Lucile MAHIEU

Health Effects

Scientific staff
Sarah BAATOUT
Louis DE SAINT-GEORGES
Hilde ENGELS
Luc HOLMSTOCK
Paul JACQUET
Lucile MAHIEU
Hubert REYNERS
Eric VAN MIEGHEM
Elva GIANFELICI DE REYNERS (guest scientist)
Jiekun YAN (guest scientist)
Jean VANKERKOM (VITO, part time)

Supporting staff
Arlette MICHAUX
Jasmine BUSET
Werner SCHOONJANS
Christophe VERDONCK
Ingrid VAN REGENMORTEL

RADIATION EPIDEMIOLOGY and radiation biology are two key areas that must interact to allow an understanding of the effects of low doses of radiation.

A retrospective epidemiological study (1953-1994), in progress at SCK•CEN, includes five Belgian nuclear facilities: SCK•CEN, Belgonucléaire, Belgoprocess, and the power plants of Doel and Tihange. This work will be part of an international multicentre programme, coordinated by the International Agency for Research on Cancer (IARC/WHO, Dr E. Cardis) in Lyon and combining data on radiation workers from 14 countries. Such a large-scale study aims at estimating the cancer risk of prolonged exposure to low doses of ionizing radiation.

By its multidisciplinary approach, radiobiology provides the indispensable scientific background for radiation protection, radiotherapy, and nuclear medicine, and thereby contributes, in a crucial manner, to public health. With regard to radiation protection, radiobiological research aims at improving the evaluation of the potential risks of low doses delivered at low dose rates by exploring the mechanisms of action of ionizing radiation at the molecular and cellular levels and the consequences on the organism. Several crucial problems remain to be solved, in particular those related to radiation-induced developmental defects and genetic damage in the child in utero and soon after birth. Our research programmes focus primarily on the radiosensitivity of the developing mammalian organism and are supported by the Nuclear Fission Safety programme of the EC and by the Belgian Federal Services for Scientific Policy.

Our activities, carried out in close collaboration with the Belgian and European scientific community, are essential for maintaining at SCK•CEN the scientific know-how needed to provide national and European authorities with advice concerning potential hazards from exposure to ionizing radiation in normal and accidental situations.

Objectives For epidemiology, we intend

- to study cancer mortality and morbidity in nuclear workers in Belgium;
- to document the feasibility of retrospective cohort studies in Belgium;
- to participate in the IARC study.

For radiobiology, we intend

- to elucidate the mechanisms of the effects of ionizing radiation on the mammalian embryo during the early phases of its development;
- to assess the genetic risks of maternal exposure to ionizing radiation;
- to elucidate the mechanisms by which damage to the brain and mental retardation are caused in man after prenatal irradiation.

In addition, the Health Effects study group has

- to keep abreast of new advances that are potentially relevant for SCK•CEN with regard to the medical applications of ionizing radiation and radionuclides;
- to advise authorities and to provide the general population with adequate information concerning the health risks arising from radiation exposure.

Cancer risk among nuclear workers in Belgium In 1997, we further completed the data collection and control in the five participating facilities. We also strived to obtain, for scientific purposes, a direct access to the National Population Registry, in order to allow future follow-up (cancer mortality) of the study cohort: we started the procedure and had the Ministry of Science approve the scientific importance of the study.

Moreover, the participation of the Belgian nuclear workers study in a concerted action "Studies of Cancer Risk among Radiation Workers in the Nuclear Industry," in collaboration with the IARC and four European countries (Belgium, France, Germany, and the United Kingdom), was approved by the EC Nuclear Fission and Safety programme.

In 1998, we will analyse the data of the nuclear workers study and write the final report, in collaboration with UCL (Prof. A. Wambersie). We will also update the cancer mortality study on

populations living in the Mol-Dessel region and initiate the follow-up (cancer mortality) study of the nuclear workers cohort.

