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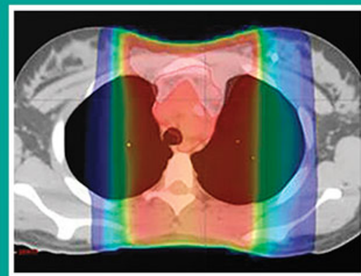

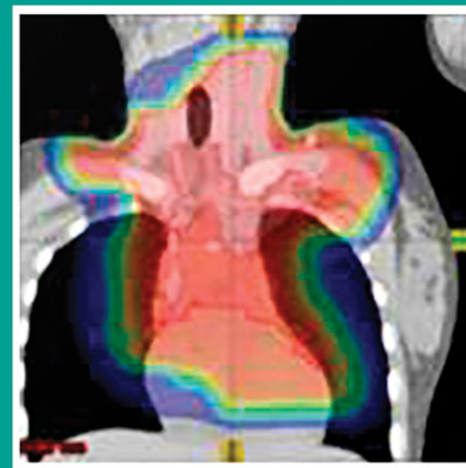

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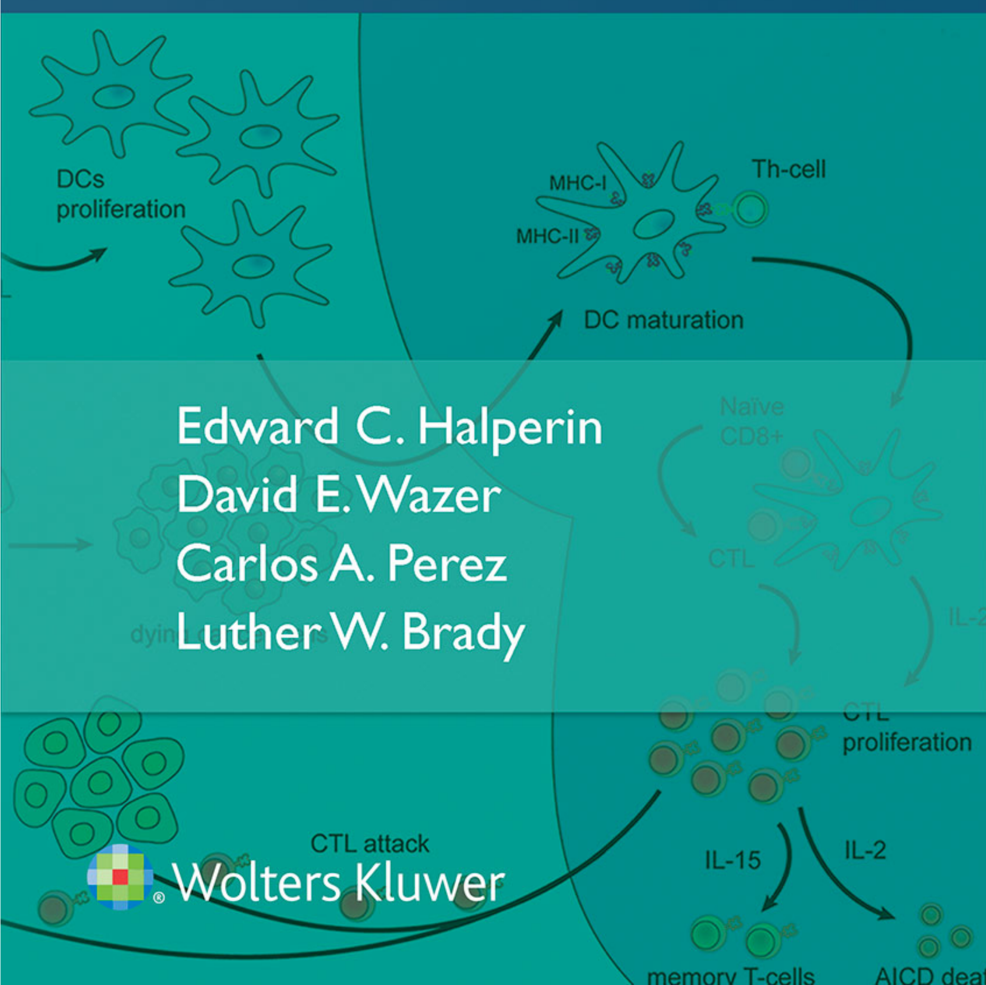

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Principles and Practice of Radiation Oncology

Seventh Edition

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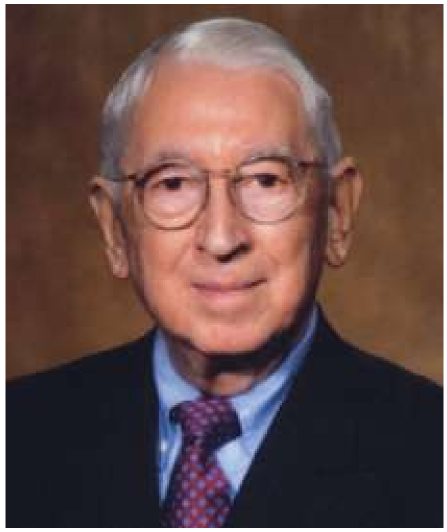

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To our patients, who have taught us through both their courage and their suffering,

To our teachers, who inspired and mentored us with knowledge and wisdom,

To our trainees, who will make the cancer care of tomorrow better than today's,

To the universities where we work—institutions that are committed to generation, conservation, and dissemination of knowledge about the causes, prevention, and treatment of human disease and disability:

To our families, who unselfishly endorsed our work on this book.

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Preface

The first edition of *Principles and Practice of Radiation Oncology* was published in 1987. This seventh edition is being published in 2018. After 31 years, approximately 11,000 pages of printed text, many tens of thousands of pages of typed and computer printed text, and an immeasurable number of meetings, phone calls, letters, e-mails, faxes, and text messages utilized to produce these seven volumes, many things have changed and others have stayed the same.

What has stayed the same? For 31 years, radiation therapy has remained a major component of the curative and palliative therapy of cancer and plays a major role in the management of many benign diseases. Patients with cancer are generally best managed by a combined modality approach that requires the participation of a well-informed, well-trained, and well-equipped radiation oncologist collaborating with a radiation oncology team. The radiation oncologist must be capable of taking a detailed medical history; performing a thorough and accurate physical examination of the patient; assessing and integrating the information from diagnostic imaging, from gross and microscopic pathology—incorporating a growing list of chemical and molecular markers that guide therapy and predict outcome—and from clinical chemistry; and formulating and implementing a treatment plan that is cognizant of the wishes of the patient and realistic in its goals. For this book, in particular, what has also stayed the same since 1987 is the vision and participation of Carlos A. Perez and Luther W. Brady, of Edward C. Halperin since 2004, and of David Wazer since 2008. We recognize that having such stability in the editorial team is exceptional in the history of textbook publishing and a blessing for the four of us. As we note below and in our acknowledgments, we remember and mourn those who contributed to previous editions of this book but are no longer with us: Ruth Aultman, Jonathan Pine, and Rupert Schmidt-Ullrich.

