Radiation Biophysics

(Ionizing Radiations)

Yurii B. Kudryashov

NOVA

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FOREWORD

The author of the treatise is Sc.D. (Biol.) Yu.B. Kudryashov, the Honorary Scientist of the Russian Federation, a Laureate of the USSR State Prize, Professor of the Lomonosov Moscow State University, Soros Prize Professor. His textbook is concerned with topical problems of the modern science, the characterization of radiation damage to living matter at increasing levels of its organization, beginning at the molecular level. The general theory of the mechanisms of biological action of radiations based on four logically connected principles of radiation biology is presented for the first time.

The book contains abundant factual material on primary and secondary processes of response of living systems to radiation, the mechanisms of direct and indirect radiation action through radiolysis of water and lipids; a detailed consideration of the theory of targets (DNA and biological membranes). The problems of high- and low-dose irradiation in the context of present-day views are given; and the systemic response of the cell to irradiation (oxidative stress, endogenous background radioresistance, damage and repair of biological membranes and DNA, systemic protection against radiation) is estimated. The consideration of these important problems is preceded by the up-to-date evaluation of some aspects of dosimetry.

The author of the treatise has delivered a course of lectures on radiation biophysics at the Lomonosov Moscow State University for more than fifty years. He also has lectured on this topics in educational and scientific institutions of Russia and abroad and was a supervisor of 60 doctors of philosophy and doctors of sciences in this area. He is the author of 300 publications, including 13 monographs and manuals. In 1986-87 Yu.B. Kudryashov took part in the liquidation of the Chernobyl nuclear power plant accident. Taken together, this enabled Yu.B. Kudryashov to highlight the fundamental and current problems of acute and chronic irradiation. An important point is that some leading radiation biologists were invoked to the compilation of the treatise, which supplemented successfully the versatile work of the author.

The book reads with great interest, it has been written at a high professional level, and fits all up-to-date international requirements to textbooks. The issue of the book is topical and timely. A wide circle of students, lecturers, and researchers engaged in problems of biology, medicine, and physics, as well as readership on the consequences of the Chernobyl accident and other radioecological contaminations of environment will find the book attractive and useful.

Professor Elena B. Burlakova
Head of the Scientific Council on Radiobiology,
Assistant Director of the Institute of Biochemical Physics,
Member of the Russian Academy of Sciences

ABSTRACT

The treatise gives a consecutive description of all stages of the development of radiation damage to biological systems, from the absorption of energy of ionizing radiations by biomolecules to the death of the cell and the organism. Special chapters are devoted to the units of dose and dose rates of irradiation of biological objects and systems and the mathematical modeling of radiobiological effects. Considerable attention is given to modern conceptions of the mechanisms of action of high- and low-dose ionizing radiation on the cell and the organism. In the concluding section, four principles of radiobiology are summarized. The problems of radiation biophysics have become currently a matter of great concern in view of consequences of the Chernobyl accident and other radiation accidents and the necessity of understanding the biological and medical aspects of the action of ionizing radiations on living organisms and man.

The author of the treatise has delivered courses of lectures on radiation biophysics at the Lomonosov Moscow State University and in educational institutions of Russia and abroad for more than fifty years. He is an Honorary Professor of several foreign universities (Japan, China, Bulgaria, Georgia, and other countries). He participated in the liquidation of the Chernobyl nuclear power station accident in 1986-1987.

The book is intended for students specializing in biology, physics, chemistry, radiation biology and medicine, for persons occupationally dealing with ionizing radiation sources at nuclear power stations and plants, and for people living in zones of increased background radiation.

PREFACE

This treatise contains factual material I have used when delivering lectures on radiation biophysics beginning from 1953, the year of foundation of the chair of biophysics at the Lomonosov Moscow State University, till the present time. During the fifty-year period of my work at the chair of biophysics I have organized a laboratory of radiation biophysics, gave constantly laboratory courses on radiation biology and delivered courses of lectures on biophysics, radiobiology and radioecology at the chairs and faculties of many universities of the former USSR countries, Russia, and in some countries abroad.

