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RBE and the Primary Mechanism of Radiation Action[1]

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KELLERER, ALBRECHT M., AND ROSSI, HARALD H., RBE and the Primary Mechanism of Radiation Action. *Radiat. Res.* **47**, 15–34 (1971).

The dependence of RBE on dose appears to follow a simple relation for a variety of effects on higher organisms and for a broad range of doses. The data indicate that the biological effects are due to primary lesions that may be produced by one or two high LET particles but require the action of at least two electrons when electromagnetic radiation is applied. The interaction distance exceeds 1 μm.

I. INTRODUCTION

There have been numerous attempts to analyze the biological action of radiation in terms of reaction kinetics. This is the essence of all hit- or target-theory studies. Although the approach has met with some success in interpreting the action of radiation on some molecular or microbiological systems, it has failed for higher plants and animals. In the usual approach an attempt is made to account for the shape of the dose-effect curve. This often poses difficulties and ambiguities attendant to the numerical specification of the effect. An even more serious difficulty is that the complex reactions of cells and tissues implicate too many free parameters to allow valid conclusions.

These difficulties are reduced or eliminated if one considers dose-RBE relations instead of dose-effect relations. In this case there is no need to find or construct a numerical scale of effect as one asks by definition only for equality of the effect. Since RBE is the ratio of doses for equal effect, both coordinates in a graph of RBE versus dose refer explicitly only to physical quantities. Another advantage is the elimination of complicating features that are common to both radiations. In some cases there is no such simplification or at least it is not obvious. Thus at the median

[1] Work performed under Contract AT-(30-1)-2740 for the United States Atomic Energy Commission and Bureau of Radiological Health, U. S. Public Health Service.

lethal dose for whole-body exposure of mice, most of the animals exposed to x-rays die because of hemapoietic damage, while those exposed to neutrons die principally because of intestinal injury. Hence the nature of the critical cells is different. On the other hand if one compares skin damage produced by x- and neutron radiations, one may assume that the cells involved are the same. If cell killing, in turn, depends on the production of primary lesions, the unknown influence of this dependence is eliminated provided each lesion is produced independently.

These considerations suggest that attention to RBE rather than to the degree of effect may help to unravel some of the intricacies of radiobiological action. An earlier study (*1*) has indeed demonstrated that in the case of three quite different biological effects a plot of the logarithm of RBE of low energy neutrons relative to x- or γ-rays, versus the logarithm of neutron dose results in a line of slope $-\frac{1}{2}$ over a wide range of doses. This was taken to indicate that the biological action of neutrons is due to the action of single particles, while inactivation by electromagnetic radiation requires two electrons. We have extended this compilation of data on the dose dependence of the RBE in higher organisms. With one possible minor exception all slopes were found to be either $-\frac{1}{2}$ or between $-\frac{1}{2}$ and 0. The latter cases merely reinforce the thesis since they were obtained under conditions where high-energy neutrons very likely produce inactivation by both 1-particle and 2-particle mechanisms.

It is the purpose of this presentation to formulate these conclusions quantitatively and to arrive at some additional results which follow from microdosimetric reasoning. In view of the importance of the subject to radiobiology in general and to radiation protection in particular, we consider it essential that the argument be presented in as general and thorough a manner as practical. This requires unavoidably extensive discussion and some mathematical formalism. It may, therefore, be useful to provide a summary outline of the arguments which will be given.

II. SYNOPSIS

A variety of data will be presented all of which indicate that there is a simple relation between the logarithm of RBE for higher organisms, and the logarithm of dose. This relation suggests that all of the effects are due to primary lesions that are produced by one or by two particles in the case of neutrons having energies up to about 14 MeV and by two electrons in the case of x- and γ-rays.

A general treatment is given of systems comprising states subject to first-order transitions. As a result of this analysis, one can identify the meaning of the coefficients in a power series expansion of the dose-effect relation. There is considerable evidence that low-energy neutrons must at low doses produce primary lesions through the agency of a single charged particle. This leads to the conclusion that for the effects under consideration and within the dose range for which the effects have been established x-rays are essentially incapable of producing these elementary

lesions through the agency of single electrons but can do so through the agency of two electrons. This does not rule out the possibility that a larger number of particles may also cause inactivation but such an assumption is unnecessary. It is furthermore shown on the basis of microdosimetric arguments that such an inactivation mechanism could not exist under conditions where the primary lesion requires a certain threshold of energy deposition in a single spherical or even approximately spherical region (the site). We believe that up to this point no other conclusions can be drawn.

We then proceed to an analysis of the dependence of primary lesions on the specific energy, z, produced in the site by one charged particle track or by a superposition of several tracks. It is concluded that the effect probability is proportional to the square of z in a region larger than 1 μm.

Arguments are presented which indicate that the dependence on z is at least approximately equal for x-rays and neutrons of intermediate energy. For particles of LET exceeding 100 keV/μm, for example for the heavy recoils of high-energy neutrons, the effect probability is less than proportional to the square of z. A subsequent discussion is concerned with some implications of these conclusions.

III. DEPENDENCE OF RBE ON DOSE

Figure 1 is a compilation of data on the dependence of RBE of neutrons on dose of the reference radiation (usually x-rays). The solid lines represent the results of experiments involving various higher organisms. These have been collected from all the work known to us according to a number of criteria.