What has changed? There has been an explosion of knowledge concerning the molecular biology of cancer and tumor physiology. Concepts that were unknown in the 1980s are now considered fundamental building blocks of knowledge concerning cancer. As it concerns the technology of this specialty, when the first edition of this book was published, some radiation oncology residents were training, in part, on orthovoltage units; cobalt-60 machines remained in widespread use; simulation using diagnostic radiographs still vied with clinical setups of treatment fields using surface anatomy; and many radiation oncologists carried slide rules, protractors, right angle drafting triangles, and rulers to calculate and map radiation dose distributions. Now, elaborate linear accelerators with multileaf collimators, particle machines, intensity-modulated and/or image-guided radiation therapy, complex brachytherapy devices, dose painting, image fusion, metabolic imaging, and increasingly powerful computers that support the preceding list of technologies have become the norm in the developed world. (And, unfortunately, the paucity of even the most minimal radiation therapy services remains the norm in many parts of the economically less-developed world, and economic and racial disparities persist in cancer care and outcomes in the economically developed world….) In some diseases, the diagnostic and staging workup has changed profoundly in the past quarter of a century—for example, the role of staging laparotomy in Hodgkin disease. In other diseases, the role of radiotherapy in treatment has shifted dramatically, as demonstrated by the decline in the role or frequency of use of radiation therapy in the management of retinoblastoma and Wilms tumor, following balloon angioplasty and stenting for coronary artery disease, or for AIDS-associated malignancies, and the change in the use of radiation therapy for breast and prostate cancer.

The editors have striven to be cognizant of change by constantly adding and pruning chapters to document the current state of knowledge of cancer biology, medical radiation physics, dosimetry, cancer epidemiology, clinical radiation oncology, and radiation oncology economics, education, ethics, and policy. Particular attention in the fifth through seventh editions has been devoted to an attractive and useable design of the printed version of this book and the new electronic versions. We have taken care to have this book evolve with the times, and we have simultaneously striven to be true to the core mission of being “the book of record” for clinical care, providing the data that justify treatment recommendations as well as comprehensive illustrations and references in radiation oncology. We take this responsibility very seriously.

We have been gratified by the public reception of this book. Sales of the fifth edition rose dramatically compared to the fourth edition—an atypical pattern in the medical book business. It is, we like to believe, evidence that the pact wordlessly exchanged between the editors, the chapter authors, and our readers is being honored by all parties.

The editors sincerely hope that this seventh edition of *Principles and Practice of Radiation Oncology* will continue to advance understanding of the causes, prevention, and treatment of human cancer. We pray that this new edition will contribute to the cure of some malignancies, the amelioration of suffering for many patients and their families, the relief of pain, and the ultimate triumph of human knowledge over cancer.

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In Memoriam

Luther W. Brady, MD (1925–2018)

The founding co-editor of this book, Luther W. Brady, died as the seventh edition of *Principles and Practice of Radiation Oncology* was being printed. As we note in the Acknowledgments section, this book has been through so many editions that we, as co-editors, have now sadly experienced the deaths of four of our collaborators: Ruth Aultman, Jonathan W. Pine, Jr., Rupert Schmidt-Ullrich, and now Luther W. Brady.

Raised in North Carolina, Luther Brady arrived at George Washington University (GWU) as, in his own words, a "wet-behind-the-ears 16-year-old" to encounter the professors, the packed lecture halls, and "the salacious lectures." He would go on to earn three degrees from GWU (AA in 1944, BA in 1946, MD in 1948) and serve on its board of trustees.

Writing 72 hours after his death, it is impossible for us to do justice to his life and career and meet the demands of publishing this book on time. This will be rectified in the lengthy tributes that will follow in the next few months.

Dr. Brady received post-graduate training in radiology and radiation oncology at the U.S. Naval Hospital in Bethesda, Jefferson Medical College, and the Hospital of the University of Pennsylvania. Except for a year at Harvard and a brief time at Columbia University, his entire academic career was in Philadelphia, first at the University of Pennsylvania and then at Hahnemann University Hospital and Drexel University School of Medicine. He was named professor in 1963; in 1970, he was appointed chair of the Department of Radiation Oncology and Nuclear Medicine. In 1975, he was named the Hylda Cohn/American Cancer Society Professor of Clinical Oncology. Hahnemann established the Luther W. Brady Pavilion in 1980.

He was president of the American College of Radiation Oncology, American Radium Society, American Society for Therapeutic Radiology and Oncology, American Board of Radiology, Intersociety Council for Radiation Oncology, Radiological Society of North America, Society of Chairmen of Academic Radiology Departments, and Society of Chairmen of Academic Radiation

Oncology Departments. He was chair of the Radiation Therapy Oncology Group and of the radiation oncology committee for Accreditation Council for Graduate Medical Education.

Dr. Brady worked on behalf of the Philadelphia Museum of Art, chaired its executive committee, and was a member of the board of trustees. The museum established the Luther W. Brady Curatorship of Japanese Art. The Luther W. Brady Art Gallery at GWU was also created in his honor. He served on the board of directors of the Opera Company of Philadelphia, the Opera Company of New Mexico, the Santa Fe Opera Company, the Settlement Music School, and the Curtis Institute of Music.

In addition, Dr. Brady received multiple medals from universities and scholarly societies and honorary degrees, delivered many named lectures around the world, and was elected to honorary fellowships of many European scholarly societies.

His scholarly interests ranged from tumors of the eye and orbit to cancers of the breast, lung, and cervix to lymphoma. He had more than 600 publications to his name, was editor-in-chief of the *American Journal of Clinical Oncology,* and was a member of the editorial advisory boards of many other professional journals.

Dr. Brady was passionate about this book. He loved telling and retelling his "founding story" wherein, he claimed, he flipped a coin with Philip Rubin and thus decided who would become the founding editor of the *International Journal of Radiation • Oncology • Biology • Physics* and who would become the founding editor of this book. In the preparation of the fourth edition of this book, the representative of Lippincott Williams & Wilkins, J. Stuart Freeman, Jr., proposed the use of a specific thickness and type of paper for the pages. Dr. Brady strongly disagreed. One of us (ECH) gently suggested that after all, Mr. Freeman was in the publishing business and he probably knew what he was talking about when it came to paper. Mr. Freeman pressed his point. Dr. Brady responded in arched tones. "Don't tell me about paper, Stuart. I know paper. I am on the board of trustees of the Philadelphia Museum of Art and I know quality paper. I'll tell you the type of paper appropriate for our text and our illustrations."

Needless to say, when the dust settled, Dr. Brady got the kind of paper he wanted.

He was a gracious host and a cultured gentleman. We shall not see his like again.

May his memory be for a blessing.

Edward C. Halperin, MD, MA
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July 16, 2018

Acknowledgments

We are grateful for the scholarly, meticulous, and thorough work of the contributors to this volume. Through seven editions, this book has become the "book of record" for the specialty of radiation oncology. It has achieved that distinction through the hard work of the individual chapter authors.

The staff of Wolters Kluwer have professionally seen this work through from planning to distribution. We are in their debt.

Our fellow faculty members, residents, and medical students have supported our work, providing consistent intellectual stimulation, valuable suggestions, and materials that have contributed to this book. We are grateful to the many librarians of our respective institutions who have come to our aid in finding the necessary books and articles to support the preparation of this book. Rupert K. Schmidt-Ullrich, MD, of the Medical College of Virginia/Virginia Commonwealth University, served as co-editor of the fourth edition. A consummate physician–scientist, a man who held himself and others to very high standards, and a valued colleague, his positive contributions live on. Ruth Aultman faithfully served as secretary to Dr. Halperin for 21 years and diligently worked on the fourth through sixth editions. She died in 2012 and was working on the manuscript for Chapter 1 until shortly before her death. Jonathan Pine served as our publisher's supervising editor for the fifth and sixth editions of this book. Jonathan was an endearing gentleman, kind, and possessed of gentle sense-of-humor. The four of us did not know of his long-standing diagnosis of lymphoma until what was perceived by us as his unexpected death in 2013. An obituary in *The Baltimore Sun* quoted one of Mr. Pine's friends, who calls him the "perfect gentleman. He had manners you don't see anymore, and he also had his first job. He was a rarity for this generation." Special recognition is due to Vilma Bordonaro, Mary Lou Chin, and Chris Trimble, who diligently worked on the preparation of materials for this volume. Our families have patiently endured the loss of time and attention to other matters that occurs as a result of the demands of a project of this magnitude. To them, especially, we express our

gratitude and love.

