Sarah Baatout
Editor

Radiobiology Textbook

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Foreword

I feel immensely delighted and consider it an honour to write the foreword for the *Radiobiology Textbook* edited by Prof Sarah Baatout. I went through the textbook with utter curiosity and found it irresistible to stop reading from beginning to end. Indeed, the book will prove a boon and treasure of knowledge for radiobiology researchers, physicians, clinicians, environmentalists, nuclear workers, industry professionals/managers, and radiation technology developers.

New Discoveries and Early Excitements

With the discoveries of X-ray in 1895 and radioactivity in 1898, unusual excitement was witnessed among scientists and researchers all over the world. It was commonly perceived that a new revolution had arrived in science, which might prove a panacea for every enigma. Besides researchers and academicians, the general public was highly enthusiastic and saw the emergence of new discoveries as an auspicious signal to humankind. Interestingly, physicians were quick to show the courage and enthusiasm to apply newly discovered radiation for treating cancer. That was a great medical challenge at that point in time. It was remarkable learning that X-radiation could kill living cells, including cancer cells, and had the potential to provide marked relief to cancer patients. In fact, X-radiation and radiation emitted from radioactive materials like radium became a public curiosity and an object of fun for those who wanted to have new experiences such as visualizing bones in the body and using radium lipsticks. In early years, both the scientists and common people were unaware and unmindful of the harmful effects of radiation. However, over a short span of time, it became known that radiation researchers suffered from harmful effects of radiation such as induction of cancer.

Radiobiology Was Born

It soon became apparent that understanding the mechanisms of biological effects of ionizing radiation like X-ray and gamma ray was important, and the field of radiobiology was born. Scientists also realized that setting safety standards for radiation was most urgent. Since radiation cannot be seen, tasted, or smelled, scientists began studying the interaction of radiation with matter, including radiation effects on living systems. Early studies showed that radiation could kill living cells, including tumour cells. How radiation kills living cells became the main focus of radiobiological researchers. Those who engaged themselves in radiobiology research came from diverse backgrounds, such as physics, chemistry, and biological sciences (life science, zoology, microbiology, etc.). Researchers from specific disciplines started intense investigations on physical effects (radiation physics), chemical effects (radiation chemistry), and biological effects (radiobiology) of radiation. One of the most significant contributions of radiobiological research was the discovery of the oxygen effect, which emphasized free radical production mechanisms in the radiation action on biological and chemical systems. Experiments on cellular colony formation showed that, in the presence of oxygen, more cell death occurred for the same irradiation dose.

Further radiobiological studies then laid the foundations for setting the safety standards and regulations for radiation exposure. The international radiation research community established organizations of experts, and the International Commission on Radiation Protection (ICRP) was formed in 1928 to provide recommendations and guidance about protecting humans against the risks of ionizing radiation. The United Nations Scientific Committee on Effects of Atomic radiation (UNSCEAR) was then formed in 1955 to determine the level and effects of ionizing radiation from atomic bombs and nuclear accident exposures. The same year, the US Academy of Sciences Committee on Biological Effects of Ionizing Radiation (BEIR) was established to determine and guide risks of radiation exposure on living organisms. The International Atomic Energy Agency (IAEA), created in 1957, aimed to guide and advise on safe radiation dose regulations for workers and the public.

With the intensive use of X-rays and gamma rays in medical practice, radiation has now become a household word amongst the public. In fact, medical science has acquired an extraordinary capability to diagnose and treat human diseases by radiation-based devices and protocols. Against this backdrop, the need for a comprehensive textbook was made clear by researchers and clinicians. This *Radiobiology Textbook* is designed to meet the demands of radiation and medical professionals, provides a thorough description of radiobiology, and stimulates young talents to engage in research and accept the challenges of advancing knowledge to serve humankind. More radiobiological research is needed to answer and explain several controversial issues, such as the dose-response curve, the observed differences in individual radiosensitivity, the radiation resistance of cancer cells, and many other questions. The radiation effect on somatic cells can be immediate or delayed, but radiation genetic effects are displayed only years and centuries later, something that needs to be further investigated in the future.

How Radiation Kills Living Cells/Tissues

Fundamentally, radiobiologists aim to understand the effects of radiation on cells, tissues, organs, and organisms, for animals, plants, microbial systems, and eventually humans. In this context, the discovery of DNA structure, as double-stranded helix with nucleotides as the basic units by Watson and Crick in the 1950s, propelled radiobiological studies on the mechanism of radiation-induced cell death. Radiological studies showed that radiation can kill exposed cells by damaging the DNA in the nucleus, which if not repaired prove fatal for cells. Since tumour cells divide faster than normal cells, it was hypothesized that radiation could kill these cells more efficiently. However, due to hypoxia in the tumour core, tumour cells showed resistance to radiation, leading to disappointment amongst radiation therapists. Therefore, research was undertaken to develop sensitizers of tumour cells to radiation, oxygen being the best radiosensitizer. These developments in radiobiological concepts and understanding of radiation cell killing mechanisms sustained the active research excitement in radiobiology. The medical field witnessed revolutions in caring for and treating cancer patients by using newer radiation technologies. Today, more than 40% of cancer patients are treated by radiation for therapeutic and palliative procedures. The technology consists of carefully targeting radiation beams and certain radiopharmaceuticals to destroy cancer cells while minimizing the damage to nearby healthy cells. Radiobiological studies in the 1920s helped design patient treatment protocols in what is popularly called fractionated radiotherapy.

