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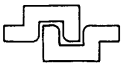

Series A: Life Sciences

Epidemiology and Quantitation of Environmental Risk in Humans from Radiation and Other Agents

Edited by

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ENEA, Energy Research Center, Casaccia
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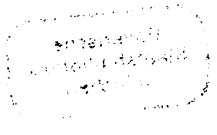

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CONTENTS

FUNDAMENTALS OF DOSIMETRY AND MICRODOSIMETRY AND THE RELATIVE BIOLOGICAL EFFECTIVENESS OF IONIZING RADIATIONS

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INTRODUCTION

The effects of ionizing radiations have been explored in innumerable biological experiments, but they have also been inflicted - often with tragic negligence or irresponsibility - on human populations. The worldwide fascination with x-rays immediatedly after Röntgen's discovery was motivated by optimistic expectations and permitted little attention to biological damage seen immediately, such as skin-lesions, or to the later occurrence of leukemias in radiologists. Several decades after their discovery x-rays were still widely assumed to have general positive effects and nearly universal medical applicability. A painful process of learning then led to the stepwise development of adequate radiation-protection procedures and to a more realistic assessment of the beneficial and detrimental potential of ionizing radiations. As a reaction to past industrial misuses of radio-isotopes and errors in their medical application one has, today, in many ways gone to the other extreme. Beyond this, it has become difficult, after Hiroshima and Nagasaki, to draw a rational balance between the uses and the misuses of nuclear energy.

The resulting attitude and public perception of ionizing radiations has made it difficult to discern similarities and dissimilarities between the actions of ionizing radiations and other agents, such as chemical carcinogens. In a discussion of fundamentals of dosimetry and microdosimetry one may, therefore, consider first presumed or real particularities of ionizing radiations and their

biological effects. The subsequent short survey will deal with some of the essentials of radiation physics, with the attendant problems in dosimetry, particularly in epidemiological studies, with parameters that characterize radiation quality, and with some general implications for the action of radiations.

Absorbed dose is - in a simplified formulation - the energy transmitted from a radiation field to a small element of matter divided by its mass (1). The macroscopic distribution of absorbed dose in an irradiated body and the microscopic random fluctuations of energy deposition are the two essential factors that determine the effectiveness of different types and energies of ionizing radiations. The former are the objective of conventional dosimetry, the latter the objective of the more recent branch of radiation physics, microdosimetry. Before these two areas are considered it is helpful to illustrate the order of magnitude of the energy densities that cause observable biological effects.

It is sometimes thought that ionizing radiations produce specific deleterious effects, and that they produce them by extraordinarily small amounts of energy. Both assumptions are erroneous. There is no effect of ionizing radiations that can not also be produced by chemical compounds. The remarkable feature of ionizing radiations is merely the extremely broad spectrum of biological end points. The energies required to produce biological effects would seem to be minimal if compared to thermal energy. A lethal dose to man transfers an energy to the body that increases its temperature by less than 0.001 degree centigrade. However, the comparison to temperature - the most degraded form of energy - is misleading. It is somewhat more informative to consider the total energy corresponding to a lethal dose of 5 gray, which is 350 joule or 350 watt*seconds. An even better illustration is the comparison to mechanical energy. One gray corresponds to the energy required to lift the exposed object by 0.1 metre in the earth's gravitation; the lethal dose corresponds to an elevation by 0.5 metre, evidently sufficient energy to produce damage. Visualizations of the effects of ionizing radiations on the microscopic or the atomic level can be similarly disparate. At a dose of 1 gray, only one out of ten to hundred billion electrons in the exposed material is disturbed. On the other hand, there are, at this dose, roughly 100 000 electronic displacements in the nucleus of a mammalian cell.

CONVENTIONAL DOSIMETRY

The Macroscopic Distribution of Energy

All ionizing radiations work ultimately through the action of electrons. Electrons can be the primary radiation, or they can be produced as secondary radiation by x-rays or gamma-rays. The electrons can also be the secondary radiation produced along the tracks of heavy charged particles. Finally they can be the tertiary radiation occurring with high energy neutrons; they are then released by the heavy charged recoils of the neutrons. In radiation protection one deals mostly with uncharged primaries, i.e. with x-rays, gamma-rays, or neutrons, when the body is exposed to external sources. Charged primaries are of concern mostly in connection with internal emitters.