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SECTION I

Overview and Basic Science of Radiation Oncology

CHAPTER 1

The Discipline of Radiation Oncology

Edward C. Halperin

SKETCHES OF SOME IMPORTANT HISTORICAL FIGURES IN THE DEVELOPMENT OF RADIATION ONCOLOGY

Wilhelm Conrad Röntgen (1845–1923)

On March 27, 1845, in Lennep, Germany, a son, Wilhelm Conrad, was born to Friedrich Conrad Röntgen and his wife, Charlotte Constanze (Fig. 1.1). Röntgen's father was a textile merchant. When Wilhelm was 3, the family moved from Prussia to Apeldoorn in the Netherlands, about 100 miles to the northwest, where Wilhelm's maternal grandparents lived. Wilhelm enrolled in the Utrecht Technical School in 1862. A fellow student caricatured a teacher on the fire screen of the schoolroom. The schoolmaster demanded the name of the unflattering artist, but Wilhelm refused to betray his classmate and was expelled. There was a risk that his education would come to an end after this episode. Fortunately, the Polytechnical School in Zurich, Switzerland, accepted students based on stiff entrance examinations. The black mark of expulsion was no impediment. Röntgen began classes in 1865 and received his diploma in mechanical engineering in 1868.[1–3]

Röntgen's considerable skill in designing and constructing precision instruments for measuring physical phenomena attracted the attention of Dr. August Kundt, a theoretical physicist. Röntgen became Kundt's assistant at the University of Zurich. When Kundt moved, in turn, to the University of Würzburg and then to the University of Strasbourg, Röntgen followed. In 1879, Röntgen struck out on his own as a professor at the University of Giessen.

In 1888, Röntgen accepted a professorship of theoretical physics at the University of Würzburg (Fig. 1.2). On November 8, 1895, Röntgen saw the effects of an unusual phenomenon while doing laboratory experiments. He presented his results to the president of the Physical Society at Würzberg on December 28, 1895[2–5] (Fig. 1.3).

There are many accounts of Röntgen's discovery. Among the multitude of reporters who rushed to interview Röntgen was H. J. W. Dam, an Englishman who was a correspondent for the Canadian *McClure's Magazine*. Dam had a letter of introduction but, like all other reporters, when he arrived in Würzberg, he was turned away. Dam, however, was persistent and wrote a letter in French to Röntgen insisting upon an interview. "You are very difficult, much more difficult than Berthelot, Pasteur, Dewar, and other men of science about whose discoveries I have written." Apparently taken by Dam's audacity and, perhaps, willing to have a sensible article written by a knowledgeable reporter, Röntgen granted Dam an exclusive interview.

Dam's lead story in the April 1896 *McClure's* is generally regarded as an accurate depiction.[6] Dam told his readers that "in all the history of scientific discovery there has never been, perhaps, so general, rapid, and dramatic an effect wrought on the scientific centers of Europe as has followed, in the past four weeks, upon an announcement made to the Wurzburg Physio-Medical Society, at their December meeting, by Professor William Konrad Röntgen, professor of physics at the Royal University of Wurzberg…. Röntgen's own report arrived, so cool, so business-like, and so truly scientific in character, that it left no doubt either of the truth or of the great importance of the preceding [newspaper] reports."[6]

> Dam, who was able to converse with Röntgen in English, French, and German, conducted an on-site interview in Röntgen's laboratories and had him describe the circumstances related to the discovery. Dam's charming description, excerpted here, gives an excellent insight into Röntgen the man and the nature of his scientific inquiry.
>
> "Now, Professor," said I, "will you tell me the history of the discovery?"
>
> "There is no history," he said. "I have been for a long time interested in the problems of the cathode rays from a vacuum tube as studied by Hertz and Lenard. I had followed theirs and other researches with great interest, and determined as soon as I had time to make some researches of my own. This time I found at the close of last October. I had been at work for some days when I discovered something new."
>
> "What was the date?"

“The eighth of November.”

“And what was the discovery?”

“I was working with a Crookes’ tube covered with a shield of black cardboard. A piece of barium platinocyanoide paper lay on the bench there. I had been passing a current through the tube and I noticed a peculiar black line across the paper.”

“What of that?”

“The effect was one which could only be produced, in ordinary parlance, by the passage of light. No light could come from the tube, because the shield which covered it was impervious to any light known, even that of the electric arc.”

“And what did you think?”

“I did not think; I investigated. I assumed that the effect must have come from the tube, since its character indicated that it could come from nowhere else. I tested it. In a few minutes there was no doubt about it. Rays were coming from the tube which had a luminescent effect on the paper. I tried it successfully at greater and greater distances, even at two metres. It seemed at first a new kind of invisible light. It was clearly something new, something unrecorded.”

“Is it light?”

“No.”

“Is it electricity?”

“Not in any known form.”

“What is it?”

“I don’t know. Having discovered the existence of a new kind of rays, I of course began to investigate what they would do. It soon appeared from the tests that the rays had penetrative power to a degree hitherto unknown.

> They penetrated paper, wood and cloth with ease, and the thickness of the substance made no perceptible difference within reasonable limits. The rays passed through all the metals tested with the facility varying, roughly speaking, with the density of the metal. These phenomena I have discussed carefully in my report to the Würzburg Society and you will find all the technical results therein stated. Since the rays had this great penetrative power, it seemed natural that they should penetrate flesh, and so it proved in photographing the hand I showed you."

A detailed discussion of the characteristics of his rays the professor considered unprofitable and unnecessary. He believes, though, that these mysterious radiations are not light, because their behavior is essentially different from that of light ways, even those light rays that are themselves invisible. The Röntgen rays cannot be reflected by reflecting surfaces, concentrated by lenses, or refracted or diffracted. They produce photographic action on a sensitive film, but their action is weak as yet, and herein lies the first important field of their development. The professor's exposures were comparatively long—an average of 15 minutes in easily penetrable media, and half an hour or more in photographing the bones of the hand. Concerning vacuum tubes, he said that he preferred the Hittorf, because it had the most perfect vacuum, the highest degree of air exhaustion being the consummation most desirable. In answer to the question, "What of the future?" he said:

> "I am not a prophet, and I am opposed to prophesying. I am pursuing my investigations, and as fast as my results are verified I shall make them public."
>
> "Do you think the rays can be so modified as to photograph the organs of the human body?"
>
> In answer he took up the photograph of the box of weights. "Here are already modifications," he said, indicating the various degrees of shadow produced by the aluminum, platinum, and brass weights, the brass hinges, and even the metallic stamped lettering on the cover of the box, which was faintly perceptible.
>
> "But, Professor Neusser has already announced that the photographing of the various organs is possible."

“We shall see what we shall see,” he said; “we have the start now; the developments will follow in time.”

