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THE THEORY OF DUAL RADIATION ACTION*

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The theory of dual radiation action arose from the finding that for a wide range of effects on higher organisms the RBE (relative biological effectiveness) of various ionizing radiations exhibits a simple and consistent dependence on absorbed dose. It is postulated that the common fundamental cause of these effects is the production of elementary lesions which proceeds at a rate that is proportional to the square of local energy concentration within regions termed "sites". The concepts of microdosimetry permit a quantitative characterization of this process in terms of the specific energy (z), and it is deduced that the diameter of sites is comparable to the nuclear diameter (i.e. is of the order of μm). The domains of primary interaction between radiation and the biological substrate, which are termed "loci", are several orders of magnitude smaller.

A dependence of effect on the square of local energy concentration has often been postulated for the production of chromosome aberrations. The theory of dual radiation action leads to a rigorous formulation of these considerations and permits the derivation of the dose-effect curves for different radiation qualities. For other cellular effects the theory accounts not for the explicit shape of the dose-effect curve but for the dose-RBE relation. While the analysis explains the general features of the RBE-LET relation, saturation corrections must be applied at high values of LET. These as well as corresponding modifications in the case of anoxia are not unambiguously established.

The theory permits a systematic treatment of the effects of various temporal distributions of absorbed dose (varying dose-rate, fractionation). Departures from the theory are considered but their significance appears uncertain.

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1. Introduction

In the biological action of ionizing radiation the complex interactions between radiation and matter are compounded with the much greater intricacies of life processes. The dose-effect relation is commonly used as the quantitative description of the over-all phenomenon but it is of limited value as a characterization of the central biophysical step which is the transmutation of radiation energy to biomolecular change. This process clearly depends not only on the mean energy absorbed by the irradiated tissues (i.e. the absorbed dose) but also on the microscopic energy distribution. It is subsequently followed by a series of further alterations or reactions that sooner or later proceed in the same manner regardless of the type of radiation applied. Some of these steps may be the same even for other deleterious agents. However any physiological or other factors that influence these subsequent changes must affect the shape of the dose-effect curve. One cannot therefore expect that a formalism which in the analysis of the dose-effect relation neglects all factors except the statistics of energy deposition will clarify the primary mechanisms of radiation action. An additional complication is that the dose-effect relation is often affected by a necessarily arbitrary choice of the scale of effect.

These general considerations might be illustrated by the concrete example of the dose-effect curve for skin damage. Such a relation needs to be established on the basis of some kind of scale which is based on increasing degrees of severity (reddening, desquamation, ulceration etc.) and the curve obviously depends on how this scale is constructed. It also depends on such factors as field size, the presence of subsequent irritations etc. and although it may be of pragmatic utility it gives little or no information to the radiation biophysicist concerned with basic mechanisms. However if two radiations of different quality are employed and one compares the ratio of doses for equal effect (RBE) as a function of dose [Rossi, 1970] one finds that a simple relation emerges that in the case of the skin seems identical for a variety of mammals [Field, 1969]. The reason for this is presumably that in the case of either radiation one is dealing with random cell destruction, and if subsequent manifestations as well as their numerical assessment are the same they are cancelled if one considers RBE rather than effect.

This approach is particularly useful if one of the radiations is of high linear energy transfer (LET). It appears well established that for neutrons having

energies of a few hundred keV cell killing is accomplished predominantly by single secondary protons. Hence the neutron dose provides in essence a linear scale (at least at small doses), and a more revealing interpretation of a graph of neutron RBE versus neutron dose is to consider it as a representation of the inefficiency of x rays as a function of effect level. It should be noted that the term "effect" need not refer to the already more complex process of cell inactivation but could denote the production of subcellular injury that leads to cell death.

These considerations lead to the following generalization: If the effect in question is reached in a series of steps between a number of states, the curve of neutron RBE versus neutron dose (for neutrons in the energy range under discussion) reflects the variation with dose of the inefficiency of x rays in inducing the first of the states in which the changes brought about by the two radiation qualities are qualitatively indistinguishable. This may be considered as the comparison state.

In the following, the assumption will be made that a wide range of effects on higher organisms is due to impairments taking place at the sub-nuclear level in the cell. These impairments will be termed *elementary lesions*. The comparison state in RBE experiments is not necessarily the elementary lesion. If an effect can be caused by injury to either of two types of cells having unequal differential sensitivity to the two radiations, the comparison state becomes, strictly speaking, the effect itself. Even when only one cell type is involved, the same complication arises if there are variations in radiosensitivity (as for example during the division cycle) that differ for neutrons and x rays. The concept of the elementary lesion if applied to RBE experiments is thus likely to be an idealization and any quantitative statements must be assumed to pertain to averages over various cell types or cell states.

The principal advantage of the concept is that it permits a formulation of the kinetics of cell inactivation in which only first and second order processes occur with the former dominant at low doses particularly for high LET radiations. Since this mechanism seems to be common to what appears to be at least the great majority of cells, elementary lesions can be invoked to explain RBE effects not because they occur in the same cell types but because they are subject to the same inactivation kinetics.

Numerous attempts have been made in the past to explain dose-effect relations obtained with ionizing radiations by the assumption of two basic mechanisms, a single-event and a multi-event action. The single-event component is dominant for densely ionizing radiations; it leads to exponential dose-effect relations and is independent of dose rate. The multi-

event component, on the other hand, causes sigmoidal dose-effect relations and it is dose-rate dependent. This distinction is common to a wide range of models applied to dose-effect relations. The numerical form in which the two components are represented varies in the different models. In general the inactivation cross-section for the single-event action is made a function of LET, restricted LET, or some related parameter of the charged particles. The functional dependence is chosen in an empirical way so that it agrees with a particular dose-effect relation or with a set of dose-effect relations. The multi-event component is either taken to be independent of the track structure – then statistics for randomly distributed ionization and multi-target equations are used – or alternatively the LET concept is used to construct multi-hit or multi-target response curves. The resulting curves contain, in general, enough parameters to fit all dose-effect relations. This is convenient, but it is also a weakness of the approach which introduces another element of uncertainty in addition to the fact that the analysis neglects all but the primary physical factors involved in the dose-effect relation. As pointed out above these difficulties are avoided by the study of dose-RBE relations instead of dose-effect relations.

A second essential point is that it will not be necessary to invoke two separate modes of radiation action; instead, it is assumed that the primary lesions in the cell depend on the local energy concentration in a way which is the same for all radiation qualities. Microdosimetric concepts can be used to analyze this dependence, and evidence will be presented which indicates that the formation of primary lesions is proportional to the square of the local energy concentration. This then leads directly to an explanation of the linear and quadratic dependence on absorbed dose, and of the ratio of the two components for different radiation qualities. The linear component reflects interaction of damage produced by one and the same particle track, while the square component is due to the interaction of lesions produced by different charged particles. The approach presented here is a formalization of arguments which have first been used by Lea [1946] and which have been extensively applied by Wolff et al. [1958] and later by Neary [1965] to the analysis of chromosome aberrations. It is also in agreement with ideas expressed by Powers, Lyman and Tobias [1968].

2. Observed RBE relations

In the introduction some of the difficulties have been mentioned which are involved in the numerical analysis of dose-effect relations, and it has been

stated that these difficulties are reduced or eliminated if one considers dose-RBE relations instead of dose-effect relations. Fig. 1 represents such relations, namely the dependence of RBE of neutrons on neutron dose for various experiments involving higher organisms.

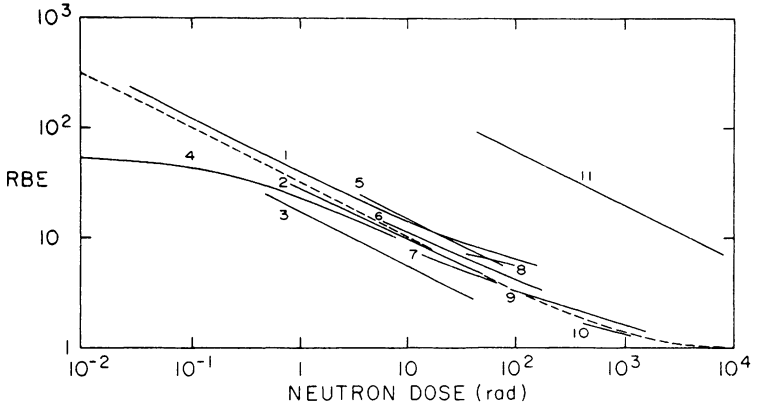


Fig. 1. Relative biological effectiveness of neutrons as a function of absorbed dose of neutrons for various biological endpoints. The dotted line corresponds to eq. (3.17). The experimental curves belong to the cases listed in table 1.

A suitable error analysis has often not been provided by the experimenter. For this reason and also because RBE values had to be obtained by interpolation between data points (no extrapolations were made) no confidence limits are given with the solid lines in fig. 1. It can however be stated that the line segments are almost certainly within the accuracy of the experiments. Some of the data in the region of larger doses suggest a slight curvature similar to that of the theoretical curve which is indicated by a dotted line and which corresponds to a formula* given in section 3. All the slopes are between $-\frac{1}{2}$ and 0; in several cases the value $-\frac{1}{2}$ is reached. In the latter instance the RBE is inversely proportional to the square root of the neutron dose.

In the case of the lens opacification in the mouse the data do not only extend over a considerable range of doses, but they have also been subjected to a statistical analysis which requires no interpolation between data points. In fig. 2 the results for 0.43 MeV neutrons are given in the form of the 95% confidence range for the RBE as function of neutron dose. The curve drawn through the confidence region will be discussed at the end of section 3.

* The theoretical curve results from eq. (3.17) with $\lambda_n = 1000$ rad.

TABLE 1

Author and number of curve in fig. 1		End point	Neutron energy	Estimate of ζ_n (rad)	Diameter $d(\mu m)$
Bateman et al. [1972]	1	Opacification of the murine lens	430 keV	150	3
	2	Opacification of the murine lens	1.8 MeV	840	2
	3	Opacification of the murine lens	14 MeV	260	3
Sparrow et al. [1972]	4	Mutations of *Tradescantia* Stamen Hairs (blue to pink)	430 keV	800	1.8
Vogel [1969]	5	Mammary neoplasm in the Sprague–Dawley rat	Fission	2200	1
Biola et al. [1971]	6	Chromosome aberrations in human lymphocytes	Fission	1300	1.4
Hall [unpublished]	7	Growth reduction of *Vicia Faba* Root, aerated	3.7 MeV	600	2
	8	Growth reduction of *Vicia Faba* Root, anoxic	3.7 MeV	2000	1.3
Field [1969]	9	Skin damage (human, rat, mouse, pig)	6 MeV	1200	1.5
Withers et al. [1970]	10	Inactivation of intestinal crypt. cells in the mouse	14	800	2
Smith et al. [1968]	11	Various effects on seeds of *Zea Mays*	Fission	400, 000	0.15

Dolphin and Purrot [1970] have given RBE values of fission neutrons as function of dose for the production of chromosome aberrations in human lymphocytes. Their data would result in a line segment in fig. 1 which is parallel to the one which represents the data by Biola et al. [1971].

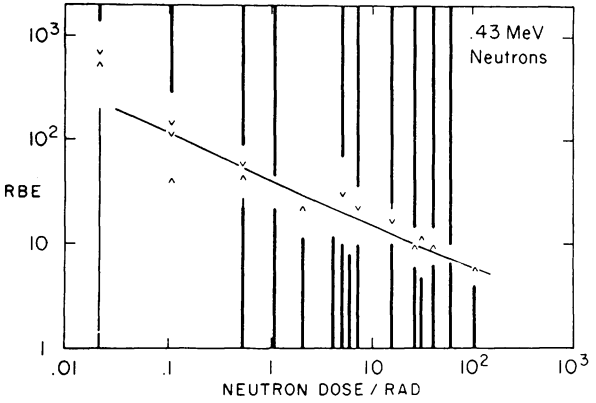


Fig. 2. RBE of 0.43 MeV neutrons relative to x rays for the induction of lens opacification in the mouse as a function of neutron dose [Bateman et al., 1972]. The solid bars indicate the ranges of RBE values which, according to the comparison of x ray and neutron doses, are excluded. Broad bars: significance exceeding 99%; narrow bars: significance exceeding 95%; arrows: non-significant differences. The solid line corresponds to eq. (3.14) with $\lambda_n = 150$ rad, $\lambda_x = 4$ rad, and a constant k which is 4 times larger for neutrons than for x rays. This curve is discussed in section 3.

RBE-dose relations obtained from cellular inactivation *in vitro* are not included. This case is discussed in section 5.5.

There is strong evidence from microdosimetric considerations [Barendsen, 1967; Rossi, 1967] that for low doses of low-energy fast neutrons the cell is very unlikely to be traversed by more than one charged particle. One can, therefore, assume that various cellular effects are produced by the passage of a single densely ionizing particle through the cell. In the range of low doses it is therefore justified to set the yield ϵ of elementary lesions proportional to absorbed dose:

$$\epsilon = k_n D_n \,. \tag{2.1}$$

The inverse relation between the RBE of neutrons and the square root of the neutron dose:

$$\frac{D_x}{D_n} = \text{RBE} = \sqrt{\lambda / D_n} \tag{2.2}$$

can be used to express D_n by the equivalent x-ray dose D_x:

$$D_n = D_x^2/\lambda \,. \tag{2.3}$$

Inserting this in eq. (2.1) one obtains:

$$\epsilon = k D_x^2 \,, \text{ with } k = k_n/\lambda \,. \tag{2.4}$$

One concludes that in the dose range where one deals with single particle action for low energy fast neutrons the primary effect is proportional to the square of the x-ray dose.

One should note that eqs. (2.1) to (2.4) are approximations valid only in a certain dose range. Figs. 1 and 2, however, make it clear that this range of validity is broad, and that one finds the same characteristic dependence for a wide spectrum of biological end points. It is, therefore, a likely hypothesis that the primary mechanisms underlying a variety of radiation-induced biological effects are related or identical. One may assume that the equations for the primary damage in the case of neutrons and x rays

$$\epsilon = k \lambda D_n \tag{2.5}$$

$$\epsilon = k D_x^2 \tag{2.6}$$

are merely approximations of the general relation:

$$\epsilon = k(\lambda D + D^2) \tag{2.7}$$

where λ depends on radiation quality and has such a small value for x rays that the linear term in D can be neglected as long as the dose is not too small, while in the case of neutrons it has such a large value that except for very large doses the quadratic term in D can be neglected. It will be seen in the next section that eq. (2.7) is indeed the dose dependence for the elementary lesions, and it will be the object of the following discussion to clarify the meaning of the quantity λ which has the dimension of a dose. Differences in radiation quality do not result in qualitatively different electronic or molecular disturbances, the difference instead is one of the microscopic patterns and relative positions in which these disturbances are produced. One must therefore seek the explanation for different dose relations observed for different radiations in a dependence of the yield of elementary lesions on the local concentration of absorbed energy or, in microdosimetric terminology, the specific energy z. The next section will be devoted to an analysis of this problem. It will be shown that eqs. (2.5) and (2.6) imply that the yield of elementary lesions is proportional to the square of the specific

energy in domains or *sites* whose diameter in most cases exceeds 1 μm, and that λ can be considered as an average increment of specific energy z produced when a single charged particle traverses such a site.

3. The quadratic dependence of effect on specific energy

In this section the formulae for the dose dependence of RBE and the method for the derivation of the interaction distances between absorption events will be given. The formal analysis in this section will be followed in section 4 by a discussion of the possible interpretations and by an illustration in terms of one specific effect, namely the production of chromosome aberrations for which the quadratic dependence on the local energy concentration has been established earlier [see e.g. Lea, 1946; Wolff et al., 1958; Neary, 1965; Savage, 1970].

A dose-effect relation is never a precise reflection of the relation between energy absorbed in a cell and the biological effect. At a certain value of absorbed dose the amount of energy actually absorbed in a cell or its sensitive structure varies. Microdosimetry is concerned with these statistical fluctuations. If one considers a certain microscopic region; then the actual energy deposition in this region at a given value of absorbed dose can only be described by a probability distribution. The quantity specific energy, z, is defined as absorbed energy divided by the mass of the reference volume [ICRU, 1971]. It is the random variable which corresponds to absorbed dose D; the mean value of z is equal to D, but the actual values of z vary around D. The variations of z are described by the probability distribution $f(z;D)$. The probability that at absorbed dose D the specific energy has a value between z and $z+\mathrm{d}z$ is $f(z;D)\mathrm{d}z$. The function $f(z;D)$ depends on the shape and size of the reference volume and on the radiation quality. For smallest volumes and for the most densely ionizing radiations the fluctuations are greatest. For large volumes and large doses of sparsely ionizing radiations most values of z are near to D.

Ideally it would be desirable to obtain the yield of elementary lesions as a function of the value z of specific energy in the sensitive sites of the cell instead of studying only its dependence on absorbed dose which always represents a wide variation of z values. With the possible exception of certain microbeam techniques there are at present no experimental methods to observe this more direct relation between cellular damage and z. But the z-dependence can in principle be derived from the dose dependence if the

microdosimetric distributions $f(z;D)$ are known*. Assume that the relation between the yield of elementary lesions in the critical sites and the specific energy z is $\epsilon(z)$, then the dependence on dose is:

$$\epsilon(D) = \int_0^\infty \epsilon(z) f(z;D) \mathrm{d}z \,. \tag{3.1}$$

The function $f(z;D)$ is known from microdosimetric measurements [see Rossi, 1967]. Therefore, if the dose dependence $\epsilon(D)$ is known, one can in principle invert the integral equation and determine $\epsilon(z)$. In the present context it is sufficient to point out that there is a unique relation between $\epsilon(D)$ and $\epsilon(z)$, and an actual numerical technique to derive $\epsilon(z)$ from $\epsilon(D)$ need not be discussed.

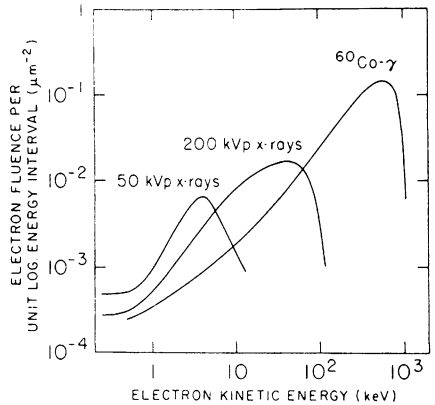


Fig. 3. Distribution of electron fluence in kinetic energy E per rad of absorbed dose for x rays and γ rays. The density $E\phi_E$ relative to the logarithmic scale of E is given. The curves are derived from data given in ICRU report 16 [1970].

