

Biology of Radiation Carcinogenesis

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Microdosimetry and Its Implication for the Primary Processes in Radiation Carcinogenesis

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Carcinogenesis has many aspects, and a variety of these aspects are discussed and compared in this conference. In a complex situation, one is naturally forced to simplify. Although this is often necessary and desirable, it can also lead to erroneous interpretation of experimental data and to distorted comparisons. This is particularly true with regard to basic biophysical concepts, such as absorbed dose, relative biologic effectiveness, and the time factor.

The following remarks deal with these three concepts and their relation to radiation carcinogenesis. The first problem is that of absorbed dose and of its inadequacy when applied to cellular or subcellular structures. The second problem is that of the relative biologic effectiveness (RBE) and its change with absorbed dose. The third problem is that of the dependence of the time factor on absorbed dose. Not only the complexities of these factors but also their interrelation and their connection to microdosimetry will be considered.

ABSORBED DOSE AND SPECIFIC ENERGY

All ionizing radiations work essentially by the same mechanism. Ionizing particles as different as photons, electrons, neutrons, heavy ions, and mesons produce the same primary alterations, namely ionization and excitation. Furthermore, the various radiations produce about the same number of such alterations per unit energy imparted to the irradiated medium. This is the justification for applying the same quantity, absorbed dose, D , to all ionizing radiations. The quantity is defined as the energy imparted to an irradiated medium per unit mass.

Equal absorbed doses of different radiations do not, however, produce equal effects. The differences are, as stated, not due to differences in the primary radiation products; they are due to the different microscopic distribution of ionization and excitation in charged particle tracks. Such radiations as α particles, or the heavy recoils of neutrons, that produce ionizations closely spaced along their tracks cause considerably more cellular damage per unit of absorbed dose than do sparsely ionizing radiations.

The fact that the cellular effect depends strongly on the microscopic pattern of energy distribution implies that absorbed dose is not a meaningful concept if one deals with small sites that may be traversed by only one or a few charged particles. Absorbed dose determines only the mean value, or statistical expectation, of the imparted energy; the actual energy in the microscopic region may differ greatly from the expectation value. This is the reason why the quantity specific energy, z , has been introduced (Rossi, 1967; ICRU, 1971). Specific energy is the statistical counterpart of absorbed dose; it is defined as energy actually imparted, divided by the mass of the region.

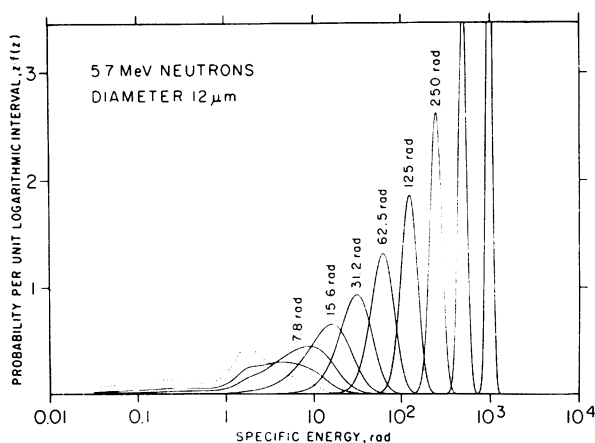


FIG. 1. Probability per unit logarithmic interval of specific energy, z , at various doses of 5.7 MeV neutrons in a spherical tissue region of diameter $12 \mu\text{m}$. The distribution of the increments of z produced in single events is shown (---). (Rossi and Kellerer, 1975.)

The statistical fluctuations, i.e., the differences between z and D are most important for small volumes, for small doses, and for densely ionizing radiation. Microdosimetry is the extension of classic dosimetry to those situations for which the concept of absorbed dose is not applicable. Its object is therefore the experimental and theoretical determination of specific energy in cellular and subcellular regions. Since specific energy is a random variable, and not a single valued quantity, such as absorbed dose, one can only give probability distributions of its possible values. Figure 1 represents such distributions, namely, the probability distribution of specific energy in regions of approximately cellular dimension upon exposure to monoenergetic neutrons. One notes that the relative fluctuations are very large at small doses, and less at higher doses. Accordingly, absorbed dose is a meaningful concept only if it is sufficiently high in value. The figure is merely an illustrative example; a detailed discussion of microdosimetric concepts relevant to radiation carcinogenesis can be found elsewhere (Rossi and Kellerer, 1975).