“You know the apparatus for introducing the electric light into the stomach?

“Yes.”

“Do you think that this electric light will become a vacuum tube for photographing, from the stomach, any part of the abdomen or thorax?”

The idea of swallowing a Crookes tube, and sending a high frequency current down into one’s stomach, seemed to him exceedingly funny. “When I have done it, I will tell you,” he said, smiling, resolute in abiding by results.

“There is much to do, and I am busy, very busy,” he said in conclusion. He extended his hand in farewell, his eye already wandering toward his work in the inside room. And his visitor promptly left him; the words, “I am busy,” said in all sincerity, seeming to describe in a single phrase the essence of his character and the watchword of a very unusual man.[6]

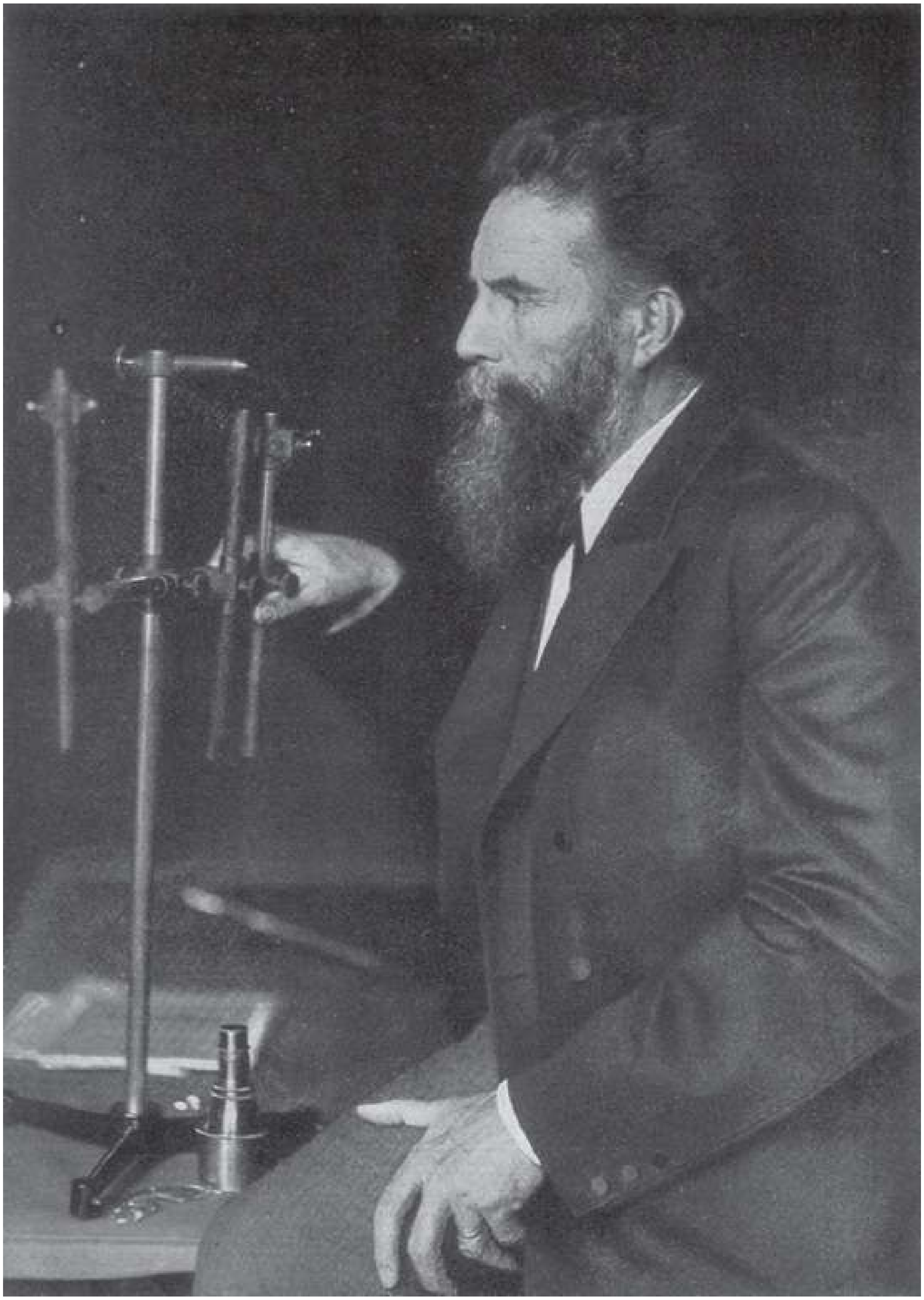

FIGURE 1.1. Wilhelm Conrad von Röntgen. He is shown in this photograph with physics instruments. (From Glasser O. *Wilhelm Conrad Röntgen and the early history of the Roentgen rays*. Springfield, IL: Charles C. Thomas, Publisher, Ltd., 1934, with permission.)

FIGURE 1.2. Photograph of the Physical Institute of the University of Würzburg from 1896. Professor Röntgen and his wife lived on the top floor. On the left side of the upper story can be seen the conservatory, of which Röntgen and his wife were particularly fond. (From Glasser O. *Dr. W.C. Röntgen*. Springfield: Charles C. Thomas, 1945, with permission.)

