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MECHANISMS OF RADIATION INTERACTION WITH DNA: POTENTIAL IMPLICATIONS FOR RADIATION PROTECTION

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Introduction

The following is an overview of presentations and discussions which took place at the U.S. Department of Energy/Commission of European Communities (DOE/CEC) workshop on "Mechanisms of Radiation Interaction with DNA: Potential Implications for Radiation Protection," held at San Diego, California, January 21-22, 1987. The Department has traditionally supported fundamental research on interactions of ionizing radiation with different biological systems and at all levels of biological organization. The aim of this workshop was to review the base of knowledge in the area of mechanisms of radiation action at the DNA level, and to explore ways in which this information can be applied to the development of scientifically sound concepts and procedures for use in the field of radiation protection.

Dr. Charles DeLisi, Director, Office of Health and Environmental Research (OHER) of the Department of Energy, was the initiator of the idea to hold such a workshop. The workshop was organized by Drs. Matesh N. Varma and Benjamin J. Barnhart of OHER. Thanks are due to Drs. Aloke Chatterjee (Lawrence Berkeley Laboratory), Charles Geard (Columbia University), Robert Griffith (Lawrence Livermore National Laboratory), Eric Hall (Columbia University), H. Paretzke (Institut für Strahlenschutz, Munich), Kenneth Wheeler (Bowman Gray School of Medicine), and Robert Yoder (DOE) for their valuable contributions

to this summary. We also acknowledge and thank Dr. John Ward who with his staff hosted the workshop at the University of San Diego School of Medicine.

I. Summary of Presentations

Concepts of RBE and Absorbed Dose: Biological Response to LET and Dose

Improvements in risk estimates of exposures to occupational, environmental and diagnostic low-LET radiation require more human data from exposures to high doses and appropriate models of dose response on which to base extrapolation from high to low doses. Molecular and chromosome studies will improve the understanding of mechanisms and therefore in developing better dose-response relationships for the initial events. Although the initial events are obligatory, the host or constitutional factors determine expression of the initial events and thus the incidence of cancer. The host factors also have to be studied at the tissue and whole-animal level.

In the case of high-LET radiation, risk estimates must depend upon experimental animal data, and perhaps human chromosome studies, because there are no appropriate human cancer data except for lung cancer induction by inhalation of radon daughter radionuclides. There is some discontent with the current RBE concept. One alternative is to determine directly the risk of induction of specific cancers by neutrons, and other high-LET radiations, in experimental animals and to extrapolate the risk across species. Such an approach entails validation and acceptance of the methods of extrapolation. While studies at the molecular level are important, studies at the whole-animal level are essential.

Concepts of RBE and Absorbed Dose:

The RBE Concept, Its Inadequacies and a Suggested Replacement

Appropriate dosimetry is central to the determination of dose-effect responses. While absorbed dose may be an appropriate description for high-level exposures that involve multiple hits in cells it is quite unsuitable in the single hit regime, i.e., for such effects as cancer induction at low exposure levels. Dose is one useful quantity that confounds physics with biology and it is suggested that a better approach to dose and biological effectiveness involves, e.g., the use of the hit-size effectiveness function (HSEF). The HSEF represents the probability of a biological response as a function of the lineal energy density. The use of this function allows responses to be related to the deposition of energy in a more meaningful way than dose. The deficiencies of absorbed dose become particularly apparent in the determinations of relative biological effectiveness (RBE). In its current use, there is the implication that RBE is a measure of both the probability and severity of the effect combined in one variable. But, in fact, severity is not appropriately represented. The use of the HSEF and hit-size distribution can replace RBE. This approach appears to have promise but further research is required to bring its potential to fruition and establish how it can be applied in practical radiation protection and fundamental radiation research.

