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Biological Implications of Microdosimetry: II Spatial Aspects*

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ABSTRACT: If the theory of dual radiation action is applied not to temporal phenomena but to the analysis of spatial interaction of cellular damage, additional complexities arise. As far as the interaction of sublesions is concerned, the quadratic dependence of the effect on specific energy, z, appears to be well established. It explains the observed RBE of different radiation qualities in a good first approximation. One must, however, also consider the effectiveness with which various radiations produce sublesions. Recent studies have indicated that this effectiveness is not completely independent of LET, and the specific energy at the nanometric level could therefore be a determining factor.

The question is discussed with special reference to cellular inactivation cross-sections in the presence and absence of oxygen, and with reference to the very high RBE values observed at low doses of neutrons with energy of the order of 1 MeV.

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The concept of primary cellular damage.

The study of dose-RBE relations has led to the conclusion that the primary cellular lesions in a variety of effects of ionizing radiations on higher organisms are proportional to the square of the specific energy, z, in the cell nucleus or in subnuclear regions of several μm diameter. From this quadratic dependence on z the linear-quadratic dependence on absorbed dose is readily derived:

$$\epsilon(D) = k\,(\zeta D + D^2) \qquad (1)$$

ζ is the dose average of the single event spectrum $f_1(z)$. The influence of the temporal distribution of absorbed dose has been treated in the first part of this contribution; for the purpose of the present discussion only instantaneous application of the dose will be considered.

The primary cellular damage is not necessarily proportional to the observed experimental endpoint, and $\epsilon(D)$ should therefore be considered merely as an auxiliary concept. As such it is, however, highly useful because it separates the complexities of the physics of energy absorption from the chemical and biological complexities which also enter the dose-effect relation. In cases, such as the induction of cataracts (1), the relation between observed effect and absorbed dose is necessarily complicated, if only because of the arbitrary choice of the effect scale. However, if one utilizes the concept of ϵ, it is sufficient to invoke only one universal function, $C(\epsilon)$, for a particular effect which is valid for all radiation qualities:

$$C(\epsilon) = C(\zeta D + D^2) \qquad (2)$$

Without the use of microdosimetric concepts it would be considerably more difficult to bring order into the observed phenomena since one would have to deal with a variety of functions, C, for different radiation qualities. The auxiliary concept of primary cellular damage is therefore of obvious value.

There are, however, cases in which the quantity ϵ is closely related to the observed cellular effect, and the study of dose-RBE relations is therefore not the only method to examine the dependence of radiation

effects on specific energy. In the following some of the sources of relevant information will be considered.

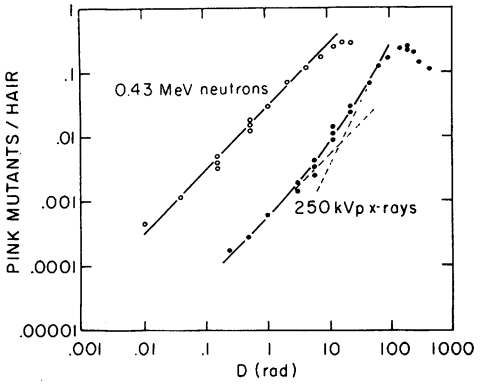
The linear-quadratic relation in the case of cytogenetic effects

Two-break aberrations in the chromosomes of eukaryotic cells are an example where the linear-quadratic dependence on absorbed dose can be directly observed. The quadratic dependence of the yield of dicentrics and of centric rings on the square of the energy concentration has in fact been postulated before microdosimetric concepts had been established. Although the treatment within the limitations of the LET-concept had to remain semiquantitative, Lea (2) has given a lucid and still valid presentation of the main arguments. We have recently made an attempt to juxtapose the formulation in terms of LET with the corresponding microdosimetric equations (3).

