

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

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

OPENING LECTURE: A Glance at 25 years of Radiation Research <i>J. W. Boag</i>	1
1. RADIATION CHEMISTRY	9
1.1 Track Effects in Radiation Chemistry (Symposium)	
Theoretical aspects of heavy-ion tracks in radiation chemistry <i>A. Mozumder and J. A. LaVerne</i>	11
An overview of the oxidation of ferrous ions in the Fricke dosimeter by heavy ions <i>J. A. LaVerne and R. H. Schuler</i>	17
Chemical aspects of high energy heavy ion tracks <i>A. Appleby</i>	23
Biophysical aspects of track structure <i>G. Kraft and W. Kraft-Weyrather</i>	29
1.2 New Trends in Radiation Chemistry	
Congress Lecture: The Chemistry of Synchrotron Radiation <i>Y. Hatano</i>	35
SYMPOSIUM: NEW TRENDS IN RADIATION CHEMISTRY I GENERAL	
Modern trends in experimental radiation chemistry <i>R. H. Schuler</i>	42
New trends in radiation chemistry: aqueous radiation chemistry <i>K-D. Asmus</i>	48
Some aspects of the radiation chemistry of ethanol and cyclic organic amides <i>G. A. Salmon</i>	54
Gas phase pulse radiolysis <i>C. D. Jonah, A. Liu and W. A. Mulac</i>	60
SYMPOSIUM: NEW TRENDS IN RADIATION CHEMISTRY II PRIMARY/REACTIVE SPECIES	
New trends in radiation chemistry II <i>N. V. Klassen</i>	66
Excited states in hydrocarbons <i>S. Lipsky</i>	72
Chemical reactivities of radical anions studied by pulse radiolysis <i>S. Takamuku</i>	78

1.3 Redox Processes, Free Radicals and Oxygen Toxicity

SYMPOSIUM: RADIATION INDUCED REDOX PROCESSES

- Mechanisms of electron transfer between radicals and molecules: The addition-elimination route (inner-sphere electron transfer)
S. Steenken 84
- The radiolytic approach to the understanding of model photochemical systems for energy conversion and storage
Q. G. Mulazzani 90
- Effects of energy, distance and orientation on electron transfer rates studied by pulse radiolysis in organic media
J. R. Miller 96
- Congress Lecture: Radiation Chemistry in Microheterogeneous Systems
M. A. J. Rodgers and S. M. Hubig 102

SYMPOSIUM: FREE RADICALS AND OXYGEN TOXICITY

- Radiobiology and the superoxide radical
I. Fridovich 109
- Generation and reactivity of activated oxygen species — the influence of hyperthermic conditions
E. Lengfelder and R. M. Fink 116
- Progress and trends in superoxide research
B. H. J. Bielski 122
- The function of specific genes to enhance tolerance to oxygen
M. Morimyo 128

1.4 Peptides, Proteins, DNA and Cell Death

SYMPOSIUM: RADIATION EFFECTS IN PEPTIDES AND PROTEINS

- Radical transformations in peptides and proteins
W. A. Prütz 134
- Peptide irradiation products and crosslinking mechanisms
M. G. Simic, L. R. Karam and M. F. Desrosiers 140
- Radiation effects in histone octamer complexes and in isolated histones
W. Schnabel, L. Katsikas and K.-H. Deeg 146
- Radiation-induced protein-DNA interactions
H. Schuessler 152
- Congress Lecture: DNA strand break formation and biological consequences
D. Schulte-Frohlinde 158
- Congress Lecture: Radiation chemical mechanisms of cell death
J. F. Ward 162

SYMPOSIUM: RADIATION DAMAGE IN DNA

- The mechanism by which metal compounds cause site specific DNA damage
G. Czapski and S. Goldstein 169

