

INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY
BIOLOGY·PHYSICS

VOLUME 5, NUMBER 7

JULY 1979

TABLE OF CONTENTS

● ORIGINAL CONTRIBUTIONS

- Cancer of the Bilharzial Bladder**
E. M. Chevlen, H. K. Awwad, J. L. Ziegler and I. Elsebai 921
- Correlation of Radiation and Surgical Parameters in Complications in the Extended Field Technique for Carcinoma of the Cervix**
M. A. El Senoussi, G. H. Fletcher and B. C. Borlase 927
- The Effect of Pelvic Irradiation on the Absorption of Bile Acids**
J. A. Stryker and L. M. Demers 935
- Low Dose Elective Brain Irradiation in Small Cell Carcinoma of the Lung**
D. D. Beiler, R. C. Kane, A. M. Bernath and M. R. Cashdollar 941
- A Pilot Study to Investigate Skin and Tumor Thermal Enhancement Ratios of 41.5–42.0°C Hyperthermia with Radiation**
R. J. R. Johnson, T. S. Sandhu, F. W. Hetzel, S.-Y. Song, H. I. Bicher, J. R. Subjeck and H. S. Kowal 947
- The Response of Pig Skin to Single and Fractionated High Dose-Rate and Continuous Low Dose-Rate ¹³⁷Cs Irradiation. Part II. Theoretical Considerations of the Results.**
I. Turesson and G. Notter 955
- Potentialiation of Cytotoxicity of 5-Thio-D-Glucose on Hypoxic Cells by Hyperthermia**
C. W. Song, D. P. Guertin and S. H. Levitt 965
- Quantitation of the Radiotherapeutic Importance of Naturally Hypoxic Normal Tissues from Collated Experiments with Rodents Using Single Doses**
J. H. Hendry 971
- The Role of Radiation Therapy in the Treatment of Small Cell Undifferentiated Bronchogenic Cancer**
B. S. Ajaikumar and H. T. Barkley 977

● RAPID COMMUNICATIONS

- Misonidazole Neurotoxicity in the Mouse**
P. J. Conroy, R. Von Burg, W. Passalacqua, D. P. Penney and R. M. Sutherland 983

Single Dose Total Lymphoid Irradiation Combined with Cyclophosphamide as Immunosuppression for Human Marrow Transplantation in Aplastic Anemia T. H. Kim, J. H. Kersey, F. M. Khan, W. Sewchand, N. Ramsey, W. Krivit, P. Coccia, M. E. Nesbit and S. H. Levitt	993
---	-----

● **BRIEF COMMUNICATIONS**

Immunosuppression and Reconstitution with Thymosin after Radiation Therapy W. M. Wara, D. W. Wara, A. J. Ammann, J. L. Barnard and T. L. Phillips	997
Nodular Lymphomas: Involvement of Epitrochlear Nodes W. Saunders, E. Glatstein, R. Hoppe and H. Kaplan	1003

● **EDITORIAL**

Pre-Operative Irradiation of Patients with T3 Carcinoma in Bilharzial Bladder W. L. Caldwell	1007
--	------

● **CURRENT CONCEPTS IN CANCER**
Updated Cervix Cancer—Stages 0 and 1A

Introduction P. Rubin	1009
Staging Classifications H. Ulfelder	1013
Histologic Types and Prognosis of Cancers of the Uterine Cervix J. W. Reagan and Y. S. Fu	1015
The Subclinical Stages of Carcinoma of the Uterine Cervix and Possible Precursor Lesions W. M. Christopherson	1021
Radiotherapeutic Approaches R. R. Million	1027
Surgical Approaches to Stages 0 and 1A Carcinoma of the Cervix J. H. Nelson	1029

● **UNITED STATES-ITALY COOPERATIVE SEMINAR ON RADIATION SENSITIVITY: FACTS AND MODELS**

Preface	1033
Introduction: The Role of Models in Radiation Science G. Gorin	1035
Physical Aspects of Radiation Sensitivity A. M. Kellerer	1041
Chemical Processes Induced Radiolytically in Well-Defined Aqueous Systems J. K. Thomas	1049
Radiolysis of DNA and Other Biopolymers L. S. Myers and E. Kay	1055



