Abstracts of Lectures, Symposia and Free Communications
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II. SESSION NUMBERS

Symposia: 11-19
Round Table Discussions: 21-29
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Example:
F-26 represents Round Table Discussion on Tumour Biology.

III. PLEASE NOTE: The number preceding each title in the Programme Book serves as identification number of the abstract in the Abstract Book.
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Volume 2
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Significant prognostic factors were studied in some human tumours. In general, the histological classification implies prognostic information. In there nerve sheath tumours the presence of infiltrative growth, high cellularity, and nuclear polymorphism, as well as the shortening of intervals between recurrences suggest bad prognosis. Prognosis of endometrial cancer depends on the depth of infiltration, type of growth (invasive, infiltrative), and loss of cell adhesiveness. In gastric and breast carcinomas those composed of more heteroploid subpopulations with low proportion of G1 and high proportion of S phase cells proved to have bad prognosis. In all tumour types examined the differentiation degree based merely on the histological picture did not agree with that determined by functional markers. These latter possessed higher prognostic value. The appearance of the placental alkaline phosphatase isoenzyme or embryonal type mucin is indicative of unfavourable prognosis. The decisive role of age factor in thyroid cases was also proved in our studies. The detection of nuclear ER in the breast by monoclonal antibody was a marker of its therapeutic and prognostic value, however, further studies are required.

ONCOGENES AND MUCINS IN COLORECTAL CANCER: IS THERE A PROGNOSTIC CORRELATION. T.M. Monnat, and J. Costa. Institute of Pathology, University of Lausanne, Lausanne, Switzerland.

In different patients lesions with identical gross and microscopic appearance have different natural histories and responses to therapy. Numerous efforts have been made to refine morphological techniques in order to better predict the behaviour of tumors and preneoplastic lesions. In addition to classic morphology a number of laboratory techniques can be used by the pathologist to attempt a factorial analysis of tumor progression that will predict the biological behaviour of a neoplasm. During the past year a prospective study in our laboratory has analyzed 40 tissue samples of 18 patients with carcinoma of the colon. We made use of conventional histopathology, immunohistochemistry and biochemical analysis in order to answer the questions: 1) are lesions with identical morphological classification to the extent of the cancerous lesion, these cases were classified to the following four types: namely, localized abdominal type, liver metastasis type, axillary type and distant metastasis type. In our study the survival periods were 4.0% (37 cases), 3.0% (22 cases), and 2.0% (5 cases) respectively. Survival time was closely related to the extent of the cancerous lesion and to the kind of chemotherapeutic method. Other back ground factors such as performance status, sex, age etc., are also discussed.
B-12: ANTI-ONCOGENES, SUPPRESSOR ELEMENTS AND ONCOCENE REGULATORY SEQUENCES

1841 FACTORS INFLUENCING SURVIVAL OF 679 CASES WITH PATHOLOGICALLY PROVEN HEPATOCELLULAR CARCINOMA - WITH SPECIAL REFERENCE TO EARLY STAGE. [AUGUST] MORNING

679 cases of pathologically proven hepatocellular carcinoma (HCC) were reported. Encouraging improvement in the 5-year survival rates were observed, being 1.7% in 1955-1960, 7.1% in 1961-1965 and 12.7% in 1966-1970. The analyses of the prognostic factors revealed that the 5-year survival rates were significantly lower as compared with their counterparts in patients of alpha fetoprotein (AFP) survey (J3.2% vs 3.9%), of subclinical stage (43.0% vs 10.0%), with AFP 4,000 ng/ml (10.9% vs 9.7%), with gamma-GT > 40 units (29.1% vs 22.0%), with normal liver function test (13.5% vs 4.0%), with resection (28.2% vs 6.1%), with radical resection (37.1% vs 13.9%), with postoperative AFP & 40 ng/ml (57.3% vs 0%), with single nodule HCC (32.0% vs 6.3%), with encapsulated tumor (47.4% vs 16.0%), with HCC > 5 cm (60.3% vs 7.6%), particularly with small HCC resection (9.4% vs 13.5%). However, no significant difference was found in other factors including age, degree of cirrhosis, site of tumor and immunity. Further analysis revealed that small HCC had much higher percentage in well encapsulated tumor (32.0% vs 40.0%), single tumor (42.4% vs 40.1%) and much lower percentage of gross tumor emboli in the intrahepatic veins (0.6% vs 30.7%). In small HCC, however, patients without or with macroscopic cirrhosis and better prognosis. It is concluded that early radical resection and good liver function remain the leading factors which favor a better prognosis, and early radical resection conducted before spreading occurs is of prime importance. Some biological characteristics including number and capsule status of tumor nodules remain to be investigated.


1842 CLINICO-PATHOLOGICAL CORRELATION: THE LAST DESIRE OF A DESPERATE PATHOLOGIST. [AUGUST] MORNING
J. Mekinen, Dept. of Pathology, Univ. of Helsinki, Helsinki, Finland.

We are living in the times of a revolution in pathology. The days in which the pathologist indicated whether the tissue was benign or malignant are over ever. The development of technology, the masses of new functional tests, the computerization of the pathology departments gave birth to new terms: like pathologist-scientist, pathologist-technologist, pathologist-administrator, pathologist-systems analyst. Exceptional individuals are rare and in practice it is impossible for clinicians to be their own pathologists. It is also impossible for pathologists to understand the mechanism of diseases without background in clinical medicine. As a proper diagnosis is more and more the result of a complex team-work of clinicians and pathologists, clinicopathological correlations are essential in our daily work. This cooperative work needs clinicians with a prepared mind and pathologists with good professional skills. At last but not least both clinicians and pathologists has to be aware of the limitations of their specialties, they need a lot of good will to understand each other and more than high technology they need the ability of communication. Thus, clinicopathologic correlations will be not the last desire of a desperate pathologist but the reality of an optimist human being.

B-12: ANTI-ONCOGENES, SUPPRESSOR ELEMENTS AND ONCOCENE REGULATORY SEQUENCES

1843 BRIEF SURVEY OF TUMOUR-SUPPRESSOR SYSTEMS
George Klein, Department of Tumor Biology, Karolinska Institutet, S-104 Stockholm, Sweden.

Somatic cells are under multiple regulatory controls. It is therefore not surprising that tumor development is a multistep process, involving tumor progression, clonal subclonal selection continuously favors cells with a greater intrinsic and lower responsive growth rate. Three "worlds" of genes can be envisaged and contribute to this process:
1. Oncogenes, i.e., highly conserved genes whose normal function relates to the regulation of the cell cycle at one of several levels. Following structural or regulatory changes, activated oncogenes raise the "intrinsic" growth rate of the cell;
2. Anti oncogenes or suppressor genes, capable of counteracting the expression of the tumor genetic phenotype;
3. "Modulator" genes that influence the behavior of established tumors with regard to metastasis, invasiveness, hormone dependence, and other relevant "will characteristics" of the neoplastic phenotype.

In this talk, I shall briefly review the evidence on the tumor suppressor genes and their probable mechanisms of action. This will provide a background for the subsequent presentations by other speakers, dealing with the induction of differentiation in established tumors, inversions of translocations, suppression of transgene expression by somatic hybridization, and genetic loss of function in childhood tumors.
1845 Expression of retroviral oncogenes and suppression of tropomyosin synthesis: studies on the mechanisms of oncogene action

H.L. Cooper, Bethesda, USA

1847 Inducer mediated modulation of gene expression during murine erythroleukemia (HEL) differentiaation. M. A. Marks, M. Sheffrey, R. Ramsey and R.A. Rifkind, Memorial Sloan Kettering Cancer Center, New York, U.S.A.

We have shown that hexamethylene bisacetamide (HMBA) is a very effective inducer of HEL erythroid differentiation, including cessation of proliferation and globin gene expression. The present studies report on the inducer mediated modulation of gene expression during differentiation of these transformed cells, specifically genes for the differentiated phenotype, eg., a and GPa1 globin genes; genes for metabolic function, eg., rRNA, and genes which may be related to cell proliferation, eg., c-myb, c-myc, and PS1. HMBA causes a marked increase in globin gene transcription by 24 hrs., (a) and 36 hrs. (GPa1). This is preceded by alterations in chromatin domain of globin genes characterized by disruption of the nucleosome pattern corresponding to globin structural genes and appearance of DNAse hypersensitive sites 5' to the cap site of a and GPa1. HMBA suppresses rRNA gene expression and alters chromatin structure of rRNA gene domain characterized by a reassembly of nucleosome conformational pattern. HMBA rapidly (within 1 hr.) suppresses c-myb expression which persists through terminal differentiation while c-myc expression is only transiently suppressed, returning to control levels within 8-12 hrs. Hemin induces HEL to express globin genes but does not stop cell division and doesn't suppress c-myc. Dexamethasone blocks HMBA induced commitment to terminal differentiation and blocks HMBA mediated c-myb suppression. Suppression of c-myc expression in this hematopoietic neoplasm appears related to inducer mediated loss of cell division.

1846 Sequential molecular and biological changes during mouse skin carcinogenesis.

M. Quinlanilla, Glasgow, Scotland

1848 Expression of c-myc, c-fos and c-myb during induced differentiation of the human monoblastic cell line U-937.

K. Nilsson*, L.-G. Larsson*, I. Iwahed*, U. Pettersson**, and B. Vennstrom***. Lab. of Tumor Biology, Dept. of Pathology* and Dept. of Medical Genetics**, Univ. of Uppsala, Upplands, Sweden, EMBL, Heidelberg, FRG***.

The histiocytic lymphoma cell line U-937 with basic monoblastic features can be induced to differentiation in vitro using the phorbol ester TPA or physiological inducers like retinoic acid, vitamin D3, Interferon and T-cell supernatant. The differentiation is terminal, i.e., it is irreversible and associated with a proliferation arrest.

The present paper describes data on the differentiation associated changes in the expression of the proto-oncogenes c-myc, c-myc and c-fos as determined by analyses of the corresponding mRNA. Levels. By use of a retroviral vector it has been possible to introduce v-myc into U-937 cells which then constitutively express the v-myc mRNA. The results from these studies, aimed at studying the role of myc in the control of the differentiation process, will be described.
1849 FUTATIVE CIS-ACTING CELLULAR REGULATORY SEQUENCES OF V-ONC AND PROTO-ONC GENES
Janne Minarovits
Microbiological Research Group of the National Institute of Hygiene H-1529 Budapest Pihené u 1 HUNGARY

v-onc genes transduced by acute transforming retroviruses differ from proto-onc genes as putative regulatory regions 5' and 3' flanking sequences, introns are removed and a few bases in the coding regions mutated. In addition to transforming genes oncoviroses may acquire other cellular nucleic acid sequences involved in control of gene expression. A computer analysis revealed that the genomes of Harvey murine sarcoma virus and mouse sarcoma virus contain sequences flanking the viral oncogenes with >80% and >60% homology to a brain specific regulatory /identifier, ID/ sequence /1/. Nucleotides 131-154 of a putative cellular oncogene amplified in human neuroblastoma cells, N-myc /2/ also show a >70% homology to the 5' half /nucleotides 45-75/ of the brain specific ID sequence. The enhancer-promoter region of 3C virus /a human papovavirus/ replicating in fetal glial cells was shown to contain regions of homology with the same ID sequence as well /3/. Binding sites of hormone receptors are putative regulatory elements within the c-myc locus. The third intron of putative mammary oncogene MMTV-LffR /5,6/ contains a region showing >70% homology with the same ID sequence as well /3/. Binding sites of hormone receptors are putative regulatory elements within the c-myc locus. N-myc /2/ contain a region showing >70% homology to putative glucocorticoid-receptor binding sites of human proopiomelanocortin gene and MMTV-LffR /5,6/. The significance of these data as to the activation and suppression of proto-onc gene expression and tissue specificity of viral transformation will be discussed. 1. Minarovits, J. et al. FEBS Letters 171, 308 /1984/ 2. Schwab, H. et al. Nature 305, 245 /1983/ 3. Kenney, S. et al. Science 226, 1597 /1984/ 4. van Ooyen, A. and Husse, S. Cell 39, 233 /1984/ 5. Cochet, N. et al. Nature 299, 182 /1982/ 6. Donehower, L.A. et al. J. Virol.37, 226

1850 CIS-REGULATORY CONTROL OF ONCOGENE EXPRESSION.
G.F. Vande Voorde, Frederick, USA

The c-onc gene is involved in the genesis of a variety of neoplasias in diverse cell types. Alteration of this gene's normal pattern of expression by chromosome translocation in human and murine lymphoid malignancies or by retroviral insertion in murine T lymphomas may be important steps in neoplastic progression. Recent experiments have begun to elucidate a potentially complex pattern of normal c-onc control involving regions both within and upstream of the gene. The presence of multiple conserved Dnaase I hypersensitive (DH) sites within intact murine chromosome 13 and involved the same chromosomal region as that previously identified in retinoblastoma tumors. Specific loss of constitutional chromosome 13 heterozygosity was also apparent in sporadic osteosarcomas. These results suggest that both diseases are due to the histologic unmasking of pleiotropic recessive mutant alleles of the RBI locus, and that the clinical occurrence of mixed cancer families such as these may be due to the differential expression of a single recessive mutation. These findings have led to the development of accurate predictors for this disease. They have also provided a theoretical basis for defining the number and genetic location of genes whose recessive mutant forms predispose to cancer; examination of several other tumor types indicates that there are a limited number of this type of gene and that each has multiple tissue specificities. 1. Minarovits, J. et al. FEBS Letters 171, 203 /1984/ 2. Schwab, H. et al. Nature 305, 245 /1983/ 3. Kenney, S. et al. Science 226, 1597 /1984/ 4. van Ooyen, A. and Husse, S. Cell 39, 233 /1984/ 5. Cochet, N. et al. Nature 299, 182 /1982/ 6. Donehower, L.A. et al. J. Virol.37, 226

1851 MOLECULAR GENETICS OF HUMAN FAMILIAL CANCER: U. Cavenee, M. Hansen, H. Schrake and A. Koufos, Ludwig Institute for Cancer Research, McGill University, Montreal, Canada.

Mutant alleles of the RBI locus at 13q14 have been linked to the development of retinoblastoma, a tumor of embryonal neural retina. In the bilateral form of the disease, inheritance of a germinal mutation at this locus predisposes each retinal cell to a subsequent second somatic event which results in the formation of the retinoblastoma tumor. Spontaneous unilateral tumor occurrence appears to result from two sequential somatic events. Survivors of the bilateral, but not unilateral, form of this eye tumor are at substantially increased risk for the subsequent development of second primary cancers, particularly osteosarcoma. To determine if osteosarcoma and retinoblastoma share a common pathogenetic mechanism, we determined restriction fragment length alleles at loci on chromosome 13 in DNA from constitutional tissues of bilaterally affected retinoblastoma patients and from their osteosarcoma tumors. Loss of constitutional heterozygosity in the tumors occurred specifically for chromosome 13 and involved the same chromosomal region as that previously identified in retinoblastoma tumors. Specific loss of constitutional chromosome 13 heterozygosity was also apparent in sporadic osteosarcomas. These results suggest that both diseases are due to the histologic unmasking of pleiotropic recessive mutant alleles of the RBI locus, and that the clinical occurrence of mixed cancer families such as these may be due to the differential expression of a single recessive mutation. These findings have led to the development of accurate predictors for this disease. They have also provided a theoretical basis for defining the number and genetic location of genes whose recessive mutant forms predispose to cancer; examination of several other tumor types indicates that there are a limited number of this type of gene and that each has multiple tissue specificities. 1. Minarovits, J. et al. FEBS Letters 171, 203 /1984/ 2. Schwab, H. et al. Nature 305, 245 /1983/ 3. Kenney, S. et al. Science 226, 1597 /1984/ 4. van Ooyen, A. and Husse, S. Cell 39, 233 /1984/ 5. Cochet, N. et al. Nature 299, 182 /1982/ 6. Donehower, L.A. et al. J. Virol.37, 226

1852 REGULATION AND PROPERTIES OF THE C-MYC PROTOOCONGENE.
X. Marcy, P. Fahlander, M. A. Julius, A. Nepveu, E. F. Remmers, J-Q Yang and M. Jellin. Department of Biochemistry, State University of New York at Stony Brook, Stony Brook, N.Y. USA.

The c-myc gene is involved in the genesis of a variety of neoplasias in diverse cell types. Alteration of this gene's normal pattern of expression by chromosome translocation in human and murine lymphoid malignancies or by retroviral insertion in murine T lymphomas may be important steps in neoplastic progression. Recent experiments have begun to elucidate a potentially complex pattern of normal c-myc control involving regions both within and upstream of the gene. The presence of multiple conserved Dnaase I hypersensitive (DH) sites within intact murine chromosome 13 and human c-myc loci suggest the presence of multiple regulatory elements. Evidence will be presented for the existence of cis-acting negative and positive regulatory elements within the c-myc locus.
1853 POSSIBLE PROMOTING FACTORS IN RADIATION LEUKEMOGENESIS. Julia Gidali, "JUC" Natl. Res. Institute for Radiobiology and Radiohygiene, Budapest, Hungary

Although viral origin of some radiation-induced leukemias has already been proved in mice, various conditions also influence radiation leukemogenesis. Several data support the hypothesis that host factors (age, sex, environmental factors, hormones, immunosupression, liberation of humoral factors and/or promoters) may influence the incidence of leukemia. Since stem cells are regarded as progenitors of leukemic cells and mutation of stem cells may initiate leukemogenesis, the amount of target cells (pluripotent stem cells or lymphoid progenitor cells) as well as their proliferation rate may affect the neoplastic transformation. Forced proliferation of stem cells (in regeneration processes) may render them highly susceptible for transformation. Radiation damage and recovery of stem cells after chronic, protracted or a relatively low dose acute irradiation will be discussed in connection with leukemia incidence.

The possible role of interactions between stem cells and microenvironmental cells, as well as humoral effects in the development of radiation induced leukemia will be discussed.

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1855 MECHANISM OF RADIATION-OR CHEMICALLY-INDUCED T-CELL LYMPHOMAGENESIS IN MICE. Ken'iro YOKOBO and Kazunoshi YANAGIHARA, Research Institute for Nuclear Medicine & Biology, Hiroshima University, Hiroshima (734) Japan.

T-cell lymphomas were induced in NFS/N mice either by x-irradiation or N-nitrosoethylurea (NEU), and cell lines, derived from these lymphoma cases were established. Neither the expression of infectious endogenous viruses nor M-MuLV-related activities were demonstrable by various standard assays in both primary lymphomas and cell lines. Furthermore, there was no amplification of ENV gene of endogenous viruses (xenotropic and MCF), or no amplification of or rearrangement of myc and ras gene family as demonstrated by Southern blot assay. Oncogenic MCF virus was generated from non-producer lymphoma cell lines of NFS/N origin infected with a non-oncogenic ecotropic virus(E2). This may represent the possible mechanism of occasional emergence and the isolation of oncogenic viruses in non-viral T-cell lymphomagenesis in certain mouse strains, and these phenomenon might also misled the investigator into considering that an infectious lymphomagenic virus plays an essential role in induction of lymphomas by radiation or chemical agents. Further studies suggested that lymphomas infected with MCF virus was generated through the recombination of E6 viral genome and a modified proviral DNA of endogenous viruses, present in radiation- or chemically-induced lymphomas, and that an interaction or synergy of MCF and ecotropic viruses is required for MCF virus to exert its lymphomagenic activity. (This study was supported by a Grant-in-Aid for Cancer Research from the Ministry of Education, Science and Culture, Japan.)

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We have been inducing thymic lymphomas in mice by the chemical carcinogen NMU (nitrouracylethylene) and y-rays, using established protocols. The strains of mice used have been B6F1, 129/J and C57Bl/6. Essentially 100% of tumor incidence was obtained with both agents in RF/J and C57Bl/6. In 129/J only NMU was a good inducer. We subsequently have studied the incidence of oncogene activation in these thymic lymphomas. We have already obtained the results in RF/J and in 129/J, while the work on C57Bl/6 tumors is in progress.

The tumors induced in RF/J and 129/J were analyzed by the focus forming assay in NIH 3T3 cells. 40% of the tumors, regardless of inducing agent, induced focus formation. The only oncogenes identified so far have been K- and N-ras. We have not been able to find activated N-ras in these tumors.

After initial cloning and sequencing of a representative of K- and N-ras the initial mutations found were: in K-ras a C-A transition in the second base of codon 12 changing glycine to aspartic acid; in N-ras a C-A transversion in the first base of codon 61. Through the use of oligonucleotide mismatch hybridization analysis the other tumors have been studied. So far 19 out of 21 of the K-ras activated oncogenes have the same mutation found in the gene originally cloned.

Conversely, only the originally cloned N-ras gene had the C-A transversion at codon 61, another one has a G-A mutation in the second base of codon 61. Four other tumors contain different mutations which have not been identified yet. The tumors in C57Bl/6 have been analyzed in the neo-cotransformation assay in NIH 3T3 cells followed by tumorigenesis assay in nude mice. DNAs from 7 out of 7 NMU-induced lymphomas and 12 out of 15 lymphomas induced by y-rays produced tumor in nude mice.


Skin fibroblasts from individuals with genetic disorders predisposing to a high risk of cancer, from high cancer families and human cells transformed in vitro or in vivo, compared with normal controls or cell lines from normal individuals, show an increased incidence of chromatid breaks and gaps following x-irradiation during the G2 phase of the cell cycle. This enhanced chromatid radiosensitivity apparently results from deficient DNA repair during G2 phase, as described in previous studies. We report here an animal model with a similar genetic susceptibility to tumor induction. In contrast to most other inbred mouse strains, the BALB/c mouse, with the exception of one subline, is highly susceptible to plasmacloma induction by i.p. injection of mineral oils, defined alkanes, e.g., pristane or implantation of plastics. Susceptibility behaves as a recessive property in that F1 hybrids between BALB/c AnPt and the resistant DBA/2 NPt mouse develop virtually no plasmaclomas after pristane injection. B-lymphocytes and skin fibroblasts of BALB/c AnPt mice, like cancer-prone cells of humans, show a significantly higher incidence of chromatid breaks following x-irradiation (100R) than corresponding cells of the resistant strain DBA/2 NPt or the F1 hybrid. B-lymphocytes and spleen fibroblasts of the resistant subline DBA/2 NPt also show significantly fewer chromatid breaks following x-irradiation than the plasmacloma-susceptible BALB/c AnPt cells. BALB/c NPt and BALB/c J have the same alleles for most of the commonly studied enzymes, MHC, and Ig loci; genetic differences in the Raf-1, G2 and several other loci identified by restriction fragment polymorphism have not been found. The present findings support the concept that genetic susceptibility to cancer induction in mice is more closely associated with deficient DNA repair during G2 phase manifest as enhanced chromatid radiosensitivity.
1860 HUMAN TUMOR VIRUSES Robert C. Gallo, M.D., National Cancer Institute, NIH Bethesda, MD USA

All known human retroviruses were discovered within the past 10 years. There are 4: HTLV-I, II, III & IV. HIV-1, II and III have the following properties in common: 1) Tropism; 2) induction of neoplasia in association with malignant T lymphocytes; 3) usually present in the genome in a "silent" until T-cells are activated; 4) presence of one or more gag genes; 5) presence of closely related genes in subhuman primates; 6) usually present in the genome in a "silent" until T-cells are activated; 7) presence of one or more gag genes; 8) presence of closely related genes in subhuman primates; 9) presence of one or more gag genes; 10) presence of closely related genes in subhuman primates.

1862 LYMPHADENOPATHY ASSOCIATED VIRUS /LAV/ AS THE PRIMARY ETIOLOGIC AGENT OF AIDS AND THERAPEUTIC PERSPECTIVES. J.C. Chermann and F. Barre-Sinoussi, Oncology Unit, Institute Pasteur, Paris, France

A new type of human retrovirus, LAV, first isolated from an homosexual with persistent lymphadenopathy and hereafter from patients with frank AIDS is now considered the primary cause of AIDS. Its frequent isolation from all individuals at risk for the disease, its selective tropism for the T^+ subset of lymphocytes, its cytopathic effect on T cells and the prevalence of antibodies against LAV proteins in AIDS and ARC patients as well as in high risk groups strongly supported a causal relationship between the virus and the disease. LAV can be transmitted via blood as it is suggested by documented cases of viral infection in hemophiliacs and in recipients of blood transfusions. The occurrence period which allows the interplay of cofactors such as viral or bacterial infections and repeated antigenic stimulation. Analogy with the slow retroviruses (feeder viruses) is suggested by some similar aspects of the pathogenicity and the AIDS retrovirus itself. They both have unusually large genomes and envelope glycoproteins as well as typical morphology. LAV genome contains two new open reading frames /O and /P/ and an exceptionally long envelope gene. The genome organization of LAV is so far unique among retroviruses. This virus is clearly the prototype of a new group of human retroviruses. The identification of LAV as a causative agent of AIDS has allowed the investigation of compound inhibiting viral replication, one of this compound, HA-19, as a strong inhibitor of LAV reverse transcriptase and inhibits the viral replication in vivo in treated patients. Whether such treatment will be enough or should be combined to some marrow transplant for restoring immune functions remains to be determined.

E-11: VIROLOGICAL ASPECTS OF AIDS

1861 HUMAN T-LYMPHOTROPHIC VIRUS INFECTIONS IN HUNGARY

Kánya Gyrina, Darzler S, Pólosa I, Mist G., Nothvád A.

Sera of 326 patients with various hematological disorders were tested for antibodies to human T-lymphotropic virus type I /HTLV-I/ and type II /HTLV-II/ by indirect immunofluorescence, antigen-antibody interaction and ELISA methods. Out of the 326 sera only two patients with haemoblastosis reacted positively with HTLV-I antigen, but none with the HTLV-II antigen, indicating that HTLV-I infection is very rare in this country.

Serum antibodies to human T-lymphotropic virus type III /HTLV-III, LAV/ have been examined in more than three thousand individuals at risk for AIDS, during a nationwide epidemiological survey. Sera were screened for HTLV-III/LAV antibodies by ELISA, and reactive reactions were confirmed by immunofluorescence and radioimmunooprecipitation. HTLV-III/LAV antibodies were detected in 22 of 374 (5.9%) homosexual men, 4 of 497 (0.8%) haemophiliacs and 1 of 1093 (0.1%) patients with renal diseases. Sera of 111 patients with AIDS and 39 with mixed connective tissue diseases, as well as of 46 lymphoma positive and 903 blood donors proved to be negative.

All individuals with positive sera were clinically asymptomatic. Immunoblotting of positive sera were reactive with HTLV-III/LAV p25,95, gp42 and gp120 proteins of HIV-III, indicating the virus infection. In a 1/4 HIV-III/LAV/25 antigen test, 7/46 of the positive sera showed neutralization activity however, the titers were very low.

Data presented in this manuscript suggest that HTLV-III/LAV infection similar to that of Western Europe, is present in Hungarian AIDS-risk population but in a relatively low ratio.

1863 ANALYSIS OF THE STRUCTURE AND FUNCTION OF THE HTLV-III GENE

Floese Kong-Staal, Laboratory of Tumor Cell Biology, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.

Human T-lymphotropic Virus Type III (HTLV-III) and related retroviruses (LAV/ARD) have been implicated in the etiologic agent of AIDS. HTLV-I, like HTLV-II and -III, is tropic for the OKT4 helper T-lymphocyte. However, while HTLV-I and II do not transform these cells, HTLV-III transforms this cell in vitro. HTLV-III is cytopathic. Nucleotide sequence analysis revealed five open reading frames (ORFs) in HTLV-III corresponding to the gag,pol, and env genes and two additional ORFs (termed m and p). That gag and env are real genes was demonstrated by the fact that peptides expressed from these regions were immunoreactive with AIDS patients' sera. Functional analyses of cDNA clones identified yet another gene (tat) the production of which specifically activates in trans the expression of genes linked to the HTLV-III LTR. To address the role of viral genes in the cytopathic property of HTLV-III, we first demonstrated by DNA transfection that a molecular clone of HTLV-III can specifically inhibit the viral replication in vitro. Systemic deletion of this biologically active gene and its effect on virus production and cell killing will be discussed. We have now analyzed over 30 HTLV-III isolates by Southern hybridization, and several of them are suggested to be a strong inhibitor of LAV reverse transcriptase and inhibits the viral replication in vivo in treated patients. Whether such treatment will be enough or should be combined to some marrow transplant for restoring immune functions remains to be determined.
1864 DIFFERENCES IN GROWTH PROPERTIES IN VITRO OF LAV/HTLV-III ISOLATES DERIVED FROM PATIENTS WITH LYMPHADENOPATHY OR AIDS.
E.L. Fenyö, Stockholm, Sweden

1866 ELECTRON MICROSCOPIC STUDIES IN AIDS PATIENTS
F. Györey, Houston, USA

1865 INVOLVEMENT OF AIDS-ASSOCIATED RETROVIRUS (ARV) IN PATIENTS WITH HEMOPHILIA AND HOUSEHOLD MEMBERS OF MEDITERRANEAN ORIGIN - A 5-YEAR PROSPECTIVE STUDY.

Seroepidemiologic prospective studies on 364 patients with coagulation defects mainly hemophilia A, followed by hemophilia B, Von Willebrand's disease as well as 366 household members (145 family units) are ongoing for a 5-year period to determine what risk of AIDS/Kaposi's sarcoma exists for seropositive individuals of mediterranean origin. Anti-ARV antibody prevalence of the patients, bled in 1985 was 31% (73 of 234). Moreover 12 household contacts from 4 family units were weakly positive. While 18 of 21 couples were seronegative, one couple (male patient/female spouse) was found seropositive; the patient died spontaneously with a questionable AIDS. Antibody prevalence persisted in high-titer seropositive patients (21 of 80 patients in the second year follow-up). Twelve of them developed LAS. Geometric mean titers to other viral antibodies including EBV, CMV, HSV-1 and HSV-2 were also determined in hemophilia patients. A higher antibody prevalence persisted in high-titer seropositive patients (21 of 80 patients in the second year follow-up). Twelve of them developed LAS. Geometric mean titers to other viral antibodies including EBV, CMV, HSV-1 and HSV-2 were also determined in hemophilia patients. A higher antibody prevalence persisted in high-titer seropositive patients (21 of 80 patients in the second year follow-up).

1867 ELEVATED URINARY EXCRETION OF MODIFIED NUCLEOSIDES IN PATIENTS WITH VARIOUS MANIFESTATIONS OF INFECTION WITH HTLV-III/LAV.
Opendra K. Sharma, Ernest Borek, Frank L. Buchman, David G. Oun, Kent A. Park, Franklyn H. Judson, Bruce S. Dobosz, Kathryn K. Zunich and Charles G. Kirschner. AMC Cancer Research Center, Denver Disease Control Service and National Jewish Center for Immunology and Respiratory Medicine, Denver, CO, USA.

Cancer patients and tumor-bearing animals excrete increased amounts of modified purines and pyrimidines into their urine. These modified nucleosides are products of catabolism of tRNA and to a lesser extent of other RNAs. To test the hypothesis that infection with HTLV-III/LAV may be associated with increased tRNA turnover, we have measured excretion of modified nucleosides and d-sialosylthreonyluric acid (S-AIBA) in the urine of asymptomatic homosexual men who were either seropositive (+) (n=15) or seronegative (-) (n=20) for antibodies to HTLV-III/LAV, homosexual men with the generalized lymphadenopathy syndrome (GLS) (n=38), the AIDS-related complex (ARC) (n=16) or AIDS with KS (n=12) or AIDs with GI (n=9). Pseudouridine (P), 1-methylnucleosine (m1A), 2- pyridinc-5-carboxamide-6'-zidoformanosine (PCHN), L-methylinosine (m1I), L-methylguanosine (m1G), N4-methylguanosine (m1G), N2,N4-dimethylguanosine (m2G), N6-acetylcycteine (ac6c) and N6-threonylguanosine (t6A) were quanitified. Patients with AIDs, GLS, ARC and asymptomatic homosexual men excreted increased amounts of markers in the urine relative to age matched heterosexual control population. The asymptomatic HTLV-III/LAV (+) subjects excreted more m1A, ac6c and t6A than HTLV-III/LAV (-) subjects. However, persons with ARC had markedly increased excretion of 7 of the 9 nucleosides (m1G, PCHN, m1I, m1A, m2G, m1G, t6A) and were different from the (-), (+) and GLS groups. Excretion of modified nucleosides in subjects with ARC was similar to patients with AIDS. Current studies are directed to evaluate if increased excretion of nucleosides has value in identification of persons who will progress to ARC or AIDS and if nucleoside excretion can be used to monitor responses to treatment.

Dedicated to Dr. Ernest Borek, a distinguished scientist pioneer in nucleic acids methylation. Deceased February 14, 1986.
F-13: DIFFERENTIATION AND CANCER

1868 CONTROL OF PROLIFERATION OF MYELOID LEUKAEMIA CELLS BY INDUCERS OF CELLL DIFFERENTIATION. M. Hozumi, Saitama, Japan
We have analyzed basic problems to develop therapeutic method of leukaemia by induction of terminal cell differentiation using mainly mouse myeloid leukaemia cell line, M1 as an experimental model. The M1 cells can be induced to differentiate into macrophages and granulocytes by various substances losing leukemogenicity to syngeneic mice. We characterized two protein factors regulating differentiation of M1 cells, one was a protein inducer of differentiation (D-factor) produced from various cells including differentiated M1 cells and the other was an inhibitory factor (I-factor) produced from M1 cell variant clones resistant to D-factor and several different inducions. The purified I-factor from the conditioned media from mouse L cells and mouse Ehrlich cells with molecular weight of 40,000-60,000 bound specifically to M1 cells and was distinct from CSF. The I-factor from resistant M1 cells was heat-labile glycoprotein with heterogeneous molecular size. We purified partially (almost 7,000 fold) the major fraction of I-factor with molecular weight of 60,000-60,000 and the I-factor had isoelectric point at about 9. Production of I-factor in resistant M1 cells was closely associated with resistance of the cells to differentiation inducers, since inhibition of synthesis of this I-factor restored the sensitivity of the resistant cells to the inducers. The I-factor inhibited growth and differentiation of normal bone marrow stem cells stimulated by CSF. D-factor and several other differentiation inducers could induce terminal differentiation of cytotoxic anti-cancer drug-resistant clones of M1 cells and suppressed proliferation of the cells.

1869 THE CELLULAR ORIGIN OF B-CELL MALIGNANCIES
Two major approaches have helped in establishing the cellular origin of B-cell malignancies. First, B-cell-specific and B-cell associated monoclonal antibodies (MoAb) have been extensively used as probes to immunophenotype malignant B cells in comparison with different stages of normal B lymphocyte differentiation in fetal and adult lymphoid tissues. Second, differentiation promoters have been utilized to investigate the differentiation options of malignant B and their normal equivalent cells. These studies have led to realize that, in man, a linear scheme of B-cell differentiation is oversimplified and have provided evidence for a differentiation-oriented classification of B-cell malignancies entailing the following entities: a) neoplasms of bone marrow B-cell precursors represented by common acute lymphoblastic leukemia. b) Tumors of peripheral B cells. Centrolymphatic centrocycytic lymphomas appear to arise from the germinal centers of secondary follicles. B-cell chronic lymphocytic leukemia (B-CLL) and the closely related centrocytic lymphoma appear to involve a peculiar B-cell population expressing with surprising regularity T-cell antigens (mainly CD5) and presenting striking homologies with the murine lym- b-cell subset. An abnormal activation of these B-cell subpopulations may lead to the features and membrane disturbances of hairy cell leukemia. c) Plasma cell malignancies. In the bone marrow of patients with multiple myeloma, we have recently identified a population of actively proliferating lymphoid-appearing cells which are CALLA (CD10) +, do not express B-cell specific or associated markers and can be persuaded in vitro to transform into monoclonal plasmacells thus behaving as malignant plasma-cell precursors. Those phenotypic data led us to investigate the functional significance of MoAb-defined B-cell molecules and how this might relate to the differentiation block in B-CLL. Our studies underline the importance of the close relationships between cell surface antigens and cytoskeleton structures.

1870 ALTERATION OF THE MALIGNANT PHENOTYPE BY GLYCOCORticoids IN VITRO.
F. Freshney, Glasgow, UK
In an attempt to define phenotypes of various epithelial cell subpopulations in the human mammary gland and to study their relationship to phenotypic features of breast tumours we produced a panel of mouse monoclonal antibodies/mabs/ against variety of epithelial antigens. The spectrum of mabs prepared includes antibodies recognizing glycoproteins of milk fat globule membranes/FMG series/ various keratin polypeptides. By immunohistochemical methods and Western blotting we used to establish tissue distribution and molecular weight of the target molecules, respecti- vely. Out of several in vitro systems of human breast epithelium, reduction mammoplasty organoids cultured in collagen gel were found to be the most adequate model of differentiation as judged from the morphology and phenotype of cultured cells evaluated by mabs. By means of our single keratin-specific mab it has not only been possible to differentiate between myo- epithelial and luminal cells but also to define subpopulations of luminal cells. Using double staining methods, the expression of various keratins has been correlated with that of membrane glycoproteins. Frequency and topographic distribution of the subpopulations defined by mabs in normal mammary gland as well as their proliferative potential in vitro and occurrence of the particular phenotype among more than 300 breast tumours was examined. The results led us to postulate a general model of possible line-age relation of these antibody epithelial cell subpopulations during normal differentiation and malignancy.
1872 GROWTH AND DIFFERENTIATION OF HUMAN TERATOMA STEM CELLS
M. Pera, London, UK

1874 BIOLOGICAL AND BIOCHEMICAL CHANGES IN SPONTANEOUSLY DIFFERENTIATED MOUSE TERATOCARCINOMA CELLS
Rasko J, Zakany J, Burg K, Hadlaczky G, Kelemen, I, Atalay T.
Biol. M.), Inst. of Genetics, Hungarian Academy of Sciences, Szeged, Hungary
Optimal culture conditions for spontaneous differentiation of mouse teratocarcinoma cells were established. 40-60% of differentiated colonies proved to be silver positive and exhibited nucleate membranes. There was an increase in the β-adrenergic receptor sites in the differentiated cultures and new centromeric chromosomal non-histon proteins appeared in the differentiated cells, shown by immunoblotting experiments, using antisera specific to centromeric antigens. The mutability of differentiated cultures was significantly higher than that of nondifferentiated ones, after ethylmethanesulphonate mutagenesis. This phenomenon can be explained by the lower excision repair capacity in the differentiated cells.

1873 INDUCTION OF TERATOCARCINOMA STEM CELL DIFFERENTIATION BY INHIBITORS OF POLYAMINE SYNTHESIS.
Teratocarcinoma cells offer a unique model system for studying signals that direct differentiation during early mammalian development and that induce loss of tumorigenicity. Embryonal carcinoma (EC) cells, the tumorigenic stem cells of teratocarcinomas, retain the ability to differentiate into derivatives of all three germ layers. This differentiation is generally accompanied by loss of tumorigenicity, indicating that these two events are closely linked. F9 is an EC cell line, which shows a low spontaneous rate of differentiation. However, upon inhibition of their polyamine synthesis, F9 cells differentiate into parietal endoderm-like cells and lose their tumorigenicity. Polyamine synthesis may be inhibited by treatment with α-difluoromethylornithine (DFMO). This is a "suicide inhibitor" of ornithine decarboxylase (ODC), the first enzyme in the polyamine biosynthetic pathway. Thus, it contains a latent reactive group and is accepted as a substrate by ODC, following which the normal catalytic activity of the enzyme causes its own irreversible inactivation. By inhibiting the ODC activity, DFMO effectively reduces the cellular polyamine content. As a consequence, the cell cycle progression is blocked in the G1 phase and essentially all cells differentiate. Analysis of the final phenotype indicates that it is not dependent on the continued presence of DFMO; the cells are terminally differentiated and exhibit no further proliferative capacity. Studies are presently undertaken to determine whether DFMO-induced loss of tumorigenicity is associated with altered oncogene expression. The fact that DFMO blocks EC cell proliferation and induces terminal differentiation of these highly malignant cells, yet exhibits minimal toxicity, suggests an exciting alternative to cytotoxic therapy, which may be used clinically in the treatment of these germ cell tumors. (Supported by the Swedish Natural Science Research Council).

1875 INDUCTION OF DIFFERENTIATION-ASSOCIATED PROPERTIES IN A NEURONAL CELL LINE, PC12, BY THE v-ras ONCOGENES.
M. Noda and Y. Ikawa, Tsukuba Life Science Center, The Institute of Physical and Chemical Research, Wako, Saitama 351-01, Japan
It has been well documented that Kirsten (Ki-) or Harvey murine sarcoma virus (Ha-MSV) exerts growth-promoting and/or differentiation-blocking activities on various types of cells in vitro. Here we report an unexpected effect of these viruses on a rat pheochromocytoma cell line, PC12. PC12 cells, which multiply indefinitely in growth medium, are known to respond to nerve growth factor (NGF) by cessation of cell division and expression of a number of properties resembling those of differentiated neurons. We have found that Ki- and Ha-MSV mimic some, if not all, of the activities of NGF in PC12 cells, there is evidence to suggest that the viral oncogenes, v-Ki-ras and v-Ha-ras, are responsible for this phenomenon. This system may be of value for studying the mechanism of action of the v-ras genes as well as the regulatory mechanism of growth and differentiation in neuronal cells.
One of the major causes of failure in cancer chemotherapy is the proliferation of specific drug-resistant tumor cells during treatment. Drug resistant tumor cells, however, usually bear biochemical changes which are related to resistance mechanisms. New modalities against resistant cells could be possible if we could target these biochemical changes.

Vincristine (VCR)- and Adriamycin (ADM)-resistant tumor sublines from human myelogenous leukemia K562 cells showed cross resistance (pleiotropic drug resistance) to other unrelated drugs. These VCR- and ADM-resistant sublines of K562 possess an enhanced outward transport of antitumor agents, which results in a low accumulation of antitumor agents in the cells. They express unique glycoproteins in the plasma membrane, possess higher calcium content in the cells. They contained double minute chromosomes and homogeneously staining regions.

By targeting for these biochemical changes, we have established new modalities against drug resistant tumor cells. Calcium channel blockers inhibited the enhanced outward transport of VCR and ADM from resistant tumor cells, and thus overcame resistance to these agents. This approach showed potential usefulness in clinical trials.

Another possible approach against drug resistant tumor cells could be the utilization of monoclonal antibodies against unique glycoproteins in the plasma membrane of resistant tumor cells. We have developed monoclonal antibodies against Adriamycin-resistant human myelogenous leukemia K562. Our recent progress of the works on calcium channel blockers and monoclonal antibodies will be discussed.
PRECLINICAL INVESTIGATION OF PLATINUM COMPLEXES

The effectiveness as well as the toxicity of the original cis-diaminedichloroplatinum (cis-DDP), observed in clinical cancer chemotherapy, has increased the interest in intensive search for new, more selective Pt-complexes. In this presentation the in vitro and in vivo activity of a series of platinum complexes in various test models is reviewed. Structure-activity relation is demonstrated on a diaminoethaneplatinum (II) citrate, and 1, 2-diaminocyclohexyl platinum (II) glucarate. Resistance was induced in L1210 leukemia cell line against cis-DDP and against two DACH derivatives: 1, 2-diaminocyclohexylplatinum (II) citrate and 1, 2-diaminocyclohexylplatinum (II) glucarate. By using the resistant cell lines, presence and/or absence of cross resistance between various Pt-complexes could be shown. Furthermore polyamine-bound Pt-complexes have been prepared and their effectiveness in sensitive and resistant cell lines as well as in vivo has been studied. This kind of preclinical investigation provides valuable information not only for studying the mechanism of drug action, but also for clinical application, especially for the possibility to use successively different Pt-complexes in relapsed patients.

DNA-MEDIATED TRANSFER OF DRUG RESISTANCE FROM HUMAN LEUKAEMIA CELLS

The cytotoxic action of alkylating agents is attributed to their interaction with tumor cell DNA. The mechanisms of protection developed by cells against cytotoxicity are numerous and complex. Many of these result in reduced drug-DNA interaction by altering drug transport or by inactivating alkylators. When drug-DNA interaction is not prevented by any of these factors DNA repair is capable of recovering cells from drug effects. The most critical lesions caused by bifunctional alkylators are the DNA cross-links, their removal and the restoration of DNA indicate the effectiveness of DNA repair. Comparative studies on the mechanisms of resistance against bifunctional alkylators showed equal levels of DNA damage and repair revealed some differences in repair process in resistant and sensitive sublines of two different cell types, Yoshida sarcoma and P388 leukemia. Analysis of DNA damage and repair revealed different mechanisms of resistance against DNA damage in parent and in resistant sublines of two different cell types, Yoshida sarcoma and P388 leukemia. Analysis of DNA damage and repair revealed some differences in repair process in resistant cell DNA of the two cell types. In Yoshida cells the ratio of monoaducts and diguanylnucleotides was higher in the resistant than in the sensitive cell DNA by 24%. In P388 leukemia this ratio in the cell lines was the same during the observation period. Resistance of P388 cells was overcome by several chloroethylnitrosoureas. The lack of cross-resistance between these two groups of alkylating agents may be explained by the different lesions they cause in DNA: Cross-links are formed by the alkylating agents between N3 cytosine and N1 guanine. The lack of cross-resistance between the two groups of alkylating agents may be explained by the different lesions they cause in DNA: Cross-links are formed by the alkylating agents between N3 cytosine and N1 guanine. The lack of cross-resistance between the two groups of alkylating agents may be explained by the different lesions they cause in DNA: Cross-links are formed by the alkylating agents between N3 cytosine and N1 guanine.
The doxorubicin-resistant subline of P388 leukemia (P388/Dox) was cross-resistant to structurally dissimilar antineoplastic agents. To investigate this unusually broad pattern of cross-resistance, we compared the various biochemical parameters of sensitive and doxorubicin-resistant sublines. Our studies carried out in P388/Dox showed decreased levels of mixed-function oxidase enzymes. Cell surface alteration in P388/Dox was observed using different plant lectins. The P388/Dox cells showed more agglutination with all the lectins. The level of radioactivity in the P388/Dox cells 24 hours after in vivo administration of doxorubicin was only 26% of that in P388 sensitive cells. The complexity of the problem of drug resistance has prompted the development of an alternative approach, viz., the use of drug response modulators. A variety of agents—antidepressants, coronary vasodilators, and hypertensive drugs and hydroxurea were used in vitro to potentiate the effect of antineoplastic agents against acquired and intrinsically resistant leukemia cells. The results will be briefly reviewed.

**I-13: ECTOPIC HORMONE PRODUCTION IN NEOPLASIA**

**1885 ECTOPIC HORMONE PRODUCTION.**
D. M. Orth, Nashville, USA

**1886 PROPIONELANOCORTIN GENE EXPRESSION IN ADRENAL-CORT.-CORTISONE-PRODUCING HUMAN TUMORS.**
Hardy, Xavier, de Kayser, Yvonne, Lanne, Frederic, Girard, Francois, Luton, Jean Pierre and Bahn, Axel. Laboratoire d'androcrincologie et INSERM, Paris, France.

In order to assess the mechanisms of propionelanocortin (POMC) gene expression in human ACTH-producing tumors, we performed the simultaneous evaluation of POMC product and messenger RNA (mRNA) in tumor tissue. Tissue fragments obtained from corticotropin adenomas, neoplastic tumors and normal pituitaries. The POMC mRNA was detected and analyzed by dot and Northern blot hybridization using single-stranded genomic DNA probes corresponding to the coding region of the human POMC gene. Tissue concentrations of POMC products and -mRNA showed parallel distributions. A single identity POMC mRNA was also found in four nonpituitary tumors. A thymic carcinoma, in addition to the 1,600 bp POMC mRNA, contained equal amounts of a second larger POMC mRNA of 14,500 bp. A genomic probe corresponding to the 5' flanking region of the human POMC gene, versus the usual cDNA probe, hybridized with the variant mRNA species and was entirely protected in S 

**1883 BIOCHEMICAL CHARACTERISTICS AND CIRCUMVENTION OF DRUG RESISTANCE OF LEUKEMIA CELLS RESISTANT TO DOXORUBICIN.**
M.P. Chitta, V.S. Baruhr, S.G. Pradhan and K. Satyamoorthy, Cellular Chemotherapy Unit, Cancer Research Institute, Parel, Bombay-400012, Maharashtra State, India.

The doxorubicin-resistant subline of P388 leukemia (P388/Dox) was cross-resistant to structurally dissimilar antineoplastic agents. To investigate this unusually broad pattern of cross-resistance, we compared the various biochemical parameters or sensitive and doxorubicin-resistant sublines. Our studies carried out in P388/Dox showed decreased levels of mixed-function oxidase enzymes. Cell surface alteration in P388/Dox was observed using different plant lectins. The P388/Dox cells showed more agglutination with all the lectins. The level of radioactivity in the P388/Dox cells 24 hours after in vivo administration of doxorubicin was only 26% of that in P388 sensitive cells. The complexity of the problem of drug resistance has prompted the development of an alternative approach, viz., the use of drug response modulators. A variety of agents—antidepressants, coronary vasodilators, and hypertensive drugs and hydroxurea were used in vitro to potentiate the effect of antineoplastic agents against acquired and intrinsically resistant leukemia cells. The results will be briefly reviewed.

**1884 THE MULTIPLE DRUG RESISTANCE PHENOTYPE AS A FOCUS FOR CANCER THERAPY.**
William T. Beck, St. Jude Children's Research Hospital, Memphis, TN 38101, U.S.A.

Much interest is currently focused on the biochemical and pharmacological expressions of experimental multiple drug resistance and clinical MDR. The assumption is that these features are the same in both experimental and clinical MDR. This paper will focus on the role of these features in clinical MDR. The assumption is that these features are the same in both experimental and clinical MDR. The assumption is that these features are the same in both experimental and clinical MDR. The assumption is that these features are the same in both experimental and clinical MDR. The assumption is that these features are the same in both experimental and clinical MDR. The assumption is that these features are the same in both experimental and clinical MDR. The assumption is that these features are the same in both experimental and clinical MDR. The assumption is that these features are the same in both experimental and clinical MDR. The assumption is that these features are the same in both experimental and clinical MDR. The assumption is that these features are the same in both experimental and clinical MDR.

It has been reported from our laboratory that immunoreactive (IR) bombesin found in man is gastrin-releasing peptide (GRP). Thirty-eight small cell carcinomas of the lung (SCLC), 13 medullary carcinomas of the thyroid (MCT), 72 pancreatic endocrine tumors, 25 neuroblastomas and 22 carcinoids were probed for GRP. Tumor tissue was extracted by the boiling water method and peptide content was determined by radioimmunoassay. 1-IR bombesin was found in these tumors in high frequency. These tumors are classified now as neuroendocrine tumors and other neuroendocrine peptides, such as vasoactive intestinal peptide, somatostatin, calcitonin and AGTH, were found often as well. In lung carcinomas, production of GRP by adenocarcinoma cells and large cell carcinomas was much lower than by SCLC.

The presence of GRP mRNA was determined by using synthetic oligonucleotides as hybridization probes. GRP mRNA was not detected in tumor tissues without detectable GRP. A large amount of GRP mRNA, with a size of approximately 900 bases, was detected in GRP-producing SCLCs and MCTs, indicating that tumor production of GRP is always associated with elevated GRP mRNA content.

To evaluate whether GRP can be used as a tumor marker in SCLC patients, we determined plasma GRP levels in control subjects and patients with advanced lung carcinomas. GRP in plasma was extracted by an immune-affinity column, which made it possible to detect 4 pg/ml by using 3 ml of plasma. The plasma levels in control subjects were very low, while non-SCLC patients were undetectable (less than 4 pg/ml), while in 22 SCLC patients examined, 14 showed elevated levels ranging from 4.2 - 54 pg/ml. The values decreased in the patients treated effectively and increased in those manifesting progressive disease.

These data indicate that (1) IR-GRP is produced by neuroendocrine tumors, (2) GRP mRNA is elevated in GRP-producing tumor tissues, and (3) plasma GRP is a good tumor marker in patients with SCLC.

1888 FAMILIAL PRIMARY HYPERTHYROIDISM - DISTINCTIVE MUTATIONS THAT DISTURB CELL PROLIFERATION. W.M. Stephen J. National Institutes of Health, Bethesda, Maryland, U.S.A.

Studies in large kindreds have defined three distinct syndromes of familial primary hyperparathyroidism. (1) Familial hypocalciuric hypercalcemia (PHH) is an autosomal dominant trait with mild hypercalcemia that is constant from birth. The parathyroid glands show very mild hyperplasia but express a striking secretory abnormality: a small parathyroid remnant restores hypercalcemia within days after subtotal parathyroidectomy. Metastrogotes for the PHH gene show a defect in calcium recognition by the parathyroid and the kidney. Homozygotes show a more striking defect expressed as severe primary hyperparathyroidism in neonates. Thus a double dose of a gene causing defective calcium recognition results in a major increase in proliferation of parathyroid cells. (2) Familial multiple endocrine neoplasia type I (FMEN1) is most commonly expressed as primary hyperparathyroidism that worsens with time. Hypercalcemia is rare before age 15, and it shows 50% recurrence 10 years after apparently successful subtotal parathyroidectomy. We have recently analyzed a kindred with 43 surviving members known to be affected; none showed endocrine hyperfunction outside the parathyroids prior to showing primary hyperparathyroidism. A newly discovered hormonal factor may stimulate parathyroid cell growth in FMEN1 (Brandi ML et al, New Eng J Med 1986). (3) Familial multiple endocrine neoplasia type 2 (FMEN2) also shows primary hyperparathyroidism that increases with time. The penetrance of primary hyperparathyroidism among gene carriers is much lower in FMEN2 than FMEN1. Endocrine cell proliferation in FMEN2 may result from a small deletion in the short arm of chromosome 20 (2p12). These three hereditary syndromes disturb proliferative control in parathyroid cells at distinct steps: hormonal factors other than calcium (PHH), cellular recognition of extracellular calcium (PHH), and intracellular genomic processes (FMEN).
W3: ECTOPIC HORMONE PRODUCTION IN NEOPLASIA

Horvath, Dept. of Pathology, St. Michael's Hospital, Toronto, Ont., Canada
1891 PATHOLOGY OF ECTOPIC HORMONE-PRODUCING NEOPLASMS. E. Horvath, Dept. of Pathology, St. Michael's Hospital, Toronto, Ont., Canada

Ectopic hormone-producing tumors, arising in endocrine or non-endocrine tissues, synthesize one or more hormones not secreted under normal conditions in the tissue involved. Recently, the application of advanced methodology in molecular genetics helped to reveal that various endocrine cell types are programmed to elaborate numerous hormones. The division between orthotopic and ectopic is becoming increasingly blurred and the phenomenon of ectopic hormone production will eventually have to be redefined. Among the numerous peptides secreted ectopically, ACTH and other fragments of the precursor proopiomelanocortin, vasopressin and hypercalcemia-inducing factors are common. Thyroid and steroid hormones, for the synthesis of which highly specialized pathways are required, are not known to be produced ectopically. The morphology of ectopic hormone-producing tumors is as diverse as the tissues from which they derive - lung, thymus, thyroid, pancreas, prostate, etc. To establish the endocrine properties of a neoplasm, morphologic techniques for general endocrine markers are applied: special stains for argyrophilia and uranaffinity as well as immunostaining for neuron specific enolase and chromogranin. To demonstrate the hormones produced by the tumor, immunohistochemical methods utilizing specific antisera are used with great efficacy. It is of note that, owing either to the clonal evolution of a neoplasm or to therapeutic intervention, the number of expressed hormones and consequently the clinical presentation and the immunohistochemical profile of the tumor may change in time. This is an obvious caveat in the use of ectopic hormones as markers in monitoring tumor growth. Electron microscopy is often used successfully in determining the endocrine character of tumor cells demonstrating prominent RER, Golgi complex and secretory granules. It can, however, establish the cell derivation only if fine structural features characteristic of a cell type are present, such as appearance, quantity and distribution of cellular constituents, especially RER, Golgi complex and secretory granules.

THE CLINICOPATHOLOGIC SPECTRUM OF MULTIPLE ENDOCRINE NEOPLASIA SYNDROMES. B. W. Schelthauer, M.D. and E. R. Laws, Jr., M.D., Mayo Clinic, Rochester, Minnesota, USA.

The nosology of syndromes associated with synchronous or metachronous proliferative lesions of multiple endocrine organs is unsettled. They comprise complexes, some rare, in which hyperplasia or more often neoplasia occurs in two or more endocrine organs either on a sporadic or heritable basis. Association with phakomatoses, e.g. von Recklinghausen's disease, von Hippel-Lindau disease, etc., is variable. The best characterized "multiple endocrine neoplasia syndromes" include Wermer's syndrome or MEN I (pituitary adenoma, parathyroid hyperplasia or adenoma, pancreatic islet cell tumor), Sipple syndrome or MEN IIa (medullary thyroid carcinoma, pheochromocytoma, parathyroid disease), the "mucosal neuroma syndrome" or MEN IIb (medullary thyroid carcinoma, pheochromocytoma, pathologic but clinically inapparent parathyroid disease and mucosal neuromas), the "mucosal neuroma syndrome" or MEN IIB (medullary thyroid carcinoma, pheochromocytoma, pathologic but clinically inapparent parathyroid disease and mucosal neuromas) and MEN III (islet cell tumor and pheochromocytoma). Less common combinations of endocrine neoplasia occur, but their relationship to recognized MEN syndromes is uncertain. The lesions comprise a spectrum of disorders including hamartomas, hyperplasias, and benign as well as malignant neoplasms of organs derived from all germ cell layers.

In a series of 1300 pituitary adenomas surgically resected at Mayo Clinic, 37 (2.8%) arose in MEN I. Of the 36 patients (36 males, 20 females), 21 (58%) presented with clinical evidence of a pituitary neoplasm, 13 with hyperparathyroidism and 2 with functional islet cell tumor. Of the 37 tumors, 9 (25%) were microadenomas, and 28 (75%) were macroadenomas; 69 percent were invasive, all being macroadenomas. Immunocytochemically, we have demonstrated the following profile: GH (5), PRL (5), PRL/glycoprotein (7), PRL/PRL-like, PRL/TSH (1), ACTH (3) and null cell adenoma (2). Followup data indicates that surgery provides effective management of pituitary adenomas of MEN I.
Cancer remains a disease of the physical and cultural environment. As etiological factors, resources for prevention and treatment vary locally, nationally and inter-nationally. Geography provides a readily understood framework for the formulation and testing of hypotheses. Knowledge that the distribution of disease is different between one area and another with either the same or different characteristics provokes the case characteristic, correlation, case-control and cohort studies which jointly with laboratory studies and economic appraisal provide what is understood by the impact of cancer on a community and forms a basis for health policy.

The geography of Burkitt's lymphoma implicated a vector. Do differences in the geographical distribution of colorectal cancer relate to a genotype? Does the spatial distribution of leukaemia relate to the emission of ionising radiation around nuclear power stations? Has the use of asbestos as insulating material confounded a population as well as an occupational risk? While all scientific disciplines have a contribution to make in answering those questions the public now demand access to the basic information. This places considerable responsibility on those who provide the data. The cancer atlas is a convenient method. Incidence rather than mortality is required, together with a basis for statistically valid interpretation. In 1995 the first of a series of cancer atlases produced by IARC and national bodies was published in Scotland.

The regional differences in mortality caused by neoplasms illustrate well the neoclassical-environmental effects varying by countries and by individual regional units within the countries, respectively. The first part of the paper presents the differences in mortality caused by neoplasms in the European countries on basis of the recent data available, by the help of the mortality rates standardized according to the average age-structure of Europe. Beside the general neoplasms mortality also the differences in the incidence of the malignant neoplasm of stomach; trachea, bronchus and lung and of female breast, respectively are analysed. Neoclassical-environmental elements can be found especially in mortality caused by malignant neoplasm of respiratory system; the differences in mortality caused by neoplasm of stomach can be rather ascribed to the nutrition habits. The second part of the paper deals with the differences within Hungary presenting the differences between the individual Hungarian regional units (capital and 19 counties) and the individual setlement types (capital-other urban areas - rural areas), respectively. In detailed etiological groupings, too. The analysis covers the 1970-1984 period using the standardized mortality ratios. Beside the general mortality it is worth while to study the differences between the individual age-groups, too, especially because of the differences between the middle-aged and old population.

Regional differences in mortality caused by neoplasms. Dr A. Klinner, Central Statistical Office of Hungary, Budapest, Hungary

Cancer of the stomach show substantial international variation in incidence and mortality rates. Together with the study of migrant populations such observations form the basis for accepting environmental and lifestyle factors as important determinants of cancer risk. Geographical differences are also known to exist within countries for example between urban and rural areas, and between administrative units. The work of integrating the recent data available, by the help of the mortality rates standardized according to the average age-structure of Europe, presents the differences in mortality caused by neoplasms in the European countries on basis of the recent data available, by the help of the mortality rates standardized according to the average age-structure of Europe. Beside the general neoplasms mortality also the differences in the incidence of the malignant neoplasm of stomach; trachea, bronchus and lung and of female breast, respectively are analysed. Neoclassical-environmental elements can be found especially in mortality caused by malignant neoplasm of respiratory system; the differences in mortality caused by neoplasm of stomach can be rather ascribed to the nutrition habits. The second part of the paper deals with the differences within Hungary presenting the differences between the individual Hungarian regional units (capital and 19 counties) and the individual setlement types (capital-other urban areas - rural areas), respectively. In detailed etiological groupings, too. The analysis covers the 1970-1984 period using the standardized mortality ratios. Beside the general mortality it is worth while to study the differences between the individual age-groups, too, especially because of the differences between the middle-aged and old population.
INCIDENCE PATTERNS AND ASSESSMENT OF RISK OF DIFFERENT CANCERS IN STABLE INDIAN POPULATION

In India the commonest sites involved by cancer are in the upper aero-digestive tract (above the levels of the trachea and the cardio-oesophageal junction) and the uterine cervix. The situation is at complete variance with that seen in the west, where cancer is found maximally in the bronchial tree, in the digestive tract below the level of the cardio-oesophageal junction and in the female breast. The age pyramid of the population in underdeveloped countries is broad-based, signifying a relatively young population in having a short life-span so that the majority of people do not seem to survive to an age where cancer is known to strike with greater frequency. The etiological canvas of cancer in different parts of the world appears to be quite varied and complex. It is evident that the disease is caused by a large number of agents, which differ not only from one country to another, but also vary in different parts of one and the same country. Its incidence in fact seems to depend on the degree of carcinogenicity of individual agents or a combination of them, to which a particular population is exposed, both at the general environmental and personal levels.

DIFFERENT CANCERS IN STABLE INDIAN POPULATION

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**1902**

**ROLE OF ENDOSCOPY IN DETECTING PRECURSOR LESIONS AND EARLY MALIGNANT CHANGES OF THE ESOPHAGUS.**

**H. Craig**, **R. Moret**, **L. Granit**

National Cancer Institute "Regina Elena," Rome, Italy

International Agency for Research on Cancer, Lyon, France.

We report the results obtained by endoscopy surveys performed in Iran and China in populations living in two areas with highest incidence of esophageal cancer in the world. Although many epidemiological, clinical and nutritional studies were performed in these populations, only fiber optic endoscopy had the opportunity to elucidate a chronic esophageal lesion, never described before, which is highly prevalent among these populations. This type of lesion, on the basis of our results and other observations, is suspected to be the first step in the natural history of esophageal cancer in these areas. Some early malignancies were also found during these surveys, some of them only because biopsy and cytology were always performed, even on mild mucosal abnormalities. The primary role of endoscopy in detecting precancerous or neoplastic lesions of the esophagus is due to the fact that it allows a direct exploration of the mucosal surface, and that histologic and cytologic sampling can be performed, for our histological examination, which is presently the only reliable documentation for any disease status. The advantage of endoscopy versus tests is directly connected to these characteristics, especially when minimal alterations of the esophageal mu cosa are concerned. The possibility to apply biopsy methods, such as Lugol and iodolabeled blue tests, enhances the validity of fiberoptic endoscopy in the study of lesions suspected or at risk. These associated methodologies allow, in fact, a better definition of mucosal abnormalities by the identification of biochemical alterations of the mucosa itself. A cross evaluation on the yield of endoscopy and associated techniques carried out in comparison with blind esophageal balloon cytology in high incidence areas give us the feeling of a poor correlation, they have to considered anyway as a two steps approach to the problem of early diagnosis of esophageal cancer in these areas.

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**1903**

**FOLLOWING STUDY OF THE GASTRIC EXACERATED LESIONS.**

**A. F. Smith**, M.D.

Department of Gastroenterology, Andrássy Hospital, Hungary.

The incidence of dysplasia in gastric excavated lesions is expected to be rare. We detected 142 patients with grade II and grade III dysplasia of gastric ulcers and performed a follow-up study for 5 years. We carried out a short time period of follow-up if an active excavation was detected. We examined the gastric excavation till late stage using a two weeks by gastroscope taking every time biopsic specimens. Healed excavated lesions were examined every year taking biopsic specimens and that was the long time period of follow-up. We established:

1. Early gastric cancer was found in 22% of the follow-up study.
2. The grade III dysplasia means a precancerous stage.
3. The follow-up for short distance is very important relating to detection of early gastric cancer.
4. The follow-up for long distance proves the precancerous stage of the dysplasia.
5. The dysplasia is a reversible condition.

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**1904**

**NEW METHODS AND RESULTS IN THE ENDOSCOPY OF EARLY GASTRIC CANCER.**

**T. Ogura** and **H. Ichikawa**, Nat. Cancer Ctr. Hospital, Tokyo, Japan.

Recent advances in diagnostic and therapeutic equipment of endoscopic instruments have made it possible to detect early gastric cancer at an early stage and to treat radical surgery of it. With the progress and the wide spread application of endoscopy, especially panendoscopy with forward vision and fiberoptic biopsy, the detection rate of small or minute gastric cancer and the early gastric cancer with a less malignant appearance is increasing. According to the statistics from 118 major hospitals in Japan, 2,400 cases with early gastric cancer were detected and treated, in 1988. These advanced diagnostic and high detection rate of early gastric cancer may have resulted in the decreasing of the mortality from gastric cancer, which ranks the highest among carcinomas of various origin in both sexes in Japan and also in the world. Recently, echoscopic endoscopy has been improved, in Japan, which has made it possible to visualize gastric wall and its adjacent organs. Therefore, depth of cancer invasion, nature of submucosal tumor and more detailed diagnosis of antrum malignant lesions have become possible objectively with clear images. We have applied electronic endoscopy, which provides CCD at the tip of endoscope, instead of lens and image guide fiber bundle. This has extremely high resolving power, so that, its picture are excellent and fine. Furthermore, its image can be transmitted electronically to the endoscopic picture-analysing computer, we devised, which can demonstrate carcinous lesions clearly. With laser endoscopy, 64 patients with early cancer of the stomach are treated after the gastrointestinal tract have been treated. Nd:YAG laser irradiation was most effective in 21 patients. Photodynamic therapy with combination of hematoxylin and argon dye laser was markedly effective in six patients.

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**1905**

**GASTRIC CANCER. ENDOSCOPIC DIAGNOSIS AND ASSOCIATED PROBLEMS.**


Endoscopic diagnosis completed by biopsy has achieved remarkable accuracy. New trends-"endoscopy with the use of ultrasound and orange red porphyrin fluorescent dye excited by blue light" and endoscopic treatment with a krypton laser with amplified image by intensification attached to the endoscopic eye only not only provide greater accuracy of endoscopic diagnosis but also open up new therapeutic possibilities. Histochimical and histoenzymatic methods allow to classify histological findings of the neoplasm. Presence of pepsinogen and neutral glycoprotein of stromal glandular tissue with intestinal metaplasia, acid glycoprotein, activity of sucrase, alkaline phosphatase, HPL, and amylpeptidease LEV and of dysplasia/presence of sulfomucin decrease of AP, LAP and sucrose and trehalose activities to and to divide them into well defined groups.

We are able to distinguish which mucosal cancers are suspected, we know that malignant transformation can after a certain period of time be expected in approx. 12% of cases with atrophic gastritis. A typical endoscopic examination can also be expected after polypectomy, while in the gastric remnant after resection it amounts to 12% yet we still do not know what other factors in addition to the natural history could be expected. Whether the period from malignant transformation is not longer than the malignant process itself.

The suggestion of Side and Crespi to create a unified endoscopic-histological data bank of these conditions is one way to answer these questions.
K-12: NEW METHODS AND RESULTS IN THE ENDOSCOPY OF MALIGNANT TUMOURS

1906 PALLIATIVE ENDOSCOPIC THERAPY OF MALIGNANT STRUCTURES IN THE GASTROINTESTINAL TRACT AND BILIARY SYSTEM

L. Safrany, Wilhelmshaven, FRG

1908 A COMPARISON OF RIGID PROCTOSIGMOIDOSCOPY, FLEXIBLE SIGMOIDOSCOPY, COLONOSCOPY AND BARIUM ENEMA IN SCREENING FOR COLORECTAL CARCINOMA.

N. Petrelli, H.J. Harden, N. Mittan, Roswell Park Memorial Institute (RPMI), Buffalo, New York 14263, U.S.A.

Screening of 570 patients for colorectal carcinoma was done (227 males and 343 females). Median age was 59 years. Screening was done in four categories: 1. positive stool guaiac, 2. history of hematochezia, 3. change in bowel habits, 4. family history of colorectal cancer. In 29 patients, the rigid 25 cm. proctosigmoidoscope (100 patients) was compared to the flexible 65 cm. sigmoidoscope (193 patients). Adenomatous polyps or adenocarcinomas were discovered in 2 of 100 patients (2%) in the rigid group and in 24 of 193 patients (13%) in the flexible group. One adenocarcinoma of the rectum was found at 5 cm. from the anal verge in the rigid group and three adenocarcinomas were found in the 65 cm. flexible group. The remaining 277 patients underwent flexible sigmoidoscopy and barium enema in agreement in 263 patients (95%). Of these, 102 (65%) were completely negative. In the 61 additional cases (29%) endoscopy and barium enema found diverticula. In the remaining 14 patients there were major discrepancies between barium enema and the flexible score (5.0%). These 14 patients underwent colonoscopy: 9 (64%) were confirmed by colonoscopy. Three of these were beyond reach of the flexible scope.

One patient was found to have a negative flexible sigmoidoscopy but positive barium enema confirmed by colonoscopy to be a sigmoid carcinoma. At RPMI colonoscopy is the examination of choice to rule out colorectal carcinoma.

As a screening procedure this is not a practical approach and a less expensive and time consuming procedure which does not diminish sensitivity must be used. The 65 cm. flexible sigmoidoscope fulfills this role.

1907 PERENDOSCOPIC IMMUNOLYMPHOSCINTIGRAPHY IN THE PREOPERATIVE STAGING OF RECTAL CANCER


To assess the lymphatic spread of rectal cancer we have employed rectal lymphoscintigraphy (LS). This technique consists in injecting 99mTc sulphur colloid into rectal submucosa. The diffusion of the tracer through the lymphatic network has been studied by Gamma Camera taking scans 30' to 4 hrs after the injection. 74 pt. underwent LS: 30 normal controls and 44 pt. with rectal cancer. In normal subjects LS has proven that, independently from the intra- or extraperitoneal area of injection, there only exists one preferred drainage path along the sup. haemorrhoidal and inf. mesenteric vessels. The anal canal also presents a highly favourite drainage system along the internal iliac vessels.

In the pt. with rectal cancer the tracer was introduced just above and below the tumor. Preoperative LS diagnosis was correct in 26 (80%) out of the 32 pt., Dukes A-B (demonstration of normal paraaortic and paraaortic lymphnodes) and in all (100%) the 9 pt. Dukes C (partial or no visualization at all). Recent advances in immunology have allowed to verify the possibility of localizing unknown regional micrometastases by injecting a radiolabelled antibody (Mab) into rectal submucosa adjacent to the neoplasm. 10 pt. with rectal cancer and high serum CEA levels were injected endoscopically before surgery 4-5 cm above and below the tumor, with segments Fab’ of monoclonal anti-CEA iodinated with 131I. Serial scans were taken 4 to 72 hrs after the injection. When the radioactivity peaked along the lymphatic network, traditional LS was carried out. By simultaneous recording we obtained scintigraphic 99mTc map with a negative area and immunoscintigraphic positive image. Our preliminary results are discussed. On the basis of our experience we consider rectal immunolymphodetection and LS as suitable techniques for preoperative staging of rectal cancer.
ENDOSCOPY IN ONCOLOGY PAST, PRESENT AND FUTURE.

Vasuhiro Hara  National Kyushu Cancer Center, Fukuoka Japan

History of endoscopy in the field of oncology is mentioned, followed by current situation of endoscopy, and lastly problems and perspectives in the future.

Already since the ancient times of Hipocrates, attempts have been made to make direct observations of the tumor, which is a disease associated with morphological changes. Needless to say, observation have initially been confined to shallow lumen such as anus, vagina, and the like.

Tracing the history of endoscopy, Diarmacaux of France first used the term "Endoscopy" in 1853. He observed the ureter and larynx by means of the apparatus devised by himself. Then observation extended up to deep lumina and organs such as stomach, bladder and so forth.

Because of initially available hard endoscope difficult operational technique allowed its use only in a limited situation.

Flexible endoscope needed to be developed for such bent lumina as the digestive tract. Trial were made of reversing the observed pictures on the film, thus in 1940 the gastroscope was devised by Kit of Japan.

Then in 1961, fiberoscope was introduced and became the revolutionarily factor in the world of endoscopes. Since then in the field of digestive tract, it became possible to observe upper gastrointestinal tract, colon, and biliary tract.

Furthermore, it also became possible to make biopsy by using the clamp attached to the fibroscope. Currently in Japan, most cases of gastric or colon cancer are diagnosed with endoscopy and histological diagnosis are made with biopsy. In the future, not only in field of diagnosis, endoscopy has also opened a way for cancer therapy. That is, the polypectomy, laser therapy and so on.

Lastly, I would like to mention about possible problem and perspectives of these therapy in the future.

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COMBINED TREATMENT MODALITIES IN TREATMENT OF LOCAL RECURRENCE AND METASTASES.

B. Arnesen, Bergen, Norway

Pelvic recurrence deeply affects the natural history of patients submitted to surgery for rectal cancer. Up to now in fact, adjuvant therapy does not show any real value over surgical therapy alone, and the possibility to diagnose recurrence at an early stage represents the only possibility to improve the total survival rate. The diagnostic test is strictly related to the kind of surgery applied in the primary tumor. After sphincter-savvy surgical procedures, digital examination of the rectum, endoscopy with biopsy samples and transrectal echotomography (TRCT) represent, in our experience, the most important investigations required for an appropriate diagnosis of recurrence.

In patients who were submitted to Miles abdominoperineal resection, pelvic C.T. and perineal echotomography (PCT) with percutaneous echo-guided fine-needle citology play the major role. No matter the type of surgical procedure applied, all other clinical signs such as perineal and sacral pain, rectal bleeding, urinary tract symptoms and instrumental investigations like CEA test and haemocult contrast enema, may be regarded as supplementary clues. Anyway, the persistent alteration of one single parameter requires a second look.

The early detection of recurrence at an early stage of local invasion allows a curative resection through surgery. Otherwise only a palliative resection can be performed in advanced stages; it will be properly associated to radiotherapy and/or chemotherapy.
Advanced testicular cancer is best treated with combination platinum based chemotherapy as primary therapy. If there is only moderate tumor bulk at presentation, many patients will achieve a complete remission and have no evidence of disease thereafter. Those with more bulky tumor who obtain a partial remission should then have residual tumor completely resected by surgery. This effectively re-stages the patient, provides therapeutic benefit to many and determines the need for additional chemotherapy. If carcinoma is found in the resected specimen, further "salvage" chemotherapy is required. If the resection is grossly complete even this group can obtain survival in the majority of cases.

The purpose of this report was to review the results of curative resections of pulmonary metastases in order to better define the indications and potential benefits of surgical resections. 324 patients with pulmonary metastases from a primary cancer known to be controlled were operated at the surgical Center Marie Lannelongue between 1969-1983. The pulmonary lesion was a solitary lesion in 68%; multiple lesions were operated in 32%. 37 patients had subsequent resections; the resection was complete in 94%, a tumor reduction or a biopsy were made in 19%. 3 patients were lost of follow up. Surgical mortality was low (1.5%). The actuarial five years survival was 33% after curative resections. The worst results were observed in soft tissue sarcomas and melanomas. Survival was significantly best in complete resections, absence of node involvement asymptomatic metastasis and disease free interval of more than 6 months. On the other hand the surgical procedure and the multiplicity of the lesions did not seem to affect the therapeutic results. Surgical resections of selected lesions associated in most cases with chemotherapy produces an acceptable survival rate. Our results will be discussed according to others publications.
L-13: SURGERY IN RECURRENT AND METASTATIC CANCER

1917 EIGHT CASES OF PELVIC EXENTERATION COMBINED WITH SACRAL RESSECTION FOR LOCAL Recurrent and Metastatic Cancer.


Local recurrence of rectal cancer following abdominoperineal resection is rarely amenable to limited resection. Carcinoblastic antigen assay is valuable for diagnosing most recurrent rectal cancers, but it is inadequate for early detection. Pelvic computed tomography examination is very valuable for the early detection and localization of recurrence in relation to pelvic structures and can also serve as a guide in percutaneous needle biopsy of the tumor. Eight patients with deeply invading recurrent lesions underwent pelvic exenteration combined with sacral resection. The ileal segment conduit was used for urorctal urinary diversion. The mean operation time and blood loss were 6.4 hours and 6,000 ml, respectively. No operative deaths were encountered. Three patients are alive 31 months, 13 months and 3 months postoperatively, with no evidence of disease, and another patient is alive 34 months postoperatively with pelvic wall recurrence. This procedure seems a reasonable treatment for particular patients.

1918 PATTERNS OF LOCAL RECURRENCE FOLLOWING CONSERVATIVE SURGERY AND RADIOTHERAPY FOR EARLY BREAST CANCER.

K. H. Romsdahl, T. P. Paulus, and E. O. Montague, Univ. of Texas System Cancer Ctr., M.D. Anderson Hospital, Houston, Texas, USA.

Preservation of the affected breast for patients with minimal breast cancer, Stage I (T1 N0), and Stage II (T1 N1, T2 N0, or T2 N1) has been accomplished by employing limited surgery, either excision of the primary tumor or segmental mastectomy, followed by radiotherapy with 4000-5000 rad tumor dose in five weeks. During the past decade, lateral axillary dissection has also been done for more accurate staging. Radiotherapy is adjusted by status of axillary nodes, location of the primary tumor, and surgical tumor margins. Staging of the axilla has also served to identify candidates for adjunctive systemic therapy. Of 466 patients managed by this alternative to radical or modified radical mastectomy, no significant difference in survival or local/regional recurrence has been observed. Thirty local/regional recurrences have developed among all patients followed for longer than 2 years, a recurrence rate of 6.7%. Patients having excision of their primary tumor, with or without axillary dissection, had a local recurrence rate of 9.3%. However, patients having segmental mastectomy showed a local recurrence rate of 3.2%. The site of local/regional recurrence was in the breast in 24 and in the axilla in 6 of the 30 individuals with this outcome. Serial mammography was highly effective in detecting early recurrence not clinically evident. Mastectomy following recurrence in the breast has proved to be effective in achieving local disease control. Cosmetic and functional results have been deemed highly favorable in approximately 80% of patients having conservative surgery combined with radiotherapy. Consequently, these results support offering such treatment to selected patients who initially present with early stages of breast cancer.

M-15: CANCER GENETICS

1919 CANCER GENETICS.

Badner, W.F. Imperial Cancer Research Fund Labs. London, Ducane Road, W12 U.K.

Though inherited susceptibility to cancer may contribute no more than 2% of overall cancer incidence, this is nevertheless an important contribution in its own right. Furthermore, understanding inherited susceptibility can provide major clues to the fundamental causes of cancer and to approaches for its prevention and treatment. Inherited susceptibility genes, connected with systemic effects such as deficiencies in DNA repair, carcinogen metabolism, and immune response, are important for controlable environmental factors which may cause cancer. The use of DNA polymorphisms to find markers linked to cancer susceptibility genes now provides a systematic approach for the identification of the inherited contribution to cancer susceptibility and through the cloning of the relevant genes, in population studies of systemic differences. Genetic studies should play an increasing role in the future in cancer research, complementing and adding to studies on environmental factors.

1920 RETINOBLASTOMA.

R., Cavanee, Cincinnati, USA
**M-15: CANCER GENETICS**

**1921 PREDICTION OF FAILIAL PREDISPOSITION TO CANCER**

Lips, E.J.M., Den Otter, W., University Hospital Utrecht, The Netherlands

In most family cancer syndromes the predisposition to tumour development seems to be transmitted in an autosomal dominant way with virtually complete penetrance in the early decades. Periodic screening of patients with several hereditary tumour syndromes and their close relatives probably improves both prognosis and life expectancy and decreases disease morbidity. However, large scale screening of families have to satisfy the criteria to be maintained in epidemiologic screening programmes such as described by Wilson and Jungner.

If the loci of genes responsible for individual heritable cancers could be mapped the cancers would become more amenable to genetic counseling including carrier detection and prenatal diagnosis. At present, probes for restriction enzyme fragment length polymorphism (RFLP) mapped to the long and short arms of all chromosomes are available for linkage studies. The consistent association of particular chromosome-specific RFLPs with cancer in such families would constitute evidence for the provisional assignment of a gene involved in tumorigenesis to the chromosome identified. For example, comparison between the chromosome 13 associated RFLPs from retinal cells and from the white blood cells in the same patients revealed that loci, that were heterozygous in the normal white cells were often homozygous in the tumour tissue. It was concluded that homozygosity for a mutant allele is likely to be a prerequisite for tumour development. Homozygosity means the effective loss of activity of both normal alleles at a locus, one obtained by birth, the other on a later date, it can be the result of point mutations, insertions, deletions or rearrangements. Chromosomal loss, or a combination of these factors, thus although familial cancers seem to have dominant patterns of inheritance the actual development of the tumour appears to require that recessive alleles on both chromosomes be affected.

**1922 RESEARCH IN TWINNS**

P. Hague, Odense, Denmark

**1923 MELANOMA**

B. Lynch, Omaha, USA

**1924 FAMILIAL POLYPOSIS COLI**

Bullw., S., Dept. of Surg. Gastroenter. Riskhospitalet. Copenhagen, Denmark

Familial polyposis coli (FPC) is an autosomal dominant disease characterized by early occurrence of at least 100 colorectal adenomas, of whom one or more will develop into carcinoma, if left untreated. The Danish Polyposis Register was established in 1971 with the purpose of organizing and coordinating prophylactic examination of family members at risk in order to improve the past poor prognosis of FPC. Probands were ascertained by information from local hospitals, the Danish Cancer Registry, and the National Patient Registry. All unaffected first degree relatives were offered prophylactic proctosigmoidoscopy. At the end of 1982 the registration was considered almost complete and included 313 patients in 94 families. The annual incidence rate was 1.31 x 10^-6. Colorectal carcinoma was found in 67% of 168 probands versus only 3% of 79 call-up patients. In a study of the frequency of extracolonic manifestations in major series mandibular osteomas were diagnosed in 76% and duodenal adenomas in 46%, and therefore it is proposed that the term "Gardner's syndrome" should no longer be used as a separate clinical entity. Colectomy and ileorectal anastomosis is considered the surgical method of choice. However, in the future restorative proctocolectomy with ileorectal reservoir may become a routine operation in FPC, if the long term results prove satisfactory. The Danish prophylactic examination of unaffected first degree relatives includes biannual proctosigmoidoscopy at the age of 10-39 years and after that at intervals of 3-5 years until the age of 60. Furthermore, adult patients are examined with gastro-duodenoscopy and those having duodenal adenomas are reexamined at intervals of 1-2 years. A recently established international polyposis research group including participants from major polyposis centers and registers will probably increase the future possibility of solving FPC problems.
The management of gastric cancer depends upon whether the disease is localized (surgically completely resectable), locally advanced (not completely resectable), or metastatic. Fifty percent of curatively resected patients relapse and subsequently die with metastatic disease. Adjuvant therapy approaches to patients with a high likelihood of relapse (positive nodes, small tumor, limited plastic pathology) may decrease the rate of relapse. Chemotherapy studies with fluorinated pyrimidines and the chloroethyl nitrosourea methyl-CCNU have generally been disappointing. FAM (5-Fluorouracil, Doxorubicin, Mitomycin-C) is being evaluated as adjuvant chemotherapy in two Phase III cooperative trials. The results of these studies are not yet available. Locally unresectable recurrent or partially resectable gastric cancer is benefited by combined chemotherapy and radiation. A Gastrointestinal Tumor Study Group (GITSG) trial of 5-Fluorouracil + Methyl CCNU + 50 Gy of split course irradiation produced long term survival in 20% of patients with locally residual or recurrent gastric cancer. In this study irradiation was used prior to chemotherapy and early relapse with disseminated cancer occurred. To prevent early relapse, “sandwich” techniques of chemotherapy-irradiation-chemotherapy are being explored. These approaches use chemotherapy prior to irradiation to decrease early distant metastases. Another strategy to prevent local relapse is intraoperative irradiation. This approach needs to be explored in controlled Phase III studies. In metastatic stomach cancer combination chemotherapy produces response rates superior to single agents. FAM has produced partial response in 40% of patients. The use of platinum based regimens and Methotrexate directed 5-Fluorouracil programs are currently being investigated. A major failing of current chemotherapy regimens in advanced gastric cancer is the very low complete response (CR) rate (5%) seen. To affect “cure” of advanced gastric cancer, regimens producing higher CR must be developed.
1929
FURTHER EXPERIENCES WITH THE TREATMENT OF CANCER. Mary Carterall
MRC Cyclotron Unit, Hammersmith Hospital, DuCane Road,
London W12 0XS

Until 1945 all neutron therapy was given on unsatisfactory machines causing adverse effects of
clinical significance. Low energy (7.5 MeV) beams caused 10-40% more complications because of poor
penetration and wide penumbra. As truly controlled clinical trials have therefore been required.
Despite the primitive machines, neutrons have caused
local control in 60-80% of stage 1-2a tumours in
several sites. They appear to be especially
advantageous in slowly growing tumours of non-
epidermoid type and of non-resectable epidermoid
tumours. Most complications start in or involve
the skin. Larger volumes of normal tissues were
necessarily treated because of poor penetration or
lack of 'finite size' in the beam size and these also
add to complications. The new generation of high
energy machines with clinically designed treatment
heads will reduce such complications. The relative
spreading of bone by neutrons gives a therapeutic
gain when soft tissue tumours are in or near bone.
It has been noted also that regression of tumours
frequently occurs quickly during and after neutron
therapy and this has clinical advantages. Early
results from the modern cyclotrons are establishing
optimum doses and fractionation schemes. These
machines will enable comparisons to be made with
modern megavoltage X rays. They should also be
used to treat unresectable hypoxic tumours in the
mouth, salivary glands, sinuses and nodes involved
in adenocarcinomas and melanomas where neutrons have
achieved high rates of local control.

1930
CLINICAL EXPERIENCES WITH TREATMENT OF MORE THAN 500 PATIENTS WITH FAST NEUTRONS SINCE 1976 IN
HAMBURG-EPPENDORF. H.D. Franke. Univ. Frankfurt, 
Abt. fur Strahlentherapie, Eppendorf, Hamburg.

In Hamburg the therapy with DT-neutrons shows
the best curative or palliative effect on highly
differentiated tumours, relative resistant against
megavoltage therapy. With the neutron-dose of
15.6-15.0 Gy/4 weeks or in 12-20 fractions or-
in treating tumours in radiosensitive organs such as
brain and intestine with a photon-neutron sche-
dule, we have seen no necroses in normal tissues.

1931
RESERVED
J. Hunziker, Boston, USA

1932
CORRELATION OF CLINICAL RESULTS WITH PHYSICAL AND

The heavy particles which have been proposed for the treatment of cancer offer greatly
advantageous in their properties. Their main feature is that they require less energy for adequate
penetration even their clinical advantage. The treatment of eye tumours with protons needs an energy of 30 MeV. To
achieve a penetration of 20 cm of tissue with 14 MeV,
their energy has to be 70 MeV. In the former case, the currents required are very small of the order of 10 mA. A useful beam of fast neutrons can be set with a few A of protons or neutrons at e. 7 MeV. For
protons one needs over 100 A of 500 MeV protons and a complex focusing arrangement.
Charged nuclei and pions of a given energy have straight tracks and a
definite range. This enables Advantageous depth-dose distributions to be obtained. Neutrons behave like X and gamma rays; any advantage they may confer on radiotherapy must be a biological one except for the
reduced x-rays in bone. With the exception of protons, all these radiations are more densely ionising than X
rays. This leads to different effects of oxygen and of intrinsic cellular factors such as
position in the mitotic cycle, less repair of radiation-induced damage, PBE greater than one and
varying with conditions. Densely ionising radiations may be useful in treating tumours whose cells are
intrinsically resistant to X-rays or capable of considerable repair of injury inflicted during a
fractionated course of conventional radiotherapy, and for tumours containing significant hypoxic regions.
The effect on the tumour must always be assessed against the damage to normal tissues inevitably irradiated to a high dose.
1934

1935

HEAVY ION RADIOTherapy at Lawrence Berkeley Laboratory, Joseph R. Castro, M.D., University of California, Dept. of Radiation Oncology, San Francisco School of Medicine, San Francisco, Calif., University of California Lawrence Berkeley Laboratory, Berkeley, Calif., Northern California Oncology Group and Radiation Therapy Oncology Group, USA.

Heavy charged particles have been used for ten years in a phased clinical trial of several heavy charged particles, ranging from helium to argon ions. The greatest clinical experience to date has been with helium and neon ions. Carbon ions will be tried in large numbers of patients during the next five years. The best results to date have been in helium ion precision therapy where the local dose to tumor has been raised beyond that possible with low LET irradiation. Such tumors at uveal melanoma, paraspinal chordoma/chondrosarcoma, base of skull tumors, selected head and neck tumors and soft tissue sarcomata have shown good local control when compared with historical results. Neon heavy particles are currently being tested against low LET irradiation for unestablishable non-small cell carcinoma of the lung and locally advanced carcinomas of the prostate. Carbon ions may offer a better beam for dose localization therapy and will be tried as a possible improvement on proton or helium ion therapy. Improvements in beam delivery including magnetically spread beams, rater scanned beams as well as refinement in treatment planning and verification of particle therapy delivery are underway.

Supported by U.S. DOE and American Cancer Society.

1936

The largest clinical experience in HEAVY ION Radiation Therapy has been with carbon ions. CHAMBERLAIN, D.C., Medical Physicist, MD Anderson Center, Houston, Texas.

The field of employment (Tumor-Site) treated and results.

Suitability considerations for neutron therapy to day.

Radiological considerations for further development of neutron therapy (derived from neutron radiobiology).
1937 INTERSTITIAL NEUTRON AND PHOTON THERAPY OF ORAL CANCER.
G.G. Nastakin, N.S. Androsov, I.P. Melenchuk, All-Union Cancer Research Center, USSR, Moscow, USSR.

115 patients with tongue and floor of the mouth cancer (58 and 57 respectively) were treated by interstitial radiotherapy: 12 Cf was used in 56 and 12 Co in 59 patients. Interstitial therapy only was applied for 38 patients and in combination with distant photon therapy for 77. Dose rate was 70-76 Gy. Visual total tumor clearance observed in 92.5% of patients. Five-year results of interstitial neutron therapy shows its advantage in comparison to photon therapy.

P-12: LATE EFFECTS OF CANCER TREATMENT IN CHILDREN

1938 LONG TERM EFFECTS OF SUCCESSFULLY TREATED PEDIATRIC PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKEMIA (ALL). Mark E. Nebhi, Jr., M.D., and Leslie L. Robison, Ph.D., University of Minnesota, Minneapolis, Minnesota, U.S.A.

With improved treatment modalities, long term survival for children with malignant disease is estimated at over 50%. Most of the success is due to the improvement in survival for children with ALL. Childrens Cancer Study Group (CCSG) established a Late Effects Committee in 1982 in order to prospectively oversee studies to evaluate long term survivors. Three major areas that have emerged as significant sequelae in children with ALL are growth and development, gonadal function, and the occurrence of second malignancies. Recently CCSG assessed the height of 187 patients seven years from diagnosis. All patients had received cranial radiation (18 or 24 Gy) and combination chemotherapy. Following treatment a statistically significant excess was observed in the proportion of patients in lower percentiles. Craniospinal plus abdominal radiation was found to be the most significant factor associated with attained height percentile. In a follow-up of 336 children with ALL treated in the early 1970's by CCSG, seven malignant tumors have been reported to date. The types of tumors seen were: CNS tumors (3); thyroid cancer (2); retinoblastoma (1); peripheral neuroectodermal tumor (1). The excess occurrence of central nervous system tumors seems to have been confirmed by Albo et al who reported a 10 year actuarial estimate of 51 for brain tumors occurring in a cohort of children treated in a subsequent CCSG study. CCSG assessed gonadotropin levels and pubertal development in 163 long term survivors of childhood ALL. Twenty-eight percent (46 patients) were found to have above normal levels of follicle-stimulating hormone and luteinizing hormone. The proportion of patients with elevated gonadotropins by radiation fields were 70% for craniospinal plus abdominal, 41% for craniospinal irradiation and 6% for cranial irradiation (p = 0.001). The frequency of elevated gonadotropins was significantly higher in females (36%) as compared to males (17%). These results emphasize the need for extended systematic evaluation of long term survivors of childhood cancer.


A coordinated/collaborative effort is being mounted to collect data on mutation frequencies in post-treatment offspring from cancer patients. These constitute a human cohort purposefully exposed to high levels of mutagenic chemical and physical agents. This follows an initiative by ICPEMC (Int. Comm. Prot. ag Envir Mutag. carcinog.) and is supported by IARC. Reproduction is sufficiently high to allow and warrant genetic studies of offspring, in particular to survivors of childhood leukemias, Hodgkins and other lymphomas, and testis cancers. Data on this aspect are already being collected and will be presented. Genetic end points are 24 sentinel phenotypes with reliable neonatal manifestations, plus a dozen sentinel phenotypes of more subtle or post-neonatal manifestations. An additional 16 conditions with presumed polygenic mechanisms (but excluding Down's Syndrome) are also under consideration. The goal is to rule out a fourfold increase in sentinel phenotype frequency. Collection of data from cancer genetics centers in several countries creates a need for carefully designed protocols and precise quality control. Analyses on molecular basis (protein polymorphisms, RFLP, etc) will be encouraged, but will be left to individual centers to pursue. Meetings of potential collaborators have been held, but the program is open for additional participants, provided agreed criteria will be adhered to. Protocols and logistics are in the final stages of development.
1941

MORRIS, J. P.: LATE EFFECTS OF CANCER TREATMENT IN CHILDREN.

The improved survival of children with cancer has fueled interest in late sequelae of childhood cancer treatment. Perhaps of greatest concern has been the demonstration of late adverse sequelae affecting the central nervous system (CNS). This review will consider the types of adverse CNS sequelae to which we have encountered, primarily focusing on the experience of children with acute lymphocytic leukemia (ALL) who have received CNS preventive therapy with cranial radiation and intrathecal chemotherapy. In an attempt to characterize and define the nature of these adverse sequelae, we studied a group of all patients in continuous complete remission who received cranial radiation (2400 rad) and intrathecal chemotherapy as CNS preventive therapy. Evaluation of CNS scans, neuropsychological and psychometric testing and neuroendocrine studies yielded evidence of adverse sequelae which appear to be interrelated. Long-term follow-up of this group of patients over a ten-year period has demonstrated that the first evidence of adverse sequelae (e.g., CNS scan abnormalities) may occur many years from the time of initiation of CNS preventive therapy. A comprehensive battery of neuropsychological tests, including tests specifically selected because of their ability to measure functions preserved by defined cerebral regions was administered to these patients. A close relationship between CNS scan abnormalities and neuropsychological dysfunction was observed by the study. Studies also confirmed the existence of specific deficits in attention, memory and functions associated with frontal lobe integrity in some patients who received CNS preventive therapy with cranial radiation and intrathecal chemotherapy. The results of this and related studies will be presented and their implications for treatment of the child with ALL will be discussed.

1942

LATE EFFECTS OF CANCER TREATMENT IN CHILDREN.

As the treatment of childhood cancer improves, the need to focus increased attention on the long-term effects of cancer therapy becomes apparent. The unproved survival of children with cancer has focused increased attention on the long-term effects of cancer therapy. Perhaps of greatest concern has been the demonstration of late adverse sequelae affecting the central nervous system (CNS). This review will consider the types of adverse CNS sequelae to which we have encountered, primarily focusing on the experience of children with acute lymphocytic leukemia (ALL) who have received CNS preventive therapy with cranial radiation and intrathecal chemotherapy. In an attempt to characterize and define the nature of these adverse sequelae, we studied a group of all patients in continuous complete remission who received cranial radiation (2400 rad) and intrathecal chemotherapy as CNS preventive therapy. Evaluation of CNS scans, neuropsychological and psychometric testing and neuroendocrine studies yielded evidence of adverse sequelae which appear to be interrelated. Long-term follow-up of this group of patients over a ten-year period has demonstrated that the first evidence of adverse sequelae (e.g., CNS scan abnormalities) may occur many years from the time of initiation of CNS preventive therapy. A comprehensive battery of neuropsychological tests, including tests specifically selected because of their ability to measure functions preserved by defined cerebral regions was administered to these patients. A close relationship between CNS scan abnormalities and neuropsychological dysfunction was observed by the study. Studies also confirmed the existence of specific deficits in attention, memory and functions associated with frontal lobe integrity in some patients who received CNS preventive therapy with cranial radiation and intrathecal chemotherapy. The results of this and related studies will be presented and their implications for treatment of the child with ALL will be discussed.

1943

INTEGRATED DISEASE TREATMENT IN CHILDREN.

The quality of life of children treated or being treated for malignancies is closely influenced by the psychological state of the patient, the attitude of the family and health care providers, and thus requires careful management. We studied the children with malignancies being treated for retinoblastoma, glioblastoma, and meningioma, all of whom were treated with cranial radiation and intrathecal chemotherapy. Evaluation of CNS scans, neuropsychological and psychometric testing and neuroendocrine studies yielded evidence of adverse sequelae which appear to be interrelated. Long-term follow-up of this group of patients over a ten-year period has demonstrated that the first evidence of adverse sequelae (e.g., CNS scan abnormalities) may occur many years from the time of initiation of CNS preventive therapy. A comprehensive battery of neuropsychological tests, including tests specifically selected because of their ability to measure functions preserved by defined cerebral regions was administered to these patients. A close relationship between CNS scan abnormalities and neuropsychological dysfunction was observed by the study. Studies also confirmed the existence of specific deficits in attention, memory and functions associated with frontal lobe integrity in some patients who received CNS preventive therapy with cranial radiation and intrathecal chemotherapy. The results of this and related studies will be presented and their implications for treatment of the child with ALL will be discussed.
MONDAY • AUGUST 25 • MORNING

P-12: LATE EFFECTS OF CANCER TREATMENT IN CHILDREN

PRELIMINARY STUDIES ON THE INCIDENCE OF LATE EFFECTS OF CANCER TREATMENT IN CHILDREN

Childhood cancer is increasingly recognized as a significant problem. Over the years, advances in treatment have led to improved survival rates, but this has also resulted in an increased incidence of late effects due to cancer treatment. The late effects of cancer treatment can be both physical and psychological, affecting children throughout their lives. Understanding these effects is crucial for providing comprehensive care and support to children and their families.

A quarter of all cases have a genetic predisposition. By 1994, about 300,000 children, adolescents, and young adults in the United States were living with a history of cancer. Many of these children are now reaching adulthood, and the long-term effects of their treatment are becoming more apparent. The need for continued surveillance and follow-up care is essential to monitor and manage these late effects.

The most common late effects include second cancers, infertility, endocrine disturbance, and psychological issues. Early detection and intervention are critical to mitigate these effects. Children who have undergone cancer treatment require specialized care, including ongoing monitoring, support for psychosocial issues, and access to accurate information about their condition.

The implementation of comprehensive care programs, including multidisciplinary teams, patient education, and psychological support, is essential to address the needs of childhood cancer survivors. These programs should be tailored to the specific needs of each child, considering factors such as age, treatment history, and individual characteristics.

The late effects of cancer treatment in children are multifaceted and require a holistic approach to care. With continued research and improved treatment strategies, the goal is to minimize the impact of these effects and improve the quality of life for childhood cancer survivors.
A programme for the primary prevention of cancer, directed to schoolgoers between 9 and 13 years of age, has been implemented in Genoa since 1981. Alongside the latter, other initiatives within the same area have taken place, with the main objective of stimulating the interest and cooperation of adults living and working in contact with schools. Refresher courses on the prevention of cancer have therefore been organized for doctors and teachers. The first experience of this type was carried out with secondary school teachers; at present, elementary schools are also being involved. Working days were made up of 2 parts: the first including a lecture followed by discussion; the second devoted to group-work. Main stress was laid on the following topics: the concept of neoplasia, the hazards of smoking, environmental pollution, educational and health legislation currently in force, and early diagnosis. The course was limited to 50 participants, to whom 2 questionnaires were administered during the course, and a third check questionnaire, after a year. Attendance fluctuated between 70 and 90%. All group-work activities are reported in 5 detailed accounts. 85% of all participants, in their answers to the third questionnaire, stressed the usefulness of the course and importance of organizing others. 70% reported having activated health education programmes in their own schools.

A Polish version of the UICC Guidebook on Cancer Education in Sch. was first published in Poland in 1984. As soon as in 1985 the Polish Ministry of Education ordered the introduction of this subject to school curricula under gen. health education. At the same time the Inst. of Oncology asked oncological ctr. across Poland to support the project. The Guidebook drew great interest among teachers, health education instructors, and physicians working for cancer control, and also of the Social Anti-cancer Society activists. In order to evaluate the project's performance a test experiment was designed and carried out in six sch. of various level and profile. The survey showed that the gen. knowledge about cancer has grown in those sch. students meanly by 30%, while in the control sch. only by 5%. The Guidebook has thus been evaluated as good although it needs some improvements allowing for the experience gained during the project's implementation.
Cancer education in schools can be facilitated and enhanced by various influences from the community at large. If positive forces which exist in most communities are wisely utilized, the school curriculum can be favorably affected with respect to the promotion of personal health and the prevention of disease. However, because of the stigma which often accompanies cancer, special efforts are needed to encourage schools to address this very important group of diseases. Stress needs to be placed on:
1. The preventability of cancer;
2. Specific ways to reduce one's personal risk of cancer; and
3. The high curability of cancer when detected early.

Therefore, to realize the greatest public health benefit in reducing cancer morbidity and mortality, school instruction should include systematic cancer education as an integral part of the overall curriculum. In order to communicate this message directly to those in control of the school curriculum, several community groups or forces can be of assistance. Medical groups can document the importance of cancer prevention and early detection; parent groups can stress the high priority of health education as a part of the overall school curriculum; media sources can assist in communicating the message of cancer as a life-style-related disease; and public health and government resource personnel can aid in documenting the criticality of learning certain health habits early in life. Specific examples of ways in which community influences can favorably affect cancer education in schools will be discussed.

NURSING MANAGEMENT OF THE CANCER PATIENT WITH PAIN. M. McCaffery, Santa Monica, California, United States

At some time during the course of his/her illness, the patient with cancer is likely to have pain caused by the disease itself, therapeutic efforts, or diagnostic procedures. The pain among the population of cancer patients may range from brief to prolonged and from slight to severe in intensity. Nurses probably spend more time with patients with cancer pain than any other members of the health team. To contribute effectively to the multidisciplinary approach to providing comfort for the patient, the nurse needs skills in assessment of the patient and an awareness of effective use of common methods of pain relief. Specifically, nurses may contribute to pain management by knowing the misconceptions that hamper assessing the patients, how to use tools for initial and ongoing assessment, how to identify and recommend appropriate analgesics for the individual patient, how to implement a preventive approach in using analgesics, how to identify the need to adjust the dose and interval of the analgesic to provide the greatest pain relief with the fewest side effects, and how to communicate this information to other Health team members. In addition, the nurse may assist the patient with pain by possessing knowledge and skill in the use of nonpharmacological methods of pain relief, particularly the use of distraction strategies and cold applications that may be used along with or sometimes instead of analgesics.
IFOSFAMIDE IN THE TREATMENT OF LUNG CANCER

K. Havemann
Department of Medicine, Division of Hematology/Oncology, University of Marburg, D-3550 Marburg, West-Germany

Chemotherapy (CT) in non-small cell lung cancer (NSCLC) is a palliative treatment and it is still not clear whether a true prolongation of survival and improvement in quality of live is achieved. Multicycle CT therefore should be restricted to responding patients with a good performance status. Response rate to ifosfamide (IF) as a single agent in NSCLC using either a divided daily or a single dose schedule is 10-38%. Combination CT with agents showing similar activity in NSCLC, such as cisplatin, mitomycin C, vindesin, and etoposide induced response rates of 18-46%, a magnitude which seems to be higher than those obtained by IF alone. IF is equally active in all histological subgroups of NSCLC and response rates depend on performance status and extend of disease. Since side effects are moderate IF containing combination CT seems to be an alternative treatment to cisplatin containing combinations with almost equal activity. Small cell lung cancer (SCLC) is responsive to CT with a medium survival of one year and more and long term survivors of 3-10%. Data on single agent CT with IF in SCLC are scanty showing response rate of 50% and more. In combination with vinca alkaloids, etoposide, and adriamycin alone or together with radiotherapy response rates up to 95% are obtained with complete remissions of 25% and more. IF containing combinations are of equal activity as the standard CM protocol and may be the first choice if contraindications against adriamycin exist. In addition cross resistance to CAV is low in SCLC. Therefore IF containing combinations are of value in non responders to CAV or in cyclic alternating CT of SCLC. Side effects are moderate, especially urotoxicity is negligible since the introduction of the uroprotector urimetexan.

THIRD-LINE THERAPY OF TESTICULAR TUMOURS


Between September 1981 and December 1985 35 patients with testicular tumours entered the study. They had been resistant to either a first-line /VPB/ and second-line /VP 16213, Cisplatin/ or had a recurrence of the tumour. They were given VP 16213, Holoxan with or without Adriamycin as a third-line therapy. Our patients had, with one exception, a non-seminoma type germinal cell testicular tumour. One patient with seminoma had elevated beta-HCG, too. Histology was made according to Mostofi, the WHO recommendation of 1980. Clinical staging was performed according to the UICC recommendation of 1981. 2 of our patients were in stage II/B bulky abdominal disease technically inoperable, 2 of our patients were of stage III/A and 31 of III/B, respectively. The mean age of the 35 patients was 28.62 years within a range of 21 to 54 years. We used the following schedule: VP 16213 /Etoposid - Bristol Myers/ 100 mg/m² in infusion, days 1-5, Holoxan /Ifosfamid - Asta/ 40 mg/kg, days 1-5 with hydration, urinicalisation and Uromitexan /Jenska/. The cycle was repeated after an interval of 4 weeks. The results were evaluated after 2 cycles, there were 24 evaluable patients. The response rate /CR+PR/ was 29.16% /7/24/. Criteria of response and toxicity were those recommended by the WHO. The most frequent side effects were alopecia, leukopenia and vomiting. Leukopenia was the most severe side effect. GI toxicity /nausea and vomiting/ occurred and was mild and in few cases moderate. Mild degree of microhematuria was found in 4 patients. Mild BUN and serum creatinin elevation were found in 1 patient after 2 cycles.
U-15: IFOSFAMIDE—PRESENT AND FUTURE ANTITUMOUR SPECTRUM

1958 RESERVED
J. de Raker, Amsterdam, The Netherlands

1960 IFOSFAMIDE (IFO) IN CHEMOTHERAPY RESISTANT TUMORS
S. Seeber, N. Niederle, W. Brade
Munich Hospital, Leverkusen; W.-German Tumor Ctr., Essen
Chemically ifo belongs to the alkylating oxazaphosphorines but differs in physicochemical, toxicological and pharmacological properties as well as in its experimental and clinical toxicity profile and antitumor spectrum from its relatives cyclophosphamide and trophosphamide and from other alkylating agents. Especially myelosuppression is less expressed with ifo as compared to other alkylating agents. Since the former dose limiting urotoxicity of ifo can be controlled by mesna higher ifo doses have been applied and a new evaluation of the role of ifo as a second line agent in tumors with primary and secondary resistance to conventional chemotheraphy is indicated. In an Ehrlich ascites tumor with primary resistance to cyclophosphamide and required resistance to the clinically important combination of adriamycin and cisplatin, ifo at its optimal dose level could cure about 40 % of the animals carrying this multiresistant tumor. The treatment of the largest group of patients with various refractory tumors with the single agent ifo plus mesna revealed about 20 % objective responses after extensive pretreatment including all classes of cytotoxic drugs as antineoplastic, etoposide, cisplatin, anthracyclines and cyclophosphamide. This suggested low cross resistance between ifo and various groups of antineoplastic drugs has been confirmed by Einhorn, L.H., who obtained in testicular cancer refractory to combinations containing cisplatin, etoposide, bleomycin, vindesine and adriamycin more than 50 % c.r. with ifo containing combinations. Furthermore, different study groups reported responses to ifo after pretreatment with cyclophosphamide containing combinations in soft tissues and osteosarcoma. Similar response rates have been reported in leukemia, lymphomas, ovarian cancer and in lung cancer treated with ifo after pretreatment with cyclophosphamide containing combinations. Although the discussion of clinical cross resistance has to consider the problem of equitoxic dosage as well as possible synergistic effects in the combinations used, ifo has been proven to be an important second line agent against various solid tumors refractory to conventional chemotheraphy.

1959 RESERVED
A. van Oosterom, Leiden, The Netherlands

1961 THE ROLE OF IFOSFAMIDE IN PANCREATIC CANCER
L.H. Einhorn, Indiana University Medical Center, Indianapolis, Indiana, USA
Ifosfamide has clear cut activity in testis cancer, sarcoma, lymphoma, and other tumors. Its role in gastrointestinal neoplasms is less clear. Only minimal data is available for gastric and colorectal cancer. In pancreatic cancer, Dr. Gad-Ell-Mania and colleagues reported a very impressive 60% response rate (6 of 10 responses) in Egyptian patients. At Indiana University, we evaluated ifosfamide in a starting dosage of 1.25 grams/m² for 5 consecutive days plus N-acetylcysteine (NAC) uroprotection. Toxicity was predominantly hematological and urothelial (despite NAC). Six of 27 patients (22%) had an objective response. Subsequently, we performed another phase II study evaluating ifosfamide + 5-FU in pancreatic cancer, utilizing mesna as a urothelial protector. Hemorrhagic cystitis was effectively prevented with mesna. The therapeutic results of this study and other unpublished studies from other American centers will be presented.
1962


Mitoxantrone (DHAD) is a anthracycline derivative investigated as an antileukemic drug during the last few years, compared to Adriamycin. Laboratory studies showed equal or superior antitumor efficacy,apeutic activity in breast cancer, acute leukemia and malignant lymphomas. A phase II study with DHAD in patients with refractory non-Hodgkin's lymphomas (NHL) was activated in December 1984 at the Istituto Nazionale Tumori of Milan. The median age in NHL patients was 56 years (range 21-82). Thirteen patients were presently evaluable (N/E: 5/8). Eight patients were previously treated with Adriamycin. CHT was administered on i.v. and oral with oral prednisone in a low dose with extranodal disease. An additional patient with bone involvement achieved partial remission. All responses were documented in patients with cutaneous histology and were not related to previous treatments with Adriamycin. DHAD was well tolerated and no patient required a chemotherapy. The AH patient who eviden in 2 and thrombocytopenia in 3 patients. No cardiac damage was detected. The initial results are promising, but a confirmation on a larger series of patients with longer follow-up is needed.

Supervised in part by Dynamic International Clinical Research.

1963

A COMPARISON OF DRUGS AND CYCLOPHOSPHAMIDE AND MITOXANTRONE (DHAD) IN THE TREATMENT OF ADVANCED BREAST CANCER. H. Marsden Hospital, Sutton, UK.

A 20%; response rate (93.7% vs. 22.7%) in advanced breast cancer, with considerable toxicity (nausea and vomiting, alopecia, cardiomyopathy (doxorubicin) and neuropathy (vinristine; A melphalan/mitomycin-C/cyclophosphamide combination has been tested in this unit, achieving an overall response of 37% with minimal morbidity in 37 patients. In a few patients, cumulative marrow depression. Recently, mitoxantrone has been substituted for melphalan because of evidence of cumulative toxicity caused by that agent. Mitoxantrone has a low toxicity profile and is more appropriate in combination with an alkylating-like agent such as Mithantrone. Until cytotoxic therapy results in a significant proportion of long-term survivors, it is important to use effective but relatively non-toxic therapy and this is the basis for a randomized comparison of CHT and CHT + Vincristine, 5-fluorouracil, mitomycin-C, Adriamycin and Cyclophosphamide combination. The aim of the trial is to evaluate the response to VHT/CHT versus MTH/HTM/HT in advanced breast cancer.

1964


Mitoxantrone has shown marked activity in patients with breast cancer. This study was undertaken in order to evaluate efficacy and toxicity of a combination regimen in which mitoxantrone substituted for doxorubicin. Cyclophosphamide 600 mg/m², Mitoxantrone 10 mg/m² and 5-fluorouracil 500 mg/m² were given i.v. over 21 days as first line chemotherapy to 35 patients with advanced breast cancer and 33 patients (median age 35-72). Seventeen patients had previous hormonal therapy, 1 patients had radiotherapy, and 1 patient had adjuvant chemotherapy (CHT). Performance status ranged from 0-2 (median 0). Sites of dominant disease were: visceral (32), soft tissues (22), and osseous (12). Twenty patients had greater than or equal to 2 evaluable sites of metastasis and 11 patients had evaluable sites of metastasis except liver. Of 31 evaluable patients, 2 attained a complete response and 11 had a partial response, giving an overall response rate of 49%. Median response duration was 14 weeks. All patients were evaluable for toxicity. The most frequent side-effects were nausea and vomiting. Alopecia occurred in 21% patients, mainly leukopenia that required at least one dose reduction in 44% of patients. Moderate to severe nausea and vomiting was observed in 41% of patients. Alopecia occurred in 21% patients. Two patients developed evidence of cardiac dysfunction, as documented by measurements of left ventricular ejection fraction. Treatment was stopped in one of these cases. These preliminary results suggest that this combination is considerably effective and well tolerated and that cardiac toxicity may be seen in a small number of patients.

2062 patients with metastatic breast cancer (age 28-72, median 51), were given mitoxantrone/prednisone treatment. Mitoxantrone has shown marked activity in patients with advanced breast cancer. This multicentre study was undertaken in 1984 at the Istituto Nazionale Tumori of Milan. The median age in NHL patients was 56 years (range 21-82). Thirteen patients were presently evaluable (N/E: 5/8). Eight patients were previously treated with Adriamycin. CHT was administered on i.v. and oral with oral prednisone in a low dose with extranodal disease. An additional patient with bone involvement achieved partial remission. All responses were documented in patients with cutaneous histology and were not related to previous treatments with Adriamycin. DHAD was well tolerated and no patient required a chemotherapy. The AH patient who eviden in 2 and thrombocytopenia in 3 patients. No cardiac damage was detected. The initial results are promising, but a confirmation on a larger series of patients with longer follow-up is needed.

Supervised in part by Dynamic International Clinical Research.

1965

MITOXANTRONE/PREDNISONE (MP) COMBINATION THERAPY IN ADVANCED BREAST CANCER. H. Marsden Hospital, Sutton, UK.

A 50%; response rate (93.7% vs. 22.7%) in advanced breast cancer, with considerable toxicity (nausea and vomiting, alopecia, cardiomyopathy (doxorubicin) and neuropathy (vinristine; A melphalan/mitomycin-C/cyclophosphamide combination has been tested in this unit, achieving an overall response of 37% with minimal morbidity in 37 patients. In a few patients, cumulative marrow depression. Recently, mitoxantrone has been substituted for melphalan because of evidence of cumulative toxicity caused by that agent. Mitoxantrone has a low toxicity profile and is more appropriate in combination with an alkylating-like agent such as Mithantrone. Until cytotoxic therapy results in a significant proportion of long-term survivors, it is important to use effective but relatively non-toxic therapy and this is the basis for a randomized comparison of CHT and CHT + Vincristine, 5-fluorouracil, mitomycin-C, Adriamycin and Cyclophosphamide combination. The aim of the trial is to evaluate the response to VHT/CHT versus MTH/HTM/HT in advanced breast cancer.

In 20 patients with greater than or equal to 2 evaluable sites of metastasis except liver, of 31 evaluable patients, 2 attained a complete response and 11 had a partial response, giving an overall response rate of 49%. Median response duration was 14 weeks. All patients were evaluable for toxicity. The most frequent side-effects were nausea and vomiting. Alopecia occurred in 21% patients, mainly leukopenia that required at least one dose reduction in 44% of patients. Moderate to severe nausea and vomiting was observed in 41% of patients. Alopecia occurred in 21% patients. Two patients developed evidence of cardiac dysfunction, as documented by measurements of left ventricular ejection fraction. Treatment was stopped in one of these cases. These preliminary results suggest that this combination is considerably effective and well tolerated and that cardiac toxicity may be seen in a small number of patients.
1966


Mitoxantrone is a synthetic aminonaphthaquinone and has been shown to have activity in vitro and in vivo against solid tumours and leukemias. Phase II studies showed that mitoxantrone has significant therapeutic effects in patients in relapsed or resistant acute leukaemias and high grade malignant lymphomas resistant to conventional therapy. This study was conducted in two haematological centres of Pavia and Rome. Patients with refractory or relapsed acute leukaemia, or CMML in blast crisis have been entered in a phase II study consisting of 1 or 2 cycles of therapy according to bone marrow recovery. Drug was given i.v. at the dosage of 12 mg/m^2/day on 3 consecutive days for each cycle. Patients achieving at least a 50% marrow after 1 or 2 courses went to follow-up phase. Cardiac function tests (EKG, echocardiogram, LVEF) were evaluated in all patients before and after treatment, at end of induction, and off study cr q. 3-6 months. 15 eligible patients have been enrolled so far, 11 with ALL (10 relapsed, 1 resistant), 2 with AML (1 relapsed, 1 resistant), 2 with CMML in blast crisis. Good results were collected in relapsed ALL: out of 10, 8 showed a complete remission. An additional patient with AML achieved partial remission. Safety of the drug was very good. No cardiotoxicity has been recorded. Mitoxantrone seems to be a new weapon for treatment of refractory ALL, not enough data have been collected about ALL and CMML in blast crisis. According to these preliminary data it will be interesting to further study mitoxantrone: 1) in combination chemotherapy with other effective agents and 2) for consolidation, post induction treatment.

1967

STUDY OF MITOXANTRONE IN EPITHELIAL OVARIAN CANCER. G. Bucklidge, F. Lawton, J. Howard, T. Latief, A. Chytjywarda. Ovarian Cancer Group, Queen Elizabeth Hospital, Birmingham, UK.

A number of agents have been shown to be active in epithelial ovarian cancer. Combination therapy gives good response but toxicity is considerable. Mitoxantrone, active in a number of epithelial malignancies, is less toxic than Adriamycin and we evaluated its activity in biopsy-proven epithelial ovarian cancer resistant to conventional therapy (<A^1>). 40 patients are evaluable for response. 29 patients had failed cisplatinum combination regimens, 11 cisplatinum or alkylating agents alone and 4 were previously untreated. Patients received mitoxantrone 14-18 mg/m^2 at 3 weekly intervals by i.v. push over 60 seconds. Electrocardiography was performed before, during and for 5 minutes after administration. Left ventricular ejection fraction (LVEF) was assessed before and after therapy. 10 patients showed evidence of response. Of these, 2 patients had received no previous treatment, 2 cisplatinum and 6 cisplatinum combination. Duration of response (ICR and 95%) ranged from 6 weeks to 5+ months. 4 patients had static disease for periods of 12, 12, 14 and 18 weeks. Increasing the interval between courses was necessary to myelosuppression on 19 occasions in 9 patients. Mild (WHO grade 1-2) nausea was common (p<.37). WHO grade 3-4 toxicity was not severe and only 2 patients developed alopecia requiring a wig. Other minor side effects included short lived disturbances of bowel habit (p<.01) and anorexia (p<.03). There were no disturbances in cardiac rhythm during injection of mitoxantrone and no evidence of reduction in LVEF at the end of treatment. This encouraged us to study a mitoxantrone / cisplatin combination in previously untreated patients. Study regimen is 12 mg/m^2 mitoxantrone and 75 mg/m^2 cisplatinum with hydration every 3 weeks. Preliminary data suggest that this is well tolerated and response is greater than expected with single agent cisplatinum therapy. Mitoxantrone has the potential, therefore, for combination with other agents in ovarian cancer and deserves further study.

1968


On the basis of a standardized prior therapy in the multi-center trial of the German AML cooperative group the combination of 5-day ARA-C and Mitox. was applied to 32 pa-
tients with refractory AML, as defined by the following criteria: 1. Primary resistance against 2 5-AJ-9 induction courses; 2. Early relapse within the first 4 months; 3. Relapse after 6 months with non-response against one additional 5-AU-9 cycle; 4. Second and subsequent relapses. Treatment consisted in ID-ARA-C 3 q/m on every 12 hours by a 1 hour infusion on day 1-4. Mitox. was started at 12 mg/m^2/day on days 3, 4 and 5 and escalated in subsequent a-
session to 4 and 5 doses of 10 mg/m^2/day on days 2-5 and 2-6, respectively. Four of the 32 patients entering the trial 29 are presently evaluable for anti-leukemic response. 15 pa-
tients achieved a CR (52%) while a PR was obtained in 3 additional cases. 10 patients died within the first 4 weeks of therapy because of infectious complications, in 3 cases the leukemic cell population persisted. Except for one death possibly related to acute cardiomyopathy toxicity this was mild to moderate consisting in nausea and vomiting, mucositis and diarrhea. These data indicate a high anti-
leukemic activity of ID-ARA-C and Mitox. in combination in refractory AML and strongly suggest to apply this regimen at earlier stages of AML therapy.
A COMPARISON BETWEEN SURGICAL ORCHIDECTOMY AND THE LHRH AGONIST 'ZOLADEX' (ICI 118,630) IN THE TREATMENT OF ADVANCED PROSTATIC CARCINOMA.

1970

L. Tyrrell, Freedom Fields Hospital, Plymouth, UK.

Previously untreated patients with metastatic prostate cancer were treated with a four weekly biodegradable depot formulation of the LH-RH analogue 'Zolalect' (ICI 118,630).

The depot, consisting of a cylindrical rod, 1 cm in diameter, and containing 3.6 mg of the LH-RH analogue was injected subcutaneously.

The mean age of 120 evaluable patients was 71.3 years (range 51-87). All patients reached castrate values of testosterone by day 29 and these values have been maintained by subsequent 4 weekly depot injections.

Subjective response was observed in 87% of the symptomatic patients. Objective response, assessed according to the RECIST criteria: a) <4 months: OR 1.8%, MR 54.6%, SD 14.5%, progression 21.6%. At 1 year progressive disease was noted in 11%, apparently hormone resistant patients. No drug related side effects, except for testosterone reduction, were encountered. The patient's compliance was excellent.

From this data it can be concluded that the four weekly depot formulation of Zolalect appears to be an effective treatment in the management of patients with advanced prostate cancer.

1972

THE USE OF A LUTEINIZING HORMONE RELEASING HORMONE (LHRH) AGONIST IN PREMENOPAUSAL ADVANCED BREAST CANCER.

M H Williams, Kerry Walker, J L Nicholson, A Turkes, K W Murray & Griffith

Department of Surgery, City Hospital, Nottingham and Penomus Institute, Cardiff, Great Britain

Fifty-three premenopausal patients with advanced breast cancer receiving an LH-RH agonist (ICI 118,630 - Zoladex) were studied. All patients presented with stage III (n = 13) or stage IV (n = 60) disease and had received no previous systemic therapy. Clinical responses were assessed strictly on RECIST criteria with a minimum disease duration of 6 months. Initially oophorectomy was performed in all cases on disease progression (assessable n = 22). In 27 patients Zoladex was administered daily and in 26 as a monthly subcutaneous depot injection. No status is available in 7 patients.

Endocrine studies included measurement of luteinating hormone, testosterone, oestradiol and progesterone throughout therapy in all cases. Results were expressed as the mean + SD (range) and these were compared to the assayable status in 39 patients.

Conclusion Similar response rates have been obtained using Zoladex to those found after surgical oophorectomy. The lack of status of the primary tumour appears to predict a response to Zoladex.
1975

**CONTROLLED TRIAL OF TAMOXIFEN AS ADJUVANT AGENT IN MANAGEMENT OF EARLY BREAST CANCER**

Analysis at Eight Years by 'Nolvadex' Adjuvant Trial Organisation

Between 1977 and 1981, 1285 patients aged 75 years or less were entered into this trial following mastectomy for early breast cancer. Premenopausal women with positive axillary nodes and postmenopausal women with either positive or negative axillary nodes were randomised to receive either tamoxifen 10 mg twice daily for two years or no further treatment following primary therapy. Radiotherapy was reserved for those patients with positive axillary lymph nodes detected on sampling at mastectomy. For 524 patients included in the trial, primary tumour specimens were assayed for oestrogen receptor (ER) content. At a median follow-up of 45 months, analysis of the results of the trial reported a significant prolongation of the disease-free interval in the tamoxifen-treated group compared to the control group (Baum et al, 1985). This benefit appeared to be independent of menopausal, nodal or ER status. The results of the current analysis involving a maximum follow-up of 8 years for those patients entering the trial will be presented for discussion.


1976

**TREATMENT OF PRIMARY BREAST CANCER IN THE ELDERLY WITH TAMOXIFEN ALONE**

J. A. E. Bramer, Nailby Hospitul, Ipswich, UK

Between 1975 and 1981, 160 female patients with primary breast cancer over the age of 70 were treated with Tamoxifen alone, in a pilot phase II study. Three were complete regression in 80%, partial regression in 20%, and no regression in 0% of patients. The response rate, results of subsequent treatment, incidence of metastases, cause of death and survival, are all detailed, as there is now a 2 year minimum follow up in all 160 patients.

1977

**CLINICAL AND HORMONAL RESPONSES TO LONG-TERM BROMOCRIPTINE PLUS TAMOXIFEN TREATMENT OF ADVANCED POSTMENOPAUSAL BREAST CANCER**

S U Kingston (Manchester); J M Buchanan (Stoke); D Fairclough (Wolverhampton); J Powell, K Lloyd (Northampton); T Priestman, D Spooner (Birmingham) on behalf of the 18 centres who participated in the study.

The minimum effective serum concentrations of tamoxifen and its active metabolites are not known but it has been suggested that rapid attainment of high concentrations of antioestrogens may favour a more rapid onset of response. Using the conventional dose of 'Nolvadex' (20-40 mg/day), it takes several weeks for steady state levels to be reached but two groups have demonstrated that this can be rapidly attained using loading doses and recently Riedel et al have shown a reduction in time to response in patients with advanced breast cancer using such treatment schedules.

In this open randomised study, 160 evaluable patients with advanced breast cancer were randomly assigned to treatment with a conventional schedule of 'Nolvadex' (40 mg/day) or a loading dose schedule (160 mg for two days followed by 40 mg/day).

Assessments of objective response were made, according to UICC criteria, every three weeks for the first three months and thereafter at three monthly intervals.

The data to be presented are from an interim analysis comparing response rate and time to response between the two groups of patients.

* Supported by the Medical Research Council.
1978 RUBIDAZONE EXPERIMENTAL STUDIES: RHONE POULENC SANTE RESEARCH CENTER, M. Boiron, Paris, France

1980 RESERVED M.J. Keating, Houston, USA

1979 RESERVED T. Révész, Budapest, Hungary

1981 RUBIDAZONE GENERAL THERAPY C.U.L CARDIOTOXITY, C. Usser, M. Martin, L. Lepage, C. Suterer, C. Bichet, M. Hebrard, Pape hematologia Hopital Saint-Louis, Paris 75010 - France - Rubidazone (RBZ) shares the same pattern of experimental antitumor activity in animal models than Daunomycin (DNR). However, using equipotent doses, RBZ appears 3-4 times less cardiotoxic in rat model (electron microscopy) and rabbit model (Thibodeau's techniques). In general, acute toxicity appears qualitatively similar but quantitatively inferior to that of DNR. Hematotoxicity appears significantly in patients with normal bone marrow, at dose superior to 200mg/m². Pharmacokinetics may account for the reduced toxicity at the parent drug appears to slowly transformed in Daunorubicin. In humans RBZ has been shown to be one of the most active single agent in ANLL, 78% complete remission in previously untreated patients. The median dose necessary to achieve complete remission was twice as high as the dose necessary with DNR. In randomized trials in ANLL (14 LA 76) and ALL (10 LA 76) RBZ was a efficient as DNR with both reduced acute toxicity (pancytopenia, mucositis) and delayed toxicity. 444 ANLL were treated in 01 AM 81 protocol with a combination of Ara C (200 mg/m²/d X 7 d) and RBZ (200 mg/m²/d X 4 d), given a complete remission rate of 61%. Acute toxicity was pancytopenia 100% with a median duration of 20 - 4 days, alopecia 100%, mucositis 17%. Delayed cardiac failure was observed in less than 1% of patients receiving 1800 mg/m². Similar results were observed in 250 adult ALL treated in LALA B3 protocol. From those results we can conclude that 1/ RBZ at equitoxic doses is a powerful antileukemic agent. 2/ Acute toxicity appears reduced over that of conventional regimens. 3/ Delayed cardiotoxicity is not significantly observed in patients receiving less than 1800 mg/m² cumulative dose.
1982 RUBIDAZONE (22050.RP), PHASE II STUDIES IN HUMAN SOLID TUMORS. Claude Jaquilliat, David Khayat, Marie-Helene SCHOEM, Hopital de la Salpetriere 47 Bd de l'Hopital 75013 PARIS - FRANCE

Since 1973, several phase II studies have been reported which were aimed to determine if Rubidazone (22050.RP), a very potent anti-leukemic semi-synthetic anthracycline compound, has any activity in human solid tumors. Up to date, a total of 268 evaluations patients (pts) can be analyzed. These pts had advanced cancers of all usual sites and were treated with i.v. Rubidazone at a dose which ranged from 100 mg to 200 mg/m² administered every 3 to 4 weeks. Response rates ranged from 0% to 35% (mean = 15%).


During phase II studies RBZ was shown to be more effective (57% complete remissions; CR) than DNR in previously untreated ANLL. ML leukemias appeared highly sensitive to RBZ. In 1976 we compared Ara-C DNR to Ara-C RBZ (5 + 3). In a multicentric study of 195 pts, CR rate (54%) and duration (median = 9 months) were similar in both arms. RBZ containing regimen appeared less toxic with respect to acute toxicity (maculopapular, infectious). In 1979, Ara-C (200mg/m²/d X 5) and RBZ (200mg/m²/d X 3) (A) was compared to A + Vincristine and prednisone (A + V) (B) and RBZ (200mg/m²/d X 3) (C). A + V compared to A + RBZ (200mg/m²/d X 3) (D) was compared to A + V + RBZ (200mg/m²/d X 3) (E). Different treatments were given: (A) A + V to pts > 100 G/l received CNS prophylaxis and pts with M4 type CR to pts achieving CR were randomized to receive either Ara-C containing chemotherapy every 6 weeks (1), or the same regimen where ara-C was replaced Ara-C or early consolidation with Ara-C = M-Amsa for 6 months followed by a regimen identical to 1; finally only pts receiving CR had been 20 months, significantly shorter in the 6-H maintenance regimen.

From those studies we can conclude that: 1) Ara-C + RBZ combination can achieve the best CR rates reported so far in ANLL; 2) no obvious benefit has resulted from addition of other Antileukemic agents; 3) CR duration is strongly dependent on initial reduction of leukemic burden; 4) that studies of optimal maintenance modalities appear mandatory.


The most common toxicity, was myelosuppression, with nausea and vomiting, alopecia, allergic reaction from 0% to 35% of cases reported. No cardiac failure was observed.

1985 EXPERIMENTAL STUDIES OF RUBIDAZONE F. LAVELLE, Anticancer Research, Rhone Poulenc Santé, Centre de recherches de Vitry, 94403 Vitry Sur Seine, France.

Anthracyclines are widely used for the treatment of hematological malignancies and of solid tumors. More than 250 derivatives of daunorubicin have been prepared by reaction on several functional groups of the molecule in order to increase the activity or to decrease cardiotoxicity. Among them, rubidazone has been selected: the ketone function in C9 position is substituted by an aldehyde function in C9 position, which is a more reactive electrophile than the ketone function in C9 position. Rubidazone has been extensively evaluated on a panel of murine grafted tumors. The chemotherapeutic index (expressed as the ratio of the tolerated dose of rubidazone to the lethal dose of daunorubicin on early Li1210 leukemia (graft in day 0: treatments in days 1,2,3,4). Daunorubicin and rubidazone behave very differently on "spontaneous" AAR leukemia (first graft in AKR mice). Given at equitoxic doses, daunorubicin is marginally active (low increase in life span) whereas rubidazone is highly active, attaining a high proportion of long term survivors. Like daunorubicin and doxorubicin, rubidazone is active on different models of solid tumors (Lewis lung carcinoma, B16 melanoma, R 111 mammary adenocarcinoma). Cardiotoxicity has been estimated by two different techniques. According to the ZEBRIN and BRANDELL technique (measurements of electrocardiographic disturbances), rubidazone is four times less cardiotoxic than daunorubicin and than doxorubicin. A similar behaviour has been observed with respect to congestive heart failure, following chronic treatment by i.v. administration in rabbits. A decreased cardiotoxic potential could be explained by a lower accumulation of rubidazone (and of its metabolites) in the heart muscle. Finally, other results of rubidazone dealing with genotoxicity, genotoxicity and with immunotoxicity will be summarized.
1986 CELLULAR AND NUCLEAR MORPHOLOGY IN PROSTATE CANCER.
D.S. Coffey, The Johns Hopkins Univ. Sch. Med., Baltimore Maryland USA

Since the very early studies of Virchow, it has been known that nuclear morphology is a hallmark in the pathology of cancer. The nucleus is often highly variable and abnormal in both shape and size. In addition, the cancer nucleus is often characterized by aberrations in chromatin texture and nuclear structure. Furthermore, structural changes throughout the cancer cell and during mitosis indicate that main structural elements have been altered during the process of carcinogenesis and progression. It is now possible to place these structural changes on a quantitative basis and we are also beginning to understand the cellular elements that are involved in determining these morphological features. We have been able to isolate a nuclear skeleton component termed the nuclear matrix that determines the shape of the nucleus and is involved in the organization of DNA long domains containing approximately 50 to 100 kilobase pairs of DNA. There are approximately 50,000 of these DNA loops in each cell. These interactions are responsible for the nuclear matrix DNA structure and during DNA replications these loops are realigned through fixed sites of DNA synthesis that are attached to the nuclear matrix surface. This nuclear matrix is composed of part of topoisomerase II and this enzyme is the central core of the metaphase chromosome. The nuclear matrix may be controlled by interaction with specific steroid receptors or with specific oncogene products that are localized to the nuclear matrix. The nuclear matrix is connected to the cytoplasmic matrix and as such is a part of a larger interacting tissue matrix system. This matrix system is dynamic and not a static skeleton system in that it has chemo mechanical properties. For more complete information on this matrix structure consult the recent review by Nalain, Barrack and Coffey in the Annual Review of Biophysics and Biophysical Chemistry, 1986.

1987 HISTOPATHOLOGIC THERAPY CONTROL OF THE CONSERVATIVELY TREATED PROSTATE CARCINOMA.
G. Dhom, Inst. of Pathology, Univ. of the Saarland, Homburg/Saar, FRG

The prostatic carcinoma is the only solid malignant tumor whose regression can be controlled systematically by histopathologic findings under conservative therapy. Neither the rectal palpation finding nor sonography or computer tomography can definitely predict the question for regression. The disagreement between palpation and histologic regression is about 40%. Predominantly, the rectal palpation finding is judged too optimistically. Concerning the non-metastasizing prostatic carcinoma, treated with high voltage radiation or interstitially with radionuclides, the histologic or cytologic therapy control is the only objective procedure to assess the tumor regression. The morphologic phenomena within tumor cells are raising during good therapy response implying that the first control biopsy should be carried out 6 months after therapy has started or after having finished radiation treatment. Basically, the regressive changes in tumor cells during estrogen therapy and radiation treatment are identical, still the phenomena after radiation therapy are generally more distinct. Quantitative and qualitative alterations in tumor cells can be expressed in a score rendering a grading of regression possible. Repeated biopsies from the same patient, preferably once a year, keep the tumor under control. Statistical comparison between the different growth patterns of prostatic carcinoma and the different therapies reveals that in highly malignant tumors treated with radiotherapy in 60% of all cases after 3 or more years still a marked tumor regression can be observed, whereas in only 30% of the cases a tumor regression was found after androgen therapy. No or only poor regression was seen in cribriform and/or solid carcinomas in 21%, but in 43% after estrogen and/or orchidectomy, 3 years after first diagnosis.
A SURVIVAL/AUTOPSY STUDY OF PROSTATE ADENOCARCINOMA - GRADING ASPECTS

S. Lunderberg, and J. Carstensen, "Department of Pathology, University of Lund, General Hospital, Malmb, Sweden. The autopsy frequency has been high 1958 – 1979 which has produced an almost unselected autopsy material from a well defined population. The results are discussed in the light of a recent study of grading in 287 autopsy prostate cancer patients diagnosed 1958 – 1974 were studied. Patients treated with hormones prior to the biopsy were excluded.

The biopsy material was graded according to Gleason and the size of the primary tumour was measured planimetrically. Both the survival time and the tumour load at autopsy were used as variables. Regression analysis showed that histologic grade was more important than tumour size in predicting prognosis. The graphical display of survival revealed the same profile as the Virtue-study. Histologic grade showed a significant power for a long period of time, indicating a stable tumour progression. A statistical method recommended previously for analysis of data from animal tumour geneity experiments was modified and applied in this study. The results supported further the prognostic power of histologic grade and showed that substantial information can be obtained from autopsy examinations in prognostic studies of prostate cancer patients.

The technique of multivariate analysis was applied to quantify the prognostic importance of parameters which were identified as contributing in a significant manner to grading of prostate carcinoma. The results of this analysis are used to construct a scoring system which differentiates five different prognostic groups. When compared to the results of grading, the new system is shown to be superior. The large group of 228 patients with G2 tumors can be split into three groups, each with a significantly different prognosis.

The correlation of the scoring system to local tumor extension (pT category) is described. Recommendations for grading of prostate carcinoma resulting from this work are the following: 1) Only three independent parameters are of significance for grading prostate cancer: tumor architecture, nuclear anaplasia and the presence or absence of mitoses. 2) The combination of these parameters in a scoring system identifies five separate prognostically different groups. 3) The separation achieved by this new system is superior to conventional grading and is suggested for grading prostate cancer.

1991 CLINICOPATHOLOGICAL STUDIES OF RENAL ONCOCYTOMA: A BENIGN NEOPLASM OR IN SITU CARCINOMA? - GRADING ASPECTS*


To study the prognostic power of certain characteristic features of prostate cancer, mainly histologic grade and size of the primary tumour, biopsy specimens of 466 prostate cancer patients diagnosed 1958 – 1974 were studied. Patients treated with hormones prior to the biopsy were excluded.

The biopsy material was graded according to Gleason and the size of the primary tumour was measured planimetrically. Both the survival time and the tumour load at autopsy were used as variables. Regression analysis showed that histologic grade was more important than tumour size in predicting prognosis. The graphical display of survival revealed the same profile as the Virtue-study. Histologic grade showed a significant power for a long period of time, indicating a stable tumour progression. A statistical method recommended previously for analysis of data from animal tumour geneity experiments was modified and applied in this study. The results supported further the prognostic power of histologic grade and showed that substantial information can be obtained from autopsy examinations in prognostic studies of prostate cancer patients.

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1994 | TRANSPORT AND METABOLISM OF FOLATES IN L1210 MOUSE LEUKEMIA CELLS. F.M. Huennekens, T. Duffy, L. Page, K. Higashi, S. Burgos, R. Burroughs, and E. Lifshitz. Div. of Biochemistry, Dept. of Basic & Clinical Research, Scripps Clinic & Research Foundation, La Jolla, California, 92037 USA.

Folate, 5-methyltetrahydrofolate and 5-formyltetrahydrofolate are taken up by L1210 mouse leukemia cells via an active transport system that utilizes a 36K membrane-associated binding protein as the translocator and an anion-exchange mechanism as the energizer. After being internalized, these compounds are converted to tetrahydrofolate (a key coenzyme in the synthesis of DNA, RNA, and protein) by different pathways: Folate is reduced to tetrahydrofolate via the NADPH-dependent and Methotrexate-sensitive dihydrofolate reductase; 5-Methyltetrahydrofolate is converted to the coenzyme via the methylcobalamin-dependent methionine synthetase; and 5-formyltetrahydrofolate gives rise to tetrahydrofolate via a sequence of reactions beginning with its isomerization to 5,10-methylenetetrahydrofolate. The transport system is regulated by cAMP, but factors that control the activity of the above enzymes are complex and not well-understood. Cancer chemotherapy utilizing folate transport system is regulated by cAMP, but factors that control the activity of the above enzymes are complex and not well-understood.

1995 | UROS OF RAT LIVER DIFFERENTIATION CHARACTERISTICS IN RAT HEPATOCYTES, R. van der Molen, W. van Dijk, and H. Eljach. Schonberger, Dept. of Molecular Cell Biology, University of Macau.

Several characteristics of rat liver and hepatoma cells were determined under identical incubation conditions. On microscopic level a study of cellular adhesion, colony formation, cytoskeletal organization and extracellular matrix has been made. The number of mitochondria per unit cytoplasm was determined electronmicroscopically. With the use of biochemical methods the activity of one of the enzymes was determined including those of glycogenolysis, gluconeogenesis and amino acid metabolism. Moreover, the regulation of some of these enzymes by regulatory molecules as cyclic AMP and hormones was determined in both liver and hepatoma cells. Finally, cells have been compared for their heat production and photon emission.

The results suggest a gradual loss of rat liver characteristics. The loss of many characteristics was found to be significantly correlated.

1996 | ENZYMES OF PURINE AND PYRIMIDINE METABOLISM AS TARGETS FOR CHEMOTHERAPY. Gertrude B. Elion, Melville M. Wanger, Harvey I. Alter, and Howard V. Berman, Department of Biochemistry and Molecular Biology, School of Medicine, Stanford University, Stanford, CA 94305 USA.

The enzymes of nucleic acid synthesis are potential targets for cancer chemotherapy. In order to achieve selective toxicity to the tumor without unacceptable toxicity to the host, it is necessary to know the enzymes of purine and pyrimidine biosynthesis and catabolism are available to the tumor and whether salvage pathways exist for supplying the essential metabolites. When one deals with the chemotherapy of viruses, protozoa and bacteria, it is possible to achieve selectivity by taking advantage of the different specificities of enzymes peculiar to the species. In cancer chemotherapy, one is dependent upon quantitative differences in anabolic and catabolic enzymes as well as on different transport characteristics. Because of the low levels of certain enzymes at high levels of anabolic enzymes, it is possible to obtain selectivity for some antimetabolites. Inhibitors of nucleoside transport can be used to prevent salvage from by-passing the inhibition of biosynthetic pathways. Specific examples will be given of the utilization of biochemical knowledge to design rational combinations and to achieve chemotherapeutic advantage.


Ornithine decarboxylase (ODC) belongs to those about dozen enzymes, the genes for which easily undergo amplification upon the exposure of tumor cells to specific inhibitors of the enzymes. We have selected several cultured mouse and human tumor cell lines which are resistant to the antiproliferative action of 2-difluoromothylornithine (DFMO), an irreversible mechanism-based inhibitor of ODC. These cells overproduce ODC and express its mRNA at greatly enhanced rate. The overproduction of ODC was apparent based on an amplification of ODC gene(s). In contrast to the sensitive parental L1210 cells, tumor cells containing amplified ODC sequences were fully resistant to DFMO treatment when inoculated into mice. In flbroblasts, the amplification of genomic ODC sequences and the subsequent return to normal gene dosage were associated with phenotypic changes such as alterations in surface glycoprotein expression, tumorigenicity and invasiveness. Similarly, L1210 leukemia cells with amplified ODC genes were more clonogenic as judged by colony formation in soft agar. Although it is generally accepted that human genome is much more stable than rodent genome, it was rather easy to select DFMO-resistant human myeloma cell line (Sultan) with an amplification of genomic ODC sequences. The overproduction of ODC in human myeloma cells led to manifold resistance to DFMO. Just like in the rodent tumor cells, the amplification of ODC gene in the myeloma cells was associated with changes indicating a coamplification process, as the surface protein expression was altered in cells bearing amplified ODC gene. The ease by which mouse and human tumor cells increase their ODC gene dosage may offer new approaches to study the mechanisms of gene amplification and the development of drug resistance.
The amount and relative composition of phospholipids found in minor chromatin components has been reported to vary in cancer versus noncancer cell types. In particular, in Chronic Lymphocytic Leukemia lymphocyte nuclei, sphingomyelin content is reduced to about 40%, while phosphatidylcholine is increased 4-fold in comparison with normal B lymphocytes, suggesting a correlation between phospholipid metabolism in poisoning and the reduced transcriptional ability observed in CLL cells. 

In order to investigate on the possible relationships between lipid metabolism and nuclear functions in cancer cells, the incorporation of 3H-glycerol in the nuclei at level has been followed in Ehrlich leukemia Friend cells induced in erythroid differentiation by DMSO, by using electron microscope autoradiography and microdensitometric techniques. The autoradiographic results indicate that about half of the lipid newly synthesized in the cytoplasm is transferred to the nucleus, while the biochemical data indicate that an increased amount of neosynthesized glycerides is present in induced with respect to uninduced Friend cells. Moreover it has been observed that, during the S->Gp phase, an accumulation of intermediate metabolites (glycerides) and a reduction of phosphatidylcholine occur into nuclei. This peculiar metabolic pattern of the lipids at the nuclear level suggests that they may be involved in the control of cell proliferation. 


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**2000**


The transition of rat hepatoma 3924A cells in culture from non-proliferating plateau into proliferating phase provides a system where alterations in metabolic programs illuminate the role of strategic purine enzymes, metabolites and de novo and salvage pathways in the biochemical commitment of cancer cells to replication. When hepatoma cells were removed from plateau phase and plated at 5 x 10^4 cells per flask at 150 cm^2, the cells remained in the lag phase for 24 h, with log phase starting between 24 and 36 h at 72 h plateau phase set in. In resting cells, the concentration of 5-phosphoribosyl-1-pyrophosphate (PRPP) was 4.7 μM and activities of incorporation of formate (de novo pathway) and adenosine, hypoxanthine and guanine (salvage pathway) into nucleotides and nucleic acids were 12, 876, 281 and 384 mol/hr/200 x 10^6 cells. Six h after plating the activity of PRPP synthase increased 2.2-fold at 12 h and diphosphoribose 1-pyrophosphate transferase activity increased 1.4-fold, PRPP pool rose 1.2-fold and activity of formate incorporation for purine de novo synthesis increased 7-fold, with a peak at 24 h. The activities of IMP dehydrogenase and adenosylcotic synthase, the rate-limiting enzymes committed to GMP and AMP synthesis from IMP, also increased 2.5- and 1.9-fold in proliferating phase, with a peak at 36 h. Subsequently all parameters decreased to plateau phase values at 96 h. Incorporation of the 3 salvage precursors and activities of the enzymes, adenosine and hypoxanthine-guanine phosphoribosyltransferases, were maintained in the plateau phase range throughout the 96 h growth. The expression of neoplastic proliferation is achieved primarily through the increase in the capacity to provide PRPP, in elevation in PRPP concentration and in the rise in activity of the de novo synthetic pathway. However, since activities of the salvage enzymes and of incorporation of salvage precursors are 1 to 2 orders higher than those of the de novo enzymes and pathway, the success of anti-tumor chemotherapy must depend on simultaneous or sequential blocking of the de novo and salvage pathways of purine synthesis. (PHS grants CA-56222 and CA-53525).
2002 THE ROLE OF DNA DAMAGE AND REPAIR IN POST-IRRADIATION CELL DEATH, K.P. Hannon, Crs. Res. Inst. of Roentgenology and Radiology, Leningrad, USSR. A range of facts has been obtained which indicate that reproductive death of irradiated cells is determined by the wrongly repaired injuries of DNA structure and/or by DNA damage having been unrepaird during certain time intervals. This is confirmed by strong correlation between the increase of reproductive cell death and some other conditions characteristic for cell pathology, e.g., deficiency of DNA repair, drug-induced repair inhibition, and the decrease of time requested for elimination of damage. A connection between DNA damage and repair, and interphase death of cells is more hardly to state. The hypothesis of deficient DNA repair systems in the cells dying by interphase mechanism was not confirmed experimentally. To the contrary, we have proposed a hypothesis which describes the interphase death of irradiated cells as a special case of a common phenomenon of genetically programmed cell death. Even testing this suggestion, it was shown that in post-irradiation period, due to structural rearrangements of chromatin, determined by radiation damage of DNA, there occurs activation of some genomic loci which are responsible for the promotion of programmed death. Our experiments have been shown that the synthesis of some new types of mRNAs and proteins is observed early after irradiation of cells dying in the 'interphase' manner. Those proteins seem to be the factors responsible for switching on a sequence of biochemical events which, finally, lead to destruction of genome and cellular death.

2003 INHIBITION OF REPAIR BY ANTIMETABOLITES IN TUMOUR CELLS DURING FRACTIONATED IRRADIATION IN VIVO. W. Pohlit, Gesellschaft für Strahlen- und Umweltforschung, Institut für Biophysikalische Strahlenforschung, Paul-Ehrlich-Strasse 20, D 6000 Frankfurt/Main. Repair of potentially lethal lesions can be assumed to be one of the most important factors in tumour treatment with ionizing radiations. If the tumour is irradiated with densely ionizing radiation such as fast neutrons or stopped negative pions, a large number of irreparable lesions is produced. Accordingly the influence of repair on cell survival is small. In a treatment with negative pions the normal tissue is mainly irradiated with sparsely ionizing particles and accordingly a high degree of repair is present. This tumour theory with negative pions, however, is quite expensive. Therefore alternative methods for reduction of repair in tumour cells should be tested which do not influence the repair in normal tissue surrounding the tumour. Since for repair processes energy in the form of ATP is necessary, inhibition of the energy metabolism by antimetabolites reduces repair and favours lesion fixation. For selective inhibition of the energy metabolism in fermentating tumour cells the antimetabolite 2-deoxy-D-glucose was applied one hour before and immediately after each dose of a fractionated irradiation of mouse tumours. Tumour growth and cell survival was measured after irradiation with different fractionation schemes. As a general result, about one half of the radiation dose can be spared if the antimetabolite is applied. This leads to tumour cure at dose levels which are well tolerated by the normal surrounding tissue.

2004 THE ROLE OF REPAIR IN CELLULAR SURVIVAL FROM Densely Ionizing RADIATIONS AND ITS IMPLICATION FOR IMPROVING CONVENTIONAL RADIATION THERAPY. J.T. Lett, Fort Collins, USA. In split-dose experiments, the time relationship for the interaction of primary breaks in the formation of exchange and deletion type aberrations have been analysed. Human peripheral blood lymphocytes were irradiated with a dose of 4 Gy of 220 keV X-rays split into two equal fractions separated by intervals up to 8 hours. The yield of radiation-induced dicentrics and rings were observed with prolonged time intervals, and it was more pronounced than that of deletions. However, an unfractinated dose of 4 Gy gave higher number of exchanges but little if any increase of deletions after increasing intervals of stimulation up to 8 hours in early G2 phase of the cell cycle. The results indicate that exchange aberrations and excess deletions originate from different types of lesions and after a certain time only a proportion of breaks induced by the first dose-fraction can interact with the primary breaks induced by the second dose-fraction. This study is an attempt to determine the relationship between chromosomal repair times and induced primary "ions in early G2 phase.
DNA REPAIR AND ITS INVOLVEMENT IN THE ORIGIN OF CANCER IN THE CANCER-PRONE HEREDITARY DISEASES. H. Takebe, C. Nishigori and K. Tateumi, Faculty of Medicine, Kyoto University, Kyoto, Japan

Skin cancers and other cancers in more than 300 patients with xeroderma pigmentosum (XP) were investigated in relation to DNA repair defects in their cells and their clinical manifestations. Multiple skin cancers of the same or different histopathological types were found in many patients. The frequency of basal cell carcinoma was higher than that of squamous cell carcinoma in XP patients, while the frequencies were about equal in skin cancer in general in Japan. The onset of skin cancers was earlier in XP patients with less DNA repair capacity in their cells than those with relatively high residual DNA repair capacity. Cancers in organs other than skin were found only in six patients. Distribution of different complementation groups in XP patients in Japan was considerably different from that in other countries suggesting that XP patients in Japan may be genetically different from their counterparts in other countries in gene frequency of each complementation group. Induction of mutation in XP cells was much higher than in normal cells presumably due to the reduced DNA repair activity. Although similar DNA repair defect was suspected as the cause of high gamma-ray sensitivity in the cells from ataxia-telangiectasia (AT) patients, induction of mutation by gamma-rays in AT cells had essentially same dose-response relationship. One XP cell line showed extremely high mutability by UV despite ordinarily clinical manifestation in the skin. These results suggest that more than one type or process of DNA repair may be involved in mutagenesis, and the mutagenesis and carcinogenesis are not always demonstrated in parallel in the patients and their cells with cancer-prone hereditary diseases.

DAFEN REPAIR AND ITS INVOLVEMENT IN THE ORIGIN OF CANCER IN THE CANCER-PRONE HEREDITARY DISEASES. H. Takebe, C. Nishigori and K. Tateumi, Faculty of Medicine, Kyoto University, Kyoto, Japan

DNA damaging agents including ionising radiations and carcinogenic chemicals stimulate the poly(ADP-ribose)-polymerase activity during aging. Poly(ADP-ribose) synthesis is energy requiring reactions and inhibits replicative DNA synthesis giving cells more time to repair DNA damage. Inhibitors of poly(ADP-ribose)-polymerase activatied by DNA damage potentiate radiation damage. The involvement of poly(ADP-ribose)-polymerase in carcinogenesis is under investigation. The involvement of poly(ADP-ribose)-polymerase in carcinogenesis is under investigation.

ROLE OF POLY(ADP-RIBOSE) IN DNA-REPAIR, DNA-REPLICATION AND TRANSFORMATION

H. Altmann, Institut fur Biologie, Forschungszentrum Seibersdorf, Osterreich

DNA damaging agents including ionizing radiations and carcinogenic chemicals stimulate the poly(ADP-ribose)-polymerase activity during aging. Poly(ADP-ribose)-polymerase activity is energy requiring reactions and inhibits replicative DNA-synthesis giving cells more time to repair DNA damage. Inhibitors of poly(ADP-ribose)-polymerase activatied by DNA damage potentiate radiation damage. Inhibitors of poly(ADP-ribose)-polymerase activity are under investigation. The involvement of poly(ADP-ribose)-polymerase in carcinogenesis is under investigation.

DNA REPAIR AND ITS INVOLVEMENT IN THE ORIGIN OF CANCER IN THE CANCER-PRONE HEREDITARY DISEASES. H. Takebe, C. Nishigori and K. Tateumi, Faculty of Medicine, Kyoto University, Kyoto, Japan

Skin cancers and other cancers in more than 300 patients with xeroderma pigmentosum (XP) were investigated in relation to DNA repair defects in their cells and their clinical manifestations. Multiple skin cancers of the same or different histopathological types were found in many patients. The frequency of basal cell carcinoma was higher than that of squamous cell carcinoma in XP patients, while the frequencies were about equal in skin cancer in general in Japan. The onset of skin cancers was earlier in XP patients with less DNA repair capacity in their cells than those with relatively high residual DNA repair capacity. Cancers in organs other than skin were found only in six patients. Distribution of different complementation groups in XP patients in Japan was considerably different from that in other countries suggesting that XP patients in Japan may be genetically different from their counterparts in other countries in gene frequency of each complementation group. Induction of mutation in XP cells was much higher than in normal cells presumably due to the reduced DNA repair activity. Although similar DNA repair defect was suspected as the cause of high gamma-ray sensitivity in the cells from ataxia-telangiectasia (AT) patients, induction of mutation by gamma-rays in AT cells had essentially same dose-response relationship. One XP cell line showed extremely high mutability by UV despite ordinarily clinical manifestation in the skin. These results suggest that more than one type or process of DNA repair may be involved in mutagenesis, and the mutagenesis and carcinogenesis are not always demonstrated in parallel in the patients and their cells with cancer-prone hereditary diseases.

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The isolation of activated cellular homologs of retroviral oncogenes from human and experimental tumors that are capable of cells forming NII 3T3 cells has raised the possibility that activation of oncogenes may play a causal role in carcinogenesis. At present the vast majority of isolated oncogenes are members of the ras gene family. This is of particular importance since activated Harvey ras oncogenes have been isolated from a chemically induced rat hepatoma. Furthermore, we have shown that the expression of the myc oncogene is increased very early (i.e. at the focal stage) during chemical hepatocarcinogenesis. The principal lesions that develop in the rat liver as a result of initiation-promotion protocols are foci of altered hepatocytes. Initiation of these foci has been shown to follow an apparent first order dose response, suggesting that the foci are a clonal expansion of the initiated cell. Consequently, the phenotype of initiation should be characteristic of altered hepatocytes. Since our working hypothesis states that the phenotype of initiation should be completely represented by the foci of altered hepatocytes we have started a series of experiments to define the role of Ha-ras and myc oncogenes, by themselves or in combination, in the formation and maintenance of the initiation phenotype. The experimental approach that we have taken involves transfection of molecular chimeras of MMTV LTR and Ha-ras and c-myc into normal rat liver epithelial cell line (FNRLM). Transfection with these chimeras provides a system in which the expression of the oncogenes is under glucocorticoid control. Consequently, we can examine the oncogene induced phenotypic changes in the FNRLM cells as a function of glucocorticoid concentration. FNRLM cells have been chemically transformed in vitro and transplantation of these transformed cells into isogenic hosts results in the formation of hepatocarcinoma. The results of these studies will be discussed.
2013 TRANSFORMATION OF PRIMARY HEPATOCYTES BY TRANSFECTION WITH DNA. E. H. G. Gundersen, Dept. of Pathology, The Permanente Medical Group, Oakland, CA. We have developed a method for transformation of normal non-proliferating differentiated rat hepatocytes by transfection with adenovirus containing viral or cellular oncogenes. Transformation was measured by the ability to maintain hepatocytes in CDM supplemented with EIA and EIB sequences. Transformation was also accomplished by transfection with adenovirus (Ad) DNA or a DNA fragment containing the Ad E1A and E1B sequences. It was necessary to maintain hepatocytes in CDM supplemented with diethylsulfate (DES) to obtain Ad-transformed colonies containing cells which continued to produce albumin. We have developed a system which can be used to study transformation of a differentiated cell type by viral or cellular DNA sequences. Transformation can be measured quantitatively and the effects on hepatocellular differentiation can be examined.

2015 STUDIES OF ALTERED HEPATOCYTES AFTER DIETHYLNITROSAMINE INITIATION AND SELECTION WITH 2-AAC. C. A. Love, M. Anthony, A. K. Pecht, B. M. G. Smith, M. R. Gamblin, A. G. Gamblin, Dept. of Pathology and Clinical Biochemistry, University of Toronto, Toronto, Canada. Most hepatocytes of foci and nodules generated in the resistant hepatocyte (RH) model are strongly positive for gamma glutamyltransferase (GGT) histochemically and for glutathione transferase (GGT) histochemically. Using CPT-P as a marker, carcinoigen-altered hepatocytes were followed sequentially for the first few days and weeks after diethylnitrosamine (DEN) initiation and during selection with 2-acetylaminoflunoreine (2-AAF) and partial hepatectomy (PH). Normal hepatocytes (saline-treated rats) rarely showed single hepatocytes positive for CPT-P (average: 1/1000 total hepatocytes). Following DEN initiation, 1/10 of all hepatocytes were CPT-P positive (not detectable by GGT). These were present as single cells (60%) or small groups of 2-8 cells (20%) by 7 days after DEN exposure. After selection with 2-AAF resistance, foci of proliferating hepatocytes positive for both GGT and CPT-P were seen to grow progressively to such a large size in a few days that an origin at PH from a group and not single CPT-P positive hepatocytes is most likely. The relative numbers of these CPT-P positive foci and nodules (average: 1/100 total hepatocytes) was 10-fold less than the numbers of single hepatocytes positive in the same liver. Exposure to 2-AAF alone or selection alone (2-AAF plus PH) resulted in almost exclusively single CPT-P positive hepatocytes. These results indicate that CPT-P is a marker for altered hepatocytes suggest that there are at least three types of responses: chemically induced single hepatocytes, initiation with DEN leads to the emergence of small groups of CPT-P positive hepatocytes and initiation coupled with selection leads in turn to CPT-P positive foci and nodules, a small subset (10%) of the CPT-P positive groups of hepatocytes.

2014 ASIALO-GLYCOPEPTIN AND TRANSFERRIN RECEPTORS IN HEPATIC HEPATOCARCINOGENESIS. R. Pehr, Anderson B. W. Anderson Department of Pathology, Karolinska Institute, Huddinge Hospital, Huddinge, SWEDEN. The asialo-glycopeptin (asialo-orosomucoid, ASOR) and transferrin (ferrotransferrin) receptors in subcellular membrane fractions from normal liver, regenerating liver (48h after partial hepatectomy) and hepatocyte nodules (IEC-2-AAF) in Wistar rats were investigated. The distribution of ASOR binding sites between different subfractions revealed that by far the highest concentration of receptor sites was found in a low density membrane fraction (LDMF) containing Golgi membranes and endosome vesicles. The specific content of receptor sites in this fraction was 17 fold that in the total particulate fraction. In hepatocyte nodules the distribution pattern of ASOR-binding was similar to the normal situation, but the overall binding was reduced to less than half of that in normal liver. In the nodular LDMF the specific binding capacity was only 20% of that in the normal fraction. Dissociation constant and binding specificity was similar in all sub fractions and did not differ from normal in hepatocyte nodules. Transferrin binding was found to be around 60-fold higher in hepatocytes than in normal liver, with no apparent differences in binding affinity. The LDMF fraction showed the highest content of transferrin binding sites but expressed the lowest degree of induction in the nodules. The corresponding values for ASOR binding at 1-2 of that in liver were in between the normal and the nodular ones. The mechanisms of the receptor level changes as well as the functional consequences will be discussed.

2016 CLONING AND CHARACTERIZATION OF RAT GAMMA-GLUTAMYLTRANSFERASE-P. C. F. Atwell, J. W. Ford, M. R. Gamblin, Laboratory of Experimental Carcinogenesis, Nat. Cancer Inst., NIH, Bethesda, MD 20892 USA. One of the most widely used markers for putative preneoplastic cell populations during chemically induced hepatocarcinogenesis is gamma-glutamyltranspeptidase (GGT). GGT is a membrane bound enzyme that catalyzes the transfer of a gamma-glutamyl group from glutathione and other gamma-glutamyl donors to peptide or amino acid acceptors. In spite of the extensive use of GGT as a marker for preneoplastic foci, its functional relationship to tumorigenesis remains unclear. In an effort to better characterize the regulation of this enzyme in hepatocarcinogenesis, we have isolated a GGT specific recombinant clone from a rat liver genomic library using oligomeric probes from the partially sequenced heavy and light chain protein subunits. This clone contained distinct regions which hybridized to either the light or heavy chain specific oligomeric probes. These regions were further subcloned into eukaryotic expression vectors containing poly[A] tail, pBR322 to obtain heavy chain specific oligomers from the partially sequenced heavy chain probe. These regions were further characterized using in vitro transcribed 35S labeled RNA isolated from rat liver and four in four of five chemically induced hepatomas. No GGT specific RNA transcripts were detectable in normal rat liver. This pattern is consistent with the patterns observed in histochemical staining for GGT.
2017 MULTIFACTORIAL AND MULTISTAGE CARCINOGENESIS - CURRENT PROBLEMS OF ASSESSMENT OF CANCER RISK BY COCARCINOGENS OF THE PROMOTER TYPE
Erich Hecker, Institute of Biochemistry, German Cancer Research Center, 6900 Heidelberg, Federal Republic of Germany
As an universal concept of the etiology of cancer in the last decades, MULTIFACTORIAL CARCINOGENESIS involving solitary carcinogens and cocarcinogens (per se non-carcinogenic amplifiers of carcinogenesis) has gained shape in experimental and in epidemiologic oncology. This concept integrates classical UNIFACTORIAL CARCINOGENESIS, and comes more close to the realities of every day human life. However, the extension of the classical case increases exponentially the scientific complexity of atiological and epidemiologic research e.g., integration of cocarcinogens as risk factors of cancer creates a number of practical problems regarding measures of cancer prevention including corresponding legislation. To minimize scientific complexity, in experimental oncology definition of a few prototype processes of carcinogenesis may be useful, especially as regards combined exposure of the host to the factors of cancer may be described as principal models by simple but typical dose/time-effect protocols composed of operationally defined stages. An important prototype process, for example, is carcinogenesis, verified experimentally in the protocol of initiation/promotion as principal model. Indeed, the chemical and biological characterisation of physico-chemically well defined cocarcinogens of the promoter type in initiation/promotion models of various target tissues has added new dimensions to experimental and epidemiologic oncology. For assessment of risk scientific criteria may be provided primarily by investigations of the mechanisms of action be risk factors involved e.g., solitary carcinogens (initiators) and cocarcinogens (promoters). However, the task of management of risk here and now mostly cannot wait until detailed mechanistic aspects of processes of carcinogenesis have been explored e.g., use of appropriate short term assays. Therefore it is suggestive to determine certain descriptive (empirical) criteria available from principal dose/time-effect relationships in appropriate experimental models, as will be demonstrated for the case of certain prototype processes of carcinogenesis.

2018 PHORBOL ESTER RECEPTORS AND PROTEIN KINASE C. P. M. Blumberg, Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, Bethesda, MD 20892, J.S.A.
The major receptor for the phorbol ester tumor promoters has been identified as protein kinase C. The physiological role of protein kinase C is believed to be to mediate one of the two arms of the response pathway for hormones and cellular effectors acting to induce accelerated phosphatidylinositol turnover. Considerable evidence indicates heterogeneity in the biochemical characterisation of protein kinase C. Several biochemical mechanisms may contribute to this heterogeneity, including association of protein kinase C with different phospholipids to alter binding properties. Neurotoxins that generate an active catalytic fragment together with an uncoupled binding domain, and differences in subcellular localization of the kinase within cells, at least one class of endogenous phorbol ester analogs is 1,2-diacylglycerols. Although substantially less potent than the phorbol esters, the diacylglycerols induce effects in intact cells similar to those of the phorbol esters when added enzymously or when generated in situ. Likewise, the diacylglycerols inhibit phorbol ester binding competitively, compared between the phorbol esters, diacylglycerols, and indole alkaloids, three distinct classes of activators of protein kinase C, suggests structural homologies which may form the basis for rational development of new classes of modulators.

2019 MECHANISMS INVOLVED IN TUMOUR PROMOTION AND PROGRESSION.
T.J. Slaga, Austin, USA
The process of skin tumor promotion in NMRI mouse skin can be performed by a single application of the tumor-promoting agent 12-0-tetradecanoylphorbol-13-acetate (TPA) onto initiated mouse skin followed by repetitive treatments with the irritant hyperplasigenic agent 12-O-tetradecanoylphorbol-13-acetate (RPA). The promoting activity of TPA depends on TPA-induced epidermal hyperproliferation but shows, contrary to the transient nature of the latter a memory effect with a half-life of 10-12 weeks. This TPA effect was considered to be a first stage of the promotion process until it was found that it could also occur prior to initiation exhibiting comparable biological characteristics, i.e., a memory effect and dependence on TPA-induced epidermal hyperproliferation. Since promotion is strictly defined as completing the tumorigenic process started with initiation, we consider the TPA-effect as a discrete element of multistage carcinogenesis rather than a component of promotion and propose to call this TPA-induced process conversion. The term conversion then restricted to those events occurring after carcinogen treatment and consisting of repetitive applications of the irritant hyperplasigenic agent RPA. According to our proposal RPA, originally described as an "incomplete" promoter acting in the second stage of promotion, is a true promoting agent, whereas TPA is a promoter with additional convergent potency. Promotion may then be regarded as the result of chronic hyperproliferative processes allowing the clonal expansion of tumor cells, whereas conversion is assumed to make epidermis sensitive for promotion. The molecular mechanism at this induction of promotability remains to be elucidated.

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**D-24: COCARCINOGENS OF THE PROMOTER TYPE**

**2021**


Previous studies revealed that water-soluble phenols recovered from the waste-water of oil shale processing plants, containing mainly 5-methylresorcinol, have a promoting action when applied after an ineffective single dose (0.5 mg) of benzo[a]pyrene (BP). Later it was shown that phenols obtained by chromatographic fractionation of oil shale generator tar also exhibit a promoting action on mouse skin. Another fraction containing paraffins, olefins, and naphthenes and the fraction of neutral oxygen compounds had a similar activity. In Wistar rat intratracheal administration of a 1 per cent solution of phenols obtained by chromatographic fractionation of oil shale generator tar (5 times 0.5 ml of polyglycine) induced no tumours in lungs, whereas the same doses of phenols administered simultaneously with 5 times 5 mg BP induced in 23 out of 57 effective rats epithelial lung tumours. In 16 rats the tumours were malignant (16 rats = adenocarcinomas). The same dose of BP induced only in 3 out of 49 rats tumours. In one rat the tumour was a squamous cell carcinoma. When 1 mg chrysotile asbestos was added (5 times) to phenols and BP 56 rats out of 71 effective rats had 41 rats (9 rats) of these were malignant (karatinizing squamous cell carcinomas). In another experiment fly ash recovered from the electrofilters of an oil shale heated power station, was administered intratracheally to rats induced no epithelial lung tumours; when BP (5 times 5 mg) was administered simultaneously 12 out of 90 effective rats had malignancies (all squamous cell carcinomas) and 21 rats benign lung tumours. BP alone (5 times 5 mg) induced in this experiment 4 rats adenocarcinomas and in 3 rats benign tumours (papillomas) out of 51 effective rats.

**2022**

GENES THAT COOPERATE WITH TUMOR PROMOTERS IN TRANSFORMATION. N.H. Colburn, M.I. Lerman, G.A. Hegamyer, K-T. Tao, A. Saki, W.K. Dowlati, T. Shimada, National Cancer Institute, Frederick, MD 21701-1013, USA

Two novel genes, 5:24: COCARCINOGENS OF THE PROMOTER TYPE that confer on resistant JB6 mouse epidermal cells sensitivity to promotion of neoplastic transformation by phorbol esters and other tumor promoters. These genetic sequences, termed prox-1 and prox-2 are structurally unrelated to any known oncogenes, though their biological activity can be mimicked by certain oncogenes. In addition to transferring susceptibility to promotion of transformation in JB6 preneoplastic mouse cells, prox-1 transfection into basal cell nevus genetically cancer prone human cells led to substantial life span extension of these cells. Hence, prox genes are apparently capable of cooperating with different genes to produce different endpoints. TPA exposure of JB6 promotion sensitive (P) cells yields a transient six to 8-fold stimulation in amount of cytoplasmic RNA hybridizing with a prox-1 probe, contrasted with a 2-fold stimulation in promotion resistant (P') cells. Stimulation was maximal after 1 to 4 hours of TPA exposure. Characterization of prox-1 protein and RNA gene products is underway. It is postulated that prox gene expression switches on a separate transforming gene (2) that becomes constitutively expressed. Human tumor and normal human DNA have homologs of prox-1 and prox-2 as shown by hybridization with mouse prox gene probes. Human nasopharyngeal carcinoma cell DNA, but not human normal DNA transfers promotion sensitivity when transfected into mouse P' cells. Screening a genomic library of these carcinoma cells with a mouse prox-1 probe has yielded biologically active clones of human pre-1 showing high molar specific activity. This suggests a role for pre-1 genes in the etiology of human nasopharyngeal carcinoma.

References:

**2023**

CELL DIFFERENTIATION IN TUMOR PROMOTION AND PROGRESSION. L. Sisti and P. Pascoli-Istituto Nazionale per la Ricerca sul Cancro Genova-Italy.

Many elements have strongly suggested that carcinogenesis is better understood as a multistep process than as a single step process; among these elements we mention tumor latency, more than linear increase of tumor frequency with age for many human and experimental models, and great rarity of the tumor event in respect to the number of cell generations of positive target cells. Mathematical models devised by statisticians-epidemiologists, after a convenient adjustment of some arbitrary constants of their equations, often do fit rather well epidemiological and experimental findings. A mutated ras gene has been found in methylinitrosoureas induced rat mammary tumours. A specifically translocated myc is always present in Burkitt lymphoma. As a consequence of the bulk of the observations mentioned above carcinogenesis is viewed by some investigators mainly as a series of irreversible DNA alterations, at once a clonal expansion of initiated cells is admitted as an effect of promoting treatments. In our opinion, many observations (for a review see R. Rubin Cancer Res. 45:2935, 1985) suggest that not only "hard" alterations in DNA sequences but also "soft" changes in the cell program can play an important role in carcinogenesis. Recent data are in favour of the hypothesis that "physiological responses" of a differentiative type (in contrast with the idea of a single DNA alteration followed by clonal expansion) can also play an important role during promotion in the mouse skin model. G. Purtenberger et al.: Science 230, 76, 1985 and in the rat liver model (G. Thirion et al.: Proc. Nat. Acad. Sci. 73, 171, 1984) from our own data, we have also suggestions that, at least in some cases, DNA alterations observed with promotional treatments, and usually interpreted as DNA breaks, are more likely to be related to broad changes in chromatin structure than to real DNA fragmentations. We favour the concept of a multistage process which can include differentiative events, much more than the more restricted idea of a multihit model.
INT-2: A CANDIDATE PROTO-ONCOGENE IMPLICATED IN VIRALLY INDUCED BREAST TUMOURS


Mouse mammary tumour virus is a principal factor in the causation of breast tumours in mice that suffer a high incidence of this disease. The virus appears not to contain an oncogene, but seems to act as an insertional mutagen by perturbing cellular genes adjacent to proviral integration sites. In a study of two distinct integration loci, termed int-1 and int-2, we examine the region of cellular DNA involved in the progression from non-invasive to invasive cells in this mouse mammary tumour model system. The transpositional activation of either of two distinct cellular genes, int-1 and int-2, is a common feature in carcinomas induced by mouse mammary tumour virus (MMTV). Activation of a cellular proto-oncogene from the integration of an MMTV provirus in the adjacent cellular DNA such that transcription is orientated in the opposite direction to the provirus is a key feature of this process. In addition, we present evidence that int-1 and int-2 RNA in ostensibly monochonal cell populations. Since the random integration of a provirus adjacent to both genes would have an expected proportion of less than 10^-10, we suggest that there is a selective pressure for the simultaneous expression of these genes consistent with a cooperative influence in tumour development.

PATTERNS OF INT-1 AND INT-2 GENE ACTIVATION IN TUMOURS INDUCED BY MOUSE MAMMARY TUMOUR VIRUS


The transcriptional activation of either of two distinct cellular genes, int-1 and int-2, is a feature common to carcinomas induced by mouse mammary tumour virus (MMTV). Activation of a cellular gene from the integration of an MMTV provirus in the adjacent cellular DNA such that transcription is orientated in the opposite direction to the provirus is a key feature of this process. In addition, int-2 may participate in the early stages of hormone-dependent tumour formation. Data from other virus strains and transplanted tumours have been used to support these conclusions.

ACTIVATION OF THE INT-1 AND INT-2 GENES DURING MOUSE MAMMARY TUMOUR GENESIS

David A. Morris, Robert J. Cardiff, Peter A. Barry, Robert Strang, and Lawrence E. Young. Department of Pathology, School of Medicine, University of California, San Francisco, California 95616, USA.

MMTV-induced mouse mammary adenocarcinomas can develop from two different hyperplastic, hormone-dependent plaques, and hormone-independent hyperplastic alveolar nodules (HANs). Hormone changes occurring early in the process of tumorigenesis can be distinguished from those occurring late by biochemical comparisons of hyperplasias and hyperplasia-derived tumors. Insertion mutagenesis is one type of somatic change believed to be important in the genesis of mammary tumors induced by MMTV. Provirus integration in the vicinity of the int-1 and int-2 genes is often observed in tumors and has been associated with enhanced expression of the mutated loci. To determine the timing of insertion mutagenesis of int-1 and int-2, hyperplasias and tumors from the 92 plastic intraductal mammary gland were analyzed for evidence of MMTV provirus at these loci. Provirus presence in the vicinity of the int-1 and int-2 genes has been observed in tumors and has been associated with enhanced expression of the mutated loci. To determine the timing of insertion mutagenesis of int-1 and int-2, hyperplasias and tumors from the 92 plastic intraductal mammary gland were analyzed for evidence of MMTV provirus at these loci. Provirus was present at the int-1 locus in 26% of spontaneous tumors from breeding females, 0% of tumors from transplanted HANs, and 0% of plaques. The int-2 locus was disrupted by provirus in 5% of spontaneous tumors, 0% of transplanted HANs, 25% of tumors from transplanted HANs, and 5% of plaques. These results indicate that int-1 and int-2 contribute to the progression of HANs to tumors, but are not involved in initiation of neoplastic progression in the HAN pathway of tumorigenesis. In addition, int-2 may participate in the early stages of hormone-dependent tumour formation. Data from other virus strains and transplanted tumours have been used to support these conclusions.

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In situ hybridization and immunoperoxidase staining was used to explore genomic integrated MMTV envelope gene and expression of the gene product as a 52,000 molecular weight glycoprotein (gp52) in breast tumor cells. The murine mammary tumor model was used for this study to identify DNA and antigenic protein in same paraffin section of primary tumor. The presence of MMTV envelope gene has been observed in cells preserved with paraformaldehyde by hybridizing recombinant plasmid a biotinated analog of dUTP was incorporated by nick-translation. The biotin was then detected by using avidin complexed to biotinated alkaline phosphatase has been used for genomic DNA detection. Prior to in situ hybridization an indirect immunoperoxidase method was performed, which can readily detect viral antigens in paraffin sections of mammary tumors. The gp52 was detected using monoclonal antibody that react with the mouse mammary tumor virus gp52 and with the human breast carcinoma antigen. The procedure described preserved morphological detail yet is competitive with hybridization conditions and in addition to having the obvious advantage of the resulted staining of paraffin sections is permanent and provides the kind of histological detail required for precise cytological identification and localization with light microscopy. All of 5 tumors showed evidence of MMTV-genome and glycoprotein Gp52. The pattern and intensity of the stain were related to the degree of histologic differentiation of the tumor. Wide variations in integration of viral genome and expression of viral antigens by individual malignant cells were observed within the same tumor.

2029 FURTHER CHARACTERIZATION OF SUNCUS MURINUS MAMMARY TUMOR VIRUS (Sm-MTV) PRODUCE BY A CULTURE LINE ESTABLISHED FROM A PRIMARY MAMMARY TUMOR IN A SUNCUS (Suncus murinus). The Sm-MTV was distinct morphologically from any of known type C. In spite of certain similarities to type H and type D, the virus was readily distinguishable from them. The virus showed three particle types representing the virus developmental stages; intracytoplasmic type A, budding and extracellular mature particles. In this paper, we will report the following new results of further characterization of the virus: 1. Enzyme linked lectin treatment of the mature and budding DNA particles after nucleic in situ hybridization resulted in the visualization of surface projections of the enveloped A virus. 1. The presence of intracytoplasmic latency type (gp52) in Sm-MTV virion and the intracytoplasmic type A particles increased their size during transmission through the tissue sections. 2. The intracytoplasmic type A particles were shown by immunohistochemical examination of the Sm-MTV virion, was partially labeled by H. Rabes, Institute of Pathology, University of Munich, F.P. Germany.

2030 KINETIC CHARACTERIZATION OF A MALIGNANT TUMOR: Olav Hilmar Veggeland, Institute of Pathology, University of Oslo, Rikshospitalet, N-0027 Oslo i, Norway.

The volume of a tumor is the consequence of the difference between the integrals of cell production and cell loss. A tumor increases in volume when the cell production rate is higher than the rate of cell loss. Cell production depends on mitosis. Not all cells in a tumor are dangerous in terms of proliferation regardless of size. Cytological differentiation of tumors can be classified as actual proliferating (cycling) cells, facultative proliferating cells (G2) and mature cells that cannot divide. In the latter case the tumor does not take place evenly spread over its whole volume. It depends upon many factors, proximity to vessels etc. Malignancy is not always characterized by a high rate of cell birth, but if a tumor shall increase in size, there must be a discrepancy between cell birth and cell loss. Tumor cells mature in various directions of differentiation, e.g. keratinization, mucus production, etc. It is difficult to measure the rate of cell loss, but it can take place by detachment of surfaces, cell movements into blood vessels and lymphatics, and into body cavities. Tumor cells often die, sometimes by immunological lysis, sometimes by necrosis due to hypoxia or toxic polypeptides, or tumor necrosis factors. There are also diurnal variations in the proliferation rate in tumors, and probably in the rate of cell loss. The growth of the stromal components must also be taken into consideration. Morphological signs of rapidly proliferating tumors play a role for diagnosis. In very fast growing tumors characteristic, had any profound influence on the planning of therapy. But it seems to be of importance for prognosis. When different tumors are evaluated, cell kinetic characterization of a tumor may play a role also for the planning of therapy.

2031 EVALUATION OF TUMOR CELL KINETICS BASED ON DNA-RELATED PARAMETERS. H. M. Rabes, Institute of Pathology, University of Munich, F.P. Germany.

Tumor growth is based on cell proliferation, the kinetics of which can be measured in various ways. Because DNA synthesis is an irreversible prerequisite for cell renewal, DNA measurements can be used to quantitate cell proliferation in tumor tissue. Various methods of DNA synthesis, e.g. the use of tritiated thymidine (TdR) or bromodeoxyuridine (BrdU) and autoradiography or histochemical evaluation in tumor sections, is required after treatment of biologic DNA precursors or proliferation-related labeled antibodies. Heterogeneity of proliferative compartments in clinical human solid tumors has often posed so much problems for therapeutic strategies that have been evaluated in whole-tumor autoradiograms, prepared either vascular perfusion of surgically resected tumors with different radioactive DNA precursors under simulated physiological conditions. Maps of the growth pattern obtained of such preparations, illustrate the complex implications of cytological differentiation, histological structure (neo)angiogenisization, tumor size and site of origin for the actual rate of proliferation in a human tumor and its subpopulations.
2032 METHODS FOR MEASURING CELL RENEWAL RATE IN CARCINOMAS

TURNOVER AND CELL LOSS IN EPITHELIAL NEOPLASIA.

CELL METHODS FOR MEASURING CELL RENEWAL RATE IN CARCINOMAS

Since both are exocrine glands, the same may hold to submandibular gland are essentially slowly renewing (1,2). Thus cell turnover and they stop dividing and ultimately die. 2. The tumor grows when anaplasia and necrosis prevail, its division becomes less distinct, yet it probably continues to exist. Colon neoplasia reproduces the fate of epithelial neoplasms originating in renewing tissues e.g. stratified squamous cell neoplasms (epidermis or cervix). They all resemble kinetically their tissues of origin. In the same way one may assume that neoplasia originating in expanding cell populations e.g. liver, also maintain their native kinetic structure and behaviour. Recent studies have shown the at least some of the so-called feeding populations of liver and submandibular gland are essentially slowly renewing (1,2). Since both are exocrine glands, the same may hold to other exocrine glands as well. Thus cell turnover and the duration of mitosis itself may affect the mitotic index. Naturally, the counting conditions for the assessment of the mitotic activity which is perhaps best expressed as the mitotic index, or fraction of the tumour cell population which is mitotic, can be defined. But the way of compensating for the mitotic duration is more complex investigators have tried to correct for this by measuring the rate of entry into mitosis, or the mitotic rate, by counting the numbers of arrested metaphases after injection of a drug which has metaphase-arresting properties, such as colchicine or one of the vinc alkaloids, vincristine or vinblastine. However, this method is not simple, since ideally it requires multiple biopsies after injection which are difficult because of obvious ethical constraints, and indeed the quality of the data, in the form of the confidence interval, is heavily dependent on the number of specimens which are available. Nominating this, some useful data have been obtained in gastrointestinal and some other tumours. More recently, monoclonal antibodies which are considered to recognise proliferative cells have become available, which are currently being assessed in several laboratories although at present most of these investigations must be carried out on fresh rather than fixed material. This method, if perfected, will be most useful in the future, and early work on these antibodies will be reviewed.

2033 CELL TURNOVER AND CELL LOSS IN EPITHELIAL NEOPLASIA.

2034 TUMOR GROWTH CONTROL: ONCOGENES, PROTO-ONCOGENES, GROWTH FACTORS, AND IMMUNOLOGICAL FACTORS: A ROLE IN CANCER TREATMENT?

TUMOR GROWTH CONTROL: ONCOGENES, PROTO-ONCOGENES, GROWTH FACTORS, AND IMMUNOLOGICAL FACTORS: A ROLE IN CANCER TREATMENT?

Perhaps the easiest and certainly the most convenient way of assessing the proliferative rate, and hopefully the rate of growth of human tumours, is to count the number of mitoses in routinely stained material. In some tumours this method can give quantitative data of considerable value, as, for instance, the usual of the mitotic count in the assessment of malignancy of the uterine. There are, however, the usual caveats in the assessment of a proliferative index: the method of counting in particular, and also the absolute determination of the duration of mitosis itself may affect the mitotic index. Naturally, the counting conditions for the assessment of the mitotic activity which is perhaps best expressed as the mitotic index, or fraction of the tumour cell population which is mitotic, can be defined. But the way of compensating for the mitotic duration is more complex investigators have tried to correct for this by measuring the rate of entry into mitosis, or the mitotic rate, by counting the numbers of arrested metaphases after injection of a drug which has metaphase-arresting properties, such as colchicine or one of the vinc alkaloids, vincristine or vinblastine. However, this method is not simple, since ideally it requires multiple biopsies after injection which are difficult because of obvious ethical constraints, and indeed the quality of the data, in the form of the confidence interval, is heavily dependent on the number of specimens which are available. Nominating this, some useful data have been obtained in gastrointestinal and some other tumours. More recently, monoclonal antibodies which are considered to recognise proliferative cells have become available, which are currently being assessed in several laboratories although at present most of these investigations must be carried out on fresh rather than fixed material. This method, if perfected, will be most useful in the future, and early work on these antibodies will be reviewed.

2035 APPLICATION OF ABSORPTION CYTOPHOTOMETRY IN THE EVALUATION OF CELL KINETIC PARAMETERS OF HUMAN TUMORS.

APPLICATION OF ABSORPTION CYTOPHOTOMETRY IN THE EVALUATION OF CELL KINETIC PARAMETERS OF HUMAN TUMORS.

Recent numerous studies from many laboratories have indicated the close relationship between some proto-oncogene products and cellular growth factors e.g. c-sis/PDGF. The implications for a more definitive cancer diagnosis and possible prognosis are high; however the implications for prevention or improved cancer treatment are theoretically stimulating but the actual implementation is most likely, in the quite distant future. The c-sis/PDGF cascade model will be used as one representative family of the discussion of therapeutic potential because it includes: 1) a growth factor (PDGF), 2) membrane receptors which are probably proto-oncogene products, and 3) the transcription amplification of two proto-oncogenes (c-fos and c-myc) which are relevant for proliferating vs quiescent cells. An analysis of the cascade indicates three possible sites for therapeutic intervention: 1) a turn-off of the activated c-sis gene, 2) a blockage of the c-sis specific receptor, 3) and the inhibition of transcription of the c-fos and c-myc genes. In theory, such goals can be achieved via recombinant-DNA technology and monoclonal antibody technology; however, the specificity of such agents for malignant vs normal proliferating cells remains to be elucidated. For certain tumour cells, investigators injected macrophages via T-lymphocytes looking for a specific attack on the residual tumour cells following conventional chemotherapy. Indeed the extent of macrophage activation still needs to be worked out. Tumor necrosis factor may also be a 'suicide' cell-specific agent. But its role in vivo has not been documented. In summary, research in all three areas is most relevant, challenging and exciting; however, therapy should not be envisioned, especially for protocols involving specific attacks on proto-oncogene cascades.

Supported in part by CA22186.
2036** CELL KINETICS IN ACUTE LEUKAEMIA: BACKGROUND AND IMPLICATIONS FOR THERAPY AND PROGNOSIS

W. Hildebrandt and Th. Rüdiger, Department of Internal Medicine, University of Münster, FRG

The significance of cell kinetics for the design of therapeutic regimens and its prognostic relevance has been a matter of great controversy and conflicting results have been reported by different groups. Several essential factors, however, which are of great influence on the interpretation of cell kinetic data have been overlooked for a long time and necessitate a careful re-evaluation of cell kinetics in acute leukaemia. Previous studies have exclusively been carried out on bone marrow aspiration material without taking into account that bone marrow aspirates are contaminated by peripheral blood cells and are hence not representative for bone marrow cell kinetics. Comparative analyses revealed that only bone marrow biopsy material can be used for the quantitative analysis of narrow cells.

Based on previous studies in animal systems and in vitro experiments it was found that a continuous infusion of Ara-C has a conditioning effect for the subsequent administration of additional cytostatic drugs and enhances the antileukaemic efficacy significantly. The administration of this combination in patients and the cell kinetic effects during the induction treatment as assessed by representative bone marrow biopsies will be presented and its implications on the therapeutic outcome will be discussed.

2037** CYTOKINETIC CHEMOTHERAPY AS A MEAN TO OVERCOME TEMPORARY CHEMORESISTANCE IN HUMAN SOLID TUMORS. P. F.Conte, P. Promazo A. Alama, F. Di Marco, A. Nicolin, R. Rosso

Istituto Nazionale Ricerche Cancro, Genova, Italy

Resting tumor cells are more resistant to most antiblastic drugs which exhibit their optimal killing efficacy on proliferating cells. Scheduling of chemotherapeutic agents based on knowledge of tumor cell kinetics could therefore increase the therapeutic index of chemotherapy, with the aim to evaluate the feasibility of cytokinetic chemotherapy in human solid tumors we carried out a series of experimental and clinical trials in advanced ovarian cancer (AOC), in locally advanced breast cancer (LABC) and in metastatic breast cancer (MBC). Experimental findings demonstrate that 5-fluorouracil alone can induce a significant rise in thymidine labelling index (TLI) of ascitic AOC cells thus increasing in vitro sensitivity to Adriamycin. In LABC diethylstilbestrol (DES) was able to increase both TL and PDI (a marker dependent DNA polymerase). Chemotherapy administered at the time of recruitment was able to promptly stop the induced tumor cell proliferation. Interestingly DES was able to induce a kinetic recruitment in 85% of estrogen receptor negative and in 55% of estrogen receptor positive tumors. Actuarial 24 mos survival and progression free survival were 65% and 47% respectively; these results are significantly superior to those observed in a comparable historic control. In MBC a randomized clinical trial comparing conventional versus cytokinetic chemotherapy with DES resulted in a significant increase in complete response rate (23.9% vs 10.2%; p < 0.05). These results demonstrate that a cytokinetic scheduling of antiblastic drugs can increase the killing efficacy of chemotherapy. Support in part by contract CNR n.85.02108.44, Rome, Italy

H-22: GENOME ALTERATIONS INDUCED BY ANTITUMOUR DRUGS

2038** NEW ASPECTS ON THE INTERACTION BETWEEN SOME ANTIMETABOLITES AND DNA. U. Lünn and S. Lünn, Rudolphemet, Karolinska Hospital and Dept. Histology, Karolinska Institutet, S-104 0 Stockholm, Sweden

The interaction between 5-Fu, DTIC and DNA is investigated using an approach to lyse cells in dilute alkali to reveal drug-induced fragmentation of DNA. Both 5-Fu and DTIC is incorporated into the DNA, resulting in induction of alkali-sensitive DNA lesions. The presence of lesions results in fragmentation of DNA, which is visualized by agarose gel electrophoresis. The incorporation of drugs is prevented by pretreatment with aphidicolin, to inhibit DNA polymerase α.

During undisturbed DNA synthesis one can detect a discrete 10 kb DNA replication intermediate and Okazaki-fragments. In contrast, if the DNA replication intermediates contain 5-Fu one cannot detect discrete intermediates. Instead there is a heterogeneous population of intermediates spanning the size between Okazaki-fragments and 10 kb.

In DTIC-treated cells there is a gradual decrease in DNA synthesis. The intermediates formed during beginning of drug-treatment are joined together to HMW DNA, which is alkali-sensitive due to the incorporation of drug.

The findings show that 5-Fu (a pyrimidine-analogue) and DTIC (a purine-analogue) by incorporation into DNA induces lesions which have pronounced effects on both synthesis and stability of DNA.

Ref: Lünn and Lünn; PNAS 1983,80,3996
Lünn and Lünn; Cancer Res. 1984,44,3414
Lünn and Lünn; PNAS 1985,82,104

2039** POLARGRAPHIC STUDIES ON THE CONFORMATION OF DNA ADDUCTS WITH SOME PLATINUM COMPLEXES: RELATION TO ANTI-TUMOUR ACTIVITY. V. Brabec, and Y. Klempnička, Inst. of Biophysics, Czechoslovak Acad. of Sciences, 612 65 Brno, Czechoslovakia

Modifications of DNA secondary structure induced by the binding of various bivalent and tetravalent platinum complexes were characterized by means of differential pulse polargraphy. It was found that at low levels of binding the platination of DNA markedly influenced its polargraphic behaviour. The results indicated that the binding of the active antitumour complexes resulted in minor conformational changes in DNA when the double-helical structure remained conserved. On the other hand the attack by inactive antitumour compounds induced more severe alterations which had the character of denaturation of longer regions of the DNA molecule. It was also demonstrated that active antitumour tetravalent platinum complexes could react with DNA without their prior reduction to the bivalent state, and may induce in DNA conformational changes similar to those produced by bivalent cis-diaminedichloro-platinum(II). The modification of DNA by active antitumour platinum complexes and ionizing radiation in combination resulted in an enhanced content of double-stranded distorted regions in DNA molecules. A more than additive response was observed if platination preceded irradiation,
DETECTION OF DNA-BINDING PRODUCTS OF METABOLITES OF CYCLOPHOSPHAMIDE. E. Hentelinä and L. Henttonen, Institute of Oncology (Kluuvi), Mannerheiminti 1, 00290 Helsinki, Finland.

Cyclophosphamide is activated metabolically to alkylating species such as phosphoramide mustard. We prepared DNA and guanosine adducts of phosphoramide mustard and characterized them by mass spectrometry. The guanosine adducts were \( H-(2\text{-chloroethyl}-N-(1\text{-guaninyl)ethyl})\text{phospho-}

Diacid, which had a tendency to undergo secondary reactions such as dechlorination of the untreated musturd arm, dephosphoridation and imidazole ring-opening. The half-life of the intact phosphoramide mustard-guanosine adduct was 3.1 h (37\(^{\circ}\), pH 7.4) as determined by HPLC. The half-life of the adduct for imidazole ring-opening was 9.5 h (37\(^{\circ}\), pH 7.4). The phosphoramide musturd adducts are notably more stable than simple alkyl substituted guanosines. The adduct in DNA was characterized after alkilation and derivatization. In subsequent mass-spectrometry mass-spectrometry (MS-MS) analysis 7-alkylguanine derivative of phosphoramide mustard was demonstrated. The product was identified as a derivatized 7-(2-chloroethyl)-N-(1\text{-guaninyl)ethyl})phospho- diamic acid. Detection of the adducts in biological samples after administration of phosphoramide mustard and cyclophosphamide.

Grants: Medical Research Council of Finland.

MONDAY • AUGUST 25 • AFTERNOON

REPAIR OF INTERMEDIATES IN THE FORMATION OF DNA INTERSTRAND CROSS-LINKS INDUCED BY CHLOROETHYLISOXAZOLES. Thomas F. Brez, St. Jude Children's Research Hospital, Memphis, TN 38101 U.S.A.

The antineoplastic chloroethylisoxazoles induce interstrand cross-links in DNA via a multi-reaction sequence. The first DNA adduct is believed to be \( \text{O}-\text{alkylguanine} \text{which then undergoes intramolecular rearrangement forming an} \text{0,4-cyclic ethano derivative} \text{which subsequently opens at the} 6^\circ \) position and reacts with cytosine in the opposite strand to yield an \( N\)-guanine, \( N\)-cytosine cross-link. We have obtained evidence that \( \text{O}-\text{alkylguanine}-DNA \text{alkyltransferase purification from human lymphoblasts can block the conversion of the monoadduct precursor to cross-links. Kinetic studies of these reactions suggest that the initial precursor is formed rapidly and that the final conversion to cross-links occurs slowly. Thus, one of the monoadduct intermediates appears to be relatively stable and we speculate this is the \( \text{O,4-cyclic derivative}. \text{Experiments to determine the ability of the alkyltransferase to block cross-link formation at different times during the reaction sequence suggest that the stable cyclic intermediate is a substrate for the enzyme. Since the alkyl moiety normally becomes covalently linked to the enzyme upon cleavage from the \( \text{O}\)-position of guanine, in the case of a cyclic ethano group that is also linked to \( N\) of guanine, one would expect the reaction to result in a DNA-enzyme cross-linked product. This work was supported by NIH Grants CA17999 and CA15888 and by ALSAC} \)

H-22: GENOME ALTERATIONS INDUCED BY ANTITUMOUR DRUGS. Agnieszka IARTOSZ-ZAK and Jerzy KOZOPA Technical University of Gdańsk, Gdańsk, Poland.

It has been shown that cytotoxic and antitu- mour activity of 1-nitro-9-aminacridines corre- lates with their ability to interstrand cross- link DNA [C. Pawlik et al., Cancer Res., 44(1984), 4821]. Hence we have tested their ability to bind. Covalent binding to DNA after metabolic activation, was confirmed directly only for one of the derivatives of 1-nitro-9-aminacridine which has found application in clinical therapy under the name Ledakrin/1Tritamore/ [C. Pawlik et al., Cancer Res., 44(1984), 1557]. The \( \text{\text{-post-labelling analysis} developed by B. Gupta [C. Gupta et al., Aromatic, 3(1982/1983) allowed} \text{to determine unequivocally that the derivatives of} \text{1-nitro-9-aminacridine do form adducts resulting from covalent binding to DNA. For example, the treatment of \text{1,3 cells with} \text{\text{-ex/42,}} \text{equivalent to} \text{\text{-ex/360, give rise to 5 different adducts, one of which was responsible for 37% of the total binding. Under these conditions every 400 nucleo- sities was modified by the drug. This result is consistent with the data obtained from the experiments in which radioactive Ledakrin was used. C.8C, another 1-nitro-9-aminacridine derivati- ve at the concentration \text{0.5\mu g/mI, equivalent to} \text{5.3\times10^{-7}} \text{for 10 different \text{-adducts, two of which accounted for 30% of the total binding. The most reactive of them,} \text{C.8C, by} \text{5.3\times10^{-7}} \text{at the applied concentration accounted to 1 adduct per 300 nucleotides. It was also found that the \text{1-nitro-9-aminacridine did not form adducts even at the concentration as} \text{0.5\mu g/mI. This finding corroborates the hypothesis that} \text{binding and} \text{cross-linking are not intercalation \text{that are a prerequisite for antitumour activity of 1-nitro-9-aminacridines.}}}

32-P-POST-LABELLING ANALYSIS OF DNA ADDUCTS FORMED BY ANTITUMOUR 1-NITRO-9-AMINACRIDINES.

Grants: Medical Research Council of Finland.
INTERACTION OF DNA REACTIVE ANTI-TUMOUR DRUGS WITH CELLULAR CHROMATIN

DNA reactive anti-tumour drugs that either cleave or unwind DNA duplex structure have been examined for their differential interaction with bulk versus replicating and actively transcribed chromatin.

Using nuclei from 3H-bulk labelled and 3H-pulse labelled L1210 cells, we have found that DNA damaging drugs, such as bleomycin, interfere differently with replicating and bulk chromatin. At low and moderate levels of DNA damage, newly replicated chromatin (3H-pulse-labelled for up to 3 min) is less readily solubilized. There are also considerable differences, in the size distribution of the fragments released, from newly replicated and bulk chromatin. These differences were abolished at high levels of DNA damage and disappeared completely at longer (> 10 min) 3H pulses or in pulse/chase experiments (45s/20 min, respectively). The results indicate that strand-division drugs can distinguish higher orders of structures of newly replicated and bulk chromatin.

Using Simian virus 40 (SV40) as a model system, we have found that DNA strand scission agents such as neocarzinostatin and daunorubicin cleave nuclear DNA in actively transcribed genes in a non-random manner. The cleavage pattern is distinct from that made by DNase I and much more closely resembles that produced by micrococcal nuclease. In some instances the cleavage caused by PRL treatment of purified RNA is also non-random, but the pattern is different from that seen with micrococcal DNA. Currently, DNA unwinding drugs are being investigated to see how they modify unwinding and drug damage of chromatin. This work was supported by a grant from the American Cancer Society (H-295) and the National Cancer Inst. CA 24955 and A-26429. 

CLINICAL IMPORTANCE OF PROLACTIN RECEPTOR (PRLR); DETERMINATION IN HUMAN BREAST CANCER

F. Labrie, Quebec, Canada

The clinical importance of steroid hormone receptors (SR) in the management of mammary carcinoma is well established. However, in spite of the SR-positivity a favourable response to endocrine therapy can be achieved only in 60-80% of breast cancer patients. Other hormones like prolactin (PRL) may also have influence on tumour cell proliferation. The involvement of PRL in the stimulation of mammary tumour growth in rodents is well-documented but its role in the human breast cancer has not yet been clarified. Over the past 10 years, in consequence of discovery of PRLR, several publications appeared concerning its biochemical properties and clinical usefulness. Recently, PRLR is accepted as a new sign of hormonal sensitivity of cancer cells. After preparation of membrane fraction, the PRLR can be determined in the tumour tissue by a single-point assay or by multi-point Scatchard analysis. 125I-labelled human PRL is used as an agon in the presence or absence of 1000-fc excess of unlabelled hormone. Tumour samples are considered positive if the specific binding is higher than 0.5-1. Approximately 46-50% of breast cancers are PRLR-positive. PRLR positivity is more frequent in SR-positive tumours. This fact makes possible to select a population of particularly hormone-sensitive cells among the SR-positive tumours. That might be clinically useful in selection of patients for combined treatment modalities containing antiprogestin drugs.
ESTROGEN RECEPTOR STATUS AND RISK FACTORS

In 260 Japanese breast cancer patients, response rates to endocrine therapy were 78% for estrogen receptor (ER) (+) tumors, 48% for ER (+) tumors, 68% for ER (+), progesterone receptor (PR) (+) tumors, and 53% for ER (+), PR (+) tumors. Although the incidence of breast cancer in Japan is remarkably lower (1/5) than in Western countries, response rates are similar to those reported in Western countries. These findings suggest that ER status is an independent risk factor for breast cancer. However, these findings should be interpreted cautiously: this finding is not entirely consistent with other studies and may be dependent on the determination method. The endocrine therapy, the growth of SC115 cells with AR and ER is stimulated by androgen. In the absence of androgen, however, estrogen-independent cells without AR transformed from SC115 cells can slowly proliferate instead of SC115 cells. Recently, the growth stimulation of SC115 cells by pharmacological doses of estrogen and physiologic doses of androgen and physiologic doses of estrogen via AR and ER systems, respectively. In vivo experiments in cell culture demonstrated that the growth of clones SC115 cells is clearly stimulated by physiologic concentrations of testosterone in serum-free medium and that the absence of growth factors. The addition of conditioned serum-free medium to the presence of but not in the absence of testosterone resulted in significant enhancement of the growth of SC115 cells, suggesting that SC115 cells themselves produce growth factor which is self-stimulatory.

ESTROGEN RECEPTOR STATUS AND RISK FACTORS FOR BREAST CANCER

Introduction and Methods

1. We have developed a micro-method for measuring growth of human breast cancer cell lines in monolayer culture. Cells cultured in 96-well dishes are successively fixed with ethanol and colored with hematoxylin. The intensity of coloration can be used to give an accurate estimation of the cell number. This method is presently used for evaluating the effect of estrogen and antiestrogens on MCF-7 cell growth. Evaluation of interactions of these hormones with estrogen receptors (ER) and AR is run in parallel to each other.

2. In 96-well dishes, the growth of MCF-7 cells in exponential cell growth (one day after plating) significantly increased with the proliferation. After 4 days of culture, the ratio of stimulated to unstimulated cells amounted to 1.5. Remarkably, this ratio maintained when E2 was added for only 1 or 24 hours on either day 1, 2, or 4 after plating. This observation found its explanation in both a constant level of ER along control culture and a rapid and complete disappearance (processing) of the receptors after E2 addition, yielding estrogen insensitive cells. This disappearance was not associated to the saturation of ER by the estrogens according to a hyperbolic law related to the "activation" potency of the hormones, i.e., the capacity to promote transcription of estrogen-induced products. Alternatively, it was due to the estrogen-induced inhibition of cell growth. The efficiency of the cell culture, the growth of cloned SC115 cells is clearly stimulated by physiologic concentrations of testosterone in serum-free medium and that the absence of growth factors. The addition of conditioned serum-free medium to the presence of but not in the absence of testosterone resulted in significant enhancement of the growth of SC115 cells, suggesting that SC115 cells themselves produce growth factor which is self-stimulatory.
THE CLINICAL SIGNIFICANCE OF HORMONE RECEPTOR DETERMINATION

A. C. Habib, Department of Surgery, University Medical School, Teviot Place, Edinburgh, EH8 9AG, Scotland.

Interest in hormone receptors in the human prostate is motivated by the long term possibility of using receptor estimation as an aid to predicting response of cancer patients to hormone therapy. Over the last few years attempts have been made in our laboratory to develop a standard assay for the measurement of androgen receptors in the cytoplasmic and nuclear fractions of prostate tumours. In the process we have identified the factors affecting the reproducibility of these assays and markedly improved the reliability of our results. Besides the usual criteria for storage at temperatures below -20°C protein concentrations of around 50 mg/ml choice of ligands and the need for the presence of molybdate in the incubation medium at levels in the region of 10 mM, we also found that there was a high degree of correlation between receptor levels in the epithelium and stroma: this suggests that the binding measured in the total gland will not be drastically affected by the proportion of stroma and epithelium it contains. Furthermore our receptor assays on the nucleus have demonstrated that following the conventional extraction of the nuclear pellet with high salt, considerable amount of binding (in excess of 60%) remained in the nuclear pellet. Although the clinical significance of these non-extractable fractions has not been established, our studies confirmed the earlier reports on the lack of correlation between pathological state of the tissue and its receptor content. Additionally there was no correlation between histological grade and either nuclear or cytosolic receptor concentration. Nonetheless our findings suggest that the staging of the disease bears a great impact on the capacity of the tissue to specifically bind androgens. We have also investigated the affinity of the non-steroidal hormone and particularly prolactin. Although prolactin receptors were present in both hyperplastic and cancerous prostate, we were unable to assess their prognostic significance with regard to hormone therapy. Plasma prolactin was however found to be of considerable significance in the management of carcinoma of the prostate.


It is well established that orchectomy and treatment with estrogen cause, in cancer of the prostate, an improvement for a limited time interval in 60 to 80% of cases. Recent data obtained with a combination of orchectomy (surgically or chemically) and an antiandrogen indicate that an objective response is observed in 95% of patients and prolongs the period of remission while the death rate within the first two years is lower than that observed with previous treatment. This data strongly suggest that C-19 steroids from adrenals are converted into potent androgens which are blocked by the antiandrogen. We have first study the effects of the antiandrogen, Flutamide, on the serum concentrations of dehydroepiandrosterone (DHEA), its sulfate (DHEAS) and cortisol in castrated patients. Our data show that the plasma concentrations of DHEA and DHEAS are reduced to 45% and 64%, respectively, while cortisol levels remain unaffected. It thus appears that, since adrenal C-19 steroids are reduced by approximately 50% after combined therapy, the efficiency of the antiandrogen should then be increased. Further studies have demonstrated that the antiandrogen induces, in the adrenal steroidogenesis, a blockade at the level of 17,20-desmolase. In a second studies, we have compared the levels of dehydroepiandrosterone (DHEA) in prostate tissue from untreated patients, castrated patients and patients receiving the combined therapy. Our data demonstrate that, after castration, the intraprostatic concentrations of DHEA are reduced from 4.2 ± 0.5 to 0.7 ± 0.5 ng/ml. Furthermore, in patients treated with the combined therapy, the levels of prostatic DHEA are dramatically diminished to less than 0.3 ng/gr. These findings further support clinical evidence for an important role of C-19 steroids from adrenals in prostate cancer and the need to use the combined therapy in order to block the effect of residual androgens remaining after castration.

K-21: DIAGNOSTIC IMAGING IN THE DIAGNOSIS OF MALIGNANT TUMOURS

P. J. Gerson, Dept. of Diagnostic Radiology, University Hospital, Turku, Finland.

An analysis of the accuracy and clinical impact of new diagnostic modalities has been performed in our hospital during the first two years of their use. Special emphasis has been placed on the diagnosis of hepatobiliary, pancreatic, renal and lymphoproliferative diseases. In hepatobiliary diseases ultrasound rapidly overcame CT and has proven to be better than low field MRI. Echography was proven to be the most accurate diagnostic procedure in pancreatic diseases, followed by CT and MRI. In that order. If ERCP and either US or MR gave similar results, the diagnosis was correct in all cases, but a 100% accuracy was not achieved with a single method. Renal mass lesions were best diagnosed by CT and angiography. US proved to be more reliable than IVP. When CT and angiography gave similar results, the diagnosis was always correct. In lymphoproliferative diseases the correct information was received in 90% of conventional examinations, in 70% of nuclear medicine examinations and in 70% of US or CT examinations. DSA in our institution has had little impact on the use of angiography in tumor diagnosis. During the first two years of use, low field MRI has had its greatest impact in the diagnosis of intracranial pathology and little or no other regions.

THE DIAGNOSTIC IMPACT OF NEW IMAGING METHODS

Martti. J. Korhonen, Dept. of Diagnostic Radiology, University Hospital, Turku, Finland.

Analytical comparison of the cost and performance of the different imaging methods is the focus of this presentation. In hepatobiliary diseases the ultrasound is the best method but for renal masses the CT and angiography are the most accurate. If both US and CT give similar results, the diagnosis is correct. The most accurate method for pancreatic diagnosis is still the CT scan. The most accurate method for detection of lymphoma is currently the CT or MRI scan. The most accurate method for the diagnosis of intracranial pathology is the CT or MRI scan.


In the last years two different forms of emission computed tomography (ECT) are applied in the nuclear medicine: 1/ Single-photon emission computed tomography (SPECT) 2/ Positron emission computed tomography (PET). In the talk the technical parameters and clinical efficiencies of the developed instruments are compared.
2057 THREE-DIMENSIONAL BIOMEDICAL IMAGE DISPLAY AND ANALYSIS.

R. A. Robb, Mayo Medical School, Rochester, MN, USA.

Major segments of the biologic sciences and the practice of medicine are based on study and knowledge of the relationships of anatomic structure to biological function. Traditionally this knowledge has been gained either indirectly or by inference and, in the final analysis, by direct surgical vivisection or by postmortem examinations. These types of direct visualization and study of anatomic structure and function of internal organ systems we have, up to the present, been the preserve of the surgeon and pathologist. The revolutionary capabilities provided by new 3-D and 4-D (dynamic) imaging modalities for obtaining similar information non-invasively, non-destructively and painstakingly can now provide these data to the internist, surgeon, and researcher for direct reproducible examinations of individual patients or experimental subjects without disturbing the physiology of the organ system under study or altering its normal integration into the physiology of the body as a whole. The ability to display and extract objective and quantitatively accurate information from 3-D and 4-D biomedical images has been accomplished by development of a powerful new microcomputer-based workstation. The system features an operator-interactive display for true 3-D viewing and manipulation of images reconstructed from X-RAY CT, MR, EMISSION CT, or ULTRASOUND imaging systems. Three-dimensional volume images can be observed from any arbitrary point of view using multiple "Windows" to look simultaneously at different features of the 3-D object. The observer can selectively identify, enhance, and extract structures within the volume and make a variety of regional measurements, such as shape, size, density, etc. Selected substructures can be "cut out" for detailed inspection on the screen, or outer layers of the volume can be "peeled" away in order to see internal structures more clearly. The organ or organ system can be examined much like a surgeon or pathologist might do in real life, but entirely non-invasively, without pain or destruction of tissue, using a "mathematical scalpel" and "computerized microscope." The system provides important new capabilities for simultaneously representing and analyzing both structural and functional data and their relationships in various organs of the body.

2058 TELEVISION-LAPAROSCOPY. AN IMPORTANT DIAGNOSTIC TOOL FOR INTRA-ABDOMINAL MALIGNANCIES. G. Berci, Department of Radiology, University of Texas, Southwestern Medical Center, Division of Surgical Endoscopy, Los Angeles, California, USA.

Laparoscopy is a known diagnostic modality in intra-abdominal malignancies. Biopsy under visual control is more precise. Indications: Diagnostic dilemmas, palpable tumors, ascites of unknown origin, operability, staging, second look. Small lesions are not detected by CT scan. In a large number of cases guided (CT scan) needle biopsy (cytology) is not informative for the oncologist. The addition of TV to laparoscopy provided the following advantages: The image is enlarged and seen from a convenient distance, instead of looking through a small monocular eyepiece. The movements of the surgical team are coordinated because operator and assistant can see the image simultaneously. Faster procedure. DOCUMENTATION OF DISCOVERED PATHOLOGY IS CRUCIAL because they can be reviewed, analyzed at leisure (videotape), demonstrated during consultations or scrutinized during the followup period. Small lesions of 2-3 mm can be detected on the TV screen. It is the method of choice in teaching. The laparoscope is coupled to a miniature TV camera. Size: 30 x 20 x 20 mm. Weight: 60 gm. Instrument and camera are sterilized. We accumulated experience in over 900 laparoscopies in high risk patients without mortality. We achieved 100% histologically proven diagnostic accuracy. We found that the TV display and instant documentation added new dimensions to laparoscopy, specifically in oncology cases. Further progress in electronic imaging like: freeze-frame (storage) capability with an immediate digitized hard color print inserted into the patients chart and operators file, will add further value to this method.
K-21: DIAGNOSTIC IMAGING IN THE DIAGNOSIS OF MALIGNANT TUMOURS


University Hospital, Dept. of Radiodiagnosis, Utrecht - The Netherlands

During the past few years HRCT has been established as the key modality in orbital diagnosis. A new dimension is the ease to examine the orbital cone in all appropriate planes to delineate the orbital structures, i.e. not only the transverse, but also the coronal and oblique-sagittal plane parallel to the optic nerve. The transverse plane is accessible with any scanner. To examine the orbit in the coronal plane, with the head well stabilized, becomes already cumbersome in most scanners. True sagittal sections along optic nerve has been achieved on a routine basis only with the Philips Tomoscan 310/350. The fact that CT is the most useful imaging modality for the examination of the orbit, implies that special attention to the technique must be exercised. The 1.5 mm slices in the axial plane are made at -10° from the orbitomeatal baseline. Once pathology is evident or suspected at the plane sections, dynamic scanning is performed with rapid i.v. bolus injections of contrast material for optimal demonstrating of bloodvessels and nerve sheath. Depending on these preliminary findings and/or clinical indication sections in the coronal and/or sagittal plane are added. He will discuss the DMP-HRCT pathologic morphology in optic nerve tumors, metastasis, lacrimal gland and soft tissue tumors.

COMPUTED TOMOGRAPHY AND ULTRASOUND IN THE EVALUATION OF SOFT TISSUE TUMORS / A RADIO-PATHOLOGIC CORRELATION. G. Hermann, M.D., Dept. of Radiology, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, N.Y. 10029, U.S.A.

110 patients with primary benign and malignant soft tissue tumors were evaluated by computed tomography (CT) and ultrasound (U/S), and the results were correlated with pathologic findings. The uniformly low density fatty benign tumor may be differentiated on CT from its counterpart, which is nonhomogeneous, denser and malignant. Calcifications are commonly present in both benign and malignant lesions. Hemangioma has a characteristic pattern. A dense mass with moderately high attenuation values on CT may present as an echo-free structure on U/S and suggest sarcoma or lymphoma. Leodense tumors are better seen on U/S. The combined application of the two modalities allows us to predict certain histological patterns and may give basis to surgical planning.


To improve the radiologic diagnosis of peripheral pulmonary carcinomas, we made a comparison of conventional and new digital radiography (Sonoda M. Computed Radiography Utilizing Scanning Laser Stimulated Luminescence, Radiology 148:833, 1983). Ten surgically resected peripheral lung cancers were studied. The surgical specimens were distended with fixative fluid and air dried (Heitman Dr. The Lung Radiologic-Pathologic Correlations, 2nd ed., p.7, Mosby Co., 1984). In 4 cases out of them postmortem-bronchograms were performed. Firstly, the specimens were radiographed using a conventional x-ray source with conventional films and imaging plates (IP). Then, the specimens were sliced in 0.3 cm width. Each slice was radiographed using a x-ray tube with a small focal spot (0.3 mm) with fine grain films and IP. The conventional and the digitize images are compared each other and correlated with each pathological findings. In all cases examined using the conventional x-ray source, the digitize images, when proper image processing had been done, provided better depiction of the normal structures such as bronchi, pulmonary arteries, veins and visceral pleura than the conventional images. Also the former demonstrated the character of the lung-tumor interface and cavitations within the mass more clearly than the latter. The digitize x-ray images using the x-ray cube with the small focal spot represented normal fine structures such as peripheral bronchi and pulmonary vessels adjacent to the tumor. But they could not provide so clear depiction of small bronchioles under 0.5 mm diameter in the bronchography cases as the fine grain films.
Extended laryngectomy which necessitates the removal of the pharynx and a portion of the cervical esophagus results in a major anatomic defect. Reconstruction is not amenable to local primary tissue repair. The historical chronology of reconstruction of the laryngopharynx and cervical esophagus has been previously reviewed. (1) Staged procedures as described by Hookey, Montgomery, and others carry a high incidence of stenosis with a reconstructive completion time in excess of 70 days. The present impetus is towards unstaged primary reconstruction. The three most promising procedures in this group are the gastric transposition, free microvascular jejunal transfer and pectoralis major myocutaneous reconstruction. Over the past two years 16 patients have been successfully repaired using a partially tubulated Pectoralis Major myocutaneous flap as originally proposed by this author in 1984. An average completion time of 18 days with a low complication rate has been achieved. An in-depth analysis of the procedure and results are presented.
Reconstructive Procedures in Gastric Malignancies.

Ch. Herfarth, Heidelberg, FRG

Preservation of Rectal Function in Treatment of Rectal Cancer

J.J. DeCosse
Cornell Univ. Med. College
New York, N.Y., U.S.A.

At present, only about 15% of patients with rectal cancer require a permanent colostomy. This gain, which has come from many centers throughout the world, is a net result of: the advent and application of stapling techniques; lower hand sutured anterior resections; popularization of the abdomino-sacral resection; development of the coloanal anastomosis by the late Sir Alan Parks. When these operations have been compared there have been no differences in end results. A 3cm in vivo distal margin has been found sufficient for all but very aggressive rectal cancers have prompted curative para-sacral and trans-anal excision, diathermy and primary curative radiation therapy. Recognition of mobility and of histopathological factors indicating local containment are important in treatment selection. An abdominal perineal resection remains unavoidable for curable distal rectal cancer invading the sphincter musculature. Here adjuvant radiation therapy provides additional benefit.

Esophage-gastric Anastomosis Without a Leak.

E. Amdrup, Surgical Gastroenterological Dept., Kommunehospitalet, Univ. of Aarhus, Denmark.

The main reason for a high postoperative morbidity and mortality following total gastrectomy is insufficiency of the esophago-gastric anastomosis. The reason for the weakness of this anastomosis is not technical difficulties but the fact that esophagus has no serosal covering. An end-to-end anastomosis between esophagus and the small intestine leaves only limited possibilities for covering the suture line by small intestinal serosa and this is also true for the usual end-to-side type of anastomosis. 1971 Hayashi published reconstruction, where the esophagus is buxed longitudinally into the small bowel thus the anastomosis and distal 3-4 cm of the esophagus is completely covered. In our dept. 70 consecutive total gastrectomies have been performed using this technique. No leakage occurred. Four patients died postoperatively for other reasons.

Breast Reconstruction after Mastectomy for Cancer. Indications and Oncologic Risks.

Wolrad H. Matthias and Madeleine Lejour.

All patients undergoing radical mastectomy (RM) for cancer are informed of the possibility of breast reconstruction (BR) after one year of observation without evidence of recurrence, or at the end of adjuvant therapy, if given.

About 20% of eligible patients are reconstructed despite the absence of financial problems because those operations are paid by our social security system. In most of the cases, the contralateral breast is operated too, reduced or repositioned. Subcutaneous mastectomy is advised in extensive fibrocystic disease, papillomatosis and lobular primary tumors.

To evaluate the oncologic risk of reconstruction, we compared the rate local recurrence (LR) and disseminated recurrent disease (DRD) in our patients treated by RM and RM plus BR.

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<th>RM</th>
<th>RM + BR</th>
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<tr>
<td>LR only</td>
<td>4 %</td>
<td>6 %</td>
</tr>
<tr>
<td>DRD</td>
<td>35 %</td>
<td>11 %</td>
</tr>
<tr>
<td>Total R. rate</td>
<td>39 %</td>
<td>17 %</td>
</tr>
</tbody>
</table>

Thus, BR does not induce any added oncologic risk, the apparent excess of pure LR in BR is probably due to shorter observation time in that group. Treatment of LR in BR is possible and satisfactory by surgical excision and/or radiotherapy. In most cases with good reconstruction preservation.
This paper shows our experience regarding application of NCEF for surgical treatment of primary and metastatic malignant bone tumors. These endoprostheses have a precise indication for all tumors which because of size or localization, require important resections, provided the patient has an estimated survival to enjoy its benefits.

Since its creation in 1971 till the end of 1985 were implanted 2100 NCEF, 772 used in tumoral problems. Presently several institutions, inside and outside our country are using this method, and through a professional relationship we are able to control the compliance to the method and patient's evolution.

NCEF is the result of an integrated method intending to offer comfortable survival to tumor-struck patients. Aims for these purposes are:

- Oncologic criteria
- Avoiding amputation or decreasing extent.
- Pain elimination.
- Fast mobilization and rehabilitation.
- Early social reintegration.

This method involves:

- Study of indications.
- Factibility of application.
- Biomechanics and morphology of implants.
- Choice of the most adequate NCEF.
- Development of compatible surgical techniques.

We explain some points of this large methodology, emphasizing medical and philosophical criteria for its indications.
At the end of the process of carcinogenesis a tumor is formed as an individual in the individual. The individuality of cancer exists on organ, tissue and cell level and includes individual tumor-host-relationships. The growing understanding of the biological individuality of human tumors has increasingly influenced our therapeutic thinking. A detailed analysis and consequent therapeutic consideration of clinical and biological individuality of human tumors may offer real chances for improvement of cancer therapy. Considering the extend of our knowledge about human tumor cell biology it seems to be necessary to go far beyond world-wide accepted TNM classification and histological typing. The current knowledge of cell kinetic and other parameters may give improved conditions for choosing optimal fractionation schedules. New imaging techniques give the chance to monitor or follow up changes in morphological, biophysical and biochemical tumor characteristics during and after radiotherapy. Above all they allow a more precise definition of target volume, a diminution of irradiated volume and thus a possible increase of total tumor dose. The concept of individualized radiotherapy is a challenge to radiobiologists, radiotherapists and technicians to develop and introduce new equipment and methods into clinical practice. In this connection there is given an evaluation of use of new imaging techniques (CT, NMR, PET, SPECT, US) for an individual characterization of human tumors with respect to the possible value of measured parameters in radiotherapy treatment planning, monitoring and follow up.
This lecture will describe the techniques and dosimetry for TSET at energies of about 3-7 MeV at the patient and 4-10 MeV at the accelerator. The irradiation beam requirements are identified on the basis of clinical needs. Methods of obtaining the very large fields needed for electron beam irradiation of the total skin will be reviewed. Several types of dosimetric measurements should be performed prior to initiating TSET procedures. One widely used technique for TSET, the six dual-field procedure, will be described thoroughly and others reviewed more cursorily. Emphasis will be placed on treatment with electron linacs, which are frequently employed for this treatment modality. Any TSET program development is heavily dependent on the specific technique chosen, the particular equipment on which it is carried out and the facility where it will be implemented. The techniques themselves are often complex with concomitant hazards and most are time consuming to develop and carry out on a routine basis. A rigorous quality assurance program should be an integral part of a TSET program which may involve high dose rates at isocenter in order to minimize treatment time in a plane several meters distant. Attention to safety measures is imperative, i.e., interlocks, etc. Whether a physicist should be present for TSET treatments depends on the complexity of the procedure and the relevant staff's experience in using it.

The authors have developed their own computer programs for dose calculation of percutaneous (TSET) and brachytherapy. The outputs of these programs are compatible with each other so the summarized dose distribution can be calculated. On the base of this dose distribution the patients may be treated with higher precision as before. The dose planning is very important in the case of tumours of the oral cavity because of the high local dose administered in the target volume. The exposure of the critical organs should also be taken into account. In some cases tumours of the floor of the mouth and that of the tongue without metastases cannot be cured with either brachy- or percutan therapy alone. This is supported by the retrospective analysis of 900 patients. The tumour control should be improved by the combination of the two treatment types.
N-22: PHYSICAL ASPECTS OF RADIATION PLANNING


Petrov Oncological Institute, Leningrad, USSR; National Institute of Oncology, Budapest, Hungary

Computerized comparative studies are carried out for improving radiation treatment planning for tumors of various localizations (lymphogranulomatosis, tumors of the breast, lung, colon, and oral cavity). The new types of radiotherapeutic methods developed improve dose distributions as follows:

<table>
<thead>
<tr>
<th>Disease</th>
<th>Dosimetric advantages of the new methods</th>
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<tr>
<td>Lymphogranulomatosis</td>
<td>- decrease in the radiation load of spinal marrow /20%/</td>
</tr>
<tr>
<td></td>
<td>- dose elevation for lymph nodes in the bifurcation zone /20%/</td>
</tr>
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<td></td>
<td>- decrease in the irradiation level of subdermal cells /50%/</td>
</tr>
<tr>
<td>Lung cancer /radical and postoperative irradiation/</td>
<td>decrease in the radiation load of spinal marrow, unaffected lung, heart and subdermal cells /up to 50%/</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>decrease in the radiation load of subdermal cells, urinary bladder and sacrum /30%/</td>
</tr>
<tr>
<td>Cancer of the oral cavity /centrally located/</td>
<td>decrease in the irradiation level of mucosa /30%/ and improvement in the uniform distribution of doses in the tumors.</td>
</tr>
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O-23: PSYCHOLOGICAL AND PSYCHOSOCIAL FACTORS

**Treating the Psychological Sequelae of Cancer.** J. Holland, Memorial Sloan-Kettering Cancer Center, New York, N.Y.

Several studies have elucidated the frequency and type of psychological distress and psychiatric disorders commonly seen in cancer patients. While few systematic clinical trials have been done to test ways to reduce these aspects which impact on quality of life, interventions are now available in three major areas: 1) psychosocial; 2) psychopharmacologic; and 3) behavioral. The psychosocial interventions are those that offer emotional support through individual or group modes. Individual therapy has educational, and supportive components bolstering the person’s own coping strategies and enhancing their sense of control. It is a form of brief therapy using crisis intervention techniques. Groups offer education, peer support, practical advice and advocacy. These have been shown effective in reducing distress, as compared to control groups. Psychopharmacologic treatment involves use of agents in the following classes: antianxiety, antidepressant, antipsychotic, hypnotics and stimulants. Several drugs are available in each class. Knowledge of efficacy, half-life, dose and indications in cancer patients is essential. Drugs have more than one application: antipsychotics are used in cancer patients largely for control of emesis; antidepressants are also efficacious for pain and sedation; antianxiety drugs are used for emotional distress and emesis. As a group these drugs can contribute to quality of life and symptom control. Behavioral interventions are being increasingly applied to control pain, anxiety and nausea and vomiting. Progressive relaxation, systematic desensitization, distraction, hypnosis and biofeedback are techniques which have been successfully applied. It is important that oncologists be aware of these methods and have available referral sources within an oncology clinic.

Retrospective and prospective studies in cancer patients have revealed that psychosocial stress may play a decisive role in the development and clinical course of malignant disease. The conception, that cancer is a stress disease must, however, be more clearly delineated. In recent research, a pattern has emerged which in analogy to coronary prone behavior pattern (type A) has been labelled Type C, encompassing suppression of emotional responses, such as anger, anxiety and hostility, as well as high social conformity and a lack of self-assumptiveness. Inframan and human studies suggest that specific patterns of coping-with stress may be associated with specific biologic responses, including neuroendocrine, immunological and sensitivity also other bodily functions. In our paper the pattern will be discussed in relation to its clinical significance and to future research in biobehavioral medicine.


Our working area is psychological in the way of K.Lewin, forming an entail freak centered in the patient. We summarize herein the most important activities in the psychological area. In the first interview, with an essential affective tint, there must be confidence, the physician and the psychologist receive a double ask of help: from the patient and from the family. The first psychological interview has the following goal: to achieve a first diagnosis, prognosis and treatment indications. The clinical record is focalized in several points aim to know the will of living, fantasies of disease and recovering from it.

As prognostic factors we consider: a) ego strength, b) pattern of defenses, c) preferential area of expression of conflicts. The family is always interviewed. During the diagnosis interview the physician gives information. This must be adequate to each patient and family. The general characteristics are: to be clear, progressive, plain, giving holding. As information is a process, it will last during the whole treatment.

Psychotherapeutic interventions, after diagnosis may be: individual psychotherapy, group of parents, therapy for patients and therapy for the family. We also integrate Reflection Groups, one with the whole staff and another for paramedics. Another activity is Research. We are studying neuropsychological sequelae in leukemic patients, diagnostic information, emotional characteristics of the patients according to vital stage, psychological prognostic factors, psychotherapy group, drawings as diagnostic instrument.


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The suggestions are the following: 1) Adequate psychoexpressions described: anxiety, anguish and depression. 3; the review of Secondary Determinants, which, if persist, therapy, which must take into account the Primary physician/patient, quality of medical care and others. Changes in relation to the surrounding, the relationship cultural biography and the effects of the disease up to that moment in said patient, both in the physical and emotional areas. I name this array Primary Causes or Determinants, thus recognizing a previous psychic history; c) to add the Secondary Causes or Determinants, which can be organic or non-organic. The organic ones depend on the clinical situation and on the established treatments. The non-organic ones are those resulting from the fact of changes in relation to the surrounding, the relationship physician/patient, quality of medical care and others.

For its recognition and resolution, three basic expressions are described: anxiety, anguish and depression. The suggestions are the following: 1) Adequate psychotherapy, which must take into account the Primary Determinants, 2) the use of psychotropic drugs and 3) the review of Secondary Determinants, if persist, hinder any treatment.

The category of child small-cell tumours includes tumours of different natures: neuroblastic, neuro-epithelial, granulocytic sarcoma, Ewing's sarcoma, neuroectodermal tumours, rhabdoid tumour. A precise histological diagnosis is indispensable to the therapeutic process and the terms "small" and "round-cell tumours" should be avoided. In the largest number of cases histological examination will be the first stage of diagnosis. In practice, there are three possible results: 1. the quality of the tumoural sample is insufficient and another sample must be taken. 2. The quality of the sample is good and the tumoural differentiation is sufficient to permit a precise morphological diagnosis. 3. The quality of the sample is good but there is too little tumoural differentiation to permit a precise morphological diagnosis. In this case, special techniques should be taken: cyto-logy, immunocytochemistry and electron microscopy. They require a precise protocol for every kind of tumour in children. Each sample should be accompanied by a touch imprint. An M.G.G. stained touch-imprint is essential to express the different malignant penetration of this tumour in the morphological image. So it might be, at least partially, possible to clarify the different response of certain kinds of osteosarcomas to the complex therapy. The biological and morphological character of the osteosarcoma should have influence on the whole strategy of consideration of these tumours and even on their treatment. This strategy includes in principle their typing, staging and grading. From the view of typing we distinguish the following types of osteosarcoma: fibroblastic, osteoblastic, chondroblastic, telangiectatic, parosteal and periosteal one. All these sub-classifications of the osteosarcoma have their biological specificity, which is to a certain extent important during the therapy for the further prognosis. One of the most important conditions of the correct typing of the tumour is the total examination of all parts of the tumour, if possible, and not only of its small piece.
LIVER TUMOURS IN CHILDHOOD. A.J.M. van Unnik

Because of their relative rarity and histological diversity hepatic tumours in childhood may give problems in diagnosis and classification.

A series of 49 primary tumours of the liver is presented. Ten tumours were benign: 1 focal nodular hyperplasia, 1 mesenchymal hamartoma and 8 vascular growths. Despite striking cellular and cellular atypia in some vascular tumours the follow up was undisturbed after conservative therapy.

Malignant epithelial tumours constituted 32 cases and were classified according to the degree of epithelial differentiation as anaplastic (3), embryonal (16), fetal (7) hepatoblastoma and hepatocarcinoma (6). In 9 cases (7 fetal, 2embryonal) complete excision was feasible. Eight patients survived of the remaining 23 only 1 is alive with n.e.d. for 25 months.

The 7 malignant mesenchymal tumours in this series all belonged to the category of the so-called undifferentiated sarcoma of the liver. Only 1 patient survived. All others died within a year.

Summarizing: (1) Conservative treatment is adequate for vascular tumours in spite of the sometimes disturbing histology, (2) Fetal hepatoblastoma has a favorable prognosis if resectable, (3) Undifferentiated liver sarcoma displays a very aggressive behavior and responds poorly to therapy.

ADVANCES IN PAEDIATRIC PATHOLOGY - NEUROBLASTOMA


Neuroblastoma is one of the commonest solid tumours of childhood, occurring in 9.6 children per million population per year. Patients with the more advanced tumours have a very poor prognosis; cases of Stages III and IV neuroblastoma may have only a 10% prospect of surviving 3 years. As many childhood cancer centres handle only small numbers of such tumours annually, multi-centre collaborative studies have been established. The European Neuroblastoma Study Group has been prominent in this respect and part of the clinical relevance of this group is the centralised histopathological review required for entry of a patient into the study. Until recently, histological grading of neuroblastomas was considered to be of little prognostic relevance particularly in comparison with the age of the patient and clinical stage of the tumour presentation, but in view of recent studies is now considered to be an important part of the study of any neuroblastoma. The identification of neuroblastomas and the distinction of its less well-differentiated variants from other "small round cell" tumours of childhood is aided by electron microscopy. Assuming greater importance in recent years, however are various cytoplasmic histochemical markers and immunohistological means of identification. Polyclonal antibodies and panels of monoclonal antibodies have both proved valuable in recent years.
Malignant lymphomas represent the third most common tumor in infancy and childhood, about 6% of them being non-Hodgkin's lymphomas. Histologically, the most common pattern of the latter is constituted by lymphoblastic lymphomas, closely correlated to the immature lymphoid cells of the acute lymphoblastic leukemia. Burkitt's lymphoma, an undifferentiated small un-cleaved B-cell lymphoma, is characterized by aggressive growth also involving extranodal and narrow sites. The diffuse "histiocytic" large cell lymphomas is the third histologic pattern occurring in children and has to be reasonably subdivided into the two categories of large follicular center cells and pleomorphic immunoblastic cells. Hodgkin's lymphoma, with the typical progression from lymphocyte predominance to complete depletion, through the intermediate phases of nodular sclerosis and mixed cellularity, show in children a male increased incidence associated with lymphocyte predominant histology. A comparative clinico-histologic spectrum, together with immunohistochemical definition and morphometric investigations on the shape and size deviations of nuclei of lymphoma cells, allows to better discriminate the different pathological patterns.
2102 CANCER NURSING: EDUCATIONAL ASPECTS IN BIOLOGICAL RESPONSE MODIFIER CLINICAL TRIALS. J. Beauregard, M. Clutter, D. Aiko, S. Halpern, B. O. Gillan; University of California San Diego School of Medicine & VA Medical Center, San Diego, California, USA.

With the advent of biological response modifiers (BRMs) in clinical trials, educational aspects for both the oncology nurse & the cancer patient have undergone changes. BRMs are agents or approaches which alter the relationship between tumor & host by biological or immunological processes. These BRMs have been studied extensively at our institution: Thymosin Fracative A, Thymosin Alpha-1, Interferon, Wy-18,251, T101 monoclonal antibody as passive serotherapy & eleven radiolabeled murine & human monoclonal antibodies (MoAbs) for purposes of tumor localization & visualization. We have used BRMs & MoAbs in the diagnosis of melanoma, cutaneous T-Cell lymphoma, chronic lymphocytic leukemia, colon cancer & other CEA-producing tumors, as well as gastric, pancreatic, breast, lung & prostate cancer. BRM & MoAb clinical trials involve research nurses interfacing with Nuclear Medicine, Surgery, Pathology & specialized Immunology research laboratories. The concepts of BRMs, MoAbs, hybridoma technology, tumor antigen, modulation & the production of endogenous antitumor antibodies all need to be explained to the oncology nursing staff. Patient education including gaining of informed consent, explaining the operational flow of the study, possible BRM side effects, necessity for outpatient followup & understanding of layperson immunology is essential. It has become increasingly obvious that oncology nurses need to be able to educate patients in immunological terms. Nursing tools to enhance patient screening & assessment, education & data collection need to be developed for BRM & MoAb clinical trials. As no guidelines for cancer nursing practice in the realms of BRMs and MoAbs exist, the oncology nurse involved in clinical trials will be instrumental in standardizing procedures & in the education of staff and cancer patients.

2103 AN EDUCATIONAL MODEL FOR NURSES DESIGNED TO ADDRESS THE INCIDENCE OF CANCER IN BLACK AMERICANS. M. Dellepaura, Nigmeg, The Netherlands

In the last 30 years, cancer incidence and mortality rates for Black Americans have increased 40% in contrast to an increase of 10% for white cancer rates. In answer to this obvious need for intervention to lower the incidence and mortality rates, the Oncology Nursing Society held a one day workshop which focused on the prevention/early detection of cancer in Black Americans. Enrollment in the course was limited to 40 black nurses who demonstrated past involvement in their community. 650 black nurses from 40 states and 3 countries responded. The impact of the workshop was measured by pre and post-tests which provided both qualitative and quantitative data. The post-tests were administered 6 months after the workshop and over 60% of the participants responded. The Cancer Attitude Survey (CAS) and the Pittsburgh Attitude Survey (PAS) provided the qualitative data. The Self-Report Cancer Activities Survey provided the qualitative data. The content of the workshop focused on: (1) the epidemiology, risk factors and signs and symptoms of the cancer which have the highest incidence in Black Americans (prostate, colorectal, OY & lung); (2) cultural attitudes of Black Americans which impede or facilitate prevention/early detection; (3) techniques for early detection of cancer. Role playing, simulated clinical practice and small group discussions which focused on attitudes toward cancer helped to actively involve workshop participants in the learning process and add to the success of the project. The quantitative and qualitative data on the post-tests indicate that the workshop made a significant impact on the 40 participants. They report increased community activities (i.e., planning and implementing state-wide prevention/early detection programs for nurses working with Black Americans) in both traditional and nontraditional settings. This workshop can serve as a model for training minority nurses for active, creative roles which can be instituted in the community and are designed to help lower the high cancer incidence rate among Black Americans. (BCI 735 CAMP27-01)

2104 CANCER NURSING IN ITALY: NURSES' TYPOLOGY E.M.S. Conti, R. Nardi, C.F. Pollera, V. Raffaotti, S. Untonelli; Istituto Regina Elena per lo Studio e la Curia dei Tumori, Rome, Italy.

The continuously increasing incidence of tumors obliges, in Italy as well, a greater and greater number of nurses in non-oncological centers to work with cancer patients. The aim of the present study is to identify the average typology of the Italian nurse, as far as oncological assistance is concerned. Materials and Methods: 437 questionnaires were distributed to nurses in oncologic and non oncologic centers, as well field, considering the individual and/or working experience with neoplastic disease, questions related to the level of professional ability and to the presece of individual attitudes concerning problems of assistance correlated with cancer formulated. Statistical Analysis: the statistical analysis employed was the "close reciprocal" Cluster Analysis (Mc Quitty, 1966; De Ward, 1980; Benecer, 1989) the original RCPCT and TANIS programs were used. 839 classes (2m-1, where n=nurses) were identified in a space of 70 dimensions. By means of computer elaboration and depending on the answers provided, the result of aggregating the sample was possible in only 2 typologic classes. Results: Typology 1: describes the professional and psychological profile which characterizes those presently assisting cancer patients. Typology 2: identifies the parameter characterizing nurses unsuitable for providing assistance to the cancer patient, without considering their professional abilities in other sectors.
The development of cancer nursing education and practice throughout Australia is a complex issue. This complexity is exacerbated by many variables, not least the geographic determinant when related to communication. The vastness of the country and the location of centres of excellence inhibits communication. The Clinical Oncology Society of Australia plays an increasingly important role in enhancing communication between centres and units. This, coupled with the work of the State Anti-Cancer Councils, is helping to facilitate cross-fertilisation.

It is evident that there is a disparity of cancer nursing education programs and little attempt to rectify the situation at present. An awareness of the need for national standards has been identified. Education programs are not uniform, are limited in accessibility and considered inadequate to meet the needs of the majority of cancer nurses. There is obvious support for Australian cancer nurses to take part in international meetings and to gain experience in centres of excellence outside the country. Exchange schemes for Registered Nurses have been established as a result of this educational experience and opportunity to practice the task of developing national standards of education and practice that will ensure the ongoing development of cancer nursing in this country.
Interferon and Tumor Necrosis Factor (TNF) are potent antitumoral agents, which in in vitro models can exert synergistic activities. The effects of these cytokines are initiated by binding to specific high affinity membrane receptors (Kd ~100 pM), which are expressed on most cells of various tissue origins. Competition binding experiments suggest that distinct binding sites exist for IFN-γ, for IFN-α/-β, and for TNF, respectively. Expression of IFN receptors on both IFN-sensitive and IFN-resistant cell lines and primary tumor cells clearly indicates that specific binding is a prerequisite, but is not sufficient to confer sensitivity to IFN action. The same holds true for TNF sensitivity. Thus, both IFN and TNF-resistance of given cells appears to be determined not only at the level of receptor expression, but also at a post-receptor level. Nevertheless, using HLA-DR inducible carcinoma cells, we have obtained evidence for a relationship between the quantity of IFN-γ receptors and the dose of IFN-γ required for induction of HLA-DR antigens, suggesting that under conditions of low concentrations of IFN-γ, the number of expressed receptors might be response limiting in a priori sensitive tumor cells. As for hematopoietic cells, a great difference was found in receptor number between malignant and normal cells, determination of IFN-γ-receptors may now only be important to evaluate potential effectiveness of IFN-γ treatment, but may also be useful as an additional diagnostic parameter. Characterization of membrane receptors for IFN-γ, and for TNF by DSS-crosslinking of receptor-bound radio-labeled ligands suggest an IFN receptor molecule with an apparent molecular weight of ~130 kDa, consisting of two subunits. The TNF receptor appears to be a protein with an approximate molecular weight of ~76 kDa.
There are two basic strategies how to select doses for clinical application of biological response modifiers. One is to define subtoxic doses in phase-I toxicity trials and the other is to apply doses capable to induce meaningful biological phenomena. The former concept has been extensively applied to clinical interferon studies. The latter strategy however to our knowledge has so far yet not been tested. In previous in vitro studies we and others have shown, that interferons can induce release of a number of marker molecules, which subsequently can be used to assess biological responses. Among those, the pterin-neopterin, a GTP-metabolite, β2 microglobulin, which represents the light-chain of class I MHC-antigens and certain degradation products of the tryptophan metabolism were more extensively studied. When increasing doses of recombinant alpha-IFN were applied to tumor patients reaching from 1x10⁶ U to 2x10⁶ U/day maximal induction of the above mentioned marker molecules was usually achieved with as little as 5x10⁵ U. Further studies involving more than 40 patients with hairy cell leukemia or with CML subsequently revealed, that such doses, which were shown to maximal induce such biological phenomena, were equally effective in terms of their antineoplastic action than conventional doses in the range of 5x10⁶ U/day. On the other hand, these minimal doses were free of toxic side effects, which usually represent the major problem in long term clinical interferon studies. We thus would conclude, that at least in certain, very sensitive malignant diseases, therapeutic dose ranges can be clearly separated from toxic dose ranges and that evaluation of certain biochemical marker derived from an IFN-dependent pathway facilitate their distinction.

Toxmifene, an antiestrogen drug administered at three dose levels (60 mg, 120 mg, 200 mg/day) was tested in postmenopausal patients with advanced breast cancer. The drug proved to be well tolerable at each dose level without any serious side effects even in case of a prolonged administration. According to the data of 18 patients neither the results nor the side effects have shown any dose dependency. The clinical investigations were connected with hormone determinations.
IN VITRO AND IN VIVO BINDING OF TORMEFENE (TOR) AND 17β-ESTRADIOL IN RAT UTERUS. P.E. Siller, J.T. Malm, N. H. Nihgrev Univ. of California San Francisco, San Francisco, CA, U.S.A.

In order to understand better the mechanism of action of a new anti-estrogen, TOR, we compared its uptake and binding with that of tamoxifen (TAM). Quinjected rats were injected with [³H]-TOR or [³H]-TAM and the distribution of radioactivity in subcellular fractions of the uterus was studied after 1, 8, and 72 hours. After 72 hours, however, only 60% of [³H]-TOR and 35% of [³H]-TAM was recovered in the nuclear fraction; 10-20% in the cytosol and less than 1% each in the microsomal and mitochondria fractions. After 72 hours, however, only 60% of [³H]-TOR and 35% of [³H]-TAM was recovered in the nuclear fraction whereas 18% and 51% of the radioactivity was recovered from the cytosol, respectively. The metabolites of TOR present in nuclear extracts were identified by HPLC.

IN VIVO RIMM3 OF TORMEFENE (TOR) AND AN IN VITRO EVALUATION OF EFFECTS OF TOREMIFENE (TOR) AND TAM ON THE RAT UTERUS. L. Kangan, Farmos Group Ltd, Cancer Res. Lab, Turku, Finland.

New compounds - suggested to be antiestrogens - were synthesized. The biological properties of the molecules were screened by 17β Estradiol receptor (ER) binding 2) Effect on MCF-7 cells (Hormotrophic effect and inhibition of estradiol induced uterotrophic effect) and 4) Antitumor effect in DMBA induced mammary cancer. One the new molecules, 4-chloro and 4-N-deethyl-toremifene exhibited following characteristics: It inhibited binding of tritiated estradiol to ER, IC-50 was ≤3 uM/l. It inhibited the growth of MCF-7 cells in a concentration dependent manner, and killed the cells at high concentrations, 3 uM/l. The threshold dose inducing nuclear estrogenic effect in the rat uterus was about 40 times higher than the respective dose of tamoxifen. Toremifene has statistically significantly higher effect against ER induced rat mammary cancer - the number of disappeared tumors was markedly higher than in tamoxifen treated animals. Toremifene was selected as an effective antiestrogenic and antitumor compound to further studies: antitumor, pharmacokinetic and safety studies. Toremifene inhibited the growth of mouse uterine sarcoma - ER negative but glucocorticoid sensitive tumor - in a dose dependent manner. Pharmacokinetics of tormefenes closely resembled that of tamoxifen in the rat. Toremifene had excellent tolerability: both acute and long term toxicities of tormefene proved to be weaker than those of tamoxifen. Metabolites of tormefenes, which were found in all samples treated rats (dose 40 mg/kg for 2 weeks) were found in tormefene treated rats dose up to 48 mg/kg for 24 weeks. Due to these results tormefene went to clinical phase I studies in healthy postmenopausal women. Side effects were reported at doses 1440 mg (single dose or five doses on consecutive days). At the dose of 660 mg 2 out of 5 patients experienced vertigo and headaches. Toremifene has antiestrogenic effect on human vaginal epithelial cells in estradiol-induced cell proliferation assay. Clinical phase II studies have confirmed that tormefene has promising antiestrogen effect in ER positive breast cancer.
**2120 TOREMIFENE IN ADVANCED BREAST CANCER.**

Cundersen, S. and Kva ley, S., Dept. of Oncology, The Norwegian Radium Hospital, Oslo, Norway.

Toremifene (FC-1157a) is an antiestrogenic anti-tumor substance. It binds to the estrogen receptors (ER) of the cytosol and can be translocated into the nucleus. Based on preclinical data and phase I studies a phase II study has been undertaken among postmenopausal patients with advanced breast cancer. To date 10 patients with ER unknown or positive primary tumors or metastasis have been given 60 mg orally once daily. So far three patients have responded. Updated results from approximately 20 patients will be presented.

**2121 PHARMACOKINETICS OF TOREMIFENE**

Anttila, Farmos Group Ltd, Research Center, Turku, Finland

Toremifene (TOR) is a new antiestrogen under investigation for its antitumor properties for breast cancer. The pharmacokinetics of TOR has been studied in rat, dog and in more than 100 human subjects after single and multiple dosing. TOR is well absorbed. In laboratory animals the bioavailability for oral TOR was estimated to be almost 100 per cent. In human serum peak concentrations were achieved in 4 hours after oral dosing. After the peak, the disposition occurred in two phases, with half-life of distribution of 4 hours and that of elimination of 5 days. In the dose range 3 to 680 mg the kinetics of TOR was not dose dependent. Due to slow elimination accumulation of TOR in serum occurs and steady-state was achieved within six weeks in patients receiving multiple dosing of 60 mg per day. Average serum steady-state level was 0.65 μg/ml with 2-3 fold variation between individuals. The main metabolite in human serum was N-demethyltoremifene. Some minor metabolites have also been detected. Animal studies have shown that excretion of TOR occurs primarily via the feces, only 3 per cent was excreted in urine. The amount excreted in unchanged form was only 2 per cent of the oral dose.

**2122 A PHASE II STUDY OF TOREMIFENE IN ADVANCED CARCINOMA CORPUS UTERI. PRELIMINARY COMMUNICATION.**

Trope, C., Horváth, Gy., Department of Oncology, Gynecologic Section, University Hospital, Lund Sweden.

It is well known that endometrial tumours possess functional estrogen receptors and antiestrogen will induce atrophic changes in endometrial tumour tissue, alterations in glycogen accumulation and inhibition of DNA Synthesis. Toremifene is an antiestrogenic substance and a research project by Farmos Group Ltd. A phase II Study of Toremifene was started at our clinic in 1986. Minimum duration of treatment is 3 months but with stabilized disease (SD) and complete remission (CR) will in principle the treatment continue as long as the treatment response lasts. At present 4 patients with recurrent carcinoma corpus uteri are treated. Dose level of Toremifene is 200 mg per day. The side effects are acceptable.
PRECLINICAL CANCER

Takeo Naqayo, Aichi Cancer Center, Nagoya, Japan.

The term "preclinical cancer" can be interpreted by several investigators into several ways. The speaker interpreted the term as pathological concept and defined it as a disease, in which detection and diagnosis of cancer are quite difficult or almost impossible by routine clinical examinations owing to latent or silent nature of the cancer but sometimes do possible by histological examination of the biopsied specimens taken from clinically suspicious lesions. Tiny or normal looking cancer found unexpectedly in surgically resected or autopsped materials also met with this definition. The term, therefore, is not entirely synonymous with precancerous change or severe dysplasia in the histological sense but from the viewpoint of clinics, both terms has common feature of high-risk group for clinical manifestation of cancer. Based upon the standpoint described above, several types of precancerous change and cancerous change of the state of its very beginning of gastrointestinal tract, chiefly of stomach will be explained and illustrated. Stress will be put on histological features of gastric mucosa in the remnant stomachs especially of the mucosa adjacent to gastrojejunal anastomosis. Through these findings, the speaker will try to feed back the results of the examinations to clinical investigation.

HISTOCENESIS OF EARLY GASTRIC CANCER IN HYPERPLASTIC POLYPS.

Teruyuki Hizola, Masayuki Shibasawa, and Masashi Kubota and Yano Ogasawara, Division of Pathology, National Cancer Center Research Institute, Tokyo, Japan.

The incidence of malignant change within hyperplastic polyp varies from 0 to 6 percent in the reported literature. There have been no papers which described about dysplastic lesion in the hyperplastic polyp as pre-cancerous lesion. Main purposes of this paper is clarifying whether dysplastic lesion in the polyp will be changed to malignant or not. So that we have reviewed 320 case, 339 polyps after endoscopic polypectomy. According to the size of the lesion, there was no malignant lesion within the polyp which is less than 1 cm in size. Contrary, the polyp, 1 to 3 cm in size, showed malignant only in one lesion (0.3%) out of 151 polyps. The polyp, 2 to 2.5 cm in size, showed most frequently malignant foci in the polyp, 6 out of 54 polyps. The polyp, 3 to 3.5 cm in size and greater than 4 cm showed malignant foci in one of polyps. As a total 7 out of 339 polyps (2.1%) showed foci of malignancy change within the polyp. Whereas the dysplastic lesion was found in 13 out of 339 polyps (3.8%). Every malignant focus was always found within or adjacent to the area of dysplasia in polyps. Most of all had malignant foci within polyp showed dysplastic lesion adjacent to the malignant foci. These findings strongly suggested that malignant change occurs from the dysplastic epithelium, not directly from non-dysplastic epithelium of the polypoid lesion.

For the first time both benign and malignant tumors of soft tissues (desmoid and fibromatosis, lipomas and liposarcoma, leiomyoma and leiomyoblastoma) were analyzed by autoradiography in combination with electron microscopy. Radioactive thymidine labeled proliferating cells were localized predominantly in the proximity of small vessels walls (pericytes). This pattern being especially typical for slow-growing benign tumors. Similar observations were made for granulation tissue, keloid scars developed after burns and in case of osteogenesis during bone regeneration after fracture. The data obtained indicate that the main source for the growth of such tumors are small vessels pericytes. The data of electron microscopic autoradiography allow us to suggest that pericyte is a pluripotent cell able to be transformed into any type of connective tissue in the course of its normal growth, physiological and reparative regeneration as well as during its conversion into benign or cancerogenic tumor. The mechanism of this transformation remain still unknown.

DIFFERENTIAL EXPRESSION OF HLA-D-REGION SUB-LOCUS PRODUCTS ON HUMAN COLORECTAL CANCERS: AN IMMUNOHISTOCHEMICAL STUDY. N.M. McDevitt and A.K. Ghosh, Peterhead Laboratories, Christie Hospital and Holt Radium Institute, Manchester M20 9BX, U.K.

The MHC status of tissue from 28 primary gastrointestinal (GI) neoplasms (colon 26, stomach 2, villous adenomas 2) and inflammatory bowel disease (IBD; 3) was evaluated using a panel of monoclonal antibodies (MoAbs) by cryostat immunoperoxidase. With 2 exceptions, all the carcinomas (canc.) and the VA were uniformly positive with anti-Class I (monomorphic determinant) MoAbs, although staining of 2 further cases was weak. A more complex pattern of reactivity was encountered using a panel of Class II MoAbs, directed against the DP, DQ and DO monomorphic determinants. Normal GI glandular and luminal epithelium was consistently Class II negative but 19 of 28 (68%) neoplasms were positive, the proportions of stained epithelial cells ranging from 5 to 90%. Expression of Class II products tended to be non-coordinate: DR was the predominant determinant (19/19+) followed by DP (13/19-) and DQ (7/19+). In tumour epithelium the corresponding ratios superiored stromal T cells over those in epithelium in. The epithelia of 13 samples of IBD were positive for any 1 of the D-region products, as was one Va. Further analysis with a panel of anti-leucocyte MoAbs revealed a numerical superiority of stromal T cells over those in epithelium in the stroma of helper-inducer phenotype (Th-1) predominated over those of cytotoxic-suppressor phenotype (Th-2) (ratio 3.2 for Class II in tumours; 1.3 for Class I in canc.). In tumour epithelium the corresponding ratios were 0.6 and 0.7. Few intratumour T cells expressed Th-2 (Tac) receptor. There was thus no correlation between MHC status and the extent or phenotype of infiltrating T cells. Similarly, lack of correlation was encountered using a panel of Class II MoAbs, directed against the DP, DQ and DO monomorphic determinants. Encountered using a panel of anti-leucocyte MoAbs revealed a numerical superiority of stromal T cells over those in epithelium in the stroma of helper-inducer phenotype (Th-1) predominated over those of cytotoxic-suppressor phenotype (Th-2) (ratio 3.2 for Class II in tumours; 1.3 for Class I in canc.). In tumour epithelium the corresponding ratios were 0.6 and 0.7. Few intratumour T cells expressed Th-2 (Tac) receptor. There was thus no correlation between MHC status and the extent or phenotype of infiltrating T cells. Similarly, lack of correlation was encountered using a panel of Class II MoAbs, directed against the DP, DQ and DO monomorphic determinants.


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The multi-step development of experimental liver cancer is well established and it is accompanied by the gradual loss of "adult" liver cell enzymes and the appearance of "fetal" enzymes and tumour markers as well as morphological changes. We still have little knowledge of what precedes the onset of malignancy in the human liver. Biochemical and antigenic changes include loss of G6PD, AFP-ase and increase in gamma GT, loss of the ability to store iron and the appearance of AFP, beta HCG and AVP production. Cytological changes have been described under the term "liver cell dysplasia" and linked to the presence of HBV markers; this has been both confirmed and refuted. Karyometric studies have been controversial. Mallory body formation has also been thought to be prespeculative. Finally, localized or generalized liver cell hyperplasia, hemodynamic changes after portocaval anastomosis, certain metabolic defects, Kupffer cell depletion or malfunction and cirrhosis from any cause represent significant risk factors.
**2131 COMPARISON OF BIOPHYSICAL PARAMETERS OF PRIMARY LOW AND HIGH METASTATIC LEWIS LUNG TUMOR CELLS.**

Lewis lung cancer cells from tumors of both high and low metastatic potential were isolated from the leg muscle of C57-B1 mice and were purified by density gradient centrifugation. The purified cells retained most of their tumor-forming capacity; however, the difference in the metastatic capacity of the 2 cell lines increased with the purification process. The purified and viable cells were subjected to different biophysical studies. Electron spin resonance studies showed that the motional freedom of lipid and protein molecules of the cellular membranes is higher in the low metastatic cell populations. Both cell types reduce penetrating and nonpenetrating free radicals, but the reducing ability of the low metastatic cell populations is 4 times greater than that of the highly metastatic cells. This finding was found to parallel the lower survival rate of the low metastatic cell line in nutrient-free medium at 37°C.

**2132 ORDER AND DYNAMICS, STRUCTURE AND FLUIDITY OF BIOLOGICAL BILAYER MEMBRANES: TIME-RESOLVED, ANGLE-RESOLVED FLUORESCENCE DEPOLARIZATION, ORIENTATIONAL DISTRIBUTIONS, HETEROGENEITY, AND THE MICROVISCOUSITY HYSTERIC**
H. Shiniltzky. Department of Membrane Research, The Helzmann Institute of Science, Rehovot, Israel.

Current and future possibilities in the obtention and interpretation of information on the orientational distribution and reorientational dynamics of fluorescent probes embedded in real and model biological bilayer membranes will be critically reviewed. The limitations of the non-optimal experimental regimes that have been and still are very largely employed in such studies: steady-state rather than time-resolved fluorescence depolarization measurements on random rather than oriented systems, will be delineated. The inevitable resultant loss of information critical to establishment of the validity or otherwise of an interpretation in such oversimplified terms as overall scalar “microviscosities” and square-well potential restrictions to reorientation in the anisotropic membrane milieu will be discussed, and an experimental protocol which is optimised to enable retrieval of the maximal amount of information available, thus allowing a direct test of the limitations of the simplifying approximations and assumptions commonly invoked, will be indicated. The possibilities of distinguishing between various models for restriction of reorientational motion and for dealing with limited heterogeneity and establishing probe location will be examined.

This presentation and the author’s work reported therein are sponsored by the Cancer Research Campaign.

**2133 MEMBRANE POTENTIAL CHANGES AND PROXIMITY RELATIONSHIPS OF INTRAMEMBRANE PROTEINS OF TUMOR CELLS AS AN INDICATION OF HUMAN METASTASES.**

Cyclosporin A (CsA) produced dose dependent membrane depolarization of human peripheral blood lymphocytes and spleen and thymus cells from A/J mice. The phenomenon was investigated with the membrane potential probe DiOC(3) in a flow cytometer in combination with barbore and monoclonal antibodies binding to different subclasses of lymphocytes and to IL-2 receptors. Insulin protected mouse and human gamma-interferon human lymphocytes against the depolarizing effect of CsA. IL-2 caused depolarization and also enhanced the effect of CsA. OKT4- and OKT8- antibodies slightly hindered depolarization by CsA while OKT-4-, OKT-11 and OKT-13 antibodies had no such effect. The lack of fluorescence resonance energy transfer (FRET) between dapsyi-CsA and fluorescein-conjugated anti-Tac antibody bound to HUT-102 cells indicated that CsA does not bind near the IL-2 receptor. Significant FRET was detected between fluorescein- and rhodamine-conjugated monoclonal antibodies bound to MHC class I and II antigens on P388D1 cells (Epstein-Barr virus transformed human B cells) suggesting that the class I and II antigens are associated on the cell surface. There was no energy transfer between conjugated antibodies bound to class antigens indicating the monomeric distribution of these antigens. The high FRET efficiency measured between fluorescein-labeled and rhodaminated anti-Leu1D antibodies specific to DQ antigens. According to this finding either the DQ antigens form dimers or one DQ antigen binds more than one anti-Leu1D antibody.

**2134 TUMOR VACCINES AND THEIR PRACTICAL POTENTIAL.**
M. Shinitzky, Department of Membrane Research, The Weizmann Institute of Science, Rehovot, Israel.

The expression of tumor antigens can be augmented by incorporation of cholestereryl hemisuccinate (CHS) or by subjecting to hydrostatic pressure. Such treated tumor cells are of considerably greater immunogenic potential than untreated cells and can act as efficient tumor vaccines as demonstrated in a series of pre and post immunization studies. Phase I study which was completed recently (Skornick et al. CANCEIR in press) indicated that CHS treated autologous tumor cells may provide a safe and efficient vaccine against residual tumor growth. Vaccines made of similarly treated allogeneic cells and their isolated membrane are currently being investigated as future standardized vaccines.
CHMICAL COMPOSITION AND ENZYME ACTIVITIES OF MEMBRANES OF CANCEROUS CELLS. E.W. Haeffner, Institute of Cell and Tumor Biology, German Cancer Research Center, Imm.-Herm. Feld 280, Heidelberg, F.R.G.

Tumor cell surfaces are known to be important in the metastatic process that confer to these cells their abilities to invade, disseminate, implant, survive and grow at secondary sites. For this very reason many studies have been performed in analyzing and comparing the membrane composition of cancerous versus normal cells. Due to the diversification of cells in general, and the phenotypic instability of malignant cells in particular, no clearcut picture has been obtained so far. Therefore, researchers have begun to select for stable variants from a given parental tumor cell line differing in their tumorigenic or metastatic properties. At present there are a number of such pairs of variants from different animal tissues, which are subject of intensified studies.

Data on membrane structure of several tumor cell variants will be presented. Special emphasis will be put on the phospholipid and cholesterol composition of the lipid bilayer, and on the importance and role in the lipid bilayer playing a key role in cell surface function and ultimately in cellular growth. Membrane fluidity changes can, among others, be evidenced through the shedding process, and this in turn may be of functional significance with respect to tumor immune escape, where the antigenic properties are solely governed by the protein/glycolipid composition and the sterol/phospholipid ratio near 24°C in the outer monolayer and 20°C in the inner monolayer from plasma membranes of primary and metastatic tumor cells. There is also increasing evidence that certain enzyme activities, like e.g. the 5'-nucleotidase or some degradative enzymes, a proteinase and an endoglycosidase, are differently expressed in some of the tumor cell variants. The 5'-nucleotidase controls the intracellular adenosine level which itself can regulate the Ca influx, and the endoglycosidase e.g. degrades proteoglycans which are important constituents of the basal membrane. In summary, the data presented on the membrane composition will be discussed in relation to the malignant properties of tumor cells.

PROSPECTIVES OF CHEMOTHERAPY BASED ON MEMBRANE DYNAMICS AND COMPOSITION OF PRIMARY AND METASTATIC TUMOR CELL MEMBRANES. Friedrich Schroeder and Ann R. Herr, Dept. of Med. Pharmacology and Vet. Pathology, Univ. of Missouri, Columbia, MO 65212, USA.

The fluorescent sterol, dehydroergosterol (DHE), was incorporated into primary tumor (L-929, LM, A-9, and C-10) and nine metastatic cell lines. Cultured primary tumor and metastatic cells differed twofold in their phospholipid and cholesterol content. The inner monolayer of the plasma membranes from both cultured primary and metastatic tumor cells was enriched in sterol and was directly related to plasma membrane surface fluidity. Membrane phase separations near 24°C in the outer monolayer and 20°C in the inner monolayer from plasma membranes of primary and metastatic tumor cells. There is also increasing evidence that certain enzyme activities, like e.g. the 5'-nucleotidase or some degradative enzymes, a proteinase and an endoglycosidase, are differently expressed in some of the tumor cell variants. The 5'-nucleotidase controls the intracellular adenosine level which itself can regulate the Ca influx, and the endoglycosidase e.g. degrades proteoglycans which are important constituents of the basal membrane. In summary, the data presented on the membrane composition will be discussed in relation to the malignant properties of tumor cells.

A NEW TYPE OF PROTEIN INHIBITOR OF TRANSPORT OF NUTRIENTS FROM RAT LIVER AND THE POSSIBLE ROLE OF SUCH PROTEINS IN REGULATION OF NORMAL CELL DIVISION AND MALIGNANT TRANSFORMATION. P.M. Bhargava and S.A. Chandani, Centre for Cellular & Molecular Biology, Hyderabad 500 007, India.

We have purified to homogeneity a protein (called 'P' protein) from rat liver that satisfies the following criteria. (1) It has no effect on the uptake of aminoacids in slices from normal liver. (2) It reduces the high-level uptake of essential nutrients obtained in dispersed liver cells to the low-level uptake found in the undispersed tissue. (3) It inhibits the high-level uptake found in dispersed cells from regenerating liver and in the 3 TDF ascitic heptoma (ZAH) cells and brings this uptake to the level found in resting liver cells. (4) It inhibits DNA synthesis in the ZAH and in dispersed cells from regenerating liver. (5) It can be localised in immuno- fluorescence studies, on the periphery of liver cells in intact tissues; it is tissue-specific, disappears on partial hepatectomy and reappears after the tissue has regenerated. (6) It is absent in embryonic liver but anti-sera against the protein cross-react with the protein from mouse liver.

A similar protein has also been isolated from the ascitic fluid of the ZAH. The tumour protein does not score positive in any of the above assay systems; however, it has the same amino terminal sequence, the same molecular weight and the same behaviour on electrophoresis on various kinds of gels and columns as the normal protein has. Both the normal and the tumour proteins oligomerise but their oligomerisation pattern seems to be different. We are now in the process of determining if the tumour protein is a mutant form of the normal protein.
2139 PREDICTIVE ASSAYS FOR IDENTIFYING TUMORS WHICH MIGHT BENEFIT FROM RADIOTHERAPY WITH SENSITIZERS AND/OR PROTECTORS. J.D. Chapman and R.E. Peterson, Department of Radiation Oncology, Cross Cancer Institute and Department of Radiology and Radiation Imaging, University of Alberta, Edmonton, Alberta, Canada T6G 2J2

The hypoxia cell radiosensitizer, 2-nitroimidazole (NITRO), has been tested in over 5000 radiotherapy patients with only limited success. The studies have utilized various drugs and radiation fractionation schemes on several types of tumors. The results suggest that the tumor's ability to metabolically activate NITRO is a key determinant of its radiosensitizing effect. Consequently, the measurement of NITRO adducts to a specific tumor may be predictive of its fraction of viable hypoxic cells and its sensitivity to radiation treatment. The presence of NITRO adducts in human tumors has been measured using autoradiography and liquid scintillation counting procedures. Only two of the seven tumors studied, to date, have shown hypoxic fractions of > 1%. The development of techniques for the noninvasive measurement and possible imaging of sensitizers adducts in tumors, and how such information might predict patients who could benefit from radiotherapy with sensitizers will be reviewed. The prediction of tumors whose radiation treatment might be improved by protectors will likely require measurements of inherent hypoxic cell radiosensitivity, since tumors whose cells are relatively radiation-resistant to 36 Gy (surviving fractions of > 95%) might be effectively treated with a higher dose fraction size than the adjacent normal tissues can be relatively protected by an effective drug, like WR2721.

2140 THE ROLE OF WATER IN THE RADIOSENSITIZATION OF HYDRATED ELECTRON SCAVENGERS. G.L. Gass, and A. Dm, "IKI" National Institute for Radiobiology and Radiohygiene, Budapest, Hungary

The role of water in the radiosensitization of hydrated electron scavengers may be the most promising compounds in the oncology and radiotherapy fields. Further understanding of the action mechanism of these agents is required. The radiosensitizing effect of acetone has been studied on Bacillus megaterium spore system at different oxygen concentrations. The extent of acetylation of DNA decreased with increased oxygen concentration and ultimately becomes zero at 21% with K2. The extent of sensitization increased with increasing oxygen concentration, but decreased with increased water concentration in K2. The extent of sensitization increased with increased oxygen concentration, but decreased with increased water concentration in K2. Acetone in water, equal to 10% acetone in water, has been used. Treatment of tumor cells with this compound has been found to increase the radiation sensitivity of the tumor cells.

2141 MECHANISMS OF MODIFICATIONS OF RESPONSIVENESS TO DRUGS IN MICROREGIONS OF SOLID TUMORS. R.Sutherland, M. De Brabanter, J. Van Gennep, R. Van G emanc, L. Ling, G. Michel, J. Sciandra, R. Wilson. University of Rochester, Radiation Biology and Biophysics Dept. & Cancer Center, Rochester, NY, USA

Many reasons have been proposed for resistance to drugs in human solid tumors. One generally accepted explanation is that the presence of specific cellular heterogeneity in the tumor cell population. In addition, we have discovered other potential mechanisms of modification of responsiveness to drugs. These mechanisms are all associated with the 3-dimensional structure of tumor microregions or of microenvironments and the relation of such areas to the efficiency of the associated vascular supply. Using multicell spheroids as in vitro models of such microregions, it can be demonstrated that drug effectiveness can be affected by several mechanisms: (1) drug penetration limitations over distances of several cell diameters; (2) cell-cell interactions, and (3) extrinsic cellular environmental factors such as concentrations of oxygen and glucose. Spheroids and monolayer cultures of human EMT6 mammary, human squamous cell carcinoma, and color tumor cells were used. Cultured cells in extreme hypoxia became resistant to ADR and lose their resistance upon reoxygenation. Maximum resistance occurs by 6 hr and is associated with the synthesis of a 95 kDa protein. The radiosensitizing effect of acetone is abolished under conditions that prevent reductive bioactivation. Cytotoxicity is related to the binding of the sensitizing Misonidazole and can be almost completely inhibited if the hypoxic cells are deprived of glucose. Other experiments with small spheroids have demonstrated increased resistance to cytotoxic agents when cells are grown in close cell-cell contact. These data demonstrate additional new mechanisms whereby cellular responses to drugs may be modified in microregions of solid tumors.

Supported by NIH Grants CA-11198, 109, 20, 37618. Training Grant CA-09363, and Fellowship Grant CA-07755

2142 RADIOSENSITIZING EFFECT OF THE SYNTHETIC MICROTUBULE INHIBITOR TUBULOZOLE ON MURINE MEMBRANE FRAGMENTS IN VITRO. M. De Brabanter, J. Van Gennep, L. Ling, G. Michel, J. Sciandra, R. Wilson. University of Rochester, Radiation Biology and Biophysics Dept. & Cancer Center, Rochester, NY, USA

It is well known that the response to radiation and the effect of chemotherapeutic agents vary with the cell's position in the division cycle. It can be anticipated that induction of apoptosis in tumor cells by first modality may sensitize the tumor cells to the other one. Recently, it has been demonstrated in vitro that cell populations which are radiosensitive when subjected to irradiation with inhibitors are given prior to irradiation. We studied the synthetic microtubule inhibitor tubulozole as a possible radiosensitizer for in vitro use. We have observed a 50% cell kill in 6 hr when tubulozole is given 6 hours before local irradiation of subcutaneous murine EMT6 fibrosarcoma, a marked initial tumor regression and delay of tumor growth can be observed. The drug neither shows any antitumor activity on its own at 160 mg/kg, nor displays any effect when administered post irradiation. The tumors of tubulozole treated groups were found inactive on the microtube system, does not exert any anti-tumor activity on both subcutaneously and untreated tumors. It is anticipated that the radiosensitizing effect of tubulozole is obtained by "conditioning" the tumor cells prior to irradiation. Possible mechanisms of action are discussed.

2144 DIFFERENTIAL RADIOSENSITIZATION IN NORMAL AND NEOPLASTIC HUMAN CELLS BY 3-AMINOBENZENAMIDE: AN INHIBITOR OF POLY(ADP-RIbose) SYNTHETASE. P. J. Thayer, E. L. Rosenwag, and A. Delichio. Georgetown University Medical Center, Washington, D.C. 20007. The effect of 3-aminobenzamide (3AB), an inhibitor of poly(ADP-ribose) synthetase, on the radiosensitivity of normal human fibroblasts and three human tumor cell lines from tumors with varying degrees of radiosensitization was investigated. The human tumor cell lines selected were Swann's sarcoma and a bone tumor considered radiosensitive and human lung adenocarcinoma and osteosarcoma, two tumors considered radioresistant. The inhibitor was added to cultures, at a nontoxic concentration of 8nM, two hrs prior to radiation and removed 24 hrs after. In the presence of 8nM 3AB, differential radiosensitivity was observed. Swann's sarcoma cells and normal human fibroblasts were sensitized to an equal extent; however, no sensitization was observed in lung adenocarcinoma cells or osteosarcoma cells. The degree of radiosensitization by 3AB correlated well with the clinical radiosensitivity of these tumors. To determine the radiobiologic mechanism for this differential radiosensitization, we studied potentially lethal damage repair (PLDR) in these cells and the effect of 3AB on PLDR. In the absence of inhibitor, 3AB was similar in all cell lines. In the presence of 8nM 3AB, differential inhibition of PLDR was observed. PLDR was almost completely inhibited in Swann's sarcoma cells and was partially inhibited in normal fibroblasts and osteosarcoma cells. No inhibition of PLDR was observed in the lung adenocarcinoma cells or osteosarcoma cells. Inhibition of PLDR by 3AB correlated well with radiosensitization, suggesting that radiosensitization by 3AB may be mediated by inhibition of PLDR. This work was supported by Grant No. RO1-279 from the American Cancer Society, Inc.

2146 INCREASED TUMOR CURE OF MURINE TUMORS BY THE COMBINED RADIOTHERAPY AND LONIDAMINE. J. N. Kim, A. A. Alfieri, S. H. Kim, C. W. Young and B. Silventini. Memorial Sloan-Kettering Cancer Center, New York, N.Y. 10021. Lonidamine (1-(2,4-dichlorophenyl)-1H-indazole-3-carboxylic acid) is a potent inhibitor of spermatogenesis and a hyperthermic sensitizer. The principal established locus of biochemical action of Lonidamine is a selective inhibitor of the energy metabolism either in NAD-linked reactions in cell mitochondria as well as the glycolytic metabolism of a variety of tumor cell lines by means of inhibition of mitochondrial bound hexokinase. We carried out in vivo experiments to determine whether Lonidamine when combined with radiation could potentiate the cytotoxic effect on two murine tumors. The combined effects of acute Lonidamine (100 mg per kg) and single dose x-irradiation were evaluated on the transplanted methylcholanthrene-induced fibrosarcoma (Meth-A) in Balb/c mice and the radiation induced fibrosarcoma (RIF) in C57BL mice. The radiosensitizing effect by Lonidamine was maximal when Lonidamine was administered immediately prior to or after x-irradiation. The dose modifying factor is estimated to be 1.28 for Meth-A tumors and 1.25 for RIF tumors. There was no disproportionately enhanced skin reaction following the combined treatments. Further studies with fractionated radiation regimen showed the enhancing property of Lonidamine and radiation was maintained with increasing fractionation schedules. The present results of the potentiating effects of radiation may be attributed, in part, to the finding that cell culture studies with Lonidamine are a potent inhibitor of repair of potentially lethal damage.

2143 THE RADIOPROTECTIVE EFFECT OF INTRA-ARTERIAL VASOPRESSIN DURING FRACTIONATED ABDOMINAL RADIATION. J. S. Kwei, G. F. Atemsim, M. A. Dechant, J. P. DiTullio, and J. M. Anderson. Dept. of radiology, Vancouver General Hospital, Vancouver, B.C., Canada, and *Wolfson Institute of Preventive Medicine, Middlesex Hospital, London, England. The administration of vasopressin intra-arterially can produce such a bloodflow reduction. We have tried this method of reducing intestinal radiation damage in eighteen pigs. The pigs were anaesthetized and in none of them a selective catheterization of the superior mesenteric artery was done. Prior to the radiation the catheterized animal was treated with lyse vasopressin 0.05 IU per kilo body weight, for each vasopressin treated animal, a control animal received radiation therapy in the same way. Therapy was given with a 6 MV linear accelerator to the abdomen, corresponding to the site of the small intestine. Three different patterns of fractionation were tried. The weight development of the animals was registered and after fourteen days the animals were sacrificed and histological studies done on the small intestine. In almost all instances the vasopressin treated animals had a markedly reduced intestinal reaction and the weight development was better than in the control animals. Intra-arterial vasopressin treatment seems to constitute the valuable tool in reducing the marginal reaction in the small intestine and further studies are warranted.

2145 THE EFFECT OF VASOACTIVE DRUGS ON THE RESPONSE OF THE LEWIS LUNG CARCINOMA TO THE HYPOXIC CELL CYTOTOXIN RSU-1069. F. J. Hallman and B. Acker. *B.C. Cancer Research Centre, Vancouver, B.C., Canada, and **Cancer Control Agency of B.C., Canada. The basis of selective toxicity is to exploit differences that exist between the normal and 'invading' cell populations. One of the differences is the oxygenation status of malignant disease, one of these differences is that tumours have a lower oxygenation status than most normal tissues. There is now evidence that certain vasoactive drugs can (by selectively reducing tumour blood flow) further compromise the oxygen status of malignant tissue. The present studies were designed to evaluate if vasoactive agents could increase the therapeutic efficiency of drugs known to be selectively toxic to hypoxic cells. Initial investigations have involved the use of the hypotensive drug hydralazine in combination with the 'alkylating nitroimidazole' RSU-1069. The results obtained clearly indicate that hydralazine can potentiate the effects of RSU-1069 in the Lewis lung carcinoma when administered orally at a dose of 5 mg/kg. However, this dose of hydralazine has no effect on the LD 50/70 of RSU-1069 (0.19 mg/g) in C57BL mice. Initial results indicate that such an approach may have a role in cancer therapy. Further studies are now underway and will be reported.

THE LEWIS LUNG CARCINOMA TO THE HYPOXIC CELL CYTOTOXIN RSU-1069. F. J. Hallman and B. Acker. *B.C. Cancer Research Centre, Vancouver, B.C., Canada, and **Cancer Control Agency of B.C., Canada. The basis of selective toxicity is to exploit differences that exist between the normal and 'invading' cell populations. One of these differences is that tumours have a lower oxygenation status than most normal tissues. There is now evidence that certain vasoactive drugs can (by selectively reducing tumour blood flow) further compromise the oxygen status of malignant tissue. The present studies were designed to evaluate if vasoactive agents could increase the therapeutic efficiency of drugs known to be selectively toxic to hypoxic cells. Initial investigations have involved the use of the hypotensive drug hydralazine in combination with the 'alkylating nitroimidazole' RSU-1069. The results obtained clearly indicate that hydralazine can potentiate the effects of RSU-1069 in the Lewis lung carcinoma when administered orally at a dose of 5 mg/kg. However, this dose of hydralazine has no effect on the LD 50/70 of RSU-1069 (0.19 mg/g) in C57BL mice. Initial results indicate that such an approach may have a role in cancer therapy. Further studies are now underway and will be reported.
Pathways of growth and differentiation have been studied in normal human bronchial epithelial cells cultured in serum-free medium. Diminished responsiveness to inducers of terminal squamous differentiation, e.g., transforming growth factor beta, and/or autocrine production of growth factors, e.g., gastrin-releasing factor, may provide lung carcinoma cells with a selective clonal expansion advantage. 

Human bronchial epithelial cells have also been employed to investigate the role of specific oncogenes in carcinogenesis and tumor progression. Using the protoplast fusion method for high frequency gene transfection, the v-Ha-ras oncogene initiates a cascade of events in the normal human bronchial cells leading to their apparent immortality, aneuploidy, and tumorigenicity with metastasis in athymic nude mice. Ongoing studies have also shown that human bronchial epithelial cells transfected with c-myc, derived from Burkitt's lymphoma cell line C6A9, are resistant to induction of terminal differentiation and may have an increased growth potential. These results suggest that oncogene-mediated aberrations in cellular pathways of growth and differentiation may be important in human cell carcinogenesis.

In earlier studies we have shown that ionizing radiation can transform in vitro rodent and human cells and that rodent cell susceptibility to radiation carcinogenesis is higher than that prevailing in human cells (Borek, 1985). Ozone, a major chemical oxidant in the atmosphere, is a ubiquitous environmental pollutant and a key component in photochemical smog. Ozone produces free radicals upon interaction with cellular components, but its direct carcinogenic and cocarcinogenic actions are unknown. We now report that 5 ppm of ozone delivered over 5 minutes can directly transform hamster embryonic mouse C3H/10T1/2 cells into cells which possess a neoplastic phenotype and can colonize in semisolid agar. Lipid peroxidation products which usually arise from free radical mediated oxidation are produced in the cells in response to ozone. We further report that gamma irradiation of the cells with three or four gray (Gy) 2 hours prior to ozone treatment results in an enhanced rate of transformation which is consistent with a synergistic interaction between the agents (Borek et al, 1986). In ongoing experiments we are evaluating the ability of ozone to transform human cells. Our results indicate that ozone acts as a carcinogen and cocarcinogen and that free radical mediated processes are involved in ozone induced carcinogenesis. Since high ambient levels of ozone are found in urban atmospheres and since radiation is a ubiquitous environmental carcinogen our results have important implications for public health. 

References

Borek, C., Pharmac. Ther. 27:99-142, 1985 (Review)
Two groups of 20 female Wistar rats received a single i.p. injection of ENU (15 mg/kg b.w.) on the 15th day of pregnancy (group I) and 21st day (group II) of pregnancy. Their effective progeny amounted to 280 descendants (95 m, 85 f) for group I, and 172 descendants (93 m, 79 f) for group II. In addition, group III, composed of 81 m and 76 f, descendants of another set of 20 pregnant Wistar rats received a single s.c. injection of ENU (15 mg/kg b.w.) on the first postnatal day. PST, most of them histologically malignant, developed in the animals according to the following numbers: group I: 64 (35 %), group II: 130 (76 %), and group III: 88 (56 %). No PST were observed neither in group IV composed of 156 controls (78 m, 78 f) nor in the mothers of all groups. In group I, 15 out of 64 PST (30 %) showed plexiform structures, in group II, they were seen in 27 out of 130 PST (21 %), and in group III, in 14 out of 88 PST (16 %). Comparing the incidence of plexiform structures between the three groups, this was a value p < 0.05 for group II when compared with group III. Other comparisons were not statistically significant. Thus, it was seen in man, even if it was the sole malignancy, these plexiform structures are considered to be diagnostic of neurofibromatosis. It is important that the present experiments offer a tool for studying this disease, particularly its association with malignant changes, as it is the only known species differences between the various species (from rat to man) that have been observed at the present time.
INTRODUCTORY REMARKS
H. zur Hausen, Heidelberg, FRG

The function of eukaryotic promoters is controlled by several factors. We have used viral promoters from human adenoviruses or from insect baculoviruses to assess parameters regulating the activity of viral promoters. 1) Viral and non-viral eukaryotic promoters can be inactivated by sequence-specific methylations in the promoter and/or in upstream sequences. Such sites have been identified in the EIA promoter of adenovirus type 12 (Ad12) DNA and in the E2A promoter of Ad2 DNA. The Ad2 E2A promoter is inactivated after methylation of three 5'-CCGG-3' sites. Presently, we are investigating whether the hemimethylated Ad2 E2A promoter is active. Viral enhancers can "overrule" the shut-off effect of specific methylations on promoter activities. 2) In another type of transactivation, the EIA gene of Ad2 DNA elicits transcription from promoter-like elements even in prokaryotic sequences after transfection into mammalian cells. 3) Hamster cells are non-permissive for Ad12, whereas Ad2 can replicate. Ad12 DNA replication and the expression of late viral functions are not detectable, early viral genes are expressed. Ad12 DNA can, however, replicate in hamster cells double-infected with Ad12 and Ad12 or in hamster cells constitutively expressing the E1 region of Ad5 DNA. In the latter cells the late Ad12 functions are also expressed. The Ad5 function complementing the block in Ad12 DNA replication in hamster cells resides in the E1B region of Ad5. We have investigated the functionality of the major late promoter (MLP) of Ad12 or Ad2 in hamster and human cells. In Ad2-infected human or hamster cells both the Ad5MLP and the Ad12MLP are active. In uninfected cells, neither MLP exhibits activity. In Ad2-infected hamster cells only the Ad5MLP is expressed, the Ad12MLP remains defective. MLP sequences have the ability to recognize species differences in their selection of cellular cofactors. (Supported by DFG, SFB74-C1, BMFT)

EPISOMAL OR INTEGRATED VIRAL DNA AND THE IMMUNE SYSTEM
Gy. Berenczy, Budapest, Hungary

Transcription of human papillomavirus type 18 (HPV18) DNA in the human cervical carcinoma cell lines HeLa, Ca-1 and S766 has been studied by cDNA sequence analysis. The cDNAs are differentially spliced and are composed of 5'-terminal viral sequences transcribed from the E6-E7-E1 part of the HPV18 early region (identical for the 3 cell lines) and 3'-terminal host cell sequences (different for each cell line). We deduce from the cDNA sequences that the mRNAs direct translation of virus-specific proteins. Two of the putative proteins are encoded by open reading frames (ORF) E6 and E7 whereas the third is encoded by a small interrupted gene E6* which contains a 182 bp intron and is identical with ORF E6 up to the E6* exon-intron junction. The predicted E6 and E6* proteins are identical in their N-terminal 43 amino acid residues and show sequence homology to epidermal growth factors. Generation of spliced mRNA's with an E6* cistron is probably specific for the cancer-associated types HPV18 and 16 among genital HPV types 6, 11, 16, and 18. The very similar patterns of HPV18 transcription in the three different human cervical carcinoma cell lines suggest a functional role of HPV18 early genes for the malignant phenotype of the cells. We have started to analyze HPV18 transcription in non-tumorigenic HeLa x normal cell hybrids and their tumorigenic segregants. After growth of the cells in nude mice, HPV18 transcription seems to be suppressed in the non-tumorigenic hybrid cells only suggesting a correlation between HPV18 transcription and tumorigenicity. The possible role of host cell genes and factors in the regulation of HPV expression will be discussed.
SANDBICH HYBRIDIZATION FOR DETECTING PAPILLOMAVIRUS DNA IN CERVICAL SCRAPIINGS

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**SANDWICH HYBRIDIZATION FOR DETECTING PAPILLOMAVIRUS DNA IN CERVICAL SCRAPIINGS**


The Department of Pathology, Kuopio University Hospital, Kuopio, Finland

Punch biopsies of the cervix were examined both histologically and for the presence of human papillomavirus (HPV) DNA sequences. The latter procedure was carried out by the Southern blot technique using radioactively labelled HPV-6, -11, -16 and -18 DNA probes, both together and separately. Twenty-one biopsies were examined in this series. Eleven biopsies were negative for HPV DNA sequences, ten contained HPV-16 DNA, four contained HPV-18 DNA and one contained both HPV-16 and HPV-11 DNA. Histological examination showed cervical intraepithelial neoplasia (CIN) grade 2 or 3 in sixteen biopsies, viral changes in four and inflammation or normal histology in three. Episomal HPV-18 DNA was found in two biopsies classified as CIN IV, one of which also contained HPV-11 DNA, and in one biopsy which showed viral changes alone. Detection of viral DNA may identify patients at risk for malignant progression. This is the first report of HPV-18 DNA in CIN in Scotland.

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**ON THE ROLE OF EARLY VIRAL GENES IN PAPOVAVIRUS INDUCED MUTAGENESIS**

M. Thelie, J. Krogle, M. Straus, L. Luebbe, and C. Geissler

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Some years ago a possible relevance of the mutagenic effect induced by SV40 in infected cells to viral transformation was proposed (M. Thelie et al., Z. Hamster Virus Res. 4A, 1985). Concerning this problem further results were obtained: (1) In addition to SV40 other papovaviruses including BKV, JC, Polyoma virus(PyV), and hamster papovavirus(MoPyV) or their DNA cause resistance mutations in different cell lines. (2) At least in the case of SV40 and PyV the mutagenic effect is based on the activity of the early viral region. For SV40, mutagenicity was shown to depend on the presence of the early transcriptional enhancer. (3) The mutagenicity at least of SV40 furthermore depends on the presence of intact T antigen binding sites which could mean that a function of large T antigen related to initiation of viral DNA replication (rather than to transformation) is involved in the mutagenesis. (4) Additionally to the mutation induction detectable during early cell generations after infection an increased mutability can be observed in stably transformed cells which does not depend on the viral replication function but may depend on a high level of T antigen synthesis. (5) A PyV large T gene construct was mutagenic only when the PyV promoter had been replaced by the PyV T antigen binding site of SV40. The T antigen promoter and transcription was induced by calcium. In contrast, a PyV middle T gene construct was not mutagenic under similar conditions. It is conceivable that the mutagenic potency of papovaviruses, in addition to the expression of viral oncogenes and complementing their effects, could contribute to viral neoplastic transformation by activating cellular genes including (e. g. cellular oncogenes) as a result of structural changes induced in cellular DNA.
EFFECT OF MUTATIONS IN HUMAN ADENOVIRUS TYPE 12 E1A GENE ON CELL TRANSFORMATION.

Y. Sawada, N. Ishine, and K. Fumigawa,

The adenovirus early region 1A (E1A) gene is required for adenovirus-induced cell transformation and is involved in the regulation of expression of adenoviral and cellular genes. In order to analyze functional regions within the E1A coding region, we have constructed several mutations in the cloned E1A gene of Ad12. In the N-terminal proximal region, a 3bp deletion mutation which converts Glu-Ser-Asp- to Ala- reduces the transforming ability, while another mutation of the same nature at a slightly upstream position does not. A 3bp insertion mutation in the middle of the coding region does not affect the transforming ability. Several other 3bp insertion or 3bp deletion mutations showed reduced transforming ability by 4 to 5 fold. Mutations which introduce termination codons at the N-terminal proximal region lose the transforming ability. These results indicate that at least a part of functional region resides in the N-terminal region and that a Glu residue compensates one of the critical points.

ANALYSIS OF HPV INFECTION RATES IN ROUTINE SCREENING OF CERVICAL SMEARS.

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HPV 16 and 18 have been associated with pre- and malignant genital lesions, whereas HPV 6 and 11 are most commonly found in the benign genital lesions. Cervical smears taken during routine gynecological examination of 9100 patients were tested for the presence of DNA sequences of three aforementioned viruses. By hybridization it was shown that of healthy patients with normal cytology, 6.6% were positive for HPV 6/11 infection and 7.2% positive for HPV 16/18 infection. About 3% of these proved to be double infections, i.e., HPV 6/11 and HPV 16/18 infection in the same patient.

STIMULATION OF NONSPECIFIC RESISTANCE BY RADIODETOXIFIED ENDOTOXIN.

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The immune deficiency and decreasing of nonspecific resistance/NSR/ are frequent problems of medicine. These are caused by many factors, e.g. viruses, ionizing radiation, cortison, ACTH, cytostatic drugs, antilymphocyte serum, radio-sensitizers etc. The serious decrease of NSR might be the cause of opportunistic infections by various microbial agents. We have found that our radio-detoxified endotoxin preparation /RD-LPS/ has a stimulating effect in the lympho-reticular-immune system. The RD-LPS can produce significant proliferation of lympho-reticular-immune system in germfree/practically immune deficient/ animals, too. RD-LPS/retreatment can prevent the majority of animals from the various experimental infections and shock forms. On the basis of our experimental results we can conclude that the RD-LPS /TOLERIN/ is a potent stimulator and regenerator of lympho-reticular-immune system. For this reason we would like to call the attention to this preparation as a potential prophylacticum or therapeuticum of immune deficiencies like AIDS manifestation or cancer.

G-32: IMMUNE POTENTIATION BY ENDOTOXINS AND POLYSACCHARIDES

Effect of endotoxin on the lateral immunity of mice to experimental tumors.

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It was observed that the transiently experimental lateral immunity of mice to experimental tumors is not altered by the administration of a single injection of bacterial endotoxin. In order to study the possible effects of endotoxin on tumor growth, mice were injected with tumors and then treated with endotoxin. The results showed that endotoxin, when given in a single injection, had no effect on the growth of tumors. However, when the endotoxin was given in two injections, the tumors were inhibited.

The possible factors influencing these differences in tumor growth will be discussed.

Analysis was supported by U.S. Public Health Service grants RO 49531, 16924, and 05351, and N.I.H.S. and 07074.
RESTORATION OF IMMUNORESPONSIVENESS BY BACTERIAL ENDOTOXINS AND THEIR DERIVATIVES IN LEUKEMIA VIRUS-INFECTED MICE. Bendinelli M., Matteucci D., and Giangregorio A.M., Inst. of Epidemiology, Hygiene and Virology, Univ. of Pisa, Pisa, Italy.

It is well established that animals infected with leukemogenic retroviruses exhibit strongly reduced immune responses and that such deficit facilitates the progression of the induced leukemia. Previous studies have shown that the administration of appropriate doses of bacterial endotoxins greatly restores the responsiveness of mice infected with viruses of the Friend leukemia complex (FLC). However, under certain conditions the same treatment can enhance leukemogenesis by FLC, probably due to an expansion of target cells for transformation. In an attempt to develop treatments capable of restoring immune responses, we have investigated the mechanisms whereby endotoxins from E. coli and B. marcescens and selected derivatives reconstitute the antibody responsiveness of spleen cell cultures from FLC-infected mice. The results show that the beneficial effects of such products are independent of the lipid moiety and are not due to the mitogenic action on B lymphocytes. Rather, they appear to act at least partly mediated through effects on accessory cells, for example, when incubated with such products, adherent spleen cells of infected mice reacquired a normal ability to cooperate with nonadherent cells. A key role for accessory cells is also suggested by the fact that supernatants generated by spleen and peritoneal macrophages pulsed with endotoxin proved as active as, or even more active than, endotoxin itself in restoring the antibody response. The activity of the supernatants was not attributable to carryover of endotoxin and was not mediated solely by interleukin-1. Induction of and response to this monokine was not appreciably compromised in mice carrying FLC-induced leukemias.


The immunomodulatory effect of a new group of branched polypeptides characterized with the general formula poly Lys-\(\frac{n}{x}\)-DL-Ala, e, where \(n\times 0\) \(\overline{LAK}\), Leu\(\overline{LAK}\), D-\(\overline{LAK}\), H16\(\overline{HAK}\) was investigated. Levanosol, an immunomodulator in clinical use was applied to compare the immunoadjuvant activity of these polypeptides. The dose and time dependent stimulatory effect of the immune response to SRBC induced by these polypeptides was studied in normal and tumor-bearing BDF mice using the hemolytic plaque-forming cell assay and rosette-forming cell assay. The qualitative and quantitative features of the antibody response induced by polypeptides was also characterized by IGM and IGG type antibody levels. Correlation was found between the chemical structure and the immunomodulatory potential of branched polypeptide with poly-L-lysyl backbone. LAK, D-LAK and HAK - similarly to levamisole - were able to compensate for immunosuppressive effect of the anti-tumor agents Dianhydrogalactitol, S-Fluorescein Vincristine/ applied in therapeutic doses both in normal and P388 tumor animals. Tumor inhibitory effect of cytostatics was not diminished by these polypeptides. Suppression of humoral immune response induced by ionizing radiation could be compensated by LAK while could be only reduced by D-LAK or HAK pretreatments. The E-rosette formation of B-lymphocytes inhibited by radiation was restored to different extent by polypeptides when applied before irradiation. In conclusion the branched polypeptides can be regarded as immunomodulators, perspective adjuvants in cancer chemo- and radiotherapy.
G-32: IMMUNE POTENTIATION BY ENDOTOXINS AND POLYSACCHARIDES

Elimination of severe toxicity and pyrogenicity of endotoxin glycolipids, without impairment of their ability to potentiate immune responses, has been achieved. The nontoxic monophosphoryl lipid A (MPL) retained the ability to interact synergistically with trehalose dimycerate (TDM) and cell wall skeleton (CWS) of mycobacteria to induce regression of tumors with concurrent induction of tumor immunity. Combinations of these immunostimulators caused regression and elimination of metastasis of the transplantable hepatocarcinoma in guinea pigs with induction of tumor immunity. A mixture of all three (HPL + TDM + CWS) in an oil-in-water emulsion containing 1-2% oleic acid, when injected directly into tumors, was effective, without noticeable harmful manifestations, in effecting the regression of bovine ocular squamous cell carcinoma (of 13) and equine sarcoma (of 5). In some of these latter cases, low doses of cyclophosphamide (thought to reduce T-cell suppression) were required to manifest the antitumor effects of the immunostimulators.

Preliminary clinical trials were undertaken in humans with malignant melanoma or Kaposi's sarcoma that were refractory to other therapies. Six of 14 evaluable patients, treated intralesionally with a MPL-CWS combination, achieved a complete response to the therapy, and two patients displayed partial responses. These studies demonstrated the potential applications of immunostimulatory agents alone, or in combination with other therapies in the treatment of certain cancers.

LOCAL TREATMENT WITH INTERLEUKIN 2: INHIBITION OF TUMOR GROWTH AND ACTIVATION OF KILLER CELLS.

Repeated peri-tumoral injections of purified interleukin 2 (IL 2) from several mammalian species inhibited growth of chemically induced sarcomas in syngeneic mice (1, 2). The IL 2 preparations could also induce cytotoxicity of lymphocytes from tumor bearers which was quantitatively comparable to that induced by IL 2 treatment of lymphocytes from non-tumorous controls. It is suggested that the activated killer cells may play a significant role in the local tumor inhibitory effect of IL 2.


H-32: PREDICTABILITY OF TESTING AND PRECLINICAL TOXICOLOGY

DEFINITION AND EVALUATION OF TOXICITY

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Therapy by medicinal compounds possesses nowadays the priority in the treatment-strategies of patients. As consequence, doctors and layman expect precise informations about desirable and undesirable effects and events caused by drugs; parallel, there are increasing numbers of national and international legal aspects and Guidelines, many of them as consequence of the contorgan-catastrophe and drug induced mortality.

The risk evaluation has increased considerably in all phases; there are growing databases world wide collecting events in the post marketing surveillance; there are growing databanks collecting preclinical findings; there is a growing knowledge about the right choice of the animal-models and their possible alternatives and complementary methods; and there are growing insights in the limitations about the predictability. This paper highlights the difficulties in how to define toxicity and how to evaluate clinical, clinico-chemical and postmortal findings. We like to demonstrate experimental findings reflecting the problems of preclinical research.
IN VITRO EFFECTS OF NEW ANTHRACYCLINE DERIVATIVES ON RAT HEART METABOLISM. G.Cini-Marzi*, M. Bandinelli*, and B.Meri**, Istituto di Patologia Generale e Istituto di Clinica Medica II, Universitá di Firenze, Italy.

In our previous study on doxorubicin, we spoke of the possibility of predicting the cardiotoxicity of anticancer drugs by estimating certain metabolic parameters in vitro. As a case in point, impairment of respiratory control and inhibition of protein synthesis in rat heart slices were found to correlate significantly with the histological lesions induced in vivo by doxorubicin.

- Epoxycytostatic effects of doxorubicin derivatives. - Increased level of cytochrome c. - Impaired electron transport chain. - Inhibition of protein synthesis.

Doxorubicin and its metabolites were investigated in a Warburg manometric apparatus at 37°C and compared to control values. The results were compared to the doxorubicin dose that, administered i.p. in vivo, caused the above-mentioned alterations. In terms of our parameters, the new anthracycline derivatives are significantly less cardiotoxic than doxorubicin (p < 0.01). However, it is well to bear in mind that impairment of respiratory control and inhibition of protein synthesis are only one of the aspects of cellular damage leading to doxorubicin-induced cardiomyopathy.

HARMONIC AND TOXICOLOGY OF SPARMINCIN.

- Pharmacokinetics and toxicology of minocycline.
- Evaluation of biochemical parameters in the assessment of gastrointestinal side effects of cytostatic agents.

Doxorubicin (Dox) is the major reduction product of doxorubicin (Dox). It is present in substantial concentrations after administration to humans. Dox's metabolism in normal and abnormal hepatic function was assessed in 6 New Zealand white rabbits given dox 3 mg/kg i.v. Four weeks later, the same rabbits were given 1.5 mg/kg of allyl alcohol i.v. followed 24 hrs later by dox 3 mg/kg. Doxol was a more potent inhibitor of relaxation than doxorubicin.

Doxorubicin is water soluble and has minimal plasma protein binding. Its effects on endogenous respiration and on the rat heart can lead to diminished of known side effects a.o. on the eye. Doxorubicin is water soluble and has minimal plasma protein binding. Alter in blood injection of 0.1 mg/kg the plasma elimination curve follows the three compartment model. The T1/2 is 1.1 h. Under serum about 70-80% of the dose is excreted in urine and the renal clearance is 8.5-6.8 ml/min. The % renal clearance depends on urine flow and creatinine clearance. A marked capacity of active tubular secretion has been observed with low urine flow. Tubular resorption results in slow Y phase (T1/2 8.5 h). With high urine flow tubular resorption decreases and the Y phase was not detectable.

Successful 9 daily doses (0.1 mg/kg each) were lethal to one out of five dogs. Additional hydration with saline/glucose sol. (0.5/1), i.d. did not prevent the increased renal clearance that was seen in all dogs. Mild to moderate increase of transaminases was observed in all animals. Plasma albumin, fibrinogen and coagulation factors were most affected by Sm. There was no bone marrow toxicity. Moderate leukopenia was seen in four animals. All abnormalities have returned to normal within 10 days. No eye fundus abnormalities were seen during or after therapy. The eye histology of two autopsied dogs was normal. The presented pharmacokinetic and toxicological data should lead to better understanding of Sm toxicity and optimization of therapy.

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DESIGN OF TREATMENT SCHEDULE ACCORDING TO THE PATTERN OF ALKYLATING AGENT-INDUCED DNA SYNTHESIS INHIBITION

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The optimal schedules for different types of cytotoxic agents vary depending on their mechanism of action. In the same time, the knowledge on differential responses and kinetic features of normal and malignant tissues is necessary. The paper will describe our experiments on evaluation of the effect of bis-2,2-dichlorodiethyl ammonium salt of dinitro-2,4-dinitro-3-phenyl glutaric acid, a newly synthesized alkylating agent on the replicative DNA synthesis in normal and tumour cells and analysis of data in respect of drug scheduling. According to the kinetic of U-thymidine incorporation into LLC (max 72% inhibition, up to 2.5 h after treatment) and P388 tumour cells (max 90% inhibition, up to 24 h after treatment) and normal active proliferating cells, time dependent drug-induced DNA inhibition was found. The data shows relationships between antitumour activity and level and duration of DNA-synthesis in tumour cells, as well as the correlation between optimal therapeutic schedule and pattern of DNA inhibition/restoration in normal and tumour cells. The results led us to confirm that the information of the effect of cytotoxic agents on DNA synthesis inhibition might lead to a design of more efficacious schedule for the selective killing of tumour cells.

ANTICANCER DRUGS - A NEW INITIATIVE FROM THE CANCER RESEARCH CAMPAIGN

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It has become clear to many scientists and clinicians engaged in the development of new anticancer drugs that the currently employed drugs are likely to be sub-optimal because they were originally selected by comparative studies in rodents bearing animal tumours with little similarity to cancer in man. Furthermore, the metabolism of a drug by a patient may be sufficiently species-specific to decrease the predictability of dose-limiting information from animal studies.

With these ideas in mind, the Cancer Research Campaign (CRC) is supporting an initiative incorporating specialists in antitumour drug development and senior medical oncologists in the UK to seek out potentially anticancer chemical substances from chemistry and biochemistry groups throughout the country and to support the necessary detailed preclinical toxicology required to transfer a greater diversity of these agents from the laboratory bench into early Phase I trials in the clinic.

Since 1981 14 drugs have entered the system and their progress to date will be discussed.

THE USE OF HUMAN TUMOR XENOGRAFTS IN PRECLINICAL EVALUATION OF NEW ANTICANCER AGENTS.

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The value of using human tumors xenografted into athymic, nude mice in evaluating the antitumor efficacy of chemotherapeutic drugs is well established. By an large, the xenografts retain the characteristics of the original tumor, even during years of consecutive passaging in the animal host. Importantly, the model permits testing of the drugs in vivo, thus involving the aspects of drug activation, pharmacology and toxicity to normal tissue. In a screening program for new anticancer drugs short term in vitro and in vivo assays should be used during the early stages of screening. If positive effects are seen in these assays, the new compound should be tested in nude mouse models. By using tumor lines from different types of cancer a preclinical in vivo phase II study can be performed on xenografts. In such studies a panel of tumors of each histological type should be included to account for the variability in chemosensitivity of tumors of the same tumor type. If this is done, it may be possible to select types of cancers in which the chances of obtaining significant clinical responses are high. This type of studies should always be done before new drugs are entered into clinical trials, hopefully making it possible to reduce the number of ineffective drugs given to patients. An example of the usefulness of this approach will be demonstrated.
2182 **PEPTIDE HORMONES AND PULMONARY CANCER**, G.D. Sorenson, C.C. Cato, and D.S. Pettengill, Dartmouth Med. Sch., Hanover, NH USA

Peptide hormones are occasionally produced by multiple forms of pulmonary carcinoma but are most commonly associated with small cell carcinoma (SCLC). SCCLC can be demonstrated to be produced by SCLC. However, hormone production is a variable characteristic. There are differences between tumors in the hormones which are produced as well as the amount of any individual hormone. It is also apparent that this is not a random association between hormone production and SCLC. Some hormones are produced more commonly, e.g., bombesin/staurin releasing peptide, calcitonin (CT), POMC and neurophysins, whereas some are produced only rarely or never, e.g., PTH and insulin. Current studies indicate that hormone content in pulmonary carcinoma cells is structurally comparable to the analogous one in normal endocrine cells. The reason for the limited expression of these genes is not clear. Is this a matter of genes already affected in the cells of origin or are a variety of transcription factors more or less selectively activated in "normal" cells in spite of the presence of "factors"? If the latter answer, what is involved? Currently available evidence does not indicate correlations between activation of hormone genes and the expression of a variety of hormone genes. Clinically it has been found that hormone content is selective in tumors and that it can be used as a marker for the only consistent result of tumor shrinkage, evaluation of the efficacy of treatment, and differentiation of tumors occurred and that it is not a characteristic of normal tissue. The results have several important problems of inconsistency and clinical usefulness. The hormone production and their physiologic effects.

2183 **EXPRESSION OF NEUROENDOCRINE (NE) PROPERTIES BY LUNG CANCER CELL LINES**, A.P. Czader, R.J. Uemoto, P. Nelsen, K.L. Becker and H.R. Ole, R.E. Russell, National Cancer Institute and National Naval Medical Center, Bethesda, MD 20814; and VA Medical Center, Washington, DC 20042, USA

We have established over 90 human lung cancer cell lines by continuous culture and compared their expression of NE properties with corresponding tumors. Pulmonary carcinoids and small cell lung cancer (SCLC) are currently recognized as NE neoplasms. However, human tumors cannot accurately be classified as NE, carcinomas, and adenocarcinomas. NE carcinomas and small cell lung cancer (SCLC) are currently recognized as NE neoplasms. In addition, studies of non-SCLC lung cancers express multiple NE markers. NE characteristics include the presence of dense core granules, the enzymes -diaphylink and neuron specific enolase, serotonin and multiple peptide hormones, especially bombesin-like, calcitonin, neurophysins, ACTH and arginine vasopressin. Most SCLC tumors and lines have typical morphology and express all of the NE properties. Some variant SCLC lines have altered morphology and selective loss of NE properties. They frequently have amplification of the c-myc oncogene. Classic SCLC lines selectively retain hormone-like peptide, which functions as an autocrine growth factor. Pulmonary endocrine cells, the presumed precursor cells of NE lung cancers, can be cultured for long periods. They express all of the NE properties. All 5 of the NE tumor types have been established in long term culture and characterized. They demonstrate that all NE tumors represent a continuous spectrum, and that they share a common endodermal origin.

2184 **COEXPRESSION OF NEUROENDOCRINE AND EPITHELIAL MARKERS IN NEUROENDOCRINE NEOPLASMS OF THE LUNG**, Victor E. Gould, I. Lee, R. Mall, B. Wiedemann, W.W. France, Rush Medical College, Chicago, USA; and German Cancer Research Center, Heidelberg, FRG.

A group of 12 carcinoids, 8 well differentiated neuroendocrine (NE) carcinomas (WDNC), 14 intermediate cell (ICNC) carcinomas and 15 small cell carcinomas (SCNC) were studied immunohistochemically with antibodies to NSE, serotonin, a broad spectrum of neuropeptides, synaptophysin, cytoplasmic polypeptides, neuroendocrine proteins (NFP) and desmoplakins. The most prominent NE characteristics of these tumors were determined by electron microscopy. All neoplasms so studied were immunoreactive for NSE and at least one and often several neuropeptides. Serotonin was frequent in carcinoids and WDNC, but was less frequently expressed in ICNC and SCNC. A similar pattern of immunostaining was observed with synaptophysin. All NE markers were readily demonstrable in conventionally fixed and embedded sections, and in cryostat preparations. All tumors expressed cytokertin polypeptides, NFP, B, BL and, to a lesser extent, NFP. NFP were expressed in a number but not all the carcinoids, WDNC and ICNC; no NFP immunostaining was noted in the SCNC studied. Desmoplakin immunoreactivity was noted in all these tumors but was more consistently observed in the carcinoids, WDNC, ICNC than in the true SCNC. Intermediate filaments and desmosomal proteins were readily demonstrated in frozen sections and high magnifications. Results on conventional sections and cryostat sections were consistent. We conclude that desmoplakin immunostaining is not a consistent feature of NE carcinomas and not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers and that it is not as tumor markers. A subset of these neoplasms is characterized by the coexpression of cytokertin-NFP. Consistent immunohistochemical analysis with NFP antibodies and other that recognize "neurone" features should result in a more realistic, reproducible and clinically significant classification of lung epithelial tumors.


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We present the results of a prospective multicenter trial on the treatment of small cell lung cancer with polychemotherapy and irradiation performed before each cycle of chemotherapy and during the follow-up period every four weeks. A deep frozen serum sample was sent to the central tumor marker laboratory in Marburg to determine CEA, calcitonin, ACTH and neuron specific enolase (NSE). The results refer to the interim analysis on 250 patients. Approximately 90% of the serum samples could be evaluated. A total of 980 marker analyses was performed on 816 sera. The following results could be obtained:

1. The incidence of elevated marker levels was lower than in retrospective studies.

2. A marked elevation of the markers indicated the presence of distant metastases. In addition, there was a direct relationship between tumor burden and the height of the marker.

3. At the time of diagnosis a negative correlation between marker level and survival could be demonstrated.

4. Multivariate analysis indicated a relationship between marker levels and other prognostic variables such as weight loss, performance status, and the number of cycles of chemotherapy.

5. Patients with no decrease of a certain marker or of tumor mass in chest x-ray during the first two cycles of chemotherapy had a significantly worse prognosis indicating an immediate switch to a second line therapy.

6. Because of the different marker profiles obtained in the marker levels during the later course of therapy was of little value to detect relapse earlier.

7. In a considerable number of patients originally normal calcitonin and ACTH raised at the time of relapse indicating overgrowth of resistant hormone-producing clones.

Human small cell lung cancer (SCLC) is a neuroendocrine tumor which produces high levels of neuroendocrine enzymes such as dopamine decarboxylase and polypeptide hormones. In particular, high levels of bombesin (BN)-like peptides are present in SCLC biopsy specimens and all classic SCLC cell lines examined (3.1-18.3 pmol/mg protein). These BN-like peptides are secreted from SCLC cell line NCI-H345 in vitro by secretin or vasoactive intestinal peptide (VIP) which elevates the intracellular cAMP levels 4-fold. Similarly elevated plasma levels of BN-like peptides are present in patients with extensive disease and secretion infusions causes a 7-fold elevation of plasma levels of BN-like peptides. Thus SCLC cells have receptors for VIP and activation of these receptors causes increased secretion of BN-like peptides in vitro.

Some SCLC cell lines have plasma membrane receptors for BN-like peptides. SCLC cell line NCI-H345 binds (Tyr'BN, a potent BN analogue, with high affinity (500-5000 nM)) to a single class of sites (1500/cell). Binding is specific, reversible and saturable. Pharmacological studies indicate the terminal of BN or the structurally related peptide gastrin releasing peptide (GRP) is essential for the high affinity binding activity. The BN-like peptides appear to bind to a protein with a subunit molecular weight of 78,000 daltons. In contrast, radiolabeled VIP binds to a slightly smaller protein weighing 42,000 daltons.

Also, exogenous addition of BN stimulates growth of SCLC cells in vitro, thus BN-like peptides function as autocrine growth factors in SCLC. The use of anti-BN agents, such as monoclonal antibodies, inhibits the growth of human SCLC. 

HORMONE PRODUCTION OF LUNG CANCER: Jeffrey S. Halcon, Baltimore, USA
The most rational interpretation of the signal changes which occur, on migration from one country to another, in the risk of cancers of stomach, large bowel, breast and prostate is that they are mediated directly or indirectly by diet. One of migration is likely to be important. Although the US National Academy of Sciences concluded in 1982 that cancers of major sites are influenced by dietary pattern, the committee considered that the data available did not permit quantitation of the contribution of diet to the overall cancer risk nor determine the degree of reduction that might be achieved by dietary modifications. Apart from aflatoxin, tryptophan metabolites and a few food additives, few dietary carcinogens have been identified. Endogenous formation of nitrosamines is receiving increasing attention - those may influence gastric cancer risk. Protective factors in fresh fruit and vegetables, including fibre, continue to be studied. Study of diet is bedevilled by a lack of reliable methods to assess past diet and, for dietary fibre, a lack of clear chemical definition and of appropriate analytical methods. The epidemiologist has tended to derive hypotheses from correlation studies, correlating food disappearance with cancer risk, frequently ignoring possible induction periods. The case-control approach has frequently been discredited with relative risks often less than two and inconsistent results. Ideally, the prospective cohort study should resolve many problems, but it is difficult to continually monitor an individual's diet, even on a sampling basis for a long time. Probably the best approach is to assess diet and store biological material so that this can be examined on a case-control basis. Several suitable population exist, regrettably few are studied. Details of studies and possible ideas are discussed.

For the last two decades we have been conducting studies of dietary fats, total calories, fibre, carotene, retinol, and ascorbic acid as well as obesity and caloric expenditure, as related to risk of cancer at various sites. Our findings have been based on case-control studies carried out among patients at Roswell Park Institute, in the three counties of western New York State, and throughout New York State. We have found carotene associated with reduced risk of cancer of the mouth, esophagus, larynx, lungs, bladder, and cervix. Our inquiries on fats have yielded conflicting findings but it would appear that they may be associated with increased risk of cancer of the colon and prostate. Ascorbic acid has been found in our studies to be associated with increased risk of cancer of the mouth, larynx, and esophagus but not stomach or intestine. It is important to note that obesity has been found associated with elevated risk for a number of sites and that physical activity via exercise appears to be associated with decreased risk of cancer of the colon. Plant foods appear to be associated with reduced risk of cancer at a number of sites including, particularly, the squamous cell sites and stomach cancer.
A randomized double-blind intervention trial was carried out in Nuxian, Henan Province. People's Republic of China, to determine whether combined treatment with retirol, riboflavin, and zinc could lower the prevalence of precancerous lesions of the oesophagus. 610 subjects in the age group 35-64 were randomized to receive once a week the active treatment (15 mg 150 00 IU retinol, 250 mg riboflavin, and 50 mg zinc) or placebo. Both at entry to the study and at the end of the treatment, 15-6 months later, the subjects were examined, with an emphasis on signs of vitamin A and riboflavin deficiencies, and retinol, caroten, and zinc levels were measured. Compliance was excellent. The final examination, on 567 (93%) subjects, included oesophagoscopy and at least two biopsies. The intervention did not affect the prevalence of oesophageal lesions: after one year, the prevalence of oesophagitis with or without atrophy of dysplasia, was 58.3% in the placebo group and 48.9% in the vitamin zinc treated group.

Despite evidence from epidemiological observations and animal experiments that dietary fat intake may influence breast cancer risk, there is little information about the effects of dietary fat on human breast tissue. We have elected initially to study the effects of dietary fat on the breast by examining the influence of dietary fat reduction on the radiological manifestations of breast dysplasia. The goals of the study were to determine if dietary fat intake may influence breast cancer risk, there is little information about the effects of dietary fat on human breast tissue. We have elected initially to study the effects of dietary fat on the breast by examining the influence of dietary fat reduction on the radiological manifestations of breast dysplasia. The goals of the study were to determine if dietary fat reduction on breast dysplasia, to assess compliance with a reduced fat diet, and to assess the effect of dietary fat reduction on breast dysplasia by comparing mammograms taken before and after a 12 month period of dietary intervention. Patients with mammary dysplasia were recruited from a breast diagnostic unit and randomly allocated to a control group who received advice about maintaining a balanced diet according to Government guidelines (40% of calories as fat), or a study group who received advice, education, and an individual diet prescription, to reduce dietary fat to 15% of calories. 270 patients (61% of those eligible) consented to randomization. After one year of follow up 20% of the study group and 5% of the controls have dropped out. The remaining patients show close adherence to the dietary goals of the study, with a mean fat intake close to target, as assessed by food records, duplicate meals and serum lipid measurements. These data thus show that dietary fat reduction has a long term reduction of dietary fat are feasible, and that good compliance with a reduced fat diet can be achieved. The influence of dietary fat reduction on the radiological manifestations of breast dysplasia is now being examined with conventional and digital radiography.

The ether-potroleum ether extract and acetone soluble fractions of 12 kinds of vegetables were tested on the development of mutagenicity of 2-acetylaminofluorene (AAF) by Ames test. The mutagen depressive effect was seen in 9 kinds among the tested vegetables, except green peppers, garlic and pears. The acetone soluble fraction was further purified by two successive treatments using column chromatography of silicic acid. In the first procedure, the solvents system of n-hexane-ethyl ether was applied, and the mutagen-depressive substance was recovered from the n-hexane eluate. In the second procedure, heptane, benzene and methanol were applied successively. And the benzene fraction contained the active agent. Experimental studies were carried out on the mutagen-depressive effects on the mutagenicity of benz(a)pyrene(BaP). Metabolites of BaP on rat liver microsome in vitro and on stomach gavage were measured using high pressure liquid chromatography. Both of the experimental results showed that the active substance accelerates the formation of phenolic compounds and inhibits the formation of diols, thus decreasing the non-metabolites of BaP in vivo.
Percutaneous biopsies with computed tomography control have become over the past years standard procedures in the diagnosis and staging of malignancies. Advantages of computed tomography in the guidance of percutaneous tissue sampling are represented by high spatial resolution, recognition of hypervascularity and tumor necrosis, collapsed digestive and vascular structures, precise documentation of the progression of the needle tip to the target, reproducibility of the procedure and the high degree of medical confidence of computed tomography shared by referring physicians.

Among more than 700 percutaneous biopsies performed with computed tomography control, an overall correct diagnostic rate was achieved in 92 %. In 8 % inadequate cytological material or a false negative result was present. False positive results are exceedingly rare. On the other hand, in lymphoma patients, diagnostic accuracy of percutaneous biopsies is dramatically decreased: 12 % of correct diagnoses only are obtained in the diagnosis of Medek's disease.

In order to gain economical benefits from methotrexate sampling with computed tomography, percutaneous biopsies should be alternated routinely in a standard computed tomography schedule in oncology patients. Computed tomography is also helpful in monitoring other percutaneous interventional methods performed in cancer patients, e.g. percutaneous needle biopsies, percutaneous catheterizations, intratumoral injection therapy and interstitial radiotherapy, percutaneous chemotherapeutic placements, and percutaneous interventional radiological procedures such as embolization or percutaneous catheterizations.

Valid anatomic and tissue density data are necessary for the exact dose planning with high energy beams to assure this either in the conventional radiology or in the modern procedures, as for instance regarding computer tomography need more thorough attention and precision. These activities mean a special escalation of the periodical Quality Control and Assurance.

**2200** THE SIGNIFICANCE OF CT FOR STAGING, THERAPY AND RELAPSE DIAGNOSTICS OF MALIGNANT TUMOURS.

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CT has acquired an extraordinary significance for primary diagnostics, staging, therapy and relapse diagnostics of malignant tumours, because it often renders possible the accurate localization of the extent of organic invading tumours and the identification of metastases in all anatonic regions. It will be reported on the limits of this method especially in case of relapse diagnostics. Besides the therapy simulator CT has developed into an indispensable resource of modern radiation planning and new computer controlled planning systems as well as stereotactic therapies use the informations gained from computed tomograms. In case of renal carcinoma and carcinoma of the urinary bladder conventionally produced radiation drafts have to be modified in more than 50 % due to the CT findings, leading to a considerable influence on the radiation doses. Modern CT machines often allow a direct tumour volumetry and therewith a quantification of the success of therapy. In different therapies schemes, for example in case of soft tissue sarcoma, the results of tumour volumetry became determinant for therapy. New software programs as there are the contour program or secondary reconstruction techniques have also proved true for tumour diagnostics and therapeutics, others like 3D-planning, dual-energy CT (electron density) CT are still clinically examined. It will be reported on these new methods and the perspectives of CT.
The purpose of the study was to show the clinical value of CT in the diagnosis of primary and secondary cardiac tumors. Using a non-contrast protocol, CT can be performed after contrast enhancement of the blood pool. We can adequately identify cardiac structures at the expense of time.

Out of 480 patients studied by CT, hazards of various cardiovascular problems were seen. In addition, primary or accessory cardiac tumors, as primary cardiac tumors, have been described in recent years. Pleomorphic malignant lymphoma, lipoma, and metastases, as well as cardiac tumors, benign or malignant, can be detected.

All patients were evaluated with computed tomography and cardiac magnetic resonance imaging. The results show that tumors larger than 2 cm in diameter are detectable using unenhanced CT. The overlapping-free visualization of the cardiac chambers and structures as well as of the large heart vessels is helpful to distinguish the results of cardiomegaly caused by the heart itself or by the tumor mass.

In conclusion, CT of the heart is a useful non-invasive method in finding or in excluding cardiac tumors. It provides information of the type, size, and spreading of the tumors in the heart and pericardium. It helps to determine whether surgery or radiation therapy or surgical procedures should be performed. Cardiac CT is also a suitable method for follow-up studies of patients under treatment.

THE VALUE OF PATIENT PREPARATION TECHNIQUES AND RECENT MULTIDETECTOR CT IN THE DIAGNOSIS OF MALIGNANT TUMORS

Proper patient preparation rules mean the difference between good and unqualified examinations. Protocols have been defined for bowel preparation, intravenous contrast administration technique and timing, use of a vaginal tampon, prevention of patient motion and bowel peristalsis. The study of the tumour extent often depends on the visualization of double tissue interfaces, interface between tumour and normal tissue and destruction of thin bone plates as findings. The visualization between single and multiple tumour volumes, in the first case scans have to be made in a plane perpendicular to the tissue interface to maximize visualization, and in the second case the plane has to be parallel to the direction of the tumour growth. Longitudinal visualization, in both cases the patient has to be positioned in the desired scan plane. We have developed such positioning techniques for almost all parts of the body. We will describe our preparation techniques and illustrate our scan technique with a number of cases.

K-31: CT IN THE DIAGNOSIS OF MALIGNANT TUMOURS
**L-33: MULTIMODALITY TREATMENT OF HEAD AND NECK TUMOURS**

**2208**

**THE CLINICAL SIGNIFICANCE OF PATHOLOGICAL FINDINGS IN Surgically resected margins of the primary tumour in head and neck carcinomas: patient and the incidence of local recurrence and clinical outcome** is presented. These margins are in five categories: Negative (no invasive carcinoma at least 0.5 cm from margins); Close (invasive carcinoma less than 0.5 cm from margins); Positive (invasive carcinoma at margins); Insitu carcinoma at margins; and Gross tumor at margins. The oral cavity, oropharynx, hypopharynx, and larynx were included in this retrospective study of 269 consecutive surgical patients - 234 with negative margins, 22 positive, 10 close, 2 insitu carcinoma, and one gross tumor - treated between 1977-1982. Local recurrence rate was 17% for negative margins; 55% for positive; 40% for close, 50% for insitu carcinoma; and 100% for gross tumour. The estimated 5-year disease-free survival was 39% for negative and 78% for positive margins (P=0.051). All patients with close margins, who developed local recurrence, died within 24 months except one who is alive at 36 months. The insitu carcinoma patient who developed local recurrence is alive at 58 months. The patient with gross tumor at margins died at 18 months. Patients with negative margins from tumor of the hypopharynx, oropharynx, oral cavity and larynx had an estimated 5-year disease-free survival of 11%, 20%, 38% and 30% respectively (P=0.0440). Adjuvant therapy - postoperative radiation was more effective than chemotherapy, 48% vs. 17% in estimated 5-year disease-free survival. Local recurrence rate for T1 and T2 lesions with free margins was 14% and 24% for T3 and T4 (P=0.0414). Patients with well differentiated squamous carcinomas did best, compared to patients with moderately and poorly differentiated. The results of this study indicate that pathological evidence of complete excision of the primary tumor is important and attempts should be made to obtain pathological clearance. Local recurrence rate for T3 and T4 lesions, even with negative margins, are high. Adjuvant therapy is indicated and the type of adjuvant therapy will be discussed.

**2209**

**DILEMMA IN THE RESTORATION OF FUNCTION FOLLOWING RADICAL AND CONSERVATION SURGERY OF THE LARYNX**

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In surgery of laryngeal cancer a surgeon is often faced with a sequence of questions especially those regarding the reconstruction of speech, deglutition and respiration. Between 1964 and 1984, 760 total laryngectomies were performed, of whom 62% developed oesophageal speech thanks to systematic early rehabilitation in our Phoniatric Clinic. Over the period 1981-1984, 48 total laryngectomies were performed on a selected group of patients by creating the phonatory neoglottis following Staffieri method. The success regarding speech and deglutition in this second group was 78% (32 patients) with the main mean of aspiration smaller than 3%. In these patients with vocal fistula an active sphincter mechanism will give better results with the satisfactory fistula voice and freedom from significant leakage of secretions, food and drink. The tracheo-oesophageal puncture technique with valved prostheses is a simple and secure technic giving excellent results and it will be further developed. Conservation surgery of the larynx removes the cancer and makes all efforts to preserve the deglutition, respiration and phonation. Conservation surgery should be above all meticulous, and special attention should be paid to an astute selection of both, the patients and the procedure. Today there are at least 27 modifications of the surgery. Consequently, the dilemma arises: which procedure to use? Our experience in this field is comparatively rich and includes a total of 310 cases. Our principle, especially in hemilaryngectomies (110 cases), is not to perform an immediate reconstruction of the larynx. On the contrary, the final closure should be delayed for four to six months after the resection of the tumor, reconstruction of the laryngeal lumen and the postoperative irradiation therapy.
MANAGEMENT OF CANCER OF THE RETROMOLAR AREA - A MULTIDISCIPLINARY APPROACH. A.B. Chandra, Chittaranjan Cancer Hospital, Calcutta, West Bengal, India.

Squamous cell cancer of the retromolar area is now a clinical entity in the eastern India. Other oral cancers seldom become symptomatic till late stage. Pain, local infection and trismus are more frequent in retromolar cancers. Out of 4800 oral cancers, the third largest cancers in Indian patients treated during June 1966 to May 1985, 235(5%) cases belonged to retromolar cancers. Retromolar cancers were found more in younger patients. Women were more often affected. The left side was more frequently involved. These features are directly related to chewing habits of 'pau' and tobacco and longer period of retained 'quid'. 239(8%) cases when came for treatment were found to have far advanced disease associated with gross malnutrition, anaemia and cachexia and were excluded from further studies. Only 20.2% of cases were considered to be early cancers. 79.8% of cases belonged to the late stage with partial or complete trismus having poor prognosis. Proper evaluation was difficult in majority of cases. Pretreatment examination under anesthesia, prior tracheostomy, dental extractions and often emergency operation were carried out for opening of the mouth and treatment. 98 cases were in control group treated by radiotherapy and/or surgery during 1966-1975 and 114 patients in study group treated by combination of chemotherapy with radiation and/or surgery during 1976-1985. The early cases in both the groups showed equally good results. The induction of chemotherapy with single agent Methotrexate by weekly i.V. injection 50-100 mg/m² with radiation and/or surgery dramatically changed the outlook of late cases in the study group by improving quality of life and survival rate from 10% of the cases in control group to 35% cases in the study group. Before the systemic use of chemotherapy trismus was considered to be worst prognostic factor. Multidisciplinary approach with Methotrexate in combination with radiation and/or surgery was found to be beneficial in the late cases of the study group by decreasing the recurrence rate and delaying the incidence of cervical metastases.

CHANGING PRINCIPLES OF RADICALITY IN THYROID CANCER SURGERY: K. Keminger, and F. Kober, Dept. of Surgery, Kaiserin-Elisabeth-Hospital, Vienna, Austria

From 1949 to 1981, 1128 cases of thyroid carcinomas were treated. According to four different department heads, the operative and postoperative policy had varied. The statistical evaluation of this retrospective study proves:

1) Patients with highly differentiated thyroid carcinomas showed the best survival rates after 25-year follow up, if they had been treated by thyroidectomy and neck-dissection (papillary carcinomas), postoperative radioactive iodine therapy, and a suppressive dosage of thyroid hormones.

2) Anaplastic carcinoma should be treated by ultraradical surgery and chemotherapy or external radiation.

Low differentiated follicular carcinoma and high stage thyroid carcinomas are today problems of special interest, our investigations showed the following results:

In evidence of progression of disease under radioactive iodine therapy of low differentiated follicular carcinoma treatment should change to chemotherapy. High stage thyroid carcinoma has to be operated under aspect of extensive reduction of tumor mass. Although there is only an inferior effect on survival rate, quality of life improves significantly.
2214 THYROID CANCER IN CHILDHOOD.
Gy. Balazs, Debrecen, Hungary

2215 LASERS IN THE TREATMENT OF HEAD AND NECK TUMORS
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The development of experimental and clinical laser surgery and laser microsurgery over the past 20 years has contributed to major advances and provided new alternatives in the treatment of head and neck tumors. These techniques provide greatly simplified and less invasive cure of benign and early malignant tumors of the oral cavity and larynx. In the case of more advanced cancer, precision detection and cytoreduction of the cancer burden results in less radical surgery and greatly improve effectiveness of combined modality treatment. More than 5 years of experience has shown that following endoscopic control of the primary laryngeal tumor, subsequent cervical metastases can be handled separately. Thus, the en-block removal of the larynx and cervical lymph nodes is not necessary.

Endoscopic laser surgical removal of small cancers in the trachea and bronchi can provide cure. It can also provide prolonged palliation in some cases of more advanced cancer. A new generation of laser surgical systems will make it possible to treat more advanced cancers of the larynx by combining endoscopic laser surgery with external laser surgery. These new systems will also have special advantages in the treatment of cervical metastases. It is estimated that even when current state-of-the-art equipment and techniques are utilized, 20% of laryngeal cancers worldwide can be eliminated or postponed for several years.

References

2216 PREDICTION OF OUTCOME OF RADIOTHERAPY IN HEAD AND NECK CANCER.
E. Nordman, Department of Radiotherapy, University of Turku, 20520 Turku, Finland

The response of head and neck tumours to radiation treatment does not necessarily correlate to the local radiocurability of the tumour. The tumour may diminish fast during therapy, even disappear, but nevertheless recur within some months. On the contrary, the tumour may persist all through the treatment and still disappear some weeks later never recurring.

There is a great need for the prediction of the outcome of radiotherapy of an individual tumour in the head and neck region; this will help to combine other forms of treatment, such as surgery, in the treatment schedule. Following methods are suggested:

1. Histological changes such as keratinization in the tumour, or lymphocyte infiltration in the vicinity of the tumour, have been reported to be in correlation to the radiocurability of the tumour.

2. Electronmicroscopic changes in the intercellular contacts seem to be predictive for the outcome of the malignant disease.

3. The tumour functions of the cancer patient are seldom predictive for the prognosis, even though immune-suppression, induced by the disease itself or by different treatment forms, is often present.

4. Tumor specifically antigen substances such as glucose analogues labelled with 125I-fluorine may reflect the activity of the tumour.

5. Flow cytometry visualizes the differences in ploidy, DNA content and different cell cycle phases in tumours. It may reflect the final outcome of radiotherapy.

6. Mononuclear antibodies marked with radioactive isotopes may reveal the tumour cell burden and changes in it during therapy; these may be predictive for the therapy result.

7. Magnetic resonance imaging is developing and may be a new tool in examining tumours during treatment.

2217 INTRA-ARTERIAL CHEMOTHERAPY AND RADIOTHERAPY IN THE TREATMENT OF 720 ADVANCED HEAD AND NECK CANCER.
A. Raporto, J.de Andrade Sobrinho, J.P. Kowalski, M.B. de Carvalho, A.S. Fava, J.F. de Cós Filho, J.F. Salles Chagas, J.L. Kanda, O. Torres, Hélioopolis Hospital/INH5P, São Paulo, SP - Brazil

Advanced head and neck cancer remain as one of the greatest problems for the oncologist. The results obtained with irradiation in such cases are uniformly poor. At the Head and Neck Service of the Hélioopolis Hospital, 720 patients with advanced cancer of the head & neck region were treated from 1971 to 1983 by the association of intra-arterial chemotherapy and radiotherapy. All of them had Clinical Stage III or IV tumors, not amenable for surgical resection or curative irradiation. Most Patients (71%) had histologically proved squamous cell carcinoma. The therapeutic approach consisted on the association of intra-arterial chemotherapy (mono or polichemotherapy) followed by irradiation (5000 to 7400 Rad). The drugs were used in different schemes of one to four drugs, which include methotrexate, bleomycin vincristine, cisplatinum, triebulimetaphosphoramide and adriamycin. Responses were usually incomplete with remission duration of a few months. The survival at 12,24 and 36 months ranged from 39 to 46%, 14 to 15% and 2 to 5%, respectively. They concluded that the frequency of complete remissions after intra-arterial chemotherapy is small and duration brief. Previous untreated patients seem to be more sensitive to this approach. There are several factors influencing the success of the treatment. Intra-arterial chemotherapy on the treatment of advanced cancer of the head and neck has been associated to considerable morbidity and limited benefits. Efforts in this area as well as continued programs evaluating new drugs should be encouraged.
L-34: ADVANCES IN LIMB-SAVING SURGERY OF MUSCULOSKELETAL TUMOURS

2218 LIMB-SAVING SURGERY IN TREATMENT OF MALIGNANT BONE TUMOURS. Z. Mateljovsky, Orthopaedic Clinic, Institute for Postgraduate Studies, Prague, Czechoslovakia

In surgical treatment of malignant bone tumors two principles are to be respected: 1. Complete removal of the tumor according to its grade of malignity - 2. Preservation of the best possible function of the affected region. In order to achieve an oncologically radical removal of an extremity tumor, formerly mostly ablative surgery was performed. In recent years, due to better understanding of different malignity grades of musculoskeletal tumors, limb-saving procedures are increasingly indicated in bone tumors of low grade malignity. In addition, preoperative chemotherapy has become extremely effective and may result in extensive regression in tumors of high grade malignity, making limb-saving procedures possible. In our center, preoperatively osteosarcoma and malignant fibrous histiocytoma is treated according to Rosen's system: T 10 and T 12 and Ewing's sarcoma T 11. The effect of chemotherapy is evaluated both clinically and histologically from the resected specimen. In responders limb-saving operations are performed. For replacement of resected bones either bone transplants or endoprostheses are applied. Different procedures for treatment of tumors in the shoulder, hip and knee region are demonstrated. The proportion of limb-saving surgery against amputations is evaluated in different kinds of 473 treated primary malignant bone tumors. Principles of Enneking's surgical staging system and classification of surgical procedures are applied. Limb-saving surgery is substantially more difficult than ablative, it should be performed by surgeons with experience in oncologic surgery, in fully equipped centers. The preservation of oncologic radicality remains the main condition of a favourable final result.

2219 MALIGNANT TRANSFORMATION OF BONE TUMOURS. T. Virkeley, Budapest, Hungary

OSTEOGENIC SARCOMA: AN ANALYSIS OF 91 CASES. H. S. Poulsen*, G. Santen*, G. Srnepen*+, and O. M. Janzen*+. The Institute of Cancer Research, Radiotherapy, Aarhus Kommunehospital, *Orthopedic Hospital and Aarhus Amts Hospital, Aarhus, Denmark.

This study consists of 91 cases which were admitted at the tumor centre of Aarhus, Denmark over a twenty-five year period. To qualify in the present study, the proliferating cells of the neoplasm must produce osteoid substance or material histologically indistinguishable from it. The material was divided into histologic categories according to the predominant malignant type of cell: osteoblastic, chondroblastic, fibroblastic, and telangiectatic osteosarcoma. Of the 91 cases 63 patients could be microscopically radically operated, of these, 39% were alive 10 years after the primary treatment. When the cases were divided according to histologic features, it was observed, that patients harbouring osteoblastic tumors did worse as compared to non-osteoblastic tumors. 100% 10 years crude survival as compared to 88% 10 years crude survival. The patient were staged by physical-, X-ray-, and CT-scan examination. An multiparameter analysis of possible features, which can subclassify prognosis different patient populations will be presented.

OSTEOGENIC SARCOMA USING ISOLATION PERFUSION.

M. Pan, M. A. Santoni, F. Bell, M. Santoni, A. Frada, M. Santoni; A. J. Castiglione, C. C. M. Santoni, R. J. Santoni, Italy, Italy.

Eleven patients affected by osteogenic sarcoma of extremities, for whom the only possible treatment was amputation or amputation, were treated at National Cancer Institute of Milan, Italy, according to this schedule: two intrarterial infusions with CDDP 40 mg, b. i. daily for three days) plus high dose of MTX for six intravenous 7/2 per b. i. (corticosteroids, per fusion with CDDP 300 mg, b. i. for lower extremities, 200 mg, b. i. for upper extremities). Three intrarterial infusions of CDDP plus high dose MTX for six intravenous 7/2 per b. i. On relevant side effects were noted in these patients, neither during infusion nor during hyperthermic perfusion at 47°C. In particular no kind of bone marrow depletion or renal toxicity were evidenced. In all cases after perfusion appeared an extensive area which regressed spontaneously in 2-3 weeks leaving extremities normal at all by a functional and histologic, rarely hypersegmented. Clinically and radiologically the tumor regression and the rearrangement of the bone were so impressive that, till now, out of 11 patients 4 underwent conservative surgery with an "en bloc" resection plus endoprostheses. One was amputated for tissue retraction due to previous radiotherapy while two were operated for technical impossibility to perform a conservative surgery. Histology in these 3 operated patients showed 100% of necrosis in 6 patients and 70% in one. The other 4 patients with identical clinical and radiographic features are still in treatment for a possible conservative surgery; needle-biopsies performed in these patients after perfusion showed a necrosis of grade 1 in all cases. Two patients developed lung metastases that were resected. Even if the number of cases and the short follow-up don't allow any definitive conclusion, this treatment schedule suggests the possibility of avoiding in many cases a destructive surgery.

From 1980, 200 bone sarcomas of limbs and girdles have been treated by multidisciplinary limb salvage procedure. Histology include 55 high grade osteosarcoma, 30 chondrosarcoma, 5 fibrosarcoma, 6 treated as recurrent lying sarcoma, 2 angiosarcoma, and 1 liposarcoma. Localisations were distal femur 35%, proximal tibia 15%, upper humerus 19%, ilium 10%, scapula 8%, fibula 6%, proximal femur 5%, tail 3% distal tibia 5%, distal humerus 3%, and metaphysis 1%. According to Skeen's staging, 2 tumors were T1, 1T2, 6T3, 8T4, and 21T5. As defined by the pathologist, 51 resections were large, 56 marginal and 9 intra-focal. Adjunct post-operative radiotherapy were given in 62 cases and chemotherapy in 70 cases. With a average follow up of 27 months (7-64) we observed 6 local recurrences (3 in osteosarcoma, there were differentiated chondro-sarcoma and one in lying sarcoma). 24 months after diagnosis, 62% of patients have a functional limb evaluated as elegant (61) or good (52) except in 4 cases. These results show as good as those obtained after amputation or distraction, except for differentiated chondromas. In conclusion, with the help of technical bone tumor imaging, large surgical experience, adjuvant chemotherapy and/or radiotherapy, our feasibility rate of conservatice surgery has been 97% in spite of local tumoral radius going 15 cm, presence of fracture in 8 patient, local infection in 6,5, multilocal lesions in 3, and necrosis in 3, and only 3 patients died. 21 cases. Including differentiated chondrosarcoma, amputation were needed only after inadequate initial management, or at risk of tumor imaging or surgical experience.

2223 APPROPRIATE TREATMENT OF SOFT TISSUE SARCOMAS OF THE EXTREMITIES


Soft tissue sarcomas are rare tumors constituting only 0.4% of all malignancies in the National Cancer Registry of GDR. Between 40% and 60% of all sarcomas are localized in the extremities, often requiring the decision between a mutilating operation or a local tumour excision. Including the risk of incurable recurrences, the multidisciplinary treatment approach must consider all prognostic factors especially the histological type, the grade and stage, the localization and size of the tumour, and the age of the patient. The most important prognostic factor is an adequate operation result in combination with postoperative irradiation and/or chemotherapy especially in infancy and childhood and administered systemically or by perfusion of an extremity. The 5-year-survival of 295 soft tissue sarcoma treated after 1969 in a multidimensional manner are significantly better than the results of 209 sarcomas of the extremities treated between 1945 and 1965.

2224 LIMP-SALVAGE SURGERY FOR OSTEOSARCOMA

Fujinori Endo*, Norihiko Yashida**, Goumu Inoue***.

*) Department of Orthopedic Surgery, Chiba University, Chiba, Japan. **) Chiba Cancer center Hospital. ***) Nihon University.

The preoperative radiotherapy and systemic chemotherapy is effective in reducing the size of the tumor and the making the tumor resectable. The results achieved with systemic chemotherapy are ultimately reflected in improved survival. Limb-salvage procedure has become possible with rationality in carefully selected patients.

Since 1972, ninety-seven patients with osteosarcoma were treated in our institute. Thirty-five out of 97 patients with osteosarcoma underwent en-bloc resection of the femur (23), the tibia (3), and the humerus (4).

Result: No patients in this series showed local recurrence of the tumor. Nine patients died of metastasis. Overall 26 patients are alive without distant metastasis after 10 to 125 month-follow-up period. Cumulative 5-year survival rate is 76.6%.

Functional results after limb-salvage surgery will be presented based on Enneking's evaluation. Our indication for limb-salvage is also presented.

2225 NEOADJUVANT REGIONAL CHEMOTHERAPY AND LIMP SALVAGE FOR SOFT TISSUE SARCOMAS OF THE EXTREMITY

A.A. Zaccaria, V. Magi, V. Andreolo, S. Corcelli, I. Guernari. Instituto Nazionale Tumori, Via Venezian 1, 20133 Milano-Italy.

Since '81 at our Institute, patients with large soft tissue sarcomas of the extremities are treated with intraarterial infusion of Adriamycin according to different schedules (ADR alone for 1 preop. cycle, ADR alone for 2 cycles, ADR+cisDPPotinum for 2 cycles). Up to now the regimen which gave the best results is ADR alone (100mg/m2) continued infusion i.v. over 8 days for 2 preop. cycles. After infusion all the patients were radically operated on with preference for limb salvage. Postop. XRT was delivered after marginal operations. Two cycles of postoperative adjuvant i.v. ADR was scheduled in responders. Up to now 44 cases entered the study: 8 of superior and 36 of the inferior limbs. Clinical response was evident in 14 (32%) cases and pathological necrosis in 27 of 34 (80%) evaluated cases. Toxicity after infusion was typical with alopecia in all patients, mild nausea during infusion, more severe with vomiting during infusion of cisDPP. Leucopenia was evident during the 12th-14th day after the first day of infusion, with a median nadir of 1,700 WBC (range 250-4000). No disturbance of the wound recovery was related to the infusion. Of 48 operations 31 were conservative versus 9 amputations (limb salvage rate 78%). Four cases developed local recurrence after conservative and 1 after ablative surgery. Four-year actuarial survival with a median exposure to follow up of 26 months, is 35%, and free-of-disease interval 52%. No relationship was documented between local response and histotype or grade of vascularity, and between local response and final outcome. More cases are demanded for a proper statistical evaluation. Conclusion: neoadjuvant preoperative regional infusion is really effective in local control of primary soft tissue sarcoma of the extremities, but does not seem to protect against metastases. Open questions: preoperative chemotherapy is really more effective when given intraarterially rather than intravenously? Is there a better regimen than ADR alone? What is the real role of XRT? Is postoperative chemotherapy indicated in responders?
2226  **PROGNOSTIC IMPORTANCE OF LYMPH NODE METASTASES versus BONE INVOLVEMENT IN SOFT TISSUE SARCOMAS of the EXTREMITIES.** M. Rudek and J. Mayza. Dept. of Surgery, Inst. of Oncology, Warsaw, Poland.

The AJC staging system for soft tissue sarcomas /STS/, accepted also by UICC, is valid in unchanged form until 1986. According to this system stage IIIc /G1-3 T2-3 N1 M1/ groups the pts with lymph node metastases /LNM/ and stage IVa /G1-3 T3-4 N1 M1/ with bone involvement /BI/. The sequence in this classification suggests better prognosis for LNM than for BI. The incidence of local recurrences /LR/, distant metastases /DM/, and 5-year survival were analyzed in 24 pts stage IIIc and 28 pts stage IVa selected from a total number of 176 pts with STS treated by surgery only in years 1950-1980. LR occurred in 52% pts in stage IIIc and 18% in stage IVa. 5-year survival rate was 4% and 16% respectively. The percentage of DM /lung/ was similar in both groups. These results indicate clearly that prognosis is worse for pts with LNM than with BI. Our findings confirm opinion that LNM in STS pts are prognostically comparable to DM. Natural course of STS and presented results suggest the need of a shift in AJC staging, in particular to accept:

- BI as stage III /G1-3 T2-3 N1 M1/ 
- LNM as stage IV /G1-3 T3-4 N1 M1/.

2227  **SIGNIFICANCE OF PREOPERATIVE CHEMORADIOThERAPY FOR PREVENTION OF LOCAL RECURRENTS AFTER LIMB SALVAGE PROCEDURES IN OSTEOGENIC SARCOMA.** A. Mirjalilzadeh, All-Union Cancer Research Ctr, USSR ANS, Moscow, USSR.

Since 1977 a study on the efficacy of limb salvage procedures for local osteogenic sarcoma in the combination with chemo-radiotherapy has been initiated in the All-Union Cancer Research Center, USSR ANS. The technique of limb sparing operations for osteogenic sarcoma envisages:

- intraarterial adriamycin infusion;
- preoperative and postoperative preventive chemotherapies;
- rehabilitation measures.

108 patients received complex treatment: in 20 patients bone allografts were utilized for bone replacement; in 86 - metal fixator knee joints. Under morphologic examination of tumour tissue following preoperative chemo-radiotherapy marked therapeutic pathomorphosis was noted in all the cases. Out of 106 patients in 27 (19,8%) following adriamycin infusion and telecurie therapy under studying a large number of specimens tumour cells were not found at all. Following complex treatment free of metastases 3 years survived 35,2% of patients. In patient group with chemotherapy alone free of disease survival rate was 7,0%. Recurrences were not observed in the patient group.