In order to obtain a practical criterion for the applicability of absorbed dose, one must determine the range of site diameters and of absorbed doses where the mean deviation of specific energy from absorbed dose is less than a specified value, for example 20%. In Fig. 2, three different radiations are considered, namely, α particles, 430 keV neutrons, and cobalt γ -rays. The ranges of site diameters and absorbed doses for which the mean deviation of specific energy from absorbed dose exceeds 20% are shaded. Above the shaded areas, the quantity, absorbed dose, can be applied directly; within the shaded areas, one must consider specific energy instead of absorbed dose.

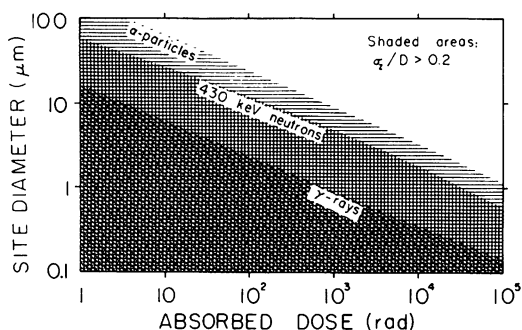


FIG. 2. Diagram of site diameters and absorbed doses for which the specific energy, z , must be distinguished from absorbed dose, D , for three different radiations. Those areas where the mean deviation of z from D exceeds 20% are indicated by shading.

Even without going into the details of microdosimetry, one can make general statements relevant to radiation carcinogenesis at low doses. This will be the subject of the remainder of this section.

Consider the case in which isolated mammalian cells are exposed to an absorbed dose of 1 rad of α particles. Then, 99% of the cell nuclei are entirely free of energy deposition by particles; they are not traversed by even a single charged particle. But 1% of all cell nuclei are traversed by one α particle. This single α particle produces specific energies in the nucleus, of the order of 100 rad. The probability that more than one α particle appears in the nucleus is only 10^{-4} and can therefore be neglected. In this situation, the dose-effect curve must be linear. This follows from the fact that only those cells that are traversed by a charged particle can be affected and that the number of cells actually traversed is proportional to absorbed dose. One may use the term *small dose* to designate the cases in which the event frequency in the nucleus of the cell is much smaller than one. Regardless of the cellular mechanisms one can then state that the dose-effect curve for any action of ionizing radiation on individual cells must be linear; it follows equally that there is no dependence on dose rate, since all effects are produced by individual particles.

At the same absorbed dose, the event frequencies are much larger for sparsely ionizing radiations than for densely ionizing radiations. Figure 3 illustrates the differences for the same radiations which have been compared in Fig. 2. In the figure, those ranges of site diameter and absorbed dose are shaded in the area where the mean number of particle traversing a given cell region is less than one. Whenever one deals with critical sites, and with absorbed doses that correspond to a point substantially inside the shaded regions, the dose-effect curve must be linear. On the other hand if, as in the results of Shellabarger et al. (1974) and Vogel (1969) on the induction of mammary tumors in the Sprague-Dawley rat, one finds nonlinearity at small doses of neutrons, one must conclude that the effect does not reflect

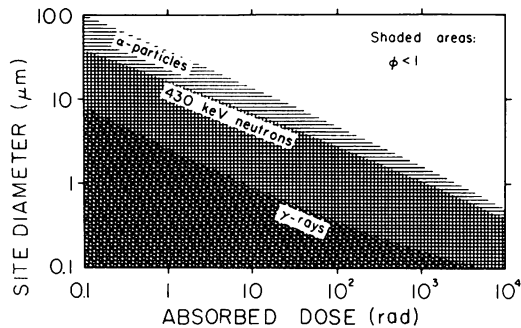


FIG. 3. Diagram of site diameters and absorbed doses for which the mean event frequency, ϕ , is less than one. The areas with ϕ less than one are indicated by shading for three different radiations.

damage to independent cells, but that there is interdependence between damaged cells (Rossi and Kellerer, 1972, 1975).

