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MICRODOSIMETRY AND ITS ALTERNATIVES*

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ABSTRACT: The relation of microdosimetry to LEA's associated volume method, to LET-theory, and to the various modifications of these approaches is analyzed, and the alternative interpretations of microdosimetric quantities and functions are discussed. The argument underlying the derivation of interaction distances and site diameters in the cell is examined, and possible lines of future development are considered.

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This is the 3rd International Conference on Microdosimetry, but microdosimetry still has the characteristics of a very new field. One of these is that it receives more attention than systematic evaluation, and that the attention concerns microdosimetry itself rather than its achievements. It has therefore been only proper that Professor Rossi who has founded and developed this field has given us a report of some of the actual achievements. Let me try to make a few remarks on the more doubtful subjects which come to the mind when one attends this symposium.

Three aspects appear critical in the present development of microdosimetry. First, there is little consistency in the terminology used by the various contributors to this field. Matters of terminology are, or course, minor questions. But they may point to major issues insofar as they are indicators of an underlying confusion, or at least, of the absence of a common point of departure. A consensus on fundamental definitions and on terminology is necessary if microdosimetry is to be not only an interesting field of research but also a useful routine tool in radiobiology. The first point is therefore closely connected with the second point, the appliciability of microdosimetry. There have been excellent radiobiological contributions to these symposia. But one cannot escape the feeling that the major effort goes into technical problems of microdosimetry, rather than its application, and that if microdosimetry is being developed for its own sake it may lose relevance to radiobiology. Finally, one must ask whether there are clearly defined approaches which can lead to a successful future development of microdosimetry. I am well aware that these are difficult questions, and one can hardly expect detailed answers or a complete synopsis. But it may be useful to list some of the thoughts which arise if one deals with microdosimetry and asks: What is it based on, what is its purpose, and what will be its future course?

FUNDAMENTALS

The necessity for microdosimetric analysis arises from the fact that electronic disturbances, e.g., ionizations in the irradiated matter are not distributed in the simplest form of randomness which would follow Poissonian statistics. The latter would only be the case if there were no correlations at all between the positions of adjacent ionizations or excitations.

The first attempt to account for the correlation in the position of neighboring ionizations has been based on the concept of mean linear ion density[1] and of linear energy transfer[2]. This is a valid approach which can be used with advantage if one stays aware of the fact that it offers a heuristic principle rather than a quantitative description. In certain special cases one finds that the LET concept or related quantities such as Z^2/β^2 are also quantitatively applicable. The applicability and the limitations of such concepts have for example been discussed in the report of ICRU[3] on linear energy transfer. In the general case one deals with the full complexity of the microscopic pattern of overlapping tracks, and no single parameter will be sufficient to describe radiation quality.

Microdosimetry in its present form has originated from experimental studies of radiation quality[4]. The point of departure has been the insight that it is not always the most effective procedure to start out with the concept of LET and then account for the various limitations of this concept by a series of corrections and approximations. Instead a formal scheme has been developed which is directly applicable to all questions concerning the microscopic distribution of energy deposition.

To understand this change in approach is important. One is tempted to use an analogy. Mathematics, for example, can always be formulated without infinitesimal calculus. In Greek mathematics integration was extensively used, but it was used as an approximative device without clearly defined concepts, and this is the reason that it never caught on. The same method when given a precise definition at a later age proved to be infinitely more powerful. I am not sure whether the

new methods in the theory of radiation quality have caught on, or whether each individual worker still uses his own approximative devices. Let me therefore draw some connecting lines between the concepts of microdosimetry and their alternatives.

Questions posed in microdosimetry or in related approaches are concerned with local energy concentration: Given a certain type of radiation and a certain dose, what is the probability of finding a specified amount of energy deposition in a specified microscopic region? What is the mean event frequency per rad in this region? What is the concentration of ionizations around an ionization? What fraction of the neighboring ionizations belongs to the same particle track, what fraction is produced by separate events? In order to deal with such questions and to understand the common element in the answers one may consider a schematic representation of the microscopic patterns of energy deposition.