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**M-32: CHRONIC MYELOPROLIFERATIVE DISORDERS**

2228  **RESERVED**

A. Georgii, Hannover, FRG

2229  **RESERVED**

J. Fleischer, Dresden, GDR
2230  XEMORRHAGIC AND THROMBOEMBOLIC PROBLEMS IN CANCER

DEATH of cancer patients in a large cancer center. The most important cause of death was infection; the second: hemorrhage and/or thromboembolism (including DIC). Changing DIC activity levels, fibrinolysis, and platelet-systems were studied prospecively. In a series of 100 patients with bronchogenic cancers, findings were: (1) increased fibrinogen turnover rate (often with increased fibrinogen levels), (2) increased production of antiplasmin (both types), and (3) decreased AT III levels with relative clinical resistance to heparinization, (4) there was significant increase in fibrin deposition products (FDP), in isolated perfused liver experiments FDP's produced increased synthesis of fibrinogen and antiplasmin.


DEATH of cancer patients in a large cancer center. The most important cause of death was infection; the second: hemorrhage and/or thromboembolism (including DIC). Changing DIC activity levels, fibrinolysis, and platelet-systems were studied prospecively. In a series of 100 patients with bronchogenic cancers, findings were: (1) increased fibrinogen turnover rate (often with increased fibrinogen levels), (2) increased production of antiplasmin (both types), and (3) decreased AT III levels with relative clinical resistance to heparinization, (4) there was significant increase in fibrin deposition products (FDP), in isolated perfused liver experiments FDP's produced increased synthesis of fibrinogen and antiplasmin.

The hypothesis is presented that in the abnormal, poorly reactive, tortuous, A-V anastomosis rich circulation of tumors there is a continuous defibrination and fibrinolysis resulting in increased production of FDP's, which in turn act on the liver, increasing synthesis of fibrinogen and antiplasmin. In premature leukemias and related conditions, the increased thromboplasty, activity results in similar phenomena. Consumption of AT-III results in relative resistance to therapeutic heparinization. Relative resistance in patients can be returned to normal by transfusion of plasma or AT-III preparations. Inhibitors of tumor cell produced plasminogen activators may be useful in helping to promote occlusion of vascular beds of tumors. These inhibitors interfere with tumor angiogenesis by promoting thrombotic occlusion of newly formed, yet blindly ending capillaries. This was shown in experiments with intracranial implants of rabbits and monkeys.

2230  CANCER AND HEMOSTASIS
MONDAY • AUGUST 25 • AFTERNOON


The liver contains a network of sinusoids which is a very unique part of the body. The sinusoids are able to produce a large number of proteins which are important for the health of the body. The sinusoids are also able to destroy a large number of proteins which are harmful to the body.

In this study, we have found that the liver is able to produce a large number of proteins which are important for the health of the body. The sinusoids are also able to destroy a large number of proteins which are harmful to the body. This is important because it shows that the liver is able to maintain a healthy balance of proteins in the body.

2232  STUDY OF THE FIBRINOLYSIN SYSTEM IN MALIGNANT MELOMANA PATIENTS. C. M. Ambrus, C. Karakousis, and J. L. Ambrus. Children's Hospital of Buffalo, Roswell Park Memorial Institute and the State University of New York at Buffalo, New York 14222 USA.

Two hundred and twenty patients with malignant melanoma at various stages were studied with respect to the fibrinolysin system. In the first 104 consecutive patients only 26 showed a decreased fibrinolysin level. In the second group of 100 patients, 12 showed an increased fibrinolysin level. The study shows that the fibrinolysin system is important in the prognosis of the disease and that it can be used as a prognostic indicator.

In conclusion, we have found that the fibrinolysin system is important in the prognosis of the disease and that it can be used as a prognostic indicator. The study shows that the fibrinolysin system is important in the prognosis of the disease and that it can be used as a prognostic indicator.
THE COAGULATION-CANCER INTERACTION: CLINICAL AND LABORATORY ASPECTS. Leo R. Zacnyiński, Veterans Administration Hospital Hematology Section and Dartmouth Medical School, White River Junction, Vermont, USA.

The proposed role for blood coagulation reactions in dissemination of experimental animal malignancies led to establishment of several prospective, randomized clinical trials of antithrombotic drugs in human malignancy. These clinical trials are intended to evaluate drug efficacy but also provide a setting in which basic mechanisms can be explored through laboratory tests. Two controlled trials of warfarin have shown a significant survival advantage and a significant increase in the incidence of complete tumor regression from anticoagulation of patients with small cell carcinoma of the lung (SCL). A double-blind trial of the platelet-antagonist, RA-233, in several types of human malignancy has enrolled over 700 patients and will be completed in June 1986. Laboratory data from these studies have increased understanding of coagulation test abnormalities in cancer. Using immunospecific techniques on fresh frozen tumor tissue sections, tissue factor (the putative initiator of clot formation) has been identified on the surfaces of small cell tumor cells. Blood coagulation factors VII and X (but not certain other clotting factors) also exist on tumor cell surfaces and in intercellular spaces, and abundant fibrin is present in the connective tissue surrounding tumor nodules and clusters of tumor cells. These findings suggest that formation of fibrin by way of the extrinsic coagulation pathway may support the growth and spread of SCL. Opportunities exist for further testing the anticoagulant hypothesis through clinical trials of a variety of drugs used individually and in combination.

2235 THE ROLE OF HEMOSTATIC FUNCTION IN TUMOR GROWTH AND METASTASIS

Max C. Kwangs, Chicago, IL.

Using a histochemical fibrin slide technique, we demonstrated that the presence of melanoma tumour tissues is associated with high levels of fibrinolytic activity in blood vessels in the tumour tissue suggesting that there is an inhibition by melanoma. Therefore, there is a need to investigate whether or not the above mentioned inhibitor binding is responsible for such inhibition. The result of this study confirms the presence of alpha-1-antitrypsin, alpha-2-antiplasmin and alpha-2-macroglobulin in malignant melanoma tissues. The role of fibrinolysis in tumour growth was studied through the application of therapeutic fibrinolysis and therapeutic fibrinolysis in experimental tumors aimed at the removal of fibrin and surrounding tumour tissue. In Lewis Lung Carcinoma in mice we observed that the sustained chronic fibrinolysis by the administration of Ancrod did not affect the tumour growth nor response of the tumour to cyclophosphamide therapy. Similarly, the addition of fibrinolytic therapy with streptokinase was ineffective. However, the number and size of metastatic lesions in the defibrinated mice were significantly less than in the untreated control animals. Anticoagulants with fibrinolytic enzymes reduced the number and size of experimental tumours. Tumour growth and metastases are governed by multiple factors, which in light of these recent studies, must now include any local and systemic perturbation of the hemostatic functions.

2236 ANTIPLATELET THERAPY WITH RA233 FOR SMALL CELL LUNG CANCER. A. Lipton, R.A. Harvey, M.A. Simmons, C. Valdivia, J. Barnes, B. Walker, B. Dixon, and R. Gordon. The Milton S. Hershey Medical Center, Hershey, Pa. 17033 and The Central Pennsylvania Oncology Group, Harrisburg, PA.

Platelets have been implicated in the metastatic spread of tumors. Both animal and human tumor cells can activate platelet in vitro. This result in the release of proteolytic factors contained in the platelet (Platelet Derived Growth Factor and Transforming Growth Factor-β). RA233 is a potent dipyrindimide (Pentrationone) derivative. Like dipyrindimide, it inhibits platelet aggregation by irreversibly inactivating Prostacyclinase and increasing intracellular cAMP. Besides its antiplatelet-phospholipase activity, dipyrindimide has also shown to directly inhibit in vitro tumor cell multiplication. Ninety-two patients with Small Cell Lung cancer were all treated with Tcytoxan (C) 75 mg/m^2, Adriamycin (A) 50 mg/m^2, Vincriazine (V) 2 mg I.V. on Day 1 + VP-16 100 mg/m^2 daily X 2. This chemotherapy cycle was repeated every 21 days for one year. In addition, patients were randomized to receive RA233 10 mg/kg p.o. t.i.d. or Placebo for 2 years. Patients were stratified according to extent of disease and by ECOG performance status. At the completion of 3 cycles of chemotherapy patients were evaluated and decision was made to administer therapy to the primary lung lesion and whole brain. Data will be presented on time to progression and survival of patients treated with C + A + V + RA233.

2237 INCREASED t-PA-INHIBITOR LEVELS IN MALIGNANCY.

J.W. ten Cate, L. de Jong, E.A.P. Emelie-Morlert, G. van Weerden, M. Bijnen, Division of Hematology and Thrombosis, Academic Medical Center, Amsterdam, and Catharinum Institute, Leiden, The Netherlands.

We investigated t-PA activity (spectrophotometric, t-PA antigen (enzyme immunoassay), t-PA inhibitor (filtrated with pure t-PA) and urine fragments antigen (ELISA)) in 72 consecutive patients with malignancy. The t-PA inhibitor and t-PA antigen were significantly increased in patients with age- and sex-matched control group (table).

<table>
<thead>
<tr>
<th>Test</th>
<th>Patients (n=72)</th>
<th>Control (n=26)</th>
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<tbody>
<tr>
<td>t-PA activity</td>
<td>Median 0.06</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Range (0.02-2)</td>
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<tr>
<td>t-PA antigen</td>
<td>Median 36.0*</td>
<td>49.5</td>
</tr>
<tr>
<td></td>
<td>Range (21.4-56.1)</td>
<td>(24.1-77.5)</td>
</tr>
<tr>
<td>t-PA inhibitor</td>
<td>Median 4.0*</td>
<td>3.20</td>
</tr>
<tr>
<td></td>
<td>Range (0.24-28.3)</td>
<td>(0.06-4.54)</td>
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<tr>
<td>UR-antigen</td>
<td>Median 98.3</td>
<td>89.4</td>
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<td></td>
<td>Range (54-847)</td>
<td>(53-178)</td>
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*p<0.001; Wilcoxon test

No differences were observed between patient groups with or without objectively diagnosed metastasis. Pathophysiological implications of these findings will be discussed.
CARCINOMA OF THE LIP, CLINIC AND THERAPY.
N. Schwenzer, Tübingen, FRG

Regional and general chemotherapy were employed in more than 300 cases. Patent blue staining, eye fundus, xeroangiography and scintigraphy were carried out in an effort for controlling the regional treatment. Patent blue staining and eye fundus examination serves as an instant control at the operating table for the location of the end of the catheter. Angiography and isotop examinations were performed via the indwelling catheter. On the xeroradiographic photographs, the bones and their soft portions can be depicted well simultaneously. The isotop flow rate, its distribution and the proportions in which the supply area of the individual arteries were perfused were analysed.

CONTROL OF INTRA-ARTERIAL CHEMOTHERAPY OF HEAD AND NECK TUMOURS. G. Szabó, Semmelweis Univ. of Med. Dent. of Oral- and Maxillo-Facial Surgery, Budapest, Hungary

Thus a treatment dependent prognostic index ”TPI” was constructed which is considered to be eligible for clinical cancer research. However, to affirm the accuracy of ”TPI” its application to an independent data material is necessary. Therefore a second observational study, the "Prospective DOSAK Study on Carcinomas of the Oral Cavity" has been performed. This study comprises a data material of about 3000 patients, the most recent results will be available in 1986. Changes in the validity of prognostic factors, both clinical and therapeutic, have occurred. The most recent version of ”TPI” is presented as a basis for clinical cancer research. Its use in uncontrolled and controlled clinical studies will be explained.

"Deutsch-Osterreichisch-Schweizerischer Arbeitskreis für Tumoren in Kiefer- und Gesichtsbereich." German-Austrian-Swiss Association for Head and Neck Tumors.
Surgical treatment of oral cancer has undergone considerable changes in recent years especially by introduction of microsurgical techniques.

Simultaneously with the development of microsurgical tissue-transfer new types of transplants were designed. Myocutaneous and osteomyocutaneous flaps in plastic-reconstructive measures have often become standard procedures. The osteomyocutaneous iliac crest transplant is primarily suitable and has been used by us on 30 patients during the last three years for reconstruction of the mandible and soft tissue defects microsurgically.

In selected cases we have subsequently used enossal tooth implants into the iliac crest bone transplant rebuilding favourable conditions for prosthetic restoration of masticatory function.

Frequently these reconstructive measures have been used in cases after preoperative radiotherapy (70 Gy maximum dose) and the method will be discussed in regard to technique, indications, and results, also mentioning the use of myoperitoneal flaps in cheek reconstruction when more than one tissue layer is required.

The techniques of arterial infusions of cytostatic drugs to the tumor area have been rediscovered in the last years by surgical oncologists for nearly all regions of the body. In the head and neck region this method is used for thirty years. In the meantime with new catheter types and improved techniques in the placement of catheters selective infusion of the tumor area can be realised. Longterm infusions of drugs like Bleomycin, Adriamycin, Cisplatin even with reduced dosage cause proliferation block and cell death of the tumor growth fraction. In every case partial or complete remission of the primary tumor can be provided, cellkinetic effects being monitored by flow cytometric DNA measurements. The advantages of this preoperative procedure are:

1. Shrinkage of the tumor mass.
2. Lower risk for the spread of tumor cells by killing the proliferating fraction.
3. Possibility of surgical removement.
4. Improvement of survival time.

The following treatment protocol was administered: BLEO 15mg/2 hrs/day i.a.; RADIATION 200 rad/day; MTX 30mg/2 hrs/day i.a.; Antidote CITROVURMFAK 4.3 mg/day.

The average survival time for the above mentioned 68 patients was 20.6 months (max, 126m., min, 3m). Complete remission was documented in (n=10) 15% partial remission in (n=36) 50%. No response occured in (n=26) 35%.

Out of 12 analysed clinical factors 6 showed a statistically significant influence on survival-time: age of patient, x-ray documented bone destructions by the tumor, over all dosage of BLEO, over all dosage of irradiation, irradiation mode, blood chemistry dates (Fe, BCC, WCC, LDH, GOT, GPT).

Sideeffects were moderate and reversible (Mucositis occured n=34 cases, leucopenia n=2 and thrombopania n=4 cases).
**Clinical Malignancy and Prognosis of Early Invasive Carcinoma**

T. Amagasa and S. Shioda, Tokyo Medical and Dental University, Tokyo, Japan

The accurate diagnosis of carcinoma in its early stage is an important aspect in obtaining more effective results of cancer therapy. There are few literary data about clinical findings and treatment results of oral early invasive carcinoma. Five hundred sixty-six early invasive carcinomas were examined in this study. Thirty-three were male and twenty-one were female. The age ranged from thirty-seven to eighty-one years. Sixty-three were found on the tongue, thirteen on the floor of the mouth. Based on the macroscopic feature of lesion, we classified them into six types. The incidence of each type was as follows: leukoplakic, 32%; granular, 25%; papillomatous, 18%; erythroplakic, 15%; ulcerative, 7%. The size of lesion ranged from four to forty-two millimeters. Thirty-five cases were treated by surgery, 15 by radiotherapy, and four by surgery and radiation. The follow-up period ranged from one to eighteen years. Sixty-seven percent of the cases had neither recurrence nor lymph node metastasis. Recurrence (and/or metastasis) was found in 9.2% in the surgery group and 13.3% in the radiation group. The lesions belonging to the mixed or erythroplakic types, larger than two centimeters, and found on the floor of the mouth had higher recurrence rate than the others. The cumulative survival rate of all cases was 94.6% in five years and 89.1% in ten years. The rate of surgery was 97.4% in ten years but that of radiotherapy was 79.4%. From these results, it may be concluded that early diagnosis of oral cancer is an essential factor to produce the maximum therapeutic result and the most suitable therapy is prompt surgery.

**Involvement of the Nervous System in Lymphomas and Leukemias**

Hochberg FH, Miller D, Massachusetts General Hospital, Boston, Massachusetts, USA

Several factors have changed our conception of Primary Non-Hodgkin Lymphoma of the Central Nervous System (NHL-CNS): A. Formerly rare (fewer than one case per two years) the tumor now accounts for 10 cases per year. B. A population predisposed to develop NHL-CNS has been delineated. Patients include those with inherited immunosuppressive disorders (A-TEL, Wiskott-Aldrich), combined immunodeficiency diseases (Ataxia-Telangiectasia, Combined Immunodeficiency Disease, Wiskott-Aldrich), acquired immunosupression (transplant recipients and AIDS patients), and an increased risk of developing NHL-CNS in patients with NHL-CNS. C. New immunohistochemical studies have revealed B cell monoclonal populations in biopsy samples as well as CSF and vitreous aspirates. E. Neuroradiologic evaluations (CT/MRI) have indicated periventricular, multicentric and steroid responsive features of the tumor deposits. F. Major sites of relapse include the brain parenchyma and cerebrospinal fluid. Fewer than 10% of patients demonstrate systemic lymphoma. G. Prognosis is intimately related to the histologic subtype of NHL-CNS, and is improved by techniques which take into account the diffuse parenchymal and subarachnoid spread. Two therapies—high dose Methotrexate by vein and cranio-spinal irradiation will be discussed.
2249 INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM IN PRIMARY NON-HODGKIN'S LYMPHOMAS

W. Janisz, Humboldt-Univ., Berlin, DDR

A retrospective study of the CNS in autopsies with non-Hodgkin's (NHL) and Hodgkin's (HL) lymphomas was performed. In every case the brain and the spinal cord were sliced at 1 cm intervals after fixation in formalin. Bilateral cerebral, parietal, temporal, and occipital slices as well as those of the cerebellum and lower brain stem were examined in paraffin wax. The spinal cord, including spinal nerve roots and spinal ganglia was investigated at 5 cm levels at least. Involvement of the CNS was proved only when separate segmental lymphoma tissues were found. Invasion of the CNS from NHL in the bones and extracranial soft tissues were not expected. Isolated CNS foci were found in NHL only. No separate deposits were detected in HL. Tumour manifestations of the CNS were present in 4% of the low grade and 34% of the high grade malignant NHL. One fourth of the NHL infiltrations in NHL showed naked-eye appearance. CNS involvement was most common in generalized immunoblastoma, immunoblastomas and in the tissue stage of multiple lymphomas. The cause of the different incidence of NHL manifestation in various types of NHL is obscure. All primary malignant NHL of our material were reviewed in accordance with the Kiel classification. First of them were lymphoblastomas. In primary NHL occurred. However, the group of lymphocytes is not the only pattern to evaluate the morphologic appearance of NHL. The classification of the primary lymphoma of the CNS is unknown. From there the tumour cells invade the brain tissue and the meninges. A typical sign of primary lymphoma of the CNS is unknown. To infer these primary signs or the clinical signs or events, in this paper is not expected in literature.

2250 PRIMARY NON-HODGKIN'S LYMPHOMAS OF THE CENTRAL NERVOUS SYSTEM


135 primary Non-Hodgkin's lymphomas (NHL) of the brain (109 autopsies, 26 biopsies) were observed among 10,000 intracranial neoplasms (incidence 1.35%). Three costs were immunocomprised. There was clear male predominance of 1.5:1. Median age of diagnosis was 57 years, range from birth to 89 years. Duration of symptoms ranged from days to years. Elevated CSF protein was frequent. CSF cytology was positive in 45% of the examined cases. CCT showed solitary or multiple enhancing foci. The most common sites were the cerebral hemispheres (44%), basal ganglia (16%), brain stem (12%), corpus callosum (10%), while 20% showed multiple lesions of the brain and meninges. There was only one autopsy case of primary NHL of the intracranial cord in a female aged 82 years. Histologically, the most common types according to the Kiel Classification (LENNERT 1981) were immunoblastomas (43%) and immunocytomas (40%), less frequent were lymphoblastomas (12%), and simple cases of centroblasto ma and unclassified NHL. The ultrastructure of primary NHL millenniums and immunoblastomas were classified and compared to biopsies obtained from the massif in the biopsies. Immunocytochemistry showing intracytoplasmic monoclonal immunoglobulins in both solid tumours and CSF tumour cells indicates that the majority of the primary CNS NHLs are B cell type. Biclonal immunoglobulins observed in single cases indicate an intratumoral heterogeneity of CNS NHLs, known in acute and systemic NHLs. Median survival without treatment after surgery was 1.2 months, after radiotherapy (10 cases) 12.5 months, and after combined radiochemotherapy (13 patients) 17 months, with poor prognosis of lymphoblastomas and immunoblastomas (1-year survival 10 and 12%, respectively), while immunocytomas showed a mean survival of 36 months (range 2 to over 240 months) with 1-year survival of 75% and a two-year life-expectancy of almost 40%. Clinical-pathological and immunological problems are discussed.

2251 RADIOTHERAPY OF CENTRAL NERVOUS SYSTEM LYMPHOMAS

Schrinner D., Giordana M.T., Mauri A., Gobbiello S., Soffietti R.

II Neurological Clinic and Institute of Pathology, University of Turin, Italy

A prospective analysis of 30 cases of primary central nervous system lymphoma is reported. All cases were studied from the clinical, pathological and therapeutic point of view. Clinically the most common presenting symptoms and cerebrospinal fluid abnormalities, especially the cytological ones, were analyzed, as well as the angiographic and tomographic features. Cerebral metastases and cerebellum were most often involved. The pathology study was carried out on surgical biopsies and in few cases also on autopsy material. Histological and immunohistological procedures were employed for classification purposes according to the new classification system of non-Hodgkin's lymphomas and the working formulation of non-Hodgkin's lymphomas. Half the patients underwent whole-brain irradiation and a few also chemotherapy mostly with nitrogen mustard derivatives. The survival time of untreated and treated patients was analyzed, even though the response to treatments was variable, whole-brain irradiation being the exception. We present the prognosis of central nervous system lymphomas. All our clinical, pathological and epidemiological data confirm that there tumours do not represent a uniform group of neoplasms. Other prognostic factors, both clinical and pathological, are discussed.

2252 NEW PATHOLOGIC PERSPECTIVES ON PRIMARY CNS LYMPHOMA

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We reviewed all cases of Primary Non-Hodgkin Lymphoma of the Central Nervous System (NHL-CNS) between 1958 and 1984 at the Massachusetts General Hospital. The International Working Formulation was used to classify the 61 cases evaluated. Beginning in 1980 these NHL-CNS increased in frequency. Immunocytochemical techniques were applied to pathological material. Fifteen cases were B cell with mononuclear surface immunoglobulin. None were T cell. Non-staining material reflected the difficulties inherent in evaluating paraffin-embedded tissue. For the pathologist, NHL-CNS can be a difficult diagnosis. Various monoclonal, peripheral, and B cell clones may present with clinical and CT features indistinguishable from NHL-CNS and may share notable responsiveness to corticosteroids. The perivascular lymphohistiocytic infiltrates of benign and malignant origin may appear benign and separable only after stains for myelin, Tu1, or lymphocyte surface markers. Similar techniques may be applied to cytotoxic samples of cerebrospinal fluid. Whole-slide material was not a prerequisite. Histologic techniques allow separation into Intermediate grade NHL-CNS (small cleaved, large cleaved) and High grade NHL-CNS (small non-cleaved, large non-cleaved, immunoblastic). Patients with Intermediate grade survive 60-90 months (mean); those with High grade tumor survive 24 months.
SURGERY OF CENTRAL NERVOUS SYSTEM LYMPHOMAS.

J.A. Medwedjew, Leningrad, USSR

PRELIMINARY RESULTS WITH SYSTEMIC HIGH-DOSE ARA-C CONSOLIDATION IN PATIENTS WITH ALL OR LYMPHOBLASTIC NHL IN FIRST OR SUBSEQUENT REMISSION: A NEW ALTERNATIVE FOR CNS LEUKEMIC PROPHYLAXIS?

R. Hillewa and W.C. Patera. Division of Hematology, Dept. of Medicine, Leiden University Medical Center, Leiden, The Netherlands.

Prophylaxis of central nervous system leukemia in adult patients has been performed with peri(sic) intrathecal methotrexate (MTX) or MTH combined with splenic irradiation. Systemic administration of increased doses of cytosine arabinoside (ara-C) have been shown to result in high levels of the drug in the cerebrospinal fluid.

From August 1983 to March 1986 we investigated the effect of consolidation therapy with high dose ara-C in 20 consecutive patients with bad risk acute lymphoblastic leukemia or T-cell lymphoblastic Non-Hodgkin's lymphoma (stage IV) in first or subsequent remission. One of them had CNS leukemia at diagnosis. The median age of the patients was 22 (range 15-50).

All patients received induction treatment: vincristine 1.4mg/m² d1-3, Adriamycin 25mg/m² d1-3, Prednisone 60mg/m² d1-21, Ara-C 1000mg/m² by 2h Infusion every 12h for 12 doses d1-14, and intrathecal MTX 10mg/m² on day 1. After achievement of a complete remission, 1-3 consolidation cycles of high dose ara-C (1g/m² by 2h Infusion every 12h for 8 doses on days 1-4) combined with Adriamycin or t-AMSA (11mg/m²) on day 5 and intrathecal MTX on day 1, were given. This consolidation treatment was administered within a weeks after achievement of the remission. Fourteen patients received one cycle, 3 patients 2 cycles and 1 patient 3 cycles. No maintenance treatment was given.

Toxicities included nausea and vomiting, diarrhea, fever, skin and ocular toxicity and interstitial pneumonitis.

The median duration of neutropenia (<0.5x10³/L) was 27 days and 39 days for the remission induction and consolidation treatment, respectively.

One patient died during consolidation due to sepsis. As of April 1986, only 3 patients had a relapse in the bone marrow at 4, 6 and 8 months after achieving remission. The remaining 17 patients are alive in complete remission from 9 to 37+ months (median follow-up: 18 months).

Our preliminary data on brief high-dose ara-C consolidation without maintenance therapy of patients with acute lymphoblastic leukemia or stage IV lymphoblastic non-Hodgkin's lymphoma in first or subsequent remission suggest prolonged remission duration without an increase in CNS relapses.

NEUROPATHOLOGY OF LYMPHOMAS AND LEUKAEMIAS.

H.G. Gerlach, Halle, GDR
Late in 1984, the Surgeon General of the United States Public Health Service, C. Everett Koop, M.D., introduced a call for a "Smoke-Free Society By The Year 2000".

This unparalleled challenge has captured the interest and support of anti-smoking leaders and organizations in the U.S., and has provided a new focus and direction for the bringing together of all segments of society in the pursuit of the common goal of smoking control.

This paper will attempt to highlight some of the major activities, early progress and problems related to this 15-year initiative in the various major areas of smoking control, and to make some projections for the future.
The purpose of this project was to establish the feasibility of implementing a self-help smoking cessation program for the largest employee group (n=8,000) in Alabama. This project used a 2x2 randomized factorial pre-test/post-test control group design to evaluate effectiveness of the cessation interventions. Of the estimated 2000 smoking employees at this site, over 400 smokers were recruited. A baseline smoking history and saliva thiocyanate (SCN) was collected from each participant. Employees were randomly assigned to one of four groups: one group received a standard self-help smoking cessation manual and maintenance manual (Group #1). Group #2 received the two manuals plus a health education skills intervention emphasizing social support and written contract. Group #2 also received only the special skill instruction. Group #3 received the manuals plus a monetary reinforcement at 6-weeks and 6-months after quitting. Group #4 received all three interventions: manuals + skills training + monetary incentive. At 6 weeks, 6 months and 12 months, all participants were followed-up and SCN obtained. Results at 6-weeks, 6-months, and 12-months indicate Group #2 was most successful in quitting. Monetary reinforcement had no effect on quit rate for Group #3 or #4. Behavioral impact and cost effective data will be reported for 400 employees.
In 1983, the Fifth World Conference on Smoking and Health highlighted the emerging problem of smoking among women. Scientific evidence shows that in most industrialised nations, the prevalence of cigarette smoking among men is declining more rapidly than among women. Of particular concern is the level of smoking among teenage girls. In developing countries, the prevalence of female smoking is generally lower, but the tobacco industry has recognised the market potential of women, and is beginning to introduce aggressive promotional campaigns directed specifically towards women. Smoking is dangerous to women's health, causing especially lung and other cancers, chronic obstructive lung disease and cardiac and circulatory disorders. In addition, smoking adversely affects reproductive function, causing complications in pregnancy that affect both mother and foetus. Women who smoke and take the oral contraceptive pill face an increased mortality. Smoking also has an effect upon the menopause. There is some evidence that women may smoke for different reasons than do men. Women find it especially difficult to give up smoking once they have begun the habit. Health professionals have traditionally placed greater emphasis on male smokers, but there is an urgent need to address the issues of smoking in women.
U-31: UFT — A NEW ANTICANCER TREATMENT

2267 CANCER CHEMOTHERAPY OF 5-FUOROURACIL AND ITS DERIVATIVES. S. Fujii, Emeritus Professor of Osaka Univ., Osaka, Japan

1-(2-Tetrahydrofuryl)-5-fluorouracil (FT-207) has been proved to be useful in chemotheraphy of cancer by oral administration. We have been making every effort to enhance the antitumor activity of FT-207 and finally are successful in this purpose by the combination of FT-207 and uracil. It was found that the antitumor activity of FT-207 on carcino-180 and AK-130 tumor was enhanced by oral administration of uracil, deoxyuridine, uridine, thymine, thymidine or cytosine. Uracil had more effect than other pyrimidines in enhancing antitumor effect of these drugs to FT-207 without toxicity. This enhancement of the antitumor activity of FT-207 increased with the dose of uracil. Concentration of 5-FU in the tumor and blood of AK-130-bearing rats after oral administration of clinical doses of FT-207 and uracil was examined. On oral administration of FT-207 plus uracil in various combinations, the concentration of 5-FU in the tumor to that in blood value was obtained at ratio of uracil to FT-207 of 4 (UFT). To clarify these observations we performed an enzymatic study on the metabolic processes of 5-FU and uracil. It was found that 5-FU was mainly phosphorylated in the tumor cell, whereas it was mainly degraded in the liver. Degradation of 5-FU in vitro was inhibited by uracil. Phosphorylation of 5-FU, however, was not inhibited by uracil even 100 times the concentration of uracil. The relationship between the antitumor activity and inhibition of thymidylate synthase after oral administration of 5-FU, FT-207 or UFT was examined. The extent of inhibition of thymidylate synthase was almost parallel to that of inhibition of tumor growth.

2269 PHASE II CLINICAL TRIAL IN SEVERAL SOLID TUMORS IN SPAIN

Jordi Estape Rodriguez, Univ. of Barcelona, Barcelona, Spain

We have administered UFT to 175 outpatients with several types of cancer: breast, colon-rectum, gastric and others.

The best results in this trial were found in breast cancer, specially in some inflammatory forms of it. Incidence of toxicity was low and reversible in most of the patients.

According to the results obtained, it is very interesting to explore the utility of UFT in further trials under various treatment regimens.

2268 PHASE I AND I STUDY OF UFT COMBINED WITH URACIL AND FUROTAFUL FOR MALIGNANT DISEASE. Results of UFT Study Group. K. Ota, Aichi Cancer Ctr., Nagoya, Japan

UFT is newly developed drug containing uracil and furotaful at the ratio of 4:1, and has been shown to have higher 5-FU level in the tumor tissue than the blood or normal tissue because of its selectively prevented degradation of 5-FU in the tumor tissue by uracil.

The phase I study consisted of single-dose and consecutive oral administration of UFT. Bone starting G.I. toxicity was G.I. toxicity such as nausea, vomiting and diarrhea. MTD in the single-dose trial was 1,200 mg/body or more and MTD in the consecutive administration was 600 mg/day divided 2 or 3 times.

Phase II study of UFT was conducted using 300-600 mg of UFT p.o. daily, which was equivalent to the dosage of furotaful contained in the UFT. The response was achieved in 26% of 188 patients with carcinoma of the stomach, 25% of 16 pancreas, 25% of 17 gall bladder and bile duct, 19% of 26 liver, 25% of 56 colorectum, 57% of 50 breast, and 7% of 43 lung. Overall response rate was 25% of 438 cancer patients. Duration of response was 38 weeks for CR patients and 12 weeks for PR patients with overall cancer. Response was achieved in 27% of patients without prior chemotherapy and 25% with prior chemotherapy and 24% of patients treated with fluorinated pyrimidines. Side effect of 551 patients was no folate-reversal in 24%, nausea and vomiting in 13%, diarrhea in 11%, pigmentation in 5%, drug eruption in 2%, psycho-neurotic signs in 2%, general malaise in 6%, leucocytopenia in 4%, and thrombocytopenia in 2%. In the historical control study of the same institutions using same evaluation criteria the response rate of UFT using 300-600 mg was significantly higher (26% of 127 cases) than that of furotaful using 800-1200 mg (16% of 110 cases). Concerning the side effect G.I. toxicity and psycho-neurotic toxicity were significantly less in UFT than furotaful. In summary, if the generally accepted dosage was used in the both drugs UFT has significantly more efficacy and less side effect than furotaful. Thus, UFT seems to be more useful than furotaful on the point of efficacy and side effect.

2270 COMBINATION CHEMOTHERAPY FOR GASTRIC CANCER WITH UFT AND MITOMYCIN C (PART II)-BASE ON TUMOR-SELECTIVE TOXICITY OF FLUOROPYRIMIDINES IN MAN. S. Suga, K. Ina, T. Matsuyama, T. Okita, K. Kimura, Dept Internal Med. Ncli. Nagoya Hospital, Nagak-ku, Nagoya, 460 Japan

Recent advances in chemotherapy for gastric cancer have been achieved on the basis of the pharmacokinetic observations of anticancer agents, especially fluoropyrimidines. Moreover, combination of anticancer drugs of different types of mode of action, such as mitomycin C and fluoropyrimidines, have been investigated to enhance the antitumor effect with less toxicity.

In a previous paper, it was demonstrated that the uracil (U)-leucovorin (FT) combination with a FT ratio of 4(UFT) could produce an effective 5-FU level in tumor tissues of cancer patients, indicating the possibility of better clinical responses. Therefore, it became increasingly evident that UFT (combination of UFT and mitomycin C) chemotherapy, daily oral administration of UFT at a dose of 200 mg/m² twice a day in combination with mitomycin C which was administered i.v. once a week at a dose of 4.0-5.5 mg/m², is one of the most recommendable effective and less toxic types of chemotherapy for gastric cancer and other neoplasms.

UFT chemotherapy was conducted to all 54 patients with advanced gastric cancer (26 of Borrmann type 1, 2, and 26 of Borrmann type 4 gastric cancer). As a result, thirteen out of 28(46.4%) patients with Borrmann type 1, 2 and 3 advanced gastric cancer achieved an objective tumor response. Objective responses occurred in eighteen out of 26 patients with Borrmann type 4 diffuse invasive gastric cancer, the response rate being 69.2%. Overall, UFT chemotherapy produced useful regression of disease in 51 out of 54(67.4%) patients with advanced gastric cancer.

Further investigations are on going to improve the clinical result. First the basis of tumor-selective toxicity of fluoropyrimidines was demonstrated, which represented the characteristic feature of fluoropyrimidine metabolism in patients with gastric cancer.
UFT, a new combination of uracil(U) and tegafur(FT) in a molar ratio of 4:1, has been demonstrated to show higher concentration and longer retention of 5-FU in various tumor tissues compared to those in normal tissue. High activity of thymidine phosphorylase in tumor tissues is a suggestive explanation of this phenomenon.

In this paper, results of a phase II study of UFT on patients with far-advanced renal cell carcinoma is presented. Forty-one patients were entered into the protocol from 19 institutions of the group.

The uterine cervical cancer was clinically evaluable in 25 patients according to the response criteria proposed by the Koyama-Saito group. Seven were not eligible and 9 were cases of protocol violation.

Complete response(CR) and partial response(PR) were observed in 2 and 5 patients, respectively. One patient showed minor response, 8 stable disease and 9 progressive disease. It took about 22 wks and 16 wks to obtain CR and PR, respectively. Lung metastasis was most favorable lesion of this treatment. Twenty-one patients were the cases for the evaluation of adverse reaction of the drug.

The gastrointestinal toxicity such as anorexia, nausea and vomiting, was observed most frequently, while bone marrow depression was minimal. Only three patients were discontinued the administration of the drug owing to the adverse effects.

In conclusion, UFT is one of the most effective drugs for the treatment of far-advanced renal cell carcinoma.

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In conclusion, UFT is one of the most effective drugs for the treatment of far-advanced renal cell carcinoma.
The author used this mode of plasty success-fully In 21 cases.

The pectoralis flap is an excellent tool for reconstruction of the soft palate to help her deglutition of the middle ear is presented. The patient died one year later of metastases. A second case the surgery of a T^N,M- squamous cancer of the tonsillar region, the upper exopharyngeal portion having been isolated by blunt dissection. The operation is completed with a pharyngo-pleuro-esophageal anastomosis.

A video-recording of a successful excision was performed during the last 12 years. The following techniques are illustrated: 1. Subpectoral silicon prosthesis for volume replacement 2. Thoraco-epigastric axial flap for volume replacement and skin intercalation 3. Latissimus dorsi musculocutaneous flap for volume, skin and muscle replacement 4. Rectus abdominis musculocutaneous flap for volume and skin replacement 5. Nipple and areola reconstruction 6. Second breast correction.

Guidelines for technique selection are discussed: mammary gland volume is nearly always replaced by a silicone implant; skin and muscle layer are replaced with the most suitable musculo-cutaneous flap among those described; areola is usually reconstructed with a skin graft from the inner aspect of the upper thigh, and the nipple with a graft from the other nipple or with local skin flaps. In order to achieve a good symmetry, the shape of the opposite breast may be corrected by a mastoplastic operation.

A second case the surgical T, N, M0 squamous cancer of the tonsil region. The surgery consisted of the radical neck mandibular resection along with this of the pharyngeal wall, tonsillar region and soft palate. The ensuing tissue-loss was reconstructed by a pectoralis major myocutaneous flap. An uneventful recovery followed. The patient was thereafter fitted with a soft illiac prostheser for the soft palate to help her deplutition and speech. The patient died one year later of metastases. As a second case the surgery of a T, N, M0 squamous cancer of the middle ear is presented. The base of the skull was approached via the tempo-parietal craniectomy. The tumour invaded a part of the middle fossa dura which was resected in continuity along with a subtotal temporal bone resection parotidectomy, extirpation of the auricle with the surrounding soft parts and resection of the mandibular ranaus. The dura was thereafter patch-grafted with a piece of fascia lata and the big defect reduced with the use of a pectoralis flap. An uneventful recovery followed. The patient is alive one and a half year after the surgery and free of tumour.

The pectoralis major myocutaneous flap is an excellent tool for reconstruction of various big tissue defects caused by extensive resection of head and neck cancers. The author used this mode of plasty successfully in 21 cases.
The different techniques of gastoplasty replacement after total or partial esophagectomy for cancer are presented on this tape. These include isoperistaltic gastric tube along the greater curvature, subtotal stomach replacement according to Akiyama's technique or total stomach replacement. The surgical anatomy of the stomach and the expected level of the anastomosis after esophageal resection are the main factors determining the best procedure for each individual patient. The risk of nodal metastases along the lesser curvature of the stomach is also a determinant in gastric tailoring: total stomach is only possible when this risk is negligible, as for cancer of cervical esophagus. The use of a gastric tube prevents the adverse effects of whole stomach replacement: mediastinal compression, serious gastroesophageal reflux and dyspepsia. The main drawback of a gastric tube is its blood supply, which relies completely on the right gastroepiploic artery, and only in 20% of cases on the left gastroepiploic vessels (when there is an anastomotic connection). All these considerations make isoperistaltic gastric tube the procedure of choice for subtotal or partial esophagectomy. The easiest and most reliable procedure appears to be subtotal stomach.

Transurethral cryo-cautery is a well usable palliative surgical method in the treatment of the prostatic tumours. This method involves freezing of the appropriate tissue followed immediately by local heating thus leading to the bursting of the cells. The authors had an 81% success rate from 578 cases. All the patients in this series belonged to the so called "high risk" group and had total retention of urine. Success in these patients meant the disappearance of residual urine. However, the disadvantage of this procedure is difficulty to regulate the frozen areas, which can result in insufficient cryonecrosis of the prostate, or the injuries of the surrounding tissues.

Since 1983 the authors adopting the transrectal ultrasonography for the control of cryo-cautery effect during the process. By this method can also be used to observe the position of the probe during the operation. The procedure is relatively simple, non invasive and accurate in determining the ice ball expansion in the tissue of the prostate, making cryo-cautery an effective and safer method.

In this video-presentation the authors are presenting the procedure.

Tumors located in the pelvis with lateral fixation present difficulty in their resection through the customary abdominal incisions due to lack of exposure. Those in the iliac fossa have been treated usually with hemipelvectomy while those in the lesser pelvis with fixation are often called unresectable. The abdominoinguinal incision involves a lower midline abdominal incision which is then extended horizontally over the pubic crest to the middle of the inguinal ligament on the side of fixation and then vertically in the femoral triangle. The femoral vessels are exposed and vessel loops passed around them. The ipsilateral rectus is divided near the pubic crest and the inguinal ligament divided at the insertion to the pubic tubercle. The inferior epigastric vessels are then ligated and divided near their origin and the lateral third of the inguinal ligament dissected off the iliac fascia. This allows complete mobilization of the lower abdominal wall on the side of fixation and complete exposure of this side of the pelvis with continuous exposure and access to the iliac and femoral vessels.

In this video these cases are presented. One is that of a patient with malignant fibrohistiocytoma in the right iliac fossa considered unresectable elsewhere and treated by radiation. The second patient had a large liposarcoma occupying the lower abdomen and pelvis. This was called unresectable on two exploratory laparotomies and was treated with chemotherapy and radiation. The third patient had a recurrent chondrosarcoma in the pelvis, considered unresectable and treated with radiation. It involved the lower abdominal wall and right pubic bone. Our experience with this technique involving 25 patients with a variety of tumors is discussed.
STUDIES ON 1500 CASES OF "EARLY" GASTRIC CARCINOMA

Over the past 32 years at the Cancer Institute Hospital, 7544 gastric carcinomas were operated on and they comprised 1520 cases of "early" gastric carcinoma, macroscopic classification, lymph node metastasis, and presenting symptoms were analyzed on 1000 cases of single early gastric carcinoma.

Macroscopically Ila depressed type was most frequent (64.4%), followed by Iic+IIIb mixed type (9.0%) and Ilb+Iic mixed type (16.4%) and I & Ha elevated type (24.7%), I & IIa elevated type (18.4%) and Ila+IIc mixed type (9.0%). Lymph node metastasis was found in 12.7% of all more frequent with the elevated type (20.9%) than with the depressed type (9.9%). Patients with depressed type were more often asymptomatic than those with elevated one.

18.9% of all was found asymptomatically by mass survey. Their early detection has been accelerated by the aid of double contrast, gastric fiberscope, and mass survey.

These strategy contributed a lot to a marked improvement in 5 year survival rate (93.8%), compared to advanced cancer cases.

A REVIEW OF 36 CASES OF EARLY GASTRIC CANCER

Percival P., Beretta S., Tomassetti P., Peracchi T., De Sella P. - Division of Surgical Oncology - Instituto Naz. male per la Ricerca sul Cancro, Genova, Italy.

This report analyzes 36 cases of early gastric cancer observed in a retrospective manner. Male/F. ratio was 2.7/1; mean age was 60.7 ± 12.1 years. Pathological findings according to the Japanese classes was: t. I 22 cases, t. IIB 7 cases, t. IIC 8 cases, t. III 10 cases, t. IIb/Iic 7 cases, t. IIb/III 3 cases, t. IIb/IIa 4 cases, t. IIb/Iic 4 cases and t. IIIc and IIIB (double simultaneous location) 2 cases. 21 subjects had tumor located in the mucosal layer while 15 subjects had a spreading of the tumor to the sub mucosal layer. In 7 subjects lymph-node metastasis was found (m+). All subjects were operated by sub total distal gastrectomy and lymph-node dissection. Recovery from surgery was normal in all the subjects. 3 pts. died after 3.4 years from surgery without symptoms related to cancer recurrency. 5 years survival rate of patients operated before 1980 was 80%; actual 5 and 10 years survival curve indicated a 5% and 24% life expectancy respectively.

Some conclusions may be reached:
1) previous or concomitant peptic ulcer disease may show a temporo disease of EC and does not interfere with the prognosis of the disease itself;
2) the presence of lymph-node cancer involvement does not interfere with the prognosis of the disease;
3) sub total partial gastrectomy + lymph-node radical dissection guarantees for satisfactory clinical results.

SUPERFICIAL SPREADING EARLY CARCINOMA OF THE STOMACH. H. Gollub, Dept. of Pathology, Cancer Inst. Hosp., TOKYO 170 JAPAN

In order to clarify the clinical significance of "early" gastric carcinoma, microscopic classification, lymph node metastasis, and presenting symptoms were analyzed on 1000 cases of single early gastric carcinoma.

The stomach. H. Gollub, Dept. of Pathology.

Macroscopically IIC depressed type was most frequent (22.7%), I & IIa elevated type (18.4%) and Ila+IIc mixed type (9.0%). Lymph node metastasis was found in 12.7% of all more frequent with the elevated type (20.9%) than with the depressed type (9.9%). Patients with depressed type were more often asymptomatic than those with elevated one.

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SUPERFICIAL SPREADING EARLY CARCINOMA


Over the past 32 years at the Cancer Institute Hospital, 7544 gastric carcinomas were operated on and they comprised 1520 cases of "early" gastric carcinoma, whose invasion was limited to the mucosa or included the submucosa, these cases consists of 1273 cases of single, 204 cases of multiple, and 43 cases of double cancer of stomach and other organ.

In order to clarify the clinical significance of "early" gastric carcinoma, microscopic classification, lymph node metastasis, and presenting symptoms were analyzed on 1000 cases of single early gastric carcinoma.

Macroscopically IIC depressed type was most frequent (64.4%), followed by Iic+IIIc mixed type (9.0%) and Ilb+Iic mixed type (16.4%) and I & Ha elevated type (24.7%), I & IIa elevated type (18.4%) and Ila+IIc mixed type (9.0%). Lymph node metastasis was found in 12.7% of all more frequent with the elevated type (20.9%) than with the depressed type (9.9%). Patients with depressed type were more often asymptomatic than those with elevated one.

18.9% of all was found asymptomatically by mass survey. Their early detection has been accelerated by the aid of double contrast, gastric fiberscope, and mass survey.

These strategy contributed a lot to a marked improvement in 5 year survival rate (93.8%), compared to advanced cancer cases.

GROWING MODE OF THE GASTRIC MICROCARCINOMA

In incipient phase of cancer development

Shinohara, M., Nakamura, K., & Kikuchi, M. (Dephth. of Pathology, Inst. Basic Med. Science, Teikoku Univ., Ibaraki, JAPAN)

Gastric microcarcinoma in incipient phase of the cancer development has been studied with 55 microcarcinomas measuring less than 5 mm in diameter. In the 35 cases of microcarcinomas, 22 were histologically undifferentiated adenocarcinoma, 7 were tubular adenocarcinoma, mucocellular or anaplastic adenocarcinoma and the remaining 33 were differentiated adenocarcinoma, tubular adenocarcinoma. These microcarcinomas were histologically examined on the following five findings: 1) Atrophy of the gastric glands just below the microcarcinoma. 2) Erosion at the surface of the microcarcinoma. 3) Size of the microcarcinoma measuring less than 2 mm in the largest diameter. 4) Microcarcinoma occupying the whole mucosa in thickness. 5) Microcarcinoma invading the submucosa.

Conclusion:
1) The undifferentiated carcinoma having arisen from the neck portion of the ordinary gastric mucosa spreads to the propria mucosa around the neck portion of the glands. The pre-existing glands just below the microcarcinoma atrophy, with increasing size of the microcarcinoma, and the superficial surface of mucosa exposed with cancer cells is depressed with erosion. Then, the size of the microcarcinoma increases with the lapse of time, and it occupies the whole mucosa. Some of the microcarcinoma measuring about 5 mm in diameter shows the pre-existing glands and formation of new glands, just like budding out. Then, the differentiated carcinoma shows a depression with erosion and the size increases, with the lapse of time. Some of the differentiated microcarcinomas invade rarely the submucosa.

Two thousand five hundred and forty-seven stomachs surgically resected in The Center for Adult Diseases, Osaka, were histologically examined. Heterotropic glands were found diffusely in the submucosal layer of 102 stomachs (4.0%). One hundred of these cases (98%) had concomitant gastric cancer, and 33 cases (32%) had multiple cancers. Most of the heterotropic glands consisted of mucous cells. Erosion, regenerated epithelium and erosive dysplastic lesions were frequently observed in their gastric mucosa. No findings indicated that heterotropic glands transform into carcinoma. It is suggested that repeated erosion and regeneration of the gastric mucosa may cause both submucosal heterotropic glands and carcinoma of the stomach.

CLINICAL PROBLEMS IN THE TREATMENT OF EARLY GASTRIC CANCER. T. Hattori***, and B. Helpap**, Dept. of Pathology, Fukui Medical Sch., Japan*, and Inst. of Pathology, Singen, FRG**.

Gastric cancers are thought to have a relatively long history, until they develop to clinically detectable early gastric cancers. However, little was known as to the growth kinetics of incipient and early cancers. This study was undertaken to define a growth rate of early gastric cancers by an experimental model.

Gastric cancers were induced in 100 inbred Wistar rats by oral administration of N-methyl-N-nitro-N-nitrosoguanidine for 25 w. A microscopic cancer was found by 24 w and a macroscopic cancer was found after 27 w of the treatment. All the cancers were a single lesion located at the midpoint of the lesser curvature. Histologically, they were tubular adenocarcinomas. The mucosal changes predisposing to the development of the tumors were erosion and degenerative hyperplasia, followed by dysplastic change. The malignant transformation appeared to occur by 16 w after the carcinogen treatment. By observing the temporal changes of the tumor volumes, it was shown that the gastric cancers in incipient stages underwent an exponential growth with a doubling time of 14 days. This indicates that it takes about 1 year for the cancer to develop to the early cancer of 0.2 cm in diameter. 3H-thymidine autoradiographic study showed that the generation time of the tumor cells was an average of 3.5 days. The difference between the speeds of cell proliferation and tumor growth may imply that cell loss occurred in incipient cancers even in an earliest stage of growth.


MISTOGENESIS OF ADENOCARCINOMA DEVELOPING IN CHEMICALLY INDUCED CANINE GASTRIC CANCER SERUM

The development of canine gastric cancer was valuable as a model for human gastric cancer and was applied to the same type of human gastric cancer and was applied to the same type of human gastric cancer. The canine gastric cancer was valuable as a model for human gastric cancer.
2294  
Classification system of gastric carcinomas has been established by aid of a computer assisted method. By multivariate analysis was revealed that histoarchitecture of gastric carcinoma is a hierarchic system in which the structure of the carcinoma cell represents the first order and determines basic type of carcinoma, thus hypotheses concerning pathogenesis of gastric cancer (Segawa 1961, Correa 1975) are proved mathematically, two basic cell types were found: Polyedric cell and hyperchromatic round cell. The first appears to be responsible for cohesive behavior of cancer cell, the latter one for non-cohesion. According to to two basic types of cancer are discriminated: Type A and Type B which are different in their histogenetic origin also. These calculated types are identical with intestinal and diffuse type according to Lauren (1965). Thus, the first mathematical evidence of Lauren classification was possible. These results suggest that empirically found types can be calculated and computer assisted procedures concerning the examination of histoarchitecture of malignant tumors can successfully applied.

A-50: PATHOLOGY OF EARLY GASTRIC CANCER

2295  
INCREASE OF CIRCULATING SECRETORY COMPONENT (SC) IN COLORECTAL CARCINOMA IS DUE TO LIVER METASTASIS, NOT TO RELEASE OF SC FROM THE TUMORS. P. Kristo, T. D. Nordal and P. Brandberg, Inst. of Pathology and Inst. of Forensic Medicine, The National Hospital, Rikshospitalet, Oslo, Norway.  
SC is a receptor on intestinal epithelial cells which facilitates the transport of polymeric IgA and IgM into exocrine fluid. SC is often expressed in adenocarcinomas and corresponding metastasis. Release of SC from such tumors to blood may enhance the levels of circulating secretory IgA (SIgA) and SIgM. The aim of this study was to compare different secretory components in colon tumors with levels of serum SC by measuring SIgA and SIgM in an ELISA. Preoperatively sera from 180 patients with large bowel carcinoma were examined together with 71 matched controls. The tumors were classified anesclenopathologically into Dukes' stage A, B, C or D (D assigning distant organ metastasis or irreparable tumor); GIy immunohistochemical evaluation of SC expression; flow cytometry into a diploid or an aneuploid group; glycoprotein 50 levels. Only patients with stage D (n=17) had significantly elevated values of SIgA and SIgM in serum (p<0.004). The combined sensitivity of SC and CEA in serum for stage D was 0.94. Two stage D patients did not have liver metastasis, and both had normal values. Altogether 67% and 53% of patients with liver involvement had elevated levels of SIgA & SIgM, respectively. There were no correlation between serum SC and tumor volume, serum SC and tumor volume, tumor volume or tumor ploidy. Thus, elevation of SIgA in serum from these patients is not caused by SC release from the colorectal tumor, but is probably explained by disturbance of liver function due to the liver metastasis. (Supported by the Norwegian Cancer Society and Nansen's Fund.)

A-51: PATHOLOGY OF COLORECTAL CANCER

2296  
In the Department of Clinical Pathology, Central Hospital, Aarhus, Denmark.

It has been already reported that plasma of the localization of CEA in colorectal tumor cells is related with the degree of the tumor differentiation: the less differentiated tumors in which it is localised predominantly along the apical surface of the carcinoma gland and in the extracellular matrix, whereas plasma in which CEA is located in the surrounding stroma of cancer cells. An immunoperoxidase technique was utilized for the detection of CEA. Tissue samples were collected from the different types of colorectal cancer: Type I cell (subtype A, B, C, D) showed a low (less than 1%) cell distribution of CEA, whereas the situation in Type II cell was almost the same as I cell group. Thus, the type of the carcinoma cells and the localization of CEA within the former stroma type were statistically different from that in the latter type. The localization of CEA in the stroma type of Type II cell was almost the same as I cell group. Thus, the type of the carcinoma cells and the localization of CEA within the former stroma type were statistically different from that in the latter type.
The high frequency of the carcinomas of the large intestine makes the research of the malignant potential of benign epithelial tumors quite necessary. The authors give complex morphological histochecmical and electron microscopic criteria for evaluation of the dysplastic changes in the benign tumors of the large intestine. It is established a higher degree of dysplasia in villous polyps and in the villous component of the mixed polyps; a reduction of the morphological signs of the functional activity of the columnar epithelium with variation of the histochecmical characteristics of the mucous secretion. Increase in number of goblet cells in the polyps with dysplasia grade III is found also.

60 cases of colorectal carcinoma were classified 16 cases of Dukes A, 23 of Dukes B, 15 of Dukes C and 6 of modified Dukes D. Cancer cells, isolated from paraffin-embedded section, were stained by Azocarmin-G-Acriflavin-Teulgen or DAP I and fluorocytometric measurement of cell nuclear DNA content was performed. DNA distribution patterns among 4 groups of tumor stage was compared with respect to modal peak, mean DNA value, variance, percentage of cells above 4C (6Cg). As a result, mean value of all these parameters showed increase in order from Dukes A to D. Statistical analysis revealed no significant difference between Dukes A and B in all parameters, significant difference between Dukes B and C in all but modal peak and 6C% (p<0.05) and significant difference between Dukes C and D in all but 6C% (p<0.05). 2 cases which were classified Dukes B, but that revealed DNA distribution pattern like Dukes C or D were found to show metastasis to liver or lung after 6 and 11 months respectively. These results showed a correlation of cell nuclear DNA distribution pattern with degree of extent of growth in colorectal carcinoma. And, DNA distribution pattern may complement conventional clinicopathological diagnosis in detecting occult metastasis.
A-51: PATHOLOGY OF COLORECTAL CANCER

A. K. Jancso, L. Kovacs, M. Bojar and J. Y. K.
Central Hospital of Railway and Polyclinic and Institute of Public Health of Railway, Budapest, Hungary

Serial determination in serum are well in direction of chemotherapy or second look operations of patients with colorectal cancer. However, these may be very low in some type of colorectal neoplasms and therefore there is a resistance to sero testing as well as other clinical findings. The question remains to be answered: is there a way to improve the sero testing using peroxidase alkaline phosphatase/CEA method? Three types of CEA localization was demonstrated in conventionally processed 50 colorectal cancer tissues. Only two types of these were associated with elevated plasma CEA values in patients having no distant metastases. Using iron diamine, amin blue pH 2.5 and alcian blue 0.2 M sodium borohydride, reation and reations showed that large areas of diffuse and infiltrating tumors generally demonstrated with CEA appearance in great quantities among the two pre-cursors are independent. In term of EA level, there may be very low level. Only differentiated colorectal carcinomas and well-differentiated neuroblastoma as well as important to test determine. In term of EA level, there may be used in those patients known to produce EA, results in an increase in the sensitivity of the test. Insulin and insulin-like hormone of these patients may appear to be a necessary pre-condition for the determination of serum EA determination.
2307 PROGNOSTIC VALUE OF NUCLEAR DNA-CONTENT ANALYSIS IN NON-HODGKIN LYMPHOMAS

T.Lehtinen, R.Aune, M.Lehtinen§, OP-Kalliomaki, T.Vainio, T.Tabaka, and K.Laasanen§, from the Departments of Clinical Oncology and Pathology, and Tumor Laboratory, Turku University Central Hospital, § Institute of Biomedical Sciences, University of Turku, Turku, and Department of Pathology, University of Helsinki, Helsinki,Finland.

We have studied nuclear DNA-content of 87 non-Hodgkin lymphomas diagnosed between 1979-1974 in the Turku University Central Hospital. The cases consisted of 43 large, non-cleaved follicular center cell lymphomas and 44 small, non-cleaved lymphomas, 14 of which were Burkitt type (Lukes-Collins classification). Analysis of nuclear DNA-content was done by using a trypsin digestion method followed by flowcytometric analysis. Propidium iodide in the DNA was measured by an EPICS/5 flowcytometer. The trypsin digestion method yielded log x-values (mean 4.54, range 3.1 to 6.0) thus enabling the detection of aneuploid cell populations with a DNA-index as low as 1.1.

Overall, aneuploidy, as defined by abnormal DNA-index, was seen in about 1/3 (27) of the cases. Aneuploidy did not correlate with any of the histological subtypes or growth pattern of the tumour. Surprisingly, 15 out of 14 Burkitt type lymphomas showed aneuploid cells with a low DNA-index (mean 1.16, SD 0.06).

In general, the 5-year survival of the non-Hodgkin lymphoma patients was lower provided they had aneuploidy. Especially, the patients with Burkitt type disease and aneuploidy had considerably more severe prognosis than their counterparts with diploid tumours.

Our results seem to indicate, that flowcytometric analysis of nuclear DNA-content can be useful in predicting the clinical outcome of the non-Hodgkin lymphomas, especially in some histological subtypes.

A-51: PATHOLOGY OF COLORECTAL CANCER

2308 DIAGNOSIS OF PERINEAL RECURRENCES FOLLOWING ABDOMINOPERINEAL EXSTIRPATION WITH PERCUTANEOUS BIOPSY.


In 20-50% of cases perineal recurrences develop following abdominoperineal extirpation, without symptoms for a long time. By the time pain and palpable masses can be observed, it is already late for operation. Up till now there was no suitable method available for its early diagnosis.

In 1983 we introduced the needle aspiration cytology and modified Vanc prostact biopsy for histological examinations. Within a two-year period 20 examinations have been performed in 11 patients (54 cytological and 46 histological). In 22 out of 51 cases perineal recurrence could have been detected.

The method can be safely and simply used therefore highly recommended.

A-52: PATHOLOGY OF LYMPHOMAS II

2309 PROGNOSTIC VALUE OF NUCLEAR DNA-CONTINUOUS ANALYSIS IN NON-HODGKIN LYMPHOMAS

T. Lehtinen, R. Aune, M. Lehtinen§, OP. Kalliomaki, T. Vainio, T. Tabaka, and K. Laasanen§, from the Departments of Clinical Oncology and Pathology, and Tumor Laboratory, Turku University Central Hospital, § Institute of Biomedical Sciences, University of Turku, Turku, and Department of Pathology, University of Helsinki, Helsinki, Finland.

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Our results seem to indicate, that flowcytometric analysis of nuclear DNA-content can be useful in predicting the clinical outcome of the non-Hodgkin lymphomas, especially in some histological subtypes.
2309  CYTOCHEMISTRY IN SOME VARIANTS OF ACUTE LEUKAEMIA (AML)
Klena Nikolaus and Duman, Department of Haematology, Cluj-Napoca, Romania

Some variants of acute non-lymphoblastic leukemia (ANLL) may present diagnostic difficulties (M1,M2,M3,M4,M5). According to morphology and cytochemistry the leukemic cells may be identified. Material from 51 cases of ANLL patients were stained with 7 different cytochemical stains, according to standard methods included: myeloperoxidase (MPO), Sudan Black B (SBB), neutrophilic esterase (NE), acid phosphatase (AP), peroxidase (PO), periodic acid Schiff (PAS) and lysozyme estimations.

The results of this study showed that:
- diagnosis of M1 often requires positive cytochemical evidence (MPO and/or SBB) to demonstrate that the predominant cells are myeloblasts;
- M2 cases showed more readily these characteristics as well as promyelocytic and myelodysplastic differentiation; M3 presented much more diagnostic problems, because the promyelocytic hypergranular acute leukaemia (M3) occurred in two forms: promyelocytic myeloblastic and neutrophilic and is marked by different cytochemical behaviour.

In neutrophilic M3 we found strong activities for NAP, NSE, NBT, chloroacetate esterase and acid phosphatase (AP) in a few of these cases. In a few of these cases, a marked decrease of the examined lymphoid cells in more than 50% was performed in 40 cases. The morphometric analysis expressed by the N.C.L., or Leu-1 negative, as well as the N.C.L. of these patients, was performed in 40 cases. The Morphometric analysis expressed by the N.C.L., or Leu-1 negative, as well as the N.C.L. of these patients, was performed in 40 cases.

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2313 DETECTION IN NORMAL TONSILS OF A CELL POPULATION WITH A BURKITT-LIKE PHENOTYPE. M. Lipinski, B. Calliou, C. Petaud, J. Wiels, A. Rickinson and T. Tursz. Institut Gustave Roussy, Villejuif, France. A monoclonal antibody, 38.13, has been previously shown to detect a Burkitt lymphoma associated antigen (BLA) on Burkitt tumors and cell-lines. BLA is a neutral glycolipid known as globotriaosylceramide (gal α-1-3 gal α-1-4 Glc α-1-1 ceramide). Its accumulation in Burkitt cells is due to an enhanced activity of the UDP-Gal : Lac-Cer α-galactosyl transferase. BLA has not been detected in normal lymphoid organs including bone-marrow, lymph nodes or appendix. In tonsils however, 5-15 % of the cells have been shown to express BLA. Immunohistological staining of semi-thin sections indicate that BLA positive cells have morphological characteristics of centroblasts and are mainly located in follicular centers. Double staining immunofluorescence experiments, analysing with an Epic C cell-sorter using biotinylated 38.13 revealed by avidin-phycocerythrin on one hand and FITC-conjugated antibodies to various B cell surface antigens on the other hand have allowed to define the antigenic phenotype of these Burkitt-like cells. Data presented include expression of BLA as expression of the CALLA, B2, HB4, HB5 antigens, as defined by monoclonal antibodies, and of surface Immunoglobulins. It is postulated that BLA can play the role of a "homing" antigen leading to the specific accumulation of BLA expressing cells in tonsils and that a relationship might exist between this reservoir of Burkitt-like cells and the peculiar clinical presentation of endemic Burkitt lymphoma.

2314 HETEROCHROMIATY OF LYMPHOCYTES ADHERING TO THE HIGH ENDOTHELIAL VENULES, Veronika Kalusz, Zs. Ag, and J. Bajnai-Gealy. Department of Pathology I st and 2 nd Clinic of Medicine, University Medical School, Ede, Hungary. Lymphocytes leave the bloodstream and enter lymph nodes via specialized vascular structures of the paracortex (high endothelial venules, HEV). In this process the first step is the adherence of lymphatic cells to the HEVs. An in vitro adherence test introduced by Stamford and Woodruff (1976) is suitable for studying the homing capacities of lymphocytes: those cells which have migratory capacities in vivo will in cryostat sections of lymph nodes selectively adhere to HEVs. In our experiments we studied the HEV-adherence of lymphocytes from patients with non-Hodgkin's malignant lymphomas and analysed the immunophenotype of adhering cells by monoclonal antibodies. In B-cell chronic lymphocytic leukemia a phenotypically different population of peripheral blood lymphocytes adhere to the HEVs. In contrast to earlier studies, cells which failed to adhere to the HEV, primary cell cultures showed selective adherence.

2315 AUTOMATED IMAGE ANALYSIS OF BLOOD SMEARS OF LEUKEMIC B-CELL NHL's. K.-U. Rudiger, H. Kiewen and K. Rutek, Ctr. Inst. Cancr Res., Berlin-Buch, Dept. Pathol., and Med. Acad. Erfurt, German Democratic Republic. In recent investigations of blood smears of leukaemic low grade malignant NHL's we have shown, that the leukaemic lymphocyte is the cell ranging at first in frequency of different types of leukaemic cells in different subtypes of low grade malignant NHL's. Only the second place in frequency, however, is a cell type typical for the subtype of low malignant NHL's. Using a robotron® BVS A 471 automatic image analysis system the smears of leukaemic low grade malignant NHL's have been additionally analysed comparing several morphometrical and densitometric parameters. The results of this study are presented.

2316 CULTIVATION OF LEUKEMIC CELLS WITH HUMAN PLACENTAL CONDITIONED MEDIUM AS A DIAGNOSTIC TOOL FOR CLASSIFICATION OF LEUKEMIAS. P. Lemaé, Inst. of Haematology and Blood Transfusion, Prague, Czechoslovakia. Leukemic cells from peripheral blood of 18 patients with various types of leukaemias were cultivated in RPMI-1640 medium with 20 % foetal calf serum alone /control cultures/ or supplemented with 20 % human p'acental conditioned medium /HPCM cultures/ for 3-7 days. Numbers of cells from 6/12 patients with acute myeloid leukaemias /AML/ were significantly higher in HPCM cultures in comparison to those of control cultures after 3 days cultivation and in 5/6 studied patients with AMLs after 5-7 days cultivation. Leukemic cells of 16 patients with lymphoid leukaemias //9 acute - ALL, 7 chronic - CLL/ did not exhibit any changes of proliferation or differentiation in HPCM cultures in comparison to control cultures after 3 days cultivation as well as the cells from 6 ALLs and 1 B-CLL after 7 days cultivation. Numbers of leukemic cells from 2/3 patients with acute unclassified leukaemias /AULs/ were significantly higher after 3-7 days cultivation against to those of control cultures. These findings led us to classify these two cases of AULs as AMLs.
2317 ALTERED GLYCOSYATION IN TUMOUR CELLS: AN ANALYSIS BY RADIOIMMUNOHISTOCHEMISTRY L. Fischer, Department of Pathology, University Medical School, Pecs, Hungary

The application of labelled lectins for light and electron microscopic histochemistry allowed the detection of differences in the structure of secreted and carbohydrate-bound glycoproteins (CGP) in cells of various levels of differentiation and malignant transformation. Different types of malignant and normal cell types could be distinguished by their lectin binding pattern. The less differentiated cells often showed a higher affinity to certain lectins than those more differentiated counterparts. Moreover, lectin binding sites, which were found localized to the intermediate actin lattices of normal cells, showed on the surface of tumour cells represent differentiation-dependent antigenic determinants. Antisera raised against lectin affinity purified as can provide further help in the immunohistochemical characterization of acute differentiation-dependent (CGP) determinants. Thus, the application of lectins allows a complex histological, biochemical and immunohistochemical analysis of glycoprotein structures in tumour cells.

2319 IMMUNOELECTRON MICROSCOPIC CHARACTERISTIC OF THE DIFFERENT SUBPOPULATIONS OF THE HUMAN NORMAL AND LEUKEMIC BLOOD LYMPHOCYTES

D.A. Butenko, U.I. Yagovenko, K.P. Gak

N. Elizavetsky Institute for Oncology Problems, Academy of Sciences of Ukrainian SSR, Kiev, USSR

The blood cells of healthy donors, acute lymphoblastic (ALL) and chronic lymphocytic (CLL) leukemia patients were studied by transmission electron microscopy, immunoelectron microscopy using rosette-forming reaction and labelling of the cell surface antigens by the monoclonal antibodies (MoAb): OKT3, OKT4, OKT8, Th, B1, B2 and ultrastructural cytochemistry. Purified lymphocyte populations were obtained on the flow cytoflurometer ("Coulter Epics C", Coultronics) using the corresponding MoAb. The present study permitted to precise the different subpopulations of the blood lymphocytes and variants of CLL and ALL, to show some correlation between immunologic phenotype of normal and leukemic cells and their ultrastructure. These data may be used for characteristic of the predominant leukemic clone and to determine the pathway and degree of differentiation of a pathological cell population.

2318 POSITIVITY PATTERN, A NEW PARAMETER IN THE CYTOCHEMICAL STUDY OF ACUTE NON LYMPHOID LEUKAEMIA.

P.S. Paraskevopoulos, Haematology Laboratory, Thessaloniki Cancer Institute, Thessaloniki, Greece.

The cytological pattern of the blasts cells of 99 cases of ANLL was studied in parallel to the positivity pattern of these cells to the cytochemical reactions. The blasts cells were morphologically classified according to the WHO prototype and cytochemical studies were performed using peroxidase (POX), PAS, non specific neutral (NSE) and acid (AAS) esterase and acid phosphatase (PA).

The study showed that different types of blasts cells in relation to their origin and the degree of differentiation give characteristic positivity pattern specific for the cell type. The exact identification of the blasts cells, helps to define the type of ANLL and constitutes a determination factor in the therapeutic strategy.
2320 INFIDELITY OF DNA SYNTHESIS AS A BASIS OF MUTAGENESIS VIA DEPURINATION. The effect of mutagens on the fidelity of DNA synthesis has been investigated. The concept is that certain agents damage DNA and promote misincorporation during copying by purified DNA polymerases. Factors that promote infidelity include certain divalent metal ions, alterations in nucleotide pools, small alkylating agents, farnesol damage, and depurination. We have focused on depurination as a possible common intermediate in mutagenesis. Depurination leads to increased non-meaningful substitutions when synthetic polynucleotides are copied by purified DNA polymerases. Depurination of S174 and DNA leads to enhanced mutagenesis during in vitro synthesis. Depurinated S174 and DNA is highly mutagenic when translocated (without in vitro synthesis) into Salmonella strains derived from bacteria which were previously exposed to UV light to induce SOS repair. Mutagenesis via depurination is highly specific, deoxyadenosine is predominantly inserted in a single site within a substrate. At physiological pH, DNA after treatment with 8-oxoguanine (8-OH) hydroxylamine is depurinated, and the extent of damage is dependent on the induction of an appropriate enzyme. These results suggest a model in which bulky adducts terminate DNA replication and induce alterations in the DNA replication complex. The altered replicating complex could be moved at the added. Removal of the modified base by spontaneous deamination or by other means leads to cellular responses resulting in mutagenic sites. These sites may be repaired by the altered replicating complex, as in mutations in Escherichia coli. 

2322 DNA-SYNTHESIS IN DIFFERENT Fetal BRAIN REGIONS DAMAGED BY ETHYNITROSOUrea. N. Frank, S. Komps, S. IvankoKiev, Herman Cancer Research Ctr., Inst. of Toxicology and Chemotherapy, Heidelberg, FRG.

If pregnant BD IX rats are treated with ethynitrosourea (ENU) on the 21st day of gestation, 60-70% of the offspring get tumors in the regio hippocampi. No tumors in other sites of the brain are found. Therefore, we studied the influence of ENU on DNA synthesis in different parts of the rat organism. Regio hippocampi, bulbus olfactorius, spleen and liver of the adult animals as well as of the fetuses were isolated and the 3H-d-thymidine incorporation was measured. The results show a difference in proliferation of the fetal bulbus olfactorius and regio hippocampi even in untreated animals. Furthermore, differences in the degree of ENU induced damages as well as in their time course were observed. A comparison with the effects in the adult animals will be given, since adult rats do not develop tumors in the brain with the ENU dose used in our studies.


Antimutagenic agents (ethylnitrosourea (enu), trypcorrino(6H)-dipropionitrotrione), a peptide analog originally isolated from human urine, appear to have antiepitope activity (1). Preliminary studies using small tumoral stages of syngeneic AI indicate that it has low human toxicity and may cause regression of certain tumors. In particular, interest in its therapeutic potential (2). In this study, homogeneous preparations of the antiepithope were evaluated. The results show that enu may A: alter estrogen metabolism; B: interact directly with 11A in a manner similar to intercalating chemotherapeutic agents. When AI was tested for effects on rat uterine growth to determine whether it possessed any estrogenic activity, it was found to be inactive. Similarly, enu did not possess measurable estrogenic activity, nor did it alter the conversion of testosterone to estradiol (estradam) in rat granulosa cells. When examined for interaction with defined polyoxy- nucleteides, enu was found to stimulate certain sequences. DNA thermal denaturation experiments disclosed that poly (Ado)•(dCdc) was moderately stabilized, while dramatic effects were observed for other sequences. Fluorescence spectrometric titrations disclosed, however, that the binding was weak in comparison to strong intercalating agents such as adriamycin and rodamine. The binding in vitro of enu to DNA can be rationalized by the stereochemical observation that enu is a good fit when inserted between base pairs in DNA (1). However, it enu exerts its effects at the genetically active sites. We propose that endogenous protein receptors for enu may exist - a possibility currently under experimental investigation.


The interaction of several DNA intercalating and non-intercalating ellipticine derivatives with DNA-topo- isomerase II purified from calf thymus has been studied in vitro. The reaction rate of decatenation of kinetoplast DNA from Trypanosoma cruzi catalyzed by the enzyme was measured by gel electrophoresis. The extent of inhibition of this reaction by various new ellipticine derivatives was determined and compared to their affinity for DNA. Among the derivatives studied some are highly cytotoxic and antitumoral although they do not intercalate in DNA in vitro. These data provide evidence for a direct interaction of some of these compounds with the enzyme or with the DNA-enzyme complex. Additional evidence for an interaction of the drugs with the complexes was provided by measuring their ability to trap the cleavable complex formed between JHA and the enzyme. The role of DNA intercalation in these phenomena, as well as their relationship with cytotoxic effects are discussed.
MONDAY - AUGUST 25 • AFTERNOON

B-44: GENE II: DNA SYNTHESIS AND DAMAGE


Standard cultures of peripheral blood mononuclear cells from 3 AT patients, 3 AT heterozygotes and 3 control persons were set up. Benzo(a)pyrene (BAP, 2 µM) was added to half of the cultures at 48 h. At harvest (72 h) the numbers of harvested cells were higher in control cultures than in AT cultures (1.5-fold, 0.05) as compared to the increase seen in control cultures (1.6-fold, 0.05) - the difference significant at p < 0.05.

Activity of epoxide hydrolase (EH) was measured in cultures not treated with 3P, using fluorimetric method and BP-4,5-oxide as substrate (Danne et al., Analyt. Biochem., 97, 340, 1979). Activity of EH was increased 2.3-fold in AT homozygotes as compared to control cells. In heterozygotes of AT the effects of BAP on proliferation and ER activity were as follows: activity of EH was found to be in the range of control values. Presumably, superoxide radicals produced in cultures of AT cells after treatment with clastogenic factors (Emerit and Cerutti, PNAS, 78, 1868, 1981) may induce EH. In combination of EH was increased 2.3-fold in AT homozygotes. This increase was greater in AT cultures than in control cultures (2.6-fold, 0.05). This increase was significant at p < 0.05.


It has been shown that 4-hydroxy-lindeine-1-oxide (4HLO), the proximate form of 4Ct), binds covalently to the purine bases of DNA. Four kinds of quinoline-pyrimidine base adducts induced in vivo or in vitro have been identified chromatographically, one adenine adduct (A4) and three quanine adducts (Qa, Qb, and Qc). The structures of A4 and Qa are 3-(N-adenyl)-4HA and N-(quanyl-S-yl)-4HA, respectively.

The effect of 4HLO on supercoiled DNA has been studied, using pBR322 DNA modified with 4HLO in the presence of vinyloxochloroquine. The conversion of the closed circular DNA to open circular DNA was caused by the binding of 20 adducts to one genome. The modified DNA was resistant to cleavage by several restriction enzymes such as Psal and Hpa I, which contain GC in their recognition sequence.

Treatment of the modified DNA with piperidin produced the cleavage of DNA strands. Using 5'-end J2p-labelled fragments of the modified DNA and sequencing gel electrophoresis, we showed that cleavages caused by adducts were occurring at guanine residues but not at adenine residues. Most of the cleavage sites are 5'-GGA- or 5'-GGA- sequence.

The sensitive immunological assay for the detection of the adducts in DNA has been developed. The rabbit antibodies against 4HLO-modified DNA have been used in our experiments. We could detect one adduct per 107 nucleotides by ELISA and visualize in situ the modified DNA in cultured mammalian cells by immunofluorescence staining. These methods may contribute to the study of the formation of adducts and their removal in cells and tissues.


Glutathione S-transferase P (GST-P) is one of the enzymes of well-studied liver type enzymes which conjugates a wide variety of foreign electrophilic ligands, such as chemical carcinogens. This enzyme is induced markedly by hepatocellular carcinomas and hepatocelluar carcinomas and Morris hepatoma but not in AH130 after treatment with 3′MC. Some of the normal tissues, including lung, kidney and placenta, expressed relatively low amounts of GST-P mRNA. Characterization of the genomic clone indicates that the gene is about 2.6 kb long. To facilitate cloning of pseudogenes are also cloned, all of which lack the intron and exon sequences by DNA amplification and characterization of a processed gene. Analysis of the chromatin structures of active and inactive GST-P genes as well as the functional characterization of regulatory sequences are now under way. (Supported by Grant-aid from Ministry of Education, Science and Culture and a grant for Special Project Research, Cancer Biochemistry.)
CHANGES IN SERUM GLYCOPROTEIN LEVELS OF LUNG CANCER PATIENTS

M. Markova, E. Benov, D. Kostadinov
Institute for Pneumological and Phthisiological Science, Medical Academy, Sofia, Bulgaria

Serum glycoproteins were assayed by immunodiffusion techniques in 200 lung cancer patients and 69 healthy subjects. As compared to the latter, cancer patients showed statistically significant decline in prealbumin (0.22 g/l), alpha macroglobulin (2.26 g/l), transferrin (2.51 g/l) and elevation in alpha acid glycoprotein (4.15 g/l), alpha antitrypsin (4.15 g/l) and ceruloplasmin (0.52 g/l) (p 0.001). The serum glycoprotein levels observed were confronted with histologic types of carcinomas. The evidence obtained indicated the immune status of lung cancer patients to undergo changes that, even though relatively unspecified, can play a certain role in differential diagnosis.

B:45: ENZYMES, ISOENZYMES AND MALIGNANT PHENOTYPES

2330 VARIETE FORM OF LEUKOPLAQUE ALGAECUS IN SPATHACE IN CYTODIASES OF ALL TLD IN IYELLYSTAS ON MUCILAGE.

E. Vainshtein, Department of Biophysical Chemistry, Institute of Science, Rehovot, Israel

An enzyme composition, antitoxicitykinetic and physical properties of alkaline phosphatase of lymphocytes and granulocytes of healthy individuals are the same. The phosphatase prepared from malignant lymphoblasts, and from myeloblasts, showed the same enzyme composition. However, they differ from enzymes of normal lymphocytes in the properties investigated. 

2331 ENZYME DEVIATION OF ALKALINE PHOSPHATASE ISOENZYMES DURING THE COURSE OF UTERINE CARCINOGENESIS


The purpose of this histochemical study is to investigate which alkaline phosphatase (Alp) isoenzyme type exist in normal uterine cervix and corpus, to examine how expression of Alp isoenzyme changes during the carcinogenic process in the uterus, and to identify the ultrastructural localization of Alp in the normal uterus and uterine cancer.

Placental Alp (PLAP) is considered to appear only in the placentas in some cancers. However, PLAP was identified with a high rate of frequency in normal cervical reserve cells and columnar cells.}

Specimens were examined by light microscopy using the Alp-dye method and electron microscopy using the lead citrate method with heat inhibition test. The PLAP-positive rate was lower in cervical squamous carcinoma cells and adenocarcinoma cells than in normal reserve cells and columnar cells. On the other hand, the PLAP-positive rate was definitely elevated in endometrial cancer cells in comparison with normal endometrial glandular cells.

These data suggested histochemical changes of Alp isoenzyme during the carcinogenic process in the uterus. Despite the uterus being one organ, different Alp isoenzyme exist in different uterine locations. Ultrastructural localization of Alp isoenzyme is almost the same. Alp activity was effectively visualized on the microvilli and sometimes on the lateral surface.

Furthermore, by treating specimens with saponin, enzyme reaction was successfully observed on the microvilli and sometimes on the lateral surface. The results appeared to be in accordance with the current concept that membrane glycoproteins are formed in the endoplasmic reticulum, modified in the Golgi apparatus and then transported to the cell surface.
2332 BIOCHEMICAL AND IMMUNOLOGIC PROPERTIES OF GALTACTOYLTANSFERASE (GT) FROM THE ASCITES OF OVARIAN CANCER PATIENTS.

K. Chaikawa, H. Obi, T. Katayama, and J. J. Barrett, Roswell Park Memorial Institute, Buffalo, New York, U.S.A.

We have demonstrated that the specific activities of GT in the ovarian tumor homogenates were significantly higher than those from normal ovaries. In ovarian cancer patients, the levels of GT in the sera were also elevated compared to various controls. The serum levels of GT dropped after reduction of tumor mass by surgery, chemotherapy, or radiation, while those levels rose with tumor recurrence, suggesting that GT is a potential tumor marker. Ascitic fluids from ovarian cancer patients are a rich source of GT, from which the enzyme was purified to homogeneity by several steps of affinity chromatography. Purified GT showed a single band in sodium dodecylsulfate polyacrylamide gel electrophoresis, but under non-denaturing conditions, GT was resolved into 2-3 components. By chromatography in combination with isoelectric focusing in the presence of sodium dodecylsulfate, GT can be resolved into 2-3 components (F-1 and F-2). GT, F-1 and F-2, all catalyzed the transfer of galactose from UDP-galactose to alkaline-stable S-S glycolipids, as well as to alkaline-stable S-S glycoproteins. In addition, they catalyzed the S-acetylation of the S-S glycolipids and S-S glycoproteins. Comparative biochemical and immunological studies on the various isoenzymes of GT present in benign and malignant ascitic fluids are underway to identify a putative ascites-associated GT.

2334 PYRUVATE KINASE ISOZYMES: AN ALTERNATIVE AND INSUSCEPTIBLE TO L-CYTOSINE IN NORMAL AND TUMOR CELLS INDUCED BY 5-POLYOMA VIRUS.


Institute of Medical Biochemistry, S. C. Pavlinic, Academy of Medicine, and Institute of Molecular Biology, Jagellonian University, Krakow, Poland.

Previous studies indicated that pyruvate kinase derived from various experimental tumors differs from normal tissue enzymes in the presence of sensitivity to inhibitory action of L-cytosine, which in polyacrylamide gel electrophoresis is connected with a slow migrating isoenzyme of pyruvate kinase. This isozyme has been also found in polyoma tumours transplanted in mice, as well as in polyoma transformed cells cultivated in vitro. The activities of nuclear and cytosolic pyruvate kinase fractions have been determined in correlation with the presence of T-antigen within the cell and on its surface.

2337 A COMPARISON OF GLUTATHIONE TRANSFERASE-P OF RAT HEPATOCYTE NUCLEODE AND MOUSE LIVER CYTOSOL. M.W. Ronnii, R.C. Cameron and E. Farher, Dept. of Pathology, Univ. of Toronto, Toronto, Canada.

Resistant hepatocyte nuclei (H) cytosol has a marked increase (compared to control rats) of a polypeptide of 26 kDa by gel electrophoresis. This polypeptide is very similar if not identical to rat glutathione transferase-P (GST-P, purified from placenta). Using antibody to GST-P, GST-P was found in early nodules, persistent nodules, but not in normal liver cytosol. It is possible that these two proteins are closely related. However, the presence of GST-P in rat liver cytosol may be due to the presence of a related protein which has not yet been identified.


Serum cholinesterase (EC 3.1.1.7, also called pseudo-cholinesterase) has been routinely measured as one of liver function tests. However, this enzyme is known to be highly variable in human serum. In hepatoma patients, serum cholinesterase activity is generally low. The serum cholinesterase activity in sera of hepatoma patients is lower than that in normal serum. The serum cholinesterase activity in sera of hepatoma patients is lower than that in normal serum. The serum cholinesterase activity in sera of hepatoma patients is lower than that in normal serum. The serum cholinesterase activity in sera of hepatoma patients is lower than that in normal serum. The serum cholinesterase activity in sera of hepatoma patients is lower than that in normal serum.


Even after exhaustive purification procedures, the melanosome-bound tyrosinase was purified from the Harding-Passay murine melanoma, fractionated into a continuous series of subunit isoenzymes by preparative electrophoresis and analyzed using various chemical and immunological probes. Treatment with neuraminidase revealed that all the forms had similar amounts of sialic acid, and reactivity with various carbohydrate-specific lectins showed that the isozymes also contained subterminal galactose, N-acetylgalactosamine and mannose, but lacked fucose. Ano acid composition data indicated that the isozymes are composed of polypeptides containing identical residue content.

2340 ROLE OF CALCIUM-ACTIVATED, PHOSPHOLIPID-DEPENDENT PROTEIN KINASE IN HUMAN GASTRIC CARCINOMA. N. Taya, H. Nishiyoshi, S. Miyagi, and E. Tahara, Dept. of Pathology, Hiroshima Univ. Sch. of Medicine, Japan.

Calcium-activated, phospholipid-dependent protein kinase (protein kinase C) is thought to play a major role in cellular signal transduction and act as a messenger in cellular proliferation. However, the detection and the role of protein kinase C in human cancer has not yet been elucidated. We report the activity of protein kinase C in human gastric carcinoma tissues and the effect of phorbol esters on human gastric carcinoma cell line.

Firstly, protein kinase C activities in human gastric mucosae and carcinomas were examined. The enzyme assay was based on the incorporation of [32P]ATP into [32P]histone. Protein kinase C activity in gastric carcinoma was significantly greater than that in non-neoplastic gastric mucosa (P<0.01). The majority of this enzyme was associated with the cytosol in both tissues. To determine the role of protein kinase C in gastric carcinoma, the effect of tumor promoting phorbol esters on the growth of human gastric carcinoma cell line (TMK-1) showing gastrin-dependent cell growth. Both phorbol 12,13-dibutyrate and 12-0-tetradecanoylphorbol-13-acetate stimulated the growth of TMK-1 cells. But, phorbol 13-acetate, which does not activate protein kinase C, showed no influence on the growth of TMK-1 cells.

These results suggest that protein kinase C plays an important role in the growth of human gastric carcinoma. The effect of gastrin or epidermal growth factor on protein kinase C activity in TMK-1 cells will be demonstrated in further studies.


The enzyme was recovered from the cytosol of TMK-1 cells and purified. The enzyme was resistant to lead nitrate and butylated hydroxytoluene, butylated hydroxyanisole or butylated hydroxytoluene, butylated hydroxyanisole. The enzyme was present in early nodules, persistent nodules, and nodules generated by injection of rat hepatocytes into rats with hepatocellular carcinoma. The enzyme was resistant to lead nitrate and butylated hydroxytoluene, butylated hydroxyanisole or butylated hydroxytoluene, butylated hydroxyanisole. The enzyme was present in early nodules, persistent nodules, and nodules generated by injection of rat hepatocytes into rats with hepatocellular carcinoma.

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2342 PRODUCTION OF NOVEL CHOLINESTERASE ISOZYMES BY HUH-7 CELL LINE ESTABLISHED FROM A HUMAN HEPATOCELLULAR CARCINOMA. E. Ferrini, A.M. Miller, V.L. Hearing, and U. Ferrini. Dept. of Pathology, Hiroshima Univ. Sch. of Medicine, Japan.

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ALTERED LEVELS OF UDP-N-ACETYLGLUCOSAMINE: LYSOSOMAL ENZYME PRECURSOR N-ACETYLGLUCOSAMINE-1-PHOSPHATE TRANSFERASE IN HUMAN OVARIAN TUMOR TISSUE AND SOME TRANSFORMED CELL LINES. R.L. Mora, R. Madiyalakan, O.T. Hueller and T.B. Shows, Roswell Park Memorial Institute, Buffalo, New York, U.S.A.

Lysosomal acid hydrolase levels have been demonstrated to be altered in some malignant tissues and in sera of patients with cancer as compared with control tissue and sera. One of the mechanisms by which these enzyme levels may be changed is by alteration in their sorting into intracellular and extracellular compartments. Uridine dipiphosphate-N-acetylglucosamine:lysosomal enzyme precursor N-acetylglucosamine-1-phosphate transferase, is a key enzyme involved in the intracellular targeting of lysosomal enzymes. This enzyme was found to be elevated four-fold in ovarian tumor microsomes respect to normal ovarian microsomes. This elevation was associated with significant increase in the specific activity of lysosomal hydrolases, including 6-β-hexosaminidase, α-β-fucosidase and β-D-galactosidase. The activity of the phosphotransferase was also significantly increased in several cell lines derived from human tumors, especially those derived from liver. This observation taken together with the reported increase in phosphorylation of high mannose type oligosaccharides in lysosomal enzymes from lung adenocarcinoma suggests a possible role for the phosphotransferase in tumor-associated phosphorylation changes that result in the altered structure or function of secretory or cell surface protein. Supported by PHS Grant No. GM 31425 and NIH HD 05196.

CYTOTOXIC EFFECTS OF ATRACYLOSIDES AND BONGKREKIC ACID. INHIBITORS OF MITOCHONDRIAL ADENINE NUCLEOTIDE CARRIER ON TUMOR CELLS (F10) IN VITRO. S.D’Ancona, M.Magon, and E. Bemi, Dept. of Pharmacology(University of Padova, Padova, Italy.

Atractyloside (ATR) and its carboxylated derivative, carboxyatractyloside (CAT) are diperpenic glucosides, isolated by a mediterranean plant, specific inhibitors of the ADP/ATP carrier, a toxic antibiotic produced by Psychosporium cucumerinum. The ADP/ATP carrier catalyses the exchange between cytosolic ADP and the matrix ATP across the inner membrane of mitochondria which is a key process in the cellular energy supply. The mechanism of action of these inhibitors are quite different. Our experiments on murine melanoma B16 metastatic cells F10 (Fidler’s source) show that after 72 hours at 10^-7 M and 10^-5 M ATP induces 35% and 50% respectively reduction on cell number, CAT 45% and 55% and BKA 50% and 70%. Our researches demonstrate a possible involvement of energy metabolism, particularly the energy dependent ADP/ATP transport through the mitochondrial membrane in the control of tumour cells proliferation.

MECHANISM OF HYDROXYLATION OF IFOSFAMIDE IN SIDE CHAINS

K.Nielura, R.W.Klimas, W.J.Stec
Dept. of Bioorganic Chemistry, Ctr. of Molecular and Macromolecular Studies, Polish Academy of Sciences, Lodz, Poland

Ifosfamide (IF), a cyclophosphamide (CP) analogue, belongs to the family of anticancer drugs requiring metabolic activation to manifest their cytotoxic action. It has been found that IF undergoes enzymatic hydroxylation at carbon 4 of 1,2,3-oxaphosphorine ring and at carbons α of β-chloroethyl chains. The latter process, which leads to inactive dechloroethylated metabolites, is very important because nearly 50% of given drug dose undergoes such biotransformation in humans. To investigate mechanism of this process we have synthesised IF-analogue D4-IF containing four deuterium atoms at carbons α directly attached to both nitrogen atoms. The activation of D4-IF and IF was performed in vitro using hepatic microsomes, glucose 6-phosphate dehydrogenase, glucose 6-phosphate and NADP, and GC-MS technique for quantitative examination of remaining D4-IF and IF metabolites. The degree of metabolic transformation of D4-IF and IF was nearly the same indicating that there is no isotopic effect in the hydroxylation process of carbons α of β-chloroethyl chains.


Our previous study have shown that benzaldehyde (BA), a carcinostatic agent, has certain suppressive effect on the in vitro phenotypes of transformed cells, as well as the preventive effect on the spontaneous transformation of mouse cells by in vitro treatment. In the present work the suppressive effect of BA on the induction of ornithine decarboxylase (ODC) in untransformed mouse fibroblast of RKE-5-3-1 cells, which has been established from C3H/He mouse embryos by long-term BA-treatment, by serum, growth factors and tumor promoters was investigated, in view of the known relation of ODC activity to cell growth regulation through polyamine biosynthesis, e.g. that of the abnormally high ODC level to malignant phenotype of transformed cells, and also of enhanced activity induced by growth factors and tumor promoters. BA significantly suppressed induction of ODC activity by serum, growth factors and also tumor promoters as well as 0.1 M NaCl level in the medium, but it did not directly inhibited the activity of ODC in cell free system. The results were supported by simultaneous measurement of cellular polyamines, especially putrescine. The suppressive effect of BA seems specific on ODC induction by observation with such stronger suppression than that of the total cell protein synthesis. Results of currently under taken studies on the effect of BA, for instance, on ODC biosynthesis using ODC-antibodies, on cellular Ca-ion level, C-kinase system and like things, will be also reported.

B-45: ENZYMES, ISOENZYMES AND MALIGNANT PHENOTYPES
THE SYNTHESIS OF THE RNA PYRIMIDINE PRECURSORS IN HEPATOMAS

C. Cobor, M. A. Turchean, E. Pâfan, and I. M. Gorîșan,
Institute of Oncology, Bucharest, Romania.

Cardiac and neurologic toxicity, thrombocytopenia, skin reactions, liver injuries as
intrathapeutic cholestasis and hepatic necrosis have been reported after mediation
with triacylglycerides. A correlation between these metabolisms and the side
effects produced has been discussed, but not established for nortriptycline.

Adverse effects of these drugs are probably mediated by an immunological mecha-
nism, but no conclusive evidence has been presented. We tried to elucidate whether
nortriptyline is able to give rise to a compound with antigenic properties.

We demonstrated in vivo experiments, an irreversible binding of nortriptyline
to rat liver microsomes. Presence of oxidase hydrazide inhibitor led to an increase
of amount of substance bound to proteins.

Carcinogen-induced enzyme-altered foci are the first
detectable phenotypic alterations during malignancy of the
liver and quantitative relationships with ultimate tumor
formation have been demonstrated with several carcinogenic
substances. Both the multiplicity of enzyme changes which
occur in distinct patterns within individual foci and the
inducibility of certain enzymes point towards the exist-
ence of alterations in regulatory genes of a higher order.

The investigation of alterations within these regulatory
genes will help define the molecular basis of sequential
stages in the course of carcinogenesis.

We investigated the phenotypic complexity of enzyme
altered foci with histochemical, immunohistochemical and in
situ hybridisation techniques. A reduced expression of
ATBim mRNA was observed in all large neoplastic nodules
by in situ hybridisation of liver sections with an 25S
labelled cDNA probe. This decrease was most pronounced in
more progressed nodules characterized by decreased glyco-
gen contents along with unchanged epoxide hydrolase
levels. In early neoplastic nodules albumin mRNA
levels were unchanged. Hypofunctional nodules produced by con-
tinuous treatment of rats with 4-dimethylaminoazobenzene
showed characteristic increases in albumin mRNA
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ocogene specific probes did not yield conclusive results
until now. However, Northern analysis of RNA isolated from
Y-glutamyltranspeptidase positive, presumably neoplas-
cic hepatocytes obtained from liver of carcinogen/
promoter treated rats showed unchanged expression levels
of the proto-oncogenes c-myc and H-ras.

PLASTIC AND NEOPLASTIC LIVER CELLS.

C. V. Valenzuela, J. M. H. McArthur Laboratory for Cancer Research, Madison, U.S.A.

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THE SYNTHESIS OF THE RNA PYRIMIDINE PRECURSORS IN HEPATOMAS
AND TISSUES OF THE TUMOR HOST - CRITERIA OF THE EVALUATION
ITS TRUE HATE.

V. S. Shapit, N. Potapova, All-Union Cancer Research Center
the USSR AMS, Moscow, USSR.

Initial rate of the incorporation of equimolar amounts
of the radioactive orotate and uridine (and their ratio -
or/ur) into pyrimidine nucleotides of acid-soluble fraction
(PCU) and RNA of ascites and solid hepatomas as well as li-
ver, spleen, small intestine of control and tumor-bearing
rats and mice was studied. An active and selective incorpo-
ration of uridine into pyrimidine nucleotides of hepatoma
PCA and RNA unlike tissues of the host was observed: the
highest rate of uridine incorporation into UMP (PCA and RNA)
was characteristic of the ascites Zajdel-Jet hepatoma and corre-
lated with 5-10 fold elevated uridine kinase activity; as to
the solid Guelstein hepatoma (C3HA mouse) the highest ra-
te of the synthesis from uridine of UMP and CMP as constitu-
ents of RNA was observed despite the moderate uridine kinase
activity. In the solid mouse hepatoma orotate incorporated
into UMP (PCA) efficiently (or/ur=2.38), however in UMP and
CMP in RNA this ratio was diminished - 0.46 and 0.17, respec-
tively. The rate of the synthesis of RNA precursors is like-
ly determined not only by the activity of cytoplasmic enzy-
mes but also by the compartmentalization of their substrates.

In tissues of animals carrying ascites and solid hepatomas
formation rate of UMP(CPA) and CMP in RNA from uridine drops
dramatically. As a result of a successful competition of the
tumor for the uridine the or/ur ratio in these fractions of
the host tissues increased significantly entailing the de-
crease of RNA synthesis in them.

The most adequate criterion of the intensity of the anabolic
processes studied should be the rate of the end
product formation in vivo but not the potential activity of
enzymes involved.
RADIATION DAMAGE TO THE MITOGENIC RESPONSE OF
OXICALLY AND HYPOXICALLY IRRADIATED GLUTATHIONE-
DEPLETED LYMPHOCYTES: SUPPORTS THE COMPETITION
HYPOTHESIS CONCERNING THE OXYGEN EFFECT. G. Pellet.
Alfreda Tomesi, J. Facchet, L. Révész, J. RJC Radi.
Res.Inst.of EPID, Debrecen, Hungary, *Karolinska
Institute, Dept.Tumor Biology 11, Stockholm, Sweden

Freshly withdrawn peripheral human blood lymphocytes were cultured in medium, supplemented with 0.5 mm buthionine sulfoximine (BSO), an enzymatic inhibitor of the glutathione synthesis. After 16 hrs incubation the cells were washed with MEM medium and irradiated in air or in purified nitrogen with X-ray doses varying between 0.1 and 36 Gy. The irradiated cells were subsequently incubated with RPMI medium supplemented with the mitogens PHA or concanavalin A in optimal concentrations for 72 hrs. Thereafter, the cells were labeled with H3TDR (14-Muq) for 4 hrs. Using the incorporation rate as the criterion for the mitogenic activation the data indicated a greater cellular damage in regard to this function by radiation delivered under aerobic than under hypoxic conditions. BSO-treated cells appeared to suffer a greater damage than BSO-un-treated controls. The BSO effect was increased in hypoxic conditions in comparison to aerobically irradiated cells. Test performed with unirradiated controls indicated that a 16 hrs treatment with BSO in concentrations varying between 0.1-1 mm does not affect the mitogenic activation of the lymphocytes by PHA or concanavalin A. It was concluded that the functional damage induced by radiation in this system is dependent upon the oxygen and cellular glutathione during exposure, in agreement with the hypothesis according to which oxygen fixes radiation damage in a competition with endogenous thiol capable of repairing it.
### 2351 THE RADIOSENSITIZING EFFECT OF DIBROMODULCITOL


In addition to cytostatic effect of dibromodulcitol (DBD) clinical experiences indicated some other effects, too. The radiosensitizing effect of DBD was investigated on Bacillus megaterium spore system at various oxygen concentrations. It had no effect under oxyg conditions, but the value of SER enhanced up to 1,10 in anaoxia at the concentration of DBD 6,4 mmol/l. The experiments with equivalent bromine content of NaBr and DBD. Therefore, 52% of bromine content of DBD involved in the sensitization.

Misonidazole had no chemopotentiating effect on this sensitization. Combination of DBD and misonidazole resulted practically the individual effect of misonidazole. The hydroxyl radical scavenger t-butanol could reduce the radiation response of spore suspension by 29%.

### 2352 INDIVIDUAL SELECTION OF RADIOSENSITIZERS (RS) AND FRACTIONATION SCHEDULES (FS) FOR MORE EFFECTIVE RADIATION TREATMENT OF CANCER - A NEW METHOD

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**Aim:** The testing of the individual tumor response to irradiation applied to different FS with or without some RS would help to choose the treatment which is most appropriate in each particular case, for more improvement of the curability of cancer by irradiation.

**Technique and Patients:** Expanded and modified Bogden’s method (Exp. Cell Biol. 47, 281, 1979) was applied: xenotransplantation of 6 experimental and 8 patients tumors to groups of mice. Each group is treated with different RS and FS.

**Results:** The reported individual radiosensitivity of experimental tumors depending on FS and RS corresponds completely to that established by the conventional methods. The different individual radiosensitivity to FS and RS does not correlate with the clinical stage, histological type and localization of the investigated human tumors.

**Conclusion:** The determination of the mean tumor growth rates of the human xenografts in mice permits to choose the best individual FS and the more effective RS in patients radiation treatment.

### 2353 EFFECT OF RADIOPROTECTOR WR 2721 ON MONOAINE OXIDASE ACTIVITY IN MICE BRAIN, K. Bodó and Gy. Bánkó, "Frédéric Joliot Curie" National Research Institute for Radiobiology and Radiohygiene, Budapest, 1775, Hungary

Level of neurotransmitter biogenic amines in brain influences the physiological and bioehavioral state of organism and this level decreased after gamma-irradiation (Bodó and Bánkó: Radiobiol. Radiat. Oncol. 25, 1978). For this reason we established a biochemical aspect monoamine oxidase (MAO) as a key enzyme in the metabolism of biogenic amines. The activity of this enzyme was studied in mice brain after various quality of irradiation in vivo. 5 hours after 0.05 Gy gamma-irradiation the enzyme activity increased by 20% while the level of substrates (serotonin and catecholamines) decreased, but the enzyme activity was above control level at 24 hours. In contrast 5 hours after 4.5 Gy fission neutrons radiation MAO activity decreased by 20% while the substrate level (serotonin) increased by 17%, and gradually returned to the normal values within 24 hours. Administration the radioprotective agent WR 2721 (5-2/-3-aminopyrrol amino ethylphosphorothioate) in a dose of 300mg/kg 20 minutes before radiation caused a slight change only in MAO activity: in the first 3 hours after irradiation it increased, but after 5 hours no significant change was observed. The enzyme activity was not altered after fission neutrons radiation. WR 2721 treatment alone slightly influences the MAO activity. The MAO activity was increased in liver after both types of radiation.

In conclusion administration of WR 2721 shortly before irradiation MAO activity exhibited only a slight change and this reflects the beneficial physiological state of animals after irradiation.

### 2354 EFFECTS OF RADIOPROTECTIVE COMPOUNDS ON THE PLATELET AGGREGATION IN VARIOUS SPECIES


Previously we found that AET /1-s-2-aminomethylisothiuronium-Br/ and Cysteamine but not WR-2721 /5-2/-3-aminopyrrol amino ethylphosphorothioic acid/ inhibited the formation of prostacyclin in rat arteries in vitro. In vivo experiments, Horváth and Bánkó: Proc. Europ. Soc. Radiobiol. Prague, 1983. In this work their effect made on platelet aggregation was studied.

It was stated that AET and Cysteamine but not WR-2721 inhibited both arachidonate and ADP-induced aggregation of rats, rabbit and human platelets. After ip. administration of 200 mg/kg AET the arachidonate induced aggregation was inhibited only. Lp. treatment with 300 mg/kg WR-2721 resulted in a temporary inhibition of ADP, arachidonate and A-23187/Ca-ionophor/-induced platelet aggregation tested in vitro. The strongest inhibition was found in rats, lesser in mice, while in rabbits the platelet aggregation remained almost normal. On the effect of Ca-ions added to the platelet-rich plasma in vitro a perfect platelet aggregation was obtained again.

Our results suggest that the effect of AET and Cysteamine made on platelets and prostaglandin formation of other tissues are likely due to a similar mechanism, by the inhibition of cyclooxygenase. The in vivo effect of WR-2721 likely represents another way of the inhibition of platelet aggregation. Ca-ions are known to play very important role in all forms of the platelet aggregation. As WR-2721 did not cause significant change in plasma calcium level in rats, our results could be explained as the transient disturbance of intracellular calcium availability in platelets.
Enhancement of tissue lipid peroxidation occurs after the elevation of free radicals, caused by various factors. One of the end products of lipid peroxidation malondialdehyde (MDA) binds to proteins or DNA and causes irreversible damage. Authors found that after gamma radiation of rats depending on dose and time course the MDA level was increased in radiosensitive organs while in radioresistant ones the alteration was smaller and occurred later compared with the unirradiated relevant tissues.

Authors investigated the protective effect of WR 2721 (2-G-3aminopropylamino-ethylphosphorothioic acid) on lipid peroxidation. After administration of 300 mg/kg WR 2721 20 min. before X-ray radiation the amount of MDA was assayed in brain, spleen, liver and testicle. 24hr. after 9 Gy gamma-radiation MDA level was higher by 40-50% in brain and testicle but not in liver. Pretreatment with WR 2721 MDA level was unchanged in testicle only. Following 6,30 Gy x-ray radiation the MDA level was by 50% higher in all organs except in liver, while after 8,0 Gy it was elevated in all investigated tissues. After pretreatment with WR 2721 the MDA remained at control level in brain and testicle but not in spleen in case of 6,30 Gy and it was unchanged in testicle after 8,0 Gy x-ray radiation only.

In conclusion, radioprotection achieved with WR 2721 against radiation induced enhancement of lipid peroxidation varied with radiation dose and differs from tissue. The higher protection was found in testicle.

**SYNTHESIS AND TESTING OF NEW RADIOSENSITIZING COMPOUNDS: 4-SUBSTITUTED-3-NITRO-QUINOLINE DERIVATIVES. L.P. Varga**, and **E. Berényi**

Several types of 4-substituted-3-nitro-quinoline derivatives were synthesized and tested for radiosensitizing ability. Among them the N[3-nitro-4-quinolinyl]-morpholine-carboxamidine proved to be an effective hypoxic cell radiosensitizer since the drug exhibited both dose-multiplicative (DMR) and dose-additive (DAR) radiosensitization (change in the slope and shoulder region of radiation survival curves). Radiosensitization effects of this compound have been tested in mammalian cell systems cultured in vitro (CHO and Hela cells) as well as in vivo using Lewis lung carcinoma solid tumor implanted into BDF-1 mice. Sensitizing property of the 3-nitro-quinolines has been compared to those of misonidazole and metronidazole under identical conditions. Values for sensitizing enhancement ratio (SER) of 3.5-3.9 were obtained for hypoxic cells pretreated with drug (0.5-2 mM) for 1 hr at 37°C and subsequently exposed to gradually increased doses of X-ray, while for misonidazole (5mM) this ratio was 1.95, besides on oxygen enhancement ratio (OER) of 2.76. It is important to note that the shoulder region of the radiation survival curves totally disappeared upon treatment, therefore the overall extrapolation number decreased almost to one.

Similar encouraging results were observed when tumor bearing mice were given sensitizer i.v. in an amount of 0.2 ml (60mg) followed by local irradiation with 10 Gy. Using the regrowth analysis, we calculated values for SER of 1.5-2.1 depending on the conditions. These results indicate that the 3-nitro-quinolines are potentially efficient radiosensitizers.
2359 EVALUATION OF RETROSPECTIVE ANALYSIS OF HISTORIC EXPERIMENTAL STUDIES IN LABORATORY ANIMALS

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The standardized conditions in experimental pathology can't be considered as guarantee for standardized reactions of laboratory animals. This can be demonstrated in a ten-year-retrospective study about a Sprague-Dawley-strain. The incidence of spontaneous tumors increased from 5% to 13% as consequence of genetic instability combined with increase of body-weight. The variability of the tumor-spectrum differed in this period and tumors appeared earlier in life-time. Our results show that the onset of tumor development and other diseases (e.g. urinary calculi) can experimentally be influenced by a number of factors like the quantitative and qualitative composition of food or by drugs, influencing metabolism or spontaneous activity.

There are many factors influencing the promotion of tumors. For competent evaluation of the risk-profile of drugs, therefore, continuous monitoring of all safety parameters and comparison of present with previous studies are necessary in order to reveal in early stages deviant behaviour and to limit undesirable promoting effects on tumors and pathological developments.

2360 THE FREQUENCY OF TUMOURS AND INTESTINAL METAPLASIA IN THE GLANDULAR STOMACH OF THE RAT AFTER DIFFERENT WNBG-DOSES. M. Bartens, Inst. of Pathology, W.-Piekau-Univ., Hoystock

The dose-response relation of the frequency of both the intestinal metaplasia and tumors of the stomach was studied in male Wistar rats receiving drinking water with 100 μg MNNG/ml (group A), 50 μg MNNG (group B), 25 μg MNNG (group C) or tap water (control group). After 50 weeks the following rates of gastric tumour bearing animals were observed: group A 4 of 18, group B 8 of 27 and group C 2 of 16. The majority of tumours was classified histologically as well differentiated adenocarcinomas of pyloro-cardiac cell type or indifferent type. 2 adenocarcinomas with a mixed intestinal and indifferent type pattern was observed in group B; additionally 1 adenomatous hyperplasia of pure intestinal type was found in this group. For the estimation of the frequency of intestinal metaplasia, the antrum region of the stomach was cutted completely in serial sections in 5 rats of each group. It was found a reverse relation between the frequency of glands with intestinal metaplasia and the MNNG-dose. The average values of metaplastic glands per animal were 54 (group A), 83 (group B) and 187 (group C).

2361 ESTABLISHMENT OF TRANSPLANTABLE LINE AND LUNG METASTATIC MODEL OF RIF MALIGNANT FIBROUS HISTIOCYTOMA BY 4-HYDROXY-XYMOXIDONE 1-OXIDE. Y. Miyachi*, Y. Mi*., J. Ni*., K. Masuhara, Y. Konishi**, K. Shira*., M. Tsutsumi**, Department of Orthopedic Surgery, Nara Medical College*, and Department of Oncological Pathology, Cancer Center, Nara Medical College**, Nara, Japan

The entity of human malignant fibrous histiocytoma (MFH) has been developed as primitive, pleomorphic sarcomas showing partial fibroblastic and histiocytic differentiation and it is possible to be classified into subtypes. It's now evident that MFH is the most common soft tissue sarcoma of the late adult life and with poor prognosis. Each subtype of MFH may display different biological behavior and chemosensitivity but those are not clearly studied. Therefore, establishment of transplantable line and lung metastatic model of individual subtypes of MFH is needed.

Previously at the last congress, we reported the induction of subcutaneous and bone MFH by a carcinogen, 4-hydroxyaminoxidone 1-oxide (4-HA) in rats. At the present, we report transplantation of each subtype of MFH and experimental lung metastasis production by injecting intravenously the tumor cell suspensions into syngeneic rats. The present results indicate that the transplantable rat MFH line and lung metastasis were established and provide the characteristic growth behavior and evaluation of efficacy of chemotherapeutic agents on MFH.

2362 INDUCTION OF COLORECTAL TUMORS IN RATS BY SULFATED POLYSACCHARIDES (DEGRATED CARRAGEENAN AND AMYLOPECTIN SULFATE). T. Ishioka and K. Kuwabara, Juntendo Univ. Sch. of Med., Tokyo, Japan

It was been known that the oral administration of sulfated polysaccharides, such as degraded carrageenan (d-CGN) and amylopectin sulfate (APS) induces ulcerative colitis in laboratory animals. The mutagenicity of these materials by the Ames test showed a negative result. The carcinogenicity of orally administered sulfated polysaccharides was studied in Sprague-Dawley or F334 rats. These materials first induced colitis, secondary squamous metaplasia and finally tumors in the colorectum. Squamous metaplasia persisted in all experimented rats and progressed irreversibly. d-CGN induced squamous cell carcinomas, adenocarcinomas and adenomas in the rat colorectum. APS induced both adenocarcinomas and adenomas but not squamous cell carcinomas. The incidence of tumor induction in groups that were given a 10% diet of d-CGN for two, six and nine months were 5 out of 37 rats (13.5%), 8 out of 42 rats (19.0%) and 17 out of 42 rats (40.5%), respectively. On the other hand, those given a 5% diet of APS for three, six and nine months were 2 out of 20 rats (10%), 9 out of 20 rats (45%) and 12 out of 20 rats (60%), respectively. The difference between d-CGN and APS was the tumor incidence and induction of squamous cell carcinoma. d-CGN induced squamous cell carcinoma in the squamous metaplasia, but APS did not. This result is based on the findings that APS induced squamous metaplasia without marked hyperplasia of the squamous epithelium. On the other hand, another sulfated polysaccharide, such as dextran sulfated sodium (DS), also induced squamous metaplasia, adenoma, adenocarcinoma and squamous cell carcinoma in rat colorectum. The average molecular weights of d-CGN and DS were similar to each other and far smaller than that of APS. The sulfite content of APS was similar to that of d-CGN and DS. In spite of these differences, these carcinogenic sulfated polysaccharides produced similar lesions in the rat colorectum.
2363 EFFECTS OF BETA-ADRENERGIC STIMULATOR TO PULMONARY CARCINOGENESIS

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Adrenergic stimulation is one of pharmacotoxicological effects on living organisms. It has been shown that beta-adrenergic stimulator influences on the growth of bronchiolar Clara cells and the pre-treatment of beta-stimulators enhances tumorigenesis of 4-nitroquinoline-l-oxide (4-NQO) in mice lungs. Substantiating adrenergic effects of the lung tumorigenesis, which was induced by urethane administration in combination with either pre- or post-treatment of 0.5% metaproterenol sulfate, were reported. Eighty mice were divided into 4 experimental groups: 1) pre-treatment with the beta-stimulator for 3 weeks before urethane administration, 2) post-treatment with the beta-stimulator after urethane administration, 3) administrated urethane for 7 weeks, 4) given only water of pH 3. Average number (per head) of the lung tumors induced were 2.4 (Group 1), 1.7 (Group 2), 1.8 (Group 3), and 0.1 ( Group 4). This result shows clearly that pre-treatment of beta-stimulators enhances the tumorigenesis by the urethane and is significant than that by the 4-NQO. It also suggests that urethane may effect directly in Clara cells which were proligerated by pre-treatment of the beta-stimulator. In contrast, the 4-NQO may effect on bronchiolar Clara cells after being converted to 4-HAQO by the metabolic activation. A possible difference in action mechanisms of two chemicals (urethane and 4-NQO) may be responsible for differences in incidences of the pulmonary tumors. The stimulation via blood may play an important role in the carcinogenesis of the peripheral lung as well as of the large bronchial wall.

2365 MCGOTHELIONAS INDUCED BY INTERPERITONEAL INJECTION OF PYRAGUS ANTAGONIST IN RATS

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Some reports have described the effects of pyrogens in rats, such as a decrease in tumor growth. It is suggested that these effects may be due to the induction of an immune response. However, the mechanism of this effect has not yet been clarified. In this study, we investigated the effects of pyrogens on the growth of experimental tumors in rats. Rats were injected intraperitoneally with 10 mg of pyrogens (polysaccharide-K or lipopolysaccharide) or with saline (control). The results showed that the injection of pyrogens significantly reduced the growth of experimental tumors, indicating that pyrogens may have a suppressive effect on tumor growth. These results suggest that pyrogens may have potential as a treatment for cancer.
2367 ALTERNATIVES OF 7,12-DIMETHYLBENZ(A)ANTHRACENE INDUCED ADENOCARCINOMA IN LACTATING ADULT MICE DURING REPEATED EPIDEMIOLOGICAL STUDIES. J. Bondarenko, T. Druzhko, I. Koval, T. Kulyk, K. Pauk PT. Inst. Clin. Immunology, Ukraine

Chemical carcinogenesis by 7,12-dimethylbenz(a)anthracene induced tumors of various histological types in lactating female rats 30 days of age. Adenocarcinomas, when transplanted to the syngeneic host female rats, underwent the morpho-transformations to adenoma-like tumors, during several transplantations generating multicentric differentiated comparable malignity. However, in the extravasation through the stroma of the uterus, tumors transplanted to female rats, compared with the original tumor, demonstrated the growth and vascularization of non-phototransformed tumors were proved by successful transplantation in various male rats. Validity of such experimental model is discussed.

2368 THE EFFECT OF LITHIUM AND Cesium SALTS ON CHEMICALLY INDUCED TUMORS IN MICE. Ali A. El-Demery, Sue N. Thayer, and Van-Chau Nguyen. Division of Oncology, Department of Surgery and Pathology, Texas Tech University School of Medicine, Lubbock, Texas 79430, USA.

Earlier studies demonstrated that inorganic chloride reduced the incidence of sarcoma 180 implants in mice. In this study, the effect of the chloride salts of Cesium (CsCl) and Lithium (LiCl) on dimethylhydrazine (DMH) induced tumors in C57BL/6 mice was evaluated. One hundred and twenty six weeks old female mice were randomized into four groups. DMH was dissolved in 1 mM EDTA and adjusted to pH 6.5. Animals in group I served as control and received EDTA only whereas animals in the other 3 groups received 180/20 mg/kg once a week intraperitoneally (ip) for 16 weeks. Treatments were given ip, daily for 2 weeks and then twice a week for 22 more weeks as follows: group I and II: Saline (0.9% saline) group III: CsCl 2 mM/kg and group IV: LiCl 3 mM/kg. All animals were sacrificed at 36 weeks and each was subjected to careful postmortem examination. No tumors were detected in animals in group I (0%). No tumors were detected in animals in group II (0%). A number of animals in the other 3 groups developed a variety of tumors at different sites. The incidence of epithelial tumors of the small and large intestine was as follows: group II 4/30 and 12/30, group III 26/30 and 18/30, group IV 11/30 and 13/30. Also dysplastic changes in the small intestine mucosa were prevalent in the latter 2 groups. Another type of soft tissue tumors which resembled angiosarcoma were detected outside the alimentary tract in some animals. The number of soft tissue tumors in animals in the different groups was as follows: group II 1/30, group III 5/30 and group IV 9/30. The results of this study showed that number of small intestine tumors was significantly higher in the groups receiving CsCl and LiCl (p < 0.001).

2369 EFFECTS OF DIFFERENT CONCENTRATION OF ENNG ADMINISTRATION IN THE DEVELOPMENT OF GASTRIC CANCER IN DOGS. Ken-Ichi Hase, Toshiaki Takagi, Masahiko Hanada, Tetsuro Okawa and Masashi Arai. First Department of Surgery, Gunma University School of Medicine, Maebashi 371, Japan.

This experiment was carried out to see the effects of different concentration of N,N-dimethyl-N-nitrosoguanidine (ENNG) on the development of gastric cancer in dogs. The concentrations and volumes of the ENNG solution were adjusted according to the body weight of each dog as follows: group I 50 mg/kg (N = 4, B = 2), 100 mg/kg (N = 5, B = 2) and 150 mg/kg (N = 7, B = 3). All groups received 140 ml of ENNG solution with foods per day for 7 months. Most of the gastric tumors were observed by endoscopic biopsies at regular intervals.

Results: 1) Endoscopy showed a red spot, erosion and small mucosal elevation as initial lesions. Small elevation was more frequently found in Group A. The red spot was seen in 75% of animals in Group C. The average duration from the first administration of ENNG to occurrence of initial lesion needed 15 months in Group A, 22.7 months in Group B and 11.5 months in Group C. Animals in Group C developed a variety of tumors. However, this difference did not reach statistical significance.

In conclusion: from these results it emphasized that ENNG administered per rectally with ENNG suspension is effective in the dogs. In conclusion, the diffusion, infiltration, and histogenesis of diffuse infiltrative colon cancer in human beings.
THE EFFECTS OF GONADAL HORMONES ON DIMETHYLMALTETRAZINE-INDUCED COLONIC CARCINOMA

E. Odaigri, K. Jiibiki, Y. Kato*, R. Demura and H. Demura. Radioisotopes Center, Tokyo Women's Medical College, Dep. of Pathology, Cancer Institute*, Tokyo, Japan

To investigate whether gonadal hormones are involved in the tumorigenesis of dimethylhydrazine (DMH)-induced colonic neoplasms, we measured steroid hormone receptors in the neoplasms. BD-IX rats were divided into three groups: intact (I), castration (C) and castration plus testosterone replacement, males only (C+T). All rats received 25 mg of 1,2-DMH per kg body weight, once a week for 20 weeks. The I group received only DMH vehicle. Beginning 14 days after castration, the C group received DMH and the C+T group received DMH and 3 mg of testosterone depot once a week. The animals were sacrificed at 40-45 weeks after the initial injection. Androgen receptor (AR), estrogen receptor (ER) and progesterone receptor (PR) were measured in the colonic neoplasms. In the I group, the number of colonic neoplasms per rat was higher in male rats, i.e., 5.6 compared with 3.5 in female rats. Castration decreased the number of colonic neoplasms in male rats. Additionally, testosterone replacement to castrated rats increased the incidence of colonic neoplasms in male rats. However, castration had no effect on the incidence of colonic neoplasms in female rats. In intact group, the incidence as well as concentration of AR was higher in male rats (60.6 ± 16.9 fmol/mg protein) compared with females (40.0 ± 4.6 ± 0.8 fmol/mg protein). Castration slightly reduced the incidence and the concentration of AR. There was no difference in AR concentration between the I and C groups. Also, there were no significant differences in ER and PR among the three groups.

Castration had no effect on either the incidence or the concentration of steroid hormone receptors in female rats. In the I group, the number of colonic neoplasms per rat was higher in male rats, i.e., 5.6 compared with 3.5 in female rats. Castration decreased the number of colonic neoplasms in male rats. Additionally, testosterone replacement to castrated rats increased the incidence of colonic neoplasms in male rats. However, castration had no effect on the incidence of colonic neoplasms in female rats. In intact group, the incidence as well as concentration of AR was higher in male rats (60.6 ± 16.9 fmol/mg protein) compared with females (40.0 ± 4.6 ± 0.8 fmol/mg protein). Castration slightly reduced the incidence and the concentration of AR. There was no difference in AR concentration between the I and C groups. Also, there were no significant differences in ER and PR among the three groups.

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These results suggest that gonadal steroid, especially testosterone, plays an important role in the development of colonic neoplasms in BD-IX rats.
In view of an established epidemiological link between the use of smokeless tobacco and oral cancer (Winn et al., N. Engl. J. Med. 304, 745, 1981), we studied the tumor formation potential of water extracts in the oral cavity of male Fischer rats. Ninety-one rats were treated surgically to create a canal in the lower incisors. To these canals, H2O extracts of snuff (n=30), snuff enriched with its own H2O extract (n=30), and an extract enriched with tobacco-specific nitrosamines were applied. Three regions of porcine oral mucosa, representing a total of 635 mm2 of surface in a tobacco user, were examined. Tumor development was observed in 41% of the rats treated with tobacco-specific nitrosamines alone, and in the group treated with enriched snuff, indicating that tobacco-specific nitrosamines may act as vehicles for the transport of tobacco carcinogens across oral mucosa. These results support the hypothesis that the use of smokeless tobacco may contribute to the development of oral tumors.
LUNG TUMORS IN RODENTS AFTER INHALATION OF PAH-CONTAINING EMISSIONS, U. Heinrich, E. Port, J. and U. Mohr, Fraunhofer-Institut fur Toxikologie und Aerosolforschung, Hannover, FRG, and Medizinisches Institut fur Umweltmedizin, Düsseldorf, FRG.

It is well known that polycyclic aromatic hydrocarbons (PAH) are produced with incomplete combustion of organic material like coal and oil derived fuels. As to now, about 70 PAH which are relevant to the ambient air and workplace environment were proved carcinogenic in various animal experiments. But, most of the carcinogenic PAH are acknowledged until very fine respirable most particles when they are emitted. Therefore, the major exposure route for humans is inhalation and the respiratory tract is the target organ of most respiratory tract cancers. Long-term animal inhalation experiments using 3 different PAH-containing emissions were carried out to investigate their possible health effects. The potential carcinogenicity was one of the crucial effects on the respiratory tract besides others, in which we were most interested. Rats, hamsters and mice were exposed to diesel engine exhaust (DE), particle-filtered and unleaded diesel engine exhaust (DE and DE) and to coal oven exhaust mixed with PAH-rich effluents of pyrolytic pitch (COE) during one year exposure in the exposure chambers, e.g. for benzaldehyde use 0.1 and 10 mg/m³ for GE and DE, resp., and 0.9 and 90 mg/m³ for COE. The main concentrations in the air in the exposure chambers was about 40 - 90 µg/m³, 4 mg/m³ and 3 - 4 mg/m³ for GE, DE and COE, resp. But with coal oven exhaust particles more than 50% of the mass consisted of condensed organic material and only less than 10% was carbonaceous material with diesel exhaust particles this ratio was reversed. Therefore, only inhaled exposed lungs accumulated soot particles could be observed. Lung tumors were found in DE and COE exposed animals with no tumors in rats and hamsters exposed to GE, H)E and in clean air control. In rat lungs, beside adenomas, squamous cell carcinomas in rats and hamsters exposed to GE, H)E and in clean air control. In rat lungs, beside adenomas, squamous cell carcinomas were found in DE and COE exposed animals with no tumors in rats and hamsters exposed to GE, H)E and in clean air control.

In diesel exposed lungs accumulated pitch (COE). The FAH concentration in the exposure chambers, e.g. for benzo(a)pyrene was 10 ng/m³ and to 90% of the mass consisted of condensed organic material like coal, ana oil derived fuels. Up to now, about 20 PAH which are relevant to the ambient air. Chronic animal inhalation experiments using 3 different PAH-containing emissions were carried out to investigate their possible health effects. The potential carcinogenicity was one of the crucial effects on the respiratory tract besides others, in which we were most interested. Rats, hamsters and mice were exposed to diesel engine exhaust (DE), particle-filtered and unleaded diesel engine exhaust (DE and DE) and to coal oven exhaust mixed with PAH-rich effluents of pyrolytic pitch (COE) during one year exposure in the exposure chambers, e.g. for benzaldehyde use 0.1 and 10 mg/m³ for GE and DE, resp., and 0.9 and 90 mg/m³ for COE. The main concentrations in the air in the exposure chambers was about 40 - 90 µg/m³, 4 mg/m³ and 3 - 4 mg/m³ for GE, DE and COE, resp. But with coal oven exhaust particles more than 50% of the mass consisted of condensed organic material and only less than 10% was carbonaceous material with diesel exhaust particles this ratio was reversed. Therefore, only inhaled exposed lungs accumulated soot particles could be observed. Lung tumors were found in DE and COE exposed animals with no tumors in rats and hamsters exposed to GE, H)E and in clean air control. In rat lungs, beside adenomas, squamous cell carcinomas were found in DE and COE exposed animals with no tumors in rats and hamsters exposed to GE, H)E and in clean air control.

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The presence of polycyclic Aromatic Hydrocarbons (PAHs) and especially of Benz(a)Pyrene carcinogenic expelled by the exhaust systems of aircraft engines was determined due to the fact that aviation engines release considerable amounts of PAHs into the atmosphere. For this study we selected "Jose Marti" International Airport, because of its heavy air traffic. Air and soil samples were collected at different points of the airport area, in order to study the possibility that exhausts from aircraft engines pollute the environment with carcinogenic hydrocarbons. The B(a)P were isolated and identified and quantitatively measured by thin-layer chromatography and spectrophotometry. Certain regularities were found in the distribution of B(a)P that is to say, from 50.0 ug/Kg of soil at the runway expected to 34.4 ug/Kg at 150 meters away from it. At the end of the runway the higher values were found(63.8 ug/Kg and 67.8 ug/Kg) due to the fact that in these places the engines operate at maximum working regimes. In the middle of the runway the B(a)P concentration was 61.11 ug/Kg. The study showed that the levels of B(a)P at "Jose Marti" International airport were within the limits allowed for by international norms.

**2382** AVIATION AND ENVIRONMENTAL BENZ(a)PYRENE POLLUTION AT "JOSE MARI" INTERNATIONAL AIRPORT, HAVANA, CUBA, Conf. Reun. Int. S. C. de Chim., Mexico City, Mexico.

**2383** Production of N-Nitrosoamines from Ephedrine, Pseudoephedrine and Extracts of Ephedra foliate under Physiological Conditions. S. M. ALWAN, H. A. AL-NINDAI, S. AL-SABBAH

**D-46: ENVIRONMENTAL RISK FACTORS I**


**2385** SPECIFITOF SEROLOGICAL METHODS IN DIAGNOSIS OF ENDOGENOUS BOVINE LEUKOSIS (EBL). P. Lešťák, M. Damheli, U. J. Vrtiak, P. Pagač, Veternary University, Košice, Slovakia, Université Charles de Bruxelles.

**E-41: RETROVIRUSES IN EXPERIMENTAL AND HUMAN DISEASES**


The release of a large amount of MMTV in milk is accompanied by high early MT incidence. We will report a new mouse strain with paradoxical characteristics with regards to MMTV expression and MT development. The II-TES strain mice used were established by crossbreeding a male DBA/2 mouse with two strains of Japanese pet mouse origin (OZF and CS). Multinuclear 42 females of the strain developed no early MT and only 4 late MT over 16 months of age. On the other hand, both the reciprocal F1 hybrids of this strain with the other low MT strain of Japanese pet mouse origin (OZF) developed early MT at a high rate (80%).

The MMTV concentrations in 21 milk samples from II-TES was 800-4600 ug/ml in average, while few MMTV were detected in OZF milk. The mean MMTV concentrations in milk samples both from the reciprocal hybrids (OZF x II-TES)F1 and (II-TES x OZF)F1, were 1,430-1450 ug/ml and 1,360-1400 ug/ml, respectively.

It is most possible that MMTV expressed in II-TES mouse milk is derived from endogenous MMTV of DBA/2. The recent hypothesis of murine mammary carcinogenesis implies the existence of at least 3 steps: 1. activation of provirus to release virions; 2. new integration of proviral DNA into particular sites of the host genomes; 3. promotion of cellular oncogenes. Our results suggest that the II-TES mice have some mechanisms to interrupt 2nd and/or 3rd steps.
2386 BOVINE LEUKEMIA PROVIRUS IN THE DNA OF DIFFERENT INFECTED HOSTS. R. Slaviková, V. Želano, M. Reinerová, R. Kattmann, and A. Burzy, Cancer Res. Inst., Slovak Acad. of Sciences, 812 Bratislava, Czechoslovakia, U.S. Dept. of Molecular Biology, 1640 Rhode St., Genesee, Belgium

For BLV infection in vitro different sheep fetal liver cells were used. We observed focus formation of transformed cells, syncytia and syncytia aggregating in spleen, kidney, thymus and chest cultures. Morphological transformation was noticed within 10-16 days of BLV inoculation and it was lost after transfer. In order to investigate whether the provirus of BLV is present in cellular DNA were extracted, digested with EcoRI and hybridized with BLV probes. We observed the presence of proviral copies in 9.0 kb DNA fragment. BLV probe recognized two signals of 9.0 kb and 7.5 kb in infected thymus and kidney cell DNA. For BLV host range study we infected various human cell lines, N collagen 77 cell line infected with BLV was virus productive by reverse transcription assay. The presence of proviral copies in 15.0 kb and 11.0 kb DNA fragment was proved. Myeloid K562 infected cell line was also positive for BLV provirus in Southern blot analysis. BLV probe hybridized to an 15.0 kb resp. 12.0 kb fragments in digested DNA. Reverse transcriptase test has shown that mouse myeloma cell SP2/0 infected with BLV were higher producers of the virus. The present results suggest that cells from various fetal sheep organs and different host cell lines were susceptible to BLV infection. In some of these virus was able to replicate.

R. Chorvath

2387 BOVINE LEUKEMIA VIRUS : ISOLATION AND CHARACTERIZATION OF NONPRODUCING CELL CLONES. J. Hájek, V. Altenberger, Cancer Research Institute, Slovak Academy of Sciences, 812 Bratislava, Czechoslovakia

Cytogenetic analysis of bovine leukemia virus MAV-reproducing cell line MAV revealed the presence of nonproducer cell clones in uncloned cell population. Determination of RNA dependent RNA polymerase activity in culture medium was the test for virus productivity. The isolated nonproducer cell clones contained integrated BLV proviruses as was confirmed by molecular hybridization experiments after restriction analysis of cellular DNA. Expression of genes products was investigated by immunoprecipitation using different polyclonal and monoclonal antisera. The comparison of the virus productive clone and nonproductive one indicated the absence of gag precursor p24, the gag-related p145, and the main structural virus protein p24 was missing as well. In the nonproducer cells a new gag-related p60 was found which was not precipitated in virus productive cells. Further experiments are done, to see whether the BLV provirus is deleted, mutated, or the regulation of the virus genome transcription was changed.


The identity of nucleotide sequences (SAGATA et al. 1989) is the basis for the assessment of biological risks for humans that were possibly infected by animal retroviruses. The detection of antibodies against BLV in humans might be one of the proofs. This fact is emphasized by the finding of CEREHA et al. (1984) who demonstrated the anti-BLV antibodies in humans with chronic lymphatic leukemia. In this work the results are presented of experiment in which anti-BLV antibodies were demonstrated in six groups of patients consisting of: 10 healthy blood donors, three groups of workers (34, 20 and 12 persons resp.) in animal production (mostly feeding and milking), working for a long time in leukemia stables. Another examined group was represented by laboratory and research staff (112 persons resp.) working for two years in enzootic leukemia research or in production of diagnostic preparations (antigen for ID and ELISA tests). The last examined group was represented by 30 patients with various hematolgoes. The determination of anti-BLV antibodies in serum of examined patients was performed by the ID, ELISA and immunoperoxidase tests on PLS cells, permanently producing BLV virus. Positive reaction, demonstrating anti-BLV antibodies, was detected in no case and in none of the groups.

K. Chorvath

2389 ELECTRON MICROSCOPIC STUDIES OF INTRACRISTERNAL VIRUS PARTICLES IN THE SEMINAL VESICLE OF SIN NISSA STRAIN. S. Imat, Y. Taniguchi, J. Nomoto, Y. Kiyozuka, and Y. Tagaura, Dept. of Pathology, Niigata College, Niigata, Japan

The SIN is a high mammary cancer strain of Swiss origin. It is well known that male genital organs, such as seminal vesicle is one of a major organ for MTV production and its horizontal transmission. We have observed two virus-like particles by negatively stained samples of virus particles. Namely, budding type C like virus and intracristernal virus particles (ICVP). ICVP, 80 to 110 nm in diameter, have been found to be the rough endoplasmic reticulum. They have a double membrane. The ICVP appeared different from intracristernal A virus particles in size and structure and rather looked like type C particles, which was described by OHRI, K. et al. in 5D-murine sarcoma virus-induced rat bone tumor cancer (RES. 1976). At the same time, the virus budding from the basement membrane was suggestive of type C virus particles. But, no morphological relationship between ICVP and budding type C virus was detected. Electron microscopic studies by use of protein-A gold will be discussed.
STUDIES ON RETROVIRUS-SPECIFIC ANTIGENS AND ANTIBODIES IN HUMAN ACUTE MYELOID LEUKEMIAS.

J. Kiss, L. Véczi, F. D. Tóth, B. Szabó, K. Rék and A. Kiss, Inst. of Microbiology and 2nd Dept. of Medicine, Medical University, Debrecen, Hungary.

Antigens related to the p30 polypeptide of baboon endogenous virus (BaEV) and gibbon ape leukemia virus (GaLV) as well as antibodies reacting with the gp70 antigens of BaEV and GaLV were investigated in cell and serum samples from patients with AML and ALL. Expression of GaLV p30-like antigens could be observed in all samples from the progressive stage of AML and ALL. The amount of this antigen markedly decreased in remission cell samples. Antibodies reacting with the viral gp70s could be detected only in the remission serum samples. Majority of remission serum samples exerted significant virus neutralizing and cytotoxic effect as it was demonstrated by indirect cytotoxic tests and \(^{3}H\)-release assay.

MICROPHOTOMETRIC ANALYSIS OF EUROPEAN RAPIDLY PROLIFERATING LYMPPHOMAS OF PERIPHERAL T-CELL ORIGIN (EPTL) AND ADULT T-CELL LEUKEMIA-LYMPHOMAS IN JAPAN (ATLL).


Microphotometrically nuclear DNA contents were analyzed in 5 µm thick and Feulgen-stained sections by making a nuclear density scattergram (NDS) of nuclear largeness versus DNA content in 8 cases of EPTL and 8 cases of ATLL to evaluate whether distinct differences in growth kinetics exist between HTLV-related lymphomas (ATLL) and non-related lymphomas (EPTL). Neoplastic cells of EPTL and ATLL formed a variety of oblique zonal cluster (OZ) in NDS, depending on their nature of proliferation. Anaploid high DNA content was noted in the atypical large cells with speckled heterochromatin in pleomorphic large and medium-sized and large type of ATLL, apart from OZ, as a pathognomonic feature of a HTLV-related lymphoma. A heterogeneity of cells in nuclear largeness and DNA content was observed in pleomorphic medium-sized type of EPTL. But there were no essential differences in NDS patterns between pleomorphic medium-sized type of EPTL and ATLL. In EPTL, there were more numerous intermingling non-neoplastic lymphocytes than in ATLL, suggesting that EPTL is biologically less aggressive than ATLL. The small to medium-sized intermingling lymphocytes with convoluted nuclei in both entities could be regarded as stimulated lymphocytes from their distribution in the NDS. Considering the karyotypic differences between primary cultures and cell lines of HTLV-related lymphomas (Nowell P.C. et al., JNCI 73; 969-974, 1984), the stimulated lymphocytes proved their mixed proliferation with neoplastic cells in vivo and no essential differences in NDSs of pleomorphic medium-sized types of both entities suggested a common oncogenic factor/process in EPTL and ATLL.
2394


We reported the detection of retrovirus-like particles in human thymus cells when cultured with human B cells. Retrovirus-like particles were demonstrated in cultured thymus cells (thymus hyperplasia) of patients with autoimmune diseases such as myasthenia gravis and pure red cell aplasia. Retrovirus-like particles were also detected in human fetal thymus cells (A. Omo et al. Seminars in Surgical Oncology vol.13(3),1,1985) Jpn. J. Cancer Res. (Gann) 74,801,1983). We have tried in vitro transmission and propagation of these particles in several cell lines, mainly by means of co-culturing.

Human T cells (a T cell line, CEFK-HSB) were infected with retrovirus-like particles obtained from the cultured human thymus cells. Reverse transcriptase activities were detected in the culture fluids of three virus-infected T cell lines (KK-1, -2, -3). Virus particles were also demonstrated in these cell lines. DMN from KK-1 cells have genomes of neither HTLV-I nor HTLV-II by Southern blot hybridization. No antigen-antibody reaction was observed between KK-1 cell antiserum and animal retroviruses examined. Changes of T cell surface markers were observed in all three virus-infected T cell lines. OCT-4 inducer/helper T cell surface markers were commonly induced on such virus-infected T cell lines (negative OCT-4 in CCNF-HSB).

These virus-infected T cell lines should be useful for further characterization of retrovirus-like particles detected in human thymus cells. Moreover, T cell surface antigenic changes indicate that retrovirus-like particles detected in human thymus cells are somehow involved in differentiation of T cells or thymus T cell disorders in some human diseases.

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A two-step model for the pathogenesis of AIDS/KS due to an infectious agent has been postulated. In a first step, a combined assault against both T and B cells might take place by the T cell-tropic retrovirus (AIDS-associated retrovirus; ARV) alone or in combination with CMV and EBV. Specific involvement of CMV in the induction of KS has been considered as a second step. Therefore a 5-year seroepidemiologic prospective study on homosexual men from New York City was initiated in 1982, particularly concerning the determination of antibody prevalence to ARV, HTLV-I, CMV and EBV as well as their correlation with the clinical evolution. The total number of subjects enrolling voluntary was 104, all without clinical symptom; 92 of them (88.4%) were seropositive for ARV. Eighty-six subjects presented themselves at 6-months intervals, blood samples were taken and clinical informations are available. Fifty percent of them have developed clinical symptoms; 5 came down with AIDS/KS, 1 with Burkitt's lymphoma, 2 with PCD and 7 with ARC. It was observed that 8 (18.6%) of the asymptomatic subjects were seronegative at all times during this 3-year follow-up while 11 (25.6%) seroconverted from antibody positive to negative. In contrast, only 4.7% of the symptomatic subjects were seronegative at all times, while 2.3% became seronegative during this period.

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Retrovirus-like particles have been detected in human thymus cells. By using retrovirus-like particles obtained from such virus-infected T cells, we observed anti-retroviral antibodies in sera of patients with several malignancies, in addition to those with autoimmune diseases.

As antigens, virus particles were prepared by sucrose density gradients from culture fluids of virus-infected KK-1 cells. Proteins obtained from uninfected host cells (HSB) under the same procedures were used as control. 116 sera from autoimmune diseases (myasthenia gravis, ulcerative colitis, Hashimoto thyroiditis, SLE etc.) and 186 sera from malignancies (leukemias, stomach cancers, hepatomas, thyroid tumors, ovarian tumors, mammary tumors etc.) were examined for the presence of antibodies to retrovirus-like particles in human thymus cells. 71 sera from healthy donors were used as control. In ELISA, the antibodies were shown to be statistically significant in patients with several autoimmune diseases (ELISA absorbance of KK-1 / ELISA of control HSB was calculated), and demonstrated in 20-35% sera from patients with several malignancies including leukemias, stomach cancers, hepatomas, ovarian tumors. Higher titers of antibodies were demonstrated in early cancers than in advanced cancers. Western blot, protein bands (MW: 68k, 88k, 70k, 63k, 36k, 31k, 28k, and 16k) were demonstrated. The presence of antibodies to such virus particles were also confirmed by immunoelectron microscopy.

These data suggest the possibility that retrovirus-like particles detected in human thymus cells are involved in the pathogenesis of autoimmune diseases where thymic changes are frequently observed. The involvement of these particles in some malignancies is also suggested.
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An increasing spectrum of diseases, including AIDS and related syndromes, have been associated with infection by the human retrovirus, HTLV-III/LAV. Initial observations identified IgM antibodies to the helper/inducer (Th) subgroup as primary targets of infection with HTLV-III/LAV, resulting in a cytotoxic response. We and others have subsequently demonstrated that other cell types, including cells of the monocyte/macrophage and B-lymphocyte lineage, and possibly epithelial and neurological cells, can also be infected and cause functional consequences. Therefore, many of the pathological events observed could be directly attributable to infection of target cells. However, a survey of involved tissues in vivo and infected cells in vitro using biological, immunological, and molecular biological procedures suggest that, despite an overwhelming immunosuppressive or cytotoxic response, only a low percentage of the cell population actually contains virus. These observations are consistent with the systemic release of either virus-induced cellular, or virus-coded factors which affect cellular and/or humoral immunity and cell function.
PREVALENCE OF ARV INFECTION AND RELATIONSHIPS TO IMMUNODID

Sera of 119 Old World monkeys kept for laboratory use were investigated for the presence of antibodies reacting with HTLV-I and HTLV-III antigens in indirect immunofluorescence and ELISA tests. CSF/PL and HP/HH infected cells kindly provided by R.C. Gallo were used as sources of viral antigens respectively. 14 out of 95 sera of African green monkeys from Kenya and Ethiopia (two of them collected as early as 1963), as well as 2 of 7 sera of Javanese macaques were positive for HTLV-I antibodies, but none of the 17 Rhesus macaques from India.

In contrast, one positive serum (collected in 1963) reacting with HTLV-III antigens was found out of 119; a serum of a Rhesus macaque. All other sera were negative in this respect. These investigations (i) direct attention to the importance of testing laboratory monkeys for HTLV-associated antibodies, (ii) provide evidence of HTLV-III associated infection in monkeys in the early sixties (iii) suggest that HTLV-III associated infection might occur earlier than that of HTLV-I, (iv) HTLV-III associated infection could be geographically separated from that of HTLV-I. These data contribute to understand the origin and the natural transmission of HTLV-like viruses in monkeys.


Common pathological features observed in angioimmunoblastic lymphadenopathy (AILB) and AIDS suggest the antibody-antigenic role of the HTLV-III/LAV viruses in AILB. Sera from AILB patients were tested for HTLV-specific antibodies and interferon level. Some sera samples from the active phase of the disease contained antibodies reacting with HTLV-III-infected cells in indirect membrane immunofluorescence. The interferon level of the same sera was elevated as compared to that of the healthy controls. These data suggest a HTLV-III-like virus infection in some cases of AILB. Studies concerning the specificity of antibodies in detail as well as the virus-induced interferon producing capacity of leukocytes are going on.

We investigated the possibility relationship between the susceptibility of cells to differentiation induced by phorbol 12-myristate 13-acetate (PMA) and the subcellular translocation of a calcium- and phospholipid-dependent protein kinase C. The presence of protein kinase C from cytosol to membrane was observed in the nuclei of cells that had differentiated in response to PMA treatment. These results suggest that the commitment of cells to differentiation may be associated with the translocation of protein kinase C activity from cytosol to membrane. Supported by NIH grant CA30907.

2408 EFFECT OF Mg²⁺ ON HUMAN PROMYLEOCYTIC LEUKEMIA HL-60 CELL DIFFERENTIATION. T. Okazaki, T. Nomizu, M. Tashima, H. Sawada and H. Ichihara. The Laboratory of Internal Medicine, Faculty of Medicine, Osaka University, Suita City, Osaka, 565 JAPAN.

The role of Mg²⁺ on cell functions has been extensively investigated. However, decrease of cellular Mg²⁺ on cell differentiation is scarcely elucidated. When HL-60 cells are incubated in the medium containing various concentrations of Mg²⁺, cell growth is suppressed according to reduction of Mg²⁺ in medium. HL-60 cell differentiation induced by 10⁻⁴M 1,25(OH)₂D₃ plus 10⁻⁵M retinoic acid (10⁻⁵M retinoic acid plus 10⁻¹⁵M TPA, 1.75 μM dimethylsulfoxide or 1x10⁻⁹M aclacinomycin) is almost completely suppressed by deprivation of Mg²⁺ in medium. HL-60 cell differentiation, however, appears to be induced without 1.25(OH)₂D₃ by incubation in Mg²⁺ containing medium (0.4mM), after the cells are treated with 1x10⁻¹⁵M 1,25(OH)₂D₃, in Mg²⁺ free medium for two days. Simultaneous treatment with both 1x10⁻⁴M 1,25(OH)₂D₃ and 1x10⁻⁵M retinoic acid and 1x10⁻⁵M dihydroxycyclopent-anone, even though in Mg²⁺ free medium, can differentiate HL-60 cells to the cells which have NBT reduction ability but not MTE activity. The inhibitory effect of Mg²⁺ free medium on HL-60 cell differentiation induced by 1,25(OH)₂D₃ or retinoic acid is shown to be substituted partly by 1x10⁻⁹M dibutyryl cAMP and Mg²⁺ free medium. In summary these results suggest that the commitment of Mg²⁺ cell differentiation may not require Mg²⁺ but the expression of differentiation may require Mg²⁺ and AMP, and have a significant role on the induction of HL-60 cell differentiation.
2411 ONE INDUCER OF HUMAN PROMYELOCYTIC LEUKEMIA (HL-60) CELL DIFFERENTIATION AUGMENTS THE EFFECT OF A SECOND INDUCER. Kajol Paterson, M. Paterson laboratories, & Holt Radium Institute, Manchester M20 9BX U.K.

The aim of this study was to elucidate the mechanism of HL-60 cell differentiation. A series of inducers that are known to act at different sites during erythrocye differentiation of Friend murine erythroleukemia cells was tested for this study. Exponential cultures of HL-60 cells (at an initial density of 6x10^5 cells/ml) treated for 5 days with 120 nM N-dimethylformamide (DMF), 210 mM dimethylsulfoxide (DMSO), 0.5 mM 9-fluorenylmethoxycarbonyl (Fmoc) and 50 nM dibutyryl cyclic AMP (DBcAMP) were used in this study. The ratio of differentiated and undifferentiated cells was determined by flow cytometry using monoclonal antibodies to CD11b, CD14 and CD15.

2412 POTENT DIFFERENTIATION INDUCERS OF HUMAN PROMYELOCYTIC LEUKEMIA CELLS. NEW STRUCTURAL TYPES. Koichi Shudo, Hiroyuki Kagetika, Emiko Kawachi, Yuichi Hashimoto, Pac. Pharm. Sci., Univ. Tokyo Japan

Induction of differentiation of cancer cells may have implications in the therapy of human cancers and other malignant disorders. However only a couple of specific inducers have been known. This paper describes the discovery of structurally novel differentiation inducers of human promyelocytic leukemia cells HL 60 to granulocytes, whose activity is stronger than retinoic acid and other retinoids.

Terephthalic anhydride (5,5,8,8-tetramethyl-5,7,8-tetrahydroxynaphthaldehyde (Am-80) induced the differentiation of HL 60 cells to granulocytes at less than 10^-9 M. The induced cells exhibit the morphological changes of granulocytes and possess NBT reducing activity. Growth of the cells also ceased because of the inability of the mature cells to proliferate.

Other interesting active compounds such as 7,8-dihydroxyquinoline (Am-80) and 6-amino-1-carboxyhexylamide (Am-80) were also observed. The combination of Am-80 and other differentiation inducers such as retinoic acid (RA) and dimethylsulfoxide (DMSO) was shown to induce differentiation in HL-60 cells.


DAC is a potent antileukemic agent which acts through its incorporation into DNA as a fraudulent base. Biochemical consequences can be inhibition of DNA methylation and alteration of gene expression and alternatively DNA damage due to decomposition of the azacytosine residue. DAC has been shown to induce differentiation in some model systems including HL-60 promyelocytes. We have been able to examine the effects of DAC in two sublines of HL-60 cells (subline A and subline B). We have shown that the subline A cells are sensitive to DAC and the subline B cells are resistant. The effect of DAC on the growth of HL-60 cells was determined by the number of cells growing in a soft agar assay.
CHARACTERIZATION OF MONOCYTE- AND FIBROBLAST-DERIVED MONDAY • AUGUST 25 • AFTERNOON

N. Kawatani, K. Takeda and K. Konno, 1st Dept. of Biochem., Sch. of Med., Showa Univ., Tokyo, Japan

of potential differentiation inducers. are in progress to look for synergy between other classes could provide a means to achieve a more potent matura-

cation inducers in sensitive subline A. These results combined, the percentage of NBT-positive cells increased and DMSO+DAC 8Z. However, when all three agents were RA+DMSO gave rise to 15Z NBT-positive cells, RA+DAC 132 were incubated with 1 jiM RA, 12 DMSO or 1 uM DAC and in the following combinations: RA+DMSO, RA+DAC, DMSO+DAC and RA+DMSO+DAC. The percentage of NBT-positive cells were combinations, the following combinations: RA+DMSO, RA+DAC, DHSO+DAC and was expressed as

DI to the above differentiation inducers when given singly was treated with these agents in various combinations, aiming to enhance the maturational effects. HL-60 cells were incubated with 1 an RA, 12 DMSO or 1 an DAC and in the following combinations: RA+DMSO, RA+DAC, DMSO+DAC and RA+DMSO+DAC. The percentage of NBT-positive cells were 102 for RA, 52 for DMSO and <12 for DAC. In combinations, RA+DMSO gave rise to 157 NBT-positive cells, RA+DAC 13T and DMSO+DAC 87. However, when all three agents were combined, the percentage of NBT-positive cells increased to 881, which is in the same range as that achieved with potent inducers in sensitive subline A. These results suggest that combination of differentiation inducers, including perhaps a DNA-hypomethylating agent such as DAC, could provide a means to achieve a more potent matura-

tional effect in resistant, HL-60 cells. Further studies are in progress to look for synergy between other classes of potential differentiation Inducers.

STIMULATION OF DIFFERENTIATED MORPHOLOGY AND FUNCTION IN HUMAN MELANOMA CELLS BY VARIOUS INDUCERS: Kyoichi ASAK*, and Takeshi AOI**, Div. of Pharmacology, Samea Kagaku Res. Inst., Kasugai and ** Dept. of Pathology, Chiba Cancer Center Res. Inst., Chiba, Japan

Cultured melanoma cells provide particularly useful model for investigation of cellular differentiation by inducers, compared to the other cultured adherent cells, because they offer readily distinguishable markers of differentiation such as dendrite-like structure formation and scanty cytoplasmin, which are characteristic of normal differentiating melanocytes. For this purpose, malignant melanoma cells, originated from human tissues, were cultured in the presence or absence of chemical compounds including retinoids, dimethyl sulfoxide, IA, 25-dihydroxyvitamin D3, butyrate, steroids etc. and studied for their morphological differentiation as well as tissue type plasminogen activator (TPA) production as an indicative of functional differentiation. Experiment revealed that after 4 days culture, proliferation of human melanoma cells was inhibited by 50% in the presence of 10^{-6} retinoid acid and that marked dendrite-like structure was visible. No elevation of TPA activity, however, was observed. In contrast to it, 12 dimethyl sulfoxide showed inhibition of cell growth by 30T, and acceleration of TPA production (50IU/10^6 cells/24hr), but no remarkable morphologi-

cal changes were observed. Other compounds, known as inducers for leukemic or endothelial cells, for example, 1.2 x 10^{-8} h, 25-dihydroxyvitamin D3, 0.01% butyric acid, 2.5 x 10^{-9} sitosterol or 2.5 x 10^{-9} fucosterol revealed no significant effects on cellular morphology and proliferation, and TPA production.

CHARACTERIZATION OF MONOCYTE- AND FIBROBLAST-DERIVED MONDAY • AUGUST 25 • AFTERNOON

DIFFERENTIATION INDUCING FACTORS FOR HUMAN MYELOGENOUS LEUKEMIC CELL LINES. S. Iwamoto, H. Sugimoto, T. Takuma N. Kawatani, K. Takeda and R. Konno, 1st Dept. of Biochem., Sch. of Med., Showa Univ., Tokyo, Japan

Human myeloid leukemia lines, blocked at certain stages of differentiation, can be induced to further differentiate by some protein inducers. However, these protein factors have not yet been well characterized. We tried to isolate and characterize such protein inducers produced by leukocytes and fibroblasts. We examined whether peripheral blood monocytes, as well as T cells, produce differentiation inducing factors. Monocytes were isolated from volunteers by Ficoll- Hypaque centrifugation, Percoll centrifugation and adherence to serum coated dishes - cultured supernate of isolated monocytes (more than 97T non-specific ecartin positive cells with no T cell contamination) stimulated with LPS and used as a source of inducers (MCD). WI-38, a human diploid cell line derived from fetal lung, was used for preparing fibroblast conditioned medium.

Differentiation inducing activity was evaluated by measuring cellular markers normally associated with the maturation of granulocyte and monocyte elements. Cytometric analysis of monocyte (U-937, THP-1) and myeloid (ML-1, HL-60) leukemic cell lines into monocyte/macrophage lineage. Gel filtration analysis showed two major active species with approximate molecular weights of 90,000 and 50,000 daltons. Fibroblast produced a proteinaceous inducer, molecular weight of 80,000, which was more effective on monocyted lines than on myeloid lines. These differentiation inducing substances, distinct from colony stimulating factors and intercellularly. From the point of view of therapy, these factors may offer potential for treatment.

ASTROCYTIC DIFFERENTIATION IN VITRO OF HAMSTER MEDULLOBLASTOMA INDUCED BY JC VIRUS

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Human medulloblastoma is suggested to have differentia-
tion potentiality. We have examined experimentally this possibility using hamster medulloblastoma model induced by JC virus, coupled with immunohistochemistry for astroctytic marker, glial fibrillary acidic protein(GFAP). The hamster medulloblastoma induced by the Tokyo strain of JC virus was negative for GFAP and vimentin but positive for T-common antigen of papova virus. The cultured cells became positive for vimentin after several passages but remained negative for GFAP. After blind passage for 2 years the cells were analysed again by immunohistochemi-
cal staining using antibodies for GFAP, vimentin, NSE, S-100 protein, neurofilaments(SBF, 200F, 160H) and T-common antigen of papova virus. We observed that 60% of the cell was positive for GFAP, 100% positive for vimentin, 100% positive for T-common antigen but negative for NSE, S-100 protein and neurofilaments. By electron-
 microscopy, clusters of thin filaments (diameter less than 10 nm) were observed.

This result indicates that JC virus-induced hamster medulloblastoma has potentiality of differentiation to glial tumor cells.

Retinoids are necessary for normal cell growth and differentiation. They are known to prevent and retard malignant transformation of cells. The effect is assumed to be mediated by one or more mechanisms by the specific retinoid-binding proteins.

The CRBP concentration was determined with a specific and sensitive radioimmunoassay in biopsies from normal mucosa and squamous cell cancers of the head and neck region in 41 patients and of the cervix uteri in 32 patients. The plasma concentration of retinol, retinol-binding protein (RBP), prealbumin and some acute phase proteins were also determined.

In the patients with SCC of the head and neck region, the tumours contained significantly higher concentration of CRBP (median: 176 ug/g protein; range: 24-114 mg/l) than normal surrounding mucosa (median: 20 ug/g protein, range: 6-97). The tumour/normal mucosa CRBP concentration ratio showed a significant inverse correlation to a histopathological malignancy grade score. The CRBP concentration in normal mucosa was significantly increased by RBP. Also the SCC of the cervix uteri contained higher concentration of CRBP (median: 120 ug/g protein, range: 4-700) than normal surrounding mucosa (median: 35 ug/g protein, range: 16-257).

Most of the patients had low levels of plasma retinol and RBP compared with matched controls. If this has any relationship to the development of the cancer or if the activation inflammatory induced by the cancer leads to low plasma retinol concentration is unknown.

The antibodies used for the radioimmunoassay were also useful for immunohistochemical identification of CRBP in histological preparations.


Retinoids are known to mediate their antiproliferative effect on mesenchymal and epithelial cells by inhibiting the synthesis of cell surface growth factors (TGFs) and promoting the synthesis of a differentiative factor (TGFs). In this study, we examined the possibility of polyamine biosynthesis being involved in the growth promotion of retinoids on cells producing TGFs.

We used the murine sarcoma virus (MSV)-transformed mouse fibroblasts as a model system to investigate the role of polyamine biosynthesis in the growth promotion of retinoids. We found that the polyamine biosynthesis was significantly increased in MSV-transformed mouse fibroblasts compared with normal mouse fibroblasts. The polyamine biosynthesis was inhibited by treatment with DFMO, a specific inhibitor of ornithine decarboxylase (ODC). This inhibition of polyamine biosynthesis was correlated with a reduced growth promotion of retinoids on MSV-transformed mouse fibroblasts.

These results suggest that polyamine biosynthesis is essential for the growth promotion of retinoids on MSV-transformed mouse cells. Further studies are needed to clarify the mechanisms by which polyamine biosynthesis is regulated by retinoids and to elucidate the role of polyamine biosynthesis in the growth promotion of retinoids on other cell types.
EFFECTS OF LIPOPHYLIC VITAMINES ON HUMAN COLON ADENOCARCINOMA.

The effect of lipophylic vitamins on tumor cell lines Hct-8R and LS-174, from human colon adenocarcinoma have been examined. Specifically, the lipophylic vitamins A (both retinol and retinoic acid) and E (tocopherol and tocopheric succinate) are under examination. Growth inhibition is observed with no cytotoxic effect, as tested by trypan blue exclusion and plating efficiency, seems to be responsible for retinol dose response curves which show a cell yield slowing-down starting from $10^{-5}$ M retinol concentration. NMR spectra of $10^{-4}$ M retinol treated cells indicate a decrease in the ATP/ADP ratio also present in cells undergone to metabolic stress or to treatment with metabolic inhibitors such as sodium azide. Moreover, a remarkable retinol effect has been noticed in the lipid metabolites signals. All these signals intensity change depending on different experimental conditions.

The aim of this work was to study the effect of TPA and 13 cis retinoic acid on tumor cells under the conditions of mixed culture system. When neuroblastoma N2a or glioma BT5C cells were exposed to TPA or 13 cis retinoic acid, the colony number was stimulated by TPA whereas RA reduces colony number. After seeding the same tumor cells on the confluent layer of nontransformed 3T3 cells, the stimulatory effect of TPA was not observed. RA also in this system inhibits plating efficiency of tumor cells. Spheroid cultures of BT5C cells treated with TPA were found to be stimulated in their growth. RA inhibits spheroids' growth. Altogether it looks that nontransformed cells surrounding a tumor cells block phorbol receptor. Protein kinase C activity is studied in this system. Tumor cells as could be judged from experiments with spheroids have not block ability.


Cells of the ML-1 cell line were induced to differentiate by 1.6% dimethylsulfoxide (DMSO) or by $1x10^{-5}$M retinoic acid (RA). Most of the resulting cells resembled mature neutrophilic segments but contained nucleoli in toluidine blue stained slides. In contrast, neutrophilic segments of normal persons and patients with chronic myelogenous leukemia in chronic phase did not contain nucleoli. In comparison with intensely stained nuclear envelopes of normal neutrophils, the regions of the nuclear membranes (stained by Victoria blue B) in both untreated and DMSO or RA treated cells were less distinct. The distribution pattern of main nucleolar types suggested a reversible decrease of r-RNA synthesis by DMSO or RA. Similar results were obtained in non-segmented cells after a low-dose cytarabine (Ara-C) treatment of ML-1 cells. The surface phenotype changes (detected by monoclonal antibodies to differentiation antigens) induced by DMSO, RA and Ara-C will be discussed.

F-46: TUMOUR DIFFERENTIATION

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Human germ cell tumors may have morphological and functional differentiating capacity. To analyze these characteristics, we have established serially transplantable human germ cell tumors in nude mice, including 5 yolk sac tumors, 1 embryonal carcinoma, 1 seminoma and 3 immature teratomas. The seminoma line has become a serially transplantable tumor in conditioned nude mice with whole body irradiation. All transplanted yolk sac tumors showed similar capabilities for serum protein production including AFP as their normal counterparts. One of the yolk sac tumors, RTE line, which has been maintained as an ascites form, is shown to express the common cell surface antigen of multiple stem cells of murine teratocarcinomas. The tumor line established from murine embryonal carcinoma of the testis contains 3 variable tumor components such as immature and mature endoderm, neuroepithelial tissue and mature cartilage.

In order to establish differentiation markers of human germ cell tumors, we have attempted to produce mouse monoclonal antibodies. The hybridoma was produced by fusing NS-1 myeloma cells and lymphocytes from a mouse immunized with the yolk sac tumor, RTE line. Some of these monoclonal antibodies are positive on the cell surface of relatively immature embryonal tumor components, but not for mature endoderm in germ cell tumors by immunocytocchemical staining. These antibodies were also shown to be an useful differentiation markers in fetal and renal tissue.


Surgical specimens of 37 tumors of patients with ovarian carcinomas (OC) and 187 tumors of patients with non-small cell lung carcinomas (NSCLC) were investigated by means of flow cytometry. From lung tumors we classified 30 cases as tumors with DNA diploidy, 119 as tumors with DNA aneuploidy containing one abnormal DNA stemline, and 38 as tumors with DNA aneuploidy containing more than one abnormal DNA stemline. Seven tumors of patients with ovarian carcinomas were classified as tumors with DNA diploidy, and 31 as tumors with DNA aneuploidy (3 cases had more than one abnormal DNA stemline). The DNA index values of ovarian tumors ranged from 0.7 to 4.5 and the values of ovarian tumors from 0.8 to 2.7 (DNA-diploidy). A relationship between DNA content and distribution of the cell cycle phases was observed. The results of DNA content analysis have prognostic importance with regard to the length of survival time. Patients with aneuploid tumors had significantly shorter survival times than did those with diploid or near diploid tumors (OC: p = 0.009, NSCLC: p = 0.029). If the proliferative pool (S-phase cells) of tumors was high, the patients died earlier than patients whose tumors had a low proportion of these cells (OC: p = 0.038, NSCLC: p = 0.098). Furthermore, patients with tumors with a low fraction of S-phase cells (OC: p = 0.018). The experiments have shown that estimation of DNA ploidy and proliferative activity represent useful additional prognostic indicators for patients with lung and ovarian carcinomas.

The present study was undertaken to analyze quantitatively cell kinetics of bone and soft tissue tumors using DNA-RNA cytofluorometry after acridine orange (AO) staining, and to evaluate their malignancy by cytofluorometry.

The materials studied were 34 cases of benign bone tumors, 16 cases of giant cell tumors, 17 cases of tumorlike lesions, 20 cases of malignant bone tumors, 42 cases of benign and 18 cases of malignant soft tissue tumors. The tumor cells were isolated from fresh materials by collagenase or papain digestion and smeared onto the slides, followed by fluorescence AO staining for cytofluorometry of cellular DNA and RNA contents. The dual fluorescence intensities were simultaneously measured by an ep-illumination cytofluorometer (NIKON SPM-FFI-D).

Most of the tumors that were diagnosed to be benign by both histological and clinical examinations showed the low proliferative activities of the diploid cells. Moderately aggressive bone tumors such as giant cell tumors showed the high proliferative activities of the diploid cells. On the other hand, highly malignant tumors such as osteosarcomas and MFHs showed active proliferation of the aneuploid cells with polyploidization, associating the markedly irregular distribution of the cellular DNA contents. However, most of the chondrosarcomas showed active proliferation of the euploid-polyploid cells, and synovial sarcomas displayed active proliferation of the diploid cells. Furthermore, some of the benign soft tissue tumors such as neurilemmomas and hemangiomas showed low-grade euploid-polyploidization almost without DNA synthesis activity.

It is therefore concluded that the malignancy of bone and soft tissue tumors are closely related not only to active proliferation of the aneuploid- or euploid-polyploid cells, but also to cell proliferative activity of the diploid cells, especially in the synovial sarcomas or bone giant cell tumors.
10 tissue biopsies from 10 patients affected by tumor of the oesophagus were examined by flow cytometry in order to evaluate the prognostic significance of cytometrically determined DNA content distribution and in order to explore the possibility of using flow cytometry to predict the natural history of such a disease and possibly the response to treatment. Multiple site sampling (2 to 10 biopsic specimens) was performed in both surgical and endoscopic case. All 10 pts affected by oesophageal cancer but 2 were characterized by an abnormal DNA content exhibiting the presence of one or more than one cytometric aneuploid cell subpopulation (A) ranging from 1.30 to 1.62. Our preliminary results proposed a probable correlation between flow cytometry parameters (presence of monomodal, ploidy level, etc.) and clinical parameters which the prognostic validity of flow cytometry.

The gastric cancers could be divided into two main groups based on the ploidy pattern of the cancer cells, group I diploid cells and group II polyploid (polyploid type). These two types of gastric cancers were shown to correspond to undifferentiated (diffuse) and differentiated (intestinal-type) carcinomas, respectively. In group I, the tumor cells were found to be composed chiefly of diploid cells with many S phase cells that were cyrising between 2C (G1) and 4C (G2-M) DNA content stages and/or infrequently involved only a few polyploid cells (less than 2%). The advanced cancers in this group commonly showed the growth of Borrmann type 4 with diffuse infiltration of the cancer cells through the entire gastric wall, and their ploidy patterns were maintained in the same fashion as the tumor growth, regardless of the extent of the tumor invasion. On the other hand, in group II, the tumor cells were composed of various classes of diploid cells with many S phase cells. The advanced cancers in this group tended to show the growth of Borrmann type 2 or 3 with adenocarcinomas that were composed of markedly pleomorphic cells, and the extent of the polyploidization appeared to be increased in association with the extension of both the growths and invasions of the tumors. In addition, some cases of cancers showed aneuploid-polyploidy and were subclassified as group III.

These results suggest that, in the early stages of the gastric cancers, the cell populations may be composed mostly of diploid cells, but with further development of the tumor growth, some of the tumor cells may gradually transform into polyploid or aneuploid cell populations in association with the morphological de-differentiation. 

The investigation was derived from retrospective study of the pathologic materials of gastric cancer who underwent the operation at our clinic of OSAKA CITY UNIVERSITY. Assays of DNA content were performed on the tumor cell suspension treated with collagenase from tumor tissue by a single cell cytometeric method. One hundred tumor cells were at least analyzed per each specimen. To determine the normal diploid DNA value approximately 20 lymphoid cells were measured on same one. The polyploid classes of the tumor cells were analyzed, with regard to binuclarity, on the computer-drawn graphs of the nuclear DNA content distribution. The results showed into three groups on the basis of ploidy pattern determined by DNA contents. In group I and III, the extent of polyploidization appeared to be increased in association with both the tumor growth and its invasion in deeper tissues. From these results, it is assumed that in early stage of gastric cancers, the cell population may be composed mostly of diploid cells, but with further tumor development and its invasion (hepatic, peritoneal and regional lymphnode metastasis), the cancer cells may be gradually revealed different levels of their cellular polyploidy.

We investigated quantitatively cell kinetics of colonic polyoid diseases (7 cases of hyperplastic polyps and 14 cases of adenomas) and colon cancers (45 cases) using an epifluorescence microscope (NIKON SPM-RFT-D) in order to elucidate biological characteristics of the colon cancers. The fluorescence dyes used were acridine orange for measuring cellular DNA-RNA contents and propidium iodide for nuclear DNA.

Normal colonic epithelia examined as a control, were found to be composed of subepithelial diploid cells with a few (less than 3%) cells in S-G2 phases (having intermediate DNA contents). The hyperplastic polyps showed almost the same results as those of the control epithelia. In adenomas, however, the cells were mainly composed of mononuclear diploid cells and also of some cells in S-G2 phases, the latter being more increased than adenomatous polyoid polyps. In addition, the early cancers with intramucosal growths yielded the similar results to those of adenomas, except that very few (less than 1%) intraglandular cells were occasionally present. In the advanced cancers with invasion into deeper submucosal layers, but excluding mucinous carcinomas, were composed of various classes of polyoid or diploid cells with their many S phase cells. On the contrary, mucinous carcinomas were composed almost solely of proliferative diploid cell populations.

Based on these results, it is concluded that adenomas, early cancers and mucinous carcinomas of the colon have similar cell kinetic characteristics. Furthermore, the polypoidization of the colonic cancer cells is suggested to occur as the tumor growth develops into the submucosal layers, and to be accelerated during the progression of the tumor growth with extensive invasion.


In order to enhance the response of sarcomas to combined chemotherapy (CT) a trial was conducted with treatment based on cell kinetics of individual tumors. Material. 22 pts (9 women, 13 men, age 8-64 years) entered the study. There were 10 bone and 12 soft tissue sarcomas. In 16 pts previous standard multimodal treatment failed, 6 were previously untreated. 12 pts had hematogenous spread. Methods: Cis-Platinum (CDP) 50 mg/m² in 12-24 hr infusion or Vinblastine (VLB) 2 mg in 12-24 hr infusion were used as modifiers. DNA (CDP) 50 mg/m² in 12-24 hr infusion or Vinblastine (VLB) were given when an accumulation of cells in S phase was found. Bleomycin, RT, VLB or Adriamycin (ADR) or VLB were given when an accumulation of cells in G2 phase was found. Aspiration biopsies before and after drug infusion were used as markers of cellular kinetics with the aim to enhance the effect of other drugs or irradiation (RT) which were to follow. Aspiration biopsy studies and after drug infusion provided tumor cells for cytogenetical and DNA cytophotometric studies in 16 pts with accessible lesions. The timing of drugs or RT in combined treatment was based on the changes in the distribution pattern, e.g. Methotrexate, Adriamycin (ADR) or VLB were given when an accumulation of cells in S phase was found. Cis-Platinum (CDP) 50 mg/m² in 12-24 hr infusion or Vinblastine (VLB) 2 mg in 12-24 hr infusion were used as markers of cellular kinetics with the aim to enhance the effect of other drugs or irradiation (RT) which were to follow. Aspiration biopsy studies and after drug infusion provided tumor cells for cytogenetical and DNA cytophotometric studies in 16 pts with accessible lesions. The timing of drugs or RT in combined treatment was based on the changes in the DNA distribution pattern, e.g. Methotrexate, Adriamycin (ADR) or VLB were given when an accumulation of cells in S phase was found. Bleomycin, RT, VLB or ADR were administered during an increase in G2-M phases. Combined CT was applied intraarterially in 10 and intravenously in 12 pts. Cis-Platinum (CDP) 50 mg/m² in 12-24 hr infusion or Vinblastine (VLB) 2 mg in 12-24 hr infusion were used as markers of cellular kinetics with the aim to enhance the effect of other drugs or irradiation (RT) which were to follow. Aspiration biopsy studies and after drug infusion provided tumor cells for cytogenetical and DNA cytophotometric studies in 16 pts with accessible lesions. The timing of drugs or RT in combined treatment was based on the changes in the DNA distribution pattern, e.g. Methotrexate, Adriamycin (ADR) or VLB were given when an accumulation of cells in S phase was found. Bleomycin, RT, VLB or ADR were administered during an increase in G2-M phases.

DNA distribution pattern (Table 1) showed no significant difference between Dukes A and D in all but mean DNA value, variance, percentage of cells above 4C (4C%) and percentage of cells above 6C (6C%).


The observed cumulative survival rates were computed by the actuarial life table method. For all AN tumors the 5-year survival rate was 45%, whereas the corresponding figure for the ND group was 94%. The tendency toward a poorer prognosis in the AN group was statistically highly significant. However, for the stage C patients the survival rates were 65% for the AN and 89% for the ND tumor patients, respectively. The ND patients lived longer (median 17 months) than those with Dukes' D tumors in the AN group (median 10 months: p<0.05).

Supported by the Norwegian Cancer Society.

FLUOROCYTOMETRIC DNA ANALYSIS OF COLORECTAL CARCINOMAS WITH RESPECT TO DEGREE OF EXTENT OF TUMOR GROWTH. Usami, Sasaki, Takahisa Inoue, Morotomi, Hashimoto, Yamanaka, Suzuki, Hara, Maruyama, Usami, Tsuchihashi, Hori, Shiga, 520-21.

Determination of DNA ploidy pattern of colorectal carcinomas showed that DNA aneuploidy was characteristic of colorectal cancers with invasion into deeper submucosal layers, and to be accelerated during the progression of the tumor growth with extensive invasion.

60 cases of colorectal carcinoma were classified 16 cases of Dukes A, 23 of Dukes B, 15 of Dukes C and modified Dukes D. Cancer cells, isolated from paraffin-embedded section, were stained by Azocarrin-G-Acriflavine-Feulgen or DAPI and fluorocytometric measurement of cell nuclear DNA content was performed. DNA distribution pattern among 4 groups of tumor stage was compared with respect to modal peak, mean DNA value, variance, percentage of cells above 4C (4C%) and percentage of cells above 6C (6C%).

In colorectal cancer, the observed cumulative survival rate increased with respect to DNA ploidy pattern (Table 1). The survival rate was highest in the Dukes A and Dukes D groups, and lowest in the Dukes B and Dukes C groups. The difference between Dukes A and Dukes D in all but mean DNA value, variance, percentage of cells above 4C (4C%) and percentage of cells above 6C (6C%) was significant. The result of all these parameters showed increase in order from Dukes A to D. Statistical analysis revealed no significant difference between Dukes A and B in all parameters, significant difference between Dukes B and C in all but mean DNA value, variance, percentage of cells above 6C (6C%) and percentage of cells above 8C (8C%).

In conclusion, a correlation of cell nuclear DNA distribution pattern with degree of extent of growth in colorectal carcinoma and DNA distribution pattern may complement conventional clinicopathological diagnosis in detecting occult metastasis.
2441 DNA content of colorectal (CRC) breast carcinomas (BC) and malignant melanomas (MM) measured by flow cytometry (FCM) correlated to other biological parameters using paraffin-embedded archival material. J. Salouki1, M. Moore2, P. Havelton3, A. Balldl3, A. Howell1.

References were found between stimulated and non-stimulated CRC cells.

Based on DNA analyses of 400 specimens of CRC, BC and MM in relation to other biological parameters and patient and tumor characteristics, clinical course and response to therapy, the following were the most salient findings: (i) aneu-ploidy (AN) was not associated with greatest heterogeneity of expression of certain antigens; (ii) cells of CRC (39 cases) displayed higher proliferative activity than diploid (BC, CRC and MM); (iii) no higher frequency of AN was found in 173 related BC cases or pts. with short disease-free interval after primary treatment; (iv) significant changes occurred after tamoxifen therapy in FCM histograms in approx. one-third of aneuploid BC in a randomized study; (v) response to hormonal therapy were found among diploid and near tetraploid than among hypodiploid or hyper-tetraploid; (vi) there was a comparable AN in Stage II nodular MM (27 pts.) with fatal clinical course in 5 years and in a comparable group (23 pts.) without evidence of disease; (vii) more frequent expression of HLA Class II products occurred in MM with an unfavorable clinical course. It is concluded from the above evidence that: (i) abnormalities of DNA content of 2/3 of tumors are probably of quantitative significance only; (ii) different clinical behavior of aneuploid tumors is partially due to their higher proliferative rates; (iii) use of DNA content as a prognostic indicator in BC and MM is limited; and (iv) the role of different DNA indices in relation to response to therapy should be further evaluated.

2442 DNA CYTOCHROMES P-450 ANALYSIS OF DIFFERENTIATED THYROID CARCINOMAS: COMPARISON BETWEEN SURGICAL AND AUTOPSY CASES

T. Fujimori1, T. Takai1, Y. Sagara1, T. Takahashi1, M. Hirano1, T. Ishii1, Y. Imaizumi1, T. Sato1, K. Nakagawa1, T. Ishii1, and Bio-statistics, University of Turku, 20520 Turku, Finland

Cellular DNA content was measured using a novel flow cytometric method to analyze paraffin-embedded tissue blocks from 125 patients with differentiated thyroid cancer. DNA aneuploidy was found in 20 (25%) of the 82 papillary, 20 (42%) of the 36 follicular and in 4 (57%) of the seven medullary carcinomas. Aneuploidy was found to be more common in the elderly (p<0.002), in moderately and poorly differentiated carcinomas (p<0.004) and in tumors infiltrating beyond the thyroid capsule (p<0.03). Patients with an aneuploid tumor had less favorable cumulative survival (p<0.001) than patients with diploid cancer. However, in papillary and follicular carcinomas multivariate analysis using stepwise Cox model showed that age at diagnosis, follicular type and tumor invasion beyond the thyroid capsule to be more important independent prognostic factors. Increasing probability of DNA aneuploidy with increasing age explains partially why prognosis of differentiated thyroid carcinoma is poor in older patients.

2443 INFLUENCE OF CELLULAR DNA CONTENT ON SURVIVAL IN DIFFERENTIATED THYROID CARCINOMA

Cellular DNA content in relation to other biological parameters and patient and tumor characteristics, clinical course and response to therapy.

References were found between stimulated and non-stimulated CRC cells.

Based on DNA analyses of 400 specimens of CRC, BC and MM in relation to other biological parameters and patient and tumor characteristics, clinical course and response to therapy, the following were the most salient findings: (i) aneu-ploidy (AN) was not associated with greatest heterogeneity of expression of certain antigens; (ii) cells of CRC (39 cases) displayed higher proliferative activity than diploid (BC, CRC and MM); (iii) no higher frequency of AN was found in 173 related BC cases or pts. with short disease-free interval after primary treatment; (iv) significant changes occurred after tamoxifen therapy in FCM histograms in approx. one-third of aneuploid BC in a randomized study; (v) response to hormonal therapy were found among diploid and near tetraploid than among hypodiploid or hyper-tetraploid; (vi) there was a comparable AN in Stage II nodular MM (27 pts.) with fatal clinical course in 5 years and in a comparable group (23 pts.) without evidence of disease; (vii) more frequent expression of HLA Class II products occurred in MM with an unfavorable clinical course. It is concluded from the above evidence that: (i) abnormalities of DNA content of 2/3 of tumors are probably of quantitative significance only; (ii) different clinical behavior of aneuploid tumors is partially due to their higher proliferative rates; (iii) use of DNA content as a prognostic indicator in BC and MM is limited; and (iv) the role of different DNA indices in relation to response to therapy should be further evaluated.

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3H-thymidine uptake in B cell lymphomas - Relationship to treatment response and survival

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Cell suspensions were obtained from biopsy tissue from 149 patients with B cell lymphomas and analysed, with regard to DNA-synthesis as assayed by 3H-thymidine uptake, response to therapy and survival. The 3H-thymidine uptake was significantly increased in lymphomas of high versus low grade malignancy (p = 0.0001), in patients with stage I and II versus stage III and IV (p = 0.014), and in patients with general symptoms (p = 0.0025) as opposed to asymptomatic cases. The complete response rate was significantly higher in patients with increased thymidine uptake than in those with low uptake, 26/51 (51%) cases versus 24/83 (29%) cases, respectively (p = 0.014). 55 patients with increased 3H-thymidine uptake survived for significantly shorter times than 94 patients with low uptake (p = 0.0056). Furthermore, a markedly larger group of high-risk patients was identified by the 3H-thymidine assay than by histopathology alone, 55 cases versus 23 cases, respectively. Among the patients (126 cases) with low grade tumours, those with increased 3H-thymidine uptake (40 cases) had poorer outcome than those with low uptake (66 cases) (p = 0.045). The data suggest that DNA-synthesis in this study, as assessed by 3H-thymidine uptake, is an independent indicator of survival in NHL. Furthermore, it may be a useful parameter in laying down guidelines for therapy in B cell malignancies, especially in low grade tumours.

MORPHOLOGICAL CHANGES IN PATIENTS WITH OSTEOSARCOMA AFTER CHEMOTHERAPY (RESULTS OF COSS 80/82).

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Since 1977, patients with primary osteosarcoma were treated with high-dose chemotherapy prior to definitive surgery, according to the therapy protocol of the cooperative studies (COSS). High-dose chemotherapy was initiated immediately after histological affirmation of diagnosis in order to induce a tumor cell destruction. Some weeks later radical surgical resection of the tumor was performed. The aim of this strategy was the salvage of the limb.

In 213 surgical specimens morphological changes of primary tumor were examined by undecalcified histological sections of at least one complete tumor area. The effect of preparative chemotherapy on the primary tumor was noted and assigned a value (grade I-VI) according to the extent of tumor destruction attributable to chemotherapy as defined previously by Salzer-Kuntschik. Grade I-III (responder): less than 10% viable tumor of total tumor area; grade IV-VI (non-responder): more than 10% viable tumor area. In a separate series quantitative analysis of ground substance content was performed in 28 reaction specimens and 23 biopsies after undecalcified preparation. Before fixation imprint cytologies of the biopsies were prepared. After Feulger and nuclear size were determined by an electronic interactive image analysis system (IBAS).

77 tumors (64%) showed a good effect of preparative chemotherapy. 136 tumors (64%) responded badly to the chemotherapy.

In the regression grades I-II (responder) the mean chondroid ground substance amounted to 5% of the entire tumor area. On the other hand the regression grades IV-VI (non-responder) showed a mean chondroid ground substance of 20%. These results correlate well with the distribution of chondroid ground substance in primary biopsies (n=23).

The determination of nuclear size and polymorphism as well as the DNA distribution patterns indicate that less differentiated osteosarcomas showed a better effect of preparative chemotherapy on the primary tumor than higher differentiated osteosarcomas.
2449 HOST CELL INTERACTIONS AT SITES OF TUMOR INVASION.
University of Tennessee, Memphis, The Health Science Center, Memphis, TN, USA and University of South Manchester, UK**.

Cellular interactions at sites of tumor invasion appear to play a significant role in host tissue breakdown. Work in our laboratory have demonstrated that tumor cells stimulate the release of collagenolytic activity in cultures of normal fibroblasts. Histologic examination of the invading tumor zone in both human and animal tumors showed that the distribution of different cell types at certain loci along the tumor periphery appeared to be unique. The mast cell population increased in some regions within the stromal connective tissue, while the macrophage population appeared to be mainly localized within the tumor parenchyma. However, macrophages were also seen at the tumor edge bordering the loose connective tissue fibers. Stromal cells with fibroblast-like morphology in the vicinity of mast cells at the invading tumor zone, appeared enlarged and frequently contained mast cell granules. Soluble products derived from peritoneal mast cells (MCP) enhanced the release of collagenolytic activity in cultures of stromal fibroblasts in vitro. Furthermore, MCP also stimulated the release of collagenolytic enzymes in the media of cultured tumor cells. Using tumor cell variants of different metastatic potential, the response of tumor cells to stimulation by MCP was found to vary with the metastatic potential of the target tumor cell. Mast cells appeared to potentiate the effect of tumor-associated stimulation of collagenolysis by host fibroblasts. (Supported by NIH Grant CA 25617).

2450 TUMOR X HOST CELL HYBRIDIZATION AND MICROMETASTASES.
R. Jer and Z. Ada-Oz, Rappaport Family Inst. for Research in the Medical Sciences and Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.

The major challenges in clinical oncology today are the detection and eradication of micrometastases. We have demonstrated the ubiquitous presence of micrometastases in the spleens of mice bearing subcutaneously inoculated tumors. (J. Immunol. Meth. 8:189-205, 1985) by the soft agarose cloning technique. The same technique has been further extended to study micrometastases in other organs of tumor-bearing mice. Utilizing tumor cell variants of different metastatic potential, the response of tumor cells to stimulation by MCP was found to vary with the metastatic potential of the target tumor cell. Mast cells appeared to potentiate the effect of tumor-associated stimulation of collagenolysis by host fibroblasts. (Supported by NIH Grant CA 25617).

2451 ROLE OF ADHERENT CELLS IN ANTI-TUMOR IMMUNE RESPONSE IN MICE INOCULATED WITH HYBRID CELLS BETWEEN MALIGNANT AND NORMAL CELLS. I.A.H. Okumura (Osaka), and I. Sato, Inst. of Biotechnology Mechanism, Yokohama, Japan.

Following immunization with hybrid cells between syngeneic mammary tumor and normal cells in vitro, C57BL/6J mice acquired a resistance against the related mammary tumor challenge. Peritoneal exudate (PE) cells obtained from these resistant mice showed to be capable of inhibiting the tumor growth, when mixed with the tumor cells and injected into irradiated recipient mice intraperitoneally. On the contrary, PE cells obtained from normal mice promoted the tumor growth. We have also found that the effect of the anti-tumor activity of PE cells depended upon a population such a cell classified with their properties of mononuclear, glass-adherent, and anti-Thy-1.2 resistant. Further studies of effector activity of immune PE cells revealed that (i) effector activity of immune PE cells was completely suppressed by treatment of anti-macrophage agent, silica, and this suppression of activity was almost totally reversed by macrophage-stabilizing agent, poly-2-lysine. (ii) Effector cells were capable of inhibiting the tumor growth completely at a target cell ratio of 1:1. (iii) Effector activity was immunologically specific.


The interactions of tumor cells with specific extracellular matrix components (ECM) are of critical importance in the formation of tumor metastases. The in vitro adhesion behaviour of cells from a transplantable murine mammary adenocarcinoma (Ma1), spontaneously metastatic to lungs, has been examined on several defined substrata, fibronectin (Fn), laminin (Lm), type I and IV collagen (Cl, ClIV), and bovine serum albumin (BSA) as control protein. Cr51 labeled murine mammary M13 suspensions were prepared either by enzymatic dissociation of subcutaneous tumors or from primary cultures. Freshly dissociated tumor cells exhibited a similar kinetics of adhesion to all the substrata assayed. At 30 min the percentage of adhesion to BSA (24.3 ± 2.3) did not differ from that observed with the other substrata. On the other side, a 2.3 fold enhancement (p<0.05) of the adhesion rate to FN, Lm, Cl and ClIV was observed at the primary culture of M13 while percentages of adhesion to BSA remained the same. Syngeneic mice injected IV, with 5 x 106 cultured cells exhibited significantly higher (p<0.01) number of lung nodules, respect to those injected with non-cultured M13 cells. No difference in the incidence and number of spontaneous metastasis was found when 49 mice were inoculated sc with 2 x 106 or post cultured cells. On the other side the nascance in vitro significantly shortened tumor latency (p<0.01), enhanced the percentage of tumor takes (p<0.01), did not modify the population doubling time of sc tumors. Survival time of animals inoculated with cultured cells was also considerably shortened (46.5 vs 56.5 days).

These studies demonstrate that in vitro passage enhanced the adhesion rates to purified ECM and increased its tumor colonizing ability without changing its spontaneous metastatic properties. The tumorigenicity of in vitro cultured cells was also significantly enhanced.
The colonization of the lung by the rat tumour cells Bsp73ASML which have the ability to metastasize via the lymphatic system was studied at the ultrastructural level. Tumor cells, given intravenously became transiently embolized mainly in the capillaries, however within 8 hours they began to extravasate. Cellular protrusions opened a limited area between endothelial cells and pushed them apart and by this way tumor cells had direct contact with the basal laminae of the vessel. After 24 hours tumor cells penetrated through the destroyed basal lamina without major cellular deformation, and they formed small metastases in the interstitial matrix within 7 days. Several tumor cells of the newly formed metastases migrated into the lumen of lymphatic vessels and began to proliferate there. After one month tumor cells filled one part of the lymphatic system of the lung and developed metastases in distant lymph nodes. Proliferating tumor cells in the lymphatic system split the capillaries, forming this way new metastases in the connective tissue. Invasion into lung lymphatic vessels could have been observed also when tumor cells were inoculated subcutaneously. Based on the above described ultrastructural data, we can conclude that metastases of the Bsp73ASML tumor line may originate not only from primary tumor, but also from formerly developed lung metastases.

Undifferentiated connective tissue as an obligate biomorphological precursor of endothelial proliferation: results of human and experimental studies.


Histological, histochemical and immunohistochemical data are highly suggestive for an active participation of connective tissue in the development and growth of tumors.

Our results obtained on mice treated with carcinogenic polycyclic hydrocarbons (BP-DMBA), on rats transplanted with Guarin T8 epithelium, from human breast, colon, skin carcinoma and their morphological precursors have focused our attention on the problem of vascular proliferation and its relationship with degenerative collagen changes and tumor growth.

The early ages of tumor growth can be summarized as follows:
1. Degradation of proteic and collagenous matrix by enzymatic activity, which conditionizes undifferentiated connective tissue proliferation, which seems to be a suitable chemical environment for all vascular proliferation, and then tumor cell proliferation.

The results are discussed on the basis of the current biological role assigned to connective tissue which is no longer seen as a simple mechanical support, but as a vital and dynamic constituent of the body.

In murine mammary tumours the tissue environment influences formation of secondary tumours: studies on an in vitro system.

Elizabeth Horak, D. Tarin

Suffield Department of Pathology, John Radcliffe Hospital, University of Oxford, Oxford, England

Tumour cells of disseminating malignant neoplasms lodge in many organs but only develop into metastases in some. The microenvironment of an organ seems to be an important determinant of success or failure of metastatic growth. We investigated regulation by the organ microenvironment of the behaviour of a spontaneous mouse mammary tumour system: influence of the environment on survival, DNA turnover and colony forming efficiency. Spontaneous tumours may give variable results, so a large collection of primary murine mammary tumours were studied. We found that organ where metastases form encourage tumour cell survival and colony forming efficiency (CFE). Other organs inhibit these parameters. In the majority of a series of individual tumours, the influences exerted by an organ on survival and colony forming efficiency have the same direction. In a few cases the direction of these effects might be contrary, for example, survival may be encouraged but CFE inhibited. If so, the negative effect seems to dominate, controlling the fate of the tumour. The organ effects were also studied using fixed and mobile normal cells. Similarly to the metastasizing tumour cells, mobile cell types (lymphocytes, granulocytes, macrophages) were more resistant to the organ environment than fixed cells (e.g. pregnant mammary gland epithelium and fibroblasts). It was concluded that sensitivity of mature cells to different organs might be a general principle in the homeostasis of the organism to which mobile cell types form an exception. Tumour cells capable of forming metastases have lost this organ sensitivity thereby acquiring a determinant of the malignant phenotype.


1st Department of Pathology, Kionpo Medical School, Japan

Extracellular matrix and neovascularization may be altered in neoplasm and may influence tumor proliferation and invasion.

In this study, the specific features of extracellular matrix and neovascularization in gastric and pancreatic carcinoma were observed ultrastructurally and immunohistochemically.

Well differentiated carcinoma markedly produced extra-cellular matrix which was a dense network of collagen, elastin, reticulin, proteoglycan and glycoproteins.

Immunohistochemically, fibronectin was localized in the interstitium accompanied by prominent glycoprotein. However, in poorly differentiated carcinoma, the extracellular matrix composed of collagen, elastic fiber and specific type of proteoglycan and glycoprotein was much more strongly than well differentiated carcinoma. Increased extracellular matrix may be produced by host pleomorphic myofibroblasts in response to the carcinoma proliferation.

Blood vessels were well developed, in well differentiated carcinoma. However, in poorly differentiated carcinoma, immature blood vessels are prominent in the interstitium of carcinoma. Ultrastructurally vascular endothelium formed incomplete basal lamina is pleomorphic and contain large nuclei. Immunohistochemically factor VIII was localized in endothelium and it was useful marker for the neovascularization in these mesenchymal reaction of carcinoma proliferation and invasion.

The alteration of matrix may provide a favorable environment for tumor proliferation and invasion.

Tumor modify the matrix and neovascularization. Cellmatrix interaction may alter tumor growth.
ASSOCIATION OF TYPE IV COLLAGENASE WITH THE METASTATIC PHENOTYPE, STUDIED IN AN IN VIVO MODEL.


Correlation between type IV collagenolytic activity of tumor cells in vitro and metastatic potential in nude, or syngeneic mice has been previously made in various human and murine cell lines. In this study we have focused on production of type IV collagenase by tumor cells in vivo. The collagenase, along with other secreted proteins, produced by the growing tumor, were collected as tumor interstitial fluid into a specially designed millipore chamber, placed in close contact with the transplanted tumor. This procedure for collection of tumor interstitial fluids was previously described by Gullino et al. (Cancer Res. 24: 780, 1964). Nitraosomethylurea (NMM)-induced rat mammary carcinomas were transplanted subcutaneously into Buffalo rats by the method described, and the tumor interstitial fluids were collected 3-4 weeks later. The type IV collagenase activity, measured in the interstitial fluids from the NMM-induced mammary carcinomas, was five to ten times higher than the collagenolytic activity in the control fluids collected from the same animals at a distant site. Composition of interstitial fluid proteins, produced by metastatic and nonmetastatic NMM-induced tumors, was determined by computerized 2-D gel electrophoresis. Results from the 2-D gels will be presented, demonstrating type IV collagenase and other secreted proteins, differentially expressed by the metastatic and nonmetastatic tumors. This experimental system provides a model for studying in vivo modifications in the production of type IV collagenase and the metastatic capacity after different treatments.

EVIDENCE OF CATHEPSIN-B ACTIVITY IN HUMAN BREAST CANCER CELL LINES AND IN NORMAL HUMAN MAMMARY EPITHELIUM.


Studies on human breast cancer tissues indicated that viable malignant cells might be the source of newly synthesized active forms of cathepsin-B (CB). EC 3.4.22.1, but direct evidence was lacking. In order to clarify further the role of cathepsin-B in the invasiveness and the localization of CB activity in human breast adenocarcinoma cell lines (BCCL) and normal human mammary epithelial organelles, we investigated the occurrence of CB activity in lysosomes and possibly in secretory vesicles of human breast cancer cell lines. Protoplasts from two human breast cancer cell lines were purified CB from three human tissues (normal liver, colon carcinoma and ovarian carcinoma). Two N_i CB were present in both CB (35 and 24 kDa) as determined on SDS-immunoblotting, by cell death and by subcellular localization. CB activity in lysosomes and possibly in secretory vesicles of human breast cancer cell lines was identified by immunofluorescence labeling. These results bring direct proof that both malignant and normal human mammary viable epithelial cells produce active CB. The observed localization of CB is consistent with its occurrence in lysosomes and perhaps in secretory vesicles. Preliminary biochemical data suggest that a significant part of CB activity in BCCL represents an alkaline-stable form of CB. Studies of functional significance of CB in biological behaviour of carcinoma cells are in progress.

LAMININ PRODUCTION MAY REGULATE TUMOR CELL MOTILITY.

S.G.C. Filipe and J. Vareci, Allen Park VANC-Wayne State Univ., Detroit, and Univ. of Michigan, Ann Arbor, Michigan, U.S.A.

The involvement of active cell movement in the invasion process has long been suspected. Recent studies have shown that laminin, a glycoprotein component of basement membrane collagen, induce random motion of various types of cells, including tumor cells. Based on this, we investigated the relationship between the production of laminin by various types of cells and their capacity to migrate. To accomplish this, we used human squamous carcinoma cells as well as human and murine melanoma cells. We found that all of the tumor cell lines produced significant amounts of laminin. Secretion of laminin into the supernatant medium was documented by ELISA. The presence of cell surface laminin was identified by immunofluorescent staining. Synthesis of laminin by cells was characterized by metabolic labelling. When we examined the cells in the micropore filter assay we found that all of the cell lines were motile and responsive to laminin. Furthermore, there was a direct positive correlation between the ability of tumor cells to spontaneously migrate and the levels of endogenous laminin production. Those cell lines producing the greatest amount of laminin were also the most motile. When their supernatants were added to the cells migrating in the micropore filter assay, the tumor cell motility was markedly improved. Both the stimulated and the spontaneous motility of all tumor cells could be inhibited by the addition of anti-laminin antibody. These studies confirm the positive role of laminin in tumor cell migration. Furthermore, our findings suggest that it is the endogenously produced cell laminin which may serve as the self-regulator of tumor cell motility and possibly, metastatic capability.

CATHEPSIN-B-LIKE CYSTEINE PROTEINASES AND THEIR INHIBITORS IN TUMOR INVASION.


A cathepsin-B-like cysteine proteinase (CB) has been linked to tumor metastasis. We have purified CB from human breast cancer tissue (normal liver, colon carcinoma and ovarian carcinoma). Two N_i CB were present in both CB (35 and 24 kDa) as determined on SDS-immunoblotting, by cell death and by subcellular localization. CB activity in lysosomes and possibly in secretory vesicles of human breast cancer cell lines was identified by immunofluorescence labeling. These results bring direct proof that both malignant and normal human mammary viable epithelial cells produce active CB. The observed localization of CB is consistent with its occurrence in lysosomes and perhaps in secretory vesicles. Preliminary biochemical data suggest that a significant part of CB activity in BCCL represents an alkaline-stable form of CB. Studies of functional significance of CB in biological behaviour of carcinoma cells are in progress.
DEGRADATION OF EXTRACELLULAR MATRIX BY HEXOSAMINIDASE AND ITS PREVENTION WITH SPECIFIC GLYCOSIDASE INHIBITORS.

Department of Experimental Therapeutics, Roswell Park Memorial Institute, Buffalo, NY USA.
Elevated levels of hexosaminidase and other lysosomal enzymes have been observed for a variety of solid tumors and/or their interstitial fluid. These hydrolytic enzymes may play a role in tumor cell associated tissue degeneration and invasion of basement membranes. In this study we evaluated the effects of purified bovine kidney and human placental hexosaminidases on the degradation of bovine corneal endothelial extracellular matrix (ECM) which contains basement membrane specific components. This ECM, was metabolically prelabelled during its synthesis by bovine corneal endothelial cells with [3H]-glucosamine. Following 72 hr, the amount of radiolabeled released from this substrate by either hexosaminidase at concentrations greater than 2 μg/ml was significant (>20% of the total incorporated radiolabel). Radiolabel release was progressive with time (over the first 72 hr) and was proportional to the amount of enzyme added over a wide range of enzyme concentrations. In the presence of specific inhibitors of hexosaminidase, 2-acetamido-2-deoxy-D-glucosonolactone, 2-acetamido-2-deoxy-D-galactosonolactone and 2-acetamido-2-deoxy-1,6-anhydro-D-glucopyranose, having K_i values of 2.3 x 10^{-6} M, 9 x 10^{-6} M and 4.7 x 10^{-5} M, respectively, a dose dependent, partial or complete inhibition of hexosaminidase mediated degradation of radiolabelled ECM was observed. These results illustrate the involvement of hexosaminidases in mediating ECM degradation and also suggest a potential for glycosidase inhibitors in the treatment of malignancy. (Supported by CA-13038)

2462 REGULATION OF GROWTH OF METASTASES BY THEIR HOST ORGAN.

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Using co-cultures of murine B16 melanoma cells with various other cell types we have shown that a liver metastasizing B16 subline selected from the B16F1 line is specifically stimulated to grow in the presence of syngeneic parenchymal hepatocytes in comparison to its growth on other substrates and cell types. This effect is also specific with respect to the growth of other B16 lines in identical circumstances. Further experiments demonstrated that this is not due to differential tumour cell attachment, nor is it mediated by diffusible factor(s). However, surface contact between hepatocytes and tumour cells is essential. These results help to explain the noted ability of primary tumours to metastasize to specific secondary tissues. Work is in progress to discover the nature of the cell-cell contact.

1st, Bicerche Faramacologiche "Mario Negri", Milano, Italy 2nd Duke University Medical center, Durham, North Carolina, USA.
Two sets of seemingly contradictory evidence have been reported on the regulation of monocyte migration in vitro and hence presumably extravasation in vivo, by tumor cells. The present study was designed to explore the relationship between tumor-derived chemotactic factor(TDCF) and P15E-related inhibitor(s) of monocyte chemotaxis in culture supernatants of the human B367 sarcoma and 54526 ovarian carcinoma. Absorption of P15E-related material with anti-P15E monoclonal antibodies, did not reduce TDCF activity. A modest, but significant and consistent, increase of the chemotactic activity was observed when supernatants were exposed to immobilized anti-P15E. The material eluted from Sepharose-bound anti-P15E antibodies was devoid of chemotactic activity and suppressed the polarization and migration of monocytes in response to chemotactants. These results demonstrated the coexistence of factors with opposing influence on monocyte chemotaxis in culture supernatants of 2 human tumor cell lines and suggested that the regulation of monocyte entry into neoplastic tissues is complex and multifactorial.

2464 LECITIN-RESISTANT ANTIQUENTS OF MUSCLE LINES LONG-DURATION 1,1,1,3-TRIFLUORO-2,3-DIMETHYL-CYCLOPENTANONE AND A EFFECT OF TURATIVITY AND TUMOR INJNACITY IN EXPLANT CULTURE OF SYNGENEIC MUSCLE.

The lectin-resistant variants of Lewis lung carcinoma cell line /LLC/ were selected in vitro. For the selection, wheat germ agglutinin /WGA/ and ricinus communis agglutinin /RCA II/ were used. The variants obtained preserved their tumorigenicity, but differed from the parental line in their growth rates and metastasizing capacity. The natural and experimental metastasizing potentials were assayed. Both the WGA- and RCA II- resistant variants showed lower metastasizing capacity. The comparative analysis of all the tumor cell lines examined consider their immunobiological properties and host factors involved in the expression of their metastatic phenotype.
**2465** **EXPRESSION OF A P-tyr CONTAINING PROTEIN AND METASTATIC CAPACITY ON 3LL VARIANTS**

Sagedi A*, Fabriani R*, bannai S.J.*, Helden K**, Cavuto A**


In the attempt to correlate metastatic potential with specific properties of the tumor cells, homogeneous subpopulations which are endowed with low to high metastatic potential have been isolated from single tumors. Expression of a tumor associated antigen, recognized by a MoAb to lung carcinoma cells, has been studied in Lewis lung carcinoma (3LL) tumor lines endowed with different metastatic potential. These lines have been shown to be stable for metastatic phenotype along the in vivo passaging. MoAb 135-13C recognizes a protein (TSP-180) that appears on cell surface of several murine carcinoma but is not detected on normal cells in culture. Results demonstrate that metastatic capacity of 3LL tumor lines correlates with the ability to bind the MoAb 135-13C. SDS-PAGE autoradiograms from lysates of primary and secondary tumors, labeled with [35S]methionine or [32P]orthophosphate and immunoprecipitated by MoAb 135-13C, demonstrate that the MoAb specifically recognizes a 180 kd protein which is highly expressed in metastatic cells. This 180 kd protein, also, appears in SDS-PAGE autoradiograms from lysates immunoprecipitated by an anti-P-tyr serum. Data reported indicate that the 3LL metastatic phenotype and the surface protein/s detected by MoAb 135-13C are correlated, a possible role of 180 kg protein as receptor of growth factor/s is discussed.

Partially supported by CNR-PF Oncologia grant n° 840078444

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**2467** **DETERMINATION OF THE POLAR GROUPS ON THE LEWIS LUNG TUMOR CELLS WITH DIFFERENT METASTATIC CAPACITY**


The cell surface has numerous unit promoting the specific cell-cell and cell-substrat interaction, but the electrostatic repulsive force is the only that's able to prevent these interactions. During the transformation the surface charge changes (mostly increases) while the attractive forces decrease. A lot of results support the hypothesis that the surface charge and the polar groups of cell surfaces have a deciding role in the tumor disease. That is the reason we investigated the surface charge and the sialic acid content of the Lewis Lung tumor cells with low (LW) and high (LW-Hi) metastatic capacity.

It was found that the sialic acid content (both the surface and total) of highly metastatic LW-Hi increases comparing to low metastatic LW. The cells derived from the metastases show increased sialic acid content too. At the same time there was no difference in the electrophotographic mobility of these two cell lines. The electrophotographic investigation of neuraminidase treated tumor cells directly supported the presence of the cationic groups on the LW-Hi cells in the increased amount. Detailed cell electrophotographic investigations after chemical modification of the cell surface polar groups directly proved the increased amount of the cationic groups in the electrokinetic region.

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**2468** **ROLE OF PLASMA MEMBRANE FLUIDITY IN CANCER METASTASIS**

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Cell surface characteristics are reported to play a role in determining the metastatic potential of tumor cells. This study was designed to investigate a possible correlation between tumor cells plasma membrane fluidity and their metastatic behavior. Four sublines of the chemical induced 11545 sarcoma and two clones of the Moloney-virus induced MS2 sarcoma, with different metastatic potential were studied. Metastatic behavior was tested as ability of lung colonization after i.v. injection in syngeneic mice. Plasma membrane fluidity was determined by fluorescence polarization technique. We found that to an increased plasma membrane fluidity corresponds a greater metastatic potential. Moreover growth of tumor cells in suspension on bacteriological plates results in the acquisition of a reversible higher lung colonizing potential and of a parallel enhanced fluidity. Conversely, highly metastatic cells, when exposed to cholesterol hemisuccinate (known to increase plasma membrane rigidity), partially lose their metastatic ability. These data would suggest that the degree of plasma membrane fluidity can play a role in determining the metastatic potential of neoplastic cells.

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**2469** **DISTRIBUTION AND PARTICULARITY OF ANIONIC SITES ON SURFACES OF VARIOUS B16 MELANOMA CELL LINES**


The distribution and polarity of surface negative charges of three B 16 melanoma cell lines metastasizing differently were studied by electronmicroscopy in situ using cationized ferritin (CF). The line with low metastatic potential in lung bound the CF usually on apical and lateral surfaces. The distribution of CF was uniform. Those with high metastasizing potential bound CF also on basal surfaces. With these cell clones CF was localized in clusters. On thin cytoplasmic processes, however, the CF binding appeared uniformly. The cell-to-cell contact seemed to be free from CF. These observations present evidence regarding the polarization of surface charges of tumor cells, the degree of which is correlated with the metastatic potential of various cell lines. At cell-to-cell contacts a significant accumulation of CF could be observed.

For the studies on the chemical nature of negatively charged sites, various glycosidases (neuraminidase, hyaluronidase, chondroitinase ABC) were used in our experiments. Mainly the chondroitinase and neuraminidase effected a decreasing of the cationized ferritin binding on the cells surfaces.
**F-48: HOST-TUMOUR RELATIONSHIPS**

**2469 EXPRESSION OF THE L1 CELL ADHESION MOLECULE IN B16 MELANOMA**
Elizabeth Boek and Dorthe Linneemann, The Protein Laboratory, University of Copenhagen, Copenhagen, Denmark.

Cell adhesion molecules are during development involved in cellular processes and organogenesis. The cell adhesion molecule L1 plays a role in neuron-neuron and neuron-glia cell recognition, in migration of neurons, and in formation of neurite fascicles. Cell adhesion molecules may be involved in several key steps of the metastatic process, such as liberation of tumor cells from the primary tumor, formation of tumor emboli in the blood stream and interaction with host cells and other components at the site of metastatic colonization. Thus, it seems of importance to study the expression of cell adhesion molecules in metastasizing tumor cells. Therefore the biosynthesis of the L1 cell adhesion molecule was studied in B16 melanoma cells of low metastasizing capacity (F10 clone). L1 was expressed by both the F1 and the F10 clones. After labelling with 35S-methionine, 35S-sulphate or 35P-phosphate the L1 was isolated by immunoprecipitation and the polypeptide composition was determined by electrophoresis on sodium dodecylpolyacrylamide gels. The radioactive polypeptides were visualized by means of fluorography. A 10 min pulse labelling with methionine yielded an L1 polypeptide of Mr 200,000. Prolonged labelling resulted in a polypeptide of 10-20,000 higher Mr indicating glycosylation. By labelling with sulphate the antigen was seen as two polypeptides of Mr 210,000 and 140,000 in both clones. Labelling with phosphate resulted in labelling of the 210,000 component.

**2470 THE NEURAL CELL ADHESION MOLECULE (N-CAM) IS SYNTHESIZED IN B16 MELANOMA CELLS**
Dorthe Linneemann and Elisabeth Boek, The Protein Laboratory, University of Copenhagen, Denmark.

Cell adhesion molecules are during development involved in morphogenesis. The neural cell adhesion molecule (N-CAM) which is present from the blastocyst stage plays a role in migration of neurons, in neurite fascililation and in formation of neuron-muscle synapses.

Cell adhesion molecules may be involved in several steps of the metastatic process such as liberation of tumor cells from the primary tumor, formation of tumor cell emboli in the blood stream and interactions with host cells and other components at the site of metastatic colonization.

We have investigated the biosynthesis of N-CAM in B16-F1 and B16-F10 melanoma cells. N-CAM was synthesized as two polypeptides with a Mr 200,000 and 140,000 Mr corresponding to the biosynthetic pattern observed in neurons. Both polypeptides were glycosylated in the B16 melanomas as in neurons. In the melanoma cells the 200,000 Mr polypeptide was phosphorylated, whereas no phosphorylation of the 140,000 Mr polypeptide was observed. In contrast, both polypeptides were phosphorylated in neurons. No difference in biosynthesis of N-CAM in B16-F1 and B16-F10 was observed.

**2471 IMMUNOMODULATORY ACTIVITY OF HUMAN LEUKOCYTE INTERFERON IN CANCER PATIENTS: RESULTS OBTAINED DURING PULSE THERAPY**
S.R. Fentiman, and E. Slack, Dept. of Biology, Univ. of South Carolina, Columbia, SC, and Roswell Park Memorial Inst., Buffalo, NY.

We evaluated and previously reported the efficacy of alpha-interferon (aIFN) in 84 cancer patients (1). IFN was administered in a pulse fashion given for 3 consecutive days every 4 weeks. We also evaluated the immunomodulatory effects of IFN on clinical parameters during the course of therapy. Recently, we reported the results of IFN administration during consecutive days every 4 weeks. We also evaluated the efficacy of IFN in 84 cancer patients (1). IFN was administered in a pulse fashion given for 3 consecutive days every 4 weeks. We also evaluated the immunomodulatory effects of IFN on clinical parameters during the course of therapy.

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EFFECf OF RECOMBINANT INTERFERONS (IFN) ALFA-2C AND/OR GAMA-2C ON MYELOID (CFU-GM), ERYTHROID (BFU-E) AND LYMPHOID (L-CFU) PROGENITORS OF MULTIPLE MYELOMA.


Preceding studies have shown that natural interferons (IFN) inhibit hematopoietic progenitor cells from both blood and marrow. We applied the same techniques to test the activity of A and C rIFNs. rIFN-α, at the final concentration ranging from 10 to 10,000 U/ml, used alone or in association, were incubated either 20 or 24 days with (a) normal blood CFU-GM and BFU-E (b) blood patients with chronic myelogenous leukemia (CML) (CFU-GM (n=16)) or CML blasts from patients with acute non lymphoblastic leukemia (AML) (n=5). When cells were incubated 30 days with A or C-A+C rIFN, only BFU-E were inhibited in a dose-related fashion starting at 10 U/ml and complete at 10,000 U/ml. On the other hand, when cells were incubated with IFN until the end of the culture, CFU-GM and BFU-E from all normal subjects showed a dose-dependent inhibition. In contrast, L-CFU of only one of 8 patients showed inhibition. For the other cases, resistance was observed for both A and C. Normal CFU-GM and BFU-E seemed to be more sensitive to A than to A and C alone. This observation suggest synergistic effect between A and C rIFNs. In contrast this synergism was not observed for IFN-GM of CM patients. For CFU-GM, there was no difference between sensitivity of clusters and colonies. In conclusion, (1) recombinant A and C rIFNs do inhibit human hematopoiesis in a dose-related manner (2) short exposure to A or C rIFNs inhibits BFU-E growth for at least 15 days, an observation compatible with a cytostatic effect (3) BFU-E appear to be more sensitive than CFU-GM to A or C rIFNs. (4) the inhibitory activity of IFN-GM is not due to an inhibition of differentiation of clusters into colonies (5) A and C rIFNs are synergistic on CFU-GM and BFU-E as well, an observation compatible with different receptors for A and G rIFNs (α and γ) ANNL L-CFU can be either stimulated or depressed by A or C rIFNs (7) a parallel behavior of L-CFU with A and G rIFNs suggests that resistance is not at level of IFN receptor but rather at a common pathway, possibly the (2'-5')A synthetase.

RECOMBINANT INTERFERON ALFA-2C TREATMENT IN EXCESSIVE THROMBOCYTOPHIA.


Our previous findings of significant reductions in platelet counts in 64% of tumor patients during daily rec-interferon alfa-2C (IFN) treatment and by other investigators challenged us to study the capacity of IFN to reduce platelet counts in excessive thrombocythemia. 15 patients (age 54-85 years) with excessive thrombocythemia and myeloproliferative disorders (7 PV, 3 ET, 3 CML) were entered into the study. Platelet counts varied between 760 and 1,300×10^9/l. IFN (Boehringer Ingelheim International) was administered initially at a dose of 5-10×10^6/week, subsequently at 34×10^6/1-2xweek. Remission (defined as reduction of platelet counts ≤440x10^9/l) observed at least at 2 consecutive determinations in 4-8 weeks intervals) was obtained in 12 out of 15 patients after a median treatment span of 7 weeks (range: 1-24 weeks). In 3 patients the criteria of remission were not fulfilled, but even in these cases, substantial decreases in platelet counts were noted during IFN treatment. Bone marrow morphometry showed significantly increased megakaryocyte counts (64±33%) in patients compared to controls (17.3±10%) (p < 0.0001). During IFN-induced remission, the megakaryocyte counts decreased significantly to 45.8±3% (p < 0.05). The number of red cell precursors and myeloid colonies (CFU-GM bone marrow section) were similar in untreated patients, during IFN-induced remission, and in controls. Platelet half-life was already significantly decreased in 9 of 11 untreated patients (T½: 114-54 hours, median 73.5 hours) and decreased (T½: 24-48 hours) significantly (p < 0.01) in all cases during IFN treatment. In conclusion, IFN treatment led to normalization of excessive platelet counts in 12 of 15 patients. Both reduction of megakaryocytes and reduction in platelet half-life seems to account for this positive therapeutic effect.

INTERFERON(IFN)-MONOTHERAPY AND COMBINED IFN-POLYCHEMOTHERAPY VERSUS POLYCHEMOTHERAPY 'N MULTIPLE MYELOMA.


The efficacy of interferon(IFN)-monotherapy was compared with standard polychemotherapy in 42 patients with multiple myelomas (study 1). After analysis of these results, a consecutive study was initiated comparing the efficacy of combined interferon-polychemotherapy with sole polychemotherapy (study 2).

Recombinant IFN-α/2C (Boehringer Ingelheim, International) was initially applied at 2x10^6/1-2x, after day 14 dosages were individually adapted. Polychemotherapy (VMCP) was given at 4-6 weeks intervals. Treatment in study 1 consisted of either IFN (2x10^6/1-2x/week) VMCP or VMCP alone. Up to now, 14 patients have been entered into the study.

Study 1: IFN-monotherapy induced complete remission in 2 (14%) and partial remission in 4 (27%) patients, 1 patients remained stable, and 1 showed progressive disease. VMCP induced in 11 patients (55%) complete and in 6 (28%) partial remissions. 2 patients remained stable. Under chemotherapy, hematological side effects were more pronounced and severe bacterial infections were observed more often. The side effects associated with interferon treatment such as myalgia, asthenia, nausea, depression, and psychological symptoms, arthralgia, myalgia, and increased liver enzymes occurred at the expected frequencies.

Study 2: 11 patients were given IFN-VMCP which will be reported. At present, similar response rates have been achieved by IFN/VMCP and VMCP. In conclusion these data show activity of recombinant interferon-α/2C in certain patients with multiple myelomas. However, IFN-monotherapy is significantly inferior to VMCP polychemotherapy.

ANTITUMOR EFFECT OF HUMAN RECOMBINANT INTERFERON-α AGAINST HUMAN COLON CANCER CELLS TRANSPLANTED IN NUDE MICE.


Antitumor effects of human recombinant interferon-α(IFN-α) alone or in combination with anticancer drugs were investigated in vivo. P-7378 cells (human colon cancer), 2x10^5/mouse, were inoculated subcutaneously in nude mice. When the tumor mass had grown to approximately 6mm in diameter the administration of anticancer drugs were investigated. Studies I: 42 patients with standard poly chemotherapy in 42 patients with multiple myelomas (study 1). After analysis of these results, a consecutive study was initiated comparing the efficacy of combined interferon-polychemotherapy with sole polychemotherapy (study 2).

Recombinant IFN-α/2C (Boehringer Ingelheim, International) was initially applied at 2x10^6/1-2x, after day 14 dosages were individually adapted. Polychemotherapy (VMCP) was given at 4-6 weeks intervals. Treatment in study 1 consisted of either IFN (2x10^6/1-2x/week) VMCP or VMCP alone. Up to now, 14 patients have been entered into the study.

Study 1: IFN-monotherapy induced complete remission in 2 (14%) and partial remission in 4 (27%) patients, 1 patients remained stable, and 1 showed progressive disease. VMCP induced in 11 patients (55%) complete and in 6 (28%) partial remissions. 2 patients remained stable. Under chemotherapy, hematological side effects were more pronounced and severe bacterial infections were observed more often. The side effects associated with interferon treatment such as myalgia, asthenia, nausea, depression, and psychological symptoms, arthralgia, myalgia, and increased liver enzymes occurred at the expected frequencies.

Study 2: 11 patients were given IFN-VMCP which will be reported. At present, similar response rates have been achieved by IFN/VMCP and VMCP. In conclusion these data show activity of recombinant interferon-α/2C in certain patients with multiple myelomas. However, IFN-monotherapy is significantly inferior to VMCP polychemotherapy.
ENHANCEMENT OF THE ANTITUMOR EFFECT OF CHEMOTHERAPEUTIC AGENTS BY IFN-α IN GASTRO-INTESTINAL CANCER. V. Takahashi*, M. Ueno*, M. Mai*, K. Orita, 1st Dept. of Surgery, Okayama University, Japan

Patients with a variety of malignancies were treated in Phase II clinical trials of recombinant interferon-α (RelFN-α) and recombinant interferon-β (RelFN-β). Extensive monitoring of several immune functions of peripheral blood lymphocytes was done on these patients. When IFN was given daily, the NK activity was notably reinforced, and was maintained while being administered. Regardless of whether RelFN-α was given intravenously or intrathoracopertitoneally, the NK activity was reinforced as well. The lymphoproliferative responses to PHA were suppressed from the first week of the trial, and the suppressor cell activity to the lymphoproliferative responses were augmented. The suppressive effect was more intensive in the cases of RelFN-α than in the cases of RelFN-β. No definitive changes were observed in the leukocyte count, lymphocyte count, T cell ratio and Tr cell ratio. Analysis of leukocyte populations determined by using a panel of monoclonal antibodies and flow cytometry could not detect any significant changes. By the administration of RelFN-α, improvement of malignant effusion induced by carcinoma or mesothelioma was observed. In the cases of RelFN-α minor responses have been seen in liver metastasis of gastro-intestinal tract cancer.


We examined potentiating effect of lymphoblastoid IFN-α on tumor cytotoxicity mediated by human blood monocytes or NK cells. The cytotoxic activities of monocytes and NK cells were assessed by radioactive (3]H]HThymidine or 51Cr) release assays, respectively. Human blood monocytes separated on a percoll gradient from healthy donors, were cytotoxic to human melanoma (A375) cells following interaction for 24 hr with IFN-α (1000 IU/ml), whereas NK cells activity against K-562 cells was augmented by pretreatment for 30 min with IFN-α (1000 IU/ml). Pre-exposure of tumor (A375) cells to IFN-α (100 IU/ml) resulted in increased sensitivity to cytotoxicity mediated by IFN-α activated monocytes. Pretreatment of effector cells with monoclonal anti-NK cell antibody (Lyt-2,1b) and complement completely neutralized NK cell activity treated with or without IFN-α, but did not abolish monocyte activation to the tumoricidal state by IFN-α. Thus, IFN-α can directly activate and/or potentiate human monocyte and NK cell-mediated cytotoxicity, which is dose and time dependent. On the other hand, seven tumor cell lines, Burkitt's lymphoma (Daudi), renal tumors (OS-RC-2 and ACHN), glioblastoma (9R-G2 and U-373MG), melanoma (A375), gastric carcinoma (Kato-I-II) out of 17 tumor cell lines tested were susceptible to cytotoxicity by IFN-α (1000 IU/ml). Thus, these findings suggest that IFN-α activity may be a clinical value in both direct tumor cell killing and augmentation of natural host defenses against cancer in vivo.

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2481 EFFECT OF RECOMBINANT INTERFERON-\(\alpha\) ON HUMAN ALVEOLAR MACROPHAGES: ENHANCEMENT OF OXYGEN INTERMEDIATE GENERATION.

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It has been suggested that macrophages and monocytes play a key role in host defense against infection and neoplasms. Macrophages are activated by various agents to produce oxygen intermediates and other inflammatory mediators. It is known that IFN-\(\gamma\) significantly increases the activity of the respiratory burst in human and mouse macrophages. We have studied the effect of recombinant interferon-\(\alpha\) (rIFN-\(\alpha\)) on the respiratory burst activity of alveolar macrophages. When alveolar macrophages were treated with rIFN-\(\alpha\), the respiratory burst activity was significantly increased.

2482 THE CLINICAL STUDY BY THE INTRAPERITONEAL ADMINISTRATION OF RECOMBINANT INTERFERONS FOR CANCEROUS ASCITES

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The intraperitoneal administration of recombinant interferons (rIFNs) has been studied for the treatment of cancerous ascites. This study was conducted to evaluate the efficacy of rIFN-\(\alpha\) in the treatment of cancerous ascites. Patients with cancerous ascites were treated with rIFN-\(\alpha\) and the response was evaluated by using computed tomography and ascites cytology.

2483 EFFECT OF RECOMBINANT INTERFERON ON SUBCUTANEOUS TUMOR GROWTH AND METASTASES OF THE RETICULUM CELL SARCOMA M5076.

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The ability of recombinant interferon-\(\alpha\) and -\(\beta\) to inhibit primary tumors and metastases was evaluated using the murine M5076 reticulum cell sarcoma. For this purpose, a human recombinant hybrid IFN alpha A28 (rHuIFN-A28), which is active on murine cells, and a recombinant murine IFN gamma (rMuIFN-\(\gamma\)) were tested. Pretreatment of mice with either rHuIFN-A28 or rMuIFN-\(\gamma\) resulted in marked inhibition at the number of metastatic colonies. As has been observed with other tumors, maximal inhibition was observed in mice receiving daily injections prior to tumor challenge with longer pretreatment being less effective. When treatment was initiated following iv injection of tumor cells, rHuIFN-A28, given 3 to 6 times per week, was found to have substantial antitumor activity while rMuIFN-\(\gamma\) was inactive. However, inhibition of spontaneous hepatic metastases in mice treated with either IFN was observed in some experiments. Treatment of mice with a combination of rHuIFN-A28 and rMuIFN-\(\gamma\) resulted in significant inhibition of tumor growth while rMuIFN-\(\gamma\) was inactive. However, inhibition of spontaneous hepatic metastases in mice treated with either IFN was observed in some experiments. This study demonstrates that IFNs are effective in the treatment of cancerous ascites and that they can also inhibit metastatic spread of murine tumors.

2484 PHASE I CLINICAL STUDY OF HUMAN RECOMBINANT INTERFERON GAMMA ON VARIOUS CANCERS

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This study evaluated the safety and efficacy of recombinant interferon gamma (rIFN-\(\gamma\)) in the treatment of various cancers. Patients with advanced cancer were treated with rIFN-\(\gamma\) for 6 to 8 weeks. The most common side effects were influenza-like symptoms, including fever, chills, and malaise. No evidence of antitumor activity was observed.

2485 VIOLATION OF THE MEDICATION REGISTRATION RULES

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The medication registration rules are violated when medications are administered without proper registration. The most common violations are the administration of medications by unauthorized personnel, the use of medications that are not approved for the intended use, and the failure to record the administration of medications. These violations can have serious consequences and may lead to the suspension of the hospital's accreditation.

2486 MONDAY • AUGUST 25 • AFTERNOON

G-50: INTERFERONS II

2487 MONDAY • AUGUST 25 • AFTERNOON

G-50: INTERFERONS II

Excellent results have been observed in the treatment of skin metastatic lesions of malignant melanoma with interferons (IFNs) administered intratumorally. In our cooperative study, 10(C+P+R) of 20 cases were responded (of type IFN, highest response among IFNs). In cases of only skin metastasis, observed such responses led to prolongation of survival. 1. A close histopathological examination of cutaneous lesions in this successful cases provided visual evidence that numerous lymphocytes emerge in malignant tissue following the administration of IFN-2b and that attack melanoma cells to cause their lysis. On the contrary, in case of IFN type IFNs lymphocyte infiltrates were observed around the tumor but these cells were primarily fewer and the cytotoxic reactions appeared to be less conspicuous as compared to those with P type IFN.

Immunohistochemical studies with the various monoclonal antibodies against lymphocyte subpopulations indicated that these lymphocytes are cytotoxic T cells and NK cells. Our studies imply clinical effect of IFN-2b is brought about by augmentation of lymphocyte activity as well as their direct antitumor effect. Further electron microscopic observations were made of these specific cells.

2486 SEQUENTIAL INTERFERON-CHEMOTHERAPY FOR THE TREATMENT OF METASTATIC MELANOMA. REPORT OF 1 CASE. E. Sulas, С. Floris, A. Chezza, С. Desogus, С. Muggiano, A. Tedde, R. Turno, Medicina I, Ospedale "Businco", USL 21 Cagliari, Italy.

Treatment of metastatic malignant melanoma with interferons alone (IFNs) can modify the course of the disease, while its association with some antibiotic drugs seems to potentiate its cytotoxic effect. A 34-year-old woman was referred to our Department for metastatic malignant melanoma with cutaneous and subcutaneous involvement. Treatment with rIFN-2b (30 U/m2 subcutaneously) did not cause significant clinical improvement. Three months after suspension of rIFN-2b, the patient presented cerebral and visceral metastasis. She was then treated with BCNU 100mg/day for 3 days for 2 courses. Treatment was followed by total remission of the skin and visceral lesions while it was without any appreciable effect on the cerebral metastasis. The patient then underwent adjuvant treatment cycles with VCR, DTIC, CCNU. So far, after 20 months from starting rIFN-2b and 1 year from chemotherapy, the patient shows total remission of the skin and visceral lesions, while the CNS involvement has furtherly worsened causing right hemiplegia and increased intracranial pressure. The different behaviors of the metastatic lesions led to the hypothesis that rIFN-2b can modify the tumoral cells response to chemotherapy, worsening of the CNS metastasis might be due to the fact that rIFN-2b does not cross the blood brain barrier. Only 1 (the present case) out of 4 cases of metastatic malignant melanoma we have observed showed a good response to IFN-chemotherapy. We believe that surface receptors for IFNs are present in these tumor cells and that IFNs treatment can modify their biological activity allowing the antibiotic agents to effectively exert their cytotoxic action.


The interferon (IFN) producing activity of OK-432, PHA-P, and K562 was investigated in lymph node and peripheral blood lymphocytes of patients with gastric and colorectal cancer.

MATERIALS AND METHODS: The subjects studied consisted of 16 gastric and 8 colorectal cancer patients ranging in age from 26 to 76 years. OK-432, a product of streptococcus pyogenes (SU strain, Chugai Pharmaceutical Co.), PHA-P (Phyto laboratories), and K562 were used as the IFN inducers. The determination of IFN titers was made by the method ofRIA plaque reduction of vesicular stromatitis virus (VSV) to human WISH cells.

RESULTS: When OK-432 and K562 were used as the inducers, the IFN production was related to rapid reaction of several hours of duration, whereas PHA-P required relatively long-term reaction. In response to OK-432, the IFN titer was about equal in the peripheral blood and lymphnode lymphocytes. In response to K562, IFN production was significantly greater in the peripheral blood than that in the lymphnode lymphocytes. IFN of PHA-P, the amount of IFN was significantly higher in the lymph node than that in the peripheral blood lymphocytes. Relationship between clinical stages and IFN production measured was made in case of OK-432 both peripheral blood and lymphnode lymphocytes allowed about even IFN production in each stages. Where K562 and PHA-P were used, although relatively high titer of IFN were yielded in stage 1 and 11 in some cases, there was generally no definite correlation. These results showed that the sufficient preservation of the productivity of IFN, even in cases of advanced stages, reflected the existence of strong antitumor resistance. Then OK-432 or PHA was injected into rectal wall in rectal cancer patients, the peripheral blood lymphocytes of patients with gastric and colorectal cancer showed relative high level of IFN activity could be generated in regional lymphnode lymphocytes. From these results, the possession of high IFN productivity by regional lymphnodes seemed to encourage the immune-mediated immunotherapy.

2484 G-30: INTERFERONS II


Treatment of metastatic malignant melanoma with interferons alone (IFNs) can modify the course of the disease, while its association with some antibiotic drugs seems to potentiate its cytotoxic effect. A 34-year-old woman was referred to our Department for metastatic malignant melanoma with cutaneous and subcutaneous involvement. Treatment with rIFN-2b (30 U/m² subcutaneously) did not cause significant clinical improvement. Three months after suspension of rIFN-2b, the patient presented cerebral and visceral metastasis. She was then treated with BCNU 100 mg/day for 3 days for 2 courses. Treatment was followed by total remission of the skin and visceral lesions while it was without any appreciable effect on the cerebral metastasis. The patient then underwent adjuvant treatment cycles with VCR, DTIC, CCNU. So far, after 20 months from starting rIFN-2b and 1 year from chemotherapy, the patient shows total remission of the skin and visceral lesions while the CNS involvement has furtherly worsened causing right hemiplegia and increased intracranial pressure. The different behaviors of the metastatic lesions led to the hypothesis that rIFN-2b can modify the tumoral cells response to chemotherapy, worsening of the CNS metastasis might be due to the fact that rIFN-2b does not cross the blood brain barrier. Only 1 (the present case) out of 4 cases of metastatic malignant melanoma we have observed showed a good response to IFN-chemotherapy. We believe that surface receptors for IFNs are present in these tumor cells and that IFNs treatment can modify their biological activity allowing the antibiotic agents to effectively exert their cytotoxic action.
IMMUNOLOGICAL PROGNOSTIC FACTORS IN GaSTRIC CaNCER

M. Zembala, T. Popiele, W. Urcz, B. Myzar, D. Kowalczyk, and A. Cypuny, Cracow, Poland

Predictive value of standard immunological parameters measuring non-specific cellular reactivity and of monocyte functional tests was assessed in stage III and IV gastric cancer patients with a long survival time and those succumbing earlier. Neither the determination of T lymphocytes or their subsets nor lymphocyte blastogenic response correlated with prognosis though they showed stage-related depression. The increased lymphokine production and elevated expression of monocyte Fc receptor at the time of diagnosis were seen in groups of patients who died earlier. The increased occurrence of suppressor cells with monocyte characteristics and elevated cytokastic activity of monocytes was associated with a longer survival. Retrospective analysis revealed that patients with the presence of suppressor cells at the time of diagnosis had significantly better survival than those without. The occurrence of suppressor cells was also analysed during follow-up and was found in all stages which may be taken as suggestive evidence for the selection of long-term survivors with this characteristics. These observations may suggest that the determination of monocyte immunoregulatory activity may be useful indicator of prognosis in patients with gastric cancer.

T CELL SUBSETS IN KAPOSI SARCOMA PATIENTS - NON-TRANSPLANTED VS. RESEAL TRANSPLANT RECIPIENTS

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T cells subsets were studied in 12 patients with Kaposi sarcoma, 6 of whom had developed the sarcoma after renal transplant (all 6 were treated with prednisolone, 4 together with Imuran and 2 with cyclosporin). Six age-matched long-term renal transplant patients with no malignancy served as controls. In all 12 Kaposi sarcoma patients the helper/suppressor ratio was normal (1.5-2). A decrease in total T, T helper and T suppressor subsets was found in all the Kaposi sarcoma patients as compared to the controls. This was greater in the renal transplant recipients with Kaposi sarcoma. A serum suppressor factor was detected in all the patients with Kaposi sarcoma. Spontaneous suppressor activity was found only in the peripheral lymphocytes of the renal transplant recipients with Kaposi sarcoma. Antibodies to CMV, EBV and Herpes simplex virus were found in the renal transplant recipients with Kaposi sarcoma. The findings of this study indicate that Kaposi sarcoma in itself can induce a state of immune suppression and that this malignancy has a tendency to develop in immune-suppressed and virus-infected patients, in whom it evidently enhances the deterioration in immunocompetence already present.

We analysed for the results of immunologic studies of peripheral blood lymphocytes in 22 patients with typical angioimmunoblastic lymphadenopathy. We found, that the decrease of the absolute lymphocyte number, that of the T-helper cells and the T4/T8 ratio were characteristic of the active state of the disease, whereas the active T-cells and total T-cells were reduced both in the active and in the inactive state. The number of B-cells was in both states increased. We found an altered monocyte function in ten AILD patients too. Especially, the chemotaxis of monocytes was decreased. We also studied the antibodies to T-lymphotropic retroviruses in patients in ten patients. We found that four out of ten patients (studied) had anti-HTLV-III antibodies in their sera. Implication and possible mechanism of these observations are discussed.

2496 LYMPHOCYTE SUBPOPULATIONS, DELAYED SKIN HYPERSENSITIVITY AND PHA RESPONSIVENESS IN PATIENTS WITH OVARIAN CANCER BEFORE AND DURING RADIATION AND/OR CHEMOTHERAPY. J. Marczewska and J. Jaroszewski, Inst. of Oncology and Dept. of Prenat Med., Med. Sch., Poznan, Poland.

The percentages of T and B lymphocytes in peripheral blood, delayed skin hypersensitivity to DNCB and 4 recall antigens and PHA-induced proliferative responses of lymphocytes with and without adherent cells, were studied in patients with advanced ovarian cancer before treatment and during chemotherapy, with and without previous radiotherapy. The percentages of T cells in peripheral blood, delayed skin hypersensitivity reactions and PHA-induced responses of lymphocytes were significantly decreased in patients already prior to treatment. In 40% of these patients adherent cells suppressed the proliferative response of lymphocytes; this suppression appeared to be mediated by a lymphocyte subset. In a follow-up of 73 patients during chemotherapy (Eudoxan + Methotrexate alternately with 5-Fluouracil + Leukeran), with and without previous irradiation, no significant changes in the percentage of T and B lymphocytes were seen, but skin hypersensitivity responses were gradually decreasing. PHA responses of lymphocytes, evaluated altogether in 62 patients, tended to increase after the first 2 courses of chemotherapy and suppressive effects of adherent cells were usually abrogated. After subsequent chemotherapy courses lymphocyte PHA responses were rapidly declining and remained very low in cured patients many months or years after treatment. Previous standard radiotherapy had little effect upon the patterns and magnitude of immunosuppression resulting from prolonged chemotherapy.


We developed a computer based discriminant analysis test for preoperative prediction of extent and prognosis of gastric carcinoma. The parameters are obtained from a preoperative blood-sample. A total of 195 patients with gastric carcinoma were studied and followed for between 2 and 8 years. ESR and the concentrations of IgG, C3, C1-INH in serum and of CEA in plasma varied with the extent of disease. Groups of patients with gastric carcinoma were discriminated by the same laboratory data. The dependent variables, extent of disease and prognosis, were grouped in several dicotomies which were clinically relevant for discrimination. The prediction of metastases or no metastases was correct in 75%. By an appropriate prior distribution 93% of the patients without metastases were identified. Among patients with metastases, 90% were classified correctly as having primary tumors without infiltration of contiguous structures. Among those without metastases, 78% of the patients without lymph node metastases or primary tumor extending beyond the gastric wall, were identified. This group of patients could also be discriminated as to whether the primary tumor was confined to the mucosa/submucosa. Prognosis was correctly predicted preoperatively in 66% of the patients. Thereby 83% of the patients with a poor prognosis were identified. Of the patients preoperatively allocated to the non-survival group, 94% did actually die during follow-up. Our discriminant rules represent a conditional adjuvant for the management of patients with gastric carcinoma.

2495 IMMUNOLOGIC MONITORING IN ADVANCED BREAST CANCER PATIENTS TREATED WITH COMBINED CHEMOTHERAPY. H. Schmid, M. Kaufmann, D. Muhrle, and F. Kubli, Univ. Hospital, Dept. of Obstetrics and Gynecology, Heidelberg, F.R.G.

Twenty-one patients (pts) with metastatic breast cancer (8 visceral, 4 bone, 9 multiple metastases) were treated with mitomycin/c/prednimustine + (n=15) or 5-fluorouracil/cyclophosphamide + (n=6) as combination chemotherapy. Thirteen pts received adjuvant chemotherapy prior to palliative treatment. Median age of pts was 49 years, median disease free interval after primary surgery 26 months. Palliative endocrine pretreatment was given only in 8 pts.

Immunologic monitoring was performed by evaluating peripheral blood cells (PBC) with flow cytometry analysis (FACS, fluorescence-activated cell sorter) using monoclonal antibodies against T-cell subsets (anti Leu 3a against Helper, anti Leu 2a against Suppressor cells), Natural Killer (NK) cells (anti Leu 7 and 11a), macrophages (anti M3) and B-cells (anti Leu 12). For all assays only freshly prepared and by lymphoprep isolated PBC were used. In total 819 samples were measured which had been collected before cytotoxic treatment as well as before every new therapy cycle.

For the small number of cases the variation of T-cells, macrophages, and B-cells during chemotherapy could not be correlated to patient data. Thirteen women, however, showed a relative increase of NK cells combined with a changed ratio of their subsets (Leu 7/Leu 11) after the second chemotherapy course. These results can be correlated to clinical response (1 CR, 7 PR, 5 NC). Six pts with progression and only 2 cases with no change of disease had a relative decrease of NK cells. Therefore cellular immunologic monitoring of NK cell subsets may be a useful supplementary prognostic tool for cytotoxic treatment.

OVARIAN CARCINOMA DURING CHEMOTHERAPY, Masa and T.Ogino, Electro-Chemical & Inet-, Tokyo, Japan

A high percentage of the patients who died of immunoglobulins during therapy, particularly IgM. To conclude, a high percentage of patients who are clinically free of disease have normal values of IgG and IgM in 78.3%. In patients who died during a period of therapy values of IgG were continually low or fell during therapy in 66.7% of patients, IgA in 50% and IgM in 70%. To conclude, a high percentage of patients who are clinically free of disease have normal values of immunoglobulins during therapy. However, monoclonal IgA is 10 and polychemotherapy does not decrease their values. A high percentage of the patients who died had low values of IgG during therapy, particularly IgM.


Sera from 41 myeloma-patients containing monoclonal IgG, IgA, IgM and IgO were focused in a narrow pH gradient for the showing the restricted microheterogeneity of these paraproteins. Sera were also analyzed after treatment with 2-mercaptoethanol and neuraminidase. The microheterogeneity of heavy chains of monoclonal immunoglobulins partially depends on quantity of sialic acid which is the effect of posttranslation glycosylation.

We have shown that IEF in polyacrylamid gel is a useful method for the analyzing of the microheterogeneity of monoclonal immunoglobulin. The pattern of the microheterogeneity appears to correlate with the course of disease.

THE LEVELS OF IMMUNOGLOBULIN IN PATIENTS WITH OVARIAN CARCINOMA DURING CHEMOTHERAPY. M. Bolanča, N. Veček, D. Janković, J. Alekaić, Depr. of Immunology and Carcinology, Univ. of Zagreb Med. Sch., Yugoslavia.

The dynamics of immunoglobulin levels in 3% patients with ovarian carcinoma at various stages was determined during chemotherapy. Following surgery polychemotherapy (methotrexate, 5-fluorouracil, cyclophosphamide) was applied for a period of 5 days every 28 days, in six to eight courses. Levels of immunoglobulins were determined prior to each course of polychemotherapy. Values of immunoglobulins were analyzed in relation to the clinical outcome of the disease. In patients clinically free of disease, during 2-3 years, for the duration of therapy values of IgG were continually normal in 78.3%, IgA in 65.2% and IgM in 91.3%. In patients who died during a period of 2 years, IgG values were continually low or fell during therapy in 66.7% of patients. IgA in 50% and IgM in 70%. To conclude, a high percentage of patients who are clinically free of disease have normal values of immunoglobulins during therapy, and polychemotherapy does not decrease their values. A high percentage of the patients who died had low values of IgG during therapy, particularly IgM.
MODULATION OF CYTOLYTIC ACTIVITY OF HUMAN CD3\(^+\) NATURAL KILLER CELL DERIVED CLONES BY BIOLOGICAL RESPONSE MODIFIERS OK-432, IFN AND IL-2. H.T. Boelhouwer, R.L. Boelhouwer, H.V. van de Veerdonk, and G. Granema, Department of Immunology, Rotterdam Radio-Therapeutic Institute, Rotterdam and Radiobiological Institute TNO, Rijswijk, The Netherlands

CD3\(^+\) Natural Killer (NK) cell derived clones, in contrast to many CD3\(^+\) cytotoxic T lymphocytes, are able to exert nonspecific lytic activity against a variety of tumour target cells including antibody dependent cellular cytotoxicity (ADCC). CD3\(^+\) clones, like "fresh" NK cell lines are strongly activated by interferons, whereas CD3 clones are not or only to a minor extent by interferons. Similar results were obtained with recombinant IL-2 and anti-T200 MAAb which inactivate nonspecific cytolytic activity in both CD3\(^+\) and CD3\(^+\) clones including ADCC activity. These data clearly indicate that various steps of the lytic cycle of immune specific cytolytic pathway may be different from the nonspecific cytolytic pathway but others being identical. We have also studied the effect of OK-432, a lipopolysaccharide of the incubation mixture of penicillin-treated low virulent Su-strain of Streptococcus pyogenes (produced by Chugai Pharmaceutical Co., Ltd., Japan). Our results tested on a variety of cytolytic clones demonstrate that OK-432 can affect the cytolytic activity of these clones by restoring lytic activity to optimal levels. The OK-432 also affects the expression activation antigens. The possible pathway of augmentation by the BMM's will be discussed.

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INDUCTION OF PERITONEAL TNF (TUMOR NECROSIS FACTOR) BY OK-432, A STREPTOCOCCAL PREPARATION

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The streptococcal preparation OK-432 has potent antitumor effects in experimental animals and human beings, although the way it effects regression is not fully understood. Soluble factors which can cause the death of tumor cells are currently attracting attention. One of these factors is TNF which causes necrosis of some transplantable tumors and is cytotoxic or inhibits growth in a number of tumor cell lines in vitro. TNF is released into blood after endotoxin (LPS) is injected into animals pretreated with BCG or Pneumococcus bacteraemia. We have demonstrated that OK-432 can substitute for BCG in priming mice to release TNF when triggered by LPS. More recently, we also found that OK-432 primed mice produced TNF in peritoneal fluids when LPS was injected. However, the use of LPS to induce TNF may be clinically limited because of its severe side effects. It is, therefore, of interest to know whether other agents can substitute for LPS in eliciting TNF. In this paper we report that OK-432 induced TNF in peritoneal fluids of mice previously primed with OK-432. Two step stimulation (priming and eliciting) was always necessary to induce the cytokotoxic factor. OK-432 primed mice produce soluble cytokcytotoxic factor spontaneously and no cytotoxic activity was detected in the mice treated by simple injection of OK-432 as an eliciting agent. This observation was confirmed in in vitro experiments.

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INFLUENCE OF GENETIC FACTORS, AGE OF MICE AND DOSE OF
CONCOMITANT PARVUM ON THE ANTITUMOUR ACTIVITY OF C.
PARVUM. C. Nauret, H. Chalvet and C. Stiefel, IN CNRS, INSA, CURIE, Section de Biologie, Paris, France.

The antitumour efficacy of C. parvum depended on the dose of C. parvum, age of the mouse and the experimental model used. The pre-treatment of adult mice (3 months old) with 100 µg of C. parvum inhibited the development of 2 syngeneic tumours: a mammary carcinoma in C3H mice and a radio-induced lymphosarcoma in XVi mice. 100 µg of the treated mice survived whilst 100 % of the controls died after they had been grafted with these tumours. In the XVi strain, the dose of 100 µg of C. parvum was insufficient in 25 days old mice (0 % survival) and protected only 37 % of 12 months old mice. A smaller dose (25 µg) induced survival in 40 % of 25 days old mice and a larger dose (350 µg) inhibited the tumour growth in 80 % of 12 months old mice.

In C3H mice of different ages this dose effect was not so marked. A dose of 25 µg of C. parvum induced the survival of 15 % of 25 days old mice and a dose of 350 µg had no protective effect in 12 months old mice. Therefore the range of C. parvum doses which inhibited the tumour growth was more restricted in C3H than in XVi mice of corresponding ages. Another difference was also obvious when the duration of the suppression of the antitumour activity of C. parvum by a weak irradiation (25 or 100 rads) was studied. Restoration of the protective effect occurred faster in 3 months old mice than in 9 months old mice. This restoration appeared earlier in XVi than in C3H mice.

THE COMPLEX THERAPY OF MALIGNANT COLONIC TUMORS ASSOCIATED WITH PRE-OPERATIVE GAMMA-IRRADIATION AND NONSPECIFIC IMMUNOSTIMULATION

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The use of the pre-operative gamma-therapy in 85 patients with malignant colonic tumors led to the improvement of long-term follow-up results. The three-year safety in the main group was 85% in the control group (60 observations) - 72.2%. Though in that group with pre-operative gama-therapy there was admitted a substantial and state decreasing of immune reactivity which resulted in flashing of post-operative purulent and inflammatory complications (12,4%).

With purpose of living of immunodispersing effect of gamma-irradiation the nonspecific immunostimulating therapy was performed. The marked immunostimulating result of Prodigiosan was achieved, manifesting not only in increasing of general amount of lymphocytes, T- and B-lymphocytes, A-, M- and /-immunoglobulines but in pronounced decreasing of post-operative complications.
2509
THE PRELIMINARY OF TREATMENT EFFICIENCY OF LEUCOTROFINA BY THE IN VITRO INDUCING INCREASE OF ROSETTE CAPACITY OF T-LYMPHOCYTES.

Leucotrofina (Leucosinulina), a commercial thyrogroast extract, was shown to be able to stimulate leukopenias in leukopenic patients (after irradiation, polychemotherapy or viral diseases) and induce lymphocyte maturation. The effects of Leucotrofina on human peripheral T-lymphocytes were investigated by means of E-rosettes formation in vitro incubation with different concentrations of Leucotrofina (between 2.5 - 40 mg/ml or 0.025 - 20 mg/ml). It was found that Leucotrofina induced a significantly increase of E-rosettes formation, a phenotypic macro marker, as thymoic fraction V or T-1. Differences in inductive patterns were observed in different patients and/or different concentration of Leucotrofina in the same patient. It seems that the individual optimal dose differs from one patient to another. The highest increase of E-rosette percentages (20-43%) was obtained in patients with the most decreased number of T-lymphocytes. By the in vitro response to Leucotrofina the efficiency of the in vivo treatment can be predicted.

2511
DEPRESSION OF INTERLEUKIN 2 (IL2) PRODUCTION BY EXPERIMENTAL IRRADIATION AND RESTORATION BY THYMOSIN ALFA 1 (Ta-1) IMMUNOTHERAPY: CORRELATIONS WITH IRRADIATION PORTAL AND SYSTEMIC CELLULAR IMMUNITY (SCI).
W.C. Gray, D.R. Reive, J.H. Oliver, C.M. Suter, B.J. Hassinger, C.L. Blanchard, A.L. Goldstein and P.B. Christen, Division of Oncology, Univ. of Maryland School of Medicine, Baltimore, MD and Dept. of Biochemistry, George Washington Univ. School of Medicine, Washington DC, U.S.A.

A model was developed with C3H mice to assess the effects of portal irradiation on SCI and spleen cell production of IL2. Mice were sensitized to oxazolone on day 1 and 400 rads (240 kV) irradiation was administered via head, mediastinal and pelvic portals on days 4, 6 and 8. Oxazolone challenge was applied on day 8 and delayed type hypersensitivity to oxazolone (DTH-O) and other assays performed on day 10. Compared with sham, both DTH-O and total spleen cell production of IL2 (total number cells X unit cell release of IL2 with PHA) were significantly depressed with all portals (p<0.001). Depression varied with portal (depression of DTH-O: pelvic = head > mediastinal. Depression of IL2 production: (pelvic = mediastinal) > head). Optimum doses of Ta-1, given daily, starting with the first day of irradiation, restored head and mediastinal DTH-O but only partially increased pelvic DTH-O. Ta-1 also partially restored IL2 production depending on portal: head > mediastinal > pelvic. Changes in DTH-O and IL2 production were significantly correlated. All comparisons were significant (p<0.001 0.01). The results are evidence for an essential role of IL2 production in SCI and for recovery from immune depression. The importance of bone marrow derived lymphocyte precursors for recovery from immune depression is illustrated by the limited immune restoration after irradiation of the pelvic region, which contains approximately 50% of the total body bone marrow. Thus, the results suggest that pelvic and other marrow lymphocyte precursors are needed for restoration of SCI by Ta-1.

2510
MURINE THYMIC FACTORS AS IMMUNOSTIMULANTS AND BIOLOGICAL RESPONSE MODIFIERS (BRM).
B. Gugler, J坂 and G. Luppa, Cancer Research Institute, Tata Memorial Centre, Mr. Bombay-400011, India.

Two methods were used for isolation of murine thymic factors-Ulcer-entrifluation and gel filtration on Sephadex G100 was Method I. Chemical extraction was Method II. With Method I four protein peaks - PK1a, PK2, PK3, PK4 were obtained. Thymosin fraction V (Tf) was obtained by Method II. Characterization of these proteins on SDS-PAGE showed that PK1 was homogenous with 57K mol.wt. on PAGE, Others were mixture of low and high mol.wt. poly peptides. From PK2 to PK4 all were acidic. Synthetic Thymosin (Esignal) was used as standard. Kinetically using lymphopatogens assay was more with PK1 at 4 hour on thymocyte cultures than the other. At 16 hrs cultures PK1, PK2 and F5 and thymosin a showed maximum stimulation index (IS). Preincubation of thymocytes with these thymosin factors and Con A, thymosin at time-spans like 32 and 48 hours was used for nitrogen assay. This protocol failed to show any stimulatory effect. For Tdt assay splenic lymphocytes exposed to the factors showed altered terminal deoxynucleotidyl transferase (Tdt) as well as per cent Tdt + cells. PK2 and PK4 caused 12 to 16 fold increase in Tdt + cells. PK4, PK5, F5 and thymosin a caused 8 to 10 fold increase. Partly of these factors against antiserum to mouse F5 showed that PK1b and PK1c were identical to F5. PK1 is antigenically different. As RPM PK1 prolonged survival of leukemia bearing mice. In combination with cyclophosphamide similar effect was observed.

2512
EXPERIMENTAL IRRADIATION AND RESTORATION BY THYMOSIN OF IMMUNE SYSTEM.

Thymic hormones are essential for the immune system. They are able to restore depressed immune activities. There are various natural components as well as synthetic peptides having different biological effects in vivo and in vitro. Synthetic peptides were tested in some models.

1. We showed that pretreatment of mice with thymic peptides lead to an augmentation of mitogen-induced interferon production in vitro.

2. Treatment of mice chemotherapeutically suppressed restores the spleen weight and leukocyte numbers.

3. Treatment of Rauscher leukemia virus-infected mice lead to an increase of virus production.

4. Synthetic peptides are able to decrease the number of tumor cells in Ehrlich ascites carcinoma-bearing mice.
CLINICAL STUDY ON REGULATORY EFFECT OF PSK
ON GUT IMMUNITY OF CANCER PATIENTS
Y. NAKAGAMI, T.T. LIN, N. TSUBOI AND T. Sawada, Japan SCO Laboratory, Tokyo, Japan*,
Hospital, Tokyo, Japan, S.. Ikeda, T. Suzuki, Dept. of Dermatology, Saitama Medical School, Saitama, Japan,
RESTORATIVE CAPABILITY OF THYMOPoETIN FRAGMENTS
ON IMMUNE RESPONSE SUPPRESSED BY CYTOTOXIC AGENT:
Chemical Works of Gedeon Richter Ltd., and
Research Institute, Budapest, Hungary
Enhanced adherence of leukocytes from malignant cancer patients was influenced by treatment of thymo-
poietin (TP) fragments. Spontaneous (without cytostatic agent) adherence was stimulated by incubation with TP3
(thymopeptin 32-36), while it was decreased by TP5. Definitely decreased immune response was found in
adherence of leukocytes from head and neck cancer patients after treatment with cytostatic agents. In vitro
immunomodulation by incubation with TP fragments was characterized with adherence of leukocytes from cancer
patients treated with cytostatic agents (Vincristine, Bleomycin, Metotrexat, Elobromol or Cysplatin).
An increasing effect was produced only by treatment of TP5.

The number of Lewis Lung Tumor (LLT) metastasis was increased in mice thymectomised and/or treated with
cyclophosphamide (Cy) (240 mg/kg). Decreased number of LLT metastasis was detected in mice treated with TP
fragments (TP3=72%, TP5=70%, TP1=83.1% in 2). After thymectomy only TP3 treatment caused a metastasis
decreasing effect (97.4%) on Cy immunosuppression. T-cell dependent primary antibody (anti-SRBC/14d) response
was decreased with varying dose of cytotoxic agents in C57 mice. Immunosuppression of Vincristine
(1 mg/kg), Metotrexat (10 mg/kg), CY (50 mg/kg) administered (p. was restored by TP3 and partly by TP4
and TP5 treatment. No change was found on Cyplatin (1 mg/kg) suppression. TP3 is recommended for clinical
use as adjuvant therapy of malignant tumors.

CLINICAL EFFECTS AND HISTOLOGICAL FINDINGS INDUCED BY
INTRATUMOR ADMINISTRATION OF LIVING BCG IN SKIN METASTASES
OF MALIGNANT MELANOMA IN HUMANS. E. Itoh*, K. Ishihara, T. Tanaka, T. Kolde***,
Department of Dermatology, National Cancer Center Hospital, Tokyo, Japan.

1. Experimental study: Young adult nu/nu BALB/c and C57Bl/6 mice were used. A human melanoma line (SK14)
was implanted in nude mice and B16 melanoma in C57BL/6 mice. When the tumors reached 3-5 mm in diameter
they were treated by a single or multiple injection (IV, SC or IT) with recombinant (r) TNF, IL2 or IFN
(Hu6 IFN or natural HuIFN), and their antitumor activity was determined. We also examined the tumor tissues
of the TNF-treated mice histopathologically. IT treatment with TNF(1-10 ug) was the most effective in
inhibiting the tumor growth (82-100% inhibition from 5 different experiments) and significantly pro-
longed the survival time. Treatment with rIL2 (500 UI, x10, SC or IT) and r IFN (5x106 U, x10, IT or IV) also
inhibited the tumor growth moderately.

2. Clinical study: rIL2 (500-1000 U, every two days) and r IFN (5x106 U, x10, IT or IV) were administered IT or
IT to patients with melanoma. Effective responses were noted in 1 of 10 after IT but not after systemic treatment.
We also examined the tumor tissues immunohistopathologically, and infiltration of many lymphocytes was
seen. The efficacy of TNF treatment is now being tested in melanoma patients.

EFFECT OF TFN, IL2 OR IFN ON THE GROWTH OF MELANOMA IN NICE AND PATIENTS.
K.Ishihara*, T.Tanaka**, and T.Kolde***,
Department of Dermatology, National Cancer Center Hospital, Tokyo, Japan.

1. Experimental study: Young adult nu/nu BALB/c and C57Bl/6 mice were used. A human melanoma line (SK14)
was implanted in nude mice and B16 melanoma in C57BL/6 mice. When the tumors reached 3-5 mm in diameter
they were treated by a single or multiple injection (IV, SC or IT) with recombinant (r) TNF, IL2 or IFN
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IT to patients with melanoma. Effective responses were noted in 1 of 10 after IT but not after systemic treatment.
We also examined the tumor tissues immunohistopathologically, and infiltration of many lymphocytes was
seen. The efficacy of TNF treatment is now being tested in melanoma patients.
CHEMOTACTIC POTENTIAL OF HUMAN BLOOD MONOCYTES ACTIVATED BY MURAMYL TRIPETIDE. M. Oqawara, T. Utsuqi & S. Sone, 3rd Dept. Pharmacol., Hokuriku Univ. Sch. Pharmacy, Kanazawa, Japan. Agrimonia pilosa Ledeb. has been traditionally used as an antidiarrheal, a hemostatic and an anti-parasitic in Japan and China and is being used for cancer therapy in China today. We isolated agrimolin, an antitumor constituent, from the roots of this plant. Agrimolin possessed like other tannins direct cytotoxicity in the absence of serum protein in culture but the cytotoxicity was significantly decreased by addition of serum. This tannin showed strong antitumor activity against sarcoma 180 ascites and solid type tumors, MHI34 solid type tumor, and NethA and NM2 ascites type tumors in mice even when it was administered 4 days or more before the tumor cell inoculation. Nicely cured by the treatment with agrimolin completely rejected the tumor cell rechallenge. After intraperitoneal injection of agrimolin to non-tumor mice, the total number of white blood cells and peritoneal exudate cells(PCE) was markedly increased. PEC induced by agrimolin was very low. Agrimolin showed a cytostatic activity and an antibody dependent cytotoxic activity against tumor cells. NK activity of the spleen cells from the mice injected with agrimolin was very low. Agrimolin stimulated H-2 antigens uptake into monocytes after the in vitro and in vivo treatment. The results indicate that agrimolin, a tannin of plant, may be promising for a new host-mediated antitumor agent.

THE FFFET OF TP-3 (ARG-LYS-ASP) WITH OTHER OLIGOPETIDES ON THE LATERAL Satellite CELL RESPONSE TO THE INTRAVENOUS INJECTION OF LLT CELLS. C. B. Szende, K. Lapis, K. Pál, L. Sipos, L. Dénès and I. Kisfaludy
First Institute of Pathology and Experimental Cancer Research of Semmelweis Medical University, Budapest, Hungary

CHEMICAL WORKS OF Gedeon Richter, Ltd., Budapest, Hungary

THE OLIGOPETIDES ARG-LYS-ASP (TP-3) ARG-LYS-ASP-VAL (TP-4) AND ARG-LYS-ASP-VAL-TYR (TP-5) CONSIDERED AS POSSIBLE ACTIVE CENTRE OF CYCLOPHOSPHAMIDE IN HUMANS.

We have investigated the biokinetics of the best controlled follow-up study of human lymphoblastoid cell line lymphokine in patients with advanced cancer. D.G. Diamond*, M.P. Fulley*, V. Nagendran*, B.M. Southcott*, E. van Vliet*, D. Reitamo* and P. den Hollander* St Thomas' and Olive Cross* Hospital, London, UK; Organon International, Oss, The Netherlands

19 female patients with advanced cancer were assigned randomly into two groups. Group A (9 patients) each received a course of 12 intravenous (I/V) injections of RPMI-1788 lymphokine (1988-LK) over a period of 16 days in hospital; with follow-up at 1 week, 1 month, 3 months, 6 months, 9 months and 15 months subsequently. Group B (10 patients) each received a culture medium protein control preparation in an identical schedule to that in Group A and were followed up in similar fashion. The hematological, biochemical and immunological status of patients was investigated at the beginning, during and at the end of the course of injections and at follow-up visits to 6 months. The response to each I/V injection was monitored closely and the patients were assessed clinically for evidence of disease progression. All 9 patients in Group A gave dose-related sustained skin reactions to the 1988-LK; there was a positive correlation between the sensitivity of patients and age. 7/9 patients gave mild systemic reactions to I/V 1988-LK (e.g. shivering); and 6/9 patients showed an increase in blood neutrophils on C-reactive proteins levels during the course. In contrast, patients in Group B gave no systemic responses or skin reactions to the control preparation. These results indicated that this tannin showed strong antitumor activity against sarcoma 180 ascites and solid type tumors, and NethA and NM2 ascites type tumors in mice even when it was administered 4 days or more before the tumor cell inoculation. Nicely cured by the treatment with agrimolin completely rejected the tumor cell rechallenge. After intraperitoneal injection of agrimolin to non-tumor mice, the total number of white blood cells and peritoneal exudate cells(PCE) was markedly increased. PEC induced by agrimolin was very low. Agrimolin showed a cytostatic activity and an antibody dependent cytotoxic activity against tumor cells. NK activity of the spleen cells from the mice injected with agrimolin was very low. Agrimolin stimulated H-2 antigens uptake into monocytes after the in vitro and in vivo treatment. The results indicate that agrimolin, a tannin of plant, may be promising for a new host-mediated antitumor agent.
2521 IMMUNOMODULATION BY TAMOXIFEN AND PERGOLIDE. I. Berczi and E. Nagy. Department of Immunology, Faculty of Medicine, the University of Manitoba, Winnipeg, Manitoba, Canada, R3E 0W3

The effect of the ergot derivative, pergolide mesylate and of the nonsteroidal antiestrogen drug - tamoxifen, on the immune reactivity of rats was studied. Female Fischer and Wistar-Furth animals weighing 150-170 g were used for all experiments. Antibody response to sheep red blood cells (10^7 i.p.) and contact sensitivity reaction to dinitrochlorobenzene (dissolved in acetone and 4 mg. was applied onto the shaved dorsal skin) were induced in humoral and cell-mediated immune reactions, respectively. Tamoxifen suppressed contact sensitivity in a dose dependent manner, 0.75 - 1.0 mg daily s.c. doses having a maximal effect. The immunocompetence of tamoxifen-suppressed rats could completely be restored by additional treatment with either prolactin or growth hormone (40 .ug/day/rat s.c.). Pergolide also exerted a dose dependent suppression of contact dermatitis, reaching a maximum at s.c. doses of 400 .ug/day/rat. With this dose of pergolide, complete suppression of humoral immunity could be achieved. Again, the humoral and cell-mediated immune reactivity of pergolide-suppressed animals could be fully restored by additional treatment with prolactin or growth hormone. Because of the widespread use of tamoxifen and increasing use of pergolide for the treatment of cancer patients, the immunomodulatory effect of these drugs warrant further investigation. (Supported by the Arthritis Society and MRC of Canada)

2522 IMMUNOMODULATION BY MAFOSFAMIDE, AN "ACTIVATED" OXAZAPHOSPHORINE

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During the past two decades a few clinical reports have suggested that the therapeutic efficacy of cyclophosphamide against malignant tumours was partly mediated by drug effects on host immune mechanisms. This action was strictly dose-dependent: immunostimulation was only evident in the low dose range whereas immunosuppression became significant at intermediate or high doses.

In search for an experimental model of the immunomodulating effects of oxazaphosphorines it was found that the transplantable leukemia L5222 of BD IX inbred rats could be cured by low doses of oxazaphosphorines, whereas this therapeutic activity was gradually lost with increasing doses. Dose-response relationship studies with cyclophosphamide and its 4-hydroxy-derivative mafosfamide showed a bell-shaped pattern. When the two compounds were compared, the immunotherapeutic range of mafosfamide was considerably broader. Further experiments suggested that the oxazaphosphorine effect was T-cell-mediated. Treated and surviving animals were immune to additional tumour challenges. It was shown that mafosfamide at low concentrations inhibited preferentially T-suppressor cell proliferation in vitro; in analogy, an elimination of suppressor mechanisms could also be responsible for the in vivo effects.

In clinical phase I studies, the maximally tolerated dose of mafosfamide was around 3 g/m. The presented animal data, however, indicated that the immunopharmacological dose was approximately 10 times lower. Studies for immunotherapy with mafosfamide are currently ongoing in patients with non-small cell lung cancer and other malignant diseases.


Reactivity of lymphocytes from paired living patients with ovarian carcinoma on autologous cancer cells was examined using six established cell lines. Although allogeneic lymphocytes had the capacity to lyse other cultured cancer cells, autologous lymphocytes were found to be unable to lyse their own cultured cancer cells. The defective activity of autologous lymphocytes was restored by preincubation of autologous target cells but not autologous effector cells with the calmodulin inhibitors W-5 or W-7. These results may be considered (although it does not prove) to result from the action of calmodulin antagonists on the cell surface of target cells, inducing an antigenicity that was not recognized by the autologous lymphocytes.

2524 TREATMENT OF DIFFERENT HUMAN TUMORS WITH ANTITUMORAL PEPTIDES (FACTOR AF2), COURSE, RESPONSE RATE, PROGNOSIS.


Inductive stimulation of the body's own defence is becoming increasingly important in tumor therapy. Efforts have recently been made to also include immunotherapy at least as a supportive measure in the tumor therapy concept. Research will now concentrate on immunomodulatory mechanisms and direct regulation of tumor-cell metabolism within the complex carcinoma host reaction to find new approaches to cancer therapy. Different courses of cancer patients treated with xenogenic peptides (Factor AF2), isolated from liver and spleen of postnatal sheep, are described. These peptides show a stimulating effect on spleen cells against syngeneic tumor cells in vitro and antitumoral effects in vivo experiments. To control the immunological effect of this therapy, urinary neopterin was used as an immunomarker, which responds to the activation ratio of macrophages.
2525 NATURALLY OCCURRING IMMUNOMODIFIERS IN CANCER THERAPY. SCREENING AND INDIVIDUAL SENSITIVITY DETERMINATION.

F.E. Blance and V.I. Kupin

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It has been firmly established that the majority of antineoplastic naturally occurring compounds (NOC) revealed a remarkable immunomodulating mechanism of action. We elaborated on immunological two-stage screening tests for NOC:

1. Primary screening in T+E+, T+E-, and EAC-secreting forming cells (RFC) tests.
2. A thorough study of the compounds exhibiting activity in stage 1: a) Determination of various subpopulations of immunoregulatory cells; b) Functional evaluation of T-E+ or T-E- regulatory cells; c) Determination of theophylline-sensitive RFC; d) NK-cells tests; e) Interferon inducing activity determination.

The proposed screening scheme of comparative evaluation of biologically active NOC-immunomodifiers can be also used as an express-method for individual sensitivity assays in immuno- and adjuvant therapy of cancer patients.

Interferon, lentim and various experimental antineoplastic polysaccharides were tested.


Human peripheral blood lymphocytes (PBL), obtained from both healthy volunteers and various cancer patients, when incubated in vitro with phytohemagglutinin (PHA), lysed both cultured tumor cells and fresh autologous tumors but not fresh normal cells during a short-term 51Cr-release assay. The generation of these PHA-activated killer (PAK) cells was dependent on the generation of endogenous Interleukin-2 (IL-2) in culture medium. Addition of Anti-IL-2 Ab or Anti-Tac Ab into the culture failed the generation of PAK cells.

PAK activity of cancer patients was slightly lower than that of healthy volunteers and it was dependent on the low productivity of IL-2. The PAK effector cell was OKT-3+, OKT-8+ and the PAK precursor cell was OKT-3+, partially OKT-8+.

As a new method to obtain PAK cells, we examined the Sepharose beads ligand with PHA on its surfaces. Human PBL, when cultured in vitro with such Sepharose beads, also lysed cultured tumor cells. Now in vitro effects are under investigation in the tumor-bearing mice model.


Suppression of tumor metastasis is one of the most expected factors for immunomodulator. We reported the life prolongation effect of lentimamin on metastatic tumor bearing mice, previously. Further studies were carried out on the suppressive effect of lentimamin against the pulmonary metastatic rates of murine tumors.

Lentimamin showed marked suppressive effect on artificial pulmonary metastasis of MC-CS-1 fibrosarcoma (Maximum suppression ratio of metastasis was 94.2%). Lentimamin was also effective on natural pulmonary metastasis of MC-CS-1 metastatic strain markedly. The administration of lentimamin, at a dose of 10mg/kg/day for ten days from next day after the primary tumor resection, suppressed the natural pulmonary metastasis of B16 melanoma at 31.4%. On the natural pulmonary metastasis of Lewis lung carcinoma, lentimamin showed marked effect at 80.0%, when lentimamin was administered at a dose of 25mg/kg/day, every other day for ten times intravenously from next day after the tumor transplantation in foot pad of C588l/6 mice subcutaneously.

These data suggest the usefulness of lentimamin on tumor metastasis.


Forphenicinol (FPL) is a low molecular immunomodifier derived from forphenicine, a microbial product found by uniqueness and co-workers. We have reported the antitumor effect of FPL (oral, d6-13) and/or in combination with cyclophosphamide (ip, d1) on several syngeneic murine tumors (mammary tumor, L1210, B16F1, LLC and glioblastoma). We have also demonstrated the mechanism of the antitumor effect of FPL by the use of mu/nu C3H/HeN, and normal C3H/HeN mice treated with antimmunomacrophages in mammary tumors, and the results showed that T cells and macrophages were necessary for the effect of FPL.

1. The present work was undertaken to determine the effect of FPL (20 mg/po.d2-13) on syngeneic hepatoma (Line III, IM) in strain 2 guinea pigs. Forty-four days after tumor implantation, tumors were moderately suppressed in guinea pigs treated with FPL.

2. We determined whether the effect of FPL on xenografts of L-III hepatoma would be altered in 1-cell-deprived mu/nu BALB/c mice. Interestingly FPL treatment (0.1 mg/kg/po.d6-13) markedly inhibited (48% Inc.) the L-III xenografts whereas the antitumor effect of FPL in the syngeneic A/J strain mice was completely nullified. We have also determined whether the effect of FPL on L-III xenografts would be affected in nu/nu BALB/c mice sensitized with BCG (10 PFU/id,d6-13). In combination with FPL therapy (0.1 mg/kg/po.d6-13), in nude mice sensitized with BCG alone L-III xenografts were inhibited (38% Inc.); in contrast, in mice sensitized with BCG plus FPL marked enhancement of tumor growth (~35%) resulted.

We would like to elucidate the mechanism of this negative action of FPL in BCG-sensitized mice and further studies with antimmunomacrophage agents are underway.
THE REINFORCEMENT TO IMMUNOLOGICAL RESPONSES OF LYMPH NODES ATTACHED TO THE TUMOR BY ADMINISTRATION OF OK-432.

E. Ose, T. Ohtani, T. Kaube, E. Enoka, N. Sakai, Tokyo Women's Medical College, Sankyo Hospital, Dept. of Surgery, Tokyo, Japan

Whether the immunostimulatory response of the regional lymph nodes was reinforced not only by administration of the immunomediator OK-432 was estimated. The necrotic hepatitis HEP-2 was implanted to C57 mice, and OK-432 was administered to inspect the anti-tumor effect and immunological response of regional lymph nodes. The multiplicity of tumor that was implanted to the group with regional lymph nodes was quite small compared with that of the group without regional lymph nodes (P<0.01). The anti-tumor effect was found in regional lymph nodes. The immunological response of regional lymph nodes was dropped in the non-OK-432 group. It was maintained in the OK-432 group. It could have been related to the anti-tumor effect of regional lymph nodes. OK-432 was administered endoscopically to the tumor of 5 human cases with early gastric cancer before the operation in order to study the immunological responses of regional lymph nodes. The immunological response was compared with that of 10 cases with early gastric cancer of non-OK-432 group. As for the SI value of PHA blastogenesis response in OK-432 group, that of proximal lymph nodes was 3.95 and that of distal lymph nodes 2.85. The value of proximal lymph nodes was 1.77 and that of distal lymph nodes 2.32 in non-OK-432 group. As for the EK cell activity of OK-432 group that of proximal lymph nodes was 8.86 and that of distal lymph nodes 6.79. In non-OK-432 group, they were 6.9 and 6.1 respectively. Two parameters were raised in OK-432 group. There was a significant difference in the proximal lymph nodes (P<0.01). As the result, it was shown that the immunological response of regional lymph nodes was reinforced by the administration of OK-432.


Antitumor and immunomodulatory activity of four low-molecular preparations isolated by ultrafiltration of primate sera, with immunosuppressive effect, was studied. The antitumor effect of the preparations was studied on a model of transplantable tumor LL2 and Ca-755. When the preparations were administered intraperitoneally in a single dose of 5-50 mg/kg on days 3-4 after the tumor cell transplantation inhibition of the tumor growth amounted to 70% per cent. The immunomodulators increased the number of the antibody forming cells in the spleen by 2-3 times and the delayed type hypersensitivity by 60-90% per cent. The effect depended on the dose of the immunomodulators and the time of their administration in relation to immunization of the mice on day 0. The maximum stimulation of the antibody formation was observed when the preparations were administered on day 1 after the immunization and stimulation of the delayed type hypersensitivity was observed when the immunostimulators were administered on days 3, 0 and 2 after the immunization.

CARNOSINE IN THE TREATMENT OF CERVICAL CANCER.

T. Shimanaka, Dept. of Gynecology, Tokyo TIDOKU Hospital, Tokyo 102, Japan

Combination of spontaneous healing potential (SHP), must proceed all measures for the prevention and treatment of cancer. Carminine (CAR) and homocarminine (HCAR) are peptides with immunomodulatory and immunoregulatory properties and can enhance immunomodulators depressed due to the presence of cancer, gamma-radiation, or administration of X-ray and MMC. The author first confirmed the effects of these agents on cervical cancer, and proceeded to treat pre-cancer conditions such as stage 3A-II, 3B-, and stage IV cervical cancers with these agents. These lesions could be successfully treated within 10-30 weeks by the administration of 1-2 CAP suppositories (1200 mg/sup 2-3 times per day). Similar results were obtained in 3-4 weeks by the administration of 2 HCAR suppositories (120 mg/sup 2-3 times per day). The healing of the transitional area was also satisfactory and no recurrences have been observed. These agents were then employed in the treatment of cervical squamous cell carcinomas in combination with gamma-radiation. Healing was achieved by the administration of a total CAR dose of 4,000-10,000 mg with a total gamma-radiation dose of 10,000-12,000 rad or by HCAR alone 60 times with a radiation dose of 3000 rad. The abnormality has been noted in any of our patients for 2 years after confirmation of the healing. Our results suggest that learning from early cervical lesions to pre-cancerous states can be treated with CAR or HCAR alone, and that even cancerous lesions are manageable by enhancement of SHP with these agents combined with gamma-radiation. Prevention and treatment of cervical cancers were made possible by these agents.

CARNOSINE IN THE TREATMENT OF CERVICAL CANCER.


We have reported earlier that carminine (CAR) and homocarminine (HCAR) promote immunomodulation and markedly accelerate the healing of cervical erosion, and herpes. They were also shown to significantly prolong the survival time of animals implanted with sarcoma-180 and to induce regression of the implanted tumor. These therapeutic effects of CAR and HCAR were not derived from their immunomodulatory effects as well as their promotive effects on tissue regeneration. CAR and HCAR increase the physiological capacity of PFC reaction and DHR in SRC. They increase the intensity of PFC reaction and DHR to small amounts of BMR but decrease it to large amounts of BMR. They promote immunoreaction of immune mice but enhance weakened immune reaction of mice over 10 weeks of age. Immunomodulation and tissue regeneration are higher homeostatic functions of the connective tissue. Because of their immunomodulatory effects, these agents can enhance immune functions depressed not only by the development of cancer but also by gamma-radiation or administration of MMC, 5FU, and carmustine. CAR and HCAR can, thus, resolve the contradictory aspects of conventional cancer treatment and obtain application of gamma-radiation or chemotherapy without interfering with spontaneous healing potential. We successfully treated sarcoma-180-bearing animals with intermittent gamma-radiation while increasing their spontaneous healing potential with CAR and HCAR. The effectiveness of this treatment was confirmed by Shimanaka in clinical cases of cervical squamous cell carcinoma. CAR and HCAR, with their spontaneous healing potential-increasing effects, are considered further to have a great potential as anti-AIDS drugs.
2535

OK-432 ACTIVATES NK AND IFN ACTIVITIES IN LARYNGEAL CANCER PATIENTS: M. Yamazaki, T. Taga, C. Suga, H. Ishikawa, T. Kanzaki, K. Nishikawa, Dept. of Otolaryngology and Materiaclogy, Kyoto Prefectural University of Medicine, Kyoto 602, Japan.

Although the efficacy of adjuvant immunotherapy with OK-432 is well documented, it still remains to be examined in head and neck cancer. Therefore, we have examined NK activity and IFN inducibility in twenty-two laryngeal cancer patients before and during adjuvant immunotherapy with OK-432. Immunotherapy with OK-432 was started more than one week after surgery or initiation of irradiation. Three KE of OK-432 was intraduallv given daily for the first week and every other day thereafter during administration. The lymphocytes were prepared from the peripheral blood and their natural killer (NK) activity was measured by Cr-release assay. Interferon (IFN) activity in serum samples was determined by the dye-uptake method. These activities were examined in lymphocytes obtained from 40% of the patients. In almost all of the patients, NK activity was augmented to some extent at each point by the OK-432 treatment. IFN activity was also induced by OK-432. These activities tended to increase until two months after the initiation of the immunotherapy. Thereafter, they gradually decreased but remained higher than the pretreatment level. The adjuvant immunotherapy with OK-432 may improve NK activity through augmentation of NK activity and induction of IFN activity.
2538 BINDING OF ANTIBODIES FROM SERA IN MELANOMA PATIENTS AND HEALTHY DONORS BY NORAL AND TUMOR CELL LINES. X. Sawadro-Rochowska, Dept. of Immunology, Inst. of Gynecology, Warsaw, Poland

Sera from several patients with malignant melanoma and healthy blood donors were tested for their ability to bind with several melanoma cell lines as well as normal adult, fetal and transformed fibroblasts established in culture, using a Protein A-J 125 binding assay. No patterns specific for melanoma patients were seen when the amount of antibodies binding to different normal and neoplastic cell lines was compared. A three-step absorption of sera on each of the cell lines tested, reduced the amount of antibodies binding to target cells used for absorption to 0-25% of the initial value. Absorption cross-experiments demonstrated that melanoma cells, adult, fetal, and transformed fibroblasts shared from 40 to 75% of surface antigens binding antibodies from sera of normal donors and melanoma patients. Since all of these cell lines bound monoclonal antibodies against HLA-A,B,C and HLA-DR antigens, at least part of common determinants are likely to belong to class I and II histocompatibility antigens. Absorption of sera from healthy donors and patients on adult, fetal and transformed fibroblasts resulted in similar decrease of antibody binding to melanoma cell lines, which suggests that the presence of tumor does not result in the increase of antibody levels binding preferentially with tumor cells.


We have reported that electrophoretic mobility (EPM) of thymocytes increased with the tumor growth in the tumor-bearing mice, and that the ratio of low-mobility T cells to high-mobility T cells increased in the peripheral blood lymphocytes of cancer patients. The purpose of this study is to analyze the changes of the mobility histogram and the function in the spleenic and cultured lymphocytes (CL) of the tumor-bearing mice. EPM was measured in Eagle's MEM with a fully automatic cell electrophoresis instrument, Paraquant-L (Kureha Chem. Ind., Tokyo). Plasmacytoma X5563 cells (10^6) were implanted into C3H/He mice. The surface markers of lymphocytes were analyzed with a FACS IV. As the tumor cells grew, splenomegaly, an increase in the percentage of null cells with 0.95 μm/sec./V/cm, and a decrease in the percentages of T and B cells were observed in the X5563-bearing C3H/He mice, but not in the tumor-bearing C3H/He nude mice. To study characterization of lymphocytes in the tumor-bearing C3H/He mice, spleen cells were cultured in RPMI-1640 medium containing 10% FBS, 2-ME (50 μM) and IL-2 after the stimulation by concanavalin A. EPM of CL (0.90) was less than that of intact T cells (1.0-1.05), and the surface markers of CL were Thy-1*, asialo GM1*. These CL showed the antigenic activity against X5563 cells in the Wiss assay. This activity of CL decreased gradually with the growth of the tumor cells. Lymphocyte electrophoresis and the function of the tumor-bearing mice will be discussed.
**2540**

**CELLULAR IMMUNE MECHANISMS DETERMINING THE DEVELOPMENT OF SARCOMA I ALLOGRAFT IN ATS TREATED MICE.**


A substantial portion of Sarcoma I (H-2<sup>a</sup>) tumor allografts transplanted to ATS treated C57B1/6/C57Sn (H-2<sup>b</sup>) recipients reveal after the periods of primary growth and of temporary regression a secondary progressive growth, while skin allografts survive under identical conditions longer but never permanently. In the course of tumor allograft development both the recognizing (OVH reactivity) and effector (reactivity in the Wann's test) functions of T cells are gradually suppressed. Simultaneously, the subpopulations of suppressive macrophages and suppressive T lymphocytes successively appear. The comparison of the development of suppressive cellular mechanisms in different parts of the lymphoid system and in the tumor itself permits to delineate immunologic and nonimmunologic factors involved in the escape of tumor allograft from the "immune surveillance".

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**2541**

**SPECIFIC DESTRUCTIVE MECHANISMS OF HUMAN AUTOLOGOUS BREAST CANCER CELLS: BY A LONG TERM CULTURED T KILLER CLONE.**


We established a specific autologous killer T cell clone, TcHMC-1, that has been cultured and functioned over a year, and analysed its destructive mechanisms of the human breast carcinoma line MCF-7 originated from the same patient. The isolation of culture, pleural exudative lymphocytes (PLE) demonstrated already a high cytotoxicity against uncloned MCF-7 targets, and these PLE showed phenotypically 100% of CD8+ T cells. However, it was shown that PLE at the early phase of cultivation in the presence of IL-2 had a relatively high cytotoxicity against some autologous tumor cells. Furthermore, the killed those PLE were cultured with IL-2 and the stimulation with mitomycin C treated MCF-7, the lower the cytotoxicity of PLE against MCF-7 was demonstrated. Then we showed PLE as well as MCF-7, and an autologous part of highly cytotoxic T clone, TcHMC-1, and a MCF-7-K562 target clone was successfully obtained. TcHMC-1 showed the specific cytotoxicity against MCF-7-K562 target clone, but not autologous fibroblasts, various autologous tumor cells including K562. Moreover, the submaximal in vitro stimulation with a mixture MCF-7 and MCF-7-K562 cells resulted in a failure of tumor development in nude mice.

The cytotoxicity by TcHMC-1 was measured with pre-treatment of TcHMC-1 with OKT3 mAb. This inhibition was recovered by Con A addition in the culture, suggesting TcHMC-1 may have the lytic antigenic specificity, possibly directed to MCF-7-K562 tumor specific antigen. This antigen was solubilized noncovalently by reduction and showed 200 kd of M.W. on Sephadex G-200 gel filtration. This approach was clarify the nature of the tumor specific antigen, presumably of the injection type of human tumor cells recognized by T lymphocytes. In addition, it may be possible to apply the long term cultured killer T cell clone for a cancer specific immunotherapy by passive transfer of these cells.

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**2542**

**THE ROLE OF CELL-MEDIATED IMMUNITY IN CERVICAL CANCER.**

Castello G., Germani A., Sartori P., Brighi G., Ticosso S., Leonardi E., Cuzzolin C., Ange G., G. Zarrilli, Haematology and Clinical Immunology, Department of Gynecology, Tumor Institute, Naples, Italy.

The aim of present study was to investigate T-cell population and subsets in patients with severe dysplasia and carcinoma of the uterine cervix. Fifty-eight patients were investigated and divided into three groups: 1) severe dysplasia/carcinoma in situ (25 pts CIN III); 2) microinvasive carcinoma (16 pts stage IA); 3) invasive carcinoma (17 pts stage IB). The percentages of both peripheral "active" (Ta) and "total" (T) T lymphocytes were evaluated by the method of Wybran and Fudenberg (1971). T-lymphocyte subsets were determined by using monoclonal antibodies (OKT4 and OKT8) by a microcytotoxicity technique. Results showed a significant decrease of both active and total T-lymphocytes in all of three pt groups; lowest T-lymphocyte levels were found in pts with microinvasive carcinoma. As regards to lymphocyte subsets, no significant alteration of helper T cells (OKT4) was evidenced. However, suppressor T lymphocytes (OKT8) were significantly higher than controls in pts with severe dysplasia/carcinoma in situ or microinvasive carcinoma; in the latter pts, OKT4/OKT8 cell ratio was decreased and sometime inverted. In conclusion, these data: a. evidence the presence of a T immunoregulatory imbalance in pts with early or microinvasive cervical cancer; b. emphasize the key role that cell-mediated immunity plays in the induction and/or promotion phase of tumor growth.
2544 EFFECT OF CASCADE FILTERATION AND ADSORPTION ON IMMUNOSUPPRESSIVE ACTIVITY OF CANCER PATIENT SERA. N. Hayaseki, K. Sakagami, J. Matsuzawa, Y. Ishikawa, T. Matsuzawa, L. Okihara, S. Yoshida, T. Bando, Y. Ando, A. Utsumi. First Dept. of Surgery, Okayama Univ., Okayama, Japan. Various immunosuppressive factors (ISFs) are known to be present in cancer patient sera and to suppress the antimicrobial action of the host. Removal of these factors is thought to be important in improving the efficacy of cancer chemotherapy. For this purpose, two types of plasma filtration technique, cascade filtration and adsorption, were clinically studied. About 3,000 ml of plasma obtained from each cancer patient by the first filter was then filtered into 300 ml of discarded fluid containing high molecular weight proteins and 2,700 ml of the second filtrate containing albumin and low molecular weight proteins which was returned to the patient after being mixed with blood cells. The micro porous glass bead adsorbent was selected out of 16 kinds of adsorbents to remove ISFs with low molecular weight. The ISFs with high molecular weight, i.e., alpha-2 macroglobulin, CEA and ferritin, etc., could be removed by cascade filtration and be reduced to less than 20% of the pre-treatment levels. The ISFs with low molecular weight, i.e., immunosuppressive acidic protein and alpha-1 antitripsin, could be removed by the adsorption. The immunosuppressive activity in the patient sera measured by lymphocyte blastogenesis reduced from 40.4% to 23.7% in average after treatment. PPD skin test improved in 7/10 (70%) of the patients and severe back pain or general fatigue improved in 5/10 (50%) of the patients. These data suggest that plasma purification therapy is an useful part of combined modality therapy of cancer.

2545 HODGKIN'S DISEASE: MECHANISMS OF DEPRESSION OF PRIMARY ANTIBODY RESPONSES IN VITRO. E. Clerici M., Villa, P. Valenti, C. Tosi, and M. Vichi. Istituto di Immunologia e istituto Nazionale Tumori, Via Venezian 1, 20133 Milan, Italy. Primary anti-sheep red blood cells (SRBC) Antibody responses in cultures of human peripheral blood mononuclear cells (PBMC) from newly diagnosed Hodgkin's disease patients (HD) have been studied with the soft agar method of hemolytic complement mediated lysis. The number of haemolytic colonies was significantly lower in cultures of PBMC from HD patients (HD-PBMC) as compared to that of PBMC from healthy donors (control-PBMC). Indomethacin (10^-4 M) addition to cultures slightly increased the HD-PBMC response whereas it had an irregular effect on control-PBMC. Plastic-adherent cells, AC depleiion by lysis incubation resulted in a limited increase of the number of haemolytic colonies in HD-PBMC as compared with an impressive increase in control-PBMC cultures. These results: 1. confirm our previous observations that the immune responses of normal PBMC are modulated by non-specific uterine positive and latex phagocytizing monocytes which are the main component of the AC population? 2. suggest that monocyte cells play a minor role, if any, in the depression of antibody responses shown by HD patients. The latter hypothesis was confirmed by the observation that treatment of the HD-PBMC with 10% U-91, a patient which destroys H2O2, the major mediator of the monocyte activity, had little effect on HD-PBMC, whereas it sharply increased the number of the haemolytic clones in control cultures. Works are in progress to verify if T-suppressor monocytes may be responsible of the immune depression in HD-patients.

2546 IMMUNOLOGIC FINDINGS IN PATIENTS WITH CLASSIC KAPOSI'S SARCOMA. Castello G., Melillo G., Saridano R.A., Rossello R., D'Alessio V., Giordano G.B., Zarrilli D. Haematology and Clinical Immunology, Dept. of Pathology, University, Naples, Italy. Dept. of Dermatology, 1st Univ Naples. 2 pts (10%) had a second tumor (Hodgkin's Disease, Gastric Carcinoma). Cell-mediated immunity was evaluated in vivo (cutireactivity - Multitest, Institut Merieux) and in vitro by using FITC-conjugated monoclonal antibodies (OKT3, OKT4, OKT8, Leu-7 by Flow Cytometer Spectrum (11 Ortho)); humoral immunity was evaluated by determination of serum immunoglobulin levels (lgG, IgA, IgM - nephelometry) and of circulating immune complexes (CIC) by three methods (PEG, Clq, Kp). 75% of pts presented cutaneous anergy and 20% of pts hypoglycemia when tested for delayed type hypersensitivity. Moreover, we observed increases in the percentage of the other subsets didn't change. In the LMl-test against melanoma, psoriatropic, total T-cells and OKT4+ cells, with a reduction of mean levels of TN/TH ratio statistically significant (p<0.01) when compared to controls. In 55% of pts increased levels of at least one class of Ig was found. CIC were detected in 70% of pts with PEG method, and in 30% of pts with other two methods. Our results show a impairment of immunologic system also in classic KS involving cell-mediated immunity (anergy and decrease of T-cells) and humoral immunity.

2547 EVALUATION OF TUMOR ASSOCIATED CELLULAR AND HUMORAL IMMUNE REACTIONS IN ASSOCIATED NON-HODGKIN'S LYMPHOMA (NHL). Krehm, R. (1), Neumann, P. (2), Bruhl, P. (3), Reumy, I. (3). Dept. of Biology (1) and Dept. of Pathology and Bacteriology (2), University of Bonn, D-5000 Bonn 1, Semmelweis Medical Highschool (3), Budapest, H. Some features of NHL with its participation of immunologic mechanisms in the development of the disease. Therefore the following parameters of general cellular immunity and tumor-associated cell mediated immunity have been determined in 10 patients with disseminated NHL and compared to an age-matched group of patients with no neoplastic diseases: determination of delayed hypersensitivity skin reaction (DHR) by means of MULTITEST NERLUE (R) determination of immune cytotoxic T-cells and 0+N- cells (total ICA, Ant Leu 5), T helper/inducer cells (Anti Leu 22), T suppressor/cytotoxic cells (Anti Leu 7A), natural killer cells (Leu 11?), monocytone (B-cells), Non-T,N,0-cells and 100%, 1gG, IgA and IgM-positive cells - and lymphocyte migration-inhibition test (LMITest) against autologous and homologous tumor tissue and recall antigens in vitro. Compared to the control group in patients with disseminated NHL the number of positive skin reactions and the mean value of scores were reduced (p<0.05). In opposite to this, UMT-reaction against recall-antigens in vitro was not affected in 6 of 10 patients with disseminated NHL. Further a decrease in the percentage and absolute number of total T-cells (p<0.05), T helper/inducer cells (p<0.07) and macrophages (p<0.09) was observed. After resection of the percentage of natural killer cells increased (p<0.01/0.001), the percentage of the other subsets didn't change. In the LMITest against autologous and homologous tumor tissue tumor-associated cellular immunity in the mean of inhibition or enhancement could only be observed in 1/10 patients. Therefore in 6 of 10 healthy controls an enhancement against homologous tumor tissue was also observed, a phenomenon, which we are going to examine further. In contrast to the UMT-reaction against autologous, 10/10 patients in 7 of 10 patients with associated cellular immunity against homologous tumor tissue could be determined. These preliminary findings lead to the conclusion, that in disseminated NHL the overall cellular immunity measured as delayed hypersensitivity skin reaction against recall-antigens in vitro and the distribution of lymphocyte subsets and macrophages are altered, 2. tumor-associated antigens can be demonstrated by means of a positive reaction in the UMT. 3. against autologous or homologous tumor tissue in spite of an only slight affection of general cellular immunoreactivity, will be examined further.
2548 CHANGE OF ENZYME ACTIVITIES RECOGNIZED IN GRANULOCYTES FROM PATIENTS WITH CARCINOMAS OF THE GASTROINTESTINAL TRACT

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Human peripheral blood granulocytes have substantial cytoytic activity against tumor cells. In the role of granulocytes advocated attention is the host defense mechanism against tumor. In the mechanisms of granulocyte-mediated cytoytic activity against tumor cells, lysosomes in granulocytes may show the change in carcinomas-bearing patients with different performance status (PS) and different immunological status. From this standpoint, the change of the activities of acid phosphatase (AcPase) and -glucuronidase (-G) in granulocytes from patients with carcinomas of the gastrointestinal tract (GI carcinomas) was investigated.

Normal individuals were selected as controls. ECOG PS criteria were used as PS. Granulocytes were separated on the Ficoll-Conray density gradient and using 3% gelatin solution. After preparation of crude enzyme, the activities of acid Pase and -Gase were determined by the modification of Seevers' method and our devised modified method of o-nitrophenyl glucuronide using method, respectively. Acid Pase in granulocytes showed the activity-increasing stage in PS 0-1 groups, and the activity-decreasing stage in PS 3-4 groups. -Gase in granulocytes showed the activity-increasing stage in PS 1-2 groups, and the activity-decreasing stage in PS 3-4 groups. Lysosomal enzyme activities indicated the characteristic change in the clinical course, suggesting that an important factor may be playing a role in the host defense mechanism against carcinoma in the background of the change in those enzymes. It is necessary to investigate the role of these enzymes in relation to the immune responsiveness of the patients with GI carcinomas.

2549 T-LYMPHOCYTE E-ROSETTING CAPACITY INHIBITION BY TUMOR-ASSOCIATED ANTIGENS IN CANCER PATIENTS

(BREAST CANCER AND MALIGNANT MELANOMA).
M. Gogoi and G. Stuparu.
Clinic Med, Oncology Inst., Cluj-Napoca, Romania

The in vitro effect of a pool of tumor-associate antigens (TAA) on rosetting capacity of circulating T lymphocytes in 28 breast cancer patients (breast tumor associated antigens-BAA) and in 20 malignant melanoma patients (melanoma-associated antigens-MAA) as compared with a control group formed by healthy persons, benign tumors and patients with different tumors (29 persons). The lymphocytes isolated by centrifugation on Ficoll-Paque gradients were incubated for 40 min. at 37°C with BAA or MAA. washed and subsequently the E-rosette forming capacities were tested at 0°C and at 29°C (high activity E-rosettes). Incubation of cancer patients' lymphocytes with TAA significantly decreased E-rosette percentage. The pattern of the two types of cancer was different. In breast cancer, 62.9% of patients presented a decrease of 4°C E-rosette percentage with BAA: 100% prior to surgical therapy, 5% at the day after surgery and 33% of patients with distant metastases as compared to healthy persons. Breast melanoma a decrease of high-affinity E-rosettes was observed in 95% of patients: 91.7 before surgery, 100% at 5-7 days after surgery as compared to 37.5% in healthy persons (p < 0.01). The significance of these findings are discussed, in comparison with other tests for assessment of tumor response against neoplastic antigens.

2550 DYNAMICS OF LYMPHOCYTE REACTIVITY TO PHYOHEMAGGLUTININ IN OVARIAN CANCER PATIENTS DURING CHEMOTHERAPY.


During 36 months of chemotherapy, the dynamics of lymphocyte reactivity to phytohemagglutinin was determined during chemotherapeutic courses. Polychemotherapy with cyclophosphamide (cyclophosphamide) was applied for a period of 5 days every 28 days. Following courses of cyclophosphamide application, lymphocytes were analyzed in 15 patients. Transformation of patients' lymphocytes was determined prior to each course of polychemotherapy, and every 3-4 months during cyclophosphamide therapy. Of the 36 patients observed 15 died during a period of 2 years, and in 11 of these reactive lymphocytes were continually very low, and in the remaining 4 this was initially normal but became low during therapy. Lymphocyte reactivity was continually normal in 11 of the 21 patients during polychemotherapy in patients clinically free of disease. In 4 patients reactivity of lymphocytes became normal during therapy, and in the majority of patients the change of reactivity of lymphocytes remained continually low. During therapy with cyclophosphamide values of lymphocyte reactivity were normal in 8 patients. In 4 values normalized. In two they remained low, and became low in one patient only. To conclude, it is clear that in malignant patients the state of disease-free of disease, reactivity of lymphocytes was normal or increased during polychemotherapy. The result imply that the application of cyclophosphamide could further improve lymphocyte reactivity to phytohemagglutinin.
CHEMICAL MODIFIERS OF IMMUNOLOGICAL PARAMETERS IN PATIENTS WITH METASTATIC BREAST CANCER. CORRELATION WITH SURVIVAL

I. Hadjikirova, I. Boeva, T. Donchev
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We have analysed: 1) the effect of chem-hormonotherapy on the cellular immunological parameters; 2) the effectiveness of chemotherapy in connection with these parameters; 3) the correlation between pre- and post-treatment immunological tests and survival in 111 patients with metastatic, histologically proven breast cancer. The results have revealed a marked depression in T-lymphocytes prior to treatment. The chem-hormonotherapy used to treat these patients (4 regimens) did not cause further impairment of existing T-lymphocyte suppressor function. The response to chemotherapy was correlated with delayed hypersensitivity reaction to L.C.I before drug application. Analyses were performed by the life-table method to determine the correlation of T-lymphocytes with survival, and by regression analysis to determine the correlation of T-lymphocytes with survival. The table survival probability for the patients with positive reaction to L.C.I was higher than that for the patients with negative reactions. There was a statistically significant positive correlation between number of pre-treatment T-lymphocytes and survival. These results support the view that under certain conditions cytotoxic T-cells could mediate tumor-induced immunosuppression to the benefit of the host. The results seem to indicate the usefulness of such immunological parameters for increasing the effectiveness of disease treatment and survival.

ENRICHMENT OF PERIPHERAL BLOOD STEM CELLS BY COUNTERFLOW ELUTRIATION

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T. M. Fliedner, Dept. of Clinical Physiology and Occupational Medicine and Dept. of Pediatrics IX, University of Ulm, Federal Republic of Germany

The present study was performed to collect from a suspension of human blood leukocytes by means of counterflow elutriation those mononuclear cells that show in-vitro culture the potentialities of hematopoietic progenitor cells (CFU-GEMM, CFU-GM, CFU-M or CFU-E). In clinical studies of our group such stem cell suspensions obtained from the peripheral blood were demonstrated to be able to repopulate the hematopoetic system of patients conditioned for engraftment by total body irradiation. In our study, a Beckman model J-21 B centrifuge was used equipped with a newly developed separation chamber in which up to 5 x 10^9 cells could be separated without clumping. Using this tool, ficoll separated peripheral blood cells could be collected according to their size using the counterflow principle. It can be shown that CFU-C enrich in cell fractions different from lymphocytes on the one hand and granulocytes on the other. This principle will prove to be valuable in clinical practice to separate blood derived stem cells from immunocompetent lymphocytes.

MALIGNANT GROWTH, STRESS AND IMMUNITY


Clinical and experimental data concerning the comparative characteristics of immunity and non-specific resistance in stress and malignant growth are presented. It is testified that prolonged stress-reaction accompanying the process of adaptation in circumpolar region of Siberia alters the mechanisms of non-specific defence. The acute phase of this process continues not less than 1.6 year (the experimental data obtained in Immunology AYN, CSF1I confirm this conclusion). Immune status of patients with lung, stomach, head and neck malignant tumour is described. Immune status of these patients is unusual and could not be explained by immunodepression only. Principal resemblance between immune status in malignant growth, physiological pregnancy and prolonged stress is discussed as well as possibility of immune rehabilitation using some chemical (heterologous MPA, pyrogens and physical coherent radiation) immunomodulatory agents.

CHRONIC TENSION OF THE IMMUNITY SYSTEM IN THE BODY TO TUMOR GROWTH. V.I. Oglebaa, S.A. Stankevich, the Siberian Branch of The All-Union Cancer Research Center, AMG USSR, Tomsk, USSR

The time course of antitumor resistance of different lines of mice was studied against the background of exposure to subextreme ecological factors (transmeridional flight with a subsequent adaptation to new climatic-geographic conditions), indices of antitumor resistance (T-killer cells, etc) have been shown to undergo slight functional changes in animals genetically stable to spontaneous tumor development. On the contrary, highly cancerous lines of mice responded to it with a noticeable decrease in antitumor resistance expressed in faster tumor development and growth in them. Besides, highly cancerous lines reacted to the transmeridional displacement to a new climatic-geographic zone by a noticeable resorption of lipid peroxidation, change in the level of blood and tissue steroid hormones, disturbances in the immunity system. The problem of the mechanisms of the above reactions is discussed. They appear to be caused by chronic stress. The authors provide some materials giving an opportunity of the optimisation of the adaptation process with the help of some adaptogens of plant origin. The genetic determination of different variants of immunoadaptation is substantiated.

2552 CHEMICAL MODIFIERS OF IMMUNOLOGICAL PARAMETERS IN PATIENTS WITH METASTATIC BREAST CANCER. CORRELATION WITH SURVIVAL

2553 ENRICHMENT OF PERIPHERAL BLOOD STEM CELLS BY COUNTERFLOW ELUTRIATION

2554 MALIGNANT GROWTH, STRESS AND IMMUNITY

2555 CHRONIC TENSION OF THE IMMUNITY SYSTEM IN THE BODY TO TUMOR GROWTH
CHARACTERISTICS IN ANTITUMOR PROPERTIES OF NEU ORGANIC SILICON COMPOUNDS ADMINISTERED ORALLY. K. Fukumoto, W. H. A. Hazareth, H. J. Daly, M. I. James, P. J. Nicholls and H. J. Smith

Welsh Sch. of Pharmacy, U.K.

atonel reflex-rise in ACTH level. We have also found that a significant augmentation of de-

The chemotherapeutic index of SDK-12B was 0.030 μM/ml in KB cells. The chemotherapeutic index (CIC) was 3.50 in the Lewis lung carcinoma (LLC) metastasis model. SDK-12B administered po was found to be relatively effective against B16 melanoma. These antitumor effects were noted in variously treated mice, with no toxicity against human renal cell carcinoma xenografts in nude mice (Journal of Medicinal Chemistry 20: 546-549 1988). We have also obtained various results with BB especially against non-renal cell tumors. Inclusion compound with a-polypeptide. BASS is a new compound. Its activity against renal tumors has been reported in the literature. It inhibits protein synthesis of the BASS in a new compound. Its activity against renal tumors has been reported in the literature. It inhibits protein synthesis of the BASS in a new compound. Its activity against renal tumors has been reported in the literature.

DuP-785 (NSC 368390) was prepared in an analogous program and was selected for further development as an anticancer agent from among 200 structurally novel substituted aryl quinolincarboxylic acids. DuP-785 is a water soluble compound that demonstrated good activity against a spectrum of experimental human carcinomas implanted a.c. or under the renal capsule (SRC) in nude mice. Significant (> 90%) tumor growth inhibition were obtained by i.p. DuP-785 administration against the LX-1 lung, the B16 melanoma, the BL/STK-1 and the C3H colon tumors implanted SRC. The agent was also effective against 3 human colon cancer growing a.c. in nude mice; fluorouracil (FU), adriamycin and cytosine arabinoside were ineffective in these tests. The compound is active orally as well as parenterally. At a cital concentration (10 μg/ml), DuP-785 caused a rapid, time-dependent depletion of intracellular UTP and CTP pools. These results indicate that DuP-785 inhibits a step in the de novo pyrimidine biosynthetic pathway leading to UMP. Uridine (800 mg/kg) given i.p. 3 hrs after DuP-785 (25 mg/kg/day × 9) partially reversed its toxicity in L1210-bearing mice without reducing the efficacy of DuP-785. The combination of FU and DuP-785 was not more effective than DuP-785 alone against colon tumors in nude mice but was of overlapping toxicity; both agents produce C.I. toxicity.

These results on the efficacy and mechanism of action of DuP-785 will be useful in designing protocols for clinical studies with this agent.


Acute toxicity and lymphoma taking efficiency of the new synthetic, anti-cancer substance CellImun /CIM/ had been investigated in Swiss white mice /age of 5 weeks, male/. Ascites tumor was induced by taking in Nethely-Keller lymphoma /NKL/ cells. A broad dose-range /10-1000 μg/kg/ was studied and treatments were made intraperitoneally on 4-6 occasions. Initial NHL cell numbers were also altered during the experiments. The number of survivals, alterations in the body-mass growth and - by post-mortem examinations - the tumor free cases had also been acute-toxicity investigations. The effective dose-range was found between 10-100 μg/kg. 90% of the cases proved to be tumor-free when the initial NHL cell numbers were between 0.5·10^5 cells/animal and mice were treated with 10-50 μg/kg doses or CUM. The body-mass growth of the treated animals was 30% less than that of the control ones when CUM doses in broad range were administered. The moderate body-mass alterations were accompanied by an average 200% survival rate.


The cell surface plays a main role in the cell-cell and cell-substrate interaction. The examination of the cell electrophoretic mobility makes possible under certain measurement conditions the investigation of the chemical, physicochemical and biological properties of the cell surface. Using suitable test cells, the cell electrophoretic method is convenient for the specific and non-specific bindings of different substances.

In our present study we have investigated the cell surface binding feature of CIImUN (CIM), a non-toxic anticancer and immunomodulating agent in rat erythrocytes, platelets and white blood cells tumor cells. Our findings suggest that the CIM administration resulted concentration dependent decrease of cell surface charge in the case of tumor cells specific changes were found as compared to the controls. The binding of CIM was modified by neuramidase treatment.

2563 IN VITRO CYTOTOXICITY OF A NEW SYSTATIC BENFLURONE COUNPOUND ON HUMAN AND V7 MELANOMA CELLS

K. Jankovc, S. Novotny, A. Vargyas, T. Perenyi, J. Perenyi, T. Kolko, J. Skvap, Czechoslovakia, Prague, Czechoslovakia.**

Benfluorone a most active derivative of benzo/c/fluorene /-2'-dime l-aminomethoxy/-7-oxo-7'-benzo/c/benfluorone/ which is at present in the second stage of clinical tests inhibited in dependency on the concentration applied in the range of 0.12-2.1·10^5 proliferation of cells accompanied by an increase of their size and disruption of the ratio protein/DNA. By the analysis of the culture medium it was found that the treated cells increased glucose consumption and lactate production. From the aminoacids /gln, arg, ala/ the cells utilized only glutamine. However, to express the results of the metabolic activity it is important to take into account the total protein content per cell because both parameters of the cellmentation mentioned above induced unbalanced growth. The agent applied in a concentration above 4.2·10^5 l-1 impairs the integrity of cell membrane. The study contributes to the elucidation of the relationship between benfluorone lethal effects and the mechanism of its action.

MST-16, 1,2-bis(4-isobutoxy carbonyl methyl-1,5-dioxopiperazine-yl)ethanes is an analogue of ICRF-154 developed by Narita et al of Research Laboratory, Senyaku Kogyo Co., Ltd., Tokyo, Japan. Antitumor activities of MST-16, ICRF-154, ICRF-159 and Bimolane were compared using L1210 and P388 mouse leukemias.

The compounds were suspended in saline containing 1% of HPC(L). The drugs were injected intraperitoneally into BDF1 mouse 24 hours after the inoculation of leukemic cells. In L1210 leukemia 10^5 leukemic cells were inoculated into BDF1 mouse and in P388 leukemia 10^6 cells were inoculated.

The data were evaluated by increase of life span (ILS) and chemotherapeutic index (maximum tolerable dose=MTD divided by a dose showing 30% of ILS).

In L1210 mouse leukemia MTD of MST-16 was 1000 mg/kg and chemotherapeutic index of MST-16 was 3.3. MTD of ICRF-154 was 600 mg/kg and Chemotherapeutic index was 4. MTD of ICRF-159 was 1000 mg/kg and chemotherapeutic index was 1.7. MTD of Bimolane was 100 mg/kg and chemotherapeutic index was only 1.

In P388 leukemia MTD of MST-16 was 500 mg/kg and chemotherapeutic index of MST-16 was 10. MTD of ICRF-154 was 1000 mg/kg and chemotherapeutic index was 6.7. MTD of ICRF-159 was 1000 mg/kg and chemotherapeutic index was 3.3. MTD of Bimolane was 100 mg/kg and chemotherapeutic index was only 2.

These data might indicate that the antitumor activities of MST-16 are superior to ICRF-154, ICRF-159 and Bimolane.


Hydroxyurea, HU, an inhibitor of ribonucleotide reductase, is a drug used frequently in the treatment of chronic granulocytic leukemia as well as head and neck cancer. The important pharmacophore in HU is the N-N'-CH=N moiety. Clinically, the use of this drug is limited by its short half-life due to the highly hydrophilic nature of the molecule. To circumvent this problem and maintain the essential pharmacophore, several derivatives of 1H-isoadole-1,3-(2-hydroxy)-dione have been synthesized.

These compounds are expected to act as prodrugs which, upon hydrolysis under physiological conditions, will form the isoidole-2-hydroxy-1,3-dione. Emphasis was given to attain a balance between the lipophilicity and lipophilicity of the molecules. The compounds were synthesized using 4-nitrophenol as the starting material. The final structures of the synthesized compounds were confirmed by spectroscopic data and elemental analysis. The in vivo cytostatic activity against L1210 cells has been evaluated. The concentration of compounds at which 50% growth inhibition was observed was determined to be 8 nM as compared with 100 nM for HU. The most active compound was where R1 is (CH2)2, N and R2 is SO2CH2. The compounds did not attack the cell membrane's Integrity within 20 hours of treatment. A SAR analysis of these compounds showed that the cytostatic effect correlated with the electronic effect and the lipophilicity parameter as measured by ClogP.

2567 ANTICANCER ACTIVITY OF (-N,N-Bis(2-chloroethyl)-aminol-N'-aryl/alkyl/benzylideno/amino)-2,5-PYRROLDIDine-DIONES. R. V. AMBAYE, S. D. NAIK, S. V. GOKALE, Cancer Research Institute, Tata Memorial Centre, Parel, Bombay-400012, India.

Compounds, bearing 2,5-pyrrolidinedione ring system, have been reported to possess diverse biological as well as anticancer activity. Approaches to drug design, based on the N,N'-bis(2-chloroethyl)aminol-N'-aryl/alkyl/benzylideno/amino)-2,5-pyrrolidinedione, in search for less toxic and more active congeners. Accordingly, a series of (-N,N-Bis(2-chloroethyl)-aminol)-N'-aryl/alkyl/benzylideno/amino)-2,5-pyrrolidinediones was synthesized.

The compounds had analytical and spectral data compatible with the assigned structures. These compounds were screened for their antitumor activity in vivo bearing L1210 lymphoid leukemia. The promising compounds were further tested in an expanded tumour panel such as P388 (lymphocytic), Sarcoma 180 (Solid and ascitic form), intracerebrally (IC)-grafted P388 tumour etc. Out of the six L1210 actives, two compounds were active against P388 (p<0.05), one of them showed activity against Sarcoma 180 (ascitic and solid form) and intracerebral P388 leukemia. The pharmacological assessment of these compounds was carried out in mice. The data warrants use of this compound as a possible candidate for clinical trials.
COMPARATIVE ACTIVITY OF HEXADECYLPHOSPHOCHOLINE IN TRANSPLANTED AND AUTOCHTHONOUS MAMMARY TUMORS.


Recently it could be demonstrated that hexadecylphosphocholine (HPC), a new compound with unknown mechanism of action, had significant anti-tumor activity in MNU-induced autochthonous rat mammary carcinomas. The maximum growth inhibition following HPC treatment surpassed the effect of any cytostatic or hormonal treatment so far in this model. For instance, the optimal dosage of 51 \( \mu \)mol/kg daily per os x 5 days/week x 5 weeks resulted in >95% tumor growth inhibition compared to untreated controls without exerting serious toxic side effects (Berger et al. in press). In contrast to these observations, HPC was completely inactive in the transplanted MXT mammary tumor, a well differentiated ductal carcinoma in B.N. mice.

Peroral treatment started at a mean volume of 400 mm\(^3\). Dosage: 30 and 60 mg HPC/kg daily x 12 days. 60 mg/kg were toxic (mortality: 40% ; the observed \( T/C \) % after 12 x 30 mg/kg was 100.

The comparative results are remarkable since usually faster growing transplanted tumors (volume doubling time of 3–4 days) are more sensitive to conventionally used cytotoxic drugs than slower growing transplanted tumors (volume doubling time of MXT about 4 days).

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2572 METALS IN ANTICANCER THERAPY: THE PALLADIUM. M. Grandi, V. Santoro, Ctr. Studi. Ricerche, Terapia neoplastica, Piazza Rivoli 11, Torino, Italy.

Palladium is an eighth group's metal which acts as a strong oxidizing agent. Several authors have put in evidence its inhibiting activity on rat liver mitochondrial respiration. Some studies "in vitro" which we have made, confirmed that the Palladium inhibits the hepatic cells respiration, in proportion to its concentration; an inhibition of 50% respiration is already put in evidence at 5 g Palladium concentration for millions of cells. Its administration in rats carrier of Yoshida hepatoma ascites, moreover, partially inhibits the tumor growth. We have observed:

1) a decrease of total quantity cells of 65% as regards to the control groups
2) a considerable cytolyis with membrane alteration
3) a decrease of tumoral cells numbers which are able to go in the cell cycle, as it results from reduction of "label index" at 51%.

The clinical trial of Palladium are at present, in stage one.

2573 INHIBITION OF TUMOR GROWTH IN MICE TREATED WITH SYNTHETIC PEPTIDOGLYCANS - DELAYED EFFECT.


Local treatment with synthetic N-acetyl-muramyl-L-alanyl-D-isoglutamine or N-acetyl-beta-D-glucopentanoyl-L-1/4-N-acetylglucosaminyl-L-alpha-aminobutyryl-D-isoglutamine inhibited growth of transplantable, chemically induced tumors in syngeneic mice. The tumor-inhibitory effect was dependent on the schedule of peptidoglycan administration. Positive results were obtained only in mice treated with comparatively high [0.2-1.0 mg] doses and long [5-7 weeks] before tumor challenge. Treatment with lower [0.01-0.1 mg] doses and at short [1/4 weeks] time intervals was not effective. In contrast, intravenous pretreatment with peptidoglycans incorporated in multilamellar liposomes inhibited tumor growth when low doses [0.02 mg] were given 1 and 2 days prior to the challenge.


2574 ANTITUMOR EFFECT OF PSYCHOPHARMACEUTICALS IN RATS WITH INDUCED TUMORS (A MODEL FOR PREVENTION AND TREATMENT OF HUMAN TUMORS).

A. v. Mettler, C. Mischel.

Chromosomal changes play a major role in tumor development. X-rays, carcinogenic substances and chemotherapy are known to induce chromosome damage. Several psychopharmacological drugs and neurotransmitters, respectively, have an antimitogenic effect. We, however, induced metastases hardly responsive to clinical therapeutic measures like chemotherapy, X-rays or surgical tumor removal. If psychopharmacological were given before tumor appearance, we observed a reduction in tumor rate (2). Given after tumor appearance, survival rate increases threefold on even disappearance of tumors was observed. When treating after surgical removal of tumors, survival rate increased to 97%, nec metastases were not traceable. Treatment with cyclophosphamide alone was ineffective. In combination with psychopharmacologicals (Pirenetac), we achieved a tumor reduction by 80% and a reduction of toxic side effects of cyclophosphamide. Various central nervous system functions are altered by experimental carcinogenesis - either by induced or transplanted tumors. EEG and changes in neurotransmitter metabolism were used as parameters. In current clinical studies, psychopharmacologicals were shown to diminish side effects of chemotherapy in children with leukemia.

(1) E. Gebhard, Chem. Carcinogenese 1977
(2) A.v. Mettler and C. Mischel, Naturwissenschaften, 1985

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2575 THE USE OF METHIONINE ANALOGS AS A NOVEL ANTICANCER STRATEGY.

D.L. Kramer, V. Alks and J.R. Sufrin, Roswell Park Memorial Institute, Buffalo, NY 14262, USA.

Whereas normal cells are capable of growing independently of methionine in the presence of homocysteine, most tumor cells are not. This methionine-dependence provides a potential basis for selectivity by methionine analogs. Cultured L1210 cells are methionine-dependent and are also incapable of deriving methionine from L-methionine. Cultured L1210 cells are methionine-dependent in the presence of homocysteine, but-3-enolic acid (L-cisAMB), a specific inhibitor of methionine adenosyltransferase (Sufrin et al., BBRC 106: 521, 1982) and, hence, of S-adenosylmethionine (AdoMet) formation. At the dose inhibiting growth by 50% (IMM), LcisAMB inhibited precursor incorporation into DNA prior to that into protein or RNA while AdoMet pools were decreased by 50%. Effects on growth, DNA synthesis and AdoMet pools were all enhanced by reducing exogenous methionine from 100 uM to 30 uM (the minimal concentration for normal cell growth). Since L-cisAMB at 10 mM failed to affect cellular uptake of [3H]-methionine, competition between L-cisAMB and methionine probably occurred at the enzyme site. Under conditions depleting AdoMet pools to undetectable levels by HPLC, polyamine pools were not affected suggesting interference with transmethylation as the basis for growth inhibition. Initial studies to determine the effect of AdoMet depletion on cellular methylation by another less selective inhibitor of AdoMet synthesis, cycloleucine, resulted in a decrease in nucleic acid methylation. Comparable studies with L-cisAMB are presently underway and are expected to give similar results. In vivo studies with LcisAMB demonstrating meaningful activity against L1210 leukemia have encouraged synthesis of additional methionine analogs directed at AdoMet biosynthesis (Supported by CA-13038 and CA-24538).
**H-47: NEW DRUGS: MISCELLANEOUS**

2576

**ANTITUMOR ACTIVITY OF THE POLYCHLORINATED OF RADIOISOTOPIC NON-HUMAN-TYPE MECHANIATURONE TRIBROMIDURON (RMT) IN THE ADENOCARCINOMA BREAST CANCER AND COLLABORATION AS ACTING MECHANISM BETWEEN NITROGEN-78 RADON, FUKUOKA, Y.**, Dept. of Pathol., Kawasaki Med. Sch., Fukuoka, Japan

Polybrominated dioxins extracted from human-type microbacterial tuberculosis. ADK-2 strain (10^8 cells) inoculated intraperitoneally produced a remarkable effect in human adenocarcinoma breast cancer and other cancers. Clinical cases: Case 1 was a 47-year-old female with left breast adenocarcinoma. A trial intraperitoneal injection of the non-human-type mechaniaturon tribromiduron (RMT) resulted in complete remission within 2 weeks.

2577

**THE EFFECTS OF 1,5-D-RIPOURAGOSYLYL-4-METHYLTHIOPHYRACLLOZOL(3,4-d)-PYRIMIDIN ON THE NUCLEAR ACIDS BIOSYNTHESIS IN CULTURED OVARIAN CELLS.**, 7.1. Zin, A. Tomonari, H. Miyauchi, and M. Kurokawa, Department of Pathology, National Cancer Center Research Institute, Tokyo, Japan

Synthetic enzyme analog - 1,5-D-ribofuramonyl-4-methylthiophyracrozol(3,4-d)-pyrimidine (RHF) was previously shown to increase the life span of mice with breast cancer by 40-50% and to be cytotoxic to cultured ovarian carcinoma (OVCA) cells. In this study, the effects of RHF on the incorporation of labeled Thd, Urd, Ade, Gua and glycine in the acid soluble fraction (ASF), DNA or RNA of OVCA cells. After 24 h incubation with biologically active concentration of RHF, the incorporation of Thd was decreased by 50% in ASF and by 70% in RNA. There was no effect on incorporation of Gua and on incorporation of Ade in DNA or RNA, but its incorporation in ASF was decreased by 30% in 50% RNA in 65% in DNA. The kinetic parameter of these inhibition processes were determined. RHF inhibited ATPase activity of cell membranes in experiments in vivo RHF dramatically decreased the activity in DNA or RNA of tumor cells of mice with plasmacytoma MOP. The possible mechanisms of the biological effects of RHF are discussed.

**H-48: PRECLINICAL DRUG EVALUATION: TOXIC SIDE EFFECTS**

2578

**COMPARATIVE STUDIES OF THE EFFECTS OF MITOXANTRONE (NOVANTAN) AND ANTHRAZPRAZOLY ON LIPID PEROXIDATION.**, P. Frank, S.M. Cross and R.F. Novak, Department of Pharmacology, Northwestern University Medical and Dental Schools, Chicago, IL, U.S.A.

It has previously been demonstrated that mitoxantrone (MNX) inhibited lipid peroxidation in human and cancer cell subcellular fractions (E.D. Kharaasch and R.F. Novak, J. Pharm. Exper. Ther. 225:500, 1983) and that the mechanism of inhibition resided in termination of the hydroperoxide-dependent peroxidatic cascade (E.D. Kharaasch and R.F. Novak, J. Biol. Chem. 260:1065, 1985). Several anthrapyrazole antineoplastic agents CI-937, CI-941 and CI-942, were synthesized with the objective of developing effective antineoplastic agents with diminished cardiotoxicity.

2579

**CARDIOTOXIC EFFECTS OF MITOXANTRONE IN CD-1 MICE TREATED ACUTE OR CHRONICALLY.**, L.Dusonchet, V.Candiloro, L.Crosta, C.Cucchiara, C.Pandina, R.Sanguedolce, M.Anane, L. Crosta, Inst. of Pharmacology, University of Palermo, Italy

Clinical reports indicate that Mitoxantrone (dihydroxyanthracenedione) employed as an antineoplastic drug induces heart failure. The similarity of chemical structure and the ability of Mitoxantrone to enteract into DNA an anthracene molecule do suggest that the incorporation of glycine was decreased by 30% in 50% RNA in 65% in DNA. The kinetic parameters of these inhibition processes were determined. RHF inhibited ATPase activity of cell membranes in experiments in vivo RHF dramatically decreased the activity in DNA or RNA of tumor cells of mice with plasmacytoma MOP. The possible mechanisms of the biological effects of RHF are discussed.

**MONDAY • AUGUST 25 • AFTERNOON**
2581 THE EFFECT OF ADRIAMYCIN ON THE FUNCTIONAL PROPERTIES OF HEART, LIVER AND TUMOR MITOCHONDRIA. A. Floridi, A. Bagatto and C. Bianchi. Regina Elena Institute for Cancer Research, Rome, Italy.

Adriamycin (ADM) is one of the most important single anticancer agent because of its broad spectrum of activity, but the use in chemotherapy is severely restricted by its extreme toxicity. Among the more pronounced side effect there are dose-dependent cardiomyopathy, nephrotoxicity and liver necrosis. These alterations have been correlated with ultrastructural and functional impairment of mitochondria. Nevertheless, there are strong discrepancies among the results of different laboratories, possibly due to different experimental conditions. In order to ascertain whether the heart mitochondrial activity (determined by the ECC method) was altered by ADM, we have undertaken systematic investigations on the effect of ADM on some functional properties of rat heart, liver and tumor mitochondria. The results obtained show that ADM inhibits electron flow through all three energy-conserving sites of respiratory chain in all mitochondria tested, without any significant difference. Moreover, ADM modifies the redox state of respiratory carriers with a pattern which is consistent with modifications of the physical state of the inner mitochondrial membrane lipid layer. This observation is further confirmed by the fact that the effect of ADM is counteracted by those agents, such as tocopherol and mitoxantrone, which inhibit lipid peroxidation. The possible mechanisms of the protective effect are also discussed.

Work supported by A.I.R.C.

2582 ECG CHANGES INDUCED BY ADRIAMYCIN TREATMENT IN RATS: THE IMPORTANCE OF THE SaT SEGMENT. D. Tocchi M., Del Tocchi M. and Soldani C. Institute of Pharmacology, University of Pisa School of Medicine, Pisa, Italy.

The rat ECG has proved to be a suitable tool in the characterization of the toxic cardiac effects of anthracyclines; however, disagreeing opinions are reported in literature about the most reliable ECG parameter for the detection of cardiotoxicity. Among the present study was the reevaluation of the SaT segment in order to test its sensitivity. The results obtained are compared with those previously proposed for the detection of the cardiotoxicity of adriamycin (ADR) and related drugs. Sprague-Dawley female rats were treated with ADR 3 mg/kg i.v. weekly for 3 weeks; periodic recording of ECG was performed and ECG data were analyzed by means of online biosignal processing. Results indicated that during the study no changes occurred in the PR and RR intervals or in the PQ, QT, or R- and S-wave amplitudes, whereas significant changes were observed consisting of a widening both of the QRS complex and of PR and QT intervals and a flattening of the SaT wave. The earliest and most consistent ECG alteration observed, however, was a progressive, irreversible widening of the SaT segment which was detected in all the tracings at all the times examined. This effect became significant at the end of the last week of treatment and continued to increase throughout the experiment. These results indicate that among the alterations induced by ADR in the rat ECG, the measurement of the SaT segment provides the most sensitive and reliable method for the evaluation of ECG signs of cardiotoxicity induced by ADR and related drugs in the rat experimental model.

(Supported by grants from National Research Council (CNR), Rome; Target Projects "Oncology" and "Preventive Medicine and Rehabilitation").

2583 INVESTIGATION ON CARDIOTOXICITY INDUCED BY ADRIAMYCIN (ADR) IN RATS. Del Tocchi M., Danesi R., and Soldani C. Institute of Pharmacology, University of Pisa School of Medicine, Pisa, Italy.

There is increasing interest in the role of adriamycin (ADR) in the induction of the cardiotoxicity of anthracyclines, since it has been demonstrated that: 1) ADR induces cardiac levels markedly increase in time during the administration of ADR; 2) ADR induces the generation of cytotoxic peroxides (De 1 Tacca et al., Pharm. Acta Toxicol., 17, 381, 1985). The present study investigates the effects of repeated administration of synthetic ADR in rats. Sprague-Dawley female rats were treated with ADR or ADR 3 mg/kg i.v. weekly for 3 weeks and periodic ECG recordings were performed. At the end of the study (6th week) the animals were sacrificed; plasma and heart samples were collected to measure the amount of ADR and ADR metabolites by HPLC and to analyse the cardiac tissue histologically. Results indicated that ECG parameters (QRS, SaT and SaT duration, wave amplitude) and the histological cardiac picture were significantly affected by ADR and to a lesser extent by ADR metabolites. In cardiac tissue from ADR-treated rats, high levels of both ADR and ADR metabolites were found, whereas in hearts from rats treated with synthetic ADR only low levels of the metabolite were detected without any trace of ADR. From these results it may be concluded that: 1) the low cardiac levels of ADR following treatment with the synthetic C14-ADR derivative may depend on the polarity of the metabolite which scarcely enters the cell; 2) the cardioxic effect of ADR-ol may depend on its interaction with the mitochondria.

(Supported by grants from National Research Council (CNR), Rome; Target Projects "Oncology" and "Preventive Medicine and Rehabilitation").
The hematotoxicity of oxoplatin and other platinum analogs was investigated in mice and rats. The compounds were administered i.p. and the effects on hematopoiesis were monitored. The results showed that oxoplatin caused a decrease in white blood cell count, platelet count, and hemoglobin levels. The toxic effects were more pronounced in rats than in mice. The study also revealed that the toxic effects of oxoplatin were dose-dependent and that the magnitude of the effect was correlated with the dosage administered. The study concluded that oxoplatin had significant hematotoxic properties and could be a potential drug for future medical applications.}

**Keywords:** Oxoplatin, hematotoxicity, platinum analogs, mice, rats.

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**Reference:**


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**Study Design:**

A new in vitro method and apparatus (MUTACALC) was developed to measure the mutagenicity and toxicity of chemicals by the aid of a 17 phage- E. coli B system. In the MUTACALC a whole phase development cycle takes place and the characteristic parameters: the latency period, the multiplicity of the infection can be determined. There is a correlation between the magnitude of the effect and the changes in the parameter values. The mutagenicity of chemicals is characterized by the mutagenicity index and it can be determined from the phage inactivation kinetics. Up to now we have investigated about 100 chemicals among them some standard alkylating agents and cytostatic drugs, mainly dihydro- and dihydrocarboplatin derivatives. On the bases of the mutagenicity indexes the following series was found in increasing mutagenicity: DIB (dibromomannitol) > <DHDA> (dihydroxylated) > <BCNU> (biscycloethylenemethylenemine) > <MM15> (methyl methacrylate). Compared with the standard alkylating agents mainly the dibromo derivatives proved to be weak mutagens in our system. In addition the toxic effect of the chemicals was measured by the influence on the hard bacteria or on the phage—bacteria complex. Among the sugar alcohol derivatives only the water soluble DAB and DAB inhibited weak toxicity. The results are compared with the results of other screening tests.
2588 EFFECT OF REPEATED DOSES OF DISOXANIL-DIAMINOHYDROCHLORITOL ON MYOCARDIAL BIOPHOSPHATASE ACTIVITY IN RATS WITH EXPERIMENTAL HEPATITIS CaH S. Knaps & J. C. Green, Dept. of Pharmacology, University of Western Ontario, London, Ont., Canada N6A 5C1.

Our results indicate that chronic administration of disoxanil-diaminohydrchloritol, a new antitumoral agent with a favourable therapeutic ratio in some animal tumors (Donna, et al., J. Nat. Cancer Inst. 48: 301, 1972), results in a decrease in myocardial biophosphatase activity. The mechanism of this effect is currently under investigation.


In an attempt to determine the mechanism of the anticirrhotic and cytotoxic action of choline lactate, two series of experiments were carried out. In the first, rats were intoxicated with cyclophosphamide and treated with choline lactate before and after the injection of the drug. The results indicated that choline lactate inhibited the development of the disease and accelerated the rate of regeneration. In the second series of experiments, the effects of choline lactate on the distribution of degenerative muscular lesions in rats were studied. The results showed that choline lactate inhibited the development of muscular lesions and accelerated the rate of regeneration.
PREVENTION OF OVARIAN DAMAGE INDUCED BY CYCLOPHOSPHAMIDE (CPA) IN ADULT FEMALE MICE BY CYCLOSPORINE A: COMPARATIVE STUDIES WITH MIPF AND MIFE

Conclusions

1. Evidence from a small number of patients with cancer who received CPA treatment suggests that CPA might be a useful therapeutic agent for the prevention of ovarian damage.

2. The long-term effects of CPA on the ovaries in female patients are unknown. Further studies are needed to determine the safety and efficacy of CPA in the prevention of ovarian damage.

3. The potential for CPA to prevent ovarian damage should be considered when selecting patients for CPA treatment.

4. CPA may have the potential to prevent ovarian damage and improve the outcomes for patients with cancer who require CPA therapy.

References


Twenty fresh human non-small cell lung cancers and nine ovarian cancers were transplanted under the subcutaneous capsule of immunocompetent mice. Grafted lung cancers were treated by combinations of cis-Pt + V710 and CBDA + V710 and ovarian cancers by cis-Pt + Melphan or CBDA + Melphan. Chemotherapy was administered on days 2 and 3 after implantation. Macroscopic responses were taken via an ocular microscope (of the 19 tumours, 11 could be macroscopically evaluated - according to macroscopic criteria of \( |S| > 0.5 \text{ cm} \) while all 9 ovarian tumours were evaluable). It appeared that 18% of lung xenografts responded to cis-Pt alone, 63% to cis-Pt + V710, while 44% of ovarian xenografts responded to cis-Pt alone vs 5% to cis-Pt + Melphan or CBDA + Melphan. However, macroscopic values did not correlate with the microscopic evaluation. An histological study of the xenografts detected tumour tissue in only 4 of the 11 lung control groups - while inflammation or fibrosis was observed in all cases - and in 4 of the 9 ovary control groups on day 6 post-implantation (day of evaluation). A histological study of xenograft fragments placed in those control groups and treated groups was conducted in both control and treated groups. Only 19 of 197 fragments contained tumour cells; 100 of the 143 human specimens (22) and 15 of the 55 ovarian specimens (45). Our results suggest that an immunocompetent control of the biopsy should be conducted before transplantation to ensure the presence of tumour tissue in the xenografts.

(Supported by a grant by Loterie Nationale, Belgium.)


Human tumor xenograft lines have been developed from squamous cell carcinoma of the tongue HT 77 and its cervical lymph node metastasis HT 78. The xenografted tumors preserved their morphology after several passages in nude mice. Tumor biologically sensitive to both were compared after subcutaneous (SC) and transoral (SRC) transplantation. For SC assay, xenograft fragments of about 3 mm of diameters were implanted and their growth was estimated by serial caliper measurements. Tumor growth inhibition was assessed on day 21 after treatment comparing tumor sizes of control and treated groups. Drugs were given - in most cases - in maximally tolerated single dose i.p. for SC assay, tumor pieces of 1 mm were placed under the renal capsule of immunocompetent (IC) and immunosuppressed (IS) mice. The tumor growth inhibition was calculated from the change in the mean diameter from day 0 to day 6. Treatment was performed at day 1. Applying 6 clinically active agents the sensitivity of the two lines was similar. The SC and SRC assay (using either IC or IS mice as recipients for SRC) again showed similar ranking of the drugs, in the tumor, that in each instances 2 of 3 i.e. Cyclophosphamide, 5-fluorouracil, Vinblastin) most active agents were identical. Our experiments support the view that SRC assay is able to select those compounds which would have the greatest chance to act against the patients tumors. Using IC mice, it is necessary to check the morphology of the tumors at the day of drug evaluation.


A new transplantable tumor strain in human cancer nodal tumors origin (TAVS) was created. The tumor has been maintained since 2002 by serial subcutaneous transplantation. TAVS showed established biological and morphological characteristics between 1/2 and 250 transplant genera- tion. The new well established subcutaneous, intramuscular or intracerebral transplantation. The subcutaneous TAVS showed a differential sensitivity against some cytostatic drugs and anti-estrogens - cyclophosphamide, sarcoylin, ethotrexate and 5-fluorouracil but against some clinically approved and some new synthesized nitroreducing agents against cyclophosphamide, ethotrexate and 5-fluorouracil but against some clinically approved and some new synthesized nitroreducing agents against cyclophosphamide, ethotrexate and 5-fluorouracil. Cyclophosphamide plus 5-FU gave better enhancement of antitumour effect of the cyclophosphamide plus levamisole. The results indicated that TAVS in the three forms may be an useful experimental model for oncological and pharmacological research.


We performed the six-day subcutaneous capsule assay (SRCA) for the estimation of antitumour effect of various human tumor xenografts in BALB/c mice for 80 advanced cancer bearing patients. Among 97 SRCA, 9 were not evaluable because patients either received no chemotherapy or non tested drugs. 8 were non interpretable because of control implants lack of growth. 100 correlations were established between test results and clinical response. 64 retrospective (chemotherapy then test) and 56 prospective (test then chemotherapy). Among the 64 retrospective correlations there are 35 true negative (-/-) and 29 false positive (+/-) corresponding to 48 poor clinical responders and 0 true positive (+/+). Among the 56 prospective correlations there are 15 true negative (-/-) and 5 false positive (+/-) corresponding to 20 poor clinical responders and 17 true positive (+/+). Further analysis of the various SRCA before a surgical procedure may provide results relevant to cancer site and reflecting previous treatment status.
CHEMOSENSITIVITY OF THE SOLID P388 TUMOR OF BDF, 1 MICE. J. Bence, S. Somfai-Relle, National Institute of Oncology, Budapest, Hungary

P388 mouse tumor is a widely used model in screening for potentially active new anticancer agents. In primary screening inoculum site is intraperitoneal, the drug is administered as ip. daily for 9 days and criterion of evaluation is median survival time, which is prolonged by treatment of nearly all clinically useful cytostatic agent. To obtain more relevant model composed of the same cell type but bearing closer similarities to human tumor situation, P388 cells were inoculated subcutaneously and the drug sensitivity of the solidly growing P388 system was compared to that of the ascites model. Cyclophosphamide, nitrosourea derivatives, CDDP and di-nitrohydrogalactitol were active on both tumor forms. Adriamycin, actinomycin D and vincristine treatment resulted in long time survival of the ip. inoculated tumor bearing mice, while caused but marginal effect in the solid model. C-mercaptopurin and dibromodulcitol were inactive in either models. In addition to preclinical screening of new drugs the solid P388 has been successfully used for testing drug combinations. Components of different combinations could be separated by giving one test-substance orally and the other intraperitoneally.
**2604 GROWTH PROPERTIES AND CHEMOSENSITIVITY OF SOLID MURINE TUMORS IN CONVENTIONAL AND IN NUDE MICE. G. Pratesi and G. Perossi, Istituto Nazionale Tumori, 20139 Milano, Italy.

In order to investigate whether tumor biological features are maintained when growing in athymic mice, the same murine tumors, B16-F1 lung carcinoma and M567/B3A (HS) rat mammary carcinoma, have been implanted in syngeneic conventional mice or in allogeneic Swiss nude mice. After tumor implantation in the left flank of the two recipient hosts, B16-F1 growth properties like tumor appearance, doubling time and growth curves, and mice survival time were maintained. Growth characteristics were similar even after fragment transplantation in both flanks of nude recipient mice, whereas syngeneic BALB/c mice injected on either sides showed a comparable tumor growth but a definitely lower (p < 0.01; Student’s t-test) mice survival time, probably due to greater tumor metastasizing capacity in the natural host as compared to the nude mouse. Tumor growth patterns and mice survival time were comparable also after s.c. injection in the left flank of C3H/B6 syngeneic mice or in both flanks of athymic Swiss mice of syngeneic tumor cells. To compare tumor chemosensitivity in the two hosts, B16-F1-bearing mice (C3H/B6 in 1 flank; and Swiss nude in both flanks) were treated when the tumors were palpable (< 100 mm), usually i.v., according to a weekly schedule. Representative of the major chemical and functional classes of clinically useful anticancer drugs were tested. cis-Diamminedichloroplatinum II was the most active drug in both systems, inducing tumor growth inhibition > 80% at three tolerated dose levels. Therefore, the response observed in the nude mice seems to reflect tumor chemosensitivity in its natural host.

Partially supported by a Research Grant from Consiglio Nazionale delle Ricerche of Rome (Italy).

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Intensively investigated spores of the anaerobic, ato- generic bacterium clostridium oncolyticum M55 (Mose 1955) cause cell destruction in vitro in the incipient stage of many animal and human malignant solid tumors. The basic events of this "tumorspecific" phenomenon are unknown. We developed on in vitro model to test the direct effect of clostridium on tumor cells in tissue culture. Indicator cells were two human squamous cell carcinoma lines of laryngeal carcinomas, established by M. Vetterlein, in whose heterotransplants in athymic nude mice oncolysis was demonstrated previously. After adding clostridial spores, tissue cultures were perfused with a mixture of different percentages of 0%, 5%, and 10% up to 7 days. 18 O 2 in the atmosphere was found to be enough for control cells to survive, whereas clostridial spores were unable to inoculate and proliferate and reach an extreme mortality leading to necrosis of the tumor cells (dehydrogenase, proteinase, and cytolysis). p.o., p.o., and p.o., in the culture media (BMHE) were added with 3.3 or 4.1 UF 97 were measured. Media containing clostridial had a lower pH (13.2-20 mHg) than controls without clostridia (pH 30 mHg), both held in the same atmosphere of 18 % O2. Our experiments demonstrated that the oncolysis by clostridium M55 effects directly tumor cells without mediation by other cells. Clostridia do not enter tumor cells and are not lost to release surfaces. Thus, oncolysis is most probably caused by substances, produced by the mobile clostridia. At the moment we are analyzing the post-tumoric and are testing clostridia and range of different equipment and non-malignant cell lines.

Supported by BMHB Contract HFI-CH-57719.

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**2605 PRELIMINARY RESULTS WITH AN IN VITRO SCREENING MODEL FOR SELECTIVE DETECTION OF DRUGS ACTIVE AGAINST SOLID TUMORS. Ladislav J. Hanka, Shirley A. Gerpheide, Res. Lab., The Upjohn Company, Kalamazoo, Michigan, USA and Thomas H. Corbett, Wayne State Univ., Sch. of Med., Detroit, Michigan, USA.

While there is available a reasonable number of clinically useful antineoplastic drugs there is a need for new and better drugs for chemotherapy of most solid tumors. In 1984, Dr. T. Corbett et al. described a new in vitro prescreen that could selectively detect compounds active in vitro against several solid tumors while inactive against leukemia. It is based on differential effect of the drug against cells of one leukemia and one solid tumor cultivated together in a semisolid agar. In a cooperative project with Dr. Corbett’s laboratory we have tested this system during the past 2 years. Over 2,600 of the fermentation broths were evaluated. Less than one percent of these demonstrated selective in vitro activity against one or more solid tumors, while inactive against L1210 leukemia. Thus, while such materials are found rather infrequently it appears that the approach is indeed feasible. Specific examples of materials detected by this screening system will be presented.

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Intensively investigated spores of the anaerobic, ato- generic bacterium clostridium oncolyticum M55 (Mose 1955) cause cell destruction in vitro in the incipient stage of many animal and human malignant solid tumors. The basic events of this "tumorspecific" phenomenon are unknown. We developed on in vitro model to test the direct effect of clostridium on tumor cells in tissue culture. Indicator cells were two human squamous cell carcinoma lines of laryngeal carcinomas, established by M. Vetterlein, in whose heterotransplants in athymic nude mice oncolysis was demonstrated previously. After adding clostridial spores, tissue cultures were perfused with a mixture of different percentages of 0%, 5%, and 10% up to 7 days. 18 O 2 in the atmosphere was found to be enough for control cells to survive, whereas clostridial spores were unable to inoculate and proliferate and reach an extreme mortality leading to necrosis of the tumor cells (dehydrogenase, proteinase, and cytolysis). p.o., p.o., and p.o., in the culture media (BMHE) were added with 3.3 or 4.1 UF 97 were measured. Media containing clostridial had a lower pH (13.2-20 mHg) than controls without clostridia (pH 30 mHg), both held in the same atmosphere of 18 % O2. Our experiments demonstrated that the oncolysis by clostridium M55 effects directly tumor cells without mediation by other cells. Clostridia do not enter tumor cells and are not lost to release surfaces. Thus, oncolysis is most probably caused by substances, produced by the mobile clostridia. At the moment we are analyzing the post-tumoric and are testing clostridia and range of different equipment and non-malignant cell lines.

Supported by BMHB Contract HFI-CH-57719.
CHARACTERIZATION OF A MURINE SARCOMA WITH LOW SENSITIVITY TO DOXORUBICIN. F. Zacchini, C. Bertero, G. Gatta, and F. C. Giudici, Farmatit-A Carlo Erba Res. Ctr., Milvano, MI, Italy.

A murine independent carcino sarcoma (H2A-Sa) was derived during serial transplantations of a hormone dependent mammary tumor line (H2A-CSA). The tumor was histologically characterized as a sarcoma, probably derived from hormone independent stroma cell types. Inoculation of 10^6 cells/mouse in 0.01 ml B6F1 tumors caused 100% tumor take. The average time for tumor appearance was 6-7 days and the median survival time was 36 days (21-62). Lung metastases were detected at autopsy and by biopsy. Doxorubicin (224, tested i.v., once a week for three weeks, was not effective on advanced tumors. Tumor growth inhibition was 0-1 at 6 mg/kg and 1-3 if at 9 mg/kg with no significant increase of life span. When DX was administered i.v., twice a week for three weeks, its toxicity increased. Tumor growth inhibition was 16-29 at 3 mg/kg and 43-46 at 4.5 mg/kg but no effect on life span was observed at either dose. The H2A-Sa was established in vitro as a monolayer cell line. The activity of DX was evaluated after 48 hrs of drug exposure. The H2A-Sa cell line also showed low sensitivity to DX. Dox was 1.5-3.3 times greater than DX. The H2A-Sa was characterized in vivo with respect to its sensitivity to different chemotherapeutic agents; the tumor was sensitive to 5-fluorouracil while cyclophosphamide and melphalan were only moderately active against H2A-Sa.

This experimental tumor provides a useful model for in vitro and in vivo investigation of new drugs effective on Doxorubicin resistant tumors.


We examined systematically the use of embryonated chick to evaluate the drug sensitivity for primary and metastatic cancers. Mouse B16 melanoma cells were used as a model experiment, and usual anticancer drugs such as adriamycin (ADM), cisplatin (CDDP), cyclophosphamide (CPM), and nitrosourea hydrochloride (ACNU) were tested. As a chemosensitivity test for primary cancer, B16-F10 melanoma cells (2x10^6) were injected into the chorioallantoic membrane (CAM) of 11日-old chick embryo. The drugs were injected to vein on CAM 3 days after tumor inoculation. Four days after the tumor was cut on CAM was dissected out and weighed. ACNU, ADR, CDDP, CY, and SFU inhibited the growth of the tumor on CAM; their inhibition ratios were 81, 80, 77, 92, and 81%, respectively.

In the chemosensitivity test for experimental metastasis, B16-F10 melanoma cells (10^6) were injected into CAM vein of 11-day-old chick embryo. The drugs were injected to vein on CAM 3 days after tumor injection. Embryos were sacrificed 7 days after tumor inoculation and the brain, lungs, and liver were dissected. Visible tumor nodules on the surface of each organ were counted. The results showed slightly different sensitivity for the metastases of the organs tested. Only ACNU was effective for brain metastases. All drugs tested were strongly inhibited the lung metastasis and inhibition ratio (IR) was more than 72 at the same dose as that of the primary tumor. ACNU, ADR, CDDP, and CY showed a strongly anti-metastatic effect on liver. CY was the most effective drug for liver metastasis and inhibited the metastasis at a dose of 100 g/kg. The metastases of the other organ were relatively low (34.0% at this dose). There is no experimentally useful model of chemosensitivity for human-tumor metastasis. Our current assay system used embryonated chick is attractive model for the quantitative study of the chemosensitivity for primary and metastasis, and also for development of new anticancer drugs including a so-called masked compound, because its reproducibility, rapidity, sensitivity, convenience and low cost.
2613 APPLICATION OF A NEW IN VITRO DROG SCREENING SYSTEM FOR DETECTION OF PLEOTROPIC DRUG RESISTANT TUMOR CELL POPULATIONS. A. Monks, M.C. Alley, D.A. Scudiero, R.H. Shoemaker and D.P. Boyd. National Cancer Institute-Frederick Cancer Research Facility, Frederick, MD 21701, USA.

For the purpose of large scale screening of potential anticancer agents in a panel of cultured human tumor cell strains, we have studied an automated cell growth inhibition assay which requires enzymatic reduction of a tetrazolium salt to formazan by living cells [T. Mosmann, J. Immunol. Meth., 65: 55, 1983]. We have modified the method by substitution of 100% DMSO for solubilization of formazan, thus improving the stability and magnitude of the optical density readings. To evaluate the sensitivity of this assay to the presence of a small population of drug resistant or sensitive cells within a heterogeneous cell strain, we have examined mixtures of a resistant, drug resistant cell strain with the parent strain. When MCF-7 human breast carcinoma cells, were mixed with 25 to 100% of an adriamycin (Adr) resistant strain, there was a significant difference (p < 0.05) in growth inhibition data generated in response to treatment with Adr for 6 days. Using pleiotropic drug resistant P388 (P388R) and sensitive (P388S) murine leukemia cells which have more comparable growth kinetics than MCF-7, we can distinguish the survival profile (p < 0.05) of a mixture containing 10% P388R cells following a 4 day exposure to Adr. Furthermore, resistance to mitoxantrone (MTX) and vincristine (VCR) was transferred to P388 cells by co-cultivation with P388R cells. These results suggest that this screening system by testing a series of new compounds in colorectal cancer. Basically, this system consists of 3 human colorectal cancer cell lines (COLO 205, COLO 320C, and HT-29) that have been shown to manifest in vitro responsiveness consistent with the sensitivity of this assay to the presence of small populations of drug resistant cells and appears well suited for large scale screening of potential cytotoxic agents. (Research sponsored by NC1, DCR, DTP under Contract No. NO-01-23910 with P41.)

2614 HUMAN TUMOURS STEM CELLS CLOMOGENIC ASSAY AND IN VITRO RADIOSENSITIVITY TESTING. S. Caminii, S. Lucchi, A. La Pers, G. Plessert-Porta, C. Biagioni, Istituto Tecnologie Biomediche CNR, Roma, Italy, and Istituto Radiologia, Universita Roma, Italy.

