Editors: MICHAEL EBERT
ALMA HOWARD

RADIATION EFFECTS IN PHYSICS, CHEMISTRY AND BIOLOGY

RADIATION EFFECTS IN PHYSICS, CHEMISTRY AND BIOLOGY

PROCEEDINGS OF THE SECOND INTERNATIONAL CONGRESS OF RADIATION RESEARCH
HARROGATE, GREAT BRITAIN, AUGUST 5–11, 1962

EDITED BY

MICHAEL EBERT

Paterson Research Laboratories, Christie Hospital & Holt Radium Institute
Withington, Manchester

ALMA HOWARD

British Empire Cancer Campaign
Research Unit in Radiobiology, Mount Vernon Hospital and The Radium Institute
Northwood, Middlesex

1963

NORTH-HOLLAND PUBLISHING COMPANY – AMSTERDAM

FOREWORD

The problem of scientific communication at large congresses presents a challenge, in response to which the organizers of the Second International Congress of Radiation Research employed the rapporteur method for the presentation of about half the proffered papers. Each Rapporteur reviewed a group of related papers. This volume contains the Rapporteurs' reports on some 300 papers, and summaries of the discussions to which the reports gave rise. In a unique way, therefore, it presents the thought of several hundred leading scientists, drawn from over forty countries, on twenty-five topics broadly representative of the advancing frontiers of radiation research.

It is a fine tribute to the quality of both the reports and the discussions that some nine hundred copies of this volume were sold in advance to Members at the Congress. It is no less a tribute to the original research which formed the basis of the reports, and I should like to offer my personal thanks to the authors for the self-effacing manner in which they entered into the spirit of the rapporteur experiment.

I think this volume is remarkable not only for its contents but for the speed with which it has been published. This has only been achieved by the very close cooperation between the Contributors, the Editors, and the North-Holland Publishing Company, to all of whom we offer our congratulations. The Editors deserve our special thanks for their part in the preparation of this volume.

During the five days of the Congress, which began with messages from two of our Honorary Presidents, Dr. Bugher and Professor Kuzin, and the Opening Address by Lord Adrian – a characteristic blend of wit and wisdom – and which ended with the remarks of Dr. Hollaender at the Closing Ceremony, much was said that was memorable but cannot be recorded in this volume. Happily, however, it has been possible to include an historical sketch of the development of radiation research which was given by Dr. Hollaender in reply to the Chancellor of the University of Leeds on behalf of the four Congress Members upon whom Her Royal Highness The Princess Royal had conferred the Degree, Doctor of Science, *honoris causa.*

FOREWORD

At the outset we were greatly disappointed when ill health robbed us of the presence of our senior Honorary President, Professor George de Hevesy, to whom the Officers and Editors respectfully dedicate this volume, as a token of our affection and of our esteem for his outstanding contributions to radiation research.

L. H. GRAY
(PRESIDENT)

British Empire Cancer Campaign
Research Unit in Radiobiology
Mount Vernon Hospital and The Radium Institute
Northwood
Middlesex

January 1963

ACCEPTANCE SPEECH

by ALEXANDER HOLLAENDER

Biology Division, Oak Ridge National Laboratory, Oak Ridge, Tenn. (U.S.A.)
(Operated by Union Carbide Corporation for the
U.S. Atomic Energy Commission)

(On occasion of Conferment of Honorary Degrees, Doctor of Science honoris causa *to Louis Harold Gray, Alexander Hollaender, Alexander Mikhajlovich Kuzin and Raymond Latarjet)*

Your Royal Highness and Chancellor, Members of the Faculty, Ladies and Gentlemen:

We feel highly honored to be given Honorary Degrees on this great occasion.

As you probably know, several of us have approached the problem of radiation research from a physical or physicochemical point of view, though not all of us have received Physics or Physical Chemistry Degrees. We therefore feel especially honored to receive the Degree from a University which for many years has been and now is so outstanding in physics and physical chemistry and, especially in the last decade or so, in radiation chemistry. These fields form the foundation stones of radiation biology.