The statement concerning the linearity of cellular dose-effect relations at small doses is valid regardless of the mechanisms involved in the effect. Linearity, however, may extend to doses higher than the doses that would be predicted by using Fig. 3. There are experimental results on various higher organisms that indicate that this is indeed the case. It will be useful to summarize these results.

The microdosimetric analysis of various effects produced in eukaryotic cells by sparsely ionizing radiations and by neutrons has led to the conclusion that the cellular damage is proportional to the square of energy deposited in sensitive sites, which are somewhat smaller than the nucleus of the cell (Kellerer and Rossi, 1972):

$$\epsilon(z) = k z^2 \quad (1)$$

A quadratic dependence on specific energy will not result in a quadratic dependence on absorbed dose. The reason is that even at smallest absorbed

doses considerable energy concentrations occur in those cells traversed by a charged particle. This results in the linear component discussed above. One can formulate this quantitatively, and finds that the quadratic dependence on specific energy corresponds to a linear-quadratic dependence on absorbed dose:

$$\epsilon(D) = k(\zeta D + D^2) \quad (2)$$

The coefficient, ζ , in the linear term has a simple microdosimetric interpretation. It is the mean specific energy produced by individual charged particles in the sensitive site. This quantity, ζ , is proportional to the dose average linear energy transfer, \bar{L}_D , in those cases where the concept of linear energy trans-

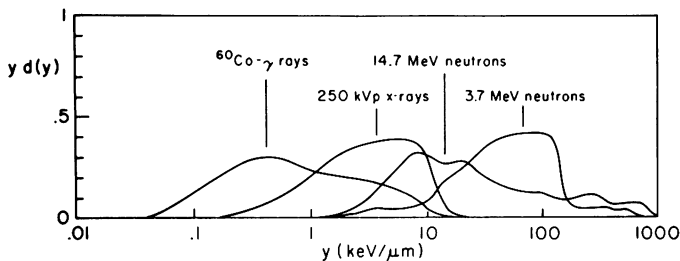


FIG. 4. Distribution of dose in y for single events in spherical tissue regions for various radiations. The curves refer to a diameter of $1 \mu\text{m}$ (Kellerer and Rossi, 1972). The value of z in rad is equal to $20.4 y$.

fer (LET) is applicable. But, the formulation in terms of microdosimetry is more rigorous and accounts for various factors neglected in the LET concept.

Figure 4 gives examples for the actual probability distributions of the energy concentrations produced in a region of $1 \mu\text{m}$ diameter by individual particles of different radiations. One can express these distributions either in terms of specific energy or in terms of lineal energy, y , which is the microdosimetric analogue of LET (ICRU, 1971). One may note the marked differences between the various radiations, but it is equally interesting to realize that even with one and the same radiation one can have energy distributions that differ by orders of magnitude. In the present context, it is sufficient to point out that the mean value, ζ , of the distributions is the coefficient in the linear term of the dose-effect relation. One can also see, from Eq.(2), that at an absorbed dose equal to ζ the linear component is equal to the quadratic component. Although ζ may be only a few rad for sparsely ionizing radiation, it is equal to hundreds of rad for densely ionizing radiations (Kellerer and Rossi, 1972).

Equation (2) appears to be well established for cellular effects at small doses, such as mutations in plants (Sparrow et al., 1972; Kellerer and Brenot, 1974) or chromosome aberrations in mammalian cells (Schmid

et al., 1973; Biola et al., 1971). It furthermore appears that the logarithm of the survival probability in various *in vitro* studies with mammalian cells follows the same linear-quadratic relation (Gray Conf., 1974). The restriction of Eq.(2) is that it does not apply to tissue effects that may depend on complex interactions of damaged cells, partially damaged cells, and undamaged cells. But the analysis of RBE can, as has first been pointed out by Rossi (1970), lead to general statements even in such complex situations.

RBE AS FUNCTION OF ABSORBED DOSE

According to the linear-quadratic dose-effect relation, the RBE of two radiation qualities must be constant in cases when the linear term is dominant for both radiations at very low doses. The asymptotic value of RBE is proportional to the ratio of the mean increments, ζ , for the two radiation qualities, and this ratio can be quite large. Some examples are given below.