	Radiation damage of the nucleobases in DNA <i>C. von Sonntag</i>	175
	Direct effects of ionising radiation on DNA and related compounds <i>J. Cadet, A. Shaw, M. Berger, C. Decarroz, J. R. Wagner and J. van Lier</i>	181
	Radiation damage and biologically active DNA <i>M. V. M. Lafleur, J. Retel and H. Loman</i>	187
1.5	Industrial Applications of Radiation Chemistry	
	SYMPOSIUM: RADIATION CHEMISTRY AND THE NUCLEAR INDUSTRY	
	Radiation chemistry in the nuclear industry <i>W. G. Burns</i>	193
	The radiation chemistry of water and aqueous solutions at elevated temperatures <i>K. Sehested and H. Christensen</i>	199
	The effect of radiolysis on the chemical forms of iodine species in relation to nuclear reactor accidents <i>K. Ishigure</i>	205
	Radiation-induced formation and dissolution of colloidal transition-metal oxides <i>G. V. Buxton, D. W. Cartmell and R. M. Sellers</i>	212
	SYMPOSIUM: A NEW LOOK AT THE RADIATION PRESERVATION OF FOOD	
	Food preservation by irradiation <i>G. Campbell-Platt</i>	218
	Public health aspects of food irradiation <i>E. H. Kampelmacher</i>	224
	The identification of irradiated foods <i>W. Bögl</i>	230
	Assessment of the wholesomeness of irradiated food <i>D. W. Thayer</i>	236
2.	PHYSICS, BIOPHYSICAL MODELS AND MICRODOSIMETRY	243
2.1	Physics	
	Congress Lecture: Prospects and Problems of Fusion Power <i>W. M. Lomer</i>	244
	SYMPOSIUM: FUNDAMENTAL RADIATION PHYSICS	
	Introductory review: Physics of electron slowing-down processes <i>M. Inokuti</i>	250
	Time dependent degradation of energetic electrons in gaseous and condensed media <i>M. Dillon and M. Kimura</i>	255
	Experimental studies on the interactions of slow electrons with molecules in solid films <i>L. Sanche</i>	260

	Differential inelastic scattering cross sections for low energy (100 eV—few keV) electrons in solids	266
	<i>S. Tougaard</i>	
	SYMPOSIUM: CHARGE TRAPPING AND MIGRATION OF ENERGY	
	Charge migration and localisation	272
	<i>J. M. Warman</i>	
	Theoretical aspects of trapping and transfer of charge	278
	<i>W. M. Bartczak</i>	
	Charge trapping and migration in liquids	284
	<i>Y. N. Molin</i>	
	Charge trapping and migration in solids	290
	<i>M. C. R. Symons</i>	
2.2	Quantitative Models of Radiation Action	
	Kaplan Lecture: Target Theory, Linearity and Repair/Misrepair in Radiobiology	296
	<i>M. M. Elkind</i>	
	SYMPOSIUM: BIOPHYSICAL MODELS OF RADIATION ACTION	
	Biophysical models of radiation action—Introductory review	306
	<i>D. T. Goodhead</i>	
	The cellular consequences of binary misrepair and linear fixation of initial biophysical damage	312
	<i>S. B. Curtis</i>	
	Pairwise lesion interaction — extension and confirmation of Lea's model	318
	<i>D. Harder</i>	
	A concept relating DNA repair, metabolic states and cell survival after irradiation	325
	<i>K. T. Wheeler</i>	
2.3	Microscopic Deposition of Radiation Energy	
	SYMPOSIUM: APPLICATIONS OF MICRODOSIMETRY	
	Applications of microdosimetry	331
	<i>J. Booz and L. E. Feinendegen</i>	
	Microdosimetry: Recent trends and applications to radiation biology and radiation chemistry	338
	<i>A. M. Kellerer</i>	
	Applications of microdosimetry in radiation protection	345
	<i>H. G. Menzel</i>	
	Applications of microdosimetry in radiation therapy	351
	<i>A. Wambersie</i>	
	SYMPOSIUM: EFFECTS OF INTERNAL AUGER EMITTERS	
	Effects of internal Auger emitters	357
	<i>D. Ackery and K. F. Baverstock</i>	
	Local effects of Auger electron cascades	363
	<i>D. E. Charlton</i>	