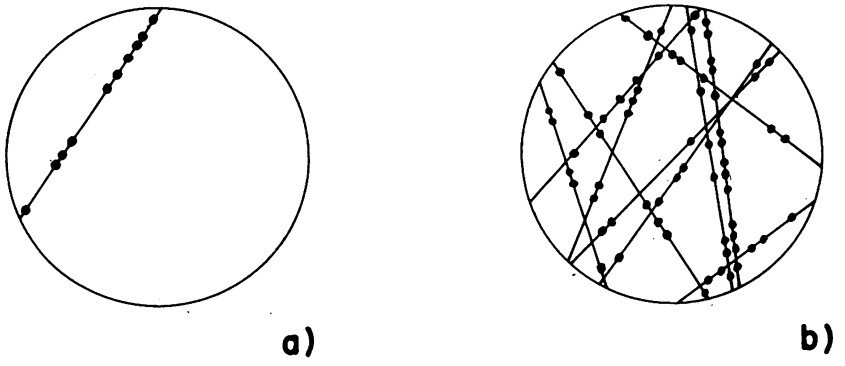
The scoring of radiation-induced dicentric chromosomes is laborious. It has therefore not been possible to achieve sufficient statistical accuracy in the region of small doses to clearly define the initial linear component for sparsely ionizing radiations. As a consequence, simple proportionality of the yield to a power of the dose intermediate between 1 and 2 has often been postulated instead of the linear-quadratic relation. Recently, however, Schmid et al (4) have been able to establish the linear component for the production of dicentrics by low doses of fast electrons and of 220 kV x rays in human lymphocytes. The values of ζ obtained by these authors correspond to site diameters of the order of 1 µm, and it is particularly noteworthy that for x rays ζ is about twice as large as for fast electrons. This is in agreement with microdosimetric data. *

In other systems the observations are simpler and permit a higher degree of statistical accuracy although they are not directly linked to actually observed chromosomal aberrations. Examples are the observations by Sparrow et al (5) on certain color mutations in Tradescantia and the study of yg_2-mutations performed by Smith on maize (6). The results for pink mutations produced in Tradescantia stamen hairs by x rays and neutrons are represented in Fig. 1. If one disregards the plateau and the subsequent decline of mutations at large doses, one can

* In this context see also the contribution of BRENOT et al. to this Symposium.



1) Induction of pink mutant cells in the stamen hairs of Tradescantia by x rays and 430 keV neutrons (5). The spontaneous rate is subtracted. The solid line for x rays corresponds to Eq.(1) with ζ = 16 rad.



2) Schematic diagram of intra-track (a) and inter-track (b) effect.

represent the data by the linear-quadratic equation. This is apparent from the logarithmic plot in which lines of slope 1 correspond to proportionality of the effect to absorbed dose, while lines of slope 2 correspond to a quadratic dependence on dose. As a result of a least-squares fit one obtains the value ζ = 16 rad for x rays and the value ζ = 750 rad for 430 keV neutrons. These values correspond to a site diameter of about 2 µm. Once can readily see from the logarithmic plot that the RBE of neutrons has a constant value of approximately 50 at low doses while, with increasing dose, it decreases in the same form which has been observed in a wide variety of different higher organisms.

Although Eq.(1) can be derived rigorously and without further assumptions from the quadratic dependence of the cellular effect on specific energy, it may nevertheless be useful to illustrate this relation by a simplified argument. In Fig. 2 the "site ",i.e. the region over which pairs of sublesions can interact, is symbolized by circles. In the example of cytogenetic effects the sublesions, represented in the diagrams by dots, can be considered as "single breaks." The total number of sublesions is proportional to dose. The probability for each sublesion to interact with another sublesion is proportional to the number of neighbouring sublesions in the site. These other sublesions can either be from the same particle track, or they can be produced by other charged particles. The mean number of the former is proportional to ζ, i.e. to the mean specific energy produced by one particle; the number of the latter is simply proportional to dose. The total effect is therefore proportional to the product of absorbed dose and the term $(\zeta + D)$:

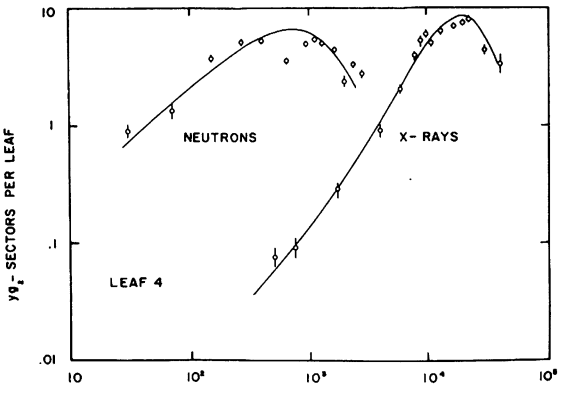
$$\epsilon(D) = k\, D(\zeta + D) = k(\zeta D + D^2) \qquad (3)$$

It is obvious that at low doses (Fig. 2,a) the linear component, i.e. the intra-track effect, dominates, while at large doses (Fig. 2,b) only the quadratic component, i.e. the inter-track effect, needs to be considered. Experimental observations, such as the results for Tradescantia, show this simple relation in particularly clear form. From the value of ζ one readily infers the site diameter, which can also be interpreted in a less specific way as an effective interaction distance of sublesions.

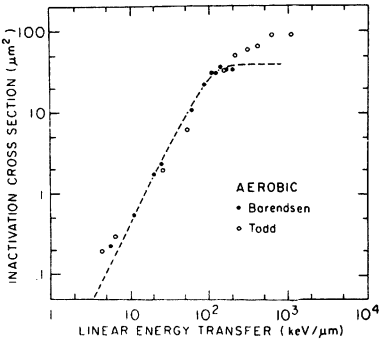
Results very similar to those in Tradescantia are obtained for yg_2-mutations in maize. This is depicted in Fig. 3. The main difference here is that the values of ζ are considerably larger than those found for other effects on eukaryotes. This is, however, not surprising since in this case one deals with dry seeds and must therefore expect that the interaction distances between sublesions are reduced. The least-squares estimate of ζ for x rays is 2100 rad; this corresponds to a diameter of .2 to .3 μm. As in the case of the mutations in Tradescantia the value ζ for neutrons is so large that the quadratic component in the linear-quadratic equation can be neglected. It appears that in this system the limiting value of RBE of neutrons at small doses is even larger than the value of approximately 50 which is expected from the ratio of the microdosimetric quantities ζ for neutrons and x rays. Similarly large limiting values of the RBE of neutrons have been found for the opacification of the murine lens (1) and for the induction of mammary neoplasms in the Sprague-Dawley rat (7). The observation indicates that densely ionizing radiations can be even more effective than predicted on the basis of the quadratic dependence of the cellular damage on specific energy. The point will be further considered in the next section. One possible interpretation is that the coefficient k in Eq.(1) is not entirely independent of radiation quality, but that it is larger for neutrons because the increased energy concentration in the tracks of the recoil protons leads to an increased yield of sublesions (8). No systematic studies of the spatial distribution of energy deposition on the scale of nanometers and of its biophysical implications have as yet been performed. But future work in this direction will be of considerable interest.

Connection between track segment experiments and microdosimetric studies

The dependence of cellular effect on specific energy has been studied by examination of the dependence of RBE on dose or of effect on dose. An alternative method is the study of the effect as a function of lineal energy, y, or of the corresponding quantity LET. Studies of the dependence on LET have been performed in the so-called track



3) Mean number of yg_2-sectors for maize in leaf 4 as a function of x-ray and neutron dose.
The spontaneous incidence is zero. The solid line for x rays corresponds in its initial part to Eq.(1) with ζ = 2100 rad.



4) Cross section of heavy charged particles for inactivation of mammalian cells <u>in vitro</u> as a function of LET under aerated conditions (9,10).
The broken line corresponds to Eq.(5) with L_o = 110 keV/μm or Eq.(6) with y_o = 124 keV/μm.

segment experiments; microdosimetric studies have mainly been performed with monoenergetic neutrons, but more recently also with fast heavy ions. In the following the interrelation of these experiments will be considered.