The microscopic fluctuations of energy deposition and therefore the functions $f(z;D)$ are significantly different for low and medium energy x rays on the one hand and γ rays and fast electrons on the other hand. The difference is due to the fact that the x rays produce a higher fluence of low energy electrons at a given dose. This is illustrated in fig. 3 where the electron fluence per rad and per unit logarithmic energy interval is given for x rays and γ rays. The difference can also be seen directly from the microdosimetric spectra. As an example the distributions of z in a sphere of 1 μm diameter and at a dose of 30 rad are given for x rays and Co-γ radiation in fig. 4. Because for most experimental end points the dose-effect relation differs only slightly

* For a definition of microdosimetric quantities see Appendix 1.

when γ rays are applied instead of x rays one concludes that the fluctuations of energy deposition are irrelevant. This means that the sensitive sites in the cell must be large enough that within the dose range of interest the statistical fluctuations of z can be neglected for sparsely ionizing radiations. The specific energy z can then be set equal to D, and one concludes from the quadratic dependence on absorbed dose (eq. (2.6)) that the dependence on z is also quadratic:

$$\epsilon(z) = k z^2 . \tag{3.2}$$

This quadratic dependence indicates that the elementary lesions are of dual nature, i.e. that they are the result of the interaction of two *sublesions* whose production is independent of energy concentration (and thus simply pro-

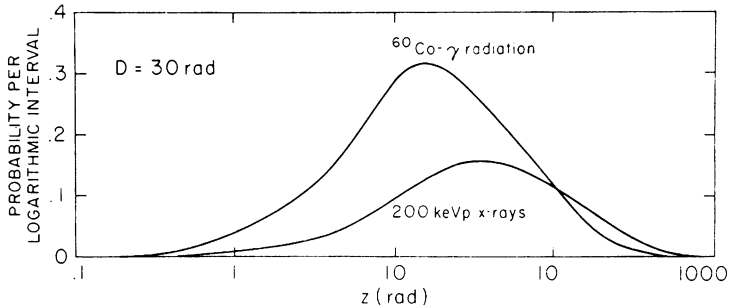


Fig. 4. Distributions $f(z;D)$ of specific energy z in a spherical tissue region of 1 μm diameter at 30 rad of 200 keVp x rays and at 30 rad of ^{60}Co-γ rays. The curves are based on data given by Hug and Kellerer [1966].

portional to absorbed dose) or, more generally speaking, that they are the result of a second order reaction.

The relation (3.1) between $\epsilon(D)$ and $\epsilon(z)$ depends on the distributions $f(z;D)$ of specific energy z and thereby on the size of the sensitive volume. Before actual numerical relations will be discussed, the general form of the effect dependence on dose will be discussed which results if one inserts eq. (3.2) into eq. (3.1).

From eq. (3.1) and (3.2) one obtains:

$$\epsilon(D) = \int_0^\infty k z^2 f(z;D)\mathrm{d}z = k\overline{z^2}(D) . \tag{3.3}$$

The expectation value $\overline{z^2}(D)$ of the square of z at absorbed dose D is

$$\overline{z^2}(D) = \zeta D + D^2 \tag{3.4}$$

where ζ is the "energy mean" of the increments of specific energy z produced in single events. It is defined in terms of the single event spectrum $f_1(z)$ (see Appendix 1) which determines the relative frequency of energy deposition events producing certain increments of z:

$$\zeta = \int_0^\infty z^2 f_1(z)\mathrm{d}z \Big/ \int_0^\infty z f_1(z)\mathrm{d}z \,. \tag{3.5}$$

This quantity was formerly designated by $\bar{z}_D$ [Kellerer and Rossi, 1969]. The shorter symbol ζ has been adopted here because of the prominence of this quantity in all applications of microdosimetry to radiation biology. Eq. (3.4) is a fundamental relation. Its derivation requires some formal mathematical considerations; they are given in Appendix 1. According to eqs. (3.3) and (3.4) one has:

$$\epsilon(D) = k(\zeta D + D^2) \,. \tag{3.6}$$

This is in agreement with the general relation (2.7) which has been discussed at the end of section 2. It identifies the parameter λ with a quantity which has direct microdosimetric meaning, namely with the average increment ζ of specific energy produced in the critical site by a single charged particle. The meaning of the equation becomes more apparent if one writes it in the form:

$$\epsilon(D) = k(\zeta + D)D \,. \tag{3.7}$$

The yield $\epsilon(D)$ of elementary lesions is proportional to the product of the number of sublesions and the mean energy concentration around the sublesions. The number of sublesions is proportional to D and the mean energy concentration around the individual sublesions is proportional to $(\zeta + D)$. Within the bracket ζ represents the energy concentration produced by the same particle track (*intratrack action*), D represents the contribution from other particle tracks (*intertrack action*). This interpretation will be discussed in more detail in section 4.

One concludes that even sparsely ionizing radiations should exhibit an initial linear component in the dose dependence. But because the value ζ is much smaller than for densely ionizing radiations the linear component is not evident except at very small doses. Fig. 5 gives the quantity ζ for different radiation qualities and for different sizes of the reference volume; the values are a compilation of experimental as well as theoretical data [Biavati et al., 1965; Biavati and Boer, 1966; Hug and Kellerer, 1966; Braby and Ellett, 1971]. As a rough rule one concludes from this figure that the value ζ for

430 keV neutrons is about 30 to 50 times larger than that for sparsely ionizing radiations.

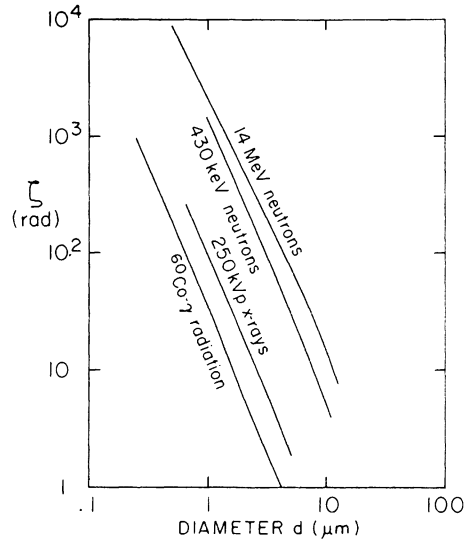


Fig. 5. Energy mean, ζ, of specific energy produced in an event as a function of the diameter, d, of the tissue sphere.

It should be stated at this point that λ can be larger than ζ if there is a linear component in the dependence of the primary damage on specific energy z. Eq. (3.2) would then take the form:

$$\epsilon(z) = k(\lambda_0 z + z^2) \tag{3.8}$$

and one obtains the modified dose dependence:

$$\epsilon(D) = k((\zeta + \lambda_0)D + D^2)\,. \tag{3.9}$$

The presence of such an additional term could not be detected at doses much larger than λ_0. Strictly speaking one can therefore not equate λ with ζ, but one must state that ζ is a minimum value of λ. At very small doses the RBE should approach the value:

$$\mathrm{RBE} = \frac{\zeta_n + \lambda_0}{\zeta_x + \lambda_0} \leqslant \frac{\zeta_n}{\zeta_x}\,. \tag{3.10}$$

Only on the basis of experimental data at small doses can one decide whether λ is actually equal to ζ. As discussed at the end of this section the

ratio λ_n/λ_x reaches the value of roughly 50 for at least two experimental endpoints, namely opacification of the murine lens and the induction of a specific mutation in *Tradescantia*, so that λ_0 is to be neglected. In the following discussion it will accordingly be assumed that the dependence of primary damage on z is purely quadratic. For certain test systems, and isolated mammalian cells in culture may be an example, the evidence is less clear; this point will be taken up in section 5.5.

By comparing the square component in the effect relation for sparsely ionizing radiation with the linear component for neutrons one can derive the value of ζ for neutrons and thereby deduce a size of the critical region of interest. Before this will be quantitatively described it may be useful to make some remarks on the interpretation of the quadratic dependence of elementary lesions on specific energy.

For an understanding of eq. (3.2) and its result (3.6) one may assume that one deals with critical sites in the cell which have the diameter d. The site may be interpreted as a region which comprises numerous sensitive loci in which the sublesions are produced which can then interact to produce the dual elementary lesions. More formally one may state that within this region radiation induces a reaction of second order, i.e. a reaction with a yield proportional to the square of the energy deposition. Alternatively one may interpret the quadratic dependence without invoking geometrically defined sensitive sites. One may instead merely postulate that the primary radiation-induced changes are of second order, that there is a characteristic (or mean effective) interaction distance, d, and that the effectiveness of an ionization increases proportionally to the number of other ionizations within a region of diameter d around it. In the next section a more detailed discussion of the different interpretations of the quadratic dependence of the effect on the local energy concentration will be given; from this discussion the meaning of the characteristic distance d as site diameter or as interaction distance may become clearer. At the present stage one can proceed with the numerical analysis of experimental data without restriction to any particular interpretations. Because the following formulae for the dose dependence of RBE are valid regardless whether one identifies the quantity λ in eq. (2.7) with ζ, the symbols λ_x and λ_n will be used instead of ζ_x and ζ_n. One may however note that within the present context one can substitute λ_x and λ_n by the dose mean event size ζ_x and ζ_n for x rays and neutrons. If the x-ray dose is designated by D_x one has the following dose dependence of the primary effect:

$$\epsilon(D_x) = k(\lambda_x D_x + D_x^2)\,. \tag{3.11}$$

For neutrons one obtains the analogous equation:

$$\epsilon(D_n) = k(\lambda_n D_n + D_n^2) . \tag{3.12}$$

The iso-effect relation is therefore:

$$k(\lambda_x D_x + D_x^2) = k(\lambda_n D_n + D_n^2) \tag{3.13}$$

and from this one obtains the following equation for the x-ray dose D_x equivalent to the neutron dose D_n:

$$D_x = \frac{2(\lambda_n + D_n) D_n}{\lambda_x + \{\lambda_x^2 + 4(\lambda_n + D_n) D_n\}^{\frac{1}{2}}} . \tag{3.14}$$

And the relative biological effectiveness, $\mathrm{RBE} = D_x/D_n$, as a function of neutron dose is:

$$\mathrm{RBE} = \frac{2(\lambda_n + D)}{\lambda_x + \{\lambda_x^2 + 4(\lambda_n + D_n) D_n\}^{\frac{1}{2}}} . \tag{3.15}$$

Relations (3.14) and (3.15) are depicted in figs. 6 and 7 for various ratios of λ_n and λ_x.

Fig. 7 corresponds to the plot in fig. 1. According to the formula derived

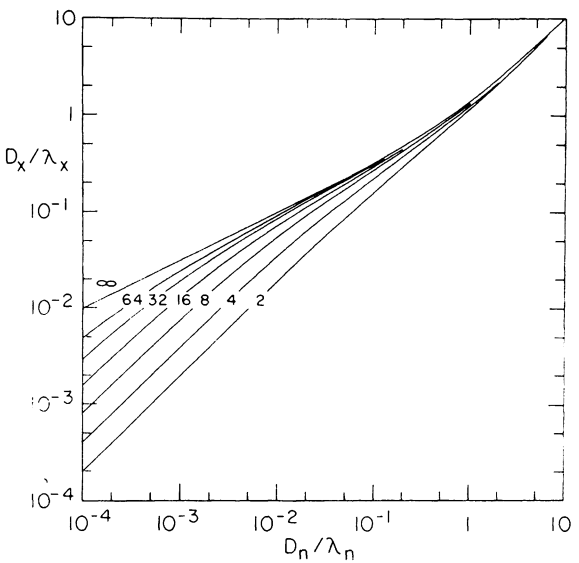


Fig. 6. Relation between equivalent x-ray doses, D_x, and neutron doses, D_n, according to eq. (3.14). The doses are given in multiples of the quantities λ_x and λ_n; the parameter of the curves is the ratio of λ_n to the corresponding quantity λ_x of the reference radiation.

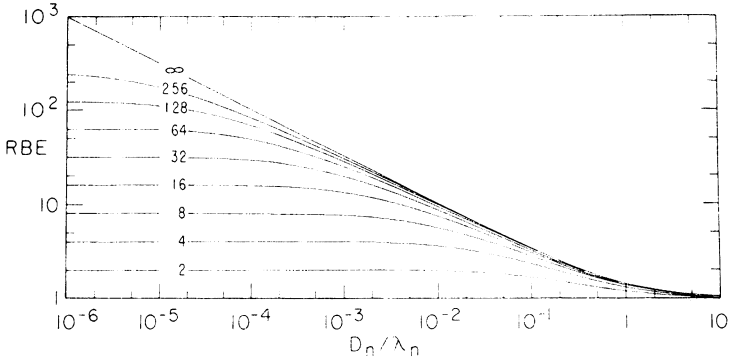


Fig. 7. Relation between RBE and dose according to eq. (3.15). The dose is given as multiple of the quantity λ_n; the parameter of the curves is the ratio of λ_n to the corresponding quantity λ_x of the reference radiation.

here, RBE is constant at very low doses and has the value λ_n/λ_x there. In most of the experimental data no plateau at low doses is seen. That means that within the range of experimental observations λ_x can be neglected. Eqs. (3.14) and (3.15) then simplify to

$$D_x = \{(\lambda_n + D_n) D_n\}^{\frac{1}{2}} \tag{3.16}$$

and

$$\mathrm{RBE} = (1 + \lambda_n/D_n)^{\frac{1}{2}} . \tag{3.17}$$

This simplified relation corresponds to the curve for $\lambda_n/\lambda_x = \infty$, i.e. to the top curve in fig. 7. It also corresponds to the theoretical curve in fig. 1. One may note that the asymptote to this curve intersects the abscissa, RBE = 1, at the value $D_n = \lambda_n$. One can further use the relation:

$$\lambda_n = \mathrm{RBE}^2 D_n = D_x^2/D_n \tag{3.18}$$

which holds for all points on this straight line. Identifying λ_n with ζ_n one obtains the relation:

$$\mathrm{RBE} = (\zeta_n/D_n)^{\frac{1}{2}} \tag{3.19}$$

or:

$$\zeta_n = \mathrm{RBE}^2 D_n \tag{3.20}$$

for this part of the RBE relation. By using this approximation or by fitting the various experimental data in fig. 1 to the curves in fig. 7 one obtains estimates of the values ζ_n and thereby also estimates of the diameter, or interaction distance, d. Table 1 gives a compilation of estimated values ζ_n and of the corresponding diameters, d, which are obtained for the various experiments.

The results all indicate interaction distances or site diameters of at least 1 μm. The only exception are the data obtained on dry corn seeds [Smith et al., 1968] where the estimated value of d is 0.2 μm. In the presence of a linear component $\lambda_0 z$ in the z-dependence of the primary damage the values of ζ would have to be somewhat smaller than the observed value λ. This would lead to somewhat larger site diameters.

On the basis of fig. 5 and the values from table 1, one can derive the values ζ_x which belong to given values of ζ_n and one can thereby predict minimum values for the linear term of the dose effect relation for x rays or γ rays. For doses below ζ_x the linear term must exceed the quadratic term even for these sparsely ionizing radiations.

These considerations must however be used with caution because the constant k in eq. (3.2) to (3.9) has not necessarily the same value for all radiation qualities. One may expect that the submicroscopic distribution of energy deposition within the sensitive site is not completely irrelevant and that this influences the coefficient k. If a given amount of energy is homogeneously spread over a critical site of a few micrometer diameter, it may be less effective than if it is deposited in this site by a short, densely ionizing particle track in a submicroscopic concentration. This would result in an increase of the value of the constant k. The RBE data for lens opacification given in fig. 2 indicate such an increase of the constant k. If one attempts to fit one out of the series of curves in fig. 7 to the confidence range derived for the lens opacification studies represented in fig. 2 one obtains no full agreement. One can ask for a curve according to eq. (3.15) which most nearly fits into the confidence region; this curve is not completely confined within the 95% confidence ranges. If however k depends on radiation quality the RBE curves are shifted vertically and under this condition one can achieve a complete fit. The solid curve drawn in fig. 2 corresponds to the assumption that for neutrons k is four times as large as for x rays. To achieve the fit one must further assume that in eq. (3.15) $\lambda_n = 150$ rad while the corresponding quantity λ_x is 5 rad or less.

The diameter of d of the site given in table 1 for this particular experiment is derived from the value $\lambda_n = 150$ rad. If one were to base the analysis on the unmodified eq. (3.15) one would obtain the larger value $\lambda_n = 1900$ rad and a site diameter of roughly 1 μm. The reason that a dependence of the constant k on radiation quality may occur in the opacification studies may be due to the fact that the lens is a poorly oxygenated tissue [Bateman et al., 1972; see also discussion of the oxygen effect in section 5.3].

On the basis of the presently available RBE data one can probably make

no definite statement on the possible dependence of the constant k on radiation quality in various experimental systems and under varying experimental conditions. In all cases except the lens opacification studies with 430 keV neutrons no dependence of k on radiation quality has been assumed. The diameters d in table 1 may therefore be somewhat smaller than the actual values of the site diameters or interaction distances of elementary lesions.

One should finally note that the opposite effect, namely a decrease of k in the case of very densely ionizing radiation is possible, because the effectiveness of a given energy deposition decreases if it occurs at too high a local concentration (see discussion of the saturation effect in section 5).

These modifying factors make it likely that deviations from the theoretical relations will be found in the range of high doses. Such deviations must also be expected because sensitivity variations within an irradiated population express themselves most strongly at large doses where only the more resistant fraction of the population survives. The experimental evidence supporting the quadratic dependence of elementary lesions on specific energy is strongest in the region of smallest doses and we are less certain of the validity of extensions of our considerations to the region of higher doses where the RBE decreases less slowly than the inverse square root of the neutron dose and finally reaches a plateau. It is however of interest to note that a recent analysis of T. Alper [1972] which is concerned with the dependence of RBE on neutron dose at large doses yields a formal relation which agrees with the high dose region of the curves in fig. 6 [see Kellerer and Rossi, 1972].

4. Intratrack and intertrack effect

In the preceding section results have been derived which follow from the quadratic dependence of the yield of elementary lesions on the local energy density in the cell. Because the considerations have been general in nature and somewhat abstract, it may be useful to retrace the argument, illustrated with a specific example, and to derive the formal relations in the somewhat more familiar LET concept. This allows only an approximate treatment, but it will facilitate an understanding of the geometrical conditions for interactions of sublesions produced within one and the same charged particle track and sublesions produced by different charged particle tracks. The LET-concept would be entirely valid if energy were transferred to the cell by charged particles in straight tracks with no radial extension and with con-

stant rate. In practice there are no radiations for which these conditions are even approximately fulfilled, and this is the reason that one must use microdosimetric quantities instead of LET. In many cases where one deals with regions which are not too small the validity of the LET concept is however satisfactory. Moreover one may assume the hypothetical case of a radiation to which the conditions mentioned above apply, and then use this hypothetical case to explain and clarify the structure of the arguments. For a treatment which is quantitatively valid one can later substitute microdosimetric quantities for the quantities expressed in LET. The form of the equations then changes back to that given in the preceding section.