	Radiobiological effects of Auger emitters <i>in vitro</i> and <i>in vivo</i> <i>D. V. Rao and K. S. R. Sastry</i>	369
3.	CELLULAR AND DNA REPAIR	375
	Congress Lecture: Aspects of DNA Damage, DNA Repair and Radiosensitivity: Responses of Mammalian Cells to Acute Doses of Radiation <i>J. T. Lett, A. B. Cox, R. Okayasu and M. D. Story</i>	376
3.1	Inducible Repair of Damage Caused by Ionising and Non-ionising Radiation (Symposium)	
	<i>recA</i> -dependent repair of DNA gaps and double-strand breaks after UV irradiation <i>K. C. Smith, T-C. V. Wang and R. C. Sharma</i>	382
	Cellular functions required for UV and chemical mutagenesis in <i>Escherichia coli</i> <i>J. R. Battista, T. Nohmi, C. E. Donnelly and G. C. Walker</i>	388
	Inducible DNA repair of ultraviolet light damage in <i>E. coli</i> and related species <i>S. G. Sedgwick</i>	394
	Non-ionizing radiation and inducible responses in eucaryotes <i>R. M. Tyrrell and S. M. Keyse</i>	400
3.2	Molecular Studies on DNA Repair in Mammalian Cells (Symposium)	
	Reversion and interspecies transfer of genes responsible for repair in <i>xeroderma pigmentosum</i> <i>J. E. Cleaver, D. Karentz, L. H. Lutze, A. N. Player and D. L. Mitchell</i>	406
	Homology of mammalian, <i>Drosophila</i> , yeast and <i>E. coli</i> repair genes <i>D. Bootsma, M. H. M. Koken, M. van Duin, A. Westerveld, A. Yasui, S. Prakesh and J. H. J. Hoeijmakers</i>	412
	DNA repair in tissue specific genes in cultured mouse cells <i>C. M. Haqq and C. A. Smith</i>	418
3.3	Radiosensitive Human Cells (Symposium)	
	The radiosensitivity of cultured human cells <i>C. F. Arlett</i>	424
	Novel pattern of post- γ ray DNA replicative synthesis in cultured radioresistant fibroblasts from affected members of a cancer-prone family <i>M. C. Paterson and R. Mirzayans</i>	431
	The human genetic disorder ataxia-telangiectasia (A-T): New insights into the basis of radio-sensitivity <i>P. G. Debenham and J. Thacker</i>	437
	High sensitivity to radiation and chemicals in relation to cancer and mutation <i>H. Takebe, K. Tatsumi, A. Tachibana and C. Nishigori</i>	443
3.4	Fractionation, Low-dose Rate and Repair Kinetics (Symposium)	
	Repair kinetics in normal tissues <i>H. D. Thames</i>	449

	The dose-rate effect and recovery in human tumour cells <i>G. G. Steel, A. M. Cassoni, J. M. Deacon, G. M. Duchesne, A. Horwich, L. R. Kelland and J. H. Peacock</i>	455
	The influence of proliferative status on responses to fractionated and low dose rate irradiation <i>J. S. Bedford</i>	461
	Chromosome break rejoining and cellular recovery from X-rays <i>M. N. Cornforth</i>	468
4.	ONCOGENESIS AND MUTAGENESIS	475
4.1	Cellular and Molecular Aspects of Oncogenesis	
	Congress Lecture: Genetic and Epigenetic Influences on Oncogene Activity <i>J. A. Wyke, J. Akroyd, A. Green, C. Poole and M. Welham</i>	476
	SYMPOSIUM: CELLULAR AND MOLECULAR ASPECTS OF ONCOGENESIS	
	Search for genes involved in thymic lymphomagenesis <i>M. Janowski, B. Borremans, R. Hooghe, J. Merregaert, P. Reddy, J. Boniver and M. P. Defresne</i>	482
	Radiation-induced carcinogenesis in dogs <i>M. E. Frazier, T. M. Seed, L. L. Scott and G. L. Stiegler</i>	488
	Studies on radiation myeloid leukaemogenesis in the mouse <i>A. Silver, G. Breckon, W. K. Masson, D. Malowany and R. Cox</i>	494
	The action of chemical carcinogens and oncogenic retroviruses in mouse skin tumour induction <i>A. Balmain, K. Brown, R. Bremner, M. Quintanilla and M. Archer</i>	501
4.2	Oncogenic Transformation	
	Congress Lecture: Oncogenic Transformation by Radiation and Chemicals <i>E. J. Hall and T. K. Hei</i>	507
	SYMPOSIUM: CELL TRANSFORMATION BY RADIATION	
	Cell killing in radiation tumorigenesis <i>M. M. Elkind</i>	513
	Somatic mutation and cell differentiation in neoplastic transformation <i>E. Huberman and F. R. Collart</i>	519
	Mechanisms and modifications of radiation induced neoplastic transformation <i>J. B. Little</i>	526
	<i>In vivo</i> activation of mouse oncogenes by radiation and chemicals <i>L. E. Diamond, E. W. Newcomb, L. E. McMorrow, J. Leon, S. Sloan, I. Guerrero and A. Pellicer</i>	532
4.3	Cellular and Molecular Aspects of Mutagenesis (Symposium)	
	LacI sequence changes and the mechanisms of UV mutagenesis in <i>E. coli</i> <i>C. W. Lawrence, J. E. LeClerc, J. R. Christensen, R. B. Christensen, P. V. Tata and S. K. Banerjee</i>	538
	Radiation mutagenesis in bacteria and mammalian cells <i>J. Thacker</i>	544

