# Biological effects of low-level radiation

by Tamiko Iwasaki*

The application of nuclear energy in industry, medicine, and agriculture is increasing remarkably. Currently, nearly 10% of total world electricity generation comes from nuclear energy, and further growth in nuclear power generation is expected in coming decades. This expansion in the peaceful use of nuclear energy is likely to increase the risk of human exposure to low doses of ionizing radiation, whose potential effects cannot be ignored.

There is sufficient data concerning the effects of exposure to high doses of ionizing radiation, but relatively little reliable information on the consequences of exposure to lower doses. The dose-effect relationship for humans at low doses of radiation must be determined by extrapolation from human data obtained at higher doses, or experimental data at low dose or low dose-rate. Thus, it is very important to study the biological effects of low dose or low dose-rate radiation using various experimental systems, as well as to carry out epidemiological studies of human populations exposed to ionizing radiation.

Many groups are doing research both experimentally and epidemiologically, with particular reference to dose-response relationships at low dose and low dose-rate. There are however still considerable uncertainties concerning genetic and somatic effects. The IAEA held two symposia at which these topics were discussed, one in 1975 and one in 1978; much experimental data has been accumulated since then and new methodologies and techniques have been developed. In particular, dose limitations have been reviewed. In April this year the IAEA and the World Health Organization (WHO) organized another**, with the objective of reviewing the current status of understanding of the biological effects of low-level as well as low dose-rate radiation from external and internal sources. It was expected to lead to a clearer understanding of the mechanisms of damage and repair of the genetic material, dose-response curves, and more precise risk estimates. It was also intended to elucidate the linkage between the radiobiology of cell damage and the possible forms of harm that may result. When the risk of low dose effects of ionizing radiation is being considered, it is essential that risk estimates be formulated within a wide perspective of possible applications. Modification of the effects of ionizing radiation by interaction with other agents such as chemicals was therefore also discussed.

**Dose re-evaluation**

A topical subject was the re-evaluation of the biological effects of the radiation exposure received by atomic bomb survivors, in the light of current dose revisions. Epidemiological studies of the effects of the A-bomb have provided invaluable quantitative data for use in the assessment of the risk of exposure to ionizing radiation. Recently, the total dose received by the exposed population and the relative contributions of neutron and gamma-ray components in the presently-used Tentative 1965 Dose (T65D) have been called into question. At this meeting, one of the invited speakers made clear the situation concerning research in this area.

The T65D has been revised over the past few years by groups at the Oak Ridge National Laboratory (ORNL) and the Lawrence Livermore National Laboratory (LLNL), taking into account new radiation spectra calculated for the two bombs. In addition, individual exposures are being re-calculated by a Japanese scientific group. Thus, the new dose-effect curves differ from those used in the past. For Hiroshima, the neutron component of dose will be reduced and the gamma component slightly increased, but for Nagasaki the revision of dose is less prominent. For the time being it appears that the dose-effect curves for both cities will be more similar for leukaemic and other malignancies than indicated by T65D. Reappraisal of risk using the A-bomb data should be withheld until the joint Japanese-US working group carrying out the current dose re-assessment programme announces its results. All data presented so far must be regarded as highly tentative and speculative until some dosimetric parameters have been investigated in more detail.

A group at the Hiroshima Radiation Research Foundation has made an attempt to re-calculate dose-effect relationships on the basis of dose assessments made by ORNL using leukaemia deaths and chromosome aberrations among survivors of Hiroshima and Nagasaki:

1. The mean kerma doses of gamma rays and neutrons are smaller for ORNL than T65D although the neutron doses in Hiroshima calculated by ORNL are still larger than those in Nagasaki;

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2. The Hiroshima-Nagasaki inter-city differences in dose response are smaller for ORNL, but the risk is still higher for Hiroshima;
3. The estimated risk coefficients for gamma rays based on a linear model are larger for ORNL and the ratios of coefficients (ORNL: T65D) were in the range 1.2 to 1.7; and
4. As the ORNL neutron dose becomes very small even in Hiroshima, estimates of risk coefficients for ORNL may not be warranted. However, estimates similar to those for gamma rays suggest that the risk coefficients are larger for ORNL than for T65D, and that ORNL: T65D ratios are in the range of 4 to 6. It was concluded that the values for the relative biological effectiveness of neutrons are larger for the ORNL than for the T65D dose.

In this connection, the incidence of cancer death for the 0–9 rad (0–90 mGy) exposure group based on T65D and for the population "not in the cities", in comparison with national rates of incidence as "control", was analysed. The reported elevation of rates of incidence for leukaemia, breast cancer and thyroid neoplasia in the 0–9 rad group and in the group "not in the city" was attributable to possible exposure to fallout in these populations. Yet doses due to fallout are not available; and local circumstances with respect to factors contributing to development of neoplasia are also uncertain, so the conclusions of this paper remained open to question.