Limitations in Radiotherapy

Radiation acts equally on normal and tumour cells. Therefore, radiation therapy of cancer patients is limited by any toxicity towards normal cells. The next goal of radiobiology was to inflict selective damage on a tumour whilst sparing normal cells. Based on radiobiological effectiveness of different cell types to the same dose of radiation, particle radiation therapy and ion beam therapies were being developed to improve the radiotherapy for patients. In addition, the rapidly increasing applications of radiation in research, industry, medicine, biotechnology, and the environment required more intensified radiobiological studies. Today, the public's major radiation exposures arise from medical applications such as diagnostic X-rays and CT scans to diagnose diseases, and cancer radiotherapy, including treatment of injuries. Therapeutic drugs with radioactive material attached, known as radiopharmaceuticals, are also routinely used in clinics to diagnose and treat some diseases. These procedures are a valuable tool to help doctors save lives through quick and accurate diagnosis.

The Book Contents

This *Radiobiology Textbook* is a comprehensive, advanced, and up-to-date volume, carefully designed and meticulously compiled by experts and practicing radiobiologists in the field drawn from reputed universities and institutes across the world. Both the experts and contributors to each chapter have remained focused to create an outstanding book useful to young radiation researchers, mid-careerists, accomplished scientists and radiation researchers in biology, biotechnology, medicine, environment, industry, and workers in nuclear power plants. There are 12 chapters written by international specialists, followed by a thorough review from experts in the respective fields. A notable and marked feature of the book is the coverage of a wide range of relevant radiobiology topics and applications. To make learning easy and enjoyable, and to enable the basic principles and core concepts to be grasped, each chapter has been designed to provide rich and up-to-date contents together with the learning objectives, chapter summary, a few exercises, key references, and suggested future readings. It is hoped that learners find the book smooth reading and a gradual building of their knowledge repository, stimulating curiosity for a deeper insight to the subject. The book begins with a brief account of the history of radiobiology, followed by the chapter on basic concepts in radiation biology, which covers basic mechanisms of radiation damage to cellular molecules, direct and indirect effects, and low-dose radiation effects with relevance to health and environment. Chapter 3 on the molecular radiation biology describes molecular details of radiation-induced lesions in DNA, types of DNA damage and mechanisms of DNA damage repair, mis-repair, and consequences to the life of cells. The following chapter on mechanistic, modelling, and dosimetry radiation biology covers the basic principles of radiation dosimetry, micro-dosimetry, dose-response and related issues. The chapter on clinical radiation biology for clinical oncology makes it attractive reading for radiation therapists and nuclear medicine physicians but will also hopefully stimulate interest of basic researchers as well as tumour therapy professionals. The objective of treating cancer patients effectively by radiation involves understanding the radiation damage mechanisms of tumour and normal tissues and the prediction of radiation response. Going over the contents of Chap. 6 provides the required specialized knowledge on clinical radiation oncology modalities such as external and internal (brachytherapy) radiation treatments, high LET therapy, and rationale of dose fractionation. Chapter 7 describes individual radiosensitivity and biomarkers for disease and treatment outcomes in therapies. Radiobiology has a crucial role in situations of nuclear plant accidents and mass exposures expected from terrorist groups. The chapter on radiobiology of accidental, public, and occupational exposures deals with the radiation accident scenario, radiation health effects, radiation risks and bio-dosimetry aspects to provide safety to workers and general public. The chapter on environmental radiobiology is most timely and relevant, describing the mobility and distribution of radionuclides in water, air, and soil with the safety and environmental perspectives. Studies on radiation effects on non-human organisms such as plants and microbial systems to measure, assess, and monitor the impacts of radiation exposures are equally important. A most fascinating chapter in this book describes various aspects of space radiobiology, which is a futuristic and young branch of radiobiology to which bright curious minds are expected to be attracted and to engage in radiobiological research. The last but one chapter concerns radioprotectors, radiomitigators, and radiosensitization, which are topics of practical importance to ensure human and environmental safety and strategies for protection. The last chapter covers ethical, legal, and social issues of radiation exposure, which re-defines the values of ethics in the radiation research field and addresses legal and social aspects of professional and public concern. The much-publicized negative aspects of radiation technology (radiophobia) are misconceived perceptions that need to be corrected by considering the diagnostic and therapeutic power and future promise of radiobiological research and applications. Without doubt, both radiation research professionals and curiosity-driven general readers will find the book stimulating, interesting, and informative.

Perspectives and Future Scope in Radiobiology

I must re-emphasize that with the ever-increasing applications of radiation technology in health and society, environment, industry, space research, and nuclear power, the radiobiology textbook of this high quality and with the coverage of frontline topics in the field is invaluable and highly warranted. The wide range of topics covered in this book with updated knowledge will prove a boon to researchers, policy makers, academicians, clinicians, and industry professionals. It is hoped that the book will arouse renewed interest among young students and will prove useful to beginners as well as senior researchers in radiobiological research and applications. More importantly, the book will prove a good reference and will help catapult future advances in radiation science and technology especially in the understanding of biological effects of radiation on living cells, tissues, and organs relevant to human health.

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Preface

Welcome to the *Radiobiology Textbook*, which was built upon the expertise of 126 international specialists, at the forefront of various aspects of radiobiology, to bring the reader the latest and most comprehensive update in the field.

Radiobiology is the branch of biology concerned with the effect of ionizing radiation on organisms. It is also a field of clinical and basic medical science that involves the study of the health effects of radiation, and the application of biology in radiological techniques and procedures for treatment and diagnostics. Multidisciplinary radiobiological research forms the scientific basis of various disciplines such as radiation protection, radiotherapy, and nuclear medicine. The goal of radiobiological research is to understand better the effects of radiation exposure at the cellular and molecular levels in order to determine the effects on health. Therefore, radiobiology encompasses various disciplines including biology, clinical applications, pharmacy, environmental and space life sciences, which make radiobiology overall a broad and rather complex topic. Throughout this textbook, we tried to organize the information from the multifaceted fields of radiobiology to enable the reader to see the Big Picture. To accomplish this synthesis of the information, unifying themes were necessary. These themes are represented by the various chapters.