It is interesting to follow the path that radiation research has taken during the past 30 years. With the increasing understanding of basic phenomena in the nuclear science field, interest in radiation biology was reawakened. Physical approaches have been and are being used extensively with great succes in the interpretation of effects in radiation biology. However, it has become more and more obvious, especially during the past 10 or 15 years, that radiobiology will require also a broad interpretation from the chemical point of view. This attitude has, as you know, taken hold of us very strongly during the last few years and changed our outlook on the mechanism of radiation effects. Modern developments in biochemistry and molecular biology have given us a much broader point of view in looking at living cells, seeing how they function, how they maintain their status, how they protect themselves against environmental factors, such as radiation, and how they repair damage. These are points of view which have emerged very strongly during the past 20 years. Even in the late Thirties and early Forties, the mention of repair mechanism in living cells was regarded as rather unusual and not considered essential enough to be mentioned in important reviews. It is only with the new developments in these fields, which are being brought out so strikingly in so many papers at this Second International Congress of Radiation Research, that we feel we are getting closer to an understanding of how radiation affects living cells.

What are the fields necessary for the radiation biologist to have at his finger tips to be able to follow these developments? He has to be well-versed in physics and in chemistry. He has to be in contact with the newest developments, especially in biochemistry, which have made possible so many strikingly new interpretations of the function and structure of the nucleic acids, the physical and chemical structure of chromosomes and genes, as well as of a variety of cytoplasmic particles. The new developments in our knowledge of the transfer of information from the nucleus to the cytoplasm which is involved in nucleic acid and protein synthesis have opened entirely new fields and ways of looking at biology. These developments have not only influenced radiation research, but radiation research has often opened the way for these advances. Radio- and stable isotopes have made possible investigations which were formerly impossible. What would our status be in these fields without advances in modern chemical genetics which were initiated by mutations produced and analyzed by radiation? The development in our understanding of genetic coding, which has become so important in the last few months, would have been impossible without the progress made in radiation biology. Developments in biology have often to wait for new advances in physics and chemistry. The new and very elegant biochemical tools, like the special mutations in microorganisms and viruses with highly specific properties, have helped extensively the new advances in molecular biology.

Radiation research also has given the immunologist, the radiologist, the cancer investigator many modern tools that have helped in interpreting medical problems, as well as in developing therapeutic methods. Let me follow this thread in a different direction.

Today we know more about the effects of radiation on living cells than of almost any other agent. And not only the effects on cells, but on living organisms in general. This became obvious to me when a survey was made on chemical mutagenesis. It turned out that radiation mutagenesis actually leads the way in the development of this important field, which is becoming more and more important with the wide use of insecticides, of food additives, and certain types of medicine. Here the new advances lie in directions pointed out by radiation research, and it looks again as if the systematic and thorough investigation of a fairly narrow field like radiation research has produced tools and approaches and ways of following things which will be most useful in the field of cancer, toxicology and in developmental biology.

Several of these areas have been approached in a routine manner by screening compounds for their effectiveness, whereas they should have been developed by studies on the mechanism of the function of such compounds. Here radiation studies, as exemplified by many papers at this Congress, can point the way. The new developments in genetics, cytology, biochemistry, and physiology – the most important research in radiation chemistry, the new thrilling approach to radiation absorption and measurement, and isotope developments – all these different fields brought together have helped to advance science in many ways, and not the least in the peaceful application of atomic energy. A survey of the abstracts of the more than 700 papers given at this congress is most impressive. They illustrate the productive cooperation between physicists, chemists, biologists, and medical investigators. This congress is indeed an excellent demonstration of peaceful cooperation of the scientists from the 40 nations represented at this meeting.

Development in sciences that border on radiation biology, which is beautifully illustrated in the development of basic science at the University of Leeds, has given us the interpretation and approaches which are so very important to modern biology. The discovery of a new method of crystal analysis, without which the new concept of the structure of nucleic acid would not be possible, was made here at the University of Leeds by Professor William Bragg many years ago. The physical chemistry necessary for modern approaches to biology has been developed most impressively here at the University of Leeds. Again, I want to say how much we feel honored to receive Honorary Degrees from a University which has played such an important role in these fields that border on, and strongly support, research in modern biology.

PREFACE

This book contains the twenty-five reports given by Rapporteurs at the Second International Congress of Radiation Research at Harrogate, Yorkshire, August 5–11, 1962. Following each Rapporteur's report is an account, written by a Discussion Secretary, of the discussion which took place after the report.