Radiolysis of Heterogeneous Inanimate Systems	
J. H. Fendler	1061
Modification of Radiation Sensitivity: The Oxygen Effect	
M. Quintiliani	1069
DNA Repair and Mutagenesis in Bacterial Systems and Their Implications in Oncology	
M. Errera	1077
Sensitivity to Ionizing Radiations and Damage Repair in Yeast	
G. E. Magni, L. Panzeri and S. Sora	1085
DNA Repair and Cell Repair: Are They Related?	
M. M. Elkind	1089
Differences in Radiation Sensitivity in Subpopulations of Mammalian Multicellular Systems	
G. Briganti and F. Mauro	1095
Facts and Models Applied to Tumor Radiotherapy	
R. F. Kallman	1103
Immunological Effects of Irradiation: Waiting for a Model	
G. Doria	1111
Intrinsic and Extrinsic Variables Affecting Sensitivity to Radiation Carcinogenesis	
J. M. Yuhas	1117
Life Span Shortening	
P. Metalli	1123
Summing Up the Seminar	
J. W. Boag	1131
● ANNOUNCEMENTS	1135
● MEETINGS	1137

ERRATA

Due to production problems associated with the prolonged postal strike in Ireland, the following compilation errors have recently occurred:

“Management of Advanced Glottic Cancer: 10 Year Review of the Toronto Experience,” by A. R. Harwood, N. V. Hawkins, F. A. Beale, W. D. Rider and D. P. Bryce (*Int. J. Radiat. Oncol. Biol. Phys.* **5**: 899-904, 1979) was designated as the second article in the June 1979 issue and should have appeared as an *Original Contribution*, not a *Brief Communication*.

“Preoperative Irradiation of T3 Carcinoma in Bilharzial Bladder: A Comparison Between Hyperfractionation and Conventional Fractionation,” by H. Awwad, H. A. ed-Baki, N. el-Bolkainy, M. Burgers, S. el-Badawy, M. Mansour, O. Soliman, S. Omar and M. Khafagy (*Int. J. Radiat. Oncol. Biol. Phys.* **5**: 787-794, 1979) should have appeared as the lead article in this issue.

Radiation Sensitivity: Facts and Models

PHYSICAL ASPECTS OF RADIATION SENSITIVITY

ALBRECHT. M. KELLERER

Institut für Medizinische Strahlenkunde der Universität Würzburg, D-8700 Würzburg, Versbacher Str. 5

A characteristic feature of ionizing radiation is the high energy concentration that occurs in the tracks of charged particles regardless of the level of absorbed dose. It is this feature that accounts for cellular radiation sensitivity at low doses. A survey is first given over the energies required to inactivate various microorganisms, and these energies are then related to the average number of DNA single strand and double strand breaks that are produced at the mean inactivation doses. It is pointed out that the production of DNA double strand breaks is always a single particle effect except at very high doses or in aqueous solution. However, a consideration of sigmoid dose effect curves and of the LET dependence of various biological effects indicates that a synergism of energy transfers or of radiation induced sublesions occurs over much larger distances. Individual double strand breaks cannot, therefore, be the lesions responsible for cellular radiation effects. However, they may be the sublesions that combine to produce the observed effects. The microdosimetric analysis that permits an estimation of the interaction distances of sublesions and the earlier analysis by Lea¹⁶ are described in their essentials. A more recent analysis, based on an explicit description of the spatial correlation of energy transfers in charged particle tracks, is also discussed. This analysis utilizes the so-called "proximity functions." The use of these functions is exemplified by the application to a recent experiment of Rossi *et al.*¹⁹ where cells are exposed to pairs of deuterons with variable lateral separation.

Ionizing radiation, Cellular effects, Tracks of charged particles.

INTRODUCTION

Imperceptible transfer of energy to the exposed object is the striking characteristic of ionizing radiation that has led to the common but erroneous notion that ionizing radiation produces substantial biological effects by singularly small amounts of energy.

Comparison with thermal energy would seem to support the view that organisms are remarkably sensitive to radiation energy. The mean lethal dose to a mammalian cell of about 5 Gy raises the temperature of the exposed object by merely 0.001 °C. However, heat, as the most degraded form of energy, is not a suitable basis for comparison, mechanical energy content is more appropriate. A simple calculation shows that the absorbed dose of 1 Gy transfers an amount of energy to the irradiated object that is sufficient to lift it by 0.1 meter. It is in no way surprising that such a sizable amount of energy should produce substantial effects. Nevertheless, there is reason to speak about the special effectiveness of small amounts of radiation energy in the cell. This special effectiveness is because even at extremely low levels of absorbed dose, energy is imparted to the cell in discrete, finite portions that can produce a wide spectrum of cellular lesions. The 'concentrated

dissipation of energy along the tracks of individual particles which is a unique feature of the ionizing radiations' (L. G. Gray in his preface to Lea's book¹⁶) has been a central theme of radiation biophysics from the beginnings of theoretical biophysics (see e.g.⁶); approaches towards a better understanding of radiation sensitivity must still be based on the study of the microdistribution of energy imparted to the cell.

