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RADIATION BIOLOGY

Donald J. Pizzarello

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Radiation Biology

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Editor-in-Chief
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CRC SERIES IN RADIOTRACERS IN BIOLOGY AND MEDICINE

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FOREWORD

This series of books on Radiotracers in Biology and Medicine is on the one hand an unbelievably expansive enterprise and on the other hand, a most noble one as well. Tools to probe biology have developed at an accelerating rate. Hevesy pioneered the application of radioisotopes to the study of chemical processes, and since that time, radioisotopic methodology has probably contributed as much as any other methodology to the analysis of the fine structure of biologic systems. Radioisotopic methodologies represent powerful tools for the determination of virtually any process of biologic interest. It should not be surprising, therefore, that any effort to encompass all aspects of radiotracer methodology is both desirable in the extreme and doomed to at least some degree of inherent failure. The current series is assuredly a success relative to the breadth of topics which range from in depth treatise of fundamental science or abstract concepts to detailed and specific applications, such as those in medicine or even to the extreme of the methodology for sacrifice of animals as part of a radiotracer distribution study. The list of contributors is as impressive as is the task, so that one can be optimistic that the endeavor is likely to be as successful as efforts of this type can be expected to be. The prospects are further enhanced by the unbounded energy of the coordinating editor. The profligate expansion of application of radioisotopic methods relate to their inherent and exquisite sensitivity, ease of quantitation, specificity, and comparative simplicity, especially with modern instrumentation and reagents, both of which are now readily and universally available. It is now possible to make biological measurements which were otherwise difficult or impossible. These measurements allow us to begin to understand processes in depth in their unaltered state so that radioisotope methodology has proved to be a powerful probe for insight into the function and perturbations of the fine structure of biologic systems. Radioisotopic methodology has provided virtually all of the information now known about the physiology and pathophysiology of several organ systems and has been used abundantly for the development of information on every organ system and kinetic pathway in the plant and animal kingdoms. We all instinctively turn to the thyroid gland and its homeostatic interrelationships as an example, and an early one at that, of the use of radioactive tracers to elaborate normal and abnormal physiology and biochemistry, but this is but one of many suitable examples. Nor is the thyroid unique in the appreciation that a very major and important residua of diagnostic and therapeutic methods of clinical importance result from an even larger number of procedures used earlier for investigative purposes and, in some instances, procedures used earlier for investigative purposes and, in some instances, advocated for clinical use. The very ease and power of radioisotopic methodology tempts one to use these techniques without sufficient knowledge, preparation or care and with the potential for resulting disastrous misinformation. There are notable research and clinical illustrations of this problem, which serve to emphasize the importance of texts such as these to which one can turn for guidance in the proper use of these powerful methods. Radioisotopic methodology has already demonstrated its potential for opening new vistas in science and medicine. This series of texts, extensive though they be, yet must be incomplete in some respects. Multiple authorship always entails the danger of nonuniformity of quality, but the quality of authorship herein assembled makes this likely to be minimal. In any event, this series undoubtedly will serve an important role in the continued application of radioisotopic methodology to the exciting and unending, yet answerable, questions in science and medicine!

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Dr. Colombetti graduated from the Litoral University in his native Argentina with a Doctor in Sciences degree (summa cum laude), and obtained two fellowships for postgraduate studies from the Georgetown University in Washington, D.C., and from the M.I.T. in Cambridge, Mass. He has published more than 150 scientific papers and is the author of several book chapters. He has presented over 300 lectures both at meetings held in the U.S. and abroad. He organized the First International Symposium on Radiopharmacology, held in Innsbruck, Austria, in May 1978. He also organized the Second International Symposium on Radiopharmacology which took place in Chicago in September, 1981, with the active participation of more than 500 scientists, representing over 30 countries. He is a founding member of the International Association of Radiopharmacology, a nonprofit organization, which congregates scientists from many disciplines interested in the biological applications of radiotracers. He was its first President (1979/1981).