The Association for Radiation Research proposed in 1959 that the Second International Congress of Radiation Research should be held in Great Britain. At the same time it was decided to devote a large part of the Congress time to the Rapporteur method as an experiment in scientific communication. The subjects for the Rapporteur sessions were chosen to represent the growing points of radiation research as defined by the scientific material submitted to the Congress. The Rapporteurs were selected from workers in this country and were given a number of papers to summarize and present in a way which would be comprehensible to a non-specialist audience.

Over three hundred papers are included in these reports. It is our duty to point out to the reader that the scientific content of this book is almost entirely based on these papers, and that the Rapporteurs acted as reviewers of current research in progress.

We would like to express our thanks to all the Rapporteurs and Discussion Secretaries, whose promptness in completing their manuscripts has made possible the early publication of this book, and to acknowledge the cooperation and help of the publishers towards the same purpose.

MICHAEL EBERT

ALMA HOWARD

CONTENTS

Physical Parameters in Radiobiology

LINEAR ENERGY TRANSFER

L. F. LAMERTON

Physics Department, Institute of Cancer Research, The Royal Cancer Hospital, Clifton Ave, Belmont, Sutton, Surrey, Great Britain

a) P. ALEXANDER and Z. B. MIKULSKI,
Qualitative differences between the action of α and X rays on lymphoma cells in tissue culture.
Chester Beatty Research Institute, London SW 3, Great Britain

b) TIKVAH ALPER, D. K. BEWLEY and J. F. FOWLER,
Alpha-particle irradiation of bacterial spores in dormant and germinated forms.
Medical Research Council, Hammersmith Hospital, Ducane Road, London, Great Britain

c) D. A. BARBER and M. EBERT,
The effects of neutrons and X rays on extension growth and survival of barley roots.
D.A.B.: *Agricultural Research Council, Letcombe Regis, Wantage, Berks., Great Britain*
M.E. : *Medical Research Council, Hammersmith Hospital, Ducane Road, London, Great Britain*

d) G. W. BARENDSEN and H. M. D. WALTER,
Differences between densely and sparsely ionizing radiations with regard to modification of radiation damage in human tissue culture cells.
Radiobiological Institute, TNO, Rijswijk (ZH), Netherlands

e) R. J. BERRY and J. R. ANDREWS,
Some observations of relationships between ionization density (LET) and lethal efficiency studied by irradiation and assay of surviving mammalian tumour cells *in vivo*.
Radiation Branch, National Cancer Institute, National Institute of Health, Bethesda, Maryland, USA

f) J. F. FOWLER, D. K. BEWLEY, G. W. BARENDSEN and H. M. D. WALTER,
Technique and dosimetry for irradiation of mammalian cells in tissue culture with cyclotron accelerated particles of various LET.
J. F. F. and D. K. B.: *Medical Research Council, Radiotherapeutic Research Unit, Hammersmith Hospital, Ducane Road, London, Great Britain*
G. W. B. and H. M. D. W.: *Radiobiological Institute, TNO, Rijswijk (ZH), Netherlands*

g) J. F. FOWLER, S. HORNSEY, D. K. BEWLEY, R. L. MORGAN, J. A. SILVESTER, B. A. TURNER and G. SILINI,
Differences in macroscopic damage to pig skin not predictable from cell population studies as exemplified by ascites cells in mice after X ray and cyclotron neutron irradiations.
Medical Research Council, Hammersmith Hospital, Ducane Road, London, Great Britain

h) G. J. Neary, J. R. K. Savage, H. J. Evans and J. Whittle,
Limiting values of the RBE of fast neutrons and gamma rays at low dose rates.
Medical Research Council, Harwell, Didcot, Berks., Great Britain
i) L. D. Skarsgard,
A comparison of some of the biological effects of heavy ions and X rays on mammalian cells.
Biophysics Department, Yale University, New Haven, Connecticut, USA
j) G. F. Whitmore and D. O. Schneider,
Comparative effects of neutrons and X rays on mammalian cells.
Ontario Cancer Institute, 500 Sherbourne Street, Toronto, Ontario, Canada

1. INTRODUCTION

The subject of this, the first of the rapporteur sessions, is the significance of radiation quality in radiobiological studies, radiation quality here being defined by Linear Energy Transfer, or LET, as the mean rate of energy loss along the paths of the ionizing particles. One reason why LET and the related subject of RBE were chosen for the first session was clearly because Linear Energy Transfer and Relative Biological Effectiveness are both basic concepts in radiobiology. Another reason was, I suspect, because the terms LET and RBE can themselves express very well the philosophy behind the rapporteur session:

Let Everybody Talk?

