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A Generalized Formulation of Dual Radiation Action[1]

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Dual radiation action is a process in which cellular lesions are produced as a result of the interaction of pairs of sublesions that are molecular alterations produced by ionizing radiation. Previous formulations of this process have employed a number of simplifying assumptions that limit the accuracy and the range of application of theoretical analysis. The formulation presented here removes some of these restrictions by introducing three functions that describe the geometry of the sensitive material in the cell, the geometry of the pattern of energy deposition, and the interaction probability of sublesions as a function of their separation. The relation derived is similar to that obtained previously, in that lesion production is found to depend on two terms that are proportional to the first and the second power of the absorbed dose. However, the coefficients of these terms are now derived on the basis of a more realistic treatment.

INTRODUCTION

The term *dual radiation action* can refer to a variety of mechanisms. Common to these is that *sublesions* are produced depending on the pattern of energy transfers to the cell, and that these sublesions can interact in pairs to produce *lesions* which in turn determine the observed effect. The general notion of dual radiation action thus comprises a broad spectrum of mechanisms, and it is very difficult to provide a mathematical formulation which covers all the possible mechanisms in such a way that the microdistribution of imparted energy as well as the geometry of the sensitive structures in the cell is accounted for. It had been necessary, therefore, to rely on various simplifications which restrict the applicability and the accuracy of theoretical treatments. In the following a formulation is presented that avoids many—although not all—of the restrictions. The necessarily complex mathematical treatment leads to a relatively simple general

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formula, and it is followed by a number of practical applications. However, before this material is presented, it will be useful to recall briefly related earlier approaches.

Lea (*1*) analyzed the production of chromosome aberrations by ionizing radiations. He assumed that the sublesions, which he termed *chromosome breaks*, were produced along charged-particle tracks. These charged-particle tracks were, for simplicity and for lack of a more accurate description, treated as straight lines with energy transfer rates corresponding to the LET of the particle. Furthermore, it was assumed that a pair of chromosome breaks could interact and, with a certain probability, produce a lesion, i.e., an observable aberration such as a dicentric chromosome. Lea postulated that an interaction between two sublesions could take place provided they were formed at a distance less than a specified value h.

In spite of its obvious simplifications, Lea's analysis proved to be successful. His comparison of X-ray-induced and neutron-induced chromosome aberrations led to the conclusion that the critical distance h for the combination of chromosome breaks is of the order of a micrometer. This result has been confirmed by various authors (*2–4*), and the works of Lea and related investigations have exerted an important influence on many subsequent detailed studies of radiation-induced chromosome aberrations (see, for example, (*5–7*)).

With the development of microdosimetry a more rigorous treatment of dual radiation action became possible (*2*). This approach was based on the probability distributions of specific energy z in spherical sites. It assumed that sublesions are formed within spherical sites in the cell with a yield proportional to the energy imparted to the site. Furthermore, it postulated that sublesions in a site have a fixed probability of interacting pairwise. Under certain simplifying assumptions the expected number of lesions is then proportional to the square of the specific energy in the site, and the yield $\mathcal{E}(D)$ of lesions at a dose D is, therefore, proportional to the expectation value of the square of specific energy. This led to the linear–quadratic dose–effect relation

$$\mathcal{E}(D) = k\bar{z^2} = k(\zeta D + D^2), \tag{1}$$

where ζ is an average of specific energy produced in individual events in the site.

This relation was found to be applicable to a wide range of cellular effects produced both by sparsely ionizing radiations and by neutrons. In particular, it proved valuable in the prediction of the very high relative biological effectiveness of low doses of neutrons.

In its current form, however, the theory of dual radiation action is also based on various simplifications the most conspicuous of which is the somewhat arbitrary assumption of spherical sensitive regions in the cell. The number and the spatial distribution of such sites in the nucleus of the cell have been left unspecified. In fact, the notion of spherical sensitive sites within the nucleus serves merely as an approximation. A more realistic assumption is that sublesions can be produced throughout the nucleus of the cell but can combine with appreciable probability only over distances smaller than the dimension of the nucleus.

The approximation in terms of spherical sensitive sites has been necessitated by the fact that microdosimetric data usually refer to spherical sites. Moreover, the approximation may often be satisfactory and sufficiently accurate to bring out the characteristic differences in the actions of various types of ionizing radiations. It is doubtful, however, whether certain limiting cases are adequately treated by this formalism. An example is the action of low-energy X rays. For such radiations the particle ranges are substantially smaller than the site diameters of one or a few micrometers. Energy transfers produced by such tracks are, therefore, much more closely spaced than energy transfers randomly situated in the site. This may lead to an increased combination probability of sublesions and, accordingly, to an increased biological effectiveness (*8–11*). As illustrated in Fig. 1, the close spacing of energy transfers within the site is disregarded if one refers merely to the specific energy in the site. The established formalism is, therefore, not sufficient, and a more general description is desirable. It will be presented in this article.

The principal limitation of the formulation given here is that it applies only if one is dealing with one type of effect. Since a variety of effects, including not only cell death but also specific injuries (transformations, specified somatic mutations, etc.), appear to result from dual action (*2*), it must be concluded that there are various types of lesions (or combinations of lesions) responsible for these effects. This, in turn, leads to the possibility that there can be mutual interference between sublesions which reduces the frequency of lesions resulting in any particular effect. Although this is of substantial practical importance, it will not be considered here.