Energy Deposition at the Molecular and Cellular Levels

Reviews were presented of work aimed at understanding and describing energy deposition from ionizing radiation (charged particles) in molecular and

cellular dimensions. Research in this area has involved development and use of computer codes that predict the spatial distribution of energy from charged particles with a range of LET values. The problems associated with accurate dosimetry of particles having ranges that are short compared with cellular dimensions were discussed, as were the results of calculations that predict the dose responses of individuals, using ICRP concepts. These calculations illustrate the degree of statistical variability associated with the biological response, and thus indicate the need to avoid placing undue emphasis on the exact shape of the dose response curve.

Sample calculations were presented from a Monte Carlo code, developed at ORNL, that simulates the energy deposition patterns from charged particles in water, and the subsequent migration of the reactant chemical species (OH, H, e^-_{aq}, H_3O^+, OH^-, and H_2O_2). These species were tracked from 10^{-11}s to $2.8.10^{-7}$s. Calculations have been performed for electrons, protons and alphas that illustrate energy deposition patterns in relation to DNA molecular dimensions. These predict the number of direct physical and indirect chemical reactions that occur with the DNA as a function of time after primary particle passage. G-value calculations are in good agreement with data from other researchers. An experimental technique was proposed for studying individual charged particle interactions using optical detection of electron interactions by light emission from excited gas molecules.

Models of Radiation Action on DNA

Many models of radiobiological action have been proposed over the past half a century, and at different times have played a significant role in the development of the field. Some models are restricted to a specific in vitro

situation and serve little purpose other than curve fitting. Other models are "global" in the sense that they attempt to describe the behavior of intact cells to lethal damage or to heritable non-lethal effects such as mutagenesis and carcinogenesis. Most earlier models attempted to describe observable biological effects in terms of early physical events and were concerned with the pattern of energy deposition. Later models attempt to introduce repair of radiation damage, and therefore also to take into account the time sequence in which radiation is delivered.

Within a given class of models, the basic philosophy and explanation for the sequence of events may be very different for the various models, but nevertheless they are all sufficiently flexible that they provide an acceptable fit to the data! The basic problem is that experimental data are never sufficiently precise, nor predictions of the various models sufficiently different, for definitive choices to be made between rival hypotheses or models from a comparison of theory and experiment.

There is a distinction between models which fit data and may be useful to extrapolate and interpolate and models which are based on a theory or a hypothesis. A model should do two things. First, adequately fit the data with an acceptable number of meaningful parameters and second, be formulated in such a way that the basic hypothesis or premise can be tested by experiment.

Radical Production in DNA by Radiations

Reviews focused on the role of radical production on DNA damage. These included theoretical concepts involved in DNA strand breaks. Base release

always accompanies OH radical attack resulting in a single strand break. The hydroxyl radicals are most important, and the damage that results from them may be more important than direct ionization of the DNA molecule for low-LET radiation. For high-LET radiation, however, direct ionization of the sugar moieties is most important, and RBE values greater than 1 are due to direct interaction by the charged particle. In systems that are highly scavenged, such as the cell, double strand breaks vary linearly with dose.

Experimental studies primarily focused on production of radical species in DNA. Measurements were made at 77°K using electron spin resonance (ESR) spectroscopy. Measurements at higher temperatures are difficult because other processes compete with electron transfer. Thymine anions and guanine cations were the only radicals detected using ESR, and sugar radicals have not been found. Recent work on plasmids suggests that these ion radicals are likely to lead to double strand breaks which may dominate those produced by hydroxyl radicals.

Molecular Changes in DNA and VI. DNA Repair Processes

Although it has been known for decades that radiation can cause cells to mutate, to transform and to die, the exact mechanisms responsible for these biological phenomena remain largely unknown. The data argue convincingly that the genetic material is usually the critical target. Radiation induced energy deposition events interact with the DNA and its associated proteins to initiate a chain of further processes that results in the cell being either indistinguishable from its unirradiated state or mutated, transformed or killed. Evidence is rapidly accruing that most, if not all, the biological

consequences of these energy deposition events are potentially modifiable by repair processes; e.g., the presence of repair genes or changes in temperature during repair can alter the slope of dose-response curves that have no shoulder.