This textbook aims to provide a solid foundation to those interested in the basics and practice of radiobiology science, and its relevance to clinical applications, environmental radiation research, and space research. It is intended to be a learning resource to meet the needs of students, researchers or any citizen, with an interest in this rapidly evolving discipline who is eager to learn more about radiobiology, but it is also a teaching tool with accompanying teaching materials to help educators. This book offers a unique perspective to students and professionals, covering not only radiation biology but also radiation physics, radiation oncology, radiotherapy, radiochemistry, radiopharmacy, nuclear medicine, space radiation biology and physics, environmental radiation protection, nuclear emergency planning, radiation protection, molecular biology, bioinformatics, and DNA repair.

The Contributors

The world is a better place thanks to those people who want to help others. What makes it even better are the people who share their expertise to mentor and educate future professionals. We have invited some of the leading writers and thinkers in the field of radiobiology to provide, in this textbook, an overview of the major considerations associated with the topic of radiobiology.

This textbook is an international endeavour, which started during the worldwide COVID pandemic and gathered 126 experts from all over the world. It includes leading radiation biologists, physicists, and clinicians from all over the world. Many contributors to this textbook regularly teach this material at both national and international levels and have many years' experience of explaining, elaborating, and clarifying complex theoretical and practical concepts in their particular field of radiobiology. Each contributor has a unique expertise and set of competences related to radiobiology, always with a critical and open mind. Where needed, they did not hesitate to address the challenges, the pitfalls, the limitations, and the beauty of the various aspects of radiobiology.

Various Chapters and Themes

The textbook is organized into chapters that can be used to support student/reader preparation in any type of educational arrangement. The chapters are intended to be complete in themselves and as such can be read independently and out of sequence.

This resource is intended to provide readers with a high-level view of the most relevant topics related to radiobiology. It is also intended to include all content a learner would need about a particular subject area within radiobiology. Furthermore, this textbook combines the best attributes of many different educational formats into one single resource that best supports the learning environment of the reader interested in the subject of radiobiology.

The textbook intends to cover all sub-disciplines involved in radiobiology. With its 12 chapters, it provides a comprehensive review of the history of radiation biology, the development of therapeutic evidence, and the basic concepts, an understanding of the molecular mechanisms induced by radiation as well as clinical, environmental, and space radiobiology. It deepens our knowledge of individual radiation sensitivity and biomarkers and gives a complete update on the use of potential radioprotectors, radiomitigators, and radiosensitizers. Finally, it discusses the legal, epistemological, ethical, and social concerns regarding radiation exposure.

A brief description of each chapter is given below:

Chapter 1, entitled “History of Radiation Biology”, describes the discovery of X-rays in 1895 by Wilhelm Röntgen and of radioactivity by Pierre and Marie Curie shortly after. It details the early observations of radiation effects that promoted the early development of radiotherapy. It then presents the first evidence of radiation epidemiology and radiation carcinogenesis.

Chapter 2 (Basic Concepts of Radiation Biology) reviews basic radiation biology and associated terminology to impart a better understanding of the importance of the basic concepts of interactions of ionizing radiation with living tissue. The chapter familiarizes the reader with basic and important radiation biology concepts, the use of radioactivity and its applications, the various types of interactions of radiation with living tissue, and possible effects from that exposure. It then focuses on theoretical dose–response curves and how they are used in radiation biology, and discusses stochastic versus non-stochastic effects of radiation exposure, and what these terms mean in relation to both high- and low-dose radiation exposure. Finally, a part dedicated to targeted and non-targeted effects, as well as low-dose radiation effects, ends the chapter.

Chapter 3 concerns molecular radiation biology, which has become a powerful discipline and tool for detailed investigations into biological mechanisms of modern radiobiology. The chapter reviews the types of radiation-induced lesions in DNA, the types of DNA damage repair pathways as well as the importance of chromatin architecture in DNA damage and repair. It also describes the cytogenetic, oxidative stress and clonogenic cell survival methods, as well as the impact of radiation on cell cycle progression, cell death mechanisms, telomere shortening, and on the connectivity between cells. Finally, it highlights omic changes (genetics, lipidomics, proteomics, and metabolomics) as well as the involvement of specific pathways and the epigenetic factors modified by radiation.

In Chapter 4 (Mechanistic, Modeling, and Dosimetric Radiation Biology), the principles of radiation dosimetry are explained and the relationship of track structure to early DNA damage and the importance of microdosimetry are addressed. The chapter establishes the relation between target theory and dose-response models.

Chapters 5 (Clinical Radiobiology for Radiation Oncology) and 6 (Radiobiology of Combining Radiotherapy with Other Cancer Treatment Modalities) are both clinical chapters. Chapter 5 is dedicated to the principles of tumour radiotherapy, the therapeutic window and therapeutic ratio, tumour growth and tumour control, and the 6Rs concept. The next part of the chapter reviews the principles of dose fractionation, whole body irradiation, and the impact of tumour hypoxia. Tumour resistance and progression, and the role of tumour microenvironments are also considered and discussed. Chapter 5 finishes with sections dedicated to normal tissue damage, response to radiotherapy, the importance of stem cells and the microbiota in radiotherapy, as well as radiomics.

Chapter 6 reviews the various conventional and alternative radiation schemes and analyses the various radiotherapy modalities in combination with other cancer treatment modalities (e.g. chemotherapy, targeted therapy, hormone therapy, and hyperthermia). Specific sections are dedicated to brachytherapy, radionuclide therapy, charged particle therapy, and the use of nanoparticles in cancer therapy.