Experiments on cells in tissue culture have been excluded primarily because of uncertainties in dose-effect relations at low doses. The small degree of effect does, of course, present problems for all observations at low doses, but in the case of tissue cultures such aspects as multiplicity corrections and variable plating efficiency introduce additional sources of error. Certain considerations also suggest that for cells in tissue culture, the sites which are susceptible to the primary lesion can be of the same nature but be in a different condition (see discussion).

It is difficult to specify the accuracy of the solid lines in Fig. 1, because a suitable error analysis has often not been provided by the experimenter and also because RBE values had to be obtained by interpolation between data points (no extrapolations were made). However, we believe that the line segments are almost certainly within the accuracy of the experiments. Some of the data suggest a slight curvature similar to that in the theoretical relation (dotted line) which corresponds to a formula to be given in Section VIII.[2]

It will be noted that with one exception (curve 2a) all lines have slopes between -1 and 0; in several instances the value -1 is reached.

There is strong evidence from microdosimetric considerations (*2*, *3*) that for low doses of low-energy neutrons the cell is very unlikely to be traversed by more than

[2] Equation (20) with $(\bar{z}_D)_x = 0$ and $(\bar{z}_D)_N = 1000$ rad.

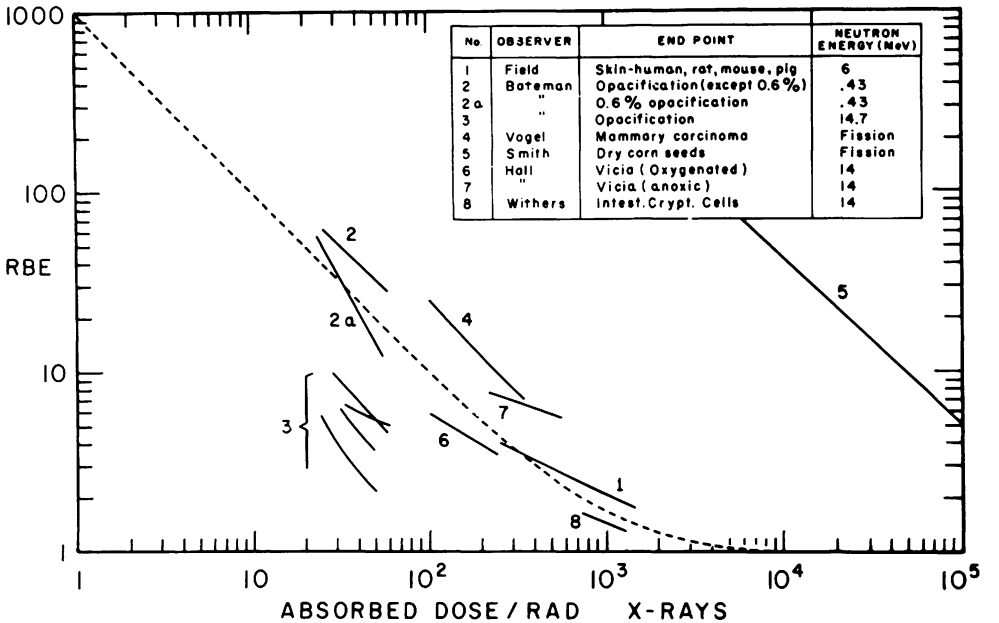

FIG. 1. RBE of neutrons as a function of absorbed dose of x-rays for various biological end points. The data are from Refs. (*7*, *13–17*).

one charged particle. Based on this premise we shall demonstrate that for the range of effects and doses represented in Fig. 1, neutrons of energy in excess of a few MeV can produce primary lesions through the agency of one or two particles while the electromagnetic radiations can not with appreciable probability produce these lesions through the agency of a single electron.

IV. GENERAL CONSIDERATION

One may expand a dose-effect relation into a power series in absorbed dose:

$$E(D) = k_1 D + k_2 D^2 + \cdots \tag{1}$$

This relation applies no matter what the effect in question. However, in the following it will be assumed that $E(D)$ represents the frequency of primary lesions. This may be related in a complex manner to cell inactivation or another biological effect in question.

It is plausible to associate the coefficient of the linear term with a one-step process, and the second-order term with a two-step mechanism. This interpretation is supported by the fact that radiation energy is deposited in the cell in discrete events which are statistically independent. We will in the following speak of *energy*

deposition events (sometimes merely referred to as *events*) and denote by this term energy deposition by one charged particle and/or its δ-rays. An energy deposition event may in some region merely cause a simple electronic excitation or ionization, but it may also generate a large number. The latter is almost invariably the case when the region in which the event occurs is large and the LET of the particles is high.

Although the meaning of the coefficients in a power expansion of the effect as a function of dose may intuitively seem clear, it is nevertheless necessary to prove this by a mathematical analysis. Several considerations will be employed to demonstrate without recourse to a particular model that the linear coefficient is always due to a one-step effect, that is to radiation action produced by a single event. Further, it will be shown that a positive coefficient in the second term always implies that the effect can also be brought about in two absorption events. This is not true for higher order terms; as will be seen, these can be positive even if no reaction of this order is taking place. If however, a power relation starts with the term of order n, then the effect can be produced in n steps and in no less than n steps. We will ultimately only be concerned with the meaning of the first and second term. But the above remarks may indicate that interpretation of the first- and second-order term, though intuitively obvious, is by no means trivial.

It has been mentioned that the energy deposited in an event in a particular region can vary widely. In view of this fact and of the complexity of the cellular structures, it is necessary to start with a rather unspecific formulation of the primary processes. Assume that the occurrence of an energy deposition event changes the state of a subcellular unit (hereafter termed a *site*). The change may result in the effect, it may also create an intermediate state of damage from which the effect can eventuate following one or more additional energy deposition events. Naturally one could assume a continuum of possible states of damage or predamage; one may, however, without too much loss of generality restrict the discussion to a discrete number of possible states of the object.