Mechanisms of the effects of ionizing radiation on the mammalian embryo Exposure to ionizing radiation can induce a delay in the cell cycle, either before DNA synthesis (G1 arrest) or after DNA synthesis (G2 arrest). The G2 arrest delays cells from entering division, thereby, presumably, allowing time to repair DNA damage. Recently, the molecular mechanisms of cell-cycle control in eucaryotic organisms have been partially elucidated, shedding new insights into the mechanisms of radiation-induced G2 arrest. Research in this area at SCK•CEN is integrated into a co-operative EC programme with five European institutes. Our laboratory contributes to this project by studying, in mouse preimplantation embryos, various factors involved in the cell-cycle control. In 1997, we pursued investigations on Maturation Promoting Factor (MPF), a protein complex whose activity determines the passage from the G2 stage to mitosis. In the context of the other studies carried out in the EC contract, an understanding of radiation effects on this factor in the early embryo promises new insights, not only on how radiation damage could be transmitted to later embryonic, foetal, and postnatal stages of development but, more generally, on how radiation-induced changes in the feedback control of the cell cycle affect the evolution from the initial DNA damage to permanent cellular modifications.

One-cell embryos of the BALB/c strain exhibit a peculiar sensitivity towards the radiation-induced G2 arrest. Thus, in contrast to most other cells, the proportion of blocked embryos, and not the duration of the block, increases with the dose of radiation. Even after a dose as high as 2.5 Gy, some embryos are still able to escape completely the drastic G2 arrest and to divide in time. In 1997, studies on the radiation-induced G2 arrest and its mechanisms were extended to one-cell embryos of the Heiligenberger strain, in collaboration with our EC contract partners from Essen. Heiligenberger embryos reacted to irradiation in a more "classical" way than BALB/c embryos, in that nearly all irradiated embryos suffered a G2 arrest whose duration was proportional to the dose delivered. After a dose of 2.5 Gy, the effects of radiation were even more pronounced than those obtained in BALB/c embryos, in that almost no recovery occurred in irradiated embryos. At a dose of 1 Gy, however, the G2 arrest was much less, and all embryos were able to undergo a mitosis after a corresponding delay.

The modifications of MPF activity during G2 arrest were studied in embryos of the Heiligenberger strain, using the "histone H1 kinase assay" developed last year for BALB/c oocytes and embryos. In this test, MPF activity is evaluated on the basis of its capacity to phosphorylate the histone H1 protein. Histone H1 kinase activity of irradiated Heiligenberger embryos remained at a very low level during G2 arrest, while this level was slightly, though not significantly lower than that of the controls during delayed mitosis. Results obtained last year with BALB/c embryos suggested that a relationship could exist between the levels of histone H1 kinase activity in mitosis and the health status of the embryo: levels of activity lower than normal would be indicative of some remaining damage incompatible with the embryonic survival; the lower the level of activity, the quicker the embryos would die after division. The exact link between these two parameters remains to be defined for the Heiligenberger strain.

Preliminary results have also been obtained on the levels of histone H1 kinase activity in BALB/c embryos irradiated at the two-cell stage. These studies will be completed in 1998, and similar investigations will be performed in Heiligenberger embryos. In addition, we intend to extend the comparison of histone H1 kinase activities to one-cell and two-cell embryos from a third strain, chosen on the basis of a very low sensitivity to the radiation-induced G2 arrest.

The activity of the cdc2 subunit of MPF changes throughout the cell cycle and these changes of activity are accompanied by modifications in the state of phosphorylation of the subunit. Immunoblotting is the method of choice to study such changes in early embryos. It is currently being used to study the state of phosphorylation of the protein present in lysates of control oocytes and embryos. The next step, planned for 1998, will be to investigate the

changes in the state of phosphorylation of cdc2 in function of the state of G2 arrest in the first embryonic cell cycle from sensitive (BALB/c and Heiligenberger) and nonsensitive (CF1 or C57 black) strains. This work will be done in collaboration with our EC contract partners of Munich and Essen.

The G2 arrest is considered as an active response of the cell to irradiation, allowing time to repair DNA damage before division. In 1998, DNA repair will be studied in irradiated one-cell embryos undergoing a G2 arrest, using the "comet assay" (which measures DNA repair at the biochemical level) and the techniques of "Premature Chromosome Condensation" (PCC, which measure DNA repair at the chromosome level). These studies will be performed in collaboration with our contract partners at Essen and Athens, respectively.

Genetic risks of maternal exposure to ionizing radiation Developmental abnormalities such as malformations or dwarfism could arise as a result of various types of chromosome aberrations induced by radiation in female germ cells and then transmitted to the embryo. The genetic radiosensitivity of the different stages of female germ cells and the role of chromosome aberrations in the aetiology of developmental anomalies remain, however, poorly defined due to the lack of a suitable animal model. We could demonstrate in our laboratory that the structure and sensitivity of guinea-pig female germ cells correspond much better to those of the human female than those of the mouse used previously. Our studies on radiation-induced translocations in parental oocytes and in the guinea pig embryo aim at providing a better estimate of the genetic risks in irradiated women.