	New methods of analysis of radiation mutagenesis in mammalian cells: Shuttle virus <i>C. F. M. Menck, M. R. James and A. Sarasin</i>	550
	Mechanisms of gamma ray mutagenesis inferred from changes in DNA base sequence <i>F. Hutchinson and K. R. Tindall</i>	557
	Ionizing radiation induced point mutations in mammalian cells <i>B. W. Glickman, E. A. Drobetsky, J. de Boer and A. J. Grosovsky</i>	562
4.4	Application of Cytofluorimetry	
	Congress Lecture: Chromosome Abnormalities, Transformation and Reproductive Death in Mammalian Cells Studied with Different Radiations and Flow Karyometry <i>G. W. Barendsen</i>	568
	Congress Lecture: Analytical cytology applied to detection of induced cytogenetic abnormalities <i>J. W. Gray, J. Lucas, T. Straume and D. Pinkel</i>	574
5.	RADIATION EXPOSURE AND RISK	581
5.1	Radiation Exposure	
	Congress Lecture: Recent Reactor Accidents and Their Effects <i>L. B. Sztanyik</i>	582
	Congress Lecture: Revisions in the Dosimetry of the A-Bomb Survivors at Hiroshima and Nagasaki and Their Consequences <i>W. K. Sinclair and D. L. Preston</i>	588
	Congress Lecture: Radiation Effects in Space <i>R. J. M. Fry</i>	595
	SYMPOSIUM: RADIATION LEVELS IN THE ENVIRONMENT	
	Introductory review: Radiation and the Environment <i>H. J. Dunster</i>	601
	The radiological impact of the Chernobyl accident in OECD member countries <i>O. Ilari</i>	608
	Radiation in the global environment <i>A. A. Cigna</i>	614
	Lung cancer risk from environmental exposure to radon daughters <i>W. Jacobi</i>	620
5.2	Radiation Risks and Epidemiology (Symposium)	
	The status of the assessment of radiation risks to humans <i>W. J. Schull</i>	627
	Methods and models in the epidemiological assessment of radiation risks <i>C. E. Land</i>	634
	Probability of causation in radiation injury and its application <i>S. Jablon</i>	640
5.3	Animal Studies and Extrapolation to Man (Symposium)	
	Some aspects of extrapolation of late effects studies to man <i>R. H. Mole</i>	646

