The Eighth

International Congress of Radiation Research

Patron: H.R.H. The Duke of Edinburgh, K.G.

The Eighth International Congress of Radiation Research was organized by the Association of Radiation Research at the invitation of the International Association for Radiation Research. The Officers of the Congress were appointed by the Association for Radiation Research.

G. E. Adams, President
Sir Alastair Currie and Lord Dainton, Hon. Vice Presidents
E. M. Fielden, Secretary-General

ORGANIZING COMMITTEE: The Officers and

I. V. Chapman (Local Committee)
J. F. Fowler (Scientific Programme)
A. Tallentire (Fund Raising)
P. Wardman (Treasurer)
D. K. Bewley
N. M. Bleehen
J. A. Dennis
N. E. Gillies
J. H. Hendry
J. L. Moore
Sir Oliver Scott

INTERNATIONAL ASSOCIATION FOR RADIATION RESEARCH

A. C. Upton (U.S.A.) — President

ASSOCIATION FOR RADIATION RESEARCH

A. Tallentire — Chairman

Radiation Research

Proceedings of the 8th International
Congress of Radiation Research
Edinburgh, July 1987

VOLUME 2

Edited by

E.M. Fielden
J. F. Fowler
J. H. Hendry
D. Scott

Taylor & Francis
London • New York • Philadelphia

Contents

1.1 **Track Effects in Radiation Chemistry (Symposium)**

1.2 **New Trends in Radiation Chemistry**

SYMPOSIUM: NEW TRENDS IN RADIATION CHEMISTRY I
GENERAL

SYMPOSIUM: NEW TRENDS IN RADIATION CHEMISTRY II
PRIMARY/REACTIVE SPECIES

1.3 Redox Processes, Free Radicals and Oxygen Toxicity

SYMPOSIUM: RADIATION INDUCED REDOX PROCESSES

SYMPOSIUM: FREE RADICALS AND OXYGEN TOXICITY

1.4 Peptides, Proteins, DNA and Cell Death

SYMPOSIUM: RADIATION EFFECTS IN PEPTIDES AND PROTEINS

SYMPOSIUM: RADIATION DAMAGE IN DNA

1.5 **Industrial Applications of Radiation Chemistry**

SYMPOSIUM: RADIATION CHEMISTRY AND THE NUCLEAR INDUSTRY

SYMPOSIUM: A NEW LOOK AT THE RADIATION PRESERVATION OF FOOD

2.1 **Physics**

SYMPOSIUM: FUNDAMENTAL RADIATION PHYSICS

SYMPOSIUM: CHARGE TRAPPING AND MIGRATION OF ENERGY

2.2 Quantitative Models of Radiation Action

SYMPOSIUM: BIOPHYSICAL MODELS OF RADIATION ACTION

2.3 Microscopic Deposition of Radiation Energy

SYMPOSIUM: APPLICATIONS OF MICRODOSIMETRY

SYMPOSIUM: EFFECTS OF INTERNAL AUGER EMITTERS

3.1 **Inducible Repair of Damage Caused by Ionising and Non-ionising Radiation (Symposium)**