The other limiting case is that of large absorbed doses. In this case, the quadratic term dominates for both radiation qualities, and the value of RBE will be equal to one if the constant, k , in Eq.(2) is the same for both radiation qualities. In the intermediate dose range, the RBE will decline as the absorbed dose increases. In the present context, it is sufficient to consider the characteristic dependence of RBE on absorbed dose. But Fig. 5 represents the actual curves from Eq.(2) for different ratios of ζ .

It has been found that these characteristic curves do not only apply to cellular effects but also to effects at the tissue level, including carcinogenesis (Kellerer and Rossi, 1972). This is remarkable as the linear-quadratic, dose-effect relation cannot be postulated for many of these effects. In studies of

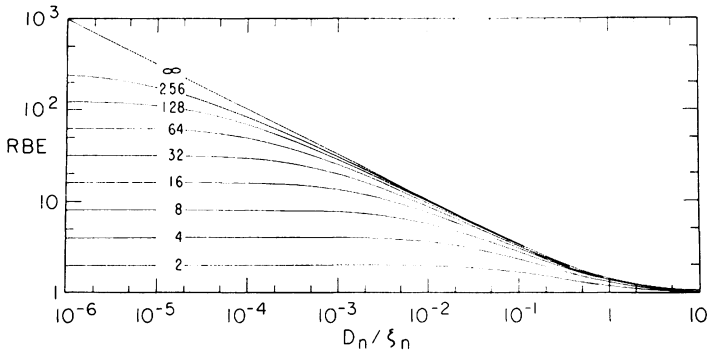


FIG. 5. Relation between RBE and dose resulting from Eq.(2). The dose is given as multiple of the quantity ζ_n ; the parameter of the curves is the ratio of ζ_n to the corresponding quantity ζ_x of the reference radiation.

the skin reaction, for example, there is no natural numerical scale of the effect, and the very notion of a linear or a nonlinear, dose-effect relation therefore loses its meaning. In carcinogenesis, one may determine the time to reach a certain incidence, or one may measure the incidence at a specified time; both procedures are meaningful, but they may not lead to the same numerical relations.

The complicating factors that enter into the dose-effect relation are presumably the same, or nearly the same, for different radiation qualities. Accordingly, they cancel if one studies RBE, and this explains the fact that one obtains the characteristic RBE-dose relations even in such complex situations as carcinogenesis.

The induction of mammary tumors in the Sprague-Dawley rat is a particularly clear example of the applicability of RBE-dose analysis. In the studies of the induction of mammary tumors in Sprague-Dawley rats (Shellabarger et al., 1974; Vogel, 1969), the dose dependence of the incidence of tumors up to 11 months after irradiation with neutrons has been found to be highly nonlinear (Rossi and Kellerer, 1972, 1975). The nonlinearity is not of the commonly observed type that corresponds to a quadratic dependence on absorbed dose. Rather, it has been found that the effect is nearly proportional to the square root of the absorbed dose of neutrons. This is the case at small doses of neutrons, in which the fraction of cells traversed by a charged particle is small. One must therefore conclude that the observed effect reflects the interdependence of damaged cells. The nature of this interdependence has not been clarified; it may be related to virus release, to hormonal factors, or it might even be explained by the presence of clusters of sensitive cells, which cannot lead to separate tumors. It is likely that the anomalous dose-effect relation for neutrons is linked to the anomalous nature of the biologic system, i.e., to the high spontaneous incidence of mammary tumors in the Sprague-Dawley rat. More detailed information on this experimental system is presented by Shellabarger (1975) at this conference. The essential point in the present context is that, in spite of physiologic complexities, the RBE depends on absorbed dose in a simple way that can be understood in terms of microdosimetry.

Figure 6 represents the RBE for the induction of mammary tumors by 430 keV neutrons as a function of the neutron dose (Shellabarger et al., 1974). The vertical bars cover those values of RBE excluded on the basis of the statistical analysis. The curve is the best estimate of the neutron RBE. Although these data are based on a preliminary analysis of an experiment just now being terminated, one can already infer extremely large values of RBE at small neutron doses. This means that sparsely ionizing radiations are much less carcinogenic at small doses than are densely ionizing radiations. It also illustrates that it is meaningless to quote values of RBE for a radiation without specifying the level of absorbed dose.