According to the quadratic dependence of cellular damage on energy concentration, one might simply assume that the cross section for the inactivation of mammalian cells by heavy charged particles is proportional to the square of the stopping power:

$$\sigma(L) \sim L^2 \tag{4}$$

This is obviously an oversimplification since the inactivation cross section can not increase indefinitely with increasing LET, but must reach a plateau which is related to the geometrical cross section of the cell or its nucleus and to the lateral extension of the particle tracks. A more realistic assumption is therefore that the primary cellular damage, ϵ, increases with the square of LET, while survival decreases exponentially with ϵ. Therefore:

$$\sigma(L) = \sigma_\infty \left(1 - e^{-(L/L_o)^2}\right) \tag{5}$$

In Fig. 4 this relation is compared with the experimental findings by Barendsen (9) and Todd (10). There is overall agreement of the experimental results with the broken line which represents Eq.(5) with the value L_o = 110 keV/µm. Discrepancies arise, however, at small values and at high values of LET. At small values of LET the experimental data lie above the theoretical curve. Todd (10) and Powers et al (11) have accordingly used an equation which corresponds to Eq.(5) but contains a term linear in L. This linear term is a reflection of the inadequacies of the concept of LET. If one considers the microdosimetric quantity lineal energy, y, instead of LET, the linear component disappears. This can be understood as follows. At moderate and high values of LET and for particle tracks which have a lateral extension small as compared to the dimensions of the cell nucleus, the quantities y and LET can be nearly equated. For low LET, however, energy straggling plays a role and leads to a significant broadening of the y spectra even at a fixed

value of LET. The average, $\bar{y}_D$, of the y spectrum is then considerably larger than LET. Since this average determines the biological effect, the observed cross sections at low values of LET are significantly higher than expected on the basis of LET alone.

At high doses, one has essential agreement of the theoretical relation and the data of Barendsen, but there are strong discrepancies to Todd's data. These discrepancies have been extensively discussed (see, for example, Curtis (12)). For the present discussion it is sufficient to note that Todd has used particles which were fast enough that the maximum range of delta rays is comparable to the dimensions of the cell nucleus. This can at least partly account for the fact that at very high LET's he obtains cross sections which are significantly larger than the actual geometrical cross section of the cell nucleus. A quantitative microdosimetric evaluation of Todd's results would be of considerable interest. Such an evaluation is, however, complicated by the fact that in these experiments the charged particles enter the cells after traversing a gaseous medium, and that one therefore deals with what one could call reversed wall effects. In view of these complexities the discussion will be confined to Barendsen's results which are obtained with particle tracks sufficiently narrow that their lateral extension can be neglected. One concludes that the data for cellular inactivation by monoenergetic charged particles are in substantial agreement with Eq.(5) or its microdosimetric equivalent:

$$\sigma(y) = \sigma_\infty \left(1 - e^{-(y/y_o)^2}\right) \qquad (6)$$

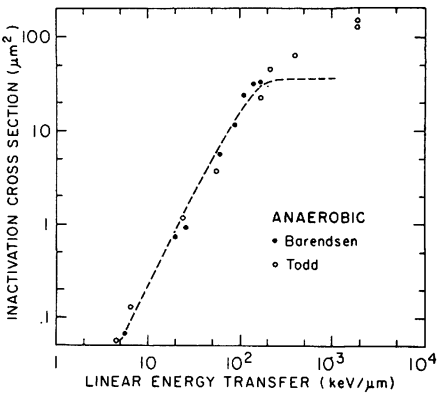
It is of interest to inquire whether the same agreement is found for hypoxic conditions. The simplest assumption concerning the oxygen effect and its dependence on LET is that in the absence of oxygen the yield of sublesions is reduced by a constant factor, ρ. The cross section under hypoxic conditions then takes the form:

$$\sigma_H(y) = \sigma_\infty \left(1 - e^{-(\rho y/y_o)^2}\right) \qquad (7)$$

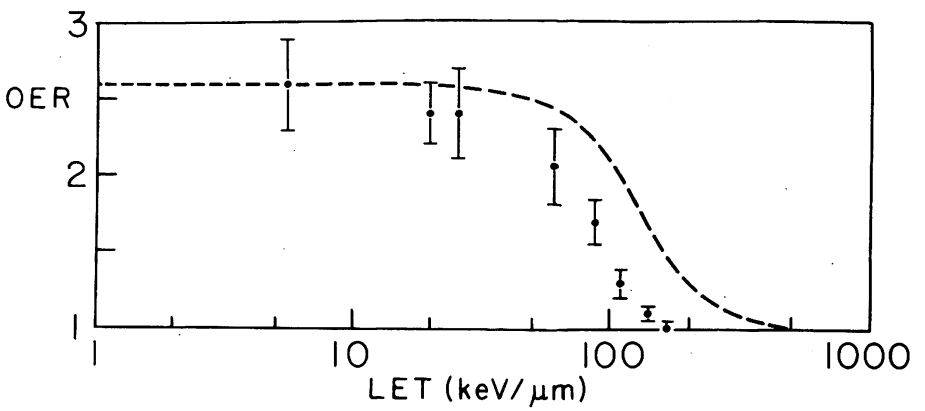
This results in a curve of the same form as in Fig. 4, but shifted to

the right by a distance corresponding to the factor ρ. In Fig. 5 the theoretical curve is compared with the experimental results. If the discussion is again confined to the data by Barendsen, one finds that at values of LET near 100 keV/µm the experimental results rise somewhat more steeply than the theoretical curve. While this appears only as a minor deviation in the logarithmic plot of cross section vs. LET, it has a significant effect on the dependence of OER on LET. Fig. 6 is a comparison of the observed dependence of OER on LET with the broken line which would result if the theoretical curves in Figs. 4 and 5 were valid. Due to the steeper increase of the experimental cross sections under hypoxic conditions the OER drops more rapidly with increasing LET than expected. Formally one could describe this by stating that the reduction factor ρ is significantly different from 1 only at small and moderate values of LET.

Barendsen's result is of considerable interest because it would indicate that the disappearance of the oxygen effect for very densely ionizing particles is not merely the trivial result of saturation in its simplest form. There has been speculation involving particular mechanisms, such as production of oxygen in the tracks of densely ionizing particles, which could account for an intrinsic disappearance of the oxygen effect for densely ionizing radiation. A simple microdosimetric explanation is, however, equally sufficient to explain the observations. This explanation is based on the assumption that for LET values near 100 keV/µm the energy concentration in charged particle tracks reaches sufficient values to increase the yield of sublesions. The apparent increase of ρ in Fig. 6 would then merely be due to the increased yield of sublesions, both under aerated and hypoxic conditions. Under aerated conditions, this increased yield may not be observable since one is already too close to the maximum observed cross sections. In the hypoxic case, however, the increased yield leads to a substantial increase of the observed cross sections at values of LET near 100 keV/µm. A schematic representation of this situation is given in Fig. 7 where inactivation cross sections are plotted as a function of the microdosimetric quantity y. The broken curves represent the simple quadratic model without modifications. The full lines indicate the increase of the cross sections due to an increased yield of sublesions



5) Cross section of heavy charged particles for inactivation of mammalian cells in vitro as a function of LET under hypoxic conditions (9,10).
The broken line corresponds to Eq.(7) with y_o = 124 keV/μm and ρ = 0.62.



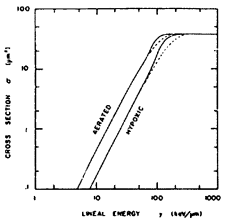
6) OER as a function of LET. The experimental points are for inactivation of mammalian cells in vitro (9) and correspond to the data in Figs. 4 and 5.
The broken line corresponds to the two broken lines in Figs. 4 and 5.

at higher values of y.