Dr. Colombetti is a member of various scientific societies, including the Society of Nuclear Medicine (U.S.) and the Gesellschaft für Nuklearmedizin (Europe), and is an honorary member of the Mexican Society of Nuclear Medicine. He is also a member of the Society of Experimental Medicine and Biology, the Coblenz Society, and the Sigma Xi. He is a member of the editorial boards of the journals *Nuklearmedizin* and *Research in Clinic and Laboratory*.

PREFACE

In many ways radiation biology cannot be considered a study unto itself. Exposure to ionizing radiations in particular, produces no unique effects. Rather, its action is to increase the frequency of occurrence of a wide variety of phenomena that naturally occur in living populations. Consequently, radiation biology is simply the study of natural phenomena—heightened in incidence by irradiation. It is an immense, diffuse discipline, far too large to be placed between two covers.

This book, then, which calls itself, *Radiation Biology*, is much less than that. For example, not all radiations are considered, only ionizing radiations. Also, most, though not all, the essays restrict their remarks to mammalian cells, tissues and organs, leaving out nearly all the animal kingdom and, practically speaking, all the plants.

Even so, the title, *Radiation Biology*, may not be so wide of the mark, for the effects of ionizing radiations (at least) are considered on many of the fundamental life processes; cell replication, transmission of genetic material, mutation, reproduction and development as well as on functions depending on intercellular relationships, tissue and organ functions, and immune response.

The book was not planned as a primer, but for advanced biology students. It includes an essay on physics basic to understanding interactions of ionizing radiations and living matter, but little basic biology.

No effort was made to achieve uniformity of style or form of exposition among the various essays. Each contributor is an expert in his or her discipline, and it was felt best to permit each to tell his or her story in the way that best suited them. The assumption was was that their theme development and language is the result of many hours of intense throught and research and would be hard to improve upon — and — in any case, variety among essays can only be refreshing to the reader.

The editor considered it his function to cull out inevitable repetition that occurs when a number of authors separately consider related topics, to correct occasional lapses in English and the even more occasional error of fact that he was capable of noticing. There is, nevertheless, some repetition and overlap, but this is deliberate. Repition, per se, is not necessarily bad and where it served as reinforcement or a convenience to the reader, it remained. Doubtless, there also remain lapses in English and errors in fact. This proves only the fallibility of even the most careful scrutiny and effort of both author and editor.

The book may be used as a text and read from cover to cover. However, the intention was that each essay would stand alone as well. To an extent all lean on the physics chapter and, of course, the reading of the essays in sequence enhances understandings of each of them.

The book has several unusual features. The long essay by Wolsky is an attempt to explain effects of irradiation on developmental processes rather than, as in the usual case, on development alone. Grdina's essay describes an exciting new technique and its power to extract information. There is a section about at least one application of radiation biology—that to various branches of medicine. This is included so that students can read and appreciate how facts learned in the laboratory can be put to work and how much remains to be learned to be pressed into the service of humankind.

There are gaps. An essay on sensitizers and protectors, normal tissue models and regeneration and repopulation are desirable. However, none could be obtained without waiting so long that material in hand would become seriously outdated. Even with these gaps, this is a strong book, one that makes an important contribution to the teaching and reference literature.

Lelio G. Colombetti
Donald J. Pizzarello

THE EDITOR

Donald J. Pizzarello is Professor of Radiology at New York University Medical Center in New York City. He is the author of numerous research reports and co-author of three books, *Basic Radiation Biology,* which is going into its third edition, *Medical Radiation Biology,* going into its second edition and *Concepts in Cancer Care,* which appeared in mid-1980.

He is much in demand as a lecturer, having served as Visiting Professor in medical centers in nearly all parts of North America, most frequently discussing presumed hazards of exposure to low doses of ionizing radiations. In addition to these professional audiences, Dr. Pizzarello frequently addresses lay groups concerned, generally, about current and future exposure of human beings to artificial sources of ionizing radiations.

Aside from the foregoing, Dr. Pizzarello regards himself as an ordinary fellow who loves his family; music; literature; good food, drink and conversation; despises all physical exercise (except swimming, which he thinks of as a form of lying down) and excessively hot weather.