Time for repair appears to be an important consideration in estimating risk. Complete recovery or repair may require days or weeks rather than minutes or hours. The data suggest that when cell lethality is used as the endpoint, complete repair or recovery is possible even at moderately high total doses if the dose rate is low enough or the time interval between doses is adequate. Furthermore, the number of transformed foci induced in some cell systems seems to be dose rate dependent for both low- and high-LET radiation. Repair rate may also be important for mutation induction. Delaying repair for a few hours can increase both cell killing and the mutation frequency in repair proficient or repair deficient mammalian cells.

The spectrum and distribution of lesions may also be important for assessing the risks from exposure to radiation of different qualities. The spectrum of lesions induced in DNA can vary with radiation energy and type, size of the energy deposition event, base sequence, conformation of the DNA and redox state of the cells. The distribution of strand breaks and base lesions on opposite strands of the DNA can create situations where no template exists to insure that the correct base sequence is restored during repair. The probability of inducing these local multiple damage sites increases with increasing size of the energy deposition events. Repair of these sites must involve recombination mechanisms, if such mechanisms exist in mammalian cells.

To determine the relative role of each of these mechanisms in the production of the biological consequences of exposure to low and moderate

doses of radiation requires the development of sensitive assays for detecting chemically distinct DNA lesions. Monoclonal and polyclonal antibodies, high performance liquid chromatography (HPLC) and gas chromatography combined with mass spectrometry (GC/MS) techniques are being developed for the detection of specific DNA lesions. HPLC with fluorescence detection of adenosine damage products and GC/MS are able to detect quantitatively nucleoside damage at doses below 10 Gy in mammalian cells; this is approaching the dose range required to provide information relevant to many risk assessment questions.

Chromosomal Aberrations

In considering the biological consequences of ionizing radiations it is a logical progression to move from the physics of energy deposition, to the induction and early dispersion of radiolytic products, to the formation of radicals in or around DNA, to molecular changes in DNA, their repair and/or misrepair and ultimately to chromosomal changes. Chromosomal alterations are responsible for a significant proportion of cellular lethality and of genetic mutations, as well as being specifically associated with certain human cancers. Given that chromosomal alterations are the harbingers of later change, information pertinent to the nature of the responsible lesions, the spectrum of aberration types as a function of LET, and their relevance as a source of comparatively readily obtained data for the regulation of human radiation exposures are matters of considerable importance.

Among the extensive array of lesions induced in cellular DNA by ionizing radiations, [single strand breaks (SSB's), double strand breaks (DSB's), base damage, mismatches, DNA-DNA cross links and DNA-protein cross-links] double strand breaks seem to be of most importance in the production of chromosomal

aberrations. A number of approaches using selective inhibitors of DNA repair/replication and enzymes to modify radiation-induced damage in viable cells were considered. The use of Neurospora endonuclease that recognizes SSB's in DNA and converts them into DSB's; of restriction endonucleases as inducers of specific lesions, either blunt or cohesive ended DSB's; and of DNA repair inhibitors along with an evaluation of chromosomal types and frequencies all indicate the importance of the DSB in aberration formation. However, analyzing chromosomal aberrations at mitosis is still far removed in time from the initial energy deposition events. This has been elegantly circumvented by examing chromosomal changes in interphase using the premature chromosome condensation (PCC) technique, which also allows elucidation of the role and timing of repair processes in the formation of chromosomal aberrations. The results of such studies have reinforced the importance of the DSB in aberration formation.

Developing further from this understanding is the realisation that aberrations form largely from the interaction of pairs of entities (breaks/lesions/DSB's) and hence interaction distance can control aberration formation. This is at present puzzling in that (for low-LET radiations) interaction distances for lesion interaction appear to be of the order of a few to a few tens of nanometers in the initial (linear) part of the dose-response curve and micrometers in the latter (quadratic) part of the dose-response curve. Overall, for ionizing radiations an important determinant of aberration frequency is the linear energy transfer (LET) of the radiation. When studying radiations of well characterized LET, knowledge of the morphometry of the irradiated cell leads to a direct estimate of aberrations per particle. One energy deposition event per nucleus is the ultimate low dose and such an approach bypasses traditional concepts of absorbed dose and

relative biological effectiveness. Furthermore, while there are variations in sensitivity to aberration induction through the cell cycle which must be accounted for, as LET per particle increases linearly, aberration frequency increases quadratically. For example, if one particle per nucleus at 100 keV/μm induces about 1 aberration in every 10 cells, then one particle per nucleus at 1 keV/μm induces 1 aberration in every 10^5 cells (based on in vitro studies).