Another, related limitation of the treatment given below is that it disregards complications that can arise when the combination probability of any pair of sublesions is influenced by the presence of other sublesions. In such circumstances the treatment is valid only when the specific energy is low.

This presentation should therefore be regarded as a major step toward the development of a still more general formalism.

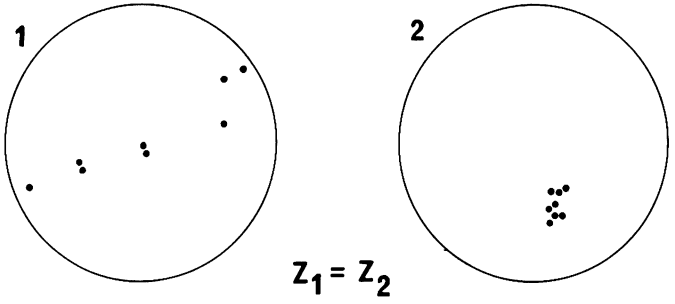

FIG. 1. Schematic diagram of energy deposition by (1) a particle of large range and (2) a particle of short range. The specific energy z is equal in the two sites, but the biological effectiveness is larger for the short-range particle because of the smaller distances between sublesions.

STATEMENT OF THE PROBLEM

Sensitive Matrix and Inchoate Distribution of Energy

Ionizing radiation produces a certain microscopic pattern of energy transfers in the cell. To describe this pattern one needs the concepts of transfer point and energy transfer (*12*). The term *transfer point* designates a point T where an ionizing particle undergoes an interaction with the irradiated medium. The term *energy transfer* designates the energy which is, at the point T, transferred from the radiation field to the material.

The concept of energy transfers is fundamental in the considerations which follow. It is therefore appropriate to state its definition more formally. If E is the kinetic energy of the incident ionizing particle and $\sum E_\nu$ is the sum of the kinetic energies of all ionizing particles leaving T, then the energy transfer at T is $(E - \sum E_\nu)$. It will be noted that $\sum E_\nu = 0$ if no ionizing particles are leaving T. Changes of rest mass resulting from the interaction (pair production, nuclear transformations) are disregarded here. A rigorous definition would have to be analogous to that of *energy-imparted* (*13*).

The temporal distribution of energy transfers will not be considered in this article; i.e., instantaneous exposure will be assumed. Formulae derived earlier (*2*) for the dose-rate dependence will, however, remain valid.

The microscopic pattern of energy transfers has been termed the *inchoate distribution* (*12*) in order to indicate that it is the initial pattern which exists before subsequent processes, such as energy conduction or diffusion of free radicals, lead to a different spatial distribution of initial radiation products. Figure 2 represents the situation schematically. Each of the heavy dots stands for an energy transfer. The light contour represents the outline of the cell; the

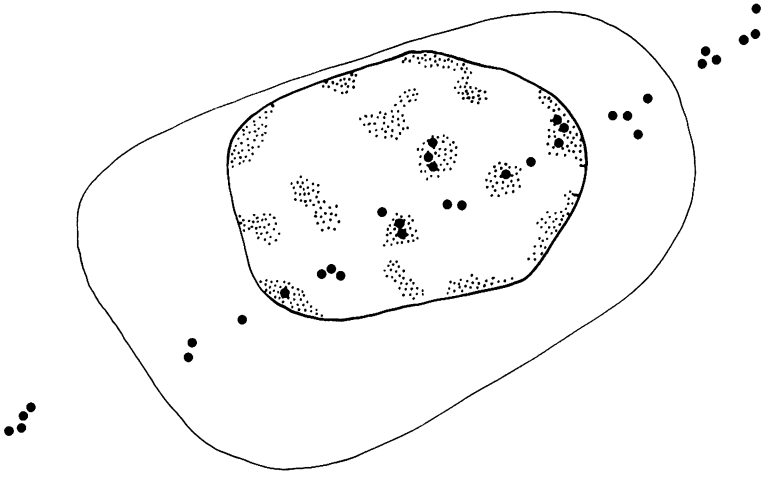

FIG. 2. Schematic diagram of a cell and its nucleus taken as the gross sensitive volume. The lightly dotted regions represent the sensitive matrix, i.e., the volume collectively occupied by the loci. The heavy dots represent energy transfers due to a charged particle.

heavy contour indicates the nucleus of the cell. It is assumed that the nucleus contains a large number of smaller regions termed *loci*. If an energy transfer is in a locus a sublesion may result. The volume collectively occupied by the loci will, in the following, be termed the *sensitive matrix*. In Fig. 2 it is represented by the lightly dotted areas. As indicated in the figure, the sensitive matrix will in general not be uniformly dispersed throughout the nucleus of the cell. Sublesions created anywhere in the sensitive matrix can interact to form lesions, but the interaction probability may be small if their separation is large.