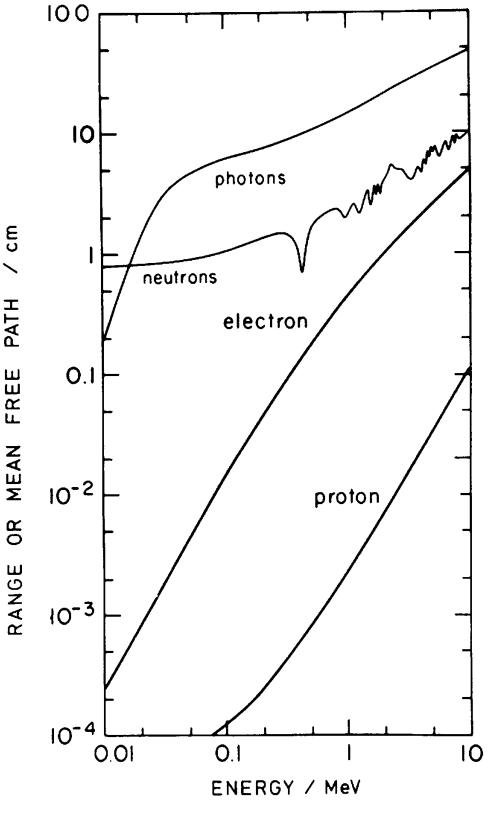

Fig. 1
Comparison of the mean free path of photons and neutrons in tissue, and of the ranges of their charged secondaries, electrons and protons.

The dosimetry of ionizing radiations is never trivial when one is concerned with large exposed objects, such as the human body. With energetic photons or neutrons beyond 20 MeV the total body irradiation may be nearly uniform. However, for these very energetic radiations cross-sections, and specifically the nuclear cross-sections, are still inadequately known. At the more common intermediate energies, in the range of 0.1 to 20 MeV, the cross-sections are adequately known, but the penetration of the radiation is then limited, and dose distributions in an exposed body are complex and depend on numerous parameters.

Fig.1 gives for uncharged and for charged particles their mean free path and their range for energies between 10 keV and 10 MeV. The essential observation is, that the mean free path of the uncharged particles is always considerably larger than the ranges of the charged secondaries. For many purposes one can, therefore, simplify dosimetric computations by neglecting energy transport by the charged secondaries. With this simplification one obtains the quantity kerma (Kinetic Energy Released in MAtter) instead of absorbed dose. It is evident that kerma and absorbed dose can be used interchangeably if, in a specified geometry, all dimensions of interest exceed the maximum ranges of charged particles. If this condition is not fulfilled, one must account for the different spatial distributions of the two quantities. Absorbed dose includes a further degradation process; the gradients of absorbed dose are therefore always less than those of kerma.

Beyond the facilitation of computations, the concept of kerma permits a further simplification. Kerma for any specified material is defined even in a receptor free geometry, e.g. in free space. A similar possibility does not exist for absorbed dose, which is always a complex result of attenuation and backscatter, and of the build-up of charged particle equilibrium in a specified geometry. These complexities of absorbed dose are sometimes disregarded with the silent assumption of a reference volume large enough to attain charged particle equilibrium but small enough that attenuation and backscatter can be disregarded. For crude estimates this may be an admissable procedure. In rigorous statements the reference to absorbed dose without specified geometry must be avoided. Fig.1 illustrates the difficulty by showing that the ranges of the released electrons can, at high energies, be equal to several percent of the mean free path of photons.

Although the use of exposure and its units röntgen or C/kg is now discouraged one may note that this quantity,

too, is defined regardless of energy transport by charged particles, and that it is, therefore, defined even in receptor free conditions.

For dose planning and dose assessment in radiotherapy inaccuracies must not exceed a few percent. Precise measurements and accurate computations are thus required. Similar requirements for dose specification can be met in many radiobiological studies, either with cell cultures or with small laboratory animals. In epidemiological studies the inaccuracies are far greater and far more complex.