In Fig.1a ionizations belonging to different particle tracks, i.e. different energy deposition events, are indicated by different symbols. One may regard a spherical site of diameter d and ask for the probability to find a given number of ionizations in this site. This is the problem which has been treated by LEA's associated volume method[5]. The idea underlying this method is to consider spherical regions around the ionizations instead of spherical regions centered at a reference point R. The result is the same whether one counts the number of ionizations in the region surrounding R (see Fig.1a) or whether one counts the number of spheres around ionizations which overlap in the point R (see Fig.1b). The total volume represented by the spheres in Fig.1b is called associated volume.

In Fig.1c the regions of various degrees of overlap are indicated by different degrees of shading. This density profile determines the fractions of the total volume which correspond to different values of energy concentration. Due to the equivalence mentioned above the probability to find a given amount of ionization in a sphere of diameter d is equal to the fraction of the total volume with this concentration. The profile is therefore described by the differential microdosimetric

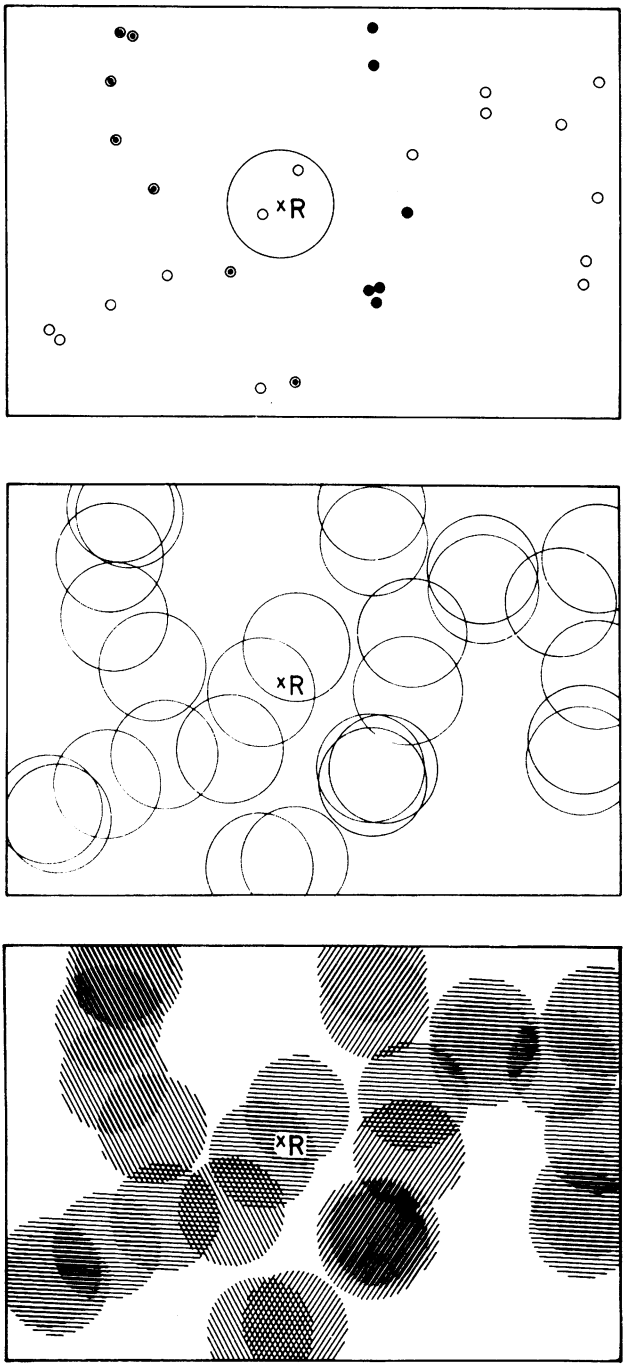

Fig.1 Schematic diagram of charged particle tracks, the definition of the associated volume, and the representation of the profile of specific energy z.

distribution f(z;D) or by the sum distribution F(z;D)*. The fraction of the total volume which belongs to a specific energy between z and z+dz is equal to f(z;D)dz, the fraction of the total volume which belongs to higher concentrations than z is equal to F(z;D).