Chapter 7 addresses individual radiation sensitivity and biomarkers. From general considerations and classification of biomarkers, it then moves on to the collection of samples for radiation studies and the existing predictive assays. It then reviews the variation of radiation sensitivity as a function of age, biological sex, and genetic syndromes. The chapter ends with a perspective on personalized medicine.

Chapter 8 provides in-depth coverage of radiobiology in accidental, public, and occupational exposures, reviewing the various radiation exposure scenarios, the long-term health effects of low-dose radiation in exposed human populations, and the problem posed by radon. A technical part of the chapter is dedicated to triage methods used after a radiation accident and to the available biodosimetry techniques.

Chapter 9 (Environmental Radiobiology) provides an overview of the behaviour and fate of radioelements in the environment. It then reviews the impact of ionizing radiation on non-human biota (plants, invertebrates, vertebrates, microorganisms) and discusses the specific case of NORM (naturally occurring radioactive materials) contamination.

Chapter 10 (Space Radiobiology) starts with a thorough review of the history of space radiation studies, followed by a description of the space radiation environment. It continues with a description of the impact of space travel on human health. It then reviews the various models (animals, plants, small organisms, microorganisms) sent to space and the biological changes induced by space radiation. It then focusses on space radiation resistance and gives a thorough description of the irradiation tests with ground-based facilities similar to the space environment.

The authors of Chapter 11 present a review of radioprotectors, radiomitigators, and radiosensitizers, as well as internal contamination by radionuclides and possible treatment. It provides an exhaustive overview of molecules and the mechanisms able to intervene in the biological effects of ionizing radiation and discusses their potential clinical use in radiotherapy or in the field of radiation protection following accidental exposure to radiation and/or nuclear emergencies.

Finally, Chapter 12 explores the ethical, social, epistemological, and legal considerations relevant to radiobiology. The chapter provides an overview of the basic principles relevant to each aspect whilst discussing contentious topics and potential future developments, along with more in-depth analysis where relevant.

Didactical and Pedagogical Approach

To write such a textbook, a strong didactical and pedagogical approach was crucial. To be effective, a textbook must be readable, challenging, and also exciting to the reader. Special care was taken to make the reader read, the teacher teach, and the student study this textbook, and to motivate and maintain their interest through the textbook. To make complex concepts or material easily understood, we provided the readers with thorough explanations, free of unnecessary terminology.

The general title *Radiobiology Textbook* illustrates the intention to provide detailed information about the entire field of radiobiology for anyone who is studying or is interested in this field. The textbook includes a table of contents in which all topics are listed with page references to enable the reader to locate topics quickly within a chapter. The standard chapter outline begins with an introduction giving a brief overview statement about what the reader can expect from the chapter and how the book can be used to teach a course. The learning objectives are intended to give a clear list of the educational scope and aims of the chapter. Before starting to read or study a chapter, the reader is encouraged to scan the introduction and learning objectives to understand the relationship of the material to be read. A set of keywords at the start of each chapter highlights the most significant words used specifically as an index to the content of the chapter.

The textbook is also enriched with high-resolution images, graphs, figures, and high-quality supporting illustrations, to make it as clear, didactical, and appealing as possible to the reader. In all figures, for which we used a consistent colour code for all chapters, particular attention was paid to aid understanding, summarizing, and visualizing of the concepts detailed in the text. Simplicity was the most important consideration in figures, to help the reader grasp and interpret clearly and quickly. The easy access to the complex ideas presented in the figures and in the text is one of the important hallmarks of this textbook. Many figures in this textbook are true pieces of art meant to teach, but also to astonish with their beauty, the different aspects covered by radiobiology. Various types of graphs (bar charts, pie charts, histograms, plots, line graphs) are also used to display quantitative relationships between variables.

Where needed, the text has been enhanced with tables to help summarize existing literature, present the results of epidemiological studies, or convey specific variables or statistical data on a particular domain. Tables have also been used as an alternative to numerical or listed data in order to make the text more readable, accessible, and understandable. In some cases, published figures, graphs, or tables have been used. Where needed, the necessary copyright permission was obtained.

In each chapter, textboxes have been added to draw the reader's attention to the section highlights, and these will be helpful to remember the most important topics covered within the chapter. These textboxes are embedded within the text narrative and summarize the content of the chapter at a glance, and enable the reader to rapidly scan and preview the content and direction of a chapter at a high concept level before beginning the detailed reading.

Abbreviations have been used with moderate frequency in the textbook. These allow concepts that would otherwise require many words, were they to be written out completely, to be communicated quickly and effectively. Each nonstandard abbreviation is defined clearly when it is first introduced in the chapter and then used consistently throughout the chapter.

The exercises and self-assessment at the end of each chapter allow the reader to evaluate and test their understanding of the chapter's material but also to apply what they have learnt. The exercises are aimed at requiring the reader to use critical thinking skills. The questions are tied directly to the concepts taught in the chapters and are meant to help the reader determine whether they have mastered the important concepts of the chapter. The questions cover important information presented in the chapter. Answers are provided for each exercise.

Recent reviews of publications in radiobiology suggest that the volume of research literature has been on the rise. Therefore, a careful analysis of the literature in the field from major databases (such as Web of Science, PubMed/Medline) was conducted ensuring highly relevant material is cited in this textbook. The list of references provided at the end of each chapter summarizes the main publications in the field addressed within each topic. Supplemental information in the section "further reading" is also included as appropriate at the end of each chapter. This is intended for readers who wish to deepen their knowledge and understanding. The "further reading" sections helps to illustrate, clarify, and apply the concepts encountered in the chapter.

An index at the end of the textbook offers the reader an informative and balanced picture of the textbook's contents, and serves as a concise and useful guide to all pertinent terms used in the textbook. These terms are presented as an alphabetically ordered list of the main entries.