Our investigations on the sensitivity of the guinea-pig oocyte to the induction of transmissible chromosome aberrations by radiation were pursued. Oocytes are X-irradiated by 1, 2, or 4 Gy at different stages of follicular growth (0, 1, 2, 3, 4, 8, or 15 weeks before ovulation). Two days before ovulation, they are collected, cultured in vitro to the MI stage (the metaphase of the first meiotic division), fixed, and analysed for translocations and other chromosome aberrations. For each individual group, at least 100 oocytes are analysed. The results obtained in 1997 suggest that the sensitivity of the guinea-pig oocyte to the induction of translocations and other chromosome aberrations diminishes as the time interval separating them from ovulation increases, i.e., when less and less mature oocytes are irradiated. This is particularly evident when one considers the results obtained with the highest dose of X-rays (one week before ovulation: 20% of oocytes with translocation(s); two weeks before: 12%; three weeks: 8%). However, this has still to be confirmed for the following time intervals (4, 8, and 15 weeks before ovulation), for which only partial results are available at present. Oocytes irradiated two days before ovulation showed the highest sensitivity, with about 35% of cells with one or more translocations after a dose of 1 Gy. In experiments undertaken in 1996 and completed this year, we found that all youngs originating from guinea-pig females irradiated with 1 Gy two days before ovulation were morphologically normal and did not show any translocations in their germ cells. This suggests that either all oocytes carrying chromosome aberrations are eliminated before fertilization, or that the embryos resulting from the fertilization of such oocytes are selectively eliminated before birth.

Data on the induction of chromosome aberrations in the guinea-pig oocyte at different stages of growth and maturation will be completed in 1998, so that a precise dose-effect relationship is obtained for the various stages tested, from the immature stage up to the preovulatory one. Our results, together with those obtained in the progeny of irradiated females, will provide a better basis for the estimation of the genetic risks in irradiated women.

Effects of ionizing radiation on the central nervous system Low doses of ionizing radiation can induce mental retardation in children, particularly when radiations have been delivered between weeks 8 and 15 of prenatal life. To elucidate the mechanisms and the risks of this effect, the EC is supporting the efforts of SCK•CEN to co-ordinate the works of eight other European radiobiological laboratories also involved in this area, dealing in par-

ticular with the extent of damages and repair in the brain DNA, the mapping of radiosensitive cerebral areas, the up- and down-regulation of a series of genes or gene products, and the beneficial effects of the addition of growth factors in vitro. It has been shown that brain produces during its development a considerable amount of superfluous or redundant nerve cells which die naturally (by apoptosis) and are eliminated; the reasons for such a waste of cellular material are still unclear, but the newly produced brain cells apparently compete for establishing cellular contacts or connections between each other and only those dividing more rapidly survive this struggle. The outcome is controlled by a series of growth factors. In the future, the understanding of the signalling pathways involving these growth factors and their receptors should pave the way to a possible compensation for the cell losses caused by a prenatal irradiation. Testing this hypothesis in the rodent brain could also help reach a better understanding of the laws that rule the complex development of the human brain.

Recent advances were registered along four lines of investigation; they confirm the great variability in radiosensitivity of the developing brain according to the morphological area studied, the time at observation, and the endpoint investigated. First, we noted that the atrophy of the cingulum (the most radiosensitive area of the rat brain) induced by a prenatal irradiation increased markedly after birth, between the ages of one and three months, after dose levels as low as 200 mGy. The mechanism for this late consequence of the irradiation remains unknown but, as we found out, the origin of this atrophy is to be searched for outside the cingulum, most probably in the cerebral cortex. Second, in the hippocampus of the adult rat, the density of the synapses (labelled by synaptophysin) was found to have decreased after a prenatal irradiation at day 17 of the pregnancy (E17) but, here, the dose required is very high: 800 mGy of X-rays. Third, the strong expression of a cell proliferation marker, the PCNA antigen, was down-regulated to zero four hours after an E15 or E17 prenatal irradiation, except in the dying apoptotic cells. Such apoptosis was often detected even after doses as low as 100 mGy of X-rays. PCNA labelling reappeared 24 hours after the irradiation but, at that time, all apoptotic cells had already disappeared. Finally, the p53 antigen (a marker of the integrity of the DNA) was found to be up-regulated in many apoptotic bodies four hours after irradiation but, here too, the dose required was high: 400 mGy of X-rays.