The profile in Fig.1c consists of regions of overlap of ionizations from the same particle track (shaded by parallel lines) and of regions which correspond to the overlap of ionizations from separate tracks (shaded by crossed lines). If recovery takes place and if the dose rate is low enough, one need only consider the overlap between ionizations belonging to the same track, i.e. one must disregard the overlap indicated by crossed lines. The resulting profile is described by the single event spectra $f_1(z)$ and $F_1(z)$. The fraction of the total associated volume which corresponds to a specific energy between z and z+dz is equal to $f_1(z)\,dz$; the fraction of the associated volume which has a higher overlap density than z is equal to $F_1(z)$. These functions are independent of dose.

It has been mentioned that the two approaches symbolized by Fig.1a and Fig.1b or 1c are equivalent. Fig.1a evokes the notion of a geometrically defined sensitive site; the corresponding point of view may therefore be termed site model. Fig.1b and 1c on the other hand call forth the notion of radiation products or radiation induced cellular lesions which interact with each other over a characteristic distance d; one may therefore label this point of view as diffusion or distance model. It is important to understand the formal equivalence of these alternatives. Any consideration which is formulated in the site model, has its counterpart in the distance model. This is the reason why in the application of microdosimetry to radiobiology one derives distances which can either be interpreted as site diameters or interaction distances. It is also the reason that the two approaches which are sometimes labeled as track analysis and as ordinary microdosimetry

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*For a definition of microdosimetric quantities and functions see reference[6] or [7].

are completely equivalent, and that the same quantities and functions are applicable to both approaches.

The microdosimetric distributions $f(z;D)$ and $f_1(z)$ have here been discussed from the viewpoint of the distance model. This is not the usual approach. Although both interpretations have been given before[8], it is commonly assumed that the microdosimetric approach is linked to the notion of geometrically defined sensitive regions. This has in the past led to a certain bias in the application of microdosimetry. An understanding of the equivalence between site and diffusion model may eliminate this bias, it may also contribute towards the development of a common language for chemists and for physicists working on radiobiological problems.

LEA's associated volume concept is, as has been seen, closely connected to microdosimetric quantities. One may well consider LEA's calculations as the first precise studies in theoretical microdosimetry. There are, however, reasons why the associated volume method has not been closely tied to microdosimetry.

The main difference between LEA's studies and microdosimetry is due to the fact that the associated volume method has been developed for an understanding of the action of radiation on small objects such as enzymes, viruses, and bacteria, while microdosimetry has been mainly applied to relatively large objects such as mammalian cells. In enzymes, viruses, or small bacteria one deals with sensitive regions whose diameters are of the order of magnitude of 100 Å. The relative biological effectiveness of different radiations is then determined by the saturation effect. One ionization is sufficient to produce the effect; if the ionization density of a radiation is so high that more than one ionization is produced in the sensitive region, then part of the energy is wasted and the RBE decreases. Accordingly one is only interested in the total associated volume and not in the actual profile of energy concentration. In the terminology of microdosimetry one would say that the effect on very small objects is merely determined by the event frequency ϕ or by its inverse the mean event size $\bar{z}_F$; the quantity ϕ is proportional to the associated volume. A further

simplification which applies to the associated volume method is that one deals only with single event action; overlap of ionizations belonging to different particle tracks can be neglected because excessive doses are necessary to produce multiple events in regions of diameter less than 100 Å.

Microdosimetry, on the other hand, has been mostly applied to mammalian cells, to other animal cells, or to the cells of higher plants. In these cases one deals with a reverse situation. As evidenced by the sigmoid dose dependences, the effects are due to the interaction of several absorption events. Accordingly the RBE increases with ionization density, and saturation effects are relevant only in the limiting case of very densely ionizing particles. The interaction distances are of the order of magnitude of 1 µm. Due to these factors one has to know the actual distributions of specific energy and not merely the event frequencies. The distributions $f(z;D)$ are needed for diameters d of the reference region of the order of 1 µm or larger. Some details will be mentioned in the next section; in the present context it is sufficient to point out the relation between the associated volume calculations and microdosimetry in general.