Because of the shortage of educational literature, we often were aware of a sharp need for timely publication of manuals and textbooks. Therefore, in 1962 a Laboratory Course on Radiation Biology and in 1979 and 1982 lectures and a textbook on radiation biophysics were issued. The co-author of the textbooks, my follower Boris S. Berenfeld, soon after the publication of the textbook left to lecture biology at the Harvard University. I recollect with sorrow and gratitude this time when we worked, full of enthusiasm, on the first in the world textbook on radiation biophysics.

Thus, two decades have passed since the publication of the first textbook. Unwittingly, one puts himself a question whether it is much or little, the gone twenty years. For the compilation of an up-to-date textbook, it is very much because during this time principally important events happened, which opened a new period in the history of radiation biology. Among these are primarily the discoveries in the field of molecular and cellular biology and the turn of radiation biology to low "technogenic" radiation doses, which happened due to radioecological contamination of our planet.

Today I follow with great satisfaction the rapid development of investigations of oxidative processes in lipids and formation of geno- and cytotoxic oxyradicals and oxy adducts in critical biological structures, biological membranes and DNA, which are currently performed in numerous laboratories of the world.

Priority researches of our laboratory and investigations concerned with the verification of the hypotheses of radiotoxins (1956-1987), endogenous background radioresistance, and general radioresistance (1980-2001) have stood the test of time. And, of course, I mean the triumph of the ideas of the deceased Prof. Boris N. Tarusov, my dear teacher and friend, the founder of the chair of biophysics, who has put forward and advanced the theory of primary chain mechanisms of radiation damage (1954-1962).

Even 20 years ago these ideas forced with great difficulties their way. Now the hypotheses about the key role of lipid peroxidation (lipid radiotoxins) in radiation pathology and stress, about the indirect action of radiation via lipid oxyradicals, the involvement of "endogenous background" in the formation of resistance of biological objects and systems to ionizing and nonionizing agents, and the role of biological membranes as a critical target – all these ideas have gained wide recognition and become the subject of thorough study.

The investigations of another Russian radiobiological school headed by the Academicians Nikolai M. Emanuel and Elena B. Burlakova were concerned with the role of free oxygen radicals and oxidants in norm and pathology. These ideas, too, have long been subjected to sharp criticism and fortunately have also successfully stood the severe test of time.

A splendid confirmation of these ideas is the recent discovery of the possible formation of geno- and cytotoxic oxy adducts (adducts of reactive oxygen species and lipid radicals with DNA) in norm, carcinogenesis, and by the action of radiation. The discovery of another class of regulatory agents, reactive nitric oxy compounds, extended the ideas on the role of oxidative reactions in primary mechanisms of radiation action.

At present the theories of B.N. Tarusov and E.B. Burlakova have not only gained the recognition of the world scientific community but also supplied the practical medicine with novel means of prophylaxis and treatment of acute and chronic radiation pathology.

The investigations of the Russian scientific school headed by Aleksander M. Kuzin have also made a considerable contribution to studies of natural background radiation and the stimulating effect of radiation. The extraordinary conceptions of A.M. Kuzin have sometimes raised sharp objections among his opponents.

However, the impartial judge, Its Majesty Time, has placed its own emphasis in radiobiology and instilled into it a fresh understanding of the nonlinearity of a living system. Probably, the first attempts along this line have been made by the theoretical science thermodynamics, which declared the principles of nonlinearity and nonequilibrium of open systems. The response of living matter to weak perturbations, namely, its exit from the stationary state, also proceeds by the laws of nonlinearity.

Recent experimental achievements of molecular biology and radiation biology made possible the revision of the previous idea of the linear dependence of biological effects on radiation dose ("high doses - strong injuries; low doses - the same injuries but of lesser magnitude"). The studies of low-dose effects indicated a different, nonmonotonous character of the systemic biological response, which differed from the effect of lethal doses of ionizing radiations.

The unusually high sensitivity at superlow doses (bell-shape effect); the opposite, stimulating effect of radiation (hormesis) and adaptive response; the inverse effect of dose rate and the quasi-radiation action of toxic substances secreted by irradiated cells into a microspace («bystander effect») – all this opened a new world of changes of a living system in response to low-intensity ionizing radiations.