In the following discussion no state transitions will be considered that are not caused by radiation. Processes which are not radiation induced will in general proceed at rates that are controlled by physiological or biochemical rates and this leads to dose-rate effects. In particular, "recovery" might be regarded as a reverse transition. Although dose rate effects are of great interest, it is necessary to first establish a framework of general relations before the analysis is to be carried further. In the present paper only nearly instantaneous application of the dose is considered.

V. THE MEANING OF THE EXPANSION COEFFICIENTS

According to the approach outlined above, the behavior of a homogeneous population of cellular and subcellular objects under irradiation is described by the fractions of the exposed population in the different states at various levels of the ab-

sorbed dose. Speaking of the fraction of a population in a particular state or of the probability of a particular member of this population to occupy this state is, of course, equivalent. Assume that the possible states are numbered from 1 to n, that states 1 to $n-1$ do not exhibit the effect, and that the effect in question (i.e., the irreversible lesion) is associated with a state n. Let $x_i(D)$ be the fraction of objects in state i at absorbed dose D. Then the behavior of the system is governed by the system of differential equations:

$$\frac{dx_i(D)}{dD} = \sum_{k=1}^{n} a_{ik}x_k(D), \quad i = 1 \ldots . n. \tag{2}$$

The linearity of Eq. (2) is due to the fact that in addition to the statistical independence of energy deposition events, there is also no interaction between the members of the population. The constants a_{ik} ($i \neq k$) represent the frequency of transitions per unit absorbed dose from state k to state i for an object which occupies state k. In the diagonal of the matrix of coefficients one has the constants a_{ii} which are equal to $-\sum_{k \neq i} a_{ki}$, the negative of the exit frequency from state i per unit dose. The coefficients a_{ik} will be termed *transition frequencies* or *matrix elements*.[3]

The system of Eq. (2) describes a linear stochastic process familiar from such applications as for example the so-called multicompartment models. It is practical, although merely a matter of convenient shorthand notation, to write Eq. (3) in matrix form:

$$\frac{d}{dD}\vec{x}(D) = \mathbf{A} \cdot \vec{x}(D), \tag{3}$$

where $\vec{x}(D)$ is the state vector with the components $x_i(D)$ and $\mathbf{A}$ is the so-called transition matrix consisting of the elements a_{ik}.

The solution of Eq. (3) is familiar from the application to linear stochastic systems:

$$\vec{x}(D) = e^{\mathbf{A}D}\,\vec{x}(0), \tag{4}$$

where $\vec{x}(0)$ is the state vector at dose zero. Its only nonzero component is $x_1(0) = 1$.[4]

The matrix $e^{\mathbf{A}D}$ is given by the power series:

$$e^{\mathbf{A}D} = \mathbf{I} + \mathbf{A}D + \frac{\mathbf{A}^2D^2}{2!} + \frac{\mathbf{A}^3D^3}{3!} + \ldots . , \tag{5}$$

where $\mathbf{I}$ is the unit matrix. Thus one has:

$$\vec{x}(D) = \left(\mathbf{I} + \mathbf{A}D + \frac{\mathbf{A}^2D^2}{2!} + \ldots .\right)\vec{x}(0), \tag{6}$$

[3] To avoid confusion with the coefficients of the power series, the common term "transition coefficients" is not employed.

[4] This presumes no previous irradiation of the system. Extension of the model to multiple irradiations (such as fractionation with recovery or change of radiation type) will be considered in later articles.

or if one merely asks for the component $x_n(D)$ which is equal to the effect probability $E(D)$:

$$E(D) = a_{n1}D + \frac{\sum_k a_{nk}a_{k1}}{2!} D^2 + \frac{\sum_{k,r} a_{nk}a_{kr}a_{r1}}{3!} D^3 + \ldots \tag{7}$$

as can be easily verified from the rule for matrix multiplication. One should note that this relation can be deduced from Eq. (2) by elementary methods applicable to systems of linear differential equations and without use of matrix notation. However the derivation would be much more complicated.

Equation (7) is the general relation which applies to the power expansion of any effect as a function of dose. The coefficients are made up of products of transition frequencies between different states. Each represents a possible pathway between state 1 and the effect which corresponds to the state n.

From Eq. (7) one can derive a scheme which make it possible to derive the power expansion without involved calculations for any model one may want to choose. Depict a particular model by a linear flow system consisting of state points and connecting lines which represent the transitions between these states. The expansion coefficient of order ν is then made up of all products of transition frequencies which consist of exactly ν terms with matching indices, i.e., indices which represent pathways leading from state 1 to the final state n. Such a concatenation of transitions may contain matrix elements, involving no change of index and represented by factors a_{ii}. If there is an odd number of such steps among the ν factors the contribution to the sum representing the coefficient of order ν is negative. The method will be applied in section VIII, where a specific model of radiation action is discussed.

Equation (7) defines the meaning of the coefficients in the power expansion of $E(D)$. The first-order coefficient is the one-step transition frequency a_{n1}. The second-order coefficient is the sum of all products formed between the matrix elements a_{nk} and a_{k1}. The second-order coefficient can be negative since it includes the product $a_{n1}\, a_{11}$ which can be negative. One can, therefore, state in general that the two-step inactivation probability is always at least as large as indicated by the second-order coefficient, k_2 :

$$\frac{\sum_{k \neq 1} a_{nk}a_{k1}}{2} \leq k_2 . \tag{8}$$

Thus if the effect can be produced by one energy deposition event, the second-order coefficient may be positive, zero or negative although two-step inactivations may occur with appreciable probability.