The difficulties and complexities of the dosimetric problems are exemplified by the studies on the atomic bomb survivers. The current reevaluation of the dosimetry has been necessitated by inaccuracies of the input data for the tentative Oak Ridge dosimetry of 1965 (TD 65). There were uncertainties concerning the yields and the energy spectra of the neutrons and the gamma-rays as well as the geometry of the bomb assemblies and the humidity of the atmosphere at the time of the bombings. Improvements in the transport codes, particularly for neutrons, are equally important. As a result the tissue-kerma values in air have been substantially changed. However, as a new consensus on the dosimetry appears to emerge there remain large areas of uncertainty. Perhaps most importantly, new individual shielding factors remain to be established. The free air kermas have to be reduced to kermas in the buildings where individuals were at the time of the bombing; the reduction can be appreciable and it depends strongly on energy. The further reduction from kerma within the building to organ doses is also substantial. For the deeper organs the reduction factors are 0.7 to 0.85 for gamma-rays, and 0.1 to 0.2 for neutrons (2,3). For the superficial organs, such as the breasts, there is the additional complexity of a dependence on the orientation of the person at the time of the explosion and during the subsequent seconds of delayed irradiation.

The relative contribution of the delayed radiation is still inadequately known. So are possible contributions from fall-out, including the possible role of the so-called black rain.

It is characteristic for radiation epidemiology that the dosimetric problems are further complicated by far less tangible uncertainties. Rules of compensation and medical care for the atomic bomb survivers were partly dependent on dose received; they may therefore have influenced the statements of individuals concerning their localization at

the time of the blasts. There could also have been an opposite effect due to the desire to avoid any social stigma linked to heavy exposure. To name still another possible difficulty, there had been severe shortages of x-ray films in the period after the bombing, and this may have led to extensive use of fluoroscopy and thus to radiation doses in addition to those from the bomb.

The dosimetric studies for Hiroshima and Nagasaki have been referred to as examples of difficult and partly unresolved problems in radiation epidemiology. The same studies are, however, also exemplary and impressive efforts. Such efforts must continue, because the various collectives of substantially exposed persons are unique and will, hopefully, remain so.

The numerous investigations of the effects of internal emitters pose problems of comparable or even higher complexity (see for example (4)). Internal emitters produce - with few exceptions such as tritium - highly non-uniform exposures. For example in patients that have been exposed to the short lived radium-224 by far the largest doses were produced in narrow regions on the bone surfaces (5). Still further complexities occur with inhaled activity such as radon daughters. The study of the distribution of the radon daughters in different areas of the lung is, by itself, a specialized field of inquiery, as is the investigation of the dose dependence and the geometric and temporal distribution of lung tumors induced by the inhaled activity.

The microdistribution of absorbed dose in the vicinity of particulate alpha-emitters in the lung is an additional complexity of inhalation studies. This hot spot problem exemplifies further the wide range of dosimetric problems, and poses problems intermediate between conventional dosimetry and microdosimetry (6); it reaches beyond the scope of this survey.

MICRODOSIMETRY

The Microscopic Distribution of Energy

Absorbed dose is defined in terms of the expected value of the energy transferred by ionizing radiation to a mass element. It is, accordingly, a statistical concept that loses applicability when one deals with small doses, with small structures, and, especially, with densily ionizing radiations. The microscopic fluctuations of energy deposition can then be considerable. Fig.2 indicates, for sparsely and for densely ionizing radiations, the sizes of spherical regions in tissue and the doses where the standard deviations of energy deposition exceed 20%.

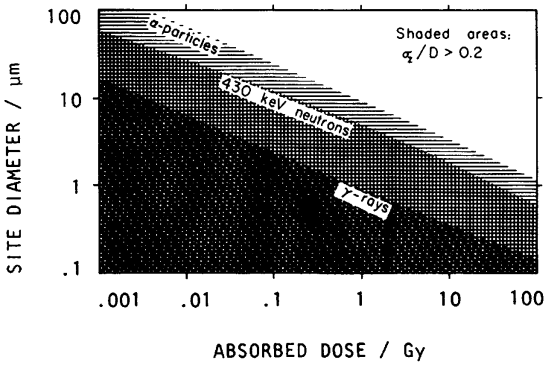

Fig.2. The shaded areas indicate those combinations of site sizes and absorbed doses where the standard deviations of energy imparted exceed 20%. Absorbed dose can then not be applied naively, and a treatment in terms of microdosimetry is required.