It has been shown that the relative biological effectiveness of neutron irradiation compared to x rays can be explained on the basis of the assumption that various radiation effects are due to cellular lesions whose yield is proportional to the square of the energy absorbed in critical sites in the cell. This conclusion is in formal agreement with treatments which have earlier been applied in the analysis of chromosome aberrations [see for example Lea, 1946; Wolff, 1954; Wolff et al., 1958; Conger and Johnston, 1956; Neary, 1965]. According to these considerations the yield of chromosome breaks is proportional to dose and independent of radiation quality while the yield of chromosomal exchanges is proportional to the product of the number of breaks and their spatial concentration. This results in a dependence of the number of exchanges on the square of the dose for x rays and a linear relation for neutrons. The preceding analysis has indicated that the same formal relations apply to elementary lesions underlying a wide range of observed effects. This does not necessarily imply that the underlying cellular lesions are exclusively and in all cases chromosome aberrations, but it implies that the lesions in the cell follow the same kinetics as chromosome exchanges and are of dual nature. One can, therefore, use the production of chromosome aberrations by ionizing radiation and the possible models to describe this process as an illustration for the more general mechanisms which are responsible for other radiation effects which follow the same kinetics. In the following discussion the notions of sublesions and of chromosome breaks will therefore be used interchangeably. Sublesions are assumed to be proportional to z. One may prefer to use Platzman's [1967] more general term *activation event* instead of the term sublesion. The term *sublesion* is used in the present context because in cellular radiation effects one obtains such large interaction distances (~ 1 μm) and such long durations of possible interaction (minutes to hours) that it is strongly indicated that the interaction occurs at the biological level. In similar ways the terms lesions, dual lesions,

or chromosome aberrations will be used interchangeably; chromosome aberrations produced by the interaction of chromosome breaks are merely specific illustrations of one type of radiation effect for which the quadratic dependence on local energy concentration holds.

It may be noted that the following section is of relevance also if one is merely concerned with chromosomal effects. It offers a formalization of arguments developed on the basis of various models for the production of chromosome exchanges. These models have frequently been discussed and used in a semi-quantitative form in order to derive interaction (rejoining) distances, and a compilation and comparison of formulae corresponding to the different approaches is therefore of practical value.

4.1. SITE MODEL AND DISTANCE MODEL

The example of the production of chromosome aberrations may serve as an illustration of two alternative interpretations of the mechanism of interaction between sublesions produced in the cell. One can either assume that the interaction is determined by the geometry of sensitive sites in the cell, or one can assume that the interaction is determined by the diffusion and interaction of radiation products within the cell or by the interaction of damaged subcellular structures over certain distances.

In the present example the sublesions can be identified with chromosome breaks. One may assume that the number of breaks is proportional to dose and independent of radiation quality [see Lea, 1946; Giles, 1954; Neary, 1965]. According to estimates made by Lea [1946] and by Wolff et al. [1958] a large number of chromosome breaks are produced for each observed aberration. One may, therefore, treat the number of radiation-induced chromosome breaks, i.e. the number of sublesions, as a continuous variable and set it proportional to the energy deposited in the sensitive region of the cell. It can be further assumed that breaks are produced throughout a certain part of the cell nucleus in spatial patterns which are determined by the distribution of the absorbed energy. It can then be postulated that the probability for joining of two breaks is a function of their distance, or, in more general terms, that the probability for the formation of a primary lesion is a function of the distance of the sublesions. To a first approximation one may assume that this probability is constant up to a certain distance and zero if the two sublesions are separated by a larger distance. This approximation has, for example, been invoked by Lea [1946] but in section 4.3 the equations will be given in the general form which holds for an arbitrary functional

dependence of the interaction probability on distance. In the following this situation will be designated by the term *distance model.* Wolff et al. [1958] choose a somewhat different model insofar as they postulate that the aberrations cannot occur randomly throughout the nucleus, but that there are only a few potential sites where two chromosomes are close enough that the production of two breaks can lead to an exchange. Two sublesions must then be formed within a site in order to form a dual lesion. This assumption will in the following be designated as *site model.* Both models will be treated, and it will be shown that they are both subject to essentially the same analysis, and that this analysis leads to equations equivalent to those given in section 3. From the ratio of the linear and the square component in the dose effect relation one obtains a characteristic distance of interaction of sublesions. This distance can either be understood as the diameter of sensitive sites which are subject to dual damage or it can be interpreted as the effective diameter of the sphere of potential interaction around an ionization or a sublesion produced by this ionization. In section 4.5 it will be pointed out that these interpretations are not mutually exclusive and that in reality one may be dealing with a mixed situation. It will further be seen that the characteristic interaction distance is meaningful also in case the sensitive structures in the cell are distributed in thin layers, for example near the nuclear membrane.

4.2. DERIVATION OF THE SITE DIAMETER

A sublesion in the critical site can interact either with sublesions formed within the site by the same particle track, i.e. by a charged particle and/or its delta rays, or it can interact with sublesions produced independently by another charged particle. In the first case one can talk about *intratrack* interaction and in the second case about *intertrack* interaction*. It should be noted that the word interaction is used in a general sense. One may speak of the interaction of ionizations or of activation events rather than of the interaction of sublesions and one must then keep in mind that such interaction need not occur at the level of primary molecular disturbances; one may instead be dealing with the interaction of free radicals or of structural changes in the cell. In fact it is one of the main results of the analysis presented here that the interaction distances are so large that the latter possibility has to be assumed. In the example of chromosome damage intratrack interaction is the joining of two breaks produced by the same charged particle in a site, while intertrack interaction is the joining of two breaks produced by two

* Frequently the terms one-track action and two-track action are used for these processes.

independent charged particles in the site. The probabilities for the two mechanisms as a function of dose are derived in Appendix 2. One obtains the following relation* for the yield of aberrations:

$$\epsilon(D) = k\left(22.9\,\frac{\bar{L}_D}{d^2}\,D + D^2\right) \tag{4.1}$$

where the linear term represents the lesions formed within the same particle track and the quadratic term represents the lesions formed due to the interaction of different particle tracks. $\bar{L}_D$ is the dose-average LET of the radiation field. In this equation it is assumed that only a small fraction of all potential sites is affected, i.e. the saturation effect [see Wolff et al., 1958; Savage and Papworth, 1969] is not considered.

Eq. (4.1) is equivalent to the relation (3.6) given in section 3. This can be derived on the basis of a relation for ζ which approximates the microdosimetric quantity in terms of the LET concept (see Appendix 1):

$$\zeta = 22.9\,\frac{\bar{L}_D}{d^2}\,. \tag{4.2}$$

If one treats the site model within the approximation of the LET-concept one finds therefore the same interpretation of the experimentally observable formal quantity λ (see eq. (2.2) or (2.7)) which has been obtained by the more exact treatment where λ had been equated with the microdosimetric quantity ζ:

$$\lambda = 22.9\,\frac{\bar{L}_D}{d^2}\,. \tag{4.3}$$

This relation can be used to determine the site diameter d:

$$d = 4.8(\bar{L}_D/\lambda)^{\frac{1}{2}}\,. \tag{4.4}$$

λ is equal to the dose where the linear and the quadratic component in the effect relation are just equal.

There are different ways in which one can obtain λ from experimental data and thereby infer the site diameter d. The most direct way would be to fit a dose-effect relation obtained with sparsely ionizing radiation to eq. (2.7). This approach is, however, limited for several reasons. With few exceptions, such as the results depicted in fig. 8, it has not been possible to obtain a dose-

* The numerical constants in (4.1) and the following equations reflect the choice of units. $\bar{L}_D$ is measured in keV/μm, and D as well as ζ are in rad. The same units are used throughout this chapter.

effect relation which reveals both the linear and the quadratic component. Furthermore, if one deals with effects other than chromosome aberrations the functional dependence between the observed effect and the elementary lesions may not be simple proportionality. Both reasons make it necessary to analyse dose-RBE relations instead of dose-effect relations. It is nevertheless useful to consider an example in which the direct evaluation of the dose-effect curve is possible.

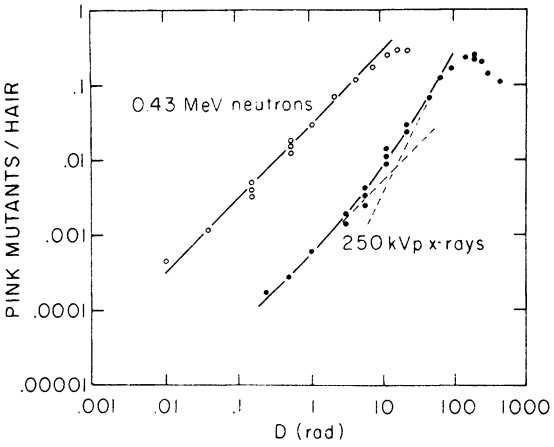


Fig. 8. Induction of pink mutant cells in the stamen hairs of *Tradescantia* by x rays and 430 keV neutrons [Sparrow et al., 1972]. The spontaneous rate is subtracted. The solid line for the neutron irradiation corresponds to a linear dose-effect relation; the solid line for x rays corresponds to the linear-quadratic dose effect relation according to eq. (4.5). The constant λ_x is equal to 16 rad; at this dose the linear and the quadratic component (indicated by broken lines) are equal.

Fig. 8 represents the production of pink mutants in *Tradescantia* [Sparrow et al., 1972] by neutrons and x rays. The corresponding dose-RBE relation in fig. 1 has been derived from these two dose-effect relations. In this particular case one can however base the analysis directly on the dose-effect curve for x rays by fitting this curve to the linear quadratic equation:

$$\epsilon(D) = k(\lambda D + D^2)\,. \tag{4.5}$$

The best fit is obtained with the value $\lambda = 16$ rad and the solid line in fig. 8 represents the resulting curve. λ is equal to the dose where the linear and quadratic components are equal (intersection of the two broken lines).

According to section 3, the value λ is equal to the energy mean event size ζ in the critical sites; inserting the value 16 rad in fig. 5 one obtains the site

diameter of approximately 2 μm. This is nearly equal to the value 1.8 μm obtained from the analysis of the neutron RBE (see table 1). If on the other hand one wants to use eq. (4.4), one needs the dose average $\bar{L}_D$ for x rays. This value depends strongly on the choice of the cut-off value of the delta ray energy (see Appendix 1). Due to the uncertainty of this choice but also due to the fact that LET does not account for energy straggling along the electron tracks eq. (4.2) may not be fulfilled. This can lead to an inaccurate determination of site diameters. The error is however modest because the site diameter varies only slowly with $\bar{L}_D$. One may estimate that the value $\bar{L}_D$ for a cut-off energy of about 5 keV and for 250 kV x rays lies between 1 and 3 keV/μm. Entering these values in eq. (4.4) one concludes that the site diameter lies between 1.2 and 2.1 μm, and this is consistent with the more accurate value determined on the basis of ζ.

Frequently it is not possible to determine the linear component in a dose effect curve for x rays. If at the dose D the reaction is predominantly quadratic, one can however conclude that λ is smaller than D and this permits the determination of a lower limit of the site diameter d:

$$d > 4.8\,(\bar{L}_D/D)^{\frac{1}{2}}\,.$$

Whenever one has data both for x rays and neutrons one can obtain λ from the comparison of the two radiation qualities. The simplest possibility is to determine the effect relation for densely ionizing radiations, such as neutrons, in the range where one need only consider the linear component of the primary damage, and also determine the effect relation for sparsely ionizing radiation in the range where the quadratic component is dominant. One then has according to eq. (3.18):

$$\lambda_n = \mathrm{RBE}^2\, D_n = D_x^2/D_n \tag{4.6}$$

and if one inserts this in eq. (4.4) one obtains the site diameter:

$$d = 4.8\left(\frac{\bar{L}_D}{\mathrm{RBE}\; D_x}\right)^{\frac{1}{2}} = 4.8\,\frac{(\bar{L}_D D_n)^{\frac{1}{2}}}{D_x} \tag{4.7}$$

D_n, $\bar{L}_D$, and RBE are dose, dose average LET, and RBE of the densely ionizing radiation. D_x is the dose of the sparsely ionizing radiation.

One can again use the data in fig. 8 as an example. At the effect level 0.05 the response to x rays is nearly quadratic, the response to neutrons linear, D_n is equal to 1.8 rad, D_x equal to 35 rad, and with the LET average 80 keV/μm for the neutron radiation one obtains the site diameter 1.9 μm which is also in close agreement with the value in table 1.

Finally whenever it is not possible to neglect the square component for the densely ionizing radiation and the linear component for the sparsely ionizing radiation, one can determine the value λ_n by fitting the RBE-relation to one of the curves in fig. 7. The diameter d is then obtained by inserting the resulting value λ_n in eq. (4.4). The more exact microdosimetric method is to determine d by entering λ_n in fig. 5; this method has been used in section 3. But in principle both methods are equivalent, and in view of the limited accuracy of the experimental data the approximate analysis in terms of LET is often sufficient.

4.3. DETERMINATION OF THE INTERACTION DISTANCE

The analysis in the preceding section has been concerned with the site model, i.e. with the situation where one deals with one or more geometrically distinct sensitive sites which are affected with a probability proportional to the square of the energy concentration. The interpretation of the quadratic dependence of the yield of elementary lesions on local energy density is, however, not restricted to this special case, and one can show that one obtains nearly the same relations for the distance model, i.e. if it is assumed that elementary lesions are formed throughout the cell nucleus or a part of it and that these lesions result from sublesions interacting with a probability that depends on their separation. In the example of the chromosome aberrations this corresponds to the postulate that aberrations can be formed throughout the nucleus of the cell whenever breaks are produced in sufficient proximity.

Assume that the probability for a sublesion to interact with another sublesion at a distance x is $\rho(x)$. In the simple approximation one may postulate a sphere of potential interaction, i.e. one may assume that the probability $\rho(x)$ is constant up to $x=h$ and that it is zero for larger values of x. The equations will, however, be given for an arbitrary function $\rho(x)$. As in section 4.2 the specific case of the production of chromosome aberrations can be used as illustration. In this example the function $\rho(x)$ is the probability for two breaks to join when their distance is x. The yield of elementary lesions produced within the same track and those due to the interaction of different particle tracks are calculated in Appendix 3. One obtains the following equation:

$$\epsilon(D) = k\left(22.9\,\frac{\bar{L}_D}{\Delta^2}\,D + D^2\right) \tag{4.8}$$

where the term Δ is defined by:

$$\Delta^2 = 9 \int_0^\infty x^2 \rho(x) \mathrm{d}x \Big/ \int_0^\infty \rho(x) \mathrm{d}x \tag{4.9}$$

and can be considered as an effective diameter of the region of interaction around a sublesion. The numerical coefficient in this definition has been chosen so that Δ is the equivalent of the diameter d in formula (4.1) which holds for the site model. If one chooses the distance model and wants to derive the interaction distance, one can therefore use the same approach which has been discussed in section 4.2 (see eqs. (4.4) to (4.7)). The only difference is that the resulting value d is not interpreted as the diameter of the site, but instead as an effective diameter of the region of potential interaction around a sublesion, or chromosome break. If one assumes a specific analytical expression for the interaction probability $\rho(x)$ as a function of distance, one can use the experimentally determined value Δ to specify the numerical parameter involved in the function. The simplest model which has been chosen by Lea [1946] and has later been invoked by various other authors is that of an interaction probability which is constant up to a distance h and zero for larger distances:

$$\rho(x) = \begin{cases} \rho & \text{for } x \leqslant h \\ 0 & \text{for } x \geqslant h \end{cases}. \tag{4.10}$$

In this case one has

$$\Delta^2 = 9 \int_0^h x^2 \mathrm{d}x \Big/ \int_0^h \mathrm{d}x = 3\, h^2 \tag{4.11}$$

and therefore:

$$h = 0.58\, \Delta\,. \tag{4.12}$$

This means that if in the site model one derives the diameter d, then this corresponds to a maximum interaction distance of about $0.6\, d$ in the distance model. One can rewrite eq. (4.8) for this special assumption of a constant interaction probability up to distance h and has:

$$\epsilon(D) = k \left(7.65 \frac{\bar{L}_D}{h^2} D + D^2 \right). \tag{4.13}$$

This is the formula which corresponds to the semiquantitative arguments given by Lea [1946].

The essential result of this and the preceding section is that regardless of the particular model used one can deduce a distance which can either be interpreted as a diameter of sensitive sites in the cell which are subject to

dual lesions or as an interaction distance between ionizations or sublesions produced by ionizations. The meaning of this quantity which is derived from the ratio of the quadratic to the linear component, either for one radiation quality or for two different radiation qualities, is therefore not restricted to a particular model.

In the site model as well as the distance model one obtains equations which are equivalent to the more accurate microdosimetric relation expressed by eq. (3.6).

4.4. SENSITIVE SITES AND GROSS SENSITIVE VOLUME

The concept of a site or of the region of interaction of sublesions must be distinguished from that of the overall sensitive region in the cell. For the latter one may use the expression *gross sensitive volume* [Rossi, 1964]. One can formally define this as the smallest convex region in the cell which contains all the sensitive sites relevant to the effect which is being studied. In other words, the gross sensitive volume is a region such that energy deposition outside of it is irrelevant to the effect. According to this definition the total volume of the sensitive sites may be smaller than the gross sensitive volume. This would be the case if the sites were separated regions in the cell nucleus. In the same way the combined cross-section of the sites could be smaller than the cross-section of the gross sensitive volume. Experiments with α-particles [Barendsen, 1967] have resulted in cellular inactivation cross-sections which are approximately equal to the cross-section of the cell nucleus. One concludes from this that the nucleus is the gross sensitive volume and that the combined cross-section of the sites which are relevant to loss of proliferative ability is not smaller than the cross-section of the nucleus which is approximately 40 μm^2. If one assumes a site cross-section of roughly 3 μm^2, corresponding to a site diameter of 2 μm, one concludes that the nucleus must contain more than 15 sites. One could object that the measured cross-section is larger than the actual combined cross-section of the sites because sites can be affected by indirect events, i.e. those events where the charged particle passes outside the site but injects some δ-rays into it. In the experiments with α-particles, however, the maximum range of δ-particles is about 0.1 μm and can be neglected in comparison to the site diameter of 1 to 2 μm. The observed cross-section can therefore be equated with the actual geometrical cross-section.

The actual number of sites in the nucleus may be considerably larger than the figure given above. In fact the whole nucleus may be more or less homo-

geneously sensitive, and one may then speak of overlapping sites or one may apply the distance model which does not invoke the notion of a geometrically defined site. In section 4.3 the distance model has been discussed without regard to the geometrical confines of the gross sensitive volume. The modifications of the analysis which are necessary if one accounts for the fact that the gross sensitive region is of finite size, will be discussed in the next section. It will be found that these modifications are minor and that the results derived in section 4.3 remain valid.