The regulation of radiation exposures on the basis of frequency of chromosome breaks or measurable alterations in DNA is appealingly simple but it can only be considered in relation to an established baseline. The variability in the frequency of genetic diseases, the susceptibility to specific cancers and heterogeneity of the human species emphasizes the importance of differences. Ongoing surveys examining individual cellular sensitivities to a variety of agents (including radiation) and establishing correlations will provide a benchmark, but it is not improbable that establishing causality between dose and effect at low doses will be masked by inherent variabilities. Establishing individual sensitivities raises the possibility (or specter) of genetic screening of individuals for particular occupational roles. Alternatively (or concomitantly) understanding the biochemical basis of sensitivity and hence mechanisms allows consideration of reducing risk by designed intervention.

Establishment of benchmarks is particularly pertinent for germinal mutations in man. Though the number of well characterized genetic diseases in man is increasing rapidly and frequencies of many can be readily established from studies of newborns and/or older cohorts the rarity of new events renders difficult ascertainment of probable cause. Protein electrophoretic patterns,

hemoglobin variants and enzyme deficiencies ponderously establish some estimates of genetic change while the frequency of sentinel phenotypes and of the pre- and post-natal mortalities allow other estimates. Clearly chromosomal abnormalities are associated with spontaneous abortion and gross chromosomal changes overwhelm single gene mutations in early mortality, however, estimating genetic change per se in survivors is undergoing a transformation. Newer techniques, such as 2D electrophoresis and direct examination of DNA sequences by restriction endonuclease digestion, by DNA-DNA hybridisation, and by DNA-RNA hybridisation, can establish unique heritable changes in offspring that are not present in parents. It should however be noted that these approaches allow addition to the data base on overall genetic change while not necessarily contributing to the data base on genetic load.

The extensive recent studies of chromosome aberrations, particularly with human lymphocytes, add weight to the contention that double strand breaks are probably, either directly or indirectly, the most important lesions that lead to aberration formation. The evidence, while still circumstantial, is very convincing.

One of the most exciting areas to evolve in recent years has been the observation of an association between certain cancers and specific chromosome changes. This has two most important implications. First, it is one of the most encouraging pieces of evidence that it may one day be possible to put a "signature" to a specific malignancy - i.e., to know with some certainty whether radiation, chemical or virus was the causative agent. Second, it provides observable and convincing support for the mechanisms of cancer induction at the molecular level.

An important area is the use of chromosome observations as a biological

dosimeter. It is important to develop techniques to improve sensitivity at low doses (less than 10 rads).

Genotoxic Survey

A presentation was made on the potential of screening in human populations for variations in responses to certain genetic assays (i.e., a genotoxic survey). The assays include those for unscheduled DNA synthesis, ionizing radiation sensitivity, susceptibility to cross linking agents, (mitomycin C) and susceptibility to alkylating agents (MNNG, etc.). Some preliminary studies had already been undertaken in a volunteer population but no very significant differences have been observed.

In another human population of special clinical interest, measurements of radiosensitivity indicated lower values of Do (the reciprocal of the slope of the exponential survival curve for cloned cells) than for normal people in AT homozygotes. A small number of AT heterozygotes had intermediate values.

These studies are very preliminary and the potential of genotoxic screening has yet to be explored.