Corresponding statements can be made regarding higher order expansion coefficients, but these will not concern us here. One should, however, note that, for example, the third-order coefficient can be positive even if there is no three-step action. This is due to the fact that the term $a_{n1}\, a_{11}^2$ is positive.

VI. APPLICATION TO THE RBE-DOSE RELATION

With this information on the expansion coefficients one may now consider RBE and its dependence on dose. At the lowest level of effect, it suffices to examine the first nonzero expansion term for the two radiations which are involved. The indices N and x will be used to indicate the case of neutron or x irradiation.

One knows that there is one-event action for low-energy neutrons and one, therefore, has the effect probability:

$$E_N = k_N D_N . \tag{9}$$

The lowest significant reaction order for x-rays will be designated by n_x. One then has:

$$E_x = k_x D_x^{n_x}. \tag{10}$$

Since RBE $= D_x/D_N$ when $E_N = E_x$, it follows that

$$\text{RBE} = k_x/k_N \, D^{1-n_x}. \tag{11}$$

The experimental evidence compiled in Fig. 1 indicates that at low doses of low-energy neutrons the RBE is proportional to D_x^{-1}. Therefore:

$$n_x = 2. \tag{12}$$

Thus an initial slope of -1 of the RBE relations in Fig. 1 shows that in the dose range observed x-rays do not work by one-event mechanisms, but that they can indeed bring about the effect in two statistically independent energy deposition events. An obvious extension of these considerations is to conclude that in cases where the slope is between -1 and 0 both one- and two-event processes are involved for neutrons. The applicable relations will be given in a later section.

VII. PHYSICAL DIMENSIONS OF SITES

In the following some considerations will be given which eliminate certain models and which indicate that the site is structured.

Electrons in traversing a volume of dimension 2 μm or less exhibit such extreme fluctuations of energy deposition that the probability of reaching any particular value of energy deposition in one event is never small as compared with the probability to reach this value in two events. Figure 2 illustrates the point for the case of spherical tissue regions of 0.5, 2, and 7 μm diameter. The curves represent the probabilities $P_1(z)$ and $P_2(z)$ that a specific energy[5] larger than z is produced in one or two events. These curves are computed from experimental data for ^{60}Co γ-radiation (4). The ratio of the probabilities is never large; over a wide range of z it does not exceed

[5] The "specific energy", z, unlike absorbed dose which is only a mean value, represents the actual energy density in a given region. For the formal definition of z and its probability distributions see Appendix.

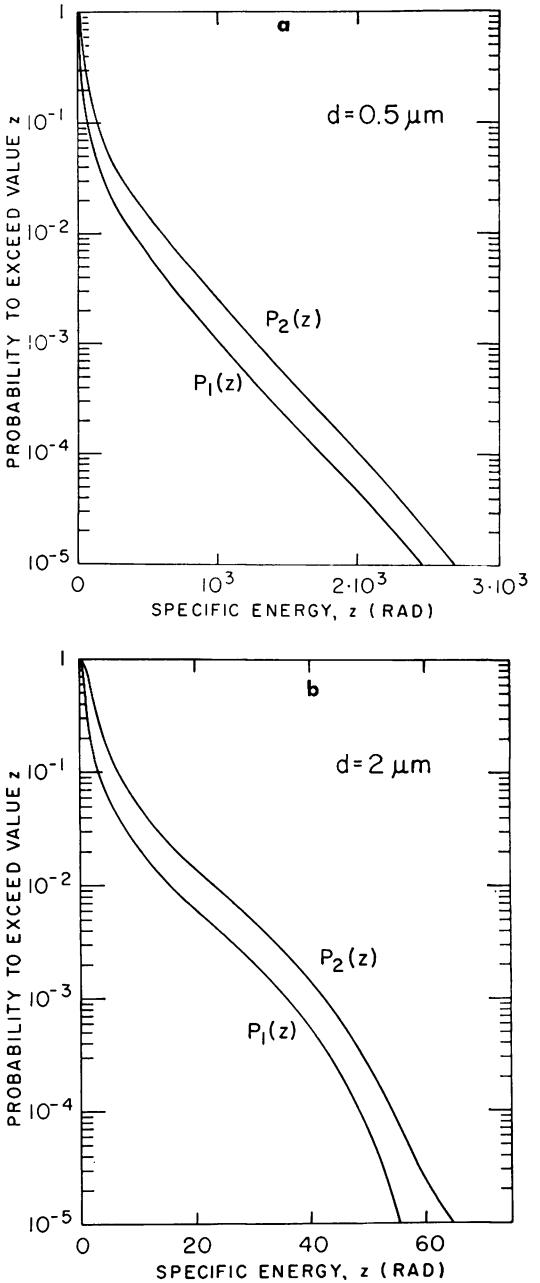

FIG. 2. The probability to exceed the value z of specific energy in one and in two events. The curves are for ^{60}Co γ-radiation and for tissue spheres of 0.5, 2, and 7 μm diameter.