The textbook is open access as a support to worldwide education. It is targeted at an international audience, but in particular at those countries facing challenges in accessing educational material. The creation of this open access resource was also intended to address one of the predominant challenges in education, namely the cost of textbooks. The most commonly required textbooks in undergraduate and graduate education remain traditional and discipline-based. In the absence of an integrated resource, students are requested to purchase and juggle preparation materials from many different discipline-based textbooks. With no fee required for readers to access or download this textbook, we hope to achieve the highest level of accessibility and to contribute to a better and more widespread knowledge of radiobiology as a discipline, as well as to facilitate efficient and focused learning by the reader.

Reviewing

This textbook has been reviewed extensively. As it contains an important amount of information, the editor and authors have taken the utmost care to ensure accuracy and minimize potential errors or omissions. Each chapter has been cross-reviewed by authors of other chapters, after which each chapter was reviewed by more than 20 external experts, all renowned in their field of competence.

We hope that each reader will feel gratified by the knowledge gathered from this textbook and that the textbook will become the radiobiologist's trusted companion.

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Acknowledgements

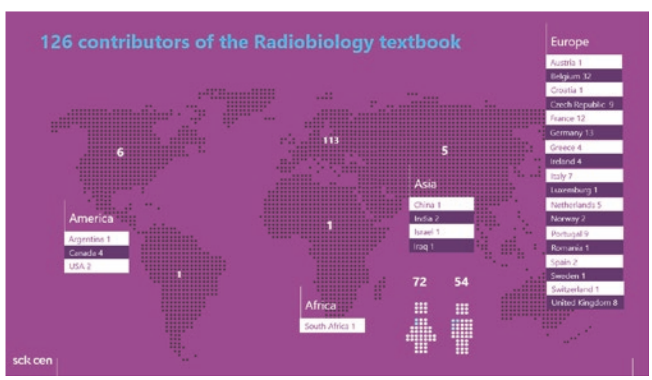
As editor, and on behalf of all the contributors, I am pleased to provide readers the required theoretical and practical tools at a time when all areas of radiobiology are expanding rapidly.

One hundred twenty-six international experts contributed to this textbook, sharing their endless expertise. Each one has contributed in significant ways and *strived to help readers learn. Each one has* provided their extraordinary insights into the complex subject of radiobiology. *They have been an inspiration and foundation for this textbook. Without their expertise, support, and dedication, this book would not exist.*

It took just more than one year to write this textbook from the day of the kick-off meeting at the height of the COVID pandemic. During this period, online meetings dedicated to each chapter were held every 3 weeks to discuss the progress of the writing of each chapter and to review the content of each chapter.

I would therefore like to express my immense gratitude upon the completion of this tremendous collaborative work and would like to thank each contributor warmly for their time, their energy but also the wonderful friendship, kindness, and teamwork that made each meeting and each part of the written text such a wonderful and constructive experience.

The figure below indicates the geographical distribution of the contributors according to their country of employment.



Of all the contributors, I have particularly appreciated the dedication of Dhruti Mistry (for making most of the beautiful figures of this book), Alexandra Dobney (for taking care so patiently of all the copyright permission issues), Kristina Viktorsson and Judith Reindl (for checking all issues related to plagiarism).

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More than 20 external reviewers willingly agreed to carefully review parts of the textbook and we would like to thank them for taking the time and effort needed to review this textbook. Their insightful recommendations and suggestions were very helpful in evaluating the quality of the writing and the relevance of each section of the textbook.

I would also like express my gratitude to SCK CEN general management, legal department, and communication department for their support throughout the process of the preparation of the textbook and for covering all the publishing costs related to this textbook in order to make it open access. A special thanks to the staff of the radiobiology unit who were extremely supportive during this endeavour.

Figures were made thanks to the use of Biorender software.

I would also like to thank the publishers and authors of the published data used in this textbook for having allowed their published figures, tables, and graphs to be used for free.

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The final words of thanks are for my family. To my brother Akim, my father Sammy, my mother-in-law Brenda, and my father-in-law John who are no longer with us, but who were always wonderful supporters. To my Mum, Elise, teacher with a deep respect for education at all levels, for her generosity, never ending support, and kindness. To my rather wonderful husband, Andrew, a patient and uncommonly discerning critic, for his love, support, and encouragement in this adventure. To our children, Alexandra and William, for their love, kindness, unconditional support, and honesty, and for making it all worthwhile.

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History of Radiation Biology

1

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Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.

—Marie Curie.

Learning Objectives

- To learn about the lives and scientific achievements of the pioneers in radiation
- To understand the logic behind the applications of ionizing radiation in modern times
- To understand the progression of the scientific knowledge of the physiological and biological effects of ionizing radiation

1.1 Introduction

In November 1895, Wilhelm Conrad Roentgen discovered X-rays; in March 1896, Henri Becquerel discovered natural radioactivity; and in December 1898, Marie and Pierre Curie produced polonium and later radium.

Almost immediately after these discoveries, radiation biology, defined as the study of the effects in biological systems of exposure to radiation, began (Fig. 1.1).

A plethora of clinical observations, initially on the skin, contributed to a better knowledge of the biological effects of ionizing radiation. The first molecular and cellular mechanistic models of the radiation action were proposed in the 1930s and 1940s and then after the discovery of the DNA structure in the 1950s. It is noteworthy that the first theories unifying molecular and cellular features of irradiated human cells emerged in the 1980s during which the first quantitative features of human radiosensitivity were pointed out [1–4].

These great discoveries at the turn of the twentieth century initiated a new era in human history. Especially, medicine has greatly profited from their applications in diagnosis and treatment of various diseases, revolutionizing our understanding of diseases. The discoveries had a vast impact on society in general and on healthcare in particular.