II. Summary of Panel Discussion

A number of selected speakers set the scene for discussions of subjects ranging from the pragmatic approach to the setting of radiation protection standards and their application, to the salient radiation-induced molecular, chromosomal and cellular changes involved in genetic effects and cancer. Ionizing radiation is ubiquitous, in the form of natural background radiations but, in addition, an appreciable number of persons are exposed occupationally. However, the average occupational dose is low and in fact is comparable, but additional, to that received by the general population from natural sources. Two major sources of population exposure, radon from natural sources and x rays and radionuclides in medical procedures, vary considerably in their contribution to individual population doses. Because all of these doses, including occupational, are low, it is the effects, if any, of low doses that are of special interest in radiation protection. At these low doses the biological effects of concern are cancer and genetic effects.

The increasing amount of data from the study of atomic bomb survivors and from some other sources will allow better risk estimates of cancer induction from low-LET radiation as time goes on. However, the improvement in risk estimates will largely be for doses greater than about 50 rem. Therefore, the estimates of risk from low-LET radiation at low doses will still depend on the dose-response models used for extrapolation. Currently, linear-quadratic responses are considered appropriate for all solid cancers except breast and thyroid, for which linear responses are favored. Although the simplicity of these dose-response models has practical advantages, such a complex process as cancer induction by radiation, involving a number of time- and dose-dependent factors requires considerable sophistication. Indeed, experimental

observations of animal tumors show a wide variety of responses. Since occupational exposures are at low-dose rates or in small fractions it is essential to understand the effects of dose rate and fractionation at low doses. Some experimental observations of the effects of protraction and fractionation, with high-LET radiation, appear to be at odds with biophysical and biological models developed from low-LET experience because the effect with protraction is greater than with single doses. A better understanding of the variety of phenomona observed is required and particularly, little is known about the role of repair in the induction of cancer following irradiation.

In the case of high-LET radiation, risk estimates will, for some time, still depend on the use of RBE values determined on experimental systems and more and more information is needed on the more relevant of these systems. Alternatives, however, must also be sought. Some of the discussants were quite optimistic about the possibilities of extrapolating risk estimates instead of RBE values across species. Possible methods of extrapolation across species can be tested using the accumulating data from human and experimental animal studies.

A driving force in the radiation protection field is the As Low As Reasonably Achievable (ALARA) principle. Improvements in technology and the comparatively minor economic impact of reducing exposures have made it possible to decrease occupational exposure levels, especially in the nuclear industry. These reductions instigated by the industry have preceeded the decreases in maximum permissible doses considered by the regulatory bodies.

In health physics, improvements in dosimetry must be practical and cost effective. The advantages of measurement of Y spectra instead of dose are

limited, but important in the case of mixed fields that occur in certain activities in the nuclear industry. Such measurements can be carried out by small portable proportional counters that have been developed in Europe and the U.S. For radiation field measurements, a size of a 7 m sphere was considered practical and suitable on the criterion that it would represent a "dose" at a size comparable to a cell. It was emphasized that for most of the experimental work in radiation biology, information and measurements are needed on energy deposition at the much smaller sizes appropriate to the question being asked, perhaps, of the order of nanometers. It was stressed that there was a need for continual intercommunication between those in health physics and in basic sciences.

In considering a different approach to radiation protection of workers the question was raised whether molecular techniques could be applied to the identification of radiosensitive subpopulations. If such sensitive populations could be identified, would screening exposed worker populations be worthwhile? We know little about the distribution of sensitivity to radiation-induced chromosome aberrations and the implications, or whether or not heterozygosity for certain traits carries any increased susceptibility to radiation. It was pointed out that other screening programs had not met with success. Based on current knowledge, selection of nonsmokers and support of programs to help workers stop smoking should be a better choice of action.

The formal presentations at this workshop had concentrated largely on techniques and phenomena and some felt that theories and models of carcinogenesis had been given too little attention. It is a tall order to develop a theory or a model for the entire trail of relevant changes that link the initial events caused by deposition of energy (with important times

limited to fractions of a second) to those that end with some increased probability, perhaps decades later, of an overt cancer. This is nevertheless, our overall aim, but because it is so complex we often deal with parts of the problem. These parts need integration eventually into a comprehensive whole.