The figure is based on microdosimetric computations and measurements, but its meaning can be understood even before the principles of microdosimetry are formally introduced. At doses of several mGy, i.e. at the level of radiation protection, the absorbed dose is never meaningful, even if the entire nucleus of the cell or the cell itself is con-

sidered. Most cells receive, in this dose range, no energy deposition at all; those cells that are traversed by a charged particle receive energies that can be far in excess of the expectation value corresponding to absorbed dose. Although the affected cells are only a minor fraction of all cells, their total number is, of course, very large. The important consequence of this basic feature of ionizing radiations is that no threshold in absorbed dose can hold for cellular effects. For smaller cell structures, such as individual chromosomes, the dose concept remains inapplicable even at the highest doses of biological interest.

The discontinuous energy transfer by ionizing radiations has attracted attention early in the development of radiation biology. It has led to the hit and target theories (for surveys see (7-9)). Such theories, although they were valid as heuristic principles, have had only limited pragmatic success. They were based on the postulate of equal and statistically independent hit processes and of hypothetical cellular targets which have never been identified. A more successful approach requires realistic physical parameters of radiation quality. The most simplified, but still the most common, parameter is linear energy transfer (LET), also called collision stopping power, of charged particles. It characterizes the average local concentration of energy along the track of a charged particle, and it is still the parameter that determines the quality factor employed in radiation protection (10). However, LET itself is merely a statistical expectation value. Energy-loss straggling, the radial transport of energy away from the particle track by delta-rays, and the change of LET along the particle trajectory are factors that co-determine actual microscopic concentrations of energy. For heavy ions there are conditions where LET and its probability distributions permit adequate estimates of energy transfer by individual charged particles to the nucleus of the cell or comparable sites. For electrons the LET concept is never adequate (11).

The shortcomings of the LET concept have been responsible for the development of a new branch of radiation physics. When H.H.Rossi attempted to determine the LET distribution of the recoils produced by high energy neutrons he found that these distributions were not directly measurable. He then recognized that the seemingly inadequate response of the proportional counters was, in fact, more meaningful than the theoretical LET values. The spherical proportional counters - now known as Rossi counters - respond to energy actually imparted to their gas volume which simulates a microscopic tissue region. The basic

principle of microdosimetry is that cellular effects are determined by actual energy concentrations, not by their expectation values. When this simple but fundamental principle was understood (12), the subsequent steps followed of necessity. A conceptional framework of microdosimetry was established and suitable experimental techniques were developed that could be applied to any radiation field to determine the probability distributions of energy concentrations on the microscopic scale (13-15).

There are a number of closely interrelated microdosimetric quantities:

The energy imparted, e, is the radiation energy transferred to a given reference volume of matter.

The specific energy, z, is the energy imparted, as defined above, divided by the mass, m, of the reference volume of matter:

$$z = e/m$$

The lineal energy, y, is the energy imparted, as defined above, divided by the mean chord length, l, resulting in straight random traversals of the reference volume *) :

$$y = e/l$$

The specific energy, z, is the random variable corresponding to the non-stochastic quantity absorbed dose, D. The linear energy, y, relates only to individual energy deposition events (i.e. individual charged particles), it is the stochastic counterpart of the non-stochastic quantity LET. In view of the simple relation between z and y, it is usually sufficient to use the specific energy, z, as will be done below.

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*)
If the reference volume is a sphere of the diameter d, the mean chord length is $l = 2d/3$. For any convex volume the mean chord length is equal to four times the volume divided by the surface (16).

4000 simulations are performed per decade of dose for each graph. The decreasing number of points at low dose is due to the increasing number of events with zero specific energy.