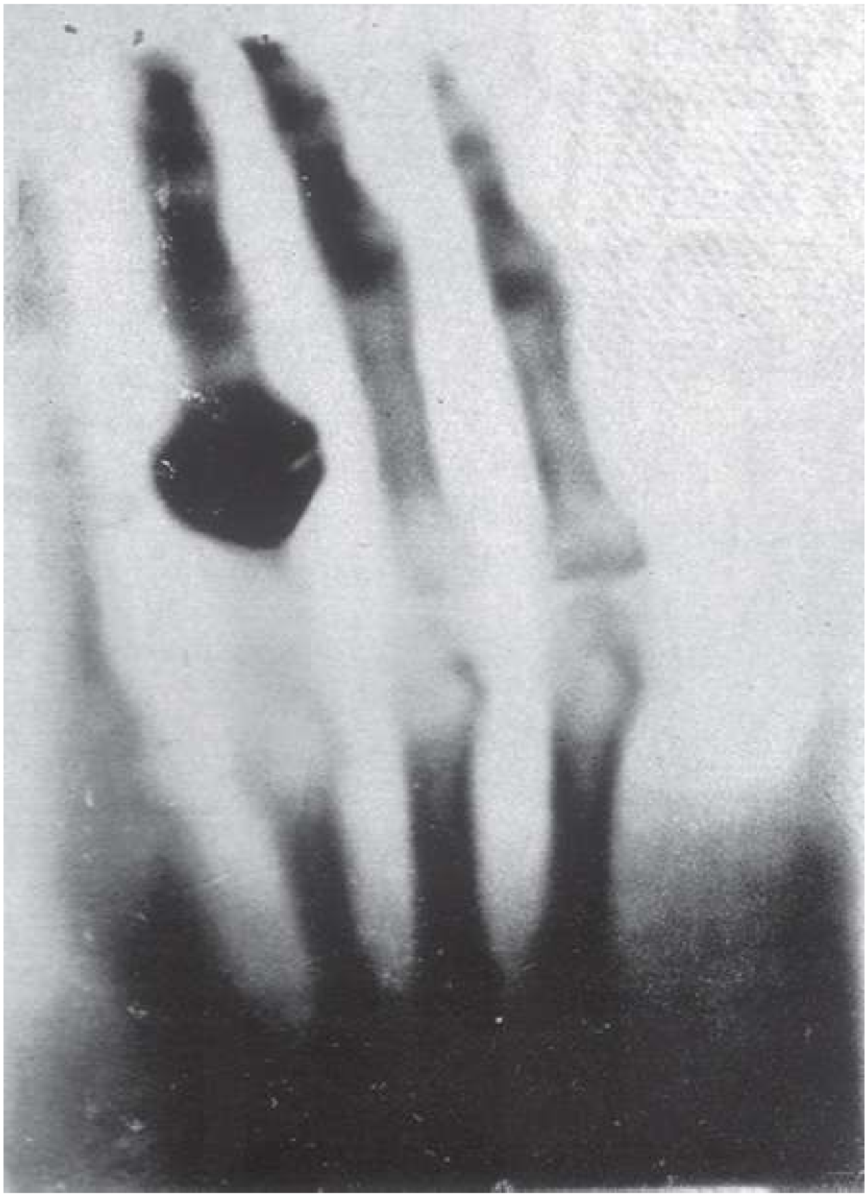

FIGURE 1.3. Röntgen made this image on December 22, 1895, and sent it to Vienna physicist F. Exner. (From Glasser O. *Dr. W.C. Röntgen*. Springfield: Charles C. Thomas, 1945, with permission.)

Kaiser Wilhelm II invited Röntgen to the imperial court at Potsdam in January 1896, shortly after the scientist had mailed out reprints to prominent physicists. Röntgen demonstrated his findings and was decorated with the Prussian Order of the Crown, Second Class. On January 23, he gave a lecture to the Würzburg Physical-Medical Society and was startled and overwhelmed by the cheers of the audience. At the end of the talk, Röntgen invited Albert von Kölliker, one of Germany's most distinguished anatomists, to come to the podium and have his hand x-rayed. When the audience saw the bones of his hand, it erupted in thunderous applause. This was one of Röntgen's last formal lectures on x-rays. He became flustered before large groups and, when lecturing to small groups of students, was generally regarded as lusterless and dull.

Röntgen received the Nobel Prize in Physics in 1901 from the Swedish king. He thanked him but gave no speech. He willed the prize money to the University of Würzburg.[1] In the presentation speech, the president of the Royal Swedish Academy of Sciences, C. T. Odhner, commented on the enormous potential of Röntgen's discovery for diagnosis and therapy:

> The Academy awarded the Nobel Prize in Physics to Wilhelm Conrad Röntgen, Professor in the University of Wurzburg, for the discovery with which his name is linked for all time: the discovery of the so-called Röntgen rays, or, as he himself called them, x-rays. These are, as we know, a new form of energy and have received the name "rays" on account of their property of propagating themselves in straight lines as light does. The actual constitution of this radiation of energy is still unknown. Several of its characteristic properties, however, have been discovered first by Röntgen himself and then by other physicists who have directed their research into this field. And there is no doubt that much success will be gained in physical science when this strange energy form is sufficiently investigated and its wide field has been thoroughly explored. Let us remind ourselves of one of the properties that has been found in Röntgen rays—the basis of the extensive use of x-rays in medical practice. Many bodies, just as they allow light to pass through them in varying degrees, behave likewise with x-rays but with the difference that some that are totally impenetrable to light can be penetrated easily by x-rays, whereas other bodies stop them. Thus, for example, metals are impenetrable to them; wood, leather, cardboard, and other materials are penetrable as are the muscular tissues of animal organisms. Now, when a foreign body impenetrable to x-rays (e.g., a bullet or a needle) has entered these tissues, its location can be determined by illuminating the appropriate part of the body with x-rays and taking a shadowgraph of it on a photographic plate, whereupon the impenetrable body is detected immediately. The importance of this for practical surgery and how many operations have been made possible and facilitated by it is well known to all. If we add that in many cases severe skin diseases (e.g., lupus) have been treated successfully with Röntgen rays, we can say at once that Röntgen's discovery already has brought so much benefit to mankind that to reward it with the Nobel Prize fulfills the intention of the testator to

a very high degree.[7] (Figs. 1.4 and 1.5).

Antoine Henri Becquerel (1852–1908)

Antoine Henri Becquerel was born in Paris in 1852 into a family of scientists. His father was a professor of applied physics who had conducted research on solar radiation and phosphorescence. His grandfather was the inventor of an electrolytic method of extracting metals from ores.

Becquerel's early scientific work concerned the plane polarization of light, phosphorescence, terrestrial magnetism, and the absorption of light by crystals. Becquerel first heard of Röntgen's discovery in January 1896 at a meeting of the French Academy of Science. He wondered if there was a connection between phosphorescence and x-rays. He had inherited, from his father, a supply of uranium salts, which phosphoresced upon exposure to light.

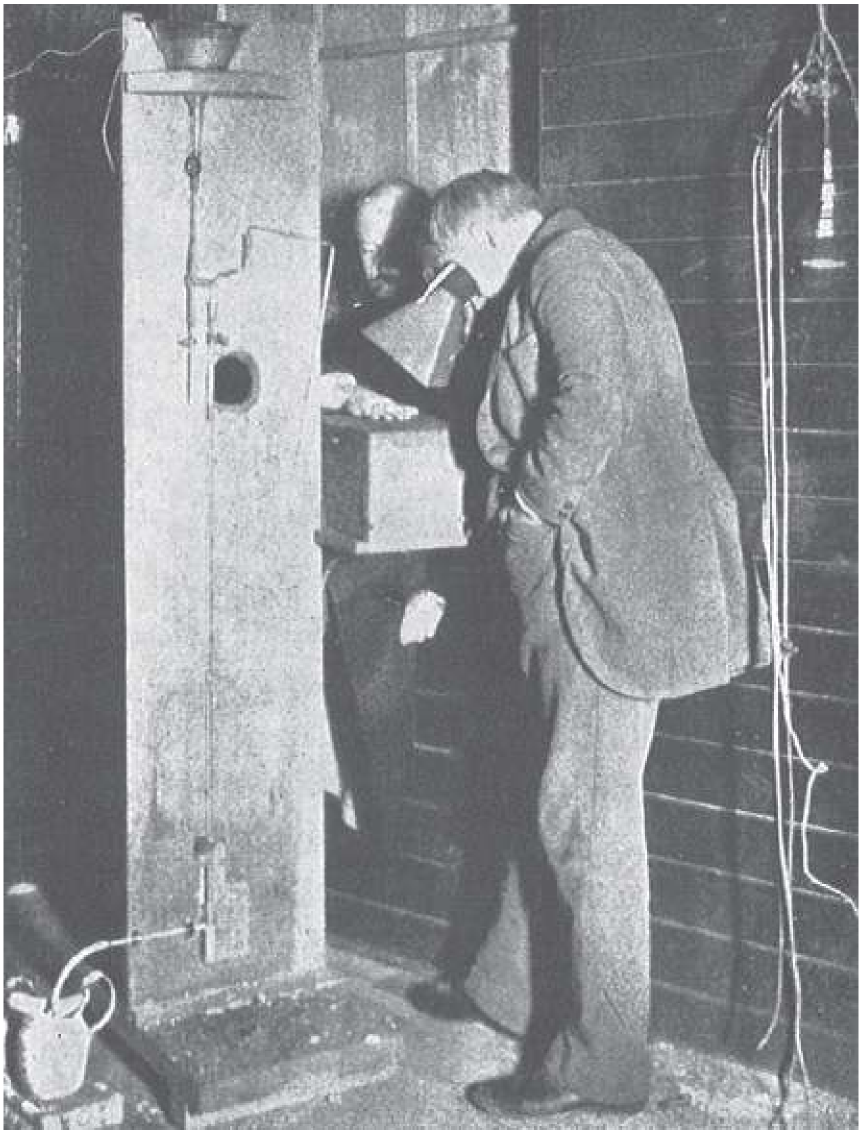

FIGURE 1.4. Thomas A. Edison experimenting with x-rays with, obviously, no radiation protection. (From Glasser O. *Dr. W.C. Röntgen*. Springfield: Charles C. Thomas, 1945, with permission.)