One of two future objectives aims at linking function with structure target. The quantitative evaluation of the density of the electrochemical connections between nerve cells (the synapses) has now been developed for the hippocampus of the rat; the present method is based on a quantitative automatic image analysis of a specific deposit of gold microparticles on the synapses. However, the exact time of maximum radiosensitivity for this parameter is still unknown. Such an information is required for correlating synaptic losses with the memory failures observed in the functional and behavioural tests carried out at the NRPB.

The other objective regards the control of natural and radiation-induced cell death (apoptosis). This two-step study will involve a mapping of the regions where apoptotic cells are seen during normal brain development, and an assessment of the time schedule for such events. This knowledge is requested for the future projects which will aim at stopping or reducing cell death in the irradiated brain in order to compensate for cell losses due to radiation death: a regenerative attempt based on the specific brain capabilities for neuron overproduction and the natural elimination of redundant cells during the prenatal development.

Medical applications of ionizing radiation and radionuclides Contacts of a general nature with specialists in nuclear medicine and radiotherapy may be useful to advise the management on new developments and potential opportunities for SCK•CEN. On the other hand, uncertainties remain about the radiobiological foundation and consequences of techniques using X- or γ-rays and radionuclides for medical diagnosis and treatment. A study related to the mechanisms of radiation-induced fibrosis was initiated in 1995, as part of the long-standing scientific collaboration with the radiotherapy department of ULg. Our study aims at establishing whether determination of circulat-

ing Transforming Growth Factor γ (TGF-γ) levels before, during, and after treatment of patients for lung cancer may be helpful to predict patients at risk for the development of pneumonitis and late normal-tissue injury.

The effectiveness of human cancer treatment is usually limited by the tolerance of normal tissues to high doses of radio- or chemotherapy. TGF-γ is a key cytokine involved in the cascade of events that leads to radiation-induced fibrosis. Recent studies suggest that fibrogenesis is mediated by the local production of TGF-γ in normal tissue, but is also increased by TGF-γ produced by the tumor and released in the circulation: TGF-γ has been shown to function in an autocrine and a paracrine manner, but it may also have endocrine effects. The results of a pilot study clearly indicated that the evolution of serum TGF-γ paralleled the platelet counts, due to the large amount of TGF-γ in the γ-granules of platelets.

In 1997, methods for drawing blood and preparing plasma were specially designed to minimize platelet degranulation, using different anticoagulants; the γ-ThromboGlobulin (γ-TG), a sensitive γ-granule marker, was measured in parallel in each plasma sample by a quantitative Enzyme-Linked ImmunoSorbent Assay (ELISA) technique. Plasma was collected by different operators in a large series (over 50) of voluntary blood donors; the values of TGF-γ, using EthyleneDiamineTetraAcetate (EDTA) as anticoagulant, were highly dependent on the dexterity of the technician; much better results were obtained by using a complex Platelet Inhibitor Mixture (PIM). Moreover, the γ-TG levels were about 10 times higher in the EDTA than in the PIM plasma, confirming a significant contamination by degranulated platelets in the former samples.

In 1998, the methodology will be applied to primary lung-cancer patients, before and during treatment, but also to patients suffering from miscellaneous pulmonary diseases, in order to assess whether the plasma TGF-γ level may be considered as a prognostic indicator or as a marker of therapeutic efficacy or side effects. Experiments using rats, irradiated at the Radiotherapy Unit of ULg, will be carried out in parallel. The contribution of our laboratory to this part of the programme will be limited to the determination of TGF-γ in the blood plasma of irradiated animals.

Partners, sponsors, and customers

Scientific partners Institut für Strahlenhygiene, Bundesamt für Strahlenschutz — National Centre for Scientific Research Democritos — Universitätsklinikum Essen — Paul Scherrer Institute (PSI) — University of Aachen — University of Athens — University of Barcelona — University of Freiburg — University of Krakow — University of Uppsala — Commissariat à l'énergie atomique (CEA) — International Agency for Research on Cancer (IARC) — National Radiological Protection Board (NRPB) — Institut national de la santé et de la recherche médicale (INSERM) — Deutsches Krebsforschungszentrum (DKFZ) — Université catholique de Louvain (UCL) — Université de Liège (ULg)

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