RADIOSENSITIVITY AND ENERGY CONCENTRATION ON THE MOLECULAR SCALE

The notion of radiosensitivity is ambiguous. A comparison of the total energies necessary to inactivate biological structures would indicate that a mammalian cell is almost a million times more resistant than a simple entity such as a single strand phage. Even if only that energy is considered that is directly absorbed in the DNA, the ratio is still far greater than 1,000. If, on the other hand, radiosensitivity is related to dose, one arrives at the opposite conclusion. A mammalian cell appears then to be 1,000 times more sensitive than the single strand phage.

General statements on radiosensitivity are difficult,

Table 1.† Single and double strand breaks produced in various biological structures by sparsely ionizing radiation at their respective mean inactivation doses (condition of suppressed indirect action).

Object	Molecular weight of DNA m/dalton	D_{37} Gy	E_{DNA} eV	Number of single strand breaks n_{SSB}	Number of double strand breaks "DSB"	
					intra-track action	inter-track action
Single strand phage $\phi x174$	$1.7 \cdot 10^6$	4000	70	1	N‡a‡	N‡A
Phage T7	$2.5 \cdot 10^7$	1000	260	4	0.2	0.001
<i>E. coli</i>	$2.8 \cdot 10^9$	25	730	10	0.5	0.0001
Mammalian cell	$4 \cdot 10^{12}$	5	200 000	3000	150	0.005

† Assumptions:

1. E_{DNA} : energy directly imparted to the DNA molecule

$$E_{DNA}/\text{eV} = 1.04 \cdot 10^{-8} \cdot \text{m/dalton} \cdot D/\text{Gy} \quad (\text{a})$$

2. Probability of single strand break (SSB) per base pair (600 dalton): $P_{SSB} = 8. \text{g} \cdot 10^{-8} D/\text{Gy}$ (70 eV per SSB) (b)

3. ratio 1:20 of double strand breaks (DSB)_S to SSB_S

4. Inter-track formation of DSB_S if 2 SSB_S are produced by different particles on opposite strands with a separation of no more than 3 nucleotides. Resulting probability of DSB per base pair.

$$P_{DSB} = 4.3 \cdot 10^{-9} (D/\text{Gy}) + 3.2 \cdot 10^{-14} (D/\text{Gy})^2 \quad (\text{c})$$

For a mammalian cell:

$$n_{DSB} = 28 \cdot (D/\text{Gy}) + 2.1 \cdot 10^{-4} (D/\text{Gy})^2 \quad (\text{d})$$

where the linear term represents the intra-track mechanism, and the quadratic term the inter-track mechanism. For densely ionizing radiations the coefficient of the linear term is probably larger¹⁷ but there is not sufficient information on this point.

‡Not applicable.

and it is necessary to examine in some detail the efficiency of ionizing radiations in producing cellular lesions and the efficiency of cells in coping with such lesions. A consideration of the most fundamental radiation-induced lesions, namely single and double strand breaks in DNA, can help to clarify these matters.

Table 1 gives a synopsis of data on breaks for a single strand DNA phage, a double strand phage, a bacterium, and a mammalian cell. Rough values are given in column 2 for experimentally determined mean inactivation doses D_{37} . They apply to sparsely ionizing radiations and they are used to derive the energies E_{DNA} that are, at these doses, imparted to the DNA molecules. The quantity E_{DNA} (= absorbed dose \times mass of the DNA) may not appear pertinent, because lesions in DNA do not result exclusively from energy directly imparted to the DNA. However, it is a suitable reference quantity insofar as one

obtains on this basis, for various organisms, a yield of roughly 1 single strand break per 70 eV absorbed in DNA. The yield of double strand breaks is less well known, but a ratio of 1:20 for double to single strand breaks is in reasonable agreement with experimental observations for phages as well as for cells^{2,9}. With these values one obtains the data given in columns 4 and 5. These are the average numbers of single strand breaks and double strand breaks that are produced at the respective mean inactivation doses D_{37} .

One single strand break is sufficient to inactivate the single strand phage $\phi x174$, and single strand breaks can also lead to the inactivation of other phages and even of bacteria. In comparison, it is striking that a mammalian cell can tolerate and efficiently repair several thousand single strand breaks and also, apparently, a considerable number of double strand breaks.

It is occasionally postulated that only 1 or, at most,

a few double strand breaks are produced at the mean inactivation dose of a mammalian cell, and that 1 double strand break is sufficient for the inactivation of a mammalian cell.⁴ This argument is based on the presumption that all double strand breaks result from the random coincidence of 2 single strand breaks produced by separate charged particles (*inter-track action*). As shown in the last column of Table 1, one obtains far less than 1 double strand break by this random mechanism at a dose of 5 Gy. Clearly, this mechanism, which goes with the square of the absorbed dose, is entirely insignificant compared with the term that is linear in dose and that results from the production of double strand breaks by 1 single particle (*intra-track action*).