The effect of radiation on mammalian cells is determined by the specific energy profiles which result according to the scheme of Fig.1c if the diameter of the spheres of dissipation is taken to be 1 µm or more. There are, however, as pointed out by Dr. Rossi certain indications that RBE may also to some extent be determined by the submicroscopic energy concentrations measured over regions of the order of magnitude of 10 Å. Investigation of this potential second order effect which may be of relevance to the oxygen effect will necessitate microdosimetric studies on a submicroscopic scale. This may lead to a more direct link between microdosimetry and the methods developed by LEA.

It may in this context be mentioned that the associated volume method has recently - and possibly without awareness of the precedence of LEA's work - been applied to the case of heavy ions. The analysis has been based on calculations valid in the range of extremely high values of LET. A particle track is treated as a cloud of ionizations

which has the same mean radial energy profile as the particle track. One can understand the approximation by comparing the particle track to a worn out test tube brush with numerous short and a few long hairs, the delta rays. If the brush is oscillated rapidly parallel to its axis one obtains the cloud like configuration which corresponds to this approximation of the particle track. The result is a certain increase in the associated volume because the energy concentration in the delta rays is washed out. In the limiting case of an extremely dense delta-ray halo one can neglect the effect, but in the remaining cases more precise microdosimetric experiments or computations will be desirable.

Other approximative approaches to microdosimetric analysis are more seriously limited. This seems to be especially true for attempts to deal with the action of radiation on mammalian cells in terms of an arbitrary bisection of the effect into a LET dependent single event process and a multi-hit component represented by a target theory formula. Such target theory formalism will always lead to accurate curve fitting if enough free parameters are involved. But mere book-keeping in terms of formal parameters will hardly lead to insights into the mechanisms of radiation action or into the actual interaction distances of cellular lesions.

APPLICATIONS

After the discussion of some principles of the theory of radiation quality one may attempt to identify the common element in the various approaches towards an understanding of the interaction of absorption events or cellular lesions. This section can be kept brief because Dr. Rossi has presented what appears to be a general and consistent scheme of analysis. It will therefore be sufficient to point out the general context of such studies.

As indicated in Fig.1c one has to distinguish between intratrack interaction of ionizations and intertrack interaction. Intratrack interaction, i.e. the interplay of ionizations or sublesions formed in the same particle track, has the characteristics of a single event mechanism and leads to damage which is proportional to dose. Intertrack

interaction on the other hand produces effects which increase more than linearly with dose.

The relative level of the intratrack and the intertrack effect and its dependence on radiation quality, dose, and interaction distances can be qualitatively understood on the basis of the LET concept. The argument will therefore be first formulated in terms of LET, the results will then be expressed in terms of the corresponding microdosimetric quantities. One may first consider the region of interaction around an ionization and ask for the mean energy $\bar{\varepsilon}_1$ deposited inside this region by the same particle track. One obtains curves which for different values of LET are represented as full lines in Fig.2. At very small diameters $\bar{\varepsilon}_1$ is nearly constant. This accounts for the fact that ionizations are very closely spaced within the clusters formed in primary collisions and that no attempt is made in this representation to resolve their spatial separation. The limiting value of $\bar{\varepsilon}_1$ is taken to be 100 eV which is approximately the mean energy per ionizing collision. With increasing values of d the mean energy deposition goes up as Ld. The mean energy $\bar{\varepsilon}_2$ deposited by separate events in the sphere around an ionization, on the other hand, goes up as the third power of d and it is proportional to dose. The values $\bar{\varepsilon}_2$ for different doses are given in Fig.2 by broken lines. These curves can be used to illustrate the derivation of interaction distances or site diameters. If the initial part of a dose effect relation can be approximated by a linear and a quadratic term in dose then one may determine the value D of the dose for which the square component is equal to the linear component. At this dose one must have a value $\bar{\varepsilon}_2$ which is at least equal to the value $\bar{\varepsilon}_1$. This yields a minimum value d for the interaction distance or site diameter. The relation between d and D is represented in Fig.3 for various values of LET.