Before the detailed discussion of the distance model it is useful to examine whether the data which are used to determine the overall cellular inactivation cross-section are consistent with the result that the site diameter is between 1 and 2 μm. Such a consideration does not lead to essentially new results, but it can be considered as an additional check of the results derived in the preceding sections.

For particles in the most effective LET range, i.e. particles with a stopping power of about 100 keV/μm, one obtains nearly exponential survival curves. At the dose $D_{37,\alpha}$ of α-particles which leads to 37% survival one has on the average one particle traversal through the nucleus. At this dose the square component in the dose dependence of the primary damage produced by the α-particles can be neglected. For x rays, on the other hand, the linear component can be neglected at the 37% survival dose. According to eq. (3.19) one has then:

$$\mathrm{RBE}_{37} = (\zeta_\alpha / D_{37,\alpha})^{\frac{1}{2}} \tag{4.14}$$

where RBE_{37} is the RBE at the 37% survival level. Because the experiments are performed with densely ionizing particles and with the so-called track segment method one may base the argument on the LET concept. Within this approximation one can equate ζ_α with the dose per particle traversal through the site and $D_{37,\alpha}$ with the dose per particle traversal through the gross sensitive volume. The dose per particle traversal through a microscopic region is inversely proportional to the square of the diameter of this region and the ratio $\zeta_\alpha / D_{37,\alpha}$ can be set equal to δ^2/d^2 where d is the site diameter and δ is the diameter of the gross sensitive volume, i.e. of the cell nucleus. One therefore finds that for the most effective LET the RBE at the 37% survival level should be equal to the ratio of the diameter δ of the cell nucleus and the distance d which can be interpreted as site diameter or as diameter of the sphere of interaction:

$$\mathrm{RBE}_{37} = \delta / d\,. \tag{4.15}$$

Barendsen [1967] finds a value of about 4.5 for this RBE_{37}; if one assumes a diameter of 7 μm for the nucleus of the cell this would indicate a site diameter of roughly 1.7 μm. The result is therefore consistent with the site diameter obtained in section 3 for various experimental end points.

The use of LET may result in somewhat too small a value of the ratio $\zeta_\alpha/D_{37,\alpha}$. In a more exact microdosimetric formulation $D_{37,\alpha}$ is the frequency mean event size in the gross sensitive volume and this mean is smaller than the dose mean event size. The ratio ζ_α to $D_{37,\alpha}$ is therefore somewhat larger than δ^2/d^2, and accordingly one concludes from the observed value of RBE_{37} that the site diameter exceeds 1.7 μm.

4.5. DISTANCE MODEL IN THE CASE OF A FINITE SENSITIVE REGION

The discussion in section 4.3 has been an oversimplification insofar as each activation event, or each sublesion produced by such an event, has been treated as if it were completely surrounded by potential interaction partners. In reality the gross sensitive volume is of finite size and a sublesion may be produced near the border of the gross sensitive volume; it then has a smaller region of potential interaction than a sublesion formed in the center of the gross sensitive volume. This situation is treated in Appendix 4. It is seen that the site model and the distance model are special cases of this more general model and that the essential result remains unchanged. Specifically it is shown that one can use the distance model in its simple form (see section 4.3) without taking into account the finite size of the cell nucleus. If the maximum interaction distance, h, is 1 μm the error involved in this simplification is well below 15%.

Finally one can show that the derivation of an interaction distance remains valid even if the sensitive structures are distributed in thin layers in the cell, for example, as some studies indicate [T. Alper, 1969] in the vicinity of the nuclear membrane. Assume that the sensitive layer has a thickness ε and that sublesions can interact with constant probability up to a distance h. This case is analyzed in Appendix 5 and one obtains the dose dependence:

$$\epsilon(D) = k\left(\frac{7.65\,\bar{L}_D}{h^2}\left(1+\tfrac{2}{3}\ln(h/\varepsilon)\right)D + D^2\right). \tag{4.16}$$

One can then use the expression for the coefficient λ to derive h (see eq. (2.7)):

$$\lambda = \frac{7.65\,\bar{L}_D}{h^2}\left(1+\tfrac{2}{3}\ln(h/\varepsilon)\right). \tag{4.17}$$

The relation differs from the corresponding eq. (4.13) in section 4.3 by the presence of the logarithmic term. This term has the effect that for a given value of λ and $\bar{L}_D$ one deduces a larger interaction distance. The equation must be evaluated numerically and fig. 9 compares the value h_L which results for the maximum interaction distance in a thin layer with the values h which result for the unmodified distance model. The comparison is given for a layer thickness of 0.1 and of 0.01 μm. One notes that the interaction distance in a thin-layered sensitive structure must be about twice as large as in a spherical site for the same ratio of intratrack and intertrack effect. These are only approximate relations. In reality the validity of the LET concept is very

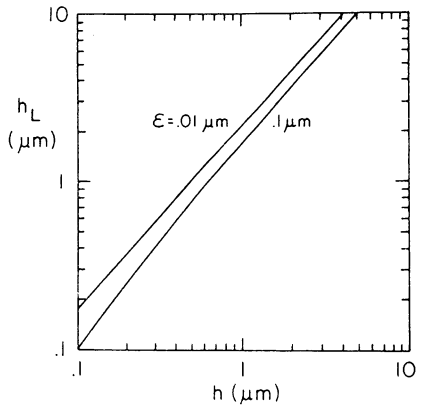


Fig. 9. Comparison of the maximal interaction distances h_L and h which result in the case of a thin sensitive layer and of an unbounded sensitive region.

limited when one deals with thin layers and it is then essential to use the microdosimetric quantities; due to the energy loss straggling of the charged particles the relevant microdosimetric quantity ζ can considerably exceed the value which would be indicated by the value of LET. This leads to the fact that the interaction distances derived according to eq. (4.17) are somewhat too small. Without detailed microdosimetric analysis one must therefore consider the numerical values of h_L as lower limits. It is thus quite consistent with the preceding analysis that DNA may be the sensitive target, that in part of the cell cycle it may be distributed near the nuclear membrane and that sublesions can interact throughout this sensitive shell.

5. Detailed considerations

The relations which have been derived in section 3 should be regarded as general statements of the basic kinetics of radiation action. Thus ϵ has been termed the "yield of elementary lesions" without specification whether the "yield" is a probability (as for instance expressed by that fraction of a limited number of sites that has been affected) or an absolute number (as might be considered if one were dealing with an indefinite number of potential lesions). The diameter of the region for which ζ in eq. (3.6) should be taken has been termed the "site diameter" although as explained in section 4 the concept of the site may only be an abstraction. All that has been deduced is that the biological effects under discussion are determined by the square of the energy concentration in regions having a diameter of the order of 1 μm.

This finding is too limited to permit definitive answers to some fundamental questions in radiobiology. However various simplifications or assumptions permit tentative conclusions that may at least be useful approximations.

5.1. SATURATION EFFECT

An increasing concentration of radiation energy in any sensitive region of a system must ultimately lead to the point where there is waste with the result that the overall effect of a given total absorbed energy becomes less than it would be for a less heterogeneous energy distribution. This has been generally accepted as the explanation of the decrease of RBE observed for particles having an LET that is more than about 100 keV/μm. In the framework of the theory presented here there are at least two possible interpretations of this saturation effect. One is the possibility that the specific energy in a site reaches such a value that the yield $\epsilon(z)$ of elementary lesions saturates. An alternative possibility is that $\epsilon(z)$ is proportional to z^2 even for large z but that the elementary lesions produced by a particle traversing the cell nucleus greatly exceed the level necessary to produce the cellular effect. At present it is not clear which of these situations obtains, and the phenomenon of saturation must be examined in general terms. In the following the correction will tentatively be applied to $\epsilon(z)$, but one may assume that the results would be similar if one were to consider cellular saturation instead of site saturation.

The simplest assumption one could make in order to account for the saturation effect is that the effect probability, while being proportional to z^2 at low levels, approaches a maximum value at large values of z. One can express this by the relation:

$$\epsilon(z) = kz_0^2(1 - e^{-(z/z_0)^2}) \tag{5.1}$$

where z_0 is a parameter which determines where saturation sets in. For values of z much smaller than z_0 eq. (5.1) reduces to the simple quadratic relation:

$$\epsilon(z) = kz^2 . \tag{5.2}$$

One must then average this term over the full spectrum of z in order to obtain the effect at a given dose. This will be dealt with in the next section. The situation is however simplified in the case of the so-called track-segment method where cells are exposed to a beam of nearly monoenergetic heavy charged particles. Data obtained with this method offer the simplest possibility to check the validity of the assumption expressed in eq. (5.1). If one deals with track segment experiments one can, to a first approximation, set z proportional to the LET of the particle. In agreement with the formulation proposed by Powers et al. [1968] one then obtains the following equation for the inactivation cross-section per particle:

$$\sigma(L) = \sigma_{max}(1 - e^{-(L/L_0)^2}) . \tag{5.3}$$

Cellular inactivation cross-sections per particle as a function of LET are given in fig. 10a and 10b. The full dots represent data by Barendsen [1967], the circles data by Todd [1964]. Both experimenters have used the same cell line, but while Barendsen has applied α particles and deuterons of varying speed in order to obtain varying values of LET, Todd has used different ions of constant speed to obtain different values of LET. The broken lines correspond to eq. (5.3). The value of L_0 is assumed to be 110 keV/μm in the aerobic case which is represented in fig. 10a. In the anoxic case the curve is shifted towards higher values of LET; this will be taken up in section 5.3 where the oxygen effect is considered.

Barendsen's data in fig. 10a fit the curve well, with the exception of the point at LET = 5.7 keV/μm. It is to be expected that the experimental cross-sections at low LET are higher than the values which result from eq. (5.3). This reflects the fact that due to energy loss straggling of the charged particle the microdosimetric quantity $\bar{y}_D$ is larger than LET (see Appendix 1) and this can at least partially account for the fact that the observed cross-sections lie above the broken line at low values of LET. There is also, as will be discussed in section 5.5, the possibility of a linear component in the relation between primary damage and z [see Todd, 1964]. One would have to have additional and more accurate data on cellular inactivation cross-sections for sparsely ionizing radiations in order to determine the relative importance of the two

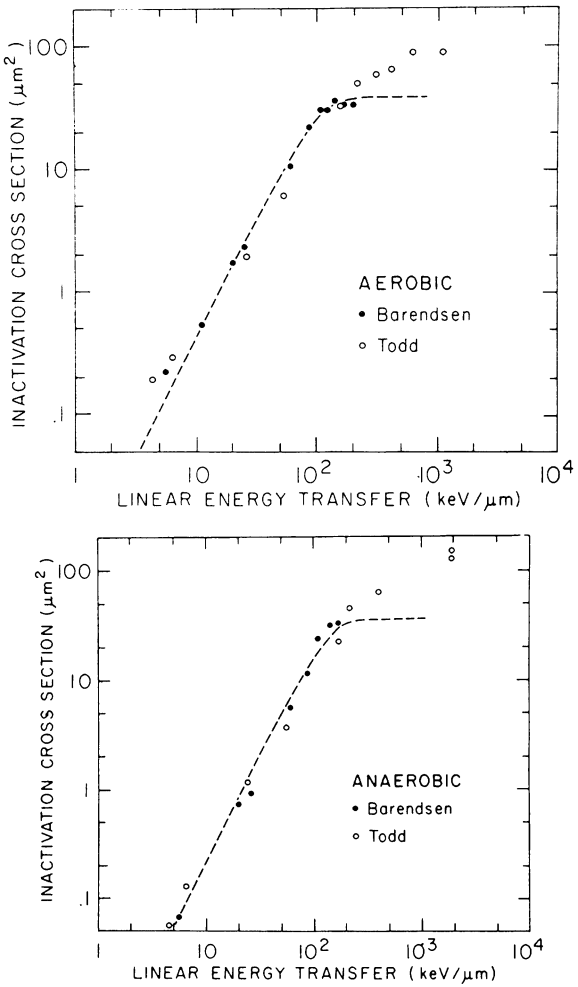


Fig. 10. Cross-section of heavy charged particles for inactivation of mammalian cells *in vitro* as a function of LET. Fig. a refers to oxygenated, fig. b refers to anoxic conditions. The broken lines correspond to eq. (5.3) with $y_0 = 124$ keV/μm and with a reduction factor $\rho = 0.62$ (see section 5.3) in the case of anoxia.
● data by Barendsen [1967], ○ data by Todd [1964].

possible factors. That Todd's data reach no well defined maximum of the cross-section at high values of LET may be explained by the fact that the particles employed in his experiments, have constant velocity and therefore a considerable radial extension of tracks even at very high values of LET. In Todd's experiments the energy per nucleon is 6.8 MeV and the maximum

delta ray range is approximately 4 μm. For very high stopping powers the cells can therefore be inactivated by indirect events in which the heavy charged particle misses the nucleus of the cell but injects enough delta rays to inactivate the cell. This leads to the fact that the inactivation cross-section at high values of LET can considerably exceed the geometrical cross-section of the nucleus. In Barendsen's experiments this effect plays no role because the maximum delta-ray range of alpha particles at LET values beyond 100 keV/μm is very small as compared to the diameter of the nucleus of the cell. The situation is further complicated by the fact that in Todd's experiments the charged particles enter the cells directly from the surrounding gas atmosphere; this "reversed wall effect" leads to a decrease in energy concentration. For these reasons one cannot expect a rigorous analysis based on LET. Curtis [1969] has shown that at least part of the discrepancy between Todd's and Barendsen's data disappears if instead of LET one uses the parameter Z^{*2}/β^2 which corresponds to a restricted LET. Ideally one would have to apply microdosimetric data to the comparison of the two experiments.

According to these considerations one may assume that the deviations of Todd's data from the theoretical curve reflect the limitations of the LET concept. There is however some indication also in Barendsen's data that the agreement is not complete. It appears, and this is especially true in the anoxic case, that in the vicinity of LET = 100 keV/μm the cross sections increase more steeply than would be expected according to eq. (5.3). This could be due to the fact that in Barendsen's experiments high LET values are achieved by the use of slower particles. A decrease of particle velocity leads not only to an increase of LET but also to a radial contraction of the track, and the energy concentration increases therefore somewhat faster than LET. The increase of the cross section is however more marked in the anoxic case; the discussion in section 5.3 will show that this is a separate effect which is also borne out when neutrons are applied under anoxic conditions.

It should furthermore be remarked that a perfect fit of the experimental data to the broken line which corresponds to eq. (5.3) is not to be expected because the data are obtained in experiments with non-synchronized cells. One would have to deal with a superposition of terms such as in eq. (5.3) for the different phases of the cell cycle if one were to give a more accurate analysis. Moreover the variations of chord length and the concomitant variations of energy deposition in the traversal of the nucleus of the cell by charged particles are neglected. In view of the limited data available at present an approximate treatment may be all that can be achieved, and one concludes that the experimental findings are in fair agreement with eq. (5.3). Accord-

ingly one may assume that eq. (5.1) is a useful approximation for the dependence of the elementary lesions on z.

In the next section these considerations will be applied to a microdosimetric analysis of RBE in neutron fields or other fields where one deals with a mixed spectrum of heavy charged particles. It is however useful to give first the formula for RBE in the low dose range (i.e. for single event action) for the case of the track segment experiments. Since the dose per particle is proportional to LET the RBE (i.e. the relative effect per unit of dose) is equal to the ratio of cross section per particle and LET. If one uses eq. (5.3) one obtains:

$$\text{RBE} \sim \sigma(L)/L \sim \frac{1}{L}(1-\mathrm{e}^{-(L/L_0)^2}). \tag{5.4}$$

For values of LET much smaller than L_0 the saturation effect can be neglected and RBE is simply proportional to L. One may therefore rewrite relation (5.4) in the form:

$$\text{RBE} \sim L^* = \frac{L_0^2}{L}(1-\mathrm{e}^{-(L/L_0)^2}) \tag{5.5}$$

where L^* can be considered as an "effective LET value" which is modified so that it accounts for saturation. In this expression the normalization factor, L_0^2, is employed to achieve equality between L^* and L for low values of the latter. Use of the value L^* in the relations derived in section 4 eliminates the

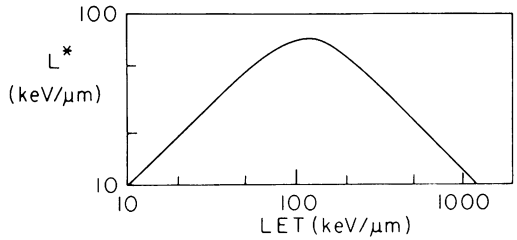


Fig. 11. The quantity L^* (see eq. (5.5)) as a function of LET.

need for corrections which reflect the saturation effect. Fig. 11 represents the relation between L^* and L according to eq. (5.5) and with the parameter L_0 set equal to 110 keV/μm. One finds that L^* reaches a maximum value of 70 keV/μm at $L = 110$ keV/μm and that it declines rapidly when L increases significantly beyond this value.

Before these considerations are extended to mixed radiation fields it

remains to examine an apparent conflict between the site diameters or interaction distances derived in the present study and conclusions which Barendsen [1967, 1969] has obtained from his data. Barendsen subjects the dependence of the inactivation cross-section on LET to a multi-hit analysis combined with an accurate evaluation of the statistics of energy loss straggling. He finds that the lesions responsible for cellular inactivation must be due to energy deposition which comprises 10 to 15 ionizations produced over a distance of roughly 10 nm. This is a much smaller distance than the one derived in the present study from the action kinetics of x rays and from its comparison to that of neutrons. The rigorous interpretation of Barendsen's result is, however, that the effect must be due to interaction of energy deposition over distances *not less* than 10 nm. This distance is a minimum value which would result if all ionizations or primary ionizations had unit action probability. In the general case of intermediate probabilities one obtains larger interaction distances. The present analysis indicates in fact that each individual ionization has only a very small probability to be involved in an elementary lesion. The results are therefore not inconsistent with Barendsen's studies.

5.2. RBE IN THE PRESENCE OF SATURATION

One can apply the findings of the preceding section to the analysis of RBE of heavy charged particles or of neutrons. The term $(1-e^{-(z/z_0)^2})$ in eq. (5.1) which determines the effect probability must then be averaged over the full spectrum of z:

$$\epsilon(D) = kz_0^2 \int_0^\infty (1-e^{-(z/z_0)^2}) f(z;D)\,dz \tag{5.6}$$

this is a modification of eq. (3.3) in section 3 which accounts for the saturation effect, i.e. the decreased effectiveness at high values of z. There are, however, limitations in such an approach. First the resulting expression is not a simple function of D; it must therefore be evaluated numerically for each value of D. Secondly the relation can only be an approximation insofar as one may not be dealing with one single site in the cell but with a number of sites dispersed throughout the cell nucleus. For a rigorous analysis one would then have to take into account the correlation of energy deposition in adjacent sites. There are as yet no microdosimetric data which would make such an approach possible.