3.2 **Molecular Studies on DNA Repair in Mammalian Cells (Symposium)**

3.3 **Radiosensitive Human Cells (Symposium)**

3.4 **Fractionation, Low-dose Rate and Repair Kinetics (Symposium)**

4.1 Cellular and Molecular Aspects of Oncogenesis

SYMPOSIUM: CELLULAR AND MOLECULAR ASPECTS OF ONCOGENESIS

4.2 Oncogenic Transformation

SYMPOSIUM: CELL TRANSFORMATION BY RADIATION

4.3 Cellular and Molecular Aspects of Mutagenesis (Symposium)

6.3 Chemical Modification of Radiation Response

SYMPOSIUM: CHEMICAL MODIFICATION OF RADIATION RESPONSE

7.1 In Vivo Radiobiology

SYMPOSIUM: NEW DEVELOPMENTS IN INTERPRETATIONS OF NORMAL TISSUE RESPONSE

SYMPOSIUM: VASCULATURE-MEDIATED ASPECTS OF TUMOUR RESPONSE

SYMPOSIUM: PREDICTIVE ASSAYS OF HUMAN TUMOUR RESPONSE

7.2 **Radiotherapy, Low LET Radiation**

SYMPOSIUM: TOTAL BODY AND TOTAL LYMPHOID IRRADIATION

7.3 **Radiotherapy, High LET Radiation**

SYMPOSIUM: CLINICAL RESULTS WITH CHARGED PARTICLE BEAMS

7.4 **Diagnosis**

SYMPOSIUM: HYPERTHERMIA: CLINICAL, PHYSICAL, *IN VITRO* AND ANIMAL

MICRODOSIMETRY

Recent Trends and Applications to Radiation Biology and Radiation Chemistry

A.M.Kellerer
Institut für Med. Strahlenkunde, University of Würzburg

1. Historical Note

A quarter of a century ago microdosimetry had just been conceived by Harald H.Rossi and his colleagues (1,2), but it was still unnamed, and 1962, at the Second International Congress of Radiation Research - the first in this country - a symposium could well have been devoted to 'Stochastic Dosimetry and its Applications'. The topic would have been appropriate and the designation might have been equally fitting, since Otto Hug had noted, at about the same time, that the Greek word 'stochazein' had the two meanings of 'hitting a target' and 'making a guess' (3,4), two processes central to target theory and radiation biology (5,6,7).

That the different term 'microdosimetry' was chosen for the new branch of science, may not have been entirely the intention of its inventor. However it gave due regard to the remarkable fact that actual energy concentrations could henceforward be measured in microscopic regions which correspond to cellular or subcellular domains. Experimental microdosimetry developed explosively in these last twenty-five years. It was recognized that stochastic quantities can be more real and more relevant to radiation biophysics than their more tractable and more readily understood mean values. Surprising as it may have been at first, the ICRU has even ranked the stochastic microdosimetric variables among the fundamental radiation quantities (8).

In the pragmatic applications to radiation protection and to the clinical uses of ionizing radiations, microdosimetric concepts and techniques have found a number of important and lasting applications. Many of these applications are unspectacular, because they are natural. When it is proposed by a liaison committee of ICRP and ICRU that the quality factor in radiation protection be linked to lineal energy, rather than LET, (9) no fundamental change from present practices is introduced. In fact it is merely suggested that measured quantities - often in unknown radiation fields - need not be artificially corrected to transform actual energy concentrations into values of a more abstract parameter. But this interpretation does not mean that LET can not serve useful purposes; in fact it can be shown that LET and lineal energy are interchangeable under certain conditions (10,11). Similarly, in medical physics microdosimetric measurements have become essential and even routine, because they are the most direct way to characterize the properties of the radiation field at different locations in a beam.

Microdosimetry may have been less successful where the aims and expectations were far more ambitious. To understand the reason for such failure, or seeming failure, may be crucial for the future development not only of microdosimetry, but of radiation biology in general.

It is, therefore, important to consider the established uses of microdosimetric data in radiation biology (section 2), but equally the more tentative applications towards the elucidation of molecular mechanisms of radiation action (section 3).

2. Established Uses of Microdosimetry

One of the simplest uses of microdosimetry has proved to be particularly important. Ionizing radiations impart energy to matter in finite portions, and on the scale of the cell and of subcellular structures these portions can be very substantial. At doses relevant to radiation protection one deals frequently with a situation, where most cells or cell nuclei receive no energy at all, while few cells which are traversed by a charged particle receive disproportionally large amounts of energy. The quality of the radiation, not the dose, determines then the fate of the affected cells; dose determines merely their number. Whether this condition prevails, can be ascertained on the basic of microdosimetric data. If it prevails, any dose-effect relation for cellular effects must be linear, a conclusion fundamental to risk assessment, and even a highly political issue in the past year. The dependences can be nonlinear, if the fate of the cell is co-determined by energy deposition in the cytoplasm, by energy deposition in adjacent cells, or, finally, by reactions of the irradiated tissue. Whether action on 'autonomous' cells - to use a phrase coined by Harald Rossi (12) - can be assumed or an extracellular effect of the exposure needs to be taken into account, is to be judged on the basis of microdosimetric data.

In experiments on the induction of mammary tumours in rats by 430 keV neutrons (13,14), which were thoroughly randomized studies, a dose dependence with negative curvature in the region of 1 to 16 mGy was found. This implied that the effect can not be merely a matter of inducing individual cells which then have a small dose independent probability to cause a neoplasm. Microdosimetric data have identified the problem; tumour biology has not yet provided the answer.

Similar microdosimetric considerations have been important with the finding by Hill, Han, and Elkind of a striking reversed dose-rate effect for the transformation of mammalian cells by small doses of neutrons (15). It has been suggested that such a dose-rate effect is incompatible with the paucity of multiple events in the cell nucleus. Measured nuclear areas and microdosimetric data for event frequencies have then shown that event frequencies are indeed higher (16) than original believed, and that the effect might therefore be due to the induction of a repair system by one particle and its influence on a subsequent event. The molecular mechanisms remain unresolved, and it is puzzling why an analogous effect is not seen in the same cell system when it is exposed to α-particles (17). Even with α-particles there are still sufficient events that a dose-rate effect, on the basis of cellular mechanisms, is conceivable at a dose of 100 mGy.