Consequences of prenatal irradiation in mice: Cancer and CNS damage as a basis for human risks <i>S. Sasaki</i>	652
The role of pathology in late effect studies <i>W. Gössner, A. Luz and A. B. Murray</i>	658
Experimental radiation carcinogenesis <i>A. C. Upton</i>	664
6. MODIFICATION OF RADIOSENSITIVITY, IN VITRO AND IN VIVO	671
6.1 Sulphydryls and Radiation Response (Symposium)	
Molecular and cellular aspects of the role of thiols in radiation response <i>B. D. Michael</i>	672
Role of glutathione and other thiols in cellular response to radiation and drugs <i>J. E. Biaglow, M. E. Varnes, E. P. Clark and E. R. Epp</i>	677
Radiation response of human cells genetically deficient in glutathione <i>M. R. Edgren</i>	683
Interactions of radioprotectors and oxygen in cultured mammalian cells <i>K. D. Held</i>	689
6.2 Oxygen and Radiation Responses	
SYMPOSIUM: TISSUE OXYGENATION AND HYPOXIA	
Tissue oxygenation and hypoxia in tumours <i>D. G. Hirst</i>	695
Determinants of spheroid oxygenation <i>W. Mueller-Klieser</i>	701
Tissue oxygenation of primary and xeno-transplanted human tumours <i>P. Vaupel and F. Kallinowski</i>	707
New trends in improving oxygen delivery to tumour tissues <i>D. W. Siemann</i>	713
SYMPOSIUM: MANIPULATION OF TISSUE OXYGENATION FOR THERAPEUTIC BENEFIT	
Benefit Exploitation of bioreductive agents with vasoactive drugs <i>J. M. Brown</i>	719
Oxygen delivery and tumour response <i>R. P. Hill and D. Stirling</i>	725
Hypoxia-targetted chemotherapy: a role for vasoactive drugs <i>D. J. Chaplin</i>	731
Manipulation of tumour oxygenation by hydralazine increases the potency of bioreductive radiosensitizers and enhances the effect of melphalan in experimental tumours <i>I. J. Stratford, J. Godden, N. Howells, P. Embling and G. E. Adams</i>	737

6.3	Chemical Modification of Radiation Response	
	Congress Lecture: Recent Developments in Combinations of Radiotherapy and Chemotherapy	
	<i>M. Tubiana</i>	743
	SYMPOSIUM: CHEMICAL MODIFICATION OF RADIATION RESPONSE	
	The non-hypoxic cell sensitizers: Their use in radiobiology and in radiotherapy	
	<i>E. P. Malaise</i>	750
	Predictive assays for identifying tumours which might benefit from radiotherapy with sensitizers and/or protectors	
	<i>J. D. Chapman, J. H. L. Matthews and R. C. Urtasun</i>	756
	Radiosensitization – the clinical position 1987	
	<i>S. Dische</i>	762
	The influence of thiol modulation on the chemotherapy and radiation response	
	<i>J. B. Mitchell, J. A. Cook and A. Russo</i>	768
7.	IN VIVO RADIOBIOLOGY AND RADIOTHERAPY	775
7.1	In Vivo Radiobiology	
	SYMPOSIUM: NEW DEVELOPMENTS IN INTERPRETATIONS OF NORMAL TISSUE RESPONSE	
	New developments in interpretations of normal tissue responses	
	<i>J. H. Hendry</i>	776
	Radiosensitivity and kinetics of target cells in relation to tissue responses —as exemplified by the epidermis and the intestine	
	<i>C. S. Potten</i>	782
	The role of the vasculature in normal tissue responses	
	<i>J. W. Hopewell</i>	789
	The tissue rescuing unit	
	<i>E. L. Travis</i>	795
	SYMPOSIUM: VASCULATURE-MEDIATED ASPECTS OF TUMOUR RESPONSE	
	Attacking tumour vasculature	
	<i>J. Denekamp</i>	801
	Effectiveness of interventional radiology	
	<i>K. Jonsson</i>	807
	Tumour blood flow response to hyperthermia and pharmacological agents	
	<i>R. K. Jain</i>	813
	Angiogenesis and anti-angiogenesis	
	<i>P. Twomey</i>	819