As far as the numerical evaluation is concerned it is a reasonable simplifica-

tion to apply the correlation only to the single event component of the effect. This is justified insofar as the correction is significant only for high values of z, and in this case the single event action is dominant. One can then merely substitute a modified quantity for the coefficient λ in the relation for the primary damage which has been derived in section 3:

$$\epsilon(D) = k(\lambda D + D^2) . \tag{5.7}$$

In order to account for the saturation at high values one can in analogy to eq. (5.5), set:

$$\lambda = \zeta^* = z_0^2 \int_0^\infty (1 - e^{-(z/z_0)^2}) f_1(z) dz \Big/ \int_0^\infty z f_1(z) dz . \tag{5.8}$$

The modified quantity ζ^* takes the place of the energy mean event size ζ:

$$\zeta = \int_0^\infty z^2 f_1(z) dz \Big/ \int_0^\infty z f_1(z) dz \tag{5.9}$$

and whenever all values of z are small as compared to z_0 the quantity ζ^* reduces to ζ.

The value z_0 can be obtained from the experimental data depicted in fig. 10. To facilitate comparison with the LET-studies it is however useful to rewrite the microdosimetric relations in terms of the variable y which is closely related to z and is defined as the energy deposited in a microscopic region divided by the mean chord length in this region (see Appendix 1). y is the microdosimetric analogue of LET; it is related to z by:

$$z = \frac{20.4}{d^2} y \tag{5.10}$$

and one has

$$\epsilon(D) = k \left(\frac{20.4}{d^2} y^* D + D^2 \right) \tag{5.11}$$

with

$$y^* = y_0^2 \int_0^\infty (1 - e^{-(y/y_0)^2}) f(y) dy \Big/ \int_0^\infty y f(y) dy . \tag{5.12}$$

This definition corresponds to the definition of L^* in eq. (5.5). The equation is merely complicated by the fact that one has to average over the whole spectrum $f(y)$. One could write the equation in terms of LET instead of the microdosimetric quantity y. The spectrum $t(L)$ of LET [see ICRU, 1970] would then take the place of the distribution $f(y)$.

In the case of sparsely ionizing radiation where all values y are small as compared to y_0, the quantity y^* reduces to the unmodified definition of the dose average event size:

$$\bar{y}_D = \int y^2 f(y)\,dy \Big/ \int_0^\infty y f(y)\,dy . \tag{5.13}$$

The parameter y_0 can be chosen in accordance with the experimentally determined value L_0. From the data represented in fig. 10 one has $L_0 = 110$ keV/μm. As demonstrated in Appendix 1 equivalent values of y_0 and L_0 are connected by the relation $y_0 = 9/8\ L_0$. The values of y^* for monoenergetic neutron fields which result for $y_0 = 125$ keV/μm are given in fig. 12 as a solid line. The data correspond to a site diameter of 1 μm but the curve would be

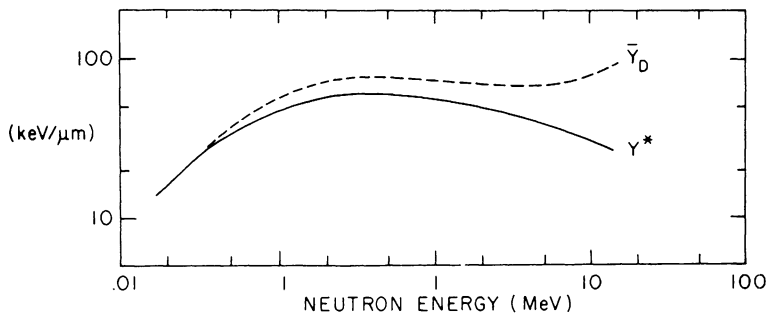


Fig. 12. Dose mean lineal energy density, $\bar{y}_D$, for neutrons of energy E (broken line), and the corresponding quantity, y^*, which results if the saturation effect is taken into account (solid line).

nearly the same for a site diameter of 0.5 or 2 μm. For comparison the values $\bar{y}_D$ which result if one disregards the saturation effect are given as a broken line.

The corresponding values ζ^* are plotted in fig. 13 in a representation analogous to the one in fig. 5. One finds from the comparison of both figures that the use of the corrected data does not lead to greatly changed values of d except in the case of 14 MeV neutrons. In the latter case use of the modified values z^* leads to diameters d which are decreased by a factor less than 2. Except for this difference the conclusions obtained in section 3 remain valid.

The limiting RBE in the range of low doses where one need only consider the single-track action is given by the relation:

$$\mathrm{RBE} = y^*/\bar{y}_{D,x} \tag{5.14}$$

where the quantity y^* is calculated according to eq. (5.12) for the radiation in question. $\bar{y}_{D,x}$ is the dose average event size for x rays.

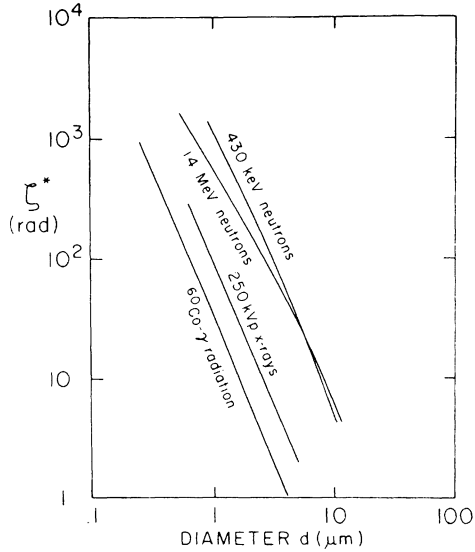


Fig. 13. "Effective" energy mean, ζ^*, of the specific energy produced in an event as a function of the diameter, d, of the tissue sphere.

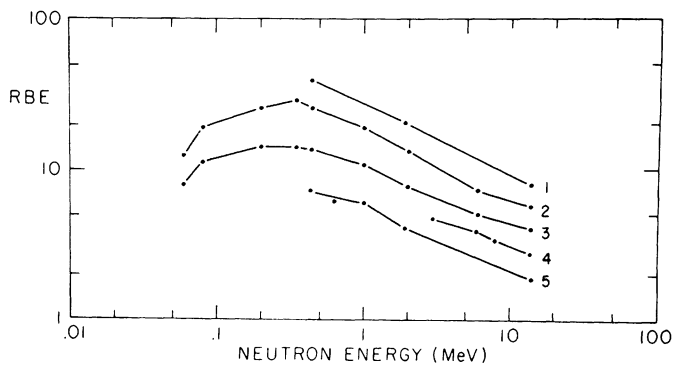


Fig. 14. Observed dependence of RBE on neutron energy.
1: Lens opacification at x ray dose 40 rad [Bateman et al., 1972]
2,3: 50% growth reduction of *Vicia Faba* (anoxic, and oxygenated) [Hall, unpublished]
4: Cellular inactivation (initial part of the survival curves) [Barendsen, 1971]
5: 37% depletion of spermatogonia [Bateman et al., 1968].

In fig. 14 the RBE as a function of neutron energy is plotted for several biological systems. The normalization of these values relative to x rays is uncertain because the effect relation for small doses of x rays is not known with sufficient accuracy. This implies that the vertical position of the RBE

relations is irrelevant. The general shape and the position of the maximum agree for the experimental and the theoretical curves. The theoretical curve is however more shallow than the observed relations. This could be due to the fact that at neutron energies of several MeV the heavy recoils have ranges too short to traverse the whole cell nucleus. The saturation effect may then be less expressed than it would be according to the data from track segment experiments. This has been postulated by Bewley [1968a,b] in connection with the RBE of neutrons for inactivation of mammalian cells *in vitro*. It would mean that one deals with cellular saturation and not merely with site saturation. For neutron energies below several MeV the heavy recoils can be neglected but a qualitatively similar argument could be applied to the protons which retain their maximal or near maximal stopping power only over a range of the order of 1 μm at the Bragg peak. This could also lead to a certain reduction in energy waste and therefore to increased values of RBE.

5.3. OXYGEN EFFECT

The simplest explanation of the oxygen effect is based on the assumption that in the absence of oxygen the production of sublesions is reduced by a constant factor. Such an assumption has been invoked by Barendsen [1967] who observes that the cross-sections for cellular inactivation depend on LET in such a way that the curves for the aerobic and the anoxic case are roughly parallel, merely shifted by a constant factor in LET. He concludes that this may imply that the amount of damage induced locally in certain sensitive structures or molecules in the cell is reduced by the removal of oxygen, and that this reduction is independent of radiation quality.

While this may be at least a reasonable approximation one can at present not discount the possibility that the deviations of the data in figs. 10a and 10b from parallelism are real and that accordingly the reduction is less at high values of LET. At the end of this section it will be seen that the observed values of the oxygen enhancement ratio (OER) for neutrons support this assumption. The experimental evidence is still limited, but since the problem is of considerable practical and theoretical importance some of the possible implications will be discussed.

The assumption made by Barendsen that oxygen is a constant modifying factor can in microdosimetric terminology be expressed by the statement that oxygen is a z-modifying factor. Under this assumption the number of sublesions is proportional to z both under aerobic and anoxic conditions, but the two theoretical curves in fig. 10a and 10b are shifted by the factor 0.6,

i.e. the coefficient of proportionality is decreased by about 40 % in the case of anoxia. Two facts should be pointed out which apply if this assumption is valid. First, it is then not necessary to invoke a special radiochemical mechanism which supresses the oxygen effect in the track of high LET particles. The decrease of the oxygen effect at high values of LET would merely reflect the saturation effect, i.e. the fact that at very high values of LET the passage of a particle through the cell nucleus is sufficient to inactivate the cell regardless whether more or less sublesions are formed within the particle track. The necessity to invoke additional mechanisms, such as the production of oxygen within the track of densely ionizing particles, arises only if there is experimental evidence that the reduction factor in the yield of sublesions is larger at smaller values of z.

A second important point is that the assumption of oxygen being a z-modifying factor is not completely equivalent to what is commonly called the assumption of oxygen as a dose modifier. This can be seen most readily if one restricts the discussion to the case of low to intermediate LET values where one can neglect saturation effects. This restriction will be adopted first, and the following relations will therefore apply only to sparsely or moderately ionizing radiations. The more general case will be dealt with at the end of this section.

If ρ is the z-modifying factor, then the yield of sublesions produced at a certain value of z under aerobic conditions is cz while the yield under anoxic condition is ρcz. The primary damage under aerobic conditions is, therefore:

$$\epsilon(z) = kz^2, \text{ with } k = c^2 \tag{5.15}$$

while the primary damage under anoxic conditions is:

$$\epsilon'(z) = \rho^2 kz^2 . \tag{5.16}$$

According to eq. (3.6) in section 3 one therefore obtains the dose effect relation:

$$\epsilon(D) = k(\zeta D + D^2) \tag{5.17}$$

in the aerobic case, while in the anoxic case one has:

$$\epsilon'(D) = k(\zeta \rho^2 D + \rho^2 D^2) . \tag{5.18}$$

If oxygen is a z-modifying factor, it is therefore not strictly a dose-modifying factor. The linear component is more strongly suppressed than it ought to be if oxygen were merely a dose-modifying factor; in the latter case one would

have to have the factor ρ and not ρ^2 in the linear term in eq. (5.18). The situation could best be examined in systems where both the linear and the quadratic component of the dose effect relation can be determined. Data on the oxygen effect in these systems are still limited. According to Barendsen's results [1967] the OER may be largest at small doses. Observations by Humphrey et al. [1963], Van Putten [1968], and Révész and Littbrand [1966], on the other hand, seem to indicate that the linear component in cellular survival curves is less depressed than it should be if oxygen were a z-modifying or even a dose-modifying factor. This would be in line with the assumption that in the anoxic condition restitution of sublesions or correlated molecular alterations can take place while it is suppressed in the presence of oxygen. The oxygen effect should then be less expressed for the dual lesions produced by a single track than for those produced by two tracks. If this particular explanation applies one would have to expect a reduction of the oxygen effect in experiments performed with ultra-high dose rate; no such observations have yet been made. Another possible cause of a reduced OER at small doses could be the diminished reduction factor at higher values of LET which has been mentioned earlier. In the following the problem of the dependence of OER on dose will be left open and the discussion will be restricted to neutrons where the linear term in eq. (5.18) dominates.

In the following the OER for neutrons will be calculated both under the assumption of a constant reduction factor and a reduction factor which approaches 1 as LET increases. The results will then be compared to experimental observations.

It will again be practical to formulate the relations in the variable y. This has the double advantage that the equations can readily be reformulated in terms of LET and that they are nearly independent of the site diameter. In the preceding section the dose-dependence of the primary lesions has been given:

$$\epsilon(D) = k\left(\frac{20.4}{d^2}\, y^* D + D^2\right) \tag{5.19}$$

with:

$$y^* = y_0^2 \int_0^\infty (1 - e^{-(y/y_0)^2}) f(y) \mathrm{d}y / \bar{y}_F. \tag{5.20}$$

In the anoxic case one obtains the analogous relation:

$$\epsilon'(D) = k\left(\frac{20.4}{d^2}\, y_A^* D + \rho^2 D^2\right) \tag{5.21}$$

with

$$y_A^* = y_0^2 \int (1 - e^{-(\rho y/y_0)^2}) f(y) dy / \bar{y}_F \,. \tag{5.22}$$

For sparsely ionizing radiation where all values of y are small as compared to y_0 the quantity y_A^* reduces to $\rho^2 \bar{y}_D$ and eq. (5.21) is then equivalent to eq. (5.18).

The OER in the range of low doses where one need only consider the single-track action is

$$\mathrm{OER} = \frac{y^*}{y_A^*} = \frac{\int_0^\infty (1 - e^{-(y/y_0)^2}) f(y) dy}{\int_0^\infty (1 - e^{-(\rho y/y_0)^2}) f(y) dy} \,. \tag{5.23}$$

In the case of sparsely ionizing radiation this reduces to

$$\mathrm{OER} = \frac{1}{\rho^2} \,. \tag{5.24}$$

Eq. (5.23) can be evaluated either for a constant or for a variable reduction factor ρ. In the latter case one can choose the functional dependence of ρ on LET or its microdosimetric analogue, y, in accordance with the ratios of

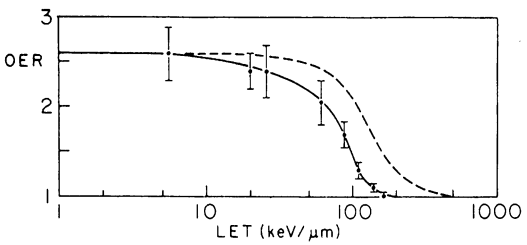


Fig. 15a. OER as a function of LET. The experimental points are for inactivation of mammalian cells *in vitro* [Barendsen, 1971]. The solid curve is fitted to the experimental data; the broken line results from eq. (5.25) with a constant reduction factor $\rho = 0.62$.

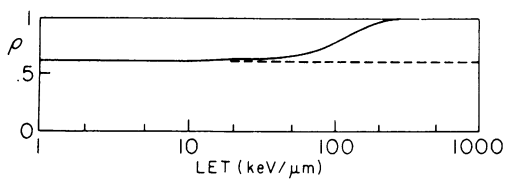


Fig. 15b. The dependence of the reduction factor ρ on LET which corresponds to the solid curve in fig. 15a.

cross-sections represented in figs. 10a or 10b. The ratios, i.e. the values of the OER, as functions of LET are plotted in fig. 15a with their standard errors as given by Barendsen [1967]. The OER which results if one assumes that the cross-sections follow the theoretical curves in figs. 10a and 10b and that ρ is constant and equal to 0.62 is indicated by the broken line. The solid line follows the actually observed values of OER. The functional dependence of ρ on LET which corresponds to the solid line can be derived by solving the equation:

$$\mathrm{OER} = \frac{1-\mathrm{e}^{-(L/L_0)^2}}{1-\mathrm{e}^{-(\rho L/L_0)^2}} \tag{5.25}$$

for ρ. The result is represented in fig. 15b.

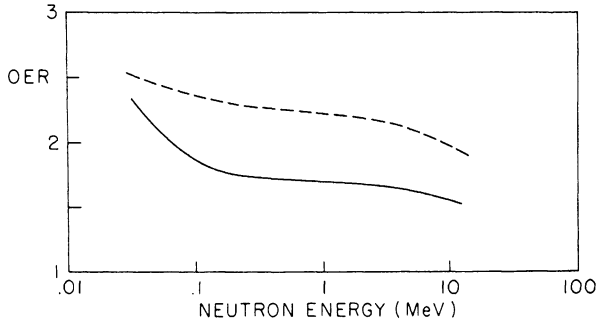


Fig. 16. Oxygen enhancement ratio for neutrons according to eq. (5.23) with constant reduction factor $\rho = 0.62$ (broken line) and ρ depending on y in accordance with fig. 15a (solid line).

In fig. 16 the oxygen enhancement ratios for monoenergetic neutrons are given which are obtained if eq. (5.23) is evaluated either with the constant reduction factor ρ (broken line) or with the variable reduction factor (solid line). The computations have been performed with y-spectra for a site of 1 μm diameter [Biavati et al., 1965], with the value $y_0 = 125$ keV/μm, and with the variable $\rho(y)$ set equal to $\rho(L)$ with $L = 8/9\,y$.

The values of the OER obtained under the assumption of a constant reduction factor ρ are markedly higher than the values which have been observed for inactivation of mammalian cells. But the values obtained with the variable reduction factor ρ according to fig. 15b agree with the OER values given by Broese and Barendsen [1966] for neutrons. Barendsen's results obtained with heavy charged particles and with neutrons are therefore mutually consistent. On the other hand, one may note that the theo-

retical predictions are at variance with the strong increase of OER with neutron energy which has been reported by other authors (see survey by Fowler [1969]). As mentioned at the end of section 5.2 the cross-sections of the short ranged heavy recoils could be higher than assumed in the present analysis; this would lead to slightly lower values of OER at neutron energies of a few MeV. Because the present analysis is based on actual microdosimetric spectra the corrections, if necessary at all, would be much smaller than those which have to be applied if LET distributions are used [Curtis, 1968].