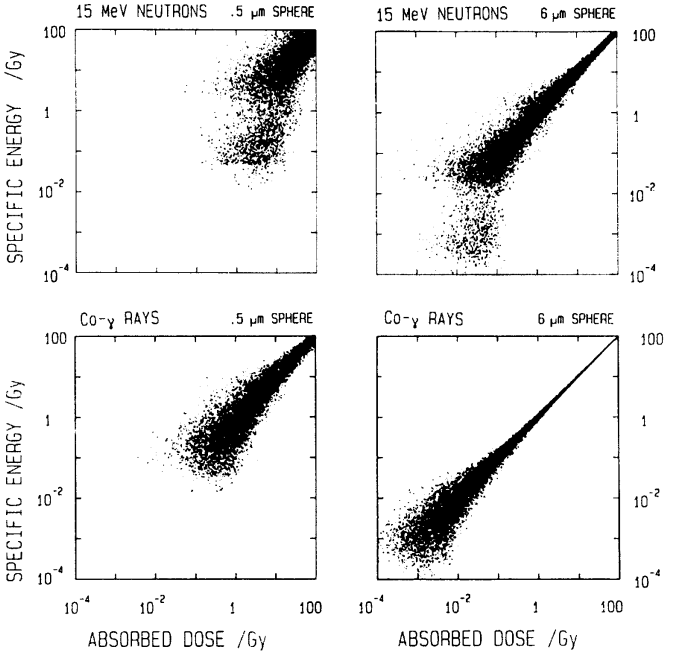

Fig.3. Scatter diagrams of the distribution of specific energy in small and large sites and for sparsely and densely ionizing radiation.

A definite value of the specific energy can not be predicted for a microscopic volume, even under fully defined irradiation conditions. Instead the possible values of the specific energy are described by a probability density, f(z;D). The objective of microdosimetry is the calculation or the experimental determination of the probability densities of the specific energy for various types of radiation and specified reference volumes. The experimental determinations are carried out not directly in solid material, but in tissue equivalent gas volumes simulating microscopic regions in tissue. Without going into the technical details of the construction of the Rossi counters it is sufficient to note that the instruments can be used for measurements in a wide variety of radiation fields. It is possible to simulate tissue regions down to a diameter of about 0.3 micrometer. Microdosimetric data for much smaller regions are also of considerable interest, but they have to be obtained by computations. Experimental techniques to determine such data have not, as yet, been developed.

It is not necessary to measure the spectra of z for different values of the absorbed dose. Instead it is sufficient to determine the single-event spectra, f (z), i.e. the densities of the increments of the specific energy due to single charged particles including their secondaries. If the single-event spectrum is known, it is possible to calculate the dose dependent spectra as solutions of a compound Poisson process (17). Fig.3 illustrates, in the form of scatter diagrams, the distributions of specific energy for a densely ionizing and a sparsely ionizing radiation and for sites of 0.5 and of 6 micrometer diameter. These diagrams illustrate the large fluctuations of specific energy; they also show, by the absence of points at small doses, the increasing probabilties for no energy deposition.

In most applications of microdosimetry to radiobiology and to radiation protection it is not actually required to utilize the dose dependent distributions of specific energy. Important conclusions can, instead, be based directly on the single-event spectra and their moments.

Typical examples of single-event distributions are shown in Fig.4. These spectra relate to spherical tissue regions of 1 micrometer diameter. The pronounced differences between sparsely ionizing and densely ionizing radiations are evident, but the very wide range of values of z for the different radiation types are equally notable. They extend over several orders of magnitude, i.e. a

densely ionizing radiation can always produce events with relatively small energy deposition, and, vice versa, moderate to high values of z occur even with sparsely ionizing radiations. There is, accordingly, no sharp dividing line between densely ionizing and sparsely ionizing radiations.

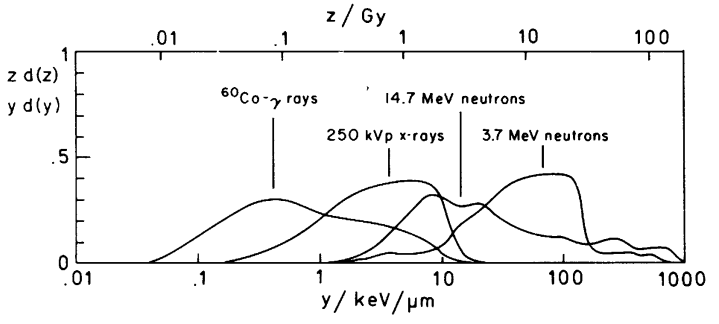

Fig.4. Single event distributions of specific energy and lineal energy for a spherical tissue region of 1 micrometer diameter. Distributions of dose, rather than event numbers, are given relative to the logarithmic scale (18).