Becquerel thought that the phosphorescent uranium salts might absorb sunlight and, in turn, re-emit the energy as x-rays. He placed crystals of the uranium salts on top of photographic plates wrapped in opaque black paper. After placing the experimental setup in the sun, he developed the plates and saw an outline of the crystals. When he placed coins and other metal objects between the crystals and the plates, he could produce outlines of the shapes of the metal objects. These initial experiments seemed to confirm his suspicions.

When he encountered several overcast days in February 1896, Becquerel put his uranium crystals and photographic plates in a drawer. On March 1, he opened the drawer and developed the plates. It is not clear why he did this. Nonetheless, he saw a clear image of the crystals on the plates. He had demonstrated that the uranium crystals were emitting x-rays on their own and had discovered spontaneous radioactivity.

Becquerel subsequently showed that the radioactive emissions from uranium could ionize gases and be deflected by electric or magnetic fields.[8–10]

Half of the 1903 Nobel Prize in Physics was awarded to Becquerel. The other half was given to Pierre and Marie Curie.[11]

Marie Sklodowska Curie (1867–1934) and Pierre Curie (1859–1906)

Marya Sklodowska was born in Warsaw on November 7, 1867. The youngest of four sisters and a brother, she lived under Russian rule in partitioned Poland. At 17, she left home to work as a governess to the daughters of the supervisor of a large sugar beet factory northeast of Warsaw in order to save enough money to attend university. In 1891, Sklodowska enrolled at the Faculte des Sciences at the Sorbonne in Paris—one of just 23 women in a student body of about 1800. She completed degrees in mathematics and physics and in 1893 was hired by the Society for the Encouragement of National Industry to study the magnetic properties of steel. While in the process of securing additional laboratory space, she was introduced to Pierre Curie.

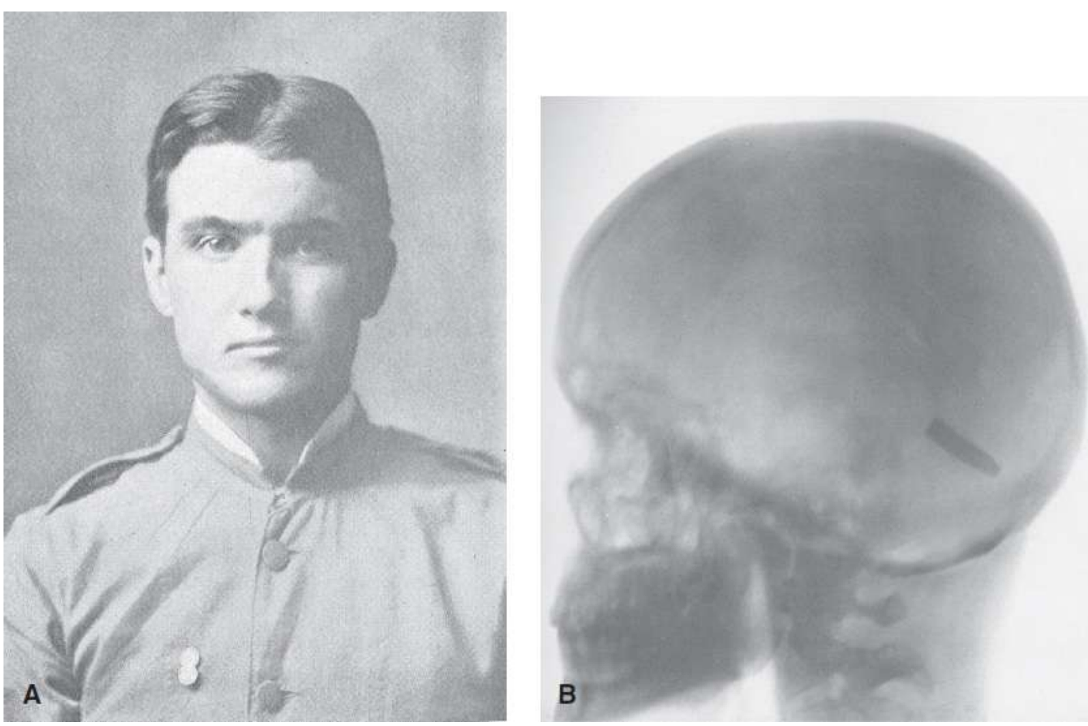

FIGURE 1.5. **A** and **B:** Private John Gretzer, Jr., Company D, First Nebraska

Volunteers, U.S. Army injury, wounded above his left eye at long range in combat at Mariboa, Philippines. Five months after the injury, he returned to duty in the military mail service. Diagnostic x-ray units were utilized by the U.S. Army Medical Department in the 1898 war with Spain and the Philippine insurrection—within 4 years of the discovery of the x-ray. (From *The use of the Roentgen ray by the Medical Department of the United States Army in the war with Spain (1898)*. Washington, DC: Government Printing Office, 1900.)

Curie was the son of a physician who had worked in the laboratory of Louis Pierre Gratiolet (1815–1865), who described the occipital visual pathways. Pierre Curie's doctoral thesis, "Magnetic Properties of Bodies at Diverse Temperatures," evaluated changes in magnetic properties of materials heated to high temperatures. He found that the magnetic properties of a substance change at a very specific temperature. This temperature is called the "Curie point" and is of great importance in studying plate tectonics, understanding extraterrestrial magnetic fields, and measuring the chemical contents of liquids. Curie also found that when crystals were pressed along their axis of symmetry, they produced an electric charge. This phenomenon is called "piezoelectricity," from the Greek word *piezin*, meaning "to squeeze," and is of importance in the operation of quartz watches, ink-jet printers, autofocus cameras, and medical ultrasound.

Marya Sklodowska (now using the French form of her first name, "Marie") and Pierre Curie wed on July 26, 1895.

For her doctoral thesis, Marie chose to investigate Becquerel's rays. She found that the intensity of the rays was affected neither by external conditions nor by any chemical process—they were an atomic property of the element. Marie observed that "it was obvious that a new science was in the course of development…. I coined the word *radioactivity.*"[12]

After confirming Becquerel's observations, Marie and Pierre Curie in 1898 published a paper entitled "Sur une substance fortement nouvelle radio-active, continue dans la pechblende on a new, strongly radio-active substance contained in pitchblende." The new radioactive substance was called polonium (named in honor of Poland). In late 1898, while working on polonium, they noticed another substance, chemically akin to barium and more radioactive than polonium. Demarçay found specific spectral characteristics of this new element, which was called radium (from the Latin word for "ray"). The Curies declined to patent their findings because, in Pierre's words, "it would be contrary to the scientific spirit." In 1903–1904, radium-226 began to be used in the treatment of patients with skin cancer and uterine cancer.[12] On June 25, 1903, Marie defended her thesis “Researches on Radioactive Substances” and became the first woman in France to receive a doctorate. Later that year, the Curies and Becquerel shared the Nobel Prize in Physics.