The human tumours stem cells assay is an in vitro culture system performed in a semisolid media. Since this technique was described (Hamburger, Salmon Science, 1971:461-467) there has been a marked increase in the use of such assay for in vitro chemoresistance and radiosensitivity testing. Despite the extensive literature, many questions remain about the biological significance, technical performance and clinical utility of such assay. Tumoral samples were processed: (1) cervix, (2) uterus, (3) lung, (4) head and neck. Results and mutant effec-
sions (5). Our studies have been directed toward the identification of es- thodological improvements in order to increase cloning efficiency. These include: (1) optimal conditions for biopsy, (2) cloning in semisolid media, (3) clonal analysis in vitro and clinical re-
psonse of patients observed in the clinical trials. Our results are encourag-
ging, ongoing developmental research is needed to improve patient's therapy. Supported by grants from Special Project Oncology.
THE EFFECTS OF N-METHYLFORMAMIDE ON ARTIFICIAL AND SPONTANEOUS METASTASES FROM A MURINE HEPATOBLASTOMA. Philip D. Talalay, Charlotte M. Vines, and Luka Milas, M. D. Anderson Hospital and Tumor Institute, Houston, Texas, USA, 77030.

The effects of the differentiation-inducing polar solvent N-methylformamide (NMF) on artificially induced and spontaneous metastases from a murine hepatoblastoma (HFB-1) in C3H/HeN mice were investigated. Exposure of HFB-1 cells in vitro for 6 days to 10% or 12.5% NMF resulted in an increase in the number of lung nodules formed in mice where these cells were injected into their tail veins. This in vitro NMF exposure increased cell volume and induced only a slight amount of cytotoxicity. Administration of NMF to mice 1 day before i.v. tumor cell inoculation resulted in a dose-dependent increase in the number of lung nodules formed, beginning at an NMF dose of 400 mg/kg. NMF caused a similar magnitude of metastasis enhancement in immuno-suppressed mice. However, when the maximum dose tested (1,800 mg/kg) was administrated as six daily fractions of 300 mg/kg each, no increase in artificial metastases was detected. Administration of NMF to mice one day after i.v. tumor cell injection resulted in a dose-independent decrease in the number of lung nodules. In mice bearing 5-6 mm HFB-1 leg tumors, treatment with six daily fractions of NMF (180 mg/kg each) significantly reduced the number of spontaneous pulmonary metastases, yet had very little effect on the growth of the primary tumor. These data suggest that, in a clinically relevant treatment setting, NMF can reduce metastasis formation.

Supported by the National Institute of Health (NIH) research grant CA-62924.

NEW MODELS FOR STUDYING TISSUE SPECIFICITY AND CHEMOSENSITIVITY OF TUMOR CELLS. TWO HUMAN MELANOMAS METASTASIZING IN NUDE MICE.

O. Fodstad,*, S. Aamdal,*, R. H. Shoemaker**, and A. Fidler*. Inst. for Cancer Res., The Norwegian Radium Hospital, Montebello 2, 0210 Oslo 2, Norway* and DTP, Nat. Cancer Inst., NIH, Bethesda, MD 20205, USA**.

Two melanoma tumor lines which give rise to metastasis in adult Balb/c nude mice have been developed. The two lines differ significantly with respect to growing lung colonies after iv injection of 104 cells, leading to death of the animals in an approximately growing 10% daily. Results in the formation of spontaneous lung metastases. Another subgroup of LOX gives, after iv injection, eccentric tumors which kill the animals in a dose dependent manner, permitting chemosensitivity studies using survival as end point. In contrast, the melanoma line FMEX, never gives lung colonies, even though the same fraction of labelled tumor cells is initially retained in the lungs. However, these cells consistently produce metastasis in lymph nodes. These first appear in the neck region and become macroscopic visible after 45-50 days. The two tumor lines were compared with respect to growth rates in vivo and in vitro, karyotype, and expression of membrane antigens. Attempts are made to prepare monoclonal antibodies distinguishing between the two melanomas. Attempts to select sublines with increased metastatic potential were made by serial iv injection of cells from FMEX metastases. In contrast to current views these time increased and the iv and jr survival growth rates decreased with increasing number of passages.

STEREO RECEPTORS IN INTRACRANIAL TUMORS.

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The appreciation of functional steroid receptors in breast cancer is in progress nowadays. For the demonstration of estrogen receptors in the summary tumoral tissue the biochemical and immunohistochemical methods, like the biochemical ones, make use of the properties of receptor binding. Some methods exist now which determine the molecule of Tamoxifen - a nonsteroid antiestrogen - within the cell, using its fluorescent properties. Tamoxifen, 20 mg/day, was administered before operation, for 8 days, in women with operable breast carcinoma, at premenopause or menopause. Intraoperatively tumor samples were taken and smears were prepared and stained using Papnicolaou hyperchromatic method. The cells were examined alternatively at ordinary light and after UV excitation (excitation filter 450–490 nm, emission filter 515 nm). The negative cells were dark green, showing no fluorescent spots. The positive cells showed yellow fluorescent granules in the cytoplasm sometimes associated with fluorescent nuclei. The smears were considered positive if more than 25% of the cells presented intracytoplasmic fluorescent granules. The authors discuss the use of Tamoxifen fluorescence for the appreciation of functional receptors of estrogen. This is a useful method for cytohistological differentiations and for the detection of the presence of progesterone receptors.

2621 Estradiol and progesterone receptors in 30 cases of soft tissue sarcomas.

FLUGUER Y, KOH WAGGON, H.C. ULRIK, H.C. , DELPY J, HAINT J. Department de l'Anatomie L.M. Hors Donnier, University of Liège, Belgium.

The concentration of estradiol E1 and progesterone P1 receptors was determined in a series of 30 soft tissue sarcomas, S.T.S., and in a series of breast tumors, B.T.C., since of different histological origin mostly, fibrosarcomas F.S., L.F. and P.F. contents are estimated by active charcoal classical method. The results are summarized in next table:

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No correlation was observed with age, sex, size of tumor, histologic type or degree of differentiation. In addition, 6 EP cases received antigestrogen therapy, by tamoxifen after chemotherapy failure, but no response was observed.

2622 Retrospective evaluation of ER and PR in 694 primary breast tumors, C. De Frangis, B. Corradini, V. Cuppilletti, C. Marini, G. Chiarini, Istituto Oncologico per i Studio Fisiologici dei Tumori, Via Venezia 1, 19100 Milan, Italy.

We report the results of a study aimed to explain the upward shift of estrogen (ER) and progesterone (PR) receptor percentages in human breast tumors observed during the last 10 years. Data on tumors were collected from 1974 through 1984, and within each year cumulative frequency graphs and frequency histograms were computed. In the case of ER there was a progressive increase in the yearly positivity percentage calculated using 10 fmol of protein as cutoff. A significantly higher frequency of ER cases was observed for the subgroup ranging from 1981 to 1984 in comparison to that from 1974 to 1980. A 10% to 15% positivity rate was observed in the 10% to 20% class, which was statistically significant. Similarly, PR values were measured on 167 cases from 1977 to 1984 using two different thresholds for positivity rate determination. 10% of cases have positive PR, and 20% of cases have the positivity rate increased in comparison to the previous years. The positivity rate increased from 1977 to 1980 in the ER and PR groups. The distribution of ER values did not vary over the considered period.


The relationship of biological behavior to estrogen receptor (ER) and progesterone receptor (PR) status of primary breast cancer has been studied in 421 and 303 patients respectively. In this series the ER-positive rate is 53.6%, the PR-positive rate is 38.5%, and the PR-positive rate in ER-positive patients is 30.4%. These rates are lower than those reported in Western countries. All patients were followed up and several factors which influence the prognosis of breast cancer have been elicited. ER and PR status are correlated with tumor grade, lymph node metastasis, size of tumor, stage of disease, disease free interval and survival. Furthermore, the ER status, especially the PR status, can be used to select good or bad progesterone groups. PR-positive patients have a good prognosis, all patients in this group being surviving without recurrence or metastasis. The prognosis of ER-negative patients is better than that of ER-positive patients, and ER-negative tumors tend to have local recurrence while ER-negative tumors tend to have bone or visceral metastasis. The status of ER and PR are helpful in planning the treatment of breast cancer.
2624 SIGNIFICANCE OF HORMONE RECEPTORS IN BREAST CANCER MANAGEMENT - KUWAIT EXPERIENCE. DR. HASSAN R. IBRAHIM, MD, PhD, SENIOR SURGICAL ONCOLOGIST. KUWAIT CANCER CONTROL CENTER, KUWAIT
Since the establishment of the Kuwait Cancer Laboratory in 1993 in Kuwait Cancer Center 105 breast cancer patients (50 tissue samples) were investigated for the presence of estrogen (E) and progesterone (P) receptors. The overall aim of the study was practical application of receptor presence in prognosis evaluation and determination of the most suitable treatment protocol, as well as an evaluation of tumor hormone sensitivity relationship with stage, histological grade, its multifocality and patients' therapeutic response.

Near 75% of Kuwait women with breast cancer were E(-) and P(-) definitely positive. Some data are basically parallel to those reported in non-Arab breast cancer population. The frequency and levels of progesterone (cytoplasmic) receptors down to the positive in 35% of patients. However, definitely strong positivity was evidenced in only 19%. Both receptors jointly have been in one half of analyzed breast cancers (47/98) but only 7% of women had both receptors at all.

The largest group of patients (42/98) down to have only one receptor (for nuclear estrogen). No hormone differences have been seen in receptor expression in breast cancer tissue.

If main women's positive for (E or P), addition were also positive; however, qualitatively different being in these women with higher than main main. Metastatic spread down to display considerably low of qualitative measured levels of any hormone receptor being even negative. No significant correlation was noted between tumor size, its anatomic location and receptor status however, such higher levels of P(+) was noted to above 100% dense. No direct correlation was observed between receptor and histological appearance of tumors. Nevertheless, significant parallelism was seen between estrogen positivity and histologically proven elements.

Near 15% of patients with E(+) and P(-) did not respond to hormonal treatment and that figure was lower in E(-) and P(-) cases. The overall response to hormonal manipulation was in E(-) P(-) cases was evidenced to be 25%. Local recurrences were decreased to be such lower in E(+) patients (12%) than those being E(-) (over 25%).

Last group showed no better to chemotherapy f(-) status than positive to predict receptor manipulation of response to hormonal therapy.

Purpose We have so far conducted comparative studies between the Dextran coated charcoal (DCC) technique using breast cancer tissues and the fluorohistocemical (FHC) technique, as means of breast cancer estrogen receptor determination especially in Japan. We have also studied cancer cells obtained by the aspiration biopsy cytology (ABC). For presence or absence of ER, the ABC cytology was prepared a sample on a slide-glass by A.B.C.FITC conjugated estradiol (17-ß-600mg-BSA-FITC) was made to react on it. The breast cancer tissue that had been removed before or during operation and preserved by freezing below -70°C was sliced in 4 um by Cryostat and evaluated in the same manner by the tissue-FITC technique. In the FITC technique, we evaluated the tissues containing more than 10% of positive cells as positive. Results The positive rate by the FITC technique was 53.3% (24/45) for A.B.C. and 62.2% (28/45) for the tissue. The positive rate by the DCC technique was 57.8% (26/45). The coincidence rate between the DCC and tissue-FITC techniques was 82.2% (37/45), while that between the DCC and A.B.C.-FITC techniques, 77.8% (35/45) than the former. Six of 10 disagreement cases were DCC(+) and A.B.C.-FITC(-) including one misdiagnosis case in A.B.C. Conclusions The FITC technique using the A.B.C. sample is simple and available for evaluation in a short time and showed a good result of coincidence rate at 77.8%. We consider that it will be an effective means to confirm the presence of ER in small tumor breast cancer which is difficult to be detected by the DCC technique and to find the change with time of ER by the endocrine therapy of metastatic lesions.

2626 ESTRADIOL AND PROGESTERONE RECEPTORS IN BREAST CANCER.
EVALUATION DURING PRIMARY CYTOXIC CHEMOTHERAPY. M. KUVE, T. POUILLART, T. DORVAL, E. GARCIA-GIRALT, P. POUILART, INSTITUT CURIE, PARIS, FRANCE
29 patients (7 pre and 22 post-menopause) with histologically proven stage III or rapidly progressive stage II breast cancer entered in this prospective study. They were given before loco-regional treatment, 3 courses (17 cases), 4 to 8 courses (12 cases) of a monthly regimen of cytotoxic chemotherapy including : Adriamycin 25mg/m2 on days 1 and 8, Cyclophosphamide : 400mg/m2 on days 1 and 8, 5 Fluoro-uracile 500mg/m2 on days 1, 3, 5, 8 and Prednisone : 20mg/kg for 10 days. Determination of hormone receptor (R.H.) status (estriol (ER) and Progesterone receptors (RP)) were performed once before chemotherapy and then before loco-regional treatment. The variation of hormonal receptor status is presented on this table.

AFTER 3 COURSES OF CHEMOTHERAPY
Increase 11
Steady state 7
Decrease 2
This results indicate that chemotherapy does not change the hormonal receptor status and that in hormonal dependent tumor there is rationelle for alternate cytotoxic and hormonal therapy.
Calcium plays a very important role in a specific function of epithelial breast cell metabolism. During periods of lactation, an enormous quantity of calcium passes through these cells. Protective systems against this massive cell influx for calcium-binding proteins are apparently produced as a result of the activity of 1,25-dihydroxycholecalciferol receptors (D3R). These receptors seem to be also a significant feature of tumor breast cells. We determined cytosolic D3R simultaneously with estradiol and progesterone receptors (ER and PR, resp.) in 61 samples of human breast carcinoma tissue with dextran-coated charcoal method evaluated by Scatchard analysis. About 70% of tumor tissue were D3R (+ 25 fmol/mg protein in cytosol). Absolute values varied from 10 to 91 fmol/mg protein. Frequency of ER+ and PR+ in this group was lower. There was only 1/5 of tumors with all 3 receptors positive. We correlated the presence of D3R with menstrual status, histological classification, tumor invasion, mammography, and concentration of α-lactalbumin in tumor tissue. The prognostic relevance of this examination will be evaluated after a 3 year follow up. The prognostic relevance will be evaluated after the follow up. The prognostic relevancy of this examination will be evaluated after a 3 year follow up. The prognostic relevancy of this examination will be evaluated after the follow up. The prognostic relevancy of this examination will be evaluated after the follow up. The prognostic relevancy of this examination will be evaluated after a 3 year follow up. The prognostic relevancy of this examination will be evaluated after the follow up. The prognostic relevancy of this examination will be evaluated after the follow up. The prognostic relevancy of this examination will be evaluated after the follow up. 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We studied the distribution of ER and Ki-67 in lightly fixed, frozen sections of breast tissues using crosslinking antibody methods with immunoperoxidase staining and monoclonal antibodies to the estrogen receptor (H222, H226) or Ki-67 proliferation antigen. Both of these antigens were found to be located exclusively in cell nuclei. In the normal mammary gland staining for ER was predominantly in terminal, intra- and extracellular ductules while the epithelial cells of segmental and subsegmental ducts were weakly stained or not stained. Terminal alveoli or tubular epithelial cells were rarely stained for ER and myoepithelial cells were uniformly unstained. In fibroadenomas the mesenchymal compartment was unstained for ER, while the epithelium ranged from weakly staining (atrophic lesions) to substantial staining (proliferating foci), consistent with the generally low quantitative ER assays for these tumors. With breast cancers we found a good correlation between the immunohistochemical staining for ER and quantitative ER assays. Cells of highly differentiated carcinomas, such as tubular or papillary, generally showed strong nuclear ER staining. Heterogeneous ER staining was most commonly found in medullary carcinomas. Peripharal, proliferating and newly developed marginal areas were found generally to show stronger staining than central atrophic or degenerated parenchyma. Around necrotic areas tumor cells were found to lack ER staining even though no apparent cytological alteration had occurred. There appears to be a good negative correlation between Ki-67 and ER in breast cancer. Tumors with high nuclear or histological grade, those associated with lymph node metastasis, or otherwise those showing more Ki-67 positive cells. These tumors are ER negative or ER poor. In the breast cancer strongly stained for ER there were fewer Ki-67 stained cells.

CORRELATION OF ESTRODIOL RECEPTOR (ER) LOCALIZATION AND CYTOMETRIC MEASUREMENT OF ER IN HUMAN BREAST TUMOR CELLS. K. Wernoust, B.A. Lane, J. Peit, V. Chrenko, Research Institute of Clinical and Experimental Oncology, Brno, Czechoslovakia

Determination of estrogen receptor (ER) and progesterone receptor (PR) in the tissue of breast tumors can be used as diagnostic factor, and also as a marker for prediction of hormonal responsiveness of mammary tumors.

Histochemical or cytometric methods for ER quantitation should be preferred to biochemical methods, as they consume substantially lower amount of material. The specificity of directly binding estradiol derivatives used for localization of high affinity ER is questionable.

In the group of primary breast cancer patients cytotoxic ER and FR were determined by dextran-coated charcoal (DCC) method. Comparison to histochemical visualization of ER with estradiol-carboxymethylxime-bovine serum albumin-fluorescein isothiocyanate. The same substrate was used for quantitative fluorometric measurement of ER in mammary tumor cells in cytologic imprints of the tumor tissue.

Correlation in positivity or negativity of ER simultaneously assessed by DCC and in histochemical method was observed in 50% of patients. Slightly higher was found between cytometric measurement and histochemical method. These correlations were not statistically significant correlating an intense nuclear fluorescence no, or reverse relation was found with respect to their nuclear ER content measured by DCC method.
2636 STEROID HORMONE RECEPTORS IN PATIENTS WITH ENDOMETRIAL CARCINOMA
Dept. of Gynecology and Obstetrics and Dept. of Pathophysiology, Univ. Zagreb Med. School, Yugoslavia

In period from 1980 to 1985 in 76 patients with endometrial carcinomas level of steroid hormone receptors has been correlated with age, stage of disease, maturity of tumor and depth of invasion in myometrium. The level of cytosolic estrogen (ER) and progestogen (PR) receptors was estimated by the method of Mac Quilhe and all. The values were expressed in fmol/mg of cytosol protein. The ER values under 20 and PR under 50 were considered very low, resp. negative. In 28%, patients ER and PR were negative, in 53%, positive both, in 15,6% ER positive and PR negative, while in 5,2% ER negative and PR positive.

Younger patients often have positive both receptors. Well differentiated tumor has positive receptors in 12 of 15 patients, moderate differentiated in two thirds and undifferentiated tumor in one third of patients.

Patients with advanced disease and with deeper invasion of tumor in myometrium have significantly more negative hormonal receptors.

2637 STEROID RECEPTORS IN ENDOMETRIAL CARCINOMA IN CLINICAL PRACTICE.
B. Lindahl, P. Ahn, M. Fern, H. Grundsell, A. Nuren, and C. Trope. Depts. of Obstetrics & Gynecology, Pathology, and Oncology, University Hospital, Lund, Sweden.

The 5-year survival rate of patients with well and moderately differentiated stage I-II endometrial carcinomas is around 90%, whereas that of the poorly differentiated ones is only about 30%. At present there is difficulty in selecting patients most likely to benefit from additional chemotherapy. This study measured the E2 and R receptor concentrations in endometrial carcinomas and correlated these with staging, histologic grading, degree of myometrial invasion and response. The concentrations of E2 and R receptors were assayed with isoelectric focusing and those of P by a multipoint dextran-coated charcoal technique. The study shows that more than 80% of the relapses in the poorly differentiated tumors belong to the low E2 receptor concentration group. Via a combination of low E2 receptor concentration and myometrial invasion more than one third of the thickness of the myometrium it is possible to select patients at risk of developing relapse. These patients constituted 60% of the women studied and more than 40% relapsed. Thus the determination of E2 receptor concentration in endometrial carcinomas might be useful for selecting patients likely to benefit from aggressive adjuvant chemotherapy.

2638 STEROID RECEPTORS AND HUMAN MIXED SALIVARY GLAND TUMOURS.
L. Vasa, T. Norvath, A. Silveyri, T. Szekely, Dept. of Pathology - Cytology and Dept. of Otolaryngology, Piro F. Hospital, Kerepestasza, Hungary

During a 5 years period we saw 170 cases of mixed salivary gland tumours. Analysing these tumours it seems that female sex influences the occurrence of the mixed tumours -as far as age and sex is concerned- show some parallelism. Using the histohormonal classification of the mixed salivary gland tumours turned out to have steroid receptor positive cells not only in the cytoplasm but also in the nuclei as well. Three patients of primary mixed salivary gland tumour developed a second primary breast cancer. Consequently, mixed salivary gland tumours seem to be strongly steroid hormone dependent in both sexes.

2639 PHARMACOLOGICAL EFFECTS INDUCED BY INTRAVENOUS ADMINISTRATION OF A SUSTAINED-RELEASE FORMULATION OF D-TRP-6-LH-RH IN PATIENTS WITH HORMONE-DEPENDENT PROSTATIC CARCINOMA.
F. Borcardo, A. Decensi, D. Faini, P. Mantoni, F. Massi, M. Paganetti and L. Martini on behalf of the ITALIAN PROSTATE CANCER PROJECT (P.I.N.C.A.P.), Istituto Nazionale per la Ricerca sul Cancro - 16132 Genova - ITALY.

Serial measurements of the following hormones: Testosterone (T), LH, FSH, Progesterone (P), Estradiol (E2), Prolactin (PRL), Thyroid Stimulating Hormone (TSH), and Sex Hormone Binding Protein (SHBG), were made in 21 patients receiving monthly i.m. injections of a depot formulation of D-TRP-6-LH-RH for stage C prostate carcinomas. Results are summarised below:

<table>
<thead>
<tr>
<th>Days/No pts</th>
<th>LH</th>
<th>FSH</th>
<th>TSH</th>
<th>T</th>
<th>PRL</th>
<th>E2</th>
<th>PRL+P</th>
<th>DHEA-S</th>
<th>A</th>
<th>SHBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>5.0</td>
<td>7.0</td>
<td>0.7</td>
<td>2.0</td>
<td>1.4</td>
<td>1.0</td>
<td>5.5</td>
<td>0.7</td>
<td>5.0</td>
<td>7.0</td>
</tr>
<tr>
<td>5-10</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.2</td>
<td>2.0</td>
<td>1.0</td>
<td>0.7</td>
<td>3.0</td>
<td>5.0</td>
<td>7.0</td>
</tr>
<tr>
<td>&gt;10</td>
<td>1.0</td>
<td>2.0</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

In patients treated for 6 mos or longer LH and T levels were measured on d. 0, 21, 28 following a single injection. In all pts LH and T levels were maintained significantly below the normal range. In particular the increase occurred on d. 21 following the 1st administration was no longer evident, just indicating the achievement of a complete desensitization at the pituitary level and down regulation of LH receptors in the tests. Conclusions: The administration of this sustained-release formulation of D-TRP-6-LH-RH produced a persistent suppression of T levels, comparable to castration starting from d. 21. Differences in T and DHEA-S in pts studied were not statistically significant. Injections of this or other LH-RH analogues.
This paper discusses screening for cervical cancer in Britain today. There has been an established test, the Pap smear, available for many years now. However, the following report shows that for some reason most women in the U.K. have never received such a test; 92% of all women who die from cervical cancer in Britain have never had a smear test at all.

Individual screening programmes, both in Britain, Europe and the United States, have significantly reduced the ages at which women are diagnosed with cervical cancer, but in Britain this decrease in mortality conceals a rising trend in mortality in women under 35.

This paper examines the positive value of centralised screening programmes for cervical cancer in women in the U.K. Since most women in the age group 20-59 years have not been tested, this programme aimed to concentrate on those generations of women covered by the screening programmes. Finally, individual follow up of screened women shows a 48% reduction in the 5-year probability for development of cervical cancer in women with one negative smear, and a 69% reduction for women with 2-4 negative smears.
A STRATEGY FOR SCREENING COLORECTAL CANCER

J.H. Czalbert

The author examined the possibilities of early detection of colorectal cancer using several diagnostic and computer methods. As a new procedure he made the patients do the faecal occult blood test in the self administered way with the aid of a special probe (CHINGLY). Moreover to apply in the screening the author studied different laboratory methods. Among others LAL/Lipolysaccharide adherence inhibition test/ and for the detection of human hemoglobin in the stool by ELISA (enzyme linked immunosorbent assay, PEGA-ELA probe/ /Labsystem Oy-Finnland/ and their critical analysis were performed. 11 polyps and 4 cancers were discovered in 1100 patients during the systematic and continuous screening system between 1984-85. On the basis of the elaborated microcomputer program a suitable alternative can be realised for mass screening and follow-up for colorectal cancer.

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ORGANIZATION OF HEMOQUANT SCREENING PROJECT FOR COLORECTAL CANCER

N.J. Goelerer, M.E., D.A. Ahlquist, M.D., H.C. Cancor

Colon cancer is a major public health problem as one in 20 Americans and Europians will acquire this disease, the cause of which is unknown. Therapeutic advances have not improved survival in recent decades. Improved survival depends on early diagnosis. As colorectal cancer is brought to diagnosis, measurement of fecal blood appears to be the most cost-effective screening approach. However, available tests, largely guaiac-based, are chemically unreliable. A new assay, HemoQuant detects the fluorescence of hemoglobin in formalin treated feces, in quantitative and specific, and appears to have major biochemical and clinical advantages over guaiac tests. Preliminary studies have shown that HemoQuant highly discriminates asymptomatic colorectal cancer patients from healthy subjects. Our study aims to: 1. Assess the validity of HemoQuant in detecting symptomatic or occult neoplasms and compare this with hemoccult results and 2. Optimize the HemoQuant screening process. This can be accomplished most efficiently by studying a population at higher risk than average risk for colon cancer. The North Central Cancer Treatment Group (NCCDG) and the Mayo clinic are existing structures to facilitate achievement of these goals. Together these centers provide colorectal cancer surveillance for cure (group 1) and an estimated (group 2) first order relative risk of colorectal cancer: current group 1 (I) during the annual periods. Group 1 subjects will be screened postoperatively for three years with hemoccult and HemQuant; routine precautions and stool charts will serve as "gold standards." Group II subjects will be screened with HemQuant and Hemoccult once yearly and undergo diagnostic studies if either fecal blood test is positive. This study represents the final phase of HemoQuant testing prior to its application in a controlled screening trial of a general population. The HemoQuant Research Center has been set up at the Mayo Clinic to handle and coordinate this rather large task. The methodology and system developed by this Research Center are the subject of this presentation.

MASS SCREENING FOR COLORECTAL CANCER WITH FECAL OCCULT BLOOD TEST

S.Kobayashi, T. Yashii, and A. Matsuda

The purpose of this study is to evaluate mass screening for colorectal cancer with fecal occult blood test in combination with gastrectroscopic examination already established in Japan. 21,661 persons principally over age 48 were included in this study. After the second screening in three successive years with hemoccult slides on a meat-free diet, 728 persons (3.4%) were referred to a detailed survey which 537 persons (79.8%) received. Thus, this study could detect 11 cases (0.05%) of colorectal cancer (4 early and 7 advanced) and 66 of polyp. The authors would stress that this combination designated as postgastrointestinal mass screening is useful and widely acceptable from the viewpoints of cost benefit and detection of curable colorectal neoplasms. In order to expand this mass screening program, education to the public via mass media and cooperation between medical personnel and anticancer organizations would be very important.

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PROSPECTIVE STUDIES OF TUMOR MARKERS IN CANCER SCREENING AND PREVENTION OF CANCER

Tetsuo Kiyosu, Teruo Saito, and Futaba Akiyama, National Cancer Center, Tokyo

We screened 172 asymptomatic persons aged 50 or over in 2 areas in Japan. We carried out simultaneous determinations of carcinoembryonic antigen, ferritin, the ratio of ferritin:serum iron, immune suppressive activity, and H.pylori antigen, heat-stable antigen, lipase, immune suppressive activity, alkaline phosphatase, isoenzymes, and glicic acid. The individuals were divided by tumor marker evaluation and classified into A tumor stage group (IV), B precurser (III), C clinical (II), and D (I) groups. The incidence of elevated values for each tumor marker showed correlation with tumor stage. The percentage of low risk group increased with each age group while the higher risk groups increase. The distribution of tumor markers are not significantly different among the 4 groups. The incidence of elevated values for each tumor marker increase with the progression through each tumor stage. Our tumor marker combination assay can identify a population of individuals at higher risk for colorectal cancer (stages V and IV). This rate varied with the cumulative cancer incidence ratio up to age 74 in Japan. The development of a tumor marker combination assay can identify a population of individuals at higher risk for colorectal cancer (stages V and IV). This rate varied with the cumulative cancer incidence ratio up to age 74 in Japan. The development of a tumor marker combination assay can identify a population of individuals at higher risk for colorectal cancer (stages V and IV). This rate varied with the cumulative cancer incidence ratio up to age 74 in Japan. The development of a tumor marker combination assay can identify a population of individuals at higher risk for colorectal cancer (stages V and IV). This rate varied with the cumulative cancer incidence ratio up to age 74 in Japan.
A PROSPECTIVE STUDY OF NASOPHARYNGEAL CARCINOMA BY TESTING ANTIBODIES AGAINST EBV DNASE AND VIRAL CAPSID ANTIGEN.


Depts. of Bacteriol., Public Health, and Otorhino-laryngol. (Coll. of Med., Natl. Taiwan Univ. and Dept. of Health**, Taipei, Taiwan, R.O.C.

From 1984, 7,146 serum specimens (5546 in 1984 and 1600 in 1985) were collected from the male who visited the government employees' clinic center (control group A and B) for health examination. Meanwhile, 4873 and 900 sera were also collected in 1984 and 1985 respectively from the nasopharyngeal carcinoma (NPC) high risk areas, where different ethnic groups of people (test groups A and B) residing. The sera were tested for the antibody against viral capsid antigen (anti-VCA) of Epstein-Barr Virus (EBV) in IGA and the neutralizing antibody against EBV-specific DNAse.

The titer of anti-EBV VCA antibody in IGA equal to or greater than 1:10 was regarded as positive. In 1984 serum specimens, 57 persons (1.18%) from test group A and 36 persons (0.65%) from control group A showed positive reactions respectively. In 1985, 1.92% (17 among 900 persons) of test group B and 5.87% (9/1600) of control B revealed positive results respectively. As to anti-EBV DNAse antibody test one ml serum capable of neutralizing more than 2 units of DNAse activity of EBV was considered as positive. In 1984, 557 cases (11.573) from test group A and 369 cases (6.652) from control group A showed positive reactions. In 1985, 6.85 (78 in 900 persons) from test group B and 5.42 (87/1600) from control group B revealed positive reactions. The differences of the positive rates between test and control groups were all statistically significant. (P < 0.01)

Clinical follow-up of the persons with positive anti-VCA and/or anti-EBV DNAse antibody reactions revealed that 7 cases were suffered from NPC. Among them, one with stage I and the other one with persistent RFC had both anti-VCA and anti-EBV DNAse antibody. On the contrary, the NPC patient has not been detected from control groups. In the rest 5 remission cases 3 patients had anti-EBV DNAse antibody but not anti-VCA. The results supported the value of testing antibody to EBV DNAse as a marker, in addition to anti-VCA, for the early detection of NPC.
2652 EARLY DETECTION IN BREAST CANCER.
Authors: E.L. Buch, L. Fernández, M. Caraballo, K. Pardo. Natl. Inst. of Oncology and -— _
-—- Haematology.

Breast cancer is the first cause of incidence and death in female population in Cuba according to National Cancer Registry. In order to attain the National Control Program of Breast Cancer many tasks in early diagnosis had been developed. A uniform methodology for initial attention in mammary pathology at oncology institute was developed. An assay was developed to establish a "National Control Program of Breast Cancer". The strategy for total breast care should rest on cancer prevention, education, early detection, effective treatment and rehabilitation. Cancer care may be: (1) Primary, (2) Secondary and (3) Tertiary. The variable types of care need to be delivered within the community based organization. The scheme should provide continuum of care and utilize the existing infrastructure of the health care system in Cuba. A trial in the Havana Province is currently being organized. The strategy components include: (1) Health education, (2) Screening and (3) Treatment. The strategy components are being developed in small centers and the main centers of the health care system in Cuba. The research module has been developed in the project "Early detection of breast cancer".
Six years ago a collaboration was developed between both the gynecological institute of Tallinn and the gynecological department of the Hospital of jännerö. The area of jännerö belongs to low risk area of view of gastric cancer, the district of Tallinn belongs to high risk area.

A follow up study was carried out by us at a determined group with gastric disease through 6 years. The infragastric diseases which were cared by us as follow up patients with gastric ulcer, low patients with gastric antrum and 50 with gastric polyp, the same method of diagnostic procedures was used i.e. gynaecology with hysteroscopy, intactic acid determination etc. As in Tallinn in jännerö.

The rate of the development of gastric cancer was the same in both districts. The collaboration provided an opportunity for us to do more further conclusions.
DEVELOPING A NATIONAL CANCER EDUCATION PROGRAM ON NUTRITION AND CANCER: FIRST PHASE

C.A. Moyer, Canadian Cancer Society, Toronto, Ontario, Canada.

In September 1983 the CCS adopted a policy on the possible prevention of cancer of the colon and rectum through diet and directed the PE Committee to develop an educational program. PE identified several necessary steps. The first was to develop a unified, single-to-understand policy on all aspects of diet and the possible prevention of all forms of cancer. The second was to increase knowledge of diet and cancer among the scientific and educational CCS leadership. Both steps were accomplished by summer, 1985. The need for expertise on nutrition throughout the national, provincial and local levels of the CCS led to the establishment of an official liaison with the CDA, a professional organisation for dietitians. The CDA offered expertise in program development, internal training and delivery of the program to the public. As a third step, it was identified that the food industry is a major current educator of the public regarding nutrition; this led to a pilot project with a major manufacturer of a high fibre cereal. A fourth factor identified was that a diet which would help reduce the risk of developing cancer also helps in the reduction and control of heart disease and diabetes, two other major chronic diseases in Canada. Therefore, the development of a common "Canadian diet" is being explored. These shifts in expertise and program emphasis will thoroughly be explored in the presentation.

CASE-CONTROL STUDY OF DIET AND PROSTATE CANCER IN HAWAII.

L.M. Koong, U.M. Hankin and C.N. Yoshimasa, Cancer Research Center, University of Hawaii, Honolulu, Hawaii, U.S.A.

A case-control study of prostate cancer was conducted among the multiethnic population of Hawaii. During the period 1974-1983, all newly-diagnosed patients with prostate cancer on the island of Oahu were identified through the Hawaii Tumor Registry. Community controls were randomly selected and matched to the cases on sex and age (±5 years). Each subject was interviewed about his diet, occupation, medical and social history, and other demographic information. The dietary information consisted of a quantitative diet history in which both frequency and portion size were assessed. The final sample consisted of 452 cases and 899 controls. At present, the data have been analyzed for dietary fat and vitamin A. Fat intake, particularly saturated fat, was greater for cases than controls (Relative risk, RR = 1.7 for highest vs. lowest quartile of intake among the men >70 years of age, p<05). Vitamin A intake also showed a direct association with prostate cancer in these older men (OR = 1.9 for highest vs. lowest quartile of intake, p<05). These results indicate the importance of diet in prostate cancer risk and suggest that the effect of vitamin A may be to enhance carcinogenesis in some circumstances.

WHEAT BRAN FIBER SUPPLEMENTATION FOR COLON CANCER PREVENTION: A FEASIBILITY STUDY IN THE ELDERLY.

E.K. Re, Cynthia Abrams, and Frank Neveskas, Arizona Cancer Center, Univ. of Arizona, Tucson, Ar, U.S.A.

Increasing dietary fiber intake has been recommended by the U.S. National Cancer Institute for reducing colon cancer risk. A feasibility study using daily wheat bran fiber supplements was conducted in 180 older individuals at high risk for developing precancerous colon polyps. The subjects were randomly assigned to three study groups for three months duration. Group 1 (Minimum Contact): Subjects were encouraged to use 2-3 cups of 100 % wheat bran cereal daily as fiber supplementation for colon cancer prevention. Group II (Supplementation): Subjects received three month's supply of cereal supplements in daily packages and were encouraged to use them everyday. Group III (Supplementation + Education): Subjects received supplementation like Group II, and an additional educational program throughout the duration of the study. Subjects from all three groups were interviewed at the clinic and completed questionnaires assessing their general and colon cancer specific health attitudes, beliefs, knowledge and habits, at the beginning and the end of the study. The educational program was designed to provide general maintenance function and individualized problem solving mechanism. Its activities included contingency contracts, newsletters, group meetings, recipe books, and personal counselling, etc. Each educational activity was identified by specific variables as compliance barriers or benefits which were intended to change. Data analysis showed that compliance rates differ significantly among the groups. The education program successfully affected compliance rate and other variables of health attitudes and knowledge. Results indicated that well planned educational program can effectively improve the compliance rate and therefore the feasibility of a cancer prevention intervention.
2663 DIETARY PREVENTION OR RECURRENCE OF ADENOMATOUS POLYPS IN THE COLON AND RECTUM. G. McKewon-Evensen and E. Bright-Shepp, Ludwig Institute for Cancer Research, Toronto Branch, Toronto, Canada.

A number of dietary factors have been suggested to be associated with the risk of colorectal cancer. Randomized controlled trials are being undertaken to determine the effect of two types of diet on the incidence of adenomatous polyps in the colon and rectum. Results of a subset of 101 patients with colorectal cancer, 71 were nonmetastatic, 72 were metastatic, and 12 were contained in situ. Follow-up of all patients will be completed in the 2nd quarter of 1986 and the rates of polyp occurrence will be reported in relation to the presence or absence of vitamin supplementation.

The second investigation is similar in design, but the dietary alteration is more substantial. Patients are randomized to receive a supplement containing 400 mg of ascorbic acid and 400 mg of vitamin C or a placebo. After 2 years, patients are examined by colonoscopy to establish whether polyps have recurred. Polyps are identified and counted at colonoscopy for the first 136 patients to complete 2 years of follow-up. Among polyps examined for pathology, 93% were adenomas, 7% were hyperplastic, and 12% contained in situ cancer. Follow-up of all patients will be completed in the 2nd quarter of 1986 and the rates of polyp occurrence will be reported in relation to the presence or absence of vitamin supplementation.

The present study was initiated to test the null hypotheses that the risk for colorectal cancer could be augmented by the intake of fiber-rich and salt-rich diets (simulations of the Japanese traditional diet), and that the risk for colorectal cancer in patients with colorectal cancer may be related to a disorder of endogenous steroid hormones that are linked to the metabolization of fat and fat-soluble vitamins (fibroproplasia and vitamin D deficiency). The effects of 2 risky diets on the growth of rat colorectal adenomas were studied and the hormonal and epidemiological aspects of gastric cancer patients were investigated. In the praxis of the hormonal study, a liquid chromatographic assay was employed to estimate the excretions of over 100 urinary steroids for each subject. Results obtained are as follows: 1) both the fiber-rich and salt-rich diets for the long-term experiment produce an atrophic change in the glandular stomach as mucosa. 2) Evidence is available to indicate that a reduction of endogenous androgens combined with an increase of endogenous glucocorticoids is induced by the intake of risky diets. 3) For the production of stomach cancer in mice. 4) The human study is in consonance with the animal data in that the patients with gastric cancers, as compared with the normal controls, have more affinity for fiber-rich and salt-rich diet, and also suffer from a dual disorder of adenocarcinoma and low hyperplastic lesions. All these findings seem to support our proposal that the risk for gastric cancer could be conditioned by a diet-related disorder of steroid metabolism.
2667 AN INFLUENCE OF FRESHLY EATEN FOODS ON CANCER RISK: K. Kitagawa*, T. Okuma*, A. Hara, K. Sasaki, M. Hattori, and T. Sawada**, Tsuchiura Hospital, Ibaraki-ken, Japan

A protective effect of dietary intake of a mushroom-herbal compound, called "ENOKI-MUSHROOM" in Japanese, was evaluated in an epidemiologically and experimentally study. "ENOKI-MUSHROOM" is a daily consumed in Nagano prefecture in Japan and its post-dependent antitumor effect had been well studied.

A retrospective case-control study of about 1000 male patients with prostate cancer was conducted in the years 1981 to 1983. Following age-adjustment, the death rate in relation to the mean age at death was 50% lower in the Nagano area than in other areas in Japan.

The present study was supported by partial financial aid from the laboratory for laboratory epidemiology. A list was made of the patients with prostate cancer and the mortality rate was calculated. The results showed that the mortality rate was significantly lower in the Nagano area than in other areas in Japan.

2668 POLT IN THE DEFICIENCY OF VITAMIN B12 IN THE GASTRIC CANCER PATIENTS. S. Kyotani, K. Nakamura, T. Horiguchi, H. Hirota, and K. Ishii, National Hospital, Nagano, Japan

The present study was conducted in the patients with gastric cancer who were diagnosed at the National Hospital, Nagano, Japan. The patients were divided into two groups: one with vitamin B12 deficiency and the other without deficiency.

The results showed that the patients with vitamin B12 deficiency had a significantly higher mortality rate than the patients without deficiency. Therefore, it is suggested that vitamin B12 deficiency may be a risk factor for gastric cancer.

2669 GASTRIC CANCER IN POLAND - A DECREASED MALIGNANCY DUE TO CHANGING NUTRITIONAL HABITS OF THE POPULATION. W.A. Dądrychowski1, T. Popiela2

2/ I. Surgical Clinic, Med. School, Cracow, 40, Kopernika Street, Krakow, Poland

The paper deals with the mortality patterns from stomach cancer over the period of last 20 years in Poland. The decrease in the incidence of stomach cancer was discussed in the light of data regarding the food consumption in several past decades and the results of the case-control study on stomach cancer and diet. In men the mortality rates dropped over 20 years by about 50% in younger and by about 40% in older age groups. Among women the drop in the rates was slightly faster than in men with the exception of age group 40-44 years. When examining the consumption of specific food products per capita over the period of last few decades, one has to note a marked increase in meat and drop in the consumption of cereals and fats in Poland. The case-control study showed that the high risk of stomach cancer run the people with low level of vegetable and fruit consumption. Analysis confirmed the downward trend in stomach cancer rates in Poland over the last 20 years and explained the pattern observed by the marked changes in the nutritional habits of the population at large.
2671 A PRIORI SURVEY OF DIETARY HABITS OF PAST DECADES TO RELATE STOMACH CANCER INCIDENCE


2673 "CHEF. D. M. Public Health Organization of Japan, Pre-Pediatric, Pre-Medical, Pre-Veterinary


Relationship between colorectal cancer mortality and bread supply or total cereal carbohydrate supply was analyzed using the regional statistical data of the Hungarian Central Statistical Office. In the 5 regions of Hungary the bread supply of pensioners for home consumption changes between 30 and 200 kg per year. Analyzing the bread supply and the standardized mortality ratio (SMR) of rectum cancer in different regions a significant negative relationship was found. The relation remained significant, when Budapest (representing a special region of Hungary) was omitted from the analysis. A similar relationship was observed, when the total amount of cereal carbohydrate supply and the SMR of rectum cancer was studied. The SMR of colon cancer also was negatively related with the supply of bread, but when the Budapest region was omitted the relationship was no more significant. No similar relationships were found between the supply of bread and the SMR of stomach cancer, of bronchus / lung cancer and of breast cancer. Bread is a major source of dietary fiber in Hungary. The findings could be explained by the protective effect of dietary fiber and/or some other components of bread.
While several studies have shown lower rates of cancer of some sites in population subgroups with above-average intakes of vegetables and fruits, there are exceptions—some having shown higher rates. An ongoing follow-up of 16,713 subjects who had reported their dietary habits in 1967-69 allowed an initial exploration of the varied relationships, with respect to individual food items, cancer sites, as well as to cause-specific mortality. Analyses were stratified on age, sex, residential characteristics and cigarette smoking, and included tests for a linear trend in the proportion affected with increasing frequency of use, and for departure from trend. Selected observations from this population will be presented. Such analyses indicate the importance of the relationship of total mortality from all causes before making preventive recommendations.

In order to study incidence and survival from malignant melanoma in Rome, a retrospective study was planned to find all cases of the tumour diagnosed during the period 1970-84. All the cases in 116 patients who had been under treatment in Rome and in the hospital during that period, both public and private hospitals were involved in the study. A standard form was filled in for each identified case. The diagnosis, place and cause of death has been ascertained from death certificates. Survival to 5 and 10 years have been estimated through the life table method. The observed survival rates were as follows: for women and 41, 39, 29 and 24 years, the corresponding 15-year survival were 54, 40, 29 and 24. The best survival rates were obtained in women, and the worst were observed in men. A Cox regression model for survival data has been applied to investigate which of the following parameters, age, sex, period of diagnosis, and site of origin and level of treatment, has a significant influence on the survival probability. In this study the last level of invasion emerged as the most significant variables on survival of melanoma patients.
2679 METHODOLOGY TO ASSESS THE RELIABILITY OF VITAL CERTIFICATE DATA. Germaine M. Buckle1, Diane L. Cookfair2, Arthur M. Michalek3, Philip C. Nasca3. Roswell Park Graduate Division/USF, Roswell Park Memorial Institute, b66 Elm Street, Buffalo, NY 14263, Department of Social and Preventive Medicine, SUNY, Buffalo, NY 14214, Department of Education, Roswell Park Memorial Institute, b66 Elm Street, Buffalo, NY 14263, New York State Health Department, Division of Epidemiology, Albany, NY 12237, U.S.A.

Cancer vital statistics are often used as a primary database for many cancer-related research projects, and also in the regional/national reporting of cancer information. The purpose of this study was to measure the degree of reliability of vital statistics abstracted from birth and death certificates for a sample of infants in Upstate New York during 1974. Hospital medical records were obtained for all infants (n=285) along with autopsy records (n=260) for infants who died suddenly during the first year of life. These records were abstracted and compared with birth and death certificates in order to measure the degree of concordance for each study variable. Further information will be presented on the methodology involved in conducting a reliability study and low tests of reliability are made. Strengths and weaknesses of vital statistics data will be presented along with the applicability of reliability studies to other databases and disease registries.

2680 MICROCOMPUTERS IN ONCOLOGY PRACTICE. Nagida Amer, Vera Saleh and A. Al Abdulwahab. Departments of Oncology, Nursing and Data Processing, King Faisal Specialist Hospital (KFSH), Riyadh 11211, Saudi Arabia (SA).

KFSH is the main cancer centre in SA with over 1400 new cancer patients (PTS) referral a year. All PTS are fully staged and intensively treated according to well defined protocols. The complexity of these clinical trials have placed an increasing burden on practising physicians and oncology nurses. Accordingly, an attempt was made to computerize oncology records using a microcomputer with hard disc storage capacity and data processing program. The system stored basic clinical data, final diagnosis, stage of disease, previous history, physical findings, measurable lesions, protocol outline, response to treatment and future plan. Warning messages for physicians and nurses were incorporated. The system generated two extra reports, one to the primary physician and the second for PTS and families to be utilized in case of emergencies. The later proved to be extremely helpful especially with PTS living in remote areas. Weekly reports were produced to define PTS attendance and results of therapy. To evaluate the usefulness of this system, data were obtained on the average number of PTS per cliner (PAT/CLINIC), average PTS time spent at the clinic each visit (PAT/CLINIC and physician time per each PAT (HR-TIME)). Data were used to evaluate clinic performance during each clinic visit and the % of good reporting were recorded. Information were collected over 3 months (M) prior and 4 M after the initiation of this system.

The actual cost of the whole system was US $5000 and the average time required to train clinic personnel was four hours. The use of microcomputer in oncology practice is relatively an inexpensive investment and proved to be extremely useful to every one involved.


Quality control of data is a crucial part of medical research, and in particular, of cancer registries. Poor quality data will often result in failing to obtain significant findings, or worse, in obtaining spurious findings. In the United States, the Comprehensive Cancer Patient Data System (CCPDS) collected data on 250,000 cancer cases. Quality control was energetically pursued by the Statistical Analysis and Quality Control Center (SAPC). The experience and wisdom arising from this effort are summarized in a manual entitled "Quality Control for Cancer Registries," available from SAPC, Fred Hutchinson Cancer Res. Ctr., 1124 Columbia St., Seattle WA 98104, USA. In addition to summaries of good quality control methods, the manual contains reprinted articles and forms, etc. The manual lists and describes the following as essential components of a quality control system: (1) standardization and definition of reportable cases, with written definitions of reportable criteria and review of questionable cases; (2) definitions of data items, with a form for data entry; (3) assessment of completeness of case finding, with a list of case-finding sources and documentation of procedures; (4) examination of data capture by systematic monitoring; (5) assessment of data accuracy, by manual or computerized edit checks and by reviewing and reviewing of abstracting and coding; (6) training for personnel, especially new personnel. Listed as very desirable are (7) active check on outside sources of cases; (8) monitoring of use of codes for 'unknown' and of the capture of therapy information; (9) standards for rates of data registration and follow-up; (10) systematic reabstracts of samples of routine cases to check accuracy; (11) intra-institutional workshops and documentation of unusual cases for training.

2682 A COMPUTER PROGRAM PACKAGE FOR CANCER SURVIVAL ANALYSIS. T. Hakulinen, and K. Abeywickrama. Finnish Cancer Registry, Liikunnapu 27 B, SF-00170 Helsinki, Finland

A computer program package has been constructed for use in patient survival analyses for cancer based on aggregated data. The central concept of the analyses, the relative survival rate is used to measure survival, with a list of causes of death of individual patients. The package contains three alternative methods estimating the relative survival rates, two different ways of estimating the expectation of life for the patients, and five methods of testing the relative survival patterns using information on the whole follow-up period. Conventional survival and competing risk analysis can also be performed with the package. It is hoped that the package will facilitate standardization of statistical methodology and terminology in long-term survival studies in cancer.
A retrospective study was made on 251 consecutive cases of female cancer breast who were examined during (1978-1980) at Tanta Cancer Institute. A relative of 13.7% to total number of malignancy was noticed. About 66% of cases occurred below the age of 49.72 and 73 cases constituted 76% and 74.25%. Lymph node involvement was found in 89% of cases. Out of 251 patients, 196 were submitted to radical or modified radical mastectomy and the remaining were considered inoperable. The most frequent histological type was infiltrative duct carcinoma 74%, comedocarcinoma 12%, medullary carcinoma 7% and lobular carcinoma 4%. The incidence of pathological nodal involvement in 1-3 nodes was found in 26% of patients and more than 3 nodes in 63% of patients. Out of 196 patients 72 received no further adjuvant therapy and 124 received adjuvant irradiation. Out of 251 patients, 72 received no further adjuvant therapy, 124 received adjuvant chemotherapy, 74 patients postoperative irradiation and 26 patients received both radiotherapy and chemotherapy. The incidence of locoregional recurrence 33% was encountered in the surgery alone group, 5% for chemotherapy group and 4% for postoperative irradiation group. Patients followed up for a period of one to three years. The incidence of distant metastases was 19% for surgery group, 4% in chemotherapy group and 6% for radiotherapy alone group.

Five questions were addressed by systematic review of the interim results of all relevant randomised trials in early breast cancer: /i/ radiotherapy, /ii/ immunotherapy, /iii/ oophorectomy, /iv/ tamoxifen, and /v/ cytotoxics. Radiotherapy was shown not to prolong life; immunotherapy was inadequately evaluated but unpromising, and oophorectomy was inadequately evaluated and but the results were very promising. Among women over 50 years of age, tamoxifen conferred a moderate /20% but a highly significant reduction in 5-year mortality, while the cytotoxic regimes thus far tested appeared to have less effect. Conversely, among younger women the opposite was true.

Monoclonal antibodies to membrane antigens of human small cell lung cancer (SCLC) were produced in our laboratory against breast, ovary and colon antigens. First, some reagents were selected for their specificity against normal and tumor epithelial cells utilizing their capacity to detect metastatic carcinomas in situ. A “in situ” application was investigated. Our results indicate that selected MoAbs may improve survival. In fact, in all of the above experiments there were no negative cytopathological changes from breast, ovary or colon patients. Furthermore, they also grow in xenograft model. In 13% of these mouse xenografts were in all of the above experiments there were no negative cytopathological changes from human tumor xenografts. The previously described MoAbs are not suitable for “in situ” application because of their specificity against normal epithelial cells, we attempted to produce MoAbs to tumor-specific antigens, we managed to estimate those highly immunogenic, MoAbs having specific structural features, recognized by the first selected MoAbs, by using immunizing materials which does not express these antigens. With this system we have obtained some MoAbs selective for every carcinoma which seem to be negative in all normal tissues tested so far. Different studies are being carried out to utilize such reagents in clinical agony for “in vivo” applications.

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MONOCLONAL ANTIBODIES IN LYMPHOMA ASSOCIATED ANTIGEN (IAA)


Biochemistry Department, Cancer Institute, Madras, India, IJAM, and the Netherlands Cancer Institute, Amsterdam, The Netherlands.

Lymphoma associated antigen (IAA) has been isolated from pooled lymph node fluids of patients with different histological types of Hodgkin's and non-Hodgkin's lymphomas. Hybrid mononuclear antibodies to IAA have been developed by in vitro immunization technique. Splenic cells of BALBc mice were immunized in culture with 11I-125 IAA in thymocyte conditioned medium, the immune spleen cells harvested after 4-6 days and fused with SP2/0 myeloma cells. The hybrid clones were tested by ELISA attachment, 1-2 weeks after IAA, resulting in 3 specific clones. All three hybrids were stable on cloning. The diagnostic potential of these monoclonals is being evaluated. The stable hybrid cells were used for production of ascites in BALBc mice. The culture supernatants of these monoclonal antibodies designated 15A3, 15B1, and 15D2 were used in immunofluorescence and serological immunoassay studies using malignant cells of lymphoma patients, normal peripheral lymphocytes, and tissue extracts. Preliminary results using monoclonal antibody 15B1 showed reactivity with the tumor cells of lymphoma patients and the test was reactive with normal lymphocytes.
DETECTION OF A 90K ANTIGEN BY MONOCLONAL ANTIBODIES IN THE SERA OF PATIENTS WITH BREAST CANCER. S. Iacobelli, G. Bartolini, T. Arno, L. Guidi, N. Gentilini, and R. Baroni. Immunology Department, Istituto Clinico Omezzeria e Ginecologia, and Istituto di Clinica Medica, Università Cattolica S. Cuore, 00168 Rome, Italy.

Monoclonal antibodies were produced from a Balb/c mouse immunized with proteins released into tissue culture fluid of human breast cancer cells. One antibody, BP-2 (14G11 class) identified an Mr 90k antigen which appeared to be a product of intracellular synthesis. By immunoprecipitation assays, BP-2 reacted with the large majority of human breast cancer as well as with some selected cases of gastrointestinal, ovarian cancer and lung cancer. A sandwich-type ELISA assay was developed to measure the levels of 90k in the sera of patients. Seventy-five of 99 patients with advanced breast cancer, 10 of 166 patients without evident disease (after mastectomy) and 5 of 48 patients with benign breast disease (mostly fibrocystic disease) showed serum antigen levels above 1.4 units/ml. Patients with non-breast cancer also demonstrated elevated serum levels of antigen in 52% of cases. The BP-2-defined antigen appeared to be distinct from carcinoembryonic antigen and other monoclonal antibody-defined breast cancer antigens of similar molecular weight. Also, it differed from the antigen defined by monoclonal antibody CA 19-9 and from the gastrointestinal antigen defined by monoclonal antibody CA 19-9. BP-2 may prove useful in breast pathology as tissue and serum marker.


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The monoclonal antibody (CA 19-9) 14G22 was generated through the fusion of the myeloma mouse myeloma cell line P3/X63-Ag8.1, and splenic cells of a mouse immunized with peripheral blood mononuclear cells (PBMC) from a breast cancer patient. CA 14G22 was tested by direct immunofluorescence technique in cell suspensions of the peripheral blood of healthy donors, splenocytes, lymphocytes, patients and culture cell lines. Also, a dynamic and micro-anatomical study of the expression of IgA-22 antigen in fetal organs and pediatric tumors was performed. The results show that the high percentage of peripheral blood cells containing this antigen in fetal and pediatric tissues was compared. In contrast, a high proportion of the P3/X63-Ag8.1 myeloma line was IgA-22 positive cells. CA 14G22 recognized a new antigen preferentially expressed in fetal tissues. It was concluded that IgA-22 or HAB identifies a new antigen or related, but not s-restricted antigen, best expressed during a definite stage of the ontogenetic development of the thymus.
2695 MONOCLONAL ANTIBODIES TO ANTIERS OF HUMAN PROSTATE ADENOCARCINOMA. Susan S. Leong, Julius S. Borgerding and Linda A. Niedorf, Department of Biological Resources, Roswell Park Memorial Institute, Buffalo, N.Y. 14263, U.S.A.

Monoclonal Antibodies (MoAb) are potentially powerful tools for cancer detection. In our study, we determined the antigenic status of human prostatic adenocarcinoma cells using monoclonal antibodies. These antibodies were produced by fusing myeloma cells with spleen cells from mice hyperimmunized with cells from a well-characterized human prostatic malignant cell line, LNCAP. These cells produce the soluble biochemical markers, prostate specific antigen (PSA) and prostate acid phosphatase (PAP), characteristic of human prostatic epithelium. Hybridoma supernatants were screened for binding activity to plasma membranes isolated from LNCAP cells and normal human fibroblast cells using the Enzyme Linked Immunosorbent Assay (ELISA). 21 of 28 wells containing the normal and tumor cell lines showed reactivity. 12 reacted with intact LNCAP cells and 76 reacted with normal human fibroblast cells. Screening by ELISA and by immunoperoxidase staining of normal and neoplastic cell lines and by immunoblotting of cytoplasmic and membrane fractions from LNCAP cells identified 3 hybridomas of interest. Cell culture and tissue culture fluids were the source of antibodies used for further studies. MoAb JF1, an IgG1 immunoglobulin, strongly reactive with the membrane fraction of LNCAP cells, but not reactive with the soluble cytoplasmic fraction of LNCAP cells was further characterized. No reaction with PAP and PA was evident. Indicating that the MoAb was not directed against antigens within the MoAb target. MoAb JF1 showed strong reactivity to LNCAP cells but much weaker reactivity to two other established prostatic cell lines, 22RH and PC-3. Weak reactivity was also detected to human bladder cancer cell line 786. The indirect immunoperoxidase staining technique was used to demonstrate that this antibody binds to prostatic epithelium. We have developed hybridoma culture and tissue culture supernatants for the purpose of analyzing the antigenic status of normal and tumor cells. The use of monoclonal antibodies for the detection of prostate carcinomas is being evaluated in several clinical studies.

2696 DEVELOPMENT OF MONOCLONAL ANTIBODIES AGAINST UTERINE CERVICAL CARCINOMA AND STUDY OF THEIR REACTIONS TO SURFACE ANTIGEN'S SITES IN EXTRACTED EPITHELIAL CELLS. L. Kortekaas-Saraka, S. Zielke[, A. Bon**, and M. Herlyn**.


Several monoclonal antibodies developed against human cervical carcinoma binding neoplastic but not normal epithelial cells in 71-90% of cervical cancer tumor tissue imprint and appear are of potential diagnostic value. One of these monoclonal antibodies, for the development of which a cervical carcinoma cell line containing fragments of human papilloma virus was used, occasionally also reacts with so-called "repair" cells in smears of patients with severe cervicitis. The procedures leading to the development and characterization of these monoclonal antibodies, results of their study, documentation of results, and discussion of significance will be presented.

2697 CLINICAL APPLICATION OF MONOCLONAL ANTIBODIES IN OVARIAN CANCER. M. Driscoll, S. Y. Schindel, and J. J. Barlow, Roswell Park Memorial Institute, Buffalo, New York, U.S.A.

We have developed and characterized several murine monoclonal antibodies (MoAb) to ovarian cancer-associated antigens, at least 3 of which (12A, 22A, and 24A) seem to have potential clinical application. MoAb 12A reacts with a high molecular weight oncoprotein (Mr 10,000) that has a very restricted distribution pattern. The antigen is found in ovarian cancer, 51% of colon carcinomas, 31% of breast carcinomas, 82% of pancreatic carcinosarcoma, and 90% of normal tissues. Only normal colon had a barely detectable antigen level. Also, the antigen was found in breast tissue. It is a putative tumour-specific antigen which is produced extracellularly in large amounts by normal human colon tumours, vascular tumours, and some gastrointestinal tumours. MoAb 22A was not found in several different ways: for immunohistochemical studies on sections of tumours and on cell-surface staining of sarcoma and breast tumours, for detection of cell line specific antigens and retained or isolated cells in high molecular weight carcinoma, or in bone marrow aspirates of breast cancer patients and patients with metastatic colorectal cancer. MoAb 24A reacts with a single chain portion specific lesion in ovarian cancer. We have developed a monoclonal antibody (MoAb) which binds to the distal end of the antigen and is present in the circulation, as well as in ascites and pleural fluids and in body fluids of patients with ovarian cancer. The MoAb has been shown to react with the following ovarian cancer antigens: anti-MoAb 12A, anti-MoAb 22A, and anti-MoAb 24A. MoAb 12A shows strong reactivity against ovarian carcinomas, 51% of colon carcinomas, 31% of breast carcinomas, 82% of pancreatic carcinosarcoma, and 90% of normal tissues. Only normal colon had a barely detectable antigen level. Also, the antigen was found in breast tissue.
APPLICATION OF ISOTOP LABELLED ANTI-MBP MONOCLONAL ANTIBODY FOR THE IN VIVO DIAGNOSIS OF CAKERM

V.Kőves, K.Kohari, B.Pekete, I.Szilvási, L.Kocsár, V.Sigy, G.Szabó

According to our previous work the myeloma basic protein (MPB) used in our experiments seems to be a common carcino-antigen reacting with all epithelial malignancies. MPB antigen has been used in humoral leukocyte adherence inhibition assay. 93.2% of the cases gave positive reactions, while there were no false positive among the controls.

In the in vitro immunohistochemical study the anti-MBP monoclonal antibody only bound to the cancerous tissue but not to the controls except of the brain. After this study the monoclonal antibody was iodinated with 131 I with chloramine T method. Lewis lung cancer mice and Walker 256R rats were treated intravenously with the labelled monoclonal antibody. Repeated gamma camera radiophotography and scintigraphic study were done for five days.

The results showed that the isotope labelled monoclonal antibody had bound specifically to the tumor, except of the brain. After this study the monoclonal antibody was iodinated with 131 I with chloramine T method. Lewis lung cancer mice and Walker 256R rats were treated intravenously with the labelled monoclonal antibody. Repeated gamma camera radiophotography and scintigraphic study were done for five days.

The results showed that the isotope labelled monoclonal antibody had bound specifically to the tumorous tissue only and furthermore had not transferred the blood brain barrier.
K-43: MONOCLONAL ANTIBODIES IN DIAGNOSIS (CLINICAL STUDIES)

2703 POSSIBILITIES AND LIMITATIONS OF THE "IN SITU" DIAGNOSIS OF TUMORS WITH MONOCLONAL ANTIBODIES

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The possibility of use of the direct enzyme-linked antibodies in the clinical diagnose of tumors in a higher range of survival for the patient were discussed, including the new methods associated with ELISA. The sensitivity and specificity is increased by the natural combination of the iodinated antibody, and the iodinated antibodies to the introduction. This leads to an increased sensitivity. Elisa is clearly more sensitive than the usual test, but is less specific. The test is more specific for the antigen, but is less sensitive. It is clear that the presence of the specific antigen is associated with the presence of the tumor. It is not clear whether the antibodies are themselves specific or non-specific.

2704 THE SENSITIVITY AND SPECIFICITY OF FERRITIN BEARING LYMPHOCYTES (FBL) TEST FOR BREAST CANCER DIAGNOSIS AND THE RELATION BETWEEN POSITIVE FBL RESULT AND RISK OF BREAST CANCER IN A POPULATION OF ISRAELI WOMEN.

Chaya Moroz, Moshe Kahan, and Chaim Chaimof, Hopewell-Medical Research Institute, Beilinson Medical Center and Dept. of Surgery, Hasharon Hospital, Peha-Tikva, Tel-Aviv University Medical School.

The FBL test measures the presence of carciinofetal ferritin on the surface of peripheral lymphocytes by a competitive binding assay with [125I]-CM-H-9 McAb which is specific for placental ferritin. In the current study an attempt was made to determine the sensitivity and specificity of the FBL test and to correlate positive results with risk factors such as age 50 yr, family history, first pregnancy 31 yr, ethnic origin-Ashkenas and menopause age 50 yr. The FBL test was performed on 292 women who were also examined clinically and/or by mammography. 28% of the women underwent a breast biopsy. The results obtained revealed that 92% of the women with breast cancer stage I,II were FBL positive. Of the women without any clinical evidence of breast cancer 5% were negative and 3% were positive. However, in the latter group, a significant increase in the proportion with positive FBL was observed in those women who had 3 or more of the above risk factors. A computer analysis of all the possible combinations of the above risk factors including, as one, the positive FBL was carried out on the 292 women who underwent biopsy. The association (odds ratio) of these risk factors to malignancy, was determined. It was found that the highest Gamma (3.580+0.115 p<0.001) was observed in 4 groups of women who had different combinations of risk factors. Two of the factors were included in all 4 groups these were age >50 yr and positive FBL. The other two factors (family history, ethnic origin) were not present in all the groups.

Supported by a grant from the joint German-Israeli Research Program.

K-44: TUMOUR ASSOCIATED ANTIGENS (EXPERIMENTAL STUDIES)

2705 CHROMATOGRAPHIC PURIFICATION OF TUMOUR-ASSOCIATED ANTIGENS OF EXPERIMENTAL MOUSE LEUKEMIA


Two water-soluble antigens are identified in the solid form of a CaCl2-induced leukaemia in BALB/c mice. It is established that these antigens are cell proteins, they are not cell-localized and possess different antigenic specificity, molecular weight and electrophoretic mobility. The antigens were isolated using separation gel chromatography, affinity gel chromatography, Affi-gel affinity chromatography, and Fast protein liquid chromatography (FPLC).

The degree of purification is checked by ELISA and polyacrylamide gel electrophoresis.

2706 DETECTION OF TUMOUR-ASSOCIATED ANTIGENS IN HUMAN LUNG TUMORS BY DIMENSIONAL AND ONE-DIMENSIONAL ELECTROPHORESIS


We have reported several tumor associated cellular proteins in human clinical samples, as detected by two-dimensional gel electrophoresis (2-D PAGE). In this study we made an attempt to detect tumor associated cellular proteins in tumors from 554 lung cancer (514 cases) obtained from carcinoma and control groups on the greater localization of the antigen. These were isolated in 2-D PAGE and 1-D PAGE, which were analyzed by computerized image analysis. The tumor proteins were detected using the spot-detection program that was developed by Chai et al. The patterns of cellular proteins in carcinoma and control groups were compared with each other. The spot patterns of cellular proteins in human lung carcinoma were relatively similar in contrast to those in control group. Some spots were different quantitatively and qualitatively. The results are as follows:

Protein spot 1 - Control carcinoma

(1) Protein spot 2 - Control carcinoma

(2) Protein spot 3 - Control carcinoma

The three spots, 1, 2, and 3 were decreased in cancer as compared to control mice. In addition, the spots, 2 and 3 were decreased in cancer in comparison with control mice. The above results suggest that the tumor associated cellular proteins in human have been producing monoclonal antibodies against these protein in two-dimensional gel spots and also characterizing them.
2707 2708 2709 2710
The properties of tumor-associated antigens (TAA)s expressed on neoplastic bovine leukosis (EBL) were investigated using monoclonal antibodies. According to the reactivities of 12 monoclonal antibodies with individual EBL tumor cells, TAA were classified into three groups: common TAA, partially common TAA and individually distinct TAA. Common TAA expressed on all EBL tumors tested was a glycoprotein with a molecular weight of 74,000 and had at least two independent antigenic regions. Monoclonal antibodies (c14, c532) recognized common TAA on EBL tumor cells but not on normal adult bovine peripheral blood lymphocytes (PBL). However, a small number of adult bovine PBL (5 to 10%) became reactive to the antibodies when these cells were cultured for 48 hrs with con A (5 ug/ml) by flow cytometry. Bovine fetal thymus cells and sporadic bovine leukemia cells also showed reactivity with the antibodies. These results suggest that the TAA expressed on EBL tumor cells might be a differentiation antigen or an embryonic antigen which is reexpressed on tumor cells during neoplastic transformation.

A mouse monoclonal antibody (TAA-B11) produced in BALB/c mice immunized with rat mammary carcinoma cells induced by oral administration of dimethylbenzanthracene (DMBA) in Sprague-Dawley rats. In immunoelectron microscopy, it reacted with 7 of 8 mammary carcinomas of rat, whereas 7 tissues of DMBA-induced benign mammary disorders, such as fibroadenoma and mammary dysplasia, and normal mammary gland showed no immunostaining. DMBA-induced extramammary disorders (malignant and benign) and 5 normal adult tissues did not exhibit any detectable staining. TAA-B11 did not react with 15 specimens of human mammary carcinoma and 6 of human mammary dysplasia. Rat mammary carcinomas exhibited immunopositive staining diffusely in the cytoplasm. The antibody reacted with about 20% of estrogen-dependent mammary carcinoma cells with mild growing activity and with over 90% of more malignant, estrogen-independent mammary carcinoma cells with more extensively growing and metastatic activities. It also reacted with fetal hair follicles tissues of rat, especially with cells of the most outer layer of hair follicle and/or its surrounding mesenchymal cells. We consider this antigen recognized by TAA-B11 as one of oncofetal antigens associated with cell growth. We discuss the biochemical characteristics and the biological function of this antigen in ontogeny and cancer development of mammary tissue.

Monoclonal antibodies which differentiated epithelial and myoepithelial cells in the breast have been developed. Human mammary carcinoma cell line HBL-AD was used for immunization kindly provided by Dr. H. Sugano in Cancer Institute, Tokyo. Monoclonal antibodies E48B2F10 (ep-10), E1H2 (F-10) with light subgroup was examined using paraffin tissues from diseased breast by avidin-biotin-peroxidase assay. Ep-1 antibody reacted with epithelial cells, while myo-1 antibody reacted with myoepithelial cells in the mammary gland and ductule. The reaction was markedly visible in fibroadenoma, cystic disease including micro cells in duct papillomatosis and papillomas which showed clear two-cell-type structures. In the infiltrating ductal carcinoma, ep-1 antibody reacted with carcinoma cells, while myo-1 antibody reacted stromal cells rather than carcinoma cells and the reaction of myo-1 antibody against carcinoma cells was almost negative. Therefore, it will be possible that myo-1 antibody will be utilized to differentiate carcinoma and benign lesions.
MONOCLONAL ANTIBODIES AGAINST SOLUBILIZED MONOCLONES AGAINST TUMOR-ASSOCIATED ANTIGENS FROM CHRONIC MYELOGENOUS LEUKEMIA (CML) CELLS.

Three hybrid clones (NN3-I, NN3-H & NN3-S) producing specific cytotoxic monoclonal antibodies (MoAbs) against a fraction of BSA / mice spleen cells immunized with solubilized tumor-associated antigens from CML leukocytes with myeloma cell line P3HS. These clones reacted only with CML peripheral blood leukocytes (PBL)/bone marrow (BM) cells, while no reactivity was seen either with other leukemic and non-leukemic PBL/HM cells or with normal PBL cells. When tested against established cell lines of various origin and with many solid tumor cells, specific reactivity was seen with CML myelocytes alone and with the cell lines of myeloid origin. These MoAbs were identified as belonging to the IgG class of immunoglobulin by immunoprecipitation followed by SDS/PAGE. Immunoelectrophoresis and immunodiffusion characterized that these MoAbs are of IgG1 subclass. The indirect immunonephelometry on CML leukocytes revealed peroxidase localization only in the proagglutinins and in a few matured myelocytes. These MoAbs may have wide range of diagnostic, prognostic and therapeutic implications.

Generally, the cellular diagnosis is made from an evaluation of morphological and histochemical staining patterns. However, many cases remain difficult to characterize using these standards. Thus, the use of these MoAbs as cell surface markers could be helpful to improve diagnostic certainty.

THE EVALUATION OF SPENT MEDIA FROM AN ESTABLISHED PANCREATIC CANCER CELL LINE AS A SOURCE OF TUMOR ANTIGEN IN THE MICROPLATE LEUKOCYTE ADHESION INHIBITION (LAI) ASSAY


The primary objective of this study was to determine if the spent media of an established pancreatic cancer cell line could be used as a source of tumor antigen in the microplate LAI assay. The spent cell-free spent media (FSM) of pancreatic cancer cell line (PANC-1) was concentrated, incubated and evaluated in the microplate LAI assay. FSM was recognized as a pancreatic organ specific neovascular type (OSH) by 31/57 (34.1%) patients with pancreatic adenocarcinoma (PAC) and by 57/74 (7.6%) control patients. FSM was fractionated by gel filtration chromatography on a Sepharose CL-6 column. Two peaks of FSM precipitated the activity. Peak 1 with an apparent molecular weight of 20,000 was recognised as a tumour in G1 in 6/7 (6.7%) tests by PC patients but not by control patients (0/6) in the LAI test. Electron microscopy studies revealed the presence of vesicular material in peak 1. Peak 2 was opened on a pancreatic in 9/10 (90%) tests by PC patients but not by control patients (0/6) in the LAI test. Each and every peak was reactive specifically with the microplate LAI activity by an indirect IF (ELISA), i.e. anti-144 (Thompson, Int. J. Cancer:35, 77, 1985) recognized peak 1 but not peak 2 in the microplate LAI assay. The results of these studies indicate that pancreatic cell activity in the spent media is due to antigen present in medium retrieved vehicles and in soluble form.

THE UNIQUE SUBUNIT STRUCTURE OF CARCINOFOetal FERRITIN ISOLATED FROM CANCER CELL LINES BY ANTI-HUMAN PLACENTA FERRITIN M MONOCLONAL ANTIBODIES

S. H. MITRA, J. J. NADKARNI, J. S. NADKARNI, L. S. NADKARNI, and D. BANDYOPADHYAY.

In many tissues involved by cancer, the level of ferritin is elevated. It was suggested that they have specific carcinofetal ferritin sequences or they are acidic because of a higher proportion of the normal H subunit (20 Kd) than the L subunit (18 Kd). The use of the monoclonal antibodies (MoAbs) developed in our laboratory against placental ferritin, H-9 which is specific to placenta ferritin, and G-8 which has a specificity common to all ferritin isoforms, enabled for the first time to characterize the structure of carcinofetal ferritin synthesized by breast cancer cell lines (HT-29 and MDA-MB-231). It was found that these cells synthesized two types of molecules: one was precipitated by G-8 MoAb and constituted 3 subunits L (18 Kd), H (20 Kd) and a third subunit not described previously of a high molecular weight (43 Kd). The second was precipitated by H-9 MoAb and consisted of the high molecular weight 43 Kd subunit only. In contrast, HBL-100 cell line which originated from normal breast epithelium, synthesized ferritin which consisted mainly of L subunits with one H subunit (20 Kd). Gold monol subunit.

It is suggested therefore that the 43 Kd subunit is characteristic of oncocyfin ferritin derived from breast cancer cells. Moreover, since H-9 MoAb reacted exclusively with these 43 Kd subunit it is of significance as a potential tool in cancer diagnosis. In fact, ferritin reacting with H-9 MoAb has been detected in the blood of breast cancer was successfully used as a marker for the diagnosis of breast cancer.
THE RELATIONSHIP BETWEEN CEA STAINING IN PRIMARY BREAST CANCER AND SERUM CEA CONCENTRATION AT PRESENTATION OF STAGE IV DISEASE. M.R. Williams, J. Elkin, Jane A Bell, Hospital, Nottingham, England

Forty-five paraffin embedded primary breast cancer tumours have been assessed for their ability to stain with a polyclonal antibody raised against CEA (Baker). All tumours were stained using an immunoperoxidase technique and have been graded (1-3) for staining intensity (1 - A strong staining, 2 - An intermediate staining, 3 - A weak staining) independent of clinical information. At the presentation of symptoms, distant metastases were found in 32 patients. A clear relationship exists between CEA staining intensity of the primary tumour and the development of distant metastases. CEA staining intensity in stage IV disease has a significant influence on survival. Conclusion: 1. A strong staining in the primary tumour indicates a shorter disease free interval. 2. Sequential CEA estimation in these patients may be of use in assessing response to systemic therapy.
ENDOSCOPY DEPARTMENT OF THORACIC SURGERY UNIT, EXPERIENCE FROM 1970 EXAMINATIONS.

D. Antypas and St. Makaris.

Thoracic Surgery Department, Division of Endoscopy, Nafplia's Memorial Hospital, Piraeus, Greece.

We present the experience of our special team in lung tumor endoscopy. One thousand patients involved in a protocol of a study in which we researched:

a. the size of the tumor and the involvement of the bronchial tree.

b. the histology type and the special endoscopic findings.

c. the position of tumors and the involvement of the bronchus.

d. the findings in several stage of the disease.

Our results indicate that the most after cancer involves the bronchi and the involvement of bronchial tree and there is no correlation with the size of the tumor. In contrary no one correlation exists between the stage of the disease and the endoscopic findings.
INCIDENCE OF THE COLO-RECTAL LESIONS REVEALED BY ENDOSCOPIC MASS SCREENING IN JAPANESE ADULTS

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The results of endoscopic examination of the whole colon and rectum in recent 2 years (1981-1983) of our hospital were studied. 2,220 persons, 1,886 males and 334 females, admitted to our hospital in the 2 years to receive endoscopic screening for cancer detection of the gastrointestinal tract with no symptoms related to gastrointestinal tract or, if any, very slight abdominal discomfort such as light pain or nausea. The peak age for either sex was in the fourth decade and the mean was 37.8. The lesions in colo-rectal regions were found in 571 persons (25.8%) in 2,220 persons. 388 cases (17.5%) of the elevated lesions, 138 cases (15.8%) of the polyps, and 87 cases (3.9%) of the diverticulosis were recognized endoscopically. All of biopsy material, mechanically polypectomized polyps and the resected materials were examined histologically. 4 cases of adenocarcinoma, 1 case of early carcinoma, 288 cases of adenoma and 279 cases of non-adenomatous polyps were confirmed histologically. As mentioned above, about 3.4% of the persons examined had little abdominal symptoms, therefore, it can be said that the population examined this time was composed of healthy people. The fact indicates that the distribution of the colo-rectal lesions detected in this study represents the natural distribution of the colon diseases of Japanese adults.

STUDIES ON EARLY GASTRIC CANCER DETECTION IN THE REGION OF SOUTH-EAST POLAND

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Endoscopic examinations performed in three groups of patients aimed at early gastric cancer detection. Group I included 3,681 patients attending the outpatient's gastroenterological departments because of the initial symptoms of upper section of gastrointestinal tract. Group II consisted of 2,761 patients requiring endoscopic examination because of the diagnosed disease of stomach or duodenum, who in the opinion of the leading physicians required surgical treatment. Group III included 3,315 factory workers treated as a sample of general population.

Degree of early gastric cancer detection was evaluated on the basis of the percentage of early gastric cancer as compared to the total number of gastric cancers detected by endoscopic examinations.

It was discovered that the highest percentage, i.e., 24.0%, in relation to the total number of gastric cancers detected by endoscopic examination characterized the group of patients attending the outpatient's gastroenterological departments with the initial symptoms of upper section of gastrointestinal tract.
PREOPERATIVE AND PALLIATIVE ENDOSCOPIC PAPILLOMY AND ENDOSCOPIC-TRANS-PAPILLARY BILE DUCT DRAINAGE BY A PIGTAIL-CATHETER

A. Hölzgrove, G. Kautz, G. Roland, C. Pfieller, B. Reers, Surgical Clinic of the Univ. of Münster, West-Germany.

The endoscopic bile duct drainage was attempted in 70 patients with tumor-induced occlusion of the common bile duct and was achieved in 41 cases (59%). The second operation was performed in another 11 patients. In 11 patients a pancreatid carcinoid tumour and in 5 patients the endoscopic drainage was performed just as a palliative treatment because of age and surgical risk. Four of the patients who had undergone surgery are still alive (4, 6, 28 and 40 months past surgery), two died 15 months after the surgery. The survival time of the patients with endoscopic drainage alone was 1 - 14 months. In 10 of the 31 patients with carcinoma of the pancreas the pancreatid drainag was not successful. The success rate was increased, however from 74 to 90 % after using modified guiding wires and an endoscope with 2,8 mm side canal. The serum-bilirubin level decreased 1 - 3 mg/ dl/day.

ORAL CLAIM CELL TUMOR OF THE ESOPHAGUS, CLINICAL, PATHOLOGICAL AND IMMUNOHISTOCHEMICAL STUDY OF 5 CASES. P. Scappini, F. Hernandez, J. Stelz, P. Scappini, F. Scappini, Division of Internal Medicine* and Institute of Anatomic Pathology*, S. Chiara Hospital, Trento, Italy.

Granular cell tumor (GCT), or granular cell myoblastoma, or myoblastoma myoepitheliale can occur on any site along the gastrointestinal tract, particularly in the oral cavity, particularly along the base of the tongue, and for the skin (1). Considering that, only 60 cases of esophageal GCT, have been reported, out of 1.200 of these tumors described since the first paper by Albrichoff in 1926, we can conclude that esophageal GCT is a rare site for this neoplasm. This lesion frequently appears as a non-specific painless mass and it is rarely correctly diagnosed prior to biopsy or surgical excision. Histogenesis has been subject of controversy, and immunohistochemical studies have not yet resolved this question. Here we report 5 cases of esophageal GCT discovered in our institutions from 1979 to the present. The patients (2 male and 3 female) aged from 31 to 66. The lesions were all demonstrated on endoscopy performed for atypical gastrointestinal symptoms (epigastric pain, burning). Gastrintestinal pathology (i.e. bulbar ulcer, diffuse erosive gastritis or bulbar duodenitis) could be observed in every case. The mean distance from the incisor teeth and the tumor was 3.2 ± 6 cm. The mean dimension of the lesion was 5.1 ± 2 cm. Immunohistochemical study of the tumor cells was performed. S-100, O-1-antitrypsin and O-1-antichymotrypsin immunoreactivities were tested. Our experience, as regard the localization of S-100 protein in the GCT, parallels that of others authors (2, 3). The evidence of a Schwann cell origin of these neoplasms. Conversely, light, tissue did not show immunoreactivity for O-1-antitrypsin and O-1-antichymotrypsin antigens. The prevalence of epigastric pain in our patients is probably related to their particular gastrointestinal conditions, since dysphagia and substernal discomfort are the most common presenting symptoms. It is our opinion however, that the GCT of the esophagus will be more commonly encountered as more endoscopy is performed.

References

A NEW DIAGNOSTIC EQUIPMENT FOR CANCER BY MEANS OF EXCIMER DYE LASER

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Hematoporphyrin derivative has an affinity for malignant tissues and emits red fluorescence when exposed to exciting light. Therefore it is theoretically possible to make a diagnosis of cancer localization by observation of the fluorescence. A krypton ion laser is used as a light source for excitation of hematoporphyrin derivative. In 73 out of 78 cases with lung cancer the fluorescence could be recognized by this method. However with this previous methodology it was difficult to examine the precisely localize the lesion because of the darkness due to a lack of white observation light and also to clarify the borderline between normal tissue and malignant tissue because the autofluorescence from normal tissue with a peak at 580 nm wavelength. The authors have been developing a new imaging system for cancer diagnosis using an excimer-dye laser. This excimer laser has 368 nm ultraviolet beam emitted by XeCl. Simplification and accuracy of the fluorescence diagnostic procedure was achieved by use of the nature of the pulse and a polychromator. The diagnostic system permits endoscopic examination under ordinary observation light. The investigations were performed in the animal tumor models which are FH- mouse (breast cancer) and beagle dog (esophageal cancer). Hematoporphyrin derivative was injected intravenously in beagles and intraperitoneal injection were performed in the mouse. Tumor tissue showed a distinct fluorescence and surrounding tumor tissue revealed relative fluorescence, however no fluorescence could be observed in normal tissues 72 hours after hematoporphyrin derivative administration. This system is still under development and will be completed in the near future.
**THE USE OF HYSTEROSCOPY IN ONCOLOGY**

2738

M. Popov - Rea. Inst. of Oncology, Sofia, Bulgaria

The contact, survey and microhysteroscopy are being used for the early diagnosis of the endometrial and endocervical cancer at the Gynecologic Clinic, Rea. Inst. of Oncology, Sofia. The hysteroscopy and the endometrial curettagewere used by 1400 patients. The data from the hysteroscopic were compared to the hystological results. The accuracy of hysteroscopy was 97.39%. This method was used also to determine the intrauterine tumor progress and subsequently to indicate an individual treatment. The first attempts have been made for LASER-treatment under hysteroscopic control.

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**SKIN MELANOMA**

2737

A. M. Caraballo et al. - C. R. Inst. of Oncology, Sofia, Bulgaria

Between 1957 and 1976, 184 patients with malignant melanomas were treated in our hospital. The ulcer incidence seemed to increase over the years. The male/female ratio was 1/1.

The most frequent localization of the tumor was the extremities. 10 patients had multiple tumors classified by tumour (T) classification, T3 or T4 in 11 cases and T4 in 7 cases.

Although not completely cleared, our cases were clinically advanced since 50% of the patients were of the medium type IV; invaded levels II-IV and 4% were thicker than 1.5 mm.

Surgery was performed in 11 patients; in 10 excision was done and skin graft was applied in one case (5%).

Histologically, a primary melanoma in the extremities was 100% of the cases. In 31 of the patients there was local recurrence in patients with melanoma III+IV only in level II and/or B know thicknesses were greater than 0.75 mm.

Of these patients having local recurrence, 10 had microscopic metastases in the lymph nodes. They were the high risk group of Stage IV melanoma with bad prognostic factors (ulceration, maximum thickness greater than 1.5 mm, and Clark level IV or V) who had high probability of LNM metastases statistically significant (p<0.05).

Loco-regional morbidity was high, 43% mostly in melanomas of the lower extremity. We had no surgical mortality.

The 6-year survival rate calculated by the actuarial method was 60%. Stage I 51% and Stage III 17%.
PREPARED FOR: RHOADES, H. H., AND BERRY, R. R.


test.

The skin and its appendages, particularly the epidermis and the dermis, play an important role in the body's protection against various environmental insults. The epidermis, being the outermost layer of the skin, is subjected to a myriad of external factors such as sunlight, friction, chemical, and bacterial agents. This layer is composed of several layers of keratinized cells, which provides a barrier against water loss and infection. The dermis, on the other hand, is the inner layer of the skin and contains blood vessels, nerve endings, and connective tissue elements which are crucial for the skin's functionality.

In the context of treatment methods, both surgical and medical approaches are employed. Surgical treatments often involve the removal of the affected skin area, which can be done through excision or more minimally invasive procedures like biopsies. Medical treatments, on the other hand, may involve topical or systemic therapies, which target the skin or the underlying tissues to treat conditions such as infections, diseases, or injuries.

In summary, the skin and its appendages are integral components of the body, providing protection, sensory input, and a vast array of functions. Understanding the structure and function of the skin is crucial for the development of effective treatments and the management of skin-related disorders.
SURGICAL TREATMENT OF RECURRENT MELANOMA. C.P. Karakousis
M.A. Niemi, J.J. Enrich, E.O. Holyoke. RoseWell Park Memorial Institute, Buffalo, New York, U.S.A.

The overall estimated 5-year survival rate for 56 patients with ilioinguinal node dissection and histologically positive nodes (mean number of positive nodes 5.4) was 40.1%, being 36.7% for 48 patients with palpable, positive nodes and 49% for 11 patients with non-palpable positive nodes. The 5-year survival rate was 46.0% for 38 patients with positive inguinal nodes only, and 29.0% for 18 patients with clinical and histological involvement of both inguinal and deep nodes. Among patients with palpable involved inguinal nodes, 44% had involvement of the deep nodes also. None of the patients with histological, but non-palpable involvement of the inguinal nodes had positive deep nodes. The estimated 5-year disease-free survival rate of another group of 66 patients who had axillary nodal metastases and histologically positive nodes (52 palpable) was 23% (mean number of positive nodes 5.3, median 3.3), being 60% when one node was involved, 32% when two nodes were involved and 8% when three or more nodes were involved (P<0.001). In another group of 160 patients with metastatic melanomas, complete resection of the gross tumor was accomplished in 33%. Among the latter the estimated 5-year survival rate was 41%, being 23% for those with solitary lesions and 29% for those with subcutaneous metastases removed completely. Chemotherapy with DTIC or nitrosourea combinations was used. The 5-year survival rate of patients treated with chemotherapy alone was 0%. In conclusion, ilioinguinal dissection with in-continuity removal of the deep nodes by dividing the inguinal ligament provides an improved survival than previously reported including patients with positive deep nodes. Survival following node dissection varies according to the number of histologically positive nodes. Resection of hemotogenous metastases is indicated when they are solitary or involve subcutaneous sites exclusively.

HYPERTHERMIC PERFUSION USING DTIC IN PATIENTS WITH MALIGNANT MELANOMA OF THE EXTREMITIES

S. PlesniCar, J. Rudolf and B. Zakotnik, The Institute of Oncology, Ljubljana, Yugoslavia.

Based on previous studies which demonstrated synergy between interferon and cytotoxic drugs, a Phase II trial was designed for treatment of patients with advanced malignant melanoma. Human leukocyte alpha interferon was applied in doses 1.5x10^6 units 3 times weekly for three weeks. During the second week epidoxorubicin (70 mg/m^2) combined with dacarbazine (250 mg/m^2/5 days) was applied. Courses were repeated every 4 weeks. Fourteen patients (age 25 to 70 yrs) entered the study. The involved sites were the skin, subcutaneous tissue, lymph nodes, subcapsular glands, pleura, peritoneum, central nervous system, lung, skeleton and liver. There were 2.9 metastatic sites per patient. Performance status ranged from 20% to 90%. To-date the 14 pts have completed at least two courses of combined treatment. The treatment was stopped when the maximum dose of epidoxorubicin was reached. In two pts a complete remission was achieved, in 3 a partial response, no change was observed in 4 patients, and in 3 patients the disease progressed. Among the two complete responders, one had metastases in the subcapsular glands and subcutaneous metastatic nodules, the second had lymph node and skin metastases. The three pts with progressive disease had metastases in the liver, bone, lung, lymph nodes and skin. During interferon treatment fever and chills were observed in the majority of pts. Nausea and vomiting appeared during the application of cytotoxic drugs. In general the treatment is well tolerated. A synergistic activity of interferon with epidoxorubicin and dacarbazine seems to be effective, however, time to maximum response and optimal duration of treatment remain to be determined.
A new international system for staging lung cancer has been accepted by the Union Internationale Contre Cancer, The Japanese Cancer Society, The International Association for the Study of Lung Cancer and the American Joint Committee on Cancer. The new system retains the valid and useful components of present systems and has new elements to meet the needs of treatment specialists for classification relating to contemporary treatment planning—as well as for prognosis. Six categories of patients with similar prognostic expectations and therapeutic options are identified by the TNM definitions and stage grouping rules.

Stage I refers to patients with carcinoma in situ. Stage II includes only patients with the best prognostic expectations—those with T1 n0 m0 and no evidence of metastasis (T1 N0 M0; T2 N0 M0). Stage II disease includes patients with T1 or T2 tumors and metastasis to the intrapulmonary (including hilar) lymph nodes (T1 N1 M0, T2 N1 M0).

Stage IIIa disease designates those patients, usually within the realm of the surgical oncologist with limited extrapulmonary extension of the primary tumor, T2, and ipsilateral mediastinal node metastasis, N2, but no distant metastasis (Any T2, Any N2 M0). Stage IIIF includes patients with more extensive extrapulmonary extension, T4, or malignant pleural effusion, T4, and those with metastasis to the contralateral mediastinum, hilum, or ipsilateral or contralateral supravacular or scalene lymph nodes, N3 (Any T4, Any N3 M0). Stage IV is reserved for patients with metastasis to distant sites, M1. These recommendations for staging fill the need for specific definitions for "limited" and "extensive" disease that can be reproduced and compared. They meet the goal of modifying present classifications to provide specific definitions for "limited" and "extensive" disease that is responsive to the needs of all those involved with the study and treatment of this disease.

In conclusion, in our experience bone biopsy discovered row metastases were seen at this second analysis. Given the low yield of positive marrow involvement in our cases only 6% had the marrow as the only site of metastasis. In 1 case only 6% had the marrow as the only site of extrapulmonary disease. Of the positive marrow biopsies we re monolateral.

Given the low yield of positive marrow involvement in our series, we performed additional histological sections (one section 4 mm thick every 4th cm to 7th cm length) on adequate specimens (1 cm length) no more marrow metastases were seen at this second analysis. In conclusion, in our experience bone biopsy discovered only a small number of cases that were classified an extensive on the sole basis of Marrow involvement (3%).
PAPYRUSITIC LIVER VENOUS TUMOR: A MODEL FOR CLINICAL LUNG CR tolerant of standard therapy.


Department of Surgery, Tokyo Medical School, Tokyo, Japan.

Twenty patients with lung cancer were studied in this research. Photodynamic therapy was performed for its potential to reduce the recurrence of tumors. Specifically, patients had stage II disease. In Stage II disease, photodynamic therapy was suggested in all 20 cases.

The main purpose of this research was to evaluate the potential of photodynamic therapy in lung cancer. The results showed that photodynamic therapy can effectively reduce tumor recurrence. In Stage II disease, the survival rate of patients treated with photodynamic therapy was significantly higher compared to patients treated with standard therapy.

This study suggests that photodynamic therapy can be an important tool in the treatment of lung cancer.
INTRAPEERIC EXPANSION OF DIFFERENTIATED FORMS OF LUNG CANCER (DATA OF EXPLORATIVE THORACOTOMY).

I.Y. Kasianenko, K.V. Jorgina, V.V. Sycheva, A.I. Lisitsa, E.M. Yermakovsky, N.E. Kvetovsky Institute of Oncology Problems, Kiev, USSR

With the purpose of establishing the rationality of conservative treatment of lung cancer patients after exploratory thoracotomy, we evaluated data on extension of the lesion in 154 patients who underwent this procedure. Squamous cell carcinoma was found in 74 patients, adenocarcinoma in 50 patients. Operative treatment was preceded by clinical, bronchoscopic and roentgenologic examination. The cause of inoperability in 71 patients with squamous cell carcinoma was involvement of the mediastinal lymph nodes, in 15 - extension of the lesion to the adjacent organ and large vessels, in 15 - associated involvement of lymph nodes with infiltration of the adjacent organs, in 20 - involvement of the peripheral and visceral pleura, in 12 - tumour involvement of the large vessels, adjacent organs and pleura. In adenocarcinoma these values were correspondingly 117, 15, 16, 28, 14%. Thus, these data suggest the rationality of using in these cases telegraphametaphy with psychosomotherapy. Data on the information value of current methods of examination of lung cancer patients for determination of the kinds of chemoradiation treatment after exploratory thoracotomy will be discussed in the presentation.

From 1976 to 1984 3 groups of patients with operable cancer of the lungs were formed by method of blind randomisation. Patients with non-differentiated forms of the carcinoma and patients over 65 years of age were excluded. Group I consisting of 30 patients includes cases where only radical operative treatment was performed. A 4-course pre-operative chemotherapy with Cyclophosphamide, Methotrexat and 5-Fluorouracil was performed upon 35 patients forming group II. Group III includes 31 patients who were treated to pre-operative X-ray therapy (5 x 4 Gr 36,57 cGy).

34.5% of I group of patients survive 3 years and 29.51% survive 5 years or more, 43.80% of II group of patients survive 3 years and 37.46% - 5 years or more, 45.76% of III group of patients survive 3 years and 36.59% - 5 years or more. Combined treatment definitely improves results mainly in the first 3 post-operative years.

2760 Survival In Operated Bronchus Carcinoma Patients According To Tumour Volume And Immuno Response E. Kayser, H. Bulsbruck, H. Ebert, H.H. Kerke

Tumour volume of 282 bronchus carcinoma patients was measured and immuno reaction of host tissue was analyzed by grading amount of lymphocytes, plasmacells, macrophages at tumour boundary. Lymphocytic subpopulations of 46 surgical specimens were analyzed by use of monoclonal antibodies (OKT-sera). Survival of patients was measured by KAPLAN-MEIER estimations. Survival depends strongly on pT-, pN-stage and upon tumour volume. Maximum tumour diameter is only a fair estimator regarding prognosis of patients. T-helper cells in lymphocytic subpopulations at tumour boundary were increased, T-suppressor cells (cytotoxic cells) were remarkably decreased. Immuno response of host tissue has important influence on survival of operated bronchus carcinoma patients in tumours with similar tumour volume.

2761 MALIGNANT PERICARDIAL EFFUSION TREATED BY DRAINAGE AND INTRACAVITARY BLEOMYCIN. A. Volckaert, L. Van Belle, V. Taeuman, Department of Internal Medicine, Oncology and Cardiology, Academisch Ziekenhuis, Vrije Universiteit Brussel.

Pericardial tamponade is an uncommon complication of malignant disease, but an asymptomatic involvement of the pericard is estimated to occur in about 10% of disseminated cancers. Since such a situation is often life-threatening and requires urgent therapy, local treatment has to precede systemic chemotherapy as first choice. There is no general non-surgical therapy without complications. Recently we introduced a combined technique of catheter drainage and intra-cavitary application of bleomycin. This method and our first results are described in four patients, with a pericardial tamponade secondary to a bronchial carcinoma (3 oat-cell carcinoma's, 1 adenocarcinoma and 1 squamous cell cancer). Diagnosis was always confirmed by cytology of the pericardial fluid. A pigtail catheter (French 6) was introduced into the pericardial sac using a Seldinger technique through a sub-xyphoidal approach. After X-ray controlled positioning, the fluid was removed over a period of 24 hours. Once the drainage was less than 100 cc/24 hours, bleomycin (30-60 mg) was injected and 10 min later the catheter was definitively removed. We observed no local or systemic complications of this technique. Echo cardiological control 30 days later, showed no recurrence in all cases. Survival, in combination with systemic chemotherapy, was excellent (10-40%) and there was no local recurrence at any time during the evolution, as confirmed in two patients by autopsy. From these preliminary results we can conclude that the combined technique of drainage and intra-cavitary bleomycin application is a new, safe and effective local therapy for malignant pericardial effusions.

2762 CLINICAL FEATURES OF PLEURAL MALIGNANT MESOTHELIOMAS. A. Károlyi, E. Kanitz, E. Juhász

KONÁNY NATIONAL INSTITUTE OF TUBERCOLOUSIS AND PULMONOLOGY, BUDAPEST, HUNGARY.

33 histologically proved pleural malignant mesotheliomas patients were treated during the period 1982-1984 in Hungarian pulmonological institutes. Out of this population 7 were detected by mass miniature radiography. The authors examined the feasibility of arriving at a diagnosis, the therapy and its impact on the survival rate. The most important conclusion is that the longest survival is found among the operated patients.
SUPERIOR VENA CAVA SYNDROME. BY-PASS PROCEDURES IN ACUTE CASES.

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Thoracic Surgery Department. Metaxa's Memorial Hospital. Piraeus - Greece.

The superior vena cava syndrome has as mainly cause the lung cancer. These cases are inoperable and we try to treat them with combined chemotherapy or radiotherapy. In the patients with a rapid proliferative disease where there is no time to practise the above treatment we perform a by-pass technique with Goretex ring between jugular or axillary veins and femoral veins. This produce a better general condition of patients giving us the time to treat later with the standard methods.

We present here our experience with twenty patients to whom different by-pass techniques were performed in a period of three years.


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221 patients were attended on account of gastric malignancy at our Department from 01.01.1980, to 31.12.1984. During this 5-year period the esophago-gastro-duodenoscopy became routine procedure in the diagnosis of the gastric disorders. This period has been compared with a previous 5-year period (1971-1975), when we did not perform endoscopy at all. From 1980 till 1984 the annual number of the endoscopic examinations doubled but the number of the discovered tumours did not change essentially. In fact the number of the patients underwent an operation decreased year by year. On the other hand the gastrectomy rate increased from 5% to 26% regarding the former 5-year period. A real early gastric cancer was discovered only in 4 cases (2%) at our patients. Further 18 cases (8%) were so-called "superficial-type" classified in the I/b stage, 14 cases (6%) were ulcer-cancer. The tumour arose in the pyloric and antral part of the stomach in 43,5% (96 cases), it was positioned in the middle part in 19,5% (49 cases) and in the upper third in 31% (69 cases). We discovered a stomach-remnant cancer following a partial gastrectomy in 13 cases (6%). The rate of the proximal tumours increased with 10% regarding to the former 5-year period. There were 37% total gastrectomy, 5% proximal partial gastrectomy and 58% distal partial gastrectomy of the 168 operations performed in this period. The total lethality was 6,5%.

The routine endoscopy has to be considered essential for the early diagnosis and for the improvement of the results. To this latter the extension of the operative radicality is necessary.


From 1971 through 1984, 49 new cases of gastric cancer were seen. From this thirty nine patients (9,3%) with early gastric cancer (ECG) were studied. The male/female ratio was 1.7, and the mean age was 57.9 years. The ECG was diagnosed endoscopically in 46,4% and by radiographic methods in 27,3% of the patients. Endoscopic types IIC and III were the most found. The ECG was localized in the antrum in 65.7% cases, one case was localized next to the gastric cardia, and another in the gastric stump after previous gastrectomy. There were no spread disease except for regional lymphnodes which occurred in 9,3% of the cases. The surgical approach was subtotal gastrectomy with radical lymph node dissection performed in 26 cases and total radical gastrectomy in 6 other cases. There was no surgical mortality. One patient was reoperated on because of an afferent loop torsion in a Billroth II reconstruction.

Four patients were lost in the follow up. From the eighteen patients operated on until five years ago, ten were traced for more than five years and are free of disease. The remain 17 cases operated on after 1979 are alive and free of illness.
MONDAY, AUGUST 25, 1969

L-51: STOMACH CANCER

2766

The patient, Mr. J. D., a 51-year-old man, was admitted to the hospital on August 20, 1969, for evaluation of an abdominal mass that had been noted for several months. The patient had no significant past medical history, and his physical examination was unremarkable.

Mammography of the abdomen revealed a mass in the upper abdomen, just to the left of the midline. A Barium meal and enema examination showed no evidence of gastrointestinal obstruction. A Technetium 99m scan revealed a focal area of increased uptake in the region of the stomach.

A biopsy of the mass was performed, and the biopsy specimen was sent for histological examination.

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The histological examination of the biopsy specimen revealed adenocarcinoma of the stomach. The patient was scheduled for surgery to remove the tumor.

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A subtotal gastrectomy was performed, with the tumor being resected. The patient tolerated the procedure well, and he was discharged from the hospital on August 27, 1969.

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The pathologist's report noted that the tumor was a well-differentiated adenocarcinoma of the stomach. The patient was referred to medical oncology for further evaluation and treatment.
2770 RADIAL SURGICAL TREATMENT OF STOMACH CANCER: N. Georgiev, S. Ivanov, E. Jeramoy, Res. Inst. of Oncology at the Med. Academy, Sofia, Bulgaria

We have studied 3 groups of factors influencing the outcome of a radical operation in 2000 patients: the tumour spread, morphological and biological features and tumour-body relations. The penetration, the lack of lymph metastases and the tumour size proved to be of importance. Results - were unfavourable in treatment of PI, N2, N3, tumours from 5 - 10 cm and duodenal infiltration. Differentiated giant tumours with a well defined stromal reaction showed favourable development. Expressed immunity supression was established in young patients with undifferentiated tumours, increased much in the case of a stromal reaction. In such cases dissemi nation was present in small-sized tumours. Results were usually better in women and also in young patients with favourable biological features. Anaplastic forms had the highest metastatic index (22.11%), while the lowest level (12.20%) was recorded in well differentiated adenocarcinoma. The authors suggest a differentiated approach in the radical surgical intervention and in some cases organ-preserving operations are recommended.


According to the traditional experience, the mortality of gastrectomies (sleeving and gastroduodenal fistula) outweighs the morbidity of gastroujunctomy (auricular, appertent / entfernt-loops syndrome, alkaline reflux gastritis, pancreatic fistula, acid reflux esophagitis). Nonetheless, the occurrence of these complications very often requires conversion from gastroujunctomy (GJ) to gastroduodenostomy (GD). Furthermore the probability of a primary on the gastric stump is as high as 10% after GD, and negligible after GJ. The main purpose of the present study is to invalidate the current concept of major surgical risk and higher local recurrence rate related to GD in the management of distal gastric cancer, when the latter is performed with the new available tools. After the standard procedure for subtotal gastrectomy (extensive Hyster's mobilisation of duodenum and head of pancreas, and section of phrenico-esophageal ligament), the section of the stomach begins at the point of Van Gastro (GIA stapler transverse to greater curvature), then isoscelaristatic gastric tube is performed (GIA parallel to greater curvature) ending at the cardiac. Left gastric artery and vein with certain nodes are left within the value of resection. Warm-string valve is performed 1 - 2 cm. Distal to pylorus and gastric-tube-duodenostomy is performed by E44 or 115 stapler (26 or 31 mm). During the last five years, 27 consecutive patients have been treated in this way in our departments: 19 for cancer and 2 for benign diseases. Pathological staging (UICC 76) resulted: I - 7, II - 6, III - 4, IV - 3. Operative mortality was absent. Early complications included a sub-serous abscess and a lueta-dramatic abscess (both healed spontaneously); delayed anastomotic stenosis was observed in 2 cases and managed by endoscopic dilatation. After a median follow-up of 30 months, we have observed no loco-regional recurrences. 4 patients developed distant metastases, 3 of them are still alive; 2 patients died for causes unrelated to cancer, 11 and 40 months after surgery.


It has been generally accepted that a total gastrectomy for a gastric cancer is superior to a subtotal gastrectomy for the upper third of stomach is combined with a splenectomy, in order to dissect possibly metastasized lymph nodes in splenic hilus. Then the organ function of the spleen, has been neglected. Recently, however, there have been found a lot of immunological and hematological evidence against cancer growth and the spleen is one of the most important organs in these fields.

Results: Only at the 13.3% out of 155 splenectomized patients the metastases were histologically determined and the splenectomy were justified. In other words 86.7% cases the splenectomies could not be justified. Postoperative survival rates were compared between the groups of cases splenectomized and non-splenectomized in same cancer stage. In the each stage there was found no statistically significant difference, but that of non-splenectomized cases seemed slightly better than that of splenectomized cases. The postoperative change of non-specific immunological, hematological parameters, i.e. skin reactions to PPD and PHA, the number of lymphocytes, T- and B-cells, serum albumin, various immunoglobulin, compliments, thrombocytes in peripheral blood showed more unstable in the splenectomized group. These results suggest that the indication for the splenectomy should be more strict and that the spleen could be necessary for the immunotherapy, i.e. with OK-432.

2773 "ADVANCES GASTRIC CANCER" (AGC) SURGICAL TREATMENT: J.A. Ans-Cruz, R. Gonzalez, C.A. Lonco, C.A. Alvarez Rennert, J.C. Stiel, C.A. Branida, A. Lopez Rosende, S.M. Quintana, B. Pardaro, Departament Surgery Army Central Hospital, Teaching Hospital, University of Buenos Aires, Av. Luis Maria Campos 726 Buenos Aires, Argentina.

Between the years 1960/1980, have been operated 210 patients with AGC, according to the embryiotic developing of the neogastroanterior and posteriorly, the mesenteric superior arc. The pancreatic cord and tail are considered the limit that we call the superior neogastrectomy. In order to test this hypothesis we have made, in 107 cases Super Amplified Total Gastrectomy (SATC) with partial panproctectomy, glandular-recto-lymphadeneotomy of the entire region and splenectomy and splectomy. In 153 cases Total Gastrectomy and splectomy in 57 cases and unselecte pistonial surgery in 46 cases. We used some techniques to reestablish the digestive tract (Micle - Longmire, Tomoda I-II, "Y" of Roux, Rossco Graham with a Braun at the bottom etc.) with the later technique the morbidity index was reduced, the falling of wellbeing got better for so long, the nutritional state was improved and the immunity index was increased as well. The 92% of the tumores were adenocarcinomas. We were 74.5% in mesmagnification tumors. The results at 1, 2, 3, 4 and 5 years were, respectively: 35.5%, 37.5%, 32.4%, 27.1% and 21.4%. This percentage is similar to the classic data that we have obtained in our previous works. During the last five years 43 patients have been operated in this way in our department, 19 for cancer and 24 for benign diseases. Pathological staging (UICC 76) resulted: I - 7, II - 6, III - 4, IV - 3. Operative mortality was absent. Early complications included a sub-serous abscess and a lueta-dramatic abscess (both healed spontaneously); delayed anastomotic stenosis was observed in two cases. After a median follow-up of 30 months, we have observed no loco-regional recurrences. 3 patients developed distant metastases, 3 of them are still alive; 2 patients died for causes unrelated to cancer, 11 and 40 months after surgery.

The aim of this report is to present a prospective study of total gastrectomy versus sub-total gastrectomy on 121 cancers of the stomach, localized in the lower half of the organ. For all cases the histology was diffuse-type, according to Lauren. All the cases that underwent a “radical” operation were admitted in this study.

Criteria for exclusion was:
- age of the patient above seventy
- 11 and T4 stages.

The recurrence occurred in 53% of the cases within 12 months, and in 95% of the cases within 48 months. Metastases in the liver and recurrence in the surgical bed were the first symptom of recurrence in nearly 90% cases. The 5 year survival for the patients who underwent total gastrectomy resulted of 50%, and for the patients who underwent sub-total gastrectomy resulted of 17,6%. The difference is statistically significant (p < 0.01): this result suggests that sub-total gastrectomy is an inadequate surgical treatment for diffuse-type cancer of the stomach.


The paper is a review of the studies carried out at the Inst.of Oncology during the past 5 years. Mortality of 19.0% was caused by suppurative complications following stomach resection. Analogous microflora was established in the stomach content of 97%, in the tumour of 83% and in the regional lymph nodes of 63% of the operated subjects. The higher the pH of the gastric juice, the bigger the incidence and the amount of microorganisms and in the majority of treated patients these were above the threshold value (5x10^5/ml). In 20 cases with stomach resections treated with a mixture of 2 mg of Metronidazole (Flagyl) and 20 mg of 5-nitro-S-hydroxichinoline (5-Nitrox) in 100 ml of water through the nasogastric tube no suppurative complications occurred.


Prognosis of resected stomach cancer patients was studied by means of multiple regression analysis and considered to the effect of blood-transfusion. As for 629 cases of resected stomach cancer charged from Jan. in 1970 to June in 1985, multiple regression analysis was done using survival time as dependent variable and sex, blood-transfusion, stage, curability as independent variables.

Results were obtained as follows:

\[ Y = 1.2062 + 0.313X_1 - 0.062X_2 - 0.150X_3 - 0.1794X_4 \]

\[ X_1 = \text{sex}, X_2 = \text{transfusion}, X_3 = \text{stage}, X_4 = \text{curability} \]

T values of each independent variables were calculated using standard error, and obtained as: sex: 1.5419, transfusion: -3.1095, stage: -3.1301, curability: -5.1552

Conclusion: blood-transfusion was found as a disadvantaged factor to the prognosis of resected stomach cancer.

2777  PERTOPERATIVE NUTRITIONAL SUPPORT IN PATIENTS WITH GASTRIC CANCER. F. Kallfarnantos, C. Tzoracoletakis, A. Bibas and I. Andreouakis, University of Patras, Department of Surgery, Patras, Greece.

In a five years prospective clinical study the contribution of perioperative nutritional support into the decrease of operative morbidity and mortality of gastrectomized patients with resectable gastric cancer and malnutrition, was assessed. Forty three patients were randomized in three groups (A, B, C).

Group A consisted of 10 patients operated without any nutritional support. Group B consisted of 18 patients with 0-5 days preoperative and 8-28 days postoperative nutritional support by total parenteral nutrition. Group C consisted of 16 patients receiving needle jejunostomy enteral nutrition for 10-32 days during the immediate postoperative period. Mortality and mortality was as follows: Group A consisted of 0 patients, Group B with 5 complications (27,7%) and 2 deaths (11,1%) and group C with 7 complications (38,8%) and 1 death (5,5%). Groups B and Chad 12 complications (33,2%) and 3 deaths (8,3%) totally. The comparison of the group A to B and C as well as group B to C didn't yield any significant statistical difference. The comparison of groups B and C as a whole to the group A yielded a statistical value of 0,1, p > 0,05.

The effectiveness of surgical treatment as well as surgical treatment with adjuvant chemotherapy [5 Fluorouracil] or chemoinmunotherapy [5 Fluorouracil + BCG] was evaluated in the group of 380 patients with gastric cancer treated between 1977-1981. Patients with histopathologically confirmed gastric cancer were qualified to four groups depending on the stage of cancer according to UICC classification.

In group 1 and II [65 patients] there was performed only radical surgery, while in groups III and IV [335 patients] surgical treatment was combined with the adjuvant chemotherapy [5FU] or chemoinmunotherapy [5FU + BCG] due to the gastric cancer advancement. Evaluation of effectiveness of the treatment was based on the analysis of survival curves characterizing the individual therapeutic groups during the period of 5-year prospective observation.

It was discovered that surgical treatment with adjuvant chemotherapy has statistical significance for the prolongation of survival in patients with advanced diffused gastric cancer, however it does not change the prognosis in patients with intestinal cancer.

THE EFFECTS OF LYMPH NODE DISSECTION AND ADJUVANT CHEMOTHERAPY STUDIED BY THE LOCATION OF GASTRIC CANCER. O. Yasuna, Shizuoka Univ. Sch. of Med., Matsumoto, Japan.

Three hundred twenty patients with gastric cancer were treated by curative gastrectomy between 1967 and 1981. Among them, the 5-year actuarial survival rates of patients with cancer limited to the upper (C), middle (M) and lower (A) third of the stomach were 68% (121 cases), 78% (82) and 70% (121), respectively. In the study of the effects of lymph node dissection, in the C area, 5-year survivors were not found among patients with positive node. The survival rates of patients with positive node in the M area and with positive node of the second group in the A area were significantly higher than those of patients whom had undergone R2 (complete removal of Group 1, 2 and 3 lymph nodes).

In group I and II (65 patients) there was performed only radical surgery, while in groups III and IV (300 patients) the lymph node dissection was combined with the adjuvant chemotherapy (5FU) or chemoinmunotherapy (5FU + BCG) due to the gastric cancer advancement. Evaluation of effectiveness of the treatment was based on the analysis of survival curves characterizing the individual therapeutic groups during the period of 5-year prospective observation.

In group I and II (65 patients) there was performed only radical surgery, while in groups III and IV (290 patients) the lymph node dissection was combined with the adjuvant chemotherapy (5FU) or chemoinmunotherapy (5FU + BCG) due to the gastric cancer advancement. Evaluation of effectiveness of the treatment was based on the analysis of survival curves characterizing the individual therapeutic groups during the period of 5-year prospective observation. It was discovered that surgical treatment with adjuvant chemotherapy has statistical significance for the prolongation of survival in patients with advanced diffused gastric cancer, however it does not change the prognosis in patients with intestinal cancer.
USE OF TOLUIDINE BLUE FOR INTRAOPERATIVE DIAGNOSIS OF RECURRENT GASTRIC CANCER

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Twenty-seven patients with recurrent gastric cancer were treated from 1979 to 1985. Thirteen patients underwent radical reconstructive surgery according to Kouk, while seven patients received symptomatic surgery and seven - test laparotomy. Three patients (11%,) died during the early postoperative period. The following procedure: after radical reconstructive surgery (7,7%) and 2, following gastroenteric anastomosis resulting from suture failure (28,6%). Among patients who received radical treatment, 2 patients died within one year, 5 patients survived for 1-2 years, and 3 patients survive more than 3 years (23%). Only radical treatment can prolong survival for patients with recurrent gastric cancer.

BENIGN NEOPLASMS OF THE DUODENUM


Early diagnosis of gastric lesions due to endoscopy produces a necessity of precise differentiation between benign and malignant ulcers intraoperatively when a diagnosis was not confirmed by biopsy before operation. We used a method of in vivo staining using Toluidine Blue /18/. The trial was performed in 21 patients operated for gastric lesions. All of them received per os 500 mg of TB. One day later intraoperative evaluation of lesion was performed. A positive result, i.e. a presence of neoplastic tissue was established if any part of gastric mucosa turned blue. Microscopic examination was performed. Blue colour of a lesion was observed in 13 cases - microscopically cancer was found. No change of tinge of mucosa was observed in 8 cases. Five of them were benign and 3 were malignant lesions. False negative results were caused by improper preparation (2 cases) and early stage of cancer (1 case). General specificity of the method is 100% for benign ulcers and 93% for malignant lesions (one false-negative). No side effects was observed.

Early diagnosis and a curative operation of non advanced cancer gives 90% of five-year-survival. For this reason improvement of early diagnosis is of major importance. In many poor countries and regions where endoscopic examination is of difficult attainment TB may be easy used before elective surgery of stomach. We wish to emphasize that the method is cheap, simple, safe and accurate. The staining has no influence on pathomorphological examination and therefore may be useful in small hospitals where intraoperative microscopic examination is impossible. The method allows to plan the limits of resection showing so-called satellite tumors.

GASTRIC CANCER AND TOTAL GASTRECTOMY

Prof. Dr. I. Chililieanu, Dr. N. Turleanu, Dr. G. Ducu, Dr. M. Lazacu, I. Acoianovachi, Third Surgical Department of Cluj-Napoca, Romania.

An analysis was made on 101 total gastrectomies performed in the Third Surgical Department in the period 1977-1985. The authors consider that total gastrectomy is an alternative of the palliative or exploratory interventions and not of curative partial resection with the intention of radicality. In the authors' conception curative total gastrectomy should be a "mild" operation achievable from a technical point of view without any remarkable risk by gently handling and avoiding fragmentation of the piece. Widening of total gastrectomy is to be made in unitary block by fixing still at the beginning a convenient approach technique through unwounded tissues. Reestablishment of the digestive tube continuity is the phase creating the main difficulties on which most postoperative complications are dependent. The authors prefer esophageal anastomosis on excluded loop.

The immediate and late results are analysed. In the 101 total gastrectomies 21 deaths occurred (20,3%). Digestive fistulae showed a high incidence, but the authors included absolutely all the cases detected clinically or radiologically only. Thus, in the 101 cases of gastrectomy 46 fistulae (45,5%) occurred. Despite of this, the digestive fistulae were the cause of death only in 10 cases (10/101, 9,9%).

The late results are satisfactory if we remember that total gastrectomy was performed in patients with a prognosis of several months' survival without this operation.
2786 CONTRIBUTION TO REDUCTION OF POST-OPERATIVE COMPLICATIONS IN COLON CARCINOMA. V. Dimitrov, Z. Doudoumov, K. Halchev. Res. Inst. of Oncology at the Med. Academy, Sofia, Bulgaria

To reduce the incidence of anastomotic leakage in complicated forms of right colon carcinoma a side-to-side ileotransversotomy with a temporary anti-peristaltic colostomy of the colon stump is performed. The latter is restituted extraperitoneally on the 15th day from the intervention. To avoid the risk of peritonitis in possible anastomotic leakage the anastomosis is isolated by a pedunculated omental, while the region is drained with a polythene tube. A sign of anastomotic insufficiency is the faeces running out of the drain. It necessitates the wide opening of the abdominal wall to form a colostomy at the drain place. It is usually closed spontaneously in one month.


Local treatment of cancer of the rectum can be applied in the following cases:
- Cancer at stage A or at low grading
- Cancer which cannot be operated on due to local or general conditions of the patient (palliative treatment).
- Cancer localized under the peritoneal reflection.

The techniques we used for such a treatment were the following:
- Excision through colonoscopy.
- Electrocoagulation.
- Electroflogoration Radiotherapy (through contact or penetration).
- Cryotherapy.
- Laser therapy.

The authors refer their experience.

2788 Alternatives by using the stapling apparatus for cancer of the lower rectum.

Professor Samuel Fain M.D., Ph.D.
Los Angeles, California, USA

Since 1967 I am using the stapling machine for low anterior resection for cancer of the colon and since 1978 I am using a new surgical device ELA-31 with a disposable loading unit. This apparatus is different from other machines because it is intended for a very low anterior resection and facilitates anastomosis as low as 3-6 cm above the anus. Usually this would be extremely difficult if not well impossible however caution must be advised and some tricks will be discussed.

I remember when the first stapling machine was introduced a great number of skepticism was obtained. Many famous surgeons mentioned that the hand sutures are safer, easier etc. but after initial reaction a era of excitement appeared. I think now we have no major hospital in the world where the stapling machine is not used. This is a great accomplishment. For the last year new voices of pessimism: Do we have after anterior resection with the stapling device more recurrences comparing with hand suturing? My answer is NO everything depend on the indication for this procedure. In choosing the operation for rectal cancer and determining how radically it should be performed the surgeon must consider: 1. the site of the tumor, 2. the anatomy and histological structure, 3. the stage of the disease and the extent of spread, and 4. the general condition of patient. For the last years due to wide use of stapling machines it became possible technically in 70% of cases to perform sphincter-saving operations especially low anterior resections.


It is now established that with modern techniques particularly the stapling instrument, most low rectal carcinomas can be resected with restoration of gastrointestinal continuity and continence. In recent years the policy for dealing with low rectal cancer in our Dept. changed. The introduction of a new technology has led us to preserve the anal sphincter in a much greater proportion of patients with low rectal cancers than was the case previously. Between January 1980 and October 1985, 87 patients with a rectal carcinoma situated between 3 and 10 cm from the anal verge presented to our Dept. 31 patients underwent sphincter-saving resection (SSR), 35 abdominoperineal resection (APR). The techniques used to preserve the sphincter were: low anterior resection with MEAD-2 anastomosis device 22, with hand sewn anastomosis 6, rectotomy posterior (MASON) 1 and excision of tumour 2. There were 1 postoperative death (3.4 per cent), 1 (3.2 per cent) in patients who underwent radical SSR. The mortality rate in patients who underwent radical APR was 2 (5.7 per cent). For tumours below 10 cm, the respective number of patients with local recurrence were 6 (of 35) (17.1 per cent) following APR and 2 (of 31) (6.4 per cent) after low SSR. No patients was lost to follow up. There was no significant survival during this period between APR and SSR. The authors stressed that although some "rules" may be broken in the desire to preserve the sphincter most still persist.
2790  THE CRYOSURGICAL TREATMENT OF ANORECTAL CANCER.

M. Sušterič, The Inst. of Oncology, Ljubljana, Yugoslavia.

Cancer of the anus and the lower third of the rectum is still a considerable local therapeutic problem. If the patient is in good general condition and the tumor is technically resectable the treatment of choice remains the abdomino-perineal resection and definitive colostomy. In combined therapy preoperative and postoperative radio- and chemotherapy can be added. The problem appears when the tumor is locally non-resectable, when a higher risk patient is considered for surgery, when the patient refuses the operation and follows up. We believe that local recurrence of the disease in most of these cases the radiotherapy was performed with more or less poor results. At the surgical department of the Institute of Oncology in Ljubljana 35 patients were treated by cryosurgery alone or in combination with radiotherapy, or local excision of the tumor. In our material all patients were treated with a closed cryosurgical unit with a contact probe cooled with liquid nitrogen. General or regional anesthesia was required in all our patients. In lithotomy position the operative procto- or rectoscope was inserted and the tumor exposed and frozen. The freezing was controlled by direct inspection and palpation or by thermocouple or by measuring of the impedance of the surrounding tissue. The exact control of freezing is not always possible therefore some empirical experience is necessary. In the group of patients with inoperable or recurrent disease the least benefit of this therapy was the relief of pain and in most cases also the disappearance of other local symptoms. The last group comprised the patients with locally operable tumors, with major general contraindications for abdomino-perineal resection or the patients who refused this operation. They were all treated cryosurgically with very good results. In most cases a complete tumor regression was achieved after one or more cryosurgical sessions. All these patients were under strict follow-up. We believe that local recurrence of the disease can be properly controlled by additional cryosurgical treatment, if recognized in time.

2791  SURGICAL MANAGEMENT OF CHALLENGING CARCINOID TUMORS.

S. Keator, M.D., Anaheim General Hospital, Anaheim, California, U.S.A.

Four cases of carcinoids are presented. 1. Duodenal carcinoid adjacent to a bleeding duodenal ulcer discovered at time of surgery. There may contain active peptides (Gastrin). 2. Symptomatic Papilla of Vater carcinoid. These manifest symptoms early. 3. Carcinoid of the liver originally resected as primary hepatoma without evidence of a primary site, later with multiple metastases to bones and lungs. In some cases, like this, primary not found. 4. Obstructive (Zen) carcinoid of the base of appendix with appendicitis. This type tumor has greater tendency to metastasize early. Surgical treatment is discussed of each, as per their exigencies.

2792  HARTMANN POUCH CARCINOMAS. Delmar A. Atten, MD, Loma Linda Univ. Med. Ctr., Loma Linda, CA, USA.

Carcinomas arising in a rectal Hartmann pouch are a rare occurrence. Four individuals have been seen with carcinomas arising in this isolated segment of bowel. The Hartmann procedures had been performed to control a benign rectovaginal fistula (1), to isolate an area of post-prostate radiation proctitis at the time of sigmoid colectomy for a primary colon carcinoma (2), and to close the rectum following resection of low anterior anastomotic tumor recurrences (2). Bleeding was the sole presenting symptom in all cases and occurred from 1-10 years following the Hartmann procedure. The Hartmann pouch was resected in all cases. The Hartmann pouch tumors were due to primary rectal carcinomas (1), a drop metastasis (1), and tumors arising as a part of the spectrum of multiple primary colon carcinomas (2). The results are two alive NED (2 5 yrs), one alive with disease, and one deceased due to tumor progression. It is recommended that bleeding from a Hartmann pouch alerts one to the possibility of a rectal carcinoma.

2793  IS HYPERCHOLESTEROLEMIA A RISK FACTOR IN THE TREATMENT OF COLON CARCINOMA? M. Bartók, M.Fehér (Department of Proctology, Time Hospital, Budapest, Hungary).

Risk factors of the alimentary tract tumors have been discussed in detail in numerous reports. This postoperative state has been studied from the point of view of colon carcinoma and compared to literature data. In the present report the frequency of complications following various types of surgical interventions are investigated. It was found that hypercholesteremia as a postoperative complication can be minimized with the application of modified Nusskay surgery. Authors claim that this postoperative state can not be considered to be a risk factor. Random digital examination of the colon and bariumpas test are to be performed as a follow-up examination. In case of positive findings additional examinations are needed. If the former examinations yield still negative results the modified Nusskay operation is the intervention of choice for the performance of the ureterosigmoidostomy.

The authors report on their experience obtained with their colostoma patients. Between 1975 and 1985 they treated 342 patients because of colorectal cancer. The postoperative treatment procedure is described. Favourable experience was gained with the stomahesive preparations of the Convatec Company. The importance of education of nurses specialized on enterostoma therapy as well as the supply of colostoma patients with appropriate devices are greatly emphasized.


In surgery the stapling has a number of advantages if compared to sutures. The former gives reliable tightness, a 3 to 5 times shorter reconstruction time, helps the anastomosis and asepsis in the destruction period, ensures the maximum preservation of tissues and organs. Thus, early or distant post-operative complications are rare. The authors applied 400 circular anastomoses (esophagus, colon and rectum) on 850 cancer patients and made 1550 linear stapling (shaping the stomach remnant, closing the duodenal stump, liver and pancreatic resections, etc.) using the Soviet staplers UO, SPTU, PKS, KZ, NJKA. In the early post-operative period 5 cases of esophageal anastomotic leakage(1.6%) came to a lethal end and 6 colonic patients(7.9%) were successfully treated by a temporary colostomy. 26 of them had stenosis due to excessive Lambert sutures and esophageal reflux. No linear stapling insufficiency has been observed. Thus, postoperative suppurative complications were 4 times rarer.

2796 MALIGNANT TUMOURS FOUND IN THE COURSE OF URGENT ABDOMINAL SURGERY. L.Badii and L.Molnár, Csepel Hospital, Dept. of Surgery, Budapest, Hungary

In the last five and half years we have performed 176 surgeries due to malignant tumour. During this period we have found malignant tumour in 16 cases among patients urgently operated because of acute abdominal symptoms. At 46 patients the tumour complication induced the urgent surgery. Among these in 7 cases we have found peritonitis caused by tumour perforation. In 24 cases tumour obstruction of the bowel was the indication of the surgery. At different sections of the small or large intestine 27% the patients were operated because of post-intestinal tumour bleeding.

The other 11 patients were operated because of acute appendicitis, which surgery proved in 4 cases to be incorrect. In one case we took a false indication. The part of the urgent surgeries performed in 176 patients the up to date were treated infracostal or infrahilar in view of intraperitoneal sparing the resection of the development of inflammatory process.

2797 RADIOLOGIC POSSIBILITIES IN THE DIAGNOSIS OF COLON CANCER RECURRENCE T.A.Ostapenko, M.D.

USSR, Kiev Scientific Research Institute of Roentgenology, Radiology and Oncology

To develop a complex of roentgenologic techniques for predicting cancer recurrence, 248 patients were studied, following radical surgery for colon cancer. It was established that X-ray examination of patients with suspected recurrence of cancer should be performed in two steps. The first step should employ double-contrast irrigoscopy, combined with polygraphy and pharmacologic relaxation. The second step includes the use of pneumography, the examination of stomach, small intestines and urinary ducts. For the first step the correctness of prediction was 90.5 ± 3.8% for the colon, and 76.4 ± 5.7% for the rectum, increasing to 95.2 ± 2.4% and 99.9± 2.9% respectively.
2798 ANORECTAL MOBILIZATION OPERATION, A NEW SURGICAL ACCESS TO RECTAL LESIONS, by Ahmed Shafik MD, Professor of Surgery, Faculty of Medicine, Cairo University, Cairo / Egypt

Based on recent anatomical findings, 'Anorectal Mobilization Operation' serves as a new type of sphincter-saving operation for lower third rectal cancer. Its essential feature is the preservation of the levator tunnel which is responsible for a normal voluntary continence and defecation.

The abdominal part resembles the combined excision operation, the descending colon, sigmoid and rectum being mobilized. In the perineal part dissection proceeds upward between external and internal sphincters, taking the tunnel septum as a guide for proper plane, till the pelvic cavity is entered. Sigmoid and rectum are brought outside the perineal wound and excised. The colon is then sacralized and angulated before being sutured to the perineal skin.

The technique was performed in 40 patients who had undergone surgery 5 to 10 years ago. Post-operatively, the mean pressure for the colonic anus is normal for the levator in all cases and for the external sphincter in only 22 patients. All patients control feces and flatus, can differentiate between both, and feel the desire to defecate. 25 patients (62.5%) survived more than 5 years.

In view of the results achieved in the treatment of growths in the lower half of the rectum by the described technique, combined excision operation seems no longer indicated.

2799 REVERSION TO NORMAL DEFECTION AFTER COMBINED EXCISION OPERATION AND END COLOSTOMY FOR RECTAL CANCER, by Ahmed Shafik MD, Professor of Surgery, Faculty of Medicine, Cairo University, Cairo / Egypt.

21 patients with combined excision operation for rectal cancer were subjected to rectographic study of levator ani, puborectalis, and external sphincter. Active puborectalis and levator ani were detected in 12 patients, 8 of whom had normal myoelectric activity for both muscles. The remaining 5 patients had reduced activity of levator ani and of puborectalis muscles, indicating that these muscles were not excised but left in the patient.

The 12 patients with active levator and puborectalis muscles were operated upon to restore defecation through the normal perineal route. The technique comprises freeing of the colostomy and mobilization of the entire left colon. The perineal scar is then excised and the colonic and fixed in the perineal skin, to be under the control of the levator and puborectalis muscles.

Full fecal control was achieved in 7 patients, and incomplete control in 5.

It is concluded that excision of the levator, puborectalis and external anal sphincter should not be considered a standard part of the radical operation for lower and mid third rectal cancer, and that combined excision operation has no place in the treatment of rectal cancer.

L-53: LIVER TUMOURS

2800 EFFECTS OF TRANSCATHETER ARTERIAL EMBOLIZATION IN HEPATOCELLULAR CARCINOMA. Ta-Cheng Wei, Yik-Ming Tang* and Hey-Chi Hsu**, Departments of Surgery, Radiology* and Pathology**, Natl. Taiwan Univ. Hospital, Taipei, Taiwan, R.O.C.

Transcatheter arterial embolization (TAE) has been well established as an effective palliative therapeutic method for unresectable hepatocellular carcinoma (HCC) in recent years. From 1982 to 1984, a total of 129 cases of HCC was treated by TAE. The 1-year and 2-year survival rates were 38% and 20%, respectively. Seventeen cases with large HCC of 6 to 15 cm in the largest diameter were surgically resected 3 to 12 months after TAE for histologic assessment of the effectiveness. Another 2 cases autopsied 3 and 8 months after TAE were also studied. These patients, 16 males and 3 females, aged from 20 to 64 years and were asymptomatic. Serum HBsAg was positive in all cases. Alpha-fetoprotein (AFP) was elevated in 16 cases and markedly dropped or dropped to normal level in 10 cases. An effective massive tumor coagulative necrosis of 99% already occurred 3 days after TAE. A necrosis of more than 50% was achieved in 9 cases and 1, judging one autopsied large HCC with 3 times of TAE in 6 months. This strongly indicates the effectiveness of TAE in the destruction of HCC. However, the presence of viable residual tumor tissues in 18 cases also strongly indicates the necessity of surgical resection whenever it is possible. The failure of complete tumor necrosis is related to the tumor capsule formation, intra- or extracapsular extension, liver invasion, satellite nodules, portal vein invasion, and collateral and portal vein blood supply.

2801 TRANSCATHETER CHEMODOMBOLIZATION OF HEPATOCELLULAR CARCINOMA. Nishizawa Yutaka*, and Takagi Tatsuya**, Dept. of Radiology* and Surgical Oncology**, Research Institute for Microbial Diseases, Osaka Univ., Osaka, Japan

Since February of 1979, we have treated more than 200 patients with hepatocellular carcinoma (hepatoma) by performing transcatheter chemoembolization (TCE) in which either Adriamycin 80 mg or Mitomycin C 20 mg and gelatin sponge (Gelfoam) pieces are infused into the hepatic artery. More recently, in April of 1983, we began to perform TCE with additional use of an oily contrast medium (Lipiodol) and obtained even better results. The results by these two methods are reported.

A study of cases in which resection was performed after TCE showed that TCE produced marked effects against encapsulated hepatoma. Even without using Lipiodol, TCE results in a high incidence of complete necrosis when the hepatoma is not greater than 5 cm in diameter, although the therapy was not satisfactory against daughter tumours in the portal vein. In contrast, TCE with Lipiodol was found to lead to more satisfactory results.

In 83 cases of unresectable hepatoma treated by TCE without Lipiodol, the cumulative survival rate was 88.7% at 6 months, 44.6% at 1 year, and 12.6% at 2 years. The results of TCE with Lipiodol in 69 cases were more satisfactory; the survival rates at 6 months, 51.4% at 1 year, and 47.4% at 2 years. It appears that, because Lipiodol slows the release of anticancer drugs and causes embolization at a more peripheral position compared with Gelfoam, the use of Lipiodol enhances the effects of antitumor therapy.
CHANGES IN DISTRIBUTION OF HEPATIC BLOOD FLOW INDUCED BY INTRA-ARTERIAL INFUSION OF ANGIOTENSIN II IN HUMAN HEPATIC CANCER.

T. Imaseki, M.D., T. Takeda, M.D., Y. Hasegawa, M.D.**, S. Nakano, M.D**, O. Ishikawa, M.D**, H. Ohigashi, M.D**, K. Taniguchi, M.D**, H. Koyama, M.D**, T. Iwanaga, M.D**, N. Tsukada, M.D**., and Y. Sasaki, M.D**, S. Imaoka, M.D**, Y. Hasegawa, M.D.**. Nuclear Medicine, The Center for Adult Diseases, Osaka, Japan. Changes in the distribution of the hepatic blood flow induced by intra-arterial infusion of angiotensin II (AT-II) were studied in human hepatic cancers using extremely short-lived radioisotopes (Krypton 81m or 81Kr; half-life, 13 seconds). After the start of continuous infusion of AT-II, the radioactivity of the tumor showed a two-fold increase, whereas that of the nontumor region decreased to about one half as much as the level before the infusion. Consequently, the mean ratio of the arterial blood flow in the tumor region to that in the nontumor region (T/N ratio) increased to 1.30±0.09 (P<0.05). The T/N ratio showed a peak before the peripheral blood pressure reached the maximum, and thereafter tended to decrease. Intra-arterial infusion of AT-II raised the T/N ratio more obviously than did intravenous infusion of the drug, with less rise in the peripheral blood pressure. It is believed that intra-arterial infusion chemotherapy with local use of AT-II enables better accessibility of chemotherapeutic drugs to tumors.

A lipid contrast medium (lipiodol) injected into the hepatic artery remains in the liver tumor selectively. Lipiodol remained in the tumor but was pushed out by the hepatic venous blood and blood flow remained relatively constant. At the same time the T/N ratio more obviously than did intravenous infusion of the drug, with less rise in the peripheral blood pressure. It is believed that intra-arterial infusion chemotherapy with local use of AT-II enables better accessibility of chemotherapeutic drugs to tumors.

Nuclear Medicine, The Center for Adult Diseases, Osaka, Japan. T. Terasawa, M.D.*, *Dept. of Surgery, **Dept. of Nuclear Medicine, **Dept. of Surgery.
2806 INTRA-TUMORAL INJECTION OF DRUGS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA. N. Hashioka, S. Matanobe, H. Kagawa, K. Terada and S. Shiroi. Department of Internal Medicine, Kagawa Medical School, Takamatsu, Japan

Hepatocellular carcinoma (HCC) is the most frequent primary liver tumor and patients are usually at an advanced stage when the diagnosis is made.

Recently, in our department, considering the progress in HCC therapy has been made, the result of a study on the intratumoral injection of drugs with the guidance of ultrasound was presented.

In the present study, the effectiveness of the intratumoral injection of immunostimulator and alcohol is presented with special reference to the immune parameters including interleukin-2, NK cells, and lymphokine activated killer (LAK) cells.

Intratumoral injection of OK-432 (25,000 IU) was performed in 10 patients with HCC and that of ethanol (100% 5 ml) in patients. Reduction of more than 40% of tumor volume was obtained in 68% of the patients with HCC.

Tumor volume was calculated by CT scan. Injection of ethanol was more effective than OK-432.

In one patient who received intratumoral injections of OK-432 (times) and ethanol (12 times), no tumor was found in CT scan.

Activities of interleukin-2, NK cells and LAK cells were significantly enhanced in the group with smaller tumor load but unchanged in the group with larger tumor load.

Intratumoral injection of OK-432 and ethanol may be effective in treatment of HCC.

2807 RANDOMIZED STUDY OF INTRAHEPATIC (IH) VS. SYSTEMIC (SYS) INFUSION OF FLUORODEOXYURIDINE (FUDR) IN PATIENTS WITH LIVER METASTASES FROM COLORECTAL CARCINOMA. N. Kemény and J. Daly. Memorial Sloan-Kettering Cancer Center (MSKCC), New York, USA.

Hepatic metastases represent a common site of dissemination for gastrointestinal neoplasms. Initial work with direct hepatic infusion suggested higher response rates and longer survival. Studies at MSKCC have demonstrated the importance of the percentage of liver involvement and initial lactate dehydrogenase (LDH) on survival. Therefore, to determine the true impact of hepatic infusion, a prospective randomized study between IH and SYS continuous infusion of FUDR was initiated.

All patients (pts) had exploratory laparotomy to evaluate the extent of liver involvement, assure the absence of extrahepatic disease, and a performance status of 0-1. In the IH group, the P was connected to the hepatic artery (HA) in the SYS group the P was connected to a vein catheter. In one patient who received intra-tumoral injection of OK-432 and ethanol, no tumor was found in CT scan.

Activities of interleukin-2, NK cells and LAK cells were significantly enhanced in the group with smaller tumor load but unchanged in the group with larger tumor load.

Intratumoral injection of OK-432 and ethanol may be effective in treatment of HCC.

2808 INTRAPERITONEAL INFUSION OF FLUORODEOXYURIDINE (FUDR) IN COLORECTAL LIVER METASTASES. Y. Tsuchida, M. Okada, K. Mizumoto, K. Oto, H. Nomura, and H. Niwa. Department of Surgery, Teikyo University School of Medicine, Japan.

A phase-1 clinical trial of FUDR in hepatic metastases of colorectal cancer was performed in 12 patients. The purpose of the study was to evaluate the safety of FUDR in patients with colorectal liver metastases and to determine the maximum tolerated dose (MTD) and the effective dose of FUDR.

Intraperitoneal infusion of FUDR (150-300 mg/m²) was tolerated by all patients. The MTD was 300 mg/m². Four patients developed grade 3-4 gastrointestinal toxicity. One patient developed grade 3-4 hepatic toxicity. The median survival time was 13 months. The median time to progression was 10 months. The median time to treatment failure was 6 months.


A phase II clinical trial of FUDR in patients with colorectal liver metastases was performed. The purpose of the study was to evaluate the efficacy of FUDR in patients with colorectal liver metastases.

The FUDR was administered intraperitoneally at a dose of 150-300 mg/m². The MTD was 300 mg/m². Four patients developed grade 3-4 gastrointestinal toxicity. One patient developed grade 3-4 hepatic toxicity. The median survival time was 13 months. The median time to progression was 10 months. The median time to treatment failure was 6 months.
**2811**

**TREATMENT AND PREVENTION OF SCLOEHRING CHOLANGITIS RELATED TO CHEMOTHERAPY DELIVERED BY INFUSATION PUMP**

\[\text{Author: } L. C. Kaspar, Patricia Meadgatt, Ito, Flay, Stephen Melicamp, Joe B. Desdy, Miguel Miranda} \]

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To prevent the occurrence or recurrence of sclerosing cholangitis, a serious and frequent complication of chemotherapy with FUDR given intra-arterially to the liver, the administration of low doses of dexamethasone given intra-arterially continuously through the infusion pump was devised. This has allowed the administration of chemotherapy with FUDR at full dose without evidence of sclerosing cholangitis.

Ten patients (pts) received steroids; 3 pts as treatment and 7 pts as prophylaxis for sclerosing cholangitis. In February 1984 our first case of jaundice related to chemotherapy was diagnosed as sclerosing cholangitis by ERCP and treated with placement of intraductal stents to bypass the areas of obstruction. Initial bilirubin of 16 mg/dl dropped to 7 mg/dl. Chemotherapy, along with dexamethasone 2.5 mg/day (d) via Infusion pump was reintiated and normal serum liver function tests were noted. Three episodes of sclerosing cholangitis occurred requiring stent change and antibiotics prior to patient's death due to progressive illness in July, 1985.

Two other pts had sclerosing cholangitis, both had ERCP within 24 hours of confirmation of jaundice. Treatment with prednisone (po) or prednisolone (iv) 80-160mg/d was given. Resolution of the clinical and biologic abnormalities seen was seen but the biliary tree abnormalities persist by ERCP. Chemotherapy with FUDR along with dexamethasone 2.5 mg/d via Infusion pump was reintimated without recurrent picture of sclerosing cholangitis. Since July 1984, 7 pts have received dexamethasone 1.0-2.5 mg/d via Infusion pump along with 0.3-0.5 mg/kg of FUDR for two weeks every four weeks, without evidence of sclerosing cholangitis. Steroidal side-effects were mild; cushionoid face, pedal edema, edematous with thinning of the skin in limbs.

**2812**

**IMMEDIATE AND LATE RESULTS IN LIVER TUMOURS**


The Authors report their experience and the efficacy of hepatic resection for tumors made in the last 10 years with the McEliurry, J. O. technique of hepatic resection and chemoembolization of vascular-satiary arteries. The mortality mortality was 9% and only 5% in the primary malignant tumors without chemoembolization, 15% in the primary malignant tumors with chemoembolization, and 15% in the liver metastases.

The survival survival in 50% of patients after liver transplantation, in the primary malignant tumors with chemoembolization, and 15% in the liver metastases.

**2813**

**HEPATIC RESECTION AND REGIONAL PERFUSION, A RANDOMIZED PROTOCOL OF TREATMENT OF HEPATIC METASTASES**

**Author: D. Goebel, M. E. Mitter, J. D. Tzucz, City of Hope, Radiation Medical Center, Duarte, California, USA**

One hundred fifteen patients have been entered on a randomized prospective protocol to evaluate the effectiveness of hepatic resection (H.R.) of single as well as multiple hepatic metastases from colorectal primaries in combination with continuous hepatic arterial infusion/chemoembolization (CHAI) of FUDR via the implantable pump (Infusaid). The 11 patients with single metastases were randomized to H.R. alone (6 patients) or H.R. plus CHAI (5 patients). The 25 patients with resectable multiple metastases were randomized between receiving the CHAI only (11) or CHAI after resection of all metastases (14). Patients who had positive portal lymph nodes (15) were all treated with CHAI. Patients with unresectable metastases (38) were randomized between IV 5FU or CHAI of FUDR. The FUDR is alternatively infused every 2 weeks at a dose of 1 mg/kg/week escalated to 10 mg/kg/week at a rate of 2 mg/kg/week at a rate of 10 mg/kg/week at a rate of 2 mg/kg/week at a rate of 10 mg/kg/week at a rate of 2 mg/kg/week at a rate of 10 mg/kg/week. The median follow-up of all patients is 20 months. The patients with solitary metastases who had resection only had a higher rate of recurrent disease than those treated with resection and CHAI of FUDR. All patients with multiple resectable metastases had a least a partial response (PR) to the pump (PR defined as a 50% decrease of the sum of the products of the diameters of the lesions measured on CT scans). Patients with resection and pump had a better survival than patients with pump only. Patients with positive portal nodes and who had lower PR (361) than patients with unresectable disease treated with pump (567). Patients with positive portal nodes or metastatic disease outside of the liver did significantly worse than patients with unresectable disease treated with pump (567). Patients with treated with 5FU failed treatment and were crossed over to CHAI of FUDR. Response, survival, and complications will be discussed.
TREATMENT OF LIVER TUMORS - CURRENT CONCEPT
Singel C. Ghosh MD, Charles C. Koh MD, W. Hamilton MD
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Cancer is the second leading cause of death among the population of the United States. In the year 1978, 396,922 persons died due to cancer. It is second to heart disease and the rate is increasing. Cancer of the liver, although it is very rare, carries a very poor prognosis. Even in rare instances, patients with malignant tumors both primary or metastatic, do not live long and the average survival is about 8-12 months.

During the year 1983, 13,000 new patients with cancer of the liver and biliary passage were recorded in the United States and 12,000 patients developed colon and rectal cancer. A large number of the patients with colon and rectal carcinomas when the disease progressed will develop metastasis in the liver only. Many primary cancers will behave similarly. Resection of the liver was not popular until Carl Logenbach reported his first successful resection in 1873 in Berlin. William Lunneman from John Hopkins University popularized liver resection in the United States. Although resection of tumors of the liver carried the best possible cure, during the recent years, palliative therapy, chemotherapy ligation of the hepatic artery and intrahepatic arterial profusion by external or implantable pump is becoming popular. During the last 4 years we have reviewed (major and minor) 47 liver tumors in this institution with or without intrahepatic arterial profusion of chemotherapeutic drugs with implantable pumps (when no hepatic artery). We have no experience and no mortality in this procedure. It is in our opinion, if resectable, even by multiple areas of liver the both primary and metastatic cancer should be removed, and in cases where the tumor invaded extensively, an implantable pump with access to intrahepatic arterial profusion be the best therapeutic option.
"RESECTION IN LIVER CANCER"
D. Manfreldi, M.D. G. Sorvelli, M.D. F. Grauso, M.D.P. Sega, N.E.F. Romano, M.D. L. Cappelli, M.D.
II DEPT. OF SURGERY-CANCER INSTITUTE "REGINA ELENA" ROMA
During our experience of 270 hepatic resections, it appeared to observe 8 patients, two of them affected with primary liver tumour and six of them with hepatic metastasis from colorectal cancer. Those, in a period of time which goes from 8 months to 3 years from the first hepatic resection, presented a new tumoral localisation in the liver without metastasis in other organs.
In those 8 patients was been executed the hepatic resection. One particular patient has had in the last five years one hepatic resection and two hepatic resections for metastasis for colorectal cancer.
The authors present the latest and previous results of their experience.

RESULTS OF CEA-DIRECTED RESECTION OF MULTIPLE LIVER METASTASES. John Peter Minton, M.D., Ph.D., FACS. The Ohio State Univ. College of Medicine, Dept. of Surgery, Columbus, Ohio 43210, U.S.A.
Multiple liver metastases have been associated with short survival. Using an early rise in carcinoembryonic antigen (CEA) after primary resection of colorectal cancer to indicate a second-look operation, small hepatic metastases have been discovered and resected. Twenty consecutive patients underwent resection of 2-12 liver metastases (total, 102 metastases; average, 5/patient). Blood loss averaged 435 cc/patient (minimal to 1,000 cc). Tumors were from .5 to 9.5 cm in diameter; 29 were 2 cm. Hepatic artery and portal vein catheters were placed intraoperatively. Resected tumors were grown in stem cell cultures and tested against chemotherapeutic agents for sensitivity, and patients were trained in the self-administration of appropriate chemotherapy during their hospitalization. 5-FU, methotrexate, vinblastin, and cytosine arabinoside most often showed cell kill capability. All 20 patients survived 12 months postoperatively, and 75% were alive at 2 years. The longest survivor is free of disease 57 months postoperatively. These results indicate that prolonged disease.

The most patients with malignant hepatic tumors, who are unamenable for surgery for reasons of multiple tumors, had been treated by intraarterial chemotherapy. However, with conventional infusion treatment, the infused drugs are eliminated swiftly from the drainage veins. In attempts to set up intra-arterial micro-depots for accumulation of the antitumor drug in the target tumor area, we devised biodegradable albumin microspheres (MS) containing mitomycin C (MMC) with an average diameter 45 ± 8 μm and we have treated 20 pts with inoperable hepatic cancer with these MMC MSs. These 20 pts had the average performance status of about 3.6 of 7 pts with hepatocellular cancer (HCC) had hepatic cirrhosis and 8 of 13 pts with metastatic cancer had extrahepatic metastases. The administered doses of MMC MS were 11.7±2.1 mg as MMC in the 13 pts with hepatic metastatic cancer and 6.9±2.1 mg as MMC in the 7 pts with HCC. An objective tumor response was obtained in 14/20, and the average level of CEA in the 13 pts dropped from 57.7 ng/ml to 16.5±2.1, that of alpha-FP dropped in all of the 7 pts with HCC. Six pts from colorectal cancer lived for 18.3±10.8 months, 3 are alive with a long life expectancy, and 7 pts from gastric or pancreatic cancer lived for 10.1±4.9 months. Seven pts with HCC lived for for 6.1±2.7 months, 3 of whom died of esophageal bleeding. Improvement of a variety of complaints such as right upper abdominal pain, right flank pain, anorexia and fever was seen at the earlier stage of this therapy, in all pts. The toxicities of MMC MS treatment were within acceptable limits, in all these pts. These results indicate that chemoebolization treatment with MMC MS via percutaneous arterial catheterization is efficacious for far-advanced hepatic cancer with poor performance status.
2821 MITOXANTHON POLYCHEMOTHERAPY IN ADVANCED BREAST CANCER


Twenty-two patients (pts) with advanced breast cancer were treated with a combination of Mitoxanthron, Cyclophosphamide and Fluorouracil to evaluate response (R) and toxicity (T) of this scheme. Patients were postmenopausal, median age 60 (range 21-72). Without prior chemotherapy.

Dominant site of disease was: skin (10 pts), bone (8 pts) and visceral (4 pts). None regimen was Mitoxanthron (12 mg/m2, infusion over 30, 17), Cyclophosphamide (500 mg/m2, IV, 1st & 2nd), Fluorouracil (500 mg/m2, IV, 1st & 2nd). Cycle repeated 3 weeks. Disease modification was done according to values of CBC and platelets. R and T were defined according to WHO criteria respectively. To date 19 pts were evaluated for R. 3/19 pts obtained complete R (CB) and partial R (PR). Duration of R were: 3, 5, 13, 24, 61, 75, 78, 84 months. 3 pts were evaluable for T. Major objective was dose-limiting myelosuppression mean WBC nadir was 2300/mm3 (range 100-10000). Effects over platelets or haemoglobin were less evident. Mean platelet nadir was 105000 (range 5000-250000). There weren't evidence of cumulative hematological toxicity. Mild nausea and vomiting was present in 7 and moderate or severe was 3 pts. Mild alopecia was in 4, moderate in 1 and severe in 1 pts. Mild alopecia was in 7, 1 severe in 9 pts. No evidence of clinical or ECG signs of moncardial dysfunction. There were neither changes in renal and liver function test nor tissue necrosis fibrinolytic in 4, moderate in 1 and severe in 1 pts. Mild alopecia was in 4, moderate in 1 and severe in 9 pts. No evidence of clinical or ECG signs of moncardial dysfunction. There were neither changes in renal and liver function test nor tissue necrosis fibrinolytic. This combination was clinically useful and well tolerated in breast cancer patients.

2822 SUBMITTIN FOR REJECTION OF SUBMITTED INVESTIGATIONAL EXPERIMENT (C1) FOR STATUS B Reeves (AR) ADMINISTRATION OF COMBINATION CHEMOTHERAPY FOR METASTATIC BREAST CANCER (583). N. Cortesig, M. Storl, D. Pribin, M. User, A. M. Priel, C. Priel, J. P. Storl, M. A. Anderson Hospital and UW Memorial Hospital, 7030 USA.

Two-hundred and seventy-five patients (PFS) with MBC were treated with D-containing combination chemotherapy in 3 sequential studies. D was administered either by R (113 pts) or by C1 over 96 hours (63 pts) or 48 hours (29 pts). The total dose of D was limited to 450 mg/m2 for pts receiving 48 hrs but not treated by C1 continued 0 for 24 months or progressive disease or evidence of early cardiotoxicity. In populations in the 3 groups were comparable by age, disease-free interval, performance status, site of disease, extent of tumor burden and receptor status. The objective response rates (CR + PR) were 81, 75 and 74.5 respectively for pts receiving treatment by C1 over 96 hours or 48 hours of C1. Median duration of response was 16 months for all 3 groups. The N survival for the 3 groups were 26, 27 and 36 months respectively. Pts achieving complete remission after C1 D had a longer duration of remission (30 months) and survival (48 months) compared to similar pts in bolus group (18 and 34 months respectively). The total cumulative dose of D was significantly higher in the 3 groups (722, 755 and 727 mg/m2). The median duration of D was 12 months (range 1-45). Responders had more >400 mg/m2. Moderate or severe nausea and vomiting was observed in 55% of pts treated by C1 chemotherapy and 73% with D. This group had a 3.5% of the pts developed clinical congestive heart failure (CHF) while only 3.5% of the pts developed CHP in the C1 arms and most of these were observed in pts who received D over 48 hours. Cardiac monitoring with serial non-invasive cardiac evaluation and endomyocardial biopsies revealed a substantially lower incidence of subclinical myocardial damage in the C1 administration group. The data from these studies illustrate that the acute toxicity of D-containing combination chemotherapy was markedly reduced and after doses of D were administered by C1. The ability to continue D-containing chemotherapy in pts achieving complete remission has resulted in significant prolongation of duration of remission in this subgroup of pts.


During 1983 and 1984, 175 patients (pts) with advanced breast cancer and similar parameters were enrolled in this multicentric study. 1 received cyclophosphamide, doxorubicin and Mitoxanthron; 30 mg/m2 (CMF); All drugs were delivered IV, on the same day, at 4 pts. of 62 evaluable pts in the CAP arm (mean 251.4) achieved an objective response (CR + PR) of 44% (mean 251.4) achieved in 28 (CMF and MITOXANTHON). It is still too early to report duration of remission and survival.

The major toxicity was myelosuppression in CAP. Causes of treatment delay was chemotherapy delivered after the 15th day compared to the B administration (10 pts) or Mitoxanthron (10 pts). All pts achieved CR over 48 hours. Cardiac monitoring with serial non-invasive cardiac evaluation and endomyocardial biopsies revealed a substantially lower incidence of subclinical myocardial damage in the B administration group. The data from these studies illustrate that the acute toxicity of D-containing combination chemotherapy was markedly reduced and after doses of D were administered by B. The ability to continue D-containing chemotherapy in pts achieving complete remission has resulted in significant prolongation of duration of remission in this subgroup of pts.

2824 RANDOMIZED TRIAL OF CYCLOPHOSPHAMIDE, FLUOROURACIL AND DOXORUBICIN OR MITOXANTHONE AS FIRST LINE CHEMOTHERAPY IN ADVANCED BREAST CANCER (CAF or MITOXANTHON). C. L. Storl, K. Williams (Ottawa Cancer Clininc, Ottawa, Ontario) and K. N. MacKinnon (Victoria Cancer Clininc, Victoria, British Columbia). E. Pestchard (Women's College Hospital, Toronto, Ontario).

Since December 1982, 103 patients with advanced inoperable breast cancer were randomized to receive CAF (500 mg/m2, 500 mg/m2 and 50 mg/m2 or M 10 mg/m2) and 15 cycles of either CAF or MITOXANTHON. Twenty-two patients (pts) were entered in the CAF arm, and 31 in the MITOXANTHON arm to date. Median cycles of therapy for CAF was 15 and MITOXANTHON was 12. Median duration of response was 15/2 weeks (CAF) and 15/2 weeks (MITOXANTHON). The objective response rate was 56% (CAF) and 51% (MITOXANTHON). No patient developed congestive heart failure. Finally the major preliminary results show a similar response rate for CAF and MITOXANTHON with major differences in toxicity and a slight advantage for MITOXANTHON in regard to appetite and quality of life, nausea and vomiting.
2825 WEAKLY LOW-DOSE ADRIAMYCIN VERSUS FARMARUBICIN IN METASTATIC BREAST CANCER: A MULTI-CENTER RANDOMIZED PHASE III STUDY

Kvaløy S', Gundehn S', Kvissland S', Lund E' and Telega W'

'Department of Medical Oncology and Radiotherapy, The Norwegian Radium Hospital, Oslo, 'Dep. of Oncology, Haukeland Sykehus, Bergen and Department of Oncology, Regionssykehuset i Trondheim, Trondheim

We recently showed that weekly administration of Adriamycin was comparable to combination chemotherapy (VAC) in terms of activity and survival in patients with advanced breast cancer. The toxicity was markedly reduced in patients receiving weekly Adriamycin and they experienced better life quality, which are important features in a non-curable disease.

Farmarubicin, a new anthracyclin has been claimed to show a similar therapeutic efficiency but less toxicity than Adriamycin. It was therefore of great interest to compare these two anthracyclines. 151 hormone resistant patients were randomized to receive either Adriamycin (A) 20 mg i.v. weekly (76 patients) or Farmarubicin (F) 50 mg i.v. every 14 Days (77 patients). Their pretreatment status were similar. 112 cases are at the present time evaluable for response: In the low dose A group: CR+PR 20/65 (31%), NC 21/65 (32%), PD 24/65 (37%) vs. in the F group CR+PR 14/67 (21%), NC 30/67 (45%), PD 21/67 (31%). The differences in the two groups were not statistically significant. However, weekly low-dose A was significantly less toxic than F given every 14 Days. The results will be roupdated and presented in details.

2826 WEEKLY-DOSE ADRIAMYCIN AS FIRST LINE CHEMOTHERAPY IN ADVANCED BREAST CANCER. Per-Ebbe Jonsson, Mats Ericsson, Stefan Ryde'n, Departments of Surgery, Helsingborg, Kristianstad and Lund Hospital, S-251 87 Helsingborg, Sweden.

In advanced breast cancer weekly administration of Adriamycin (WDA) has been used as second or third line chemotherapy. This phase II-study was aimed to investigate the objective response rate and toxicity when WDA was given as first line chemotherapy. Until now 41 patients have been included in the study (39 - 31 years, median 61 yearn) and a weekly dose of 20 mg Adriamycin was used as second or third line chemotherapy. This study is still in progress and additional patients will be included. The dominating metastatic sites were in lungs and bone. Thirtythree patients are now evaluable (at least eight courses of therapy) for response and toxicity. The study is still in progress and additional patients will be included. The preliminary evaluation of WDA in advanced breast cancer confirms the beneficial effects with lower toxicity earlier reported. The response rate when given at first line chemotherapy seems to be comparable with when it is given as second or third line therapy. A more detailed analysis with definitive conclusions will be reported at the meeting.

2827 5 DAY AMBULATORY CONTINUOUS I.V. INFUSION OF 5 FU IN PATIENTS WITH METASTATIC BREAST CANCER RESISTANT TO CHEMOTHERAPY PROGRAM INCLUDING ADRIAMYCIN. T. PALANIGE, R. BASTIAN, C. DEMARCO, T. DURIO, M. JUVÉ, É. GARCA- GIRALT, J. VEDRENNE, M. FASAND, N. BERTHAU, M. COUTANT, P. POULIART - INSTITUT CURIE, PARIS, FRANCE

34 patients with histologically proven metastatic breast cancer were included in this phase II trial. They were given every 15 days, a five day course of continuous intravenous infusion of 5FU at the daily dose of 500mg/m2 associated with on iv push of Vindesine 2mg/m2 and Cyclophosphamide 300mg/m2 on days 2 and 5 of each course. All the patients treated were totally ambulatory. 26 patients were objectively resistant to previous cytotoxic treatment including Adriamycin and the other patients presented a metastatic dissease early after they stopped adjuvant therapy with Adriamycin. Pharmacokinetic study of 5FU and major metabolites was performed in 3 cases. The median follow up is now over 12 months. The immediate tolerance was good: leukopenia was observed in 2 cases, a thrombocytopenia without hemolitic complication in 2 cases, a mucositis in 1 case, on complete alopecia probably related to Vindesine injection in 5 cases and partial alopecia in 14 cases, a red "hand/foot" syndrome was seen in 2 cases. These minor complications allowed us to continue the treatment with 20% reduction of the given doses. A complete response was seen in 4 cases, a major response over 50% in 13 cases (RC+PR: 17/34, 50%). minor response in 7 and failure in 10. The median duration of response was 9 months (5 to 14 months) for major responders. In all the responders a rapid improvement of performance status was obtained.


*Med. Univ.Klinik, Bonn; **Städtisches Klinikum, Oldenburg, DDR.

Patients who have been treated successfully for metastases from breast cancer invariably suffer from further metastases. Due to this less than satisfactory result 2 novel cross-reactive chemotherapies were introduced in 1976 namely Adriamycin and Vincristine in addition to Cyclophosphamide, Methotrexate and Fluorouracil as part of the so called Second-line therapy. The remission rate has been subsequently reported to be between 20% and 50%. A paucity of information exists for drugs used in Third-line therapies. We have treated 40 patients with metastasizing breast cancer, who have been Second-line treated with either CMF or 5FU for 8-14 months. Of the 40 patients undergoing the Third-line treatment, 15 experienced a new remission, 13 of which were partial remissions and 2 were complete remissions. Tumor reduction was observed in 8 patients although this reduction was less than 50%. The average remission rate was 6.5 months - however remissions up to 19 months were observed. In spite of the massive Second-line therapy which normally included 2 cytostatic combinations, hormone and radiation therapy, overall tolerance was good. The most prominent side effect were bone marrow toxicity and erythropoiesis. Blood transfusions are therefore indicated for those patients in remission who undergo long-term therapy.

Third-line therapy in metastasizing breast cancer with Miloxycin, Vincristine and Prednisone resulted in a 27% remission rate with a good subjective tolerance to the side effects of the drugs.
M-51: BREAST CANCER: MEDICAL ONCOLOGY III

2830 A RANDOMIZED TRIAL OF DOXORUBICIN, CYCLOPHOSPHAMIDE IN COMBINATION WITH Fluorouracil (FAC) or Etoposide (EC) IN METASTATIC BREAST CANCER. A. Sufrin, G. YAitskevich, and C. Horobagyi. M.D. Anderson Hospital and Tumor Institute, Houston, Texas 77030 USA.

One hundred and sixty evaluable patients (pts) with metastatic breast cancer were randomized to an induction regimen of either FAC (27 pts) or EC (83 pts). Pts were crossed over to an alternate regimen after either achieving a maximum response with induction therapy or upon progression of disease or maximum dose of doxorubicin. The crossover regimen for FAC pts consisted of vinblastine, methotrexate, and prednisone (VM). For EAC pts VM (vinblastine, methotrexate, and fluorouracil) was used. All estrogen receptor positive and unknown receptor pts were given tamoxifen both in the induction and crossover phase of chemotherapy. Distribution of pts by age, receptor status, disease-free interval, performance status, and site of disease were similar between the two groups. With induction regimen in FAC pts, 15 pts (52%) had complete remission (CR), 13 (43%) partial response (PR), 12 (39%) no change and 5 pts (17%) had progressive disease. In EAC pts 40 pts (49%) had CR, 27 (33%) PR, 9 (11%) no change and 3 pts (4%) had progressive disease. Of those 6 were in CR, 27 were PR, 9 stable, and 14 had progressive disease. Of those 11 pts (28%) showed objective improvement, 31 FAC pts were crossed over to VM, of these 6 were in CR, 27 were PR, 9 stable, and 14 had progressive disease. Of these 15 pts (45%) showed objective improvement in their response. All CR that crossed over remained CR, 6 pts (13%) in the FAC group and 5 FAC pts (22%) became CR with crossover therapy. The median duration of progression free interval was 18 months for FAC and EAC groups. In conclusion both FAC and EAC regimen had similar response rate and time to progression and with the crossover regimen, a significant fraction of pts response status was further improved.

2831 THE WHO EXPERIENCE WITH FAC AND CMF IN PATIENTS WITH METASTATIC BREAST CANCER. Galvez CA, Teige JG, Garbovesky C, Baro E, Tempeley G, Tzapanik CJ, Pizlak C, Hittell J, Goodwin PC. Hospital Municipal de Oncologia, Bs. As. ARGENTINA.

A retrospective analysis of 224 women (98 premenopausal and 126 postmenopausal) with metastatic breast cancer were treated between 1974-83 with FAC or CMF.

Of the 98 pts. premenopausal, 52 (53.06%) received FAC and 46 pts. (46.94%) CMF and of the 126 pts. postmenopausal, 71 (56.57%) received FAC and 55 pts. (43.43%) received CMF. The median age of all pts. was 52 years (18-76 yrs), 43 pts. (premenopausal) and 63 pts. (postmenopausal) were over 50 yrs. The dominant metastatic site was visceral 54.73%, oesophageal in 38.21%, soft tissue in 19.39%, and SNC 4.94%.

Estrogen receptor data were not available during this study. Criteria for evaluation of response were those advocated by the UGEC.

Results: 123 pts. received FAC: (premenopausal: 52 pts.; CR: 17 (32.7%); PR 22 (42.3%) CR + PR: 75.1% postmenopausal: 71 pts.: CR: 10 (14.1%); PR 26 (36.6%); CR + PR: 36.7%);

101 pts. received CMF: (premenopausal: 46 pts.: CR 17 (37.8%); PR 22 (47.8%) CR + PR 49.6% postmenopausal: 55 pts.: CR 6 (10.9%); PR 17 (30.9%) CR + PR 44.2%);

The median duration response was: FAC = 10.6 months (premenopausal: 9.4 mos; postmenopausal: 11.9 mos);$\text{CMF} = 9.6$ months (premenopausal: 8.5 mos and postmenopausal: 10.7 mos).

The median survival time from the start of treatment was: FAC = 18 months (premenopausal: 21.6 mos; postmenopausal: 16.2 mos); CMF = 14 months (premenopausal: 15.8 mos; postmenopausal: 12.3 mos).

Conclusions: The response rate, the median duration response and median survival time were superior in the premenopausal women.

Response to second line chemotherapy in patients (pts) with advanced breast cancer (ABC) is uncertain. Neither is clear if inclusion of agents of the first line regimens are useful in the second line.

Thirty seven pts with primary failure or recurring to first line chemotherapy or failing to adjuvant therapy with Adriamycin in cyclophosphamide + vincristine were randomly allocated in a two arms protocol: Regimen A (21 pts); Cyclophosphamide 100 mg/m² po d1-14; Methotrexate 40 mg/m² iv d 1 & 8 and Fluorouracil 600 mg/m² iv d 1 & 8. Regimen B (16 pts) Methotrexate 40 mg/m² iv d 1 & 8 & Fluorouracil 600 mg/m² iv d 1 & 8 B; both regimens every 28 days. Pts in both arms were comparable in age, menopausal status and metastatic pattern. Response was observed in both arms:

Reg. A Reg. B

- CR 2 (9.5%) 0
- PR 2 (9.5%) 5 (31.2%)
- T.R. 4 (19.0%) 5 (31.2%)
- SD 4 (19.0%) 1 (6.3%)
- PD 13 (62.0%) 10 (62.0%)

Responders in both arms had disease involvement of only one area, so when this group of pts was considered separately response rate was 4/11 (36.4%) for Reg. A and 5/13 (38.5%) for Reg. B. Mean duration of response in Reg. A was 13.5 mos and in Reg. B 7 mos. Median survival of the 37 pts was 11 mos; 19 mos for responders and 6 mos for non responders (p<0.01). In Reg. A there was no significant survival interval between responders and non responders. In Reg B median survival of responders was 15 mos and that of non responders 4 mos (p<0.01). Response to any of the two arms was not related with response to first line chemotherapy. Toxity was mild with no toxicity related deaths. Leukopenia in Reg A was more severe than in Reg B (p<0.001). Both second line regimens were usually evaluable in ABC pts with only one area involved with disease. Inclusion of agents utilized in first line regimen only added toxicity.


Selected alkylating agents have been demonstrated in experimental systems to possess non-cross resistance, therapeutic synergy and in conventional clinical trials a steep dose response curve. In previous studies, a dose-related, enhanced tumor volume regression rate was seen with high dose combination of alkylating agents used with autologous bone marrow support (AMS). For these reasons, we have undertaken a Phase II trial of a single treatment with high dose cyclophosphamide (9625 mg/m²), cisplatin (161 mg/m²), and carboplatin (600 mg/m²) with autologous bone marrow support as initial chemotherapy for metastatic breast cancer. Ten premenopausal patients with estrogen receptor protein negative, measurable metastatic disease and no evidence of bone or bone marrow metastases have been treated. Six of seven currently evaluable patients have achieved a complete response within 45 days, (median 18 days). Two of these patients have relapsed in 3 and 4 months at sites of previous visceral disease.5 cm in size; the remaining patients continue in CR from 4-28+ months (median 7 months). One patient has achieved a partial response. Two patients are too early for evaluation. Toxicity was frequent but, in general, manageable. Hematologic reconstitution to AMS <10000 occurred in a median of 16 days. Platelet recovery was slower (median time to transfusion independence of 25 days). There was one episode of pulmonary hemorrhage and two episodes each of reversible cardiotoxicity and hypertension. One patient experienced veno-occlusive disease, and there was one episode of fatal renal failure and severe electrolyte derangements. The results indicate that high dose combination alkylating agents with autologous bone marrow support can produce a high complete response rate when utilized as initial chemotherapy for metastatic breast cancer and is likely to be most effective when tumor volume is small.


High dose chemotherapy or combination of chemotherapy and radiation therapy followed by rescue with cryopreserved autologous bone marrow transplantation is a potential curative therapeutic modality in patients with stage III and IV breast cancer. Since the marrow may be contaminated by breast cancer cells, successful application of such a procedure depends upon adequate purging of breast cancer cells prior to cryopreservation in order to reduce the risk of reintroducing tumor cells into the patient. Previous reports have demonstrated binding of soybean agglutinin (SBA) to malignant breast carcinoma cells in frozen and paraffin embedded tissue sections. Whereas studies by Reimer et al have shown that SBA does not agglutinate the human marrow stem cells. The SBA negative cells from human marrow were shown to successfully reconstitute patients with malignant hematological disorders conditioned by high dose chemotherapy. The following study was carried out in order to develop a model system for studying a new approach for purging breast cancer cells toward autologous BMT. Artificial mixtures of normal human marrow aspirates and radiolabeled breast cancer cells (derived from cell line, T-47D) were mixed with either soluble SBA or SBA covalently bound to 0.7 µ, 2.5 µ, and 5.0 µ magnetic beads. Cells which were bound to the magnetic beads were removed by a magnetic field. Cells which were agglutinated by the soluble SBA were separated by gravity through 4% bovine albumin gradient. Efficacy of tumor cell depletion was assayed by comparing radioactivity before and after cell separation. A median of 2 log depletion was accomplished after one cycle of separation procedure. When 2 successive cycles of cell separation were carried out, a median of 3 log depletion was accomplished. We suspect that a similar procedure could be useful for purging autologous marrow in patients with advanced breast cancer.

TREATMENT OF ADVANCED BREAST CANCER WITH CMF + AMINOGLUTETHIMIDE (AG) AND HIDROCORTISONE ACETATE (HC)


Since 1983, 102 patients with advanced breast cancer not selected because of the presence of high number of radioreceptors received CMF (CTX: 600mg/m², MTX:140mg/m², AGR:100mg/m²) iv d 1, 4, every 21 days during 5 cycles and AG:500mg/d p.o. + HC: 60mg/d p.o. during 15 days, followed by AG:2000mg/d and HC:400mg/d until progression. At the present moment, 61 patients are evaluable. Median age was 53 years. The results were the following (according to WHO criteria):

<table>
<thead>
<tr>
<th>No. patients</th>
<th>CR</th>
<th>PR</th>
<th>CR+PR</th>
<th>NC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>61</td>
<td>16</td>
<td>24</td>
<td>40</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>(26,2)</td>
<td>(39,3)</td>
<td>(65,5)</td>
<td>(6,5)</td>
<td>(27,8)</td>
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</tbody>
</table>

The percentage of response per site of dominant lesion was as follows: soft tissues 22/22 (100%); bone 11/21(52%); visceral 6/7(85%). 25 patients (out of the 40 that responded to treatment) completed the 5 cycles of CMF with a duration of response of 14,1 mos and a median survival of 18.5 mos. Toxicity was mild to moderate: digestive disorders (nausea-vomits), alopecia, asthenia and dermatitis. 2 pat. interrupted treatment momentarily due to asthenia, and 1 successfully due to digestive disorders. CONCLUSION: The data up to now allow us to affirm that the combined therapy of CMF+HC+AG is active in the treatment of advanced breast cancer.

Prospective controlled studies have been realized in the past recent years at our Oncology Department, evaluating in patients with measurable disease in an inoperable stage an association of some cytotoxic drugs (CMF, ETC) with hormone therapy (HT), and the association CT + HT.

Therapeutic results by WHO criteria (Cancer 1981, 47:207) in consecutive untreated patients admitted to the study from January 1980 to September 1983 are as follows:

<table>
<thead>
<tr>
<th>Treatments</th>
<th>N. Response</th>
<th>MD</th>
<th>MSO</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAM/HT/MPA/AGT</td>
<td>225</td>
<td>274</td>
<td>51</td>
</tr>
<tr>
<td>2nd line:CMF</td>
<td>all 67</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>Folatrexed/AV</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Response appears on the same line with the usual literatue subs. Toxicity has been limited, and fully acceptable.

From 1984 we are studying in newly occurring pts the comparative value of 1) TAM versus polyHT (TAM/FLU), and -as 2nd line- AGT (500 mg/d) versus MPA (oral, 1500 mg/d); 2) all 1 iv CMF, comparing our results with those of Carstensen et al. (CMF 300 mg/m2 days 1 & 8); 3) polyIC + concomitant HT (F/M daily high dose MPA) versus CT placebo (double-blind study).

At present we have only the preliminary results of the 2 study (45 entered pt), in which the OR of high-CMF (20%) is statistically superior to low-CMF (18%) (p<0.02, at test), however with no difference in toxicity, median duration of response and survival.

Intermediate, more mature data will be available for presentation by next August 1986.

M-51: BREAST CANCER: MEDICAL ONCOLOGY III

2839 COMPARISON OF SEQUENTIAL ENDOCRINE- AND CHEMOTHERAPY IN ADVANCED BREAST CANCER. T. Adachi, N. Suzuki, A. Kamachi, K. Koyasugi, T. Ohmura, K. H. Abe. Hospital and Research Institute, National Cancer Center, Tokyo, Japan.

Advanced breast cancer patients were randomized and treated either with sequential endocrine- and chemotherapy or combined one. Their estrogen receptor (ER) was positive or unknown. They were subjected to previous endocrine therapy, had the measurable lesions and 70 years old. The objective response was assessed using the system recommended by EECG. The protocol was as follows. A-group: tamoxifen (TAM) alone was prescribed, and whenever the treatment showed PD, it was switched to Adriamycin + cyclophosphamide (AC). B-group: both TAM and AC were administered. AC consisted of 20 mg/m2 of M and A, and 60 mg/m2 of C po days 1 to 14, and this schedule was repeated every 28 days. When the total dose of A reached 350 mg/m2, the patients responding to this regimen were switched to C + MTX + Procarbazine (CMF). In the A-group, TAM was administered.

CMF consisted of 60 mg/m2 of M and A days 1 to 14, 30 mg/m2 of M days 1 and 8, 600 mg/m2 of F po days 1 to 16. This schedule was also repeated every 28 days. The patients showed PD to AC were changed to.

Prognosis was assessed using the system recommended by EECG. The protocol was as follows. A-group: tamoxifen (TAM) alone was prescribed, and whenever the treatment showed PD, it was changed to CMF. In the B-group, TAM was administered.

CMF consisted of 60 mg/m2 of M and A days 1 to 14, 30 mg/m2 of M days 1 and 8, 600 mg/m2 of F po days 1 to 16. This schedule was also repeated every 28 days. The patients showed PD to AC were changed to TAM. If the RR patients entered to the study were eligible for evalution, 40 belonged to the A-group and 61 to the B-group, and their characteristics were fairly evenly distributed. In the A-group, the objective response (CR + PR) was achieved in 4/2 (10.41%) to TAM alone and in 23/9 (25.2% to TAM + CMF, and the overall response rate was 48.5 (19/35) with TAM. In the B-group, it was observed in 54/7 (66.7%) with TAM + CMF, and the higher response rate was observed in the visceral metastases.

There was no significant difference in the response rates between the A- and B-groups, but the OR rate was significantly higher in the B-group (p<0.05). The survival rate up to 3 years was significantly higher in the patients belonged to the B-group (Greenwood, pr 0.03).

It can be concluded that combined endocrine- and chemotherapy is more effective than sequential one in the patients with ER positive or unknown tumors.

226 previously untreated adults (median age 50, range 15-81) received induction therapy with Ara-C (200 mg/m²/d CI x 7) and daunorubicin (45 mg/m²/d x 3). 133 pts (56%) achieved complete remission (CR) including 67/69 (92%) pts < age 40, 68/77 (63%) pts age 40-60, and 37/71 (52%) pts > age 60. Successful courses of pts in CR were assigned to receive 4 courses of single agent Ara-C intensification by CI (250-400 mg/m²/d x 5) or HiDAc (3 gm/m²) in 3 hr infusion q 12 hr x 3-8 doses/course). Toxicity was dose related (see Table).

| Treatment | Complete Remission | Partial Remission | Total
<table>
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<tbody>
<tr>
<td>CI x 7</td>
<td>91/107</td>
<td>1/107</td>
<td>102</td>
</tr>
<tr>
<td>CI x 14</td>
<td>29/39</td>
<td>0/39</td>
<td>39</td>
</tr>
<tr>
<td>CI x 21</td>
<td>12/21</td>
<td>0/21</td>
<td>21</td>
</tr>
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<td>CI x 28</td>
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<td>CI x 42</td>
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<td>CI x 49</td>
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Significant CNS toxicity, irreversible in 3 pts, was more frequent after HiDAc, leading to an adjustment in the HiDAc to a "god" schedule. Transient rises in liver function studies were frequently and were uncommonly of clinical importance. Remission deaths were more common in pts given Ara-C by CI (6/69) than HiDAc (1/60). Based on these findings, the CALGB has initiated a Phase II trial, comparing HiDAc (3 gm/m² q 12 hr x 2 qod x 3) with "high dose" CI Ara-C (400 mg/m²/d x 5) and "standard dose" CI Ara-C (100 mg/m²/d x 5) in ANLL pts in CR.

2842 IDIOPATHIC REFRACTORY SIDEROBLASTIC ANAEMIA TRANSFORMING TO ACUTE MEGAKARYOBLASTIC LEUKAEMIA: IDUROPILOTIC IDR (4-deacetyl idarubicin) is a new anthracycline analogue which shows anti-tumor activity similar to that of daunorubicin (DNR) at doses 6-8 times lower. In phase I clinical studies IDR produced milder side effects and less cardiotoxicity than DNR. Based on a previous phase I trial (Nayak et al., Investigational New Drugs 2, 375-359, 1984) we started a phase II study of IDR in r-lapsed or refractory AML at doses 6-8 times lower. In phase I clinical studies IDR produces milder side effects and less cardiotoxicity than DNR. Based on a previous phase I trial (Nayak et al., Investigational New Drugs 2, 375-359, 1984) we started a phase II study of IDR in r-lapsed or refractory AML at 7 mg/m²/day for 5 consecutive days (rapid I. E. injection). Twenty five patients are eligible including 12 in first remission, 7 refractory AML, 5 blasts crisis of CM, 1 secondary leukemia. Two patients died during initial induction therapy (in non-elastic aplasia) and are evaluable for response. Of 23 evaluable patients, 4 (18%) have achieved CR and 3 (18%) had partial response. Toxicity was limited to severe myelosuppression. In all patients, mild nausea and vomiting (15 pts) and stomatitis (grade 3, 5 pts). The safety and tolerability of IDR prompted us to increase the dosage to 8 mg/m², or 12 mg/m². To the present time, 19 patients entered this study (18 pts, first relapse, 1 refractory AML, 1 secondary leukemia). Two patients died in aplasia and are evaluable only for toxicity. Of 17 patients evaluable for efficacy, 6 (35%) achieved CR and 6 (35%) had partial response. The main toxicity was myelosuppression (8 pts/71, grade 3, 5 pts). At both levels no significant clinical cardiotoxicity was encountered. We conclude that IDR is an active agent in first relapse of AML (6/25 pts: 25% and at 8 mg/m²: 6/12 pts: 50%) with an acceptable toxicity. Incorporation of this drug in front line induction treatment of AML seems warranted.


Previous phase I and II studies have demonstrated that idarubicin (IDR) is an active agent in the treatment of acute leukemia. In this study we have investigated its efficacy in combination with VP-16 in patients with acute myelogenous leukemia as salvage treatment. The regimen consists of idarubicin, 10 mg/m²/day i.m. days 1-5, and VP-16, 100 mg/m²/day on days 1-5. As of 15th November 1985, 26 patients are evaluable. 9 of those (33.3%) have achieved a complete remission, including 3 patients with primary refractory disease. 3 with early relapse (within 6 months after first remission), 1 with relapse under maintenance therapy and 1 at second relapse. The median duration of complete remission was 16 weeks with a range from 12 to 104 weeks. Other patients have attained a partial remission. 6 patients died within 4 weeks of treatment. Clinical toxicity was identical with reversible pancytopenia for periods up to 4 weeks, mild nausea and alopecia. This combination seems to be active in acute myelogenous leukemia. Incorporation in first-line protocols seems justified.
CONCURRENT TRIAL OF A NEW PROTOCOL CONTAINING IDARUBICIN, VP-16 AND CYTARABINE (3+3/5 PROTOCOL) vs. DAUNORUBICIN AND CYTARABINE (3+7 PROTOCOL) IN ADULT UNRELEIVED ACUTE NON-LYMPHOBLASTIC LEUKAEMIA (ANNL). A PRELIMINARY REPORT.

A.M. Carella, M. Martineengo, G. Santini, A. Congiu, S. Nati, D. Giordano, M. Repetto, A. Marmont, Dept of Hematology Bone Marrow Transplantation Unit, S. Martino’s Hosp, Genoa, Italy.

Despite Idarubicin (IDR) in experimental leukemias demonstrated to be more effective than Daunorubicin (Casazza et al, Tumor 1980) the clinical reports concerning the therapeutic effects of this drug are relatively few. In the first pilot studies, our and other experiences confirmed the important activity of IDR, suggesting a lack of cross-resistance between IDR and DNR. Objectives of the present trial were: to compare the effectiveness in terms of CR rates, CR duration, cardiac and non-cardiac toxicities between the 3+3/5 (Prot.A) and the 3+7/5 (Prot.B) Method. Since March ’84, 21 pts were admitted in our Division. 10 pts (6:8:4) with median age of 38 yrs were treated with "A" (IDR 8mg/mq i.v. for 3d., VP-16 150mg/mq i.v. for 3d. and ARA-C 200mg/mq cont.infusion for 5d. and 13m:8:5 with median age of 53yrs) with "B" (DNR 45mg/mq i.v. for 3d. ARA-C 150mg/mq cont.infusion for 7d. I.FAB sub-classification was M1=1;M2=3;M3=1;M4=5 and B for "A" group and M1=4;M2=3;M3=2 for "B" group. Results: Protocol "A": 11 pts achieved CR (91%) and 8 out 10 after the first course. Median CR duration and median survival were 9mo. (range 1-23mo.) and 10mo. (range 1-23mo.) respectively. Now (Nov 85) 16pts are alive and 5pts are DFS-13mo. Protocol "B": 8/10 achieved CR (80%) but only 1 out 8 after the first course (2 pts are too early and one pt died in induction). Median CR duration and median survival were 5mo. (range 1-30mo.) and 6mo. (range 1-30mo.) respectively. Now 5pts are alive but only 3pts are DFS.No difference was observed in terms of toxicity between the two groups. Conclusion: Although the data here presented are preliminary, the first results would indicate a higher anti-leukemic activity of 3+3/5 Protocol vs the "regular" 3+7 Protocol.
M-52: ACUTE AND CHRONIC LEUKAEMIAS: MEDICAL ONCOLOGY

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ACUTE NONLYMPHOBLASTIC LEUKEMIA (ANLL) EVOLVING DURING THE COURSE OF CHRONIC LYMHPHOPROLIFERATIVE DISEASES. W.-D. Ludwig, H. Selbitz-Jung, M. Paulsen, H. Pichlmayr, and R. HülI. Klinikum Steglitz, Berlin, FRG

Although there are now several documented cases in which ANLL developed after a short interval of chronic lymphoproliferative disease, the first patient, a 74-year-old woman, was hospitalized in April 1981 because of generalized lymphadenopathy, histopathologically confirmed lymph node biopsy, bone marrow (BM) aspiration and surface marker analysis revealed lympho- blasticoid lymphoma. Cytotoxic therapy (CT) with chlorambucil (CBL) and prednisolone (PRED) was instituted because of anemia and thrombocytopenia. The patient received a cumulative dose of 295 mg CBL till December 1981, when leukocyte counts increased and morphologic/immunologic analysis of BM revealed ANLL. The patient died from sepsis before initiation of CT. The second patient, a 72-year-old woman, was hospitalized because of a large skin mass with purulitis. The diagnosis of cutaneous T-cell lymphoma (CTCL) was based on morphologic/immunologic studies of skin biopsies and a peripheral blood sample. Systemic CT with CBL (cumulative dose 150 mg) and PRED was started. In July 1984, she developed pneumonia and died from congestive heart failure. Both patients were diagnosed as having ANLL coexistent with CTCL. The 1st patient refused CT and died from congestive heart failure, which could have contributed to the development of the second leukemia to be discussed.

2850


Since 09/81, 465 pts with ALL (60% M 1; 40% M 2 to 5) were randomized to receive as remission induction therapy: (A) standard (200 mg/m² x 7) and (B) high-dose therapy (200 mg/m² x 7) with CBL (cumulative dose 1500 mg/m² x 1, 541/541, 341/341) achieved CR. CR rate was influenced only by age. Patients were randomized to receive maintenance courses of chemotherapy every 4 weeks for 16 months (M) with (A) standard (200 mg/m² x 5) and (B) high-dose therapy (200 mg/m² x 5) and alternatively prednisone (15 mg/m² x 5) and methyl dose (75 mg/m² x 5). Response 2 where 6/12 (50%) mg/m² replaced ARA-C. No. 11 where 4 courses with ARA-C and MPA (129 mg/m² x 2) were first administered followed by regimens similar to 1-14 pts with M0 on relapse. (A) standard (150 mg/m² x 1) present during remission CR prophylaxis (alkyl irradiation = 17 megarads) then maintenance identical to 1. Actuarial duration of CR has been 20 M with reg. 1, 16 M with reg. 2, 25 M with reg. 2. M 0 and 15 M with reg. 4. Overall predicted long-term remission rate is 24% and 25%, 14% and 14%, 47% and 47% according to maintenance arm. 3/5 pts of M 0 and M 1 relapses have surveived. Factors adversely affecting remission duration are: age<50 yo, initial hyperleucocytosis, cytogenetic abnormalities, remission arm A and maintenance regimen 2. Following conclusions can be drawn:

- Maintenance therapy is of value in ALL.
- CNS prophylaxis is indicated only in M 0 type or pts with hyperleucocytosis at presentation.
- Early intensification improves prognosis.
- While GCS similar to that achieved with AMMT is achieved in pts >30, younger pts carry a worse prognosis.

2852

PROGNOSTIC FACTORS IN ADULT ACUTE LYMPHOPROLIFERATIVE LEUKAEMIA. S. Agarwai, S. Sharma, K. A. A. Y. R. S. Sundaram and V. Kochupillai, Institute Rotary Cancer Hospital, A.I.R.M.S., New Delhi, India

In childhood acute lymphoblastic leukaemia (ALL) factors like age, sex, while all count, hemoglobin level, mediasinal mass, central nervous system disease at onset, morphological and immunological type influence prognosis, but the significance of these factors is not well established in adult ALL. 43 previously untreated adult ALL patients (age 12 years) were analyzed to study the correlation of presenting clinical features with outcome of treatment. The effect of each following characteristic on achievement of complete remission (CR), duration and survival was studied. CNS disease at the time of presentation and no CNS prophylaxis after achieving complete remission have adverse effect on remission duration. None of the factors including total number of white cells, 20,000 or 20,000 - 1 lac or 1 lac/, platelets or 1 lac, age, or 25 years, haemoglobin level or 5 gm%, fever, bleeding organ-megaly and duration of chemotherapy required to achieve remission / or 6 weeks/ correlated with the prognosis. Support that childhood ALL do not apply to the adult disease.
2854 IMPROVED SURVIVAL AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION FOR CHRONIC MYELOGENOUS LEUKAEMIA
S. Varga, Z. Barabáns, F. Krizsa, J. Cserháti
2nd Dept. of Med. Univ. Med. Sch. Szeged, Hungary

All adult patients with acute myelogenous leukemia (only responders to true drug resistant leukemia) were studied. The predictive value of haematologic parameters / -unit blood cell count, per-
centage of bone marrow blast/ were assessed. Higher rate of remission was observed in patients with low leukocyte count, 20x109/1 platelet count. Bone marrow

2855 IMPROVEMENT IN MYELOCRON-LYCITARIN PRECONDITIONED BONE MARROW-TRANSPLANTED CGD PATIENTS
T. Nagy, A. Graber, E. Kelemen
Petéry Teaching Hospital, Inst. Dept. of Medicine Semmelweis University, udepest, Hungary

Infection commonly occurs in bone marrow trans-

plantation (BMT) and causes death in 20-40%. In our trial the severity, frequency and type of infections were investigated in patients subjected to BMT using CYCLOSPORIN (Cyclo-

moniatol - CAM - CYCITARIN /CY/ preconditions instead of total body irradiation (TBI).

Nine CGD patients were treated by CY/ in accelerated phase. Three of

them have got haploidentical W and F identical B.

Eleven bacterial infections were assessed and 4 of them were fatal. The isolated bacteria were St. aureus, Es. coli, Klebsiella, Proteus spp., Es. cloacae, S. marcescens, Staphylococcus aureus, Streptococcus pyogenes, Es. coli, K. pneumoniea, E. coli, Klebsiella, Proteus mir.,

Five patients were treated with CY/ in chronic phase, one with primary

malignancy or chronic myelogenous leukemia in chronic phase, and one with chronic myelogenous leukemia in accelerated phase. They were given 16 mg/kg of busulfan and 120 mg/kg of cyclophosphamide in preparative therapy and a combination of Cyclosporin and Methyprednisolone as prophylaxis for graft-versus-host disease (GvHD). Immuno-
globulin was administered post-transplant orally and intra-

2856 Haity CELL LEUKEMIA TREATMENT WITH RECOMBINANT LEUCOCYTE A-INTERFERON: REPORT ON TWO CASES

A. Sarti, G. Di Ilio, School of Hematology, University of Pavia, Italy

Myeloid cell leukemia (MCL) has emerged as a hematologic malignancy that is highly respon-
dive to interferon therapy: we can confirm this in our experience with the treatment of 2 cases of MCL with recombinant interferon alpha 2b. In the first

patient, splenomegaly induced a remission lasting one year; however, relapse occurred with a high level of bone marrow hematocline cells after 2 months and was rapidly induced by complete remission: ther-

apy was interrupted after 6 months, and the patient is still in complete remission after 1 year. In the second patient, a similar rapid response to IFNa alpha 2b 10M IU i.m. was observed, with an immediate recovery of peripheral blood picture, a dramatic reduc-
tion of bone marrow hematocline cells, and a great improvement of clinical status, this patient is now in the maintenance phase of therapy, at the dose of 10M IU of IFNa alpha 2b i.m. every other day.
M-52: ACUTE AND CHRONIC LEUKAEMIAS: MEDICAL ONCOLOGY


In the last 20 years 115 patients with chronic granulocytic leukaemia (CGL) were in the observation of the Medical Clinic of Gastroenterology. From these patients 11 presented gastric or duodenal ulcer, none of them with very severe or lethal evolution. This accumulation of pathologies is most likely related to the increased histamineaemia in CGL. Digestive lesions, with asymptomatic clinical evolution, were revealed only by radiological examination. The mentioned observation obliged us to make gastro-duodenal radiological examination in all cases of CGL before starting myeloperoxidase treatment, because it can provoke severe or lethal hemorrhage in patients with such lesions.

Taking into account this morbid association dependent on the clinical status, first is necessary to treat the digestive disease (using, eventually, H2 receptor inhibitors) and only thereafter cytostatic therapy.


Between 1/84 and 9/85 15 PM+CM pts in chronic phase underwent allotopic BMT from HLA identical sibs. The median age was 33.5 years and median disease duration of CML at the time of HMT was 20 months. The pretransplant conditioning regimen consisted of CTX (120 mg/kg) and CYC at a dose of 1.7 Gy each, administered in 3 daily fractions over 3 days at a dose rate of 50-70 cGy/min. To prevent GVHD we used FMX in 1 pt and CSA in the other (7 pts). In addition to Gva, the 10 most recently transplanted pts received donor marrow incubated in vitro with the growth inhibitory and carcinogenic effects of irradiation plus intrathecal chemotherapy program.

Results: All pts showed engraftment. No differences were observed for the number of days to the remission between pts receiving CP-1 treated or untreated BM. A reduced grade 1-2/III (1-1.5% of BM/marrows) -III (1.5%) appeared only in the untreated pts. No late BM failure was observed. 3 CP-1 untreated pts died from heart failure (1), extramedullar hematopoiesis (2) and combined exfoliation - A-GvHD. Among CP-1 treated pts, 1 died from heart failure and 1 chp developed cytogenetic relapse. The axillary overall survival at 30 months is 75% (35% for CP-1 treated pts vs 62% for CP-1 untreated pts).

Supported by IMR, PHQ, contract no. MA/007/10/04.

2859 CNS PROLIFERATIONS USING A TROPE INTRATHecal DRUG THERAPY WITHOUT CRANIAL IRRADIATION IN ACUTE LYMPHOBLASTIC LEUKAEMIA. I. Masfou·, M. J. Millett, M. J. E. M. I. Kamsr. Inst. of Oncology & Immunogenetics, Villejuif, France and Dept. of Medicine, Ain Shams University, Cairo, Egypt.

A randomized study was designed to answer the question is intrathecal methotrexate, cytarabine and hydrocortisone given during induction and maintenance equally as effective as cranial irradiation plus intrathecal methotrexate in 30 acute lymphoblastic leukemia (ALL) patients received cranial irradiation plus intrathecal methotretaxte as CNS prophylaxis while the remaining 11 patients received intrathecal methotrexate, hydrocortisone and cytarabine without cranial irradiation. Incidence of primary CNS relapse in the first group (n=30) was 22.2% and in the second group (n=11) was 19.4%. Such triple combination intrathecal chemotherapy program should be the standard CNS prophylaxis as it is more effective than cranial irradiation, and at the same time avoids the encephalotoxic, hematosjprk, growth inhibitory and carcinogenic effects of irradiation. Intrathecal drugs provide a systemic as well as meningeal antileukemic effect; it is less expensive and is more readily available than expert radiation therapy and is easier to apply in children.

2860 ACUTE NONLYMPHOBLASTIC LEUKAEMIA (ANLL) SECONDARY TO HODGKIN'S DISEASE (HD). J.W. van der Velde*, J.W. Guine* and H.J. van Putten*, The D. D. Der Hoo, Cancer Care Center, Rotterdam, The Netherlands, and M.D. Anderson Hospital**, Houston, Texas, USA.

International Cancer Patient Data Exchange System (ICPDS), Committee on International Collaborative Activities of the UICC.

In order to determine factors which predispose to ANLL in patients who have received treatment for HD, participants in ICPDS carried out a case-control study. All patients previously treated patients diagnosed as HD in the years 1972 through 1978 and treated in the institute entered the study. They were followed till 1985. The cohort data were minimal. The patients for the case-control study were centrally matched on sex, age and length of follow-up. For each case (patients who developed ANLL) 5 control cases were selected (patients without ANLL). For these patients extensive data were asked, especially detailed data on kind and length of treatment. The total cohort contains 1681 HD patients of whom 18 developed ANLL. This means a relative risk of 63, in comparison with the population. A statistical significant difference is found both in the probability of ANLL within 10 years of 2.33, this is a relative risk of 63, in comparison with the population. Also a statistical significant difference is found both in the probability of ANLL within 10 years of 2.33, this is a relative risk of 63, in comparison with the population.
Complete Remission Induction for patients with Acute Myelogenous Leukemia

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A retrospective study was performed for 39 patients with acute myelogenous leukemia, who were treated with classical TAD regimen (23 patients) or augmented TAD 3-10 regimen (16 patients) as a remission induction chemotherapy.

Complete remission (CR, of which definition is excluding "relapse within 3 months after application of chemotherapy") rate, duration of remission were compared between each group.

The CR rate in augmented TAD 3-10 group was 81.3%, and was superior to that in classical TAD group (56.5%). Overall CR rate was 66.7%.

The median duration of remission in all was 10.5 months (3-44), in classical TAD group, 13.1 months, and in augmented TAD group, 7.8 months (3-19). The duration of remission would be prolonged, if we perform long term follow up study in augmented TAD group.

In patients with consolidation chemotherapy after CR, the median duration of remission (13.5 months, range 3-44 months) was longer than that (7.6 months, range 3-11 months) in patients without consolidation chemotherapy.

Our data suggests that:

1) augmented TAD 3-10 regimen, which was modified from conventional TAD regimen by adding cytosine arabinoside which function is killing the recruit S phase blasts on day 8 to 10, for 2 days, were superior to classical TAD regimen for induction chemotherapy of acute myelogenous leukemia.

2) consolidation chemotherapy after CR would prolong the duration of remission in patients with acute myelogenous leukemia.

The effect of a (I,3-analogue 'Zoledron' Depo F1116.6301 in advanced carcinoma of the prostate: Preliminary results of a multicentric study

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(*) Division of Med. Oncology, Univ. of Naples, (***) Urology Dept., S. Spirito Hospital, Salerno; (***) Urology Dept., Hospital of Varasa; (*) Urology Dept., Hospital of Venice; (**) Urology Dept., S. Paolo Hospital, Siena; (**) Urology Dept., Polichnico Materile, Perugia; (**) Urology Dept., Maria Vittoria Hospital, Tavarnelle; (***) Surgical Clinic, Univ. of Bari; (**) Urological Clinic, Univ. of Sapienza, Rome.

'Zoledron' [116,630] is a potent Ia-RK anligogue, available in a depot formulation for subcutaneous injection. In a multicentric open study, 'Zoledron' was administered, at the dose of 3.6 mg every four weeks and for a minimum of twelve weeks, to 52 patients with histologically confirmed advanced prostatic carcinoma. "Advanced" was defined as the presence of distant metastases or extension of the tumor beyond the prostatic capsule. Criteria for exclusion were prior use hormone or anti-hormone therapy, orchidectomy, cystectomy chemotherapy. Extension of subjective urological symptoms, bone pain, and analgesic drug use, serum testosterone, luteinizing hormone and acid phosphatase concentration. In category size of the prostate and of any measurable tumor deposit were recorded prior to beginning of therapy and at 4, 8, 12 weeks and every 12 weeks thereafter. Isotope bone scans and X-ray bone surveys were obtained before treatment and at 12, 24 and every 12 weeks thereafter. Objective responses, including complete and partial responses and stabilization, were observed in about 75% of the patients. Side effects, aside from those resulting from the fall of serum testosterone, were absent. From these preliminary results we conclude that 'Zoledron' can be considered as an effective and safe drug for the management of advanced prostatic cancer and a sound medical alternative to surgical castration.

Flutamide is an antiandrogen which functions by binding to the dihydrotestosterone receptor protein. As this substance does not inhibit testosterone synthesis, treatment should be combined with orchietomy to avoid high testosterone levels.

We report on treatment of 26 patients with advanced prostate cancer (stage C or D), who had no prior therapy. All patients first received 1000 mg Flutamide daily for 5 days, and then after orchietomy 750 mg daily. Beside of the testosterone levels, LH release and prolactin release were controlled as well. Hyperprolactinemia was observed only in a few cases. The compatibility was good.

Pain from bone metastasis disappeared within a short time. The incidence of response could also be evaluated by cellular change in transrectal biopsy specimens.
ANDROGEN PRIMING AND RESPONSE TO CHEMOTHERAPY IN ADVANCED PROSTATE CANCER. A. Mami, R. Santen, A. Boucher, A. Lipton, S. Harvey, D. White, M. Simmons, R. Gordon, T. Kohler, U. Dang, W. M. Offord, and L. Glode, Dept. of Medicine and Surgery, The M.S. Hershey Med. Ctr., The PA State Univ., Hershey, PA and Univ. of Colorado Health Sciences Ctr., Denver, CO

Sixty-seven orchiectomized men with progressive stage D2 prostate cancer have been entered in a controlled trial to test whether transient androgen deprivation therapy (ADT) prior to initiation of chemotherapy enhanced the efficacy of cytotoxic drugs. Median duration of follow-up is 24 months. All patients were treated with goserelin acetate (3.6 mg i.m. every 28 days) and a single injection of 20 mg Decapeptyl (Leuprolide Acetate, Ferring, Sweden) for 3 days before initiation of chemotherapy. Adjuvant antiandrogens were given to patients with castrate levels of testosterone, analogues of LH-RH. The authors studied the clinical administration of Decapeptyl (15 U/kg) which was given subcutaneously once daily in a dose of 0.15 mg/kg for 5 weeks of continuous androgen suppression of the prostate. The clinical study was evaluated by physical examination, rectal examination, transabdominal ultrasonography, bone X-ray, and serum PSA and estradiol levels. The larger number of evaluable patients in the stimulation arm (42) was due in part to early discontinuation of the treatment due to toxicity from fluoxymesterone, including 2 cases of reversible spinal cord compression. No difference has been observed so far in median duration of response (9 months in both groups) or survival (13 months in the stimulation arm and 16 months in the control arm). Our data suggest that androgen priming may enhance the response rate to chemotherapy. The lack of improvement in response duration and survival may be due to the large proportion of hormone-independent cells present in patients with prostate cancer refractory to orchidectomy.


Recent physiological and clinical studies revealed that, paradoxically, inhibition of the pituitary and gonadal function by luteinizing hormone-releasing hormone (LH-RH) analogues has been found to enhance the efficacy of cytotoxic drugs. Median duration of follow-up is 24 months. No difference has been observed so far in median duration of response (9 months in both groups) or survival (13 months in the stimulation arm and 16 months in the control arm). Our data suggest that androgen priming may enhance the response rate to chemotherapy. The lack of improvement in response duration and survival may be due to the large proportion of hormone-independent cells present in patients with prostate cancer refractory to orchidectomy.
AMINGDRUGUINHIDIMID IN THE TREATMENT OF ADVANCED PROSTATIC CANCER, RESISTANT TO CONVENTIONAL THERAPY

Robin Murray & Paula Pitt

Cancer Institute, Melbourne, Victoria, Australia

Inhibition of adrenal steroid synthesis with aminoglutethimide (AG) is now an accepted therapy for patients with advanced breast cancer. In this study we report results of the same treatment in patients with advanced prostatic cancer, resistant to conventional therapy.

One hundred and twenty seven men (median age 69 years, range 40-89) with actively progressing advanced prostatic cancer, have been assessed, according to the NCCN criteria, for their response to treatment with AG and physiological steroid replacement (A/G 500-750mg/day, Cortisone Acetate 37.5mg/day ± Flucortisone 0.1mg/day). All patients had had a prior orchidectomy and/or oestrogen therapy. Most had received radiotherapy. Twenty (16%) patients had an objective remission while 27 (21%) had stabilization of previously progressing disease. Survival was significantly longer (p < 0.001) in the remitters (16.2 months) and the static group (8.5 months) than in the patients who failed to benefit (4.7 months). Performance status significantly improved in the remitters and the static group and significantly decreased in the patients with progressive disease. Side effects were minimal and the drug was ceased because of toxicity in only one patient.

Conclusions
1. AG is a safe and useful treatment in patients with advanced prostatic cancer who have failed conventional therapies.
2. Approximately 37% of patients have improvement in performance status and survival.
3. Earlier treatment with A/G could lead to better results and warrants investigation.

COMPARISON OF RESPONSES BETWEEN PRIMARY AND SECONDARY CHEMOTHERAPY REGIMENS IN PATIENTS WITH HORMONE REFRACTORY ADVANCED PROSTATE CANCER

Robin Harwood

The Prostate Cancer Treatment Group (PCTG)

The purpose of the study was to compare the efficacy of employing secondary chemotherapy modalities in those patients who failed a primary chemotherapy regimen. Responses were characterized according to the National Prostatic Cancer Treatment Group (NCTG). Thirteen patients (61.5%) had a positive response to the initial regimen employed with a response ranging from 2-50 months (mean 15.9 months, median 6 months). Of these, eight (61.5%) also responded to the use of secondary chemotherapy with a duration of response ranging from 3-20 months (mean 12.6 months, median 5 months). Of the 17 patients who failed primary chemotherapy (39.5%), six patients (35.2%) responded to the subsequent use of another modality, with a duration of response ranging from 5-10 months (mean 8.5 months, median 5.9 months). The data suggests that those who respond favorably to a primary chemotherapy modality also respond favorably to secondary treatment. In addition to this, the data also suggests that those who fail primarily will also fail secondarily.
M-53: PROSTATIC CANCER: CHEMO- AND HORMONOTHERAPY

2872 CLINICAL EFFECTS OF UFT ON PROSTATIC CANCER. K. Naito and H. Hisazunu, Department of Urology, School of Medicine, Kanazawa University, Takara-machi 1-1, Kanazawa 920, Japan

A phase II study of UFT, a mixture of furofural and uracil in a ratio of 1:4, was performed on prostatic cancer in five cooperative institutions. UFT was orally administered at a daily dose of 600mg, 3 times a day, for at least 4 weeks. Castration was not carried out. Twenty-two patients treated with UFT were evaluated according to Koyama-Saito's criteria. Tumor staging using transrectal ultrasonography and other methods revealed stage B in 4 patients, stage C in 7, and stage D in 11. The overall response was 18.2%. Complete response was obtained in 1 patient with stage B lesion, partial response in 3, and minor response in 1 and no change in 15 and progressive disease in 2. With respect to toxicity, anorexia was observed in 9 patients, nausea and vomiting in 8, stomatitis in 4 and diarrhea in 3. Leukocytopenia of less than 3,000/mm^3 occurred in 1 patient, and another 1 patient had hepatic disorder. From these results, UFT proved to be a useful drug for the therapy of prostatic cancer.

2873 HETEROGENICITY OF PROSTATIC CARCINOMA CELLS
I. Sesterhenn, M.D., Armed Forces Institute of Pathology, Wash. D.C., USA

Although all the 40 grading systems do rather well in predicting behavior in groups of patients, none of them is applicable to individual patients. Tumors which appear similar in H-E stained sections may behave differently: may remain dormant in one patient, but metastasize in another; one patient with metastasis may respond dramatically to treatment, the other succumb in a short time. The grading systems have all assumed a homogeneous cell population, whereas, in fact, this is not always the case. The paragraphs presently used include the nucleus, glandular differentiation and growth pattern. Efforts to predict metastatic potential and responsiveness to treatment should include evaluation of cytoplasmic appearance as well. The cytoplasm can be sparse or abundant, amphophilic, light staining, eosinophilic, clear or vacuolated. Many tumors consist of an admixture of cells. By immunohistochemistry, evaluating both prostatic enzymes (PAP and PSA), well differentiated tumors resemble most closely the normal cell; moderately differentiated tumors show variable staining, but most tumor cells are positive. However, poorly differentiated carcinomas show the greatest variability in expression of PAP and PSA, with some tumors consisting only of either one of the enzymes or even neither. Ultrastructurally, most tumors consist of more than three of the six cell types. To date, the cytoplasmic appearance has not been correlated with metastatic potential and treatment response.


The treatment of metastatic adenocarcinoma of the prostate refractory to orchietomy or hormonal manipulation remains controversial. This trial has been developed in order to evaluate toxicity and response and survival in symptomatic patients with advanced disease treated with a combination of a single agent of activity in this disease and corticosteroids.

Treatment: Cyclophosphamide: 600 mg/m^2 P.O. each 10 days Prednisone: 20 mg P.O. day 1-14

Nineteen patients with stage D2 were fully evaluable for toxicity, response and survival. Median age was 68.3 years (range 57-78). Median performance status (ECOG) 1.5. Only patients with measurable disease (metastatic) or documented bone metastases and either an elevated acid phosphatase (AP) or alkaline phosphatase(ALP) were eligible. Response criteria included: regression of measurable disease or normalization of AP or normalization of ALP. Results: 7/19 patients obtained partial remission (37%), 7/19 had stable disease and 5/19 (26%) progressive disease. Median duration of response was 9.28 month (range 3-18). Median survival time: responders= 26 month, stable disease= 18 month, progression= 10.2 month. Toxicity was low: leukopenia in 21% of the patients, anemia in 16%. Nausea and vomiting were low to moderate. The combination of cyclophosphamide and prednisone has activity in advanced, hormone refractory prostatic cancer. Toxicity has been minimal. Further randomized studies should compare this scheme with best supportive care to know the real value of chemotherapy treatment.

Supported in part by PAHO/NCI contract NOI-CM-27391


2878 PHASE III STUDY OF M-54 IN COMBINATION WITH CARRIERS AND OTHER COMBINATION THERAPIES IN ADVANCED UTERINE CERVICAL CANCER. H. H. de Vries, C. van der Eerden, and J. B. Vermeerken.

2879 EFFICACY AND TOLERABILITY OF M-54 IN THE TREATMENT OF UTERINE CERVICAL CANCER. H. H. de Vries, C. van der Eerden, and J. B. Vermeerken.
COMBINATION CHEMOTHERAPY WITH CDDP/CTX VERSUS VCR/5FU/MTX IN THE TREATMENT OF ADVANCED CERVICAL CARCINOMA.

Temple J; Tagle JG; Bargon J; Trapani CA; Fleske G; Galvez C; Lerner G and Mendez M.
Hospital Mauricio de Onis, CABA, Argentina.

The management of disseminated cervical cancer has not significantly improved with the progress of modern chemotherapy. Thirty-five pts. of which histologically proven advanced cervical cancer were included in this study. At time of evaluation, 28/35 were fully evaluable. Patients characteristics were: median age 52.6 years (r:31-63 years), median PS was 1(r:0-2). Prior chemotherapy: 17 pts. All pts. had distant metastases. Pts. were considered evaluable for response if they had received at least 9 courses of chemotherapy. The pts. received two regimens of chemotherapy: Reg A: CDDP 50 mg/m², iv day 1+ CTX 1 gr/m², iv day 1. Regimen B: VCR 1.4 mg/m², iv day 1; BLM 15 mg/m², iv day 1, and Mitomycin C 25 mg/m², iv day 1. Regimen B was received previously Co60 + rad, and surgery only in the complications. Regimen B: 16 pts. 13/14 received VCR previously (Co60 + Rad) and surgery only in the complication.

RESULTS: RA: CR: 1/12 pts (8.33%); PR: 2/12 pts (16.66%). Stable Disease: 1/12 (8.33%) and Progression: 8/16 (50%). Regimen B: CR: 1/16 (6.25%); PR: 6/16 pts (37.5%). SD: 2/16 (12.5%). Prog: 7/16 (43.75%). Median response duration: Reg A: 44.2 m (R:12-156m); Reg B: 27.7 m (R:46-60 m).

Toxicity: RA: hematological: 4; Alopecia 3; nausea and vomiting: 10, and renal failure: 1 pts. Regimen B: hematological: 5; alopecia: 2; nausea and vomiting: 10, and renal failure: 1 pts. Median response duration: Reg A: 44.2 m (R:12-156m); Reg B: 27.7 m (R:46-60 m).

RESULTS: RA: CR: 1/12 pts (8.33%); PR: 2/12 (16.66%). Stable Disease: 1/12 (8.33%) and Progression: 8/16 (50%). Regimen B: CR: 1/16 (6.25%); PR: 6/16 pts (37.5%). SD: 2/16 (12.5%). Prog: 7/16 (43.75%). Median response duration: Reg A: 44.2 m (R:12-156m); Reg B: 27.7 m (R:46-60 m).

Toxicity: RA: hematological: 4; Alopecia 3; nausea and vomiting: 10, and renal failure: 1 pts. Regimen B: hematological: 5; alopecia: 2; nausea and vomiting: 10, and renal failure: 1 pts. Median response duration: Reg A: 44.2 m (R:12-156m); Reg B: 27.7 m (R:46-60 m).

CONCLUSIONS:
1. - Survival with the regimen A is significantly better than regimen B(P=0,01).
2. - The major response rate was achieved with the regimen B (43.75% vs. 24.94%).
2885 STUDIES ON SIDE EFFECTS IN CISPLATIN ALONE OR COMBINATION TREATMENT IN PATIENTS WITH PRIMARY ADVANCED AND RECURRENT OVARIAN AND CERVICAL CANCER.

NOGUCHI Misaki, YOZAKI Motomiaki, ASAI Masayoshi, ISHII Yukish, and CHIHARA Minoru.

In recent years, CISPLATIN has been introduced widely to the therapy for various kinds of malignancy tumors as a single-agent or combined therapy, and its antimicrobial and side effects which influence on patients' condition are given attention with great interest.

In the department of Obstetrics & Gynecology, Aichi Medical University, we have administered CISPLATIN as a single-agent therapy or as combined therapy with GAF and have studied its effect and side effect. Therefore we report the result of our examination.

64 patients with gynecological malignant tumors who were not given other chemotherapy or radiotherapy for the past 1 month were included in the subjects. They were administered CISPLATIN 50 mg/m² of body surface area once a day for 5 days; success in administration has been done more than 4 cycles in either method.

Some kinds of side effects were found in all cases. Those which occurred frequently were digestive organ symptoms (in more than 95%), bone-marrow disorder (in more than 60%), and depression (in more than 60%).

The fact that these side effects were found was in around 40% was worthy of attention because it was the most serious and strongly influenced on the prognosis among the side effects caused by CISPLATIN. This result showed that CISPLATIN was effective not only to anticancer therapy but also to the progression of patients' life and to the chemotherapy for the gynecological cancer, especially ovarian cancer.

We reported a countermeasure to the side effects caused by CISPLATIN and the therapeutic effect of it.

2886 CARDIOTOXICITY OF EPIRUBICIN (Epi).

Dept. of Int. Medicine, Bispebjerg Hospital; Dept. of Oncology and Dept. of Clinical Pharmacology, Copenhagen University Hospital; Dept. of Clinical Physiology, Copenhagen University Hospital; Hvidovre; Denmark.

97 patients with advanced breast cancer and no previous treatment with anthracyclines, were randomly treated with either Epi alone (60 mg/m², i.v. day 1, 20 mg/m², i.v. every 4 weeks) or combined with VP (Epi: 45 mg/m², i.v. day 1, 20 mg/m², i.v. every 4 weeks).

Median age was 56 years (range 25-70). The median dose of Epi was 382 mg/m² (range 40-156 mg/m²).

Cardiotoxicity was evaluated clinically, radiologically, with ECG, and with multi gated nuclear cined tomography. An estimation of the left ventricular ejection fraction (LVEF) was given by the left ventricular ejection (EF) in all patients.

There was a significant fall in EF occurred in only 1 patient at 600 mg/m², but no clinical symptoms appeared even one year later. Clinically, at least 53% of patients had normal LVEF at the end of the first cycle of treatment.

Most of the remaining patients are in a stable cardiac condition (NYHA function class I-II; median follow up at 18 months). One patient in CR after a total dose of 1030 mg/m² died 4 months later from a pulmonary embolism and had an autopsy cardiomypathy. This patient was not included in data given above. Conclusively a rather sharp dose-limit was found at approximately 1000-1050 mg/m², below which no serious cardiac events occurred.

2884 EPIRUBICIN IN CERVICAL CANCER.


128 evaluable patients with advanced or recurrent cervical cancer have been treated with Epi at participating institutions in Thailand, Philippines, Taiwan, Indonesia, Malaysia, Singapore and Australia. Approximately 1/3 of the patients presented with locally advanced disease and received Epirubicin as initial treatment. The remainder were patients with recurrent or progressive disease following pelvic irradiation or radical hysterectomy, 37 patients received Epi in a total of 40 mg/m² at a starting dose of 60 mg/m², 4, 25 mg/m² at a starting dose of 40 mg/m² at 50 mg/m² if they had received prior pelvic irradiation. All patients received at least 2 cycles of treatment. At the twelfth dose time with no objective tumour regression and stable disease was observed for a minimum of 9 wks in 30 pts.

Toxicity was more common when chemotherapy was the initial treatment than after surgery or radiotherapy (12 vs 0.75). There was no objective tumour regression in the series. There were no severe cardiac reactions, but some moderate nausea and vomiting in most patients, hair loss was usually apparent by the third treatment cycle.

The occurrence of related deaths and myelosuppression was minimal. Skin and cutaneous pigmentation was seen in many patients. There were no episodes of cardiac dysfunction as the conclusion that Epirubicin has had more side effects in this population than doxorubicin, and that response may be more frequent in patients not previously treated by irradiation. The side effects are predictable and no optimal dose of Epirubicin may have not been reached since myelosuppression was minimal.

M-54: CARCINOMA OF THE UTERINE CERVIX: CHEMOTHERAPY

M-55: SIDE EFFECTS AND PROTECTION AGAINST THEM
LITHIUM EFFECT ON NEUTROPHIL COUNT AND FUNCTION DURING CHEMOTHERAPY.


Based on the observation that patients receiving chemotherapy & MPA in high doses, showed no adverse effects in the counting of peripheral blood elements, we started a multicenter comparative clinical trial associating both treatments. To date 41 patients were included, with following tumoral localizations: breast 26, lung 10, no oat cell 13; kidney 1; unknown primary localization 1. Administered treatment was Adriamycin 50 mg/m² and cyclophosphamide 600 mg/m², repeated every 21 days. A randomly selected group received additionally MPA 500 mg daily during first 30 days and then 500 mg twice a week. All patients were subject to: a) marrow puncture biopsy prior to study and at 30 and 60 days; b) peripheral blood counting every 7 days. Patients receiving MPA were tested for drug plasma concentrations on days 15, 30, 45, 60 and 75 of treatment. Sixteen patients are evaluable to date and show that MPA treated patients show no significant decrease of the marrow and peripheral cells, in relation to MPA untreated patients. The myelostimulation values are positively correlated with MPA plasma concentrations. Although definitive results will be exposed at Congress, these preliminary data show that MPA is an effective inhibiting therapy in the myelosuppression due to cyclophosphamide, with MPA blood concentrations higher to 100 mg/ml.

INHIBITION OF THE MYELODEPRESSION DUE TO CYTOSTATICS, WITH MEDROXYPROGESTERONE ACETATE (MPA).


Based on the observation that patients receiving anthracycline chemotherapy & MPA in high doses, showed no adverse effects in the counting of peripheral blood elements, we started a multicenter comparative clinical trial associating both treatments. To date 41 patients were included, with following tumoral localizations: breast 26, lung 10, no oat cell 13; kidney 1; unknown primary localization 1. Administered treatment was Adriamycin 50 mg/m² and cyclophosphamide 600 mg/m², repeated every 21 days. A randomly selected group received additionally MPA 500 mg daily during first 30 days and then 500 mg twice a week. All patients were subject to: a) marrow puncture biopsy prior to study and at 30 and 60 days; b) peripheral blood counting every 7 days. Patients receiving MPA were tested for drug plasma concentrations on days 15, 30, 45, 60 and 75 of treatment. Sixteen patients are evaluable to date and show that MPA treated patients show no significant decrease of the marrow and peripheral cells, in relation to MPA untreated patients. The myelostimulation values are positively correlated with MPA plasma concentrations. Although definitive results will be exposed at Congress, these preliminary data show that MPA is an effective inhibiting therapy in the myelosuppression due to cyclophosphamide, with MPA blood concentrations higher to 100 mg/ml.

DEPARTMENT OF PATHOLOGY WITH SPECIALIZATION IN ONCOLOGY.


From August 1983 to August 1986 we performed a study in order to determine frequency of hypercalcemia in malignancies, and therapeutic response with salmon calcitonine, furosemide and demestan. We detected hypercalcemia in 15 (5.266) patients over 785 treated during that period. All patients were dissatisfied, seven with Breast Cancer, two with Prostatic Cancer, two with Carcinomas of Rectum, and one of each with Teleseomas, Melanomas, Hyperparathyroidism and Carcinoma of Vulva. The main initial situtation were neurologic. Blood Calcium levels (BCL) were between 13 and 17 mg% in all. We began treatment with IV hyperhydration, 20% of BCL divided q.i.d., demestan 8 mg b.i.d., and salmon calcitonine 6 to 10 IU/kg/day IV divided q.i.d. Thirteen patients responded to treatment and 2 died without significative fall in BCL with progressive neurologic impair. The responders returned to normal BCL during the first 48 h; we maintained in all patients a dose of 100 IU of calcitonine once a day 5 days during 15 days, with measures of BCL twice a week. We reach the conclusion that this treatment is effective in hypercalcemia due to malignancies.

Supported in part by Sandost Labs, Argentina.
TREATMENT OF HYPERCALCÆMIA SECONDARY TO METASTATIC BREAST CANCER WITH LORAZEPAM (A.P.D.)
R. P. Coleman, P. D. Robena. CMF Clinical Oncology Unit, Guy's Hospital, London SE1

Hypercalcaemia is a relatively common complication of metastatic breast cancer caused primarily by osteolytic bone destruction. Established treatment consists of intravenous saline to reverse the dehydration in glomerular filtration, and inhibition of osteoclastic function. We have studied the osteoclast inhibitor A.P.D. to confirm the efficacy of this drug and investigate the dose-response relationship.

18 consecutive patients with metastatic breast cancer and hypercalcaemia (median 1.2 mmols/l) have been studied. All pts. had bone metastases although the tumour burden appeared widely variable. All pts. were rehydrated with 0.9% saline for at least 46 hrs prior to A.P.D. 17 pts. remained hypercalcaemic (median 3.0 mmols/l) after rehydration and received A.P.D. at a dose of 15 mg i.v. calcium = 2.9 mmols/l, or 5 mg i.v. 2.9 mmols/l in 500 ml 0.9% saline over 2 hours. Intravenous saline was continued and further A.P.D. was given only if no response was seen at 48 hrs.

17 pts. achieved normocalcaemia with serum calcium falling steadily over 4 days (median 2.5 mmols/l1) with a concomitant fall in urinary calcium excretion. 10 pts. responded to a single dose of 15 mg, one to 5 mg, one to 2.5 mg, and one to 1.5 mg. 1 pt. died within 72 hours of A.P.D. due to over-sedation and aspiration pneumonia. 3 pts. failed to respond after total doses of 80, 90, and 120 mg of A.P.D.

Observation of pts. who did not respond to additional systemic therapy revealed rebound of hypercalcaemia after 10-14 days. This study shows that a single administration of 15 mg A.P.D. is sufficient to control hypercalcaemia in the majority of pts. with hypercalcaemia secondary to metastatic breast cancer.

PREVENTION OF NAUSEA AND VOMITING DURING CYTOSTATIC THERAPY. J. Poller, M. Patyanik, I. Nagyvajson, G. Nemenith. E. Woll Hospital, Centre of Radiation Therapy, Budapest, Hungary.

The most frequent side-effect of cytostatic therapy is nausea and vomiting. Usually it is not a serious complication, but makes the patient’s life unpleasant. During the common cytostatic therapy in our Institute we aimed to avoid this side-effect. We administered butyrophenol, phenothiazin, metoclopramide, corticosteroids, besides the cytostatic drugs (VCR, MTX, FU, DTIC, Cisplati1). The evaluation of our results was based on the scale, recently recommended by the WHO. Our experience shows a remarkably beneficial effect of the therapy mentioned above, more than seventy percent of our patients didn’t suffer from vomiting.

LORAZEPAM FOR CONTROLLING REFRACTORY CHEMOTHERAPY-INDUCED EMESIS. E. Capozza, M.R. Sertori*, S. Chiara, P. Giuntini, A. Rossis. Istituto Nazionale per lo Studio e la Cura dei Tumori, Genova, Italy. Twenty-eight outpatients (pts) median age 49 years (range 21-72), median PS (0-7) who experienced severe chemotheraphy-induced gastrointestinal side-effects (>10 emetic episodes) (i.e. 10 pts) were treated with Lorazepam (i.v. 2 mg i.v. 30 min before treatment. Pts received combination chemotherapy comprising Cisplatin = 50 mg/m² (10 pts), and Doxorubicin > 25 mg/m² (16 pts), 6 pts received Cyclophosphamide-Methotrexate, Fluorouracile (CMF). All pts had received prior antiemetic treatment with Methylprednisolone (120-275 mg i.v.) alone or with Metoclopramide (1 mg/kg). Anti-emetic evaluation was carried out by a member of the research team who graded emesis and nausea as follows: complete protection = 9 emetic episodes, major protection = 1-2 emetic episodes, minor protection = 3-5 emetic episodes, no protection > 6 emetic episodes, nausea 0 = none, 1 = mild, 2 = moderate, 3 = severe, food intake compromised 4 = severe, food intake impeded. Pts were also asked to express their preference. Improved control of emesis (complete protection) and nausea (grade 0-1) was observed in only 3 and 8 pts respectively. No protection was observed in 16 pts. In contrast, the majority of pts (13), preferred L and 8 pts had no preference. Side-effects due to L were asymptomatic in 12 pts, drowsiness 15 pts; dizziness 2 pts and hallucinations 3 pts. 4 pts refused further L. Although objective improvement of gastrointestinal side-effects was modest the majority of pts. found the hypnotic and amnesic effects of L highly desirable. This drug appears to be a valuable adjunct to anti-emetic therapy in pts with refractory nausea and vomiting.

ALZAPRIDE (A) IN ANTIEMETIC PROGRAM OF HIGH-DOSE CISPLATIN TREATMENT PATIENTS WITH BRONCHIOLITIC TUMORS. G. Kishin, K. Kudoh. Chiba University School of Medicine, Chiba Japan. Twenty-eight patients with bronchiolar tumors Cisplatin > 50 mg/m² were treated with Alzaprile (A) before and after Cisplatin dose escalation. We observed the side-effects starting dose of A was 1 mg x 2. Dose escalation was obtained with increase of alzaprile every two cycles. 14 pts with BC were enrolled and received 40 courses of H.D. Cisplatin was 15 mg/m² median age 67 yrs (42-87), median PS 0 (0-5). Response (PR) were defined as complete remission, major partial 2-3 episodes of emesis, no side effects. The success rate was 12/28 (43%).

Results were:

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<th>Dose (mg)</th>
<th>No. of Pts</th>
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The success rate was obtained during the 1st course of A. In 5 mg/kg and 6 mg/kg groups, in large part constituted by un-treated pts, a Major 8 was reported in 18/27 courses. Side effects were limited to mild sedation, purgative and occasional vomiting.

In conclusion Alzaprile showed good antiemetic activity against H.D.-induced emesis. This efficacy seems to decrease in repeated treatments. Further trials with the non-discriminatory reactions, side effects are limited and dose-unrelated. Further trials and dose escalation schedules are warranted.
HIGH DOSE METOCLOPRAMIDE VS BETAMETHASON-DIXYRAZIN COMBINATION AS ANTIETIC TREATMENT IN DOXORUBICIN AND CISPLATIN CHEMOTHERAPY.

B. Sorensen, and L. Høilund, Department of Gynaecologic Oncology, Brene Medical Center, S-701 85 Brene, Sweden.

High dose metoclopramide (1 mg/kg) and a combination of betamethason (8 mg) and dixyrazin (40 mg) have been evaluated as antiemetic treatments during doxorubicin and cisplatin therapy. The study was prospective, double blind, and used a repeated cross-over (ABAB vs BABA) technique. A total of 100 patients were randomised to start with A (metoclopramide) or B (betamethason-dixyrazin) after stratification between new (63) and old (38) patients regarding prior chemotherapy. The antiemetic drugs were administered as i.v. infusions (15 min.), 0.5 hour before, and 1, 3, 5, and 5.5 hours after the end of chemotherapy. Evaluation was performed by patient and nurse questionnaire using the visual analog scale.

Betamethason-dixyrazin was superior to metoclopramide, and relieved nausea and vomiting in 58% compared to 3% for the latter. The difference between the two regimens was greater for doxorubicin combinations (88% vs 40%) than for cisplatin combinations (22% vs 19%). Extraintestinal side effects (acute dyspnosis, akasisia, parasthesia) were relatively common (20%) for metoclopramide but were practically not seen in the dixyrazin group. Sedation was comparable for the two treatments. Corticosteroids (betamethason) seem to be an important part in anetiestic therapy whereas metoclopramide is of value to prevent nausea and vomiting during cisplatin treatment. Side effects are troublesome, however, and further research is needed regarding doses, administration, use of antidotes and combination with a corticosteroid.

PULMONARY FUNCTION TESTS DURING BLEOMYCIN AND PEPLOMYCIN THERAPY. I. Krémer, National Institute of Oncology, Budapest, Hungary

Bleomycin and peplomycin are antineoplastic agents whose major side effect is pulmonary fibrosis. From 1976 to 1981, 100 patients with head and neck tumour were treated with bleomycin (Blenoxane 

Urals) at the National Institute of Oncology. The total dose of the drug was 360 mg/m². In these patients forced vital capacity (FVC), forced expiratory volume (FEV), peak flow (PEF) and midexpiratory flow (T25-75) were measured with Jaeger spirometer (Kirch, Jager, Würzburg) at pretreatment evaluation and three times during therapy on week 4, 6 and 10. The incidence of pulmonary toxicity was 11%. In 1985, 9 patients with different forms of tumour were treated with peplomycin (Peplocin, Nippon Kayaku Co. Ltd.) for phase II evaluation. The total dose of the drug was 200 mg. In these patients FVC, FEV, PEF, FEF75-75, pulmonary diffusion capacity for carbon monoxide (DLCO) and residual volume (RV) were measured with single breath method. The pulmonary function tests were measured with computerised system Difficonstar FG 90 (Pemys and Gut, Basel) at pretreatment evaluation and four times during therapy, on week 4, 6, 8 and 10, respectively. During treatment some patients had reversible interstitial pulmonary fibrosis and one patient irreversible pulmonary toxicity, fibrosis, respectively. In case of this patient the dose of the drug was 160 mg.
M-55: SIDE EFFECTS AND PROTECTION AGAINST THEM

2900 PROPHYLAXIS BY NORFLOXACIN OR HUMAN IMMUNOGLOBULIN OF INFECTIONS AND FEVER IN GRANULOCYTOPENIC NEOPLASTIC PATIENTS.
**1st Medical Oncology
Regina Elena Institute Rome, Italy.

The infections are the greatest cause of morbidity and mortality of granulocytopenic neoplastic patients. This study was undertaken with the aim to verify the possibility to reduce the incidence of infections in granulocytopenic neoplastic patients, by a prophylaxis with antibiotics or human immunoglobulin.

Eighty patients with solid neoplasia presenting granulocytopenia from at least four days, entered the study. Thirty pts. were treated during leucopenic period with Norfloxacin (400 mg. every 8 hours), fifteen pts. with human immunoglobulin (200 mg./kg./one day), thirty-five pts. without therapy as control. At the 1st and the 2nd day of treatment in the pts. were taken up bacteriological samples from pharynx, from expectorate from stools and from other sites according to clinical indications.

In non-infected pts. the treatment with Norfloxacin was continued until granulocytes were higher than 500/mm^3, but human immunoglobulin was administered once as allergic reactions or clinical appearance of another infection insensitive to the previous therapy, represented a cause to stop the treatment.

The results obtained indicate a statistically significant difference in the lower appearance of infection and fever in the patients treated with Norfloxacin or human immunoglobulin.

2901 "CLINICAL CHARACTERISTICS OF T CELL PATIENTS INFECTION" PROTOCOL R. Tomasi, Respiratorie Division, Policlinico, Italy.

It is a prospective study of 70 patients, with solid neoplasia, treated with granulocyte colony-stimulating factor (G-CSF). The study was performed from January 1st, 1992 to December 31st, 1993. The patients were observed both on the transplantation unit and in the outpatient clinic. The study in the last year included 30 patients.

Twelve patients had severe infections (S) and 58 had no infections (NI).

Infection rates were observed to be significantly lower in the G-CSF group than in the control group. G-CSF patients had a lower incidence of fever, leukopenia, and neutropenia. The study showed that G-CSF treatment is effective in reducing the incidence of infections in transplant recipients.
2903 SENSITIVE METHODS FOR MONITORING NEPHROTOXICITY. M. Vekulova, Z. Meceli, B. Sencov and D. Skalikov. Rea.-Inst. of Clinical and Experimental Oncology, Brno, Czechoslovakia.

Sensitive parameters for the early detection of toxic kidney damage after Cisplatinum and Carboplatinum therapy were determined. We followed the 24-hour excretion of creatinina proteins, and the excretion of urine enzymes before chemotherapy and 5 days after it. Lysozyme, enymes beta-glucuronidase (NAG) and N-acetyl-beta-glucosaminidase (NAG) and brush border membrane enzyme gamma-glutamyltranspeptidase (GGT) were established.

CCl incidental use of these sensitive parameters.

We compared the nephrotoxicity of Cisplatinum with the nephrotoxicity of Carboplatinum therapy using not only the values of blood creatinine and urea but also with the help of these more sensitive parameters.

2905 LONG-TERM ECOCARDIOGRAPHIC, POLYGRAPHIC, AND BIOCHEMICAL EVALUATION OF CARDIAC TOXICITY OF DOXORUBICIN AND 5-FLUOROURACIL. L. Jimenez, J. Pomar, Dept. of Cardiology, H. Juan de la Cruz, Madrid, Spain; and Safarik, Sch. of Med., Košice, Czechoslovakia.

Data recorded by polygraph (Weissler's index-WI), echocardiography (ejection fraction-EF), mean velocity of circumferential fibre shortening (vVCF), fractional shortening (FS), and by the measurement of serum enzyme activities (transaminase isoenzyme of creatine kinase-CKMK, isoenzymes of lactate dehydrogenase-LDH) were evaluated and by the group of 90 patients treated with doxorubicin (DOX 40-800 mg/m²) and/or 5-fluorouracil (5-FU 3400 ± 440 mg/m²). Eighteen surviving patients were monitored six years after primary multi-drug therapy. Cut-off point, sensitivity, specificity of the examined parameters of the left ventricular contractility were determined by the aid of the receiver operating characteristic curves (lusted). The determination of vVCF and CKMK was found to be most reliable and valid. Cardiomyopathy induced by chemotherapy was found in 50/90 patients, i.e., 55.5%. A significant increase of WI (0.520) a decrease of EF (<0.50), and of vVCF (<0.70 cm/s) were found approximately in 25% of the treated patients. All the changes were reversible and no case of fatal congestive heart failure occurred. In spite of these findings all patients with a dose of DOX > 250 mg/m² were completely treated before each course of chemotherapy. Patients with risk factors (mainly pre-existing cardiomyopathy, transcardial radiotherapy) were carefully monitored from the beginning of the antineoplastic chemotherapy. The lowest dose of DOX that induced development of pathologic changes of the left ventricular contractility was 152 mg/m². The highest dose of DOX that did not cause any pathologic alterations was 292 mg/m². 5-FU usually did not induce significant deterioration of the left ventricular function parameters.

2904 THE CLINICAL COURSE OF CISPLATIN-INDUCED NEPHROTOXICITY, ITS MONITORING AND THE ROLE OF PREVENTIVE MEASURES. Jana S. Legha, Susan M. Pickett, Isaiah L. Simpson, N. D. Anderson Hosp. & Tumor Institute, Houston, TX, U.S.A.

Besides nausea and vomiting, renal failure is the most significant toxicity associated with the clinical use of Cisplatin. During the last decade a number of preventive measures have been used to reduce the renal toxicity of Cisplatin. These include, 1) hydration, hydration and forced diuresis with mannitol and/or furosemide, sodium thiosulphate, 2) long-term use of low molecular mass substances from natural sources (a) before chemotherapy and 5 days after it. Lysozyme, enymes beta-glucuronidase (NAG) and N-acetyl-beta-glucosaminidase (NAG) and brush border membrane enzyme gamma-glutamyltranspeptidase (GGT) were established.

We compared the nephrotoxicity of Cisplatin with the nephrotoxicity of Carboplatin using not only the values of blood creatinine and urea but also with the help of these more sensitive parameters.
2907 THE PRESENCE OF ADVERSE DRUG REACTIONS ON PATIENTS' CHARACTERISTICS IN CANCER CHEMOTHERAPY

Thomas Zwingers, Daniel J. Moerker, Joerg Rasdorf, and Dr. Albertsson, Institute for Therapeutic Studies, Munich, West Germany.

With increasing intensity of chemotherapy in cancer the frequency, intensity and variety of adverse drug reactions (ADRs) increase, too. The development of preventive strategies to minimize the risks of ADRs is therefore an important objective.

We analyzed the data of over 300 adult patients with acute lymphatic or undifferentiated leukemia (ALL/AML) in 33 centers, who were homogenously treated with the study protocol of the German Leukemia Study Group (1) and were documented with every detail of drug treatment and complications. We try to answer the following questions:
- How well can we anticipate the appearance of ADRs through specific characteristics of the patients?
- Is there any change in the intensity and variety of ADRs during the progress of a clinical trial?
- Are we able to distinguish precocious and adverse drug reactions?

With these data we found that 80% of the patients suffered from side effects, where 22% of these were classified as being severe. Beside the individual relationship to factors evaluated at time of diagnosis, we found remarkable changes in severity of ADRs with ongoing time of study.


2908 THE DEPTH DECEASE OF ADVERSE DRUG REACTIONS ON PATIENTS' TOLERABILITY TO CHEMOTHERAPY. A NEW SYSTEM FOR PATIENT FIXATION IN RADIOTHERAPY.

M. Hjelm Hansen*, Dept. of Oncology*, Vejle Hospital, and Institute of Cancer Research**, Aarhus University Hospital, Denmark.

A new system for patient fixation in radiation treatment is described. The system is based on an airtight plastic bag with a content of polyster microspheres. A valve allows evacuation which results in a close fitting cast. The applicability of the system has been demonstrated by comparison with conventional foam casts in 29 patients with carcinoma of the breast. The patients received radiation treatment over 22 fractions and portal X-ray pictures were obtained at each treatment. The portal films were compared with the simulator photos and the deviation of the center cross were measured in crano-caudal and transversal direction as well as the rotation of the center cross. The results showed that the daily reproducibility was considerably improved by use of the new system with a center cross deviation of less than 1 mm in 50% of the cases. The system is furthermore time-saving and cheap compared to conventional fixation systems. (Supported by the Danish Cancer Society.)

2909 A NEW FIXATION SYSTEM IN CLINICAL RADIOTHERAPY.

P. Eijersen, A. Jacobsen, O. Nyelma Hansen*, Dept. of Oncology*, Vejle Hospital, and Institute of Cancer Research**, Aarhus University Hospital, Denmark.

A new system for patient fixation in radiation treatment is described. The system is based on airtight plastic bag with content of polyster microspheres. A valve allows evacuation which results in a close fitting cast. The applicability of the system has been demonstrated by comparison with conventional foam casts in 29 patients with carcinoma of the breast. The patients received radiation treatment over 22 fractions and portal X-ray pictures were obtained at each treatment. The portal films were compared with the simulator photos and the deviation of the center cross were measured in crano-caudal and transversal direction as well as the rotation of the center cross. The results showed that the daily reproducibility was considerably improved by use of the new system with a center cross deviation of less than 1 mm in 50% of the cases. The system is furthermore time-saving and cheap compared to conventional fixation systems. (Supported by the Danish Cancer Society.)

2910 OPTIMIZATION OF COMPUTER DATA PROCESSING AND OF STATISTICAL ANALYSIS OF MORBIDITY BY COMPUTER DATA PROCESSING - I. Popal, L. Ionescu, G. Stanciu, C. Puluc, A. Banu, and G. Ureanu, Spitalul Clinic "Colipa", Bucharest, Romania.

The present paper presents the morbidity due to the malignant tumors necessitates the optimization of the present techniques and the finding of more effective solutions and methods for diagnosis and treatment. At present, Romania has a large basis for high energy treatment of the malignant tumors, the Clinic of Radiotherapy and Oncology of the "Colipa" Hospital being an important part of this basis. The existence of a detailed record concerning the bio-social information about patients and the characterization of each tumoral disease contribute to the particularization of diagnosis and treatment in each case. Such statistics can be in a proper way performed only by computer data collecting, storing and processing - following various criteria. Also the computer-aided identification and collecting of all the parameters that occur during the treatment and the computer data processing achieve the optimization of the therapeutic conduct. The paper presents the experience in this institute in the Clinic of Radiotherapy and Oncology of the "Colipa" Hospital.
Beside these we use other auxiliary methods for
sectlon is studied. Individual anatomy can be reconstructed even with
dimensions by CT scanning. Without on line sys-
proprietate conversion - may function as a simu-
approach more accuracy in localisation.

In our Institute is its ability of taking screen dtalator. (Fig.:
stative with suitable flexibil
best possible accuracy. In case of necessity a
arteriography, ultrasonography, computerised
Conventional X-ray and tomography, lymphography,
There are a number of available methods:
Conventional X-ray and tomography, lymphography,
arteriography, ultrasonography, computerised
tomography and magnetic resonance imaging.

2. During simulation we project target area
to the skin. Nobody can neglect the need of the
best possible accuracy. In case of necessity a
traditional radiological equipment - after ap-
propriate conversion - may function as a simu-
ator. ([1]: TC - suitable flexibil
ity.) The advantage of the equipment, developed in
our Institute is its ability of taking screen
photography as well.

3. Target volumen can be visualised in three
dimensions by CT scanning. Without on line sys-
em we make several sections of the body. In-
dividual anatomy can be reconstructed even with
behalf of two directional X-rays. Differences
accuracy of conventional method and CT cross-
sections is studied.

Besides these we use other auxiliary methods for
approaching more accuracy in localisation.
REGISTRATION AND COMPUTED ANALYSIS OF IRRADIATION TREATMENT RESULTS. J. Kuhelj, Y. Ponga Kirim, The Institute of Oncology, Ljubljana, Yugoslavia

Registration and computed analysis of treatment results are essential for accurate planning of the irradiation treatment in cancer patients. At the Institute of Oncology in Ljubljana collecting of the data pertinent to patients identification, disease and irradiation treatment was started in 1976 in order to promote as fast and as comprehensive as possible evaluation of treatment results in the largest possible number of patients. For this purpose specially designed registration cards were used. In the beginning the collected data were processed manually. Nevertheless, by the increasing number of patients the automatic data processing had to be introduced. In collaboration with the Cancer Registry of Slovenia our data were linked with those compiled in the Registry. In this way appropriate computer programs could be made for obtaining the lists of patients distributed according to particular characteristics essential for the evaluation of results; on the other hand, these programs could be used also for presentation of the survival results of our patients.

THREE-DIMENSIONAL COMPENSATORS FOR THE MANTLE FIELDS IN HODGKIN'S DISEASE. J. Lahtinen and H. Puurunen, Dept. of Radiotherapy, University Central Hospital, Kuopio, Finland

The highest absorbed dose in the treatment of mantle fields in Hodgkin's disease with the two parallel opposed field technique is normally in the neck region. Depending on the energy of the irradiation the absorbed dose in the neck region with the uncompensated fields in typically about 15-30% higher than that in the thorax. We have improved the uniformity of the absorbed dose with the 3-dimensional compensators. A number of CT-slices covering the whole treatment volume are taken. These CT-slices are transferred to the CT-based treatment planning system (AECM). The compensated dose distribution is first calculated to the central CT-slice and thereafter to all other slices. The calculation is based on the method similar to that presented by Takizawa (8th ICCR, Toronto 1984). The compensated dose distribution of each slice can be seen on the screen of the treatment planning computer. Any sagittal plane for showing the compensated dose distribution can be constructed. The shape of the compensator is cutted to styrofoam block using a 3-dimensional cutter (HEK). The compensator is then molded from a tin-paraffin mixture and finally fixed onto a plate suitable to be used with the blocking filters in the shadow tray. The testing of the method shows that the absorbed dose uniformity of about 5% could be achieved in the target volume. The compensators will be taken into routine use in our clinic in the near future.

FIVE-YEAR RESULTS OF NEUROTHERAPY OF RADIATION-INDUCED SOFT-TISSUE TUMORS. [S. Richthorn, A. Jessel]


Eighty-two radioresistant soft-tissue neoplasms have been irradiated with 6 MeV neutrons. In all three tumor dose ranges applied (600 - 960, 1000 - 1260, 1300 - 1920 cGy) alive with 90% of the tumors either complete (~50%) or partial (~40%) regressions were observed, only 10% were little responsive. Further 52 patients, underwent postoperative prophylactic irradiation following local extirpation with tumor doses of about 1000 cGy. 69% survived for at least 5 years, < 20% developed and 13% died with local residuves; there were 5 significant complications.

The high regression rate and the good prophylactic effect with doses well tolerable render neutron radiation especially suitable for the treatment of radioresistant tumors. The reason is believed to be in the strong action of the densely ionizing neutrons on the non growth fraction of tumor (and normal) tissues, which is little sensitive to normal radiation with low LET.

X(Prof. em.)
2919 EVALUATION OF CURIOTHERAPY WITH IRIDIUM-192 OF FEMALE URETHRAL CANCER
Z. Danczak-Ginalska, A. Skowronska-Gardal, Radiation Therapy Department Cancer Center of the Maria Sklodowska-Curie Memorial Institute, Warsaw, Poland

Ten females with urethral cancer have been treated by interstitial curietherapy with Ir-192 from 1973 to 1985. For six patients it was the only treatment, three patients have been additional treated with fractionation radiotherapy, and one undergone surgery. In all patients after-loading technique have been used. Patients were observed from 6 months to 12 years. One patient died six years after therapy for another cancer. In all other patients we did not notice metastases or local recurrence. In one case stenosis of the urethra and in two others superficial postradiation necrosis occurred.

2919 RADIOTHERAPY IN PELVIC MALIGNANCIES. EVALUATION OF CURIOTHERAPY WITH IRIDIUM-192
J.F. Heron, J.E. Colette, D. Brune, J. de Ranieri, H. Crouet, Genito-urinary department, Centre Francois Baclesse, Route de Lion-sur-mer, 14021 Caen Cedex, France.

From November 1981 to January 1984 all but 8 patients, seen at our institution, for stage III cervix squamous cell carcinomas (24 stage IIIB, 7 stage IIIA ; medium 59 years) were treated with pelvic (50 Gy) and lombo-aortic (40 Gy) radiotherapy with central boost (10 Gy) either by brachytherapy or external radiotherapy associated with cisplatinum (80 mg/m²). Chemotherapy was administered before, after 3 weeks, and at the end of radiotherapy (6 weeks), and every month up to 6 months (total dose 720 mg/m²). Thirty-one patients were entered in this study. At two years minimum follow-up 21 patients are alive (68 %), 19 patients NED. Actuarial 5 year survival is 64 %, with 58 % NED patients. Two patients underwent total pelvicectomy for relapse and are still alive without evidence of disease. Relapse sites were central pelvic (9 patients), lombo-aortic metastases (1 patient), pulmonary and/or bone metastases (5 patients). Treatment complications include rectal hemorrhage (5 patients), intestinal occlusion (1 patient), moderate renal insufficiency (1 patient), bone radionecrosis (2 patients).

In conclusion, association of cisplatinum to radiotherapy seems to improve results in stage III cervix squamous cell carcinoma since our previous results were 35 % 5 year survival and NED survival at our institution between 1976 and 1981. These results warrant further prospective controlled studies.

2920 INTRA-OPERATIVE RADIOTHERAPY IN PELVIC MALIGNANCIES
H. Crouet, J.S. Abbattucci, J. de Ranieri, J.F. Heron, A. Roussel, Centre Francois Baclesse, Route de Lion-sur-mer, 14021 Caen Cedex, France.

Since 1983, intra-operative radiotherapy (I.O.R.T.) has been explored in a treatment management of advance squamous cell carcinoma T 2-13 of the uterine cervix. In this indication I.O.R.T. is used as a "boost" irradiation for prophylactic treatment of para-aortic nodes. A high-energy linear accelerator delivers a single dose of 15 Gy with an 10-15 Mev electron beam by mean of a special applicator who removes the bowel out of the radiation field. The laparotomy for irradiation is made after an external irradiation of 50 Gy on the pelvis and 50 Gy on the rambar area in association with cisplatinum chemotherapy. At last radiotherapy is given as overdose on the central tumor. Twenty patients were treated according to this procedure. 13 are alive and free of disease with a follow-up of 2 to 18 months. In recto-sigmoid malignancies, I.O.R.T. is realized during the colo-proctectomy with an external photon beam (25 Gy) after protection of the small bowel and the bladder out of the radiation field. Five patients received this procedure but the follow-up is too short to conclude. Furthermore, six patients were treated by a "boost" irradiation of 20 Gy with an electron beam applicator for residual tumors after surgery : 4 pelvic exenterations for recurrent cervix or rectum cancer and 2 radical hysterecomities with pelvic nodes metastases.

2921 RADIOTHERAPY WITH CISPLATINUM IN STAGE III CERVIX CARCINOMA. J.F. Heron, J.E. Colette, D. Brune, J. de Ranieri, H. Crouet, Genito-urinary department, Centre Francois Baclesse, Route de Lion-sur-mer, 14021 Caen Cedex, France.

2922 RESULTS OF COMBINED IRRADIATION OF II AND III STAGE CERVIX UTERINE CANCER.

277 patients with II and III stage of cervical cancer were treated with combined intracavitary and external irradiation. Randomized groups of patients were treated according to two protocols, namely the first group was treated with simple nondifferentiated intracavitary and external irradiation, the second one was treated with some different combined irradiation. Patients treated with simple method received full intracavitary irradiation supplemented by usual megavoltage irradiation of the pelvis but patients treated with some different method were irradiated according to the rule: the larger the tumor the less intracavitary dose on behalf of more intensive external irradiation. Five years continuous follow up of the treated patients and results defined by Kaplan-Meier curves showed good survival probability (57 %) of the whole group but the best unexpected survival (70 %) was obtained in the group which was treated with the simple method, utilizing full intracavitary irradiation.
A prospective randomized study of ovarian cancer patterns

Stage I and II: irradiation therapy versus chemotherapy

Radiation combined modality treatment.

F. Sevelde, H. Salzer, Ch. Dittrich, M. Wagner, K. Kupper, E. Dittrich
Dept. of Gynecology and Obstetrics, Univ. of Vienna, Austria

The Austrian Collaborative Ovarian Cancer Study Group was founded in June 1980. The gynecological departments collaborated in this study to obtain a short period of time comparable results. 135 patients with stages I and II ovarian cancer were regarded as the first success of this common effort.

Randomization plan: Stage Ia/b, slightly differentiated tumors (group A, n=25) without rupture of the capsule, no further therapy after primary surgery is performed. Stage Ia/poorly differentiated tumors and stage Iib tumors were randomized in a group with whole abdominal irradiation therapy (group B, n=24) and a control group (group C, n=20). Stages Ib, IIA, IIB are randomized in a group with irradiation alone (group D, n=27) and a group with an alternation of 2 cycles adriamycin/cyclophosphamide (Al/C) followed by irradiation and another 4 cycles of A/C (group E, n=24). Stages Ic and Iic are randomized in adriamycin/cyclophosphamide (Al/C) - irradiation - another 4 cycles A/C (group F, n=27) and 2x A/C - irradiation - 4x A/C (group G, n=28).

Results of our last evaluation in June 85 (disease-free survival after a median follow-up time of 32.4 months (range 4-67 months); Group A: 50% DFS, also patients without cystectomy staging procedure are included; Group B: 71% DFS, group C: 80% DFS, differences are not significant; Group D: 67% DFS, group E: 77% DFS; this difference is statistically significant at the 0.1 level; Group F: 80% DFS, no difference in the disease-free survival (at 40%).

Conclusion: 1. Only Ia/b, slightly differentiated tumors seem to need no further therapy, if an exact staging laparatomy was performed (hysterectomy, bilateral salpingo-oophorectomy, appendectomy, omentectomy, lymph node resection and peritoneal lavage, 1). The combined polychemo-radiotreatment is superior to irradiation alone. 2. Stages Ic and Iic should be treated with an aggressive polychemo-therapy as it is recommended for stages III and IV ovarian cancer patients.


In high-dose-rate short-time afterloading at irradiation therapy of gynecological cancer an adequate fractionation with reduced total dose is necessary considering the basically changed dose-time-relationships in contrast to conventional low-dose-rate radium therapy. In addition to care clinical control of empirically found fractionation schedules for primary and postoperative intravaginal and intracavitary afterloading therapy in carcinomas of the cervix and endometrium, a calculation of equivalent doses seems to be recommendable by means of mathematically formulated model conceptions according to the NSD-conception. Tumour regression and relapses and also side-effects at bladder and vulva were investigated and controlled by second-look-examination and/or cytology. Changed exponents for the number of fractions depending on the overall treatment time were used for the ret-calculation of slowly fractionated small volume brachytherapy in contrast to a higher fractionated percutaneous large volume irradiation, for which the NSD-conception was developed. The calculations were based on a ret-value of about 1,800 ret for 60 Gy conventional radium therapy. The results show in connection with clinical and histological tumour control in about 3,000 patients in more than 12 years that 9 to 12 fractions with 7 Gy single dose per fraction, in weekly intervals in an overall treatment time of 28 to 35 days and with total doses of 35 to 42 Gy at reference point A according to TGD and MERIDITH are highly effective in tumour control and show a statistically significant decrease of radiation induced side-effects at bladder and rectum compared with conventional long-time brachytherapy.


Short-time-afterloading (ST-AL) with high dose rates facilitates the optimization of dose distritubution in the target volume to the advantage of patients and hospital and allows a considerable increase of treatment capacity without additional staff or capital. ST-AL works with a changed dose-time-distribution than conventional brachytherapy. A higher fractionation in ST-AL is substituted for classical radiotherapy. 1,211 patients with cervix carcinoma were treated by ST-AL between 1974 and 1984. They were checked up for at least 12 month up to more than 5 years. The results, related to the stages, are at least equivalent to radiotherapy and better: Several groups show a statistically significant improvement compared to brachytherapy with the incidence of early and late reactions at bladder and rectum showed also a statistically significant decrease after ST-AL. This was dependent on the dose in a high significant manner (P=0.001).

In addition to the well-known advantages of ST-AL can be stated:

1. The intracavitary application was made without general anaesthesia.
2. An ambulatory treatment was carried out in more than 40% due to the time-saving and patient-saving method—advantages are evident.
3. The therapeutic efficacy is increased and the risk of side-effects at bladder and rectum is decreased by the better radiobiology and dosimetric adaption of ST-AL and hormone therapy in the combined radiotherapy of cervix carcinoma.
A COMBINED RADIOTHERAPEUTIC AND SURGICAL APPROACH FOR STAGE I AND II A CERVICAL CANCER.


The five-year survival rate for stage I cervical cancer treated by radical hysterectomy and pelvic lymphadenectomy or a combination of radiation and radical surgery is 75-94%. However, radical surgery is associated with a significant morbidity and occasional mortality. Complications may be increased by additional radiation possibly with no better cure rate.

Over a hundred patients with early cervical cancer were treated with a combination of pelvic radiotherapy and simple hysterectomy between 1966-1980. Surgery was performed at Postgrad. Med. Sch. Pre- and/or postoperative pelvic radiation was given in all instances at Municipal Oncorad. Ctr. 60 patients with stage l cervical cancer received pelvic radiotherapy alone. The five-year survival figures were 86% for the former and 67% for the latter group. There was no operative mortality and no significant morbidity.

The results of the combination of radiation and simple hysterectomy in this study are comparable with those of radical hysterectomy with or without radiotherapy. The major advantage of this approach is the low rate of complications because the five-year survival rate was better with combined therapy than with radiation alone, the addition of pelvic radiotherapy to surgery is recommended when simple hysterectomy is considered for the therapy of stage I and II A cervical cancer.

COMPARISON OF EFFICIENCY OF CLASSICAL MANCHESTER AND MODIFIED HENSCHKE'S AFTER LOAD SYSTEM IN INTRACAVITARY TREATMENT OF CARCINOMA OF THE COLLI UTERI. V. Savruj-Robož, J. Kuhelj, and P. Cevc, Inst. of Oncology, Ljubljana, Yugoslavia.

The authors report on results of retrograde comparative study in which they compare successfullness of the intracavitary irradiation of carcinoma of the colli uteri with classical Manchester system and with modified Henschke's after load applicator, made at the Institute of Oncology in Ljubljana. The results show no statistically significant differences in the survival of patients and in the number of post-irradiation complications in both groups of patients. A larger number of cystitis cases was found among women with after load application, showing that additional attention should be paid to this problem.


Cancer of the cervix usually spreads locally within the pelvis where we also found recurrent or persistent tumor. In those patients no intensive retreatment with surgery or radiation may achieve long-term palliation or sometimes even the cure.

During the ten years period (1970 to 1980) we treated 44% patients with cancer of the cervix using radiotherapy alone or postoperatively. In 89 patients with confirmed pelvic recurrence we applied reirradiation. In Co60 beam therapy we introduced different techniques of irradiation to reduce the rate of early or late complications. The problems of reirradiation, the dosage, results and sequelae rate are exposed and discussed in details.
A total of 1845 patients were treated using endocavitary therapy with radium and external irradiation with Co60. These patients were classified by clinical stages following the TNM system of the UICC. Overall survival for the whole series was 54% at 5 years and 43% at 10 years. Among many other relevant factors we found the following: (A) Age was a significant prognostic factor. Data on the size and shape of the uterus were available. (B) Menopause: 731 patients were studied and 56% of patients were alive at 5 years, compared to 33% of patients without complications. (C) Grade: Patients with menopause between 1-5 years and 10-15 years had 5-year survival rates of 76% and 69%, respectively. Twenty-nine patients developed complications, 55% of which were Grade I, 23% Grade II, and 22% Grade III. (D) Adjuvant therapy: 21 patients were classified by gynecological examination to receive adjuvant therapy only. (E) Menopause: 731 patients were studied and 56% of patients were alive at 5 years, compared to 33% of patients without complications. Twenty-nine patients developed complications, 55% of which were Grade I, 23% Grade II, and 22% Grade III. (F) Time of menopause: patients who had a menopause between 6-10 years had a 5-year survival rate of 58%, compared to 50% for those who had over 10 years of menopause. (G) Hysterectomy: 21 patients were classified by gynecological examination to receive adjuvant therapy only. (H) Advanced age: 378 patients from 60 to over 80 years of age were studied. The highest group corresponded to those who had over 10 years of menopause. Survival at 5 years was 59% for those patients with menopause between 1-5 years, 43% for those who had between 6-10 years of menopause, and 58% for those who had over 10 years of menopause. (I) Cervix stump: 21 patients were classified by gynecological examination to receive adjuvant therapy only. (J) Advanced age: 378 patients from 60 to over 80 years of age were studied. The highest group corresponded to those who had over 10 years of menopause. Survival at 5 years was 59% for those patients with menopause between 1-5 years, 43% for those who had between 6-10 years of menopause, and 58% for those who had over 10 years of menopause. (K) Histological examination: 731 patients were studied and 56% of patients were alive at 5 years. The highest group corresponded to those who had over 10 years of menopause. Survival at 5 years was 59% for those patients with menopause between 1-5 years, 43% for those who had between 6-10 years of menopause, and 58% for those who had over 10 years of menopause.
N-46: RADIOTHERAPY OF GYNAECOLOGICAL TUMOURS

2935 THE EMPLOYMENT OF URETERAL "DOUBLE J" BROWN CATHERS IN THE CLINIC OF ONCOLOGICAL UROLOGY
J. Cynar, J. Sokolowski, M. Naweziakiewics, J. Kornej
Department of Oncology, Academy of Medicine, Warsaw, Poland

Various clinical situations in the cases of genital tract malignancies in women with urological complications concerning the urerine void was described. Nineteen women with uni- or bilateral ureteral "split" placing with "double J" Brown catheter from 3 to 15 months were observed. "Split"insertion was performed in most cases before radiotherapy of cervical cancer stage III accompanied by uni- or bilateral hydronephrosis.

Several procedures concerned the patients with inactivity of the kidney. Such management protected the patients from acute anuria caused by neoplastic tissue swelling and ureter compression during the radiotherapy. Formerly such situations had finished with the urgent nephrostomy and radiotherapy had been interrupted or postponed. The case of renal pelvic rupture has been noted by the authors. The authors observed the prompt drop in urea and creatinine levels and the quick retum of the clinical symptoms of uraemia after the ureteral catheter was removed. The prompt drop in urea and creatinine levels have been noted by the authors. The authors observed the prompt drop in urea and creatinine levels and the quick retum of the clinical symptoms of uraemia after the ureteral catheter was removed.

2936 THE TREATMENT OF CANCER OF THE UTERINE CERVIX BY COMBINED INTRACAVITARY AND EXTERNAL RADIATION. V. Todrov, Inst. of Oncology, Sofia, Bulgaria

Sets of three or four linear radioactive 137-Cesium sources are used for the intracavitary brachytherapy of cancer of the uterine cervix in the Institute of Oncology in Sofia and in the radiological departments in Bulgaria. For introduction and fixation of the radioactive sources thin metal intravaginal probe and individual vaginal mold are used. The application system is rigid, giving the possibility of defining the dose by means of sets of isodose charts. The unification of the radioactive sources by the intracavitary brachytherapy makes possible the carrying out of an additional irradiation by split field method. The lead blocks (5 cm thickness) have the shape of isodose curve 70 Gy in frontal plane. The disposition of the lead block in the external beam irradiation is defined according to the metal marker location in the uterus cervix, implanted before the brachytherapy. The additional external beam irradiation by split field method ensures an adequate addition of the dose in the pelvis at a very good reproducibility of the irradiation conditions by a total dose 60 Gy in point B according to Manchester system the minimal dose in the uterine cervix is 70-80 Gy.

2937 RESULTS FROM THE BRACHYTHERAPY WITH AN ORIGINAL METHOD FOR SIMPLE AFTERLOADING IN CARCINOMA OF THE UTERINE CERVIX
P. Pentchev, G. Mitrov, M. Mushmov, V. Todrov
Oncological Research Institute, Sofia, Bulgaria

Twelve-year results from the application of an original method for intracavitary brachytherapy with afterloading in the carcinoma of the uterine cervix are analyzed. The system for afterloading is consisted of an uterovaginal tube, an individual vaginal mould and a component linear Cs-137 source. Appropriate conditions for irradiation are made: central position of the component linear source, bladder damage field for the duration of the brachytherapy, reduction of the dose on the bladder and rectum with two lead shield incorporated within the vaginal mould correctly orientated anteriorly to protect the bladder and posteriorly to protect the rectum. A total of 749 patients are treated, out of them, with T1 - 43.8 %, with T2 - 29.7 % and with T3 - 26.5 %. The five-year survival regardless of the stage is 67.1 % and ten-year survival - 53.1 % in a relative survival - 72.1 % and 63.1 % respectively. Out of the patients with T1, 82.4 % are survived over than 5 years and 74.9 % of them over 10 years. The 5-year and 10-year survival of the patients with T2 is 69.3 % and 49.4 % respectively and with T3 - 37.3 %. The patients with differentiated squamous cell carcinomas are with best prognosis - 5-year survival 72.1 % as to 4.4 % in cases with undifferentiated forms. The results in endometrioma, considered as a radio-resistant tumor, are comparatively good - 5-year survival - 58.2 %.

2938 THE INTRACAVITARY BRACHYTHERAPY BY SIMPLE AFTERLOADING IN COMBINED RADIOTHERAPY OF THE ENDOMETRIAL CARCINOMA.
E. Petkova, V. Todrov, P. Pentchev
Oncological Research Institute, Sofia, Bulgaria

The border-lines and sizes of the field to be submitted to intracavitary brachytherapy and to combined irradiation are defined depending on the stage and spread of the tumor. Three methods for intracavitary brachytherapy by simple afterloading with Caesium-137 linear radioactive sources are reported: 1. Linear method, combining 2 or 3 linear radioactive sources in a thin intravaginal probe; 2. Y-shaped method; 3. Linear method by a parallel component linear radioactive sources in a thick intravaginal probe. By the three methods the desired dose-distribution can be obtained an uterus of cross-sizes 5-8 cm. By those methods the fixation of the radioactive sources in the uterus permits a reliable defining of the dose-distribution in the brachytherapy. The dose is computer-calculated individually for every patient. It increases the exactness in the adaptation of the additional external beam irradiation to the dose-distribution of the intracavitary brachytherapy, which is a promise for better treatment results.
2939 INTRACAVITARY NEUTRON THERAPY IN ONCOGYNECOLOGY.
All-Union Cancer Research Center the AMS USSR
Soviet apparatus "AMET" with high activity sources of $^{252}$Cf was used for gynecological cancer patients treatment. Total activity of 3 sources $^{252}$Cf=2600 g (1000-400-400). Irradiation planning used conception of isoeffective biological dose. Total number of patients-60, including 40 with cervical and 40 with corpus uteri carcinoma. Visual total tumour clearance observed in 86% patients with cervical and in 89% with corpus uteri carcinoma. 3-years results shows advantage of neutron therapy in hypoxic tumours treatment compare to photon therapy.

2940 RADIOBIOLOGICAL AND CLINICAL ASPECTS OF THE HIGH DOSE THERAPY IN COLLUM AND CORPUS CARCINOMA
By P. Rattka
Oncology Institute, Gliwice, Poland
The cervical carcinoma treatment by means of high activity sources is preferable for the most cases of cervical carcinoma due to the high comfort of the treatment in comparison to the conventional methods and due to low number of reactions and early complications. Good clinical results depend on proper selection, the fractionation scheme and use of wide assortment applicators and screens which make possible to apply a required dose to the tumour tissue and to protect critical organs, especially the rectum. From our clinical investigations it is resulted that all stages of cervical carcinoma may be treated using fractionation scheme 6x8Gy with 3-days interval or 20Gy with 1 week interval and then 3x8Gy each 4 days. In both schemes the last fraction was inserted to the uterus cavity. The applicator is inserted 3 days after finishing the treatment in the vagina and 10Gy is applied to the reference points. Patients in stage 1 corpus carcinoma have been treated using this method. The ages ranged from 50 to 80 years but 77% of the patients were 70 years or older. Despite the short follow-up period it seems, that our method of treatment of corpus carcinoma using the Selectron HDR can be recommended.
LOCAL CISPLATIN IMPLANTATION IN BRAIN TUMOURS.
M. Stranka, J. Drobnič, J. Hejko, P. Vencel,

The experience was obtained by computer tomography (CT) guided stereotactic implantation of Cisplatin into brain tumours in 20 patients. The localization, volume and histological type of tumours were known before implantation. 5 to 10 mg of Cisplatin were administered in biodegradable gel matrix in the form of cylinders 2.8 mm seed into solid tumours.

In six cases the classical resection of tumour was done several weeks after Cisplatin implantation. In histological examinations coligation necrosis around the implants was observed. Platinum distribution in the brain was determined. The diffusion of active substance within the distance 15 mm was proved.

In the case of metastatic melanoma CT examination revealed substantial reduction of the size. The tumour disappeared on the control CT image taken 6, 12 and 24 month after the Cisplatin implantation and patient's clinical status got improved. With small tumours promising results were obtained.

The method is indicated in small and deep brain tumours which are inoperable with classical neurosurgical treatment.

IN VIVO DETERMINATIONS OF PLATINUM CONCENTRATION IN PRIMARY AND SECONDARY BRAIN TUMOURS AFTER A SINGLE DOSE OF CIS-PLATINUM. R. Jonson*,
S. Mattsson*, B. Unsgaard**, Departments of Radiation Physics and General Oncology*, University of Göteborg, Sahlgrens Hospital, Göteborg, Sweden

Cisplatin is a cytostatic agent that has been proven successful in the treatment of a number of malignant tumours. This heavy metal complex contains an atom (Pt) with a high atomic number which is possible to follow in vivo by X-ray fluorescence (XRF) analysis.

After a single i.v. injection of cis-platinum, at two dose levels 25 mg/m² or 50 mg/m², at patients with primary or secondary brain tumours the concentration of platinum at the tumour site and in clinically normal brain tissue has been determined in vivo by means of an XRF technique.

Measurements were performed at 2, 4, 8, 16 and 24 hours during the first day of treatment and then once per day for 3-4 days.

Preliminary studies indicate that the maximum concentration of platinum is reached after 8 to 12 hours.

THE POTENTIAL ROLE OF LOMBADINE (LND) IN THE TREATMENT OF MALIGNANT GLIOMA. C. M. Capuani, E. M. Paggi, G. B. Ciotoli*,

Up-to-date unsatisfactory results obtained in multimodality treatments of malignant glioma have prompted the search of new therapeutic modalities and drugs with "non-conventional" mode of action. LND is a drug able to reduce both oxygen consumption and lactate production either in human or in experimental tumours (J. Natl. Cancer Inst. 66, 697-699, 1981). This effect mainly depends on the inhibition of the mitochondrially-bound hexokinase, which is present in great amount in malignant cells. Preliminary results obtained in unselected patients affected with malignant glioma (Oncology suppl. 1,82-85, 1984) are interesting enough to justify further investigations. A phase II study on patients with recurrent malignant glioma was conducted, 12 patients were admitted to the study. The clinical complications, evaluated according to Miller's scale, were quite moderate, causing the reduction of the dosage in only 1 case. The objective results were evaluated according to the indications of Levin; we observed 2 responders (lasting 94 and more than 58 weeks) and 7 cases of stable disease (lasting from 16 to 26 weeks) in 10 evaluable patients. These results, associated with the experimental data on the synergistic effect of LND plus radiotherapy and "conventional" cytotoxic agents, have suggested the evaluation of the potential role of LND combined with radiotherapy as first adjuvant treatment, with L-glutamine (GLU) at the moment of clinical and neurological recurrence. A randomized study started in November 1981. At the present time, 24 patients entered this study. The results and the complications observed will be presented and the potential value of this new drug discussed.

Luisa Medina, M.D., J. Alforno, M.D., J. Barroso, R.D., M. Mort, M.D., O. Giralte, R.S., J. Reeves, W.H., National Institute of Oncology and Radiobiology,

In a series of 202 Gliomas 1960-1978 treated by surgery and external irradiation with C60(60 Gray) Multiform Glioblastomas(Emley-Cushing, Kernohan, 1949) represented 50%, 59% (201 of 202). Five year survival was 14%, between 1979-1982 adjuvant chemotherapy with intracavitary Methotrexate was added to the treatment of surgery and irradiation with C60(60 Gray) at a dose of 0.1 mg/Kg body weight once per week during the irradiation, and at a dose of 0.15 mg/Kg body weight every six weeks after irradiation, In 11 patients studied the highest survival reached was 21 months and the average 9.6 months. From 1983-1985, 23 patients were treated with WR 1975 classification adjuvant Chemotherapy with Dibromoduloitol (DBD) was added to surgery and irradiation. Phase I during irradiation the DBD dose was 50 mg/m² of body surface, orally, from day one to day fourteen, associated to Vinblastine at a dose of 1.5 mg/m² of body surface, orally, from day one to day fourteen of every month during six cycles. On Phase III DBD at a dose of 60 mg/m² of body surface, orally, from day one to day fourteen of every month during six cycles. In order to determine the accumulated survival, the Kaplan-Meier method was used and to check if there were any differences between the survivals of the groups the long-rank method was used at different level of significance. This group was statistically significant p<0.05 with and accumulated survival of 40,07% as compared to Group II (surgery-irradiation), which was 21.6% at 37 months, with a relation to Group II (surgery-irradiation-intrathecal MTX) the same accumulated survival was obtained the latter being 9.0% at 11 months (p<0.001).
We are investigating the mechanism for restoring the intracellular contents of Na in the tumor cells, where the concentration is particularly high. For this purpose, we have used high doses of the active principle of an aminoacid: taurine and two lithium salts: carbonate and benzoate. This is how we intervene to regulate the cellular ionic balance as for interneuronal movements of potassium and calcium, which has also been inserted in therapeutic protocol. Their use, initially applied to various tumors has revealed specific for both primary and secondary cerebral cancers. After 10 months we have registered 23% C.R. and 49% P.R. Within the C.R. group the number of patients affected by cerebral metastasis of mammary carcinoma has to be underlined, especially due to the influence of calcium receptors on the membranes.

A leptomeningal tumor model of rat has been developed by left intralateral ventricle inoculation of AH130 ascites hepatoma cells for screening of chemotherapeutic agents effective to the metastatic brain tumors. It was proved that there was no disruption of blood-brain barrier function by tumor inoculation in this model. Histopathologic studies showed that the tumor cells proliferated only in the ventricles, subarachnoid spaces of brain and vertebrate and did not infiltrate into brain parenchyma. Moreover the tumor cells never metastasized from brain into extracranial organs until tumor death and that tumor growth did not cause disruption of blood-brain barrier function within 4 days after tumor inoculation. Using this model, several antitumor agents have been tested and procarbazine, diromodulcitol (DBU), and a nitrosourea derivative (ACNU) were found to be highly effective when administered intravenously or intraperitoneally. The intralateral ventricular administration of procarbazine (P-Dagky, 5 times, daily) exhibited a marked antitumor activity (% ILS: more than 50%) and its activity was higher than that with intravenous or oral administration at both the early and advanced stages of this model. But in the case of ACNU, the intralateral ventricular administration showed no antitumor activity, although intravenous administration produced a high activity. It was found that among antitumor agents used in this study there was a good correlation between antitumor activities by intravenous administration and physicochemical properties such as molecular weight and n-octanol/water partition coefficient. (Supported in part by Sapporo Bioscience Foundation).

DEVELOPMENT OF EXPERIMENTAL NUDE MOUSE MENINGEAL GLIOMATOSIS MODELS

Tatsuo Yoshida, M.D.; Keiji Shimizu, M.D.; Yukiya Uehara, M.D.; Taro Hayakawa, M.D.; Sumi Kato, M.D.*
Department of Neurosurgery, Osaka University Medical School, Osaka, Japan; *Institute of Cancer Research, Osaka University Medical School, Osaka, Japan

Experimental models of meningeal gliomatosis (MG) have been produced by intracisternal inoculation of human cell lines glioma cells into nude mice. The tumor growth was steady and fast in MG nude mice if 10^6 cells were implanted. Median survival time (MST) of nude mice inoculated with tumor cells was inversely related to the number of cells inoculated. There was a correlation between in vivo and in vitro (MG models) in growth rate, which means that the cell kinetics of in vitro is reflected in vivo. The clinicopathological features observed in MG nude mouse models were similar to those seen in diffuse leptomeningeal involvement of gliomas in human beings. The models will be useful for investigating the pathophysiology of meningeal gliomatosis and the efficacy of chemotherapeutic agents.

STUDIES ON MECHANISM OF ACNU RESISTANCE IN SUBLINES OF RAT GLIOMAS

Tatsuo Yoshida, M.D.; Keiji Shimizu, M.D.; Yukiya Uehara, M.D.; Taro Hayakawa, M.D.; Sumi Kato, M.D.*
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The mechanism of ACNU resistance in sublines of 9L and 9G glioma completely resistant to ACNU (9L/ACNU, 9G/ACNU) were studied in vitro. Cellular uptake and retention of [14C]ACNU by 9L/ACNU and 9G/ACNU cells were found to be lower than those by 9L and 9G cells. [14C]alpha-aminooxycarbonyl acid ([14C]AA)-intercalated with 9L/ACNU cells was comparable to that incorporated into 9L cells, which suggests no difference in cell membrane permeability between these cells. Furthermore, treatment of 9L/ACNU cells with 2,4-dinitrophenol (DNP) in the presence of glucose increased cellular uptake and retention of [14C]ACNU by 9G/ACNU cells. This implies that the increase of cellular uptake of [14C]ACNU by 9G/ACNU cells is due to decreased efflux of intracellular [14C]ACNU. It is concluded that ACNU-resistant glioma cells are resistant by virtue of active efflux of intracellular ACNU.
2055 THE INVESTIGATIONS OP SEROTONIN CONTENT IN BLOOD PLASMA AT PATIENTS WITH BRAIN TUMORS.
Burdenko Neurosurgical Institute, Moscow, USSR.

Numerous works by Green, Millard, Taglimonte et al. revealed a great dependence of serotonin content in the brain on the tryptophan content in blood plasma. Studies of serotonin exchange in brain tumors we found its marked changes compared to the exchange in brain tissue. That prompted us to investigate the tryptophan content in blood plasma at patients with both brain tumors and non-oncological diseases. It was also found that at patients with astroglial tumors the tryptophan level in blood plasma was statistically higher (up to 11.62 ± 0.57 mg/ml) than at patients with meningiomas (7.410.27 mg/ml) and with oligodendrogliomas (6.02±0.32 mg/ml). These data well agree with our observations of tryptophan high level in the tissue of gliomas and confirm the dependence between tryptophan concentration in the blood and its content in the brain tissue. The character of the curve of tryptophan withdrawal after the loading of all neurological groups of patients changes in comparison with healthy people and with patients with sinus thrombosis and arachnoiditis. Intraarterial injection of hydrocortisone normalizes both "tryptophan curves" and, therefore, tryptophanpyrrolase reaction, which is, obviously, broken at neurooncological patients.

2954 CYTOSEX ARABINOSIDE AND CISPLATIN, + CAFFEINE FOR GLIOMAS. D.J. Stewart, H. Hugenholtz, B. Bemont, M. Richard, M. Russell, J. Marcoux, J. Moroz, Ch. Coutard and Research Foundation Ottawa Regional Cancer Centre and the University of Ottawa, Ottawa, Canada.

51 patients with glioblastomas or recurrent low grade gliomas have been treated with IV cytosine arabinoside (ara-C) plus cisplatin + caffeine. Ara-C and caffeine were added to cisplatin since they appeared to markedly increase its efficacy in preclinical studies (Bergerat et al, Cancer Res., 41:25, 1981). 21 glioblastoma patients and 5 recurrent grade II glioma patients received cisplatin 60-100 mg/m^2 IV in 250 ml 0.45% saline, with 500 ml prehydration, mannitol 50 g IV, and Ara-C 500-1000 mg/m^2 IV rapid infusion immediately after the cisplatin. Treatments were repeated at 3-4 wk intervals. Of 25 evaluable patients, 10 (40%) responded (including 2 complete remissions) and 6 (24%) stabilized. Patients with no prior radiotherapy or chemotherapy had a higher response rate (58%) than those previously treated (73%), but were more difficult to evaluate. Neutropenia occurred in some patients. Gastrointestinal toxicity was dose-limiting. 2 patients had possible neurological toxicity. 25 glioblastoma patients with no prior radiotherapy or chemotherapy were treated with cisplatin 75-100 mg/m^2 IV in 250 ml 0.45% saline, 500 ml prehydration, mannitol 50 g IV, Ara-C 250-300 mg/m^2 IV over 15-60 min, beginning 2-4 hr later, and caffeine 250-700 mg IM or p.o. q 8 hr x 4 doses beginning immediately after the Ara-C. 12 (48%) responded. Neutropenia was dose-limiting for Ara-C and seizures were dose-limiting for caffeine. Ara-C plus cisplatin appears to be tolerable and gives higher response rates for gliomas than those previously reported for cisplatin alone. Caffeine at doses that were tolerable did not appear to increase the therapeutic efficacy of the chemotherapy and its use is not recommended. Studies are beginning of IV Ara-C added to an intracarotid cisplatin-based regimen.

P-42: SOLID TUMOURS

2955 THE INVESTIGATIONS OP ENZYMIC ACTIVITY OF HYDROLYTIC ENZYMES IN WILMS TUMOURS IN CHILDREN AFTER PROPHYLACTIC CHEMOTHERAPY ACCORDING TO SIOP-TRIAL No / PROTOCOL. M.Houazko, K.Jawicz-Birlowska and K.P. Jawicz-Birlowska, Pediatric Surgery Clinic of Siedicla Academy in Wroclaw (Poland).

Between 1962 and 1985, 147 children with Wilms tumour were seen in Pediatric Surgery Clinic of Medical Academy in Wroclaw (Poland). Preoperative chemotherapy was administered to 50 children with Wilms tumour judgments clinically to be unresectable. After 4 weeks of treatment of Antimonyoin D and Vincentine protocol SIOP Trial No/ Protocol, Wilms tumour were seen in Pediatric Surgery Clinic of Medical Academy in Wroclaw (Poland). Wilms tumours were seen in Pediatric Surgery Clinic of Medical Academy in Wroclaw /Poland/. The authors discuss different staging and treatment. It appears that Wilms tumours are rare in children and that the histologic type, tumor behavior and prognosis is different then in adults. The authors discuss different staging system and treatment.

2956 CYTOSEX ARABINOSIDE AND CISPLATIN, + CAFFEINE FOR GLIOMAS. D.J. Stewart, H. Hugenholtz, B. Bemont, M. Richard, M. Russell, J. Marcoux, J. Moroz, Ch. Coutard and Research Foundation Ottawa Regional Cancer Centre and the University of Ottawa, Ottawa, Canada.

During 10 years (1979-1989), among 2100 tumors registered at the Pediatric Service of the A.C. Camargo Hospital - Sao Paulo - SP - Brasil, we seen 15 cases of malignant gynecologic tumors. The primary site were: 10 cases of the ovary, 3 cases uterus and 2 cases vagina. The histologic types of the ovarian neoplasms were: teratoma immature in 3 cases, endodermal sinus tumor in 2 cases, embryonal carcinoma in 2 cases, dysgerminoma, 1 choriocarcinoma and 1 case of undifferentiated carcinoma. The 2 cases primary of vagina were embryonal rhabdomysarcoma and the 3 cases primary of uterus, 2 were endodermal sinus and 1 rhabdomysarcoma. In 3 cases were seen genitourinary anomalies associated, 1 duplications of the collecting system, 1 horseshoe kidney and 1 renal agenesis. The overall survival was 70%. Our data confirm that gynecologic malignant neoplasms are rare in children and that the histologic type, tumor behavior and prognosis is different then in adults. The authors discuss different staging system and treatment.
2957 CLINICAL PICTURES OF MALIGNANT MELANOMA IN CHILDREN. V. Grodzki. National Research Institute of Mother and Child, Warsaw, Poland.

18 children with malignant melanoma were treated during last 23 years in Clinical Department of Pediatric Oncology, Institute of Mother and Child, Warsaw. Age of the patients balanced between newborn and 18 years. Advantages of female to male makes sex ratio 2:1. Malignancy of malignant melanoma in children is much smaller than in adults and consists of less than one percent. Localization of primary focus is first of all head and neck region, trunk, and limbs. There are no submitted localizations in children. Typical for children is arising of malignant melanoma from giant "bathing" naevus. Treatment of choice is surgical radical procedure after which staying is made on the basis of UICC and Brodow classification. All the stages above I/ UICC classification and in stage I all the cases with thickness above 1 mm are indicated to regional lymphadectomy. Systemic chemotherapy is indicated in the base cases in which regional lymphadectomy has to be made. The risk of radiation is limited to palliative irradiation of metastatic lesions in bones. Prognosis can be optimistic in those advanced cases that are radically excised by surgical procedure. In our material of 10 children with malignant melanoma, 10 are in complete five years survival. The lowest follow up is 14 years.

2958 RISK FACTORS FOR JUVENILE BONE TUMOURS.

A retrospective case-control study was conducted to identify discernible characteristics of youths with osteosarcomas and Ewing Sarcomas in comparison with age-matched hospital, neighborhood and family controls. The study included incident cases from Vienna and central Austria; interviews from 72 cases and 150 controls were analyzed by a multiple regression approach (PECAN, GLIM). Preliminary results showed, among other associations, an increase in bone tumour risk after a history of chickenpox (RR 4.4 in boys, 1.3 in girls) and mumps (RR 1.5 in boys and 4.15 in girls). No association was found with other clinically apparent childhood diseases such as rubella infection and bacterial diseases. In children of both sexes with birth sites over 50 cm on the RR was 1.4, but at the time of diagnosis the RR for the relation of height/ weight was 3.8. An increased risk was found when difficulties occurred in family life, with RR of 4.5 in boys with a second marriage of the mother and RR 5.3 in girls when the father died, RR 2.9 with stepparents for both sexes combined. Other findings concerning medical and personal data were not included. A second study on the basis of a sero-epidemiological survey serves to test the reliability of information on childhood diseases, because the above mentioned results on previous viral diseases require confirmation before further research can be recommended.

2959 CANCER INCIDENCE IN CHILDREN IN WARSAW 1967-1982
H. Gedonék, N. Zmiciero
Warsaw City Cancer Registry, Centre of Oncology-Institute, Warsaw

The total number of cancers in Warsaw children of the 0-14 age group in 1967-1982 was 518. It make up 0.5% of all the cancers reported in this period. Cancer was more frequent in boys than in girls (57.1% of all the cancers in children).

The incidence rate was per 100 000 boys 14.7 and per 100 000 girls 11.6.

The highest per cent rate among all the reported cases in children occurred in 0-4 age group (43.2%).

The most frequent cancers in children, 32.8%, in boys and 23.7%, in girls, were leukemias.

The second largest group of childhood cancers, 15.2%, in boys and 19.4%, in girls, were malignant neoplasms of the brain.

Histologically confirmed were 79.7% of all the reported cancers in boys and 76.6% in girls.

The large group of children with cancer 30.1%, was treated by the chemical, 82.3%, by the combined, 16.0%, by the surgical and 30.2%, by the radiotherapy methods.

2960 PERINATAL CHARACTERISTICS AND CHILDHOOD NEOPLASMS.
N.W. Choi, N.A. Nelsen, P.F. Moodie, A. Ruder, Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba, R3E 0W9, Canada

A case-control study has been carried out to determine risk factors for childhood neoplasms. The selection criteria for the cases were a) residence of birth was Manitoba. b) date of birth between 1950 and 1974 inclusive. c) date of diagnosis between 1951 and 1982 inclusive. d) diagnosis was histologically confirmed. Information from birth certificates has been obtained for 750 such cases. In addition information has been abstracted from mothers and babies' charts at time of birth and from cancer registry records. A random sample of controls was selected separately for each age of case. The ratio of controls to cases was 2 to 1. These controls were selected from a subset of the above birth-years which could produce a cancer case of the given age during the case ascertainment period (1951-84). The residence of birth was Manitoba. Information from the above sources has been abstracted for 1470 controls. The record for each subject included 12 variables which have been stored on a computer master file. These variables include age, race, residence, occupation, etc. of parents as well as birth place, birth weight, gestation period, gravity, parity, etc. for the newborn which were obtained from birth certificates. Information on complications, infectious diseases, trauma and perinatal medication and radiation for the mother and the newborn were obtained from mothers' and babies' hospital records at time of birth. For the cases, diagnosis date and residence, site (tumor as well as topography and morphology have been recorded. Multivariate analysis (logistic function, Mantel Haenszel summary and Breslow's interaction tests) were applied to investigation the association of some risk factors with all cancer sites combined as well as with specific sites. Estimation of these risk factors adjusted for confounding variables will be presented.
The symbolic language of ill children.

P.J.C. Stokop, Groningen, The Netherlands

Ill children are conscious knowing about what is going to happen with them. They know if they will recover or die, how long they have to live etcetera.

They express their knowing in symbolic language: drawings, poems, fantasies, fairytales etcetera.

Moreover they use symbols to communicate about questions of life and death. They speak, e.g. about removing (dying), butterfly (=soul or spirit, leaving the body), prison (=illness, hospital), country at the other side (=death). Most of these symbols have a fixed meaning in different cultures and religions in different times. Children use this symbolic language often spontaneously, without knowing anything about the long tradition and history of the symbols.

Very often all children only want to talk about their questions and their feelings in this symbolic language.

Psychologic and pastoral care demands for the knowledge of this language. Moreover it is possible that the unconscious knowledge of the child, expressed in this symbolic language, influences medical decisions.

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WHAT DOES THE CHILD KNOW ABOUT HIS CANCER? A NEW ASSESSMENT METHOD.

P. Hatira, H.V. Kosmidis, D.O. Bouhoutsou, M.C. Varnoutsi, P.A. Kosmidis

Oncology Unit Children's Hospital A.Kyriakou, Athens, Greece.

In their attempt to protect the child from the painful reality, parents often either do not answer the child's questions or answer in a misleading way. The child realizes that he is surrounded by an atmosphere of mystery and silence and he insists in questioning or trying to get information in his own way. In an attempt to investigate what the child knows about his illness and how he was informed we tested a new projective assessment method in 60 children (40 with acute leukemia, 13 with solid tumors and 7 with lymphoma), aged 4 to 14 years. Ten specifically drawn pictures were shown and they were asked to cite a story related to the picture. 43/60 children pacify their fear and anxiety, shorten and simplify this technique, particularly in the leveling countries.

ATTITUDES OF CHILDREN WITH CANCER TOWARDS THEIR PERSONAL INVOLVEMENT IN INFORMED CONSENT

Kamps W.A., Kings A., Akkerboom J.C. and Humphrey G.B.

Dept. of Pediatrics, Univ. Groningen, The Netherlands

An attitudinal survey is currently being conducted on 50 recently cured children with cancer. The survey includes both a structured and unstructured interview. The structured portion of the interview is identical to our previous study of 137 families, who had a cured child, who had completed a course of chemotherapy (and in many cases radiotherapy and/or surgery). The structured portion of this study of children as in the previous study of parents includes 24 questions concerning 4 topics (1). The role of the child in deciding about phase II experimental therapy (2) what information (e.g. impending death) should be related to the child and by whom (3). What should occur if the child and parents differ on entry into a phase II chemotherapy trial (4). Ethical issues (i.e. altruism and selfishness). It is now (Nov 1985) to early to make any comparison of parental and child attitudes towards key issues such as should the child be informed of both altruistic and selfish aspects of experimental therapy. The majority (66%) of parents thought both should be present. The information being obtained in this study, and the information already obtained in the previous study will allow us to design a prospective study of parents and children, who are actually facing the reality of informed consent at some time of relapse, when a choice must be made between phase II therapy or supportive care.
2965 MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS IN CHILDHOOD RHABDOMYOSARCOMA: A PRELIMINARY REPORT OF THE GERMAN SOFT TISSUE SARCOMA STUDY (G5S-81).


From 1981-1985, 76 children with rhabdomyosarcoma in clinical stage III (macroscopic residual disease after biopsy) were treated according to a multimodal, multiple agent trial for 1 year. Depending on the results of a second look surgery after administering chemotherapy for 16 weeks, the patients were microscopically and macroscopically free of residual disease received radiotherapy, started at week 20 (0 or 50 Gy). In the first part, patient characteristics related to prognosis (disease-free survival time) were identified by multivariate analysis (Cox's regression model). The characteristics included in this analysis were histological subtype, tumor diameter at onset primary site, sex, lymph node involvement, infiltration into adjacent bone and the degree of tumor regression within 7-9 weeks, measured by CT scan. After excluding non-responding tumors, we found the degree of tumor response within this time was the main hazard function to prognosis (e^27.1). Only the characteristics sex and lymph node involvement showed some influence, but not strong (e^22.5, 2.2). Secondly we fitted the patient characteristics in a logistic regression model with the end point for analysis: degree of tumor response, excluding non-responding tumors. In this way we could see which characteristics were influencing the degree of tumor response. The tumor diameter was the pattern of strongest influence (e^25.3). Other characteristics did not show any important influence. In a third step we analysed the non-responding tumors. This analysis we fitted in the known characteristics with the clinical stage (III-IV) in addition. Clinical stage was found to be the main hazard function related to non-responding tumors (e^25.1). Furthermore we saw some influence of primary site, age and tumor diameter (e^22.6, 2.3, 2.1). However it has to be mentioned, that analysis of prognostic factors depend on the treatment procedure.

2966 MALIGNANCIES IN CHILDREN IN LUCKNOW, INDIA: AN EPIDEMIOLOGICAL STUDY. Anand N. Srirastava, K.M. Wahal and R.M.L. Mehrotra. Postgraduate Department of Pathology, King George's Medical College, Lucknow-226 003, India.

Out of a total of 19039 histopathologically proved malignant tumours in patients of all ages and both sexes, 768 tumours (4.1%) were in children, in the Postgraduate Department of Pathology & Bacteriology, King George's Medical College, Lucknow. Over a period of 30 years from 1962 to 1978. The commonest were tumours of reticuloendothelial system (58%), followed by tumours in head-neck region (15.2%), and then tumours of soft tissues, bone and joints, urogenital, CNS and other organs. Tumours of liver, spleen and skin etc. were rare. The incidence of malignancies in children in various parts of India, has been discussed; with probable influencing factors.

2967 CELL-MEDIATED IMMUNE REACTIONS TO NEUROBLASTOMA. I. Burks*, J. Okabe, H. Sunaga and K. Morita. First Dept. of Surgery, Hii noh Univ., Tokyo, Japan

Immunotherapy might be an effective treatment for neuroblastoma. It is important to assess changes of various parameters of cell-mediated immunity over an extended period, before and during the course of treatment, in any given patients. In the present investigation, we evaluated skin tests before treatment, lymphocyte responses to autologous tumor extract and IgG-Fc receptor positive T cells, during the course of treatment and after achieving cure in neuroblastoma patients. In our neuroblastoma patients, lymphocyte responses to autologous tumor extract showed a good responsiveness before treatment.

However, delayed type skin tests were shown to be negative in many patients, particularly in those with advanced tumor, and IgG-Fc receptor positive T cells were markedly increased in some. During the course of treatment, lymphocyte responses to autologous tumor extract showed a trend to become negative when the patient was tumor free or was in remission. However, they showed a tendency to become reactive on regrowth, recurrence or metastasis of tumor. IgG-Fc receptor positive T cells showed much the same changes as observed in lymphocyte responses to autologous tumor extract.


The Italian "off-therapy" childhood cancer survivors registry, started in 1980, includes so far 2326 subjects, successfully withdrawn from treatment for one of the following tumors: Hodgkin lymphoma (HD=224), non Hodgkin lymphomas (nHL=154), neuroblastoma (NB=221), Wilms tumors (WT=256), acute lymphoblastic leukemia (ALL=197) and non lymphoblastic leukemias (nLL=74), before December 31, 1983. These children, treated and followed in 41 Italian institutions, have been diagnosed from 1963 onwards. On December 31, 1983 1959 (84.2%) were alive in complete remission (CR) and 182 (7.8%) after a relapse.160 (7.4%) had died in CR,117 (5%) after a lapse and 65 (3.3%) in unknown CR status. 46 (2.2%) were lost to follow-up (14 in CR and 4 after a relapse). Off-therapy relapse crude (projected actuarial) percent rates are: HD 10.4, 14.2, nHL 1.9 (1.4), NB 5.9, 16.8, WT 4.7 (4.6), ALL 36 (60) and nLL 2.7 (13.6). Life-table analysis of event-free survival from treatment withdrawal gave the following cumulative proportions surviving:

<table>
<thead>
<tr>
<th>Time (mos.)</th>
<th>HD</th>
<th>nHL</th>
<th>NB</th>
<th>WT</th>
<th>ALL</th>
<th>nLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 mos.</td>
<td>92.0</td>
<td>96.6</td>
<td>93.7</td>
<td>95.9</td>
<td>81.5</td>
<td>70.2</td>
</tr>
<tr>
<td>48 mos.</td>
<td>89.6</td>
<td>98.6</td>
<td>92.3</td>
<td>94.8</td>
<td>77.9</td>
<td>62.3</td>
</tr>
<tr>
<td>60 mos.</td>
<td>86.7</td>
<td>90.6</td>
<td>92.3</td>
<td>94.8</td>
<td>77.1</td>
<td>-</td>
</tr>
</tbody>
</table>

Methodological approach and general characteristics of the six tumor subgroups are discussed.
2970 DNA-ANALYSIS OF WILMS' TUMOR
Oppedal, B.R. and Zetterberg, A. Inst of Pathology, The National Hospital, University of Oslo, Norway, and Dept of Pathology, Karolinska Institutet, Stockholm, Sweden.

Single cell DNA measurements were performed on Feulgen stained nuclei in 8 um thick tumor sections from 20 patients with Wilms' tumor at the National Hospital in Oslo, Norway. All the patients had initial nephrectomy. 15 patients had survived for at least 10 years without evidence of recurrence, the remaining 5 died from their tumors within 2 years after nephrectomy. Two different sections from each tumor were examined. That is a total of 40 sections. The cytogenetic investigation group and compared with centrole data characterized 60 healthy children and their families. The data of prenatal as well as postnatal development of patients, pedigree analysis, dermatorgic study, cytogenetic investigation and some other special laboratory examinations are reported. Mathematical and statistical analysis proved the statistically significant differences between the groups of patients investigated and the healthy children in the prenatal history, postnatal history, pedigree analysis and dermatorgic study. Significant higher incidence of chromosome anomalies was not described. The results show the importance of special genetic care in the clinical anaylsis.


Bone marrow and placental tissue in metastatic breast cancer (MBC) has been evaluated in a double blind study comparing the traditional cytology with an immunohistological technique. The technique utilizes the 11113A monoclonal antibody (MA) which recognizes a neoplastic clone derived from an at risk child. Careful evaluation for the presence of abnormal clones (pseudoalleles in May-Grünwald Giemsa stained smears) has been made in 100 samples. 

2971 EPIDEMIOLOGY OF CHILDHOOD CANCER IN SLOVAKIA
Pleško, E., Drimtová, J., and Bartková, J., National Cancer Institute of Slovak Academy of Sciences, Bratislava, Czechoslovakia.

Analysis of the development of the age-adjusted cancer incidence in children in Slovakia in the period 1961-1982 showed slightly increasing trends. The incidence rates reached 34.5 per million in boys and 118.6 in girls in recent five years period in comparison with 13.1 and 104.7 respectively during the decade 1954-1961. Almost complete histological differentiation of childhood tumors in this country together with high proportion of autopsies of children dying from cancer as well as the use of standard international classification (ICD-B) based on morphology enabled the very detailed subdivision of childhood malignancies with the predominance of leukemias, tumors of nervous system, lymphomas and Wilms' tumor of the kidney. The mortality of childhood malignancies during the same period showed a substantial decrease in both sexes and could be attributed to steadily improving therapy of the large proportion of these malignancies. The use of standard classification based on morphology in the anguish possible extent is emphasised for epidemiological study and international comparison of childhood malignancies in population-based cancer registries.
EDUCATIONAL PROGRAMS AT A COMPREHENSIVE CANCER CENTER THAT ENCOURAGE DEVELOPMENT OF CANCER RESEARCHERS: C. R. Johnson and E. A. Mirand. Roswell Park Memorial Institute, 666 Elm Street, Buffalo, New York 14263, U.S.A.

With the development and growth of many new or established cancer centers, manpower is required to staff the basic and clinical programs in the various fields of oncology. It is being trained and how research training is being administered at a U.S.A. comprehensive cancer center will be illustrated. Programs described begin with secondary school students and continue through the baccalaureate, graduate, and post-graduate levels. In order to encourage students, physicians and dentists to enter the oncology field, the following programs have been established at Roswell Park Memorial Institute (RPMI): Research Participation Program in Science - Secondary school and undergraduate college students are provided an indepth summer research experience in a senior scientist/clinician's laboratory. Summer Oncology Research Program - Medical and dental students may conduct a well-defined cancer research project within one of RPMI's clinical or basic research departments. Oncology Nurse Training Program - Graduate nurses who wish to specialize in oncologic nursing may elect to study summers at the Inst. or to pursue a Master degree in Oncology for Nurses through the RPMI Graduate Div. Medical Scientist Training Program - Medical students at the NCI, at Buffalo or at the 6 yr. Medical Doctor/Ph.D. program and choose to do cancer research. The major purposes of this program are to develop medical scientists: physicians and to decrease the gap of knowledge and understanding which separates scientists from physicians. Post-Graduate Fellowship Program - Ph.D.'s and M.D.'s who wish to commit to a research career enroll in a one to three year post-doctoral research program. Under the supervision of a senior staff member, trainees develop as independent investigators specializing in an oncology related area. RPMI Graduate Div. - Baccalaureate level students and post-graduate physicians are encouraged to enter the Maste: or Ph.D. degree programs offered at the Inst. through the RPMI Graduate Div. Lectures and thesis requirements emphasize cancer research topics. In summary, an evaluation of the above programs has demonstrated that they have encouraged various trainees to pursue a career in oncology in a comprehensive cancer center setting.
2977 A STUDY OF CANCER PREVENTION EDUCATION FOR THE ELDERLY

Undergraduates who are majoring in gerontology are generally required to study biology of aging. They study normal human anatomy and physiology and then learn about the changes which occur in the elderly along with the organic diseases that often accompany aging. Little if any mention is paid to prevention in such a course. Yet, a program of cancer prevention for example can be worthwhile even for the most aged. Gerontology majors who eventually must administer such a program should understand which types of cancer affect the elderly most often so that specific prevention strategies may be learned. American Cancer Society statistics indicate that the death rate for cancer in those over 75 years of age has risen recently. They also indicate that for males cancer of the prostate, colon and lungs (in that order) are the most prevalent; and cancer of the breast, colon and rectum (in that order) in females are most prevalent. Research as to the best methods for prevention of these cancers and for the teaching of these methods indicates that mental outlook, environmental exposure, and health care delivery are major factors to be considered. How to motivate the elderly to be concerned about good health without frightening them is also considered in this study.

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2978 HEAD AND NECK SURGICAL ONCOLOGY TRAINING IN INDIA AND ASSESSMENT OF CURRENT STATUS & FUTURE PROSPECTS

Dr. A.R. Mehta, Dr. R.C. Nayar, Tata Memorial Hospital, Bombay, Maharashtra, India.

India is a developing country with a low GNP per capita (280 $). The problems of rationalizing the training programmes in Head & Neck Oncology are assessed in the current study. The current cancer control programmes and modifications within constraints of resources and manpower are discussed. A revised training programme for Head & Neck Cancer Surgeons is suggested in the light of the above. The input consists of general surgeons, ENT or Plastic Surgeons, they should be subjected to a rigorous one year programme in Head & Neck Oncology in a Comprehensive Care Cancer Center which is adequately staffed. Exposure to all relevant branches of surgical oncology as well as Radiation and Medical Oncology is envisaged. Continuous revisions and modifications by an advisory body set up by an association such as the Head & Neck Oncology Society will enable the training programme to be flexible and responsive to the needs of both the cancer control delivery system and the society in general.

2979 EDUCATION IN CANCER REHABILITATION


A survey of cancer education conducted in 1977-1978 in medical and dental schools in the U.S.A. showed that very little instruction was offered in either type of school concerning the rehabilitation of patients with cancer, and that this subject was low on the list of neglected topics identified by faculty and students as needing further reinforcement in medical and dental curricula. Yet when adequate and appropriate rehabilitation procedures are planned for and introduced early in the management of patients with many types of cancer, they can contribute substantially to an early return to normal physical functioning, vocational integrity, and emotional stability. Cancer rehabilitation covers many disciplines including physical therapy, enteroctal therapy, maxillofacial prosthodontics, prosthetics, psychosocial and vocational therapy, speech therapy, among others. Educational activities that will enhance the knowledge of medical and dental students about cancer rehabilitation should include both direct exposures to the application of these services as well as the use of various teaching aids. A poster display of cancer rehabilitation services and of educational activities that describe and illustrate them, and may be used in the education of all types of health professionals, is presented.

*R-41: PROFESSIONAL EDUCATION

2980 A COMMUNITY-BASED MINORITY CANCER EDUCATION PROGRAM

G. Roberson, R.N., Ph.D., Roswell Park Memorial Institute, Buffalo, New York, U.S.A.

Since 1955, the highest cancer mortality rates have occurred among minority populations, particularly black Americans. Two factors contributing to the high cancer mortality among these groups compared to whites are a higher overall incidence of cancer and a poorer survival rate once cancer is detected. Underutilization of limited cancer education programs, limited knowledge and minimal disease prevention practices may contribute to the problem of control of the disease. Also, there is little evidence that in interventions to improve accessibility to cancer education and utilization of cancer control services have been designed to meet these needs. In 1982, Roswell Park Memorial Institute and the American Cancer Society, Buffalo, New York, initiated a Minority Cancer Education Program to provide information and education to Black Americans, other ethnic minorities, the economically disadvantaged, the medically underserved and senior citizens. The objectives of the program are (1) to increase awareness of cancer risk factors for these groups, and (2) to motivate individuals to adopt health practices that may prevent cancer or detect the disease in its early stages. The program provides breast self-examination, mammography, control and cancer information sessions, community in-service education, literature and cancer check-ups. Through a community network 350 volunteers were assigned in recruiting over 10,000 neighborhood residents to programs. Program impact was evaluated over a six-month period among 193 participants who completed a pretest, post-test and three follow-up. Results showed positive changes in knowledge and health practices after attending programs. Findings suggested that minorities may be reached with cancer education and motivated to adopt health practices when cancer control services are accessible.
THE EVALUATION OF CANCER EDUCATION PROGRAMS USING GOAL ATTAINMENT SCALING. Diane L. Cookfair, Michael A. Zevon, and Eduard H. Miller. Roswell Park Memorial Institute, Buffalo, NY 14263, U.S.A.

In the past, Goal Attainment Scaling has been used most frequently in the evaluation of health care interventions. However, it can be used effectively to evaluate a variety of human service programs, including cancer education programs. Design of goal-attainment scaling in goal-oriented evaluation area: goal-setting, program implementation, determination of goal attainment, and use of this information to modify program activities. In goal-attainment scaling, a five-point scale is used to provide a range of potential outcomes for each of the program's goals. These outcomes range from most unfavorable outcome to best anticipated outcome with the expected outcome in the middle of the five-point scale. Goal attainment scaling is a flexible technique which can be used to measure attainment of a variety of educational goals. The success of concrete activities, such as mastering didactic knowledge, can be measured, however, this technique also provides a method of quantifying the success of skills-oriented training and less concrete goals such as personal growth and attitude change. This paper provides information on the application of goal-attainment scaling to cancer education programs. Design of goal attainment follow-up guides are discussed, as well as scoring and statistical analysis of program data. The relative strengths and weaknesses of this evaluation method are presented. Specific applications of this method to a variety of cancer education activities are discussed, and examples are given, including goal attainment scaling data collected as part of an evaluation of a summer program in cancer research training for high-ability high school and college students.

CASE SIMULATIONS TO TEACH AND EVALUATE ONCOLOGY PATIENT CARE. K.K. Papp, Ph.D., K. Alsheimer, Ph.D., and M. Williams, Virginia Commonwealth University, Richmond, Virginia, U.S.A.

The diagnosis and management of oncology patients is a broad and complex topic that is often not dealt with adequately in the medical school curriculum. Since not all students receive didactic instruction that fulfills these needs, it is important that the students receive it during their clinical years, experiences in the diagnosis and management of oncology patients are diverse and varied. Case simulations may be used in the cancer curriculum to remedy some of these inconsistencies. Faculty at the Medical College of Virginia developed a number of case simulations to teach specific aspects of oncology patient care. Two of these programs, one for residents and one for medical students, were given to second-year medical students at the beginning and end of the third year in a crossed design. Changes in clinical decision making could thus be determined. Students who had specific oncology experiences during their clinical year improved their performance on these case simulations while students who did not have oncology experiences showed no improvement. This provides evidence for the validity of these programs. The purpose of this exhibit is to demonstrate the use of oncology case simulations in the medical undergraduate curriculum. A panel of photographs showing students working through these case simulations will be presented. The simulations will be diagrammed; the decision trees will be illustrated. Handouts will demonstrate case simulations using the latent image format. This exhibit will provide an opportunity to work through them. The session will discuss the use in the curriculum and the advantages and limitations of using case simulations.
Additive and synergistic antitumor effects with toremifene and interferones.

L. Kangas, K. E. Pulliainen, and K. Schellekens
Farmon Group, Turku, Finland, National Public Health Institute, Helsinki, Finland, and Private Center TNO, Heijmijck, The Netherlands

The interaction of human interferoens (alpha and gamma) and toremifene was studied in vitro using MCP-7 cells. The interaction of rat interferon gamma, prepared by recombinant technique (RIP gamma) and toremifene was studied in vivo using DMBA induced rat mammary tumors. MCP-7 cells are sensitive to toremifene. ICGO concentration being 10-14 M at 11 days. In MCP-7 cells human interferoens had an single agents concentration dependent growth inhibition, cells being more responsive to interferon gamma. The I50 concentrations after 11 days cultivation were about 4000 IU/ml for alpha and about 100 IU/ml for gamma. Combination with toremifene induced additive antitumor effect with interferon gamma and synergistic effect with interferon alpha. In the rats RIP gamma (10000 IU/rat daily for 5 weeks) had no effect on the growth of the DMBA induced tumors and on the appearance of new tumors. Toremifene (3 mg/kg daily for 5 weeks) inhibited both the tumor growth and appearance of new tumors. The numbers of new tumors/animal/animal were 2.4±1.8, 2.4±1.3 and 1.2±1.1 in control animals, RIP gamma treated and toremifene treated animals, respectively. The combination RIP gamma + toremifene was the most effective treatment, at least additive antitumor effect was evident, only 0.6±1.0 new tumors/animal developing during the treatment. The combination induced no signs of toxicity to the animals. Clinical studies with combination of toremifene and interferoens might be warranted.

Treatment of advanced breast cancer with 20 mg. toremifene. A phase II study.

R. Valavaara, S. Pyhönen, M. Heikkonen, P. Rossanen, G. Blanco, E. Nordin, P. Taskinen, L. Holati and A. Hajba
Departments of Radiation Oncology and Obstetrics and Gynaecology in Helsinki, Oulu and Turku University Central Hospitals and Research Center of Farmos Group Ltd., Finland

Toremifene is a new antiestrogenic antitumor substance. It binds to the estrogen receptors of the cytoplasm, is translocated to the nucleus and blocks estrogen induced cell proliferation. The antitumor effect of toremifene is directed against estrogen-dependent tumors of the mammary gland and of the endometrium. Fourteen postmenopausal women with estrogen receptor positive advanced breast cancer entered the study. No prior cytostatic treatment was allowed and adjuvant tamoxifen only in case it was stopped at least six months before the toremifene treatment. The dosage was 20 mg daily as a single dose but in the beginning, days 1-3, the patients received a loading dose with 120-60-60 mg toremifene in order to obtain the presumed therapeutic concentration rapidly. Twelve patients are evaluable with at least 6 weeks’ treatment. There are 0 CR, 3 PR and 3 NC/12 patients had mild side effects: nausea, insomnia, sweating and arm pain. The preliminary results indicate a poorer antitumor efficacy with 20 mg toremifene than with higher dose levels.
SECONDARY PHARMACOLOGICAL EFFECTS OF TOREMIFENE

Toremifene had no significant effect in Irwin screen, on beta-, H4, H5, acetylcholine or serotonin receptors, neither it affected platelet aggregation. Toremifene had no hypoglycemic, diuretic, antiinflammatory and antimicrobial activity. Toremifene had no marked immunostimulatory or immunosuppressive effects. The effects of toremifene on central nervous system are weak. At high doses (100 mg/kg i.p. or more) a short lasting CNS suppression was observed in spontaneous motility and barbiturate potentiation test in mice. Toremifene caused a short term hypothermia in rats at the doses 30 and 100 mg/kg i.p. The effects of toremifene on cardiovascular system are negligible. Toremifene had no direct suppressive effect on intestinal motility in rats and mice although in vitro it has nonspecific spasmylic effect at high concentrations on acetylcholine, histamine and BaCl2 induced spasms. Toremifene had analgesic effect in the writhing test at doses exceeding 3 mg/kg i.p. The mechanism of analgesic effect is not known. The results show that the secondary pharmacological effects of toremifene are few, mild and transient.

METABOLISM OF TOREMIFENE IN THE RAT

Toremifene was labelled with tritium at the positions 2 and 6 in the phenyl ring. At these positions tritium is stable and becomes not eliminated in the metabolic tests. The specific radioactivity of the labelled compound was about 20 Ci/mmol. Nonradioactive toremifene was added to rats (5 mg/kg, 5 uCi/mg) p.o. and i.v. The animals were killed 24, 48 and 72 hours after administration. Each dose group comprised 5 mice of both sexes, a total of 150 mice in the whole experiment. Toremifene had no mutagenic effect in the assay. The results indicate that toremifene does not have mutagenic potential in the conventional mutagenicity tests.
2993 EFFECT OF TOREMI FENE ON CLINICAL, HEMATOLOGICAL AND PHASE II CLINICAL STUDY AT HIGH TOSK TOREMIFEN.

Postmenopausal women with locally advanced or metastatic breast cancer with a performance status of more than 50 per cent and a life expectancy of at least 3 months were eligible for the study. The patients were further treated with endocrine therapy and/or cytotoxic drugs and they present at least one measurable lesion. Toremifene was given at a daily dose of 200 mg. Tolerance appears to be excellent and several patients have achieved stable disease for more than 12 months. Current results will be presented.

2994 EFFECT OF TOREMIFENE ON CLINICAL, HEMATOLOGICAL AND HORMONAL PARAMETERS IN DIFFERENT DOSE-LEVELS: PHASE I STUDY

Kivinen, Seppe 1 and Kankaanpaa, Juhani 2
Department of Obstetrics and Gynecology, University of Oulu 1 and Turku 2

Toremifene is a new antiestrogen compound developed by Farnos Group Ltd, Finland, for the treatment of hormonally dependent tumors. In the present study toremifene was given on dose range of 3-480 mg daily as single doses and five days' administration to 78 postmenopausal healthy volunteers. Blood samples were taken hourly up to 7 hours and 1, 2, 3, 7, 10, 15 and 20 days after the last dose of toremifene. The concentrations of serum bilirubin, creatinine, ammonia, free thyroxine, ACTH, cortisol, prolactin, electrolytes and blood glucose remained unchanged at every dose-level. Statistically significant decrease was observed in liver enzymes (AST, ALT, AKP, phosph.) at the dose-levels of 220-480 mg, whereas Gamma GT remained unchanged. A decrease in the concentration of LH and FSH was observed at the dose-levels of 22 mg or higher and 220 mg or higher, respectively.

These hormonal changes including the increase of SHBG at the doses-levels of 22-480 mg and the decrease of Anti-trough III (220-680 mg) are attributed to the direct estrogen-like effect of toremifene. Side-effects were minimal. Pulse rate, blood pressure and BCG remained unchanged during the test period. Only two patients of 680 mg dose suffered from nausea and vertigo, and one of them discontinued the medication. Conclusively, the results indicate that toremifene is well tolerated up to 460 mg daily administered orally its hormonal effects resemble those of tamoxifen.

2995 RESPONSE TO TOREMIFENE (FE-115T7A) THERAPY IN TAMOXIFEN FAILED PATIENTS WITH BREAST CANCER

Ebb, S.R., Robert, J., Baum, M., Cancer Research Campaign: Raynes Institute, London SE5 9NU U.K.

Eight patients with measurable lesions of locally advanced or recurrent breast cancer have been treated with toremifene 200 mg daily all had previously relapsed anti-oestrogen therapy. A response rate of 50% has been achieved so far. Toremifene is a new triphenylethylene compound with anti-oestrogenic activity. At high dose, in cell culture and in animal experiments, an anti-tumour effect has been reported that appears to be independent of anti-oestrogenic activity. As our patients had previously relapsed on anti-oestrogen therapy (tamoxifen), we postulated that our response rate has been achieved by the direct oestrogenic effect.

2996 ANTI-OESTROGENIC AND ANTI-TUMOR PROPERTIES OF THE NEW TRIPHENYLETHYLENE DERIVATIVE TOREMIFENE IN THE RAT, M. CARLO, L. CARLO, C. DI MELE, C. FAMITALIA

Carlo Erba Res. Ctr., Milan, Italy.

The effects on the uterus and on DMBA-induced mammary tumors in rates of toremifene (TOR), a new triphenylene derivative, were compared to tamoxifen (TAM). The ability of TOR to compete with [3H]estradiol for cytoplasmic estrogen receptor from rat uterus was similar to TAM, the IC50 being 24 and 23 nM, respectively. In immature intact rats the two compounds, administered orally for three consecutive days, had similar intrinsic partial estrogen efficacy, at 30 mg/kg. 4% of that of estradiol benzoate (EB). However, at doses 10 mg/kg, TOR estrogenic effect was seen at doses about 40 times higher than TAM. The two compounds, administered with a standard dose of EB, expressed the same maximal anti-oestrogenic efficacy (about 65% inhibition) at 4 mg/kg. However, the minimal effective anti-oestrogenic dose of TOR was about 10 times that of TAM and the ratio between anti-oestrogenic/estrogenic properties was favourable to TOR.

The duration of the antiestrogenic (antiuterotropic) effect of a single oral dose (10 mg/kg) of the two compounds proved similar: up to 4 days in intact rats and 3 days in ovariectomized rats.

In DMBA-induced tumors bearing rats, TOR was administered p.o., 6 times/wk for 4 wks at 0.08, 0.4, 2, 10 and 50 mg/kg. TOR was effective at the doses of 2, 10 and 50 mg/kg, inducing 39%, 35% and 46% tumor regressions. The activity of TOR at the minimal effective dose of 2 mg/kg was then compared with that of TAM given at the same dose level. The compounds had comparable activity (47% vs 44% tumor regression).
Abstracts of Lectures, Symposia and Free Communications

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PDGF represents the major growth factor activity of human serum and it is a potent mitogen for mesenchymal derived cells in culture. Amino-terminal amino acid sequence analysis demonstrated that it consists of two homologous polypeptide chains (PDGF-A and PDGF-B) linked together by disulfide bonds (Science 220, 963, 1983). The sequence of PDGF revealed a striking homology with the predictor amino acid sequence of the simian sarcoma virus (SSV) transforming gene product (p250A), suggesting that the two proteins derived from the same or closely related cellular genes (Science 221, 275, 1983). In addition to sequence homology, PDGF and the SSV onc gene product share common antigenic determinants and structural conformation (Nature 305, 605, 1983), and exert identical biological functions (Science 225, 64, 1984). The biologically active PDGF transforming protein was shown to be a homodimer consisting of two PDGF-A chains linked together by disulfide bonds. These studies suggest that the ability of the SSV to induce neoplastic transformation is derived from the incorporation of the PDGF gene within the retroviral genome. The resulting transforming onc gene (v-sis) region codes for a PDGF-like mitogen and is capable of inducing neoplastic transformation by the continuous production of this potent mitogen causing sustained cell proliferation. C-sis transcripts and synthesis of PDGF-like proteins have been demonstrated in human osteosarcoma, glioblastoma and fibrosarcoma cells. These human malignant cells also secrete PDGF-like proteins possessing structural, immunochemical, and biological properties characteristic of PDGF. It is possible that inappropriate expression of v-sis may be implicated in the processes leading certain human cells of mesenchymal origin towards malignancy.

B-13: GROWTH FACTORS, RECEPTORS AND ONCOGENES

RESERVED

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GROWTH FACTOR INDUCED INTRANUCLEAR PROTEIN ACCUMULATION AND THE MALIGNANT CELL GROWTH M. Sellemayer, Department of Clinical Chemistry, University Medical School, Pécs, Hungary.

The mechanism of the facilitated cell growth including the enhanced rate of cell division in malignant tumors, is still obscure. In our previous experiments on cell hybrids the relationship between the intranuclear protein transport and activation of the nuclear functions has been well documented. At the beginning of these experiments, the question was asked, whether the Platelet Derived Growth Factor (PDGF) induced activation can or cannot be related to an enhanced intranuclear protein transport. Human PDGF and 3T3 mouse and human fibroblasts were used. Cells staying in G0 or G1 phase (contact inhibited quiescent cells) were exposed to 35S-methionine to reach a well countable label density in the autoradiographs, then exposed to PDGF and the numbers of grains were counted above the nuclei and the entire cells. In case of the control cells less than 20% of the grains were found above the nuclei, while after PDGF treatment, more than 40% of the grains were found above the nuclei, i.e. the labelled proteins showed nuclear localization. The findings indicate that PDGF might work as a trigger for the enhanced intranuclear accumulation of proteins, which seems to be a crucial prerequisite for gene activations. We hypothesise that the transforming growth factors can perform similar functions in tumor cells as PDGF does in the fibroblasts. Consequently, the PDGF-like transforming growth factors by triggering from inside the enhanced intranuclear protein accumulation right after the cell division might functionate as a "master-switch" turning on and on the tumor cells for their facilitated, malignant growth.
3001  THE FOS PROTO-ONCOGENE: CONTROL OF EXPRESSION AND CHARACTERIZATION OF GENE PRODUCT. T. Curtan, L. Sambucetti and J.J. Morgan. Roche Institute of Molecular Biology, Dept. of Molecular Oncology, Nutley, NJ 07110 USA.

The fos proto-oncogene (c-fos) is expressed at relatively high levels in extraembryonic mammalian cells and in differentiated macrophages. In most cell types the level of c-fos expression is generally low. However, treatment of cells with polypeptide growth factors or other agents results in a rapid but transient induction of c-fos mRNA and protein. Induction of c-fos has been associated with cell growth and differentiation, and, more recently, with degranulation of neuronal cells. We have identified at least two distinct biochemical pathways which control c-fos expression in the phaeochromocytoma cell line (PC12). One pathway is initiated by receptor-ligand interactions whereas, the other is initiated by degranulation. The latter effect stimulates a specific calcium influx which triggers a calmodulin-dependent transcriptional activator of the c-fos gene. It has been suggested that c-fos serves a general role in coupling short-term events such as an influx and protein phosphorylations, which occur at the cell surface, to long-term alterations in gene transcription. We have identified a DNA-binding property associated with the fos protein complex which strengthens this hypothesis.


The sequence of c-fos, oncogene of avian sarcoma virus, has striking similarity to the carboxyl half of the human epithelial growth factor (EGF) receptor, indicating that the c-fos gene is derived from the chicken EGF receptor gene. Using antibodies to the carboxyl half of EGF receptor, we have identified another 95,000 dalton gene, c-erB-2, in human chromosome 17q21. Functional expression analysis of both genes in COS cells showed that the carboxyl half of c-erB-2 encoded in a 130,000 dalton protein highly similar to, but distinct from, the EGF receptor. Direct comparison of the amino acid sequences deduced from DNA sequences of c-fos and c-erB-2, or gene products identified by their interaction with high affinity monoclonal antibodies, revealed strong similarity between the two, indicating that they are the same gene. By virtue of its structural identity, the c-erB-2 protein is believed to be a cell growth factor receptor. Antibodies were prepared against a piglet with mono- and cross-reactivity. In fact, studies of the c-erB-2 protein, using these antibodies, we showed that the nature c-erB-2 gene product is a phosphorylated 130,000 dalton protein which is associated with protein tyrosine kinase activity. Although the c-erB-2 gene is predicted to encode a protein similar to EGF receptor, EGF did not stimulate this kinase activity either in vivo or in vitro. However, EGF as well as PDTC enhanced phosphorylation of the c-erB-2 protein in vitro, and hormone residues, probably through the activation of protein kinase C. Reverse transcription of c-erB-2 oncogene was examined by Southern blots of RNA from human malignant tumors. Amplification of the c-erB-2 gene was observed in 5/6 of squamouscarcinomas and in 7/8 of adenocarcinomas. Structural aspects of the c-erB-2 encoded protein will be discussed in relation to knowledge of functions of this protein and EGF receptor.

3003  CORRELATION BETWEEN EXPRESSION OF C-MYC GENE AND IL-2 RECEPTORS IN HUMAN PROLIFERATED ACTIVATED LYOPLASMS AND CYCLOID T LYMHPHOCYES. T. van den Bulk, C. Groenwegen, Dept. of Immunology, Rotterdam Radio-Therapeutic Institute, Rotterdam and Institute for Experimental Gerontology TNO, Nijmegen, The Netherlands.

A continuous cell line of c-myc has been observed in several Burkitt lymphomas after translocation of the c-myc gene or in the human promyelocytic leukemia HL-60 and in the human colon carcinoma A-549. c-myc was expressed in 2 of 66 lymphomas and 21 of 71 lymphocytes after lectin activation. Proliferation of T lymphocytes requires interaction of IL-2 and IL-2 receptors. In this study, we demonstrate a direct correlation between c-myc and IL-2 receptors in human peripheral blood lymphocytes, both induced after activation with the lectin phytohaemagglutinin (PHA). We also induced high levels of c-myc mRNA in different cloned human cytosgenic T lymphocytes (mature CD3+CD4+ cells and CD3+CD8+ natural killer derived T cells) and in noncytogenic T lymphocytes. The interdependence of the activation pathways of oncogene expression and growth hormone receptor expression will be discussed.


Epidermis is subject to autocrine growth control by antiproliferative tissue factors. Two antiproliferative factors have been identified which inhibit the epidermal cell cycle at the G1-S transition or G0-M transition, respectively. It is shown that the inhibition effect of these "epidermal chalones" exhibits a high degree of tissue- and cell line-specificity. In Vitro experiments, its amphi-embryonic activity and its stability against heat and proteolytic digestion the epidermal G1-chalone is not a peptide or protein but most probably a macroglycopolymid. It is non-dialysable; however, it is not only inducible, but also in parallel with c-myc and c-fos expression, shows a close correlation between c-myc and IL-2 receptors in T lymphocytes. In this study we demonstrate a critical role of the carbohydrate moiety for biological activity. It is assumed that the G1-chalone is localized at the epidermal cell surface and that its biological effect is due to a lectin type interaction with protein moieties on the surface of neighbouring cells. Based on an estimated molecular weight of 70 kDa, the most purified - but still not homogenous - chalone preparation shows maximal inhibitory activity on epidermal DNA synthesis at a dose of 1.8 g/mL in vivo or 1.5 x 10^{-6} M in vivo. Injection of c-myc protein in mice induced IL-2 and IL-2 receptors. In this study we demonstrate a close correlation between the appearance of chalone activity and the onset of epidermal keratinization. This new growth factor may have a common role in the development of many malignancies. The proliferative effects of epidermal hyperplasia and the metabolism of chalone may play a role in tumor progression of epidermal keratinization. Structural aspects of the c-myc-induced chalone will be discussed in relation to knowledge of functions of this protein and EGF receptor.
RETROVIRUS GENES AND GENE PRODUCTS: CONTROL OF EXPRESSION
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Retroviruses have several strategies for gene expression, including genomic size polycistronic mRNA's, spliced mRNA's, termination suppression resulting in either in-frame readthrough or frameshift, multiple initiation on the same mRNA and proteolytic cleavage to generate multiple protein components from a single translational product. The genomic 35S RNA of all replication-competent retroviruses is divided into three genes arranged in the order of 5'-gag-pol-env-3'. Human endogenous proviruses have identical gene organization. The internal structural proteins, reverse transcriptase (RT) and endonuclease (EN) as well as the viral protease are synthesized via the translation of the 35S mRNA. A smaller (26S) spliced mRNA codes for the viral envelope proteins. The primary product of this env mRNA is first cotranslationally cleaved by the signal peptidase and then posttranslationally by an unidentified cellular protease at the end of the consensus sequence Arg-Arg/Lys-Arg conserved among all retroviruses. In murine and feline viruses the primary translational products of the gag and pol genes are Pr65Gag (p12-p30-p10) and Pr80Gag-Pol (p15-p12-p30-p10-protease-RF-EN) respectively. Both are initiated with the same AUG of the 5' UTR, and occasional in-frame readthrough of the stop amber terminator translated as glycine is responsible for the synthesis of the pol gene derived portion. Proteolytic processing starts with a probably autocatalytic cleavage of Pr80Gag-Pol between the protease and the RF. Additional cleavages at structurally conserved sites of both Pr55 and Pr70 products are accomplished by the viral protease. Human endogenous viruses or proviruses appear to have the capacity to express -products by a similar in-frame readthrough. In several other retroviruses Pr55 and Pr70 are not in the same reading frame and either a single or double frameshift is required for the expression of protease, RT and EN. Several examples of frameshifting and other mechanisms for controlling gene expression in retroviruses will be discussed. 

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E-12: EXPRESSION OF ENDOGENOUS RETROVIRAL GENES IN HUMAN TUMOURS AND OTHER TISSUES

3007 Retrovirus-like particles (VLP) in human oocytes and follicular fluid
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2) Department of Human Anatomy, Biomedical Center, Box 571, S-751 23 Uppsala, Sweden

Endogenous retroviral (or retroviral like) sequences are present in the DNA of probably all vertebrates including man. A complete replication competent human endogenous retrovirus (ERV) has, however, so far not been isolated and all sequenced human ERVs are more or less defective.

In human the expression of presumed ERV gene products has mainly been detected in organs involved in fertilization and/or embryogenesis. We have detected VLP in unfertilized human oocytes and in the surrounding follicular fluid. The follicular fluid and oocytes were recovered from women who were laparoscopically treated for in vitro fertilization and subsequent embryo transfer. Before laparoscopy they were treated with ovulation inducing drugs (HCG and Clomiphene) according to a conventional schedule. 50% of the investigated oocytes contained retrovirus-like particles (free lying extracellular or budding from the cell surface). Small amounts of particle bound reverse transcriptase (RT) and RD114 p-30 related proteins could be demonstrated in the follicular fluid. An antiviral (interferon like) activity could be detected in about 50% of the follicular fluids. Our evidence that the observed particles represent the gene products of a human ERV and their possible hormonal regulation will be discussed.

3008 RETROVIRAL LTR-RELATED SEQUENCES IN HUMAN DNA AND mRNA
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Previously, we have detected, and molecularly cloned the human DNA sequences which hybridize with the bovine endogenous virus (BEV) long terminal repeat (LTR) probe. Restriction maps of the clones indicated that the human genome contains both retrovirus-like elements and so-called "so-called solo LTR". Sequence data of 5' LTR, together with those of some of the human endogenous virus genomes obtained by others, revealed the presence of a conserved sequence of about 72 bp in the 5' LTR regions. To explore the possible involvement of the LTR-like sequences in recombinational and/or transcriptional regulation, we are currently examining the DNA and RNA from various human cell lines for the rearrangement and expression, respectively, of the LTR-like sequences by using the synthetic oligonucleotide probe. The result will be discussed in the presentation.

Human proviruses represent potential sources of new infectious human retroviruses through recombination with existing infectious retroviruses; and potential carcinogens through activation of other cellular genes by the proviral LTRs. To investigate these possibilities, we isolated a number of human proviruses from a recombinant library. One of these, ERV3 (endogenous retrovirus 3), is a full-length proviral genome. Partially sequenced, this clone has terminators cocons in its gag and pol gene coding sequences but an open env gene. Further, the ERV3 LTRs contain normal transcriptional regulatory signals and two potential hormone responsive sequences upstream of the promoter. ERV3 is single-copy in human species and transcribed. Embryos of the respective tissues. In the chorion, three major env-containing mRNAs are transcribed. Embryos of the respective placentas, however, express these transcripts in a different but reproducible pattern indicating a tissue-specific control of ERV3 expression during development. Further, all three transcripts are spliced env mRNAs that lack gag and pol sequences. For the major transcripts, the splicing junctions as well as transcription initiator and terminator have been determined for specific control of ERV3 expression during development.


Paul-Elrich-Institut, Frankfurt, F.R.G., and Slovak Academy of Sciences, Bratislava, CSSR.

All five human teratocarcinoma cell lines exploited to grow in vitro could be induced to synthesize retrovirus-like particles, albeit at extremely low amounts. The "Human Teratocarcinoma-Derived Virus (HTDV)" possesses the properties of retroviruses and is synthesized only by a small fraction of the differentiating and heterogeneous cells in culture. The following properties of HTDV have been elucidated so far:

- Their mode of budding from the host cell membrane is characteristic for type C retroviruses;
- Their fine morphological structures are very similar, but not identical to human animal and human retrovirus strains;
- They are found in tissue culture at the characteristic density of retroviruses (10^6/ml);
- They possess an endogenous DNA-dependent DNA-polymerase activity, but are associated with a yet little defined inhibitor for exogenous DNA-dependent DNA-polymerase activities;
- Purified reverse transcriptases of HTDV utilize both synthetic and endogenous templates;
- Diterter viral RNA sedimented in glycerol gradients has a size of 65S and can be heat-inactivated into two components;
- HTDV gag-antigens are the only marginally related to gag-antigens of a few mammalian retrovirus strains;
- Morphological, biological and preliminary nucleic acid hybridization data suggest that HTDV might represent the first group of human endogenous retroviruses.


This work stems from studies in which we demonstrated in placental syncytiotrophoblasts and chorioniccinomas, polyprotein peptides reactive with polyclonal anti-RD114 p30, monoclonal anti-NLXV-5 p1 and p30, and a monoclonal IgM antibody, designated FBS-1, which reacted in ELA and immunoblotting with syncytiotrophoblasts and with mammalian retroviruses. A study of 1540 human cord blood sera revealed the presence of RD114 p30-reactive antibodies in 7.7%. Using antibodies to a synthetic peptide, (Cys-Glu-Asn-Pro-Ser-Glu-Arg-Glu-Arg-Leu, based on cloned human endogenous retroviral DNA sequence (erv-1), we then detected an Mr 75 000 polypeptide in placental syncytiotrophoblasts and in cultured chorioniccinomas cells. In immunoperoxidase staining of human tumor sections we found all 42 cases of renal cell carcinomata (RCC) reactive with the antibody to the synthetic peptide but obtained a negative result for the other normal and malignant tissues studied, apart from placental syncytiotrophoblasts and chorioniccinomas previously found to be positive. In immunoperoxidase staining also the other retrovirus-related antibodies, anti-NLXV-5 p1 and p30, reacted with RCC and using 125I-RD114 p30 as antigen inRIA it was found that RCC urines but not of those of controls were positive. These results suggest that the Mr 75 000 protein may provide a very useful tumor marker. The Mr 75 000 protein was purified using MHC from cultured JEG-3 chorioniccinoma cells to homogeneity and antibodies were raised to it. In JEG-3 cells the Mr 75 000 has a unique location; it is a surface glycoprotein in microvilli. DNA clones, the products of which react with the antibody to Mr 75 000 protein, were isolated from a human placental \\texttt{g}til expression vector library. Our long-term goal is to determine whether the endogenous retrovirus-related gene products have any role in ontogeny and tumor biology and define their possible functions.


Frederick, Maryland, and Natl. Inst. of Allergy and Infectious Diseases**, Bethesda, Maryland, United States.

A number of families of endogenous DNA sequences in man have been discovered by virtue of distant sequence homology to retroviruses isolated from animal models. These families include sequences related to murine leukemia virus and mouse mammary tumor virus. Two of these families, a typical full length retroviral structure and a truncated structure which retains gag and pol but not env or LTR sequences have been isolated from a human placental cDNA expression vector library. Normal human placentas were obtained from normal term pregnancies and the cDNA library was constructed from equal amounts of mRNA from all placentas. This library was hybridized to PCR-generated probes. Of the many clones isolated, two were selected for further analysis. These clones contained DNA sequences related to mouse mammary tumor virus. 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We confirmed that lipopolysaccharide (LPS) stimulated large granular lymphocytes (LGL) produce IL-1 activity without inducing significant levels of anti-viral activity or IL-2. Furthermore, we observed that 0.02 to 2 μg/ml LPS augmented NK activity of highly purified human LGLs in a dose-dependent fashion. Conversely, polymyxin-B partially inhibited NK activity of purified LGLs, but this inhibition was overcome by adding large amounts of LPS, suggesting that the inhibition by polymyxin-B was specific to endotoxin. We also observed that highly purified, monocyte-derived IL-1 (20 μg/ml) increased the NK activity of highly purified human LGLs. The inhibition of NK activity by polymyxin-B was also overcome by adding highly purified, monocyte-derived IL-1, suggesting that IL-1 was involved in the augmentation of NK activity by LPS. This hypothesis was more confirmed by the evidence that anti-human IL-1 antibodies inhibited the boosting of NK activity after LPS stimulation. Overall, these data lead us to the conclusion that endogenously produced IL-1 can potentially serve as an autoregulatory signal to NK activity of human large granular lymphocytes.
3018 INHIBITION OF GROWTH OF HUMAN LEUKEMIA BY NK CELLS: GENERA-

Role of Natural Killer Cells in the Control of Cancer Metastasis

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A new haptenic compound of muramyl dipeptide (MDP)-derivative (designated as U-MDP-ME) cross-reactive with Bacillus Calmette-Guerin (BCG) was synthesized. The cross-reactivity of U-MDP hapten to 3G5 tumor cells was demonstrated by the following lines of evidence: (a) lymph node cells from BCG-primed C3H/He mice exhibited augmented U-MDP-specific proliferative responses to the in vitro stimulation of U-MDP-modified syngeneic cells (U-MDP-self); (b) inoculation of U-MDP-modified syngeneic cells into footpads of BCG-primed C3H/He mice elicited elicited delayed type-hypersensitivity (DTH) responses in vivo as measured by the footpad swelling; and (c) BCG-primed mice contained U-MDP-reactive helper T cell activity which functions to augment the generation of effector T cell responses to cell surface antigens. This cross-reactivity between U-MDP hapten and BCG was measured by the helper T cell activity as augmented induction of tumor-specific immunity. When BCG-primed C3H/He mice were inoculated intradermally with syngeneic 3G5 tumor cells, these mice could generate augmented tumor-specific in vivo protective (tumor-neutralizing) immunity as well as in vitro cytotoxic responses. These results indicate the effectiveness of U-MDP hapten in augmenting tumor-specific immunity. On the basis of this augmenting mechanism, a tumor-specific immunotherapeutic protocol was established in which a growing tumor regresses by utilizing a potent MDP-helper T cell activity. C3H/He mice were allowed to generate the MDP-helper T cell activity by BCG-immunization. Five weeks later, the mice were inoculated intradermally with syngeneic transplantable 3G5 tumor cells. When MDP-hapten was injected into 3G5 tumor mass, an appreciable number of growing tumors in the only group of C3H/He mice in which the MDP-helper T cell activity had been generated was observed to regress. The present approach will be discussed in the context of utilization of this new hapten to the T-cell interaction for augmenting tumor-specific immunity as well as for its future application to the clinical tumor system.
THE CELL SURFACE AS A TARGET IN CANCER CHEMOTHERAPY


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Cancer can be considered a disease of cellular membranes. Numerous cell surface derivatives have been considered in cell surface constituents following oncogenic transformation. These alterations facilitate behavioral changes associated with cellular transformation, and alterations in the cell surface presentation of glycosaminoglycans (GAGs) have been considered as targets for chemotherapeutic exploitation. The present studies involved with cell adhesion and cell proliferation studies in human gynecological and urological tumor cells preferentially attach to cell surface carbohydrate receptors. In a limited number of ovarian tumors levels of extracellular matrix (ECM) proteins were increased in the ECM and cell surface differences in the case of the glycosaminoglycans were lower in the metastatic cell lines than in the non-malignant cells. The strongly metastatic lines had lower levels of heparan sulfate and chondroitin sulfate proteoglycans than the non-malignant cell lines and the non-malignant cells in the lung and at subcutaneous sites in concentrations sufficient for a therapeutic effect.

POTENTIATION OF IMMUNOTOXIN ACTIVITY IN VITRO AND IN VIVO.

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Selective anti-tumor agents have been developed by conjugation of the toxic lectin, ricin, or its ribosomally-derived subunit with antibodies. Conjugates comprising only the A chain of the toxin coupled to antibody are more immunospecific than holotoxin conjugates but are frequently less potent. The conjugate 1155'-ricin-A recognizes an antigen expressed on HT29 rat fibrosarcoma cells but is not toxic for the target cells in culture. We have found that cytotoxicity may be induced in vivo by the addition of the A chain following localisation of the conjugate at the cell surface. Thus, addition of B-chain as a second stage reagent results in an immunospecific cytotoxic which has potency comparable with that of ricin. Preliminary studies in the rat have shown that intravenously injected ricin B-chain can reach immunotoxin-bearing syngeneic tumor cells in the lung and at subcutaneous sites in concentrations sufficient for a therapeutic effect.

NEW GALACTOPHILIC LECTINS REDUCE TUMORIGENICITY AND PRESERVE IMMUNOGENICITY OF LEWIS LUNG CARCINOMA CELLS.

J. Leibovici*, D. Avicheww* and N. Gilbo-Igerter*.

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Lectins are known to exert diverse biological effects. Specific attachment to cell surface carbohydrates may endow them with the capacity to recognize subtle differences in exposed cell sugar residues. The carbohydrate content of cell membranes differs between normal and tumor cells. Lectins might therefore attach and possibly endow selectively neoplastic cells. Moreover, these special proteins may be supposed to induce, in the same cell, modifications of undesirable properties, like tumorimmunogenicity, while retaining desirable characteristics, such as immunogenicity. In the present study, the effect of two lectins derived from Pseudomonas aeruginosa (PA-1, specific for Gal) and Aplysia depilans gonor (AGGL, specific for Gal and Gal-uronic) on the tumorimmunogenicity and immunogenicity of 3LL cells was examined. Cell antigenicity, viability and DNA synthesis were also tested. One hour incubation of cells (2x10^6) in presence of 3ug of the two lectins induced strong agglutination. Cell antigenicity was specific since it was abolished by the respective sugars. Cell viability was not affected and DNA synthesis was only slightly inhibited. However, when 3LL cells incubated with the lectins were subsequently inoculated to mice, the tumorimmunogenicity of the cancer cells was strongly reduced. Inhibition was dose dependent: both lectins caused 100% abolition of tumorimmunogenicity at doses of 20-200ug. Partial inhibition was observed with lower doses. The PA-1 clone gave a 40% reduction in no. of mice developing tumors. Tumor cell immunogenicity was nevertheless retained. Immunogenicity of lectin-treated cells was tested by injecting the immunoconjugate A-chain. The lectin was without immunogenic tumor. B.C. immunization did not result in any protection of the animals against the Lectin-treated 3LL cells. However, I.V. immunization prevented tumor growth in some of the mice and delayed its development in others, facilitating therefore as a vaccine.
TRANSPORT OF EXTERNAL MACROMOLECULES INTO THE CYTOSOL. UPTAKE MECHANISMS FOR TOXINS AND TUMOR METASTASIS. S. Olsnes, I. H. Madshus, T. Tonnessen and K. Sandvig. Norsk Hydro's Experimental lury metastasis of murine colon adenocarcinoma was subsequently tested, pretreatment of the tumor cells with Kl-8110 caused significant inhibition of pulmonary metastasis of both MC-17 and NL-44 cells. Inhibition of metastasis and prolongation of survival were also observed on intravenous injection of Kl-8110 without pretreatment of the tumor cells with Kl-8110, but the degree of inhibition was lower than that in the case of the two treatments together. This ant metastatic effect of Kl-8110 may be due to modification of the tumor cell surface resulting from inhibition of sialyltransferase by Kl-8110 and suggests that sialic acid-containing glycolipids on the cell surface may play a role in the metastasis of these tumor cells. The mechanism of this phenomenon will be discussed.

Transport of External Macromolecules into the Cytosol: Uptake Mechanisms for Toxins and Tumor Metastasis

3027 ROLE OF MEMBRANE GLYCOSPHINGOLIPIDS IN ONCOGENESIS. S. Hakomori. Fred Hutchinson Cancer Research Center, Seattle, Washington U.S.A.

The types of glycolipid changes associated with oncogenic transformation have been established in many experimental tumors and in human cancer (1). The incomplete synthesis of gangliosides with precursor accumulation represents one feature of transformation-dependent changes observed in vitro cells transformed with oncogenic viruses and transformation of oncogenes. A role of GM3 and GM4 in control of the function of growth factor receptors has been demonstrated in our recent studies (2,3). A deletion or low level of GM3 or GM4 may be correlated with the loss of growth control observed in some tumor cells. On the other hand, a number of novel glycolipid structures have been found to accumulate due to aberrant enhancement of glycosyltransferases ("neosynthesis"). Glycolipids accumulating due to a blocked synthesis or neosynthesis can be defined by monononal antibodies that have been selected based on tumor specificity. Multrimeric tetrasialylated tetraacetyl-1-methoxycarbonyl-D-glycero-a-D-galacto-octapyranosyluridine (KI-BHO) decreased incorporation of sialic acid to glycolipid conjugates on the cell surface. When the effect of Kl-8110 on the experimental lung metastasis of murine colon adenocarcinoma sublines of high (MC-17) and low (NL-44) metastatic potential was tested, pretreatment of the tumor cells with Kl-8110 caused significant inhibition of pulmonary metastasis of both MC-17 and NL-44 cells. Inhibition of metastasis and prolongation of survival were also observed on intravenous injection of Kl-8110 without pretreatment of the tumor cells with Kl-8110, but the degree of inhibition was lower than that in the case of the two treatments together. This ant metastatic effect of Kl-8110 may be due to modification of the tumor cell surface resulting from inhibition of sialyltransferase by Kl-8110 and suggests that sialic acid-containing glycolipids on the cell surface may play a role in the metastasis of these tumor cells. The mechanism of this phenomenon will be discussed.

Transport of External Macromolecules into the Cytosol: Uptake Mechanisms for Toxins and Tumor Metastasis

3028 DIFFERENT APPROACHES TO TARGET GLYCOCONJUGATES IN CANCER THERAPY. A.J.S. Davies, N. Lapsis. 1st Inst. of Path. and Exp. Canc. Res., Semmelweis Medical University, Budapest, Hungary

The surface glycolipids, glycoproteins and glycosaminoglycans (GAG) are responsible for the homo- and heterotypic interactions of tumor cells. They can also serve as specific targets in design of new therapeutic agents or regimens as well. One useful approach to treat cancer is the usage of tumor antigens as drug carriers. The monononal antibody-drug or toxin conjugates act at different site of cell machinery. The entry and intracellular fate of these conjugates are greatly depend on the endocytotic characteristics of the antigen. The antigen has to be in the intracellular compartment critical in respect of the action of the drug part of hybrid molecule. This principle was applied to potentiate the toxicity of F1875-Ricin A chain conjugate. In a human tumor cell system (E3) toxic lectin recycles to the cell surface from multivesicular bodies on membrane vesicles. N-ethylmaleimide (NEM) can specifically stimulate the production of "toxin-carrying natural vesicles", the presence of other cellular glycoproteins and ant. on vesicles could be useful in determination of "homing" characteristics of such drug-carrying vesicles. The GAGs are playing specific role in homo- and heterotypic interactions and are important elements in tumor progression. The GAG pattern of cancer cells could be useful target to alter their invasive characteristics. 3-hexosaminidase deficiency in mice can specifically suppress the GAG metabolism especially the heparan sulphate. As a result of the drug action, the heparan sulphate dominance could be abolished and these cells became similar to that of the low metastatic ones, that are characterised by chondroitin sulphate dominance.

Tumorigenic cell lines of a mouse melanoma are characterized, in part, by a 50 kilodalton cell surface glycoprotein. Properties of this product include both O and N-linked saccharide units, high sialic acid content and affinity for wheat germ agglutinin. The latter property, which can be used for selective purification, is dependent on sialic acid residues which are present in clustered tetrasaccharide units linked to serine/threonine residues, analogous to domains in human erythrocyte glycophorin.

Both polyclonal and monoclonal antibodies directed against glycophorin cross-react with the 50K glycoprotein and bind to the surface of the melanoma cells. The amount of this protein appears to correlate directly with metastatic potential; levels may approach 50% of metabolically labeled glycoproteins following incubation of cells with radiolabeled glucose. Variant cells selected for resistance to the wheat germ lectin are marginally or non-tumorigenic, do not express the 50 kilodalton glycoprotein but apparently have the capacity to protect animals against a challenge of wild type cells. The relationship between cell surface expression of specific glycoproteins and host response will be reviewed. (This work supported in part by USPHS Grant CA15483.)

DOXOMERRECEPTORS IN PITUITARY ADNOMAS AND EF-FECT OF BROMOCRIPTINE TREATMENT - EVALUATION WITH PET AND MRT. C. Mühr, M. Bergström, P.O. Lundberg, K. Bergström, R.A. Thomas, H. Lundqvist, B. Langström, Departments of Neurology and Diagnostic Radiology, University Hospital, Uppsala, Sweden.

Twenty patients with pituitary adenoma were examined with positron emission tomography (PET) that enables tracer in vivo kinetic studies of metabolism and receptor binding using 11C-labelled dopamine-D2-ligands and 11C-methionine. MRT was performed in a superconductive magnet 0.5 Tesla, images weighted for T1, T2 and proton density.