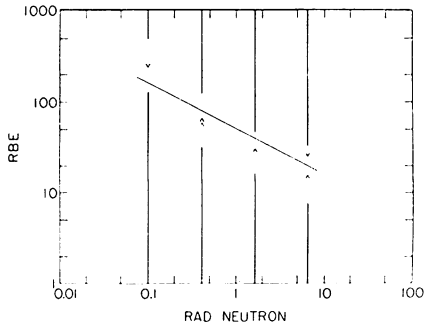


FIG. 6. The RBE of 430 keV neutrons relative to sparsely ionizing radiation for the induction of mammary tumors in the Sprague-Dawley rat (Shellabarger et al., 1974). The vertical bars indicate the ranges of RBE values, which are excluded with statistical significance exceeding 95%.

These considerations are particularly relevant to the problem of the linear extrapolations in radiation protection. The primary mechanisms of radiation carcinogenesis are not sufficiently known to exclude a linear, dose-effect relation for any type of radiation. But we can conclude that linear extrapolations from large to small doses cannot be simultaneously valid for sparsely ionizing radiation and densely ionizing radiation. This follows from the characteristic change of RBE with absorbed dose; if the dose relations for both radiation qualities were linear over a wide dose range, the RBE would have to be constant.

As an example of particular importance one may consider the incidence of leukemia in the survivors of the nuclear explosions in Hiroshima and Nagasaki. A substantial part of the absorbed dose in Hiroshima was due to neutrons, whereas the radiation in Nagasaki was essentially γ -rays. The data on leukemia incidence are not extensive enough to permit a definite statement whether the dose-effect relation in either of the two cities is linear or nonlinear. A nonparametric statistical analysis of the data (Rossi and Kellerer, 1974), however, indicates that the RBE of the radiation in Hiroshima as compared to that in Nagasaki follows the typical dose dependence observed in many other cases. As indicated in Fig. 7, the result is established only on a 86% confidence level. But it cannot be dismissed, since it is in agreement with basic biophysical considerations.

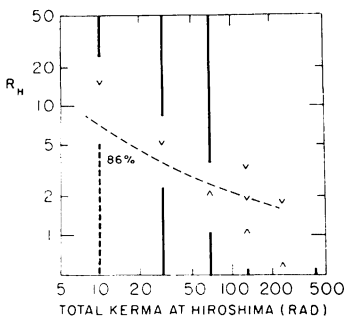


FIG. 7. The RBE of the radiation in Hiroshima for the induction of leukemia compared to that in Nagasaki as a function of kerma in Hiroshima (Rossi and Kellerer, 1974). The bars indicate those values that can be excluded with 95% confidence; the broken bar stands for a level of confidence of 86%. The broken curve is the result of a least-squares fit.

DEPENDENCE OF THE TIME FACTOR ON ABSORBED DOSE

The preceding section has dealt with RBE and its dependence on absorbed dose. An analogous dependence on absorbed dose must apply to the time factor. This will be the object of the present section.

The time factor is defined as the ratio of absorbed doses that produce the same effect at different irradiation times or dose rates. A quantitative treatment of the time factor is complicated by the fact that there is an unlimited number of different temporal distributions of a given absorbed dose. One may compare two dose-effect curves established with two different irradiation times; alternatively, one may compare dose-effect relations established with two different dose rates. The latter method is more commonly applied. The two methods, however, can lead to significantly different results (Kellerer and Rossi, 1972). Further complications arise when one deals with fractionated irradiation. The results presented by Yuhás (*this volume*) illustrate the complexities in the study of the time factor in carcinogenesis. They also illustrate the fact that the time factor depends on absorbed dose and that it is therefore meaningless to quote its value without specifying the absorbed dose. The following remarks will deal with one special case.