The predominance of the intra-track formation of double strand breaks underscores the fact that radiation sensitivity is, at least for eukaryotes, determined by the dense concentration of energy transfers along each charged particle track. However, energy concentration within dimensions comparable to those of the DNA-double helix cannot be the only relevant factor. This follows from the fact that many cellular effects of sparsely ionizing radiations increase more than linearly with absorbed dose. In these cases inter-track action must be present. However, knowledge of the underlying mechanisms is still incomplete.

CORRELATED ENERGY TRANSFER ON THE CELLULAR SCALE

There is now general agreement that the relative biological effectiveness (RBE) of ionizing radiations is linked to the spatial correlation of the energy transfers[†] that occur along the tracks of charged particles. However, the agreement does not extend far beyond the recognition that the RBE for effects on eukaryotes increases with increasing linear energy transfer (LET), and that it decreases after an optimum value of LET is passed that corresponds fortuitously to the stopping power of protons at their Bragg peak ($\approx 100 \text{ keV}/\mu\text{m}$). It remains a point of controversy whether the critical factor is the energy concentration in the DNA double helix and its immediate surroundings^{4,7}, or whether the concentration in sites that are up to 1000 times larger is of greater importance^{10,13}.

The increase of the RBE with LET, a single particle effect, and sigmoid dose effect relations, a 2 particle effect, are both expressions of the fact that the biological effect considered increases more than linearly with energy concentration. The non-linearity

must result from the interaction of energy transfers or of radiation products such as free radicals, or from the combination of cellular sublesions. An identification of the nature of the interaction processes or of the sublesions can be achieved only on the basis of detailed knowledge of the spatial and temporal separations that are involved. Microdosimetry has been developed towards this objective, but the analysis in terms of microdosimetry is closely related to earlier approaches.

Microdosimetric analysis

Lea was the first to derive distances involved in the interaction of radiation induced sublesions¹⁶. He compared the nearly quadratic dose dependence for chromosome aberrations produced by X-rays with the linear dependence that results, with neutrons. Lea based his analysis on the assumption that neutrons and X-rays produce sublesions (chromosome breaks) with equal effectiveness. He assumed further that any pair of sublesions separated by a distance less than a critical value, h , can combine to form a lesion (aberration). The yield per unit dose is then proportional to the average energy, ΔE , contained in a region of radius, h , around an energy transfer, ϵ . For neutrons, ΔE is equal to the average energy contained in a segment of length $2h$ of the particle track that contains ϵ ; energy transferred to the region by other charged particles is disregarded. For X-rays, the energy from the single particle track is disregarded, and ΔE is set equal to the energy that is imparted to the vicinity of ϵ by all the other charged particles.

Lea found that h cannot be less than fractions of a micrometer if the ratio of the values ΔE is to be equal to the ratio of observed effects for neutrons and X-rays. By this argument he excluded the possibility that certain chromosome aberrations, e.g. dicentric, result from a lesion, such as a double strand break, that involves only short range interaction of energy transfers or of sublesions.

The microdosimetric argumentation is entirely similar. The essential difference is that measured microscopic distributions of energy concentration are utilized instead of rough estimates.

The microdosimetric quantity specific energy, z , is defined as the energy actually imparted to a site divided by the mass of the site.¹¹ It is therefore the stochastic (i.e. random) counterpart of the non-stochastic (i.e. average) quantity absorbed dose. The energy average, ζ , of the possible increments of specific energy in the site as a result of individual charged particles (and/or their secondaries) can be

[†]The term *energy transfer* is used in the sense of energy transferred at a point from the radiation field to the irradiated matter. The energy transfer at a point is therefore equal to the

kinetic energy of the incident ionizing particle minus the kinetic energy of any emerging ionizing particle¹².

determined experimentally or theoretically for different site diameters and for different radiation qualities.

Consider an energy transfer within a site. Then ζ is the average energy concentration in the site that results from the single particle track. The probability for the occurrence of independent particles is unchanged by the presence of the reference track; this is one of the essential properties of a Poisson process. Accordingly the average contribution of other, independent particles is equal to the absorbed dose D . If the observed effect is due to lesions that result from a combination of pairs of sublesions within the site, one obtains the linear-quadratic dose effect relation that represents the intra-track and the inter-track action:[†]

$$\epsilon(D) = k(\zeta + D) \cdot D = k(\zeta D + D^2) \quad (1)$$

The examination of numerous dose-effect relations and RBE-dose relations for effects of sparsely ionizing radiations and neutrons on cells and tissues has led to the conclusion that the values of ζ are always such that they correspond to sites with diameters from a fraction of $1 \mu\text{m}$ up to several μm ^{10,13}. It has therefore been concluded that various effects of ionizing radiations on higher organisms result from lesions that involve interaction of energy transfers or sublesions over distances up to a few micrometers.