On April 19, 1905, Pierre Curie was killed while crossing the Rue Dauphine near the Seine—run down by a horse-drawn carriage carrying 13,000 pounds of military equipment. Marie returned to work and described the radioactive decay series of polonium. In 1911, she became the first person to win the Nobel Prize twice, this time in chemistry.

When France entered World War I, Marie Curie assembled hospital and mobile x-ray units for the care of the wounded. The mobile units were dubbed “petites Curies.”[12] In March 1912, a glass tube containing 20 mg of radium was declared the international radium standard after comparison with a similar standard prepared in Vienna. The radioactivity unit was called Curie and defined as the emanation in equilibrium with 1 g of radium. In 1975, the International Commission on Radiation Units and Measurements replaced the Curie with the Becquerel (1 Curie = 3.7×10^{10} Bq). Marie Curie died on July 4, 1934, from the consequences of radiation exposure.

Irene (1897–1956) and Frederic Joliot-Curie (1900–1958)

In 1924, Marie Curie interviewed Frederic Joliot for a position in her laboratory. Joliot had a recommendation from the famed physicist Paul Langevin (1872–1946). Marie Curie’s daughter Irene also worked in the laboratory. Romance blossomed and Frederic and Irene were married in 1926. The two worked together in the laboratory.[13] A reporter for *Time* magazine wrote:

> Husband and wife work like one person with two heads, four hands, 20 fingers. “We compare notes,” says M. Joliot, “and exchange our thoughts so constantly that we honestly don’t know which of us is the first to have an original idea. Don’t you agree, ma chere?”[13]

Toward the end of 1931, the Joliot-Curies were studying the effects of alpha-particle irradiation of elements such as boron and beryllium. These metals gave off secondary radiations more penetrating than the gamma rays of radium. Interposing substances containing hydrogen in the beam, such as paraffin or cellophane, increased the intensity of secondary radiation. The couple considered these secondary radiations to be high-energy x-rays that knocked out protons from the atomic nucleus of hydrogenated substances. In England, James Chadwick conducted similar experiments with superior equipment.

Remembering that Ernest Rutherford had predicted the probable existence of a nuclear chargeless particle, Chadwick correctly deduced that the secondary radiations were this chargeless particle, the neutron. Frederic Joliot-Curie admitted that he had not read Rutherford's Bakerian Lecture where he had predicted the existence of this particle and said the credit for the discovery ought go to Chadwick.

In 1934, Irene and Frederic Joliot-Curie, by bombarding aluminum targets with alpha particles, transformed a naturally stable element into radioactive phosphorus. Additional radioactive isotopes were produced by the irradiation of fluorine, sodium, and other metals. The induction of "artificial radioactivity" created the field of nuclear medicine—but Frederic always insisted that so-called artificial radioactivity was identical with natural radioactivity. In 1935, they learned that they had been awarded the Nobel Prize in Physics for their work. Husband and wife divided the Nobel Lecture between them Frederic predicted that researchers would find ways of exploiting progressive transmutations of elements by irradiation such that "veritable chemical chain reactions" would be produced—intimating the creation of self-sustaining nuclear fission chain reactions. In 1936, Irene Joliot-Curie was appointed by the Socialist President of France Léon Blum as undersecretary of state for scientific research.[12–14]

Frederic Joliot realized the possibility of atomic release of large amounts of energy and the potential of this for warfare. He pursued experiments designed to establish that a sustained chain reaction could be produced through nuclear fission leading to the production of vast amounts of energy.

Joliot may well have been the first to achieve a sustained nuclear chain reaction had not the German invasion of France and the capture of Paris intervened. Frederic Joliot-Curie and his scientific collaborators spirited their stock of heavy water and uranium out of France just ahead of the Germans. The Joliot-Curies hid their scientific papers on nuclear fission in a vault. Frederic joined the French Resistance, whereas Irene, her health in decline, moved to the French Alps with the couple's daughter. Eventually, mother and daughter crossed over to Switzerland in 1944. One wonders what would have been different in the history of science if the couple had taken the opportunity to escape to England in 1940 and continue their work. They would, perhaps, have played an even greater role in the development of atomic energy.[13]

The work of Joliot-Curie was invoked in the famous letter Albert Einstein signed sent to President Franklin D. Roosevelt on August 2, 1939. The letter, written by the Hungarian American physicist Leo Szilard, was designed to spur

American action to assure that the United States would acquire nuclear weapons before Nazi Germany.

Einstein wrote:

> Some recent work by E. Fermi and L. Szilard, which has been communicated to me in manuscript, leads me to expect that the element uranium may be turned into a new and important source of energy in the immediate future. Certain aspects of the situation which has arisen seem to call for watchfulness and if necessary, quick action on the part of the Administration. I believe therefore that it is my duty to bring to your attention the following facts and recommendations.
>
> In the course of the last four months it has been made probable through the work of Joliot in France as well as Fermi and Szilard in America—that it may be possible to set up a nuclear chain reaction in a large mass of uranium, by which vast amounts of power and large quantities of new radium-like elements would be generated. Now it appears almost certain that this could be achieved in the immediate future.
>
> This new phenomenon would also lead to the construction of bombs, and it is conceivable—though much less certain—that extremely powerful bombs of this type may thus be constructed. A single bomb of this type, carried by boat and exploded in a port, might very well destroy the whole port together with some of the surrounding territory.
>
> In view of this situation you may think it desirable to have some permanent contact maintained between the Administration and the group of physicists working on chain reactions in America.
>
> I understand that Germany has actually stopped the sale of uranium from the Czechoslovakian mines which she has taken over. That she should have taken such early action might perhaps be understood on the ground that the son of the German Under-Secretary of State, von Weizsacker, is attached to the Kaiser-Wilhelm Institute in Berlin, where some of the American work on uranium is now being repeated.[13]

After the war, France created a civilian atomic energy authority. Frederic was appointed head of the Commisariate de l”Energie Atomique (CEA), the French

Atomic Energy Commission. In 1946, he was promoted to Commandeur de la Legion d'Honneur and was awarded the Croix de Guerre for heroism during the Nazi occupation of France. A member of the French Communist Party, Joliot was dismissed as high commissioner for atomic energy in 1950 because of his political views.

Irene Joliot-Curie died of acute leukemia in 1956. Frederic Joliot-Curie died in 1958.[13,14]

James Ewing (1866–1943)

For much of the 20th century, if a person was selected by the editors of *Time* magazine to appear on the weekly newsmagazine's cover, it was a mark of distinction. Individuals on the cover of the magazine were "newsmakers": important, notable, and worthy of your attention. The January 12, 1931, issue of *Time* portrayed a dignified pathologist in a drawing. "Cancer Man Ewing": The "weapon" referred to dedicated cancer institutions. "He wants six $10,000,000 weapons" (Fig. 1.6).