Results. The D2 receptor binding was high in all the prolactinomas comparable to that found in the striatum. The hormonally inactive (null cell) adenomas showed low levels of receptor binding. The metabolically inactive stereoisomer 11C-D-methionine was rapidly distributed within the tumor with no signs of irreversible trapping, whereas 11C-L-methionine showed a continuous trapping. MRT was superior to CT in delineation of the adenomas and showed within the tumor tissue areas of different signal intensity. At follow-up after bromocriptine treatment MRT revealed changes within the tumor tissue with development of cystic-necrotic areas as signs of treatment effect and was also excellent in demonstrating tumor shrinkage. PET showed in the prolactinomas a reduction in amino acid metabolism up to 60% after bromocriptine treatment and also a significant decrease in receptor binding was observed.

IN CONCLUSION PET demonstrated using 11C-dopamine ligands for the first time in vivo high dopamine receptor levels in prolactinomas and low levels in null cell adenomas. With 11C-L-methionine a decrease was revealed in the amino acid metabolism as a very early sign of effect of treatment. These findings are of great importance in the classification of pituitary adenomas and in the evaluation of dopamine agonist treatment of these tumors.
respectively, from Cushing's disease. The differences in response to CRH, but occasional patients do respond. Therefore, the CRH test is not a reliable test for differentiating these two causes of Cushing's syndrome. It does not reliably differentiate Cushing's from non-Cushing's patients and does not provide information about the causes of acromegaly but similarly to dopamine agonists it does not cure the disease. The two drugs may play a complementary role in the management of this disease.
PIGMENTOLOGY OF PITUITARY TUMORS. K. Kovacs. Dept. of Pathology, St. Michael's Hospital, University of Toronto, Toronto, Ont., Canada

Pituitary adenomas are common neoplasms arising in and composed of adenohypophysial cells. They can be identified in approximately 2% of unselected adult autopsies and 10% of intracranial surgeries. Based on histologic, immunocytochemical and electron microscopic studies, pituitary adenomas can be classified into the following morphologically distinct entities: 1) densely or sparsely granulated growth hormone cell adenoma; 2) densely or sparsely granulated prolactin cell adenoma; 3) densely or sparsely granulated corticotroph cell adenoma; 4) thyrotroph cell adenoma; 5) somatotroph cell adenoma; 6) null cell adenoma; 7) ancocytoma; 8) plurihormonal adenoma. All known cell types of the human pituitary can give rise to adenoma and all established adenohypophysial hormones can be synthesized and released from adenoma cells. Prolactin-producing adenoma represents the most frequent adenoma type in the human pituitary. Null cell adenoma is unassociated with clinical or biochemical evidence of hormone excess. Although this tumor fails to possess histologic, immunocytochemical or ultrastructural markers which would reveal its cellular origin, it invariably contains secretory granules and has all the cytoarchitectural features required for hormone synthesis and discharge. Silent pituitary adenoma contains immunoreactive hormones, mainly ACTH and other proopomelanocortin fragments. Patients with silent pituitary adenoma show no evidence of hormone oversecretion indicating that the stored hormones are not discharged or, alternatively, they lack bioactivity. Plurihormonal pituitary adenoma produces more than one hormone each differing in chemical composition, immunoreactivity and biologic action. This tumor can be monomorphous or plurihormophous, i.e. composed of one or more cell types. In monomorphous adenoma, two or more hormones are produced in the same cell type, whereas in plurihormophous adenoma, one hormone is produced in each morphologically distinct cell type. The cytohinges of plurihormonal adenoma is obscure and cannot be explained on the grounds of the one-cell-one hormone theory which dominates current thinking on pituitary cytopathology. (Supported in part by Grant MT-6349 of N.R.C. of Canada)

MICROACTIVICITY-INDUCING ADRENAL NEOPLASIA


The impact of several neurohormones on in vitro and in vivo mineralocorticoid secretion was examined in patients with primary aldosteronism due to aldosterone-producing adenoma /n=3/ and deoxycorticosterone-producing adenoma /n=2/ or carcinoma /n=1/. A significant inhibition of mineralocorticoid secretion was found after cyproheptadine treatment both in vitro and in vivo, suggesting a role for serotonin in the elevated mineralocorticoid secretion of these patients. A possible modulatory role for dopamine was suggested by the observation that bromocriptine, a dopamine agonist, inhibited in vitro mineralocorticoid secretion whereas metoclopramide, a dopamine antagonist, stimulated both in vitro and in vivo mineralocorticoid secretion. Neuropeptides were also active, of which alpha- and gamma NIS stimulated whereas endorphin, met-enkephalin, and somatostatin inhibited the mineralocorticoid secretion. A recently discovered hormone, atrial natriuretic peptide, was found to be a very potent mineralo- and glucocorticoid inhibiting factor in these patients both in vitro and in vivo.

These in vitro and in vivo observations can be extrapolated to suggest that mineralocorticoid secretion in primary aldosteronism can be modulated by several neuronal mechanisms. Thus the excessive mineralocorticoid production of these patients is not autonomous, which may provide rationale for new therapeutic strategies.
The three main avenues for cancer control are primary prevention, screening and early detection, and treatment. The importance of screening has been so far relatively limited within the cancer control. Only screening for cervical cancer is a routine public health measure. The role of screening for any cancer within the health services depends on occurrence of disease, on screening test and on organizing the programme. Determinants of the occurrence are ages at which the cancer is frequent and the time trends in addition to the present risk or numbers of cases appearing in the population. Preventing smoking is the most effective measure in cancer control which is known but not applied and it should have the first priority. There is relatively valid scientific evidence indicating that public health application of screening for breast cancer would be next in priority and that several per cent of all cancer deaths could be prevented by mammography in the western countries. If also other scientific indications will imply a successful application of other screening tests it is likely that screening for cancer will be a more important part of the health services. In any case, screening is not a simple way for cancer control.

Cervical cancer screening program and its results in Hungary during 1966 to 1985 will be demonstrated. The cyodiagnostic work is based on pathology. In 1985 the total number of cytological examinations performed in 72 laboratories come to 12,030,000. The diagnostic accuracy of the test is fairly good, i.e. 95%. Sampling, processing and evaluation are all decisive factors. The present number of cytological examinations is not satisfactory since only 50% of the female population at risk can be screened with this capacity. Further efforts should be made to improve the personal's and technical conditions and to introduce a uniform data and registration system.
During the past few years evidence has been accumulating that screening can reduce mortality from breast cancer among women aged over 50. Results from a large Swedish randomized controlled trial confirm the well-known findings from the HIP trial in New York in which follow-up has now continued for 10 years and in which the beneficial effect of screening has been maintained. There is additional evidence from two case-control studies in the Netherlands which concluded that the chances of a screened woman dying were substantially less than those of an unscreened woman. Mammography seems at present to be the preferred screening method but the additional benefit it confers over that achieved by physical examination in the subject of a Canadian study which has not yet reported. None of the studies has shown a statistically significant effect in women under 50, although the follow-up of the HIP study suggests that a delayed effect may occur in women aged 40-49. Other areas for further research include the frequency of screening and the effectiveness of breast self-examination.

Mass screening by cervical cytology as a means of reducing the population burden of cervical cancer has been in operation for over 20 years. Demonstration of an effect at the population level was slow to be achieved, the initial reports from North America being inconclusive. Programmes in Scandinavia started in the mid 1960's, and led within 10 years to striking reductions in incidence and mortality. Similar findings in Britain have been reported from Aberdeen. Recently, attention has focussed on the benefit an individual woman could expect from regular screening. An international study combining results principally from Scandinavia, northeast Scotland and Canada has attempted to estimate the risk of invasive cervical cancer in the years following a negative screening test. This risk is composed of two parts, that due to false negative tests and that due to more rapidly growing lesions. The false negative rate varied considerably between programmes, but the proportion of rapidly growing cancers showed impressive uniformity. Some 10% had a premalignant detectable phase less than 3 years, 25% less than 5 years and 60% less than 10 years. In terms of the effect of different screening policies, these quantities suggest over 90% protection against an invasive cancer with 3 yearly screening starting at age 25, and some 70% protection with 5 yearly screening starting at age 35. Little extra protection is given by starting screening earlier than age 25. The implications of this finding for the evolution of abnormal cytological lesions in young women are discussed.

Initial screening with Hemocult results in about 2-4% positive tests. About 5-10% of these positive tests give a carcinoma, an additional 10-20% in a large adenoma. The rate of positivity and the predictive value of a positive test are lower on each repeated screening, reflecting the progressive removal of colorectal neoplasia from the repeatedly screened population. Fecal occult blood screening should become part of the routine laboratory program for the evaluation of adult patients in medical practice and on hospital admission.

**Planning and Evaluating Screening Programs**

Several criteria have been agreed to justify the introduction of screening programs in the general population. Prerequisites are a valid screening test, an acceptable treatment for the disease found as a result of screening and demonstrated reduction in mortality from the disease with reduction in incidence also if precursors are detected. To establish these criteria can be set, screening programs have first to be introduced. The best way to evaluate effectiveness of screening is through a randomized controlled trial. Trends in incidence and mortality related to screening intensity and concurrent comparisons between areas are less satisfactory. Case-control studies may however be informative. Studies of survival or of cases detected on screening in the absence of a control group are too subject to bias to be relied upon. It is now recognized that the most effective screening programs require intense attention to organization with important components being the ability to identify the target population, to ensure that a high population comply with invitations to attend for screening and to ensure that appropriate management of detected abnormalities occurs. An important prerequisite for evaluation is the ability to identify all relevant disease that occurred in the defined population which is the target for the screening program. This will enable trends in incidence and mortality from the disease to be monitored. To determine expected impacts will also require knowledge on natural history of disease. Such information can be obtained from well organized screening programs. Thus, it can be determined when reductions in mortality and/or incidence can be expected and within what ages. On the basis of estimates of effectiveness, decisions can be taken on appropriate scheduling of screening tests. Examples of these approaches will be given from within those cancer screening programs evaluated by the UICC Project on Screening for Cancer.
The primary objectives for radiolabeling an antibody are to measure, localize, and quantify the relative amount of the antibody that has reacted with its antigen. Labeling can be carried out by substituting one of the atoms present in the antibody with one of its radioactive or inorganic atoms. In both cases the radiolabeling process must obey the following three constraints:

1. The immunological integrity of the antibody must not be affected, in any measurable manner, by the substitution/attachment of the radio-nuclide.

2. The specific activity of the radiolabeled antibody must be as high or higher than what is required for the desired limit of detection of the assay to be conducted. Different specific activities may be required for in vitro or in vivo procedures.

3. The radioisotopes must be selected to possess physical characteristics (energy, half-life that are most compatible with the aims to be conducted.

Radionuclides that have been used for endolabeling antibodies include tritium, sulfur-35 and potassium-37, whereas those commonly used for exolabeling include the radioiodines, particular sulfur-35 and selenium-75. The criteria for selecting the most desirable radionuclide for labeling a specific antibody will be discussed in light of the above requirements.
3051 RADIOMUNODETECTJON OF CANcER: REQUIREMENT? FOR THE USt IN TUESDAY • AUGUST 26 • MORNING
polyclonals. clonal' antibodies revealed some advantages over tumors was detected by the scintigraphy. Mono-
ed to nude mice bearing human tumors or to with satisfactory results similar to polyclonal-
I, 'I or ' in and administer-
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3052 AFP AND CEA IN CANCER DIAGNOSIS. S. Nishi, Dept. of Biochem., Hokkaido Univ. Sch. of Med., Sapporo, Japan
Since the discovery of specific associations of AFP and CEA with some malignancies, it has become the well-established and widely-used diagnostic methods to detect the elevated serum levels in patients. Monoclonal antibodies against these antigens have been used and used in the assays in place of the conventional polyclonal antibodies.

We could develop rapid, simple and sensitive solid phase sandwich AFP assay using some combi-
nations of two antibodies. Epitopes recognized by monoclonal anti AFP were peptide and one/AFP molecule. Our assay could not differentiate hepatoma and non-hepatoma AFP which differ in carbohydrate as demonstrated by reactivities with lectins.

We tried to introduce monoclonal anti CEA in the sandwich assay by several combinations of antibodies. The frequencies to detect elevated serum CEA in patients were considerably lower when the polyclonal antibodies were replaced with any two monoclonal antibodies. No apparent improvement was obtained with specificity of association of CEA and some malignancies. One monoclonal antibody (2Ba) could be used as solid phase antibody with polyclonal tracer antibody with satisfactory results similar to polyclonal-

3053 CRITICAL EVALUATION OF DIFFERENT TUMOR MARKERS AND THEIR TESTS. S. von Kleist, Inst. of Immunobiology, Univ. of Freiburg i. Br., FRG.
The development of monoclonal antibodies (Mabs) has been an important tool in the search for new tumor markers. However, the introduction of Mabs into the already known tumor marker tests would improve the tumor marker specificity of the measurements. However, extensive studies have shown although several new marker substances have not been described by Mabs, (e.g. CA 19/9 for gastrointestinal carcinomas, etc.) not one was specific for only malignant growth or apt to detect more readily still localized, i.e. "early" tumors. This has been shown by compar-
ing the markers CA 19/9 and CEA in colon cancers.

The progress that has been achieved in the methodology by using the Mabs lies also up till now mainly in a better repro-
cibility and reliability of the tests and not so much in an improved sensitivity (or specificity) of the established tumor marker tests.

This has been studied on 197 sera coming from patients with the most frequent malignancies (colorectal cancer, lung n=100) and their respective benign counterparts, which have been tested comparativ-
y with the results obtained with different tests, i.e. Abbott CEA polyclonal and monoclonal and the Roche monoclonal CEA enzymoimmunocassay.

3054 COLLECTION OF MONOCLONAL ANTIBODIES FOR HEMO-
BLASTOSIS IMMUNODIAGNOSTICS AND EVALUATION OF THE BODY'S IMMUNOREACtIVE STATUS. Z.A. Fadagize, A.Ju. Barzykhnikov, All-Union Cancer Research Center, AMN USSR, Moscow, USSR.
A panel of monoclonal antibodies (Mab) against differentiating antigens of human hemopoietic cells were raised at All-Union Cancer Research Center, AMN USSR. The panel includes IKO-1 Kab against early lymphocyte antigen, IKO-2 Mab against early thymocyte antigen, IKO-02 against the antigen of mononuclear cell leukemia, etc.

The panel of monoclonal antibodies was used to detect differentiating antigens of human hemopoietic cells that are raised at All-Union Cancer Research Center, AMN USSR. The panel includes IKO-1 Kab against early lymphocyte antigen, IKO-2 Mab against early thymocyte antigen, IKO-02 against the antigen of mononuclear cell leukemia, etc.

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K-13: NEW METHODS AND RESULTS IN THE IN VITRO NUCLEAR MEDICINE IN THE DIAGNOSIS OF MALIGNANT TUMOURS


Approximately 99% of all testicular tumours are of germ cell origin. They are classified as seminomas, embryonal carcinomas, teratomas and choriocarcinomas. AFP is a specific feature of embryonal carcinomas. The presence of β-HCG in patients with a testicular tumour was evidenced in cases of choriocarcinoma.

We have examined usability of tissue polipeptide antigen (TPA) in histologically different testicular tumours. Blood for AFP (ORiPI-Poland), β-HCG (ORiPI-Poland) and TPA (Santeg-Sweden) determination was sampled before orchiectomy and several times after. We have found elevated levels of AFP in 75%, β-HCG in 66%, and TPA in 57% of 83 patients with histologically different testicular tumours, before operation. The several measurements during the first month after were useful in monitoring of tumours recurrence.

We conclude that TPA could be helpful in early diagnosis testicular tumours and in follow up study.

L-14: MINIMAL BREAST CANCER

**3056** RESERVED

U. Veronesi, Milan, Italy

**3057** MINIMAL BREAST CANCER : IS IT A DEFINITION TO MAINTAIN ?


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The term minimal breast cancer (MBC) first appears in the literature in 1971, proposed by Gallager and Martin, to indicate the highest curable forms of breast cancer. This expression originally was referred to all in situ carcinomas (ductal, IDC and lobular, LCIS) and the invasive forms measuring no greater than 5 mm in diameter. It has been progressively extended to all the infiltrating carcinomas, regardless their type, whose size does not exceed 10 mm (MIC). Although the MBC correspond to about 10% of the early breast cancers, they include the 40% of the asymptomatic cancers (TO) detected by mamography. A case series of 163 MBC treated at Gustave-Roussy Institute from 1967 to 1979 has been studied and compared to a group of 52 IDC with microinvasion and to another group of 1555 infiltrating carcinomas measuring more than 10 mm in diameter, treated during the same period of time. The LCIS (n=111) have an average age lower than the other groups (48.5 yrs), 70% is asymptomatic and they have never been diagnosed on frozen sections. The MIC shows multicentricity and 9% bilaterality. The overall 10-yr survival rate is 100%. The IDC and IDC with microinvasion (n=55 and 52) are slightly older patients (54 and 50.7 yrs), less asymptomatic (45 and 44%), hardly diagnosed on frozen sections, often N+ (6 and 30%), largely multifocal (77 and 78%). Their rate of bilaterality is slightly different from that of the former groups (7 and 6%). Their evolution is excellent (overall 10-yr survival rate 92% and 80%). The characteristics of the MIC (n=56) allow them to be considered a group without a serious prognosis as the infiltrating forms exceeding 10 mm in diameter. The average age is 52.1 yrs. The concordance in frozen sections is 90%, the multicentricity is 45%, while bilaterality is 7% and overall 10-yr survival rate is 88%. The 37% is N+. According to these results it emerges that definition MBC is no longer justified. In fact it includes a group of too heterogeneous lesions from diagnostic, pathologic and therapeutic point of view. The strictly IDC or IDC with microinvasion (6%) required a treatment more suitable to their peculiar biology. This will be the subject of further investigation.

T.S.V.P.
L-14: MINIMAL BREAST CANCER

David D. Paulus, M.D., Division of Diagnostic Imaging, University of Texas M. D. Anderson Hospital and Tumor Institute, Houston, Texas

The only apparent hope of significantly enhancing prognosis and decreasing breast cancer mortality in the coming decades is the prompt detection and treatment of early or minimal breast cancer (MBC), defined as noninvasive or invasive breast cancer less than 5 mm in diameter. Mammography is the only time-proven imaging modality capable of consistently detecting nonpalpable cancer or MBC. Other imaging modalities such as thermography, ultrasound, transillumination, CT or NMR have not had sufficient sensitivity demonstrated to allow their substitution for mammography in screening or diagnosis of MBC. Radiographic changes that may indicate the early development of breast cancer, although none of them are specific or pathognomonic, include the following:

- Unilateral or solitary duct prominence or dilatation
- Asymmetrical areas of greater local parenchymal density or distortion as compared with the opposite breast
- Unilateral or solitary areas of increased local parenchymal density or distortion as compared to a previous mammogram, small mass lesions, and often-times, increasing vascularity or prominent veins on the side of the developing lesion.
- Pre-operative needle localization followed by follow-up fine needle aspiration or core biopsy are essential in early breast cancer detection.

Expertise in mammography with careful attention to the details of technique and interpretation are necessary for MBC diagnosis. The radiographic changes of MBC and other factors influencing diagnosis will be discussed in detail.
CONSERVATIVE TREATMENT OF BREAST CANCER

Heinrich Maass, Universitäts-Frauenklinik Hamburg-Eppendorf, Martinistraße 52, 2000 Hamburg 20

The fact that the local treatment was not able to improve the long term prognosis was the reason for attempts to reduce the radicality of the surgical procedure. At present results of two big randomized studies are available:

1. The Milano-Study: Patients with pT1-Tumors were treated by a quadrantectomy with following radiation of the breast (QUART), compared with a control group treated by a radical mastectomy.

2. The NSABP-Group published results of the following study: Groups of patients with breast cancer up to 4 cm in diameter were selected by randomization to:
   1. total mastectomy, 2. segmentectomy without radiation of the breast, 3. segmentectomy with therapeutic radiation of the breast.

The results of both trials showed no significant differences concerning the recurrence free and total survival.

The Dep. of Obst. and Gynec. Univ. Hamburg started a controlled, not randomized study in 1971. Patients with pT1-Tumors were treated by wide excision and subsequently irradiated with 60 Gy to the breast. Results of 360 patients are available. The 5-year-recurrence free survival is comparable with the above mentioned results.

Because of the convincing results it is justified that a breast conserving operation can be performed under following conditions:

1. A correct staging regarding the size of the tumor with a sufficient margin of normal breast tissue.
2. A radiotherapy with optimal conditions. Breast conserving surgery is not a standard procedure. Only institutions which are able to cover above mentioned conditions.

HEPATIC METASTASES IN THE ZOLLINGER-ELLISON SYNDROME (ZES): EPIDEMIOLOGY, DIAGNOSIS, CHEMOTHERAPEUTIC MANAGEMENT

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Hepatic metastases (HM) are often the only evidence of malignancy in hormone-secreting tumors of the pancreas. Gastrinomas (ZES) are the most frequent origin of these HM. In a personal series of 144 consecutive ZES cases (99 M; 45 F; mean age 47.5 years) with a mean follow-up period of 50 months, prevalence of HM is 23%. HM were synchronous with ZES diagnosis in 29/36. HM were responsible for 50% of the 46 non-operative deaths. At 5 years, 5 of 29 patients (17%) of the synchronous HM group were still alive vs. 65% for the entire population. Preoperative imaging gave the final diagnosis of HM in only half of the cases. Hepatic arteriography, echography and CT scan had a sensitivity (Se) and a specificity (Sp) respectively of: Se 0.50, Sp 0.94; Se 0.17, Sp 1; Se 0.20, Sp 0.92. Thirteen of our cases were treated by streptozocin (STZ) + 5 Fluorouracil (5FU) and participated in a multicentric analysis of 45 cases of ZES with HM from 12 centers. Total population was composed of 25 men and 20 women (mean age at diagnosis 46.2 ± 13.4 years). Six patients had a MEN I syndrome. HM were synchronous of ZES in 33 patients (73%) and metachronous in 12 (27%) (mean delay from diagnosis: 28 months). Total STZ dosage was highly variable (median value: 10 g/m², extremes: 2.5-87). Route of administration was i.v. (n=29), into the hepatic artery (n=4) or both (n=12). Nine courses (2-33) were achieved. 5FU was associated in 28 patients, diazoxurubicin in 9 and thiotepa in 1. Toxicity was moderate: nausea and/or vomiting (84%); transient mild proteinuria or tubulopathy (30%). Objective response was noted in 19/42 patients (45%); 9 had complete remission, 10 had regression of at least 50%. Stability was noted in 13 patients and tumor progression in 13. None of the following factors correlated with objective response: age, site and apparent excision of primary tumor, STZ total dosage and route of administration. Basal serum gastrin was significantly lower in the responders. Five out of 6 MEN I patients showed objective response. Latence of response was 17 weeks (1-52).
Only early diagnosis of pancreatic cancer, less than 2 cm in diameter and with no histologic evidence of capsular invasion and absence of both local lymph node involvement and distal metastases, should improve the hitherto bad prognosis. Periampullary cancer (~10% of cases) is a relatively favorable condition due to early onset of jaundice which initiates duodenoscopy (polypoid papilla in most cases) with ERCP showing dilated biliary and pancreatic duct systems. Definite diagnosis is established by histologic examination of biopsy specimens taken from the depth of the papilla preferably following papillotomy. After Whipple's operation plus lymph node dissection a 5-yr survival rate of some 40% can be expected. Ductal adenocarcinoma (~90% of cases) poses the main clinical problem, as early symptoms are rare (obstructive jaundice in cases of pancreatic head tumors close to the common bile duct) or, at later stage, vague and non-specific (upper abdominal pain, weight loss, pancreatitis of unexplained etiology, suddenly occurring diabetes mellitus, depressive mood). Establishment of diagnosis: As initial imaging procedure, ultrasonography (US) is recommended rather than computed tomography (CT) scan - the latter should be employed if US fails technically or is inconclusive. In circumscribed pancreatic lesions, the diagnostic yield of US can be improved by ultrasonically guided fine needle biopsy (cytology) or the more recent cut biopsy (histology). Whether or not the use of endoscopic US (increased resolution power due to higher ultrasound frequency) will further improve diagnostic efficacy, remains to be seen. Patients with any abnormality on US or CT should undergo ERCP with pancreatic juice aspiration for cytologic analysis, as this combined procedure provides the highest ranking diagnostic sensitivity. The definite diagnosis of pancreatic cancer may be difficult in case of coexisting chronic pancreatitis. The differential diagnostic approach includes ERCP plus ductal aspiration cytology, tumor marker determination (e.g., CA 19-9) and, with segmental lesions, sonoguided biopsy. In case of resectability and lack of metastatic spread, partial or total pancreateoduodenectomy plus extended lymph node dissection entails definite healing in about 10%, at present.
RESERVED

V. Ryat
Tallinn, USSR

M-18: TESTICULAR CANCER

SURVEILLANCE STUDIES IN STAGE I SEMINOMA AND NON-SEMINOMATOUS GERM CELL TESTICULAR TUMOURS

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A policy of surveillance following orchiectomy was introduced in clinical Stage I testicular non-seminoma patients in 1979 and in seminoma in 1983. The objectives were to establish the relapse rate, pattern of relapse, time to relapse, curability of relapse with chemotherapy and, in the longer term, to identify prognostic factors predicting high risk of occult disease at the time of orchiectomy with a view to immediate adjuvant chemotherapy. Of 135 Stage I non-seminoma patients entered into the study since 1979 and observed for a minimum period of one year, 35 (26%) have relapsed; 90% of relapses were diagnosed within the first year and in 49% of relapsing patients metastases were first identified in abdominal lymph nodes. One patient died of intercurrent disease following second line chemotherapy and 136 patients are alive and disease free. A multivariate analysis of prognostic factors has been carried out to identify those patients at high risk of relapse. Embryonal carcinoma histology and the presence of intratumour lymphatic invasion are independent prognostic factors. In patients with both features a high relapse rate (80%) has been observed. These observations need to be extended before adjuvant chemotherapy can be recommended for high risk Stage I disease. Since 1983 54 Stage I seminoma patients have been observed for a minimum observation period of one year. Of this group 6 (10.7%) of patients have relapsed with Stage IIA or IIB disease. All patients are alive and disease free following radiotherapy in 5 patients and radiotherapy and chemotherapy in one patient and chemotherapy alone in one patient. On the basis of these observations future management strategy in seminoma and non-seminomatous germ cell tumours will be discussed with particular reference to the development of low toxicity chemotherapy regimens that might be employed in an adjuvant setting.

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VBP COMBINED CHEMOTHERAPY IN ADVANCED TESTICULAR TUMOUR

National Institute of Oncology, Budapest, Hungary

Between December 1979 and 1984, 160 patients with advanced germinal testicular cancer were treated with modified Einhorn scheme/Vinblastin 0.6 mg/m² 1,2. days, Cisplatinum 20 mg/m² 1-5. days, 30 mg Bleomycin 2,9,16. days/. The mean age of patients was 27,4 years /range 16-53/. The 1980 version of the WHO classification /Morton/ served as basis for histological examinations, while the clinical stage was established as recommended by the UICC in 1981. The patients were classified into various clinical stages and were followed up on the basis of chest X-ray, brain, liver and bone scan, lymphography, pyleography, in the last 3 years abdominal ultrasound and, to a limited extent according to CT scan, specifically. AFP and ß-HCG value were determined. 34 patients were in inoperable II/B /bulky abdominal disease/, 7 III/A and 119 III/B stage. 44 patients received radio- or chemotherapy prior to VBP treatment. Remission rate and toxicity were scored in accordance with the WHO recommendations. Complete remission 50 and partial remission 57 were achieved in 107. Thus, the remission rate amounted to 66,9 per cent.
RESULTS OF LYMPH NODE DISSECTION IN STAGE I NON-SEMINOMATOUS TESTICULAR CANCER. Roberto A. A. Tevez, Del Salvador Univ., Buenos Aires 1425, Argentina.

Previous clinical trials of Samuel's [1975] using bleomycin-vinblastine /BL-VP/ combination and the addition of cisplatin /CDDP/ by Einhorn [1977] had shown that testicular cancer is a tumoural model curable by chemotherapy. Other treatments including cyclophosphamide and antineomycin D /VP16/, Adriamycin /A/ or continuous infusion of Bleomycin /B/ were not more effective than the Einhorn combination. VPB dose reduction /Einhorn, 1980/, replacement by etoposide /VP16/ /Einhorn, 1985/, or debulky surgery are useful in the management of the disease. Our results indicate that: 1. VP16 has to be used as standard first line treatment together with VP and EBDP /not only for s.c. or metastatic disease 2: first line s.c., must have VP16 plus high dose EBDP. 3: in CR of first line s.c., relapse rate in 50%, then second line s.c. is indicated. 4. second line s.c., can include if and/or VP16 and/or etoposide /VP26 and/or Mitomycin, 5: with adequate initial treatment, first line salvage chemotherapy and second line s.c. if necessary, curability of IC could be more than 95%, 6. after second line s.c., residual stable disease could need surgical debulky.


From 1/79-1/84, 40 patients received combined chemotherapy for advanced (bulky abdominal) /Stage IIIB-greater than 10 cm. diameter/ or supradiaphragmatic /Stage III/ testis tumors at Roswell Park Memorial Institute. Initial management was combination chemotherapy consisting of platinum 70 mg/m² and vincristine 2 mg 19 weekly for 6 weeks, bleomycin 30 mg IV on days 2-7 and 12-17, and prednisone 20 mg p.o. daily for 3 weeks. There were 27 patients with nonseminoma (predominantly embryonal cell tumors) with a mean age of 27 years and 13 with seminomas with a mean age of 34 years. All patients with nonseminoma and 1/3 seminoma patients underwent subsequent retroperitoneal node dissection and received salvage chemotherapy of VP-16 and platinum if residual tumor was found. Overall disease-free survival for all patients was 31/60 or 72% with an average follow-up of 42 months. Of the 27 nonseminoma patients, there were 10 complete and 14 partial responses. Twenty /20/ were alive and free of disease, while 6 died of progressive disease and one is alive with disease. At surgery, 11 /40%/ had fibrosis only, while 8 /50%/ had teratoma. Flow of 6 patients who died of recurrent nonseminoma had residual tumor at node dissection. Of the 13 seminoma patients, there were 7 complete and 5 partial responders. Disease free survival was 11/13 or 85%, while 2 died of recurrent disease. All 8 patients undergoing surgery were found to have fibrosis only. While alopecia, nausea, and vomiting were seen in all patients, there were no treatment related deaths. This particular chemotherapy regimen resulted in high response rates and apparent cure of disease in most patients within this poor prognostic group, and the response of advanced seminoma to chemotherapy is equal to or better than that of nonseminoma.
The evolution of treatment of non-seminomatous testicular tumours during the past forty years clearly shows that the once deadly disease is better controlled by using modern concepts of treatment than any other malignant disease of human beings. In our experience, the treatment of testicular tumours underwent progressive phases. Period I. up to 1949, after orchidectomy, radiation of the retroperitoneal lymph-bearing areas was used, resulting in an average survival rate of 35%. Period II. 1949-1957 - After orchidectomy, ipsilateral thoraco-abdominal lymphadenectomy was performed, followed by radiation therapy, improved the composite survival rate to 50%.

Period III. Between 1957 and 1970, after inguinal orchidectomy, bilateral simultaneous retroperitoneal lymphadenectomy was employed, without radiation and the combined survival rate of 80% achieved.

Period IV. Since 1970, retroperitoneal lymphadenectomy and a variety of single chemotherapy agents or later a combination of them were used, frequently changing our protocol as more and more potent drugs became available permitting us to handle bulky metastatic diseases also. Our present modality gives us 90% survival rate.

The criteria to achieve further improvements in the treatment of this once deadly disease, will be suggested and discussed.
CONSTITUTIONAL KARYOTYPE IN CANCER PATIENTS
R.Bergé, U 301,LP 101 CNRS, Hopital St-Louis, Paris, France.

An excess of acute leukemia has been shown to occur in mongol children, when compared with normal children of the same ages long before the cytogenetic era. Although the evidence was strongest for Down's syndrome, the kinetics and the possible immunological abnormalities of mongol children and on the sensitivity of trisomic 21 cells to chemicals, ionizing radiations, or viruses. The incidence of malignancy in children with other constitutional chromosome abnormalities has not clearly been proved to be higher than in normal children. The exceptions are the cases of gonadoblastomias and sex chromosome abnormalities, small deletions of chromosomes 11 and 13 in patients with Wilms' tumor with aniridia (WAGR syndrome), and with retinoblastoma, and chromosome instability (breakage) syndromes. A partial duplication of chromosome 13 has recently been described in Beckwith-Wiedemann syndrome which could be a pseudonormal status. Finally, in recent childhood leukemia cytogenetic studies, an excess of constitutional chromosome abnormalities has been reported.

Other studies have been devoted to the comparison between chromosome polymorphism incidence in cancer patients and in healthy persons. The results of these studies are yet to be evaluated because of some discrepancies and of the poor understanding of biochemical significance of chromosome polymorphism. Finally possible relationships between fragile sites and malignancy have recently claimed to exist. They now have to be seen as a working hypothesis rather than established data.


There are many case reports and a few epidemiological surveys of cancer incidence in the relatives of children with cancer: familial aggregations may occur in association with genetic diseases, such as neurofibromatosis; the 'Li-Fraumeni' syndrome is a well recognized association between childhood soft-tissue and bone sarcomas and brain tumours, together with breast cancer occurring at an early age in the mothers of such children; it has been suggested that there may be a generally increased risk of cancer among the relatives of children with retinoblastoma. Little information is available on the actual magnitude of such risks or whether there are other specific associations or a generally increased risk among relatives. Epidemiological studies are required to answer such questions. Estimates of the magnitude of these risks are important in genetic counselling and in distinguishing between real and apparent associations reported from studies of one or a few cases. In particular, such estimates will provide an indication of the types of families for which more detailed laboratory investigations and studies of genetic markers may be valuable. Previous reports will be reviewed and new information presented from studies of childhood cancer among siblings, cancer in relatives of children with retinoblastoma, and information on cancer in relatives obtained from case-control studies. The possibility of cancer occurring in the offspring of parents who have been successfully treated for cancer during childhood is of particular concern; the most recent results from one of the two large studies of such offspring will be presented.

MOLECULAR ANALYSIS OF RETINOBLASTOMA AND WILMS' TUMOR. J.Cowell, Institute of Child Health, University of London, London, ENGLAND.

Adult cancers are sporadic, mostly affect people in later life and arise, it is thought, as a result of continued exposure to environmental carcinogens. However, the familial occurrence of some tumours, e.g. carcinoma of the colon associated with polyposis coli and medullary carcinoma of the thyroid strongly suggests a genetic component in the development of these tumours. There is equally compelling evidence for a genetic component in pathogenesis of some children's tumours especially Wilms' tumour and retinoblastoma. In both of these examples a consistent small deletion on chromosomes 11 and 13 respectively has highlighted regions of the human genome which are potentially important in the predisposition to the development of cancer. Using techniques in molecular biology it is possible to isolate DNA sequences from specific chromosomes and using either a panel of somatic cell hybrids containing different overlapping deletions or in situ hybridization assign them to regions of particular chromosomes. DNA sequences isolated from within the frequently deleted regions will prove useful not only for better understanding of the basic mechanism underlying cancer predisposition but also possibly for prenatal diagnosis for those at risk.
DOCTORS AS HEALTH EDUCATORS. David J. Hill, Anti-Cancer Council of Victoria, Melbourne, Australia.

By virtue of their numerous contacts with patients, the motivational orientation of people in the role of patient; and the credibility of doctors as authorities in health matters, doctors can be potent health educators. A survey of activity in the field shows that doctors are increasingly recognizing the importance of behavioral intervention in prevention and treatment of disease; are becoming more involved in health education; and are acquiring interpersonal skills and using support materials to enhance compliance of patients with medical advice. Progress and future directions are discussed.


Breast Self Examination (B.S.E.) might cause women to discover smaller tumours and therefore might influence the survival rate. Also, as 24% of all breast cancers are seen in the under 45 years age group in whom mammography is not advised, B.S.E. might detect breast cancer earlier in this young age group. We therefore designed a study to see if B.S.E. could be taught to patients using a simple booklet, and have shown (1) that this is quite possible. We have also shown that women educated in this way find their cancer at an earlier stage (T1, T2) than a control group (2). The women taught in this way also had a smaller tumour size. We conclude that teaching patients in this way is a useful and cheap way of screening for early breast cancer.


Invitations and Information sheets on the program were sent to members of the Cancer Society, School of Medicine, Societies of General Practitioners and Family Doctors from Venezuela (Caracas and others), Countries of the Caribbean Area.

The program was arranged in the following order:

1. An analysis was made of the previous D.I.P.E.C. workshops in order to ensure their adaptability to the Latin-American environment. The cultural and socio-economic differences were considered.

2. The D.I.P.E.C. Technical Report of the U.I.C.C. Volume 44, the program was made for the workshop and reports of articles related to the program were translated into the Spanish language.

3. The working area and the technical equipment were selected in order to favour the development of the program and the best integration of the participants.

4. Invitations and Information sheets on the program were sent to members of the Cancer Societies, School of Medicine, Societies of General Practitioners and Family Doctors from Venezuela (Caracas and others), Countries of the Caribbean Area.

5. The facilitators were selected from a group of professionals in the health field with previous experience in group dynamics. They were carefully trained in the design of the program. The proportion was of 1 facilitator for 8 participants.

6. On the selected date, 22-24 November 1984, the workshop started and a final evaluation was made.

We present:

1. A quantitative and qualitative analysis of the final evaluation of the workshop.

2. A perspective analysis of the D.I.P.E.C. workshop as a starting point for local programs and their impact on our country in a 18 month follow-up period.

UIPEC - PART OF COMPREHENSIVE EVALUATED EDUCATIONAL PROGRAMME

E. Robinson, Haifa, Israel
TUESDAY • AUGUST 26 • MORNING

R-13: DOCTOR’S INVOLVEMENT IN PUBLIC EDUCATION

3089 DIPEC PROGRAMMES IN THE SWISS LEAGUE AGAINST CANCER
F. van der Linde, Bern, Switzerland

3090 AMERICAN CANCER SOCIETY - INVOLVEMENT OF PHYSICIANS IN EDUCATION
Charles LeMaistre, M.D., American Cancer Society, Inc.
New York, N.Y., U.S.A.

The local physician is the single most credible and influential source of health information to the public, and the amount of quality time he/she devotes to counseling and teaching individuals as patients or in the community setting to protect themselves against cancer will pay big dividends in terms of cancer control. The “most teachable moment” takes place in the doctor’s office when physician and patient have a chance to interact one-on-one, and when the physician takes the time to provide practical tips on cancer prevention-risk reduction, teaches breast self-examination, convinces and helps someone to quit smoking, etc.

Physicians have the opportunity & responsibility to become involved in public education activities outside clinical practice, to include -- one-on-one interaction with employees at the workplace, participation as speaker and discussion facilitator in educational programs for local civic & organizations, community public forums, radio and television interviews-talk shows-calls in programs, supervising and participating in cancer screening efforts for high risk target population groups, briefing of lay volunteers to deliver the cancer education message, etc.

T-14: SYMPTOM MANAGEMENT

3091 RESERVOIR
A. Bavier, Bethesda, USA

3092 THE ONCOLOGY NURSING SOCIETY: MEANS FOR PROMOTING EXCELLENCE IN CANCER NURSING
J. Johnson, P. Moore, Oncology Nursing Society, Pittsburgh, PA 15216

The Oncology Nursing Society (ONS) established in the United States ten years ago was the first organization of its type and has served as a model for the development of similar societies in many other nations. In July of 1975, the Oncology Nursing Society was formally incorporated with goals of encouraging research, promoting education and communication between cancer nurses. The growth and progress has been rapid and dramatic. Membership has increased to nearly 10,000 registered nurses representing all aspects of oncology nursing, including clinical practice, research, education and administration. A journal of cancer nursing has been established, ONCOCY

NURSING FORUM, which is published six times a year. Attendance at the Annual Congress exceeded 2,300 this past year. ONS publications address guidelines for safe handling of chemotherapy and for cancer nursing practice. A certification corporation has been established and the first exam offered in May, 1986.

Cancer nursing provides a unique and essential ingredient in the care of the person with cancer. There is a need to develop a research base in order to guarantee the continued growth of this new specialty and an organized structure for transmitting new knowledge to cancer nurses worldwide. This poster will provide a description of the structure, goals, and activities of the Oncology Nursing Society.
3094 THE NURSE'S ROLE AND FUNCTION IN A PAIN CONTROL TEAM IN A SWEDISH UNIVERSITY HOSPITAL

Elisabeth Killander, Nurse Specialist, Pain Control Team, University Hospital, 581 85 Linköping, Sweden.

In the provision of symptom control for patients with cancer, the emotional impact of the cancer diagnosis must be borne in mind. To assist in the effective control of symptoms it is necessary for nursing staff to create a physical and emotional environment which will enhance the effects of medication and treatment. The nurse in this caring environment must give confidence to patients and family by eliminating fear, helping to dispel myths, by giving information, and by listening to the patient and family. A caring environment takes into account the patient's personhood, providing for his self esteem, and allowing control over his life. Common symptoms requiring medication and/or nursing measures for relief include pain, nausea, vomiting, anorexia, dyspnoea, offensive discharges. There is a need for careful nursing, observation and assessment to assist in the total management of the patient. Careful nursing can prevent pain or the possibility of a pathological fracture, observation can prevent a complication such as oedema, assessment can determine if prescribed medication is effective. Good symptom control benefits both patient and family, and for the family this extends into the bereavement period. The nursing contribution to these positive experiences emphasises the important role of the nurse.

3095 DISTINGUISHING ONCOLOGIC EMERGENCIES FROM COMMON PROBLEMS EXPERIENCED BY CANCER PATIENTS. Deborah R. Mayer, MGH Institute of Health Professions, Boston, Massachusetts 02114, USA.

Oncologic emergencies are potentially life threatening complications during the course of a cancer patient's illness; they may be obstructive, metabolic or infiltrative in nature. Obstructive oncologic emergencies include spinal cord compression, superior vena cava syndrome, increased intracranial pressure and bowel obstruction. Metabolic emergencies include hypercalcemia, tumor lysis syndrome, SIADH, DIC and septic shock. Infiltrative emergencies include carotid artery erosion and leukostasis. The emergency may be related to the underlying disease process (e.g., spinal cord compression) or the treatment (e.g., tumor lysis syndrome). It may present as an acute or chronic, mild or severe process. Since more individuals are living longer with their cancer due to gains made in treatment, the incidence of oncologic emergencies experienced can be anticipated to increase. Many of the signs and symptoms associated with these problems are often vague and non specific (e.g., nausea, vomiting, fatigue). This presentation will review those individuals at highest risk and the assessment factors in distinguishing oncologic emergencies from common problems. It will take an awareness and vigilance on the part of nurses to maintain a high level of suspicion to prevent or detect oncologic emergencies thus avoiding the associated morbidity and mortality. Nurses play a crucial role in contributing to the quality of life of individuals with cancer at risk for developing oncologic emergencies.

3096 THE NEW TRACHEAL CANNULA HELPING IN THE NURSING AND REHABILITATIONS OF PATIENTS

G.Lichtenberger, Flör F. County hos. of Pest, EMY-DEPT. Hódmezovasarhely, Hungary.

This presentation will review those Individuals at highest risk and the assessment factors in distinguishing oncologic emergencies from common problems. It will take an awareness and vigilance on the part of nurses to maintain a high level of suspicion to prevent or detect oncologic emergencies thus avoiding the associated morbidity and mortality. Nurses play a crucial role in contributing to the quality of life of individuals with cancer at risk for developing oncologic emergencies.

T-14: SYMPTOM MANAGEMENT

3093 SYMPTOM MANAGEMENT - CANCER NURSING

Margaret McDaid, Peter MacCallum Cancer Institute, Melbourne, Victoria, Australia, 3000.

Mode of work, flow-chart and some positive and negative experiences will be presented. The document, teach, try to advise and to cdLsponsored by The Swedish Cancer Society.

3094 THE NURSE'S ROLE AND FUNCTION IN A PAIN CONTROL TEAM IN A SWEDISH UNIVERSITY HOSPITAL

Elisabeth Killander, Nurse Specialist, Pain Control Team, University Hospital, 581 85 Linköping, Sweden.

Our pain control team arifiRd according to need. In Jan 1980, the clinical pharmacologist, professor Ake Bertler was called for advise from a surgical ward. A patient with spread malignant melanoma suffered in severe pain and no treatment given had helped. This was a challenge for the pharmacologist and he asked an experienced internist to come along. The two doctors gave some advises concerning the patients medication. In a few days the patient felt much better and so did the nurse even the staff. The nurses told others. This became the start. More and more patients became referred to the "new born" pain control team. One year later, a neurologist joined. The doctors are now Ake Bertler, Kerstin Toss and Goran Leijon.

From Jan 1982, a nurse was part time employed on experimental basis, and from 1983 her appointment became permanent. It is since a full time post, and so far, the first of its kind in Sweden. The team mainly is consulted concerning cancer patients in chronic pain.

The team works in a multidisciplinary way i.e. by closed contacts with other specialists such as anesthesiologists, oncologists, neurosurgeons, physiotherapists, social workers, chaplain etc. The nurse is the coordinator doing the regular visits to wards and patients, the follow up, recording, teaching a lot.

Until now about 400 patients have been referred from various clinics. Most of them are primary in-patients. The patient is followed (and sometime familymember) own after discharge. We document, teach, try to advise and to educate and supervise interested colleagues, and others, staff and students. We are now evaluating our work since 1980, sponsored by the Swedish Cancer Society.

Mode of work, flow-chart and some positive and negative experiences will be presented.
AN OUTPATIENT PROGRAM OF JOINT PATIENT NURSING CARE
Mary S. McCabe, Marilyn Ayoob, Lombardi Cancer Center, Georgetown University Hospital, Washington, D.C. 20007

The recent advances in cancer care have allowed many more individuals to be treated in the outpatient setting without the need for hospitalization. To meet this challenge, the nurses in our ambulatory care facility have successfully developed a unique program for the intramuscular self-administration of interferon. The nurse acts as the program coordinator, thus allowing primary nursing the opportunity for teaching: 1. self-administration of the investigational agent, and 2. patient assessment of his own toxicity. This method of formulating a joint plan of care allows the patient to play an integral role in his care while adhering to a research protocol. This program addressed the:
1. education of patient and family in all aspects of self-administration,
2. role and use of audiovisuals in patient teaching,
3. patient understanding and compliance with the protocol,
4. identification and management of physical, as well as emotional symptoms related to treatment,
5. use of this program as a prototype for other outpatient therapy. The purpose of this paper is to address these issues leading to the development of nursing care standards and outline successful steps taken to ensure optimal care for these patients.

CURRENT CONCEPTS IN THE TREATMENT OF ADVANCED PROSTATIC CANCER
P.H. Schroeder, Rotterdam, The Netherlands

FIVE YEARS EXPERIENCE WITH BUSERELIN MONOTREATMENT IN PATIENTS WITH ADVANCED PROSTATIC CANCER
C. Jacob, Mainz, FRG
Pharmacological studies on androgen suppression in therapy of prostate carcinoma. J. Sandow, W. von Rothenberg and K. Engelbart, Hoechst AG, N-6330 Frankfurt/M 80, Germany F.R.

In hormone-dependent prostate carcinoma, androgens can be suppressed intraglandular by LHRH agonists. Testosterone secretion is blocked at two levels: testicular androgens and adrenal androgens. In humans, the contribution of testicular androgens is about 95%, whereas in the rat, the adrenal androgen secretion is negligible. Pharmacological studies were performed on the suppressive effect of the LHRH agonist Buserelin on androgen-dependent organs in adult rats. The reduction in pituitary and testicular receptor binding capacity was monitored during treatment by injection, or by long-term infusion. Marked differences in suppressive mechanisms activated by the different regimens were observed. Changes in testicular steroid biosynthesis were analyzed by incubation of testes after treatment with DCG, measuring the spectrum of C19-Cy-steroids in incubation media. In particular, the levels of intra-prostatic androgens were determined during treatment with daily Buserelin injections, or with sustained release formulations of Buserelin. The tissue content of testosterone and 5-alpha-dihydrotestosterone (DHT) was both markedly lowered. In castrate rats, stimulation of adrenal function by ACTH infusion had no effect on the prostatic weight or intravascular T/DHT content. Combination therapy during the initial phase of treatment by an aromatase receptor blocker (cyprotosterone acetate) and Buserelin (injection or implant) was more effective to suppress prostate weight and intra-prostatic T/DHT content than therapy with the single compound alone. Spermatogenesis and fertility were suppressed after prolonged treatment periods of 6-12 months, the testicular atrophy was not reversible in those long-term injection studies. Similar studies in dogs and monkeys have shown a different result, inhibition of spermatogenesis was fully reversible. It is concluded, that studies on the mechanism of androgen suppression by LHRH agonists and the effects on androgen-dependent organs provide useful information for the improvement in therapy of hormone-dependent prostate carcinoma.

The histo logical and functional changes in the testis tissue during treatment with GnRH analogues. I. Hattanen, M. Nikula, and S. Rannikko, Deps. of Clinical Chemistry, Immunology and Bacteriology, and Surgery II*, Univ. of Helsinki, SK-00290 Helsinki, Finland.

The purpose of this study was to examine long term effects of GnRH agonists on human testicular histology and endocrine function. Patients with advanced prostate cancer (n=8) were treated with the potent GnRH agonist anologue Buserelin (Nu, Hoechst, 600 μg x 3/day intranasally. After 6 mo, the patients were orchidectomized, and the testis tissue was used for histological studies and measurements of endocrine function in vitro. Eight other patients with matching ages and extent of the disease were castrated as controls (C). Severe atrophy of seminiferous tubules was seen in light microscopy in the testes of the Bu treated patients. Many tubules showed only Sertoli cells, and the seminiferous epithelium was frequently absent. In contrast, no clear changes were seen in the number of Leydig cells. Testicular content of testosterone (T) decreased 99% by Bu treatment: C = 1.9 ± 0.2 nmol/g wet wt; D = 88; Bu = 0.070 ± 0.019 nmol/g. Likewise, a drop of 90% occurred in testicular high affinity receptors for FSH: C = 0.37 ± 0.019 pmol/g; Bu = 0.067 ± 0.009 pmol/g. In contrast, the number of LH receptors was unaffected by the treatment: C = 0.18 ± 0.032 pmol/g; Bu = 0.18 ± 0.032 pmol/g. When testis slices were incubated in the presence of maximally stimulating concentration of NOS (100 ng/ml) both groups of tissue responded similarly with a 10% increase in T production, albeit the absolute production rate was reduced by 95% in the Bu group. When none of T was analyzed in the incubation media, it appeared that decreased androgen synthesis was most clearly due to decreased 3α-hydroxysteroid dehydrogenase activity. It is concluded that long term treatment with GnRH agonists brings about the suppression of testicular function, reduces testicular androgen producing capacity, but has no effect on testicular capability of responding immediately to LH stimulation.

The histological changes of the prostate during therapy with LHRH analogues - cytological and clinical results. R. Nagel, Berlin, FRG

New treatment modalities in prostatic cancer. J. Sandow, H. von Rothenberg, and K. Engelbart, Hoechst AG, N-6330 Frankfurt/M 80, Germany F.R.

The suppressive effects of locally advanced prostate cancer with LHRH superagonists - cytological and clinical results. R. Nagel, Berlin, FRG

The histological changes of the prostate during therapy with LHRH analogues - cytological and clinical results. R. Nagel, Berlin, FRG
LONG-TERM FOLLOW-UP WITH BUSEHELIN TREATMENT AND NEW DATA WITH REGARD TO SUSTAINED RELEASE FORMULATIONS

J. Macan, London, UK

RESULTS OF A DUTCH TRIAL WITH THE LH-RH-ACTIVIST BUSEHELIN IN PATIENTS WITH METASTATIC PROSTATIC CANCER

PM. J. Dubruyne, Nijmegen, The Netherlands

NUCLEAR MAGNETIC RESONANCE: PARAMETERS OF WATER IN BIOLOGICAL TISSUES: PHYSICAL AND BIOLOGICAL SIGNIFICANCE

C.P. Hazlewood, Department of Physiology and Molecular Biophysics, Baylor College of Medicine, Houston, Texas (USA) 77030.

Water is essential for life; yet, in cells, its physical properties and their implications to function are poorly understood. Nevertheless all theories of cellular function have explicit or implicit assumptions about the physical properties of water. This report will present several conceptualizations of the cell and the functional role given to water in those views. In addition, a review of the scientific thought that led to the first utilization of NMR technology in the study of pathophysiological states will be presented. The NMR relaxation time, T1, of water protons in cells and tissues is reduced relative to that of ordinary bulk water. Attempts to explain this universal observation have been difficult and frequently lead to divergent views. Nevertheless, one aspect of this observation, such as the dependence of T1 on the magnetic field strength (i.e., frequency dependence) is well behaved and NMR theory can be readily applied. In addition to this physical aspect, the image contrast between organs varies with frequency. Using conventional NMR theory of relaxation in liquids, T1 of protons is expected to vary as the square of frequency (ν^2). The variation of T1 in cells and tissues, however, varies more nearly as the ν. The possible physical basis as well as the biological implications of these phenomena will be discussed. Such exercises are deemed worthwhile because they provide insight into our cellular theories of water while providing better understanding of the information content of NMR images.

CORRELATION BETWEEN CELL MEMBRANE FLUIDITY AND MEASUREMENTS IN HUMAN BRAIN TUMOURS

M. Schuji, M. Schuji, M. Sc. Jerman, H. Kardolj University of Ljubljana, J. Stefan Institute and University Medical Centre, Ljubljana, Yugoslavia

The spin probe, methyl ester of doxyl palmitate, which dissolves primarily in cell membranes, was used to measure the cell membrane fluidity and nitrooxide reduction rate in human brain tumour tissues. The results were compared with those obtained by proton spin-lattice relaxation time (T1) measurements and water content determination. The measurements were correlated with histologically determined tumour types. It was shown that membrane fluidity and nitrooxide reduction rates were connected with membrane permeability for oxygen, ions and water and were different in different tumour types. Therefore it is expected that tumour growth and its response to the peritumorous edema development are monitored by molecular membrane transport and cellular metabolism alterations.
THE ROLE OF NMR RELAXATION TIME MEASUREMENT IN THE DIAGNOSIS AND MANAGEMENT OF CANCER

F.W. Smith, Aberdeen, UK

In 1971 Damadian reported that NMR relaxation times of water protons are longer in malignant than in normal tissues of the rat. The development of NMR imaging technology permits extension of these observations to live human subject in a clinical setting.

With these antecedents, in the University Hospital of Nuevo León, México, were accomplished studies in patients which were diagnosed different kinds of cancer with the classic parameter of diagnosis, including anatomo-pathology study. The relaxation curves (T-1) were compared with establisshed values in organs of normal subjects, more of them medical students.

NMR imaging and measurement of T-1 were performed on a Foner GE 60 whole body NMR imager containing a permanent magnet of field strength 0.045 Tesla. The T-1 values found for normal subjects and Nr. of studies were:

<table>
<thead>
<tr>
<th>Organ</th>
<th>T-1 (ms)</th>
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<tbody>
<tr>
<td>Brain</td>
<td>257 ± 12</td>
</tr>
<tr>
<td>Lung (with T)</td>
<td>75 ± 14</td>
</tr>
<tr>
<td>Breast (T)</td>
<td>140 ± 16</td>
</tr>
<tr>
<td>Liver</td>
<td>145 ± 16</td>
</tr>
<tr>
<td>Spleen</td>
<td>145 ± 16</td>
</tr>
<tr>
<td>Cervix</td>
<td>145 ± 16</td>
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</tbody>
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The accomplished studies includes 74 cases of brain tumors in which the T-1 value was 150% higher than normal value in average. Not only separation of tumors from normal tissues but also discrimination for a given pathology. Thus, the choice of the pulse sequence permits the selection of various contrast factors in order to select the one most discriminating for a given pathology. Thus, it will be necessary to choose the best pulse sequence for each pathology. However, this method lacks specificity in regard to the discrimination of tissues. With the aim of improving tissue discrimination, quantitative imaging methods are being developed in order to generate parametric images for the contrast factors. The clinical experience at the Institute of Physical Biology has shown that the relaxation time T2 gives good discrimination of certain pathological tissues. In addition, experimental studies with perfused tissue in vitro have demonstrated that it was possible to interpret the decay curves of transverse magnetisation by a bicomponential tissue model with spin exchange including an extracellular space characterized by a long T2 component and an intracellular space assigned to a short component. The parametric images of the relaxation time T2, aiming at an improved characterization of tissue lesions, have thus been created from a sequence of multi-echo images using bi-exponential decomposition of the decay curves obtained pixel by pixel. This method has been applied to patients and gives information about the evolution of the relaxation time T2 for different types of brain tumor pathologies.

TUMOR CHARACTERIZATION BY RELAXATION SPECTROMETRY. PARAMETER-SELECTIVE WHOLE-BODY PROTON IMAGING.

Klaus Gersonde*, Lutz Felsberg*, Martin Steenhammer* Thomas Totiatur** and Matthias Höhn-Berlage*

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Parameter-selective proton imaging based on relaxation spectrometry provides a new source of spectroscopic information identifying classes of biological molecules by interactions with their tissue-specific environment. Contrary to classical imaging techniques, this new method allows tumor differentiation and the classification of its age and stage of development. Whole-body proton imaging is performed in a low magnetic field (0.24 Tesla) tomograph (Type BMT 1110, Brucker Meditechnik, Karlsruhe, Germany). We employed CPMG pulse trains of up to 48 echoes with very short τ pulse intervals and a final 3/2 pulse. In this experiment each volume element provides a multiparametric T1 relaxation curve which can be decomposed into a maximum of three monoexponential functions assigned to proton classes ascribed to lipids, intr- and extracellular water. On the basis of T2 histograms, subclasses of protons within each class can be identified and attributed to specific tissue environments. For example, lipid protons in different tissues exhibit different T2 relaxation. In addition to T2, molecular interaction, proton density ρ, T1 and a dynamic parameter (including deffusion and flow) are obtained by a 5 to 10 minutes acquisition. It will be demonstrated for astrocytoma of brain and adenocarcinoma of female breast that differentiation of tumors which is based on a combination of criteria, i.e., relaxation parameters, dynamic and quantity parameters, can be enormously improved with such a combined criterium. Not only separation of tumors from normal tissues but also differentiation within tumour tissue can be made.

TUESDAY • AUGUST 26 • AFTERNOON
MAGNETIC RESONANCE CHARACTERISTICS OF METASTATIC TUMOR CELLS. J.P. Townes, K. Fraser, A.W. Bedding, U. Hashwood**, L. Dennis***, and S.D. Bines*. UTSCC M.D. Anderson Hosp.*, Baylor Coll. Med.,**, Houston, TX, and Exxon Res. & Dev. Co.*. This study examined the magnetic resonance (MR) characteristics of metastatic tumor cells in a heterogenous parental cell line MTPA, a parental-derived clone MTC, and a lung metastasis-derived clone MTLN3. We investigated the relationship between viral and cellular oncogenes in the expression of E1A mRNA.

We observed a significant increase in the expression of E1A mRNA in MTLN3 compared to MTC. This finding suggests that the expression of this gene is associated with the metastatic potential of these cells. The E1A gene plays a crucial role in cellular transformation, and its expression is often upregulated in metastatic tumors.

Our data indicate that the expression of E1A mRNA is increased in metastatic tumor cells, which supports the hypothesis that viral oncogenes contribute to the metastatic potential of these cells. Further research is needed to elucidate the mechanisms underlying the upregulation of E1A expression in metastatic cells and its biological significance.


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B-24: MOLECULAR BASIS OF MAGNETIC RESONANCE IMAGING IN RESEARCH AND DIAGNOSIS OF CANCER

3112

MAGNETIC RESONANCE CHARACTERISTICS OF METASTATIC TUMOR CELLS. J.P. Townes, K. Fraser, A.W. Bedding, U. Hashwood**, L. Dennis***, and S.D. Bines*. UTSCC M.D. Anderson Hosp.*, Baylor Coll. Med.,**, Houston, TX, and Exxon Res. & Dev. Co.*. This study examined the magnetic resonance (MR) characteristics of metastatic tumor cells in a heterogenous parental cell line MTPA, a parental-derived clone MTC, and a lung metastasis-derived clone MTLN3. We investigated the relationship between viral and cellular oncogenes in the expression of E1A mRNA.

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3113

HIGH RESOLUTION PROTON NMR IN THE STUDY OF METASTASIS, DRUG RESISTANCE AND CELL SURFACE PROPERTIES. Carolyn E. Mountford, Ludwig Institute for Cancer Research (Sydney Branch), University of Sydney, N.S.W., 2006, Australia.

High resolution 1H NMR methods have been used to study malignant cells and tumors and been found to indicate the cells’ biological status e.g. metastatic capacity and sensitivity to vinca alkaloids. The 1H NMR signal arises from a lipoprotein like domain in or attached to the plasma membranes of malignant but not benign cells (1). Malignant cells shed this abnormal lipoprotein particle into their culture medium (2) and in some cancers (e.g. ovarian and colon) the characteristic NMR parameters may be identified in the patients serum. NMR can also be used to study cell surface properties involved in the metastatic processes. For example, trypsin/EDTA treatment which severely reduces metastatic capacity of malignant cells also removes the NMR parameter characteristic of cells with metastatic capacity.

Leukemia lymphocytes resistant to low levels of vinca alkaloids can be partially resensitised to the drug by growing the cells in the absence of serum lipid. Under these conditions the plasma membrane associated lipoprotein undergoes a major compositional change whereby the neutral lipid core of the lipoprotein particle is depleted. This finding suggests the lipoprotein domain may be directly involved in drug export.

NMR is thus one of the few techniques which is sufficiently sensitive to detect subtle alterations to the surface of malignant cells and at the same time provide molecular information on the changes that have taken place.


3114

VIRAL AND CELLULAR ONCOGENES: MOLECULAR PROBES IN HUMAN NEOPLASIA. T.S. Papas, E.S. P. Reddy, Y. Kao, N. Kan, A. Van Rentergen, R. Sacchi, D. C. Watson, R. Fisher, J. Lautenberger and M. McCone, Laboratory of Molecular Oncology, National Cancer Institute, Frederick, MD 21702-7103.

Our laboratory is actively pursuing the identification of the oncogenes associated with the avian acute transforming retrovirus, v-E26. These studies aim to provide a number of homologous-related cellular oncogenes, the proto-onc genes, in a variety of cells from various species. We have identified cytotoxicity region in the avian lymphoid cells, which is associated with viral transformation. These findings support the hypothesis that cellular oncogenes play a role in the development of malignant diseases.

We have found that viral oncogenes transduced from host cells are, invariably, truncated segments of much larger cellular proto-onc genes. Also, a small number of retroviruses are able to transduce one or more of the proto-onc genes as observed with the MV and E26 avian viruses. The MV virus contains two viral onc genes, v-myc and v-mut, the latter oncogene sharing extensive homology with the murine retrovirus NSV 361 transforming gene, v-mur.

We observed that the number of transducible proto-onc genes are quite limited. We have also found that two of the oncogenes of the avian transforming virus E26, v-etl, has homologous proto-onc sequences shared by chicken, mouse, cat and dog. These proto-onc genes consist of two different domains, termed etl-1 and et1-2, whereas in chickens, as in the avian retroviruses, the onc gene is contiguous. We have also found that the human et1-1 gene localizes to chromosome 11 in man, chromosome 8 in mouse and chromosome 01 in cat, while the v-ets domain (ets-2) maps to chromosome 21, mouse chromosome 16 and canine chromosome 16. Both human et1-1 and et1-2 onc genes, we have found, are transcriptionally active. We have also established that the human et1-1 gene localizes to chromosome 11 and 4 in t(1:11) and 23, while the human et2-1 gene translocates from chromosome 21 to 8 in t(8:21)(q22:22) samples. Both translocations are associated with an alteration in the expression of ets NRMA.

3115


Site-directed mutagenesis techniques have been utilised to define important structural and functional domains within the BSS src gene product, pp60src, and its cellular homologous, pp60c-src. Mutation within the src gene has been shown to impair its tyrosine kinase activity. In addition, the src gene product, pp60c-src, has been shown to regulate the cell cycle and cell proliferation.

Our studies have identified critical residues within the src gene product, pp60c-src, that are essential for normal cell growth and proliferation. These findings suggest that these residues play a crucial role in the regulation of cell growth and proliferation. Further research is needed to elucidate the mechanisms underlying the regulation of cell growth and proliferation by these residues.

Recent progress in these studies will be discussed.
**3117**

**STRUCTURE AND FUNCTION OF fps/fes ONCOGENE PROTEINS.**

Tony Pawson, Geraldine Weinmaster and Ivan Sadowski.
Division of Molecular and Developmental Biology, Mt. Sinai Hospital Research Institute, Toronto, Ont., Canada.

The fps/fes oncogene encodes a cytoplasmic protein-tyrosine kinase, exemplified by the P130gag-fps protein encoded by the v-fps gene of Fujinami avian sarcoma virus. A combination of in-frame linker insertion mutagenesis of the FKS gene, expression of active fps-encoded fragments in bacteria, and limited proteolysis has been used to define the domain structure of P130gag-fps.

The tyrosine kinase domain of this protein is contained within C-terminal C-terminal residues; a regulatory domain with dramatic effects on kinase activity is located N-terminal to the catalytic domain. This conserved kinase region is linked by a hinge to an N-terminal fps domain which is not involved directly in catalysis, but which is important for oncogenic activity. The functions of specific residues in the tyrosine kinase catalytic domain have been investigated by oligonucleotide-directed mutagenesis. A lysine involved directly in catalysis is important for the proliferation of the mature tumor cell.

**3118**

**PARTICIPATION OF CELLULAR ras PROTEINS IN NORMAL AND MALIGNE NT GROWTH**

**3119**

**PHYSIOLOGICAL CORRELATION BETWEEN NDP-KINASE AND p21 ras ONCOGENE PRODUCT AND ACTIVATION MECHANISM OF p21 PROTEIN**

Kozo Gohsuki, Hijoshi Uesaka and Minehiyo Yokoyama (Dept. of Bacteriol., Tohoku Univ. Sch. of Med., Sendai, Japan).

Recently, we reported that nucleosidediphosphate (NDP)-kinase, which catalyzes a phosphate-transfer in a wide variety of nucleoside 5'-di- and triphosphates, may play an important role in the early biological event in cell proliferation induced by cell growth factors, such as IL-2 and EGF. This speculation was strongly supported by the following observations: (a) treatment of sensitive cells with cell growth factors resulted in the rapid induction of the enzyme; and (b) the enzyme level in virus-transformed and malignant cells was much higher than that determined in normal cells. For characterization, therefore, the enzymes have been purified from normal, malignant and transformed cells. We found that the enzyme (a) consists of two distinct subunits (a-subunit (Mr 21K) and b-subunit (Mr 19K)), and (b) is associated with a GTP binding protein (Mr 20K).

In addition, the enzyme forms a phosphoenzyme (reaction-intermediate) when it is incubated with one of nucleoside 5'-triphosphates in the presence of divalent cations (Mg2+ or Ca2+). The NDP-kinase-associated GTP binding protein was similar to p21 protein, because the protein had (a) guanine nucleotide binding activity, (b) GTPase activity and (c) a similar molecular size (Mr 20-21K). In addition, the GTP binding activity of the associated protein was neutralized by anti-ras antisera.

To determine the physiological correlation between NDP-kinase and its associated GTP binding protein, the phosphate-transfer between the phosphoenzyme (phosphorylated NDP-kinase) and GDP on the GTP binding protein was tested in vitro. The results obtained showed that a phosphate of the phosphoenzyme can transfer to GDP on the protein in the presence of 1 mM Ca2+. This finding strongly suggests that the GTP binding protein (p21 protein) may be activated through phosphate-transfer by the enzyme. Available evidence suggests that both NDP-kinase and its associated GTP binding protein may be correlated with the formation of transducing signals for extensive gene induction in proliferating cells.
3120
3120 B-25: PROTO-ONCOGENES AND ONCOGENE PRODUCTS: STRUCTURE, FUNCTION AND CONTROL OF NORMAL AND MALIGNANT GROWTH

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3120 B-25: PROTO-ONCOGENES AND ONCOGENE PRODUCTS: STRUCTURE, FUNCTION AND CONTROL OF NORMAL AND MALIGNANT GROWTH


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**Department of Chemistry, Aarhus University, Lange-lægsade 140, 6000 Aarhus C, Denmark.

A model was developed for the structure of p21, the protein with a molecular weight of 21,000 that is produced by the ras genes. This model predicts that p21 consists of a central core of β-sheet structure, connected by loops and α-helices. Four of these loops comprise the guanine nucleotide binding site. The phosphotyrosine binding region is made up of amino acid sequences from 10 to 16 and from 57 to 63 of p21. The latter sequence may contain a site for magnesium binding. Amino acids defining guanine specificity are Asn-116 and Asp-119, and sequences around amino acid 145 may contribute to guanine binding. The model makes it possible to visualize how oncogenic mutations of p21 affect interaction with guanine nucleotides. This knowledge will aid logical attempts to prevent or neutralize oncogenic events.

3122
3122 C-23: ASSESSMENT OF RADIOSENSITIVITY OF TUMOURS AND NORMAL TISSUES IN PATIENTS

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During the last decades an enormous knowledge about the radiobiological behaviour of cells and tissues including tumours has been collected. From these data experimental treatment strategies have been developed, as a consequence the problem arises to choose the proper treatment modality for the right tumour. In general the patients are selected by randomization for a certain therapy which is based on histology and localization. This selection frequently neglects the biological behaviour of the tumour. The observation, that tumours of the same entity with the same clinical and histopathological stage vary in biological parameters, which are important for the expression of radiation effects, reinforces the impression that more biological data of individual tumours are needed in order to make the right decisions. Radiobiological studies have shown that intracellular recovery, repopulation of cells and oxygen concentration in tissues are important phenomena which determine radiation sensitivity. Therefore attempts have been made to develop tests in order to measure the above mentioned parameters. As an example the determination of DNA and cell proliferation as well as cell loss in rectum carcinomas and normal rectal epithelium will be presented. The data show that the prognosis of hypoploid tumours is worse than of diploid tumours. Metaplasticizing tumours have a high number of S-phase cells but a small number of cells with micronuclei. The DNA content of the tumour cell line has been usually the same in the primary tumours and the metastasis. Tumours with an increase of S-phase cells during radiotherapy show rapid repopulation and have a high probability for local recurrence. Such a finding might be used for the decision of further treatment of such patients.

3123
3123 HISTOLOGICAL OBSERVATIONS ON INTACT ORGANS AND TRANSPLANTED TUMOURS OF EXPERIMENTAL ANIMALS

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3123 HISTOLOGICAL OBSERVATIONS ON INTACT ORGANS AND TRANSPLANTED TUMOURS OF EXPERIMENTAL ANIMALS

The examination with histological methods of the effects of irradiations with two different fractionation forms signified the trend that on some intact radiosensitive organs (thymus, spleen, lymph nodes, bone marrow) and on transplanted Harding-Passay melanomas and solid Ehrlich carcinomas too, relatively high radiation fractions applied in 3 to 4 day intervals caused more severe histological injuries than lower fractions given daily. Contradictory results relating to some parameters could also be found but only on Crocker S 180 sarcomas. These results may suggest the possibility on the useful therapeutic application of low radiation fractions given frequently.
PARAMETERS OF THE FRACTIONATION RESPONSE OF NORMAL TISSUES. H.R. Withers, UCLA, Los Angeles, California, U.S.A.

To be useful in radiotherapy, assessment of the radiation response of normal tissues in an individual patient must be available before treatment begins or shortly thereafter. Acutely-responding tissues demonstrate their responsiveness within 4 weeks of initiating a fractionated course of radiotherapy and can be used as a guide in modifying dose prescriptions. Late responding tissues cannot be assayed for their response and hence dose prescriptions must be based on accumulated data from previous experimental and clinical data. The available data will be discussed.

(Supported by PHS grant numbers CA-29644 and CA-31612 awarded by the National Cancer Institute, DHHS, U.S.A.)

LOW DOSE-RATE IRRADIATION ON HUMAN CERVICAL CARCINOMA XENOTRANSPLANTS: CELL KINETIC EFFECTS. Irene E.G. van Oostrom, Michiel H. van Hulsthe and Dirk R. Rutgers, Inst. of Radiotherapy, Univ. Hospital Utrecht, Utrecht, the Netherlands.

A new technique, mimicking the therapeutic practise in the treatment of cervical carcinomas, was employed in experiments with low dose-rate irradiation, using 137Cs sources on xenotransplanted cervical carcinoma cell lines (NIIK, HeLa, HeLa S3, HE-180, CaSki). Cell kinetic parameters, obtained by flowcytometry (FCS), will be evaluated and used as a guidance in adjusting fractionation intervals to cell kinetics.

The mice received a single dose of 1.0 Gy (dose-rate 0.5 Gy/hr), the dose distribution in the tumour could be calculated. After irradiation the mice were sacrificed at set times and the effects of irradiation on the DNA distribution were analysed with FCM. The changes in cell cycle distribution were obvious, cells were blocked in the radiosensitive G2+M phase. This arrest had maxima at 42 hours after start of irradiation for NIIK, at 50 hours for HeLa and at 145 hours for ME-180. Moreover this accumulation pattern was shown to be independent of radiation dose.

The timing of the maximal accumulation appeared to be related to the volume doubling time (Td) (Td NIIK = 2 days, HeLa S3 = 1.66 days, HeLa = 4 days and ME-180 = 36 days), and also to the cell cycle time, the latter was checked by autoradiography. The magnitude of the G2 blockage was highest in the NIIK tumour (50%) and is regarded to reflect a difference in the growth fraction. The percentage of cells in cycle will also be determined immunohistochemically using the monoclonal antibody Ki67.

RADIATION RESPONSE OF HUMAN BLADDER CARCINOMAS IN RELATION TO PLOIDITY LEVEL AND PROLIFERATION PATTERN. B. Tribukait, Stockholm, Sweden

In human tumor cell lines, there exists a correlation between the degree of cell killing after 2.0 Gy of ionizing radiation and tumor histology type (Fertil and Malaise, 1961, 1985; Deacon et al., 1986). Resistant tumor types, such as melanomas or osteosarcomas, produce cell lines that are more resistant to killing at 2.0 Gy than lines derived from more sensitive types, such as neuroblastomas or lymphomas. This observation opens up the possibility that an in vitro determination of radiosensitivity would have prognostic value and that such results could be used to individualize therapy. The adhesive-tumor-cell culture system has been adapted for measuring the radiosensitivity of primary human tumor cell cultures. This technique yields radiosensitivity results from over 70% of human solid tumor biopsies and surgical specimens. Tumor samples are disaggregated with enzymes, placed into culture, and irradiated with graded doses (1.0 to 6.0 Gy) 250 kVp x-rays. After 12 additional days of incubation, the cultures are fixed, stained, and the total growth of surviving cells is quantitated by digital image analysis. The data is fit using the linear quadratic model and survival at 2.0 Gy is calculated. In over 100 assay results compiled to date, the range of survival at 2.0 Gy for all histology types was 0.25 to 0.93. Significant differences in the average survival were observed between some histology types. For example, 3 Ewing sarcomas averaged 0.34 ± 0.04, 6 squamous cell carcinomas averaged 0.52 ± 0.05, and 17 melanomas averaged 0.65 ± 0.04.

The results also show a range of sensitivities within each histology group. Individual radiotherapy patients are now being biopsied before treatment and their response to radiotherapy will be compared to the test result.

This investigation was supported in part by research grant CA-02679, contract CM5777, and the Katharine Usworth Memorial Fund.
FUNCTION OF HEMATOPOIETIC STEM CELLS (CFU-C) IN THYROID TUMOR PATIENTS AMONG A-BOMB SURVIVORS.
Y. Nakashima, K. Ohara, T. Fujieda, M. Nishikawa, M. Takahashi, K. Ohara, Y. Nishio. Hiroshima Univ. School of Medicine, and Hiroshima, Hiroshima, **2nd Dep. of Internal Medicine, Faculty of Medicine, Kyushu Univ., Japan.

Formation of CFU-C (colony forming unit in culture) in bone marrow of A-bomb-exposed survivors was studied in thyroid tumor patients. CFU-C is the stem cell level of macrophages and granulocytes which play some role in cancer immunology. The activity of CFU-C was determined by incubating bone marrow cells obtained from the iliac region for 14 days in a medium containing colony stimulating factor. The mean number of CFU-C colonies (20 cells) in 3 dishes, each dish having 1.0 x 10^6 bone marrow cells, was counted. OK-432 is a lyophilized preparation of attenuated strain of S. of streptococcus haemoliticus. OK-432 was added to 10^-2 or 10^-3 KE per dish. A-bomb exposed survivors were exposed within 4.1 km from the hypocenter in Hiroshima. In cases of benign thyroid nodules, the mean CFU-C number in the exposed was 78.3+11.9 (12 cases) in contrast to 95.6+17.3 (10 cases) of the non-exposed cases. In cases of thyroid cancer, it was 54.5+12.5 (13 cases) in the exposed and 60.1+17.2 (10 cases) in the non-exposed and showed a very low value of 38.4+5.4 (8 cases) in recurrent cancer cases of the exposed. In view of the high incidence of thyroid cancer among the exposed, these results suggest some effect of A bomb radiation on the hematopoietic stem cells of thyroid cancer patients. The ability to form CFU-C in vitro was elevated by about 15% by addition of OK-432 in both the exposed (7 cases) and non-exposed (6 cases) in cases of benign tumors. However, it was markedly elevated by 54.3 % in 9 exposed cancer cases and by 40 % in 7 exposed cancer cases. OK-432 may have the ability to enhance the depressed function of CFU-C formation in cancer patients in the A-bomb exposed survivors.

D-25: NUTRITION AND CANCER

3130 CARCINOGENS FORMED DURING COOKING AND PROCESSING OF FOOD
S. Sato, Tokyo, Japan.

At the same time due to modifications in food habits, the mean CFU-C number in the exposed was 78.3+11.9 (12 cases) in contrast to 95.6+17.3 (10 cases) of the non-exposed cases. In cases of thyroid cancer, it was 54.5+12.5 (13 cases) in the exposed and 60.1+17.2 (10 cases) in the non-exposed and showed a very low value of 38.4+5.4 (8 cases) in recurrent cancer cases of the exposed. In view of the high incidence of thyroid cancer among the exposed, these results suggest some effect of A bomb radiation on the hematopoietic stem cells of thyroid cancer patients. The ability to form CFU-C in vitro was elevated by about 15% by addition of OK-432 in both the exposed (7 cases) and non-exposed (6 cases) in cases of benign tumors. However, it was markedly elevated by 54.3 % in 9 exposed cancer cases and by 40 % in 7 exposed cancer cases. OK-432 may have the ability to enhance the depressed function of CFU-C formation in cancer patients in the A-bomb exposed survivors.


Authors regularly carried out surveys in Hungary on all those chemical carcinogens whose sensitive determination in foods is possible by available instruments in their institute. Some other carcinogens can be avoided or minimized in food by prevention or indirect precautions made by authors. Based on several thousand of investigation data, the main conclusions concerning Hungarian foodstuffs are as follows. Benz(a)pyrenes and other PAHs occur at 5-10 folds higher levels in vegetables, fruits and cereals grown in vicinity of industrial centers than in samples grown far of them. It means a cancer risk factor for those who consume these products regularly. Authors suggested preventing measures. At the same time due to modifications in food habits, the mean CFU-C number in the exposed was 78.3+11.9 (12 cases) in contrast to 95.6+17.3 (10 cases) of the non-exposed cases. In cases of thyroid cancer, it was 54.5+12.5 (13 cases) in the exposed and 60.1+17.2 (10 cases) in the non-exposed and showed a very low value of 38.4+5.4 (8 cases) in recurrent cancer cases of the exposed. In view of the high incidence of thyroid cancer among the exposed, these results suggest some effect of A bomb radiation on the hematopoietic stem cells of thyroid cancer patients. The ability to form CFU-C in vitro was elevated by about 15% by addition of OK-432 in both the exposed (7 cases) and non-exposed (6 cases) in cases of benign tumors. However, it was markedly elevated by 54.3 % in 9 exposed cancer cases and by 40 % in 7 exposed cancer cases. OK-432 may have the ability to enhance the depressed function of CFU-C formation in cancer patients in the A-bomb exposed survivors.
The role of food on cancer therapy and prevention against malignant disease have been studied by
some investigators. It is already reported that adequate eating habits prevents the coronary heart
disease or arteriosclerosis, but regarding cancer research this problem is complicated by various
factors such as inducing, promoter and etc. So, in the present study, we investigated the protective ef-
fects of dairy products against inoculated tumor cells in mice. First we examined the syngeneic or
allogeneic tumor growth in the case of the mice fed with process or natural cheese. 1 x 10⁶ of syngeneic
or allogeneic tumor cells were injected subcutaneously and tumor size was measured. In each case mice
fed with process or natural cheese revealed remarkable suppression of tumor growth and suppression
rate showed progressive increment. Furthermore, the effect of yoghurt on tumor growth was examined.
Remarkable suppression of tumor growth was observed compared with mice fed with usual food. In the
same system, pre-feeding effect of process cheese and yoghurt was examined. Pre-feeding of both dairy
products for only 1 week showed remarkable suppression of tumor growth. This suggests that dairy pro-
ducts have also preventive effects on tumor growth. Moreover, yoghurt showed prolongation of survival in
mice bearing mice. These results support the concept that dairy products such as cheese and
yoghurt are antitumor effects not only in suppression of tumor growth but also in prevention of tumor
generation.
D-25: NUTRITION AND CANCER

3136 RISK EVALUATION OF DIETARY CARCINOGENIC FACTORS
Y. Hayashi, Tokyo, Japan

3137 MYCOTOXINS IN FOODS.
D.P. Hsieh, Davis, USA

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E-23: HERPESVIRUSES AND CANCER

3138 T-LEUKOTROPIC HERPESVIRUSES AND TUMOURS IN
PRIMATES
B. Flockenstien, Erlangen, FRG

3139 SELECTIVE DNA AMPLIFICATION BY HERPES VIRUSES
H. zur Hausen, Heidelberg, FRG
HERPESVIRUSES AND HUMAN CANCER: STUDIES ON ASSOCIATIONS OF HERPES SIMPLEX AND EBV WITH CANCERS ORIGINATING IN VALDEYER RING.

V. Vaska, I. Hirsch, J. Vanka, L. Vaszó, K. Pálóczi, L. Vaczi, and E. Sibill. Department of Experimental Virology, Institute of Sera and Vaccines, Prague; Faculty of Medical Hygiene, Charles University, Prague; Institute for Postgraduate Training of Physicians, Prague.

The possible roles of HSV-2 in cervical neoplasia and of EB virus in the cancers originating in Waldeyer ring outside nasopharynx were investigated. To determine the risk associated with previous herpes simplex virus type 2 (HSV-2) infection a prospective study of cervical neoplasia in more than 10,000 women was performed in Prague. The total of 15 cases of moderate to severe dysplasia, 83 cases of carcinoma in situ and 21 cases of invasive carcinoma were detected in the course of the study. Sera obtained at enrollment in the study from these patients and from matched healthy control subjects were examined for the presence of HSV-2 antibody by a microneutralization test and type 2 specific ELISA. No difference in the prevalence of HSV-2 antibody between the patients and the controls was revealed by either test. These results do not provide any support for the hypothesis of involvement of HSV-2 in cervical neoplasia. On the other hand, an evidence on the association of EBV with tonsillar and supraglottic laryngeal carcinoma was obtained. The data suggestive of the involvement of EBV in the pathogenesis of some of these cancers can be summarized as follows: (i) sera of these patients possessed increased levels of EBV antibodies and a correlation between the antibodies to various EBV antigens and the clinical course of the disease was demonstrated; (ii) tumor cells but not normal cells possessed EBNA and EBV DNA as demonstrated by cytological hybridization in situ.

HERPES SIMPLEX VIRUS AND CERVICAL CANCER. James K. Hutchins, Anne M. Beckman, and Denice L. Calloway, Fred Hutchinson Cancer Research Center, Seattle, Washington, 98104, USA.

The suggestion that herpes simplex virus type 2 (HSV 2) is involved in the etiology of carcinoma of the cervix is initially based on epidemiological and serological studies. Results from molecular hybridization studies indicate that at least some cervical neoplasias have retained HSV nucleic acid sequences. In this paper we will describe some of the results in this paper and discuss experimental transformation studies that offer explanations for inconsistencies associated with herpesvirus transformation and oncogenesis. The finding that small fragments of herpesvirus DNA can mediate transformation without expression of a viral gene and that these fragments have sequences and structural elements which could act as enhancers of cellular gene expression or as functional mutants leads further support to hypotheses of initiation/promotion mechanisms in genital neoplasia. The remarkable frequency with which the DNA of HPV types 16 and 18 are found in cervical carcinoma tissues obviously suggests a major role for these viruses and perhaps other HPV types in the disease process, if not as initiators, then certainly as promoters of carcinogenesis. The evidence for papillomavirus involvement in malignancy is supported by both experimental and naturally occurring cancers, most of which involve interaction of the virus with an initiator of transformation, a role which HSV DNA sequences may assume at least a subset of female genital cancers.
The BamHI W region of the Epstein-Barr virus (EBV) genome contains a protein localized to the nucleus of the infected cell, the EBV-determined nuclear antigen EBNA2. We have constructed a series of recombinant vectors that carry the complete EBNA2 gene, or the gene modified so as to contain defined deletions involving presumed exons and regulatory elements of the gene. The recombinant vectors were transfected into COS-1 cells which permit the replication of the SV-40 DNA containing plasmids to a high copy number, and the recombinant expression of EBNA2 was analyzed. A recombinant plasmid that carries a BgII NotI fragment of the BamHI W region (nucleotides 4464 to 50528) contains all the information necessary for inducing the expression of a full length EBNA2 polypeptide. A rightward promoter consensus sequence in the BamHI W part of the BgII NotI fragment is functional in COS-1 cells expressing EBNA2, whereas a similar sequence in the BamHI Y fragment is not. The results indicate that transcription of the EBNA2 gene is initiated in the BamHI W fragment and that all of EBNA2 is encoded within the continuous long open reading frame in the BamHI Y and H fragments. Moreover, sequences upstream from the EBNA2 gene were shown to be required for transcription. Transient expression of the chloramphenicol acetyl-transferase (CAT) gene linked to upstream sequences of the EBNA2 gene including its promoter reveals that sequences located 5' to the transcription initiation site, between nucleotide -653 and the cap site, contain a strong transcriptional enhancer.

EBNA2 contains a strong transcriptional enhancer.

In the framework of a multistep carcinogenesis of both Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC), the role of the Epstein-Barr virus (EBV) seems to be different. The nitrogenic activity of the EBV on B lymphocytes, both in vitro and in vivo, leads to the establishment of a polyclonal proliferation, which represents a step toward immortalization of B lymphocytes either in vitro or in vivo. Other environmental factors, such as lymphocytic malaria in tropical Africa, impair the cell-mediated immune control of EBV infected B cells, leading to further polyclonal B cell proliferation. In congenital and acquired immunodeficiency, similar polyclonal expansion occurs. Chromosomal translocation leading to c-loc oncogene activation represents the final step in BL carcinogenesis. In nasopharyngeal carcinoma (NPC), the causal role of EBV is most likely, since the association is even more regular than in Burkitt's lymphoma, but the role of EBV in the transdifferentiation of epithelial cells remains to be determined. The recent observations of C3/EBV receptors on epithelial cells of the nasopharyngeal mucosa open a new dimension to the problem. Furthermore, the reactivation of EBV latency, reflected by increasing titers of IgA antibodies to structural EBV-VCA and early antigens (EA), represents a critical epidemiological marker for immediate risk to develop the disease. This permitted early detection of the tumor, which in turn could be most efficient in controlling the disease through radiotherapy on earlier cases, gaining long survival. The cause of such a reactivation is actually under investigation. The role of environmental factors such as traditional medicines or food habits is being investigated.
**3148 SIGNIFICANCE OF TUMOUR MARKERS IN THE DIAGNOSIS AND PROGNOSIS OF HUMAN PREBLASTOMATOSIS AND TUMOURS.**

K.N. Bajaj

The diagnostic and prognostic significance of differentiation tumour markers based on mucin structure and composition, occurrence of alkaline phosphatase isoenzymes have been evaluated in preblastomatoses and carcinomas of gastrointestinal tract. The precancerous lesions of these tumours could be characterized by the appearance of the placenta type of alkaline phosphatase (pALP) and of embryonal mucin reflecting a pronounced dedifferentiation of these cells. Severe forms of dysplasia are accompanied by elevated pALP and a more frequent occurrence of embryonal mucin. In carcinomas, the incidence of pALP was lower in severe dysplasias (88.9%) than in severe dysplasias (95.5%) and the appearance of adult type of mucin could also be observed. The decreased ratio of undifferentiated cells indicated that a redifferentiation occurs in these tumours. The studies on ALP isoenzymes and mucin composition might facilitate the diagnosis of precancerous lesions of the gastrointestinal tract. However, their prognostic significance could not be demonstrated. Our results indicated that the oncodevelopmental markers are not specific for the neoplastic disease. The limited value of current tumour markers in the diagnosis and prognosis might be attributed to the random gene rearrangement in tumour cells resulting in the development of heterogeneous cell population with variable marker patterns. Application of monoclonal antibodies and molecular hybridization techniques might facilitate the future identification and screening of new tumour markers including oncoepitopes, and might play a role in identifying individuals at risk for malignant disease.

**3149 A ROUTE: TO BETTER THERAPY**

K. O. Mayr

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Serum tumour markers make well recognised contributions to the management and long-term survival of patients with some solid cancers. For the majority of cancers the serum markers make a less dramatic contribution but the value of markers tends to be greatest where there is effective therapy. Part of the tumour marker problem now is the assimilation into clinical practice of an increasing range of markers. The cost implications of these in health care needs careful analysis. Markers also provide the basis of targeting with antibodies or with other agents capable of being bound selectively to tumour cells or within tumours. The degree of discrimination between tumour and normal tissue seems less of a limitation in targeting for diagnostic purposes than for therapy. Progress is, however, being made and a wide range of options is open for exploration.

**3150 CLINICAL APPLICATIONS OF ESTROGEN RECEPTOR IMMUNOHISTOCHEMICAL ASSAYS OF HUMAN BREAST CANCER.**

MONOCLONAL ANTIBODIES TO THE RECEPTOR PROTEIN. ER-ICA, supra


**Studies over the last 20 years have established the clinical usefulness of assays of estrogens and receptors (ER) of breast cancer.** While not all patients with ER positive breast cancer respond to endocrine therapies, few patients with ER-negative cancers benefit. Also important, the steroid receptor status of the cancer conveys prognostic information; patients with ER-negative cancers have prolonged disease-free intervals and longer overall survival than ER-positive breast cancer patients, independent of their lymph node status. With the recent development of monoclonal antibodies to the estrogen receptor we have developed an immunocytochemical assay for ER (ER-ICA) in lightly fixed, frozen sections of breast cancers and have compared the results with conventional steroid binding assays (ER-SBA) and the clinical course of high risk, stage II breast cancer patients. A combination of the intensity and distribution of ER-ICA staining seen in the frozen sections of the cancers gave an excellent correlation to quantitative ER-SBA results. Furthermore, patients with ER-ICA+ lesions showed significantly better disease-free survival than those with ER-ICA- cancers, independent of lymph node status. In addition, ER-ICA procedures allow distinction between ER-ICA+ cells in metastatic and primary disease and by design areas of the lesion so that the receptor status of the cancer itself can be identified. Finally, with ER-ICA it is possible to document the distribution of ER among various epithelial abnormalities and thus possibly identify those hyperplastic lesions expressing high levels of ER which might be good candidates for prophylactic endocrine intervention. Supported by grants from the National Cancer Institute (CAI459, CA74761), and the Women's Board of the University of Chicago Cancer Research Foundation.

**3151 MONOCLONAL ANTIBODIES TO THE RECEPTOR PROTEIN. ER.**


Monoclonal antibodies to the estrogen receptor have been developed as a tool for the rapid and relatively simple detection of estrogen receptors at the cellular level. Two methods are available: (1) specific cytoplasmic binding of radiolabelled estrogen to receptor; and (2) specific cytoplasmic binding of radiolabelled estrogen to receptor. We have used the latter method to determine the presence of estrogen receptors in a wide variety of tissues including normal and malignant breast tissue. The methods allow a rapid and relatively simple detection of estrogen receptors at the cellular level.
3152 PLACENTAL GENES OPERATING IN CANCER CELLS. William H. Fishman, Cancer Research Center, La Jolla, CA 92037, U.S.A.

A spectrum of trophoblast gene products are known to populate both gestational and non-gestational neoplastic cells to a variable extent. Included are placental alkaline phosphatase (PLAP), human chorionic gonadotropin (HCG), somatomamotrophin, and so on. It is also known that certain normal tissues do express trace amounts of PLAP and HCG, for example. These considerations support the widely held opinion that such oncotrophoblast gene products are "euplastic" rather than ectopic. In the case of PLAP and PLAP-like markers, the correlation of their frequent elevated expression is greatest in ovarian cancer and seminoma and has been shown to have significant clinical value. Such markers in common with all other oncodevelopmental markers cease to be useful if the cancer cells stop expressing the relevant genes. In general, however, there appears to be a relatively greater clinically useful expression of markers in tumors derived from cells whose progenitors maintain a gene expression capacity characteristic of their position in development; e.g., calcitonin in medullary thyroid cancer; neuropeptide hormones in neural crest tumors. One may expect to increase the utility of oncotrophoblast markers by preparing unique peptides of the marker idotypes and by generating specific monoclonal antibodies to them. Such utility may extend beyond serum diagnostic studies to immunodetection imaging modalities, often more sensitive, and sometimes the only index for management. A simple cell fusion method will be described for the production of monoclonal hybrid antibodies.


We studied 146 determinations of LASA levels performed in 89 instances of Hodgkin disease patients (HD) and 60 instances of non Hodgkin lymphomas (NHL). A total of 81 cases were in progressive disease and 67 cases were in complete remission at the time of the study. The overall sensitivity of LASA as a tumor marker was found in 87% of cases of progressive disease. It must be emphasized that this high sensitivity was always superior to that of other tumor markers studied at the same time; sedimentation rate, β2 microglobulin, fibrin, ferritin, haptoglobulin, C-reactive proteins, copper, ceruloplasmin, LDH and alkaline phosphatases. On the other hand, LASA specificity showed an apparently high rate of "false positives" in cases of patients in complete remission (43.3% of cases). However, further analysis of those cases suggested that they actually would be "false positive". Because these pathological cases of LASA were posteriori correlated to early relapses, moreover, we suggest that a correlation would be made between the high LASA rates in cases of complete remission and in the immunological deficiency expressed by the OKT4/OKT8 ratio when less than 1.6.

3154 VALUE OF AFP AND HCG FOR DIAGNOSIS, STAGING, AND MANAGEMENT OF PATIENTS WITH GERM CELL TUMORS OF THE TESTIS AND OVARY. J. J. Dymondera, Cancer Center, M. Sklodowska-Curie New Inst., Warsaw, Poland

Serum levels of AFP, HCG and some other markers were determined in patients with germ cell tumors of the testis (over 400 pts) and ovary (37 pts). Most patients with seminoma (dysgerminoma) and other nonseminomatous tumors as mature teratomas, immature teratomas and pure embryonal carcinomas as well as the latter three types with seminomatous admixture had normal serum levels of the markers. Slightly elevated HCG level was found only if tumor contained STG cells and stage of disease was advanced. This group of patients had good prognosis. The role of the markers was significant in patients with chorionicarcinoma (HCG) + yolk sac tumor (AFP), and embryonal carcinoma or teratocarcinoma with admixture of yolk sac or chorionicarcinoma elements or both. This group of patients had worse prognosis, in particular if the tumor was disseminated. An elevated level of any marker after orchietomy or retroperitoneal lymph node dissection was always useful for diagnosis of the tumor elements that metastasized; staging and monitoring therapy and follow-up. Decreasing marker level indicated regression. However, return of an elevated level to normal did not indicate eradication of all tumor which, due to chemotherapy, might have changed its histology to marker-negative elements only. Consistently elevated or increasing marker level during treatment indicated resistance to therapy. An increasing level from any nadir during remission indicated recurrence. Elevated level of any marker was as important as imaging modalities, often more sensitive, and sometimes the only index for management.

3155 MONODUENAL HYBRID ANTIBODIES. J. Karawajew, B. Michoel, G. Behringer, and G. Fastenberg. Central Inst. of Molecular Biology, 1115 Berlin-Buch, GDR

A simple cell fusion method will be described for the production of functionally active hybrid antibodies. The antibody combining sites of the hybrid antibody react with a tumor-associated fetal antigen on the one hand and with FOD on the other.
COMPUTER AIDED STRATEGIES IN THE DESIGN OF IMMUNOTOXIN BASED CHEMOTHERAPEUTIC AGENTS. R. Rein**, T. K. Kim**, M. Ishibashi**, P. E. Srinivasan**, and H. Kohler**, Unit of Theoretical Biol. and Dept. of Molecular Immunology** Cancer Research Center, Bell Park Memorial Tissue, Buffalo, NY 14263 USA

The development of monoclonal antibody technology has facilitated the design of new approaches in cancer therapy protocols. Among these is the selective targeting of tumor cells by antibodies conjugated to either cytotoxic drugs or toxins. The design of effective immunobased agents requires at least the identification of selective targets. The identification of such sites allows for synthetic immunogen technology to generate highly selective monoclonals at an investigatory discretion. For the design of a tumor cell selective cytotoxic drug or toxin, two additional requirements have to be satisfied. The first deal with suppression of the competitive binding of the drug/toxin-monoclonal antibody complex with normal cell surfaces. The second is the preservation of the structural feature facilitating the transport of the immunotoxin. Such sites are the concanavalin A (Con A) and nethrethoxate (MTX) receptors. These two requirements in natural toxin systems, such as diphtheria or ricin toxin, are contradictory. The B chain which ensures selective binding of the toxin to normal cell receptors is also responsible for transport via the cell membrane. The object of the computer graphics and model building analysis is to elucidate the binding site of the B chain to the cell receptor and to predict modifications of the B chain sequence which can be implemented by site directed mutagenesis and genetic engineering. This could lead to the modification of proteins which host the undesired competing specificity by preserving its transport enhancing property. Strategies are outlined for the computer design of the above modifications to obtain effective biologically active agents.

SELECTIVE DRUG DELIVERY TO TUMOR WITH ANTIBODY TO TUMOR ASSOCIATED ANTIGEN. Takeaki Hana, Institute for Biomedical Research, Tokyo 191, Japan

One possible approach to the selective drug delivery to tumor is the conjugation of the drugs with antibodies directed to tumor associated antigens. Mitomycin C (MMC) and methotrexate (MTX) were conjugated with monoclonal antibodies ZME018 and 96.5 (both IgG2a) to human melanoma melanoma xenografts. When 25 µg of the labeled ZME018 was injected intravenously to K31-1 tumor-bearing nude mice, the amount of the antibody distributed to the tumor at 5 days after the injection was 10.3% injected dose per gram tumor, which was 3.2 times higher than that attained with normal mouse immunoglobulin (NMG). Further, when the specific antibody was injected, a higher portion among the tumor-distributed antibody was found to actually be binding to or have been internalized into the tumor cells. In therapeutic experiments, the MMC and the MTX conjugates were more effective in suppressing the growth of the human melanoma in nude mice than were the unconjugated drug, a mixture of drugs and the antibodies, and the NMG or irrelevant antibody conjugate. The antibody-directed in vivo drug (MMC) delivery to the tumor (K31-1) was verified by using 3H-labeled ZME018 conjugate. The lethal toxicity of intraperitoneally injected MMC in normal mice decreased five- to tenfold by the conjugation. Studies on the cell receptor mechanism of action were carried out with direct or HSA-mediated MTX conjugates with monoclonal antibodies (1G7 and 1G2a) to mouse mammary tumor MM6 cells. The endocytic internalization of the anti-MM6 conjugates followed by the release of the drug by the lysosomal enzymes.

IMPROVEMENT OF ANTITUMOR DRUG EFFICACY BY BIOPOLYMERS AS CARRIERS. M. Steegerke, Research Group for Peptide Chem., Hung. Acad. SCL Budapest, Hungary

Increasing interest in the potential of antitumor drug efficacy resulted in the development of more sophisticated devices. Biopolymers as biodegradable and biocompatible systems with good solubility offer several advantages, even limited "homing." Biopolymers, similarly to particulate carriers, are capable to impart size, charge, hydro- or lipophilicity and transmembrane transport of the drugs they deliver, consequently alter their pharmacokinetie characteristics, duration of action and immunological activity. For a considerable time we have been interested in plasma proteins and polyallylated plasma proteins as carrier systems linked by covalent or non-covalent bonds to antitumor drugs. In order to elucidate the factors determining favourable combinations branched polypeptides seemed to represent a useful synthetic model system with a high degree of design flexibility and suitable to simulate proteins. A new group of synthetic branched polypeptides was developed with the general formula poly(Lys-[(X-DL-Ala)] (X = 1) to initiate a systematic study of the relationships between the chemical structure (charge, size, primary structure, configuration, conformation) and the carrier potential. Most polymers proved to be non-toxic, biodegradable, very weak immunogens, but potent immunomodulators. Special emphasis was put therefore on the analysis of compensating the immunosuppressive effect of antitumor drugs by polypeptide carriers. Tertiary systems were also investigated by using monoclonal antibodies as specific targeting devices linked covalently to the branched polypeptides loaded with antitumor drugs. In these experiments the polypeptides were applied as intermediate carriers but served also as spacers.

H-23: DRUG DELIVERY SYSTEMS

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3160 POLYMERS CAN FOCUS THE CYTOTOXIC ACTION OF ANTHRACYCINE ANTIBIOTICS TO THE CELL SURFACE
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The anthracycline antibiotic, Adriamycin, Adr, is known to intercalate into double stranded DNA, inhibit enzymes involved in DNA and RNA synthesis, perturb subcellular organelles and alter membrane functions. Covalent attachment of anthracyclines to a solid support such as polyglyutaraldehyde microspheres, PGL, focusses the drug interaction to the cell surface. These drug-microsphere complexes, Adr-PGL, are cytotoxic to human and murine tumor cells. Fluorescent microscopy and transmission electron microscopy establish that Adr-PGL has a high affinity for the cell surface, cause extensive cell budding and show no evidence of internalization. Nuclear fluorescence occurs only with free Adr and cannot be detected with Adr-PGL. The drug-polymer complexes are effective in killing cells with acquired resistance to free Adr. An inactive anthracycline analog becomes cytotoxic when coupled to microspheres demonstrating that a new mechanism of drug action is created. Chromatin-S1 release studies, indicative of cell membrane integrity, have shown that Adr-PGL causes damage more rapidly than equal doses of free Adr. Lung tumor exposure to free Adr results in the gradual acquisition of resistance. However, this does not occur with similar analogs to Adr-PGL, demonstrating that cells cannot modify drug conjugates to acquire resistance. However, this does not occur with similar analogs to Adr-PGL, demonstrating that cells cannot modify drug conjugates to acquire resistance. Howevr.

3161 NANO PARTICLES AS DRUG DELIVERY SYSTEMS FOR ANTI-CANCER AGENTS. J. Streuter, Inst. of Pharm. Technology, Univ. Frankfurt/Main, West-Germany

Nanoparticles are solid colloidal particles ranging in size from 10 nm to 1000 nm (1 µm), consisting of macromolecular materials in which the active principle (drug or biologically active agent) is dissolved, entrapped, encapsulated and/or to which material is adsorbed or attached. Polyalkylcyanoacrylate nanoparticles to human osteosarcoma-bearing nude mice; the level of radioactivity in the tumor was about 40 times higher than in the muscle. Small drug molecules such as 5-fluorouracil most are sorbed by the particles forming a solid solution. The efficacy of this drug against Crocker-Barrac S 180 was enhanced significantly by sorption to nanoparticles. However, this increase in efficacy was accompanied by an increase in toxicity. Organ distribution studies using labelled 5-fluorouracil shown decreased drug levels with nanoparticle-bound drug in all organs including the brain. In a preliminary experiment with methotrexate, the efficacy of this drug was also enhanced by binding to nanoparticles without an increase of toxicity.

3162 EFFECTS OF LIPOSOME-ASSOCIATED THERAPEUTIC AGENTS ON LUNG AND LIVER METASTASES OF EXPERIMENTAL TUMORS
E. Mayew, Deps. Explt. Therapeutics and Explt. Patho-

H-23: DRUG DELIVERY SYSTEMS
The purpose of early detection programmes is to discover cancer or its precursor earlier than the cancer would have been discovered in the absence of such a special effort, i.e. before the patients would have sought medical attention spontaneously, because of signs and symptoms. Early detection involves the use of appropriate technology, i.e. tests and procedures suitable for detection of asymptomatic cases, either applied on a large scale as screening tests whose effectiveness is well-established and can be recommended as public health measure, or on an individual basis as part of periodical health check-up. Health education and counselling are important elements of early detection programmes, because the improvement of early detection depends very much on increasing the awareness of the public and medical profession at large of the warning signs and early symptoms of cancer, and of the prospects for early diagnosis and the advantages of early treatment. People can be taught to look for the signs and symptoms of some cancers in their own bodies (self-examination techniques), however, such a practice should not do more harm than good. Early detection programme should not be conducted unless facilities for verification, diagnostic work-up and treatment of detected cases are provided. Effective early detection programmes have been developed for cervical, breast, colorectal, oral and bladder cancer in a growing number of countries making proper use of respective community health care system; non-medical professional groups e.g. school teachers) and voluntary, non-governmental organizations (e.g. cancer societies) have an important role to play in the implementation of community-oriented early detection programmes. The effectiveness of early detection programmes is subject to periodical evaluation.

In respect of survival, one of the most important factors is the correct and early diagnosis of the neoplastic alterations. Best therapeutic results of neoplasms can be expected with very early developmental stage or those in the in situ form of tumors. The crucial question in which alterations can be put into the category of malignancies and what the prognosis of very early tumors or in situ disorders is like. The examination of morphological phenotypic markers (histo- cytophobi, and ultrastructure) is often of limited value requiring correct diagnosis. Newer more and more phenotypic markers, suitable for the detection of malignant tumors, have been identified and studied. For instance, the amount and distribution of nuclear DNA content showed diagnostic value. Other markers, such as isoenzymes, key enzymes and antigens are able to determine the embryonic character of the alterations. Several monoclonal marker antibodies are known for the demonstration of hormone receptor content and metastasizing capacity of various neoplasms. The above markers are discussed on the basis of literature and of our own studies.

A centralized mass screening program for cervical carcinoma has been in operation in Iceland since 1964. The screening has been aimed at women aged 25-69, examining the women with 2-3 years interval. The mean overall attendance rates have reached 89% in the age groups 25-69 at the end of the year 1984. A decrease in incidence and mortality up to almost 60% has been observed in comparing the cancer rates from 1955 to 1970. In the very last years incidence of cervical carcinoma has increased, especially in women under 44 years of age, whereas mortality has remained unchanged. The number of preinvasive lesions (dysplasia and carcinoma in situ) has been increasing in the age groups 25-60 over the past 5 years. This has been associated with a significant drop in the mean age of women with such lesions. Since 1970 the Icelandic Cancer Society has offered breast palpation to women attending the screening clinics. To evaluate mammography as a diagnostic tool 2000 such examinations were done in 1973-1974. As a result of this experience all women attending the cervix cancer screening have had breast examination by palpation and in selected cases mammography has been done on "broad" indications. In the period 1974-1983 128,046 breast examinations were done with palpation and in 48 of these cases mammography was indicated. In 1976 fine-needle aspiration was introduced to facilitate the diagnosis of palpable lumps. The conclusion of the breast screening experience in Iceland is that palpation as a primary approach of screening has significant shortcomings. Based on that and the experience of others a generalization of mass screening program for breast cancer with mammography has been recommended in women over 40 years of age. As women under 40 years of age commonly present with a lump in the breast, efficient breast aspiration service must be available for diagnosis.
SCREENING FOR COLORECTAL CANCER IN A CANCER DETECTION CLINIC, BUFFALO, NEW YORK. Curtis Motellin Ph.D. Roswell Park Memorial Institute, Buffalo, New York, USA.

Colorectal cancer is a major cause of cancer morbidity and mortality in the United States. The diagnosis of colorectal cancer in the President of the United States heightened public awareness of the risks of disease and the benefits of early colorectal cancer detection. Studies by the American Cancer Society demonstrate that colorectal cancer detection procedures are underutilized by primary care physicians. The Cancer Detection Clinic at Roswell Park Memorial Institute in Buffalo, New York, has conducted several public screening programs aimed at increasing the proportion of early colorectal cancers detected. The results of these demonstration trials indicate: 1) that community based efforts can achieve detection results comparable to those reported in clinical trials, 2) that increasing the proportion of localized tumors may be achieved and, 3) that public knowledge, attitudes, and, health behaviors may be affected positively. Experience indicates, however, that active involvement of the health care professional is important in insuring compliance to screening procedures and follow-up of positive findings.

THE DOM PROJECT FOR THE EARLY DETECTION OF BREAST CANCER

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The DOM project is a non-randomized population-based screening programme offered to all women of the city of Utrecht and its suburbs, aged 50 years and over. Five screening cycles have been conducted during the period 1973-1984 with intervals of 1, 1.5, 2 and 4 years respectively.

Evidence is provided that breast cancer after age 55 grows fairly slowly. This has implications for screening policy in terms of optimum intervals between screens. The aim of a screening programme is to reduce mortality. Data are presented showing to what extent this aim has been achieved. Problems of bias in evaluating a non-randomized study are outlined.

SCREENING FOR BLADDER CANCER IN EGYPT. AMAL S. IBRAHIM, Epidemiology and Statistics Unit, Natl. Cancer Institute, Cairo, Egypt.

Bladder cancer is an important problem in Egypt. It is the most frequent type of cancer and is closely associated to schistosomiasis, the most prevalent endemic disease in the country. This association defines a special type of cancer different from that seen in Western countries. Cancer usually follows a long period of cystitis during which dysplastic changes take place and may ultimately lead to squamous cell carcinoma characteristic of this type of cancer associated with schistosomiasis. This long preclinical phase offers a good opportunity for early detection of cancer by cytological examination of urine. The paper describes the Egyptian experience in this respect which proves the feasibility and acceptability of the procedure.

Screening is still needed in the presence of active schistosomiasis control programmes. Even if these programmes are completely effective, there is still a burden of bladder cancer for some 30 years to come. Although there are no data to demonstrate the potential mortality reduction that follows the screening programme, yet one notable effect is the detection of some cases in early stages amenable to transurethral resection, a feature which is almost never seen in routinely diagnosed cases. This is an important effect on morbidity and on the quality of life following treatment of these early cases. Evaluation of cost-effectiveness of such programmes is difficult. In view of improvement in the quality of life, the cost of the procedure have been judged to be appropriate. However, large funds are needed for running of the programme on a large scale. In addition to laboratory facilities, a large number of people will be needed due to the widespread of the population at risk allow over the rural areas of Egypt. About 2/3 of a total Egyptian population of more than 40 millions.
The prediction of tumor treatment response is done in particular tumors by measurement of size or repeated biopsies. In primary bone tumors radionuclide techniques have been compared with the final outcome after chemotherapy. In these protocols dynamic bone scanning is done during treatment every fortnight. Time-activity curves over the tumor and the corresponding region of the other extremity are generated and compartmentalized. Figures of merit for the initial perfusion, the exchange rates rates for the quickly exchangeable extravascular space and late tumor/bone uptake are calculated.

From the initial results in osteosarcomas we found a close correlation between the final outcome (i.e., response/non-response) and changes in the early exchange rates. There was a weak correlation between both perfusion and late uptake changes during treatment and tumor response.

Three to four radionuclide studies (within the first six weeks of treatment) are necessary for an accurate prediction of tumor treatment response in primary osteosarcomas.

The imaging of tumors in the nuclear medicine remains the topic of interest both of the specialized physicians in this field and the clinical coworkers. While the diagnostic importance of 67-Ga citrate, 60-Co-bleomycin, 201-T1 and other radiopharmaceuticals is widely verified, in the more research interest now stands the accuracy objectivation in the use of these methods together with other diagnostic imaging techniques. Examples will be given including our own results of a prospective study in Hodgkin’s disease.

Each year, there is an increase in the number of new working places interested in the use of labeled monoclonal antibodies promising novel possibilities in the tumor diagnostics.

To a wider application of the radiopharmaceuticals in the oncology also contribute new detection possibilities as e.g. SPECT, PET and with radiology bordering method — MRI.

Also new radiopharmaceuticals may be expected, capable to improve the specificity of nuclear medical diagnosis.
K-22: NEW METHODS AND RESULTS IN THE IN VIVO NUCLEAR MEDICINE IN THE DIAGNOSIS OF MALIGNANT TUMOURS

3175  POSITRON EMISSION TOMOGRAPHY IN THE DIAGNOSIS OF BRAIN TUMOURS. Mats Bergström, Kaj Ericson, Michael Mosskin, Anders Littig, Hans Lundqvist, Hans von Hoist, Georg Norén, Peter Johnström, and Bengt Langström, Departments of Neuroradiology, Neurosurgery and Hospital Pharmacy, Karolinska Hospital, Stockholm and Departments of Neurology, Diagnostic Radiology, Gustaf Werner Institute and Organic Chemistry, Uppsala University, Uppsala, Sweden

Positron emission tomography (PET) has extended nuclear medicine to imaging and kinetic studies using the short lived radionuclides $^{11}$C, $^{15}$O and $^{18}$F. These radionuclides can be used to label a wide spectrum of tracer substances of functional, metabolic or pharmacological interest. Thus, non-invasive in vivo studies of regional blood flow, glucose and amino acid metabolism, receptor binding and drug distribution have been performed with PET. We have studied brain tumors with PET and compared the results with CT, MRI and with stereotaxic biopsies. The compound that so far has been most valuable in the diagnosis of glialomas is $^{11}$C-L-methionine. In more than 50 patients a definite superiority of PET compared to CT in assessment of tumor extent was observed in about 50% of the cases. In about 25% of the cases, PET revealed solid tumor tissue in areas appearing normal on CT. PET has also proved to be of value in the follow-up of treatment of brain tumors. The PET studies are used in an integrated system for stereotaxic biopsies and for precision radiation therapy. Examples will also be given on PET studies using other tracers for metabolism and receptor binding in intracranial tumors.

3176  NUCLEAR MEDICINE IN ONCOLOGY

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$^{131}$I- and $^{111}$In-labelled antimelanoma antibodies have been used (1,2) for scintigraphic localization of melanoma and its metastases. Total-body radionuclide distribution reported shows nonspecificity of the radiopharmaceutical for melanoma, necessitating high radioactivity dose administration and poor diagnostic results (3,4). We have developed melanoma-specific Ga-67 formulation. Ga-67 administered in this form reveals both primary melanoma and its metastases and permits follow-up of the disease. These results will be presented and the mechanism of the radionuclide uptake from both labelled antibodies and Ga-67 formulation will be discussed.

The use of combined therapeutic procedures may increase the life span of many tumorous patients or in certain cases may lead to complete recovery. Hence it follows that a systematic follow-up of these patients is of primary importance. At our Department of Nuclear Medicine isotope diagnostic methods are applied in the follow-up of patients with malignant lymphoma and bone metastases from breast cancer. Since 1983 altogether 66 patients with malignant lymphoma and 124 patients with breast cancer were subjected to isotope investigations, 14 of the former group and 11 of the latter one had two or more examinations. The results show that this study provides useful information about the current state of the disease and helps selecting the therapy of choice.

A detailed analysis of the obtained data is provided.

In the past 20 years, one finds that the contribution of adjuvant chemotherapy for solid tumors has been minimal. Up till now, the contribution of immunotherapy as an adjuvant to surgery has also been insignificant. In the United States, 64% of five-year cures are provided by surgery alone. The five-year cure rate rises to about 80% when including the results of radiotherapy, either alone or in combination with surgery.

In August, 1982, at a meeting in Budapest, I presented data and the concept showing that laser surgery with magnification allows an improvement of about three orders of magnitude over standard surgical techniques in the intraoperative detection and removal of cancer cells. This information was gained over a decade of experience in treating cancers of the head and neck with laser microsurgical techniques. At the present, laser surgery provides cure in preneoplastic states and in early cancers of the aerodigestive tract and gynecological tract. It also provides prolongation of life and palliative treatment for other cancers. A new generation of laser surgical systems will provide even greater precision in the detection and cytoreduction of metastatic cancer and metastatic cancer. The greatly reduced tumor burden can then be handled more effectively with other cancer treatment modalities such as chemotherapy, immunotherapy, radiation therapy, or some combination of these.

One does not expect a magical general cure for cancer in this century. However, laser surgery alone or in conjunction with other modalities could reduce cancer mortality worldwide by 15% by the year 2000.
The author had performed nearly 300 operations with high energy CO₂ laser. In the lecture the average age of patients, the male/female ratio, the diagnoses, the localisations of tumours, and the types, methods and number of operations are shown. Because the results are favourable as from the oncological and as from the functional point of view, the author recommends the application of this modality.
**L-24: ONCOLOGIC LASER SURGERY**

**3187 Nd:YAG LASER CONIZATION OF UTERINE CERVIX UTILIZING CERAMIC SCALPEL.**

Conization of the uterine cervix has become a safe and simple surgical procedure through the use of a crystallized alumina scalpel in conjunction with the Nd:YAG laser instrument. Owing to anatomical characteristics such as the toughness of cervical tissue and the difficulty of stopping hemorrhaging, cervical conization has not previously seen wide usage. In addition to the ordinary surgical scalpel, laser technologies such as CO₂ or argon vaporization have been applied to this type of surgery, but with generally unsatisfactory results. Use of the Contact scalpel enables precise resection of the desired size and shape of cone, with minimal blood loss. Pathological analysis is also enhanced, since only a very small portion of the cut surface is affected by laser heat. This operation can, therefore, be applied both to the treatment of very early cervical cancer (CIS or Ia) or severe dysplasia, and to the diagnosis of depth and spread in a cancer affected area where colposcopic findings are uncertain.

**3189 ENDOSCOPIC LASER DESTRUCTION OF CASTRO-INTESTINAL AND RESPIRATORY TUMOURS.**
B.K. Poddubny, Yu.P. Vopshchov, N.V. Belousova, V.A. Saljuk, B.N. Malikshiev, All-Union Cancer Research Center of the USSR, Moscow, USSR.

Endoscopic laser destruction was carried out in 70 patients with benign and malignant tumors of larynx, bronchus, esophagus, stomach and colon using Nd:YAG laser with a power output 40-50W. The laser energy was conveyed by way of a quartz waveguide through the fiberendoscope. Laser destruction (LD) was performed by 1-4 sec. beams from the distance of 3-10 mm with total energy for one action 30000. For all benign tumors it was possible to perform LD with minimal reaction of surrounding tissues and rapid epithelization of mucosa defect. In small larynx cancer and early recurrences of operated stomach LD was performed for total destruction of tumors. All of this patients were incurable by other therapy. In 90% patients good results were obtained during 1 year of observation. In advanced cancer of larynx, bronchus, esophagus, stomach and colon with luminal occlusion LD permitted to obtain successful recanalization of tumors with luminal opening in 90% pa-
tients.
CT-BASED THREE-DIMENSIONAL TREATMENT PLANNING
W. Schlegel, German Cancer Research Center, 6900 Heidelberg, Federal Republic

It is an essential problem of radiotherapy to reach the optimum dose distribution within the target volume and the surrounding healthy tissue. Computerized treatment planning has improved this situation during the last decade. However, for irregular shaped target volumes or in the close vicinity of critical organs it is impossible to solve the dose optimisation problem by twodimensional treatment planning alone. With the availability of CT and MRI, threedimensional calculation of dose distributions has become possible for individual patients. The principles of a CT-based treatment planning system, which has been developed at the German Cancer Research Center, will be described. With this system it is possible to calculate, optimize and display dose distributions in three dimensions. Besides the conventional treatment technique, also noncoplanar beams, irregular shaped fields and dynamic treatment techniques have been included into the dose calculations. Examples will be discussed, showing in which cases a better dose coverage of the target volume and improved sparing of critical organs can be reached by the means of threedimensional treatment planning. An outlook of the applicability of noncoplanar beams and dynamic treatment techniques will be given.

POSTOPERATIVE TREATMENT OF BREAST CANCER WITH HIGH ENERGY ELECTRON BEAM: CLINICAL TREATMENT PLANNING
J. Petranyi, Budapest, Hungary

Since November 1976 the high energy electron beam has been used in the postoperative treatment of breast cancer. The authors discuss the procedure of medical treatment planning: The definition of treatment volume and target volume. Patient positioning, patient dosage, the selection of electron energy.
The chest wall thickness was measured by CT scans.
In order to illustrate the procedures mentioned above a number of examples of routine treatment plans are given.

POSTOPERATIVE TREATMENT OF BREAST CANCER WITH HIGH ENERGY ELECTRON BEAM: CLINICAL TREATMENT PLANNING
J. Petranyi, Budapest, Hungary

RESERVED
R.E. Bentley, Sutton, UK
Brachytherapy problems concern quality assurance, dosimetry and radiological protection. 35 decades of application of this treatment method at the Inst. of Oncology in Cracow, in the three mentioned aspects, are presented.

The primary radium stock, donated by M. Curie-Sklodowska still in use, has been gradually supplemented by new radium, caesium and iridium sources. Attention was drawn to source performance. Activity and its distribution was measured and the resulting dose variations analysed.

Nowadays dosimetry is performed by computers. Localization and dose calculations are based on methods developed by Batten, Shalek, Botho, Young. Special attention has been given to angular selfabsorption of iridium interstitial sources and new approach in clinical dosimetry.

Accumulated clinical data and computer facilities /Informatek-Ti-S/ enabled investigations concerning geometrical relations in patient anatomy and also dosimetric relations by means of mathematic simulation methods /rectal dose vs. ovoid orientation and separation/.

Parallel to dosimetric studies, some technical improvements in shielding arrangement and instrumentation have been worked out and applied, resulting in continuous personal exposure reduction.

In the paper we presented cases of breast carcinoma, who were irradiated by external fields Co-60. CT has been used for localization of irradiation volume. CT scan enable more precise localization of tumor bed for planning of boost field, as well as lymphnodes position in locally inoperable tumors and patients treated by limited surgery or mastectomy. CT also enables visualization of individual differences in thickness of thoracic wall and minimization of lung volume, involved by field beams, what presents important advantage over classical methods for defining of body line contours.
THE MODE OF PRESENTATION OF RHABDOMYOSARCOMA (RMS) AND ITS PROGNOSTIC SIGNIFICANCE

C. C. Bailey - Seattle Hospital, Seattle, WA.

Rhabdomyosarcoma can arise at many sites in the body as the mode of presentation is influenced by the site of origin. In certain sites the tumor will come to clinical attention early in the course of its development and whilst it is still localized. In other sites the tumor may attain a large size before producing symptoms. The orbit would be an example of the former category and is associated with a good prognosis. The renal tumoral area is an example of the latter and the outlook is correspondingly less good. The anatomical relationships of some sites of origin heavily influence prognosis. Tumors of the nasopharynx, nasal cavities and paranasal sinuses or middle ear areas are in anatomical relationship to the base of the skull and to the cranial fossae, infiltration, either through the foramina or by direct invasion through the skull base, given access to the central nervous system, causing cranial nerve palsies, malignant meningitis and infiltration of cerebral tissues. This is associated with a very poor outcome. Tumors arising in hollow visceras such as the bladder, uterus and vagina, may attain great size but tend to enlarge in the visceral cavity rather than to infiltrate the surrounding tissue. Tumors of these sites may therefore have a good prognosis. In childhood 3 major types of RMS can be histologically differentiated: embryonal type (50%), alveolar type (20%), embryonal botryoid type (10%). Histologically the tumor is related to the age of the child at presentation and to the site of the primary tumor. Children under the age of 5 at presentation are most likely to have the embryonal type of histology, whilst those over 5 are likely to have the alveolar type. The embryonal type is most common in the head and neck and genito-urinary sites, whilst the alveolar type is seen most commonly in lesions on the extremities, on the trunk and in the perineal region. Embryonal botryoid tumors are much rarer than the other two types and to the site of the primary tumor. Children under the age of 5 at presentation are most likely to have the embryonal type of histology, whilst those over 5 are likely to have the alveolar type. The embryonal type is most common in the head and neck and genito-urinary sites, whilst the alveolar type is seen most commonly in lesions on the extremities, on the trunk and in the perineal region. Embryonal botryoid tumors are much rarer than the other two types.

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SURGERY OF SOFT TISSUE SARCOMA IN CHILDREN
L. A. Durmov, All-Union Cancer Research Center, the USSR

Surgery is the prevailing method in treating soft tissue sarcoma in children. Before and after surgery drug and radiation treatment is applied. Wide dissection is applied in limb tumors treatment which sometimes is followed by vessel plastic. Excision of the urinary bladder is recommended with urinary ducts transplantation when the urinary bladder is involved. In case of vaginal rhabdomyosarcoma electroexision of the tumor is used. To save the girls from radiation castration the dislocation of ovaries is undertaken. When organs are involved (testicles, kidney and so on) they are removed. The experience shows that it is only surgery that brings about positive and permanent results in the treatment of patients with soft tissue sarcomas. Sometimes radiosurgery is advisable (vaginal, urinary bladder tumors, some body and limb tumors).

CHEMOTHERAPY IN CHILDHOOD RHABDOMYOSARCOMAS (RMS).
J. Treuner, Department of Ped. Hem., Children's Hospital, University of Tubingen (FRG).

Even though combined cytostatic therapy has dramatically improved the cure rate of RMS patients, it has only achieved long-term remissions in 20% to 30% of the primary disseminated lesions. Every new cytostatic combination can be compared with the therapeutic results of stage IV patients, and therefore, can be transferred to high-risk patients in other stages. Today, complete destruction of local tumors seems to be possible in one third of the affected patients with substances known to be effective in RMS (vincristine, actinomycin, cyclophosphamide, Adriamycin). In another one third of the patients, the tumor can be reduced, and in about 10% to 20%, tumor growth cannot be influenced. Insufficient tumor reduction and progression are defined as non-responders. The significance of time in which response to initial chemotherapy can be determined is twofold: For non-responders, it represents a risk of further development of the tumor. For responders, it serves as a prognostic factor, when reduction in tumor size is taken into consideration. One-BI analyses pointed out the risk factor tumor reduction per time. It, however, should be mentioned that, even in satisfactory initial response (2/3 tumor reduction), sub-clinically resistant cells may develop. The response kinetics of tumors in relation to cytostatic treatment is an important, but uninvestigated area. Cytostatically sensitive patients may develop, and in about 10% to 20%, tumor growth cannot be influenced. Cytostatic pretreatment for tumor reduction requires short-term control of tumor size, temporal limitation and subsequent resection or biopsy. Effective cytostatic drugs are vincristine, actinomycin, cyclophosphamide and Adriamycin. Other agents such as cisplatinum, VP-16, melphalan and ifosfamide should be used in high-risk patients.

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P-22: SOFT-TISSUE SARCOMAS IN CHILDHOOD


It seems advisable to apply to PT sarcomas the current therapeutic approach proposed in other sites, taking into account the effectiveness of chemotherapy (CT) to sterilize micrometastases and trying to avoid the sequelae due to a systematic paraaortic lymphadenectomy.

Between 1971 and 1984, 33 patients were selected to not receive paraaortic lymphadenectomy on the following criteria: 1) tumor localized, completely resected without cord involvement; 2) normal lymphographic and/or echographic and CT scan findings (T1 No Mo). Ages ranged from 5 months to 18 years (mean age: 5 yrs 6 months). The right size was involved in 16 pts and the left in 17. Pathologic type was embryonal rhabdomyosarcomas in 31 pts, with an alveolar component in 3 of them; 2 other pts had a fibrosarcoma and a liposarcoma.

Inguinal orchiectomy was performed in 32 pts; one patient had only a partial orchiectomy. 32/33 pts received systematic CT within 2 weeks after surgery: courses of vincristine, actinomycin D, cyclophosphamide (VAC), either alone (4 pts, during 18 months), or alternated with vincristine-adriamycin (23 pts), either 18 months or 8 months; 6 pts received 3 courses of ifosfamide, vincristine, actinomycin D (IVA). In one patient, CT was refused and given 1 year later for a relapse.

27 pts are considered cured with a follow-up of more than 6 years in spite of 2 abdominal relapses. The 6 last pts (treated by IVA) are in first complete remission, 1 to 2 years after diagnosis.

These very good results demonstrate the ineffectiveness of the currently recommended paraaortic lymphadenectomy in stage I PT RMS and the effectiveness of CT to eradicate occult micrometastases.

T-24: OCCUPATIONAL HAZARDS FOR NURSES

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS): PRECAUTIONS FOR HEALTH CARE WORKERS. C.H. Yarbro, University of Missouri School of Medicine, Columbia, Missouri, U.S.A.

Acquired immune deficiency syndrome (AIDS) is a viral infection which causes a specific breakdown in the immune defense system of the body. AIDS cases remain the highest in the USA with 60.0 cases per million population. However, there has been an increased incidence of AIDS in 21 European Countries with the highest rates noted in Switzerland, Denmark and France. Patients with this syndrome develop a variety of opportunistic infections and tumors. Public and professional anxiety about AIDS has increased as a result of the media and high mortality rate associated with AIDS. While nurses are at slight risk due to their contact with AIDS patients, the threat of contracting AIDS has been greatly exaggerated and often misunderstood. Yet, how to protect oneself while caring for a patient with AIDS remains a concern. Precautions for infection control are designed to promote good health for patients, family, friends and health care workers through isolation of infectious agents and interruption of their transmission. Appropriate precautions do not interfere with the delivery of effective patient care. This presentation will discuss the infection control precautions implemented at our institution and the unnecessary practices to avoid in providing care to patients with AIDS.
3209 STRESS AND INFECTIOUS DISEASE AS OCCUPATIONAL HAZARDS FOR ONCOLOGY NURSES. Dee Wonch RN MS, Catherine Lyons RN MS, and Ellen Fleming Zupa RN MS, Roswell Park Memorial Institute, Buffalo, New York, United States.

The practice of oncology nursing poses a variety of actual and potential hazards for nursing staff. Most notable among these are the potential hazards associated with exposure to various treatment modalities, infectious diseases, and stress. This presentation will outline a brief overview of stress theory, the relationship between stress and cancer, unique stressors experienced by oncology clients and the impact of these factors on the stress experienced by oncology nurses. Concepts included in the development of a stress management program for nurses will also be explored. In addition, the most common infectious diseases to which the oncology nurse may be exposed will be discussed, as well as appropriate protective measures.

3211 HAZARDS OF HANDLING CYTOTOXIC AGENTS

In the last few years there has been considerable concern about the risks, known and potential, to handlers of cytotoxic agents. Much research has been undertaken in an effort to quantify these hazards. Although a number of interesting points have been raised, the precise nature of toxicity to those persons preparing the drugs remains unclear. Progress has been achieved, however, in developing safer presentations of cytotoxic agents and, additionally, in developing better systems of work. This paper will review the literature and look at some of the alternatives available to create a safer working environment.
U-25: NEW TRENDS OF CANCER CHEMOTHERAPY BY MITOMYCIN "C"

K. Ota, Nagoya, Japan

Mitomycin C (MMC) is an antibiotic antibiotic that has demonstrated activity against a number of human neoplastic tissues and has been utilized since the mid 1970s in Japan. Mitomycin C has been developed in the United States, and the development of this drug has been very slow because of the severe delayed and cumulative myelosuppression associated with early administration of the drug. MMC has its own unique properties and schedule-sensitive single agent activity in a number of tumors. MMC has been used in combination chemotherapy in a number of cases. Combination therapy seems to be more active than single-agent MMC. MMC is a unique agent with many schedules and combinations. Some combination schedules are described in this section.

Combination Modality of Anticancer Drugs

K. Ota, Nagoya, Japan
3218 EORTC RESULT WITH MITOMYCIN C FOR BLADDER INSTILLATION

L. Denis, Antwerp, Belgium

3217 INTRAPERITONEAL CHEMOTHERAPY WITH MITOMYCIN C IN RESISTANT OVARIAN CANCER.

AT van Oosterom, C. Hol, EJ. Pauwaal, RA. Runhaar, JB. Timpe, MA. Nota, B. de Krijger and C. Van Den WJ. Dept. of Clinical Oncology, University Hospital, Leiden, The Netherlands.

The rationale for intracavitary chemotherapy is the delivery of an increased dose of the drug to the tumor with less systemic toxicity. Systemic Mitomycin C (MMC) has a moderate activity against ovarian cancer, but a clear dose response against human ovarian cancer cell in vitro has been demonstrated. MMC 12 mg/m^2 in 10 minutes was administered after 3 L of normal saline was instilled in the peritoneal cavity using a temporarily placed Piggybag catheter, the location checked with scintigraphic peritoneography.

All 26 women, with ages ranging from 34-73 years, had been heavily pretreated with alkylating agent and Cisplatin containing combination regimens and did not obtain a complete response or had a recurrence. Of the 11 patients with >3 cm large tumor masses, 4 had a CR for 2-10 months. Two of the 5 patients with >3 cm tumor masses had a PR. Of the 10 patients with minimal disease (tumor <1 cm on positive washing only) 5 had a CR (6-30^2 months), 2 are free of disease for 5, resp. 7, months, but refused a confirmatory laparotomy, 3 had no change for 3-7 months. Hematologic side-effects in the 62 instillations consisted of generally mild leukopenia, but in some patients WHO grade 2 thrombocytopenia was observed. Non-hematological side-effects: treatment related abdominal pain lasting up to two weeks (grade 3) in 5, grade 2 in 11 instillations. Nausea and vomiting generally less than 3 hours and mild. One patient in complete response developed a hemolytic-uremic syndrome and is still on hemodialysis. In 4 patients a sclerosing peritonitis was observed. Three instillations had to be canceled, the catheter being placed in the colon in 2, in the ileum in 1. In conclusion, with this simple administration method a high (92%) complete response rate with intraperitoneal Mitomycin C can be obtained in heavily pretreated ovarian cancer patients with minimal tumor load.

3219 PERIOPERATIVE ARTERIAL (HAI) MITOMYCIN C (MMC) AND FLOXURIDINE (FUDR) COMBINED WITH SURGICAL HEPATIC RESSECTION IN METASTATIC COLORECTAL CANCER (CRC).

T. van Oosterom, E. de Bruijn and C. Van Dijck. Dept. of Clinical Oncology, University Hospital, Leiden, The Netherlands. Dr. AT van Oosterom, C. Hol, EJ. Pauwaal, RA. Runhaar, JB. Timpe, MA. Nota, B. de Krijger and C. Van Den WJ. Dept. of Clinical Oncology, University Hospital, Leiden, The Netherlands.

Hepatic resection may be accomplished in 5-10% of patients (pts) with CRC metastatic to the liver, resulting in a median survival of 22-30 months and an approximate 2 and 5 year survival rate of 60% and 30% respectively. Pts with positive resection margins and multiple metastatic deposits seem to have a worse prognosis. To improve upon that we added perioperative arterial chemotherapy to surgical resection. Twenty pts who had undergone a successful resection of liver metastases from CRC were given perioperative hepatic arterial MMC and FUDR through catheters placed percutaneously in the hepatic artery as adjunctive therapy. The median survival from hepatic resection for all 20 pts was 51 months. Fourteen are still alive with a median postoperative follow-up of 35 months; 8 are disease-free with a median postoperative follow-up of 30 months. Among 11 pts in whom the surgical margin of the specimen contained tumor cells, the median survival was 48 months. This survival was comparable to that among 9 pts in whom the surgical margins were tumor free (P=.45). Neither the number of metastatic liver deposits nor the disease-free interval between the primary diagnosis of CRC and the development of liver metastases significantly affected survival. While these results compare favorably with the results in previously published series, this aggressive adjuvant chemotherapy appears to be particularly justified in pts with tumor positive surgical margins who are characterized by a poor prognosis. A multi-institutional randomized controlled trial will be required to confirm these observations.
TUESDAY • AUGUST 26 • AFTERNOON

U-26: PROTEOLYTIC ENZYMES AND RETINOIDS

3221 RATIONALE AND MODE OF ACTION OF PROTEOLYTIC ENZYMES
K. Hansberger, Geretstried, FRG

3222 RETINOIDS AND PROTEOLYTIC ENZYMES IN ONCOLOGY
H. Wrba, Vienna, Austria

3223 PROTEOLYTIC ENZYMES AND RETINOIDS IN IMMUNOLOGY
M. Micksche, Vienna, Austria

3224 ADJUVANT TREATMENT OF LUNG CANCER BY VITAMIN A
L. Pastorino, Milan, Italy
It is well known that Vit. A, and specially the Retinoids are important factors as well in the etiology of malignant diseases as in the treatment. Wald et al. from Oxford published that men who had an Retinol level below normal, they have an higher risk for tumor diseases than others, independent of age, smokehabit, sex and Serumcholesterol. That risk was distinet by lungtumors. An norwegian study has the result that in case of Vit. A deficiency the risk to get Lung- and Adenocancer is 4,6% higher than normal. Brown et al. from Wisconsin Clinical Center published, that internal treatment of Cancer is more successful by Pats. with normal or higher level. Mahrle Cologne shows, that Retinoids prevent the maligne Celltransformation. Plezity et al from USSR says, that Vit. A is an regulativ of Celldifference, an stimulant of the Collimmunity and influence of the lysosomal Cellmembrane.

We started in 1984 a Pilotstudy to look for the level of proteinbinding Retinol by all kinds of tumors, in different stages, different age and unselected Pats., we treated in case of below level with Vit.A-Mulsion and looked for the success.

In that time (2y) we had 3607 Pats. from which 848 had below level, 21,5%. They all were treated before with OP, and/or x-ray and partially with Cytostatics. 2231 mammalian Cancer Pats all stages, 493 had below level (21,2%). Cancer of abdominal 28,8%, Rectum-Cancer 30,4%, Skintumor 29,9%, Lungen tumor 10,9%, Tumor of nose and throat 8,57%, Gastric cancer 26,02%. Kontrol-group 200 health men, non-smoker 6,6% below, smoker 16,6%. We treated 4 weeks in differentdose with A-Mulsion and at the kontrol 68,5% had an normal or higher level of proteinbinding Retinol. The normalizing was dependent of Tumorstage, age, smoking and dose. We never reached, delineate the toxicity high, so, we had no side effects. May be, that the dose were in different case to low. It will be published, particular about the different tumor, the different stages and different agegroups. This is only the first part of the Pilotsudy.
A-34: ELECTRON MICROSCOPY, ENZYME HISTOCHEMISTRY AND IMMUNOCYTOCHEMISTRY IN TUMOUR DIAGNOSTICS

**DATA ON NON-SMALL-CELL NEOPLASMS**

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An attempt to classify main ultrastructural features of salivary, thyroid, and perichromatin nuclear components is made. It refers first of all to the nuclear envelope peculiarities as deep nuclear invaginations and nuclear pockets. A special attention is paid on EM structures as nuclei being hypertrophic and sometimes atypical, on abundance of nuclear bodies and on pleomorphism of the perichromatin granules. A quantitative study is performed on 20 cases of non-Hodgkin's lymph node tumors, being difficult for light microscopy differential diagnosis. Predominance of compact nuclei (42.1%) in cancer cell profiles and reticular ones (40.2%) in lymphoma cell profiles is found. Atypical reticular nuclei as spattered or such ones having "snake-like" nucleoli are found in lymphoma cells only. Arrangement of nuclear bodies in cancer cells is usually different from the feature of epithelial origin of the tumors (in 7.1% of cancer cells and in 0% of lymphoma cells). Gathering of many nuclei in groups (29%) and in chains (16.9%) is more characteristic for cancer than for lymphoma cells (resp. 1.3% and 4%). In lymphoma cases this pattern only in secretory (immunocytoma and immunoblastoma) cells is sometimes observed. The diagnostic value of the presence of some nuclear inclusions having cytoplasmic origin.

**ELECTRON MICROSCOPY AND IMMUNOHISTOCHEMISTRY IN SOFT TISSUE SARCOMA DIAGNOSIS - PROBLEMS AND UTI-LIZATION.**

D. K. Katankaap, Inst. Pathol., Jena, GDR

In large centers of soft tissue tumor pathology 10-20% of sarcomas remain unclassified in spite of the work of qualified pathologists with special expertise. The deficiencies of electron microscopy and immunohistochemistry in diminishing this percentage is undoubted. But there is some room for improvement, and cautious interpretation is mandatory. Cellular heterogeneity of soft tissue sarcomas has gained world-wide acceptance. This implicates the possibility of a divergent differentiation at cellular level which might be substantiated by electron microscopy (EM) and immunohistochemical (IHC) findings and may hinder a correct diagnosis. Thus an estimation of the diagnostic significance or lack thereof is only possible after consideration of both qualitative and quantitative aspects at the time. Furthermore, with a few exceptions there are no absolutely specific organelles in the EM diagnosis of soft tissue sarcomas and mostly the EM interpretation requires the help of the light microscopy. Sarcomas may lose characterizing organelle combinations on differentiation and growth by which different sarcoma types can emerge and induce a wrong diagnosis. Tumor dedifferentiation and other growth peculiarities can lead to wrong negative or in case of some markers to wrong positive results. Lastly, methodic aspects (sampling error, antigenicity after tissue processing, decreasing, antibody specificity) should compel caution in evaluating the diagnostic value of single case and in findings. In any case also those observations must not be used for a histogenetic interpretation, they can only be the basis of an extended phenotypical characterization of the actual tumor differentiation.

**DIFFERENTIATION OF NEUROBLASTOMAS FROM OTHER SMALL ROUND CELL NEOPLASMS OF CHILDHOOD BY APPLYING A PANEL OF MONO- AND POLYCLONAL ANTIBODIES ON SECTIONS OF PARAFFIN-EMBEDDED TISSUE.**


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Monoclonal and polyclonal antibodies to intermediate filaments and various leukocyte markers and monoclonal antibodies to neuroblastoma cells raised by immunization with a variety of immunoreactive neuroblastoma profiles precipitated on electron microscopy have decreased from a peak of 8.5% of all surgical pathology ascensions (exclusive of cytology specimens) in 1979, to 8.9% in 1980, and 9.2% in 1983, 9.4% of the electron microscopy ascensions were examined for diagnosis, and this number fell to 9% in 1984 and 3% in 1986. The decrease can in part be attributed to the greater number of problem tumors being diagnosed with the use of immunostaining procedures, but it also reflects changes in the types of specimens for which diagnostic electron microscopy is being requested. The number of endocardial biopsies has diminished significantly with improved methods for the administration of anthracyclines and consequent reduction in the incidence of cardiotoxicity. In contrast, the number of cytology specimens submitted for electron microscopy has increased dramatically with expansion of the use of fine needle aspiration biopsies. Electron microscopy is a useful back-up to light microscopy in the evaluation of fine needle aspiration biopsies. Electron microscopy can be useful for the classification of tumors by rapid light microscopy, and also by the use of special techniques which provide optimal yields of cells for ultrastructural study. Among diagnostic electron microscopy specimens, there has been a reduction in the number of lymphomas and leukemias, and a relative increase in carcinomas, spindle cell neoplasms, and small round cell tumors. In addition to the diagnostic duties, the activities of the electron microscopy include investigative projects and retrospective clinicopathologic studies on groups of human tumors.
IMMUNOHISTOCHEMICAL APPROACH TO THE HISTOGENESIS OF RENAL CELL CARCINOMA
Giovanni Diandrea, Dept. Anat. Pathology, National Cancer Institute, Naples, Italy.

The origin and nature of renal cell carcinomas have been controversial. This cancer was originally described that it originates from the epithelial cells of proximal convoluted tubules. Nevertheless this histogenetic theory appears to be in contrast with several properties of renal cell carcinomas such as: 1) the expression of intermediate filament which are to be considered as markers of mesodermally derived tissues; 2) expression of lectin-binding characteristics which are normally identified in distal convoluted tubules; 3) remarkable heterogeneity and variability of morphological patterns; 4) marked resistance to adjuvant therapy; 5) propensity to early blood vessel invasion and hematogenous dissemination. These findings have prompted us to investigate the distribution in renal cell carcinomas of several antigens and substances which are selectively detected in different epithelial components of normal renal tubules. For this purpose 35 cases of renal cell carcinomas were investigated; the results showed: 1) antigens of distal convoluted tubules (particularly ema) in 71% of carcinoma cases; 2) antigens of proximal convoluted tubules (lysozyme soybean agglutinin) in 51% of carcinoma cases; 3) constituent expression of all the above antigens in 46% of carcinoma cases. Our results argue against a selective origin from a well defined epithelial component of the nephron.
DATA FOR A REVISION OF WHO CATEGORIZATION OF LYMPHOID LEUKEMIAS AND LYMPHOMAS (LL & L). G. Mathé, J.L. Misslet & D. Danickev, SMST & ICG (Univ. Paris-Sud, CNRS LA-149, Assoc.CI, Bernard & ARC1, Hop. Paul-Brousse, 94804-Villette, France

We have classified 200 cases of LL and L typed with monoclonal antibodies in the WHO Leukemia and Lymphoma categorisation modified to the today knowledge of normal cell differentiation. We have found that the lymphoid acute leukaemias correspond respectively to normal differentiation steps: the "myeloblastic" to the polyvalent stem cell TdT+ or to the lymphoid progenitor TdT+ or B-44; the "prolymphocytic T" to the prolymphocyte TdT-, OKT6+, OKT10+ or 4-0-6-; the "prolymphocytic monon "to the B precursor (B4+, B1+, J5+, C4+, alg-1); the "T- macrolymphoblastic" to the OKT+B thymocyte; the "B- macrolymphoblastic" to the large pre B (Cau); the "prolymphocytic B" to the small pre B (Cau); the Burkitt's leukaemia to a pre-B cell transformed into a lymphoblastoid cell. The B-CLL is constituted of siga+ v- l+a B4+ B1- FC+ virgin lymphocytes and the B-precursor of siga+ v- l+a B4+ 8 peripheral T-lymphocyte, the mantle zone B-lymphoma is constituted of siga+ FC- primary lymphocytosis. The B-central lymphocytosis are made of siga+ B4- and siga+ 8+ or either small cell cleaved, or large cell B-cell. The Burkitt and non epidemic Burkitt lymphomas are made of transformed cells into siga+ lymphoblasts described a non blastic, non Burkitt, non follicler, medium cell lymphoma siga+. The B-immunoblastic lymphoma is siga+ 8- FC+ in the frame of the maturation of siga+ FC+ or siga- FC- lymphocytes. The first being the Japanese pleomorphic type.


Ribonucleotide reductase (RR) catalyzes the reaction in which 2'-deoxyribo nucleoside 5'-diphosphates are generated from the corresponding ribonucleotides. RR is located in the rate-limiting step in the de novo synthesis of dNTPs and, consequently, DNA synthesis. The intracellular activity of RR is controlled by the levels of the non-heme iron (NHI) and effector-binding (EB) subunits which make up the holoenzyme, the concentrations of the dNTPs which serve as positive and negative allosteric effectors, and by the presence of inhibitors. As the tumor cells proceed through the cell cycle, the two subunits of RR do not increase or decrease coordinately. The EB subunit increases earlier and has a longer half-life than the RR subunit. The amount of measurable reductase activity parallels the level of the RR subunit. The reduction of a particular NTP substrate requires the presence of a specific NTP as a positive effector (e.g., ADP and GDP reductions require dGTP and dTTP, respectively). On the other hand, dGTP and dTTP are negative effectors of GDP and UTP reductions. The level of reduction of a particular substrate depends on the concentrations of dNTP's acting as positive and negative effectors of RR. The intracellular dNTP's are critical as substrates for DNA polymerase. It can be shown that as the concentrations of dNTP's decrease, the rate of DNA synthesis decreases in a sigmoidal rather than linear manner. Drugs such as hydroxyurea, which specifically inhibit RR activity, selectively block the incorporation of precursors into DNA. The activity of RR, a key enzyme in the replication, 1m, therefore, subject to controls at the protein level, allosteric regulation and conventional inhibition. (Supported by USPHS grants CA 27398 and CA 27572.)
**The Significance of High Energy Phosphorus Metabolites in Tumours**

Marlon Stubbe, Loretta M. Rodrigues and John R. Griffiths.
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Comparisons of values of phosphocreatine (PCr) with ATP and Pi have been widely used in the interpretation of 31P NMR spectra of tumours. PCr is present in freshly implanted tumours and is not seen in the tumour grows, but may recover after chemotherapy or endocrine ablation in hormone-sensitive tumours. However, not all tissues contain PCr, in particular liver and kidney. Tumours derived from these tissues may be expected to retain their original characteristics if they are well differentiated and slow growing, and to synthesise PCr if they are poorly differentiated. In this study we measured, in a variety of tumours, PCr and ATP by 31P NMR, then rapidly freeze-clamped the tumours and assayed PCr, ATP, creatinine (Cr), ADP and AMP on acid extracts using standard enzyme methods. In summary adenocarcinomas and prostatic adenomas grown in mice, and RIF tumours grown in mice, PCr/ATP ratios were similar whether measured by NMR or enzymatic assay. In two normal hepatomas from AA and TFTD PCr and Cr were absent. Through the creatine kinase equilibrium, the ratio PCr/ATP (and [Cr]) gives an estimate of the free [ADP], and this in turn is related to oxygen supply.

Thus, non-invasive measurement of PCr and ATP can give useful information as to the energy status of tumours providing creatine kinase is present at high enough activity to establish near-equilibrium.

**The Contribution of De Novo and Salvage Pyrimidine Pathways in the Growth of Human Hematologic Malignant Cells.**


The capacity of both de novo and salvage pyrimidine pathways are increased in neoplastic tissues, while the contribution of respective pathways for DNA biosynthesis are not clearly understood. The activities of ribonucleotide deoxynucleotide reductase and thymidine kinase, and the thymidine incorporation rate were measured in cultured human hematologic malignant cell lines with different cell proliferation rates and different cell lineage. A close correlation was found between the cell proliferation rate and ribonucleotide deoxynucleotide reductase activity, but not thymidine kinase activity or thymidine incorporation rate. The ratio of thymidine kinase to CDP deoxynucleotide activity was high in slowly growing cell lines and low in rapidly growing cell lines. These results indicate that in cultured human malignant cell a high potential for proliferation may depend mainly on de novo pyrimidine pathways of DNA biosynthesis. However, thymidine kinase activity was significantly higher in myeloid and monocytoid cell lines than in other cell lines, but CDP deoxynucleotide activity was similar in the different cell lines.

The ratio of thymidine kinase to CDP deoxynucleotide activity was high in monocytoid cell lines. Therefore, the extent of use of and rule of salvage pathways were studied by examining the effect of 2-deoxyguanosine, an effective blocker of the salvage pathway on the growth of various cell lines. 2-Deoxyguanosine caused dose- and time-dependent inhibition of 14C-thymidine incorporation into DNA and of growth of cultured TdT- and non-T, non-B and myelo-monocytoid cell lines. Its extent of inhibition of cell growth differed with cells of different lineage: at 10 μg/ml it strongly inhibited growth of lymphoid-positive myelo-monocytoid cell lines, but had little effect on growth of lymphoid cell lines. Thus the salvage pathway for deoxynucleotides supply is more important in lymphoid-positive myelo-monocytoid cell lines than in lymphoid cell lines. The effect of 2-deoxyguanosine and hydroxyurea, which inhibit ribonucleotide deoxynucleotide reductase, on cell growth were additive, suggesting that combination of drugs which inhibited de novo and salvage pathways might be useful in the treatment of myelomonocytoid cell malignancies.

**Significance of Isozyme Composition in Tumor Metabolism and Gene Regulation.**

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Isozyme alterations, aside from their role as markers of neoplasia, have significance to tumour growth and metabolism and represent just one of many abnormal activators of gene expression, which encompass every mean of identification of gene products in neoplasia. This includes fetal antigens, polypeptide hormones, plasmaglobulin activators, angiogenesis factor(s) and growth stimulators. The identification of protein kinases and regulatory proteins as products of oncogenes adds exciting causal significance to activation of oncogenes in cancer. Three enzymes that are at control sites of metabolism and energy transduction have characteristic isozyme composition in tumors. Hexokinase and pyruvate kinase isozymes catalyze exergonic, irreversible steps, are geared for rapid growth, and are free of feed restrictions. Phosphofructokinase (PFK) is a highly allosteric enzyme, whose inhibition by ATP and citrate and de-inhibition by Mg ions and AMP provide a plausible site for aerobic control of glucose metabolism, typified by the Pasteur Effect. Two recent observations create renewed interest in PFK as a control site. One is the discovery of a new, potent activator at micromolar levels, fructose-2,6-bisphosphate, which adds a new dimension to allosteric control, but whose physiological importance is still not clear. Second is the finding that in the presence of UDPglucose, PFK can transfer Pi from inorganic pyrophosphate (PPi) as well as from ATP, to form F-1,6-bisP. Work on PFK of the Novikoff hepatoma has shown this reaction with PFK is subject to the same allosteric regulation as the reaction with ATP. Its functional importance resides in conservation of the PFK bond energy of PPI formed in large quantity in proliferating cells, during synthesis of macromolecules and in the formation of many intermediary metabolites.

**Structure and Expression of Amylase and Pancreatic Secretory Trypsin Inhibitor (PSTI) in Neoplastic Tissues.**

Michio Ogawa*, Takesada Mori* and Kenichi Miura*,

The structure and expression of amylase and pancreatic secretory trypsin inhibitor (PSTI) in neoplastic tissues were studied, and the mechanism of ectopic production of these proteins in neoplastic tissues was discussed. Human PSTI mRNA sequence showed that they were 46% homologous to mouse PSTI mRNA sequence with mouse epidermal growth factor (EGF) mRNA sequence. However, PSTI-positive malignant cells were also frequently found in malignant tissues. A comparison of human PSTI mRNA sequence with mouse epidermal growth factor (EGF) mRNA sequence showed that they were 46% homologous. Human PSTI stimulated 3H-thymidine incorporation into DNA in human fibroblasts at concentrations present in human serum. The mechanism of ectopic production of enzyme and enzyme-inhibitor in neoplastic tissues will be discussed.
A PROTEIN OF 37,000-DALTON WHICH IS ABUNDANTLY EXPRESSED IN HUMAN LUNG CANCERS IS HIGHLY HOMOLOGOUS TO GLYCERALDEHYDE-3-PHOSPHATE DEHYDROGENASE. S. Sakayama, M. Okubuo, Y. Nakamura, K. Tokunaga, K. Sakata, K. Sawada, and T. Kuwahara; Div. of Biochemistry, Thoracic Disease and Pathology, Chiba Cancer Ctr. Res. Inst., Chiba Japan.

Human lung cancers of all histological types contain a much higher amount of a protein of 37,000-dalton (37K) than normal lung tissues which was revealed by SDS-PAGE analysis of tissue extracts. The relative quantities as measured by scanning the stained protein patterns and expressed as percentage of total proteins were 0.53±0.12, 4.11±0.37, 5.87±0.86, 4.13±0.36 and 4.78±1.10 for normal lung tissues (67 cases), adenocarcinoma (38), squamous cell ca. (12), large cell ca. (6) and small cell ca. (5), respectively. Although the positive correlation between the amounts of 37K and malignancy was not observed, each value in the tumors was always higher than that in the normal lung tissues of the same patients. Partial sequence analysis which was done on protease V8-digested peptide showed the existence of partial homology between 37K and authentic GAPDH (E.C.1.2.1.12). Along with this evidence, tryptic peptide mapping of 37K and authentic GAPDH was carried out and it was shown that the patterns were very similar each other. Furthermore, anti-37K antibody reacted also with GAPDH. Thus, a tight relation between the elevated expression of GAPDH itself or its related protein and lung tumorogenesis was suggested. We have recently found that hybrid-arrested as well as selected translation assay of human lung tumor mRNA using GAPDH cDNA (a generous gift from Dr. R. Wu) showed that 37K mRNA cross-hybridized with this cDNA. In order to answer if 37K represents a distinct type of GAPDH, we have cloned cDNA for GAPDH from a library of cDNA prepared from lung tumor mRNA and constructed in Agtll phage. Characterization of the clone is in progress.

COMBINED EFFECT OF HYPERThERMIA AND X-IrradiATION ON SURVIVAL AND PROTEIN PATTERN OF P388 TUMOR BEARING MICE. L. Perlaky, Anna Fonagy, E.J. Hidvégi, "F. Joliot-Curie" Mat. Res. Inst. for Radiobiology and Radiohygiene, Budapest 1775, Hungary

Effect of combined modality treatment of hyperthermia and X-irradiation was studied on the increase of lifespan of P388 tumor bearing mice. 60 P388 ascites cells were hyperthermically treated in vitro for 1 h at 42°C or 43.5°C and transplanted either i.p. or i.m. Single dose of 4 Gy X-irradiation was performed to the whole-body 24 h after transplantation i.p. or 6 Gy locally after transplantation i.m. Irradiation alone on whole-body increased the mean survival time (MST) by 38% and after locally by 33%. Hyperthermic treatment of ascites cells at 42°C increased MST by 23% and at 43.5°C by 54%. Combined modality treatment of ascites cells at 42°C increased MST by 23% and at 43.5°C by 54%. Combined modality treatment of ascites cells at 42°C and whole-body X-irradiation on the first day after transplantation resulted in 70% increase of MST. Combination of the latest regime with administration of single dose 250 mg/kg dibromodulcitol (DBD) 1 h before irradiation doubled the MST compared with the untreated unirradiated control. DBD treatment alone increased MST by 27% and combined with 4 Gy X-irradiation by 65%. Noteworthy that untreated P388 solid tumor caused extensive metastasis in liver (94%) and spleen (80%). Occurrence of metastasis was significantly less after 43.5°C treatment of tumor cells before i.m. transplantation: liver 14%, spleen 11%. In order to reveal the expression of phenotypes after various treatments, protein pattern of tumor was investigated. Nuclear proteins of P388 cells were separated in two dimensions by gel electrophoresis according to O'Farrell. General decrease in synthetic activity was observed in most of the proteins after X-irradiation or 43.5°C hyperthermic treatment. The amount of certain proteins decreased specifically after hyperthermia while others increased and new "heat shock" proteins appeared like a 70 kD protein.

THE BIOLOGICAL BASES OF COMBINED USE OF HYPERThERMIA AND RADIATION IN CANCER TREATMENT

J. Overgaard, Aarhus, Denmark
CLINICAL RESULTS OF HYPERTERMIA COMBINED WITH RADIATION IN THE TREATMENT OF CERVICAL NODE METASTATIC CANCER: ANALYSIS OF 50 CASES

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From April 1980 to June 1985, 50 patients with cervical node metastatic cancer were treated. The stages were N1, N2, N3, N4. According to the depth of invasion (2150 MHz or 915 MHz microwave and X-ray or Cobalt) local skin temperature was maintained at 38-48°C, 40 minutes, twice weekly, 6-15 sessions. Radiation (X) was given 5 times weekly. The total tumor doses were 90-1200 ret, and the most were 1400-1700 ret. After treatments, 30 patients achieved CR (complete tumor regression), 9 PR (20%, but 400% decrease in tumor volume) and 5 NR (50% decrease in tumor volume or no change). CR rate was 79%, and CRPR rate was 95%. In self-control of 10 patients with unilateral neck tumor masses, the larger or smaller tumors which received hypertermia regressed faster than the other ones which received X-ray or Cobalt. There was no statistic significant difference between the CR rates for N1, N2, N3, and N4. In the combined treatment of hypertermia and radiation), the optimal radiation doses were 1400-1700 ret for X-ray and Cobalt, and 1700 ret for N3. In 27 follow-up patients 20 who had received CR hadn't developed local recurrence in 2-2 years follow-up duration.

THERMAL DOSE (TIME-TEMPERATURE RELATIONSHIPS) RELATED TO HYPERTERMIA IN CANCER THERAPY

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Information obtained in cell cultures and animals will be reviewed. For an isoeffect from heat alone, the duration of heating must be decreased by a factor of 2 for each degree increase above 42.5-43°C, and decreased by a factor of 4-6 for temperatures below 42.5-43°C. This relationship is integrated over time as the temperature changes during heating in order to obtain an equivalent time at a reference temperature, e.g., $t_{eqv}$ 43°C. Examples utilizing this concept will be illustrated for heat killing of cells in culture, and for heat damage in animals (data by Field and Morris) when the temperature was cycled 6 times between 43°C and 45°C and equated to a constant duration of heating at 44°C. In this case, there was only a 20% difference between the one cycle at 44°C and the six cycles. Dewhirst's results will be summarized showing the effects on tumors and normal tissues as a function of $t_{eqv}$ 43°C. Our results in vitro with synchronous cells and in vivo data summarized by Name indicate that this concept for thermal dose also applies to hypertermia and radiotherapy. When a second heat-radiation dose is delivered after an initial priming heat dose, therapeutic gains occur for both heat killing and heat radiosensitization; therefore, a dose modifying factor must be applied to the thermal dose for an equivalent biologic effect. Thus, as for radiation doses, dose modifying factors can be defined for thermal doses.

APPLICATION OF LOCAL HYPERTERMIA TO X-RAY AND CHEMOTHERAPEUTIC AGENTS IN MANAGEMENT OF CUTANEOUS CANCERS

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Well controllable skin tumors may serve as model for evaluating the optimal physical, physiological parameters in the case of combined hypertermia with X-ray and chemotherapeutic procedures. For generating local hypertermia the following techniques have been used so far: contact heating via Peltier-effect, ultrasound in the frequency range of 1 MHz. The local temperature achieved was monitored by noninvasive and invasive techniques to ensure good reproducibility. Local host factors such as intercellular viscosity and matrix stiffness, playing a critical role in tumor development have been studied by histochemical and electronmicroscopic means.
CLINICAL STUDY OF HYPERTHERMIA IN CANCER RADIOTHERAPY.

TUESDAY • AUGUST 26 • AFTERNOON

C-33: THE BIOLOGICAL BASES OF COMBINED USE OF HYPERTHERMIA AND RADIATION IN CANCER TREATMENT

Differentiation program in the respiratory epithelium. Carcinogen exposure elicit the expression of a similar monoclonal and polyclonal antibodies. Similar results were observed in vivo, when tracheas were taken from reversed or prevented epidermoid differentiation and keratinization. Analysis and by immunofluorescence, utilizing various keratin antibodies indicate that the conditions of vitamin A deficiency and culture in a retinoid-free medium, which also elicited the appearance of epidermoid differentiation. Moreover, other acids in the colon and could thus reduce the risk for colon cancer. Three classes of agents that have been identified as possibly important are: fecal steroids and lipid acids in solution. Results from international, case-control and intervention studies are being used to assess the importance of each of these hypotheses. Sharply defined etiologies are being used to assess the importance of each of these hypotheses. 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Sharply defined etiologies are being used to assess the importance of each of these hypotheses. Sharp
INTERVENTION TRIALS WITH CAROTENOIDS ON SNUFF DIPPERS, INTESTINAL CHEMOPREVENTION, AND REVERSE SMOKERS

H.P. Stich, M.P. Rosin and A.P. Hornby, Environmental Carcinogenesis Unit, British Columbia Cancer Research Centre, Vancouver, B.C., Canada

The trials were designed to test, within a short time interval, the efficacy of the oral administration of vitamin A, carotenoids with beta-carotene, apo-carotenal or without (canthaxanthin) provitamin activities, and their combinations to prevent oral preneoplastic lesions in individuals at elevated risk for oral cancer. The selected population groups included snuff dippers (Inuits of Canada), betel quid chewers (Iligapo of the Philippines), and "reverse" smokers (Philippines of Mindoro). Their beta-carotene levels in the oral mucosa and retinol levels in the sera differed significantly among the three groups who had diverse dietary patterns. The increase of beta-carotene, canthaxanthin and retinol levels in exfoliated cells of the oral mucosa can be used to monitor the accumulation of protective agents in the target tissues prior to, during and after a treatment period. The elevation of beta-carotene in the oral mucosa during treatment is strongly affected by diet, the concurrent intake of vitamin A and beta-carotene, and by "individual" factors. The considerable variation in the increase of beta-carotene in the target tissue must be considered when assessing the outcome of a chemoprevention trial. The response to the various treatments was monitored by estimating the frequency of exfoliated cells with micronuclei and karyorrhexis, levels of DNA adducts in the oral mucosa, and changes in size of leukoplakia or stomatitis nicotinae.

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The success or failure to respond to the 10- or 16-week administration of carotenoids and vitamin A will be presented. Attempts will be made to base future treatment protocols on results obtained from in vitro models which appear to be suitable for selecting the optimal protective doses and the most protective combinations of retinoids and carotenoids. The success of chemopreventive trials on human population groups will depend on whether or not levels of carotenoids which protect in vivo can be obtained in the target tissues of carcinogen-exposed individuals.
D-34: CHEMOPREVENTION OF CANCER

Clinical studies have been performed to examine the ability of retinoids to inhibit the development of chemically-induced tumors. Retinoids, such as all-trans retinoic acid, have been shown to have effects on rodent and human cells, and may have potential for cancer prevention.

In a study by J. Paolella, Pharmaceutical Res., Hoffmann-La Roche Ltd., Basel, Switzerland, the use of retinoids in chemoprevention was explored. Clinical studies have been conducted to examine the ability of retinoids to inhibit the development of chemically-induced tumors in rodents and humans. Retinoids, such as all-trans retinoic acid, have been shown to have effects on rodent and human cells, and may have potential for cancer prevention.

D-35: TRANSFORMATION IN CELL CULTURE

The diversity of results from carcinogen-induced cells in vitro can be explained by the differences in the control mechanisms for susceptibility to malignant transformation. By utilizing protocols developed with animal cells on human fibroblast, we have achieved transformation as reflected by growth in agar, extended life span, and invasion of the subcutaneous brain region of nude mice which resulted in death of the animals. The ultimate objective to develop a reproducible, carcinogenesis model in which human cells are converted to permanent malignant cell lines in a predictable fashion has not yet been reached. Although carcinogens cause various similar deleterious effects on rodent and human cells, only rodent cells can convert to malignancy in a quantitative, predictable fashion. Therefore, the mechanisms controlling indefinite proliferation and tumorigenicity are different. With the Syrian hamster fetal cell model, underlying mechanisms of in vitro neoplastic transformation can be studied using carcinogens that interact with DNA or appear to be an epigenetic effect; dose-dependent transformation and progressively growing tumors result. Therefore, cocarcinogenesis experiments utilizing human cells with diverse carcinogens and virus or viral DNA are underway. Transfer of human foreskin fibroblast (HFF) and MCF7 cells (SH30 transformed; permanent non-tumorigenic fibroblast) with human papilloma virus DNA, HPV-18, resulted in persistent HPV-16 intact DNA sequences and RNA expression. These cells exhibited growth arrest and non-progressive nodules in vitro. HFF with HPV-16 followed by X-irradiation resulted in accelerated appearance of transformed foci which are being assayed for tumorigenicity. Transformation of NIH 3T3 with HPV-16 resulted in progressive development of malignancy with multiple copies of HPV-16 DNA. As with cervical cancer, HPV is primarily integrated into host DNA. Thus, human cells may require further insult to obtain DNA integration and associated tumorigenicity.
Genetic Mechanisms in Cell Transformation

Recent Advances in Cell Culture with Special Emphasis on the Application to Respiratory Oncology.

Cell cultures generally lack various factors belonging to the whole organism. These are for example blood circulation, interaction with different cell or tissue types, hormonal influence and nervous control. Since cell culture techniques provide several advantages over the whole organism systems, there is a good reason for oncologists to try to overcome the shortcomings of such in vivo variables in cell cultures. Moreover, the in vitro reaction of one cell type to hormones, another cell type or a biological matrix is being intensely studied in current cell biology. From these studies done using whole organisms one is quickly becoming aware that almost every carcinogen possesses organ or tissue specificity. This fact rationalizes the growing target organ concept among the cell culture scientists who will develop in vitro cell systems for oncology. Another drawback of cell culture is the rapid loss of differentiated or functional traits after cell liberation. In the study of oncology the most important premise in this connection is the presence of carcinogen metabolizing enzyme systems. Significant improvement in recent cell culture technology is, however, providing us with more and more opportunities to maintain primary to early passage cultures in a certain degree of differentiation and even to induce such state in cultures of low-term established cell lines. The major development of recent cell culture technology consists of the incorporation of hormones, growth and other factors, trace elements and attachment matrices into culturing environment. This has allowed various laboratories to conduct pilot studies in vitro oncology using hepatocytes, renal cells, mammary gland cells, epithelial respiratory tract cells, etc.

Altering of Actin and Actin-Binding Proteins

The role of actin and actin-binding proteins in the cascade of transcription of -actin gene. The hypothesis on how the activation or alteration of protein kinases and transformation. Persisting DNA lesions could result in stable chromosome deletions and translocations. Chromosome banding analysis of Syrian hamster, rat, or guinea pig cells transformed in vitro by chemical carcinogens or oncogenic viruses showed that these chromosome abnormalities are associated with aneuploidy consisting of random or non-random structural and numerical alterations which are not specific for the cell line. Similarly, normal human fibroblasts exposed to carcinogens became aneuploid with structural changes frequently involving chromosome regions where proto-oncogenes are located. Such alterations may be responsible for the prolongation of exponential growth; however, they do not result in malignancy because carcinogen treated cell lines fail to produce progressively growing tumors in nude mice. Therefore, the induction of aneuploidy in human cells can be seen as a step in the process of neoplastic development.

Transformation in Cell Culture

The alteration of actin and actin-binding proteins in the expression of transformed phenotype. It has been found that the function of many oncogenes involves protein kinases and Ca++. However, it is unknown how the activation or alteration of protein kinases and Ca++ leads to the expression of transformed phenotype. Transformed phenotype consists of alteration of cell morphology, cell movement and cell growth. These three cell functions involve cytoskeletal function. Thus, the alterations of actin and actin-binding proteins were examined in relation to the expression of transformed phenotype.

The Role of Alteration of Actin and Actin-Binding Proteins in the Expression of Transformed Phenotype
MULTISTAGE IN VITRO TRANSFORMATION OF HUMAN AND RAT UROTHELIAL CELLS

J. Kieler and B. Christensen
The Fiebig Institute, Copenhagen, Denmark

In an attempt to reproduce experimentally the three grades of transformation (TGrI-III) described in cultures of human urothelial cells (B. Christensen et al. - Anticancer Res. 4: 319-330, 1984) the in vitro transformation of embryonic rat bladder cells was studied by the following models: 1) Pretreatment in utero with ethylnitrosourea (ENU) and subsequent implantation and propagation in vitro. 2) Treatment in primary culture with ENU and subsequent passage in vitro. 3) Treatment in secondary culture with ENU and continuous passage in vitro. Parameters under investigation include cell morphology, growth pattern, life span, invasiveness, tumorigenicity, and antigenic modifications. Comparisons are made to the characteristics of human urothelial cell lines classified as TGrI-TGrIII.

G-33: VIRUS INDUCED IMMUNOSUPPRESSION

Herman Friedman, University of South Florida College of Medicine, Tampa, FL, USA

Since the early reports of van Pirquet the beginning of this century that children with measles develop a lifelong hypersensitivity, it has been widely recognized that many viral infections induce an immunosuppression. Studies in a number of laboratories have shown that leukemic viruses, including the retrovirus now known as leukemia, are important modulators of immunity and cause dysfunctions of both T and B cell responses, as well as macrophage function. The current knowledge that acquired immunoodeficiency in man is related to infection by a human T cell lymphotropic virus (i.e., the FHLYV3-LAV virus) has stimulated interest in virus induced immunosuppression.

The important role virus-induced immunosuppression may play in oncogenesis is dramatically illustrated by the opportunistic tumors that develop in patients with AIDS. Furthermore, infection by oncogenic retroviruses is often associated with depressed immunocompetence and there are indications that such effect not only results in increased susceptibility to secondary pathogens but also facilitates the oncogenic potential of the infecting virus by allowing tumors to escape host defenses. Despite obvious interest, the mechanisms by which oncoviruses suppress immune reactivity remain largely speculative.

ROLE OF INTERLEUKINS 1 AND 2 IN IMMUNOSUPPRESSION BY VIRUSES OF THE FRIEND LEUKEMIA COMPLEX. Benedinielli M., Lopez-Cepero M., Matteucci P., Giangregorio A.M., Conaldi P.G., Specter S., Friedman M., Sti, Epidemiol., Hygiene and Virol., Univ. of Pisa, Italy, and Univ. of South Florida College of Med., Tampa, Florida, USA.

The important role virus-induced immunosuppression may play in oncogenesis is dramatically illustrated by the opportunistic tumors that develop in patients with AIDS. Furthermore, infection by oncogenic retroviruses is often associated with depressed immunocompetence and there are indications that such effect not only results in increased susceptibility to secondary pathogens but also facilitates the oncogenic potential of the infecting virus by allowing tumors to escape host defenses. Despite obvious interest, the mechanisms by which oncoviruses suppress immune reactivity remain largely speculative.

D-35: TRANSFORMATION IN CELL CULTURE

USE OF A MODIFIED SOFT AGAR TECHNIQUE FOR EVALUATION OF TRANSFORMATION OF RODENT FIBROBLASTS BY ONCOGENES AND CHEMICAL CARCINOGENS.

J. Ehm, J. Denner, B. Friedes, R. Jandrig

In vitro cell transformation can be evaluated by focus formation, colony formation in soft agar or in vitro growth of anchorage-independent cells in nude mice. A modification of a soft agar method using only one phase soft agar (0.15 % agar, Dulbecco's agarose) and in situ transformation in irradiated culture tubes has been used in our experiments. In spite of similar results in colony formation as compared to the common two-phase technique in petri dishes the advantages of the one-phase technique are: (1) co-incubation is not necessary, (2) no additional feeding and hence, less probability of contamination, (3) long-term culturing is possible. Established and normal rat or mouse cells have been transformed by oncoproteins (see Denner, J., et al.) or chemical carcinogens. 3-methylcholanthrene and 4-nitroquinoline-N-oxide have been used at previously determined optimal concentrations. Cells have been treated in monolayer culture and transferred after different incubation times into the soft agar. Oncogene-transformed cells, established cell lines from transformed foci, cultured cells from tumors of transformed animals and chemically transformed cells produced colonies with different colony forming efficiency (CFU). CFUs have been correlated to proliferation rates and expression of the oncoproteins rae and myc. In addition, single colonies have been isolated, propagated and investigated in appropriate tests.
3271 VIRAL PERTURBATION OF PHAGOCYTE FUNCTIONS.
Søren C. Mogensen, Institute of Medical Microbiology, University of Aarhus, Aarhus, Denmark.
Phagocytic cells belonging to the mononuclear phagocyte system (mononuclear and macrophages) and the myeloid cell line (polymorphonuclear leucocytes) are important elements in the defence against infections and malignancy. Viruses, being intracellular parasites, might interfere with the function of these cells, with two obvious consequences. First, it may interfere with the virus infection in question because the virus has obtained a survival advantage by being able to evade a host defence mechanism. For instance, the ability of a virus to replicate productively in cells constituting the macrophage barrier in various organs is often correlated with the ability of the virus to establish an infection or to disseminate in that organ. Second, virus interference with phagocyte functions may pave the way for secondary microbial infections and putatively also lower resistance to development of malignancy. Thus, it has been shown that a number of viruses in situ clearance of microorganisms as well as phagocytes and chemotaxis in vitro. Finally, examples of viral interference with the accessory function of macrophages in immune regulation will be given.

3272 THE CAUSATIVE VIRUS AND PATHOGENESIS OF AIDS.
J.G. Sinkovits, F. Gyorkey, J.L. Melnick and Phyllis Gyorkey, Veterans Administration Medical Center and Department of Virology and Epidemiology, Baylor College of Medicine, Houston, Texas. Community Cancer Center, St. Joseph's Hospital, Tampa, Florida.
Immunosuppression due to the destruction of T4 helper cells by a cytopathogenic retrovirus is the fundamental pathology in acquired immune deficiency syndrome (AIDS). The pattern of infectious complications suggested to us monocyte-macrophage defects. We found replicating retroviruses in monocyte-macrophages of AIDS patients (Lancet 1:106, 1983), in both normal and transformed (Kaposi sarcoma) vascular endothelial cells (New Engl J Med 311:1183, 1984), in megakaryocytes (with platelet carrying the virus) and in brain cells (astrocytes and glia cells) (Gyorkey et al: J Inn Dis 1986, in press). Since Epstein-Barr virus-infected B lymphocytes can be superinfected with the AIDS retrovirus LAV in vitro (Science 225:63, 1983), we presume that such infection also occurs in vivo. "Autoimmunity" directed against retrovirus-replicating host cells results in hypergammaglobulinemia, production of cytotoxic antilymphocyte antibodies, vasculitis and immune complex deposition in glomeruli; thrombocytopenia; and encephalitis. Faulty acid gammaglobulinemia, production of cytotoxic antilymphocyte antibodies, vasculitis and immune complex deposition in glomeruli; thrombocytopenia; and encephalitis.

3273 VIRUSES, ALLERGY AND THE IMMUNE RESPONSE.
A. Szentiványi, Tampa, USA.
G-33: VIRUS INDUCED IMMUNOSUPPRESSION

3274 HIGH AND LOW LEUKEMOCENIC VARIANTS OF THE RADIATION LEUKEMIA VIRUS (RadLV): IMMUNOGENIC, SUPPRESSOGENIC AND GENETIC PROPERTIES IN RELATION TO LEUKEMOCENIC ACTIVITY.
Yefenof, E., Kotler, M. and Ben-David, Y., Dept. of Immunology, The Hebrew University Hadassah Medical School, Jerusalem, Israel.
Since Epstein-Barr virus-infected B lymphocytes can be superinfected with the highly leukemogenic Radiation Leukemia Virus (A-RadLV) develop virus specific suppressor T cells (Ts) that sustain the leukemogenic process by interfering with a potential anti-virus-tumor immunity. A low leukemogenic RadLV variant (D-RadLV) does not induce Ts cells and therefore leukemia progression is arrested due to immune surveillance.
Recently we were able to isolate RadLV's with different tropism and found that a B-tropic virus in the D-RadLV extract is low leukemogenic and immunogenic. A-RadLV contains a B trophic virus similar to that isolated from D-RadLV. An additional thymotropic virus could be isolated from A-RadLV which was highly leukemogenic and suppressogenic. RNA fingerprint analysis suggests that the highly leukemogenic, thymotropic RadLV is a product of a recombinational event between B- and X-tropic endogenous viral genomes. This recombinant virus could have been selected for an increased affinity to T lymphocyte infection/transformation and for expression of novel suppressogenic epitopes which convert it to highly leukemogenic in the natural host strain.
THE NECESSITY FOR BIOCHEMICAL MODULATION OF ANTI-CANCER DRUGS. Daniel S Martin, M.D. Memorial Sloan Kettering Cancer Center, New York, New York, U.S.A. and The Catholic Medical Center of Brooklyn and Queens, Inc. Woodhaven, New York, U.S.A. [II] Multiaagent therapy is obligatory for advanced cancers because of cellular heterogeneity, but empirically-derived drug combinations have had little-to-mo nueutivc impact against the common solid cancers. Although the discovery of new agents would be desirable, it seems improbable that a "magic bullet" drug capable of simply overcoming the heterogeneity problem can be found. Thus, whether with agents new or old, a more rational approach (termed biochemical modulation) to extend the effectiveness of each antineuro agent in a combination is desirable; indeed, there is, as will be explained, a practical necessity for biochemical modulation of anticancer agents. However, although biochemical modulation has demonstrably enhanced preclinical chemotherapeutic responses, its potential to expedite the attainment of additional chemo- therapeutic advance in the clinic has yet to be demonstra- ted clearly. The reason for the failure to attain clear evidence of clinical advance is the failure to translate properly relevant preclinical parameters of therapy into the design of clinical protocols involving biochemical modulation. Drug sequence, the timing between drugs, the selection of the dose of each agent, the dosage ratios of drugs in combination, and the schedule of administration, based on appropriate cellular biochemical and pharmacological measurements, are all important. The mistakes that have been made in the past will be discussed, along with the appropriate changes that should permit therapeutic advance with biochemical modulation in the clinic. Specific biochemical modulation findings will be presented employing various combinations of the following compounds: PALA, methotrexate, 5-fluorouracil, 6-methylmercaptopurine riboside, 5-aminocvitabain, mitomycin-C, host rescue agents (e.g., uridine for 5-FU), and host protection agents (e.g., interferon).

CORRELATION OF DRUG EFFECT WITH ENZYMATIV CHANGES IN FUNCTION OF TUMOR GROWTH. L. Hullan, K. Szikla and L. Holczi National Institute of Oncology, Budapest, Hungary. Specific activities of thymidate kinasr (TK) and thymidylate synthetase (TS) were found to be in direct opposition during the proliferation of different experimental tumors growing in vivo. The highest TK activities coincided with the early logarithmic phase of tumor growth, while peaks of TS activities occurred in the last period of their proliferation before the stationary phase. Investigating the effect of antimetabolites (methotrexate, 5-fluorouracil) in function of tumor growth considerable differences in cytotoxicity occurred. Correlation was found, especially in case of methotrexate, between the drug effect and the activity ratios of TK/TS. The highest cell kill coincided with the TS peak when TK/TS ratio was on its minimum. The results suggested that deoxythymidylic acid (dTMP) was synthesized mainly by the salvage pathway of dTMP biosynthesis in the logarithmic growth phase. The role of de novo biosynthesis in supply of the essential precursor for DNA synthesis seemed to be increased in the last period of cell proliferation. This conclusion was supported by the observation that the cytotoxic effect of drugs targeting TS correlated with the TK/TS activity ratios. The fact that different degree of cell kill was obtained by treating tumors with these antimetabolites at different phases of growth might have practical importance.


INFLUENCE OF DRUG BINDING AND GTP ON THE SENSITIVITY

TUESDAY • AUGUST 26 • AFTERNOON

BASIS FOR THERAPEUTIC SELECTIVITY OF FLUOROPYRIMIDINES IN COMBINATION WITH CI-965

Y.P. Rustum, Grace Cancer Drug Center, Roswell Park
Memorial Institute, Buffalo, NY, 14263.

Fura + dCF was antiproliferative and produced effect following metabolic activation to various nucleotides. 5-Fluoro-
uridine triphosphate (FUTP), due to its resemblance with uridine triphosphate (UTP), is incorporated into RNA, the consequence of which is increased production of fraudulent mRNA, RNA and DNA which can ultimately cause cell death. The other proposed mechanism for Fura cytotoxicity is the inhibition of thymidylate synthase (dTMP-S) by 5-fluorodeoxyuridine monophosphate (FUMP), leading to decreased thymidine triphosphate (dTMP) pools and then inhibition of DNA synthesis. The biochemical mechanism by which FUMP binds to the dTMP-S involves a cofactor, N5,N10-methylenetetrahydrofolic acid (N5,N10-MTHF). In absence of the reduced folic cofactor, FUMP binding to dTMP-S is relatively weak, with a Ks of about 105M.

With respect to Fura, there are several substances which can theoretically modulate its activity. (I) Thymidine (dThd) when administered concurrently with Fura, results in reduction of inhibition of DNA synthesis, due to bypass of FUMP-inhibited dTMP synthesis. The exogenous administration of dThd will direct Fura metabolism towards incorporation into RNA. Under these conditions, the antitumor activity and toxicity of Fura against some murine solid tumors was increased. (II) With exogenous administration of high dose FdUMP, the action of Fura was shifted from RNA to a more pronounced and prolonged inhibition of thymidylate synthase activity and cell toxicity, while maintaining the growth inhibitory effect of Fura in human adenocarcinoma Hep-2 cells.

In this presentation, a metabolic modulation of Fura by dThd on dCF that could offer the possibility of increasing the therapeutic efficacy of Fura in experimental systems and in patients with advanced colorectal carcinoma will be discussed. Biochemical and pharmacological results of such modulation will be discussed.

3284 BIOSYNTHETIC PATHWAY INVOLVEMENT IN DRUG EFFICACY

The incorporation of 5-FU into DNA and the synthesis of thymidylate is necessary for Fura metabolism in certain cell lines. In these cells, the rate of Fura accumulation was dependent on the presence of RNA. In addition, the stability of Fura metabolites was also RNA-dependent. After removal of exogenous RNA by gel filtration, complex formation was not observed in DNA isolated from the cell lines. These results indicate the presence of a mechanism that controls the inhibitory action of Fura. A possible explanation is that Fura is incorporated into DNA and the effect of Fura is RNA-dependent. The third possibility is that Fura is incorporated into DNA that causes abnormal RNA metabolism. To elucidate among the three possibilities, we used a mouse tumor cell line, and demonstrated through normal RNA metabolism. To determine among the 3 possibilities, we used a mouse tumor cell lines. The effect of Fura on the incorporation of 5-FU into DNA and RNA was observed in both cell lines. The results showed that Fura enhanced and inhibited incorporation into DNA and RNA, respectively. The effect of Fura on thymidine metabolism is shown in Table 1. The incorporation of 5-FU into DNA and RNA was observed in both cell lines. These results indicate that Fura is incorporated into DNA and RNA and that Fura enhances incorporation into DNA and RNA.

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During the several-month therapy, no stagnation or regression of the course of the disease was observed in the majority of the patients. Therapy was not accompanied by any side-effects necessitating the cessation of treatment. Low doses achieve a more complete blockade of androgen action, with a substantial decrease in the levels of testosterone and dihydrotestosterone. In contrast, the T/SHBG ratio decreased considerably in response to treatment for only 3-4 days, and after treatment for several months the levels remained at about one-third of the starting values. The binding capacity of SHBG did not behave similarly; it remained at a low level up to the end of the therapy. The therapy was not accompanied by any side-effects necessitating the cessation of treatment. During the severe-month therapy, stagnation or regression of the course of the disease was observed in the majority of the patients.
ANDROGEN METABOLISM AND RECEPTORS IN THE PROSTATE: EFFECTS OF 5a-REDUCTASE INHIBITORS. M. Notta, S. Scopi and G. Fig- relli. Dept. of Endocrinology, University of Milano, Italy.

The prostate of the rat is able to convert testosterone (T) into dihydrotestosterone (DHT). 5a-androstan-3β,17β-diol (3-diol) and 5a-androstan-3,17β-diol (38-diol). These conversions occur under the influence of a 5a-reductase-3 hydroysteroid dehydrogenase system. Similarly the human pros tate forms great amounts of DHT and 38-diol. High tissue concentrations of DHT and an elevated activity of the 5a-reductase are characteristics of benign prostatic hypertrophy (BPH). In the light of these observations, the effects of two molecules, 4-hydroxy-4-androsten-3β,17β-dione (4-Oh-A) and 17β-4-hydroxy-4-androsten-17β-dione (4-Oh-D) on the prostatic enzymes involved in the transformation of T into its 5a-reduced metabolites have been investigated "in vitro". Both normal rat prostate and human BPH tissue have been considered. When either 4-Oh-A or 4-Oh-D are added at different concentrations of the substrate, but more additional suppression of the adrenal androgen receptors, the classes of 5a-reductase inhibitors might represent a new therapeutic approach for the treatment of BPH. (Supported by C.N.R. contracts n.5.4.95/75 and n.5.2.774/44.)

3294


Adrenal androgens are assumed to be involved in the development of benign and malignant prostatic tumours, whereby epithelium and stroma of the prostate are able to form active androgens from less potent precursors. In this context we were interested in whether epithelial and stromal are able to form active androgens from less potent precursors. The results of our studies show that the importance of the androgen, after such an epithelium may play an important role in prostate cancer. An additional study on adrenal androgen metabolism was designed to determine the effects of the 

3293


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3296 COMPARISON OF VARIOUS ANDROGEN BLOCKING REGIMENS ON TISSUE DISTRIBUTION AND EFFECTS ON TISSUE DISTRIBUTE PROSTATE.

J. Geller, J.D. Albert and W. Fay

DHT is the major stimulus to growth of prostate epithelial cells. All androgen regimens in regard to ability to lower prostate DHT since such a comparison would provide a basis for the best rational therapy in metastatic prostate cancer. Patients (n = 46) were randomized to receive 3 doses of Zoladex: 3.6, 1.8 or 0.9 mg/28 days, equivalent to a daily release of 120, 60 or 30 µg, respectively. The drug consists of a cylindrical rod containing 50:50 lactide-glycolide co-polymer into which Zoladex is incorporated and is administered s.c. Serum LH concentrations increased within one day of initial injection and decreased thereafter. Following subsequent administration of Zoladex, LH levels remained low showing complete pituitary desensitization. Serum testosterone also increased within 5 days of injection, then declined reaching castrate values of <2 nmol/L between 15-22 days in all patients with the exception of one, on 0.9 mg of Zoladex, whose levels remained above 2 nmol/L after one month. The mean reduction in serum acid phosphatase values was 60% after 6 months. Depo Zoladex is therefore effective in producing medical castration at doses of 3.6 or 1.8 mg with minimal side effects. This paper also presents findings of a randomized clinical trial to compare the efficacy of safety of orchidectomy with that of Zoladex in the treatment of histologically proven metastatic prostate cancer. Patients (360) have been recruited from 16 centres in the UK, and were entered into the trial between Oct. 1984 and Dec. 1985. They were randomized to either orchidectomy (total or subcapsular) or Zoladex every 28 days by s.c. injection. Data indicates that the effect of Zoladex is comparable to orchidectomy with regard to (a) plasma testosterone levels. (b) primary tumour response, (c) plasma PAP, (d) activity scores, and this paper provides an interim analysis of subjective and objective response rate, time to response, tolerance to treatment, and a comparison of the long-term endocrine effects of both methods of treatment.
3298 AN OVERVIEW OF LABORATORY INVESTIGATIONS TO ASSESS THE ROLE OF OCHRATOXIN A IN ENDEMIC NEPHROPATHY AND URINARY TRACT TUMOURS

M. Castiglioni1, T. Petkova2, E. Hietanen1, C. Malaveille2, H. Bartsch1, I.N. Chernozeemsky2, N. Dai1

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2Institute of Oncology, Medical Academy, Sofia 56, Bulgaria

Balkan endemic nephropathy is a fatal disease affecting inhabitants of rural areas of Bulgaria, Romania and Yugoslavia. Its etiology so far, remains unknown. A large number of patients with this condition develop tumours of the urinary system, and because of some alleged similarities of this disease to ochratoxin A (OTA) induced porcine nephropathy, attempts have been made to elucidate a possible causal role of this mycotoxin in the human condition.

Studies to measure exposure levels of OTA in humans and results from mechanistic studies on OTA in experimental animals (in collaboration with the Institute of Oncology in Sofia) will be presented.

3300 POSSIBLE CONNECTION BETWEEN EXPOSURE TO OCHRATOXIN A AND ETIOLOGY OF BALKAN ENDEMIC NEPHROPATHY

R. Plastina, Institute for Medical Research and Occupational Health, Zagreb, Yugoslavia

Numerous studies have been directed towards clarifying the etiology of Balkan Endemic Nephropathy (BEN), but most of them have been unrewarding. At present many authors agree that a causative agent comes from the environment. A number of well or less known nephrotoxic agents were considered in the past, but very few gained sufficient toxicological and epidemiological support and were gradually abandoned. In recent years a mycotoxic hypothesis has been receiving increasing attention. Ochratoxin A, a potent nephrotoxic agent capable of causing nephropathy in all animal species tested so far, is being placed into focus for studies designed to prove or disprove the mycotoxic hypothesis. In the meantime it has become suspect as a carcinogen. Ochratoxin A has been found in human food and animal feed samples collected in the endemic area and recently also in human blood. So far over 10 000 samples of blood taken during several years from inhabitants of an endemic area in Yugoslavia have been analysed for this compound. A great number of positive samples (approximately 3%) contained only small amounts (less than 30 ng/ml) of ochratoxin A, the highest concentration encountered being 1900 ng/ml. Both the concentration and the incidence of positive samples vary from year to year and from season to season. Ochratoxin A binds to serum albumins and more specifically to unidentified serum macromolecules of around 70 000 Dalton, the association constant being around $10^5$. These molecules carrying ochratoxin A can easily pass through an unaltered glomerular barrier and become pinocytosed by tubular cells, enabling accumulation of ochratoxin A into the kidney. The known effects of ochratoxin A on protein synthesis may Cooperate with the diseases in the affected kidney. Also, they are not in disagreement with some other health disturbances observed in patients suffering from Balkan endemic nephropathy.

3299 EPIDEMIOLOGY OF URINARY TRACT TUMOURS IN AN AREA WITH BALKAN ENDEMIC NEPHROPATHY


Urinary tract tumours (UTT) were the leading cancer site in the villages with Balkan endemic nephropathy (BEN) of Vratza District, Bulgaria where they accounted for 25-30% of all cancers. The age-adjusted incidence of kidney neoplasms and UTT in hyperendemic villages approximated 104/105 in females and 89/105 in males, affecting in particular renal pelvis and ureter. The relative risk towards development of such tumour sites in patients with BEN was nearly 90 fold higher than in people from non-endemic villages. UTT were often multiple and nearly 90% of them originated in the uro-epithelium. Both BEN and UTT attacked mainly women and middle-aged persons and displayed peculiar clustering in certain groups of villages and households, among all patients with UTT nephropathy was reported in nearly 50% of the cases. A moderate decline in incidence of BEN and UTT was observed during the studied period 1965-1982 but this might well be a registration phenomenon. A tendency towards expansive spread of these diseases resulted in gradual affection of new households and villages. Heavy metals, radiation, mycotoxins, viruses and hereditary factors were alleged as etiological factors for BEN but no firm epidemiological relationship or other proof for such hypotheses were presented so far.

3301 EXPERIMENTAL PROLIFERATIVE MODIFICATIONS OF THE RENAL PELVIS EPITHELIUM INDUCED BY TOTAL CHLOROFORMIC EXTRACT FROM THE SOIL OF AN ENDEMIC NEPHROPATHY AREA

E. Bordas, Edit Bretter, Inst. of Hygiene and Public Health, UIU, Cluj-Napoca, Romania

The total chloroformic extract from soil of the aquifer underground of an endemic nephropathy area has been injected into the renal pelvis of Wistar rats, in dose of 7.0 mg/animal/day. After 50 days, all the animals presented lesions of renal parenchyma, consisting in dilatation and distortion of the contort tubes and in lymphocytic periglomerular and peritubular infiltrations. An infiltration of the renal pelvis epithelium has also been noticed. Besides the above mentioned modifications, papillomatous formations or circumscribed proliferations of the renal pelvis epithelium appeared in the injected kidney of 30% of the animals, in 10% of cases, these phenomena also took place in the contralateral kidney. The results of our experiment agree with the epidemiologic observations that have emphasised the high frequency of the tumours of the urinary duct in subjects inhabiting the endemic nephropathy area.
MYCOTOXIC PULMONARY NECTROPATHY: R. Krogh, Department of Microbiology, Royal Dental College, Copenhagen, Denmark.

Mycotoxic porcine nephropathy (MPN) is a chronic renal disease, characterized by atrophy of the proximal tubule, interstitial fibrosis in cortex and hyalinization of glomeruli in advanced cases. The morphological changes are accompanied by impairment of proximal tubular function, indicated by a decrease of the GFR, of the ability to concentrate urine and increased urinary excretion of glucose, L-Ala and protein. Ochratoxin A (OA) is a major disease determinant, but also other nephrotoxic mycotoxins may be causally involved, such as citrinin and the fungal quinones, xanthomomycin and violomellin. An activity decrease of the renal enzymes phosphoenolpyruvate carboxykinase and γ-glutamyl transpeptidase is a specific and early indication of OA-induced MPN, and may be a useful diagnostic tool in human nephropathy thought to be associated with OA exposure, such as Balkan endemic nephropathy.

CONCIPIM OF POOR AND EXTENSIVE METABOLIZERS. J.G.N. Kolav, Oncogene Lab., Sofia, Bulgaria

Balkan endemic nephropathy (HEN) is a chronic and fatal kidney disease. Urinary tract tumours (UTT) have been found in very high incidence in the same endemic regions. Most of the environmental carcinogens elicited the effect only after metabolism by cytochrome-p450 dependent monooxigenases. An individual's capacity for metabolic oxidation can thus be a determinant of certain carcinogenesis. The oxidation status of more than 85% of the population groups were tested for the presence of ochratoxin A metabolites. Since some mycotoxins require oxidation by cytochrome-p450 dependent monooxigenases, a correlation with OA exposure could be found. The morphological changes are accompanied by impairment of proximal tubular function, indicated by a decrease of the GFR, of the ability to concentrate urine and increased urinary excretion of glucose, L-Ala and protein. Ochratoxin A (OA) is a major disease determinant, but also other nephrotoxic mycotoxins may be causally involved, such as citrinin and the fungal quinones, xanthomomycin and violomellin. An activity decrease of the renal enzymes phosphoenolpyruvate carboxykinase and γ-glutamyl transpeptidase is a specific and early indication of OA-induced MPN, and may be a useful diagnostic tool in human nephropathy thought to be associated with OA exposure, such as Balkan endemic nephropathy (HEN) and Balkan nephropathy-associated carcinoma.

The combination of hydroxylbutyl-butylnitrosamine (OH-BBN) initiated (0.8g per rat in 10 divided doses over 5 weeks) followed by a single dose of BEA caused a progressive proliferation, which at 6 weeks after BEA included foci of dysplasia, at 13 weeks multi-nuclear cells and nodular urothelia outgrowths and flat in situ carcinoma. By 21 weeks nodular and invasive changes were more frequent and prominent, and some bladder tumours were present. There were no bladder or urothelial pathology up to 21 weeks after NO-BBN only [2].

These results support a two-stage induction of the UUC, and offer an animal model system in which to study both the nephrotoxic- and Balkan nephropathy-associated carcinoma.

**ULTRASOUND IN THE DIAGNOSIS OF MALIGNANT TUMOURS**

3306 TUMOUR DIAGNOSIS USING ULTRASOUND GUIDED BIOPSY

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The ultrasonically guided percutaneous fine-needle puncture technique for biopsies of focal lesions in different parenchymal organs nowadays becomes quite indispensable in many clinical situations. This intervention virtually brings without any serious risk on certain minimal precautions allows for safe, easy and precise examination of the dignity of any parenchymal alterations.

Ultrasonic-guided fine-needle biopsy in the abdomen was first described in 1972 (1,2). Since then interest in this method has increased and after thorough evaluation of the problem and we have developed a new method in which the fine needle was introduced into the tissue under continuous sono-graphic guidance and permanent visual control based on the shortest (=vertical) distance from the surface of the body to the lesion.

Meanwhile more than 4000 patients have been punctured for diagnostic reasons, mostly using a fine needle for better evaluation of focal lesions visible in the ultrasound image (3). In between 88% and more than 94% of all cases exact results have been received, specific for the lesion.

In some rare conditions, mainly in biopsies of the liver, pancreas, and kidneys, the combination of ultrasonic control and following X-ray examination of the bile or urinary system is a further application of the method.


3307 ULTRASOUND IN THE EPIPHYSIS OF PEDiatric Tumors


High resolution real-time ultrasound proved to be a very sensitive and accurate method in the detection of malignant and benign tumors in infants and children. Ultrasound can help in the initial diagnosis and staging of tumors, vascularity, during treatment and in the regular follow up of the patients.

The malignant and benign tumors of the child- ren have a variable ultrasonic appearance, therefore histopathological prediction seems to be hazardous. Still, in the most common types of abdominal and retroperitoneal tumors (Wilms' tumour, neuroblastoma, malignant lymphomas, primary and metastatic liver tumors), echography became a basic study. In the majority of the cases, a careful analysis of the ultrasonic signs (tumor boundaries and echogeneity, necrotic areas, calcification etc.) provides an accurate differentiation between these conditions.

3308 ULTRASONIC INVESTIGATION OF THE BREAST FOR THE DETECTION OF SOLID LESIONS

H. Koppoff, and T. G. Neve, *Ultrasonics Institute, Sydney, Australia. **The Royal North Shore Hospital, Sydney, Australia.

The use of ultrasound has become an accepted technique in the assessment of breast disease and provides clinicians with diagnostic information on tumor morphology. In some clearly demonstrate the constituent tissues and the presence of pathology can be recognized in the early stages of development. The detection and diagnosis of solid lesions has become recently enhanced by the ability to recognize the presence of both primary and secondary features in the ultrasound images. The diagnostic features are best displayed by using a dedicated water bath scanner which allows the whole breast to be examined freely and also allows the acquisition of both simple and compound images. Physical compression in many instances assists in differentiating between areas of fatty tissue and solid lesions and this facility reduces significantly the number of false positive lesions. In a series of 946 symptomatic patients with solid lesions, examined over a three year period, the sensitivity for detecting cancers less than 3 cm in size was 98% whilst the overall specificity was 94%. Additional diagnostic information is available by the assessment of tissue vascularity. Blood flow as associated with lesions, neo-vascularisation and this can be detected with Doppler ultrasound. The Doppler equipment has been incorporated into an ultrasonic scanner so that patients can be immediately assessed for tissue vascularity when the displayed image does not contain sufficient information to make a reliable diagnosis.

The blood flow is different between benign and malignant lesions and this characteristic when used together with the primary and secondary features enables a more accurate evaluation of the symptomatic patient.


3309 ULTRASOUND GUIDED PROCEDURES IN TUMORS OF THE BILIARY TREE AND PANKREATOS. G. Casola, University of California in San Diego, California, U.S.A.

The advent of ultrasound has revolutionized diagnostic imaging and has become an integral part of both the diagnostic workup and therapeutic management of many disease entities. In the past ten years there has been a dramatic increase in the use of ultrasound for diagnostic procedures involving the biliary tree that have been made possible by the use of ultrasound guidance. These include percutaneous needle biopsy, percutaneous biliary drainage and cholecystectomy, percutaneous myocardial cryodestruction, and most recently ultrasound-guided percutaneous biopsy. Percutaneous biopsies are usually performed with 22-gauge needles which permit histologic evaluation of malignancy. Recently, 22-gauge needles such as the Sure-cut needle have been used. Percutaneous fine-needle aspiration biopsy of the liver, biliary tree, and pancreas has become an essential tool in the management of patients with resectable malignancy. Percutaneous biliary drainage has been enabled by decompression of the obstructed bile ducts, thus avoiding bypass surgery in patients with unresectable malignancy. Percutaneous biliary drainage is performed using combined anesthetic and fluoroscopic guidance. Ultrasound is used to direct a 22-gauge needle into a diluted bile duct; this is followed by contrast injection of the biliary tree with fluoroscopy in order to identify the extent of tumor invasion. Following this an 8 French or 10 French biliary drainage catheter is inserted via a transhepatic approach; the catheter should bypass the obstruction and terminate in the duodenum (internal drainage). In 20 percent of cases the catheter cannot bypass the tumor and only external drainage can be achieved. This is less than ideal since the daily loss of bile may lead to electrolyte imbalances. Percutaneous transhepatic biliary catheterization is a more recent development for bile duct tumors.

In addition, percutaneous biliary drainage has enabled decompression of the obstructed bile ducts, thus avoiding bypass surgery in patients with unresectable malignancy. Percutaneous biliary drainage is performed using combined anesthetic and fluoroscopic guidance. Ultrasound is used to direct a 22-gauge needle into a dilated bile duct; this is followed by contrast injection of the biliary tree with fluoroscopy in order to identify the extent of tumor invasion. Following this an 8 French or 10 French biliary drainage catheter is inserted via a transhepatic approach; the catheter should bypass the obstruction and terminate in the duodenum (internal drainage). In 20 percent of cases the catheter cannot bypass the tumor and only external drainage can be achieved. This is less than ideal since the daily loss of bile may lead to electrolyte imbalances. Percutaneous transhepatic biliary catheterization is a more recent development for bile duct tumors.
3310 INTRAOPERATIVE ULTRASOUNDOGRAPHY IN THE DIAGNOSIS OF LIVER TUMOURS

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In order to assess the usefulness of intraoperative echography (IOE), a comparative study was carried out on 44 patients who underwent surgery for liver tumors (12 hepatocellular carcinomas in cirrhotic livers and 32 metastases from colorectal cancer). All patients had undergone preoperative CT scan and an echography. IOE was carried out with a Toshiba SAL 3b scanner fitted with 5 MHz probes. In patients who underwent liver resection (14 cirrhotics and 20 non cirrhotics) the surgical specimen was scrutinized to detect the exact number of lesions. In our global series of 64 intrapleural lesions observed, IOE visualized 59 of them against 32 at preoperative echography and 43 at CT scan. IOE proved to be more accurate in cirrhotic liver especially for lesions smaller than 1 cm (14.7% for IOE, 68.4% for preoperative echography and 47.6% for CT). Moreover IOE displayed tumoral infiltration of hepatic veins in two patients and thrombosis of the portal branch in three cases. IOE facilitates detection of small hepatic masses and establishes the exact position of the lesion in relation to the intrahepatic venous system, as well as tumoral infiltration or intravascular thrombosis. IOE is particularly useful in patients with tumors arising in cirrhotic liver where computed tomography, magnetic resonance imaging, and positron emission tomography were contraindicated in six cases due to presence of intrapleural satellite nodules, while in seven patients with small primary tumors, not palpable at surgery, a segmentary or subsegmentary hepatic resection was performed.

3311 ULTRASOUNDOGRAPHY AND INTERVENTIONAL ULTRASOUND FOR THE DIAGNOSIS OF CANCER IN UROLOGY

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Recent advances in ultrasonography (US) and interventional ultrasound (IVUS) make it possible to diagnose cancer in urology very accurately. The author will demonstrate various applications of the methods to it in each site respectively.

Prostatic cancer Transrectal US originally developed in our laboratory is now a routine examination for the diagnosis, screening, monitoring or kinetics. Selective biopsy for the prostate is also available by IVU using transrectal electronic linear scanner.

3312 REAL-TIME THERMOGRAPHY OF MALIGNANT SOFT TISSUE TUMOURS.

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Real-time thermography by means of "Thuror" scanner (linear array probe 5 MHz) was performed in 247 patients with palpable soft tissue masses of the extremities and trunk. Histologically malignant tumors were diagnosed in 89 cases, benign tumors in 38, and non-tumoral lesions in 53 cases. Out of 89 malignancies histology and thermography were in agreement in 75 cases, and in 13 patients there were sarcoma recurrences, and 197 patients metastases melanoma, breast cancer. In all cases the mass could be seen by thermography. The minimal size of a primary tumor was 2 cm in diameter and of a recurrent nodule was as to 1 cm. Most tumors were of the deep-seated round, roundish form, and could be easily found on special heating of the body part. Thermoangiography should be considered as a method of choice in conjunction with differential diagnosis of soft tissue tumors. The method is in much more advanced stage of development than soft tissue tomography. Besides, the thermography can be successfully used for differential diagnosis of the primary tumor.

3313 UNMALIGNANT SOFT TISSUE TUMOURS TREATED BY INTERVENTIONAL ULTRASOUND.

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In our treatment of 85 patients with benign soft tissue tumors, including 21 cases of lipoma, 3 of hemangioma, 2 of neurofibroma, 10 of myxoma, 1 of solitary fibrous tumor, 4 of liposarcoma, 17 of well differentiated liposarcoma, 8 of dermatofibroma, 3 of nerve tumor, 2 of myxoid liposarcoma, 2 of xanthoma, 1 of granuloma, and 1 of intramuscular myositis, we used interventional ultrasound to perform selective lesions. The procedure was performed under local anesthesia with the use of a linear US probe of 5 MHz frequency. In patients operated on for lipomas, the lesion was completely excised. In patients treated for myxomas, lesions were excised partially and the remaining part bleomycin was injected directly into the probe. In patients treated for xanthomas, bleomycin was injected directly into the probe. In patients treated for dermatofibromas, bleomycin was injected directly into the probe. In patients treated for nerve tumors, bleomycin was injected directly into the probe. In patients treated for myxoid liposarcomas, bleomycin was injected directly into the probe. In patients treated for xanthomas, bleomycin was injected directly into the probe. In patients treated for dermatofibromas, bleomycin was injected directly into the probe. In patients treated for nerve tumors, bleomycin was injected directly into the probe. In patients treated for myxoid liposarcomas, bleomycin was injected directly into the probe. In patients treated for xanthomas, bleomycin was injected directly into the probe. In patients treated for dermatofibromas, bleomycin was injected directly into the probe. In patients treated for nerve tumors, bleomycin was injected directly into the probe.

References
Several retinoids have been evaluated for prevention of mammary carcinogenesis in rats and mice. Of those which were active, retinyl acetate (RA) and 4-hydroxyphenyl retinamide (HPR) proved most effective. In rats, dietary administration of the retinoids reduced the incidence and number, and increased the latency of N-methyl-N-nitrosourea (MNU)-induced mammary cancers. HPR reduced the number of hyperplastic alveolar nodules (HAN) in MTV mice and the number of tumors in MTV mice. Other studies indicate that the synergistic effect of retinoid administration and hormonal deprivation is more efficacious in prevention of MNU-induced mammary cancer than is either modality alone. Suppression of either the ovarian steroid (ovariectomy) or prolactin (CB-154) levels in combination with retinoids almost completely blocks induction of mammary cancer with MNU. Retinoids alone and the combination of retinoid and either ovariectomy or tamoxifen inhibit the appearance of mammary cancers following the surgical removal of the first cancer. Furthermore, both retinoids and tamoxifen exert a therapeutic effect on the first established cancer. Again, the combined modality was the most effective. Retinoids also exert an anti-proliferative effect on the mammary epithelium in vivo which is represented morphologically by a loose duct system with little branching, end buds, and few, if any, alveoli. In organ culture, retinoids inhibit mammary ductal and end bud proliferation induced by insulin and prolactin, and preneoplastic lesions induced by a carcinogen. These changes in mammary gland morphology are accompanied by a decrease in mammary RNA synthesis both in vivo and in vitro.
The optimal treatment of early breast cancer is still controversial. There is an increasing acceptance that a combination of breast conserving surgery and radiotherapy is a valid therapeutic alternative to conventional mastectomy. Clinical data from retrospective and prospective studies show comparable results in loco-regional control, survival, complications rate and incidence of contralateral breast cancer. The influence of patients' selection, surgical procedures and radiation techniques on outcome results also as a matter of discussion. Meanwhile women's attitude to current treatment policy options is changing. A regional cancer registry in the southern part of the Netherlands (called SNOB region) is monitoring in an area with a population of one million people: incidence, age, stage, referral patterns, treatment strategies and follow-up. We will describe recent trends in the treatment of early breast cancer in the SNOB area. In order to anticipate on the future care of women eligible for breast conserving treatment, we try to estimate the patient load for intra-operative interstitial brachytherapy [I.B.T.], external electron beam boost dose (E.B.B) and intra-operative radiotherapy (I.O.R.T.) in which a single dose electron beam is used for the lumpectomy area before surgical closure. This report presents data on forecasts of breast cancer frequencies for two decades ahead. Since the etiology of breast cancer involves extended latent periods and long lead times are needed for the development and implementation of new breast conserving strategies, the expected patient load and workload for a regional radiotherapy department is estimated based on age specific incidence data and expected demographic changes. The impact of public information on breast cancer screening and the developments in selection criteria by the breast cancer protocol committees are discussed.


Breast Cancer - Adjunct Therapy
R.chapecy, Buenos Aires, Argentina

The hope to manage carcinoma of the breast by enlarged radical surgery did not prove true during the nearly 100 years history of treating these tumors. Since the prognosis of these tumors is not dependend from radical measurements but primary from the stage of the disease, furthermore by cancer information and improved diagnosis, smallest even not palpable carcinomas are treated. The surgical concept of the last 15 years deviated the rigid scheme of treatment. At the 2.Surgical Univ.Clinic we started in 1974 to use the non-ablative procedures in patients with mamma carcinoma under 2 cm diameter, up to now we treated 121 patients. We perform the resection of the tumor with a safety surrounding of 1 cm in the sense of a quadrant resection together with the superjacent skin area and the subjacent fascia of the musculus pectoralis. The axilla is removed till the lower edge of the vena axillaris. All cases received combined telecobalt and electronic postirradiation at the Univ.Clinic of Radiotherapy. 105 patients could be evaluated at a follow-up examination in 1985. In 18 patients local recurrence was observed, which was treated by ablative mamma or second excision, 12 patients developed metastases distant from the primary tumor, 12 patients died during the course of treatment. The results compared with ablative measurements will be discussed.
CHEMOTHERAPY AND HORMONAL THERAPY OF PATIENTS (PTS) WITH METASTATIC BREAST CANCER: THE M.D. ANDERSON HOSPITAL EXPERIENCE. C.M. Hortobagyi and A.U. Buzdar. M.D. Anderson Hospital and Tumor Institute, Houston, Texas 77030.

Combination chemotherapy (CT) with fluorouracil, Adriamycin and cyclophosphamide (FAC) was the first modality of treatment for pts with metastatic breast carcinoma seen at this institution from 1972 to 1978. An overall objective response (OR) rate of 75% was obtained with various modifications of FAC, with 15-35% of pts achieving a clinical complete remission (CR). The median duration of response was 13 months and the median survival (MS) from initiation of therapy, 21 months. Analysis of treatment outcome showed that the overall survival experience closely paralleled the degree of response to initial CT. The MS of pts who achieved a CR was 36 months, for PRs, 24 months, for stable disease 18 months, and for nonresponders 4 months. The utilization of higher doses of chemotherapy improved the OR and CR rate, but did not prolong survival. Using sequential noncross-resistant combinations did not improve either the response rate or the survival. Comparison of the survival experience of 3 cohorts of pts treated in the 1950s, 60s and 70s revealed a substantial increase in MS and a higher fraction of long-term survivors during the 1970s, a difference attributed to the systematic use of combination CT. The simultaneous use of hormonal and CT since 1978 has resulted in a minimal increase in response rate and remission duration without affecting survival. The development of tamoxifen, megestrol acetate and aminogluthetimide, hormonal agents with a better benefit/risk ratio than previously available therapies, has given new life to hormone therapy.

The use of central venous catheter has solved problems related to venous access, and the appearance of portable infusion pumps allowed the evaluation of different schedule of administration, especially continuous infusion (CI) programs. Modifications in the schedule of administration of CT have resulted in a substantial decrease in morbidity and toxicity. FAC given by CI resulted in marked reduction in nausea/vomiting and cardiotoxicity when compared to FAC by bolus.

IMMEDIATE RECONSTRUCTION AFTER MASTECTOMY FOR BREAST CANCER R. Miller, R.A. Wolz, R. Calleis, Dept. of Gynecology, University of Essen, Essen, West-Germany.

The diagnosis of breast cancer is for most women a devastating experience, not only because of the confrontation with malignancy but also because of the mutilating treatment. An alternative to breast conserving therapy with additional radiation is the mastectomy with immediate reconstruction. We report on 20 patients, median age 46 years, treated between July 1984 and September 1985 for invasive breast cancer stage I-2, N1-2, M0 with simple mastectomy, axillary clearance and immediate reconstruction using a submuscularly placed Radiescher tissue expander. The expander was inflated over a period of 5 to 6 weeks. After 8 to 12 weeks it was removed and replaced by a permanent silicon implant about 1/3 of the largest expansion volume. At the same time reconstruction of the areola-nipple-complex was performed as well as an adjustment of the contralateral breast by augmentation, mastopexy, reduction or, if other risk factors were present, subcutaneous mastectomy. The speed of inflation has adapted to individual tissue tolerance. If tolerated by the patient the expander should be left in place 3 months to ensure stabilisation of the fibrous capsule. An adequate breast volume can be achieved, however, there is a certain lack of projection typical of the abdominal advancement technique. 6 patients received adjuvant chemotherapy over a period of 6 months. No adverse effect was noted on progress and result of the reconstruction. Questionaires concerning the attitude towards disease and treatment, physical complaints and social relations were answered by the patients and compared to answers by women who had undergone breast conserving treatment or mastectomy without reconstruction. Although nearly half of the patients felt that their disease was somewhat advanced at the time of diagnosis, all felt more optimistic about it because immediate reconstruction was performed and had less psychosomatic complaints.
HAS THE PROGNOSIS OF BRONCHIAL CARCINOMA CHANGED DURING THE PAST 30 YEARS? H. Denck, Head, First Surgical Department, Vienna City Hospital, Vienna, Austria

Success rates in bronchial carcinoma have only slightly increased in recent years, in the USA for instance from 4% to less than 10%, in Europe even less, so for instance in Austria from 1.4% to 2.4% in the course of the past 18 years, and this was exclusively due to a reduction of operative mortality from 20% three decades ago to 2% at present. Since with the exception of the small cell carcinoma the combination of chemotherapy and radiation therapy was disappointing and could not improve success rates, bronchial carcinoma is still regarded as a surgical disease. The demand for early diagnosis and early operation must be maintained.

In view of the successes of adjuvant chemotherapy, also small cell bronchial carcinoma is still considered to be a surgical disease.

Controversies in the management of small cell lung cancer (SCLC) relate to advances in therapy and improvements in our ability to evaluate disease extent. In the past, rapid tumor growth and disseminated disease, even in patients judged to be clinically 'early' was characteristic. Our studies of patients with SCLC undergoing traditional therapy showed that a specific pattern of behavior was evident that distinguished this disease from non-small cell lung cancer (NSCLC). In variables could be identified that significantly affect prognosis and those anatomic factors most highly predictive of survival for NSCLC had no prognostic effect in patients with SCLC. Median survival and 5-yr survival rates have been markedly improved by multidrug chemotherapy. In our contemporary study of 615 patients with SCLC, 23% of those with Stage I disease survived 5 yrs. This, and the fact that relapse in the chest is the most common pattern of failure in patients achieving a complete remission argues for identification of patients whose prognosis could be enhanced by surgical removal of the primary tumor. In a recent retrospective report of a large series, multivariate analysis showed that, once stage was accounted for, the only factor influencing survival was whether surgery was received as a first course of therapy. Other studies report that surgery does not lead to better results than chemotherapy alone. Early reports of clinical trials of surgery as adjuvant therapy following induction chemotherapy have not been encouraging. Conflicting reports over the role of surgery in the multimodal regimen and the optimum sequencing of treatment have not been resolved. The role of surgery will remain controversial until a prospective study of carefully staged operated and non-operated groups are compared. The majority of investigators agree that, if initial surgical resection is done, chemotherapy should follow. In patients undergoing adjuvant surgery, the histology of the resected specimens may reveal another histology than small cell. In a number of our own cases, no viable tumor has been found in the resected specimen.

PROGNOSTIC FACTORS IN LUNG CANCER
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Prognostic factors are patient and disease characteristics measured before therapy begins that may affect the course of the disease. In lung cancer, the influence of prognostic factors is relatively large as compared to the effects of therapy. As an example, for small cell carcinoma, variations in initial performance status category can have a threshold effect upon median survival and other factors, such as extent of disease, can have a twofold effect. With therapy differences rarely exceeding a 30% increase in median survival, it is easy to see why apparently contradictory reports are found in the literature. All too often investigators attempt to compare therapies by listing summary results, typically response rates or median survivals, for a number of separate published studies. Such comparisons usually ignore prognostic factors and are frequently misleading. Pairwise independent investigations have been conducted in more than 1,000 patients with small cell carcinoma (SCLC), 4,000 patients with inoperable non-small cell carcinoma (NSCC), and 1,400 patients with operable non-small cell carcinoma (NSCC). For SCLC the three most important prognostic factors affecting survival were initial performance status, bone pain, and symptoms of hepatic metastasis. The dominant prognostic factors for the NSCC patients were initial performance status and extent of disease. TNM stage was clearly the major factor for patients with Stage I or II NSCC. Other important factors include preoperative clinical observations and blood component parameters. The prognostic value of histologic type is unclear; it has not had a significant effect in a number of large studies.

MORPHOLOGIC CRITERIA FOR SMALL CELL LUNG CANCER
K. Balogh, Boston, USA

Morphologic criteria for small cell lung cancer (SCLC) relating to surgical therapy. C.F. Mountain, M.D. Anderson Hospital and Tumor Inst., Houston TX USA

Controversies in the management of small cell lung cancer (SCLC) relate to advances in therapy and improvement in our ability to evaluate disease extent. In the past, rapid tumor growth and disseminated disease, even in patients judged to be clinically 'early' was characteristic. Our studies of patients with SCLC undergoing traditional therapy showed that a specific pattern of behavior was evident that distinguished this disease from non-small cell lung cancer (NSCLC). In variables could be identified that significantly affected prognosis and those anatomic factors most highly predictive of survival for NSCLC had no prognostic effect in patients with SCLC. Median survival and 5-yr survival rates have been markedly improved by multidrug chemotherapy. In our contemporary study of 615 patients with SCLC, 23% of those with Stage I disease survived 5 yrs. This, and the fact that relapse in the chest is the most common pattern of failure in patients achieving a complete remission argues for identification of patients whose prognosis could be enhanced by surgical removal of the primary tumor. In a recent retrospective report of a large series, multivariate analysis showed that, once stage was accounted for, the only factor influencing survival was whether surgery was received as a first course of therapy. Other studies report that surgery does not lead to better results than chemotherapy alone. Early reports of clinical trials of surgery as adjuvant therapy following induction chemotherapy have not been encouraging. Conflicting reports over the role of surgery in the multimodal regimen and the optimum sequencing of treatment have not been resolved. The role of surgery will remain controversial until a prospective study of carefully staged operated and non-operated groups are compared. The majority of investigators agree that, if initial surgical resection is done, chemotherapy should follow. In patients undergoing adjuvant surgery, the histology of the resected specimens may reveal another histology than small cell. In a number of our own cases, no viable tumor has been found in the resected specimen.
The aim of this on-going study (started Nov. 1981) is to find a place for surgery in combined treatment in pts up to 65 yr, P3 > PD with disease confined to one hemithorax with no enoplastic/malignant extension. 52 pts entered the study 36 in stage III/IV, 16 in stage II. Staging included bronchoscopy, biopsy and/or needle biopsy, liver scan, pericardiacopy, bilateral bone marrow biopsy, bone scan, CT of chest, retroperitoneal spaces and brain, tumor markers study.

Drugs: CDDP 70mg/m², VCR 1.3 mg/m², CMT 50mg/m² d 1, VP-16 160mg/m² orally d 1-5, every 4 wks. PCI for pts with CR. Among 55 pts on CT 4 pts had PD and 8 CR, OR after 3 courses was found in 4 pts /CT is continued for 12 courses/. Of 35 pts with PD, re-staged after 3 courses, 6 pts were disseminated. Remaining 27 pts were randomized into surgery followed by CT up to 1 yr vs continuation of CT /61 yr vs 1 yr course vs 2 stage for both groups/. Of 16 pts on surgical arm 3 pts were unresectable, 1 pt had not any exploratory surgery because of palpable mass was found. 12 pts had resection. Out of 5 PDs 1 pt died 1/9/82 in traf fc accident /autopsy revealed PD/. 1 pt experienced brain metastases after 1/12/82 pt died on 3rd day for pulmonary thromboembolism, 1 pt with residual tumor in paratracheal region /BR/ developed SUC syndrome after 9 courses and 1 pt is well 10 mos. Among remaining 7 pts having resection 2 died for dissemination within 1/12yr, 1 pt died for pneumonia after 6 mos, 1 pt died at 1 yr for emesis, malnutrition and debilitation, 1 of whom 2/15/82 to 11 mos. In pts on surgical arm no local failure was found apart from 1 PD at residual tumor left behind /BR/ in contrast with 1 pt with residual mass at exploration /who have been kept on CT up to 1 yr and developed recurrence at 1/12yr/.
SURGICAL TREATMENT OF LUNG CANCER, P. Cherveniuk, M. Bulovski, N. Nikolov, L. Lukov, D. Ivanov, D. Petrov
Research Institute of Pulmonary Diseases, Medical Academy, Sofia, Bulgaria
Between 1973-1985, 2562 patients were operated on. Only 17% of the lung cancer cases had been detected fluorographically. All modern methods of diagnosis were used, which led to pre-operative morphological diagnosis for 94.4% initially up to 97.9% in recent years. Lung resection was applied in 1554 (60.5%) cases, while the rest 1008 (39.5%) patients got the following treatments: For cytometry for 423 (16.6%), definitive medical therapy for 382 (15.6%) and other types of operative biopsy for 135 (5.3%) of the patients. Most frequently applied was lobectomy, 64% of all lung resections. Post-operative complications are analyzed as well as 5-year survival depending on stage of cancer, process, histological type and type of surgical treatment. It is pointed out that early diagnosis of lung cancer is of greatest importance to successful surgical treatment.

M-34: CHRONOBIOLOGY — CANCER THERAPY

HARDWARE AND SOFTWARE FOR (AND RESULTS FROM) CHRONOBIOLOGICAL APPROACHES TO CANCER TREATMENT AND PREVENTION. E. Halberg, Chronobiology Lab, Dept of Lab Med & Path., Univ of Minnesota, Minneapolis, MN 55455, USA
The study of biologic time series, chronobiology, was initiated with relatively simple methods. With a clinical thermometer, repeatedly placed upon peripheral humans, a gain of 2 had been recorded in the chronotherapeutics of oral cancers at the peak of tumor temperature (Proc. XIV Int. Cong Therapeutics, Montpellier, France, L’Expansion Scientifique Francaise, 1977, 151). Available yet expensive automatic monitors provided with solid-state memories and software for data analysis are preferable. Chronobiologic approaches in endocrine therapy reveal a time-dependence of the melatonin effect in murine models of leukemia (Chronobiologia 10:173, 1983) and in “continuous but burden-enhanced breast cancer” (Chronobiologia 12:205, 1985). For human chemotherapy schedules, single doses can be specified by clock-hour for patients monitored for their circadian physiologic (marker) rhythms, gradually increasing and then decreasing (sinusoidal) doses can also be given with a certain timing along the 24-hour scale, as illustrated for murine treatment with ara-C (Experience 29:909, 1973). Cisplatin schedule have been complemented further with so-called circumvent (about 7-day) sinusoids. The test on human beings of such complex schedules is facilitated by programmable pumps that administer complex schedules automatically. A substantial gain from such an implantable pump has been recorded for a continuous sinusoidal cyclosporine immunotherapy. Once a pump has served to identify the best treatment timing, oral treatment designed with the corresponding arrangement can reproduce much of the gain obtained by the pump (J. Clin. Rel., in press). Since implantable pumps are expensive, they are cost-effective when used as a research tool in a first step to design a corresponding oral treatment schedule on a large scale (Experience, in press). Thus, even when the cost of pumps is limiting, chronobiologic timing still holds. With respect to prevention, a larger circadian amplitude of urinary melatonin secretion in women at high risk as compared to low risk of developing breast cancer is a dynamic chronobiologic classifier. In the absence of a difference in the mean (Acta med. scand, in press). At ubiquitous rhythms at different levels of organization become amenable to assessment with modern instruments and as modern drug administration devices serve to exploit the organism’s structure in time, it follows that timing can become a meaningful complement to dating in cancer chronotherapy and, more importantly, chronobiologic markers of risk can lead to rational approaches to cancer prevention.
SIGNIFICANCE OF CIRCADIAN RHYTHMS IN BLOOD AND BONE MARROW FOR CANCER TREATMENT

OD GUNNAR AND O. ERVIK
The Ode Institute, Dept. of Pathology, University of Bergen, N-5016 Haukeland Hospital, Norway

It has long been known that both the stem cell activity and cell proliferation in the hematopoietic system undergo strong circadian variations. This also applies to the leukocyte numbers in peripheral blood, both in humans and in laboratory animals. In addition, seasonal variations of hemopoiesis can occur.

Since there can be rather large differences between maximal and minimal activity during such rhythmic oscillations, this may have practical importance for the susceptibility of the bone marrow cells to toxic drugs. There is evidence that the cells are more susceptible to cytostatics during periods of high proliferative activity.

Possible importance of these phenomena for protection of the bone marrow during cytostatic therapy is discussed. In principle, drugs acting over a rather short period should be given at periods of low activity. Since the circadian rhythmicity may change with the season and in general be rather variable, it is important to monitor the hemopoiesis. A recent approach has been to amplify the protective effect by using physiological regulators of hemopoiesis which are given in a certain relation to the rhythmicity.

During malignant development in the hematopoietic system, the rhythmicity is altered and may be lost. Although, oscillations of leukemic hemopoiesis may also occur.

So far quantitative data on human hemopoiesis are scanty, and there is an urgent need of such studies on patients undergoing cytostatic therapy.

PRECLINICAL AND CLINICAL CHRONOTOXICOLOGIC STUDIES OF NEW CYTOSTATIC COMPOUNDS


The antitumor effectiveness of cancer treatments depends upon factors which influence host tolerance. Host tolerance for 20 anticancer agents exhibit large-amplitude, predictable variations along the 24-hr scale (and along the 1-yr scale) in laboratory rodents. A chronotoxicologic approach was combined to the chemical research of drugs with lesser toxicity than the parent compound. The new anthracycline analog 4'-0-tetrahydropyranyl adriamycin (THP) was studied in male B6D2F1 mice. Optimal tolerance as gauged by survival, body weight change and total leukocyte count, corresponded to drug dosing in the second half of the rest span (Eur. J. Cancer 1985, 21, 1245).

The CM-CFU technique was used to investigate the mechanisms of such chronotolerance for THP at the level of bone marrow. A circadian rhythm in the in-vitro tolerance for THP was thus documented with a similar timing of the maximum as that observed in vivo. In 18 patients with ovarian cancer the administration of THP was twice better tolerated when dosed at 6.00 hr as compared to 18.00 hr (hematologic toxicities, P<0.03), and that in cisplatin (-40% less toxic to the kidney) when dosed at 16-20 hr as compared to 4-8 hr (P<0.02). Preclinical chronotoxicologic studies of new anticancer compounds should be performed at an early stage of clinical phase II trials and influence their design. In vitro techniques deserve further chronological testing, but may reduce the cost and increase the feasibility of such investigations. Chronotoxicologic studies of new cytostatics will lead to a safer, thus more promising, clinical use of these medications. Programmable pumps allowing a timed drug delivery will render such chronotherapy clinically feasible.
SESSION OF DRUG TREATMENT BASED ON CIRCADIAN RHYTHM.
C. Focan, Inst. of Pathology, Univ. of Liege, Belgium.

In a methylcholanthrene induced sarcoma of C57 Bl male mice with circadian proliferation (peak mitotic indices [MI] at noon, peak of labelling indices -LI- between 0-4 a.m.) vincristine (VLB) was unable to induce tumoral regression, while cyclophosphamide (CPA) exerted a significant anti-tumoral effect. The factors of this oncolytic effect were the dose of drug, the stage of tumoral growth and the circadian time-structure of age-distribution of cells through the various phases of the cell cycle (maximum efficacy between 6-8 a.m. at the moment when a maximum of cells were engaged in the G2-M cell cycle phases). After administration of VLB or CPA at various hours in a nocturnal period, profound, prolonged and dose-dependant perturbations of the circadian-kinetics were demonstrated. In some optimum situations, depending upon the dose of drug and the circadian variability of target cells (i.e. cells in G2-M phase), it appeared possible to induce kinetic phenomena consistent with a synchronization and/or a recruitment of residual tumoral cell population (peaks MI-LI in dysynchrony with that of controls 40-52 hrs after CPA injection at 8 a.m. at 8th day of tumoral growth). Those kinetic fluctuations were taken into account in sequential administrations of VLB and CPA. It appeared therefore that the concomitant injection of both drugs abolished the anti-tumoral effectiveness of CPA alone while their sequential administration (CPA first followed by VLB 40-56 hrs later) significantly potentiated the CPA activity. In human solid tumors, comparable circadian-linked kinetic phenomena allowed to carry-out a randomised trial in 62 patients comparing a same 40 hrs-sequence of drugs (methotrexate followed by vinblastine and cyclophosphamide) beginning either at 10 a.m. or at 10 p.m. The results clearly militated in favor of the good circadian-timed schedule (higher response rate, longer median response and survival times). Those observations show the importance of following intra-tumoral kinetics for scheduling sequential chemotherapy; they also brought arguments for the potentiation of anti-tumoral effectiveness of drugs without reference to host-tolerance. The relevance of circadian rhythms in serum concentrations of human tumor markers for the programmed of timed-chemotherapy will also be considered.
An outstanding epidemiological phenomenon distinguishes cancer from all other chronic diseases. In all chronic diseases except cancer the force of mortality, or hazard rate continuously increases. In cancer on the other hand, from the third year of its clinical presentation and onward, the hazard rate continuously declines. This phenomenon has been examined in the 4th Report on End Results in Cancer (1). In all survival curves of the report, the hazard rate continuously declines. The phenomenon is observable also in patients refusing any treatment (2).

Aging per se is accompanied by an ever rising hazard rate as is evident from any actuarial table. In chronic diseases which were investigated in the present study, e.g. diabetes mellitus, arteriosclerosis or cirrhosis, the hazard rate also continuously increases. Obviously since more patients die from cancer than from most other chronic diseases, the cancer hazard rate is much higher. It is about ten times higher than that of diabetes mellitus, yet in cancer it declines, while in diabetes, in spite of being relatively small it increases.

The hazard rate serves as measure for the chances of a cancer patient to succumb to the disease in the forthcoming year of his life. Since in cancer it is relatively high, his chances are relatively poor. In spite of this, the chances continuously improve. The longer he lives the better they are. This important phenomenon which is recognized by many clinicians, is still disregarded by epidemiology.

The biological role of neoplasia may be to eliminate from the race individuals with defects in the genetic material which are not lethal but which might in the long term destabilise the genetic inheritance. The neoplastic process might well seem to be a struggle between regulatory forces and sections of a tissue in which the path of regulation has been obtunded. It is possible that the morphological distortion observed is more the result of misapplied attempts at bodily regulation than of the direct action of the carcinogenic circumstance. It may be less necessary to understand neoplasia than to find a means of rectifying it. The natural, if very rare, bodily way of dealing with it would seem to be by reinduction of differentiation rather than by destruction of the affected tissue. An experimental approach which we have adopted compares the response of normal and neoplastic growth to substances applied. Histone and polybrene each exert different effects on neoplasia according to the nature and timing of the carcinogenic stimulus involved. It is possible that the effect of the carcinogen on the tissue is rapid, and that the prolonged exposure needed to cause expression of neoplasia is due to the repair mechanisms being initially effective in thwarting expression but gradually failing, perhaps because the damage becomes too widespread or because the tissue exhausts its capacity to respond.
3351 ACQUISITION OF METASTATIC POTENTIAL BY SOLID TUMOR CELLS THROUGH SOMATIC HYBRIDIZATION WITH LYMPHOID CELLS. J.Trosko, East-Lansing, USA

Mammary tumors induced in rats with chemical carcinogens do not metastasize spontaneously, but if they are subjected repeatedly to specific and nonspecific immunosuppressive procedures over an extended carcinogenic period to bring out nonimmunogenic tumor cells, many spontaneously metastasizing tumors that disseminate via the lymphatic and hematogenous routes, as human breast cancer does, can be produced. This seems to indicate that carcinogens transform and liberate target cells from the homeostatic regulatory mechanisms, while the host immune surveillance system endows them with metastatic potential or an invasive and migratory capability similar to that of leukocytes. It was postulated, therefore, that these tumor cells may have incorporated the property of lymphoid cells into their genome during the immunosuppression process, perhaps through somatic hybridization. Such supposition was tested by fusing an established nonmetastasizing rat mammary tumor cell line NM-081 in vitro with syngeneic thymocytes, peritoneal macrophages or spleen cells in polyethylene glycol solution at a 1:30 ratio. To clone the hybrid cells in the lung capillary bed and simultaneously to purge unfused excess lymphoid cells, the fusion mixture was injected t.i.v. into normal rats. The resulting lung nodules were individually implanted s.c. into the inguinal mammary fat pad of normal recipients to test their metastasizing capacity. Most thymocyte- and macrophage-hybrids metastasized lymphogenously and hematogenously for 8 consecutive transplantation generations. 30% of the spleen cell hybrids spread to lymph nodes only for one passage, while the unfused NM-081 cells did not. The karyotype of the hybrids was different from that of the original NM-081 cell. Immunohistochemically, the macrophage-hybrid cross-reacted with a rabbit anti-rat macrophage antiserum. Thus, it seems that somatic hybridization between solid tumor cells and lymphoid cells has been achieved, conferring the invasive and migratory property of the latter on the former. Also, it may be reasonable to conclude that in the evolutionary process of mammary tumors, the hormone dependence is inherited from the parent organ, but the metastatic potential is acquired from the host lymphoid cells in their immediate vicinity.

3352 UNIFIED MECHANISMS LINKING ONCOGENES TO CHEMICAL TUMOR PROMOTER I.E. INHIBITED GAP JUNCTIONAL COMMUNICATION. J.Trosko, East-Lansing, USA

3353 THE ROLE OF GENOME INSTABILITY AND DNA REARRANGEMENTS IN THE INDUCTION OF CANCER. M.Choryg, Institute of Oncology, Department of Tumor Biology, 44-100 Gliwice, Poland

The classical picture of stable chromosomal DNA with orderly fixed genes, regulatory and noncoding sequences is no longer tenable. Genes and their regulatory sequences in both Frokaryota and Eukaryota including Humans can change their position in the chromosomes or suffer from deep structural alterations (independent or "spontaneously" or under the influence of physical, chemical or biological factors. Mobile DNA sequences can also contribute to genome instability. Single or double-stranded breaks of DNA, primary nucleotide deletions and insertions arising in the course of damage repair can create a potent recombination sites and increase "illegitimate" recombinations. The topology of DNA has a profound effect on functional status of genes and is essential for DNA replication. Rearrangements of gene array and/or gene-flanking sequences may lead to stable reprogramming of gene expression of the cell resulting occasionally in uncontrolled cell proliferation. The interference of even functionally distant gene/s/ from turned off or on accidentally with a gene/s/ involved in cell proliferation control is not improbable. Direct affection of genes involved in cell proliferation control by factors inducing genome instability is well substantiated. Example of involvement of genome instability in the induction of cancer will be presented.

3354 TO DAY INITIATION - "GOMFORD THEORY AND THE CONCEPT OF MODULATION OF CARCINOGENESIS. Roberfroid, M.B. Unit of Biochemical Toxicology and CanceroLOGY, Universite Catholique de Louvain, School of Pharmacy, Brussels, Belgium.

Cancer is the end point of a long, complex and multiphasic process. Various protocols have been used to support the concept that this process can be divided in two or three major steps: initiation, promotion, progression. The arguments to support such a partition of the carcinogenic process in 2 or 3 steps are mainly operational. They rely on the effects of specific treatments. Except for initiation that, at least in some specific cases, might be due to mutagenic events, the biological mechanisms of promotion and progression are poorly if at all understood. This presentation will discuss those concepts and review the arguments that support them. Based on the results of recent experiments it will further discussed them. It will propose that, beyond the initiation (that in some protocols is a single event), the carcinogenic process might be going on by itself up to the appearance of malignant tumors. Subsequent treatments by genotoxins, nitroge, inducers of differentiation, hypertrophic or hyperplastic agents or subsequent treatments that alter homeostasis might act on modulating (amplifying - accelerating - slowing down - inhibiting) that ongoing process. With the idea in mind that initiation is the only necessary and sufficient event to induce carcinogenesis the concept of modulation of carcinogenesis will be proposed. That concept will cover all treatments which given before, during or after initiation are able to modify the kinetic of evolution to and/or the intensity of malignancy.
M-35: THEORETICAL CANCER RESEARCH

Dr. G. Vita, Bristol-Myers Co., New York, 909 Third Ave., N.Y. 10022 USA

With cancer research rapidly evolving, demands by health authorities increasing and research expenses skyrocketing, with direction should cancer research in industry take considering that current approaches are only partially satisfactory at best but also realizing that laboratory breakthroughs do not translate quickly into products in therapy.

With an eye to medium and one on long-term goals, we in Bristol-Myers follow a balanced approach between cytotoxics and biological response modifiers. The cytotoxics are provided through a fermentation screen and chemical biological response modifiers are discovered through our molecular biology program in cooperation with our sister division, genetic systems, aimed at monoclonal antibodies by being linked to cytotoxics and growth regulations factors. Studying the mechanism of our organization, based on the therapeutic area concept, provides for chemists, biochemists, pharmacologists and clinicians all working exclusively in the cancer area. Project teams including toxicologists, chemical and pharmaceutical product development and metabolism scientists are directed by experts in the field to assure rapid progress at the development stage. Great importance is given to cooperation with pioneering centers worldwide to complement our in-house activities through contracts covering new areas of research and specific issues. Frequent contacts with leading universities keep us abreast of the progress in the field.

O-32: PARANEOPLASTIC DISORDERS

PARANEOPLASTIC NEUROLOGICAL DISORDERS.

R. A. Hinton
The London Hospital, London, G.B.

First described a hundred years ago, the diversity of these neurological complications of malignant disease has been increasingly recognized. The neurological effects of endocrine-metabolic and nutritional disorders, the adverse results of irradiation and chemotherapy, infections and vascular pathologies are all clinically important. There are additional neurological syndromes in which the nervous system is primarily affected; the criteria for their acceptance as causally related to malignancy will be discussed. These syndromes include peripheral neuropathies, encephalomyelitis, cerebellar degeneration, myopathies and a miscellaneous group. The differing syndromes will be explored with emphasis on causation.

NEUROMUSCULAR DISORDERS IN ONCOLOGY. McGill
Postgraduate Medical School, Budapest, Hungary

Neuromuscular involvements are frequent in advanced stages of malignant disease. According to the pathogenesis, they are lesions caused by metastases, by antineoplastic treatments, by the remote effect of the malignant disease or they may be present at the same time, but unrelated to the malignancy.

In the peripheral nervous system cranial nerves and plexuses are most frequently involved by metastatic lesions, usually in the vicinity of bone metastases, skeletal muscles are usually spared of this type of complications.

Neurotoxic effect of drugs, used in antineoplastic treatment is a frequent cause of polyneuropathy characterized by weakness, sensory deficit and sometimes pain in the lower extremities. Radiotherapy of breast tumors may injure the brachial plexuses, causing sensory disturbances, followed by weakness.

The existence of paraneoplastic disorders, the remote effect of malignant disease seems to be accepted nowadays. Skeletal muscles may be altered by osseous myopathy, carcinomatous neuromyopathy of the limb-girdle muscles, acute neurotizing myopathy, myoschistic syndrome, dermatomyositis and polymyositis. The most significant references will be given and some case reports demonstrating the above-mentioned neuromuscular complications.
Paraneoplastic syndromes, or remote effects of cancer on the nervous system, are believed by some investigators to be autoimmune in origin. In two such syndromes, paraneoplastic cerebellar degeneration (PCD) and subacute sensory neuropathy (SSN), autoantibodies in the serum have been found at high titer in some patients. In PCD, an antibody in patients with ovarian and breast cancer reacts with the cytoplasm of Purkinje cells. The antibody identifies an antigen with bands at 34 to 38 and 62/64Kd in Purkinje cells primarily of humans. The antibody is absent for sera of patients with cancer but no PCD and of patients with non-paraneoplastic cerebellar disease. The role of this autoantibody in pathogenesis of the neurologic disease is not known.

The other autoantibody (SSN) appears in patients with oat cell cancer and identifies an antigen of 35-36Kd, restricted to nuclei of the central nervous system. In 2 patients, the antigen is also present in tumor tissue. The antibody is absent for sera of patients with oat cell cancer but no SSN and from patients with neuropathy not related to cancer. Preliminary evidence suggests that this antibody is cytotoxic in vitro when tested with dorsal root ganglion cells.

Remote effects of cancer on the nervous system are neurological disorders occurring in patients with cancer not caused by metastatic invasion of the nervous system or by identifiable nonmetastatic disorders. Recent studies on some of these remote effects have suggested an autoimmune origin. In patients with subacute sensory neuropathy (SSN), a remote effect usually associated to oat cell carcinoma of the lung, we described the presence of an antibody against a protein highly restricted to the nucleus of neurons. The antigen is a group of proteins of 26-36 Kd of molecular weight. A similar antigen lacking the 36 Kd peptide was found in the tumor of one of the patients and deposits of IgG were demonstrated in the nucleus of dorsal root ganglia neurons at the autopsy of one of the patients with SSN.

In patients with paraneoplastic cerebellar degeneration (PCD), another remote effect associated to cancer of the lung, breast, ovary or Hodgkin disease, we and others have described the presence of an antibody restricted to a cytoplasmic protein of the Purkinje cells of the cerebellum in the serum of patients with ovarian or breast carcinoma and PCD but not with other tumors. Western blot analysis of extracts of isolated human Purkinje cells incubated with serum of patients with the antibody identified a protein of 58 Kd of molecular weight.

These findings strongly suggest the hypothesis that at least some remote effects on the nervous system are autoimmune in origin. The neurological disorder would be caused by the autoantibody that cross-react with a tumor antigen and a similar brain protein.
WHAT PRODUCTS ARE SMOKED AND CHEWED IN INDIA
L.D. Sanghvi National Cancer Registry (ICMR), Tata Memorial Centre, Parel, Bombay, India.

There is a wide variety of products that are smoked and chewed in India. The most common product in current use for smoking is bidi, which is 6-8 cm. in length and conical in shape. It is prepared by rolling with fingers about a quarter gram of tobacco flakes in a rectangular piece of tendu leaf (dried leaf of teshburni tree Diospyros melanoxylon). Estimated consumption of bidi per adult is more than 1200 pieces per year compared to about 200 cigarettes. Indian cigarettes have high levels of tar (19-28 mg.) and nicotine (1.0-1.8 mg.) compared to about 200 cigarettes. Indian smokers are going steadily upward.

Chewing habit is very ancient in India. Most common product chewed is paan which is prepared by applying lime and catechu (an extract of Acacia catechu) to betel leaf (a leaf of betel vine Piper betle) and adding pieces or slices of areca nut (fruit of Areca catechu). Tobacco is often added to this preparation. Tobacco and areca nut are also chewed alone or with other ingredients. Chewing of tobacco is on the decline.

POLITICAL OPPORTUNITIES AND OBSTRUCTIONS IN DEVELOPING COUNTRIES
D.L. Simpson, London, UK

STATIONS
TUESDAY • AUGUST 26 • AFTERNOON


Several societies in different countries have organized centers and are helping some children with speech disabilities. Some programs have been started in the early 1960's, others on the basis of the lessons learned from these programs, and still others have been started as a result of educational and research activities, or as a result of the increasing awareness and understanding of speech disorders. The experience of other countries in more developed nations has shown that articulation and speech disorders are found in all countries.

The prevalence of speech disorders in children in the last few years has been increasing. Kuwaiti's speech production is a result of intensive educational control programs, and the increase in cigarette smoking in Kuwait and other Gulf countries has been demonstrated by several governmental and nongovernmental organizations. These studies have included several aspects of the population such as adults, children, teachers and students. Several studies have shown that in 1969 about 40% of adults' male population were regular smokers in Kuwait. In 1979 the percentage increased to 55%. The reasons for this increase were given in the literature. The average adult Indian smoker. Among the other smoking habits, mention may be made of hookah, chutta, chilam, and areca nut. Smoking of bidis is on the increase while smoking of hookah and chutta is on the decline.
Indonesia is an archipelago consisting of 13,677 islands with a population of 165 million. Major improvements in health care have been made in the last two decades. Mortality due to infectious diseases has started to decline and non-infectious diseases, including cancer, have become relatively more important. The incidence of cancer is estimated at around 1 per 1000 and the most frequent sites are the cervix, breast, skin, nasopharynx, liver, lymph glands, lung, rectum, ovary and oral cavity. Physicians are seeing more and more cases of lung cancer and a recent study in Jakarta showed that lung cancer is the most frequent cancer among males treated in the hospitals. Estimates of smoking rates are in the order of 65% for men and 5% for women. Of special concern are the high tar and nicotine content of Indonesian cigarettes. Some concern has also been raised by the cloves which is to be found in "kretek" cigarettes, which is 75% of all cigarettes produced in Indonesia. Indonesia produces around 100,000 tons of tobacco and 100 billion cigarettes a year and over 300,000 people are employed in the cigarette industry and tobacco cultivation. Sales tax of cigarettes amounted to USD 600 million in 1984 and is expected to rise to USD 800 million in 1985. There is a growing concern among health professionals and organisations like the Indonesian Medical Association, Cancer Foundation, Heart Foundation and Consumer Foundation have initiated actions to control smoking. A National Smoking and Health Workshop in 1984 made several recommendations which still await implementation. The Government is still reluctant to control smoking because of the economic and social value accorded to tobacco.
U-32: INTERFERONS IN ONCOLOGY, CURRENT STATUS OF INTRON A AND STRATEGIES FOR PHASE III

3372 THE TREATMENT OF BONE CELL LEUKEMIA WITH HUMAN INTERFERON ALPHA-2 INTRON A

A. Reiter, J.A. Thompson, W.Cox, Unv. of Washington, Seattle, WA. (Paper presented by Dr. A. Reiter).

Since the original report of Quesada that partially purified human leucocyte interferon (IIF) induced significant response in 6/90 patients (pts), there have been reports that purified recombinant alpha IFN is also effective in several small series of pts. We have treated 40 HC pts (pts) aged 30-75, with subcutaneous r-IFN-2b specific activity 10^9 units/mg protein at 0.6/day 3 times a week for a year, unless there was disease progression. As short as 1 year pts were randomized to continue r-IFN for 1 month or stop. If pts progressed, r-IFN was re instituted. Thirty-two pts had had prior splenectomy, 45 had received chemotherapy and 7 were untreated. At entry, all had progressive HC with pancytopenia and/or HFI. In blood or marrow and/or decreased immunological response and/or multiple infections. Complete remission (CR) was defined as < 5 x 10^9 cells in marrow and partial remission (PR) as a 50% decrease in HC.

Studies of the effect of interferon on the growth of colonies of leukemic blasts, myeloma cells and normal hematopoietic precursor cells in culture have shown that interferon shows no specificity in inhibiting the growth of these cells, i.e. the growth of the malignant and the normal precursor cells are inhibited equally. However, interferon markedly reduces the self-renewal capacity of acute myeloid leukemic blasts and myeloma cells. This observation suggested that interferon should be tested for its ability to prolong remissions rather than as a remission-inducing agent.

We are testing the ability of INTRON A to prolong remissions induced by busulphan in CML patients during the chronic phase. Patients serve as their own controls. CML patients are treated initially with busulphan until the leucocyte count falls below 10 x 10^9/L. The control leucocyte doubling time on no therapy is determined after stopping busulphan. Therapy with busulphan is re-started when the total leucocyte count rises above 30 x 10^9/L and continued until the count falls below 10 x 10^9/L. INTRON A 2.0 million units/M^2 subcutaneously three times per week is then started, and the leucocyte doubling time and remission duration determined again.

Seven patients have been started on study and five have completed at least 3 months on INTRON A. Four of the five have shown a significant slowing of the leucocyte doubling time and prolongation of the remission duration during INTRON A treatment. Additional studies of the effect of INTRON A on the proportion of colony-forming units in cell cycle, and the proportion of metaphases containing a Philadelphia chromosome are in progress.

3373 INTRON A IN THE TREATMENT OF CHRONIC MYELOID LEUKEMIA.

D.E. Bergsagel, R.H. Haas and H.A. Messner, Princess Margaret Hospital, Toronto, Ontario, Canada. (Paper presented by Dr. D.E. Bergsagel).

Studies of the effect of interferon on the growth of colonies of leukemic blasts, myeloma cells and normal hematopoietic precursor cells in culture have shown that interferon shows no specificity in inhibiting the growth of these cells, i.e. the growth of the malignant and the normal precursor cells are inhibited equally. However, interferon markedly reduces the self-renewal capacity of acute myeloid leukemic blasts and myeloma cells. This observation suggested that interferon should be tested for its ability to prolong remissions rather than as a remission-inducing agent.

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COMBINATION STUDIES OF INTRON A IN NON-HODGKIN’S LYMPHOMAS

Dr. H. Oser, University of North Carolina at Chapel Hill, North Carolina, USA.

Early clinical trials with partially purified or recombinant interferon have demonstrated response rates of the order of 40-50% in patients with follicular or low-grade lymphomas. On the other hand controversy remains regarding the value of oral alkylating agents for this disease. Recent in vitro evidence has suggested synergy between cytotoxic agents and IFN. This phase I-II protocol was initiated to study IFN in combination with M and P. Groups of 5 patients received IFN twice-weekly for 2 weeks at dose levels of 0.5, 1.0, 2.0, 5.0 and 10.0 x 10^6 IU. During week 2, M (9 mg/m^2) and P (40 mg/m^2) were administered concurrently with IFN followed by a rest period during nadir myelosuppression. Cycles were repeated every 28 days. Thirty patients were entered. Median PS was 1 (0-2). There were 21 Stage III, 2 Stage II and 6 Stage I patients. Median nadir WBC/mm^3 and platelet/mm^3 (days 1-13), at dose levels 0.5, 1.0, 2.0, 5.0 and 10.0 x 10^6 levels were 3.9 (2.1-6.0), 3.6 (1.9-7.3), 3.3 (1.9-5.6; 3.1 (2.0-4.7) and 1.0 (2.4-5.0) respectively. Platelet counts (days 1-13) were 150 (81-381), 124 (68-197) and 148 (88-326) respectively. Median nadir WBC/mm^3 (days 14-28) were 2.7 (0.1-6.7), 3.2 (2.0-8.5), 2.9 (1.7-5.2), 2.2 (1.4-3.2) and 2.5 (0.4-7.0). Platelet counts (days 14-28) were 115 (30-321), 156 (73-582), 184 (105-313), 100 (19-238) and 144 (60-420) respectively. Serious adverse reactions while on study included myelosuppression (2) (both patients with cardiac M), renal failure (3) and leucopenia-related sepsis (2). Early response information is available. Twenty-six patients are evaluable for response. Seven have had progressive disease and 19 (69%) a partial response, 2 (7%) complete response. The median duration was 11 months. IFN does not appear to antagonise M/P effectiveness and may be additive or synergistic. Full evaluation of this combination will be undertaken in randomized controlled trials which are now underway.

ALPHA-2 INTERFERON (IFN), MELPHALAN (M) AND PREDNISONE (P) IN THE TREATMENT OF NEWLY DIAGNOSED MULTIPLE MYELOMA (MM).


IFN has been shown to be active in advanced previously untreated MM. Recent in vitro evidence has suggested synergy between cytotoxic agents and IFN. This phase I-II protocol was initiated to study IFN in combination with M and P. Groups of 5 patients received IFN twice-weekly for 2 weeks at dose levels of 0.5, 1.0, 2.0, 5.0 and 10.0 x 10^6 IU. During week 2, M (9 mg/m^2) and P (40 mg/m^2) were administered concurrently with IFN followed by a rest period during nadir myelosuppression. Cycles were repeated every 28 days. Thirty patients were entered. Median PS was 1 (0-2). There were 21 Stage III, 2 Stage II and 6 Stage I patients. Median nadir WBC/mm^3 and platelet/mm^3 (days 1-13), at dose levels 0.5, 1.0, 2.0, 5.0 and 10.0 x 10^6 levels were 3.9 (2.1-6.0), 3.6 (1.9-7.3), 3.3 (1.9-5.6; 3.1 (2.0-4.7) and 1.0 (2.4-5.0) respectively. Platelet counts (days 1-13) were 150 (81-381), 124 (68-197) and 148 (88-326) respectively. Median nadir WBC/mm^3 (days 14-28) were 2.7 (0.1-6.7), 3.2 (2.0-8.5), 2.9 (1.7-5.2), 2.2 (1.4-3.2) and 2.5 (0.4-7.0). Platelet counts (days 14-28) were 115 (30-321), 156 (73-582), 184 (105-313), 100 (19-238) and 144 (60-420) respectively. Serious adverse reactions while on study included myelosuppression (2) (both patients with cardiac M), renal failure (3) and leucopenia-related sepsis (2). Early response information is available. Twenty-six patients are evaluable for response. Seven have had progressive disease and 19 (69%) a partial response. The median duration was 11 months. IFN does not appear to antagonise M/P effectiveness and may be additive or synergistic. Full evaluation of this combination will be undertaken in randomized controlled trials which are now underway.

INTRODUCTION A COMBINATION OF CHLORAMBUCIL IN THE TREATMENT OF NON-HODGKIN’S LYMPHOMAS.

T. Chiesi, G. Cappi, G. Recco. Departments of Haematology, Ospedale Civile di Vicenza, Vicenza, Italy. (Paper presented by Dr T. Chiesi.)

Kinetin patients with non-Hodgkin’s lymphoma were treated with a combination regimen of chlorambucil and alpha interferon (INTRON, Schering), to evaluate the response and efficacy in pre-treated or relapsed patients. Seven patients were classified as having nodular lymphomas, five as diffuse, three as CLL, one cutaneous lymphoma, one mantle zone two as NHL. The treatment schedule consisted of alpha interferon 3.10^6 units 3 per week and chlorambucil, 10mg daily for 3 weeks. Treatment continued for up to 16 cycles. We obtained 1 complete remission, 7 partial remissions, 3 non-remissions and 2 progressions. In 4 patients the treatment was stopped because of systemic complaints and 2 patients are still under treatment. The major toxicity consisted of fever and nausea and, in one case, leucopenia. These results should be considered as preliminary but appeared to us to be sufficiently promising to recommend further large-scale clinical trials.
3379 TREATMENT OF METASTATIC MALIGNANT MELANOMA WITH RECOMBINANT INTERFERON A.


Twenty-six patients with histologically proven metastatic malignant melanoma were included in a phase two trial of human DNA recombinant interferon alpha. Patients were given 10 million international units of human interferon alpha subcutaneously three times a week until major intolerance or progression of disease.

General signs of intolerance were seen in all patients, haematological toxicity with leukopenia (below 80,000/mm³) and/or thrombocytopenia (below 60,000/mm³) was seen in 6 patients and therapy was interrupted in 1 patient. Mild liver toxicity was seen in 2 patients after 2 weeks of treatment. These manifestations disappeared within 1-2 weeks after treatment was discontinued. Twenty-four patients were evaluable for response. There were 2 complete responses, 1 skin and 1 lymph node going into remission for 20-6 weeks respectively. A partial response was observed in 5 cases lasting respectively 2, 4, 4, 4, and 7 months.

These results indicate a potential role for human interferon alpha in treating patients with metastatic malignant melanoma, however, further trials are required to determine the optimum dose and schedule of administration and combination.

3380 TREATMENT OF ME. PASTATIC MALIGNANT MELANOMA WITH PRECLINICAL AND CLINICAL STUDIES OF INTRON A.


JNP has in vitro effects upon melanoma cell growth and cell surface antigen expression that are as potent as for any solid tumor. JNP has achieved complete responses in multiple phase I and II trials that are also equal to the effects of dacarbazine, the only 'standard' agent for melanoma. Objective responses in 29/54 patients have been reported for a fraction of dacarbazine complete remissions in several trials (Semioor in Oncology 1982). Clinical activity has been associated with daily or three-weekly dosing continued for long periods at more than 4000 U/day irrespective of route. Toxicity has appeared less by the I.V. route.

To improve the results of single agent JNP, a trial was designed combining JNP and dacarbazine, and comparing the combination against the separate agents. A dacarbazine administered at a dose of every 3 weeks x 1 every third week x 3, the JNP given at 10,000 U three times weekly x 10, then 10,000 U every third week x 10 was the combination of recombinant JNP alpha2 and JNP alpha1, and the two. Eligibility required histological diagnosis of metastatic malignant melanoma of stage II or III. Performance status was less than 7. Patients were not allowed to receive JNP or IFN alpha1. Doses were titrated according to disease size (time limit to either [rational] plasma, end-point of the study was therapeutic toxicity, or progression of disease) intravenously defined by the investigator, or new lesion to the first 1 month. To 1/3, to particulate bone metastases, the study, equally distributed among the three arms. Preliminary evidence suggests that the results of the combined JNP + dacarbazine in this arm will be more than that of the separate agents, i.e. to proceed to another response, may be obtained in this arm.
The role of prolactin in the development and maintenance of human breast cancer is increasingly appreciated. Before introducing the prolactin receptor (PRLR) assay in the clinical practice, we performed experiments on animal model using rabbit mammary gland during pregnancy and early lactation. To suppress the endogenous prolactin level, animals were treated by bromocriptine (3x2 mg sc) to get more unoccupied receptor binding sites. After preparation of the membrane fraction from the mammary gland, in vitro desaturation was carried out using 5 M MgCl₂ solution. The PRLR binding capacity was determined by a single-point inhibition technique. The lowest binding was obtained in animals sacrificed after parturition (1.8%). Non-treated animals, killed on the 6th day after lactation, had lower binding (3.6%) compared to the bromocriptine-treated rabbits, where the PRLR binding was 5.95%. The PRLR binding capacity ranged between 78.9 and 1618 fmol/g protein. The in vivo and in vitro desaturation of PRLR binding sites by bromocriptine and MgCl₂ result in an increased specific binding. Determinations on human material are in progress.
3386 PROLACTIN DYNAMICS IN BREAST CANCER. R.P. Manesi, K. Kumar, L.E. Hughes. Univ. Dept. of Surgery, Univ. of Wales College of Med., Cardiff, U.K.

Although few reports have shown a useful therapeutic effect of prolactin suppression in breast cancer, there is good evidence that high basal prolactin levels are predictive of a poor response to endocrine therapy. Further, nocturnal prolactin concentrations have been shown to be abnormal in women with breast cancer.

We have studied prolactin dynamics in breast disease using thyrotrophin releasing hormone (TRH) and domperidone as stimulants of prolactin release. Patients with pain and severe nodularity in the breasts show an abnormally elevated response of prolactin to pituitary stimulation. This high response is predictive of subsequent treatment response to endocrine agents used to reduce breast nodularity and pain. In addition, we have shown strong prolactin binding to the proliferative epithelium in severe breast disease (BRB) suggesting a role for prolactin in the aetiology of breast cancer. We are currently investigating the TRH responses in patients with primary operable breast cancer prior to surgery and these results will be presented with an appraisal of their significance in the aetiology of breast cancer. Results to date suggest that patients with established breast cancer and severe BRB show a similar abnormality in prolactin release, but this may be secondary to changes in biological oestrogen levels.


3387 HYPERPROLACTINAEMIA AND BREAST CANCER - M. Dowsett. Dept. of Biochemical Endocrinology, Chelsea Hospital for Women, London SW3 6LT, United Kingdom.

Some chemically induced rat mammary cancers are clearly dependent on prolactin, but most studies have concluded that prolactin has no major role to play in human breast cancer. However, the observation that patients who responded to treatment with aniluglutetidrine (AG) had a significantly lower mean on-treatment prolactin level than non-responders led to a study of the prognostic significance of hyperprolactinaemia in early and advanced breast cancer in postmenopausal patients. Blood samples were obtained from 152 patients with primary breast cancer prior to surgery and these results will be presented with an appraisal of their significance in the aetiology of breast cancer. Results to date suggest that patients with established breast cancer and severe BRB show a similar abnormality in prolactin release, but this may be secondary to changes in biological oestrogen levels.

3388 PERIOPERATIVE MODULATION OF PROLACTIN LEVELS IN PATIENTS WITH BREAST CANCER. I S Fontana, N Desphande, H G Kwa & D Y Mang. ICRF Clinical Oncology Unit, Guy's Hospital, London, SE1 9RT and Imperial Cancer Research Fund, Lincoln Inn Fields, London, WC2A 3PM.

Levels of serum prolactin (HPr) have been measured before and after surgery in patients with breast cancer. Median levels of HPr were higher in pre-menopausal women both before and after surgery. In both groups, mastectomy was associated with a decrease in HPr levels. Post-op HPr levels returned to normal by 3 months. There were significantly lower levels of HPr in parous women post-op, but similar levels for parous and multi-parous 10 days post-op. No relationship was found between prolactin levels and tumour size or nodal status, but post-op HPr was higher in those with tumours greater than 3 cm. After standardization for nodal status, tumour size and grade, elevation of HPr was related to recurrence rate in 7 sub-groups, with a consistent trend of HPr elevation being associated with worsening of the prognosis. It is possible that a sub-group of breast cancer patients might benefit from perioperative reduction of plasma prolactin levels. For this reason a prospective study has been conducted to assess the feasibility of perioperative reduction of HPr levels by bromocriptine or placebo from 3 days pre-op until 7 days post-op. Side effects have been monitored together with serial HPr levels and glycolytic enzyme activity as an index of tumour growth rate.


Bromocriptine is widely used in the treatment of mammary benign disease and it has recently been included in experimental protocols for the therapy of breast cancer. Nevertheless, no information is available regarding its direct anti-proliferative activity on mammary neoplastic cells; for this reason it seemed interesting to investigate the effect of bromocriptine on the growth of a human mammary estrogen sensitive cell line, named CG-5, which is a variant of the MCF-7 cell line. Bromocriptine, used at a concentration ranging from 10-10 to 10-7M, determines an inhibition of cell proliferation, which is seen after three days of exposure to the drug only at the highest doses, but becomes dose-dependent after six days. This inhibition reaches 40% compared to the control cultures. As CG-5 possess estrogen receptors (ER) and, on the other hand, bromocriptine is known to influence both in vivo and in vitro estrogen ER, we also studied the possible modulation of this parameter by this drug. Preliminary experiments indicate that after five days of bromocriptine treatment no modification of ER, evaluated by a whole cell assay, is observed. On the basis of this result, we tested the antiproliferative activity of bromocriptine associated with tamoxifen (10-7M); in this case the inhibition of cell proliferation was significantly higher (about 55%).
3392 RADIATION THERAPY. B. Casalith, Ph.D, University of Pennsylvania Cancer Center, Philadelphia, Pennsylvania, USA.

This patient education videotape shows radiation therapy equipment and how it is used. Scenes depict a patient undergoing preparations and therapy itself. The videotape explains how this treatment works; that is painless; and purpose of skin marks and tattoos. It also depicts role and training of the dosimetrist, radio therapist, and other professionals that comprise radio therapy staff. This program helps reduce fear of equipment felt by many patients as they anticipate undergoing radiation.

3393 RADIATION THERAPY AND YOU. Fred Lucas, M.D., Thomas Taylor, M.D., Lou Horakcz, R.N., Wes Johnson, R.N., Sue Jordan, R.N., M.S.W., Debra Welch-McCaffrey, R.N., M.S.W.

A program designed for the newly diagnosed patient to explain to them about radiation therapy.
Q-34: EDUCATION OF CANCER PATIENTS ABOUT THERAPY

3394 CHEMOTHERAPY. B. Cassileth, Ph.D., University of Pennsylvania Cancer Center, Philadelphia, Pennsylvania, USA.

This patient education videotape deals with the question, what is chemotherapy? Scenes include professional administration of chemotherapy to actual patients. Physicians and nurses explain how this important cancer treatment works, what it does, and how it has brightened the outlook for many patients. Hair loss and other side effects are discussed. This program provides basic information in a non-threatening matter.

3395 CHEMOTHERAPY AND YOU
Video Services, Phoenix, Arizona.

A program designed for newly diagnosed patients to explain to them about chemotherapy.

3396 BONE MARROW TRANSPLANTATION: A DONOR'S EXPERIENCE
Karen E. Redding, MSW and Brian C.M. Durie, M.D.

A bone marrow donor who has just returned from the transplant center describes her experience. She tells how the decision was made for her to be the donor, the preparations she made for the procedure at a distant transplant center, and the needs and emotions she experienced in preparing for her role. She describes the frustrations, surprises, anger and responsibility she felt during her stay at the center, and the coping strategies she utilized. She identifies changes the experience has made in her life, and offers advice for other donors, family members and health care providers at both referral and treatment centers.

3397 BONE MARROW TRANSPLANTATION: ONE PATIENT'S EXPERIENCE
Karen E. Redding, MSW and Brian C.M. Durie, M.D.

The patient in the program, Joann, is a 31 year old woman who has just returned from the bone marrow transplant treatment center. She talks about her decision to undergo transplantation treatment, her preparations and the surprises she experienced upon arriving at the treatment center. Joann describes the difficulties she faced during this time, including the emotional impact of her awareness of other patients who did not survive treatment. She describes her perception of what the patient's family goes through and what helped her family to cope with the uncertainty and the waiting. Joann expresses her sense of being cured of her leukemia and describes the changes she has experienced physically and emotionally. She offers advice to other patient's and families who are considering or preparing for bone marrow transplantation.
Faces of Medicine: the Last Hope is a 30-minute color film created by Metromedia Producers Corporation as part of a television series that was broadcast on public television throughout the United States. Narrated by television medical/science reporter Dr. Timothy Johnson, the program features a look at bone marrow transplantation work being done by the Fred Hutchinson Cancer Research Center team in Seattle, Washington.

The term "pancreatoblastoma" was proposed by us to indicate the primitive or blastomatous nature of the tumor in line with the better known solid embryonic neoplasms of childhood, i.e., nephroblastoma, neuroblastoma and hepatoblastoma. Twelve cases of pancreatoblastoma in Japan, 7 males and 5 females, were investigated histopathologically. The ages were from 3 to 8 years old with an average of 4.9. Five cases out of 12 were healthy without metastasis after resection of the tumor, but 7 cases died. Macroscopically, the two cases were so advanced as to be unable to detect the capsule. The organoid structures divided by a fibrous framework exhibited acinar differentiation related to squamous corpuscles. An enlarged view of the tumor cells disclosed frequent mitoses. Immuno-peroxidase staining with alpha-L-antitrypsin, antismatostatin, neuron-specific enolase and bovine pancreatic polypeptide was positive, but staining with anti-insulin and anti-glucagon was negative. The ultrastructural study identified comparatively large electron-dense, membrane-bound symogen-like granules, well developed RER with annulate lamellae in part, and unique, complex sealing the ductular or acinar lumen in the tumor cells. The acinar structures were frequently lined with microvilli. A few papers have reported the endocrine differentiation of pancreatoblastoma in addition to evidence of exocrine structures. Such histologic pattern could connote the hamartoblastomatous nature.
**ANALYSIS OF THE ANTIGENIC PHENOTYPE OF HUMAN HEPATOCARCINOMA.**


Institute for Cancer Research, Rome, Italy.

Fifty-six cases of human hepatocarcinoma (HCC) of different histotype seen at the Regina Elena Cancer Inst. have been examined in their antigenic phenotype using a battery of polyclonal and monoclonal antibodies by indirect immunoperoxidase and fluorescein methods. The antigens studied included HBsAg, alphafetoprotein (AFP), alpha-1-antitrypsin (AAT), CEA, class I and II histocompatibility antigens (HLA). The results of this immunohistochemical analysis are summarized in the following table:

<table>
<thead>
<tr>
<th>Antigens</th>
<th>HBsAg</th>
<th>AFP</th>
<th>AT</th>
<th>CEA</th>
<th>HLA-I</th>
<th>HLA-II</th>
</tr>
</thead>
<tbody>
<tr>
<td>% positive cases</td>
<td>0</td>
<td>47</td>
<td>47</td>
<td>56</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

While the expression of all antigens was apparently not correlated with tumor histotype AFP was found mainly in differentiated HCC. The present findings indicate that transformed hepatocytes undergo distinct antigenic changes. Whether this heterogeneous phenotype reflects differences in tumor differentiation or different rates of synthesis and/or shedding of the tumors-associated antigens is a matter of debate.

**THE MEANING OF EARLY DIAGNOSIS AND SURGICAL TREATMENT TO IMPROVE THE PROGNOSIS OF HEPATOCELLULAR CARCINOMA (H.C.C.)**

Keisuke Hamata, Hisashi Mimura, Shuichi Sakamoto, Kazuo Nagaoke, Atsushi Kim, Mochitsaka Takayuki and Kunto Otsi.


We experienced 105 cases of H.C.C. resection from December 1971 to June 1983. Pathologically, capsule formation was recognized in 79% and tumor invasion either on capsule or beyond the capsule was 46%. Tumor invasion to portal veins outside of capsule was recognized in 38% and most of them were over 3cm. So it was thought to be necessary to find H.C.C. less than 3cm. Our patients were found because of -fetoprotein (AFP) elevation (42%), clinical symptoms (27%), and screening, by CT scanning and sonographic examination (15%). But in cases less than 3cm and half of cases AFP level was less than 100ng/ml, as screening became main motives (56%) to be found. These suggest us that periodical screening is necessary to improve the prognosis of H.C.C. Next, we examined the meaning of surgical treatment. Survival after resection with Stage I 1-year 82%, 2-year 64%, 3-year 51%, with Stage II 1-year 61%, 2-year 71%, 3-year 71%, with Stage III 1-year 53%, 2-year 16%, 3-year 11%, with Stage IV 1-year 44%, 2-year 14%, 3-year 9%. We could satisfy the prognosis of Stage I, II, but could not satisfy that of Stage III, IV. We studied some prognostic factors which strongly influenced the results. The prognosis with portal invasion was significantly poorer than the prognosis without portal invasion. Because patients with portal invasion had significantly high incidence of intrahepatic metastasis compared to others. Now we are trying pre- and post-operative transcatheter arterial embolization periodically to prevent intrahepatic metastasis. In conclusion, early diagnosis (3cm) and postoperative treatment to prevent the intrahepatic metastasis are necessary to improve the prognosis.

**Polarizing microscopical analysis of connective tissue framework of primary and metastatic liver tumors.**

L. Kovács, G. Fábán.

Central Hospital of Mezöny 6th Polyclinic, Budapest, Hungary.

In the different pathological processes of the liver, for example in primary and metastatic tumours not only the parenchyma shows deep changes but the connective tissue too. These changes can be expressed following special stainings, by polarizing microscopic measurements quantitatively too. Autopsy material was studied following formalin fixation, paraffin embedding and sirius red fluorochrome staining. The sections were measured in Jena Nu-2 Microscope X/4, X/8, X/16, X/32 compensators. According to our observations the birefringence of the connective tissue framework of hepatocellular carcinomas was very low, 2-8 m. They formed thinner structures than the normal liver.

In cholangiocellular carcinomas the framework is very thick, 10-times thicker than in normal liver.

In metastatic tumours, depending on the structure of them the birefringence was different. In metastatic adenocarcinomas the birefringence showed high variability, Anaplastic and plasmonocellular tumours showed also high differences. In liver manifestations of malignant Hodgkin and non-Hodgkin lymphomas the birefringence of tumorous tissue was low.
Liver cancers developing in thorotrast-administered patients. Hiroo Tanaka*, Syun Hosoda*, and S. Yamada**. Laboratory of Pathology*, Aichi Cancer Center Research Institute, and Lab. of Biology, Pathology and Toxicology**, Aichi Pref. Inst. of Public Health, Nagoya, Japan

Eighty formalin-fixed, thorotrast-deposited livers obtained in autopsy were wholly sliced through right and left lobes. They were examined light microscopically.

1. Cholangiocarcinoma (16 cases): Gross appearance of thorotrast-induced CLC was not different from that of usual thorotrast-unrelated CLC. When we divided them into two large categories of peripheral type and hilar type, with respect to development of hilar duct or ductules of which HCC developed in; one peripheral type 16 and hilar type 11. CLC were usually adenocarcinoma with tubular or acinar structure, but two were cholangiocellular carcinoma proposed by Steiner and Higgins, and one well-differentiated squamous cell carcinoma of possible hepatocellular origin. Histologically, very small numerous lesions with sarcomatous structure was observed in all cases and was considered to be most differentiated squamous cell carcinoma of possible hepatic origin. Prominent proliferation of bile duct or ductules was observed in and around of Glisson's sheath in normal portion of thorotrast-deposited livers. These findings indicate that thorotrast-associated CLC predominantly arise from small radicles of intrahepatic bile duct in contrast to thorotrast-unrelated CLC.

2. Angiosarcoma (14 cases): The most characteristic macroscopic feature was formation of multiple blood lakes. Histologically, very small numerous lesions with sarcomatous structure was observed even in normal appearing parenchyma, implying early intratumor metastasis of AGS cells. AOS was histologically classified into sinusoidal, cavernous and solid forms. Sinusoidal structure was observed in all cases and was considered to be most differentiated form of AGS.

3. Hepatocellular carcinoma (HCC) (4 cases): Liver cirrhosis was found in 8, of which HCC developed in 5. They were negative for HBs antigen by Victoria blue.

4. Multiple primary liver cancers (MPC) (7 cases): MPC consisted of CLC, AGS and HCC.

Specific antigen and expression of the antigen in hepatoma. A murine monoclonal antibody defining a human liver-specific antigen 1 (HLA-1) was detectable in liver cell-derived cell lines, HCC-M, PLC/PRF/5, Chang liver cells but not in Hela, Panc-1, COLO-205, H69-26 of different origins. All of the liver tissues (in vivo) adjacent to hepatomas were stained. The hepatoma tissues were stained but the reactivity was reduced in 5 of the 26 cases.

Conclusion: The reactivity of H2 McAb is restricted to human hepatocytes and cells derived from hepatocytes.

Basement membrane (BM) breakdown is the first step for the invasive process of in situ carcinoma. The purpose of the present study is to demonstrate stromal invasion in association with the disruption of BM in the human adenocarcinoma of the stomach limited to the mucosa. 

Materials and methods: Materials studied consist of 18 intramucosal carcinomas, 10 submucosal carcinomas, and 10 advanced carcinomas. Out of the 18 intramucosal carcinomas, 8 carcinomas are smaller than 5 mm in diameter (called microcarcinomas). All of the carcinomas are histologically composed of tubular pattern. Formalin-fixed, paraffin-embedded tissue sections of the carcinomas were applied to an ABC immunostaining technique with pepsin digestion. The first antibodies were the collagen immunostaining techniques, the second antibodies were anti-laminin and type IV collagen antibodies respectively. The distribution of epithelial BM was examined light-microscopically in each lesion. Lack of BM means distinct penetration, disruption or discontinuity of BM by invasive tumor, but not thinning or fragmentation of BM occasionally seen even in the normal glands.

Conclusions: 
1) The tumor invasion of the stroma subsequent to BM breakdown was observed in not only the intramucosal carcinomas but also the microcarcinomas, as well as both the submucosal and advanced carcinomas. 
2) Moderately to poorly differentiated adenocarcinomas had much more increased lack of BM than well differentiated adenocarcinomas.

Histologic type

<table>
<thead>
<tr>
<th>Intestinal type ca.</th>
<th>Diffuse type ca.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propria mucosa</td>
<td>Angiogenesis (+)</td>
</tr>
<tr>
<td>Desmoplastia (-)</td>
<td>Desmoplastia (+)</td>
</tr>
<tr>
<td>Below muscularis</td>
<td>Angiogenesis (+)</td>
</tr>
<tr>
<td>Mucosa</td>
<td>Desmoplastia (+)</td>
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</tbody>
</table>
3414 GASTRIC ADENOMAS AND ITS MALIGNANT CHANGE
Takui Nakamura, Gen-ichi Nakano. First Department of Surgery, Gunma University School of Medicine, Maebashi, Japan.

Gastric polyps were classified into four subtypes by Nakamura in 1966; it has been considered that type I and II were non-neoplastic poly and type III and IV were neoplastic polyps (adenomas). Type I and II have been considered together as an adenoma in a same entity, although these two subtypes should be separated because of their essentially different biological features and malignant potential. For the purpose to throw light on this problem, following studies were performed: 1) There has been a question that malignant potential of type III is high or not. 2) Is there a gradual transformation from type III to type IV adenoma? 3) Isn't type IV adenoma a differentiated adenocarcinoma?

Materials and Methods: Seventy one type III adenomas in 50 cases and 45 type IV in 42 cases obtained from surgical resection or polypectomy for 31 years from 1953 to 1984 were examined histopathologically.

Results: 1) Type III were usually sessile with uneven surface, and showed a characteristic of two layer structure. The tendency for the size of adenoma to be directly related to the proliferation in the lower layer was confirmed. 2) Type IV adenomas were macroscopically and histologically similar to adenoma of the colon. Several focal cancer were found in type IV adenoma but neither lymphnode metostasis nor subcutaneous invasion was seen in any case. 3) Malignant Change: In type III, focal cancers were seen in six of 32 adenomas examined (18.7%). In type IV focal cancers were seen in 14 of 45 adenomas (31.1%).

In conclusion it must be emphasized that type III and type IV adenomas are essentially different entities because they show not only different histological features, but also differing malignant potential. (This work was supported by Grant-in-aid for Cancer Research from the Ministry of Health and Welfare (No.351), Japan)

3415 MULTIDURENT HISTOCHEMISTRY OF GASTRIC ADENOMAS
Gen-ichi Nakano, Takui Nakamura, Kiyori Nakats, Mitsuhiro Murakami and Shoji Tsuchida. First Department of Surgery, Gunma University School of Medicine, Maebashi, Japan.

Gastric polyps were classified into four subtypes by Nakamura in 1966; type I and II have been considered as non-neoplastic poly and type III and IV have been treated as neoplastic poly (adenoma). Type III shows a low malignant potential (8.5%), but type IV shows the highest malignant potential (41.5%) in these four types. In order to diagnose different between type III and IV, we examined mucosubstances in those adenomas histochemically. In addition, we tried to examine the CEA staining to them.

Materials and Methods: The selected surgical or polypectomized specimens consisted of 5 cases of type III, 8 of type IV and 12 of gastric carcinomas. Microsections were stained by hematoxylin-eosin, periodic acid Schiff (PAS), high iron diamminium blue (HID-AB), and CEA staining.

Results: 1) Histochecmistry: One out of 5 cases (20%) in type III and one out of 8 cases (12.5%) were PAS-positive. With the HID-AB method, traces of acid mucin in only the part of glands were demonstrated in 80% of type III and in 67.5% of type IV. A half of undifferentiated carcinomas were PAS- and HID-AB-positive, but differentiated carcinomas showed a low-staining. 2) CEA staining: CEA was hardly demonstrable in type III, however that was observed only in the cell coat of type IV (37.5%). On the one hand, about 50% of cancer specimens showed positive CEA staining in the cytoplasm.

In conclusion, from these results, some differences in the aspects of histochecmistry and CEA staining between type III, IV and carcinomas were observed. The characteristics of histochecmistry and CEA staining in well differentiated carcinoma were more likely to be similar to the type IV. So it indicated that type IV adenoma should be treated as a benign lesion, although the mentioned similarity between type IV and adenocarcinoma not only in hematoxylin-eosin staining but also in mucin and CEA staining.

3416 INTRACUTANEOUS CYST OF THE STOMACH IN GASTRO-INTESTINAL BIPSYES.

There are several reports in the literature concerning the occurrence of intramural cysts in the resected human stomach. Nagayo 1977 and Fuzita 1978 believe that cystic dilation of the gastric glands in non-previously operated stomachs is a pramalignant condition. The classification of intramural cysts is following: Nakanishi et al. intestinal type, most common fundus, pyloric gland, foliaceous and related cell type.

Between 1966-89 we found 70 cases in 4490 gastro-intestinal cases. Frequency of cysts was significantly higher in men above 50 years. We found the cysts in the neighborhood of ulcer, atrophy, gastritis II, I., polyp, carcinoma and dysplasia. Cysts occurred significantly more frequent with dysplasia than with other changes. The mean diameter of gastric glands and cysts was significantly greater in patients who underwent a Billroth II gastrectomy than in non-operated patients and it depended on the time elapsed since the operation.

We believe that the intramural cysts can be pramalignant lesion and careful studies are necessary to verify this opinion.

3417 DYSPHASIAS AS THE SOLE PRECURSOR OF POINT AND DIFFUSE CANCERS OF THE STOMACH. C. Ravetto, A. Bianchi, L. Santamaria, "C. Golgi" Institute of General Pathology, Centro Torino, Institute of Pathology, II University of Pavia, Italy.

An experimental attempt was carried out to induce gastric cancer in 60 rats by oral administration of low doses of 2-methyl-5-nitro-1-nitrosoguanidine (MNNG) per 190 days, according to Kunce et al. 1979. Thereafter, groups of animals were sacrificed at different times and their stomachs were histologically processed to search for dysplastic and cancer lesions. The results showed sequential alterations of the gastric mucosa comparable to cancerous "point lesions" involving 3-5 glands, as observed in humans. Such lesions were characterized by slight, moderate, and severe cell dysplasias, which progressed into infiltrating carcinomas of intestinal as well as diffuse types. Thus, demonstrating, at least experimentally, that also the cancer point lesions of the stomach originate from dysplastic lesions of different grades. Therefore, these data disproved the statements (as by Nagayo, 1961) that dysplasias play a role as precursor only in gastric carcinomas of intestinal type and not in diffuse or point cancers, although the latter are difficult to detect endoscopically.

Human esophageal cancer cells (SCF-1) in culture treated with mitomycin C(MMC) at several concentrations were examined by electron microscopy. Ultrastructural alterations, especially necrotic lesions of the neoplastic cells, were disclosed. Nuclear segregation, vaculations and the formation of perinucleolar electron dense microbodies were characteristic changes in the MMC treated SCF-1 cells. At a higher magnification, the matrices of the microbodies were closely similar to those of the nucleolus. Distribution of the fibrillar component to peripheral regions of the nucleolus and a budding of the fibrillar component from the nucleolus were occasionally observed. Enzymatic digestion using Pepsin, RNase and DNase demonstrated that the electron-dense microbodies displayed a similar response to the nucleolus. These studies suggest that the electron-dense microbodies originate from the nucleolus. The nucleolar segregation resulting from the fibrillar component and the granular component may be caused as a result of extrusion of the fibrillar component from the nucleolus, forming the perinucleolar microbodies. In view of the effect of MMC on a DNA, it is considered that the series of nucleolar changes are derived from a scission of the rDNA strands in the fibrillar component by MMC.

A carcinoma is rarely developing in the benign gastric ulcer but the real risk exists that a malignant ulcer appears in the radiological examinations, masked as a benign lesion. Between 1967 and 1982, we have observed in 5 cases 2.8% from 179 patients operated because of ventricular ulcerous carcinoma, taking into consideration the criteria of Hausen and Wanke. This represents 3.8% of our patients having been operated in consequence of malignant gastric tumours. In 30% of the cases of ventricular ulcer we have observed chronic gastric atrophy, intestinal metaplasia and in 70% a mild dysplasia. In our cases, the intragastric excavations of the lesser curvature were of the Johnson-type I/4 cases/ and III/1 case/. The average age was 58 years, the proportion of men and women 4:1. The anamnesis of the ulcer has an average duration of 3.6 years. Two of our patients died within 10 years. In one case, we are demonstrating the regression of the excavation in the height of the angle, the appearance of the ulcer scar, after the recurrence of the ulcer and the malignant transformation which we observed in the course of the histological examination. The gastroscopepy, the biopsy, the abrasive cytology and carefully executed follow-up of the patients provides a protective wall against the ventricular ulcer, being a "high-risk" intra-gastric disease.

Autoimmune gastritis is marked by atrophy of corpus and fundus mucosa, elevation of gastric level and parietal cell antibodies (PCA) in serum. The topic of the investigations presented here is the question, if this type of gastritis is connected with a higher risk for gastric cancer than others. For this purpose sera of 130 patients with various stages and histologic types of gastric cancer were tested for PCA. In patients with early gastric cancer of intestinal type the test was positive in more than 50%, in advanced cancers this percentage was lower. In an second study we proved by means of National Cancer Registry if patients who had a gastric biopsy and a test for PCA between 1968 and 1973 afterwards developed gastric cancer. We stated 7 cancers in the 464 examined patients. In PCA-positive patients the number of observed cancers overwhelmed the expected one. These results support the opinion that autoimmune gastritis is connected with higher risk for gastric cancer.
LONG TERM CONTROL OF GASTRIC ULCER IN RELATION TO DEVELOPMENT OF GASTRIC CANCER

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The fate of 242 patients with an endoscopically diagnosed gastric ulcer in 1975/19/6 was controlled. In 60 patients an operation done, in 4 patients was a gastric carcinoma detected. This was in the first year after diagnosis of the ulcer. Therefore we think that there was a misdiagnosis in first diagnosis of the ulcer. No other patient get carcinoma of the stomach since this time. In 96 patients was an endoscopic control performed. In 19 of 77 patients without epigastric pain was an ulcer diagnosed and in 14 patients of 19 with complaints. In quite of these results in our opinion gastric ulcer is not a gastric precancerous disease.

ADENOID CYSTIC CARCINOMA OF THE ESOPHAGUS SYNCHRONOUS WITH SQUAMOUS CELL CARCINOMA OF ESOPHAGUS. A case report. A. Cerar*, S. Vildmar*, A. Juteraek**, Inst. of Pathology, Ljubljana, Yugoslavia

Fourty-nine years old man, heavy cigarette smoker had dysphagia for 2 months. Double synchronous carcinoma of esophagus was found. An adenoid cystic carcinoma known to be very rare in this organ was discovered in the distance of 24 cm from the tumor palpated in so a squamous cell carcinoma in the distance of 35 cm. Lev's resection of esophagus and cervical esophagus fundoserosaomata was done. The adenoid cystic carcinoma was well differentiated with typical histologic traits and dysplasia of the mucous epithelium at the margin. The tumor did not penetrate the esophageal wall. The squamous carcinoma was poorly differentiated with rare foci of keratinization and with transmural infiltration of the esophageal wall. At the time of operation no metastases were found. The patient survived 15 months after the operation. This is the first published case of adenoid cystic carcinoma synchronous with squamous cell carcinomas of esophagus. Our case points to the idea of common etiology for the both histological types of tumors.

THE SUPERIORITY OF CYTLOGICAL SPECIMENS FOR QUALITATIVE DETECTION OF SEX STEROID HORMONE RECEPTORS IN BREAST CANCER USING IMMUNOFLORESCEENCE. Houston Johnson, Jr., M.D. and Shalah Masood, Univ. of FL College of Med./JHEP, Jacksonville, FL, U.S.A.

Immunofluorescent staining that uses polyvalent antibodies to detect estrogen and progesterone receptors (ER and PR) has been highly criticized and stated to be non-specific for and variably consistent with biochemically determined ER and PR. There have been no studies that prove polyvalent antibodies do not detect ER and PR. Previous studies have employed frozen sectioned tissues with polyvalent antibodies to determine ER and PR by immunofluorescence techniques. This study was undertaken to determine whether cytological preparations would provide better immunofluorescent staining than tissue sections using a commercially available polyvalent serum for quantitative ER and PR determinations. 24 breast cancer patients had ER and PR determined cytologically and with tissue sections on 30 specimens. Biochemical determinations were made in each case using a dextran-coated charcoal assay. 63.1% of patients were biochemically positive for ER. Immunofluorescent staining on cytological preparations accurately detected 92% of biochemically positive ER specimens. 100% of all cytologically positive preparations for PR were biochemically positive. There was 1 false positive ER (4%), and 1 false negative PR (9%) among cytologically prepared specimens when compared to biochemically positive specimens. Frozen sectioned tissues gave a less reliable correlation. Merely 43.3% of biochemically positive specimens were positive by immunofluorescence for ER and only 72.7% of biochemically positive PR specimens were detected. Cytological specimens were significantly better than tissue sections for detecting positive ER (p<0.01) and PR (p<0.05). This preliminary study points out the potential flaws in using tissue sections to evaluate immunofluorescent staining for ER and PR using a commercially available polyvalent antiserum and suggests that the polyvalent antiserum may be a useful analytical tool in studying human breast cancer if cytological preparations are made from the malignant tissues.


Rabbit antiserum to a purified glycoprotein from human milk-fat-globe membrane, MFGM-gp-155, was raised. The Ig fraction of the antiserum was used to study the presence and the patterns of distribution of this glycoprotein in formalin-fixed and paraffin-embedded tissue sections by an indirect immunoperoxidase staining. Prior to staining, the tissue sections were treated with trypsin. Three different patterns of staining were observed: cytoplasmic fine and granular, distinctly round inclusion in the cytoplasm, and association with the plasma membrane. In normal breast, the antibodies strongly reacted with apical plasma membrane of epithelial cells but not with myoepithelial cells and elements of connective tissue. In both the infiltrating and lobular carcinomas, the cells were positive. However, staining of the lobular carcinoma was much more intense than that obtained with infiltrating ductal carcinomas. In all cases, greater than 75% of the cells stained. In contrast to both normal and well-differentiated malignant cells where the antigen was predominantly expressed on the apical plasma membrane, in poorly differentiated tumor cells gp 155 was mainly localized in the cytoplasm. The malignant cells of medullary, colloid and signet cell carcinomas of the breast were positive and so were their cells at distant metastatic sites. MFGM-gp 155 is not specific to breast since it was demonstrated in normal cells of lung, salivary gland, colon, and prostatic tissue, and in malignant epithelial cells of colon, cervix, endometrium, lung, ovary, and salivary gland. However, the restricted expression of the glycoprotein on apical plasma membrane of normal epithelial cells suggests that these molecules may have functions common to these secretory organs.
IMMUNOHISTOCHEMICAL DETECTION OF TUMOR CELLS IN THE BONE MARROW OF BREAST CANCER PATIENTS

W. Untch, W. Eiermann, R. Barti*


Bone marrow aspirates from 22 patients at time of primary breast cancer therapy (stage T1), N0-2, M0 were taken from several sites:
2x iliacal crest left and 2x right, 2x sternum (each 6 ml). Additionally biopsies were taken in 12 patients with an myelodilysis drill from the iliac crest. Tumor cells in bone marrow aspirates were detected by an immunocytochemical method using monoclonal antibodies against EMA (epithelial membrane antigen) and LCA-LON-M8.

Myelodilysis biopsies were morphologically examined. In 6/22 bone marrow aspirates staining of single tumor cells (6-32 cells) could be demonstrated. 2 of the 6 patients were stage I, 4 stage II disease at time of clinical admission (histologically proven). Bone scan and radio-photography showed no pathological changes. In all patients myelodilysis tumor spread could not be detected. Conclusions about diagnostic and prognostic value and therapeutic consequences cannot be drawn at this time since follow up of the patients is no longer than 12 months and some patients are still under adjuvant chemotherapy.

IMMUNOLOGICAL STUDY ON CARCINOEMBRYONIC ANTIGEN (CEA), LACTALBUMIN (LA), LACTOHEMAGGLUTININ (LHA), MYOSIN(FM) AND S100 PROTEIN(S100P) IN MAMMARY PLAND CARCINOMA


Sections of 100 invasive carcinomas were examined by the PAP method to clarify the relation of antigens to 1) the histogenetic type of tumors, 2) the age of the patients, 3) the epithelial and myoepithelial characters of tumor cells and 4) the histogenesis of the tumor cells.

These tumors were obtained from 99 females and 1 male of 30 -91 years old. Of the carcinomas, 76 were invasive ductal(1D), 6 were ID with a predominant intraductal component (IDIC), 1 was an invasive lobular(1L), 12 were medul- lary(MED), 1 was papillary(PAP), 3 were tubular(TUB) and 1 was an apocrine(ACP) type typed according to WHO. The 10 and IDIC types were classified on 15 papillotubular(PF), 24 solid-tubular(ST) and 43 scirrhous(SCC) typed according to the Japanese Hamamy Cancer Society.

The following results were obtained: 1. Antigens were demonstrated in these tumors in the following order of frequency: CEA in 81 cases, ACT in 74, M0 in 52, S100P in 47, LF in 33 and LA in 20 of the 100 cases. This order of frequency was almost the same in PT, ST and SCI, but different in MED. 2. CEA, LA, ACT and M0 were found most frequently in SCI and LF in MED, while S100P was found at similar frequencies in PT, CEA and LF were less frequent in the intermediate age group(young and older). The frequency of LA increased with age of the patients, while those of ACT and M0 decreased. S100P was seen with similar frequency in patients of all ages. The frequencies of CEA, LF and S100P appeared to be greater in postmenopausal patients, whereas those of LA, ACT and M0 were greater in premenopausal patients. 4. Both epithelial(CEA, LA or/and ST) and myoepithelial(M0 or/and S100P) markers were found in 76 of the tumors, only epithelial markers in 14, only myoepithelial once in 5 and neither markers in 5 of the tumors.
In this paper we are pointing out the importance of stroma in breast carcinomas in order to reach an accurate diagnosis. From the ultrastructural point of view we can see in non-invasive breast carcinomas the presence of fibroblasts in stroma with dilatation of ergastoplasm without any transformation of these fibroblasts. When carcinomas invade stroma the fibroblasts become myofibroblasts, as a reaction of stroma to invasion of malignant cells. This event allows the pathologist to prove early infiltration of carcinomas based upon the presence of myofibroblasts in stroma. Elastosis has been also investigated in carcinomas and benign lesions. Intraductal carcinomas may have an important elastosis followed in second place by invasive carcinomas. Benign lesions of breast such as fibroadenoma, adenosis, etc. have no significant elastosis.

In discussing the precancerous potential of intraductal breast papillomas, according to recent literature data, author distinguishes two distinct type of pathology: 1. the solitary intraductal papilloma of a major duct; 2. the most rarely type, the macroscopic multiple intraductal papillomas, that develops in 20-40 per cent into carcinoma. In authors 2000 cases in the course of breast operations 86 proved to be simple, while 14 multiple papillomas. From the multiple papillomas 5 became cancers: the average age of latter was 35 years. Author shows on the poster in coloured macro- and micro-photos the cytomorphological and histological characteristics of the malignized multiple papillomas. As an introduction he describes the benign cyto-histological pictures commonly occurring up to the precarcinomas. Finally he summarized the histologic caser-types of papillomas which got cancerous: 3 cases corresponded to adenocarcinoma muciparum, in two patients the intraductal apocrine-papillary and cribriform carcinoma has occurred, well known by Haagensen as well. The patients are so far free of recidiva and metastasis.

The investigation was based on a series of 300 biopsy specimens in which estrogen /ER/ and progesterone /PR/ receptors were determined. The specimens were obtained from women with primary breast cancer operated at the Dept. of Oncology in the years 1982-1985. ER and PR contents were determined at the same Dept. by radioisotope /dextran-coated charcoal/-analysis. The cut-off between positive and negative tumors was 10 fum estradiol/cell tissue protein. The status of ER and PR was correlated with the following pathomorphological patterns: 1. Histopathological type of the tumor and 2. Grade of histological malignancy. We have found a strong correlation between the ductal and eino-ductular differentiation and the values of ER and PR. The receptor content and histological grade of malignancy also showed a distinct correlation: the well-differentiated tumors had a higher incidence of ER and PR than the poorly differentiated ones. The medullary carcinomas had very low or non-detectable ER levels. The mucinous carcinomas appeared to have generally higher ER levels than the infiltrating duct carcinomas.
MULTINUCLEATED (OSTEOCLAST-LIKE) GIANT CELLS OF STROMAL ORIGIN IN BREAST CARCINOMAS. T. Zilari, L. Lamovac, M. Va Krasovec, L. R. Obis, The Inst. of Oncology, Ljubljana, T. U.

Multinucleated giant cells of osteoclastic type are not so rarely found in various breast neoplasms. We en countered them several times in metaplastic carcinoma of the breast and in phyllodes tumors - not only in cases with well developed osseous metaplasia but also in those without it - and in 3 cases of infiltrating papillary carcinoma. We separately analyzed these 3 papillary carcinomas by means of aspiration cytology and light microscopy using H&E, special stains and immunoperoxidase reactions. In one case EM examination was also employed. Our results are as follows: 1) Grossly, these were relatively bulky, well circumscribed tumors varying in size from 2.5 to 9 cm in their largest dimension, and were usually cystic and reddish-grey in color. 2) Axillary lymph nodes were negative in all 3 cases. 3) Microscopically, they were well to moderately differentiated infiltrating papillary carcinomas with various number of osteoclast-like giant cells in the stroma. Immunohistochemically, these giant cells were characterized by negative reaction to keratin, but also to lysozyme and acid phosphatase. EM in one case showed that the nature of giant cells was consistent with histiocytic origin. 4) Factor VIII related antigen and reticulin stain could not demonstrate any special degree of vascularity of these tumors in contrast to other reports. 5) We believe that the presence of giant cells of osteoclastic type in breast carcinoma is not so rarely seen, if only sought for. It may well be that giant cells are first discovered in aspiration cytology smears. 6) The meaning of these findings is not clear for the moment neither from our cases nor from the literature. It is of interest to note that all our cases were infiltrating papillary carcinomas which was not reported previously.

Recurrence of the Breast - Carcinoma or Second Primary?

German Democratic Republic

Exploring late recurrences and late metastasis of the Breast-Carcinoma the question arises: Are Carcinoma-foci observed after long intervals always late recurrences? Can de novo second carcinomas have developed in remained breast tissue? From these aspects the biopsies are analyzed retrospectively and prospectively and the autopsies post mortem. Up to now remainders of the breast tissue have been found in 13 of 103 local recurrences resp. recurrences in the operation area in the biopsies of the period 1966 to 1973 with a latency from two months to 26 years. During September 1962 till December 1984 remainders of breast tissue have been discovered in the autopsies at 9 out of 38 deceased women after radically mastectomy of the Breast-Carcinoma with the survival time from 5 weeks to 15 years. These residues may be the matrix of a de novo second carcinoma.
UKRAINE-LIKE PLASMINOGEN ACTIVATOR IN BREAST TUMORS: A ROLE IN METASTASIS AND BREAST CANCER DEVELOPMENT

S. A. Fedotov, I. Shevchenko and D. D. Strukov

The present study investigated the expression and localization of plasminogen activator (PA) in various breast tumor tissues. The results indicated that PA is a key molecule in breast cancer development, playing a role in metastasis and breast cancer progression. The study also suggested that PA could be a potential target for the development of new therapeutic strategies.

LOCALIZATION OF PLASMINOGEN ACTIVATOR IN HUMAN COLONRECTAL CANCERS AND ADENOMAS

S. Kohga, J. Suzuki, T. Ito, Y. Hasui and A. Sumiyoshi

The study examined the localization of plasminogen activator (PA) in human colorectal cancers and adenomas, using immunohistochemistry and other techniques. The results showed that PA was localized in the tumor cells, especially in the invasive and metastatic areas, suggesting a role in cancer progression. The study also suggested that PA could be a potential target for the development of new therapeutic strategies.
Carcinomyo-Phosphate Synthase II in Rat Bone Marrow and Action of Acivicin

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Earlier work from this lab showed that the activity of the L-glutamin dependent carcinomyo-phosphate synthase II (CPS II; EC 6.3.5.5; CPS II) was increased in hepatomas in a transformation- and progression-linked fashion and in other animal and human neoplasms (J. Biol. Chem. 257: 435, 1982). It was also demonstrated that the antitumor agent, acivicin, now in Phase II trials, inactivated CPS II in vitro and in vivo in rat hepatomas and in vitro in human colon carcinoma (Bioclinic. Pharmacol. 31: 927, 1982). Since acivicin has an important side effect in depleting bone marrow, the purpose of this study was to elucidate the action of this drug on CPS II activity in bone marrow. Bone marrow was removed from rat femurs and in the 100,000 x g supernatant fraction enzyme kinetic studies were carried out and the action of acivicin was examined. The bone marrow extracts were treated with Sephadex G-25 chromatography to remove glutamine. The kinetic studies showed that for the bone marrow CPS II K for glutamine, ATP, and BDP, were 16.6, 1.2 mM and 2.0 μM respectively and the pK optimum was 7.4. The bone marrow activity measured under linear enzyme kinetic conditions was 95 nmol/hr/mg protein. Acivicin in vitro competitively inhibited against glutamine with Ki ~1.7 μM. Acivicin in vitro inactivated CPS II with an inactivation constant of 0.01 μM and a minimum inactivation time of T = 0.65 min at 37°C. These results indicate that the CPS II in the rat bone marrow is similar in its kinetic behavior to the enzyme in rat liver and hepatomas. The in vitro inactivation of the bone marrow CPS II by acivicin is in line with the observations of Prajda et al. (in this Congress) showing the in vivo inactivation of CPS II and other glutamine-utilising enzymes in the rat bone marrow after acivicin treatment. (Supported by USPH grants CA-15326 and CA-05034).

Body fluids (sera, ascites, pleural effusions) from cancer patients suppress glucose utilization by murine peritoneal exudate macrophages in vitro. The cancerous sera affect only the glycolytic pathway. The target enzyme sensitive to the sera is phosphofructokinase (ATP: Fructose-6-phosphate 1-phosphotransferase, EC2.7.1.11)(PFK). The "PFK INHIBITION TEST" for the detection of cancer has been established after examining thousands of sera. 58% of cancerous sera were positive regardless of cancer origin. 54% of early gastric cancer were also positive. This method was applicable for monitoring cancer patients. Mechanism of PFK inhibition relates to lower buffering capacity of sera against acidic solutions. It elucidated that the measurement of pH after mixing serum and 40 mM acetic acid identify the onset of malignant neoplasms anywhere in body. The "acetic acid-pH method" identified 78% cancerous sera as positive. Sera from pregnant ladies, patients with chronic renal failure, diabetes mellitus, acute peptic ulcer, partial liver cirrhosis, SLE receiving steroid hormone, and heavy anemia showed pseudopositive. Although the pH-method is simplest, it remains problems in reproducibility and reliability for routine work. Total scoring recommends the PFK inhibition test for detection of tumors, and for monitoring patients after therapy. We investigated the mechanism of formation of substance(s) with lower buffering capacity, and clarified that overproduction of lactic acid by tumors might cause as one of the factors in changing serum components to active upon onset of malignant neoplasms.

PLASMINOGEN ACTIVATORS. BIOCHEMICAL PHENOTYPES FROM THE URINE OF A LUNG CARCINOMA PATIENT. H.A. Toth, Zs. Molnar, National Institute of Oncology, Budapest, Hungary

Serum coeruloplasmin (Cp)/, haptoglobin (Hp)/, C-reactive protein (CRP)/ and lactate-dehydrogenase activity (LDH)/ were examined in the sera of patients with histologically confirmed non-Hodgkin's lymphoma. The patients were in clinical stage IV according to Ann Arbor classification. The purpose of this study was to determine the usefulness of the examined serum parameters for the prediction of prognosis and for therapeutic monitoring. In 97 untreated patients raised Cp values (> 150 U/l) were found in 37.1%, while abnormal Hp values (> 7.5 g/l) were measured in 56.7%. Pretreatment serum Cp and Hp levels of both were normal in 32.8%. Normal values were indicators of a better response to therapy and a longer survival. Cp and Hp values together or one of them were elevated in 67% of the patients. Their high levels were associated with poorer response to therapy and shorter survival. The regular determination of Cp and Hp during the cyclic combined chemotherapy may help to recognize the therapeutic effect. Unchanged normal values of both parameters or their early rapid fall during the therapy were followed by complete remission. Unchanged high levels or frequent alteration are reliable indicators of therapeutic failure. Before treatment pathological CRP (> 10 mg/l) were found in 42.8%, while raised LDH activity (> 240 U/ml) were measured in 36.6%. Observations suggest that the determination of LDH or CRP besides Cp and Hp from the same serum sample may reduce the number of false predictions and yield better information about the effect of treatment and survival as well.

ISOLATION AND CHARACTERIZATION OF 5-CARBOXYMETHYLURIDINE FROM THE URINE OF A LUNG CARCINOMA PATIENT. H.A. Toth, Zs. Molnar, National Institute of Oncology, Budapest, Hungary

Serum coeruloplasmin (Cp), haptoglobin (Hp), C-reactive protein (CRP) and lactate-dehydrogenase activity (LDH) were examined in the sera of patients with histologically confirmed non-Hodgkin's lymphoma. The patients were in clinical stage IV according to Ann Arbor classification. The purpose of this study was to determine the usefulness of the examined serum parameters for the prediction of prognosis and for therapeutic monitoring. In 97 untreated patients raised Cp values (> 150 U/l) were found in 37.1%, while abnormal Hp values (> 7.5 g/l) were measured in 56.7%. Pretreatment serum Cp and Hp levels of both were normal in 32.8%. Normal values were indicators of a better response to therapy and a longer survival. Cp and Hp values together or one of them were elevated in 67% of the patients. Their high levels were associated with poorer response to therapy and shorter survival. The regular determination of Cp and Hp during the cyclic combined chemotherapy may help to recognize the therapeutic effect. Unchanged normal values of both parameters or their early rapid fall during the therapy were followed by complete remission. Unchanged high levels or frequent alteration are reliable indicators of therapeutic failure. Before treatment pathological CRP (> 10 mg/l) were found in 42.8%, while raised LDH activity (> 240 U/ml) were measured in 36.6%. Observations suggest that the determination of LDH or CRP besides Cp and Hp from the same serum sample may reduce the number of false predictions and yield better information about the effect of treatment and survival as well.
**3449**

**STUDIES OF THE INTERCALATION OF CARCINOGENIC HYDROCARBON METABOLITES INTO DNA.**

P.R. LeBreton, Department of Physiology and Pharmacology, School of Medicine, Loma Linda University, Loma Linda, CA 92350, USA.

Ellagic acid (EA), a plant phenol found in a variety of foods humans consume, is reported to possess antimutagenic and antioarcinogenic activity. Wood, et al (PNAS 79:5513-5517) reported the formation of adducts between EA and the diol-epoxide of benzo(a)pyrene (BaP) in aqueous solutions. Other reports indicate that EA inhibits the metabolism of polycyclic aromatic hydrocarbons (Mukhtar, et al. BBRC 185:434-441; 188:224-31). EA inhibits carcinogenicity series the lowered carcinogenic activity of the ring-halogenated dimethylaryl-triazene compounds of both series convincingly showed that the carcinogenic activity of the carcinogenicity region diol, 

The evidence so far obtained favours the selective in vivo tumor inhibition by that series of tumor inhibitory compounds. The evidence favours the involvement of 3-hydroxymethyl-3-methyl-1-aryl-triazenes, or their as yet unknown conjugates. The active species may exist in an equilibrium with their corresponding triazines (iminium) ions that selectively react with cellular biopolymers.

**3450**

**STUDIES OF THE INTERCALATION OF CARCINOGENIC HYDROCARBON METABOLITES INTO DNA.**

P.R. LeBreton, Department of Physiology and Pharmacology, School of Medicine, Loma Linda University, Loma Linda, CA 92350, USA.

Studies of the intercalation into DNA of nonreactive metabolites and metabolite model compounds of BP, have been carried out. The molecules examined include trans-7,8-dihydroxy-9,10-dihydro-BP, trans-4,5-dihydro-BP, 1,6,9,10-tetrahydroxy-7,8,9,10-tetrahydroxy-7,8,9,10-tetrahydroxy-BP, 7,8,9,10-tetrahydroxy-5,6-dihydro-BP, and pyrene. Of all the metabolites of ultimate carci nogen, 1, which is a precursor of the ultimate carci nogen region diol, 2, in vitro solubilization studies with protein free DNA further indicate that maximum DNA uptake of 1 is more than one hundred times greater than that of the parent hydrocarbon BP. Finally, kinetic studies indicate that intercalation enhances hydrocarbon epoxide reactivity. For epoxides that are poor intercalating agents this enhanced reactivity is highly sensitive to changes in DNA structure and environment. For good intercalating agents, 3 for example, this enhanced reactivity in less sensitive to such changes.

1Abbreviation: BP, benzo[a]pyrene

**3451**

**CORRELATION STUDIES BETWEEN THE BINDING OF AFLATOXIN B1 TO THE CHROMATIN COMPONENTS AND THE INHIBITION OF NUCLEAR AND NUCLEAR DNA SYNTHESIS.**

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Aflatoxin B1 (AFB1) is a potent inhibitor for rat liver nuclear and nuclear DNA synthesis. Recently, we have also found that it binds preferentially to the active chromatin in vivo and in vitro (Carcinogenesis 4, 889, 1983). However, since the binding is to both DNA and chromosomal proteins (Proc. Amer. Assoc. Cancer Res. 20, 91, abstr. #358, 1984), the question is which of the binding is responsible for the inhibition of DNA synthesis. Male Springer-Dawley rats, 200g, were given i.p. injection of 10, 50, 100, 300, and 500 μg AFB1; per 100g body weight containing 100 μCi [3H]AFB1 (sp. act. 25 Ci/mmol), the animals were sacrificed 2 h later. Liver nucleoli and nuclei were isolated and the binding of AFB1 to DNA and protein of each fraction were determined by DNAase 1 digestion and 5% TCA hydrolysis. We found that the binding of AFB1 to both nuclear and nuclear DNA plateaus at 300 μg AFB1; per 100g body weight with values around 100 and 400 pmol AFB1 per mg nuclear and nuclear DNA, respectively. On the other hand, the binding to protein is linear, although with different slopes, for both nuclear and nucleolar fractions even at 500 μg AFB1; per 100g body weight, the highest dose used. Since AFB1 only inhibits de novo nuclear and nuclear DNA synthesis plateaus respectively at 60% and 90% inhibition levels at the dose of 300 μg AFB1; per 100g body weight, these results suggest the binding of AFB1 to DNA, not to protein, is responsible for the inhibition of DNA synthesis (supported by NIH grant CA-30091).

**3452**

**ELLAGIC ACID BINDING TO DNA AND INHIBITION OF DNA-BINDING OF BENZ()APYRENE IN CULTURED EXPLANTS OF THE RAT AND HUMAN.**

Robert W. Tegt, Department of Physiology and Pharmacology, School of Medicine, Loma Linda University, Loma Linda, CA 92350, USA.

Ellagic acid (EA), a plant phenol found in a variety of foods humans consume, is reported to possess antimutagenic and antioarcinogenic activity. Wood, et al (PNAS 79:5513-5517) reported the formation of adducts between EA and the diol-epoxide of benzo(a)pyrene (BaP) in aqueous solutions. Other reports indicate that EA inhibits the metabolism of polycyclic aromatic hydrocarbons (Mukhtar, et al. BBRC 185:434-441; 188:224-31). EA inhibits carcinogenicity series the lowered carcinogenic activity of the ring-halogenated dimethylaryl-triazene compounds of both series convincingly showed that the carcinogenic activity of the carcinogenicity region diol, 

The accepted current hypothesis claims that carcinogenesis in humans.

In vitro solubilization studies with protein free DNA further indicate that maximum DNA uptake of 1 is more than one hundred times greater than that of the parent hydrocarbon BP. Finally, kinetic studies indicate that intercalation enhances hydrocarbon epoxide reactivity. For epoxides that are poor intercalating agents this enhanced reactivity is highly sensitive to changes in DNA structure and environment. For good intercalating agents, 3 for example, this enhanced reactivity in less sensitive to such changes.

1Abbreviation: BP, benzo[a]pyrene

Recently, we have also found that it binds preferentially to the active chromatin in vivo and in vitro (Carcinogenesis 4, 889, 1983). However, since the binding is to both DNA and chromosomal proteins (Proc. Amer. Assoc. Cancer Res. 20, 91, abstr. #358, 1984), the question is which of the binding is responsible for the inhibition of DNA synthesis. Male Springer-Dawley rats, 200g, were given i.p. injection of 10, 50, 100, 300, and 500 μg AFB1; per 100g body weight containing 100 μCi [3H]AFB1 (sp. act. 25 Ci/mmol), the animals were sacrificed 2 h later. Liver nucleoli and nuclei were isolated and the binding of AFB1 to DNA and protein of each fraction were determined by DNAase 1 digestion and 5% TCA hydrolysis. We found that the binding of AFB1 to both nuclear and nuclear DNA plateaus at 300 μg AFB1; per 100g body weight with values around 100 and 400 pmol AFB1 per mg nuclear and nuclear DNA, respectively. On the other hand, the binding to protein is linear, although with different slopes, for both nuclear and nucleolar fractions even at 500 μg AFB1; per 100g body weight, the highest dose used. Since AFB1 only inhibits de novo nuclear and nuclear DNA synthesis plateaus respectively at 60% and 90% inhibition levels at the dose of 300 μg AFB1; per 100g body weight, these results suggest the binding of AFB1 to DNA, not to protein, is responsible for the inhibition of DNA synthesis (supported by NIH grant CA-30091).

The evidence so far obtained favours the selective in vivo tumor inhibition by that series of tumor inhibitory compounds. The evidence favours the involvement of 3-hydroxymethyl-3-methyl-1-aryl-triazenes, or their as yet unknown conjugates. The active species may exist in an equilibrium with their corresponding triazines (iminium) ions that selectively react with cellular biopolymers.
**INHIBITORY EFFECTS OF ELLAGIC ACID ON DNA DAMA-
GE BY N-NITROSO COMPOUNDS**

T. Górska, E. Górska, J. Poczobut-Odlaniola.
Sanitary-Epidemiological Station in Lodz, Poland.

Ellagic Acid is known as an inhibitory factor with reference to the mutagenicity and cytotoxicity of known ultimate carcinogenic metabolite of benzo/a/pyrene. In our experiments DNA - N-nitrosodimethylamine and Ellagic Acid were injected intraperitoneally 4 hours before killing the rats. The quantity of particular fraction of liver DNA was determined by alkaline elution procedure. The percentage of DNA undergone fragmentation passing through the filter was a basis for the evolution of the exponent of DNA damage. DNA fraction was marked with fluorochromes 3,5-diaminobenzolc acid dibydrochloride. Fluorescence intensity was measured by SPF "Anino-lumilum". Dlmethylsulfoxide was used for DMNA and Ellagic Acid dissolution.

Studies show that ellagic acid distinctly inhibits the genotoxicity of DMNA.

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**THE INFLUENCE OF DIFFERENT SUBSTANCES UPON THE LETHAL EFFECT OF N-METHYL-N-NITROSUREA IN NEW BORN RATS.**

Kroger, H. R. Gratz and A. Dietrich
Robert Koch-Institut, Nordufer 20, D-1000 Berlin 65

After a single injection of N-methyl-N-nitrosurea (1) mainly thymic lymphomas are induced. We applied 1 to 10 day old rats. The animals injected with 1 started to die around 100 days after the application of the substance. At day 250 only few animals were still alive. Thymidine, theophylline, nicotinamide, nicotinamide + caffeine, bromodesoxyuridine are given together with 1, the animals are dying much earlier. This is not the case, if 1-methyl-nicotinamide, L-methionine, L-tryptophan + methionine, guanosine, caffeine are applied with 1. It has to be elucidated if the potential effect of some substance is due to an interference with the repair mechanism.
3457 IDENTIFICATION OF BENO[APYRENE (BP)-DEOXYGUANOSINE (dG) ADDUCTS FORMED BY ONE-ELECTRON OXIDATION. E. Ragan, E. Cavalleri, S. Cavalleri, and F. Cavalleri. Yorktowne Inst., Univ. of Nebraska Medical Center, Omaha, NE 68105, USA.

Evidence on the mechanism of activation of carcinogens in biological systems can often be established by the identification of the carcinogen-DNA adducts formed. Model adducts of known structure are essential in such identification. Model adducts of DNA were synthesized by anodic oxidation of BP in the presence of dG. Adducts were purified by reverse-phase HPLC on a 5 μm ODS column using a water-methanol gradient. Complete structures have been determined for 3 adducts: (a) BP bound to the C-6 of dG ("C6dG") or the C-8 of guanine ("C8G") and BP bound at C-6 to the N-7 of guanine ("N7G"). Structure determinations have been conducted by NMR spectroscopy, including 2D proton-proton NMR. Atomic bombardment mass spectrometry coupled with collisional activation mass spectrometry confirmed the structures of the 3 adducts. These model compounds have been used to identify adducts formed in vivo in the horsehair penicillium/N, N-catalyzed DTNB of [14C]BP to calf thymus DNA. After incubation of BP, DNA, enzyme and cofactors for 1 hr at 37°C, DNA was precipitated with ethanol and redissolved in buffer for enzymatic digestion to mononucleotides. The adducts released from DNA by depuration during the binding incubation, found in the ethanol-water supernatant, were analyzed by HPLC, as were the adducts in the DNA digest. About 10 times as much N7G adduct was observed in the supernatant compared to the digest, indicating that the N7G adduct destabilizes the guanine-deoxyribose bond, leading to depuration of DNA. However, the ADDUCTS FORMED BY ONE-ELECTRON OXIDATION. E. Rogan, E. Cameron, J. Justin McCormick and R. Michael Liskay—Carcinogenesis Laboratory, Michigan State University, East Lansing, MI 48824, and Department of Pathology, Yale University School of Medicine, New Haven, CT 06510, U.S.A. Mouse liver cells lacking thymidine kinase (tk-) activity were transfected with a recombinant plasmid containing two different mutated forms of the herpes tk gene. These tk- mutants were tested for their ability to produce tk+ revertants in cells containing single, stably-integrated copies of the plasmid in order to stimulate tk activity by the tk+ transfection. Tk+ transfections were selected by subsequent selection in HAT medium. Each agent tested, i.e., RCo, UV, N,N-dimethyl-N-nitrosourea (MNU), and N,N,N-7,8-diol-9,10-epoxide of benzo[alpyrene (BPEP), was tested using tk- cells which lowered the cell survival to between 80% and 10% of the untreated control and c-10-15 determination was made from 2 ± 10^6 surviving target cells. The spontaneous frequency per 10^8 viable cells averaged 18 ± 1. UV, MNU, and BPEP caused a linear dose-dependent increase in tk+ recombinants. The tk+ cell line used is a tk- variant of the Htk- line isolated from the strain C57BL/10Sn. The order of activity of the agents, compared at 34°C survival doses, was: MNU, BPDE, UV, N,N-dimethylhydrazine, N,N-7,8-diol-9,10-epoxide benz[a]pyrene (BPEP). At least 90% of the tk+ cell line was tk- resistant. The tk+ activity was not lost when exposed to 34°C survival doses, and only a single tk+ gene conversion with the tk- cells returning the Htk gene duplication and the tk- gene. In 10% of the events, the tk+ gene was lost and the only single tk+ gene (w.t.) returned (single reciprocal exchange). Southern blot analysis showed that each tk+ recombinant tested contained an Xho I resistant (w.t.) Htk gene. No evidence of spontaneous or carcinogen-induced recombination was found in cells containing only a single mutant copy of Htk. NIH Grants CA12175, CA12174, and a Leukemia Society Scholar Award.

3458 THE CHICK EMBRYO MODEL IN ONCOLOGY FOR A WIDE SPECTRUM OF GROWTH DISORDERS INCLUDING CARCINOGEN-INDUCED HOMOLOGOUS RECOMBINATION. C. Cameron and G. Feuer. Depts. of Pathology and Clinical Immunology, University of Toronto, Toronto, Canada M5S 1A8.

Liver nodules generated by exposure of male rats to initiation by diethylnitrosamine (DEN) and selection for resistance with or without acetylsalicylic acid, lead to a hyperplastic hepatocytosis (Selt-Farber model) show characteristic changes in the architectonic organization and in the activities associated with the metabolism of xenobiotics. Phase I components (microsomal cytochrome P-450 content and aminopyrine N-demethylase) are significantly decreased and Phase II components (glutathione transferase, epoxide hydrolase, UDP-glucuronosyl transferase and DT-diaphorase) are increased when compared to normal liver or surrounding hepatocytes. All of these changes can represent a coordinated package contributing to the functional resistance of nodule hepatocytes to the cytotoxic effects of xenobiotics, which may be the key event of selection-promotion in the resistant hepatocyte model. Recently using the same initiator (DEN) but different promoters (choline-deficient diets, orotic acid diets and phenobarbitol) to generate nodules we have shown an identical pattern of Phase I and Phase II changes (M.W. Roomi et al. Cancer Res. 45: 564-571, 1985). When nodules are induced in female rats using the resistant hepatocyte model, Phase I components are once again decreased and Phase II components increased. In addition, microsomal prostaglandin synthetase and microsomal prostaglandin binding are decreased in nodules of female or male rats compared to control and surrounding liver tissue. These observations suggest that the event of selection-promotion in the initiation phase is consistent with a consistent pattern of enzyme modifications in preneoplastic hepatocytes of male and female rats with the progression phase and it is independent of the nature of the promotion, Supported by N.S.E.R.C. and the Medical Research Council of Canada.
INFLUENCE OF DIETARY RIBOFLAVIN DEFICIENCY ON THE MECHANISM OF CARCINOGENESIS BY DIMETHYLNITROSAMINE (DMN) IN RATS. R.C. Gupta, E. Berkeley and P.E. Berger, Baylor College of Medicine and N. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030, USA.

Riboflavin has been shown to have some effects on chemical carcinogenesis, primarily through its influence on metabolic pathways. For nitrosamines, metabolic activation and the interaction of their metabolites with DNA are believed to be the rate-limiting steps in carcinogenesis. Formation of methylated bases in DNA, especially 6-methyl guanine (6-MeG), has been widely recognized as a critical lesion. The influence of dietary riboflavin deficiency on the metabolism of DMN, DNA damage and alkylation was investigated. In riboflavin deficient rats, the in vivo metabolism, measured as the disappearance of DNA from plasma, increased 4 fold. This finding was supported by in vitro studies which demonstrated that the activity of microsomal DMN-demethylase 1 in both liver and kidney was enhanced significantly. The amount of DNA damage, evidenced as single strand breaks, was estimated by measuring the template activity of isolated DNA with E. coli polymerase I. Liver DNA from DMN treated rats fed riboflavin deficient diet showed a 146% increase in the template activity above the untreated control level whereas, those of the control animals showed only a 14% increase in the template activity. This result indicated either more priming sites for the enzyme and/or more single stranded regions which reflected more damage in the DNA of the riboflavin deficient rats. Interestingly the level of 6-MeG in DNA was also higher in riboflavin deficient animals. These findings demonstrated the effect of riboflavin deficiency on the crucial steps in DMN-induced carcinogenesis, were the susceptibility of the host to carcinogenic effect of this compound.

ANALYSIS OF DNA ADDUCTS IN HEPATIC NODULES AND NON-TARGET TISSUES DURING 2-ACETYLAMINOPERIDINE (AAP) CARCINOGENESIS. R.C. Gupta, E. Berkeley and P.E. Berger, Baylor College of Medicine and N. D. Anderson Hospital and Tumor Institute, Houston, TX, 77030, USA.

Exposure of rats to a standard four-cycle feeding regimen of o-DMN 2-acetylaminofluorene (AAF) results in the formation of hepatic nodules, but nothing is known as to the types of DNA adducts formed in these putative premalignant nodules. By using a sensitive radiolabel assay (R.C. Gupta, Cancer Res., 45, 1956-1956, 1985), we have analyzed the DNA adducts in individual hepatic nodules during the carcinogenic process. Kidney, spleen and testis were included as non-target tissues. No qualitative difference was observed in the DNA adducts found in hepatic nodules when compared with the DNA adducts seen in the non-target tissues; however, quantitative differences occurred. Two known (6-CC-AF and 6-CC-AAP) and at least two unknown DNA adducts were detected, with 6-CC-AF being predominantly (95%) formed, in all tissues examined. At the end of the first three weeks of AAF feeding, DNA binding in liver (200 fmol adducts/µg DNA) was found to be about 2, 6 and 16 times higher than the DNA binding in kidney, spleen and testis, respectively. By the end of the last AAF feeding cycle, the liver exhibited numerous nodules that could be dissected free from the surrounding tissue. DNA adducts measured in these hepatic nodules ranged from 30 - 90 fmol adducts/µg DNA, while kidney, spleen and testis showed about 200, and 75 fmol adducts/µg DNA, respectively. Three months following the cessation of AAF, the binding in persistent nodules and the non-target tissues had decreased to 10 - 20% of the adducts measured at the end of the fourth cycle. These data indicate that AAP-DNA adducts are found in non-target tissues as well as in putatively premalignant lesions and that persistence of adducts per se is not an unique characteristic of susceptible cell populations.

Supported by USPHS Grants CA 30066 and 20657.
The carcinogenic effect of N-nitrosochlor-diazepoxide (NCD), synthesized in our institute, alone or in association with vitamin A was studied in groups of 20 female Wistar rats. The incidence of tumors following oral treatments was: two breast fibroadenomas in the group receiving NCD, one breast fibroadenoma in the group with vitamin A and two invasive malignant abdominal fibrosarcomas (likely originating in the retroperitoneum), in the group treated with NCD and vitamin A.

Carcinogenic dialkylnitrosamines are subjected to enzymatic hydroxylation to nitrogen to give hydroxy-alkyl derivatives. The latter are reactive and readily lose an aldehyde fragment. These intermediates are too unstable to study directly and were converted into their ester conjugates. El and E isomers of the acetylated nitrosamines are readily prepared and separated chromatographically. The isolomers are configurationally stable as indicated by H NMR studies and this is borne out by ab initio calculations of the energy barrier to rotation for the esters and for the free hydroxy compounds. If the E and Z forms are generated separately, they will react as discrete species. The isomeric ester conjugates undergo hydrolysis under both enzymatic and basic conditions to generate the respective E and Z electrophilic alkyl diazohydroxides. Esterases selectively hydrolyse the E ester to generate the Z alkyl diazohydroxide. The rate of hydrolysis depends markedly on the nature of both R1 and R2. The observed stericselectivity of E and Z alkyl diazohydroxides on sensitive DNA base sites leading to lesions, including the critical carcinogenic G guanine alkylation, were interpreted by ab initio calculations in terms of the Hard and Soft Acids and Bases Theory. The observed steroselectivity of enzymatic hydrolysis of these ester conjugates of the dialkylnitrosamines metabolites leading to the generation of site-selective electrophiles contributes to the understanding of their carcinogenic action.

Nine-day-old rats were treated with a single intraperitoneal dose (100 mg/kg body weight) of 3-methylcholanthrene (3-MC) and 24, 48, 72 and 120 h later the properties of the heterogeneous nuclear ribonucleoprotein (hnRNP) particles derived from the livers were analyzed and compared with the properties of the hnRNP particles derived from control animals of similar ages. There were no observable differences in the physical properties among the particles isolated from livers of 3-MC treated and untreated rats. When the protein composition of the hnRNP particles was compared the 35 000-M subunit polypeptide which is normally not found in the hnRNP particles of the young rats prior to the 11th day life appears on the 10th day after 24 h 3-MC exposure. In addition, the minor polypeptide components of the particles were also found in higher quantity. The polypeptide patterns of the hnRNP particles derived from treated animals resembled those of the older animals and not those of controls of similar age. The possible mechanisms for the effect of 3-MC will be discussed.
3468 DIETHYLNELPHTHALATE IN A NEW TEST STRATEGY FOR ELUCIDATING BIOLOGICAL ACTIVITIES OF CHEMICAL CARCINOGENS. B. L. Palf, T. Schreiner, D. Konstam.

D-48: ENVIRONMENTAL RISK FACTORS II

3469 ENHANCED RISK OF CANCER AFTER LONG-TERM EXPOSURE TO MICROWAVE/RADIOFREQUENCY RADIATION. B. Czapiewski, M. Bielecki, A. Szudzik, S. Litvak. Med. Sch. Poland

3470 CANCER ACCELERATING EFFECT OF 2,450 MHZ OF MICROWAVE RADIATION ON BENZ(2a)PYRENE-INDUCED SKIN CARCINOMA IN MICE. B. Szporacki, A. Szmidt-Mazlak.

TUESDAY • AUGUST 26 • AFTERNOON
SYNERGISTIC ENHANCEMENT OF TUMOR INUULI'iOH IN MICE BY COMBINED ADMINISTRATION OF ONCOGENIC MYCOTOXINS


COMB iNED ADMINISTRRTION OF ONCOGENIC MYCOTOXINS

Univ. Sen. of Hed., YoXuha,na , Japan.

H.Kanisawa and A.Shimizu: Dept . of Pathol., Yokohama City

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Supported by the Italian Society for Cancer Research.

effects should be considered for acid contamination,

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improving results for acid-sensitive biota or obstructive diseases

in human respiratory apparatus, but other biological

are associated to sub-lethal acid exposure

Monitoring of Exposure to Alkylating carcinogens results

in the covalent binding of the active genotoxic species to cellular macromolecules. Human exposure to these alkylating agents may be monitored by determination of the extent of this binding. We have developed methods based on the use of capillary gas chromatography-mass spectrometry (GC-MS) for the quantitative determination of alkylated amino acids in protein and of alkylated bases in DNA, and the use of haemoglobin adducts as an indicator of the amount of circulating genotoxic agents has recently excited much interest. For example exposure of rats to acrylamide at 10 mg/kg/day for 3 months showed its adducts in haemoglobin, stable isotope labelled 14C-labelled acrylamide with haemoglobin have been used as internal standards for these analyses. Exposure of rats to methylating agents (e.g. methyl methanesulphonate, methyl nitrosourea, nitrosated 2-aminoiminothyl) may similarly be determined from measurement of molecular weight changes.

Supported by the Italian Society for Cancer Research.
ARECOLINE HYDROBROMIDE ISOLATED FROM THE BETEL NUT
Daniel A. Brotsky, M.D.
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This Alkaloid is very carcinogenic in comparison to the other isolated Alkaloids. On the Pacific Islands of the United States trust territories, investigations revealed high frequency of Cancers of Oral Cavity due to this Alkaloid. The Rhesus Monkey was used for Animal experiment and Omava Reservoir was built into the Buccal mucosa, containing the Arecoline Hydrobromide.

PROTECTIVE EFFECTS OF 4-CAROTENE AGAINST PSORALEN PHOTOTOXICITY: RELEVANCE TO PROTECTION AGAINST CARCINOGENESIS
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Division of Toxicology, Food and Drug Administration, Washington, D.C. 20204

ß-Carotene (car) is a naturally occurring antioxidant known to prevent photosensitization by endogenous photosensitizers. This ability of car has been applied clinically to relieve symptoms of patients suffering from certain light sensitive skin diseases. Recently, we were able to demonstrate in an experimental model that dietary car was effective in in vivo protection against phototoxicity (PT) induced by ß-methoxypsoralen and UVA light. No such protection was observed against UVB-induced PT. It has been shown both in animal models and clinical studies that chronic psoralen PT can lead to carcinogenesis. Thus, the observed protective effect may have implications for protection against carcinogenesis.

In the last few years, based on both experimental and epidemiological studies, interest has evolved in carotenoids as potential cancer-preventative agents. Various mechanisms for this phenomenon, i.e., involving the unmetabolized carotenoid, the provitamin A property of ß-carotene as well as alteration of the immune function of the host by carotenes, have been proposed. The capacity of our experimental model for future studies on protective effects of carotenoids against PT and carcinogenesis will be discussed.

LEUKEMOGENICITY OF HALOPERIDOL IN MICE
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Haloperidol (Hp), a butyrophenon, is widely used for the treatment of psychotic disorders in man. Recently we reported that Hp causes, in high incidence, the development of monocytic-myeloid leukemias in male NMRI mice upon 5 x 5 mg Hp/kg ip administration (Fey et al., Carcinogenesis 3, 223 '82). Here we present evidence for a leukemogenic effect of Hp in two other strains of mice (XVII x AKR hybrids, low leukemia BALB/Bom). The strain-dependent incidence of Hp-induced leukemias ranged both in males and females between 34 % and 69 % with average latencies between approx. 200 and 600 days. On the basis of cytological and cytochemical criteria the predominate type of leukemias was classified as monocytic-myeloid. These leukemias were serially transplantable. Cell-free extracts of leukemia tissues did not induce the disease indicating that no virus was activated by Hp. When Hp was administered after a suboptimal dose of nitroso-methylurea (NMU), a higher incidence of mixed-type leukemias was observed as with Hp alone. NMU alone induced lymphatic leukemias with a clear-cut viral involvement. The tumor promoter 12-O-tetradecanoylphorbol-13-acetate did not influence Hp leukemogenesis.

We reported previously that serial passages of oncogenic Marek's disease virus (MDV) in culture resulted in structural change of its DNA with loss of oncogenicity (K. Hirai et al. Virology 125:385,1981). The structural difference between oncogenic and nononcogenic MDV strains was found in the Bam HI-U and H fraggments, which contain a portion of the long inverted repeats of the MDV genome. DNA of the oncogenic MDV strain BCI-1 contains three units of tandem direct repeats with 132 bp in the terminal repeat and internal repeat, respectively, of the long region of MDV genome, whereas the attenuated, nononcogenic viral DNA contains multiple units of the tandem direct repeats. Inspection of the nucleotide sequences in the 132 bp direct repeats indicates the presence of four sets of inverted repeats with 6 or 7 bp. The region containing the direct repeats does not share homology with the DNA of herpesvirus of turkeys, which has been used as a vaccine against Marek's disease. The 1.22 and 7 fraggments containing the direct repeats was found to be hybridized to the poly(A) DNA of approximately 2.6 kb. The MDV DNA in two lymphoblastoid cell lines MDCC-MS51 and -RP1 has a structure similar to that of the oncogenic MDV. None of the viral DNA in these cell lines was found to be in a circular, plasmid state. In situ hybridization of viral DNA fragments to metaphase chromosomes of these cell lines demonstrated that the viral DNA localizes to the short arm of chromosome 2 of MS51 and RPI cells and to the short arm of chromosome 6 of MS51 cells.


As we reported previously (Iwata et al., Int. J. Cancer 35, 397, 1989), we have isolated the monoclonal antibodies (McAbs), which react with Marek's disease virus (MDV)-specific phosphorylated proteins in infected cells. Using these McAbs, cytoplasmic antigens were demonstrated by immunofluorescence test in lymphoblastoid cell lines established from Marek's disease (MD) tumors when, in culture temperature was shifted from 41°C to 33°C or when treated with 5-iodo-2'-deoxyuridine. The McAbs were found to immunoprecipitate at least three phosphorylated proteins of 30K, 36K and 24K from MDV serotype 1-infected cells or from an MD cell line MDCC-MS51 by two dimensional gel electrophoresis and Western blotting method. The phosphorylated polypeptides are immunologically, structurally different from the gag proteins specific to avian leuokemia virus. The MDV-specific phosphorylated proteins appeared to be located in the mononuclear fractions of infected cells and NC cell lines, but not on the cell surface. The phosphorylated amino acid of these proteins was found to be a phosphoserine. The McAbs directed to the phosphorylated proteins are useful for the serotype classification of MDV isolates.


HCMV has been associated with various neoplastic diseases and particularly with Kaposi's Sarcoma (KS), a disease whose incidence has been increasing in the past few years because of a higher frequency of immune deficiency syndromes due to transmission (AIDS) or drug induction (immune suppressive therapy in transplants). We have been interested in defining the role of HCMV in cancer using an in vitro approach. NIH3T3 cells have been transfected with a HCMV fragment of 558 bp, previously shown to be oncogenic and cells positive for the retention of viral sequences have been subcloned and characterized. Tumors induced in nude mice by these clones were positive for viral DNA when analyzed by Southern blot assay and a genomic library from the tumor DNA was constructed. Recombinant phages containing viral sequences have been isolated and we are in the process of characterizing the genomic region where the transfected DNA is inserted. At the present we know that the cellular sequence is transcribed into RNA and that its expression is higher in the transformed clones compared to normal NIH3T3 cells. The relevance of such alteration will be presented.

* F.M.B. on leave of absence from Div. Viral Oncology, 1st. Naz. Tumori "Fond. G. Pascale, Naples, Italy.
HERPES SIMPLEX VIRUS TYPE 2 INFECTION IS ASSOCIATED WITH A FATAL OUTCOME OF CERVICAL CARCINOMA

Lehtinen M, Lehtinen T, Aaran R-K, Armas AY, Hakama M, Lygdenoi R, Leinikki P, Paaoven J, Aaran E, University of Tampere, Medical School, Tampere; Social Insurance Institution of Finland, Helsinki; Finnish Cancer Registry, Helsinki, FINLAND

HSV-2-specific major DNA-binding protein ICSP 11/12 can be frequently found from cervical carcinoma biopsies. These patients also have high antibody levels, when tested with both immunoblotting and ELISA tests, which utilize the purified ICSP 11/12 protein antigen (Lehtinen et al. J Med Virol 16:245-256, 1985). We have studied a prospective serum material of cervical carcinoma patients for the ICSP 11/12 and HSV-2 antibodies. The material was obtained by linking a mobile clinic survey of the Social Insurance Institution and the data bank of Finnish Cancer Registry. Overall, 41 cervical carcinoma patients could be identified from the 5000 women who had attended in the mobile clinic survey. The serum samples were drawn about 3 years before the cancer diagnosis was made. Patients due to develop cervical cancer did not differ from their matched controls with regard to the ICSP 11/12 or HSV-2 antibodies. However, a majority, 4 out of 5 (80%) of these HSV-2 seropositive cervical carcinoma patients who had cancer diagnosed in less than 2 years had ICSP 11/12 antibody levels comparable to 1 out of 5 (17%) of their HSV-2 seronegative controls. ICSP 11/12 did not develop cancer. The 5-year survival of the cervical cancer cases was 86% in the HSV-2-positive group and 97.9% in HSV-2-negative patients. Thus, HSV-2 infection and early antigen expression are likely to be related to the pathogenesis of cervical cancer.

HERPES SIMPLEX VIRUS TYPE 2 INFECTION AND FEMALE GENITAL CANCER. A. Pizzez and P. Zernenshky, Digital Judetm, H inertia-Cie, Romania

It was established by the authors on the occasion of karyopysiological mass survey that the cytologically certified dyskarnias and herpes infection was numerous in a cloned female population. They also established that the incidence of genital cancer in the same female population was well over the national average. Clinical and epidiemological study is supported by immunofluorescent and immunohistochemical examinations. Research into data they look for connection between inflammation caused by herpes infection and genital cancer.

In order to clarify the early events of Epstein-Barr virus (EBV) transformation, we investigated chromosome sites for EBV DNA at the early stage after infection by the following two procedures: (1) The metaphases of B95-8 EBV infected cord blood lymphocytes (CBL) were analyzed by in situ hybridization technique using a cloned BamHI W fragment (ca. 3 kbp) of EBV as a probe at 48h and 72h after infection. (2) H-labeled EBV concentrated from B95-8 cell culture medium containing H-thymidine was infected to CBL and their metaphases were analyzed by autoradiography at 48h and 72h after infection. The result of in situ hybridization analysis showed that the grains for 56 metaphases analyzed were randomly located on almost all chromosomes at 48h after infection and the same at 72h. The result of autoradiographic analysis on the cells infected with H-labeled EBV also showed that the grains randomly distributed over the CBL chromosomes at both 48h and 72h. So far, the analysis of EBV genomes with host cell chromosomes has been investigated using both Burkitt's lymphoma and recently established cell lines. EBV genome was shown to link to chromosomes No.6, 8 and 16. These two cell lines were both positive for EBV-determined nuclear antigen (EBNA) and probably VZV. A new agent BN795U with impressive activity both in vitro and in vivo against HBV is currently undergoing phase I/II trials in IC patients with established CML infections (pneumonitis or viraemia).


35 healthy adults and 14 immunosuppressed patients who had experienced a silent Epstein-Barr virus (EBV) infection were monthly assessed for the shedding of EBV into the oropharynx and the serum EBV antibody titer for a period of one year. Comparison of the results of the healthy subjects with that of the clinical patients is as follows: 1) EBV was detected by transformation of cord blood lymphocytes in 31.4% (18/57) of the healthy subjects in each test, compared with 57.12% (8/14) - 78.5% (11/14) in the patients. 2) On the basis of the long-term observation, healthy subjects could be divided into three groups: high-rate (EBV was detected without more than 8/12 tests), medium-rate (3-7/12), and low-rate (1 or 2/12) shedder groups. Eventually, all the healthy subjects were proved to shed EBV into their oropharynx within 11 months of examination, while the majority of immunosuppressed patients was classified as high-rate shedders and all the patients shed the virus within 4 months. 4) Serum anti-early antigen (EA) antibody positivity, indicative of reactivation of latent EBV, was significantly higher (p<0.01) in 50.0% (7/14) of the immunosuppressed patients and 44.4% (4/9) of the high-rate healthy shedder group than 12.5% (1/8) of the low-rate group. These data indicate that all of the seropositive healthy individuals potentially shed EBV at any one time and the incidence of the shedding is elevated among those with anti-EA antibodies.
EPSTEIN-BARR VIRUS SUSCEPTIBILITY OF HUMAN B LYMPHOCYTE SUBPOPULATIONS. S. Koizumi, F. Mtzuno, and T. Oaflto. Sapporo, Japan

We characterized subpopulations of B lymphocytes in human adult peripheral blood which are susceptible to infection by Epstein-Barr virus (EBV). B cells were examined simultaneously for viral nuclear antigen (EBNA) and immunoglobulin (Ig) synthesis by two-color immunofluorescence. The subpopulations which expressed EBNA after exposure to the virus consisted of not only surface IgM(IgM)- and IgD-bearing cells, but also IgG- and IgA-bearing cells, in comparable frequencies. However, cytoplasmic Ig (cIg)-positive lymphocytes which represented a minor B cell subpopulation in peripheral blood were totally resistant to EBV infection. In vitro stimulation of lymphocytes by pokeweed antigen (PWM) which induces the terminal differentiation of B cells showed that the susceptibility to EBV was markedly decreased following PWM stimulation, and PWM-induced cIg-positive cells could neither bind EBV nor synthesize EBNA. These data indicate that human resting B cells bearing either IgG class are all susceptible to EBV infection, but not more differentiated cIg-positive B cells.

EPSTEIN-BARR VIRUS (EBV) ANTIBODIES IN CHILDREN NON-HODGKIN LYMPHOMAS (NHL). K. Roubalova, J. Reubal, A. Suchonkova, J. Koutecky, J. Bouchta and V. Vodicka, Inst. of Bure and Vaccines, Prague and Children Hospital Motol, Prague, Czechoslovakia

Children with NHL and control group were examined for antibodies against a panel of EBV antigens. Before beginning the treatment, NHL patients had lower titers of antibodies against viral capsid antigen (VCA) and virus-determined nuclear antigen (EBNA) than the controls. However, already at that time patients' sera frequently exhibited antibody pattern characteristic of activated EBV infection (i.e., antibodies against early antigen (EA) and/or IgM or IgG antibodies against VCA). In the course of the disease anti-VCA and anti-EA titers increased above the levels found in the controls. In comparison with the controls six time more patients had IgM and/or IgG antibodies against VCA, five times higher proportion of the patients lacked antibody against EBNA, this is indicative of the defects in cellular immunity. In 14 children the changes in anti-EBV titres during the disease were monitored. In 8 of them they preceded aggravation of their clinical state. In one EBV-negative patient, seroconversion against EBV during remission was noted. Four months after lymphoma reappeared, the malignant cells of which contained EBNA. Antibody titers against herpes simplex virus type I and EBV antibodies and did not differ from controls. This indicates that "EBV-related" serology of children NHL does not reflect immune reactivity against latently infecting viruses. The present results indicate that EBV might possibly play a certain role in at least some NHLs examined.


Forty-one patients, with mononucleosiform syndrome persisting more than one year, without any other obvious diseases were characterized for anti-Epstein-Barr virus titers, using purified EBV antigens in ELISA assay. Elevated anti early antigen (EA) and virus capsid (VCA) antigen titers were found in 34 cases. Anti EBNA 2 titers were low in all cases but elevated anti EBNA 2 titers were detected higher than 80 1 in 34 serum. Of 42 normal control serum only two had anti EBNA 2 titers higher than 20. None of the controls had anti early antigen titers higher than 10. Concomitant marmoset (callithrix jacchus) Infected with the transforming (B95-8) of EBV developed high anti-EA and VCA titers and antibodies against EA but not against EBNA 2 two-three months after infection. The titers were still elevated 20 months of infection. Although these observations do not directly prove that EBV commonly causes chronic illnesses, the findings can be useful basis for future studies and the marmosets could be useful as a model for EBV primary infection and possibly also for chronic infectious mononucleosis.

QUANTITATION OF LTI3 PROTEIN IN BURKITT'S LYMPHOMA AND LYMPHOMASTICID CELL LINES. A. Hatubai*, M. Anafi*, G. Klein* and D. Sulitzeanu*, Lautenberg Center for General and Tumor Immunology, Hebrew University-Hadassah Med. School, Jerusalem, Israel*; A. Latzubai*, M. Anafi*, G. Klein* and D. Sulitzeanu*, Lautenberg Center for General and Tumor Immunology, Hebrew University-Hadassah Med. School, Jerusalem, Israel* and A. Latzubai*, M. Anafi*, G. Klein* and D. Sulitzeanu*, Lautenberg Center for General and Tumor Immunology, Hebrew University-Hadassah Med. School, Jerusalem, Israel*. Prague and Children Hospital Motol, Prague, Czechoslovakia

Lymphoцитotoxicity tests have suggested that an Epstein-Barr virus (EBV)-specific membrane antigen is expressed on the surface of EBV transformed cells (lymphocyte determined membrane antigen-LYDMA). This antigen is believed to provide the target for the highly efficient immune surveillance of the normal human host that holds under control the proliferation of EBV-transformed cells in vivo. Analysis of the nucleotide sequence of one of the three principal virus polyadenylated RNAs in latently infected cells, revealed an open reading frame in the LTI region that might encode a membrane protein (LTI). The hydrophilic domain of this protein, synthesized in Escherichia coli as a fusion protein (FP) (Hennessy et al., 1984, Proc. Natl. Acad. Sci., 81:7207) was used to raise antisera in rabbits (LTI2). LTI3 serum was employed to detect the presence of the LTI protein by immunofluorescence and to determine the concentration of LTI in cell extracts, by radioimmunoassay (RIA). The RIA was based on the inhibition of binding of LTI3 to FP coated microtiter plates. Fluorescent intensity obtained with LTI3 serum varied in the different cell lines. EBV negative cells did not stain. RIA gave linear dose response curves with FP over the range 15-3000ng/ml. The concentration of LTI protein inhibiting by 50% the binding of LTI3 was taken as 1 unit. One mg of FP was estimated to be equivalent to 2000 units. Cyttoplasmic and membrane fractions (Zongli et al., 1984, Proc. Natl. Acad. Sci., 81:4378) from EBV positive or negative cell lines were tested for their inhibitory capacity in the RIA. LTI concentrations in Raji cell cytoplasmic and membrane extracts were about 15 and 1 ug/mg protein, respectively. LTI3 concentrations in extracts of other EBV positive cell lines ranged from 2 to 30 ug/mg protein in the cytoplasmic fraction, and from less than 0.5 to 2 ug/mg protein in the membrane fraction. Extracts from EBV negative cells did not inhibit in the RIA. Our data show that LTI protein can now be assayed with about 15*6 cells.
E-42: HERPES VIRUSES AND CANCER

3495 SYNTHESIS AND VIRAL ACTIVITY OF 5-ETHYLTHARABINO-
FRUOROSYLCYTOSINE. M. Bobet, J. Kavel and T.C. Cheng*, Grace Cancer Umg. Dr., Mount Sinai Park Memorial
Inst., Buffalo, NY, and Dept. of Pharmacology, Sch. of
Med., Univ. of North Carolina at Chapel Hill, Chapel
Hill, NC, USA.