### Occupational exposure

In addition to the human data relating to A-bomb survivors, a number of papers on epidemiological studies on occupationally exposed human populations were presented. A detailed analysis of mortality among Japanese radiological technologists who were thought to have been exposed to high radiation doses before 1955 indicated that a small excess of deaths due to malignant tumours was observed and that relative risk increased with radiation exposure; but the relationship between risk of cancer death and dose did not appear to be statistically significant. Results from a comparative study of radiographically observed changes in the bone structure of two groups of former radium dial workers who were exposed predominantly before 1926 indicated that severe non-stochastic changes were observed in workers with intakes of 100 microcuries ($3.7 \cdot 10^6$ Bq) or more. The data suggest that clinically significant changes in bone structure will not occur at intakes below one microcurie ($3.7 \cdot 10^4$ Bq) of either radium-226 or radium-228. Preliminary epidemiological studies in three corporations covering the complete Canadian nuclear fuel cycle indicated an excess of lung cancer deaths in underground uranium miners exposed to high concentrations of radon daughters in early years, but no excess of cancer death among nuclear workers exposed primarily to gamma radiations at levels below ICRP recommendations for maximum exposure. Although a further analysis of job-related risks of Hanford workers was reported, it was concluded that the radiation exposure of these workers caused excess cancer deaths. The analysis stimulated a lively discussion.

Progress to date was reported from a mortality study of radiation workers employed by the Central Electricity Generating Board in the UK. The cumulative and annual exposures are both low and no detectable effects are anticipated unless ICRP risk estimates are too low by an order of magnitude or more. Various epidemiological studies on radiation workers in the UK were surveyed. Since these studies are looking for a very small excess in cancer mortality, very careful data collection and analysis are necessary to avoid bias due to unidentified factors. Even so, random variations in the number of cancer deaths in any given group may dominate.

Occupational exposures to ethylene oxide in terms of rad-equivalents was another interesting topic. If the assumed conversion factors are correct, it appears that occupational exposures to ethylene oxide might be very high, approaching several tens of rad-equivalents per year in some cases.

### Environmental sources of radiation

An interesting attempt to relate the effect on human populations exposed to higher than normal natural background radiation in India, Brazil, and China was reviewed by WHO groups. In addition, vital materials such as building materials, drinking water, and gas for domestic uses appear to show appreciable variations in concentrations of radioactivity under different conditions and living habits. Some instances were quoted where remedial action has been deemed appropriate to avoid unnecessarily high exposure due to enhanced concentrations of activity associated with certain technologies, or certain ways of using natural resources – typically, building materials. As it is, it is quite understandable that international agencies, such as WHO, have been asked to consider the problem in a general way and perhaps to suggest some recommendations. This has been recognized as a difficult task because of consideration of costs versus benefits which are influenced by the decisions on the level at which epidemiological studies ought to be done and on the end-points that should be investigated.

Some results were reported from Japan, where among a large number of potential indicators only a few have provided a significant correlation with variations in background levels, and it remains to be seen whether some positive correlations are just a matter of chance – taking into account the many other co-factors in carcinogenesis, in addition to radiation.

### Basic research

Two papers introducing new experimental end-points for the study of irradiated cells were presented: when rats were injected with a certain number of radioactive nuclides, lymphocytes became more fluorescent to UV light excitation. This might reflect changes in amino acids such as tryptophane, tyrosine or phenylalanine of cellular proteins, but the physical chemistry of this induced fluorescence needs further clarification. Such increase in cellular protein fluorescence is also observed after chronic external irradiation. As these changes in fluorescence decrease after several days, they might constitute a signal for the renewal of some populations of lymphocytes, but these relationships and the significance of these induced fluorescence changes need further investigation. Another report was on membrane changes in irradiated cells as well as changes in membrane binding capacity of concanavalin A which showed some transit membrane changes after low doses of X-irradiation or of various treatments with $^{3}$H-thymidine or water. Both these papers stressed the importance of approaching cellular radiobiology with methods enabling the study of cell constituents or organelles which may not have received so far all the attention they deserve.

Theoretical analysis of radiobiological problems is of importance when risk assessments are made. The application of microdosimetry to the "hit" theory, to explain responses of cell populations exposed to radiation with different energies, was proposed. An observed effect will depend on a stochastic transfer of energy to a critical volume within the cell. If sufficient energy is transferred or if a certain "hit size" is reached, a biological effect will result. There is no necessity to make a prior assumption on the molecular events which occur between the energy deposition in the critical volume and the end effects considered (i.e. carcinogenic, mutational, etc.). Radiations of several levels of linear energy transfer (LET) were used to construct single-cell hit size response functions that in principle replace relative biological effectiveness (RBE) and permit prediction from microdosimetric hit size spectra of the incidental quantal effect in cells exposed to any quality or mixture of radiation qualities. Excellent fit was obtained when results on pink mutations in staminal hair cells of Tradescantia were treated. Similar treatments can be applied to cell death and organ failure in a variety of irradiation conditions. The advantage of such a treatment, simply by taking into account the energy transferred, obviates the usual requirement for RBE in such calculations and enables predictions for the effect of radiations of different energies. The "classical" non-stochastic effects such as animal death can be treated in mathematical terms similar to those for stochastic effects such as single cell death. The assumption is made that a double-strand break in DNA can cause cell death, malignant transformation or mutation. When the whole organism is considered, one can assume that it cannot survive the impairment of a vital organ caused by excessive loss of cells of that organ. The present treatment certainly stresses that some non-stochastic effects can be explained and expressed in terms comparable to stochastic ones, and can be closely related to the cellular effects observed. These observations certainly suggest that terminology like single- and multi-cellular effects would seem less ambiguous then stochastic and non-stochastic.