In this chapter, we present the main landmarks in the history of X-rays and, more generally, of ionizing radiation. Brief biographies of the pioneers in this field are presented in a chronological description of the whole field and emphasis is placed on the continuity in the development of the application of ionizing radiation to human life.

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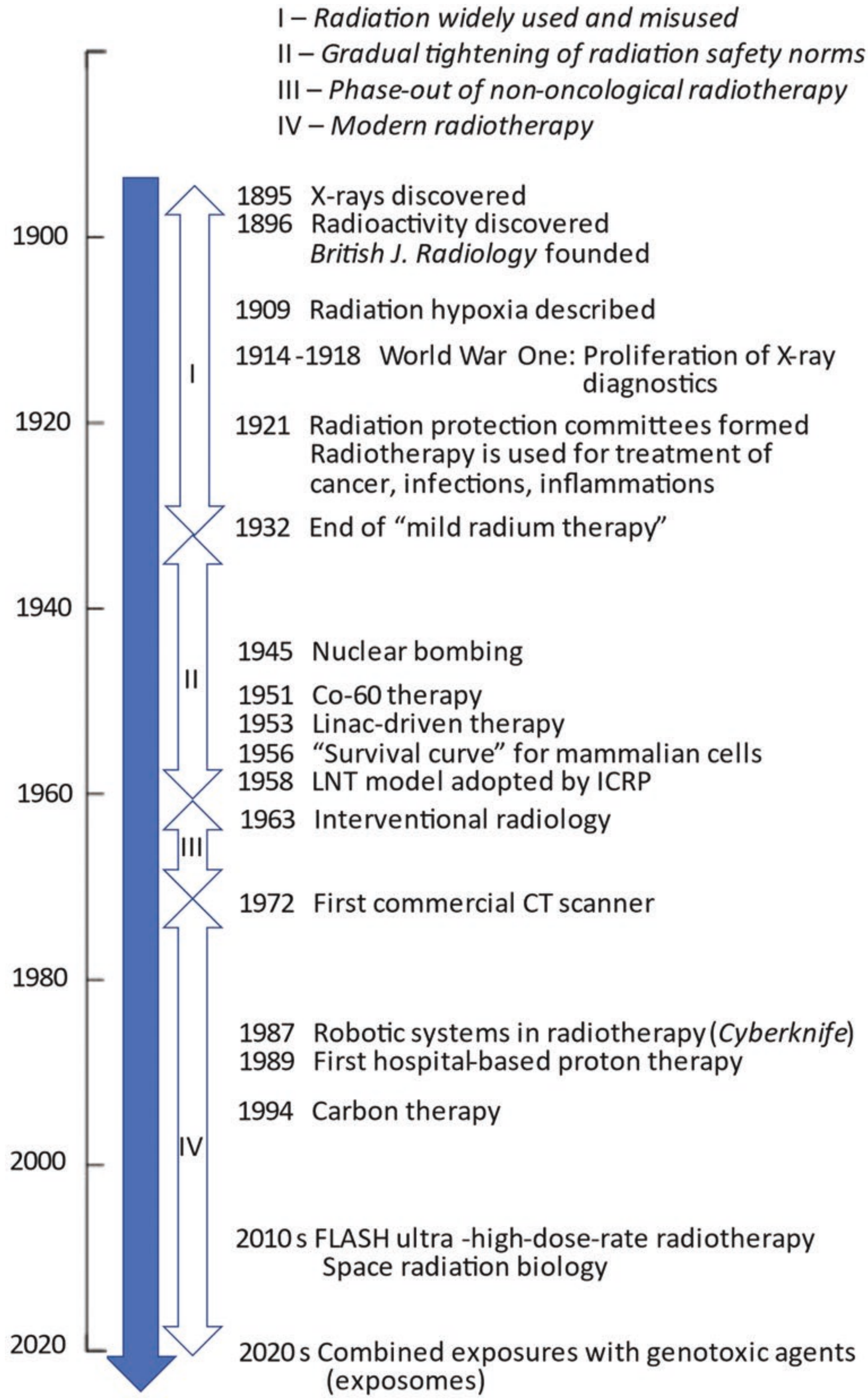

Fig. 1.1 Milestones of radiation biology

1.2 Early Observations of Radiation Effects

1.2.1 The Discovery of X-Rays and Radioactivity

By the end of the nineteenth century, "Newtonian" physics had explained nearly all the phenomena involving mass, speed, electricity, and heat. However, some questions remained unanswered, notably the origin of the luminescence phenomena observed either in glass vacuum tubes subjected to a high voltage (e.g., the Crookes tubes—Fig. 1.2) or on certain ores [4]. In both cases, one of the major questions was their inducibility vis-à-vis the sunlight. The German physicist Wilhelm Conrad Roentgen addressed the first challenge by putting some opaque boxes on the Crookes tube, while the Frenchman Henri Becquerel focused on the second one by studying light emitted by uranium ores in the darkness. The two series of experiments became legendary and led to two Nobel prizes in physics [4].

In November 1895, Wilhelm Conrad Röntgen (Roentgen) (1845–1923) detected electromagnetic radiation of a subnanometer wavelength range, today known as X- or Roentgen rays. For this discovery, he was awarded the first Nobel Prize in Physics in 1901. Although he investigated these X-rays and learned much about their interactions with matter, for a long time, he was not entirely convinced that he had made a real discovery [5] (Box 1.1).