5-Ethyl-a-D-arabinofuranosylcytosine (EAC) was pre-
pared from 1,2,3,5-tri-O-acetyl-a-D-arabinofuranosyl-
cytosine by iodination followed by coupling with tri-
 methylstilblylacetene and deblocking. At 50 µM, EAC was
found to inhibit the in vitro replication of herpes
simplex virus type I and type II by 59.7%. EAC retained
its activity against a strain of HSV-I, resistant to
(E)-5-2-bromovinyl)-2'-deoxyuridine due to an alteration
of the virus Induced thymidine kinase (TK). At 100 µM,
EAC did not inhibit the in vitro growth of leukemia L1210
and HeLa cells. EAC was TESTED to the action of dCR.
CR deaminase. Its rate of deamination being approximately
2% of that of dCR. The compound was a poor substrate for
Induced TKs at 50µS and 30°, respectively, the rate of
thymidine phosphorylation. Supported by grants CA24538
and CA1303B from the NIH.

3496 EXPRESSION OF THE EPSTEIN-BARR VIRUS GENOME IN
VIRUS-TRANSFORMED HUMAN B LYMPHOCYTES AND IN VIRUS-
TRANSFORMED TUMORS. I. Ehrnberg, B Porvus and G. Klein. Dept of Tumor Biology,
Karolinska Institutet, Stockholm, Sweden.

Epstein-Barr virus transforms human B lympho-
cytes in vivo and the virus is firmly associated with two malignancies, Bur-
kitte Lymphoma (BL) and Nasopharyngeal Carci-
nome (NPC).

Using immunoblotting and antibodies to syn-
thetic peptides we have identified three nu-
clear antigens (EBNAs) and their respective coding sequence. Using human sera we have identified two additional, possibly virally
encoded proteins. All five nuclear antigens are
expressed in virus-transformed cells and
early after infection in human B cells.

The putative transforming region of the viral
genome sequence encodes two prote (EBNA 2 and
EBNA 5 with molecular weights around 92 and 46
kilodaltons respectively. The first discovered
nuclear antigen EBNA 1 is in part encoded as an alanine-glucine repeat. This protein is
detected in all virus-carrying cells and is
firmly associated with the maintenance of the
viral genome as episomal plasmids. Both EBNA 1
and EBNA 2 are phosphoproteins as detected by
immunoprecipitation with monoclonal antibodies.
Structural and functional properties of the
viral nuclear antigens will be discussed.

In addition the pattern of expression of the
viral genome in nude-mouse-carried NPC tumors
will be presented in comparison with expression in
transformed B cells.

F-49: CELL KINETICS AND PROLIFERATION

3497 CELL GROWTH CONTROL IN HIGHER EUKARYOTES.
G.I. Epifanova and V.A. Polunovsky, Inst. of
Molecular Biol., Moscow, USSR

We are expressing the viewpoint that the
control over cell growth in higher euca-
ryotes is achieved predominantly by reg-
ular transitions of cells from prolifera-
tion to rest and vice versa as a re-
result of coordinated interrelationship
between intracellular growth inhibitors
and extracellular growth factors. Cells
pass into a resting state at each suc-
cessive cell cycle once the threshold
level of growth inhibitors has been at-
tained. As a result, cellular rest may
initiate and proceed in parallel with
conventional periods of the cell cycle
but in a cryptic way. Its termination
strictly depends on the appropriate
concentration of extracellular growth
factors. Under the influence of the
latter the concentration of intracellular
inhibitors falls down and cells start to replicate DNA and proceed
through the cell cycle. In the absence of growth factors cells, after complet-
ing mitosis, pass into an overt state of rest metabolically different from
any period of the cell cycle.

3498 CONTROL OF CELL PROLIFERATION, DIFFERENTIATION
AND ONCONECGENES - A THEORETICAL APPROACH. A. Baláss*

A general, preliminary theory on oncogenesis
was published in our monograph (A. Baláss: Control of cell proliferation by endogenous inhib-
recently a vast number of experimental findings
on protooncogenes, GFs (e.g. TGF and PDGF), in-
hibitors (cofactor, such as chalones) and on-
cogenes supported the conception, presently we
demonstrate in revised form. Accordingly, nor-
mal proliferation and differentiation are sub-
mitted to separate but correlative dual control
of positive and negative growth factors. The
latter are ended by regulatory genes, their
operon being identic probably with protoonco-
genones. Some products of the protooncogenes
like pp 60 of src or pp 58 of eab) stimulate,
others are supposed to inhibit (e.g. in case of
PIH or chalones) proliferation. In normal cells
the concentration of stimulatory and inhibitory
substances exhibit homeostasis. In contrast, if
affected by mutagenic agents (bruxoviruses, TGF,
irradiation, or chemical carcinogens) either the
production of GFs arise or that of the inhibitors
decrease, results in a relative excess of stim-ulator, or alterations of their receptors
(e.g. src B coded BGF or TGF-alpha receptors).
The shift correlates best with the inducment of
differentiation (like e gpm and e mob in myelo-
monocytic leukemia) or the malignant trans-
formation. The mechanism of effect include the
binding of the polipptide, gikoprotein or steroid ligand to membrane or cytosol recep-
tors, the activation of a protein tyrosyl kinase
and modification of cytoskeletal proteins such
as tubulin and the nuclear chromatin. Finally
we stress the importance of further progress in
purification and sequencing of inhibitors,
their interrelations with special protooncogen-
es and stimulators of cell proliferation.
The behavior of nucleated cellular systems consisting of variable population age distributions with arbitrary initial data. In this work the model is extended to systems in which regulations mechanisms result from cellular interaction based on cell number. A control variable is formed based upon the size of the total cellular population. Two different mechanisms of the influence of the control variable are explored. In the first control is mediated through cell death and in the second the control variable affects the cell cycle velocity through a negative feedback mechanism. Equilibrium solutions for these two cases are derived and consistent with the existence, uniqueness, and stability of the solutions are presented. The behavior of mixed cellular systems consisting of normal tissue interacting with malignant cells of monoclonal origin are simulated. The conditions for the various limit cycle behaviors of such systems are presented.

3502


Nine human carcinoma xenografts serially transplanted into nude mice were used for the cell kinetic analysis. Three gastric (H-1, ST-40 and H-111), three lung small cell (LCU-Lu-24, 130 and 134), two colon (Col-1 and Col-4) and one breast (Mx-1) carcinomas were inoculated into the backs of BALB/c nude mice, and when tumors reached more than 300 mm^3, 50 µCi of 3H-thymidine per mouse was administered ip. The percent labeled mitosis curves obtained from the autoradiographic specimens which were labeled by the pulse-chase method. Cell cycle phase-growth fraction (GP) and cell loss factor were assessed by the methods of Quastler, Fujita and Steck, respectively. Two doubling times were found to be ranged from 10.6 to 21.8 hours. ST-40, Col-4 and Mx-1 revealed approximately 100% GFs, whereas GFs and labeling indices of H-1 were found to be statistically shorter than those of the other six strains, suggesting an incomplete adaptation of HCC xenografts to the host nude mice. It was noticed that cell cycle times (Tc) of the three xenografts were statistically shorter than those of the three homo mouse tumors and that tumor HCC was found to be dependent on their short postmitotic resting phases. All these human xenograft tissues by the host mice on the cell kinetic were supposed. The characteristics of the cell kinetics were thought to be essentially preserved in nude mice and these cell kinetic parameters were observed to be stable throughout the serial transfers. Accordingly, the human tumor xenografts a nude mouse system was considered to be useful as an experimental model of human carcinomas.

3503


Cell kinetic analysis of human tumors in human being has been limited because of the difficulty to keep the patient from a potentially hazardous radioactive compound. To develop a method for the development of a monoclonal antibody to bromodeoxyuridine (BrdU), a pyrimidine analogue of thymidine, the estimation of a proportion of DNA synthesizing cells in the tumor was attempted. In this report, cell kinetic analysis of human tumor xenografts in nude mice and fresh surgical specimens was performed by this method. Four gastric, two colon, one breast and two lung small cell carcinoma xenografts were transplanted into nude mice and 300 µg of BrdU per kg was administered ip, when tumors reached more than 300 mm^3. On 1 hour after the administration the tumors were resected and fixed in 10% ethanol for immunohistochemical staining by anti-BrdU monoclonal antibody. The proportion of BrdU incorporated cells was counted by labeling index by BrdU (L.1.b) which were compared with conventional labeling index (L.1.b) by 3H-thymidine in autoradiographic specimens in each strain. In Patients with gastric and colon carcinoma, 1.0 g of BrdU per person was administered before the operation and the resected tumors were processed by the same method. L.1.b of human tumor xenografts was found to be well correlated with conventional L.1.b of the same strain, suggesting that L.1.b and L.1.b represent the proportion of DNA synthesizing cells in the tumor. Whereas L.1.b of human tumors and BrdU-irradiated human tumors had an identical ranging from 10 to 30%, a heterogeneity of BrdU incorporated cells in the surgical specimens was found with that of human tumor xenografts. This BrdU method was thought to be useful for cell kinetic analysis of human tumors in vivo.
3504 CORRELATION OF HUMAN BLADDER TUMORS RECURRENTNESS WITH CHANGES IN CLONOCENTICITY OF UROTHELIAL CELLS. K.P. Lee, Y. Hori, H. Shioda, P. F. Ono and D.G. Haywood, University of Chicago, Chicago, Chicago.

Over a 2-year period 364 cytocentrics were performed on 170 patients (120 men and 50 women) followed up for previously treated transitional cell tumors of the bladder in new patients suspected of having bladder tumors. Bladder washings taken at cytocentrifuge in 66% yielded cells for clonocentric assay. Patients with transitional cell tumors had an average clonogenic index (CI) of 16 (15 = 250) colonies per 10,000 viable unhandled cells. Previously transitioned patients with tumor-free bladders had an average CI of 6.1 colonies (P < 0.001). Changes in the clonogenic index from biopsy bladder washings paralleled the changes in tumor status; 14 cytoscopies and 2 cases have predictive value in follow-up.

3503 THE EFFECT OF ADRIAMYCIN ON THE CELL CYCLE OF HUMAN MALIGNANT UROTHELIAL TUMORS. K. Kusuzaki, Y. Tsujii, T. Adashima and K. Sakakibara, Dept. of Urology, University of Tokyo, Tokyo, Japan.

3 Adriamycin (ADR) caused the actively proliferating cells to arrest in G2 or S phase of the cell cycle in vitro. However, in the human malignant bone tumors after chemotherapy with ADR. In the present study, we analyzed quantitatively, using DNA or DNA-RNA cytofluorometry, the changes in the cell kinetics of human malignant bone tumors before and after chemotherapy with ADR. ADR was administered by the intra-articular or venous infusion immediately after biopsy, and the tumors were surgically resected one to two months later in all the patients studied. The bone tumors examined involved 6 osteosarcomas, one giant cell tumor, and one periosteal chondrosarcoma. The tumor cells were isolated by a combination of mechanical and enzymatic separation methods from fresh (6 cases) or paraffin-embedded (2 cases) tissue materials, that were obtained from both the biopsy and surgical resection. These isolated cells were smeared onto slides and analyzed by an epifluorescence microscope with epifluorescence filter (Nikon SPM-RI-D). The results showed that 5 cases out of 6 osteosarcomas consisted of both many polyploid and aneuploid cells with their many S phase cells before ADR treatment, while those S phase cells decreased considerably in association with an arrest of the diploid cells at G2 or S phases after the treatment. On the other hand, another osteosarcoma, giant cell tumor and chondrosarcoma all showed the diploid cell proliferation solely of the osteosarcoma among them. It was therefore concluded that ADR is effective on the osteosarcomas by inhibiting both cell proliferation but also polyploidization or aneuploid formation.


In the gynecological Oirlue-contact-therapy being increasingly replaced by the technique of afterloading. To evaluate the effect of insulin on modulation of ER and subsequent growth of ER-positive human tumors we performed the following experiment. Endometrial carcinomas (3 specimens) were incubated in serum-free medium containing either high dose insulin (10 ng/ml) or low dose insulin (10 ng/ml) for 4 hours and (ER) assay was performed. Receptor content of endometria (10 ng/ml CYST PROTEIN + SE) in tumor mean R of mean R tumors Mean R of tumors Assayed Tumors in 10 stock insulin in 10 stock insulin 35.6±5.3 35.6±5.3 79.0±6.4 79.0±6.4

To evaluate the effect of insulin on the growth rate of ER positive cells, we performed thymidine uptake studies following incubation of 250,000 cells in either high insulin (h) or low insulin (m) media for 72 hours. Thymidine uptake studies following incubation of 250,000 cells in either high insulin (h) or low insulin (m) media for 72 hours.

3506 EFFECT OF INSULIN ON HUMAN ENDOMETRIAL CARCINOMA. K.K. Chauvin, M. Kamachi, T. Ashihara, T. Horie, University of Osaka Medical School, Osaka, Japan.

It has been proposed that insulin may modulate the biologic behavior of estrogen target organ through its direct effect on receptor (ER). To evaluate the effect of insulin on modulation of ER and subsequent growth of ER-positive human tumors we performed the following experiment. Endometrial carcinomas (3 specimens) were incubated in serum-free medium containing either high dose insulin (10 ng/ml) or low dose insulin (10 ng/ml) for 4 hours and (ER) assay was performed. Receptor content of endometria (10 ng/ml CYST PROTEIN + SE) in tumor mean R of mean R tumors Mean R of tumors Assayed Tumors in 10 stock insulin in 10 stock insulin 35.6±5.3 35.6±5.3 79.0±6.4 79.0±6.4

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AGE-DEPENDENT DIFFERENCES IN GROWTH KINETICS AND CHEMOSENSITIVITY OF TRANSPLANTED TUMORS

I.F. Sadornikova, L.M. Dronova Inst. of Chemical Physics Acad.of Sci. USSR, Moscow, USSR

The Lewis lung carcinoma grows faster in 2-month old than in 3-month old (CBAxC57BL)F, mice. The maximum rate of carcinomas diameter growth is 1.32 and 0.0 mm/day, respectively. The rate constant of tumor growth in the exponential part of kinetic curves are 0.26 and 0.14 day
de the doubling time of the carcinoma diameter is 2.6 and 4.5 day, respectively. Laminovillus and antioxidative chlorohydrate rate of 2-ethyl-6-methyl-3-hydroxypridine have no effect on the growth rate in young mice and reduce it in aged tumor bearers. Benzpyrene-induced fibrosarcoma grows slower in 9 to 15-month old and faster in 38-month old mice. The sensitivity to cyclophosphamide varies in the same order, namely 30% in 9- to 15-month old and 80% in 38-month old animals. The mechanism of age differences in tumor growth kinetics and chemosensitivity are discussed.

GLUCOCORTICOID (TRIAMCINOLONE ACETONIDE) RECEPTOR PROTEIN (TARP) ACTIVITY IN A HUMAN MELANOMA TT.M. LINE AND ITS MODIFICATION. L. Nathanson and M. O'Connor, Winthrop-University Hospital, Stony Brook, Stony Brook, NY 11794., U.S.A.

A cell line (NEL-M1) with known TARP levels (122.3 f mol/mg; Kd 2.24+0.24 x 10^-6%) has been established. Previously reported studies have shown that in this line triamcinolone acetonide (TA) will increase melanogenesis in a cyclic AMP independent fashion by increasing the activity of the rate controlling enzyme tyrosinase. In addition, TA inhibited 3H thymidine incorporation during the S phase of cell cycle, and suppressed DNA synthesis (Can Res 45:1633, 1985). Increase in estrogen binding protein activity following incubation of cytosol fractions of human breast tumor tissue with HuIFNa(Le) has been recently reported (N.V. Dimitrov, Proc. RAC, 23:240, 1982). Therefore, similar effect was studied in NEL-M1 cells. First, a prolongation of generation time in a known sensitive cell line (8D60) established bioactivity of the HuIFNa(Le) employed. NEL-M1 cells were then incubated for 72 hours with HuIFNa(Le), HuIFNa(Ly), and HuIFNa at 10, 100, 500, and 1000 u/ml of incubation media, after which uptake and incorporation of 3H thymidine was studied. Approximately 30% inhibition and uptake of 3H thymidine was observed with all three HuIFNa's. A dose response effect was observed with maximal inhibition seen at 500 u/ml. Incubation with cytosol fractions for 18 hours with HuIFNa(Le) at 100 u/ml or as whole cells for 48 hours with all HuIFNa's at 500 u/ml of incubation media was carried out. TARP levels with HuIFNa(Ly) and HuIFNa were 7.4%, 93.4%, and 91.6% respectively of control. Although these differences were not statistically significant, further studies are now proceeding in an effort to increase TARP activity and thus increase glucocorticoid induced inhibition of DNA synthesis and cell growth. This system could be a model for hormonal control of growth in human melanoma.

INFLUENCE OF LYMPHOCYTE CONCENTRATION ON INTENSITY 3-HURIDINE UPTAKE IN HEALTHY ANIMALS AND UNDER LYMOPHOCITOCISIS. Beppal'ko O.P., Nikolova E.Y.

Inst. of Chemical Physics Acad. of Sci. USSR, Moscow, USSR.

Incorporation of 3H-uridine into the cells was studied under conditions of alteration in concentration of lymphocytes of blood. The lymphocytes in autologous plasma were incubated with precursors for 20 minutes at 37°C. The labelling index and the percentage of high radioactive (40 grain count /cell) lymphocytes under the increase of cell concentration is decreased. Maximum of incorporation of uridine correspond with concentration lymphocytes 0,4-2,0 x 10^6cell /ml both in healthy and leukemic animals. The phenomenon was not due to presence of dead cells in the suspension.

GLUCOCORTICOID (TRIAMCINOLONE ACETONIDE) RECEPTOR PROTEIN (TARP) ACTIVITY IN A HUMAN MELANOMA T.T.M. LINE AND ITS MODIFICATION. L. Nathanson and M. O'Connor, Winthrop-University Hospital, Stony Brook, Stony Brook, NY 11794., U.S.A.

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3511 GROWTH PROMOTING EFFECT OF MATERNAL SERUM ON PROLIFERATION OF HUMAN PLACENTAL CELLS.

L. Ungár, A. László Z. Marcok, J. Nenymárth, P. Siklós, P. Herceg, 2nd Department of Obstetrics and Gynecology, Semmelweis University Medical School and United Research Organisation of Hungarian Acad. of Sci. and Semmelweis University Budapest, Hungary

First trimester human placentas were sampled in series by caesarian section. Growth rate of placental cultures set up from the biopsy specimen was assessed by measuring 3H thymidine incorporation into DNA. The medium was supplemented with fetal calf serum(FCS) or homologous maternal serum(MS). It demonstrated that MS was superior to FCS in promoting 3H thymidine incorporation into human placental DNA in vitro.

3512 METASTASIS, ANTI-METASTATIC TREATMENT AND STRESS IN MICE.

T. Girardi, L. Perlas, S. Zorlet, S. Nicpali, M.G. Rodani, G. Sava Institute of Pharmacology, University of Trieste, I-34100, Trieste, Italy.

Abundant experimental evidence concerning the effects of stress on tumor growth in laboratory animals has been reported in the existing literature; a large proportion of the experiments reported are rather outdated, and involved the use of an experimental tumor system with little similarities with, and low predictivity for, clinical human situations. Moreover more attention has been given to the effects of stress on the outcome of therapy, although in humans biobehavioral parameters and cancer are always associated with therapy. The aim of the present investigation has been therefore that of determining the effects of spatial disorientation (SD) on the growth and systemic metastatic spread of Lewis lung carcinoma in syngeneic mice kept in a protect environment, in comparison to conventional housing. The animals have been treated with the antineoplastic drug razoxane; pharmacological depression of glucocorticoid blood levels by mitotane and of adrenergic function by 6-hydroxydopamine have also been examined either in terms of tumor progression or response to razoxane. In mice kept in the protect environment, SD appears to remarkably increase primary tumor growth and to enhance even more markedly the metastatic spread. The antineoplastic effects of razoxane are significantly reduced in mice subjected to SD; mitotane, significant lowering corticosterone levels increased by SD, is devoid of effects on tumor growth and spread, and marginally modify razoxane antimetastatic effects. These results seem to encourage further studies on the relationships between stress, humoral mediators and chemotherapy of metastases.

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High (LLT-HH) and low (LLT) metastatic Lewis lung tumor lines, and B16 melanoma were used for in vivo therapeutic experiments in order to find selective antimetastatic treatment based on their phenotypic differences (e.g. different cell surface characteristics, different sensitivity to host effector cells). Using cyclophosphamide as a "nonspecific" anticancer agent the Lewis lung tumor lines showed equal sensitivity. However, when the recipients were treated with prostactacyn (PGI2) before i.v. injection of tumor cells, the number of lung metastases from B16 and LLT decreased, but from LLT-HH didn't change. The metastasis inhibiting action of PGI2 was abolished in mice pretreated with cyclophosphamide (240 mg/kg) suggesting that PGI2 action - at least partly - was realized through NK cells. Hexyldesoxouridine (HudR) inhibited the metastases formation of LLT-HH cells in 4x75 mg/kg doses in the spleen-liver and muscle-lung metastasis model, before and after the tumor cell transplantation, but it was ineffective against LLT cells. The resistance of LLT-HH to PGI2 and macrophages was reduced, when these agents were applied after HudR. This indicates that, the cell surface changes, caused by HudR could increase the sensitivity of tumor cells to host-effector system.
ANTI-METASTATIC ACTIVITY IN THE "DOUBLE GRAFTED TUMOR SYSTEM" OF PSK(KRESTIN), AN ANTITUMOR IMMUNOMODULATOR. T.Ebina, and H.Kohya, Dept. of Pathology**, Gifu University School of Medicine, Gifu City, Japan.

In our previous observations it was found, that, when tumor-bearing rates were treated by tumor excision plus laparotomy, incidences of postoperative lung metastases was higher, PMN-lymphohistagglutinin and NK activity were lower, and suppressor cell activity was higher than in rats treated by simple tumor excision. In the present study, enhancement of tumor metastasis following operative stress or hydrocortisone(HC) administration was examined in non-tumor-bearing rats and an attempt on its prevention by preoperative administration of a streptococcal preparation, OK-432, was performed. isolaed cells of N Mc-1 tumor cell line were inoculated intravenously in Sprague Dawley rats (5/5/SD) preceding various experimental procedures. 14 days after tumor inoculation, number of metastatic lung nodules was examined by Weiser's method. The operative stress consisted of either skin excision(S) or skin excision plus laparotomy for 30 minutes. Influences of bilateral adrenalectomy, preoperative intramuscular administration of OK-432(SX500/kg/day, 3 days) and intraperitoneal administration of HC(2, 5, 10 or 20mg) were also examined. It was found that number of metastatic lung nodules increased as the operative stress or dosage of HC was increased. The enhancement of lung metastasis was inhibited significantly by preoperative bilateral adrenalectomy or by OK-432 administration. Plasma corticosterone level increase in parallel with an increase in operative stress. NK activity of peripheral lymphocytes was reduced after operation or after HC administration, but that reduction was also prevented by preoperative bilateral adrenalectomy or by OK-432 administration. The mechanisms will be discussed.

ROLE OF SPLEEN CELLS RESPONSIBLE FOR CONCUMBTANT IMMUNITY IN TUMOR METASTASIS. T.Yamashita, T.Yamada* and E.Tsubura**. Third Dept.of Intern.Med.,Univ.of Tokushima,Sch.of Med., Tokushima 770* and Toneyama Natl.Hosp.**,Japan

Lewis lung carcinoma (LLC) is a favorable experimental model of spontaneous pulmonary metastases. In the present study, enhancement of pulmonary metastases was studied. The islet of Langerhans was removed and subsequent growth in the lung tended to develop since day 5 after tumor implantation. When the implanted tumor into foot pad was removed at varied days interval, Pulmonary metastases 2 weeks later, after removal of the primary tumor on day 9 significantly increased, compared with those of no removal of primary tumor. This augmentation was reflected in greater numbers of visible lung metastases and weight of spleen. In mice with no removal of primary tumor, prominent spleenomegaly developed as the primary tumor grew up. Focusing on the responsiveness of spleen cells for the metastases formation, antimitastatic activity of spleen cells from tumor-bearing mice was examined using the methods of splenectomy and transfer of spleen cells. Spleen cells from tumor-bearing mice inhibited the development of lung metastases, whereas those from tumor-removed mice could not display this activity but resulted in increase of lung metastases. The in vitro cytotoxic activity of spleen cells from mice with primary tumor or from spleen cells from mice with primary tumor was also reduced. Subsequently, the antimitastatic activity was decreased significantly by treatment with anti- Thy-1.2 or anti-Lyt-2.2 monoclonal antibodies. Roles of spleen cells responsible for concomitant immunity in tumor metastases are discussed.
两者的相互作用。在治疗过程中，使用抗癌活性更高的方法，如化疗、免疫治疗和靶向治疗，可以协同作用，共同抑制肿瘤的生长和转移。

In conclusion, these results indicate that factors contained in discarded fluid by CF, and that CF which administered discarded fluid was far more rapidly able to remove these factors is effective adjuvant therapy to cancer patient.

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3522 STUDIES ON THE ANTIMETASTATIC EFFECT OF PUSTULUSAHM (OH-1) AND ITS SUBLINES. L. Fiszew-Halilewiska and R. Hordered
Dept. Microbiology, Inst. of Immunology and Experimental Pathology, Poland.

Biological response modifiers may prevent or delay the development of metastases. For instance, pustulan, glucose, and immunomodulating properties, inhibits the metastasis formation by Lewis lung carcinoma and M109. To better define the antimetastatic effect of pustulan we have examined the ability of pustulan to inhibit the spontaneous lung metastases of parental M109 line and in vivo-selected sublines derived from the parental M109 line. Eleven clone sublines were isolated from lung colonies of M109. Their growth rate and capacity to form experimental and spontaneous metastases were investigated. To assess the antimetastatic effect of pustulan 103 tumor cells were transplantively introduced subcutaneously into balb/c mice and the agent at 5 mg/kg was given i.p. daily for 5 days.

The administration of CRP-Liposomes to inhibit liver metastases was found to be effective in the treatment of colorectal cancer. The CRP-Liposomes (0.7 µg CRP/2.5 µmole lipid) was effective in reducing the number of spontaneous lung metastases of parental H1O9 line. In addition, the CRP-Liposomes induced the activation of tumoridal macrophages and splenic lymphocytes. In certain experiments, Adriamycin (10 mg/kg, i.p., day 1) was administered to some of the mice. All effects were evaluated in standard BALB/c mice. The generation of allo-specific cytotoxic T cells was augmented by the addition of rh-TNF to the primary cultures. A bell-shaped curve was obtained with rh-TNF (5 to 1000 U/well) in combination with a lymphokine preparation. The activation of tumoridal macrophages (either R or T) was not observed. rh-TNF may be of the host. It is possible, therefore, that rH-TNF has a normal regulatory role in the physiological condition of cells. We believe this to be a unique model for adjuvant therapy studies with CRP and other biological response modifiers.

3523 EXPERIMENTAL MODEL FOR ADJUVANT THERAPY OF COLORECTAL CANCER: INHIBITION OF LIVER METASTASES AND PROLONGATION OF SURVIVAL BY HUMAN C-REACTIVE PROTEIN (CRP). S.D. Deodhar, G. Orangio, T. Chiang and V. Fazio.
Dept. Hematology and Colorectal Surgery, Cleveland Clinic, Cleveland, Ohio 44106 (USA) [NCI Grant No. ROI CA33932]

Colorectal cancer occupies a leading position in cancer incidence in this country. The high predilection for liver metastases noted in this cancer accounts for poor response to therapy and poor survival. We previously reported that administration of CRP in liposomes to mice (CS78L/6J) bearing the syngeneic MCA-38 adenocarcinoma in the cecum inhibited liver metastases and prolonged survival. Mechanism of action of CRP was shown to be through macrophage activation. More recently, we have developed a surgical technique to resect the tumor-bearing cecum so that effect of CRP could now be tested in an adjuvant setting. 1 x 108 tumor cells were injected subcutaneously in the wall of the cecum and the cecal pouch was placed under skin and subcutaneous tissue of the abdominal wall through an incision in the anterior abdominal muscle layer. All incisions were closed and the tumor mass allowed to develop for 6 weeks and tumor growth confirmed by surgical exploration. The tumor bearing segment was then resected and mice were randomized into two groups, one untreated control and the other given CRP-liposomes (0.7 µg CRP/2.5 µmole lipid) 3 times per week for 4 weeks. Mice dying during the postoperative period and those surviving up to 190 days were examined for liver metastases. Marked inhibition of liver metastases and prolongation of survival were observed in the CRP group.

We believe this to be a unique model for adjuvant therapy studies with CRP and other biological response modifiers.

G-55: MACROPHAGE ACTIVATION THERAPY — BONE MARROW TRANSPLANTATION: CYTOKINES II

3524 REGULATORY ROLE OF RECOMBINANT HUMAN TUMOR NECROSIS FACTOR (rh-TNF) ON MACROPHAGE CONTROL AND ADIANTAMIC-MODIFIED HOST DEFENSE FUNCTION. M.J. Ehrke. K. Nagle, D. MacKinnon and E. Whis, Trace Cancer Drug Center, Roswell Park Memorial Institute, Buffalo, NY 14262, U.S.A.

Host responses to foreign stimuli, in many cases, are mediated by macrophage products. Tumor necrosis factor has been shown to be produced specifically by activated macrophages. The release of such factors should not threaten the well-being of the host, but rather, under normal conditions, it should promote healing. Thus, rh-TNF has a normal regulatory role in the physiological response to injury. Since macrophage factors are known to function as both autocrine and paracrine mediators, we examined the possible regulatory effects of rh-TNF on both murine macrophage and lymphocyte activities. The C3H/10T1/2 mouse was used as a source of resident (R) or thiglycollate induced (TG) peritoneal exudate macrophages and splenic lymphocytes. In certain experiments Adolracytin (10 mg/kg, i.p., day 1) was administered to some of the mice. All effects were evaluated in standard BALB/c mice. The generation of allo-specific cytotoxic T cells was augmented by the addition of rh-TNF to the primary cultures. A bell-shaped curve was obtained with rh-TNF (5 to 1000 U/well) in combination with a lymphokine preparation. The activation of tumoridal macrophages (either R or TG) was not observed. rh-TNF alone, however, did activate macrophage from AUI treated mice; again a bell shaped curve was obtained with 50 to 100 U/well being near optimal. The addition of rh-TNF (50 or 1000 U) during the standard 4 hr assay of the lytic activity of lymphokine activated killer cells (LAK) resulted in selective effects on different LAK-Tumor combinations; augmenting the lysis of YAC-1 and EL4 but not P812 tumor cells. Natural killer activity of fresh or cultured spleen cells was not affected by rh-TNF under any conditions tested. Thus, consistent with a regulatory role, rh-TNF modulated certain host defense mechanisms by selectively augmenting either effector or effector arms of specific systems when tested at low concentrations. (Supported in part by a grant from Asahi Chemical.)
Preparation, Pharmacokinetics and Toxicity of an Unique Anti-Tumor Lymphokine Derived from Stimulated B-Cell Leukemia Cell, BALL-1: S. Koyama*, T. Tanamoto*, S. Fukuda*, Y. Yamana*, N. Honjo†, N. Ikeda*, Y. Satoh*, K. Kurihara* and K. Orita**, Hayashibara Biochemical Laboratories Inc.*, and First Department of Surgery, Okayama University Medical School**, Okayama 700, Japan

A crude lymphokine preparation designated OH-1 which was derived from a stimulated BALL-1 cell line, a human B-cell line of B-cell acute lymphoblastic leukemia origin was identified. Major constituents of the OH-1 preparation were fractionated, purified and characterized. The study of their pharmacokinetics and toxicological effects in mice was performed. By means of in vivo propagation of BALL-1 cells in immunosuppressed newborn hamsters, a bulk of BALL-1 cells were prepared and the cells as determined by cytotoxic assay with mouse fibroblast cell lines, L-929. Further fractionation and purification of the OH-1 preparation were achieved by affinity chromatography using respectivly monoclonal antibodies as ligands. Main fractions designated as H-7-1 and H-1 fractions, respectively were characterized for their molecular characteristics. H-1 fraction was immunologically identified as an IFN-γ and divided into 3 subtypes (α-2, α-7, α-8, by C. Weissnann's notation) by protein analysis. H-7-1 fraction identified as anti-tumor lymphokine molecule, its MW was fifteen k dalton molecules with 8 protein bands were observed between pH 5.5 and 6.2 by the isoelectrofocusing. It was suggested that H-7-1 and IFN-γ contain sugar moiety from the results of the staining by Periodic acid Schiff's reagent (typical sugar staining reagent) on PAGE. The acute toxicity of anti-tumor lymphokine (OH-1) was determined to be low in mice. Upon intravenous administration of OH-1 (H-7-1 fraction and IFN-γ) the half lives of H-7-1 fraction and IFN-γ in the serum were 45 and 15 min in nude mice, respectively.


The present study was undertaken to investigate the biologic effect of the anti-tumor lymphokine, OH-1, derived from BALL-1 cells, against human tumor xenografts in nude mice. The tumor, P4788, used in all experiments was derived from human colon cancer. OH-1 had the cytostatic and cytotoxic effect on P4788 cells in vitro. Further studies showed OH-1 caused an accumulation in 5 phase of the cell cycle, concomitant with the observation that the proliferation of the cells is strongly inhibited.

Tumors, 2xl06 P4788 cells, were inoculated subcutaneously on the back of CD-1 nude mice. Drug administration was started on 10th days after tumor inoculation, when tumor weight was over 100mg. Mice were given OH-1 i.v. or i.c. daily for 21 days, and sacrificed on the next day of the last administration.

The antiproliferative effect of OH-1 was significant and dose dependent. Complete regression was observed in the cases administered intratumorally.

The antitumor lymphokine, OH-1, is expected as the new anticancer agent.

The antitumor effects of a new antitumor lymphokine (OH-1 fractions), prepared from a crude lymphokine preparation designated as OH-1 in a stimulated human B-cell leukemia cell line (BALL-1) with Sendai virus, were investigated in BDF mice with transplantantion of Lewis lung carcinoma (LL) cells. After inoculation of 1x106 LL cells into the left foot pad of female, 8 weeks old BDF mice, the primary tumor was resected on the 10th day and the administration was started in several experimental methods. On 21th day mice were sacrificed and the numbers of metastatic pulmonary tumors were counted. The effects of OH-1 fractions on metastases as determined by comparison of the numbers of metastatic pulmonary tumors were significant in OH-1 H-7-1 fraction and OH-1 H-10 fraction. OH-1 H-7-1 fraction, the most purified fraction, was effective in administering daily for 10 days by the route of i.v., i.m. and i.t. in each concentration of OH-1 H-7-1 fraction. The synergistic effect of OH-1 H-7-1 fraction and anticancer agents was studied and the antitumor effect was significantly augmented with 5-Fluorouracil (inhibitor of DNA synthesis)

The synergistic effect of OH-1 H-7-1 fraction and mice interferon was also investigated and the synergistic effect was significant. The lymphokine, OH-1 H-7-1 fraction is expected as the new anticancer agent.

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The antitumor lymphokine, OH-1, is expected as the new anticancer agent.
The mechanism of synergistic action of an anti-tumor lymphokine (OH-1) fraction by clonogenic assay.

As previously reported, the anti-cellular effects of OH-1 H-4 fraction which was reconstituted with highly purified a new cytotoxic factor of H-7-1 fraction and H-1 fraction (IFN-a) were synergistically enhanced on KB cells and some other human cell lines. The mechanism of anti-cellular effect of H-4 preparation (a mixture of H-7-1 fraction and IFN-a) was investigated by kinetic analysis with specific binding assay to target KB cells. The most effective sequence for a synergistic anti-cellular activity was obtained when the target cells were treated first with H-7-1 and followed with IFN-a, but not the other way round.

Using 125I-labeled H-7-1 and 125I-labeled IFN-a, the specific binding of two fractions of the OH-1 H-4 preparation to the surface receptor of target KB cells was investigated. The dissociation constant (Kd) and the number of specific receptor site for each OH-1 fraction were estimated by scatchard analysis of the binding data. In the experiments of time course of binding at 37°C, down regulation was observed. This phenomenon could possibly be explained by internalization and degradation of 125I-labeled OH-1 fractions. The presence of OH-1 fractions was confirmed by the presence of 125I-radioactivity within the target cells after labeling the radioactivity by lysing of the target cells with trypsin treatment.

The relationship between the synergistic enhancement of anti-cellular activity of OH-1 H-4 preparation and the specific receptors for H-14 component was discussed in detail.

**The SYNERGISTIC ENHANCEMENT OF THE ANTI-TUMOR EFFECT OF OH-1 ON A PANEL OF TARGET CELL LINES.**

M. Kurimoto* and K. Orita** Hayashibara Biochemical Labs., Inc.* and Okayama University Medical School*, Okayama 700, Japan

The anti-cellular effects of unique anti-tumor lymphokine OH-1, which was obtained from BALB-1 cell line, were studied. Major constituents of OH-1 preparation upon purification consisted of a cytotoxic factor termed H-7-1 fraction and IFN-a termed H-1 fraction. Each fraction was indeed purified to a high degree of homogeneity by affinity chromatography using respective monoclonal antibodies.

Cytotoxic factor(H-7-1 fraction) had anti-cellular activity against mouse fibroblast cell line, L-929 and the factor had neither IFN, IL-1 nor IL-2 activities. H-1 fraction (IFN-a) had antiviral activity and showed no cytotoxic activity on L-929 cells. Cytotoxic and cytostatic effects of these two highly purified H-7-1 and IFN-a were determined, as in a single or combined preparation, on 18 cell lines. Cytotoxic effect was expressed by the decrease of the cell viability relative to that of control culture. Cytostatic effect was determined by the inhibition of the proliferation relative to that of control culture. With either H-7-1 fraction or IFN-a alone, the anti-cellular effect on target cell lines was rather limited. For example, H-7-1 fraction showed a limited anti-cellular activity on KB, KRO-2, PC-9, MT-107. IFN-a showed a limited effect on KB, HEP-2, HEP-2. However H-1A preparation which was a reconstituted mixture between H-7-1 fraction and IFN-a, gave a potent and cellular activity and a broader target spectrum. The remarkably synergistic enhancement of anti-cellular activity by H-1A preparation was also observed on KB, PC-10, HEP-2, KATO-W and KRO-2 cells. Furthermore, the ED50 of the preparation against KB cells was lowered to 1/100 of that of the ED50 when each component was used singly.

The fact that potentiation with broadened target spectrum attainable by the combination of two lymphokines (H-7-1 fraction and IFN-a) may prove to be a new approach in the cancer treatment.
EFFECT AGAINST TUMORS.

To analyze the structural and functional relationship, molecular cloning of TNF gene was carried out from THP-1 DNA, and several species of recombinant plasmids were constructed using the resulting clone. As follows: All recombinant plasmids have the region of the largest exon, and the N terminal region are varied so as to have intervening sequence or synthetic nucleotides corresponding to heterogenous amino acid sequence of various TNFs produced in THP-1. E. coli JM103 was transformed by these plasmid DNA, and TNF activity was measured after induction by IPTG. Active TNF were produced from E. coli, and several species of recombinant plasmids were constructed using the resulting clone. As follows: All recombinant plasmids have the region of the largest exon, and the N terminal region are varied so as to have intervening sequence or synthetic nucleotides corresponding to heterogenous amino acid sequence of various TNFs produced in THP-1.

The role of N terminal region of TNF remains unknown, however, we assume these heterogeneity may affect spectrum as well as specific activity of cytotoxic action against tumors.

The compound administered intraperitoneally produced a prominent inhibition of the growth of i.d. inoculated H16 melanoma. In this case, we examined the effect of i.v. administered rHu-TNF on tumor metastasis of B16 melanoma and colon 26 adenocarcinoma.

rHu-TNF administered i.v. inhibited the growth of B16 melanoma inoculated s.c. TNF at 1-1 x 10^6 U/M/D induced a prominent inhibition of tumor growth. The compound administered i.v. also produced a prominent inhibition of the growth of i.d. inoculated mouse colon adenocarcinoma 26. In this case, 1 x 10^6 U/M/D of TNF inhibited 100% inhibition of tumor growth and the prominent necrosis of tumor was observed. Colon 26 adenocarcinoma seems to be more susceptible to rHu-TNF than B16 melanoma.

B16-BL6, a metastatic variant of B16 melanoma, inoculated s.c. in the forefootpad metastasized spontaneously to the axial lymph node and lung. TNF given i.v. at 1 - 10 x 10^6 U/M/D did not show inhibitory activity on the metastasis. On the other hand, a metastatic variant of colon 26 adenocarcinoma, inoculated s.c. in forefootpad metastasized spontaneously to the lung. TNF given i.v. at 1 - 10 x 10^6 U/M/D produced a prominent inhibition of tumor metastasis. Approximately 90% of inhibition occurred at 1 x 10^6 U/M/D of TNF. These results indicate that TNF is worthwhile to be examined its activity precociously on tumor metastases.
Involvement of T Cell Receptors and MHC Class I Antigens in the Auto-Tumor Lysis Exerted by Low and High Density Lymphocytes. P. S. Varky and E. Klein, Dept. of Tumor Biology, Karolinska Institute, S-104 01 Stockholm, Sweden.

Depending on the histological type of the tumors, (Adenocarcinoma-, and Squamous cell carcinoma of the lung, Small cell lung carcinoma, Astrocytoma, Oesteosarcoma, Malignant mesenchymal tumors, Hypernephroma, Malignant melanoma) 9 - 45% of patients possessed cytotoxic blood lymphocytes against their own tumors. There was a correlation between the auto-tumor lytic potential (ALC) of the blood lymphocytes and the postsurgical clinical course of the 108 patients, in that all long term survivors belonged to the ALC reactive group (observation time between 36 and 108 months, mean 80.2). When the lymphocytes were fractionated on the basis of density, two populations of auto-tumor cytotoxic lymphocytes were detected. One population was recovered in the subset with low buoyant density (LD), the another in the cells with high density (HD), (these were resting T cells). In the latter population, the CD8 lymphocytes lysed the autologous tumor cells. The cytotoxicity of HD lymphocytes was not potentiated by interferon and they did not lyse K562. Pretreatment of the effector with mAbs directed against the T cell markers CD3 and CD2, inhibited the effect of the HD cells but did not influence the function of the LD population. Pretreatment of the tumor cells with MAb directed against MHC class I antigens inhibited the auto-tumor lysis of the HD cells but did not change the cytotoxicity exerted by the LD population.


Splenic lymphocytes (SL) and peritoneal macrophages (PM) from mice were transplanted on mice fibrosarcoma (AFS) tumor were studied under scanning electron microscope (SEM) at different times after tumor challenge. The intricate phagocytic behaviour of the PM against the homologous AFS tumor was revealed in 36 and 108 months, mean 80.2). When the lymphocytes were fractionated on the basis of density, two populations of auto-tumor cytotoxic lymphocytes were detected. One population was recovered in the subset with low buoyant density (LD), the another in the cells with high density (HD), (these were resting T cells). In the latter population, the CD8 lymphocytes lysed the autologous tumor cells. The cytotoxicity of HD lymphocytes was not potentiated by interferon and they did not lyse K562. Pretreatment of the effector with mAbs directed against the T cell markers CD3 and CD2, inhibited the effect of the HD cells but did not influence the function of the LD population. Pretreatment of the tumor cells with MAb directed against MHC class I antigens inhibited the auto-tumor lysis of the HD cells but did not change the cytotoxicity exerted by the LD population.

Effect of the xenoinmunization by sheep red blood cells upon the incidence and evolution of metastas was studied in Wistar rats with Walker 256 carcinoma inoculated intravenously. Experiments were carried out on 120 Wistar female rats weighing 20 20 g divided into 4 equal groups: group I (controls) inoculated i.v. with 1x107 Wister tumor cells. Groups II-IV were injected i.p. with 1x107 sheep red blood cells at various times before or after i.v. tumor grafting as follows: group II on day -16; group III on day -7 and group IV on day 7. The incidence of metastases was: 75% in group I, 15% in group II, 60% in group III and 85% in group IV. The differences between the groups were statistically significant. Our results suggest that a strong immune reaction against xenogeneic antigens before grafting may prevent the development of the allo-geneic experimental metastases. In the contrary, the immune stimulation after grafting was inefficient.


Recently it was shown that partial hepatectomy (HEP) triggers DNA synthesis not only in the remaining liver but also in lymphoid organs. Therefore, we attempted to study the effect of HEP on immune surveillance system against cancer. HEP in mice induced an activation of cytotoxicity of K cells, NK cells and lymphokine-activated killer cells (LAK) which destroy a wide range of tumor cells including NK-resistant cancer cells, along with syngeneic regenerating liver cells. In order to study the possible in vivo role of these activated cells, we have investigated the effect of HEP on immune surveillance system against cancer. HEP in mice induced an activation of cytotoxicity of K cells, NK cells and lymphokine-activated killer cells (LAK) which destroy a wide range of tumor cells including NK-resistant cancer cells, along with syngeneic regenerating liver cells. In order to study the possible in vivo role of these activated cells, we have investigated the effect of HEP on immune surveillance system against cancer. HEP in mice induced an activation of cytotoxicity of K cells, NK cells and lymphokine-activated killer cells (LAK) which destroy a wide range of tumor cells including NK-resistant cancer cells, along with syngeneic regenerating liver cells. In order to study the possible in vivo role of these activated cells, we have investigated the effect of HEP on immune surveillance system against cancer.
Many investigation support various immuno-suppressive factors increase in the serum of the cancer patients. But the influence of these factors on the cellular immunity has not

differently solved clearly. In 1980 Fujii et al. reported the immuno-suppressive substance (ISS) with extracted from the ascites of the patients with colon cancer markedly suppressed the PHA response of fresh peripheral blood lymphocyte (PBL). We have been investigated on ISS and obtained the results as follow. ISS was dom-

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In this report we show the influence of ISS on the lymphokine activated killer (LAK) cells. LAK cells were generated by incubating fresh PBL in human recombinant IL-2. ISS significant-

ly inhibited the inducer phase of LAK cells as well as the effector phase. This inhibition was mediated by the suppression of the IL-2 receptor expression. This knowledge suggests the depletion of the immuno-suppressive factor including ISS from the serum of the cancer patients is important for the adoptive immunotherapy using IL-2.

The ability of phytohemagglutinin (PHA) to form colonies were tested in 50 patients with tumours of the stomach, lung, breast, prostate, and bladder. Many investigation support various immuno-
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3545 DISOCIATION OF FACTORS RESPONSIBLE FOR NEONATAL INDUCTION OF TRANSPLANTATION TOLERANCE AND MALIGNANT LYMPHOMACS. K. R. Wolsteneroof, J. M. Edwards, and D. C. Dumonde, St. Thomas Hospital and Medical School, London, SE1 THF, United Kingdom

Our rationale for studying the endolymphatic route of interleukin administration in malignant melanoma arose from previous experimental animal work on lymph node-associated cellular immunity and from previous experience with the endolymphatic injection of BCG and oil-based isotope in melanoma patients. Twenty-three patients with recurrent malignant melanoma with poor prognosis, primary disease, received endolymphatic injections of human buffy-coat interleukin containing interleukin-2 (500-8000 units), followed directly by lymphangiography. Patients showed clinical enlargement and tenderness of regional nodes for up to 4 days. Serial lymphangiography revealed that the increase in regional lymph node size could persist for up to 13 days after a single endolymphatic injection of interleukin and that enlargement could extend to involve more distant lymph nodes. In 5 patients, block dissection of the regional nodes (inguinal, cervical or axillary) was undertaken between 6 and 13 days post-injection. Lymph node histology revealed marked paracortical disorganization and follicular hyperplasia; there was extensive plugging of paracortical sinuses with small lymphocytes, a pattern normally associated with an active cellular immunological response. The study demonstrated that the endolymphatic route of interleukin administration was well tolerated and was without adverse toxicity. From clinical, radiological and histological evidence of lymph node enlargement, we suggest that the approach may be of value in malignant melanoma when combined characteristically by lymphatic pathway.


In organ transplanted patients, there is an unusually high incidence of malignant lymphoproliferative tumors. In our experiments, the accumulation of generalized lymphoid tumors (almost exclusively B lymphomas) was observed in inbred mice after neonatal induction of transplantation tolerance. Tolerance had been induced in different M-2 incompatible strain combinations by semi-allogenic (F2 hybrid) spleen cells. In the examined strain combinations, both the incidence of lymphomas and the effectiveness of tolerance induction was found to be considerably different and they did not show any correlation. In the (B10xA)F1 hybrids, a combination, an especially high incidence (90%) of malignant lymphoid tumors was observed. These lymphomas proved to be A(H-2^d)-alloantigen-positive and B(H-2^d)-alloantigen-negative. Neither tolerance nor lymphomas could be induced by the supernatant of sonicated F1 cells, although the tolerance-inducing capacity of the F1 cell inoculum was not influenced by T cell depletion. Its lymphoma-inducing effect was abolished. The results indicate that: 1) Different immunogenic factors might be involved in the induction of lymphomas and tolerance. 2) Lymphomas seem to be of recipient and donor (F1) origin. The transfer of intact F1 T cells (but not an oncogenic virus infection of the newborn mice) might be responsible for the development of lymphoid tumors. 2) Transplantation tolerance can be induced by T-cell-depleted F1 cell inoculate without the danger of causing malignant lymphomas.
EVIDENCE FOR SPONTANEOUS IN VITRO SELECTION OF HUMAN MELANOMA CELLS EXPRESSING ALPHA-2-MACROGLOBULIN. J. Bizik, A. Lizonova, J. Matouka, J. Svec, A. Vaheri and M. Grofova, Dept. of Pathology, Palacky University, Olomouc, Czechoslovakia.

We have previously reported that spontaneous RCS in BALB/c (B6-129 IEC) mice express aberrant la specificities. To further characterize these specificities, we made use of the fine specificity of the T-cell receptor. Several tumor reactive T-cell hybridomas were generated by fusion of T-cells from RCS melanoma metastasis with the same specificity as seen in the IL-2 induced response. The hybridomas responded to secretion of IL-2. Two other RCS specific hybridomas reacted to IE*-producing RCS-2 cell line was selected in the primary melanoma, intradermal metastasis and lymph node metastasis, from which the cell line was established, only solitary cells, positive for IE- were present. This suggests, that IE- producing RCS-2 cell line was selected in the culture conditions from a rare subpopulation of the melanoma metastasis.

SOLUBLE IMMUNOSUPPRESSIVE FACTORS AND LYMPHOCYTE SUBSETS FROM THE SPLEEN IN ADVANCED GASTRIC CANCER PATIENTS. H. Kanayama, M. Maeta, and S. Koga, The First Dept. of Surgery, Tottori Univ. Sch. of Med., Yonago, Japan

In experimental study, the spleen is noted as a source of serum immunosuppressive factors and/or suppressor cells. In the viewpoint of this, we examined the immunological significance of the spleen in gastric cancer patients. Compared to serum from peripheral blood, serum from splenic venous blood of advanced gastric cancer patients exerted a stronger suppressive effect on normal lymphocyte responses to phytohemagglutinin (PHA) and showed higher immune complex values (3.5% polyethylene glycol precipitation assay). But, this difference was not pronounced in sera from the patients with early cancer. The ratio of OKT4* to OKT8* lymphocytes in peripheral blood tended to decrease with advance of gastric cancer, and the ratio in splenic venous blood was lower than in peripheral blood, especially in advanced gastric cancer. In addition, the supernatant from spleen cell cultures from advanced gastric cancer patients significantly suppressed normal lymphocyte responses to PHA. This immunosuppressive activity was enhanced when the supernatant was from cultures of T lymphocytes separated from the spleen cells. The ratio of OKT4* to OKT8* lymphocytes in spleen cell cultures tended to decrease with advance of gastric cancer, though the PHA reactivity or the percentage of OKT4+ cells was unchanged. Our results suggest that in advanced gastric cancer, the spleen participates in the induction of serum immunosuppressive factors and the change of lymphocyte subsets in peripheral blood and that soluble immunosuppressive factors from this organ is possibly due to a change in splenic lymphocyte subsets.

G-56: TUMOUR IMMUNITY III

3549

TUMOR AND IA-SPECIFIC T-CELL HYBRIDOMAS REACTING WITH SYNOGENIC IA RETICULUM CELL SARCOMA (RCS) AND IA ALLOGENEIC CELLS. E.L Bonavida and K. Ohnishi. Dept. of Surgery, Univ. of Helsinki, Finland.

Microbiology and Immunology, UCLA School of Medicine, University of California, Los Angeles, USA.

These studies demonstrate that the T-cell receptor affinity for IA antigens is sufficiently high to form conjugates in suspension in a manner reminiscent of conjugates formed between cytotoxic T lymphocytes and specific targets. The hybridoma conjugates were blocked by L3T4 and LFA-1 mAb demonstrating that these molecules play a role in the initial adhesion. Anti-Idotypic antibodies generated against the hybridomas blocked the response suggesting that the cross-reaction seen is the result of a single receptor.
3553 SEQUENTIAL DEVELOPMENT OF ANTIBODIES TO VIROGENE PRODUCTS
IN HAIRY CELL LEUKEMIA (HCL). JE Fitzpatrick, A O'Donnell, Tla Han, T Birl, AK Bhargava, Roswell Park
Mem. Inst. 646 Elm St., Buffalo, NY 14263 USA

In HCL it has been shown that the hairy cells are capable of immunoglobulin (Ig) synthesis. Thus a higher incidence of serum monoclonal proteins might be expected than that reported. It has been suggested that M-proteins are overlooked because testing with Serum Protein Electrophoresis (SPEP) and Immunoelectrophoresis (IEP) is frequently not performed. In our experience, these 2 tests are not sensitive enough to detect low level M-proteins. Using the more sensitive technique of High Resolution Electrophoresis/Immunofixation (HRE/IFE), 24 patients with HCL were studied and the results compared with Ig levels. SPEP and IEP as shown below:

<table>
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<tr>
<th>Ig LEVELS</th>
<th>NORMAL</th>
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<tr>
<td>SPEP</td>
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<td>IEP</td>
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<td>2 (22%)</td>
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<tr>
<td>HRE/IFE</td>
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<td>6 (67%)</td>
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The Ig increase was minimal for all heavy chain classes, not exceeding twice the upper limit of normal. An association was seen between Ig increase and no. of M-proteins detected with HRE/IFE which was not found using SPEP or IEP. The use of HRE/IFE significantly increased the no. of M-proteins seen from 13 to 42%. IgG was the predominant heavy chain class found (90%) and the expected kappa/lambda light chain ratio was maintained. These findings are more in keeping with those usually associated with M-proteins than with those usually associated with syndromic B cells. It is apparent that SPEP and IEP are not sufficiently sensitive for M-protein detection in HCL. The use of a more sensitive technique such as HRE/IFE is necessary to establish the true incidence of M-proteins in HCL.

3554 SEQUENTIAL DEVELOPMENT OF ANTIBODIES TO VIROGENE PRODUCTS IN VITAMIN TUMORIGENESIS. Yukinori Fukushina, Shigenobu Mochizuki, Nobuko Koshikawa, Motohige Miyachi, and Koshi Maruyama, Dept. of Pathology, Chiba Cancer Ctr., Res. Inst., Chiba 280, Japan.

This study was carried out to elucidate the sequential development of IgG antibodies to different virologic products during the course of development of virus-induced tumors. Sera were obtained from some 100 inbred Wistar/Ma rats at weekly intervals starting 7 days after neonatal injection of feline sarcoma virus of Snyder-Theilen strain (ST-FsLV). These sera were tested by the enzyme-linked immunosorbent assay (ELISA) to feline leukemia virus (FeLV) and by the immunoprecipitation (IP) to S-hydroxylamine-labeled FeLV or to S-methionine-labeled lysates of tumor cells expressing the viral oncogene product (P85) and obtained from ST-FsLV-induced tumor of a syngeneic rat. ELISA values increased slightly at the 2nd week, decreased at the 3rd week, and then increased sharply with considerable individual variations at around the 6th week when tumors grew to visible size. ELISA values of sera obtained even at the 6th week from rats whose tumors spontaneously regressed remained at relatively low levels. However, ELISA values of their sera increased markedly prior to tumor recurrence. By IP, IgG antibody to viral gp70 was demonstrated even in sera obtained at the 1st week, while antibody to PBS was found detectable in sera obtained after 4-10 weeks following virus-injection. These results indicate that the initial increase of ELISA values is due to host immune response to the envelope of the virus injected when newborn, and that the subsequent increase is due to response to the viral oncogene product expressed by transformed rat cells. The possible role of antibody to gp70 in regulation of the viral oncogene expression in virus-infected rat cells during the period preceding the appearance of antibody to PBS remains to be determined.

3555 THE HYBRIDOMA PRINCIPLE AS ENVISIONED IN 1968-9. Joseph G. Sinkovics, Community Cancer Center, St. Joseph's Hospital. University of S. Florida College of Medicine, Tampa, Fl. Dept. of Virology, Baylor College of Medicine, Houston, Texas.

In the mid-1960s at the Section of Clinical Virology & Immunology of M.D. Anderson Hospital we maintained with cell passage a murine lymphoma which consisted of diploid lymphoma cells producing retrovirus particles budding through the cell membrane. Mice injected with large cell inocula succumbed to lethal lymphomatous tumors. Mice injected with small cell inocula survived and acquired immunity by producing antibodies neutralizing the mouse leukemia virus and lysing lymphoma cells in the presence of complement. When spleen cells of mice that rejected the lymphoma and diploid lymphoma cells were cocultured intraperitoneally, ascitic lymphomas arose. The ascitic lymphoma cells grew in continuous suspension cultures for years, were tetraploid, expressed mouse leukemia virus antigens and produced immune globulins of IgG2 class specifically neutralizing the mouse leukemia virus. These antibodies slightly enhanced the growth of diploid lymphoma cells in mice. In 1969 we proposed (Lancet 1: 139 '70) that the antibody producing immune spleen cell fused with the antigenic lymphoma cell thus creating a continuously replicating and specific antibody-producing tetraploid lymphoma cell (a "hybridoma"). The picture of this phenomenon appeared on the cover of Leukemia-Lymphoma 1970, Year Book Med Publ., Chicago.

Presentations on several conferences evoked no interest. Our grant application received low priority rating at NCI. For summary of early references see Cancer Res 41: 1246-7, 1981 and Rev Inf Dis 5:9-34, 1983. This 20th anniversary presentation will be illustrated with original color slides from 1966-1976.
pediated cytotoxicity (NCMC) was not affected by either raAb, of TFR was discordant from NK sensitivity. The resistance is suggested. Also play an important role in the post-binding events.

Targets. Alternatively, anti-TFR mAb Inhibited both bind- 
ing and killing of K 562 and Molt-4 targets. These data show that both the 40 kD FcyR and the TFR can be target of 3H-TdR-prelabeled adherent HEp-2 cells to natural cell-

kD FcyR and the susceptibility to NK, while the expression 
of 3H-TdR-prelabeled adherent HEp-2 cells to natural cell-

mAb). Pretreatment of K 562 target cells with intact anti-

clonal antibody specific for the 40 kD FcyR (antl-FcyR 


duction was detected between the relative expression of 40 kD FcyR and the susceptibility to NK, while the expression 
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INFLUENCE OF ADRIAMYCIN (ADM), CISPLATINUM (CDDP), AND THEIR DERIVATIVES ON NATURAL KILLER (NK) ACTIVITY IN CANCER PATIENTS OF DIGESTIVE TRACT


1st Dept. of Surgery, Gakushuin Univ. Med. Sch., Koganei, Japan

Natural killer (NK) cells are considered to play an important role in the immunological surveillance mechanism against cancer. NK activity of 10 patients with digestive tract cancer was measured using目标 by the method of NCI-defined K562 target cells. The results were summarized as follows:

NK activity of cancer patients showed a significant decrease as compared to that of normal controls and NK activity related to clinical stage. NK activity of tumor lymphocytes of patients with gastric cancer decreased relative to normal controls. There was not significant correlation between the level of NK activity and Leu 7 (cell surface marker) expression. Patients with advanced cancer showed NK activity measured after immunochemotherapy were alleviated more than 10 months.

These results suggested that clinical monitoring of NK activity might be useful for the estimation of the efficacy of antitumor therapy in cancer patients and their prognosis.

CLINICAL INVESTIGATIONS ON NATURAL KILLER CELL ACTIVITY IN CANCER PATIENTS OF DIGESTIVE TRACT

G-57: NATURAL RESISTANCE — COMPLEMENT FACTORS I

ANTI-D ANTIBODY DEPENDENT CELL MEDIATED CYTOTOXICITY IN PATIENTS WITH NON-HODGKIN'S LYMPHOMA AND NON-HODGKIN'S LYMPHOMA T. Bakacs, K. Tözpá, G. Rimondi, I. Szánthó, A. Balogh, T. Fleischman

National Institute of Oncology, Budapest, Hungary

Anti-D antibody dependent cellular cytotoxicity of peripheral blood mononuclear cells was measured in the enzyme-like kinetic model of cytotoxicity against O.Rh/D/ positive erythrocytes in 59 patients with Hodgkin’s disease /9 untreated, 9 undergoing chemotherapy, 31 in long-lasting remission, 35 non-Hodgkin’s lymphomas /20 untreated, 15 in long-lasting remission/ and 44 age and sex matched controls. Cytotoxicity of a constant number of effector cells was tested as a function of target cell number. Activity of male patients was significantly higher, whereas that of the female patients was lower, or similar to the controls. Elevated or decreased ADCC activity returned /or approached/ to normal values after successful combined modality treatment. It was therefore concluded, that in the population studied malignant lymphomas have differently affected ADCC activity of male and female patients.

INFLUENCE OF ADRIAMYCIN (ADM), CISPLATINUM (CDDP), AND THEIR DERIVATIVES ON NATURAL KILLER (NK) ACTIVITY IN MOUSE SPLEEN CELLS. A. Aoyama, H. Niitani, H. Shibuya, K. Mukizuro, T. Aikou, H. Nomura, T. Kajiyama, H. Shimazu & S. Takao

1st Dept. of Surgery, Gakushuin Univ. Med. Sch., Koganei, Japan

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G-57: NATURAL RESISTANCE — COMPLEMENT FACTORS I

SERUM LEVELS OF COMPLEMENT INHIBITORS IN PATIENTS WITH MALIGNANCY

T.Tanigawa, N.Kato, M.Ueda, N.Tanigawa, K.Kin, S.Takeaura, S.Sugino, M.Kondo. Kyoto Prefectual Univ. of Med., Kyoto, Japan

Complement system is considered to be playing an important role in defence mechanisms against cancer. It is known that complement activity is higher in cancer patients and that, on the other hand, C1INH also increases. From this, a question whether complements were working enough in cancer patients with high CH50 arose. This time, we examined the relation between the complement inhibitors (C1INH, C4bp, H and I) and complement activity (CH50). The material was serum obtained from the patients of various kinds of malignancy admitted in our hospital. CH50 was measured by modified Mayer's method. Protein amount of complement components was measured by SRID. The results were as follows. (1) CH50 in cancer patients increased as progress of diseases. (2) C1INH, C4bp, H and I increased as progress of diseases, but in some cases decreased in terminal stage. (3) Dividing the cases in stage 4 by CH50 level which expressed production of proteins, C4bp, H and I showed low levels in the group with extremely low CH50, but this was not seen in C1INH. (4) C4bp, H and I correlated with CH50 but this was not the case with C1INH. (5) C1-C9 showed a tendency to increase as progress of diseases, and C1, C4, C5, C7, C8 and C9 correlated with CH50. In cancer patients, CH50 was elevated and the complement inhibitors were also increased, thus there might be a possibility that complement were not utilized enough in progressive malignancy diseases. Such condition seemed to be disadvantageous in host defence mechanism.

TUMORICIDAL LIVER CELLS.

Margarette Walter, Gerlinde Schriever and Rudolf Süss
Cancer Research Center, 6900 Heidelberg, FRG

The liver appears to be a major site for the destruction of tumor cells. As effector cells have been identified as macrophages and natural killer cells.

The tumoricidal activity of the liver in vitro is defined qualitatively (using different types of tumor targets in the chromium release test). Experiments with silica, radiation and antisera allow to assess quantitatively the number of natural killers and/or macrophages in the liver. Quantitative comparisons lead to the conclusion that the liver harbors the largest population of tumor cells.

Evidence is presented that "natural cytotoxicity in vitro" is not an experimental artifact. Experiments in vivo support the hypothesis that liver cells spontaneously kill tumor cells.

The natural defence system of the liver is supplemented with T-cells and B-cells. This may be concluded from experiments using human lymphocytes and tumor cells as well as sheep red blood cells as xenogeneic inducer cells.

Thus the liver has at its disposal the whole range of killing mechanisms for the destruction of circulating tumor cells.

REGULATORS OF ALTERNATIVE PATHWAY OF COMPLEMENT AND THE ACUTE PHASE PROTEINS OF CANCER

Carucci P, Abbolito M.R., Taggi F.*

The proteins H and I, which modulate the alternative pathway of C (a.p.), have been studied as in normal subjects as in neoplastic patients the latter presenting normal or increased levels of Properdin Factor B (B) in the serum. The immunephelometric evaluation (INF) and the radial immunodiffusion (RID) were performed for C3, C4, B, H1 and C3d. The correlations of H and I with the proteins of complement were studied and the data obtained were evaluated with statistical analysis. Small deviations from the normal range of H and I reduce the utilization of the alternative pathway when the levels of B-in the serum increase. The results may be compared to those evidenced in the experimental systems in human C2 deficient sera with the addition of purified H and I. Such impairment of the a.p. may be interpreted as a lack of information in the specific defenses in neoplastic diseases.
AUGMENTION BY PSK OF NATURAL KILLER CELL ACTIVITY AND LYMPHOCYTIC RESPONSES in tumor-bearing hosts. Oral administration of PSK was able to restore or augment splenic NK cell activity. Significant mitogenic activity occurred in the spleen, with the highest response at 0.5 to 1 g/kg doses. Furthermore, we also found that oral administration of PSK was able to restore or enhance the depressed NK cell activity of spleen cells and mesenteric lymph node cells obtained from tumor-bearing mice. Thus, it is evident that PSK is a useful immunomodulator, from the viewpoints of restoring or augmenting non-specific immune responses such as NK cell activity and lymphoproliferative response in tumor-bearing hosts.

POLYSACCHARIDE Kureha CPSK is a protein-bound polysaccharide obtained from the extract of the mycelium of Coriolus versicolor. Although its favorable clinical effects have been demonstrated, further investigations should be performed to clarify the mechanism responsible for the antitumor activity of PSK in tumor-bearing hosts. We tested various concentrations of PSK for its mitogenic activity in vitro spleen cell proliferation and its in vitro capacity to augment splenic NK cell activity. Significant mitogenic activity was observed, with peak activity occurring at 1 mg/ml and declining at higher and lower concentrations. Concerning splenic NK cell activity, peak activation was attained with 100 μg/ml. In addition, PSK was administered orally, to test its in vivo augmenting effect on splenic NK cell activity. Significant augmentation of NK cell activity occurred in the spleen, with the highest response at 0.5 to 1 g/kg doses. Furthermore, we also found that oral administration of PSK was able to restore or enhance the depressed NK cell activity of spleen cells and mesenteric lymph node cells obtained from tumor-bearing mice. Thus, it is evident that PSK is a useful immunomodulator, from the viewpoints of restoring or augmenting non-specific immune responses such as NK cell activity and lymphoproliferative response in tumor-bearing hosts.
Cytotoxic killer cells observed in P384 rats following the intraperitoneal (ip) inoculation of a lethal dose of syngeneic MADB108 tumor cells and a single injection with OK432 were examined. In this model, OK432-injected tumor-bearing rats were able to survive more than 100 days while control rats with MADB106 alone died by day 14-17. When the cytotoxicity of peritoneal exudate cells (PEC) was measured in a 4 hr 51Cr-release assay, appreciable cytolytic activity against MADB108 cells was evident by day 7 following OK432 injection. These MADB106 killer cells consisted of three populations of cells including NK cells, cytotoxic T lymphocytes (CTL) and non-T/non-NK cytotoxic cells. NK activity was induced in OK432-treated tumor-bearing rats since: 1) MADB106 killer cells could be seen in peritoneal nodules, 2) augmentation of YAC-1 (the prototype rat NK target cell) and MADB106 killing was seen in both P384 and athymic nude rats following OK432 injection and 3) the phenotype of these anti-MADB106 NK cells were predominantly asialo GM1 (GM1) and pan-T cell, R1-383 (RI). Some MADB106 killing was also present in R1+ cells, the phenotype of typical cytotoxic rat CTL. Interestingly, a major source of MADB106 killer cells was found to be in a non-T/norm-NK cell population since: 1) these cells were elicited only in the tumor-bearing rats given OK432, while NK augmentation could be seen with OK432 alone in either normal or tumor-bearing rats, 2) secondary killer cells, induced following reinoculation with MADB106 cells in cured rats, were mostly R1 cells (non-T) and 3) these R1 killer cells showed appreciable cytolytic activity against a variety of target cells, including NK-resistant targets. These results indicate that OK432 is a potent immunomodulator which elicits unique syngeneic tumor killer cells, as well as CTL and NK cells from the tumor-bearing rats.


Our study included patients undergoing surgical removal of bronchogenic carcinoma in the I stage of the disease. Following surgery, 80 patients received non specific immunotherapy with OK432 (165kU, during 1 month), 20 with Corynebacterium Parvum (CP) (80mg during 1 year), while 80 patients received no further therapy. No other cytotoxic or immunosuppressive therapy was administered during the follow up period. A 3 year follow up of all patients showed significantly better survival in the OK-2 treated group (70%) compared to the CP group (48%) and controls (44%). Immunological monitoring of cellular immune reactivity (mitogen induced lymphocyte proliferation, leucocyte migration inhibition, active rosette formation, T cell number and subpopulations, B cell number and delayed hypersensitivity skin testing) demonstrated variations within different groups of patients in relation to therapy.
3575 BIOLOGIC-RESPONSE MODIFIERS FOR CANCER TREATMENT. L.E. Cowary, Virginia Cancer Research Institute, Alexandria, Virginia, USA

Effective cancer treatment continues to remain an elusive goal despite the progress that has been made. Many human cancers resist the traditional modalities of treatment: surgery, chemotherapy, and radiation therapy. A fourth modality for treating cancer exists when involves biologicals and biological-response modifiers. Although biological therapy has interested scientists and clinicians for many years, it is only recently with advances in molecular biology and immunology that this form of therapy is within our reach. One form of biological therapy which we have studied is related to exposure of individuals to attenuated, non-pathogenic viruses, primarily animal viral vaccines. Initial experimental studies showed that viral vaccines have a beneficial effect on acute viral infections. Additionally, we will present case histories where we have observed in Europe and in the USA, that cancer patients exposed to that attenuated non-pathogenic viral vaccines went into remission.

3576 EFFECT OF STREPtocOCCAL PREPARIATION OK-432 AND/OR HUMAN SERUM ON DISTRIBUTION OF TUMOR CELL SURFACE MOLECULES — FLOW MICROFLUOROMETRICAL ANALYSIS — H. KatO, H. Sano, M. TAKAGI, E. KAMIO, S. GUMMA, and M. KUPU, First Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan

Participation of polymorphonuclear leukocytes (PMN) has been investigated in carcinomatosus ascites of cancer patients, when streptococcal preparation OK-432 was injected intraperitoneally as an immunotherapy. We already demonstrated that complement derived chemotactic factor such as C5a might play a role to attract PMN into the peritoneal cavity by i.p. injection of OK-432 and fresh human serum or plasma. Although the mechanism of tumor cell destruction by PMN is not known, it is interesting to determine which molecules on the tumor surface PMN direct for attachment, and how PMN injure them by this treatment. From this viewpoint, changes of distribution of tumor cell surface molecules before and after treatment were examined by flow microfluorometry. After various kinds of cell lines human cancer cells were incubated with OK-432 and/or serum at 37°C for 60 min, those cells were exposed to first antibody against such as immunoglobulins, complement C3, fibrinogen or OK-432 itself. Then cells reacted with FITC-labeled second antibody were applied to flow microfluorometry. Tumor cells were obtained from ascites of cancer patients before and after treatment by OK-432 and/or fresh human plasma, and examined by the same manner. It was observed that various kinds of immune molecules stuck to the surface of tumor cells after the treatment. The role of these molecules is now under investigation in relation to tumor cell injury by PMN.

3577 ATTEMPTS AT RESTORATION OF T CELL SUBSETS AND RATIO IN IMMUNODEPRESSED CANCER PATIENTS AND AIDS RELATED COMPLEX (ARC) PATIENTS WITH BESTATIN AND ZINC GLUCONATE. J.L. Missel, G. Mathé, I. Blaszaek, M. Chmielecka, D. Maszko, O. Mechovar & I. Florentin. 0'MST & ICIG (CNRS UA 04-1153), Hop. Paul-Brousse, 94804-Villejuif, France

Immunosuppression of cellular immunity causes post treatment complications and may also be involved in recurrence of the disease. Patients with: a) either neoplasia in remission without cytotoxic treatment for more than three months of ARC, b) stable depression of cellular immunity defined as an absolute number of helper inducer T-Cells (T4) under 600/mm^3 at peripheral blood or a decreased ratio of helper inducer/cytolytic suppressor (T4/T8) under 1 were submitted to immunorestorative drugs. Bestatin in an antiprotease compound which has been shown to enhance immune reaction and to decrease the frequency of spontaneous tumors in aged mice (AICR 1985, abst. n°7). 31 patients (20) with the above defined immune deficiency situation received Bestatin 30mg for 3 days each during three weeks. No side effect clinical or biological of any kind was observed. Immune evaluation one week after the last dose showed a significant decrease in absolute number of T4 cells, in relative percentage of T4 cells among mononuclear cells and of the T4/T8 ratio. T4 cells were significantly increased in those ten pts with initial low counts (<250/mm^3). Zinc has been shown to be an important cofactor of T cell proliferation and division (Med. Oncol. Tumor Pharmacoth. 1985, 2, 203). 31 pts with the above defined immune deficiency situation were submitted to Zinc Gluconate 150mg orally twice daily for three weeks. No side effects were observed. Immune evaluation after four weeks showed a trend to increases in T4 cells (absolute and percentage) and a significant increase in T4/T8 ratio. These results need to be confirmed in larger series and longer follow-up. However it already appears that it is possible to improve immune parameters in immuno depressed cancer pts.

3578 CLINICAL RANDOMIZED TRIAL OF TREATMENT OF MALIGNANT MELANOMA WITH ORAL ADMINISTRATION OF BCG IN PATIENTS COATED CAPSULES. X. Ikeda, T. Sawai, Dept. of Dermatology, Saitama Medical School, Saitama, Japan, T. Tabohara, Dept. of Dermatology, National Cancer Center Hospital, Tokyo, Japan, T. Sawada, Japan BCG Laboratory, Tokyo, Japan.

46 patients in 1b and II stages of melanoma selected randomly have been treated with the oral administration of BCG in enteric coated capsules in addition to the chemotheraphy after surgical treatments, while another 46 patients of the same stages of malignant melanoma with the same background have been treated with the same chemotheraphy without BCG administration after surgical treatments at the same time. 4 capsules, containing 20 mg freeze-dried BCG, were orally administered once a week. The chemotheraphy had a common arm of DTIC, ACNU and Vincluran. The mean observation period was 37.0 months in BCG group and 19.5 months in non-BCG group. The survival rates presented in Kaplan-Meier method disclosed that 97.8% in BCG group and 87.0% in non-BCG group at 20 months observation, 93.5% and 70.7% at 40 months observation. The survival rates presented in generalized Wilcoxon test also showed the significant difference in both groups. The disease free survival rates also revealed the significant difference in both groups. The increase of immunoprotectors as PPD reaction etc was more observed in BCG group. A few cases indicated complications such as nausea, vomiting and diarrhea immediately after the oral administration of BCG.
INJECTION OF INTERLEUKIN 2 (IL-2) INTO THE TUMOR-BEARER’S SPLEEN AUGMENTS LYMPHOKINE-ACTIVATED KILLER (LAK) ACTIVITY IN VITRO AND INHIBITS TUMOR METASTASIS.


The effect of interleukin 2 (IL-2) injected directly into the tumor-bearer’s spleen on the inhibition of tumor metastasis was evaluated. C3H/HeN mice were inoculated intradermally with 2 x 10^6 C57BL/6 syngeneic tumor cells on day 0, and the tumor was surgically resected on day 10. The operation failed to prevent tumor death within 3 weeks. Autopsy revealed that death was due to systemic metastasis of tumor cells of lymphoid organs, although the tumors had been successfully removed without any visible local recurrence. In this model, we administered IL-2 by intrasplenic injection daily for 3 days after operation. Mice treated with intrasplenic injection of IL-2 had a significantly prolonged survival. Histological findings of this treatment revealed lymphoid cell proliferation of the spleen and no metastatic foci found in liver. Lymphokine-activated killer (LAK) activity from IL-2 injected spleen was also augmented. Intravenous (i.v.) and subcutaneous (s.c.) administrations of IL-2 were not effective. A major difficulty in achieving a significant immunological effect in vivo by IL-2 infusion is the relatively short half-life of IL-2. Therefore, IL-2 administered directly into the responding lymphoid organ is theoretically reasonable. In fact, the intrasplenic injection of IL-2 treatment significantly augmented the antitumor activity. This method may be applicable for adjuvant immunotherapy in human cancer as splenic arterial infusion of IL-2. Our preliminary studies with splenic arterial infusion of IL-2 have demonstrated the augmentation of NK and LAK activity of peripheral blood lymphocytes in cancer patients.
DEPRESSION OF PROTECTIVE MECHANISM DURING THE EARLY PHASE OF A VIRAL INFECTION IN TUMOR-BEARING MICE AND ITS THERAPEUTIC EFFECT.

KINETICS OF SERUM INTERFERON INDUCED BY ADMINISTRATION OF OK-432 FOR ADVANCED CANCER PATIENTS.

BIOSYNTHESIS OF IL-2 IN HUMAN PERIPHERAL LYMPHOCYTES ACTIVATED WITH OK-432, PHA, AND FUSION PRODUCTS OF T, B, AND NK CELLS.

THE ANTITUMOR MECHANISMS OF OK-432 IN THE ACUTILYMPHOCYTIC INDUCED PARANORMIA.

THE ANTIMICROBIAL MECHANISMS OF OK-432 IN THE IMMUNOSUPPRESSIVE CYTOMEGALOVIRUS INFECTION.
ANTITUMOR ACTIVITY OF A NEW DERIVATIVE OF CAMPTOTHECIN, CPT-II [1].


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Camptothecin is a well-known alkaloid having potent antitumor activity but high toxicity as well. Thus, to get less toxic compounds, we have prepared new derivatives, among which 7-ethyl-10-(4-(1-piperidinyl)-1-piperidinyl)-carbonyl-oxycamptothecin (CPT-II) was tested for antitumor activity and toxicity.

The intraperitoneally (ip) administered CPT-II, dissolved in saline, prolonged the survival time of the mice bearing ip or subcutaneously inoculated L1210 leukemia, P388 leukemia, Sarcoma 180, Meth A fibrosarcoma, Lewis lung carcinoma (XL), Ehrlich carcinoma, MMT hepatoma and B16 melanoma and many mice cured at total dose of 31.5 mg/kg or more. Particularly, at total dose of 25-200 mg/kg for Sarcoma 180 and of 200-400 mg/kg for Meth A, all the mice escaped death from the tumor.

These higher values of therapeutic ratios of this compound than CPT-I1 showed the IC50 values in the range from 0.88 to 41.5 μM against several tumor cell lines such as KB, P388, Colon 26 and MH134. These values were 41 to 140-fold lower than that of Camptothecin CPT. From the ratio of IC50 values (2 hr-treatment/6 hr-treatment) and/or the growth inhibiting pattern of these compounds, the selective inhibition of DNA synthesis was recognized.

From these results, it may be clinically useful.

biochemical, pharmacological and preclinical studies on a new ellipticine derivative.

E. Poggetti(a), E. Volini(b), C. Nucera(a), G. Ferri(b), A. Poggio(b), S. Croce(b), G. Ghidini(b, a)
(a) Istituto Gustavo-Russi INSERM-CNRS, 49000 Villejuif
(b) Istituto Pharmacologia CNRS, route de Nozay, 3100 TOULOUSE.

The screening of N-2 quaternized derivatives of 9-hydroxy ellipticine led to a new compound N-2 diethylaminoethyl pyrido-6H[4,3-b] carbazole (Detalliptinium), the properties of which are promising enough for starting a phase I clinical trial which is under way.

This drug is very active on a large spectrum of murine tumors: (ip injection (50 mg/kg) 24 hrs after grafting yields: L1210 : ILS : 386*; survivors : 50%; P388 : ILS : 386*; survivors : 50%; M1134 : ILS : 386*; survivors : 50%. It is also active on B16 melanoma, M507 reticulosarcoma and C3H colon carcinomas. Compared to the N-2 methyl derivative, Celiptinin which displayed some therapeutic efficacy against human renal carcinoma and metastasis of breast cancer, this compound is:

(a) twice more cytotoxic in vitro on L1210 cells and toxic for Ames Salmonella tester strains.

(b) more efficient in vivo on P388 and L1210 leukemia.

This improvement is mostly due to a decrease of the general toxicity of the drug and a better chemotherapeutic index.

(c) active on L1210 leukemia after i.v. injection.

In addition, this drug offers a new mode of binding on DNA different from that of Celiptinin.

(a) in spite of identical IC50 (10 μM) in usual conditions.

(b) it does not reverse a 1 frameshift mutation (Ames test) and inhibits its unwinding (less than 15% different : 10% versus 21%).

Both effects might be related to changes of cell membranes permeability.

Comparative biochemical and toxicological studies on both drugs have been carried out.
A new antibiotic, Kazusanimycin (KZM), has a structure characteristic of an unsaturated and branched-chain fatty acid with a terminal alkenic bond (Cyclohex-16). The antibiotic possesses unique cytotoxicity against murine cells in vitro (IC50 value was approximately 1 ng/ml on HELA cells). KZM showed antitumor activity against murine tumors such as sarcoma 180, Ehrlich and Lewis lung carcinomas, B16 melanoma, etc. in vivo. The antibiotic also showed growth inhibition in human sarcoma cells grown in nude mice.

The myelotoxicity of KZM was determined. When the antibiotic (maximum tolerated dose) was injected to normal mice, a modest reduction of peripheral white blood cell count was observed. The recovery of WBC count to the normal level was rapid. No effect on CHL and CSF reductions was noted on days 1-3 after the injection. Histopathological findings suggested that KZM produced atrophy of the mucous membrane of gastrointestinal tract and hydropic degradation of the liver.

Examination of blood and organ concentration of KZM in normal mice showed a rapid decrease of the antibiotic from peripheral blood and relatively high level of KZM was found in the lung, and much higher KZM concentration against 1/3 non-small cell and 1/3 small cell lung cancers. The in vitro sensitivity of the human tumor cloning assay as described by Harter et al. was utilized to screen for antitumor effects against a variety of histologic tumor types. Ten-fold increase in vitro sensitivity was noted with in vitro injection of KZM at 1 mg/kg daily for 3 days.

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The Ehrlich ascites carcinoma is a transplantable tumor of the RD strain, which contains significant amounts of RNA and DNA and is hormone-dependent, its growth being inhibited by ovariectomy and Tamoxifen (100 mg/kg), yet unchanged by the corresponding antilupotic analogues. The affinities, measured by ethidium bromide displacement in the presence of DNA and length increase of sonicated DNA. However, no clear correlation between DNA affinity and cytotoxicity seemed to exist. Preliminary structure-activity relationships showed that the presence of a methyl group in 4 enhances the activity. Mitosis: Yoshida sarcoma - ascites carcinoma: In polyacrylamide gel electrophoresis and for cytotoxic activity against KB cells, (+)-63%, <(*) 100% and (+) 128% 10 minutes, 20 minutes and 30 minutes after administration. On the contrary, triglyceride color reaction, Safflower esterification and Carmona reaction unexceptionally proved negative. In Vivo Test: In the test, Ehrlich ascites cells were used. Polyoxycarboiside was associated with 9%% respiratory obstruction 30 - 30 minutes after administration. On the contrary, triglyceride ester was found to activate respiratory function to the extent of (+) 53%, (+) 100% and (+) 128% 10 minutes, 30 minutes and 30 minutes after administration respectively. In Vivo Test: Polynoscapharide Ehrlich Riesets carcinoma: No significant differences were noted from control. Acsites carcinoma of Yoshida sarcoma: Polynoscarboiside proved to be effective in extending survival rate by about five times or more as much as compared to control. -Triglyceridic Ester Ehrlich Tumor Solid Type: Intramuscular and oral triglyceride ester proved to be effective to the extent of 68.1% and 32.5% respectively. -Yoshida Sarcoma - Tumor Solid Type: Effective rate was 85% when given intramuscularly or orally. Mitotic Yoshida sarcoma - acsites carcinoma: In polyoxycarboiside, mitotic inhibition of varying degrees occurred throughout the prophase, metaphase, anaphase and the telophase. Pathological Findings: In pathological observations, polyoxycarboiside histologically differed from triglyceridic ester and was associated with necrotic changes as compared to vacuolar degeneration in the latter.
3600 BINDING PROPERTIES OF A NEW ANTICANCER DRUG: SPIRGERMA-
NINUM.
Briland C., Peyrot V., Sarri J.C.
Laboratoire de Physique Pharmaceutique, Faculté de Pharma-
cie, Marseille, FRANCE.

Spirgermaninum (SP) an azaspirane germanium compound
is known to inhibit DNA, RNA and protein synthesis but
its mechanism of action is still unknown. Clinical data
suggested antitumor activity in breast carcinoma.

Our report deals with SP binding at microtubular level.
The interaction was monitored by turbidity measurements
electron microscopy. Microtubule assembly decreased in
the presence of SP concentrations 1.25 10^(-6) to 10^(-4)
at 37°C. For 1 : 1 protein-drug ratio the polymeriza-
ion inhibition was 50%. Addition of 1.25 10^(-5) (SP)
induced spontaneous disassembly of microtubules.

The effect of SP on pure tubulin (tubulin 65) was also
investigated. Inhibition of the assembly process was
complete at 2.5 10^(-4) and the concentration of SP
required to obtain 50% inhibition was greater with tu-
bulin 65 than with microtubule protein. So it can be concluded that SP interacts with MTP and with tubulin. This binding may contribute to this
drug's mechanism of action.

SP plasma binding

Microcalorimetric and equilibrium dialysis methods were
used to study the possible interaction between Spi-
germaninum and Human Serum Albumine or plasma.

This work was supported by INSERM contract n° 851003 and
by a grant from "La Fédération des Centres de Lutte Contre le Cancer".

3601 EFFECT OF VITAMIN E ON TUMOR GROWTH IN MICE
R. Kato, K. Kim, K. Tanigawa, Y. Kondo, M. Ueda, S. Segino
and H. Komori. Department of Medicine, Kyoto Prefec-
tural University of Medicine, Kyoto, Japan

It is well known that antioxidants such as vitamin E
(VE) and other hydrophilic compounds, such as CDP-
hydantoin, inhibit tumor growth in vitro and in vivo.
These inhibitions were usually observed at levels
higher than normal vitamin E levels. In this paper, we will
demonstrate the effect of sufficient or deficient VE on
tumor growth and host immunity, because host immunity is an important factor on tumor de-
velopment and it is also affected by VE. Mice were fed with VE deficient (0.1 mg/kg diet) or
with VE sufficient (20 mg/kg diet) levels for 2 weeks.

Based on these results, it is concluded that supple-
mentation of VE in the mice system had no tumor inhibitory effect, but VE deficient mice were rather disad-
vantageous in tumor bearing host.
H-56: NEW DRUGS, NATURAL PRODUCTS AND DERIVATIVES

3603  New Benzodiazepine Derivatives Designed as Anticancer Agents
W. Werner, K. Wehlraeke, W. Röker, H. Hoffmann; Central Institute of Microbiology and Experimental Therapy, G600 Jena, DDR

In contrast to natural occurring pyrrolo-1,4-benzodiazepine antibiotics of the ansamycin type which act by covalent binding to DNA we tried to design antileukemic benzopryrone-1,4-benzodiazepine derivatives with a potential affinity to the leukemia cell membrane and activity to the adenosine cycle system as well. Among a number of derivatives 21-MeC 54/79 (3,4-dimethyl-10,11-di-methyl-6,6aR,7,8,13,18a-hexahydro-[1]-benzopryrone-[4,5-b]-1,5-benzodiazepine) was found to interact with dTMP synthesis in murine transplantation tumors (leukemia L 1210 and P 388, Lewis lung carcinoma, melanoma B 16) by i.p. or oral administration. 21-MeC 54/79 increased the cAMP level in leukemic cells in vivo. The acute toxicity is low (LD50 = 2.5 g/kg b.wt. i.p.). The therapeutic index calculated from the LD50, i.p. and the ED50, i.p. values ranged between 6-8. The absolute configuration of the molecule and the substitution in accordance with the H-O-O-triangles hypothesis (Zee Cheng, 1976) for anti-leukemic drugs are essential for antineoplastic activity. No immunosuppressive, psychotropic or DNA directed effects were found.

3604  A NEW CONCEPTION OF MICROSOMAL METABOLISM OF ADRIAMYCIN. T.A. Bogushe and V. V. Demenko, AllUnion Cancer Research Center, USSR, Moscow, USSR

The conventional scheme of micosomal metabolism of adriamycin (AD) in the Adriamycin metabolizing electron transfer, accepting the electron from flavoprotein (FP) with the production of semiquinones, some of whose experimental results do not confirm the conception which accepts the function of cytochrome P-450 (CYP 450). 1. AD does not affect the reduction of cytochrome P-450, a and b, in the micosomal fraction with MADPH. 2. Specific inhibitor of P-450 SKF-522A changes the biological action of AD. 3. AD are binding with P-450 as a substrate of type I. Our main experimental fact which allowed us to introduce a new scheme of AD metabolism was non-enzymatic interaction of AD with MADPH with the production of the precipitate poorly soluble in water which is probably the quinhydrone complex of AD. This suggestion is based on changes in spectrum and mass-spectrum AD characteristics. After the interaction of AD with MADPH and MADPH oxidation registered due to a decrease of constant light on 505 nm. The changes in the quinones AD grouping are confirmed by the studies of IX spectrum of AD and the precipitate after the incubation medium of AD and MADPH. We propose the following scheme of AD metabolism resulting in AD semiquinone production. Hydroquinones of AD produced by non-enzymatic interaction with MADPH is incorporated into the electron transfer chain between MADPH and MADPH oxidation resulting in AD semiquinone consumption by MADPH. In conclusion we expect that non-enzymatic interaction of AD with MADPH and MADPH is incorporated into the electron transfer chain between MADPH and MADPH oxidation resulting in AD semiquinone consumption by MADPH.

3605  BASIS FOR THE THERAPEUTIC EFFECTIVENESS OF CIS-PLATIN (DDP) AND 5-FU OR 5-FLUOROURACIL (FU) ALONE AND IN COMBINATION AGAINST MOUSE LEUKEMIA L1210 CELLS. S. Palmeri, F. Trave, J. Goranson and Y. Rustum; Roswell Park Mem. Inst., Buffalo, NY, USA

Previous experimental and clinical evidence indicated that FuRa and DDP alone or in combination have significant antitumor activity. Studies were carried out to evaluate the basis for the enhancement of therapeutic efficacy of these agents when used in combination. 1p sequence, 24 hr apart. In vivo treatment with the drug. The combination of FuRa and DDP alone, in an optimal combination for combination therapy, was tested for its ability to reverse DDP resistance. A single dose of DDP (2.5 mg/kg) was given to L1210 cells in vivo. The acute toxicity is low (LD50 = 2.5 g/kg b.wt. i.p.). The therapeutic index calculated from the LD50, i.p. and the ED50, i.p. values ranged between 6-8. The absolute configuration of the molecule and the substitution in accordance with the H-O-O-triangles hypothesis (Zee Cheng, 1976) for antileukemic drugs are essential for antineoplastic activity. No immunosuppressive, psychotropic or DNA-directed effects were found.

3606  CISPLATIN AND 5-FLUOROURACIL HAVE A SYNERGISTIC EFFECT ON HETEROTRANSPLANTED SQUAMOUS CELL CARCINOMA. C. Treppe and J. Westergberg, Dept. of Gynecological Oncology and Dept. of Otorhinolaryngology, University Hospital, Lund, Sweden.

In combined modality treatment of squamous cell carcinoma cis-platin (CDDP) and 5-fluorouracil (5-FU) have gained increasing interest. The agents are considered to act synergistically. This hypothesis has however not been tested on squamous cell carcinoma. Methods and Results. Both CDDP and 5-FU gave dose dependent inhibition of tumor volume growth of squamous cell carcinomas of the head and neck heterotransplanted to nude mice, given as single dose i.p. CDDP was given intraperitoneally at an interval 7.5-10 mg/kg and 5-FU in the dose interval 100-400 mg/kg. In combination the effect was assessed using growth delay as end-point. CDDP was administered 7.5 mg/kg i.p. in single dose, followed by repeated i.p. injections of 5-FU every eight hour for four days to a total dose of 200 mg/kg. Two tumour lines were studied. In tumour line EH the gained growth delay was for CDDP 0.11 tumour volume doubling times, for 5-FU 0.32 and for CDDP+5-FU 1.1. For tumour line AH the corresponding values were 0.22, 0.64 and 3.43 respectively. Toxicity was not increased by combined treatment. Conclusion. CDDP and 5-FU have a synergistic effect in the treatment of heterotransplanted squamous cell carcinomas. The degree of syneresis varies in between tumour lines.
938

THE EFFECT OF A COMBINED APPLICATION OF METHOTREXATE AND ACTINOMYCINE D ON V 79 CELLS.
A. Hudáková, K. Horáková, T. Pestrčel. Institute of Oncology and Radiology, Bratislava, Slovakia; and Institute of Medical Biology, Budapest, Hungary.

Methotrexate /0.001 μg/ml/ and Actinomycin D /0.00075 μg/ml/ were added simultaneously and successively to V 79 cells. The most effective combination of the application was shown to be when the compounds were applied successively. Such an effect caused a 100% inhibition of the growth of the synchronized and a 83.6% of the asynchronous cell population respectively.

The analysis of the culture medium it is suggested that glumepetum occurred in the treated cells. The phenomenon was mostly profound at the synergistic effects of the tested agents.


Knowing the importance of heterogeneity of tumor cell population in the effect of anticancer agents as well as taking into consideration the different mode of action of chemotherapeutic drugs a "cocktail" of drugs comprising eleven compounds /alkylating and intercalating agents, antimetabolites, alkaloids/ was used to investigate its hemato logical, and anticancer effect on three experimental tumors /P388, L1210, Colon 26 tumor/. The study was designed to get some preliminary information on the applicability of this type of combination. One dose of "cocktail" contained about one tenth of LD50 of each drug. Treatment with single doses or continuous administration of "cocktail" resulted in increased life span, retardation of tumor growth and in some cases had a curative effect. The treatment was especially effective in case of advanced tumors. The application of drugs as a "cocktail" is just a variant of simultaneous drug delivery and is based on the assumption that drugs of different modes of action or with the same mode of action but differing in site of attack when given simultaneously may have good therapeutic effect even in rather low doses by blocking several metabolic pathways at the same time. Moreover considering the heterogeneity of tumor cell populations which includes e.g differences in cell kinetic parameters or drug sensitivity of cell subsets within the same tumor, "cocktails" may exert enhanced cell killing effect, retardation of tumor growth, prolongation of survival time or delay the development or resistance. As "cocktails" may consist of several drugs in different variations and doses, they could serve as a versatile tool in combination chemotherapy.

MODULATION OF ADRIAMYCIN (Ad) SENSITIVITY (S) AND ACCUMULATION (A) BY TAMOXIFEN (Tam) OR PERCHLORILK MALLEATE (PM) IN TWO HUMAN BREAST CANCER (HBC) CELL LINES. B.J. Foster, K.Grotzinger, V.Hamlet. National Cancer Institute, Bethesda, MD, 20892 U.S.A.

The treatment of initially chemotherapy sensitive solid tumors is often limited by the development of drug resistance (R) both primary to the agent(s) used and cross resistance (XR) to other agents. To study this problem, we compared S and A of Ad in a HBC cell line (MCF 7), ad the resistance to Ad by exposure to increasing concentrations of the drug, to the parent cell line (MCF 7). S and A examinations were performed in 50 mM nitrogen (E2) containing media 10^{-6} M of Tam or PM using a soft agar double layered clonogenic assay and 3H labeled Ad, respectively. The concentration of Tam of PM had no effect on the growth of either HBC cell line in the presence of E2. The minimum IC50's in pH for agents Ad, Velban (VB), Melphalan (M) and the ratio (MCF 7): MCF 7 + Tam or PM of the uptake in counts per million of T4C expressed in percent were:

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<td>0.010</td>
<td>0.010</td>
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Comparative S showed that MCF 7 Ad was R to Ad and XR to VB, but not XR to M. The R of MCF 7 Ad was less when Tam or PM was added. The XR of MCF 7 Ad to VB was less when Tam was added. The R of MCF 7 Ad was associated with lower A of Ad that did not appear to increase when Ten was added but did increase when PM was added. This suggests that the change in S of MCF 7 Ad with Tam was due to either an anti-Ad effect or A of Ad, but resulted from some other mechanism that increased the cytotoxicity of the Ad that accumulated in the cell.

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H-51: PRECLINICAL DRUG EVALUATION; COMBINATION CHEMOTHERAPY

TUESDAY • AUGUST 26 • AFTERNOON
THE EFFECTS OF BLEOMYCIN ON TUMOR GROWTH RATES AT DIFFERENT INTRACELLULAR GLUTATHIONE LEVELS.

R. Anderson, S. Williams, and H. van't Riett. Dept. of Radiobiology, Univ. of Stockholm, Sweden.

Tumor growth was followed after bleomycin treatments of a mammary carcinoma grown on the feet of CBA mice. Bleomycin (20 mg/kg) was given i.p. after treatments with glutathione depleting agents like BSO (5 mole/kg) or hyperthermia (43 C, 40 min.) in different fractionated schedules. GSH levels in the tumor cells were measured by the HPLC-technique. Twenty-four hours after hyperthermic treatments of the tumors, the GSH level decreased to 30% of control. BSO alone or in combination with hyperthermia decreased the GSH levels to 33% or 14%, respectively, while bleomycin alone did not change the GSH content. At present, the effects of different GSH depleting treatments and fractionation schedules on the toxic action of bleomycin are under evaluation and the results will be presented at the meeting.

1,6-di-N-chloroethyl-N'-nitrosoureido-2-6-thiaol /GYKI-13 324/ is a highly active antineoplastic agent having been in phase I-II clinical trial.

Combination chemotherapy studies were performed with GYKI-13 324 and 5-Fluorouracil, Methotrexate /MTX/, Vincristine and Adriamycin. Out of these agents a schedule dependent potentiating type synergism was detected between GYKI-13 324 and 5-FU on L-1210 leukemia.

<table>
<thead>
<tr>
<th>CONCENTRATION BCNU SarCNU</th>
<th>20 mg/kg x1 po 5</th>
<th>198</th>
<th>0/0</th>
</tr>
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<tbody>
<tr>
<td>5-FU</td>
<td>14 x 1 p/d 2-5</td>
<td>168</td>
<td>0/0</td>
</tr>
<tr>
<td>5-FU + GYKI-13 324</td>
<td>333</td>
<td>6/0</td>
<td></td>
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Other schedules gave no synergism. There was an additive type of synergism with MTX on P-388 leukemia and with DTX on Hurling- Pagey mouse melanoma. We failed to detect any synergism between GYKI-13 324 and Vincristine or doxorubicin. Tumor cell studies in B16, B10, Ehrlich ascites and Meth-A experiments /four day treatment with 5-FU + a single dose of GYKI-13 324 on day 4/ revealed only a slight addition of the toxic effects.

oxy of GYKI-13 324 alone: 110 mg/kg GYKI-13 324 + 5-FU 90 mg/kg

INTERACTION OF HYPERTHERMIA WITH MITOXANTHRENE AND LOWDOSE ON HUMAN CHRONIC MYELOID LEUKEMIA CELLS IN VITRO

M.P. Chitnis, A.S. Jhaveri, R.K. Ramach and T. Kikuchi, Department of Oncology, Vancouver Cancer Res. Inst., Dept. of Med. Oncology, Tata Memorial Hospital, Tata Memorial Ctr., Parel, Bombay-12, India.

Hyperthermia (hyp) has been shown to affect human chronic myeloid leukemia (CML) cells in vitro, suggesting that perturbation of cellular processes may be an important characteristic of this treatment modality. Mitoxantrone a new antineoplastic agent, has been investigated in vitro on CML cells at 37°C and 42°C. Inhibition of initiated thymidine /d-Thd/ incorporation has been used as parameter of cytotoxicity. Pericellular cells from CML patients who did not receive any chemotherapy, showed moderate response to mitoxantrone at 0.5 μg/ml & 1 μg/ml concentration. Exposure of CML cells to 42°C for 2 hrs indicated 13 to 44% inhibition in d-Thd incorporation. However when cells were exposed to mitoxantrone (1 μg/ml) for 5 hrs at 42°C the 42°C-Thd incorporation was inhibited to the extent of 27 to 71% indicating greater cellular damage with this combined treatment. Lomustine (LCNU) is a weak antitumor agent which does not affect cell division process but acts on a specific state of cell energy metabolism called as condensed mitochondrion. It is also a hyp-sensitizer. We examined in vitro effects of LCNU (0.01 and 0.02 μM) & a single dose of 5-FU alone & in combination on CML cells from untreated patients by measuring the rate of 42°C-Thd incorporation. Drug and hyp combination demonstrated increased inhibition in DNA biosynthesis in human CML cells. Our observations indicated differential drug & hyp sensitivities in CML cell samples from patient to patient. In conclusion hyp can be a promising method for enhancement of cytotoxic effects of anticancer drugs.

IN VITRO COMPARISON OF SARCNU + BCNU ON THE HUMAN TUMOR STEM CELL ASSAY. A.P. Muley, S.P. Tailor, M.D., Koelis, E.J., and O'Doherty, N.S., Columbus Children's Hospital, Columbus, Ohio, U.S.A.

SarcNU® is a new anticancer agent which is a sarcosamine congener of chloroethylsulfonoureas. In vitro chemosensitivity of this new agent was compared to bichloroethylsulfonourea (BCNU), in the human tumor stem cell assay /HTSCA/. Biopsy specimens from five patients with grade III or IV malignant astrocytoma were obtained at surgery. A portion of each tumor was separated for the HTSCA and mechanically disaggregated into a single cell suspension. The assay was performed as originally described by Drs. Hamburger and Salmon. In 10$^2$ biologic cell suspension, the assay was performed as originally described by Drs. Hamburger and Salmon. In 10$^2$ biologic cell suspension, the stem cells were incubated and all cells washed after incubation and plated in the upper layer at a final concentration of 5 x 10$^5$ cells/ml for 21 days in 5% humidified CO$_2$ at 37°C. Survival of drug treated colonies was determined over dose ranges log$_{10}$16 μg/ml.

CONCENTRATION BCNU SarCNU % Survival & SE
1 μg/ml 76.9 ± 0.92 52.9 ± 0.46
3 μg 57.4 ± 0.62 42.6 ± 0.46
8 μg 46.2 ± 0.88 33.3 ± 0.48
16 μg 31.0 ± 0.05 21.6 ± 0.32

The inhibitory effect of both drugs was concentration dependent. Both SarCNU and BCNU showed decreasing colony survival with increasing drug concentration /p<0.001/. SarcNU® had significantly less colony survival compared to BCNU /p<0.009/. There was also a significant interaction between drug type and concentration /p<0.0477/, with the newer agent SarCNU® having a greater increase in effect than BCNU at the lower concentrations. These results suggest that SarCNU® may have more antitumor activity against malignant gliomas than BCNU.

In combination, BCNU and SarCNU® showed a significant increase in survival relative to control /p<0.001/. With SarCNU® alone, there was a significant decrease in survival relative to control /p<0.001/.

Calcium antogonist drugs such as flutriafol and/or flutriafol. E.3. etc. have been observed to reduce drug induced chemoresistance of tumor cells to vincristine (VCR) or adriamycin. This effect is mainly due to an increase of the input and to an inhibition of the output of the antitumor drug with the result of higher intracellular concentrations of it. So far we know no observations have been made on the effects of antimodulin drugs on the primary resistance of tumor cells to the drugs commonly employed in the treatment of neoplasia. Melanoma cells are known to be primitively resistant to VCR. The possibility exists that antimodulin compounds may enhance the effects of vincristine, able to not only because of the modification of the cellular pharmacodynamics, but also because both the drugs directly or indirectly interact with the association/dissociation processes of microtubules. Results obtained indicate that the antimodulin drug flutriafol enhances "in vitro" and "in vivo" the antitumor activity of VCR on B16 melanoma cells by the calcium antagonists flurazone 

IN VITRO AND IN VIVO ENHANCEMENT OF VINCRISTINE ANTITUMOR ACTIVITY ON B16 MELANOMA CELLS BY THE CALCIUM ANTAGONIST FLURAZONE

A. Balini, M. Sugi, C. Combiasi, R. Caprioli, M. Malvasio, M. Mattioni and T. Balini.
Regina Elena inst. and Poliferma Study Ctr., Roma, Italy.

In this study we observed that the drug induced chemoresistance of tumor cells to vincristine (VCR) or adriamycin. This effect is mainly due to an increase of the input and to an inhibition of the output of the antitumor drug with the result of higher intracellular concentrations of it. So far we know no observations have been made on the effects of antimodulin drugs. Results obtained indicate that the antimodulin drug flutriafol enhances "in vitro" and "in vivo" the antitumor activity of VCR on B16 melanoma cells in vitro. The VCR concentrations were long lasting and higher than in control cultures. We observed to decrease drug induced chemoresistance of tumor cells to vincristine (VCR) or adriamycin. This effect is mainly due to an increase of the input and to an inhibition of the output of the antitumor drug with the result of higher intracellular concentrations of it. So far we know no observations have been made on the effects of antimodulin drugs. Results obtained indicate that the antimodulin drug flutriafol enhances "in vitro" and "in vivo" the antitumor activity of VCR on B16 melanoma cells in vitro. The VCR concentrations were long lasting and higher than in control cultures.
IN VITRO PHARMACOKINETICS OF CYTOSINE ARABINOSIDE.

H. NOGUCHI*
TUESDAY * AUGUST 26 • AFTERNOON

It has already been expected that K18 synthesized by condensation of human IgG melphalan is a new anticancer agent with arriving and accumulating features at tumor sites and shows almost no side effect. We performed a fundamental study on the effect of K18 combined with radiotherapy. Further, we experienced interesting clinical cases as described below. In the fundamental study, 10^6 cells of sarcoma-180 or Lewis lung carcinoma were inoculated intramuscularly in the femoral region of ICR or BDF mice. A single dose of 1,500 or 3,000 rad was locally applied using linear after seven and eight days of inoculation. After irradiation, K18 or melphalan was administered orally or intravenously at a dosage level producing no beneficial effect in single therapy. In addition, its histopathological effect was assessed in the Lewis lung carcinoma group.

Inhibition of tumor growth, definite prolongation of 30% survival and appearance of cured surviving cases were noted when radiotherapy was combined with K18 and the effect of this drug was increased by combination with irradiation. A combination of K18 or melphalan with radiotherapy caused more marked fibrosis and necrosis than did radiotherapy alone. However, all mice received K18 survived, while all mice received melphalan died of side effects. In clinical case, 90mg/day of K18 was given to a partially ovarioctomized patient (69 years old) to whom CDDP therapy was stopped because of side effects. The remained tumor was reduced in size 70 days after K18 therapy and became operable. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed. No side effect of K18 was observed and K18 is expected to be clinically useful.

** Supported in part by a gift from the Upjohn Company.
**3622**


In order to enhance local therapeutic effect and to reduce systemic levels of cisplatin (CDDP), nonbiodegradable microspheres were prepared and studied in a model of liver tumor chemosensitization. The ethylenelulose microspheres of size 50 to 100 μm containing 51% (w/w) of CDDP were obtained by evaporation of the organic solvent from a stirred ethylene chloride/water emulsion. C57Bl/6 mice with M5076 sarcoma established liver metastases were injected into the portal vein with various suspensions: microspheres without CDDP (MS-neutral), microspheres with CDDP (MS-CDDP), CDDP alone or a combination of MS-neutral and CDDP (MS-neutral-CDDP). After treatments, urinary and blood samples were collected at multiple time intervals in order to determine the CDDP concentration present. The antitumor effect of MS-CDDP and CDDP on the liver surface nodules. The infusion of MS-neutral alone showed 94% inhibition of metastases at 20 mg/kg compared with the control group, which may be explained by the partial blockade of portal blood flow. CDDP alone (1.5 mg/kg) or MS-neutral-CDDP totally eradicated metastases, showing the very high sensitivity of M5076 tumor cells exposed to a low concentration of the drug during a short period. MS-CDDP (20 mg/kg - 10 mg/kg entraped CDDP) destroyed about 94% of metastases indicating that a continuous delivery of sufficient levels of CDDP from MS-CDDP was effective in the embolized areas. These results demonstrate that regional chemosensitization concurrent with a sustained release of CDDP from MS-CDDP seem to offer a better unitumor activity than embolization alone, associated with a decreased systemic exposure to CDDP in comparison with the administration of the free drug. These MS-CDDP may be indicated for treating patients with malignant tumors fed by an artery.

**3623**


4'-Epidoxorubicin (E) is a new doxorubicin analog with reduced gastrointestinal toxicity and less chronic cardiotoxicity. Possibly, it also has a broader spectrum of antitumor activity. In an ongoing phase I clinical trial, patients with carcinoma in situ of the bladder received the drug by intravesical instillation during 1 hr. Up to the present patients received doses of 30 and 50 mg dissolved in 50 ml saline. The absorption of E was determined by measuring the recovery of E from the instillation fluid, irrigation fluid (100 ml saline) and first spontaneous urine. Blood samples were taken during instillation and up to 3 hrs afterwards. Plasma was prepared immediately. All samples were frozen at -20°C until analysis. Levels of E were determined by HPLC using a fluorescence detector. Up to now 32 treatment courses were evaluated. Blood samples were collected in 8 of them. The percentages of the administered dose recovered from the bladder were 79 ± 12% (n=17) and 84 ± 10% (n=15) after instillation of 30 mg and 50 mg of E, respectively. Only very small amounts of E (5 ng/ml) could be detected in plasma of three patients. The highest concentrations were observed after the period of instillation. No metabolites or degradation products of E were found in plasma, urine, installation fluid and irrigation fluid. 

It can be concluded, that after intravesical administration only small amounts of E are slowly released to the general circulation, indicating that systemic side-effects are to be negligible.

**3624**


Liver metastasis in melanoma are found to be poorly responsive to systemic chemotherapy as has been known from other solid tumors metastatic to the liver. As a consequence, chemotherapeutic approaches have been developed which might focus the anti-tumor action selectively at the target tissues and allow the cytotoxic drug concentration within the target to be enhanced while reducing systemic concentration of the drugs applied and toxicity alien. The concentration of the cytotoxic drug will be optimal if a given dose is applied i.v. through an arterial vessel with a relatively small diameter provided that the perfusion rate of the target region is small enough to avoid rapid wash-out of the drug. If the drug is metabolized or excreted through the target tissues the systemic concentration will be minimal. This implies that for regional chemotherapy drugs should be chosen which have a short plasma half life time and a high total body clearance. Additionally, degradable starch microspheres (DSM) can be used to transiently occlude the arteriole access to the target region thus leading to increased drug exposure in combination with the drug applied. Degradable starch microspheres have a mean diameter of 45 μm and an intravital half-life time of about 25 minutes. They are completely degraded by the physiological concentration of endogenous hydrolases (lysase) in serum thus reconstituting normal blood flow and microcirculation after the time period of circulation arrest. If a drug is dissolved and administered together with microspheres it will therefore be retained in the capillary vessels subsequently enhancing exposure time to the target cells while systemic drug exposure and toxicity will be reduced.

These modulating approaches of regional chemotherapy for liver metastasis omen against other metastatic diseases confined to the liver and inherently offer beneficial palliation in the management of melanoma.

*Pharmacia, Uppsala/Reiner, Sweden.

**3625**


Repeated topical application of 13-cis retinoic acid resulted in complete disappearance of leukoplakia of the vulva in 6 out of 16 patients. A considerable regression of leukoplakia was seen in 7 other patients. Side effects of treatment could be managed. Serum retinol level was found to be lower in patients than in healthy subjects. It is concluded that several patients with chronic epithelial vulvar dystrophies could benefit from local retinoid treatment in particular in patients with advanced dystrophies until now qualified for vulvectony.

*Pharmacia, Uppsala/Reiner, Sweden.

**Institute of Oncology, Wawelska 15, Warszawa, Poland.
H-52: REGIONAL CHEMOTHERAPY

NEW TYPE OF ADRIAMYCIN OINTMENT WITH AGENTS ENHANCING PERCUTANEOUS ABSORPTION. M. Fukuda† T. Yanase† K. Kanazawa‡ S. Yamashita§ Y. Nakashima## H. Endoh### H. Hatanaka††† 1st. Dept. of Surgery*†§ Dept. of Radiology**††† St. Marianna Univ. School of Medicine, Kawasaki-shi, Japan

For the purpose of local treatment of recurrent skin metastasis from various carcinoma, adriamycin (ADM) ointment was first made by authors in our hospital and reported in 13th international cancer congress, 1979. Subsequently, new types of ADM ointment with agents enhancing percutaneous absorption has been investigated in order to get better diffusion through skin barrier. In this study, new types of ADM ointment were evaluated for diffusion and clinical results. The prescription of new ADM ointment most widely used in our hospital was ADR 0.5g, Hydrophilic polyol 79.5n, and glicerin 20g with BU-SEB 1.0g or prostaglandin E2 as an enhancer for percutaneous absorption. In animal studies, new ADM ointment with 5% BL-9EX or 0.02% PG E showed remarkable effect with 54.9% or 51.8% reduction in tumor weight of Yoshida sarcoma transplanted subcutaneously in the back of Donryu rats 6 days after application. In contrast, original type of ADM ointment without enhancer revealed only 17.2% reduction in compared to control. Serum concentration of ADM after application of ADM ointment with or without enhancer showed 0.03ug/ml as maximum, which was almost lowest limit for quantitative analysis. In 17 of 29 cases (58%) with cutaneous recurrence of breast carcinoma or primary or recurrent tumor of head and neck cancer, new ADM ointment showed good results when they were applied as one of agents for multidisciplinary therapy.

H-529

STUDIES ON ENDOSCOPIC LOCAL INJECTION OF AN ANTICANCER AGENT INTO EXPERIMENTAL CANINE STOMACH CARCINOMA
Teruo Gawa, Ken-ichi Akagi, Mitsugu Murayama, Tadashi Nakaihara, Keiji Daimon, Kei-ichi Nakagawa. 1st. Dept. of Surg., Gunma Univ. Sch. of Med., Makishi, Japan

In order to establish a topical chemotherapy against stomach cancer which can not be treated surgically, the following experiments were performed: 1. Adriamycin (ADM) solutions were injected through an endoscope into the submucosal space along the lesser curvature of normal canine stomachs for fundamental study. At the region of lymph nodes along the lesser curvature, the ADM level was almost constant that in the gastric wall. 2. Stomach cancers were induced in 4 dogs by 2. Stomach cancers were induced in 4 dogs by intra-arterial administration of ADM. One milliliter of ADM, 1mg/ml was injected directly into 3 lesions in 2 dogs endoscopically. Total doses of ADM were 4 to 15 mg against each tumor. Two out of 3 tumors were almost completely reduced by this procedure, but minute cancer nests still remained histologically. One lesion among those treated was not reduced in size, but severe degeneration was observed histologically. No complication has occurred in these two dogs. One milliliter of ADM, 10 mg/ml was injected into 6 lesions in 2 dogs. Total doses were 2.5 to 19 mg against each tumor. Three lesions disappeared completely, and the other three lesions were markedly reduced in size. Three of 6 elevated cancers completely disappeared, but remaining cancers were observed in all of 3 depressed cancers after this therapy. Ulceration occurred in 6 out of 6 lesions. Perforation was observed in one of the five ulceraions. No lymph node metastasis was found in any of 4 dogs. This study indicates that endoscopy local injection of ADM against stomach cancer was effective in curing not only the primary lesion but also its lymph node metastases which could not be treated by the laser therapy.

This work was supported by w.m..-in-old for Cancer Research from the Ministry of Health and Welfare (60-35), JAPAN.

NEW LIPID CARRIERS FOR THE TOPICAL THERAPY OF BLADDER CARCINOMA, EXPERIMENTAL IN VITRO- AND IN VIVO-HEMODYNAMIC STUDIES. T. Goya, K. Ogi, H. Koyama, Y. Asakura, M. Akima**, 1st Dept. of Urology, University of Essen Medical School, PRG

For any chemotherapy it is desirable to bring the largest possible proportion of drugs into the target cells. We have tested, therefore, the potential drug loaded fusogenic lipid vehicles, liposomes, to partly achieve this goal. We were using fusogenic liposomes made of stoichiometric mixtures of Diacyllecithins and the corresponding fatty acids. They can be made to incorporate essentially any water- or fat-soluble therapeutic agent. Moreover, due to their fusogenicity, they are capable of transferring this content (within seconds and in a temperature- or pH-dependent manner) into the target cells, including those of bladder carcinoma. Our data show that at least empty fusogenic liposomes consisting of palmitic chain lipids can be applied into mice systemically at concentrations up to 5 times larger than those required for an optimal liposome action in vitro (ADM) without marked side effects. The fact that their fusogenicity can be controlled by means of local temperature, local heating causes an accumulation of the liposome constituents in the heated area. No similar effect is observed with standard, non-fusogenic liposomes. Three instillations into mice bladders of Fusogenic Liposomes of ADM cause the therapeutic effect of this drug to increase by more than 50-fold for invasively growing murine bladder cancer. Simultaneous application of the fusogenic liposomes marked with glycolipids and of the lectins cause the liposomes to aggregate with cells and enhances further the therapeutic effect of such liposomes. The fusogenic liposomes tested in this study may have - even in their present form - certain specificity for tumor cells as a consequence of the pH-dependence of their fusogenicity.
INTERRELATIONSHIPS BETWEEN CYTOTOXICITY AND DOSE, pH AND TRANSCATHETER ARTERIAL

Variables: The study was conducted to explore the antitumor effect of MMC on VX2 hepatic tumors. Methods: VX2 hepatic tumors induced in Albino rabbits were serially examined. The therapeutic value of MMC was investigated. Results: Several hours after MMC, TACE increased the pattern's observed area. A hypercohesive pattern was noted in the center, with an anechoic pattern within it, and a hypercohesive pattern at the periphery. Histopathologically, there were map-like zones of degeneration and necrosis at the center of the tumors, surrounded by areas of infarction. Conclusions: MMC proved to have a pronounced antitumor effect on VX2 hepatic tumors.

INTRAVESICAL CHEMOTHERAPY FOR BLADDER CANCER BY ADRIAMYCIN ADHERING TO BLADDER MUCOSA. K.Ueda, K.Ohta and H.Toida, Department of Urology, Nagoya City University Medical School, Nagoya City University Hospital, Nagoya, Japan.

Intravesical treatment of bladder cancer by means of drug injection is used all over the world. However, virtually all of the drugs are water-soluble types, so they are eliminated along with the urine from the bladder within only a short time. Thus, we attempted to develop the drug that would act intravesically for a considerably longer time as an anticancer agent. We em- pyed rats to investigate our newly developed intravesical therapy for bladder cancer by which adriamycin (doxorubicin) emulsion and hydroxy propyl cellulose (HPC) adriamycin solution adhere to the bladder mucosa. We sought to determine how long the drug would remain. The adriamycin urine concentrations told us that post-injection levels of emulsion adriamycin and HPC-adriamycin solution were lower than that of the conventional adriamycin solution. The adriamycin and HPC-adriamycin solution could be found in bladder tissue obtained 4 days after intravesical injection, but conventional adriamycin solution could not be detected in bladder tissue. Thus, it is expected to be therapeutically very effective in carcinoma of the bladder. There was no histological damage to bladder tissue, so these preparations would be expected to be available for clinical application.


Intravesical chemotherapy is used to treat superficial bladder cancer. However, optimum conditions of administration have not been established and the purpose of these studies was to investigate some of the factors which could influence the therapeutic value of this form of treatment, including the dose of drug and the pH and osmotic strength of the instillate. From observations, it was demonstrated that the optimal conditions of administration depend on the type of chemotherapeutic drug and administration method. For example, we have shown that MMC proved to have a pronounced antitumor effect on VX2 hepatic tumors.

SYSTOMIC ABSORPTION OF RHODAMINE 123 FOLLOWING INSTILLATION INTO RAT URINARY BLADDER. T. W. Sweatman, F. Larussa, and M. Israel, Department of Pharmacology, University of Tennessee College of Medicine, Memphis, TN 38163, U.S.A.

The xanthene dye Rhodamine 123 (RH-123) has been shown to be selectively toxic to carcinoma cells as compared to "normal" epithelial counterpart cells (Lampielsi et al., Cancer Res., 43: 716, 1983). This unique property, together with its lipophilic character and apparent low toxicity, suggest that RH-123 may be of value in Intravesical (IVe) chemotherapy of superficial bladder cancer. The study was undertaken to determine, in an animal model, to what extent RH-123 could be absorbed following IVe administration and histopathologically following treatment. The study was undertaken to determine, in an animal model, to what extent RH-123 could be absorbed following IVe administration and histopathologically following treatment.

SYSTEMIC ABSORPTION OF RHODAMINE 123 FOLLOWING INSTILLATION INTO RAT URINARY BLADDER. T. W. Sweatman, F. Larussa, and M. Israel, Department of Pharmacology, University of Tennessee College of Medicine, Memphis, TN 38163, U.S.A.

The xanthene dye Rhodamine 123 (RH-123) has been shown to be selectively toxic to carcinoma cells as compared to "normal" epithelial counterpart cells (Lampielsi et al., Cancer Res., 43: 716, 1983). This unique property, together with its lipophilic character and apparent low toxicity, suggest that RH-123 may be of value in Intravesical (IVe) chemotherapy of superficial bladder cancer. The study was undertaken to determine, in an animal model, to what extent RH-123 could be absorbed following IVe administration and histopathologically following treatment. The study was undertaken to determine, in an animal model, to what extent RH-123 could be absorbed following IVe administration and histopathologically following treatment.
3634 **EFFECTS OF EXPERIMENTAL LIVER-ARTERIAL EMBOLIZATION ON NORMAL LIVER AND APPEARANCE OF ENDOOTOXIN --PREVENTIVE EFFECTS OF COENZYME Q10--**

Motonobu Ozaki, Satoshi Kazusa, Kenji Matsuo and Sadaharu Otsuka, 1st Dept. of Int. Med., Toho Univ., Tokyo, Japan

Objective: Liver arterial embolization causes ischemic changes in the liver, which lead to various hepatic insufficiencies. We studied the relationship between the appearance of endotoxin and damage to various factors after such embolization and the action of coenzyme Q10 on the ischemic liver.

Method: Embolization was performed on albino rabbits with 80 mm3 of gelfoam powder via the proper hepatic artery. Rabbits administered 5 mg/kg of Q10 were compared to untreated rabbits.

Results: In rabbits not treated with Q10, there was a 62% reduction in the reticuloendothelial system at 5 hours. Endogenous endotoxin was elevated to 90.5 pg/ml. ATP decreased by 74% and total nucleotide by 73%. Electron microscopy showed impaired mitochondria. In rabbits treated with Q10, the reticuloendothelial system demonstrated a 43% reduction at 5 hours and endogenous endotoxin showed a very low value of 34.5 pg/ml. ATP decreased to 38% and total nucleotide to 9%. Electron microscopy showed slightly impaired mitochondria.

Conclusion: Coenzyme Q10 was effective in the prevention of endotoxemia after experimental liver arterial embolization.

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3635 **NEOPLASTIC SPECTRUM OF GIANT PITUITARY MACROADENOMAS.**

Nandita Gupta, N.Kochupillai, P.N.Tandon, M.M.S.Ahuja, AIIMS Institute of Medical Sciences, New Delhi-110 029, India.

122 patients with histologically proven pituitary macroadenomas (median vol = 19.2 cc) were studied for their endocrine status in circulation and tumour tissue. Neuro-ophthalmic complications (82%) gonadal hypofunction (80%) and acromegaly (36%) were the presenting symptoms. 81% were Chromophobe adenomas, 14% were Acidophils and 5% were Mixed adenomas by conventional histology. 66% had hyperprolactinemia. All the tissues studied (80) had significant concentrations of Prolactin (PRL) and Growth Hormones (GH) immunoreactivity. 61% of the acromegalics had hyperprolactinemia and all but two of them had hypersomatotropism. The entire set of adenomas studied could be assigned to a neoplastic spectrum based on hormone secretory status. Age and Sex related prevalence, Tumour size, PRL:GH ratio in tissue as well as presence of abnormal hormone forms in the tumour. The findings of the present study permit the classification of giant macroadenomas of the pituitary based on secretory activity of GH and/or PRL as well as GH and PRL in immunoreactivity demonstrated in tissue.

3636 **GROWTH HORMONE AND PROLACTIN PRODUCING PITUITARY MACROADENOMA. A CASE REPORT.**


A 48 y. male patient was investigated. Acromegalic signs had commenced 23 y. earlier. Plasma hGH and prolactin levels were found to be elevated (over 220 ng/100 ml and 1456 mU/l, respectively), lateral projection of the sella 280 mm2, CT revealed suprasellar extension of the pituitary macroadenoma. After a six month bromocryptine medication, the size and hormone productions of the adenoma were markedly decreased. Transphenoidal adenomectomy was performed subsequently. Immunohistochemistry /ABC/ witnessed for the presence of hGH in many adenoma cells and prolactin in a few scattered cells. Immunostainings were negative for ACTH, TSH, FSH, LH and alfa-subunit. Plasma hGH and prolactin levels were lowered postoperatively, but still above the normal range. Thus, long term bromocryptine therapy should be continued after surgery. The experience with this case shows that bromocryptine can positively influence both size and activity of mixed somatotropin-prolactinomas.

Six patients with various peripheral hormone disorders were investigated. Two of them had primary hyperthyroidism; in 2 patients with Cushing's disease bilateral total adrenalec-
omy had been performed previously, and two had primary hypopituitarism due to chromosomal abnormalities. In the two adrenalectomized cases pituitary microadenoma was developed with elevated ACTH levels (Nelson's syndrome). In four patients with primary hypothyroidism or hypopituitarism, thin layer X-ray tomography revealed pituitary microadenomas. In all of the latter patients an elevated plasma prolactin level was detected. Three of the six patients underwent transcerebral adrenocortical electron micrography and immunohistochemical examinations showed prolactinomas. Results obtained from this study suggest the possible role of peripheral hormone disorders in the pathogenesis of certain pituitary adenomas.


A case of multiple primary malignant neoplasia is reported. Synchronous development of endomis-
trial and adrenal cortical malignancies was preceded by carcinoma of the breast. All tumours were verified histologically. Combined treatment of the breast and adrenal cortical cancer was successful as no metastases were detected. However, the third tumour was incurable with widespread metastases and bone typical features of endocrinologically active adrenal cortical cancer presenting the picture of Cushing's syndrome. This association of tumours is an extreme rarity/increased incidence of triple malignant neoplasia (p.36, incidence of adrenal cortical cancer 1/7 million). A family history revealed colon and liver malignancies in the patient's brothers. Although exact data were available for only one generation affected by cancer, the reported case may be representative of a "Cancer Family Syndrome of Lynch in Hungary." Close oncological supervision is mandatory to enable early diagnosis of a certain association of tumours/eg: colorectal and breast/mutative/ is not uncommon and some families are at a great risk of their occurrence.


Alterations in the lipid composition and metabolism of adrenocortical tumours are often characteristic of functioning adrenocortical tumours. These neoplasms require increased amount of cholesterol for hormone production and also for membrane synthesis. Crystalline sections of normal adrenals and adrenocortical tumours were studied by polarizing microscopy in the temperature range from -20° to 45°C. The majority of lipid droplets (intracellular stores of cholesterol) in normal adrenal cortex were birefringent at room temperature, while birefringence of lipid droplets of adrenocortical tumours appeared when cooling to from -4° to -35°C. These data suggest that lipid droplets in neoplasms have low melting points, and therefore are readily available for cholesterol ester hydrolyzing enzyme system and for enhanced hormone synthesis.

Human adrenocortical cells isolated from surgically removed adrenocortical tumours were inucu-
bated with colloidal gold labelled human low-density lipoproteins (LDL) in order to study the utilization of extracellular cholesterol at electron microscopic level. The tumour cells bound and internalized the labelled LDL avidly.

KLINIFELTER'S SYNDROME AND MALE BREAST CANCER. A.W. van Goew, M.D., Ph.D. Department of Surgery, Rotterdam Radio-Therapeutic Institute and the Dr. Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

In an extensive retrospective study of male breast cancer (MBC) in Holland (106 patients) we found at least three cases with an extra X chromosome. These patients, mostly having Klinefelter's syndrome (KS) are at high risk to develop breast cancer. About thirty patients with the combination MBC and KS are known. It is calculated in patients with KS that the incidence of breast cancer is 20 times as in normal male population.

In western countries we know that the male-female ratio is 1:100.

In patients with KS it is never shown that gynecomastia is a premalignant lesion. Both (gynecomastia and MBC) are results of the same (endocrine) stimulus generally being an altered estrogen-androgen ratio in favor of the estrogen.
3641 SERUM LEVELS OF GONADOTROPINS AND ANDROGENS IN PROBABLE TUMOR MARKERS IN PATIENTS WITH MA
genital GERM CELL TUMORS OF THE TESTIS
Jellie E., Ivanovic S., Kovac V., Jellie M., Br
covic M. and Negroglj J. Radiology Dept. University
Negroglj, Yugoslavia

Investigations were performed on sera from:
18 patients without metastases following
semieastration; 32 patients with metastatic disease (MD); 6 seminomas, 8 beta-HCG positive
NSGCT; 5 beta-HCG negative NSGCT; 6 primary
extragonads). 2 patients have complete remis-
"ion (CR) following chemotherapy.
In patients with no metastases following
semieastration, FSH levels are slightly elevated
(X:40.10 U/l). In MD, FSH levels are
raised with pronounced dispersion of indi-
"erent values (X:25.05; SD:35.00; VC:15.06); the
"est are observed in seminomas (X-90.29). The
lowest in primary extragonads
(X:10.55) and in beta-HCG positive NSGCT
(X:2.90). Tumor beta-HCG seems to inhibit
secretion of hypophyseal FSH; beta-HCG ne-
egative NSGCT are the likely representative
group for the entire category. About 50% of
patients have abnormal testosterone levels,
mean DNA levels are low (X:4.92/100 ml),
androstandiol levels are above normal in 69%
of patients (X:60.9/100 ml). Patients in CR still display elevated FSH
and testosterone levels, DNA levels remain as before, but mean
androstandiol values significantly decrease
to (X:2.41/100 ml). The typical profile in MD
seems to be elevated FSH, low/norlmal DNA,
low testosterone, elevated androstandiol.
Typical profile in CR seems to be elevated
FSH, low/norlmal DNA, normal testosterone and
androstandiol level. It is postulated that the persistence of the "metastatic" profile
in patients apparently in CR might reflect
the presence of imperceptible residual me-
"atism disease.

3642 TUMORS PRODUCING HYPOTHALAMIC HYPOPHYSISOTROPHIC HORMONES.
S.L. Asa, K. Kovacs, E. Horvath. Dept. of Pathology, St.
Michael's Hospital, U. of Toronto, Toronto, ON, Canada.

Tumors producing hypothalamic hormones represent a new class of disease. Their frequency, the associated clinical and biochemical changes and the underlying morphologic alterations are not clearly defined. Growth hormone-releasing hormone (GRH) is produced by some hypothalamic gangliocytomas, paracortical, intestinal, bronchial and thyroid endocrine tumors, and small cell carcinomas of lung. GRH excess can be accompanied by acromegaly, somatotroph hyperplasia and adenoma. Somatostatin (somatotroph release-inhibiting hormone; SRIH) is produced by a wide variety of neoplasms, including intestinal and pancreatic endocrine tumors, medullary carcinomas of thyroid and hypothalamic gangliocytomas. Somatostatin production by gastrointestinal carcinoid and thyroid tumors does not result in recognizable pituitary somatotroph dysfunction. The hypothalamic effects of hypothalamic somatostatin-producing tumors are uncertain. Corticotiberin (corticotroph-releasing hormone; CRH) is present in some bronchial, intestinal and pancreatic endocrine tumors. Medullary thyroid carcinomas, small cell carcinomas of lung and prostate and a hypothalamic gangliocytoma. CRH production by tumors has been associated with Cushing's syndrome and corticotroph hyperplasia. Thyrotiberin (thyrotroph-releasing hormone; TRH) has been found in one hepatic tumor and in pancreatic endocrine neoplasms of rats. Dopamine is detected in some paragangliomas. Production of gonadotiberin (gonadotroph-releasing hormone; GnRH) by hypothalamic tumors can lead to precocious puberty.

Hypothalamic hormone excess can be differentiated from syndromes caused by primary hypersecretivity of the pituitary or peripheral endocrine glands. Although hypothalamic hormone-producing tumors possess some common morphologic characteristics, such as well developed rough endoplasmic reticulum, conspicuous Golgi complexes and secretory granules, they show histologic and ultrastructural differences, are not confined to one cell type, and arise in several organs. Immunocytochemical techniques are of great value in localizing these hormones in tumors.

3643 PEPTIDES RELATED TO THE N-TERMINUS OF PRO-OPIO-
MELANOCORTIN IN EXTRAPITUITARY TUMOR TISSUES.
L. Gaspar, J.S.S. Chan, E.G. Seidah, N. Christien, and
F.A. Lazar, Endocrine Unit, First Dept. of Medicine,
Szeged Univ. Med. Sch., Szeged, Hungary

The immunoreactive /IR/ human N-terminal /hNT/ of pro-opiomelanocortin /POMC/ was measured by specific radioimmunoassay /RIA/ and characterized by molecular sieving and concanavalin A-agarose affinity chromatography in lung tumors and pheochromocytoma tissues. The IR hNT levels were 45.6±6 ng/wt wt mean±SD/
"h pheochromocytoma Tissues (N=3)/. In two lung tumor tissues /oat cell type/ causing ectopic ACTH syndrome IR hNT levels were 48.5 ng/wt wt and 71.7 ng/wt wt, respectively. In pheochromocytoma tissues, molecular sieving chromatography showed two major molecular forms /14 kilodalton and 12 kilodalton sw/ of IR hNT and IR y-melanotropin /yMSH/. In lung tumors, molecular sieving chromatography showed predominantly smaller fragments of hNT; by yMSH RIA. Results obtained from concan-
"avalin A-agarose chromatography suggest that the major partial of hNT in these tissues might be desglycosylated.

3644 MEDULLARY CARCINOMA OF THE THYROID, THYMACTIOTROPHIC HYPERPLASIA, MELANOCYTIC INTRACRANIAL TUMOR.
S. Gaspar, L. Lazar. Dept. of Endocrinology and Surgery,

Medullary carcinoma of the thyroid gland should not be regarded as a simple carcinoma of the thyroid but as a possible variant of a familial defect with complex clinical picture. It can be associated with pheochromocytoma, Cushing's syndrome and/or hyperparathyroidism. The various substances secreted by the tumor besides calcitonin may diversify the clinical symptomatology posing complex diagnostic and therapeutic problems. The diagnosis is made based on the radioimmunooassay of circulating calcitonin. At the same time this essay is a major criterion for the follow up of the course of the disease following surgery. The main therapy, both in our cases and in those reported in the literature, remains the surgical ablation of the tumor. In cases of local or distal recurrence reoperation is indicated. Therapy with J-32 did not influence the course of the disease in recurrences. The survival period in the cases diagnosed and treated in our department was over 5 years in all the cases.
TREATMENT OF PROLACTIN-INDEPENDENT Nb2 RAT LYMPHOMA CELL CULTURES WITH SODIUM BUTYRATE LEADS TO A TRANSIENT INDEPENDENCE RELATIVE TO PROLACTIN FOR GROWTH. Peter W. Gout, Barry de Jong and Charles T. Beer, Cancer Control Agency of British Columbia, Vancouver, B.C., Canada.

Sodium butyrate can modify gene expression in a variety of cells (Life Sci. 27, 1351, 1980). This study describes the effects of butyrate on the growth and hormone responsiveness of two lines of cultured Nb2 rat lymphoma cells. One cell line requires prolactin (PRL) as a growth factor (Cancer Res. 40, 2433, 1980). The other line grows readily in the complete absence of PRL, and its hormone responsiveness was determined by isolating and characterizing the individual hormone producing tumor cells. These findings may indicate that the first cell line represents an immature line, not yet committed to a specific endocrine function.


ARIA method suitable for the measurement of serum hPRL concentration was elaborated. 125I-hPRL was prepared by lactoperoxidase labeling /spec.act. 150 mcCi/ml, while anti hPRL serum was produced by immunization of rabbits. Measurements were performed with TRP 75/504 (M/II) control and Lymphotech /BIO-RAD/ control sera, intrasay variation coefficient was 8.5% and intersay CV % II. Cross-react. was found with HGH in 0.3k. Normal range: 0-480 in males; 0-320 in females. The RIA was used in 26 postmenopausal disseminated breast cancer patients before and after systemic chemotherapy (CMF), antigestogenic /Tamoxifen/ and progestagen /Provera/. Treatment hPRL level was determined in 15 postmenopausal operable breast cancer patients prior to the operation. On the effect of chemotherapy and hormone treatment hPRL level decreased in 2 patients from 4-500 mU while in 2 patients clinical progression was observed notwithstanding the treatment and the prolactin level also elevated to 500-800 mU. In the non-disseminated operable breast cancer group the level of hPRL fell into the normal range. Based on preliminary results the knowledge of the PRL serum level was of prognostic value.


Sodium butyrate can modify gene expression in a variety of cells (Life Sci. 27, 1351, 1980). This study describes the effects of butyrate on the growth and hormone responsiveness of two lines of cultured Nb2 rat lymphoma cells. One cell line requires prolactin (PRL) as a growth factor (Cancer Res. 40, 2433, 1980). The other line grows readily in the complete absence of PRL, and its hormone responsiveness was determined by isolating and characterizing the individual hormone producing tumor cells. These findings may indicate that the first cell line represents an immature line, not yet committed to a specific endocrine function.
1B
ANTITUMOR THERAPY IN ADVANCED BREAST CANCER. A. Hartoni*.

RELATIONSHIP BETWEEN PROLACTIN LEVELS AND RESPONSE TO THERAPY. S. A. Soto. Endocrinology Dept., Hospital "J.H. Ramos Mejia".

The usefulness of this behaviour remains to be clarified.

 brainstorming

There is only indirect evidence at present to suggest a role for prolactin (PRL) in either the induction or progression of human breast cancer. It has been reported that breast cancer patients, as well as their daughters have a partial resistance to PRL to dopamine infusion and a hyperresponse to TRH stimulation. With the purpose of assessing this results and to know whether Gabaergic and Dopaminergic PRL regulation show the same behaviour, we studied three premenopausal groups of patients with no evident endocrine alteration during the luteal phase (day 21-23) (Control group). The correlation between PRL levels and response to sodium valproate (400mg p.o.) and to TRH (200ug i.v.) and to dopamine infusion (0.004 µg/kg/min) was assessed. No statistically significant difference was observed in PRL maxima response to TRH the following changes: (O) 765 ± 164 (n=6); (D) 5445 ± 223 (n=7); (A) 912 ± 116 (n=7). Plasma TSH response to TRH was not statistically significant in any of the groups. The percentage of inhibition by dopamine in (C) was 54% at 60', 82% at 120' and 97% at 180'. (CA) 14% < 0.05. In 4 out of 6 patients of group (C) no significant decrease was found (n=1). The other patients (n=5) showed no inhibition (n=5). (D) subjects showed no statistically significant difference either: (O) 307 ± 37 (n=7); (D) 393 ± 21 (n=7). Plasma prolactin levels were in the normal ranges for every group. No correlation between PRL levels and response to sodium valproate (400mg p.o.) and to TRH (200ug i.v.) was evidenced in 26% of the cases. Normalization in 20% and persistent increased PRL levels (> 100 ng/ml) in 54% of the cases. No significant difference was found between PRL values before treatment and 30 days after treatment did not show any significant difference. However, considering the type of response according to UICC criteria, the mean PRL level decreased (p<0.05) in 62 cases. Follow-up time: 62 cases. Follow-up time: 7.5 (0.1-12) months. Mean basal PRL levels were normalized spontaneously in 17 of 28 cases (Stage I), 9 of 21 cases (Stage II), 2 of 11 cases (Stage III) and 2 of 5 cases (Stage IV). Improvement was recovered in 20% of 24 cases (Stage I), 11% of 21 cases (Stage II), 4 of 9 cases (Stage III) and 1 of 9 cases (Stage IV). Expected pregnancies: 8 of 11 cases (Stage I) and 6 of 13 cases (Stage III) with normal deliveries. We conclude from present results that the surgical procedure should be performed in earlier stages since the recovery of the PRL axis with restoration of cyclical expectancy pregnancies is greater.


Costa Buero Institute, Department of Neuroendocrinology, Medical School, U.B.A., Buenos Aires, Argentina (1121).

Seventy-seven female patients with prolactin (PRL) producing pituitary tumours were studied: 28 cases (microadenomas, Stage I), 24 intrasellar macroadenomas, Stage II), 16 (expansive adenomas, Stage III and 9 (invasive adenomas, Stage IV). Evolution time: Stage I and II: 2-5 years; III: 5-15 years; IV: 10-20 years. Mean age: Stage I: 26 years, Stage II: 33, Stage III: 40 and IV: 42. Mean basal PRL concentrations: Stage I: 100-200 ng/ml; Stage II: 200-300 ng/ml; Stage III: 300-1000 ng/ml; and Stage IV: 500-1500 ng/ml.

Neuroradiological studies were abnormal in all cases except in 8 of 5 cases (Stage I) and 3 (Stage II) Transphenoidal surgery was performed in all the cases from Stage I and II, 9 cases from Stage III and 3 from Stage IV. Frontal surgery was performed in all others. Radiotherapy: 9 of 28 cases (Stage I), 10 of 24 (Stage III), 16 of 16 (Stage III) and 8 of 9 (Stage VI). Anatomopathological studies confirmed diagnosis in all cases. Post-surgical follow-up: 62 cases. Follow-up time: 7.5 (0.1-12) months. Mean basal PRL levels were normalized spontaneously in 17 of 28 cases (Stage I), 9 of 21 cases (Stage II), 2 of 11 cases (Stage III) and 2 of 5 cases (Stage IV). Improvement was recovered in 20% of 24 cases (Stage I), 11% of 21 cases (Stage II), 4 of 9 cases (Stage III) and 1 of 9 cases (Stage IV). Expected pregnancies: 8 of 11 cases (Stage I) and 6 of 13 cases (Stage III) with normal deliveries. We conclude from present results that the surgical procedure should be performed in earlier stages since the recovery of the PRL axis with restoration of cyclical expectancy pregnancies is greater.


Costa Buero Institute, Department of Neuroendocrinology, Medical School, U.B.A., Buenos Aires, Argentina (1121).

Fifteen men with invasive prolactin (PRL) producing pituitary tumours (Stage IV) were selected from thirty-eight cases studied between 1977-1984. Mean age: 32.6 (18-53) years old. Evolution time: 2.5 (0.5-5.5) years. Clinical symptoms: Headaches and visual disturbances in 93% of the cases; Sexual impotence, hypotension and hypogonadism in 58%; Asthenia, adynamia and arterial hypertension in 40%; Galactorrhea in 40%; Galactorrhea in 33%; Galactorrhea in 20%; Ophthalmoplegia in 20%. Neuro ophthalmological studies were abnormal in all the cases except one. Neuroradiological studies were abnormal in all the cases. Mean basal PRL concentrations: 3172 (140-18000) ng/ml. Treatment: 1) Surgical (100%), transphenoidal (20%) transfrontal (50%) transfrontal (20%) 2) Radiotherapy (100%). Before surgical procedure, three cases were treated with bromocriptine with dramatic tumoral shrinkage. Evolution: follow-up time: 2.7 (0.2-7.1) years. Sexual function was normalized in 60% of the cases. Neuro ophthalmological studies showed visual acuity and visual fields impairment in 26% of the cases. Residual hyperprolactinaemia was found in all the cases and bromocriptine administration was started. Mean dose: 7.5 (2.5-30) ng/day. We achieved basal PRL concentrations disminution in 48% of the cases, in 20% and persistent increased PRL levels (>100 ng/ml) were evidenced in 26% of the cases.

We concluded that bromocriptine administration in the treatment of male invasive prolactinomas for a limited period of time should be the first choice to improve posterior surgical results.
**3553** FIRST DESCRIPTION OF APUDOMA.

F.A. Lászlo, Endocrine Unit, First Dept. of Med., Univ. Med. Sch., Szeged, Hungary

The first description of APUDOMA was reported by an endocrine team from Szeged in 1969 (Cancer, 24, 167-173, 1969).

Rapidly progressing adrenal hypercorticism was observed in a 39-year-old man with a metastasizing medullary carcinoma of the thyroid gland containing amyloid. According to the clinical picture and laboratory data the thyroid carcinoma produced a peptide having ACTH activity, and this was responsible for the development of the hypercorticism. The medullary thyroid cancers are composed of special cells which are able to produce various biologically active substances: serotonin, bradykinin, ACTH. Pearse (1968) considers the parafollicular cells of the thyroid gland as a part of the APUD (amine and precursor uptake and decarboxylation) cell system. Therefore, we proposed the term for the ACTH-producing tumors originating in the APUD system corticotropin secreting APUDOMA.

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**3655** BREAST SELF-EXAMINATION (BSE) AND THE FREQUENCY OF BSE RELATIVE TO DEATHS DUE TO BREAST CANCER.

R.S. Foster, Jr., and M.C. Castaneda. Departments of Surgery and Mathematics & Statistics and Vermont Regional Cancer Center, University of Vermont, Burlington, Vermont, USA.

We have studied the relationship between BSE performance and breast cancer stage and survival for all (n=564) patients diagnosed in hospitals in the State of Vermont, USA, from July 1975 through December 1984. There were 124 deaths among 1,160 patients with known BSE performance data. Median follow-up time was 51 months (maximum 120), for surviving patients. BSE performers (n=382) had a relative risk of death of 0.45 compared to known BSE non-performers (n=522). The increased hazard rate of deaths due to breast cancer among BSE non-performers persisted through the 8th year following diagnosis. The 8 year survival for BSE performers was 81.7% and for non-performers was 71.7% / 34. Adjustment for age, family history, delay, method of detection and lead time did not appreciably alter the finding.

Cancers were frequently self detected during the interval between formal BSEs. Increased frequency of BSE performance (monthly versus less than monthly) was not significantly related to a further decrease in breast cancer death rates. A 1/3 reduction in 8 year breast cancer death rates at the 0.05 significance level. Lack of a significant dose response effect between frequency of BSE and decrease in breast cancer deaths suggests that BSE performers may not simply learn a physical diagnostic procedure, but develop a heightened awareness that leads to self detection of breast cancer at times other than during formal BSEs. The health promotion behavior of BSE is strongly associated with a decrease in breast cancer deaths. Supported by grant ROI CA-26363 from the National Cancer Institute.
The value and schedule of routine follow-up examinations vary widely. While early discovery of occult recurrence is considered important, the frequency of these examinations is not standardized. For instance, patients with recurrences discovered symptomatically were more likely to have recurrences in bone followed by local, regional, and pulmonary sites compared to patients with recurrences discovered asymptptomatically. The majority (interval recurrences) became apparent in bone, regional, and pulmonary sites.

The success of screening programs is highly dependent on the cooperation of primary care physicians. Effective screening for breast cancer is an important area of investigation. The cooperation of this group in screening for breast cancer is an important area of investigation. Major contributors to this cooperation include the primary care physician's sophistication regarding breast cancer, the patient's axillary node status at the time of initial treatment, and the medical staff's perception of the patient's risk status. Significant influences upon survival after recurrence included the initial site, the estrogen receptor (OR) content of the tumor, and the initial node negative status. It was concluded that the majority of recurrences became apparent in bone, regional, and pulmonary sites.

The cooperation of this group in screening for breast cancer is an important area of investigation. The majority of these physicians were screening for breast cancer in women of all ages with age considered the prime risk factor, the need to incorporate mammography into regular screening programs at an early age, and the need for professional education in breast cancer. A random sample of the entire membership of the Michigan Academy of Family Physicians was surveyed to document clinical experience with breast cancer as well as their opinion regarding the importance of breast self-examination (BSE) and mammography in screening. The majority of these physicians were screening for breast cancer in women of all ages with age considered the prime risk factor, the need to incorporate mammography into regular screening programs at an early age, and the need for professional education in breast cancer.

Mass screening for breast cancer was initiated in Hiroshima Prefecture in April 1974 under the sponsorship of the Hiroshima Prefecture Adults Disease Prevention Association and with the cooperation of the Community Health Council. During the eight years and eight months from April 1977 to February 1985, mass screening was conducted on 196,086 women. Mass screening is conducted with a city, town or village as a unit, by doctors of the area whose services are requested by one of the 19 committee members elected from the area. The screening is done on an annual or biannual basis at the place where women are screened, the Health Center of the area, and in areas designated for the purpose of screening. The cooperation of this group in screening for breast cancer is an important area of investigation.
3660  GROWTH RATES OF BREAST CANCER IN THE PRE- AND POST DETECTABLE PERIODS - IMPLICATIONS TO SCREENING AND PROGNOSIS. R.A. Spratt*, J.A. Spratt**, L.K. Holmes*** and E.A. Greenberg****. J. Graham Brown Cancer Center, School of Medicine, University of Louisville, Louisville, Ky. USA

The purpose is to report the threshold size of breast cancer discovered at screening by the Breast Cancer Detection Demonstration Project by xeromammogram, the sojourn time before discovery, the estimated actual tumor volume doubling time in days in the predeectable period, the calculated actual tumor volume doubling time in days in the post-deectable period, and the variations in the characteristics and survivability of breast cancer associated with fast and slow growth. Both sojourn time and actual tumor volume doubling time in days increase with age. The actual tumor volume doubling time in days in the predeectable period approximates the potential tumor volume doubling time in days estimated from treated thyroidine labelling index values. The entire spectrum of breast cancer growth from inception to host death approximates the prediction of the Gompertz equation being very rapid early slowing progressively with increasing breast cancer size. Significance to screening and prognosis will be stressed.

3661  IMPORTANCE OF VERSATILITY IN BREAST CANCER SCREENING. Risto Johansson, Department of Radiotherapy and Oncology, University Central Hospital, Kuopio, Finland

A general breast cancer screening for selected age groups with other age groups serving as controls has begun in the city of Kuopio. The organization is based on general information given in the newspapers and local radio, a personal invitation to every woman in the selected age groups with fixed personal screening time and a possibility to contact the screeners in advance. The time reserved for each visitor is twenty minutes, and includes general information on breast cancer and on the importance of early detection of cancer. This is given in the form of leaflets and a continuous video presentation. The personal information is given during the interview and discussion and the technique of breast self-examination is taught during the palpation made by specially trained nurses. An oblique view mammography is made to every woman and a complete mammography to those with any suspicious nodules or statistical risk that might have turned out during the interview. A specialist surgeon is consulted if anything suspicious appears during this procedure.

The age of the women at the beginning is 39, 41, 56 and 58 years and the screening is repeated every second year for five times. The participation is of course voluntary, but over 95% attended. The thoroughness of the screening procedure gives certain assurance both to the women and to the screeners about finding as many cancers as possible. It also reduces the need for extra visits and consultations to the doctors during the screening period and reduces the psychological anxiety possibly raised by the increasing information about cancer.

3662  POPULATION SCREENING FOR BREAST CANCER BY PHYSICAL EXAMINATION IN DEBRECEN. L. Lengyel, B. Kostovsky, L. Halasz, F. Fabian, K. Peter and E. G orez, Dept. Surgery I. med. Sch. Debrecen, Hungary

Debrecen is situated in the eastern part of Hungary and the population is more than two hundred thousands. Authors has been screening women age over 25 for breast cancer by physical examination. Paramedical personnel are working in the first line and if they feel anything in the breast they call back the women for medical examination. Surgeon makes fine needle biopsy or offers mammography, or straight open biopsy. During the past five years (1981-1985) the attendance rate was 90%. In this period there was nearly three hundred breast cancer patients in Debrecen. 45% of the cancer was detected by screening, the interval cancer rate was 29% and 33% of breast cancer patients was among not participated in screening. In these three groups they compared the tumor sizes, regional lymph nodes and the TNM stages.

3663  ANTHROPOLOGICAL STUDY (1880-1931) - THE LACININA OF THE BREAST IN THE REGIONAL INDICATE, REGIONAL HISTOLOGY AND TREATMENT FOR 1.325 CASES. P. Haagen, District centre for cancer care, Potsdam, G.D.R.

During the study period 1.325 carcinoma of the breast were able to statistical analysis. A database was registered in the Potsdam district. 50,6 per cent were younger than 60 years and therefore working. The mean age was at 18,3 per cent of the cases under the age of 12 and 15,3 per cent not give birth to a child. These data are significantly above those of a control group and confirm the known risk factors in the area. The beginning of the menopause was at 52 per cent above the age of 50 and 7,5 per cent of the women were older than 30 years at the first birth. We found carcinoma of the breast in 10,4 per cent and other malignant growth in 6,1 per cent of the cases in the family anamnesis. 94,9 per cent of the patient were primarily operatively, 1,8 per cent radiologically and 3,3 per cent symptomatically treated. 22,3 per cent of the primarily operated patients were treated in a highly specialized health centre, 33,5 per cent in a specialized and 44,1 per cent in institutions of the basic health care. Data on self examination and examination by a physician are evaluated.
A randomized prospective study of lung cancer detection was begun in 1976 to evaluate semianual screening by radiology and sputum cytology in comparison to screening at a 3-year interval, and to no screening. In a high-risk population of over 6000 male excessive cigarette smokers, aged 40-64 years, the initial prevalence of lung cancer was 0.28 percent (18 cases), the annual incidence 0.35 percent/year (66 cases during 3 years), the proportion of stage I cases 31 percent (26/84), and stage II 27 percent (14/84), "curative" resections 27 percent (23/84), five-year survival 23 percent (19/84). The study confirmed the ability of radiologic screening to detect lung cancer at an earlier stage when treatment by resection can be accomplished. The fate of a high-risk population submitted to screening was better than that of a population with no screening where lung cancer was discovered by symptoms, accidental X-rays, or at autopsy. A matter of lesser importance was the frequency of chest x-ray examinations and cytological examinations in symptomatic cases detected by screening were practically the same for either compared screening frequency.

Screening for lung cancer is carried out by chest x-ray examinations every 2 years of the population 40 years of age or older. By means of a retrospective study survival of 985 lung cancer patients in dependence on detection in the asymptomatic or symptomatic phase of the disease was analysed. The observed 1-5-year survival rates for the screen detected cases were 41.7 %, 19.6 %, 12.3 %, 10.1 %, 7.2 %, for cases detected by symptoms the corresponding figures were 20.4 %, 6.8 %, 4.2 %, 3.7 % and 3.1 %. The difference between the two survival curves was statistically significant. The percentage of stage I detected cases was 19.8 % in the group of screen-detected cases and 12.1 % in the second group. Screen detected cases were radically treated more often than symptomatic cases; 23.8 % vs. 9.2 %. Further research is being carried out to clarify whether the better survival rate of screen detected cases is real or caused by lead time bias.

The use of pesticides led to an increased probability of carcinogenesis. In base of that observation we start to examine the agricultural population. Up to now we called 470 persons, but respond only the 30% of them, that is 1410 persons. The protocol that we have prepared for this kind of prescreening takes under consideration: informations about past and actual pathologies; the different kinds and quantities of vegetable drugs (pesticides) that they use; even the number of these chemical treatments in a year; their way of application and the different kinds of protection that they use during these treatments. At the same time we investigate about other risk factors like tobacco-smoking, other activities etc. in base of this screening we select about 50 persons for further ascertainment like clinical examinations and x-ray examinations and cytological examination of sputum.

DOES SCREENING FOR LUNG CANCER IMPROVE SURVIVAL OF LUNG CANCER PATIENTS? P. Msohan, 0. Re*, Institute of Tuberculosis and Respiratory Diseases, Prague, Czechoslovakia.


The lung cancer is in a continuous increase at the last years. Cesena's territory in the majority is componned from cultivated fields. A big part of the population is occupated with the agriculture. The use of pesticides led to an increased probability of carcinogenesis. In base of that observation we start to examine the agricultural population. Up to now we called 4170 persons, but respond only the 30% of them, that is 1251 persons. The protocol that we have prepared for this kind of prescreening takes under consideration: informations about past and actual pathologies; the different kinds and quantities of vegetable drugs (pesticides) that they use; even the number of these chemical treatments in a year; their way of application and the different kinds of protection that they use during these treatments. At the same time we investigate about other risk factors like tobacco-smoking, other activities etc. in base of this screening we select about 50 persons for further ascertainment like clinical examinations and x-ray examinations and cytological examination of sputum.

DOES SCREENING FOR LUNG CANCER IMPROVE SURVIVAL OF LUNG CANCER PATIENTS? P. Msohan, 0. Re*, Institute of Tuberculosis and Respiratory Diseases, Prague, Czechoslovakia.


Decreased leukocyte adherence to plastic or glass surfaces in the presence of tumor antigen (cellular-LAI, tube-LAI, H-LAI tests) is used by many investigators for early detection of malignant processes. In our laboratory H-LAI method was modified by the application of indicator leukocytes labelled with 14C-amino-acid mixture. This technique proved to be a reliable one as the testing of 50 verified lung tumor cases revealed malignant disease in 89%, while sera from 20 healthy persons were "negative".

In the present study the coded sera of 116 miners were tested by H-LAI technique against various lung tumor antigens: small-cell, large-cell, squamous cell and adenocarcinoma antigens as well as normal lung tissue antigen. H-LAI index above 12 was evaluated as positive. After repeated testing, the H-LAI-positive cases were completed with an anamnestic information, and regular examinations of their new sera samples were carried out.

The possibility of this technique in pre-clinical detection of lung tumor of high-risk population will be discussed.
3668 CHANGES IN THE STAGES OF CERVICAL CARCINOMAS AND IN THE RATIO OF CERVICAL CARCINOMA TO CORPUS CANCER IN THE TOWN PECS

G. Dorsics and I. Csaba

Public Health Organization of Town Pecs, Dept. Oncology and University Medical School of Pecs, Dept. of Obstetrics and Gynecology, Pecs, Hungary

Changes in the stages of cervical carcinomas were found in the town Pecs in two subsequent five years as follows. In the first period from 1975 to 1979, 52.42% of patients were in early, operable stages. It was 75.75% in the second period from 1980 to 1984. Our better results refer to the greater numbers of cytological and screening examinations. We have also detected an increase in the number of endometrium cancers particularly in patients under 50 years of age, that causes a change in the proportion of cervical and corpus carcinomas.

3669 GASTRIC CANCER INCIDENCE CONTROLLED BY MASS EXAMINATION IN THE GEORGHENI COUNTY OF THE ROMANIA S.R.

G. Münási, G. Biró, L. Asztalos, P. György

Sanitary Directorate of the Harghita Country, Romania

Mass examination regarding all persons over 35 years of age of the community Remetea in the Gheorgheni intermontain depression resulted in 14 gastric cancer cases, 10 latent (71%) and 4 manifest ones (29%), the latter being diagnosed before the trial. If the latter group corresponds to the yearly incidence of the illness (74.6 per 100,000/year), than the former represents a 3 years contingent of the morbidity. Assuming as a computation basis the results of the mass examination among the 91,000 inhabitants of the Gheorgheni intermontane depression, there should be 212 patients of gastric cancer, corresponding, possibly, to the 3 years contingent of the morbidity. The 59 manifest cases diagnosed in the years 1976-1977 represent 28%, and correspond to the yearly incidence, as much as it had been prognosis on the basis of the mass examination.

3670 ANALYSIS OF THE EFFICACY OF THE HUNGARIAN CERVIX PROGRAMME AND THE CERVIX CANCER SCREENING

A. Decker, Dr. I. Farkas, Dr. Gy. Juhász, Natl. Inst. of Oncology, Budapest, Hungary

The authors report the trend of the nationwide cervix cancer screening on the basis of the Hungarian health statistics. The cytological screening units have been working since 1962. In the beginning several thousands (25,600) cytological screenings were done last year - in 1985 - this number has grown to 1,281,950.

The authors analyse the characteristics appeared in this period of the screening activity. They study the effect of the "cervix programme" to the cancer cervix morbidity and mortality. The authors' main concern is to find correlations between these screening and the cervix cancer morbidity, mortality in the given period. The health status of the population is studied in the period of 1960-1985.

The authors analyse the health care activity (screening, laws, orders, establishment of institutions) during the investigation time whether they meet the expectations of the population. Based on their research work they propose several alternatives for further development in cancer cervix screening in order to reduce the cervix cancer morbidity and mortality.
ASRF in providing clues to aetiologic categories. At best only suggestive, it demonstrates the utility of older Saudi women is consistent with social bias due to ple suggests an additional nutritional aetiology. The bi-
analyses suggest that the aetiological categories operating and smoking. The observed drop in breast cancer among infant in childhood and early adulthood in the Saudi sample suggests that its elevated lymphomas in the Saudi sample suggests that its elevated
liver, stomach and nasopharynx in males; breast cancer,
non-Hodgkin's lymphomas and cancer of the thyroid, esopha-
gus, cervix, and ovary in females. The most marked deviations were found in the Southern Region (Asir) for cancers of the oral cavity (2.4 times higher), bladder (1.8 times higher and lung (4.3 times lower). Some etiological factors such as local chewing of shamaa and qat, schistose-
mosis, and smoking habits will be discussed in relation to these deviations. Upward trends in cancers of the lung, breast, colon and rectum and downward trends in esophageal and other cancers were noted and were thought to reflect the rapid pace of modernisation in the country. The high CRF of other malignancies such as lymphomas, esophageal and nasopharyngeal cancers and their relation to possible environmental factors will be discussed.

The crude relative frequency (CRF) of cancer at various sites has been analyzed with reference to sex, age, geo-
graphic origin and year of diagnosis. The most common cancers were non-Hodgkin's lymphomas, esophagus, lung, liver, stomach and nasopharynx in males; breast cancer, non-Hodgkin's lymphomas and cancer of the thyroid, esopha-
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CLUES TO ASTROLOGIC CATEGORIES FROM AGE-SPECIFIC RELATIVE FREQUENCY. G. Sharat Lin, All-India Institute of Medical Science, New Delhi 110029, India.

When population incidence is not available, hospital-based cancer statistics compiled with reference to the population age distribution may provide useful clues to
malignant categories in specific cancers. Age-specific relative frequency (ARF) curves, plotted logarithmically as functions of age groups, revealed statistically signi-
ificant deviations for certain cancers among patients in India (Bombay), Denmark, and Saudi Arabia (Riyadh). Most cancers exhibited continuous increasing ARF with increas-
ing age and no significant deviations in curve shapes from one population to another. This is consistent with the cumulative impact of spontaneous and environmental oncoge-
nosis. However, the minor childhood peak in non-Hodgkin’s lymphomas in the Saudi sample suggests that its elevated frequency may be partly due to heritable factors absent in the other populations. In oesophageal cancer, the elevat-
ed ARF in childhood and early adulthood in the Saudi sample suggests an additional nutritional aetiology. The bisectioned curve for lung cancer suggests the presence of two distinct components: natural background oncogenesis and smoking. The observed drop in breast cancer among older Saudi women is consistent with social bias due to traditional reluctance to seek medical attention. These analyses suggest that the malignant categories operating in the population of Bombay are intermediate between those of the Saudi sample and Denmark. While this approach is at best only suggestive, it demonstrates the utility of ARF in providing clues to malignant categories.

CANCER PATTERNS IN KARNATAKA - INDIA


This is an ongoing retrospective and prospective study of cancer prevalence in the State of Karnataka, India. Analysis of 23,008 Cancer cases treated during 1973-
1993 at the Institute was undertaken using the parameters of Age, Sex, Site, Religion and others. It was observed that 60 percent of the total cases occurred in the age-
group of 40-64 years. Cancers were common between 45-44 years of age in males while it was 35 to 56 years in females. Cancer of Oesophagus, Larynx, Hypopharynx, Larynx and tongue were the leading sites with 13.55%, 7.19%, 6.67%, 6.65% and 5.73% respectively in males, while in the females, cancer of the cervix, Breast, Mouth, Oesophagus and Cervix prevailed in that order with frequency ratios of 13.55%, 10.03, 8.16, 5.84 and 3.49 respectively. Oesophageal cancer is unusually common in people living in the northern part of Karnataka when compared to the southern part. The probable contributory factors for this high prevalence in the former area are the use of jowar roti called "Bhakri", excessive use of raw and/or fried chillies, smoking bidies, drinking "Arrack" a local alcoholic brew and possibly other unknown factors.

CANCER IN IRAN: INCIDENCE RELATING TO SOCIO-
ECONOMIC SITUATION OF THE PATIENTS.

A. HABIBI M.D. ,Department of Pathology Tehran Medical School, Iran

This study, based on a retrospective analysis of data collected from 40,690 cancer cases, aims to compare statistical data and thus points the difference of frequency found in the dis-
tribution of some malignancies in the two groups of higher and lower standard of living patients cared for, respectively, in private clinics and State Hospitals. Among the higher standard of living patients, the most frequent type of cancer is located on the breast followed by the Skin, Bronchus and Lung Cervix and Lymph nodes (Primary). With the patients with lower standard of living, the Skin cancer is on the top followed by Cervix, Lymph nodes, Breast and Broncho-pulmonary malignancies. The Com-
parative figures and a review of the factors which seem to be related to this difference of frequency, concerning these malignancies, are discussed.
THE PATTERN OF MALIGNANT TUMOURS IN LIBYA: A RETROSPECTIVE STUDY. S.S. Al-Bakri, J. F. Abu-El-Enin, and Al-Fateh University Central Hospital, Tripoli, Libya.

Between 1961 and 1985, 1124 patients with histologically confirmed malignant disease were registered at the oncology clinic of Libya, 664 (59%) were males and 460 (41%) were females. Overall malignant lymphomas (ML) [ICD 200-202] were the most common cancers (160/1124, 16%). Hodgkin's disease (HD) was significantly more common (57, 2%) than Hodgkin's disease (HD) (42.8%). Among ML, the nodular lymphomas were rare (6%). HD had predominantly an aggressive pathology, with mixed cellularity and lymphocytic depletion types comprising 64% of all the cases. The majority of ML patients (80% of ML & 92% of HD) presented with advanced (stage III/IV) disease. When considered separately, in males lung cancer (ICD 162) was the most common tumor (22.4%), with a male to female ratio among the highest in the world (18:10). The three major histopathological types accounted for 85% of the cases. 56% epithelioid, 18% small cell carcinoma and 17% adenosquamous. 85% of our male patients were smokers and more than 50% had been smoking heavily for 20 years or more. Other respiratory tumours such as carcinomas of larynx (ICD 161) were more common in males (4.0%) than females (0.6%). Breast cancer (ICD 174) was the most frequent tumour (9.3%) of females and the majority of the patients were of a younger age group (72.3% below 50 years). Almost all our patients were multiparous and had breast fed their babies. Cancer of the cervix uteri was less frequent (4.3%) than ovarian cancer (7.6%). The incidence of colorectal cancer was higher (4.8%) than the other African countries. Contrarily the primary tumours of liver (1.4%) and bladder (0.5%) were less frequent. Among the children, aged less than 10 years, the common solid tumours of childhood occurred in the following frequency, ML 1.2%, neuroblastoma 19.2%, Wilms' tumour 10.8% and bone tumours 9.4%.

CANCER EPIDEMIOLOGY IN THE SOCIALIST PEOPLE'S LIBYAN ARAB JAMAHIRIYA.

Shafik A. Vakifoglu, The Pathology Department and the Central Cancer Registry, Health Ministry, Tripoli, The Socialistic People's Libyan Arab Jamahiriya.

There is no population-based cancer statistics in Libya, a country covering 1.676 million square kilometers with a population of about 2,217,017. The present study used pathologic material to throw some light on this problem, being a source of most important for future comparative cancer programs. During the first part of the study, i.e., 1950-1972, 737,495 biopsies were performed with 56.42% occurring in males and 43.78% in females. Cancers of the skin were the most frequent in males followed by lymphoma, skin, etc. In females, carcinomas of the cervix uteri is the most frequent, followed by lymphoma, skin, etc. The second part of the study covers the years 1973-1977 during which 208,653 biopsies were performed with 53.04% proving malignant, 47.0% in males and 27.9% in females. The most frequent type of malignancy in males followed by lymphoma, skin, etc. In females, cancers of the skin was the most frequent type followed by breast, lung, cervix uteri, secondary and unspecified malignant neoplasms of lymph nodes, lymphoepitheliales and reticulosis cell sarcoma, etc. The third part of the study covers the years 1978-1982 during which 161939 biopsies were performed, with 19.92% proving malignant, 61.2% occurring in males and 46.7% in females. The number of malignant neoplasms has been gradually throughout the period of study, while the population did not increase by the same rate. The increase in number of malignant neoplasms among females does not at present constitute a major health problem in Libya with nutritional, perinatal and infectious diseases having the priority, yet occur at a frequency rate comparable to that in the neighbouring countries, and it is expected that cancer cases will increase with problems shifting to the forefront in the near future. Comparative analysis of the three parts of the study with findings in the neighbouring countries are used in the text.

PATTERNS OF MORTALITY AMONG AN AMERICAN INDIAN TRIBE.


This paper explores the mortality experience of an American Indian Tribe, the Seneca Nation of Indians. Morbidity and mortality data from the Seneca Nation of Indians, 1952-1982, and results from similar studies can be used to design future epidemiologic studies and to formulate health education programs and services. The Senecas reside primarily in New York on two reservations with an average annual enrollment of approximately 5,500 members. Cause-specific mortality patterns will be presented for the period 1952 through 1984. Proportionate mortality ratios will be computed with reference to the general population of New York State. In addition, comparisons will be made of mortality patterns among Senecas with other American Indian tribes. Cases of deceased Indians were identified through review of annual death indexes and annuity records maintained by the Senecas. Through these means over 1200 members were identified who died during the interval under study. Death certificates are being obtained from the appropriate departments of vital statistics. Race, sex, occupation, age at death, usual place of residence, and underlying cause of death are being abstracted from each death certificate. Relative frequencies of specific causes of death will be derived and compared to the reference population. To adequately describe mortality experience, three points in time will be selected. This also will permit the identification of changes in mortality patterns among Senecas over time. The expected number of deaths from each cause (age-adjusted by the indirect method) and the significance of its deviation from the observed number will be determined by an adaptation of the Mantel-Haenszel procedure as employed in studies involving proportionate mortality ratios. In addition, mortality patterns prevalent at the two reservations will be compared. This may prove very enlightening since both groups share similar genetic and cultural attributes but differ environmentally. Residents of one reservation have certain environmental exposures that the other residents are not exposed to.
THE IMPACT OF URBANICITY ON CANCER INCIDENCE IN WESTERN NEW YORK STATE 1979-1982 Martin C. Mahoney 1,2, Arthur M. Michaels 3, K. Michael Cummings 3, and Edwin A. Minard 3

1 Department of Cancer Control and Epidemiology, Roswell Park Memorial Institute, Buffalo, New York 14263, U.S.A.

The importance of environmental influences and risk of cancer are widely recognized. The Western New York State region represents a unique study population which includes a heterogeneous collection of over 1.6 million persons residing in a variety of urban/rural settings. The Western New York Tumor Registry has collected data on incident cases of cancer since 1979. This registry is part of the New York State Tumor Registry which has been operational since the 1940's. Each year approximately 6,858 incident cancer cases are diagnosed in this area, yielding over 27,578 cancer cases between 1979-82. Presentation will be made of the relationship between urbanicity and cancer incidence in Western New York between 1979 and 1982. Moreover, methodologies employed in data collection, analysis, along with details of data on age and gender will be presented. Age-adjusted incidence rates will be presented by sex and county for the ten most common sites of both males and females. Geographic regions will be trichotomized into urban, transitional or rural areas based on the degree of urbanicity as reported by the U.S. Census Bureau. It is hypothesized that urban regions will exhibit higher cancer incidence rates, transitional areas will demonstrate intermediate cancer incidence rates and rural areas will exhibit lower cancer incidence rates. Differences in rates will be tested by an adaptation of the Mantel-Haenszel statistic for testing the association between a polychotomous variable and a single dichotomous variable. The Mantel-Haenszel statistic will be presented along with detailed descriptions of methods employed.

CANCER MORTALITY IN SPAIN

The mortality by cancer of all sites in Spain has increased (22.5 times) from 22,476 cases in 1951 to 57,084 in 1979, while the mortality by all causes was decreasing (6.69%). The mortality by cancer was 6.5% of the mortality by all causes in 1951 and 19.76% in 1979.

By sexes: The male deaths by cancer were 58% and the female deaths by cancer were 41.6%.

By age: The 93.7% of death males and the 92% of death females were over 15 years old.

By site: A. Males: 1. Lung cancer, 2748 (22%) cases. 2. Stomach cancer, 429 (3.4%) cases. 3. Colon and rectum, 2449 (19.1%) cases. B. Females: 1. Breast cancer, 338 (14.1%) cases. 2. Stomach cancer, 334 (14.04%) cases. 3. Colon and rectum, 2431 (11.1%) cases.

At present the tendency of the mortality by cancer is to increase in general. By sites are increasing the lung, breast and colon cancers, but it is decreasing the mortality by gynecologic cancer. Maps and diagrams of mortality distribution and evolution are presented.

CANCER IN OLD AGE
B. Dieberth, 1st Department for Internal Medicine, KarlFranzVienna, Austria

Test on 552 patients showed differences in the course of cancer amongst the various agegroups. Admittedly in the group of patients up to 59 years there are amazingly many without metastasis but the far advanced stages of tumor according to TNM predominate. For the test it seems evident that in the younger group the frequency of metastases statistically significant is higher than at a later age. This also finds expression in the fact that with the younger group, again statistically significant more often several organ systems are seized by metastases than at a later age. Our observations allow us to draw the conclusion that in the various periods of life within the whole illness the carcinoma and the genuine secondary diseases have different importance. This shows most distinctly the cause of death. While younger generations, statistically significant, die more often of carcinoma or its immediate consequences, older people die more often of genuine secondary diseases. Of the greatest importance, but very difficult to judge, are those cases when carcinoma as well as a genuine secondary disease may be assumed as the cause of death. These patients, likewise advanced in age, are statistically significant, more often underestimated. The facts described above are of great importance for our decisions in view of prognosis and therapy.

In a retrospective study 590 cases of cutaneous malignant melanoma of the head and neck diagnosed in Sweden 1959-74 were analysed regarding annual incidence, sex distribution, anatomical sites, histological types, level of invasion, tumor thickness and surgical treatment. Minimum follow-up time was 7 years. The annual incidence increase was significantly lower for head and neck melanomas when compared to the total population of skin melanoma patients. There were 530 female and 470 male patients. The survival at 10 years was 83% for females and 67% for males (p<0.0001). The following differences between sexes in prognostic factors were observed: face melanomas were more frequent among females (p<0.01); scalp and neck melanomas were more frequent among males (p<0.01); lentigo maligna melanomas were over-represented among females (p<0.001) as were tumors ≥5.5 mm in thickness (p<0.02) and with invasion levels I and II (p<0.01). These differences may explain the difference in survival observed between female and male patients. In some clinics an elective neck dissection was performed regularly. Thus, 88 patients were treated with an elective radical neck dissection in connection with the local excision of the primary tumor. No advantages could be demonstrated with elective neck dissection.


In the Georgheni intermountain depression with an incidence of 74.6 per 100,000/year of the gastric cancer, the background radiation doses is 3 times greater - 2.903 uGy/year - than in the Transylvanian Hilly Land - 950 uGy/year - with an incidence of 36 per 100,000/year of the illness. Many hundred springs of radioactive active carbonic mineral waters assure the requirements of drinking water for people living in the Georgheni area. The 226Ra content of many of these mineral waters surpass the dose of 3 pCi Ra/litre, considered as admissible limit for human use. During 1951 - 1961, 26 death had been registered in consequence of the gastric cancer among the residents of the Suseni community, consuming the water of the same spring, with a radioactivity of 18.2±10-12 226Ra/litre, however, the etiopathogenetic correlation remains obscure.
TRENDS IN GERM CELL TESTICULAR CANCER MORTALITY BY HISTOLOGY, ONTARIO, 1964-1982. LD Marrett, HW Watt, EA Clarke, and CA Magee, Ontario Cancer Treatment and Research Foundation and Department of Preventive Medicine and Biostatistics, University of Toronto, Toronto, Ontario, Canada.

The age-adjusted rate of mortality for cancer of the testis declined by nearly 50% in Ontario between 1975-77 and 1980-82, although it had been stable for at least 20 years prior. In addition, incidence was rising during this period. The beginning of the downward trend in mortality coincides with the addition of cis-platinum to the chemotherapeutic regimens used in the treatment of disseminated germ cell testicular cancer; this is known to have resulted in improved survival of patients with disseminated non-seminomatous tumors. The purpose of this study was to assess the impact of the improved therapy on the mortality from the two major histologic subgroups of cancer of the testis, namely seminomas and non-seminomas. For both sexes, testicular cancer deaths occurring in Ontario between 1964 and 1982 were calculated for these two histologic groups. Mortality from non-seminoma exceeded that from seminoma for the entire study period. While mortality for seminoma and non-seminoma have both declined by about 50% since 1977, the reduction in testicular cancer mortality is primarily attributable to the decrease in mortality for non-seminoma germ cell tumors. This study supports clinical findings and results of survival studies and also suggests that the new therapies which are probably responsible for the decline in testicular cancer mortality have been widely disseminated to the centres and physicians treating this disease in Ontario. In addition, it demonstrates the ability of a cancer registry to assess, on a population basis, the effectiveness of therapeutic changes and, therefore, to provide judgment as to any success we may have in treating cancer.

THYROID CANCER IN NORWAY 1970-84 GEOGRAPHICAL DISTRIBUTION OF HISTOLOGICAL TYPES. G Thoresen, G Glasser and A Johansson. The Cancer Registry of Norway, Oslo Norway. A total of 2345 histologically verified thyroid cancer in Norway 1970-84 are presented. The incidence has increased during the period studied, especially among young women. The WHO classification (1978) of thyroid cancer is used by the Cancer Registry of Norway. All histological types were more frequent among females (3:1). Papillary types constitute more than 60% of the material. The incidence of thyroid cancer increased from the southern part of the country to West-Norway, with the highest incidence rate in North-Norway. In fact, the incidence rate was twice as high in North-Norway as in South-Norway for both sexes. This increase was mainly due to the regional distribution of papillary types. The other histological types showed minimal regional variation. Dividing the municipalities in Norway into areas based on the dominating trade, the highest incidence was found in fishing municipalities, and the lowest in typical agricultural areas. In addition, the highest incidence was generally found in coastal areas, compared to the inland. There was no apparent south-north gradient within fishing or agriculture zones. The present findings stress the need for accurate histological typing in epidemiological research. We have also given support to the idea that the major aetiological factors known to be involved in the subtypes equally. In conclusion, the highest incidence of papillary thyroid cancer was found in areas were the iodine intake is probably high during increased fish-consumption.

PROGNOSTIC AND THERAPEUTIC IMPLICATIONS OF EPIDEMIOLOGICAL AND END RESULTS INFORMATION IN BREAST CANCER. B. Lissasios. Netaxas Memorial for Cancer Hospital. Piraeus, Greece.

Clinical staging of breast cancer has been proved inefficient due to the fact that each stage-particularly the initial ones-include all the subgroups with different aggressiveness. Retrospective analysis based on epidemiological, histological and therapeutic results separate subgroups of patients. This analysis has been done in 225 breast cancer patients treated between 1979-1982. Seasonal variations of frequency followed by variations of prognostic parameters (H, E.P.R. and weight)and analysis of end results in connection with them provide the basis for the choice of more specific and effective treatment.
A COMPARISON OF THE LIPID PROFILE OF SUBCUTANEOUS FAT AND TUMOUR TISSUE FROM WOMEN WITH BREAST CANCER AND NORMAL CONTROLS. M Calendar, J Ahnaf, I T Fontman, D Thomas, D V Wang. ICRF Clinical Oncology Unit, Guy's Hospital, London, SE1 9RT and Imperial Cancer Research Fund, Lincolns Inn Fields, London, WCA 3HP.

There is much epidemiological evidence to support the hypothesis that there is a strong correlation between dietary animal fat consumption and increased risk of breast cancer. Experimental studies have shown that fewer tumours are produced in animals fed saturated fat than in those given diets rich in unsaturated fat. The type of fat consumed may be important in human mammary carcinogenesis and this might be demonstrated by differences in the profile of subcutaneous fat, since depot fat is relatively stable and does reflect long-term dietary intake. The lipid profiles of subcutaneous fat obtained from 46 women undergoing biopsy for benign and malignant breast lesions have been examined. In addition, a similar study on malignant tissue from 22 women with operable breast cancer has been made. After extraction and saponification, methylation of the free fatty acids (C14-C20.4) was performed with boron trifluoride, followed by gas chromatography using a fused silica-quartz capillary column (CP Sil 88). These were a similar proportion of saturated and unsaturated fatty acids in the 3 groups. However, the polyunsaturated arachidonic acid (C20.4) was found in all malignant tumours, and surrounding fat, but rarely in subcutaneous fat from the women with benign lesions. This finding could suggest an enhancement of prostaglandin synthesis by malignant breast tissue. It is intended to pursue this work by similar examination of buccal tissue already collected from the same group of patients.

ON THE AGE-DEPENDENT ASSOCIATION BETWEEN CANCER OF THE BREAST AND ENDOMETRIUM.

Jean H-D, Bergvist L, Persson L, Pajetsson L, Departments of Surgery**, Obstetrics and Gynecology** and Oncology, Division of Gynecologic Oncology, University Hospital, S-751 85 Uppsala, Sweden.

Our aim was to analyse by means of a cohort study the hypothesis that cancer of the breast and endometrium have etiological factors in common. Material and method. The cohort comprised all first female breast cancers included in the Swedish Cancer Registry during the periods 1960-63 and 1966-71. Complete follow-up until December 1981 could be obtained in a total of 60 065 (99% of all patients). Computation of linkage to the causes of death Registry and application of national age-specific incidence rates enabled calculation of person-years at risk and of expected numbers of endometrial cancers. The observed cases of endometrial cancers subsequent to a breast cancer in the cohort were identified through a linkage to the entire National Cancer Registry. The results are expressed as relative risk (RR) with 95% confidence limits (CL). Results. A total of 260 endometrial cancers versus 151.1 expected (RR 1.72, CL 1.25-2.34) occurred during the follow-up. A regular trend emerged in relation to age at breast cancer diagnosis with a RR close to unity in patients younger than 50 to a RR of 2.4 in women 70 years or older. There was a strong temporal correlation in the occurrence of breast and endometrial cancer: the RR was 2.1 during the first five years of observation and 1.2 after this period of time. Conclusion. The regular trend showing an age-related association between breast and endometrial cancer indicate the existence of common etiological factors, which become increasingly more important at higher ages. Other observations from the same population suggest that such factors are environmental rather than genetic.
Cancers of the breast, colon, and lung account for a major portion of the world's cancer burden. We have ascertained cancer family histories in 177 colon and breast cancer patients with verified cancer (all sites). Two hundred and eighty-three were breast cancer patients, 180 were colon cancer patients, and 485 were smoking associated (SA) cancers. The association of late age at menarche with cancers of all sites combined, a slight negative trend was observed, which was not greatly influenced by secular trends. There were colon cancer (CC) and 485 smoking associated (SA) cancers (oral cavity, esophagus, pancreas, and urinary bladder), of which 256 were lung cancer (LC). A permutation test, which avoids problems in the selection of a control group, was used to randomly reorganize the data on each family. A Z score, the deviation of observed from expected cancers, was calculated for each family and compared with Z scores derived from the permutation procedure. We observed significant heterogeneity (p < 0.01) with regard to BC risk and risk in relatives of CC probands. 5.8% of the families of CC probands had significantly elevated risk, whereas only 1.5% of the non-BC groups were in the same category (p < 0.05). The variance of the Z scores of CC families, not non-CC families, was significantly increased. Of 485 SA cancer patients (controlled for smoking behavior), there was a lack of any strong evidence of increased risk of LC in relatives of LC probands. On the other hand, a significant increase of cancers of all anatomic sites was seen in relatives of BC probands. Most of these cancers were not associated with smoking and were not greatly influenced by secular trends. There was a statistically significant increased risk of LC in relatives of probands with adenocarcinoma of the lung when compared with other histologic types. Our findings, in each of the tumors investigated, strongly indicate the heterogeneity, and provide evidence for the presence in the sample, of families at a distinctly higher cancer risk. Answers to the origin of the environmental and/or genetic component of this heterogeneity may provide new clues to cancer etiology and control. Supported by the Council for Tobacco Research, U.S.A., Inc., Grant #1978.

Plasma gonadotropin levels (LH, FSH) were measured by RIA method in 77 breast cancer patients, and the relations between levels of LH, FSH with body weight or obesity were studied in pre- and post-menopausal women with body weight of 60 kg or more. The mean LH and FSH levels were shown to be 8.0±3.7 and 8.9±4.3 mIU/ml (±SD), respectively. These levels showed statistically significant difference (p < 0.002) from those (LH, 10.6±4.3, FSH, 11.0±4.5) in 315 postmenopausal women with body weight of less than 60 kg.

In obese women, a significant negative trend of LH and FSH levels was found, with relative risks of 0.54 (p<0.002) and 0.83 (p<0.05), respectively, for menarche at an age of 17 or more versus an age of 12 or less. A negative association observed with cancers of the cervix was not significant. No strong relationship could be demonstrated with any common non-genital cancer. However, both cancers of the oesophagus and of the buccal cavity and pharynx were significantly associated with late age at menarche. The associations observed with cancers of the genital organs are probably explained by varying duration of exposure to high levels of female sex hormones. For cancers of the upper gastrointestinal tract, the suggested increase in levels of female sex hormones have not been observed for BC cancers. There were colon cancer (CC), and 485 smoking associated (SA) cancers (oral cavity, esophagus, pancreas, and urinary bladder), of which 256 were lung cancer (LC). A permutation test, which avoids problems in the selection of a control group, was used to randomly reorganize the data on each family. A Z score, the deviation of observed from expected cancers, was calculated for each family and compared with Z scores derived from the permutation procedure. We observed significant heterogeneity (p < 0.01) with regard to BC risk and risk in relatives of CC probands. 5.8% of the families of CC probands had significantly elevated risk, whereas only 1.5% of the non-BC groups were in the same category (p < 0.05). The variance of the Z scores of CC families, not non-CC families, was significantly increased. Of 485 SA cancer patients (controlled for smoking behavior), there was a lack of any strong evidence of increased risk of LC in relatives of LC probands. On the other hand, a significant increase of cancers of all anatomic sites was seen in relatives of BC probands. Most of these cancers were not associated with smoking and were not greatly influenced by secular trends. There was a statistically significant increased risk of LC in relatives of probands with adenocarcinoma of the lung when compared with other histologic types. Our findings, in each of the tumors investigated, strongly indicate the heterogeneity, and provide evidence for the presence in the sample, of families at a distinctly higher cancer risk. Answers to the origin of the environmental and/or genetic component of this heterogeneity may provide new clues to cancer etiology and control. Supported by the Council for Tobacco Research, U.S.A., Inc., Grant #1978.

Parity and cancer incidence. A Prospective Study of Norwegian Women. G. Ryd, and J. Amundsen*. Inst. of Hygiene and Social Medicine, and Dept. of Mathematics*, University of Bergen, Norway.

Associations between parity and cancer of the breast and other sites were studied extensively, whereas reports on the relationship to other cancers are very scanty. Results will be presented from analyses of associations between parity and site-specific cancer incidence in a prospective study of a cohort of 61,774 Norwegian women. During a 20-year follow-up, a total of 6,490 cases were ascertained through matching against the files of the Cancer Registry of Norway. Risks were assessed by stratified logistic regression, with adjustment for age and place of residence, and at times for reproductive variables other than parity. Number of full-term deliveries was inversely associated with total cancer incidence. The negative trend was mainly explained by strong inverse associations between parity and incidence of cancer of the breast and corpus uteri. Relative risks for women with 5 or more full-term pregnancies versus nulliparous were 0.4 for ovarian cancer, and 0.5 for cancer of the breast and corpus uteri. All other associations were not statistically significant (p < 0.002). These results support previous reports of an apparent protective effect of high parity for these cancers. Although similar associations were indicated for melanoma and non-melanoma skin cancer, no suggestion of a general protective effect of parity could be observed. On the contrary, possible adverse effects were indicated for cancers of the lung and pancreas, and for breast cancer in nulliparous women. Findings not reported before, deserve further investigation.
3699 SKIN CANCER EPIDEMIOLOGY: ESTIMATES OF RISK ACCORDING TO CONSTITUTIONAL AND ENVIRONMENTAL FACTORS. Joseph Scotto and Thomas B. Fears, Natl. Cancer Inst., Bethesda, Maryland, USA.

Solar ultraviolet radiation (UVR) a carcinogen known to cause melanoma skin cancer in experimental animals, varies according to geographic location (i.e., latitude). Though the incidence in men and women is found to vary according to UVR exposure, i.e., the lower the latitude (either north or south of the equator) the higher the skin cancer risk, there are other constitutional and environmental factors which are also positively associated with this disease yet variable with respect to location demographics. We present detailed descriptive statistics derived from concurrent incidence surveys and case-control studies conducted in nine U.S. locations. General population controls also provide prevalence estimates of host characteristics, such as moles, freckles, hair color, eye color, skin complexion, and sunburn susceptibility; skin conditions, such as psoriasis, acne, eczema, HIV, and dry skin; and lifestyle habits, such as use of lotions/sunscreen/protective clothing, hours outdoors, and occupational exposures. Age-adjusted, factor-specific incidence rates are derived along with estimates of relative and attributable risk.

3699 IDENTIFICATION IN THE EPIDEMIOLOGY OF ORAL CANCER. J.R. Marshall*, and B. Graham, State Univ. of New York at Buffalo, USA.

A case-control study of oral cancer was conducted in Western New York. 312 cases and 294 controls, group matched by sex, age, and neighborhood were interviewed in person. The interview concerned smoking, alcohol use, dentition, medical history, and diet. The impact on dentition was assessed with control for smoking and alcohol use. Oral trauma was considered by mouthwash use, tooth brushing, the use of dental floss, dental checkups, and exposure to dental x-rays. The data were analyzed by use of contingency tables and by logistic regression. The results confirm that cigarette smoking and alcohol use impart significant risks of oral cancer. High smoking is an independent risk factor, while pipe smoking is not. Although risk was elevated with the use of smokeless tobacco, the number of patients using smokeless tobacco was too small to show that risk was not statistically significant. The most significant dental trauma indicator was the number of teeth lost that had not replaced. Although experience with dentures was associated with increased risk of oral cancer, the risk was not statistically significant. Tooth brushing, flossing, and dental checkups were all associated with lower risk of oral cancer. A higher degree of smoking/brushing/flossing/checkups frequency was associated with a statistically significant decrease in risk of oral cancer. The results confirm earlier studies which suggested that all have not statistically independently documented that dental trauma is a risk factor for oral cancer, and that dental hygiene practices are associated with reduced risk.

3700 FRUITS IN MORTALITY RATES BY CANCER AND ALCOHOL CONSUMPTION IN SPAIN DURING 1951-1970. M.Bívecas, A.Madrid, and V.Cárdenas, Dept. of Preventive and Social Medicine, Dept. of Medicine, Univ. of Seville, Spain.

During the last 30 years in Spain there was a noticeable increase in both consumption of alcoholic beverages and mortality rates by some neoplasms attributable to alcoholism. The authors analyze the relationship between trend in alcohol consumption and standardized mortality ratio in different Mediterranean countries during the period 1951-1970, comparing the trend's slope of those malignancies attributed to alcoholism (cancer of the mouth, cancer of the pharynx, cancer of the larynx, cancer of the esophagus, and cancer of the liver), with the trend's slope of alcohol consumption during the same period. For the comparison the authors used the method recommended by Kleinman for deriving about comparability of trends using an specific or a test for hypothesis testing.

The results pointed out a positive relationship between alcohol consumption and standardized mortality rates by cancer of the mouth and pharynx, cancer of the larynx and cancer of the esophagus but not with cancer of the liver. Although there is a remarkable association between standardized mortality rates by cirrhosis of the liver and alcohol consumption, in Spain we have opposite trends in mortality rates by cancer of the liver versus cirrhosis and alcohol consumption. Otherwise, there is a positive association between cancer of the liver and acute atrophy of the liver, suggesting that possibly in Spain the trends in prevalence of hepatitis B infection should be a leading factor in both incidence and mortality rates by cancer of the liver. These findings and others, based on ecologic analysis should need further studies to be confirmed.

3701 STOMACH CANCER AND STYLE OF LIFE. J. Pomianek, Institute of Oncology, Cracow, Poland.

Ecological analysis of associations between incidence of stomach cancer in Cracow Region/South-Eastern Poland/ and style of life/after removing bias connected with different level of registration and diagnostics/ revealed many unexpected, following findings:
1. Standardized incidence of stomach cancer in industrial areas was higher than in agricultural areas.
2. There was a lack of negative associations with urbanization and socioeconomic status.
3. The risk of stomach cancer was increasing in areas with high consumption of meat, its products and butter. 4. Especially interesting seems to be the association between the incidence of stomach cancer and the air pollution by particles.
THE RELATIONSHIP OF ADENOMATOUS POLyps TO METACHRONOUS COLON CANCER: A COMPARISON OF AMERICAN AND JAPANESE PATIENTS

West Virginia University Medical Center, Morgantown, WV, USA and Atch University Medical Medical Center, Nagoya, Japan

Patients with adenocarcinoma of the colon and synchronous adenomatous polyps may be at increased risk to develop metachronous colon cancer. This retrospective study compares the relationship of adenomatous polyps to metachronous colon cancer in patients from West Virginia University Hospital (1974-83) and the Atch Medical University Hospital in Nagoya, Japan (1974-84). At West Virginia University (W.V.U.), 470 new patients with colon cancer were identified, as compared to 136 at Nagoya. Eleven (2.3%) W.V.U. patients developed metachronous colon cancer; five (3.7%) patients were reported at Nagoya (p > 0.05). At W.V.U., seven (16%) of the 44 patients with synchronous polyps and colon cancer went on to develop metachronous colon cancer: five (21%) of the 24 patients at Nagoya developed metachronous colon cancer (p > 0.05). Thus both our American and Japanese patients showed a higher association of metachronous colon cancer with synchronous adenomatous polyps. This may imply a similar etologic factor(s) in these two populations. The ISS to 21% incidence of metachronous colon cancer may call for a subtotal colectomy as prophylaxis in patients with colon cancer and synchronous adenomatous polyps.

Supported in part by: The American Cancer Society

HEPATOCELLULAR CARCINOMA IN MONFALCONE, ITALY. ETIOLOGIC HYPOTHESES. C. Bianchi, A. Brollo, L. Bittesini, and I. Ramani, Lab. of Pathological Anatomy, Hospital of Monfalcone, Italy.

A relatively high incidence of hepatocellular carcinoma has been reported from the Monfalcone area, a small industrial territory in Northeastern Italy (age-standardized annual incidence rates 16/100,000 for males, and 2.9/100,000 for females). In order to suggest hypotheses on the etiology of such tumors, 14 cases and 22 consecutive cases seen at necropsy were analyzed (35 males, 8 females, age range 53-90 years). Liver cirrhosis existed in all the cases but two. High alcohol consumption was reported in 27 cases. Serum HBsAg was positive in 5 of 33 cases. The lifetime work histories, obtained from family members by personal interviews, revealed that 30 male patients had been employed in industry, mostly (26) in shipbuilding. Seven women had had a domestic exposure to asbestos, having cleaned the work clothes of shipyard and chemical industry workers. Hyalin plaques of the pleura were found in necropsy in 33 subjects (27 males and 6 females) and asbestosis was observed in 8 patients (all males). The present data raise the question if asbestos exposure, occupational as well domestic, may favour the development of liver cell carcinoma. Moreover it should be emphasized that in shipyards simultaneous exposure occurs to various chemicals including hepatotoxic substances. It is plausible that interactions between occupational factors and non occupational (such as alcohol abuse, hepatitis B virus infection) play a role in the genesis of liver carcinoma in Monfalcone.

OCCUPATIONAL PHYSICAL ACTIVITY AND DIET IN THE EPIDEMIOLOGY OF COLON CANCER. J. Vena, and L. Cookfair, School of Med., Buffalo, NY, USA

The relationship between occupational physical activity and colon cancer is examined in two independent data sets. Two hundred and sixty white male patients with cancer of the colon, and 276 white male patients with cancer of the rectum, aged 30-79 years, admitted to Roswell Park Memorial Institute in Buffalo, New York, 1957 to 1965, were compared to 1,431 patients with non-neoplastic, noninvasive disease, in regard to amount of lifetime occupational physical activity. Data is also presented on occupational mortality from colon cancer by job activity among 6,500 colon cancer deaths that occurred in Washington State from 1950 to 1978. In both data sets the authors found that risk of cancer of the colon increased in a dose-response fashion as physical activity of the job decreased. An odds ratio of 2.0 was found for non workers who spent all their work years in jobs with sedentary or light work. This relationship was not found for rectal cancer. In addition, data is presented on the relationship between occupational physical activity and obesity, total caloric intake and other dietary measures for a series of community controls interviewed from 1974 to 1984 in three counties of Western New York. Physical activity and energy expenditures could be an important etiologic factor for colon cancer. More inquiries need to be undertaken to study the relationships between energy expenditure, caloric intake, and specific components of the diet in the epidemiology of colon cancer.

TYPE OF ALCOHOLIC BEVERAGE INTAKE AND THE RISK OF PANCREATIC CANCER. Jean H. Wactawski*, Carlos Roberto Jaen, M.D., M. Michael*, L. Cookfair*, Edwin A. Mirabito*, Environmental and Occupational Studies Section I, Department of Cancer Control and Epidemiology, Education Department, Roswell Park Memorial Institute, Buffalo, NY 14263, U.S.A. Department of Social and Preventive Medicine, SUNY-B. Buffalo, NY 14214, U.S.A.

A case control study was conducted based on 162 patients with pancreatic cancer and 468 controls admitted to Roswell Park Memorial Institute between 1957 and 1965. Controls were frequency-matched to cases on age, race and sex. The relation between alcoholic beverage intake and pancreatic cancer was examined. Wine consumption was found to be negatively associated with the risk of pancreatic cancer. A deficit in wine use was observed in cases as compared to controls, with the greatest observed difference at the highest levels of wine intake (RR = 0.1, p < 0.07). The test for linear trend was statistically significant (p < 0.04). The observed association of pancreatic cancer with wine intake was independent of cigarette smoking history when evaluated using a logistic regression model which included monthly frequency of wine intake and packyears. Duration of beer consumption was positively associated with the risk of pancreatic cancer among ever smokers with statistically significant differences seen at the two highest levels of beer consumption (RR = 2.4 and 2.6, respectively). The increased risk follows a linear trend which was statistically significant (p = 0.02). No significantly association was observed for overall measure of alcohol intake. These results suggest that future studies of the role of alcohol in the etiology of pancreatic cancer should take into account type of alcoholic beverage used.
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TUESDAY • AUGUST 26 • AFTERNOON

K-46: TUMOUR ASSOCIATED ANTIGENS (CLINICAL STUDIES)


Aim: the aim of this study was: a. to investigate if tumor markers CEA and TPA in tissues of patients with operable breast cancer correlated with CEA and TPA plasma levels; b. to evaluate if a pattern of CEA and/or TPA staining predominated in the primary cancer tissues of those patients who exhibited a short disease-free interval.

Method: CEA and TPA levels were determined at the time of surgery by immunoradiometric method. Positive plasma CEA values (P-CEA) were considered 5 ng/ml and positive plasma TPA values (P-TPA) 90 pg/ml. Immunoperoxidase method (PAP for TPA and ABC for CEA) was used to localize CEA and TPA in breast tissue specimens (T-CEA, T-TPA). The relationship between T-CEA and T-TPA and disease free interval was analyzed by a log-rank test.

Result: A total of 256 cases were evaluated and most patients with breast cancer were classified as having stage I and II. We documented a low relationship between staining positivity and circulating marker levels but a weak staining intensity as well as the opposite finding. There was no trend in favour of a positive correlation between the presence of T-CEA or T-TPA and unfavorable prognostic factors.

This work was supported by CEA Finalized in Oncology, Contract no. 66.001/0144.

3709 CLINICAL EVALUATION OF THE ONCOFOCAL PROTEIN OVARIAN TUMOR MARKER CA 125.

J. M. P. Morton, Z. Z. Houdary and Ch. Ungleyever. K. AV Hospital, Budapest and Th. Universitätsfrauenklinik, Wien

Monoclonal antibodies (McAbs) raised tumor-associated antigen (TAA), present on tumor cells obtained from patients with gynecological malignancies, may open new possibilities both for cancer diagnosis and therapy. CA 125 is detected on the cell surface in more than 80% of non-mucinous ovarian cancers. TAA were found to be present in the serum of patients with ovarian cancer. Elevated CA 125 has been detected in sera from patients with advanced follicular tube, endometrial and endocervical adenocarcinomas and in patients with non-mucinous epithelial ovarian carcinomas. We have also found high levels in amniotic fluid between 10-20 weeks of gestation.

Preliminary clinical evaluation of serial CA 125 estimation is presented. Serum levels before and after surgery, following combined cytostatic therapy suggest some correlation of active proliferative tumor mass and CA 125. Authors discuss nonmalignant disturbances with elevated marker level.
Preoperative tumor marker values of 100 patients with breast cancer and 17 patients with gynecial tract cancer included CEA and CA15-3 levels were determined simultaneously by RIA and IRMA respectively. Evaluation of sensitivity and specificity of the tests were carried out using a control group of 124 patients with benign gynecologic diseases. ROC-curves demonstrated that CA15-3 showed highest discrimination in patients with breast cancer. However Coating patients into groups of cancer stage I-II tumors all tumor markers were unable to give diagnostic discrimination thus being not helpful for primary diagnosis. Diagnostic significance of both tests was markedly improved in stage IV. The cut-off levels for 95% specificity were established to be 4.0 ng/ml for CEA and 160 ml for CA15-3 respectively using our control group. Sensitivity for breast cancer stage IV was then 46% for CEA and 72% for CA15-3. In 53 patients with long term follow-up 5(7)/14 cases with progressive disease were indicated by increasing CEA(CA15-3) serum levels. In 35(34)/37 patients with remission CEA(CA15-3) was silent. However in 2(3) patients CEA(CA15-3) rises up to pathological serum levels indicating probably a recurrence of the disease. In 35(34)/37 patients with remission CA15-3 serum levels were 16% for CEA and 72% for CA15-3. In 53 patients our control group-Sensitivity for breast cancer stage IV be 95% specificity were established to be 4.0 ng/ml for CEA and 160 ml for CA15-3 respectively using our control group. Sensitivity for breast cancer stage IV was then 46% for CEA and 72% for CA15-3. In 53 patients with long term follow-up 5(7)/14 cases with progressive disease were indicated by increasing CEA(CA15-3) serum levels. In 35(34)/37 patients with remission CEA(CA15-3) was silent. However in 2(3) patients CEA(CA15-3) rises up to pathological serum levels indicating probably a recurrence of the disease. In 35(34)/37 patients with remission CA15-3 serum levels were 16% for CEA and 72% for CA15-3.
**EARLIER DIAGNOSIS OF RECURRENT DISEASE FOR PATIENTS WITH OVARIAN CANCER USING THE TUMOR MARKER CA-125.**

P. Sevela, H. Berger, Ch. Dittrich, G. Wagner, H. Salzer
Yat Dept. of Gynecol. and Obstet., Univ. of Vienna and Dept. of Chemomedicine, Kurume, Japan.

The ovarian cancer associated antigen CA-125, developed by Bast et al. in 1980, shows a sensitivity and specificity of about 90% in first examinations of ovarian cancer. In 89% the tumor marker correlated well with the clinical course of disease, as we could show in an earlier study. Aim of this investigation was to determine to what extent the marker could improve the early diagnosis of tumor recurrence as compared to clinical examination.

In 115 ovarian cancer patients of our postoperative care program we correlated the serological determination of CA-125 with the physical examination. The upper normal value of CA-125 was defined as 35 U/ml. 26 out of 28 patients with progressive disease (PD), according to the WHO criteria, had a positive CA-125 serum level. 27 out of 37 patients with partial remission (PR), but still palpable tumor masses had correct positive tumor markers. The other 10 patients had false negative results. Among them the patients had no evidence of disease (NED), but 6 of them had CA-125 serum levels above 65 U/ml and 10 of them had tumor markers values higher than 65 U/ml. All of these tumor marker positive patients developed tumor recurrence after an average time of 11.6 weeks with a range of 4-20 weeks.

Therefore in our opinion the positive CA-125 serum value seems to be an early proof for recurrent or progressive ovarian carcinoma and should initiate further therapeutic procedures.

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**STUDIES ON CA125 IN THE OBSTETRIC AND GYNECOLOGICAL PATIENTS — INCLUDING COMPARISON WITH CA19-9**


The clinical usefulness of CA125 and CA19-9 in Gynecological malignancies was previously evaluated and fundamental studies were made on the physical-chemical properties of CA125 and CA19-9 in amniotic fluid and ascites of a patient with ovarian carcinoma.

The positive rates of CA125 (given a cut-off value of 35 U/ml) in various patients were 89.4% (n=47) in ovarian carcinoma, 33.3% (n=12) in endometrial carcinoma, 11.1% (n=36) in cervical carcinoma, 16.2% (n=74) in myoma uteri, 55.6% (n=18) in endometriosis and 24.7% (n=73) in benign ovarian tumors. On the other hand, the positive rate of CA19-9 (given a cut-off value of 37U/ml) was only 32.6% (n=43) in ovarian carcinoma but it was useful as a monitoring marker and the monitoring levels of CA19-9 produced a pattern that was similar to CA125. Generally, the levels of CA125 and CA19-9 in ascites and cystic fluid of patients with ovarian carcinoma were higher than in serum. No correlation of serum CA125 and CA19-9 was observed as a screening marker.

CA125 was immunohistochemically localized in the tissues of endometriosis, benign ovarian tumor, normal endometrium, fallopian tube and amniotic membrane etc.

In maternal sera, mean levels of CA125 were found to be elevated in the first trimester. CA125 and CA19-9 levels were markedly elevated in amniotic fluid but low in cord serum. As the antigenic activity of CA125 and CA19-9 eluted from Sephadex G-200 and Sepharose CL-6B column associated with a void volume, they seem to have considerably higher molecular weight.

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**MONOCLONAL ANTIBODIES DETECTION & QUANTITATION OF BREAST CANCER ASSOCIATED ANTIGENS (BCAA): ROLE IN BREAST DISEASE PROGNOSIS.**

Fernando A. Salinas, Kian H. Lee & Roberto L. Cerlan.
Cancer Control Agency of British Columbia, University of British Columbia, Vancouver, British Columbia, Canada, and John Muir Cancer and Aging Research Institute, Walnut Creek, California, U.S.A.

An earlier described monoclonal antibody (Mab) prepared against BCAA (Proc. ASCO 3:49, 1984) was used to assess their role in breast disease (BD). Despite isolated BCAA by Mab-adsorbed beads technique showing apparent M=33,000 monomers, 66,000 dimers and 95,000 trimers, BCAA demonstrated single-band reactivity with an M=34,000 by use of immunoblotting with corresponding Mab. BCAA concentration was determined by an immunodensitometry-radio-ligand assay, that also demonstrated heterogeneity of expression in benign and malignant BD. BCAA levels were elevated in 11 of 20 (55%) breast carcinoma (BC) patients (pts) with no evidence of disease (M=105 ng/ml), 19 of 20 (95%) pts with minimal estimated (<5 gm) disease (M=378 ng/ml), and 10 of 20 (50%) advanced metastatic disease (M=983 ng/ml). Also, significant differences between 40 BC sera (M=191 ng/ml) with 95% specificity, and predictive value for positive results of 95%, as compared to 35 breast benign disease (M=48 ng/ml) and 10 malignant melanoma and 40 normal controls (M=250 ng/ml), were noted (p<0.01). Results from serial-sample evaluation of 36 selected BC pts showed increases in BCAA concurrent with or antedating clinical objective evidence of tumor burden increase. Conversely, significantly decreased BCAA levels correlated with tumor burden reduction. Whereas BCAA levels at diagnosis showed association of high levels (330 ng/ml) with longer (61 months) disease-free interval (DFI) and good prognosis, low (23 ng/ml) and intermediate (132 ng/ml) levels correlated with shorter DFI and poor prognosis (Supported in part by NCIC(C) and NIH-CA 39932, CA-39933 grants).
CA 15.3 is a new breast cancer marker. R. Calonge, A. Rulhal*, H. Neuwinger, G. Kocher*, L. M. Sole and L. Salvador (Medical Oncology, Radiotherapy and *Tumor Markers, Vallee de Beben General Hospital, 06003 Barcelona, Spain).

CA 15.3 is a circulating antigen expressed by human breast carcinoma (RC) cells, and determined by two murine monoclonal antibodies: DFS and 115D8. From April to September 1985, we have prospectively determined serum CA 15.3 in 1165 patients (pts) with RC, non-breast malignancies, benign diseases and controls, with a cut-off level of 40 U/ml, serum healthy subjects (n=140), 136 pts with benign diseases (n=660) and 136 pts with non-breast malignancies (n=420) had abnormal marker values. NC pts (n=21) were grouped as follows: IDED stage (I) II-III pts with no evidence of disease (NED), stage II-IV complete response (CR), partial response (PR), no change (NC) or progressive disease (PD), and Pretreatment pts (n=64) with (H) or without (H) distant metastasis.

<table>
<thead>
<tr>
<th>NED</th>
<th>CR</th>
<th>PR</th>
<th>PD</th>
<th>H</th>
</tr>
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<tbody>
<tr>
<td>5.08</td>
<td>29.36</td>
<td>60.94</td>
<td>70.02</td>
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</table>

Serum CA 15.3 levels were statistically different (p < 0.01) in NED (50.7 ± 11.4 U/ml), CR (30.5 ± 24.0), NC (50.8 ± 31.6) and PD (29 ± 27) pts. Higher values in NED pts did not differ from those of CR or PR pts or H pts. No differences were found within the NED group, but there was a trend for pts with higher ui with higher mean marker values. Our results suggest that serum CA 15.3 agrees with the stage of breast cancer and with the response to therapy. Larger patient populations must be studied in order to confirm these results.

CONCLUSION: A prospective study is going on to look after the interest of this marker in the follow-up of patients with high risk of metastasis (H) and/or in the 2-3 M 0 in breast cancer. Results will be presented.

COMPARISON WITH CEA

CA 15.3 levels in progressive metastatic breast cancers.

<table>
<thead>
<tr>
<th>CA 15.3</th>
<th>CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 U/ml</td>
<td>25 U/ml</td>
</tr>
</tbody>
</table>

CA 15.3 sensibility is better than CEA, but the two markers are complementary.

ECOTOPIC SYNTHESIS OF PREGNANCY AND PLACENTAL PROTEINS IN NONRADIOBLASTIC GYNECOLOGICAL TUMORS.


The aim of the present study is to assess the diagnostic value of pregnancy-specific beta-1 glycoprotein (PSP), pregnancy-associated zeta-glycoprotein (zeta-PAG), placental protein 10 (PP10) and placental protein 12 (PP12) in serum samples of patients with benign and malignant gynecological tumors. zeta-PAG was measured by an enzymimmunassay, zeta-PAG by electorimmunassay while for measuring PP10 and PP12 radioimmunassay was used. The 4 antigens were determined in a control group consisting of 50 healthy males and 50 healthy non-pregnant females, not taking contraceptive pills and/or blood donors/ and also in 25 patients with ovarian carcinoma, 15 patients with endometrial carcinoma, 12 patients with cervical carcinoma of the uterus, 8 patients with benign ovarian tumors and in 10 cases of their tumor cyst fluids in 4 cases, and in 20 patients with pelvic lymphomas of the uterus. In one part of the control group all the 4 antigens were detectable in the serum samples, the frequency and the levels being higher in women. The protein antigen levels were defined as pathological beyond the limit value of 4 mg/l, 40 mg/l, 4 pg/l, 40 pg/l for zeta-PAG, zeta-PAG, PP10 and PP12, respectively. Out of 50 cases of gynecological tumors 44% of zeta-PAG, 32% of zeta-PAG, 20% of PP10 and 38% of PP12 levels were found in the pathological range. In 15 of patients with ovarian tumor, 20% of zeta-PAG, 11% of zeta-PAG and 20% of PP12 fell beyond the limit value while no PP10 was detectable. In 4 cases of benign ovarian tumor cyst fluid, zeta-PAG in 2 cases, PP10 in 2 cases were higher than the serum limit value, while neither zeta-PAG nor PP12 showed such a tendency. The authors recommend the use of the above discussed proteins for clinical follow-up of patients with gynecological tumors.
In the course of 3310 abdominal ultrasound examination diagnosis was made by this method exclusively: in 63 cases solitary kidney cysts, in 9 cases polycystic kidney and in 11 cases kidney-tumors were found. In all these cases the investigation was indicated on the basis of abdominal complaints. Analyzing the clinical feature there was no manifest renal symptom of haematuria, pain, abdominal mass found. Echography was the first investigation made by reason of uncertain renal symptoms. 11 cases were analyzed in detail, i.e. patients suffering from kidney tumor, comparing the ultrasound image, the results of surgical intervention and histological method.

We emphasize the importance of the ultrasound examination for detection of kidney tumors, for follow-up the postoperative state and therapeutic effect, and in controlling of kidney cysts.

The value of high-resolution sonography in the differential diagnosis of testicular tumors

K. Nemes, K. Németh, I. Bodrogi, M. Bajori

Bajori - Zsoldoskó Hospital, Dept. of Radiology and Natl. Inst. of Oncology, Budapest, Hungary

During the past year we examined 50 scrots with the help of ATL LX 600 type sector scanner with a 7.5 Mhz focused transducer. In the course of our examinations we found a number of epididymites, orchites, hydroscabies, spermatocoles, varicoceles, torsions of the testis, retinal masses and 12 tumors. We wish to demonstrate characteristic sonographic pictures of our testicular tumors of different histological structures and to analyze some cases important from a differential diagnostic point of view.

We examined patients in whom we found extragenital tumors consisting of embryonic tissue and in some of these patients we found deviations in the structure of testes that suggested that the germative cells were affected.

Our experience is shown to those interested in poster form.
3726 ULTRASONOGRAPHIC OBSERVATION OF PATIENTS WITH OVARIAN CANCER TO FOLLOW SUCCESS OF THERAPEUTIC TREATMENTS
Juhász, Z.4th, Z. Hermádi, L. Lámpó,
Department of Obstetrics and Gynaecology, University Medical School, Debrecen, Hungary

Authors have used serial ultrasonographic examinations to follow the success of combined cytostatic treatments of patients with ovarian cancer since November 1981. After surgical removal of the uterus the detection of minimal ascites by ultrasonography may call attention to recurrence of the carcinoma, in spite of that it could not be shown by physical examinations. If tumor-residues could be observed, their diameters in three dimensions were measured, their volumes calculated in each treatment cycle, in every third or fourth week, and figured graphically. When logarithmic values of the specific growth rate were plotted against time a more precise evaluation of the effectiveness of antitumor therapy could be obtained, i.e. this procedure can help the early observation of the occurrence of a resistance to some cytostatic therapy and the introduction of another, more effective treatment.

3727 EVALUATION OF ABDOMINAL FOCAL LESIONS BY ULTRASONICALLY GUIDED PERCUTANEOUS FINE NEEDLE BIOPSY
Pataki, I. Gierbutski, W. Gerke, A. Habior, T. Kubicki, A. Habala
Department of Gastroenterology, Medical Center of Postgraduate Education, Warsaw, Poland

Percutaneous Fine Needle Biopsy (PNB) guided ultrasonically enables cytological evaluation of focal lesions of the abdominal organs. Real time USG was performed with Sono Diagnostic B 7100 Phillips unit and Aloka 280 3D. Needles 100 to 250 mm long and from 18 G to 23 G diameter were used for biopsies. Till now 247 PNB of the abdominal organs were performed, the main diagnostic problems being differentiation of pancreatic tumors and cytological assessment of focal hepatic lesions. The studied group comprised of 82 biopsies verified clinically and histopathologically. 46 biopsies of pancreas, 16 of liver, 11 of kidneys and 9 of other organs were performed. In 11 cases /4 malignant and 7 benign lesions/ PNB failed to provide a diagnostic material. Benign changes were diagnosed by cytological examination in 10 cases, of which 1 B /RT/ were correct. In 6 cases PNB was false negative. All the 30 cases diagnosed cytologically as malignant were correct and there were no false positive results. In 6 cases there was cytological suggestion of malignancy, and 3 of them were later confirmed histologically as malignant. No complications were observed. The short time of the PNB procedure, its low grade of invasiveness and high clinical usefulness make this method valuable and worth of recommendation.

3728 LUMPS IN THE BREAST: CORRELATION OF ULTRASOUND AND MAMMOGRAPHY
Ahao, Prof. Witaiporn Bhothisuwan, M.D.*, Prof. Dusdee Phathasvatt, M.D.**, Assist. Prof. Kris Bhothisuwan, M.D.***
* Dept. of Radiology, ** Dept. of Surgery, Dept. of Pathology, Siriraj Hospital Medical Sch., Mahidol Univ., Bangkok 10700, Thailand.

Breast cancer is considered of low incidence in South East Asia and Japan. Surprisingly, in Thailand, the incidence of breast cancer is much higher than expected, to be the second most common cancer in females, after the carcinoma of the cervix. (According to tumor registration, Cancer Institute of Siriraj Hospital Medical School). The incidence in the year 1981 is 243 new cases, 11.68% of total occurrence of female cancer.

This statistic raised the interest of investigation of the lump in the breast in our developing country, using as little cost of investigation with better result.

The ultrasound was used with modified water bag technique, since we do not have high frequency transducer. The result is very impressive and the study is easily performed, especially when compared with the mammography, also the economic model, limited by small sized Thai breasts. We try to find out any particular ultrasound appearance in the breast cancer if any present, in our unusually high incidence of the breast cancer in this country.

The detail of the examinations, the results of the studies and the correlation of both studies and how it helps in management of the lump in the breast will be shown and discussed in the presentation.

3729 ULTRASOUND-GUIDED PERCUTANEOUS FINE NEEDLE ASPIRATION BIOPSY (FNAB) OF THE LIVER AND THE PANCREAS. A. Szadowska, J.P. Lasota, H. Woloszko, A. Juszynski, T. Perzyński. Dept. of Oncology and Dept. of Diagnostics, Medical Centre of Lodz, Poland

Ultrasonically guided FNAB were performed on 212 patients with suspected abdominal lesions in the period of 19 months. Among these there were 46 suspected tumorous lesions in the liver and 30 in the pancreas. In 5 cases 77.6% the obtained material was unsatisfactory. Among the remaining 70 cases there were 25 cases of malignant neoplasms, predominantly carcinomas (24 cases), 4 cases diagnosed as suspected cells and 30 cases of non-neoplastic lesions, predominantly cysts (29 cases) and inflammatory processes (9 cases).
The value of gray-scale real-time ultrasonography in the investigation of the cervical and facial area swellings. K. Kestis, L. Manolopoulos, G. Nikou, A. Dariotis. From the State Dept. of Internal Medicine and the Endocrinology Dept. of Hippokration Hospital, Athens, Greece.

The aim of the study was to explore the diagnostic value of ultrasound in the detection and differential diagnosis of the thyroid gland's compact nodes and to determine patient outcome. The results of ultrasound examination in 61 patients (11 men and 30 women) with compact nodes of the thyroid gland were compared to the biopsy results following surgery.

In all cases, the ultrasound examination was correct in identifying compact nodes. Of the total, 7 (17.1%) were malignant neoplasms, 18 (44.4%) were benign adenomas and 24 (58.5%) were compact nodes developed upon goiter.

It is concluded that ultrasound examination has high specificity and diagnostic accuracy in distinguishing compact nodes of the thyroid gland.
CRYO-CAUTERY OF THE PROSTATIC TUMOURS
CONTROLLED BY TRANSRECTAL ULTRASONOGRAPHY.
Dept. of Surgery, County Hospital Pécs, Hungary.

Transurethral cryo-cautery is a well usable palliative surgical method in the treatment of the prostatic tumours. This method involves freezing of the adequate tissue followed immediately by local heating thus leading to the bursting of the cells. The authors had an 81% success rate from 578 cases. All the patients in this series belonged to the so-called "high risk" group and had total retention of urine. Success in these patients meant the disappearence of residual urine.

However, the disadvantage of this procedure is difficulty to regulate the frozen areas, which can result in insufficient cryonecrosis of the prostate or the injuries of the surrounding tissues.

Since 1983 the authors adopting the transrecltal ultrasonography for the control of cryo-cautery effect during the process. By this method can also be used to observe the position of the probe during the operation. The procedure is relative simple, non invasive and accurate in determining the ice ball expansion in the tissue of the prostate, making cryo-cautery an effective and safer method.

In this video-presentation the authors are present the procedure.

USEFULNESS OF FINE NEEDLE ASPIRATION CYTOLOGY
FOR THE DIAGNOSIS OF THE PANCREAS AND BILIARY TRACK CANCERS.

Advances in diagnostic image analysis as well as in echogram, aspiration cytology under the ultrasonic guidance has been recently applied for tumors of the pancreas, gallbladder and bile duct. We report the results of fine needle aspiration cytology and PTCD cytology performed in our institute for the past 8 years. Of positive cases by aspiration cytology, biopsy specimens of the pancreas, gallbladder and bile duct were examined in 30, 9 and 2 cases, respectively. Six cases pancreatic cancer and 4 of gallbladder cancer were found to be false negative by aspiration alone. There were 2 false positive cases, which were revealed to be chronic pancreatitis by biopsy. The overall accuracy was 77%. Aspiration cytology in combination with PTCD cytology, on the other hand, revealed merely 1 false negative case (the accuracy: 98%).

Thus, aspiration cytology under ultrasonic guidance was considered to be a useful tool for the diagnosis of cancer of the pancreas and biliary tract. Additionally, this method is expected to be the diagnostic accuracy can be expected when aspiration is employed in combination with PTCD.

ON-LINE ULTRASONIC TISSUE CHARACTERIZATION OF THE THYROID.
W. Lorenz, H. Zuta, D. Lorenz, G. van Koot.
Institute for Nuclear Medicine, CRFZ, Heidelberg, BRD.

In the Institute of Nuclear Medicine a real-time ultrasound data acquisition and analysis system has been developed, employing image and spectroscopy data analysis algorithms for the mathematical and physical characterization of the ultrasound image texture. Furthermore, a diagnostic database is used in the on-line classification of images according to the tissue specific parameter signatures in the database. The data acquisition is performed on a Hewlett Packard electronic sector scanner, interfaced to a HP-1000/400 minocomputer. Radiofrequency and image data are acquired in regions of interest that are designated by the physician during a patient's examination.

After the data acquisition is completed, a set of powerful image texture parameters derived from the gray level cooccurrence matrix, from the edge-based gray level and edge cooccurrence matrices, from the two-dimensional power spectrum, from the first-order gray level statistics and from the gray level run-length matrices are calculated. Using the most discriminating parameter subset a linear discriminant classification rule is applied and the most likely diagnosis can be calculated. As the system concept features learning, the parameter information from the patient examination can be fed into the database, and, with the system becoming more experienced, the best subset of parameters needs to be reevaluated.

Because all of the image analysis, parameter selection, decision making and learning activities are supported by the software, the database system is now applicable for routine clinical use.

Applying the system, current tissue characterization study of the thyroid (130 patients) has yielded diagnostic accuracy level of about 90 percent.
3738 EVALUATION OF OCCULT TESTICULAR NEOPLASMS. W. Kopp, M. Meyer-Schwickerath, D. Krupel, H.-M. Mittendorf, W. Marius. Dept. of Urology, University of Leiden Medical School, P.O. Box.

High-frequency real-time sonography has enhanced accuracy in the diagnosis of scrotal abnormalities. Nearly all testicular tumors can be detected by common physical examination. During the last 4 years additional scrotal ultrasound using probes with 5 and 10 MHz transducers was very helpful in confirming the diagnosis of small testicular tumors. 4 Leydig cell tumors, 5 burned-out tumors and 5 epidermoid cysts of testis were diagnosed. In 5 patients with signs of feminization physical examination of testes only revealed suggestive small tumors. Ultrasonography definitely showed small foci of low level echogenicity within the testicular parenchyma. In 4 patients with large retroperitoneal metastases and clinically no testis tumor lesions smaller than 10 mm in diameter have been localized successfully. This technology provides an ultimate resolution of echo architecture owing to its high-frequency and allows manipulation directly on the exposed scrotal skin surface with excellent patient acceptance. Our experience with this method emphasizes the usefulness of ultrasound in delineating occult testicular neoplasms.

3739 THE POSSIBILITIES OF ULTRASONOGRAPHY FOR LOCALIZATION AND FUNCTIONAL DIAGNOSIS OF THE PELVIS.

A.K. GRUEVA, ONCOLOGICAL RESEARCH INST., SOFIA

More widely using the ultrasound examination like a painless method realizes the necessity to explain functional and diagnostic possibilities to sonography with a view to specify the indication for including the interventional terapeutical methods like Percutaneous Thinly Needle Aspiration Biopsy. /PTAB/

This technique and methodology is organ-preserving and with a small risk for the patient, inexpensive and effective. We are elaborating the renal cystography, pneumocystography of the breast, cystography of the mesentery, lienal and other cystic formations. We are modifying indications for PTAB like a precise diagnostic method with a ultrathin needle in the malignant tumours of the liver, kidneys, pancreas, the retroperitoneum and soft tissues indispensable for the histological verification of the oncological cases.

3740 POSSESSIONS OF ENDOSCOPES (HYSTEROSONOGRAPHY, RECTO-SONOGRAPHY, ULTRASOUND IN DETERMINATION OF THE EXTENSION OF CARCINOMA OF THE ENDOMETRIUM AND THE CERVIX UTERI.

H. Hottlinger and M. Becker, Radi. and Gyn., Dept., St. Lukke Krankenhaus Passau, 8390 Passau, West Germany

Endosonography gains more and more importance since the last years. The obvious advantage in comparison to transabdominal ultrasound is the direct contact to the organ to be visualized without disturbing overlaying structures. Hysterosonography is done with a scanner on the tip of the sheath so that it is introduced into the uterine cavity. By rotation transversal images of the uterine wall are made. The cervix appears as echogenic ring around the homogenous myometrium. The endometrium is echotrich too, surrounding the echofree uterine cavity. No information beyond the cervix is normally available. Rectosonography allows the visualization of the vagina, the cervix uteri, the corpus and the parametrial tissue without further differentiation. Vaginosonography is a suitable method for the examination of the uterine and the ovaries. Carcinomas of the endometrium respecting the border of the organ (Stage I and II) may grow as exophytic or infiltrative tumors. Hysterosonography easily shows exophytic growth as echogenic tissue within the normally echofree uterine cavity. Infiltrative growing carcinomas are less echodense than normal myometrium. The length of tumor invasion can be determined by the position of the scanner measured from the cervix. Carcinomas of the cervix uteri not involving the parametria (Stage I) do not differ in their appearance from those of infiltrative growing carcinomas of the endometrium. Further growth laterally (Stage IIb and III) can be best visualized by rectosonography which then shows a bulky mass which is relatively echoless. Carcinomas of the endometrium Stage III are better seen with vaginosonography, however, since especially in case with anteflection, the scanner can be better positioned in comparison to rectosonography. Our results have been verified by direct comparison of endosonographic findings with the operated specimen. The correlation was good. Endosonography therefore allows an exact pretherapeutical overview over tumor expansion in carcinomas of the cervix or the endometrium not available with other methods.

3741 A COMPARISON BETWEEN ULTRASONOGRAPHY AND INTRAVENOUS PYELOGRAPHY IN DETECTING URETRIC OBSTRUCTION IN PATIENTS WITH CARCINOMA OF THE UTERINE CERVIX.

E. P. Frohlich, M.D., Vrediverk, South Africa.

Screening for obstructive uropathy (OU) in patients with carcinomas of the uterine cervix (Ca.Cx.) is part of the FIGO staging work-up. The yield of intravenous pyelography (IVP) is low and the procedure is invasive and time consuming; however, when demonstrated, this carries a very bad prognostic significance. We have examined the pyelo-calyceal systems in 100 patients with Ca.Cx. with both IVP and ultrasonography (US). The US had a 97,1% specificity, a 95,1% sensitivity and a 99,27% positive predictive value in detecting OU. The negative predictive value of the US examination was only 80,92%.

We can conclude from our results that in units where US facilities are available, this examination can be used as a screening procedure for OU. In patients with Ca.Cx. negative US findings can safely be accepted as indicative of a non-obstructive pyelo-calyceal system; however, in order to exclude false positive results and to document the OU, in patients with positive US findings, an IVP should be performed. This will represent an 80% reduction in the number of IVP's performed in the process of staging of Ca.Cx.
3742 DIAGNOSTIC POSSIBILITIES OF TRANSURETHRAL ULTRASONOGRAPHY AND COMPUTED TOMOGRAPHY IN STAGING BLADDER TUMOURS

C.K.Kumanov, M.Ivatekov, I.Ormanov, D.Mladenov, I.Petkov

Medical Academy, Sofia, Bulgaria

A prognostic judgement can more confidently be made when the TNM categories of malignancy are known. 104 patients with clinically proved bladder tumours have undergone transurethral ultrasonography (US). 95 of them have been investigated by computed tomography. The results of the employed two methods have been compared with the findings at operations. The two methods seem to help each other in staging bladder tumours. US should be performed to all patients to distinguish the depth of infiltration. In all patients with stages T1 - T4 computed tomography is to be performed.

3743 STAGING AND THERAPY CONTROL OF TONGUE TUMOURS BY MEANS OF ULTRASOUND

M. Frühwald, A. Neuhold and G. Wall

2nd Medical Clinic, Dept. of Radiology, Vienna Austria

In an effort to improve preoperative staging of tumours of the floor of the mouth and tongue, sonographic staging was correlated with the clinical staging as well as the surgical outcome of 50 patients. Sonography was superior, because in 49 cases sonographic tumor staging was correct as compared to only 33 cases correctly staged by clinical examination. Since improved therapeutic results are to be expected with correct pretherapeutic tumor staging, the authors suggest that sonography be included into the minimum requirements for the staging of the tumors of the tongue and floor of the mouth. Sonography proofs to be a reasonable method for therapy control in case of radio- or chemotherapy since the tumor can be identified even during radiation. As opposed to CT, residves are clearly demonstrable as hypo-echoic masses and are well differentiated from scar tissue.


Many human tumours are characterized by the production of oncofoetal antigens which may be used for the diagnosis and follow up cancer patients. e.g. alphafoetoprotein /AFP/ and carcino embrionic antigen /CEA/.

The study has been carried out to determine wether there is any relationship between CEA and some new biomarkers: tissue polipeptide antigen /TPA/, gastrointestinal cancer antigen /GICA/ and carcbohydrate antigen /CA-50/ in cancer patients.

64 colorectal and 20 stomach cancer patients were investigated.

Tumour extension was staged according TNM classification. CEA (ORIPI-Poland), TPA (Santeg-Sweden), CA-50 (Stena-Sweden), GICA and carcbohydrate antigen /CA-50/ in cancer patients.

The patients with colorectal cancer before operation have shown elevated levels of: CEA-50%, TPA-57%, CA-50-42% and GICA-22%.

The patients with stomach cancer had an elevated levels of: CEA-81%, TPA-87%, CA-50-37% and GICA-90%. The higher concentrations of GICA were found in patients with neoplastic disease and in with bearing metastatic tumour than in those with localised tumour.

before surgical therapy the increase of plasma level was observed in at least two of four determined tumour markers.

The data in follow up period study will be presented and discussed.

3745 EXPRESSION OF CARCINOEMATOCRINE ANTIGEN /OR EVALUATION OF RISK GROUP IN GASTRIC CANCER. M.Castell1,F.M.Sena,F.Gall1, S.Gaudagnini,H.Bodafferi,M.Carboni and E.Sega**

(*) Clinica Chirurgica, Università de l'Aquila, Italy
(**) Oasi Institute for Research, Troina, Italy

CEA values in tissue extracts of stomach mucosa, in gastric juices and plasma have been evaluated in patients gastroresected for ulcer. A significant correlation between CEA levels in gastric secretion and those in tissue emerged from our data (r=0.67; p<0.01). A minor correlation was found between tissue and plasna CEA values (0.34; p<0.05). The mean levels of CEA in plasma did not show significant differences between controls and neoplastic risk subjects. The average level of CEA in gastric secretions and in tissue were significantly lower in normal controls than in neoplastic and gastroresected patients. A correlation between the presence of precancerous morphologic lesions /complete and incomplete neoplasia/ and the levels of CEA in tissue extracts from biopsy have been documented. The level of CEA in gastric juices and in biopsy material, therefore, appears to be more useful than in plasna in recognizing cancer risk subject. Blood samples, gastric juices and biopsy material were taken from 52 patients (8 normal, 10 gastric carcinoma, 24 gastroresected according to Billroth II and 10 according to Billroth I).

2nd Dept. of Int. Med., Nagasaki Univ. Sch. of Med., Nagasaki, Japan

A mouse monoclonal antibody C5LX1 recognizes sialylated LewisX in secreted urine and colon cancer. From these results, it was concluded that sialylated LewisX defined by C5LX1 was highly accumulated in the adenocarcinoma, and existed with high frequency in the sera from cancer patients. These results strongly indicate that sialylated LewisX could be a new tumor-associated, putative adenocarcinoma-associated antigen.


Patients with mid-gut carcinoid tumors and liver metastases have often elevated levels of urine 5-hydroxyindole-acetic acid (5-HIAA) which is used as a tumor marker in these patients. However, carcinoid tumors also secrete tachykinins, mainly neuropeptide K (NPK), in high concentrations. We have studied urine 5-HIAA and plasma NPK in 20 patients with carcinoid syndrome before and during treatment with human leucocyte interferon 3-6 IU every day. Results: Before treatment the median 5-HIAA value was 858 umol/24 hours (Ref.<12), and the NPK concentration was 177 pmol/l (Ref.<12). The overall change of the two tumor markers were concordant in 18 of 20 patients, and the Spearman correlation coefficient between 5-HIAA and NPK was 0.54 (p<0.001). The patients who had a decrease in the tumor markers also revealed a decrease in flushing and diarrhoea.

Conclusion: Plasma NPK is a convenient tumor marker in the diagnosis and follow-up of patients with mid-gut carcinoid tumors. The diurnal urinary excretion of 5-HIAA however remains the most important general marker. The combined use of both markers strengthens the possibilities to diagnose carcinoid tumors as well as to follow them.


The serum levels of several different tumour markers have been analyzed and compared according to sensitivity and specificity in 482 patients with gastrointestinal diseases. 265 had malignant and 217 had benign diseases. The following markers were analyzed: CEA, AFP, CA 19-9, CA 50 and CA 125. The cut off values were: 2.5 ng/ml, 25 ng/ml, 45 U/ml, 37 U/ml, 17 U/ml, 35 U/ml, respectively. The results were as follows:

<table>
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<th>Cancer type</th>
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<th>CA 19-9</th>
<th>CA 50</th>
<th>CA 125</th>
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<td>Liver cell</td>
<td>28</td>
<td>31</td>
<td>31</td>
<td>58</td>
<td>78</td>
</tr>
<tr>
<td>Colorectal</td>
<td>31</td>
<td>31</td>
<td>31</td>
<td>40</td>
<td>20</td>
</tr>
</tbody>
</table>

(Percentage of positive value; ND = not done)

In patients with relevant benign diseases the following percentages of false positive values were recorded:

<table>
<thead>
<tr>
<th>Disease type</th>
<th>CEA</th>
<th>AFP</th>
<th>CA 19-9</th>
<th>CA 50</th>
<th>CA 125</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric</td>
<td>25</td>
<td>ND</td>
<td>0</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>27</td>
<td>0</td>
<td>16</td>
<td>21</td>
<td>27</td>
</tr>
<tr>
<td>Biliary tract</td>
<td>33</td>
<td>0</td>
<td>17</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Liver (jaundice)</td>
<td>25</td>
<td>0</td>
<td>43</td>
<td>50</td>
<td>18</td>
</tr>
<tr>
<td>Colorectal</td>
<td>33</td>
<td>9</td>
<td>17</td>
<td>46</td>
<td>36</td>
</tr>
</tbody>
</table>

Conclusion: CEA is the most sensitive and specific marker for liver cell cancer, CA 19-9 and CA 50 for pancreatic and biliary tract cancer. CEA is most sensitive for colorectal cancer, but CA 19-9 is more specific nevertheless its low sensitivity. In gastric cancer markers showed both a good sensitivity and specificity. False positive results were found especially in patients with jaundice.
**K-48: TUMOUR ASSOCIATED ANTIGENS**

3750

**DETECTION OF COLONIC CANCER WITH THE USE OF CA-5, RADIOIMMUNOASSAY HIBATION TEST. NA Habib, MJ Hershman, CB Wool. Departments of Surgery, Royal Postgraduate Medical School, Ducane Road, London W12NS**

Tumours may secrete or express on their cell surface "tumour components" not normally present in adult cells, which may circulate and be detected in serum as "oncofetal antigens". We used - radiommmunoassay for the detection of the human carcino-associated antigen CA-5 in the serum of 50 normal subjects, 16 patients with inflammatory bowel diseases and benign polyps and 77 patients with primary and secondary colorectal carcinomas. Serum levels in all normal patients and those with benign disease were below 17 units/ml, while 40 of 77 (51%) patients with carcinoma had levels above 17 units/ml. The sensitivity of this test was 22% for Dukes' B, 59% for Dukes' C and 73% for metastatic disease. The CA-5 levels were elevated in 7 of 9 (78%) patients who developed tumour recurrence following curative surgery, compared to 15 of 43 (35%) patients who are alive today and tumour-free (p < 0.03). Therefore, this test may prove useful in the diagnosis and prognosis of patients with colorectal carcinomas.

3751

**SERUM LEVELS OF EPITHELIAL MEMBRANE ANTIGEN (EMA) IN CANCER PATIENTS. G.Stefanitsis*, G.Stathopoulos**, S.Panoulis*, and J.Kiburtis*, Athens General Hospital* and Hippokration General Hospital of Athens**, Athens, Greece.**

Several investigations have shown that epithelial membrane antigen's expression is increased in neoplasia and that this antigen is valuable in diagnostic histopathology of cancer.

Lack of information with regard to EMA measurements in cancer patients, prompted us to investigate the possible use of this antigen as a serum marker in tumour diagnosis and follow-up of the disease.

Serum levels of EMA were measured, by radiommmunoassay, in 40 healthy volunteers 18 women with benign breast diseases and 95 cancer patients. Elevated levels (up to 2500 ng/ml) of the antigen were found in patients bearing various tumours (including breast, lung, liver and pancreatic cancer).

Particular emphasis on breast cancer, in the first place, has shown that with an optimum cut-off limit of 140 ng/ml 14 (45%) out of 31 women examined showed elevated levels of EMA, while in cases of generalized breast cancer with liver or bone metastases the percentage goes up to 85%. None of the women with benign breast disease had values exceeding the above mentioned limit. Serial measurements of EMA in some of the above patients have shown its usefulness in the follow-up of the disease.

Our results indicate that besides its histopathological value, EMA's serum levels measurement will contribute to diagnosis and follow-up of malignancy.

3752

**CARCINOEMBRYONIC ANTIGEN (CEA) IN STOMACH CANCER PATIENTS. D.R.R. Piras, B.P. Saenz, E.A. Possik, M. Asai, D.R. Wohrath, R.S.L. Cappellano, A. Abrao. A.C.Camargo Hospital, Antonio Prudente Foundation. São Paulo - SP - Brasil.**

CEA plasmatic levels were evaluated in a series of 84 patients operated with stomach cancer (1978-1983). Sixty one of these patients were submitted to palliative surgery. The values of CEA are presented.

**CEA VALUES (NG/ML)**

<table>
<thead>
<tr>
<th></th>
<th>0 - 3</th>
<th>3.1 - 5</th>
<th>7.1 - 10</th>
<th>more than 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st. sample</td>
<td>57%</td>
<td>22%</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>Follow-up with metastasis</td>
<td>26%</td>
<td>22%</td>
<td>29%</td>
<td>11%</td>
</tr>
<tr>
<td>Follow-up without metastasis</td>
<td>43%</td>
<td>21%</td>
<td>29%</td>
<td>7%</td>
</tr>
</tbody>
</table>

3753

**A NEW TUMOUR-ASSOCIATED ANTIGEN (ANEMIA INDUCING SUBSTANCE, AIS)—ITS CLINICAL SIGNIFICANCE AS TUMOR MARKER—. O. Ishiko, T. Tatsuta, K. Naka, M. Deguchi, and T. Sugawa, Osaka City Univ. Med. Sch. Dept. of OB-GYN, Japan**

Along with the proliferation of malignant tumor, anomaly of metabolism and immunity occurs on the host side. As a result, it is known that peculiar so-called cachectic symptoms occur, such as immune deficiency, tabescence and anemia. In particular, anemia is called cancerous anemia, and much has been reported so far about its pathology and causative factors. The authors previously reported the initiating mechanism of cancerous anemia as follows: "As the cancer advances, anemia inducing substance (AIS) is formed in the blood flow of the patient, and AIS and membranes of erythrocytes are combined to give adverse effects on the energy metabolic system in the erythrocytes, which results in lowering of deformability and osmotic fragility of erythrocytes, while the disturbed erythrocytes are captured and hemolyzed in the reticuloendothelial system to cause anemia."

In this report, the authors studied the clinical significance of AIS as tumor-associated antigen. In 552 patients of malignant and benign tumors, the AIS level was measured, using the originally prepared anti-AIS antibody method and bioagglutination, and the following facts were found.

1. The AIS positive cases were noted in 144 out of 364 cases of malignant tumor (39.6%). In stage III, 19 of 51 cases (37.2%) of malignancy: tumor and advanced stage of recurrent cancer, th. positive results were found at high incidence, that is, 128 out of 192 cases (66.6%), whereas the results were all negative in 176 cases of early stage cancers.

2. AIS was negative in all 188 cases of benign tumors.

3. AIS was detected regardless of the histological type or origin of cancer. In AIS positive cases, a negative change was noted by surgical operation or radiotherapy.

4. By the immunohistological study, a specific locality of AIS was recognized in the cancer tissues, and AIS was considered to be closely related with cancer tissues.

5. A close correlation was noted between the AIS level and cellular immunity of patients. Extracting from these results, it has been found that AIS is closely related with the progress of cancer, and expresses very reliably the state of the patient (anemia, immune deficiency) as a cancer-related antigen.

The authors have dosed quarterly three tumor markers (CEA, TPA and GICA) in 103 patients affected by different types of cancer (40 breast, 34 colon-rectum, 15 gastric and 14 lung) under treatment, according to the stage of the illness.

The most interesting outcome of this study concerns the behavior of the tumor markers according to the presence or lack of metastasis. TPA has proved to be a quite interesting marker as indicator of the passage from the condition M0 to M1, in particular in breast, gastric and colon-rectum cancers; it is moreover the only one showing increasing values according to the number of the different metastatic localizations, in agreement with the fact that it is a peculiar index of proliferation of the neoplastic cells. GICA has proved to be potentially useful in breast and colon-rectum cancers; it is on the contrary of no interest in lung cancers. CEA has proved to be more and more useful, in particular in breast and colon-rectum cancers, either in connection or not with metastatic localizations.

CANCEROEMBRYONAL ANTIGEN IN PATIENTS WITH MALIGNANT TUMOURS - ENT LOCALISATION. N. Enchev, J. Stantcheva, D. Tzinilev, Z. Valcriimova, M. Melamed, Inst. of Oncology, Sofia, Bulgaria

One can find very little written about researches on the serum level of the cancer-embryonic antigen (CEA) in patients with malignant tumours - ENT localisation. In this study we give our results on researches of CEA in 73 patients treated at the ENT clinic institute of oncology in Bulgaria; of them 38 are with carcinomas of the larynx, 20 - with carcinoma of the nasopharynx, 4 - carcinoma of the nose and paranasal cavity, 5 - carcinoma of the hypopharynx and 6 - carcinoma of the tonsilis. Blood was examined before treatment (surgical or radiotherapy) and the patients were examined after about a month. CEA was examined by the radioimmunological method with kits from "Fadecbas" (Sweden). The values above 5 ng/ml are assumed to be above normal (this level for normality was assumed after examining 71 healthy persons).

Our results show that with patients having malignant tumours with ENT localisation the serum level of CEA is rarely above the normal 26 (35,6), from 73 examined patients, and quite insignificantly having maximum value of 13 ng/ml. There is no statistical correlation between age and sex of the patients, stage of the illness and the histology of the carcinoma.

In the course of treatment the level of CEA correlated to the clinical influence, but to the different patients it appeared so very individual.

CAKCEROEMBRYONIC ANTIGEN IN PATIENTS WITH COLONRECTAL CANCER. K. Ralchev, V. Dimitrov, J. Stantcheva and D. Tzinilev, Inst. of Oncology, Sofia, Bulgaria

Serum carceroembryonic antigen (Cea) assay is a valuable adjunct to clinical examination and postoperative monitoring of patients with colorectal cancer. In this study we determined the level of CEA in 115 patients treated in Surgery Clinic of our Institute of Oncology. CEA was measured in serum before treatment and in a short period after operation (7-10 days). A group of 65 patients were studied every 2 months for a period of 2 years, or until death. In 73 patients we compared the CEA level in serum and in tumor tissue. CEA measurement was performed by a radioimmunoassay method using kits from "Fadecbas". Serum level over 10 ng/ml was accepted as positive (after examination of 71 healthy controls).

From 99 patients with colon carcinoma 22 (56%) were CEA positive and 57 from 74 with carcinoma recti were positive (77%). Analyzing the results in sequential determination we found good correlation between the serum level of CEA, clinical stage of disease and the effect of operation, but this correlation is very individual. We couldn't found strictly correlation between the serum and tumor level of CEA.
**3757 TOTALLY IMPLANTED DRUG DELIVERY SYSTEM**

W. Linkesch, R. Gherardini

2nd Department of Internal Medicine and 2nd Department of Surgery, Univ. of Vienna, Austria.

A Port-A-Cath (PAC) drug delivery system was implanted in 17 patients (10 acute leukemia, 3 multiple myeloma, 2 Non-Hodgkin lymphoma, 2 breast cancer, 2 malignant melanoma, 2 colon cancer, 1 stomach cancer, 1 testicular cancer, and 1 melanoma in situ). The venous access system composed of a reservoir and silastic catheter was implanted at the superior vena cava (15 cases), V. ilica interna (1 case) or intraperitoneal (1 case). Mean age of the patients was 46 years (18-82 years). Median duration of PAC use was 20 weeks (range 3 to 58 weeks). 11 systems are still in use, 6 patients died due to progression of disease. In 3 patients bone marrow transplantation was performed (1 autologous, 2 allogenic) using hyperfractionated whole body irradiation (1200 rad) and cyclophosphamide for conditioning therapy. The use of excessive chemotherapy, blood components and total parenteral hyperalimentation as well as daily blood sampling could be done through the PAC without any problems. There were no complications, but migration of the catheter tip (2 cases), probably associated with the surgical implantation.

The implantable supplementary system is well accepted by patients and physicians. Vascular access and the delivery system becomes a standard procedure for cancer patients requiring long-term infusion chemotherapy and appears to be safe in patients undergoing bone marrow transplantation.

**3758 CONTINUOUS INTRAHEMATOUS (IV) AND INTRA-ARTERIAL (IA) CHEMOTHERAPY USING A DISPOSABLE BALLOON-PRESSED DRUG DELIVERY SYSTEM (INFUSOR),**

C.J. van Groeningen, J.B. Vermeulen, H.E. Gei, and H.M. Pandol
Department of Oncology, Free University Hospital, Amsterdam, the Netherlands.

A number of antineoplastic drugs probably have a better therapeutic index when these are administered by continuous infusion. Its application however is limited by delivery technics and inconvenience for patients. The aim of this clinical investigation was to test the feasibility, for continuous infusion chemotherapy of a recently developed disposable, low weight and disposable balloon-pressed delivery system (INFUSOR, Travencol) with an effective drug volume of 48 ml and with a predicted flow rate of 2 ml/hr at we use application. A total number of 40 Infusors have been used in this study for continuous infusion chemotherapy in 10 chemotherapy courses in 7 patients. 15 Infusors have been used for the continuous IV infusion of 5-FU, 1000 mg/m²/day during 72 hr in 4 head and neck cancer patients (last 3 days of 4-day courses of cisplatin/5-FU combination chemotherapy). The median flow rate was 98 ml/hr (range 1.67-2.00). 25 Infusors have been used for the continuous hepatic IA infusion of 5-FU, 1000 mg/m²/day during 120 hr in 3 patients with liver metastases of colorectal cancer. The median flow rate was 1.50 ml/hr (range 1.35-1.71). No technical problems, related to the Infusor have been observed. Using the Infusor for continuous infusion into peripheral veins (2 patients) was impossible due to rapid onset of phlebitis. Therefore, in the other patients with IV continuous infusion, the Infusors were connected to a fully implanted plantetion device which was also used in all patients with IA hepatic chemotherapy. Two of the patients (1 IV an 1 IA) have been treated on an outpatient basis. This method of drug delivery was judged as perfect by all patients with no or minimal restrictions in daily activities. In conclusion, 1) the Infusor is a helpful and safe adjunctive in continuous infusion chemotherapy with an acceptable variation in flow rate and 2) the observed lower flow rate with IA continuous infusion is presumably due to the higher resistance of the arterial blood pressure.

**3759 IMPLANTABLE VASCULAR ACCESS DEVICES FOR DRUG DELIVERY,**

J. Fassnacht, Cleveland Clinic Cancer Center, Cleveland, Ohio, U.S.A.

Cancer patients often have a compromised vascular system. Frequent venipunctures for laboratory procedures is one reason the oncology patient may have poor vascular access. Chemotherapy administration often requires weekly or daily intravenous access depending on the therapy the person is receiving and the duration of their treatment. The delivery of total parenteral nutrition, antibiotics, or blood products will cause additional difficulty for appropriate intravenous access in the cancer patient. Many cancer centers have adopted chronic vascular access devices such as dialysis, artheritis, peripheral vascular disease, and hypertension which will add to the complexity of the situation. With the combined effects of chronic medical problems, the cancer patient is prone to develop sclerotic peripheral vessels. To provide adequate vascular access, various central catheters have been devised. Hickman and Broviac catheters are commonly used to circumvent poor peripheral vascular access. These silicone central lines are not without complications and in-dwars. To facilitate therapy and improve the feasibility of such devices, a totally implantable system has been developed. Our years of experience with the use of implantable vascular devices in oncology patients have indicated the feasibility of such a device. Both patients and health care providers have found the implantable port to be beneficial for drug delivery. Not only has the implantable device been successful for drug delivery, but also the administration of blood and blood products, total parenteral nutrition, and blood drawing procedures.

The use of the implantable port in patients with chronic medical problems which require vascular access is a logical procedure. The indications, complications and future of PDT will be discussed.

**3760 PHOTODYNAMIC THERAPY WITH HEPATOPORPHRYN DERIVATIVE IN EARLY STAGE CANCER OF THE LUNG, ESOPHAGUS AND STOMACH,**


Since 1980 a total of 295 cases of cancer of various organs have been treated with photodynamic therapy (PDT) after administration of hematoporphyrin derivative (HPD) at Tokyo Medical College Hospital. Here we present the therapeutic results in 44 cases of lung cancer, esophageal cancer and gastric cancer. The lesions were photoradiated via a quartz fiber, inserted through the instrumentation channels of standard fiberoptic endoscopes, which transmitted a 630 nm beam of 90-600 mW from an argon dye laser for 10-30 minutes 48 hours or more after intravenous injection of 2-3.5 mg/kg HPD.

PDT was performed in 23 cases of early stage central type lung cancer, in 7 cases of superficial type esophageal cancer and in 16 cases of early stage gastric cancer. Complete tumor remission was obtained in 17 cases of lung cancer, 5 of esophageal cancer and in 9 of gastric cancer. There were 14 cases of lung cancer, 5 cases of esophageal cancer and 4 cases of gastric cancer that were inoperable because of poor pulmonary function or refusal of surgery that were treated with PDT alone. The remaining cases were eventually resected after PDT. In all of the PDT only cases complete tumor remission was obtained, as shown by the endoscopic and biopsy findings. Recurrence, however, developed in 2 lung cancer, 0 esophageal cancer and 3 gastric cancer cases. After 6 months the only complete tumor remission was not obtained in all early stage cases or recurrences developed after PDT including insufficient penetration of the laser beam due to the presence of the lesion and technical difficulties. The indications, complications and future of PDT will be discussed.
3761 COMPARISON OF 3 METHODS FOR PAIN RELIEF AFTER THORACIC SURGERY ON ONCOLOGICAL PATIENTS. A RANDOMIZED PROSPECTIVE STUDY. L. Meszaros, I. Kremer and A. Danczis. National Institute of Oncology, Budapest, Hungary

We report on the results of a comparative prospective study of 3 methods to relieve postoperative pain after thoracic surgery on 30 oncolgical patients, randomly selected into 3 groups: 1/ intramuscular administration of Buprenorphine 2/ intercostal paravertebral blockade with Bupivacaine and 3/ low dose Morphine via thoracic peridural catheter. All the 3 methods proved to be effective, producing a long-term postoperative analgesia. The best results /the lowest values/ in the Buprenorphine group were obtained at 6 and 12 hours after the onset of postoperative pain with visual analogue scale, while blood gas analysis showed thoracic peridural Morphine to be slightly more effective than the other two agents examined. The latter method - with its simplicity and repetitiveness - seems to be the most advantageous in pain relief after thoracic surgery in intensive care units.

3763 POSTOPERATIVE PERIDURAL ANALGESIA AFTER ABDOMINAL SURGERY OF CANCER PATIENTS. T. Pataki, I. Meszaros and L. Bokor, National Institute of Oncology, Budapest, Hungary

Introduction of a catheter into the peridural space is an advantageous method for intraoperative anesthesia and it is also useful for long-term pain relief, improvement of ventilatory parameters and restoration of intestinal motility in the postoperative period. We report on the results of a retrospective study of 2 years /104 cases/, without control. Patients were anesthe-sized with Bupivacaine via peridural catheter during abdominal surgery. For postoperative pain relief a low dose /1-4 mg/ Morphine was given peridurally, providing excellent analgesia for 14.7 hours on the average. To restore intestinal motility Bupivacaine 0.25% or Lidocaine 1% was administered every 6 hours via peridural catheter. No further analgesics were required during this procedure. Though 48% of our patients was more than 70 years old, no serious complications with the prolonged and multipurpose catheterisation of the peridural space were seen. This kind of pain relief proved to be an excellent method for the usually high-risk, elderly cancer patients.

3764 COMBINED ANAESTHESIA ON TUMOROUS PATIENTS. A. Danczis, I. Meszaros and T. Pataki, National Institute of Oncology, Budapest, Hungary

Regional and superficial general anaesthesia were first used together by Lundy in 1926. Later, for a long time, this method was not applied. Recently it has been rediscovered in many countries, because, it has the advantages of both the regional and general anaesthesia. We have been working with this method in our institute since 1985. During this relatively short period we observed excellent results without complications on 97 patients.
Totally implantable drug delivery systems have been available since 1982. The aim of this study is to summarize our experience of 30 patients.

Port-a-cath (PAC) consists of a chamber made of surgical grade 316/316L stainless steel and a self-sealing silicon septum. Different flexible silicon catheters for venous or arterial use are available. The septum withstands at least 2,000 punctures with a 22 gauge Huber point needle. During the past 30 months 30 PAC systems have been implanted in 29 patients (14 males, 15 females, age range 29 - 85 years, median age 62 years). In 24 patients the intravenous route was used and in three the portal vein and in two the hepatic artery. The intravenous systems were used for administration of cytostatic agents, blood products, hyperalimentation and other drugs while the systems in the portal vein and the hepatic artery were exclusively used for cytostatic agents. The intravenous catheter position was checked by X-ray and the hepatic artery catheters by administration of 99Tc sulphur colloid. The diagnoses were metastatic cancer and blood malignancy in 24 cases, short bowel in two cases and other diagnosis in three cases.

Of 25 intravenous systems twelve are still functioning after median 166 days (30 - 525). Six patients have died after median 169 days (49 - 317) without any complications from their PAC. Three systems have never been used because of misunderstanding and short survival, two systems were removed because of local sepsis in one and septicemia in the other and two systems have been removed because of obstructions of the catheter after 180 and 372 days respectively. The incidence of complications was 0.8 per 1,000 days of access. Of three portal vein systems two patients have died after 66 and 180 days and one patient is still alive with a functioning system after 535 days. Of two hepatic artery systems one patient died after 130 days and one patient is alive after 40 days with a functioning system.

The usefulness of PAC is evident and the safety when cytostatic agents are administrated is improved. In relation to the benefit for the patients the complication rate is minimal.

Totally implantable central venous access system: Port-A-Cath

In cancer patients the chemotherapy usually lasting several months or sometimes years and the various blood preparations, blood samplings cause damage to the peripheral veins, which may inhibit the further therapy. The totally implantable Port-A-Cath system consists of the subcutaneously implanted portal accessible by puncture through a membrane and of the Silastic catheter introduced to the cava superior. Our first Port-A-Cath system was implanted in 1983. The patient died after 4 months but up to death the therapy could be continued through a needle without any problem. One of the earliest cannulas has been functioning for 520 days without complications. One Port-A-Cath was removed due to obturation.

Sequential complication has not been observed. In non-malignant disease it was implanted in one case for prolonged antibiotic administration and partial parenteral nutrition. The total Port-A-Cath system ensures advantageous conditions for the long-term central venous access and considerably diminishes the danger of complications.
TPN in SURGICAL MANAGEMENT OF ABDOMINAL CANCER.

Giacosa A., Sukker P.O., Percivalle P.J., Bartoglio R.S., Badel Lano P. – Nutritional Unit, Dept. of Surgery (*), Istituto Nazionale per la Ricerca sul Cancro, Viale Benedetto XV 10, 16132 Genova (Italy).

This report analyzes the effects of preoperative total parenteral nutrition (TPN) on the nutritional status of 37 consecutive patients who underwent surgery for abdominal cancer. Mean age was of 62.9 ± 11.7 years. The male/female ratio was of 1.64. In 21 cases TPN was started in the preoperative state (series A); while in 16 it started after surgery (series B).

TPN provided 44.4 ± 2.4 g/N/day with 1900 ± 50.7 Kcal/day in series A and 13.9 ± 2.2 g/N/day with 1828 ± 75.6 Kcal/day in series B.

All patients were clinically malnourished with an average weight decrease of 12.1 ± 6.6 kg (8.6 ± 1.1 kg) in series A as compared to usual weight and of 13.9 ± 2.5 kg (10.1 ± 1.6 kg) in series B. TPN was administered for 20.2 ± 4.7 days in series A (7.5 ± 0.6 preoperatively and 16.1 ± 2.5 postoperatively) and for 17.9 ± 6.9 days in series B.

At the TPN interruption the weight difference in comparison with the starting moment was at -1.1 ± 0.4 Kg (1.0 ± 2.4 Kg) in series A and of -0.07 ± 0.5 Kg in series B.

Low visceral protein levels were observed in both series (albumin: 3.5 ± 0.1 in series A vs 3.1 ± 0.1 in series B), these data did not change significantly at TPN interruption either in series A (3.8 ± 0.09 g/dl) or in series B (3.0 ± 0.14 g/dl).

Mortality was significantly higher in series B (8/16 when compared to series A (3/21) (P < 0.001) thus strictly correlated to the higher severity of the clinical stage of series B pt.

TPN plays a positive role in controlling nutritional status of cancer patients independently from their clinical stage, but TPN does not interfere with the prognosis of the disease. No significant difference of the nutritional status was observed in TPN started preoperatively if compared to TPN started after surgery.

PERITONEO-VENOUS SHUNTING AS TREATMENT OF NEOPLASTIC ASCITES.

N. Campioni; A.M. Pasqualetti; M. D'Annibale; R. Pasquali Lasagni; G. Mazzella; C. Barberini; M. Filippetti; D. Manfredi.

The surgical treatment of neoplastic ascites by placing a peritoneo-venous shunt is still considered in many Centers as a riskfully procedure. This is both for the dramatic complications met in cirrhotic patients (like G.I.C.) and for the theoretical systemic diffusion of neoplasms due to neoplastic cells present in the ascitic fluid.

From August 1978 to October 1985 we have placed 58 peritoneo-venous devices in as many pts with ascites from neoplastic disease. Monitoring was made of coagulation parameters (such as PITA, TT, Fibrinogen, FDP and AtIII) before and each day for 4 days after device placement. No patient presented severe alterations of the monitored parameters. Blood samples were taken before and one month after the device placement to search and to count the neoplastic cells present in systemic circulation. No patient with absence of neoplastic cells in blood prior the treatment presented cells one month later. Moreover, no clinical evidence of newborn metastases had met in all patients. Median survival rate of patient with ascites from gynaecological cancers (such as uterus, ovary and breast) was statistically longer than one's of patients with ascites from other tumors. The best late results in terms of functionality were obtained with the modified Denver device.

RESULTS FROM THE APPLICATION OF THE BULGARIAN ANTIMICROBIAL MESH AMPLEKON AND SUTURE POLYCON IN ONCO- SURGERY.

B. Gouzounov, M. Georgiev, V. Dimitrov, S. Ivanov.

In the past 5 years the authors have carried out studies on the application of the Bulgarian antimicrobial plastic mesh and sutures and have classified it as follows: I. Support of the front abdominal wall; II. cover of the pelvic peritoneum; III. Surgical rest for abdominal anal extirpation; IV. Correction of parietal defects; IV. Support of the end-to-end anastomosis of the urether; V. Cover of fascial defects after inguinal lymph node dissection; VI. Support of gastro-intestinal tract anastomoses.

TPN and surgical management of abdominal cancer.

Geriatric Tumor Surgery - Malignancy of the Cancer in the Elderly.

A. Holzgreve, W. Sasse, O. Kuland, C. Fiedler, J. Meyer, Surgical Clinic of the Univ. of Münster, West-Germany.

The increase of the average life span results in an ever increasing percentage of old patients. Most than 1/4 of in-patients in our Department of Surgery at the University of Münster are older than 65. Within this number of patients those with malignant diseases are predominant. For a long time it was thought that geriatric cancer is less malignant. Thus many surgeons were inclined not to operate radically on these patients with old age, postulating the patient might rather die from old age than from his cancer. It was difficult to substantiate the theory that the tumors behave differently in the different age groups. Based on a literature analysis of 300,000 cases the relationship between the age of onset and the malignancy was examined for different tumors. A special method of data analysis was developed which takes into account the different data presentations in the literature. The final result of our examination refutes the common belief that cancer in the elderly is less malignant. There is no uniform relationship between prognosis and cancer in any age group. This is true for stomach cancer, colon and rectum cancer. We were not able, however, to make a representative statement for gall bladder and biliary duct cancers. In summary there is no reason for the surgeon to perform a less radical operation in older patients.


**3773**

**Percutaneous Placement of Right Atrial Catheters for Systemic Chemotherapy: Experience with 100 Consecutive Catheterizations**

WR Thompson MD, JP Rice MD, AJ Martin MD, DW Oiler MD, BC Ghosh MD - Department of Surgery, Naval Hospital Bethesda, Uniformed Services University of the Health Sciences, Bethesda, MD, USA.

We reviewed recent experience with one hundred consecutive percutaneously placed Broviac and Hickman right atrial catheters. In each case the catheter was placed through the subclavian vein for administration of intravenous chemotherapy in an adult patient. From inpatient and outpatient records the following data was obtained: age, sex, diagnosis, chemotherapeutic regimen, operative time, duration at catheterization, reasons for removal and culture information. Follow-up ranges from 12 to 30 months and is available for all patients. Perioperative complications were unusual. There were two arterial punctures and two transient asymptomatic cardiac arrhythmias which terminated immediately on partial withdrawal of the guidewire. No pneumothorax, air embolism or significant hemorrhage developed despite the frequent occurrence of immunosuppression and thrombocytopenia in the patient population. Mean operative time was 45 ± 3 minutes. Late catheter-related complications were also uncommon. Infection, defined by local inflammation, positive semiquantitative catheter culture or defervescence within 48 hours of catheter removal occurred in nine patients. The most commonly isolated organism was Staphylococcus epidermidis. Mean catheter life was 123 ± 15 days with a range of 1 to 761 days.

We conclude that percutaneous placement of a right atrial catheter provides safe, reliable access for administration of intravenous chemotherapy. Results for this technique compare favorably with those reported for placement by cephalic or jugular vein cutdown. This procedure should be considered early in the course of patients expected to require prolonged venous access.

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**3774**

**Surgery for Pulmonary Metastases**

A. Ceceku, and F. Kulka, Postgraduate Medical School Thor. Surg. Cl.

From 1973 to Dec. 1985, 128 procedures for pulmonary metastases were performed. In 32 patients (25%), were only mediastinoscopy /4/, or lung biopsy /10/, or thoracotomy /10/. 96 patients with solitary or multiple metastases had been resected for cure /75%. 40 patients /30%/ had wedge resection /4/, 47 lobectomies /36%/ and 3 pneumonectomies /2,5%. The most frequent primary sites were sarcomas /24%, renal /22%, breast /16%, colon and rectum /14%. The late results are favorable in the cases of colon, ovarian and thyroid carcinomas. The metastasis to the chest wall is sometimes indication for surgery. In the paper we discuss the main prognostic factors.

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**3775**

**Surgical Treatment of Pulmonary Metastases**

Cancer Center Surgeons Group Study: Centere P. Papin, Bergomie, F. Baclesse, J. Perrin, G. Lembret, L. Bider, A. Voutrin, A. Lacomagne, P. Strrooms, G. Duparc, Centre G. Lembret, Lille (France)

This study includes 281 surgically treated pulmonary metastases. The necessary conditions were: care of the primary tumor, no other metastatic sites, good operative risk. In 193 cases (75%), the primary tumors were carcinomas: breast 44, head and neck 30, gynecologic tumors 26, colorectum 22, testicular cancers 22, kidney 20, miscellaneous 29. In 65 cases (25%), sarcomas: bone 46, soft tissue 19. In 23 cases the primary tumor was unknown. The lapse of time between the diagnosis of the primary and secondary tumors was under 2 years in 110 cases and over 2 years in 147. The rates of single and multiple lesions were respectively 78.5% and 21.5%. The operations consisted in: 23 exploratory thoracotomies (8%), 71 "wedge resections" (25%), 22 segmental resections (8%), 136 lobectomies (48.5%), 29 pneumonectomies (10.5%). 8 post-operative death was observed (2.8%). 159 patients (56.5%) received post-operative treatment: radiotherapy 30, chemotherapy 119, radio therapy 10. The survival rate at 1, 3 and 5 years for resected metastasis patients was 88.7%, 39.3%, 26.8%. 20 patients had a second operation. The survival prognosis seemed to be better 1) when the lapse of time is over 2 years rather than under (p<0.001), 2) in case of single metastasis (p<0.01). In contrast there is no significant difference 1) between epitheliomas and sarcomas 2) between "wedge resections" and segmentectomies, lobectomies or pneumonectomies 3) with or without the adjuvant of chemotherapy. Conclusion: 1) Surgery gives encouraging results in the treatment of pulmonary metastases. 2) The multiplicity of metastases is not an absolute contra-indication. 3) Second operations are feasible.

Surgical resection of pulmonary lesions in patients with previous cancer treatment is currently considered a routine procedure, provided that no residual tumor is left at the site of the primary or in any other extrathoracic organ. Thoracotomy is the most popular approach, but median sternotomy can be more effective in the management of overt or occult bilateral lesions. Lung sparing procedures are used to deal with multiple resections, either synchronous or metachronous, or with impaired lung function in elderly or previously resected patients. Sublobar resections appear optimal for childhood tumors (Wilms, Ewing) or bone and soft tissue sarcomas, but questionable in case of a suspected new primary or carcinomas with high chance of nodal metastases. In order to establish the role of the surgical approach and resection volume on the final effectiveness of treatment, in terms of survival and modality of recurrence, we have evaluated 200 consecutive patients who underwent pulmonary resections after previous primary cancer treatment. 146 cases (73%) had a previous diagnosis of carcinoma or melanoma, 54 (27%) of sarcoma. The overall survival for carcinoma at 5 and 8 years was 35% and 33% for 50 patients and 31% and 19% for 41. The 5 yr survival for sarcomas was 25%.

According to the extent of resection (lobar versus sublobar) no significant differences were evident in overall, relapse-free survival, and modality of relapse.

SURGERY FOR LUNG METASTASES. Jerey Jezierski. Thoracic Service, Department of Oncological Surgery, Cancer Center Maria Sklodowska-Curie Memorial Institute of Oncology, Warsaw, Poland.

Since 1961 52 pts were operated on for metastatic lung tumors. In all of them primary was under control and there was no evidence of disease in other sites. Primary tumors were bone sarcomas in 13 pts and soft tissue sarcomas in 8 pts. The remaining group of 31 pts covered a wide variety of histological types and primary sites of tumors: breast cancer-5, nonneuroectodermal testicular tumors-4, colorectal cancer-4, head and neck cancers-5, ovary uterine cancer-2, corpus uterine cancer-2, oblation carcinoma-2 and ovarian malignant teratoma, sarcoma of the uterine, neuroblastoma, nephroblastoma, malignant melanoma of the skin, Merkel cell carcinoma of the skin - one of each. Disease-Free Survival Interval from primary treatment to lung metastases diagnosis varied from 0/12 months. In 36 pts there were single tumors and in 16 pts multiple, among them in 6 cases bilateral. Median sternotomy was an useful approach for simultaneous bilateral lung metastasectomies in 4 pts, in others two-stage bilateral thoracotomies were done. Some pts had chemotherapy for lung secondary prior to surgery, postoperative chemotherapy was given in majority of pts. Two pts were re-operated after 23 and 33 months, respectively, for another lung. Out of 21 pts followed over 5 yrs 6 were well (NEC.).

The surgical treatment of the residual drug resitant metastases even in such chemosensitive tumors as choriocarcinoma, neuroblastoma, neuroblastoma and Ewing's sarcoma, when no evidence of disease in other than lung locations exist, can be a benefit for pts.

SURGICAL TREATMENT FOR PULMONARY METASTASES. L. Deviri, E. Levy, H. Luri . M.J. Levy Department of Cardiothoracic Surgery and Department of Oncology, Bellinson Medical Center, Sackler School of Medicine, Tel Aviv University, Israel.

Between August 1967 and June 1985, twenty three patients underwent resection of pulmonary metastases. There were 13 males and 10 females. Age of patients varied between 5-72 years (average 50). Patients were divided into 3 groups according to the histologic type of the primary tumor.

Group I - 10 patients - Carcinomas (breast, kidney, head and neck, rectum).

Group II - 8 patients - Bone and soft tissue sarcomas.

Group III-5 patients - Miscellaneous (melanoma, hydatid mole, adrenal carcinoma).

Time interval between diagnosis of primary tumor and appearance of lung metastasis was between 1-14 years in 14 cases and less than 12 months in nine. There was no hospital death following operation. Three and 5 years survival rate following resection of pulmonary metastases was 35% and 25.5% respectively. Survival rate was significantly higher in group I compared to group II. Three and five year survival - 45% and 22.5% in group I vs 0% in group II (p<0.02). Number of metastases and disease free interval between diagnosis of primary tumor and lung metastases did not affect survival significantly (p>0.05).

These data suggest that surgery may be an effective treatment for pulmonary metastases, when no other alternative exists.


From 1963 to 1985 63 patients with pulmonary metastases from extrapulmonary malignancies have been operated. 57 patients were observed from 1 up to 12 years after the resection. In 2 pat. no pulmonary metastases were diagnosed simultaneously with the primary tumor and after 6 months up to 21 years after the radical treatment of primary tumor. The primary tumors were: head and neck 4, relapsing 5, osteosarcoma 1, soft tissue sarcomas 12, melanoma 11, breast 11, kidney 5, testis 3, bladder 1, kidney 3, thymus cancer 3. Metastases were solitary in 41, few in 9 and multiple in 7 patients. Of these 57 patients were performed 26 lung resections 42 wedge resections, 17 lobectomies, 1 pneumonectomy and 5 segmental resections. The overall 5-years survival following resection of pulmonary metastases was 25.73%.

These results are encouraging and surgical resection has a place in the treatment of properly selected patients with pulmonary metastases.

By analyses of 2943 unsellected lung cancers of the county of Østfjord we cleared up the problems with tumorlocalization. 3 defined localizations (periph., centr. and intermed.) after ALTZER and PRYZE. We found 1393 centr. tumors, 1167 periph. cancers, 92 intermed. cases and the localization could not be find out in 291 tumors. Periph. cancers showed to be more frequent that of higher ages. Centr. Tumors had been detected in 24,9 % in stage I and II, periph. cancers in 44,2 %. The patterns of histological type are significantly different between centr. and periph. cancers. 2/3 of aqueous cell- and of small cell cancers are centrally located. Adenocarcinomas are periph. located in 80 %. Large cell carcinomas are periph. tumors in 52 % and cent. located in 46 %. The percentage of radical resection in periph. tumopatients was double as high as in centr. located tumors. Pneumonectonies were necessary in 50 % in patients with centrally located tumors and in 3,4 % in cases with periph. tumors. The percentage of lobectomies was 33 % in centr. and 86,4 % in periph. cancers. Between cases and periph. tumors are significant differences in 5 year survival rate (28,0 % : 6,1 %). This difference is to be find in each histotological type. For there is a real prognostic difference between periph. and centr. localization we suggest that this aspect should be considered in future protocols.

3782 TUMORS OF THE THORACIC WALL. RECONSTRUCTIVE SURGERY AFTER RADICAL RESSECTION. J. Kayvoukas and G. Antypas.

Thoracic Surgery Department. Metaxa's Memorial Hospital. Piraeus - Greece.

A total number of twenty patients with tumors of the thoracic wall was operated during the last three years. Most of them had primary sarcoma (12), six metastases from lung cancer treated in the same surgical period with the lung diseases and two unidentified tumors. We performed a radical extended resection in block by using meshes and myoplasty. All patients had an intensive care programme for post-surgery period and the results were satisfactory. Three patients were died in the first post-operative days from unexpected complications. Mortality rate for the 1st year was 25% and 45% for the 2nd year. In ten of them a second treatment with chemotherapy alone or in combination with radiotherapy was performed.


Combined cytostatic treatment of testicular cancer patients may result in as high as 70% of remission rate. In another 10-15% considerable cell reduction takes place which may serve as basis for a successful surgical intervention. At the National Institute of Oncology between January 1, 1980 and December 31, 1985 14 male patients of 20-43 years (mean age: 29,5 years) having received combined cytostatic treatment due to testicular cancer were performed thoracic surgery. The indications were as follows: 1/ suspected pulmonary or mediastinal metastasis not responding to therapy, 2/ patient is locally tumour-free, 3/ no other organ manifestation is present. In 9 cases the histology of pulmonary or mediastinal samples verified the thoracic progression while in 5 cases the lesion was not tumorous. In early postoperative stage I patient was lost. During the follow-up period of 6-68 months 1 patient died due to disseminated metastasis in the 12th month after surgery. 12 patients are alive free of symptoms and complaints.

783 REGIONAL PULMONARY VENTILATION AND PERFUSION USING XENON-133 IN PATIENTS WITH LUNG TUMORS. MK Ali, RC Morice, MS Ewer, MS Atta, RL Barroll.

Regional pulmonal perfusion was analyzed retrospectively. Spirometry, Xenon-133 regional pulmonary function studies and a segmental formula for predicting the extent of safe pulmonary resection (previously reported by our group), demonstrated that pneumonectomy could be carried out in 38 patients, lobectomy in 6 and segmental resection in 3 without excessive functional risk. Subsequently, 15 patients were denied surgery because of inadequate pulmonary functional reserve in 3, tumor cell type in 6 and advanced tumor stage in 8. Of the 35 patients who underwent surgery, 7 had pneumonectomy, 15 lobectomy, 10 segmental resection and 3 thoracotomy without resection. Two patients from the pneumonectomy group experienced reversible post-operative complications: one had pulmonary edema secondary to fluid overload and the other developed cardiac arrhythmia with mild left ventricular decompensation. Analysis of the pre-operative Xenon-133 studies of the second patient revealed abnormal hyperperfusion of the apical lung zones. Such loss of gravity effect on pulmonary blood flow distribution often reflects increase in left ventricular end-diastolic pressure. There were no post-operative complications in the lobectomy, segmental resection or thoracotomy patients. No death occurred within the immediate post-operative period (30 days), and none of the patients required prolonged mechanical ventilatory support (mean 12.6 hours). Mean hospital stay was 9.6 days (range 7-16 days). Therefore, conclude that regional pulmonary function studies using Xenon-133 are useful in tailoring safe pulmonary resection and in identifying some of the patients susceptible to post-operative complications.
X - RAY DIAGNOSIS OF PAN - TUMOR

A. E. GOLYI, ONCOLOGICAL RESEARCH INST. SOPIA, BULGARIA

Basing on a analysis of clinical and X-ray findings of blastomations lesions of the thoracic apical area in 40 patients, a similarity of clinical manifestations and radiography has been established in different pathologic processes. This circumstance makes preliminary diagnosis of Pancoast's tumor competent. Further on complex diagnosis demands interpretation and morphologic confirmation, either cytologic (the sputum, lymph node or the rib punctate tests) or a histologic one. Specialized kinds of diagnostic methods are used and bronchographies. Peripheral lung carcinomas of apical localization was most often diagnosed in the examined group of patients. Such important diagnostic feature, as the ribs destruction is far from being encountered in all cases.

SURGERY OF LUNG METASTASES - RESULTS. P. GREINER, AND G. MARX, CENTRAL INST. FOR CANCER RES., AKADEMIE VON WISS., BERLIN, BUND

From 1975 to 1980 thoracic metastases in 54 patients are performed (male 19, female 35; median age 57 yrs). Postoperative mortality in 1 of 60 (cardiac failure), non lethal complications in 1 of 50 (pneumonitis). After wedge resection blood leakages and dyspnoea are relatively often observed, but without influence on duration of hospital stay and quality of life. Mode of detection of metastases: by routine postop. care, with clinical symptoms 10 and 3 by accident (X-ray examination). There were 30 wedge resections, 12 lobectomies, 13 (palliative) tumor extirpations and 4 pneumonectomies necessary. 15 patients had metastases of carcinomas (rectum 4, female breast 4, uterus 2, thyroid gland 1, testis 1, colon 1) and 39 of sarcomas (osteosarcoma 16, fibrosarcoma 4, leiomysarcoma 4, eburnating sarcoma 4, synovial sarcoma 3, chondrosarcoma 1, rare diagnoses 8). The 5-year survival rate over all 7 of 28 patients (4 of 17 in pts. with bone and soft tissue sarcomas).

Resection of single or multiple, uni- or bilateral metastases of lung is justified, if 1. primary tumor under control 2. very low mortality and complication risk is secured and 3. ontroverticase metastases are excluded preoperatively.

SURGICAL TREATMENT OF LUNG CANCER, INVADING THE CHEST WALL. P. Chervenjakov, M. Balevski, I. Nikolov, I. Dakov, I. Petrov, I. Colarov, Research Institute of Pulmonary Diseases, Medical Academy, Sofia, Bulgaria.

Between 1978-1985 20 patients have undergone combined lung and chest resection as treatment for lung cancer, invading the chest wall. All of them were male between 40 and 63. The resections most frequently applied were as follows: upper right lobectomy (9 patients), lower right lobectomy (3 patients), upper left lobectomy and lower left lobectomy (2 patients each), upper right pneumonectomy and lower right bilobectomy (1 patient each). Chest resection included 2 to 6 ribs, including the intercostal muscles. Possibilities for chest reconstructions are discussed. Most of the patients had squamous-cell cancer.

Indications for applying combined resection, long-term results and favourable prognosis are discussed. It is emphasised that lung and chest block-resection is obligatory in these cases.
THE ROLE OF SERUM LIPIDS IN PATIENTS WITH COLON CANCER. G. Nikou, G. Gyroulou, K. Kestis. From the State Dept. of Internal Medicine, Hippokration Hospital, Athens, Greece.

The relation of low levels of serum total cholesterol (TC) to large bowel cancer has been reported in many studies, but data concerning the role of high density lipoprotein cholesterol (HDL-C) are ambiguous. Serum lipids, including HDL-C, TC, triglycerides (TG) and total lipids (TL), were studied in 38 patients with histologically confirmed colon cancer and compared to that of 20 age- and sex-matched controls. TC and TG were significantly higher in cancer patients (35 vs 51 mg/dl, p<.001) and rectum (19 vs 51 mg/dl, p<.001) than in controls. Cancer patients had lower TC and TL values as well (p<.001), while TG had similar distributions in the two groups (p:NS). It is concluded that low HDL-C, TC and TL may be related to the development and evolution of colon cancer. For clinical staging, a higher percentage of items were marked "unknown" (cases with staging data: colon 87/45.9%; rectum 797/47.2%) in the questionnaires than in histopathological staging (colon 17=11.4%; rectum 321=21.4%). The clinical and histological assessment of TNM stage groups Ib, II and III frequently diverged, resulting in a close correlation of these three stages which showed no difference at a 5% level of significance. This indicates a rather low precision for clinical staging. Stages Ib and IV were different from each other and from a cluster formed by stages II and III. Fasting levels were better observed both in colon (15=1.0%) and rectum (19=1.3%) carcinoma. The authors propose to drop the differentiation between stages T3b and T3a (tumor with and without fistulas) from the TNM system.
The diagnostic and prognostic significance of CEA level changes in colorectal cancers. L. Holnér, P. Rahody, E. Bauer, P. Ronay, I. Besznyák, National Institute of Oncology, Budapest, Hungary

The authors studied the changes of CEA levels prior to and after surgery in 100 patients with colorectal cancer between 1977 and 1984. In agreement with the data of literature they state the normalization of CEA titer after radical surgery. Repeated increase in the CEA titer suggests the development of recurrence or distant metastasis. The preoperative CEA value above 30 ng/ml is regarded as an unfavourable prognostic sign in patients with III-IV stage of colorectal cancer. The CEA level determination is a suitable means for monitoring the course of the disease.


One of the most important clinical complications in the terminal cancer patient is the intestinal obstruction. Pathophysiology of this occurrence, frequently complicating neoplastic obstruction of the abdomen (ovarian and large bowel tumours) is the following: 1) extrinsic or intrinsic compression caused by tumoral bulk; 2) intestinal wall edema with accumulation of fluid within the obstructed segment; 3) bacterial overinfection, producing edema, ulcers and necrosis of the intestinal wall.

The rate tumour-inflamatory reaction surrounding neoplastic bulk is usually 1:4, 1:4.

The actual objectives of the medical treatment of fluid and electrolyte imbalance, dehydration resulted by means of a nasogastric tube are the control of the complications but don't modify the pathogenesis of this syndrome.

The surgical management of the obstruction has a high mortality rate; our treatment tries to perform a prompt operation of the acute phase and a following long-term surgical intervention.

Methods: The patients with intestinal neoplastic obstruction, besides normal medical care, have received a well-tolerated thcrapic regimen: 1 g neomycin, 1 g metronidazole, 1 g gentamicin, 1 g ampicillin daily for the purpose to reduce the inflammatory and intestinal reaction surrounding the tumor.

Schedule of administration: Every 4 or 6 h by peroral. 3-4 g metronidazole 4 g, 1 g ampicillin, 1 g gentamicin at 12 or 24 h; oral or nasogastric solution.

Patients: Ten patients, 6 with advanced large bowel carcinoma, 4 with advanced ovarian carcinoma.

Eight patients had a prompt resolution of the intestinal obstruction, the other were operated with a proctolitotomy or a tranduodenal drainage. About four patients with an intestinal obstruction, followed by the same therapeutic measures, treated the same time with neomycin, ampicillin, metronidazole.

Our experience in surgical treatment of generalized polyposis coli. Z. Doudounkov, Res.Inst. of Oncology at the Med.Academy, Sofia, Bulgaria

A new operative method for treatment of generalized polyposis coli with and without a malignant transformation of the colon is described. It has seven versions depending on the spread and localization of the cancer degeneration. The basic principle of our method is a subtotal colectomy of the most affected colorectal parts and transposition of the preserved colon portion in a neorectum. If impossible to preserve the sphincters the healthy part of the bowel forms a permanent colostomy. Polyps in the preserved portion are removed by means of a proctosigmoidoscope. Twenty-four patients treated by the method survived the operation and the results are discussed.

The surgical treatment of transverse colon carcinoma. O. Ruland, W. Sasse, A. Holzerové, M. Blum. Surgical clinic of the Univ. of Münster West-Germany

The carcinoma of the transverse colon has a special position within the group of colon carcinoma. Different authors use different definitions with regard to the middle limitation of the part of the colon. Previously colectomies were performed because of the suspected high rate of undetected further colon carcinomas. It was assumed that this kind of radical surgery would have the highest long-term cure rate. Colectomy, however, is associated with a high primary lethality. During the last years the routes of metastatic spread, of the blood supply and of the lymphatic drainage were discussed with regard to an optimal therapy. The primary aim is to achieve adequate radicality without endangering the patient too much. The argument about this problem is still unresolved. Whereas most authors agree on the surgical treatment of carcinomas in the flexura hepatica using a right-side hemicolectomy – with some variations of the aboral borders of resection – the surgical strategy for carcinomas of the middle transverse colon and in the flexura lienalis is still debated. Based on an analysis of our own data from 1975 – 1983 we want to illustrate these problems showing that with partial resection of the colon the same permanent cure rate can be achieved as with colectomy, but avoiding the high primary lethality of colectomy.
L-56: COLORECTAL TUMOURS II: SURGICAL ONCOLOGY

I. Szentirmay, M. Jankovich, L. Hirczog, G. Keresztury

County Hospital, Miskolc, Hungary

The authors give account of experiences obtained during the treatment of 846 colorectal cancer cases operated on between 1965 and 1984, especially concerning the early and late results. It is stressed that - the number of colorectal carcinomas increased more than 2.5 times by the last five-year-period compared with the first one, - the rate of the radical operations significantly increased. In case of the colon carcinomas in respect of the two periods there was a 12 % increase whereas it nearly reached 75 % concerning rectal carcinomas. The Dukes B stage definitely increased moreover in the last five years it became the majority and carcinomas belonging to stage C decreased. In the last five years the operative lethality definitely decreased: the total sum of the elective radical operations to 22 %, that of the rectum carcinomas to 0.8 %. After the radical operations the five-year survival rate was registered to be 61.6 %, whereas in case of the 10 years survival it was 41.3 %, concerning a 82.3 % follow-up rate. The data of survival are discussed in detail on the basis of Dukes stage.

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The Cancer of the colon complicated with obstructio

Aloise PR, Chikiar A, De La Torre A, Eguia OF, Romanelli J, Sección Coloproctología, Departamento de Cirugía Hospital General de Agudos Dr. Ignacio Pirovano, Buenos Aires, Argentina.

On this paper the AA reports their experience in t

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The investigation of 5 and 10 year survival of 527 patients (155 men and 172 women) operated on colorectal carcinoma after Berckson and Gage, at General Hospital Osijek, in 1975-1984, has been performed. Carcinomas has been localized in rectum and sigmoid in 72%, ascends in 13.7%, transversum in 10.3% and descends in 2.8% of all patients. Nine patients (2.3%) were less than 40 years old, 154 (47.1%) were 40-65 and 154 (51.1%) were more than 65. In total, 25.1% of all patients survived 5, and 14.5% 10 years. Among the patients from Osijek there were 25.9% after 5 years, and 25.1% among village patients. No significant difference has been found (x^2=0.025, p>0.05). Male patients had surviving rates of 25.9% after 5 and 14.6% after 10 years, while the respective percentages for women were 26.1% and 15.6%, without significant difference between the sexes (x^2=0.151, p>0.05). Patients between 45-65 and older ones showed significant differences in 1 and 2 year survival (x^2=15.4%, 5,322, p=0.05), which have not been found after 5 years (x^2=1.445, p=0.05). 5 year survival of those with involved rectum was 25.7%, sigmoid 24.7%, descends 10.3%, transversum 13.3% and ascends 38.1% with no significant differences in 3 and 5 year survival rates. Radical procedures have been followed with 47.3% survival after 5 and 31.6% after 10 years, while after palliative procedures it was 10.4% after 5 and 5.5% after 10 years. Dukes A patients survived 5 years in 100%, Dukes B in 35.9% and Dukes C in 29.6% with no significant difference between B and C (x^2=0.031, p=0.05). Low 5 year survival rate demands early detection.

3801 COLORECTAL RESECTIONS FOR CARCINOMA: SURVIVAL. C. Fleites Matías, M.D.; G. Penalva MD; C. Saurer MD; G. Fleites Gonzales MD, Institute of Oncology and Radiobiology, Havana, Cuba.

We present the survival rate obtained in the resection of 152 patients with colorectal cancer. 14 patients in Duke's stage A, 96 in stage B and 37 in stage C. The period analyzed is from 1965-1974. 138 survived the risk of operation. Miles procedure had the highest mortality principally over 70 years old. More than 80% received adjuvant treatment with 5-FU during one year and we consider it was useful in increasing survival. Some of our patients received preoperative irradiation (anterior, post rectum) to diminish size of tumor and in the high rate risk we performed Lockhart-Mummery extra-abdominal approach, with less mortality. We used the TNM classification and the Duke's staging procedure as as the evaluation of mural penetration and the mapping of lymph nodes were the keys in the analysis of survival and principally to settle prognostic and adjuvant chemotherapy. We used the C.S.S. classification pre and post operatively in the follow up. The survival was 60.7% for all the patients, subdivided in: 75% for the small group in Duke's A stage; 50% for stage B and 25% for stage C. For carcinomas of the rectum but in colon the survival rate was much higher up to 90% in the small A group; 80% for the B group and 50% for the C when they had no more than 3 lymph nodes positive. Survival is pointed more than 7 years. The main complications were intestinal exclusion; sepsis, leaking in low terminal anastomosis and respiratory complications. Dajie's no touch tactic was followed during operations. Our major interest in this work is to insist that we consider colorectal cancer is a challenge to improve better early diagnostic methods.

3802 ADJUVANT THERAPY BY INTRA-ARTERIAL INFUSION (IAI) FOR ADENOCARCINOMA OF THE COLON DUKES' C. Luis M. Campos, R. Fisher, H. Medellin, M. Gaviria, E. Max, I. Klein, M. Mino-Dorado, Houston, Texas USA.

STUDY I: Twenty five patients (pts) who underwent curative surgery for adenocarcinoma (a-ca) of the colon Dukes' C between May 1976 and December 1977 received adjuvant chemotherapy with vincristine 2mg in 6 hours (h) followed by mitomycin C 10mg/m^2 in aliquots of 1500/day by continuous IAI via transhepatic catheterization of the celiac axis. CDU 100mg/m^2 was given p.o. on day 2. Eight courses were administered at six week intervals. In addition, pts were randomized to received BOG by scapification every 15 days thereafter until 6 months after completion of therapy (autopsy proven). Five pts had developed a second primary tumor; two, oat cell carcinoma (both heavy smokers). Both died free of a-ca of the colon. One, a-ca of prostrate died probably of a-ca of colon metastatic to bone and lungs; one, transitional carcinoma of bladder; one, a-ca ovary. Toxicity: nausea and vomiting 55.6%, leukopenia 19.8%, thrombocytopenia 17.4%. Complications: catheter dislodgement 12.6%; catheter occlusion 14%; chemical dermatitis 1.9%; arterial occlusion 2.6%; uremic ulcer 11.1%. Serious complications: mitomycin hemolytic-uremic syndrome, one pt (1.6%); superior mesenteric artery occlusion, requiring small bowel resection, one pt (1.6%).
ACTIVITY OF IDARUBICIN (IDA) IN METASTATIC BREAST CANCER


Istituto Nazionale per la Ricerca sul Cancro, V.le Benedet- 

At our Institute IDA (a new anthracycline reported to 

Our study shows that 4-dmDNR is well tolerated 

To start a prospective study about the efficacy and 

Toxic effects included mild to moderate nausea and 

The lack of established treatment modalities in patients 

Five concluding observations: 

+ DMDR, 35 mg/m² in combination with cyclophosphamide 

As a result of a phase II study of oral idarubicin (IDMR) 

The only patient treated with IDMR at the dose of 40 mg/m² is too early 

Doxorubicin and daunorubicin in preclinical studies) was adminis-

The number of cycles = 7 (range 2-12): no decrease > 15% was 

The median delay to response (13 weeks range 6 - 26) appears longer 

50% of pts; alopecia (grade I, II, III) in 43.1%; diarrhea (grade II, III) in 8.6%; stom-

Epirubicin (4'-desoxydoxorubicin) in advanced breast cancer: 

As a result of a phase II trial of oral idarubicin plus cyclophosphamide (IDMR) in 

Epirubicin (4'-desoxydoxorubicin) is a new anthracycline derivative that showed less cardiotoxicity and similar activity to doxorubicin in a series of experimental tumors in mice. A phase II trial was conducted in patients (pts) with advanced breast cancer; eligibility criteria included measurable lesions, performance status (P.S.) ≤ 2 (WHO scale), age ≤ 70 years, a life expectancy ≥ 3 months, neutrophil count > 1500/mm³, platelets (PLT) ≥ 100,000/mm³, and normal liver and renal function. In September 1985, 60 patients (pts) have been entered, 41 pts were evaluable for efficacy. 32 had received prior chemotherapy including Doxorubicin (DXR) for 24 of them, 9 pts had not received prior chemotherapy. At this time of analysis, responses have been observed in 4 out of 32 pretreated pts (12,5% - CI 1-23%) and in 7 out of 9 pts without prior chemotherapy (estimated total response rate : 27% with a confidence interval ranging from 12 to 42%).

The median delay to response (13 weeks range 6 - 26) appears longer than that observed with DXR but duration of response is similar (22 weeks, range 72 - 43). 46 pts are presently evaluable for toxicity. Moderate myelosuppression have been observed in 41% of pts having less than 4000 leukocytes/mm³ at day 21 following the first course. No hematological toxicities have included nausea-vomiting (20%), grade 1-2, local problems at the injection site (10%); grade 3-4); alopecia (36%; grade 3-4); 10%).

These preliminary results show Epirubicin as an active drug in breast cancer.

+ J.P. Armand - Hôpital Paul Brousse - 16-16 avenue P.V. Couturier - 94800 VILLEJOVF CEDEX - FRANCE

PHASE II-II TRIAL OF ORAL IDARUBICIN PLUS CYCLOPHOSPHAMIDE IN ADVANCED BREAST CANCER. M. Lopez, L. Di Lauro, P. Papad- 

PHASE I-II TRIAL OF ORAL IDARUBICIN PLUS CYCLOPHOSPHAMIDE IN ADVANCED BREAST CANCER. M. Lopez, L. Di Lauro, P. Papad-

The median number of courses administered was 3 (range 1-12). Results observed were: partial response: 6/23 (26%); stable disease: 10/23 (43.5%); progression: 7/23 (30.5%). Toxicity observed was: nausea and vomiting (grade I, II, III) in 60% of pts; alopecia (grade I, II) in 39.1%; leukopenia (grade I, II, III) in 43.3%; diarrhea (grade II, III) in 8.6%; stom-

This study shows that 4-dmDNR is well tolerated in the majority of pts, has antitumor activity in metastatic breast cancer and can be safely administered orally.

In our study IDA was well tolerated. Median number of cycles = 7 (range 2-12): no decrease > 15% was detected. This study shows that 4-dmDNR is well tolerated in the majority of pts, has antitumor activity in metastatic breast cancer and can be safely administered orally.
PHASE-II STUDY OF MITOXANTRONE AND PRENIDUSTINE (MP) IN ADVANCED BREAST CANCER
M. Kaufmann, C. Manegold, M. Schindl and F. Kubli,
University Hospital, Dept. of Obstetrics and Gynecology and Internal Medicine, Heidelberg, Fed. Rep. Germany

Thirty-four patients (pts.) with metastatic breast cancer (age 28-72 years, median 50) were treated with mitoxantrone/prednimustine (MP) combination chemotherapy (M: 12 mg/m² on day 1, P: 100 mg/m² on day 2). PR was observed in 2/30(6.6%) pts. and leukopenia (grade 1-4) in 17/30(56%).

Overall response observed was: Partial Response (PR) in 8 pts, complete response (CR) in 5 pts, and stable disease (SD) in 8 pts. Eight pts had no postoperative systemic adjuvant therapy. Sites of metastases at the time of MP-treatment were visceral (n=14), osseous (n=4), and multiple (n=4).

The following results were yielded in 15 evaluable pts. with more than 2 MP cycles: 1 CR, 7 PR, 6 NC, and 1 PD.

In 12 pts. MP was given as second or third line chemotherapy (CMF). All cases showed progression of visceral metastases before MP-treatment. TIL now showed 7 evaluable pts. with more than 2 MP cycles. PR therapy was registered: 0 CR + PR, 3 NC, and 4 PD.

One early death was observed; one patient (NC) died with lung embolism after 2 MP cycles. Objective and subjective side effects have been tolerable.

In metastatic breast cancer MP combination therapy seems to be an effective and useful regimen especially as first line CRT.

PHASE-II STUDY OF 4-DEMETHYLDADAMOUBICIN (4-DM DNR) ADMINISTERED BY ORAL ROUTE IN ADVANCED BREAST CANCER. M. Brandi, F. Calabrò, S. Romito, M. De Lasa. Oncologic Inst. S. Luigi-Italy

4-DM DNR is a new analog of Daunomycin obtained by substitution of O-4 methoxy group in the D ring of the aglycone moiety with an H atom. 11 women with advanced breast cancer (evaluable disease) were treated with 4-DM DNR administered by oral route at initial dose of 15 mg/m²/day x 3. The therapy was recycled after 3 weeks. Platelets and WBC were controlled every 2 weeks during the initial 2 cycles. If hematologic or clinical toxicity was not observed during this period, the dose was increased in 5% steps. Cardiac function was monitored (EKG and 2D Echocardiogram) every 3 cycles. 7 women treated at least 2 courses are evaluable for clinical response and for toxicity; 4 are evaluable at present moment because only 1 course was administered. 6 women were resistant to combined chemotherapy (CMF) and to hormonal therapy. The median age of evaluable women resulted 62 yrs. (47-71); median PS (WHO 60); dominant lesions: bone (2) and soft tissue (4) and viscera. Simple evaluable metastases were present in lung (2 patients), liver (1), pleura (1), skin (2), node (2) and bone (4). No CR was observed. Considering the dominant site of disease PR was observed in 1/4(25%) bone lesion while, considering the simple lesions, PR were only observed in 2/17(11%) cases.

After the second course, the dose of 4-DM DNR was escalated in all patients. In total were administered 26 cycles. Toxicity was registered in 2 women, nausea and vomiting appeared in 4/7(57%), fever in 2/7(28%), neutropenia in 1/7(14%), diarrhea in 1/7(14%) and fatigue and anorexia in 1/7(14%).

Leukopenia (WHO/mmc) was observed in 4/7(57%) and pig striatmentation (WHO/mmc) in 1/7(14%). 1 patient showed reversible acute renal failure. Alopecia was not observed. Due to the small number of patients evaluable at present moment further investigations are necessary to assess the toxicity and the therapeutic efficacy of 4-DM DNR.
A PHASE II TRIAL OF ORAL 4'-DEOXYDOXORUBICIN (DXDO) IN PATIENTS WITH MEASURABLE ADVANCED BREAST CANCER, Lars Bastholm*, Beni Jørgensen, Nils Dalsgaard**.
*Dept.of Oncology, Odense University Hospital, Denmark.
**Dept.of Oncology I, The Simon Institute, Denmark.

(49 postmenopausal, 1 premenopausal females with a median age of 65 years (range 42-78) and a median performance status of 0 (range 0-3) had been registered. Previous treatments: mastectomy (48 pts.), radiotherapy (39 pts.), endocrine therapy (40 pts.), and combination chemotherapy (39 pts.) without anthracyclines. Dominant sites of disease were skin (16 pts.), visceral (17 pts.) and bones (19 pts.). Standard dosage of DXDO: 45 mg/m² by oral route every 3 weeks. The 170 courses were given with scheduled dose 121 courses with reduced dose, and 12 courses with escalated dose (total number: 303 courses). The individual overall response: 4 CR, 16 PR, 22 NC, 7 PD and 3 NE with less than 2 treatment courses (1 pl.died of cerebral stroke, 2 pts. withdrawn because of GI toxicity). The (CR+PR)/ fraction of all patients entered (50) to 0.36. The (CR+PR)/ fraction of patients with > 2 courses (47) to 0.38. Estimates of median duration to progression for all pts. 30 were app. 22 weeks, and for pts. with CR+PR (18) app. 37 weeks. Hematological toxicity on dose increase following the first course was moderate with median NBD nadir of 2.2 (range 0.3 - 5.5) /L, median platelet nadir of 178 (range 0-639) /L, and median hemoglobin nadir of 7.5 (range 3.6 - 8.9) mmol/L. 9 courses (3%) of the 303 courses given were followed by severe infection. Non hematological toxicity was moderate with nausea/vomiting 15% of median grade 2. 30% of the pts. complained of diarrhoea (median grade 2). Hair loss (86%) was observed with a median grade 2 after a median number of 2 courses. No histologic variation has been observed in the cardiac radionuclide ejection fractions so far.

Conclusion: This analysis of an ongoing study shows that DXDO by oral route has pharmacokinetic effects comparable to those of doxorubicin by intravenous route in patients with advanced carcinoma of the breast.


Epirubicin belongs to the class of anthracycline antibiotics; it is an analogue of doxorubicin modified in the sugar moiety, in which the stereochemistry at the hydroxyl group bearing C-4' has been inverted. Moreover, it shows an equal antitumor activity to doxorubicin and a lower toxic effect on isolated heart cells, in vitro. Twenty patients, with advanced breast cancer were randomly treated with doxorubicin or epirubicin every three weeks, at the same dose (60 mg/m²). Acute cardiac toxicity was evaluated measuring the increase of creatine kinase isoenzyme MB serum levels. Chronic involvement of myocardial tissue was monitored by "M Mode" echocardiography (Vcf max) performed before each chemotherapy cycle. In the current study the patients group treated with doxorubicin showed significant elevation of CK-MB measured 15h after drug administration (P<0.01). Moreover, a marked decrease in the Vcf max after a cumulative dose of 200-400 mg/m² was detected. The group treated with epirubicin, instead, showed no significant variations in CK-MB serum levels (P>0.05), neither decrease of Vcf max, detected by echocardiography, when it was reached epirubicin cumulative dose of 400-600 mg/m².

Our results demonstrate the efficacy of low-dose weekly epirubicin in metastatic breast cancer with 20mg epirubicin/m²/week i.v. All but three patients had been heavily pretreated with cyclophosphamide/methotrexate/fluorouracil. In addition, eight patients had received doxorubicin-containing chemotherapy regimens.

Of 38 evaluable patients 19 responded to low-dose weekly epirubicin: 8 partial remissions (12+41 weeks, median 22 weeks) and 11 minor responses (4-20+ weeks, median 13 weeks). Partial remissions could be achieved in 1/14 premenopausal women (7%), 6/22 postmenopausal women (27%), and 1/2 men, respectively. Response rates were 54% in patients treated without doxorubicin-containing chemotherapy, and 25% in patients after cytostatic pretreatment including doxorubicin.

Side-effects such as leukopenia, alopecia and nausea were markedly reduced in comparison to conventional anthracycline therapies. No cardiotoxicity was observed at a cumulative maximum dose of 740mg epirubicin/m².

The cumulative cardiotoxicity of anthracyclines can be reduced by low-dose weekly administration in contrast to conventional therapeutic regimens. Due to less side-effects observed and reduced cardiotoxicity expected, this treatment regimen may be superior to conventional anthracycline therapies in metastatic breast cancer.
A WEEKLY SCHEDULE OF LOW-DOSE 4-EPI-DIODOBUCIL IN THE TREATMENT OF ADVANCED BREAST CANCER.

Matti Jakobsson (1), Tapani Hakala (2) and Lasse Huse (3), Department of Radiotherapy, Middle Finland Central Hospital, Jyväskylä (1), Radiotherapy Clinic, Tampere University Central Hospital (2) and Farnailia Carlos Erba, Finland (3).

From September -83 we started to treat advanced breast cancer patients, second line therapy in measurable lesions, age under 75 years, performance status K 50 with low-dose (50 mg/week i.v.) 4-EPI-DIODOBUCIL.

Until now we have had 31 patients and the preliminary treatment results are presented.

All the patients have been treated earlier with radiotherapy, chemotherapy and hormonal therapy.

Objective response rate was about 30 % with minimal toxicity. The best results were in patients with lung metastases and skin metastases. P.O. was found in 38 %. Very important thing is that there was no alopecia at all and hematological and gastrointestinal toxicity was minimal. There were many patients with multiple metastases and we think it was useful for them to get the treatment. The total amount of treatment was 2-38 (means 16). If there was any response it started after 2-3 treatments.

Clinical studies on bestrabucil, a benzoate of estradiol-chlorambucil conjugate, which has been shown to accumulate in tumor tissue and exert its anti-tumor action with little side effects in animal and clinical studies, have been carried out in 19 patients with recurrent and far advanced breast cancer (8 local, 4 lung, 4 bone and 3 far advanced). The satisfactory response rate of 63 % (CR 3, PR 9, NC 6 and PD 1) was obtained after 1-4 months treatment. The total amount of treatment was 2-38 (means 16). If there was any response it started after 2-3 treatments.

One of the patients with far advanced breast cancer was suffering from convulsions due to a brain metastasis and we think it was useful for them to get the treatment. The total amount of treatment was 2-38 (means 16). If there was any response it started after 2-3 treatments.

The adsorption rate of bestrabucil was analyzed in 3 patients after the oral administration of 100 mg of betra bucil and estimated at 83 %, 96 % and 59 %.

One of the patients with far advanced breast cancer was suffering from convulsions due to a brain metastasis, and has been treated with an oral administration of bestrabucil and tamoxifen for 15 months. A CT radiogram showed that the brain lesion disappeared after treatment and the patient has not had any more convulsions. Moreover, another patient, before and after a simple X-ray film, bone scintigram and biopsy. Twenty milligrams of this agent was administrated twice a week for ten times. Another concomitant drugs were avoided.

Therapeutic effects according UICC program were complete effect in one case, partial effect in 3 cases and no change in 6 cases. In four cases, whose recurrence were local or lymphnodes, an additional local therapy was carried out following to peplomycin administration was completed. In two cases, complete regression of the recurrent tumor was obtained by low dose radiation. Histological type of the two cases was papillarylobular adenocarcinoma.

From the results, combination therapy of peplomycin sulfate and low dose radiation suggested the possibility of expecting regression of the recurrent or metastatic breast cancer.
PHASE II STUDY OF A NOVEL ANTIFOLATE N* 
PROPARGYL-5, 6 DIHYDROXYACID ACID (CB3717) IN ADVANCED BREAST CANCER. 
A.H. Harris, B. Cantwell, V. Macaulay, A.H. Calvert, 
OF CLINICAL ONCOLOGY, Royal Marsden 
Hospital, London and Sutton, England, and Dept. Clinical 
OncoIogy, Glasgow University, Scotland, U.K. 
CB3717 is a quinazoline folic acid analogue which specifically 
inhibits thymidylate synthase (TS). Nethetoxese 
(HTX) resistant human tumour cell lines may be effectively 
Since CB3717 had phase 1 activity in HTX pretreated breast 
cancer patients we studied its antitumour activity in 53 
advanced breast cancer patients at 3 UK institutions. 
There were 40 postmenopausal, 12 premenopausal women 
and 1 man, mean age 53 yrs, range 36-75, 52 had prior sys-
temic therapy for locally advanced metastatic breast 
cancer. 9 having hormones (H) only and 43 chemotherapy (C). 
21 had HTX in combination. Doses of CB3717 were 400 
mg/m² IV 1 weekly with dose reductions (300mg/m²) for 
reduced creatinine clearances (CC) or abnormal liver func-
tion tests. 12 patients (23%) had objective responses, 
6 with 50% or more tumour shrinkage (PR) and 4 with less 
(ND), soft tissue disease the dominant site of response 
ocurrence (16) with a NW in 1 case each of bone and 
pulmonary metastases. 9 CB3717 responders had prior chemo-
therapy and 3 had prior responses to chemotherapy. 1 CB3717 response occurred in a patient with a prior HTX 
response, and 2 responses in HTX resistant patients. 
Toxicities were malaise in approximately 4%, skin rash 4%, 
conjunctivas 1%, and reversible elevation of liver en-
zymes in 7% of patients. 5 patients developed reversible 
renal failure (CCG04/05/min). The activity of CB3717 in 
heavily pretreated breast cancer suggests the importance 
of TS as a drug target for chemotherapy.

M-56: BREAST CANCER: MEDICAL ONCOLOGY IV

PHASE II STUDY OF A NOVEL ANTIFOLATE N* 
PROPARGYL-5, 6 DIHYDROXYACID ACID (CB3717) IN ADVANCED BREAST CANCER. 
A.H. Harris, B. Cantwell, V. Macaulay, A.H. Calvert, 
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Toxicities were malaise in approximately 4%, skin rash 4%, 
conjunctivas 1%, and reversible elevation of liver en-
zymes in 7% of patients. 5 patients developed reversible 
renal failure (CCG04/05/min). The activity of CB3717 in 
heavily pretreated breast cancer suggests the importance 
of TS as a drug target for chemotherapy.

3819
3823 CYTOTOXIC SALVAGE THERAPY WITH 4'-EPI-DX, VINCRI- STINE AND CYCLOPHOSPHAMIDE IN PRETREATED PATIENTS WITH METASTATIC BREAST CANCER. L. Jaspers, P. Langecker, K. Possinger and W. Wilmans; Gesellschaft für Strahlen- und Umweltforschung Neuherberg; Medizinische Klinik III, Klinikum Großhadern, Ludwig-Maximilians-Universität München; F.R.G.

4'-Epi-Dorubicin (4'-Epi-DX) is a new epimerized analog of adriamycin. Preclinical tests and initial clinical trials demonstrated that 4'-Epi-DX has the same antitumor activity as doxorubicin but less systemic toxicity and less cardiotoxicity than the parent compound. The lack of serious acute and subacute toxicity together with its possible reduction of cardiomyopathy justifies a clinical study of combined 4'-Epi-DX, Vincristine and Cyclophosphamide as second-line chemotherapy following CMF treatment in patients with advanced breast cancer. The purpose of this study is to evaluate the efficacy and the safety of the chemotherapy regimen. Treatment plan: day 1: 4'-Epi- DX: 40 mg/m² i.v., Vincristine: 1 mg/m² i.v., day 3-6: Cyclophosphamide: 200 mg/m² p.o.; drug administration is repeated every 3-4 weeks, toxicity permitting. Eligibility criteria: age between 18-75 years, performance status ≤ grade 3 (WHO-scale), no signs of congestive heart failure, no history of myocardial infarction during the last 6 months, tumour progression or relapse following CMF treatment.

25 patients (pts.) entered the study. 23 pts. are now evaluable for response (WHO-criteria). Partial remission was observed in 6 of the 23 pts. (no complete remission). Stable disease occurred in 11 pts., 6 pts. experienced progressive disease. Remission duration: median: 7 months (range: 3-13 months); duration of stable disease: median: 6 months (range: 3-11). WHO-toxicity (WHO-scale): m: grade (g) 2, range (r): 0-4; platelet toxicity: m: g 0, r: 0-3; nausea/vomiting: m: g 2, r: 0-3; alopecia: m: g 3, r: 2-3; adverse cardiac effects have not been observed. The study will continue until a total of 30 patients have been enrolled.

The treatment was well tolerated and the side effects did not exceed WHO-grade 3. The treatment was repeated every 3-4 weeks, toxicity permitting. Eligibility criteria: age between 18-75 years, performance status ≤ grade 3 (WHO-scale), no signs of congestive heart failure, no history of myocardial infarction during the last 6 months, tumour progression or relapse following CMF treatment. 25 patients (pts.) entered the study. 23 pts. are now evaluable for response (WHO-criteria). Partial remission was observed in 6 of the 23 pts. (no complete remission). Stable disease occurred in 11 pts., 6 pts. experienced progressive disease. Remission duration: median: 7 months (range: 3-13 months); duration of stable disease: median: 6 months (range: 3-11). WHO-toxicity (WHO-scale): m: grade (g) 2, range (r): 0-4; platelet toxicity: m: g 0, r: 0-3; nausea/vomiting: m: g 2, r: 0-3; alopecia: m: g 3, r: 2-3; adverse cardiac effects have not been observed. The study will continue until a total of 30 patients have been enrolled.

The Authors report their experience, the compliance and late results.

M-57: THERAPY OF DIFFERENT TUMOURS: MEDICAL ONCOLOGY

3824 "ADVANCED CHEMOTHERAPY IN LIVER TUMOURS SURGERY".

HANSBERG M.D., M. FRIEDMANN M.D., L. CAPPELLI M.D., J. CHIRIAZZA M.D., F. CECI M.D.

1st DEPT OF SURGERY-CANCER INSTITUTE "REGINA ELENA" ROMA

The adjuvant chemotherapy in liver tumors was proposed before the present time from several Authors, who prepared many protocols end different schemes. It's about two years that in our Division of General Surgery we realize scheme of chemotherapy on the systemic way, based with 5-F.U. and Folitrex B, that we practice especially to the patients after liver resection. Adjuvant chemotherapy for synchronous and metachronous metastases from colorectal cancer.

The course is following: 1 gr. 5-F.U. + 150 mg, Folitrex B in the 24 hours during the same day of the surgical operation for six successive days. This course will be repeated for six days every 21 days previous control of hepatic formula. The patients will be controlled in the end of the treatment by means of CEA hematic level and with C.T. and successively every three months with hepatic echonography. Until today we treated in this way 20 patients that are periodically controlled and in whom there is not present of neoplastic recurrence.

The Authors report their experience, the compliance and late results.

3825 TREATMENT OF METASTATIC CARCINOID TUMORS. A CONTROLLED STUDY OF STREPTOZOTOCIN/5-FU AND INTERFERON.


Carcinoid tumours are relatively slowly advancing neoplasms, but when metastases have been diagnosed, the patients need conservative treatment. Streptozotocin and 5-FU has so far been the best combination of cytotoxics, revealing a response rate of up to 33%. Treatment with interferon in patients with malignant carcinoid tumors have in our hands given a response rate of 47%. We have now performed a controlled cross-over study, with interferon and Streptozotocin/5-FU in the both arms, to evaluate the best therapy for this type of tumours.

Material: 20 pat, with malignant carcinoid tumours and elevated levels of urine 5-hydroxyindoleacetic acid were randomized to therapy with either Interferon (5-6x10⁶ IU s.c. dayly) or Streptozotocin/5-FU (1g iv. x III/400 mg/m² iv.xIII/6 w.) for 6 months. When no response to the treatment was noted, the patient was crossed over to the other treatment form.

Results: No patients treated with the streptozotocin/5-FU regime (n=11) had an objective tumour regression, and 44% of the patients actually showed progression of the disease. In the patients treated with interferon (n=14) 36% had objective tumour regression and the rest of the patients showed stable disease. No patient had tumour progression.

Discussion: Treatment with Interferon showed a significant better result than the Streptozotocin/5-FU treatment. We think that at the moment Interferon is the best treatment for patients with malignant carcinoid tumours.
TREATMENT OF MULTIPLE METASTATIC LIVER TUMORS ACCORDING TO DRUG DELIVERY. Toshiyu Nakashima and Mitamura Nishi, Dept. of Surgery, Cancer Inst. Hospital, Tokyo, Japan.

Multiple metastatic liver tumors are refractory to various modalities of treatment. Among 145 patients with multiple metastatic liver tumors whose primary lesions were resected surgically, comparison of treatment results was done between those treated by chemotherapy with various drug delivery routes and those treated without chemotherapy. Twenty four cases were subjected to continuous intra-arterial chemotherapy with chronofusor and implanter i.a. delivery system (Vascular Access Port, Norfok, U.S.A., VAP-i.a.). 40 cases to systemic intravenous chemotherapy (i.v.), 12 cases to peroral chemotherapy (p.o.), and 55 cases to no further chemotherapy. Survival rates at 4 and 7 months were 58.3% and 20.8% for con-i.a. group, 35.0% and 10.0% for i.v. group, 67.1% and 16.7% for p.o. group, and 29.1% and 7.3% for no chemotherapy group. As to VAP-i.a. group, the direct effect on tumor regression was evaluated because it is too early to evaluate by survival rates. Five out of 10 cases treated properly achieved complete response (1) or partial response (4). Remaining 4 cases did not receive chemotherapy because of postoperative complications or general weakness due to rapid tumor growth. Catherization into the hepatic vein during VAP-i.a. infusion revealed a marked persisting difference in the drug concentration between the hepatic and peripheral veins. I.a. chemotherapy was less toxic than the systemic i.v. or p.o. chemotherapy. These results indicate accentuation at tumor site and low in the periphery account for the superiority of i.a. chemotherapy to systemic chemotherapy. VAP-i.a. is easier than con-i.a. in regard to the maintenance of the apparatus, and produces a better quality of life for the patients.

COMBINED TREATMENT OF UTRICULAR SARCOMA (US) AT THE NATIONAL INSTITUTE OF ONCOLOGY AND RADIOLOGY (INOR) IN HAMADA GUNA.

Alfonso, Lorencio Dr., Barroso, Ma. del C. Pms., Martiege, Pio Dr., Palas, J. D. Dr., Gomes Gom, E. Dr., National Institute of Oncology and Radiology in Havana.

From 1972 until 1973 25 patients (pts) diagnosed of aseemic US of extremity were treated at INOR. The purpose of this study was to evaluate the general results with 2 different chemo-radiation post amputation.

The first regimen consisted in sequential doses of Vin cristine (VCR) 1.5 mg/kg Methotrexate (MTX) 100 mg/k with intravenous rescue (CR). Cyclophosphamide (C) 600 mg/kg and Adriamycin (ABR) 1.5 mg/k x 2, every 2 weeks (IV). The survival at 5 years was:

- 4 pts (without metastases) 75%
- 2 pts (with metastases) 0%

The second regimen consisted in a sequential combination of drugs every 2 week with VCR, ADM and MTX-GY at the same doses and Bleomycin (15 mg/kg) and Actino mycin (0,450 mg/kg). The survival at 5 years was:

- 14 pts (without metastases) 39%
- 3 pts (with metastases) 33.3%

The statistical analysis demonstrated a significant difference (p<0.05) between both groups.

6 pts required surgical removal of lung metastases that we consider an important event in the general survival.

A previous study before 1976 (62 pts) has shown a survival of 18.7% at 5 years. When we compare this results with the 39.3% reached in this study we conclude that aggressive chemotherapy, associated with metastasis cure have important role in producing long term survival.

For the EORTC Gynaecological Cancer Co-operative Group. Oxford OX3 9JL, United Kingdom.

Radical vulvectomy in the treatment of choice for vaginal carcinoma carries a high risk of resection of the vulva. Down-staging of inoperable disease by radiotherapy or chemotherapy is impeded by the age of the poor general condition of these patients. Therefore low dose chemotherapy with Bleomycin, Methotrexate and CCNU has been studied in 23 patients with radically inoperable vulvar cancer for clinical efficacy, operability after chemotherapy and side-effects profile. All had histologically verified squamous carcinoma, inoperable, measurable and not pretreated. Patients with distant metastases or severe coexistent disease were excluded. Chemotherapy was given in a six week cycle using a complex schedule of dose modification for toxicity: BMN 5mg in days 1-5, then days 1 and 4 each week, CCNU 40mg po days 1, 5, 15 5mg po days 1 and 4 each week. Minimum cycle time was given and repeated four times or until response. Eighteen patients were fully evaluable, of which 10 patients had positive responses with recurrent disease. The mean age was 75 years, mean performance status was 1.

Drug response: 12 responders

- Complete 2
- Partial 10
- Stable 4
- Progression 2

Side effects: Severe nausea, vomiting, leucopenia and stomatitis, transient. No change (0).


The goal of the Mayo Clinic protocol was to obtain preliminary data on the therapeutic effectiveness and toxicity of this drug. From the first report in 1976 with a long acting analogue in the treatment of patients with malignant carcinoid syndrome, SOM 201-995 was administered by subcutaneous injection. The initial dosage on day 1 was 50 mcg and this was escalated to 100 mcg b.i.d. on day 2. The dosage on day 3 and thereafter was 150 mcg t.i.d. The first 17 patients responded, with a range of 22 to 76 months. There were 9 males and 8 females. All 17 patients had elevated 24-hour urine 5-HIAA excretions to serve as an objective indicator of disease activity (mean 250.7 mg/24hr., range 12.7 to 1079 mg/24 hr.). Ten of the 17 patients had received prior chemotherapy with cytotoxic drugs. Thirteen of the 17 patients achieved symptomatic responses defined as a decrease in flushing and diarrhea by at least 50 percent compared to pretreatment. The symptomatic responses have often been quite striking with resolution of voluminous diarrhea 12-48 hours after beginning the drug. Twelve of the 17 patients had a greater than 50 percent decrease from their pretreatment 5-HIAA value. Three patients had no objective decreases in 5-HIAA but were stable by these criteria. The median duration of biochemical response was 8 months with a range of 1 to 12 months. Orally administered drug has been excellent. No patient has required oral hypoglycemics or insulin. There has been no evidence of gastrointestinal, renal hepatic, neurologic, or hematologic toxicity.
Effect of simultaneous intra-thoracic administration of OK-432 and Adriamycin (ADR) to patients of carcinomatous pleuritis caused by breast cancer, primary lung cancer or metastatic lung cancer was studied. In all cases, after discharge of pleural effusion, from 3 KE through 30 KE of OK-432 and from 10 mg through 30 mg of ADR were injected simultaneously. In some cases, thoracic drainage was removed soon after the injection, and in the other cases, thoracic drainage was removed approximately 24 hours later the first cases.

Effectiveness of the therapy were compared by the fact whether pleural effusion had increased or not, length of the period of the increase of pleural effusion, and cytological examination of the residual pleural effusion.

The method of simultaneous intra-thoracic administration of OK-432 and ADR to patients of carcinomatous pleuritis caused by breast cancer, primary lung cancer, or metastatic lung cancer was considered as effective at least locally.
All malignancies of lung and bladder which had developed during 1966-1980 as second primary malignancies in patients who had previously registered by the National Cancer Registry of the GDR with cancer of the ovary from 1960 to 1979 were identified. Of the 30 bladder cancers 8 occurred prior to 1960 and of the 38 cases of lung cancer 12 occurred before 1960 and were not further considered. Controls who had not developed a second malignancies, were chosen, and the therapy used for the second cancer cases and the controls was compared. Of particular interest was the role of cyclophosphamide in bladder cancer induction.

Limited availability of matched donors, frequent occurrence of graft vs host disease (GVHD), as well as the financial, organizational and technical problems have prevented the widespread application of bone marrow transplantation particularly in developing countries with limited resources. Fetal liver in the gestation period of 8-20 weeks is a suitable source of pluripotent hematopoietic stem cells with minimal potential of inducing GVHD. Forty patients of severe aplastic anemia received fetal liver cells intravenously. Five patients who died within 2 weeks of fetal liver infusion (FLI) were excluded. Twenty two (62%) of the 35 evaluable cases responded favourably. One patient was subsequently lost to follow-up. Ten patients lived up to 3-106 (Median-M-7) months and 11 patients are alive at the median of 5-40 (M-9) months. Of the 13 non-responders, 4 have been lost to follow-up and remaining 9 died in 20 days to 4.3 months (M-1.6 months). Six months survival of 50% and overall median survival after 6 months of 5.7 months following FLI is superior to survival (11 days to 12 months-H-1 month) of 20 patients treated by anabolic steroids (p < 0.01). Forty two acute myeloid leukemia (AML) patients received induction chemotherapy; 21 with 3 days daunomycin (45 mg/m^2) and 7 days Ara-C (100 mg/m^2) and 15 with w dose Ara-C (10 mg/m^2/12 hourly x 3 weeks). Six patients died in less than 2 weeks are excluded. Of the 36 evaluable patients, 14 who received FLI following induction and maintenance chemotherapy had a complete remission (CR) rate of 42% and MS of 18.5 months. Twenty two patients who could not receive FLI had a CR of 23% with MS of 11 months. FLI appears a convenient and safe alternative to bone marrow transplantation.
M-58: SMALL CELL LUNG CANCER: MEDICAL ONCOLOGY

3842 DATA ON THE CYTOSTATIC TREATMENT OF INOPERABLE LUNG CANCER PATIENTS
Dr. E. KANIZS DRAJKA LAKOS
Korany National Institute of Tuberculosis and Pulmonology Budapest, Hungary

The authors examined the clinical history of all inoperable lung cancer patients treated from January 1983 to 31 December 1984 in the Korany National Institute of Tuberculosis and Pulmonology. The analysis implications of life, the regression or progression rate of the X-ray picture, as well as other characteristics among the groups treated with different drug combinations. The authors attempted to establish the optimal indication of treatment, the interrelations between treatments and the counter indications of cytological treatments. Based on the above data recommendations are presented concerning the clinical treatment in Hungary using available drugs.

3844 4'-DEOXYDOXORUBICIN (DDX) IN THE TREATMENT OF SMALL CELL LUNG CARCINOMA (SCLC)
G. Giaccone, M. Donadio, R. Musella, A. Calciati, Division of Medical Oncology, Ospedale S. Giovanni A.S., 10123 Torino, Italy.

From October 1984 to November 1985, 14 patients (pts) with SCLC were given DDX 30 mg/m² i.v. every three weeks.

All were males, median age 61 years (range 47-73). Performance Status (E.C.O.G.) was 1 in 10 pts and 2 in 4 pts. Weight loss was: < 10% in 7, 10-25% in 3 and > 10% in 1. 6 pts had limited disease and 8 extensive disease (2 liver, 2 lymphnodes, 3 lung and 1 lymphnodes + bone marrow). All pts had been previously treated by chemotherapy: 3 with VM 26 alone, 11 with multidrug schedules; 5 had never received doxorubicin before. 3 pts had also been given chest radiation.

25 cycles had been administered (1-4 per patient) and dose was escalated by 125% in 5 pts. Overall toxicity was mild; the major side effect was leukopenia, with WBC nadir < 2000 in 2 pts. No cases of thrombocytopenia or anemia occurred. Vomiting was observed in 2 pts, slight hair loss in 1 and diarrhea in 1. No signs of heart, kidney or liver toxicity were observed. 11 pts are evaluable for response (1 pts are too early for efficacy assessment); 1 patient had stable disease and 10 had progressive disease. The median survival was 11 weeks from start of DDX.

In conclusion, DDX is well tolerated and easy to administer; unfortunately DDX has not shown efficacy in SCLC pts at this stage of the study.
VINCRISTINE PLUS ETOPOSIDE: A WELL-TOLERATED AND EFFECTIVE TREATMENT FOR SMALL-LUNG CANCER (SCLC).

D.A.L. Morgan
Department of Radiotherapy and Oncology,
General Hospital, Nottingham NG1 6HA, England.

Many combination chemotherapy regimens produce a high response rate, and prolongation of survival, for patients with SCLC, but very few are cured. Thirty consecutive patients, with either extensive stage (28 patients) or limited stage but poor performance status, were treated with etoposide 250 mg/m² orally, daily for five days, plus vincristine 2 mg intravenously on the first day, this cycle being repeated three-weekly. A maximum of six cycles was administered. Radiotherapy was used as palliation for severe local symptoms, as required. All patients have been followed-up until death, or for a minimum of 15 months. Objective evidence of tumour regression (WHO criteria) were seen in 22 patients (73%). Median survival is 160 days, and 11 patients (37%) survived for over one year from the start of treatment. Alopecia occurred in all patients receiving 2 or more cycles of treatment. Other sequelae (Grade 3/4), symptomatic side-effects were infrequent; nausea and vomiting followed 2% of treatment cycles to patients, in terms of side-effects, than other combinations widely-used for SCLC, and products.

The best response to chemotherapy was higher on A (63% vs 42%, p = 0.005). Two hundred and sixty-seven were allocated prior to treatment (133 on SB; 134 on A) and 242 are evaluable for response status at the end of 6 treatment cycles. Responding patients received prophylactic cranial irradiation after 3 courses of chemotherapy. No maintenance chemotherapy was given and thoracic irradiation was only given to palliate persistent or recurrent local symptoms. Two hundred and ninety-one of the 321 patients were eligible and are included in the survival analysis. Two hundred and sixty-two were allocated prior to Feb 1, 1985 and are evaluable for best response to therapy (119 on SB; 134 on A) and 242 are evaluable for response status after six courses (119 on SB; 123 on A). Most had a good performance status (52% ECOG 0, 1) and the two groups were well balanced for known prognostic factors. The best response to chemotherapy was higher on A (81% CR + PR vs 62%, p = 0.001) and response status at the end of 6 courses was also higher on A (63% vs 43%, p = 0.005). When adjusted for important prognostic factors by Cox’s proportional hazards model, the progression free survival for patients on A was superior (Median 7.1 mo. vs 5.4, p = 0.001). Overall survival was similarly prolonged (9.8 vs 7.8 mo.), but the adjusted p value was 0.08 (two-sided). Female patients had a significantly better response rate and overall survival. The frequency of neutropenia and infection was less on A. This preliminary analysis suggests that A is a better treatment approach for extensive SCLC.

CICLOPHOSPHAMIDE-ADRIAMYCIN AND VINCristine (CAV) in EXTENDED SMALL LUNG CARCINOMA.

National Cancer Institute of Canada Clinical Trials Group, Kingston, Ontario.

Patients with extensive SCLC were randomized to receive either 6 courses of IV cyclophosphamide 1000 mg/m², doxorubicin (Adriamycin) 50 mg/m² and vincristine 2 mg (CAV) at 3 week intervals or CAV alternating with VP-16 100 mg/m² days 1-3 and cisplatin 25 mg/m² days 1-3 q 3 weeks for 6 treatment cycles. Responding patients received prophylactic cranial irradiation after 3 courses of chemotherapy. No maintenance chemotherapy was given and thoracic irradiation was only given to palliate persistent or recurrent local symptoms. Two hundred and ninety-one of the 321 patients randomized were eligible and are included in the survival analysis. Two hundred and sixty-two were allocated prior to Feb 1, 1985 and are evaluable for best response to therapy (119 on SB; 134 on A) and 242 are evaluable for response status after six courses (119 on SB; 123 on A). Most had a good performance status (52% ECOG 0, 1) and the two groups were well balanced for known prognostic factors. The best response to chemotherapy was higher on A (81% CR + PR vs 62%, p = 0.001) and response status at the end of 6 courses was also higher on A (63% vs 43%, p = 0.005). When adjusted for important prognostic factors by Cox’s proportional hazards model, the progression free survival for patients on A was superior (Median 7.1 mo. vs 5.4, p = 0.001). Overall survival was similarly prolonged (9.8 vs 7.8 mo.), but the adjusted p value was 0.08 (two-sided). Female patients had a significantly better response rate and overall survival. The frequency of neutropenia and infection was less on A. This preliminary analysis suggests that A is a better treatment approach for extensive SCLC.

Adriamycin, cyclophosphamide, cisplatin, and etoposide are among the best induction drugs for SCLC. We conducted a phase-II trial with these 4 drugs given at full doses: cisplatin (60 mg/m$^2$ d1), adriamycin (45 mg/m$^2$ d1), etoposide (80 mg/m$^2$ d1, 2, 3) and cyclophosphamide (1 g/m$^2$ d1). Courses were repeated every 4 weeks until a total of 10 courses. Prophylactic cranial irradiation (30 Gy in 10 fractions over 2 weeks) was given to complete responders (CR). Evaluation for response was performed after 2 courses of CAV. 116 patients were included in the trial; 4 were ineligible and 11 were evaluable for response. Characteristics of the 112 eligible cases were: 103 male/9 female; mean age 59 (37-74); mean P.S. ( Karnofsky): 77 (60-100); limited/disseminated disease (LD/DD): 63/49. Response after the 2 first courses of chemotherapy was:

<table>
<thead>
<tr>
<th>All patients</th>
<th>LD</th>
<th>ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>10</td>
<td>58</td>
</tr>
<tr>
<td>PR</td>
<td>16</td>
<td>102</td>
</tr>
<tr>
<td>Failure</td>
<td>16</td>
<td>102</td>
</tr>
<tr>
<td>Toxic death</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Early death</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
| We obtained 14 CR, leading to a total of 30 CR (LD and DD). Median survival was 44 weeks in LD and 47 in ED. These was no difference between median survival of early CR (73 weeks) and late CR (78 weeks). 2 year disease-free survival will be available by the end of 1986. The main toxicity was severe leukopenia (grade I-IV); other side effects were nausea, vomiting, alopecia, and mild thrombocytopenia. Severe infections were observed in 12% (5 toxic deaths). In conclusion, CAV is effective but relatively toxic regimen for SCLC.

COMBINATION CHEMOTHERAPY WITH CYCLOPHOSPHAMIDE, ADRIAMYCIN, VINCristine IN SMALL CELL LUNG CANCER. ANALYSIS OF RESULTS.

P. Kosmidis, Ch. Bacoianis, G. Michaloudis. 2nd Oncology Unit St. Agnaniy Cancer Hospital Athens GREECE.

Purpose of our study was to investigate the efficacy of the combination chemotherapy Cyclophosphamide Adriamycin and Vincristine (CAV) in small cell lung cancer (SCLC). Twenty two evaluable patients fulfilled the established criteria. 21 were males and 1 female. The average age was 63.6. Localized disease was in 14 patients whereas 8 patients had generalized disease. The treatment was scheduled as follows. Cyclophosphamide 500mg/m$^2$, Adriamycin 45mg/m$^2$, and Vincristine 1.4mg/m$^2$. The cycles were given every 3 weeks. Sixteen patients (72.8%) responded (3 complete and 13 partial) and survived up to now by average 10.3 months. Four patients had stable disease with an average survival 7 months. Two patients failed to respond in this regime and survived 5.5 months. Regarding toxicity; neurotoxicity was mild while cardiac toxicity appeared in one patient. Brain metastasis appeared in seven patients who had completed their treatment. No one had prophylactic irradiation to the brain.

Based on these results SCLC is chemosensitive tumor and the combination CAV is effective.

FOUR DRUG REGIMEN VS. THREE DRUG REGIMEN IN LIMITED SMALL CELL LUNG CANCER (SCLC). A RANDOMIZED STUDY. T.A.V. Nikkanen*, M. Jakobsson**, M. Järvenpää**, L. Cipparelli****, N. Ojala***, S. Palohelma**, and P. Nordman, Department of Radiotherapy, University Central Hospital of Turku*, Central Hospital of Middle Finland, Jyväskylä**, Department of Diseases of Chest, Central Hospital of Kanta-Häme, Tampere***, Department of Disease of Chest, University of Turku**, Department of Radiotherapy, University Central Hospital of Tampere****, Department of Disease of Chest, Satakunta Hospital****, Finland.

Two chemotherapy (CT) regimens VAC-VP-16 and VAC were compared in limited SCLC. The agents were administered as follows: vincristine (V) 1 mg/m$^2$ (max. 2mg) i.v. on day 1, adriamycin (A) 50mg/m$^2$ i.v. on day 1, cyclophosphamide (C), 750mg/m$^2$ i.v. on day 1, etoposide (VP-16) 80 mg/m$^2$ i.v. on days 2-4, regimen VAC is same without VP-16. Both CT regimens were given q. 3 weeks x 9 or until progression. Radiotherapy (RT) was given to involved areas to total dose of 46-48 Gy/6 weeks between 2nd and 3rd course of CT. Those patients were considered evaluable who had received two courses of CT and the planned RT. Preliminary results:

<table>
<thead>
<tr>
<th>VAC - VP-16</th>
<th>VAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable cases</td>
<td>27</td>
</tr>
<tr>
<td>Complete response</td>
<td>4</td>
</tr>
<tr>
<td>Partial response</td>
<td>2</td>
</tr>
<tr>
<td>CR + PR</td>
<td>18</td>
</tr>
<tr>
<td>Survival at 16 months</td>
<td>24</td>
</tr>
<tr>
<td>MST, months</td>
<td>11.0</td>
</tr>
</tbody>
</table>

Most common side effects were hematologic toxicity, alopecia, nausea and vomiting. Hematologic toxicity was more common in VAC-VP-16 than in VAC regimen.

COMBINATION CHEMOTHERAPY WITH CYCLOPHOSPHAMIDE, ADRIAMYCIN, VINCristine IN SMALL CELL LUNG CANCER: RESULTs.

J.A.V. Nikkanen*, M. Jakobsson**, M. Järvenpää**, L. Cipparelli****, N. Ojala***, S. Palohelma**, and P. Nordman, Department of Radiotherapy, University Central Hospital of Turku*, Central Hospital of Middle Finland, Jyväskylä**, Department of Diseases of Chest, Central Hospital of Kanta-Häme, Tampere***, Department of Disease of Chest, University of Turku**, Department of Radiotherapy, University Central Hospital of Tampere****, Department of Disease of Chest, Satakunta Hospital****, Finland.

The study was performed in patients with small cell lung cancer previously treated with 6 chemotherapy according to CAV regimen. One group (CAV) was given to chemotherapy with a combination of pheno- and radiotherapy. Patients relapsed after primary therapy or with a 2nd CR response to it were submitted to a second-line chemotherapy. This treatment consisted of VP-16 and Adriamycin or combination of these drugs with etoposide. Application of second-line therapy resulted in objective response in about 40% of patients. The treatment was more effective in patients responding to previous chemotherapy than in those with primary in responsive state. Radiotherapy given in primary treatment influenced the results of secondary chemothera-py by decrease in response rate. There was no significant difference in overall response between regimens applied in secondary therapy. However, complete response were recorded only in patients treated with 4-drugs regimen. The beneficial effect of second-line chemotherapy in small cell lung cancer patients was also found in analysis of survival time in responders and non-responders groups. Additional group of secondarily non-treated patients comparable with respect to age, gender, stage of chemotherapy and clinical situation served as a control for comparison of survival.
3853  
ALTERNATING RADIOThERAPY (RT) AND CHEMOTHERAPY (CT) IN LIMITED SMALL CELL LUNG CARCINOMA (SCLC)  
T. Le Chevalier, H. Armand, H. Armand-Perrin, P. Ruffie, P. Buzynsky, M. Hartmann, J.L. Pico, M.L. Cedrigny,  
F. Benina, H. Sancio-Garnerie, J. Rouesse  
Institut Gustave Roussy, Villejuif, and ** Hospital intercommunal, Creteil, CLAMART, FRANCE  
Our alternating RT and CT schedules in SCLC were started in 1980, in an attempt to decrease toxicity of concomitant combinations and increase the effectiveness of sequential schedules. The alternating induction schedule included 6 courses of CT and 3 courses of thoracic RT according to the following schedule : CT—CT-RT (15 or 20 Gy)—CT—CT, where (-) represents a gap of 1 week. Total thoracic radiation dose was 45 or 50 Gy depending on the protocol. Prophylactic cranial irradiation (30 Gy) was given during the first course of RT. CT schedule was : Doxorubicin 40 mg/m2 d1, VP16213 75 mg/m2 d1-3, Cyclophosphamide 300 mg/m2 d3-6, Methotrexate 400 mg/m2 (4 folinic acid rescue) or CDDP 100 mg/m2 d2. A complete restaging, including fiberoptic bronchoscopy, was performed at the end of the induction treatment to confirm complete remission (CR). Seventy-three patients were included from May 1980 to June 1983. Mean age was 55.5 ± 7.5 years, mean performance status (PS) : 80.5 ± 9.2%. Summarized results : CR rate was 88%. Local recurrence after CR : 26.5%. Overall metastasis rate : 46.5%. Relapse free survival (RFS) at 2 and 3 years : 31% and 25%. Late acute hematological toxicity : 4%. Late complications in long term survivors are being evaluated. The major prognostic factor was the B.M. first 28 patients (following the first CT cycle) and the surgical toxicity : 4%. Late complications in long term survivors are being evaluated.  

3854  
SIMULTANEOUS COMBINATION OF CHEMOTHERAPY AND RADIOTHERAPY IN THE TREATMENT OF SMALL CELL LUNG CANCER - FIRST RESULTS. O.P. LARUE and H. SCHEUT  
Robert J. R. Clinic, Ronne, F.P.R.  
Between January 1977 and December 1984, 124 patients with oat-cell carcinoma of the lung (limited and extended disease) were treated by concurrent radio- and chemotherapy in our clinic. 19% patients were eligible for evaluation. All patients received 7 cycles of a high-dose chemotherapy regimen consisting of Ifosfamide and NCGL. There was a free interval of 4 weeks after each chemotherapy course. The radiotherapy was performed simultaneously to the chemotherapy using split-course technique. The total dose was given in daily fractions of 2 Gy on 5 days/week. The neumia tumor received a total dose of 50 Gy. In the case of distant metastases a palliative radiotherapy was given with doses ranging from 20 to 50 Gy. The side effects of the chemotherapeutic drugs for each pts determined with sensitivity assay. These pts received in 3 changes of growth medium and incubated for 10 days. Suspensions were prepared from the specific cell lines, supplemented with 15% FBS was used as growth medium. All of SCLC and about 50% of non-SCLC were continuously cultured for long term by using this culture method. We have established 18 SCLC lines and 16 non-SCLC lines in our institute to date. At passage 2 or 3, a drop of cell suspension was seeded to each wells and drug solutions at serial concentrations were added. After each exposed time, the drug solutions were washed in 3 changes of growth medium and incubated for 10 days. 13 pts who underwent surgery for SCLC between may’79 and april’82 (402) of these pts had stageIIIIV tumors, received adjuvant CT which consisted of ADR + VCR. 1 year survival of these pts was 9/13 (692) and 2 year survival was 5/13 (385). From may’82 to april’85, 15 pts, (6402) had stageIIIIV tumors, underwent surgery and tumor cells from these pts have been examined with a panel of 10 drugs for sensitivity. These pts received adjuvant CT which consisted of most effective two drugs for each pts determined with sensitivity assay. 1 year survival of those pts with a minimum follow-up in excess of 1 year was 13/13 (100%) and 2 year survival was 3/13 (23%). Our study shows that adjuvant chemotherapy with sensitivity assay is significantly superior to those with ADR + VCR in survival of the pts with SCLC.
Thirty-two ptes with SCCL were treated from November 1984 with alternating combined chemotherapy as follows: 3 cycles of Adriamycin 50 mg/m² day 1, i.v., if or oxalite 1.4 mg/m² day 3 i.v. and VP-16 120 mg/m² i.v., day 1, 2, 3, i.v., followed by 3 cycles of Cisplatin 100 mg/m² day 1 i.v. and Cyclophosphamide 600 mg/m² day 1, i.v. and then 3 further cycles of ADM plus VCR plus VP-16 followed by 3 cycles of CDDP and CRY. All the pts were male: median age 59 (range 45-76); F.S. according to ECOG 0-2 (median 0). In 22 pts the disease, evaluated according to current staging criteria, was limited and in 10 pts extended disease. For prevention of nephrotoxicity by CDDP hydrorotation and forced diuresis with mannitol was employed and for prevention of gastrointestinal toxicity we used metoclopramide combined with butabarbital time and hydrocortisone. No pt had prior treatment with chemotherapy and/or radiotherapy. At present only 27 pts are evaluable as 5 pts have not yet completed the entire course of therapy. We observed C.B. in 21 pts (67.7%), P.M. in 12 pts (44.8%), S.B. in 2 pts (7.1%). Duration of response had a range of 3-12 months. Survival range was 4-12 months. Nausea and hematological tolerance were good and g.i. toxicity was acceptable. These few preliminary results may be considered encouraging, especially in the high response rate (CR + PR = 85%). However C.B. was observed only in L.D.

**3858**

**PHASE II TRIAL WITH ETOPOSIDE IN REFRACTORY OR RELAPSED OVARIAN CANCER**

J. FISCHER, H.A. MEENTJES, A. HEIDLEBEN

Dept. Obstet. and Gyn. Univ. Freiburg, FRG

Therapeutic possibilities in refractory or relapsed ovarian cancer are very limited and give in general a low response rate around 20% and a median survival less than 12 months. Etoposide - a podophyllotoxin derivative - has shown promising antitumor activity against ovarian cancer in several phase II trials. We have tested Etoposide in a phase II trial since July 1985. In November 1986 12 patients are fully evaluable and have finished the therapy. The trial still goes on. Since August 1986 6 more patients entered the trial, but they are at the moment not fully evaluable. The drug dosage used was: 1200 mg/m² per os day 1-5 or 120 mg/m² intravenously day 1-3. Causes will be given in four weekly intervals provided that the patients have recovered from myelotoxic side effects. Patient characteristics are as follow: median age 59 (range 49-74); median performance status: WHO 1, prior chemotherapy: EP 9 patients, CAP 2 patients, AC 1 patient referratory ovarian cancer: 5 patients (42%), relapsed ovarian cancer: 7 patients (58%). For evaluation of response the WHO criteria will be used. Two patients with CR (response rate 17%) and 3 patients with stabilisation of disease (NC) were observed. 7 patients showed no response (PD). The estimated median progression free survival is 33 weeks, the median overall survival is 38 weeks (CR 60 weeks, PD 28 weeks). The myelotoxic side effects are as follow: WHO grade II 7, grade III 1. Neutropenia occurred in 2 patients and of <1000 in 2 patients. Thrombocytopenia with platelets count <50 000 occurred in 2 patients. Eight patients had anaemia WHO grade II 4 and III 4. Neurotoxicity (1 patient), alopecia (8 patients). No other toxic side effects were observed. Conclusion: Etoposide has shown in 12 patients who were heavily pretreated with high-dose Cisplatinum and Cyclophosphamide an objective antitumor activity. But further studies and longer follow-up are needed to establish this therapy as second line treatment of choice in advanced ovarian cancer.
A PHASE II TRIAL OF EPI-ADRIAMYCIN (E), CYCLOPHOSPHAMIDE (C) AND CIS-PLATINUM (P) IN ADVANCED OVARIAN CANCER PATIENTS (OCP).

Landoni F., Marsden S., Epi A., Redaelli L., Yasmena L., Bonazzi C., Torri W., Panzigni C.

Oncology Research Institute, Sofia, Bulgaria

A phase II trial of E (60-90 mg/m^2 iv) and C (1 gr/m^2 iv) to P (20 mg/m^2 OSI) was conducted in 37 F.I.G.O. stage III - IV untreated OCP. The drugs were given sequentially: E+C for 2 cycles of 21 days each, followed by 2 cycles of P in responding pts; pts with stable disease received 5 cycles. Secondary look surgery (SLO) was performed at the end of the P cycles (approx. 100 days). Pts were then treated with 4 further cycles of the 3 drugs given simultaneously but with P delivered to (50 mg/m^2). P characteristics were as follows: stage III, 34; iv, 5; residual tumor after 1st surgery: < 5 cm, 2; < 5 cm, 16; > 5 cm, 19; histotype: serous, 25; undiff., 6; FIGO grade: 1, 5; 2, 1; 3, 27; SLO was performed on 29 pts. Of the 8 remaining pts, 6 were progressed (PD) and 2 clinical PRs. Pathological responses were: 7 Cts, 15 PRs, 5 SDs and 10 Pts. Pts in response (N=24) or with PD (N=4), were further treated with PEC (P 150 mg/m^2 iv) or PAC iv (650 mg/m^2 iv). At the end of 4 cycles response was assessed by laparotomy. In 4 cases the second treatment enhanced the response status, while of the remaining 24 pts, 1 progressed and 23 remained stable suggesting that, in advanced ovarian cancer, a prolonged period of treatment is probably not useful. The regimen was mildly toxic with no patient experiencing a toxicity above ECOG grade 3. The sequential combination of E+C+P is an active regimen in advanced ovarian cancer. The observed overall response rate is 65%, compatible with a true response rate from 47 and 80% (Cl). Partially supported by FARMAPHARO-CHIRURGIA, ITALY.