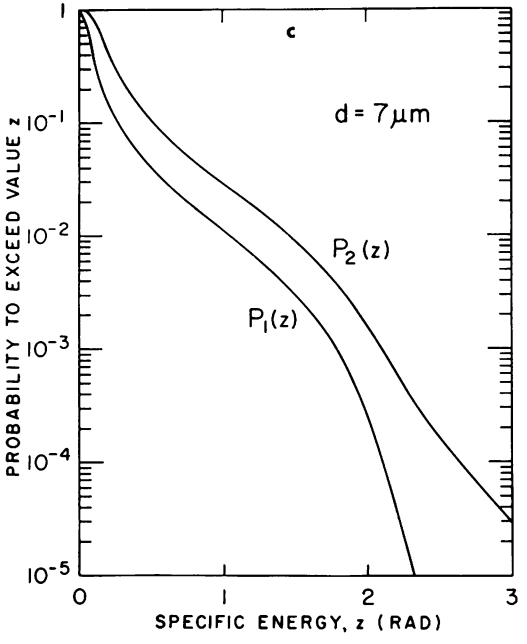

FIG. 2c

two. Because of the additional fluctuations due to the large variability of path length, the ratio between $P_1(z)$ and $P_2(z)$ must be even smaller in nonspherical regions. It must also be smaller if the volume is smaller because then the relative fluctuations of energy deposition are more extreme.

As has been shown, the relations in Fig. 1 must be explained by the improbability that a single electron produces the initial lesions while the effect can be induced by two electrons. The assumption of a compact sensitive site of the order of magnitude of 1 μm or less and with a critical threshold of energy deposition must, therefore, be dismissed according to the considerations given above.

For volumes larger than 2 μm there is, on the other hand, a certain narrow range of z values which can be reached in two events with much higher probability than in one event. This is seen from the curves for a spherical volume of 7 μm diameter. This might be taken to indicate that for larger sensitive sites a compact sensitive volume with a threshold of z could, indeed, explain the observed second-order inactivation kinetics. However, as indicated by the scale of the abscissa the values of z are between only about 2 and 4 rad. This is much less than the doses required for the effect according to the experimental observations. The idea of a compact sensitive volume with a fixed threshold of specific energy, z, must, therefore, be rejected.

This indicates that the sensitive site has structure. The site is extended over a

certain region, in the following termed the "gross sensitive volume." Since the site occupies only part of the gross sensitive volume, energy deposition in the latter has a limited effect probability. If one wants to interpret this geometrically one can say that two loci within the site have to be affected. If one wants to think purely in terms of reaction kinetics one may say that certain radiation products, either on the primary stage of electronic disturbances or on the succeeding level of free radicals, have to interact. The second-order kinetics are thus related to the diffuseness of the site and its loci and they are consistent with the fact that in the dose range of interest many more than two absorption events may occur within the gross sensitive volume.

In order that at a certain absorbed dose the mean number of events is two or exceeds two, the gross sensitive volume must have a minimum diameter. The actual values can be taken from microdosimetric results. Figure 3 gives the mean number of events at an absorbed dose of 1 rad for Co γ-radiation and x-rays. The data are taken from measurements on spherical tissue-equivalent proportional counters (*4*). The x-ray data are based on data derived with Tm 170 (*5*) and on calculations (*6*).

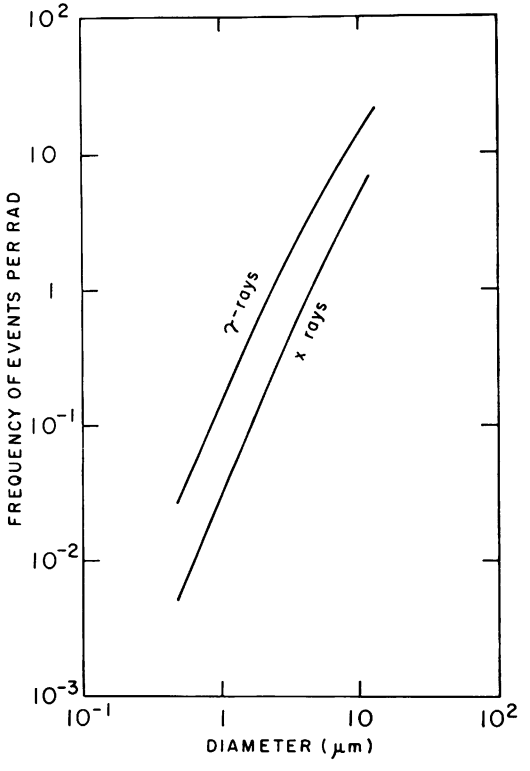

FIG. 3. Mean number of energy deposition events at an absorbed dose of 1 rad in tissue spheres of diameter *d*.

Some lines of slope -1 in Fig. 1 are in the dose range around 50 rad. In order to obtain an average number of two events at 50 rad and with x-rays, one has to have a site which extends over more than 1 μm in diameter if the site inactivation frequency is to be equal to the frequency of the biological effect under consideration.

The possibility remains that only *one* of a *number* of sites needs to be inactivated to produce the effect. In this case, each of these sites could be smaller, but due to the steepness of the curves in Fig. 3 even a tenfold reduction in probability of the dual events would lead to only an approximately threefold reduction of minimum site diameter. As will be shown later there are other considerations indicating that the sites have a diameter somewhat in excess of 1 μm.

VIII. THE TWO-STEP MODEL OF RADIATION ACTION

The preceding arguments were based on the observation that at low doses the primary lesion is produced by two electrons while it can be due to a single heavy particle. It is certainly a simplification to adopt this model in all instances. At higher doses there may be different modes of action and what has been found to be dominant at low doses need not be a relevant mode of action at higher doses.