A related example are the astonishing results by Wolff and his colleagues (18,19), that human lymphocytes are substantially less sensitive to ionizing radiations many hours after being exposed to the tiny dose of only 10 or even 5 mGy of gamma-rays. At this dose the mean number of charged particles in the cell nucleus is close to unity and it will, therefore, be of particular interest to seek analogous effects with densely ionizing radiations, and to assess the observations in terms of microdosimetric information on event frequencies in the nucleus or the cytoplasm.

Event frequencies in cellular or subcellular domains are important parameters. However, microdosimetry provides the full spectrum of events in a site. Various attempts have been made to utilize this information, and the diversity of approaches precludes their detailed consideration. In a certain overgeneralization, one may state that such attempts have failed, or are bound to fail, when they aim at correlating the reaction of the cell with 'cell dose' - presumably the specific energy in some subregion of the nucleus. One knows too little about the distribution of the sensitive DNA or DNA-membrane structures to make realistic models, but one knows that the distribution throughout the nucleus, and the distribution on the micrometer to the nanometer scale needs to be taken into account. The cell has no uniform gross-sensitive volume, nor does it carry one or a few spherical or cylindrical targets.

In a further slight overstatement one may say that microdosimetric arguments can merely exclude certain assumptions and thereby narrow down the range of possible models. But this negative function can be essential. Even wrong models - and every model is ultimately wrong - can serve a useful purpose, if they have sufficiently few parameters to be falsifiable. Dual action in its original formulation (20) was the postulate of a second order process dependent on the square of energy concentrations measured over regions of the order of a micrometer. It was a wrong model with a minimum of free parameters, and it did permit falsification through several intriguing experiments (21,22). In being partly disproved, it led to modified analyses which are less falsifiable, but may still be useful. They are closely linked to more recent trends of microdosimetry.

3. Recent Trends

Continued efforts have been made in microdosimetry to extend the measurements to submicroscopic regions of less than 50 nm or even to molecular dimensions. None of these efforts have been successful. However, a great change has been brought about by the advance of computational methods to simulate charged particle tracks (23). Some of the information may still be tentative and cross sections often pertain to gasses rather than condensed media. However, the remaining uncertainties may be of minor importance, since microdosimetric information is mainly used to compare the effects of different types of ionizing radiations and to correlate them with characteristic differences in the patterns of energy deposition; such differences depend little on the subtilities of track structure.

While there is adequate physics information, there is also a curious imbalance in pragmatic applications. In radiation chemistry it is still common to quantify energy concentrations in terms of 'blobs' and 'spurs', while microdosimetric functions show that one deals with a continuum of energy densities, not with distinct classes of events. Developments towards a more quantitative description (24) show that more use needs to be made of mathematical functions that describe the spatial correlation of energy transfers in charged particle tracks.

In the much less quantitive studies of radiobiology there is a strangely reversed situation. It is not uncommon that exact information from simulated tracks is applied to models which invoke thresholds of energy for the reaction of assumed spheres or cylinders - or pairs of such constructs. The exactitude of the physical description is then in marked contrast to the uncertainty of the radiobiological assumptions.

The use of relatively crude tools in the more exact investigations, and the application of precise data to the more qualitative studies may reflect the unavoidable imbalance of a developing field of study, but it indicates the need for more systematic and concise applications of microdosimetric data. Few steps have yet been done in the direction of a mathematical theory of the random patterns of energy deposition. But certain notions, such as the distributions of nearest neighbours among the energy transfers in charged partice tracks (23,25), are closely related to distributions and parameters familiar in the stochastic geometry of point sets (see e.g. (26)). Of even broader applicability is the proximity function. It is linked to M.J.Berger's concept of the geometric reduction factor and it has been utilized in a general formulation of dual action that accounts for the steep spatial gradient of the interaction probabilities between lesions in the cell (27). The function is largely equivalent to the spatial auto-correlation function which has wide application in the analysis of any random process and spatial or temporal pattern; it also equals the point-pair distance density of a structure times its content. In stochastic geometry, the mathematical theory of random sets, a corresponding quantity is called covariance of a point process. It is of considerable interest that notions evolved in microdosimetry are closely parallel to a variety of concepts in other fields.