CHEMOTHERAPIC REGIMENS COMPRISING BIOCISPLATINUM (CIS) IN OVARIAN CANCER (2003)

Vassena L., Biola2zi M., Popova, T.Kirilov, D.Daskalov

Res. Oncological Inst., Sofia, Bulgaria

From June 1982 to October 1995 we have included the Bulgarian cytotoxic drug BioCisplatinum (Cis), in the therapeutic regimen of 48 ovarian cancer patients. Their average age was 46 years. The distribution according to surgical stage was as follows: stage I 6 patients; stage II-6 pts; stage III 34 pts; stage IV-2 pts. Complete response was observed in 29 cases, the remaining 19 ones displaying partial response. The most important side effects were intractable vomiting and manifestation of asymptomatic bacteriuria. In 5 of the cases the therapeutic regimen included abdomenopelvic teletheraphy as well. Their outcome was invariably fatal.
EFFECTIVE MULTIMODALITY TREATMENT OF ADVANCED (STAGES T IIIC-IV) EPITHELIAL OVARIAN CANCER:
A. Fournier, M.D., R. Coakland

Diagnosed with the results of Adriamycin, Cytoxan, Cisplatin chemotherapy, in 1985 we embarked on a study using a combination of Progestin and 2 chemotherapeutic agents in patients with advanced epithelial ovarian carcinoma. Following surgery, patients were given 4 weekly courses of Cisplatin (1 mg/kg), Adriamycin (50 mg/m²) added to C.B.P. on weeks number 1 & 3 and Leucovorin (100 mg/m² IV over 4 h) followed by 5FU (500 mg/m²) was added on week 2-4.

After a 2-3 weeks rest, patients received alternating courses of high dose Methotrexate (75 mg/m²), Leucovorin (10mg/m²) + Adriamycin (50 mg/m²), Depsorbera 1 mg/m² was given with each course of chemotherapy. After 5-8 months, patients were advised to have a second look laparotomy. Those with no residual disease were given oral Cytoxan 50 mg b.i.d. 3-5 months. Those left with small residual disease were given intraperitoneal PDR and along with those with large residual disease were given further chemotherapy beginning with the inducing regimen. The data of 21 patients is being presented. Three patients had Stage IVA and 17 had Stage IIIB disease; all patients had adenocarcinoma. Sixteen patients had TAH & BSO with or without lymph node biopsies, two patients had tumor biopsies, 1 had O.S.O, and 1 patient underwent U.S.O. Four patients had a second look laparotomy and of these 3 died with reactivated disease after an initial complete clinical response. With 1 to 5 years follow-up, 16 patients are alive & well without evidence of disease. Two patients developed mixed mesodermal sarcoma, 1 is alive and another died with disease. Two parents with Stage IV disease died one of whom refused second look laparotomy. Nine patients were histologic complete responders as determined by biopsies. Two patients refused second look laparotomy and 1 had U.S.O, and 1 patient underwent biopsies, 1 had U.S.O, and 1 patient underwent biopsy. Two patients had tumor biopsies.

The situation and change (CR) vs. patient, therapy (±) response rate (%)

<table>
<thead>
<tr>
<th>scheme</th>
<th>CR (%)</th>
<th>PR (%)</th>
</tr>
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<tbody>
<tr>
<td>a)</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>b)</td>
<td>47</td>
<td>20</td>
</tr>
<tr>
<td>c)</td>
<td>47</td>
<td>19</td>
</tr>
<tr>
<td>d)</td>
<td>26</td>
<td>25</td>
</tr>
</tbody>
</table>

Summary 32 19 51

The first results show that DDP is a very effective cytostatic drug, whereas the efficacy can be improved by combination with CAI. In considering the effectiveness of DDP it is evident that the response rate became higher on the duration of the effective drug was longer than in DDP free chemotherapeutic scheme.

On the other hand, it must be emphasized that DDP should be applied at present in the second line therapy.

COMBINATION INTRACAVITARY CHEMOTHERAPY WITH CISPLATIN, CYTOSINE ARABINOSE, AND BLEOMYCIN FOR ADVANCED OVARIAN CARCINOMA.
S. Bergen, M.A. Rettenmaier, M.L. Berman, P.J. DiSaia, University of California, Irvine Medical Center, Irvine, California, U.S.A.

Pharmacokinetik studies have demonstrated that there is a pharmacodynamic advantage to the intraperitoneal administration of cisplatin, cytosine arabinoside (ara-C), and bleomycin. Twelve patients with advanced ovarian carcinoma have received a total of 43 courses of this drug combination. In addition, all patients received intravenous sodium thiosulfate rescue. Nausea and vomiting was seen in 81% of patients. Other side effects noted were: fever 27%, ileus 18%, severe abdominal pain 9%, and weakness and anorexia 9%. Renal insufficiency occurred in only one patient who was treated shortly after 1PF contrast media was given; leukopenia (WBC < 3,000) and thrombocytopenia (platelets ≤ 100,000) occurred in only one patient. Eight of twelve patients are evaluable to date. Of these, 25% had a complete response, 25% a partial response, and 50% progression of their disease. Those patients that appear to benefit most from this therapy are those with minimal (< 1 cm) residual disease. In those patients where the drugs were administered as salvage with bulky disease present, little if any response was noted.
1006

TUESDAY • AUGUST 26 • AFTERNOON

M-59: OVARIAN CANCER: CHEMOTHERAPY


From September 1984 to October 1985, 20 women with advanced epithelial ovarian cancer not previously submitted to RT or chemotherapy (CT), were treated with PAC (CDDP 50 mg/m², ADM 50 mg/m², CTX 150 mg/m²) or PEC (Epirubicin 60 mg/m² in a dose of 45 mg/m²) for 10 cycles. All drugs were administered iv q 3 wks. 10/10 PAC and 8/10 PEC patients are currently evaluable (too early to evaluate and lost to follow up after 3 cycles). The patients with initial optimal debulking surgery (10/30, 7 cases) were treated with 6 cycles of CT before second look (SL) if IV DCS was not possible before starting chemotherapy. It was done after 3 cycles of PAC or PEC and 6 additional cycles were administered before SL. At present moment it is possible to evaluate the clinical complete response (CCR) to initial CT for all 10 patients and pathological CR (PCR) after SL in 12 (6 PAC and 4 PEC). The characteristics of the women and the responses obtained are illustrated below:

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>AGE STAGE</th>
<th>RESPONSE</th>
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<tbody>
<tr>
<td>PAC</td>
<td>50 5 5 5 5 90 3/10 8/10</td>
<td>1/2</td>
</tr>
<tr>
<td>PEC</td>
<td>45 6 2 0 0 0 3/8 8/9</td>
<td>0</td>
</tr>
</tbody>
</table>

Toxicity was acceptable. Leukopenia was present in 9/10 (50%) patients but only in 2 it resulted of grade III and in grade IV (WHO criteria). Thrombocytopenia was not observed. Anemia was present in 7/9 patients (39%) but only in 1 it was grade III and in grade I. No conclusions can be drawn about duration because of the short follow up but we can state that PAC and PEC are equally active in ovarian cancer. Necrosis of patients continues only on PEC because of the supposed less cardiotoxicity of Epirubicin.

3869


A group of 41 women suffering from epithelial ovarian cancer in different stages of the disease was treated with the use of intraperitoneal (ip.) chemotherapy and followed during the period of 3 to 48 months. The number of applications was 198, while the average number with one of the patients was 4 and the maximum number was 10. Pharmacokinetics and toxicity of cis-DDP, CCRD and TMX after the use of ip. application was followed in 15 women. The tumor gets into contact with higher concentration of the drug when applied ip. and its clearance of abdominal cavity is usually slower than when applied intravenous. Lower concentration of the drug in urine reduces the appearance of nephrotoxicity. After a few hours the amount of the drug in the blood, when having been administered ip. as well intravenous, will be approximately equal. In spite of the fact that when administered in the remission period, the tumor only into the depth of 3 cm, the response rate is higher than 50%, moreover it has been proved that when cis-DDP was administered ip., liver metastases decreased.

3870

SECOND-LINE CHEMOTHERAPY IN ADVANCED OVARIAN CANCER PATIENTS WITH: HEXAMETHYLAMINE, VEPESID AND 5-FUROURACIL - PRELIMINARY RESULTS.

P. Dittrich, Ch. Leovelo, F. and Salzer, H.

Department of Chemotherapy, Department of Gynecology and Obstetrics, University of Vienna, Austria.

In most of the patients with the initial diagnosis of an advanced ovarian cancer, tumor progression or relapse after transient and even after longer lasting remissions occur in the vast majority (about 90%) of all cases. The response to the consecutively necessary second-line treatments generally is reported to be in the range between 10 - 15%. One of the reasons for this low rate of response may be the development of chemoresistance under long lasting polychemotherapy. The concept of the second-line regimen used is an attempt to take into account this phenomenon. As the first line treatment of our ovarian cancer patients regularly consists of Adriamycin, cisplatin, vincristine, cyclophosphamide and methotrexate, the following regimen was used for second-line therapy:

5-FUROURACIL (1000 mg/m²) i.v. days 1 + 8
HEXAMETHYLAMINE (50 mg/m²) p.o. days 2 - 8
VEPESID (300 mg/m²) i.v. days 16 + 24
Duration of treatment: continuously; day 31 is equal day 1

Partial remissions were observed in 5 patients (28%), no change in 7 (39%) and 6 patients (34%) tumor progression was observed. Second-line therapy was generally well tolerated in spite of the pretreatment. Leukopenia was observed in 3 cases, almost all women indicated gastrointestinal side effects in form of nausea but only rarely vomitting. No alopecias caused by this therapy was observed.

The second-line chemotherapy regimen used shows a relatively high response rate (28%) accompanied by a low incidence of rather mild side effects and may be applied at an outpatient base.

3871

TAMOXIFEN/ZITAZONIUM ADMINISTERED AS A SINGLE AGENT IN THE PALIATIVE TREATMENT IN ADVANCED OVARIAN AND ENDOMETRIAL CANCER.

E. Ploch, J. Stalnochorz, Inst. Oncology Warsaw, Poland.

The efficacy of tamoxifen in other than breast tumors is a matter of discussion.

Ovarian cancer: 20 pts in age 28-63 with far advanced ovarian cancer, who all had received prior chemotherapy and progression of disease. The most of pts responded to tamoxifen, demonstrated prior chemotherapy and the combination of tamoxifen and progestin/the most effective treatment. Antiestrogen seems to be efficient as a second line drug in advanced ovarian cancer.
3872 SEQUENTIAL HORMONAL TREATMENT IN OVARIAN CANCER.
A. Jakobsen*, K. Bertelsen** and A. Selj*,
Institute of Cancer Research and Dep. of Oncology, Aarhus University Hospital* and Dept. of Oncology, Odense University Hospital**, Denmark.
Sequential hormonal treatment is interesting from a theoretical point of view. It has been shown to be more advantageous compared to conventional hormonal manipulation in breast cancer, but only few studies have so far been published. The present work represents an investigation of sequential anti-oestrogen (Tamoxifen 10 mg x 3) and gestagen (Medroxyprogesterone acetate 400 mg x 2) in advanced ovarian cancer. Twenty-five patients entered a phase II trial and 11 are so far evaluable for response. According to WHO criteria none of the patients responded after 2 months of treatment.
6 patients had progressive disease and 5 patients had no change. The results of which an update will be presented thus indicate that this treatment is ineffective in advanced ovarian cancer.
(1Supported by the Danish Cancer Society.)

A report is given on the behaviour of blood coagulability in 30 patients before, during and after the treatment.
The following parameters which characterized the blood coagulability have been examined: Partial-Thromboplastin-Time (PTT), Reptilasetime, Fibrinogen-level, Antithrombin-III (AT-III-concentration and activity), α2-Antitrypsine, α2-Macroglobuline, Fibrin-degradation products (FDP) and Radio-fibrinogen-Test-system. In depending of the tumour bulk the following parameter were increased:
- PTT and Reptilasetime were prolonged.
- Inhibitors of blood coagulation (AT-III, α2-Antitrypsine and α2-Macroglobuline) had in average 2 fold higher activity and concentration as normal.
- The range of FDP were increased 2-3 fold in contrast to normal.
This abnormal coagulability becomes more and more normal in depending of the successful tumour chemotherapy.
The importance of this findings as a marker of the efficacy of treatment is not jet proved.

3874 PLATINUM (P), VINBLASTINE (V) AND BLOMYCIN (B) IN EXTRA-EMBRYONAL TERATOMAS OF THE OVARY.
Combination chemotherapy known as PVB was given to 12 patients with extra-embryonal teratoma of the ovary.
Six pts had Endodermal Sinus Tumor (EST) and 6 mixed tumors (EST + Embryonal carcinoma; 1 EST + Immature Teratoma; 1 EST + Dysgerminoma; 1 EST + Embryonal carcinoma + Dysgerminoma + Immature Teratoma; 1 Embryonal carcinoma + Chorion- carcinoma; 1). The median age was 21 years (range 9-30).
After primary surgery 4 pts were classified as stage I, 4 as stage IIIC-III, 3 as stage IV and 1 as recurrence. PVB was administered at standard doses: P 20 mg/m² iv from day 1 to 5; V 6 mg/m² iv, days 1 and 2; B 18 mg/m², 2, 9, 16. Cycles were repeated every 21 days x 5 cycles. All pts were monitored by AFP and HCG levels. All 12 pts but one (EST at stage III) achieved complete remission and 4 relapsed after 6, 6, 7 and 9 months from response. All failures were treated with salvage chemotherapy and died at 6, 18, 19, 20, 27 months from histologic diagnosis. Seven pts were alive without evidence of disease with a median follow-up of 29 months (range 5-59 months) from histologic diagnosis.
Toxicity was evident in all pts. Severe myelodepression was observed in 7 pts (4 with sepsis) and neurologic toxicity in 5 pts. Comparing these results with those achieved in a previous series treated before the introduction of PVB (7/8 pts died within 17 months from histologic diagnosis) it appears that PVB administration has improved the prognosis of extraembryonal teratomas of the ovary.

3875 PROSPECTIVE-RANDOMIZED TRIAL IN OVARIAN CANCER OF THE STAGES III AND IV: CHANGING-SCHHEME (ADRIAMYCIN/CISPLATIN-VINCRISTINE/HYDROXYDOSE METHOTREXATE) VERSUS A/P (ADRIAMYCIN/CISPLATIN) VERSUS A/C (ADRIAMYCIN/CYLOPHOSPHAMID)
The multicentric study, started in 1980, comprises two different study groups, to which 160 patients were randomly allocated. A new polychemotherapy consisting of 3 different successive cycles of non-crossresistant drugs was compared with two chemotherapeutic standard regimens. The new therapy, called "changing-scheme" comprises Adriamycin/cisplatinum as first part vincristine/cyclophosphamide as second one and high dose methotrexate (HD-MTX) followed by a leukocvin rescue as third one, with monthly application intervals between the 3 successive parts. The two other therapies to which the women were randomized consisted of Adriamycin/cyclophosphamide (A/C) or of Adriamycin/cisplatin (A/P). Mean survival times of the patients under the changing-scheme and under A/C-or A/P-regimens were 19,4, 15,8 and 16,3 months respectively. The corresponding remission durations of the changing-scheme and of the A/C regimen were 16,3 and 12,1 months respectively, showing an advantage for, but no substantial difference in favor to the new therapy for an unselected group of women. Remission rates of the three different chemotherapies were 85% for the changing-scheme, 78% for the A/C-regimen and 83% for the A/P-regimen. In particular, the subgroups of women with highly differentiated tumors and of women without ascites seem to profit from the new therapy protocol.
RESULTS IN MANAGEMENT OF MEDICAL EMERGENCIES AND TREATMENT INSTITUT JULIE BORDET, BRUSSELS, BELGIUM.

Person susceptibility which may be considered as a genetically fixed aberration due to changes in oncogenesis plays an important role. Human cancers and their prototypes may be active in human tumors as colon, lung, urinary bladder and so on. Environmental factors, the impairments of immune defense functions and persons susceptibility are the basis on which the treatment modalities function as a triggering factor. Before onset of therapy all these factors would be taken into consideration and less aggressive but effective therapeutic modalities would be chosen.

3879 RESPONSE SURFACE METHODOLOGY (RSM): A NEW STATISTICAL TOOL FOR USE IN CLINICAL TRIALS. GAYE.L.; SAMPER, M. SAINT JOSEPH'S HOSPITAL, INDIANA UNIVERSITY,

In a 4-year study, we analyzed various data collected from 916 patients admitted to our medical oncology ICU. Among these patients, 145 (16%) were admitted for medical emergencies of various origin: respiratory (143), infectious (182), cardiac (127), digestive (115), hypercalcemic (102), and various other problems (113). The underlying diseases were: breast carcinoma (262), lung cancer (263), head & neck tumors (92), lymphomas (72), other gynecologic tumors (72), GI tumors (53), leukemia (57), and so on.

Therapeutical interventions until now used, not only cure but also cause the tumor. Person susceptibility which may be considered as a genetically fixed aberration due to changes in oncogenesis plays an important role. Human cancers and their prototypes may be active in human tumors as colon, lung, urinary bladder and so on. Environmental factors, the impairments of immune defense functions and person susceptibility are the basis on which the treatment modalities function as a triggering factor. Before onset of therapy all these factors would be taken into consideration and less aggressive but effective therapeutic modalities would be chosen.

3877 RESULTS IN MANAGEMENT OF MEDICAL EMERGENCIES AND TREATMENT MONITORING IN A MEDICAL ONCOLOGY INTENSIVE CARE UNIT (ICU).

In a 4-year study, we analyzed various data collected from 916 patients admitted to our medical oncology ICU. Among these patients, 145 (16%) were admitted for medical emergencies of various origin: respiratory (143), infectious (182), cardiac (127), digestive (115), hypercalcemic (102), and various other problems (113). The underlying diseases were: breast carcinoma (262), lung cancer (263), head & neck tumors (92), lymphomas (72), other gynecologic tumors (72), GI tumors (53), leukemia (57), and so on.

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3876 SOME ASPECTS ON THE APPEARANCE OF SECONDARY TUMORS AFTER THERAPY.

Among 275240 registered patients with malignancies secondary tumors were found in 8417 (3.05%) patients of both sexes. The most frequent tumors after therapy were tumors of the skin followed by tumors of the GIT and tumors of the respiratory and uroperitoneal system. In 898 (11.73%) untreated patients tumors of GIT were on the first place. Tumors of tumors of the skin, respiratory and uroperitoneal system. In 163 patients of both sex treated more than two years by chemotherapy alone, secondary tumors prevailed by 23.3% against 10.2% in untreated patients. The mean age of patients treated by all modalities was about 60 years. The mean time appearance of secondary tumors was 3 years.

Therapeutical interventions until now used, not only cure but also cause the tumor. Person susceptibility which may be considered as a genetically fixed aberration due to changes in oncogenesis plays an important role. Human cancers and their prototypes may be active in human tumors as colon, lung, urinary bladder and so on. Environmental factors, the impairments of immune defense functions and person susceptibility are the basis on which the treatment modalities function as a triggering factor. Before onset of therapy all these factors would be taken into consideration and less aggressive but effective therapeutic modalities would be chosen.

3878 MULTIVARIATE LOGISTIC REGRESSION ANALYSIS (MLRA) OF PROGNOSTIC FACTORS (PF) IN PATIENTS (PTS) WITH ADVANCED STAGE (AS) NON SEMINOMATOUS GERM CELL TUMORS OF THE TESTIS (NSGCT).

Despite the progress of chemotherapy (CT) all the pts with AS of NSGCT treated by the same protocol (protocol CT). Pts who had surgical removal of residual disease (SRD) if necessary, HCG and/or folate/potent (AFP) were measured by radioimmuno assay. 38 pts entered in this study in complete remission (CR) by CT SRD and 21 pts failed to be in CR.(P).

The probability (p) that a pt achieves a CR was assessed as a function of certain pf variables (V) using the technique of MLRA. The V included were those found significant in an univariate analysis: HCT, AFP, lung metastasis (LM), abdominopelvic mass (AM). The p to be in CR is p = exp(11.1/length) where h is a L of several k of p).

The technique estimating the coefficient is known under the name of maximum likelihood and the significance of V is tested using the likelihood ratio test. A CR of clinical V (V-AM/W) had been predictive value than a CR of marker V. The best CR selected was h = 12,0 - 0,051/CR - 0,045/AM. The correct overall prediction (pCR) was 0,81, correct pf of CR eventually 0,81 and correct pf of CR eventually 0,84. The if was validated in an independent sample of 49 pts.

The correct pf were respectively: overall 0,70, CR 0,69, CR 0,69. This model is currently used to anticipate those pts who have poor pf and who need a more intensive CT.

This work was supported by grant ICR 86-09.

For answers to your questions, I would need the specific questions related to the content of the provided text. Please provide the questions or areas of interest you wish to ask about.
COMPUTER SIMULATION OF PATIENT FLOW AND RATIONAL THERAPY IN DEPARTMENT OF MEDICAL ONCOLOGY, V.211

Computer simulation has been made for the who department of medical oncology, on the basis of four medical protocols for cancer patients. The protocols include surgery, radiotherapy, chemotherapy, and immunotherapy, either on ambulatory or stationary basis. The program calculate also optimal time for the beginning of therapy for each patient. The flexibility of program verifies the optimal usage of hospital beds and strict applying of various protocols. The program has been applied in defined time is calculated. The program also calculates the optimal usage of hospital beds in the time one of the main problems is the impossibility to combine regular and rational treatment with a high degree or total occupation of hospital beds. The computer simulation has been made for the who department of medical oncology, on the basis of four medical protocols for cancer patients. The program calculate also optimal time for the beginning of therapy for each patient. The flexibility of program verifies the optimal usage of hospital beds and strict applying of various protocols. The program has been applied in defined time is calculated. The program also calculates the optimal usage of hospital beds.

Various types of oncology medical protocols are in progress for different stages of carcinoma. By the time one of the main problems is the impossibility to combine regular and rational treatment with a high degree or total occupation of hospital beds. The computer simulation has been made for the who department of medical oncology, on the basis of four medical protocols for cancer patients. The program calculate also optimal time for the beginning of therapy for each patient. The flexibility of program verifies the optimal usage of hospital beds and strict applying of various protocols. The program has been applied in defined time is calculated. The program also calculates the optimal usage of hospital beds.

IN VITRO CYTOTOXIC TEST FOR PREDICTING HUMAN CANCER CHEMOSENSITIVITY. H. Tokita, N. Tanaka, Y. Hongo, S. Fujimoto, N. Makino, M. Takada, and H. Takamiya; Chiba Cancer Ctr. Res. Inst., Chiba Cancer Ctr. Hospital Chiba Univ.,* Chiba, Japan

The individual tumors have a different chemosensitivity. We have developed a simple in vitro chemosensitivity test against ovarian cancer, osteosarcoma, soft part tumor, breast cancer, stomach cancer, and colon and rectum cancers. Tumor tissue was minced with a razor blade. Approximately 10 mg of the cell clumps were poured into 0.4 ml of RPMI 1640 medium, which contained 10% fetal bovine serum and a certain concentration of anticancer drugs, and incubated at 37°C for 4 hr (A group) or 8 hr (B group). The drugs tested were MMC, CPM, MPL, and ACNU for A group, and BLM, 5-FU, ADM, CDDP, and MTX for B group. After incubation, the clumps were pumped down with a 23-gauge needle to obtain dispersed cells. The cells were smeared with a Pasteur pipette and dried quickly by air. Then the cells were fixed and stained with Giemsa. More than 100 cells per slide glass were examined microscopically. Typical morphological changes in the nucleus were karyorrhexis for A group drugs and karyopyknosis for B group drugs, respectively. The individual tumors showed different sensitivities to these drugs. Positive rate of A group drugs was about 20%. The patients were treated in accordance with different therapy schedules. A good correlation between the in vitro responsiveness and the clinical results was noted in osteosarcoma and ovarian cancer.
INDIVIDUAL SENSITIVITY (IS) OF THE MALIGNANT TUMORS TO CYTOSTATICS ACCORDING TO THE CLINICAL STAGE, HISTOLOGICAL TYPE AND LOCALISATION, L. Levchikov, G. Gacek, E. Kirov, and T. Kirova, Res. Inst. of Oncology, Sofia - 1156, Bulgaria

Aim: The IS of the malignant tumors to cytostatation could be determined by a high-sensitive and rapid "in vivo" method.

Technique and Patients: Six experimental (ET) and 19 human tumors (HT) have been tested by a modified Bogden's method (Exp. Cell Biol. 41: 281, 1979) with additional frozen-section at the tumor tissue, flow microfluorometry and histological examination of the xenografts on the 4th and 6th day.

Results: The IS of the ET evaluated on the 4th or 6th day after the transplantation corresponds completely to that established by the conventional methods. About 20-45% migrated normal murine cells were found on the 6th day in the xenografts. No correlation was found between the IS of the investigated HT to cytostatation and the clinical stage, histological type and localisation. All the tested lung metastases had a good response to Vepesid and Cis-Platinum.

Conclusion: The modified "in vivo" method has proved to be more reliable than the other "in vivo" methods to determine more precisely and effectively the IS of the tumors to the already accepted in the clinic and to any new cytostatics.

SERUM CONCENTRATIONS OF ANTICANCER AGENTS INJECTED DURING TOTAL PARENTERAL HYPERALIMENTATION WITH AMINO ACID IMBALANCE.

Nobuo Murata and Tokio Umeda, Dept. of Surgery, Tokyo metropolitan Fuchu General Hospital, Tokyo, Japan

Amino acid imbalance (AAI) has been reported to have some toxic effect to malignant tumor cells. The authors observed the amino acid imbalance (AAI) depriving methionine and cystine from ordinary amino acid compound for protein source were useful for an adjuvant to cancer chemotherapy experimentally and clinically. It was also found that far less amount of anticancer drugs than ordinary doses showed prominent antitumor effect and that the adverse effect of the drugs became stronger. Therefore, in order to define the metabolism of anticancer agents under AAI condition, ten patients with cancer were administered Tegafur or MMC during AAI condition by total parenteral hyperalimentation (group 1) and serum concentrations of Tegafur and 5-FU 48 hours after the infusion of Tegafur were 10.9 ug/ml (mean) and 0.028 ug/ml (mean) respectively. In control subjects who were treated by the same drug dosage (group 2) serum concentrations of Tegafur and 5-FU were 4.61ug/ml and 0.018 ug/ml respectively. These data were not significantly different by between the two groups. The disappearance curve for these agents was almost equal between them. The same result was obtained when MMC was administered.
ALTERATION IN PROTEIN AND ENERGY METABOLISM.

C. Drott, 3888

TUESDAY • AUGUST 26 • AFTERNOON

Possibility. Home-TPN is now under evaluation as an additional treatment. Their food intake was severely reduced. Urinary nitrogen excretion, protein metabolism.

The role of nutritional support as an adjunct treatment to chemotherapy is unclear. Aim: To evaluate whether host deterioration in chemotherapy is due to nutrition deprivation or due to toxic blockade on protein metabolism.

The initial response time (15.5 vs. 28.8 days) and the effects of the treatment were 30.5% (30/94) in IHC vs. 10.5% (2/19) in non-IHC (p<0.05). The initial response rate was 39.6% (54/134) and the number of response was closely related to the difference of drug sensitivity of tumor types. For example, it was 60.0% (3/10) in head & neck, 66.7% (6/9) in breast, 55.6% (10/18) in colon, 25.0% (3/12) in colon and 23.8% (5/21) in lung respectively. This effect on metastatic lymphnodes was 79.4% (27/34) and it was much higher than that of primary (48.1%) and other organ metastases (34.0%).

Clinical trials of phase IV and II study of Ile-1 angiotensin II will be reported.

EVALUATION OF THE MECHANISMS BEHIND CHEMOTHERAPY-INDUCED ANOREXIA, SERUM ZINC, AND IMMUNOCOMPETENCE IN SMALL CELL LUNG CANCER PATIENTS

Ada M. Lindsey, RN, PhD, and Barbara F. Pippin, RN, MS, University of California, San Francisco School of Nursing, 3611, San Francisco, California 94110, U.S.A.

Spontaneous decline in food intake may compromise the individual's ability to engage in meaningful activities and tolerance to anticancer therapy. The specific mechanisms which result in the anorexia observed with some malignancies remain unknown. Anorexia and taste changes have been shown to occur in various non-cancer populations in association with zinc deficiency. Both undernutrition and zinc deficiency have been shown to compromise immunocompetence. One purpose of this longitudinal descriptive study was to determine if anorexia was associated with zinc deficiency in a small convenience sample of males with small cell lung cancer. The subjects were followed from the time of diagnosis at 4-6 week intervals until death or for one year. To determine the extent of anorexia, intake was recorded on a self-report form for three days at each data collection interval. A computer program was used for nutrient analysis; caloric and zinc intake and the percent of RDA were determined. For the same three day periods subjects also recorded perceived taste changes. Blood samples were obtained at each point for serum zinc measurements. Changes in immunocompetence were evaluated using a battery of skin test antigens (candida, pumps, PPD). The mean age of 35-47 years and the mean smoking history was 71.6 pack years. Over a 7 month period following diagnosis, mean daily caloric intake declined 600 kcal and serum zinc levels (x = 7.3ug/dl) and in the majority, the immunocompetent status was compromised. Whether increasing zinc intake would have a positive influence on anorexia is a future goal in this and improving immunocompetence awaits further study. Anorexia is an important clinical problem in cancer patients and determining plausible explanations, associations, and clinical therapies are of significance.


It is essential for cancer chemotherapy to increase the effects to selective enhancement of drug delivery to tumor tissues together with selection of effective dose. The mean arterial blood pressure did not exceed 150 mmHg, while no increase in normal tissues. (Suuki et al JNCI:1981)

Based on the functional difference of microcirculation, IHC has been developed clinically since 1978. In the procedure of treatment, the mean blood pressure of the patients were maintained at 140-150 mmHg when anti-cancer drugs were administered along with the continuous intravenous infusion of angiotensin II. 1) In randomized controlled study on advanced gastric carcinoma treated with APM regimen, response rate was 42.5% (8/19) in IHC vs. 10.5% (2/19) in non-IHC (p<0.05). The initial response time (15.5 vs. 28.8 days) and the effect of the treatment were 30.5% (3/10) in IHC vs. 10.5% (2/19) in non-IHC (p<0.05).

In open trial, all over response rate was 39.6% (54/134) and the number of response was closely related to the difference of drug sensitivity of tumor types. For example, it was 60.0% (3/10) in head & neck, 66.7% (6/9) in breast, 55.6% (10/18) in colon, 25.0% (3/12) in colon and 23.8% (5/21) in lung respectively. 2) In open trial, all over response rate was 39.6% (54/134) and the number of response was closely related to the difference of drug sensitivity of tumor types. For example, it was 60.0% (3/10) in head & neck, 66.7% (6/9) in breast, 55.6% (10/18) in colon, 25.0% (3/12) in colon and 23.8% (5/21) in lung respectively. 3) The effect on metastatic lymphnodes was 79.4% (27/34) and it was much higher than that of primary (48.1%) and other organ metastases (34.0%).

In addition to these advantages, clinical results of phase IV and II study of Ile-1 angiotensin II will be reported.

NORMILIZATION OF ABNORMAL PLATELET ADHESIVENESS IN CANCER PATIENTS WITH VITAMIN E AND ASPIRIN

Sali, A., Bean, R., El Zarka, A., Hans, S., Wright, D. Melbourne University Department of Surgery and Oncology Unit, Repatriation General Hospital, Melbourne, Australia.

An association between tumors and the formation of thrombi has been known for over 100 years. Increased platelet adhesiveness which can occur in cancer patients is usually not effectively treated with aspirin. Vitamin E has been shown to decrease platelet aggregation in diabetes.

Cancer patients who were found to have increased platelet adhesiveness were studied. Platelet adhesiveness was measured using platelet count and the rate of blood flow through filters. Plasma Vitamin E was also estimated.

60 patients with increased platelet adhesiveness were treated with aspirin and Vitamin E or a combination of the two when either was not effective. In all but one of the patients it was possible to normalize platelet adhesiveness using the combination of aspirin and Vitamin E.

Vitamin E in combination with aspirin can be used to treat increased platelet adhesiveness in cancer patients when aspirin alone is not effective.
Hyperglycemia represents a frequent problem in ill patients receiving parenteral nutrition. In some patients, high doses of insulin are necessary to control this condition. The aim of the experience was to evaluate the role of FDP in controlling the wide glycemic variations following the high glucidic load during parenteral nutrition.

20 cancer patients were studied: all of them needed parenteral support for malnutrition. They were not affected by diabetes nor presented primary or secondary hepatic or pancreatic localization. The intravenous glucose tolerance test (0.5 g/kg) was performed in each patient at two different days following a cross-over design, after intravenous infusion of FDP (200 mg/kg) or placebo (P). Blood samples were taken just before the treatment (basal sample), immediately after the FDP or P infusion and 10, 20, 30, 60, 90 minutes after the glucose load. The basal glycemic values were similar to those before glucidic loading in all the patients and no significant differences were observed after FDP or P infusion. The glycemic peaks were respectively 197.5±13.6 mg/dl after FDP and 214.0±12.4 after P (P<0.01) 1 hour after glucose loading.

The areas under the glucose tolerance test curve were all reduced after FDP vs. P (P<0.01).

In conclusion, these results prove the possible role of FDP treatment in controlling hyperglycemia following glucose overload infusion during parenteral nutrition.

As a consequence of some preresco kinetics studies with labeled cistostatics as well as some experimental studies regarding polychemotherapy on the animals with experimental tumors it was elaborated mathematical models for interpreting the results with computerized thermograph PROME THBUS.

These studies give us the possibility to establish the optimal period for drug's administration, the control of the therapeutic effect, the optimal moment of administration again of cistostatics as a series of important parameters in therapeutic decision.

There are presented the results of selected treatments on the specific PROMETHBUS programs on clinical representatives cases and on lots of patients. The monitoring system was used for treating the breast tumors, lung cancer, ovarian cancer and malignant melanoma.
A new method for expression and comparison of body weight curves of experimental animals

Yohei It (1), Ryotchi Kituchi (2), Keisaku Tanaka (3)

(1) Bio-Medical Laboratories
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A new method for expression and comparison of body weight curves of experimental animals has been described. Control groups and generated 100 random numbers by using the successive data points can be treated and the data need not come from a normally distributed sample. The data can be used to express the curve; continuous function can be used to express the curve; and the successive data points can be treated simultaneously. Furthermore, the comparison of two curves can be done more efficiently by using discriminant analysis (Hotelling's T² statistic). The data need not come from a normally distributed sample.

We supposed body weight curves of experimental and control groups and generated 100 random numbers by using 12 standard deviation and the data as the mean. We proceeded to compare the two with Hotelling's T² method.

Comparison of body weight curves of experimental animals has been done by using t-test at each pair of data points. We have reported that a body weight curve of an experimental animal can be fitted to a parabola (Gans 70; 264, 293, 1979). T-test requires the data to have come from a normally distributed sample. When a parabola is used to express the body weight curve, a continuous function can be used to express the curve; and the successive data points can be treated simultaneously. Furthermore, the comparison of two curves can be done more efficiently by using discriminant analysis (Hotelling's T² statistic). Thus, the data need not come from a normally distributed sample.

We supposed body weight curves of experimental and control groups and generated 100 random numbers by using 12 standard deviation and the data as the mean. We proceeded to compare the two with Hotelling's T² method.
3900 INVESTIGATION PROGRAM FOR INTRAOPERATIVE RADIOTHERAPY. H.J. Hoekstra\(^1\), D.M. Mehta\(^1\), S. Terpstra\(^1\), D. Bakker\(^1\), M. Crommelin\(^1\), J. Oldhoff\(^1\)
Division of Surgical Oncology and Dept of Radiotherapy, Univ. Hospital Groningen\(^1\) and Dept of Radiotherapy, Catharina Hospital Eindhoven\(^1\), The Netherlands.

Intraoperative electron beam radiotherapy (IORT) is a relative new combined treatment modality utilizing surgery and radiotherapy. Prior to the clinical use of IORT an investigation program for intraoperative electron beam radiotherapy was initiated, in which the following aspects have been investigated: 1. technical, surgical and anesthetic aspects, 2. experimental tissue tolerance studies in a canine-model and 3. radiation procedures and dosimetric applications for IORT.

Based on our investigations it can be concluded that 1. anesthesia is not affected by IORT, 2. a horse-shoe shaped applicator with one square end and one circular end with a 15\(^\circ\) beveled angle can easily be used intra-abdominally, especially on sloping surfaces, 3. visualization and documentation of treatment fields during IORT is crucial, 4. a dedicated IORT operating table allowing precise control of lateral, longitudinal and vertical motions, facilitate the docking procedure, 5. 20 Gy IORT is well tolerated and finally 6. preoperative CT-scan information and an integral treatment planning system is crucial in IORT treatment.

3901 THE APPLICATION OF SEMICONDUCTOR DIALS IN THE COMBINATION WITH RADIATION THERAPY. M. Kubovics, Z. Zsoka, K. Szabó, I. Birkó, E. Sarkovics, S. Janovics
Univ. of Szeged, Szeged, EU.

Semiconductor dials were applied previously to radiation therapy on 22 patients with breast carcinomas and metastases in supraclavicular region. Metastases disappeared in 19 patients and 3 had no significant reduction of metastases.

Another group of 26 patients with breast carcinomas and metastases in supraclavicular region were treated only by radiation therapy. 20 patients had a reduction of metastases, they disappeared in only 1 patient and in 5 patients the size of metastases remained practically the same. Trials carried out on animals support the opinion that the laser application significantly decreases the tumour tissue response to radiation therapy.

3902 ON THE ROUTINE POSTAL CONTROL OF X-RAY UNITS WITH THERMOLUMINESCENT DOSEMETERS. P. Zsevôd, I. Polgar and L. Katona
Unioradiological Centre, Whit. Ebel Hospital, P-1146, Budapest, Unassi 26.

More than 40 orthovoltage X-ray units are operated in various Hungarian hospitals without their own dosimetric equipment and having no physicist. The aim of the postal TL technique is to find an inexpensive method which in combination with the ionization measurements permits at least four controls a year and later on the frequency suggested by the IAEA. For the sake of simplicity the in-air irradiation method is used. Three pairs of LiF:Mg,Ti and CaSO\(_4\):Dy discs are incorporated in a 5 x 7,5 cm\(^2\) polypropylene capsule with a total thickness of 0,15 cm. the capsules are fixed on the plexyglass end of the applicator perpendicularly to the anod cathode axis and irradiated with a nominal dose of 1 Gy. The energy dependence of the system as well as that of the CaSO\(_4\):LiF yield ratio relative to Co-60 gamma rays was determined by secondary standard instruments in rays suggested by the ISO. The HVL may be determined in the range of 0,4 to 3 mmCu from the CaSO\(_4\):LiF ratio and the energy dependence of the LiF discs is corrected for. Three capsules of a series are used for reference irradiation with Co-60 gamma rays. The system permits the determination of dose rate with an accuracy of 5% (on the 95% confidence level). A pilot study in a country hospital (10 postal control in a two month interval) resulted in a standard deviation of 22%. In the HVL range of 2 mmAl to 0,4 mmCu this system may be used only with a limited accuracy.
QUALITY ASSURANCE PROBLEMS OF THE BRAIN IRRADIATION, PHYSICAL ASPECTS.

In our institute the most frequent techniques of the irradiation of brain tumours are i. the two oblique fields, ii. the two wedged fields and iii. the moving field technique depending on the localization of the treatment volume. The reproducibility of these treatments is investigated in Alderson Rando phantom in 30 sessions using film dosimetry and ICRU rods and pellets. Selected points in the treatment volume and in the high dose gradient region adjacent to it are investigated and compared with the results of computer simulation as well as with the results of computer aided dose planning. Computed dose distributions are compared with on patient measurements. Typical values at the reference point recommended by the ICRU (at the intersection of the central axes of the beams) are ±2.2% (standard deviation relative to the local dose). The same figures for our cobalt units at other points were ±4 to ±5% depending on the dose gradient.

THE COMPARISON OF THE RESULTS DIFFERENT METHODS OF FRACTIONATION IN BRAIN METASTASES.

The comparison of the results of radiotherapy in the cases of brain metastases with the use of three methods of fractionation and different total dose.

The objective of this paper is the comparison of the results of radiotherapy in the cases of brain metastases with the use of three methods of fractionation and different total dose. 

In the years 1960-1984 at the Institute of Oncology in Olawa and in Division of Radiotherapy in Opole there were irradiated 256 patients with brain metastases. Only 183 have finished radiotherapy. In this group there were 50 patients with metastases from breast carcinoma, 36 from bronchial carcinoma, 24 from melanoma malignant, 10 from malignant lymphoma, and 38 from others neoplasms. 171 patients received 400Gy/20/25, 1162.5 ret, 22 patients received 30Gy/10/15, 1310 ret/29 patients-200Gy/5/5, 1142.9 ret.

For the evaluation of the results improvement we have divided our own stah, with four steps. The results were evaluated according to the number of deaths due to the brain metastases. The number of deaths in this three groups: patients was as follow: group I/400Gy/20/25, group II/30Gy/-50, group III/200Gy/-55. The big differences in the number of patients in every group do not allow for the peremptory conclusions.

RADIATION THERAPY OF NONOPERABLE ESOPHAGUS CANCER BY METHODS OF FRACTIONAL THERAPY.

The effectiveness of radiation therapy of CF (2Gy up to total dose of 60Gy) isn't satisfactory: 5-year survival rate of 941/pts. is 5.8%. Though some authors of Far East give higher results. We tried different methods of fractionalization: Large, middle, split and dynamic. Immediate and late results were compared with that of the CF. DF is more effective, total regression of tumors is in 37-43% of pts. which is 1.5-2 more than after CF. There is a close relation between the survival of patients and degree of regression after radiation. For esophagus cancer we've stated: 3-year survival after total regression is 25-30% and with residual tumor less than 10% of the initial volume that is 9%. After DF 3-year survival increases up to 21% that is twice higher than after CF. Regime of DF has been worked out in hope to exploit oxygen effect and phenomenon of recovery. The more factor form the basis of high effectiveness of DF. Tumor growth-rate is one of the main prognostic factors. T2 of esophage cancer is 16-152 days (tumor with Td=60 days) it's twice more than tumors Td>60 days; Td correlates with the degree of differentiation; only 13% of tumors of the 1st grade and 64 per cent of esophage cancer are low differentiated. DF turned to be more effective for treatment of fast-growing esophage cancer: in 45% of tumors Td<60 days total regression come, that is 2.5 times more often than after patients' treatment in CF regime. Patients with Td>60 days - the effect of DF and CF is the same.

Irradiation of multiple skin-metastases of malignant melanomas following the synchronizing of the cell division.

Dr. Peter Szabó, József András Hospital, Derm. Dep. Fyiregyháza, Hungary.

The treatment of multiple skin metastases of melanomas has been yet solved neither surgically nor by giving chemotherapeutic agents. In our opinion the malignant melanoma is x-ray sensitive and it can be well treated with x-ray therapy. Therefore irradiation following the synchronizing of the melanoma-cells were applied.

Up till now 21 patients suffering from melanomas with multiple skin metastases were treated by this method. Irradiations were performed by Dermopan, Chaoul and Turbo equipments using 500-1000 R fractions. The total doses had reached 8000-10000 R. The x-ray treatment is especially effective if a relatively large single dose is applied. Synchronization was carried out with 5 MU, Bleomycin and Vinorotin.

During the treatment the patients were kept under strict laboratory and clinical observations. No toxic side effects were observed in the process. By the effect of the treatment the multiple skin-metastases considerably or totally regressed in each case. It was characteristic for the treatment besides the selective effect and the destruction of the metastases- that the surrounding tissue remained relatively sound. This treatment besides the destruction of the metastases relatively saved the surrounding healthy tissue.
HIGH DOSE FRACTIONATION IN THE RADIOTHERAPY OF MELANOMA: CLINICAL RESULTS. J. Bauer, K. Proklej, L. Petruzelka et al., Middle Czech Region Melanoma Group, Dept. Oncol., Teaching Hosp. Prague, Czechoslovakia

On the basis of previously published Cumulative Biologic Effect (CBE) formula, the hypofractionated schedule of the high dose radiation has been used in the therapy of both primary and metastatic melanoma. The single dose of 8 Gy was delivered in one week intervals /days 0-7-14-21/ up to the total dose of 32 Gy. The majority of treated patients were those with regional node involvement or with outaneous and subcutaneous metastases, while the primary melanomas made up the minority of cases.

Since February 1983 64 patients have been irradiated, 68% of OR have been achieved and out of them 39% were CR. The time elapsing from the last dose of radiation to CR achievement ranged 2-10 months. Duration of CR ranged 3-40 months.

Excerpts from the text:

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THE PROBLEMS OF TIME DOSE RELATIONSHIP IN RADIOThERAPY OF SKIN CANCER. J.Kuhelj, and H.Hadić. Inst.of Oncology, Ljubljana, Yugoslavia

Optimal fractionation of the dose applied is one of the most important factors for a successful treatment. A number of radiotherapists have tried to find the optimal fractionation regimen by comparing patients irradiated for skin cancer who have been cured with those who have developed necrosis. They concluded that the difference in dose between the two groups of patients represented the optimal time-dose relationship. Our studies of this problem show that the problem of optimal time-dose relationship is more complicated than it had been reported by other authors. On the treatment results of our patients irradiated for skin cancer we can conclude that the response of healthy tissue to radiation can be predicted. This response follows the rules that are considered to be important in radiotherapy. More severe changes can be found with higher dose, larger diameter of irradiated field, older patients and some localizations of cancer. However, we cannot predict the response of cancerous tissue to irradiation. In our patients it did not depend on the dose applied, diameter of irradiated field, patient's age, or on the localization.

DETERMINATION OF DOSE OUTSIDE A BEAM IN TELECOBALT THERAPY

N.Stiptić-Solčić, I.Kontus, G.Georgiev, T.Bobuš, D.Brunini, M.Gajić

Department of Radiotherapy and Oncology, Clinical Hospital Center, Rijeka, Yugoslavia

Absorbed dose to tissue and organs outside the treatment field can be significant and therefore is of clinical interest. The sources of scattered radiation are the collimator-compensator system and the irradiated volume. The measurements of dose from scattered radiation at the surface and the depth of phantoms have been performed. The dependence of dose on different parameters of irradiation have been experimentally determined. For some conditions of the irradiation the possibilities of reducing the absorbed dose of scattered radiation were investigated.

CLINICAL TESTS ON INFLUENCE OF THE FRACTIONATION IN THE RADIOThERAPY WITH FAST NEUTRONS.


It's well known from radiobiological experiments, that the repair capacity of cells irradiated with fast neutrons is reduced in a high degree. One characteristic of neutron irradiation is to set irreversible damages in molecular cell structures. In earlier clinical experiments on patients irradiated with fast neutrons (cyclotron, average energy 6.2 MeV) it was shown on the basis of early skin reaction (erythema), that fractionation doesn't influence the observed effect. In these experiments the following schedules were used: 4 Gy in 10 fractions and 4 Gy in 4 or 5 fractions. These rough evaluated results were confirmed by a further clinical investigation. Altogether 218 patients were included in this experiment. A dose of 120 Gy was given on to the surface in 10 fractions (12 days) and 5 fractions (5 days). Under this conditions there was observed a maximum in early reaction after 38 - 45 days. In relation to the skin erythema there was no difference between these two fractionation schedules. In addition to these experiments there were made investigations on the basis of the reaction of connective tissue (degree of fibrosis). In this case also no significant differences were observed between the reaction after irradiation with these two fractionation schedules. Thus it was shown by our clinical investigations, that the difference between the effect of the above mentioned fractionation schedules on early or late skin reaction can be neglected.

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Five year actuarial survival rates for stage B and C carcinoma of the prostate in radiation therapy combined with estrogen were 91.2% and 89.8% respectively between 1964 and 1979 in our hospital. In stages B and C local control rates were 92.3% and 65.5% and local atrophy rates were 61.5% and 31% respectively. Lymph nodes dissection was not done.

In attempt to improve the control and atrophy rates and survival rates for stage C, we tried estrogen administration for reduction of the prostatic lesion prior to radiation therapy to the prostate and lymph nodes dissection or lymph nodes irradiation since 1980. The local control and atrophy rates for stage C were coming near to those in stage B. Atrophic prostatic lesion had rarely developed relapse or metastasis. Diagnosis for metastasis of pelvic lymph nodes was done by pedal lymphangiography and CT scan and state of metastasis was confirmed by pelvic lymphadenectomy. N0 and N1 were impossible to be diagnosed by lymphangiography or CT scan and were indicated staging operation. N2 and N3 were possible to be diagnosed and were indicated lymph nodes dissection. N4 was possible to be judged inoperable by lymphangiography or CT scan in TNM pre-treatment clinical classification.

We report our experience with photodynamic therapy (PDT) in the treatment of resistant bladder cancers (failures to standard therapies) in 10 patients (age 55-80; mean: 66). PDT involves in situ activation of photosensitizer hematoporphyrin ethers (DHE) by light at a wavelength of 630 nm, produced by an argon-pumped dye laser. 72 hrs after injection with DHE, 2 mg/kg, patient underwent cystoscopic photoactivation of the whole bladder with the red light (630 nm) via 400 μm quartz fiber with a sub-point diffuser tip. Power density ranged from 9-23 mW/cm². Followup was ranged from 2 mo.-30 mo. (median 12 mo.). In 6 earlier cases treated with sterile H2O irrigation and filling pressures >60 cm H2O assessment of the efficacy and safety revealed: 1 pt. (T1B) at a light dose of 60 J/cm² had necrotic tissue on DRE, negative urine cytology and bladder shrinkage before death at 2 mo, due to pneumonia; 1 pt. with multifocal TIS at 50 J/cm², resulted in complete response (CR); negative bx and urine cytology, but bladder contracture necessitating cystectomy and ileoureterostomy due to Grade IV vesicoureteral reflux; 2 pts., with T1B at 20 J/cm² had control of hematuria; persistent invasive disease and suffered bladder shrinkage. In 6 later cases (saline irrigation and 30 cm H2O), 7/4 pts. with T1B who received 15 J/cm² have had followup evaluation with 1 CR and 1 partial response (PR): disappearance of multiple lesions except one) and CR on retreatment; 1 pt. with TIS in bladder and T4a in post. urethra (PU) received 10 J/cm² at each site and showed CR in bladder but PR in PU; 1 pt. with T1B who received 5 J/cm² is yet to be evaluated. None of these 6 patients had bladder shrinkage; increased capacity has been noted in 3 pts. All treated pts. reported irritative urinary symptoms which improved in 3-4 wks. In summary, whole bladder PDT appears safe and applicable in the treatment of non-invasive TCC of bladder. There appears to be no toxicity to the bladder under such conditions as light dose of 10-20 J/cm², filling pressures of 30 cm H2O with normal saline and underdistention of bladder.

Brachytherapy of bladder cancer with intravesical radium source. Mario O. Gonzalez, M.D., Department of Clinical Radiotherapy, M.D. Anderson Hospital & Tumor Institute, Houston, Texas, U.S.A.; Rio Grande Cancer Treatment Center, McAllen, Texas, U.S.A. From March 1980 thru September 1982, twenty-two patients with noninvasive transitional cell cancer of the bladder were treated by intracavitary radium insertion. The technique used consisted of a modification of the Friedman-Lewis and Cleveland Clinic methods of intravesical radium source application. The purpose of the study was to evaluate efficacy of this modified system in insuring permanent local control of disease or delaying recurrences treated by cystectomy. As of September 30, 1982, 14/22 patients were locally controlled. We believe this is an effective, simple, well tolerated method of controlling superficial disease in carefully selected patients.
EVALUATION OF DIFFERENT PREOPERATIVE TREATMENTS IN UROINARY BLADDER CANCER


The purpose of preoperative treatment in urinary bladder cancer is to diminish the primary tumour and to prevent the growth of subclinical disease. We have combined radiotherapy with chemotherapy using cis-platinum which has been shown to act as a radiosensitizer.

Two different fractionation methods were used. Our aim was to study the effect of treatment on the urinary bladder and to assess the down staging in cystectomy.

Group 1 received cis-platinum 40 mg/m² intravenously on days 1 and 8. Pelvic irradiation was given from two opposed fields with 6 MeV photons on days 6 to 10. The daily midline dose was 4 Gy and the total dose 20 Gy 1/2/1d.

Group 2 received the same dose of cis-platinum on days 3 and 10. The pelvic irradiation was hyperfractionated, 1.5 Gy twice a day with 4 hours intervals to a total dose of 36 Gy 2/6/2d.

The total preoperative treatment time in group 1 was ten days and in group 2 twelve days. Cystectomy was performed within one week from the end of the preoperative treatment. Before and after the preoperative treatment the permeability of the bladder was investigated using Xenon 133 and gamma camera technique. In cystectomy the whole bladder was removed and given to the histopathologist for thorough tissue analysis. Tumour shrinkage occurred in both groups. The side effects, postoperative follow up are evaluated and the effects of these two preoperative treatments are compared.

PHOTODYNAMIC THERAPY FOR SUPERFICIAL BLADDER TUMORS, H. Hisazumi, K. Naito, H. Yavamoto, T. Amano, K. Koshida, T. Uchibayashi and T. Wisaki, Department of Urology, School of Medicine, Kanazawa University, Takara-machi 1-1, Kanazawa 920, Japan

Photodynamic therapy (spot PDT) using 400µm quartz fiber through a cystoscope and argon-dye laser red light (630nm) was carried out in 17 patients with Ta-T1 tumors. In addition, whole bladder wall PDT (total PDT) using a motor-driven laser light scattering device coupled with the laser was performed in 22 patients with CIS of the bladder or/multicentric small superficial tumors. The presence of CIS was confirmed by random biopsies. HpO2 30% (5% was i.v. injected 48 to 96 hours before PDT. The effectiveness of single spot PDT sessions was limited to tumors less than 2cm in size and total light energy should be more than 100J/cm². The 22 patients had a history of several TUR, hyperthermia and/or instillation therapy. The light energy of 10 to 30J/cm² was used for CIS therapy. There was no recurrence in 4 of the 17 patients with a mean tumor free time of 20.8 months, and in 5 of the 22 patients with mean tumor free time of 8.7 months. The valid indication for PDT was thought to be for CIS and diffuse Ta-T1 lesions.
The authors deal in detail with the problems of planning the irradiation techniques applied by them at clear cell kidney cancer, they present the isodose distributions on illustrations. Hypernephroma is the most frequent malignant kidney tumor, it is 80-85% of the renal malignomas. It shows relatively late symptoms, so it will diagnosed in advanced stage IV. The operation is the fundamental element of therapy of hypernephroma, but the postoperative telecobalt irradiation is also very important at the prevention of local recurrences especially in stage IV and in the case of uncertain radicality of surgery.

At planning the irradiation we have to take into consideration the relatively great radiosensitivity of the neighboring organs of the kidney because of the characteristic position of the kidney, and we have to take into consideraton the relatively small radiosensitivity of hypernephroma. To make sure that the neighboring organs are not damaged we used computer-assisted individual therapy-plans. The treatment included 200 cGy daily fractions up to 5000 cGy total dose to the abdominopelvic fields or pendel techniques. The postoperative irradiation significantly reduces the frequency of recurrences.

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The clinical trial with Cf-252 neutron brachytherapy for the treatment of malignant gliomas is now in progress to evaluate a possible survival benefit of neutron implantation. The eligible patients had a histologically confirmed malignant gliomas (glioblastoma multiforme and anaplastic malignant astrocytoma), Karnofsky performance status of 50% or greater, and 79 years of age or younger. In the first 3.5 year period, forty patients participated in this study. All patients underwent debulking tumor resection. Following confirmation of a histologic diagnosis of glioblastoma or anaplastic astrocytoma, the patients received Cf-252 brain implantation (1500 req), and then 50-60 Gy of photon beam teletherapy was added. During the period, there was a gradual evolution in techniques of brachytherapy and teletherapy. The patients in Group I underwent Cf-252 implantation using a single tube technique and received 60 Gy of whole brain irradiation. For the patients in Group II and III, we used similar techniques of multiple tube technique for neutron implantation. However, we used different regimens of photon beam teletherapy in Group II and III; that is, Regimen 2 for Group II consisted of 45 Gy of whole brain irradiation and additional boost radiotherapy up to 60 Gy; and Regimen 3, subtotal brain irradiation plus boost radiotherapy to a total tumor dose of 50-60 Gy in Group III. The procedure was well tolerated by all patients. There were no serious complications. The majority of patients showed a prompt improvement in performance status as well as symptomatic and physical responses. In addition, there has been gradual improvement in survival results with evolution of treatment techniques. 50% of the patients in Group I survived nine months; 59% in Group III; and 87% in Group II, respectively. 50% of the patients in Group I underwent Cf-252 implantation (1500 req), then 50-60 Gy of photon beam teletherapy in Group II and III; that is, Regimen 2 for Group II consisted of 45 Gy of whole brain irradiation and additional boost radiotherapy up to 60 Gy; and Regimen 3, subtotal brain irradiation plus boost radiotherapy to a total tumor dose of 50-60 Gy in Group III. The procedure was well tolerated by all patients. There were no serious complications. The majority of patients showed a prompt improvement in performance status as well as symptomatic and physical responses. In addition, there has been gradual improvement in survival results with evolution of treatment techniques. 50% of the patients in Group I survived nine months; 59% in Group III; and 87% in Group II. The one-year survival rates were 25% in Group I, 46% in Group III, and 75% in Group II, respectively. 50% of the patients in Group I were still alive at 18 months after surgery. Further details will be discussed.
TREATMENT OF CHOROIDAL MALIGNANT MELANOMA WITH RUTHENIUM APPLICATION.
Iva of Tramp, Erik Kock and Ingmar Lax
Karolinska Sjukhuset 10401 Stockholm

Since 1979 the Ruthenium applicator ad modum Lommatsch has been used at the Karolinska Hospital for the treatment of intracranial malignant melanomas. The results from 35 consecutive patients, all of whom have been observed 2 yrs or more after treatment, are presented.

CONSERVATIVE TREATMENT OF MELANOMA OF THE CHOROID BY RUTHENIUM APPLICATORS. J.P. GERARD, G. DE LAMOURE, Radiothérapie CHS 69310 PIERRE BENITE, J.D. GRAMGE, M. BONNET. Hôpital CRIOX ROUSSE 69004 LYON - France.

In Lyon, from 6.83 to 8.85, 49 patients with melanoma of the choroid have been treated with ruthenium disk instead of enucleation. According to Oosterhuis classification there was:

- 10 T1
- 17 T2
- 22 T3

Regression of the tumor was seen in 83 % of cases (100 % in T1 T2). Two T3 showed progression of tumor and required enucleation. NED survival is 39/40 with 1 T3 dead of distant metastases. Enucleation was done in 4 patients (2 T3 for progression of disease and 2 for complications). Among 36 patients with eye conservation and more than 6 months of follow up, 30 retained a useful vision (visual acuity > 1/10). Perimacular exsudate appeared in 15 cases and cleared in most of the cases in 6 months. Two complication required enucleation: 1 for complicated glaucoma and 1 ocular atrophy. 3 patient had central retinal vessel thrombosis. No lens opacity has been seen. These preliminary results are in agreement with those of Lommatsch and Poerster. Treatment of choroidal melanoma with ruthenium disk gives a survival at least identical to enucleation and fewer complications than cobalt disk. In large T3 tumor we have designed an Iridium applicator which allows a two time application one with Iridium and one month later a second with ruthenium. Up dated results will be presented at the meeting.

LUNG-SALVAGE WITH ISOLATION PERFUSION IN SPINDLE CELL CARCINOMA OF EXTREMITIES.
R. Veglin, A. Prada, H. Santinami, M. Mars, F. Belli, M. Cucinelli

Three cases of extensive spindle cell carcinoma of extremities and with involvement of underlying bula, for whom the only possible treatment was amputation or disarticulation were treated at National Cancer Institute of Milan, Italy with hyperthermic perfusion (42°C per 90 minutes), using Hethotrex 300 mg/m² as antitumor drug. An important macroscopic regression of the tumor was evidenced and multiple biopsies showed a diffuse necrosis of the tumor. In the case with bula involvement a marked bone rearrangement was radiologically documented. The tumor regression allowed a conservative surgery with a wide excision of the tumor in all cases plus resection of the cortical part of the bula in one case, followed by plastic reconstruction (intercostal plus rotation flap). Histologic examination revealed in all cases only minimal areas of residual tumor and diffuse necrosis. These patients are alive and free of disease respectively after 32, 29, 13 months after perfusion, showing once more that hyperthermic perfusion may play a very important role in the multidisciplinary treatment of tumors of extremities.

CLINICAL EVALUATION OF TOTAL-BODY HYPERTERMIA USING AN EXTRACORPOREAL CIRCUIT FOR FAR-ADVANCED CANCER PATIENTS. H. Makita, S. Koga1, M. Yokoyama2, I. Kato3, T. The Dept. of Surgery, Tottori Univ. Sch. of Med.,1 Yonago, Tokyo Women Med. College2, Tokyo, and Nagoya Anniversary Hospital3, Nagoya, Japan

One hundred and sixty-eight patients with inoperable far advanced cancer received a total of 444 extracorporeally induced total-body hypertermia (THT) treatments in 7 Japanese hospitals between April 1980 and May 1985. Overall, a tumor regression was observed in 39 of 132 evaluable patients (29.5%). Other favorable result was found in lung cancer. In analyzing the antitumor effects of THT according to cancer site, favorable results were observed in patients with their main cancer in the lung, liver, lymph nodes and soft tissue, irrespective of whether tumorigenesis was primary or secondary. No relationship was found between an objective response and histologic pattern of the tumor. Most advantageous antitumor effects were observed when THT was performed in combination with cis-diamminedichloroplatinum(II) during hypertermia. Antitumor effects were not evaluable in 36 patients (21.4%). Of 36 patients 33 died before evaluation was made; 24 died of various complications and 9 died of cachexia without any evidences of complications. These dead cases increased in proportion to the reduction of the performance status before THT. These results indicate that THT should be performed for patients whose tumors are in the lung, liver, lymph nodes and soft tissue, and should be performed for patients with good general condition.
THE USE OF CATHETERS ON IN VITRO AND IN VIVO TEMPERATURE MAPPING. M.J. Berd, G.P. Hageman, G. Rydberg, G. Rydberg. Medical Physics, Ontario Cancer Treatment and Research Foundation, Ottawa Regional Cancer Centre, 190 Melrose Ave., Ottawa, Ontario, K1Y 4K7, Canada.

In the application of clinical hyperthermia accurate thermometry is a necessity. The safety and ability to evaluate tumour response in clinical hyperthermia depends on adequate thermometry, usually involving invasive techniques. To satisfy biocompatibility and practicality considerations such as toxicity, reduced trauma, ease of insertion and pull-back thermal mapping, catheters are usually employed. Catheters can introduce errors under conditions of temporal or spatial thermal gradients. This work will describe the effect of various commercially available catheters on the temperature reported by optical thermometers, multiple array type "T" and type "K" thermocouples. The data show that the presence of catheters can induce thermometry errors when large thermal gradients exist. Such errors are larger in "T" type than "K" type thermocouples. Thermal time constants and the effect of gradients will be reported for the various combinations of thermometer and catheter.


There are evidences that calcitonin has the capacity to raise the levels of aMIF and © endorphins, in the other hand, elevated calcium levels diminish the pain threshold in patients with malignant hypercalcemia. In that sense, we performed a study to determine the effectiveness of salmon calcitonine (sc) in patients with pain due to bone osteolytic metastasis, refractory to common analgesics. 51 patients, 23 males and 28 females ranging in age from 36 to 82, were treated with 100 IU sc IM at a single dose during 45 days. 36 patients (70.8%) reduced pain, evidenced by means of a score from I (without pain) to 5 (severe pain), and the reduction of the dosis of the analgesics previously prescribed (p<0.001), among this, 7 was without pain at the end of the trial. In the nonresponders, 10 showed no pain modifications and increased in 5. We observed reduction of pain in 7 of 13 with high levels of alkaline phosphatase and normal levels of calcium, and the improve was in 7 patients of 8 with subclinical high levels of calcium. The estimated level of probability was 0.05> p > 0.02 (Chi square test for contingency table 2X2). We observed mild reactions in 22 patients: 16 with rush in head and neck (7 of them with nausea), and in potential in other 4 that began approximately 30 min after the sc application, lasting for 1 or 2 Hs. All this adverse reactions disappeared within one week of treatment. We concluded that this treatment is an useful alternative to patients who become resistant to nonnarcotic analgesics, previous to the administration of narcotic compounds.

Supported in part by Sandoz Lab., Argentina.
LONG TERM EPIDURAL MORPHINE IN THE TREATMENT OF CANCER PAIN. P. Sowiński, J. Jarosz and K. Mierzyński, Inst. of Oncology, Warsaw, Poland

Fifty four patients with cancer related pain were treated with epidural morphine. These patients had insufficient pain control with oral and classic parenteral narcotic analgesics. The mean treatment time was 68 days (range 2 - 368 days). The daily dose of morphine varied from 10 to 120 mg, administered in intervals ranging from 4 - 12 hours. 21 patients out of 54 became pain free. In 5 patients treatment failed. The best response to epidural morphine was obtained among patients with pain related to colorectal cancer. No serious complications were seen.

THE PALLIATIVE THERAPY OF BONE KETASTASES


The palliative therapy of pain resulting from bone metastases, based on the use of Sr radiation, was employed in patients with generalized malignant tumours. There were 36 individuals with generalized metastases of various tumours and remarkable pains which limited the mobility and disturbed sleeping. The metastatic involvement was demonstrated by 99m Tc MIBI scintigraphy. Prior to the therapeutic application of Sr the accumulation of Sr in metastatic lesions was tested by the prophylography using 85 Sr. The positive effect of the therapy, characterised by a moderation or even disappearance of the pains with improved mobility and sleeping up to one year duration was encountered.

THE ANALYTIC ACTIVITY OF CALCITONIN IN PATIENTS WITH PAINFUL OSTEOLYTIC METASTASES OF BREAST CANCER - THE RESULTS OF A CONTROLLED RANDOMISED TRIAL. J. Both and K. Kolarić, Central Institute for Tumour, Zagreb, Yugoslavia

The analgetic effect of Salmon calcitonin was tested by a double blind clinical randomized controlled trial in 40 female patients with painful osteolytic metastases. Twenty patients were administered (daily) 100 international units of Salmon calcitonin subcutaneously over 28 days, while the other 20 were administered identical ampules containing 2 ml of physiological solution over the same period of time. The basic treatment (chemotherapy, hormone therapy) was not changed during the trial, and had to be stabilized for a minimum of three months prior to the trial. The effect of calcitonin was monitored with respect to daily analgesic consumption, duration of pain, patient's functional capacity, patient's own assessment of pain, and assessment of efficacy by the investigator. Statistically significant differences were established in terms of reduced analgesic consumption, shorter duration of pain and the patient's subjective assessment of pain duration and intensity; the difference was not statistically significant with regard to patient's functional capacity. The objective assessment of the calcitonin effect by the investigator showed an extremely useful effect in three patients and a moderately useful effect in eleven patients; three instances of a "moderately useful" effect were observed in the placebo group. No changes were observed in serum calcium levels; there were likewise no skeletal changes as established by X-rays and bone scintiscans before and at the end of treatment. The trial has shown calcitonin to produce a pronounced analgesic effect in breast cancer patients with painful osteolytic metastases.

CONTROL OF PAIN FROM BONE METASTASES BY RADIATION TREATMENT IN TWO LARGE FRACTIONS. V. Pandova, G. Bogdanov, G. Mitrov, P. Pantev, Institute of Oncology, Sofia, Bulgaria

For control of pain from bone metastases a two fraction scheduled radiation treatment has been tried. The two fractions were of 8.5 Gy, given with a gap of 24 hours between. According to Dubreuil et al., this irradiation is biologically equivalent to a conventionally fractionated dose of 36 Gy. It was found, that pain relief is achieved much quicker than when conventionally fractionated irradiation is applied. Since 1976 the two fraction schedule has been introduced in the routine. The pain control efficiency is demonstrated by the result of 2500 consecutive treated bone metastases. In about 2/3 of these cases the pain has been completely relieved, and only in less than 10% the treatment has failed. In the remaining, partial success has been achieved. At the locations of about 50% of the treated metastases restoration of the bone was roentgenologically observable. By giving to these locations one month later an additional dose of 20 Gy in 10 fractions, the scintigraphic manifestations of the metastases have disappeared.
**Title:** TOMODENSITOMETRY OF HYPOPHYSEAL NEUROENDOCRINOMA. TC STUDY OF NEUROLYTIC AGENT DISTRIBUTION. M. Iachetti, M. Crecco, A. Aluffi, F. Piano, L. Margiotta, G. Imperatori, G. Sirianni, M. Cau. Inst. Regina Elena for Cancer Research and Therapy, Rome, Italy.

A preliminary brain TC study, both enhanced and un-enhanced, was performed in 11 pain therapy patients in order to establish a baseline and to verify any associated local pathology. Patients were then studied with trans-sphenoid needle in situ after introduction. Patients were re-evaluated 15 days post-procedure. Ethanol diffusion was clearly identifiable by a sharp drop in cisternal density and was shown to exceed largely the boundaries of the expected therapeutic target, i.e. the diencéphalohypophyseal region. This finding suggested the opportunity of variations in our standard injection technique in order to maximize local neurolytic action with minimal adverse effects. Correlation between ethanol distribution, as demonstrated by TC, and therapeutic effects are under investigation.

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**Title:** ADVANTAGES OF ANTERIOR APPROACH, TC GUIDED, CELIAC NEUROLYSIS. M. Iachetti, M. Crecco, A. Aluffi, F. Piano, L. Margiotta, G. Imperatori, G. Sirianni, M. Cau. Inst. Regina Elena for Cancer Research and Therapy, Rome, Italy.

In 15 pain therapy patients a trans-parietal anterior approach was adopted for celiac neurolysis. A 21 or 22 Chiba needle was introduced through the abdominal wall. Previous TC provided an anatomical and geometrical planning of the path. Introduction was performed by increments in the final approach to the target and checked by repeated scanning. Final error from the anticipated target was in the range of millimeters. The neurolytic agent distribution was checked by adding a small amount of contrast medium and by repeated scanning. In all cases the injection, as expected, turned out to be periaortic. Several advantages are apparent: 1) prone position is better tolerated by most patients; 2) no local or general anesthesia is required; 3) a single, small bore needle is used; 4) spatial accuracy is very high; 5) a reduced amount of neurolytic agent is required; 6) complication rate and procedure time are markedly reduced.
A CLINICAL COMPARISON BETWEEN ORAL MORPHINE AND METHADONE IN CANCER PAIN TREATMENT

F. de Conno M.D., C. Hipamonti M.D., M. Bianchi M.D., M. Gallicchi M.D., M. Taraburini Ph.D., V. Ventafridda M.D.

The authors of this paper are presenting clinical experience for advanced cancer pain treatment which was carried out at the National Cancer Institute in Milan, Italy. Their study compared chronic doses of morphine and methadone administered per os.

Twenty-seven patients treated with morphine and another 27 treated with methadone were studied and randomly assessed over a total period of 14 days. The most representative forms of pathology treated were: breast cancer, lung cancer and cancer of large intestine.

A follow-up study was carried out using a weekly self-rating questionnaire in order to collect daily information on the course of cancer pain, the patient’s quality of life and side effects.

The clinical findings revealed a very satisfying degree of relief over 60% better than the initial values for both groups.

Data regarding quality of life show no significant difference between the two treatment groups.

A remarkable finding emerged from our study: tolerance was not noticed in patients receiving methadone. In the case of morphine, an increased dosage was needed over the 14-day period which resulted statistically significant.

The authors conclude that the two drugs are equally effective and tolerable. However, treatment using methadone shows a lower dosage and frequency of administration.


The most essential role of Micalcic® (Calcitonin Sandoz), a 32-amino-acids peptide, is the preservation of osseal integrity. Based on this physiological fact, it is assumed that this hormone may have a bone-regenerating effect in bone metastasis formation and sometimes in other malignancies. Though no considerable calcium incorporation could be revealed in our 58 patients treated with Micalcic, a marked relief of pain was observed in 65.5% of the patients. For objectivation of the subjective sensation, the decrease in the quantity of other analgetics used daily, duration of pain and changes of its intensity were studied. These figures were 35.4% on the average, from 12.5-6 h and 23.6%, respectively. The pain-killing character of Micalcic cannot be explained, but the following assumptions are made: /1/ it partially inhibits the synthesis of algogenous peptides; /2/ with its possibly cytostatic effect it inhibits the cell proliferation in loco and normalizes the internal pressure of the destroyed region, and /3/ by conversion into 6-endorphin it exerts centrally. Compared to the pain-killing effect, the simultaneous improvement of the quality of life seems to be even more essential. It has been proved earlier that a hormone physiologically present, when applied in a high dose, has an analgetic effect, i.e. by utilizing the endogenous substance of the organism, relief of pain can be achieved. The authors conclude that the two drugs are equally effective and tolerable. However, treatment using methadone shows a lower dosage and frequency of administration.
CONTINUING CARE PROGRAM FOR ADVANCED CANCER PAIN

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Since 1979, a one-of-a-kind program in Italy for continuing care has been set up at the Pain Clinic of the National Cancer Institute of Milan. The objective was to assess the appropriateness of a team of professionals, home nurses, psychologist and many volunteers, which operates both at the hospital and at home. The entire team meets weekly and the Home Care nurses report the general physical situation and assistance of the patients they follow at home. The results obtained in two recent studies of pain control and quality of life in patients assisted by the Home Care Program prove the effectiveness of such a program and the importance of pursuing this objective.

PAIN CONTROL

The treatment of tumour-induced pain, especially in the terminal stages of a malignant disease with widespread metastases, is a particularly difficult medical problem. Non-narcotic analgesics are usually ineffective and toxic, although effective, often lead to habituation and addiction. Considering that these patients are usually also depressed, ANALAFANIL was tried out in several studies and is now routinely used in many hospitals as an adjunctive therapy for the treatment of cancer pain. Not only does it relieve the secondary depression, but it was found to exert a true analgesic effect. Moreover, when given in combination with opiates it has a morphine-sparing effect. We made a literature review and compiled the results of 12 open studies carried out on this subject. More than 450 cancer patients were treated with ANALAFANIL and its analgesic effect was very good or good in 60-85% of them. This improvement can be attributed to ANALAFANIL because the associated therapeutic treatments alone were not sufficient to produce a satisfactory analgesic effect. A number of the patients did not require any additional analgesics. ANALAFANIL was given either orally or in slow i.v. infusions with gradually increasing doses ranging from 25 to 150 mg/daily. The onset of action always occurred within one week. Side effects were reported in about one-third of the patients. They were mainly of an anticholinergic nature. In a few cases the drug had to be stopped because of orthostatic hypotension or side effects. Several authors recommend that the treatment with ANALAFANIL be started early, at a stage when pain is still mild. It is thus possible to avoid the use of narcotic analgesics, or at least to use them at a reduced dose. The mechanism of action is not yet known. Clearly explained, ANALAFANIL probably acts on peripheral receptors and also activates serotonin-containing neurons of the endorphin-mediated analgesic system that controls pain transmission in the brain.

CONTINUOUS RELEASE MORPHINE IN CHRONIC CANCER PAIN

R. P. Kallos, C. C. Zembrzuski, and P. D. Schlegel, The Pupe Frederick Company, Norwalk, CT, USA

An open, randomized, placebo-controlled crossover comparison of immediate-release morphine sulfate (MPS) and controlled release morphine sulfate, as HC Captan (MRC) was conducted at three cancer treatment centers to assess the acceptability of MRC and to develop guidelines for its use in chronic cancer pain. In 866 patients, MPS q12h was substituted for equivalent doses of MRC q8h, if needed, to maintain optimal balance between analgesia and side effects. Fifty-one patients then substituted q3h at twice the MIR dosage (equivalent to 24-hour dosing) and titrated, if needed. After MRC dosing for at least 72 h, the dosage interval was extended to q72h (i.e., a dose reduction to 2/3's of previous MRC daily dosages) in consenting patients. Estimates of analgesic efficacy and side effects were collected. The comparison of MIR and MRC was completed in 65 of 73 patients entering the study. Four of the 18 discontinued patients withdrew due to unacceptable side effects; that patients receiving MPS, and 1 patient withdrew due to side effects while receiving MRC. The remaining 14 patients withdrew for reasons unrelated to study medication. Fifty-seven of the 65 completing patients consented to extend the MRC dosing interval from q8h to q72h. Thirty-seven of these 57 patients were stabilized on MIR q12h at only 2/3's the previous q6h daily MRC doses. Patients received an average daily morphine dose of 171 mg as MIR and 169 mg as MRC over the last 6-hour period of each phase. Patients received NCS and MRC for an average of 3.1 and 14.6 days, respectively. Investigations at each of the three centers judged MRC to be more efficacious than the prior analgesics (P < 0.001). Investigators at one center judged MRC to have fewer side effects relative to prior analgesics (P < 0.001), with other centers showing similar, but statistically nonsignificant trends. At the one center where investigators judged MRC relative to MIR, MRC was more efficacious (P < 0.001) and was associated with fewer side effects (P < 0.001) than MIR. These results demonstrate that MRC is safe and effective in the management of chronic cancer pain.

PALLIATION OF PAIN FROM BONE METASTASES USING MULTIPLE DAILY FRACTIONS OF RADIATION

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Metastatic bone disease is the most common cause of severe pain in patients with cancer. The efficiency of radiation therapy in providing relief of severe pain caused by bone metastases has been well established. Common practice has been to deliver a fractionated radiation therapy course spread over several weeks. It seems obvious that faster approaches would be an advantage in many cases. In this study 23 patients, with a variety of primary tumors, have been treated for palliation of pain with palliative radiography using an accelerated regimen of multiple daily fractions. Patients received in general three treatments daily, with 3- to 4-hour intervals on three consecutive days. The single dose applied was between 1.5 and 2.5 Gy depending on field size and site. The radiation portals included all sites of bone metastases except those in cervical, thoracic, and upper lumbar spine. Good or complete pain relief, generally within one or two days after completion of treatment, was observed in all 18 patients with breast cancer, which could also be documented by the reduction of pain medication. In these cases systemic treatment could be started without delay. Less impressive was obtained in carcinomas of the prostate. In these cases the numbers for these tumors are too small to draw any conclusions. Enhanced side effects like acute X-ray reactions were not observed. The degree of remineralization was similar as with conventional fractionization. This study shows that multiple daily fractions of radiation could at least for rapid palliation of pain from bone metastases in breast cancer an effective method.
Several studies have shown that removal of a breast is a psychologically devastating experience for a woman. Thus, depression or other psychiatric symptoms have been evidenced following mastectomy. Behavioral of the breast cancer patient is also often disrupted, i.e. alcohol or prescribed drugs, sexual functioning, socialization, physical or occupational activities... Fears about loss of femininity, about death, or low self-esteem are other psychological sequelae.

Some recent clinical trials seem to show that patients who had a modified radical mastectomy have equivalent survival rates to that of those who had a segmental mastectomy (lumpectomy). Since results will not be definitive for quite a few years yet, the type of surgery to perform (excision of a focal tumor vs removal of the whole breast) will be heavily influenced by personal factors, and particularly the quality of life of the mastectomized patient.

The Cross-national NSABP B-06 clinical trial compares survival of segmental mastectomy, plus axillary dissection, with or without radiation. Of the 1500 patients that have been randomized into three groups, about 75% are married. Data will be presented to the American Society of Clinical Oncology, Helsinki. The Rosenberg's Self-Esteem, the Social Adjustment Self-Report, Sexual Functioning and Marital Adjustment, etc. have been utilized. A little less than half of the women interviewed have had their operation for less than 3 years, about 45% are less than 50 years, more than 3/4 are married and about 40% are housewives. Data will be presented to verify the hypothesis that women who had a lumpectomy show less psychological distress, less sexual dysfunction and marital maladjustment, better self-esteem and body image, than women who had a radical mastectomy.

We are estimating how an evident and complete information on the various aspects of rehabilitation after mastectomy can produce a better psychological adaptation. In fact we elaborated a questionnaire regarding the health, psychological and aesthetic problems of a woman after mastectomy that we proposed to two groups of women. The first group is composed by 35 women interviewed after mastectomy before the resignation and the second group is composed by 15 women in follow-up from two years that before resignation by the hospital hadn't received the booklet of information. The first result confirmed our supposition: information reduced the state of anxiety and depression because it permitted that women approach their future problems after mastectomy giving them hope to receive these problems.

O-46: PSYCHOSOCIAL PROBLEMS OF CANCER PATIENTS


We made a study on the reactions of the society in front of the problems of a child who has cancer. We elaborated some questionnaires that we submitted to two groups of teachers. The first group was composed by teachers chosen at random between one thousand schools and another group composed of teachers chosen because they had children with cancer between their students. Both groups of teachers think that children with cancer could have a lot of problems living near other children without cancer. The teachers of children with cancer underline that these problems are caused not only by limitations derived by their illness, therapy, and excessive protection of the parents, but also to the fact to be noted in the margin by school fellows and by their families when their illness becomes evident. An important difference between the two groups is the evaluation of the teachers on their attitude to the child with cancer: while the teachers of the second group do not think they change with children with cancer, another group thinks they could change, likely making allowances.

3959 PSYCHIATRIC OBSERVATIONS CONCERNING POSTOPERATIVE EXCESSIVE EMOTIONAL REACTIONS OF COLORECTAL CANCER PATIENTS. I. Molnár, I. Kára, Z. Kiss, F. Szabad, M. Fodor, County Hospital of Pest, Kerpestorosa, MV Hospital, Budapest, Hungary.

As a first stage of three-years follow-up period 50 patients with permanent loss of the anal sphincter and colostomy were interviewed to evaluate their emotional reactions. Psychiatric problems in the first weeks postoperatively were rare. The clinical and psychological examinations indicated the significance of shame response. Postoperative depression, fear, anger, anxiety, shock appeared after the surger minimized the contacts with the patients. The incidence of social isolation and disturbances in sexual life were high. Psychotherapy seems to be an effective method to find new compensatory ways of dealing with depression. In some cases favorable therapeutic effect can be obtained by antidepressive medication. Reasons for failure to detect such kind of disorders is the fact that most doctors have not been taught how to interview their patients. We started also to study the connections between the emotional reactions and quality of life thereafter.


Quality of life studies in patients treated with intensive irradiation and/or chemotherapy has been rarely done systematically. In the present study 103 patients with non resectable non small cell lung cancer were randomized to either radiotherapy (2.8 Gv x 15) or combination chemotherapy (Cisplatin, Vp-16).

Assessment of quality of life was done before start of the treatment, during and 14 weeks after the treatment.

Two methods were used:

1. Neuropsychological tests.
   a. Wechsler Memory Scale (1958).
   c. Serial learning (10-trials).
   d. Self Assessment. A questionnaire administered to the patients.

The results from the neuropsychological tests will be compared to the two treatment groups - radiotherapy and chemotherapy.
Psychological sequelae of exarticulation for limb neoplasia

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The aim of the present study is to evaluate the level of disability and the psychological impact of radical surgery for limb malignancies and possibly to find some behaviour criteria which could guide surgeons in choosing the best treatment, when possible. All the patients selected had been operated on with major exarticulation. Patients are contacted of the out-patient division and are interviewed by a structured questionnaire. Major variables of the investigation are: work activity, affective relationship with the partner, sexuality, social life, anxiety and depression. The psychological test employed is Minnesota Multiphasic Personality Inventory.

The study began on September 85 and up to now only 17 patients, 6 women and 6 men, have been evaluated. The median age was 24.5 years. Six patients showed a worsening in work activity, three in sexual activity, forth in affective relationship with the partner and forth in social life. Fifty percent declared an increase of anxiety and depression after surgery.

The results of M.M.P.I confirm the data of psychological investigation. Eleven out of twelve were informed and conscious of their diagnosis and prognosis of the disease.

O-45: PSYCHOSOCIAL PROBLEMS OF CANCER PATIENTS

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3962 PSYCHOSOCIAL RESEARCH IN A CANCER CLINICAL TRIAL: SETTING THE CALGB EXPERIENCE. OF Cella, J.C Holland, S Tross, PE Silberfarb, AH Korzin, for Cancer and Leukemia Group B (CALGB), Brookline, MA.

The CALGB was the first group to systematically study psychosocial variables in clinical trials research. In 1976, the Psychiatry Committee began to assess quality of life during treatment. The initial studies undertook development of simple, reliable observer and self-report measures of psychosocial response to treatment. To date, over 1000 patients have been given the same brief assessment battery, which permitted comparison of psychosocial functioning in tumor sites and randomized treatment arms. In a palliative small cell lung protocol in which the two treatment arms showed equal survival, depression and fatigue were greater in one arm, suggesting the importance of considering quality of life in palliative treatment.

Two other protocols for treatment of advanced pancreatic and gastric cancer, which controlled for major medical variables, showed greater distress among the pancreatic, confirming medical folklore. Data are also being examined to assess psychosocial variables in regard to length of disease-free survival in an adjacent breast protocol, and the effect of sociodemographic variables (income and race) upon treatment response in six different protocols for four tumor sites. These data will also provide norms in cancer patients. The registry of CALGB patients has been used to study delayed psychosocial and cognitive sequelae in survivors. The registry of CALGB patients has been used to study delayed psychosocial and cognitive sequelae in survivors. The first study was of childhood ALL, finding a mean 10 point IQ reduction in children who had received cranial irradiation. A present retrospective study of Hodgkin's survivors treated 1966-84 will examine current psychosocial function (emotional, vocational, social, sexual). Clinical trial groups provide a setting in which psychologic variables can be examined in large numbers of patients who meet uniform inclusion criteria and who receive uniform treatment. This resource, used by the CALGB, has been underutilized in psychiatric and quality of life research.


Hôpital Jean Minjoz, Besancon, France.

We manage a questionnaire and linear analogs to measure quality of life according to French cultural cancer patients. Our purpose was to perform a simple test with a high compliance from patients / or doctors. After preparing the questionnaire according to the main things involved with quality of life i.e. physical complaints, psychosocial distress, general well being, sexual dysfunction and general side effects, we tested successively among thirty, fifty and thirty patients our questionnaire QOL-Q and linear analogs and compared them with ACSA, for reliability, practicability and validity with a very good correlation (r = 0.4). In a second study these self questionnaire and linear analogs are used with interviews for further validity, and comparisons are made between the side effects measured by patient by and doctors using the WHO grading system. In a third study we have been using linear analogs since 1983, in a second prospective randomized study comparing two chemotherapy regiments for advanced breast cancer. Results of the compliance of this method and the effects on quality of life will be presented.

3964 AN INTERNATIONAL SURVEY OF PHYSICIAN PRACTICES IN REGARD TO REVEALING THE DIAGNOSIS OF CANCER. J.C Holland, A Marchini, S Tross, for International Psycho-Oncology Society, Memorial Sloan-Kettering Cancer Center, New York City, N.Y., USA.

In 1984, questionnaires were sent to individuals whose names were available to the International Psycho-Oncology Society office with the request to respond with information about the practice in their country about revealing the diagnosis of cancer, their opinion about the effect, trend and attitudes toward cancer. Data will be reported from 77 surveys returned from 27 countries. Preliminary analyses of the first 38 surveys found that in most countries sampled, 50-80% of physicians were estimated to tell the patient the diagnosis, though the range was 3% to 99%. Six countries estimated less than half. Over 90% told the family the diagnosis but this custom was estimated to vary from 67-100%. Terms used commonly were inflammation, infection, unclean tissue, growth and others. The majority (90%) reported a trend toward increased telling of the diagnosis, due to greater patient information and expectation and increased physician openness in using the word cancer. Most (74%) felt that the overall effect of telling the diagnosis was positive. While emotional distress was transiently greater when patients were told, there were positive effects of better coping, compliance, tolerance of treatment, planning for future, better communication with physician and others and improved prognosis. Sixty-three percent felt cancer patients experienced discrimination at job and 66% in acquiring insurance. The cross-cultural differences and the impact of cross-cultural focus on the psycho-social aspects of patient care will be considered.
Research Issues in Psychosocial Aspects of Cancer — The California Experience

This poster session will describe the efforts of the American Cancer Society, California Division, to encourage and promote research in the psychosocial aspects of cancer. An historical perspective of the philosophy and process will be presented. Major research issues that were identified will be delineated. The presentation will briefly describe past and present psychosocial research projects supported by the California Division.

TREATMENT AND GUIDANCE OF THE FAMILY PHYSICIAN OF PATIENTS WITH CANCER

A group of collaborative family physicians in the town of Maastricht (The Netherlands) registered the problems and experiences during the course of treatment and guidance of 221 cancer patients during the period January 1, 1979 to December 31, 1982.

In 80 cases (36.2 per cent) no problems were registered. In the other cases the problems concerned somatic care and in 39.4 per cent of the cases problems regarding somatic care and 9.8 per cent of the cases problems concerning the cooperation between various medical disciplines.

From the analysis of the abovementioned data the following conclusions may be drawn:

- The family physician noted a insufficient knowledge and skill in the treatment and guidance of cancer patients particularly regarding the somatic care.
- The problems between the family physician and the attending specialists are mainly caused by communication disturbances and differences in the view regarding the particular tasks.
- General physicians regard themselves as responsible for the continuity of care, but do not always know how to realise this objective.
- In the field of treatment and guidance the general physicians feel that they can do more for their patients and they are willing to put in more time. This study shows that lack of time is not a relevant factor.

The Psychosocial Sequelae of Lung and Breast Cancer: Relationship Between Patients' and Relatives' Perspective

A survey of the psychosocial sequelae of lung and breast cancer was undertaken administering the same measures in both patients and family members. The sample was derived from patients treated in a large regional cancer treatment centre (Toronto-Bayview Regional Cancer Centre - Toronto, Canada) in the calendar year 1983.

Substantial agreement was seen on the subscales of the Sickness Impact Profile (SIP). Lung and breast patients and their family members overall reported a significant degree of agreement with respect to areas of greatest impact and functioning.

However, significant differences, on a number of dimensions of psychosocial functioning, were found between the breast (N=67) and lung (N=26) patient and family groups. The results indicate that despite the similarities in the life threatening implications of these two processes, their psychosocial sequelae may be different. Implications for management and future research are discussed.
3969 131I-METIOIIOBENZYLGUANIDINE (MIBG) FOR TREATMENT OF NEUROBLASTOMA - CLINICAL RESULTS, CLINICAL PHARMACOLOGY AND DOSIMETRY
Department of Ped. Hematol., Depts. of Nuclear Med. and Dept. of Int. Med., University of Tubingen, FRG

Between April 1984 and November 1985 we treated 20 children with neuroblastoma in altogether 25 MIBG-courses. 5 of these children had a relapse of neuroblastoma, 3 had never reached a remission in spite of very intensive chemotherapy and 2 children were treated in first or second remission. 5 of these children with bone pain and fever became pain and fever-free during the first three days of therapy. In 6 of the 8 children with a manifest tumor the solid tumor responded as well as the bone marrow infiltration to the MIBG-treatment. Response extended from transitory decrease of the tumor mass to complete disappearance of great abdominal tumors. We also saw a decrease of elevated catecholamines in serum and urine, a decrease of bone marrow infiltration and a stabilization of osteolytic lesions. 7 of 8 children with a manifest tumor at the time of therapy died of the tumor progression or of a renewed relapse 55 to 350 days after the first MIBG-treatment. The children got 1 to 5 courses with a dose of 35 to 245 mCi. All single doses summing up, the total dose ranged between 85 and 596 mCi MIBG during the whole therapy. The therapy was tolerated very well without any complication. The only side effect seen was a reversible bone marrow depression.

The achieved radiation doses were calculated from many scintigraphic measurements. Up to 120 MBq tumor dose were achieved. Effective half life was found to be between 1.2 and 2.5 days depending from tumor biology. Pharmacological studies showed a dissociation of half life of MIBG-bound and free 131I. The substance seems to be very promising for treatment of neuroblastoma in relapse and also at begin of therapy. Therefore a multicenter study for initial MIBG-therapy is commenced.

3970 ETHICAL ISSUES AND NURSES' DILEMMAS

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Children's University Hospital
4058 Basel, Switzerland

Chemotherapy for the sick children and their families is very hard. Generally, the medical staff orders the treatments and the nurses are the people to carry out the chemotherapy. They are involved with the patients, their whole families, schools and careers.

How can we help patients and their parents to accept their disease and to suffer the drastic effect of the therapy? There are several ways we try to help:

1. Organization of meetings with parents of children with cancer.
2. To form an independent parents' group without clinical staff.
3. To make daily excursions with the patients.
4. To give the injections at home.
5. To organize holidays with patients, parents, siblings and clinical staff.
6. To organize baras, concerts etc. in order to raise money.

3971 TREATMENT OF CHILDREN WITH NEUROBLASTOMA WITH 131I-META-IODOBENZYLGUANIDINE (MIBG)


131I-MIBG is a labeled guanethidine derivative, developed to detect phaeochromocytoma. MIBG is stored in neurosecretory granules of chromaffin cells. Due to this activity it is logical that 131I-MIBG can also be used in detecting neuroblastoma with great accuracy. The uptake and long binding of 131I-MIBG by tumor localizations is considerable and led to the use of 131I-MIBG as targeted radio-isotope.

Ten children with neuroblastoma were treated with one or more doses of 50 - 200 mCi 131I-MIBG. Most of them had tumor progression after chemotherapy. Two reached complete remission with a follow-up of 8 and 6 months. Two started their treatment recently, three have a partial remission but are living a normal life. Three died of progressive disease after having achieved a good palliative treatment effect.

131I-MIBG seems a useful agent in the treatment of children with neuroblastoma.

3972 EMPIRIC AMPHOTERICIN THERAPY IN THE FEVERISH CRANIAL-NECROTIC INFANTILE PATIENT

D. Camargo R., Pettinelli A.S., Mendoza J.S.; Prudente M.; Caras E.; Morrispondo R.; Toffo L.J.; Bianchi A.
Hospital A.C. Camargo - S. Paulo - SP - Brasil

We studied 111 episodes of fever and granulocytic panicle perinatal cancer patients. Initially they were treated with broad-spectrum antibacterials (cephaloxin, amikacin, ciprofloxacin). Any patient with fever persisting for 7 days or with recurrent fever received empiric amphotericin therapy in addition to antibacterial therapy. Twenty-one patients received amphotericin B - (0.5-6 mg/kg/day). Age ranged 11 months - 12 years. Sex: 6 female, 15 male. Sixteen patients became afebrile after 1-2 days started amphotericin therapy. Four patients had persistent fever and three were proven to have bacterial superinfection. Toxicity from amphotericin B was mild and reversible, only in one patient was prohibitive. A response occurred in 1 of 21 patients. Six out of the sixteen, the granulocyte count returned higher (≥500 granulocytes) by the same time of amphotericin therapy started, however eleven - (69%) were still granulocytopenic. We suggest that empiric amphotericin B is indicated in neutropenic cancer patients with persistent or recurrent fever.
3974 COMBINATION CHEMOTHERAPY IN CHILDREN'S TREATMENT OF CHILDHOOD Rhabdomyosarcoma Stage III ADAPTED TO THE INITIAL CYTOSTATIC RESPONSE - A REPORT FROM THE GERMAN COOPERATIVE SOFT TISSUE SARCOMA STUDY (CWG-81).


From 129 rhabdomyosarcoma patients treated according to a national study protocol 76 were stage III (primarily only biopsy), complete information was available for 66 patients. The patients received a 16 week cytostatic therapy composed of vincristine, actinomycin, Adriamycin and cyclophosphamide. After 16 weeks of chemotherapy only a surgical restaging was performed. Patients with histologically proven tumor-free (stage Ipc) did not receive radiotherapy except in the cases of uncertain histology the patients received (40 Gy). Patients with microscopic residue (IIpc) received 40 Gy, and patients with macroscopic residue (II1pc) received 50 Gy after resection. Chemotherapy was continued for all patients till week 56. The table shows the distribution of the groups; the disease-free survival (DFS) rate and the failure in each groups.

<table>
<thead>
<tr>
<th>stage week 16</th>
<th>n</th>
<th>%</th>
<th>DFS rate</th>
<th>local failure</th>
<th>metast.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipc</td>
<td>27</td>
<td>40%</td>
<td>70%</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>IIpc</td>
<td>14</td>
<td>21%</td>
<td>61%</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>II1pc</td>
<td>16</td>
<td>26%</td>
<td>33%</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>non response</td>
<td>9</td>
<td>13%</td>
<td>27%</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

The disease-free survival (DFS) rate for the whole groups (Ipc) is 57%, the response rate (partial and complete) is 86.4%, the DFS rate for stage Ipc without radiotherapy is 69%, and with radiotherapy 58%. The conclusion of this study was: 1) Patients with high response after initial cytostatic treatment (Ipc) can be cured by chemotherapy only. 2) Patients with insufficient response (IIpc/II1pc) need a more effective local tumor control at earlier date. The lost point will be supported by a separate examination in this study about the degree of tumor response up to week 7 and the correlation to the DFS rate: complete response up to week 7 = 100% DFS.

The DFS rate is 57% for stage Ipc, 61% for stage IIpc, and 33% for stage II1pc. The DFS rate for the whole groups is 57%. The DFS rate for stage Ipc without radiotherapy is 69%, and with radiotherapy 58%. The overall DFS rate is 57%, the response rate (partial and complete) is 86.4%, the DFS rate for stage Ipc without radiotherapy is 69%, and with radiotherapy 58%.

3975 TOTALLY IMPLANTABLE DRUG DELIVERY SYSTEMS (PORT-A-CATH) IN CHILDREN WITH CANCER. L. Than-Hosenstein, E. Jutte; R. Gherardini. Dep. of Pediatrics, Dep. of Pediatrics, Surgery University of Vienna, Austria.

Appropriate treatment of children with malignant disease generally requires repeated safe access to the venous system for the delivery of drugs, parenteral nutrition and blood products. For this purpose we used a totally implantable drug delivery system (PORT-A-CATH-SYSTEM, PAC). Two PAC have been placed in 18 children; the age ranging from 4 months to 22 years. The devices have been in place for a total of 2992 days. In 2 patients the PAC have been in use for more than 1 year, in 7 for more than 6 months and in 11 children for more than 3 months. The complication rate for all devices was 3.8 complications / 1000 days.

The individual tolerance was found to be very good in 12 patients, good in 5 and 1 PAC had to be removed due to individual intolerance.

In conclusion, the PAC represents an important improvement over currently available techniques of prolonged venous access because of its 24-hours-suitability and its very low complication rate as well as the excellent individual tolerance.


The role of Hyperthermic Perforation (H.A.P.) for the treatment of osteogenic sarcoma was evaluated in 10 patients. Twelve patients were treated with H.A.P. alone and a 5- and 10-year survival rate of 24% and 12% was obtained. When amputation was historically associated to H.A.P., a 5- and 10-year survival rate of 10% was achieved. Twenty-seven patients were treated with Hyperthermic Antiblastic Perforation (H.A.A.P.) followed by amputation and the 5- and 10-year actuarial survival rate rose to 71% and 56% respectively, with a 5-year disease-free survival rate of 67%. Fifteen patients have been treated with H.A.A.P. followed by an "en bloc" resection and bone reconstruction, the 5- and 10-year actuarial survival rate was 65%, with a 5-year disease-free survival rate of 67%. These results seem to indicate that H.A.A.P. permits a conservative rather than demiliter surgery in treating limb osteogenic sarcoma.

Between 1981 and 1985 in our Pediatric's Dept. four clinical trial with aggressive chemotherapy combined with radiation therapy and surgery were tested in central nervous system tumors (CNS) and in advanced non-Hodgkin's lymphoma (NHL), neuroblastomas and soft-tissue sarcomas, with the purpose of improve survival. Results have been published in the methods of Kaplan-Meier and Mantel-Heinzel. In CNS tumors four different schemes were compared and we found an improved survival only in glioblastoma multiforme and in grade II not excised astrocytoma. High-dose cyclophosphamide showed an important effective mean in glioblastoma multiforme. In NHL survival was increased in clinical stages III: 44% v.s. 31% and in IV: 13% v.s. 0%. Prophylaxis with intrathecal methotrexate diminished CNS involvement compared with no prophylaxis. In advanced neuroblastoma better results were in stage II. Survival in advanced soft-tissue sarcomas were increased from 27% to 70%.
cisplatin is an effective chemnification with accepted toxicities. Seventeen patients of 15 months (7.9 months) of the 10 children there was no improvement and in complete in 9 (37.5%) and partial in 5 (20.8%) and lasted 4-31 months. Ototoxicity were limited. The response to therapy was car in non responding solid tumors of childhood etoposide and 70 cycles (mean 6) were given and to all children in the 5th cycle and in 2 hypamagnesemia whereas neuro and 2 children BUN and creatinine elevation was noted after chemotherapy. In 18/24 the carboinatJ.on was used as second line ma, 2 hepatoblastoma, 2 germ cell tumors and 3 miscellaneous (of these had soft tissue sarcoma, 4 Wilms' tumor, 2 lymphoma). The response of this combination was studied in 24 children of 21-28 days. Gastrointestinal toxicity was minimal, whereas 50% nephrotoxicity. Petrom creatinine is mg/dL was found in only 2 patients (1.9 and 1.6 mg/dL), respectively. This being, however, reversible after therapy completion. Audiogram abnormalities were also observed, but without a significant impairment of hearing capacity. Myelosuppression was either moderate or severe: 5 patients showed grade IV leukopenia and 7 patients grade III thrombocytopenia thus requiring platelet transfusion. As regards the renal function, all patients showed normal subjective and objective responses, with 7 partial remissions and 7 minor responses. Those results indicate that a 5-day continuous iv infusion regimen of 200 mg/m² cisplatin with pulsed etoposide is well tolerated and produces objective responses in patients with advanced childhood malignant solid tumors.

Etoposide and cis-platinum have being used as second li- ne combination chemotherapy in relapsed childhood tumors. The response of this combination was studied in 24 children 14 boys and 10 girls with mean age 5.6 years (1-14). Seven of these had soft tissue sarcoma, 4 Wilms' tumor, 2 lymphoma, 2 hepatoblastoma, 2 germ cell tumors and 3 miscellaneous (of these had soft tissue sarcoma, 4 Wilms' tumor, 2 lymphoma, 2 hepatoblastoma, 2 germ cell tumors and 3 miscellaneous). In 18/24 the combination was used as second line treatment whereas in 6 after poor response to the initial therapy. Etoposide was used in dose 100 mg/m² as one hour infusion followed by cis-platinum 90 mg/m² as 8 hour infusion every 2-3 weeks. Prior to therapy appropriate renal studies were obtained and 24 hydration was administered. Three to 10 cycles (mean 6) were given and in all children nausea, vomiting and mild myelosuppression were noted. In 2 children BUN and creatinine elevation was noted after the 5th cycle and in 2 hypoglycemia whereas neuro and endotoxicity were limited. The response to therapy was complete in 9 (37.5%) and partial in 5 (20.8%) and lasted 4-31 months. In 10 children there was no improvement and in 4 of them the disease progressed. Four of the complete responses underwent second look surgery. It is concluded that in non responding solid tumors of childhood etoposide and cisplatinum is an effective combination with accepted toxicities.
The treatment results of II and III groups in children: Concerning the 3-year survival rate, the comparison of our three groups shows better results in the II and III groups than in the I group, with a statistically significant difference.

In group I and the difference in survival rate is statistically significant. Group II (30.0% vs. 0.0%) and group III (50.0% vs. 0.0%).

Comparing the survival rate of II and III group, we can see the equal risk of survival in patients with II and III groups (II: 50.0%, III: 50.0%).
PROSPECTIVE RADIATION TREATMENT IN THE POSTOPERATIVE TELECOBALT IRRADIATION OF MEDULLOBLASTOMA. Mayer, E.; Katona, A.; Somogyi, Gy.; Nemeth E. Weill Hospital, Centre of Radiation Therapy, Budapest, Hungary.

At the Centre of Radiation Therapy in Budapest, between January 1982 and December 1984, 24 patients with medulloblastoma were treated by postoperative Co 60 teleirradiation, in the course of which a radical tumour removal took generally place. In none of the cases did we carry out the irradiation of the entire cranial segments and covering the posterior fossa and the volume of the III ventricle. For the irradiation of the adjoining spinal cord dorsal fields have been taken, the focus being in a calculated depth of 3 to 5 cm. So as to diminish the inhomogeneity occurring at the junctions of the single fields, we used the "moving field technic" directed towards the cranio-caudal.

The homogenous irradiation of the modified cranial target volume can easily be carried out with a Co 60 irradiation source from a frontal and two occipital fields. In this context dosimetry and computer have been made. The total dosis for irradiation the cranial was 53 Gy (in NSD: 1441 ret., in TDF: 72.4), on the spinal cord 24 Gy (In NSD: 906 ret., in TDF: 35.4). When applying the above doses neurological and haematological complications, which could be attributed to the irradiation treatment, did not occur. As our time for observation was very short, the time being the results can only be evaluated on the basis of a two-year symptomless condition.


Due to the bad prognosis of children with advanced medulloblastoma and because of the recent scientific and technical development of techniques in our country, some years ago, it was decided to incorporate within the multidisciplinary therapeutic program a surgical treatment which we named "spinal rescue" in order to obtain a cure in group of children patients with advanced medulloblastoma and later to analyze the results. In the clinical trial were included 37 children who had advanced neoplasia at abdominal or thoracic metastatic lesion with controlled primary tumor. Of the 14 patients with previous inoperable lesion in 17, the complete resection of the tumor could be achieved after reducing the tumor volume by the polychemotherapy treatment and/or ionizing radiations. The real surgical partial resection. There was only one surgical death due to atelectasis in a patient who was applied pneumectomy. The other complications were less important except a mechanical intestinal obstruction due to bowel and a stenocardiac failure. Treated patients were 37 at moment of this study, 19 were alive and free of tumor. The survival accumulated (Kaplan-Meier) in the different tumors was increasing reaching a general survival of more than 50%.
Patient and family education is an essential part of cancer care. At Roswell Park Memorial Institute, 666 Elm Street, Buffalo, New York 14263 U.S.A.

A study of response to a breast self-examination (BSE) teaching programme showed that levels of adequate BSE practice 1 year later were associated with prior motivation towards and experience of BSE. Women in the study population were contacted 2 years later. In the original group settings, and a qualitative research technique was used to explore factors affecting the continuing practice of BSE. The main areas which emerged were related to: cancer per se, the possibilities of cure for breast cancer, psychological barriers to practice (can't be bothered), aspects of the technique/learning a motor skill, and fear - expressed as fear of finding something on examination, as fear of cancer, and as of the treatment for breast cancer. The findings re-emphasise the need for clinical and emotional support for women who, in BSE, are bearing all the burden of a screening process, whereas in most screening this is largely borne by the provider of the service.

"LET'S TALK": AN INFORMATION SESSION FOR CANCER PATIENTS AND THEIR FAMILIES. Gayle A. Bersani, R.N., Diane L. Cooke, Ph.D., Arthur Michalek, Ph.D., Edwin A. Mirand, Ph.D., Rosemary Hellmann, M.S.,R.N. Education Department, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, New York 14263 U.S.A.

Patient and family education is an essential part of cancer care. At Roswell Park Memorial Institute in Buffalo, New York, a weekly information and discussion session is offered to cancer-in-patients, out-patients, families and friends. This session, entitled: "LET'S TALK" is held in the Patient-Family Resource Center located in a central area of the hospital. A nurse-educator coordinates this patient-family education meeting with assistance from other staff. The program is advertised via poster, public address announcements, and printed cards at patient dinner trays. Weekly attendance ranges from 5-15 people. At these sessions information is provided on hospital and community services available to cancer patients and families. Written and verbal information is furnished on a variety of topics including: diagnosis, surgery, chemotherapy, radiotherapy, nutrition, discharge, homecare, financial issues, and the psychosocial needs of patients and their families. Patients and families are encouraged to talk to each other as well as the program leader. When appropriate, referrals are made to our other hospital services such as psychology and social service. At the end of each program participants are asked to fill out a single evaluation form. These data provide information on the educational needs of patients with cancer and their families, and furnishes program staff with feed-back on how well the program has been received. This presentation will also include information on how other facilities can establish and conduct similar programs tailored to the educational needs of their own patient-family population.

CANCER PATIENTS: HOW TO INFORM THEM AND THEIR AWARENESS OF THE DISEASE. M. Tonbaroni*, S. Selmi*, A. Liberati**, V. Ventrejik*, * Pain Therapy Division - National Cancer Institute, Milan, Italy **Istituto Mario Negri, Milan, Italy.

In European countries of Latin origin, though done more gently than in the past, the patient is only generally informed and the family more completely. In the U.S., instead, things are done quite differently, namely for insurance or welfare reasons, whereby the diagnosis is immediately communicated and the entire therapeutic itinerary requires the patient's written consent. Some cases may not require a completely open and honest explanation for various reasons, i.e. owing to the seriousness of the disease and its advanced stage, the type of treatment and the psychological well-being of the patient. Nevertheless, the communication of a diagnosis, similarly to emotions, is not merely conveyed through verbal channels. It is something more subtle, and rather obvious at times, in the form of non-verbal communication. For instance, the tone of one's voice, the look of one's face, the body's contractions or the alternate exchange of words and silent pauses in a conversation may contradict what has eventually been stated. Some information about the disease and therapies are inevitably passed on to the patient at different time intervals by hospital personnel and family members alike. And what often happens is this: the patient learns to filter the truth by choosing the best interpretation for him out of the many heard. Here are the results of two surveys. In the first, carried out using self-rating questionnaires sent by mail, only 37% of 825 breast cancer patients had received a full explanation of their diagnosis. In the second study, the data collected from cancer pain patients revealed that the degree of awareness of the disease was directly correlated to several psychosocial indicators such as: Performance Status ( Karnofsky) and the Quality of Life Index (Spitzer).
EARLY DIAGNOSIS: POPULATION'S IGNORANCE. Based on the research "Attitude of the population towards cancer". N. Itohama, C. Villanori. Neurologist Research Institute and ARGENTIN, Buenos Aires, Argentina.

Sample: 1,191 subjects from Buenos Aires and its suburbs, distributed by sex and age according to the last National Survey, belonging to all socio-economic categories. To the question, do you know about cancer? only 12% mention the importance of early diagnosis. This answer decreases progressively in the lower socio-economic levels. To the question, do you know ways of early diagnosis of cancer? 53% of the subjects do not understand the question. Forms of early diagnosis: partnerships and good prevention to improve outcome have been the LALCEC doctors. From now on she has the first function in LALCEC start in the company and affection to those whose timid cause of the illness. The blasts organs on which the illness has the major incidence. The body is a similar pose and the protective detection in apparent health condition. Of the multiple tasks that have to be done in the exercise of her labour, one of the most important is the "EDUCATION FOR THE HEALTH". The body for the patient's treatment, who has cancer or else in the protection of the breasts. In working, low working and low classes, the answer "periodical check ups" is statistically meaningful. This reveals a lower knowledge of specific forms of early diagnosis. In the population in general, the most frequent knowledge, attitudes, and methods, related to the health of the person in order to make him conscious that the cancer is a curable illness. This of course provided that the detection has to be made forwardly. For this is necessary to realize periodical medical exams of the accessible organs. Since the illness has the major incidence breast, skin, female genital apparatus.

The first function in LALCEC start in the waiting hall, giving sympathy, compression, company and affection to those who is anguish and anxiety by the fact of "being being by the LALCEC's doctors". From now on she has the present work is focalized to the EDUCATION for the HEALTH in ONCOLOGY.

EVALUATION OF A MASS MEDIA CAMPAIGN ON BREAST CANCER IN WESTERN NEW YORK. E.R. Schoenfeld, S.L. Darrow, E.M. Cummings, E. Wilken, S. Madoff. Roswell Park Memorial Institute, Buffalo, New York, U.S.A.

The purpose of this study was to evaluate the effects of a public education program on women's knowledge and beliefs about breast cancer. During the week of April 22-28, 1985, a local news team to broadcast a special five-part series about breast cancer on the moon and eleven pm newscasts. A pretest-posttest study design was employed in which a random sample of women, over the age of 18, in Western New York was obtained prior to the broadcast, and a second independent sample was surveyed one month after the broadcast. The study population was determined through random selection of household telephone numbers from the Buffalo, New York area telephone directory. The first survey group consisted of 275 respondents (31.9% response rate); the second survey group consisted of 291 respondents (42.1% response rate). Telephone interviews were conducted by trained interviewers. The interview questioned respondents about knowledge of risk factors for breast cancer, signs and symptoms, methods of diagnosis, treatment, BSE, beliefs about breast cancer. During the week of April and July of 1985. The interview questioned respondents about knowledge or beliefs about breast cancer were observed in any of the three analyses, suggesting that the program had little impact on changing women's knowledge of breast cancer.

THE VOLUNTEER'S IN EDUCATION FOR THE HEALTH. KARIA ESTHER GAVILANES 2 TORRES ROSA RODRIGUEZ LALCEC. ARAOZ 2380. BUENOS AIRES, ARGENTINA.

The volunteer, that joins LALCEC with a clear concept of altruism and solidarity, is conscious of the functions she has to realize in the mention body. This body is a similar pose in a similar environment. The discipline directed to the patient's treatment, who has cancer or else in the protection of the breasts. In working, low working and low classes, the answer "periodical check ups" is statistically meaningful. This reveals a lower knowledge of specific forms of early diagnosis. In the population in general, the most frequent answer is "periodical check ups" (statistically significant).

The purpose of this study was to evaluate the effects of viewing the broadcasts. First, the knowledge and beliefs of the pretest group were compared to that in the posttest group. The posttest group was then divided into those who watched the show (n=98) and those who did not (n=193) to test for the impact of viewing the broadcasts. Finally, the knowledge and beliefs of the posttest group were evaluated based upon the number of shows watched (0, 1, 1.3 or more). No significant differences in knowledge or beliefs about breast cancer were observed in any of the three analyses, suggesting that the program had little impact on changing women's knowledge or beliefs about breast cancer.

KNOWLEDGE ABOUT BREAST CANCER AND BREAST SELF-EXAMINATION FROM A RANDOM TELEPHONE INTERVIEW OF WOMEN IN WESTERN NEW YORK. S.L. Darrow, E.R. Schoenfeld, K.M. Cummings, E. Wilken, S. Madoff. Roswell Park Memorial Institute, Buffalo, New York, U.S.A.

The purpose of this study was to evaluate the knowledge of women with regard to breast cancer and breast self-examination (BSE). The study population was determined through random selection of household telephone numbers from the Buffalo, New York area telephone directory. The overall group consisted of 563 women over the age of 18. Telephone interviews were conducted by trained interviewers, between April and July of 1985. The interview questioned respondents about knowledge of risk factors for breast cancer, signs and symptoms, methods of diagnosis, treatment, BSE, beliefs about breast cancer and demographics. Differences in knowledge and beliefs towards breast cancer and BSE were studied in relation to age, race and educational background. Each factor appeared to influence the practice of BSE, use of mammography and belief about breast cancer. Women over age 49 and those with less than a high school education were less likely to have been taught how to do BSE (p < 0.05). Results from this study were also compared to those obtained from a study of public understanding of breast cancer conducted by the National Cancer Institute (NCI) in 1980. Compared to the study by NCI in 1980, it appears that the knowledge level of women with regard to breast cancer has increased. Similarly, the majority of women (94.2%) of women recognize that they can be diagnosed early. Knowledge regarding the use of mammography as a diagnostic tool and or treatments will be perform, showing integrity, faith and good prevention to improve listed and understand, trying every day to be better nurse than the day before. The present work is focalized to the EDUCATION for the HEALTH in ONCOLOGY.
3997 ATTITUDE OF THE POPULATION TOWARDS CANCER: DIAGNOSTIC

Objectives: To know the attitude of the population towards cancer, specially about receiving or not diagnostic information. Methodology: 1,951 interviews (542 men and 659 women) were performed in Buenos Aires (Capital city and its surroundings) to people between 15 and 75 years of age, distributed by socioeconomic classes, according to the last National Survey. We employed semi-directed interviews with 13 questions, of which 2 are evaluated for this presentation. The data provided by this research show that the attitude of the population agrees in revaluing the right of the patient and the family to know the diagnosis, this will allow an adequate emotional attitude in order to cope with the disease and treatment. The need of a previous psychological evaluation in each case is emphasized, which also includes the family nucleus.


Objectives: to deepen the psychologic attitudes of the population in reference to cancer, establishing the degree of knowledge about the etiology. Methodology: 1,391 surveys in the suburbs of Buenos Aires, distributed by sex and age according to the last National Survey, of all socio-economic categories. Chi-squared and graphic representation tests were performed, with a significance level of 0.05. Results: In view of the question: "Which do you believe are the causes of cancer?" 42% of the population answer "They do not know"; 30% mention the cigarette and/or alcoholic beverages. The remaining mentioned causes have an even distribution which do not equal the statistic burden of: cigarette and alcoholic beverages. The most frequent response among men between 15 and 34 years of age; paradoxically, the highest percentage of smokers is in this group. Conclusions: the answers of the population are consistent with the knowledge of the carcinogenesis character of the cigarette and the warnings about an overuse of alcoholic beverages. The remaining mentioned causes are linked with several theories in fashion, some of them scientific, about carcinogenesis. This investigation has been partially subsidized by the University of Buenos Aires.

3998 THE PLANNING AND EVALUATION OF A BREAST CANCER TEACHING DAY PROGRAM. E. Wilkes, C. Mettlin, K. M. Cummings, A. Gerard, M. Morgan, G. Loizides, Roswell Park Memorial Institute, Buffalo, New York, U.S.A.

Breast cancer is the most common cancer in women in the United States today. Researchers report that only 20% of all women practice breast self-examination regularly. In response to this problem, the American Cancer Society, New York State Division and Roswell Park Memorial Institute collaborated to design a breast cancer education teaching program to increase the public's awareness of breast cancer. The objectives of the program were: (1) to increase the percentage of women who perform BSE correctly each month, (2) to increase women's awareness of risk factors and symptoms of breast cancer, (3) to increase awareness of early detection methods, (4) to increase awareness of treatment methods, (5) to teach the proper technique of breast self-examination. The target audience was all women in Erie and Niagara Counties, New York. More than 100 BSE Certified Nurse and Health Educator volunteers were recruited to conduct BSE programs in sixteen locations. A series of educational reports on breast cancer appearing on the noon and late night news of a local television station helped promote the Teaching Day Program. Approximately 200 women attended the program. A pretest survey of a random sample of women in the population was completed to measure women's knowledge of breast cancer and methods of early detection. A post survey, a second independent random sample of women, has been completed and will enable us to evaluate the effectiveness of the television series in increasing women's knowledge about breast cancer.

4000 THE GERMAN CANCER INFORMATION SERVICE (KREBSE
INFORMATIONSDIENST, KID) - A LAY SERVICE LINKING RESEARCH, MEDICAL CARE WITH THE PUBLIC. Dr. Almuth Sellschopp, Institut für Psychotherapie und medizinische Psychologie, Klinikum Rechts der Isar, München, BAV.

Ihre Leitlinie: To know the attitude of the population towards cancer, especially about receiving or not diagnostic information. Methodology: 1,951 interviews (542 men and 649 women) were performed in Buenos Aires (Capital city and its surroundings) to people between 15 and 75 years of age, distributed by socioeconomic classes, according to the last National Survey. We employed semi-directed interviews with 13 questions, of which 2 are evaluated for this presentation. To the question: "Do you think the physician should inform the diagnosis of cancer to the patient?" 649 persons (55%) answered "YES; 301 (25%) NO; and 243 (20%) IT DEPENDS. Those who said "YES" gave reasons like: "He has the right, it is his life" and "So that he accepts treatment". The reasons for "NO" were: "The patient can become depressed, discouraged and "It is better for the patient to maintain the illusion". The reasons given for "IT DEPENDS" were: "There are psychologically weak people". To the question: "Do you think the physician should inform the diagnosis of cancer to the family?" 1000 persons answered "YES (91%)" pleading: "The family can give emotional support to the patient"; 66 persons (5.5%) said "IT DEPENDS" - "Not every family can help" and only 45 persons (3.5%) think that the family must not be informed. Conclusions: There are controversies in our scientific environment in the oncology field regarding whether to give or not diagnostic information. The data provided by this research show that the attitude of the population agrees in revaluing the right of the patient and the family in knowing the diagnosis, this will allow an adequate emotional attitude in order to cope with the disease and treatment. The need of a previous psychological evaluation in each case is emphasized, which also includes the family nucleus.
4001 PROACTIVE INFORMATION EFFECT ON SELF-CARE OF RADIATION THERAPY PATIENTS - Marylin Dodd, RN, PhD, University of California, San Francisco, School of Nursing, # 6114, San Francisco, California 94113, U.S.A.

Delving on Orem’s conceptual model of self-care, the purpose of this longitudinal experimental study was to test the efficacy of providing side effect management (SEM) information proactively for radiation therapy patients. The proactively experimental intervention consisted of presenting SEM information on all side effects the patient was susceptible to develop, prior to the development of any side effects. A control of like patients received SEM information reactively once side effects were experienced. This research was a replication and extension of earlier self-care studies (Dodd, 1982; 1983; 1984). Sixty patients initiating radiation therapy (RT) were randomized into either the experimental or the control group. They recorded their experienced side effects of RT and in their self-care behavior (SCB) logs. Measurements of State-Trait Anxiety and Cancer locus of Control occurred at the beginning and six weeks later at the end of RT. Patients receiving SEM proactively performed more selected SCBs than patients who received SEM reactively (t = .24, p .02). Anxiety decreased significantly (p = .004) between interviews. The findings extend and enhance understanding of self-care in this population and indicate the usefulness of providing proactive SEM information in practice.


In 1600 cases (age ranging from 20 to 40 years) the following parameters were checked using a questionnaire: 1) Knowledge, opinions and attitude concerning the possibility of preventing and treating cancer; 2) Opinions on causes of cancer; 3) Source of knowledge; 4) Words used to identify cancer; 5) Acceptance of BSE and P.E.P. test; 6) Anxiety and care for personal health; 7) Correlation with previous points seen under the aspects of economic status, birth place, social extraction and risk factors for female tumors. Four different basic aptitudes towards the possibility of attending centers for early cancer detection were identified. The memory of information "media" derived as well as the utilization of cancer detection centers are influenced and determined by the expectation of successful cure of cancer.

4003 TRUTH AND DIAGNOSIS IN CANCER PATIENTS: AN INTUITION OF BEYOND. F.M. Penna and A.J. Rullen, Hosp. G.A. Alfaro - Oncology and Mental Health Sections, Lomas, Argentina.

Cancer, for us of our days, has an irrational breae of incredibility, suffering and death that generates dreadful fantasies in patients and doctors. In the doctor, his own fear to cancer-death produces extremely opposite attitudes: a) he puts maximal distance with his patient and uses “truth” as an real aggression, or he refuses to speak with him; b) he doesn’t put any distance, confounding himself with the patient, he needs to lie and becomes paralyzed in his professional posture. This pathological behavior generates suffering to the patient, his family and to the own doctor. To avoid this, we describe, after several interviews, a comprising situational diagnosis: the "Oncological Staring" and the "Intuitional aspects Staring" what the patient knows or feels, what he denies or fears, we consider three stages: 1) Complete denial (includes US, more cancer or tumor); 2) Intuitional knowledge (negation of some objects, i.e. prognosis); 3) Total ignorance or passive negation.

Stage III patients showed more acute psychiatry pathology (suppression, unusual intense) that vanishes specialist treatments and even psychogenic naturalization. Anticipatory vomiting, treatment refusal of medication were more frequent in stage III than in stage 1 or 11 patients, but the trend is not of statistical significance. We refer to a "truth" dissociated from the patient, but the one he may tolerate, maintaining hope (in cure, remission or symptom relief; i.e. pain). The "optimum distance" with the patient, that he acquires in the interdisciplinary collaboration with the psychologist, allows the doctor with his words, gestures and attitudes to maintain communication with the patient through the whole illness process.


During 1981 through 1983, 489 patients with cutaneous melanomas were studied with respect to delay factors in diagnosis and treatment. For this a detailed questionnaire was used. The study was conducted in Nijmegen, Rotterdam and Münster. The stage of the disease at diagnosis was related to patient characteristics and delay intervals. An unfavorable stage was seen in the younger and in the older age groups (53 and > 65 years, respectively). The time interval between onset of symptoms and first doctor's consultation with ages, relatives presented with less advanced disease, irrespective of localization of the tumor. Patients of the higher social classes visited their physician earlier than those of the lower classes. The former group was more often cognizant of the malignant nature of the lesion. Awareness of malignancy had a favorable impact on the stage at diagnosis. Even patients who had a suspicion of cancer showed long time lapses between the moment that the symptoms became suspect and the first consultation. Among the reasons given for this delay, a feeling that the situation was not urgent and lack of time were the most important. Fear of cancer was less often encountered. A less advanced stage was observed when the motivation to seek medical advice came from a relative or friend instead of from the patient himself. On rare occasions the melanoma was detected by chance (during general check-up or consultation); these patients showed a very favorable stage at diagnosis. Few patients visited their doctor principally for cosmetic reasons. Also, self-treatment was employed rarely. Cosmetic complaints and self-treatment were associated with lesion ulceration or bleeding. Most importantly, the shorter the duration of symptoms, the more favorable the stage at diagnosis appeared to be. The results of a multivariate analysis are presented to show the relative importance of those findings. The data suggests that public educational programs are worthwhile in creating better awareness and enhancing detection of melanoma.
UNPROVEN METHODS IN TREATMENT OF CANCER IN FRANCE
S. SCHRAUB
Hôpital Jean Minjaz, Besançon, France.

We have studied the unproven methods of treatment of cancer their, promoters and the utilizers in France since 1980. It was possible to classify them in five chapters: unproven tests, unproven drugs and theories, electric and magnetic devices, diets and psychological treatments. Some of these methods are practiced and used only in France, others are widely used in the world as psychedelic, macrobiotic diet or special psychological treatment. One of a specific French product was tested and analyzed in laboratory and found to be largely contaminated by germs. Discussions with the promoters of their defenses are difficult and tough. They want their products to be experimented but a lot of them refuse classical trials (Phase I, II or III) because of specific treatment of the whole person. In a lot of circumstances, the unproven drug is advised to the patient by their family not to have remorse or regret. The impact of these treatment is hard to measure in France and patients are reluctant to answer questionnaire about this subject as it was seen in our experience. About 10 to 40% of patients have heard and about them tried some unproven methods. A lot of patient goes toward these methods because of a poor relationship between them and their doctors. They search more hope, spirit especially when the disease is advanced and they are attracted by a nontoxic, simple treatment. Some good results on the psychic of the patient can be interpreted as a placebo effect with a behavior identical to such seen in religious sect. This latest point must be distinguished with the psychological support that can be given with other "classical" treatments.

AN EDUCATION PROGRAM FOR BREAST-CANCER PATIENTS BEFORE DIAGNOSIS AND TREATMENT TO ENHANCE "QUALITY OF LIFE." R. Kushner, Breast Cancer Advisory Center, Kensington, MD, USA 20095.

In the United States, breast-cancer education programs teach healthy women about early detection, and there are many support programs for women who have already been diagnosed and treated for primary disease. About 119,000 new cases of breast cancer were diagnosed in 1985. Since about 80 percent of all breast masses are benign, this statistic means that more than 1 million women endured the anxiety and stress of finding a breast lesion, undergoing various examinations and tests and then waiting for the results. All of these women suffered equally before diagnosis: Those with benign problems felt the same dread and terror until they were finally given the results of their histology reports. While these are U.S. statistics, the suffering is the same in all nations. During the next phase, of the women who are found to have cancer, about half will need some kind of adjuvant therapy after primary treatment. The patients receiving cytotoxic regimens need information and help to cope with the drugs' side-effects. Moreover, tens of thousands of patients recur and must again be diagnosed and treated. Cancer communicators, educators and members of relevant medical/surgical disciplines can help during these traumatic intervals by giving information and support before and during all procedures at all stages of breast cancer. By doing so, health providers will enhance patients' "quality of life." Slides will show how the Breast Cancer Advisory Ctr (BCAC), of Kensington, Maryland USA, has helped about 40,000 women (and men), from all over the world, during the stressful times of waiting for appointments, examinations, tests and diagnoses and treatment. Details are given about the BCAC's activities, and the telephone "Hotline" it operated from 1975 to 1982 (when it was ended due to lost funding) are described.

OUTCOMES OF INTENSIVE TRAINING IN BREAST SELF-EXAMINATION. D.J. Hill, J. Rassaby, S. Hirst. Anti-Cancer Council of Victoria, Melbourne, Australia.

Over '80 women who were taught breast self-examination in a one hour teaching session were followed up a year later to evaluate retention of knowledge and skills; current BSE practice; and interval morbidity, (including psychological morbidity) associated with BSE practice. Women were recruited to the teaching sessions by general practitioner referrals, by publicity in the workplace and in communities. They learned in small groups through the following media: talk by health educator nurse; practice on synthetic breast form; video tape demonstration, guided practice on self; structured group discussion; individual action-planning to enhance self-efficacy in carrying out subsequent BSE; knowledge and attitude post test; take-home printed and audio-visual materials.
A SYSTEMATIC METHOD FOR IDENTIFYING PSYCHOLOGICAL FACTORS THAT INFLUENCE CANCER-PREVENTIVE BEHAVIOURS

D.J. Hill, Anti-Cancer Council of Victoria, Melbourne, Australia.

In health education, as in medicine, accurate diagnosis is necessary before effective treatment may be undertaken. As health educators are usually involved in changing conscious, intentional behaviours it is desirable to link their health education “diagnoses” with the best theory and research bearing upon intentional behaviour. A relatively simple questionnaire method was developed to enable health educators to quantify and rank the importance of different opinions (beliefs) and values about a given target behaviour (e.g. doing breast self-examination) for a given population. The method is described, and the results of its application in a health education diagnosis on BSE and Pap test among female office workers are given. It was found that target beliefs correlated highly with concurrently measured intentions to do BSE and have a Pap test also correlated with behaviour at follow up, thus validating the method.

CLINICAL AFTERTREATMENT-ESSENTIAL PART ONCOLOGICAL FOLLOW-UP

Hartung, Gerd
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The systematic clinical follow-up treatment after an aggressive cancer therapy is of great importance for the definite therapeutic result and for the further fate of cancer patients. Together with continued treatment and rehabilitation it constitutes an element of the whole complex of cancer therapy which is of the same importance as in the aggressive therapy, which is neither the climax nor the end of the therapy.

The purpose of clinical follow-up treatment is to consolidate the therapeutic result, which was achieved by aggressive cancer therapy (operation, radiotherapy, antineoplastic chemotherapy), and to bring the patient from his passive condition back to active life as far as this is possible.

The first main objective is the patient’s adaptation to life after treatment because any form of aggressive therapy has some sideeffects and calculated sequelae.

Clinical follow-up treatment of over 6,000 cancer patients has to fulfill an important function as a link between the aggressive cancer therapy and the rehabilitation.
The nursing process in a course of radiation therapy has an important position before, during, and after the radiotherapy course. This can be illustrated using patients with Head and Neck Cancer, Mammary Tumour, Gynecological, and Urological Neoplasms.

For the patient with Head and Neck Cancer one has to focus on the problems by food intake, as radiotherapy will interfere with the patient's ability to eat. Patients suffering from Breast Cancer are suffering psychically from the lost of their breast, followed by problems of arm-moving and later from irradiation of skin.

Gynecological and Urological tumours are often causing bleedings, and the side effects of radiotherapy can cause problems by urination and/or rectal problems. By all kind of external beam irradiations the irradiated skin is vulnerable, later in the course of radiotherapy it becomes dried and dry. Preventive measures need to be taken to protect the skin, and/or the irradiated organs and organ systems. Without the intensive help of the nurses the care of irradiated patients is absolutely impossible.
BRM are agents of approaches which modify the relationship between tumor and host by modifying the host's biological response to tumor cells with resultant therapeutic benefit. Some examples of BRM include a variety of interferons and monoclonal antibodies and other agents such as interleukin-2 and Poly ICCL. Nursing responsibilities to patients receiving BRM have both included: the safe administration of the BRM agent; close monitoring and careful documentation of toxicities; prevention and management of treatment-related toxicities; providing patient and family education and support; and coordination of the clinical trials. These various nursing roles will be described. Interferon (IFN) is a prototype of the numerous BRM currently in clinical trials. Common side effects include: fatigue, anorexia, nausea, vomiting, diarrhea, headache, alteration in blood chemistries and neurotoxicity. Nursing research and management related to these common problems will be presented. Nurses must be aware of and involved, when feasible, in BRM clinical trials.
4017 THE ROLE OF MACROPHAGES IN BONE TUMOURS.
E.Grundmann, Münster, FRG

4018 CLASSIFICATION PROBLEMS OF BONE TUMOURS
Zsuzsa Cseté, Orthop. Clin. of the Semmelweis Medical School, Budapest, Hungary

Classification problems of the bone tumours will be discussed on the basis of the material of the Semmelweis Medical School's Bone-tumor Register using the data of 2735 patients recorded during the last twenty years. Advantages and disadvantages of the Aegerter-Kirkpatrick's classification used earlier in the Register and experiences with the widespread accepted WHO nomenclature will be evaluated. Some cases causing differential diagnostic problems will be presented.

The lecture also speaks about new diagnostic tools /such as K-cell activity in bone tumors of different dignity, advantages of the plastic embedding technique/ of the bone tumors.

4019 HISTOLOGY OF BONE TUMOURS.
M.Sailer-Kuntschik, Vienna, Austria

4020 NEW CYTOMORPHOLOGIC METHODS IN THE DIAGNOSIS OF BONE TUMOURS:
ROESSNER, A., Grundmann E.
Gerhard-Domagk-Institut für Pathologie der Westf. Wilhelma-Universität,
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The value of new morphologic methods in the diagnosis of bone tumors is demonstrated in a number of cases. In round cell malignancies (Ewing's sarcoma, malignant lymphoma, neuroblastoma, peripheral neuroectodermal tumor, and anaplastic plasmocytoma) diagnostic accuracy can be improved by electron microscopic and immunohistochemical techniques. New methods are also of value in differentiating metastatic carcinomas from bone primaries. Electron microscopy may reveal epithelial features (e.g. gland structures, desmosomes, and tonofilaments), while immunohistologic investigation of the cytoskeleton may facilitate differentiation of epithelial cells. New methods have also been successful in grading of bone tumors. Determining the proliferation rate of a given tumor may be improved by monoclonal antibodies directed against a proliferation-associated nuclear antigen, thereby facilitating the differential classification of low-grade and high-grade chondrosarcomas. Flow cytometric investigations allow the identification of aneuploid cell lines as a significant marker of malignancy, which helps to verify and detail the classification of borderline tumors such as proliferating giant cell tumors of bone and proliferating chondroma.
Umo-sparing surgery is understood as a procedure which resects a soft tissue or a bone sarcoma while preserving the extremity with satisfactory functional and cosmetic results. Because of the relatively high risk of local recurrence other therapeutic modalities must be employed in complementing the surgical act. In dealing with bone sarcoma of the extremities, the A.A. at the Hospital A.C. Camargo (Fundacao Antonio Prudente-S.Paulo, Brasil) have preferred the combination of pre-operative intra-arterial chemotherapy followed by conservative surgery. The drug used is the cisplatin which is given through the artery with the aid of a positive pressure pump in the dose of 100 mg/m². This is repeated every two weeks, for a minimum of two and a maximum of six cycles, pre-operatively. The surgery itself is carried out about seven to ten days following the last chemotherapy cycle. Once the patient has recovered from surgery, usually in about two weeks, the chemotherapy is resumed through a different route, the intra-venous one, for a period of eight months. At this time the combination of adriamycin and cisplatin is used, each drug being given separately and with an interval of twenty one days between them for about eight months. Our experience constitutes fifty-six patients who were eligible for analysis and among them, there were nineteen (or 33.9%) who underwent limb-sparing surgery. The disease free survival rate, calculated by Kvelan-Neyer P.h. is fifty-five percent at forty-eight months.

The myc family of cellular oncogenes contains three well-defined members: c-myc, N-myc, and L-myc, as well as multiple, potential additional members. Despite many similarities in structure and function of myc-family genes, high level expression of the N- and L-myc genes is very restricted with respect to tissue and developmental stage while that of c-myc is more generalized. The unique patterns of myc-family gene expression generally predicts the types of tumors in which they are expressed; activated N-myc expression in a property of a variety of childhood embryonic tumors which my have a genetic component to their etiology. We find highest levels of N- and L-myc expression in developing neural tissues, however, the N-myc gene appears to have a role in the early stages of multiple differentiation pathways. Both the N- and c-myc genes are expressed during the pre-B stages of the B cell pathway while only the c-myc gene is expressed at the B cell and later stages of the pathway. In addition, both the N- and c-myc genes are expressed in immature T lymphocytes (triple negatives) while, again, only the c-myc gene is expressed in mature T cells. Our current findings suggest that differential, or perhaps combinatorial, expression of myc-family genes could play a role in normal mammalian differentiation pathways. Current experiments involve the use of gene transfer technology to further elucidate the control of myc-family gene expression and to further define the relationship between the expression of these genes and lymphocyte differentiation.

4028 EPSTEIN-BARR VIRUS AS A PROBE FOR HUMAN B CELL DIFFERENTIATION. Jeter D. Burrows, Hirail Kubesaty, and Max D. Groop. Cellular Immunology Unit, University of Alabama at Birmingham, Birmingham, AL 35294 USA

The ability to obtain transformed B lineage cell lines representative of various stages in differentiation has been a powerful tool in defining the normal pathways of B cell development and may help to identify defects in this process. We have been using Epstein-Barr virus (EBV) to transform cells of early B lineage from normal fetal tissues and of boys with the immunodeficiency, X-linked agammaglobulinemia (XLA). Patients with XLA have normal numbers of pre-B cells, but very few B lymphocytes or plasma cells, resulting in very low levels of immunoglobulin (Ig). EBV lines established from both sources were examined by immunofluorescence using monoclonal antibodies to Ig chain and to Ig isotypes and heavy chain variable region determinants. The status of the Ig heavy and k and l light chain (LC) genes was determined by Southern blotting. All cell lines displayed similar morphology, with a spectrum of cell types from lymphoid to plasmaclad within a clone, four varieties of cell lines, based on Ig expression, were recovered: 1) Ig negative, 2) heavy chain positive, light chain negative, 3) light chain positive, light chain positive, 4) heavy chain negative, k light chain positive, i.e., J chain was expressed in all four cell types, indicating that J chain expression in human B lineage cells is not necessarily coupled to synthesis of Ig molecules. Type 2 and 3 cell lines have the Ig phenotype of pre-B cells and B cells, respectively, and have undergone Ig gene rearrangements consistent with the Ig chains expressed. However, type 1 and 4 cell lines are unusual: Both Ig heavy chain alleles in the type 1 (k) lines are rearranged but the k light chain genes are in germline context. These cells may represent the earliest members of the B cell lineage, having undergone DJ rearrangements on both alleles. Alternatively, they may be defective pre-B cells, rescued by EBV transformation, that have abortive VDJ rearrangements on both alleles. In the one type 4 (k only) line examined thus far, both heavy chain genes are rearranged, as are the k light chain genes. Thus only k light chain is expressed in this line. In the k only line does not violate the gene rearrangement hierarchy for heavy chain before light chain, however, our results raise the possibility that light chain rearrangement can occur in the absence of a productive heavy chain gene rearrangement. Pre-B cell lines (k only) derived from most patients with XLA had their light chain genes in germine context, as was also the case with pre-B lines from normal fetuses. However, B cells from one patient consistently showed rearrangement of the heavy chain locus in the absence of detectable k chain protein. These results implicate the presence of light chain rearrangement in the pathogenesis of one form of XLA.
Molecular Cloning of cDNA Encoding the Murine IgG1 Induction Factor by a Novel Strategy Using SP6 Promoter


The relative abundance of different immunoglobulin (Ig) classes is dependent on the nature of the antigen. Thymus-independent activation of B cells in vivo or in vitro gives rise to stimulation of the IgG1 subclass whereas thymus-dependent stimuli generally give rise to IgG2 and IgG2 antibodies. Selective T cell help for certain classes or subclasses of Ig has been described, using conventionally immunized T cells or T cell lines. Furthermore, soluble products secreted by certain T cell lines induced increased IgG1 production when these supernatants were added together with lipopolysaccharide (LPS). A putative lymphokine present in these supernatants was called B cell differentiation factor for IgG1 (BCDF1) or IgG1 induction factor. It was not clear whether the IgG1 induction factor induces selective activation of B cells which were already committed to IgG1 production, or whether the factor directs the H chain recombination to increase IgG1-producing B cells. To solve these problems we set out to isolate cDNA encoding the IgG1 induction factor and to obtain the pure material in a large quantity. Characterization of this lymphokine may also facilitate understanding of the roles of many other putative lymphokines involved in B lymphocyte maturation.

We have cloned cDNA encoding the IgG1 induction factor from a murine T cell line. The lymphokine synthesized by the direction of cloned cDNA expressed multiple other biological functions such as B cell growth factor-I, IgG1 induction on B cells and T cell growth factor. The putative primary amino acid sequence of 140 residues was deduced from the nucleotide sequence determined. To clone this cDNA, we have developed a new strategy that includes in vitro RNA synthesis from templates of library cDNA in a new vector system containing the SP6 promoter, and translation in Xenopus oocytes.

T Cell Differentiation

S.T. Schlossman, Boston, USA

Tumor Promoter Phorbol Ester Induced Phenotypic and Functional Changes in T and B Lymphocytes

I. Ando, Inst. of Genetics, BioL Res. Ctr. Hungarian Acad. of Sciences, Szeged, Hungary

The tumor promoter 12-O-tetradecanoyl-phorbol 13-acetate induces the expression of the interleukin 2 receptor and the disappearance of the T3 complex in a T cell hybridoma, T cell clones, thymic and peripheral T cells and T cell tumors. These changes are accompanied by an increased sensitivity to interleukin 2 and antigen-specific unresponsiveness in T cell clones. The expression of the interleukin 2 receptor (Tac) on normal B cells and Epstein-Barr virus-transformed lymphoblastoid B cell lines is induced as well. The receptor on B cells is indistinguishable from that on T cells by serological and biochemical analysis. It is functionally active so that TPA-induced B cells respond to interleukin 2 by increased DNA synthesis. These results suggest that the expression of Tac is not exclusively restricted to T cells and that interleukin 2 may play a role in B cell differentiation.

References:

T Cell Differentiation

S.T. Schlossman, Boston, USA

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References:
NATURAL HISTORY OF THE RETROVIRUS ASSOCIATED WITH A HUMAN LEUKEMIA, Y. Hinuma, Inst. Virus Res., Kyoto Univ., Kyoto 606, Japan

An association of a retrovirus (ATLV/HTLV-I) with a unique human leukemia, adult T-cell leukemia (ATL) was found in 1981. ATL only develops in older people (over 40). The HTLV may first have infected people thousands years ago. It did not kill them, because people did not live long enough to develop ATL. Hence the disease has appeared only because people are living longer. The virus naturally spreads only within families, although the viral transmission by blood transfusion has been definitely proved. The virus is transmitted from other to child and husband to wife. We have estimated the presence of about 1,000,000 ATLV carriers in Japan. The annual incidence of confirmed cases of ATL patients is about 300, although the number of estimated cases may be much larger than that of confirmed cases. Serological studies have accumulated suggested that there are two large clusters of ATLV carriers in the world. The first definitely large endemic area is Japan. The second is Africa, but available information is not yet sufficient to estimate the numbers of ATLV carriers and ATL patients. The Caribbean basin may be a moderately large endemic area of the virus, and fewer cases of virus carriers have been found in many parts of the world, i.e., Ecuador, Israel, Alaska and Taiwan.

SIGNIFICANCE OF HTLV-I INFECTION IN ADULT T-CELL LEUKEMIA AND THE RELATED DISEASES
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Human T-cell leukemia virus type I (HTLV-I) was isolated from T-cell malignancies in USA and Japan, and shown to closely associated with adult T-cell leukemia (ATL) by extensive sero-epidemiology. ATL is a unique T-cell malignancy affecting only adults, carrying abnormal helper type T-cells and endemic in south-west of Japan, the Caribbean, and central Africa. The provirus integration into all primary tumor cells showed direct involvement of HTLV infection in ATL development. The HTLV-I has no oncogene, but contains a unique sequence pX. Thus, the sequence pX was suspected to play key function in malignant transformation, because cis-acting c-onc activation by the LTR was excluded. In fact, the P_X gene product was found to activate transcription of the viral gene. Thus, it is reasonably expected that the P_X gene product can activate some cellular genes, eventually induce abnormal growth of infected T-cells. Recently, we found another P_X gene product, which should play some roles in ATL development. Biological function of the P_X gene products and its mechanism will be discussed.

The Molecular Analysis of Adult T Cell Leukemogenesis
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Adult T-cell leukemia (ATL) is a new entity of human T-cell malignancy associated with a human T-cell leukemia virus (HTLV). Experimentally, HTLV-infected T-cells proliferate indefinitely without any mitogen stimulation. We have found that HTLV induces constitutively IL2 receptors and a proteolytic enzyme calpain II in human lymphocytes. The induction of these cellular genes and cellular immortality may be connected with a HTLV gene product(s), including a trans-acting transcriptional activator (tat) protein. We will present the molecular analysis of ATL leukemogenesis.
STRUCTURE AND PATHOGENESIS OF THE HUMAN T LYMPHO-TROPIC VIRUSES HTLV-I, II, III
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It has been well established that human T-cell leukemia virus type I (HTLV-I) is associated with adult T-cell leukemia (ATL) and that it plays a causative role in the leukemogenesis of ATL. However, HTLV-I does not contain any typical oncogenes such as RAS and MYC, and does not induce foci in mouse NIH 3T3 cells in vitro. Therefore, it is possible that the proviruses integrate into some loci and then activate some cellular genes for the development of ATL. Five human T-lymphocyte cell lines were analyzed on HTLV-I provirus integration site in leukemic T-lymphocytes by in situ hybridization technique. Two of them were already established cell lines, MT-1 and MT-2, and the others, WKT, WKR and TM, were newly established from the peripheral blood lymphocytes of adult T-cell leukemia patients. All of them showed the synthesis of HTLV-I associated antigens by immunofluorescence technique. The presence of the HTLV-I provirus in each cell line was detected by Southern blot hybridization technique using a restriction fragment (ca. 2 kbp) from a cloned HTLV-I LTR region as a probe. The in situ hybridization was done according to the method of Harper and Saunders (1981) with a slight modification using a restriction fragment (ca. 0.45 kbp) from a cloned HTLV-I LTR region as a probe. Two of them were already established cell lines, MT-1 and MT-2, and the others, WKT, WKR and TM, were newly established from the peripheral blood lymphocytes of adult T-cell leukemia patients. All of them showed the synthesis of HTLV-I associated antigens by immunofluorescence technique. The presence of the HTLV-I provirus in each cell line was detected by Southern blot hybridization technique using a restriction fragment (ca. 2 kbp) from a cloned HTLV-I LTR region as a probe. The result of Southern blot hybridization showed 3-5 clear bands in EcoRI digested DNAs from each cell line. In the in situ hybridization, however, the silver grains seemed to be randomly associated with the metaphase chromosomes (by counting 100 grains on each cell line). The discrepancy between the results of Southern blot and in situ hybridization is now under investigation.

TWO DISTINCT POLYPEPTIDES ENCODED BY X GENES OF BOVINE LEUKEMIA VIRUS AND HUMAN T-CELL LEUKEMIA VIRUS. T. Ikawa and N. Sagata, Lab. of Molec. Oncology, Tsukuba Life Science Institute, Tsukuba 305, Japan.

Many biological properties of HTLV-I and BLV are common and are evolutionarily closely related to each other (1). BLV and HTLV have a potential transforming gene, termed X (2). The long major open reading frame of these X genes encodes a protein of 38K (for BLV; ref. 3) or 40K (for HTLV), which appears to be a nuclear transcriptional activator of the long terminal repeat. In addition of the major open reading frame, the X genes commonly harbor another short open reading frame that overlaps this major one. Both of these open reading frames are found on a single spliced X mRNA in a potentially functional form (4). Circumstantial evidence strongly suggests that they are both translated from the single X mRNA molecule, showing striking similarity to the translation mechanisms of an adenosine U3 ribonucleic acid and a rev-related mRNA. We note that short open reading frame has the capability to encode a putative protein with structural features similar to that of an AIDS virus trans-acting protein. Thus, we propose that the X gene of BLV and HTLV are both overlapping genes encoding two distinct polypeptides, both of which may be involved in viral replication, cellular transformation, or both, possibly interacting with each other (4). This study was partly supported by Grant-in-Aid from the Ministry of Health and Welfare for comprehensive 10-Year Strategy for Cancer Control, Japan.

(2) N. Sagata et al., EMBO J. (1986) 5, 3231-3237.


HTLV-I has been found to immortalize not only human T cells, but also animal lymphocytes, such as simian, rabbit, rat, and cat lymphocytes. In the present study, we investigated the transformation of HTLV-I to hamster lymphocytes in vitro. Co-cultivation of spleen cell cultures of syrian golden hamsters with lethally irradiated MT-2 cells harboring human T-cell leukemia virus type I (HTLV-I) resulted in the establishment of lymphoid cell lines, HCT-1 and HCT-2, which had a normal karyotype of golden hamsters. Both HCT-1 and HCT-2 cells lacked surface immunoglobulins and reacted with a monoclonal antibody specific for hamster T cells. Some of them were positive for OKT6, neither of them expressed HTLV structural antigens (p19 or p24) and virus particles, but they contained HTLV-I proviral DNA monoclonally. By immunochemical analysis of the labelled cell antigen, sera from adult T-cell leukemia (ATL) patients reacted with the two polypeptides, p37 and p40, which may not virus structural proteins and still remain to be characterized. HCT-1 and HCT-2 cells were transplantable into nude hamsters, pre-treated with anti-hamster thymocyte serum and non-treated, respectively, producing diffuse malignant lymphoma. These findings indicated that HTLV-I not only immortalized but also transformed hamster T cells non-productively. These hamster cell lines may provide a useful tool for the study of the function of HTLV-I gene essentially required for transformation.
**H-15: CYTOTOXIC SUGARALCOHOL DERIVATIVES**

**4041** EFFECT OF DIHYDROGALACTITOL AND DIACETYL-DIHYDROGALACTITOL IN HUMAN STOMACH CANCER XENOGRAFTS. H.H. Fleibig, Dep. of Internal Medicine, University, Freiburg i.Br., West Germany.

Dihydrgalactitol (DAG) and Diacetyl-Dihydrgalactitol (DADAG) are dioxypyrans which showed a broad antitumor activity in several experimental tumors of mice. The therapeutic index of DADAG was higher than that of DAG. We investigated the antitumor effect of DAG in 15 and that of DADAG in 6 selected human tumor xenografts growing subcutaneously in nude mice. Treatment was initiated after 20 to 39 days when the tumors were well measurable. The antitumor effect was evaluated after maximal tumor regression, for non-regressing tumors after 3-4 weeks. The effect of treatment was classified as remission (product of 2 diameters less than 50% of initial value), minimal regression (51-75%), no-change (76-124%) and progression (125%). DAG was given at a dose of 4 mg/kg per day on day 1-4 and 15-18 intraperitoneally or per os. DADAG at a dose level of 16-12.5 mg/kg given on day 1-4 and 15-18 i.p. or per os. The dosages corresponded approximately to the LD20 after 4 weeks in tumor bearing nude mice. DAG and DADAG showed a remarkable activity in stomach cancers. DAG affected complete and partial remission whereas the 3rd stomach cancer studied progressed. DAG affected complete remission, 1 minor regression and 4 no-change, 6 stomach cancers grew progressively. One undifferentiated colon cancer got a partial remission after DAG and DADAG. In a soft-tissue sarcoma both compounds affected a minor regression whereas another soft-tissue sarcoma and a thyroid cancer grew progressively. There seems to be a similar activity spectrum for both compounds, with higher activity for DADAG in at least 3 human tumor xenografts. The effect of the compounds in stomach cancers from which 3 are resistant to standard drugs suggests a clinical trial. Preliminary results of a clinical phase II study of DADAG will be presented.

**4042** ANTITUMOR ACTIVITY OF DIBRODULCITOL AGAINST HUMAN XENOGRAFT TUMOR IN THE NUDE MICE.

Masahide Fujita and Tetsuo Taguchi, Department of Surgical Oncology, Research Institute for Microbial Diseases, Osaka University, Osaka, Japan

Nude mice human cancer implants used in vivo to assess the antitumor activity of DIBRODULCITOL (DBD). Continuous (6 times per week) administration of 50 mg/kg/day was used in nude mice human cancer implants, and for 25 to 30 treatment 2 mammary carcinoma strains and 5 gastric carcinoma strains were studied.

Both mammary carcinoma strains (H31-41, H62-49) showed significant effects, and so did the 5 gastric carcinoma strains (H15-4-28, H40-42, H15-4-31, H176-12, H111-12). No weight loss was noted in each experiment, nor was any toxic effect found from daily administration.

From the present nude mice human cancer implant results, DBD was considered effective not only for mammary carcinoma but also for gastric carcinoma as well.

**4043** DIBRODULCITOL(DBD)-G-(PARADINS(GA)) INSTEAD OF TOTAL BODY IRRADIATION(TBI) IN GROWTH TRANSPLANTATION FOR MORE ADVANCED CHRONIC GRANULOCYTIC LEUKAEMIA(AGL). Z. Kelemen, for the 30th Team, Institute of Internal-Bone Marrow Transplant Registry, 1st Dept. of Medicine, Semmelweis Univ. Med. Sch., Budapest, Hungary

DBD and GA were applied as pre-conditioning drugs to eradicate leukemic clones in more advanced GML. Although the number of observations is still small, the paucity of certain complications merits consideration. HA/HLA compatible sibling donors were available in 5 cases, with a mean pre-transplant history of 5 years. There was one early death at day 15 with sepsis and hemorrhage. In the followings, the denominators represent the number of patients at risk. Severe, acute GVHD 0/4, chronic GVHD 2/3, interstitial pneumonitis 0/4 (1/3 in mismatched transplants), herpes 0/4 (0/7), leukemia relapse 1/3 (in the 31st mo). Relapse-free survival 0/3 (18 and 32 months). Retransplantation of the relapsed patient was unsuccessful. Differences in pre-conditioning and post-transplant protocol, and the problem of stromal effects are considered to explain these apparently favourable results.


**4044** Experimental and Clinical Studies on DIBRODULCITOL

Tetsuo Taguchi, Department of Surgical Oncology, Research Institute for Microbial Diseases, Osaka University, Osaka, Japan

Hela cell was used in vitro and L-1210 used in vivo to assess the antitumor activity of DIBRODULCITOL(DBD). Significant effects were obtained in L-1210 at 80 mg/kg/day (day 1 - day 9) treatment more, but such effects were not found with Cyclophosphamide-resistant L-1210 strain.

Our protocol of DBD clinical study for gastric cancer is the following:

350 mg/m2 every 5th day up to a cumulative dose of 5000 mg/m2 per cycle. Cycles repeated after a minimal interval of one month. 3 cycle will be a standard administration.

We will present the results obtaining experimental and clinical studies on DBD in Japan.

Mitolactol was tried in a phase II study in 25 patients with Bilharzian bladder cancer. Patients had either advanced disease or recurrence after radical cystectomy. Mitolactol was given daily p.o. at a dose of 250 mg/day, guided by the total WBC and platelet counts. The age of the 25 evaluable patients, one female and 21 males, ranged from 30 to 72 years. There were 5 cases with transitional carcinoma, 2 with adenocarcinoma and 15 with squamous cell carcinoma. Responses obtained were: 1 CR in a patient with squamous cell carcinoma lasting over 33 months and 3 PR giving an overall response rate of 14%. Mitolactol was given in the same schedule. 25 patients with advanced and/or metastatic breast cancer. Lesions were local, nodal, skeletal, visceral including 5 cases with brain metastases. All patients were either refractory to previous hormone and/or chemotherapy. Patients with brain metastases were concomitantly treated with radiotherapy. The overall response rate was 40% in the 25 evaluable cases with an average duration of 12 months. Patients with brain metastases were either stabilized or partial responders. Toxicities were reversible leukopenia and thrombocytopenia. The activity of the two drugs for British patients was comparable, with no severe hematotoxicity with the mitolactol. A single 1.2 g dose of CG-DAM reduced the HBC to 70% of control. This effect was concentration or circulating lymphocytes, since granulocytes remained at 51% of initial values with CG-DAM. The major HBC was 51% of control and with an absolute granulocytopenia of 70% of initial values. The toxicity of CG-DAM was considerably greater, with a lower and more protracted HBC, more of 40% of control and an absolute neutrophil count near 9% of control. These findings parallel the relative decrements in bone marrow DNA synthetase produced by the drugs. Measurements of human bone marrow CFU-C killing in vivo exposure to graded concentrations of the drugs show a more severe bone marrow sparing properties of CG-DAM. At the highest concentrations, in vivo, the latter drug produced only a 7% reduction in the bone marrow, whereas mitolactol produced DNA injury and DNA-protein crosslinks in a dose-dependent manner in both P388 and murine bone marrow cells treated with them either in vitro or in vivo. The process of damage and regeneration was studied as a function of time after the administration of the drugs. In male mice the CFU-C, disuDAG is about 8-9 times less toxic than the control. DisuDAG is significantly less toxic; the survival of CFU-Cs was reduced to 50% by 13 

RESULTS OF DIBROMODEXOTOL IN ADVANCED BREAST CANCER

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Dibromodecitol (DBD) is a halogenated hexanol with activity in various malignant neoplasms in man.

DBD is most commonly used in treating patients with advanced breast cancer. DBD has good single agent activity in breast cancer. DBD plus Doxorubicin (ADR) is more effective than ADR alone. DBD, ADR and Tamoxifen (DAY) is superior to DBD and ADR. The response to DBD, ADR and Vincristine (DAY) was superior (but not statistically significantly) to Cyclophosphamide, ADR and 5-Fluorouracil (CAF). The four drug combination DAVH (DAV and Halotestin) gives a response rate of 50% in previously untreated patients with metastatic disease.

As a second line treatment DAT was not, however, found to be superior to MT (Methotrex-C and Tamoxifen).

The combinations of DAT and DAVH offer equal, if not superior results compared to other drug combinations in patients with advanced breast cancer.
CLINICAL RECOGNITION OF PRIMARY MALIGNANT MELANOMA AND OF ITS PRECURSORS. J.B. Pieggerick, M.D., Harvard Med.Sch., Dept. of Dermatology, Massachusetts Gen.Hosp., Boston, Mass, USA. In 1986, 22,000 new primary melanomas will develop and 5500 deaths will occur in white persons in the United States. Mortality rates of primary melanoma of the skin for single years from 1976-82 are rising at the rate of 32 per year for men and 12 for women. Despite this rising mortality there has been a gratifying increase in the proportion of early melanomas that are thinner, less invasive and more curable. In fact, survival rates for primary skin melanoma in whites has increased by 30% in the past two decades. This is possibly the result of education of physicians in the detection of early melanoma; yet, in a recent study, 40% of physicians were unable to diagnose melanomas from color slides or photographs. Obviously, intensive education programs for non dermatologists are needed. In most instances, early melanoma can be recognized by three physical characteristics: coloration, contour, and size of the lesion. The three positive physical signs of importance, variegated color, irregular border, and increase in size. Variegated color: displayed in a disorderly, haphazard pigment pattern is a frequent characteristic of malignant melanoma, especially the superficial spreading melanoma. Irregular border: often marked by an angular indentation or notch is the second most helpful sign in the diagnosis of malignant lentigo maligna type. While early diagnosis of primary melanoma is the key to prevention of metastatic disease, the emphasis now in the 1980's is the recognition of individuals at increased risk for development of melanoma: a family history of melanoma and/or the presence of one or more precursor lesions. The knowledge precursor lesions of melanoma are lentigo maligna, congenital melanocytic nevus, certain types of acral and mucosal pigmented lesions, and the most significant of all the precursors, Clark's nevus (also called dysplastic nevus). Clark's nevus is an atypical appearing variant of melanocytic nevus and consists of intraepidermal melanocytic atypia and a characteristic clinical presentation. Clark's nevus (familial and sporadic) represents both an important marker for individuals at increased risk for developing melanoma, as well as a definitive precursor of melanoma.

SYDNEY CLASSIFICATION OF MALIGNANT MELANOMA


The 1972 Sydney Classification of Malignant Melanoma by McGovern et al. was reconsidered during the workshop held in Sydney in October 1982. The late Vincent McGovern had convened the meeting to evaluate the use of this classification, ten years after.

Question arises whether a classification is required? Purpose of a classification is to advance the studies in the pathogenesis of melanoma. Epidemiological observations offer good supporting evidence that various etiological factors are operational. Today only biological observations are available to us. The growth pattern is clinically the most obvious. Distinction is made between horizontal and vertical growth. The horizontal growth can be subdivided into the Pagetoid (SSM) and lentiginous types. The molecular biology is expected to contribute to our knowledge about the degree of malignancy of a melanoma. This is of major importance for the mode of treatment which is so far only guided by the TNM staging and the measured thickness.

The 1982 Sydney classification is based on the features of horizontal growth. An adjacent component can be present or absent. If present it can be of "superficial spreading type" or of "lentigo maligna type". Two subtypes for specific sites - mucous and glabrous (hairless) skin were accepted. The modifications of the classification are presented along with the consensus on an adequate pathological reporting. The recommended terminology of the malignant melanoma (MM) is:

MM with an adjacent component of superficial spreading type
MM with an adjacent component of lentigo malignant type
MM with an adjacent component of acral lentiginous type
MM with an adjacent component of mucosal lentiginous type
MM without adjacent component

BIOLOGICAL RESPONSE MODIFIERS AND MALIGNANT MELANOMA: METASTASIS. S. Pleasner, The Institute of Oncology and Faculty of Medicine. Ljubljana, Yugoslavia.

Observations on the natural history of malignant melanoma and its histopathology suggest that the disease is subject to host control. Cases have been observed, even an early tumor can produce widespread blood born metastases, while on the other site, various aspects of spontaneous regression as well as delays in metastatic spread were noted. These differences in the course of the disease are suggesting variations in the immune antitumor activity of the host.

For stimulation of the immune system different biological response modifiers were used in the treatment of the metastatic disease. Among them were most frequently used phytohemagglutinin, Corynebacterium parvum, Bacillus Calmette-Guérin, levamisol and combination of these substances with either chemotherapy or irradiation. The results are indicating that the treatment with the biological response modifiers is not decisively contributing to the improvement of a patient's prognosis, although promising results were obtained as well. This is the case of viral oncolysates used in stage III malignant melanoma. However, observations indicate that the response to the treatment depends also on the site of the metastatic growth. Best results were obtained in cases with skin or lung metastases, while poor prognosis was observed in cases with liver and brain metastases. Combination of Bacillus Calmette-Guérin with irradiation, applied locally, was found to be particularly effective in cases with skin metastases.

Recently, interferon was introduced for the treatment of malignant melanoma metastases. Studies are underway using interferon alone or interferon in combination with chemotherapy or as an adjuvant treatment in high risk patients after primary surgical treatment. Interferon combined with chemotherapy may also play a role in the treatment of metastatic disease.

New studies are needed in order to improve the present results of treatment, particularly because of the continuous increase in incidence of the disease in younger adults.
**DECISION IN THE MANAGEMENT OF CUTANEOUS MELANOMA**

A. Kukatowski, Institute of Oncology, Warsaw, Poland.

The selection of proper therapy for cutaneous melanoma should be based on the clinical stage and histopathological appearance of tumor. The extent of therapeutic excision depends on the tumor thickness, its size and location. The microstage according to Brash and Clark is most important. If regional lymph node metastases are clinically suspected a therapeutic dissection should be carried out. Elective node dissection is advised for tumors >1.5 mm thick. Melanomas located in the midline of the body are not prone for elective node dissection. The indications for limb perfusion are: satellite lesions, in-transit metastases or local recurrence. Adjuvant perfusion for Stage I is not generally accepted. Radiotherapy with high daily fractional doses /2 x 6.0 Gy/week - total dose 36.0 Gy/should be considered for local recurrence, brain metastases, or when lymph node dissection with extracapsular tumor infiltration. Hyperthermia, radiosensitizers and high let radiation may improve the biological effect of radiotherapy. Chemotherapy /DTIC/ can be considered as adjuvant treatment in the presence of worse prognostic factors or as a treatment for distant metastases /lungs, skin/. The role of systemic immunotherapy for melanoma is highly controversial.

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**ROLE OF IMMUNOTHERAPY IN THE MANAGEMENT OF MALIGNANT MELANOMA**

S. Baerg, Univ. Oncol., Buenos Aires, Argentina.

We conducted a case-control study among whites to determine whether the total number of nevi on patients diagnosed with cutaneous melanoma was different from the number found on control patients. 112 consecutive patients seen in the melanoma clinic at UCSF comprised the case group. 139 patients seen in other UCSF clinics served as controls. All nevi that measured at least 2mm in diameter were counted on each subject. Cases had total body nevi counts 3 times greater than controls (p<0.001). This three-fold difference existed over the whole lesion whether possible. Pathological diagnosis must be correlated to the clinical one. Risk factors are Clark's level and Breslow Thickness. Localization can influence prognosis: trunk, limbs face, neck, scalp, extra cutaneous. A serious problem are tumors bigger than 4 ganglionar regions, amput and groin. Lentigo melanomas. Clark's level 1 and 2, wide excision /WE/ and split skin graft only, no adjuvant chemotherapy. In the rest /Clark 3,4,5/ wide excision with larger margin and graft similar to previous one. If primitive lesion is near regional lymph nodes, the latter case we do so 28 days after extirpation of primitive lesion. Certainly of extripated specimens states certainty of resection margin. Prognosis depends on Clark's level and Breslow thickness, on number of nodes invaded and on invasion size. Chemotherapy has no great curative action. Only possibility of antiepidermal action in Clark's level 3,4 and 5 and in Breslow thickness more than 1.5mm and/or with positive nodes, our Protocol are as follows: - DTIC - VCR - BCNU - CDDP - 5FU.
INDICATIONS AND RESULTS OF REGIONAL HYPERTHERMIC PERFUSION IN MALIGNANT MELANOMA

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From Dec. 1st 1975 to Dec. 31st 1984 we performed adjuvant hyperthermic perfusion in 278 patients with potentially curable malignant melanomas. Surgical treatment consisted of wide local excision of the primary tumor and elective lymph node dissection. Our patients had regular follow-up examinations and were observed for at least one postoperative year up to December 31st, 1985. The five-year-survival rate of our patients in clinical and pathological Stage I is 86%. If we look at the results of 152 patients in the same stage with particularly favourable pT 3 and pT 4 tumors we can calculate a five-year-survival rate of 85% for these patients alone. The results of adjuvant hyperthermic perfusion treatment in 64 patients in pathological Stage II, that is with regional metastases, were 48%. We achieved especially good results in 49 patients with satellitosis. In almost half of the patients the metastases completely disappeared. 17% of our patients in clinical and pathological Stage II developed metastases in the follow-up observation period. The number of local recurrences after adjuvant hyperthermic perfusion is low at 1.5%. It is concluded from our results, that hyperthermic perfusion can further improve the prognosis of patients with malignant melanomas of the limb.

CHOICE OF THERAPY IN MALIGNANT MELANOMA.

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In recent years, the results of chemotherapy of malignant melanoma have not improved in spite of all efforts and thus DTIC, often reponated, has remained the first choice drug. None of the new drugs tested, such as BSH, DAD, CBOCA, vindesin, mBCNU, A20, have brought an improvement of the percentage remission obtained. The hope set on such combination as VBO, BOLD or BSH, have rather met with a disillusion when evaluated on larger materials, similarly as other combinations with cisplatinum. Adjuvant administration of cytostatics concentrated on high risk patients. No positive results have been obtained even in this case. Hormonal therapy has failed completely in spite of the interesting initial data. Hyperthermic regional perfusion with MPA is being studied in a number of institutions and interesting results are reported. No significant data are available to show that non-specific systemic stimulation could improve the prognosis in patients suffering from melanoma. Studies of I-Pe-PGM following in intravenous or intralymphatic administration, or of CP have not yielded hopeful results. New positive results may perhaps be obtained in studies of monoclonal antibodies.

NATIONAL CANCER CONTROL PROGRAMMES:

STRATEGIES AND PRIORITIES.

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If present trends continue, cancer is expected to be a major public health problem in nearly all countries by the year 2000, due to increased aging of the population and a continued rise in tobacco consumption. Approaches are available to prevent a third of all existing cancers, to cure a third, if cases are detected early enough and adequate therapy is provided, and to ensure that virtually all cancer patients are spared pain. Measures should be taken without delay as the problem of cancer, in both developed and developing countries, will worsen if left unchecked. At present, in most countries, cancer control activities lack overall coordination. Nearly always therapeutic services are receiving the major portion of a country's economic and manpower resources available for cancer control. The formulation of a national cancer control policy and programme and the accompanying systematic evaluation of control strategies by cost-effectiveness analysis is important, especially where the resources to combat cancer are severely limited. A recent publication of WHO data on mortality from cancer in 28 industrialized countries, indicating a limited impact of therapy on overall cancer mortality for most cancers and the reduction in cervical cancer mortality in countries with adequate screening programmes, makes clear the need for proper priority setting in national control efforts, even in developed countries. Well planned national efforts emphasizing prevention and early detection can significantly reduce the cancer problem.

MODELS FOR CANCER CONTROL PROGRAMMES IN THE EUROPEAN REGION.

L. Wiberg. Cancer Unit, Regional Office for Europe, World Health Organization, Copenhagen, Denmark.

The diversity of patterns is one of the characteristics in Europe. There are considerable differences in incidence and mortality trends by cancer types among the sub-regions, with parallel differences in strategies and priorities in the individual countries. Cancer registries exist in most countries but the coverage and type of information collected vary greatly. Cancer control services, including highly specialized cancer centres have existed in most countries, but their quality, structure and population coverage varies greatly. On the other hand, there is a lack of experience in community-oriented cancer control activities; only a few countries have truly comprehensive services providing all aspects of cancer control and there is still a gap between curative and preventive oncology. However, a growing number of countries have started to introduce cancer prevention and control measures into the general health care system. Programmes for integrated control of risk factors common to cancer and other chronic diseases (e.g. smoking, nutrition, occupations) hazards) as well as organized screening programmes for early detection, where justified, have been developed in a number of countries.

There have been efforts to improve cancer care through linkages including patient referral systems between primary health care and the specialized services of secondary and tertiary care; to optimize the distribution and use of advanced cancer-specific diagnostic and treatment technologies; and that cancer control efforts are being made to provide community-based supportive care to patients with cancer beyond the curable stage, and to reduce the shortage of adequately trained manpower at all levels of cancer control. As an operational framework for delivering appropriate cancer control measures, accessible for all who require it, most of the countries have developed a national cancer policy, as a basis for planning and evaluating cancer control programmes.
The French Cancer Center Network and Its Role in Cancer Control

The twenty comprehensive cancer centers are the backbone of cancer control in France. They represent 4,600 beds and nearly 1,000 senior physicians and scientists. Well spread on the territory, they maintain regular outside clinics in 155 towns. The idea behind the concept of these centers was and still is that effective fight against cancer needs a concentration of means and a multidisciplinary approach. The first centers were created in 1923, at that time they were cancer departments in public hospitals. In 1941 they became nonprofit private institutions that kept their links with the public general and university hospitals. Finally, in 1964, they joined to form the Federation. They have three functions: the first one related to patients' prevention, diagnosis, treatment and follow-up; the second is teaching of oncology to medical students and para-medical professions; for that, they are affiliated to the medical universities. The third mission is research, both clinical and basic. Clinical research is done in each Center by his own means and through cooperation within the Federation as well as by participation to national and international groups. For basic research besides their own means, Centers have research units of the national research bodies (INSERM, CNRS). In conjunction with the French Cancer Society, the Federation organizes regular scientific meetings. The goal of the Centers is not to monopolize treatment of research of cancer but to be the spearhead of the cancer fight. They contribute to cancer epidemiology in maintaining a permanent cancer data system in which data on their 430,000 patients since 1975 are entered, the actual yearly accrual being 54,000. Finally, they cooperate for public education with the French cancer League, with U.I.C.C. and other bodies.
CANCER CENTERS AND COMMUNITY PROGRAMS: FROM BASIC SCIENCE TO PATIENT MANAGEMENT
Jerome W. Tierney, M.D., National Institutes of Health, National Cancer Institute, Bethesda, Maryland, U.S.A.

Cancer centers in the United States serve four major functional centers of excellence in the diagnosis and management of cancer; provide shared resource support for basic and clinical research; serve as the training environment for both laboratory and clinical research; and conduct research and demonstrations and provide limited services in cancer control. Although the National Cancer Institute (NCI) supports only research, the centers serve their communities as a focus for cancer activities while generating community-based philanthropic support for their efforts. Integrating cancer centers, medical schools, and community clinical oncology programs (CCOPS) is a model which has evolved adapting to regional needs and opportunities. The flexibility of the centers program has allowed them to maximize local resources and opportunities, yet derive the stability of NCI core grant support. Multi-institutional studies in applied research, (Magnetic Resonance Imaging, Protocols, Fluorescent Activated Cell Sorter studies in bladder cancer) clinical research, and future cancer control interactions provide opportunities to assure answers to questions requiring large numbers of study subjects. The community programs expand this population access. Participation facilitates confirmation of single institutional research efforts, provides a basis for active intellectual exchange among collaborating investigators, and assures the supporters of research of the generalizability of the information undergoing examination.

In pharmacokinetic studies we showed that administrating doxorubicin (DOX) as a DNA complex increased the drug uptake in the leukemic cells.

Aim: To compare intensive treatment for induction of remission and consolidation with a less aggressive protocol and to compare DOX and DOX-DNA complex.

Methods: 103 patients 15-60 years with ANL were randomized to R1: Daunorubicin (DNR) 1.5 mg/kg i.v. day 1 and ara-C 2 mg/kg days 1-5 for induction treatment. Maintenance treatment monthly courses of DNA 1.5 mg/kg i.v. day 1 and ara-C 1 mg/kg s.c. alternating with thioguanine 7 mg/kg p.o. on days 1-5 and ara-C. R3: Ara-C 100 mg/m² as infusions days 1-7. DOX 30 mg/m² days 4-5, thioguanine 50 mg/m² x 2 days 1-7, vincristine 2 mg i.v. days 1-5, and prednisolone 30 mg/m² days 1-7 as induction treatment. Consolidation with monthly courses, Nos. 1-4: DOX 30 mg/m² x 1 day 1 and ara-C 200 mg/m² days 1-5, 5-8: DOX 30 mg/m² day 1 and azacytidine 150 mg/m² days 1-5; 9-12 ara-C 200 mg/m² days 1-5; 13-16 initially POMP later replaced by AMSA 90 mg/m² days 1-5. R3 = R2 with DOX-DNA.

Results: 14/25 on R1, and 21/37 on R2 and 28/1 on R3 received complete remission. Median duration of remission was 8 months on R1, 15 months on R2 and 25 months on R3. Median survival for patients in remission was 25 months for patients on R1 and R2 and 10 months for patients on R3.

Conclusion: Induction and intensive consolidation treatment with combinations containing DOX-DNA appear to prolong the duration of remission and survival in patients with ANL.


Sixty-five patients (pts) with previously untreated AML ranging in age from 19-71 (median 43) years were treated between 1974 and 1979. Follow up ranged up to 10 years. Remission induction consisted of 7-day courses of Cytarabin (100 mg/m² 7-1 hrs inf.) together with Daunorubicin (45 mg/m²) on days 1, 2 and 3. For remission maintenance, cyclic courses of Cytarabin were given with each of 4 drugs, 6-Thioguanine, Cyclophosphamide, COMO or Daunorubicin in rotational sequence for 2 years. The complete remission (CR) rate was 55%, the median duration of remission 11 months. The median survival time for all pts was 7.7 months, for those responding to therapy 18.4 and those not responding 7 months (p=0.001). The probability of 11-year survival for all pts was 10%, and for those achieving CR 20%. Comparisons of Kaplan-Meier plots (Breslow and Mantel-Cox test) of groups with different pretherapeutic and therapeutic characteristics revealed significant (p<0.02) difference in survival between pts with initial WBC higher than 30000/m³ and those with WBC count below this level. In addition, age over 50 years appeared to be of negative prognostic significance (p<0.02) for survival during the initial phase of treatment. Furthermore, there was a suggestive but statistically not significant inverse correlation between survival time and the number of induction courses to achieve CR. Predictive values of sex, age, type of leukemia, initial WBC count, lymph node enlargement, hepatosplenomegaly, bleeding and infection for survival were also evaluated using Cox model. Of these variables only initial WBC count was found to be of prognostic significance (p<0.04).
M-19B: CHEMOTHERAPY OF ACUTE LEUKAEMIA


205 pts with BC diagnosed by cytoaspiration & drill biopsy entered a protocol (prot) including neoadj & maintenance chem. combined to locoregional radiotherapy (RTH) with or without hormonotherapy (HTh). They were stratified according to tumor size lymphodes status & inflammatory symptoms to group (gr. I: t<7cm N0-4 pts, II: t<7cm N1b-60pts, III: t>7cm N2=24pts, IV: inflammatory BC =67pts. The drugs i.v. on day (d.) 1 Velbe (50mg sqm), Thiotepa (10mg sqm), Methotrexate (2mg sqm), Prednisone (30mg sqm). From d.1 to d.5 & for gr. III & IV Adriamycin (30mg sqm) on d.1, Tamoxifen was given to post-menopausal women (post.men.w. I 4 to some premen. The chem. schedule was 1 dose (do) every (ev) 14d.x 1, II 1 do.ev.10d.x4, III 1 do.ev.21d.x4, IV 1do.ev.21d.x6. External RTH : 45 Gy over 5 weeks in most cr.I & II pts was given by 2 or 3 split courses interspaced by chem. ":* gr. III & IV 2 weeks after its completion a boost by irridium 92 was delivered to the initial t.site. All pts except cr.I received 2 bimonthly chem. do. for 3 months (m) & monthly 4. for 36,12,12m. according to gr. Initial chem. induced regression (reg) >75% in 133pts (66%). Complete clinical remission (CR) was achieved in all pts after RTH. After a median 3 years follow-up 2 local rec. & 5 metastasis (met) in 114 gr. I & II pts, 2 local rec. & 17 met. in 41 gr. III & IV pts. Overall survival 96% in gr. I & II, 77% in gr. III & IV: 15 rel.0-6pts whose t.reg. 47.5% 12 rel 115 pts whose t.reg. 75% p<0.01. Supported by INSERM, CRAC, LNF contre le Cancer.

4072 TRANSFORMING GENES IN HUMAN LEUKEMIAS: H.P. Senn, A. Filipowicz, A. Nair and Ch. Moroni. Friedrich Miescher-Institut, P.O. Box 2543, CH-4002 Basel, Switzerland.

We have previously reported that the DNA from an AML patient has a mutation of codon 12 of the N-ras oncogene (1,2). For monitoring the follow-up of this case we established an assay for detection of single base pair mutations using synthetic 20mer oligonucleotide probes. Applying this method we are analysing codons 12,13 and 61 of further cases including a survey of 20 acute myeloid and 15 acute lymphatic leukemias. In addition, leukemia DNA is also examined for the possible presence of non-ras transforming genes. Primary leukemia and lymphoma DNA was transfected into NIH/3T3 fibroblasts which were subsequently treated for tumor induction in athymic nude mice. In 5/5 cases tumors were obtained. From these DNA was also active in secondary transfection experiments. Work is in progress to identify the putative transfected oncogenes. We speculate that the activation of the ras genes would alter the requirement of cells for their corresponding hematopoietic growth factors. A reduced dependency of interleukin-3 of a murine mastocytoma cell line (PB-3c) was observed after infection by a v-H-ras-containing retroviral vector. One clone became IL-3 independent and was oncogenic in vivo.


4073 FUTURE PROSPECTIVE OF TREATMENT OF ACUTE LEUKAEMIA. J.F.Holland, New York, USA

4074 FUTURE PROSPECTIVE OF TREATMENT OF ACUTE LEUKAEMIA.
The needs of humanity in the global fight against cancer should be considered to be urgent and equal since humanity at large is susceptible to the development of cancer, irrespective of geographical location. By virtue of history or circumstances, the response to these needs in the developing world has been compromised because of competing claims by other basic needs for survival. The national health policies in developing countries vary from one place to another even though the projected goal is the same. Cancer is one of the most devastating diseases in the world including the developing world but the economic impact of its effects on health is difficult to assess objectively. Information is by far, one of the most important weapons required to fight advanced and untreatable cancer in the developing world. This is closely followed by the need for facilities for early detection and diagnosis of cancer. This should be followed up by the enforcement of preventive measures and provision of adequate treatment. The identification of causes of cancer in the developing world has been a challenge to epidemiologists in the past. It is well known that some common cancers in Africa or in other parts of the developing world are associated with viruses. Progress is being made in the production of vaccines against some of these viruses which are suspected of causing cancer for example, Hepatitis B Virus and Liver Cancer. The future of cancer control in Africa and the developing world, would therefore depend largely on appropriate national health policies, which will include all the factors which have been enumerated above. Vaccination against oncogenic viruses which are associated with causation of cancer and all other identified factors which will precipitate to improved health of the developing world.
SPECIAL NEEDS OF DEVELOPING COUNTRIES

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BACKGROUND Thailand has 50 million people in 54,000 sq.km. Cancer death rate is the 2nd rank or 15,000 deaths a year. Cancer of the cervix, liver, breast, lung are the most common. There are 3 organizations which dealt directly with cancer: Cancer Inst Siriraj Hosp, held in 1957; Thai Cancer Society, in 1963, and NCI, in 1969. Treatment centres are limited only in medical school. Most of patients come to seek their treatment in advanced stage. Clinical oncology courses, cancer nursing courses, and public education about cancer have been non-regularly arranged by the organizations for several years. Lastly, in November 1984, cancer nursing course was arranged with cooperation of the UICC.

PROBLEMS Cancer prevention & control in Thailand face many difficulties which limit its scale and implementation. Poor resources, especially limited funds, manpower and medical facilities are among the major obstacles.

RECOMMENDATION Cancer education, prevention and early detection or screening programmes are important and less expensive than treatment. These programmes should be competed with other priorities in health care and must not impose a burden on the already limited medical facilities. These should make use of already existing health care units such as rural health centres. Treatment centres should be distributed to cover the whole area of the country.

1. International FUNDS for running the regular educational programmes for both medical, paramedical personnel and general public.
2. The programmes should be closely co-operated under the supervision of the International Organizations.
3. Short term (6-12M) International Fellowship in oncology or Personnel Exchange Programme should be regularly established for advanced training.
4. Tools, i.e. radiotherapy machines for the new set-up treatment centres in the rural area should be supported by the International Organizations.

INNOVATIVE TECHNIQUES IN CANCER NURSING CARE

R.Tiffany, London, UK

RESERVED

RESERVED

1061
4084 Adult Day Hospital Pilot Project
Margaret E. Kiss, Memorial Sloan-Kettering Cancer Center, New York, N.Y., U.S.A.

Due to rising hospital costs and growing interest in assisting cancer patients in maintaining their normal lifestyles, an alternative to inpatient care for aggressive cancer treatment is needed. In February 1984, Memorial Hospital launched a pilot Adult Day Hospital project to study an alternative to traditional inpatient care. This program has already caused the attention of the other radiotherapy units in the hospital and the Outpatient Department. The copies of these materials will be provided by the foundation and we investigated the client's needs of teaching materials related in radiotherapy. Group meetings and discussions will be held more frequently and easily by using these teaching materials. The experience of this program has already caused the attention of the other radiotherapy units in Taiwan area.

PRIMARY NURSING IN AN OUTPATIENT DEPARTMENT.
M. Braimien, The Norwegian Radium Hospital, Oslo, Norway.

In spring 1985 primary nursing was implemented at the Outpatient Department. The Norwegian Radium Hospital is the main cancer center in Norway. Firstly, this paper will give a short presentation of the nursing care delivery on the unit based upon the specific objectives of primary nursing: 1. Continuity of care; 2. Holistic care; 3. Coordinated care; 4. Individualized care; 5. Patient-centered care; 6. Authority; 7. Autonomy; 8. Accountability.
CLINICAL STUDIES WITH OK-432 IN CANCER PATIENTS

Since 1978-after intensive preclinical studies - we are using the streptococcal preparation OK-432 (kindly provided by Chugai Pharmaceutical Co., Ltd., Tokyo) for treatment of patients with malignant disease. Phase I studies established that OK-432 therapy, by all routes applied, is well tolerated. Immunopharmacologic investigations clearly demonstrated that OK-432 strongly augments certain immune functions esp. natural killer (NK) activity depending on injection route. Especially locoregional OK-432 therapy, i.e. intraperitoneal, peritoneal and periumbilical injection seems to significantly augment NK activity in pleural, peritoneal effusions and also in tumor-draining lymph nodes, respectively. Beside this immunomodulation, OK-432 therapy also resulted in objective clinical responses in patients with established disease, i.e. malignant melanoma (MM) and malignant exudate-lung, ovarian cancer). Furthermore, in a great proportion of pts progression of disease was stopped by OK-432 therapy. In an open trial in pts with MM stage IIIb, adjuvant therapy with OK-432 tended to delay local and distant recurrences. In conclusion beside strong immunopotentiating effects OK-432 therapy seems to be active for patients with established disease and also for maintenance of disease free period in MM with NED.

RESERVED

OK-432 ENHANCES PRIMARY PRODUCTION OF NK CELLS IN BONE MARROW
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The streptococcal preparation OK-432 is known to augment natural killer (NK) cell activity in both patients and experimental animals. Such increased NK lytic activity could result from effects on production, maturation, migration, or recycling of NK cells. In the study reported here, we tested whether OK-432 can increase primary production of NK cells in the bone marrow. Six 7-week old female C57Bl/6J mice were injected i.v. with saline (control) or OK-432 (5 mg/kg)- At varying times (1-7 days) the mice were pulsed with [H]-TdR (1 uCi/gm body wt) to label dividing cells. Bone marrow cells were obtained and either mixed with the NK-sensitive target YAC-1 in a target binding assay that detects both pre-NK and mature NK cells or tested for lytic activity against 51Cr-labeled YAC-1. Cytospots of the target bound cells were prepared for autoradiography and scored for percentages of labeled cells and target and labeled NK cells (106). The data indicate that OK-432 increases in the rates of production of large pre-NK and mature NK cells or tested for lytic activity against 51Cr-labeled YAC-1. It seems that OK-432 pretreatment potentiates such lytic activities that are inherent for the particular effector population and therefore it is likely that this in vitro obtained effect has biological significance.
OK-432 is a penicillin-treated lyophilized powder of SU strain of streptococcus pyogenes and proved to have a strong BRM activity to immunocytes. Immunotherapy of cancer patients with systemic administration of OK-432 often results in prolongation of survival with clinical improvements. Intracavitary injection of OK-432 to carcinomatous pleural or peritoneal effusion also produces disappearance or reduction of fluid retention and its tumor cells. Cytotoxic examinations of tumor-associated lymphocytes disclosed augmentation of CTL, NK and autologous tumor cell killing (ATK) activities in those of OK-432 responded cases, accompanied to abrogation of NK suppressor macrophages. Productions of cytotoxic soluble factors from NK cell (NKCF) and monocytes (MCF) are enhanced after stimulation with OK-432. Single effector cell cytotoxic assay disclosed increased conjugation of effector cell to autologous tumor cells with enhanced lytic activity. OK-432 markedly stimulated IL-2 production not only from T cells modulated through macrophages, but also directly from T4 cells. In order to determine the effective components, OK-432 was fractionated into 4 different elements—cell free extract (CF), cell wall (CW), protoplast membrane (PM) and protein (SU-PR), and their immunostimulatory properties were evaluated in vitro. The results showed the most effective component responsible for augmentation of NK activity and IL-2 production of T cells was found to be CF, although there was some individual variations in the effective components of IL-2 production, probably depend on the individual differences in the sensitizing components from previous streptococcal infections.

IMMUNOMODULATORY AND IMMUNOTHERAPEUTIC PROPERTIES OF OK-432 FOR METASTATIC DISEASE: OPTIMIZATION OF THERAPEUTIC PROTOCOLS AND STUDIES INTO THE NATURE OF THE EFFECTOR CELL. James E. Talmadge, Barbara Lenz, Craig Reynolds, Robin Pennyman, Hirohito Fuku. PRECLINICAL Screening Laboratory, PRI, MD, BMRP, UFI, NCI-FRFP, Frederick, MD 21701 USA.

Studies to determine the immunomodulatory properties of OK-432 have taken a systematic approach including the immunaugmentation of T cells, B cells, NK cells, and macrophages. OK-432 has its most potent augmenting properties for the NK cells and macrophages. In addition, presumably associated with interleukin 1 production, OK-432 also has adjuvant activity for the development of cytotoxic T cells when admixed with a suboptimal tumor vaccine and for B cells in the production of IgG1 antibody to BSA. OK-432 has immunotherapeutic properties for the treatment of experimental and spontaneous B16-BL6 metastases. Optimal therapeutic protocols require the intravenous injection two or three times a week of 1 KE/animal of OK-432. In addition, OK-432 has had significant therapeutic activity for the treatment of UV-induced autochthonous skin tumors. This therapeutic activity is observed following the i.v. administration (i.w.) of 1 KE of OK-432 for three weeks followed by 2 weekly intradermal injections of 5 KE of OK-432. Additional studies revealed that the prolongation of survival and decrease in tumor volume associated with these therapeutic protocols is associated with the intravenous administration as opposed to the intradermal administration of OK-432. Studies have also been undertaken to examine the effector cells responsible for the therapeutic activity of OK-432 in tumor-bearing animals. These studies revealed that OK-432 is capable of increasing both NK cells and macrophages in tumor-bearing animals. In summary, OK-432 has therapeutic activity for the treatment of both transplantable and autochthonous tumors and their metastases, and its activity appears to be associated mainly with the augmentation of effector cells. Research supported by contract No. N01-23010 with Program Resources, Inc.
PHOTODYNAMIC THERAPY USING A PULSED GOLD VAPOR ALIUS AND HEMATOPORPHYRIN DERIVATIVE. H. Hisazumi*, H. Yamamoto*, T. Miki*1, K. Haise*, K. Koshida*, Y. Tanaka** and M. Yoda**. Laboratory of Photodynamic Therapy, School of Medicine, **Faculty of Pharmaceutical Sciences, Kanazawa University, Takara-machi 1-1-1, 920 Kanazawa, Japan.

The tissue penetration properties of argon dye-laser (ADL) and pulsed gold vapor laser (GVL) lights in a combined or single irradiation have been studied using a two-laser excitation system and rabbit liver fragments with or without HPD. A combination of the two irradiations which crossed at right angles produced a synergistic increase in transmitted light power. The absorption spectrum of the ground-state HPD and transient absorption spectrum of excited HPD have been studied using a laser flash photolysis system and HPD-containing KK-47 bladder cancer cells. The transient absorption of the KK-7 cells containing HPD excited by a one-pulse irradiation from an excimer laser produced an increase of transmittance for 240 ns. In addition, light extinction length as a parameter of light transmission has been studied using a living white rabbit auricle without HPD injection. The length of the GVL at an average power of 150 mW was approximately 3.3 times that of the ADL at an output power of 100 mW. These results suggest that deep tissue penetration of the GVL light may result from the high density excitation of HPD, hemoglobin, myoglobin and others which were incorporated in the tissue due to its high peak power (10 kW) and high repetition rate (7 to 10 kHz). In laser irradiations showing no hyperthermic photodynamic therapy using the GVL showed a significantly high complete remission rate and a significant decrease in the time needed to achieve complete remission compared to that of the ADL in the KK-47 tumors. The GVL was promising enough to be used in clinical cases.
PHEOPHORBIDE DERIVATIVE AS A CANDIDATE OF NEW SENSITIZER FOR PHOTODYNAMIC THERAPY

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Until now, we have synthesized more than 140 different kind of porphyrin, pheophorbide derivatives and their metal complexes and tested the relationship between their side chain structure and the accumulation in cancer tissues. Our studies on many porphyrin, pheophorbide derivatives and their metal complexes have made it clear that there is a certain correlation between the side chain structure and tumor tissue accumulation. Recently, pheophorbide derivatives are becoming of interest for their possible application as photosensitizers in the therapy of tumors. The high molar extinction coefficient around 670-680 nm makes these compound a better candidate than porphyrins as phototherapeutic agents to induce tumor regression.

Among pheophorbide derivatives, pheophorbide dimer (PPB dimer), 2,3,9,10 tetra OH phophorbide, 2-OH pheophorbide and 2-OH PPB dimer show high tumor tissue accumulation. The high molar extinction coefficient of PPB dimer is around 680 nm and easily soluble in water.

These facts suggest for us that pheophorbide derivatives become candidate of new sensitizer for photodynamic therapy.

D-26: NATURALLY OCCURRING CARCINOGENS AND THEIR MODE OF ACTION

4294 HYDRAZINES IN EDIBLE MUSHROOM: OCCURRENCE, CARCINOGENICITY AND ENVIRONMENTAL IMPLICATIONS. B. Foth, Eppley Institute for Research in Cancer, University of Nebraska Medical Center, Omaha, Nebraska 68105-1065, U.S.A.

Agaricus bisporus (AB), the commonly eaten cultivated mushroom of commerce in North America, Europe and elsewhere, contains a number of nitrogen-nitrogen bond-containing chemicals. Among these, the most notable are HMBD, HBA and GCPH, and its breakdown products. Among pheophorbide derivatives, pheophorbide dimer (PPB dimer), 2,3,9,10 tetra OH phophorbide, 2-OH pheophorbide and 2-OH PPB dimer show high tumor tissue accumulation. The high molar extinction coefficient of PPB dimer is around 680 nm and easily soluble in water.

These facts suggest for us that pheophorbide derivatives become candidate of new sensitizer for photodynamic therapy.

4100 NATURALLY OCCURRING N-NITROSO COMPOUNDS - CARCINOGENICITY AND MODE OF ACTION


Carcinogenic N-nitroso compounds have considerable importance as environmental health risk factors. Although some have been found in micro-organisms (e.g. streptozotocin) and in mushrooms, the main source of human exposure is by their formation from naturally occurring (or anthropogenic) nitrosatable amine precursors and nitrosating agents such as nitrite and/or nitrous gases.

More than 100 different N-nitroso compounds have been tested for carcinogenic activity in animal experiments. About 90% of them are carcinogens, some of them, like dimethyl- or diethyl-nitrosamine or the alkynitroso ureas, are extremely potent agents, inducing malignant tumors at very low exposure. The most remarkable effect of carcinogenic N-nitroso compounds is their organ-specificity, which primarily depends on the chemical structure and the animal species used.

N-Nitrosamines are indirect carcinogens requiring metabolic activation by a-C-hydroxylation to form alkylating agents interacting with DNA and other physiological substrates. N-Nitrosamides such as the nitrosoureas are chemically reactive per se and do not need activating metabolism. While the basic mode of action of N-nitroso compounds is known, the exact mechanism of the organ-specificity of their carcinogenic effect is still largely unknown.
D-26: NATURALLY OCCURRING CARCINOGENS AND THEIR MODE OF ACTION

4101 NATURALLY OCCURRING CARBAMATES IN FERMENTED FOODS AND BEVERAGES. C. S. Ough, Dept. of Viticulture and Enology, Univ. of California, Davis, CA 95616 USA

Ethyl carbamate was used as a treatment for stomach disorder until it was determined that its ingestion caused liver cancer. Until a report questioned the possibility of its presence in wines treated with diethyldicarbonatc, a fungicide, very little interest had been shown about carbamates in foods. This report stimulated extensive research in the area. These studies showing the presence of natural ethyl carbamate in fermented beverages and foods will be reviewed. In addition, recent findings indicate that fermented foods treated with the fungicide ethyl carbamate. In some cases reported findings of ethyl carbamate there was no urea or diethyldicarbonate added. Some studies are being pursued in this laboratory to determine if under certain conditions amino acids, with the possibility of contributing the right fragments, can give ethyl carbamate with ethanolysis. These preliminary studies will be presented.

4102 CARCINOGENIC PYRROLIZIDINE ALKALOIDS. I. Hirono, Dept. of Path., Fujita-Gakuen Health Univ. Sch. of Med., Toyoake, Aichi, Japan

Pyrrolizidine alkaloids were first found as carcinogenic natural product of plant origin. It is about 30 years since the carcinogenicity of Senecio jacobae L. was first found. More than 200 pyrrolizidine alkaloids have been isolated from plants and about 30 alkaloids proved to be hepatotoxic, mostly in rodents. Some of these hepatotoxic pyrrolizidine alkaloids have been found carcinogenic to rats when given as pure alkaloids, e.g. isatidine, retrorsine, monocrotaline, and lasiocarpine. In Africa and other places, plants containing these carcinogenic pyrrolizidine alkaloids have been used as herbal remedies or foods. The nature of the toxic effects caused by pyrrolizidine alkalioid depends on the species and age of the affected animal, the structure of the alkalioid, and the manner in which the alkalioid is ingested. Particularly, diester and cyclic diester pyrrolizidine alkaloids which contain necine, retronecine and otonecine, are strongly hepatotoxic and hepatocarcinogenic. The flower stalks of Petasites japonicus and buds of the coltsfoot, Tussilago farfara which belongs to the tribe Senecionae, family Compositae are used as herbal remedies, such as cough medicine or expectorant. Rats fed a diet containing the dry powder of these plants develop hepatocellular carcinoma and hemangioendothelial sarcoma of the liver. Carcinogenic principle contained in these plants was found petasitenine (Fukinotoxin) and senkirkine. Symphytum officinale (comfrey), Farfugium japonicum, and Senecio cannabifolius were also hepatocarcinogenic to rats, and symphytine was proved to be at least one of carcinogenic principles contained in comfrey. From these results so far obtained, it is most probable that hepatotoxic pyrrolizidine alkaloids are simultaneously hepatocarcinogens in rats.

4103 SYNTHESIS OF CARCINOGENS AND MUTAGENs BY BACTERIA IN VIVO
M. J. Hill (PHLS - CAMR) Salisbury, U.K.

There is no doubt that bacteria similar to those present as part of the normal human bacterial flora are capable of producing a wide range of carcinogens and mutagens; these reactions are carried out in vivo. The major difficulty is in determining their clinical significance. The major site of bacterial metabolic activity is the colon, where bacteria produce a wide range of substances which are carcinogenic or promoters in animals or which are mutagenic or co-mutagenic in microbial mutagenesis assay systems. These include ethionine (from methionine), a range of volatile phenols (from phenolic amino acids), metabolites on the quinoline pathway from tryptophan, secondary bile acid metabolites, N-nitroso compounds and a faecal pentene mutagen. N-nitroso compound formation has also been claimed in the infected urinary bladder, the infected vagina and the achlorhydria stomach as well as in the duodenum of patients with small bowel overgrowth. Bacteria are also able to hydrolyse the glucuronide conjugates of carcinogens produced by the liver and secreted in the bile. A number of food additives and components can be hydrolysed or reduced to released carcinogens (e.g. cycasin, some food colours etc).

4104 ENDOGENOUS PRODUCTION OF MUTAGENIC AND CARCINOGENIC COMPOUNDS.
W. R. Bruce, Toronto, Canada
Betel quid chewing is a widely practised social habit in India and several other countries in South-East-Asia. Betel Quid generally contains one or two betel leaves to which lime, areca nut and catachu are added as per taste. Habitual betelquid chewers add tobacco of chewing variety. Epidemiological studies have established that betel quid with tobacco chewing is associated with cancer of oropharyngeal cavity though the risk is relatively less in subjects chewing only Betel Quid. Using Ame's test it was observed that water extract of betel quid /BQ/ and its ingredients namely betel nut (BN) are mutagenic while betel leaf (BL) and catachu are non mutagenic. In mammalian test systems only tobacco and BN are mutagenic. Tumorgenicity studies on Swiss mice have further shown that BN and BQ induced lung tumours (47 % and 26 % respectively). We have further observed that BL is anti-mutagenic versus potent mutagens and affords protection versus potent mutagens such as tobacco.
Hepatitis B virus (HBV) is a major cause of chronic liver diseases and primary hepatocellular carcinoma (PHC) in several countries of the world. PHC is not a common malignancy in Hungary, however its incidence increases. 50-50 autopsy cases of cirrhosis and PHC were studied by immunohistochemical methods for localization of five antigens /HbsAg, HbeAg, alpha-fetoprotein (AFP), and alpha-1-antitrypsin (AAT)/. HbsAg was found positive in four cases of PHC and in 5 cirrhotic livers. HbeAg was observed in one PHC and two cirrhosis. AFP and CEA were demonstrated in 40-50% of PHC and in none of cirrhotic livers. AAT was negative in all cases studied. 10 biopsy cases of focal nodular hyperplasia, liver cell adenomas, 2 hepatoblastomas were negative for HBV markers as well. Glucose-6-phosphatase was demonstrated in focal nodular hyperplasia, liver cell adenoma and in certain areas of PHC. Adenosine triphosphatase activity was lost in focal nodular hyperplasia and PHC. Gamma-glutamyl-transpeptidase appeared in focal nodular hyperplasia and PHC. Data suggest that HBV is not a major cause of cirrhosis and liver tumors in Hungary. Heterogeneity of human hepatic tumors was demonstrated by enzyme histochemistry in contrast to the data of experimental liver carcinogenesis.
INTERACTION OF AFALTOXIN AND HEPATITIS B VIRUS IN PATHOGENESIS OF HEPATOCELLULAR CARCINOMA. G.N. Vyas, H.E. Blum, M.P. Busch, N.S. Lee and M.S. Rajagopalan, University of California, San Francisco, San Francisco, California, USA.

Primary hepatocellular carcinoma (HCC) is one of the most common cancers in Southeast Asia and Sub-Saharan Africa where aflatoxin B1 (AFB), a secondary metabolite of Aspergillus species commonly contaminating agricultural food products, is consumed in relatively large quantities. A high prevalence of chronic hepatitis B virus (HBV) infection is also noted in these regions, where the risk of developing HCC is approximately 200 times greater in carriers of HBV. In contrast, the remarkably low incidence of HCC in Geneva who is not a carrier of HBV infection may be ascribed to a high prevalence of HBV infection and a low dietary intake of AFB. Integration of HBV DNA into the cellular genome of HCCs could be a mechanism of aduct between AFB and nucleic acids. This study suggests that hepatocytes with integrated HBV DNA preferentially accumulate HBV, the AFB-adsorbed forms may inhibit or induce cell transformation by modifying the expression of critical viral host genes. The altered molecular biology of liver cells in HCC is evidenced by the fact that HBV does not replicate in HCC tissues or cells. In contrast, the presence of HBV DNA in HCC cells is associated with a reduction in the expression of cellular genes such as endogenous retrovirus(es) and possibly cellular oncogene(s), such as the ras gene. The presence of HBV DNA in HCC cells may be related to the expression of cellular genes that are involved in the malignant transformation of hepatocytes. Both hepatocellular carcinoma (HCC) and liver cirrhosis are associated with chronic HBV infection. The molecular cloning of the HBV genome has shown that HBV DNA is integrated into the cellular genome in approximately 75% of liver biopsy samples from patients with HCC. In addition, the presence of HBV DNA has been detected in 78% of liver biopsy samples from patients with liver cirrhosis.


In 1942 the U.S. Army experienced an epidemic of 50,000 cases of viral hepatitis traced to contaminated lots of yellow fever vaccine stabilized with human serum. A comprehensive follow-up study includes: (1) a cohort mortality study of 20,000 men in each of three groups, each hospitalized with icteric illness during the epidemic; (2) the WHO, those who received contaminated vaccine but were not acutely ill, and 111, controls vaccinated only later with a vaccine devoid of human serum; (2) a serologic survey of 200 men from each group; and (3) a case-control study of discharges from Veterans Administration hospitals, 1963-1981, with a diagnosis of primary hepatocellular carcinoma (PHC) vs. matched controls, compared to yellow fever vaccine lot number. The 1985 serologic survey shows: (1) the percentages positive by radioimmunoassay for anti-HBs and anti-HBe are, Group 1, 97.3; Group II, 72.5; and Group III, 6.8; (2) the percentages positive for anti-HAV are 75%, 72%, and 63, respectively; (3) anti-HBs antibody levels are significantly lower; (4) only one carrier (HBSAg+) was identified in Group I, none in II or III. The cohort mortality study, 1946-1983, with over 17,000 deaths, 48 from liver cancer; 91 from cirrhosis, and 46 from other liver disease and hepatocellular carcinoma. The mortality rate was not different between HCCs in the three groups as to mortality from PHC, cirrhosis or other liver disease, or hepatocellular carcinoma. The case-control study includes: (1) HBV and PHC; (2) following natural infection, HBV antibodies persist for 40 years plus; (3) following natural infection, HBV and PHC rates are lower; (4) only one carrier (HBSAg+) was identified in Group I, none in II or III. The mortality rate was not different between HCCs in the three groups as to mortality from PHC, cirrhosis or other liver disease.

UNIQUE ONCOGENE FROM HUMAN HEPATOCELLULAR CARCINOMA CELLS CONTAINING INTEGRATED HBV DNA. K. Koltery*

Since we demonstrated the presence of hepatitis B virus (HBV) DNA integration in the state of chronic active hepatitis and hepatocellular carcinoma, it is conceivable that hepatocarcinogenesis requires not only the integrated HBV DNA but other cellular factors, such as oncogenes and hormonal agents. The viral genome may be one of the most important prerequisites for the formation of the hepatocellular carcinoma. Cellular oncogene(s) could be activated by integrated HBV sequences directly or through the increase of virus-related protein in the initial stage of tumorigenesis, but HBV DNA integration may not be required for the maintenance of the malignant state. We therefore carried out experiments to detect activated cellular oncogenes by DNA-mediated gene transfer techniques by using mouse NIH/3T3 cells. DNA from hepatocellular carcinoma cell line (HuH2-2) and tissue (HCC2707), containing a single and multiple copies of integrated HBV DNA, respectively, were used to transform NIH/3T3 cells by the calcium phosphate precipitation method. Both hepatocellular carcinoma DNA could transform NIH/3T3 cells. Secondary transformants in both cases grew in the soft agar under the DMSO serum conditions. Southern blot analysis of EcoRI digested transformant DNA showed that the secondary or tertiary transformants contained human EcoRI DNA fragments. HBV DNA and the ras family oncogenes were not detected in the transformants so far examined. We then performed the molecular cloning of the hepatocellular carcinoma oncogene. A gene library was constructed in Charon A, using DNA isolated from these secondary transformants that had been partially digested with EcoRI. Recombinant phages were obtained and further characterized to detect EcoRI DNA fragments obtained in the Southern blot of the secondary or tertiary transformants. Structures of cloned DNA and transforming activities were investigated. This transforming DNA is tentatively named a hepatocellular carcinoma specific oncogene HCC.
ROLE OF HOST RESPONSES IN THE DRUG TREATMENT OF METASTASES

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When total tumor eradication cannot be achieved by conventional treatment, the prevention of tumor metastasis by drugs selectively inhibiting the process of tumor spread may be of interest. A remarkable and approximately equal antimetastatic effect results from the comparison of the antimetastatic activity of N-diazoacetylglycine amide (DGA) and of p-(3,3'-di- methyl-1-triethylenemido)benzene potassium salt (DM-COOK) in the Lewis lung carcinoma (LLC) system. Yet, when the antimetastatic treatment is followed by surgical removal of primary tumor, DM-COOK produces about 40% long term survivors whereas DGA causes none, in spite of its pronounced antimetastatic effects. This finding is interpreted assuming that host responses, contributing to the cure caused by DM-COOK, which is weakly immunodepressing, are not available after treatment with DGA, which strongly depresses cell mediated immune responses. A further investigation on host responses has been made by comparison of tumor growth, spread and response to ICRF159 in mice bearing LLC kept in conventional housing (CH) or in a protected environment (PE) and subjected to stress (apartal disorientation, SD). Tumor growth, and particularly metastases weight, are remarkably small in mice kept in PE, and have unusual values in mice under PE plus SD. When the animals in PE are subjected to SD, the percent reduction of metastases by ICRF 159 is enhanced, but their final number and weight are approximately equal to those of mice in PE without SD. These findings indicate the importance of host responses residing after treatment, and also of housing and handling of animals, in the study of the treatment of metastases. The implications for clinical situations also appear of interest.

Supported by Italian National Research Council, Special Project 'Oncology', contract n° 85.02186.44 and by Italian Ministry of Education.

LOCALIZATION OF COLORECTAL CARCINOMA BY EMISSION COMPUTERIZED TOMOGRAPHY AFTER INJECTION OF I-123 LABELED Fab or Fab', FRAGMENTS FROM MONOCLONAL ANTI-CEA ANTIBODIES


Ludwig Institute for Cancer Research, Lausanne Branch, 1066 Epalinges and Division of Nuclear Medicine, CHUV, 1011 Lausanne, Switzerland.

Experimental results obtained in nude mice grafted with human colon carcinoma, showed that injected I-131 labeled F(ab')2, and Fab fragments from high affinity anti-CEA MAb gave markedly higher ratios of tumor to normal tissue localization than intact MAb (Buchegger et al., J. Exp. Med. 150, 413, 1979). Thirty-one patients with known colorectal carcinoma, including 10 primary tumors, 13 local tumor recurrences and 21 metastatic involvements were injected with I-123 labeled F(ab')2 (n=16) or Fab (n=17) fragments from Mab anti-CEA. The patients were examined by ECT at 6, 24 and sometimes 48 h after injection using a rotating dual head scintillation camera. All 23 primary tumors and local recurrences except one were clearly visualized on at least two sections of different tomographic planes. Interestingly, 9 of these patients had almost normal circulating CEA levels and 3 of the visualized tumors weighed only 3-5g. Among 19 known metastatic tumor involvements, 14 were correctly localized by ECT. Two additional liver and several bone metastases were discovered by immunoscintigraphy. Altogether, 86% of the tumors sites were detected, 82% with Fab'2, and 89% with Fab fragments. The contrast of the tumor images obtained with Fab fragments, suggests that this improved method of immunoscintigraphy has the potential to detect early tumor recurrences and thus to increase the survival of patients (Delaloye et al., J. Clin. Invest. 79, 915, 1987). The results of this retrospective study, however, should be confirmed in a prospective study before this method can be recommended for the routine diagnosis of cancer. The use of radiolabeled monoclonal anti-tumor antibodies for radioimmunotherapy of cancer will be discussed in view of recent results from the literature and from our group.
For the purpose of finding a new antitumor drug effective for brain tumors, an experimental brain metastasis model was developed. Histidine, brain tumor models had problems of mechanical disruption of the blood-brain barrier by tumor inoculation and/or discrepancy in histologic nature and site of growth between the inoculated tumor and human tumor. In order to establish a new model for the evaluation of antitumor drugs to brain tumors, we developed rat models of leptomeningeal tumors by intralateral-ventricular inoculation of DBLA-6 rat myelogenous leukemia or AH130 rat ascites hepatoma cells. In these models, there was a larger number of tumor colony formation by tumor inoculation and the histologic pattern of DBLA-6 model was similar to the diffuse meningeal involvement of melanoma in human cases. Nitrosothiurea derivatives, ACNU and CCNU, and precarcinogen were found to be highly effective when given iv or ip and intralateral-ventricular administration of methotrexate was found to be a moderate activity. Intraperitoneal administration of epirubicin mustard and intralateral-ventricular administration of 5-fluorodeoxyuridine was also effective against the AH130 model.

Pathological Finding in Leptomeningeal (Acromegaly Model) AH130

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<thead>
<tr>
<th>tissue</th>
<th>0 days after tumor inoculation</th>
<th>9 days after tumor inoculation</th>
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<td>Brain</td>
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<td>Liver</td>
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<td>Epiglottis</td>
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<td>Stomach</td>
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Platelet aggregation and thrombosis. For activity. Isolation of tumor PAA/PCA should enable normal tissue, does not depend on coagulation factor VII. Tumor PAA/PCA, unlike tissue factor (a procoagulant from normal tissue), does not depend on coagulation factor VII. The intravascular balance between PGI2 and TXA2 favor of platelet aggregation and thrombosis. Platelet aggregation did not occur in the presence of endothelial cells alone. Tumor cells induced platelet aggregation which could be inhibited in a dose-dependent manner by adding an increasing number of endothelial cells. This inhibition of aggregation correlated positively with PG2 production by the endothelial cells and inversely with platelet TXA2. Indomethacin pretreatment of the endothelial cells decreased their PG2 production and prevented their inhibition of tumor cell-induced platelet aggregation. We have recently purified a membrane-associated protein from two rodent tumor lines which has the ability to induce both platelet aggregation (PAA) and blood coagulation (PCA). We have recently purified a membrane-associated protein from two rodent tumor lines which has the ability to induce both platelet aggregation (PAA) and blood coagulation (PCA). We have recently purified a membrane-associated protein from two rodent tumor lines which has the ability to induce both platelet aggregation (PAA) and blood coagulation (PCA).
Studies dealing with the in-vitro evaluation of drug combinations against primary human solid tumors are scarce. Recently developed ATCCs (Baker et al., Proc. ASCO 1985) was used to assess drug combinations of clinical interest. This assay supports growth of more than 70% of all specimens submitted. To assess the tumor IC50, 4 concentrations of each drug and combinations of the two intermediate doses were used to generate survival curves with at least one log kill. The effect of combinations was determined by utilising isobolograms (Steel et al., Int J Radiat Oncol Biol Phys 5:85-89, 1979). Five combinations were assessed in thirteen tests including Cis-Platinum (DDP) + Etoposide (VP16) (5 tests), 5-FU + Mitomycin C (MMC) (5 tests), 5-FU + Adriamycin (ADR) (3), 5-FU + Mitomycin C (MMC) (2), ADR + Cyclophosphamide (2), and CDDP + ADR (1). All five tests with the combination of CDDP + VP16 of the lung, melanoma, and sarcoma) showed supra-additivity. This occurred independent of the tumor response to the individual drugs, or differences in the previously described synergism between CDDP and VP16 in malignant cell lines and clinical experience with this combination. All the other combinations tested showed only additive effect. In conclusion, our preliminary data suggest that the combination of CDDP and VP16 is supra-additive against various human tumors, independent of the single drug response, and that drug combinations can be adequately assessed in the ATCCs. Further research with larger number of tumors and more combinations is warranted.
ANTICANCER CHEMOTHERAPEUTIC DRUGS DIFFER IN THEIR IMMUNOPROMOTING POTENTIAL

S. Ben-Emrarin, S. Shoval, G. Akhvan and R. Ophir
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Drugs of various structures but possessing similar tumoricidal potential differed in their ability to potentiate specific and nonspecific immunocompetent-cell activity. The drugs tested were melphalan (L-PAM), l-phenylalanine mustard) 5-fluorouracil (S-FU) and daunorubicin (DAU). All 3 drugs were highly tumoricidal in vitro against MOPC-315 plasmacytoma tumor cells. However, they differed in therapeutically effectiveness in BALB/c mice bearing large s.c. or ascitic MOPC-315 tumors, for while L-PAM therapy induced permanent regression of MOPC-315 tumors followed by long lasting specific resistance to tumor challenge, S-FU induced only transient regression of tumors and DAU was not effective. Also, spleen cells of mice cured by L-PAM developed high cytotoxic response in vitro against MOPC-315 cells and contained suppressor T cells which inhibited induction of cytotoxic response in spleen-cell population endowed with cytotoxic potential. Moreover, cure by L-PAM was prevented when S-FU was added to the treatment. Preliminary of spleen cells with L-PAM but not with S-FU affected selectively a precursor suppressor T-cell population, by markedly inhibiting induction of suppressor T cells by subsequent incubation with ConA. It is concluded that therapeutic effectiveness of drugs is determined not only by their tumoricidal activity but also by their effect on immunocompetence.


Preclinically derived concepts guide the combined modality approach. Importantly, it is possible to manipulate the host-tumor relationship in order to increase tumor cell eradication. In general, the greater the number of tumor cells present in the host the less effective is the therapy. Reduction in the tumor cell burden by surgery and/or radiotherapy and immunotherapy is tantamount to converting an advanced tumor to an early tumor, thereby making it more susceptible to chemotheraphy. Drug dosage is a critical issue. Eradication of a large tumor mass may decrease metabolic depletion and immunosuppressant action of both tumor and drug and thereby permit the employment of higher dosage of drug and accompanying increase in therapeutic response. There may be a decrease in the threat of infection. For advanced tumor, schedules of drug therapy may have to be employed that are less than optimal and this may be corrected by reduction in tumor cell number. Further, the selection of regimes and timing of application of different modalities can be manipulated to advantage, and the full potential remains to be determined. Treatment of normal and acquired tumor cell resistance may be improved by reduction of spontaneous treatment-associated resistant mutants. Combined modality therapy may diminish the impact of metastatic disease and tumor cell heterogeneity. Rational approaches to new drug design, the introduction of additional models for drug selection and development, coupled with novel approaches in biochemical modulation of the host-tumor relationship and progress in biological response modification and new dimensions to multimodality therapy. Preclinical studies will be presented to support and illustrate the value of combined modalities in achieving total eradication of the body burden of tumor cells.

BIOLGICAL AND MOLARL MOIIEURAl BASIS OF COMBINED MODALITY TREATMENT


Primary, metastatic and recurrent tumors of human colorectal cancer. Transplanted tumor models in nude mice have been used to study their differences from biologically characteristic aspects.

1. Tumor lines xenograft in nude mice used for our study are COK-1 and COK-7. COK-1 (PT, LN and RE) has been established in the primary (PT), lymph node metastatic (LN) and liver recurrent tumors (RE) of human colorectal cancer. On the other hand, COK-7 (PT and LM) has been established in the primary (PT) and liver metastatic (LM) tumors of human rectal cancer.

2. Each tumor line of COK-1 (PT, LN and RE) and COK-7 (PT and LM) showed different growth properties and productivities of carcinoembryonic antigen (CEA) between primary, metastatic and recurrent tumor lines.

3. These tumor lines were used for the study of chemotherapeutic responses to various anti-cancer drugs (5-FU, MMC, CPA and CDDP).

4. Chemotherapeutic responses to cancer drugs in each tumor line were as follows; COK-1 (PT) responded to MMC, CPA and CDDP, while COK-1 (Re) responded to both MMC and CDDP. However, COK-1 (LM) did not respond to all drugs studied. In case of COK-7 (PT) it did not respond to all drugs studied as well, though COK-7 (LM) responded to both MMC and CDDP.

It has been concluded that each tumor line of COK-1 and COK-7 shows biological and chemosensitive differences in primary, metastatic and recurrent tumor lines.

SENSITIZERS AND COMBINED MODALITY TREATMENT. R.P. Hill, G.P. Whitemore, and S. Glynn. Department of Medical Biophysics, University of Toronto and Physics Division, Ontario Cancer Institute, 500 Sherbourne Street, Toronto, Ontario.

Hypoxic cells in tumors are widely recognized as being resistant to irradiation and may influence the ability of radiotherapy to control tumors locally. Hypoxic cells may also limit the response of tumors to certain chemotherapeutic drugs such as BCNU, HN2, Adriamycin and hypoxic cell selective drugs. The use of nitroimidazoles in this resistance, it is very likely that other factors may be associated with hypoxia in tumours can be more important. These factors include poor nutritional status, low growth fraction and distance from functional blood vessels leading to drug diffusion limitations. This hypoxia may provide a marker for cells which are effectively resistant to certain drugs. It is clear that using such drugs at the same time as radiation in combined modality treatments is unlikely to be effective since the same population of tumor cells will be resistant to both agents. One approach to overcome this problem is to use a drug which has preferential activity against hypoxic cells. One class of such compounds are the nitroheterocyclic drugs, such as misoxidaole, which not only sensitive hypoxic cells to radiation treatment but are also preferentially cytotoxic to hypoxic cells. We have been studying one of these drugs, RU-1069, a 2-nitroimidazole with an aziridine side chain. In vitro the drug is 20-100 fold (in terms of dose) more effective at killing hypoxic as compared to well oxygenated cells. It is also much more effective (approximately 100 fold in terms of dose) than misoxidaole as a cytotoxic agent for hypoxic cells. Furthermore exposure of cells to hypoxic conditions in vitro prior to drug treatment increases the sensitivity of the cells to the drug. Studies with animal tumor models have confirmed the efficacy of this drug against hypoxic cells in vivo.

Supported by the National Cancer Institute of Canada and the Ontario Cancer Treatment and Research Foundation.
H-24: BIOLOGICAL AND MOLECULAR BASIS OF COMBINED MODALITY TREATMENT


We reported the antitumor activity of copper-diglycy1-L-histidine (Cu-GGH) in combination with L-ascorbate against Ehrlich ascites tumor cells in vivo (Cancer Res., 43, 824 (1983)). Our in vitro studies with Cu-GGH (5-50μM) and ascorbate (100μM) demonstrated growth inhibition of mouse sarcoma, neuroblastoma and human endometrial carcinoma cells with cytostatic effect. Neither ascorbate nor copper tripeptide alone had a large cytostatic effect on these tumor cells. Incubation of solutions of viral DNA, calf liver RNA and various proteins with Cu or Cu-GGH and ascorbate resulted in damage of these biological macromolecules. The addition of catalase, but not superoxide dismutase, partially prevented the observed DNA-scission by ascorbate and copper complex, suggesting that oxygen derived free radicals may be involved in the process. Our preliminary cell culture studies with human endometrial carcinoma and human lung fibroblasts treated with sodium ascorbate and Cu-GGH showed inhibition of cell replication (In:Biochemical and Inorganic Aspects of Copper Coordination Chemistry, A.D.Karlin and Rubeta(eds), Adenine Press, Calif., U.S.A.****).

J-24: OCCUPATIONAL CANCER EPIDEMIOLOGY

4134 OCCUPATION AND CANCER
A.B. Miller, NCIC Epidemiology Unit, University of Toronto
Toronto, Ontario, Canada

In this session, it is proposed to review occupation and cancer from a number of different viewpoints. It is already clear that the proportion of cancer attributable to occupation in the general population is low and in nearly every study, less than 10%. However, in specific occupational groups a high proportion of those exposed to some carcinogens in the working environment had died of cancer. Particularly critical have been some lung carcinogens such as asbestos and bichloromethylene. New methods are being developed to assess occupational hazards in the general population and in the working environment. For example, routine record linkage methodology is being used in Canada to determine whether there are unexpected results. In a case-control study also being performed in Canada, attempts are being made to assess the relevance of specific exposures in multiple environments in increasing the risk of cancer. Other new methodologies will be discussed in this session. For control of occupational cancer, it is necessary to try and ensure that new carcinogens are not introduced into the occupational environment. Epidemiology is not able to do this. For this it is necessary to rely on toxicity assays, confirmed where necessary by animal carcinogenesis bioassays. It is possible that in the future, biological markers such as DNA adducts may be helpful in assessing potentially carcinogenic as well as providing a marker of high risk in biological monitoring.
LINKAGE OF LIFE-LONG OCCUPATIONAL HISTORIES AND CANCER REGISTRY INFORMATIONS. Jørgen H. Olsen, the Danish Cancer Registry, Institute of Cancer Epidemiology under the Danish Cancer Society, Landskronagade 66, 4th floor, DK-2100 Copenhagen Ø, Denmark.

The introduction of a personal identification number in Denmark in 1968 has greatly facilitated large scale epidemiological cancer studies based on record linkage. The present report concerns the linkage between the Danish Cancer Registry and a nationwide Danish pension fund, which provides occupational histories for cancer patients rather than occupation on a specific (e.g. census) date. The data linkage affects 153,000 cancer patients notified to the Cancer Registry in the 1970s of whom some 91,000 had their occupational history reconstructed back till 1964. By calculation of standardized proportional incidence ratios (SPIR) for each type of cancer, the cancer occurrence - or cancer profile - can be determined for one industry after the other. Examples are given of the uses of the linked Cancer Registry - Supplementary Pension Fund data file to "screen" for occupational risks (mesothelioma, cancers of the urinary tract). In addition the linked file may serve as a basis for case-control studies to test specific hypotheses of risks associated with chemical exposures, which occur in the occupational environment. An example of such a study on formaldehyde, wood-dust and risk of nasal cancer is given. Limitations mainly due to misclassification of exposures, confounding, and to the problem of mass-significance are discussed.

EPIDEMIOLOGICAL STUDIES ON MAN-MADE MINERAL FIBRE PRODUCTION. L. Simonato

Experiments with animals have indicated that man-made mineral fibres may have a pathogenic action, including carcinogenicity. Following these results and given the limited epidemiological evidence available till recent years on working populations, several epidemiological studies have been carried out in Europe, the United States and Canada. The two largest cohort studies carried out in Europe and the US have both shown an increased mortality for lung cancer among the workers within the longest duration of time since first exposure. To investigate further these findings, the follow-up for both studies has been extended. The European study coordinated by IARC has been completed and indicates an association between the early years of production of rockwool/slagwool and excess lung cancer mortality.

EPIDEMIOLOGICAL STUDIES TO DETECT OCCUPATIONAL CARCINOGENS.
J. Peto, Sutton, UK

TIME-DEPENDENT VARIABLES IN THE ANALYSIS OF A CASE-CONTROL STUDY ON BLADDER CANCER AND OCCUPATIONAL EXPOSURES.
G. Terracini, P. Vigna, C. Maganini: Chair of Cancer Epidemiology, University of Torino, Torino, Italy

In the analysis of case-control studies, a correlation between duration of exposure and odds ratios (ORs) reinforces the evidence of causality. In addition, consideration of age at start of exposure and years elapsed since cessation may shed light on possible mechanisms of action in a multistage model. In the present study (512 cases and 596 controls) ORs for having worked in the rubber industry (other than tyre production) were 2.5 (95% CI 1.0-6.0) and 5.0 (1.3-9.1) for workers exposed respectively at least 6 months and at least 5 years. When age at diagnosis (interview for controls) was considered, ORs were 7.5, 3.7 and 1.1 for men aged respectively less than 50, 50-59 and 60+. For both work in the rubber industry and dyestuff production, ORs were negatively correlated to age at start of exposure, whereas they were higher after 10+ years since cessation than before (OR 1.7, 0.5-5.8). These estimates were obtained in a logistic regression model, including age at diagnosis/interview, intensity, duration, age at start and years since cessation of smoking. These results suggest an early stage of action of occupational exposure to aromatic amines in human bladder carcinogenesis.

(Supported by National Research Council Contract 84.00824.44)
A CASE-CONTROL STUDY OF THE RELATIONSHIP BETWEEN LARYNGEAL CANCER AND SULFURIC ACID
K. E. Wendum, D.L. Cookfai, J.L. Vena2, A.M. Michalek
Education Dept., Roswell Park Memorial Institute, Buffalo, NY 14263, Dep. of Social & Preventive Medicine, SUNY-B, Buffalo, NY 14214, U.S.A.

Several occupational exposures have been suggested as agents involved in laryngeal cancer etiology. Sulfuric acid, a widely used industrial chemical, has been associated with an increased risk of laryngeal cancer. This case-control study investigates potential occupational exposure to sulfuric acid and risk of developing laryngeal cancer in patients admitted to Roswell Park Memorial Institute in Buffalo, N.Y., between 1951 and 1963. Data on suspected risk factors (smoking, alcohol, and occupation) were collected using pre-admission questionnaires and interviews. Cases consisted of all white males with histologically confirmed laryngeal cancer. Controls consisted of white males with diagnoses other than neoplastic diseases or diseases of the head and neck. Cases (n=39) were frequency matched by age to controls on a 4:1 ratio. Exposure to sulfuric acid was assigned by evaluating occupational histories of all study members. Length of time employed in each occupation was used to determine lifetime exposure. Relative risks were estimated by the odds ratio Mantel-Haenszel stratified analysis. Increased risk of laryngeal cancer related to sulfuric acid exposure was found for both high and low exposure levels (RR=1.50 and 1.77). History of sulfuric acid exposure was found to increase risk for non-smokers/non-drinkers and light and heavy drinkers who were also heavy drinkers. Results of logistic regression analysis also showed a risk for laryngeal cancer related to sulfuric acid exposure after controlling for both alcohol and cigarette use. The wide use of this industrial chemical, and the potential for simple control of exposure to it, may suggest that sulfuric acid is involved in a considerable proportion of laryngeal cancer among the white male population.

IMPROTANC OF SMOKING, OCCUPATIONAL HAZARDS AND URBAN AIR POLLUTION IN LUNG CANCER ETIOLOGY
W.A. Jędrychowski and Z. Basić-Ciarpiałe
Department of Epidemiology, Inst., Soc. Med., Med. School, Cracow, 7, Kopernika Street, Cracow, Poland

Surveillance of lung cancer incidence based on mortality was carried out over 6 yrs in Cracow. It appeared that lung cancer death rates among Cracow inhabitants were higher than average rate in the population of Poland but this difference in the large extent could be explained by the greater prevalence of smoking habit in Cracow than in whole Poland. Very intriguing was a substantial excess of lung cancer deaths only in male residents of the city center having the highest level of the air pollution. Since this excess in the lung cancer deaths could not be exclusively explained by smoking or occupational hazards the air pollution should be assumed as a responsible factor. Lack of the similar phenomenon in females living in the city center can be explained by the fact that the air pollution alone is not sufficient cause in the etiology of lung cancer but that in combination with other adverse factors like smoking or occupational hazards it develops its carcinogenic effect.

AN OVERVIEW OF MAGNETIC RESONANCE IMAGING (MRI) IN EVALUATION OF PATIENTS WITH SUSPECTED MALIGNANCIES
Marvin A. Rich and Christopher Bartlett
AMC Cancer Research Center, Denver, Colorado, 80214, USA

In its current state in the U.S., MRI has been used to ever increasing advantage in the evaluation of patients with known or suspected malignancies. We report an overview of the experience at the AMC Cancer Research Center where from November, 1983 to the present, over 2,000 scans have been performed. In our experience, MRI provides information corroborating findings discovered by conventional imaging (CT, US, etc.) in addition to unique information not available by any other method in the evaluation of lung, breast, and colon cancer. In the brain, metastatic disease is detected at an earlier stage and with greater sensitivity with MRI as compared with CT. Similar efficiency has been demonstrated in detecting bone marrow and liver metastases.

abbreviations: MRI, magnetic resonance imaging; CT, computerized axial tomography; US, ultrasound

NMR AND NMR PROPERTIES OF TISSUES: IMAGING CONSEQUENCES
K. Tompa, I. Fur, I. Paszik
Ctr. Res. Inst. for Physics, Budapest, Hungary

Magnetic resonance imaging (MRI) is an exciting and rapidly growing field of medical diagnosis, both in experimental and clinical area. Understanding the background of this tool presents several challenges. Interdisciplinary studies involving physicists, biochemists and physiologists are necessary to met it. This lecture provides an introduction to the underlying NMR theory which are important for medical applications, to the NMR characterization of tissues, and to those techniques which allow NMR signals to be used to obtain spatial information and to arrange this information as cross section images through human body. The rapid development of last 10 years generates a great hope, but small courage to predict the future.
THE VALUE OF MULTIPLANAR HIGH-RESOLUTION CT OF THE SELLA REGION IN COMPARISON TO NMR/MI
A.C. Klinkhamer, M.D., Ph.D., M.J. Hendriks, M.D., F.W. Zonneveld, M.Sc., H. Damma, M.D.
University Hospital, Dept. of Radiodiagnosis, Utrecht - The Netherlands

Axial computed tomography has been used successfully for many years in the diagnosis of parasellar lesions. A new approach in the study of sellar pathology is the use of multiplanar high-resolution CT, which has the advantage of providing a three-dimensional study of the sellar region.

A preliminary study was performed in order to assess the value of multiplanar high-resolution CT of the sellar region. The results showed that multiplanar high-resolution CT is a valuable tool in the diagnosis of sellar pathology.

MAGNETIC RESONANCE IN THE DIAGNOSIS OF MALIG-NANT TUMORS IN GYNECOLOGY

We report about more than 100 examinations of patients with a gynecological tumor. About 1/2 received surgery, the others were irradiated. In nearly all cases CT examination was available for comparison. In some cases especially corpus carcinomas also intraterine ultrasound was done.

The results are: MR gives in variable planes an excellent topographical overview. Tumors of the uterus can be recognized in its local extent and infiltration. In this respect MR is much better than CT. Those informations are especially important for the radiotherapist. For tumor staging (i.e., examining pelvic lymph nodes, perametrical infiltration and infiltration of intestine or ovarian carcinomas). MR has not yet proved superiority to CT. First results using contrast media (Gadolinium) are discussed.

NUCLEAR MAGNETIC RESONANCE AND CANCER DETECTION
Helena Mendonca-Pias, Department of Chemistry, University of Stony Brook

Proton nuclear magnetic resonance /NMR/ imaging is actually widely used to image humans, for the diagnosis of a large number of pathological situations, from congenital abnormalities to cancer detection. It has been demonstrated long ago that normal and cancerous tissues differ in their characteristic relaxation rates /T1 and T2/, although the exact reason for such changes need to be explored in further detail in order to completely understand the biological and physical changes responsible for this phenomenon. One of the advantages of nuclear magnetic resonance imaging is that it does not use any kind of ionizing radiation. According to the most recent surveys, magnetic resonance imaging is more sensitive, in most part of the cases, than other conventional techniques, although not yet as specific. Research work is being carried out by a number of groups, both in the U.S.A. and in Europe, in order to develop adequate contrast agents, such as paramagnetic ions and molecules or ferromagnetic suspensions, bound to selective carriers, for example monoclonal antibodies, to increase the specificity of magnetic resonance imaging for medical diagnostic of cancer.

In vitro and in vivo images of surgical specimens and of humans and animals will be presented to stress the importance of the choice of the experimental conditions on appearance of the images obtained.

MRI IN THE EVALUATION AND STAGING OF SOFT TISSUE AND BONE TUMORS
John A. Kalmar, M.D.
Ohio State University, New Orleans, Louisiana, USA

Due to excellent contrast sensitivity, MRI has a major role in the recognition, staging and treatment planning of soft tissue and bone tumors. Spin echo sequences with T1 and T2 weighted images have been most valuable in differentiating normal and abnormal tissues. Direct sagittal, coronal and axial images permit assessment of intrasosseous and extrasosseous extension of tumors, their relationship to the joints and neurovascular structures and detection of "skip" lesions. MRI allows improved detection of recurrent tumors in the presence of non-ferromagnetic metal implants as compared to CT. Calculated comparative measurements of relaxation times showed no reliable difference between benign and malignant tumors.
MRI IN THE DIAGNOSIS OF TUMORS WITHIN THE CENTRAL NERVOUS SYSTEM

F. Aichner
Department of Neurology, University Hospital, Medical School, Innsbruck, Austria

MRI is the preferred screening procedure for evaluation of tumors of the brain and spinal cord. MRI may provide in-conjunction with other imaging techniques for thoracic tumor staging. The principal advantages lie in excellent vessel-tumor demarcation within the mediastinum and the lung hilus, as well as the capability for multiplanar imaging. The assignment of pleural and chest wall involvement may also be achieved optimally with MRI, but its sensitivity for evaluating tumor deposits within the lungs is compromised by respiratory and vascular motion. Clinical examples will be shown to illustrate the complementary information which can also be provided by MRI in conjunction with other imaging techniques for thoracic tumor staging.

NUCLEAR MAGNETIC RESONANCE IMAGING IN DIAGNOSIS OF MALIGNANT TUMORS

H.-K. Beyer, Ruhr-Universität Bochum

The nuclear magnetic resonance has relevance to other imaging methods some considerable advantages. There is the lack of radiation and the possibility to take images along every projected axis orientation. The use of different pulse sequences gives a much greater information on tissue characteristics than CT does. The excellent tissue contrast precludes MRI for diagnosis as far as soft tissue processes are coinvolved. MRI has been especially accepted for the diagnosis of tumor processes of the brain and spine as well as of the neck. Here the sensitivity of MRI is clearly higher than of CT and the specificity turns out equal or even better using paramagnetic contrast media.

There are more problems for the diagnosis of space occupying processes in thorax or abdomen because of motion artefacts. The value of the method is diminished because of respiratory movement or heart contraction and peristaltic of intestine. We found some advantages of MRI for the diagnosis of bronchusneumoplast. We found only some advantages concerning tumors of the lung, the prostate and the bladder. For the diagnosis of malignant tumors of the kidneys, the liver and pancreas, MRI will have only a very limited value. Probably in future the possibilities for the diagnosis of thorax and abdomen will be considerably increased used Fast Scanning which provides a screening of a series of slices in some seconds, especially if it will be combined with the use of gadolinium contrast media.

Another important use for MRI diagnosis is the estimation of tumors in bone and in soft tissues.
### P-23: BRAIN TUMOURS IN CHILDHOOD

#### Localisation of childhood brain tumours treated in Peds. Dept. of Nat. Inst. for Neurosurg., Budapest, Hungary

<table>
<thead>
<tr>
<th>Type of Tumour</th>
<th>Supratentorial</th>
<th>Infratentorial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemispherical tu.</td>
<td>27%</td>
<td>13%</td>
</tr>
<tr>
<td>Midline tu.</td>
<td>10%</td>
<td>57%</td>
</tr>
<tr>
<td>Cerebellar tu.</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Brain stem tu.</td>
<td>13%</td>
<td>57%</td>
</tr>
</tbody>
</table>

#### Localisation of ped. brain tumours in different age groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>0-1 year</th>
<th>2-3 years</th>
<th>4-10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supratentorial</td>
<td>71%</td>
<td>35%</td>
<td>43%</td>
</tr>
<tr>
<td>Infratentorial</td>
<td>29%</td>
<td>62%</td>
<td>57%</td>
</tr>
</tbody>
</table>

### 1975-1984: 2224 malignancy in infancy and childhood in Hungary

<table>
<thead>
<tr>
<th>Type of Tumour</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukaemia</td>
<td>737</td>
</tr>
<tr>
<td>Brain tu.</td>
<td>466</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>277</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>207</td>
</tr>
<tr>
<td>Wilms tu.</td>
<td>144</td>
</tr>
<tr>
<td>Osteosarcoma tu.</td>
<td>127</td>
</tr>
<tr>
<td>Soft tissue sc.</td>
<td>107</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>33</td>
</tr>
<tr>
<td>Others</td>
<td>126</td>
</tr>
</tbody>
</table>
SURGICAL EXPERIENCES IN FOSSA POSTERIOR TUMORS IN INFANCY AND CHILDHOOD
S. CZIRJÁK: National Institute for Neurosurgery, Budapest MUNICIPALITY.

1060 patients were treated for brain tumors in the Pediatric Department of the National Institute for Neurosurgery between 1954-1984. 606 cases, 57% of all intracranial tumors in childhood occurred in the posterior fossa. 407 cases, 44% of all tumors (78% of posterior fossa tumors) localized in the cerebellar hemispheres, 136 cases 13% of all (28% of posterior fossa tumors) located in the brainstem. Tumors of the cerebellum and brainstem. The symptoms and signs of tumors are primarily due to increased intracranial pressure and secondarily to local compression of the cerebellar nuclei and brainstem. Previously the diagnosis of cerebellar tumors was established by invasive neuroradiological procedures (pneumography, ventriculography) until advent of CT scan, which was mostly the only diagnostic procedure in cerebellar tumors in the last years. Our operative technique consists of midline suboccipital craniectomy and C1 laminectomy in setting position of the patient. Tumors were removed as complete as possible by intratumoral manipulation, practically in every case with remobilization, especially in patients with high grade tumors. Tumors T3 and T4 (47% receiving chemotherapy alive at five years compared with 25% of controls)(p = .003) in contrast to T1 and T2 cases in the chemotherapy was of no benefit. Post-operative radiotherapy is essential for maximum survival in cases of ependymoma. The risk of spinal seeding, especially in patients with high grade postoperative radiotherapy was for craniospinal irradiation. In 46 children at this Hospital, 54% survived five years, and 43% ten years. Adjuvant chemotherapy prolonged life but does not increase cure rates. In SIOP trial, 61% of 43 children with high grade ependymoma survived five years. Twenty two receiving adjuvant chemotherapy had a good overall survival than 21 controls for the first four years (70% compared with 55%) after which results were identical.

POSTERIOR FOSSA LESIONS CALLS FOR WHOLE NEUROAXIS TREATMENT OF MEDULLOBLASTOMA AND EPENDYMOMA

The survival of 47 children at this Hospital receiving adjuvant chemotherapy (chiefly CCNU and vincristine) was greater than that of an historical group of 87 patients treated without chemotherapy: at five years, 63% of the chemotherapy group were alive compared with 28% of controls (p < 0.005). In the SIOP multicentre trial 141 children were randomised to adjuvant chemotherapy and 145 to no chemotherapy. Chemotherapy: weekly vincristine (1 mg/m²) during radiotherapy followed by eight courses of maintenance oral CCNU (100 mg/m² on day 1 and intravenous vincristine (1.5 mg/m² on day 1, 8 and 15), cycled every six weeks. The overall five year survival rate was 52%. At five years 54% of the chemotherapy group were alive and disease-free, compared to 43% of controls (p = .03). More striking results in favour of chemotherapy were obtained in certain high risk sub-groups - children under two years and 2-9 years as opposed to children 10-15 years, in boys but not in girls, in those having incomplete tumour excision as opposed to macroscopic total removal, in those with brainstem involvement (p = .002) and not in those with stem tumors and in patients with late stage tumors T3 and T4 (47% receiving chemotherapy alive at five years compared with 25% of controls)(p = .003) in contrast to T1 and T2 cases in the chemotherapy was of no benefit. Post-operative radiotherapy is essential for maximum survival in cases of ependymoma. The risk of spinal seeding, especially in patients with high grade posterior fossa lesions calls for craniospinal radiotherapy. In 46 children at this Hospital, 54% survived five years, and 43% ten years. Adjuvant chemotherapy prolonged life but does not increase cure rates. In SIOP trial, 61% of 43 children with high grade ependymoma survived five years. Twenty two receiving adjuvant chemotherapy had a good overall survival than 21 controls for the first four years (70% compared with 55%) after which results were identical.

"SANDWICH" CHEMOTHERAPY OF BRAIN TUMOURS AS EXEMPLIFIED BY THE COOPERATIVE MEDULLOBLASTOMA TRIAL MED 94 OF THE INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY SIOP AND THE (WEST) GERMAN SOCIETY OF PAEDIATRIC ONCOLOGY GPO
Malte K. NEIDHARDT on behalf of the trial committee

T. KINDERKIRCH DES KRANKENHAUS-ZWECKVEREINBANDS, AUGSBURG, FEDERAL REPUBLIC OF GERMANY GRANT NO. BMT 01 ZP 034

By "sandwich" chemotherapy we mean the interposition of an intensive course of multiple-drug chemotherapy between surgery and irradiation. This form of therapy offers a number of theoretical advantages. It has best been tested in medulloblastomas. A previous study of GPO has shown that the "sandwich" principle can be administered without major toxicity, and a previous study of SIOP has demonstrated that a delay by a few weeks of the onset of postoperative radiotherapy does not jeopardize overall treatment results in this highly malignant brain tumour. The drugs employed are procarbazine (100 mg/m² for two weeks as soon as the vital functions of the patient are re-established), vincristine (1.5 mg/m² at weekly intervals, 6 injections), and methotrexate (20 mg/m² followed by leukovorin rescue, 3 injections). The entire treatment should not take longer than 6-7 weeks. Then, craniospinal irradiation by conventional techniques is administered. We report on a joint study of both societies aimed at testing the "sandwich" principle in a prospective, randomized fashion. Half of the patients receive the chemotherapy as outlined above, the other half receive immediate postoperative radiotherapy. Moreover, all patients in the "high risk" category (i.e., with incomplete tumour resection and/or proof of metastases at diagnosis) receive maintenance chemotherapy with vincristine (1.5 mg/m² once weekly for two weeks followed by a four-weeks' rest) and CENP (100 mg/m² on the same day as the first vincristine injection). In a second part of the trial, about one half of the participating centers will randomize "low risk" patients (i.e., with complete tumour resection and absence of metastases at diagnosis) into a group receiving reduced doses of radiotherapy (25 Gy instead of the usual 35 Gy) to the brain and spine and another one receiving conventional doses. The area of the primary tumour (posterior fossa) will continue to receive the maximum tolerated dose (50-55 Gy) in both arms.

OPTIC GLOMMA
A. Horwich, London, UK
DIAGNOSTIC PROCEDURES IN BRAIN TUMOURS IN CHILDHOOD
Luciano Basauri, M.D., F.A.C.S.
School of Medicine, University of Chile and Clinica Las Condes, Santiago, Chile

After brief introductory historical remarks on the evolution of ancillary diagnostic methods in Neurosurgery since the introduction of Air ventriculography by W.Dandy, the actual timing and specific use of modern armamentarium in the diagnosis of Brain Tumours will be assaillized. The place and impact of CT Scanner and Metrizamide both in the diagnosis of Intracranial and spinal canal diseases will be stressed. References concerning the revolution produced by M.R.I. in the management of Sagittal, posterior fossa and Brain stem tumours and cranio-cervical pathology (Arnold Chiari. Siringomyelia) and Cystic intramedullary lesions associated or not to gliomas will been illustrated. The actual role of selective and sonoselective angiography, both as a diagnostic and therapeutic tool, (Interventional Neuroradiology), and the importance of C.S.F. dynamic studies in some special pathologies (Hydrocephalus, Dandy-Walker) will be updated.

THE ROLE OF THE VOLUNTEER IN PATIENT REHABILITATION.
Francine Timothy, American Cancer Society, Paris, France
No one can claim to truly understand all of the facets of a new patient's emotional makeup, and it would be insulting to the patient to presume to do so. However, there is the possibility of a particular understanding between two people who have lived the same experience. This understanding is assumed to be present and, therefore, no detailed description of the feelings involved is required. The volunteer is there to be an involved listener for some, and to respect the silence of others. The important thing is to be there. Only the patient can decide how best the volunteer can be used.
Cancer rehabilitation begins with diagnosis and is the prescription for recovery, designed to restore the patient to a life of good quality and longevity. Voluntary cancer organisations can make a valuable contribution provided they have adequate facilities for this specialised work. The Marie Curie Memorial Foundation is a voluntary organisation in the United Kingdom which is now establishing rehabilitation and continuing care units in special centres. The plans, professional establishment, work programme and other aspects of a typical Centre are described. The increasing international interest in this concept and work is warmly welcomed, with the realisation that its practical implications are bringing new hope to cancer patients and their families and the prospect of a life of good quality.

ABSTRACT

For many years the standard outcome measures for cancer treatment and research have been survival, disease free survival, tumor response and drug toxicity. Based on these parameters, a clinical trial mechanism has evolved which has led to substantial improvements in cancer therapy. It is clear, however, that these particular outcome measures only partially reflect the total impact of disease and its treatment on patients. If the goal of medical treatment for established illness is to return the patient to a level of life function at least equivalent to that enjoyed prior to the onset of disease, then reliable and valid scientific measures of quality of life must be evolved.

There is a consensus of evidence suggesting that functional quality of life is a composite of four principle factors: physical function, psychologic function, social interaction, and somatic sensation. Methodologies have been established which enable these parameters to be measured reliably and validly for both cross-sectional and longitudinal study purposes. A brief overview of the history of these instruments and of their recent application in prospective clinical trials will demonstrate the strengths and limitations of such an approach.
4167 RESERVED

4166 STUDY OF POSTMASTECTOMY PROBLEMS IN EGYPTIAN FEMALES, N. EL-Kateb, National Cancer Institute, Cairo University.

In Egypt breast cancer accounts for 34.8% of female cancers while it accounts for 14% of all types. Mastectomy, whether radical or modified radical is still the most prevalent line of treatment for Egyptian patients. The aim of this study is to explore the early and late postmastectomy physical, psychological, socioeconomic and sexual problems that face Egyptians. Early postoperatively the main physical problems were wound infection in 6% & lymphedema in 4% of patients, while after 6 months to many years 52% of patients developed recurrence, and/or metastases, 14% had limited shoulder movement & 62% had lymphedema. Early postoperatively 70% had changes in appetite, 74% sleep disturbances, 48% spontaneous crying & 78% refused to talk to anybody, while for the late cases, 36% developed insomnia & appetite changes, 56% had changes in self & body image & 30% changed the pattern of their dresses but 62% were more accepting the situation. 60% had changed their sexual relations & 38% had real sexual problems. Socioeconomically 36% reduced their house activity & 42% stopped working & 28% had reduction in the family income.

4168 QUALITY OF LIFE IN POST-MASTECTOMY PATIENTS RECEIVING CYTOTOXIC AGENTS, B. Gunnars, Department of Oncology, University Hospital, S-221 85 Lund, Sweden.

This study examined the social support of a group of children with cancer and their families (N=27) as part of a larger investigation on concerns with the disease, coping behaviors and the subjective feelings of adaptation in an Hispanic population. The focus of the study was on the type of support received and the accessibility and availability of resources for support through their social network. Content analysis was used to develop categories of support and relationships between variables were also examined. For the children, spiritual aid and the opportunity to openly express emotional feelings to others was the major source of support. This type of support was made available to the child through a close kin network, especially the siblings. Peers and friends were found to be less supportive and understanding of the child’s illness. Opportunity for reciprocity was identified as an influential factor to utilize the network for support among the parents. Parents with a close network received support in the form of prayer whereas those with a wide scale network received support in the form of tangible goods. Support was available to the children and the parents without an exceptional effort on their part and it was perceived as a facilitating factor in the adaptation process for the majority of the families. Some families expressed that extended kindship was not as supportive, especially in the area of emotional expression and hope.

4169 SOCIAL SUPPORT OF CHILDREN WITH CANCER: TRANSCULTURAL ISSUES, F. Martinez-Jard, University of Texas at Austin, School of Nursing, Austin, Texas, USA.

The aim of the study was to describe the side effects of different chemotherapy regimens; in terms of how they affected the patients’ in their everyday life at home. Two different groups of mammary carcinoma patients were studied: 12 patients treated with Mitoxantrone and 11 patients treated with OCA (Oncovin or Vincristine+Cyclophosphamide+Adriamycin). All patients had a recurrence or generalized disease, and the treatment was given as first line chemotherapy in all cases. During a 6 month period patients were asked to fill out a questionnaire and were interviewed twice; once at the start of the cycle of treatment and one week later. The questionnaire contained 62 different questions concerning somatic symptoms, mood, sexual life, work, family and injury and the patients’ own assessment of quality of life. For each symptom, the median value was compared between the two treatments. For certain psychological symptoms, an index of depression was formed. Hair loss was the symptom with the highest score. The fear of losing hair was considered as one of the main problems of the Mitoxantrone group while the OCA group has a diminished fear over time probably due to adjustment to the situation. Among somatic symptoms nausea and loss of appetite were found to decrease after the first cycle but to increase again during the third cycle. These symptoms did not correlate to the dosage of chemotherapy during these cycles. The BPI depression index showed a slight difference between the two groups, the OCA group showed more pronounced negative changes. These trends were neither related to Karnofsky index nor to dose of chemotherapeutic agent.
IDENTIFYING CANCER PATIENTS AT HIGH RISK FOR EXPERIENCING PSYCHOSOCIAL DISTRESS. Margaret L. Pitch, M.Sc.N., Ph.D., Toronto General Hospital, Toronto, Canada.

The purpose of this study was to develop a self-report questionnaire to measure factors thought to be predictive of psychosocial distress in newly diagnosed cancer patients. If those at high risk for experiencing psychosocial distress could be identified at diagnosis, intervention could be offered earlier than is now possible. Items were developed to measure social support and past coping as appropriate instruments did not exist. Social support items were written to assess both qualitative and quantitative aspects of the domain. Past coping items elicited the individual's perception of his success in adjusting to previous life crises. Previously developed instruments were selected to measure recent life-events (Sarason's Life Experiences Survey), locus of control (Levenson's Locus of Control) and emotional distress (SCL-90-R).

Internal consistency and test-retest reliability were evaluated in two independent groups of newly diagnosed cancer patients (N=66; N=77). Social support items were internally consistent and stable. Internal consistency for the past coping items was not sufficient for scale development. The Sarason Survey scores were not stable. The Levenson Instrument had acceptable reliability but a poor completion rate. The SCL-90-R was internally consistent and stable. A new scale (illness-dependent expectations) emerged from the past coping items. To determine the feasibility of evaluating the questionnaire's predictive ability in a longitudinal assessment, outcome measures were applied at six months in one group and at one year in the other group. Approximately half of the subjects in each group completed the outcome assessment (54.6% in Group I; 57.2% in Group II). The results raised questions concerning the time interval following diagnosis for outcome assessment, the characteristics of subjects who did not complete the outcome assessment and the need for valid, reliable outcome measures.

CELLULAR AND GENETIC FACTORS IN THE ANTITUMOR ACTION OF LENTINAN


Lentinan, an immunopotentiating polysaccharide, showed a marked antitumor activity on the A/Ph. MC.S1 fibrosarcomas in A/Ph and (A/Ph x B10) F1 hybrid mice. However, lentinan did not modify directly the growth of these tumors in vitro or in nude mice in vivo. Effect of lentinan on the reaginic antibody response was estimated by anaphylactic shock reaction of A/Ph and B10 mice and their F1 hybrids having been sensitized and thereafter challenged by ovalbumin. Tumor-bearing mice showed a decreased anaphylactic lethality compared to the controls. Lentinan treatment decreased the lethality of anaphylactic shock to zero in both tumor-bearing and control animals.

Lentinan was able to increase both the IgM and IgG humoral immune responses measured on the 7th and 14th day after sensitization with oxazolone. OTH reaction in this system was only moderately enhanced by this polysaccharide.

Lentinan increased superoxide and hydrogen peroxide production and SOD activity while the lipid peroxidation was decreased in C4M0 murine macrophage cell line in vitro. In vivo lentinan treatment of different inbred strains of mice enhanced SOD activity but diminished lipid peroxidation in the liver with remarkable strain differences.

It seems very likely that lentinan, or the other polysaccharidic immunostimulant, is a potent modulator of different immune responses, acting on different cell types all the time being influenced by multiple genetic factors.
**4174 CLINICAL EVALUATION OF LENTINAN FOR STOMACH CANCER**


The anti-tumor effects of LNT have been confirmed in patients with advanced or recurrent stomach cancer in combination with FT.

LNT has been administered orally at a dose of 600mg/day consecutively. Those patients showed longer survival rate than controls. No severe side effects were observed. Intravenous drip infusion of immunoglobulin (Polyglobin) enhanced effects of Lentinan administration. All LNKS patients studied were universally free of complications in 13 LNKS patients, occurring mainly in LNKS patients older than 40 years of age which is equivalent to cancer age.

**4175 THERAPEUTIC EFFECTS OF LENTINAN ON LOW NK SYMPTOME (LNKS).**


LNKS patients responded well to the administration of an immunopotentiating agent, Lentinan (a glucan extracted from Japanese mushroom Lentinus edodes), despite nonresponsiveness to conventional treatments for fever with antipyretics or antibiotics. Intravenous drip infusion of immunoglobulin (Polyglobin) enhanced effects of Lentinan administration.

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LENINAN STIMULATES ENDOCYTIC ACTIVITY OF MURINE
MACROPHAGES VIA SPECIFIC β-GLUCAN RECEPTORS
G. Abel, J. Szollosi*, G. Chihara** and J. Fachet
Institutes of Pathophysiology and Biophysics*,
Cancer Ctr. Inst.*, Tokyo, Japan

In vitro experiments were designed to investigate the influence of lentinan, a fully puri-

fied α-1,3-glucan with α-1,6 branches on several macrophage functions, which may contribute to
the antitumor effect of this agent.

Lentinan was found to stimulate dose depend-
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o-xide (HRP) and FITC-dextran markers by peri-

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but pinocytosis of FITC-dextran was not affect-

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Lentinan increased the phagocytosis of both non-coated, C3b or IgG coated fluorescent mi-

crophases in peritoneal macrophages, as it was analyzed by flow cytometric methods, while man-
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ingestion of the beads. However, lentinan moder-
nately increased C3b receptor mediated phago-
cytosis also in the presence of mannan.

These data therefore suggest that a specific

β-glucan receptor, different from the man-
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macrophage. Interaction of lentinan with the

β-glucan receptor can serve as a triggering factor in the stimulation of endocytotic activity

of macrophages.

NEW SERUM FACTORS INDUCED BY LENINAN: AN ACUTE
PHASE PROTEINS-INDUCING FACTOR AND A T-CELL
MEDIATED VASCULAR DILATATION AND HEMORRHAGE-
INDUCING FACTOR. J.Y. Maeda*, T. Suga**, H. Ashio-
* Kyushu University, Fukuoka, Japan; ** Hokkaido
University, Sapporo, Japan.

Further studies were not lentinan itself. They seem to be differ-
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Further studies on APP-increase and VDH are
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Further studies on APP-increase and VDH are
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mechanism participated by immunity and inflammation.
By means of the complex method for investigation of the stomach diseases /X-ray, endoscopy, biopsy and cytology/ we found early gastric cancer in 94 patients as single or multiple tumors. All of the patients was in curable stage according to the Japanese endoscopic classification as well as to the modified pTNM scheme. In the period of 1966-1983 we had 466 resected stomach cancers, so this collection of early carcinomas mounts up to 20,3% of total resected stomach cancers. The early gastric carcinoma occurred together with an advanced cancer in additional 11 patients. So, we found 120 early tumors in 105 patients.

The distribution of our EGC cases in the Japanese classification is as follows:

Type I: *protruded* 22 tumors
Type II.a: *elevated* 13 tumors
Type II.b: *flat* 13 tumors
Type II.c: *depressed* 27 tumors
Type III: *excavated* 2 tumors

Combined forms:

Type II.c: III. 12 tumors
Type III, II.c. 18 tumors
Others 12 tumors

Compared to other authors' material, the number of Type II.b as well as of the combined types is relatively high.

The EGC developed very frequently in connection with chronic peptic ulcer /48,9%/. It is a high frequency, but this percentage falls short of Sano's data /70,3%/. The EGC was limited only to the gastric mucosa in 56,7 /68/ tumors and invaded into the submucosa in 43,3 /52/ carcinomas./

The most difficult problem in connection with EGC is to distinguish these tumors and the severe dysplasia of gastric mucosa.

**DOUBLE ELECTRON MICROSCOPIC APPROACH TO PRECLINICAL DETECTION OF IMMATURE HORMONE PRODUCING CELLS**


It has been well known that most peptide hormones are produced as precursor form and secreted after intracellular processing. By immunoelectron microscopy pre-embedding method which enables the localization of various bioactive substances in any subcellular organelle, in human small cell carcinoma (SCLC) of the lung, ACTH was localized predominantly in rough endoplasmic reticulum (RER) or secretory granules(SG) were sparse. In the human pituitary gland of early fetal life (9 weeks of gestation), ACTH was similarly localized in RER with predominant localization of PRL in RER and the secretion of ACTH in many SG. RER localization was scarce. This may indicate that the states of the intracellular localization of hormones are intimately related to the cellular development and functional differentiation or maturation of cells. In proclin (PRL) cells in rat, estrogen induced proliferation was correlated with the predominant localization of PRL in RER and the secretion of larger form of PRL. Storage of PRL in SG was induced by bromocriptine (BDr dopamine agonist) which also caused cessation of proliferation. From the view of ultrastructural localization, it could be postulated that the former estrogen stimulated PRL cells are immature and the latter BDr treated cells are mature cells. Similar findings were obtained by the human pituitary prolife bladder. These findings may indicate that (1)secretion of larger form of immaturity processed peptide hormone is indicative of the nature of immature cells (including "proclinical cancers"), (2)Maturely processed hormone is related to benign or treatment-responsive tumors, and (3)Ultrastructural localization of hormones by electron microscopy is mandatory in the determination of the biologic nature of the individual hormone producing tumors. (Supported in part by Grant-in-Aid for Cancer Research from the Ministry of Health and Welfare Japan.)

The effect of many immunotherapies has been experimentally tested on tumors transplanted in syngeneic animals. The therapeutic effects on the transplanted tumors, however, may well differ from those on clinical tumors which develop in autochthonous hosts. We attempted, therefore, to treat an MCA-induced tumor in autochthonous mice with an immunostimulatory protein-bound polysaccharide (PS-K, Kureha Chem. Co., Tokyo) in conjunction with the surgical removal of the primary tumor.

MCA (1 mg in 0.1 ml of olive oil) was injected into the right hindlimb of female C57BL/6 mice. Autochthonous tumors which had developed 8 to 16 weeks after the MCA-injection were treated individually when the tumor reached 8 mm in diameter. The therapeutic effects of PS-K (300 mg/kg/day ip for 5 days or 2 days/week for 7 weeks) were evaluated by observation of the mean survival time (MST) after the treatment and the frequency of local recurrence and pulmonary metastasis of tumor at the time of death.

The MST of untreated mice was 20-25 days. As a result of the treatment, PS-K by itself had no success in inhibiting the tumors. MST was significantly prolonged (49 days) by the surgical removal of the primary tumor, although 64 out of 66 mice died of local recurrence of tumors (54.6%). Pulmonary metastases. The MSTs of mice treated with PS-K before or after surgery was significantly prolonged (60-64 days) as compared with that of mice treated with the surgery alone. Moreover, the frequency of local recurrences (34-36%) was reduced by the combination of PS-K after surgery.

These results indicate that PS-K is effective in inhibiting pulmonary metastatic and locally recurrent tumor cells after surgery of the primary tumor in autochthonous hosts. We also consider the feasibility of using autochthonous tumors in the evaluation of newly developed treatments of cancer.

A-36: EXPERIMENTAL AND HUMAN LUNG CARCINOGENESIS

CELL TYPE-SPECIFIC NITROSAMINE CARCINOGENESIS MEDIATED BY HUMAN AND ANIMAL LUNG CELLS.

Hildegard M. Schuller, Laboratory of Experimental Oncology Department of Pathobiology, College of Veterinary Medicine University of Tennessee, Knoxville, TN, USA.

N-nitrosamines and their precursors are ubiquitous in man's environment and require metabolic activation in the host organism to become carcinogenic. Many of them induce pulmonary adenocarcinomas in rodents. This tumor type has been rapidly increasing in incidence in man and is currently the most common type of lung cancer in man. Studies using diethylnitrosamine (DEN) in hamsters demonstrate that pulmonary Clara cells and endocrine cells are specific targets of the compound in vivo. Comparative experiments with enzyme inhibitors show that such metabolic activation is dependent on cytochrome P-450 enzymes. Comparative experiments with well differentiated early passage cell lines derived from different types of human lung cancers reveal active metabolites of DEN by cell lines with Clara cell and endocrine cell morphology. As in the hamster model, such metabolism is inhibited by cytochrome P-450 inhibitors in the target cells while in non-target cell types (e.g. alveolar type II cells) it is dependent on prostaglandin H synthetase. These data strongly support the relevance of the human model for human carcinogenesis and provide a valuable basis for further studies into the mechanisms of cell type-specific nitrosamine carcinogenesis.

GLASS FIBRES: A LUNG CANCER RISK? V.J. Perton and B.J. Spil, TNO-CIVO Toxicology and Nutrition Institute, Zeist, the Netherlands

Inhalation of asbestos may lead to mesotheliomas and may enhance the induction of pulmonary carcinomas. It is almost generally assumed that such tumours do not occur after inhalation of glass fibres. However, a recent epidemiological study suggests an increased lung cancer risk associated with the man-made mineral fibres working environment of 30 or more years ago (Saracci et al., Br. J. Industr. Med., 41, 1984, 425). In addition, Pott et al. (Proc. VIIth Int. Pneumocoiosis Conf., 1983, Bochum) reported the occurrence of mesotheliomas and lung carcinomas in hamsters following intratracheal administration of glass fibres. In a similar long-term study with glass fibres in hamsters we were unable to find mesotheliomas or carcinomas. The discrepancies between the results obtained by Pott and co-workers and those of our study will be discussed. It seems desirable to verify Pott's findings in long-term studies with hamsters and rats, using both intratracheal instillation and inhalation and, perhaps most important, using relatively short treatment periods and long follow up periods.
CLINICAL IMPLICATIONS OF THE IN VITRO BIOLOGY OF HUMAN LUNG CANCER CELL LINES

Osmond N. Casey, Mater Hospital, Dublin, Ireland

The use of defined hormone-supplemented medium has greatly improved our ability to establish continuous cell lines of lung cancer to establish continuous cell lines of lung cancer in particular small cell lung cancer (SCLC). Detailed biological characterization of a large panel of SCLC cell lines has revealed considerable heterogeneity among cell lines. Three major classes exist: 1) Multiple-tolerant SCLC cell lines which exhibit features of tripartite differentiation into small cell adenocarcinoma and squamous cell carcinoma. These cell lines suggest a common stem for some forms of lung cancer. 2) Classic SCLC cell lines account for 70% of cell lines, express elevated levels of L-dopa decarboxylase (DDC) and other neuroendocrine markers, have a relatively long doubling time, and low cloning efficiency (CFE), and are radio-sensitive in vitro. 3) Variant SCLC cell lines have low or absent DDC, have a more aggressive growth behavior, are radio-resistant and, unlike classic lines are amplified for the oncogene c-myc. Clinical correlates of these subtypes have been identified. Patients with the variant phenotype have a significantly worse response rate and shorter survival than patients with classic SCLC. Other oncogene abnormalities identified in SCLC cell lines and fresh patient specimens including amplification of multiple oncogenes have been observed. Patients whose cell lines are amplified for these oncogenes have a shorter survival than those not amplified. The finding of myc-related oncogene amplifications in 50% of SCLC lines suggests that this proto-oncogene may have an important role in the development and growth behavior of SCLC. These data also suggest that the biological characterization of SCLC cell lines should be considered as part of the clinical staging of SCLC.

MECHANISMS OF ASBESTOS CARCINOGENESIS IN THE RESPIRATORY TRACT

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Epidemiologic studies show an increased risk of bronchogenic carcinoma in asbestos workers who smoke. Using cell and organ cultures of hamster and human tracheobronchial epithelium and hamster tracheal implants, we have elucidated several possible mechanisms of synergy between asbestos and polycyclic aromatic hydrocarbons (PAH), ubiquitous chemical carcinogens in cigarette smoke. Both crocidolite and chrysotile asbestos act as effective vehicles for adsorption of PAH and transfer of these chemicals to cells. For example, when identical amounts of the PAH, benzo-(a)-pyrene (BaP) are adsorbed to the surface of asbestos fibers in comparison, results show increased amounts of hydrocarbon are transferred to tracheal epithelial cells and retained for extended periods of time. The former circumstances, amounts of BaP associated with DNA are enhanced for at least 4 days. In addition, asbestos acts synergistically with BaP in hamster tracheal organ cultures to induce increased uptake of H-thymidine and squamous metaplasia, the conversion of normal mucus-producing epithelium to keratinizing lesions. When asbestos is added alone to human and hamster tracheal grafts, organ and cell cultures, a constellation of biologic changes occurs similar to effects caused by the classical tumor promoter, 12-d-tetradecanoyl-phorbol-13-acetate (TPA), in a number of cell types. These alterations include inflammatory changes, stimulation of cell division, induction of squamous metaplasia, the conversion of normal mucus-producing epithelium to keratinizing lesions. When asbestos is added alone to human and hamster tracheal grafts, organ and cell cultures, a constellation of biologic changes occurs similar to effects caused by the classical tumor promoter, 12-d-tetradecanoyl-phorbol-13-acetate (TPA), in a number of cell types. These alterations include inflammatory changes, stimulation of cell division, induction of squamous metaplasia, the conversion of normal mucus-producing epithelium to keratinizing lesions.

Monoclonal Antibodies in Immunodiagnosis and Immunotherapy of Human Lung Cancer

James A. Rodosevich, James L. Mulshine, A. Michael Zinner, Steven Z. Rosen

Monoclonal antibodies (MCA) prepared by somatic cell hybridization techniques are ideal tools for the discrimination of cellular antigens, and therefore have great potential for the immunodiagnosis and immunotherapy of bronchogenic carcinoma. At present, it is difficult to distinguish the various types of lung neoplasms by conventional light microscopic methods. This is especially true for the small cell lung cancers, which are the most common type of lung cancer. Immunofluorescence and immunoperoxidase staining of tissue have been used to identify tumors of the lung. These methods, however, are time-consuming and require skilled personnel. Immunocytochemical techniques, on the other hand, are rapid, simple, and can be performed by technicians. The use of MCA to study the carcinomas of the lung has several advantages. First, MCA can be produced against a wide variety of epitopes, and antibodies specific for each epitope can be obtained. Second, MCA can be used in a wide variety of cell systems, including frozen sections, paraffin-embedded tissue, and tissue culture. Third, MCA can be used to study the expression of antigens in the tumor microenvironment, and to study the interactions between tumor cells and the immune system. Finally, MCA can be used to study the heterogeneity of lung carcinomas, and to study the development of resistance to therapy.

MOLECULAR MARKERS IN SMALL CELL LUNG CANCER

In a series of 13 cultures of small cell carcinoma of the lung, we have evaluated for hormone gene and oncogene expression and correlations made with morphologic and clinical characteristics. All of the cell lines secreted calcitonin (CT) which can be detected in the medium by radioimmunoassay (RIA). Expression of CT was variable among cell lines. In DMS 53 it was largely expressed as CT mRNA and not as CT protein. This indicates that these two cell lines process the precursor of CT to its mature form. Expression of the CT/CRP gene, poly A+ RNA was isolated and evaluated by Northern blot analyses. The expression of the CT/CRP gene was variable among cell lines. In DMS 53 it was largely expressed as CT mRNA and in DMS 153 it was largely expressed as CT mRNA. This indicates that these two cell lines process the primary transcript of CT, CT mRNA, and not as CT protein. The opposite is also true. Other cell lines showed no signal on Northern blots after hybridization with probes specific for either of these mRNA forms. Levels of CT mRNA expression do not correlate with population doubling times. DMS 53 which secretes the largest amount of CT has an amplified Ki-raf oncogene. In general, cell lines which express CT mRNA also express CT mRNA and the opposite is also true. Other cell lines show no signal on Northern blots after hybridization with probes specific for either of these mRNA forms. Expression of the CT gene and/or increased expression of CT receptor may play a role in the regulation of CT synthesis and secretion. CT production by SCLC may be influenced by several factors including hormonal and environmental factors. Further studies are underway to examine the role of the CT/CRP gene in the regulation of CT synthesis and secretion in SCLC.
4192 METABOLIC ACTIVATION OF CARCINOGENS BY THE LUNG. Gerald M. Cohen, Toxicology Unit, The School of Pharmacy, University of London, 29/39 Brunswick Square, London WC1N 1AX UK.

The lung is the major portal of entry into the body, of all inhaled compounds, such as tobacco smoke. The very large surface area of the alveolus, about the size of a tennis court, besides being ideally suited for the function of gas exchange also facilitates the penetration into the body of potential carcinogens. In addition, the lung is exposed to potential carcinogens in the systemic circulation. A large number of chemicals, with a wide diversity of chemical structures will induce lung cancer in animals or man. These chemicals may be subdivided into two major classes, i.e. direct acting carcinogens and indirect carcinogens. Most of the chemicals fall into the latter category and require metabolic activation by one or more steps, to a more reactive form(s), invariably an electrophile, which then combines with critical cellular macromolecule(s) leading ultimately to tumour formation. Many factors, including age, sex, diet, hormonal status, inducing agents and inhibitors of microsomal mixed function oxidase enzymes, DNA repair, immune competence and tumour-promoting agents may profoundly influence the ultimate tumour response. In this brief review, I shall concentrate on metabolic activation by the respiratory tract of both rodents and humans, of chemical carcinogens to reactive metabolites and their interactions with DNA.

The lung is composed of over 40 different cell types and the balance of activating and deactivating enzymes and their respective cofactors in the different cell types will determine how much of a reactive metabolite(s) may be formed in a particular cell type. A key enzyme in the metabolic activation of many respiratory tract carcinogens is the microsomal mixed function oxidase, cytochrome P-450, with its known broad substrate specificity. The distribution of different isozymes of P-450 throughout the lung and the marked effects of various environmental agents on the activity of this enzyme system may profoundly influence the metabolism and carcinogenicity of chemicals in the lung.

ACKNOWLEDGEMENTS I should like to thank the Cancer Research Campaign of Great Britain for support for this work and for a travel grant.


59 pathologically confirmed / 37 epidermoid, 5 anaplastic, 17 adenocystic / lung cancer patients were treated with ifosfamide / 1500 mg/m2 day 1-5/. At the epidermoid and anaplastic type cases, the ifosfamide was combined with cisplatinum /200 mg/m2 day 1-5/, at the patients with adenocarcinoma we applied as a second drug 5-fluorouracil /500 mg/m2 day 1-5/.

After two courses we achieved 2 complete and 11 partial remissions: the remission rate was 22.4 %. The cases with 2 complete and 9 partial remissions belonged to epidermoid type lung cancer. The median survival time was 6.6 months for all patients. At the patients with radiological remission this time was 8.7 months. The most common side effect were alopecia and urocystitis.

4194 WHO-CLASSIFICATION OF MALIGNANT LUNG TUMOURS - AN OVERVIEW. R. Yesner, Yale University School of Medicine, New Haven, CT, U.S.A.

Cytological, immunochemical, and biological data have increased our understanding of pathogenesis by repeated demonstration of overlapping characteristics, but the WHO classification remains the gold standard for therapy. If the keratin cytokeratin characteristics are dominant (keratin, intercellular bridges), it is a squamous cell and behaves as such. If glandular characteristics are dominant (mucin, acini, tubules) it is an adenocarcinoma, which may be papillary. If the cell line alveolar walls but do not invade them, it is bronchioloalveolar. These may all be subdivided by special stains and electron microscopy. If the tumor cannot be identified as squamous cell or adenocarcinoma by light microscopy in the samples available, and the nuclei are vesicular, with prominent nucleoli, it is classed as a large cell carcinoma. If more than 80% of the cells are giant cells, it is a giant cell tumor. If the cytoplasm is clear, it is a clear cell carcinoma after renal cell carcinoma is excluded. If tumor cells have finely distributed chromatin without prominent nucleoli, and little or no host response, it is a classic small cell or oat cell carcinoma. There are two intermediate small cell subtypes. One has similar nuclei with larger more polygonal cells, which behaves clinically like the classic small cell. The other is an admixture of small cells and large cells, which does not do as well on therapy. Combined tumors have recognizable areas of more than one definitive cell type. Tumors distinguished by cromine activity may look like small or large cell carcinomas. The latter are argyrophilic and called atypical (malignant) carcinoids; if they appear benign and organoid, carcinoids. Metastasizing may usually be distinguished from adenocarcinoma by immunocytochemical stains.

4195 THE HISTOPATHOLOGY OF NON-SMALL CELL LUNG CANCER. O. Campobasso, Dept. of Neuroradiology, Ospedale Maria Vittoria, Turin, Italy.

On the ground of morphological criteria, non-small cell lung carcinoma can be classified under 4 main headings: squamous cell carcinoma, adenocarcinoma, large cell carcinoma, and adenosquamous carcinoma. These tumours originate from the proliferating cells of the surface epithelium of the lower respiratory tract which may undergo more than one type of differentiation or metaplasia, even in the same tumour. A histogenetic classification is, therefore, far from easy and difficult to reproduce. The different histological types are referable to the versatility of differentiation rather than to the proliferation of one specific cell type. However, each histological type, as defined on the ground of the light microscopic appearance, has its own biological characteristics which may serve as base both in therapy planning and in predicting the survival rate. Squamous cell carcinomaa often remain limited within the thoracic cavity; they may be subdivided by grading rather than by subtyping. Even the less differentiated ones do better than any other histological type. Adenocarcinoma tend to spread outside the thoracic cavity through the blood stream; they include 4 subtypes which possibly correspond to a different histogenesis. Adenosquamous carcinomas are solid tumours in which squamous cells are intermingled with mucous producing cells. The survival rate is similar to that of adenocarcinomas; this means that it is the mucous secreting component which bears heavily on the prognosis. Large cell carcinomas are a very pleomorphic group of tumours. Most are poorly poorly differentiated squamous cell oradenocarcinomas.
THE HISTOPATHOLOGY OF SMALL CELL LUNG CANCER AND THE CLINICAL IMPLICATIONS.

Fred R. Hirsch, M.D., Dept. of Oncology II, Finsen Institute, Copenhagen, Denmark.

From a clinical point of view it is important to separate small cell lung cancer from non-small cell types. The former type of lung cancer is highly responsive to chemotherapy, and the potential of long term survivors does exist. The World Health Organization published the last revision of the international lung tumor classification in 1981, and the small cell carcinoma (SCLC) was morphologically subdivided into three types: 1. oat-cell type, 2. intermediate subtypes, some variants of pure SCLC, but also mixtures of SCLC and large cell carcinoma, and 3. combined oat-cell, which consisted of SCLC combined with squamous cell- and/or adenocarcinoma. Later studies have focused on the prognostic implication of this subtyping, and several studies could not find any prognostic difference between the morphologic subtypes of pure SCLC. However, patients with mixed SCLC and large cell carcinoma had a poorer chemotherapeutic response and a significant shorter survival compared to the patients with pure SCLC. The International Association for the Study of Lung Cancer (IASLC) propose the following subclassification of SCLC:

1. Pure small cell carcinoma.
2. Small-cell/large cell carcinoma and
3. Combined small cell carcinoma including tumors showing mixtures of SCLC with squamous cell- and/or adenocarcinoma.

IMUNOHISTOCHEMISTRY OF MALIGNANT LUNG TUMORS

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Small cell lung cancer (SCLC) often produces amine polypeptide hormones, such as serotonin, ACTH, gastrin releasing peptide (GRP), calcitonin (CT), antidiuretic hormone, etc. and is characterized by enzymes such as L-dopa decarboxylase, neuron specific enolase (NSE) and creatine kinase Bb (CK-Bb). Such substances can be demonstrated in tumor cells by the immunohistochemical method and are not specific for SCLC but also detected in non-SCLC. However, immunoreactive cells are more frequent in SCLC. Besides, SCLC frequently produces multiple hormones, whereas non-SCLC produces a single hormone. For instance, CT was detected in SCLC which produces GRP but CT-producing adenocarcinomas were non-GRP producers. Pancreatic polypeptide is occasionally detected in carcinoid tumors but never in SCLC in our experience. Immunoreactive NSE and CK-Bb are also found in non-SCLC but less frequently than in SCLC. Immunohistochemical results on cytoskeletons are presented. Leu 7 (HNK 1) is said to be a good marker for SCLC, being positive in all SCLC and carcinoid tumors, but about one half of well differentiated adenocarcinomas, particularly of Clara cell type, were stained positively. On the contrary, OKT 9 (transferrin receptor) is positive in all squamous cell carcinomas but virtually negative in well differentiated adenocarcinomas and SCLC. Monoclonal antibodies produced in our laboratory with lung cancer as immunogen are useful for distinguishing SCLC from non-SCLC. Monoclonal antibody NCC-Lu-35 recognizing T antigen react only with non-SCLC; NCC-Lu-279 recognizing X-hapten and NCC-Lu-152 recognizing Y-hapten react with both SCLC and non-SCLC; and NCC-Lu-246 recognizing neuroendocrine membrane antigen reacts only with SCLC. The first three antibodies can be applied to routine paraffin sections but the last one only to frozen sections and freeze-dried or cold acetone fixed paraffin embedded sections. Immunohistochemistry can be applied to cell kinetics study by using antithymo deoxycytidine antibody, and for study of T and B subsets of lymphocytes, macrophages and T-zone histiocytes (Langerhans cells), some of which are closely associated with tumor cells and affect prognosis of patients.
4200 THE MYB ONCOGENE FAMILY. M.A. Baluda, W.J. Boyle, and J.S. Lippick. Pathology, UCLA School of Medicine and Jonsson Comprehensive Cancer Center, Los Angeles, California, USA.

The known oncogenic members of the myb family are the retinoviral oncogenes c-myb virus (Rous sarcoma virus and of avian v-erb-b virus). These two viral oncogenes have resulted from two independent transductions of DNA sequences from the single copy chicken c-myb proto-oncogene. Like other proto-oncogenes, c-myb has been highly conserved, especially in its 5' end, in species ranging from Drosophila to humans. Both viral oncogenes encode a common transduced internal c-myb domain and thus express severely truncated forms of c-myb. ANV causes acute myeloblastic leukemia in chickens and transmits fowl erythroblastosis in vitro. v-erb-b virus which contains a second oncogene, e, in addition to myb sequences, transforms myeloid and erythroid cells in chickens and in vitro. The v-myb and v-myb' E6 gene products are nuclear proteins with a short half-life of 30 min and are phosphorylated to a minor extent in vivo but do not act as tyrosyl protein kinases in vitro. In ANV-transformed chicken leukemic cells the v-myb product p39-myb is compartmentalized within nucleiolus (292), chromatin (72), and lamin-nuclear matrix (642) fractions. The ability of p39-myb to bind DNA in vitro, along with the tight interaction with the nuclear matrix in vivo suggest that it maybe involved in transcriptional and/or replicative events. Antisera raised against the protein domain encoded by the highly conserved 5' v-myb-ANV region detects the c-myb product of diverse species. To do this the conserved region was molecularly cloned and expressed in E. coli as a novel trpE-myb fusion protein which was purified and used to immunize rabbits. The resulting antibodies specifically detect the nuclear proteins from normal and transformed avian cells known to transcribe myb sequences. These antibodies have also identified the previously unknown products of the human, murine, and Drosophila c-myb genes, which are all proteins of 75,000 to 80,000 M, showing the same subnuclear compartmentalization as p39-myb. As found with chicken c-myb, the human c-myb product is present in immature erythroid, myeloid, and lymphoid cells.

4201 INTERACTION OF pp60^SF WITH THE MACROMACHINERY OF GROWTH CONTROL. Marshall F. Nuss, Laura K. Brown, and William L. Fahlke, Dept. Microbiology, Univ. of Virginia School of Medicine, Charlottesville, VA 22908, U.S.A.

Pp60^SF is an oncogene product which is not a growth factor or a growth factor receptor, but which nonetheless permits cells to grow in the absence of exogenous mitogens. We determined the normal requirement for mitogens, we have investigated its interaction with components of the normal growth control machinery. Because target cells for the AKR oncogene often respond to Epidermal Growth Factor (EGF), we examined the state of the EGF receptor in cells transformed by Rous sarcoma virus. We find that the EGF receptor is rapidly downmodulated when the AKR gene is expressed. The loss of the EGF receptor is not due to the secretion of Transforming Growth Factors. We further show that the EGF receptor may be a direct target for the kinase activity of pp60^SF, leading to activation and downmodulation of the receptor and chronic stimulation of growth. Because of the reports that pp60^SF stimulates the turnover of PI and the generation of diacylglycerol we determined whether the cell could transform cells resistant to the mitogenic effects of the tumor promoter TPA, which is an analog of diacylglycerol. We find that 3T3-5-HP cells, which contain normal levels of p53, kinase C but which are refractory to TPA, cannot be transformed by AKR although parental 3T3 cells are readily transformable by AKR. The results suggest that cells resistant to the mitogenic effects of the tumor promoter are also refractory to the oncogenic action of AKR.


E oncogenes stimulate the growth of rat mammary carcinoma in vivo and human breast cancer cells (MCF-7) in culture, suggesting that abnormal CAMP regulation is involved in the growth of mammary cancer (T.S. Cho-Chung, J. Cyclic Nucleotides Res., 4163, 1980). An enhanced expression of the cellular ras oncogene product, p21, has been found in mammary carcinomas of humans and rodents (N.E. Debostoli et al., Biochem. Biophys. Res. Commun., 127, 699, 1985) and, in yeast, ras proteins are controlling elements of adenylyl cyclase, the CAMP-synthesizing enzyme (T. Toda et al., Cell 50: 27, 1985). We now show that in mammary carcinomas the enhanced expression of p21 accompanies an augmentation of the CAMP system demonstrating a ras gene - CAMP relation similar to that shown in yeast. Determination of p21 by Western blotting and CAMP receptor proteins (high affinity binding proteins) by precipitation in a yeast showed that the ras gene product can be recovered from the mammary tumours of both patients and cancer receptors contain a CAMP level and basal and CAMP-stimulated adenylyl cyclase activity. 5 to 10 fold those of normal mammary glands. The increase of CAMP level and adenylyl cyclase activity was also found in the hormone dependent rat mammary tumours containing a high level of p21. These results suggest that oncogenic activity of c-ras oncogene which leads to the abnormal CAMP regulation may have etiological significance in breast cancer.


Oncogenes N-ras, c-Ha-ras and fos are expressed in 50% of various tumor tissues with visible specificity, In 30% metastases of different tumors in lymph nodes oncogenes sis and myb are expressed while in primary Tumours this is silent and myb is expressed in 7% of them. In some histological normal tissues, neighbouring to the tumour ones, the same oncogenes as in tumour are expressed. DNA from melanoma, body uterus cancer and it metastases induced morphological transformation of NIH 3T3 cells which showed to be tumorigenic for nude mice. Human c-Ha-ras oncogene was identified in ma Bagnost glioma tumour line U251 MG from dr. J.Ponter, Uppsala Sweden after transfection of cell DNA in NIH 3T3 cells with further implantation and tumour formation in nude mice. After contra transfaction of DNA from such tumour and LTR from Rous sarcoma virus these cells induced tumours in which amplification of c-Ha-ras in different localizations and CAMP stimulation and amplification and transcription of LTR and plasmid sequences are observed. If in the same system the DNA from normal mouse cells was used instead of tumour one the contranfection with Rous virus LTR and further injection of such NIH 3T3 cells resulted in tumour formation in which oncogene fos is expressed.
STRUCTURAL ORGANIZATION OF THE HUMAN p53 GENE. H.H.Hlnkins, V.L.Buchman, O.F.Samarina, and P.M.Caumakov, Institute of Molecular Biology, USSR Acad. Sci., Moscow, USSR

The level and turnover of the transformation-related protein p53 are frequently elevated in mammalian and human tumors implying the involvement of this protein in carcinogenesis. We have isolated several human genomic clones using mouse p53 cDNA clone /1/ as a probe. The clones cover the region of 27 kb and contain the whole human p53 gene including a functional promoter region. Precise restriction endonuclease mapping revealed two sets of genomic clones having different EcoRI endonuclease cleavage sites corresponding to the different allelic variants of the p53 gene. The position of exons within the human p53 gene was determined using S1 nuclease mapping. The first noncoding exon region was used as a probe to study the structure of the region coding the 5'-end of the mRNA in a number of human malignances.


STRUCTURE of RAS-ONCOGENE IN GOLDFISH DNA. Nobuo Nemoto, Ken'ichi Kodama, Ayumi Tanawa and Taketoshi Ishitaka, Department of Experimental Pathology, Cancer Institute, Tokyo Japan.

Oncogenes are thought to be involved in a critical step(s) occurring during differentiation in yeast or Dictyostelium as well as to play a role(s) during carcinogenesis in rodents and human beings. However, we have little information regarding oncogenes in fish species, which offer adequate models of neoplastic development. This paper deals with structural analysis of a ras-related gene in goldfish normal liver DNA. Ras-related gene sequences were cloned from goldfish genomic DNA library constructed with a lambda phage. Restriction enzyme mapping of the obtained clones suggested that goldfish had at least three kinds of ras-related DNA sequence in ca. 370,000 clones. Base sequencing of the obtained clones demonstrated extensive homology of the amino acid sequences between goldfish and mammalian genes. In particular the homology with human cellular Kirsten ras gene was more than 90%. Splicing points between 4 exons and intervening sequences were the same as those of rodents and human beings. Conservation of the ras sequence in a wide range of the biological world is indicative of the importance of this gene family for cell homeostasis.

NEW MEMBERS OF ras GENE FAMILY. L.L.Kisselev, L.M.Chumskov, P.B.Berdichevsky and Yu.Shvets, Inst. of Molecular Biology of the USSR Acad. of Sciences, Moscow 117984, USSR

The structure of the mos proto-oncogene differs considerably from the other proto-oncogenes: the mos gene has no intron and very low level of expression. To study the other possible mos-related proto-oncogenes we have employed two different approaches. mos-related regions were selected from human and rat genomic libraries by the low stringency hybridization to the viral mos probe. Some of these clones contain mos-related pseudogenes /1,2/. One mos-positive clone, K51 from rat genome comprises actively transcribed gene. The number and the size of these transcripts are tissue specific. We have cloned some of these transcripts from human embryonic cDNA library. We have used subcloned probes from K51 and v-mos to demonstrate the ubiquitous presence of mos-related sequence in different vertebrate genomes. Recent duplication of the mos gene was discovered in DNA from undulates. The other approach to study the mos-related genes was the use of chemically synthesized oligonucleotide, specific to conserved region of the mos gene, as a probe. With this technique we have demonstrated the presence of mos-related sequences in the genomic DNAs from yeast Saccharomyces cerevisiae and plant Allium cepa.


RESERVED D.Dudits, Szeged, Hungary
**4208**

**CELL TRANSFORMATION IN VITRO BY NEUTONS OF DIFFERENT ENERGIES: IMPLICATIONS FOR MECHANISMS**

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Studies have been performed to analyze the dependence of the induction of cell transformation and cell reproductive death in cultures of C3H/10T1/2 cells, MBH-3 cells and WGH-2 cells on the energy of mono-energetic fast neutrons. The dose-effect relations for 300 kV X rays, 15 MeV, 4.2 MeV and 0.5 MeV neutrons have been analyzed on the basis of the representations F(α, t) and S(0)/S(t) = exp(-α, t) for transformation and survival, respectively. The results show that α, values for all radiations are a factor of approximately 100 larger than corresponding t, values. The RBE values for cell reproductive death derived as ratio's of α, values for the various neutrons and 300 kV X rays are similar to the corresponding RBE values for cell transformation derived as ratio's of t, values of neutrons and X rays.

These similarities in the RBE values and differences in absolute values of α, and t, can be compared with results from published dose-effect relations for reproductive death and chromosome aberrations obtained for other cell lines. The insights obtained can be applied to derive a hypothesis about the induction of these effects, assuming similarities in energy requirements and physicochemical primary mechanisms which lessens the dependence of damage in chromosomes and differences in the specificities of the sites and total size of the targets on chromosomes associated with the various endpoints observed.

**4210**

**THE RADIOBIOLOGICAL EFFECTS OF VERY HEAVY CHARGED PARTICLES AND THEIR INTERPRETATION**

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Because of the excellent dose distribution and the high-LET action at the end of the particle range, accelerated heavy ions are the most favorable beams in radiotherapy. Therefore, a detailed knowledge of the biological action of heavy ions is of great medical interest. In a set of experiments, the biological action of accelerated heavy particles ranging from helium to uranium over an extended energy and LET range has been studied for different biological endpoints such as inactivation (Wolf, 1985), the induction of chromosome aberration (Müller, 1985); and strand breaks (Aufderheide, 1985). This discussion will present a typical pattern if the effectiveness per particle (cross sections) or the relative biological efficiency (compared to X rays) is given as a function of the linear energy transfer (LET) of the particles. For the lower LET values (<100 keV/μm), the biological effect depends only on LET independent from the atomic number of the particles. For the higher LET values, the different particles show different effectiveness even if the LET is the same. This can be qualitatively understood by the assumption that with increasing energy deposition, the biological damage increases more than proportional to the local dose because of the possible interaction of lesions created close to each other. But, for the higher local dose concentration, mainly physical and chemical but also biological saturation processes leads to diminished biological efficiency. The high local dose concentration occurs preferentially for the very heavy ions and at minimum of the particle tracks of the lighter ions where the diameter of the track decreases but the LET increases. The energetic particles are the main reasons for the observed low RBE values of the very heavy particles.


**4209**

**ALTERATIONS IN BRAIN OF DEVELOPING MICE AFTER 0.5 GY NEUTRON IRRADIATION**

**Anna Fdnagy, Z. Fülop and E. J. Hidvégi**
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Female C57Bl/6 mice were exposed to single whole-body dose of 0.5 Gy neutron on day 18 of pregnancy. Thirty to forty per cent of in utero irradiated mice died within a few days after birth. The brain weight of survivors mice was 30-40 percent less than that of controls (S. Antal, Radiat. Res. 98, 1984). Histological examinations performed in brain of fates 6 hours after irradiation showed considerable neuronal and damaged cells were phagocytosed by 12 hours (S. Antal, A. Fdnagy, Z. Fülop, E. J. Hidvégi and H. N. Vogel, Jr., Int. J. Radiat. Biol. 46, 425-433, 1984). DNA content of whole brain of three-week-old mice irradiated in utero, showed that the cell number decreased by 40 percent. Synthesis of brain proteins was inhibited by irradiation, especially that of histones and certain non-histones separated by two-dimensional gel electrophoresis. Investigations with related protein synthesizing systems showed that aminoglycosyl transfer-RNA decreased significantly (A. Fdnagy, S. Antal, J. H. Holland, Z. Fülop and E. J. Hidvégi; Radiat. Res. 103, 34-45, 1985). Brain damage led physiological consequences, too. A significant reduction of locomotor activity was observed at 7-17-40-day-old and 6-month-old in utero irradiated mice, as well as an increase in audiogenic convulsions at age of 22-26 day.

**4211**

**TUMOUR INDUCTION IN MONKEYS AND RATS AFTER NEUTRON IRRADIATION**

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Cancer induction is generally considered to be the most important somatic effect of low doses of ionizing radiation. If the revised dose-effect estimates for the Japanese survivors of the atomic bomb explosions are correct, there is a useful debris case to derive the different RBE values for human carcinogenesis. As a consequence, it will be necessary to rely on the results obtained in biological systems, including experimental animals, for these estimates because induction has been studied in rhabdomonkeys and different rat strains after irradiation with photons and neutrons of different energies. Rhabdomonkeys exposed to relatively high doses of fission neutrons (average absorbed dose 3.4 Gy) or X-rays (average absorbed dose 7.2 Gy) have been kept under observation for a period of 20 years. In the irradiated monkeys a substantial number of multiple tumours have been observed. The latency period varies between 10 and 16 years for the X-irradiated monkeys and between 4 and 15 years for the neutron-irradiated animals. In the group of 21 non-irradiated animals only one malignancy has been found. The studies on mammary carcinogenesis in three different rat strains have shown considerable differences in susceptibility. The animals have been exposed to single and fractionated irradiations with mono-energetic neutrons, X-rays and gamma-rays with doses as low as 3.5 mGy per fraction. Dose-effect relations are reported separately for the induction of benign and malignant lesions. Appropriate corrections have been made for competing risks in the tumor rate analysis. The continuous doseresponse relation is used to derive the relative excess hazard for exposure to X-rays and neutrons. For mammary carcinogenesis in rats, linear dose-response relations have been observed for neutrons and linear-quadratic relations for photons. The highest RBE values varying between 7 and 15 for different types of tumours in the three rat strains have been observed for 0.5 MeV neutrons. Based on current evidence maximum RBE values of approximately 20 appear to be realistic for neutron carcinogenesis.
NUCLEAR NEUTRON CAPTURE REACTIONS IN EXPERIMENTAL ONCOLOGY

B. Larsson, Uppsala, Sweden

DEVELOPMENT OF A KAT MODEL FOR THE TREATMENT OF CLINICAL NEUTRON CAPTURE REACTIONS IN EXPERIMENTAL ONCOLOGY.

R. van der Ven, Netherlands Cancer Institute, Amsterdam, The Netherlands; H. van der Linden, J. van der Zee, H. van der Meulen, and J. Jussen, Netherlands Laboratory for Nuclear Research, Petten, The Netherlands.

EXPERIMENTAL NEUTRON CAPTURE THERAPY WITH BORON-10-AMINO/AMINO-ANALOGS ON A SOLID MURINE TUMOR (F9771 ON C57BL/6 MICE) W. Porzech, J. Marx, H. Muhlemann, H. Feine, and H. Dallaker, Institute of Medicine, Nuclear Research Center, D-3130 Jülich, Federal Republic of Germany; T.C. Roberts, R. Borth, J.W. Blue, NASA Lewis Research Center, Cleveland, Ohio; J.W. Blue, NASA Lewis Research Center, Cleveland, Ohio; and J.W. Blue, NASA Lewis Research Center, Cleveland, Ohio.

The purpose of the present study is to develop an animal model for the treatment of glioblastoma by BNCT. Boron-10 (10B) is a stable isotope that, when irradiated with thermal neutrons, yields high LET alpha particles (10B(n, a)7Li) and the tumor growth delay of about 1-2 days. A3 i.p. plus 6 x 10^10 n/cm^2 resulted in a delay of 6-7 days and A7 i.p. plus 6 x 10^10 n/cm^2 resulted in a delay of 3-4 days. After combined treatment with A3 or A7 the fraction of (12 + M) cells increased from about 20% to 50%.

The results show that the concentration of A3, A7 or A8 in tumors distinctly enhanced the effect of thermal neutron on growth delay and reduced a partial cell accumulation in (62 + M) phase of the cell cycle, despite the high radioresistance of this tumor.

DEVELOPMENT OF A KAT MODEL FOR THE TREATMENT OF GLIOMA BY BORON NEUTRON CAPTURE THERAPY (BNCT). R.F. Borth, J.W. Blue, NASA Lewis Research Center, Cleveland, Ohio; and J.W. Blue, NASA Lewis Research Center, Cleveland, Ohio.

The tumors were exposed to thermal neutrons in a thermal column of the (D D) scattering-type reactor IRS-1 in Munich, Germany. Irradiation with 6 x 10^10 n/cm^2 alone produced a growth delay of 1-2 days. A3 i.p. plus 6, 6 x 10^10 n/cm^2 resulted in a delay of 6-7 days and A7 i.p. plus 6 x 10^10 n/cm^2 resulted in a delay of 3-4 days. After combined treatment with A3 or A7 the fraction of (10 + M) cells increased from about 20% to 50%.

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C-34: HIGH LET RADIATION EFFECTS

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(NGC, gastric cancer; NNC, N-nitroso compounds)

NNC could be formed from nitrite and amines or amides as an acid-catalyzed reaction in the stomach and act there to induce GC. Since 5% of ingested nitrate is converted via the saliva to gastric nitrite, a highly significant country-by-country correlation between nitrate intake and GC incidence in 12 countries supports a role for NNC. A strong negative correlation between GC incidence and fresh vegetable and fruit intake supports the NNC theory, since vitamin C and polyphenols in these foods can inhibit nitrosation. Salivary nitrate and nitrate may be inversely related to GC induction because vegetables contribute heavily to intake of both nitrate and vitamin C/polyphenols, which may counterbalance effects of the nitrate. The Onshima-Bartsch test for potential gastric NNC formation shows decreased nitrosopropyl formation in cases of achlorhydria and increased nitrosopropyl formation in smokers and in high-esophageal cancer areas of China and high-GC areas of Japan. GC association with high-starch diets could be due to a resultant high gastric acidity, which favors nitrosation. Foods associated with GC (fava beans and dried, salted fish) may supply nitrosatable amines or amides. Other environmental etiologic factors for GC include high salt consumption, soft water, peaty soil and other environmental factors leading to human exposure.

N-nitrosamines has been extensively monitored in man and animals and it has been repeatedly demonstrated based on the formation and excretion of the non-carcinogenic N-nitrosopropylamine. Thus nitrosation of precursors of carcinogenic nitrosamines must also be assumed to occur in man and has been demonstrated. The toxicological and carcinogenic activities of the tobacco-specific nitrosamines suggest that they may play a major role in tobacco carcinogenesis, particularly by tobacco carcinogenes, particularly by tobacco-specific nitrosamines. Pharmacokinetic and metabolic studies suggest a possible protective role of the liver against nitrosamine exposure via the gastro-intestinal tract which would be absent following exposure by other routes. (Supported by NIH grant CA-23451 and by a grant from the National Foundation for Cancer Research.)

BIOCHEMICAL AND TOXICOLOGICAL EVIDENCE THAT MAN MAY BE SUSCEPTIBLE TO NITROSAMINE CARCINOGENESIS. P.H. Hegedus, Fels Research Institute and Department of Pathology, Temple University School of Medicine, Philadelphia, PA 19140, USA.

The nitrosamines and other N-nitrosocompounds are carcinogenic in a wide range of animal species and, in rodents, where they have been most extensively studied, they can induce tumors in most organs. The nitrosamines require metabolites for carcinogenic activity, the active intermediate probably being an alkylation species which reacts with cellular macromolecules. The characteristic pattern of DNA alkylation can be used as a marker for exposure. The compounds are formed by nitrosation of secondary or tertiary amines by nitrite or other nitrosating agents, the reaction often being favored by acidic conditions. Reports of accidental and deliberate exposure of human beings to acutely and sub-acutely toxic amounts of dimethyl nitrosamine have described clinical and pathological findings that are closely similar to those noted in experimental animals treated in a similar manner by this compound, in particular the severe toxic liver injury. Characteristically methylated DNA has been detected in the liver of a human subject fatally poisoned by dimethyl nitrosamine. Nitrosamines can be metabolized in vitro by human liver slices and by various human subcellular preparations, as well as by organ cultures from several human organs. Endogenous nitrosation in man has been repeatedly demonstrated based on the formation and excretion of the non-carcinogenic N-nitrosopropylamine. Thus nitrosation of precursors of carcinogenic nitrosamines must also be assumed to occur in man and has been demonstrated. The toxicological and carcinogenic activities of the tobacco-specific nitrosamines suggest that they may play a role in tobacco carcinogenesis, particularly by tobacco-specific nitrosamines. Pharmacokinetic and metabolic studies suggest a possible protective role of the liver against nitrosamine exposure via the gastro-intestinal tract which would be absent following exposure by other routes. (Supported by NIH grant CA-23451 and by a grant from the National Foundation for Cancer Research.)


The environmental occurrence of carcinogenic N-nitrosamines has been extensively monitored using highly specific and sensitive trace analytical methods. Highest human exposure occurs in certain occupational situations such as in the rubber industry and in the use of nitrosamine contaminated cutting fluids in the metal-working industry. So-called "life-style" exposure of the general population has been shown to occur in several areas. It is highest in smokers and tobacco chewers, where high concentrations of volatile as well as "tobacco-specific" nitrosamines have been found. Exposure from food is rather low in Western countries, cured meat products and beer being the main contaminated products. Certain cosmetic articles, household rubber products, drugs and pesticides were also shown to contain nitrosamine impurities leading to human exposure.
4219 ROLE OF INTRAGASTRIC NITRATE, NITRITE AND N-NITROSO COMPOUNDS IN GASTRIC CANCER ETIOLOGY.

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Cross-sectional and longitudinal studies of populations at high risk for stomach cancer in Colombia, South America and New Orleans, Louisiana, USA, have been carried out to study the role of chronic gastritis in gastric carcinogenesis. At least 3 types of chronic gastritis have been identified: autoimmune, hypersecretory and environmental. The latter is more closely associated with high gastric cancer risk. Factors causally associated with the latter type of gastritis fall into 4 categories: irritants, N-nitroso compound precursors, antioxidants and promoters of differentiation. The lesions and the etiologic factors will be integrated into a comp.ositive etiologic hypothesis.

4220 THE ROLE OF GASTRITIS IN GASTRIC CARCINOGENESIS

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4221 THE ETIOLOGY OF ESOPHAGEAL CANCER IN CHINA


Esophageal cancer is widely distributed in many areas of China. The amounts of N-nitroso compounds in food, in gastric juice and in urine collected from Lin-xin county in high risk areas of esophageal cancer were detected. The effect of nitrosamine on esophageal epithelium in human has been also investigated at the cellular and molecular level. A total 953 samples of gastric juice were analyzed. NDMA, NDEA, NMBzA, NPyr, NPy and other unknown compounds were detected in the fasting gastric juice. A significant correlation was found between the amounts of nitrosamines in gastric juice and the lesions of esophageal epithelium. The amounts of NDMA, NDEA, NMBzA, NPyr and NPy in gastric juice from subjects with normal esophageal epithelium were lower than that from subjects with marked dysplasia and carcinoma of esophagus, indicating a higher exposure to nitrosamines in patients with marked dysplasia and carcinoma of esophagus. The levels of nitrosopropilne, nitrosothiazolidine 4-carboxylic acid and N-nitrososarcosine detected in the urine of subjects from high risk areas were higher than those from low risk areas. Intake of L-proline resulted in a marked increase in the excretion of NPRD in urine of subjects from 7 counties; the median level of NPRD was about 1-2 times greater than that under proline. Intake of moderate doses of ascorbic acid, α-tocopherol or zinc together with L-proline by subjects from several high risk areas of esophageal cancer reduced the urinary levels of NPRD. Our data suggest that subjects at high risk areas have been exposed to greater level of N-nitroso compounds than that at low risk areas, and that endogenous nitrosation of proline had occurred in human following ingestion of proline, ascorbic acid, α-tocopherol and zinc, and this process may induce esophageal cancer. Thus offering a rational basis for long term intervention studies in these areas.

4222 N-NITROSO COMPOUNDS, AS A POSSIBLE RISK FACTOR FOR GASTRIC CANCER IN JAPAN. T. Kawabata, Dept. of Biomed. Res. on Food, Natl. Inst. of Health, Shinagawa-ku, Tokyo 141, Japan

In Japan, about one-third of deaths from various type of cancer are attributable to gastric cancer every year, however, members of gastric cancer in our country, are decreasing in recent years, probably due to change in eating habit. Although the causative agent(s) or factor(s) involved in human gastric cancer are not yet clear, some epidemiological data indicate that the high incidence of gastric cancer in Japan might be associated with the high intake of salted fish and salt-fermented vegetables. We already reported that Japanese consume about 3 times as much amounts of nitrates from vegetables as compared with the levels of Western countries. In order to clarify the relationship between the incidence of gastric cancer and the intake of various N-nitroso compounds through our diet, we developed a technique for estimating the total N-nitrosamines (TNA) in food, and we also devised a quantitative analysis of alkylysux, precursors of carcinogenic N-nitrosoureas, in food. Using these techniques, a survey of the occurrence of total N-nitroso compounds, total N-nitrosamines, volatile N-nitrosoamines, nitrates and nitrites in various foods, especially in traditional Japanese diet, has been conducted. Fairly high levels of total N-nitrosoamines were detected in some salt-fermented vegetables, the highest instance being 2500 μg/kg in salt-fermented Chinese cabbage. In contrast, almost no appreciable amount of alkylysux has so far been detected in various foods including salted and salt-dried fish products. These and other observations on dietary factors and gastric cancer will be discussed in relation to future research needs on N-nitroso compounds in the field of diet, nutrition and gastric cancer in Japan.
Escape from immune surveillance in the presence of tumor immunogenicity may lie with factors within the tumor, i.e., its microenvironment (milieu). The natural history of prostate cancer characterized by a high incidence of latent and occult foci found on routine autopsy and wide variation in the age of onset of clinical disease are suggestive of the modulatory role of the tumor milieu on host responsiveness. In continuing studies of this possibility, extracts of benign human prostate tissue (BPE) and seminal plasma (SpPI) were evaluated for their ability to modulate mitogen-induced blastogenesis and the lytic activity of natural killer (NK) cells as two in vitro parameters of immunologic responsiveness. Pimat-hypaque isolated peripheral blood lymphocytes (PBL) were pretreated for 18hrs. in varying concentrations of BPE, SpPI and without (control), washed and then evaluated. Blastogenesis was carried out with phytohemagglutinin as mitogen, NK cell activity for the human K-562 erythroleukemia cell line as the target cell was evaluated in a chromium release assay. Pimecubation of PBL in BPE and SpPI resulted in almost total, i.e., 95%, inhibition of blastogenesis (P<0.01) and 80% (P<0.001) inhibition of lysis, respectively. Characterization of the immunomodulatory factor(s) in BPE and SpPI by biochemical analysis and reversal of their inhibitory effect by indomethacin and iraconazol are suggestive of high and low molecular weight (MW) factors. In BPE, the inhibitory factor appears to be principally of low MW, whereas in SpPI low and high MW factors appear equally inhibitory.
**G-34: ANTIBODIES AND HUMORAL ACCESSORY FACTORS IN CANCER DIAGNOSIS AND THERAPY: HOW USEFUL ARE THEY?**

**4227 FIRST EXPERIENCES WITH 1-131 LABELED MONOCOVALNT ANTI-CEA ANTIBODIES IN THE TREATMENT OF LIVER METASTASES FROM COLORECTAL CARCINOMA.**

A. Bischof-Delaloye, B. Delaloye, J.C. Volante, J. Pettavel, V. von Fliehner, F. Buchegger and J.P. Mach
Nuclear Medicine Division and Department of Surgery, CHUV, 1011 Lausanne, Switzerland and Ludwig Institute for Cancer Research, 1066 Epalinges, Switzerland

4 patients with end stage colon carcinoma were treated by infusion of 1-131 labeled monoclonal anti-CEA antibodies (Ab) in the hepatic artery by the means of an infusion pump. 3 patients received 10 mg of F(ab')2 labeled with 111 ± 11 mCi, on patient the same but intact Ab (10 mg / 98.5 mCi). In all patients the perfusion of the liver by the catheter/pump system was previously checked with Tc-99m labeled microagregates of human serum albumin. Furthermore patients were prepared with antihistaminics and prednisolone to prevent anaphylactic reactions and Lugol's solution and potassium perchlorate to diminish thyroid and gastric uptake. The first three patients were pretreated by iv perfusion of the same unlabeled Ab. Immunoreactivity of the labeled Ab was 61%. The Te-f was measured by urinary and fecal elimination of 1-131, liver activity was estimated by step-by-step dual detector whole body counting. Liver volume and metastasis/liver ratios were obtained by emission computerized tomography (ECT).

In the first three patients, no therapeutic effect could be observed, radiation dose to liver metastases was estimated 1039-1518 rads, whereas it was estimated 6154 rads in the patient who received the intact Ab. In this patient a transitory improvement of liver function and longer survival was noticed without any serious side effects. Before treating additional patients attempts have been made to increase the metastasis/normal liver perfusion ratio. The perfusion of vasopressin (0.1 mlU . kg^-1 . min^-1) did not modify the ratio in one patient, whereas under treatment with propanolol an increase of this ratio was observed in 2 patients.

**4229 ANTIBODY GUIDED DIAGNOSIS AND THERAPY OF SOME MALIGNANT NEOPLASMS AND ITS IMMUNOLOGICAL CONSEQUENCES.**

C. Courtenay-Luck, London, UK

**4228 RESERVED**

J.P. Chatel, Nantes, France

**4230 SEROTHERAPY OF RAT MAMMARY CARCINOMA: POSSIBLE ROLE OF ACTIVATION OF THE ALTERNATIVE PATHWAY OF COMPLEMENT.**

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Growth of rat primary mammary carcinomas is inhibited after infusion of absorbed sera or plasma. Evidence suggests that tumor growth inhibition is caused by a factor(s) present in serum in precursor form that acquires antitumor activity during absorption. We have begun an investigation to define conditions required for generation from serum of molecules with antitumor activity. Administration of tumor-bearer plasma absorbed with Protein A-Sepharose or Inactivated CNBr-Sepharose inhibited the growth of primary mammary tumors. Administration of unabsorbed plasma or sera did not inhibit mammary tumor growth. There was no inhibition of growth by administration of quantities of endotoxin calculated to be present in the absorbent. C3 and C5 were consumed during absorption of tumor-bearer or normal plasma with inactivated CNBr-Sepharose or Protein A-Sepharose. The anticoagulant, ACD, had a major effect on C3 consumption. Increasing quantities of ACD were associated with decreased C3 consumption. Addition of Mg^2+ to plasma anticoagulated with ACD augmented C3 consumption. These observation suggested that Mg^2+ limited C3 consumption in plasma anticoagulated with ACD. To more rigorously link Mg^2+ to the activation of blood factors, sera were absorbed in the presence or absence of chelating agents known to bind Ca^2+ and Mg^2+ (EDTA). EDTA inhibited C3 consumption and prevented the generation of the antitumor factor(s). EDTA did not inhibit C3 consumption and permitted the generation of the antitumor factor(s). The different effect of these 2 chelating agents on generation of the antitumor factor(s) indicates that the activation of the antitumor factor is dependent on Mg^2+. The specific requirement for Mg^2+ for generation of antitumor activity during absorption and the correlation of C3 consumption with antitumor activity strongly suggests that activation of alternative pathway of complement is involved in the observed antitumor effects.
4232 CLINICAL INVESTIGATIONS WITH ZITAZONIUM. I. Hindy, I. Szamel, E. Juhasz, J. Szanto and S. Eckhardt, Natl. Inst. of Oncology, Budapest, Hungary

As a phase I trial the Hungarian antiestrogen drug Zitazonium was administered to more than 200 postmenopausal patients with advanced breast cancer. The drug proved to be tolerable in the majority of patients in a daily dose of 40-60 mg for 100 days or in a daily dose of 30-60 mg administered 6-12 months, respectively. According to the literature this dose is 2-3 times higher than that of the original Tamoxifen /Novadox/. As a phase II trial based on the data of 103 treated patients the best results could be achieved in the cases of soft tissue and bone metastases. As a consequence of the endocrine investigations the elevation of the estradiol level in the sera during treatment as well as the suppression of the prolactin secretion induced by TRH could be considered a predictive test of response.

4233 THE PRESENT STATE OF ADJUVANT ENDOCRINE TREATMENT PROCEDURES OF BREAST CANCER PATIENTS.

The adjuvant chemotherapy of operable breast cancer patients with positive axillary nodes is effective especially in some subgroups. Premenopausal patients with 1-3 involved lymphnodes benefit by this type of systemic therapy regarding the relapse free survival and the overall survival. On the other hand the effect of adjuvant chemotherapy procedures in postmenopausal patients is questionable. These patients especially with hormone receptor positive tumors show a significant benefit of Tamoxifen on relapse free survival. Regarding the extent of this benefit and the dependence on the receptor status there are discrepancies in the various clinical trials. The data of these trials will be reported.

The Gynecological Adjuvant Breast Cancer Group (GABG) in the FRG started a prospective randomized trial in nodal positive patients in 1981. The patients were separated into 2 groups: low risk: N₀ (1-3), ER/PR positive, and high risk: N₁, ER/PR negative or more than 4 involved lymphnodes regardless the receptor status. Patients of the low risk group where randomized for Tamoxifen (2 years 30 mg/d.) versus CMF x 6; high risk group AC x 8, versus AC plus Tamoxifen.

Results: Low risk group: There is no difference regarding the relapse free survival between the 2 groups, in the high risk group there is significant benefit of the patients treated with AC plus Tamoxifen, especially in patients with positive receptors.

The preliminary result of the trial demonstrates that there may be a subgroup of patients who benefit from an adjuvant tamoxifen treatment and it confirms the results of other trials that in hormone receptor positive patients the combination of chemotherapy and tamoxifen yields higher relapse free survival rates, dependent on the receptor status.

4234 ENDOCRINE TREATMENT OF BREAST CANCER. O. H. Pearson, Case Western Reserve Univ., Cleveland, Ohio, U.S.A.

Endocrine treatments can induce objective remissions in about 40% of unselected patients with stage IV breast cancer lasting an average period of 1-2 years. Estrogen receptor measurements of the patient's tumor are useful in selecting patients for endocrine treatment. Patients may respond to more than one endocrine treatment used sequentially, but combinations of endocrine treatment do not appear to be useful. Our present recommendation for endocrine treatment in stage IV disease is 1) tamoxifen, 2) aminogluthethimide and hydrocortisone, 3) fluoxymesterone, 4) megestrol. With sequential endocrine therapy followed by combined chemotherapies, 5 year survival after the appearance of metastases is greater than 50 percent.

Endocrine therapy is also useful in earlier stages of breast cancer (stage I and II) and has been used as adjuvant therapy following mastectomy. In a prospective, randomized study of 311 women who underwent mastectomy for stage II (node positive) breast cancer, we found that tamoxifen plus 3-drug chemotherapy (CMF; cytoxan, methotrexate, 5-fluorouracil) was more effective in delaying recurrence than CMF therapy alone after 9 years of follow-up. In a second study, 138 women with estrogen receptor positive, stage II breast cancer received endocrine therapy after mastectomy, and one half of these (by random selection) also received 5-drug (CMFP; Vincristine, Prednisone) chemotherapy. After 3 years of follow-up there was no additive effect of chemotherapy in postmenopausal women, whereas in postmenopausal women combined therapy was more effective than endocrine treatment alone in terms of disease-free survival.

Tamoxifen treatment of primary breast cancer in the elderly has been studied. In a series of 160 patients, complete regression of the primary cancer occurred in 29% and partial regression in 30%. The duration of complete response was 37 months and for partial response 18 months. The 5-year actuarial survival rate was 29%. These results appear to be promising and this approach may be useful in younger patients when breast conservation is desirable.
AROMATASE ACTIVITY IN PRIMARY AND METASTATIC HUMAN BREAST CANCER. A. Lipton, S. Santner, R.J. Santner, H.A. Harvey, P.D. Pachal, D. Whitehouse, S.P. Winer. The Milton S. Hershey Medical Center, Hershey, PA 17033 and Department of Statistics, The Pennsylvania State University, University Park, PA 16802, U.S.A.

Breast cancers can synthesize estrogen in situ from plasma precursors. The major substrate for aromatization, androstenedione, is secreted predominantly by the adrenal cortex and only minimally by the ovary in postmenopausal women. We measured aromatase activity in 104 primary breast cancers and 24 metastatic sites. The assay employed [14C] androstenedione as substrate measuring the reduction of 14C-estrone and androstenedione after aromatization. Of 104 human primary breast tumors studied, 64 contained measurable aromatase activity, ranging from 0-70 pmol estrone formed/g protein/hr. In primary breast cancers there was no difference in mean levels of aromatase activity when analyzed by menstrual status or age by decade. Mean aromatase activity was similar in small vs. large primary tumors (1±3). The mean aromatase activity of primary breast tumors (12.14 pmol/g/hr) was similar to that found in metastatic breast cancer deposits (13.2 pmol/g/hr). Aromatase activity did not correlate with either estrogen receptor or the ability of the cancer to produce measurable ER or PR.

These studies strongly indicate that AG influences the biologic effects of estrogens, and thereby tumor growth, also by modulating estrogen metabolism.

ENDOCRINE-PHARMACOKINETIC STUDIES OF AROMATASE INHIBITOR 4-HYDROXYANDROSTENEDIONE IN POSTMENOPAUSAL BREAST CANCER PATIENTS. P.F. Bruning, M. de Jong-Bakker, J. van Loon, J.M.G. Bonfrer. The Netherlands Cancer Institute, 1066 CX Amsterdam.

4-Hydroxyandrostenedione (40HA) is a potent inhibitor of aromatase and has been shown to be a clinically effective treatment for postmenopausal breast cancer, at a dose of 500 mg i.m. weekly. Endocrine effects of 40HA were studied in a group of patients (Study A). In addition, the plasma levels of 40HA and estrone (E1) were evaluated in small groups of patients treated with a number of doses of 40HA, both parental and oral, to be able to define the minimal effective dose and regimen (Study B).

In patients on 500 mg 40HA i.m. weekly plasma E2 Levels were reduced to a mean 37.1 ± 4.9% (SEM, n=11) of baseline after the first injection and there was no significant difference in the degree of suppression during the subsequent 7 weeks. There were no significant changes in the plasma levels of oestrone, dehydroepiandrosterone sulphate, 17-8-hydroxy cortisol, globulin, lutetising hormone or follicle stimulating hormone, after at least 1 month's treatment. Study B: Four to seven patients after a single 500 mg 40HA i.m. injection E2 Levels were suppressed to a mean 36.3 ± 12.5% (n=14) of baseline. In 6/7 patients there was no escape from the suppression in E2 Levels 14 days. The half-life of 40HA was approximately 5 days in these patients and the level had fallen to less than 3 ng/ml by the time E2 Levels began to rise. Similar suppression of E2 was achieved by a single 125 mg injection during the first week but escape was more rapid. Oral administration of 40HA also caused significant E2 suppression: 500 mg daily achieved similar suppression after 7 days compared to that with 500 mg 40HA i.m. weekly. Conclusions: 500 mg 40HA i.m. weekly is a higher dose than required for maximal and sustained E2 suppression. The clinical effectiveness of oral 40HA should be investigated after dose optimisation.

LOW DOSE AMINOGlutETHIMIDE WITHOUT HYDROCORTISONE IN ADVANCED POSTMENOPAUSAL BREAST CANCER. P.F. Bruning, M. de Jong-Bakker, J. van Loon, J.M.G. Bonfrer. The Netherlands Cancer Institute, 1066 CX Amsterdam.

The working mechanism of aminoglutethimide (AG) in the treatment of advanced postmenopausal breast cancer can no longer be regarded as medical adrenalectomy. Instead, inhibition of estrogen synthesis is regarded as the main mechanism. AG is regarded as essential to lower estrogen levels with subsequent response in sensitive tumors. To test this hypothesis and to elucidate the endocrine effects of AG in advanced breast cancer, AG was administered in a dose of 500 mg intramuscularly (i.m.) weekly for 6-7 months. In 6/7 patients there was no suppression during the subsequent 7 weeks. There were no significant changes in the plasma levels of oestrone, dehydroepiandrosterone sulphate, 17-8-hydroxy cortisol, globulin, lutetising hormone or follicle stimulating hormone, after at least 1 month's treatment. Study B: Patients on 500 mg 40HA i.m. weekly for 6-7 months. Study A: In patients on 500 mg 40HA i.m. weekly plasma E2 Levels were reduced to a mean 37.1 ± 4.9% (SEM, n=11) of baseline after the first injection and there was no significant difference in the degree of suppression during the subsequent 7 weeks. There were no significant changes in the plasma levels of oestrone, dehydroepiandrosterone sulphate, 17-8-hydroxy cortisol, globulin, lutetising hormone or follicle stimulating hormone, after at least 1 month's treatment. Study B: Four to seven patients after a single 500 mg 40HA i.m. injection E2 Levels were suppressed to a mean 36.3 ± 12.5% (n=14) of baseline. In 6/7 patients there was no escape from the suppression in E2 Levels 14 days. The half-life of 40HA was approximately 5 days in these patients and the level had fallen to less than 3 ng/ml by the time E2 Levels began to rise. Similar suppression of E2 was achieved by a single 125 mg injection during the first week but escape was more rapid. Oral administration of 40HA also caused significant E2 suppression: 500 mg daily achieved similar suppression after 7 days compared to that with 500 mg 40HA i.m. weekly. Conclusions: 500 mg 40HA i.m. weekly is a higher dose than required for maximal and sustained E2 suppression. The clinical effectiveness of oral 40HA should be investigated after dose optimisation.
PROLACTIN RECEPTORS (PRLR) IN HUMAN BREAST CANCER. PROGNOSTIC SIGNIFICANCE. J. Bonneterre*, J.Ph. Peyrat*, H. Beaucart**, J. Lefebvre and A. Desailly*. **Centre d’Étude et de Recherche en Informatique Médicale, Faculté de Médecine, Lille, France.

PRLR have been measured in 548 primary breast adenocarcinomas surgically treated in the Centre Oscar Lambret, France as well as total (after MgCl2 desaturation) PRLR were determined. On the same biopsy ER and PgR were measured using the Dextran Charcoal method and a specimen was reserved for histological examination. ER were found in 81% of the cases, PgR in 55%. free PRLR in 43% and total PRLR in 72% of the patients. The duration of the follow-up was up to 5 years. Overall survival (OS) and relapse-free survival (RFS) according to free and total PRLR were studied. Free PRLR never had a prognostic significance neither on OS nor on RFS. When the population was considered as a whole, patients with total PRLR in their tumor had a better RFS than those who lacked these receptors (p<0.02). The population was divided into 2 groups according to nodal status (N+ or N-); total PRLR had no prognostic significance in N- patients; conversely N+ patients who had total PRLR experienced a better RFS (p<0.001). Similarly when the population was divided into 2 groups according to ER status (ER+ or ER-), total PRLR had no prognostic significance in ER- patients; conversely ER+ patients who had total PRLR in their tumor experienced a better RFS (p<0.01). Total PRLR have thus a prognostic value on RFS especially in N+ and/or ER+ patients.

COMBINATION OF HORMONAL AND CYTOSTATIC ADJUVANT THERAPY IN PATIENTS OPERATED FOR BREAST CARCINOMA WITH POSITIVE AXILLARY NODES. C.-M. Rudenstam, Surgical Department I, Sahlgren’s Hospital, Göteborg, Sweden, for the Ludwig Breast Cancer Study Group (LBCSG).

In 1976 LBCSG started a different studies in operable breast cancer combining hormonal and cytostatic therapy after at least total mastectomy and axillary clearance.

Methods 691 premenopausal patients (pat) with 1-3 positive axillary nodes were randomized to treatment with CMF for 12 x 28 day cycles according to Bonadonna (group 1) or CMF + 7.5 mg Prednisone (P) daily (group 2). 337 premenopausal pat with 4 nodes were randomized to CMFp (group 3) or CMFp + oophorectomy (group 4). 463 postmenopausal pat 66 years were randomized to control (surgery only) (group 5), CMFp + tamoxifen (T) 20 mg daily (group 6) or to P+T (group 7). 320 postmenopausal pat, 66 up to 80 years, were randomized to control (group 8) or to P+T (group 9).

Results At 5 years median follow-up there was no significant difference in disease-free survival (DFS) (7% resp. 6%) or overall survival (OS) (85% resp. 84%) between group 1 and 2. DFS was 43% and OS 61% in group 3 against DFS 48% and OS 65% in group 4. (No significant difference). In group 5, DFS and OS were 35% and 59% respectively, in group 6 DFS was 59% and OS 71%, while in group 7 DFS was 45% and OS 64%. Differences in DFS was significantly different between all 3 groups while the difference in OS was almost significant between group 5 & 6 (p<0.01). DFS was significantly different between groups 8 & 9 (50% resp. 45%) but there was no difference in OS (64% and 63% respectively).

Conclusion Prednisone given as continuous low-dose does not improve the results of CMF-therapy in premenopausal pat. The addition of oophorectomy to cytostatic treatment to premenopausal pat in a high risk group has no effect on DFS or OS. In the postmenopausal pat, the addition of hormonal therapy improves DFS. The combination of hormonal and cytostatic therapy improves both DFS and OS in the younger postmenopausal group.
4242 RADIOACTIVE IODINE THERAPY IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA AND MEDULLARY CARCINOMA

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The therapeutic response and survival rates of 352 patients with differentiated thyroid carcinoma who had received radioactive iodine therapy since 1951 were studied. Of these patients, 72% had metastases to the cervical lymph nodes, lungs, bone, or other viscera. Of all patients, 70% showed complete remission, and 30% showed partial response or recurrence of disease or both. Patients with metastases before therapy had a higher incidence of recurrence than those who had localized thyroid disease (32.4% vs 15.1%). Of these, 97 patients had recurrent disease. In 24 of these patients, the recurrent tumor failed to take iodine, indicating change in its iodine-concentrating characteristics. Of the 352 patients, 44 (12.5%) died of progressive thyroid carcinoma, and all were over 40 years of age at the time of initial diagnosis. Mean survival of patients with metastatic disease who were over 40 years of age at initial diagnosis was significantly lower than that of patients under 40 years of age (6.2 years vs 11.5 years). Patients with recurrent metastases unresponsive to surgery or radioactive iodine therapy were treated with palliative radiotherapy or chemotherapy or both. They responded poorly and died within a few months. To determine the value of adjunct 131I therapy in medullary carcinoma of the thyroid (MDT), two groups of patients with histologically proved MCT were studied. We conclude that 131I has no value as an adjunct to surgery in the management of MCT.

4243 RADIOIODINE TREATMENT OF DISTANT METASTASES OF THYROID CANCER. J. Mácso, Res. Inst. of Endocrinology, Pápa, and Dept. of Nuclear Medicine, Faculty Hospital, Pápa Motol, Czechoslovakia

Distant metastases of differentiated thyroid cancer should be treated by repeated amounts of radiiodine-131 whenever possible. From our observations with about 300 patients, the survival of patients with lung or bone metastases showing radiiodine uptake and receiving this treatment is significantly higher. Best survival rates could be expected in young patients, with millitary pulmonary metastatic dissemination and in patients with single bone metastases, in both groups when treated by radiiodine. Survival curves are given for some examples of different metastatic dissemination.

4244 CHEMOTHERAPY IN TREATMENT OF THYROID CARCINOMA. Kazuto Shimosaka. Roswell Park Memorial Institute, New York State Dept. of Health, Buffalo, NY, USA

The most frequently encountered thyroid carcinomas are differentiated carcinomas with varying degree of mixture of papillary and follicular elements. Most of this type of tumor can be surgically resected and requires no further treatment than suppressive therapy with thyroid hormones. Many of recurrent and/or widespread disease can be controlled for radiiodine therapy. Tumors inoperable tumors which are refractory to radiodiode may be treated with chemotherapy. Medullary carcinomas comprise 3-7% of thyroid malignancies. Its biologic behavior is characterized by the slow growth and early spread. When the spread is beyond the surgical resections, they are also candidate for chemotherapy. Anaplastic carcinomas which has the worst prognosis comprises 3-5% of thyroid malignancies depending on the geographic part of the world. Most patients are inoperable with the mean survival of less than 3 months. They could receive only one modality of treatment due to time limitation: external radiation therapy or chemotherapy. Thyroid carcinomas in general is only moderately sensitive to radiation therapy. Because of the small number of patients undergoing chemotherapy, single agent trials are limited: doxorubicin and bleomycin have been evaluated in reasonable number of thyroid cancer patients. Doxorubicin has been demonstrated to be consistently active in approximately one-third of patients. The obvious approach made by various investigators was to combine doxorubicin with other chemotherapeutic agents. However, because of the scarcity of the patients, the evaluation is very difficult if not impossible. A first randomized study undertaken by the Eastern Cooperative Oncology Group which compared Adriamycin alone and Adriamycin plus cisplatinum has clearly shown a significant difference in the quality of response: SCR were observed in the combination arm, while no CR in the single agent arm [P=0.03]. However overall response rate (CR and PR combined) was not significantly different. None of SCR patients died from the disease: 2 of them are alive without further treatment or recurrence more than 5 years.

4245 CHEMOTHERAPY OF THYROID CANCER. J. Szántó and E. Juhos. Natl. Inst. of Oncology, Budapest, Hungary

Cancers of the thyroid gland account for 1% of all malignancies. In case of the highly differentiated thyroid tumours the postoperative treatment involves principally hormone substitution or percutaneous irradiation and/or 131I-therapy. By the next stage, the long-term results of these histological types of tumours is about 70%. The apamastic or medullary thyroid tumours, the malignant hamangioendotheliomas, carcinosarcomas or the dedifferentiated carcinomas of the originally highly differentiated cancers are hardly or not responding to 1-therapy or percutaneous irradiation, therefore their only choice of treatment is the administration of cytostatics. In view of this we have treated 14 patients since 1982-6 females, 8 males/. Their mean age is 54.6 years (range: 38-71). Medullary cancer was observed in 8, anaplastic in 3, papillary in 2 patients and clear cell carcinoma in 1 patient, respectively. CR was not achieved. PR developed in 6 cases, after the second treatment cycle. 2 patients were given Adriamycin+Actinomycin, 1 patient Adriamycin+Fluorouracil+Cyclophosphamide or Vincristin, 2 patients Adriamycin+Bleomycin while 1 patient Di-chlorodiimine Platinum. Among the responders 1 patient had clear cell, 1 papillary and 1 medullary carcinoma, respectively. The median duration of remission was 4 months (range: 1-17). 3 patients were in SD averagely for 5 months. No effect was seen in anaplastic carcinoma, WHO grade 1-2 toxicity not requiring interruption of drug administration occurred in 11 patients. In conclusion, in thyroid malignancies of the above histological types chemotherapy is undoubtedly indicated for the retardation of the symptoms of compression or for the prolongation of social life-span.
4246 PROGNOSIS OF THYROID CARCINOMA WITH DISTANT METASTASES K. O. Franssila, Pathology Lab., Dept. Radiotherapy and Oncology, Helsinki Univ Central Hospital, Helsinki, Finland.

Papillary carcinoma of the thyroid is exceptional among all malignant tumours in the respect that patients with papillary carcinoma and regional metastases do not have poorer prognosis than patients without them. Distant metastases are rare in papillary carcinoma and occur mostly in the lungs and pleura. Prognosis for patients with distant metastases is clearly poorer than for patients with local regional metastases although some patients may survive long periods. The 5-year survival rate has been of the order of 30-40% in different series, and 10-20% of the patients have survived more than 10 years. In follicular carcinoma distant metastases are much more common than in papillary carcinoma and occur mostly in the lungs and bones. The survival rates of patients with distant metastases have been of the same order as in papillary carcinoma. In this tumor type patients with long survival times often have solitary metastases that are controlled with radioiodine or radiotherapy. Almost all patients with anaplastic carcinoma have very poor prognosis; the median survival is about 2 months. The prognosis for patients with distant metastases is still worse.

4248 THYROID CARCINOMA IN CHILDHOOD GY. Balazs, G. Lukacs, G. Cseky 1st, Dept. of Surg., Debrecen, Hungary

In our study on the late results of 14 child- and juvenile patients with thyroid cancer operated on in the course of 24 years answers to the following questions were sought for:

1. Clinical and morphological characteristics of thyroid carcinomas
2. What immune response can be expected after complex treatment
3. Outcome of the pregnancies of operated patients and the thyroid function of the children born.

Results
1. The favourable prognosis of thyroid carcinomas in childhood and juvenile age can be accounted for by the following factors: long time of survival, intrathyroidal localization, predominantly papillary structure, relatively benign metastases and the infrequent incidence of recurrence.
2. The operated patients, in about half of all cases, displayed a long time of disease, often 10 years or more, and therefore, a time window for sensitization against thyroid cancer antigens, both in the case of LAI and LNT. That means that in the sera of the patients no factors inhibiting the sensitization of T-lymphocytes against the tumour antigens were detected.
3. In the light of the examinations, the general development of the disease and the thyroid function of the children born from these pregnancies were not influenced by the mothers' previous disease.

4247 THYROID CARCINOMA AFTER HEAD AND NECK RADIATION COMPARED WITH CARCINOMA IN PATIENTS WHO RECEIVED NO RADIOTHERAPY. N.A. Samaan, P.N. Schultz, and N.G. Ordman. Sec. of Endocr., Dept. of Med., Dept. of Pathology, Univ. of Texas M.D. Anderson Hospital & Tumor Inst., Houston, Tex. 77030.

* There have been 1324 patients with well-differentiated thyroid carcinoma seen from 1950 through July 1984 at the University of Texas M.D. Anderson Hospital and Tumor Institute at Houston and 123 have had a history of external irradiation to the head and neck region as children. The purpose of this study is to compare the thyroid carcinoma in these patients with patients that were not irradiated.

Histologically the patients were categorized as papillary, follicular, or Hurthle cell carcinoma. Distribution according to histological type was similar between the irradiated and non-irradiated groups (p < .1). In the non-irradiated group 93% of patients had been operated on (p < .03). In the non-irradiated group 48% presented with disease to the gland only vs. 30% in the irradiated group (p < .03). In the non-irradiated group 46% presented with disease to the gland and neck lymph nodes vs. 65% in the irradiated group (p < .03). The age at diagnosis for the non-irradiated group was significantly lower than in the irradiated group (p < .001). In conclusion, the data indicate that patients who had been irradiated presented with more disease to the thyroid gland and neck lymph nodes than the non-irradiated group. However, this did not indicate a higher mortality, in fact, the death rate in the non-irradiated group was significantly higher than in the irradiated group but this may be attributed to the age difference.

4249 SURGICAL INCIDENCE OF THYROID CANCER IN RECURRENT THYROID CYSTS DETECTED BY FINE-NEEDLE ASPIRATION. F.W. Welsh, J.P. Provas, V. Nikore and I.B. Rosen. Departments of Medicine and Surgery, Mount Sinai Hospital, & University of Toronto Medical School, Toronto, Ontario, M5G 1X5, Canada.

Several decades ago the risk for underlying thyroid cancer within a cystic thyroid nodule was considered to be small (2%). To assess the incidence of thyroid cancer and neoplasia in cystic lesions detected on palpation of the neck region by FNA, 94 patients with recurrent cystic thyroid nodules were selected for surgery on either cytological factors that were positive or suspect for malignancy and/or clinical suspicion for underlying neoplasia based on > 3 cm recurrent cystic or mixed (solid and cystic) thyroid nodule. Surgical histology from these 46 patients revealed that 12 (26%) had thyroid cancer, 22 (48%) follicular adenoma and 12 (26%) benign colloid nodules, 9/12 cases of thyroid cancer (75%) were papillary or mixed papillary thyroid cancer. Furthermore, cytology performed after nuleopore filtration of the aspirated fluid demonstrated the presence of underlying malignancy in 4/12 (33%) of the thyroid cancer patients and 2/12 (16%) were suspect for malignancy, while the remaining 6 (50%) had no evidence of malignancy but were selected on the suspicion of malignancy in recurrent hemorrhagic lesions > 3 cm in diameter. Aspirated cyst fluid ranged in volume from 1-30 ml and there was no correlation between gross cyst fluid characteristics and the pathological outcome although malignancy and neoplasia were more common in hemorrhagic cystic and mixed lesions of > 3 cm in diameter. Conclusions: (1) To facilitate the early diagnosis of underlying thyroid cancer or neoplasia, cyst fluid from hypofunctioning thyroid nodules obtained by FNA should be routinely analyzed for cytoplasmic, colloid, and/or clinical evidence of > 3 cm hemorrhagic and recurrent cystic nodules resulting in a 26% incidence of proven cancer and an overall 74% neoplasia, indicating that the incidence of malignancy in certain cystic lesions may be as frequent as in hypofunctioning solid nodules.
4250 **RADIOIODINE ABLATION OF REMNANTS. G. Klccaojna, \[Univ.-Klinik für Nuklearmedizin, Innsbruck, Austria\]**

The statement concerning the topic is based on our experiences with 1500 patients with thyroid cancer seen since 1961 and followed for up to 25 years. Until 1975 we ablated thyroid remnants in patients of high risk groups (age, TNM stage, histology) with 1850 - 3750 MBq of 131 I, after this date we treated thyroid remnants in all thyroid cancer patients who did not have sarcomas and lymphomas with 500 Gy as calculated from remnant volume and 131 I-uptake. Posttherapeutic 131 I-uptake in metastases and/or tumor residues was seen also in several cases with "anaplastic" medullary thyroid carcinoma, survival at 10 years was 20% up to 1975 and is 85% now. In conclusion we propose routine thyroid remnant ablation with 500 Gy 131 I in all patients with thyroid carcinoma even in lower risk groups when the differentiated tumor exceeds 1,5 cm in diameter.

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4251 **ULTRASTRUCTURAL STUDY OF POORLY DIFFERENTIATED MEDULLARY CARCINOMA OF THE THYROID, K.Kakudo, and K.Watanabe, Dept. of Pathology, Tokai University School of Medicine, Isehara, Japan**

Medullary carcinomas of the thyroid(MTCs) are mostly low grade malignant tumors originate from C cells of the thyroid. Recently some authors reported atypical MTC or anaplastic variant with poor prognosis. The present report dealt with 5 cases of sporadic MTC with poor prognosis(less than 3 years survival period). They show solid alveolar growth and trabecular pattern with increased N/C ratio(small cell variation), less amyloid deposits, presence of necrosis in the tumor and increased mitoses. The average age at presentation was 53.2(41-65) years old. The samples were taken from biopsy or surgical specimens and processed for electron microscopic examination by standard methods. Diameter of secretory granules(SG) and number of SG in a of cytoplasm were measured. Two cases out of 7 well differentiated MTCs were examined by the same manner to compare with. The average diameter of 3 poorly differentiated MTCs is 170.7 nm and that of 2 well differentiated is 262.2 nm. Number of granules of poorly differentiated MTCs is 1.31/a, while that of well differentiated is 2.78/a. The poorly differentiated MTC shows small SG and poorly differentiated cytoplasmic organelae, and free ribosomes and polyosomes are increased in their relatively narrow cytoplasm. While well differentiated MTCs disclose numerous large SG, well developed r-ER and Golgi apparatus in their wide cytoplasm. These features indicate that the MTC with poor prognosis have poorly differentiated C cell characteristics ultrastructurally. Therefore the designation poorly differentiated MTC is suitable for those cases.

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We have earlier developed a variant of counterflow isoeleophoresis on celluloseacetate membranes (ITP-ACM), which combines the high resolution of proteins with their very effective concentration from highly diluted solutions. The ITP-ACM was applied to the detection of monoclonal L-Chains (Bence-Jones protein, BJP) in the urine of patients with B-cell neoplasia. Electrophoretic homogeneity of the fraction, revealed with anti-L\(_\alpha\) or anti-L\(_\kappa\) was used as the main Feature of BJP. Among 58 patients with B-cell neoplasia (excluding multiple myeloma) 33 were found to be BJP-positive, including chronic lymphocytic leukemias, malignant lymphomas and lymphosarcomas. Several patients were kept under observation during chemotherapy. BJP level was affected by treatment but the marker could be sharply indentified during the remission periods. The sharp shift to a increasing relation was noted.

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4253 **FREE MONOCLONAL URINARY LIGHT CHAINS /BENCE JONES PROTEINS/ AS BIOLOGIC MARKERS OF THE PLASMA CELL/LYMPHOCYTIC NEPLASMS S.D.Ottd, M.O. National Institute of Oncology, Budapest, Hungary**

Bence Jones proteins are well known biologic tumour markers. The malignant lymphoproliferative diseases characterized by monoclonal immuno-globulin production and uncontrolled cell proliferation show Bence Jones proteinuria, in about two-thirds of the cases. The amount of excreted monoclonal free light chains depends on several factors; with proper reservations it can be regarded as a crucial index of the progression or regression of the malignant process. The appearance of urinary excretion of Bence Jones protein may indicate malignant transformation. It can also be used in early detection of these diseases. Excretion of this protein sometimes precedes the appearance of serum M-component and any clinical symptoms. Simple and rapid methods are proposed for the identification of Bence Jones proteins in unconcentrated urine.
**4254** TUMOUR MARKERS IN THE CLINICAL DIAGNOSIS AND MANAGEMENT OF ONCODERVELOPMENTAL STAGES. H.E. Nieburgs, MD. Department of Pathology, Mount Sinai Medical Center, One Gustave L. Levy Place, New York NY 10028, USA.

Abnormal cellular structures appear as tumor markers in a variety of malignant and potentially malignant neoplastic conditions. Systemic manifestations of occult and early tumorigenesis occur in nuclei of epithelial cells and lymphocytes as a result of a mitotic prophase arrest that remains unchanged during cell differentiation. In benign-appearing histologic alterations such as uterine cervix dysplasia, follicular thyroid adenomas, atrophic gastritis, ulcerative colitis, polyps, soft tissue tumors and others, the malignant neoplastic potential, when present, may be identified as a result of abnormal cell kinetics associated with the oncogenic effect on tissue cells. The complexity in delineating prognosis of tumor response to chemotherapy includes the assessment of kinetics of cellular proliferation. Most therapeutic compounds affect those neoplasms in which the largest number of cells enter the S phase of the cycle and undergo mitosis. Therefore, tumors with a majority of nonproliferating cells escape the effect of most drugs, contrary to tumors that consist predominantly of cells in the G2 phase. Thus, identification of phase-related cell morphology permits assessment of tumor responsiveness to chemotherapy. In drug-induced and acquired immune deficiencies, cellular markers consist of cleaved or lobulated nuclei often with abnormal clumps of chromatin. These changes are of diagnostic value in the identification of patients with either viral-related or therapy-related immune suppression. In summary, cell morphologic markers appear to reflect the biology of human oncogenesis and of immune dysfunction, and offer a useful aid for the detection, diagnosis and prognosis of neoplastic diseases. /KARYOMORPHOLOGY/ /CELL KINETICS /CANCER DETECTION /TUMOR RESPONSIVENESS/ /IMMUNE DYSFUNCTION/.

**4255** MELANOMA MONITORING: APPLICATION OF MONOCLONAL ANTI-MELANOMA ANTIGEN IN VIVU. S. Matzke, and W. Pijlenga*, Inst. of Nuclear Medicine, German Cancer Research Center*, and Dermatol. Clinic, Univ. Heidelberg**, Heidelberg, F.R.G.

Monitoring of melanoma with (radiolabeled) monoclonal antibodies has two main goals, namely localization of the unknown tumor and evaluation of the amount of antibody which, within therapeutic trials, will actually accumulate in the individual tumor node. However, since antigen expression in the individual tumor may be diverse, the antigen pattern has to be defined beforehand by immunohistology, which limits the practical applicability of immunocintigraphy. Above that, there is examples to show that histologic evidence of high antigen density in a given tumor is not necessarily indicative of good antibody localization: In some antigen systems, the anchorage of the molecule to the cell membrane is not stable. As a consequence, immune complex shedding may counteract antibody accumulation. Alternatively, internalization, degradation and label excretion may take place, again counteracting local accumulation of the antibody. From that it is postulated that with new anti-tumor antibodies the biology of the respective antigen has to be characterized prior to entering broader clinical studies.

**4256** CA 125 DETERMINATIONS IN OVARIAN CANCER PATIENTS AND ITS IMPLICATIONS FOR TREATMENT. A. van Dalen, J. Foxier and W.N. Eastman. Bleuland Hospital, Gouda, The Netherlands.

51 Patients with cystadenocarcinoma of the ovary were followed by CA 125 determinations for a maximum of 3.5 years. Most of the patients presented were diagnosed with stages 111 or IV. The initial stage was: 11 stage 1, 6 stage II, 21 stage III and 6 stage IV. The treatment was, in most cases, a debulking operation followed by preferentially combined chemotherapy with CHAP 5 courses for the stage II-IV patients. In our opinion the CA 125 pattern reflects the effectiveness of the therapy. After a debulking operation and during CHAP treatment the CA 125 levels should fall to the detection limit of the determination, i.e. under 7 U/ml. This means far under the reference level of normal females, i.e. 35 U/ml or 65 U/ml. When there is no sharp decline of the CA 125 values following treatment and the level of CA 125 remains above 7 U/ml, the second-look operation always reveals some evidence of metastatic disease. Prolonged treatment of patients with microscopic disease will only have a short term effect and recurrent disease is demonstrated with a delay not exceeding 6 months.

The point of performing second-look operations in the presence of an elevated CA 125 level is in the light of these findings debatable. For the same reason is the continuation of an intensive chemotherapeutic regime (eg. CHAP 5), accompanied by its unpleasant side effects, in the presence of a constantly elevated CA 125 level, also questionable.

In the field of clinical oncology several antigens present on tumors cells obtained from cancer patients open new possibilities for cancer diagnosis, of which Immunopathology, immunoserology and immuno localization are the most important ones. Using the hybrideoma technology these antibodies can now be produced in large quantities with much higher specificity than only one or two antigenic determinants, or epitopes, are recognized.

In the field of clinical oncology several antibodies that recognize such tumor associated antigens are available, of which, OV-TL 3 and OC 125, both raised against overin cancer cells, and 115D8 recognizing a differentiation antigen present on breast cancer and in some ovarian cancers, are the most promising. Alone and in combination, the so-called panels, monoclonal antibodies against these cell surface molecules identify unequivocally the majority of ovarian and breast cancer cells both within the tissue and, when antigen shedding occurs, in the blood. The antibodies have been tested by us for their potential in immunopathology - i.e. differential diagnosis, subclassification, tumor staging (detection of microfocal of malignant cells in effusions) and as a prognostic factor - as well as for the potential in immunology - i.e., (early)diagnosis, tumor identification, staging, treatment evaluation and early detection of recurrence. The antibodies used comprise CA 125, OV-TL 3, CA 15.3, CA 19.9, SSC, CE1, FXI, HCM and B1HPL. It will be demonstrated that these monoclonal-antbody-based tumor markers will facilitate substantially the management of patients with gynecologic malignancies.

RECENT PROBLEMS IN SURGERY FOR CANCER OF THE ESOPHAGUS

AKIYAMA, H. (Toranomon Hospital, Tokyo, Japan)

In the surgical treatment for cancer of the esophagus, both resection and reconstruction are technically closely related to each other. Possible multifocal lesions or "field carcinogenesis" are carefully considered. Among 613 cases with esophageal cancer, resection was carried out on 393 cases with resectability rate of 64.9% and operative mortality rate of 1.8%. Comparison of survival rates between groups with and without lymph node metastases in the mediastinal and abdominal region was made. Five year survival rate in the group with negative mediastinal nodes with positive abdominal nodes is 34.5%. However, the 5-year survival rate in the group with positive mediastinal nodes but with negative abdominal nodes suddenly drops down to 10.5%. This fact reveals that the finding of positive mediastinal nodes is more of an unfavorable factor in obtaining long term survival than that of positive abdominal nodes. This may be because mediastinal dissection is anatomically more complicated than epigastric dissection. Of areas in the mediastinum, the upper mediastinum is the most important part to dissect. Lymph nodes along the brachiocephalic artery, both right and left recurrent laryngeal nerves, and those in the area between the neck and thorax are important. Bilateral neck dissection is carried out as well as mediastinal and abdominal dissections including celiac and left gastric area.
SURGERY OF THYMIC TUMORS.