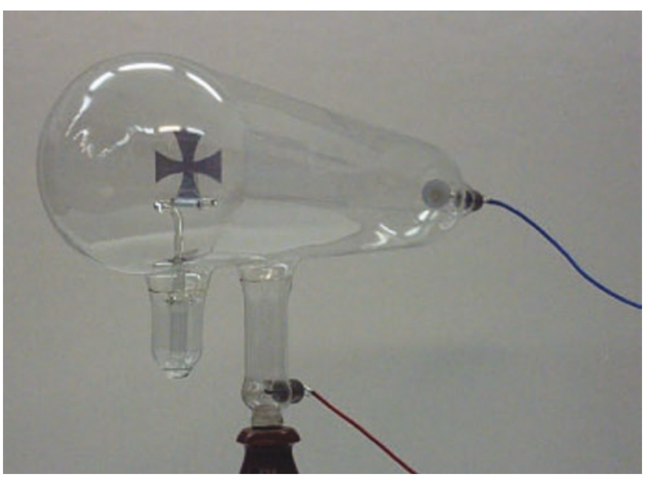

Fig. 1.2 Crookes, or cathode ray, tube. (Source: Wikimedia. Reproduced with permission)

Box 1.1 Wilhelm Conrad Röntgen

- Wilhelm Conrad Röntgen (1845–1923) experimented with Crookes tubes and in November 1895 detected electromagnetic radiation of a subnanometer wavelength range (X-rays).
- He earned the first Nobel Prize in Physics in 1901.

Roentgen was born in Lennep, Rhineland, Germany [6]. When he was 3 years old, his family moved to the Netherlands. He was an average student in the primary and secondary school, and in November 1865, he enrolled in the polytechnical school of Zurich, graduating as a mechanical engineer in 1868. After that, Roentgen remained at the University of Zurich as a postgraduate student in mathematics having August Kundt, an expert in the theory of light, as a mentor. Roentgen's first experiments in Zurich concerned the properties of gases and proved to be important for his subsequent discoveries. His doctoral thesis "Studies on Gases" led to his being awarded a PhD degree in 1869 and being appointed as an assistant to Kundt. In 1870, Roentgen, following Kundt, returned to Germany to the University of Wurzburg (Bavaria). In the autumn of 1893, he was elected Rector at the University of Wurzburg, having 44 publications and being highly respected by his colleagues and the larger academic community. Richard I. Frankel gives an excellent description of the life of W. C. Roentgen as a scientist and describes in detail the events leading up to his groundbreaking discovery.

On November 8, 1895, after experimenting with cathode rays produced in tubes developed by Johann Hittorf and William Crookes, Roentgen made his discovery. He repeated and expanded his work and gave the first description of the physical and chemical properties of X-rays. He demonstrated that these rays could penetrate not only glass and air but also other materials, including various metals. However, a thin sheet of lead completely blocked them. Roentgen inferred that the radiation he observed was in fact rays because it traveled in straight lines and created shadows of the type that would be created by rays (Fig. 1.3). While studying the ability of lead to stop the rays, Roentgen held a small piece of this metal between his thumb and index finger and placed it

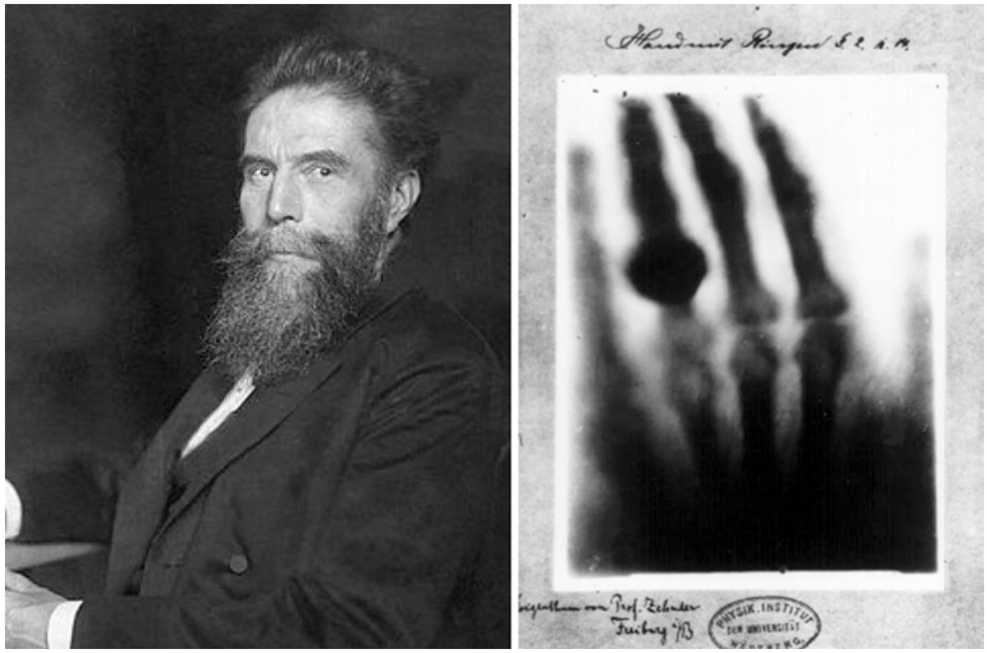

Fig. 1.3 Left: Wilhelm Conrad Röntgen (1845–1923), a portrait by Nicola Perscheid, circa 1915. Right: The first roentgenogram—the hand of Röntgen's wife after its irradiation with X-rays (Dec 22, 1895)

in the path of the rays. He noted that he could distinguish the outline of the two digits on the screen and that the bones appeared as shadows darker than the surrounding soft tissue. Roentgen continued his work over the next weeks, during which he made additional images and showed that the rays darkened a photographic plate. In his manuscript entitled "Uber eine neue Art von Strahlen" ("On a New Kind of Rays") submitted to the Physikalisch-Medizinische Gesellschaft in Wurzburg on December 28, 1895, he used the term "X-rays" for the first time [5].