Fig. 17 demonstrates the relative contribution of the different ranges of y to the effect. The curves are given for monoenergetic neutrons of 0.1, 3.7, and

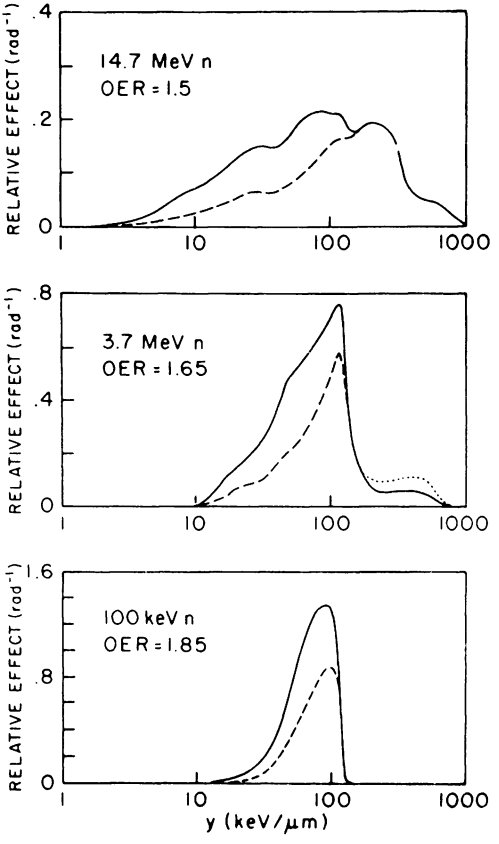


Fig. 17. Relative effect per unit dose and unit logarithmic interval of y for neutrons of different energy. Solid lines: aerated condition, Broken lines: hypoxic condition. The results are based on experimental y spectra [Biavati et al., 1965; Rodgers et al., 1971].

14.7 MeV and for oxygenated (solid line) and anoxic conditions (broken lines). A rough estimate of the possible correction for increased cross-sections which could apply to the 3.7 MeV neutrons is indicated by the dotted line segment; the decrease of the OER which results from this correction is small.

5.4. DOSE RATE DEPENDENCE

Up to this point it has been assumed that one deals with cases where either the dose is administered instantaneously or, if the exposure time is finite, recovery and recombination processes can be neglected. One can derive modified equations for the functional dependence of the primary damage on dose and for RBE as a function of dose which hold in the presence of recovery processes. The mathematical formalism involved in this derivation will be similar to that applied in section 4.3. In section 4.3 the interaction probability $\rho(x)$ between ionizations or sublesions as a function of their spatial distances has been used; in the present section an analogous function $\tau(t)$ will be introduced which determines the interaction probability as a function of the time interval between two energy deposition events or between the formation of two sublesions.

The yield of elementary lesions as a function of dose has been derived in section 3:

$$\epsilon(D) = k(\lambda D + D^2) . \tag{5.26}$$

According to the considerations in sections 4.2 and 4.3 the linear term represents the effect due to intratrack interactions while the quadratic term represents the effect of intertrack interaction. The intratrack interaction is independent of dose rate; the intertrack interaction, on the other hand, decreases with increasing exposure time and this decrease is to be analyzed in the following:

Assume that the probability of a dose element to interact with another dose element which is administered at a temporal separation t is given by $\tau(t)$. The function $\tau(t)$ can be considered as recovery function for sublesions; its initial value, $\tau(0)$, for zero time separation is set equal to 1. In order to simplify the notation in the following formulae $\tau(-t)$ is set equal to $\tau(t)$; this reflects the fact that the order of the two dose elements is irrelevant. Let 0 to T be the time interval in which the irradiation occurs and let $I(t)$ be the dose rate as a function of time. The total interaction probability between dose

elements given at different times is then proportional to the integral:

$$\int_0^T \tau(t) \int_0^{T-t} I(s) I(s+t) \mathrm{d}s \mathrm{d}t \,. \tag{5.27}$$

In the special case where one has no recovery the term $\tau(t)$ is equal to 1. The ratio of the quadratic effect in the presence of recovery to that in the absence of recovery is therefore equal to:

$$\begin{aligned} q(T) &= \int_0^T \tau(t) \int_0^{T-t} I(s) I(s+t) \mathrm{d}s \mathrm{d}t \Big/ \int_0^T \int_0^{T-t} I(s) I(s+t) \mathrm{d}s \mathrm{d}t \\ &= \frac{2}{D^2} \int_0^T \tau(t) \int_0^{T-t} I(s) I(s+t) \mathrm{d}s \mathrm{d}t \,. \end{aligned} \tag{5.28}$$

One may note that the function:

$$h(t) = \frac{2}{D^2} \int_0^{T-t} I(s) I(s+t) \mathrm{d}s \tag{5.29}$$

can be considered as the distribution of time intervals t between dose increments for a given temporal mode of irradiation. The probability that two absorption events are separated by a time interval of length t to $t+\mathrm{d}t$ is equal to $h(t)\mathrm{d}t$. The reduction factor q can then be expressed as:

$$q(T) = \int_0^T \tau(t) h(t) \mathrm{d}t \,. \tag{5.30}$$

The factor $q(T)$ applies to the quadratic component in eq. (5.26) and one therefore obtains the following relation for the dose dependence of the primary damage in the presence of recovery:

$$\epsilon(D) = k(\lambda D + q(T) D^2) \,. \tag{5.31}$$

In the special case of constant dose rate, $I = D/T$ one has a triangular distribution of time intervals between dose elements:

$$h(t) = 2(T-t)/T^2 \tag{5.32}$$

and therefore:

$$q(T) = \frac{2}{T^2} \int_0^T \tau(t)(T-t) \mathrm{d}t \,. \tag{5.33}$$

If one assumes an exponential recovery function:

$$\tau(t) = \mathrm{e}^{-t/t_0} \tag{5.34}$$

one obtains the reduction factor:

$$q(T) = \frac{2}{T^2}\int_0^T e^{-t/t_0}(T-t)dt = \frac{2t_0}{T} - \frac{2t_0^2}{T^2}(1-e^{-T/t_0}). \tag{5.35}$$

The formula for a continuous irradiation of duration T is therefore:

$$\epsilon(D) = k\left(\lambda D + \left(\frac{2t_0}{T} - \frac{2t_0^2(1-e^{-T/t_0})}{T^2}\right)D^2\right). \tag{5.36}$$

If the recovery time, t_0, is large as compared to the exposure time, T, and if one accordingly neglects all higher powers of the term T/t_0 one obtains the approximation:

$$\epsilon(D) = k\left(\lambda D + \left(1 - \frac{T}{3t_0}\right)D^2\right). \tag{5.37}$$

If, on the other hand, the recovery time is short as compared to the irradiation time, one has:

$$\epsilon(D) = k\left(\lambda D + \frac{2t_0}{T}D^2\right). \tag{5.38}$$

Fig. 18 represents the reduction factor $q(T)$ as a function of the ratio T/t_0 of exposure time to recovery time.

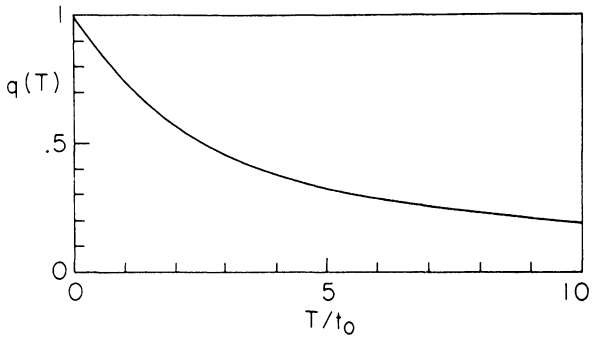


Fig. 18. Reduction factor, $q(T)$, of the intertrack effect as a function of the ratio of irradiation time, T, and recovery time, t_0.

Assume that D_0 is a dose which is applied instantaneously and that D is the dose necessary to reach the same effect when the irradiation time is T. In order to derive the time factor D/D_0 one must solve the equation:

$$\lambda D_0 + D_0^2 = \lambda D + q(T)D^2. \tag{5.39}$$

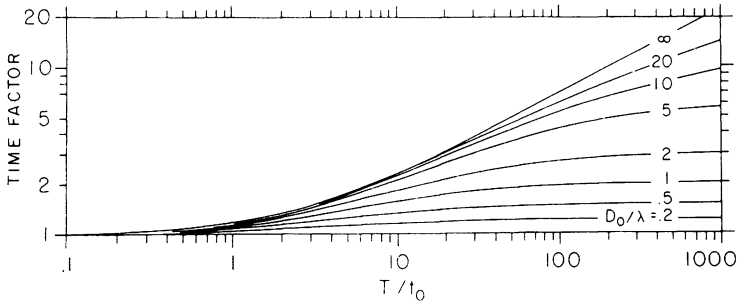
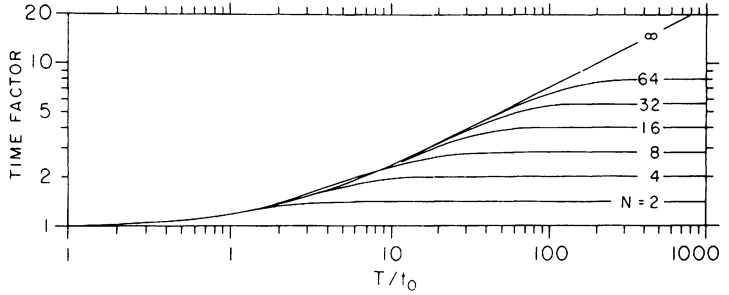


Fig. 19. a) Time factor D/D_0 for a continuous irradiation as a function of the ratio of irradiation time T and recovery time t_0. The parameter of the curves is the instantaneous dose, D_0, in units of λ.



b) Time factor D/D_0 for an irradiation in N instantaneous, equal fractions equally spaced over the time T. The recovery time is t_0. The curves apply to doses large as compared to λ.

The result is plotted in fig. 19a as function of the ratio of irradiation time T to recovery time t_0. The parameter of these curves is the ratio of the instantaneous dose D_0 to λ; if D_0 is small the intratrack effect which is independent of dose rate predominates and the time factor is small. The maximal time factor $q(T)^{-0.5}$, on the other hand, is obtained if D_0 is large as compared to λ and only the intertrack effect has to be considered.

The next important case besides that of a continuous irradiation is dose fractionation. If N equal instantaneous fractions are equally spaced over the time T one obtains the following distribution of time intervals between dose elements:

$$h\left(\frac{\nu}{N}T\right) = \begin{cases} 1/N & \text{for } \nu = 0 \\ 2(1-\nu/N)/N & \text{for } \nu = 1, 2, \ldots N\,. \end{cases} \tag{5.40}$$

Fig. 19b gives the resulting time factor. The parameter in this representation is the number N of fractions; all curves refer to the case where D_0 is large as

compared to λ. A further example is that of a dose D given in two not necessarily equal fractions D_1 and D_2 separated by a time T. In this case one obtains:

$$\epsilon(D) = k(\lambda D + D^2 - 2(1 - e^{-T/t_0}) D_1 D_2) . \tag{5.41}$$

In an analogous way one derives the effect relations or the time factor for more complicated modes of irradiation.

A general conclusion from eq. (5.31) is that in the presence of recovery processes the yield of elementary lesions remains the sum of a linear and a quadratic component regardless of the form of the recovery function for sublesions. Due to the recovery the quadratic component is decreased by the factor $q(T)$. The curves which represent RBE as a function of dose have the same shape which has been discussed in section 3 but they are shifted by the factor $1/q(T)$ towards higher dose values. The equation for the relative biological effectiveness which corresponds to eq. (3.14) in section 3 has the modified form:

$$\mathrm{RBE} = \frac{2(\lambda_n + qD_n)}{\lambda_x + \{\lambda_x^2 + 4(\lambda_n + qD_n) qD_n\}^{\frac{1}{2}}} \tag{5.42}$$

and in the special case where the linear component for x rays can be disregarded:

$$\mathrm{RBE} = \left(1 + \frac{\lambda_n}{qD_n}\right)^{\frac{1}{2}} . \tag{5.43}$$

These relations apply for constant irradiation time, i.e. a variable dose rate which is proportional to dose. If a dose effect curve is determined with constant dose rate the situation is more complicated because the reduction factor $q(T)$ is then a decreasing function of dose. The effect due to intertrack interaction is therefore less than proportional to the square of the dose. According to eq. (5.38) both the intratrack and intertrack effect are proportional to dose in the limiting case of exposure times much larger than the recovery time t_0:

$$\epsilon(D) = k(\lambda + 2t_0 I) D . \tag{5.44}$$

If one compares the result of different doses administered at *equal dose rate* one can therefore find values of RBE which are independent of dose or exponential dose effect relations, and one must be careful not to conclude from this observation that one deals exclusively with single event mechanisms. This fact is important for the evaluation of experimental data obtained at low dose rate where dose effect curves obtained at constant dose rate are some-

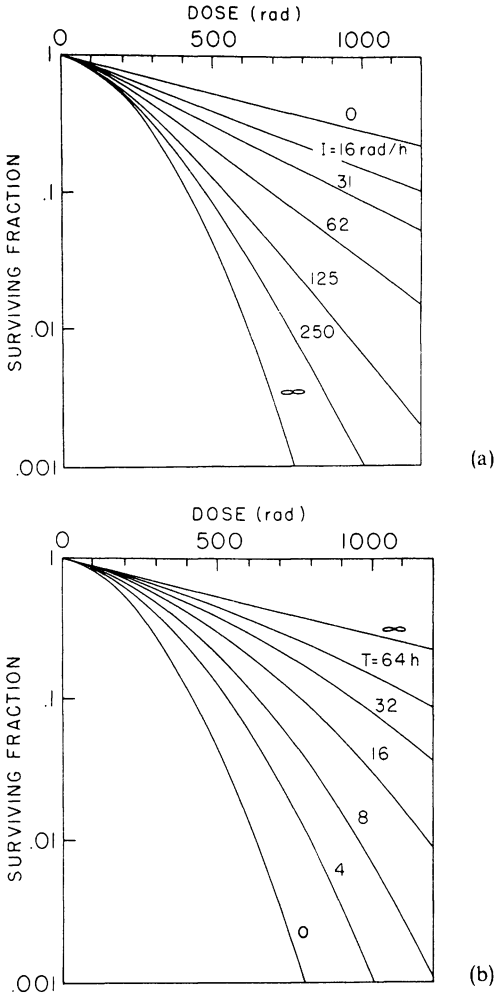


Fig. 20. Dose-effect relation according to eq. (5.45) and its modification due to recovery.
a) curves for constant irradiation time T.
b) curves for constant dose rate, I.

times used to infer the magnitude of the single event component. The situation is illustrated in fig. 20. As an example for a dose-effect relation in the limiting case of high dose rate the equation

$$S(D) = \exp(-10^{-5}(125\,D + D^2)) \tag{5.45}$$

is chosen in this figure. The value $\zeta = 125$ rad corresponds to x rays and a site

diameter of 1 μm. In fig. 20a the dose effect curves for constant irradiation time, T, are plotted. In fig. 20b the theoretical curves for the case of constant dose rate, I, are given. The recovery time, t_0, is taken as 2 hours. The example is, of course, a simplification; in reality the situation is modified by the partial synchrony of the cells which is induced by the irradiation, and which complicates the recovery phenomenon [Elkind, 1959].

5.5. DEVIATIONS FROM THE QUADRATIC DEPENDENCE

The formalism developed in section 3 allows a prediction of the linear components for x rays and for gamma rays from observations obtained by more densely ionizing radiations. This is based on the fact that to each value ζ_n obtained for example with neutrons one can deduce the corresponding value ζ_x for x rays or some other radiation quality. Because the value ζ_x for sparsely ionizing radiation is roughly 30 to 50 times smaller than the value for 430 keV neutrons it is in general difficult to test this part of the theory and compare the expected magnitude of the linear component with its observed value. The only experiment where the linear part of the x ray response has been clearly demonstrated is the study of Sparrow et al. [1972] on Mutagenesis in *Tradescantia* (see fig. 1 and fig. 8). This experiment confirms the theory, as one obtains a limiting RBE at small dose of roughly 50 and a value ζ_x of 16 rad which according to fig. 5 corresponds to a site diameter d of about 2 μm and the observed value ζ_n of about 800 rad. This agreement between theoretical prediction and experimental observation indicates that the linear component is indeed due to dual lesions produced by intratrack action. As a further test of this result it would be desirable to compare the initial part of response curves for gamma rays and soft x rays in this or in other biological systems. According to microdosimetric data the values ζ are different for the two radiation qualities by nearly a factor of 2 and the linear component should therefore be larger in the case of x rays. If on the other hand one should fail to find this difference one would have to conclude that the low dose part of the response curve is at least partly determined by primary damage which is not of dual nature.

In the other experimental data given in fig. 1 the limiting value of RBE at low doses is not yet reached. In the case of the lens opacification one finds however that the ratio of the RBE at smallest doses to the RBE at highest doses cannot be much smaller than 40 and that therefore the linear component for x rays cannot be significantly greater than expected according to the ratio of values ζ_n and ζ_x.

For the other experimental systems listed in fig. 1 one cannot exclude the possibility that part of the damage at low doses is not of dual nature, and that RBE reaches a plateau at values below 40 for 430 keV neutrons and corresponding values for other energies. Further experiments at very low doses will therefore be of great importance and may help to decide the question whether all of the cellular damage is proportional to the square of the local energy concentration or whether at low doses cells may also be subject to damage produced by single ionizations without the requirement for the interaction of radiation induced molecular changes.

Some exceptions to the quadratic dependence have to be expected. The case of cultured mammalian cells will be discussed below, and it will be found that the present data permit no clear decision whether in this system a part of the effect is due to lesions whose yield is independent of radiation quality. Another case where the experimental evidence as to the square dependence of the primary damage on energy concentration is inconclusive is that of objects which are smaller than the typical size of a site according to the data in fig. 1. A border line case is the induction of translocations in *drosophila* sperm [Gonzalez, 1971]. In these cells the DNA is packed within volumes which can be roughly approximated by cylinders of height 1 μm and of diameter 0.2 μm. According to this small size the value ζ must be of the order of at least 100 rad even for x rays, and a strong linear component in the response curve has indeed been observed. In this case it is difficult to obtain an accurate estimate of the quadratic component for x rays because it exceeds the linear component only at doses which are so high that cell killing is already quite significant. An accurate test of the theory has, therefore, in this case not yet been possible.

If one deals with smallest objects, for example with small bacteria or with viruses, the linear component of damage is dominant over the whole observable dose range. In this case the only dependence on radiation quality is due to the saturation effect as has been shown in the studies performed by Lea [1946] and by Pollard and co-workers [1955]. The excellent results obtained with Lea's associated volume method indicate that in such small objects one deals with lesions which are produced by single electronic collisions.