Formation of Sublesions

The process of random formation of sublesions in the sensitive matrix may be intuitively clear; however, it needs to be specified rigorously. Assume that there are I transfer points in the sensitive matrix and that ϵ_i ($i = 1, 2, \ldots, I$) are the energy transfers at these points. It is then postulated that the number of sublesions produced at the ith transfer point follows a Poisson distribution with mean $c\epsilon_i$. It may be reasonable to assume that $c\epsilon_i$ is generally much smaller than unity. In this case $c\epsilon_i$ is simply the probability that a sublesion will be produced by the energy transfer ϵ_i, and the probability that multiple sublesions are produced by one transfer can be disregarded. The assumption is not necessary, however; one can instead consider the more general Poisson process in the formation of sublesions.

The nature of sublesions is left unspecified in the present context. The reason is that there are at least two different mechanisms in the cell which have the characteristics of dual radiation action. One mechanism is the production of DNA double-strand breaks as the result of two adjacent single-strand breaks. The other mechanism is the formation of chromosome aberrations from pairs of chromosome breaks. Both mechanisms are relevant to cellular radiation biology. Earlier analyses (*1*, *2*) have linked the linear–quadratic dose–effect relations in cellular radiation action to chromosome aberrations or another process characterized by large interaction distances of sublesions. The formation of DNA double-strand breaks, while another instance of dual radiation action, takes place at distances which are so small that the interaction of energy transfers from separate charged particles can be disregarded except at doses much higher than those relevant to radiation effects on the cells of most higher organisms. Only the linear term in Eq. (1) is important, therefore, and the formation of double-strand breaks from single-strand breaks cannot be the process responsible for the sigmoidal survival curves of mammalian cells.

On the one hand, the production of chromosome aberrations is more closely linked to cell death or specific cellular injuries; on the other hand, it is complicated by the fact that the sublesions, i.e., chromosome breaks, are possibly themselves represented by double-strand breaks. The description of the formation of chromosome breaks by individual energy transfers serves, therefore, merely as an approximation. In actuality, the efficiency of their production may depend on radiation quality, and, as indicated earlier (*14*), modifications of the formal treatment may be required to account for this effect. This, however, will not be a

subject of the present article. The treatment given here is therefore more readily applied to the process whereby DNA single-strand breaks combine to form double-strand breaks. However, while application to this case is more straightforward and may help in visualizing the process, it is—as stated above—of somewhat less pragmatic importance than the application to the formation of chromosome aberrations.

Diffusion of primary radiation products such as free radicals is disregarded in the present context in order to reduce the complexity of the mathematical treatment. Instead it is simply assumed that each sublesion is formed at an energy transfer point, i.e., that the spatial distribution of sublesions is a subset of the inchoate distribution in the sensitive matrix. The assumption that sublesions are produced precisely at the energy transfer points is not essential, and a subsequent article will generalize the result of the present work so that it includes diffusion. No substantial changes in the mathematical formalism result from this further generalization.

Formation of Lesions

Pairs of sublesions can combine to form a lesion. The average combination probability of two sublesions with mutual distance x is designated by $g(x)$, and this is also termed the *interaction probability* as a function of distance x between two sublesions.

If only two sublesions are present, the probability of the formation of a lesion is $g(x)$. The situation is more complicated if there are three sublesions. The expected number n of lesions will then depend on all three distances x_{12}, x_{13}, x_{23}, where the indices refer to the three sublesions. The functional relation $n(x_{12}, x_{13}, x_{23})$ need not be simple because the probability that sublesion 1 will combine with sublesion 2 will be diminished because of the possibility that 1 will combine with 3, and both combination probabilities for 1 are diminished because of the possibility that 2 will combine with 3. The term *saturation of sublesions* may refer to this interrelation.

The saturation of sublesions, however, can be disregarded whenever all sublesions have a small combination probability, so that sublesions are much more numerous than lesions. One can then simply set

$$n = g(x_{12}) + g(x_{13}) + g(x_{23}) \tag{2}$$

and the analogous formula

$$n = \sum_{\substack{i,k \\ i<k}} g(x_{ik}) \qquad (i, k = 1, \ldots, J) \tag{3}$$

applies to the general case of J sublesions.

The simplified treatment is probably acceptable if one deals with the formation of double-strand breaks in DNA. In mammalian cells it is found that sparsely ionizing radiations produce about 20 times more single-strand breaks *in vivo* than double-strand breaks (*15*). Even if all double-strand breaks result from pairs of single-strand breaks produced in sufficient proximity, only 1 in 10 single-strand

breaks would be involved in a double-strand break. Similar considerations apply to the formation of chromosome aberrations, since their number is much smaller than that of chromosome breaks (*1*). It is less certain whether saturation of sublesions can be disregarded for densely ionizing radiations, but this will not be examined in the present article.

Mean Number of Lesions

Equation (3) specifies the expected number n of lesions for a given *constellation* (spatial arrangement) of sublesions in a cell. The actual number ν of lesions will follow a Poisson distribution with the mean value n.