No!

Rapporteurs for Bare Essentials.

That, at least, is the theory, but only the rapporteur who has had to summarize papers so full of information and thought as the present ones will recognize just how bare the essentials have to be.

Over the last few years there have been many developments, experimental and theoretical, in our understanding of the biological significance of LET and its exploitation in the study of biological mechanisms. One reason is the much wider range of radiations now available. In the present series of papers the LET values used range from 0.2 KeV/μ, using high energy electrons, to 2000 KeV/μ

using accelerated argon ions. Another very important reason has been the improvement in techniques and precision of dosimetry with the particulate radiations, so that much of the previous uncertainty in dose values has been removed.

A major factor, however, has been the development, initially by Puck[1]) and his colleagues, of the culture techniques which allow quantitative studies on mammalian cell survival. This has greatly extended the range of biological materials for which dose-response curves can be determined over a wide range of dose levels. If full advantage is to be taken of the range of radiation qualities available it is not sufficient to make single determinations of RBE. The whole dose-response curves have to be compared over a wide range of radiation conditions.

Ten of the twelve papers given in the programme for this session have been made available in full for this report. The main areas of work covered are:

(i) comparison of dose-response curves for a range of LET values and with a variety of biological materials, including a number of types of mammalian cells in culture, plant material and bacteria.

(ii) the modification of these curves by various factors, including fractionation and protraction of the radiation dose, degree of oxygenation and culture conditions.

2. LET DEPENDENCE OF DOSE-RESPONSE CURVES

Work already published on plant and mammalian material has established the general principle that, when there is a difference in shape of the dose-response curves for radiations of different LET, the curve for the high LET radiation is more nearly exponential than that for the low LET radiation. However, there is little published work on the detail of how the shape of the curve varies with LET.

In the present series the paper of Fowler, Bewley, Barendsen and Walter[f]), gives dose-response curves for a range of LET values from 5 to 140 KeV/μ, for survival of a culture of T-1 cells, kidney cells of human origin. These are shown in Fig. 1. The curves for the three highest LET values, 140, 85 and 60 KeV/μ, obtained with α radiation, are exponential within experimental error. Thereafter, with reduction in LET, a shoulder begins to develop on the curve. One consequence of such a change in shape of the curves is that, for any

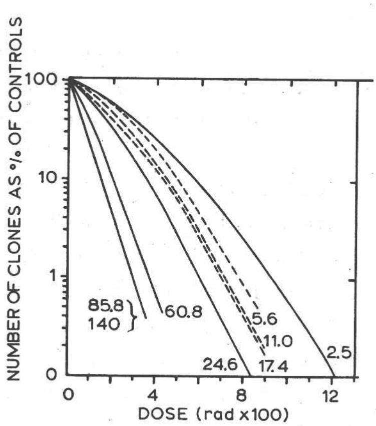

Fig. 1. Dose response curves for T1 cells. LET values in KeV/μ given on curves. (Fowler, Bewley, Barendsen and Walter.)

two radiations, the RBE will not have a constant value but will increase as the dose is reduced, except when both curves are exponential. Fig. 2, taken from the same paper, shows how the RBE value relative to that for 250 KVp X rays varies with LET for different levels of radiation damage (corresponding to 80%, 20%, 5% and 0.5% survival).

The LET value for maximum RBE is an important parameter for estimation of "target size". In these experiments the LET value for maximum RBE would appear to be about 100 KeV/μ, but is somewhat uncertain because it is at the extreme end of the LET range used.

Studies up to much higher values of LET are reported by

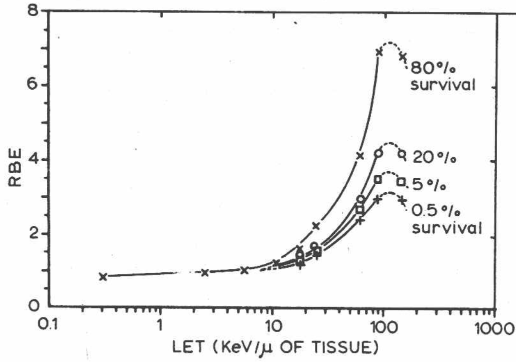

Fig. 2. RBE values for T1 cells for different levels of radiation damage, as indicated on the curves. (Fowler, Bewley, Barendsen and Walter.)