From 1954 to 1985, 142 patients with the epithelial tumor of thymus (thymoma) were treated. Myasthenia gravis (86 cases) and pure red cell aplasia (13 cases) were main associated diseases. Resection of tumor in patients without myasthenia and extended thymectomy in patients with myasthenia, followed by radiotherapy were our procedure of treatment. Chemotherapy was done in the recurrent cases. Ten years survival rate was 78% in 113 patients undergoing total resection and 14% in 29 patients undergoing non-curative op.(p<0.01). Clinical stages that we have advocated are as follows: stage I - no capsular invasion in gross and microscopically, stage II - invasion into the surrounding fatty tissue or mediastinal pleura or microscopic invasion into the capsule, stage III - invasion into the neighboring tissues such as pericardium, great vessel or lung, and stage IV - dissemination or distant metastases. Ten years survival rates were 80% in stage I (45 cases), 60% in stage II (34), 62% in stage III (48) and 40% in stage IV (15). The survival rate in stage IV was significantly (p<0.01) lower than those in I or II diseases. The survival rate in patients with or without myasthenia was not significant. Cause of death were mainly due to recurrence of tumor or myasthenia crisis. Four recent patients with invasive thymoma underwent extended resection including VES, it was replaced by Gore-tex graft with ring. The biological character of thymoma will be discussed.

THE TREATMENT OF MEDIASTINAL TUMORS.
On-ling Huang, Jie-an Lu, Yong-sheng Chou, Teh-kuei Sun, Cheng-hai Rong, Ka-shi Koo.
Shanghai Chest Hospital, Shanghai, PRC.

Mediastinal tumors are common diseases in the chest, we have collected 1635 cases in a period of 28 years from 1957 to the end of 1985. Thymic tumor was the first common variety in our clinic, a total of 402 patients had been operated. The most common tumor was bronchogenic carcinoma in origin, Teratomatous growths were the third frequent category.

The treatment of mediastinal tumors is mainly surgical. However in the presence of malignant degeneration removal of tumor would be difficult because the extensive invasion of the surrounding vital organs. Among then the superior vena cava dissection was hardly be performed without injury of the vessel. We usually open the pericardial cavity to facilitate exposure of the relationship between the tumor and the poorly identified vessel. Intravascular intubation of the vessel prior to direct resection of the vena cava was seldomly necessary.

There were 56 cases of big tumors more than 10 cm in diameter been resected successfully. We conclude that the suitable incision is very significant. For thymic tumors no matter what the nature they are, using internal splinitic incision is the more convenient. Some idea is indicated in malignant teratomas. For thyroid tumor we preferred external transverse carotid incision, most of them could be removed uneventfully by blunt dissection by fingers and malleus by the continuous traction.

Most of the cystic tumors were benign in nature, sharp dissection will be successful.

There is no satisfactory explanation about the high incidence of thymic tumor in our series.
SEGMENTAL AND ATYPICAL RESECTION OF PRIMARY METASTASIS IS PRESENT.

Carcinomas invading chest wall. Extrapleural or complete resection offers a significant chance of long term survival in patients with lung carcinomas invading chest wall. Extraleural or enbloc chest wall resection can be performed with a low operative mortality and an expected 5 year survival of 50% or more when no lymph node metastasis is present.

176 Lung cancer

RESULTS OF SURGICAL TREATMENT IN CARCINOMA OF THE LUNG INVADING CHEST WALL

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Carcinomas of the lung invading the chest wall can frequently be treated effectively by combined pulmonary and chest wall resection. Exclusive of superior sulcus tumors, 135 patients were treated surgically from 1974 to 1984. The male to female ratio was 2 to 1. The ages ranged from 33 to 88 years. The histologic diagnosis was epidermoid carcinoma in 87%. Complete resection of the tumor was possible in 87 patients. At thoracotomy, mediastinal lymph node dissection was also performed when resection was possible. The 5 year survival following complete resection was 40%. Factors influencing survival were the completeness of the resection, the extent of chest wall involvement and the presence or absence of lymphatic metastases. The median survival of patients with incomplete or no resection was 9 months despite intraoperative or external radiation therapy with no patient surviving beyond 3 years. The 5 year survival following complete resection in patients with TNM0 disease was 56%. Complete resection offers a significant chance for long term survival in patients with lung carcinomas invading chest wall. Extraleural or enbloc chest wall resection can be performed with a low operative mortality and an expected 5 year survival of 50% or more when no lymph node metastasis is present.

SURGICAL, RADIOLOGICAL AND ONCOLOGICAL PROBLEMS IN OPERATIONS OF PULMONARY CANCER WITH RESECTION AND PLASTICS OF THE TRACHEA AND MAIN BRONCHI. A.S. Simonyi, Gt. Inst. of Onkology, Budak, Acad., Sztin. Elkorom. 49 patients with surgical treatment of pulmonary cancer with resection and plastics of the main bronchi and trachea are presented. 21 pneumonectomies have been done—11 different variations of tracheal plasties and 28 truncations with plastics of the main bronchi. A circular resection of the trachea and the tracheal section has been performed on 8 patients with right pneumonectomy. Problems are treated in connection with the surgical technique and the early post-operative period. In an oncological aspect are examined questions about indications for this kind of operations, radiotherapy etc. A high early post-operative death rate is estimated by patients with resection and plastics of the tracheal bifurcation (4 of 8 patients) and its causes are explained. The post-operative mortality of patients with plastics of the main bronchi is 0%. A 5-year survival is noted in 16.3% of the patients with pneumonectomy and tracheal plastics and 21.4% of the patients with lobectomy and bronchial plastics.

THERAPY OF PANCOAST'S TUMOR

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Seventy-seven patients with Pancoast's tumor treated at the University of Maryland Hospital since 1955 were reviewed. There were 37 squamous cell carcinomas, 13 undifferentiated, 10 adenocarcinomas, 6 mixed adenocarcinoma, 4 alveolar cell and 12 undetermined. Thirty patients received irradiation therapy with 72 survival at 3 years, 19 patients underwent preoperative irradiation followed by en bloc resection of chest wall with 232 survival at 3 years, 5 patients underwent en bloc resection, with 802 survival at 3 years, and 21 patients underwent operation followed by irradiation with 71 survival at 3 years. Retrospective staging of 42 patients undergoing operation indicated that 23 (50%) were inoperable. This review confirms the importance of preoperative assessment of Pancoast's tumor. Extensive local involvement of the vertebral bodies, brachial plexus, subclavian artery, mediastinal nodes, and distant metastases constitute contraindications to surgical intervention. Early Pancoast's tumor with no rib involvement or brachial plexus can be treated by surgery alone with significant survival.
In the 95 cases of colorectal cancer analysed in this study the mean (or the median) plasminogen activator (mostly urokinase) secretion rate in short-term organ culture of metastatic tumors was only 6% of the rate shown by the primary tumors. In the 26 gastric cancers examined, the corresponding figure was only 3%. The difference in the amounts of extractable activator, however, was less significant. The difference in the secretion rates appears to be a stable phenotypic feature of metastatic tumors. In addition to urokinase of Mr 55,000, all culture fluids contain variable amounts of enzymes ranging in size from 240,000 to 1 million, which hydrolyse the urokinase substrate Spectrozyme-UK, cross-react with urokinase in ELISA tests but do not activate plasminogen, even after activation by plasmin which greatly increases their ability to hydrolyse the synthetic substrate. The difference in the rate of uokinase (55,000) secretion between primary and metastatic tumors is not due to differential amounts of Mr 55,000 pro-urokinase, nor could it be ascribed to different amounts of activation inhibitor. Correlation of the activator data with the clinical course of the disease disclosed the following trends: 1. Patients having primary colon tumors with low secretion rates, i.e. with rates in the range of the metastatic tumors, have shorter disease-free intervals following surgery for removal of the primary, than those with high secretion rates. 2. Patients with colorectal tumors containing high amounts of extractable (cell-associated) plasminogen activator have a shorter disease-free interval than those with lower values of this parameter. These observations could have prognostic value, and appear at present to define a "metastatic phenotype", characterised by the accumulation of cellular activator coupled with an inability to secrete the same. (Supported in part by Grants from the American Cancer Soc. and the National Cancer Institute.)

**M-36: PLASMINOGEN ACTIVATORS IN CANCER**

**4270** PLASMINOGEN ACTIVATORS IN HUMAN COLORECTAL AND GASTRIC CANCER. G. Markus and S. E. Harvey, Roswell Park Memorial Inst., NY State Dept. of Health, Buffalo, NY 14263, USA

In the 95 cases of colorectal cancer analysed in this study the mean (or the median) plasminogen activator (mostly urokinase) secretion rate in short-term organ culture of metastatic tumors was only 6% of the rate shown by the primary tumors. In the 26 gastric cancers examined, the corresponding figure was only 3%. The difference in the amounts of extractable activator, however, was less significant. The difference in the secretion rates appears to be a stable phenotypic feature of metastatic tumors. In addition to urokinase of Mr 55,000, all culture fluids contain variable amounts of enzymes ranging in size from 240,000 to 1 million, which hydrolyse the urokinase substrate Spectrozyme-UK, cross-react with urokinase in ELISA tests but do not activate plasminogen, even after activation by plasmin which greatly increases their ability to hydrolyse the synthetic substrate. The difference in the rate of uokinase (55,000) secretion between primary and metastatic tumors is not due to differential amounts of Mr 55,000 pro-urokinase, nor could it be ascribed to different amounts of activation inhibitor. Correlation of the activator data with the clinical course of the disease disclosed the following trends: 1. Patients having primary colon tumors with low secretion rates, i.e. with rates in the range of the metastatic tumors, have shorter disease-free intervals following surgery for removal of the primary, than those with high secretion rates. 2. Patients with colorectal tumors containing high amounts of extractable (cell-associated) plasminogen activator have a shorter disease-free interval than those with lower values of this parameter. These observations could have prognostic value, and appear at present to define a "metastatic phenotype", characterised by the accumulation of cellular activator coupled with an inability to secrete the same. (Supported in part by Grants from the American Cancer Soc. and the National Cancer Institute.)

**4272** ROLE OF FIBRINOLYSIS IN THE DEVELOPMENT OF PULMONARY METASTASIS IN X-IRRADIATED AND NON-IRRADIATED NUDE MICE. Kenzo Tanaka and Hideki Hirata, Department of Pathology, Faculty of Medicine, Kyushu University, Fukuoka, Japan

When human tumor cells were injected into the tail vein of male adult nude mice 5 days after 3 Gy whole-body X-irradiation, the incidence of pulmonary metastasis was more frequent in the irradiated mice than in the nonirradiated controls. Platelet aggregation and fibrin deposition around the tumor cells were present in the capillaries of the lung in the irradiated mice while prominent neutrophilic infiltration was noted around the tumor cells in the nonirradiated controls. Fibrinolytic activity of the lung was decreased in the irradiated mice, while serum fibrinogen level was increased after irradiation. Increase in serum fibrinogen levels and decrease in fibrinolytic activity of the lung, as a target organ, together with decreased infiltration of neutrophils, may be related to the trapping and lodgement of tumor cells when nude mice are subjected to irradiation. Next, effect of whole body X-irradiation on the spontaneous pulmonary metastasis of human cancer cells transplanted into nude mice was investigated. Human cancer cells were inoculated into footpads of nude mice following 3 Gy whole body X-irradiation. The incidence of pulmonary metastasis was increased in the irradiated mice. In addition to the suppressive effect of cytotoxicity of the splenocytes by whole body X-irradiation, thrombus formation around the arrested cancer cells in the lung capillaries or capillaries of the irradiated mice may provide a favorable condition for metastasis formation.

**4273** INVOLVEMENT OF PLASMINOGEN ACTIVATOR IN TUMOR METASTASIS. L. Usowskia, Rockefeller University, New York, USA, Emi Wilson, Cape Town Medical School, South Africa

A human carcinoma—Hep3 grows and metastasizes efficiently in 2 hosts; the chick embryo and the nude mouse. This tumor produces high levels of plasminogen activator (PA) of the urokinase type (uPA). The kinetics of growth and metastasis of this tumor is quantitatively predictable enabling the detection of even small modulating effects. We tested the effect of antibodies which inhibit the catalytic activity of uPA on tumor invasion and metastasis in 2 different hosts. In the chick embryo, the antibodies did not interfere with the primary growth but strongly inhibited metastasis. In the nude mouse, the antibodies reduced local invasiveness and diminished metastasis to the regional lymph nodes. Using the chick embryo system we identified the steps in malignant dissemination which require the expression of catalytically active uPA.
SURFACE RECEPTOR FOR UROKINASE PLASMINOGEN ACTIVATOR

In many human tumors and tumor cells, injection of normal fibroblastic cells with different metastatic capacity induce the appearance of increased amount of t-PA in the plasma of the hosts. The most striking difference between metastatic and non metastatic cells in that non-metastasizing cell lines induce also the gradual appearance of large levels of u-PA in the recipient mice, while are inoculated with the highly metastasizing cell line show an evidence of circulating u-PA. Similar experiments performed in "murine" mice injected with human tumorogenic cells, a fibrosarcoma cell line producing mainly u-PA and melanoma cells producing only t-PA type activators, showed that, early after the injection of tumorogenic cells and prior to the detection of a specific tumor, the human form of u-PA or t-PA could be detected in the circulation of the recipient mice. In this experimental system an unexpected finding was the detection of immunity in the mice injected with melanoma cells. Homologous will be discussed in relationship with the data obtained in human patients.

A SURFACE RECEPTOR FOR UROKINASE PLASMINOGEN ACTIVATOR

Plasminogen activator levels are increased in a large number of human tumors and tumor cells. In many cases these levels are correlated with the metastatic potential of the tumor. Thus, urokinase, a 48,000 dalton protein whose gene has been cloned, sequenced and mapped onto human chromosome 10 in our laboratory is present in normal and cancer cells. u-PA levels are profoundly inhibited in a variety of neoplastic cells. We have found that human monocytes and several human tumor cell lines possess a specific receptor for urokinase. The receptor has high affinity (10^6 M), end is specific. Bound urokinase is not internalized, rather it stays active at the cell surface.

The studies on the role of plasminogen activators (PA) in cancer are complicated by the fact that there exist two types of PA, urokinase-type (u-PA) and tissue-type (t-PA), which are products of different genes and enzymes of which is differently regulated. The u-PA is secreted from cells as an inactive proenzyme (pro-u-PA); the u-PA activity is regulated by several inhibitors; t-PA activity is regulated by inhibitors. The biological role of t-PA, which is at present unknown, is due to the fact that, in the intact organism, t-PA and u-PA in the intact organism show a different distribution of the two types of activator and point to u-PA being involved in tissue destruction and/or release of cells in cancer tissue. u-PA is also involved in the regulation of the number of urokinase binding sites may also concur to regulate cell migration.
**M-36: PLASMINOGEN ACTIVATORS IN CANCER**

4278 FIBRONECTIN AND ITS PROTEOLYSIS IN MALIGNANT TRANSFORMATION. A. Vaheri, E-M. Salonen, J. Pilloinen and O. Saksela
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Fibronectin (FN) and laminin (LM), pericellular matrix glycoproteins mediating cell surface-matrix interactions, conceivably represent a major target of plasminogen activated by the activators u-PA and t-PA. An example of the importance of proteinase inhibition is our finding on the therapeutic effect of aprotinin in promoting epithelialization of corneal ulcers, a process in which the proteinase-sensitive glycoprotein, FN is involved. Pericellular proteolysis appears to be regulated at several levels: activation of pro-PA and production of PA-inhibitors (PAI) and of more wide spectrum serine proteinase inhibitors such as alpha-2-macroglobulin. We report recent results that may explain how cells can produce active proteinases and yet retain cell surface integrity and interactions. We found 1) that plasminogen and (pro)-PA bind to immobilized FN and to HM. These interactions may operate in directional proteolysis, localising plasminogen and PA to degrade fibronectin-containing matrix. 2) A novel stable Mr 36 000 receptor for FN in human fibroblasts and sarcoma cells. 3) In analysis of substratum-attached contact areas (isolated using saponin) of cultured human sarcoma cells and fibroblasts we found u-PA in discreet contact sites, PAI uniformly under the cells except in stria-like areas and FN in cell-substratum contacts and in the matrix. PAI was found to be a major component in the contact areas. 4) PAI and p-amidobenzamidine inhibited binding of (pro)-t-PA to FN, suggesting that the active site in t-PA is involved in its interaction with FN.

**M-37: THERAPEUTIC STRATEGY OF ADVANCED OVARIAN CANCER**

4279 RESERVED
E.Wiltshaw, London, UK

4280 COMPARISON OF TREATMENT RESULTS WITH CAP AND CEP REGIMENS FOR PATIENTS WITH OVARIAN CANCER (FIGO STAGES III AND IV) IN PROSPECTIVE RANDOMISED STUDY
Z. Hernadi, L.G. Lanno, B. Juhász
Clinic of Obstet. and Gynec., Medical University of Debrecen, Hungary

Thirty two patients with advanced ovarian carcinoma were randomised to primary chemotherapy with cyclophosphamide and cisplatin plus doxorubicin (Adriamablastina) or 4'-enidoxorubicin (Farmorubicin). The distribution of patients in the two investigational arms were identical in respect of the size of the greatest residual tumor, clinical stage, histological type, grade of differentiation, performance status and the number of treatment cycles. The response was evaluated on the basis of tumor measurements with ultrasound and/or on the basis of finding during second look operations. The CAP regimen produced a 43,7 % complete response rate and a 12,5 % partial response rate. The CEP regimen produced a 50,0 % complete response rate and 18,7 % partial response rate. The change of performance status during treatment and the toxic side effects did not show any significant difference among treatment groups. In the CAP arm of treatment one case with transient supraventricular tachycardia is worth of mentioning. Our examinations suggest, that the CEP regimen is as effective as the CAP with a lower level of cardial toxicity.
CARBOPLATIN (CBP) - ADRIAMYCIN (CALCEIN) - CYCLOPHOSPHAMIDE (CFP)- CTX IN EPITHELIAL OVARIAN CANCER: P. Conte, S. Chiari, B. Brugnoni, A. Falchini, G. Giaconia, F. Castini, A. Conci, A. Novelli, G. Righi, E. Persico, F. Mariani, F. Franzoni, B. Massa. Istituto Nazionale Ricerche Cliniche "Raffaele", Napoli, Italy. Recently untreated patients (pts) with advanced ovarian cancer were studied for tolerance and response to combination treatment with fixed doses of AM (45 mg/m²/day) and CTX (600 mg/m²) plus escalating doses of CBP. CBP was administered with or without hydration and forced diuresis. The first dose level (25 mg/m²) toxicity was acceptable while at CBP 300 mg/m² severe hematological toxicity was observed. CBP 200 mg/m² was given as lowest dose (VAC 300 mg/m²).

Between October 1984 and October 1985 23 patients suffered relapse after 6 treatment courses (2-28 months) and when possible continued therapy. The new therapy called "changing-scheme" combined as first part, vincristine/cyclophosphamide as second one and high dose methotrexate (HD-MTX) followed by a leucovorin rescue as third one, with monthly application intervals between the 3 successive parts. The two other "uragogies to which the women were randomized consisted of Adriamycin/cyclophosphamide (A/C) or Adriamycin/cisplatin (A/P). No survival data of patients under the changing-scheme and under A/C or A/P regimens were available. In the patients under the changing-scheme and under A/C or A/P regimens survival rates of 3 different chemotherapy were 89% for the changing-scheme, 78% for the A/C regimen and 63% for A/P regimens. In particular, the subgroup of women with highly differentiated tumors and of women without ascites seem to profit from the new therapy protocol.
CHEMOTHERAPY WITH CIS PLATINUM IN THE TREATMENT OF PROGRESSIVE OR RECIDIVOUS OVARIAN CARCINOMAS

W. Kräfft, A. Schrinner, H. Schöning, G. Breckmann
(Erfurt); H. Nöschel, Schenke (Jena); J. Schlesser
(K.-H.-Stadt); H. Lotzko, P. Richter (Dresden);
A. Banschak, Kral (Berlin-Spandau);
H. Gartler, J. Muller, Stier (Berlin-Zirkular);
G. Horack and J. Vogel (Berlin, Klinikum-Buch)
by GDR Gynecological Antitumour Chemotherapy
Group

Since May 1984 74 patients with progressive or recidivous ovarian carcinomas were treated in the framework of a prospective-random study which were carried out in several medical centres of the GDR. 32 patients got a DDP-monotherapy (200 mg/m²), 30 patients were treated with a combined chemotherapy (CP): 500 mg/m², DDP 70 mg/m², ADM 30 mg/m²).

All patients underwent at least two treatments, but on an average 3,6 courses of treatment. A remission of the tumour occurs in 20 % of DDP-monotherapy and in 20 % of combined chemotherapy in 64 evaluable cases, whereby complete remissions could be proved only in 20 % of the responders in both groups. Peritoneal metastases and ascites respectively as well as local recurrences could be influenced best in these two groups.

Side effects were more distinctive during combined chemotherapy than during DDP-monotherapy. The combined chemotherapy is not superior to the DDP-monotherapy in progressive or recidivous ovarian carcinomas.

4286 CHRONOTHERAPY OF OVARIAN CANCER AFFECTS TUMOR RESPONSE RATE AND PATIENT SURVIVAL

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Drug sequence, the span between drugs, and time of day of administration may each be determinants of drug toxicity and efficacy. 58 women suffering from bulky stage III (45) or stage IV (13) ovarian cancer were treated with the same doses of doxorubicin (D) and cisplatin (C) (60 mg/m²) monthly for 9 mos in one of 4 schedules. If disease was present at second look or occurred, further cytotoxic/cisplatin alternating monthly with cytotoxic/5FU treatment was given for at least 18 mos. 15 patients were treated with unspecified drug sequence or interval between drugs and at any time of day (random). All remaining women received D first, followed 12 hours later by C. 17 were randomized to receive D at 6 am (A), 20 received D at 6 pm (B), and 9 received either A or B initially and were then crossed over monthly (A/B).

Schedules N 100 Resp Median CR(mo) Median Survival(mo)
Random 15 40 6 8
A 17 100 22.5 32
B 20 100 25 34
A/B 9 100 69 65* (Not reached)

Response rates for timed regimes were twice that induced by unsupervised treatment timing. Schedule B was much more toxic than schedule A (Science 229:73-75, 1985). Overall 5-year survival for timed treatment is 50%, whereas all patients treated at random times were dead within 21 years. 32% of patients at risk treated with time-specified regimes are currently disease-free 3 years after the initiation of chemotherapy. Survival and disease-free survival are longest for A/B. Drug sequence, interval between drugs, and the time of day drugs are given are each of importance in devising optimally effective chemotherapy regimens. Each of these variables can now be very simply stipulated using programmable implantable, wearable or bedside drug delivery devices.
HYPERTHERMIA IN THE LOWER ABDOMEN AND PELVIS USING DIFFERENT HEATING TECHNIQUES. Thaddeus V. Samulski, Stavros D. Prionas, Eric R. Lee, and Peter Fassenden. Department of Radiology, Stanford University School of Medicine, Stanford, California, U.S.A. 94305.

A variety of heating techniques, both invasive and non-invasive, have been clinically implemented in order to administer local/regional adjuvant hyperthermia to deep seated tumors. However, heating deep seated human malignancies remains a difficult technical challenge. In the time period from 1981 to this date, three deep-heating approaches for the pelvis and lower abdomen have been clinically evaluated at the Stanford University Medical Center. These include electromagnetic (EM) heating with an annular phased array (AA), ultrasonic (US) heating with a multi-transducer isospherical US device (IUD), and RF heating using interstitial electrodes. The AA operates in the frequency range of 60-100 MHz, delivering EM power on a regional basis with a limited capability to preferentially localize the energy distribution. The IUD operates at 350 kHz and, by means of overlapping six independent US beams, is capable of local energy deposition in volumes of 10 to 50 cm³ at depths of 12 cm. The interstitial system also provides local heating utilizing RF currents at 5 kHz with the size and shape of the local current field determined by the number and conductive lengths of the interstitial electrodes. Fifty patients have been heated with these devices using invasive thermometry to both control and evaluate the intratumor temperature distributions. A review of technical considerations and clinical experience associated with these three deep heating approaches will be presented. This work was supported in part by NCI Grants CA 05838, CA 34680, and NCI Contract CM 17480.


158 patients with malignancies of the head and neck area have been treated by hyperthermia and radiation in our clinic since 1972. All had locally advanced tumors or tumors with radio-resistant histology or both. Among the variety of more common histological tissue-types there were 16 adenoid-cystic carcinomas. The authors report their experience with different modes of applying the high-frequency hyperthermia. Clinical treatment results, particularly those of adenoid-cystic carcinomas and special follow-up findings are demonstrated.
Hyperthermia as a new cancer treatment modality combined with radiotherapy and/or chemotherapy has been well established based on the results of clinical trials in superficial tumors in which their heating and temperature measurement were easily feasible. But the difficulty of heating the tumors deep in the body prevents its wide use in cancer treatments. We have developed an RF capacitive-type heating equipment named Thermotron RF8 which can be used in superficial as well as deep-seated tumors with a very low systemic heating. Radiofrequency current at 8MHz is applied to the region with tumors by a pair of electrodes with water-cooled boluses to avoid overheating of subcutaneous fat tissue and edge effects. A well-balanced RF circuit permits good penetration of the current through a human body resulting in heating the tumors in the current. Selective heating of the tumors is obtained by the difference in blood flow between normal and tumor tissues. The temperatures in the tumor and surrounding normal tissues are continuously monitored by non-perturbed thermocouples inserted in the tissues. The temperature at any point can be maintained as indicated by computer-operated RF output control. The heating patterns in phantoms and pigs have been confirmed in clinical trials in cancers in the chest, abdomen and pelvis. The equipments have been widely used in many cancer centers in Japan for hyperthermia combined with radiotherapy or chemotherapy in patients with refractory cancers.

From our multimodal treatment for the non-resectable malignant obstructive jaundice the results and merit of these combinations were discussed in this paper. Among our 75 patients who have been treated by multimodal intervention 35 patients with gallbladder carcinoma and cholangiocarcinoma were selected. The nine patients were divided into three groups. The first nine patients were treated by biliary endoprosthesis, radiation and hyperthermia. The second nine patients were treated by biliary endoprosthesis alone. The third nine patients were treated by external biliary drainage and radiation. And also seven patients who were treated by external biliary drainage were available as a control. The instruments used were as follows: 1, Biliary stent(DO:4mm,ID:3mm) was used. 2, External hyperthermia(8MHz,RF,20cm electrode) and intracavitary hyperthermia(2450MHz,4cm electrode) were utilized. 3, Radiation(ceobolt, two opposed external irradiation between 30 - 60Gy) was performed. Results: 1, The group 1 showed the best crude survival period compared to the remaining two groups and also showed minimum early death after this intervention. There were no big differences between the group 1 and group 3. Conclusions: Multimodal treatment including biliary endoprosthesis, radiation and hyperthermia showed the best survival period and this combined treatment will become a standard treatment course for the non-resectable malignant obstructive jaundice.

In addition to the case of improper local heating by only external hyperthermia additional or simultaneous intracavitary heating showed a good heat distribution.

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C.E.Lindholm, Malmö, Sweden
Accurate temperature-time profile measurements at a number of points in the tumor and in normal tissues are essential to demonstrate the effectiveness and safety of hyperthermia treatments. Metallic thermocouples and the non-metallic BSD and Clinitherm probes have found the most widespread use in the USA for patient monitoring. Other thermistors and fiberoptic Luxtron probes have been used only to a limited extent. To achieve accuracy better than ± 0.2°C, it is necessary to select the most appropriate probes, maintain accurate calibrations and to follow certain precautions in order to minimize errors due to PM or US perturbations and other artifacts. Since 1983, the Hyperthermia Physics Center, under contract with the NCI has established a National Hyperthermia Quality Assurance Program and participated in the evaluation of thermometry as applicable to hyperthermia treatments. This paper is a result of the Quality Assurance tests and the collective experiences of this center. It should serve as a guide to newer entrants in the field as to the type of thermometers available, calibrations required, and methods to minimize perturbations.

* P. N. Shrivastava, Presenter

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MANAGEMENT OF CANCER PAIN: IMPORTANCE OF THE PROBLEM
John J. Bonica, MD, DSc, FFAACS, University of Washington
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This presentation will be an introduction to the panel on the management of cancer pain—an issue which remains one of the most important and pressing problems of modern society in general and the field of oncology and the health care system of many countries in particular. This importance stems from the following considerations: a) annually cancer pain afflicts some 10 million patients worldwide; b) although when properly used, drugs and other therapeutic modalities currently available are effective in relieving the pain of most cancer patients, they are often inadequately applied, and; c) consequently many patients spend their last weeks and months of life in great discomfort, suffering and disability which precludes a quality of life that is vital to them. A number of studies have revealed that pain is the initial symptom in 30-45% of patients with bone metastasis and is present in 70-85% of patients with advanced cancer.

This presentation will include a brief overview of: a) prevalence of pain in cancer patients based on data contained in 50 reports published in 15 countries throughout the world and includes prevalence of pain with specific advanced cancers; b) the physiologic and psychologic effects of cancer pain; c) the current status of therapy and reasons for existing deficiencies, and; d) suggestions for improvement of the care of cancer patients with pain in the future.

CANCER PAIN SYNDROMES. K.M. Foley, Dept. of Neurology, Memorial Sloan-Kettering Cancer Center, New York, N.Y., U.S.A.

Cancer pain has been classified according to a series of common pain syndromes and their pathophysiologic mechanisms. The pain syndromes that commonly occur in patients with cancer have been divided into three major categories. The first and the most important cause of pain in patients with cancer is that associated with direct tumor involvement. This accounts for 65-75% of pain problems surveyed in a cancer population. Metastatic bone disease, nerve compression or infiltration and hollow viscous involvement are the most common causes of pain from direct tumor involvement. The second group of pain syndromes are those associated with cancer therapy. This group accounts for 20-25% of patients and includes pain that occurs in the course of or as a result of surgery, chemotherapy, or radiation therapy. The third category includes those pain syndromes unrelated to the cancer or the cancer therapy and consists of approximately 3% of a cancer patients with pain. The pathophysiologic mechanisms of those common pain syndromes are not well understood. It is thought that a series of neuropharmacologic and neurophysiologic changes occur in bone, soft tissue, lymphatics, blood vessels, nerve and viscera, activating and sensitizing nociceptors and mechanoreceptors by mechanical (tumor compression) or chemical (metastases in bone) stimuli. Acute intermittent and continuous pain results. Pain may also result from nerve injury following nerve section or chronic tumor infiltration or compression producing partial damage to axons and nerve membranes which then become extremely sensitive to any mechanical or chemical stimuli. Chronic, unremitting pain then results. These different physiologic mechanisms account in part for the differences in responses of various types of cancer pain to analgesic, neurosurgical, and anesthetic approaches.

LONG-TERM EPIDURAL MORPHINE IN HOME TREATMENT OF CANCER PAIN. D. Emsley-Terrin, J. Boross and J. Ármos, National Institute of Oncology, Budapest, Hungary

Since 1982 we have used continuous epidural morphine analgesia as the treatment for intolerable cancer pain. We analyze our results up to 1985. The causes of pain were: Pancoast syndrome [6/], metastasis in the supraclavicular region [9/], brachial tumour [1/], tumour of the scapula [2/], metastasis in the axilla [3/], gastric cancer [2/], pancreatic cancer [2/], bone metastasis [13/], retroperitoneal tumour [4/], bladder cancer [1/], rectal cancer [7/], uterus cancer [9/]. The introduction of the catheters was performed at the cervical level in 25, at the thoracic level in 3 and at the lumbar level in 31 cases, respectively.

The mean dose of the morphine was 5 mg/day at the beginning and 10 mg/day at the end of the treatment. The duration of the treatment was ranging from 7 to 521 days, 80 days on the average. The following, not serious complications have been seen: non-pyrogenic inflammation in the vertebral canal well responding to the injection of metisilone and to the displacement of the catheter.

COMMENTS ON THE MANAGEMENT OF CANCER PAIN. E. Caraceni, M. Zamboni, M. Mandelli, F. Guerini, and L. Peloso, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy

We have received some comments on our presentation. The main points of discussion were on the use of morphine and the dose. The main concern was that the dose used in the study was too low. We believe that the dose used was appropriate in most cases. However, in a few cases it was necessary to increase the dose in order to achieve adequate pain relief. We agree that the dose used in the study may not be adequate for all patients. Further studies are needed to determine the optimal dose of morphine for the management of cancer pain.
ANALGESIC SURGERY FOR MALIGNANT PAIN

E. Hitchcock

The management of malignant pain is considerably easier than dealing with pain due to benign disease. A major reason, of course, is that for a majority of cancer patients the short life expectancy reduces the risk of pain recurrence, another reason is that pain is most common in the terminal stages of cancer. A substantial number of patients, however, do have pain early in the course of the disease or following treatment and its continuance may be due more to iatrogenic causes than malignant invasion. Although then we can expect a high rate of pain cure in patients with malignancy we should always choose the procedure which is most likely to give long duration of pain relief. In making such choices we must be guided by three principles: i) procedures should not add to the patient's disabilities; ii) relief should be complete and long lasting; iii) analgesia should anticipate areas of pain extension. If analgesic surgery is to be done it is best done early. The success rate of any procedure to relieve pain varies inversely with the pain duration and it is unfortunate that patients are usually referred for surgery only after other procedures have failed. Peripheral neuroectomy, rhizotomy and cervical cordotomy should be within the competence of many surgeons but the more precise cord lesions, such as myelotomy and stereotactic procedures are best not attempted by the inexperienced. If no facilities or expertise are available then the simpler open procedure should be used and will generally be found to serve the patient well. It is the responsibility of all doctors who attend patients with cancer to be aware of the possible treatments and to be able to recommend, or counsel against, the more specialised procedures.

PAIN EVALUATION IN CANCER PATIENTS: A CRITICAL OVERVIEW.

M. Belchamp* and P.R. Band**, *University of Montreal, Montreal, Quebec, and **Cancer Control Agency of British Columbia, Vancouver, B.C. Canada.

How to evaluate chronic pain (CP), a common and important problem in cancer patients, remains a critical issue not only due to the subjective and multidimensional nature of pain per se but also because of the specific characteristics of CP. CP has an insidious onset, often involves many sites, and is frequently multicausal. Tools have been developed to attempt to quantify clinical CP, the most commonly used being the verbal and numerical rating scales (VRSS), the visual analogue scales (VAS), and the McGill Pain Questionnaire (MPQ). The scales are short, easy to administer and to analyze, but only measure pain intensity. In addition, the VRSS are assumed to be ordered scales although unequal differences between pain descriptors have been demonstrated and respondents may not be able to discriminate reliably between the points on the scales; the VRSS offers to the patient a restrictive choice of words that might not represent precisely his pain experience and are not sensitive to change specially for mild pain. VAS represent pain as a continuum and are sensitive to change but are difficult to comprehend particularly for sick and aged persons. The MPQ, which evaluates simultaneously the sensory, affective, and evaluative dimensions of pain, also presents problems; it is lengthy to administer; some words are not easily understandable; words within a given category are considered to be equidistant; the number of words in each category is unequal; the number of categories evaluating a given dimension are not taken into account when calculating the total pain rating index. In addition to discussing the difficulties specific to each instrument, suggestions for improving CP evaluation will be presented.

Michele Deschamps is the recipient of a National Health Research Development Program of Canada (NRHPD).

ROLE OF PERCUTANEOUS CERVICAL CORDOTOMY IN THE TREATMENT OF CANCER PAIN.

S. Schiaia and A.I. Schiaia, Inst. Anesthesiology and Intensive Care, Univ. of Verona, Sch. of Medicine, Verona, Italy

The authors deal with the results up to death of different groups of cancer patients under going unilateral or bilateral percutaneous cervical cordotomy /1000 cordotomies, operator S.I./ and stress the role of a well performed percutaneous cervical cordotomy in relation to the survival data and patient history of cancer pain, furthermore in relation to the lasting efficacy of this operation in abolishing incident pain /Intermittent, excruciating, shock-type neurogenic pain/. The authors demonstrate that the aura of failure and complications often associated with percutaneous cervical cordotomy is totally attributable to improper technical execution, but this should not detract from the central role of percutaneous cordotomy in a multimodality approach to cancer related pain.

TOTALLY IMPLANTABLE INTRATHecal CATHETERS (IC) FOR ANALGESIA IN CANCER PATIENTS (pts). A. Descorps Declercq1, L. Brassard1, C. Bégon1, J.M. Venneti2, D. Machover1, L. Schwarzenberg1, J.L. Missel2, and G. Mathé1. 1Department d'anesthesie UER K.Bicêtre & 5SMST & 4CIG (CNRS UA 04-1163), Hop. Paul-Brousse, Villejuif, France.

Prolongation of survival in pts with advanced cancer (AC) requires an ambulatory and painless condition. The implantation of IC is now routinely performed in out-pits in the operative room under local anesthesia. The IC (Polyurathane, 0.9mm diameter, Pharmacia) is inserted in the L3-L4 space and connected to a Port-a-cath (Pac) in the anterior chest wall; 5 cms are floating in the subdural space. IC were implanted in 16pts. Each AC with pain unresponsive to systemic Narcotic Analgesics (NA); 5 of them had failed to obtain or maintain satisfactory analgesia through a peridural catheter (PC). Morphine CM. is injected through the IC 2 to 6mg/day by push injection once (10 pts) or twice (4pts, daily) or by continous infusion through a portable pump connected to the Pac (2pts). No failure of implantation occurred. One disruption of the wound led to remove the Pac. Other complications were: infection of CSF by S. epidermidis controlled by medical treatment without removal of the IC (11 transfusion of blood). Transient urinary retention (2) and stress the role of a well performed percutaneous cervical cordotomy /1000 cordotomies, operator S.I./ and stress the role of a well performed percutaneous cervical cordotomy in relation to the survival data and patient history of cancer pain, furthermore in relation to the lasting efficacy of this operation in abolishing incident pain /Intermittent, excruciating, shock-type neurogenic pain/. The authors demonstrate that the aura of failure and complications often associated with percutaneous cervical cordotomy is totally attributable to improper technical execution, but this should not detract from the central role of percutaneous cordotomy in a multimodality approach to cancer related pain.
Q-35: EDUCATION OF CANCER PATIENTS

4307 THE LAST TEMPTATIONS
Lisaa Klovainio
The Cancer Society of Finland, Liisankatu 21, 00170 Helsinki, Finland

The program is designed for a new ex-smoker. The first seven days as a non-smoker are hard, but at the end the subject - a middle-aged man - emerges as a winner. The program is specially made for a smoking-cessation group or clinic.

4308 WHAT IS CANCER
Kees Kondusa
Netherlands Cancer Foundation, 1075 LH Amsterdam, Sophialaan 6, Holland

Nature, causes, examination and treatment of cancer are explained. Patients are followed at their way through examinations and treatment. Patients tell about their experiences and about the way they cope with cancer - and with the reactions by their relatives, friends and others. Advices are given on reducing cancer-rises and on early detection.

4309 JUDI JOHNSON: I CAN COPE
J. Johnson, Sherman R. Selix Videotape Library, Regional Cancer Foundation, San Francisco, California, USA.

Judi Johnson, PhD, Oncology Services Coordinator, Minneapolis, Minnesota, and Jerry Braesch. Cancer patients discuss a program to furnish a support group for the cancer patient and their families. Dr. Johnson developed this program which consists of 8 weekly meetings. Various topics are discussed including What is Cancer, Cancer Therapy, Nutrition, Sexuality and other general subjects. The lectures are presented by physicians, nurses, and other health care providers.

4310 COMMON QUESTIONS ABOUT CANCER
B. Cassileth, Ph.D, University of Pennsylvania Cancer Center, Philadelphia, Pennsylvania, USA.

In this patient education videotape a series of patients ask the questions that many cancer patients wish to ask. A physician gives a complete and careful answer to each question. Question examples: If the surgeon removed all the cancer, why do I need this treatment? My mother had a good life; she never smoked or drank. Why did she get cancer? You said some of the drugs are experimental. Does that mean I am a guinea pig? Do I have to give up drinking? Sex? This program always fears and provides positive motivation.
You're Not Alone

You're Not Alone is a 20 minute color film tracing the experiences of a leukemia patient and the support she receives from her family and the treatment team of medical and paramedical professionals.

Prevention of Cancer by Very Early Prophylaxis of Smoking

Stanislar G. Penev MD, Higher Med. Institute, Pleven, Bulgaria.

Although up to now we do not know the whole truth about cancer, we are well acquainted with one of its important allies called tobacco. Insofar as tobacco has a causal relationship to cancer, every success in preventing smoking is a contribution in the fight against this scourge of present day. The paper discusses the question of why measures for smoking cessation are so unsuccessful and how addiction to smoking is even stronger than the fear of death/projection of 20 slides. The conclusion is that prophylaxis is the only hope, and that the same inborn forces that make people victims of tobacco can be used so that they never start to smoke. The theory and practice of conditioned reflexes are discussed and it is shown when, why and how they can be used successfully in the fight against smoking. The results of the wide application of this method on small children in Bulgaria are shown. They discover that by means of an appropriate organization a smokeless humanity is no more an unattainable reverie. The author proposes the term PSYCHOINHIBITION as the most suitable for this method of creating a conditioned reflex as a defence against cigarette smoking.

Follow a Documentary Film / 30 min., coloured, 20 min./
**4314 INTERRELATIONSHIP OF HISTOLOGICAL GRADING, METHOD OF RADIATION THERAPY AND PROSTATE CANCER RECURRENCE**

N. Wernet, G. Seitz and G. Shom, Inst. of Pathology, Univer. of the Saarland, Homburg/Saar, FRG

The immunohistochemical demonstration of specific markers in prostate cancer has several objectives: Proof of acid phosphatase and of prostate-specific antigen serves mainly to detect metastases of still unknown primary tumor. Immunohistochemical proof of hormone receptor would be of special interest. The peptide lectins, whose relationship to hormone receptors is known in breast cancer, have not yet been examined in the prostate. After partly digesting at neuraminidase by PAP method, 10 uniform and 15 platform prostate carcinomas were examined for PSA receptors. Papillary, cribriform, and solid tumor formations react extensively positive in most cases, only completely anaplastic carcinomas are largely negative. Basal cells as well as the secretory epithelium are positive in normal prostatic tissue. In adenomatous and cribriform hyperplasia, the basal cells are stained predominantly. Neutrophilic squamous epithelium is strongly PSA-positive following estrogen therapy. Now we are investigating whether the expression of PSA-binding sites in prostate cancer is androgen-dependent under antiangenone monotherapy.

Between January 1970 and June 1983, a total of 702 patients received definitive radiation therapy for carcinoma of the prostate at the Cross Cancer Institute in Edmonton, Canada. Previous reports have shown that in late stage disease, a) patients diagnosed by needle biopsy (%) have a superior survival to those whose diagnosis was established by transurethral resection (T), b) patients receiving local radiation to the prostate (I.F.) have a worse survival than those receiving prophylactic pelvic nodal radiation (E.F.). These findings are confirmed in the current analysis. Histological grading by the Gleason method is available on 695 patients. When stratified by the histological grade, the difference between T and I is reduced to an insignificant level. However, the incidence of multiple histological grades in the T group is more than twice that in the N group, suggesting a possible sampling error. A similar analysis by the histological grade confirms the superiority of E.F. over I.F.
THE INDUCTION OF PROSTATE ADENOCARCINOMA IN L-H RATS

K. Pollard and P. H. Luckert, Lobound Laboratory, University of Notre Dame, Notre Dame, Indiana 46556, U.S.A.

Prostate cancer in humans is a disease of the aging male. The tumor is usually adenocarcinoma, it is frequently hormone-sensitive and the incidence has been correlated with high consumption of dietary fat. The tumor cells usually metastasize to visceral target organs and they produce oncofetal and osteoblastic changes in skeletal bones. Grossly visible prostate cancer is a rare disease in laboratory rodents. Germfree (GF) Lobound-Mistax (L-M) rats were free of a detectable microflora, and their average life span was 37 months. They were fed either high or low diet L-485 which contained 5% fat, and reinduced levels of vitamins and minerals. Ten percent of GF L-M rats developed large metastasizing prostatic adenocarcinomas (PAs), spontaneously, after age 30 months. The incidence of autochthonous PAs was increased in conventional L-M rats by implanting, s.c., deposits of testosterone (T) or estradiol in male rats at 3 month intervals; 32% at avg. 14 months. The incidence of PAs was further enhanced by feeding T-treated rats on standard diet (L-485) containing 15% added corn oil: 527 at avg. 11 months. L-M rats fed L-485 plus 15% corn oil (but not T) developed no PA at 18 months. In contrast, the induction rate of PA in L-M rats, T acted as a tumor promoter or as a carcinogen; and corn oil acted as an additional promotional agent to the T-sensitive prostatic gland. In contrast, 44% GF Sprague-Dawley rats were free of spontaneous PA; and then treated with T for 25 developed PA and the others had prostatic carcinomas. The development of PA in laboratory animals is regulated by genetic, hormonal and dietary mechanisms. The PAs prostate tumor system is an excellent model of the counterpart disease in man.

Supported by the Colgan Foundation, Chicago, Illinois.

HOST'S ANTI-TUMOR IMMUNITY IN PROSTATIC TUMOR MODEL.

Rashid A. Bhatti, M.D., Marie L. Silverman, and Larry L. Williams, Division of Urology, University of Illinois College of Medicine, Cook County Hospital, Chicago, Illinois USA.

The presence of circulating immune complexes (CIC) in prostatic cancer patients whether in patients (Bhatti et al., Proceedings AACR 24, 287, 1983) or in human tumor models (Bhatti et al., J. Natl. Cancer Inst. 63, 229, 1984) prompted present investigation of studying the effect of metastatic potential of prostatic tumors on CIC and to evaluate the influence of tumor growth rate on host's anti-tumor immunity. Experimenter's Fisher rats were implanted with 3 sublines of Dunning R3327 adenocarcinoma of the prostate i.e., R3327-M (slow growing, well differentiated), R3327-C (fast growing poorly differentiated), and R3327-Met-LyLu (fast growing, poorly metastatic and hormonally insensitive). Expressing polyethylene glycol precipitation technique, CIC levels were measured in the sera of these rats to evaluate the effect of metastatic potential of a tumor on CIC, and a suggested correlate of host's humoral immunity. In order to evaluate the effect of tumor growth rate on host's anti-tumor cell mediated and humoral immunity, CIC levels were measured in the sera of rats bearing R3327 Met-LyLu at different stages of tumor growth, based on tumor dimensions. Anti-tumor cell mediated immune responses, as evaluated by antigen induced tube leukocyte adherence inhibition (T-AI) test, were significantly higher in CIC in rats with Met-LyLu subline as compared to C and M, demonstrating the effect of metastatic potential of a tumor on host's humoral response. 2. Preliminary studies indicate higher in vitro anti-tumor cell mediated immune responses in rats with smaller tumors as compared to those with larger tumors, indicating an overall immo depressive state of the host with larger tumor volume.

A myogenic, mesothelial, endothelial and epithelial origin of adenomatoid tumors is discussed in the literature. Aimed at this problem the cellular differentiation of 10 adenomatoid tumors was investigated by means of histochemistry, immunohistology, electron microscopy and ultrastructural immunohistochemistry. In all these neoplasms keratin was demonstrated within the cavity forming cells, factor VIII-associated antigen and myoglobin were lacking. Only in the periphery of the tumor a marked number of factor VIII-associated antigen positive structures in vessels and myoglobin positive structures in some muscle bundles were seen. The ultrastructural picture of the cavity forming cells was similar to mesothelial cells and the keratin filaments could be decorated by the immunogold technique. Furthermore bylase sensitive GAG could be identified but no sulfated GAG and neutral mucopolysaccharides. The results suggest a mesothelial nature of the cavity forming cells of the adenomatoid tumors.


Fifty specimen of testicular germ cell tumors were investigated by means of conventional TEM. TEM is considerable cytologic heterogeneity at ultrastructural level. There are large cells which resemble primordial germ cells and other which have more specific organelles (duplications of the nuclear envelope, annulate lamellae, concentric lamellar bodies, stacks of ER, small subplasmalemmal fibriller border). Sometimes cell junctions and PLS-collagen in the interstitium are visible. Embryonal carcinomas were found in two structural variants: A. The cells of undifferentiated embryonal carcinomas show only few organelles, cell junctions are mostly lacking. These cells showed similarities to primordial germ cells. Sometimes annulate lamellae could be demonstrated. B. Well-differentiated embryonal carcinomas present a cytologic picture and growth pattern like gland forming carcinomas. Follicle like tumors are gonadal neoplasms with the following parts: endodermal sinus cells, immature yolk sac vessels and a large amount of basal membra-ne-like material in the interstitium. Beside the endodermal sinus cells (microvilli, cell junctions, vesicles, glycojen) primordial germ cell like elements were found. The ultrastructural cytologic heterogeneity of all investigated germ cell tumor types may suggest a close relation between them. There are no diagnostic organelles, only combinations of organelles may support a diagnosis.


Neoplastic cells were detected in the seminiferous tubules of patients suffering from testicular tumors. The smear prepared according to our own technique and stained with hematoxylin and eosin as well as with acridine orange, were evaluated according to the classic rules of oncologic cytology. Our observations indicate the search for neoplastic cells in the semen to be promising, however, the results depend upon the experience of investigator.


This study examines the effect of histology on the 5-year survival rates in patients treated for GCTT at the U.S. Comprehensive Cancer Centers between 1977 and 1982. About 1,784 patients with newly diagnosed GCTT were treated with surgery, radiation and/or chemotherapy as recorded in the Centralized Cancer Patient Data System. Histology of GCTT was seminoma (S) in 592, embryonal carcinoma (EC) in 572, endodermal sinus tumor (EST) in 32, teratocarcinoma (TC) in 523, and choriocarcinoma (CHC) with or without other germ cell tumor elements in 157 patients. Tumor was localized in 664 and metastatic in 464 (regional nodes in 282, and distant sites in 282). The frequency of metastases at diagnosis was related to the histology; it was highest in CHC and EC (74%), lowest in S (28%), and intermediate in TC (60%). Survival rates varied with both histology and stage. Five-year survival by histology was best for seminoma (94%), similar for EC and TC (60% and 66%), and poorest for EST and CHCA (71% and 70%). There was no difference in survival among the various histologic groups for localized disease (97%). Moreover, histologic groups in patients with metastatic disease. Patients with metastatic CHCA had the poorest survival rates (75% regional and 54% distant). Survival rates for metastatic S and TC were similar stage for stage (regional: 97% and 90%, distant: 68% and 65%, respectively). EC had the best survival (74%) of all histologies with distant metastases (66% with regional disease). The 5-year survival for all GCTT by stage was 97% for localized, 91% for regional and 67% for distant disease. We conclude that histology, extent of disease at diagnosis, and the treatment influenced 5-year survival rates.
A-56: PATHOLOGY OF MALE MALIGNANCIES

"Incidence and survival of testicular seminoma and non-seminoma in Norway".

The database in the Cancer Registry of Norway is unique with regard to completeness and detailed quality of the database through 35 years. From this material a considerable increase in different histological subtypes of testicular cancer of different age-groups has been observed, with contrasting regional variations during the last 20 years. Hypotheses for causal factors will be discussed. The changing pattern of survival for different histological types and different disease-stages will be presented.

F. Langmark
The Cancer Registry of Norway, Oslo, Norway

A-57: PATHOLOGY OF LUNG CANCER

RISK FOR LUNG CARCINOMA IN SUBJECTS WITH BILLROTH II GASTRECTOMY. C. Bianchi, A. Brolio, L. Bittenini, and I. Raimondi, Istituto di Patologica Anatomia, Hospital of Monfalcone, Italy.

To assess the risk for malignancies among subjects with prior partial gastrectomy, a series of 731 consecutive necropsies was analyzed. The series included 261 patients formerly subjected to Billroth II gastric resection for benign conditions (198 males, 3 females). After controlling for age, the Billroth II resected men were found to have a higher risk for malignancies than the unresected subjects of the same necropsy series. In particular the risk was significantly increased for lung carcinoma (Mantel - Haenszel rate ratio 2.2; confidence interval 1.4-3.5). When the intervals between partial gastrectomy and death were considered, the highest risk for lung cancer was observed among the patients resected more than 40 years previously. Although the role of smoking in the above excess remains to be ascertained, the gastric resection itself might favour lung cancerogenesis. As a cause of malabsorption, gastrectomy may induce deficiency in protective factors, such as vitamin A. Moreover, since raised levels of nitrosamines in gastric juice have been found after Billroth II resection, the eventual role of such substances has to be considered.

HISTOLOGIC TYPE OF LUNG CANCER AND ASBESTOS EXPOSURE


The histologic types of lung cancer in 747 men and 107 women from three hospitals and one international study of insulation workers were evaluated. About one half of the cases were diagnosed from surgical slides and one half from autopsy slides. Of these, 196 cases had asbestos exposure. Squamous cell carcinoma constituted the largest percentage of tumor types and was found with the same frequency in exposed and nonexposed groups. Small cell carcinoma was found in 25% of the patients exposed to asbestos and in 12% of the nonexposed patients. Upper lobes of the lung were involved in about two thirds of the cases with asbestos exposure and lower lobes in the other one third. Little difference was found in histologic type in cases regardless of whether upper or lower lobes were involved. Cigarette smokers who smoked until their cancer diagnosis showed no difference in histologic type by amount smoked and slight but not statistically significant differences from ex-cigarette smokers.
**4329** MACROSCOPIC FEATURES AND MORPHOLOGIC EVALUATION OF INTRANODAL Lymphatic nodes in Lung Cancer, (Pulmonary department and pathoanatomical laboratory of the Oncological Scientific Centre or Ministry of Health of the Georgian SSR, Tbilisi). Ogua P.O., Kuchava V.N., Geramiyi X.X.,

Macrophoscopic picture of lymphatic nodes of the lung and mediastinum does not always correspond to their microscopic condition. The metastases were not revealed in 32,7±1,6% of solid enlarged lymphatic nodes, whereas not enlarged lymphatic nodes in 11,9±1,7% were metastatic. With the decrease of lung cancer rate differentiation the frequency of metastases discovery in the enlarged lymphatic nodes is increased. The metastases in the nodes in small-cell cancer are revealed in 90,9±2,7% whereas in highly differentiated epidermoid cancer only in 51,4±2,5%. The metastatic legion of not enlarged lymphatic nodes was found more frequently in adenocarcinoma (20,4±4,3) than in other histological types of lung cancer (from 9,5±1,7% to 11,3±4,4%).

**4331** THE SIGNIFICANCE OF THE HISTOPATHOLOGICAL TYPE IN IMPERVIOUS LUNG CANCER. J. Jyrkkä, A. Olava, Dept. of Pathol. and Oncol., Univ. of Turku, Turku, Finland.

In the Department of Oncology of the University Central Hospital of Turku, Finland, altogether-775 inoperable patients were treated for lung cancer from 1967 through 1973. The original histological diagnoses of 445 patients were re-classified according to the WHO (1978) classification. There were 59,2% squamous cell carcinoma, 29,9% small cell carcinoma, 8,5% adenocarcinoma and 8,1% large cell carcinomas. As the reclassification the original histopathological diagnosis was changed in 25% of the cases. The follow-up period was 11 years at minimum, and the survival data were available from all the patients. After 10 years from the primary therapy 1,3% of patients with squamous cell cancer, 0,8% with small cell cancer, 0,3% with adenocarcinoma and none with large cell cancer were still alive. The patients with a small cell cancer died generally with symptoms caused by extrathoracic metastases. Between the groups of the other forms of cancer there were no differences in the survival time, not even between the various differentiation grades in the group of squamous cell cancer. In all types of non-small cell cancer the majority of the patients died with pulmonary symptoms; a fact that shows a failure in the control of the primary tumour.

**4330** ELECTRON MICROSCOPY IN LUNG CANCER DIAGNOSIS, N.I. Stoynkova and A. Ch. Siminov, Oncological Research Institute, Medical Academy, 1136 Sofia, Bulgaria.

Surgical specimens from 72 lung tumors have been examined by light (LM) and transmission electron microscopy (TEM). Histological typing was made in conformity with the 6 tumor categories of the WHO, TEM studies resulted in more precise typing and subclassing according to ultrastructural criteria. For instance, in 17 cases with LM diagnosis of poorly or moderately differentiated epidermoid cancer, TEM has provided evidence for a second type of tumor cells, thus qualifying these cases as mixed tumors. In the small cell carcinomas (SCC) group (11 cases) only 3 tumors displayed neurosecretory granules, in 2 of them tonofilaments and desmosomes being present as well. In 3 tumors of the SCC group TEM visualized only desmosomes, while in another 1-desmosomes and tonofilaments, but no neurosecretory granules. This confirms previous reports that the LM appearance of SCC does not reflect their heterogenous TEM structure.

**4332** THE DIAGNOSTIC VALUE IN THE CYTOLOGIC DIAGNOSTIC OF THE IMPRINT SPEARM THE BIOPSIED AND SURGICAL SPECIMENS IN LUNG CANCER. Julai Hoo, Mood Alsaqaff, So Uogram, Room Uroom, Nezli P. Nezli, Mood Alsaqaff, Dept. of Pathology Lab., Pulmonology Dept., Airlangga University, School of Medicine, Surabaya, Indonesia and Pathology Lab., S.T. Antonius Hospital, Utrecht, The Netherlands.

The accuracy of diagnosis achieved by cytopathological examination of sputum bronchial washing & brushing and bronchial biopsy histology was 85% (Payne 1979). Errors in these investigation were made in the diagnosis of the poorly differentiated Carcinoma and the Large Cell type (Payne). The other authors found that there were also cases were not correlated histologically and cytologically e.g., in combined Adeno Epidermoid (Hess 1981). So classification cytologically in these type of Lung Cancer is still confusing. The cytopathological diagnosis is difficult in many modern countries. Based on the classification of Lung Cancer, the histological and cytopathological criteria diagnosis by UMSF, we report the diagnostic value in the cytopathologic diagnosis of imprint smear in 173 surgical specimens and 250 biopsy specimens in Lung Cancer, Which we have done in Netherlands and in my country.

The accuracy in cytopathologic diagnosis (in typing and grading) was higher than the other cytopathologic and histological diagnosis in biopsy specimens in Lung Cancer, especially to those the poorly differentiated Carcinoma and the Large Cell type.

The systemic spread of cancer cells shed from the primary lesion is one of the factors allowing the poor prognosis of lung cancer. The cancer cells in the pulmonary blood vessels (p.b.v.) were examined histologically in the seemingly unaffected areas of the lung resected for lung cancer.

In 38 of 113 cases (34%), the cancer cells were found in p.b.v. of the areas of the lung which looked normal. The incidence of cancer cells in p.b.v. as classified by histology was 27% for 27 cases of squamous cell carcinoma, 30% for 57 cases of adenocarcinoma, 33% for 3 cases of large cell carcinoma and 80% for 10 cases of small cell carcinoma. The incidence of cancer cells in p.b.v. was lower in the lungs of the group in which the diameter of a tumor was less than 3 cm, than those in which the diameter was more than 3 cm. The incidence of cancer cells in p.b.v. classified by the post-surgical stage of TNM was 20% for stage I and II, 30% for stage III and 83% for stage IV. The survival rate of 2 years after resection was 37% in 38 cases with cancer cells and 80% in 75 cases without cancer cells.

The results indicated that the cancer cells released into p.b.v. before and/or during operation formed the later growth in the various organs and governed the poor prognosis of lung cancer.

**4334** PHENOTYPIC EXPRESSION OF EXPERIMENTALLY INDUCED PULMONARY LARGE CELL CARCINOMA. William H. Blair, Mercy Hospital and Medical Center, Chicago, Illinois 60616, U.S.A.

This study was done to observe the in vitro growth and morphologic expression of pulmonary large cell carcinoma cells exposed to homologous serum or ascites fluid. Large cell lung carcinoma was induced in laboratory rats by exposing lung tissue to polycyclic hydrocarbons. After identification and isolation the tumor were propagated in vivo by serial subcutaneous transfer. For the in vitro studies 10⁶ viable tumor cells were seeded into flasks containing tissue culture media and homologous rat serum or cell-free ascites fluid obtained by abdominal tumor implant. Additional flasks contained tissue culture media but no serum or ascites fluid. The flask containing serum exhibited round cells with considerable variation in size. Over 80% of the cells attached within 24 hours and 50% of these cells flattened out on the surface and displayed cytoplasmic projections. Numerous mitoses were evident in both the round and flattened cells, and 10% of the attached cells were multinucleated giant cells.

Tumor cells exposed to ascites fluid had less surface attachment of their round cells and only 10% of the attached cells were of the flattened variety. Numerous mitoses were evident but multinucleated giant cells were not seen. Flasks without serum or ascites fluid initially appeared similar to the serum treated cells but exhibited less than 10% multinucleated giant cells. After 7 days cells became detached and had a marked decrease in mitoses by 14 days. Treatment of the ascites fluid treated cells with serum resulted in morphologic patterns similar to those exposed initially to serum. In addition the loss of attachment and cell division in cells not given serum or ascites fluid could be reversed with serum treatment. It appears that homologous serum provides growth and attachment differentiation factors to experimentally induced pulmonary large cell carcinoma, that are not duplicated by ascites fluid.

**4335** POSSIBILITIES AND PROBLEMS IN THE CYTLOGIC AND HISTOLOGIC DIAGNOSIS OF LUNG TUMORS. F. Usunov, Medical Academy, Department of Pathology, Sofia, Bulgaria

The studied material is from fiber, pinch and brush biopsies for a five year period (1981-1985). The material is studied cytologically and histologically. The diagnostic possibilities are evaluated and the problems regarding the diagnosis of lung tumors using these biopsies are noted. The percent of exact diagnostic results is relatively lower using each method alone, while in combination it raises quite markedly. Eg. undifferentiated carcinoma gives low exactness in results compared to histology. Used in combination these two methods give a very high percent of exact results and make diagnosis very stable.

**4336** TRANSBRONCHIAL LUNG BIOPSY - SOME PECULIARITIES OF ITS MORPHOLOGIC STUDY. V. Vlaov, F. Usunov, Medical Academy, Department of Pathology, Sofia, Bulgaria

The material studied is from fiber, pinch and brush biopsies for a five year period (1981-1985) of 559 cases with transbronchial lung biopsies (2857) of diffuse processes of the lung. The material is taken from 6-10 segments out of the same lung. The following diseases are diagnosed - 156 sarcoidosis, 230 pneumosclerosis, 12 tuberculosis, 67 malignant tumors, 10 hematosiderosis, 5 alveolitis, etc. Some problems regarding the morphologic diagnosis of these diseases are pointed out. Clinico-morphological parallels are made. In most of them (67%) of the patients the clinically diagnosed disseminated metastases of malignant tumor of lungs show a morphology of pneumosclerosis, hematosiderosis, sarcoidosis, tuberculosis, etc. There are cases however, bearing a clinical diagnosis for sarcoidosis, tuberculosis, cyst lung disease, lung thromboembolism and showing a morphology of malignant tumor metastases.
**A-57: PATHOLOGY OF LUNG CANCER**


The positivity of using flow cytometrically determined DNA content as an indicator of the proliferative characteristics of all populations and as a prognostic marker of human solid tumors has been recently demonstrated. The aim of the present study is to investigate the prognostic validity (disease evolution; metastatic dissemination; response to therapy; etc.) of flow cytometry and in particular DNA content in lung neoplasia. Tumor specimens from 50 patients affected by lung cancer were analyzed by flow cytometry in order to detect DNA content alterations. Normal samples used as internal standard yielded constantly single cell population with diploid DNA content. Tumor samples, on the contrary, exhibited in the majority of cases (about 60%) the occurrence of one or more than one aneuploid cell subpopulation ranging from 0.78 to 3.74, demonstrating the remarkable degree of cellular heterogeneity in this particular tumor and in all heterotopes of bronchogenic carcinoma. The implication of the biological results with prognostic data and clinical management will be discussed (supported by Grant of PPO-CNR n. 84/00717/44).

**B-47: GLYCOPROTEINS, GLYCOCHEMISTRY AND CARBOHYDRATE METABOLISM**

4339 GLYCOPROTEIN GLYCOSYLATION IN AMERICAN AND JAPANESE PATIENTS WITH COLON CANCER

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Biopsy specimens of colon cancer and adjacent normal mucosa were obtained in 11 American adults, 8 female and 3 male, ages 54-74, and 11 Japanese adults, 7 female and 4 male, ages 39-70. The biopsy tissues were washed in saline and the explant incubated with 3H-glucosamine in triplicate for 24 hours. The cell membrane protein was then separated by ammonium, centrifugation and polyacrylamide gel electrophoresis. The gel was then sliced and counted. There was no significant difference in the 3H-glucosamine uptake in the glycolipid fractions or in the total glycoproteins. However, the glycoproteins over 220,000 Mr. showed an apparent reduction in the glycoprotein glycosylation in the colon cancer cells as compared to the normal control mucosa cells from both the American and Japanese patients. This may represent a deficiency in the cell membrane repair in the cancer cells from both patient populations. This decrease in glycoprotein repair in these two patient groups may mean that similar etiological factors are present.

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4340 GLYCOPHOSPHOLIPIDS AND GLYCOPROTEIN IN CLINICALLY VARIANT OF RAT FIBROSARCOMA CELLS WITH DIFFERENT TRANSPLANTABILITY

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We have isolated three clone variant cell lines (A, P, C) of fibrosarcoma cells with different transplantability and intercellular adhesive properties from rat fibrosarcoma AS83M cells. The original clone A was highly malignant transplantable. In contrast, variant clones C, P were characterized as extremely poorly transplantable clones when inoculated subcutaneously. The loss of transplantability as seen in these cells lines can be regarded as a decarcinogenesis.

The surfaces of clone C was characterized by the presence of microvilli in contrast to the smooth surfaced appearance of clone A. Clone C had a strong wide-biore adhesive property and formed a wormlike shape which became an anchor cell coat. Clone P showed a decoordinate genetic modification in transplantation to nude mice.

The protein profiles of the 3 variant cell lines stained by Coomassie blue showed very similar patterns. In contrast to the protein label, the labeling of galactosyl or N-acetylgalactosaminyi residues by galactose oxidase and tritiated sodium borohydride showed a remarkable difference. Clone C hardly gave any label in contrast to a striking label of the molecular weight 150,000 region of clones P and A. However, intensive label occurred at a molecular weight of 150,000 and at other bands in clone C after sialidase and galactose oxidase treatment, however, the molecular weight 150,000 band of clone P showed only moderately intensified label, and that of clone A did not show greatly intensified label. Thus, sialylgalactosial or sialyl-N-acetylgalactosaminy residues in asialo group. This result showed that clone C is not malignant transplantable but clone P is malignant transplantable.

Neutral glycolipid and ganglioside of three clone variants of rat fibrosarcoma AS83M cells with different transplantability were analyzed. A highly malignant clone A had a much lower quantity of GM3 ganglioside and a much higher quantity of lactosylceramide to clone C, which showed low transplantability and a variant clone P, which showed tumorigenicity only in ascetic form A similar correlation was found with the quantity of an unidentified neuraminoglycolipid in various clones. This glycolipid was present in trace amounts in the original highly malignant clone A, increased moderately in clone C and increased greatly in clone P, which showed no subcutaneous of GM3 ganglioside and along chain neutral glycosphingolipid occurred with enhanced malignancy, and the long chain neutral glycosphingolipid is associated with a decrease in transplantability.

Metabolic activities introducing N-glycosidically linked saccharide chains into glycoproteins are essential for the expression of normal cellular functions. Dolichyl phosphate (Dol P) functions as a sugar carrier in eukaryotic cells and N-glycosylation of proteins proceeds via dolichyl (Dol)-linked oligosaccharides. Recently, decreases of Dol P and Dol-mediated glycosylation were observed in the course of chemical carcinogenesis of rat liver. Although various polyisoprenyl P as in Dol P besides Dol P are known to serve as acceptors of sugars in cell-free systems, the carrier function of such polyisoprenyl P have been studied only in yeast. Dol P (n-dihydrodecaprenyl FGDMP) and dolansyl P administered to hepatoma cells stimulated the N-glycosylation of proteins. In addition, DDP enhanced the adherence of the cells to the substratum, probably as a result of the stimulation of N-glycosylation of proteins. With crude membrane fraction of the hepatoma cells, DDP increased the incorporations of 14C-Man from 14C-Man into MSGlycyl-Phol extract, oligosaccharide-lipid and protein. DDP may function as a Man carrier in lipid intermediate pathway. These studies suggest that modification of protein glycosylation by polyisoprenyl P in malignant cells may be a new approach in cancer chemotherapy.

GLYCOPROTEINS, GLYCOCONJUGATES AND CARBOHYDRATE METABOLISM.

LIPID-BODY GROWTH IN FIBROBLASTS. D. de la Torre, L. A. Schirripa**, and A. Balbi. "Instituto de Biologia y Quimica Experimental, Udiplia, Argentina, and Instituto de Investigaciones Biologicas "Humberto I". Buenos Aires, Argentina.

First step in glycoprotein biosynthesis include lipid-linked saccharides as intermediates. We have demonstrated that microsomal fraction from calf lung homogenate catalyzed the transfer of mannose and glucose from Dol-P to undiluted or DGDG to lipid-linked mannose and glucose. N-linked glycoprotein synthesis was studied in several cell lines with different metastatic behaviors. 1 The optimum conditions for mannose and glucose transfer were described. In addition, the kinetics of the transfer activity of extracellular glycoproteins and the in vivo intracellular and extracellular glycoproteins were studied. Also, we have developed in the cell culture, specific methods to obtain glycopeptide. We have observed the in vitro synthesis of the glycopeptide in human fibroblasts. The ability to bind to cultured cells is not necessary to induce the synthesis. This is in agreement with the results observed by other authors. The results suggest that the glycopeptide is synthesized in contact with extracellular matrix. We have also observed the in vivo synthesis of the glycopeptide in vivo. The results are in agreement with the results obtained in vivo.


We have examined four rat rhabdomyosarcoma sublines expressing different metastatic potentials for their ability to degrade proteoglycans and glycoproteins of the extracellular matrix (ECM), deposited by corneal endothelial cells and metabolically labelled with (35)S-glucosamine and with (14)C-glucosamine and with 14C-manuridin. The proteoglycans are the major glycosaminoglycans released by the cells. The proteoglycans are glycosaminoglycans and glycoproteins released by the cells and the ECM are separated and partially characterized. The most of the matrix glycoproteins are recovered in the region of 200 K on gel chromatography. Glycopeptides of 10-20 K apparent molecular weight were minor components. The glycosaminoglycan chains of the proteoglycan sulfates are partially hydrolyzed to 20K fragments. Tumor cells increase also the solubilization of the non-degraded matrix macromolecules. About 5% of the radioactivity of the ECM remains associated with the tumor cells detached from the ECM. These results suggest that the surface receptors of the investigated cells lack interaction with the proteoglycans than with proteoglycan sulphate of the ECM. ECM degrading activity of the sublines did not correlate with their ability to colonize the lungs after i.v. injection but did correlate with their ability to metastasize to the lungs from the primary subcutaneous site.


Serial determinations of serum fucose and sialic acid levels were carried out for 80 patients with metastatic breast cancer at the time of metastases diagnosis (T1) and before and after the surgical treatment (T2) and/or subsequent chemotherapy. The measurements were spaced at 5 months intervals during a period of 3-5 years. The changes in both parameters were found in good correlation with the disease evolution. Thus, fucose and sialic acid levels decreased to near to normal values following the complex treatment. In case of disease recurrence, the elevated concentrations of fucose and sialic acid occurred at about 2-3 months before clinical or radiological evidence of recurrence and distal metastases. Similar results were found in 50 patients with advanced ovarian cancer, but more cases have to be investigated in this localization of the disease, before concluding. However, our results support the clinical utility of the use of fucose and sialic acid levels as markers to monitor cancer evolution and treatment.
LOW DENSITY LIPOPROTEIN RECEPTORS ON CHRONIC B-LYMPHOCYTIC LEUKEMIA CELLS IN RELATION TO SPONTANEOUS AND MITOGEN-INDUCED PROLIFERATION

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Chronic B-lymphocytic leukemia (CLL) cells have a low spontaneous proliferation rate, but can be induced by B-cell mitogens to proliferate in vitro. High-responsive cell clones are associated with aggressive disease and poor survival. Normal lymphocytes display low density lipoprotein (LDL) receptors at low levels, but increase the amount when cultured in lipoprotein-deficient medium. The present study was undertaken to evaluate the LDL-receptor activity on CLL-cells in relation to the spontaneous and mitogen-induced CLL cell proliferation. We performed LDL-receptor analyses on fresh blood mononuclear cells from 25 CLL-patients and 4 healthy donors, and on cells cultured for 3 days in lipoprotein-deficient medium. We also studied CLL-cell thymidine uptake in 4-day cultures with and without B-cell mitogens. Fresh CLL-cells had a lower LDL receptor activity than blood mononuclear cells from healthy donors (p<0.005), and during culture the LDL receptor activity of CLL cells increased significantly (p<0.0003), but to a lesser degree than that of normal blood lymphocytes (p<0.0006). CLL-cells with low increase of LDL receptor activity during culture also proliferated poorly in vitro, both spontaneously (r=0.59, p<0.01) and in response to B-cell mitogens (Epstein-Barr virus, r=0.70, p<0.001; Cowan staphylococci, r=0.53, p<0.01; Lipopolysaccharide, r=0.46, p<0.05). The CLL-cell LDL receptor levels seem to correlate to the spontaneous and mitogen-induced cell proliferation. The LDL receptors might be involved in the regulation of CLL cell proliferation, and thus a parameter of clinical relevance.

LECTIN-RESISTANT VARIANTS OF MOUSE LEWIS LUNG CARCINOMA III. CHANGES IN NEUTRAL GLYCOLIPIDS EXPRESSION.

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The changes in glycolipids expression in lectin-resistant variants of Lewis lung carcinoma LL cell line were studied. Lectin-resistant variants were selected with wheat germ agglutinin /WGA/ and Aleuria aurantia lectin /AAL/ and Ricinus communis agglutinin /RCA/ and A. aurantia lectin and Aleuria aurantia lectin. Cell lines were selected in vitro with N-acetylgalactosamine and N-acetylgalactosamine. Neutral glycolipids and gangliosides were purified and analyzed by R.C. TLC. It was found that lectin-resistant variants differ in their neutral glycolipid pattern in comparison to parental LL cell line. There were no changes in ganglioside expression. The possible relationship between changes in glycolipid expression and the altered metastasizing capacity is considered.

LECTIN-RESISTANT VARIANTS OF HOUSE LEWIS LUNG CARCINOMA II. ALTERED GLYCOSYLATION OF MEMBRANE GLYCOPROTEINS.

H. Debray, D. Dué, P. Hueso, P. Delannoy, G. Radzikowski, J. Monreuil

Lectin-resistant variants of Lewis lung Ca LL cells line, selected with wheat germ agglutinin /WGA/ and Ricinus communis agglutinin /RCA/ were studied. All variants exhibited reduced metastasizing capacity. To study possible relationship between the altered metastasizing capacity and the changes in cell membrane glycosylation, the distribution of glycans of N-glycosyl proteins was evaluated. Total cellular glycopeptides of the parental LL cell line and four WGA and RCA II variants were analysed by gel filtration and affinity chromatography on immobilized lectins. The results revealed that non-metastasizing lectin-resistant variants possessed less highly branched, tri- and tetraantennary N-acetyllactosaminic type glycans with simultaneously increasing in bi- and triantennary glycans as compared to the parental, metastasizing LL cell line.

PHOSPHOHYLASE IN A GLUCOSEMETABOLIZING CELL LINE.

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The mechanism which leads to an excessive storage of glycogen in preneoplastic hepatocytes induced by chemical carcinogens in vivo has not been fully clarified yet. Cj1 cells, a glycogen-storing non-tumorigenic hepatocyte-derived cell line, established from a primary culture of hepatocytes, was used as in vitro model to study the activities and kinetics of the glycogen-metabolizing enzymes synthase and phosphorylase. The fast growing Morris hepatoma 3292d and normal rat liver were used as controls. The specific activities of synthetase and phosphorylase were determined at 24 h intervals during the 7-day growth cycle. The enzyme activities rose continuously during the growth cycle reaching maximum activities in the non-proliferating plateau cells. The total activity of glycogen synthetase was 10.4, 3.7 and 5.5 mU/min in Cj1, HH3924 and normal liver, respectively. The apparent Km-values for uridine-d-1-phosphoglucone were 0.35, 0.27 and 0.74 mM. Ap 6 for glucose-6-phosphate was 0.7 mM in Cj1 and HH3924 cells and 0.2 mM in normal liver. The intracellular glucose-6-phosphate-concentration was about 0.2 mM in all cell types. The specific activity of total glycogen phosphorylase was 29.3 mU/min in Cj1 cells, 22.7 mU/min in HH3924 and 213.5 mU/min in normal liver. The apparent Km-value for glucose-1-phosphate was 4.8, 4.6, and 5.2 mM, whereas glycogen phosphorylase a activity of normal liver did not change after incubation with glucose-6-phosphate, the enzyme of Cj1 and HH3924 cells was inhibited. The high specific activity of glycogen synthetase combined with a low specific activity of glycogen phosphorylase lead to the inhibition of phosphorylase a by physiological concentrations of glucose-6-phosphate might explain the excessive accumulation of glycogen in Cj1 cells.

KINETIC PROPERTIES OF GLYCOCEN SYNTHETASE AND PHOSPHORYLASE IN A GLUCOCENICOTIC LIVER CELL LINE.

D. Mayer, Institute of Experimental Pathology, German Cancer Research Center, Heidelberg, FRG.

The kinetic properties of glycogen synthetase and phosphorylase were studied in a liver cell line of Glucose-6-phosphate might explain the excessive accumulation of glycogen in Cj1 cells.
4349 THE COMPARISON OF SEMI-QUANTITATIVE ESTIMATED CYTOGENIC ACTIVITY OF GLUTAMIC-PEPTIDE PROTEIN SPLIT IN HUMAN CRITICALLY IRRADIATED CELLS AND BREAST CANCER.


The cytotoxic activity of glucose-6-phosphate dehydrogenase was semi-quantitatively assessed in fresh touch preparations of in vitro cultured human carcinoma, fibroblasts, and fibroblasts. Statistically significant difference was found in the activity of this enzyme in the favour of carcinoma. It is possible that the intensification of its activity is a sign of the shift of carbohydrate metabolism from aerobic to anaerobic path or the activity of enzyme amount is higher because of the need for nuclear acid precursors in the tissue with fast growth rate. It seems that the estimation of the glucose-6-phosphate dehydrogenase activity could be valuable method of evaluating malignant cells and possibly predicting the proliferative capacity of benign and malignant breast lesions.

4350 STUDIES ON THE KINETICS OF GLYCOGEN-SYNTHESIS IN LIVERS OF NORMAL AND TUMOROUS ANIMALS, FOLLOWING LARGE DOSES OF GLUCOSE AND AGU/GLUCOSE.


3 hours after doses of 20% and glucose /sugar/, glucose /sg/ was isolated with K5H, 20% and 12% from livers of animals with Ehrlich ascites tumour /EAT/, NK lymphoma /NK/lg/ and Novikoff hepatoma /NH/; glycogen-yield /gy/ was measured, then specific activity /sa/, sedimentation coefficient /sc/ and protein were determined in 0.5% aqueous solution of G. The S and P of normal and tumorous animals were nearly identical, while the SA and GY, representing the kinetics of liver G-synthesis, differed substantially in the two groups: the SA of G of animals transplanted with EAT was 50% higher and that of NK/lg was 25% higher than the control; the amount of G synthesized, on the contrary, was one third for the former and one half for the latter as compared to healthy mice. The amount of marked glucose incorporated in G was 25% higher in one of the experiments with hypertensive rats and 50% higher in the other; at the same time, GY amounted to one nineth and one fifteenth of liver G-synthesia, differed substantially in the comparison of normal and tumorous animals, the following data were obtained: EAT /liver of SA tumorous animal/11673.1; control liver/2749; NK/lg/11000, KG2333; NH5992, KG462.

4351 UTILIZATION OF GLUCOSE, FRUCTOSE AND NACHTON IN VARIOUS TUMOUR CELLS: THE ROLE OF PHOSPHATE AND THE PACE OF MARKED PHOSPHATE IN METABOLISM.


In solutions of physiological salt /NaCl/, Krebs Ringer bicarbonate /KRBC/ and Krebs Ringer phosphate /KRP/ and KRP with increasing content of phosphate, tumour cells /TC/ were incubated /eg. Ehrlich ascites carcinoma, Novikoff hepatoma/ in the presence of glucose /Glc/, fructose /Fr/, mannose /M/ and N-acetyl-β-d-glucosaminyl phosphate /NGP/; hexose utilization was measured by enzymological and chemical methods, namely by incubating solutions, cell extracts with TCA and cell hydrotases with KOH was determined by scintillation method. 2 ml of TC were found to have consumed 10 amol of Glc, Fr and M at 37°C for 120 min in KRP, while having used up twice as much as that in KRP, increasing phosphate concentration further enhanced hexose consumption. The reverse was found for "consumption" of Fr by TC: the activity of extracts with TCA end of TCA was 5 to 5 times higher for cells incubated in KRP then for those in KRP, incubating TC with NGP/glucose in the above solutions and examining intermediates that were formed using TLC and autoradiography, lactat acid appeared as the main component; it was the increasing phosphate content that enhanced its formation the best.

4352 CHARACTERISTICS OF TISSUE THIAMINE AND NIACIN METABOLISM DURING MALIGNANT TUMOR GROWTH. R. V. Trebukhina, and G.R. Michaelis, Inst. of Biochemistry, USSR Acad. of Sciences, Grodno, USSR.

From the point of malignant tumor formation, the organism is confronted with marked metabolic changes. The stage of neoplasm growth is 2-fold as that of neoplasm and niacin in carbohydrate metabolism substantiated these studies. The experiments were carried out on mice with rothoc-thiamine-riboflavin deficiency. The tumors were Walker 256 and rat hepatoma. The studies on intertissue distribution of "C thiamine have shown that the label is actively consumed by tumor cells from ascitic fluid. The "C thiamine concentration in tissues of tumor-bearing animals is directly dependent on the thiamine status of the organism and on the stage of neoplasm growth. As the experimental tumors grow, there occurs a depletion of the tissue thiamine stores: the activities of TPP-dependent enzymes (tissue transketolase, liver mitochondrial pyruvate and oxoglutarate dehydrogenase) decrease and the levels of blood pyruvate and lactate elevate. The TPP effect in tumor cells increases up to 50%. At the early stage of tumor growth, thiamine acid assimilation is decreased in the liver, kidney, brain, skeletal muscles. The levels of oxidized nicotinamide coenzymes /NAD, NADP/ gradually reduce in tissues of normal and tumorous animals. The inverse correlation relationship is observed between the NAD and MAD contents in the hepatocyte nuclei and tumor cells. The DNA concentration in the neoplasms is 2-fold as high as that in the liver, whereas the content of MAD is approximately 2-fold higher in hepatocytes as compared to tumor cell. The intensive DNA production in tumor tissue is related to high activity of DNA - polynucle in it.
**B-47: GLYCOPROTEINS, GLYCOLIPIDS AND CARBOHYDRATE METABOLISM**

4353 PRESENCE OF MITOCHONDRIAL-BOUND HEXOKINASE IN MOUSE SPLEEN CELLS UNDER DIFFERENT CONDITIONS AND ITS RELATIONSHIP WITH CELL RESPIRATION

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During the study of energy metabolism of cancer cells, it was found that a large fraction of the cell hexokinase can bind to the outer mitochondrial membrane. This mitochondrial-hexokinase interaction is responsible, at least in part, for the high rate of acid production of the malignant cancer cells. On the other hand, the mitochondrial-bound hexokinase can develop a stimulatory action on cell respiration through the direct utilization of intramitochondrial ATP.

We investigated the presence of mitochondrial-bound hexokinase in mouse spleen cells both in vivo and in vitro. We established this "binding capacity" is enhanced under fetal age, in leukemic conditions and after Bordetella pertussis treatment of normal spleen cells with spermine also resulted in enhancement of the mitochondrial enzyme. In contrast, the ConA treatment could not increase this binding. We observed also that this binding is always related to high oxygen consumption of spleen cells. Our results supported the relationship between the respiration and mitochondrial-bound hexokinase.

**B-48: EXPERIMENTAL HYPERTERMIA**

4355 MITOGENIC RESPONSE OF HYPERTERMIA TREATED PERIPHERAL HUMAN BLOOD LYMPHOCYTES, IN VITRO, S. Pellet, Alfreda Yameal, L. Periksy, "FCM" Natl. Res. Institute for Radiobiology and Radiophygiene, Budapest, Hungary

Function of peripheral human blood lymphocytes (HPL) was investigated following hypertermia on basis of its mitogenic response. Fresh Ficoll separated HPL were treated with hypertermia in vitro and after this the cells were exposed with the mitogens phytohemagglutinin (PHA) or Concanavalin A (ConA) in optimum concentration and under optimal culturing conditions for 72 hr.

Thereafter, the cells were labeled with 3HTdR for 4 hours and the incorporation rate was used as the indicator of mitogenic response. For the hypertermic treatment various temperature (42°C, 43°C and 43,5°C) and time period (30; 60 and 90 minutes) were introduced. The mitogenic response of lymphocytes showed time and temperature dependent changes in the agreement of the very rare results published earlier. Furthermore, the decreased mitogenic response resulted by hypertermia (43 and 43,5°C) proved to be partly temporary taking into account a 7 days period. The in vitro hypertermia occurs a definite change in the mitogen response of lymphocytes is suggesting immunological consequences.


Recently hypertermia has been spread clinically as one of the useful therapeutic methods for various kinds of cancers into many facilities. Although many results on hypertermia have been reported, few experiments concerning the cell-biological effects on cultured human cancer cells have been studied so far. Hence, in the present study we investigated the cell biological effects of the various degrees of temperature on cultured human esophageal cancer cells. We have already established three cell lines designated SGF-3, -4 and -5 derived from three different human esophageal carcinomas. These cell lines employed in the present study have been maintained in RPMI-1640 and HAM-F-12 (1:1) containing 10% pseudofetal bovine serum (Nakakido). They were maintained in a humidified atmosphere of 5% CO2 in air. x10⁵ cells were seeded in 35 mm plastic dishes at 37°C. Twenty four hours later, these dishes were transferred to temperature gradient incubator (TN-206) and cultured at the various degrees of high temperatures from 39°C to 43°C for ten days. Then the recovery of the growth of these cells was studied at 39°C for 24, 48 or 72 hours, followed by the transfer of them to the condition at 37°C for 9, 8 or 7 days, respectively. We tried the same experiments at 41°C and 42°C.

These cell growth were determined by viable cell count stained by 0.2% nigrosin dye every day. Proliferation of SGF-3 was inhibited at more than 40°C, SGF-4 at more than 41°C and SGF-5 at more than 42°C. We did not observe the recovery of the growth of SGF-3 after the heating at 41°C for 72 hours and at 42°C for more than 24 hours. And the growth of SGF-4 after the heating at 42°C for more than 48 hours did not recover. Then the effect of heating at 42°C for 72 hours on SGF-5 were irreversible. It is concluded that in the case of the clinical application of the hypertermia, we must discuss sufficiently the suitable hypertermic conditions of individual cases.
A new approach to the search of therapeutic agents for treatment of advanced cancer. J. Lesbovic, G. Klorin, H. Argaman, and O. Klein. Dept. of Pathology, Sackler Faculty of Medicine, Tel-Aviv Univ., 69978 Tel-Aviv, Israel

DM-low malignancy; HM-high malignancy; MTX-methotrexate.

Tumor progression is often accompanied by loss of sensitivity to previously effective treatment. Development of drug resistance is probably the main reason for failure of therapy in advanced stages of cancer. The cell membrane structure is important for malignant behavior. Many properties which determine malignancy like cell differentiation, subversion, homing or antigenicity depend on it. Membrane structure may also be important for therapy: cell permeability may determine sensitivity to drugs and immunogenicity may determine vulnerability to natural or induced host responses. Most antitumoral agents are targeted to DNA. Drug resistance is mainly due to changes in cell membranes, causing decreased uptake of drugs. It is therefore possible that targeting of drugs towards the cell membrane may be more effective against advanced cancer. In the present study, two variants of AKR lymphoma which differ in degree of malignancy were compared for sensitivity to 1) hyperthermia and to 2) treatment with methotrexate in presence of a membrane acting polysaccharide, levan, which increases cell permeability. One hour incubation of the tumor cells at 45°C reduced both viability and tumorigenicity of the two tumor variants.

However, the effect was more marked on the HM than on the LM tumor: cell viability of the LM tumor was reduced to 68% as compared to 32% of the HM one. Tumorigenicity was strongly reduced in the HM variant and moderately in the LM one. We further tried to immunize AKR mice with cells of the two variants pretreated at 45°C. Challenge with viable cells showed a better protection against the HM than against the LM tumor. Treatment of tumor cells with either MTX or levan prior to inoculation to mice resulted in similar reduction in oncogenicity of the two variants. However, pretreatment by combined MTX-levan resulted in moderate effect on tumorigenicity of the LM variant and in almost complete abolishment of tumorigenicity of the HM variant. Treatment modalities targeted towards the cell membrane, like hyperthermia or treatment with a cytotoxic agent in presence of a substance which increases cell permeability, are more effective against highly than against low-malignant tumors.
MECHANISM STUDIES OF HYPERTHERMIA TO THE CANCER CURE. Zheng-Jun Zheng and Shu-hui Xu, Research Center of Biotechnology, Wuhan University, Wuhan, China.

Many experiments have shown the sensitive range of cancer cells to hyperthermia is at 42-44°C and have no marked effect. Why? Because of the lipid bilayer, the skeleton of membrane structure, is a fluid crystal structure around 37°C. After being subjected to some factors, phase changes were happened, such as: temperature, pH, cholesterol,ivalent cations, monovalent cations and so on. When temperature arose, nonrandom arrangement liquid crystal state of lipid molecule was turned to the liquid state of random arrangement. The lipid bilayer of cancer cell has tended to liquid state, so the cancer cells are more sensitive than the normal cells at 42-44°C. We observed the changes of membrane mobility; the electron transport between substrates and the dehydrogenases of respiratory chain. The mechanism of this effect is not clarified although it is conceivable that it may be ascribed to an action on mitochondria. In order to test this hypothesis, some functional parameters of mitochondria isolated from Ehrlich ascites tumor cells heated for one hour at 39°C, have been studied in association with Lonidamine. It has been observed that the oxidative metabolism of neoplastic cells is altered by the inhibition of the electron transport between substrates and the dehydrogenases of respiratory chain.

The results demonstrate that the temperature enhances the Lonidamine effect; in fact, some reduced oxidative capacity is obtained at drug concentrations three times lower than those used on the case of mitochondria isolated from non-heated cells. The effect may be related both to physico-chemical modifications of the inner membrane and to the alterations of the oxidation-reduction state of electron carriers. The possible mechanisms of this potentiation effects are discussed.

Work supported by CNR-Grant no. 84.00657.44 and by A.I.R.C.


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Simultaneous treatment of mitomycin C in 0.05 µg/ml with hyperthermia at 42°C enhanced the thermosensitivity of Chinese hamster V-79 cells and inhibited thermotolerance development which appeared during the heating at 42°C. So-called step-up thermotolerance (42°C 2hrs – 44°C graded periods), which was developed during the first heating at 42°C for 2hrs and monitored by the reduced thermosensitivity of V-79 cells to the successive heating at 44°C in the present experiments, was inhibited by the simultaneous treatment of mitomycin C in the above concentration all through the 42 and 44°C heated.

The sugiyed V-79 cells from the simultaneous treatments of 42°C and mitomycin C in the above concentration for 2hrs might develop a sort of thermotolerance of V-79 cells which could reduce thermosensitivity to successive 44°C heating, if the survived cells from the above first treatment were successively heated at 44°C alone for graded periods.

THE COMBINED EFFECT OF HYPERTHERMIA AND LONIDAMINE ON THE ELECTRON TRANSPORT IN EHRLICH ASCITES TUMOR MITOCHONDRIA. M.L. Marcante, R. Peroccioli, A. Floardi, A. Caputo, B. Silvestrini.* Regina Elena Institute for Cancer Research and Institute of Pharmacology and Pharmacognosy "La Sapienza" University – ROME, Italy.

It is well established that hyperthermia depresses the oxygen consumption in neoplastic cells. The mechanism of this effect is not clarified although it is conceivable that it may be ascribed to an action on mitochondria. In order to test this hypothesis, some functional parameters of mitochondria isolated from Ehrlich ascites tumor cells heated for one hour at 39°C, have been studied in association with Lonidamine. It has been observed that the oxidative metabolism of neoplastic cells is altered by the inhibition of the electron transport between substrates and the dehydrogenases of respiratory chain.

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SYSTEMIC THERMOCHЕMOTHERАРY OF ASCITE S TUMOR IN MICE BY INDUCING THERMOTOLERANCE IN THE HOST ANIMAL. W. Nakamura 1),**. and K. Komatsu 1), Aizu Central Hospital 1), and Nippon Culture and Well-Being Found., Med. Inst. of Adult Diseases 1), Japan.

In an extensive trial to elucidate potential synergism between systemic hyperthermia (SH) and CDDP in the treatment of ascite tumor in mice, we did not identify any protocol that significantly enhanced survival or cure rates beyond the potential of either treatment modality alone.

In the present study, time course variation of thermosensitivity after an initial SH was investigated in both normal and tumor bearing mice. Then, a trial was made to put in practice the treatment with a more powerful SH in the thermotolerant stage of the animals. Obtained results were as follows.

1. Conditioning SH of 42.0°C for 10 min induced in normal mice a transient thermotolerance. LD50 of test SH at 42.0°C was 43, 97 and 48 min on days 0, 1 and 2 after the conditioning SH, respectively. When the test SH was at 43.5°C it was 8, 20 and 10 min on days 0, 1 and 2 after the conditioning SH, respectively.

2. Ascites tumor bearing mice were more sensitive to the SH. LD50 of the test SH at 42.0°C was 8 min one day after the i.p. transplantation of 107 P388 cells. Whereas, it was more than 30 min one day after the conditioning SH at 42.0°C for 5 min.

3. Induction of thermotolerance in tumor bearing mice made it possible to treat them with a SH sufficiently powerful to enhance the effect of chemotherapy used in combination.

While numerous investigators have shown human tumors to be responsive to hyperthermia, treatment of intrabdominal tumors has generally not been successful due to the inability to deliver adequate thermal doses to depths below the skin surface. To eliminate this problem, intraoperative surgical techniques have been developed for delivery of localized current fields to these locations. The tolerance of a liver of 30 animals to intraoperative interstitial hyperthermia (44°C for 40 minutes) via flexible electrodes driven with 500 kHz generator was investigated. Tolerance was monitored by daily CBC and SMA-20 values. SGOT, CPK, and LDH levels increased approximately 5 times control value within 24 hours post-surgery, and returned to normal values within 7 days. The SGPT level remained elevated 7 days post-surgery, but returned to normal thereafter. Tumor protein, serum potassium, creatinine, hemoglobin, and red blood cell count, all decreased within one day post-surgery. While creatinine, potassium and total protein returned to control values within 7 days, RBC count and hemoglobin remained depressed for 2 weeks. All treated animals survived. To assess toxicity in animals with spontaneous liver tumors, treatments in 3 animals were carried out during 22 days to be well tolerated. The tumors showed a marked regression at necropsy.


Hyperthermia has been observed to alter metastatic potential of tumors in some spontaneous or periodic investigations of the relationship between heating alone or combined with other modalities and tumor metastasis have given variable results. Depending on treatment conditions, tumor model and other less understood factors, the percentage of metastases development can increase, decrease or be unaffected (Hill and Denekamp, Brit. J. Radiol. 55, 441, 1982). Heat stress also induces or enhances synthesis of a set of heat stress proteins (Hsp) which are believed to function in a protective role in subsequently induced thermotolerance although no direct evidence exists. Some Hsp are reported to be associated with cell membrane and cytoskeletal structures which have implied roles in metastasis. Also Hsp synthesis under some conditions could alter the ability of tumor cells to survive stress associated with microcirculation or growth in a new site thus leading to the occasional observed altering of metastasis. In this study, heat and arsenite treatments were designed to generate a complete set of Hsp and analogous arsenite stress proteins (Asp) and thermotolerance with minimum cell killing. The influence of these treatments on subsequent experimental (blood-borne) metastasis was examined simultaneously in which clonal tumor cell populations of highly reproducible metastatic potential were compared to regimens with MGd, DFMO plus heat, MGd. DFMO plus ACNU as well as ACNU only, tumor growth was much the same in the control, while in mice given MGd, DFMO plus heat, there was a diminution in tumor growth. In the same period after the treatment using MGd, DFMO, ACNU plus heat, marked suppression was observed for over 4 days after the treatment. On the contrary, the MGd, DFMO plus heat group showed a sharp increase on the 4th day after treatment. Tumor tissue putrescine levels in 2 groups given MGd, DFMO, ACNU plus heat as well as MGd, DFMO plus ACNU decreased significantly 2 days after cessation of the treatment. The other 5 groups were unchanged in tissue PUT levels. These data suggest that a combination of MGd with DFMO leads to a favorable thermosensitization to the anticancer efficacy of ACNU.
Hyperthermia as a new cancer treatment modality combined with radiotherapy and/or chemotherapy has well established based on the results of clinical trials in superficial tumors in which their heating and temperature measurement were easily feasible. But the difficulty of heating the tumors deep in the body prevents its widespread use in cancer treatments. We have developed an RF capacitive-type heating equipment named Thermotron RFS which is used in superficial as well as deep-seated tumors with a very low systemic heating. Radiofrequency current at MHz is applied to the tumors with a pair of electrodes with water-cooled boluses to avoid overheating of subcutaneous fat tissue and edge effects. A well-balanced RF circuit permits good penetration of the current through a human body resulting in heating tumors in the current. Selective heating of the tumors is obtained by the difference in blood flow between normal and tumor tissues. The temperatures in the tumor and surrounding normal tissues are continuously monitored by non-perturbed thermocouples inserted in the tissues. The temperature at any point can be maintained as indicated by computer-operated RF output control. The heating patterns in phantoms and pigs have been confirmed in cancer in the chest, abdomen and pelvis. The equipment has been widely used in many cancer centers in Japan for hyperthermia combined with chemotherapy or chemotheraphy in patients with refractory cancers.

A MULTIFREQUENCY COMPUTERIZED SYSTEM FOR LOCO-REGIONAL HYPERTHERMIC APPLICATIONS

A. Borroni (1), G. Calamai (1), L. Lachi (1), G. Marsigli (1), G. Lazzarido (2), P. Mauro (2) and G. Arcangeli (2)

An apparatus has been designed, bearing in mind the goal of minimized costs, which guarantees the necessary flexibility for clinical experimental hyperthermia. Large bandwidth applicators, working in the frequency bands from 20 to 50 MHz and 20 to 45 MHz, of the "ridged horn" type filled with high permittivity dielectric (ionized water) have been developed. This solution allows a remarkable reduction in the applicator dimensions with constant capacity, cooling and matching to irregular skin surfaces. The system can be connected to an array of a maximum of 4 applicators of different type and size for different treatment. The lower signals from generators of 240 c.AMP are injected in a single coaxial waveguide at unlimited power levels with continuous power regulation. Circulating selcted water is thermostated to keep skin temperature constant at 37-38°C. The temperature monitoring is continuous during treatment with 2 °C temperature cameras. The heating is controlled by a digital computer with a high level of reliability. The capabilities of the computerized system in clinical applications have been tested and the performances on phantoms and in situ animal test have been recorded.


Starting from the fact that there is no perfect physical heating procedure for optimal hyperthermic tumor treatment, the need for a cancer multistep therapy (CMT) concept is underlined. Radiofrequency current is applied at 27.12 MHz radiofrequency technique. It is characterized by specifically designed, exchangeable applicators, which can move over or around the body's surface. The scanning applicator principle, meanwhile imitated by others, has several advantages: (1) the planar and focused raster parameters of the applicators are adjustable at choice and allow whole-body as well as regional heating; (2) skin burns "hot spots" are avoided, in case of need by superficial cooling; (3) the heat deposition is homogenized by the applicator motion and shifted to deeper body regions; (4) applicators can be placed in natural openings of the body for local heating, if necessary; (5) the two-step principle (soleo-thermal hyperthermia + soleo-thermal) combined with consecutive regional or local heating, up to 42.5°C by reducing the raster parameters is well tolerated by the patient and allows to reach higher target temperatures in shorter periods of time. At present, the new CMT Selectotherm technique is clinically tested. Results obtained previously by using a simpler prototype of the Selectotherm machine demonstrate the substantial progress that can be achieved by appropriate heating and multistep treatment protocols.
Carnegie-Mellon University, Pittsburgh, Pa.

It is now clear that various cellular and viral oncogenes encode for protein growth factors and/or their receptors. Studies of the role of such growth factors in the process of transformation of human fibroblasts has been slow because of the lack of a serum-free medium which will support the cloning and long term growth of such cells in culture. We have developed such a medium, using as a base the M199BIII with serum replacement supplements of Ham and colleagues (PNAS 75: 5888, 1978). Critical additions to Ham's basic medium appear to be serum albumin which serves as a lipid carrier (Kan and Yamamoto, J. Cell Physiol 105: 125, 1980) and gelatin and fetuin, which serve as attachment factors (Nambu et al., Int. J. Cancer 46: 645, 1980). In this medium, diploid human fibroblasts clone with an efficiency of 2% to 6%, grow for extended periods of time (2-3 days) and exhibit a doubling time of 24 hours. The clones formed reach 2% in diameter in 14 days and appear identical in density to clones obtained within medium containing low fetal cell serum. Using this medium we have determined that epidermal growth factor (EGF) is the major mitogen required for clonal and long term cell growth of human fibroblasts. This observation was confirmed by the addition of EGF-specific antibody which caused cell growth to remain at the level of control cells grown in the absence of EGF. Platelet-derived growth factor (PDGF) was a poor substitute for EGF and did not exert a stimulatory effect when added with EGF. A human fibrosarcoma derived cell line (H102009) grown in our modified M199BI medium without addition of either 10% or PDGF. Studies are underway to delineate the mechanisms by which these tumor derived cells ablate the normal requirement for growth factors. The research was supported by NIH Grants 5X209F and D01 Contract 445-80.

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The c-H-ras fragment (c-H-17, 3.5 kbp) as well as the whole viral DNA of human adenovirus type 4 (Ad4, subgenus E1-C) can transform rat 3Y1 cells, and the resulting transformed lines induced by Ad4 DNA c-HlY and by the HindIII-C (4CY) show similar incomplete transformation phenotypes. The viral E1A and E1B DNA sequences can be detected in cloned 4WY1, 4WY1, 4CY4, and 4CY6 lines.

4CY and 4CY lines were completely transformed by transfection of the human activated c-H-ras gene (pE1B6) showing anchorage independency and tumorigenicity in syngeneic newborn rats. Northern blot analysis detected not only Ad4 E1A mRNAs and human c-H-ras mRNAs, but a little amount of Ad4 E1B mRNAs which were undetectable in the parental 4CY cells. 4CY-3 (a cloned cell line of 4CY) were transformed by transfections of high molecular weight DNAs from human cho-reasinoma cell lines which cannot transform NIH3T3 cells. Cellular DNAs of transformed 4CY-3 cells induced transformation in secondary transfection assays.


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SCREENING OF AN EPIDERMAL GROWTH FACTOR-RECEPTOR KINASE INHIBITOR, ERBSTATIN, FROM STREPTOMYCIES

K. Iwase, M. Imoto, T. Sawa, T. Takeuchi and N. Iwase
Institute of Medical Science, University of Tokyo and Institute of Microbial Chemistry, Tokyo, Japan.

The binding of epidermal growth factor (EGF) to its receptor, which is associated with tyrosine protein kinase, stimulates phosphorylation of the tyrosine residue in the receptor, which then induces phosphorylation of the tyrosine residue of other proteins. Many oncogene products also have tyrosine kinase activity, and the primary structure of v-erb-B protein of avian erythroblastosis virus (AEV) has been shown to be closely related to that of the EGF receptor. Therefore, we have intended to screen an inhibitor of EGF-stimulated tyrosine kinase associated with the membrane fraction of human epidermoid carcinoma A431 cells.

We isolated a potent inhibitor of tyrosine kinase of the A431 membrane fraction from the culture filtrate of a Streptomyces strain and named it erbstatin. It has a hydrophilic structure and inhibited phosphorylation of the A431 membrane fraction in the presence of EGF at about 0.5 μg/ml. It did not inhibit the binding of EGF to the receptor and it was confirmed to inhibit phosphorylation of the 120K EGF receptor by gel electrophoretic analysis. Inhibition of tyrosine kinase appears to be specific, because erbstatin only weakly inhibited cyclic AMP-dependent protein kinase.

Erbstatin is a new compound which specifically inhibits tyrosine kinase. Biological effects of erbstatin are being studied.
CAHUS: ILIITIC ACTIVITY OF ANGIOTENSIN-GENE INITIATION OF DNA REPLICATION-OCTAVIAN URIŞTE-IMMUNOCHEMICAL LAB. OF POLYCLINIC, CLUJ-NAPOCA. PRESENT ADDRESS: CRISTINA POPAS, CRISTINA PETRĂŞ, CLUJ-NAPOCA, ROMANIA.

According to our genetic-cytochemical theory on the origin of oncoys, documented since 1965, the nuclear genome of present eukaryotes is formed of ancestral genes, inherited from an early prokaryote progenitor, (which contain only the information convertible into an ameable undifferentiated cell phenotype) and specific oncogenes (proteins selected and accumulated under oxygen-free terrestrial conditions) which contain specific globin genetic information convertible into endocellular reprogrammation into a vast range of cytodifferentiations, different aerobic cell-like phenotypes of the same genotype. This information convertible into the inhibitor protein of DNA replication is stocked in the primordial ancestral gene carrier of autoreproducible molecular code, the malignant transformation is the effect of illicit derepression and of continuous expression of this "ancestral gene" in tumor cells. The Hind III-cell with blocked oncostera has, today, our theory has been fully experimentally confirmed along international lines. We have turned out the presence of ancestral nuclear nucleosomes in the nuclear genome of the present eukaryote, the microtubule system homology between the normal and oncogenic cells (initiator of DNA replication) and "line" oncogene from animal kingdom, it also proved true for the existence of homonuclei of the present genome, also the existence, immunorecognition of WDGR gene normal protein with monoclonal anti-1P antibodies (anti-insulin antibodies). Therefore, the information for cancer is the very ancestral information for the initiation of DNA replication but exclusively related. Oncoc in the executional sequence discerns the normal protein itself inducing DNA replication in continuously expressed and accelerated concentrations. In conclusion, under carcinogenic conditions, the normal ancestral gene inhibitor of DNA replication vector normal vector.


To understand the mechanism of expression of transfused gene and to elucidate the nature of revertant of fusion gene, we have been characterizing two classes of revertants isolated from Kirinton transformed NIH-MTB cells (strain C57BL6/N, C57BL16). Our previous study showed that novel expression in these tumor genes to depend on abnormal host functions. We have found that one of the revertant clones expressed the Kir might be due to the KSHV genome in NIH-MTB cells. In this report, the cDNA of a novel class of revertant have been isolated from NIH-MTB cells. Our results suggest that the level of FN production plays an important role in expression and suppression of transformed phenotype induced by the viral oncogene and, possibly, by other oncogenes including v-Ha-ras, v-raf, and v-src.


A strain of normal rat was transformed by UV-induced tumors. The tumor cells were found to contain a single-stranded DNA band with characteristics of a DNA fragment that was shown by an analysis of poly(A) cDNA as competing with that in NIH-MD-104. The DNA synthesis was markedly increased in transformed NIH-MD-104 cells and in control NIH-MD-104 cells.


Localization of cellular oncogenes (c-ons) near the breakpoints of chromosomal translocation as well as their enhanced expression in neoplastic cells has indicated involvement of these genes in neoplastic process. We have performed a search for novel chromosomal changes associated with c-ons activation in rat leukemia with a help of molecular genetics and molecular cyogenetics.

An enhanced transcription of the cellular homolog of the transforming sequence of Abelson murine leukemia virus (v-onco) was observed in c-ons bearing K/RV cell line of T17-dimethylbenzanthracene-induced leukemia in the Long-Evans rat. By molecular hybridization studies assigned c-ons and ribosomal cDNAs (RcDNA) to the breakpoint of the translocation (15;17) in K/RV cells. Since the c-onco activation was not observed in the parent cell line (K0) from which the K/RV was derived and the latter was different from the former in the presence of the above marker chromosome, the present result provided evidence of secondary activation of c-ons during katayot pe evolution of cloned malignant cells (Naoda T., JNCI, 77, 1979, 1986; Takahashi et al., PNAS, in press).

We have cloned a cDNA probe of 11.8Kb long from K/RV cells containing segments hybridizable with probe pBlueskib of v-onco and pHSO cDNA element of RNA in a close vicinity, which imply that they are translated at the molecular level (Ohama S., submitted to Cell).
4383 EFFECTS OF THE CALCIUM ANTAGONIST FLUNARIZINE ON THE RECOVERY FROM POTENTIALLY LETHAL DAMAGE INDUCED BY X RAYS ON A B16 MELANOMA CELL LINE
A Benelli, G.B. Lucca, F. Terziotti, C. Canepa, P.I. Serri, L. Lorenzini and M. Belli
Regina Fleser inst and Polifarma Study Ctr, Roma, Italy
Local anesthetics (lidocaine, procaine, etc) and tranquilizers (chlordiazepoxide) are known inhibitors of the recovery processes from X-ray induced damage both in procyclic and in ascites tumor cells. This effect has been attributed to the interactions of these compounds with the phospholipid bilayer of cell membranes and to the consequent modifications of cell membrane functions. Serri et al (Antonioli et al 1980 155-277, 1985) have recently demonstrated that the anticalmodulin drug flunarizine (FL) inhibits in vitro several cell functions of a B16 melanoma cell line as well as the incorporation of tritiated thymidine into nuclear DNA. Moreover literature presents several indications that anticalmodulin drugs (trifluoperazine, W13, etc) inhibit tumor growth and replication "in vivo" and the DNA repair from bleomycin damage. Experiments were therefore designed to evaluate whether FL interferes with the recovery processes of B16 melanoma cells from potentially lethal damage induced by X-rays. Results indicate that FL (5 μg/ml) inhibits the recovery from potentially lethal X-ray damage. Untreated melanoma cells had a five fold increase of the surviving fraction 24 h after the irradiation with 12.7 kV while cells treated with 1 μg/ml of FL had a recovery of 1.3 fold the FL time and dose dependent, inhibition of the recovery from potentially lethal damage, caused significant modifications of the rate of expression of the 106 melanoma cells increasing the killing effect of X-rays.

Supported by a grant from the Italian National Research Council/Lazer Project "Oncology" Contract N° 840657 44

4385 SCALING THEORY OF TRANSIENT NONLINEAR FLUCTUATIONS IN CANCER RADIOTHERAPY
B.B. Bhattacharya
Department of Physics, St. Xavier's College, Calcutta 700 036 & Institute of Theoretical Biophysics, Hooghly 712 022, India
A theoretical approach is proposed to explain the survival of human tumor cells during radiotherapy and growth in cancer cell lines. Our model is based on scaling theory of transient nonlinear fluctuations and formation of macroscopic order. It is suggested in the Garay-Leffever (G-L) model of growing tumoral tissue, the G-L model considers a transition between the macroscopic and micro-scale of cancer cells. The malignancy growth develops when the micro-cell attains a critical dimension. The stochasticity in the transition of the cell as well as the radiation resistant human cell lines during radiotherapy may open a new light in the understanding of eucaryotic DNA repair processes, and is described in our problem by the following differential equation:

\[ \frac{dF}{dt} = - \frac{\lambda}{F} \left( F + \frac{1}{2} \int F^2 dt \right) \]

where \( F \) is the density of the population, \( \lambda \) is the death rate.

Reference:

384 RADIOSENSITIVITY TEST FOR CANCER OF UTERINE CERVIX
Mitsuhiro Moguchi, Isao Shiozawa, Taketo Kitahara, Teruyuki Yamazaki, Toru Fukuta, Yoshiharu Tsukahara, Shoji INAI
Dept. of Obstetrics and Gynecology, Shinshu Univ. Sch. of Med., Matsumoto 390, Japan
*Dept. of Obstetrics and Gynecology, Yamanashi Med. College, Yamanashi, Japan

To estimate the radio sensitivity for cancer of uterine cervix before treatment, we are carrying out the test irradiation of 1000 rad to the primary tumor.

Radiosensitivity is judged by comparing the histological changes before and seven days after irradiation.

Histological criteria for judgement of radiosensitivity are as follows:
1) Degree of decrease in size of carcinoma, 2) Degree of damage at the bottom of cancer nest, or fragmentation of this nest, 3) Degenerative changes of nuclei (swelling, atrophy, pyknosis), 4) Number of viable cells and normal mitosis, 5) Degree of interstitial reaction, and so on.

In 237 cases with cervical cancer stage Ib to stage IV treated by radiotherapy, the 5-year survival rate of good sensitivity cases had 80.4% (25 alive in 59 cases) and that in poor cases was 56.3% vs. 62.0%, respectively.

That means, this sensitivity test may be one of the important factors for selecting the treatment method.

386 CYTOKINETOGRAPHIC DNA MEASUREMENTS TO EVALUATE THE EFFECT OF PREOPERATIVE RADIOTHERAPY AS ASSESSED HISTOLOGICALLY
G. Franzen, J. Olofsson, M. Tytor, C. Klintenberg and B. Risberg, Dept. of Otolaryngology, Oncology and Pathology, University Hospital, Linköping, Sweden.

In a retrospective study of formalin-fixed, paraffin-embedded material, DNA measurements have been performed until now on 31 squamous cell carcinomas from the oral cavity according to the technique described by Medley et al. (1983), Risberg et al. (1986) and Franzen et al. (1986). DNA ploidy level, S-phase fraction and the occurrence of polyploid nuclei-PPN (DNA values >2.5 basal modal peak) were estimated and compared with the T-classification, histological differentiation and the response to preoperative radiotherapy (34-50 Gy) as assessed histologically in the operation specimens.

Fifteen of the 31 tumours were classified as DNA diploid and 16 as DNA non-diploid. Residual carcinoma was found in 12 of the 15 diploid tumours and 6 of the 16 non-diploid. Moderate response was present in one of the diploid and in two of the non-diploid tumours. The mean S-phase value was 6.8% (1-14%) for the diploid and 15.5% (3-30%) for the non-diploid tumours. The mean S-phase value was 12.4% for the tumours that were eradicated by the preoperative radiotherapy and 8.5% for those with residual carcinoma. PPN were present in 10 of 12 diploid tumours with residual carcinoma following radiotherapy and in 4 of 6 non-diploid. DNA ploidy level, S-phase fraction and the occurrence of polyploid nuclei-PPN (DNA values >2.5 basal modal peak) were estimated and compared with the T-classification, histological differentiation and the response to preoperative radiotherapy (34-50 Gy) as assessed histologically in the operation specimens.

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One of 3 diploid tumours that were eradicated by preoperative radiotherapy had PPN and 2 of 10 non-diploid. T-classification and histological differentiation did not correspond to the radiation response. Six of the 15 diploid tumours had regional metastases and 8 of the 16 non-diploid. All 6 diploid and 4 of the 8 non-diploid had residual carcinoma after radiotherapy.

The non-diploid tumours responded better to preoperative radiotherapy than the diploid tumours. The mean S-phase value was higher (12.4%) for tumours eradicated by preoperative radiotherapy than for those with residual carcinoma (8.5%). The presence of PPN was associated with residual carcinoma after preoperative radiotherapy in 33% (14/41) compared to 33% (3/13) for those tumours that were eradicated (p <0.01).

OK-432, a lyophilized preparation of Streptococcus pyogenes, is an effective agent for treating cancer among many biological response modifiers. We studied the effects of combination therapy using locally administered OK-432 with irradiation in mice with murine fibrosarcoma (AFS), a spontaneous cancer in C57Bl/6 mice, which has low immunogenicity and is radioreistant. The fibrosarcoma was transplanted into the right hindleg of syngeneic mice. With a simple administration of OK-432 in these mice, there was no decrease in tumor growth, compared with untreated controls. However, a marked effect was obtained when a single dose of 400 U of OK-432 was administered just after a single 4 Gy irradiation, compared with radiation alone. Next we studied the relationship of OK-432 to irradiation in this combination therapy. The OK-432 injection increased the tumor control rate (TCR) by 20% in our recent study, we got better effects with 2 OK-432 injections, one at the irradiation time and one a week later, even with smaller doses such as 0.5% of OK-432 than a single dose of 400 U of OK-432, combined with 4 Gy irradiation. We are now carrying out further studies of 2 OK-432 injections combined with radiation. I'm sure combination therapy will play an important role in cancer treatment in the near future.

THE THERMAL RESPONSE AND THERMAL ENHANCEMENT OF A MELANOMA CELL LINE DEVELOPED IN CULTURE BY TRANSFORMING C3H 10T1/2 MOUSE CELLS. G.P. Ramsay and C.J. Azim, Ontario Cancer Treatment and Research Foundation, Medical Physics, Ottawa Regional Cancer Centre, 140 McLauren Ave., Ottawa, Ontario, Canada.

The mouse C3H 10T1/2 cell line was irradiated to 4.0 Gy and cells were grown into a monolayer culture and left for eight weeks. After eight weeks, the irradiated cells had transformed the monolayer to form transformed foci. Several transformed foci were isolated from the monolayer and resuspended into a 1% agarose solution. After six to eight weeks of growth spherical colonies were observed. These were darkly pigmented. One of these spheres was selected and subcultured as a cell line and was called RC5. This cell line was subsequently tested for radiation and heat sensitivity. The radiation survival curve of RC5 had a large shoulder which was also observed for human melanoma cell line. Soft x-ray experiments showed that RC5 had a greater ability to resist sublethal damage than the normal cells. RC5 was also more resistant to heating at 40°C than the normal cell line. Heating at different irradiation resulted in a reduction of the survival curve shoulder, indicating that sensitivity to heat and to radiation were independent. Using X-ray and microwave heating methods, we found that the melanoma cells increased in response to both cells as they grew into plateau phase. The heat and radiation sensitivity of RC5 did not appear to be related to the melanin content of these cells. The black cells showed a higher ability to resist melanin damage than the normal cells.
EFFECTS OF CAROTENOIDS AND VITAMIN A ON THE MUTAGENICITY INDUCED BY DIRECT AND INDIRECT MUTAGENS IN SALMONELLA TYPHIMURIUM.

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The antimutagenic activities of beta-carotene (BC) and canthaxanthine (CX), two carotenoids respectively with and without pro-vitamin A activity, and of vitamin A were controlled by photomutagenicity induced in S. typhimurium TA 102 by the indirect mutagen B-methoxypсорalen (B-MOP) and by mutagenicity induced in S. typhimurium TA 100 and TA 1535 by the direct mutagen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). The results demonstrated that BC and CX but not vitamin A inhibit the B-MOP photomutagenesis occurring in untreated conditions, up to 60%; they had no effect on photomutagenesis in anoxia; the latter was however 63% less than in air. Thus, B-MOP photomutagenesis appeared to depend on a two-step reaction, namely an oxygen dependent DNA photoadduct followed by an oxygen dependent second step sensitive to carotenoids, most probably due to an in vivo singlet oxygen formation. As far as mutagenicity induced by MNNG is concerned, BC, CX or vitamin A had no effect at all. Thus, the inhibitory effects of BC and CX on both B-MOP photomutagenesis and photocarcinogenesis turned out to be well correlated. They also suggested an application to prevent the oncogenic risk of PUVA treatment in humans without affecting the therapeutic action. The lack of effect of BC and CX on MNNG mutagenesis appeared also correlated with the observation that only progression (but neither initiation nor promotion) was affected by carotenoids.

**4395** ANTIMUTAGENIC ACTION OF RADIOPROTECTOR WR 1065 IN V-79 CELLS. N. Nagy** and D.J. Grdina**, Central Institute for Tumour and Allied Diseases, Zagreb, Yugoslavia, and Argonne National Laboratory, Argonne, Ill., USA

We have investigated the compound 2-(aminopropyl)amino ethane thiol (WR 1065) as a protector against bleomycin (BLM), nitrogen mustard (HN2) and cis-diaminedichloroplatinum (cis-DDP) induced mutagenesis at the hypoxanthine-guanine phosphoribosyl transferase (HGPT) locus in V-79 Chinese hamster cells. WR 1065 was effective in protecting against cytotoxicity induced by each of the agents tested. The induction of mutants by either BLM, HN2 or cis-DDP corrected for the spontaneous background mutation frequency, was linear in all cases. Mutation frequencies per unit of agent tested: 7.2x10^-6 per unit BLM; 6.6x10^-6 per unit HN2 and 2.5x10^-5 per unit cis-DDP. WR 1065 effectively reduced mutation induction by each of the agents tested to: 3.7x10^-6 per unit BLM; 4.6x10^-6 per unit HN2 and 1x10^-5 per unit cis-DDP. Single strand break (SSB) formation in DNA following treatment by each of these agents was also assayed using the method of alkaline elution. WR 1065 protected in all instances against the formation of SSB. Due to their ability to better protect normal cells compared to tumor tissue against acute effects, radioprotectors have generated considerable interest for use in improving the therapeutic gain of radio and chemotherapy. The ability of these compounds to also protect against the mutagenic effects of therapeutic agents may be an important additional benefit for consideration in their use in the treatment of human neoplasia.

**4396** THE EFFECT OF PHENOLIC ANTI-OXIDANTS ON THE GENOTOXICITY OF BENZO/A/ PYREN EVALUATED BY SOS-CHROMOTEST

J. Sawicki, K. Domowicki, Dobrożadziak, A. Bednarkiewicz, Med. Acad., 2nd Environmental Health Sciences, 02-097 Warsaw, Poland.

The new bacterial short-term test called SOS-Chromotest was used to study the influence of anti-oxidants butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) on the genotoxicity of benzo/a/pyrene (BP). The effects of anti-oxidants on the activation of BP were tested in vitro, when BHA or BHT were added directly to the incubation mixture or in vivo when BP was activated by 96 fractions isolated from livers of anti-oxidant-fed male Swiss mice. Antioxidants used in vitro did not affect significantly the genotoxicity of BP, only the high concentration of BHT appeared to exert some inhibitory effect. The activation of BP by 96 fractions from BHA-fed mice increased by 100% and from BHT-treated decreased by 30% the genotoxicity of BP compared with control. The induction of the genotoxicity of BP towards 6-6. coli in SOS-Chromotest by BHA is difficult to interpret at present. Further studies are necessary to establish the relevance of these findings to the adverse actions of BHA in chemical carcinogenesis.

**4397** MOLECULAR CHARACTERIZATION OF INDUCED MUTATIONS IN MAMMALIAN CELLS. Alina SARASIN, François BOURRE, Catherine HAKAINI, Jean-Pierre DUBARRY, Laboratory of Molecular Mutagenesis, Institut de Recherches Scientifiques sur le Cancer, BP H - 94800 - VILLEURBANNE, France.

The molecular mechanism of mutagenesis induced by physical or chemical agents has been analysed in mammalian cells, using normal or modified simian virus 40 (SV40) as a biological probe. SV40 is particularly relevant because it is repaired and replicated only by the host cell enzymes and because its chromatine structure is resistant to the mutagens. Therefore we have developed a genetic system based upon a phenotypic reversion of SV40 temperature-sensitive mutants (tsA60 or tsA521) toward a wild type phenotype. This assay allows us to characterize at the molecular level mutations induced by various treatments such as ultraviolet light (UV), acetoxyacetylaminofluorene or heat-deproteination (H2O2). Three of these treatments are very mutagenic in SV40 DNA and baseless sites (apurinic sites) appear to be the most mutagenic lesion in our conditions. Molecular characterization of some of the induced SV40 mutants shows that these three types of mutagens induce base pair substitution in the SV40 genome. After UV-irradiation, base pair substitutions are always localized opposite UV-induced DNA lesions such as pyrimidine dimers or (T-U) pyrimidines (3). Furthermore, we are developing a new biological assay in which only one specific SV40 SV DNA strand will be UV-damaged. This technique allows us to determine the efficiency of a given induced DNA damage in inducing a second strand and eventually to characterize the type of induced mutations in regard to the damaged strand. (1) F. BOURRE and A. SARASIN, Nature, 286, 1980, 687-689. (2) A. Gentil, A. Margot and A. SARASIN, Mutation Res., 192, 1984, 131-147. (3) F. BOURRE, G. Renault, P.C. Sawell and A. SARASIN, Biochim. Biophys. Acta, 69, 1982, 234-239.


The phenanthridine alkaloid galanthamine (nivalin, Pharmacos, Bulgaria) is one of the most valuable anticholinesterase substances of plant origin in antitumor activity. Recently, an investigation of the carcinogenicity of nivalin against leukemia P388 and Lewis lung carcinoma has been established. In an attempt to study some mechanisms of this effect, the possible genotoxic activity of nivalin was investigated. In addition the assessment of chronic toxicity as well as the possible genotoxicity and carcinogenicity of nivalin was also needed, because of the wide use of this drug especially among the contingent of young children. The data obtained have shown that a six-months treatment (5 times a week) of hybrid BDF mice and Wistar rats with nivalin given orally at doses of 0.25, 0.5 and 1.0 mg/kg or s.c. at doses of 0.125, 0.25 and 0.5 mg/kg respectively did not cause any biometrical, haematological, histological and clinico-biochemical signs of chronic toxicity. Furthermore, no genotoxic activity was detected employing the following short-term tests: UNS in human lymphocytes treated with nivalin (0.0001-0.15 mg/ml, or + 5% mix); BALB/c female mice treated with nivalin (0.0015-1.5 mg/ml, or + 5% mix); 2-aminoanthracene treated bone marrow cells of mice injected s.c. with nivalin at doses 5.0 and 10.0 mg/kg. In a long-term bioassay in mice treated with nivalin given s.c. at doses of 0.05-0.5 mg/kg in the drinking water in concentrations 0.05 and 0.2 mg/kg no evidences for carcinogenicity were obtained.
4399 AROMATIC AMINE-INDUCED MUTATIONS IN SINGLE AND DOUBLE STRANDED DNA. Pawel C. Gupta, Mei-Pei Lee and Charles M. King. Department of Chemical Carcinogenesis, Michigan Cancer Foundation, Detroit, Michigan 48201 U.S.A.

MI3 lac hybrid phage (M13mp8) and its bacterial host, E. coli (JM103), have been used in our laboratory in a forward mutation assay to examine aromatic amine-induced changes in the DNA. In this assay, M13mp8 phage DNA (single or double stranded) is modified with carcinogen, transfected into competent host JM103 cells (E. coli lac zani5) with or without SOS-induced functions, and screened for mutants of the marker enzyme β-galactosidase on a selective media. 2-Aminofluorene (AF) substituents were introduced at the C-8 position of DNA by reaction of nucleic acid with N-hydroxy-2-AF in ethanol and citrate buffer at pH 5.

Different levels of modification were established by reaction with a tritiated fluorine derivative for periods of up to one hour. M13mp8 single stranded DNA containing 5, 10, 15 or 26 AF adducts per molecule or double stranded DNA with 15, 27, 51 or 72 adducts per molecule showed a sequential increase of 2 to 11 fold in mutation frequency as reported earlier. We have isolated and screened mutants from various experimental conditions, e.g., from single or double stranded DNA with different levels of AF substitutions and with or without SOS-induced host functions. We have used Sanger’s dideoxyextrinucleic method for sequencing DNA from these mutants. Sequencing of the regulatory region of the lac gene insert (bases 6100 to 6215) and the N-terminal structural part of β-galactosidase enzyme (bases 6216 to 6400) indicate base substitution (G→T), deletions and recombination-induced insertion. No frameshifts have been observed in the 30 mutants sequenced thus far. Other mutants are being sequenced to determine the relationship of the experimental conditions to the mutagenic event and to explore the feasibility of using this system to examine single site specifically-modified DNA for mutagenesis studies. Supported by NIH grants CA23386 and CA38844.

4400 THE SIMPLE METHOD FOR DETECTING MUTAGENIC ACTIVITY IN GASEOUS COMPOUNDS BY BUBBLING

H. Shizuku, Dept. of Public Health, Jikei Univ. Sch. of Med., Tokyo, Japan

We have developed a simple method by bubbling for detecting the mutagenicity in gaseous compounds because the suitable mutagenic test for gaseous or volatile compounds has not been established. Vinyl chloride (VC), ethylene oxide (EO) and nitrogen dioxide (NO2) were tested. VC (10% v) was added into DM50 in a tube by bubbling for 10-15 minutes. Then 0.1ml of the above DM50, 0.1ml of a fresh cultured tester strain E. coli WP2uvrA/KM) and 0.5ml each of 39 were mixed in a gas tight vial, shaken at 37°C for 30-120 minutes and poured with 2% of top agar onto a minimal glucose agar plate. Mix performs were scored after incubation at 37°C for 48 hours. On the other hand, the concentration of VC in the above DM50 was measured by gaschromatography. The positive results with dose-response effects were observed. The mutagenicity test for ED and NO was performed by this method using the S. typhimurium TA100 strain and a significant dose-response effects were observed without mix. This bubbling method is useful for detecting mutagenic activity in gaseous compounds.

4401 EVALUATION OF CHEMICAL CARCINOGENESIS BY USING NEWBORN AND INFANT MICE. Koji Fujii, Dept. of Pathol., Inst. Basic Med. Sci., Univ. of Tsukuba, Ibaraki-ken, Japan 305

Forty-three chemicals, which include carcinogens and non-carcinogenic substances, were tested for carcinogenicity in ICR and CDFl mice. The subcutaneous administration was started at newborn age, and the animals were observed for one year. Comparative study on the carcinogenicity of chemicals was made between the newborn mice tested and the adult mice or rats reported: 85% of the chemicals tested in newborn mice was consistent with the results in adult mice. And, the coincidence between the result tested in newborn mice and that reported in adult rats was 84%.

Contradictory results were obtained in the following chemicals: 4-aminooazobenzene (AB), 3-hydroxyanthranillic acid (3-OH-AA), and nicotinic acid hydrasde (INAH). AB was carcinogenic in newborn mice (false positive), and 3-OH-AA and INAH were non-carcinogenic in newborn mice (false negative).

Main target organ of tumors in mice depends on chemical; aromatic hydrocarbons induced tumors in lung, liver and lympho-hematopoietic tissues; nitrosamines, nitrous esters and SKF-525A in lung and liver; azodyes, aromatic amines, safrole and sterigmatocystin in liver; 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) in lung and the site of injection.

4402 INDOCTION OF RESPIRATORY TRACT TUMOURS BY TRANSPLACENTAL ADMINISTRATION OF DIETHYLHNITROSAMINE (DEN) IN SYRIAN GOLDEN HAMSTERS OF F1-GENERATION, WITH NON TRANSMISSION OF THE TUMOURICIC EFFECT TO F2- AND F3-GENERATIONS.


Transplacentally administered N-diethylhnitrosamine (DEN) during the late stage of pregnancy is known to initiate metaplastic lesions and benign papillary tumors of the respiratory tract in the F1-progeny of Syrian golden hamsters. To determine whether the transplacental tumorigenic effect of DEN persists in the descendants of the second and third generations a long-term mutagenicity study was conducted. Thirty-six female Syrian hamsters (F1-generation) were given a single s.c. injection of DEN (dose range 1.25 to 20 mg/kg b.w.) on day 15 of gestation. Six controls received NaCl. F2-generation hamsters (total of 251 animals) and F3-generation hamsters (total of 184 animals) were obtained by mating groups of animals of the F1-generation (total of 275 animals) and F2-generation, respectively. Hamsters of all generations were raised to old age and autopsied when terminally ill. Approximately 30% of the DEN-treated mothers and 60% of their F1-offspring developed neoplasms in the respiratory tract. Morphologically, the observed tumors were papillomas of the trachea and larynx and to a lesser extent, adenomas of the lung. Neither in the control animals nor in the F2- and F3-generation descendants could a comparable lesion of the respiratory tract be detected. Thus, our results indicate that the vertical transmission of the tumorigenic effect of DEN is limited to one generation and does not persist in the descendants of F2- and F3-generations.

D-49: CHEMICAL CARCINOGENESIS: MUTAGENECITY AND CARCINOGENECITY II
MODIFICATION OF DEVELOPMENT OF 20-METHYCHOLANTHRONE-INDUCED SARCOMAS BY TRICHINELLA SPIRALI. J. Bany and Z. Liszka, Inst. Hygiene and Epidemiology and Inst. For Radiobiology and Radioprotection, Warsaw, Poland.

In the present report we show the effect of encapsulated muscular larvae of Trichinella spiralis on development of 20-Methylenanthrene (MCT) induced sarcomas. Kinetics of tumor development and percentage of tumor-bearing mice were investigated in experiments utilizing B6C3F1 mice injected intramuscularly with MCT (0.3 mg/mouse in olive oil) on 45, 60, or 100 day post injection (dpi) with larvae larvae/100 larvae/mouse.

A most pronounced growth of sarcomas was observed in a group of mice treated with MCT on 100 dpi as compared to the other groups of animals and to the MCT-injected but not infected control mice. The induction of sarcomas in animals with MCT was tended to be delayed but not prevented on 45 and 60 dpi. The results show that muscular larvae of T. spiralis modified development of chemically induced sarcomas. They also suggest that this modification depends on the period of muscular phase of the trichinellidal invasion.

This experiment is one of the attempts to make such experiment period shorter.

In this experiment, both infected mice such as C57BL/6J, C3H/HeJ, A/J strain and non-infected C57BL/6J strain were used. Each mouse group was sensitized nine weeks after a single injection of benzaldehyde of 0.5 mg or 1 mg into the muscular layer within 24 hour after birth. In C57BL/6J or C3H/HeJ mice, no pulmonary adenoma was observed at either normal control group or benzaldehyde-injected group. 0.5 mg or 1 mg. In A/J infected mice, however, the incidences of pulmonary adenomas were 77.9 per cent at normal control group and 16.4 per cent at 0.5 mg benzaldehyde group and 15.4 per cent at 1 mg benzaldehyde group, respectively. In non-infected C57BL/6J mice, the incidences were 2.0 per cent at normal control group, 4.5 per cent at 0.5 mg benzaldehyde group, and 4.5 per cent at 1 mg benzaldehyde group, respectively.

To verify the utility of this experiment, and C3H/HeJ new born mouse group, after injection of 7.5 mg of benzaldehyde, was administered red onion through drinking water for six weeks after they were weaned. It was observed that the pulmonary adenomas in the C57BL/6J mice were 6.8 per cent at the group injected 0.5 mg of benzaldehyde alone, while it was decreased to 2.2 per cent at the group administered both 0.5 mg of benzaldehyde and red ginseng, showed 10.6 per cent of the prevention effect.

It was proved from the above result the this method was useful to detect carcinogenic and anti-carcinogencity agents.


Production of Gastric Carcinoma in dogs by oral administration of ENNG in the form of wet pellic, was first reported by Kurihara et al. (Kyobokusensha, 90, 29, 1977). Some experimental method was applied in six miniature pigs, which were more similar to humman. Three 3-month old (Exp. No. 1) and three 4-month old (Exp. No. 2) pigs were given two batches of a diet per day for 15 months, each batch by soaking pellic in a solution of ENNG (700 mg/kg) in 2 % tween 60 (mg/kg). Follow-up examination by endoscopy and biopsy was performed every 2-3 months. After 17-20 months biqued materials of polyoid lesion in the formix and upper body of the stomach in the four pigs (Exp. No. 31, 41, 43, 44), revealed adenocarcinoma.

At the autopsy of pig No. 31 after 40 months, many polyoid lesions were recognized in the stomach, and four polyoid lesions were adenocarcinomas. The target organ is limited to the stomach except for the melanoma of a pigs jaw. Therefore, adenocarcinomae of pig stomach produced with ENNG could be one of the new useful experimental models.
FISH AS EXPERIMENTAL ANIMAL IN CHEMICAL CARCINOGENESIS, AN ULTRASTRUCTURAL STUDY.
L. Jánossy, K. Simon, A. Čisikó and K. Lappis
Fish are very susceptible to carcinogenic compounds and tumors grow quickly in them. Guanines (guaninethiocetic acid and tribromobenzene) and diethylnitrosamine or other chemical compounds in a dose half or quarter of LD50. Tumors developed in one month after beginning treatment. Ultrastructural studies showed appearance of structural alterations associated with both cellular injury and malignancy transformation. Few days after treatment nonuniformly-sized cells, enlarged bile ducts, accumulation of fat droplets and sometimes, also lipofuscin granules were visible. The degeneration of LRH proliferation suggest that the mixed-function oxidase function be in fish. About a year later, at necropsy, were a great number of glycogen rosettes, a mitogenesis with usual shape and in amount of KER in the transformed cells. Delta, mainly LNA membranes formed concentric lamellar complexes ("fingerprints") with or without glycogen. The huge nuclear vacuoles indicate some defects in lysosomal degradation of nucleoside metabolism of cholangiocellular carcinoma the appearance of poorly differentiated oval cells could be detected. The present studies provided data on the similarity of ultrastructural alterations in fish and rodent livers investigated in a separate experiment.

RELATIONSHIP BETWEEN CCI-1-INDUCED LIVER CARCINOGENESIS AND DIETHYL-NITROSAMINE HEPATOCARCINOGENESIS IN F-344 AND B6C3F1 MICE.
To elucidate the relationship between liver carcinogenesis induced by CCI-1 or diethylnitrosamine (DENA) and the occurrence of denoys, tumors grow quickly in them. Gynoginethiocetic acid and tribromobenzene were compared with normal and cirrhosis in F-344 or B6C3F1 rat liver. Liver carcinogenesis was induced by chronic administration of carbon tetrachloride and single or repeated doses of diethylnitrosamine (DENA) were applied as initiator of hepatocarcinogenesis. In normal and cirrhotic rats, DENA induction of hepatocellular carcinoma was substantially related to the number of formed rats treated with repeated doses of DENA. On the contrary of chronic carbon tetrachloride administration, carcinogen treatment has been followed by the induction of the hepatocarcinogenesis in all the rats examined. The same hepatocarcinogenic treatment were also applied in carcinogenic rats. There was no alteration in the number of rats and nodules evoked after single DENA treatment. Thus, the present study provided data on the similarity of ultrastructural alterations in fish and rodent livers investigated in a separate experiment.
A large number of carcinogens induce mammary cancer in female Sprague-Dawley rats. The present study was intended to test whether the mammary cancer in Sprague-Dawley rats can be induced even by other non-genotoxic carcinogens than hormones. Female Charles River Sprague-Dawley rats (CD rats) were used. Group 1 consisted of 23 female CD rats, 50 days old, each of which was fed a diet containing 2% butylated hydroxyanisole (BHA) for 300 days until the termination of experiment. Group 2 consisted of 20 female CD rats of 50 days old. They were fed a diet containing 0.5% clofibrate (Ethyl-2-6-chlorophenoxyisobutyrate) for 300 days. Another group of 21 female CD rats served as untreated controls. Three animals in Group 1 died within 8 days after the start of experiment. Remaining rats in Group 1 and all rats in Group 2 survived until the termination of experiment. All animals were autopsied, and tissues were fixed in 10% formaline, sectioned, and stained with hematoxylin and eosin. All of 20 rats in Group 1 which survived until the termination of experiment developed papillomas and carcinomas of the forestomach. However, no animals had mammary tumors. Although hepatocellular carcinomas which are usually induced by clofibrate were not encountered in Group 1, a proliferation of peritoneal tumors was encountered in Group 2. In Group 2, 17 out of 18 female CD rats which received intragastric administration of methylosilic, a genotoxic bracken carcinogen, developed mammary tumors. These results lead to an intriguing assumption that mammary cancer in CD rats can not be induced by nongenotoxic carcinogen.

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A search for nuclear RNA lost in azo dye-induced transplantable hepatoma. M. Mao, and K. Kuroda, Univ. Sch. of Med., Gifu City* Japan

Studies were conducted to characterize the nuclear RNA (nRNA) species that were lost in rat liver but absent in the azo dye-induced hepatoma. Nuclear RNA was compared between Donryu rat liver and AH136B hepatoma, a 3-methyl-4-(dimethylamino)-azobenzene-induced transplantable cell line, by DNA-RNA competitive hybridization. The hepatoma lacked 3.1-1.44 k of nRNA according to measurements of radioactivity of the hybridized *32P-labeled liver nRNA, and this loss was shown to be due to the failure of transcribing such RNA rather than to the deletion of the relevant DNA in the genome. Characterization of the lost nRNA was first made by fractionating liver nRNA by density gradient sedimentation and polyacrylamide gel electrophoresis. The comparison of the additive effects of the fractionated RNA's in the competitive hybridization indicated that the pertinent RNA was present in the large RNA molecules (>43S) but not in the low molecular weight RNA's. Then poly(A) nRNA was found to show a strong additive effect in the competitive hybridization while nuclear RNA showed little such effect, indicating that the pertinent RNA was present in the heterogeneous nRNA but not in the poly(A) RNA. Another characterization was made by fractionating DNA with regard to the repetition in the genome. The comparison of the competitive hybridizations on the fractionated DNA's showed that the loss occurred most in such RNA as was transcribed from highly repetitive DNA. In conclusion, the RNA species lost in the hepatoma was the transcript from highly repetitive DNA that was contained by the heterogeneous nRNA.

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A large number of carcinogens induce mammary cancer in female Sprague-Dawley rats. The present study was intended to test whether the mammary cancer in Sprague-Dawley rats can be induced even by other non-genotoxic carcinogens than hormones. Female Charles River Sprague-Dawley rats (CD rats) were used. Group 1 consisted of 23 female CD rats, 50 days old, each of which was fed a diet containing 2% butylated hydroxyanisole (BHA) for 300 days until the termination of experiment. Group 2 consisted of 20 female CD rats of 50 days old. They were fed a diet containing 0.5% clofibrate (Ethyl-2-6-chlorophenoxyisobutyrate) for 300 days. Another group of 21 female CD rats served as untreated controls. Three animals in Group 1 died within 8 days after the start of experiment. Remaining rats in Group 1 and all rats in Group 2 survived until the termination of experiment. All animals were autopsied, and tissues were fixed in 10% formaline, sectioned, and stained with hematoxylin and eosin. All of 20 rats in Group 1 which survived until the termination of experiment developed papillomas and carcinomas of the forestomach. However, no animals had mammary tumors. Although hepatocellular carcinomas which are usually induced by clofibrate were not encountered in Group 1, a proliferation of peritoneal tumors was encountered in Group 2. In Group 2, 17 out of 18 female CD rats which received intragastric administration of methylosilic, a genotoxic bracken carcinogen, developed mammary tumors. These results lead to an intriguing assumption that mammary cancer in CD rats can not be induced by nongenotoxic carcinogen.

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THE STATISTICAL ANALYSIS OF A CARCINOGEN MIXTURE EXPERIMENT. Thomas R. Fears and Robert M. Elashoff, Natl. Cancer Inst., Bethesda, Maryland and Univ. of California, Los Angeles, California, USA

This paper reports on the design and analysis of a series of complex chemical mixture experiments carried out to assess the interaction of chemicals in a carcinogenesis bioassay. Four groups of four chemicals each were designed to study interaction. Each chemical was fed at three nonzero dose levels to Fischer 344 rats. Each pair of chemicals was studied according to a two-way factorial design. Each chemical was given singly as well as in three combinations. Negative control groups were included. Methods of analysis designed explicitly for this study were derived to study interaction. These methods were supplemented by standard statistical methods appropriate for one-at-a-time studies. Antagonism was not discovered for any pair of chemicals. Some interactions were observed, and the statistical methods used to detect these interactions were evaluated. Implications of these findings suggest alternative designs for mixture studies that will result in improved interpretation of findings.
**4415 PHYSIO-CHEMICAL MECHANISM OF NATURAL REGULATOR’S MODIFYING EFFECT IN CHEMICAL CANCEROGENESIS MODELS**


The decelerated tumor nodules origin effect during NDEA induced hepatocarcinogenesis under vitamin C and polyunsaturated fatty acids influence as well as during mammary gland 7,12 DMSA induced cancerogenesis under vitamin A influence was discovered.

The features of molecular regulatory action mechanism which display stabilization effect of cytochrome P-450 functionality in hydroxylation system of polyunsaturated fatty acids and also display the origin appearance nitrosil complexes non haemotic iron-sulphur proteins and haemproteins electrontransport chain of mitochondri under action vitamin A.

**4417 HEPATOCELL NODULES SHOW PERSISTENT CHANGES INVOLVING XENOBIOTIC METABOLIZING ENZYMES: BEGINNINGS IN GENETIC ANALYSES OF KEY CELLS DURING LIVER CARCINOGENESIS.**


The nodules which persist during liver carcinogenesis appear to have a pivotal role between normal and cancer since not only are liver cancers seen to arise within persistent nodules but also, nodules share some of the following characteristics: (1) persistent nodules usually arise in multiple foci; (2) nodules tend to be imperceptible to the unaided eye; (3) malignant transformation of these lesions is under genetic control and is not accompanied by the dramatic changes which usually occur in the early stages of hepatocarcinogenesis. These nodules are also unique in that they share some of the properties associated with malignancy, such as independence of cell cycle and increased mitotic activity.

**4416 GLUCOSE INFUX AND GLYCOLYSIS/GLUCONEOGENESIS IN PRENEOPLASTIC LIVER FOCI**


Correlative histochemical studies of the activity of a number of enzymes, especially the enzyme controlling glucose influx in normal hepatocytes, pyruvatekinase, and pyruvatekinase activity at different sub-enzyme concentration, whereas glucosekinase is the enzyme which catalyzes the conversion of glucose to glucose-6-phosphate. The results reveal that in preneoplastic focus the pyruvatekinase L and glucosekinase show strong activities. The respective isoenzymes, hexokinase and pyruvatekinase M2 are not detectable in preneoplastic foci. However, in hepatocarcinomas the isoenzymes hexokinase and pyruvatekinase are the predominant isoenzymes. These results suggest that changes in the isoenzymes glucosekinase/hexokinase and pyruvatekinase L/M2, leading to an increase in glucose influx and glycolysis, appear relatively late during hepatocarcinogenesis.

**4418 INCREASED ERYTHROCYTE STEARIC ACID DESATURATION IN RATS WITH CHEMICALLY INDUCED COLORECTAL CARCINOMAS.**

N. Habib, R. Salem, M. El-Hattal, A. Dajani, D. Cohan, Department of Surgery and Virology*, Royal Postgraduate Medical School, Dusun Road, London W12KHS.

It has been shown that malignant transformation of cells is associated with an increase in membrane fluidity, predominantly due to increase of the oleic acid content of membrane lipids relative to arachidonic acid. Desaturation of the lipid layer of erythrocytes has been noted in patients with malignancies. This study investigated the stearic acid desaturation in red blood cell membranes of rats during the induction of colorectal tumors. Male Sprague-Dawley rats were injected weekly with 20 mg/kg dimethylhydrazine (DMH) for eleven weeks and sacrificed at four weekly intervals. Total lipid extraction was carried out on rat erythrocytes and analysed with gas liquid chromatography. In the control rats (injected with normal saline) the mean of the stearic to oleic acid ratio in erythrocyte membranes was 2.0±0.3 (n=20), compared to a mean of 1.6±0.2 (n=30), range 0.9-2.6, which is statistically significant (p<0.01). The increased desaturation occurred in parallel with appearance of tumors. These data suggest the regulation of stearic acid desaturation is an important adaptive mechanism of membrane fluidity and could be a useful chemical marker for malignancy.

Cadmium metal powder injected i.m. induces fibrosarcomas in mice and rats. The latent period can be as long as 1-2 months. (Rust and Schneider, E. Weinert, Path. Toxicol., 15:51, 1977.) An attempt to negate this action by zinc powder was unsuccessful (Rust and Cassette, Proc. Am. Assoc. Cancer Res., 17:2, 1972).

Here, however, the two powders were not mixed. A previous literature implies that selenium can counter the toxicity and even the carcinogenicity of cadmium. One of the early examples of this point is that the addition of selenium to the diet resulted in a reduced number of liver tumors induced by "Shafter polyp" (Elssmann, Cancer Res., 17:7, 1957). In the experiment (i.m.) described here, we studied the effect of selenium on cadmium carcinogenesis. Five groups of 12 male white-Kohler mice were used. Group I received 2 mg of powdered cadmium once a month for three months. Group II received a mixture of 2 mg cadmium and 1.5 mg selenium over 1 month for three months. In addition, we weekly injections of the selenium group III were given time injections of the selenium. Group IV were the vehicle controls, and Group V were the untreated cage controls. All animals were palpated and weighed weekly. Histopathological studies were made of the growths. The results were: Group I, 15/25 developed fibrosarcomas at the site, Group II, 15/25, Groups III, 1/25, 0/25. Under the conditions of this experiment, selenium did not protect the mice from cadmium-induced fibrosarcomas.


The effect of tagA and alka mutations in E. coli on the induction of the SOS system was investigated by the method of chromotest. The method developed by P. Quillardet and M. Hofnung was based on the measurement of induction of the lacZ gene, which is caused by the promoter region of the lacI gene of E. coli/V. Quillardet, P. and M. Hofnung, Mutation Res., 147, 05-78, and personal communication. It was shown that alkylating agents; methylamine sulphonate and N-methyl-N'-nitro-N-nitrosoguanidine which are known to alkylate adenine in N-3 position induced beta-galactosidase three times more effectively in tagA alka strain than in the analogous wild type E. coli strain. On the other hand benzene/Pyrene known to bind to N-2 position of guanine showed the same inducing ability in both tagA alka and wild type strains of E. coli. It has also been shown that 1,2-dibromoethene was a better beta-galactosidase inducer in tagA alka than in the wild type strains of E. coli both in background and uptake.

It is suggested that the comparison of alka gene induction in E. coli strains that possess and lack the N-glycosylase activity of adaptive response may be a useful and simple tool for the detection of the ability of chemicals to alkylate adenine in N-3 position.

4421 THE USEFULNESS OF SYNTHETIC DNA TO STUDY CHEMICAL CARCINOGENESIS. B. Knapik, M. H. Bix, Biophysics Dept., Roswell Park Memorial Institute, Buffalo, New York 14263 (USA).

Although there is considerable evidence that damage to DNA by covalent modification with chemical carcinogens can play a critical role in carcinogenesis, the subsequent biochemical events that initiate a normal cell to a cancer cell are not yet known. To understand carcinogenesis at the molecular level, it is essential to determine the complete chemical structure of carcinogen-DNA adduct, conformational change associated with it and finally, to relate the chemical and physical alteration with possible functional alteration as a consequence of modification. We synthesized a defined segment of DNA, d(TAGAGA), by modifying the photoreactive technique. The receptor was reacted with the chemical carcinogen N-acetoxy-acetyl-methyl-urea (AAM). The major product was isolated by high pressure liquid chromatography (HPLC) and characterized as 3-Acryloyl-guanine adduct of d(TAGAGA) by UV and NMR analysis. The adduct with AAM bound via the nitrogen to the (1) position of guanine has received much attention since it is the major adduct of AAM to DNA and is the major methylated adduct in vivo. GC and MS studies of AAM modified d(TAGAGA) indicated that AAM modification shifted the molecule into a minor conformation. The stabilization of this altered conformation under physicochemical conditions of salt and temperature suggests biological relevance. Proper growth requirement expresses specific DNA protein interaction. The altered conformations may induce altered genetic expression by releasing the specific interaction of protein with modified DNA. Modern biochemical tools may provide a direct method of assessing the effects of carcinogen on the structure and function of DNA. This research is supported by grant 16-246 from the National Cancer Institute.
A NO KI ONGFUTAL PROTEIN ASSOClATED WITH CHEMICAL CARCINOGENESIS. N.K. Mithal, M.W. Voigt, V.G. Matese, and R. Williams. The Department of Pathology, and Physiology State University of New York Health Science Center and the Comprehensive Cancer Center, Columbus, Ohio 43210, U.S.A.

A 45,000 dalton unglycosylated phosphoprotein, measured biochemically by its ability to induce the release of RBCs from isolated nuclei, is released from tumors and carcinoma-generated treated tissues to circulation, from fetal tissues to amniotic fluid and from transformed cells in culture medium. Although it is readily phosphorylated by protein kinase it does not exhibit endogenous protein kinase activity. Upon treatment of rats with a chemical carcinogen there is a transient appearance of the 60 kd factor in the blood plasma. The maximum concentration during this early phase has been confirmed to be at 11 days for the several carcinogens examined. The concentration of the factor then decreases and reverts background, but after exposure of vitamin A, and culture parallel with carcinogenesis. The early phase induction appears to be specific for carcinogens. All 17 chemical carcinogens tested, and representing 6 different structural categories induced the 60 kd factor at 24 hours post-treatment, in contrast none of the 9 non-carcinogenic analogs or toxins tested induced the factor. Further, the induction of the factor from the non-carcinogen was proportional to the induction of subsequent tumor incidence. The factor does not appear to be induced in normal adult cells, or in tissues by promoting agents. The 60 kd unglycosylated protein has been identified in the cytoplasm of target cells, and of normal adult target tissue of the rat with 48 hours at treatment. Using the stage hepatoma carcinogenic prorog of promoting the induction of the 60 bd factor in normal hepatocytes, it was shown that the induction of the factor in liver occurs over a 4 week period whereas it persists at the induced levels of incidence with provigen. These data are consistent with the production of the 60 kd factor by altered hepatocytes. Supported by grant CA 30627.

Exposure of Synthetic UDS in vitro to carcinogenic agents, including ionizing radiation, reactive oxygen species and alkylation agents, shows that these agents can produce multiple lesions in DNA. Numerous products produced by each of these agents in synthetic DNA dimers and tetramers have been isolated using high performance liquid chromatography (HPLC). This individual modified DNA oligomers have been characterized using nuclear magnetic resonance (NMR) spectroscopy. The proton NMR spectrum usually suffices to identify the nature of the lesion although ancillary measurements are used as necessary. An intriguing aspect of this experimental approach to the study of DNA damage is the possibility of observing stereochemical effects. Markedly different product profiles are obtained from sequence modifiers. Also, exposure of self-complementary oligomers to the agent at high temperature (70°C) as opposed to low temperature (5°C) can lead to different products. Presumably these temperature dependent differences arise mainly because of formation of a duplex structure at the lower temperature. A basic objective of this research is to discern which DNA lesions are mutagenic and which are of no biological consequence. NMR studies provide some insight into the mutagenic potential of a particular lesion by revealing the conformational changes induced in DNA by the lesion. Specific examples of stereochemical and conformational effects of radiation-induced lesions will be shown. Another objective of this research is the isolation of specifically modified DNA oligomers for in vitro testing of the mutagenic potential of specific lesions using recombinant DNA methods. Loechler et al. (1986) have described a strategy for in vivo testing of specific lesions. This research is supported by grant CA 29425 from the National Cancer Institute.


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METABOLIC PATHS OF DNA-BINDING DEPENDENT ACID HYDROLYSIS OF ARTHROPOD ACID. W. Schiller, R. Schulz, H. Schaefer, German Cancer Research Center, Institute of Toxicology and Pathobiology, in Neuherberg, 8550, BAYREUTH, F.R.G.

Arthropods and in vitro, a mixture of two naphthotheno derivatives was found to be mutagenic in cell culture. The in vivo metabolism with the isolated component revealed, a precursor-intracellular pathway under formation of the arachidonic acid-hupulating system in vitro analyzed with the 5h-postlabeling assay, shows extensive formation of DNA-adducts, mainly under anaerobic conditions. The mix DNA-adducts are formed in vivo after oral application of the two AAs. At the present time no correlation between DNA-adduct formation and carcinogenic action in different organs can be given.

Supported by Grants CA 27539 and CA 32159 by the National Cancer Institute, US PHS.
SUCCESSFUL TREATMENT OF PAPILLOMA VIRUS-RELATED CONDYLOMATA ACUMINATA AND OF BOWENOID PAPULES WITH LOW-DOSE RECOMBINANT INTERFERON-ALPHA. St. Orsola, S. Benelli, A. Zanini, V. Gaspari, V. Morfin

The preliminary results of an ongoing clinical trial of recombinant interferon alpha (IFN-α; Schering-Plough) in patients with genital condylomata acuminate (HC7) and Bowenoid papules (HC8) are presented. The dosage regimen consisted of 5 million U IFN-α subcutaneously once daily, 6 of the thus far available 10 patients achieved objective responses (6 complete and 2 partial remissions). The average duration without relapse was 8 weeks. One patient with disseminated macular Bowenoid papulosis (erythroplasia-like) of the glans achieved complete response, whereas in 2 cases multiple Bowenoid papules of the mucous external urethra and of the glans disappeared partially after 62 days of treatment, i.e., a total dosage of 310 million U IFN-α. In 5 of 7 cases with classical condylomata acuminate a complete remission after 42 days on the average was noted (i.e., 210 million U IFN-α). The 5 responding cases included 2 conditions of the urethral mucosa. All patients experienced flu-like symptoms in varying degrees being reversible after 3 days of treatment. Only in 1 case transient elevated levels of SGPT and SGOT were observed, regularly after the third day IFN-α was given by the patients themselves in the form of autoapplication without side-effects. These results suggest strongly that the low-dose subcutaneous IFN-α treatment has a beneficial effect on genital papillomavirus infections. The efficacy seems to depend on the virus type, since HPV 6 and HPV 11 induced condylomata acuminate responded earlier than did the Bowenoid papules associated with HPV 16. As derived from 1 case with nonresponding recalcitrant HPV 16-related giant condyloma of more than 2 years duration, one might assume that the treatment is less effective in older lesions undergoing fibrous changes.

INVESTIGATIONS ON THE PRESENCE OF PAPILLOMA VIRUS IN CERTAIN FORMS OF CANCER. M. Stoica, Elisabeta Mateos, N. C. Celal, "St. S. Nicoliciu" Institute of Virology, Bucharest, Romania

Two serially transmissible tumors were induced in the hamster by inoculation of human brain tumor material cell suspension or nucleic acid extracted from the malignant tissue. SV40 T antigen could be made evident in the hamster tumor cells from the experimentally induced tumors. Antibodies to SV40 T antigen were detected by indirect immunofluorescence in the serum of tumor-bearing hamsters. The same method allowed the visualization of SV40 V antigen in a section through a human brain tumor. Serological investigations revealed the presence of neutralizing antibodies to SV40 both in the cerebrospinal fluid and in the serum of patients with brain tumors (in 59.5% and 50.2% of the cases, respectively).

The authors have found 17 colo-cytological atypia according to 936 histological investigations from 3,555 patients treated in the II. Gynecological Department of István Hospital, during the last five years (1980-84). According to the histological findings 6 patients belonged to the CIN I, 6 to the CIN II and 5 to the CIN III. The average age of the 6 patients belonged to the CIN I were 27 years, the same value was found in the CIN II 30,1 years and 32,4 years in the CIN III. All these facts demonstrated the progression of the damage of HPV. Further evidence can be obtained on the carcinogenic role of HPV by the immunoperoxidase painting and electronmicroscopic and spectrophotographical investigations. All these investigations are in progress.

Key-words: HPV, carcinogen effect on the cervix uteri.


Carriage of oncogenic viruses in latent form can predispose the organism to oncogenic effect, while reactivation from latency with subsequent entire replication cycle can diminish this danger. We established latent infection in tissue cultures by a small amount of adenovirus type 5 and its temperature-sensitive mutants ts19 and ts23. For reactivation natural substances were used. Both native and radiodetoxified endotoxins of E.coli 055 were able to reactivate latent infections of three viruses at permissive temperature. This was significantly inhibited by o-tocopherol. Pretreatment of cells with endotoxin could prevent latency of subsequent virus infection, i.e. immediate replication took place. At restrictive temperature the wild type virus was reactivatable only. Prednisolone-succinate was not able to reactivates any latent viruses, but a combined treatment with endotoxin increased the virus producing capacity of cells, and at nonpermissive temperature a limited production of ts19 could be observed. PGE1 increased the production of wild type viruses and mutant ts19 at permissive temperature, while it had no influence on replication of ts19 mutant. At restrictive temperature, moderate reactivation of mutant ts19 was shown. PGE1 usually resulted in inhibition. These differences are due to alterations in p-lypeptide processing and phosphorylation. Alternative ways exist in maturation of viral proteins, presumably. Natural substances may modulate these processes.
E-43: VIROLOGICAL ASPECTS OF MALIGNANT AND NON-MALIGNANT DISEASES

4435 HEPATOCELULAR CARCINOMA AND HEPATITIS B VIRUS INFECTION IN HUNGARY. A. Gy. Decsi, Dept. of Surgery, Univ. of Szeged, Szeged, Hungary.

Sera (a total of 660) from 90 Hungarian patients bearing primary hepatocellular carcinoma (HCC), 45 patients with solitary hepatocellular carcinoma (HCC) and 90 samples from well-looking, non-symptomatic insulins were analyzed for hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (Anti-HBc), and hepatitis B surface antibody (Anti-HBs.). The results clearly show a high prevalence of HCV antibodies in HCC patients (14% for FPAg and 36% for Anti-HBc) as compared with non-tumoral healthy controls (2% and 5%, respectively) and HB patients with anti-HBs and Anti-HBc, respectively. These findings for the first time report higher rate of carriage of hepatitis B virus in Hungarian patients with hepatocellular carcinoma.

4436 THE POTENTIAL ROLE OF VIRUS-INDUCED DNA AMPLIFICATION IN HUMAN CANCER. J. H. Schilling, C. H. Krystro, J. W. Hsueh, R. A. Deschner. Stanford University School of Medicine, Stanford, CA, USA.

Similar to established chemical or physical carcinogens, certain group antigens (such as viruses, hormones, and physical agents) are potential carcinogens. In order to investigate the role of viral DNA amplification in cancer, we have developed a novel method for the detection and quantitation of viral DNA sequences in the human genome. The method involves the use of a novel technique called terminal transferase-mediated oligonucleotide ligation assay (TTOLA). The method is highly sensitive and specific for the detection of viral DNA sequences in human tissue samples. The method has been used to detect the amplification of DNA sequences in human tissues obtained from patients with various types of cancer. The results suggest that viral DNA amplification may play a major role in the development of human cancer.

4437 AUTO-ANTIBODIES AS MARKERS OF CANCER. A. A. Alani, M. A. Elsheikh, and A. A. Elsheikh, National Cancer Institute, Cairo, Egypt.

Auto-antibodies were induced in mice and rats by the administration of various antigens, such as tumor cells, viral particles, and other substances. The auto-antibodies were then used to detect the presence of these substances in blood samples from cancer patients. The results show that auto-antibodies are present in the blood of cancer patients at a significantly higher level than in healthy controls. This finding suggests that auto-antibodies may be useful as markers for the diagnosis of cancer.


We have tested sera from children with cancer for evidence of immune response to HIV-1 gag without specific IgM (both measured by ELISA). Eight patients seroconverted (median age 3.1 years), and HIV-1 was detected in the first sample. The results suggest that HIV-1 infection may play a role in the development of cancer. The neutralizing activity of the sera was also measured, and the results showed that the sera from children with cancer had significantly lower neutralizing activity than the sera from healthy children. This finding suggests that HIV-1 infection may have a detrimental effect on the immune system of children with cancer.
NEUTRALIZATION TEST FOR BK VIRUS: PLAQUE REDUCTION DETECTED BY IMMUNOPEROXIDASE STAINING. T. Fløenstad*, T. Tveit**, and K. E. Christie*, *Dept. of Microbiology and **Dept. of Pediatrics, University of Tromsø, Tromsø, Norway.

The seroepidemiology of BK virus (BKV) is usually studied by hemagglutination inhibition methods (HAI), but in the last years ELISA- and RIA-methods have been employed to investigate the specific immunoglobulin classes. Conventional neutralization tests are very time consuming, so we have developed an immunoperoxidase staining test to detect structural antigens of BKV in Vero cell cultures. Carboxymethyl-cellulose was used to impede virus diffusion in the medium after the inoculation. The cells were fixed with methanol. Rabbit antiserum against BKV structural antigen, swine antirabbit-HRP and DAB-substrate were used in the staining process. This test was used to examine the neutralizing activity of human and immunized animal sera. It was shown that sera positive for BKV antibodies by HAI and ELISA were able to prevent expression of BKV in cell cultures. The correlation between titers of antibodies asayed by the neutralization test and the neutralizing activity of human and immunized sera was high. We suggest that this type of test may be used instead of conventional neutralization tests also for other viruses with slowly developing cytopathogenic effects.

THE ROLE OF IMMUNODEFICIENCY IN THE DEVELOPMENT OF CERTAIN MALIGNANT AND NON-MALIGNANT DISEASES. Ziozi, Leukemia Research Unit, Rome, Italy.

Recent evidence suggests that the last 10 years on the human retina were marked by the individualization of the postaggregatory stage of acquired immuno-deficiency syndrome (AIDS) and of the correlated syndromes (cancer and AIDS). Recent epidemiologic data indicate an increase in the curve of incidence with geometrical progression and mortality: of AIDS promoted a study on selected cases carried out in a high-risk population for immuno-deficiency syndrome and lymphoma. A group of patients was then examined on 68 AIDS, 61 heterosexual (40 yrs 27 yrs; 37 yrs, were HAV III-IV -153 had positive hepatitis markers (HAV). In 41 pts., infection 10/10 was present (AIV). In one pt. tests for syphilis and HD were positive. AIH was found in 1 case. (cases 3 of the two had a Kaposis' tumor with cutaneous and visceral localization). AIH was found in 1 (19 yrs) and TB in 1 19 yrs, Relevant post-operative complications were not observed.

Neuropathological examination of AID-prevalence, the most common is a dramatic role in the progression and early lesions are high risk, with lymphoma. The virus, in all the cases, is a real threat and starting for a medical test is not yet an issue.

SPONTANEOUS DEVELOPMENT OF ACUTE AND CHRONIC HEPATITIS, AND LIVER CANCERS IN AN INBRED STRAIN OF LONG-EVANS RATS. N. Takeichi*, H. Kobayashi*, R. Masuda**, M.C. Yoshida** and H. Sasaki**, Laboratory of Pathology, Institute of Medicine, Hokkaido University School of Medicine, Sapporo, Japan.

Spontaneous hepatitis with severe jaundice was found to occur in an inbred strain of Long-Evans rats. Originally, two inbred strains ofrat were isolated from the virus. The inbred strain of Long-Evans rats at the Center Experimental Plants and Animals, Hokkaido University. Spontaneous hepatitis was noticed for the first time in the offspring of the LEA rats (with a cinnamon coat color) at the 23rd generation of brother-sister mating, whereas none of the offspring of the LEA rats (with an agouti coat color) developed the disease at all. The clinical symptoms were characterized by an abrupt and relatively late onset (100 to 160 days of age), pronounced jaundice, dilution of urine, and a high rate of lethality. An increase in the total serum bilirubin level and elevated levels of GGT and GPT were observed in relation to the severity of the syndrome. About 80% of the affected rats died within 2 weeks of the appearance of jaundice (acute hepatitis). The remaining 20% of the rats recovered spontaneously from the disease and survived for more than one year without a recurrence of the clinical symptoms, although the GGT and GPT levels remained relatively high (chronic hepatitis).

Recently, we have found spontaneous development of 7 liver cancers among the 18 rats with chronic hepatitis. Of the 7 tumors examined histologically, 5 were bile duct carcinoma and 2 were hepatocellular carcinomas. The average latency period of was 350 days. Of the 2 rats of hepatocellular carcinoma showed elevated levels of GGT and GPT and the production of alpha-fetoprotein. Detailed studies of the natural course, nutritional influence, possible viral or immunologic factors, and the genetics of the spontaneous development of hepatitis and liver cancers in this rat strain are now in progress.
MODULATION OF ANTIPROLIFERATIVE ACTIVITY OF TUMOR NECROSIS FACTOR-α (T) WITH INTERFERON-α (I-α), I-β, and I-γ IN HUMAN TUMOR CELL CULTURES. S. Yuk-Pavlovic, P. Sroginger, and J.S. Korash, Mayo Clinic, Rochester, Minn. 55905, U.S.A.

K. Haranaka, N. Satomi, A. Sakurai, and J.J. Nariuchi, Cancer Grant CA-15083.

Roche, Inc. for gifts of natural I-β and recombinant I-γ, Industiries, Inc. and Hoffmann-La Roche vjtrp. We thank Genentech, Inc. for gifts of recombinant T

IFNs. Synergistic activity refers to a degree of inhibition exceeding the product of the percent inhibition of each agent alone at the same concentration used in the combination.

Extent of inhibition of colony formation by T did not precede that by I-β and I-γ, and additive antiproliferative activity.

Lines of inhibition of colony formation by T did not predict sensitivity to the interferons. Despite marked differences in susceptibility to antiproliferative activity of individual cytokines among the cell lines, combinations of I-α with I-β, I-γ, and I-δ resulted in additive or synergetic inhibition of colony formation in each line. These cell lines appear to be useful models for exploring mechanisms underlying interactions of these cytokines in vitro. We thank Genentech, Inc. for gifts of recombinant T and I-γ and Toray Industries, Inc. and Hoffmann-La Roche, Inc. for gifts of natural I-β and recombinant I-δ, respectively. Supported in part by Mayo Comprehensive Cancer Center Grant CA-15083.


It was reported that tumor cells have receptors for tumor necrosis factor (TNF). In contrast, it was also reported that these cells have more receptors than malignant cells for recombinant human TNF. The presence of receptors does not sufficient to explain the sensitivity of cells to the cytotoxic action of TNF. TNF induces enhancement of endogenous lysosomal activity of tumor cells. Following the addition of TNF, susceptible tumor cells revealed decreased respiration after a certain duration and subsequently the respiration again increased. Sulfate dismutase, sodium azide and sodium fluoride remarkably increase cytoxicity of TNF. TNF increased to generate O₂⁻ and other oxygen radicals in target tumor cells. This suggests the importance of glyceroxidase system and glycolysis, that is, mitochondrial function and energy metabolism. The concentration of TNF required to induce this metabolic alteration, grows inhibition or cytotoxicity on the vascular endothelial cell. Pathological study suggests that the re-endothelialization of tumor neovascule induced by TNF administration may be a hemorrhage induced due to circulatory disturbance associated with a microvascular injury manifested by hyperemia and multiple fibrin thrombus in vascular channels of tumor tissue.

COMPARISON OF PROPERTIES, ANTITUMOR ACTIVITY AMONG TUMOR NECROSIS FACTOR FROM MOUSE, RABBIT AND HUMAN. K. Haranaka, N. Satomi, A. Sakurai, and N. Martuchi, Inst. Med. Sci., Univ. Tokyo, Tokyo, Japan

Production, purification, physicochemical properties and antitumor activity was compared using murine tumor necrosis factor (TNF), rabbit TNF and human TNF. Good production of TNF in animals was obtained using Propionibacterium acnes and subsequent administration of lipopolysaccharide. Murine TNF and rabbit TNF resembled each other, that is, the molecular weight was 39,000, was estimated by gel filtration and 18,000 by SDS-PAGE. The isoelectric point was determined as pH 3.9-4.0 by isoelectric focusing. TNF was stable within the pH range of 3.5-11.0, and was stable at 56°C for 8 hrs. It was digested by trypsin, proteinase and elastase, but was resistant to neuraminidase. The greatest difference between murine and rabbit TNF was that, murine TNF was glycoprotein, in contrast, rabbit TNF was simple protein. The amino acid sequence of rabbit TNF was determined as Ser-Ala-Ser-Arg-Ala-Leur-. Human TNF was simple protein, and physicochemical characters were similar to that of rabbit TNF. Highly purified TNF had a cytotoxic effect on mouse and human tumors tested. TNF does not show species specificity in its effect. TNF was capable of distinguishing malignant cells from normal cells. Highly purified TNF was tested against murine tumor and human tumor heterotransplanted into nude mice. Mouse was injected with intravenous or intratumoral injection of TNF, commencing when the tumors were well established. TNF showed an excellent inhibitory effect against all kinds of murine and human tumors tested. Monoclonal antibody against rabbit TNF completely inhibited both in vivo and in vitro activity of rabbit TNF, and partially inhibited that of human TNF. However, this antibody could not inhibit the activity of murine TNF.


The relationship between tumor necrosis factor (TNF) and mononuclear phagocytes/macrophage-like cell lines, especially the lysosomal enzymes, was investigated. The serum lysosomal enzymes and L-argin activities increased in proportion to the TNF production even in a different strain of mice. Lysosomal enzymes and TNF were released into the supernatant of the culture medium of macrophage-enriched peritoneal exudate cells (PEC) or spleen cells derived from Propionibacterium acnes-primed mice after the addition of lipopolysaccharide (LPS). After passage through a Sephadex G-200 column, TNF activity could not be detected in the supernatant of these spleen cells after the addition of LPS. TNF activity could not be detected in the supernatant following the destruction of TNF. These results suggest that TNF productivity is strongly related to the degree of activation of macrophage, especially the lysosomal enzymes. The macrophage-like cell lines, J 74%, also released lysosomal substance and lysosomal enzymes after addition of LPS. J 74%, derived from this factor was purified and characterized. This factor is a glycoprotein with a molecular weight of 30,000 by gel filtration and 18,000 by SDS-PAGE, and with an isoelectric point of below 4.1. J 74% derived TNF and serum TNF were identical as regards properties.

The effect of recombinant human tumor necrosis factor (rHu-TNF) was evaluated in intradermally transplanted Meth A sarcoma-bearing BALB/c mice and in normal Wistar rats. Pharmacokinetics of rHu-TNF differed by the administration routes and schedules. Distribution studies by radiometric and autoradiographic means were also confirmed.

Macromolecule synthesis was also examined using radioactively labeled amino acid and nucleoside. Selective action of rHu-TNF on the tumor tissue and early onset of action of rHu-TNF were also confirmed.

Pharmacokinetics of recombinant human tumor necrosis factor (rHu-TNF) in normal and intradermally transplanted Meth A sarcoma-bearing BALB/c mice and in normal Wistar rats.

As rHu-TNF was administered in intravenous route by a single bolus injection, continuous infusion or divided consecutive injections. As well, rHu-TNF was also given intramuscularly, subcutaneously, intraperitoneally and intratraumally. rHu-TNF in plasma, tissues and excreta was measured by cytotoxic action on LM cells (bioassay), by immunoreactivity with enzyme multiplied immunosorbent (EIA) or by radiometric means with radiolabeled preparation, with which autoradiographic studies were also performed on distribution.

Plasma levels of rHu-TNF determined by bioassay, EIA and acid insoluble radioactivity were essentially similar to each other in mice. Pharmacokinetic parameters in normal and tumor-bearing mice were similar to each other. Systemic availability of rHu-TNF differed by the administration routes. Availability of rHu-TNF in the tumor tissue was also different by the administration routes and schedules. Distribution studies by radiometric and autoradiographic means revealed that rHu-TNF was well distributed in the interstitio, spleen, lung and liver as well as in the tumor. Distribution and disappearance in the tumor was rather different from those in other tissues after intravenous administration of rHu-TNF. Total radioactivity was mainly excreted in urine, where neither immunoreactive rHu-TNF nor acid insoluble radioactivity was detected after administration of radioiodinated rHu-TNF. Pharmacokinetic parameters in rats were somewhat similar to those in mice.


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Most studies on TNF have been carried out with crude or partially purified preparation containing other cytokines. We examined in vitro the effects of recombinant human TNF on L-CFU, CFU-GM, and BFU-E. L-CFU and CFU-GM were assayed by the method of Minden et al. Thirteen patients with acute non-lymphocytic leukemia (ANLL) whose bone marrow (11 cases) or peripheral blood (2 cases) cells (containing >90% leukemia cells) and up to 2 x 10^6 colony forming units (CFUs) were selected for this study. The effect of TNF on CFU-GM was examined using bone marrow cells from 3 normal volunteers, 8 patients with hematological malignancies in complete remission and 1 patient with cirrhosis. After incubation with TNF (Akhsh Chemical Industry Co., Ltd., Tokyo, Japan) for 9-11 days, L-CFU or CFU-GM (240 cells per colony) were scored. Dose-dependent inhibitions of L-CFU and CFU-GM by TNF were found, and the inhibition of L-CFU by TNF was significantly more marked than that of CFU-GM. By the addition of 10 U/ml TNF, the mean inhibition was 52 ± 6.6 (mean ± S.E.) in L-CFU and 3.5 ± 3.0 (mean ± S.E.) in CFU-GM (p < 0.001). The extent of inhibition of L-CFU by TNF had no correlation with the number of colonies without TNF or the type of leukemia by the French-American-British classification. BFU-E appeared to be inhibited by TNF, although only 4 cases were examined. The inhibition of L-CFU was neutralized by anti-TNF monoclonal antibody. These results indicate that TNF may be of value in the treatment of ANLL, although careful observation of the effect on normal hematopoietic stem cells by TNF will be necessary for its clinical application.

POSSIBLE INVOLVEMENT OF PHOSPHOLIPASE A2 AND ARACHIDONIC ACID METABOLISM IN CYTOTOXIC ACTIVITY OF RECOMBINTANT HUMAN TUMOR NECROSIS FACTOR (rHu-TNF) AGAINST L-M CELLS. K. Nakano, K. Idoo, K. Ohkuma, S. Abe and Y. Sohmura (Research Laboratories, Dainippon Pharmaceutical Co., Ltd., Osaka, Japan)

Recombinant human tumor necrosis factor (rHu-TNF) exerts its strong cytotoxic activity against murine L-M cells. The manner of action of rHu-TNF is far from clear. It is now made clear that both rHu-TNF-sensitive and resistant cell lines as well as human diploid cells possess specific binding sites. As to other receptors, it was found that free arachidonic acid and its metabolites are released after stimulation of receptors. In the present study, in order to clarify the event following interaction of rHu-TNF with specific binding sites, it was examined how the drugs which are considered to affect phospholipase A2 activity or arachidonic acid metabolism, influence the cytotoxic activity of rHu-TNF against L-M cells.

Calcium blockers, i.e., diltiazem, verapamil and nifedipine, inhibited the cytotoxic activity of rHu-TNF. Thus, influx of calcium into cells is suggested to be involved in the cytotoxic activity of rHu-TNF. Phospholipase A2 inhibitors, i.e., quinacrine and tetracaine, inhibited the cytotoxic activity of rHu-TNF. Glucocorticoids, i.e., hydrocortisone, dexamethasone and prednisolone, that are considered to inhibit phospholipase A2 activity, did not inhibit the cytotoxic activity of rHu-TNF. These results suggest that phospholipase A2 is involved in the cytotoxic activity of rHu-TNF. Indomethacin and aspirin did not inhibit the cytotoxic activity of rHu-TNF. Therefore, cyclooxygenase pathway does not seem to be involved. On the other hand, lipoygenase inhibitors, i.e., nordihydroguaiaretic acid (NDGA) and quercetin, inhibited the cytotoxic activity of rHu-TNF. Therefore, lipoygenase pathway seems to be involved in the cytotoxic activity of rHu-TNF.
Antitumor activity of recombinant human tumor necrosis factor (rHu-TNF) was investigated against murine tumors transplanted in syngeneic mice and human tumors heterotransplanted in nude mice. rHu-TNF was produced through an expression of the cloned TNF cDNA encoding 155 amino acid residues in Escherichia coli. Purified rHu-TNF showed a single band with a molecular weight of 17,000-16,000 on SDS-polyacrylamide gel electrophoresis, at 5.9 ± 0.3 and specific activity of 2.9×10^7 U/mg. The composition and sequence of amino acid residues of rHu-TNF coincided with those presumed from the base sequence of TNF cDNA. Cytotoxic activity of rHu-TNF against L-M cells was retained after a 1-month storage at 4°C and after heating at 60°C for 1 hr. A preparation of rHu-TNF used in in vivo tests contained 10^6 U/ml. The concentration at which 50% of L-M cells were killed was defined as 1 U/ml.

rHu-TNF was found to exhibit potent antitumor activity not only against murine tumors, e.g., Meth A sarcoma, b16 melanoma, colon 26 adenocarcinoma, Lewis lung carcinoma, and M134 hepatoma, transplanted in syngeneic mice but also against human tumors, i.e., H6-2 melanoma, PC-10 lung carcinoma, MKN-45 gastric adenocarcinoma and GOTO neuroblastoma, heterotransplanted in nude mice. rHu-TNF caused necrosis of all tumors tested and inhibited their growth in a dose dependent manner. Complete regression of tumors and prolongation of survival time were observed in syngeneic mice transplanted with murine tumors except Lewis lung carcinoma, MKN-2, PC-10, and MKN-45 human tumors heterotransplanted in nude mice were also regressed completely in some cases. The antitumor activity of rHu-TNF was augmented by combination therapy with anticancer drugs such as adriamycin, cyclophosphamide or cisplatin.

In the case of murine L-cells, two rHu-TNF-sensitive sublines, L-M and L(S) cells, possessed receptors to rHu-TNF. However, human diploid cells were not affected at all. In many cases where cytotoxic effect was observed, cytoxic effect was also noticed. In order to analyse initial interaction of rHu-TNF with tumor cells, it was investigated whether or not tumor cells possess specific binding sites on their cell-surface and whether or not the sensitivity of the tumor cells correlates with the number of specific binding sites. In the case of human cell lines, both rHu-TNF-sensitive and resistant tumor cells processed specific binding sites. Moreover, human diploid cells also possessed specific binding sites. The number of binding sites did not correlate with the degree of their sensitivity to rHu-TNF. Both rHu-TNF-sensitive and resistant tumor cells internalized and degraded cell-bound rHu-TNF in a similar manner. In the case of murine L-cells, two rHu-TNF-sensitive sublines, L-M and L(S) cells, possessed comparable numbers of specific binding sites. One rHu-TNF-resistant subline, LMR cells, also possessed specific binding sites. However, another resistant subline, L(R) cells, had no or a very low number of specific binding sites. Actinomycin D made the LMR cells sensitive to rHu-TNF. However, L(R) cells were resistant to rHu-TNF even in the presence of actinomycin D.

These results suggest that tumor cells could not be damaged unless they possess specific binding sites to rHu-TNF and that even if they possess specific binding sites, the sensitivity of tumor cells could be determined at post-receptor stage(s).
PRELIMINARY RESULTS WITH THE APPLICATION OF RECOMBINANT HUMAN TUMOR NECROSIS FACTOR (rhtnf) IN CANCER PATIENTS. S. Stannenberger, J. Muller, U. Muller and H. Gortler. Acad. Sci., GDR. Central Inst. of Cancer Res., Berlin-Buch, GDR

In a phase I study 10 patients with various malignancies were given rhtnf by intravenous infusions. Study provided same data with regard to side effects and to tolerable and subtoxic doses of rhtnf. Blood levels of rhtnf were followed up with a test kit based on a rhtnf-specific monoclonal antibody. Activity of natural killer cells and effector cells of anti-body-dependent cellular cytotoxicity were estimated from peripheral blood cells before and after infusion of rhtnf.

THE ROLE OF NATURAL KILLER CELLS AND MACROPHAGES IN TUMOR-GROWTH SUPPRESSION BY ACTIVATED MOUSE PERITONEAL CELLS

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Peritoneal cells activated by a combination of indomethacin-polyIC-Synovular/anticoagulant/ given intraperitoneally to C57Bl/6 mice /5mg per kg body weight each/ suppressed the take of Lewis lung carcinoma when impregnated into syngeneic recipients at a 50:1 peritoneal cell/tumor cell ratio. After removal of the macrophages from the activated peritoneal cells by adherence to plastic and carboxyl iron plus magnetic treatment the remaining cells retained the capacity to suppress the take of the tumor. The tumor-growth inhibitory effect of activated nonadherent peritoneal cells was lost when they were incubated with 10^{-6} M neutral red /the leukocyte infusate/ with the cytoplastic activity of natural killer cells/ at 37°C for 30 min. When the activation of peritoneal cells by the described combination of drugs was performed 4 days after giving of a single dose of cyclophosphamide /2,5 mg per kg body weight/, the tumor-inhibitory capacity of the cells proved to be diminished. Macrophage-enriched populations of normal non activated peritoneal cells enhanced the growth of Lewis lung carcinoma in a dose dependent manner while plastic adherent cells from activated peritoneal cell populations inhibited the take of the tumor. Thus, both natural killer cells and macrophages contribute to the suppression of tumor growth by activated peritoneal cells.

IMPACT OF MACROPHAGE INTRINSIC ANTIVIRAL ACTIVITY IN PATIENTS AFFECTED BY NEOPLASIA. L.A. Herendinio, L. Bonina, A. Arena, V. Greco, R. Malmi, E. Chillemi and P. Mastroeni. Microbiological Institute and Oncology Institute, Clinical School, Messina University, Italy

It has been firmly established that the cells belonging to the mononuclear-phagocytic system are pivotal in the outcome of viral infections. Moreover the professional phagocytic cells are affected by neoplasia in different expressions of their functionality. We report here the results of a study carried out in order to define a possible influence of two types of neoplasia or a particular macrophage function, by which these cells can hinder the replication of viruses, called intrinsic activity. This activity has been analyzed "in vitro" on differentiated macrophages from blood-derived monocytes obtained from healthy donors and patients affected by breast cancer and melanoma. The intrinsic antiviral activity was evaluated versus an RNA virus, a recently clinically isolated Muso virus, and two DNA viruses, recent clinically isolated herpes simplex Virus type 2 and Adenovirus type 17. The challenge of the macrophages was carried out with different multiplicity of infections /MOI/, namely 1, 0.1 and 0.01. The synthesis of the viral protein was tested by evaluating the single cycle growth curve in 24 hours. The results demonstrate that the restriction of the viruses is strongly affected by the multiplicity of infection, since the major restrictions of virus replication were obtained at the lower MOI employed and this was particularly evident in the case of the Adenovirus. The macrophages obtained from neoplastics patients showed an impairment of the intrinsic antiviral activity evidenced by an active replication tested, not affected by the multiplicity of infections. No significant differences were found, in this respect, between the macrophages from patients affected by breast cancer and melanoma.
4459 ACTIVATED MOUSE PERITONEAL CELLS INHIBIT THE TAKE OF TRANSPLANTABLE SOLID TUMORS IN ADOPTIVE TRANSFER ASSAY IN VIVO

Erika Karas, Janos Minorovits and Istvan Foldes

The effect of mouse peritoneal cells on the growth of transplantable syngeneic tumors using an in vivo adoptive transfer assay was studied. Normal peritoneal cells as well as peritoneal cells obtained after injecting protease peptone or thioglycollate medium intraperitoneally /ip/ enhanced the growth of B-51 fibrosarcoma /a benzpyrene-induced/ and peritoneal cells collected after ip. injection of protease peptone or thioglycollate medium and poly I:C did not influence the take of Balb fibrosarcoma. Peritoneal cells collected 18 hours after ip. inoculation of poly I:C /5mg per kg body weight/ inhibited the take of B-51 fibrosarcoma and SP4 spontaneous adenocarcinoma but did not influence the growth of Lewis lung carcinoma at a 50:1 peritoneal cell:tumor cell ratio. Peritoneal cells activated by ip. injection of indomethacin and poly I:C and Synovar /antiagglutinant/ did not inhibit significantly the growth of Lewis lung carcinoma while a combination of indomethacin+poly I:C+Synovar /5mg per kg body weight each/ markedly suppressed the take of B-51 fibrosarcoma at a 50:1 peritoneal cell:tumor cell ratio. Peritoneal cells activated with the same combination of drugs or with poly I:C alone were unable to influence the take and growth of F361 mastocytoma.

4460 MACROPHAGE ACTIVATION DURING TUMOUR GROWTH ALTERS THE SENSITIVITY TO INTRAVASCULAR COAGULATION

G.Lazar, E.Huuskik, K.Sabo and J. Tito

The host-tumour relationship was investigated in inbred, female 8-month old rats bearing subcutaneous Yoshida sarcoma. It was observed that the growth of the tumour stimulated the activity of the reticuloendothelial system (RES). Although during tumour growth significant splenomegaly developed, the increased RES activity was due to the activation of functional cells. This was supported by organ uptake studies using 51Cr-labelled foreign red blood cells, and it was shown that the enhancement of the RES activity was independent of the presence of the spleen as it also developed in the group of animals which had undergone splenectomy 1 week before the tumour transplantation. According to our investigations the increased RES activity of the tumour-bearing animal alters the sensitivity to the consequences of the intravascular coagulation. Liquid (sodium polyanethol sulphonate, Hoffman-La Roche) in doses of 4 mg/100 g body weight, iv., induced generalized Sanarelli-Schwartzman reaction /9/ bilateral renal cortical necrosis in 90% of the control animals; however, caused only minimal morphological alterations in the kidney and only in 25% of the animals bearing subcutaneous Yoshida sarcoma. Since sodium polyanethol sulphonate induced severe thrombocytopenia and fibrinogen depletion not only in the control but in rats bearing subcutaneous Yoshida sarcoma, the refractoriness of these animals is due to the stimulatory effect of tumour growth on the RES activity. This is supported by our studies that other RES stimulants such as bacterial endotoxin or with poly I:C alone were unable to influence the take and growth of BaF1 mastocytoma.

4461 ULTRASTRUCTURAL AND ENZYMOCHEMICAL CHANGES OF ALVEOLAR MACROPHAGES AFTER 3-METHYLCHOLANETHRENE TREATMENT IN RAT.

S.Keiza, P.Erdhart, A.Tigyi

The pulmonary macrophages /PAM/ have a special place in the mononuclear phagocyty system. PAMs play a primary role in maintaining the clearing of the alveolar region of the respiratory tract and have regulatory function in the spreading and metabolism of surfactant and clean the inner surface of the lung. PAMs are constantly exposed to the external environment. Inhaled components of the live oil of the lung are phagocytosed by PAMs. A part of these components are found to be both mutagenic and carcinogenic. The metabolic activation within PAMs may play an important role in oesophaheally induced lung cancer. One of the mechanisms is the metabolic activation of 3-MC to 3-methylcholanthrene /3-MC/ is an inducer of chemical carcinogenesis. We have investigated the changes in ultrastructure /routine and electron histochemical methods/, viability and enzymology of PAMs. Male CFY rats /200g/ were treated with a single dose of 3-MC intratracheally /200mg/kg b. w./ The treated and control animals were killed after 24 and 48 hours and 1 week. PAMs obtained after bronchopulmonary lavage were used. After 3-MC treatment the electron micrographs of PAMs showed that the number of lysosomes were increased, great amount of lamellar bodies were appeared in the cytoplasm of PAMs on 1 week, histotechnical and spectra photometrical reactions of solid phosphates were increased. A maximal increased viability and metabolic activity of phosphatases were measured after 24 hours of 3-MC treatment. The number and viability of PAMs and their phagocytic activity were increased at 48 hours after ad马丁. From these results we concluded, that the PAMs were highly active metabolically during phagocytosis of 3-MC.

4462 PERIPHERAL MONOCYTE CULTURE: USEFULNESS IN FOLLOWING PATIENTS WITH RENAL CELL CARCINOMA.

University of Kansas Medical Center, Kansas City, Kansas 66163 USA.

We have shown earlier lower monocyte/macrophage counts in a group of renal cell carcinoma patients (NCI 74:1189, 1985). In this report, we applied the monocyte culture assay to follow 39 patients with Renal Cell Carcinoma. A mononuclear cell-rich fraction was cultured from peripheral blood of patients over a period of 7 days. The number of adherent matured monocytes (macrophages) was analyzed and quantitated at the end of the culture period. Functional activities were analyzed by antibody-coated sheep red blood cells and non-specific esterase staining technique. Macrophage yield in pre-treatment patients with detectable tumor burden was 2.06±2.81 x 10⁶ ml of blood and the mean value at 3, 6, and 9 months post-nephrectomy were 3.69 ± (2.21), 6.73 ± (12.13), and 9.41 (11.18) x 10⁶ cells/ml of blood, respectively. We have followed some patients over a period of 6 months. In the post-treatment, macrophage counts tend toward normal values (8.24 ± 10⁶ cells/ml of blood), and among the patients who were known to have metastasis at the time of check-up, the results were in the range of pre-surgical values. From these results the assay appears to be useful in following renal cell carcinoma patients in both pre- and post-surgical period. In particular, in the advanced stage of Renal Cell Carcinoma, the analysis of the mononuclear macrophage assay, to follow the patient's response to the treatment, seems to reflect the "wellness" of the patient.
**4464 QUANTITATIVE ASPECTS OF AUTOCRINE REGULATION OF TUMOR GROWTH: A GENERAL PHENOMENOLOGICAL MODEL.** L. Bajzer and S. Vuk-Pavlovic*, Rugjer Bošković Institute and Nuclear Medicine and Oncology Clinic, Dr. M. Stojanovic Clinical Hospital, Zagreb, Yugoslavia, and *Mayo Clinic and Foundation, Rochester, MN 55905, U.S.A.

We present a model which considers autocrine regulation of tumor growth as a feedback control system. Tumor growth is resolved into two components: one causally dependent on secretion of autocrine mediator and one which encompasses all other growth mechanisms. Tumor size (N) is a function of extracellular concentration of autocrine mediator (S) and time (t): N = f(t,S). Concentration of autocrine mediator depends on N and Q; Q is the extent of external experimental manipulation of S (e.g. by injection of autocrine mediator): S = g(N;Q). We generalize our previously developed phenomenological model, based on the modification of Gompertz growth curve (Bajzer et al., Science, 225:930-932; 1984), to accommodate any growth curve which fits the data. We define the Open Loop Gain Parameter and Autocrine Tumor Mass Gain Parameter which express the efficiency of the feedback mechanism. The model provides guidelines for design of experiments for quantification of the extent to which autocrine regulation contributes to growth of any tumor and of other measurable biological system.

**4465 THE EPIDERMAL GROWTH FACTOR SYSTEM IN HUMAN CANCER.** Authors: Rolando Perez Rodriguez, Josefa Lebarrero, Ana Maria Hernandez, Agustín Lebarrero, National Institute of Oncology and Radiobiology, Havana, Cuba, Department of Biochemistry.

We have studied the EGF-system in mammary cancer. About half of human breast carcinomas showed measurable high affinity receptors for EGF. There was an inverse association between EGF-receptors and estrogen receptors. This fact was also evident among experimental mice tumors and among cultured cells from human breast cancers. A Radioimmunoanalysis for EGF-like peptides, sensitivity to cell-cycle concentrations have been devised. Cytokines recognizing the EGF-receptor have been identified in human breast carcinomas. High dose EGF inhibited thymidine incorporation in Ehrlich ascites tumor cells. The implications of these findings for the concept of hormone dependence and biological-therapy are discussed.

**4466 INTERACTION BETWEEN EPIDERMAL GROWTH FACTOR (EGF), INSULIN AND CAMP IN THE REGULATION OF DNA SYNTHESIS IN CULTURED HEPATOCYTES.** T. Christoffersen and T.E. Sand, Department of Pharmacology, University of Oslo, Pb. 1057 Blindern, Oslo, Norway.

Cell proliferation is regulated primarily by mechanisms that determine whether quiescent (G0/G1) cells start to replicate their DNA (enter S-phase). A useful model system for this is mouse hepatocytes, which allow studies of hormonal effects on DNA synthesis under defined, serum-free, conditions. We have used this system to investigate the signal requirements of the S-phase induction, and the interactions between growth-controlling factors. DNA synthesis was measured biochemically as [3H]-thymidine incorporation and autoradiographically as nuclear labelling index.

EGF and insulin synergistically stimulated DNA synthesis. Dose-effect studies showed that EGF increased the sensitivity to insulin, while insulin increased the maximal effect that could be obtained with EGF. Insulin had to be present from an early stage after plating and was required for EGF responsiveness. Conversely, EGF administration could be postponed for 30 - 40 h after plating and maximal effect still be achieved, if the cells had been primed with insulin. With late addition of EGF the cellular sensitivity was higher and the rate of S-phase entry was more rapid. Glucagon, or dibutyryl (DB) CAMP, further stimulated DNA synthesis in cells treated with EGF plus insulin. However, this effect was critically dose- and time-dependent, since stimulation was only obtained at low concentrations (glucagon < 10^{-5}M, DBcAMP < 10^{-4}M) and early addition (30 min plating), whereas high concentrations and/or late additions produced inhibition. The results indicate that in cultured hepatocytes insulin produces competence for DNA replication, EGF strongly stimulates DNA synthesis in insulin-primed cells, and CAMP exerts a dose-dependent, biphasic, modulatory effect.

(This work was supported by The Norwegian Cancer Society and The Norwegian Society for Fighting Cancer)
STUDYING EPIDERMAL GROWTH FACTOR RECEPTORS AND THEIR FUNCTION IN CANCER.

4467 4468 4469


A low molecular weight, heat and acid stable, tryptic and dehydroaminopeptidase resistant polyepptide has been isolated from the pig skin of mice. It enhances the binding of labeled EGF to IGF-cells in the radioreceptor assay. Hence the name "enhancing factor" (EF). EF binds to the cell membrane even in the EGF-receptor cell line NCA indicating that the binding of EF is independent of EGF receptors. Autoradiographic studies with labeled A431 membranes have identified the receptor for EF in A431 cells as a new membrane resident weight protein which under reducing conditions runs with DTT. In acellular system EF interacts with EF, F. EF probably acts as a biological ligand which binds to the cell membrane through its own receptor and in turn provides a binding site for EGF. DNA synthesis has been studied in vivo in EGF-receptor cell lines. Immunoprecipitation showed that EF is not internalized into the cell membranes, but it interacts with the cell receptors. Studies on the human ef and the translation of the cDNA sequence have led to the conclusion that EF has a 50% homology with EGF.

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ROLE OF GROWTH FACTORS AND PROPOSED MECHANISMS IN THE BINDING OF EPIDERMAL GROWTH FACTOR (EGF) AND PRODUCTION OF TGF-α.


EPA.

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HIGHER LEVELS OF GROWTH FACTORS AND PROPOSED MECHANISMS IN THE BINDING OF EPIDERMAL GROWTH FACTOR (EGF) AND PRODUCTION OF TGF-α.


FURTHER STUDIES ON THE BINDING OF EPIDERMAL GROWTH FACTOR (EGF) AND THE PRODUCTION OF TRANSFORMING GROWTH FACTOR-α (TGF-α).


FURTHER STUDIES ON THE BINDING OF EPIDERMAL GROWTH FACTOR (EGF) AND THE PRODUCTION OF TRANSFORMING GROWTH FACTOR-α (TGF-α).

4472 Isolation of an Angiotensin on the Rat Kidney and its Biological Activity. 

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Confluent cultures of normal rat kidney fibroblasts, clone 49 F, release a 56 kDa protein phosphorylated at serine (pp56) into the medium as detected by SDS-PAGE and autoradiography after labelling the cells for three hours with 32P-orthophosphate. pp56 is not a dominant intracellular phosphoprotein, but is the major phosphoprotein in the medium. Incubation of the cells with EGF during the labelling period results in dramatic increase of secretion of pp56, while prolonged preincubation of the cells in low serum reduces it severalfold. The effect of EGF is reversible and can be prevented by actinomycin D. The secretion is suppressed by cycloheximide and ammonium chloride. A secretory protein with a slightly higher apparent molecular weight than 58 kDa can be labelled with 35S-methionine and is also selectively enhanced by EGF. Several other growth factors, like PDGF, NGF, TGF-β, and insulin do not affect the secretion of pp56.

In contrast, the synthetic tumour promotor, TPA, mimics the action of EGF.

4473 A NK EFFECTOR FACTOR FROM THE BURKITT ACETITES LIVER CANCELL.


We purified a factor from bovine mammary gland, inhibiting in vitro the regulation of growth of stationary Burkitt acutes liver carcinoma cells (obtained from mice 12 to 14 days after transplanting, p16). It has:
- effective in concentration of 0.2 to 2.0 ng/ml
- homogeneity in SDS electrophoresis. R = 1500
- characterized by polyclonal and monoclonal antibodies
- characterized by first data on its receptor
- antagonized by insulin, EGF, FGF in physiological concentrations
- characterized by 2'-phosphorylation, pointing to involvement of phosphotyrosine reductase in the factor effect
- ineffective in in vitro effects of the Burkitt untransformed liver carcinoma, which synthesized, however, its own inhibitor. Thus, tumour growth regulation may be altered by treatment with antigen(s).

4471 GROWTH AND TRANSFORMING FACTORS

Robert I. M. (Australia) AN I 1 AN I HAFAN I HWAR I

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WEDNESDAY • AUGUST 27 • AFTERNOON
STUDY OF GROWTH REGULATORS ISOLATED FROM CELLS IN TISSUE CULTURE. C.N-SHENOV and K.A. CHAUBAL, Biophysics Unit, Cancer Research Institute, Tata Memorial Centre, Parel, Bombay 400 012, INDM.

The normal cells have a well regulated pattern of growth passing through its cell cycle. The cells which have undergone malignant transformation do not have this self regulatory mechanism. In our investigations we have explored about the existence of growth regulatory fraction in Human Ammon (HA) cells of normal origin and HeLa, KB and Mouse Fibrosarcoma cells of cancerous origin. The growth regulatory fraction was isolated from the culture medium, in which the cells were grown, using Sephadex filtration technique. The fraction was tested on the cells of its origin and also on other cells. The fraction from HA cells inhibited mitosis of HA cells and had no effect on HeLa, KB and MFS cells, indicating specific mitotic inhibitory action. However, the MFS fraction caused stimulation of mitosis in MFS cells. These results were confirmed in independent experiment with colchicine pretreatment of these cells. Since the growth stimulatory effect on MFS cells was similar to the action of plasminogen activator, the possibility of its presence in the fraction from MFS cells was examined by carrying out fibrin overlay method and direct fluorescence assay and these ruled out its presence. These studies bring to the fore the presence of a self regulatory mechanism that controls the growth in normal cells and the absence of such a principle in malignant cells.

TRANSFORMING GROWTH FACTORS ISOLATION FROM AN INVASIVE HUMAN MELANOMA

Jorge A. GLIMILEUE,*, Norberto SAN JUAN +, Juan J. LEPRI,*, Teresa HINCH*, Gerardo F. LAMPARO,*, Ricardo VELA,*, Jorge WILL*, and Clorindo WURM

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Transforming growth factors (TGFs) are polypeptides that confer malignant phenotype on non-neoplastic cells. They are divided into two classes according to their biological activity in cultured cells: (1) α-TGF compete with epidermal growth factor (EGF) for binding to the EGF receptor; and (2) β-TGF do not compete with EGF for binding to the EGF-receptor but require the presence of either α-TGF or α-TGF for biological activity. TGF were isolated from a highly malignant and aggressive human melanoma. Tumoral tissue was subjected to acid-ethanol extraction and chromatography on Bio-Gel P-60. TGF had apparent molecular weight from 15,000 to 25,000 and from 30,000 to 45,000. TGF induced progressive colony formation of normal rat kidney (NRK) in soft agar. There was no TGF effect on enhancement by the addition of 10 ng/ml of EGF. The isolation of TGF from a human melanoma tumor provides evidence that the above factors resemble those described in media conditioned by continuous melanoma cell lines, the detection of TGF in blood and urine of melanoma patients is part of a wider study currently being carried out.
A transforming growth factor production by a human colon carcinoma cell line (LoVo).

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Inst. de Biología y Medicina Exp., Buenos Aires, Argentina.

Transforming growth factors (TGF) are low molecular weight polypeptides that confer a malignant phenotype on non-neoplastic cells. TGF have been divided into two classes according to their biological activity in cell culture: 1) α-TGF compete with epidermal growth factor (EGF) for binding to the EGF receptor, and 2) β-TGF do not compete with EGF for binding to the EGF receptor but require the presence of either EGF or α-TGF for biological activity. β-TGF was isolated from conditioned LoVo cell medium. These cells showed long term growth capability in serum-free medium. Accordingly, serum-free conditioned medium by exposure to LoVo cells was collected every ten days during forty days, dialyzed, lyophilized and applied on a Bio-Gel P-60 column. β-TGF from LoVo medium had an apparent molecular weight from 7500 to 12000. β-TGF induced progressive colony formation of normal rat kidney (NRK) cells in soft agar in the presence of 10 ng/ml EGF. This TGF failed to compete with EGF for binding to the EGF receptor. Besides, other active fractions were found, whose characterization is under way. Isolation of this factor suggests β-TGF is involved in the growth regulation of LoVo cells and could play a vital part in the growth in serum-free medium.

Inhibitory growth factors from autolysed cellular ascites fluids.

The role of autolysis in the production of growth inhibitory factors from Ehrlich ascites carcinoma cells (EACC) and Leukemia L-1210 cells was studied. The cellular ascitic fluids suspended in saline solution were kept on a rotary shaker for 1-5 days, then centrifuged and supernatants concentrated by freeze drying to 1/10 of the original volume of medium. The crude extracts obtained were tested for their antitumor activity either as such or after a partial purification. The antitumor effects of autolysed fluids (AACC) on the re-growth of EACC were dependent on certain parameters as: inoculation-harvesting interval of the cells subjected to autolysis, cells density and autolysis duration. Following partial purification of autolysed fluids (either EACC or Leukemia L-1210 cells) by 70% ethanol extraction and successive chromatography on G-15 and G-75 Sephadex columns six of the eleven tested fractions revealed notable inhibitory effects on EACC and Leukemia L-1210 cells, as well. Our findings suggest that the autolysis of tumour cells carried out under controlled conditions could serve as an useful procedure for obtaining endogenous inhibitors with a marked efficiency in the tumour growth control.

Tumour cell growth-inhibiting factors obtained by autolysis of some Penicillium strains.

Under certain culture conditions several Penicillium species (P. notatum, P. chrysogenum, P. decumbens, P. italicum) produced tumor cell growth-inhibiting factors. Thus, liquid cultures of Penicillium strains kept on a rotary shaking apparatus at 22-24°C after a stage of growth of 3 days were centrifuged and the sediment resuspended in fresh medium and maintained under shaking for 1-10 days. In this period of time, daily, the content of a fermentation flask was centrifuged, the mycelium structure was examined under microscope, the supernatant after lyophilization was tested for inhibitory effect on the growth of Ehrlich ascites carcinoma cells and Leukemia L-1210 cells. The inhibitory effect was estimated at seven days after inoculation in a treatment schedule consisting in the 3 doses of 4 ml medium/week. Microscopic examinations revealed the existence of an autolysis process expressed by continuous destruction of mycelium. The inhibitory activity was found dependent upon the autolysis duration, with a maximum as a function of the buffering capacity of the medium. The highest inhibitory effect was 95-98% of control. Further investigations concerning the nature of these inhibitory factors are in progress.
4482 EFFECTS OF MICROTUBULE INHIBITORS ON MONOCYTE PHAGOCYTOSIS
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The microtubule inhibitors (MIs) suppress a number of cell processes, including leukocyte chemotaxis, tumour cell invasion, which by inference are thought to be more or less microtubule-dependent.

A series of experiments were undertaken in order to elucidate the effects of therapeutic concentrations of microtubule inhibitors with different sites on tubulin on the monocyte phagocytes of yeast cells, assessed by a glass surface method which measures the adherence phase and the engulfment phase of phagocytosis separately.

Monocyte adherence was slightly inhibited by the microtubule antagonists. However, the main MI inhibition of monocyte phagocytosis was located to the ingestion phase. The inhibition was statistically significant and in an order of magnitude of 10-30% for Vinca alkaloids, colchicine and podophyllotoxin. In contrast, griseofulvin which inhibits microtubule-associated proteins, had no inhibitory effects on monocyte phagocytes. Experiments with podophyllotoxin suggested that part of the MI inhibition of monocyte phagocytosis was due to interference with nucleoside transport over the cell membrane.

The above-mentioned observations are consistent with the hypothesis that microtubule engulfment of yeast cells is partly dependent on microtubule function, partly dependent on nucleoside transport over the cell membrane, and that one cost of cytotoxic therapy with microtubule inhibitors is a moderate depression of monocyte function.

4483 CORRELATION BETWEEN DEGREE OF CAPping OF LECTIN RECEPTORS AND MALIGNANCY IN CLONES OF HYBRIDOMA AND MYELOMA.
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The correlation between the degree of capping of lectin receptors and the malignancy of a murine myeloma tumor line and two clones of hybridoma was examined. The percentage of cells exhibiting capping of Concanavalin A receptors was 9% for the myeloma (NS1), 10-15% for hybridoma A and 40-50% for hybridoma B. The rate of proliferation in vitro of the myeloma and hybridoma clones was similar. However, inoculation of the various lines into Balb/c mice (10^6 cells, s.c.) resulted in diverse biological expression. The tumor lines differed in local growth and metastasizing ability. Local tumor growth differed in respect to rate, maximal size reached and inflammatory response. Metastatic spread was assessed by determining organ weights relative to normal organs and by their microscopic examination. The percentage of mice bearing metastatic growths was 15, 40 and 90% for the myeloma, low-capping and high-capping hybridomas, respectively. Organs (spleen, liver, lungs and kidneys) of mice which had been inoculated with the high-capping hybridomas were by far the most extensively invaded, particularly those of the R58. None of the tumors caused cachexia. Mortality rate was the most rapid in mice injected with the high-capping hybridomas, which, in contrast, were least affected by low-capping hybridomas. The factors responsible for the malignant behavior of tumor cells are not yet known. The study of membrane and cytoskeletal structure and function in cell lines with variant levels of malignancy may contribute to a better understanding of the factors which endow tumor cells with the ability to undergo metastasis.

4484 EFFECT OF IRON OVERLOAD ON IRON BINDING PROTEINS IN NORMAL AND MALIGNANT BREAST CELL LINES. H. Shterman and C. Horoz.

The delivery of iron to cells is mediated primarily by transferrin (Tf) - an iron transport agent. A specific membrane receptor for Tf appears to be the first step in the iron uptake process. A major part of iron is stored in intracellular ferritin. In some neoplastic cells the level of ferritin is elevated, but this ferritin has a relatively low iron content and is more acidic than normal cellular ferritin. Little information is available on the events that occur after binding of Tf to its surface receptor, and incorporation into cellular metallo-proteins. Moreover, the effect of iron overload on these events is unknown. We have chosen to study the effect of iron overload on the surface Tf receptors and on the synthesis of intracellular ferritin in a breast cancer cell line (HT-29) and for comparison in a cell line which originates from normal breast epithelium (HBL-100).

The results indicate that HBL-100 cells possess a large number of Tf receptors with high affinity. Following treatment with iron-loaded cells in the presence of high iron overload for 14 days, the number of cellular Tf receptors was decreased to half with no change in their affinity. Furthermore, a significant increase in the synthesis of acidic ferritin was observed. In contrast, in breast cancer cells the number of Tf receptors was not affected by iron overload even following 30 days of culture, moreover, there was no change in the amount of ferritin synthesized by these cells. These results indicate the down regulation of surface Tf receptors and up-regulation of ferritin synthesis by iron overload in the normal breast epithelial cell line whereas breast cancer cells were unresponsive to this protective regulation of iron uptake.

4485 VITAMIN A AND ITS EFFECT ON THE LIVER.
I.A. Sadek.

The carcinogenicity of hydrocarbons for the Egyptian toads and therapeutic effects of anticancerous drugs has been demonstrated. (Sadek 1982, Oncology 33, 399, Sadek & Abdel-Meguid 1992, Oncology 44, 96-100). In a recent study, 15 animals were injected with 0.2mg or 1mg of 3-[3-deoxyglucose acid, 3 times/week for 2 weeks induced a decrease in the body and liver weights. The percentage of death was increased at a dose level of 1mg/animal. Before treatment, the mitochondria of the control liver were rounded in shape and small in size with dense matrix. After treatment, the mitochondria become larger and most of them appeared oval. Their matrix turned to be not highly condensed and with well-developed cristae. However, many giant mitochondria were also recorded. It is suggested that these well-developed cristae give structural evidence of an increase of mitochondrial protein synthesis. This could be also supported by the well-developed endoplasmic reticulum in the liver of the treated toad. Therefore, it might be concluded that vitamin A acid causes disturbance of mitochondrial protein synthesis.
Acute leukaemias are a heterogeneous group of diseases regarding cellular origin, stage of differentiation, prognosis, and response to therapy. Cell surface markers, plasmamembrane microviscosity, insulin receptors (IR), and gluconcoritcoid receptors (GR) of separated blast cells were investigated following Ficol sedimentation. Acute lymphoid and non-lymphoid leukaemic children and adult patients and CML patients in blast crisis were involved in the study. Cell surface markers were analysed with a panel of polyclonal and monoclonal sera (anti-T, -B, -HLA DR, -myeloid, -platelet antibodies) using a FACS II analyser. It has been found that blast cells have (1st) a decreased plasmamembrane microviscosity, (2nd) 1RF on their surface in some cases. (3rd) The GR level of blast cells is of prognostic value. Very low GR levels are commonly associated with other unfavourable prognostic factors and/or a poor outcome. We have found a special group among "high risk" ALL children who presented a very high GR level. Investigation of cytohistologic properties of transformed cells could give an additional help in choosing treatment protocols and understanding the disease process in acute leukaemia. Further work is needed to correlate the cell biological characteristics with established morphological and clinical prognostic factors of leukaemic patients.

The membrane fluidity of resting lymphocytes is lower than that of proliferating or malignant cells. With a polarization method the membrane fluidity of lymphocytes of patients with various lymphoproliferative diseases was determined. In addition, the density of cell surface transferrin receptors indicative of cell proliferation, was assessed immunocytochemically. The membrane fluidity (microviscosity) of lymphoid and of lymphoma cells showed correlation to the grade of the disease, low grade tumour (B-cell NHL) cells exhibiting lower, high grade tumours (lymphoblastoma) higher membrane fluidity. Transferrin receptor expression was higher in high grade and lower in low grade malignant lymphomas and in lymphoblastic leukemias. When human $T$ lymphocytes isolated from peripheral blood were stimulated by PHA, in the early phases of transformation membrane fluidity and transferrin receptor expression increased. In low grade tumours, at later phases values comparable to those of high grade tumours were seen.
4491 AUTOLOGOUS AND NATURAL CYTOTOXICITY IN PATIENTS WITH MULTIPLE MYELOMA.
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Department of Pathological Anatomy 3, Medical Academy, Wrocław, Poland.

Most cytogenetically defined neoplasias have translocations or deletions of chromosomes, but in a few cases, numerical aberrations are also seen. In chronic lymphocytic leukemia (CLL) 30% of the cases have trisomy of chromosome #12 and 10% of patients with acute non-lymphocytic leukemia (ANLL) have trisomy of chromosome #8. We derived a monoclonal B-cell line with 47,XY,+12 karyotype from a 71-year-old non-symptomatic normal male. His T-cells have a normal karyotype. A polymorphic satellite, a normal variant in chromosome #22, was non-symptomatic at the time of the chromosome study, and his blood count was normal, he may develop B-cell lymphoma of the colon, hormone kidney, absence of the left lobe of the liver, agenesis of the gall bladder and severe mental retardation and had a constitutional karyotype of 46,XY, del 3(q13q15) or del 5(q15q22) and polymorphic satellite of chromosome #12. However, in malignant follicular lymphoma, trisomy of chromosome #12 is associated with a monoclonal B-cell line with 47,XY,+12 karyotype derived from a 71-year-old non-symptomatic normal male. His T-cells and fibroblasts have a normal karyotype. A polymorphic satellite, a normal variant in chromosome #22, is present in all the cells of all the tissues examined. His 42-year-old son suffered from Gardner's syndrome, carcinoma of the colon, hormone kidney, absence of the left lobe of the liver, agenesis of the gall bladder and severe mental retardation and had a constitutional karyotype of 46,XY, del 3(q13q15) or del 5(q15q22) and polymorphic satellite of chromosome #12 cell line from the normal father is important from the point of view that even though he was non-symptomatic at the time of the chromosome study, and his blood count was normal, he may develop B-cell leukemia (CLL or SLL) because trisomy of chromosome #12 is often associated with such leukemia. In malignant follicular lymphomas, trisomy of #12 is associated with a translocation involving chromosomes #14 and #18. In the present case, trisomy of chromosome #12 is the sole abnormality seen in this cell line and thus, probably is the primary karyotypic defect. Further clinical follow-up of the case and characterization of the cell line will be discussed.

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G-59: NATURAL RESISTANCE — COMPLEMENT FACTORS II

4492 LENTIN RECEPTORS ON HUMAN NATURAL KILLER (NK) CELLS.
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The binding ability of Peanut (PM)/Lentil (LE)/Lycium (LY)/Barberry (BA)/, Wheat germ (WG)/ and Appa rugas pea (AP)/ agglutinins to human NK cells using double marker immunofluorescence technique was studied. For identification of NK cell VEP 13 positive cell VEP 13 antigen was not established. Experiments were performed on large granular lymphocyte enriched cell preparation. The receptor for FNA lectin was shown exclusively after neuraminidase treatment of cells and VEP 13 antigen was neuraminidase resistant. The majority of VEP 13 positive cells showed co-expression of FNA, LEN and WGA lectin receptors. Our results show that VEP 13 antigen and FNA receptor are two various membrane structures, whereas there is some competitive binding between LEN as well as WGA lectin and VEP 13 antibody. In double marker experiments using FNA and LEN lectin, the small fraction of VEP 13 positive cell lacking receptors for these lectins was found. No binding of SBA and ASP in spite of neuraminidase treatment of the cells was shown. These results indicate apparent heterogeneity of NK cells in respect of lectin receptor expression.
4493 ENHANCEMENT OF NATURAL KILLER (NK) ACTIVITY BY AN IMMUNO-
POTENTIATOR (OK-432) AND RESISTANCE TO HUMAN HEPATOMA CELL 
IMPLANTATION IN NUDE MICE. H.Saito, T.Moriizane, N.Kumagai, 
of Med., Reio Univ., Tokyo, Japan.

The relationship between spleen NK activity and the tumor take of a human hepatoma cell line (HCC-M) was investigated in nude mice.

MATERIALS AND METHODS: HCC-M was established from a hepatocellular carcinoma of an HBeAg-positive Japanese male in our laboratory. Nude, 4- to 6-week old female BALB/c nu/nu mice were used as recipients. 5 x 10^5 cells were subcutaneously inoculated. An immunopotentiator, a streptococcal preparation (OK- 
432) was intraperitoneally administered to a group of nude mice (n=7) one and three days prior to the implantation of HCC-M cells (1 KE dose/animal). Cytotoxic activities of spleen cells against HCC-M and YAC-1 cells were also studied.

RESULTS: Transplantability was significantly decreased to 42% by pretreatment with OK-432, whereas pretreatment with OK-432 at concentrations below 10^5 gave no effect on tumor growth. The level of NK activity in untreated patients was significantly higher than that of control (p<0.005). But by the simultaneous administration of anti-asialo GM1 antiserum, the tumor growth became similar to that of untreated groups. NK activity of spleen cells from nude mice pretreated with OK-432 significantly increased 12 to 24 hours after the administration but blocked by the in vivo treatment with anti-asialo GM1 antiserum and complement.

CONCLUSION: Splenic NK activity is closely associated with the resistance to xenograft in nude mice. The pretreatment with OK-432 in able to reduce tumor take and enhance NK activity is attributable to the effect.

4494 TCGF-MODULATION OF NATURAL KILLER FUNCTION IN BREAST CAN-
CER. R.G. Marpolese, and B.G. Brenner, From the Lady Davis Institute of the Sir Mortimer B. Davis Jewish General Hospital and the McGill Cancer Centre, Montreal, Quebec, Canada.

Native and TCGF-inducible natural killer cell (NK) activity in breast cancer was ascertained by determining the K562 cytocidal capacity of peripheral mononuclear lymphocytes. The level of NK activity in untreated patients was significantly greater than that observed in patients receiving adjuvant chemotherapy or healthy controls. The absolute level of NK activity of treated cancer patients was further reduced when compared to untreated patients and healthy controls when reductions of circulating lymphocytes occurred concomitant with cytotoxic drug therapy were incorporated into calculations of NK function. NK activity in cancer patients and healthy controls was stimulated by TCGF. The maximal stimulation of NK activity by 102 TCGF (v/v) was observed under conditions where there was no increase in cell proliferation. No stimulation of NK activity by TCGF was observed in NK-resistant RAJ1 cells. The percent stimulation of basal NK activity by TCGF in treated cancer patients was significantly greater than in untreated patients or healthy controls. Autologous plasma at concentrations below 102 (v/v) enhanced basal activity in both treated and untreated patients. Levels of stimulation of NK activity by either 102 TCGF, ST plasma, or a combination of both were not significantly different. At concentrations above 202, autologous plasma inhibited basal NK activity but TCGF could reverse this inhibition. The potential use of TCGF in adjuvant immunotherapy as a modulator of NK function has been demonstrated in vitro. TCGF stimulates in vitro NK activity, acts synergistically with plasma-stimulating factors, and can restore NK activity suppressed by plasma-inhibitory factors.

This work has been supported in part by grants from the Cancer Research Society of Montreal and Stanley A. Vineberg Research Endowment.

4495 INTERFERENCE OF ANTIBIOTICS WITH NK ACTIVITY. M.L. Villa, P. Valentii, E. Clerici, Cattedra di Immunologia e Istituto Nazionale Tumori, via Venezian 1, 20133 Milano, Italy.

The influence of some antimicrobial drugs on NK activity of human peripheral blood mononuclear cells (PBMC) was investigated in a standard chromium release assay against K562 cells. All the tests were performed in triplicate, both with and without antibiotics addition to cultures.

Penicillin and streptomycin which are usually found in cell culture systems were tested either together or alone. Results showed that penicillin (33 IU/ml) decreased the NK activity of PBMC as compared to controls, whereas streptomycin (30 mg/ml) had a minor depressive effect. A mixture of both penicillin and streptomycin sharply inhibited the NK activity.

To analyse the possibility that other aminoglycosides, besides streptomycin, might interfere with NK activity, gentamicin was examined. Results showed that gentamicin (4 mg/ml) decreased the NK activity of PBMC as compared to controls. This depressive activity was not shared by amikacin (20 mg/ml), which was the third aminoglycoside antibiotic tested. Finally, rifampin (7 mg/ml) did not modify the NK activity. We are at present trying to define the effects of other class of antibiotics, the cephalosporins, which are known to interfere with the immune response.

The mechanisms trough which antibiotics modulate the NK activity are not clear, but we feel that the evaluation of their capacity of interfering with the immune system should be part of any routine preclinical immunotoxicological screening. C.N.R. grant n. 84.00518.44

4496 RESTORATION OF ANTINEOPLASTIC ACTIVITY OF P.GRANDL0-
SIM KM-45 AND GLUCAN BY LOW DOSES OF RADIATION. SUBTRA-
TION OR CYCLOPHOSPHAMIDE. B.Onatowski, H.Janiak, and B.

One of the possible mechanisms of antineoplastoic effect of P. grandii mycelium KM-45 (PG) and glucan may be stimulation of the activity of natural killer (NK) cells in tumor-bearing host. This stimulation, however, is mediated by a marked depression of NK-mediated killing, most pronounced 7-10 days post injection of the above Biological Response Modifiers (BRMs). At the same time the activity of anti-NK suppressory macrophages was clearly demonstrated. In the present experiments i.p. injection of PG or glucan 3 days prior to a.c. inoculation of 816 melanoma cells resulted in retardation of tumor growth and prolonged survival of tumor-bearing mice. However, when these BRMs were given 7 days prior to inoculation of tumor no antineoplastoic effect was observed. When such injection of PG or glucan was accompanied by irradiation of mice with 1 Gy of neutron beam or application of 50 mg per kg cyclophosphamide CyC a marked inhibition of tumor development and prolonged survival were resumed. These results suggest, that low doses of radiation or Cy may potentiate antineoplastoic effect of PG and glucan in vivo, possibly by blocking the activity of suppressory mechanisms induced by these BRMs.
4497 THE HYPERSENSITIVITY TO THE MOST COMMON EXTRINSIC ALLERGENS IN PATIENTS WITH APOLIAPTIC DISEASES AND IN HEALTHY FAMILIES. J.Tujakowski, Outpatient Dept. of Oncology in Med.Acad.Hospital in Bydgoszcz, Poland.

The relations between atopy and malignancy are often discussed but the opinions concerning the frequency of tumors in atopic patients and atopy symptom in patients with tumors are often contradictory. In patients with tumors both low and elevated IgE serum levels were observed. In atopics specific IgE against environmental allergens are produced, it seemed therefore useful to verify what is a frequency of hypersensitivity to the above allergens in people with neoplasia. In the examined group of 167 patients with histologically confirmed malignancy, a family and personal history of atopy was found only in 6 and in 4 patients respectively. In this group the immediate type skin reactions to house dust, feathers, grass pollen and two mixed extracts of mould allergens were positive in 3,0%, in 4,7%, in 1,2%, in 0,6% and in 1,6% of cases respectively. In control group of 152 healthy persons skin tests with house dust and feather extracts were positive in 30,2% and in 19,5% of the examined subjects. The difference in the occurrence of positive reactions to the above allergens between the two examined groups was statistically significant. It seems therefore, that family and personal atopy is not common in patients with malignancy, while the hypersensitivity reactions to the most prevalent extrinsic allergens are in the above patients symptomatically less frequent that in the normal population.

4498 MODULATION OF NATURAL AND ANTIBODY DEPENDENT CELLULAR CYTOTOXICITY IN CHRONIC MYELOID LEUKEMIA (CML) PATIENTS IN REMISSION. S.G.Ganega, M.D.Dabholkar, R.J-Tatake and S.H.Adval, Cancer Research Institute, Tata Memorial Centre, Bombay 400 012, India.

Non-adherent peripheral blood mononuclear cells from 67 CML patients in the first and two subsequent remissions, and 23 normal healthy donors were tested for Natural Killer (NK) and Antibody Dependent Cellular Cytotoxicity (ADCC) activities. CML patients showed significantly reduced NK activity (16,1-19,7%) compared to normal healthy donors (47,4%). Of the patients tested, 56% showed NK levels below the mean percent cytotoxicity minus 2 SD of normal donors (low responders), while 45% could be grouped as normal responders. While, CML patients showed normal ADCC activity irrespective of their NK status. The NK responder status of CML patient was not found to be related to progression of the disease, type of drug used to bring about remission, or period in remission at the time of testing. In vitro treatment of effector cells with Interferon (IFN) or Interleukin-2 (IL-2) modulated the NK activity both in low and normal responders. Cellular cytotoxicity of effectors to NK targets (K562) could also be enhanced by monoclonal antibodies (MAB) directed against the targets. In cases, IFN and MAB showed synergistic effect. Status of suppressor lymphocytes in low responders was also investigated. The study indicated that with whichever modality of modulation used, although there was an augmentation of cytotoxicity in low responder patients, the activity still remained below the normal levels.

4499 NATURAL KILLER (NK) CELL ACTIVITY IN BLOOD AND BONE MARROW OF PATIENTS WITH MULTIPLE MYELOMA. M.Migasche, H.Gissjnger, W.Scheithauer, W.Linkesch, and H.Ludwig, Inst. of Applied & Exp. Oncology, 2nd Dept. Internal Medicine, Wiesbaden, Austria.

NK cells seem to be involved in the regulation of hematopoiesis by direct cytotoxic reactions and/or secretion of cytokines. We have investigated NK activity (anti-K562, 4hr Cr-release assay) in peripheral blood (PB) and bone marrow (BM) of patients (pts) with multiple myeloma (MM, n=32), pts with myeloproliferative syndrome (MPS, n=12), myelodysplastic syndrome (MDS, n=10) and healthy donors (HD, n=8). In PB, NK activity of pts with MM was comparable with that of HD, whereas in pts with MDS and MDS is significantly lower. In BM, NK activity was highest in pts with MM and lowest in the other groups. In MM, no influence of sex, age, pretreatment status and clinical stages on levels of NK activity in PB and BM has been detected. In pts with MM furthermore a higher percentage of BM but not of PB cells reacted with monoclonal antibody HNK-1 (which identifies a certain proportion of NK cells) in comparison to other groups. Both these results suggest an increase in number and function of cells: BM of pts with MM mediating NK activity.

4500 NATURAL KILLER CELL ACTIVITY IN LUNG CANCER PATIENTS BEFORE AND AFTER SURGERY. M.Anthony, M.Nouve, V.Penem, Cancer Res.Institute, Sofia, Bulgaria.

Natural killer (NK) cell activity was examined in lung cancer patients before and 1-14 days after surgery. NK activity of blood lymphocytes from preoperative patients against K562 target cells, labelled with 51Cr, was significantly decreased compared to controls. After surgery the patients showed further decrease in NK activity as compared to the preoperative one, but the differences were not great. When blood mononuclear cells were depleted of monocytes an increase in NK activity was exhibited only in postoperative patients. No significant differences were observed in the absolute number of lymphocytes. The possibility, that suppressor cells, presumably monocytes, could be a cause of depression of NK cell activity, was discussed.
The serum factor responsible for the observed reaction has been isolated from serum of lung cancer patients and found to be a glycoprotein of 70-80,000 daltons. The factor can be absorbed or columns coupled with crude extracts of cancer-associated antigens. Antigen specificity has been demonstrated in both breast and lung cancer.

Several biochemical properties of the factor have been studied. The activity of the factor was sensitive to trypsin, low pH, and SDS treatment. Furthermore, it was found to be partly inactivated by 2-mercaptoethanol and pepsin. Treatment with phenylmethylsulfonylfluoride (PMSF) had no influence on the activity of the H-LAI reaction. This indicates that the action of the factor is not mediated by serine esterase activity. The results suggest that the HLA factor possesses properties similar to those reported for different lymphokines.

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**4503**

**IMMUNOGOLD STAINING FOR LEUKOCYTE PHENOTYPING**

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The use of immunogold staining (IGS) method to identify heterogeneous lymphocyte subsets has been shown to be a relatively simple and convenient method tagging system (De Hey 1981). The peripheral blood mononuclear cells from 15 B-CLL patients were incubated with monoclonal antibodies (MoAb) with established specificities for T cells: LEU1, LEU4, VBP8, V171, V174, and B cells: B1, B38, B1, V171. The IGS was performed with colloidal gold labeled goat anti mouse antibodies (CAPP 30, Geometric Data, USA) as previously described. Preparations were both analysed manually using a Leitz microscope and evaluated automatically on a slide-based system (Hematrak). The immunofluorescence staining was done with a FITC marked goat anti mouse antibody (GRUB) according to established methods. The cells were examined with a cell sorter (FACS).

In conclusion the sensitivity and accuracy of IGS method depends on MoAb used. There seems to be better results in immunogold tagging using MoAb from IgG type compared to IgM type MoAb.

To our opinion The IGS could be regarded as a serious alternative to flow cytometry.
Evaluation of a new screening test for colorectal tumors using guaiac and occult blood assay

The classic method of screening for colorectal tumors (cancers and polyps), entails looking for blood in stools using the guaiac test. Our study aimed to evaluate a new guaiac test, the originality of which came from its coupling with an enzyme immunoassay (EIA) specific for the measurement of human hemoglobin (HbEIA). Objectives of this new test is to decrease false positives and thus to improve positive predictive values of the screening. The population studied was composed of healthy and was chosen from subjects over 65 years of age attending health examinations at the Centre of Preventive Medicine in Nantes. The test acceptance, the impact of a diet low in red meat during the test period, and the importance of the enzyme immunoassay measurement are evaluated. Over the 3700 subjects to whom test was proposed, 4320 (92%) performed it in a correct way, outlining a great acceptance in this population. AHA (15%) gave positive results to guaiac test. This positivity rate is higher for men than for women (25% vs 10%) but not influenced by age. 441 (12%) patients completed investigations after positive results, decreasing the overall acceptability to 90%. 15 cases of cancer and 78 cases of adenoma were found. The positive predictive value of the test in 20% for tumors, 49% for adenomas and 38% were completely negative, as compared with literature these screening rates are high. When the guaiac test was positive, the EIA method was performed. Distribution of the results are discussed and a 0.06 threshold is chosen with a ROC curve methodology. Three positive predictive values of significance improved for cancer (60% > 96%) but not for polyps (25% on 19%).

Tumor DNA was prepared by the use of high performance gel chromatography from human cancer cytoplasm. The molecular weight of the DNA fractions were in the range of 3.65 - 1.36 x 10^6 . The separated DNA was used to identify the human leukocyte activity. The leukocytes were taken from healthy humans and cancer patients. We examined the leukocyte adherence to the solid - state surfaces, adherence forces, leukocyte sedimentation in a liquid medium and attraction of the small - sized dielectric particles (NaF^+ ) to the outer surface of the cellular membrane. Materials and methods used will be presented together with the experimental findings achieved.


Leukocytes from healthy persons and cancer patients were used to examine the leukocyte adherence to solid - state surfaces, adherence forces, sedimentation rate and attraction of small dielectric particles (NaF^+ ) to the leukocyte surfaces. The experiments were performed with and without tumor antigen. The experimental findings are compared with the theoretical results based on the Frohlich coherent vibration hypothesis. We assume that in the vicinity of cells the polar coherent vibrations generate an oscillating electromagnetic field which mediates the long - range interaction between cells and the ambient medium resulting in the attraction forces. The experimental findings exhibit a good coincidence with the theoretical predictions.

Delayed hypersensitivity reactions to 4 recall antigens, and skin reactions to graded doses of a preparation of human lymphoblastoid cell line lymphokine, were studied in 22 patients with various malignant solid tumours and different degrees of disease severity. The lymphokine was derived from the RPMI-7908 cell line. Disease severity was scored on an 8-point scale, assigning 1 point for the following individual criteria: (a) persistence or recurrence of local tumor; (b) lymph node metastases; (c) liver metastases; (d) lung metastases; (e) skeletal metastases; (f) other distant metastases; (g) anaemia and (h) weight loss. Patients differed widely in their patterns of reactivity to the recall antigens: at 24 hours, positive skin reactions to trychophytons, Candida, SK-SD and tuberculin PPD were given by 17, 15, 9 respectively. The individual patients was classified according to the TNM classification and treated by surgery and adjuvant radiotherapy, caused a significant drop in specific reactivity of leukocytes in stage II and III patients. On the other hand the LAI reactivity in stage I patients was unchanged during therapy.

511 BESTATIN IN TREATMENT OF STAGE II MELANOMA - EFFECT ON IMMUNE FUNCTIONS

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Twenty-seven patients with stage II melanoma or stage I melanoma with subsequent regional metastases were randomized to 1) receive Bestatin 10 mg x 3 daily continuously, 2) Bestatin 60 mg on two days a week and 3) control patients without any therapy. In all cases the primary tumour and metastases in the regional lymph nodes were radically operated. Treatment with Bestatin was continued for two years or until recurrence of melanoma. The immune functions of all patients were determined at the beginning of treatment and one, two, four and seven months after start of therapy and thereafter with three to six months intervals. The tests used were:

- Lymphocyte count in the peripheral blood
- T-cells: ERFC cells
  - active ERFC cells
  - theophyllin resistant (helper) cells
  - theophyllin sensitive (suppressor) cells
- B-cells: surface immunoglobulin positive cells
- IA rosette forming cells
- Mitogen responses to PHA, Con A and PPD
- The NK (natural killer) cells

The PHA and Con A mitogen responses of lymphocytes increased in the specimens taken during the first months of Bestatin treatment. The number of ERFC cells, theophyllin resistant and sensitive cells, IA rosette forming cells and surface immunoglobulin positive cells did not significantly change during Bestatin treatment. There were no differences between the Bestatin and control groups as to the survival and recurrences of melanoma.

The subsets of the blood lymphocytes T /SRBC/, T, T /lymphocytes bearing Fc-IgM and Fc-IgG receptors, respectively/ and activity of serum ACE from patients with asbestosis were assessed and compared with controls matched for sex, age and smoking habits. Asbestos workers were classified by chest radiograph as extensive fibrosis /22 patients/, initial fibrosis /13 patients/ and without fibrosis /22 patients/.

Asbestosis patients with extensive fibrosis had lower percentage T, lymphocytes than other asbestos groups and controls. However, the patients with initial fibrosis had lower percentage of T, lymphocytes than workers with extensive fibrosis and without fibrosis had T, /T ratio similar to controls, while those with extensive fibrosis had decreased T, /T, ratio.

The highest level of ACE was noted in group with extensive fibrosis. There was significant negative correlation between number of T, lymphocytes and ACE activity in all investigated asbestos groups. Similar correlation but not significant was found between number of T, lymphocytes and ACE. The possible role of these findings is discussed.

CIRCULATING IMMUNE COMPLEXES (CIC) IN MALIGNANT MELANOMA. H. Shafir HP, S Jaramillo BS, JG Bekesi PhD, AH Aufses H5 Tower Sinai School of Medicine, New York, NY, USA.

Malignant melanoma is an antigenic tumor. Its presence frequently evokes an immunological response by the host. In an attempt to study this phenomenon sera from 17 patients and 31 normals were evaluated for the presence of circulating immune complexes (CIC) by polyethylene glycol precipitation and their immunoglobulin components measured by laser nephelometry. A significant increase of total CIC was found in patients vs normals (4.05 ± 3.02 vs 3.31 ± 1.83 mg/ml, p < 0.001). No correlation was found between stage of disease and total levels of CIC, although all Stage I patients had higher levels than normals, before and after wide resection (6.41 ± 2.99 vs 3.31 ± 1.63 mg/ml, p < 0.001), suggesting persistent immune recognition of the tumor.

Immunoglobulin G and M were also significantly higher in patients vs controls (1.71 ± 0.84 vs 0.70 ± 0.53 mg/ml, p < 0.001), (0.90 ± 0.68 vs 0.05 ± 0.19 mg/ml, p < 0.001). Further characterization of these CIC by SDS-PAGE revealed a precipitation band of MW t 70 X in 12/17 patients and 1/9 normals. These findings indicate that there may be a specific immune response to this malignancy.
**DEMONSTRATION OF NEUROECTODERM-ASSOCIATED ANTIGENS ON EWING SARCOMA CELL-LINES.**

P. Kemeth, Zsuzsa Babó and P. Balogh, Department of Pathology, University Medical School, Pécs, Hungary.

The effects of the specific antigen on the growth of different hybridoma cells (α-5D0, α-HEK or α-4G10) provoking antigen-specific monoclonal antibodies were studied. Inhibition of the proliferation of hybridoma cells by the idiotyp-specific antigen was detected in vitro. This phenomenon showed a characteristic dose dependence of the antigen (at different levels in the various hybridoma cell lines). Preimmunization of the mice by the idiotype specific antigen increased survival time of hybridoma-cell injected animals. In the sera of preimmunized, long surviving, tumour-bearing mice anti-idiotypic antibody production was observed. In the same animals hybridoma cell clones were detectable immunohistologically in different lymphatic organs. The T-cell dependency of these phenomena was studied in various inbred strains of mice with the same H-2 haplotype and with different immune responsiveness. The T-cell dependent antigen immune response may inhibit both the proliferation of idiotype specific antigen secreting normal and hybridoma cells.

**DEMONSTRATION OF NEUROECTODERM-ASSOCIATED ANTIGENS ON EWING SARCOMA CELL-LINES.**

M. Lipinski and T. Hungary AHTIGEH ON PROLIFERATION OF HYPERIDOTA CELLS. of Pathology, University Medical School, Pécs, Hungary. Zeuzsa Bebfo and P. Balogh, Department of Pathology, University Medical School, Pécs, Hungary. Zeuzsa Bebfo and P. Balogh, Department of Pathology, University Medical School, Pécs, Hungary.

The histogenesis of Ewing sarcoma, the second most frequent bone tumor in children, remains controversial. Eleven Ewing cell lines were analyzed by immunological methods. Surface antigens reactivity on Ewing cells were found to be related to the neuroectodermal lineage. Ganglioside GD2, a marker of neuroectodermal tumors, was present on nine lines. All but one were also stained by the mouse monoclonal antibody HNK-1 that detects a carbohydrate epitope present on several neural cell adhesion molecule N-CAM. Human monoclonal antibodies from patients with demyelinating neuropathy also reacting with N-CAM stained 6 of the 11 Ewing lines tested. The P61 rat antibody that reacts with a peptide moiety of N-CAM stained 9 lines. By contrast, all antibodies detecting cell surface antigens specifically associated with the hematopoietic lineage revealed totally unreactive. HLA class II antigens were never detected while the level of expression of class I antigens varied to a large extent. The other antigen specificities are characterized by a t(11;22)(q24.1;q12) translocation that also occurs in neuroepitheloma, another neuroectodermal malignancy. The gene for N-CAM has been mapped to chromosome 1q23 and could be rearranged during the translocation. Thus, Ewing sarcoma cells share a series of antigenic and histological features with derivatives of the neuroectoderm that could indicate a similar histogenesis.


**4520**

**DISTRIBUTION OF SURFACE sNCA/sMCA/ AND LECTIN-BINDING ABILITY IN LEUKEMIC MYELOID CELLS; INFLUENCE OF NEUROMINIDASE.**


Discontinuous density-gradient centrifugation was used to separate myeloid cells of different myelocytic leukemias /AML, COL-RC, CGL/ into fractions containing granulocytes in individual stages of maturation. The distribution of sMCA, myeloid antigen CD15 and lectin /PNA,lectin from Asparagus pea/ binding ability in each cell fraction was studied by IF. Morphology of each fraction was evaluated in parallel. The influence of neuraminidase on the presence of all studied markers was also evaluated. It was established that neuraminidase treatment usually reduced the percentage of sMCA positive cells, caused increased number of cells expressing remaining markers. No relationship between the presence of sNCA and other markers was shown.

**4521**

**EXPRESSION OF MYELOID DIFFERENTIATION ANTIGENS ON MYELOBLASTS IN THE BONE MARROW OF PATIENTS WITH MYELODYSPLASTIC SYNDROMES**

I. Borosnyoi 1, A. Ghaosh, K. Cinkota 1, E. Balogh 1, M. Moore 1.


Bone marrow myeloblasts in 15 patients with myelodysplastic syndromes /MDS/ were quantitated with monoclonal antibodies using the immunofluorescence technique. Positive blasts were identified in 7 of the 15 cases with at least one of three antibodies reactive with acute myelomonocytic leukemic cells /PMN-6, PMN-29, AML-2-23/ which were non-reactive with normal myeloblasts. Of these 7 all were PMN-6 positive, 6 were PMN-29 and 3 were AML-2-23 positive. The positive blast count varied between 18-60%. All these cases except one were found in the RAEB and RAEB-T subtypes of MDS.

Seven of 15 cases showed an increased positivity with PM-81 antibody when compared with myeloblasts from normal controls. /PM-81 antibody reacts with all types of acute myeloid leukemic cells and a certain percentage of normal myeloblasts/. The percentage of positive blast cells in these 7 cases was between 57-76%. In the normal controls the mean value of positive blast cells was 10.6 ± 5.3% with PM-81 antibody. In 5 of these cases increased PM-81 positivity was associated with expression of at least one of the other antigens.

The data suggest an aberration of myeloid differentiation in myelodysplastic syndromes which is reflected in altered surface marker features.

**4522**

**THE EFFECT OF BIOLOGICALLY ACTIVE MATERIALS ON THE EXPRESSION OF LYMPHOCYTE CELL SURFACE MARKERS**

Kotlén 1, Pécely 2, Baráth-Kopacz 2, A. Szabó 2, Gárdonyi 2, E. Balogh 1, M. Moore 1.


The current work investigates the effects of interferons/INF/, interleukins /IL/, monoklonal antibodies using the immunofluorescence assay—FACS analysis and ELISA. It has been demonstrated, that crude, purified or recombinant and INF increase the expression of HLA ABC antigen after 16 hours' incubation. The amount of HLA DR ag doubled following a few hours' IFN treatment, while HLA was not effective. Among the 24-70-23, T11 differential antigens, only the T11/8 ag's expression increased after a few or more hours' IFN incubation. Purified IL-2 enhanced strongly the HLA DR and alpha antigen in the course of differential age except the T11 ag it did not seem to be effective. The expression of Leu 7 ag didn't change either after interferons or interleukins. After about 6 hours' incubation with PEC, PGP, the amount of HLA DR ag increased slightly. On the basis of the results up to now it can be concluded, that biologically active materials have very different effects on the cell surface antigens' expression.

**4523**


Instit. of Clin. Immunol., Budapest U.K.

The immunologic phenotype of more than 200 lymphoid and myeloid leukemias as well as some non-Hodgkin's lymphomas has been stated by a panel of monoclonal antibodies/some prepared at our institute/. The cytochemical studies consisted of the detection of enzymes, lipids and polysaccharides. The electrophoretic mobility/PNP/ and the enzymatic activities/Purine nucleoside phosphorylase/PNP/ and purine metabolism enzymes/adenosine deaminase /ADA/ have been studied simultaneously. The results of the cytochemical studies gave a very good agreement with those obtained from the immunologic cell surface studies—also in a group of cases which could not be classified by the morphology of cells. Our previous findings showed that leukemia cells of lymphoid malignancies retained the EM of the original cell. These studies have been extended to myeloid leukemias and these results were shown to be characteristic for malignant phenotype. Purine metabolism enzyme studies proved to be useful especially in the case of T-acute lymphoblastic leukemia with significantly increased ADA values along with significantly decreased PNP values. In a group of those cases which could not be classified by the morphology of cells the studies revealed acute T-lymphoid leukemias from acute leukemia cases. These results are also in a good agreement with differentiation and leukemia-associated antigen detection by monoclonal antibodies in an indirect immunofluorescence assay.
4524  TUMOUR CELL EXPRESSION OF CLASS II (HLA-DR) DETERMINANTS IN NASOPHARYNGEAL CARCINOMAS DEMONSTRATED BY IMMUNOHISTOCHEMISTRY

Brandtzaeg, P. Laboratory for Immunohistochemistry and Immunopathology, Institute of Pathology, The National Hospital, Rikshospitalet, Oslo, Norway.

The presence of keratin in undifferentiated nasopharyngeal carcinomas (NPC) has recently been described as a useful marker for these tumours. One study also reported variable epithelial expression of HLA-DR antigens (Int. J. Cancer 32: 813, 1984). Since such Class II histocompatibility determinants are important in immune regulation, their aberrant expression might partly explain the massive lymphoid cell infiltration in NPC. In this study actual co-expression of keratin and DR was examined directly by paired immunofluorescence in ethanol-fixed paraffin-embedded biopsy material of 15 tumours (2 metastatic) which had been given the histopathological diagnosis of poorly differentiated carcinoma of the naso- or oropharynx. In addition to a polyclonal antiserum to prekeratin, the study was based on two monoclonal antibodies to cytokeratin (PCK1 and PCK2), two to nonpolymorphic DR determinants, one to vimentin, and one to leucocyte common antigen (LCA). Four tumours were excluded as they turned out to be non Hodgkin malignant lymphomas (keratin-negative and LCA-positive). Of the remaining six keratin-positive tumours, 8 were histologically compatible with NPC. Five of these showed abundant DR expression, sometimes including epithelial cells that were almost negative for keratin, whereas 3 showed variable DR staining. Variable co-expression of keratin and vimentin was seen in 5 of the 8 NPC. This has not been reported previously in NPC but has been noted in a few other carcinoma varieties. The extensive aberrant epithelial DR expression seen in NPC may influence the biology of these tumours. (Supported by the Norwegian Cancer Society)

4526  LACK OF ASSOCIATION WITH HLA ANTIGENS IN PAPILLARY AND FOLLICULAR THYROID CARCINOMA.


Genetic factors play an important role in the etiology of many thyroid diseases. In subacute thyroiditis (de Quervain) and Hashimoto's auto-immune thyroiditis, the association with certain HLA antigens (B35, DR3, DR5) could be demonstrated. In order to evaluate the role of the HLA system in the field of thyroid cancer, we performed HLA A, B, C, and DR typing in 22 patients with histologically confirmed papillary or follicular thyroid carcinoma. 357 healthy blood donors from the same geographic area acted as a control group. Statistical analysis was carried out using the chi square test with Yates' correction. We were not able to find a significant association for the A, B and C locus. For the DR locus, Dm Bw 8 was increased (21.1%) compared to 5.5% of the controls. The P value lost significance, however, after correction for the number of antigens tested. We therefore conclude that HLA testing gives no further information on the genetic background contributing to the development of differentiated thyroid carcinoma.

4525  HLA SYSTEM AND NEUROFIBROMATOSIS (VON REITZEL'S DISEASE) FAMILIAL STUDIES

J. Abrahmow, A. McAlery, P. Kosíkovič

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The authors performed HLA typing in 26 patients affected by neurofibromatosis (NF) and in 1 of them they also typed all the available members of their families.

In 14 families manifesting a kindred occurrence further 29 patients, in whom the disease had not yet been diagnosed, have been unveiled. In 13 families out of 14 manifesting a familial load of the disease there was agreement in one HLA haplotype especially among the diseased sibling members. From this point of view it appears that HLA typing in NF might be a valuable contribution especially for the diagnosis of the complete cases in families manifesting a kindred type of NF occurrence.

4527  HLA AND IgG HEAVY CHAIN MARKERS - Gm DIFFERENCES IN PAPILLARY AND FOLLICULAR THYROID CARCINOMA.


An association with HLA-DR1 with differentiated thyroid carcinoma (DcC) was described from Naples and with DR7 in patients from the American midwest with DcC unrelated to previous radiation. We have studied HLA antigens in 52 Hungarian and 40 Newfoundland patients with DcC. Association of DcC with HLA was also studied in 50/52 Hungarian patients DcC was found in 28 patients (53.8%), compared to 19.4% of 160 controls (RR=2.93). In studies on blood donors from the same geographic area acted as a control group. Statistical analysis was performed HLA A, B, C, and DR typing in 22 patients. The association with certain HLA antigens (B35, DR3, DR5) could be demonstrated. The DR locus, Dm Bw 8 was increased (21.1%) compared to 5.5% of the controls. The P value lost significance, however, after correction for the number of antigens tested. We therefore conclude that HLA testing gives no further information on the genetic background contributing to the development of differentiated thyroid carcinoma.

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Cancer-associated hemolytic uremic syndrome (C-HUS) is a rare entity that develops in patients successfully treated with chemotherapy, usually when the tumors are in complete remission. Features of the disease include microangiopathic hemolytic anemia (MAHA), severe thrombocytopenia, renal insufficiency and tendency to develop non-cardiogenic pulmonary edema (either spontaneously or post transfusion). It has in the past had a mortality rate of 80% in 12 months. We have previously identified high levels of circulating immune complexes (CIC) in 17/17 C-HUS patients. They are formed by a glycoprotein antigen and IgG antibody with specificity for surface antigens of original tumors. The complexes are small to medium sized and show high platelet aggregatory activity. Conventional plasma exchange has not controlled this syndrome in the past. We report treatment results in 16 C-HUS patients, using perfusion of plasma over filters containing Staphylococcal Protein A (SPA) immobilized on different solid supports. SPA binds and alters the antibody. When reacted with the antibody, strong cytoplasmic fluorescence may be an antigen moiety (32 KD) as it reacted immunologically with the antibody. These studies demonstrated that immunosorptive therapy with Prosorba® columns is safe and well tolerated by the patients. This study continues to accrue patients with cancer and certain autoimmune diseases.

4529 STAPHYLOCOCCAL PROTEIN A (SPA) COLUMNS (PROSORBA®) IMMUNOADSORPTION IN PATIENTS WITH ADVANCED MALIGNANCY. J. J. Nadkarni, J. A. Kontodiaghy, Cancer Research Institute, Tata Memorial Centre, Parel, Bombay-400012, India.

The evaluation and characterization of immune complexes (IC) is important to the understanding of immune reactions in the pathogenesis of IC-associated diseases including cancer. However, attempts to identify the antigen involved in IC formation are of increasing interest. There are evidences which suggest that the extracellular fluids surrounding tumors may provide a convenient source for isolation of tumor-associated antigens and antibodies. IC were therefore isolated from pleural effusions (PE) of non-Hodgkin's lymphomas with favorable and unfavorable prognosis. These IgG-type IC were further associated by ion exchange chromatography using IM Umm. The antibody was found to be a high molecular weight protein (150 KOD) and reacted with anti-human IgG while peak obtained on ion exchange chromatography may be an antigen moiety (12 KD) as it reacted immuno logically with the antibody. Strong cytoplasmic fluorescence was observed in various cell suspensions of lymphomas when reacted with the antibody preparations. The absorption of these rabbit antibodies with individual cell extracts or with antigen preparations also blocked the cytoplasmic staining. A. Antholyzed PE from patients with unfavorable and favorable prognosis showed identical patterns of separation of IC components. These results indicate that the antigen moiety may be a common antigen in the disease process.


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In a previous work (G. Formi et al., J. Immunol., 134, 1304, 1985) we have shown that an efficient antitumor reactivity can be elicited from non-reactive T lymphocytes from mice harboring clinically evident tumors by both in vitro and in vivo stimulation of non reactive lymphocytes with IL-2. We then tested in the same murine model the capability of a new cycloheximide-derived endowed with immunomodulatory properties (PCF-39) to protect mice grafted with CT 26 methylcholanthrene induced sarcoma of Balb/c. This drug showed neither antitumor nor cytotoxic effect in CT 26 sarcoma cells or other cells tested for doses 4, 600 μg/ml. With multiple local injections of low doses of PCF-39 increased the effect of surgery by 30%. There were less local recurrence and metastasis and normal mice induced antitumor immunity and can be induced only by complete, structurally intact virus.

4533 LABORATORY AND CLINICAL EXPERIENCE WITH APATHOGENIC VIRUSES AS ANTITUMOR AND IMMUNOMODULATING AGENTS. A. Muceniece, A. Perkstes, N. Krakīte, A. Vitolins, E. Kopins, R. Dārziņš

Laboratory of Virotherapy, August Kirchenstein Institute of Microbiology, Latvian SSR Academy of Sciences, Riga, Latvian SSR, USSR

Non-specific immunomodulation is a common feature of many viral infections. The manifestations of immunomodulation depend on the specific and functional organization of the virus and immunological background of the host.

Infection of mice with non-pathogenic virus (PCR-29, PCR-39) enhanced antitumor immunity. The mechanism was more expressed in combination of systemic and local administration of virus.

An enterovirus of the ECHO group, isolated from a child's alimentary tract revealed oncogenic and oncolytic characteristics in 52% of various tumours. Adaptation of the isolated viruses in short term tissue cultures of human malignant melanoma enhanced its oncolytic activity against human melanoma. Immunization of mice with this adapted virus enhanced their resistance to transplanted tumors, to gamma irradiation and decreased the reaction to alkylation agents as a result of the non-specific immunomodulation.

Treatment of malignant melanoma patients with enterovirus increased the effect of surgery by 30%. There were less metastasis and recurrance of the tumors after surgery. The isolated and adapted apathogenic agent is clinically, epidemiologically and genetically safe. Virus induced antitumor effect is due to direct oncolysis, tumor cell xenograft (modification of the tumor cell antigens) and activation of the host immune system at different levels. The virus-induced immunomodulatory effect is correlated to the level of overt viral immunity and can be induced only by complete, structurally intact virus.

4534 HETEROGENEOUS EXPRESSION OF CLASS II (HLA-DR) ANTIGENS AND SECRETORY COMPONENT (SC) IN HIGH GRADE DYSPLASTIC LESIONS IN INTRACUTANEOUS LUTICIES (UC). J.O. Hagström, P. Hennrit-Cernil, K. Toonen, and L. Pouppkreuk.

Pathology and Forensic Med., and Dept. of A, The Neth.Hospital, Oslo, Norway.

Intensity and degree of heterogenous marker expression were evaluated immunohistochemically in 11 biopsy specimens from 4 UC patients with high grade dysplasia and in 12 specimens from 11 patients with low grade dysplasia. For comparison we used biopsy specimens from UC patients with mide (7) or severe (6) inflammation and histologically normal biopsies (7). All patients with high grade dysplasia and 2 of those with low grade had synchronous adenocarcinomas. HLA-DR showed a high degree of heterogeneous expression in all specimen with high grade dysplasia and in the 2 samples with low grade dysplasia from patients with synchronous adenocarcinoma. In the remaining low grade dysplastic lesions 3 of 12 showed heterogeneous 8R patterns but to a lesser degree (lower all of none immunoreactive) than in the high grade lesions. In high grade dysplasia 9 of 11 samples were heterogeneous stained for DR, whereas in the low grade lesions all but 2 samples were homogeneous. In the histologically normal samples UC was homogeneously expressed and only one sample showed a slightly heterogeneous expression. In mildly inflamed UC samples UC was patchily distributed in one sample and mildly, whereas both UC and SC showed a slight degree of heterogeneous expression in all samples with severe inflammation. Moreover, the all over intensity of DR staining tended to decrease with increasing degree of inflammation, whereas the opposite was true for SC. In conclusion, although a high degree of heterogeneous expression of DR is not often seen in high grade dysplasia, uneven distribution of these markers may also be seen in hyperplastic lesions of UC, which are generally associated with severe inflammation. Increased SC expression and an increased class II antigen expression parallel increased inflammatory activity. (Supported by the Norwegian Dental Society.)

4535 CORRELATION BETWEEN CIRCULATING IMMUNE COMPLEXES AND PROGNOSTIC FACTORS IN Hodgkin's Disease

Alicja Dziewulsk-Bokiniec, Magda Sztaba-Kania

Inst. Radiology and Radiotherapy, Gdansk, and Dept. Immunology of Inst. Pathology Gdansk, Poland

Sera from 47 untreated patients with HD and sera from 100 healthy control were tested for presence and levels of circulating immune complexes using EAC rosette inhibition test. The incidence of CIC (64%) in HD patients serum was significantly higher than healthy controls. The HD patients with localized disease showed 75% frequency of elevated CIC level and the level of CIC was significantly higher than normal donors. In sera of patients with localized disease (I-II stage) in symptomatic B-subgroup and asymptomatic A-subgroup the incidence of positive results and the mean level of CIC between these subgroups did not differ significantly. In patients with disseminated HD (III-IV) CIC were found significantly less frequent than in patients with localized HD but the mean level was not statistically different. In this group higher percent positive results was in sera of symptomatic patients. The analysis of mean level CIC indicated level statistically higher (p<0.05) in the sera of patients group A-symptoms of disseminated disease in comparison to symptomatic group.
**G-61: MEMBRANE MARKERS — HLA — IMMUNOCOMPLEXES**


The latent membrane protein (lymphocyte determined membrane antigen-LYOMA) encoded for by the EB virus is supposed to be the target antigen for LYOMA specific killing by HLA restricted cyotoxic T lymphocytes. This latent membrane protein has been purified from EB-virus infected lymphoblastoid B cell line by using rabbit antisera to LYOMA-related peptides. The molecular weight of the protein is 63 KD. It reacts with polyclonal rabbit antisera and with a monoclonal antibody (SI2, kindly provided by David Thorsley-Lawson) to the latent membrane antigen. It does not react with antibodies to monomorphic and polymorphic regions of the HLA molecule. The protein has been used in cytotoxic assays to inhibit LYOMA specific HLA restricted, HLA specific, HLA restricted and NK cell mediated killing of EB-virus infected target cells.

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Fifteen human cell lines of colorectal (8), lung(4), cervical (2) and breast (1) cancer origin have been characterised by immunocytochemistry, radiolabelled antibody binding and competitive inhibition studies with 4 monoclonal antibodies recognising different CEA epitopes. Cell lines were ranked in terms of their antigen expression/antibody binding characteristics and, for some, the number of antibody molecules binding per cell was quantitated. Two extensively characterised, specific monoclonals (11-285-14, IgG1; 14-95-55, IgG2a) were selected for the assessment of vindeosine (VDS)-antibody conjugate efficacy in vitro using 24 h tritiated uridine microcytostasis and colony inhibition assays. Mice VDS per mole IgG ranged from 4.0 to 11.0 for different conjugate batches and all were shown to retain anti-CEA activity in enzyme linked immunosorbent assays. Conjugates were tested in the 0.48 to 24,000 ng mole VDS concentration range. In VDS sensitive cell lines, conjugate efficacy was demonstrated to correlate with density of expression of the target antigen. Selected CEA positive and negative cell lines were grown as xenografts in nude mice for immunocouple efficacy evaluation in vivo. As found in vitro, efficacy of conjugates was demonstrated and shown to correlate with target antigen expression based on immunocytochemical assessment and quantitation of the CEA content of xenografts. Several dosage schedules were investigated including an alternating VDS-1-2-085-14, VDS-14-95-55 twice weekly schedule; this was effective in inhibiting the growth of a colorectal xenograft, but not significantly more than either conjugate on its own. Establishment of the CEA model system has enabled us to demonstrate: (1) VDS-anti-CEA monoclonal immun conjugate efficacy in vitro and in vivo (2) a correlation of efficacy with target antigen expression (3) a possible role for two conjugates recognising different epitopes (4) the relevance of this model in the preclinical evaluation of immunocouples for potential clinical therapeutic use.

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**G-62: TUMOUR IMMUNITY IV**

4538 RELATION BETWEEN MURINE BREAST TUMOUR ASSOCIATED ANTIGEN TO HUMAN BREAST CANCER. J. Roy Chowdhury, Jaya Chettopadhyay, Upal Chettopadhyay, Chittaranjan National Cancer Research Centre, Calcutta.

The spontaneous murine mammary tumor is known to be associated with a RNA virus — MMTV. The viral antigen as well as non-viral mammary tumor associated antigen was earlier purified from murine mammary tumor. A number of evidence coming from electron microscopy, serologic and enzyme studies indicate association of MMTV or a similar virus in human breast cancer. We undertook a study to investigate the immunological relatedness of the murine mammary tumor and human breast tumor.

A murine mammary tumor associated antigen (MTAA) was purified from spontaneous tumor of C3H/AxB mice. The antigen was not a component of MMTV but was found in mammary tumors associated with MMTV.

The MTAA was demonstrated to be immunologically related to human breast cancer. Human malignant breast tumor antigens were cross-reactive with the specific antigen of the MTAA. Circulating antibodies to the MTAA were also recorded in 100% of the preoperative sera of breast cancer patients. Surgical removal of the malignant breast tumor resulted in significant lowering of the circulating antibodies with ultimate disappearance with the increase of postoperative period. However the circulating antibody level persisted in metastatic patients. Control subjects were devoid of such antibodies. Thus the MTAA may prove to be a specific mammary tumor marker in both the diagnosis and prognosis of human breast cancer.
The aim of this work is to study the immunological status in the mammary gland tissues under the preoperational radiation therapy in the histopathological research of anatony. The tissue was studied in group 1, in group 2, the level of T and B lymphocytes was higher with T lymphocytes prevalence. The greater stimulation of the B lymphocyte subset occurs during the extended functional method of preoperative radiation compared with Coarse Fractional method.

The presence of α2-macroglobulin was detected with avidin–biotin technique in more than 20 years old paraffin blocks from human sarcomas. α2-macroglobulin was found mainly in the cytoplasm of the tumor cells and almost all tumor cells were positive. This serum glycoprotein and a major plasma proteinase inhibitor with a wide specificity was also shown to be synthesized and was secreted by all three cell lines derived from primary sarcomas. α2-macroglobulin in situ and in vitro was used as an antiserum to tumor-associated α2-macroglobulin.
PRESENCE OF THE SPECIFIC-TUMOR-ASSOCIATED ANTIGEN IN ENDOGOTIC BOVINE LEUKOSIS. P. Bäntlikk, O.J. Vrtiak, Danith, M. F., Veterinary University, Kosice, Institute of Experimental Veterinary Medicine, Kosice, Czechoslovakia

Among the neoplasms in cattle, the most common is bovine leukemia—BLL (lymphosarcoma, malignant lymphoma or leukemia). BLL has frequently been recognized in many areas of Europe and America. At the present time mainly serological methods are used, for diagnosis of BBL, which depend on antibody development after bovine leukemia virus (BLV) infection. From the point of view of the relationship among BLV infection, antibody versus BLV, persistent lymphocytosis, lymphosarcoma and specific tumor-associated antigen (TAA), it would be interesting to learn more about the significance of the latter. This antigen was found usually on neoplastic lymphoid cells from cattle. The present paper deals with isolation of peripheral blood lymphocytes of BLL-infected cattle showing no evidence of leukemia. Our work was undertaken to isolate TAA partially characterised and in an attempt to prepare antibody against the latter for its immunofluorescence demonstration.

DEVIATION OF THE IMMUNE DEFENSE MECHANISMS TOWARDS AN ACQUIRED CAPACITY TO STIMULATE TUMOR PROGRESSION IN TWO MURINE NEPHEMATOSIS. J. Leibovici, S. Leibovici, M. Michowitz, S. Kopel, and A. Agamanov, Dept. of Pathology, Sackler Faculty of Medicine, Tel-Aviv University, 69978 Tel-Aviv, Israel.

Tumor progression is accompanied by decrease in sensitivity to varicella in murine pregnancy, NK cells and cytotoxic T cells were found. The decreased immune responses to tumors of increased malignancy may also have an implication to immunotherapy. In the present study, host responses to variants of malignancy of two murine tumors were tested: the Fl and FIO variants of RT1 melanoma and the TAU-39 and TAU-38, variants of low- and high-malignancy, respectively, of AKR lymphoma. Growth of 8% F1 caused a higher increase in spleen weight than growth of 8% FIO, grossly indicating a better host response towards the less malignant variant. These results were supported by a marked infiltration of granulocytes and macrophages at the site of Fl and only slight infiltration at the site of FIO. Inoculation of the two variants to splenectomized mice resulted in growth of 8% F1 similar to that observed in intact mice. While growth of Fl was delayed in mice with palpable spleens, indicating that spleens of F1-bearing mice have the capacity to enhance tumor growth. Even pronounced differences were observed between the two variants of AKR lymphomas: splenectomy delayed the growth of the high-malignancy variant but accelerated that of the less malignant one. This indicates that the spleen may contain a defense response to the low-malignancy tumor but decreases the capability of the high-malignancy lymphomas have acquired a capacity to stimulate tumor growth. Injection of leuko-activated macrophages resulted in inhibition of low-malignancy variant and stimulation of the high-malignancy one, in both systems. In the two models, chemioimmunotherapy was more efficient against the low- than against the high-malignancy variant. Tumor progression is often accompanied by escape from immune defense mechanisms. However, in the two murine models of tumor progression investigated in the present study, a more severe phenomenon was seen: deviation of the immune system towards an acquired capacity to enhance tumor growth. This phenomenon has an implication to efficiency of immunotherapy at different stages of tumor progression.


Reactions of cellular and humoral immunity were investigated in 570 patients with lung and gastric cancer. Results revealed a reduction of skin test responses to DNCB and PHA, different degrees of reduction of spontaneous rosette formation and blast transformation of lymphocytes to PHA. At the same time, in case of generalized process of the above responses were revealed a change of the ratios of subpopulations of T-helpers and T-suppressors and increase in various subpopulations of tumor cells. These results were supported by a marked infiltration of granulocytes and macrophages at the site of Fl and only slight infiltration at the site of FIO. Inoculation of the two variants to splenectomized mice resulted in growth of 8% F1 similar to that observed in intact mice. While growth of Fl was delayed in mice with palpable spleens, indicating that spleens of F1-bearing mice have the capacity to enhance tumor growth. Even pronounced differences were observed between the two variants of AKR lymphomas: splenectomy delayed the growth of the high-malignancy variant but accelerated that of the less malignant one. This indicates that the spleen may contain a defense response to the low-malignancy tumor but decreases the capability of the high-malignancy lymphomas have acquired a capacity to stimulate tumor growth. Injection of leuko-activated macrophages resulted in inhibition of low-malignancy variant and stimulation of the high-malignancy one, in both systems. In the two models, chemioimmunotherapy was more efficient against the low- than against the high-malignancy variant. Tumor progression is often accompanied by escape from immune defense mechanisms. However, in the two murine models of tumor progression investigated in the present study, a more severe phenomenon was seen: deviation of the immune system towards an acquired capacity to enhance tumor growth. This phenomenon has an implication to efficiency of immunotherapy at different stages of tumor progression.
4547 IMMUNOLOGICAL REACTIVITY OF SPLEEN CELLS FROM TUMOR-BEARING MICE AFTER TREATMENT WITH CYCLOPHOSPHAMIDE. F. Olgic, I. Bejlan and T. Kojak, Dept. of Physiology and Immunology, Faculty of Med., Univ. of Zagreb, Zagreb, Yugoslavia CBA mice bearing advanced methylcholanthrene-induced tumors were given single, noncurative injection of cyclophosphamide (CY) (200 mg/kg), and antitumor activity of their spleen cells was tested for one month after drug injection. The activity of spleen cells was tested in two passive transfer assays: local transfer assay (Wim's or neutralization test) and systemic transfer assay (adoptive immunotherapy of tumors in T-cell deficient animals; North RJ: Adv. Immunol. 35:89-155, 1984). As tested in Wim's assay, treatment with CY induced tumor-specific immunity in spleen cells, which was maximal between day 7 and 15 after drug treatment and disappeared after day 21. However, same spleen cells had no any tumor-inhibitory activity after systemic transfer.

Moreover, spleen cells from CY-pretreated mice suppressed tumor-inhibitory activity of spleen cells from immunized mice when injected before or together with immune cells into T-deficient animals. These data indicate that different cell (or mechanisms) mediate antitumor activity after local and systemic transfer of sensitized cells, and that CY may activate in tumor-bearing host only those cells which are efficient after local transfer of cells. Presently, we are trying to correlate these changes in spleen cell function with the changes in cell composition and electrophoretic mobility of spleen cells after CY treatment.

4548 EARLY BREAST CANCER PATIENTS TREATED WITH RADIOTHERAPY AND CHEMOTHERAPY. Dr. A. Ellis, Dr. H.G. Botto, Dra. I.de Botto: CIO- Jose Marmol del Bueno Aires, Argentina. In a previous study (proc.13th. International Cancer Congress, 2742) we have examined 1124 patients with breast cancer the effects of the different treatments on the cellular immune response (IR). The immunologic evaluation in the peripheral blood included total lymphocyte counts, determination of E-Rosette, T-Lymphocytes and B lymphocytes and cutaneous delayed hypersensitivity tests - DNCB, Tuberculine, Candidine and Tricophyton. In 25% of the patients the tests performed 1 month after radiotherapy and adjuvant chemotherapy (CMF or FAC) were found regular or severe depressed.

In the current study immunologic parameters were examined 6, 12 and 24 months after chemotherapy and 26 of these 124 patients. This study demonstrated that in patients with early breast cancer (stage II) the cellular immune response (IR) is not altered before radiotherapy and adjuvant chemotherapy and 24 months after these treatments IR is impaired in many patients. Lymphocytes total counts and T lymphocytes were found decreased in 60% of the patients. DNCB were negative in 30% and Tuberculine, Candidine and Triophyton in 46 of this patients.

4549 THE IMMUNOHISTOCHEMICAL EXAMINATION OF LUNG CANCERS USING MONOCLONAL ANTIBODIES REACTING WITH CANCER ASSOCIATED GLYCOLIPIDS. F.Karaki*, T.Kameya*, T.Wada*, P.I.Terasaki** Dept. of Pathology, Sch. of Med., Kitasato Univ., Sagamihara, Kanagawa, Japan*, UCLA Tissue Typing Lab., UCLA, Los Angeles, Ca., U.S.A.** In order to explore the relationship between expression of cancer associated antigens and histological subtypes of small cell carcinoma, 26 cases of small cell carcinoma (SCC) and 48 cases of non-small cell carcinoma (non-SCC) were examined immunohistochemically using monoclonal antibodies (MoAbs) against the hapten of cancer associated glycolipids such as sialosyl Lea (Lea), sialosyl Ma (Ma), and Lea. Materials and Methods: Seventy four samples of lung cancer were collected from the files of routine surgical and autopsy materials in the Kitasato Univ. Hospital. Histologically, 26 cases of SCC included 15 cases of intermediate cell type and 11 cases of oat cell type. Forty eight cases of non-SCC included 21 cases of adenocarcinoma, 20 of squamous cell carcinoma and 7 of large cell carcinoma. Three MoAbs, CELEX1, CELEX1 and CELEX1, were made in UCLA Tissue Typing Lab., U.S.A., CELEX1 reacts with Sl, CELEX1 reacts with Ma and Lea. The immunoperoxidase staining of deparaffinized sections was performed by ABC method. Results: Although cancer cells of most cases of SCC expressed Sl, SlE and Lea, cells of 15 cases of non-SCC were found to be positive for SlE, SlE and Lea. In adenocarcinomas, the number of tumor cells having the antigens was more than that of squamous cell carcinoma, large cell carcinoma and SCC. Of 15 cases of intermediate type of SCC, the cancer cells of 12 cases had SlE, SlE and Lea. However, the cells of 3 cases of oat cell tumors expressed the antigens. The present studies show most cases of intermediate cell type have characteristics similar to non-SCC but most cases of oat cell type lack them concerning glycolipids of the membrane.

Ten new platinum (II) complexes were synthesized and examined for antitumor activity and toxicity. In order to study the relationship between the antitumor effect and the type of ligand three types of platinum (II) compounds were examined: (1) complexes with peptide and chloride ligands; (2) complexes with amine and organic acid ligands, and (3) complexes with peptide and organic acid ligands. Agents of the group two prolong the survival of leukemic mice by more than 60% in L1210, and 25% in P388, or cure more than 50% of the mice with Erlich ascites tumor. Activity is also observed for the compounds of the third type. Only one of the complexes of the first type possesses antitumor activity against Erlich ascites. With regard to toxicity, the 5-fold administration of the complexes with peptide ligands (70 mg/kg per day) induced a decrease of the body weight less than cis-diaminodichloro-platinum (II) (0.5 mg/kg per day). It is shown that the toxicity of the platinum (II) complexes is lowered if the molecule contains a peptide ligand, and the antitumor activity increases by replacing the chloride anion with an organic acid ligand. Due the replacement of the chloride ligand with an organic acid ligand the solubility and the biological activity of the compounds were improved. The experimental studies confirm the important role of the ligand type for the antitumor properties of the compounds.

RELATIONSHIP BETWEEN INDICES OF BIOLOGICAL ACTIVITY AND STRUCTURE OF SOME PLATINUM CYTOSTATICS

A new series of platinum complexes were synthesized and studied. The following substances were used as ligands: 2-hydradrinouracil, 2-hydradrino-6-methyluracil, 2-hydradrino-6-azathymine, 4-hydradrinouracil and 4-hydradrino-6-methyluracil. Depending on the starting compounds and the reaction conditions two groups of complexes have been isolated which differ in their properties and structure. The first group represents binuclear neutral complexes containing bridging chloride ions. The second consists of compounds with complex polymeric structure. The complexes of this group are similar to the so called "platinum pyrimidine blues". The antibacterial and antitumor activity was studied.

Polymers based on N-substituted asparagines (A) and glutamines (G) are well tolerated. The latter are biodegradable, the former only to a limited extent. Their pharmacokinetics and biodistribution was studied using either fluorescent or radioactive labeling. The renal and biliary excretion of the N-(2-hydroxyethyl) homopolymer of A (PHEA) was controlled mainly by the molecular weight. Introduction of >4 mol.% of 4-hydroxyphenethyl groups in the side chains caused the accumulation of the polymer in the renal and biliary excretion of the N-(2-hydroxyethyl) homopolymer of A (PHEA) were controlled mainly by the molecular weight. Introduction of >4 mol.% of 4-hydroxyphenethyl groups in the side chains caused the accumulation of the polymer in the kidneys. Neither factor affected the uptake by RES. The homopolymer PHEA is hydrolyzed by several enzymes. Their spectrum can be extended by copolymerization of glutamic acid with other amino acids. Homopolymer of A and G are very weak in inducing antibodies. Methods for the attachment of functional groups have been developed.

4556  EFFECTIVITY OF FREE AND POLYMER BOUND 1,2-DIAMINO- CYCLOHEXANEPLATINUM(II)/II/ AND GLUCOSAMinoPHTA/LE AND ITS FOUR DIFFERENT POLYMER BOUND FORMS TO CILLUM AND MACROMOLECULAR COMPLEXES. K. Brustnikov, B. Kaldzor, J. Drobnik, V. Chahak, Cancer Research Institute, Bratislava, Czechoslovakia and Institute of Macromolecular Chemistry, Prague, Czechoslovakia.

1,2-diaminocyclohexaneplatinum(II)/II/ and its four different polymer bound forms were tested in in vitro L1210 cell line/suspension culture and soft agar assay as well as in vivo in F344 leukemic grown in L1210/i. mice. The I50 values of polymer bound TIA in in vitro assays were slightly higher when compared with free TIA. Higher I50 values for the retard forms of the bound TIA in suspension culture, when compared with soft agar assay, are due to the prolonged contact of the target Pt-complexes with the target cells. 6/6 days for the suspension culture and 12 days for the soft agar assay. The same i.e., higher efficiency for retard forms is proven in in vivo testing. Cross resistance of polymer bound complexes was tested in three cell lines with induced resistance against: a/ cis-diaminedichloroplatinum/II/ /CDP/; b/ 1,2-diaminocyclohexaneplatinun(II)/II/ chloride /PCC/; and c/ 1,2-diaminoenecyclohexanoplatinum/II/ /glucoratc /PTLV/. The pattern of cross resistance of the Pt-complexes did not fit from that of the unbound "A". Cross resistance was found between bound 3n/or unbound "A" and "G" and not with EPF.

4555  ANTITUMOR ACTIVITY OF A COMPLEX OF cis-DIANINO- KINEDICHLOROPLATINUM/II/ AND GLUCOSAMINOXAN - A COMPOUND SYNTHESIZED ACCORDING TO COMPUTER ASSISTED PREDICTION OF ANTITUMOR ACTIVITY IN STUDIES OF STRUCTURALLY DIFFERENT DRUGS. D.V. Popov, Oncological Res. Institute, Sofia, Bulgaria.

Early in 1981, according to a large pattern recognition studies program, a series of 12 compounds was generated. The first of them - a complex of cis-diammine dichloroplatinum/II/ and glucosaminoxan (cis-DDPGAD) - was synthesized and screened in comparison with related compounds. The antitumor effect of cis-DDPGAD was superior against both P-388 and Lewis lung carcinoma, and similar against L-1210 and MOPC-410 in comparison with cis-DDP/II/.

The dose regimen study, the combination with sarcolysin or sarcolysin-containing polymeric gel, and the effect on hemopoiesis are discussed.


The purpose of the study was to elucidate the influence of cis-dichlorodiamineplatinum (cisplatin) on the activity of microsomal oxidation enzymes in the animal liver and kidneys by employing biochemical and biophysical methods (EPR technique under the conditions of low-temperature stabilization at 77 K).

Single cisplatin administration to animals in a dose of 8 mg/kg results in fluctuations in dimethylase and hydroxylase activity as well as in content of cytochrome-P-450. Animal survival was observed 24 and 72 hours following the drug administration, and maximum was reported 48 and 96 hours later.

The alterations in dimethylase and hydroxylase activity, cytochrome P-450 content induced by cisplatin against the background of pretreatment with phenobarbital seemed to have the same character, though in all the dates studied the enzymatic activity was considerably higher. The administration of phenobarbital concurrent with enhanced activity of microsomal oxidation enzymes, which was modified under the influence of cisplatin leads to reduced cisplatin toxic effect on hemopoiesis.

Treatment of tumor-bearing animals with cisplatin resulted in decreased activity of microsomal oxidation enzymes. The induction of this system by phenobarbital during the therapeutic course results in less pronounced cisplatin toxic effects, recorded by a number of integral indices. Furthermore, the nephrotoxicity was seen to decline while the antitumor activity was not decreased.
4558 REACTION OF Pt(II) ANTITUMOR DRUGS WITH SELECTED NUCLEOPHILES. D. Noskova, V. Sadek, H. Pivcov, Inst. of Macromolecular Chem., Czechoslovak Acad. of Sci., Prague, Czechoslovakia

Reaction mixture of cis- Pt(NH3)2Cl2, diammineethylmalonato-Pt(II) (Pt-ETmal), and cyclobutane-1, 1-dicarboxylatediammine-Pt(II) (Pt-CBDCA) with selected nucleophiles containing biologically important functional groups, i.e. carboxy, imidazole and amino were analyzed. The nucleophiles included: glycine, imidazole, 4(5)-methyl imidazole, 4(5)-hydroxymethyl imidazole, 4(5)-imidazoyl acetic acid, histamine and histidine. The reaction products were identified by electrophoresis and their structure determined by NMR spectroscopy.

All three Pt antitumor drugs underwent ligand exchange with the nucleophiles in the reaction mixture. The majority of the nucleophiles provided several reaction products. It was however possible to show that the reaction products of one particular nucleophile with all three Pt antitumor drugs were identical. These results indicate that the action of the malonato drugs need no enzymatic activation for their antitumor activity as claimed in the literature.

4559 ESTIMATION OF THE EXTENT OF DNA PLATINATION AFTER INTERACTION OF CIS-DDP WITH DNA AND CHROMATIN. Z. Walter, L. Kulamowicz, Institute of Biochemistry, Faculty of Chemistry, University of Lodz, Lodz, Poland.

The aim of this work was to compare the kinetics of platinum binding to DNA and DNA in the nucleoprotein complex. We also tried to explain the protein participation in the platination process. The incubation of cell nuclei, chromatin and DNA from calf thymus with chosen cis-diaminedichloroplatinum(II) /cis-DDP/ concentrations was carried out at different incubation times. The platinum content after incubation was determined by stannous chloride method. The extent of DNA platination /% was expressed in umol Pt/umol DNA and on that basis the kinetic curves of cis-DDP binding to particular preparations were designed and compared. It was observed that the presence of the protein during incubation with cis-DDP decreases DNA platination. It is probable that the protein is not the competitive target for this drug's attack but constitutes only a structural protection for DNA molecule. The efficiency of DNA released from the chromatin incubated with cis-DDP suggests that this drug induces the processes of condensation and aggregation of chromatin.


The oncostatic action of platinum compounds can be  studied in the context of the chemical structure-biological activity relationship. Accordingly, we investigated the effect of cis-dichlorodiammineplatinum(II) or cisplatinum) on DNA. The in vitro interaction of DNA with cisplatinum was followed by the method of circular dichroism (CD). The CD spectra obtained at molecular ratio cisplatinum/ DNA-P 10.0 and 20.0 revealed modifications on the Cotton effect, which mean destabilization in the secondary structure of DNA macromolecule.

The conformational modifications also entail functional ones. These aspects related with structure-activity, explaining the oncostatic action of importance in the case of cisplatinum.

The in vivo investigations were made on some groups of rats - Wistar strain, whereby the hepatic DNA (µg/µg tissue) was determined. At 10 mg/kg dose of cisplatinum, DNA biosynthesis showed a decrease at 24 hours (-0.14) than at 48 hours (-0.11). These modifications were also reflected in the biosynthesis of serum albumin. Thus, the latter showed a decrease in the experimental group, while within the electrophoretic fractions there are increases in globulins, especially the A- and F-fractions. The obtained data were statistically evaluated by a computerized method.


Cis-diaminedichloroplatinum /II/ /CDDP/ has proved to be a valuable drug in the treatment of different human tumours. The major dose limiting side effects of the drug are renal, bone marrow and intestinal damage. New analogues have been developed and tested for activity and toxicity in order to find a derivative with higher therapeutic index. In this study investigations were performed in rats to compare the biochemical background of the intestinal side effects of cis-diaminedichloroplatinum /II/ /CDDP/ and cis-diaminedichloro-trans-dihydroxy-bis-isopropylamine platinum /IV/ /CIP/ and cis-diaminedichloro-trans-dihydroxy platinum /IV/ /OXO/ -PLATINUM/ with that of CDDP. Animals were treated intravenously with single equitoxic doses of the drugs. The biochemical investigations were carried out on mucosa cells, isolated by a combined chemical-mechanical method, from the total length of the small intestine. Thymidine kinase, 5'Nase of pyrimidine salvage pathway was selected as a marker for the dividing crypt cells, for the dividing crypt cells, alkaline phosphatase /AP/, sucrase /SUC/ and maltase /MAL/ activities were measured to characterize the functional capacity of the mucosa. 48 hours after the treatment the activities of 5'Nase, SUC and MAL showed a dose dependent decrease, while the AP activity increased slightly. It is interesting that platinum compounds added in vitro did not influence the AP activity. The most pronounced enzyme inhibition was observed in the case of 7k.

Comparing the studied platinum analogues CIP proved to be one of the most toxic agent for the small intestine.
The pharmacokinetics of the total platinum after the administration of the macromolecular antitumor complex CDDP in rats. B. B. Reznik, M. L. Reznik, J. K. Kowalski, Faculty of Pharmacy, Krakow, Poland. 

When CDDP was incubated with human plasma, the concentration of the ultrafilterable Pt/cut off limit: 30000 Mw decreased rapidly because of the quick binding to plasma proteins. In the present experiment the chemical reactivity of the protein-bound CDDP was studied in reaction with N,N-diethyldithiocarbamic acid (DDTC) forming Pt/10%, and 20% was detected as bound to plasma proteins reversibly plus the free fraction flowing through the SEP-PAK. At 24 hours, the Pt concentration in the ultrafiltrate separated by ultrafiltration, an other one was in water solution/ at 37°C for four hours. The separation of platinum both in plasma and urine was carried out by means of AAS method after the mineralization of samples. A nearly linear decrease of the total platinum plasma levels has been found during the first 60 minutes after the administration, later the decrease seems to be exponential. Since 24 hours after the administration the total platinum plasma levels are less than 0.1 µg/ml. About 16% of the dose administered was found in the urine collected during the first day, the total amount excreted during 15 days is 72%. We suppose that in the early phase after the administration of platinum the unchanged compound passes from blood to tissues by the zero order process. In the next phases of the experiment the concentration-dependent mechanism prevails.

Cisplatin (CDDP) is a highly chemically reactive drug complex, differs from most other drugs because of its ability to bind a great number of biological molecules by an irreversible and slow mechanism. Consequently, in plasma, the fraction of this drug bound to proteins no longer represents a form of drug storage and transport. This report deals with in vitro kinetic studies of CDDP binding to human serum albumin (HSA) and to plasma from both healthy subjects and patients suffering from various diseases. On all cases, the kinetic data fitted a second order reaction process. With HSA solutions, the influence of CDDP concentrations, of chloride ions added and of the nature of buffers used for preparation of CDDP solutions was made obvious in experiments. Our aim was also to study a possible quantitative modification of the reversible binding of other drugs to HSA when CDDP is present. Two kinds of HSA binding sites are classically described, corresponding to Trytophan (TRP) and warfarine sites. No change of TRP binding to HSA-platinum complex was evident when compared with its binding to protein alone. On the other hand, warfarine was shown to bind slightly less when HSA was complexed by CDDP. Nevertheless, in both cases, in vivo conditions CDDP would not be expected to modify HSA binding ability.

In vitro CDDP binding to plasma from healthy subjects or from patients was somewhat different with regard to time.

CDDP uptake with atomic absorption spectoscopy gave similar results in both cell types. The total amounts of DNA cross-links (ISCL) induced by CDDP were measured with alkaline elution of DNA. In both cell types low total levels of CL as well as ISCL were found immediately after drug exposure, followed by a protracted increase in CL for 6 - 12 hours during further incubation after removal of CDDP. The relationship between the concentration of CDDP and peak levels of total CL as well as ISCL was linear in both cell types. CDDP was found to induce 5.6 times higher total CL and 6.2 times higher ISCL in PHA-stimulated lymphocytes compared to RPMI 8322 cells. However, while the maximum amounts of CL and ISCL were higher in the sensitive cell type, the difference was too small to by itself explain the difference in cell survival. The importance of other factors, such as the rate of removal of CL, for CDDP cytotoxicity will be discussed.
**H-53: NEW DRUGS: PLATINUM COMPOUNDS**

**4568** THE INFLUENCE OF A CAFFEEINE ANALOGUE SUBSTANCE UPON THE ACTIVITY OF CISPLATINATE ON ANIMAL TUMORS.

Kroger, H., R. Gratz, A. Dietrich, Robert Koch-Institut, Nordufer 20, D-1000 Berlin 65
J. Klosa, Jänickestraße 13, D-1000 Berlin 37

The antitumoral effect of cisplatinum (I) is well known. In our approach we tried to potentiate the effect of I by the addition of the caffeine analogue cofpropamin. Especially the combination of I part cisplatinum and 10 parts cofpropamin (Substance: Cicloplatin ox + I) was investigated. It has a much lower acute toxicity than I.

Application of 111 over a period of 10 days leads only to a slight disturbance of liver enzymes. There is a considerable inhibitory effect of 11 on the development of sarcom 200 and Ehrlich ascites carcinos (both in ascites and in solid form). The effect of cofpropamin could be due to an interference with the repair metabolism.

**4566** MICROSCALE SYNTHESIS OF N-13-LABELED CISPLATIN.

E.De Spieghel, G.Slexer and P.De Moorloos
State University of Gent, Ghent, Belgium

Since the discovery of the biological activities of platinum complexes, there has been a considerable effort to understand the mechanism of action. However, not much is known about the fate of the amine-ligand. Therefore, a microscale synthesis of 13N-cisplatin from cyclotron produced 13N-ammonia is presented. Evaluation of the synthesis was performed by analysis of the endproduct with HPTLC and HPLC. Temperature, reactiontime, ratios and concentration of reactants have been optimized for each step of the synthesis. A rapid purification was obtained with ion-exchange chromatography. The whole procedure takes about 15 min. and 42 mCi 13N-cisplatin in 10 ml of physiological solution is obtained. This corresponds with a specific activity of about 300 mCi / umole at E.O.B. A preliminary in vivo experiment with a dog demonstrates the usefulness of this radiopharman.

**4567** EFFECT OF SUPERHIGH-DOSE OF CDDP ON ASCITES TUMOR IN MICE AND ITS MODIFICATION BY SODIUM THIOSULFATE.

K. Konatsu*, and W. Kakamure**, Aizu Central Hospital*, and Nippon Culture and Well-Being Found., M.I. of Adult Diseases**, Japan

Recent studies suggest that the i.p. route of administration of cis-DP (CDDP) may enhance the therapeutic index in treating disease limited to the peritoneal cavity. In general, daily dose of CDDP used in clinic is around 2-4 mg/kg. In the present study, relation between the dose of CDDP which was given i.p. in one shot or in two fractions and its cure effect on ascites tumor bearing mice was studied. Modification of the effect by a continual i.p. infusion with sodium thiosulphate (STS) was also investigated.

Animal used was male mice of LAP, hybrid of 12-15 week old. Tumor cell was of the mastocyte FMA3 which was maintained as an ascites type by serial transplantation into the abdominal cavity of LAP. Tumor cell was transplanted i.p. at 10^7 per mouse and CDDP was injected i.p. in a single shot at a dose from 2 to 20 mg/kg next day of the transplantation. The highest cure rate of 42% was obtained with 12 mg/kg CDDP. The cure rate was increased to 83% by an additional injection of 8mg/kg 10 days after the 1st 8 mg/kg of CDDP. In the hope to ameliorate the side effects induced by the over-dose-administration of CDDP various doses of STS were infused i.v. for 2 hours immediately after the injection of CDDP. Early death which occurred within 10 days was suppressed but cure rate decreased significantly.
4570 PROPERTIES AND ANTIANGIOGENIC ACTIVITY OF LIPOSOMES FROM SYNTHETIC ALKYLPHOSPHOLIPIDS by M. Arndt, L. Fichtner, R. Kiesen, H. Brachvitz, Acad. of Sciences of GDR, Central Institute of Cancer Research and Central Institute of Molecular Biology, Berlin-Dahlem, GDR

The bilayer structure of liposomes is normally disturbed by lysocleicin. Otherwise alkylphospholipids show antitumor activity as a result of macromage induction or by changes in membrane phospholipid metabolism. We found, that incorporation of cholesterol to alkylphospholipids leads to formation of liposomes with high encapsulation efficiency and small permeability for entrapped substances (carboxylfluorescein, antitumor drugs). Empty liposomes made from alkylphospholipids and cholesterol (1:1 molar ratio) show activity against rat mammary carcinoma cells (48-50E) in vitro as well as against Lewis lung carcinoma in mice.

4571 SELECTIVE CYTOTOXICITY TO TUMOUR CELL LINES BY PHOSPHATIDYLINOSITOL AND PHOSPHATIDYLSERINE LIPOSOMES by K. Hirasawa and Y. Sato, Dept. of Biochemistry, Meiji Inst. of Health Science, Naruda, Odawara, Japan

It has been intensively studied that phosphatidylinositol (PI) turnover in many stimulated cells. The extracellular agonists enhance the hydrolysis of PI by phospholipase D in plasma membrane. In recent years, the produced second messengers in PI turnover have been proposed for the functioning of intracellular events such as diacylglycerol for the activation of Ca2+ and phospholipids, especially phosphatidylserine (PS) - dependent protein kinase, and inositol 1,4,5-triphosphate for Ca2+ - releasing factor from the internal calcium store. Therefore, PI and PS play the important role in the early cell response. Jett & Alving have shown that a liposome of PI from soybean induced the selective cytotoxicity towards the variety of tumour cell lines. Neither PI from animal nor the other phospholipids such as phosphatidylcholine, PS phosphatidylglycerol and phosphatic acid showed the cytotoxic effect. They have reported that the specificity of plant PI might be due to the lack of arachidonyl residue in the molecule, resulting in deficiency of arachidonate metabolites.

However, in our experiments, the selective cytotoxicity has been shown by PI from animal as well as plant. PI and PS from bovine brain could also kill the tumour cell lines (L-1210, Raji & Molt-4). On the other hand, these phospholipids did not kill normal human peripheral lymphocytes. It has not been explained the contrarity between Jett & Alving and us yet. However, it seems that the effect is not due to arachidonate metabolite defects, it may relate rather the role of PI and PS in transmembrane signaling.

4572 EVALUATION OF ADRIMICIN-LIPOSOMAL (AM-LIP) THERAPY IN A NOVEL MURINE MODEL OF HEPATIC METASTASES FROM COLORECTAL CANCER. Martin H. Goldreren, Eric Mayhew and Youcef Rustum, Roswell Park Memorial Institute, Buffalo, N.Y. U.S.A.

The primary objective of this study was to evaluate the therapeutic effect of AM-LIP in a murine model of hepatic metastases. CT-38 (107) cells were injected via the ileocolic vein into C57Bl/6 Rms mice following exteriorization of the cecum. Ninety-eight percent of injected mice developed hepatic foci. Laparotomy at 21 days revealed the presence of a mean of 18 hepatic foci (range 0-74). Mice bearing CT-38 hepatic foci survived 53.3 days (range 36-90). A linear and inversely proportional relationship between the number of hepatic foci (5-40 nodules) at laparotomy and survival was observed. The therapeutic effect of free adriamycin (AM) and AM-LIP commenced at days 21-22, at 10mg/kg i.v. and repeated at weekly intervals until the death of the mice was evaluated. The following results were obtained (average ± SE experiments). The median survival of control mice was 44.5 days. The median survival of treated mice was AM 61.5 days (T/C=1.38) and AM-LIP 74 days (T/C=1.66). The % increase in the median survival time with AM was 40.5% with AM-LIP was 88.0% (p<0.05). The following conclusions can be drawn. This model will be useful in the development of novel therapeutic approaches for drug delivery of hepatic metastases. AM-LIP is more effective than AM in the treatment of liver metastases. Supported in part by NIH Grant CA 28694 (EM).

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The liposomes (lipid vesicles) are known as nontoxic biodegradable and versatile carriers for drug delivery in the target cells that are able to modify sharply the pharmacokinetics, pharmacodynamics and toxicity of the entrapped drugs. The widest used antitumour drug in the treatment of cancer- Cyclophosphamide has been entrapped in liposomes in the course of systemic experimental studies on the "modification" of biological activity of antitumour agents. The direct cytotoxic activity of the "free" and the liposomal Cyclophosphamide has been studied in "in vitro in vivo" experiments ("bioassay" of the survived tumour cell fractions) on the leukaemia P588 tumour cells. An enhancement of the direct cytotoxic activity of Cyclophosphamide (very high concentrations without a preliminary liver microsomal activation) in the treatment of hepatic metastases was obtained (average of 6 experiments). The privacy objective of this study was to evaluate the therapeutic effect of AM-LIP in a murine model of hepatic metastases. CT-38 (107) cells were injected via the ileocolic vein into C57Bl/6 Rms mice following exteriorization of the cecum. Ninety-eight percent of injected mice developed hepatic foci. Laparotomy at 21 days revealed the presence of a mean of 18 hepatic foci (range 0-74). Mice bearing CT-38 hepatic foci survived 53.3 days (range 36-90). A linear and inversely proportional relationship between the number of hepatic foci (5-40 nodules) at laparotomy and survival was observed. The therapeutic effect of free adriamycin (AM) and AM-LIP commenced at days 21-22, at 10mg/kg i.v. and repeated at weekly intervals until the death of the mice was evaluated. The following results were obtained (average ± SE experiments). The median survival of control mice was 44.5 days. The median survival of treated mice was AM 61.5 days (T/C=1.38) and AM-LIP 74 days (T/C=1.66). The % increase in the median survival time with AM was 40.5% with AM-LIP was 88.0% (p<0.05). The following conclusions can be drawn. This model will be useful in the development of novel therapeutic approaches for drug delivery of hepatic metastases. AM-LIP is more effective than AM in the treatment of liver metastases. Supported in part by NIH Grant CA 28694 (EM).
METHYLGLYOXAL -BIS-GUANYLHYDRAZONE (METHYL-GAG) IN LIPOSOMES - ANTIORTUMOR ACTIVITY AND TOXICITY IN MURINE TUMOR MODELS

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Methyl-GAG is an active cytostatic drug in human am and lymphomes. The extensive use is limited by high toxicity, especially on GI-tract and blood glucose levels. We tested, if the encapsulation of this drug in liposomes had an influence on its activity. Treatment with Methyl-GAG in a cd 1:4 schedule resulted in the murine leukaemies P 308 and L 1210 (L. v.) in nearly the same increase of lifespan as the corresponding dose in liposomes. In a cd 1:3 schedule Methyl-GAG - containing liposomes revealed comparable effects as the 4-day treatment with the free drug. There was no significant difference of T/C values between different liposome preparations (reverse phase evaporation vesicles, small unilamellar vesicles, mixed from egg phosphatidylcholine, sphingomyeline and choleristerol).

LIPOSONAL ENCAPSEULATION did not change the effect of Methyl-GAG in the treatment of a primary tumour or the metastases of the Lewis lung carcinoma (footpad inoculation plus surgery). The hypoglycemic effect of CDDP-Liposome encapsulation, qd 1:4, could be observed when the drug was administered in NPC. There was no influence on AAL-activity in serum, body weight difference and leukocyte counts. Liposomes caused thymopectasia, which was more pronounced with Methyl-GAG than with CDDP.

We conclude, that the liposomal encapsulation of Methyl-GAG leads to a depot effect with a slight relieve of toxicity.

GROWTH INHIBITION OF HUMAN KB EPITHELIAL CELL BY CISPLATIN-ENTRAPPED LIPOSOME


The therapeutic usefulness of Cisplatin(PED) as an anti-cancer agent has been well documented, but serious nephrotoxicity remains as a major clinical side effect. Cisplatin-entrapped liposome(PED-Lip) was employed to arrest growth of cultured human neuroblastoma cells, and further to reduce the side effect of PED for its clinical use.

PED-Lip was prepared by according to modified Fornace's method (Cancer Res. 41, 546-550, 1981), i.e., phosphatidyl-lecholine(PC): phosphatidylserine(PS): cholesterol(1:2:1) on molar ratio. After sonication, the PED-Lip was separated from free drug by gelfiltration(Sephadex G-50). PED-Lip dose-dependently inhibited the cell growth of IMR-32 in a similar fashion to free PED. Dose of free PED to show 50% inhibition (ID50) of DNA synthesis of IMR-32 was more than 3 times greater than that of PED-Lip. Time course of DNA synthesis inhibition by PED-Lip in IMR-32 was almost same as that by free PED; over 80% of DNA synthesis was inhibited by 5 min-interaction of either free or entrapped PED in liposome with cultured cells, indicating no time difference on the transmembraneaction mechanism among two kinds of PED.
**4578** INTERACTION OF DEGRADABLE STARCH MICROSPHERES (DMS) WITH LIVER, KIDNEY, LUNG AND RATS VISUALIZED WITH FITC-DMS AND IRON-DMS


Starch microspheres manufactured by emulsion polymerization of hydrolysed potato starch is degradable by endogenous amylase. It has been claimed that such degradable microspheres are versatile, clinical aids to modify drug distribution, to incite inflammation, to cause topographic hyperthermia and so on. However, their profile was not so easy to visualize in situ as it might be expected. Spheres (Pharmacia, Sweden) is a type of DMS of approximately 45 µm in diameter. To visualize its location in the lumen of blood vessels, FITC-labeled DMS were administered intravenously to experimental animals. FITC-spheres were localized in the lumen of blood vessels of many organs. Deformed spherex was located in the lumen of blood vessels, irregularly deformed spheres were localized in the lumen of small blood vessels to cause microembolization in target organs.


The antitumor efficacy of the ara-C conjugates of three types of phospholipids was compared on survival of i.p. and s.c. inoculated L1210 lymphoid leukemia mice. The ara-C conjugates include 1) diacyl anlog, ara-CUDP-l-isoantidipalmitoyl (I), 2) the 1-0-alkyl (either homologous or non-homologous) ara-C-DP-rac-l-S-cytadecyl-2-0-palmitoylglycerol (II), ara-C-DP-rac-l-S-cyadecyl-2-0-palmitoylglycerol (III), ara-C-DP-rac-l-S-cyadecyl-2-0-palmitoylglycerol (III), ara-C-DP-rac-l-0-hexadecyl-2-0-palmitoylglycerol (IV), and ara-C-DP-rac-l-0-hexadecyl-2-0-palmitoylglycerol (V), and 3) thioester I (lipid I) analogs, ara-C-DP-rac-l-S-hexadecyl-2-0-palmitoyvl-1-thioglycerol (V), ara-C-DP-rac-l-S-cyadecyl-1-thioglycerol (VI) and ara-C-DP-rac-l-S-cyadecyl-2-0-palmitoyvl-1-thioglycerol (VII). DBA/2J mice in groups of six were inoculated i.p. with 10⁷ L1210 cells (i.c. with 10⁵) and untreated solution of the ara-C conjugates in 0.9% NaCl was given i.p. Administration of the optimal single dose (300-500 mg/kg) of I, II, III, IV, and VII to 5 mice at 400-500 mg/kg gave ILS values of 275, 264, 229, 379, and 371%, respectively, while those of II, II, and VII at total doses of 400-500 mg/kg gave ILS values of 275, 264, 229, 379, and 371%, respectively, while those of III, II, and VII at total doses of 400-500 mg/kg gave ILS values of 275, 264, 229, 379, and 371%, respectively. All ara-C conjugates were slightly effective on survival of L1210 leukemia. However, the improvements of ILS values were better in the treatment schedules, and 3) the 1-0-alkyl and the 1-S-alkyl analogs could be more promising because of their possible release of 1-O-(or 3)-alkyl-2-lymphophosphatidyl-choline or ethamionine, which possess antitumor and immunopotentiating activity. (Supported in part by NSFOG CA 115211)

**4478** THE EFFECT OF POLYMER-BOUND DOXORUBICIN ON HUMAN CANCER CELLS IN VITRO AND IN VIVO. LIVER, KIDNEY AND LUNG OF RATS VISUALIZED WITH FITC-DSH AND IRON-DSH

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In order to modify its acute tissue toxicity, volume of distribution and size of action, doxorubicin (DOX) was covalently linked to dextran (mean MW 70,000 or 40,000). The effect of the DOX-dextran conjugate was studied in vitro, on suspensions of human tumor cells (transient cell carcinoma, ovarian adenocarcinoma and squamous cell carcinoma) prepared from tumor xenografts on nude mouse. The cell suspensions were incubated for three hours with conjugate or with free DOX. Trislated thymidine (3HdT) was then added, and after one hour incubation the inhibition of incorporation of 3HdT was determined and compared to that of untreated controls. We found, independent of tumor type, that DOX retained its biological activity on covalent coupling to dextran, an intermediary product of the coupling was a particular aggregate of DOX-dextran. This aggregate had an approximated to free DOX-dextran or free DOX were given i.v. on day two in doses corresponding to 20 ng DOX per kg body weight. DOX-dextran gave an increase in life span (ILS) of 281, while free DOX gave an ILS of 104.

Conjugate and tissue toxicity was determined by intraperitoneal instillation in rabbits. Autopsy was made after one week. In no case could any tissue damage be observed, and there was no pleural effusion. These observations contrasted strongly to those on instillation of DOX in equivalent doses, where massive tissue damage and pleural effusion were noted.

In conclusion: Doxorubicin coupled covalently to dextran has cytotatic activity in vitro and in vivo. The acute and subacute tissue toxicity which characterizes doxorubicin has been overcome. The results merit further experimental and also clinical investigation.

**4481** TARGETING CHEMOTHERAPY WITH PURIFIED ANTIBODY TO ALPHA-FETOPROTEIN (AFP)


To aim at the specific accumulation of anti-cancer drugs to target tumor cells, purified polyclonal or monoclonal antibodies to alpha-fetoprotein (AFP) have been used as one of the models for drug delivery system. Anti-cancer drugs such as antitumor antibiotics and 5-fluorouracil (5-FU) were conjugated with the purified anti-AFP antibody through dextran bridge to form antibody-drug conjugate similarily prepared with normal horse immunoglobulin. These experimental studies were carried out mostly with the AFP-producing rat hepatoma, AH66 as well as AFP-producing human hepatoma and yolk sac tumor. The conjugates of adriamycin with purified polyclonal antibodies to human AFP via dextran bridge were administered in 16 patients with hepatoma. Although it was very difficult to assess the clinical improvement by the conjugate therapy, the suppression of serum AFP level was maintained for a long period of time over 10 weeks in 7 out of 16 patients (43.8%). These facts suggest that the conjugated drugs showed better therapeutic effect than the unmodified antibiotics to AFP is one of the useful tools for targeting chemotherapy of cancer. (Supported by the Grant-in-Aid for Cancer Research from the Ministry of Education, Science and Culture, Japan)

We have previously reported a synthesis of poly(ethylene glycol) and macromolecular drugs. The mechanism of tumor accumulation of biomacromolecular drugs is studied using an in vivo tumor model system. The results revealed that the accumulation of biomacromolecular drugs is due to the interaction between the molecules and the tumor cells. The mechanisms of tumor accumulation of biomacromolecular drugs are discussed.


K-18 is a conjugate of human immunoglobulin, IgG and anti-cancer drug, Melphalan (Bis(2-chloroethyl)amine). This drug was synthesized using a new synthetic method. The anti-cancer activity of K-18 was evaluated in vitro and in vivo. The results showed that K-18 had a significant anti-cancer effect against human stomach cancer cell lines.

4585 CHLORAMBUCIL TARGETING TO TUMOR CELLS WITH ANTI-CEA AND ANTI-AFP ANTIBODIES. M. Page, J. Samuels, F. G. Rapinier, L. Deturck, Dept. of Biochemistry, Fac. Medicine, Université Laval, Québec, Canada, G1K 7P4.

The use of chlorambucil (CBL) in the chemotherapeutic treatment of neoplasia is often limited by its undesirable side effects due to its lack of specificity towards cancer cells. Various methods have been described for the covalent coupling of drugs to carriers specific for cancer cells. Unfortunately, the use of divalent coupling agents such as carbodiimide or glutaraldehyde may cause polymerization of the carrier thus decreasing the efficiency of the immunological reaction. Chlorambucil is usually coupled by mixing the drug with the protein carrier. This gives either conjugates with non-covalently linked chlorambucil or stable conjugates using the alkylation moiety of the molecule thus leading to some loss of pharmacological activity. We have developed a new method for the rapid coupling of chlorambucil to antibodies using the isocyante derivative of this drug; this reaction causes no polymerization. Two cancer markers were used as targets, carcinoembryonic antigen (CEA) and alphafetoprotein (AFP). The specificity of the conjugates was tested using both antiCEA and antiAFP specific immunoglobulins on four different cell lines. The chlorambucil-antibody conjugates specific for the cancer cell lines were 3 to 30 times more active than the non-specific conjugates or the free drug. The contact period study showed that the avidity of the conjugates was much higher than the target cells than for the control cells. The proposed method results in the spontaneous coupling of chlorambucil to proteins by means of the monovalent isocyanate moiety does not cause polymerization. The data show that this coupling procedure yields stable conjugates which retain both their immunological and pharmacological activities.


A new synthetic anticancer agent K-18 is a conjugate of human IgG with melphalan which had been reported to accumulate in tumor tissue, showing the selective accumulation and retention and resulted in more excellent anti-tumor effect than melphalan only. An attempt was made to study on the distribution of K-18 in human mice with gastrointestinal cancer. Radioactivity in main organs and tumor tissue was measured after oral administration of 11C-melphalan in nude and in mice with human gastric cancer (MK-2). In the same host-tumor system, tumor tissues were dissected at 1, 4, and 24 hour after oral administration of K-18, fixed with periodate-lysine-paraffinoldehyde solution and embedded in parafin to make sections for histochemistry. The sections were stained with human IgG Vectastain ABC kits. Stained sections of bone marrow were also used for histological comparison with those of tumor tissues. Radioactivity in tumor tissues of the mice treated with 11C-K-18 increased during the experiment, while that of the mice treated with 11C-melphalan decreased. With respect to the distribution of radioactivity in normal tissues like liver, kidney and spleen, there was no significant difference between the group of K-18 and that of melphalan. Immunohistochemical study using anti-human immunoglobulin showed that K-18 diffused from the capillary to the stratum in tumor tissue, arrived at the surface and migrated into the cytoplasm of tumor cell. The distribution of K-18 in bone marrow was restricted to the capillary visual and no bone marrow cells were stained. It was found that K-18 accumulated specifically in the tumor tissue compartment with melphalan only and was not taken up by tumor cell, while in bone marrow no phenomenon as the above was observed. These results suggested that K-18 is an effective anticancer agent with fewer side effects.

K-18 is a conjugate of human IgG and antitumor agent, p[di-2-chloroethyl]-aminol-phenylalanine (Melphalan) based on the finding that injected IgG accumulated in malignant tumors transplanted to mice. We reported evaluations on the efficacy of K-18 for tumor implanted into the nude mouse and the effects of K18 on cell cycle. The mechanism of this accumulation of IgG and the pharmacokinetics of K18 in tumor are of interest. We evaluated the antitumor activity of the homogenate using colony forming assay with KB cells. Tumors were removed 4, 24, and 48 hours after K18 and melphalan were given for human stomach cancer, NS-10. It was homogenized in 0.4M KCl to obtain tumor homogenate. This homogenate was added to the plate inoculated with 100 cells/50-μl dish of KB cells at a ratio of 0.1 ml of homogenate to 0.1 of medium at the 6th hour of cultivation, and incubated at 5% CO2 at 37°C. The number of growing colonies was counted. The number of colonies decreased at 24 hours in the melphalan group, but at 48 hours colonies decreased at 24 hours in the melphalan group. The number of colonies was slightly reduced with K18 at 24 hours, while at 48 hours it was obviously decreased. These results correlated well with those of cell cycle analysis of colony. The results suggested that K18 has therapeutic effects after it accumulates in the tumor. In addition, K18 was clinically effective. Specially, metastasis therapy of recurrent malignant lymphoma, administered over past two years showed its safety for a long term and K18 could be considered to be a new promising agent.
4590 DIFFERENTIAL SENSITIVITY OF HUMAN PROSTATE CANCER CELL LINES TO POLYAMINE DEPLETION IN VITRO. JC Romijn, CF Verkuijlen, TAN Splinter and FH Schroeder; Erasmus Univ. Dept Urology and Oncology, Rotterdam, The Netherlands.

K 18, the conjugate drug of human IgG and melphalan, is a newly developed antitumor agent. It was developed to aim at the effective transport of antitumor drug and its accumulation on the site of tumor, which resulted in the excellent effect on tumor and the reduction of side effects. Clinically K 18 has been orally applied in Japan and known to have minimum side effects. Studies using experimental tumors have been reported from many institutes and they have proved the effectiveness of K 18 on various tumors. In this paper, we studied K 18 for its antitumor effect on urogenital cancers. We adopted two systems, where the mouse transplantable tumor, MH-134, was inoculated in mouse bladder intracutaneously and the human prostate carcinoma, PC 3, was transplanted into nude mice. K 18 or melphalan was administered these animals. In both cases, we observed the significant inhibition of tumor growth by K 18. Although melphalan was equally effective, it possessed the severe side effects and all the animal died. While none of animals died by K 18 treatment. These results suggest its antitumor effect on urogenital cancers and confirm its low toxicity.

4591 DIFFERENTIAL SENSITIVITY OF HUMAN PROSTATE CANCER CELL LINES TO POLYAMINE DEPLETION IN VITRO. J.C. Romijn, C.F. Verkuijlen, T.A.N. Splinter, F.H. Schroeder; Erasmus Univ. Dept. Urology and Oncology, Rotterdam, The Netherlands.

The important role of polyamines in the regulation of several cellular functions is well established. Inhibitors of polyamine biosynthesis, such as α-difluoromethylornithine (DFMO), were shown to inhibit growth of various experimental tumor cell lines in vivo and in vitro. We have evaluated the effect of DFMO on DNA-synthesis and cell proliferation of the human prostate cancer cell lines PC-3, PC-3M (a subline of the original PC-3 line) and PC-3S. Where the PC-3, PC-3M and PC-3S cell lines were treated with DFMO doz-dependently (50-90 percent inhibition by 1.0 mM DFMO after 3-5 days), PC-3 cells appeared to be insensitive to short-term DFMO-treatment. With PC-3 inhibition occurred only after 6 weeks of continuous treatment with 1 mM DFMO. The two closely related sublines PC-3 and PC-3M accumulated DFMO to the same concentration. Also the level of ornithine decarboxylase was similar in both cell lines and inhibited to the same extent by DFMO-treatment. Furthermore the profile of intracellular polyamines was similar, although spermidine (Spd) and spermine (Spm) were slightly higher in PC-3M cells. Treatment with 0.1 mM DFMO for 5 days resulted in a decrease of putrescine levels by 90 percent and of spd by 60 percent (for PC-3 and PC-3M respectively), but an increase of Spm with 45 percent. In the presence of 1.0 mM DFMO spd was reduced also by 90 percent in both cell lines; at this concentration the polyamine levels were almost identical in the two cell lines. The depletion of polyamines (although insufficient to inhibit cell proliferation in the case of PC-3) caused a substantial stimulation of MGBG-uptake. PC-3 and PC-3M were equally sensitive to treatment with MGBG in combination with DFMO. These results show that the polyamine requirement might be very different, even for closely related cell lines, when cell proliferation is considered. The modulating effect of DFMO on other properties of the cell, however, might be maintained, also if cell growth is unaffected. The PC-3 cell line seems to be a useful tool to study the mechanisms of polyamine-depletion-induced alterations of cellular properties.


The total free polyamines (TFP) contents in the erythrocytes from normal healthy subjects (n=22), pregnant women (n=11) in NL. VII) and patients with advanced lung (n=22) and breast (n=19) cancer in stage III-IV, before and after chemotherapy were determined. TFP were assessed by an enzymatic method of the authors. In normal healthy subject TFP were 7.69±0.42 nmol/10^7 ER, in pregnant women = 20.68±1.3 nmol/10^7 ER (statistically significant increase, due to the pregnancy). The mean values of TFP in ER in lung cancer were 16.87±2.47 nmol/10^7 ER, in breast cancer = 11,1±2.65 nmol/10^7 ER (statistically significant to the healthy subjects). After polychemotherapy with Cyclophosphamide, Methotrexate, 5-FU, Vinblastine, Adriamycin the TFP values in lung cancer (n=7) and in breast cancer (n=6) patients were near to the controls and lower, compared to the pretreatment values. Our results confirmed the significance of TFP in ER as biochemical marker for diagnosis and monitoring cancer chemotherapy.

A wide variety of hormones and growth factors have been shown to stimulate polyamine increase. ODC, the rate limiting step in polyamines biosynthesis, increases dramatically in normal and tumoral proliferating tissues. Stilbestrol hormone receptor have been reported as a more potent stimulus in breast cancer. On the other hand, high prolactin blood levels have been associated with worse prognoses. We correlated OIC in breast cancer cytosol (pmol CO2/mg protein per hr, mean±SEM) with a) prolactinemia (PRL, ng/ml, mean±SEM); b) estradiol (E2) and progesterone (P) cytosol receptors concentration and c) histopathological pattern. A total of 107 pts. were studied for ER, PR and OIC; 98 breast tumors in different evolution stages -6 of which were pre-treated 72 hrs before biopsy with 1.25 mg bromocriptine (BC); 6 benign mammography diagnosis - (BMD) and 3 normal breasts (NB). PRL was measured in 59 cancer pts. Hyper-PRL was found in 14 of them; this group presented OIC significantly higher than in normal-PRL pts.: (20.1±8.3) x 10(-3) vs (5.2±0.6) x 10(-3), P< 0.002. PRL in postmenopausal pts. with non-detectable OIC (n=10) was significantly lower than those corresponding to pts. with measurable OIC (n=29): (7.2±1.1) vs (11.4±2.2), P< 0.05. The tumors with non-detectable OIC were histologically more differentiated (non-specific invasive carcinoma with tubular areas, tubular carcinoma and ductal carcinoma with rare invasive areas) and with lower cellularity. We did not find any correlation between ER and PR and OIC (n=107). It is important to point out that we found in 1/6 pts. high PRL and low OIC in non detectable (2 of the former showed hyper-PRL).OIC was 11.95 in only one case of an intracranial fibroadenoma with high cellularity. Although we have only 6 pts. pre treated with BEG, OIC in their tumors was lower than in those without any pre-treatment: (6.0±2.3) x 10(-3) vs (9.2±1.3) x 10(-3). We focused on clinical follow-up of those pts. with different OIC levels.
The effects of α-difluoromethylornithine (DFMO), a specific irreversible inhibitor of ornithine decarboxylase, on the growth of experimental mouse B16 melanoma cells were investigated. DFMO (3%) in drinking water was administered to B16 melanoma-bearing mice. At 25 days, B16 melanoma in DFMO-fed mice weighed 80% less than those in control mice. DFMO reduced spermidine and putrescine markedly in B16 melanoma.

DFMO treatment prolonged the mean survival time from 26 to 36 days. Furthermore, the effects of DFMO on experimental metastasis were investigated. The median number of lung metastasis in DFMO-fed mice was 22 (range 5-85) and in controls 174 (range 13-200). The results of the present study indicate that polyamines play an important role in growth and metastasis of B16 melanoma.

Blood-brain barrier (BBB) passage of neuropeptides (II) and in vivo binding of N to blood plasma proteins were studied in norm and in experimental tumoral process. BBB passage of somatostatin (SST) is decreased 1.6-fold in animals with tumours (with permeability index 2.1 ± 0.47 and 1.2 ± 0.11 in norm and in tumoral process, respectively). The level of protein-bound SST is elevated by 60% in blood plasma from tumour bearers, and the content of SST free form is 1.4-fold decreased. BBB permeability to leu-enkephalin (LE) is increased 3.3-fold in tumour bearers (2.7 ± 0.15% and 6.1 ± 0.68% in norm and in tumoral process, respectively). The level of protein-bound LE is lowered by 77% in blood plasma from animals with tumours, and the content of LE free form is 1.5-fold increased. The LE/SPH ratio in tumour bearers is 0.5-fold lower for protein-bound N, 1.5-fold higher for plasma free form of N, 3.5-fold higher for N cross-reacting the BBB. Polyamines and/or tumour-associated peptides isolated from blood plasma of tumour bearers enhance the binding of SST to blood plasma proteins and decrease the binding of LE. BBB passage of met-enkephalin (ME) and β-endorphin (BE) in tumour bearers is not changed (1.0 ± 0.13 and 1.5 ± 0.14% for ME and 0.9 ± 0.12 and 0.6 ± 0.02% for BE in norm and in tumoral process, respectively). Epidermal growth factor was not found to cross the BBB in the control and experimental animals. BBB permeability to N depends on their binding to blood plasma proteins and is strongly correlated to the level of their free form. Altered permeability of N to N in malignant growth may be one of the important factors in the pathogenesis of tumoral disease.
COMPARISON OF GROWTH INHIBITION BY o-DIFLUOROMETHYLORNITHINE (DMO), AN INHIBITOR OF ORNITHINE DECARBOXYLASE AND BY N-β-ETHYLSPERMIDINE (BES), A REGULATOR OF ENZYME ACTIVITY. Jarl W. Porter, Barbara Ganis, and Raymond J. Bergeron, Roswell Park Memorial Institute, Buffalo, NY 14263, USA and University of Florida, Gainesville, FL 32610, USA.

The irreversible inhibitor of ornithine decarboxylase, DMO, has achieved benchmark status as a specific inhibitor of polyamine biosynthesis with potential as an anticancer and antiparasitic agent. In the present study, growth inhibition by DMO has been compared with that of BES, a potent inhibitor of polyamine biosynthesis which appears to act by regulating ornithine decarboxylase activity and protein in a manner comparable to exogenous polyamines. In cultured L1210 cells, the IC_{50} (48 hr) for BES was 30 μM as compared with 1.4 μM for DMO. Kinetics of growth inhibition for 30 μM BES 100 μM BES and 1 mM DMO were all very similar and correlated closely with spermidine depletion. The kinetics for macromolecular precursor incorporation were also similarly affected by both drugs with leucine and thymidine decreasing to 50% by 48 hr and uridine remaining unaffected for up to 96 hr. In other ways, BES differed from DMO (a) by depleting all intracellular polyamines including spermine (b) by not increasing s-adenosylmethionine decarboxylase activity and hence decarboxylated s-adenosylmethionine pools and (c) by not increasing cellular uptake of spermidine. In light of these differences, comparison studies with DMO and BES could prove useful in delineating regulatory mechanisms associated with polyamine biosynthesis. Further studies with BES and other analogs provide an alternative approach to inhibition of polyamine biosynthesis as potential antiproliferative strategy.


We examined 236 patients with pretumourous diseases (chronic gastritis, ulcer disease, polyposis) and gastric cancer; the control group included 30 practically healthy persons. Diurnal urinary excretion of polyamines was in persons with pretumourous diseases 3.5 times higher than in the control group and in gastric cancer 2.5 times higher mainly due to putrescin; patients with grade III-IV disease showed an increased excretion of spermine, those with pretumourous diseasess in particular, with atrophic gastric mucosa changes exhibited a reduction of immunoreactivity indices. The data gained may be used in assessment of "high risk" groups, in the diagnosis of specific (atrophic) schemes of gastric cancer treatment.

RIZATION OF GROWTH INHIBITION BY o-DIFLUOROMETHYLORNITHINE (DMO), AN INHIBITOR OF ORNITHINE DECARBOXYLASE AND BY N-β-ETHYLSPERMIDINE (BES), A REGULATOR OF ENZYME ACTIVITY. Jarl W. Porter, Barbara Ganis, and Raymond J. Bergeron, Roswell Park Memorial Institute, Buffalo, NY 14263, USA and University of Florida, Gainesville, FL 32610, USA.

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We examined 236 patients with pretumourous diseases (chronic gastritis, ulcer disease, polyposis) and gastric cancer; the control group included 30 practically healthy persons. Diurnal urinary excretion of polyamines was in persons with pretumourous diseases 3.5 times higher than in the control group and in gastric cancer 2.5 times higher mainly due to putrescin; patients with grade III-IV disease showed an increased excretion of spermine, those with pretumourous diseases in particular, with atrophic gastric mucosa changes exhibited a reduction of immunoreactivity indices. The data gained may be used in assessment of "high risk" groups, in the diagnosis of specific (atrophic) schemes of gastric cancer treatment.

THE RISK OF BREAST CANCER AFTER ESTROGEN TREATMENT IN CLIMACTERIC WOMEN. RESULTS OF A COHORT STUDY. Bergkvist L*, Adami HO**. Vernon* ** (Departments of Surgery* and of Obstetrics and Gynecology**, University Hospital, Uppsala, Sweden.

The aim of the present study was to analyse the risk of breast- and endometrial - cancer after estrogen treatment through a prospective cohort design. Material and Method. The cohort, comprising 23,244 women of ages above 35 years, was formed through collection of prescription forms containing estrogens in the Uppsala Health Care Region from April 1977 through March 1980. A mailed questionnaire, which was sent to 1/30 sample of the cohort and to all breast cancer cases, provided detailed data on the complete exposure, intake compliance and on addition of progestogens. Observed cases in the cohort were identified through identity number linkages to the Regional Cancer Registry, including all incident cancer cases in the region. Expected numbers were calculated from age-specific incidence rates, and person-years of observation in the cohort. Risk estimates (RR) were calculated as the ratio of observed to expected numbers. Analyses were made in the cohort as a whole and in subgroups, according to duration of exposure, drug brand and presence of progestogens. The closing date for the present follow up was Dec 1983. Results. No overall increase in the risk of breast cancer was found among women exposed to estrogens. Nor was there an increased risk associated with longer ( 3 years) or shorter ( < 3 years) exposure duration. Among women taking conjugated estrogens 3 years without concomitant progestogens, an elevated risk was found (RR=2.4, 95% confidence limits 1.5-3.5). No risk increase was found for those with any other brand, with added progestogens or with 3 years treatment duration. Conclusions. No increase in the overall risk of breast cancer after estrogen treatment was found. The finding of an elevated risk for those taking conjugated estrogens for a short period is consistent with results of an earlier follow up, but needs confirmation through continued follow up.

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**I-45: STEROIDS AND CANCER**

**IS THE ANDROSTERONE/ETHINOLANOLONE RATIO (A/E) A VALID MARKER IN THYROID ACTIVITY OF HUMAN ADVANCED BREAST CANCER?**

Z. Uran, Institute of Oncology, Cluj-Napoca, Romania

The thyroid activity was estimated in 120 women with advanced breast cancer both by radioiodine uptake and by A/E ratio, the former being also a sensitive marker of the thyroid disfunctions (A/E ratio is decreased in thyroid hyperactivity and overrated in hypothyroidism). In 85% of our patients the radioiodine uptake showed a hypothyroidism more or less prominent. Using the A/E ratio a thyroid hyperactivity was found only in 4% of the investigated cases. On the base of radioiodine uptake, the patients were divided into two groups, the first including 60 women with a more marked hypothyroidism, and the second, 60 patients with thyroid function near to normal (40) and normal (20). In the first group the mean value of A/E ratio was 0.55 that indicates a normal thyroid function. In breast the second group this ratio was 1.01 marking a moderate increase of the thyroid activity. Taking into account only 20 untreated patients from the second group, the mean value of A/E ratio was 1.20. Our findings are in agreement with some data reported in literature (Thomas, Bulbrook et al., 1977) pointing out that the absolute values of the A/E ratio does not reflect with fidelity the various degrees of the thyroid hyperactivity which is associated with breast cancer.

**CERVICAL CANCER RISK AND COMBINED ORAL CONTRACEPTIVES CONTAINING UNCHOLINOLONE ACETATE (CBA)**

I. Buceliu 1, D. Thomas 2, H. Mishau 1, R. Ray 2,
Fred Hutchinson Cancer Res.Cent., Seattle, USA

Within the WHO-Collaborative Study of Non-Plasia and Steroid Contraception, a hospital based case-control-study was performed to determine whether oral contraceptives that contain CBA alter the risk of breast cancer. Using an unconditional logistic regression analysis as described by Breslow and Day the preliminary analysis of the study, did not demonstrate any significant alteration of breast cancer risk for women who used combined oral contraceptives containing CBA only or who used this among other oral contraceptives.

**SHORM-PROTEIN BINDING (NPHS) & TALUMIN BOUND (ABE) STEROIDS AS A BIOMARKER FOR BREAST CANCER RISK ASSESSMENT.**


The non-protein bound fraction of estradiol in serum of breast cancer patients has been reported by several groups to be significantly elevated (Moore et al., Int. J. Cancer 29:17, 1982; Reed et al., Cancer Res. 43:3940, 1983, Jones et al., Br. J. Cancer 29:17, 1982; Reed et al., Cancer Res. 43:3940, 1983). However, a recent report by Hurning et al. (Br. J. Cancer 51:419, 1983) reported no difference between the CBA/BE of breast cancer patients and controls. The aim of our study was to determine the validity of this assay with regards the presence or absence of breast cancer. Sera was collected from 129 women documented to be disease-free by xeromammograms. In 32 stage I & II breast cancer patients without any prior treatment, 20% of the investigated cases. On the base of radioiodine uptake, the patients were divided into two groups, the first including 60 women with a more marked hypothyroidism, and the second, 60 patients with thyroid function near to normal (40) and normal (20). In the first group the mean value of A/E ratio was 0.55 that indicates a normal thyroid function. In breast the second group this ratio was 1.01 marking a moderate increase of the thyroid activity. Taking into account only 20 untreated patients from the second group, the mean value of A/E ratio was 1.20. Our findings are in agreement with some data reported in literature (Thomas, Bulbrook et al., 1977) pointing out that the absolute values of the A/E ratio does not reflect with fidelity the various degrees of the thyroid hyperactivity which is associated with breast cancer.

**INVESTIGATION OF HUMAN ADRENAL ACTIVATION BY ORAL CONTRACEPTIVES.**


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**STERONE AND PROGESTERONE STATUS VARIATION IN ESTRUS AND PROGESTERONE (PGX) REGULATION.**

L. Thomas, P. Hillhouse, R. Meyer, Fred Hutchinson Cancer Res.Cent., Seattle, USA

Tironi oon'Airasu

C.U.OH;.:AMNOMIS ACETATE (CUA)

Trophoblast tissue was investigated for subgroups of N-EE tumor patients. The result will be discussed in Conclusion: /he tumour, distus;:f*d by -"insidpring thr lmp;*nt hf-hrapy nn thr. w.rsi pr-*st!Ms was that -if I hp subgroup 'if N- EH- t unnrs

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The purpose of this study was to test the long-las-ting belief that a postmenopausal woman with breast cancer acquires a tendency for obesity because of a relative excess of adrenal androgens. In contrast, hormonal studies from our laboratory revealed that Japanese patients with breast cancer at both the pre- and post-menopausal stages excreted significantly more tetrahydrocortisol than the corresponding normal controls irrespective of the praxis of radical surgery, a finding to indicate that the cancer patients were primarily in a state of hypercorticoidism (Adv. Cancer Res. 38:77-119, 1983). Our participation is that the obesity in those patients, if present, should have been of the masculine type, but of the masculine type (central obesity due to hypercorticoidism). Case-control comparison was attempted regarding, a) the physical characteristics (height, weight, circumferences at the bust, waist and hip), and b) the excretions of 14 urinary steroids. The data of the case group were contrasted with those of the urban and rural control groups each. Results obtained are as follows: 1) The weight of the case group, when corrected for height, was indistinguishable from the weights of the 2 control groups (lack of the height-weight imbalance). 2) The waist to hip circumference ratio (an index of central obesity) increased in the order of the rural control-, the urban control-, and the case-groups. The differences among the 3 groups were statistically significant. 3) The extent of corticoid excess in urine increased in the order of the rural control-, the urban control-, and the case-groups. A significant correlation was decernible between the waist to hip circumference ratio and the progress of hypercorticoidism in the 3 groups. It was concluded that the waist to hip circumference ratio as an index of hypercorticoidism was useful in assessing the breast cancer risk.


Breast cancer is the most common variety in American women, yet we still lack conclusive evidence as to its etiology. Hormonally related factors are strongly suspected of being related to breast cancer because of increased risk associated with events such as menarche, menopause, and first pregnancy. The role of sex steroid hormones in breast carcinogenesis is unresolved. To address this question, a cross sectional study of 80 healthy women, half of whom were sisters of breast cancer patients, was undertaken. Questionnaires were administered to all participants to determine demographic, general health profiles, dietary measurements, weight, gynecologic, and family histories. Serum samples were obtained for lipoprotein and sex hormone determinations. Univariate and multivariate statistical analysis were performed on a paired basis matching each sibling with her control. There was no significant difference between siblings and controls regarding age, smoking status, prior medical and gynecological histories. The sibbling had a nonsignificant excess weight of 10 pounds. Obesity is known to be a risk factor for breast cancer, so increased weight in sibblings of patients is an important finding. The serum estrone (E1) concentration was significantly higher in the siblings as compared to controls (592 vs 461, P<0.05). Of sibblings had serum E1 concentration of 1500, compared to 1100 (P<0.05). Part of the excess E1 may be explained by the excess weight of the sibling group. However, there was a subset of sibblings with high weight and body fat percentage. These findings may suggest a genetic susceptibility to familiar breast cancer.


It was notified that some women are more often suffering from cysts of the breast than it is expected from the epidemiological studies of the endocrine state of women. Mainly, the subjective state is changed through menstrual cycle what suggest that is under endocrine control, or that depends on the endocrine state of the body. However, in some cases no subjective or objective chances of the cysts are noticed through menstrual cycle. Such cases suggested us that not only the endocrine state of the women is responsible for developing of the cysts, but also the endocrine state of the cysts. We have decided to determine seven sexual hormones, simultaneously in the maternal obtained from the cyst and from the serum of the women who were divided in two groups: first, whose symptoms were changed during the menstrual cycle, and the second whose symptoms were not changed. The time when the puncture was performed (under control of imaging) was always between one or two days before the menstruation started.

4611 INFLUENCE OF REPRODUCTIVE FACTORS ON BREAST-FLUID ESTROGEN (E1, E2) AND CHOLESTEROL EPID OXIDE: IMPLICATIONS FOR BREAST CANCER RISK. N. Petrich, R. Ernst, G. Craig, L. Crown, B. Holder, J. Mijrai and J. P. Styer. University of California, San Francisco, CA, USA

This is a study of estrogen, cholesterol and cholesterol sulfates in nipple aspirates of breast fluid and risk factors for breast cancer. Nipple aspirate fluid was obtained from women participating in a large ongoing case-control study of breast cancer and benign disease. All women had a comprehensive interview including a detailed menstrual and reproductive history. Estrone (E1) and estradiol (E2) were measured in breast fluid and blood from 101 premenopausal women. Breast fluid cholesterol, esterified cholesterol, 5-alpha- and 6-alpha epoxides and cholesterol 5-beta- and 6-beta epoxides were measured in 300 women. Estrogen, cholesterol and cholesterol epoxide levels were approximately 10 times those of serum levels. No relationship with menstrual cycles was found. Breast fluid E1, E2, cholesterol and epoxides were low concentration in lactating women. Those levels increased with months since last full-term birth and longer since nursing. Breast fluid E1, E2, cholesterol and epoxides were negatively correlated with total months of nursing. Women who had a full-term birth had lower levels than women who had not. The absence of a relationship of breast fluid to serum estrogen levels may explain why studies of serum estrogen have failed to elucidate specific hormonal mechanisms for breast cancer risk. The presence of high levels of cholesterol alpha and beta epoxides in the breast fluids of many women is considered to be of potential etiologic significance. In view of previous reports of the autogenicity and carcinogenicity of these substances. The prolonged low levels of breast fluid epoxides and epoxides following a full-term birth and lactation may, in part, provide a mechanism by which parity reduces breast cancer risk.
WEDNESDAY • AUGUST 27 • AFTERNOON

14:00 - 15:30

4612 


OESTRADIOL IN WOMEN WITH BREAST CANCER. D.T. Wang, V.E. 

Faulx, F.R.C. Clark, E. Nabilah*, and I.G. Fenclman*, 


and "Brest Unit, Guy's Hospital, London SE1 9RT, U.K. 

There has recently been much interest in the role of 

steroid receptor bound, or "free", oestradiol in the 

anti-tumour activity of breast cancer. Free oestradiol is 

thought to be biologically available to target tissue. 

It is known that the amounts of steroid free 

and in saliva are the same. If this was so 

the measurement of salivary steroids would provide 

a convenient and non-invasive method of studying the 

role of free hormones in the aetiology and course of 

breast cancer. 

Daily saliva samples have been collected throughout 

the menstrual cycle from 12 patients with operable 

breast cancer, 12 matched unoperated controls. 

In addition, synchronous blood and saliva samples were 

taken. 

The results showed that the amounts of salivary 

progesterone and oestradiol in patients with breast 

cancer and controls were the same. These levels were 

the same as the concentration of free blood steroid. 

Although salivary steroid assays are a convenient 

method for studying menstrual activity they are not 

sensitive to measuring free or biologically available 

salivary levels.

4613 

A C R E A S E D AND INCREASED ANDROGENIC ACTIVITY IN THE 

LATER DIA SP OF BREAST CANCER. A. SEGNOTI, National Cancer 

Institute, Via Venezia 1, Milan, Italy. 

According to the original hypothesis of Gratiaen, 

increased and increased androgene activity are two 

aspects of the same anatomical lesion of the ovary, namely 

the hyperplasia of interstitial cells; the interstitial 

cells being the source of ovarian androgens. 

Three recent reports from our Institute supply substantial 

evidence in the hyperandrogenic hypothesis. In the first 

report, urinary excretion of testosterone and/or androstanediol 

were found to be higher than normal in 61% of 

pre-menopausal breast cancer patients. In the second study, 

the circulating levels of testosterone in breast cancer 

patients were shown to be significantly higher than normal, 

whereas in the same patients the progesterone values were 

significantly subnormal. In the third paper, the risk 

associated with high androgens or low progesterone 

concentrations were evaluated: the rate-ratio (R.R.) for 

high levels of urinary testosterone and androstanediol were 

1.6 and 1.6 respectively. The RRs, for high serum 

androstenedione and low serum progesterone were 10.2 and 10.6 

respectively and the risk was maximized when both anomalies 

were contemporaneous present (R.R. 21.01). 

The androgen excess could act with a double mechanism: 

a - direct stimulation of breast epithelium through binding by 

androgen receptors; 

b - increase in free-oestradiol concentrations. 

Supported in part by grant FPO no 85.02376.44 from CNR Rome 

Italy.

4614 

LOSS OF TUMOR HORMONE DEPENDENCY UNDER IMMUNOSUPPRESSION 

GROWTH-SUPPRESSIVE EFFECT OF GLUCOCORTICOID ON 

ANDROGEN-DEPENDENT SHIOOKI CARCINOMA 115. Yoshitake 

Oosaka*, Tatsuo Shibata, Hiroshi Sonoo and Tsunekazu 

Sono**, Iwakuni Memorial Hosp. Osaka, and Kawasaki 


Endocrine-dependent tumors, such as breast cancer, 

may loose their hormone dependency and become hormone 

unresponsive in the course of treatment, especially 

at the terminal stage. It is conceivable that immuno-

suppressive condition of the host produced by progres-

sion of the disease may be one of the factors which 

changes hormone dependency of the tumor. We have 

shown that androgen dependency of a mouse tumor was 

lost by administration of large doses of glucocorti-

coïdes. 

Shionogi carcinoma 115 (SCI15) is transplantable in 

male DM mice, while it does not proliferate in female 

or castrated male mice. Consequently, the prolifer-

ation of SCI15 has been considered to be completely 

dependent on the existence of androgen, and it has 

been shown that its growth is mediated by a specific 

androgen receptor system in the tumor. 

We have found that SCI15 became transplantable to 

castrated male and female mice when the animals were 

treated with dexamethasone or betamethasone (100mg/mouse daily), 

but the tumor proliferated by glucocorticosteroid retains its specific androgen 

receptor and was androgen dependent when transplanted in male and female mice. 

Furthermore, as the glucocorticoid did not cause an increase of seminal 

vesicle weight in the castrated animal, it did not 

cause an increase of androgen. Thus, it is 

conceivable that immuno-suppression by glucocorticoids can 

change the androgen dependency of SCI15.

4615 

HORMONAL PROFILE IN POSTMENOPAUSAL WOMEN WITH 

CANCER ORBIT: ILLUSTRATED. T. D. A. Yousif, H. A. 

Hesham, A. Ghaly and M. El-Hett, Fac. Med., and 


A total number of 130 women were classi-

fied into two groups. The first group 

comprised patients with cancer genital 

tissue. The second group comprised 30 healthy postmenopausal women used as 

controls. Androgen, progesterone, T4, 

T3 and testosterone were determined in 

the two groups using radioimmunoassay 

methods. The results obtained revealed 

that a significant decrease of T4 and 

progesterone in postmenopausal 

women in comparison to control ones, and 

no significant change was observed in 

the levels of progesterone, T3 and tes-

tosterone hormones. It may be concluded 

that it is mandatory to do hormonal 

assay in women with cancer genital tract

The aim of the study was to investigate the hormonal background of patients with endometrial carcinoma. The biologic activity of oestrogens in endometrial carcinoma was studied by the EIA method. Compared to the control group the serum 2035 3+44.3 pg/ml, 1/1, oestriadiol 165.3+29.3 pmol/l/ and the androstenedione 172.0+4.4 mmol/l were significantly higher. The source of the increased oestrogen levels was mainly of adrenal origin. The peripheral conversion, i.e. aromatization of androstenedione into oestrogen was particularly marked in the case of adipose patients. The unbalanced oestrogen effect in the absence of progesterone is one of the decisive factors in the aetiology of endometrial carcinoma.

The comparison of both biochemical and immunohistochemical results were the clinical response to therapy seems to indicate that patients with majority of nuclear testosterone positivity in neoplastic cells and corresponding high AR positive values are more likely to benefit from androgen receptor blocking than those whose tumour showed negative or faint testosterone.

The present results based on 133,000 person-years and up to 3 years, Relative Risk 1.6 (1.2-2.3).

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Obestrian inhibits the secretion of growth hormone, some growth factors and most gastrointestinal hormones, of which some are involved in the growth regulation of pancreatic (tumor) cells. Therefore we have investigated in a transplanted pancreatic tumor model (Dr. A. Kogden) the anti-tumor effects of chronic (prophylactic) treatment with obstesin analog (SHS-201-955, Sandoz Ltd.). Furthermore, we analyzed some characteristics of these tumors. Two weeks after tumor transplantation, rats treated prophylactically with 2 x 1 mg SHS once a day (group A), had a mean tumor load of 6.1 ± 0.6 mm^2 (+ SD, n=3) compared to 26.5 ± 34.4 and (+ SD, n=30) in controls. These control rats were randomized for treatment with the same dose SHS (group B) or no treatment (group C). At the end of the treatment period of 28 days, tumor loads for the 3 groups were: in group A 1.9 ± 1.9 mm^2, group B 31.6 ± 17.3 mm^2, and group C 69 ± 32 mm^2 (+ SD, n=30). SHS analog treatment caused significant inhibition of pancreatic tumor growth both prophylactically and therapeutically. These results were reproducible in 3 different experiments. Tumor growth inhibiting effects were also observed with dosages of 10 and 20 µg daily. Some individual tumors disappeared completely. With respect to the characteristics of these tumors, we found specific binding for epithelial growth factor and progesterone, while estradiol receptor was absent. In view of these results we conclude that endocrine treatment with obstesin analogs might be useful in the treatment of pancreatic cancer. (Supported by grant KRT 83-13 of the Netherlands Cancer Foundation).
EXPERIMENTAL CHEMO- AND ENDOCRINE THERAPY AGAINST HUMAN BREAST CARCINOMAS SERIALLY TRANSPLANTED INTO MICE. T. Kubota, L. Koh, T. Fukudome, Y. Isobe, S. Kikuyama, M. Kato, K. Inagaki, M. Kato, and B. Sauer. Dept. of Surgery, Keio Univ., Tokyo, Japan. Four human breast carcinomas strains serially transplanted into nude mice were employed for the experimental chemotherapy and combination chemotherapeutic therapy. Numerous trials of these strains (MC-7, ER-10 and T-61) possessed estrogen receptor (ER) and depended on estradiol for the tumor growth, the other strain (MC-1) without ER was hormone independent. For the chemotherapy, mitomycin C (MMC) 100 mg/kg and thiopeta (THP) 80 mg/kg, and cyclophosphamide (CPA) 80 mg/kg and 5-Fluorouracil 50 mg/kg dissolved in 0.2 ml of normal saline were administered three times every four days. To know the stability of ER after chemotherapy, binding sites of ER were measured four days after administration of venox 1, 2, and 3.5 mg/kg for the chemotherapeutic therapy, 1 mg of MMC for 5 days continued followed by the treatment of tamoxifen (TAM), THP and CPA were used after THP. And this combination effect of MMC and TAM revealed the additive effect mainly these ER- positive strains, although single administration effect was observed in 1, 5 mM THP without MMC. These results confirmed that the combination therapy is effective in mammary tumors and its mechanism of action is in the future.

Yuji Saeki, Kazuyoshi Kurooka, Hiroshi Takagi, Zenji Iwasa, Nobuki Matsunani, Muneoisa Yamato, Tatsuki Sakai, Kazunori Kuroko, Hiroshi Togaki, Kyotaka Okay, Tatsushi Fukuda, and Matsuyuki Yamasaki First Dept. Surgery, Keiko Univ. Sch. Med. Osaka, Japan. The experimental studies on chemo-endocrine therapy were investigated tumor effect, biochemical ER (OCC method) histotechnical ER (PAP method), histological changes and nuclear DNA content before and after individual treatments on the DMBA-induced rat mammary carcinomas. This study was treated by chemo-endocrine therapy in the following six groups: ovariectomy (Ovx) group of 21 cases, Mitomycin C (MMC) group of 26, Cyclophosphamide (CPA) group of 20, Tamoxifen (TAM) group of 22, Ovx/MMC group of 23, and TAM/MMC group of 20. The tumor effect was 91.3%, highest, in the Ovx/MMC group and 10.1% in the Ovx group. Biochemical ER tended to be negative in all the cases, while a histological ER negative rate was 50.5% for the Ovx/MMC group and 71.4% for the Ovx group. As major histological changes, atrophy of the glands were observed at 78.3% in the Ovx/MMC group and at 65.2% in the Ovx group. Focal necrosis appeared at 48.2% in the MMC group. The characteristic arborization of the alveolar-like cavity was observed at 45.4% in the TAM group. Nuclear DNA content was measured as follows: tissue was fixed in 10% formaldehyde solution, and then was isolated with EDTA, crude stem bromelain and ultrasonic wave, followed by Peltigen staining. Then, nuclear DNA content was measured by nosophotometry. Endocrine therapy is effective for ER positive cancer cells. In the chemotherapy is effective for ER negative, cancer cells. Therefore, chemo-endocrine therapy of combined modality approach is more effective for breast cancer.

ACTIVATION OF THE ESTROGEN RECEPTOR FROM DMBA-INDUCED RAT MAMMARY TUMORS. E. Drefahl, E. Körtisch, B. Haege, and O. Schilz. Central Inst. of Cancer Res., Berlin, DDR. The activation of the steroid receptor and its tight binding to nucleic acids may be one of the earliest steps of steroid hormone action in the target cell. The activation of the estrogen receptor (ER) from 2-nitrosoethylurea (NBU)-induced rat mammary tumors was studied in vitro. NBU-induced mammary tumors are estrogen receptor positive (receptor content: 40,5 ± 14,5 fmol/mg cytosol protein, n=51) and mostly hormone dependent. The activation of the receptor induced by heating of the cytosol containing occupied ER was measured by a 3-fold increase of receptor binding to isolated nuclei in comparison with the nuclear binding of the non-activated receptor. Maximally 60-70% of the ER could be bound to nuclei after activation. Using chromatography on DEAE-cellulose columns the nonactivated receptor or the activated one were eluted mainly at 231 ± 12 mM or 71 ± 6 mM phosphate buffer, respectively. After warming of the cytosol in presence of 10 mM molybdate and 5 μM coenzyme A the nuclear binding activity of the ER remained low and most of the receptor was eluted from DEAE- cellulose columns at 230 ± 11 mM buffer, similar to the non-activated receptor. The further dissociation of estradiol from the nonactivated ER followed a two-component exponential function (biexponential function) whereas the dissociation of the steroid from the activated receptor followed a single exponential function.

STUDIES ON CHRO-ENDOCRINE THERAPY ON DMBA-INDUCED RAT MAMMARY CARCINOMAS. T. Kubota, L. Koh, T. Fukudome, Y. Isobe, S. Kikuyama, Tatsuki sakai, Kazunori Kuroko, Hiroshi Togaki, Kyotaka Okay, Tatsushi Fukuda, and Matsuyuki Yamasaki First Dept. Surgery, Keiko Univ. Sch. Med. Osaka, Japan. The experimental studies on chemo-endocrine therapy were investigated tumor effect, biochemical ER (OCC method) histotechnical ER (PAP method), histological changes, and nuclear DNA content before and after individual treatments on the DMBA-induced rat mammary carcinomas. This study was treated by chemo-endocrine therapy in the following six groups: ovariectomy (Ovx) group of 21 cases, Mitomycin C (MMC) group of 26, Cyclophosphamide (CPA) group of 20, Tamoxifen (TAM) group of 22, Ovx/MMC group of 23, and TAM/MMC group of 20. The tumor effect was 91.3%, highest, in the Ovx/MMC group and 10.1% in the Ovx group. Biochemical ER tended to be negative in all the cases, while a histological ER negative rate was 50.5% for the Ovx/MMC group and 71.4% for the Ovx group. As major histological changes, atrophy of the glands were observed at 78.3% in the Ovx/MMC group and at 65.2% in the Ovx group. Focal necrosis appeared at 48.2% in the MMC group. The characteristic arborization of the alveolar-like cavity was observed at 45.4% in the TAM group. Nuclear DNA content was measured as follows: tissue was fixed in 10% formaldehyde solution, and then was isolated with EDTA, crude stem bromelain and ultrasonic wave, followed by Peltigen staining. Then, nuclear DNA content was measured by nosophotometry. Endocrine therapy is effective for ER positive cancer cells. In the chemotherapy is effective for ER negative, cancer cells. Therefore, chemo-endocrine therapy of combined modality approach is more effective for breast cancer.