In particular, if one excludes energy transfer over large distances, the inactivation of mammalian cells cannot result from the production of individual double strand breaks in DNA. The interaction distances that can be assumed for this process are so small that one would obtain a magnitude of ζ far in excess of values compatible with survival curves for sparsely ionizing radiations or with RBE-dose relations for neutrons (see Fig. 1). In this connection one may note that eqn (c) and (d) in Table 1 correspond to a value ζ larger than 10^5 Gy ; such a value belongs to interaction distances in the nanometer range.

The microdosimetric analysis is in substantial agreement with a wide range of experimental observations, and it has led to the prediction of unexpectedly high RBE values of neutrons at low doses that have recently been verified for lens opacification,¹ for somatic mutations in plants²², and for radiation induced tumours^{20,21}.

However, the formalism also has obvious limitations. The treatment in terms of hypothetical spherical sites had merely been chosen because available microdosimetric data relate to such sites. The actual situation is more properly described in terms of sublesions that are produced throughout the nucleus

of the cell and that combine with a probability dependent on their spatial as well as temporal separation. An approach that takes this into account has been developed recently.¹⁴ It utilizes a function that is an interesting link between microdosimetric quantities and LET, and it will be described in its essentials.

Application of the proximity function

If the biophysicist could freely choose the most suitable probe for his investigations, he would undoubtedly avoid the complexity of charged particle tracks and instead select an ideal radiation which gave pairs of energy transfers at constant distance, x , apart. The effectiveness of such a radiation, if it existed, would provide a function, $\gamma(x)$, which combined the probability that the 2 transfers should both occur within the sensitive structure of the cell and that resulting sublesions should then combine.

With real radiations one always has to deal with a distribution of distances between energy transfers. This can be represented^{5,12} by a function, $t_D(x)$, that specifies the distribution of neighboring energy transfers at distance, x , from a transfer, ϵ , randomly selected. $t(x) dx$ is defined as the average energy imparted to a spherical shell of radius, x , and thickness, dx , that is centered at ϵ . The function, $t_D(x)$, separates conveniently into 2 terms. One is the contribution from particle tracks unrelated to ϵ ; this term is proportional to absorbed dose and independent of radiation quality. The other term is the contribution from the particular track to which ϵ belongs; this

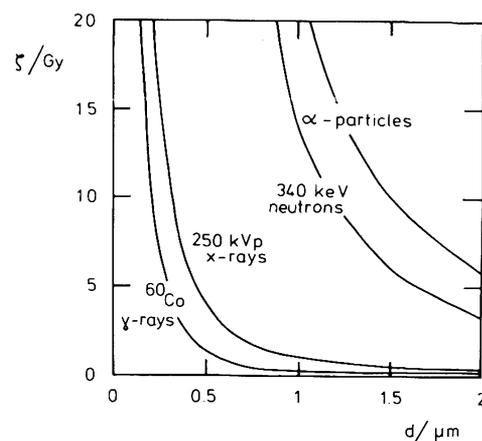


Fig. 1 Values of the microdosimetric quantity ζ in spherical sites of different diameter for γ -rays, 340 keV neutrons, and α -particles. ζ is the energy average of the increment of specific energy produced by individual energy deposition events (see,¹²) i.e. by individual charged particles and/or their secondaries.

[†]Temporal separation that affects the inter-track term but not the intra-track term is an important factor that is not

considered here.

term is independent of absorbed dose and depends on radiation quality;

$$t_D(x) = t(x) + 4\pi\rho x^2 D \quad (2)$$

The function $t(x)$, i.e. the contribution from the particular particle track, provides a useful characterization of radiation quality. It is, in fact, proportional to the probability density of all mutual distances between energy transfers (disturbed molecules) produced by a charged particle. Boag proposed such a function a number of years ago³ and he pointed out that it might be a reliable tool even if it had less pictorial appeal than stereo models of tracks. In contrast to a probability density the functions $t(x)$ and $t_D(x)$ are not normalized to unity; instead they have the dimension energy by length and their integral is equal to average energy imparted up to distance x . The function $t(x)$ characterizes the average spatial correlation of energy transfers in charged particle tracks. It refers to a uniform medium and depends on the type of the medium.

$t(x)$ stands in an interesting relation to LET and can even be considered as a generalization of LET. Within the applicability of the concept of linear energy transfer one has $t(x) = 2 \cdot \text{LET}$. However, $t(x)$, in contrast to linear energy transfer, accounts both for the increased frequency of correlated energy transfers at short distances, and for the decrease of correlated transfers at distances that are comparable to the range of the charged particles. Figure 2 gives the function $t(x)$, the so-called *proximity function*, for low energy electrons.