However, the situation is even more involved. The quantity n is the expected number of lesions resulting from a specified constellation of sublesions. At a certain dose, different specific energies may be imparted to the sensitive matrix; but even when the same specific energy is imparted a different inchoate pattern of energy transfers may result. The constellation of sublesions will vary accordingly, and one will deal with a certain distribution of n. The distribution $d_D(\nu)$ of the actual number ν of lesions is then a superposition of Poisson distributions of different mean values n. In certain cases it may be feasible to calculate this distribution $d_D(\nu)$. However, this is not attempted in the present treatment; instead, only the *expected* number $\bar{\nu}$ of lesions per cell at a specified dose D is calculated. This expected number of lesions is designated by the symbol $\mathcal{E}(D)$:

$$\mathcal{E}(D) = \bar{\nu}(D) = \sum_0^\infty \nu d_D(\nu). \tag{4}$$

One must note that this quantity does not necessarily determine the observed effect, even if the effect is a function $S(\nu)$ of the number of lesions. As has been pointed out also by others (*16*) one cannot generally equate the observed quantity $S(D) = \overline{S(\nu)}$ with $S(\bar{\nu})$:

$$S(\bar{\nu}) = S(\sum_0^\infty \nu d_D(\nu)) \neq \overline{S(\nu)} = \sum_0^\infty S(\nu) d_D(\nu). \tag{5}$$

If, for example, survival is an exponentially decreasing function of the number of lesions,

$$S(\nu) = e^{-k\nu}, \tag{6}$$

then substitution of the mean value of $\bar{\nu}$ for the actual averaging procedure leads to an overestimate of the effect:

$$S(\bar{\nu}) = e^{-k\bar{\nu}} \leq \overline{e^{-k\nu}} = S(D). \tag{7}$$

The present treatment is therefore limited. It does not aim at a precise solution, and the error will be largest if individual charged particles produce more lesions in the cell than are necessary for the effect which is being considered. However, when this saturation plays a minor role, the mean yield of lesions will closely determine the effect of an irradiation.

The following sections of this article lead to a relatively simple formula which

permits one to calculate $\varepsilon(D)$ if the geometry of the sensitive matrix and the microdistribution of energy transfers are known. It is found that this relation depends only on $g(x)$ and on two functions which may be called the proximity function of the energy transfers and the proximity function of the sensitive matrix. These functions are introduced before the general formula for $\varepsilon(D)$ is derived.

DEFINITION OF THE PROXIMITY FUNCTIONS

It is found that the quantity $\varepsilon(D)$, the expected number of lesions, can be expressed by a simple integral over two functions $s(x)$ and $t(x)$. These functions are discussed in the present section. They are closely related. $s(x)$ characterizes the geometry of the sensitive matrix; $t(x)$ characterizes the spatial distribution of energy transfers. $s(x)$ and $t(x)$ are similar to a function which in mathematical morphology (*17*, *18*) is called the covariance of a geometrical object; however, the term *proximity function* is used here.

The Function $s(x)$

The proximity function, $s(x)$, is the product of the volume of the sensitive matrix and the probability density of distances between two points randomly chosen in the matrix (*19*).

An equivalent definition which conveys the meaning of the function $s(x)$ somewhat more directly is the following:

Select points, P, randomly in the matrix. Then $s(x)\,dx$ is the average partial volume of the matrix which is contained in a shell of radius x and thickness dx centered at P.

Some examples may serve to illustrate the function $s(x)$. The simplest case is that of a uniform extended medium. In this case one obtains

$$s(x) = 4\pi x^2. \tag{8}$$

A somewhat more complicated case is that of a spherical domain of diameter d. The function $s(x)$ for this case can be readily obtained from a formula given by Kendall and Moran (*20*, Eq. (2.125)); it is also linked to the chord-length distribution (*21*) resulting from the random traversal of a sphere:

$$s(x) = 4\pi x^2\left(1 - \frac{3x}{2d} + \frac{x^3}{2d^3}\right), \qquad x \leq d. \tag{9}$$

This function was utilized earlier in the context of microdosimetric computations (*19*, *22*).[2]

Other geometries might also be considered. Thus one obtains the following function for a spherical shell of diameter d and (infinitesimal) thickness Δr:

$$s(x) = 8\pi\Delta r, \qquad x \leq d. \tag{10}$$

This result is cited here without derivation.

[2] In the earlier article (*19*) the term *distance distribution* was used and the notation $t'(x)$ was applied instead of $s(x)$.

One may note that these formulae also apply if loci are randomly distributed without the specified configurations. The reason is that $s(x)$ will then still account for the *collective* response of the cells. If clusters of loci are randomly distributed within a certain configuration, the formulae will have to be modified. This is considered in the examples at the end of this article.

The Function $t(x)$

When biological specimens are irradiated, the frequency of pairs of sublesions that are in sufficient proximity to interact depends on two factors. The first factor is the availability of neighboring loci; this is described by the function $s(x)$. The second factor is the frequency of energy transfers spaced closely enough to affect neighboring loci. To account for this second factor, one uses a function $t_D(x)$, which is analogous to the function $s(x)$ but relates to the pattern of energy transfers and not to the geometry of the sensitive matrix. The index D is added to indicate that the function $t_D(x)$ depends on absorbed dose. It will be seen, however, that $t_D(x)$ separates conveniently into a term $t(x)$ which is independent of absorbed dose and a second term which is proportional to absorbed dose and independent of radiation quality.