It will be useful to obtain the formulae which correspond to the results of section 3 in the more general case where one deals not with a purely quadratic dependence of primary damage on specific energy but with a superposition of a linear and a quadratic term and possibly also with higher powers of z:

$$\epsilon(z) = k_1 z + k_2 z^2 + k_3 z^3 + \dots . \tag{5.46}$$

This equation is the generalization of eq. (3.2) in section 3. In the same way as in section 3 one can derive from it the relation between effect and absorbed dose:

$$\epsilon(D) = \int_0^\infty (k_1 z + k_2 z^2 + k_3 z^3 + \ldots) f(z; D) \mathrm{d}z \tag{5.47}$$

$$= k_1 \bar{z} + k_2 \overline{z^2} + k_3 \overline{z^3} + \ldots$$

On the basis of theoretical relations which are pointed out in Appendix A1 one obtains the following equations between the moments of the specific energy, z, and the dose, D:

$$\bar{z} = D \tag{5.48}$$

$$\overline{z^2} = \zeta D + D^2 \tag{5.49}$$

$$\overline{z^3} = \zeta \xi D + 3\zeta D^2 + D^3 \,. \tag{5.50}$$

Where the following abbreviations have been used:

$$\zeta = \frac{\int_0^\infty z^2 f_1(z) \mathrm{d}z}{\int_0^\infty z f_1(z) \mathrm{d}z} \tag{5.51}$$

$$\xi = \frac{\int_0^\infty z^3 f_1(z) \mathrm{d}z}{\int_0^\infty z^2 f_1(z) \mathrm{d}z} \,. \tag{5.52}$$

Therefore the primary damage depends on dose in the following form:

$$\epsilon(D) = (k_1 + k_2 \zeta + k_3 \zeta \xi) D + (k_2 + 3k_3 \zeta) D^2 + k_3 D^3 + \ldots \,. \tag{5.53}$$

This is the generalization of the fundamental eq. (3.6) which has been derived in section 3. The terms containing k_3 can be eliminated because none of the experiments listed in fig. 1 indicates a steeper slope than that which corresponds to the term which is quadratic in dose. One can of course argue that higher powers of D could be relevant at higher doses but at present such an effect has not been observed. The equation therefore reduces to a form which has already been discussed in section 3:

$$\epsilon(D) = (k_1 + k_2 \zeta) D + k_2 D^2 \,. \tag{5.54}$$

The presence of a linear dependence of primary damage on specific energies z results therefore in an increase in the linear component of the dose de-

pendence. For the dose-RBE curves this results in a shift towards higher values of doses and a reduction of the limiting value of RBE at lowest doses. If the limiting value of RBE at low doses is not observable in an experiment, one cannot decide whether one deals with the purely quadratic dependence of primary damage on specific energy or with a superposition of a linear and a quadratic dependence. If one assumes a purely quadratic dependence in the case where the underlying mechanism is mixed one derives a value of ζ which is too large and therefore a site diameter or an interaction distance d which is smaller than the true value. The estimates of d derived in section 3 are therefore conservative and one would have to assume somewhat larger distances if part of the primary damage is independent of the microscopic concentration of energy deposition.

Survival curves obtained with mammalian cells cultured *in vitro* have not been used in the analysis of RBE at low doses. The reason is that survival curves of mammalian cells are of high accuracy at low survival levels but of limited accuracy in the region of low doses and small effects. This is the case in all experimental systems where one counts unaffected cells within an irradiated population and where accordingly one infers the effect probability only indirectly as the difference between two observations at zero dose and at the dose of interest. The variable plating efficiency and in certain experiments the cellular multiplicity are among the factors responsible for the absence of accurate information on the initial slope of the survival curves. It is, therefore, at present not possible to derive the functional dependence of RBE on dose at small effect levels for this test system with certainty. However, Barendsen [1971] has concluded that experiments at various neutron energies indicate a lower maximum RBE, and his results are shown in fig. 21.

Dose rate studies with unsynchronized cells have shown that the survival curves approximate exponential shape at lowest dose rates. This has been taken as an indication of a sizable linear component in the effect. Most of these studies have however been performed with constant dose rate and variable irradiation time. According to fig. 20b in section 5.4, the exponential shape can then reflect intertrack interaction and is not necessarily due to single event mechanisms.

A recent study [Hall et al., 1971] of the growth rate of mammalian cells under continuous irradiation of x rays and neutrons has been used to derive the dependence of RBE on dose under the condition of constant irradiation time. One obtains the slope of -0.5 of the RBE versus neutron dose relation as expected according to the theory. This study is therefore an indication that

the quadratic dependence of primary damage applies also to the case of mammalian cells *in vitro*.

One possible objection against this conclusion is based on the fact that with α particles one obtains survival curves which show no observable deviation from the exponential shape over the whole dose range. This would seem to be in conflict with the statement that even for densely ionizing radiation one must have a quadratic dependence on dose at highest values of D. There are, however, two reasons why the quadratic component cannot be detected in this case. First the term ζ_n is very large for α particles and one would have to go to doses exceeding this value in order to find a quadratic

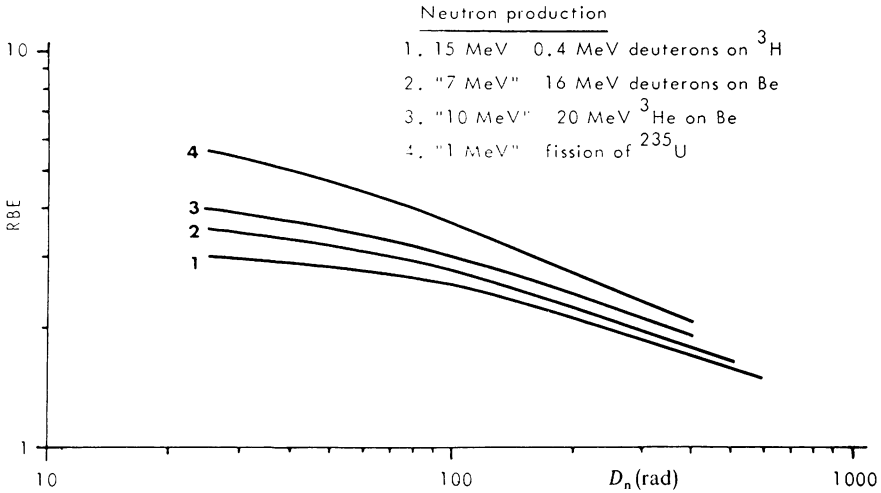


Fig. 21. RBE of neutrons for the inactivation of mammalian cells as a function of neutron dose according to Barendsen [1971].

component which exceeds the linear component. Secondly, one can show that the survival curves for a nonsynchronized population cannot be of purely exponential form if one assumes that the survival curves which apply to the individual phases of the cell cycle are exponential. Fig. 22 represents the survival curve for mammalian cells exposed to α rays which has been theoretically deduced from experimentally observed values of the sensitivity variations throughout the cell cycle [Hall et al., in preparation]. The superposition of exponential functions with different slopes leads to a curve which becomes more shallow at higher doses, as seen in the figure. The fact that due to experimental limitations this change of the slope of the survival curves

by nearly a factor of 2 cannot be experimentally observed implies that one is equally unable to detect a quadratic component in the effect which would result in a steeper slope of the curve at higher doses.

One concludes that it is at present difficult to extract accurate dose-RBE relations at low doses from survival curves obtained on mammalian cells. It

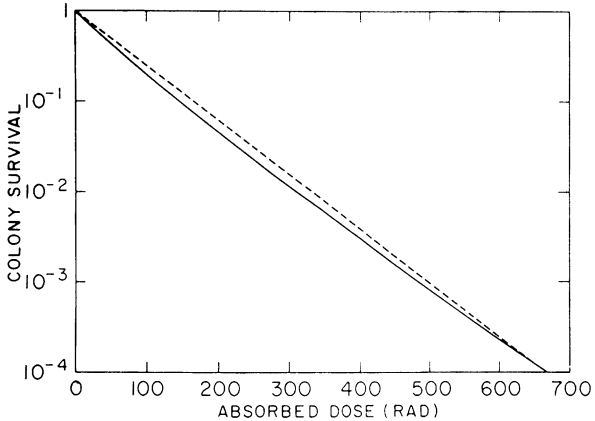


Fig. 22. Survival curve (solid line) for a non-synchronized population of Chinese hamster cells exposed to x rays. The curve is derived from the sensitivity variations with cell age which have been determined by Hall et al. [1972] and under the assumption that the survival curves for all individual cell ages are exponential. The broken line is inserted to indicate the deviations from an exponential function.

is therefore an open question, whether the nearly exponential survival curves for mammalian cells which are obtained in G1 and G2 with x rays [Sinclair, 1968] indicate that in these phases of the cell cycle the cell is in a labilized state and is therefore subject to lesions which do not require the interaction of several molecular disturbances, or whether the observed shape of the survival curves is consistent with a primary damage proportional to the square of the specific energy z.

In the latter case the increased sensitivity and the loss of the shoulder of the survival curve would merely indicate a closer concentration of the sensitive structures within the cell nucleus in certain phases of the cell cycle.

APPENDIX

A1. Elements of microdosimetry

The following is a brief survey of microdosimetric quantities and functions and their properties. An explicit introduction into microdosimetry has been given by Rossi [1967, 1968]. A list of definitions can be found in ICRU Report 19 [1971] and in more detail in a summary by Kellerer and Rossi [1969].

SPECIFIC ENERGY AND ITS PROBABILITY DISTRIBUTION AT A GIVEN DOSE

When a mass element, m, is exposed to an absorbed dose, D, then the expected value of the energy imparted to this mass element is mD. The actual energy imparted is however a random variable and can be significantly different from the expectation value, mD. The statistical fluctuations are most expressed for a small mass, m, for small doses, D, and for densely ionizing radiations. For macroscopic objects the distinction between the random variable and its mean value can be neglected, but it is essential in radiobiology where one deals with cellular and subcellular structures.

The ratio of energy imparted to mass, m, is called *specific energy*, z. This is the random variable which corresponds to absorbed dose. For a given value of absorbed dose, a specified radiation quality, and a specified microscopic region the values of z must be described by a probability distribution, $f(z;D)$. The probability that the specific energy lies between z and $z+\mathrm{d}z$ is equal to $f(z;D)\,\mathrm{d}z$.

The expectation value (or mean value) of z is equal to D:

$$\bar{z} = \int_0^\infty z\, f(z;D)\,\mathrm{d}z = D\,. \tag{A1.1}$$

Like the absorbed dose, D, the specific energy, z, is measured in rad.

The distributions $f(z;D)$ can be measured by proportional counters which simulate microscopic tissue regions. Measurement of the distributions $f(z;D)$ for different values of D is however not necessary. The distributions can be computed from the spectrum of z which is produced in single events.

THE DOSE DEPENDENT DISTRIBUTIONS OF z AND THE SINGLE-EVENT SPECTRUM OF z

An *energy deposition event* (or *event*) is defined as energy deposition in a specified region due to an ionizing particle and/or its secondaries. Different events are, by definition, statistically independent.

The probability distribution of the increments, z, produced in a single event is designated by $f_1(z)$. Thus the probability that an event induces an increment of specific energy between z and $z+\mathrm{d}z$ is equal to $f_1(z)\mathrm{d}z$. The spectrum $f_1(z)$ depends on the radiation quality and on the shape and size of the reference volume. Spherical reference volumes are the most important case, and in most microdosimetric measurements spherical proportional counters are used.

The mean value of the distribution $f_1(z)$ is:*

$$\bar{z}_1 = \int_0^\infty z f_1(z)\mathrm{d}z \,. \tag{A1.2}$$

This is the average increase of z per event, and accordingly $\bar{z}_1$ is the inverse of the event frequency per rad.

From the single event spectrum one can compute the spectra of z for any number of events. The spectrum, $f_\nu(z)$, for exactly ν events is the ν-fold convolution of $f_1(z)$.

At dose D the expected number of events is $D/\bar{z}_1$. Because events are statistically independent, their number follows the Poisson distribution, and the probability for exactly ν events is:

$$p_\nu = \mathrm{e}^{-D/\bar{z}_1} \frac{(D/\bar{z}_1)^\nu}{\nu!} \,. \tag{A1.3}$$

The dose-dependent z distributions, $f(z;D)$, can be expressed in terms of these Poissonian probabilities and the convolution products of the single event spectrum:

$$f(z;D) = \sum_{\nu=0}^{\infty} p_\nu f_\nu(z) \,. \tag{A1.4}$$

Computer evaluation of this equation yields the dose dependent z distributions from a measured single-event spectrum [See for example, Kellerer, 1969].

* The quantities which have in an earlier compilation of microdosimetric quantities [Kellerer and Rossi, 1969] been designated by $\bar{z}_F$ and $\bar{z}_D$ are in the present context symbolized by $\bar{z}_1$ and ζ.

MOMENTS OF z

The specific energy at a given dose is the sum of independent increments. The random variable z at the dose $D_1 + D_2$ is therefore the sum of the corresponding random variables at dose D_1 and at dose D_2.

The expectation value of the power z^N of the random variable z is called the N-th moment of z. The moments of the sum of two independent random variables are, in general, not equal to the sum of the moments of the two random variables (the first moment which is equal to the mean is an exception). But, while the moments themselves are not additive, certain combinations of the moments are. These are the so-called cumulants or semi-invariants, κ_N. In the present context, only the first three cumulants are needed. They are particularly simple, and are equal to the mean, and to the second and third central moment:

$$\begin{aligned} \kappa_1 &= \bar{z} \\ \kappa_2 &= \overline{z^2} - z^2 = \sigma^2 \\ \kappa_3 &= \overline{z^3} - 3\,\overline{z^2}\,z + 2\,\overline{z^3}\ . \end{aligned} \tag{A1.5}$$

Because the cumulants are additive, they must be proportional to dose:

$$\kappa_N = c_N D. \tag{A1.6}$$

The constants c_N are most conveniently derived in the limiting case of a very small dose, $D = \varepsilon \bar{z}_1$. In this case eq. (A1.4) simplifies greatly; if one neglects all terms which contain higher than linear powers of ε, one obtains:

$$f(z; D) = (1-\varepsilon)\delta(z) + \varepsilon f_1(z)\,. \tag{A1.7}$$

$\delta(z)$ is the Dirac delta function at the origin; it reflects the fact that with the high probability $(1-\varepsilon)$ no event occurs, so that z is equal to zero. From eq. (A1.7) one can directly compute the moments of $f(z; D)$:

$$\begin{aligned} \bar{z} &= \varepsilon \int_0^\infty z f_1(z)\mathrm{d}z = \varepsilon \bar{z}_1 \\ \overline{z^2} &= \varepsilon \int_0^\infty z^2 f_1(z)\mathrm{d}z = \varepsilon \overline{z_1^2} \\ \overline{z^3} &= \varepsilon \int_0^\infty z^3 f_1(z)\mathrm{d}z = \varepsilon \overline{z_1^3}\,. \end{aligned} \tag{A1.8}$$

The moments of the single-event spectrum are labelled by the index 1 in

order to distinguish them from the moments of the dose-dependent distributions. From these equations one obtains the relations for the cumulants:

$$\begin{aligned} \kappa_1 &= D \\ \kappa_2 &= \overline{z_1^2}/\bar{z}_1 D \,. \\ \kappa_3 &= \overline{z_1^3}/\bar{z}_1 D \,. \end{aligned} \tag{A1.9}$$

By entering these relations which hold for any value of D into eq. (A1.5), one obtains the general relations for the moments of z:

$$\begin{aligned} \bar{z} &= D \\ \overline{z^2} &= \overline{z_1^2}/\bar{z}_1 D + D^2 \\ \overline{z^3} &= \overline{z_1^3}/\bar{z}_1 D + 3\,\overline{z_1^2}/\bar{z}_1 D^2 + D^3 \,. \end{aligned} \tag{A1.10}$$

With the abbreviation:

$$\zeta = \overline{z_1^2}/\bar{z}_1 = \int_0^\infty z^2 f_1(z)\mathrm{d}z \Big/ \int_0^\infty z f_1(z)\mathrm{d}z \tag{A1.11}$$

one obtains:

$$\overline{z^2} = \zeta D + D^2 \tag{A1.12}$$

which is the key equation in section 3. The quantity ζ is the so-called energy average of the event size; it must be distinguished from the frequency average $\bar{z}_1$.

From eq. (A1.12) one can readily obtain the standard deviation of the specific energy, z, from its mean value, D:

$$\sigma = (\zeta D)^{\frac{1}{2}} \,. \tag{A1.13}$$

More detailed derivations of these relations have been given elsewhere [Hug and Kellerer, 1966; Kellerer, 1969].

RELATION TO LET

A quantity which is closely related to the specific energy, z, is the *lineal energy density*, y. This quantity is defined as the energy imparted to a reference region divided by the mean chord length of that region. The mean chord length of a convex region of volume V and surface S is $4V/S$. In the following only spherical regions of diameter d will be considered; in this case one has:

$$z = \frac{20.4}{d^2}\, y\,. \tag{A1.14}$$

The numerical constant in this equation reflects the choice of the units keV, μm, and rad and the fact that unit density is assumed. The quantity y is used only for single events. The distribution $f(y)$ corresponds to the single-event distribution, $f_1(z)$. The mean value of $f(y)$ is commonly called the frequency mean of y:

$$\bar{y}_F = \int_0^\infty y\, f(y)\,\mathrm{d}y = 0.049\, d^2\, \bar{z}_1\,. \tag{A1.15}$$

This must be distinguished from the energy (or dose) mean of y, which corresponds to ζ:

$$\bar{y}_D = \int_0^\infty y^2\, f(y)\,\mathrm{d}y \Big/ \int_0^\infty y\, f(y)\,\mathrm{d}y = 0.049\, d^2\, \zeta\,. \tag{A1.16}$$

Lineal energy density, y, is the microdosimetric analogue of LET. This analogy has in fact been the historical starting point of microdosimetry [Rossi, 1959; Rossi et al., 1961]. If one approximates the y-distribution by the distribution of LET, one has:

$$\bar{y}_F = \bar{L}_T \tag{A1.17}$$

where $\bar{L}_T$ is the so-called track average of LET [see ICRU, 1970]. The dose mean, $\bar{y}_D$, on the other hand, must be approximated by:

$$\bar{y}_D = \tfrac{9}{8}\bar{L}_D\,. \tag{A1.18}$$

The factor $\frac{9}{8}$ accounts for the variations in chord length in the random traversal of a spherical region. A more exact analysis [Kellerer, 1969] shows that $\bar{y}_D$ exceeds $\bar{L}_D$ by an additional term which is due to energy loss straggling. One must choose appropriate cut-off values of the delta ray energy in the definition of LET in order to obtain meaningful comparison with the y-spectra. The cut-off must be such that the maximum delta-ray range is of the order of the dimensions of the reference region. Due to its various limitations the LET concept can only lead to an approximate description of the fluctuations of energy deposition in microscopic regions; use of the y-spectra leads therefore to more accurate results.

FREQUENCY DISTRIBUTIONS AND DOSE DISTRIBUTIONS

In microdosimetry as well as in LET-theory one deals with two types of averages, the frequency averages $\bar{z}_1$, $\bar{y}_F$, $\bar{L}_T$ and the energy averages ζ, $\bar{y}_D$,

and $\bar{L}_D$. The latter quantities are applicable whenever one deals with a RBE which increases with energy concentration; the former are relevant if one deals with event frequencies regardless of event size. The difference between the two types of averages is more easily understood if one distinguishes two different types of distributions, namely *frequency distributions* and *energy* (or *dose*) *distributions*.