### Cytogenetic effects

Chromosome aberrations in peripheral blood lymphocytes are very sensitive to ionizing radiation and are a good indicator in the study of dose-response relationship at low doses.

It was reported that in the peripheral lymphocytes of patients exposed to very low levels of diagnostic X-irradiation measurable chromosomal aberrations were found; and that there is a measurable, and even sizeable, enhancement of chromosomal aberration frequency when sodium methylglucamine diatrizoate is used as a contrast medium in individuals undergoing cardiac catheterization. The higher than expected frequency of aberrations may be attributed to a synergism between the radiation and high iodine concentrations in the blood at the time of irradiation.

A large inter-laboratory study of the effects of low levels of gamma and neutron irradiation of the human peripheral lymphocytes which has been carried out under a co-ordinated research programme, initiated by the Agency, on chromosome aberration frequency induced by low-dose high-LET radiation was reported. Great care was taken to ensure uniform irradiation of the samples as well as excellent dosimetry. Slides were encoded and distributed to recognized authorities for analysis. The sizeable amount of resulting data was analysed statistically. The most astonishing result was that at levels of irradiation of a few milli-Gray (mGy), fewer aberrations were present than in the non-irradiated control. Such a finding demonstrates the futility of extrapolating below 50 mGy after gamma irradiation and 20 mGy after neutron exposure.

An extensive analysis of unscheduled DNA synthesis and sister chromatid exchange in individuals exposed to levels of radiation in the range of 4 mGy to 8 mGy millirad in half a year was presented. Individuals receiving $40 \cdot 10^{-6}$ Gy to $140 \cdot 10^{-6}$ Gy actually had more sister chromatid exchanges than those exposed to more than $140 \cdot 10^{-6}$ Gy. Moreover, there was more unscheduled DNA synthesis taking place in individuals receiving more than $140 \cdot 10^{-6}$ Gy, indicating that they had a greater capacity for DNA repair. It was demonstrated, on the basis of the analysis of dose-response

very low levels less chromosomal damage is induced than is expected by conventional extrapolation from higher doses, as substantiated by other speakers.

### Are beneficial effects considered?

In the study of low dose effects an interesting question on whether small doses of radiation can actually cause beneficial response always arises. As already stated, a number of papers indicate that positive data have been obtained. Beneficial results in the life-shortening and tumour induction in mice after neutron or gamma irradiation have been obtained; non-stochastic lung lesions were significantly reduced in a mouse group which had received less than 1 Gy of X-ray and death from malignant tumours was reduced after small single neutron doses. It was explained that such an apparent beneficial action of radiation is expressed in terms of hormesis which may be mediated via a stimulation of antibody production following cell death. However, further experiments should be continued since the population size is still small.

Four papers dealt with the non-stochastic effects involved in the sensitivity of oocytes in adult mice; the role of ADP-ribosylation to DNA repair; life-span shortening of irradiated mice; and acute effects caused by very low doses such as 0.1–0.01 Gy in bone-marrow cells. The last paper found the remarkable reduction of uptake of $^{3}$H-thymidine and $^{125}$I-deoxyuridine into bone-marrow cells four hours after whole-body irradiation. It will be a good indicator to detect the small change after low dose irradiation.

### Risk estimation

The practical assessment of risks to individuals and populations exposed to low dose radiation was analysed theoretically by French groups by means of mathematical models. Prediction of biological damage at low doses by extrapolation of observed effects at high doses can be variable according to the mode using the linear quadratic hypothesis and it might affect the threshold dose. A more refined theoretical approach and further experimental studies are needed. One of the invited speakers summarized the problem posed by low-level exposures in the optimization of radiation protection with special regard to ICRP Publication 37, which dealt with cost-benefit analysis. He stated that optimization of protection is based on the assumption that the dose-effect relationship is linear without threshold, the collective dose is measurable, and detriment and risk factors are independent of age and social conditions. However, in practical optimization some uncertain factors might be involved – the dose-effect relationship at low dose, the possible synergetic or additive effects of other toxic agents, modification of collective dose by exposure for long periods from the environment. Taking these factors into account, optimization of radiation protection is now being actively pursued by different national and international bodies.

It is beyond question that the data from human beings is invaluable in relation to accurate dosimetry. In this sense, it would seem that nuclear power workers would generally constitute the best sub-population to be studied in each country. The Agency could perform a useful service to Member States by encouraging such studies and developing guidelines for them.