The function $t_D(x)$ has been introduced and utilized in the context of microdosimetric computations (*19*, *22*); it characterizes the inchoate distribution in the same way that the function $s(x)$ characterizes the sensitive matrix. The definition of $t_D(x)$, therefore, is largely analogous to the definition of $s(x)$:

Select energy transfers, ϵ, randomly in the irradiated medium. Then $t(x)dx$ is the expected sum of energy transfers contained in a shell of radius x and thickness dx centered at the transfer point where the energy transfer ϵ occurred.

One must note that the random selection is between energy transfers rather than between transfer points. Accordingly, each transfer point T has a selection probability proportional to the associated energy transfer (*19*).

Although the function $t_D(x)$ is analogous to the function $s(x)$, it differs in that it has the dimension of energy divided by length, while $s(x)$ has the dimension of volume divided by length.

The proximity function $t_D(x)$ always separates into two terms. The first term, which in the following is designated $t(x)$, is the *intra*track contribution; i.e., it represents energy transfers produced by the same event[3] as the energy transfer at point T. This term depends on radiation quality but not on absorbed dose. The second term represents energy transfers by other, uncorrelated charged particles. This *inter*track contribution is proportional to absorbed dose and independent of radiation quality. One obtains

$$t_D(x) = t(x) + 4\pi x^2 \rho D, \tag{11}$$

where ρ is the density of the irradiated medium.

The simplest formula for $t(x)$ results if one regards the charged particle as slowing down continuously with stopping power L while moving along an infinite

[3] An event (*13*) designates the imparting of energy by an ionizing particle and/or its secondaries.

straight line. Then one has

$$t(x) = 2L. \tag{12}$$

As one can readily show, the dose average, $\bar{L}_D$, replaces the value L if a distribution of LET values is assumed.

If, instead of an infinite particle track, one of range R is considered while the linear energy transfer is taken to be constant, the following relation results:

$$t(x) = 2L(1 - x/R),\ x < R. \tag{13}$$

This is a drastic simplification which does not account for the varying stopping power along the track. Furthermore, the statistical fluctuations of energy loss along the track and the radial extension of the track are neglected. In spite of its inadequacy Eq. (13) is utilized in numerical examples at the end of this article. The reason is that this approximation has been used in an analysis of the effect of low-energy X rays on cell survival and on mutations that appeared to be inconsistent with the conventional treatment of dual radiation action (*23*). Numerical examples, even if based on Eq. (13), show that no inconsistencies arise with the present more rigorous treatment.

GENERAL FORMULA FOR DUAL RADIATION ACTION

The concepts and quantities defined in the preceding sections can be utilized to obtain a formula for the mean number of lesions. Although the discussion refers to the mean yield of lesions *per cell*, it is readily apparent how the resultant formula can be modified to apply to other cases, for example, to an irradiated medium such as DNA in aqueous solution.

The mean number ε of lesions per cell is equal to the mean number m of sublesions per cell multiplied by the mean combination probability p of a sublesion

$$\varepsilon = \tfrac{1}{2}(p \cdot m). \tag{14}$$

The factor $\frac{1}{2}$ enters the relation because two combined sublesions result in only one lesion.

The mean number of sublesions per cell is

$$m = c\rho VD, \tag{15}$$

where D is the absorbed dose, V is the (average) volume of the sensitive matrix, ρ is the density, and c is a constant introduced earlier, in the section dealing with the formation of sublesions.

The combination probability for a sublesion is determined by the expected number of neighboring sublesions multiplied by the appropriate, distance-dependent interaction probability $g(x)$.

$s(x)/4\pi x^2$ is the expected fraction of the spherical shell of radius x centered at an energy transfer (or sublesion) which belongs to the sensitive matrix. The quantity $t_D(x)dx$ is the expected energy imparted to the spherical shell. If either the radiation field is isotropic and/or the cells are randomly oriented, the fraction $s(x)/4\pi x^2$ of this energy will on the average be imparted to the sensitive matrix.[4]

[4] A somewhat more complicated relation applies if neither of the two conditions is fulfilled. The directional dependence of the functions $s(x)$ and $t(x)$ must then be taken into account.

The expected number of sublesions in the spherical shell is equal, therefore, to $ct_D(x)s(x)/4\pi x^2 dx$. Integrating this expression over all distances and including the interaction probability $g(x)$ one obtains the following expression for the average combination probability of a sublesion:

$$p = c \int_0^\infty \frac{g(x)t_D(x)s(x)}{4\pi x^2} dx. \tag{16}$$

This important and strikingly simple relation links the three aspects which determine the interaction of sublesions:

(1) distance-dependent interaction probability,
(2) microscopic distribution of energy transfers,
(3) geometry of the sensitive matrix.