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TABLE OF CONTENTS

Section I
Basic Radiation Biology

Chapter 1

BASIC PHYSICS

Robert J. Barish

TABLE OF CONTENTS

I. INTRODUCTION

A. Matter and Energy

Our concepts of energy and matter have undergone a considerable evolution in this century. The theory of quantum chromodynamics predicts the existence of hundreds of subatomic particles, many of which have already been observed in high energy physics experiments. To understand the physics of radiobiology, however, we can be content with one of the earlier atomic models where there are only three fundamental particles. In this model, electrons swing in orbits around a nucleus which is composed of protons and neutrons.

B. Atomic Structure

Each atom consists of a nucleus containing protons and neutrons, and orbital electrons which surround it. The electrons exist in orbits with discrete energy levels whose values are quantized; i.e., they can take only these energy values and not any in-between. This concept was first proposed, and its consequences worked out, by Bohr in 1913. He assumed that electrons could make a transition from one energy level to another and that the transition would correspond to the absorption or emission of radiation whose quantum energy would be equal to the difference in energy of the two levels.

The electrons can be thought of as occupying "shells" which are identified by the letters K,L,M,..., successively as one gets farther from the nucleus. The electrons in the inner shells are more tightly bound to the atom than those in the outer shells. This model accounts for the observation of such phenomena as the line spectra emitted when a material is excited in an electric spark. The wavelength of the emitted light corresponds to the energy difference between the electron shells. Some electrons are raised to higher orbits and the observed spectrum is created as they jump back to their normal orbits. By supplying enough energy, an electron can be liberated completely from the atom thus creating a positively charged atom or molecule and a free electron, each of which may interact with its surroundings. In most cases, the free electron will soon attach itself to a neutral molecule to form a negative ion so that the net result is an "ion pair". The capture of another electron by the positively charged atom or molecule will often lead to the release of energy in the form of a single "bundle" — a photon. Alternatively it may lead to the breakup of the molecule; i.e., to chemical change.

C. Mass Energy Equivalence

The mass of an atom is less than the combined masses of the component parts — neutrons, protons, and electrons — which make it up. The difference is accounted for by the binding energy holding the parts together, quantified by Einstein's famous relationship of equivalence between mass and energy, $E = mc^2$. If δm is the decrease in mass when a number of neutrons, protons and electrons combine to form an atom, $E = \delta mc^2$ is released in the process. This same amount of energy would be required to break the atom into its constituents. Mass and energy are not measured in the same units but a direct conversion is possible using the Einstein formula. For example, if an electron could be completely converted into energy, the energy would be:

$$E = (9.11 \times 10^{-31}\,\text{kg})\,(3 \times 10^{8}\ \text{m sec}^{-1})^2 = 8.2 \times 10^{14}\,\text{J} \qquad (1)$$

A special energy unit, the electron volt (eV), has long been used in radiological physics although it is not part of the S.I. system* ($1\ \text{eV} = 1.6 \times 10^{-19}$ J). E in Equation 1 is therefore 5.1×10^5 eV or 510 keV. Thus 510 keV of energy could conceivably be converted into the mass of one electron, a phenomenon that happens in certain interactions of radiation with matter.

Radiation may broadly be divided into two types — particulate in which the individual energy carriers have mass and may be electrically charged, and electromagnetic where the energy carriers are photons which have no charge and have zero mass.

D. Electromagnetic Radiation

Many familiar physical manifestations such as light, radio waves, and radar are examples of electromagnetic radiation. X-rays and gamma rays are also in this category. Their names are associated with their means of production. X-rays arise from electron transitions in the inner shells of atoms or from the deceleration of charged particles in matter. Gamma rays are associated with the release of energy from the atomic nucleus. The physical properties of electromagnetic radiation can be fully explained only if these radiations are considered to have a dual nature and to behave sometimes as waves and sometimes as particles. Using light as an example, the wave nature is demonstrated by the fact that this radiation undergoes interference, diffraction, refraction, reflection, and polarization. The waves are characterized by their velocity of propagation $c = 3 \times 10^8$ m sec^{-1} in a vacuum, and by their wavelength λ and frequency ν. These are related by the formula $c = \lambda\nu$. The particulate nature of light is based on the fact that energy carried by the radiation is always absorbed in the form of discrete "bundles" or "quanta". These individual bundles are called photons. Each photon has no mass but travels with the velocity, c, given above. The minimum amount of a particular electromagnetic radiation is one single photon of the appropriate energy. Thus, in the examples given earlier in this chapter, an electron transition in an atom can lead to the production of a photon whose energy is characteristic of a particular electron energy level difference in that material. This photon is properly called a characteristic X-ray. Similarly, a photon whose energy exceeds 1020 keV can be converted into two electrons (one negative, one positive) in the interaction mentioned earlier.