The argument which has been used here is limited because it is based on the LET concept. In reality the energy loss straggling along the particle track, the complicated shape of the delta rays, and the curvature and finite length of the tracks of the charged particles,

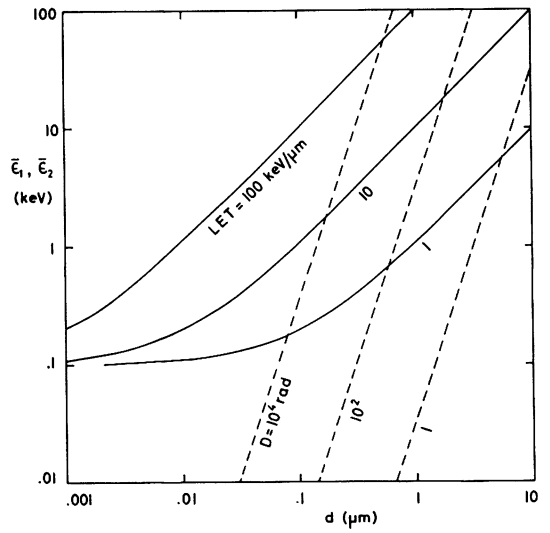


Fig.2 Mean energy $\bar{\varepsilon}_1$ around an ionization due to the same track, and mean energy $\bar{\varepsilon}_2$ due to different tracks as functions of the diameter of the sphere of reference.

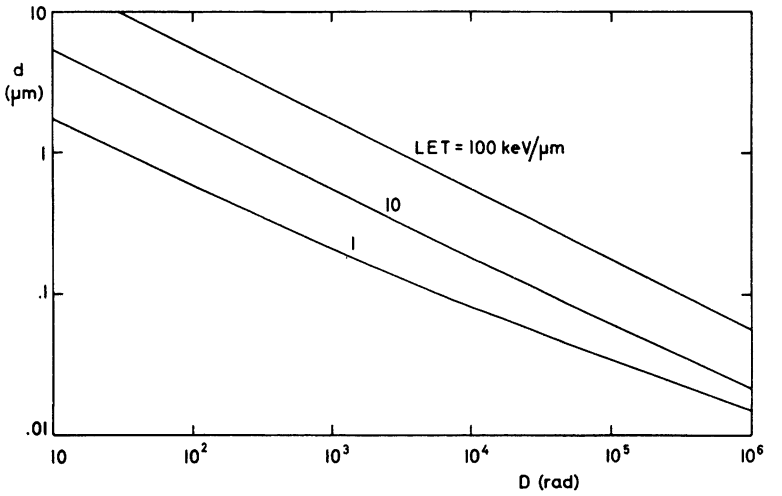


Fig.3 Dose D for equality of the linear and quadratic component of the radiation action and the corresponding diameter d of the site.

as well as the variations of stopping power cannot be neglected. It is always possible to account for these factors if starting from the fluence spectrum one uses the correct collision cross sections to derive all the characteristics of the various particle tracks; it is also frequently possible to apply special simplifications. In practice it is however wasteful to precede each radiobiological inquiry by a study in radiation physics with its own ad hoc definitions and terminology. To eliminate such unnecessary repetition is the purpose of microdosimetric quantities and functions.

In the microdosimetric analysis the plot in Fig.3 is substituted by a plot of the mean event size $\bar{z}_D$ as a function of diameter d. The quantity $\bar{z}_D$ corresponds to the ratio of the mean energy $\bar{\varepsilon}_1$ and the mass of the reference region; this means that $\bar{z}_D$ can be considered as the "dose locally produced" around an ionization due to its own particle track. The dose due to separate particle tracks is D. Therefore D must be at least equal to $\bar{z}_D$ if the quadratic component in the dose effect curve is to be equal to the linear component. The plot of $\bar{z}_D$ as a function of d can therefore be used in the same way as Fig.3 has been used to derive a minimum for the interaction distance or site diameter. The curves for LET-values of 1 keV/µm and 100 keV/µm are repeated in Fig.4 as broken lines in order to give a comparison between the analysis based on LET and on microdosimetry.