Inserting this expression and Eq. (15) into Eq. (14), one obtains the equation for the average number of lesions per cell:

$$\mathcal{E}(D) = \frac{c^2\rho V}{2} D \int_0^\infty \frac{g(x)t_D(x)s(x)}{4\pi x^2} dx. \tag{17}$$

One derives the explicit form of this equation by inserting the expression for the proximity function $t_D(x)$ which has been given in Eq. (11):

$$\mathcal{E}(D) = \frac{c^2\rho V}{2} D \left(\int_0^\infty \frac{g(x)t(x)s(x)}{4\pi x^2} dx + \rho D \int_0^\infty g(x)s(x)dx \right)$$

or

$$\mathcal{E}(D) = k(\xi D + D^2). \tag{18}$$

The coefficient k is given by the relation

$$k = \frac{c^2\rho^2 V}{2} \int_0^\infty s(x)g(x)dx, \tag{19}$$

but it need not be considered in the following. However, the quantity ξ plays a central role:[5]

$$\xi = \int_0^\infty \frac{s(x)g(x)t(x)}{4\pi\rho x^2} dx \Big/ \int_0^\infty s(x)g(x)dx. \tag{20}$$

One concludes from Eq. (18) that dual radiation action leads to a linear–quadratic dose dependence regardless of the geometry of the sensitive matrix and of the type of radiation. The quantity ξ depends on the functions $s(x)$ and $g(x)$ which characterize the irradiated specimens and the function $t(x)$ which characterizes the radiation.

[5] The symbol ξ is used here in order to indicate the close relation to the microdosimetric quantity ζ (see discussion of the site model).

It is convenient to utilize a combined function:

$$\phi(x) = g(x)s(x) \Big/ \int_0^\infty g(x)s(x)dx. \tag{21}$$

This normalized function can be considered as the distribution of "available" loci in distance x from a sublesion. The word available is used to indicate that the interaction probability $g(x)$ enters this function in addition to the distance distribution $s(x)$.

With this definition one obtains the final form of the basic relation:

$$\varepsilon(D) = k(\xi D + D^2) \tag{22}$$

with

$$\xi = \int_0^\infty \frac{\phi(x)t(x)}{4\pi\rho x^2}\, dx. \tag{23}$$

At a dose equal to ξ the linear component in the dose–effect relation is just equal to the quadratic component. The linear component (*intra*track action) dominates for lower doses while the quadratic component (*inter*track action) dominates for larger doses.

Equations (22) and (23) are the essential result of the present study, and it is desirable, therefore, to give a visualization of the quantity ξ. This can be achieved by observing that ξ is proportional to the expected number of neighboring sublesions from the same particle track around a sublesion randomly selected. ξ is obtained by integrating the product of the "available loci" $\phi(x)$ and the "conditional dose" $t(x)/4\pi\rho x^2$ at the loci.

The quantity $t(x)/4\pi\rho x^2$ is equal to the expected energy imparted to the shell of radius x divided by the mass in this shell. Therefore, the quantity can be considered as the conditional dose due to the same particle track at a distance x from a randomly selected energy transfer. Absorbed dose is always an expectation value, and it is in line with the general principles of probability that a conditional expectation value may differ from the overall expectation value. It is correct, therefore, to speak about a *conditional absorbed dose* in the vicinity of energy transfers:

$$\Delta(x) = t(x)/4\pi\rho x^2. \tag{24}$$

This, however, is merely a matter of interpretation. It does not affect the equations, and one can use these equations without introducing the concept of a conditional absorbed dose.

The function $t(x)$ can be computed for any type of radiation, and one might also consider possible methods of experimental determination. On the other hand, it may appear that Eqs. (22) and (23) are of little applicability, if there is no detailed knowledge of $s(x)$ and $g(x)$. Very general conclusions follow, however, without such detailed knowledge. For example, one can readily show that ξ must be larger than $\Delta(d)$, if d is either the maximum linear dimension of the sensitive matrix or the maximum combination distance of sublesions. Even for sparsely

ionizing radiations this excludes values of ξ below a few thousand rad, whenever d is less than roughly 20 nm.

NUMERICAL EXAMPLES

As stated earlier, the numerical examples utilize Eq. (13), which is only a rough approximation of the actual distributions $t(x)$. For purposes of illustration this is satisfactory. Future quantitative studies, however, will require more realistic data, and therefore it will be necessary to expand previous computations (*19*, *24*) which have derived the functions $t(x)$ for certain radiations.

The Site Model

The term *site model* refers to the case which was treated earlier in the theory of dual radiation action. It is assumed that loci are randomly dispersed over a spherical site of diameter d. Furthermore, the combination probability $g(x)$ is taken to be constant. One then obtains from Eq. (9), and from Eq. (21) where the combination probability cancels by division:

$$\phi(x) = \frac{24}{d^3} x^2 \left(1 - \frac{3x}{2d} + \frac{x^3}{2d^3}\right), \qquad x \leq d, \tag{25}$$

and according to Eq. (23),

$$\xi = \frac{6}{\pi \rho d^3} \int_0^d \left(1 - \frac{3x}{2d} + \frac{x^3}{2d^3}\right) t(x) dx. \tag{26}$$

It was shown earlier (*19*) that this is equal to the microdosimetric quantity ζ. Equation (26) has in fact been used (*22*) as an efficient tool to calculate ζ from simulated particle tracks (*25–27*).

The function $\phi(x)$ is given in Fig. 3 (solid line) for a site diameter 0.6 μm. As has been stated before, this is the distribution of loci in distance from a randomly selected sublesion (or locus).