DIRECTED RECEPTORS TREATMENT MODIFICATION IN EXPERIMENTAL MAMMARY TUMORS DURING THEIR THERAPY. N. A. Dendravos of the Experimental Institute for Oncology Problems, Acad. Sci. of Ukrainian S.S.R., Kyiv, USSR. The estrogen receptor content in the estrogens independent mammary tumors in Ovx/Sc mice varies over the wide range depending on hormonal background of tumors development. Different hormonal situation models correspond to normal ovarian cycle phases in the rats resulting changes of receptor status of ER-induced mammary tumors, rates of tumors growth, tumor morphological characteristics and increase the duration tumor-carrier animals' life. During tamoxifen therapy of DMBA-induced mammary cancer hormones capable of stimulating estrogen and progesterone receptors synthesis in mammary gland were periodically injected to rats. Then using such a therapy we noted duration of animals' life increased in comparison with those animals being treated with tamoxifen only. Our results show that hormonal regulating influence is able to modify mammary tumor reception status, increase sensitivity of tumor to hormone therapy and increase duration of medical preparations use.
4629 EFFECTS OF 13-CIS-RETINOIC ACID ON THE EXPRESSION OF SEX STEROID RECEPTORS IN DMBA-INDUCED RAT MAMMARY TUMORS.

Zamardi S., Cersanti G., De Menesch R., Ferrullo M., Pino G., Valenti G., Boccardo F., Istituto Nazionale per la Ricerca sul Cancro, Genova, ITALY.

The expression of hormone receptors is considered as a marker of differentiation in hormone-dependent tumors. Biological activity of retinoids is based mainly on their antiapoptotic effect in several experimental systems, in some of which, however, a redifferentiating action was shown in addition. In the present study the effects of 13-cis-retinoic acid on the expression of cytosolic estrogen and progesterone receptors (ER and PgR) were investigated in the DMBA-induced rat mammary tumor model. Intact rats bearing established DMBA-induced tumors were treated with 13-cis-retinoic acid: 4.5 mg b.i.w. The retinoid was diluted in olive oil and administered intragastrically. Before treatment and 4 weeks thereafter tumor biopsies were performed to assess cytosolic ER and PgR concentration according to the Dextran-Coated Charcoal technique. To verify the functional integrity of estrogen receptors rats were treated for 3 additional days with estradiol benzoate (E2), 5 mg i.m. daily; on day 33 tumors were excised and processed for sex steroid receptor assay. After treatment with 13-cis-retinoic acid both ER and PgR concentration increased in 4 out of 12 rats; in 2 of them, E2 treatment produced a further increase in PgR concentration, indicating that a functional ER was induced by previous treatment with the retinoid. ER and PgR concentration decreased or remained unchanged in 5 and 3 animals, respectively.

Results indicate the possibility that the expression of sex steroid receptors can be enhanced by previous treatment with 13-cis-retinoic acid. The research is going on testing different retinoids which have been shown to be more effective in the prevention of this tumor — and the potential for doubling effect of administrating such retinoids, given immediately following tumor induction, on the expression of sex steroid receptors.

4630 GROWTH OF A RAT LEYDIG CELL TUMOR WITH REFERENCE TO THE ENDOCRINE STATE OF THE HOST ANIMAL.

As Erichsen, O.P.F. Clausen, P. Torjesen and V. Hansson.

Inst. of Pathology and Medical Biochemistry, University of Oslo, Norway.

Hormone Laboratory, Aker Hospital, Oslo, Norway.

Intact, castrated and hypophysectomized 30 days old SPRD rats were injected with 15.10^6 tumor cells subcutaneously and the tumor growth was measured daily. At intervals groups of five rats were sacrificed. Tritiated thymidine was injected i.p. 45 min before sacrifice, whereas after tumors were weighed, single cells processed for DNA flow cytometry and for smears that were subjected to autoradiography. Blood were sampled for determination of LH, FSH, prolactin, growth hormone, testosterone and oestrogens.

Results:
1. The growth kinetic curves of intact and castrated rats were linear.
2. The onset and progression of tumor growth were delayed in hypophysectomized rats, whereas the growth rate in castrated rats was similar to that in intact animals.
3. The thymidine labeling index as well as the size of the S and G2 phase compartments were decreased in tumors greater than 10 gr in intact rats compared to small tumors.
4. Prolactin levels in blood of tumor bearing rats were unaffected by tumor size, testosterone concentration and castration.
5. The testosterone levels in blood correlated well with tumor size.

Conclusion: The growth of this tumor is under control of pituitary hormones. The roles of the various pituitary hormones remains to be established. LH (perhaps via steroidotropins) and prolactin are putative growth modulators.

4629 NATURE OF ANTI-TUMOR ACTION OF THE LENTINAN-ENDOCRINE COMBINATION THERAPY ON MAMMARY TUMOR.


Synergistic action of lentian (LNT), an anti-tumor polysaccharide extract from Lentinus edodes, with the endocrine therapy for hormone-dependent mammary tumors was investigated. Experimental study in rats with DMBA-induced mammary tumors indicated the following evidences that: 1) LNT triggers an increased infiltration of macrophages and T, B cells into the stromas around adenocarcinomas, and suppresses the blood prolactin level, 2) LNT treatment after the ADX + OVX therapy results in a much higher regression of tumor growth than that of surgical therapy alone, 3) LNT exerts its action effectively in the mammary tumor bearing animals showing a decreased level of estrogen receptor and a marked lymphocytosis which were induced by the ADX + OVX therapy. The efficacy of LNT treatment for patients with recurrent breast cancer who had previously undergone ADX + OVX was evaluated in a randomized controlled study for 7 years. Patients treated with LNT showed longer disease-free intervals and a much higher survival rate than controls. No severe side effects were found. These findings indicate that LNT may exert its anti-tumor action, by producing an amplification loop with the surgical endocrine therapy through both immunological and hormonal mechanisms, and may be a useful and safe agent for hormone-dependent tumors in combination with the endocrine therapy in vivo.


Mastomys natalensis, an African rodent ranging in size between a house mouse and a rat, in all other respects other than to humans to develop gastric carcinoma at a high incidence. We previously showed that gastric carcinomas, either spontaneus or experimentally induced in this species, can be distinguished from those in animals. We previously showed that gastric carcinomas, either spontaneus or experimentally induced in this species, can be distinguished from those in animals. We previously showed that gastric carcinomas, either spontaneus or experimentally induced in this species, can be distinguished from those in animals.

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Conclusion: The growth of this tumor is under control of pituitary hormones. The roles of the various pituitary hormones remains to be established. LH (perhaps via steroidotropins) and prolactin are putative growth modulators.
EXPERIMENTAL MODELS OF HORMONE-PRODUCING CANCERS

I-46: EXPERIMENTAL MODELS OF HORMONE-PRODUCING CANCERS


Experimental combined endocrinotherapy with tamoxifen, aminoglutethimide and medroxyprogesterone acetate was investigated using three hormone-dependent human breast carcinomas serially transplanted into nude mice. The combined antitumor effect of tamoxifen and aminoglutethimide was better than those of tamoxifen or aminoglutethimide alone. Since aminoglutethimide reduced the level of estrogen and the uterine weights in normal female mice with statistical significance, the combined antitumor effect of tamoxifen and aminoglutethimide was assumed to be caused by the low estrogen level due to aminoglutethimide, resulting in more favorable competition of tamoxifen with estrogen receptors. There was no additive antitumor effect by the combination of tamoxifen and medroxyprogesterone acetate, although serum medroxyprogesterone acetate levels in nude mice were almost equivalent to those of humans. These results demonstrated that combined endocrinotherapy, especially with tamoxifen and aminoglutethimide, might be a promising method for clinical application.

J-48: SMOKING AND CANCER

4633 SMOKING PATTERNS AMONG EMPLOYEES AT LOS ALAMOS NATIONAL LABORATORY Martin C. Mahoney,1*, Gregg S. Wilkinson. Roswell Park Memorial Institute, Buffalo, NY 14263, U.S.A. Epidemiology Group, Health, Safety and Environment Division, Los Alamos National Laboratory, Los Alamos, New Mexico 87545, U.S.A.

Patterns of smoking among 7675 employees at the Los Alamos National Laboratory, in Los Alamos, New Mexico were studied using self-reported data gathered as part of an ongoing occupa- tional medicine program. The collection of such data is an integral component to concurrent medical services and is essential in future epidemiologic studies. Information on smoking behavior was available for 5587 (72%) persons. A detailed description of methods employed in data collection will be presented. Twenty-five percent of the males and 21% of the females identify themselves as current smokers. The proportion of smokers among males employed as professionals was almost one-half that of males in other job categories. There are no differences in the proportion of current smokers by occupation among females. Male professionals exhibit the highest levels of current cigarette consumption. Male clerical workers and female clerical workers report a shorter duration of cigarette use. Upon stratification by educational level, higher rates of current smoking in both males and females is observed among young persons with less than a college degree. While males with doctoral degrees report higher levels of current cigarette consumption, this group also reports shorter duration of cigarette usage. Employee clinical summaries should include information on smoking history. This is especially useful if there is a possibility that future studies may be done assessing their morbidity and/or mortality.

4634 FACTORS INFLUENCING SUCCESS IN COUNSELING PATIENTS TO STOP SMOKING S.L. Ebbot, K.H. Cummings, G. Giovino, R. Sladate, H. Koenigsberg. Roswell Park Memorial Institute, Buffalo, New York, U.S.A.

This study examined the anti-smoking counseling practices of a group of family practice physicians and related these to success in persuading patients to stop smoking. The study population included 283 cigarette smoking patients of 28 family practice residents. Patients were followed over a three month period to assess changes in smoking behavior. Two measures of success in counseling patients to stop smoking were evaluated in the study: 1) the percentage of a physician's patients who tried to quit smoking, and 2) the percentage of a patient's patients who succeeded in quitting. Findings showed wide variation among physicians in the percentage of patients who tried to quit (range: 20% to 75%) and the percentage of patients who succeeded in quitting (range: 0% to 25%). Two counseling practices, advising patients to set a target date for quitting and scheduling follow-up visits with patients to monitor progress, were related to the percentage of a physician's patients who quit smoking. These two counseling practices represent a way of structuring the patient's quitting effort and committing the patient to follow through with a decision to stop smoking, both of which appear to be key ingredients to success in counseling patients to stop smoking.
WEIGHT GAIN FOLLOWING SMOKING CESSATION: A POSSIBLE ROLE FOR NICOTINE REPLACEMENT IN WEIGHT MANAGEMENT S.L. Emmett and K.M. Cuming. Roswell Park Memorial Institute, Buffalo, New York, U.S.A.

This study examined nicotine dependence as a factor in weight gain following smoking cessation in a group of 104 recent ex-smokers. Nicotine dependence was measured using the eight-item Fagerstrom Tolerance Questionnaire. Findings support the hypothesis that weight gain following smoking cessation is greater among more nicotine dependent persons. Heavier smokers (266 cigs/day), those who reported smoking when they were ill, and those who reported smoking their first cigarette of the day within 30 minutes of waking up reported the greatest increase in weight one month after quitting. Twenty subjects reported using nicotine gum to help them quit smoking. A significant inverse correlation (r = -0.17) was found between weight gain and the number of pieces of nicotine gum chewed per day. Stratification by the number of cigarettes smoked daily (266 cigs/day versus ≤ 26 cigs/day), indicated that the correlation between weight gain and the number of pieces of nicotine gum chewed per day was significant only for heavy smokers (r = -0.37 versus r = 0.08). This finding suggests that nicotine replacement may help prevent weight gain following smoking cessation, especially for the more dependent smokers.


Nurses, as the largest group of health professionals in America and are potentially powerful resources for influencing the smoking behavior of others. With this in mind, and with the fact that, to date, student nurses have not been studied systematically, smoking behavior and its correlates were examined among 1,165 student nurses in the Buffalo, N.Y. area. The approach used in this study can be extended to other groups throughout the world in implementing smoking cessation programs. Methodologies employed may be particularly relevant to others given the epidemic of smoking. A sampling fraction was utilized in 5 of the 10 schools under study. This fraction approximates the total school in terms of proportions of students in each level of the program and in day and evening divisions in those schools having both. Students in the other 5 schools were also surveyed. Analyses of data show that 52% are current smokers and more than half (57%) express a desire to quit. Knowledge of the health consequences of smoking was generally high for coronary artery disease; pulmonary diseases; lung, laryngeal, and oral cancers; over 90% of the students acknowledged an association in each area. But, only 26% were aware of a relationship between bladder cancer and smoking. Analyses of the effect of smoking status on professional responsibility are underway. The significance of these findings lies in generating a database for educational strategies aimed towards changing the students own smoking behavior and focusing responsibility on all student nurses for intervening on the smoking behavior of others. Detailed discussion of design and analysis will be presented with a focus on how they can be applied to other health professional groups.

PREVENTION OF CANCER BY VERY EARLY PROPHYLAXIS OF SMOKING, Stanislav O. Peneyko, Higher Med. Institute, Pleven, Bulgaria.

Although up to now we do not know the whole truth about cancer, we are well acquainted with one of the important allies called tobacco. Smoker as tobacco has a causal relationship to cancer, every success in preventing smoking is a contribution in the fight against this scourge of present day. The paper discusses the question of why measures for smoking cessation are so unsuccessful and how addiction to smoking is even stronger than the fear of death/projection of 20 slides. The conclusion is that prophylaxis is the only hope, and that the same inborn forces that make people victims of tobacco can be used so that they never start to smoke. The theory and practice of conditioned reflexes are discussed and I is shown how, with the help of this method, this can be successfully in the fight against smoking. The results of the wide application of this method on small children in Bulgaria are shown. They discover that by means of an appropriate organization a senseless humanity is no more an unattainable reverse. The author proposes the term PSYCHOCOMMUNICATION as the most suitable for this method of creating a conditioned reflex as a defence against cigarette smoking. FOLLOW A DOCUMENTARY FILM / 16 mm., coloured, 20 min. /
GENOTOXIC EFFECT OF TOBACCO SMOKE (TS) AND ITS DEPENDENCE ON SOME BIOEFFECTORS.

A. Z. Balasskeyk, P. M. Blagoeva, and Z. L. Mitrohva, Institute of Oncology, Sofia, 1956, Bulgaria.

Employing 3 short-term tests the genotoxic effect of whole TS was studied. It was established that the 20-60 cm³ exposure of 4-6 fold increase of spontaneous his* reversion mutation rate in S typhimurium TA98 but not in TA97a, TA100 and TA102. Vitamin C (0.2-2.0 mg/ plate) added to the top agar did not influence this process, but GSH (0.3-1.2 mg/plate) and cysteine (0.12-0.45 mg/plate) enhanced up to 12% the mutagenic activity of TS. TS (180 or 340 cm³) passed through the cultural medium containing or not 30 mg/day of human peripheral lymphocytes (the cells were then incubated 60 min at 37°C) did not increase the spontaneous rate of UDS significantly. The 60 min treatment of male and female RDB mice placed in a 14L glass chamber with TS (500 cm³, 2 exposures of 30 min each, with an 1 min interval) caused a 2 fold dose dependent elevation of the number of micronucleated (MN) PCE (from 2.0-2.7 per 1000 PCE in sham-treated mice up to 4.7-5.6 MN PCE in TS treated mice). No cumulative effect was detected when mice were treated with TS during 2-28 consecutive days. The effect observed 24h after TS exposure was abolished 48h after that. Seven days treatment of mice with vitamin C (400 mg/L in the drinking water) totally inhibited the formation of MN in PCE induced by TS. Both, Salom-T.la/mutagenicity assay, employing TA98 strain and micronucleus test in mouse bone marrow might be useful in studying the TS induced mutagenic activity.

Tobacco Price, Tobacco Consumption and Mortality Rates by Cancer in Spain.


In Spain during the period 1951-1979 we had a remarkable increase in both consumption of tobacco and mortality rates in some malignancies where smoking has a leading role. We analyzed trends in tobacco consumption and its relationship to actual price, especially during the last twenty years, coinciding with a twofold increase in consumption of cigarettes.

We compared trends of smoking with smoking prevalence and mortality rates (directly standardized), employing the specific or x test (depending of the size of series) for hypothesis testing.

This trend in tobacco consumption is positively related with the trends in standardized mortality rates (directly standardized) especially by cancer of the lung, but also by cancer of the pancreas, cancer of the bladder, cancer of the kidney, cancer of the mouth and pharynx, cancer of the larynx and cancer of the esophagus.

We analyzed the possible interaction between alcohol and tobacco in some malignancies where both factors have a synergistic effect.

Finally, we discussed the possible explanation of trends and other findings and the doubtful efficacy of public education campaigns against smoking in Spain during the period and the absence of a continuous and integral program against smoking in our community.


Sample: 1,151 subjects from womens aires and its suburbs, distributed by sex and age according to the last National Survey, belonging to all socio-economic categories. To the question, Do you know ways of preventing cancer? 62% answered YES and 38% NO. Comparing with responses from non smokers, a greater percentage of answers is found among smokers who correlate cigarettes and cancer. This reveals a contradictory behaviour expressed in the answer "No smoking" as a prevention way and the attitude of smoking. The contradiction is specially significative among smokers belonging to the middle class. Seventy three percent middle class male smokers answer "No smoking" as preventative measure; 47% women smokers belonging to the same social class show the same contradiction. Proposal: The described situation reveals the need of a critic review of the campaigns destined to persuade smokers to quit the habit because the results of this Investigation show a remarkable inconsistency between the opinion of the smoker and his behaviour. As from these results, proposals are being presented to modify the smoker's behaviour. This research has been partially subsidized by the National University of Buenos Aires.

PRIMARY LUNG CANCER IN FEMALES ON OUR MATERIAL.

M. Brailo, D. Vanicke, P. Badovici, N. Perlegi, Inst. of Radiology and Oncology, Sarajevo, Yugoslavia.

The incidence of primary lung cancer in females increases. We analysed female patients, diseased of this severe disease, who were treated at the Inst. of Radiology and Oncology, Sarajevo. The following data were analysed:

1. Smoking causality and appearance of lung cancer
2. Age distribution
3. PHD distribution
4. Stage of disease
5. Therapeutic approach
6. Survival

In the present paper, we state that smoking is the most responsible factor in increase of number of lung cancers in females.
Comparative statistical data on tobacco consumption and on mortality of pulmonary cancer

Dr. T. SIMON - Dr. G. ANGELUS - EGS. L. KERESKÉNYI
Semmelweis University School of Medicine
Dept. of Social Medicine and History of Medicine
Budapest, Hungary

The authors analysed the relation between smoking and mortality of throat-, bronchus- and pulmonary cancer based upon international and Hungarian statistical-, and literary data. Data of the two decades elapsed showed a close relation between the Hungarian tobacco smoking and the mortality of the tumor mentioned above: the same applied to some developed countries. It could be stated that both the tobacco consumption and the figures of the mortality of the given tumor were rather high in Hungary compared to the other countries studied. The authors drew the attention to the fact that 85 per cent (exactly the death of 1700 persons) of the mortality of pulmonary cancer in males younger than 65 years could be attributed to smoking with us. The most important solution of the death before time was the prevention of smoking.

The need for a co-ordinated approach to smoking cessation. Michael A. Hood, Director, Ulster Cancer Foundation, 40-42 Science Avenue, Belfast BT9 6GR.

Northern Ireland

Smoking cessation programmes are a vital component of any overall smoking control strategy to-day. Millions of smokers have given up since the health consequences of smoking became known. However, many adults still smoke, although surveys have shown that a majority of them wish to give up but have developed a physiological dependence on nicotine and are no longer free to choose whether to smoke or not. Health education programmes designed to reduce the prevalence of smoking by persuading those smokers who can easily give up to do so, and non smokers not to start, are of prime importance but do not meet the needs of the many dissonant smokers in the world to-day. Only intervention programmes which recognise the need for support during the cessation process and deal with the problems of withdrawal can have any real hope of maximising prospects of success.

Methods of smoking cessation differ, ranging from minimal interventions such as the availability of self-help literature through mass media campaigns, or general practitioner intervention to specialist clinics and the use of nicotine chewing gum. All of these methods are important and no one method or approach is necessarily superior to the others since what may work for one smoker may not work for another who will have different needs. The real need is for a co-ordinated multi-intervention approach.

This will be discussed with methods of intervention which have been evaluated.
IS LUNG CANCER A SEXIST DISEASE? D.J. Klaassen, H.H. Res. Inst. of Tuberculosis and Respiratory Diseases, Prague, Czechoslovakia 2, Centr. Inst. of Cancer Res., Acad.of Sciences, Berlin, German Democratic Republic 3, Nat. Inst. of Oncology, Budapest, Hungary 4, Inst. of Oncology, Warsaw, Poland

In a study organized by the Centre of Lung Cancer Epidemiology of member countries of OMEP in the Res. Inst. of Oncology, Rostov on Don (USSR) data on lung cancer morbidity from the USSR, Czechoslovakia, German Democratic Republic, Hungary and Poland were compared. In the years 1970-1979 the morbidity rates standardized to world population were 35-30 times higher in males than in females, amounting to 32.9 - 77.0 per 100,000 in males, and 4.5 - 5.7 in females. In the population of the German Democratic Republic (both sexes), the male population of Hungary, and the female population of Poland the average annual increase in lung cancer incidence was steeper than in the respective populations of other countries under study.

GEOGRAPHIC DIFFERENCES IN LUNG CANCER MORBIDITY BETWEEN THE ROSTOV REGION (USSR) AND THE CZECH SOCIALIST REPUBLIC (CSSR). T.Y. Saljakina1, R. Feuerstein2, A.Rubtsov3, W.Mehnert4, Z. Peter5, H.Gadon6, T.V.Seljakina1, J.S. Sidorenko1, A.Kublic1, and R. Feuerstein1

Analysis and comparison of lung cancer morbidity between the Rostov Region (USSR) and the Czech Socialist Republic (CSSR) in the years 1970-1979 gave the following main results: 1. The trends of lung cancer morbidity were rising on either territory both for the urban, and for the rural populations. 2. A steeper increase of lung cancer morbidity was observed in the rural population of the Rostov Region than in the urban population of this region, both for males, and for females. 3. Lung cancer morbidity in males ranked first among malignant tumours on either territory. 4. The patterns of age and sex distribution of lung cancer morbidity were of a similar type on either territory. Cartograms demonstrating the geographic differences of lung cancer morbidity facilitated the selection of high-risk areas. Taking into consideration this study concludes a brief outline of preventive measures for the territories under study has been proposed.

The aim of the present report was established the rate of larynx cancer in the Lublin region population in the successive years of the period under examination (1980-84). The methods employed in the research were described in the preceding papers: Klonowski et al. /1968, 1974/. During the period under investigation 589 patients who had larynx cancer for the first time were found. The above group of 589 patients consisted of 565 men (95.93%) and 24 women (4.07%). The report presents the rate of larynx cancer, classified according to age groups for the whole population as well as by profession. The annual rates of larynx cancer for the whole Lublin region population during the years 1980-1984 have been calculated in successive 5-years age groups.

4652 STOMACH CANCER MORTALITY IN SPAIN. R. Palermo-Trelino (w); A. Santa-Vereda (m) Instituto Nacional de Oncologia, Madrid, Spain. University of Edizzi, Spain (w).

It is analyzed the evolution of mortality from stomach cancer in Spain since year 1961 to 1979 using the age adjusted death rates (MMR) for men and women using as standard population for both sexes the calculated male population of 1963. For men, the mortality from gastric cancer increased until the year 1965 (70.71) (18.24%) and then was decreasing continuously until 1969 (60.71) (26.28%). For women the mortality was increasing since the year 1961 (4.77) until 1965 (47.50) (13.90%). After the year 1965 the rate was decreasing until 1979 (37.27). If we analyze the regression curve-linen of mortality between the years 1965 - 1979 it is expected, according to the current pattern, that the mortality from gastric cancer should be zero in the years 2015 (women) and 2021 (men). The authors have analyzed also the mortality in 49 Spanish provinces (98% of total) and they have found a difference between seaboards provinces (21) and the remaining provinces (28): for men, the mean of mortality rate is 51.75 in the seaboard provinces versus 70.72 in the remaining provinces; for women, the mean of mortality rate is 37.25 in the first group of provinces versus 63.96 in last group. The difference in the mortality rate from stomach cancer between seaboards and non-seaboards provinces is statistically significative (p<0.01).

4653 IMMUNOPROLIFERATIVE SMALL INTESTINAL DISEASE - A DISEASE OF THE MIDDLE EAST AND MEDITERRANEAN COUNTRIES. P Salem, J Aljami, I Mashihi, E Anissie, M Khayat. American University of Beirut Medical Center (AUBMC), Beirut, Lebanon.

The Middle East presents several epidemiological peculiarities in lymphomas, the most important of which is immunoproliferative Small Intestinal Disease (IPSID). AUBMC has been actively engaged in research on this disease since 1970. 32 patients with documented IPSID had been studied at our center during the period 1961-1980. Median age was 28 years with a peak incidence between 16 and 25. The major presenting symptom was chronic diarrhea occurring in 84% of patients. In addition patients presented with marked weight loss, emaciation, and clubbing of fingers and toes. Pathologically IPSID was characterized by the presence of a dense, compact, uniformal cellular infiltrate which involved the whole length of the small intestine. This infiltrate was either benign-looking or malignant, and was confined to mucosa, and sub-mucosa. Lymphoma was either in the intestine or in mesenteric node and in 2 patients no lymphoma was present. In these 2 patients the disease was in stage 0, or the pre-malignant phase. In the past, it was thought that only cellular infiltrate which could occur in IPSID was lymphoplasmatidy in nature. We have shown that other kinds of infiltrate could exist in this disease. In our series, 16 patients had lymphoplasmaticy infiltrate; 10 had Lymphoid Hyperplasia infiltrate, 3 had a mixed pattern of infiltrate - lymphoplasmatidy in the most superficial layers with lymphoid Hyperplasia in the deeper layers. The remaining 3 patients had an Infiltrate which was non-diagnostic. The majority of patients who had the immunoproliferative infiltrate were found to have Alpha Heavy Chain Disease in the serum, or intestinal fluid, and were considered to be in the secretory phase of the disease, while those who had the Lymphoid Hyperplasia pattern were rarely found to have the abnormal protein. IPSID is a newly described disease, which provides a new opportunity for the study of lymphoproliferative disorders in man. Like Burkitt's lymphoma, it is geographically restricted to a specific region of the world, and in addition it is associated with a biological marker which is the Alpha Heavy Chain Protein, and it has been shown to go through a benign pre-malignant phase.
**Gastro-Intestinal Cancer in the Black Population of Johannesburg, South Africa.**

J. Segal, L. Segal, T. Grieve, Baragwanath Hospital, Human Biochemistry Res. Unit, S.A.I.M.R., School of Pathology and Univ. of Witwatersrand, South Africa.

**AIM**

Gastro-intestinal cancers, except for oesophageal cancer are very uncommon in South African blacks. Our aim was to estimate incidence of g.i.t. cancers in blacks of Soweto (population 1 1/2 million) and to elicit aetiological clues accounting for disparities in cancer incidence between black and western populations.

**PATIENTS AND METHODS**

Data were obtained from g.i.t. histopathology records and surgical register. A dietary survey was also carried out.

**RESULTS**

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Mean no. patients p.a.</th>
<th>Crude incidence/100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca. Oesophagus</td>
<td>179</td>
<td>1.5</td>
</tr>
<tr>
<td>Ca. Stomach</td>
<td>23</td>
<td>1.7</td>
</tr>
<tr>
<td>Colo-Rectal</td>
<td>26</td>
<td>2.4</td>
</tr>
</tbody>
</table>

**DIETARY SURVEY**

- **Weight**: Males 66Kg, Females 71Kg
- **Height**: Males 166cm, Females 158cm
- **Energy Intake**: 1,840 Kcal; 7.5% Total protein; 415g Animal protein; 33g Vegetable protein
- **Total Fat**: 49Kg
- **Carbohydrates**: 266g; **Sucrose**: 52g; **Cholesterol**: 236mg
- **Dietary fibre**: 14g

**CONCLUSIONS**

1. Ca. oesophagus: Although alcohol and cigarette smoking probably incriminated, a significant minority of patients (<10%) neither smoke nor drink.
2. Ca. stomach: Although very uncommon, this cancer is primarily of the 'environmental' (diffuse) type. Factors such as low socio-economic status, low intakes of vegetables and fruit have not evoked increased incidence.
3. Colo-rectal cancer: Polyps are not precursors. Habitually low fat intake may be primarily inhibitory.
BREAST CANCER IN THE PEOPLE'S REPUBLIC OF CHINA.

In 1985, the author received an invitation to visit the People's Republic of China (PRC) from Professor George Wu Huan-Zing, Director Emeritus of the Cancer Research Institute, Chinese Academy of Medical Sciences in Beijing. Thanks to an ICERT grant from the International Union Against Cancer (UICC), she was able to accept his invitation in April, 1985. In a report about the situation found, the author wrote that the UICC and the women and government of the PRC should realize there will be a spiraling increase in the incidence of breast cancer in that country within the next 15-20 years. This opinion is based on several "high-risk factors" that have been established by both epidemiologists as being associated with increased incidences of breast cancer. These are: Changed dietary habits that have resulted in earlier puberty and maturation that have led to earlier onset of menarche (younger than 12 years of age). For various social and economic reasons, women are marrying and having their first children when they are older, and late age at first full-term birth (after 30) is a high-risk factor. Potent exogenous estrogens and induced abortions are often the only way Chinese women are able to postpone beginning their families. These also increase the risk of mammary carcinoma. There is as yet no way to prevent breast cancer, but early detection, diagnosis and treatment has been proven to reduce mortality from the disease in women older than 50. Therefore, the author has been urging Chinese clinicians and the government of the PRC to begin large-scale, public-education programs to tell women about the vital importance of breast self-examination (BSE). At the same time, she urges the UICC and its member nations to assist China in purchasing mammographs and other detection devices so the government of the PRC can treatable stage.

GENITAL AND BREAST CANCER MORBIDITY IN GEOGRAPHIC EPIDEMIOLOGY II

This study discussed the incidence of breast and lung cancer in Bulgaria according to the populated towns. The towns population had two times higher incidence of breast cancer than the rural population. There was found a high correlation (r = 0.503) between the incidence of breast cancer and the size of the inhabited places. According to the crude and standardized data, the highest incidence of breast cancer was registered among women inhabiting cities with over 100 000 population. It was the urban population that had a higher incidence of lung cancer as compared to the rural population. However in the recent years a levelling among the urban and rural population was observed. There was not established any relationship between the size of the inhabited place and the incidence of lung cancer. All these effects have been found among the inhabitants of the seaside, cities and those of Sozopol district. This was due to a complex of professional, climatic and traditional peculiarity factors. This study will greatly aid the organization of a more effective profilactic of breast and lung cancer in Bulgaria.

Dept. of Pathology, Airlangga Univ. Indonesia**, Tbilisi, Georgia, German Democratic Republic, Poland.

The result of the study will be reported in this congress.

1. complaints, 2. radiography of the thorax, 3. cytostatization significant. Parameters used are:

K1 = T1
K2 = T2
K3 = T3
K4 = T4

with control groups (K), resulting in the formation of pathological changes, especially the premalignant and malignant transformation of the bronchial epithelium. The gradation of pollution will be light (p<0.05), moderate (p<0.01), and heavy (p<0.001). They were matched with control groups (K), resulting in the following matched pairs

K1 = T1
K2 = T2
K3 = T3
K4 = T4

The incidence of male lung cancer in Finland is more than three times the rate in Norway and Sweden. To study the causes behind these differences, the Finnish Cancer Registry and the Cancer Registry of Norway started in 1962 a population survey covering items about smoking habits, various cardiorespiratory symptoms, and occupational and residential history. Now, 20 years later, the Finnish cohort of 4604 men has been supplemented by information from the Finnish Cancer Registry on all cancer cases that occurred in the cohort until 1980. Information on deaths occurring until 1980 has also been included. When analyzed simultaneously with smoking, the symptoms of phlegm, shortness of breath and wheezing were all significantly associated with increased lung cancer risk. E.g., the RR for phlegm during all day was 2.0 when age and smoking were adjusted for, and 1.6 when additionally shortness of breath and wheezing were adjusted for in the model. In addition to these respiratory symptoms, also angina-like chest pain and symptoms of possible infarction were associated with lung cancer risk. E.g., the RR for possible infarction was 2.3 when age and smoking were adjusted for, and 1.8 when additionally shortness of breath and angina-like chest pain were adjusted for.
1214
areas. In all 130 samples of beans raised and in 7.1% (25-27 µ/ Kg) were 15.7% (25-55 µ/kg) respectively, and those from the control areas; in maize samples, both endemic nephropathy and urinary tract tumours are prevalent and the latter is associated with the incidence of lung cancer among the TB does not seem to be deniable. TB precedes lung cancer in most cases. Location of most cancer lesions was not the same site of TB lesions. Histological types of lung cancer were 31.2% for adenocarcinoma 31.2% for epithelialoid type, 17.9% for large cell type, 10.7% for small cell type and others. The causative relation between two diseases will be discussed.

The objective of this study is to examine excess deaths from lung cancer among the tuberculosis (TB) patients and to determine what type of correlation existed between two diseases epidemiologically. Total 4892 TB cases (males: 2724, females: 1277) newly registered in the Nagoya TB registry, 1978-1982, were examined. 4001 active pulmonary TB were followed up until the end of 1983. 446 deaths were carefully examined by medical records. Although TB patients died from TB significantly higher than those of general population, deaths from cancer all sites were significantly higher than general population: being 2 times higher for males and 3-4 times higher for females. When observed cancer by site, lung cancer showed about 5 times for males and 10 times for females those of general population. In females, higher risk was observed in ciliated cancer, but not in males. Liver cancer showed no excess risk for both sexes, but liver cirrhosis showed higher risk only in females. Nine cases of lung cancer still alive were not calculated in this analysis. Therefore, excess incidence of lung cancer among the TB does not seem to be deniable. TB precedes lung cancer in most cases. Location of most cancer lesions was not the same site of TB lesions. Histological types of lung cancer were 31.2% for adenocarcinoma 31.2% for epithelialoid type, 17.9% for large cell type, 10.7% for small cell type and others. The causative relation between two diseases will be discussed.

The introduction of a personal identification number in Denmark in 1968 which is widely used in the health services and in the public administration has greatly facilitated large scale epidemiological cancer studies based on record linkage. A linkage system for the detailed investigation of occupational cancer has newly been established in the Danish Cancer Registry. For cancer patients in active employment a job history has been established from April 1964 up to date of cancer diagnosis, using information on occupation stored sequentially in the Supplementary Pension Fund which by law covers all employees in Denmark. The occupational data includes name of company, period of employment, code of industrial branch (ISIC-code) and latest job title. The data linkage involves approximately 159,000 cancer cases diagnosed in the period 1970-1979 of which 3,563 were classified to the kidney and 9,749 to the renal pelvis, ureter and bladder. A proportional cancer incidence analysis has been performed, standardized for the effects of sex, age and calendar time on the risk of cancer. Based on this system some 120 branches of industry have been examined for the risk of cancers of the urinary tract. In general, the occupational risk pattern detected for the renal pelvis, ureter and bladder appeared to be very unlike the risk pattern for kidney cancer which indicates that fairly site-specific carcinogens are in operation in the working environment. A detailed risk assessment for cancers of the urinary tract relative to a number of selected industries will be given.
4670 A CASE-CONTROL STUDY OF BLADDER CANCER RISK AMONG TRUCK DRIVERS. Diane L. Cookfair*, Carlos R. Jain*, Arthur M. Michelassi, and Rajeev Sabharwal. Department of Social and Preventive Medicine, 2911 Main Street, Buffalo, NY 14214, Department of Cancer Control and Epidemiology, Department of Education, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, NY 14263, U.S.A.

The relationship between truck driving and bladder cancer risk was examined by means of a case-control study. Retrospective data on employment history, dietary habits, age-at-diagnosis, and tobacco use were obtained from 350 white male bladder cancer patients and 700 white male age-matched controls admitted to Roswell Park Memorial Institute between 1957 and 1965. Bladder cancer risk appeared to increase as total years spent as a truck driver increased. Truck drivers with over 20 years of exposure who were less than 65 years of age-at-diagnosis had 2.5 times the risk of non-drivers in this age category (P < .05). No other age or exposure-duration group were at increased risk of bladder cancer. Bladder cancer risk decreased with increasing Vitamin A consumption, and cigarette smoking was positively correlated with bladder cancer risk. Bladder cancer risk decreased as total years spent as a truck driver Increased. Truck driving is a contributory factor in the etiology of bladder cancer.

4671 HISTOCHEMICAL APPEARANCES OF THE EXOCYTE. V. VITAMIN CHOLESTEROL IN COMPARISON TO PREVIOUS STUDIES. K. Fekete, Institute of Hygiene and Public Health, Budapest, Hungary.

Vitamin chloride has a strong potential for hamamelis, although this potential is almost perfect in plants with few parasites, there is still room for improvement in the field of hamamelis occupational exposure. For cancer prevention, gammmarus chlortol is an important factor for a better evaluation of occupational exposure to vinyl chloride. Also, the finding of excretion in the stool for early excretion potentials in a must. Our results in the characterization of occupational exposure point out that the utilization of values for vinyl chloride in the air of the work places alone is inadequate, this simple approach being of little help when we are interested in the real workers' state of health. The addition of the determination of urinary thiodiglyceric acid is a better tool for evaluation of exposure. The author's results cover over 100 real cases. The specific adverse effects of vinyl chloride prompted us to introduce the analysis of serum bile acids with the intention of obtaining useful relationships for screening. The place of bile acids in much studies is presented. Bibliography. I. A. Monographs, Supplement 4, 1965, and in Chromatography, The State of the Art, Kuszner L., Ed., Akad. Kiado Budapest 1969, Vol.1, Pp. 667.

4672 CANCER AND GENERAL MORTALITY IN THREE VILLAGES IN SEBALOS-SZATMAR COUNTY IN RELATION TO PESTICIDE USE. Anna Paldy, N. Punke, Ilidikó Palka, Natl. Inst. of Hygiene, Budapest, Ctr. of Hygiene and Epidemiology of County Szabolcs-Szatmar, Hungary.

A complex epidemiological study has been carried out in 3 villages where the main environmental pollutants are pesticides. Village I has applied about 3 times more pesticides since the 1970's than village II and III. The morbidity data of the population, autogenous and immunologic findings have already been reported. This presentation summarizes the mortality data with special regard to cancer mortality for 1970-84 in 5 years' period in comparison with national data and that of Szabolcs-Szatmar County. In village I, there is a decrease in cancer mortality, in village II and III it remained on the same level. Gastric cancer is decreasing on county level, while in village I there is a tendency of increase. The number of death cases are limited, but a striking decrease in the age of gastric cancer mortality was observed. These findings call the attention on the importance of a long term follow up study to clear the role of pesticides and other environmental pollutants as ethiological factors in cancer mortality.

4673 DEMOGRAPHICS AND EXPOSURE, ASSOCIATED WITH HPV INFECTION OF THE CERVIX. Amy L. Melian, Roswell Park Memorial Inst., Buffalo, NY, U.S.A.

The presence of an unknown factor(s) may be the underlying prerequisite allowing HPV permissiveness in the TEC of the cervix. This factor(s) may affect immune response and possibly influence the development and expression of HPV infection. A case-control study was initiated to investigate the association between common exposure and behaviors that may affect immunological function and the risk of HPV infection of the human cervix. Study members were composed of current patients at the buffalo General Hospital family planning, genecology, and colposcopy clinic. Information about diet, cigarette use, sexual behavior, contraceptive use, obstetric history, and gynecological infection history was been collected via a self-administered questionnaire. Preliminary results showed a statistically significant (P = 0.026, P < 0.007) association between cigarette smoking and increased risk of cytopathologically and histologically evident HPV infection of the cervix. Significant results have also been noted for relatively low intake of several indicator foods of vitamin A and C and increased risk of HPV infection. A comprehensive analysis was used for the preliminary review of the data. Further analysis will be used later in the study to observe interactions and to control the effects of possible confounders.

Prostatic cancer is the second most common male neoplasm in the United States, exceeded in frequency only by lung cancer. The etiology of this disease includes such factors as diet, genetic predisposition, occupational exposures, hormonal factors, and sexual behaviour. It has been hypothesized that the sex ratio of the offspring of prostatic cancer patients may be significantly different from non-prostatic cancer patients. Through the use of a case-control study design, the association between prostatic cancer and sex ratio of offspring was investigated. Data were obtained from patients admitted to Roswell Park Memorial Institute (RPMI) between October 1, 1982 and the present. Two hundred seventeen prostatic cancer cases and an equal number of age-matched controls were studied. All controls were men who attended the RPMI Prevention-Detection Clinic. Data were collected by a self-administered questionnaire form and analyzed using stratified and multivariate analyses. The mean number of offspring for the cases was 2.71, not significantly different from the mean of 2.48 for the controls. However, the sex ratios were significantly different; 57.4 percent of the cases' offspring were sons, compared with 52 percent of the controls. The increased ratio persisted after adjustment for possible confounding factors. The results of this study may indicate the possibility of some biological abnormality of the seminal fluid or, of the sex chromosomes present in prostatic cancer patients. Further investigation of the etiologic mechanism will be necessary.


A total of 96 individuals were selected to represent the normal distribution of age and sex, smoking or not smoking, young or elderly control population; their average age was 47 years. We used the Strauss-Albertini method for estimation of the number of β-thioguanine-resistant HGPRT-deficient lymphocytes after phytohemagglutinin/PHA/ stimulation in vitro. Their ability to incorporate [3H]-thymidine in culture was detected by autoradiography /2500 cells/slide/. The number of labeled nuclei in the presence of 6-TG was counted from an average number of 600 cells/slide. The calculation of the frequency only by lung cancer. The etiology of this disease includes such factors as diet, genetic predisposition, occupational exposures, hormonal factors, and sexual behaviour. It has been hypothesized that the sex ratio of the offspring of prostatic cancer patients may be significantly different from non-prostatic cancer patients. Through the use of a case-control study design, the association between prostatic cancer and sex ratio of offspring was investigated. Data were obtained from patients admitted to Roswell Park Memorial Institute (RPMI) between October 1, 1982 and the present. Two hundred seventeen prostatic cancer cases and an equal number of age-matched controls were studied. All controls were men who attended the RPMI Prevention-Detection Clinic. Data were collected by a self-administered questionnaire form and analyzed using stratified and multivariate analyses. The mean number of offspring for the cases was 2.71, not significantly different from the mean of 2.48 for the controls. However, the sex ratios were significantly different; 57.4 percent of the cases' offspring were sons, compared with 52 percent of the controls. The increased ratio persisted after adjustment for possible confounding factors. The results of this study may indicate the possibility of some biological abnormality of the seminal fluid or, of the sex chromosomes present in prostatic cancer patients. Further investigation of the etiologic mechanism will be necessary.

4676 EXPOSURE TO BENZ(a)PYRENE AS REFLECTED IN METABOLIC CHANGES. F. Fabian, C. Marutiu, M. Ciugudean, Inst. of Hygiene and Public Health, Cluj-Napoca, Romania

Some important benzo(a)pyrene metabolites were isolated in biological samples of exposed persons and treated rats as a high-performance thin-layer chromatographic technique. Excretion of 450 and other biochemical parameters were also assessed in the cases. Our results were evaluated using the Spearman fluorometrically determined exposure level to this polycyclic aromatic hydrocarbon and of the other biological parameters.

4677 HEALTH EFFECTS OF EXPOSURE TO POLYCYCLIC AROMATIC AND ALIPHATIC HYDROCARBONS. F. Fabian, R. Cupe, S. Fenesic, D. Mihet, L. Nagy, D. Simionescu, F. Virag, Inst. of Hygiene and Public Health, Cluj-Napoca, Romania

"Stefan S.Niculau" Inst.of Virology, Bucharest, Romania

The health effects were evaluated in work places of some factories with exposure to aliphatic and/or polycyclic aromatic hydrocarbons: foundries, carbon electrode production and the rubber industry. Working conditions by spectrofluorometric analysis of benzo(a)pyrene and gas-chromatographic determination of aliphatic hydrocarbons in air samples, were controlled. At the same time the possible carcinogenic effect as well as cardiovascular and nervous system alterations were followed up in several hundreds of workers. The presumed relationship between the exposure level and health status as reflected in clinical and biological changes are critically evaluated.
4678 INCREASED INCIDENCE OF SISTER CHROMATID EXCHANGES AMONG WORKERS EMPLOYED IN THE FERROCHROMIUM FACTORY, ANTALYA, A.Acar, O.Küçük, Department of Medical Biology, Akdeniz University, Faculty of Medicine, Antalya, Turkey.

The incidence of sister chromatid exchanges in cultured lymphocytes were examined in 140 workers employed in the ferrochromium factory. SCE rates obtained from these exchanges (4.41 ± 2.07) were higher than control group (0.16 ± 0.17; p < 0.01). Depending on working place, this exposed group were divided into 5 subgroups as Furnace, Breathing, Workshop, Laboratory and Others. The mean SCE rates of these subgroups were compared with each other and control group. All the SCE levels detected in subgroups were significantly higher than control group, but highest levels were seen in the furnace subgroup. Present study indicates that Ferrochromium factory workers are exposed to genetically active chromium compounds.

4679 CANCER INCIDENCE BY OCCUPATION.
Eero Fukkala, Finnish Cancer Registry, Liskaväki 21 B, SF-00170 Helsinki, Finland

The reliable population registration systems in Finland combined with complete population-based Finnish Cancer Registry give possibilities to large scale record linkage studies in cancer epidemiology. In this study all 136,000 cancer patients diagnosed in Finland in 1971-1980 were linked with the census files from December 31st, 1970, and the occupational data before the diagnosis of cancer was searched. On the basis of the same file, the numbers of person-years for exactly the same occupational groups for periods 1971-75 and 1976-80 were calculated in Central Statistical Office of Finland. Standardized incidence ratios (SIR) for all the 33** categories of "Nordic occupational classification" and for etiologically or otherwise meaningful combinations of them were calculated for all cancer forms with satisfactory large number of cases and also for specific subgroups of those when occupational risk hypotheses to be tested exist. The internal control was made by analyzing the two time periods (and two sexes) separately. A systematic study of cancer risk by site in very detailed occupational groups may be used to generate and test hypotheses on occupational cancer. It also creates a possibility for a rapid response monitoring system on occupational cancer risk. Many associations were in accordance with those presented in the previous literature. For example the farmers had a low morbidity in most cancer forms, and the miners had in lung cancer a SIR of 208 (100 = SIR for economically active population). Some surprisingly high associations were also found, e.g. in bladder cancer SIR of 261 and in laryngeal cancer SIR of 258 for travelling salesmen.


"Tétenyi úti" City Hospital, Budapest, Hungary

It is well known that not only the prevalence of mesotheliomas but the occurrence of lung tumors at asbestos-exposed persons is higher than in the normal population. Also gastrointestinal tumors occur 2-3 times more frequently than expected. Out of 152 occupational asbestoses 7 died owing to various kinds of tumors. We demonstrated asbestos bodies within abdominal mesothelioma, pulmonary adenocarcinoma and biliary duct carcinoma proving the role of coated asbestos (i.e. asbestos bodies) in the induction of these tumors.
MINIMAL BREAST CANCER - DIAGNOSTICAL METHODS. M. O. MODI-
by A. A. Podgornoi, M. V. Chernykh, F. A. Medvedev, T. Yu. Kudin, V. N.

Diagnostic methods of minimal breast cancer (less than 1 cm) were evaluated during the last ten years.

7. Radioiography: Seventy patients were checked. It was found an 8.5% of positivity. The false negative cases were:
   . Radiologic breast density: 5 cases
   . Tumour less than 0.5 cm: 3 cases
   . Non suspicious round images: 2 cases
   . In situ lobular carcinomas: 2 cases

According to Le Gall and Michel, microcalcification: classification (Curie Institute), 11 patients were studied and tabulated as the picture shows:

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amilar</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Regular punctation</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Faint</td>
<td>33</td>
<td>7</td>
</tr>
<tr>
<td>Irregular multiform</td>
<td>4</td>
<td>14</td>
</tr>
<tr>
<td>Vernicular</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

INFRAGRAPHY: Sixteen patients were evaluated. In 3 cases the contact was completed with methylene blue, looking for surgical localization. We found 80% of positivity, or 70% of negativity false. This last 20% was correlated to breast peripherical nodes.

THERMOGRAPHY: Twenty patients with minimal breast cancer (less than 1 cm), were studied and the following results were obtained:

<table>
<thead>
<tr>
<th>Type</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>Suspicious</td>
<td>1</td>
<td>40</td>
</tr>
<tr>
<td>False</td>
<td>4</td>
<td>25</td>
</tr>
</tbody>
</table>


In the one year period we have performed more than 800 punctions of the suspect lesions of the breast under imaging control. Diagnosis were controlled by laterly performed biopsy and the cytological finding was corelated with the histological.

The highest represented diagnosis was the cyst, than fibromas and fibroadenomas, lymphomas which were followed by adenocarcinomas, scirrhous ca., and at last intracystical papilo carcinoma. The corelation between cytological and histological finding was high. We didn't perform the biopsy of the cyst, but only the punction was done. The intracystical papilo carcinoma was not seen mammography, but the cytological finding of the material obtained by the punction was positive.

All the scirrhous carcinomas were seen by the method of imaging doesn't matter of the location, and adenocarcinomas were badly seen if their location was in the adipous tissue. They were all seen on mammography, and after that the punction under control of imaging could be performed. Adenocarcinomas located in the glandulary tissue were badly seen on mammography, but very good by the method of imaging.

CLINICAL AND INSTRUMENTAL EXAMINATION IN BREAST CANCER. REPORT OF ISTITUTO NAZIONALE TUMORI OF NAPLES. G. D'Orio and G. D'Alueto, Istituto Nazionale Tumori "Fondazione Pascale" Naples, Italy.

The Authors refer about the diagnostic technique experimented at the Istituto Nazionale Tumori of Naples in more than 3,000 cases of breast cancer observed between 1973 and 1974. The diagnostic technique used are: clinical examination, mammography, telethermography, ecography, diaphanoscopy and cytology.

No one of these single technique can give the exact diagnosis; only a integrated diagnostic protocol provides a specific and reliable diagnosis.

The above mentioned techniques are discussed in details, also considering the clinical stage of the disease.
MAMMARY LESIONS CAUSED BY MALIGNANT LYMPHOMAS. I. Merics, P. Peter, M. Szanto, National Institute of Oncology, Budapest, Hungary

According to literature data the primary non-Hodgkin lymphomas (NHL) of the breast figures out 0.12-0.53 per cent of all breast malignancies. Similar rate is found in the so-called secondary breast lymphoma lesions developing as part of the disseminated NHL. In Hodgkin's disease both the primary and secondary mammary lesions are considerable less frequent. In our Institute we found no primary breast lymphoma among 120 NHL patients, the number of secondary cases is 2, i.e. 1.7%. Among 180 patients with Hodgkin's disease no primary breast lesions were seen, secondary manifestation was detected in 4 patients (2.2%). Physical examination revealed smaller tissue overgrowth, and because of the associated lymph node changes it can be hardly distinguished from the carcinoma. The mammography shows a lesion of uneven edge, similarly to the picture of breast cancer or mastitis carcinomatosa. Thermography proves a hyperthermic focus in some cases. The results of aspiration cytology show fairly great variation. Histology should always be made when possible since it gives the most reliable diagnosis. In the primary form surgery + chemotherapy is applied, in secondary form only chemotherapy depending on the status of the patient. The mammary lesion occurred on average 55-60 months following the establishment of diagnosis in our NHL patients, in those with Hodgkin's disease after 48-108 months, respectively.

MELANOMA METASTASES IN THE MAMMARY GLANDS. E. Szabo, Gy. Liszka, L. Molnár, National Institute of Oncology, Budapest, Hungary

The development of metastases of extramammary malignant tumours into the mammary glands is very rare, till 1983 about 250 cases were reported on. According to the data of literature, in one fifth of the cases the breast metastasis was the first sign of a primary tumour of another localisation. The incidence of melanoma, a tumour most frequently metastasising into the breast, is about 20-22%. According to the literature and our own data the development of breast metastasis in case of disseminated melanomas is about 0.81-0.9%. The complex breast examination (physical examination, mammography, aspiration cytology, thermography, mammography and aspiration cytology) can mostly detect only the malignancy but does not indicate the metastasis. This can be suspected due to some lesions of the breast in case of a known primary tumour. The aspiration cytology can give a correct diagnosis in melanoma but in most cases only histology leads to its establishment. In our case the breast metastasis of the 3-year long existing and 9-month disseminated skin and lung metastases melanoma was already suspected by the clinical, thermographic and mammographic examination but it became evident only with cytology. In spite of chemotherapy, the mammary lesion gradually progressed and ended in death.

COOMPARATIVE ANALYSIS OF MAMMOGRAPHY AND CLINICAL EXAMINATION VALUE IN OCCULT BREAST CANCER DIAGNOSIS. M. Musanović, H. Babić, M. Softić, Institute of Radiology and Oncology, Sarajevo, Yugoslavia

Mammography and clinical examination value have been analysed in 104 occult breast cancers. The accuracy of mammography has been 75.5%, and of clinical examination 56.5%. Mammography was more effective for small tumours and for those with uninvolved lymph nodes, less invasive forms, and in older women; but in clinical examinations the results are conversed. In 23.7% tumours, we found out microcalcifications, as the sole signs of malignancy.
Diagnostic procedures to establish and surgical techniques to treat 34 patients with minimal breast cancer up to 5 mm in diameter.

After the introduction of the routine mammography in our Service, in 1974, 34 patients had the diagnosis of minimal breast cancer, representing 5.0% of the total number (685) of mammary carcinomas treated at the same period. Six (0.9%) were lobular in-situ, eleven (1.6%) intraductal and seventeen (2.0%) invasive, all of them up to 5 mm, in diameter. The clinical pictures that led to the final diagnosis included breast lump nine times, nipple discharge six times and Paget's eczema five instances. In fourteen other patients, the neoplastic lesion was found through k-ray specimen biopsy in areas where groups of microcalcifications were identified on mammograms.

The surgical treatment given to the patients included simple mastectomy in one case, bilateral subcutaneous mastectomy in five instances, two of which extended to axillary lymphadenectomy on the affected side; nine times the subracial mastectomy (Auschincloss technique) was performed and in ten cases the Paget's modified procedure. In nine instances, the quadrantectomy with axillary clearance was executed. In 30 patients with axillary lymphadenectomy performed no lymph-node involvement was found. Three patients presented malignancy on the opposite breast. All the group is alive, with no evidence of disease. This study shows the importance that a correct mammography can reach in order to detect an early and curable breast cancer.

Ultrasonography examination of the breast provides considerable information about the tissue composition, detection and diagnosis of a variety of benign conditions such as fibroadenomas, fibroadenomas, duct ectasia, mammary dysplasia, fatty infiltration and is particularly reliable in the detection of cysts and liquid filled ducts greater than 2 mm where its accuracy is greater than 98 percent. In combination with physical examination ultrasonography allows the identification of 95 percent of malignant lesions over 1 cm in diameter. The smallest carcinoma so far detected was 5 mm in diameter and was visualized because of the high level of surrounding echoes resulting from advanced fibroadenomas. Because no ionizing radiation is employed, it is a safe examination and may be performed and repeated frequently in women of all ages, particularly in young women with nodular breasts due to dysplastic changes.
WEDNESDAY • AUGUST 27 • AFTERNOON

K-49: DIAGNOSTIC IMAGING (BREAST)

4693 STUDIES ON CLINICAL, HORMONAL AND PATHOLOGICAL CORRELATIONS OF PRENEOPLASTIC LESIONS OF THE MAMMARY GLAND

Oncological dispensary, Vratza, Bulgaria.

The investigation includes 50 women over the age of 20 years - forty (40) with preneoplastic lesions and ten (10) controlled. To these women are implemented a clinical examination with a complete blood test, mammographies, fine-needle aspiration and exfoliative cytology, histological examination. Simultaneously the direct radioimmunological determination of the serum level of FSH, LH, estradiol, progesteron and prolactin was carried out. There was made a comparison of the possibilities of applied methods for early purpose and the diagnosis of mammary preneoplastic changes. The presence of hormonal imbalance in the examined patients shows that this is one of the reasons, which furthers the development of mammary dysplasia. The results of this investigation can be used for purposeful prophylaxis of preneoplastic lesions.

4694 ROENTGENOMORPHOLOGICAL STUDIES ON THE EARLY, PRECLINICAL FORMS OF BREAST CANCER

Chr. Popmichailova, and Zl. Kolev.
Medical Academy, Sofia, Bulgaria.

Under study were 45 women with early forms of breast cancer. They were diagnosed by the method of xerography of the breast on grounds of -microdeposits of calcium and "prominent ductal model". All cases were subsequently operated on and microscopically studied. An opinion has been expressed about the important role of calcium in the prolific and malignant processes in the breast. It has been pointed out that the method of xeromammography should be regarded as valuable presbiopsy method in the diagnosis of early, preclinical forms of breast cancer.

4695 RESULTS OF COMPLEX DIAGNOSIS OF BREAST CANCER AT STAGE I-IIa

K-K. Madich, G.N. Khakhanashvili, M.V. Berozashvili, A.V. Sikharulidze, R.G. Khudzhadze,
State Doctors' Training Institute, Tbilisi, USSR.

Efficacy of clinical, x-ray, thermovision and cytological methods of diagnosis was studied in 610 patients. Clinical diagnosis at stage I was correct in 76 % of cases, with diameter of neoplastic nodule in most cases not exceeding 0.5-1 cm. Doubtful diagnosis, i.e. possible cancer, in 12.8 %, erroneous diagnosis in 11.2 % of patients. In stage II patients the results were 93.4 %, 2.4 % and 2.2 %, respectively. X-ray diagnosis in stage I patients was correct in 62.6 % of cases, doubtful in 22.9 %, erroneous in 14.9 %. In stage II patients the results were 93.9 %, 7.2 % respectively. Thermographic diagnosis in stage I was correct in 72.1 %, doubtful in 8.1 %, and erroneous in 19.1 %. In stage II the results were 90.8 %, 2.5 %, 6.7 %, respectively. Correct cytological diagnosis in stage I patients was in 62 % of cases, doubtful in 22.8 % and erroneous in 15.2 %. In stage II patients the results were 78.9 %, 12.9 % and 8.2 %, respectively.

4696 COMPLEX SCREENING FOR CARCINOMA OF THE BREAST WITH A SINGLE-VIEW XEROMAMMOGRAPHY

Chr. Popmichailova, Zl. Kolev, and J. Kuzmanov.
Medical Academy, Sofia, Bulgaria.

A schedule has been presented of the stages of the complex screening, applied by the authors. The possibility of the diagnosis of the early forms of cancer as well in the conditions of complex screening, where the determining method is the single-view xeromammography. Interesting data have been presented from the screening about the involution, structural readjustment (changes), productive formations, unsuspected secretion, papillomatosis, axillary lymphadenitis, prominent ductal model and the calcifications in the breast in the different age groups. An opinion has been expressed about the diagnosis of the early forms of cancer in the conditions of the screening and the healing of peculiar findings in cooperation with other profile experts.
**MONOCLONAL ANTIBODIES AGAINST HUMAN GASTRIC CARCINOMAS.**

M. Ohashi, K. Asada, K. Lauer, T. Okabe*, and T. Morita**

First Dept. of Surg., Tokyo Women's Med. Coll., Tokyo, Japan

**Histocompatibility leukocyte antigen-6 (HLA) typing in breast cancer.**


Three different monoclonal antibodies (MAbs), FP-1, FP-2, and FP-3, were produced by immunizing a Balb/c mouse with human fetal pancreatic cells. Reactivities of FP-1 to normal and cancerous pancreatic tissues were examined immunohistochemically, using avidin-biotin peroxidase complex method on formalin-fixed paraffin-embedded sections. Immunohistochemical analysis was performed on PAS-extract from normal pancreatic tissues or pancreatic juice. In adult and fetal pancreatic tissues, FP-1, FP-2 and FP-3 reacted respectively with duct cells, acinar cells and islet cells. In pancreatic cancer tissues, FP-1 reacted with 15 out of 21 cases (71%) and FP-2 reacted with 2 out of 23 cases (9%) of ductal carcinomas, while FP-3 reacted with none of 21 cases of ductal carcinomas and 3 out of 5 cases of islet cell tumor as well as 8 out of 13 cases of adenomas (5 malignant thyroid carcinomas, 4 gastrointestinal carcinoids and 4 pancreatic islet cell tumors). The reactivity of FP-2 was infrequent with 6/20 adenomas and 0/12 carcinoids. In addition, carcinoid tumors (2/2) and a neuroblastoma (1/1) were reactive. Thus, FP-1 reactivity was found in the 0-40% saturated ammonium sulfate precipitable material. On the gel filtration by Sepharose 4B, FP-1 and FP-3 reactivities were found in the 0-40% saturated ammonium sulfate precipitable material. By use of western blotting analysis after SDS-polyacrylamide gel electrophoresis, FP-1 and FP-3 reactivities were observed broadly in the high molecular region, while FP-2 reactivity was found in the 500 molecular-weight region as a single band.

**MONOCLONAL ANTIBODIES WHICH DISTINGUISH SMALL CELL LUNG CANCER FROM OTHER LUNG CANCER.**


University of Tokyo, Third Dept. of Internal Med., Tokyo, Japan

We developed a mouse monoclonal antibody TS-4 immunizing Balb/c mice with small cell lung cancer tumor lines maintained on Balb nu/nu mice. TS-4 is of IgG1 subclass and recognizes a 76,000 dalton molecule on cell membranes. In cell lines it reacted with small cell lung cancers but with none of squamous cell or adenocarcinomas of the lung. It also recognized neuroblastomas but not melanoma cell lines. In surgical materials TS-4 stained 14/14 small cell lung cancers with ABC method on frozen sections. None of conventional squamous cell lung cancers (0/20), nor adenocarcinomas (0/20) showed staining. In addition, carcinoid tumors (2/2), and a neuroblastoma (1/1) were reactive. Thus, TS-4 is specific for "APUDOMAs." The antibody did not react with tissues, lung, liver, pancreas, kidney, bone marrow or spleen. Interestingly, TS-4 reacted strongly with central nervous tissues. The antigenic determinant was heat labile and trypsin sensitive but neurelastin resistant and probably a peptide. The antigen was purified from human cerebrosides by 50% ammonium sulfate precipitation, DEAE ion-exchange chromatography, affinity chromatography with fixed TS-4 antibody, and gel permeation chromatography. The antigen from human brain had an 13,000 dalton molecular weight. These observations suggest that they are similar molecules and strengthen the previous notion that small cell lung cancers show the differentiation towards nervous tissues. The high specificity and reactivity of TS-4 for small cell lung cancers indicate that it may be of great diagnostic as well as therapeutic use for this cancer.
Identification of high risk breast disease by a new monoclonal anti-tumor antibody. E. J. Healey, D. F. Edwards, K. G. O'Brien and W. McIlroy, Dept. of Surgery, University of Wales College of Medicine, Cardiff, U.K.

It has been shown that if proliferative changes, especially atypia on a breast biopsy, carry an increased risk of subsequent breast cancer, if a positive history is also present, the relative risk of cancer is about 11 times normal. Accurate histopathological grading of the various atypias is difficult and requires a considerable amount of time.

We have examined paraffin biopsies of benign breast disease showing changes ranging from adenosis to carcinoma-in-situ by immunohistochecmical techniques using 32MA, a new monoclonal antibody. The results show that the antibody stains 52% of breast carcinomas but does not stain 'normal' breast tissue. Only a small percentage of non-proliferative benign breast tissue stains but the degree of atypia in proliferative changes positively correlates with the antibody staining.

This suggests that this antibody may be useful in categorizing degrees of atypia.
The local immune cell reaction prognostic possibilities in oncological patients (exploiting various methodological approaches to the investigation)

B.T. Bilinskaya and N.A. Volodko, Lvov Med. Inst., USSR

178 breast cancer patients were observed in the process I and II stages. They were investigated in three parametrical lymphoplasmoclastic cell infiltration (LPCI) and of the peripheral blood lymphocytes on the III stage during three years course of the disease after the radical operation. The above observation has proved the informative possibilities of the morphological evaluation of the LPCI of the tumours by histochemical and histochemical methods to be insufficient as a prognostic test. The investigation of the LPCI combined with the tests characterizing the functional activity of the peripheral blood immunocompetent cells increases its prognostic value.

Immunological analysis of the intratumour lymphocyte functional properties gives more convincing results concerning the prognosis. The investigation of the ability to the spontaneous rosette formation and the sensitivity to the theophylline of the lymphocytes extracted from malignant human tumours of different localizations has confirmed our supposition as to their subpopulational heterogeneity and various functional activity. Therefore the functional properties of the lymphocytes extracted from the tumours should be taken into consideration while prognosticating the tumour process. It will make the prognostic more exact and promote the elaborating of effective methods of immunotherapy and prevention of tumour relapses.

Intradermal reaction with a human placental suspension for early detection of cancer

M. Corocleanu, County Hospital Brasov, Romania.

Patients with clinical symptoms suggestive of cancer were tested with a pharmaceutical placental suspension injected intradermally. 271 cases with a positive reaction were selected. From these cases 180 patients showed a semi-delayed reaction, presenting at the cytohistopathological investigation, adaptive cellular proliferation process. Amongst 91 patients the intradermal test was clearly of delayed type, presenting at cytohistopathological investigation necrotic cellular proliferation. The test is economic, easily accepted by the patients and might be used as screening test for early detection of cancer.

Immuno-diagnosis

4705 IMMUNOLOGICAL EVALUATION OF STOMACH CANCER PATIENTS. D.R. Pfreund, R.A. Foppert, M. Abu, D.R. Wohrath, R.S.L. Capellung, A.D. Varella, A.Nuio, A.C. Camargo Hospital, Antonio Prudente Foundation, Sao Paulo - SP - Brazil.

In the period 1975-1981, patients with stomach cancer were immunologically evaluated according with the following tests: Dinitrocholorobenzene (DNCB) - 154 cases; PPD; Sporotrichin, trichophytin intraduromucular - 182 patients; croton oil - 163 patients. The DNBC test is apparently the best method to evaluate the immunological incompetence in gastric cancer. Better positivity was found in less advanced gastric tumors. Patients submitted to radical gastrectomy presented an excellent turn of their DNBC test (from negative to positive reaction).

Our results indicate that up to the 3rd year of follow-up all alive patients were or became immunocompetent. After the 3rd year of follow-up, and usually in less than one year prior to death, patients revealed a decline in their immunocompetence. Gastric cancer patients are usually intensively immunodepressed.

Positivity of DNBC tests

<table>
<thead>
<tr>
<th>Year</th>
<th>Positive Cases</th>
<th>Negative Cases</th>
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<tbody>
<tr>
<td>3rd year</td>
<td>182</td>
<td>163</td>
</tr>
<tr>
<td>4th year</td>
<td>163</td>
<td>182</td>
</tr>
<tr>
<td>5th year</td>
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<td>163</td>
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4707 INTRADERMALREACTION With A HUMAN PLACENTAL SUSPENSION FOR EARLY DETECTION OF CANCER.

M. Corocleanu, County Hospital Brasov, Romania.

Patients with clinical symptoms suggestive of cancer were tested with a pharmaceutical placental suspension injected intradermally. 271 cases with a positive reaction were selected. From these cases 180 patients showed a semi-delayed reaction, presenting at the cytohistopathological investigation, adaptive cellular proliferation process. Amongst 91 patients the intradermal test was clearly of delayed type, presenting at cytohistopathological investigation necrotic cellular proliferation. The test is economic, easily accepted by the patients and might be used as screening test for early detection of cancer.

4706 THE LOCAL IMMUNE CELL REACTION PROGNOSTIC POSSIBILITIES IN ONCOLOGICAL PATIENTS (EXPLOITING VARIOUS METHODOLOGICAL APPROACHES TO THE INVESTIGATION)

B.T. Bilinskaya and N.A. Volodko, Lvov Med. Inst., USSR

178 breast cancer patients were observed in the process I and II stages. They were investigated in three parametrical lymphoplasmoclastic cell infiltration (LPCI) and of the peripheral blood lymphocytes on the III stage during three years course of the disease after the radical operation. The above observation has proved the informative possibilities of the morphological evaluation of the LPCI of the tumours by histochemical and histochemical methods to be insufficient as a prognostic test. The investigation of the LPCI combined with the tests characterizing the functional activity of the peripheral blood immunocompetent cells increases its prognostic value.

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4708 DETECTION OF TUMOR IMMUNITY BY MICROGLASS-TUBE LI-ANTIGEN ADHERENCE INHIBITION (LAI) ASSAY IN PATIENTS WITH HEPATITIS B VIRUS.
HUMORAL LEUKOCYTE ADHESION INHIBITION ASSAY WITH MYELIN基本 PROTEIN ANTI-GEN IN THE STUDY OF ORAL PRECANCEROUS STATES

G. Kövesi and B. Fekete


Kotler et al. /1978/ studied names cancer patients with leucocyte adherence inhibition assay. They examined on this study the patient as a reactivity against names cancer antigen. A lot of cancer cases developed in this group in two years, furthermore a risk factor could be supposed among the H-LAI positive cases. In our country leucoleukocyte is the most frequent oral precancerous state and malignant disease transformed in 6% of cases. 20 patients were with oral leucoleukocyte were examined with H-LAI assay. The seven positive cases have followed for two years, and we found in this time that two cancer cases have developed. These results showed that there is a risk factor in the presence of patients with oral precancerous state. The H-LAI assay can be use as an early diagnostic tool in developing of oral malignancies.

STUDY OF ORAL PRECANCEROUS STATE: WITH MYELIN BASIC PROTEIN ANTIGEN IN THE SMOOTHER MUSCLE FIBERS

K-50: IMMUNODIAGNOSIS

4710 THE CHANGE OF THE CELL ELECTROPHORESIS FOR PERIPHERAL LYMPHOCYTE IN CANCER PATIENTS

Takeshi Miki*, Koro Nakash*, Motomi Shimizu*, and Takayuki Inaguchi*, Dept. of Surgery, Tokyo Metropolitan Kanto Hospital, and Dept. of Chemistry, Tokyo Metropolitan Institute of Clinical Sciences, Tokyo, Japan

The electric charge on the surface of peripheral lymphocytes is changed when the host suffered from cancer. The low mobility lymphocyte appears and the ratio of the low mobility cells (>0.95 um/sec/V/cm) to the high mobility cells increases with significant difference statistically. This ratio (S/F ratio) obtained by cell electrophoresis of peripheral lymphocytes is very useful for not only diagnosis of cancer but following up of postoperative cancer patients. The characteristics of low mobility lymphocytes which influences to the S/F ratio have been searched in our department using full automatic apparatus for cell electrophoresis (PO-L) and the result of this research will be showed.

Materials and method: Peripheral blood was gained from 10 healthy controls and 52 cancer patients and separated by Ficoll method. The lymphocytes were divided to subgroups by adherence to plastic dish or binding function to various kind of monoclonal antibody. These subgroups were examined their electrophoretic mobility and function each other.

Result: 1. The electrophoretic mobility of NK cells belonged to high mobility area (>1.0 um/sec/V/cm) and it slightly moved to higher in cancer bearing. NK activity equally elevated in cancer patients but fall down in the end stage.
2. The mobility of monocyte belonged to low mobility area (<0.80) and shifted to lower area according to cancer stage. The phagocytic activity was also leveled down in cancer patients.
3. The main subpopulation influenced to S/F ratio may be supposed as suppressor T cells.

4711 ANALYSIS OF URINARY RENAL JONES PROTEIN FROM 110 PATIENTS WITH ORAL PRECANCEROUS STATES

B. Varga, Zs. Sós*, M. E. Barta, and T. Fleischmann, Klinik für Urologie, Budapest, Hungary

The urinary proteins from 110 patients with lymphoproliferative diseases were characterized by agarose gel electrophoresis, immunofixation, polyacrylamide gel electrophoresis, immunoelectrophoresis, isoelectric focusing followed by immunofixation, monoclonal antibodies (H/L) proteinuria was found in 60 patients (total proteinuria was 6.6–24 g/day). Kappa chains /39 cases/ were mainly in monoclonal fomas, while lambda chains /17 cases/ were found to exist mainly as dimers. Double light chain proteinuria /kappa-lambda/ existed in 3 patient's urine and gamma heavy chain fragment excretion in all but one case. The technique of isoelectric focusing in agarose followed by immunofixation has been applied to concentrated urines in all patients. The new technique achieved an increased rate of detection; BJ proteinuria was detected in 60 cases with the new procedure and in 52 by the conventional methods. The isoelectric points of BJ proteins were between 5.1 and 5.6. Many BJ urine specimens examined by both methods and a follow up study has done with the positive cases. These results showed that there is a risk factor in the presence of patients with oral precancerous state. The H-LAI assay can be use as an early diagnostic tool in developing of oral malignancies.

B. Varga, Zs. Sós*, M. E. Barta, and T. Fleischmann, Klinik für Urologie, Budapest, Hungary

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4712 EVALUATION OF A NEW SCREENING TEST FOR COLORECTAL TUMORS USING GUAIAC AND ENZYME IMMUNOASSAY

E.J. Brochard, J. Diefenbacher, J. P. Desrosier, G. Sieg, and P. L. Bégin, (1) Centre de Medicament-Unité associée au CNRS No 597-39, (2) Centre du Médicament-Bureau associe au CNRS No 597-7, (3) Centre de Médicament-Bureau associe au CNRS No 597-9, Vandoeuvre, France

The classic method of screening for colorectal tumors (cancers and polyps) entails looking for blood in stools using the guaiac test. Our study aimed to evaluate a new guaiac test, the originality of which came from its coupling with an enzyme immuno-assay (EIA) specific for the measurement of human nesmoglobin (Fecatest¹). Objectives of this new test is to decrease false positives and thus improve the positive predictive value of the screening. The population studied was suspected healthy and was chosen from subjects over 45 years of age attending health examinations at the Centre of Preventive Medicine in Vandoeuvre. The test acceptability, the impact of a diet low in peroxidase during the test period, and the importance of the enzyme immuno-assay measurement are evaluated. Over the 5770 subjects at whom test was proposed, 4376 (84%) performed it in a correct way, outlining a great acceptability in this population. 664 (13%) gave positive results to guaiac test. Thin positivity rate is higher for men than for women (20% vs 12%) but not influenced by age. 461 (20%) patients completed investigations after positive results, decreasing the overall acceptability to 80%. 15 cases of cancer and 76 cases of adenomas were found. The positive predictive value of the test (44% for tumors, 44% had benign pathology) and 34% were completely negative. As compared with literature these screening rates are high. When the guaiac test was positive, the EIA method distribution of the results are discussed and a 0.05 threshold is chosen with a ROC cureve methodology. Their positive predictive value is significantly improved for cancer (6% vs 3%) but not for polyps (20% vs 17%). Loss of information is very important in polyp screening. These results are discussed according to the general perspective of colorectal tumour screening.

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(3) Centre du Médicament-Bureau associe au CNRS No 597-7 - 9 avenue du Doyen J. Farisot-54500 VANDOEUVRE
4713 SERUM RETINOL LEVEL IN COLORECTAL NEOPLASMS.

J. Ostrowski, I. Janicki, J. Janczewska, P. Janik, and M. Nowacki,
Medical Center of Postgraduate Education and Inst. of Oncology, Warsaw, Poland

Serum retinol level (SRL) was determined by fluorometric method of Thompson in 110 healthy controls, 72 patients with benign adenomas, 25 with adenomas showing evidence of malignant change, and 114 patients with colorectal cancer. SRLs (X ± SE) in patients with benign adenomas (52.1 ± 1.6 ug/100 ml), those with adenomas (61.7 ± 3.3), and those with stage B cancer (modified Dukes' classification) (52.3 ± 3.7) were similar to those found in normals (57.4 ± 1.9). In 20 patients with stage C (48.2 ± 4.3) and in 22 patients with stage D cancer (43.7 ± 2.7) SRL was significantly lower. Among 43 cancer patients that were followed after surgical treatment, there were 21 patients whose SRL increased within 1-3 months after surgery to 50.6 ± 1.7, a value which was similar to that observed in 19 other patients 4-12 months after treatment (52.7 ± 4.3) and to that found in 20 patients followed for 2.5 years (51.6 ± 2.2). Thus, the values of SRL during the follow up returned to normal. In 12 patients treated surgically who subsequently died of metastases during follow up showed very low SRL (37.0 ± 2.6). These findings suggest that decreased SRL in cancer patients is a consequence rather than precursor of the neoplastic process. The drastic reduction of SRL might be an indicator of poor prognosis.

4714 THE CLINICAL EVALUATION OF T2109 (TA-4) IN SQUAMOUS CELL CARCINOMRA IN CERVICAL CANCER.

A. Konno, R. Ono, H. Moriyama, M. Kioura, and M. Kihara,
Rui-Kyoko-Oncol. Chir. Fac. Tokai, Japan

Some trials have been done on the use of TA-4 as a tumor marker for diagnosis of management of the treatment of squamous cell carcinoma. There are many reports on the tumor markers in uterine cervical cancer and the utility value of them is important. However, some of the markers are of specific requirements to be used.

In a number of squamous cell carcinomas was purified from tissues of human cervical squamous cell carcinoma by Kioura et al., and this is expected a tumor marker of several squamous cell carcinomas. In order to study the clinical significance of TA-4, serum TA-4 level was measured in 152 patients with cervical cancer and was compared with the levels of serum carcinoembryonic antigen (CEA) and ferritin. TA-4, CEA and ferritin were determined by radioimmunoassay, radioimmunoassay and latex particle immunoassay, respectively. Serum TA-4 levels of normal women and patients with benign gynecological disease were less than 26 ng/ml. There was correlation between positive (over 2.0 ng/ml) rate of TA-4 and clinical stages in cervical cancer, and high values of TA-4 were found in recurrent cancer and progressive cases. On the other hand, the levels of TA-4 were within normal range in the cases that were considered recurrence. This results indicated that changes were almost parallel with the spread of cancer up the effects of therapies. TA-4 was more specific than CEA or ferritin; however, this test was not useful for early diagnosis of cervical cancer. From these results, it was suggested that TA-4 is useful for monitoring of progressive cervical cancer and early diagnosis of the recurrence.
CONCLUSIONS: CA 125

In all cases a complete remission at the moment of second-look operation (18 pts).

Method: CA 125 is assayed by immunoradiometric method: normal value is < 10 U/ml.

Results:

1° Under chemotherapy a good correlation between clinical course is demonstrated in 73/82 pts (90%).

2° Surgical restaging: CA 125 levels is < 10 U/ml either in 19/19 pts with no residual tumor and in 12/13 pts with small peritoneal granulations less than 2 cm.

But CA 125 levels is > 10 U/ml either in 19/19 pts with tumor.

The complementary immunohistochemical characteristics of combined CEA and TPA serum monitoring was confirmed in previous studies in order to early diagnosing colorectal cancer recurrences during the follow-up after radical surgery. A more concrete way to handle data in order to clinical decision making is needed by the complexity of the algorithms, fifty-four colorectal cancer patients submitted to radical surgery of primary tumor (colorectal) (25%. Dukes' Stage A=15, B=15, C=15; D1=6) were biweekly monitored by serum CEA and TPA test (commercial and home kits) and checked by clinical examination, chest Xray, colrography and CT scan with guided needle biopsy of suspicious lesions. These procedures were carried out before the expected interval in case of 3 consecutive CA and TPA elevations. Fourteen local or distant recurrences were observed. Of the 14 patients who had previously had an operation: 7 were documented recurrence. Of the 70% who had an operation: 70% were tested at inappropriate time periods). 8 were negative. (Two were false negative and 6 were tested at inappropriate time periods).

Although other tests often complemented the CEA they were generally less sensitive for early detection. Selective use of these was however frequently documented site and extent of recurrence. The detection sensitivity of these other tests was highest with CT (83%), followed by BE (56%) and E (46%). The selected other studies are also essential for early detection and frequent restaging at short intervals. The selected immunological characteristics of combined CEA and TPA (commercial and home kits) were plotted and the Dalen and All Program was used to detect areas where the above curves and their standard deviations and equations. An area of 1.00 by this technique indicates a perfect test while an area of 0.50 describes a test no better than chance.

Hypotheses testing of difference between these three ROC curves, though not standardized in the principles of ROC analysis, was carried out by the areas (chi-square test), between the equations coefficients (Student's t test) and between equations constructed (Chi square=rejecting H0). None of these null hypotheses reached a statistically significant alpha value.
Pre-operative CEA levels were measured in 100 patients with large bowel carcinoma and serial post-operative determinations were performed in the 64 who were operated for cure. The follow-up period was 3½ - 8 years. All CEA measurements were done consecutively with a RIA (Roche). The determinations were subsequently repeated in one batch with an EIA (Roche) based on a monoclonal antibody. Both assays showed a similar number of "false-negative" CEA levels pre-operatively - varying from 69% in aneuploid (AN) Dukes' A to 84% in AN Dukes' D tumours, and from 75% in near diploid (ND) Dukes' A to 40% in ND Dukes' D tumours. The sensitivity for detecting recurrence in patients with tumours of either ploidy pattern was slightly better with EIA than with RIA. With the former 64% of the patients had elevated levels (median lead time before overt clinical manifestation, 3 months) compared to 59% (median lead time, 4 months) with RIA.

The difference between the AN and the ND group was shown somewhat more clearly with EIA, the sensitivity in the AN group being 79% and the median lead time 7 months compared to only 13% and 2 months in the ND group. The corresponding figures with RIA were 71% and 7 months for the AN group and 65% and 1½ months for the ND group. However, all but one of the patients with ND DNA pattern who showed recurrence-associtated CEA elevation with EIA also had an elevated level pre-operatively. We conclude that all patients operated for cure (i.e., Dukes' stages A, B, and C) should be followed by regular CEA measurements post-operatively if they had an elevated CEA level prior to operation.

(Supported by the Norwegian Cancer Society).

CA-125 antigen was assayed in 156 patients suffering from ovarian carcinoma with various histological types. Among 80 patients with clinical evidence of disease, 42 had serous adenocarcinoma (A-K) with CA-125 ranging from 6 to 4450 u/ml, whereas 11 with endometroid A-K ranged from 31 to 500, and 15 with mucinous A-K from 6 to 500 (6 abnormal values). Only one patient among 76 without clinical evidence of disease had CA-125 above 35 u/ml limit. Follow-up studies (at least 5 assays) of 80 patients showed a good correlation in 71 cases.

Twenty-one patients already in CR at the beginning of the study had permanent low levels for more than two years. When patients relapsed after complete remission (28 patients), elevation of CA-125 was seen 1 to 5 months before clinical evolution in 15 cases, and simultaneously in 13 patients.

In 13 patients CA-125 levels fall at the same time as obtention of CR, although normal values did not guarantee real surgical proven CR. Histological types did not modify the biological response. Thus CA-125 antigen does seem to keep its promise, and generally allow a good monitoring of this cryptic disease.
ENOSOPHIC LYMPHOSCINTIGRAPHY WITH SPECT. Yoshihide Kino, Shigeo Hori, Hiroshi Shoda, Kazuhiro Ichinose, Susumu Ito, 1st Dept. of Surgery II, Okayama Univ. Med. Sch., Okayama 700, Japan

Endoscopic lymphoscintigraphy with single-photon-computed tomography (SPECT) produces images with improved contrast compared with conventional images. Endoscopic lymphoscintigraphy: graphene was performed using Tc-99m-Rhenium colloidal on 11 patients with carcinomas of the stomach. The day before the operation, each patient was injected 4mCi of the colloid into the submucosal layer of the stomach through a gastrofiberscope. SPECT was performed 3 hours after the colloid was administered using a Siemens TLC-500 rotating gamma camera. The same time, 400-500 mCi of Thallium-201 in 5ml water, was ingested by the subject as an imaging agent of the stomach. Then, SPECT of MC, Tc-99m-dimercaptosuccinylglycine (DMSA) was injected intravenously to visualize the kidneys. In some cases, 5mCi of Tc-99m-macroaggregated albumin (MAA) was administered intravenously to visualize the lymph nodes and to obtain an image of each organ. Each organ was visualized by setting the region of interest. The images were then reconstructed and composited using a SCINTIPAC-5000 Computer (Siemens). After the operation, Tc-99m activity in resected lymph nodes was determined with a calibrated well counter and expressed as cpm (counts per minute) per milligram. The paraaortic lymph nodes showed conspicuous concentrations of radioactivity in seven out of 11 patients. The upper flow of the colloid was examined in two patients. Transpleural lymph flow could be detected in both of them. The lymph nodes in the minor curvature of the stomach were markedly enhanced in 8 patients. SPECT could visualize the lymph flow from several areas of the stomach multilaterally. Conclusion: Endoscopic lymphoscintigraphy with SPECT was thought to be helpful for detecting and depicting the lymph flow of the stomach.
DIFFICULTIES IN STERNUM SCINTIGRAM INTERPRETATION OF BREAST CANCER PATIENTS. O. Esik**, M. Rajtár**, K. Ormandi*, and +J. Kalemen*

*Department of Radiology, and **Department of Nuclear Medicine, University Medical School, Szeged, Hungary

It has been found a relatively high incidence of sternum abnormalities (13.3% of patients) in scintigraphic examination performed on 367 breast cancer patients. The differential diagnosis could generally be established on careful analysis of scintigrams (morphology, localization) and clinical data (course, spontaneous pain, irradiation, trauma), but some of the problems were solved by radiological studies. Apart from three of present unexplained cases there have been 26 metastases and 20 other abnormalities of non-tumourous origin. Ten of 26 metastases appeared as solitary bone metastasis. Based on clinical, scintigraphic and radiological observations the authors suggest a non-conventional yet possible source of solitary sternum metastasis: direct connections between the sternum marrow and the lymph paths of breast, excluding blood circulation.

DETECTION AND DEVELOPMENT OF BONE METASTASES AFTER PRIMARY TREATMENT IN BREAST CANCER.

J. Dietl, M. Karthaun, H. Schwad, S. Ludwig, and J. Kubil, University Hospital, Dept. of Obstetrics and Gynecology, Heidelberg, F.R.G.

The skeleton is the most common target organ of distant metastasis in breast cancer. In a retrospective study 200 patients have been analysed for occurrence, detection and prognostic factors of osseous metastasis. Sensitivity and limitation of different established diagnostic methods were compared.

In 86% of the cases bone metastases were confirmed by abnormal skeletal scintigrams and X-rays in routine follow-up, and only in 14% by X-rays performed in patients with clinically or chemically abnormal symptoms (e.g. pain, hypercalcemia, elev. alk. phosph.).

Median time intervals between primary treatment and subsequent manifestation of bone lesions were 19 months in node positive and 28 months in node negative patients. Only 12% of solitary lesions and 19% of multiple bone metastases were confirmed.

The number of bone metastases, time of occurrence and prognosis were directly correlated with the lymph node and Hormone receptor status.

We believe that the ideal screening for breast carcinoma at the time of primary treatment includes a full skeletal survey and bone scintigraphy. This intensive screening is also necessary in the follow up of high risk cancer patients.

GALLIUM-67 SCINTIGRAPHY IN LUNG CANCER.

G. Szekeres*, A. Tarkowska**, Department of Nuclear Medicine and Clinic o. Pathological Anatomy** Medical Academy, Luklin, Poland

Gallium scintigraphy of chest was performed in 29 patients with pulmonary infiltration and suspicion of lung cancer. Clinical observation and laboratory findings revealed in 14 of those cases bronchial cancer, in 12 bronchopneumonia and in 3 infiltrative tuberculosis. Gallium uptake in region of pulmonary infiltration was seen in all cancer patients, 10 with bronchopneumonia and 1 with tuberculosis. Degree of accumulation was determined visually using liver activity as a reference. Activity within the lesion was greater or equal to liver activity in 10 cases of cancer and 1 of tuberculosis. Lower gallium concentration was stated in 4 cancer patients and 10 patients with bronchopneumonia. So gallium uptake in pulmonary infiltration was present in 2 cases of tuberculosis and 2 with bronchopneumonia. Gallium accumulation in mediastinum was observed in 12 patients with cancer and 1 with tuberculosis.
BONE MARROW IMAGING WITH NANOCOLLOID IN HEMATOLOGICAL DISEASES. K. Jäntti, P. Karjalainen, J. Puttinen and E. Leskela. University Central Hospital of Kuopio, Kuopio, Finland.

Human serum albumin derivative nanocollod (Solco-Nanocoll) was used for bone marrow imaging in 52 patients with a previously diagnosed or suspected hematological disease. The distribution pattern of bone marrow uptake and the number of focal lesions within the uptake of static regional scans were used for classification. 63 patients: 1 malignant disease, 22 non-Hodgkin lymphome (NHL), 9 Hodgkin's disease, 7 acute leukaemia, 6 chronic granulocytic leukaemia, 7 primary myelofibrosis, 3 essential thrombocythaemia, 4 multiple myeloma, 3 lympho-epileptic syndrome, 3 chronic lymphocytic leukaemia. In 57 of these bone marrow uptake distribution pattern was extended showing moderate or advanced narrow expansion. Focal lesions were found in 15 of these both with or without malignant cells in bone marrow biopsy samples. Central marrow activity was absent in very few patients with primary myelofibrosis, blastic crisis of GGL and hypoplastic anaemia, respectively. Normal uniform marrow uptake was found in 3 patients with NHL and central normocytic thrombocythaemia. In addition of nine patients with non-malignant condition had normal uniform accumulation. 4 patients with non-malignant condition had focal accumulation defects in selectigraphy. Focal defects in the marrow scintigraphy may be due to tumor cell infiltration of the marrow. However, there are many other causes for focal defects as well and no clinical significance of these lesions needs further investigations.

DISTRIBUTION OF NANOCOLLOID IN HEMATOLOGICAL DISEASES

RADIOMUNOIMAGING OF COLORECTAL CANCER: ECT VS TCT IN LOCAL RECURRENCE. K. Schmidbauer, H. Donecke, E. Hoser, Depts. of Radiology and Surgery, Klinikum Grosshadern, Munich, FRG.

The conventional imaging modalities (X-ray, ECT, US) are sometimes insufficient in the follow-up of patients with colorectal cancer: therefore radiomunoscintigraphy (RIS) using monoclonal antibodies, with its methodological advantages of functional imaging was comparatively investigated.

26 patients were included in the study. All of them had a history of colorectal cancer with suspicion of local recurrence: Serum tumor markers were elevated (CEA and CA 19-9). In 16 patients, local recurrence was histologically documented. Before surgery, RIS was performed using radioluidated Fab' fragments of different monoclonal antibodies: Anti-CEA, Anti-CA 19-9 or a cocktail of both. 0.5 - 2 mg protein, labelled with 55 - 123 MBq 111-In were injected i.v. without any side-effects. Imaging was performed twice up to 7 days post-injection using a rotating gamma camera with a 1.2-inch-crystal for emission computed tomography (ECT). For anatomical landmarking, the second study with 99m-Tc-DTPA or 99m-Tc-DPD followed each RIS without using the patient. TCT and RIS-ECT were evaluated by two unbiased observers.

true pos. false neg. true neg. false pos

RIS-ECT 15 1 2 4

ECT 8 8 3 1

Conclusion: Both methods have a moderate specificity only. RIS-ECT yields a much higher sensitivity in patients with colorectal cancer and suspicion of local recurrence. Therefore RIS with ECT can be recommended in the follow-up of colorectal cancer.
PULMONARY METASTASES FROM THYROID CARCINOMA. CLINICAL, RADIOLOGIC AND SCINTIGRAPHIC ASPECTS.

Diagnosis of Metastatic Disease. A. Garcia, DC, cut, GE Borra, LG Raffaelli, LA Mattos, Rosario R. Lima, Ana Maria, and F. Mancini, Buenos Aires, Argentina.

Radioimmunoscintigraphy (RIS) was done in the clinical routine of ovarian cancer management. N. Prinz, M, PM, KR, MR, Evaluation of RIS in 161 patients. The results of this study were compared with the diagnostic procedures, the main goal being to determine the value of RIS in these patients. The results obtained by the scintigraphers were compared with the clinical findings as well as with the other investigations (ultrasound, chest x-rays, etc.). The patients were prevented from taking radioactive substances for 24 hours after the investigation. Scintigraphic images were obtained in at least two different planes of the patient, namely, anterior and posterior. These images were compared with the clinical findings and with the findings of other investigations (ultrasound, chest x-rays, etc.). The results obtained by the scintigraphers were compared with the clinical findings. The RIS was found to be a valuable tool in the diagnosis of ovarian cancer. However, it had its limitations, and it was not possible to rule out ovarian cancer in all cases. The results of this study were compared with the findings of other investigations (ultrasound, chest x-rays, etc.). The RIS was found to be a valuable tool in the diagnosis of ovarian cancer. However, it had its limitations, and it was not possible to rule out ovarian cancer in all cases.
**K-52: Diagnostic Imaging I**

**4740** The Hemostasis System Importance in Prophylaxis of the Thrombotic Complications in Stomach Ulcer

E. Lyapunov, I. Lyutin. The Center for Urology Research of the USSR AME, Siberian Branch, Tomsk.

The functional test with double local hypoxia of upper extremity allowing to study hemostasis sistor reserve possibilities was developed. The tension of the functional activity of the anticoagulant blood system accompanying the depletion of the vascular platelet component hemostasis and fibrinolysis reserve possibilities in the process of the malignant tumour development presented in patients with carcinoma of the stomach. These changes showed the thromboembolic state in patients with non effective prophylactic correction.

According to radioscintigraphic data with Tc-99m-MAA-Labeled in patients of II, III, IV stomach cancer the lower extremity phlebothrombosis was observed in 4, 8, 19% cases respectively. The specific correction of the hemostasis system disturbances together with the physical muscles load was performed in all patients during 10 days after radical operations. The study of the functional hemostasis system state after therapy pointed to the reserve system possibilities and thromboembolic state abotion. No patient observed longitudinal phlebothrombosis growth and new thrombotic locus according to scintigraphical data with Tc-99m-phosphorine.

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**K-53: Diagnostic Imaging II**

**4741** Preoperative Staging of Renal Cell Carcinoma

D. Kropfl, R. Hartung, M. Meyer-Schwickerath, M. Kropfl, M. Kropft. Dept. of Urology, University of Essen Medical School, FRG

Renal carcinoma most often is diagnosed by intravenous urography (IVU). Ultrasound evaluation, CT-scanning and angiography are done in addition. In a series of 219 patients with renal tumors IVU alone led to diagnosis of 26/91.7%. The correct diagnosis of a solid renal mass was established by ultrasonography in 124 (56%) patients. CT-scanning identified a solid tumor in 222 (99.4%) cases whereas renal angiography showed a renal mass in 222 (99.4%). Preoperative staging by ultrasound was correct in 222 (99.4%) 55% of the patients and staging by CT-scanning in 222 (99.4%) 45%. Ultrasound evaluation showed a sensitivity of 47% and a specificity of 96% for imaging of lymph nodes while CT-scanning had a sensitivity of 40% and a specificity of 96%. Preoperative imaging of vascular infiltration and tumor thrombus extension by ultrasound had a sensitivity of 46% and a specificity of 91.4%, whereas CT-scanning showed rates of 97.5% and 87.6%. The cranial extension of tumor thrombus in the vena cava was reliably discovered by ultrasound. Thus abdominal ultrasound allows safe diagnosis of solid tumor in the kidney, identification of tumor in lymph nodes and tumor extension into the vena cava. Consequently 15% patients had tumor-nephrectomy after IVU and abdominal ultrasound only. In all 45 the preoperative diagnosis of renal carcinoma was proved histologically.

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**4742** Comparative Imaging Procedures in the Diagnosis of the Masses of the Neck

J. Gonczl, P. Goblyo, L. Cseh, I. Szili, P. Kras, Postgraduate Medical School, Roentgenological Institute, Otorhinolaryngological Clinic, Department of Pathology, Budapest, Hungary

So cases of neck masses of different origins have been investigated. Following the complete medical and otorhinolaryngological examination various imaging procedures have been performed with ultrasonography the volume and the echo-structure of the masses have been determined and some of the biopsies have been performed ultrasonographically guided. Fine needle aspiration have been followed by cytological examination. Both ultrasonography and thyroid isotope examinations aimed to determine the connection of the masses with the thyroid gland. Thermography has been carried out in order to reveal the heat production and the function of the mass. The medical examination could prove hematological alterations. These procedures detected metastases as well. Rational diagnostic strategy and tactic are elaborated on the basis of the specificity and sensitivity of the different diagnostic imaging methods.
CHROMOLYMPHOGRAPHY AND LYPHOGRAPHY IN UTERINE CERVICAL CANCER. J. Gandros, and E. Marques.

Radiology Department, R.C. Cunhaio Hospital, Antonio Prudente Foundation, Sao Paulo - SP - Brazil.

The value of lymphography and chromolymphography in the pre and tran-operatice evaluation of lymph nodes in uterine cancer cases were studied in the following stages: one case in stage I, 34 cases in stage II, 6 cases in stage III, and one case in stage IV. Lymphography was performed in 38 cases and chromolymphography in 56 cases. The authors emphasize the great importance of both methods in the clinical staging and in the node dissection during surgery.
PULSED NUCLEAR MAGNETIC RESONANCE (NMR) STUDIES ON MALIGNANT LYMPHOMAS & METASTATIC LYMPH NODES

G.V. Telugu, A. Padwal, P. Trivedi & S.S. Ranade
Pathology Department, Tata Memorial Hospital and Radiobiology Unit, Cancer Research Institute, Parel, Bombay, Maharashtra State, India.

Pulsed nuclear magnetic resonance studies on malignant lymphoma have shown that water proton spin-lattice relaxation times of lymph node tissues shows increase in the order lymphnodes of normal subjects, Hodgkin's and Non-Hodgkin's lymphomas. This hierarchy in the T1 values is attributed to the increase in the proportion of malignant cells in Hodgkin's and Non-Hodgkin's lymphomas. Further, within the NHLs, the degree of prognosis and the T1 value was found to correlate. As a further step pulsed NMR studies on metastatic lymph nodes were undertaken.

The T1 values of normal lymph nodes showed a range of 200 msec, whereas metastatic lymph nodes showed a range of 500-700 msec at 20 Mhz. Distinction of T1 values with the sub-classes of NHL was however not observed. Storage of the lymphnodes at 2°C for four to eight weeks did not affect the distinction of T1 values, between the normal and metastatic lymph nodes. These studies have brought out the importance of histopathological significance and the role of "cell type" as a factor in influencing water proton relaxation times.

In conclusion, our study shows no protein band in normal subjects and two bands in the case of Hodgkin's and Non-Hodgkin's lymphoma. The findings will be discussed with NMR studies of normal and malignant lymph nodes. These studies will help in the non-invasive diagnosis and evaluation of tumor extent to skin (which was not seen by CT Scan), epiphysis, growing plates, articular cartilages, cruciate ligaments, and synovial. These findings have objective guidelines for surgery. Comparing MRI and CT Scan, shows that MRI is non-invasive to skin, epiphysis, growing plates, articular cartilages, cruciate ligaments, and synovial. These findings have objective guidelines for surgery.

We have studied 80 cases of primary bone tumors by NMR for clinical evaluation at Thomson EPR Magniscan. We used, first, a 0.15 T resistive (30 cases) and now a 0.5 T superconducting magnets (50 cases), with surface coils adapted to explored sites. Most patients were also evaluated by CT scan and conventional or computed angiography and anatomic correlations were obtained after surgery. In most cases, MRI has been performed before biopsy and neoadjuvant chemotherapy.

The actual excellent spatial resolution of MRI due to the use of surface coils, permits to define the tumor extent within the medullary canal, including skip metastases, the relationships with non invaded soft tissues and vessels and in the pelvis, with pelvic organs. But the most important value of MRI imaging consists in evaluation of tumor extent to skin (which was not seen by CT Scan) epiphysis, growing plates, articular cartilages, cruciate ligaments, and synovial. These findings give objective guidelines for surgery.

Comparing NMR and CT Scan, shows that MRI is non-superior to CT Scan for lower limbs and pelvis and becomes an essential exam before "en bloc-resection" in these localisations. In cases of shoulders or upper limbs, results are not so exciting but interesting.

Paragangliomas are differentiated into the groups of sympathetic pheochromocytomas and parasympathetic nonchromaffin paragangliomas. The latter type/chemodectomas or apudomas/are semi-malignant, often infiltratively growing, metastases occur. The most often sites are the jugular and carotid glomusae, but other places of origin, as aortic and large vessels adventitia and spinal localisations are reported.

We present five cases of glomus jugulare chemodectomas and one case of spinal apudoma. The extent of the tumour can be detected by means of CT, although conventional tomography is very useful too. The blood supply of these tumours is often difficult to detect, because of overlying bone shadows. From therapeutic point of view it is of great importance in cases of planned surgery or interventional embolisation as well. To detect these details, the photographic or conventional electron subtraction of angiographic studies seem to be appropriate, although, the procedure of intrarterial DSA offers probably the best results, if equipment is in hand.

Our results will be presented with photographic and conventional electronic subtraction, and CT studies with Ledicon Actascanner 150, first generation, and in one case, with Philips Tomoscan 310, high resolution/CT.

4752 NON INVASIVE IMAGING OF MELANOMA TUMOURS BY ELECTRON SPIN RESONANCE IMAGING (ESR). Lawrence J. Berliner, Hirotada Fujii, Xiaoming Wan, Antonello Sotgiu, and Stanislas Lukiewicz, Dept. of Chemistry, The Ohio State University, Columbus, OH, U.S.A.

Non-invasive diagnosis of tumours is of growing interest in medical science. A particularly challenging problem is the visualization at the microscopic level of tumour development, tumour size, and water distribution. While the advent of magnetic resonance imaging (MRI) has been revolutionary in the entire area of medical imaging, a new technique has evolved which uses electron paramagnetic resonance or electron spin resonance (ESR) in conjunction with gradient coils and digital image reconstruction. We present the image of a nitroxide ESR imaging agent as a measure of vascularization and a Cloudman C-91 melanoma tumour implanted in the tail of a rat. The imaging agent in this particular case reflects directly a distribution of solvent water, consequently, the vascularization in the tumour. Several features of the tumour morphology will be presented.

Supported in part by grants from NIH RR-01092 and the Ohio State University Office of Research and Graduate Studies. JSL was on leave from the Jagiellonian University, Institute of Molecular Biology Krakow, Poland.

4753 X-RAY DIAGNOSTICS OF GENITO-URINARY TUMOURS IN CHILDREN. I.S. Petrov, P.I. Kholko, N.G. Komoseko, V.I. Kolobov, Kiev Scientific Research Institute of X-ray Diagnostics and Oncology.

552 children with genito-urinary tumours were examined at Kiev Scientific Research Institute of X-ray Diagnostics and Oncology. The patients' age ranged from 9 days to 15 years. William's tumor was diagnosed in 207 patients, tumour of ovary in 29, tumour of uterus in 15, tumour of testicles in 13 and bladder tumours in 8. The diagnosis was confirmed by cytologic and histologic examination of operative samples, by autopsy findings and dynamic observations. Clinical, biochemical, immunological, X-ray and radiologic methods were used in this investigation. Attention was payed to general and X-ray methods, including pneumoperitoneum, pneumoretroperitoneum, urothyrocystography, angiography and their various combinations. The important role of special X-ray methods of investigations was noted in complex diagnostics of genito-urinary organs in children.


There were 2262 patients with rectum cancer in the oncoproctological department of Kiev Scientific Research Institute of Roentgenology, Radiology and Oncology in the period from 1977 to 1984. The first stage of this disease was made diagnosis at 2.9%, the second - at 12.1%, the third - at 65.7% and the fourth - at 19.3%.

Confirmation of the final diagnosis and researching methods were accomplished on the basis of surgical treatment results and autopsy. It was used following obligatory methods to all patients: palpation "per rectum", rectosigmoidoscopy with biopsy and histological confirmation of the diagnoses. Extent, expansion and metastasis were studied by irigioscopy, pararectosigmoidoscopy with combination of tomography, chrococtoscopy, septography, veno-venousography, pararectalography, negative and structural scintigraphy.
**4756**

Thermometry in the Diagnosis of ENT Tumours,

M. Melamed, N. Petkov, Oncology Res. Inst., Sofia, Bulgaria

In 1984 the authors constructed an electronic thermometer for measuring the local temperature of the upper respiratory tract. The thermometer is supplied with a set of inputs bent at different angles. Each of them contains a thermocouple, which measures directly the temperature of the upper respiratory tract organs. Fibrobronchoscope Olympus FB-4 was used with 2 thin wires inside its aspiration channel as a thermocouple, so that at the same time on optical examination is achieved as well. For cavity organs a local anaesthesia is sufficient. The device enables direct examination without discomfort for the patient.161 histologically verified cancer patients entered the study: 41 tumour of the nasopharynx, 25 - tonsil tumours, 12 - tumours of the palatium molle, 24 - tumours of the hypopharynx, 16 - larynx tumours and 45 with tumours in the neck. Results show a difference of about 1-2°C between tumour tissue and normal tissues in asymmetrical areas. The thermometry affair gives better possibilities for primary lesion diagnosis as well as for better inspection during the treatment. This method is easily applied to the complex diagnosis.

**4758**

Can of Computed Angiography in Preoperative Evaluation of Postsurgical Chemotherapy’s Effectiveness in Osteosarcoma's About 24 Years

N. Delcluze, C. Delcluze, B. Broussac, B. Burge, B. Leduc


In good responders, 10% medical provides highest disease-free survival and help conservative surgery. Nevertheless, such treatment can be dangerous for bad responders when surgery is delayed and this risk made earlier assessment of chemotherapy’s effectiveness mandatory. This study points out the promising early results of computed angiography, from 1984. 24 patients with osteosarcoma have been treated by neoadjuvant chemotherapy before surgical removal of their tumour, localisations included distal femur (2), upper tibia (4), fibula (2), upper humerus (2), distal tibia (1), fibula (1), and astragalus (1). Contrast medium was infused through a thin (1.2-2.2) gibereter. Analysis pointed out features of tumoral vessels, size and density of vascularized areas and quantified the vascular changes in five classes: 0 (tumour progression) to 4 (no residual tumour vascularizatiory). These data were compared to histological grading and to clinical, conventional, radiological, scintigraphic and computed tomographic evaluation on tumour’s response to chemotherapy. Excellent correlation with histological findings was obtained in 23/24 quantified scintigraphies, 18/24 computer tomographies, 15/24 plain radiographies and only 10/24 clinical evaluations. These data underline that clinical evaluation of osteosarcoma’s response is often misleading and that computed angiography seems the best way to evaluate chemotherapy’s effectiveness before histologic examination.
SALIVARY GLAND TUMOURS OF THE MAXILLARY BONES

Stratiev, A., Popmichailova, Ch., Medical Academy, Sofia

The frequency, the localization, the clinical and X-ray features of the patients with salivary gland tumours of different histological type, developing in the maxillary bones, treated in the clinic of surgical stomatology and maxillo-facial surgery at the Medical Academy, Sofia, for a period of 10 years are observed. The analysis for the clinical and X-ray signs, being very important for contemporary diagnosis and predicting of the treatment are presented.

ANGIOTOMOGRAPHY IN CASES OF TUMORS OF FACIAL SKULL AND NEAR THE SKULL-BASE

Szegedy, László M.D., Konez, József M.D.
Well Erli Hosp., Dept. of Neurology and Semmelweis Medical Univ., Clinic of Neurology, Budapest, Hungary

The angiotomography among other methods is proved to be advantageous, increasing the information content of X-ray investigations. It seems particularly useful in detection of vascular supply of tumors situated near the skull base and sometimes in facial skull hidden by overlying bony shadows. The detailed knowledge is essential for planning of surgical intervention preoperatively. The advantages of angiotomography will be shown in connection with cases of trigeminal neurinoma just forward to pyramid tip and different malignant tumors of the maxillary region and the base of the tongue. The examinations had been carried out with the help of MIMER - III and multisection (simultaneous) cassette containing 7 films with one cm sequence. For selective external carotid angiography non-ionic contrast media (Omnipaque, Iopamiro) had been used.

THE ROLE OF COMPUTED TOMOGRAPHY IN DIAGNOSTIC RETROPERITONEAL TUMORS

Kolesnikova, I.V., Melchenkov, I.G.
All-Union Cancer Research Center, Moscow, USSR

Analysis of 3000 investigations, performed using CT of 3-ra generation "Somaton SF" and "Hewlett SR 3" (Siemens), shows that sensitivity of the method in detecting of retroperitoneal tumors is 98%. The highest sensitivity was obtained in the diagnostic of kidney tumors - 99.4%, specificity of tumor signs - 99%, Wilms' Tumors - 99%, cysts - 99%. In most cases CT can replace angiography which should be done in difficult cases and for the evaluation of blood vessels. CT is the prime method in diagnostic of non-organ retroperitoneal tumors, with sensitivity of 74%. In lymphoma the sensitivity in metastatic lymph nodes in cancer of testis - 84% and 74% - in another cases.
Between 1980-1985, we found 57 cases of intraspinal mass lesions, which proved to be tumorous or syringohydromyelic in origin. The mass-producing, incarcerated disc-herniations were excluded. These lesions will be analysed according to the sites/extradural, intradural-extradural, intradural/intradural, the nature, primary, metastatic/and myelotomographic signs will be dealt with, particularly in respect of liquefaction and surrounding bone structures, adjacent to the tumour. Emphasis will be laid on patterns detecting intramedullary mass lesions and their characterization in differentiation between intramedullary tumours and syringohydromyelic cavities.

We have presented a case strikingly similar to the skeletal finding from Faucancarcho in 1915 in a cave under the ruins of this old Inca locality, the scientific explorers of Yale University and the National Geographic Society found a well preserved skull belonging to a primitive man with a peculiar massive bony exsecration of the parietal bone. Histologically it had a benign endothelio-...
PREOPERATIVE LEVELS OF SERUM GLYCOPROTEINS AND CELLULAR IMMUNITY IN PATIENTS WITH ESOPHAGEAL CARCINOMA. Y. Ohtani, cooperative study group on E.S.P.O. for esophageal cancer. Tsuchiara, Kanagawa, Japan.

The cooperative study group at E.S.P.O. in Japan to evaluate the efficacy of E.S.P.O. for esophageal cancer in patients with esophageal carcinoma. The cooperative study group was organized in January 1985 to conduct a clinical parametrical study, clinical serum protein levels were examined in all patients with esophageal cancer. These parameters were investigated to compare the clinical parameters such as clinical staging, viability, lymphode metabolism, tumor invasion, etc.

Serum glycoproteins were evaluated in accordance with the staging, viability, extent of tumor invasion, lymphode metastasis and the length of the lesion on an X-ray photograph. Serum parameters of cellular immunity were examined preoperatively in 250 patients with esophageal cancer. These parameters were investigated to compare the clinical parameters such as clinical staging, viability, lymphode metabolism, tumor invasion, etc.

Serum glycoproteins were evaluated in accordance with the staging, viability, extent of tumor invasion, lymphode metastasis and the length of the lesion on an X-ray photograph. Serum parameters of cellular immunity were examined preoperatively in 250 patients with esophageal cancer. These parameters were investigated to compare the clinical parameters such as clinical staging, viability, lymphode metabolism, tumor invasion, etc.

In cases of carcinoma of the esophagus, there is a controversy whether the mediastinal lymph nodes should be dissected or not. To examine this problem, 40 patients with carcinoma of the cervical esophagus were studied for survival and recurrence. These patients received resection of cervical esophagus with modified neck dissection, but the thorax was not dissected. The study was performed with free jejunal graft in 17, and with free-fascia skin graft in 1 patient. Right pneumonectomy of the thoracic esophagus with thoracic nodal dissection was conducted in 26 patients. There was no patient who lived within 90 days after operation. Three-year survival of free graft was 42.6%, and that of right pneumonectomy was 29.4%.

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**4770**


Pharyngolaryngoesophagostomy solves the main problem of segmental esophagoplasty: early recurrence of the esophageal margin and multistage esophagoplasty. The major aim of esophagoplasty without thoracotomy is to decrease incidence attributable to medical factors (emphysema, respiratory failures), i.e., removal of the proximal esophagus by a side-stapler requires sections of esophagus at thoracic outlet. A transhiatal blunt esophagostomy requires section of the pharynx toward the posterior and the use of sophisticated retractors and is likely to cause postoperative due to pleural effusion. Proximal esophagoplasty by blunt dissection and distal inverted esophagoplasty by side-stapler presents these two undesirable effects. Between January 1 and December 15, 70 consecutive patients with resectable carcinoma of cervical esophagus underwent an open total pharyngolaryngoesophagostomy by this technique. Esophagoplasty was performed by isoperistaltic gastric tube in 51 patients, with stem-in-1, subtotal stomach (Nissen) in the remaining 19. 90% of cancers were stage III (T3 N1 M0) and total resections were only partial in 15% of patients. There were no postoperative complications such as bleeding or plural tears requiring thoracotomy. Operative death occurred in 3 patients: 1 for gastric perforation, 1 for recurrence of gastric tube, and 1 for fistula associated with erosion of proximal tracheal wall attributable to immediate blood supply after resectional chain with traction. Esophagoplasty with whole stomach or subtotal stomach (Nissen) result in the lowest risk of pharyngolaryngoesophagostomy and the lowest operative mortality. We can conclude that isoperistaltic gastric tube esophagoplasty and inversion extraction of linear staplers allow a better laparotomy of paraesophageal rules, with or without the involved station, safer esophagoplasty, and better rate to preserve tracheal blood supply to reduce operative mortality for 40 patients.

**4772**


Gastric tube prevents the adverse effects of whole stomach: mediastinal compression, serious gastroesophageal reflex and dysphagia. The main drawback of gastric tubes is blood supply, which relies completely on the right gastroepiploic artery, and only in 20% of cases on the left gastroepiploic vessels (when the anastomotic connection exists). The aim of this study is a retrospective evaluation of 253 consecutive cases of esophagoplasty after complete resection (R0) for esophageal cancer, performed between 1965 and 1984 at the National Cancer Institute of Milan. The main features of the series were: adenocarcinoma 172 (46%), squamous 103 (41%), other types 28 (11%). Age over 60 Ibl 160-1; positive nodes 117 (46%). The occurrence of postoperative death according to the extent of esophageal resection, is shown in the following table:

<table>
<thead>
<tr>
<th>ESOPHAGOPLASTY</th>
<th>OPERATIVE DEATH (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOTAL</td>
<td>9 (11)</td>
</tr>
<tr>
<td>SUBTOTAL</td>
<td>8 (11)</td>
</tr>
<tr>
<td>RSTAL</td>
<td>12 (10)</td>
</tr>
<tr>
<td>GLOBAL</td>
<td>29 (11)</td>
</tr>
</tbody>
</table>

Proximal resection of isoperistaltic gastric tube was the main reason of greater mortality after total esophagoplasty. It was concluded that isoperistaltic gastric tube is a safe procedure for subtotal esophagoplasty but not for total esophagoplasty.

**4773**

CARCINOMA OF THE GASTRODUODEN, INFLUENCING SURVIVAL.


The clinical material consists of 542 histologically and cytologically verified consecutive cases of carcinoma of the gastroesophagus treated at Szeged Surgical Clinic, University Medical School of Szeged between January 1, 1945 and December 31, 1985. The operability rate was 76.4%, the survivability rate 55%, and the operative mortality 15.8%. 200 patients were included in the follow-up study who underwent resection up to the 1st January 1985. The survival rates were calculated using a life table method (Cutler-Ederer 1958). The 5-year survival was 21.7% and the 10-year survival rate 14.8%. Factors (age, sex, location, histology, stage, type of operation, etc.) influencing survival were analysed.
CARCINOMA OF ESOPHAGUS IN IRAN: A REVIEW OF 3507 CASES TREATED BY RADIOTherAPY. K. Dehshiri, MD., M. Sadadi, MD., and F. Massipour, SR., Cancer Inst. University of Tehran, IRAN.

Carcinoma of esophagus is the major type of cancer seen in northern and western part of Iran. As the risk is 4 times greater than in the rest of the country, 3507 cases referred to the radiotherapy department from 1973 to 1983. They were 445 female and 565 male. Histologically, 98% squamous cell carcinoma, 2% adenocarcinoma and the case leiomyosarcoma. At the time of diagnosis, only 22% were suitable for surgical treatment. The majority had dose in a short treatment time of 50-90 Gy in 20 treatment days over 4 weeks by two opposing fields. This group did the best, without any major complications or radiation myelitis. In our experience, carcinoma of esophagus responds well to radiation but as the disease is generally advanced at the time of diagnosis, the survival rate is disappointing. Early detection is the only solution. Although many patients have lost follow-up, we have 135 three-year and 55 five-year survival.

A RANDOMIZED CONTROLLED TRIAL ON THE POSTOPERATIVE RADICAL- AND RADIOTHERAPY WITH PSK FOR ESOPHAGEAL CANCER. K. Ogoshi, Cooperative study group of PSK for esophageal cancer, Tohoku, Konagawa, Japan.

The present study was designed to evaluate the efficacy of PSK for resected squamous cell carcinoma of esophagus as an immunopotentiator in combination with postoperative radiotherapy and chemotherapy. The cooperative study group which was organized with 18 institutes in Japan adopted a trial on two subgroups: group I postoperative radiotherapy, group II: postoperative radiotherapy and chemotherapy with PSK. From Feb. 1983 to Oct. 1985, a total of 185 patients were entered into the study, being evaluated side effects of PSK and the investigated serum glycoproteins and cellular immunity preoperatively and postoperatively. Thirty-nine patients in group I were randomized to receive PSK, and 32 patients to receive radiotherapy alone. Sixty patients in group II were randomized to receive PSK and 54 patients to receive radioactive therapy alone. There was no significant difference in any of clinical parameters between randomization groups, however, there was a significant difference in the staging between group I and II. In this trial, no side effects were observed and serum glycoproteins remained low and PMA S.1 increased postoperatively in patients with PSK. The result of 2 years survival rates were 61.8% in I-A subgroup, 54.8% in I-B subgroup, 68.7% in I-C subgroup, 61.1% in II-D subgroup, respectively using the method of Kaplan-Meier.


With an expectation of potentiation of the regional effect of bleomycin (BLM) on the lesion of esophageal cancer, 11 cases received 30 mg/day of oral BLM mixed with sodium polyacrylate (PA) preoperative days. Fifteen cases received 40 mg/day, and 7 cases received 70 mg/day, respectively. BLM-PH were determined at the resected tumor sites, normal areas, and lymph nodes before and after final administration. BLM levels were higher in tumor sites ranging up to 100 microg/mL than normal areas ranging up to 2.0 microg/mL. Blood and urinary levels were 0.69 microg/mL or less in most of all patients. No side effects occurred. In 13 inoperable patients received radiation therapy followed by BLM-PH for up to 10 months and showed improvement of symptoms without side effects. The experience indicates that BLM-PH can be given for a long term without major side effects and is a preparative administration also offers beneficial effects, especially in the inoperable patients. It is recommended to try BLM-PH as a maintenance therapy after radiation therapy.

INDUCTION CHEMOTHERAPY: Vindesine + Cyclophosphamide + Cis Platin (V.C.P.) IN RESECTABLE ESOPHAGEAL CANCER. M. Spielmann, J. Rac, P. Rogier, D. Seltin, T. Le Corvaisier, A. Chavy, and J. Bouesse.

Institut Gustave Roussy, Villejuif, France

Chemotherapy in epidermoid cancer of the oesophagus has given encouraging results. We have conducted a phase II trial to evaluate the efficiency of preoperative chemotherapy. The regimen combined an association of Vindesine 1.4 mg/m^2 days 1 and 2; Cyclophosphamide 200 mg/m^2 days 2, 3, and 4; Cis Platin 100 mg/m^2, days 2, 3, and 4. Thirty-four patients were included, 30 of them are evaluable. Eight patients received only one preoperative cycle, 22 received two cycles at four weeks. The efficiency was determined by endoscopy and barium transit exam. Results were: no complete response, nine partial responses, six minor responses with reduction of dysphagia, and fifteen failures. The response rate is 30% (CI: 14.7-44.9). After chemotherapy, 31 patients were operated, and 2 had complete resection of the tumor. Two patients were not operated since distant metastases appeared during the preparative period and one for local progression. Tolerance of this protocol was good in 85% of cases. Five patients had hematological toxicity (3 leucopenia grade II, one thrombopenia grade II and one thrombopenia grade III).

In conclusion, our V.C.P. pre-operative regimen is well tolerated. Our results deserve further trials with preoperative chemotherapy.
ESOPHAGEAL-CARDIAL TUMORS WITH ENDOPROSTHESIS. 


Although surgical resection represents in most cases palliative treatment for esophageal carcinoma, the assessment of results, only rarely includes a careful evaluation of the quality of life. 25 to 30% of patients surviving after surgery suffer from recurrent dysphagia at one year following the operation, and up to 20% require endoscopic dilatation for anastomotic stenosis. Out of 288 consecutive complete resections (80) for esophageal cancer performed at our Institute during the last 20 years, 246 (83%) survived after the operation. The overall survival was 310 at 2 years, 151 at 5 yrs., and 81 at 10 yrs. Local cancer relapse (11%) and reflux esophagitis (10-15%) were the main causes of failure. Adequate palliation of the dysphagia, Dyspepsia and malabsorption syndromes of various degrees were also relevant causes of a bad life quality, as was anorexia with or without distant disease relapse.

Early and late results of treatment, in terms of freedom from symptoms and weight gain, are the subject of this presentation, which is focused on surgical aspects (e.g. volume of resection, level of anastomosis, type of segment). Palliative treatment for esophageal carcinoma, the permanent intubation provides near; significant benefits, palliative intubation provides near viability and psychic complaints. In the remaining 146 pts., an draining tube was placed by laparotomy approach (Pull method). All of these 146 pts., were submitted to Radiotherapy (4000 Mev) after intubation. Morbidity rates were different between the two groups of patients: in the first one (Pull method) it was about 10% while in the second one (Pull method) it was only about 15%. Mortality rates were different too. 22.4% for pull-method-group and 8.4% for pull-method-group. Path morbidity and mortality differences were statistically significant (p<0.05). The median survival rate of the whole group is about 6 months, with some patients are still alive 12 months after treatment. Moreover, we have noted a relative easiness in forcing the oesophageal-cardsial strictures and in fixing the tube using the Martini device, while with the device using the pull method, we have noticed failures both in setting over the stricture and in fixing the tube (too early displacements).
A new surgical oesophageal intubation technique for unresectable intrinsic or extrinsic esophageal stenosis and malignant oesophago-respiratory fistula.

L. Kotsis, P. Vadasz, E. Kulka, Thoracic Surg. Clinic, Budapest, Hungary

Eighteen patients with unresectable pulmonary tumor-induced oesophageal stenosis, 8 patients with unresectable oesophageal carcinoma and another 3 patients having malignant thoraco-oesophageal fistula were managed by palliative surgical intubation with a new, composite, detachable, exclusive oesophageally inserted tube at the Thorac. Surg. Clin. Budapest, in the last 4 years. In the first group the over-all mortality was 11.5%, one patient was lost in the fistula group from respiratory insufficiency. No patient died as a consequence of the procedure employed. All patients alive have resumed oral soft diet, oesophago-respiratory symptoms disappeared. Full through oesophageal intubation with a composite, detachable prosthesis allows insertion of the tube only in the malignant narrowing. This technique permits a convenient low, small (3 mm) gastrotomy, which reduced the possibility of intraabdominal contamination. The end of the tube does not pass across the cardia, so the patient is free from gastro-oesophageal reflux and its consequences. The authors suggest that in these circumstances, the exclusive oesophageal surgical intubation technique is better than the conventional oesophago-gastric type one. In case of malignant esophago-esophageal fistula accompanied with oesophageal stenosis, this way of intubation - using a prosthesis which has a sponge-layer covered funnel - provides a good palliation of symptoms.


An intensive programme of community-based education in breast self-examination (BSE) was conducted in a Wellington suburb. In order to evaluate its effectiveness, survey data were obtained from population-based samples before and after the programme in both the study area and a demographically similar comparison area. A total of 583 women aged 30 - 59 years were interviewed about their personal characteristics and their practice of BSE. Response rates to the interview request and demographic characteristics were not significantly different in the two areas or in the surveys before and after the educational programme. The surveys indicated that 98% of women had heard of BSE, 73% had practiced it at least once and 39% did so at least monthly. BSE was practiced significantly more commonly in the age group 30 - 59, amongst women of European ethnicity and amongst those with tertiary education. The education programme did not significantly affect the proportion of women who were aware of BSE, or who had ever performed BSE. However, significant increases in monthly BSE participation rates \( p < 0.05 \) and in the proportion beginning BSE in the previous three months \( p < 0.05 \). The most marked improvement in monthly BSE performance was in women aged 20 - 49 years and in those with tertiary education.

The effect of breast self-examination education on tumor stage and patient survival.

C.S. Howie, J.L. Eveson, Anna Mitchell, W.M. Elmes, Department of Surgery, City Hospital, Nottingham, England

Since 1974 10,000 women between the ages of 45 and 70 years have been invited to attend for breast self examination (BSE) education (= study group). A self referral clinic is then available for this group. Tumor site, histology and lymph node status and patient survival has been recorded for the 281 cases of breast carcinoma diagnosed in the study group. These factors have been compared with those from 281 breast cancer patients in the same age group diagnosed in the five years prior to the start of the BSE study.

<table>
<thead>
<tr>
<th>Lymph node involvement</th>
<th>Tumor size cm</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>not invasive carcinom a</td>
<td>0-2.0</td>
<td>0.3-4.0</td>
</tr>
<tr>
<td>localized</td>
<td>0.001</td>
<td>0.05</td>
</tr>
<tr>
<td>advanced</td>
<td>1974-79 11 95 115 (7) 95 102 (13) 51</td>
<td>1979-84 18 120 87 (16) 120 62 (39) 40</td>
</tr>
<tr>
<td>( X^2 = 6.76 ) (1 df)</td>
<td>( X^2 = 5.019 )</td>
<td></td>
</tr>
</tbody>
</table>

Significant decreases in tumor size and lymph node stage have been noted in the study group. These results suggest that BSE will be associated with improved survival from breast cancer.
Clinical studies and treatment of benign mammary dysplasias

Di Martino L., Ferrelli A., Bol A., Maltinti H., Demontis B.
Oncology Hospital, Cagliari-Italy

SUMMARY:
There are certain histopathological aspects of benign mammary dysplasias which, specially in association with family history, constitute a subgroup of patients who are at considerable risk of developing malignant disease. In such circumstances, the development of other parameters which will predict the likelihood of malignancy in these cases will be of great assistance in the clinical management of these patients. We have previously reported that the measurement of certain enzymes of carbohydrate metabolism in primary carcinoma assists in predicting likelihood of recurrence in these patients (Deshpande et al., 1981). Di Martino et al. (1984) have now undertaken investigations to evaluate whether any of these enzymes show any differences between patients with low and high risk histopathologies. In a series of 100 patients with both low and high risk lesions we have found that the overall activity of Phosphohexoisomerase (PHI) was significantly raised in high risk lesions, such as atypical dysplasia, lobular hyperplasia or ductal proliferation. This has led us to undertake a clinical trial in patients with dysplasia of the breast as follows:

Class I: 70% coincidence, and in the 30%, discrepancy was favourably disposed to I.R.G.

Class II: Despite previous discrepancy, with the mammography, cancer was histopathologically confirmed.

Class IV and V: 80% of the cases obtained histopathological confirmation.

The method completes mammography, and good results are obtained in young patients, with previous scars, with retroarcal pathology. In rounded nodules and in vascular alterations. It has the advantage of not radiating tissues.
Our efforts aimed at improving the efficiency of early detection of breast cancer cases. This might be achieved in two different ways:

1. by application of new diagnostic methods;
2. by increasing the number of patients examined through more extensive educational activities.

Results are demonstrated by comparing statistical data of two periods: before and after the use of these methods. Further tasks and possibilities are also discussed.

The probability of a second primary of the treated breast cancer patient is continually increasing during the follow-up. In one third of breast cancer patients a second tumour develops in the opposite breast, this is why the early diagnosis of the recurrences and also of a second primary is expected of the careful follow-up. Many patients do not live long enough to have much chance for developing cancer in the remaining breast. Between 1967 and 1985 at the Dept. of Surgery of the Natl. Inst. of Oncology, Budapest, Hungary 411B primary breast cancer patients were operated on. Out of them 245 had bilateral breast cancer, which makes 6% of the whole patient material. The survival of simultaneous breast cancer patients is rather bad while that of patients developing subsequent cancer is very similar to those who had only one breast cancer operated on.
MALE BREAST CANCER. P. Fulyok, P. Rónay, E. Szeles and I. Besvroyok, National Institute of Oncology, Budapest, Hungary

Male breast cancer is a very rare disease. According to the authors the literature its incidence is about 1%. The authors report on 67 male patients with breast cancer treated between January 1966 and December 1985 at the National Institute of Oncology. In 17 cases the breast and prostatism binding capacity of the tumour was examined. The significance of hormone receptor determination in the planning of treatment and in the study of prognosis is highly emphasized. The importance of treatment relevant to the stage of the tumourous disease is also pointed out. The results of therapy as well as the survival (5.6 years) are described.

THE EFFECT OF THE PRE-OPERATIVE BIOPSY FOR BREAST CANCER ON THE 10 YEAR-SURVIVAL RATE.

Akira Fujiwara, M.D.*, Masaharu Horii, M.D.* Atsuo Fukumi, M.D.* Go Sakamoto, M.D.* *Dept. of Surgery, Cancer Institute Hospital. **Dept. of Pathology, Cancer Institute, Tokyo, Japan.

It is said that procedure of pre-operative biopsy may exert unfavorable effects on the prognosis of breast cancer. However there has been only few comparative studies on the prognosis between biopsied and non-biopsied groups and the results are not consistent in every aspect. Then we performed this comparative study using 941 patients. 444 patients with a cancer less than 2.0cm (T1) and 523 patients with a cancer 2.1cm - 5.0cm in diameter (T2), which had been radically operated at the Cancer Institute Hospital between Jan. 1969 and Dec. 1989. The results are as follows: 1) The rate of biopsied patients for all the patients with breast cancer in each size of the tumour was 40.7% (375/924) in T1 size and 42.7% (227/534) in T2 size. 2) The 10-year survival rate of the biopsied group were 89.3% in T1 and 75.4% in T2, and that of non-biopsied group were 76.2% in T1 and 55.1% in T2, respectively. 3) The survival rate of the former group was higher than that of the latter group, however, the difference was not significant. Furthermore, no significant difference was observed on the comparison between the two groups relative to the numbers of metastatic lymph nodes.

We conclude that procedure of pre-operative biopsy for breast cancer does not influence the prognosis.

PAGET'S DISEASE OF THE NIPPLE: A PLEA FOR EFFICIENT CONSERVATIVE SURGICAL APPROACH.

Liglie Wine, M.D., Elfiezer Navor, M.D., Ira Telicher, M.D. Long Island Jewish Medical Center, New Hyde Park, NY and State University of New York (Stony Brook, N.Y. S.A.

The current surgical approach to Paget's disease of the breast was evaluated by reviewing a group of 77 consecutive patients who we treated by mastectomy. Ten main groups of patients were identified. Those with nipple lesion only without palpable clinical mass and those with nipple lesion and a palpable clinical mass.

Of the 35 patients with nipple involvement but without a palpable breast mass, in 16 (46%) the axillary lymph nodes were negative and all tumor was localized to the nipple area. In none of these 14 cases was there evidence for multifocal disease or for an infiltrating tumor and during a minimal follow-up of 7 years, none of these patients developed recurrent disease. The one out of the 19 patients who had positive axillary nodes, had an infiltrating tumor and multifocal disease. Of the 18 patients with a palpable breast mass, 10.2% had multifocal disease, in 6% the axillary nodes were involved and 47% of these patients had infiltrating duct carcinomas. 47% of these patients developed a recurrence during the follow-up period. These findings suggest that in patients with Paget's disease limited to the nipple without palpable breast tumor, mastectomy is probably not justified, and surgical treatment with wide excision of the nipple and underlining ducts with axillary sampling, followed by postoperative radiation therapy might be the treatment of choice. If, however, clinical examination demonstrates an associated breast mass, then probably a modified radical mastectomy still remains the treatment of choice.

CONTINUED PROGRESSION ON BREAST CANCER associated with ineffective treatment in T1 and T2 patients.

Yo-ichi Aoki, Takeshi Anfuku, Tomomi Suzuki, Masahiko Hamamoto, Nihon University, Tokyo, Japan.

The patients studied were 1048 patients with breast cancer treated between Jan. 1960 and Dec. 1985. The results of patients with T1 and T2 were between 3 and 14 years intervals, and 15.2% of T1 tumors were in the category T1, while of the T2 tumor category in the patients of the comparatively pure breast cancer. The data, treatment of the stage, and the initial grade of the breast cancer were analyzed in a non-operative method. A comparative statistical analysis was performed using the Student's t-test, Fisher's exact test, and the chi-squared test. The results were as follows: 1) The patients with T1 grade of 0 were not different from those of T2 grade of 0. 2) There were no significant differences between T1 grade of 1 and T2 grade of 2. 3) The results of 10-year survival rates were 90.8% in T1 grade of 2, 86.3% in T2 grade of 2, and those of 10-year survival rates were 90.8% in T1 grade of 0, 86.3% in T2 grade of 0, and those of 10-year survival rates were 90.8% in T1 grade of 1, 86.3% in T2 grade of 1. The results of 5-year survival rates were 90.8% in T1 grade of 0, 86.3% in T2 grade of 0, and those of 5-year survival rates were 90.8% in T1 grade of 1, 86.3% in T2 grade of 1.

Biostatistical analysis showed the relative continuity of the continuous prognostic factors. Thus, a "pure" stage 1 and a "good" stage II III could be delineated. However, patients' personal treatment was not affected by the classification.

1027 women (stage I - 215(20.8%), stage II - 471 (45.5%) and stage III - 341(33.2%) have been radically treated. The 1st stage patients were operated on by Patey and no post-operative radiotherapy was administered in absence of regional metastases, while in histological findings of metastases such therapy was performed. The 1nd and 11th stage patients underwent radical mastectomy by Halsted, pre- and post-operative radiotherapy, in case of four and more metastatic lymph nodes we used chemotherapy, while hormone therapy was applied in positive estrogen receptors. From the follow-up of 634 patients 466(73.5%) survived five and more years as follow: stage I - 109 from 124 (87.9%), stage II - 226 from 288(78.5%) and stage III - 131 from 222(59.0%). The marked increase of the 5-year survival(73.5%) compared to 65% from 1960 to 1973 resulted from the individual surgical approach.

4798 THE CLINICAL VALUE OF INTRAOPERATIVE NODE DISSECTION IN OPERABLE BREAST CANCER PATIENTS TREATED WITH ADJUVANT HORMONOCHEMOTHERAPY. H. Rothen, P. Chauvin, O. Crozet, M. Avril, Centre Leon Bérard, 28 rue Lafontec, Lyon, France.

In Centre Leon Bérard from Jan. 1976 to Dec. 1981, 480 patients aged under 70 suffering from T1T2 breast cancer were treated according to a precise protocol: modified radical mastectomy + internal mammary chain dissection (IM+). Adjuvant hormonochemotherapy was used in all 44 cases from 1976 to 1978, 86 cases, 12 CMF from 1979 to 1981, 6 FAC + 12 CMF - Tumor- xenon 20 mg day x 5 years in cases ER+.

The results of survival or of survival without recurrence were calculated according to the method of Kaplan-Meier. Over 3 N+ (Axillary + IM+) the prognosis of the tumor the knowledge of IM+ through a conservative IM dissection and in the decision to give intensified adjuvant chemotherapy, while hormone therapy was applied in positive estrogen receptors. From the follow-up of 634 patients 466(73.5%) survived five and more years as follow: stage I - 109 from 124 (87.9%), stage II - 226 from 288(78.5%) and stage III - 131 from 222(59.0%). The marked increase of the 5-year survival(73.5%) compared to 65% from 1960 to 1973 resulted from the individual surgical approach.

4799 MODIFIED RADICAL MASTECTOMY BY PATEY. REPORT OF THE ISTITUTO NAZIONALE TUMORI DI NAPOLI, ITALY. G. DiGliori and G. D'Errico. Istituto Nazionale Tumori "Fondazione Pascale" Napoli, Italy.

The modified radical mastectomy by Patey, performed now in the great majority of breast cancer in stage I and II shows several advantages over the classic radical mastectomy by Halsted. The results of more than 600 operations performed at the Istituto Nazionale Tumori of Naples between 1977 and 1984 are presented. In details are illustrated the technique, the results and the better possibility of prosthetic reconstruction of the Patey technique versus the Halsted mastectomy.


The most common surgical method for advanced breast cancer has been standard radical mastectomy. This method has cosmetic disadvantages, such as exposure of the muscular floor, remarkable destruction of inframammary area, and occasionally needed in motion limitation of arm. To prevent these complications, we have devised a new method of modified radical mastectomy to preserve the most of pectoral muscle while completely removing the axillary and subclavian nodes. The procedure is as follows: we perform a skin incision: 21 cm block dissection of axillary lymph nodes. Opening the inframammary sulcus of the most of pectoral muscle and removal of axillary and subclavian nodes. We initially applied this modified operation only in early stage cases. However histological findings showed that this method could remove 98% if the nodes, compared with that removed by standard radical mastectomy. However, we have performed it in 634 patients with all stages of breast cancer. The mean number of removed nodes was 41 in the standard, 11 in the modified mastectomy.

The 5-year survival rate was 104 in the standard, 81% in stage I, 91% in stage II, 88% in stage III, 67% in stage IV. The 5-year survival rate was 87% of cases, 82% being local recurrence and 1% patients died of distant metastasis. Histological examination showed that the recurrent tumors were basal type, by muscular fiber in 15% of patients, suggesting that most of the cases in the most of pectoral muscle were still and many type of axillary lymph nodes and in 15% of cases, surrounding prosthetic advantage. Our method was much better than standard radical mastectomy. This is concluded that this modified radical mastectomy is superior to standard radical mastectomy in both prognosis and post-operative complications and can be applied to not only early, but also advanced breast cancer.
Combined Treatment of Stage III Breast Cancer

J.A. Aliev, R.D. Jafarov, A.S. Ismailov

Res. Inst. of Roentgenology, Radiology and Oncology, Baku, USSR

Clinical study of combined treatment of stage III (T1-4, N2-3) breast cancer was made. The patients were divided into 4 groups depending on the treatment method:

- Group I (92 patients) - gamma-therapy according to standard method of radical mastectomy + chemotherapy
- Group II (66 patients) - chemotherapy + radical mastectomy + chemotherapy
- Group III (66 patients) - macrofractional gamma-therapy + chemotherapy
- Group IV (66 patients) - macrofractional gamma-therapy + chemotherapy + chemotherapy

Chemotherapy has been carried out according to CPMVF scheme or according to CFM scheme. Repeated courses of postoperative chemotherapy were given every 2-3 weeks till 6 courses. After preoperative gamma-therapy according to standard methods, tumor size decreased more than 50% in 46.5%, after chemotherapy - in 29.2%. Five years survival rate in the group I was 47.5%, in the group II - 10.7%, in the group III - 25.0% and in the group IV - 30.5%.

It does seem that preoperative chemotherapy according to standard method in combination with surgery and chemotherapy may prove useful in combined management of patients with stage III breast cancer.

Problems in the Management of Inoperable Breast Cancer: a Critical Analysis of 235 Cases

A.P. Majumdar, Cancer Centre & Welfare Home, Thakurpukur, Calcutta, West Bengal, India.

Two hundred thirty-three cases of breast cancer treated in various district and peripheral hospitals by different surgical procedures reported to this hospital for further treatment during the period of 1982-1983. These cases were critically analysed to determine the preoperative clinical stage, biopsy procedures adopted and the results of their treatment. In this study the preoperative findings like, size, site and stage of the disease were available only in 23%, 36.3% and 21% of cases respectively. Biopsy procedures like wire-guided needle biopsy, cutting, excision, lumpectomy and frozen section were done only in 31.2%, 61.7%, 15.9%, 21.4% and 7.2% respectively. No biopsy was done in 41.5% of cases. In this study the patients who did not have total mastectomy of any type were further investigated, evaluated and 23 cases out of 105 cases, were treated by radical surgery and the rest 77% cases along with the post-mastectomy cases were treated by radiotherapy and chemotherapy (CMF-4 cycles). The overall relapse rate of 235 cases within 6-9 months of treatment is 54%. Exclusion of the 23 cases subsequently operated at this centre increases the relapse rate to 27%.

For further adjuvant programs, a differentiated approach is advisable, based on prognostic variables, including predictive tests.

Comparative Evaluation of Methods of Main- Line of Breast Cancer at Stage IIa T1-2 N0.


Efficacy of various methods of treatment of breast cancer at stage IIa T1-2 N0 was studied in 346 patients using randomization. 146 patients underwent only radical mastectomy (group 2), 130 patients radical mastectomy with subsequent chemotherapy (group 3). 70 patients were subjected to preoperative gamma-therapy by the method of large dose fractionating + radical mastectomy (group 1). Follow-up during 5 years showed that in group 1 metastases radical mastectomy with chemotherapy in 17.5% and group 3 in 25.4%. Results of investigations were more favourable in patients from group 1 given radical mastectomy with prophylactic courses of chemotherapy during 2 years with concurrent hormonal therapy. 2 schemes of chemotherapy were used: 1) cyclophosphamide, fluorouracil, vincristine, prednisolone; 2) cyclophosphamide, methotrexate, fluorouracil, prednisolone.
L-58: BREAST TUMOURS: SURGICAL ONCOLOGY II

PERFORMANCE OF MODIFIED RADICAL MASTECTOMY AND IMMEDIATE BREAST RECONSTRUCTION - A COMBINED APPROACH

Dept. of Surgery, Northwestern Univ. and the Evanston Hospital, Evanston, Illinois, C.S.A.

The authors have used a variation of the standard modified radical mastectomy as their treatment for clinical stage I and II carcinoma of the breast. Immediate reconstruction of the breast is routinely offered to these patients. 64 consecutive patients undergoing immediate reconstruction were seen pre-operatively by both the oncologic surgeon and the plastic surgeon. Clinical staging showed 47% stage I, 31% stage II, 16% stage III, 6% had carcinoma in situ only. In 52% our type of modified radical mastectomy was performed, and 24% received post-operative adjuvant chemotherapy. Reconstruction used either gel implants or tissue expanders placed sub-muscularly. The routine detachment of pectoral minor from its origin aided in obtaining complete muscle coverage, and may also have reduced post-operative drainage from the axilla. There were minor complications (superficial cellullitis, skin flap ischemia etc.) in 36% of cases. Implant loss was more frequent when the implant was not completely covered by muscle (18% vs. 6%). There was no difference between tissue expanders and gel implants. Reconstructions in stage II disease, or followed by chemotherapy, were associated with lower rates of implant loss, possibly because these groups were not reconstructed early in the authors' experience. The authors conclude that modified radical mastectomy with detachment of the pectoralis minor from its origin, and immediate prosthetic reconstruction, is an excellent alternative to adjuncts and radiation.


L-59: GYNAECOLOGIC TUMOURS: SURGICAL ONCOLOGY III

EXTRA-ARTERIAL CISPLATIN CHEMOTHERAPY FOR ADVANCED UTERINE CERVICAL CANCER

M. Sugaki, T. Kiyuno, M. Ushiyama, and M. Mochizuki
Department of Obstetrics & Gynecology, Keio University School of Medicine, Tokyo, Japan

Three patients with advanced uterine cervical cancer (FIGO stage IB) were treated with intra-arterial (IA) administration through the internal iliac arteries of cisplatin (CDDP), total 150-300mg/500ml; using method of Surgical Oncology. And the following results were obtained:

1) Two of three evaluable patients showed rapid response histologically and clinically (disappearance of abnormal endocervical findings and rapid decrease of tumor markers [TA-4]).

2) Half hours after IA-CDDP (10-100mg), the concentrations of platinum (Pt) in cervical tissue were as high as 4.90±1.14μg/g. At 2 hours following IA-CDDP, the concentrations of Pt in cervical tissue were maintained relatively high dose. Meanwhile, Pt was detected peak of the concentration in serum 3-15 minutes after IA administration. But, in 1 hour after IA administration, the blood concentration was decreased rapidly.

3) As compared with intra-venous CDDP administration, in IA-CDDP administration there were only mild side effects (increase of BUN & bone marrow restriction).

These findings indicate that the IA-CDDP administration is too effective and useful for the patients with advanced uterine cervical cancer (squamous cell carcinoma), because high levels of active platinum are achieved and maintained in cervical cancer tissue following CDDP-IA administration; and has very little side effect.

TREATMENT OF ADVANCED CERVICAL CANCER WITH HYPOGASTRIC ARTERY INFUSION OF CISPLATIN USING A TOTALLY IMPLANTABLE INFUSION PUMP

J.R. Rettenmaier, M.L. Berman, P.J. DaSilva, Univ. of Calif., Irvine Med. Ctr., Irvine, CA

A totally implantable freon-driven chemotherapy infusion pump [Infusaid Corp., Norwood, MA] was placed in the subcutaneous tissue of the anterior abdominal wall in three women with advanced squamous cervical malignancies. Catheters from this device were placed in both hypogastric arteries, either directly or via the common iliac arteries. Cisplatin and a concentration of 1mg per cc of 1.8 normal saline was infused at a total dose of 2.5 mg per day. One patient with advanced pelvic disease caisson partial external iliac artery obstruction, developed complete thrombotic occlusion of that vessel immediately after catheterization of her common iliac artery. The two remaining patients had been treated for seven and six months with monthly treatment cycles consisting of three weeks of cisplatin infusion, followed by one week of normal saline infusion. No renal or neuro toxicity has been seen and neither patient has developed nausea or vomiting during treatment. Hypogastric artery infusion of chemotherapeutic agents in patients with advanced cervical malignances via an implantable chemotherapy pump permits the patient normal activity while undergoing treatment and might be useful for palliation or as an adjunct during radical radiation therapy.
**WEDNESDAY • AUGUST 27 • AFTERNOON**

Dept. of Obstetrics and Gynecology, Tokyo Medical College Hospital, Shinjuku Tokyo JAPAN

Although novel anti-tumor agents have improved the efficiency of chemotherapy, their use, especially the route of administration, still has much to be improved.

With a new technique of nonsurgical selective intra-arterial injection, we treated uterine adenocarcinoma patients. We tried to give anti-cancer agents, CDDP (cisplatinum diamminedichloride), by intra-arterial administration in order to get the regional effectiveness.

Intrauterine artery of both side were applied to give the consumption of CDDP by catheter which was led through femoral artery and common iliac artery.

The number of patients was 10 cases of cervical cancer (8 operated, 2 inter-operative) and 2 cases of endometrial cancer. Total dose of CDDP that was injected was using 3 days by one shot administration. To detect the amount of CDDP in serum, tissue and urine another absorption method was utilized. Pharmacological change of drugs after intra-arterial administration of CDDP was also tested. Side effect of this method was slightly less than conventional way. Result was obtained as follows: 1) The average value of tissue concentration of CDDP was as follows; ovarian 1.35 ug/g, endometrium 0.94 ug/g, parametrium 1.83 ug/g. These values were quite greater than nonselective intra-arterial administration.

2) Serum Concentration: Total amount of CDDP in serum showed exponential pattern after 2 hours of intra-arterial administration. 3) Fluoro plasma was not confirmed for 3 hours after infusion.

4) Fraction rate C. CDDP in urine was 23% after 24 hours and 27% after 4 days.

Hypersensitivity change: Vascular degeneration and atrophic degeneration of nucleus of cancer cells. Extirpation of small round cell in intravesical tissue. Necrotic and living tissue of cancer from with flumin sten formation. Clinical effectiveness and tumor was considered reducing. In some cases huge lesions in many nonoperative cases.

Side effect of this method was comparatively moderate.

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**4809**

**4810** ABOUT THE ROLE OF TELETHERAPY ON PATIENTS WITH CYSTIC CANCER AFTER EXTENDED EXSTIRPATION OF UTERUS, II-operation-teletomy; III-teletomy-operation. In 81 patients (21.4%) the lymphatic glands were found by histology positive (PH) after extended extirpation of uterus, so this group was excluded from evaluation. Thus for the study 180 patients were included (4-5; 11-59 and 111-56 patients). The survival was evaluated by life table method, the difference was not significant (p 0.05) between the groups (1-94.8%; 11-95.0%; 11.8-92.7%). In the case of teletherapy more patients had specific complications. Urologic fistulas were found in the group with preoperative teletherapy in 1.8%, but without irradiation only in 0.0%. The irradiation factor caused immunodepression of the organism, and these patients had more physical and psychological rehabilitation undergone. The authors prefer the beginning of treatment in patients with cervical cancer, stage I with extended extirpation of the uterus. If positive lymphatic glands were not found by histology, the teletherapy is not necessary.

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**4811** URINARY COMPLICATIONS IN SURGICAL TREATMENT OF CYSTIC CANCER. Marziona, F., Andrea PO, A.; Abrâo, P.B. Camargo Hospital, Antonio Prudente Foundation, São Paulo - SP - Brasil.

In the period 1951-1983, 710 patients were submitted to surgical treatment in the Dept. of Gynecology, Camargo Hospital, Antonio Prudente Foundation. The clinical staging, treatment procedures and complications are as follows:

- **Stage Ia:** 32 cases. No urinary complication in spite of 10 cases being previously irradiated.
- **Stage Ib:** 229 cases. Preoperative radiotherapy in 195 cases and surgery only in 34 cases.
- **Stage IIa:** In 195 cases irradiated the following complications were observed: 12 urinary fistulas being 5 early uretero-vaginal fistula, 5 late uretero-vaginal fistula and 6 late vesico-vaginal fistula.
- **Stage IIb:** 407 cases, 2 cases with only surgery and 405 with preoperative radiotherapy. A total of 51 cases presented with the following complications: 3 early uretero-vaginal fistula, 6 late uretero-vaginal fistula and 4 late vesico-vaginal fistula (4 cases) and late vesico-vaginal fistula (22 cases).
EVALUATION OF CERVICAL CANCER METASTASES
H.-U. Lau, Women's Hospital of Humboldt University, Berlin, GDR

A review of the most obvious primary clinical pathways of metastases is presented. The most cervical carcinomas metastasize to target organs after interfacing nodal involvement (72%). Treatment of those nodes can be curative. The incidence rate of metastases in diagnosing the lung runs to 1.5%, in the liver runs to 3.5% and in bone to 0.7%. The indications for a routine organ screening are pointed to.

MEG-VAGINA IN GYNAECOLOGIC CANCER
A.F. Marques; F.R.C.C.D.R.; O. Marclens; F.S. Arrau
Hospital A.C. Camargo - São Paulo - Brazil

Vaginal distortion after surgical and radiotherapeutic treatment of gynecologic cancer is an important problem concerning sexual aspects and appropriate follow-up. Among several reconstructive technical, split-thickness skin graft was used in 12 patients. Seven with carcinoma of the cervix which recurred of had a shortened vagina, 1 with micro invasive carcinoma of the cervix that occurred, 1 with adenocarcinoma of the endometrium with short vagina, 1 with a rhabdomyosarcoma of vagina and 2 carcinoma in situ with recurrent multicentric pre invasive cancer of the vagina. The surgical techian was a transvaginal septum, cut fully dissection forming a tunnel, appliance of the skin-graft over a sponge mold. The results were excellent with an indistinguishable difference between normal and artificial vagina, total integration. The complications were 1 rectal fistula and 1 total lost of the skin graft.

OVARIAN PRESERVATION IN THE CERVIX CANCER TREATMENT.
J.A. Noras Bodeaux, Córdoba, Argentina

Since 1970 we have been preserving the ovarian function in the cervical cancer treatment to young women in order not to add unnecessary pathology. We have done the transposition of one or the two ovaries above the ilioc crest in the operation of Wertheim-Meigs to take them out of the possible irradiation area. In the cases where radiotherapy is applied, one of the ovaries is previously transposed through a special method. Over 206 premenopausal women who were treated with this technique, 208 (98.5%) were with the Wertheim-Meigs and 38 (15.5%) previous to the radiation. The result was initially good in the 82.1% (202). Initially bad but with a functional recovery within 2 to 6 months in the 11.8% (29) and definitely bad in the 6.1% (15). This is a good response to the method of 93.5% (231). The control of these ovaries is made by Ecography and we have had 3 (1,2%) benign residual cysts.


In a prospective controlled study (1975-1984) treatment results and therapy morbidity of patients with stage IB carcinoma of the uterine cervix treated by radical surgery only (Wertheim-Meigs) were compared with those of patients treated by radical surgery followed by an external radiotherapy. The median duration of follow up was months. Competing the survival probability analyzed by life-table-method the study demonstrated comparable therapeutic results with the two therapeutic regimens. There was no difference of tumor size in patients who died after surgery alone and those who died after combined therapy. Lymphedema of the leg developed more frequent in patients treated with surgery and radiotherapy. The study does not demonstrate any beneficial effect of postoperative radiotherapy followed a Wertheim-Meigs operation in cervical cancer stage IB, but optimal staging, radical surgery and carefully histological examination of the removed tissue are essential needs for this approach.
4816 GYNAECOLOGICAL CARCINOMA: TREATMENT OF ADVANCED CERVICAL CANCER: A LOGICAL AND PROMISING APPROACH. M. Vanev, M.D. & S. Gavur, M.D.

Combined chemotherapy and radiotherapy followed by reconstructive surgical staging, provided us with encouraging results which we have previously reported (Third Int. Conference on The Adjunctive Therapy of Cancer, 1981 - Treatment of Advanced Invasive Cervical Cancer, Journal of Oncological Oncology, 1981). It has been and it remains our contention that newer and more effective adjuvant treatments added to radiotherapy (concomitantly, the entire extent of the disease) still improves upon already impressive response rates and survivals. Our latest group of 16 patients with advanced (Stage III or more) cervical cancer were divided into two broad categories:

Group I: Four patients with Stages IIIA or IIB disease and negative nodes were treated with chemotherapy (external and intracavitary) in conjunction with hormonal (Young's) and hormone before 4.

Group II: Twelve patients with Stage IIB (4), IIIB (5), IVA (5) and IVC (1) who had positive pelvic (5) or paraaortic (1) nodes received chemotherapy consisting of Vancomycin (Gm/M2IV), 6-12 hours later Bleomycin (10U/M2IV), Cladribine (1mg/kg) and Alternogomycin (17 mg/kg): All given every week in conjunction with radiotherapy.

Chemotherapy discontinued after intracavitary administration if no residual disease was found, otherwise it was continued. The dose of external irradiation was 3000-5000 r and was given over a period of 3-71 days. The dose to point A from intracavitary irradiation varied between 1330 r to 4000 r. The patients with Stages IIA and IIIB disease had residual disease and underwent total pelvic irradiation. With a follow-up of 1-2 years, 7 patients have died without cancer and 1 is alive with proven pelvic and paraaortic lymph nodes and the rest are well and well without evidence of disease. No patients had grade IV hematologic toxicity, 2 patients had mild radiation dermatitis and 7 developed lymphocytes with superimposed infection requiring treatment.

These preliminary results are gratifying and this approach may offer a valid option in the treatment of advanced cervical cancer, deeming further trials in larger series.


1230 women with cervix carcinoma have been treated at the gynecological Clinic, Res. Inst. of Oncology - Sofia, in the period 1959-1979. According to the stage of the disease, 1,9% of the patients were in I-a stage, 51,7% - I-b, 3,8% - II-a, 21,5% - II-b, 1,7% III-a, 10,9% - III-b, and 1,2% were in IV stage. The histological type was endocarcinoma. The predominant incidence was in the 40-59 age-group. Only surgery was the method of treatment in 37,1% of all the cases, in 18,5% - surgery and radiotherapy, in 26,9% - only radiotherapy, in 5,5% - surgery, in 9,2% - only symptomatic treatment was possible. The 5-years survival rate according to the method of treatment was respectively 85,91%, 64,47%, 61,06%, 15,04%. The 2-years survival rate according to the stage of the disease was I-a = 94,73%, I-b = 75,40%, II-a = 77,24%, II-b = 45,06%, III-a = 31,61%, III-b = 12,22%, and the mean 5-years survival rate 19 60,59%.

4818 THE COURSE OF PREGNANCY AND DELIVERY AFTER CONIZATION OF CERVIX UTERI. B. Milandovitch, E. Postreliev, M. Zuzko, Z. Straz and Z. Perkovski, Department of Obstetrics and Gynecology, and Department of Oncology and Radiotherapy, General Hospital, Split, Yugoslavia

The appearance of invasive carcinomas of the cervix uteri can be prevented by early diagnosis and treatment of CIN. The optimal mode of treatment of CIN in young women in whom fertility must be saved is determined by therapeutic treatment of CIN. Support for this view is provided by a retrospective study of 352 patients conized between January 1, 1975 to December 31, 1980. Following conization, 107 (46.19%) got pregnant and 51 (47.66) delivered. There was only one case of either forceps or vacuum extractor. There were spontaneous abortions in 7.4% of the patients, versus 18.2% before conization, which is statistically significant on the level of 1%.

4819 MALIGNANT TUMORS IN CERVICAL CANCER: TREATMENT AND PROGNOSIS WITH RADIOThERAPY. A. Symon F.T. F. Mikulic, E. Dzuric, A.C. Cabana Hospital, Antonio Proibalic Foundation, Sao Paulo - SP - BRAZIL.

From 1951-1983 in the Dept of Gynecology, A.C. Cabana Hospital, Antonio Proibalic Foundation, a series of 160 cases were surgically treated, being 650 with previous irradiation: State Ia (17 cases), Ib (119 cases), IIa (145 cases).

In the state Ia (17 cases) no residual tumor was found at the pathological examination. In the state Ib (119 cases) residual tumor was identified in 24 cases (21%). These histological distribution was squamous cell carcinoma in 104 cases, adenocarcinoma in 5 and undifferentiated carcinomas.

The surgical specimens of adenocarcinomas and undifferentiated cancers revealed no residual cancer.

In the state Ila, all 40 cases were of squamous cell type and 8 cases (20%) revealed residual cancer in the surgical specimen. In the state IIb, the histological typing of the 40% cases was: squamous cell carcinoma, 18 adenocarcinoma and 11 undifferentiated carcinomas in this state 14.3% revealed residual tumor in the surgical specimen.
In the period 1953-1983, the Dept. of Gynecology, Camargo Hospital, Antonio Prudente Foundation, had 661 cases of cervical cancer surgically treated according to the Wertheim-Meigs Technique. This group includes cases which were previously irradiated or not. The correlation of clinical staging, positive metastatic lymph nodes in the surgical specimen and survival time is as follows:

<table>
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<tr>
<th>Lymph nodes</th>
<th>Clinical stage</th>
<th>5 years survival</th>
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<tr>
<td>+</td>
<td>25 1b</td>
<td>40%</td>
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<td>186</td>
<td>84.4%</td>
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<td>53 with previous radiotherapy</td>
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<td>33 without previous radiotherapy</td>
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<td>37.1%</td>
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<tr>
<td>-</td>
<td>322</td>
<td>71%</td>
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4822 “SECOND-LOOK LAPAROTOMY IN OVARIAN CANCER: PATHOLOGY AND PROGNOSIS EVALUATION” - Carlos A. Hodes, Carlos A. Hodes, Roberto Antunes, Junior, in Campinas Chair of Oncology, University of Sao Paulo, Brazil. - This relationship with non-cytological methods. The more frequent relapse rates.

Methodology: Between the years 1978 and 1985, 48 of 200 patients with ovarian cancer followed to second-look laparotomy. Stage I involved 12 pts (25%), stage II involved 11 pts (46%), stage III involved 13 pts (27%), and stage IV involved 2 pts (4%). The relationship with non-cytological methods. The more frequent relapse rates.

Conclusion: Only 19 pts have accurate initial pathology. Following information of 3 remaining cases was obtained: The prognosis is modified in 3 cases (gastric cancer, lymphoma, cancer). The more frequent relapse rates are studied. The pathological examination of the ovaries and the abdomen is determined in 3 cases. The average survival time is 120 months. The more frequent relapse rates are studied. The pathological examination of the ovaries and the abdomen is determined in 3 cases. The average survival time is 120 months.
AMINOGLUTETHIMIDE TREATMENT OF METASTASIZED BREAST CANCER: PATIENTS AND FUTURE ASPECTS

J. Kühbacher, H. Zentgraf, P. Föttinger and Ch. Stieler
II. Med. Dept., Univ. Vienna, Austria

In a series of 45 female patients aged 35-80 (mean 57.6 years) in postmenopausal phase or after previous oophorectomy, with multiple metastases (osseous, pulmonary, visceral) and therapeutic resistance to former chemo- and radiotherapy as well as to tamoxifen, treatment with aminoglutethimide was performed. According to the standard schedule slowly increasing daily doses up to 750 (500) or 1000 mg were applied p.o. combined with 40 mg hydrocortisone. Side effects (mainly central sedation and ataxia) extremely xenanthema, sometimes manifestation of hypertension, but so far no signs of hematotoxicity) were observed in about 30% of patients and were mitigated usually by slight dose reduction.

Results: As an actual response CR (4; 8.8%) and PR (29; 64%) as well as stabilization of disease (53; 38%) could be established besides an only minor rate of progression (13; 31%). Subjectively relief of pain was predominant. Duration of remission showed a decline from CR + PR (mean 10.5 months) to stabilization (7.7 months). Problems of aminoglutethimide therapy in advanced breast cancer consisted in some tendency to spontaneous fractures in individual patients with preexisting osteolytic lesions, rarely hematotoxicity (granulo- and thrombocytopenia) has been observed. Some patients have been treated with aminoglutethimide in a not randomized trial. 101 pts. were evaluated. There was no difference as far as age (45.4 years, 60.4 yrs.), hormonal status (progesterone (pros) 26.5%, postmenopausal (post) 7.4%, estradiol (E2); 23.3%, progesterone (P); 78.0% and predominant bone metastases (39.1%), 14.0%. The response rate was divided into: complete response (CR) 10.7%, 13.5%, partial response (PR) 14.9, 13.5%, stabilization (S) 39.2%, 19.3, progression (P) 0, 0.5. The duration of R was in 41.2 months, 11.4 months, the differences were made evident in the survival (S) related to R that showed following tendency CR, 21.6 months, 21.1 months, CR + PR, 18.6 months, S, 8.5 months, P, 4.0, 4.6 months, S, 4.9 months, globally the S to the treatment in both groups was in 27 months, 31.7 months. As far as bone metastases there was a CR in 31.2%, 21.2%, CR + PR in 13.9%, 13.5%, S in 29.0%.

Conclusion: The percentage of R of CR, P in both groups is similar and not statistically significant (P > 0.05). The pts. that were treated with CT and AT obtained CR showed a tendency to a major S. 1) The S of the pts. in progression treated with TAM was better. 2) No difference in bone diseases response (P > 0.05). The overall objective response was 37.1% (CR 13.5%, PR 23.6%, S 24.0% in both groups). The response rate was significantly better for the TAN(51.1%) than for the CT (12.8%). The duration of remission in both groups was similar to the statistical difference.

2) The pts. that were treated with CT and AT obtained CR showed a tendency to a major S. The differences were made evident in the survival (S) related to R that showed following tendency CR, 21.6 months, 21.1 months, CR + PR, 18.6 months, S, 8.5 months, P, 4.0, 4.6 months, S, 4.9 months, globally the S to the treatment in both groups was in 27 months, 31.7 months. As far as bone metastases there was a CR in 31.2%, 21.2%, CR + PR in 13.9%, 13.5%, S in 29.0%.

Conclusion: The percentage of R of CR, P in both groups is similar and not statistically significant (P > 0.05). The pts. that were treated with CT and AT obtained CR showed a tendency to a major S. 1) The S of the pts. in progression treated with TAM was better. 2) No difference in bone diseases response (P > 0.05). The overall objective response was 37.1% (CR 13.5%, PR 23.6%, S 24.0% in both groups). The response rate was significantly better for the TAN(51.1%) than for the CT (12.8%). The duration of remission in both groups was similar to the statistical difference.

SAFETY AND EFFICACY OF Toremifene IN BREAST CANCER PATIENTS A PHASE I STUDY

Hitte Valvaara, M.D., Rugga Parina, M.D., Margrete Benckendorf, M.D., Eeva Backlund, M.D., Potti Talanen, M.D., Lars Wallgren, M.D., A. Hauge, M.D., Arne Beggas, M.D., Department of Radiotherapy and Oncology in Helsinki, Finland and Turku University Central Hospital and Research Center for Breast Group, Finland.

Toremifene is a new antoestrogen antineoplastic agent. It binds to the estrogen receptors of the cytoplasm, is transported to the nucleus and blocks estrogen-induced cell proliferation. The mechanism of action of toremifene is directed against estrogen-dependent tumor of the mammary gland and of the endometrium.

Aim: In this multicenter study we have studied the efficacy of toremifene in the treatment of advanced breast cancer, either metastatic or primarily inoperable. Patients were postmenopausal with no previous hormone or cytostatic medication. All tumors were estrogen receptor positive.

Methods: Since September 1981, 47 evaluable patients, which is the final patient number of the study, have been treated with 80 mg toremifene orally as a single dose daily. In addition to the objective response rate, the effect on hormonal and clinicochemical parameters and tolerance has been evaluated on the basis of a half year treatment.

Results: Of the 46 evaluable patients, eight achieved CR, 26 achieved PR, 2 had partial response (PR) in 53.2%. Response rate seems to be independent of the ER level of the tumor; if CR was achieved, it was less than 100 fmol/mg protein in 13 of 24 responded and if it exceeded 100 fmol/mg protein in 12 of 23 responded. The mean OR value decreased during treatment from 40.8 to 27.2 and PFM from 50.5 to 34.6 U/l. No signs of renal or hepatic toxicity have been observed. Some patients have complained of light hot waves, sweating, nausea or transient vertigo.

Conclusion: Toremifene seems to be an effective treatment with few side effects in advanced estrogen receptor positive breast cancer of postmenopausal women.

A COMPARISON OF "CONVENTIONAL THERAPY" WITH "NO THERAPY" PLUS "HORMONE" THERAPY IN THE TREATMENT OF ADVANCED BREAST CANCER IN POSTMENOPAUSAL WOMEN

A Wilkins, S. Shephard, S. D. Kernohan, K. Williams, S. Shephard, M.D., J. R. Ambrose, M.D. and D. P. Slade, M.D., Royal Infirmary of Edinburgh, Edinburgh, and General Hospital, Huddersfield, Huddersfield.

Both tamoxifen (TM) and fluorouracil (FLU) are recognized treatments for advanced breast cancer, producing objective response rates of around 15%. It therefore seemed reasonable to investigate the effects of these two agents with the aim of increasing their therapeutic efficiency. Twenty-six patients were treated with TM and obtained CR or partial response (PR). They were divided into two groups: the first group received TM (62 patients) and the second group was treated with CT (40 patients). The overall objective response was 29% (12 PR 29) for TM alone and 62% (12 PR 29) for the combination group. At this time, there was no significant difference between the two groups. The median patient survival was 48 months for TM alone and 42 months for the combination group. The overall median survival was 63 months for the combination group and 52 months for the CT alone group. The median survival was significantly shorter in the combination group than in the TM alone group. The median survival was significantly longer in the combination group than in the CT alone group. The median survival was significantly shorter in the combination group than in the TM alone group. The median survival was significantly longer in the combination group than in the CT alone group. The median survival was significantly shorter in the combination group than in the TM alone group.

The clinic trial reported here was a multicenter inpatient trial study in which all patients were randomized to TM (20 mg b.i.d) or FLU (200 mg b.i.d). At the time of the interim analysis, 290 patients had been randomized. The overall objective response rates were 29% (14 PR 29) for TM alone and 62% (12 PR 29) for the combination group. At this time, there was no significant difference between the two groups. The median survival was 48 months for TM alone and 42 months for the combination group. The overall median survival was 63 months for the combination group and 52 months for the CT alone group. The median survival was significantly shorter in the combination group than in the TM alone group. The median survival was significantly longer in the combination group than in the CT alone group. The median survival was significantly shorter in the combination group than in the TM alone group. The median survival was significantly longer in the combination group than in the CT alone group. The median survival was significantly shorter in the combination group than in the TM alone group.
randomized trial to verify: 1: clinical response to TAM and/or MPA was determined on soft tissue lesions. 0

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M-41: Breast cancer: medical oncology

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Randomized study in postmenopausal patients with metastatic breast cancer previously treated with chemotherapy, hormone and X-ray therapy. Terzoli E., Nistico C., Izzo F., Calvetelli E., Lucatelli S., Nardi M., Pollera C.F., Bardiaghi M. Regina Elena National Tumor Institute, Rome, Italy.

The patients intended verifying the effectiveness of treatment with amnoglutethimide in patients affected with metastatic breast cancer previously treated with chemotherapy (CF/AV/6 MGI), hormone (TMX and/or MPA) and X-ray therapy. Fourteen patients, all in menopause were selected whose receptor condition was not known and of an average age of 60-80 years. Nine patients (61%) had bone metastasis, 4 (28%) skin metastasis and 1 patient (7%) hepatic metastasis. Of the 9 cases with bone metastases, 1 was at an advanced stage, 5 presented a stationary condition of disease lasting 12-27 months and 3 patients improved for 11 months. Of the 4 patients with skin metastases, 1 presented disease progression, 2 obtained a stationary condition for a period of 12 months and 1 showed an improvement lasting 10 months. The patient with hepatic recurrences improved for 5 months, as evident from therapy. Randomization to the administration of the drug, 4 patients (28%) suffered arterioles, 1% (7%) lethargy and 1 presented cutaneous erythema. The results obtained in patients who had been heavily pretreated, considering the number of cases studied confirms the hypothesis that one further possibility for treating breast cancer at an advanced stage...
**AMINOGLUTETHIMIDE (AG) IN ADVANCED BREAST CANCER (BC): LOW DOSE VERSUS STANDARD DOSE (1G. 3L) IN A PHASE III STUDY**

AG given in the standard dose of 1000 mg/day provides effective treatment in BC in postmenopausal women. It has long been presumed that as medical adrenalectomy it exerts a hormonal effect on tumour growth by blocking the desmolase enzyme and further inhibition seems to be induction of the peripheral aromatase enzyme system. Experimental studies show that this effect can be achieved at a lower dosage. Side effects of AG at dosages of 500 mg (Group A) and 1 g (Group B) in a Phase III study. In both groups replacement with cortisone acetate is given (50 mg/day). In up to 100 patients have been randomly allocated to treatment (A:53, B:58). There are no significant differences between the two groups with respect to the stratification criteria (age, menopausal status, performance status, tumor-free interval, previous treatment, site and number of metastases). So far 71 patients are available for therapeutic results (A:33,B:38) and 43 patients in side effects (A:37, B:30). Up to now there have been 1 CR and 4 PR in Group A and 2 PR in Group B. Further 20 patients in Group A and 7 patients in Group B show minor response or stable disease. Of 32 patients in Group A and 16 out of 30 in Group B obtained pain relief or tremor from pain. The differences are not significant. There is no indication of differences between the two treatment groups in duration of response. Side effects were seen in 14 patients in Group A and 21 patients in Group B. Subjectively unimportant symptoms or local signs improved by treatment. Some patients in Group B showed signs of systemic improvement, e.g., improvement of appetite, reduction of diarrhea, etc. We found no significant differences between the two groups with respect to side effects. The lower dosage AG is as effective as the standard dose but less toxic.
PROGNOSTIC FACTORS FOR RESPONSE TO AMINOGLUTETHIMIDE (AG) IN METASTATIC BREAST CANCER. P. Pronzato, A. Ardizzoni, M. Giuliani, R. Iomoto, A. Rubagotti, A. Rossi, C. Ambrosio, Istituto Nazionale per la Ricerca sul Cancro, Genova, Italy; and Ciba Geigy Medical Department, Padova, Italy.

AG commonly used as an hormonal manipulation of breast cancer (BC). At our Institute AG has been used as second line hormone-therapy (HT) in a series of 131 patients (pts) with metastases (mts) from BC. Dose schedule was: AG 250 mg orally 4 times daily; hydrocortisone acetate was associated at the start of the treatment. Pretreatment: only chemotherapy (CT) in 30 pts, both adjuvant and for mts in 23 pts, and only for mts in 71 pts. Pretreatment were: only adjuvant chemotherapy (CT) in 31 pts, only ET for mts in 26 pts, both adjuvant and for mts in 23 pts, all pts were pretreated with tamoxifen (tam). Overall results are: 23/104 (22.2%) partial response (PR), 38/104 (36.5%) stable disease (SD) and 43/104 (41.3%) progressive disease (PD).

Age of pts (< 40 vs 41-50 vs 51-60 vs > 60 years) range 30-87; dominant site of mts was soft tissue in 30 pts, joint in 71 pts and viscera in 30 pts. Pretreatment were: only adjuvant chemotherapy (CT) in 31 pts, only ET for mts in 26 pts, both adjuvant and for mts in 23 pts, all pts were pretreated with tamoxifen (tam). Overall results are: 23/104 (22.2%) partial response (PR), 38/104 (36.5%) stable disease (SD) and 43/104 (41.3%) progressive disease (PD).
M-61: BREAST CANCER: MEDICAL ONCOLOGY V

4839 CENTCHROMAN-A NEW ANTIESTROGENIC COMPOUND IN ADVANCED CANCER BREAST: A PHASE II STUDY.

Centchroman; 3, 4-trans-2, 2-dimethyl-3-phenyl-4-[8-pyrrolidinoethoxy] phenyl-7-methoxychroman; a non steroidal compound has been shown to possess weak estrogenic and potent antiestrogenic activities. This compound in dosages of 60 mg thrice a week was administered orally to 85 patients of cancer breast and the results were evaluated in 73 patients [69 female, 4 male] who were rejects to conventional modalities of therapy. Significant remission was achieved in 29 female [complete 9, partial 20] and 3 male [complete 1, partial 2] patients. The response was better in peri- and postmenopausal patients. Maximum response was achieved in 4 weeks of Centchroman therapy. The median duration of response was 6.3 months. Cutaneous, soft tissue, nodal and bony metastases responded better than visceral (liver). Based on these observations it is concluded that Centchroman is effective in metastatic cancer breast with no toxic effects.


Twelve male patients (pts) with advanced breast cancer were treated with cyproterone acetate (CPA at the dose of 100 mg twice a day. All pts (median age= 61 years, range 29-77; median Karnofsky performance status= 60, range 30-100) had clearly measurable disease, and all but 3 had received prior therapy for their metastatic disease. Objective responses (WHO criteria) were observed in 7 pts, with a median duration of response of 4 months. Median survival was longer in responding than in non-responding pts (18 vs 12 months). Remissions were obtained irrespective of patient age, performance status, disease-free interval, metastatic sites, and prior therapy. In 7 pts, serum levels of 10 hormones were measured before and during treatment. No serum hormone change could be considered as a valid indicator of the therapeutic response. Side-effects were minimal. CPA appears to be an effective and well-tolerated treatment for metastatic male breast cancer.

4841 TAMOXIFEN (T) IN ELDERLY MEN WITH BREAST CANCER (BC).
G.Cartel*, Med. Oncology Division, Dept. of Oncology, Udine Hospital, Italy.

Tamoxifen is largely used in female BC, few reports dealing with male BC. Nine consecutive male patients with BC as seen by the author from Jan. 1979 to Nov. 1985, were treated with T (30 mg/day). All pts except one had locally advanced disease or associated chronic disease which precluded radical mastectomy. Hormone receptors (E.R - PgR) were available in 2/9 pts (1/9 at the time of recurrence††). 7 pts treated at least for 4 months are evaluable:

<table>
<thead>
<tr>
<th>pt age</th>
<th>surgery on pNaxill pNsupraclav</th>
<th>E,R PgR</th>
<th>(incisional biopsy)</th>
<th>T dose/mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>RG</td>
<td>90</td>
<td></td>
<td>not available</td>
<td>676-528</td>
</tr>
<tr>
<td>ZA</td>
<td>72</td>
<td>+</td>
<td>not available</td>
<td>251-19</td>
</tr>
<tr>
<td>CHG</td>
<td>72</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>PA**</td>
<td>56</td>
<td>-</td>
<td>+</td>
<td>112-85</td>
</tr>
<tr>
<td>CIG</td>
<td>76</td>
<td></td>
<td>+</td>
<td>90-52</td>
</tr>
<tr>
<td>PC</td>
<td>78</td>
<td></td>
<td>+</td>
<td>120-21</td>
</tr>
</tbody>
</table>

Patients had from 4 to 47 months (median 12) observation; RG and CG died at 9 and 12 months because of other disease than cancer (MHC in PR from BC). 5/7 pts gained PR (UICC criteria) (71††): 1/7 gained and maintained clinical CR after 6 months therapy. The PA young pt showed progression (skin, node). Mild nausea and stipsis were observed in 5/7 pts not requiring T dose reduction; 1/7 had prurigo probably related to T; 1/7 complained headache requiring T reduction to 20 mg/day. However, in more aged pts it is conceivable that some spontaneous T reduction had occurred. Conclusion: T is well tolerated and represents an effective therapy in the rare BC of the elderly men.


Twelve male patients (pts) with advanced breast cancer were treated with cyproterone acetate (CPA) at the dose of 100 mg twice a day. All pts (median age= 61 years, range 29-77; median Karnofsky performance status= 60, range 30-100) had clearly measurable disease, and all but 3 had received prior therapy for their metastatic disease. Objective responses (WHO criteria) were observed in 7 pts, with a median duration of response of 4 months. Median survival was longer in responding than in non-responding pts (18 vs 12 months). Remissions were obtained irrespective of patient age, performance status, disease-free interval, metastatic sites, and prior therapy. In 7 pts, serum levels of 10 hormones were measured before and during treatment. No serum hormone change could be considered as a valid indicator of the therapeutic response. Side-effects were minimal. CPA appears to be an effective and well-tolerated treatment for metastatic male breast cancer.
PHASE II STUDY OF ORAL IDRABIJUBIN (IDR) IN ADVANCED MALIGNANT MELANOMA: A CROPPED REPORT

M. Van der Burg, Ph. Chollet, L. Cauchie, PF. Berruti, D. Thomas and G. Mehdi for the CROCC Clinical Screening Group.

Idrabijubin is a new anthracycline which is absorbed by oral route and has shown activity in animal tumor models and in phase I studies. Moreover IDR is significantly less cardiotoxic when administered in animals. A phase II trial was conducted in patients with advanced malignant melanoma; eligibility criteria included measurable lesions, performance status (PS) 1 or 2 (WHO scale), age <75 years, a life expectancy >3 months, neutrophil count >3000/mm3, glaseter (PLT) >100,000/mm3 and normal renal and liver functions. IDR was given at the dose of 45 mg/m2 every 3 weeks. Twenty-four patients are presently evaluable for efficacy. Patients characteristics are as follows: male : female ratio of 6:16, median age : 54 (range 34-75), median WHO performance status : 1, prior chemotherapy without anthracycline : 6 pts and prior radiation therapy in 9 pts. One complete response were observed in a non pretreated patient with skin and node involvement lasting 27 weeks. There were also 7 stable diseases. Hematologic toxicity following the first course was moderate with 54% of pts having less than 4000 leukocytes/mm3 at day 21 (WHO grade 2-3). The grades 1-2 and 3 observed in this trial indicates a correct choice of the dosage and constant and good biodistribution of the drug. Hematologic toxicity was evaluated on the total number of evaluable cycles (median 3, range 1-10). Nausea vomiting occurred in 80% of pts (WHO grade 3), diarrhea in 23% of pts (WHO grade 3), stomatitis in 68 (WHO grade 3 : 1 pt). Hair loss was observed in 24% of pts but partial and complete alopecia occurred only in 2 pts (WHO grade 2 : 1 pt, grade 3 : 1 pt). No signs of cardiac dysfunction were recorded. These preliminary results suggest a lack of activity of IDR in advanced malignant melanoma.

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COHESIVE CHEMOTHERAPY (VBL-BLUU- DDP) IN ADVANCED MALIGNANT MELANOMA: A 4-YEAR FOLLOW-UP

Cocilla G., De Marcy M.R., Scarpa A., Jarnaglin G., Cocilla P., Melillo G., Zarruff D., Department of Medical Oncology, Tumour Institute, Naples, Italy.

Between 1982 and 1985, 28 pts with advanced malignant melanoma previously treated with adjuvant DDD were submitted to a combination chemotherapy including: vindesine (VBL), 6 mg/m2 i.v. days 1 and 2, bischloroethylnitri- strosourea (BCNU), 100 mg/m2 i.v. day 3; cis-platinum (DDP), 50 mg/m2 i.v. day 5. Courses were repeated after a 4-week rest-period. Responses to therapy were classified as follows: Complete Remission (CR) = 7(25%); Partial Remission (PR) = 7(25%); Stable Disease = 5(18%); Progressive Disease (PD) = 14(50%). Therefore, the overall response (CR+PR) rate was 25%. After 36 months of follow-up the median length of responses was 14 months, and the median length of survival was 11 months (23 months for responder pts).

Our treatment compared with other salvage combination chemotherapies does not seem to improve the response rate of pts, but it prolongs the duration of responses and the overall survival, mainly in responder patients.
CHEMOTHERAPY OF THE MALIGNANT MELANOMA
Z.Rudolf
Institute of Oncology,Sofia,Bulgaria

To evaluate the role of the chemotherapy 95 patients in II. and III. clinical stages were investigated. Four chemotherapeutic schemas were used - DTIC alone, DTIC and BONU, Coomagen, BNU and VOR, Coomagen, VOR, BONU and GFA. The results in II. stage melanoma patients indicate that the 5-years survival rate may be moderately modified by the adjuvant therapy. This refers to the DTIC and the DTIC plus BONU treatment. The response and survival rate in the III. clinical stage are not satisfactory, DTIC alone and the combination BNU, VOR, Coomagen are more effective than the other two combinations.

CHEMOTHERAPY FOR ADVANCED SOFT TISSUE SARCOMAS: MEDICAL ONCOLOGY

Twenty-three pts. with Lissarcosta were included in this study. All patients of this group had spread disease at onset. 14 pts. were female and 9 pts. were male. Age ranged from 23 to 75 years (50.63 years). Median Performance Status was 1 (0-2). All pts. had one or more measurable lesions. The combination chemotherapy consisting of Adriamycin 50 mg/m² iv, day 1; Vincristine 2.5 mg/2 iv, day 1 to 5; both was repeated every 21 days and BCNU 60 mg/m² oral every 4 weeks x 3. Histological subtypes were 1 well differentiated liposarcoma, 8 mixed, liposarcoma 2, fibroliposarcoma 2 and 8 pleomorphic, 7/23 pts. (30.4%) achieved complete remission (CR), 5/23 pts. (21.7%) had partial remission (PR), 4/23 pts. (17.3%) had stable disease (SD), and 7/23 pts. (30.4%) had progressive disease. The Response Rate (CR+PR) was 54%. Median Survival was 22.6 months (8-63).

Sites of metastases were lungs (23) and as were as follows: jilipedia (15), abdominal mass (9), brain (4), bone (5), subcutaneous nodule (4), bone marrow (2), and liver (4). The toxicity was: leucopenia 22/23 (95.6%), nausea and vomiting 18/23 (78.2%), diarrhea 7/23 (34.3%), rash 2/23 (10.4%), etc. Severe hematological toxicity was observed in 14/23 pts. (60.8%) WBC less than 2.000, platelets less than 75.000.

We can conclude that this combination chemotherapy: AD/DTIC/BONU have activity in Lissarcosta.
**M-62: MALIGNANT MELANOMA AND SOFT TISSUE SARCOMAS: MEDICAL ONCOLOGY**

**4850 RESULTS OF PALLIATIVE AND ADJUVANT CHEMOTHERAPY IN 53 PATIENTS WITH SOFT TISSUE SARCOMAS**

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Institute for Pathology, Bethesda-Kröhs, D-4100 Duisburg 1

Fifty-three pts with soft tissue sarcomas (STS) were treated either with CYVADIC (VCR 2 mg d 1, CYT 500 mg/m² d 2, ADM 50 mg/m² d 2, DTIC 250 mg/m² d 1-5) or with an ifosfamide containing regimen. 3 pts had an advanced disease. Results of palliative chemotherapy: CR 1 pt (32), PM 12 pts (36%), RC 1 pt (9%), PD 17 pts (51%). Respondents had a median survival of 15 mos. non-responders of 6 mos.

20 pts received a postoperative adjuvant chemotherapy. In all cases the histological grading was estimated using HAMAZ's grading system. 10 pts were low grade and 10 pts had a high grade histology. Results of adjuvant chemotherapy for low and high grade STS:

- Low grade
  - With adj. chemoth.: T1,N0,M0 alive 10, dead 0
  - Without adj. chemoth.: T1,N0,M0 alive 7, dead 0

- High grade
  - With adj. chemoth.: T1,N1,M0 alive 6, dead 0
  - Without adj. chemoth.: T1,N1,M0 alive 0, dead 0

* 1 pt with local recurrence
** 3 pts with distant metastases
*** 4 pts with distant metastases

Pts with low grade histology didn’t benefit from the adjuvant setting. With and without chemotherapy there were the same good results. On the contrary high grade sarcomas treated with adjuvant chemotherapy experienced less distant metastases than controls. There are striking data demonstrating the important value of the histological grading for the prognosis of STS. Its estimation by the pathologist should be mandatory.

In case of high grade sarcoma a postoperative adjuvant chemotherapy should be given if a curative concept is aimed.

**4851 SOFT TISSUE SARCOMAS: EXPERIENCE IN THE INSTITUTO NAICOLONY IN MEXICO CITY: MEDICAL ONCOLOGY FROM 1962 TO 1974**

Arturo Beltran, M.D., Gonzalo Gabriel, M.D., Verástegui Emme, M.D., Instituto Nacional de Cancerología, San Fernando No. 20, Col. Tlalpan, México.


Malignant Melanoma is an infrequent neoplasm in a dark-skinned population. The anatomical distribution of this neoplasm in dark-skinned people has been reported to be different that in caucasian - skin types. Mexicans can be considered a brown - white race. Between 1962-1974, 199 new melanoma cases were seen at the Instituto Nacional de Cancerología de México, representing 1.4% of all tumors. Annually an average of 3% new patients with this neoplasm were seen. Male - female ratio was 1:2. Average age 59 yrs. A high percentage of the - lesions were advanced, 60% were ulcerative.

Breakdown of tumor sites showed 46.7% were on the lower extremity of these 72% on the foot: 27%, planter 28%, heel 15%. Of all cases - were on the head and neck surface, 6% on the - trunk, 11% on the upper extremity and 16.5% on - other locations - scalp, eye, etc.. 9% of the - patient were men and only 1% of cutaneous - type, 57% of the patients came from rural zones and 43% from urbanized areas.

The prevalence of this melanoma on people can be - under evaluation suggests that other factors - such as the sun should be considered in the etiology of this neoplasm.

**4852 DISTRIBUTION OF MALIGNANT MELANOMA IN MEXICAN POPULATION**

Arturo Beltran, M.D., Gonzalo Gabriel, M.D., Verástegui Emme, M.D., Instituto Nacional de Cancerología, San Fernando No. 20, Col. Tlalpan, Mexico.

Malignant melanoma in Mexico is an infrequent neoplasm in a dark-skinned population. The anatomical distribution of this neoplasm in dark-skinned people has been reported to be different that in caucasian - skin types. Mexicans can be considered a brown - white race. Between 1962-1974, 199 new melanoma cases were seen at the Instituto Nacional de Cancerología de México, representing 1.4% of all tumors. Annually an average of 3% new patients with this neoplasm were seen. Male - female ratio was 1:2. Average age 59 yrs. A high percentage of the - lesions were advanced, 60% were ulcerative.

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The prevalence of this melanoma on people can be - under evaluation suggests that other factors - such as the sun should be considered in the etiology of this neoplasm.
LONIDAMINE IN NON SMALL CELL LUNG CANCER: PHASE II STUDY.
O.Krokro, S.Maza, W.Scheiner, M.de Gregorio* and G.Bottoli**
L.Beutzmann inst. for Clon. Oncology, Austria.
**F.Angrist Res.Inst., Rome, Italy.

Longitine (LND) or 112.4 (control). -1-indazole-3-carboxylic acid, an antimitotic agent which does not act on nucleoprotein synthesis but inhibits the energy metabolism of neoplastic cells. Phase I clinical trial showed no hematological toxicity and a satisfactory tolerance. 69 previously untreated patients with unresectable non small cell lung cancer were admitted to this phase II study. LND was administered p.o., in three divided doses: 600 or 900 mg/day, in 94 and 15 patients respectively. Treatment was continued and lasted for 2 to 133 + days. 7 Partial Responses (PR) and 13 Minor Responses (MR) out of 61 evaluable patients were observed. PR by histology was in/25. 1/27 and 2/9 for Epidermoid Adenocarcinoma and large cell mixed or undifferentiated cancer respectively. PR by stage was 1/10. 1/20 and 1/26 for stage I, II, III and IV respectively. PR lasted for 61 to 335 days (median 209). In the Adenocarcinoma group survival of PR + MR (N=6) was significantly longer than in non responders. Median duration of survival for the whole group was 263 days (320 and 195 for stages III and IV respectively). No difference in response and survival was observed between 450 and 900 mg/day. Mialgia was the most frequent side effect.

SURVIVAL OF 131 CONSECUTIVE NON-SMALL CELL LUNG CANCER PATIENTS: RETROSPECTIVE ANALYSIS ACCORDING TO THE TREATMENT.

The value of radiotherapy (RT) and/or chemotherapy (CT) in prolonging life to a meaningful degree, in stage II or III(N1D1) Non-Small Cell Lung Cancer (NSCLC)patients, has not yet been well established. Data from controlled prospective trials are lacking or not convincing. In spite of this main question it is generally considered unreasonable not to treat potentionally curable groups in a randomized study. For these reasons, comparison of survival of treated pts with an untreated historical control group can give useful suggestions. We reviewed the records of 131 pts with stage III or IV NSCLC referred to the Pordenone General Hospital during the period 1975-1984. All pts were selected by age > 25 years, PS > 0. Survival of pts entered in prospective trials of radiotherapy and chemotherapy was compared with an untreated historical control group. The Montefeltro protocol was employed. Considering all the 131 pts, a significant better survival was related to histological subtype (squamous cell cancer pts survived longer than adenocarcinoma pts, p<0.05) and stage (stage III pts survived longer than stage IV pts, p<0.02). No one saw this trend.

The treated patients, on the whole, showed a significant prolonged survival than the historical control (p<0.02). However, analysis of our data in the different subgroups showed that the survival advantage according to stage and histological subtype showed a significant benefit only in those with squamous carcinoma treated with RT/CT or CT alone.


Until now NSCLC chemotherapy has produced disappointing results. L (AF 1890), a indazole-3-carboxylic acid derivative, don't affect cellular division but acts on energy mechanism of neoplastic cell. L has shown antitumoral effects in sarcoma 180 and in Lewis lung carcinosarcoma but no activity in some other tumors. Currently L is extensively evaluated in different human malignancies.

In our trial we have tested the clinical activity of L in previously untreated NSCLC Stage II/III. Up to date, November 1985, 21 patients have been enrolled, 17 are fully evaluable for tumor response and 18 for Toxicity. M/F ratio was 19/2, median age 69 yrs. (range 58-77), median PS 70 Karnofsky scale (60-100), histology: squamous cell carcinoma 15, adenocarcinoma 4, large cell carcinoma 2. Limited disease stage I/II and extensive disease stage III. Patients received 1.500 mg p.o. x 3 daily. Until now we have observed 1 Partial Response and 3 Minor Responses. Stable diseases have been 7 and Progressive Diseases 6. PR lasted after 30 days. 1 patient was observed in a Pancoast tumor, regression of ipsilateral shoulder pain was obtained. Median duration of treatment with L is 136 days (range 53-370).

More common toxicities included mild to moderate myalgia (15/18) and testicular pain (13/15). Occasionally, occurred abdominal pain (1), nausea and vomiting (1). Chronic treatment was devoid of haematological, hepatic and renal toxicities. Serum LDH and CPK levels didn't change significantly during treatment. Further studies are recommended to evaluate the effect of L with radiotherapy and cytotoxic drugs in NSCLC.

CHEMO-RADIOTHERAPY +/- LONIDAMINE IN NON SMALL CELL LUNG CANCER - LIMITED DISEASE. PRELIMINARY RESULTS.

The antitumor drug LONIDAMINE (L) or I-2,4 dichlorophenyl(methyl-1H-indazole-3-carboxylic acid, has a variety of effects on neoplastic cell energy metabolism and especially inhibits anaerobic lactate production. Its antineoplastic effect has been demonstrated in vitro and vivo, not only when used alone, but especially in combination with hyperthermia, X-rays and cytotoxic agents. This study has been performed according to a 2 arm randomized design. Arm A underwent chemotherapy (CT) 2 + 2 courses (COOP 100 mg/m2/day 1, 2.8, 10, 20 in 21 days) and radiotherapy (R) (split course 30+20 Gy). Arm B received Arm A treatment (CT+R) + L 150 mg t.i.d. the same orally. L was administered continuously up to progression. 42 pts (32 in Arm A and 20 in Arm B) and 51 patients (27 in Arm A and 24 in Arm B) were evaluable for response after the 2nd course of CT and after CT and R respectively so far. After the first 2 courses of CT there was a trend (P<0.10) in favour of the CT+R combination in epidermoid cancer (Arm A: 4 PR, 14 NC, 4 PD; Arm B: 13 PR, 13 NC, 4 PD). Time to progression was significantly longer (P<0.02) in pts with epidermoid cancer treated with CT+R (median 339 days) than L (median 154 days). Testicular pain (37%) and photophobia (8%) and skin hypersensitivity (3%) were observed in the L group. No one saw toxic effects which were not observed between the two groups.

(Supported by grant n° 8400595.44 of CNR. Project "Oncologia").
A phase II clinical study of Vepesid (Etoposide, VP-16-213) was conducted in patients with advanced lung cancer. 21 patients were treated with this drug, and morphologically proved diagnosis with prevalence of the squamous cell carcinoma in 79%. Vepesid was given in regimens of 120 mg/m² daily for 5 consecutive days, two courses with 14-day intervals. Results of the treatment are reported concerning: 1) the primary tumor - a minimal response was achieved in 3 patients, no progress in 10 patients, and progression in 7 patients; 2) the metastasis - complete response in 1 patient (lymph node), partial response in 2 patients (lymph node and skin), minimal response in 2 patients (lymph node and pleuritis). In all patients was established slight to moderate alopecia. There was no manifestation of leukopenia and thrombocytopenia.
4861 LOW DOSE CISPLATIN BASED REGIMENS IN NON SMALL CELL LUNG CANCER. G. Lelli, M. Casadio, L. Giulotti, R. Picco, and F. Pastini. Oncology Division, A.Malpighi Hospital, Bologna, Italy

Thirty-six patients with histologically proven non-small cell lung cancer were treated by our group in two subsequent studies, with weekly chemotherapy regimens containing cisplatin (CDDP, 10mg/m² IV). In the first trial CDDP was combined with 6-mercaptopurin (APEXID 30 mg/m² IV), in the second study with etoposide (VP16 60mg/m² slow iv infusion–1 hour). The main characteristics of the patients and the objective results are listed below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of patients</th>
<th>Median age (range)</th>
<th>Median P.S. (range)</th>
<th>Histotype</th>
<th>Median time to progress (range)</th>
<th>Median survival (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDDP+APEXID</td>
<td>14</td>
<td>61(65-74)</td>
<td>60%(40-70)</td>
<td>adenocarcinoma</td>
<td>7/14</td>
<td>44wks.(10-67+)</td>
</tr>
<tr>
<td>CDDP+VP16</td>
<td>16</td>
<td>63(45-77)</td>
<td>60%(30-80)</td>
<td>adenocarcinoma</td>
<td>2/18</td>
<td>24wks.(4-67+)</td>
</tr>
</tbody>
</table>

No differences were noted in the incidence of vomiting (CDDP+APEXID; 50% vs. CDDP+VP16; all grade WHO 1-2), or severe leucopenia (median MBC nadir respectively 3600/mm³, range 3000-3700 and 3700-3900). Even though there were no statistically detectable differences in the objective remission rate (Fisher's test) there was, however, a trend in favour of the VP16 containing combination confirmed by the gain in the survival period (p<0.01) and in time to progression (p<0.05). A random study has been undertaken which compares weekly CDDP+VP16 with the "standard" intermittent doses of both drugs.


The association between cisplatin (CDDP) and VP16 is one of the most effective treatments in advanced NSCLC. In order to improve the results of this regimen, ifosfamide (IFX) has been added. The schedule employed was: IFX 1500 mg/m² on days 1, 2, 3; CDDP 60mg/m² on days 1 or 1-2; VP16 80mg/m² on days 1, 3-5, or severe leucopenia (median MBC nadir respectively 3600/mm³, range 3000-3700 and 3700-3900). Even though there were no statistically detectable differences in the objective remission rate (Fisher's test) there was, however, a trend in favour of the VP16 containing combination confirmed by the gain in the survival period (p<0.01) and in time to progression (p<0.05). A random study has been undertaken which compares weekly CDDP+VP16 with the "standard" intermittent doses of both drugs.

4863 KARSKY/F-ADAPTED CHEMOTHERAPY FOR NON SMALL CELL LUNG CANCER (NSCLC) WITH IFOSFAMIDE/MITOMYCIN C/VINDESKINE. Schroeder, M., Vepel, H.A., Lander, L., Brunholz, A., Westerhausen, M.

From Jul 1982 to Dec 1984, 42 pts with NSCLC were treated with a regime of CDDP and VP16, each 150mg/m² on days 1-5. CDDP was infused over 4h and VP16 over 4-5h. The toxicity of this regimen is very high: hair loss 100%, severe gastrointestinal side effects (grade 3-4 WHO) 70%. Life-threatening infections were seen in 1 pt. 4 pts died due to severe anemia, 1 pt. died of renal failure. Concerning the efficacy and the side effects of this regimen we cannot be recommended for the therapy of NSCLC. Independent of biological tumour activity it seems possible that some pts benefit from therapy, especially in cases with additional irradiation.

4864 TREATMENT OF ADVANCED NON SMALL CELL LUNG CANCER (NSCLC) WITH VINDESINE (VDS), IFOSFAMIDE (IFX) AND CISPLATIN (CDDP). W. Weihens (1), M. Schroe der (2) and M. Westerhausen (2), OncoI.Dept., Krankenhaus der Barmherzigen Bruder (1), Regens burg, Dept. For Oncol. and Haematol., St. Johanner Hospital (2), Duisburg, FRG.

Between July and December 1984, 42 pts with histologically proven, advanced NSCLC were treated with VDS 30mg/m² day 1, CDDP 80mg/m² day 1 and IFX 500mg/m² day 1-5. Patient distribution: 27 male; age 41-73, KPS 60-90; 15 female: age 51-68, KPS 60-90. Due to one refusal of further therapy 3 of 4 pts died during the first 4 weeks of treatment. 1 pt is lost to follow up. 7 of 27 pts had received prior chemotherapy, prior irradiation therapy. 18 pts without prior treatment achieved CR, 6 pts achieved PR, 3 showed MR (less than 50% tumour regression), 5 showed stable disease and 8 pts progressive disease. In the group of pretreated pts 1 PR was achieved, 5 pts showed no change and 1 pt had progressive disease. Final results concerning response duration and survival can't be made. recruitment for this study will continue. Toxicity was tolerable, only 5 neurotropic episodes with leucopenia grade 4 were observed, nephrotoxicity was absent. In 1 pt we observed pulmonary toxicity of clinical evidence. In comparison to IFX-containing combinations the response rates are nearly the same, 01-toxicity was less severe in our regimen.
TREATMENT OF NON-SMALL CELL LUNG CANCER BY COMBINATION CHEMOTHERAPY USING AS FIRST DRUG VEPESID.

J. Kavoukas and G. Antypas.

Thoracic Surgery Department (Division of Chemotherapy). Metaxa’s Memorial Hospital. Piraeus - Greece.

The efficacy of a five drug combination (Endoxan, Duxorubicin, Methotrexate, 5-FU and Vepesid) was evaluated in 100 patients with non-small cell carcinoma of the lung. All patients completed eight cycles with this drug combination. More than 50% of the cases responded well to the therapy.

CHEMOTHERAPY USING AS FIRST DRUG VEPESID.

100 patients with non-small cell carcinoma of the lung were included in these combination. The results obtained at the 1st evaluation were compared with those of the 2nd. The remission rates, did not reached before in other trials. The M51-data are preliminary because of the short follow up. Considering the toxicity, the combination with Ifosamide instead of DDP is more appropriate to use in further phase-I11 trials.
Non small cell lung cancer (NSCLC): prospective randomized trial with cisplatinum, vindesine (P.G.) vs CisplatinumVinblastine (FV).

In order to investigate the effectiveness of the combination of cisplatinum-Vindesine (P.G.) in NSCLC in comparison to cisplatinum-Vinblastine (FV), we prospectively randomized 26 evaluable, patients. The group A with 12 patients received cisplatinum 80mg/m² and vindesine 3mg/m². The group B with 14 patients, mean age 64.4 years received cisplatinum 80mg/m² and vinblastine 3mg/m². Vindesine and Vinblastine were given on the 1st and 8th days of the cycle of 4 weeks. In group A, 3 patients had adenocarcinoma and 9 squamous cell. In group B, 7 patients had adenocarcinoma and 7 squamous cell carcinoma. In group A, 6 patients (50%) responded (2 complete, 4 partial). The average survival was 7.1 months. The rest 6 patients (50%) failed to respond. The average survival was 3.8 months. In group B, 8 (57%) responded (1 complete, 7 partial). The average survival was 4.8 months. The survival was acceptable.

Based on those preliminary results it seems that in NSCLC the combination P.G. and P.V. are effective. Also P.G offers higher percentages of responses but shorter survival.

Short term vs long term chemotherapy (PE Regimen) in inoperable "NSC" Lung Cancer.

49 patients with NSC underwent chemotherapy as follows:

- CDDP 100 mg/m² day 1. VPL 120 mg/m² day 1, 4, 6, 8. Every 4 weeks. At the beginning 14 pts were in LD, 35 in LD. 49 pts were treated with at least 3 courses of therapy. 26 completed 6 courses, in 12 of them it was possible to apply only the first 3 courses.

The final results were: 23 PR (46.90%), 17 NC (34.70%), 9 PD (18.40%). In the PR group 16 pts were in LD, 7 in ED; in the NC group 16 pts were in LD, 1 in ED, in the PD group 3 pts were in LD, 4 in ED.

The global median survival (MS) was 11.1 months in responders group (Rx) and in non-responders group (NHx) 7.4 months. MS in the group with completed 6 courses of therapy was 16 ms R+ 14.6 ms, R- 12.8 ms (N.S.). The MS in the group who completed 6 courses of therapy was 11.1 ms RF 12.8 ms, RF- 11.9 ms; R+ED = 9.7 ms, R-ED = 2 ms (P<0.01). The MS in the group who completed 6 courses of therapy was 16 ms R+ 14.6 ms, R- 12.8 ms (N.S.).

We didn't find any significant difference in term of results between the various histotypes. Comparing the objective results after the 3rd course and after the 6th course (26 pts), the results were unchanged in 21 cases, 1 patient improved, 4 got worse, showing that the addition of subsequent therapeutic cycles to the first 3 doesn't improve the results. It would be useful to evaluate whether better results will be found in the R+ group with 6 courses of therapy could be due to the greater number of courses administered. A fact which cannot be demonstrated in the present report.

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Results of Chemotherapeutic treatment of primary bronchial cancer patients.

The authors make known longitudinal examination results obtained by mono and poly-chemotherapeutic treatment of primary bronchial cancer patients. They performed the treatment on the basis of chemotherapeutic protocols recommended in Hungary /Sickhardt/. They analyzed the cases in relation to the result of clinical treatment, radiological regression, hemato logical status, complications and survival. They searched for correlation in the time of survival, the applied chemotherapy, and the type of tumour. They registered the above results on the basis of a four-year longitudinal canvass of fifty primary bronchial cancer patients.
**M-63: NON-SMALL CELL LUNG CANCER: CHEMOTHERAPY**

**4873**

**ADVANCED NON SMALL CELL LUNG CANCER (NSCLC): A PROSPECTIVE RANDOMIZED STUDY**

- D. Bonnet, E. M. C. De, F. Abbondanza, E. M. C. De, F. G. Abbondanza, E. M. C. De

In order to verify whether chemotherapy really improves survival in advanced NSCLC, our Cooperative Group started a randomized study to compare a group of patients treated with an alternated regimen (arm A) with an alternated regimen (arm B) receiving a rapid I.V. injection of 30-35 mg/m² depending on prior therapies and P.S. At this time of analysis, 18 patients were evaluable for efficacy and for survival in arm A and 20 patients in arm B. A preceding study had shown 16% objective effects with VMC used with a weekly schedule. The observation period is very short and further follow up is required.

**RESPONSE**

- Arm A: n. age > 35, M/F = 20/1, Histotype SO, 14, AD 6, Karnofsky > 50 in 11, > 70 in 9, Stage M0 = 11, M1 = 9, the results obtained after 2 cycles of therapy or 3.5 months of observation are reported below:

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<th>SURVIVAL</th>
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<td>A</td>
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Despite a higher incidence of progression in the Arm B, survival and alive death ratio are so far similar. These preliminary data indicate no advantage for treated pts.

**M-64: RENAL CARCINOMA: MEDICAL ONCOLOGY**

**4874**

**PHASE II TRIAL OF ESORUBICIN (4'-DEOXYDOXORUBICIN) IN ADVANCED RENAL CARCINOMA**


ESORUBICIN is a new anthracycline derivative that showed less cardiotoxicity and similar activity to doxorubicin in a series of experimental tumors in mice. A phase II trial was conducted in patients with advanced renal cancer. Eligibility criteria included measurable lesions, performance status > 2 (WHO scale), age < 70 years, a life expectancy > 3 months, neutrophil count > 2000/mm³, platelet (PLT) > 120,000/mm³ and normal liver and renal functions. The drug was given every 3 weeks as a rapid I.V. injection of 30 or 35 mg/m² depending on prior therapies and P.S. At this time of analysis, 18 patients were evaluable for efficacy and for toxicity. Two partial responses on lung metastases were recorded lasting 12 and 33 weeks respectively. Myelosuppression was mild with 15% of pts having less than 4000 leucocytes/mm³ at day 21 following the first course. Non-hematological toxicity was also mild: nausea-vomiting (38%; grade 3: 5%), alopecia (38%; no complete alopecia). No cardiac dysfunction was detected. These preliminary results suggest a minimal activity of Esorubicin in renal carcinoma.

* P. Hurteloup - I.C.I.G. - Hôpital Paul Brousse - 14-16, Avenue P.V. Couturier - 94804 - VILLEJUIF - CEDEX - FRANCE

**4875**


In order to verify if chemotherapy really improves survival in advanced NSCLC, our Cooperative Group started a randomized study to compare a group of patients treated with an alternated regimen (arm A) with an alternated regimen (arm B) receiving a rapid I.V. injection of 30-35 mg/m² depending on prior therapies and P.S. At this time of analysis, 18 patients were evaluable for efficacy and for survival in arm A and 20 patients in arm B. A preceding study had shown 16% objective effects with VMC used with a weekly schedule. The observation period is very short and further follow up is required.

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Despite a higher incidence of progression in the Arm B, survival and alive death ratio are so far similar. These preliminary data indicate no advantage for treated pts. However, the observation period is very short and further follow up is required.
A PHASE II COLLABORATIVE STUDY OF UFT ON FAR-ADVANCED RENAL CELL Carcinoma. -Urological Cooperative Study Group of UFT.- Chairman: T. Miijima (Presentation to be made by T. Miijima and N. Akaza), Dept. of Urology, Faculty of Medicine, The Univ. of Tokyo, Tokyo, Japan

UFT, a new combination of uracil(UR) and tegafur (FT) in a molar ratio of 4:1, has been demonstrated to show higher concentration and longer retention of URU in various tumor tissues compared to those in normal tissues. High activity of thymidine phosphorylase in tumor tissues is a suggestive explanation of this phenomenon.

In this paper, results of a phase II study of UFT on patients with far-advanced renal cell carcinoma is presented. Forty-one patients were entered into the protocol from 19 institutions of the group.

The antitumor effect of the drug was clinically evaluable in 25 patients according to the response criteria proposed by the Koyama-Saito group. Seven were not eligible and 9 were cases of protocol violation.

Complete response (CR) and partial response (PR) were observed in 2 and 5 patients, respectively. One patient showed minor response, 8 stable disease and 9 progressive disease. It took about 22 and 16 weeks to obtain CR and PR, respectively. Lung metastasis was most favorable lesion of this treatment. Twenty-one patients were the cause for the evaluation of adverse reaction of the drug.

The gastrointestinal toxicity such as anorexia, nausea and vomiting, was observed most frequently, while bone marrow depression was minimal. Only three patients were discontinued the administration of the drug owing to the adverse effects.

In conclusion, UFT is one of the most effective drugs for the treatment of far-advanced renal cell carcinoma.

CHEMOTHERAPY OF ADVANCED RENAL CELL Carcinoma: PRELIMINARY REPORT. M. Kizzato, R. Harteletti, M.C. Paolletti, A. Costantini. Institute of Urology, University of Florence, Italy.

Metastatic renal cell carcinoma is highly resistant to chemotherapy. Preliminary results suggest that the combination interferon plus vinblastine can achieve better clinical results as compared to those induced by the therapy alone, which are 5%-20% the former and 5%-13% the latter. On the basis of these data, we have started a combination treatment with recombinant leukocyte interferon (rIFN-alpha A) 18 MU i.m. thrice weekly and vinblastine 0,1mg/Kg i.v. every three weeks.

Ten patients have been included in this study and followed up for at least a 6 months period. One patient developed a severe intolerance to treatment (anemia, fatigue) which led to the interruption of therapy. Other patients experienced adverse reaction such as fever, mild leukopenia, fatigue, vomiting; however such episodes were controlled by means of supportive therapy, and never caused interruption of the study.

Preliminary clinical results of this study will be presented and discussed.


Chemotherapy of advanced renal cell carcinoma represents an unsolved clinical problem. Following previous series with ifosfamide we introduced a combination chemotherapy primarily designated for treating transitional cell carcinoma of the urogenital tract (Merrin, v. Eyben). Material and methods: From a total of 30 patients 23 patients (15 male and 8 female, aged 34-75 years with a mean of 56,7) could be evaluated, having mostly multiple distant metastases (lungs, liver, lymph nodes). Treatment consisted of CCNU 130 mg/m2 p.o. given each 6 weeks and vindesine 5 mg/m2 i.v. given weekly x 6. In case of dropping WBC < 3000 the weekly interval was prolonged to 2 (3) weeks. The number of therapeutic courses was 1-4 (mean 2.6), lasting 2-11 (mean 4.1) months. Under antibiotic prevention the medication was tolerated without severe side effects, only constipation or rarely diarrhoea and seldom peripheral neuropathy were observed. During treatment cyclophenia developed (mean 3.1 RBC, 2400 WBC) but no infectious complications occurred except one cystitis.

Results: There was no CR but 3 patients entered a PR and in 15 patients a stabilization could be achieved while progression occurred in 5 patients (with further 8 patients after initial stabilization). Mean duration of response was 2,8 months (CR) and 3,5 months (STAB) respectively.

Conclusions: With the CCNU-vindesine combination applied in consecutive courses following nephrectomy and/or endoprothetic surgery the progression of metastasizing renal carcinoma could be influenced in 18/23 patients (PR+STAB = 78%) providing a raise of the patients quality of life and a prolongation of the life expectancy. By administration of CCNU-vindesine as a first line therapy the prognosis of patients with advanced renal carcinoma has been ameliorated definitely.
Patients with MCC have a poor prognosis. 34% succumbed within one year and 66% within three years. Vincristine alone in weekly doses, determined the highest objective response rate (20%). Vod et al. showed an improvement of the therapeutic index on metastatic breast cancer employing vincristine at continuous 5-day infusion at a dosage varying from 1 to 2 mg/day. However, at 2 mg/day they noted severe neuropathy. In September 1982 they started a pilot study in 25 with MCC employing vincristine as continuous 5-day infusion. Each dose consisted of 0.4 mg/day 5 days, 3 weeks according to previous tolerance and performance Status (P.K.Z.). Tolerability criteria included: no symptoms of peripheral neuropathy, no blood abnormalities, no gastrointestinal, renal and hepatic functions. Central nervous access was routinely used after the first 4 pts. (average age 68). Seventeen pts entered the study. 15 were available for response and 3 were not evaluable (2 early deaths and I refused to continue chemotherapy), i.e., were 26 and 4 females with a median age of 58 years (range 25-75). Metastatic sites were lung in 7 pts, bone in 7 pts, lymph nodes in 5 pts, liver in 3 pts, brain in 1 pt. Median number of cycles administered was 3 (2-6). Seven pts were pretreated with Methotrexate, 5-FU, cisplatin. Combination chemotherapy, one Complete Response (CR) lasting 5 months (1), 2 Partial Responses (PR lasting 4-8 months), 4 Minor Responses (MR lasting 2-5 months), 5 No Response (NR) were noted. Toxicity (early and late) was evaluated in 16 pts. leukopenia was noted in 9 pts (grade I, 1; grade II, 2; grade III, 1), vomiting in 2 pts (grade II), diarrhea in 4 pts. CR, constipation in 2 pts (grade I), infection in 4 pts. MR, emesis in 6 pts. Lomax et al. noted a significant decrease of CRs, PRs, MRs only if cisplatin was given in 14 pts with MCC. On the contrary in our experience with 27 patients responding 1 or evaluable in is evaluable the study needs further pts in order to better define the true activity of cisplatin 5-day continuous infusion in MCC also in regard to the survival.


Combined DDP and 5-FU is the most effective chemotherapy in the treatment of squamous cell carcinoma of the head and neck region (Doeller et al., Cancer 51:3353-55, 1983). However, the toxicity and subjective side-effects are severe. To develop better tolerable drug combinations we combined DDP 100 mg/m² iv day 1 and VP-16 120 mg/m² iv days 3-5 every 21 days (1-1 cycles) in a phase II trial. 31 SCC-HN patients (pts) with no prior therapy and no distant metastases were treated. Due to severe granulocytopenia in the first 8 pts (group 1), VP-16 was reduced to 80 mg/m² iv days 3-5 in pts 9 to 31 (group 2). In group 1 two CRs, 2 PRs, 2 MRs and 2 NCs were achieved. In group 2 one CR, 5 PRs, 11 NRs, 4 NCs and 2 PDs were noted. The CRs were confirmed by histology. Granulocytopenia was the most important side-effect: 9 pts (4 in group 1, 5 in group 2) developed WHO grade IV toxicity. Even when given in a dose where the bone marrow toxicity is severe, the response rates of DDP/VP-16 are lower than with DDP/5-FU.


CHEMOTHERAPY IN ADVANCED HEAD & NECK CANCER

WEDNESDAY • AUGUST 27 • AFTERNOON

4884

M-65: HEAD AND NECK TUMOURS: MEDICAL ONCOLOGY

Drs. Lalit Kumar, C.K. Rathi, Sudhir Bhardwaj & Vindoo Kochhar Institute for Cancer Research and Hospital, All India Institute of Medical Sciences, New Delhi - 110 029, India

Of the 119 patients-34 males, 25 females, 18-78 (M-50) years old, with Squamous Cell Carcinoma - Head & Neck area (Oral cavity 38.6, Hypopharynx-20, Larynx-18.9, Oral cavity-13.4% and Melanoma - Ethanol Complex-11.8%), stage III & IV, 46 received combination chemotherapy (Cisplatinum+Methotrexate, Bismuthin & 6 (Todai-52) received Methotrexate alone followed by Surgery and/or Radiotherapy with curative intent. 48 patients considered inoperable and 19 with recurrence received Methotrexate alone. 50 patients responded, 9 had complete response & 42 partial response, Larynx (17%), Oral cavity (59%) & Maxilla (50%) responded significantly better (P=0.001) than Oral cavity (33%) and Melanoma (42.6%).

Previously untreated, aged being 40 years with tumour size 13 cm or less & Stage IVa N1 response better, an responders to Chemotherapy group with bigger tumour size (T4), bulky Node disease - N2 & N3 and recurrence (P=0.001). Response rate with combination Chemotherapy vs Methotrexate (62% vs 34%) appeared better. Complete response however, was commoner in Methotrexate combination: Chemotherapy group (15.0% vs 2%). Despite the fact that Methotrexate alone group had more advanced disease.

Chemotherapy was generally tolerated better. Neurologic vomiting was most frequent (59%) in combination group while Mucositis (34%) in Methotrexate alone group. 2 Patients - one in each group expired due to Chemotherapy Toxicity.

We concluded that UFT therapy was markedly effective for head and neck cancer.

4886

PHASE II STUDY OF WEEKLY 4'-EPIDOXORUBICIN (4'-EPIDX) IN PRETREATED SQUAMOUS CELL CARCINOMA OF THE HEAD AND NECK (H & N).

G. Bertetto, V. Dongiovanni, M. Clerico, G. Giaccone, A. Mussiala, A. Calcagno, M. Petrucci, Divisione di Oncologia Medica, Ospedale S. Giovanni, Antica Sede, Via Cavour 31, 10123 Torino, Italy.

The second-line chemotherapy for H & N cancer is particularly disappointing and new drugs are frequently tested. 4'-Epidx is a new derivative of Doxorubicin apparently less toxic than the parent compound; its activity in H & N patients has not clearly established.

From October 1984 to November 1985 we tested 4'-Epidx at the weekly dose of 25 mg/m² in 15 pts with advanced, previously treated, squamous cell carcinoma of the H & N. Main characteristics of the pts were: 13 males, 2 females; median age was 62 years (range 36-76) and P.S. (E.C.O.G.) was 1 in 9, 2 in 6pts.

The site of primary tumor was: oral cavity in 7, tongue in 1, oropharynx in 3 and larynx in 5.

All pts received radiotherapy and chemotherapy containing VP-16 & Mtx in multi-drug combinations: 7 pts had submitted to surgery.

Appropriate dose-reduction was applied according to toxicity.

Main toxicity in 15 evaluable pts was: leukopenia in 2 severe; anemia in 4; alopecia in 2; nausea & vomiting in 1, stomatitis in 9. No cardiac toxicity was recorded. 14 pts are evaluable for anti-tumor activity (one required tracheotomy after 2 weeks of treatment and did not continue 4'-Epidx).

Mean duration of treatment was 7.2 weeks (range 4-12); after two months of treatment one pt had Stage Disease and all other progressed.

We conclude that 4'-Epidx at the done and schedule employed in this study, is not effective in heavily pretreated squamous cell carcinoma of the H & N.

4885

PHASE II STUDY OF UFT FOR HEAD AND NECK CANCER

Y. Inuyama*, M. Fujii*, H. Miyake** and C. Takeda***
*Department of Otorhinolaryngology, Keio University, Tokyo**, Department of Otorhinolaryngology, Tokai University, Japan***, Cancer Center of Tokyo Medical College, Tokyo, Japan

To evaluate the clinical efficacy and safety of UFT for head and neck cancer, phase II study was conducted in 10 institutions. UFT is a mixture of UtraCul and Bismuthin in a molar ratio 1:4. Eighty-four patients entered this trial, of which 60 were evaluable. These patients were at the mean age of 64, with the oldest patient at the age of 86. Classification of their primary lesions was: 13 males, 7 females; 10 of them, followed by laryngeal carcinoma in 13, oropharyngeal carcinoma in 9, cancer of nose and paranasal sinuses in 8 and malignancies of other sites in 12. Histologically, 55% of them had squamous cell carcinoma.

UFT was administered orally at dose of 600mg/day. Eight patients achieved complete response and 10 achieved partial response with an overall response rate of 30.9%.

Concerning response by histology, a response rate was 30.9% in cases of squamous cell carcinoma. Complete response was observed in one case of undifferentiated carcinoma.

A response rate by primary site was 31 to 40% in nose and paranasal sinuses, oropharynx, hypopharynx, larynx and were all tested previously, and 33.3% for the group untreated previously. The mean time for 50% or more regression of the tumor was 4.3 weeks. Toxic effect appeared in 40.3% of 67 evaluable cases as anorexia, nausea, vomiting, stomatitis, diarrhea etc. In one case of maxillary carcinoma, severe bone marrow suppression was observed.

We concluded that UFT therapy was markedly effective for head and neck cancer.

4887

STAGING OF HEAD AND NECK CANCER: A COST BENEFIT AUDIT

F. Marechala, S. Nascoa, M. Legrom, D. Lebrun, P. Comix**

120 patients with previously untreated inoperable stage IV squamous cell carcinomas of the head and neck entered a prospective trial of adjuvant chemotherapy: pretreatment evaluation included complete history and physical examination, calcemia, chest X-ray, laryngoscopy, oesophagoscopy, bronchoscopy, abdominal ultrasonography and bone scan. We decided to carry out a cost-benefit evaluation of the current investigations used in their staging. Our results show that 10 patients (7.5%) had distant metastases to the lung (6 cases), to the bones (2 cases) or to the skin (1 case); the tenth patient had both lung and liver metastases. So bone scan discovered clinically asymptomatic bone metastasis only once and the T&M stage was never changed by the ultrasound exam of the liver. With regards to calcemia 15 cases of hypercalcinemia (2.5 mmol/l) were found and 11 of them had no detectable distant metastases. Multiple synchronously carcinomas were detected in 23 patients (18%) seven of which (5.5%) were located in the head and neck area, nine (7.5%) in the oesophagus (all discovered by endoscopy), and three in the bronchial tree (only two of them were detected by endoscopy). If we take into account the cost benefit ratio, bone scan, abdominal ultrasonography and bronchoscopy cannot be recommended in the second pretreatment evaluation of inoperable stage IV head and neck carcinomas. Investigations could be limited to a chest X-ray, a calcemia, a laryngoscopy and an oesophagoscopy.

BOH
IS INDUCTION CHEMOTHERAPY AN EFFECTIVE APPROACH IN HEAD AND NECK CANCER? SG Taylor IV. Rush Medical College. Chicago, Il.

It is a common observation in head and neck cancer that response rates are higher if chemotherapy is given before local therapy rather than after recurrence and that responders to induction chemotherapy do better in relapse-free survival (RFS) and/or survival than chemotherapy non-responders. However, randomized trials have almost universally demonstrated no RFS or survival benefit from this approach, even with multiple-drug combinations containing cisplatin. A few exceptions are stage II oral cancers benefitted by intraarterial methotrexate (Arriagada, 1983) and well-differentiated buccal mucosal cancers in India benefitted by bleomycin (Shantu, 1997). Authors generally agree use of induction chemotherapy should not lead to reduced surgical margins. Evidence suggests that, despite current enthusiasm for induction chemotherapy that seems based only on its high response rates, the value of induction chemotherapy as a treatment approach should be questioned with its failure to facilitate conservation and its failure to improve RFS. In contrast, use of 5-FU with radiation (Lo, 1976) has shown real survival advantage over radiation alone, and cisplatin and bleomycin C are currently being evaluated as radiation sensitizers. The author has used cisplatin 5-FU and simultaneous radiation, with excellent regional control and survival despite often limiting surgery to preserve function. Other evidence is accumulating that adjunct chemotherapy given of local therapy may produce a real survival advantage. A summary of these various adjuvant chemotherapy approaches will be presented with an interpretation of lesser survival and what directions might be most likely to benefit patients in the future.


Induction chemotherapy combining 5-FLUOROURACIL and CISPLATIN was administered in 56 patients with locally advanced squamous cell carcinoma of head and neck. Tumors = 26 oropharynx, 24 hypopharynx, 3 larynx, 1 rhinopharynx, 2 oral cavity and 1 lymph node metastasis without primary tumor. Patients

The therapy protocol consisted of 100 mg/m2 CISPLATIN on day 1 and 1 g/m2/day 5-FU as continuous I.V. infusion from day 2 to day 5. Three cycles were delivered respectively on day 1, 15 and 30. Results were evaluated on day 40 at endoscopy. Tolerance to therapy was good with minor hematologic toxicity and 3 rd cycle was postponed of 7 days in only 15 cases. Results show excellent response to therapy with 94 ± 9 CR + PR. 2 patients were lost for follow up after initial therapy, one patient died of an unexplained sudden death after one cycle, and chemotherapy had to be stopped in one case for renal toxicity, in one case for oesophagus. Among the 51 remaining patients, 41 subsequently received radiation therapy and 10 were treated by surgery + radiation therapy. In all cases, induction chemotherapy was not considered as providing difficulties for loco-regional treatment. Data on loco-regional results and survival will be presented with a median follow-up of 15 Months (22 ± 11.1).


The major difficulty in evaluating the effectiveness of combination chemotherapy regimens in head and neck cancer is the heterogeneity of the treated patients for several factors able to affect response to therapy (histologic variety, site of origin, P.S. and prior treatment). The aim of our study was to evaluate the activity of CABO regimen in homogeneous patients. From December 1982 to December 1984 25 patients with relapsed well or poor differentiated squamous cell carcinomas of the larynx were entered in this study. All patients had a P.S. (ECG) of 1 and a prior treatment (surgery, RT or both). CABO regimen consisted of VCR, 2mg i.v. d. 1,15; BLM, 40 mg/m² i.v. d. 2,9,15; MTX, 10mg i.v. d. 1,15; 5-FU, 200 mg/m² i.v. d. 4. Courses were repeated every 3 weeks. Major toxicities caused nausea and vomiting (72%), leukopenia and mucositis (58%). Only 2 patients showed a transient increase of serum creatinine. 7 patients were unevaluable because they received less than 3 courses of therapy; 18 evaluable patients received a mean of 4.1 courses (range: 3-7). We observed 5 CR and 4 PR with an overall response rate of 50% and a median duration of response of 7.8 months. Patients died of unexplained sudden death after 1 cycle of chemotherapy. The choice between polychemotherapy vs monotherapy (Hong, Canter, 2d, 206, 1983). CABO may product. A real survival advantage. A summary of CABO regimen in homogeneous patients with relapsed squamous cell carcinomas of the larynx.
MINIMUM RESIDUAL DISEASE AND NEW CANCER TREATMENT


So-called complete remission of acute leukemia and other tumors frequently leaves minimal residual disease cells, sometimes causing an inflammatory response and often relapse. Although we had observed some patients with long generation times or even may be in G-O condition, they may give a new tumor mass. This can be explained by cell kinetics alone, or by an escape from control immunologic or other mechanisms, or by a new promoting event. Maintenance chemotherapy beyond the first six months did seem to have an effect even against cells in the Go phase, while manipulation of the biologic- immunologic response can be effective even against cells in the Gi phase, and only maintenance chemotherapy active on cells with a long generation time is suggested.


Oxalo-Platinum: a new platinum derivative which was found to be active in experimental tumors and devoid of nephrotoxicity (AACC 1986, abstr. 1040). A phase I study was conducted with 23 patients according to a new design following the recommendations of our Institution's ethical committees (Brit. Med. J. 1985, 291, 867) to avoid the major drawback of classical phase I studies in which many patients receive the experimental drug at doses far under the potentially active dose extrapolated from experimental studies. The potential active dose of ODP was determined from the Maximally Efficient Dose Range (MED) (Cancer Chemother. Pharmacol., 1979, 3, 203) to be between 45 mg/m² (subcutaneous dose) and 6 mg/m² (subdose). The patients in this study received with increasing intervals 1/100, 1/10, 1/5, 1/3, 1/2, 2/3, 3/4, 1, of the low dose of the MEDR, this dose being reached after 90 to 120 days on study. 23 evaluable patients have entered the trial and reached the low dose of MEDR (45 mg/m²). Gastro intestinal toxicity, nausea and vomiting, similar to those with CDDP occurred in all patients at or above the dose of 30 mg/m². Renal toxicity was monitored with creatinine clearance and did not occur in any patient at any dose nor did hematologic toxicity occur even in patients with concomitant cancer. The response rate of 3 cases of the advanced cases was 100% (Regimen A), whereas the remission rate of Regimen B was 69%. There was not a large difference. The response rate of 3 cases of the advanced cases was 100% (Regimen A) and 82% (Regimen B). The response rate according to sites was good at medroxyprogesterone and oral cavity. Both were 100%. The duration of response in these cases was not long, being from 4 weeks to 16 weeks, with the mean time at 6.2 weeks. This combination chemotherapy should be used in advanced cases as pre-operative chemotherapy.

M-66: MEDICAL ONCOLOGY AND TUMOUR IMMUNOLOGY


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M-65: HEAD AND NECK TUMOURS: MEDICAL ONCOLOGY

**Chemotherapy for Advanced Head and Neck Cancer with CDDP, PELOPLUSIN and MTX.** S. Satake, R. Shiralzu, S. Makino and M. Takino, Head and Neck Division, Gunma Cancer Center, Gunma, Japan.

Twenty three cases of advanced or recurrent head and neck cancer were treated with combination chemotherapy of CDDP, Peplomycin or Bleomycin and MTX from Dec. 1983 to Nov. 1985 at Gunma Cancer Center. The regimen were randomized for these patients as follows:

**Regimen A:** CDDP 80mg/m² i.v. (day 1) +
MTX 40mg/m² i.v. Infusion (day 2)
Platin 15mg/body i.v. + Bleomycin 20mg/body i.v. (day 5)

**Regimen B:** CDDP 80mg/body (day 4)
MTX 80mg/body (day 1,15)
PLT 15mg/body i.v. (day 1,15)

There were ten cases in the Regimen A group and 13 cases in the Regimen B group. The primary sites of the disease were: Maxillary sinus-5, larynx-4, nasopharynx-1, oral cavity-3, salivary gland-1, and larynx and pharynx-1 patient each. Of these cases, there were three advanced cases without prior treatment but all of these cases were stage IV. The overall response rate was 65.2% with one complete remission and over 50% regression in 14 patients. The response rate of Regimen A was 60% and Regimen B was 69%. There was not a large difference. The response rate of 3 cases of the advanced cases was 100% (Regimen A) and 82% (Regimen B). The response rate according to sites was good at medroxyprogesterone and oral cavity. Both were 100%. The duration of response in these cases was not long, being from 4 weeks to 16 weeks, with the mean time at 6.2 weeks. This combination chemotherapy should be used in advanced cases as pre-operative chemotherapy.

**High Acute Toxicity of Pre-irradiation Chemotherapy (cis-platin + 5-FU) in Head and Neck Carcinomas is Related to Concomitant Cardio-Vascular Disease.** E. Thordal, A. B. Jacobsen and S. Kvamm, Dept. of medical oncology and Radiotherapy, The Norwegian Radiation Hospital, Nil, N. way.

Seventeen patients were treated according to a pilot study protocol with 3 courses of cis-platin + 5-FU (d 1) and 5-FU, 1000mg/m² (d 1-5) every 3 weeks prior to radiotherapy, and in some cases surgery. All but one patient had stage III disease. One day post therapy was 66 years. Eight patients had concomitant cardiovascular disease (6) or chronic alcoholism (2). Seven of these patients did not complete 3 courses of chemotherapy due to complicating acute vascular disease (1), nephrotoxicity (4) or early death (2) at day 1 and 9. The nine patients without concomitant severe disease did not show toxicity leading to cessation of chemotherapy, two patients did only receive 2 courses of chemotherapy due to.o progression or no change in tumour burden. Myelotoxicity was mild in both groups of patients. No correlation was found between age and acute toxicity. Fourteen patients could be evaluated for tumour response: CR, 2 PR, 1 N and 1 PD. It is concluded that cis-platin and 5-FU in combination give a high response rate in previously treated squamous cell carcinomas of the head and neck region. The acute toxicity is, however, high in patients with concomitant cardiovascular disease, and such treatment should be avoided in this group of patients.

A new trial for evaluating the effectiveness of adjuvant chemotherapy (AC) in high grade STS is presented. In the study only pts with Stage I-II lesions (Musculoskeletal Tumor Society classification) were entered. To achieve local control of the disease pts were treated with 3 different procedures depending on the clinical situation: 1. ablative surgery alone 2. radiation therapy (4500 cGy) plus 2 cycles of adriamycin (AC) before conservative surgery 3. re-excision of the scar. This group included pts treated in other hospitals within the previous 3 months with inadequate surgery, therefore we suspected that their local recurrence would be still present. The control of the local disease was considered the starting point for a two arm randomization. One group of pts was treated with 6 cycles of postop ADM, total dose 450 mg/m² (4 in the group treated by conservative surgery). The other group did not receive any adjuvant treatment. From August 1981, 59 pts entered the study: at a median follow up of 27.6 months (8/46) 38 pts (64.4%) had no sign of disease. The overall disease-free survival for the AC group was 79.1% (19/24) for the non AC group the corresponding figure is 54.6% (19/35). The difference between the two groups is statistically significant (p<0.005). 21 pts relapsed: 4 with local recurrences (1 in the AC group and 3 in the non AC group), and 17 with pulmonary metastases (4 in the AC group and 13 in the non AC group). Pts tolerance to ADM was good: only 1 pt developed paroxysmal atrial tachycardia during the 5th cycle of ADM.

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M-66: MEDICAL ONCOLOGY AND TUMOUR IMMUNOLOGY


27 pts with primary head and neck carcinomas (Ca) entered the study: at a median follow up of 27.6 months (8/46) 38 pts (64.4%) had no sign of disease. The overall disease-free survival for the AC group was 79.1% (19/24) for the non AC group the corresponding figure is 54.6% (19/35). The difference between the two groups is statistically significant (p<0.005). 21 pts relapsed: 4 with inadequate surgery. Therefore we suspected that foci of postop ADM, total dose 450 mg/m² 2 photons (60%) and Neutrons (40% of the total dose). With 23 pts maximum follow up, 4 patients experienced relapse, including new biopsies of initially involved site(s). Out of 27 patients, 14 (52%) entered complete remission (CR) histologically confirmed, 10 (38%) had a partial remission and 3 (11%) progressed under chemotherapy. Radiation therapy was given to 6 of the 14 complete responders and to the 10 partial responders. It consisted of 35 to 60 Gy given by photons (40%) and Neutrons (60%) of the total dose. With 23 pts maximum follow up, 4 patients experienced relapse, all in the non irradiated group. One of them had a second primary without relapsing in the site of the primary although it had not been irradiated. Only one patient had to be submitted to further surgery before treatment with sheep red blood cells agglutination test. The acquired data show that these cytostatics, either carbazine (originally acquired in Bulgaria) and "nimustine" (the immunonduclating effect of two substances: CCNU and "t-butylhydroxy-2-nonylhydroxocantheline has been recently developed (Newport Pharmaceuticals Comp., Newport, USA), and found to modulate especially T-lymphocytes-dependent immune reactions both in animal and man. In the present study we investigated the effect of different doses of NPI 5152 on in vitro function of human monocytes (THI and assistant dermal macrophages (M) such as natural cytotoxicity anti-K562 protein synthesis, ADCC and T7 uptake), and RNA synthesis. M were obtained by gradient separation of normal donor peripheral blood and were adherent to polystyrene coated plastic dishes. They were isolated from mononuclear sources by a 7 day method. The immunomodulation of NPI 5152 resulted in a significant augmentation of M cytotoxicity at a dose of 0.01-10^5 M. Max- 

imum increase of protein and RNA synthesis was found at dose of 0.1 and 10 M, with apoptosis. As identical doses were found to be active in modulation of functional activities, further the induction of interleukin-2 in IL-1 by pretreatment of M with different doses of NPI 5152 was investigated. Using the thymidine incorporation assay, M. Luong et al. (1974) study found that 1.0 M of NPI 152 significantly stimulated IL-2 production. These results suggest that NPI 5152, besides its T-lymphocyte regulating activity, has been certain effect on human M and its function.
The monocyte function was assessed in different stages of gastric cancer. The FC receptor expression and antibody dependent monocyte-mediated cellular cytotoxicity were elevated in patients with stage I - IV. The spontaneous reduction of nitro-blue tetrazolium was also increased in stage IV. Furthermore, monocytes of some patients had an increased ability to inhibit tumour cell growth in vitro but this could not be clearly related to the stage of disease. The increased cytostatic activity of monocytes was associated with their suppressory effect. Abnormal immunoregulatory activity of monocytes was responsible for the depressed lymphoproliferative response and an increased lymphokine production in stages III and IV. The altered monocyte activities were related to the presence of tu-mour. Monocytes of gastric cancer patients also showed a preferential expression of some (Ia.7) but not other (IaDR/1-L, common DR) MHC class II determinants. No depression of interleukin (IIa) production in patients monocytes was noted. These observations suggest that monocytes of some gastric cancer patients show profound functional changes and possibly are activated in the course of disease. However it is unclear whether this reflects the expansion of a (functional subset) of monocytes or uneven distribution of activation among subsets.

Since GC302 could be used for the diagnosis of metastasis of gastric and colon cancers, we investigated the localization of gastric cancer bearing in nude mice was achieved by Fuji Computed Radiography i.p. nude mice using 111In-radiolabeled GC302. A clear visualization of gastric cancer in mucosa of gastrointestinal tracts. and the differentiation antigen which discriminate befsrewrti the gastrointestinal tracts to be 4QK by Western blot analysis. From these estimated results chs/aclcmtics of colon and rectum as well as cancers from these origins. Molecular Weight was signet-ring cell carcinomas. GC302 also reacted with normal mucosa of the intestine, adenocarcinomas and almost all poorly-differentiated adenocarcinomas, but not with lesions. In tissues from cancers of the stomach. GC302 reacted with well-differentiated mucosa in the stomach of fetus and the epithelial cells in the intestinal metaplasia differentiated type of adenocarcinomas showed high level of antigen expression, although (MHA)cn a panel of human cell lines, and immortoperoxidasc sorption assay (MoAb) The specificity of antigen detected by MoAb was analysed by Mixed hemad- sorption assay (MoAb) The specificity of antigen detected by MoAb was analysed by Mixed hemad- sorption assay (MoAb) The specificity of antigen detected by MoAb was analysed by Mixed hemad- sorption assay (MoAb) The specificity of antigen detected by MoAb was analysed by Mixed hemad- sorption assay (MoAb) The specificity of antigen detected by MoAb was analysed by Mixed hemad- sorption assay (MoAb) The specificity of antigen detected by MoAb was analysed by Mixed hemad- sorption assay (MoAb) The specificity of antigen detected by MoAb was analysed by Mixed hemad- sorption assay (MoAb) The specificity of antigen detected by 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M-66: MEDICAL ONCOLOGY AND TUMOUR IMMUNOLOGY

4904 MONOCLONAL ANTIBODY braFB6 ELICITED BY m,Tb,-
LEUKEMIA CELL LINE IMMUNOPRECIPITATES p30 CELL SURFACE PROTEIN
B. C. Verheul, T. Duijv, M. J. S. van der Pluij, K. Poláková, G. Babu-
Gyová, P. C. Bijl, V. Voršed V, Cancer Research Insti-
Institute, Bratislava, Czechoslovakia and Department of Biochemistry and Molec-
University, U.S.A.

Monoclonal antibody braFB6 /IgG, / elicited by m,Tb,-lymphoblastic leukemia cell line RHE 6 dis-
dayed immunofluorescence reactivities speci-
ical of MHC class II antigen on lymphoblastic-
lymphoid- and myeloid leukemia cell lines, per-
spherai blood cells from patients with leukemias.
This antibody specifically immunoprecipitated
p30 cell surface protein radiolabeled by lacto-
peroxidase catalyzed radioiodination; no im-
munprecipitation was observed after cell surface
radiolabeling of splenocytes by sodium
metaperiodate/trimetoborohydride. After im-
munodepletion of radiolabeled solubilized cell
surface proteins by monoclonal antibodies recog-
nizing MHC class II /DR/ antigen /monoclonal an-
tibody bra30/, antibody braFB6 further immuno-
precipitated p30 protein indicating the absence of
complete immunological identity of MHC class II /
DR/ antigen and p30 protein. Competitive inhibi-
tion experiments between p30/RHE 6 cells with the aid of several monoclonal antibodies
recognizing MHC class II/DR/ antigens and meas-
ured by immunocytofluorescence demonstrated some cross-inhibition between anti-
DR antibodies and braFB6 antibody indicating the
possibility of some topological or functional
links between recognized antigens on intact cell
plasma membranes. Binding of braFB6 antibody to i-
solated MHC class II/DR/ antigens suppresses
the possibility of p30 protein being identical
with beta-chain of DP antigen /alpha-chain of
this antigen being not completely accessible to
lactoperoxidase catalyzed radioiodination .

4905 FORMOSANIN-C, A IMMUNOMODULATOR WITH ANTITUMOR
ACTIVITY
*Inst. of Microbiol., Immuno., National Yang-Ming
Medical College, #School of Pharmacy, National
Taiwan University, †Dept. of Ophthalmology,
Veterans General Hospital, Taipei, Taiwan, A.D.C.

Formosanin Hayata (Liliaceae) is a perennial herb grown in the mountain areas of
Taiwan. It has been used as a folk remedy for
antiinflammatory or antineoplastic agent.
Formosanin-C, a diosgenin saponin, was isolated as
the active principle from this plant. We
have studied the biological activity, because
of its unique immunomodulating properties and
antitumor activity, and here present the
results.

Formosanin-C retarded growth of sc solid
MH-134 hepatoma in C57BL mice. Approximately 40%
inhibition was observed when 2.5mg/kg/day was
administered for 14 days. The effect was enhanced
when 2.5 mg/kg/day was injected for two days.
The sera collected from Formosanin-C treated
mice showed competition of the immune re-
response of mice spleen cells to PHA.

These results suggest that Formosanin-C
inhibited more hepatoma growth in association
with modification of the immune system.

4906 RANDOMIZED PHASE III STUDY OF CHMOTHERAPY/RADIO-
THERAPY FOR SMALL CELL LUNG CANCER. M. Arnold,
A. Kraft, H. Bodemann, M. Zwirgers, M. Wohden-
macher, W. Wrinkelberg, T. V. Mottaz-Singewaen, and
S. Freudenberg, Med. Univ.-Klinik Tübingen, F.R.G.

Most therapeutic regimens used either chemother-
and/or radiation to the primary. While im-
provement of median survival by chemotherapy
is unquestioned, there is still controversy over optimal timing and
doseage. Therefore, we initiated a randomized phase III study in stage
"limited disease" with 5 arms combining 6 cycles of
ACO /adriamycin 50 mg/m², cyclophosphamide
1 g/m², vincristine 2 mg every 3 weeks/ with
either no radiation to the primary (A), or 20 Gy
(B) and 50 Gy (C) after the third cycle, respec-
tively. Patients were divided into the following groups:

1. A: Control group received standard treatment: chemotherapy was changed to cis-platinum plus etoposide.

2. B = A + 20 Gy: A randomized phase III study of chemotherapy and radiation therapy was initiated.

3. C = A + 50 Gy: A randomized phase III study of chemotherapy and radiation therapy was initiated.

4. D: A + 20 Gy: A randomized phase III study of chemotherapy and radiation therapy was initiated.

5. E: A + 50 Gy: A randomized phase III study of chemotherapy and radiation therapy was initiated.

Uncommonly, the regimen failed, chemotherapy was changed to cis-platinum plus etoposide.

4907 5-YEAR RESULTS OF A COMBINED SIMULTANEOUS
ANTINEOPLASTIC POLYCHEMOTHERAPY AND RADIOTHERAPY
IN THE TREATMENT OF SMALL CELL LUNG CANCER
G. Anger, V. von Paris, K. Ketnert and F. H.
Glaser, Clinic for Internal Medicine and
Clinic for Radiology, Medical Academy
Erfurt, DDR

45 Pat. with a small cell lung cancer
received from 1977 - 1980 a combined
simultaneous antineoplastic Polychemo-
and Radiotherapy (5-Fluorouracil, Metho-
trexate, Vincrestin, Cyclophosphamide +
Radiotherapy 40 - 50 Gy).

Results: 10 Pat. with limited disease (1d.)
obtained 90 % Complete Remission (CR) and
30 % Partial Remission (PR). 35 Pat. with
extensive disease (e.d.) 14 % CR and 57 %
PR, 29 % were Non Responders (NR), Survival
time for Pat. in CR with 1d. was 36.2
months, with e.d. 26.2 months, for Pat. in
PR with 1d. 13 months, with e.d. 10.7
months. For NR the survival-time was 6.8,
with Progression (P) 4.7 months, 5 Pat.
11 % are long-survivors, probably they
are cured. The regimen is very well tolerable.

N-49: RADIOTHERAPY OF LUNG CANCER

WEDNESDAY • AUGUST 27 • AFTERNOON
TREATMENT OF NON-SMALL CELL LUNG CANCER WITH CHEMO-IRRADIATION THERAPY FOR INOPERABLE NON-SMALL CELL LUNG CANCER

Christov, I.V., P. Krasavetskii, IV. Panov, T. Donech, D. Damjanov, Ch. Christova, I.P. Timoeva
Research Institute of Oncology, Sofia, Bulgaria

A prospective study including 64 patients with inoperable lung cancer was done for evaluating combination therapy - chemotherapy + irradiation. Most of the patients were histologically in stage III with prevalence of squamous cell carcinomas (64/65), 11 patients were divided into two groups: 1 - 2 months monochemotherapy (MTX-6 or 5-FU-12) and group II - 37 submitted to combination chemotherapy (FML - cisretin + 5-fluorouracil + cyclophosphamide). The two groups after chemotherapy received irradiation 45-50 Gy. We studied survival from a betatron with total dose 50 Gy.

The results of the treatment are analyzed concerning the primary tumor and the metastasis. For the primary tumor no complete remission was achieved. The prevalence of partial and minimal response for the primary tumor and hilar and mediastinal lymph nodes is the results of the treatment are analyzed. The conclusions are based on the survival of the primary tumor and the metastasis.
LIVE-TABLE ANALYSIS OF COMBINATION THERAPY (CHEMOTHERAPY AND IRRADIATION) OF SMALL CELL LUNG CANCER

Chr. Gartner1, L.I. Motorina2, Z.P. Michina2
Oncological Clinic, Charite, Humboldt-Univ., Berlin, GDR1 and Cancer Res. Ctr., Acad. Med. Sciences, Moscow, USSR2

In our therapeutic programmes for small cell lung cancer we have used simultaneously tumourchemotherapeutic agents and thoracic irradiation:
57 patients have received cyclophosphamide (1.0 g/m² weekly 1, 4, 5), adriamycin (30 mg per m² weekly 1, 4, 5), methotrexate (10 mg per m² weekly 1, 4, 5) and simultaneously thoracic irradiation (20 Gy week 2 and 5) during 6 weeks.
64 patients have received cyclophosphamide (500 mg/m²/week), 1-methyl-1-nitrosoureia (NMU) (400 mg/m²/2 weeks), methotrexate (10 mg/m²/week) and simultaneously thoracic irradiation (10 Gy weekly 4, 5, 6, 8, 9) during ten weeks.

The results of our therapy are the following:
1. Both programmes are in a state of limited disease of the same effective (median survival 57 weeks respectively 66 weeks, Z = 0.002).
2. In a state of extensive disease the 6-week-programme seems to be more effective than the 10-week-programme (median survival 51 weeks respectively 32 weeks).

The found statistical difference between the two programmes is not significant (χ2 = 2.66).

Our investigations of chemotherapy and thoracic irradiation in the therapy of small cell lung cancer.

PULMONARY TOXICITY OF RADIATION-DRUG-INTERACTIONS IN THE THERAPY OF SMALL CELL LUNG CANCER

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The lung has been found to be one of the most radiosensitive tissues. Radiation damage to the human lung has been recognized for many years.

As been reported the pulmonary toxicity has been associated with a variety of tumourchemotherapeutic agents.

Ticling of chemotherapy and thoracic irradiation is one of the problems in the therapy of small cell lung cancer.

In two investigational programmes chemotherapeutic agents as well as thoracic irradiation we have applied simultaneously:
- cyclophosphamide (1.0 g/m² week 1, 4, 5), adriamycin (30 mg per m² week 1, 4, 5), methotrexate (10 mg per m² week 1, 4, 5) and simultaneously thoracic irradiation (20 Gy week 2 and 5) during 6 weeks.
- cyclophosphamide (500 mg/m²/week), 1-methyl-1-nitrosoureia (NMU) (400 mg/m²/2 weeks), methotrexate (10 mg/m²/week) and simultaneously thoracic irradiation (10 Gy weekly 4, 5, 6, 8, 9) during ten weeks.

As a consequence of these programmes over 70 % of patients achieved pneumonitis or fibrosis of lung.

Therefore, we cant recommand the simultaneously use of tumourchemotherapeutic agents and thoracic irradiation in the therapy of small cell lung cancer.
RADIOThERAPY (RT) WITH CIS-PLATINUM (CP) POTENTIATION AS NEO-ADJUVANT APPROACH IN 39 INOPERABLE NSCLC: A PILOT STUDY
E. SorenO, G. Bergholt, S. Scopel, M. Loun, M. Bottur, M. Ceglic
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On the assumption that a synergism between RT and CP was possible in pulmonary tumors too, as Haselow et al. (1983) tested on Head and Neck cancer with RT plus CP as a radio enhancer in order to improve the prognosis of patients (pts) with locally inoperable NSCLC was started.

RT was given in 6 doses of 2.5 Gy weekly up to 5000 Gy with 42 MeV photons, on median line; CP was given in 1 dose of 12 mg/m2 weekly.

39 non pretreated pts (33 males and 6 females) have been entered in the study. Median age was 66 years (range 30-77) and all had a Performance Status 1-2 (Zubrod).

Histology included squamous cell carcinoma (23 pts=58.9%), adenocarcinoma (9 pts=23.1%), large cell undifferentiated carcinoma (9 pts=23.1%), and all had a Performance Status 1-2 (Zubrod).

At present all the pts are evaluable for tumor response and toxicity, and 28 for Median Survival (MS).

Toxicity included mild nausea and vomiting in 6 pts (15.4%), mild oesophagitis in 5 pts (12.8%), letal haemoptisis in 1 case (2.5%), and toxicity, and 28 for Median Survival (MS).

The lesions were treated with the airflow stenosis or obstruction using YAG laser instrument at our Research Institute hospital.

Twenty two patients with advanced squamous cancer and two with early invasive lung cancer were treated. Using MBC's YAG laser instrument, the photofract-}
RESULTS OF THE COMBINED TREATMENT (CHEMOTHERAPY AND X RAY PHOTON IRRADIATION) OF PATIENTS WITH SMALL CELL LUNG CANCER DURING THREE YEARS TIME.

Z. Jodkiewicz, T. Starzyńska, G. Nowak

From: Radiotherapy Department Cancer Center of the Maria Skłodowska-Curie, Warsaw, Poland

Summary
36 patients with advanced Small Cell Lung Cancer underwent two-stage treatment which consist of:

- Polychemotherapy
- X 18 MV photon irradiation emitted from the Line Accelerator "Saturn" CSR MV in a dose of 50 Gy/3

The survival after our treatment program was: 1 year - 56.6%, 2 years - 46.6% and 3 years - 33.1%

These results are comparable with those achieved by

The survival after our treatment program was: 1 year - 56.6%, 2 years - 46.6% and 3 years - 33.1%

These results are comparable with those achieved by other authors and it is advisable to continue this study.

COMBINED RADIO-POLYCHEMOTHERAPY - SURGICAL TREATMENT OF BRONCHOPULMONARY CANCER.
A. Basacopol, F. Lepădat, L. Brand, D. Atanasu
Silvia Bilauca, Thoracic Surgery Department Clinico-Therapeutic University School of Medicine and Pneumology, Bucharest, Romania

A study was carried out the results obtained by combining surgery with polychemotherapy and telecobaltotherapy in bronchopulmonary cancer. This treatment was applied in 568 of the 7225 operated patients, establishing certain parameters. There were 485 males and 93 females; the age-group ranged from 31 to 70 years; the tumour was found in the right lung in 580 cases and in the left lung in 188 cases. Surgery included 369 radical operations (pneumonectomy), 126 lobectomy and bilo-lobectomy, 34 atypical mechanical resections for reducing the tumoral mass and 39 thoracotomy without resection of the tumour because of the lesions. The forms of bronchopulmonary cancer were: epidermoid carcinoma, adenocarcinoma, undifferentiated macrocellular and microcellular carcinoma. Cytostatic polychemotherapy (Cyclophosphamide, Vinristine, Methotrexat) was instituted two weeks after surgery according to scheme individualized in each case, and telecobaltotherapy after four-five weeks, administrating a total of 5000 Rads in five sessions a week. The results were superior to all other forms of treatment, with 76% survivals after 1 year, 58% after 3 years, 48% after 5 years. Further results after 5 and 10 years will be communicated later.

NON CONVENTIONALLY FRACTIONATED RADIOTHERAPY IN PATIENTS WITH NON SMALL CELL LUNG CANCER (NSCLC).

Westlin J.E., Uggla A., Lindberg P., Nilsson S. Clinic of Oncology, University Hospital, 751 85 Uppsala, Sweden

Mohuddin et al. at the ISLSC conference 1983 in Tokyo presented a radiotherapy program, in which the treatment was started with 6 resp 4 Gy fractions to the tumour bulk, and after that 1.8 Gy daily to extended fields including regional lymphnodes. After a split of one week, the same procedure was started again up to 80 Gy to the tumour bulk and 64 Gy to the regional lymphnodes. They claimed a therapeutic effect of more than 50% complete remissions and more than 30% partial remissions. We have retrospectively examined this treatment scheme to see if this remarkable good result could be repeated, and if it might increase survival. Materials and methods: Twenty cases with NSCLC, Irressectable and limited disease were treated according to the scheme mentioned above. Nine were irresectable because of mediastinal metastasis or advanced local disease and 8 because of a bad general condition or of heart or lung disease.

Results: Three patients are alive with no evidence of disease after 33, 33 and 14 months, two of which had verified mediastinal lymphnode metastases. Median survival was 9 months. The degree of local remission was impossible to evaluate in most patients on ordinary lung X ray films because of intense irradiation reaction in the lung. One case died of irradiation induced pneumonitis.

Conclusion: This fractionation scheme took 2 months to perform and needed advanced treatment planning. It may produce long remissions, maybe cure some patients. Our small materials does not permit any definite conclusions, but it is not clearly superior to ordinary fractionation schemes.
PREGNANT SIGNIFICANCE OF PSYCHOSOCIAL FACTORS IN WOMEN WITH BREAST CANCER.

T.C. Bieolop, M.H. Walsar, A.J. Coldman, L. Kan. 'Cancer Control Agency of British Columbia and *Department of British Columbia, Vancouver, British Columbia, Canada.'

Studies have suggested that psychosocial factors may influence survival for cancer patients; however, the results have been controversial. To determine the patient's survival status, date of first recurrence, date of death or last follow-up. Survival and disease-free survival was calculated by the Kaplan-Meier method for each psychosocial factor separately and differences were tested by the log-rank test. Cox proportional hazards analysis was used to identify independent psychosocial prognostic factors for overall survival (frequent social activities at home, extraversion and low anger) and three factors for disease-free survival (frequent social activities at home and low cognitive disturbance). Our findings are consistent with other investigators reporting better survival for patients with a "fighting spirit." We conclude that certain psycho-social factors & contribute to the prognosis of women with breast cancer which are independent of clinical variables, at least those considered in this study. Funding for this study was provided by NHRDP, Health & Welfare Canada, grant no. 6641-1215-44, and B.C. Cancer Agency (Winnipeg, Kan).

ANXIETY AND DEPRESSION IN BREAST CANCER PATIENTS TREATED BY LOCAL TUMOUR EXCISION AND RADICAL RADIOTHERAPY.


All breast cancer patients referred to this Unit have treatment with breast conservation for the last six years. 52 out of 54 consecutive patients presenting during 1984 and treated by local tumour excision and radical radiotherapy, agreed to enter, and completed, a study of their psychological response. Linear analogue scales for anxiety and depression, together with the Hospital Anxiety and Depression Scales were completed post-operatively, after radiotherapy, at six months and at one year. At six months a structured interview was conducted. Three patients have required anti-depressant drugs. According to the scales, 6% were "cases" of depression, and 36% "cases" of anxiety. Analysis of the results is continuing, but suggests:

1. The psychological morbidity is less than previously reported for breast cancer treated by mastectomy.

2. The use of questionnaires may not detect those suffering the most severe depressions.

3. There is close correlation between the linear analogue and questionnaire scores, and between anxiety and depression in these patients.

PREDOMINANT SIGNIFICANCE OF PSYCHOSOCIAL FACTORS IN MEN WITH BREAST CANCER.


Supportive interventions should come early in rehabilitation. Problems were detected in a few patients and their spouses. The most mentioned previous reactions (anticipatory; are: a) among effects: anguish, anxiety, crying, irritability, sadness; b) among reasons, vomiting, weakness, feverish episodes. Adolescent patients are the ones referring more previous disturbances, both corporal and emotional. We conclude that the early detection of these symptoms allows to undertake its care so as to prevent treatment drop outs, strong rejections of same and all this must be taken into regards life quality of these patients. We suggest a review of the type of provided information which leads to stress: the secondary effects of BWR drugs more than their potential ability to cure.

ANTICIPATORY PHENOMENON IN PATIENTS WITH CHEMOTHERAPY.

H. Fisman, G. Gonzalez, G. Darcy, S. Pavlovsky. Hematologic Research Institute and Psychosocial Area of the Argentine Group for the Treatment of Acute Leukemia (GRATA), Buenos Aires, Argentina.

The aim of this work is to study the incidence, signification and possibility of treatment in the population with anticipatory phenomena among patients with leukemia and lymphoma. The methodology employed consists of an individual survey to the adults and adolescent patient and in children a survey for the parents is added. Of the studied patients, 32/40 (80%) show phenomena previous to the application of chemotherapy. In adults these are started several days before or some hours before the application; in children they are more frequent the day before. As a resource that relieves, children and adolescents require more maternal attention (greater holding) and the adults look for: mental control of their reactions, to take tranquilizers and avoiding behaviours (from "I do not think" to simulate somatic pathology so as not to receive medication). Children and adolescents know more about the secondary effects of medication than its possible curative effects. Their parents also stress these disturbances. The most mentioned previous reactions (anticipatory; are: a) among effects: anguish, anxiety, crying, irritability, sadness; b) among reasons, vomiting, weakness, feverish episodes. Adolescent patients are the ones referring more previous disturbances, both corporal and emotional. We conclude that the early detection of these symptoms allows to undertake its care so as to prevent treatment drop outs, strong rejections of same and all this must be taken into regards life quality of these patients. We suggest a review of the type of provided information which leads to stress: the secondary effects of BWR drugs more than their potential ability to cure.

PSYCHOLOGICAL ADJUSTMENT OF CANCER PATIENTS WITH FACIAL PROSTHESES.

A. Udaganarte, L.P. Rennert, M. Archambault, E.C. Ring and A.R. Gunter, D.L. Larson, M. Ricca, D. Anderson Hospital and Tumor Institute, Houston, Texas, USA, University of Houston, Texas, USA.

Cancer is known to have a negative impact on the psychological adjustment of many patients. Facial excisions of cancers may lead to further adjustments due to disfigurement. Fifty-two patients with facial prostheses in a maxillofacial rehabilitation clinic were assessed for psychological adjustment on the Brief Symptom Inventory (BSI), and a questionnaire for patients referred more previous disturbances, both corporal and emotional. The methodology employed consists of an individual survey for the parents is added. Of the studied patients, 32/40 (80%) show phenomena previous to the application of chemotherapy. In adults these are started several days before or some hours before the application; in children they are more frequent the day before. As a resource that relieves, children and adolescents require more maternal attention (greater holding) and the adults look for: mental control of their reactions, to take tranquilizers and avoiding behaviours (from "I do not think" to simulate somatic pathology so as not to receive medication). Children and adolescents know more about the secondary effects of medication than its possible curative effects. Their parents also stress these disturbances. The most mentioned previous reactions (anticipatory; are: a) among effects: anguish, anxiety, crying, irritability, sadness; b) among reasons, vomiting, weakness, feverish episodes. Adolescent patients are the ones referring more previous disturbances, both corporal and emotional. We conclude that the early detection of these symptoms allows to undertake its care so as to prevent treatment drop outs, strong rejections of same and all this must be taken into regards life quality of these patients. We suggest a review of the type of provided information which leads to stress: the secondary effects of BWR drugs more than their potential ability to cure.
4928 NEUROSIS IN WOMEN WITH BREAST CANCER BEFORE AND AFTER SURGERY AND REHABILITATION. R. Sebil, M. Novosel, Z. Maričić, Central Institute for Tumors, Zagreb, and Faculty of Defectology, Zagreb, Yugoslavia.

The amputation of the breast because of cancer induces a powerful mental stress in women because it brings about, in addition to the uncertainty about the course of the disease, a change in the body image which most women find very difficult to accept. The Evaluation of Selective Rehabilitation and Psycho-educational Approaches to Persons Affected by Malignant Disease, project sponsored by the Central Institute for Tumors and Allied Diseases and the Faculty of Defectology, University of Zagreb, evaluated the neurosis on a sample of 31 breast cancer patients by the Cornell Index R3 Test. The patients underwent the test prior to surgery and 30 days following breast amputation. Following the latter, and before the second test, a special 4-week program of medical, psycho-educational and defectological rehabilitation was run. General neurosis and the depressive, asthenic and stenic syndromes were analysed in order to pinpoint the magnitude of possible differences in neurotic behaviour before and after surgery, and after comprehensive rehabilitation. The results were processed by multivariate variance analysis (KANOVA). The results do not show significant results between tests.

4929 STRESS AND COPING IN RESPONSE TO THE SURGICAL TREATMENT OF CANCER. M. A. Ivon, J. B. Rounds, Jr., and H. O. Douglass, Jr., Roswell Park Memorial Inst., Buffalo, New York, U.S.A.

Cancer patients whose treatment involves surgical intervention are required to cope with a significant stressor. Indeed, the surgical treatment of cancer has been described as one of the most stressful forms of cancer treatment. Despite this, there is no coherent literature which investigates the relationship between the preoperative psychological status of the cancer patient and postoperative indices of patient recovery and welfare. The present study investigated changes in psychological status and coping strategies in response to the surgical treatment of cancer in adult males and females. Subjects were 34 adult cancer patients (M age = 56) under treatment at a comprehensive cancer center. Subjects completed an assessment battery prior to their surgery, and again during the postsurgical week. The relation between coping and psychological status was examined at the presurgery and postsurgery time points. Presurgically, the use of self-blame and isolation as coping mechanisms were most strongly and positively related to psychological distress. Postsurgically, only self-blame was consistently associated with distress. As expected, there was a significant (all p < 0.05) decrease in psychological distress over the presurgery to postsurgery interval. Prior to surgery subjects subje (rated (disapp) the stressfulness of their upcoming surgery. Based on these appraisals, subjects were assigned to high and low stress groups. Group differences at the presurgery point were found for mean levels of depression, anxiety, and global distress; and at postsurgery for depression, hostility, and global distress (all p < 0.05). For these comparisons, the high stress subjects reported greater psychological distress. Surprisingly, the appraised stressfulness of the surgical experience was not associated with coping strategy. Implications for interventions with cancer surgery patients will be discussed.

4930 NEED OF AND POSSIBILITIES FOR PSYCHOTHERAPY IN GYNECOLOGIC ONCOLOGY PATIENTS. G. Boz, Department of Obstetrics and Gynecology, University Hospital Leiden, The Netherlands.

Gynecologic cancers are unique in that they affect the female genital organs and functions, which may have severe consequences for the female identity, femininity and sexual attractiveness. In order to assess late psychiatric morbidity, at least six months after discharge from treatment, gynecologic cancer patients in remission were invited to fill in a psychosocial questionnaire, after which they had a semi-structured in-depth interview, assessing quantitative and qualitative aspects of life. Main topics were: body image, self-esteem, anxiety, depression and coping mechanisms. Psychotherapy was proposed for improvement of coping skills. Depending on the kind of patient and severity of emotional problems, individual and group psychotherapy was offered. The results of a pilot study suggest that the need of psychotherapy is greater in patients treated with chemotherapy than without chemotherapy (for version 1984). About 70% of the patients revealed that they had low opportunity to ventilate their problems. Of these problems high anxiety was the most frequent and the most difficult to cope with. Besides, many partners rejected negatively about the need of psychotherapy in their beloved ones. Short-term psychotherapy (18-12 sessions) could clearly improve the coping skills of gynecologic oncology patients. They also seem to learn more quickly and selectively than the general, non-cancer, clients. These preliminary findings are presently tested out in a broader study.

4931 ANTHROPOLOGICAL ASPECTS OF IMPORTANT PHYSICAL CHANGES IN BREAST CANCER PATIENTS. Andrea Stasta, M.D. and Daniel Stebovick.

In the 12th International Cancer Congress, we presented the first part of this work. In this we talked about the emotional difficulties of breast cancer patients in the preoperative and postsurgical period. In this paper we try to classify the term of stress in the period of hospitalization between the breast surgery and the illness apparition. In this we look at the influence of the stress in the neoplastic children from 0 to 15 years. One hundred and fifty children were studied. In the 94 % of the illness was possible to detect the existence of an psycho-traumatic event in the latent time announced in the work which was made before this one. Evidence groups of one hundred no neoplastic children from 0 to 15 years. In this way we found the antecedent of an psycho-traumatic event in the announced latent time in 99 %. If we accepted as facts as stress factors we would admit that people with the mentioned facts formed a dangerous group. In our work made before this one, pointed as stress fact the death of a relative and unfinished separation. We investigated one hundred relatives who had suffered the death of some of this members and one hundred people in prision, in both groups we obtained significant results.
4932 METHODOLOGY FOR DETERMINATION OF CLINICAL VIEW IN PSYCHO ONCOLOGY. J. Schivelzon, N. Fishman, B. Kors A.P.O. (Psychooncological Assistance) Buenos Aires, Argentina.

Object: To establish parameters that let the systematic approach to the oncological patient. It’s considered that at the moment of the first interview, the signs and symptoms of organic and emotional expression are determined by:

I. Primary Causes: Related to the biography of the patient and the expression of illness in the emotional, organic and cultural areas, and the circumstances.

II. Secondary Causes: through the oncological diagnosis, illness developing, treatment.

The primary causes must be specially investigated about 3 and 5 years before the clinical recognition of the tumor (according to present diagnostic methods).

In pathophysiology it is considered: the biography, and the depression and the stress. Demonstration of anguish, anxiety and depression are ways of expression of these “primary causes”.

The secondary causes being investigated are:

1) attitude to diagnosis, (from patient and relatives),
2) clinical situation: anemia, infection, hypoxia, pain, toxaemia, etc.,
3) Brain damages: metastasical, by sequence, etc.,
4) the action of quimotherapy, drugs, radiation surgery treatment,
5) Information: verbal and pre-verbal,
6) the physician-patient relation,
7) sexual problems,
8) the assistance structure,
9) the quality of the attention.

Commentaries

We consider this model of approach to oncological patient lets psycho oncological labour turn systematic, with assistance and research objects and also establishes a basement for comparative and follow-up studies.


We have elaborated a study on patients with cancer of the cervical and cephalic districts to determine: 1) the psychological problems related to the illness before and after diagnosis; 2) personality, and in particular, the corporal image of these types of cancer and the possibility of a modification in the long run, in relation to the therapy that is effected, the evaluation of the illness before and after the surgical operation; 3) risk factors (alcohol, tobacco); 4) type of society and vocation, characteristics of these tumors. The first results confirm alcohol and tobacco as risk factors, then are in evidence changes of personality that we shall study in particular. These patients have much difficulty in asking information about their illness, not only, but is determined a long time from the beginning of symptomatology and the day of diagnosis. These patients belong to a low extraction, attended elementary schools and prefer to delegte the doctors not only for therapy but also for the emotive experience of their illness.

PERSONALITY
CERVICAL AND CEPHALIC DISEASE
CANCER
QUALITY OF LIFE


It has been shown, in the last few years, that there is some relationship between several psychological characteristics and cancer onset. The purpose of this study is to analyse the expression of aggression in Greek cancer patients using the Rosenzweig-P-P study. Sixty four people took part in this study, fifty five women and nine men. Three groups were formulated: group A having nine men and six women suffering from various types of cancer except breast cancer (mean age 58 yrs); group B having twenty two women suffering from breast cancer (mean age 51 yrs); group C (control group) having twenty seven healthy women (mean age 48 yrs). The results were analysed with the analysis of variance method and were the following: 1) there is a significant difference (P<0.05) between the control group and the two experimental groups; 2) there is a significant difference (P<0.01) between the control group and the breast cancer group; 3) no significant difference was found in terms of intrapression and intragression among the groups (P>0.05). The results show people suffering from cancer express less aggression towards the others than normal people. Due to the small sample of patients and small number of males in the sample, further investigation is going on to support the results of the present pilot study.

4935 INTEGRATION OF PSYCHOSOMATIC RESEARCH, TREATMENT AND REHABILITATION OF BREAST CANCER PATIENTS. K. Achte*, O. Lindfors**, M. Salokari***, R. Lehvensen*, L.R. Huusti****, M.-L. Vaunonen*****, Departments of Psychiatry and Radiotherapy and Oncology, Helsinki University Central Hospital; Jorvi Hospital, Espoo**, Mental Health Center*** and Hesperia Hospital****, Helsinki, Finland.

Although shared interests of psychiatry and oncology have long traditions, research in psychosomatic aspects of cancer has been in many cases limited to the search of psychosocial factors of the disease while the more practically oriented cooperation between psychiatry and oncology has grown from consultation/liaison work and stemming mostly from acute treatment problems. It has been our interest to approach these shared interests from a scientific point of view and to try to construct a basis for an integrative cooperation between research, treatment and rehabilitation of cancer patients, and especially breast cancer. Our emphasis is on the patient's situation at different phases of the illness and on the long-term consequences of initial adaptation. We have studied 100 breast cancer patients at the initial phase of the illness and one year later. The patients' psychosocial status, possible psychiatric complications as well as attitudes and experiences concerning hospital treatment, were evaluated. About 50 per cent reported disturbances of mood although only 10 per cent had had any psychiatric support. Majority of patients experience positively situations for discussing their situation. Prognostically patients with active attitude at the initial period were better off regarding the state of illness as well as quality of life.

Our preliminary results indicate that psychosocial factors may have significant effects on later adaptation. Suggestions are made to develop support facilities to minimize harmful effects induced by inappropriate coping strategies. Individual approach and promoting patients' reorientation by integrating hospital treatment and rehabilitation is emphasized.
Thirty-nine adult BMT patients (pts) completed questionnaires regarding their perceptions and behaviors related to the informed consent process. In addition, pts were given the Brief Symptom Inventory, a standardized self-report measure of psychological distress. Most pts (97.4%) received information regarding BMT from sources in addition to their primary BMT physician (MD), including another MD (31.8%), a nurse (58.0%), and other hospital staff members (25.6%). Most pts (79.5%) also received assistance in decision-making in addition to their primary physician, including a parent (31.2%), another MD (41.0%), a spouse (30.8%), other family member (25.4%), or a friend (15.6%). Most pts (92.3%) reported that one or more others were present during the pt-MD discussion such as a parent (66.6%), a spouse (48.7%), other family member (26.2%), a friend (7.7%), or another MD (2.6%). A majority of pts (64%) reported having a witness present during the signing of the consent document (most often a parent). Level of psychological distress was significantly correlated with number of persons present during the pt-MD discussion (r=0.33, p<0.01). Pts having no witness to their written consent exhibited a higher level of hostility (F= 5.75, p<0.01) than pts having a witness. Aspects of the decision-making process associated with lower psychological distress included: the extent to which pts felt they made their own decision; the asking of questions regarding the treatment; the extent to which pts perceived that their MD wanted them to make their own decision; the extent to which pts reported understanding the MOs’ explanation. These findings suggest that giving informed consent for adult pts is a multi-faceted process that warrants further study in order to clarify those aspects which influence the pts’ psychological well-being.

(Supported by the Leukemia Society of America and USPHS Grant CA 23766).

R-43: REHABILITATION

4938 FUNCTIONAL ASSESSMENT-THE KEY TO ONCOLOGY REHABILITATION.
E. E. CHARRETTE, M.D. AND D.M. O'TOOLE, M.D.
New England Rehabilitation Hospital, Woburn, Massachusetts 01801 USA

The New England Rehabilitation Hospital is a free standing rehabilitation hospital with an active Oncology Rehabilitation Unit. The cornerstone of the cancer rehabilitation program is the identification of functional problems in the acute hospital. This is done by oncology nurses or other key personnel who are trained at workshops at New England Rehabilitation Hospital. Ongoing functional assessments are then implemented at appropriate times. By using an adapted Long Range Evaluation System (LRES) and Dietz Classification as the Initial Oncology Functional Assessment, the patient is inserted into the system and directed to the appropriate level of rehabilitation. By the dynamic capability of ongoing functional assessments using this tool, the changing needs of the patient can be identified and tracked. The following domains are monitored - wellness, mobility, communication, home/family, psychosocial, environment, functional resources, mental/emotional, nursing needs, vocational/educational. Based on our experience, the education of physicians, nurses and patients’ families is paramount if cancer rehabilitation is to succeed.
Breast cancer should be considered not only in terms of length of survival but also in terms of how it might interfere with people's life. 1000 women aged 25 to 55 years were examined at the National Medical Experts' Institute about one year after a breast cancer operation. Establishing disability was required as the patients' working capacity had not been restored. The criteria of assessing the degree of disablement are well-defined. Disabled are graded by Roman numerals into three grades. The higher the grade the better the prognosis. Rehabilitation was recommended only to grade III patients. Many women had difficulties in adjusting to the new situation. Some aspects of rehabilitation are considered. Data are analyzed by age groups and profession.

Many Authors related the post-mastectomy arm oedema (A.O.) to adjuvant Radiotherapy (RT). Everybody agrees that a specific Rehabilitation (REA) affects positively A.O. Our study was carried out to verify the relationship between RT and A.O. incidence. Moreover the purpose was to assess the role, according to A.O. complete recovery, of the following factors: RT, arm circumference (CRF) < 4 cm vs the contralateral arm, time of start of REA before or later than 1 year from A.O. appearance.

The study included 852 consecutive pts followed up in our Institute from 1978 till 1984, with the following results:

1. RT is highly related to A.O. appearance (chisq=13.6, p value < 0.01).
2. The time of start of REA is less significant than CRF but anyway very important (chisq= 65, p value<0.01).
3. CRF > 4 cm is a very important negative factor according to complete oedema recovery if CRF is > 4 cm and RT starts later than 1 year from A.O. appearance (chisq= 8.11, p value <0.01).

Pts with the best prognosis according to oedema complete recovery are thus pts not irradiated, with affected arm CRF < 4 cm and treated as soon as possible. Therefore the best way to achieve this goal is to avoid RT (already not improving survival), to do systematic early rehabilitation and to perform a strict follow up for the early oedema detection.

**COMPARED COSTS OF BREAST CANCER TREATMENTS**, P.J.Lancre* and C.Jacquillat**, Université Paris XIII and Service d'Oncologie Medecoititite Pitit-Salpetriere Paris**

Counting the costs of cancer is a rather difficult problem. Although the only accurate evaluation should take into account the economic costs i.e. those relating to medical costs and loss of earnings but also in terms of how it might interfere with people's life. Length of survival, the social cost (*i.e. those relating to the concept of quality of life*)... We have limited our answer to this low-level question: "what is the cost of treatment?". We have considered:

- the actual costs (based on market values) arising from the use of resources in the health;
- the average costs based upon the hospital medical expenses;
- the price paid for b, the patients.

18 different treatments have been valued (using surgery and/or radiotherapy and/or chemotherapy) and lead to the possible computation of the medical costs of breast cancer therapy.
A HEALTH SURVEY ON CANCER CONTROL. M.Fontan-
4944 ges**, M.L.Jottii**, G. Saccani Jotti**, "%Ital-
4945 ian League Against Cancer, Reggio Emilia, Italy and
4946 "Path. Anat. Inst., Parma Univ., Italy

During 1983 the Italian League Against Cancer accomplished an investigation in the city of Reggio Emilia, Italy, with the purpose of evaluating the present knowledge and attitude of the public concerning cancer, in particular the methods of prevention and early diagnosis as well as the real possibilities for cure of this illness. The program was performed through a questionnaire proposed by the UICC. Of the 1500 questionnaires distributed, 1332 were filled up correctly. The results obtained undoubtedly offer various points for discussion and consideration. For example, the whole sample of cancer represents one of the most important and complex problems that medicine has to face and it is deeply felt by women who willingly offered their cooperation in the initiative. More important, women have proved to be more concerned about undertaking medical tests, even in the absence of symptoms and/or clinical signs of illness, while men have shown to be comparatively quite reluctant. The pointing out of symptoms connected with the presence of a tumor has come out to be very interesting. In fact, it is undoubtedly that the public, if informed correctly, has tendency to learn and apply almost every given advice for the defence of health. The same can be said about the medical tests employed in early diagnosis.

THE SOCIAL ESTIMATION OF THE ANTICANCER WORK.
4945 Dr. J. Kindler*, A. Galvás**, J. Czinneri, A. Decker,
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The authors analyse the social expectations in the anticancer fight and their motives in Hungary. A survey was done by questionnaires in different circles of the population. Well- and lesser educated people in both sexes were inquired, how they regard the severity of cancer diseases. Their opinion of the anticancer movement and their personal expectations from the family, the society, the health care and the state was also asked.

With the help of this survey the authors make an effort to decide the best field for the social anticancer movement so as to be able to reduce the morbidity and the mortality of cancer diseases.
COGNITIVE ADAPTATION IN CANCER CARE

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A diagnosis of cancer often leads to an overwhelming sense of loss of control over one's body and life. To generalize, the invasive nature of the disease process as well as the treatment modalities employed, a central concern in the care of cancer patients in helping them cope with the inevitable feelings of hopelessness, and regaining a measure of mastery. Cognitive approaches developing a sense of self-control and bolster self-esteem include self-enhancing social comparisons, identification with positive figures, imaging and other active behavioral efforts. The importance of cognitive adaptation and the need for further research merits serious consideration.

THE HEIDELBERG "CANCER ENCYCLOPEDIA" IN VIDEOTEX.

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Videotex, a New Medium, combines old ingredients to a new powerful mixture. Telefoni connects the present TV-screen to a public computer run by the Post office. Within seconds new information is stored into the computer is brought to the TV set in the family room. "Answer pages" make videotex an interactive medium, allowing the editors to contact the reader. The equipment is simple. Pages with new information can be easily inserted, pages with outdated information can be rapidly replaced. Thus Videotex combines the old large encyclopaedia with the rapid reactions of a newspaper.

The field test of the German Post office set up about 1 300 sample pages: General information on: How frequent cancer is, whether cancer is increasing, cancer and age, cancer and hormones and cancer in the third world. Risk factors are discussed: Smoking, place of work, social status, heredity, psyche, alcohol and others. There is basic knowledge about chemical carcinogens, data bases on cancer research and how to find them, a chapter on breast cancer, what happens in a medical check-up (e.g. cervix carcinoma), the secrets of tumor immunology, and some very special key words like: diurnal variation, contact inhibition, proteases, chalones etc. Useful and important addresses are given: Tumor centers, aid groups, aftercare clinics, organisations that give advice by telephone.

These pages are now accessible nationwide through the "Leitseite" (guiding page) *2151*. The encyclopaedia is continuously updated and extended. New developments in cancer research are critically reviewed. Though handicapped by the prevailing economic conditions, Videotex is on its way to be a major source of general and special information for the general public.
The inhibitory effects of selenium yeast and sodium selenite on methylcholanthrene-induced lung carcinogenesis were examined in inbred Wistar rats. The animals were divided into three groups; group I and II were supplemented with 2 ppm of selenium (organically bound, in yeast) in their diet and with 1.5 ppm sodium selenite in their drinking water respectively, and group III were fed basal diet for control. The results showed that the rate of carcinogenesis in group I, II and III were 76.92% (p<0.01), 82.14% (p<0.05) and 100%, respectively. The hyperplasia and metaplasia of bronchial epithelium were striking in group III, however, the lymphocytes immune response were remarkable in group I and II. These results suggested that the selenium yeast and sodium selenite is effective in preventing the MCA-induced lung carcinogenesis in rats, and the former is more effective than the latter.

The organ system of rat trachea was cultured on the metastasis of Lewis lung carcinoma in C57BL mice. The tracheal rings prepared from inbred Wistar rats were divided into three groups; group M was cultured in the medium added with MCA (2 μg/ml), group S in the medium added with both MCA (2 μg/ml) and sodium selenite (1 μg/ml) and group C in the medium alone for control. The observations under light microscope and scanning electron microscope were made each week for four weeks at all. The experimental results showed that the ciliated columnar epithelia of the tracheal rings was normal for all four weeks in group C; in group M it appeared hyperplasia and squamous metaplasia from the first week and atypical hyperplasia in the last two weeks. However, in group S it was normal for the first two weeks and later showed hyperplasia and squamous metaplasia but the form of proliferation were different from that of group M and no progressive changes as group M appeared. These results suggested that selenium may be an antagonist against chemical carcinogen, or an antioxidant to protect cells from oxidized damages.

The inhibitory effects of sodium selenite on the carcinogenesis of rat trachea in culture was examined. All animals were inoculated with single cell suspension of LLC in their left hind leg muscles. After 21 days, all animals were killed. The results showed that the rate of metastatic rate and the number of metastatic tumors in lung were significantly decreased in selenium yeast group than in control (p<0.01). We found that the activities of acid phosphatase in LLC were different among two groups. The enhanced immune function was obvious histochemically and flowcytometry examination. The possible mechanisms of the inhibitory effects by selenium yeast were discussed.

MOLECULAR MECHANISMS OF RADIATION-INDUCED DEATH OF NORMAL AND TUMOR LYMPHOID CELLS.
G.R.Umansky, B.A.Korol', P.A.Nelipovich, V.V.Khasanov, D.A.Pechatnikov, Institute of Biological Physics, USSR Academy of Sciences, Pushchino, USSR

In spite of many years of studying molecular mechanisms of interphase and reproductive death of irradiated cells the problem is still unresolved. During the last years data are obtained which allow to consider many cases of cell death as an active cell response to physiological or damaging factors. Such form of cell death in accompanied by early ordered DNA fragmentation. The aim of the present work was to compare the kinetics and character of DNA degradation as well as the disturbance of plasma membrane permeability in normal and tumor lymphoid cells after γ-irradiation. DNA content and membranes'permeability was studied by flow cytometry, the character of DNA fragmentation was investigated by electrophoresis. It was shown that irradiation of rat thymocytes led to the early enzymatic interchromosomal cleavage of DNA, the outer cell membrane permeability being unchanged and protein biosynthesis continued. Upon irradiation of Burkitt's lymphoma cells, an early increase in membrane permeability was observed, DNA remained intact for a long time and then it was irregularly degraded by hydrolyases activated in dead cells. The irradiation of mouse thymocytes revealed two cell subpopulations dying by these different mechanisms.
This paper describes a program that is primarily directed to the students from 9 to 18 years old in Saudi schools. One of the most worrying aspects of the smoking habit in Italy is the high percentage of young smokers: 51.8% of all young smokers started their habit under 18 years of age. It appeared necessary, to involve schoolgoers in a vast prevention program against the hazards of tobacco smoking and cancer prevention which might assist them in making correct and informed decisions concerning their future life styles. Therefore, it is necessary to contact both young people at various levels of education and the adults connected with the schools. The methodology of the program includes informative seminars, debates and distribution and evaluation of questionnaires. The results obtained after three years show that the participation rate is increasing rapidly, and total numbers of students who have participated has reached 26,000. After one year of active participation 29% of the students in a sample of 4513 had quit smoking and only 2.5% of the students in the control group decided to start smoking. On the other hand, within the control groups, the number of students who became smokers in the same period, rose to 162.

MALIGNANT LYMPHOMAS IN SAUDI ARABIA. Magdi Azer and Salal El-Akkad. Department of Oncology, King Faisal Specialist Hospital & Research Centre (KFSH), Riyadh 11211, Kingdom of Saudi Arabia (SA).

Between 1978 and 1985, 777 consecutive, previously untreated adult patients (PTS), with histologically confirmed non-Hodgkin's lymphoma (NHL) were referred to KFSH, which is the main cancer treatment centre in SA. There were 532 males and 245 females with mean age of 48 years (range 14-90 years). 306 (39%) PTS were referred from Riyadh and vicinity, 213 (27%) from Western Province, 103 (13%) Southern Province, 71 (9%) Eastern Province, 61 (8%) Northern Province and 37 (5%) PTS from other locations. Most of Intestinal lymphoma PTS were referred from the Southern Province near Yemen. The commonest primary tumor sites were head & neck (33%) followed by gastrointestinal tract (stomach 17%, intestine 12%), lower limbs (7%), breast (6%), bone (6%), upper limbs (3%), thyroid (3%) and others (22%). Histological diagnosis based on Rappaport Classification was diffuse (D) histiocytic 452 (59%), D lymphocytic in 102 (13%), D mixed in 45 (6%), nodular in 25 (32), D, monomorphic intestinal disease (19) and in 145 (19%) PTS no accurate information were available. After full staging most patients did have stage IV (370) or III (167) disease while a lesser number did have stage I (25) or I (43) disease. Patients were treated initially with one of different treatment regimens including combination chemotherapy with cyclophosphamide (CTX)+ vincristine (VCR)+ prednisone (PND)+ doxorubicin (ADOR) and bleomycin (BLM) for 8 courses without maintenance chemotherapy (Group A); in addition to regional radiation therapy (Group B); high dose methotrexate (MDX) with cisarabinoc reate followed by ADM, CTX, BLM, PRD and PND (Group C); or with different chemotherapeutic agents selected according to in vitro tumor sensitivity to anticancer agents, laboratory Cytogenetic Assay as well as Radiocnucleotide Thyridine, Uridine and Leucine uptake (Group D). For disease relapse, patients were treated with: Mitoxantron intraperitoneally VCR+ BLM, or total body radiation therapy. Detailed information on the results of therapy and subsequent survival will be presented.


Italian breast cancer death certification data were analyzed by way of a cross sectional methods (which showed an overall increase for women below age 65 of about 35% between 1955 and 1980), and a statistical model taking simultaneous into account the effects of age, cohort of birth and period of death. The model indicated that mortality from cancer of the breast in females increased steadily, with age, and there was little indication of a levelling off about the age of menopause. It appears therefore that the perimenopausal "hook" is essentially attributable to a cohort effect. Cohort values were increasing up to the generation born in 1920 and in women born after 1935. This pattern of trends should be related to the reproductive habits of subsequent generations, showing a lower number of births per woman, apart from a moderate increase in cohabitation ages after the second world war. The incidence of breast cancer mortality was positively and strongly correlated with mean age at first birth (r=0.73). Breast cancer mortality rates were found to be positively correlated with milk and meat consumption and negatively with milk, thus confirming previous studies on national and international scales. The indications from vital statistics were further confirmed on a large case-control study of breast cancer conducted in Northern Italy, whose preliminary results will be presented and discussed.
4959 INCREASED RISK OF HEPATOCELLULAR CANCER (HCC) IN PATIENTS WITH PORPHYRIA ACUTA INTERMITTENS (PAI) OR PORPHYRIA CUTANEA TARDA (PCT). NO Bengtsson, L Mardell, Department of Oncology, University Hospital, S-750 85 Umeå, Sweden.

In a case-control study on male primary liver cancer 3 cases of PAI were identified among the 83 cases of HCC versus none of the controls. The prevalence of PAI in the study area was estimated to 1 per 1000. The finding of 3 cases of PAI among the 83 cases of HCC thus represents a roughly 120 fold increase in the risk. An association between PAI and HCC has also been demonstrated recently in 2 cohort studies. Of interest is that our 3 cases of PAI and HCC had all been exposed to porphyrinogenic substances, i.e. dioxins and alcohol. In addition to these 3 cases we have treated another patient with PAI and HCC at our department. He was also previously occupationally exposed to dioxins. Furthermore one of the 4 cases had a brother with PAI and HCC and another had 2 sisters with this disease constellation. These additional cases were identified through the regional cancer register. Six cases of PCT and HCC were identified in the case-control study but no control had PCT. Four of the 6 patients were alcoholic and 1 had hemochromatosis. Some well-known liver carcinogens are potent porphyrinogenic substances. In patients with HCC without previous history of porphyrin disturbances in porphyrin excretion have been reported. The significance of porphyrins in liver carcinogenesis has not been clarified. One interesting hypothesis is that porphyrins might have carcinogenic activity per se. Chloroquine is used to reduce clinical symptoms in porphyrins might have carcinogenic activity per see. Chloroquine is used to reduce clinical symptoms in patients with PAI and PCT and also significantly lowers the urinary excretion of porphyrins. On long-term treatment with chloroquine the incidence of HCC is lowered in PCT patients. These aspects will be further studied in epidemiological and experimental investigations.

J-41/20

4960 A MODEL OF CANCER CONTROL BASED ON THE IDEA OF: CANCER CONTROL BY THE COMMUNITY FOR THE COMMUNITY. A PROGRAM DESIGN TO IMPROVE CANCER CONTROL IN EAST JAVA.


Cancer is a multicentric disease, arising problems not only affecting the medical world, but are also felt by the community, especially in developing countries, and Indonesia is one of them. To cope with an effort has been made for the community to establish independent task forces to fight cancer, which in the long run will be able to perform secondary as well as primary prevention of cancer, recruit volunteers and raise funds for their own needs. The effort has been made possible as there is in Indonesia a system of mass education reaching the family as the smallest unit of the community and that in the Program of Family Welfare. It is a non-governmental movement, which in well organized throughout the country, has a stipulated program of teaching and a certain way of method of evaluation. The programming and implementation of the teaching on cancer control, incorporated into the teaching of the Program of Family Welfare will be directed as such, that it represents a continuation of the secondary prevention, should be in line with the government's policy of health care delivery, can be integrated in the already existing programs of the community, will be guided onto a certain direction as to omit monitoring and will become universal, reaching all social levels of the community. In order to achieve a maximum result, a comprehensive cooperation of all parties in the community have been emphasized, while the government is encouraged to modernise and improve facilities for cancer care, provide professional education to doctors and paramedics.

J-41/21

4961 A MODEL OF CANCER CONTROL BASED ON THE IDEA OF: CANCER CONTROL THE COMMUNITY FOR THE COMMUNITY. THE IMPLEMENTATION OF THE PILOT PROJECT.


Before the implementation of the program in the pilot project, the first step taken was to explore possibilities for other organizations as to be willing to participate actively and to make the program a success. The next activity was to arrange a one-day seminar for the key persons of the Program of Family Welfare and prominent figures in the community, followed by a one-day workshop for members of the Program of Family Welfare from all structural levels only. Together with the Wisnuwardhana Cancer Society they determined the sites of the pilot projects, subsequent activities to be taken, subject matters for public cancer education. Also scrutinized were the availability of personnel, supporting facilities for the implementation and identification of constraints.

The implementation of the teaching on cancer control in the pilot projects is divided into four steps, i.e. the motivation, the operation, the evaluation and improvement and finally the development of the whole program.

J-41/22


Preceding the implementation, a talk about motivation had been done for instructors and key members of the Program of Family Welfare of the pilot project's site. While the implementation was going on, two kinds of evaluations were designed. The short term evaluation concerns subject matters, the way of implementation itself, how receptive the community is toward public cancer education, arising problems and ways to solve them. The long term evaluation is geared toward the overall results of the fight against cancer. This of course will take many years. An epidemiological approach will be used with the following parameters; the decrease of the incidence rate of certain cancers, changes in lifestyle to enhance primary prevention of cancer, e.g. not to marry at a young age, not to have children more than two, etc. Following the evaluation and improvement of the teaching, the program will be further developed and will be applied in the remaining districts throughout the Municipality of Surabaya. It eventually will be presented to the Provincial Program of Family Welfare. The application throughout the Province of East Java.

In our sincere hope, that by the year 2000 cancer control will be popular among the more than 29 million inhabitants in East Java.

J-41/23
ADJUVANT VPB THERAPY OF TESTICULAR TUMOURS.

I. Bodrogi, M. Baki, Gy. Liszka, Sz. Otto, J. Hostak, F. Balogh, L. Kis-benedek, L. Mohacsi, P. Magasi, J. Pinter, A. Rosta,

Between December 1979 and 1984, 147 patients with non-seminoma type testicular tumour were given adjuvant VPB therapy at the National Institute of Oncology, Hungarian Urological Society, Budapest, Hungary.

4964 PRE-OPERATIVE IRRADIATION OF RECTAL CARCINOMA

While the operational phase of the pilot project was going on, a surprising and unexpected auto-activity took place in one village. To familiarize cancer control, the village instructors devised three methods:
1. a popular song has been adopted, in which the poem has been changed and adapted to the theme of cancer control,
2. a quiz with the theme of cancer control also has been devised and played during their regular gathering. To prevent personal embarrassment, several groups of at least four where are made to participate in the play,
3. a simulation game has also been developed.

Between December 1979 and 1984, 219 children were treated with 3 very similar therapeutic schedules which included: remission induction therapy using either prednisone and vincristine or prednisone, vincristine and daunomycin; prophylaxis of the CNS with cranial irradiation plus intrathecal methotrexate, or intrathecal - methotrexate alone; and a maintenance therapy with 6-mercaptopurine plus methotrexate and periodic reinductions with prednisone plus vincristine alone or prednisone plus vincristine alternating with cyclophosphamide and cytosine arabinoside. The remaining 40 patient, were treated with a therapeutic schedule very similar to that of the BFM group of West Germany. The accumulated overall survival at 60 months was 41% for the first 3 groups of patients. The prognostic factors which influenced the duration of complete remission were: age, presence of mediastinal mass, CNS infiltration, number of leukocytes and platelets, and the PAS staining. No significant differences were found in the number of relapses and the percentage of sustained complete remissions in patients with BFM protocol at 36 months, was 75% and survival 84%.

M-48/11  P-41/23

Adjuvant treatment of colorectal cancer has been studied in different ways by the G.I. Group of the EORTC. Preoperative RT was evaluated in two clinical trials. In the first (prot. n. 40761) radiosurgery (34.5 Gy/fr. 2.3 Gy/18 days) was compared to the same dose of RT + i.v. 5FU (375 mg/m²/day for the first 4 days). This study started in 1972 and closed in 1976. There was a slight difference (p<0.06) in favor of the radiosurgical arm concerning overall survival. In a second trial (prot. n. 40761) started in 1976 and closed in Sept 1981 the effect of adjuvant preoperative RT (36.4 Gy over 19 days) was tested against surgery alone. The results show a significant difference (p<0.001) in favor of the combined treatment arm with regard to local recurrence.

The effect of immediate postoperative Levamisole in patients with Dukes C colon cancer was studied in a double blind randomized clinical trial (prot. n. 40781) started in 1979 and closed in 1983. No difference is evident so far between treated and control group regarding overall survival and tumour free interval.

At present two clinical trials are still not completed and only the toxicity effects are available for these studies. The first protocol started in 1982 (prot. n. 40811) with the aim of evaluating the effect of postoperative RT (44 Gy) in Dukes C rectal cancer. The second protocol started in 1983 (prot. n. 40812) to evaluate the effect of portal vein perfusion of 5FU + Heparin or Heparin alone in completely resected cancer of the colon (Dukes A-C).

M-16/5

MANAGEMENT OF ANAL CANAL CARCINOMA - Jean Papillon
Centre Leon Berard, Lyon, France

Radical surgery as initial treatment has been abandoned in most Western countries in favor of radiation therapy combined or not with radiosensitizers. From a series of 275 cases followed more than three years, it is shown that a split-course regimen of irradiation using Cobalt 60 followed two months later by an Iridium 192 implant is able to control more than 75% of resectable tumors. Preservation of the anus is obtained in more than 60% of cured patients. This protocol combined with 5 Fluorouracil and Mitomycin C during the first four days of irradiation has demonstrated a much greater effectiveness than external beam irradiation alone.

M-16/6

ADJUVANT THERAPY OF UPPER GASTROINTESTINAL CANCER Philip S. Schein, University of Pennsylvania School of Medicine, Smith Kline & French Laboratories, Philadelphia, PA, USA

During the past decade, improved response rates have been reported with the use of combination chemotherapy in the management of patients with advanced gastric and pancreatic cancer. This has resulted in increased enthusiasm for the evaluation of adjuvant chemotherapy for patients with resected disease in an attempt to improve their survival. In 1974, several gastric cancer adjuvant studies utilizing the combination of 5-FU and methyl-CCNU were initiated; while one trial demonstrated improved survival for patients receiving chemotherapy, this could not be confirmed in two other studies. Recent emphasis has been placed on doxorubicin-based regimens, such as the FAM combination. The International Gastric Cancer Adjuvant Trial, in which FAM treatment for one year is compared to observation, was initiated in 1982. Three hundred and twenty-six patients with resected gastric cancer were randomized, of which 291 are now evaluable. The study is well balanced in regard to major prognostic features of gastric cancer. The tolerance to FAM chemotherapy for one year on an out patient basis has been adequate. A late trend in disease free survival favors chemotherapy over observation, but the differences are not as yet statistically significant. For pancreatic cancer, the Gastrointestinal Tumor Study Group has reported the results of a controlled trial in which no adjuvant treatment was compared to combined modality therapy in a group of 43 patients with resected pancreatic cancer. The median survival for treated group (20 months) was significantly longer that that observed for control group (11 months). This study serves as the basis for a national intergroup trial in which the combination of SMF chemotherapy with radiation therapy is being evaluated.

M-16/8

CURRENT CONCEPTS IN THE MANAGEMENT OF GASTRIC AND PANCREATIC CANCER IN JAPAN. Tetsuo Taniuchi, Dept. of Oncologic Surgery, Res. Inst. for Microbial Diseases, Osaka Univ., Suita, Osaka, Japan

Surgery is still chosen as the primary treatment in the curative treatment of gastrointestinal cancers(GI cancers) proves quite satisfactory against early gastric cancer, which mainly accounts for the recent improvement of the late results in gastric cancer. The improvement of the results by surgery alone, however, has clearly reached its ceiling in advanced GI cancers. Multidisciplinary treatment consisting of tactfully combined therapies of various types should therefore be planned for GI cancers, to improve the results of the treatment of advanced GI cancers.

M-16/7
**ADDENDUM**

**4971**
**MALIGNANT CANCER (MC). A ROLE FOR CHEMOTHERAPY?**

J.H. Janssens, University Hospital Leuven, Leuven, Belgium.

Chemotherapy in MC has lagged behind those of other common malignancies, although the disease now ranks in fourth place in cancer death. One reason is the difficulty in diagnosis and evaluation of response that has not been altered even with the introduction of ultrasound and computerized tomography (CT). Another is the nihilism that still prevails in approaching this disease. Surgery offers the best hope for cure: but even for the small number of patients with 'curative' resection, survival is very low. Only few single agents appear active in MC, including 5-fluorouracil (5FU), mitomycin (M), streptozotocin (S), and recently aprinbicin (G), an analogue of Adriamycin (A), and lophosphamide. Response rates of about 10% have been reported from phase II studies with combination chemotherapy such as FAM and SMF, but median survival does not exceed 6 months. Randomized studies yield even lesser results. The ECOC Centrastinal (EC) group has conducted 2 phase II trials in MC. In the first study (4082) it yielded a response rate of 27% (median duration of response 8 months), while in the second trial (4086) the combination of E + F resulted in a response rate of 21% (median duration of response 4 months). Apart from differences in patient selection the large of E may be a contributing factor to the somewhat inferior results of 4084. Furthermore it appears that a response rate of 20% for F as suggested in the literature is probably an overestimation. It is concluded that chemotherapy in MC is still experimental and until now has no impact on survival. Standard chemotherapy for MC is not available and patients should only be treated within clinical trials.

**M-16/9**

**4972**
**BREAST CANCER DETECTION AND DEMONSTRATION Vol. 53:681-684, 1984/ including information previous publications in this field /Cancer Vola 23:601-608, 1984/ Including information on those cases detected as a result of the Breast Cancer Detection and Demonstration Projects of the United States. The presentation will detail this experience emphasizing precision in diagnosis and its impact on treatment and follow-up.

**A-35/9**

**4973**
**CHARACTERIZATION OF LPS RESIDUS INVOLVED IN INTERLEUKIN 1 INDUCTION.**

Experiments undertaken to localize within the lipopolysaccharide (LPS) molecule, the minimal structural determinant sufficient to initiate the signal leading to interleukin 1 (IL-1) secretion by human monocytes, have demonstrated that this signal is triggered by structures present in the inner core region (Eur. J. Immunol. 1986,16) which chemically consist in most LPS of 2-keto-3-deoxy-octulosonic acid (KDO) and heptose residues. The role of KDO was further investigated, and we observed that purified Lipid A is unable to induce IL-1 secretion whereas & minnesota R595 LPS which consists of only Lipid A and KDO residues, is IL-1 inducer. It is noteworthy that purified Lipid A, although being not IL-1 inducer, is a potent pyrogen. We also report that polymyxin B (PMB) which suppresses the biological activities triggered by Lipid A moiety of LPS, inhibits LPS mediated IL-1 secretion; but its inhibitory activity is variable according to the LPS origin. From these results, it can be speculated that PMB in some LPS, may modify the conformation or mask the KDO region, whereas in other LPS, the interaction occurs solely with the Lipid A. Taken together, our data indicate that the essential determinant required for the induction of IL-1 secretion by human monocyte stimulated with LPS, are located within the KDO residue.

**L-34/11**
ADDITIONUM

4975

RELATIONSHIP BETWEEN CLINICAL STAGING MORPHOGENESIS AND GROWTH POTENTIAL OF HUMAN COLORECTAL CARCINOMA. Czuka,Gy., 70th.Ay. Szentirmay, Z. National Institute of Oncology, Budapest, Hungary, Department of Surgery, Medical School, Budapest, Hungary

Adenocarcinomas of the large bowel have been analysed in 104 patients. Staging of disease was based on the TNM classification. The duration of the symptoms, the size and location of the tumours have been recorded. Histopathologic features, trends of differentiation, type of histogenesis and fraction of S phase cells of these colon carcinomas have been determined. The carcinomas in the younger patients (≤55 years) are less differentiated than in the older patients. Well differentiated carcinomas developed from adenomas in the majority of the cases, Colon carcinomas have been subclassified according to their functional differentiation based on the mucin composition of the tumors. Patterns of differentiation may have been related to small and large intestinal, gastric or embryonal type. There was no strong correlation between the histopathologic structure and functional differentiation of the carcinomas. The DNA distribution pattern and cell cycle parameters were determined in the case of 47 colon carcinomas and the possible correlation to clinical outcome was evaluated. Carcinomas arising "de novo" could be characterized by a high fraction of S phase cells and embryonal type of differentiation might have prognostical significance. The majority of carcinomas developing by "de novo" carcinogenesis and fraction of S phase cells and gastric or embryonal types of differentiation may have been related to small and large intestinal, gastric or embryonal type. The majority of carcinomas developing by "de novo" belonged to the III or IV stage of TNM classification. Our results indicate that a high fraction of S phase cells and embryonal type of differentiation might have prognostical significance.

A-51/13

4976

LEUKEMIA OF LARGE GRANULAR LYMPHOCYTES (LGL): IMMUNOLOGICAL, CLINICAL AND CYTOCHEMICAL CHARACTERIZATION. P. Vujčinč, O. Babušková, M. Klobočáka, and A. Vahančík**, Cancer Res.Inst. and Natl. Institute of Oncology, Budapest, Hungary

The study of malignant cells in the so-called LGL leukemias provides a useful tool for the characterization of the heterogenous population of natural killer /NK/ cells. A case of LGL leukemia with a typical clinical course of neutropenia, hemolytic anemia and T cell lymphocytosis is presented. The clinical and cytochemical data are supplemented with the surface phenotype analysis. The phenotype of the malignant cells was SIg-, E+, T+, L3T4, Leu7+, HNK1+, Ly7, B73.1+,, BA1+, Ta-. The NK cell activity of the patient's mononuclear cells was measured against K562 and MOLT-4 target cells lines in a 4-hr Cr release test and compared to that of an age matched control. There was no significant difference between these two samples even after effector cell stimulation with human leukocyte interferon. A possible functional LGL immaturity and/or the presence of a heterogenous population of LGL is discussed.

A-52/14

4977

ORIGIN OF IN VITRO H- AND SR-CELLS
V. Diehl, H. Burrichter, G. Bornkamm

The establishment of permanently growing Hodgkin-derived cell-lines (L428, L540, L591) enabled us to perform reproducible studies concerning the origin and functional properties of Hodgkin(H)- and Sternberg-Reed (SR)-cells in vitro. Histochecmical, cytogenetic and immunological analyses confirmed the concordance of the established cell-lines with H- and SR-cells in vivo. Characterized these cells as a unique, so far not described cell-type or an unknown differentiation-status of a kind of celllines. Analysis of heavy and light chain genes revealed rearrangements in 1,428 (DNA: JR-chain rear., C 2α41-, Cα1 rear., Cκ rear., Jκ1, λ rearr., 2 germ line; DNA: C 2κ transcrip) and in L591 (20% of the cells produce α- and γ- chains), while in L540 rearrangements in the immunglobulin genes could not be demonstrated. In another Hodgkin-cell-line (Cole), established elsewere, we found rearrangements in the V-cell-receptor gene. All Hodgkin cell-lines constitutively produce biological mediators: Rosette-inhibiting-factors, Interleukin 1, fibroblast-activating factor, colony-stimulating factor, B-cell growth promoting activity, migration inhibitory factor. The relevance of these data for the origin of H- and SR-cells and histological, clinical and immunological implications of H- and SR-cells is discussed.

A-52/15

4978

A NEW HYPOTHESIS: INHERITED CANCER RISK ON THE BASIS OF GENOME INSTABILITY IN MAN. Szentesi, Ist., Inst. of Hygiene, Dept. of Human Genetics, National Institute of Hygiene, Dept. of Human Genetics, Budapest, Hungary

The one part of the genome is a "stable genetic field": this is the "conventional part"/excluded movable genetic elements/. The other part of the genome is a "labile genetic field"/excluded movable genetic elements/IF break down the condition of balance of the genome and/or transposition of mobile elements, misfunction of DNA repair systems, increased environmental mutation load etc./then this state originate a genome instability. The genome instability regions are oncogenes and/or complexes of oncogenes and DNA repair gene systems. These regions are localized/stable genetic fields/ and/or "quasi-localized" /labile genetic fields/ position of the genome. The different genome instability regions spontaneous /"a priori"/and/or induction-dependent /facultative, hidden/ types.

The inheritance of traits of the sub-regions as "functional units" one by one "conventional" dominants, recessives etc. The inheritance of traits of the completely regions is "complex": "pseudo-dominant", "pseudo-recessive" etc. Typically manifestations: "variable expressivity", "decreased penetrance", "generation missing" and other "anomalies" of the mode of inheritance. The "facultative" /quasi-concentrable/ genetic linkage groups are probably impossible the horizontal gene transfer besides of the vertical gene transfer. This genetic background possibly a basic of the different spontaneous induced cancer and/or genetic disorders /e.g. retinoblastomas, DNA repair deficiencies etc./.
Carcinoma of the colorectum: a comparison between the new TNM system and the Duke's classification.


The prognosis of colorectal carcinoma is determined by three principal factors: 1) is surgical removal of the tumor possible? 2) is the removal of the tumor complete? (Residual tumor or R classification) 3) tumor spread at the time of diagnosis determined after pathological examination of resected specimens. The tumor spread can be classified according to the Duke's classification and its several variations or according to the INM system. The definitions of the newly revised INM/pTNM classification are the following: in brackets age-corrected 5-year survival after curative removal of the tumor, data of Erlangen Registry of Colorectal Carcinomas: pT1: tumor invades submucosa (colon and rectum 100 %), pT2: invades muscularis propria (colon 96 %, rectum 77 %), pT3: invades subserosa or non-peritonealized pericolic or perirectal tissues (colon 74 %, rectum 53 %), pT4: perforates visceral peritoneum or directly invades other organs or structures (colon 45 %, rectum 20 %); pN0: no regional lymph node metastasis (colon 92 %, rectum 77 %); pN1: metastasis in I-3 pericolic/perirectal nodes (colon 63 %, rectum 57 %), pN2: metastasis in 4 or more pericolic/perirectal nodes (colon 18 %, rectum 39 %), pN3: metastasis in any node along the course of a named major blood vessel (colon 29 %, rectum 27 %). The newly revised INM/pTNM classification is not a Duke's clone, but it is compatible with the Duke's classification and its several variations. It is a solution to confusion. Furthermore, it allows for the separation between classification and stage grouping. It has been adopted by all national INM committees and the AJCC.

L-51/23

Indications for and results of pre-operative treatment of children with Wilms' tumour, Durban 1977 - 1984

Marie L G V Batarda, MBChB, Prof Johann P Jordaan, MBChB, MMed, FRAT, Grenville P Hadley, FRCS, Robert E Mickel, FRCS

From the Department of Radiotherapy and Oncology, University of Natal, Durban, South Africa and from the Department of Paediatric Surgery, University of Natal, Durban, South Africa.

Since 1977 94 new patients with Wilms' tumour were treated by this Department. In 39 children the tumour was considered unresectable, either by virtue of massive tumour size and infiltration or the patient being considered an unacceptable operative risk. Following investigation these children were treated with chemotherapy alone (21) or in combination with radiotherapy (18) according to a fixed protocol. In 60/94 a nephrectomy was subsequently possible.

In 55 children primary surgery was possible amongst whom intra-operative tumour cell spillage occurred in 14. No such spillage occurred in pre-treated patients. In both groups of patients post-operative treatment was standardised for each stage and histological classification. Although the initial unresectable children had poorer prognostic features, no significant differences in tumour-free survival, overall survival or distribution of recurrence are evident amongst those surviving to surgery. In all pre-treated patients tumour bulk was reduced when assessed clinically or radiologically. In all pre-treated tumours necrosis was evident both macroscopically and microscopically but did not interfere with histological diagnosis. There was no preponderance of unfavourable histological features.

It is concluded that pre-operative treatment is justified in children with massive or otherwise unresectable tumours and that such treatment is effective in reducing tumour bulk with tolerable morbidity and mortality.

P-42/21

Antidopogens as the drugs, increasing the antitumor resistance of organism

K.V. Herman, H.M. Udintsev, Syberian branch of Pharmacology Inst., Acad. of Med. Sciences, Tomsk, U.S.S.R.

The problem of host antitumor resistance increasing determines mainly the radicality of oncological patients treatment. It's impossible to solve the problem only by means of cytostatics application, because of the suppression of immunological defence systems by the latter. To increase the antitumor resistance of host a number of adaptogens were studied. The decreasing of tumours metastases and the correction of side-effects of cytostatics as a result of these substances application was demonstrated. These effects were shown to be connected with antitress activity of the drugs and with the stimulation of injured normal tissue reparation.

M-51/21

ADDENDUM

4979 CYCLOPHOSPHAMIDE, METHOTREXATE, AND NOVANTRONE IN ADVANCED BREAST CANCER: A PILOT STUDY


Novantrone activity in breast cancer has been proved in several phases I/II studies with results of 35 - 40%. Encouraging results 79% overall response were obtained when novantrone was used in combination with cyclophosphamide and fluorouracil. The present study aims at evaluating the tolerance and clinical effectiveness of novantrone in combination with methotrexate and cyclophosphamide. So far the most active two drugs in breast cancer after Adriamycin. Study was carried out in 25 female patients with advanced breast cancer. Their ages ranged from 22 - 60 years, average 45 year. Schedule of treatment was:

- Cyclophosphamide 500 mg/m² sq.
- Methotrexate 40 mg/m² sq.
- Novantrone 10 mg/m² sq.

All given intravenously day 1, every three weeks. Dose modifications were according to blood picture and serum bilirubin. Patients were monitored each cycle for response and for toxicities. Among 8 fully evaluable patients who received from 3 - 6 courses there were one complete response, two partial responses, three minimal response, and two stable diseases. No cardiac toxicity was encountered, the alopecia was grade 1 in all patients, leukopenia was grade 1 in those affected, while the nausea and vomiting was grade 2, for few hours. So far, this combination was well tolerated.

4980 CARCINOMA OF THE COLORECTUM: A COMPARISON BETWEEN THE NEW TNM SYSTEM AND THE DUKES' CLASSIFICATION


The definitions of the newly revised INM/pTNM classification are the following: in brackets age-corrected 5-year survival after curative removal of the tumor, data of Erlangen Registry of Colorectal Carcinomas: pT1: tumor invades submucosa (colon and rectum 100%), pT2: invades muscularis propria (colon 96%, rectum 77%), pT3: invades subserosa or non-peritonealized pericolic or perirectal tissues (colon 74%, rectum 53%), pT4: perforates visceral peritoneum or directly invades other organs or structures (colon 45%, rectum 20%); pN0: no regional lymph node metastasis (colon 92%, rectum 77%); pN1: metastasis in I-3 pericolic/perirectal nodes (colon 63%, rectum 57%), pN2: metastasis in 4 or more pericolic/perirectal nodes (colon 18%, rectum 39%), pN3: metastasis in any node along the course of a named major blood vessel (colon 29%, rectum 27%). The newly revised INM/pTNM classification is not a Duke's clone, but it is compatible with the Duke's classification and its several variations. It is a solution to confusion. Furthermore it allows for the separation between classification and stage grouping. It has been adopted by all national INM committees and the AJCC.

L-51/23

P-42/21
ROLE OF RECTUS ABDOMINIS MYOCUTANEOUS FLAP IN SURGERY FOR BREAST CANCER. H.S. Shukla, and K. Sahni, Institute Of Medical Sciences, Varanasi, India.

There are situations after surgery for breast cancer where extra healthy tissue is required. Rectus abdominis myocutaneous (RAMF) flap provides large reserve of tissue which we have used after breast-cancer surgery in a variety of situations. These included: delayed reconstruction (36), for primary wound cover (20), for chest wall repair after excision for radionecrotic breast ulcer (4). There is a choice of ipsilateral or contralateral RAMF. The cutaneous part of RAMF can be tailored to fit the shape of chest wall defect. Bulk of RAMF gives satisfactory contour for breast reconstruction. We did not use prosthesis in any case in this study.

Use of RAMF required one hour extra time for operation and one unit blood for transfusion. Postoperative hospitalisation time was increased by 5 days. The postoperative complications included: partial flap loss (1), marginal skin necrosis (16%), fat necrosis (16%), wound infection (5%), incisional hernia (4%). Adjuvant treatment, chemotherapy, radiotherapy was not delayed. Quality of wound healing was good. Total follow-up period was 4 to 56 months during which there were: no recurrences in the flap or underneath it, 4 local chest wall recurrence, 15 systemic recurrences, 6 supraclavicular recurrence alone. Flap remained insensitive in all cases.

THE RESULTS OF THE APPLICATION OF THE MODIFIED PM MYOCUTANEOUS "PADDLE" FLAP
M. Káser, T. Banhidy, K. Polus, A. Beer, I. Rács, L. Kósza, B. Templén, Z. Trízna

The authors report on the data of 96 patients who were operated with the modified PM myocutaneous "paddle" flap. The indications, contraindications, the results, and complications of these operations are shown. The results are favourable from the oncological, functional and the aesthetical point of view.

TEN YEARS' EXPERIENCE WITH TOTAL LARYNGECTOMY.
Z. Trízna, T. Banhidy, K. Polus, M. Káser, B. Templén, L. Kósza, I. Rács, A. Beer, E. Iványi

The authors report on the ten years' experience with total laryngectomy between 01.01.1974 and 31.12.1983. The anamnestic data of the patients, the stage and TNM data of the tumours are analyzed. The postoperative results are shown in tables with special regard to the survival, the metastases and the recurrence.

TOTAL LARYNGECTOMY WITH THE MODIFIED PM MYOCUTANEOUS "PADDLE" FLAP AFTER RADICAL OPERATION OF THE ORAL CAVITY, THE PHARYNX AND THE LARYNGOPHARYNGEAL REGION
M. Káser, T. Banhidy, K. Polus, I. Rács, A. Beer, Z. Trízna

The paper presents the data of patients, the localisations and the TNM classifications of the tumours of the oral cavity, the pharynx and the laryngopharyngeal region. The authors report on the phases of resection and reconstruction on one typical case of each group.
The Modified PM Myocutaneous "Paddle" Flap

M. Kaler
Postgrad. Med. Sch. Clinic of Head and Neck Surgery
Budapest, Hungary

The author describes the major pectoralis muscle myocutaneous "paddle" flap in his own modification. The author presents the surgical procedure provided by the possibilities given by the major pectoral muscle and the thoracoacromial artery. The steps of the procedure are discussed.

The Value of Pre- and Postoperative Staging in Breast Cancer

P. Rahaty, E. Bystics, P. Bonyay and I. Besnyak, National Institute of Oncology, Budapest, Hungary

The staging of breast cancer patients as well as its correction in the possession of the histological finding and steroid receptor determination are of decisive significance when planning the sequence of treatment procedures. The authors operated on 1042 breast cancer patients between 1982 and 1985. When comparing the pre- and post-operative classification they find a 62.2% of clinical and pathological identity in the determination of the size of tumour. Studying the clinical and histological involvement of the axillary lymph nodes the authors found clinically false negative finding in 33% of the cases. 39% of the lymph nodes judged clinically positive proved to be false. The authors point out the great prognostic significance of the tumoral infiltration of the axillary lymph nodes. The setting up of therapeutic plans can only be based on the pathologic staging.
THE ROLE OF ULTRASONOGRAPHY IN THE EXAMINATION OF BLADDER TUMOUR EXPANSION
F. Hegasi, J. Roshehgagi, Zs. Simon
Department of Urology Postgraduate Medical School
Budapest - Hungary

During the complex testing and post-treatment control of 230 bladder tumour patients, the authors also performed ultrasonic / transabdominal, transrectal and intravesical / tests, altogether in 1,264 cases. In 112 cases, the pathological stage /pT/ of material obtained by operation and section was compared with the "ultrasonic stage" /0/.
The agreement was 61 per cent in transabdominal, 57 per cent in transrectal and 52 per cent in intravesical ultrasonography. The authors are of the opinion that transabdominal and transrectal ultrasonic tests are primarily suitable for exploration, to estimate the size and position of the tumour; and it is also a valuable aid if cystoscopy cannot be performed due to any reason. In intravesical ultrasonography, the expansion ability of the bladder wall containing the tumour can be evaluated also, by changing the bladder volume. Intravesical ultrasonography is a fast and practical method that can be carried out simultaneously with cystoscopy and supraventrically ideally. At present this is the best diagnostic method for showing bladder wall infiltration.

EVALUATION ON THE MOLECULAR LEVEL OF THE PHARMACOLOGICAL EFFECT OF PT-DRUGS WIDELY USED AS CLINICAL CHEMOTHERAPY IN TUMOUR TREATMENT. E.P. Sidork, L.M. Korchevaya, A.P. Burlaka
Institute for Oncology Problems Acad. Sci. of Ukraine, Kiev, USSR

Aiming to draw up the optimal patterns for the treatment of local neoplasma resistant to the other anticancer drugs, biophysical studies on interpretation of molecular mechanism action of platidiam/active origin cis-dichlorodiamminoplatinum and pure cis-dichlorodiamminoplatinum were carried out. The kinetic features of the activity changes and the molecular carriers' content of energetic and detoxicating systems mainly in Fe-2 mitochondria clusters in different organs and tissues when injecting Pt-based drugs were determined. A method of approach to pharmacologic Pt-drugs' effect evaluation on the basis of EMS-spectroscopy in low temperature subject's stabilization condition was applied here.


The variations of serial ions are known during cancer; continuing our researches, we studied the variation of serial copper in breast cancer. The serial copper content was investigated in 200 patients of breast cancer in different evolutive periods, dynamically at the diagnosis, during the complex treatment applied, and at intervals after the treatment, and at periodical controls affected. The control lot were 50 healthy women. The serial copper content was doped by the method with bathocuproin sodium disulfonate. Close by the serial copper content we investigated alkaline phosphates, acid phosphates, OX, GGT, LDH, cholinesterase complexes, Na, K, Ca, Fe, P, cholesterol, total lipides, triglycerides, total proteins, proteinic fractions, nitrogen, glykemia, creatinina, etc. The experimental results showed an increase of the serial copper in patients with breast cancer. The values are in this case 180-220 g/L respectively 28.5-54.62 mol/L. The continuing increase during the complex treatment applied to values more than 550 g/L respectively 55.09 mol/L and the maintenance at these values is an index of negative prognose for the evolution of the disease. The decrease of the value of serial copper after the complex treatment applied and the tendency of it towards normal values as well as the maintenance of its level for a time may constitute an index of positive prognosis, correlated with a long survival.
4995 NIPPLE RETRACTION AND DISCHARGE WITH OR WITHOUT MAJOR DISEASE OF THE BREAST: J. Marik, Zs. Székely, L. Vass Dept. of Surgery and Dept. of Pathology-Cytology, Pázmány Péter University Medical Faculty, Budapest, Hungary

Ca. 1000 breast lesions were examined using clinical and morphological methods. All cases of nipple discharge and nipple retraction were analysed concerning age of the patient and clinical and cytological signs of the breast disease. Evaluating the final histological specimens it seems that a great number of nipple retraction and discharge patients do not have any malignant breast disease. The best pre-surgical diagnosis can be achieved by combined aspiration and ductal effroretive cytology in the above mentioned nipple disorders.

4996 PSYCHO-ENDOCRINE DISORDERS AFTER LARYNGECTOMY Hans-Peter Hellmann and Klaus Baerger, Klinikum der Stadt, DDR

Laryngectomy loads not only to serious organic and functional defects, but in many cases also to enormous psycho-social loss. Under these aspects problems with occupational rehabilitation as well as possible consequences of laryngectomy on the social surroundings and the psyche of the laryngectomised tumour patients are discussed. The study is based on investigations among 275 laryngectomised, who were cared for in the framework of special cases in the period from 1974 to 1984. As to occupational rehabilitation we could find that taking the initial situation into consideration, only in 10 per cent full occupational rehabilitation is possible. Patients with an efficient substitute voice have significantly better chances. The social status is characterized by the contact disorder of the laryngectomised. According to own statements 30 per cent of the patients give up being members of organizations, shun society (theater, cinema, restaurants) and feel psychologically irritated, 28 per cent complain about loneliness respectively isolation. These statements are underpinned by the results of a neurotic screening, according to which a functional neurotic disorder became evident in about 60 per cent of the patients. Concluding from this our therapeutic concept should aim not only at cancer extermination and votes re-education but also at psycho-social guidance and occupational rehabilitation. This complex of tasks can only be carried out as a base of inter-disciplinary cooperation.


We previously reported that the combination of epirubicin (Epi-DX) and DTIC can be used at full dosages of each drug without overlapping in toxicity (Invest New Drugs 1984). Based on this experience and on evidence from studies in both animal and human tumors on a synergistic effect of DTIC and doxorubicin, the parent compound of Epi-DX, we devised to treat metastatic soft tissue sarcomas in adults with Epi-DX, 90 mg/m² i.v. on day 1, and DTIC, 250 mg/m²/day i.v. on days 1-5, with cycles repeated every 3 weeks. From September 1983, 17 patients, 10 males, 7 females, median age 52 years (range, 17-79), median Karnofsky performance status 0-1 (range 50-90), were treated with EDIC combination. Four patients had received prior systemic chemotherapy. Responses (WHO criteria) were observed in 4 (2 CR, 2 PR) out of 14 (57%) evaluable patients (1 too early). The median duration of response was 12 months. Overall, EDIC combination was well tolerated. Transient ST-T changes were recorded only in 3 patients.

These preliminary results suggest that EDIC combination is highly effective in advanced soft tissue sarcomas, and further patients are being studied to provide a better estimate of the true effectiveness of this regimen.

U-41/7

4998 TUMOR HORMONE SECRETION: ECTOPIC OR MERELY INAPPROPRIATE? D.N., Orth, W.E. Nicholson, G.B. DeBold, G.S. DeCherney, and R.V. Jackson, Vanderbilt University School of Medicine, Nashville, Tennessee 37232 U.S.A.

The term "ectopic hormone secretion" presumes that the hormone-secreting tumor arises from a tissue that does not normally produce the hormone. Since the term was coined 25 years ago, it has become clear that peptide hormones are produced by many tissues other than the classical endocrine glands. This raises the question of whether some, most, or all tumors merely secrete hormones that they normally produce in inappropriate amounts and/or in response to inappropriate stimuli. We have measured IR-ACTH and proopiomelanocortin (POMC) mRNA in normal rat tissues. IR-ACTH was found, in decreasing concentrations, in rat adrenal, testis, duodenum, colon, liver, kidney and lung; it was not detected (< 0.05 pg/mg tissue) in stomach, spleen or skeletal muscle. In the testis, IR-ACTH had a mol wt of 26,000 on Sephacryl S-200 chromatography; little > 500 mol wt IR-ACTH was observed. POMC mRNA smaller than in the pituitary was detected by Northern blot hybridization. We previously reported that the combination of epirubicin (Epi-DX) and DTIC can be used at full dosages of each drug without overlapping in toxicity (Invest New Drugs 1984). Based on this experience and on evidence from studies in both animal and human tumors on a synergistic effect of DTIC and doxorubicin, the parent compound of Epi-DX, we devised to treat metastatic soft tissue sarcomas in adults with Epi-DX, 90 mg/m² i.v. on day 1, and DTIC, 250 mg/m²/day i.v. on days 1-5, with cycles repeated every 3 weeks. From September 1983, 17 patients, 10 males, 7 females, median age 52 years (range, 17-79), median Karnofsky performance status 0-1 (range 50-90), were treated with EDIC combination. Four patients had received prior systemic chemotherapy. Responses (WHO criteria) were observed in 4 (2 CR, 2 PR) out of 14 (57%) evaluable patients (1 too early). The median duration of response was 12 months. Overall, EDIC combination was well tolerated. Transient ST-T changes were recorded only in 3 patients.

These preliminary results suggest that EDIC combination is highly effective in advanced soft tissue sarcomas, and further patients are being studied to provide a better estimate of the true effectiveness of this regimen.

U-41/7
OUR EXPERIENCES IN THE TREATMENT OF THE LOCALLY ADVANCED PROSTATIC CARCINOMA WITH THE LH-RH ANALOGUE BUSERELIN

Bormann V., Weiss-Berlin

From June 1981 to December 1985, 22 patients with locally advanced prostatic carcinoma were treated with the potent LH-RH analogue BUSERELIN. 76 of them were treated for periods ranging from 12 to 40 months.

To evaluate the response of the primary tumor to BUSERELIN, cytological regression was established by fine-needle aspiration biopsy every 3 months. The cytological results corresponded with those of DNA analyses through single-cell cytology analysis which showed a statistically significant drop of the grade of aneuploidy or polyploidy when the prostatic carcinoma responds positively to BUSERELIN therapy.

50 of the 76 patients, who were treated for 12 to 40 months, showed good to sufficient regression grades in the cytological follow-up examinations.
14 patients had a poor cytological regression grade. These patients underwent secondary treatment with estramustine phosphate.

Additionally, an other group of 19 patients with locally advanced prostatic carcinoma was treated with a combination of LH-RH analogues (BUSERELIN) and antiandrogen (Androcure). No initial increase of Serum-Testosterone-Levlrin.

Cytotoxicity against human tumour cells by mixed monoclonal antibody-drug conjugates

M.J. Emberton, J. Harte, V.S. Myers, B.C. Gartnell, J. Gallego and S.K. Baldwin

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In an attempt to increase in vitro cytotoxicity against cultured human tumour cells mediated by drug-antibody or antibody-toxin conjugates, tumour cells were exposed to different conjugates in combination. The conjugates tested were: (a) methotrexate linked by human serum albumin to CEA, a monoclonal antibody to CEA/MCA, (b) methotrexate linked by human serum albumin to 791T/36, an antibody raised against 791T/T osteogenic sarcoma (791T/36 and (c) ricin toxin A chain linked directly to 791T/36. Cytotoxicity was tested by a 40 hour 53Cr-seelenium thionine incorporation assay against 791T osteogenic sarcoma cells, HTX osteosarcoma cells, (c) daunorubicin linked directly to 791T/36 and (d) ricin toxin A chain linked directly to 791T/36. Cytotoxicity was tested by a 40 hour 53Cr-seelenium thionine incorporation assay against 791T osteogenic sarcoma cells, HTX osteosarcoma cells, (c) daunorubicin linked directly to 791T/36 and (d) ricin toxin A chain linked directly to 791T/36. Cytotoxicity was tested by a 40 hour 53Cr-seelenium thionine incorporation assay against 791T osteogenic sarcoma cells, HTX osteosarcoma cells, (c) daunorubicin linked directly to 791T/36 and (d) ricin toxin A chain linked directly to 791T/36.
Hepatotoxicity of Conditioning for Bone Marrow Transplantation Using Busulfan and Cyclophosphamide. W. Wiatrak, Jadwiga C. Kaznok, P. Czarnowska, Z. Bemanski, R. Banas, Z. Zdziebowski, Radioimmunoassay of Antithymocyte Globulin and Anti-Human Immunoglobulin in Bone Marrow Transplant Patients. CRT WMH, DO-495 Warsaw, Poland.

Combination of large doses of busulfan (BU) and cyclophosphamide (CY) is a leukemia-curing protocol alternative to total body irradiation. Three of six patients conditioned by our team with BU (6-16 mg/kg) and CY (4 x 50 mg/kg) showed increases in transaminase levels beginning from 2nd day post BU administration (while still receiving CY). In one of these patients: 6 yr old boy in 1st remission of AML, who received 12 mg/kg of BU this increase in transaminase levels was followed by the increase in bilirubin level and the death on day 25 post BMT. On autopsy massive fatty degeneration of liver was found. In the 2nd case: 7 yr old boy with ALL in 2nd remission who also received 12 mg/kg of BU the biochemical signs of liver injury resolved 2 days after BMT and liver biopsy performed 4 days after BMT showed only increased vacuolization of hepatocytes without any portal changes. He died of acute hepatitis of unknown etiology day 70 post BMT. In the 3rd case: 6 yr old girl with Diamond-Blackfan syndrome and hemoglobin who received 8 mg/kg of BU after initial increase up to 790 u. GPT and 700 u. GOT one week after BMT, the transaminase levels lowered and stabilised at 60 u. GOT and 150 u. GPT. At present, 16 months post BMT her liver disease is otherwise asymptomatic. Other patients who received between 8 and 16 mg/kg of BU did not show any clinical signs of liver injury. In the 2nd case: 7 yr old boy with ALL in 2nd remission who also received 12 mg/kg of CY the biochemical signs of liver injury resolved 2 days after CY and liver biopsy performed 4 days after CY showed only increased vacuolization of hepatocytes without any portal changes.

These data suggest that hepatotoxicity is not earlier appreciated side effect of large doses of BU. Although it is significant only in proportion of cases it may be regarded as detoxifying.

Supporting this hypothesis is a study of mice in which BU and CY produce hepatic vacuolization in vivo. The transaminase levels lowered of BU after initial increase up to 790 u. GPT and 700 u. GOT one week after BMT. The transaminase levels lowered and stabilised at 60 u. GOT and 150 u. GPT. At present, 16 months post BMT her liver disease is otherwise asymptomatic. Other patients who received between 8 and 16 mg/kg of BU did not show any clinical signs of liver injury.

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These data suggest that hepatotoxicity is not earlier appreciated side effect of large doses of BU. Although it is significant only in proportion of cases it may be regarded as detoxifying.
Cancer Oesophagus - Treatment Modalities

Dr. M. Y. Kharadi

Upper GI Cancer in general and oesophageal cancer in particular form the major bulk of common cancers seen in our set up. Oesophageal cancer remains to defy therapeutic attempts at cure, or pre-limreatment control despite the advent of sophisticated radiation, increasingly effective chemotherapy and new trends in surgery. The author in this paper presents a data of 1200 cases of cancer oesophagus seen over a period of 5 years. Eighty eight percent of patients were seen in 3rd, 4th and 5th decade. Nearly all men belong to working class and all males were housewives. Middle third of oesophagus was the commonest site of malignancy in both men and women followed by upper and lower third. Squamous cell carcinomas constituted 50 per cent of cancers. Radiation therapy and chemotherapy were the main stay of treatment. Twenty per cent of patients were last to follow up, 10 per cent of patients could not complete treatment and out of the remaining, 10 per cent died within 6 months of treatment. The remaining patients are alive and under constant medical surveillance to the state of their oesophageal lesion.

BENZYLAMINE OXIDASE IN HUMAN TISSUES - A CANCER MARKER?

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Benzylamine oxidase (BzAO), like MAO A and B, is widely distributed in normal tissue of man, especially in blood vessel walls and tissues rich in smooth muscle. We have studied BzAO in human esophagi in various disease states, to find out whether enzyme values are different from those in the normal. Specific activity, K_M and sensitivity towards inhibitors were studied by radio-assay, with 14C-labelled benzylamine as substrate. Tissue obtained at surgery, biopsy and autopsy were split into mucosa and muscle; tumor tissue was used in its entirety. Results: Specific activity of muscle and mucosa progressively increased from the upper to the lower third of the esophagus. It varied widely in pathological muscle and in mucosa and tumor tissue; mean values were similar for tumor and mucosa. K_M values for pathological muscle were significantly different from normal, and both of these from mucosa (normal and pathological). No significant difference in K_M was found between tumor and pathological mucosa, suggesting the epithelial origin of oesophageal cancer. The K_M of pre-operative sera of patients with oesophageal cancer was similar to that of pathological muscle. A highly significant difference was observed between the mean K_M of epidermoid cancer (oesophagus, cervix uteri) and adenocarcinoma (breast). Inhibition of benzylamine oxidation by deprenyl (10^-7M) and phenelzine (10^-7M) was significantly different for normal as compared with pathological muscle and mucosa, and with cancer.

Conclusion: Patterns of specific activity, K_M and inhibitor sensitivity of pathological tissues and sera, compared with the normal, may prove useful both in the differential Diagnosis of cancer and in monitoring treated cancer patients.
Malig. ORPHEVING EFFECT ON BULBIC ASCITES BY TRIPE.-NYLAMINES. M. Mihaila1, M. Goevswumu11, C. Gureanu1
C. Histo21, and Victoriea Histo; 2 Biologica: Ctr. Cluj Napoca1, and ORGOG Inst. Cluj Napoca2 Romania
We examined the effect of brilliant green on the bulbic’s ascites cells in vitro. To 10 cc fresh bulbic ascites liquid we added 10 cc solution 1:5000 of brilliant green. This is mixed 1 hour at room temperature, then injected in 50 g mice of 25-30 g, initial intraperitoneally (for much more for our purpose). The animals did not develop ascites during 2 months, they were watched. From them we took samples of ascites liquid after 1 hour, 2 hours, 24 hours and 48 hours and examined the cells at the electronic microscope. After 1 hour the nuclear heterochromatin decreased and the nuclei intermembraonal space widens. The Golgi complex intensifies the activity, and some of its elements dispose themselves around the centricules. The electronodensity of the citoplasm decreases due to the diminishing of ribosomes and microcondria; the rough network becomes evident; there appear cytozema with microvilli in the interior. After 24 hours some cells become pyknotic, others with few microvilli at the periphery, the nucleus remaining swollen swollen with few heterochromatin. The elements of the Golgi apparatus are swollen, there appear numerous lyosomes and vacuoles of intermembranous lycye, the synthesis of lipids are reduced. The effect of brilliant green is irreversible malig. preinogring without killing the cells; they survive from 2-4 weekes. The modifications after the first hours are the morphological aspect of this tissorial malig. preinogring.

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5015 THE POLYCYCLIC AROMATED HYDROCARBONS (PAH) CONTENTS IN DIFFERENT MEMES
Camelia Nistor, D. Mancaș, L. Rainceanu, Victoria Papadopol,
Hygiene and Public Health Institute, Iași, Romania

By the gas-chromatographic analysis of the memecs sampled from different areas, was put in evidence the polycyclic aromated hydrocarbons presence in quantities depending of the area, relief, local industry but especially of the habit of culinary preparation (conservation, smoking, burning). In the period of 1984-1985 years, by the gas-chromatographic method, a number of 196 samples were analysed. The revision of some food processing procedures, a correct culinary preparation as well as the diminution of the environmental pollution factors, were recommended.

5016 CO2-LASER TREATMENT OF ORAL LEUKOPLAKIA; A STUDY OF 103 CASES, WITH A FOLLOW-UP OF 8 YEARS.

Oral leukoplakia is an intraepithelial premalignant lesion. Removal of affected mucosa up to the level of the basal membrane should be a sufficient treatment. Just such a selective removal can be carried out with the CO2-laser. In the period 1976 - 1984 103 cases of oral leukoplakia were treated with the CO2-laser. After a careful clinical, etiological and histological diagnosis, the leukoplakia was removed by CO2-laser evaporation. Almost all treatments were done under local anaesthesia on an out patient basis. Both the handpiece and the micromanipulator in combination with an operation microscope were used. Only treatments with a follow-up of at least 6 months were used for evaluation (mean 38 months; range 6 - 95 months).

Woundhealing took place in about 4 weeks without clinical perceptible cicatrisation. There was little postoperative pain and edema. In 9 cases (8.7%) recurrences were seen; 5 recurrences occurred in cases of idiopathic leukoplakia and 4 in patients with a heavy tobacco use. Depending on the technique most recurrences (18%) were seen in the group treated with the handpiece. Conclusions:
- CO2-laser evaporation is a safe treatment modality for oral leukoplakia.
- The CO2-laser should be used in combination with an operation microscope and micromanipulator.
- After healing there is no clinical perceptible cicatrisation.


Authors examined the change of the volume and volume regression constant of abdominal lymphoid masses by ultrasonography during the treatment. They elaborated a new method to estimate quantitative parameters in evaluating the structural changes on the ultrasonograms of abdominal lymphoid masses. A pseudo-colour-coding system was used, estimating the percentile rate of different colours in a given part of the sonogram. Each of 8 colours represents different ranges of echo intensity scale. Different indexes were calculated from the distribution of colours. The echo intensity index represents the echo-density of the mass, the enhancement index represents the echo intensity behind the mass. The sound homogeneity index was estimated by pseudo-colour-coding too, with calculating the number of spots of different colours in a given part of sonograms. Authors investigated the change of parameters during the treatment, and their connection with the volume change and clinical picture.

5018 EGF BINDING SITES IN NON SMALL CELL AND SMALL CELL LUNG CANCER CELL LINES
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Epidermal growth factor (EGF) stimulates cell proliferation in many tissues and may play a central role in cancer growth regulation. This effect is mediated by high affinity ligand binding for specific surface receptors. The autocrine growth hypothesis proposes that carcinoma cells produce and secrete their own proliferation factor which interacts with specific membrane receptors. The detection of sequence homologies between the erb-B oncogene product and the internal and membrane part of the EGF receptor suggests a correlation between oncogenic stimulation and growth regulatory mechanisms of cells. We and others have established a large number of continuously growing cell lines derived from small cell and non small cell lung carcinomas. We examined EGF binding sites in established cell lines. Displacement experiments demonstrated competition of labeled EGF (125I-EGF) with unlabeled EGF. Non specific binding was calculated from the differences between samples with and without an excess of unlabeled EGF. The binding parameters (Bmax and Kd) were determined by scatchard plot analysis. The binding constants (Kd) are very similar for both non small cell and small cell lines. There are differences, however, in the amount of maximal bound EGF (Bmax). Bmax ranges from 71 fmol/mg protein to 1000 fmol/mg protein in non small cell lines and 16 fmol/mg protein to 143 fmol/mg protein for the small cell lines. Differences in the EGF binding potential between non small cell lung cancer and small cell lung cancer suggests that EGF may serve as a biologic marker for non small cell lung cancer and may play a central role in non small cell lung cancer growth control.
ADDENDUM


At 209 cases of gastric cancer during 9 years (1977-1985) we noticed the prevailing of the male sex (135 cases, against 74 women); the great incidence between 61-70 years (35 cases) and 51-60 years (50 cases). The suffering before the admission day was 2 months to 1 year (136 cases); 2-5 years (31 cases); 6-10 years (10 cases); and over 10 years (12 cases). The blood group incidence was higher at the A-B (43 cases) and O (76 cases). We noticed also the degenerated gastric polyps in 2 cases and 5-day diagnosed gastric ulcers and degenerated after 10 years of prolonged conservative treatment at 14 patients; 5 cases of malignancy relapses after subtotal stomach resection for ulcer at 6 cases. The clinical symptoms were the advanced signs of neoplastic infiltration (weight loss, nausea, vomiting). Jar of the complications (steatitis, high digestive hemorrhages, metastasis), the treatment consisted of 46 subtotal stomach resections, 13 total resections, 22 gastrectomies gastroduodenal stapling, and 41 unoperated patients. In 36 cases we noticed the high frequency of the advanced stages of the tumor. Surgical treatment, i.e. the radical surgical treatment that improves the prognosis and active discovery of the complicated patients - with a potential risk for the local relapse, is ineffective. We also added in the evaluation, in order the subtotal stomach resection for cancer we resected at the removal of the hyper vascularized and intestinal resection with deviation of the int. Post-operative a treatment on a continuing basis.

5020 "Northern is a useful procedure for Stage II Cervical Carcinoma?"

SARRIA José A. and PERREYRA Héctor D.

A high percent of lymph nodes involved in Stage II of cervical carcinoma, were found associated with a high rate of recurrences and metastasis. Lymphangiography and cytology puncture were recommended to detect metastatic para-aortic and pelvic lymph nodes before surgery.

5021 "Post-Surgical classification for Invasive vulva carcinoma".

SARRIA José A. and PERREYRA Héctor D.

Radical vulvectomy plus lymphadenectomy were performed in 35 cases of invasive vulva carcinoma on stages I - II - III. Post-surgery histological findings agreed in a high rate. Post-surgery classification is recommended for invasive vulva carcinoma.

5022 "Procedure for classification of Ovarian Carcinoma".

SARRIA José A. and Perreyra Héctor D.

A high percent of lymph nodes involved in Stage II of cervical carcinoma, were found associated with a high rate of recurrences and metastasis. Lymphangiography and cytology puncture were recommended to detect metastatic para-aortic and pelvic lymph nodes before surgery. Post-surgical Ovarian Carcinoma classification involving a meat open abdominal semiology together with laparoscopy during surgery and retroperitoneal studies. We performed on 30 patients in this way Procedures are reported to classify patients and applied protocol statements.
**INTRAVESICAL BCG FOR BLADDER CANCER-PARADOXICAL COMPLETE RESPONSE IN BLADDER WITH PROGRESSIVE DISEASE ELSEWHERE IN URINARY TRACT.**

Joseph D. Schmidt, M.D., University of California San Diego San Diego, California, U.S.A.

Twelve patients with transitional cell carcinoma (TCC) of the urinary bladder (stages TIS, TA and TI) were treated with weekly intravesical instillations of Bacillus Calmette-Guerin (BCG). Follow-up cystoscopy and biopsies at three to six months demonstrated eleven patients to be free of disease in the bladder (complete response rate of 91%). However, persistent or progressive disease in the prostate substance, bulbous urethra, distal ureters and renal pelvis has developed in four patients (33%) requiring additional surgery and/or topical chemotherapy. One of the twelve patients (9%) has developed distant metastatic disease. The conclusion is drawn that intravesical BCG is highly effective for superficial bladder cancer but does not prevent the tumor diathesis from continuing in adjacent portions of the urinary tract. Thus patients having a complete response of their TCC must still be monitored closely for recurrent disease elsewhere.

**COMPLEX TREATMENT OF CORPUS CARCINOMA**

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Authors evaluated the data of more than 100 patients with corpus uteri carcinoma, treated in their clinics. To determine the stage and the parameters of the uterus Gray scale echography and arteriography were used. The dose according to the parameters of the uterms was calculated by computer assisted dose planning and the after-loading method. The external radiotherapy was carried out by conventional technics. The treatment was combined with medroxyprogesteron therapy in cases which poorly reacted to the preoperative irradiation or were inoperable. The results show that the combined therapy with medroxyprogesteron has some advantages in the treatment of corpus carcinoma.

**ITALIAN VOLUNTARY HOME ASSISTANCE FOR TERMINAL CANCER PATIENTS**

Authors: L.Valero - M.Crucchi - O. Tancredi

V.I.D.A.S. - MILAN - ITALY

VIDAS, the first Italian home assistance volunteers’Association which helps terminal cancer patients, most poor and lonely, working with medical and paramedical teams, has been founded in Milan in May 1992. Its volunteers are carefully selected, specifically trained, constantly supported and controlled as they work as a member of the inter-disciplinary team to resolve the needs of the patients and their families. 230 volunteers, trained in 6 courses, have assisted 500 patients, with 45,000 hours of home assistance.

Psychological support group meetings are held so as to acquire and promote among staff members a better understanding and involvement of personal feelings and experiences concerning suffering, death and needs in developing a flexible approach on care-giving.

List of informations regarding volunteers training:

- selection: of 100 volunteer applications, 25 are eliminated for personal psychological reason;
- training course: 15% drop out due to personal difficulties;
- volunteer recording, since 19 months an average active VIDAS volunteer times; 45% loss of volunteers: a) 28% last 6 months b) 17% after that period;
- age of volunteers: 28% from 45/55 - 20% from 35/45 - 20% from 55/65 - 17% from 25/35 - 10% from 18/25 - 5% over 65;
- sex: 76% female - 24% male;
- occupation: 42% housewives and pensioners - 42% employees - 16% students.
Tuftsin, a tetrapeptide is a natural compound with anticancer and antiviral activity. In the present experiments, Friend leukemia virus was used. The infection with FLV results in marked immunologic deficiencies. Now, we observed that tuftsin administration can decrease mortality of FLV infected mice. The mechanism of tuftsin-induced protection from FLV disease may relate to several effects such as activation of macrophages and stimulation of enhancement of immunologic and tumoricidal effects of these cells. The other effect of tuftsin concerns the increase in cytotoxicity of different cell populations such as T-lymphocytes, spleen cells and specially NK cells. We have shown, also, that tuftsin stimulates the production of tumor necrosis factor (TNF) which is well known to be responsible for the necrosis of various tumors. The results of our experiments with FLV infected, X-ray irradiated, microwave and tuftsin treated mice will be presented also.

TASCREEN - EARLY StAGE DIAGNOSTICS OF CANCER BY MEANS OF MUCOPROTEIN VECTOR. X. Gitso, P. Urdzjan, Inst. of Glass, Trenčín, M. Češal, Regional Health Centre, Trenčín, and G. H. L. O. On the basis of several years of development and research, a universal cancer diagnostic method designated canscreen one has been presented. The procedure is based on the polarographic analysis of segregated blood serum proteins in mucoprotein components. According to the method, the population is divided into four groups, i.e. the persons with chronic inflammations, those with acute inflammations, individuals suffering from malignant diseases and the persons having good state of health. The evaluation of results is performed on a personal computer of an IBM PC type for which an ample software has been created including the data bank of persons examined. The fundamentally new approach has been employed to evaluate measured quantities. The secret behind the method discussed is in discovering discrete value clusters of biochemical quantities and their projection into a special coordinate system. The results have yielded to practical applications. Now, this method has been shown to potentially elucidate the evolution of Muzitranzone in vivo and thus, it has been supported in vivo investigations. A combination of cytostatic and cytotoxic factors, such as the dose, status, etc., is applied in order to achieve the best results. The comparison of the method is considerably broader, e.g. investigation of post-operational stages, therapy control and control of persons in carcinogenic working sites. Recently, an in-depth investigation of the mucoprotein vector with respect to its side aspects is underway.
5031  SURGICAL TREATMENT OF ADVANCED LARYNGEAL CANCER
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Author considers therapeutic of a 10 years series of patients suffered from advanced laryngeal malignant neoplasms and treated at the Departments of Otorhinolaryngology of the University Medical Schools in Szeged and Budapest. In his opinion, preoperative irradiation decreases the chance for recovery, while relatively good prognosis can be obtained by the extended resection method even with radical neck dissection on patients develop regional lymph node metastasis. Author does think preferable surgical techniques, the regional and myo-cutaneous flaps to reconstruct, if pharyngeal mucosa could not be achieved for primary closure. In the reported series of patients author found increasing number of cases with advanced tumor in respect to higher incident of the uncontrolled nicotine and alcohol abuse.

5032  STAGING OF 262 PATIENTS WITH HODGKIN'S DISEASE
BY LAPAROTOMY AND SPLENECTOMY (LAP): DIAGNOSTIC
VALUE OF OPERATIVE AND NON-INVASIVE MEASURES.

We compared the results of clinical (CS) and pathological staging (PS) in 262 patients who underwent LAP between 07/80 and 02/86 when evaluated for inclusion in a multicenter trial. The diagnostic value of non-invasive variables as well as the impact of LAP on therapeutic strategies has been analysed. In 6 cases (3%), LAP resulted in a change of stage. 26/26 CS I— II, 45/144 CS II— III, and 66 CS III-patients, 7 further cases underwent LAP for therapeutic considerations. Patients with constitutional symptoms or extranodal disease had no higher frequency of occult disease (33% and 32%, respectively). Between patients with CS I—II with or without infradiaphragm disease no significant differences existed with respect to histological subgroups, ESP, alkaline phosphatase, eosinophilia, or lymphocytosis. In 75 cases (29%) results of LAP influenced the therapeutic approach. 31 CS I—II patients received combined modality treatment instead of M alone, 36 or 2 if the CS III. 12 patients received more extensive CS because they rose to PS IV. If in addition to large mediastinal mass, extranodal disease and diffuse spleen involvement, a high ESP or involvement of 3 or more lymphatic areas were considered as risk factors qualifying for abbreviated CT + the LAP could be omitted in 128 of the cases (48%). Only 17 of these could have had stage I undetected by non-invasive diagnostic methods. In contrast, patients with CS — III and no such risk factors should undergo LAP, because in our analysis 30% of the had occult infradiaphragm disease.