The basic argument which has been outlined here has various modifications. It can, for example, also be applied to dose response curves for which one knows merely the overall shape but not necessarily the exact shape of its initial part[9]. But one can go a considerable step further, and as Dr. Rossi has reported, it has been possible on the basis of studies of RBE to derive a relation between primary damage in the cell and specific energy z. The primary damage for a wide spectrum of effects appears to be proportional to the square of the local concentration z averaged over regions larger than 1 µm. In order to determine the effectiveness of a given radiation dose one need then only calculate the value z^2 averaged over a density profile as in Fig.1c. One can show that the mean, $\overline{z^2}$, of the square

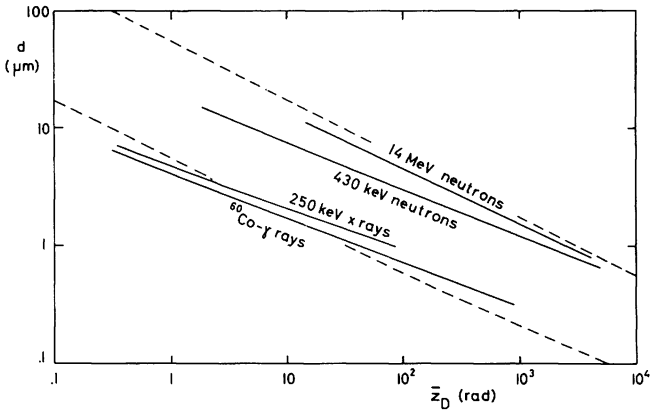
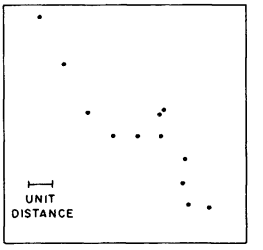


Fig.4 The relation between the mean $\bar{z}_D$ of the single event spectrum of specific energy and the diameter d of the spherical reference volume. The broken lines correspond to LET values of 1 and of 100 keV/μm.



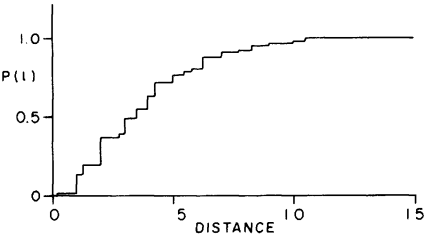


Fig.5 Diagram of a track pattern and the sum distribution of the distance between ionizations.

of specific energy is equal to $\bar{z}_D\ D + D^2$ and accordingly one obtains the equation for the primary damage:

$$E(D) = k(\bar{z}_D\ D + D^2) \qquad (1)$$

which connects the linear term with the quadratic term in the initial part of the dose effect relation. This equation has been discussed in detail in the context of the theory presented by Dr. Rossi.

The analogue to eq.1 can be given in terms of the LET concept:

$$E(D) = k(c\bar{L}_D/d^2\ D + D^2) \qquad (2)$$

The value of the numerical constant c is 22.9 if the track average $\bar{L}_D$ of LET is measured in keV/μm and if the site diameter or interaction distance, d, is given in μm. This relation is obtained if one postulates a spherical site of constant sensitivity or a fixed interaction sphere of diameter d. Somewhat different forms of the relation result if one assumes diffuse sites or interaction probabilities which are continuous functions of distance. In terms of LET such modified solutions can be easily formulated, for example one can assume a Gaussian shape of the interaction probability as function of distance. The LET concept has however, as has repeatedly been mentioned, various limitations. Eq.2 and its possible modifications are therefore applicable only in special cases. It is an open question whether useful microdosimetric quantities can be defined which relate to diffuse reference regions or to continuous interaction probabilities.