The quantity ξ depends on the function $t(x)$, i.e., on radiation quality. As an example, electrons of different initial energies are considered, and $t(x)$ is taken from Eq. (13). With electron ranges for water (*28*) one then obtains results which are plotted in Fig. 4 as solid lines; the site diameters have been chosen as 0.6 and 0.4 μm.

The Distance Model

The site model was utilized in earlier work to permit the application of microdosimetric data as they are obtained experimentally. A more realistic assumption, however, is that loci are contained in a sensitive matrix which may be dispersed throughout the nucleus of the cell, and that sublesions within this matrix can combine with a probability $g(x)$ that decreases with distance x.

For interaction distances small compared to the diameter of the matrix, one can disregard the latter and use the function $s(x)$ from Eq. (8) which refers to an infinite site.

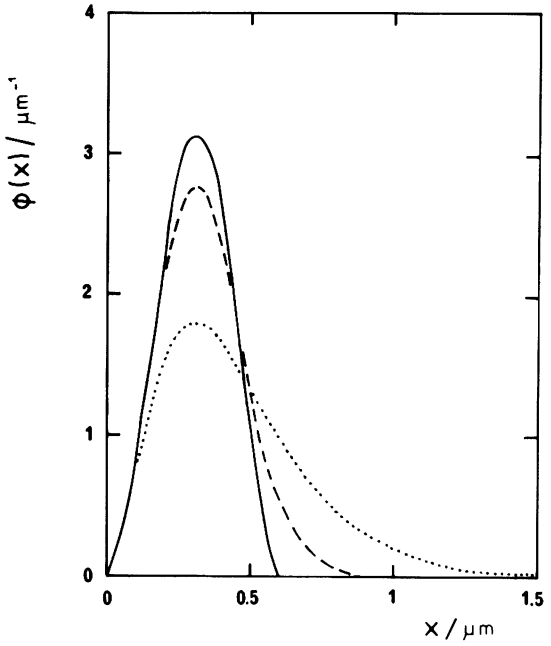

FIG. 3. The functions $\phi(x)$ for the site and the distance model. Full line: site model; Eq. (25) with $d = 0.6$ μm. Broken line: distance model; Eq. (29) with $a = 0.3\mu$m. Dotted line: distance model; Eq. (30) with $a = 0.15$ μm.

If a slowly varying interaction probability is considered one might set

$$g(x) = Ce^{-(x/a)^2}, \tag{27}$$

or alternatively,

$$g(x) = Ce^{-x/a}. \tag{28}$$

One then obtains from Eq. (27)

$$\phi(x) = (\pi^{\frac{1}{2}}/6)a^3x^2e^{-(x/a)^2} \tag{29}$$

and from Eq. (28),

$$\phi(x) = a^3x^2e^{-x/a}. \tag{30}$$

These two functions are also plotted in Fig. 3. For Eq. (29) the value $a = 0.3$ μm is assumed; for Eq. (30) the value $a = 0.15$ μm. The three functions in Fig. 3 are of generally similar shapes; one therefore concludes that the site model and the distance model are substantially equivalent.

This is borne out in the example of the simplified electron tracks. Figure 4 permits a comparison of the values of ξ for the different models. One obtains the same characteristic dependence on electron energy in all three cases.

In actuality, one deals neither with the site model nor with the distance model but with a combination of both, i.e., the matrix has finite dimensions and the interaction probability depends on distance. Equation (20) can readily be evaluated for this combined case. Taking into account a diameter of 6 μm for the cell nucleus one obtains values for ξ which are about 5% higher than those for the

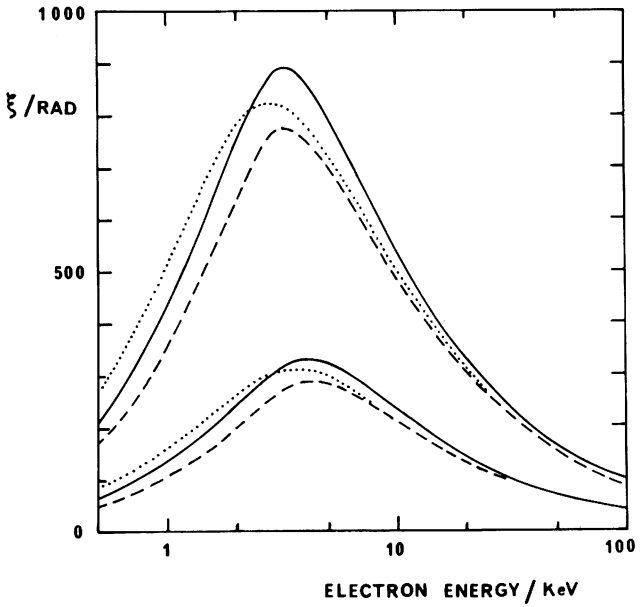

FIG. 4. The quantity ξ for electrons as a function of their initial energy, with $t(x)$ approximated by Eq. (13). Full lines: site model; Eq. (25) with $d = 0.4$ μm (upper curve) and $d = 0.6$ μm (lower curve). Broken lines: distance model; Eq. (29) with $a = 0.2$ μm (upper curve) and $a = 0.3$ μm (lower curve). Dotted lines: distance model; Eq. (30) with $a = 0.1$ μm (upper curve) and $a = 0.15$ μm (lower curve).

simple distance model. Therefore, the finite diameter of the cell nucleus need not be considered in calculating ξ.