Various interesting properties link the function $t(x)$ to the established microdosimetric quantities and to LET. These will not be considered here. However, an equation will be reported that permits the determination of the function $\gamma(x)$.

If cellular lesions result from the combination of pairs of sublesions, their yield is determined by the integral over the product of $\gamma(x)$ and $t_D(x)$:

$$\begin{aligned} \epsilon(D) &= kD \int_0^\infty \gamma(x)t_D(x) dx \\ &= kD \left(\int_0^\infty \gamma(x)t(x) dx + 4\pi\rho D \int_0^\infty x^2\gamma(x) dx \right) \quad (3) \end{aligned}$$

With the convenient normalization $4\pi\rho \int_0^\infty x^2\gamma(x) dx = 1$ one obtains:

$$\epsilon(D) = k(\xi D + D^2) \quad \text{with } \xi = \int_0^\infty t(x)\gamma(x) dx \quad (4)$$

This relation is illustrated in Fig. 3. It takes the place that eqn 1 held in the earlier microdosimetric treatment.^{13†} Applied to recent experiments, it has led to significant conclusions and to some definite revisions of earlier notions.

The actual form of the function $\gamma(x)$ is not very important, as long as one deals exclusively with radiations that produce charged particles with ranges that are large compared to cellular dimensions. However, it is critical for short range particles, such as electrons liberated by low energy photons. These parti-

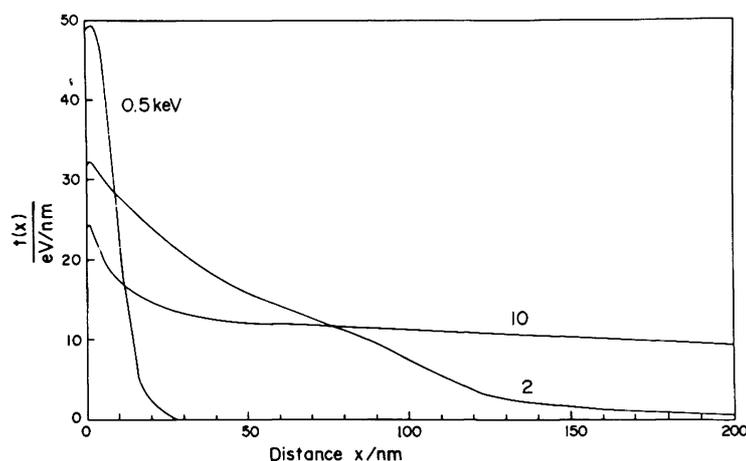


Fig. 2. Proximity functions, $t(x)$, for electrons of energy 0.5, 2 and 10 keV in tissue. $t(x) dx$ is the expected energy transfer at distance x to $x + dx$ from an energy transfer randomly chosen. Only energy transfers from the same particle track are considered (data from¹⁸).

[†]Eqn 1 is the special case of eqn 4 that results with

$$\gamma(x) = \left(1 - \frac{3x}{2d} + \frac{x^3}{2d^3}\right); \quad x < d$$

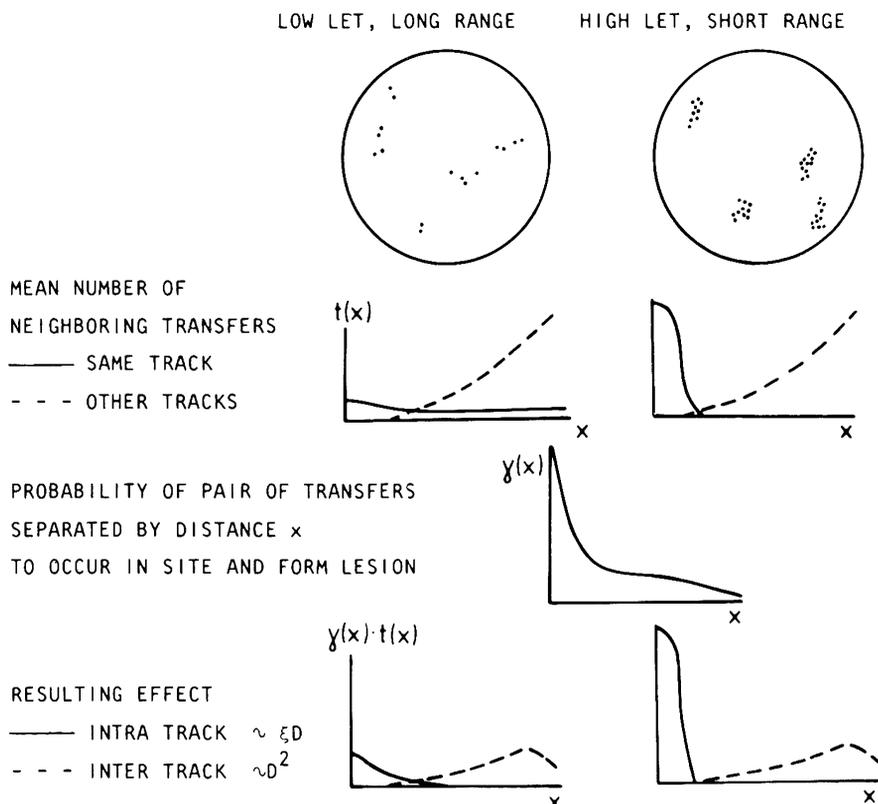


Fig. 3. Derivation of Eqn 4.