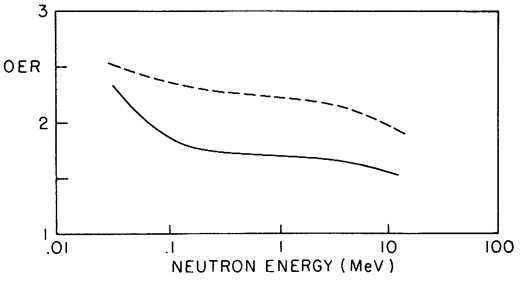
The situation can be further examined in the light of results obtained with neutrons. For this purpose one has to integrate the microdosimetric y spectra for neutrons over the curves in Fig. 7. Fig. 8 represents the results. The lower OER values given by the solid curve result from the integration over the solid lines in Fig. 6, the broken line results from the integration over the broken lines in Fig. 5 which correspond to the uncorrected model. Experimental data for the OER of monoenergetic neutrons, such as the observations by Hall et al (13) are consistent with the solid and not with the broken line. The results from neutron experiments are therefore in agreement with the rapid decrease of OER with LET observed by Barendsen and with the conclusions concerning an increased yield of sublesions in the tracks of densely ionizing particles.

Further information on the same problem is provided by the growth reduction studies of Vicia faba with fast nitrogen ions (14). Microdosimetric measurements have been performed for these experiments (15), and the theoretical analysis (16) has shown that in this case the observed values of OER are in accordance with the broken lines and not the solid line in Fig. 7. This difference to the track segment experiments and the observations with neutrons is expected on microdosimetric grounds. At a given value of y the tracks of the faster nitrogen ions are much less concentrated radially than the tracks of lighter particles, such as protons. The energy concentration on a scale of several nanometer is therefore smaller for nitrogen ions and the increase of the yield of sublesions should be less prominent.

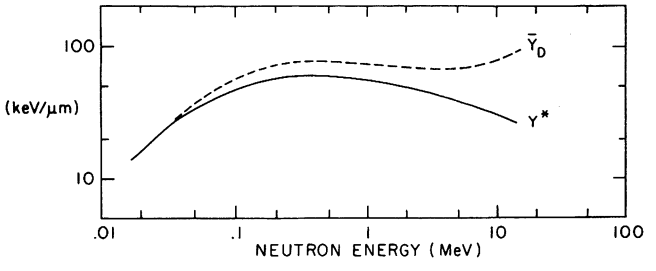
Further information on the dependence of cellular damage on the microdosimetric quantities z or y is obtained from studies of the RBE of monoenergetic neutrons or heavy ions. In the simplest approximation, corresponding to Eq. (4), the RBE at low doses should be proportional to the dose average, $\bar{y}_D$, of lineal energy. This quantity is plotted as a broken line in Fig. 8. As pointed out, one must instead introduce a quantity which is corrected for saturation (for details see (3)):



7) Schematic representation of the dependence of the cross section σ on lineal energy y. With the broken line segments the curves correspond to Eqs.(6) and (7) with constant ρ. The solid curves result if the yield of sublesions increases at values of y near 100 keV/μm; formally this could be represented by a decrease of y_o with increasing y.



8) Oxygen enhancement ratio for monoenergetic neutrons as a function of their energy. The solid line results from the solid lines in Fig. 7, the broken line from the curves with the broken line segments in Fig. 7.

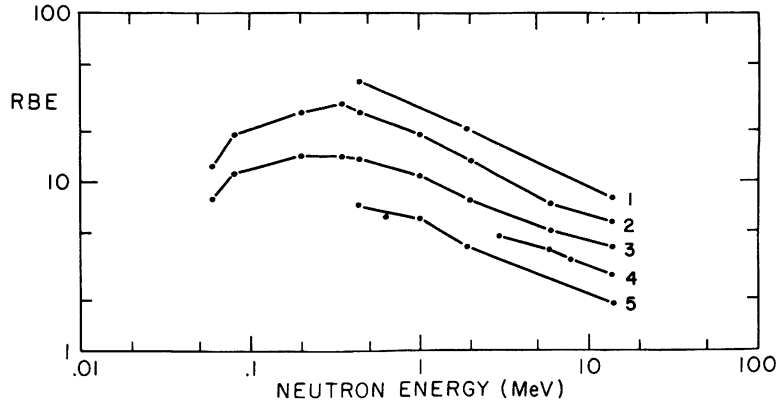


9) Dose mean lineal energy, $\bar{y}_D$, for neutrons of energy E (broken line), and the corresponding quantity, y^*, which results if saturation is taken into account according to Eq.(8).