The larger the increments of specific energy per event, the smaller is the mean number of events per unit of absorbed dose. Table 1 shows event frequencies for various types of radiation. Fig.5 indicates, largely in analogy to Fig.2, those site sizes and doses where the mean event frequency is less than 1. These data permit important conclusions. In particular, dose-effect relations must always be linear when the mean event number in the cell or in the sensitive cell organelles is much smaller than 1. With densely ionizing radiation this condition is met even at doses of the order of several gray. However, the argument applies only to dose-effect relations for autonomous cells, i.e. to cells that are not influenced by energy deposition in adjacent cells or by radiation induced reactions of the tissue (22).

The postulate of radiation action on autonomous cells appears to apply to hereditary effects which are due to

Table 1: Event frequencies in spherical tissue regions of specified diameter.

SITE DIAMETER (μm)	TYPE OF RADIATION			
	^{60}Co-γ-Radiation ϕ (Gy^{-1})	NEUTRONS ϕ(Gy^{-1})		
		.43 MeV	5.7 MeV	15 MeV
12	2000	55	51	61
5	360	4.2	8.6	11
2	58	.39	1.2	1.6
1	12	.08	.32	.38
.5	1.7	.02	.07	.09

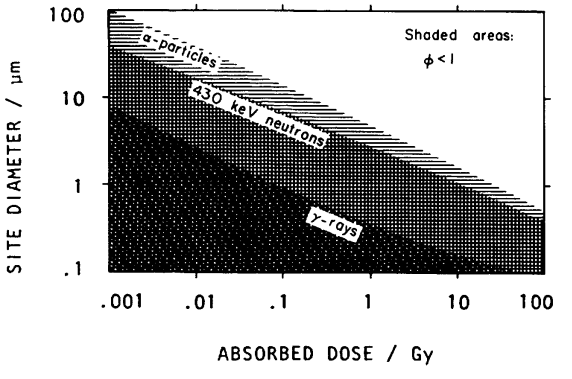

Fig.5. The shaded areas indicate combinations of site sizes and absorbed doses where the expected number of energy deposition events is less than 1, and dose dependences - for autonomous response - must accordingly by linear.

mutations or chromosome aberrations in individual cells. It is far less certain when applied to radiation carcinogenesis. In fact, non-linear dose-effect relations have been found at neutron doses far too small for an appreciable probability of multiple events in the cell (19-21). One must conclude that radiation tumorigenesis is co-determined by dose dependent tissue factors that are, as yet, unresolved. Linearity at low doses remains, therefore, a mere hypothesis for radiation carcinogenesis.

IMPLICATIONS FOR RADIATION PROTECTION

Dosimetry

Absorbed dose and the related quantity dose equivalent are utilized in the limitation principle of radiation protection. This principle is based on annual dose-equivalent limits which obviate the need to retain information on exposures of individuals in earlier calendar years. Another convenience has been - up to a recent change - that the maximum dose equivalent in any organ rather than a more complex quantity has been limited. A further feature of the limit system is the absence of any hypothesis concerning the form of the dose-effect relations.

However, there has been in past years a gradual change away from the limit to the assessment system. H.H.Rossi has recently analysed the change and its consequences in depth (22), and only some of the essentials will be considered here. For what has been called non-stochastic effects (10) -perhaps a somewhat artificial notion - the limit system has been retained. For the stochastic effects, i.e. hereditary effects and radiation carcinogenesis, which are of predominant concern in radiation protection, ICRP has shifted towards an assessment system that aims at an optimization of detriment and benefit. To be practicable such a system requires the assumption of linearity of the dose-effect relation at small doses, a postulate that is, at least for radiation carcinogenesis, entirely hypothetical.