The distinction between the two types of distributions is well established in LET theory [ICRU, 1970]. One can either consider the distribution, $t(L)$, of track length in LET, or one can consider the distribution, $d(L)$, of dose in LET. The track average, $\bar{L}_T$, is the mean of $t(L)$, while $\bar{L}_D$ is the mean of $d(L)$.

An analogous distinction can be made for the microdosimetric distributions. While $f(y)$ determines the frequency of events which produce the lineal energy y, one can also use the distribution $d(y)$ of dose in y. The two distributions are directly related:

$$d(y) = y\,f(y) \Big/ \int_0^\infty y\,f(y)\mathrm{d}y = y\,f(y)/\bar{y}_F\,. \tag{A1.19}$$

The mean value of $f(y)$ is $\bar{y}_F$, the mean value of $d(y)$ is $\bar{y}_D$.

In the same way one can use the dose distribution $d_1(z)$ for single events and the dose distribution $d(z;D)$ at a given value D of absorbed dose:

$$d_1(z) = z\,f_1(z) \Big/ \int_0^\infty z f_1(z)\mathrm{d}z = z f_1(z)/\bar{z}_1 \tag{A1.20}$$

and:

$$d(z;D) = z\,f(z;D) \Big/ \int_0^\infty z\,f(z;D)\mathrm{d}z = z f(z;D)/D\,. \tag{A1.21}$$

$\bar{z}_1$ and $\bar{z} = D$ are the mean values of the frequency distributions $f_1(z)$ and $f(z;D)$. The mean values of $d_1(z)$ and $d(z;D)$ on the other hand are ζ and $\zeta + D$ (see eqs. (A1.11) and (A1.12)).

The dose mean is always larger than the frequency mean. The ratio of the dose mean to the frequency mean determines the width of the underlying distribution.

Because the frequency and the dose distributions are closely related one can avoid the explicit use of the dose distributions. The dose averages are then defined as the ratio of the second and the first moment of the frequency distributions.

The dose distribution is proportional to the frequency distribution multiplied by the variable. This multiplicative factor must be distinguished from the same factor which appears whenever the distributions are plotted

versus a logarithmic scale of the variable. In the latter case the factor appears because the logarithmic differential is equal to the linear differential divided by the variable. If the random variable is multiplied into the differential distribution the meaning of the area under the curve as a probability is preserved; if, for example, one takes the case of the single-event distribution of z:

$$f_1(z)\mathrm{d}z = z f_1(z) d \ln z \,. \tag{A1.22}$$

Therefore, whenever the frequency distribution is given on a logarithmic scale of z one must plot $z f_1(z)$. Whenever the dose distribution is given on a

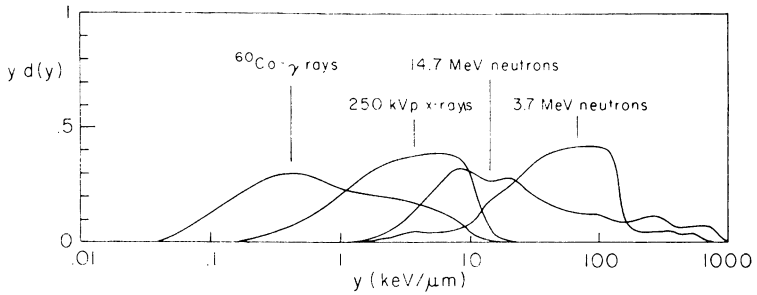


Fig. 23. Distribution of dose in z for single events in spherical tissue regions for various radiation qualities. The curves are based on experimental [Biavati et al., 1965, 1966] and theoretical data [Hug and Kellerer, 1966]; they refer to a diameter of 1 μm.

logarithmic scale one must plot $z d_1(z) = z^2 f_1(z)/\bar{z}_F$; this function gives the fraction of the dose per unit logarithmic interval of z. Fig. 23 is an example of this representation of single-event distributions of dose in y.

A2. Formation of intratrack and intertrack lesions in a site

Consider an ionization* in the site. The probability that this ionization will result in a sublesion (chromosome break) is, according to the assumption discussed in section 4, independent of the energy concentration within the site. However, the probability that a sublesion produced by the ionization will in turn, interact with another sublesion formed by the same track seg-

* As pointed out in section 4 the term "ionization" is used as a convenient abbreviation. It stands for "small increment of absorbed energy", and one may equally use the term "activation event" [Platzman, 1967].

ment within the site, is proportional to the energy, E_s, deposited in this track segment. The energy E_s can, within the approximation of the LET-concept, be set proportional to the length x of the track segment and the value L of the LET of the particle, and one accordingly has:

$$p_1 = \kappa E_s = \kappa x L . \tag{A2.1}$$

In order to obtain the average interaction probability $\bar{p}_1$ per ionization one must integrate the value p_1 over all ionizations in all events with different chord lengths x and LET value L. If the distribution of chord length is designated by $h(x)$ and the crack distribution of LET is $t(L)$ [ICRU, 1970], one has:

$$\begin{aligned}\bar{p}_1 &= \kappa \int_0^\infty \int_0^\infty p_1 x L h(x) t(L) \mathrm{d}x \, \mathrm{d}L \Big/ \int_0^\infty \int_0^\infty x L h(x) t(L) \mathrm{d}x \, \mathrm{d}L \\ &= \kappa \int_0^\infty x^2 h(x) \mathrm{d}x \Big/ \int_0^\infty x h(x) \mathrm{d}x \cdot \int_0^\infty L^2 t(L) \mathrm{d}L \Big/ \int_0^\infty L t(L) \mathrm{d}L .\end{aligned} \tag{A2.2}$$

The second ratio of integrals in this expression is the so-called dose average of LET [ICRU, 1970]:

$$\bar{L}_D = \int L^2 t(L) \mathrm{d}L / \int L t(L) \mathrm{d}L . \tag{A2.3}$$

The first ratio of integrals is the analogous definition of a mean of the chord-length spectrum. If one considers a spherical site of diameter d, one has:

$$h(x) = 2x/d^2 \tag{A2.4}$$

and accordingly:

$$\int_0^d x^2 h(x) \mathrm{d}x \Big/ \int_0^d x h(x) \mathrm{d}x = \tfrac{3}{4} d . \tag{A2.5}$$

Therefore the average probability for intratrack interaction is:

$$\bar{p}_1 = \kappa \tfrac{3}{4} d \bar{L}_D . \tag{A2.6}$$

As a second step the probability per ionization to interact with an ionization produced by a different charged particle can be calculated. At dose D the expected value of the energy deposited in the region is:

$$\bar{\varepsilon} = \tfrac{1}{16} D V . \tag{A2.7}$$

The numerical constant reflects the choice of units. ε is measured in keV, the dose D is in rad, and V is in μm^3. The density of the cellular material is

assumed to be 1. Accordingly the probability of an ionization to interact with a sublesion formed by a different energy deposition event is:

$$\bar{p}_2 = \kappa\bar{\varepsilon} = \kappa\tfrac{1}{16}DV\,. \tag{A2.8}$$

In order to obtain the yield of dual lesions in the cell at a certain dose, D, one must multiply these values by cD where c is a constant. The total probability for the intratrack and intertrack formation of dual lesions is therefore:

$$\begin{aligned}\epsilon(D) &= cD(\bar{p}_1 + \bar{p}_2)\\ &= k\left(22.9\,\frac{\bar{L}_D}{d^2}\,D + D^2\right)\end{aligned} \tag{A2.9}$$

with:

$$k = \frac{c\kappa\pi d^3}{96}\,. \tag{A2.10}$$

For the validity of eq. (A2.9) it must be assumed, as has been pointed out before, that the interaction probabilities per sublesion are small as compared to 1. In the case of chromosome aberrations there is evidence that the condition is fulfilled; the number of single breaks exceeds the number of chromosome aberrations considerably. In the general case, however, and for densely ionizing radiation saturation must be considered (see section 5).

A3. Intratrack and intertrack lesions in the distance model

Consider an ionization within a track of linear energy transfer L. In order to obtain the intratrack interaction probability p_1 one must integrate over the energy laid down at all distances x weighted with the interaction function $\rho(x)$:

$$p_1 = 2\kappa\int_0^\infty L\rho(x)\mathrm{d}x = 2\kappa L\int_0^\infty \rho(x)\mathrm{d}x\,. \tag{A3.1}$$

This relation is analogous to eq. (A2.1). The factor 2 reflects the fact that one integrates from the reference point in both directions along the track. The average value $\bar{p}_1$ of p_1 over the whole LET spectrum is:

$$\bar{p}_1 = 2\kappa\bar{L}_D\int_0^\infty \rho(x)\mathrm{d}x\,. \tag{A3.2}$$

$\bar{L}_D$ is the dose average LET as defined in eq. (A2.3).

The intratrack interaction probability is obtained by integrating the

product of the energy per volume element and the function $\rho(x)$ over spherical shells surrounding the reference point. If one uses the units rad, keV, and μm one obtains:

$$\bar{p}_2 = \kappa \frac{D}{16} \int_0^\infty \pi 4x^2 \rho(x) \mathrm{d}x = \frac{\kappa \pi D}{4} \int_0^\infty x^2 \rho(x) \mathrm{d}x \,. \tag{A3.3}$$

The sum of the intratrack and intertrack effect probability is proportional to the product of $(\bar{p}_1 + \bar{p}_2)$ and the dose, D:

$$\begin{aligned} \epsilon(D) &= c\, D\, (\bar{p}_1 + \bar{p}_2) \\ &= k \left(\frac{8 \bar{L}_\mathrm{D}}{\pi \int_0^\infty x^2 \rho(x) \mathrm{d}x \Big/ \int_0^\infty \rho(x) \mathrm{d}x} D + D^2 \right) \end{aligned} \tag{A3.4}$$

with:

$$k = \frac{c \kappa \pi \int_0^\infty x^2 \rho(x) \mathrm{d}x}{4} \,. \tag{A3.5}$$

Eq. (A3.4) can be written in a form analogous to eq. (A2.9):

$$\epsilon(D) = k \left(\frac{22.9\, \bar{L}_\mathrm{D}}{\Delta^2} D + D^2 \right) \tag{A3.6}$$

if one defines the "effective interaction distance" Δ:

$$\Delta = 3 \left(\int_0^\infty x^2 \rho(x) \mathrm{d}x \Big/ \int_0^\infty \rho(x) \mathrm{d}x \right)^{\frac{1}{2}} . \tag{A3.7}$$

A4. Distance model for a finite site

Site model and distance model are special cases of the more general situation where one deals with sites in which sublesions (single breaks) interact with a probability dependent on their spatial separation. For the analysis of this general case one needs an auxiliary relation concerning the probability distribution of the distance between two points within a spherical site. This relation will be derived first.

Auxiliary theorem: If one chooses a point at random within a sphere of diameter δ then the probability that a second point randomly chosen at a distance x lies within the sphere is equal to:

$$\pi(x) = 1 - \tfrac{3}{2}\frac{x}{\delta} + \frac{x^3}{2\delta^3}, \qquad x \leqslant \delta \tag{A4.1}$$

Proof:

Assume a convex body K for which the integral distribution of chord length is $F(s)$; i.e. $F(s)$ is the probability that the chord length in a straight random traversal is more than s. Assume further that K is randomly intersected by a straight track of length x. This situation has been analyzed [Kellerer, 1971], and it has been found that the resultant distribution of segments in K is:

$$P(s) = k\left((x-s)F(s) - \int_s^x F(t)\mathrm{d}t + \int_x^\infty F(t)\mathrm{d}t + 2\int_s^x F(t)\mathrm{d}t\right), \qquad s \leqslant x \tag{A4.2}$$

where k is a constant. $P(s)$ is the probability that the segment in K is larger than s. The terms in the first line represent those instances where the track crosses K (crossers; in the terminology of Caswell [1966]), the term in the second line represents instances where the track is entirely inside K (insiders), and the term in the third line represents instances where the track lies partially inside K (starters, and an equal number of stoppers).

The probability $\pi(x)$ is equal to $N_i/(N_i + N_s)$ where N_i is the total number of insiders and N_s is the total number of starters. N_i and N_s are obtained by setting s equal to zero in the corresponding terms in eq. (A4.2):

$$N_i = k\int_x^\infty F(t)\mathrm{d}t \tag{A4.3}$$

$$N_s = k\int_0^x F(t)\mathrm{d}t. \tag{A4.4}$$

Accordingly:

$$\pi(x) = \int_x^\infty F(t)\mathrm{d}t \Big/ \int_0^\infty F(t)\mathrm{d}t\,. \tag{A4.5}$$

In the special case of a sphere of diameter δ one has [Kellerer, 1971]:

$$\int_x^\infty F(t)\mathrm{d}t = \tfrac{2}{3}\delta - x + \frac{x^3}{3\delta^2} \tag{A4.6}$$

and therefore:

$$\pi(x) = 1 - \tfrac{3}{2}\frac{x}{\delta} + \frac{x^3}{2\delta^3}. \tag{A4.7}$$

This ends the proof of the auxiliary theorem which is to be used in the following consideration.

Assume that the cell nucleus is homogeneously sensitive and that sublesions within the nucleus have an interaction probability $\rho(x)$ if x is their mutual distance. The diameter of the cell nucleus will be designated by δ. In order to obtain the total interaction probability for a sublesion in the nucleus one must integrate over all distances as in eqs. (A3.2) and (A3.3), but in addition one must multiply $\rho(x)$ by the probability $\pi(x)$ that the activation event formed at a distance x lies within the nucleus. Accordingly one obtains the probability for intratrack interaction:

$$\bar{p}_1 = 2\kappa \bar{L}_D \int_0^\infty \pi(x)\rho(x)\mathrm{d}x \tag{A4.8}$$

and the probability for intertrack interaction:

$$\bar{p}_2 = \frac{\kappa\pi D}{4}\int_0^\infty x^2 \pi(x)\rho(x)\mathrm{d}x\,. \tag{A4.9}$$

These formulae are valid for arbitrary shapes of the sites, in A5 they will be applied to the case of thin sensitive layers. In the special case of a sphere one has:

$$\bar{p}_1 = 2\kappa \bar{L}_D \int_0^\delta \left(1 - \tfrac{3}{2}\frac{x}{\delta} + \frac{x^3}{2\delta^3}\right)\rho(x)\mathrm{d}x \tag{A4.10}$$

$$\bar{p}_2 = \frac{\kappa\pi D}{4}\int_0^\delta x^2\left(1 - \tfrac{3}{2}\frac{x}{\delta} + \frac{x^3}{2\delta^3}\right)\rho(x)\mathrm{d}x\,. \tag{A4.11}$$

One may look at these equations as the equivalent of eqs. (A3.2) and (A3.3) with the only difference that the interaction probabilities $\rho(x)$ are substituted by the more rapidly decreasing effective interaction probabilities:

$$\rho'(x) = \left(1 - \tfrac{3}{2}\frac{x}{\delta} + \frac{x^3}{2\delta^3}\right)\rho(x)\,. \tag{A4.12}$$

If one considers interaction distances x up to 1 μm and assumes a nuclear diameter δ of 7 μm, then the maximal value of x/δ is approximately 0.15, and the correction factor lies between 1 and 0.85. It is therefore not very signi-

ficant, and one concludes that the formalism given in section 4.3 is essentially correct.

In the limiting case of a large δ eqs. (A4.10) and (A4.11) reduce to eqs. (A2.6) and (A2.8); one then deals with the pure distance model. If, on the other hand, one assumes that the interaction probability is constant independent of distance x, one finds that eqs. (A4.10) and (A4.11) simplify to formulae (A3.2) and (A3.3) which describe the pure site model. This will not be formally demonstrated here but it is easily seen by evaluation of the integrals. This leads to the conclusion that by the formulae presented in this section or their equivalents as given in sections 4.2 and 4.3 one derives a characteristic distance which can either be interpreted as an interaction distance, or a site radius, or a quantity representing both of these aspects. The difference of the numerical constants in these equations is insignificant because both models are approximations which provide only estimated values of the interaction distance.

A5. Thin layers as sensitive sites

Assume that the sensitive structures are distributed in thin layers in the cell, for example, as some studies indicate [Alper, 1969], in the vicinity of the nuclear membrane. Assume further that the sensitive layer has a thickness ε, and that sublesions within this layer can interact with the probability $\rho(x)$ dependent upon their separation x. The yield of the intratrack interactions and the intertrack interactions is then determined by the same equations (A4.8) and (A4.9) which have earlier been derived. One must merely evaluate the term $\pi(x)$ for a thin layer, instead of a sphere.

It will be assumed that $\rho(x)$ is constant up to a distance h, and it will also be assumed that the curvature of the thin layer can be neglected.

In a slab of thickness ε one has [Kellerer, 1971]:

$$F(x) = \begin{cases} 1 & \text{for } x \leqslant \varepsilon \\ \varepsilon^2/x^2 & \text{for } x > \varepsilon \end{cases} \tag{A5.1}$$

and according to eq. (A4.5) one obtains:

$$\pi(x) = \begin{cases} 1 - x/2\varepsilon & \text{for } x \leqslant \varepsilon \\ \varepsilon/2x & \text{for } x > \varepsilon\,. \end{cases} \tag{A5.2}$$

Eqs. (A4.8) and (A4.9) therefore take the form:

$$\bar{p}_1 = 2k\bar{L}_D\left(\int_0^{\varepsilon}(1-x/2\varepsilon)\mathrm{d}x + \int_{\varepsilon}^{h}\varepsilon/2x\,\mathrm{d}x\right)$$

$$= \tfrac{3}{2}k\,\bar{L}_D\,\varepsilon\left(1+\tfrac{2}{3}\ln\left(\frac{h}{\varepsilon}\right)\right) \tag{A5.3}$$

and

$$\bar{p}_2 = \frac{k\pi D}{4}\left(\int_0^{\varepsilon}(x^2-x^3/2\varepsilon)\,\mathrm{d}x + \int_{\varepsilon}^{h} x\,\varepsilon/2\,\mathrm{d}x\right)$$

$$= \frac{k\pi D}{16}\,(h^2\varepsilon-\varepsilon^3/6)\,. \tag{A5.4}$$

For $h \gg \varepsilon$ one can neglect the term $\varepsilon^3/6$ and has:

$$\bar{p}_2 = \frac{k\pi h^2\,\varepsilon}{16}\,D \tag{A5.5}$$

therefore one obtains:

$$\epsilon(D) = cD(\bar{p}_1+\bar{p}_2)$$

$$= k\left(7.65\,\frac{\bar{L}_D}{h^2}\,(1+\tfrac{2}{3}\ln(h/\varepsilon))\,D + D^2\right). \tag{A5.6}$$

This formula corresponds to the formula for the simple distance model (see section 4.3) except for the factor $(1+\frac{2}{3}\ln(h/\varepsilon))$.

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