James Ewing, born in Pittsburgh in 1866, was the son of Thomas Ewing who began his career as a teacher and undertook the study of law at age 36. He became a judge in the Court of Common Pleas in Pittsburgh, became an elder of the Presbyterian Church, and was viewed as a leading local citizen. Ewing's mother, Julia, graduated in the first class of Mt. Holyoke College and became a teacher.[15,16]

Ewing's personal life was marked by a series of illnesses and tragedies. He developed osteomyelitis of the femur when he was 14 and was bedridden for two years, his wife died after <3 years of marriage from toxemia of pregnancy, he suffered from tic douloureux and was operated on by Harvey Cushing, a urinary calculus developed later in life, and he ultimately died of bladder cancer. It was said of him that adversity, suffering, disappointment, and sorrow left their mark on him not in the form of bitterness or disillusionment but in increasing sensibleness for the misfortune of others. "His sympathy and kindliness became almost legendary during his lifetime and the very legend of his benignity impressed itself on his character…That this benignity was not of the mere sentimental variety was shown by his intolerance of sham, hypocrisy, and mental laziness, which led him to be an unsparing critic."

FIGURE 1.6. James Ewing was on the cover of *Time* on January 12, 1951.

Ewing received his undergraduate education at Amherst College and was in the first class of the College of Physicians and Surgeons of New York that graduated after the institution had become affiliated with Columbia University.[15,16]

In 1899, Ewing was appointed the first professor of pathology at Cornell Medical College and held that position for 33 years. Ewing began to focus his interest on cancer when Mrs. Collis P. Huntington (c1851–1924) established the C.P. Huntington Fund for Cancer Research in 1902. The thrice-married Mrs.

Huntington was the heiress to a railway and industrial fortune and was said, by some, to be “the richest woman in America.” Income from the fund was expended for cancer research at Cornell Medical College under Ewing’s direction. Ewing’s early studies focused on lymphosarcoma of dogs. (Many other US institutions benefited from the philanthropic support of C.P. Huntington and his wife including the Collis P. Huntington Memorial Hospital in Boston, the site of important early work in radiation therapy. After the closure of this hospital, some of its equipment was moved to the Massachusetts General Hospital.)

In 1919, after a decade of work, Ewing published the first of four editions of *Neoplastic Diseases*, the definitive reference of its time on tumor pathology. Unlike the multiauthored oncology books of today, including the one you are holding in your hands, *Neoplastic Diseases* was solely Ewing’s work with >450 illustrations and 49 chapters (Box 1.1). He wrote in the preface to the first edition:

Box 1.1

A Definition of Cancer

For many years, it has been the habit of the author to ask medical students beginning a clinical elective on the radiation oncology service or new radiation oncology residents beginning their training, “How do you define the word cancer?” For someone beginning the study of cancer, this would seem to be the most fundamental question to answer at the outset. The question is most often met by a blank stare. Faced with the likelihood that, like these trainees, many of my readers have not grappled with this question, it seems worthy of some consideration in these pages.

James Ewing, who is profiled elsewhere in this chapter, spends many pages in the four editions of his definitive textbook, *Neoplastic Diseases*, trying to present a succinct definition. He settles on “a tumor is an autonomous new growth of tissue” while citing the attempts of others. He writes “Ziegler defined a tumor as a new growth of tissue which apparently originates and grows spontaneously, possesses an atypical structure, does not subserve the uses of the organism, and reaches no definite termination of its growth…. Adami accepts White’s descriptive definition: ‘A tumor proper is a mass of cells, tissues or organs resembling those normally present, but arranged atypically. It grows at the expense of the organism without at the same time subservient any useful function.’”[17]

The National Cancer Institute (NCI) Dictionary of Cancer Terms offers the following definition: Cancer is “a term for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems.”

If you were to line up a series of dictionaries and pathology textbooks on your desk, a turn each to the proffered definition of cancer, you will find phrases such as “an uncontrolled division of abnormal cells…,” “a malignant tumor of potentially unlimited growth that expands locally by invasion and systemically by metastasis…,” and “an abnormal growth of cells which tend to proliferate in an uncontrolled way and, in some cases, to metastasize (spread)."

No matter what definition what chooses, there will always be exceptions. The best is the enemy of good, as Voltaire reminded us, and the lack of a perfect definition should not dissuade us from finding a good, working, reasonable definition. Here is the one the author recommends:

Cancer is a heritable disease of abnormal cell proliferation. In their abnormal cell proliferation the cells do not respect the usual constraints of space and time. Cancer is characterized by invasion and metastases.

Let's unpack the definition and look at its components.

Heritable: cancerous behavior is passed from mother to daughter cells;

Abnormal cell proliferation: the fundamental disease-causing aspect of cancer is abnormal cell proliferation.

Cells do not respect the usual constraints of space and time: Normal cell growth is constrained. If you cut yourself then fibroblasts being to proliferation to heal the wound. They grow and grow and then a cellular switch turns the grown off (except in keloid formation). Similarly, in embryonic development our cells proliferate to grow organs, at some point, however, the growth stops. Cancer cells don't stop growing when they bump up against adjacent cells (contact inhibition) or according to some internal time clock. Their growth is not constrained.

Invasive: As Ewing wrote "growth is infiltrative, single cells or cell groups pushing their way through and destroying adjacent tissues";

Metastases: Cancers can send forth colonizing cells via the blood, lymph, cerebrospinal fluid, or in the pleural or peritoneal spaces which can establish themselves and grow.

> Up to a very recent time it has been the prevailing impression that tumors fall into a limited number of grand classes in which the forms occurring in the several organs are so nearly related as to be virtually identical. Hence the practical physician or surgeon has been content without regard to the organ involved, and on this theory to treat the members of each class alike…I believe that this point of view has greatly retarded the progress of the knowledge of tumors, and it has been the writer's effort to combat such a conception, so far as present knowledge permits.[17]

In 1920, Ewing reported to the New York Pathological Society that he had observed a malignant tumor of the bone most frequently arising in teenagers and "composed of broad sheets of small polyhedral cells with pale cytoplasm, small hyperchromatic nuclei, well-defined cell borders, and complete absence of intercellular material." He considered the tumor to be an "endothelioma of bone" arising from blood vessels. In a second report, he called the tumor an "endothelial myeloma." Ewing commented on the tumor's marked radiosensitivity, its tendency to invade soft tissues, and its ability to metastasize to lymph nodes.[18,19]

Ewing was quick to recognize the potential of radiation therapy for cancer treatment. He called it "the first rational treatment of cancer ever devised."[20] Ewing revisited radiation therapy many times in his publications:

> "From the most unexpected source, experimental physics, a new and powerful weapon has been brought into play."[21,22]

> "Radiation therapy, by demanding a detailed knowledge of the symptoms, clinical course and pathology of tumors, has introduced a new era in the study of cancer."[21]

> "Cancer research has entered a…fruitful era of therapeutics and more intelligent descriptive study…The developments of radiotherapy have opened a new biology of tumors, have stimulated new lines of research and suggested new concepts…many new facts and principles of tumor growth have been brought to light."[22,23]

Ewing conducted experimental work on cancer, vigorously worked to secure the funding for the establishment of New York's Memorial Hospital for Cancer and Allied Diseases (now called Memorial Sloan Kettering Cancer Center), investigated the role of radium in the treatment of cancer and worked to establish the production of radium in the United States, wrote four editions of the *Neoplastic Diseases*, and helped found the American Society for the Control of Cancer (now called the American Cancer Society) in 1913 and served on the organization's governing board for more than 30 years.[24]

Ewing viewed an organized war on cancer was a societal imperative and that success would be slow and incremental (Fig. 1.6):

> It is a growing conviction that to know cancer in man, one must study the disease most carefully in the human subject. Personally, I do not look for any startling advances or sensational discoveries, since it is much more likely that a steady reduction in the mortality from cancer will come chiefly from a large number of separate factors, of which the most significant appear to be increased control of the conditions leading to cancer, more