It still seems profitable particularly with regard to radiation protection to consider the simplest form of a complex target which would appear to be a site that is impaired by a dual lesion. The lesion can either be induced by two independent charged particles or instantaneously by one charged particle.

Traditionally such models either stipulate two locations on one "target" (two-hit model) or one location on each of two "targets" (two-target model). The parameters of either model can be related to the frequencies in Eq. (2) and consequently to the coefficients in Eq. (7). However, such a course is unnecessary, and the principal conclusions can be drawn without choice between these alternatives or perhaps even other models.

One may simply consider the general scheme of a two-step inactivation process, as

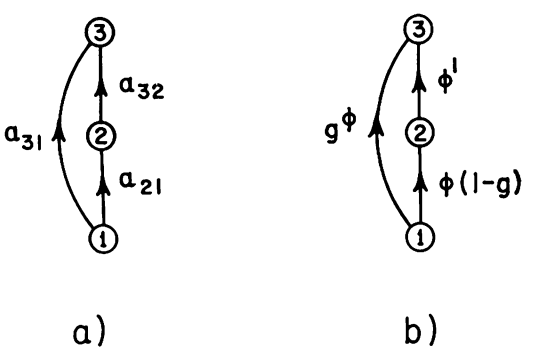

FIG. 4. General scheme of a two-step inactivation process.

represented in the sketch of Fig. 4, a. In this scheme, (1) is the state of no damage, (2) the state of predamage, and (3) represents the effect. The frequencies a_{21}, a_{32}, and a_{31} are the event probabilities per unit absorbed dose. By suitable choice of these frequencies one may select various two-step inactivation models; the only restriction lies in the fact that Fig. 4 does not include reverse processes.

In order to make the meaning of the frequencies somewhat more obvious one can rewrite the scheme according to Fig. 4, b. Here ϕ is the total frequency per unit dose of events affecting the undamaged site, and g is the fraction of events which induces the double lesion at once, ϕ' is the frequency per unit dose of events which lead from the state of predamage to the fixed damage. One should note that this implies no new assumptions; it is merely a change in notation which serves to indicate that the transition probabilities can be considered as cross sections. The relations between the elements of the transition matrix and the cross sections are as follows:

$$\begin{aligned} a_{21} &= \phi(1-g) & a_{12} &= 0 \\ a_{31} &= g\phi & a_{11} &= -\phi \\ a_{32} &= \phi' & a_{22} &= -\phi' \end{aligned} \tag{13}$$

It can be shown that the so-called two-hit model with superimposed single hit inactivation corresponds to the case $\phi' = \phi$, while the so-called two-target model is represented by $\phi' = \phi/2$. From the model one can derive the RBE-relations which result if a radiation with $g = 0$ (x-rays) is compared to another radiation with $g > 0$ (neutrons). In the limiting case of g values small as compared to 1, one obtains the dotted curve which is plotted in Fig. (1). For larger values of g, one obtains a slightly different curve. The difference is, however, quite insignificant, and moreover one finds that it makes very little difference whether one assumes $\phi' = \phi$ or $\phi' = \phi/2$. In the following it will, therefore, be assumed that $\phi' = \phi$. This is not to be taken as a choice between two alternatives; it merely reflects the fact that the limited accuracy of available data makes it impossible to distinguish between a two-hit mode of action on primary sites and a two-target mechanism.

According to the rule derived in section V and formulated in Eq. (7), one can give the power expansion of $E(D)$ directly from the scheme of Fig. 4b:

$$E(D) = k_1 D + k_2 D^2 = g\phi D + \frac{\phi^2(1-g) - g^2\phi^2}{2} D^2. \tag{14}$$

For $g \ll 1$ one has:

$$E(D) = g\phi D + \frac{\phi^2}{2} D^2. \tag{15}$$

For larger values of D the second-order coefficients predominate and RBE approaches the value $\sqrt{k_{2,N}/k_{2,x}}$. From Fig. 1 it appears that all curves are consistent with the assumption that the RBE is near to 1 for doses which are so large

that the first term in Eq. (15) can be neglected not only for x-rays but also for neutrons. This means that the second-order reaction is nearly independent of LET, and indicates that the inactivation of loci is due to single electronic collisions or to single free radicals produced in the physicochemical transformations induced by such a collision. If the inactivation of a locus were dependent on critical concentrations of energy deposition or of radiation products one would have to find strong dependence on LET and an RBE much larger than one at high doses.

While the inactivation of loci seems to be independent of LET up to the maximum LET of protons, it is also known from studies with heavy charged particles that RBE decreases at LET values exceeding 100 keV/μm. At this LET, one has about 1500 primary collisions/μm of the track, and one deduces an effective diameter of about 1/1500 μm or 0.7 nm for a locus. The result does not necessarily mean that the loci are actually well-defined volumes of this size; but whether one interprets the cross section in a geometrical or in a purely formal manner, one must conclude that an ionization or a δ-ray in the site has only a small probability of damaging one locus. This must be the case since the electron which is likely to produce several ionizations when traversing the gross sensitive volume of a site appears to have negligible probability of affecting two loci.