Two important observations must be taken into account in theories of radiation-induced cancer. First, in the case of some human and experimental tumors there are marked age-dependent changes in susceptibility. For example, in humans the risk of radiation-induced breast cancer decreases from relatively high after exposure at a young age to no observable excess risk with exposures at about 45 years or older. This suggests that if carcinogenesis is a multistage process, the later stages must be relatively radioresistant. Second, the radiation-induced excess of some cancers only starts to appear at an age when the incidence of the same type of tumor starts to increase in the unexposed population.

Although the information on the effects of radiation on DNA is considerable much remains to be done regarding the interpretation of such data. How does the spectrum of energy transfer and absorption events relate to the spectrum of molecular and cellular damage, and in turn, to the subsequent biological effects? Is the induction of malignant transformation more likely at one stage of the cell cycle than at others? We still know little about the probabilities of the occurrence of each of the sequential changes that bring about the end effect. For example, it is clear that there are many more initiated cells than cancers, and yet we know nothing, directly, about the repair of the molecular lesions in the initial events that lead to cancer induced by radiation, with perhaps the exception of those induced by ultraviolet radiation. The long latent period between exposure and the

appearance of overt solid cancers offers, in principle, a very good opportunity for intervention. Perhaps the greatest contribution molecular studies could make to radiation protection is the development of methods of detection and intervention whereby the growth and progression of initiated cells could be detected and stopped. To do so will require detailed knowledge of not only the molecular processes involved, but, also, cell-cell interaction and tissue and systemic control of growth and differentiation. The catchy phrase, "molecular epidemiology", is not yet reflected in the development of techniques of identifying either the subpopulation at risk or the tell-tale radiation-induced changes in cells that may lead to cancer. The quest for markers of potential cancer cells, if successful, could provide the criterion for intervention. Another aspect of the changes associated with cancer induction was whether the type of carcinogenic agent that caused a specific cancer could be identified by what was called the "signature of malignancy". This implies that some of the changes may be agent-dependent. For example, can a profile be prepared for a specific cancer from the information about specific chromosome aberrations, the type of oncogenes activated and from other changes in the genome and the cell membrane, and can these be shown to be characteristic of a specific causative agent? The possibility was raised that deletions involving repressor genes or anti-oncogenes might be a characteristic of some radiation-induced cancers because of the propensity of radiation to cause deletions.

It is obvious that there is a need for in vitro cell systems for investigating questions that cannot be answered at the whole-animal level. Indeed, such systems, because of the opportunity they present to observe single cell changes, offer some unique possibilities. While rodent cell systems have provided a considerable body of data about radiation-induced

malignant transformation, it is the responses of human cells, particularly epithelial cells, that are needed. Unfortunately, the morphological changes associated with the malignant phenotype that are the basis of rodent cell transformation assays are not apparent in human cells. Different and appropriate assays appear to be required for human cells.

Workers that are exposed occupationally to radiation are also exposed to many other agents that may interact with radiation. These interactions are complex and may be additive, superadditive and even subadditive. Some agents will interact with radiation at the initiation stage. For example, agents that alter levels of radiation-induced free radicals may alter initiation. Whereas, many agents, including hormones, influence expression. In vitro cell systems are well suited for the study of many of these interactions at the cell level. A number of different in vitro, in vivo-in vitro and whole-animal model systems are now available that complement each other in the study of interactions of agents.

Studies at various levels, from human epidemiological surveys to the identification of radiation-induced changes in the gene all have a role in unravelling the puzzle of the mechanisms of carcinogenesis. Experimentally, it is important that the system selected is suitable for the questions that are posed. Although the goal of understanding mechanisms is as worthy as can be, for quite some time yet, risk estimates of radiation-induced cancer will have to come from direct studies of those risks. Molecular studies have made impressive advances, some of which have been described at this workshop, but they have not as yet made a contribution to risk estimates. They may do so in the future.

III. Participants

The participants in the workshop included the following:

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