The preceding discussion has been restricted to the problem of interaction processes, the determination of their range, and of the relative level of intratrack and intertrack effect. Various other applications of microdosimetry can be based on the microdosimetric quantity, event frequency ϕ, or its inverse, the frequency mean $\bar{z}_F$ of the event size. These applications have been considered in detail elsewhere[8,10]. While $\bar{z}_D$ is the microdosimetric analogue of the dose average LET, the quantities ϕ and $\bar{z}_F$ are related to the track average

LET, or in the case of very small regions to the associated volume. ϕ and $\bar{z}_F$ are of particular importance in all considerations concerning exponential dose effect relations where one is not interested in the interaction of absorption events but merely in the determination of cellular cross-sections. It may however be noted that general theorems on dose effect relations have been derived which widen the applicability of these microdosimetric quantities considerably[11].

FUTURE DEVELOPMENTS

The history of radiobiology has been one of growing complexity; this is true for the types of radiation used, for the test systems experimentally analyzed, and for the attempts to explain the observed effects. Target theory models based on the simple postulates of critical energy thresholds and a deterministic reaction of the cell have been abandoned, and it has been recognized that the cell's reaction to the radiation insult reflects various stochastic factors[9]. Variations of cellular sensitivity, the stochastic behavior of the cell, and the statistics of energy deposition equally determine the shape of the survival curve at least in those cases where such a curve is sigmoidal. A model for cellular survival curves can therefore not be exclusively based on only one of these factors, namely the statistics of energy deposition. Indeed the very fact that such a model fits the experimental data would be sufficient proof of its inaccuracy. This lessens the value of the old curve fitting techniques.

The growing complexity has, however, led to simplification insofar as extensive model building has been reduced in favor of more rigorous and general lines of approach. The microdosimetric analysis of RBE which has been mentioned earlier is a good example for this development. A study of RBE instead of the explicit shape of the dose effect curve eliminates factors other than the statistics of energy deposition. Giving up the postulate of critical thresholds of energy deposition one obtains a general dependence between primary damage

and specific energy. This leads to an important simplification insofar as one can understand RBE on the basis of the microdosimetric quantity $\bar{z}_D$ and need not invoke the full distribution f(z;D). It will have to be the object of future microdosimetric research to extend this approach. Studies of dose rate dependence, oxygen effect, and various other modifying factors as functions of radiation quality will be equally important. The further development of the system of microdosimetric quantities and functions will have to be paralleled by the establishment of more clearly defined radiobiological concepts relating to these various factors.

While the line of future development in the radiobiological application of microdosimetry may be clearly indicated, the technical development of microdosimetry is not so easily predicted. This is especially true for potential studies of the patterns of energy deposition in the nanometer region. It seems likely that measurements of the spatial distribution of positive ions in charged particle tracks will have to be performed; the cloud chamber photography presented at this symposium point in this direction. Theoretical studies, possibly in the form of an extension of the associated volume method, may be equally important. A question of particular importance in this context is whether the established microdosimetric functions which have proved useful in dealing with regions of the typical size of 1 μm will prove equally useful on a much smaller scale. Diffusion of free radicals and direct energy transport may be the dominant factors on this scale, and in the analysis of these factors it may be necessary to use realistic interaction probabilities as a function of distance. As has been mentioned, there is at present no clear way to generalize the microdosimetric concepts to this case. It is therefore of great interest to examine alternative methods of describing the spatial patterns of the electronic disturbances or of initial radiation products, such as free radicals. Tentatively one may consider the use of distribution functions of the mutual distances of ionizations, but how this idea can mathematically be realized is an open question. One might for example consider all possible pairs of ionizations

belonging to the same particle track and calculate the distance for each pair. Thus one derives a distribution function such as the one given in Fig.5b which corresponds to the pattern represented in Fig. 5a. It is a highly interesting question whether there is a unique relation between any such pattern and the corresponding distribution of distances. In the two dimensional analogue and in such simple cases as the one depicted in Fig.5 it has indeed been found that a unique or nearly unique relation exists, i.e. one cannot only calculate the distribution function of distances for each given pattern but one can also reconstruct a pattern from the distribution function. But these considerations are still far from leading to useful general results, and it may well be that a completely different mathematical description of the spatial patterns of electronic disturbances in a charged particle track will have to be found.

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