With this information one can proceed one step further and relate the constants g and ϕ to microdosimetric quantities. This may be done with the assumption that a site consists of a large number of loci dispersed over a spherical region in such a way that electronic collisions occurring anywhere in the site have equal probability of impairing a locus. One may assume, at least in a first approximation, that this probability is independent of the velocity or mass of the charged particle; then the probability, p, that in a site that has received specific energy z one of the loci is impaired is equal to:

$$p = \phi z.$$

Because p is small, the probability, p', for the induction of a dual lesion is according to Poissonian statistics equal to $p^2/2$:

$$p' = \phi^2 z^2/2. \tag{16}$$

The frequency of site inactivation by a *single* event is obtained by integration of p' over the event size distribution, $f_1(z)$.[6] The product of this integral and of the frequency of events per rad, $1/\bar{z}_F$, is then equal to the frequency, $\epsilon g\phi$, of the one-step induction of a lesion per rad of absorbed dose:

$$g\phi = \int_0^\infty \phi^2 z^2 f_1(z)\, dz/2\bar{z}_F = \phi^2 \bar{z}_D/2 \quad \text{and} \quad g = \phi \bar{z}_D/2, \tag{17}$$

where $\bar{z}_D$ is the so-called dose mean of the event size. With these values one obtains

[6] For the definition of the distribution, $f_1(z)$, of specific energy see Appendix.

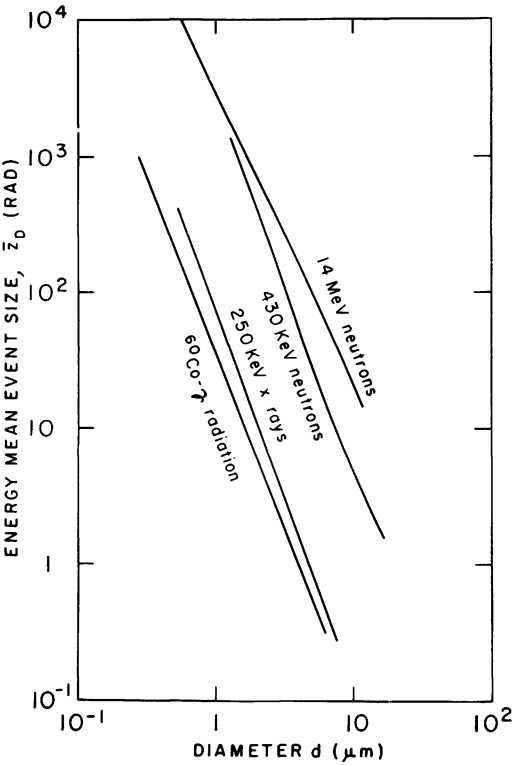

FIG. 5. Energy mean, $\bar{z}_D$, of specific energy produced in an event as a function of the diameter, d, of the tissue sphere.

from Eq. (15):

$$E(D) = [\phi^2/2]\,(\bar{z}_D\,D + D^2). \tag{18}$$

This important relation shows that the absorbed dose, D, must be large as compared to $\bar{z}_D$, if the linear term in the effect relation is to be small as compared to the quadratic term. In other words, if for x-rays at 100 rad the quadratic term is to be dominant, $\bar{z}_D$ must be much smaller than 100 rad; this as shown in Fig. 5 is the case only for sites with diameters larger than 1 μm.

Assume that the doses D_N and D_N of x-rays and neutrons have the same effect:

$$E(D_x) = E(D_N),$$

or

$$(\bar{z}_D)_x\,D_x + D_x^2 = (\bar{z}_D)_N\,D_N + D_N^2. \tag{19}$$

From $RBE = D_x/D_N$ it can be readily shown that:

$$RBE = \frac{(\bar{z}_D)_N + \sqrt{(\bar{z}_D)_N^2 + 4[(\bar{z}_D)_x + D_x]D_x}}{2[(\bar{z}_D)_x + D_x]} \tag{20}$$

It should be noted that this relation has been derived with the assumption that ϕ has the same value for x-rays and neutrons. As mentioned above this assumption appears to be approximately met in the case of electrons and protons but it is unlikely to hold for heavy recoiling nuclei where ϕ is probably less. These considerations cannot, therefore, not be applied to 14 MeV neutrons, because a substantial fraction of the absorbed dose produced by these and other high-energy neutrons is due to heavy recoils.

The characteristic difference between neutrons and x-rays is that:

$$(\bar{z}_D)_N \gg (\bar{z}_D)_x . \tag{21}$$

One may distinguish three principal regions in the RBE versus D_x relations:
(a) Very high doses:

$$D_x \gg (\bar{z}_D)_N \gg (\bar{z}_D)_x . \tag{22}$$

In this case Eq. (20) reduces to: $RBE = 1$.
(b) "Low" doses:

$$(\bar{z}_D)_N \gg D_x \gg (\bar{z}_D)_x . \tag{23}$$

Here:

$$RBE = \frac{(\bar{z}_D)_N}{D_x} .$$

(c) Very low doses:

$$(\bar{z}_D)_N \gg (\bar{z}_D)_x \gg D_x . \tag{24}$$

Here:

$$RBE = \frac{(\bar{z}_D)_N}{(\bar{z}_D)_x} .$$

Case (c) does not appear in Fig. 1, but on the basis of the model under discussion it must be presumed to exist. In fact one can take the ratio $(\bar{z}_D)_N/(\bar{z}_D)_x$ from Fig. 5 and so obtain an estimate for the coefficient of the linear component in Eq. (18), i.e., $\bar{z}_D$, with x-rays or γ-rays.