However, the nonlinear dynamics, too, has covered not all the aspects. In the classical variant, it considers only thermal effects. Thus, it was impossible to explain in terms of nonlinear dynamics the energetic paradox in radiobiology and the features of absorption of ionizing radiations by biological structures and their responses to the agent.

In view of the aforesaid, it becomes clear that it is a necessary and timely task to describe the sequence of radiation-induced changes at different levels of organization of a living system, create a general theory of the mechanisms underlying the action of ionizing radiations, and present the main principles of radiobiology as a single whole. This treatise is devoted to the solution of these tasks.

A western reader can be not adequately acquainted with Russian publications on the item.

Hence in the book a tendency prevails to cite Russian native authors. We ask to forgive us if simultaneously some gapes in the presentation of world data were tolerated.

When writing the textbook, I found it necessary to invoke materials specialists of other, sometimes very distant areas of knowledge. Many of these persons kindly have given in my disposal their materials useful to make this book. I cordially thank for this my dear colleagues:

Prof. Mikhail F. Lomanov who has edited the English translation of the textbook and let us newly comment his published materials in part 3 of Chapter 3 on biophysical aspects of radiation therapy; I consider also as very helpful his critical discussion of the material on microdosimetry, a branch of knowledge that tried to form a basis for mutual exchange of ideas between physics and radiation biology; all progress and failures of this research line tangibly affect the solution of urgent practical problems;

Prof. Viktor K. Mazurik who has undertaken a hard and intricate work of a scientific editor of the Russian version of the treatise and had written in collaboration with Prof. V.F. Mikhailov much for conception of radiation-induced instability of the genome used in the corresponding Section of the book.

Prof. Sergei V. Mamikhin who has discussed and given much material for writing the section on mathematical modeling of radiobiological effects. The wide availability of data-processing facilities gave a new impetus to the application of mathematical modeling, which has been a traditional method of radiation biophysics. At the same time, there is a lag in this area of research, which is due to the specificity of radiobiological investigations and some other problems. All these aspects were covered in the mentioned section of the treatise.

I am also grateful to Nina Kudryashova who has provided unique data on DNA and the DNA-membrane complex and its changes upon radiation-induced damage to the organism.

Of great value for the textbook are the data of the prematurely died brilliant lecturer and scientist David M. Spitkovski on radiation-induced changes of DNA and DNA repair.

My special thanks are to the head of the biophysics chair of the biological faculty of the Moscow State University the Member of the Russian Academy of Sciences A.B. Rubin for his many-year help in the hard pedagogical and creative activities without which the work on the treatise would be impossible.

I express my sincere gratitude to the Head of the Council on Radiobiology, Assistant Director of the Institute of Biochemical Physics, Russian Academy of Sciences, USSR State Prize Winner, Member of the Russian Academy of Sciences Dr. Sci. (Biology) Prof. E.B. Burlakova for constant consideration and encouragement. The collaboration with Prof. E.B. Burlakova in the Council on Radiation Biology has been a powerful beneficial impetus in my scientific activity.

My sincere appreciations are to my colleagues:

Prof. Elena Goncharenko who is a constant assistant and co-author of our joint publications on radiation biology; I thank her for the careful revision of the manuscript of the textbook and helpful advices;

Prof. I.I. Pelevina, Prof. D.S. Chernavski, and Prof. G.Yu. Riznichenko for useful remarks and advices, which also helped in the work on the book.

S.V. Sidorova for the intricate and highly qualified work on the translation of the textbook and the staff of Columbus' Publishing House which has undertaken the edition of the English version of the book.

The original edition of this textbook was dedicated to two anniversaries: the 50th anniversary of the chair of biophysics of the biological faculty and the 250th anniversary of the Lomonosov Moscow State University (2006). It is hoped that this textbook will be a timely contribution to the total wide stream of university education in different countries of the world.