SYMPOSIUM: PREDICTIVE ASSAYS OF HUMAN TUMOUR RESPONSE

	Predictive assays of human tumour response – Introductory review <i>C. Streffer</i>	825
	Prediction of tumour radiation response from radiosensitivity of cultured biopsy specimens <i>L. J. Peters, F. L. Baker, H. Goepfert, B. H. Campbell, T. A. Rich and W. A. Brock</i>	831
	Assessing radiation sensitivity of human tumour subpopulations by proliferating status, DNA content and monoclonal antibodies <i>P. C. Keng</i>	837
	Measurements of human tumour cell proliferation <i>in vivo</i> <i>N. J. McNally and G. D. Wilson</i>	843
7.2	Radiotherapy, Low LET Radiation	
	Congress Lecture: Physical Advances in Radiation Therapy <i>M. Goitein</i>	849
	Congress Lecture: Biological Advances in Radiation Therapy <i>H. D. Suit</i>	856
	Congress Lecture: Antibody Directed Radioisotopes and Chemotherapy <i>K. D. Bagshawe</i>	862
	Congress Lecture: Dose Per Fraction, Overall Time and Volume Effects in Radiotherapy <i>H. R. Withers</i>	869
	SYMPOSIUM: TOTAL BODY AND TOTAL LYMPHOID IRRADIATION	
	Clinical application of immunological effects of TLI <i>E. van der Schueren, M. Waer, Y. Vanrenterghem, M. Vandeputte and P. Michielsen</i>	875
	Immune modulating effects of fractionated total lymphoid irradiation (TLI): Experimental Studies <i>M. Waer, E. van der Schueren and M. Vandeputte</i>	880
	Early blood cell kinetics after total body irradiation – Biological and clinical significance <i>J. Dutreix, Th. Girinski, D. Hubert, G. Socie and J. M. Cosset</i>	885
	Total lymphoid irradiation combined with total body irradiation preceding bone marrow transplantation for chronic myeloid leukaemia <i>N. D. James, J. F. Apperley, K. C. Kam, S. Mackinnon, J. M. Goldman, A. W. G. Goolden and K. Sikora</i>	891
7.3	Radiotherapy, High LET Radiation	
	Congress Lecture: Problems of Neutron Capture Therapy <i>Y. S. Ryabukhin</i>	898
	Congress Lecture: An Update of Fast Neutron Therapy Results <i>R. D. Errington and H. M. Wardenius</i>	904

SYMPOSIUM: CLINICAL RESULTS WITH CHARGED PARTICLE BEAMS

	Clinical results of charged particle radiotherapy <i>J. R. Castro, T. L. Phillips, P. Petti, J. M. Collier, S. D. Henderson, S. Piluck and M. Reimers</i>	910
	Clinical results of proton beam radiotherapy in Boston <i>J. E. Munzenrider, M. Austin-Seymour, E. S. Gragoudas, J. M. Seddon, L. J. Verhey, M. Goitein, R. Gentry, M. Urie, D. Ruotolo, S. Birnbaum, K. Johnson, J. M. Sisterson, P. McNulty, H. D. Suit and A. M. Koehler</i>	916
	Clinical results of proton radiotherapy in Japan <i>H. Tsunemoto, S. Morita, K. Kawachi, T. Kanai, K. Kawashima, T. Hiraoka, S. Furukawa, T. Kitagawa and T. Inada</i>	922
	Clinical evaluation of Pimeson radiotherapy at TRIUMF <i>G. B. Goodman, R. Harrison, R. O. Kornelsen, G. K. Y. Lam C. Ludgate, L. D. Skarsgard and F. J. Vernimmen</i>	928
7.4	Diagnosis	
	Congress Lecture: Magnetic Resonance Measurements of Physiological and Metabolic Factors <i>G. K. Radda</i>	934
8.	HYPERTHERMIA	941
	SYMPOSIUM: HYPERTHERMIA: CLINICAL, PHYSICAL. <i>IN VITRO</i> AND ANIMAL	
	Clinical hyperthermia – an update <i>J. Overgaard</i>	942
	Physical and engineering aspects of hyperthermia <i>R. B. Roemer</i>	948
	Hyperthermic effects studied <i>in vitro</i> <i>W. C. Dewey</i>	954
	Hyperthermia in animals <i>S. B. Field and S. P. Hume</i>	960
9.	SUBJECT INDEX	967
10.	AUTHOR INDEX	981

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 disproportionately 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 basis 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 non-linear, 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 originally 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 over-

generalization, 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 subtleties 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 quantitative 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 particle 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.