E. Particulate Radiation

Particulate radiation may be of many types. The nuclear particles, neutrons or protons, may be liberated from the nucleus and emitted as particulate radiation following the interaction of high energy radiation with matter or as a result of nuclear fission. Alpha particles which consist of two protons plus two neutrons may be emitted from the nucleus in radioactive decay. Electrons also may be liberated from the atom. If they are produced as a consequence of radioactive decay they are called beta particles. They may also be knocked out of their orbits as a result of the interaction of radiation with matter. Physics research has led to the production of many other particles which

* Systeme Internationale, an international system of units and definitions.

are not easily found in nature. Some of these, like pi mesons, may in the future have some application in radiation biology.

II. PHOTON INTERACTIONS WITH MATTER

A. Photoelectric Effect

In the 1890s, it was observed that light falling on a metal surface could cause a loss of charge from the metal. There was a minimum optical frequency at which this would occur. Light of lower frequency (longer wavelength) would not eject the electrons which, as we now know, caused the charge loss, regardless of the intensity or the length of application of the light. These observations could not be explained by the existing theories. In 1905, Albert Einstein put forward a simple hypothesis to explain this process called the photoelectric effect. He proposed that energy of light was carried by individual quanta, called photons, each with energy $E = h\nu$, where h is Planck's constant and ν is the frequency. If the energy of the photon is great enough, (ν is high enough), an orbital electron can be ejected from an atom of material it strikes. In the photoelectric interaction, the photon gives up all of its energy and disappears. This absorption of the photon leads to the release of an electron whose kinetic energy is equal to the difference between the photon energy and the energy holding the electron to the atom. The likelihood of the photoelectric interaction per electron varies with E^{-3} and Z^3 where E is the photon energy and Z is the atomic number of the material. Thus the process dominates at low energies for a given material. In biological materials, the photoelectric effect is most important for photon energies up to around 50 keV.

In addition to the primary ionization that is a result of the photoelectric ejection of an electron, two other subsidiary processes may occur. The first is a filling of the vacancy created in the electron shell from which the photoelectron came. The jump of an outer electron to the inner vacancy is accompanied by the emission of characteristic X-radiation which may then produce its own ionization elsewhere. Sometimes the characteristic X-ray's energy is absorbed in the outer shells of the same atom, releasing electrons from these higher orbits. These are called Auger electrons, and contribute to the general distribution of secondary effects.

B. Compton Scattering

It is also possible for a photon to collide directly with any of the atomic electrons. If the binding energy of the struck electron is small compared with the photon energy, it may be considered "free" and in the collision, the photon transfers enough energy to knock the electron out of the atom. The photon is left with lower energy and is deflected away to interact again elsewhere. Thus the outcome of this event is a recoil electron and a scattered photon which share the initial photon energy (minus the electron binding energy). The physical principles of this interaction were discovered by A. H. Compton in 1923. He combined elements of Einstein's quantum theory of light and some parts of the special theory of relativity to predict the relationships of energy transfer and angle of deflection in this interaction. The Compton process is the dominant interaction in biological materials over the wide energy range of 50 keV to 20 MeV. Since the process involves relatively "free" electrons, it is independent of the atomic number of the absorber and all materials absorb about the same amount of radiation per electron by this process. There is a practically linear decrease in the likelihood of Compton scattering over its broad energy range.

C. Pair Production

Pair production provides a practical demonstration of the conversion of energy into