cles release only moderate energies, but produce the energy transfers in close proximity so that their effectiveness is greatly enhanced since $\gamma(x)$ has a maximum at small values of x .

It appears that recent cell survival data⁸ obtained with low energy photons are inconsistent with the earlier microdosimetric treatment (eqn 1) while they may be consistent with an interaction function $\gamma(x)$ that decreases rapidly with distance, but still extends with small values to the large interaction distances that are responsible for the sigmoid shape of the survival curves obtained with conventional X-rays and γ -rays,

More definite conclusions have already been drawn from a current experiment by Rossi *et al.*¹⁹ that utilizes correlated deuterons traversing the cells in pairs at specified mean lateral separations, b . The functions, $t_b(x)$, can be readily computed for the different values of b that are employed, and a preliminary analysis¹⁵ in terms of eqn 4 of survival data for G_1/S cells has yielded the interaction function $\gamma(x)$ that is given in Fig. 4 as a solid line. This function leads to the best fit. However, one can obtain rough agreement with the observations also if the broken line is assumed. No acceptable fit can be obtained without a pronounced peak of $\gamma(x)$ at short distances and without an extension to values substantially exceeding $x = 1 \mu\text{m}$.

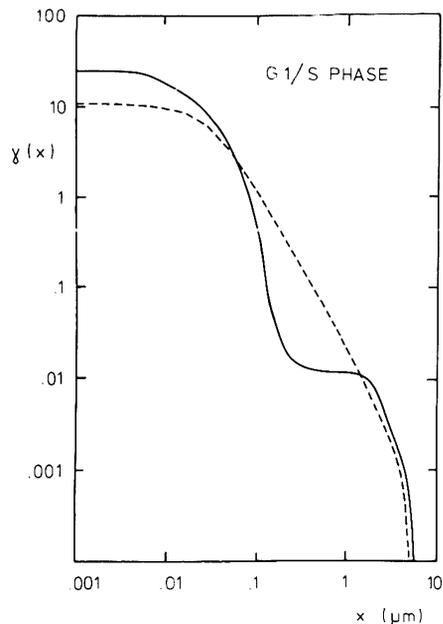


Fig. 4. Probability (in rel. units) that 2 energy transfers separated by distance, x , shall combine to form a lesion. Results inferred from cell inactivation studies with correlated deuterons (see Refs. 15,19 for V-79 Chinese hamster cells in G_1/S phase). The solid line is in best agreement with the observations; the broken line leads to a poorer fit but cannot be rejected. No function $\gamma(x)$ that does not extend beyond $1 \mu\text{m}$ is consistent with the data.

Similar results are obtained for late S cells. It is of interest that the solid line corresponds very closely to a configuration where clumps of sensitive structures (DNA) of diameter $0.1 \mu\text{m}$ are randomly distributed over a larger region that has roughly the dimension of the nucleus of the cell. This would be consistent with the assumption that the sublesions are double strand breaks in DNA, and that the actual lesions result from the combination of pairs of such sublesions. The numerical analysis shows that almost all intra-track combinations would have to occur within individual clumps (short range interaction), while most of the inter-track interactions would have to involve separate clumps (long range interaction). This characteristic difference between the linear intra-track effect and the quadratic inter-track effect has important implications.

CONCLUSIONS

It is apparent that the concentrated dissipation of

energy determines the radiosensitivity of higher organisms. The sigmoid dose-effect relations for sparsely ionizing radiations require interaction distances between energy transfers of separate particles that are of the order of a few micrometers. However, it appears that the interaction probability of energy transfers is greatly enhanced at smaller distances, and that the short range interactions predominate for the intra-track effect, i.e. for the interaction of energy transfers within charged particle tracks. Accordingly there is no clearcut answer to the question whether energy concentrations on the scale of the DNA double helix or over larger distances are the decisive factor that determines RBE. Both scales are relevant. Experiments with short range particles or with spatially correlated particles may provide further and more precise information on this point, and a recent theoretical concept, the proximity function, can be an important tool in these investigations.