A LIST OF ABBREVIATIONS, SYMBOLS, AND SOME CONDITIONAL TERMS

$\Delta\mu H^+$	gradient of proton potential
D_{37}	a dose at which 37% of biological objects remain viable
D_{se}	a "single event" dose (a dose inducing a single event)
e_{hydr}^-	hydrated electron
Φ	fluence (a measure of time-integrated particle flux, expressed in particles per square centimeter)
G	radiation-chemical yield
$HO_2^{\bullet}$	hydroperoxy radical (perhydroxide)
$LO^{\bullet}$	alkoxyl radical
$LO_2^{\bullet}$	peroxyl radical
LOOH	hydroperoxyl
NOS	nitrogen monoxide synthetase (NO-synthase)
$O_2^{\bullet}$	oxygen anion radical; superoxide
$^1O_2$	singlet oxygen
$^3\Sigma_gO_2$	oxygen in the ground, triplet state
$ONOO^-$	peroxynitrite
$OH^{\bullet}$	hydroxide radical
ROOH	hydroperoxide
AAT	aminoalkylthiols
AEI	aminoethylisothiouronium
MLD	mean life duration
AO	antioxidants
AOA	antioxidant activity
AOB	antioxidant buffer
AT	aminothiols
ATP	adenosine triphosphoric acid
ATPase	adenosine triphosphatase
BER	base excision repair
BM	biological membrane
CNPP	Chernobyl nuclear power plant
CL	chemiluminescence

CNS	central nervous system
Da	dalton
DDF	dose decrease factor
DL	dose limit
DNA	deoxyribonucleic acid
DNase	deoxyribonuclease
DNA-MC	DNA-membrane complex
DR	"death receptor" on the surface of cell membrane
DSB	double-strand DNA breaks
EHN	2,3-epoxy-4-hydroxynoneal
EPR	electron paramagnetic resonance
EBR	endogenous background radioresistance
ECL	electrochemiluminescence
ESRB	European Society of Radiation Biology (founded in 1959 in Brussel)
eV	electron-volt
GNRO	general nonspecific response of the organism
HED	Hauterythemdosis (Germ.)
HPDG	hydroxypropanodeoxyguanosines
IAA	indolylalkyl amines
IAEA	International Atomic Energy Association
IARA	International Atomic Research Association
ICRP	International Commission on Radiological Protection
ICRU	International Commission on Radiological Units
IRPA	International Radiation Protection Association
IUR	International Union of Radioecologists
LDx/y	*lethal dose for* x% *of objects over a period of* y *days:*
LD_{50}	"semilethal" dose (lethal dose for 50% of irradiated objects)
LD_{100}	"minimum lethal" dose (minimum dose lethal for 100% of all irradiated objects)
LCS	laser correlation spectroscopy
LID	linear ionization density
LP	lipoperoxidation
LET	linear energy transfer
LPO	lipid peroxidation
LPP	lipid peroxidation products
LRT	lipid radiotoxins
MDA	malondialdehyde
NBR	natural background radiation
NER	nucleotide excision repair
NMR	nuclear magnetic resonance
NQR	nuclear quadrupole resonance
OE	oxygen effect
ORT	oxyradiotoxins ($ROCC_{RT}$ and LRT)
[ORT^DNA]	adducts (oxy adducts) of ORT with DNA
PDN	polydeoxynucleotides
PK C	protein kinase C

PO	prooxidants
PS	phosphatidylserine
PS_{ox}	oxidized phosphatidylserine
RBE	relative biological efficiency of radiation
RNA	ribonucleic acid
RNC	reactive nitrogen compound
ROS	reactive oxygen species
ROCC	reactive oxygen-containing compounds
$ROCC_{RT}$	ROCC radiotoxins
SB	Schiff bases
SI	International System of Units of Measurement
SNRS	Sanitary Norms of Radiation Safety
SOD	superoxide dismutase
SSB	single-strand breaks
TNF	tumor necrosis factor
UNSCEAR	United Nations Scientific Committee on Atomic Radiation
UV	ultraviolet
WHO	World Health Organization

INTRODUCTION

Radiation biophysics is a scientific discipline that deals with the molecular mechanisms of the biological effects of ionizing and nonionizing radiation. It elucidates consecutive changes induced by irradiation, from the absorption of energy by individual molecules to complex biological changes in the cell and the whole organism. In essence, radiation biophysics solves radiobiological problems in terms of biophysics since radiobiology is concerned with the effect of radiation on biological objects and systems, and biophysics deals with molecular interactions underlying vital processes in norm and pathology.