Roentgen did not leave any autobiography, so all information regarding people and events which had an influence on his work comes from his biographers. Scientists whose work had greatly influenced Roentgen were the physicist August Kundt (1839–1894), the physicist and mathematician Rudolf Clausius (1822–1888), and the physicist and physician Hermann Ludwig Ferdinand von Helmholtz (1821–1894), all three of German origin. Of importance is his lifelong friendship with the physicist Ludwig Zehnder who served as Roentgen's chief assistant and became an occasional co-author.

It is worth mentioning the relationship between Roentgen and his contemporary German experimental physicist Philipp Lenard (1862–1947), director of the Physical Institute at Heidelberg University. Lenard (Fig. 1.4) first published the results of his experiments on cathode rays in 1894 and was awarded for this the Nobel Prize in Physics in 1905. Prior to Roentgen's discovery, the two scientists exchanged several letters regarding the aspects of the cathode ray research, and Roentgen referenced Lenard in his initial publications on X-rays and used Lenard's modified tube for his experiments (Box 1.2).

Fig. 1.4 Philipp Eduard Anton von Lenard (1862–1947)

Box 1.2 Philipp Lenard

- Philipp Lenard (1862–1947) was awarded the Nobel Prize in Physics in 1905 for "his work on cathode rays."
- However, Lenard became extremely embittered by not winning the Prize in 1901. He became one of Adolf Hitler's most ardent supporters, eventually becoming "Chief of Aryan Physics" under the Nazi regime.
- After World War II, he was not sentenced (for his prominent role in the Nazi regime) only due to his old age.

However, when Roentgen alone was awarded the Nobel Prize in 1901 "in recognition of the extraordinary services he has rendered by the discovery of the remarkable rays subsequently named after him," Lenard became extremely embittered, and for the rest of his life, he insisted that he had shown Roentgen the way to his discovery. Lenard became one of the early adherents of the National Socialism and one of Adolf Hitler's most ardent supporters, eventually becoming "Chief of Aryan Physics" under the Nazi regime. In 1933, he published a book called "Great Men in Science" in which he failed to mention not only Jews, such as Einstein or Bohr, but also non-Aryans like Marie Skłodowska-Curie and even Roentgen. When World War II ended, Lenard's prominent role in the Nazi regime led to his arrest, but due to his old age, instead of being sentenced to prison, he was sent to live in a small German village, where he died at the age of 83 [7, 8].

A few months after the discovery of X-rays, radioactivity was described. Antoine-Henri Becquerel (1852–1908) (Fig. 1.5) was a member of a distinguished family of four generations of physicists, all being members of the French Académie des Sciences. Becquerel's initial research was in phosphorescence, the emission of light of one color following a body's exposure to the light of another color. In early 1896, following Röntgen's discovery, Becquerel "began looking for a connection between the phosphorescence he had already been investigating and the newly discovered X-rays" [9] and initially thought that phosphorescent materials, such as some uranium salts, might emit penetrating X-ray-like radiation, but only when illuminated by bright sunlight. By May 1896, after a series of experiments with non-phosphorescent uranium salts, he correctly concluded that the penetrating radiation came from the uranium itself, even without any external excitation. The intensive study of this phenomenon led Becquerel to publish seven papers in 1896 only. Becquerel's other experiments allowed him to figure out what happened when the "emissions" entered a magnetic field: "When different radioactive substances were put in the magnetic field, they deflected in different directions or not at all, showing that there were three classes of radioactivity: negative, positive, and electrically neutral" [10] (Box 1.3).

Box 1.3 Henri Becquerel

- Henri Becquerel (1852–1908) discovered radioactivity in 1896 while studying phosphorescent uranium salts.
- Later in the same year, upon experimenting with non-phosphorescent uranium salts, he concluded that the penetrating radiation came from the uranium itself.
- He was awarded the Nobel Prize in Physics in 1903.

Interestingly, radioactivity could have been discovered nearly four decades earlier. In 1857, the photographic investor Abel Niépce de Saint-Victor (1805–1870) observed that uranium salts emitted radiation that darkened photographic emulsions. Later in 1861, he realized that uranium salts produced invisible radiation. In 1868, Becquerel's father

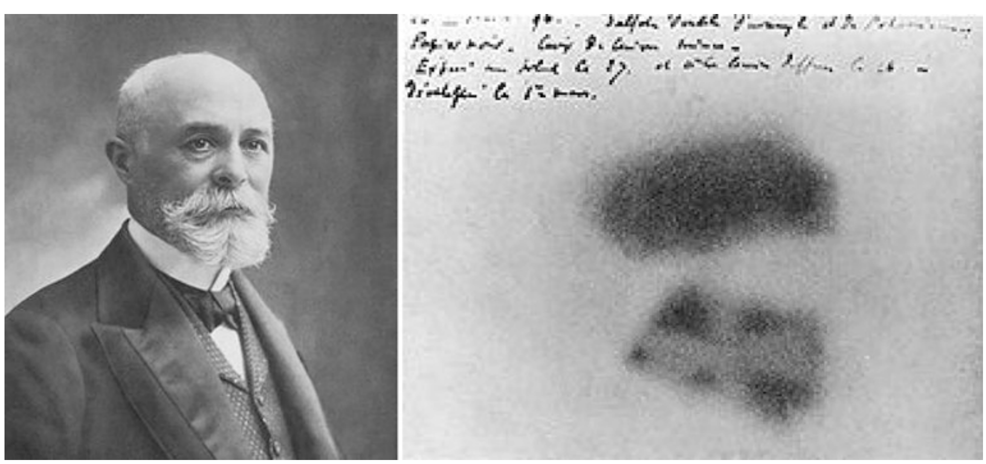

Fig. 1.5 Left: Henri Becquerel (1852–1908), circa 1905. Right: Becquerel's photographic plate exposed to a uranium salt