REFERENCES

- Bateman, J.L., Rossi, H.H., Kellerer, A.M., Robinson, C.V., Bond, V.P.: Dose-dependence of fast neutron RBE for lens opacification in mice. *Radiat. Res.* 51, 381-390, 1972.
- Blok, J., Loman, H.: The effects of γ -radiation in DNA. *Curr. Top. Radiat. Res. Qtrly* 9: 165-245, 1973.
- Boag, J.W.: Energy transfer from charged particles. In *Advances in Radiation Research*, Vol. 1, ed by Duplan, J.F. and Chapiro, J. London, Gordon & Breach, 1973, pp. 9-13.
- Chadwick, K.H., Leenhouts, H.P.: Chromosome aberrations and cell death. In *Proc. 4th Symp. on Microdosimetry* Vol. 1, ed. by Booz, J. Ebert, H.G., Eickel, R., Waker, A. Luxembourg, Euratom 5122 d-e-f, 1974, pp. 585-599.
- Chmelevsky, D.: Distributions et moyennes des grandes microdosimétriques à l'échelle du nanomètre. Report CEA-R-4785, Commissariat à l'Energie Atomique, Saclay (1976)
- Dessauer, F.: Über einige Wirkungen von Strahlen. *Z. Physik* 12: 38-47, 1923
- Gillespie, C.J., Dugle, D.L., Chapman, J.D., Reuvers, A.P., Doern, S.D.: DNA damage and repair in relation to mammalian cell survival: Implications for microdosimetry. In *Proc. 5th Symp. on Microdosimetry* Vol. II, ed. by Booz, J. Ebert H.G. Smith. B.G.R. Luxembourg. Euratom 5452 d-e-f, 1976. pp. 799-810.
- Goodhead, D.T.: Inactivation and mutation of cultured mammalian cells by aluminium characteristic ultrasoft X-rays—III. Implications for theory of dual radiation action. *Int. J. Radiat. Biol.* 32: 43-70, 1977.
- Hagen, U.: Strahlenwirkung auf Struktur und Funktion der DNS. *Biophysik* 9: 279-289, 1973.
- Hug, O., Kellerer, A.M.: Stochastik der Strahlenwirkung. Berlin-Heidelberg-New York, Springer-Verlag, 1966.
- ICRU Report 19: Radiation Quantities and Units. Internat. Commission on Radiation Units and Measurements, Washington, D.C. 1971.
- Kellerer, A.M., Chmelevsky, D.: Concepts of microdosimetry—III. Mean values of the microdosimetric distributions. *Rad. and Environm. Biophys.* 12: 321-335, 1975.
- Kellerer, A.M., Rossi, H.H.: The theory of dual radiation action. *Curr. Top. Radiat. Res. Qtrly* 8: 85-158, 1972.
- Kellerer, A.M., Rossi, H.H.: A generalized formulation of dual radiation action. *Radiat. Res.* 75: 471-488, 1978.
- Lam, Y.-M.P., Rossi, H.H., Kellerer, A.M.: Biophysical studies with spatially correlated ions—IV. Analysis of cell survival data for diatomic deuterium. In preparation.
- Lea, D.E.: Actions of radiation on living cells, 1st Edn, Cambridge University Press, London, and Macmillan, New York, 1946.
- Neary, G.J., Simpson-Gildemeister, V.F.W., Peacocke, A.R.: The influence of radiation quality and oxygen on strand breakage in dry DNA. *Int. J. Radiat. Biol.* 18: 25-40 (1970)
- Patau, J.P., Terrissol, M., Chmelevsky, D., Kellerer, A.M.: Proximity functions for electrons. In preparation.
- Rossi, H.H., Bird, R., Colvett, R.D., Kellerer, A.M., Rohrig, N., Lam, V-M.P.: The molecular ion experiment. In *Proc. 6th Symp. on Microdosimetry*, Vol. II, ed. by Booz, J., Ebert, H.G. London, Harwood Academic Publishers, 1978, pp. 937-947.
- Rossi, H.H., Mays, Ch.W.: Leukemia risk from neutrons. *Health Phys.* 34: 353-360, 1978.
- Shellabarger, C.J., Brown, R.D., Rao, A.R., Shanley, J.P., Bond, V.P., Kellerer, A.M., Rossi, H.H., Goodman, L.J., Mills, R.E.: Rat mammary carcinogenesis following neutron or X-radiation. Symp. on the Effects of Neutron Irradiation upon Cell Function, Munich, 1973. In *Biological effects of neutron irradiation*, International Atomic Energy Agency SM-179/26 Vienna, 1974, pp. 391-401.
- Sparrow, A.H., Underbrink, A.G., Rossi, H.H.: Mutations induced in tradescantia by small doses of X-rays and neutrons. Analysis of dose-response curves. *Science* 176: 916-918, 1972.