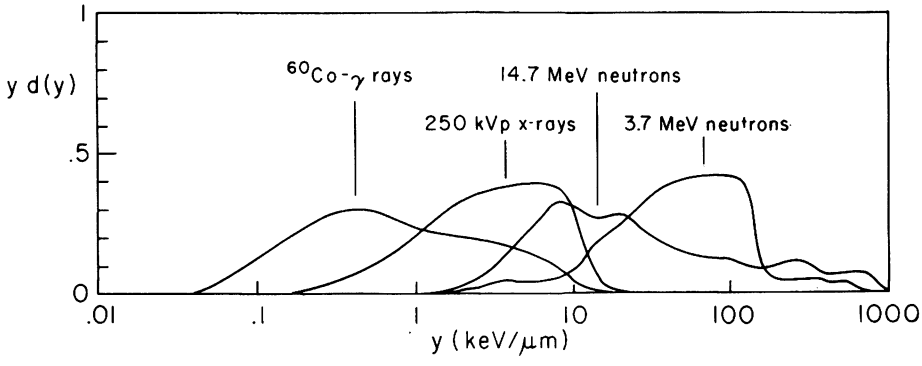
$$y^* = y_o^2 \int (1 - e^{-(y/y_o)^2}) f(y)\, dy/\overline{y}_F \qquad (8)$$

This definition of an 'effective' y corresponds to Eq.(6), but it is normalized in such a way that at low values of y it reduces to the dose average, $\overline{y}_D$. The resulting values are given as the solid line in Fig. 8. Fig. 9 contains corresponding plots of the experimentally observed dependence of neutron RBE as a function of neutron energy for various systems. Without going into the details of these results, one concludes that there is an overall agreement between the theoretical prediction and the experimental observations, and particularly that the maximal values of RBE occur at an energy of about 340 keV, as the theory predicts. However, one notes also that the difference between the RBE at intermediate neutron energies and high neutron energies is larger than theoretically predicted. This difference can be understood from the fact that the theoretical curve is derived from data obtained with particles of sufficient range to traverse the nucleus of the cell completely while in the experiments with neutrons of a few hundred keV one deals with recoil protons whose range is considerably less than the diameter of the cellular nucleus. One of the main results of the theory of dual radiation action is that the site diameters, or the relevant interaction distances in cellular action, are of the order of 2 μm. A proton of about 150 keV has sufficient range to traverse these sites, and near its Bragg-peak it reaches the most effective LET of about 100 keV/μm. On the other hand, it transfers considerably less total energy to the cell nucleus than a heavier particle of comparable LET which traverses the whole nucleus. One must therefore conclude that there is less waste of energy in the action of the low energy protons. This is borne out by the experimental observation that the RBE at neutron energies of a few hundred keV exceeds the predicted values by about a factor of 2.

This interpretation is further supported by the finding that various studies with heavy nitrogen ions have shown full agreement with the microdosimetric predictions based on the observations in the track segment experiments. In this case the agreement is to be expected since one deals with complete traversals of the cell nucleus.



10) Observed dependence of RBE on neutron energy. 1: Lens opacification at x ray dose 40 rad (1). 2,3: 50% growth reduction of Vicia Faba (anoxic, and oxygenated) (13). 4: Cellular inactivation (initial part of the survival curves) (9). 5: 37% depletion of spermatogonia (17).