The assessment system has also made it necessary to define and introduce into the practise of radiation protection a new quantity to replace the former dose equivalent. The new quantity, effective dose equivalent, is

a dose equivalent averaged with specified weight factors over all organs of concern. The rules of radiation protection for individuals retain numerically the earlier annual limits. One may note that - except for uniform exposures of the body - the limitation in terms of the new quantity is less restrictive than the earlier limitation in terms of the maximum dose equivalent in an organ. In fact, it has been necessary to introduce additional limitations on certain organ doses to ensure that non-stochastic effects be avoided.

The new system and its implied assumption of linearity have also been responsible for the increased use of concepts such as collective dose (equivalent) or committed collective dose (equivalent). It is not surprising that these new, and somewhat contrived, notions lead to novel conceptual difficulties when applied to specific situations. There have also been new problems in radiation-protection monitoring. It had been the practise to employ for purposes of area monitoring, or for personal monitoring, quantities that provide conservative rather than best estimates. Within the new philosophy this is inadequate. Accordingly the ICRU is about to present the definition of operational quantities for radiation protection that can be determined in area monitoring and personal monitoring. These quantities, ambient dose equivalent and individual dose equivalent, will serve as fair, if still somewhat conservative estimates of effective dose equivalent. When these quantities are introduced into the practise of radiation protection a reasonable compromise between the limit and the assessment system might be achieved. However, it must be noted that any epidemiological investigation will require information beyond the summary doses determined for radiation protection monitoring. The rules of radiation protection are aimed at keeping the risk sufficiently low to be unobservable statistically. If exposures beyond such safe levels occur, dosimetric information is needed beyond routine requirements. Effective dose equivalent, or its operational substitutes, can not be suitable reference parameters for radiation epidemiology.

Microdosimetry

The change from dose equivalent to effective dose equivalent is to account for the macroscopic distribution

of absorbed dose. Another current development in radiation protection relates to the microscopic distribution of radiation energy. This is the possible revision of the quality factors.

Microdosimetric considerations (23) had first led to the recognition that the linear component of the dose-effect relation is related to the average energy concentration produced in subcellular regions by single events, while the quadratic component reflects a cumulative damage due to the interplay of several events. There is no certainty, as yet, on the critical distances for which the energy concentrations are relevant. However - largely independent of the distances - one has a ratio of average single event sizes for fast neutrons and for sparsely ionizing radiations of 30 to 60. At low doses where the linear component of the radiation action predominates one expects, therefore, RBE values of neutrons versus sparsely ionizing radiations of this magnitude. For neutrons of about 400keV the RBE was indeed found, in various experiments, to reach such values or still larger ones (23). Perhaps even more importantly, an inverse dependence of the neutron RBE on the squareroot of the neutron dose has been consistently found in these experiments, which corresponds to a linear-quadratic dose dependence of the underlying damage for both radiations. This has been so, even when the dose-effect relations were substantially different from the linear-quadratic relation. One concludes that the RBE-dose dependence is more fundamental and more closely indicative of the initial steps of radiation action than the dose-effect relation which may be co-determined by complex tissue factors.

On the basis of the T65 Oak Ridge dosimetry it appeared that the dose-effect relation for leukemia in Hiroshima compared to the one for Nagaski was in agreement with the high neutron RBE (24,25). The resultant high risk values for neutrons may have been an added motivation for the revision of the T65 dosimetry. As of now, the estimates of the neutron doses are so small, even for Hiroshima, that no conclusions on neutron RBEs can be expected from the Japanese data. This gives added importance to experimental data and to new evidence on high neutron RBE, such as the life shortening data from the Argonne experiments (26) and the transformation data obtained by Han et al.(27) with fractioned neutron exposures.

In view of these developments certain changes are envisaged. If, as it appears now, the RBE of densely ionizing radiations continues to rise at small doses below

a few mGy, higher quality factors will have to be adopted for stochastic effects. The change will be unavoidable, because it is a basic tenet of the assessment system that risk estimates be realistic and that optimization be applicable even to doses substantially below annual limits. A substantial change of the quality factors will, on the other hand, make the new values inapplicable to non-stochastic effects. For these effects the limiting principle is still retained, with dose-equivalent limits in excess of 0.1 sievert. It is difficult to ignore the dualistic nature of the present system of radiation protection.

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INDEX