Assume that the cellular effect follows the linear-quadratic dependence on absorbed dose expressed in Eq.(2). One may then consider the time factor between irradiation over a short period, during which no recovery of sublethal damage occurs, and irradiation over a long period, during which recovery from sublethal damage is complete, and accordingly, the quadratic component in the absorbed dose can be disregarded. The doses for the short period of irradiation will be designated by D_s , the doses for the long one by D_l . The condition for equal effect is then:

$$\zeta D_l = \zeta D_s + D_s^2 \quad (3)$$

The time factor, TF , is equal to D_l/D_s , and therefore one obtains

$$TF = 1 + D_s/\zeta$$

This is represented graphically in Fig. 8. As one would expect, the time factor is largest for sparsely ionizing radiations, i.e., if the mean increment produced by individual charged particles is small. For densely ionizing radiations, where ζ is large compared to the absorbed dose, the time factor is close to one, i.e., the temporal distribution of absorbed dose is of relatively little influence. In all cases, however, the time factor is proportional to absorbed dose. It is therefore meaningless to quote time factors without specifying the effect level or the absorbed dose. Furthermore, one cannot apply time factors observed at high absorbed doses to the small doses that are relevant in radiation protection. Observations at high absorbed doses are relevant to questions of radiation protection only, insofar as they yield information concerning the linear component in the dose-effect relation.

These considerations apply only to cases in which the time factor is due to the recovery of sublethal damage. It has been pointed out that the induction of mammary tumors in the Sprague-Dawley rat involves a more complicated mechanism. The incidence per unit dose decreases with increasing neutron doses, and for X-rays one obtains a nearly linear, rather than a quadratic, dose dependence. A process that counteracts oncogenesis at larger doses should be most effective at short irradiation times. The time factor may therefore be small, or even negative. In fact, Shellabarger (1975) found very little reduction of tumor incidence if a certain X-ray dose is administered over a longer time.

A negative time factor need not always be due to intercellular effects. Borek (*this volume*) presents results to show that even in isolated cells one may deal with a negative time factor. It has been found that the transforma-

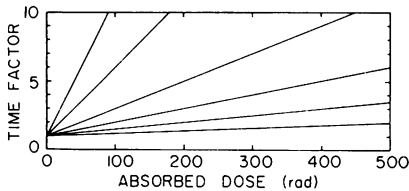


FIG. 8. Time factor for irradiation over a short period versus that over a long period, where complete recovery from sublethal damage occurs. The slope of the lines is proportional to ζ . The values of ζ are: 10, 20, 50, 100, 200, and 500 rads.

tion yield in cloned hamster embryo cells increases if an X-ray dose of 50 or 75 rad is given in two separate fractions instead of a single fraction. There is, as yet, no definite explanation of this interesting phenomenon; but one may surmise that the increased transformation rate at longer irradiation times is due to the fact that misrepair of sublethal damage can then play a greater role.

The occurrence of a negative time factor in the production of bone sarcomas by α particles poses a related problem (Gössner et al., 1975). It is an open question whether, in this case, one deals with intracellular or intercellular mechanisms.

CONCLUSIONS

Three biophysical concepts relevant to radiation carcinogenesis have been considered. Due to the statistical fluctuations of energy deposition on a microscopic scale, the absorbed dose loses its meaning whenever its value is not sufficiently large and whenever one deals with cellular or subcellular regions. Criteria have been given to indicate whether for a given site diameter and a given value of absorbed dose the statistical fluctuations are important. It has been pointed out that, at very small doses, all cellular dose-effect relations must be linear, but that at higher doses, the quadratic term in absorbed dose must be taken into account.

The statistical nature of energy distribution is responsible for the different relative biological effectivenesses of different radiations; it furthermore is responsible for the increase of RBE with decreasing absorbed dose. It has been found that the characteristic dependence of RBE on absorbed dose applies not only to cellular effects, but also to such processes as radiation carcinogenesis, which may depend on the interaction of damaged cells.

Not only RBE but also the time factor depends on absorbed dose. As with RBE, it is therefore meaningless to quote its value for a certain radiation and for a certain biologic system without specifying absorbed dose. The problem of the time factor is in many ways more complicated than the problem of RBE. Microdosimetry permits numerical predictions only as far as one deals with recovery from sublethal damage. Additional cellular and inter-cellular processes can lead to a negative time factor, i.e., to increased carcinogenesis at the same absorbed dose but at longer irradiation times. These processes are only incompletely understood.

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