11) Distribution of dose in y for single events in spherical tissue regions for various radiation qualities. The curves are based on experimental (18) and theoretical data (18); they refer to a diameter of 1 μm.

Conclusions

It has been found that the basic tenets of the theory of dual radiation action are supported by the study of dose-RBE relations, by the analysis of track segment experiments, and by various studies of the RBE and OER obtained with monoenergetic neutrons as well as with heavy ions. There are, however, indications that the dependence of cellular effect on the square of specific energy is accompanied by an increase in the yield of sublesions in the track of sufficiently slow heavy charged particles. Furthermore saturation occurs in all those cases where one charged particle deposits more than a few hundred keV in the cell nucleus.

Although a relatively simple quantitative treatment of saturation is in agreement with the experimental observations, we have not yet reached sufficient understanding of the underlying mechanisms. The assumption that the yield of sublesions increases in the tracks of densely ionizing particles is supported by various experimental results, but since no systematic studies of the patterns of energy deposition on a scale of only a few nanometers have as yet been performed, these conclusions must remain tentative. It is, however, noteworthy that the same quadratic kinetics with only slight modifications appear to be valid for a wide range of experimental observations in higher organisms and for a wide variety of radiation qualities whose microdosimetric spectra as shown in Fig. 10 extend from values of lineal energy below .1 keV/μm to values exceeding 1000 keV/μm.

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D I S C U S S I O N

Mr BICHSEL

I would like to ask a question about Mr Rossi's paper. In radiotherapy a formula or expression is used to calculate the effective dose in fractionated irradiation. It is the Ellis-formula. I wonder whether you have made any attempt to relate your approach to the problem of time dependence of radiation effects to the Ellis-formula?

Mr KELLERER

The Ellis-formula is closely related to the older Strandquist equation. This equation can be derived from a recovery function, which is proportional to a negative power of time but which can also be closely approximated by an exponential recovery function with a certain non-recoverable part of the sublethal damage. The Ellis-formula therefore agrees closely with the equations presented by Mr Rossi for incomplete recovery and for doses which are large in comparison with $\int$.

Mr KATZ

I wanted to ask a question about the slide you showed concerning the cross-section versus LET for Todds and Barendsen's data. You claimed that these data had a quadratic dependence on the cross-section with LET. Are your data from the initial or final slope of the survival curve?

Mr KELLERER

The discussion related to the initial slope of the survival curves.

Mr KATZ

Our analysis of the "ion-kill" cross-sections of these and other data for mammalian survival curves, which correspond to initial slopes of survival curves, give a slope of 2.5 or 3 for such plots, while we get slope 4 for bacterial spores. Is this in any way contradictory to your analysis? I think it very unlikely that our analysis can yield slope 2?

Mr KELLERER

The points I raised relate to eukaryotic cells. They can naturally not apply to systems which are so small that the inter-action of lesions over distances of the order of micrometers is out of the question purely for geometrical reasons. As to your other point, namely the statement that the cross-section for inactivation of mammalian cells goes with the power of 2.5 of LET, I am doubtful and can merely refer to the graphs which I have presented. We do have a certain deviation from the quadratic dependence, but it goes in the other direction. I am referring to the slope below 2, at low LETs. Under hypoxic conditions and at LET values near 100 keV/μm one observes a slope of the cross-section versus LET relation which is larger than 2. This particular point was treated in detail in the preceding analysis. It is indeed important as it leads to the assumption that the coefficient K may increase at large LET.

Mr KATZ

Well, in our analysis of what we call the ion-kill cross-section and in mammalian cells we were never able to achieve slope 2. The 2.5 is always a little uncertain but for us it veers towards 3 and in fact for some cells, in both aerobic and anoxic conditions, the figure is 3 but never 2.

Mr KELLERER

I have to be somewhat hesitant about this statement as it is based on a curve for Todd's data which does not contain the actual experimental points. I have also mentioned the reasons why we have not included Todd's data in the present analysis.

Mr KATZ

Just one final comment. Of course the drawing of initial slopes in experimental curves is open to a great deal of discussion.