This textbook is devoted to the biophysical mechanisms of the action of ***ionizing radiation***. In the broad spectrum of electromagnetic and corpuscular radiation occurring in nature and generated by artificial sources created as a result of human activity, ionizing radiation has received the most study.

A part of the electromagnetic radiation spectrum, from γ-rays to low-frequency waves, and the main parameters and radiation sources are presented in Table 1.

At present the most comprehensive information has been obtained on the biological effects induced by ionizing radiation as well as ultraviolet and visible light. The studies of the mechanisms of action of infrared, long-wavelength electromagnetic radiation and so-called zero radiation, i. e., permanent electric and magnetic field, are being considerably extended.

The interest of physicists and biologists in various kinds of radiation has led to the emergence of a number of new scientific disciplines, such as radiation biology of ionizing radiation, photobiology (concerned with the effects induced by radiation of the optical spectrum, e. g., photosynthesis, photodynamic effect) and electromagnetic biology (deals with the effects of radiation in the radiofrequency range).

Electromagnetic and corpuscular radiation of different types are a very important tool when investigating living matter. Modern biology is unthinkable without the use of X-ray diffraction analysis, ultraviolet, visible and infrared spectroscopy, radiation ultramicrometry, light and proton microscopy, and radioactive isotopes. In the past few years, radically new methodical improvements (use of radioactive indicators, X-ray electron and atomic spectroscopy, selective ion- and mass spectrometry, cryoelectron tomography, and other modern methods) formed the basis for the highly sensitive specific identification of labile biological structures, including oxyradicals and oxyadducts with biomacromolecules in norm and pathology. The most impressing advances in the investigation of the structure and properties of living matter have been made possible by the wide use of the methods of radiation biophysics. The solution of this task requires a complex approach, which should take into account the physical principles of radiation energy transfer, the discrete nature of radiation, and the character of interaction with the atoms and molecules of biological structures, on the one hand, and the unique features of the structural and functional organization of the living thing, on the other.

It is evident from Table 1 that only a narrow region of the electromagnetic spectrum belongs to ionizing radiation. This is the shortest-wavelength high-frequency radiation whose quanta carry a huge energy of many thousands and millions of electronvolts. Owing to their physical properties, they are able to penetrate into a substance and are therefore often called *penetrating radiation.* The term *ionizing radiation* was introduced to designate radiation of various physical nature whose most typical property is the ability to ionize, directly or indirectly, the atoms and molecules of an absorber.

Ionizing radiation includes electromagnetic and corpuscular radiation with energies exceeding the value of the *ionization potential* (12.6 eV for water). X-rays and γ-rays of radionuclides are the electromagnetic radiations capable of ionization. Radiowaves and the optical spectrum also belong to electromagnetic radiation; however, they are classified with nonionizing radiation because, due to low intrinsic energy (and correspondingly, long wavelengths), they are unable to ionize atoms and molecules.

Corpuscular radiation encompasses charged particles: β-particle (electron or positron), ionized hydrogen (proton), deuterium (deuteron), helium (α-particle), and other nuclei; and many neutral particles: neutron, π^0 meson, and others which are unstable if they are emitted.

The urgency of studies on the biological effects of ionizing radiation has been dictated by numerous scientific and social problems.

First, it is known that all living things are constantly exposed to the natural background radiation (1-2 mSv/year), which is composed of cosmic radiation and radiation from radioactive elements that occur in surface layers of Earth's crust and are incorporated into living organisms themselves and the products of their nutrition.

Second, the background radiation in many districts of our planet has substantially increased due to human technogenic activities, nuclear weapon tests, and accidents at nuclear atomic power and other industrial plants. The extremal impact of ionizing radiation, particularly in combination with other kinds of environmental contamination, adversely affect the ecology of the animate Nature and human health and life. All this stimulated the extension of studies in the fields of radiobiology and radiation ecology.