The dotted line in Fig. 1 corresponds to Eq. (20) and to the values:

$$(\bar{z}_D)_x = 0, \qquad (\bar{z}_D)_N = 1000 \text{ rad}. \tag{25}$$

From Eq. (23) one can see that $(\bar{z}_D)_N$ is equal to the absorbed dose at the point

TABLE I

Author and No. of cures in Fig. 1		*Estimate of* $(z_D)_N$ *(rad)*	*Diameter* d *(m)*
Field	(1)	1200	1.5
Bateman	(2)	1700	1.3
	(2a)	950	1.7
	(3)	100–200	3–4
Vogel	(4)	2500	1.0
Smith	(5)	400 000	0.15
Hall	(6)	600	2.0
	(7)	2200	1.1
Whithers	(8)	700	1.9

where the extrapolation of the line of slope -1 intersects the line $RBE = 1$. Estimated values of $(\bar{z}_D)_N$ for the different experiments and corresponding diameters of the sites according to Fig. 5 are listed in Table I. It will be seen that the values are similar except for the case of dry corn seeds (*7*).

One must note that these relations have been derived under the simplifying assumptions that the sites of the primary lesions can be represented by spherical regions which contain the sensitive loci homogeneously dispersed. In so far as this is probably only an approximation for a situation which may more properly be represented by a diffuse site, one has to assume a somewhat larger diameter of the site.

IX. DISCUSSION

The concept that radiobiological effects require energy deposition in two sites was proposed by Wolff and Neary (*8*) to explain chromosome interchanges and by Rossi (*3*) to account for the RBE of neutrons of different energy in the opacification of the murine lens. The deductions made here are very similar to those made by Wolff and Neary who assumed that in their system loci ("targets") are chromosome strands and that the site is the volume within which recombination of broken chromosomes can occur. One might extend this interpretation and conclude that all of the effects shown in Fig. 1 are due to chromosome aberrations involving two chromosomes. Such a generalization seems hardly justified at this stage. However, the arguments presented here are entirely consistent with the notion that large numbers of small targets are aligned in filamentous structures within a site.

The model which has been presented is one for primary lesions and it applies to the dependence of RBE on dose only for those effects which are produced by primary lesions which are statistically independent. If there is interdependence for neutrons, and several primary lesions are necessary for the effect, then the slopes in the RBE plots should be steeper than observed.

The various factors which influence the relation between primary damage and the overall cellular effect vary from system to system and may also depend on experimental conditions. It is, therefore, in general not possible to derive explicit dose-effect relations from the kinetics of the primary lesions.

It is, however, of interest to consider the simplest assumption that a single primary lesion is sufficient for cell inactivation. If one assumes that the total number, N, of sites is large, then one obtains the survival probability $S(D)$ from Eq. (15):

$$S(D) = (1 - g\phi D - .5\,\phi^2 D^2)^N = e^{-g\phi ND - .5\phi^2 ND^2} \tag{26}$$

This is the so-called autocatalytic or logistic curve (*9*) which fits certain survival curves of cultured mammalian cells (*10*). One must, however, note that in this particular system the survival curves depend on various biological and physical parameters. The observed dose-effect relation can, therefore, not directly reflect the simple kinetics of the dual lesions.

Certain survival curves, particularly those for cells in S-phase exposed to x-rays, have too wide a shoulder to fit Eq. (26). One can in fact show that these curves have a shape which is incompatible with any model which leads to the effect in less than four statistically independent energy deposition events (*6*). In these cases the effect can therefore not be due to a single dual lesion.

On the other hand there are examples of survival curves which are consistent with Eq. (26) but which seem to indicate a linear component ($g > 0$) even with x-rays. This has been observed when mammalian cells are irradiated in interphase (*11*) and in certain phases of the cell cycle (*12*). The observation has a number of possible explanations:

1. Sites have a range of values of ϕ and g.
2. Although the nature of the site is the same its physiological condition is not (e.g., some loci are already affected by agents other than radiation).
3. The model is not applicable since the data in Fig. 1 refer predominantly to cells in the "G_0" phase.

It must be established whether these or other alternatives are correct before the model can yield further conclusions concerning basic mechanisms in the action of radiation upon the cell.

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APPENDIX

Definition of Specific Energy and its Probability Distributions

The specific energy, z, is defined as the energy deposited by ionizing radiation in a certain volume divided by the mass in this volume. Due to the statistical nature of radiation and its interaction with matter z is a random variable, the mean value of z is the absorbed dose, D.

The relative fluctuations of z are larger for smaller volumes, for lower doses, and

for less densely ionizing radiation. A quantitative description can be given in terms of the probability distribution, $f(z; D)$, of z at an absorbed dose D. The probability for a value between z and $z+dz$ is equal to $f(z; D)dz$. The probability, $P(z)$, that the specific energy exceeds the value z at dose D (see Fig. 4) is given by the integral:

$$P(z) = \int_z^\infty f(z;D)\, dz.$$

The dose-dependent distribution $f(z;D)$ can be calculated from the probability distribution, $f_1(z)$, of values z brought about in a single energy deposition event. An event is energy deposition in the volume of interest due to one or more ionizing particles which arise from the same quantum-mechanical event (e.g., disintegration event, or accelerated particle).

The mean event size, $\bar{z}_F$, is the first moment of the distribution $f_1(z)$:

$$\bar{z}_F = \int_0^\infty z\, f_1(z)\, dz.$$

This quantity is also called "frequency mean" in order to distinguish it from the "energy mean" or "dose mean":

$$\bar{z}_D = \int_0^\infty z^2\, f_1(z)\, dz \,/\, \int_0^\infty z\, f_1(z) dz.$$

The frequency of events per rad of absorbed dose in a region is equal to $1/\bar{z}_F$. The variance of z at an absorbed dose D is equal to $\bar{z}_D D$. Both mean values are of practical importance. $\bar{z}_D$ is always greater than $\bar{z}_F$.

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