A fundamental relation in microdosimetry (see e.g.(28)) shows that the yield of a second order process is a simple integral over the proximity function of a radiation and the corresponding function that characterizes the irradiated structure or substrate. This dependence and a modified formula apply to such diverse mechanisms, as the reaction of two free radicals, the combination of two adjacent DNA breaks in misrepair, or the far more complex process of the fusion of two chromosome breaks. The same theorem applies to all problems that arise when arbitrary structures are randomly superimposed (29). The relation expresses the weighted average (and also the second moment) of the intersection, u, of two bodies T and S (of contents V_T and V_S) under uniform isotropic randomness in terms of the point-pair distance distributions $p_T(x)$ and $p_S(x)$ of the two bodies:

$$\overline{u^2}/\bar{u} = V_T V_S \int \frac{p_S(x)\ p_T(x)}{4\pi x^2}\, dx$$

This fundamental relation, and similar results and their implications can not be elaborated in this brief discussion. But their existence needs to be noted, if uses of microdosimetry are sought which go beyond a merely descriptive correlation between the patterns of energy deposition and the varying degrees of effectiveness of different ionizing radiations. Methods and concepts of stochastic geometry are bound to determine the further development of microdosimetry and its utilization in radiobiological or radiochemical studies.

References

1) Rossi, H.H., Radiat. Research, 10, 522-531, 1959.
2) Rossi, H.H., Radiat. Research, Suppl. 2, 290-299, 1960.
3) Kellerer, A.M., Hug, O., Biophysik 1, 33-50, 1963.
4) Hug, O., Kellerer, A.M., Stochastik der Strahlenwirkung, Springer Verlag, Berlin-Heidelberg-New York, 1966.
5) Dessauer, F., Quantenbiologie, Springer, 1964.
6) Timofeeff-Ressowsky, N.V., Ivanov, V.I., Korogodin, V.J., Die Anwendung des Trefferprinzips in der Strahlenbiologie, Fischer, Jena, 1972.
7) Lea, D.E., Actions of Radiations on Living Cells, Cambridge University Press, London, 2nd ed., 1955.
8) ICRU, Report 33, Radiation Quantities and Units, 1980.

9) ICRU, Report 40, The Quality Factor in Radiation Protection, 1986.
10) Blohm, R., Harder, D., Rad.Prot.Dosimetry 13, 377-381, 1985.
11) Kellerer, A.M., Hahn, K., Considerations on a Revision of the Quality Factor, submitted for publication, 1987.
12) Rossi, H.H., Kellerer, A.M., Biophysical Aspects of Radiation Carcinogenesis, Cancer 1, 2nd ed., 569-616, 1982.
13) Shellabarger, C.J., Chmelevsky, D., Kellerer, A.M., J.Nat. Cancer Inst. 64, 821-833, 1980.
14) Shellabarger, C.J., Chmelevsky, D., Kellerer, A.M., Stone, J.P., Holtzman, S., J.Nat. Cancer Inst. 69, 1135-1146, 1982.
15) Hill, C.K., Han, A., Elkind, M.M., Int. J. Radiat. Biol. 46, 11-15, 1984.
16) Rossi, H.H., Kellerer, A.M., Int. J. Radiat. Biol. 50, 353-361, 1986.
17) Hieber, L., Ponsel, G., Roos, H., Fenn, S., Fromke, E., Kellerer, A.M., Absence of a Dose-Rate Effect in the Transformation of C3H 10T1/2 Cells by α-Particles, Int. Journal Radiat. Biol. to appear.
18) Shadley, J.D., Wolff, S., Mutagenesis 2, 95-96, 1987.
19) Wolff, S., Afzal, V., Wiencke, J.K., Olivieri, G., Michaeli, A., Int. J. of Radiat. Biol., 1987.
20) Kellerer, A.M., Rossi, H.H., Current Topics in Radiation Research Quarterly, 8, 85-158, 1978.
21) Rossi, H.H., Bird, R., Colvett, R.D., Kellerer, A.M., Rohrig, H., Lam, Y.-M.P., Proc. 6th Symp. on Microdosimetry 2, 937-947, Harwood, London, 1978.
22) Goodhead, D.T., Thacker, J., Cox, R., Proc. 6th Symposium on Microdosimetry 2, 829-843, Harwood, London, 1978.
23) Paretzke, H.G., Radiation Track Structure Theory, In: Kinetics of Nonhomogeneous Processes, Ed. by Gordon R. Freeman, John Wiley & Sons, 89-170, 1986.
24) Maggee, J.L., Chatterjee, A., Track Reactions of Radiation Chemistry, In: Kinetics of Nonhomogeneous Processes, John Wiley & Sons, 171-214, 1986.
25) Berger, M.J., Proc. 7th Symp. of Microdosimetry 1, 521-531, EUR 7147 d-e-f, Harwood, London, 1981.
26) Stoyan, D., Kendall, W.S., Mecke, J., Stochastic Geometry and Its Applications, John Wiley & Sons, 1987.
27) Kellerer, A.M., Rossi, H.H., Rad. Res. 75, 471-488, 1978.
28) Kellerer, A.M., Models of Cellular Radiation Action, In: Kinetics of Nonhomogeneous Processes, John Wiley & Sons, 305-375, 1986.
29) Kellerer, A.M., J.Appl.Prob. 23, 307-321, 1986.