And finally, ionizing radiation is the well-known diagnostic and therapeutic means in the treatment of many diseases. The application and future development of radiation therapy are unfeasible without deep knowledge of the mechanisms of interaction of radiation with the substances and radiation-induced changes in cells, tissues, and the whole organism.

Radiobiology is a complex science. It requires combined efforts of physicists, chemists, mathematicians, clinicians, biophysicists, and the researchers engaged in classical biological disciplines. In view of this, extensive research is currently conducted in many fields: radiation ecology and genetics, radiation biochemistry and cytology, radiation medicine and sanitation. *Radiation biophysics* occupies a special place among these disciplines because its main goal is to determine the physicochemical and molecular mechanisms of *primary radiation-induced changes* occurring from the moment of generation of ionized and excited atoms and molecules till the appearance of visible structural and functional changes. The solution of this problem requires a thorough analysis of processes occurring at each stage of *energy exchange* in a living system, the description of these processes in terms of molecular events, and the creation of a total picture reflecting the sequence of all reactions that lead, depending on radiation dose, either to radiation-induced changes or radiation damage. Before turning to the range of problems facing modern radiation biophysics, it is necessary to consider the main periods in the history of radiobiology, the origination and development of radiation biophysics, and the emergence of separate lines of research into the biological effect of ionizing radiation many of which remain timely today.

Radiobiology is a science of the 20th century. Its advent dates back to the discovery of X-rays, radioactivity, and the first mention of the effect of X-radiation on the living organism. In December 1895, the head of the chair of physics at the physical faculty and the rector of the Wurzburg University Prof. Wilhelm Konrad Roentgen demonstrated to the Physicomedical Society the first X-ray photograph of his hand and a manuscript with the description of the discovery of penetrating cathode X-rays, which were soon named after the discoverer. As soon as January 1896, the booklet of Roentgen entitled "A new kind of rays" was published in Russian, English, French, and Italian. The book soon became the property of the world community.

The Roentgen discovery stimulated new investigations in physics, biology, and medicine. In March 1896 Professor of physics at the Paris Museum of Natural History A. Becquerel discovered a new phenomenon, an arbitrary emanation of invisible penetrating radiation (α-, β-, and γ-rays) emitted by uranium salts. Two years later, Marie and Pierre Curie isolated hitherto unknown elements from uranium tar, which, like uranium, emitted rays. The elements were named radium and polonium. The peculiar property inherent in these elements and in related elements discovered later was called **radioactivity**.

The discovery of uranium and thorium rays has marked the beginning of research into **natural radioactivity**.

Later in 1934 Irène and Frédéric Joliot-Curie, while studying the nuclear reaction of $^{27}Al(\alpha, n)^{30}P$ registered a new hitherto unknown radionuclide ^{30}P. This is how the new phenomenon, **artificial radioactivity,** was detected.

The discoveries in physics evoked a ready response among biologists. The birth of radiobiology, in early 1896, almost completely coincides with the date of discovery of X-rays. At this time the Petersburg physiologist Ivan R. Tarkhanov (Tarkhanishvili) performed his first experiments on irradiation of frogs and insects with X-rays and reached the conclusion that "by using X-rays, it is possible not only to photograph but also affect the living function".

Another pioneer, the Russian radiobiologist Efim S. London, initiated also in 1896 year-long extensive studies on roentgenology and experimental radiobiology.

The first official information on the pathological effect of radiation on skin appeared as late as 1901 in the paper of P. Curie and A. Becquerel in which they reported on the burns on their skin caused by careless handling of radium.

At that time, the main problem of radiobiology was the precise quantitative estimation of radiation dose. It is reasonable that roentgenologists were the first to discover the necessity of dosing radiation because they had to empirically specify if only arbitrary units of biological doses of X-rays. The first unit of measurement of dose, which was "registered" biologically within several days or weeks after irradiation, was Haut Erythem Dosis (HED, German; "skin erythema dose").