Skarsgard[i]), who has studied the response of Chinese hamster cells in culture to irradiation from X rays (LET 2 KeV/μ) and to accelerated heavy ions up to a maximum LET of 1950 KeV/μ, for argon ions. The RBE-LET relationship found for cell survival and for mitotic delay is shown in Fig. 3. For cell survival the peak RBE occurs at an LET of between 100 and 200 KeV/μ. It will be seen that both RBE values and LET values for peak RBE are different when mitotic delay is the end-point. I will return to this result again later.

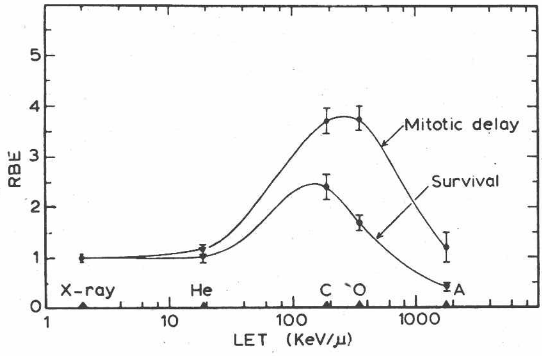

Fig. 3. Relationship of RBE and LET for mitotic delay and survival in Chinese hamster cells CH2B$_2$. (Skarsgard.)

A basic question, in any review of radiation quality, is how far radiation quality can be adequately characterized by the mean LET, and whether two different types of radiations will necessarily have the same biological effect because they have the same LET. This, and the question of what precisely is meant by "mean LET", are not specifically the subject of any of the papers contributed. However, Berry and Andrews[e]), in their studies of the response of mouse lymphatic leukaemia cells, irradiated and assayed *in vivo*, have employed two very different types of radiation but having the same mean LET of about 0.5 KeV/μ. One was ^{60}Co γ radiation and the other accelerated protons of 340 MeV energy in the plateau region. They found similar values, not only of RBE, but also of the oxygen effect. A further demonstration of the significance of LET was their finding, *in vivo*, of different RBE's for the same accelerated α beam, depending on whether the plateau region or the Bragg peak was used.

3. LIMITING VALUE OF RBE

When the dose-response curves vary with LET in the way shown in Fig. 1, one may ask whether the RBE of high LET to low LET radiation will increase indefinitely as the dose is reduced, or will reach a limiting value. This is a matter of considerable theoretical interest, as well as of practical importance in radiation protection.

On a target theory the interpretation of the change in shape of dose-response curve with LET is that the passage of a single ionizing particle through the target is sufficient to produce the effect for high LET radiation, whereas more than one passage may be required for low LET radiation. If, for the low LET radiation, more than one passage is always required, the RBE of high to low LET radiation will increase indefinitely as dose is reduced. However, if there is a finite, though perhaps only small, probability that the effect can be produced by a single passage with low LET radiation, there will be a limiting value of RBE, given by the ratio of the coefficients of the linear dose terms for the two radiations. On a simple target theory one would expect this limiting value of RBE to apply to very low doses at any dose rate and, if repair mechanisms operate between successive passages, for low dose rates at any total dose level. As a number of the present contributors point out, experiments to test this involve many difficulties, because of the low doses or long exposure times needed.

However, Neary, Savage, Evans and Whittle[h]) present, in their paper, a study of this problem based on chromosomal aberrations in Tradescantia microspores, using ^{60}Co γ rays and 3 MeV fast neutrons as the radiation sources. They have analysed the dose-response data for short exposures and for exposures up to 48 hr and have computed the coefficients of the linear dose terms and square dose terms. The conclusion is that there is a linear term for the low LET radiation, but much smaller than that for the high LET radiation, so that the limiting values of RBE are high, as shown Table 1. These RBE values are much higher than those that have been previously reported for Tradescantia.

Several of the contributors working on survival of mammalian cells in culture conclude that here also the RBE has a limiting value. Barendsen and Walter[d]), in their paper on the response of T-1 cells, use their data on X ray fractionation to infer the limiting