From a comparison of the curves in Fig. 4 one might conclude that the various models of dual radiation action always lead to roughly the same results. This would then imply that experimental data which do not fit the simple site model will be equally inconsistent with other models of dual radiation action, as recently concluded with some qualifications (*23*). The argument is erroneous however, as is shown in the next section.

Enhanced Short Range Interaction

The three models represented by Eqs. (25), (29), and (30) are, as seen in Fig. 4, similar in that the majority of the potential reaction partners lie at an intermediate distance from a sublesion. In reality the situation may be different, insofar as short-range interaction can play a larger role.

One possibility is that the interaction probability declines steeply at small distances but still has a considerable tail to larger distances. Thus one might deal with the function

$$g(x) = C_1 e^{-(x/a_1)^2} + C_2 e^{-(x/a_2)^2} \qquad \text{with } C_1 \gg C_2 \text{ and } a_1 \ll a_2. \tag{31}$$

The effectiveness of short-range particles can be greatly enhanced by the first

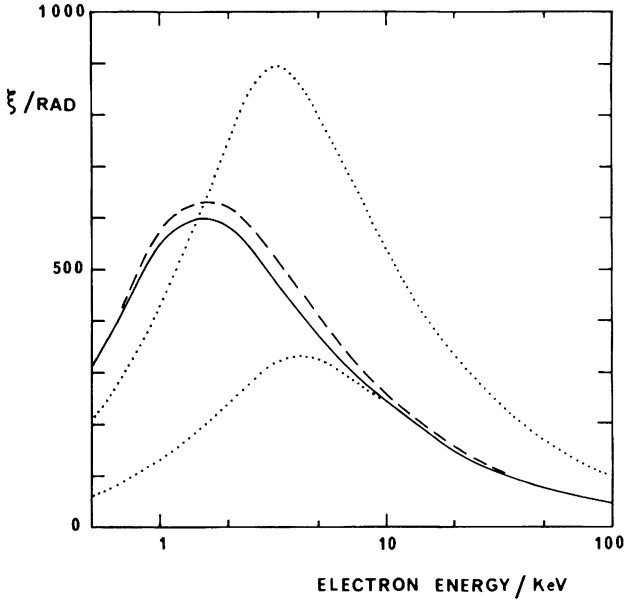

FIG. 5. The quantity ξ for electrons as a function of their initial energy, with $t(x)$ approximated by Eq. (13). Dotted lines: site model; Eq. (25) with $d = 0.4$ μm (upper curve) and $d = 0.6$ μm (lower curve). Full line: distance model; Eq. (31) with $C_2/C_1 = 0.004$, $a_1 = 0.05$ μm and $a_2 = 1$ μm. Broken line: distance model (Eq. (27) with $a = 1$ μm) for a random arrangement of clusters in a large site (Eq. (32) J with $d = 0.1$ μm and $\tau = 0.004$).

term, while that of long-range particles may be little affected. One must therefore expect a shift of the maximum values of ξ toward lower particle energies.

This is indeed the case, as can be seen from Fig. 5. The solid curve in this figure results for the distance model with Eq. (31) and $a_1 = 0.05$ μm, $a_2 = 1$ μm, and $C_2/C_1 = 0.004$.

A comparison with the site model (dotted curves) shows that at higher energies the values ξ correspond to larger diameters ($d = 0.6$ μm), at lower energies to smaller diameters ($d = 0.35$ μm).

A recent publication (*11*) deals with a comparative study of cell killing and mutation induction by 1.5-keV photons and higher-energy radiations. The statistical accuracy of the data is not sufficient to quote ξ values with much accuracy. It has been stated, however, that the results for the high-energy radiations require larger site diameters than those consistent with the data for 1.5-keV photons. The possibility of dual action in its usual interpretation has therefore been excluded, and it has also been stated that the alternative treatment in terms of the distance model will not overcome all of the difficulties (*23*). As seen from the example in Fig. 5 this does not necessarily follow.

Similar results are obtained if, instead of a short-range component in $g(x)$, one considers a sensitive matrix which consists of clusters of loci in a larger site. If spherical clusters of diameter d are randomly distributed in a large (infinite)

site one has

$$s(x) = 4\pi x^2\left(1 - \frac{3x}{2d} + \frac{x^3}{2d^3}\right) + 4\pi x^2\tau, \tag{32}$$

where τ is the fraction of the site filled with the clusters which belong to the sensitive matrix.

The broken line in Fig. 5 is a solution for this case. The diameter d of the clusters is taken to be 0.1 μm, τ is 0.004, and $g(x)$ is set proportional to $\exp[-(x/a)^2]$ with $a = 1$ μm. The overall result is similar to that for the distance model with Eq. (31). It is evident that the finite diameter of the nucleus of the cell can be readily taken into account. However, this has little influence on the results.

It should be noted that the evidence provided by electron microscopy (*29*) does in fact indicate that DNA is arranged in clusters during interphase.

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