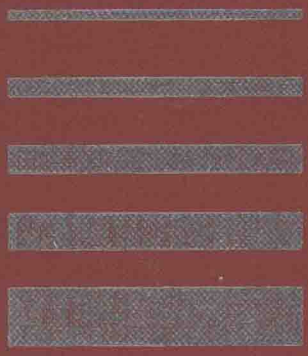

MOSS' RADIATION ONCOLOGY

Rationale, Technique, Results

Seventh Edition

James D. Cox

MOSS' RADIATION ONCOLOGY

Rationale, Technique, Results

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To the students whose inquiries have led us to greater understanding and to the teachers whose efforts have led us to better care for our patients.

Preface

Radiation oncology plays an essential and often pivotal role in the care of patients with cancer. Its role has been more clearly defined and expanded—as curative treatment for many patients with malignant tumors, as integrated therapy with resection and cytotoxic drugs and hormones, as a means to palliate those for whom curative treatment is not yet available. An impressive amount of new information has been published in the last few years. In preparation of this edition, efforts have been made to incorporate the new data into the framework of previous editions. To that end, all chapters have been revised extensively, many have been entirely rewritten, and new chapters have been added. Discussions of effects of ionizing radiations on normal tissues have been preserved and expanded. Large bodies of data have been synthesized and carefully documented to permit both a rapid survey of a subject, if necessary, and reference to the original manuscripts as desired. Emphasis has been placed, as in all previous editions, on the clinical care of patients as practiced by the radiation oncologist. The conceptual framework for the use of radiation therapy has been emphasized, and techniques have been outlined broadly, with no intention of suggesting there is a single solution to a specific clinical problem. Each author has been allowed to present his or her own views without regard to treatment philosophies represented in prior editions.

Many individuals have contributed to this effort, beyond those who are authors of chapters. Our associates and families have borne the consequences to our commitment to this endeavor. Our colleagues have provided critique, advice, and support. Most of all, we acknowledge the assistance of Evelyn B. Heinze in developing the manuscript; it would not have been possible to complete it in a timely manner without her contribution.

James D. Cox, M.D.
William T. Moss, M.D.

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CHAPTER 1

Physical and Biologic Basis of Radiation Therapy

Eric J. Hall
James D. Cox

HISTORICAL BACKGROUND

Radiation has been an ever-present ingredient in the evolution of life on earth. It is not something new, invented by the ingenuity of man in the technologic age; it has always been there. What *is* new, what is manmade, is the *extra* radiation to which we are subjected, largely for medical purposes, but also from journeys in high-flying jet aircraft and from the nuclear reactors that are used to generate electrical power.

X-rays were discovered in 1895 by the German physicist, Wilhelm Conrad Roentgen. He found that "this new kind of ray" could blacken photographic film sealed in a container and stored in a drawer and could also pass through materials opaque to light, including cardboard and wood. During a public demonstration of the production of x-rays, Roentgen asked his colleague, Herr Kölliker, to put his hand in front of the x-ray machine and, with a sheet of photographic film, he made the first radiograph displaying the bony structure of the hand. Roentgen was thus the father of diagnostic radiology, as well as of radiation physics. There is some controversy about who was the first to use x-rays therapeutically. In 1897 Professor Freund demonstrated before the Vienna Medical Society the disappearance of a hairy mole by the use of x-rays, and by the turn of the century x-rays had been used in Europe and America in primitive therapeutic applications.

Parallel to the discovery of x-rays, Becquerel discovered radioactivity in 1898. Three years later, he performed what is arguably the first radiobiologic experiment when he inadvertently left a container with 200 mg of radium in his vest pocket for 6 hours. He subsequently described the erythema of the skin that became evident in 2 weeks, and quite unexpectedly, the ulceration that developed and required several weeks to heal.

During the early 1900s, radiobiologic experiments were conducted with simple biologic systems in parallel with the development of radiation therapy. One of the most well-known results, still cited today, was the so-called law of Bergonié and Tribondeau, which states that radiosensitivity is highest in tissues with the highest mitotic index and lowest in differentiated tissues. From 1912 to 1940, a number of investigators, first in Germany and later in the United Kingdom, demonstrated the dependence of radiation response on oxygen. Using seedlings of *Vicia faba,* the magnitude of the oxygen effect was determined and the possible implications for radiation therapy discussed.

In Paris in the 1920s and 1930s famous experiments were performed in which the testes of rams were irradiated with x-rays. It proved to be impossible to sterilize the animals in a single dose without a severe reaction to the skin of the scrotum, whereas if the dose was fractionated over a period of time, sterilization could be achieved with little apparent skin damage. It was argued that the testes were a model for the rapidly growing tumor, while the skin represented a normal tissue response. On this basis, fractionation was introduced into clinical radiation therapy.

Brachytherapy underwent a similar conceptual evolution following its first use in the early years of this century. As fractionation was recognized to be advantageous in exter-

nal irradiation, protraction in brachytherapy, i.e., using low-activity sources for longer periods of time, was thought to improve the therapeutic ratio although radiobiologic studies of dose-rate effects were still decades away. This became the hallmark of the "Paris" approach to intrauterine and intravaginal radium therapy for cancer of the cervix. In Manchester, England, optimal arrangements of radium sources were sought to achieve a consistent dose rate and a more nearly homogeneous dose distribution through the tumor-bearing volume while sparing surrounding normal structures; this led to a more systematic application of the Paris concepts. In more recent times, afterloading systems have been developed in brachytherapy that employ the use of nonradioactive applicators, so that the radioactive sources are introduced only after the desired relationships of sources are assured; the afterloading approach reduces radiation exposure to professional personnel.

Large quantities of radium were gathered in some centers to produce a telecurietherapy unit, i.e., one that would permit the treatment of patients with gamma rays at a distance, in contrast to the placement of encapsulated radium in body cavities or directly into tumors (brachycurietherapy). Clinical experience with these units suggested advantages of high-energy radiations over the widely available 200 kVp x-ray generators. Between 1930 and 1950, technical advances permitted the development of much higher energy x-ray generators. In the 1950s, ^{60}Co teletherapy units became widely available, and the first generation of medical linear accelerators was developed.

In the wake of World War II and the use of atomic weapons on Hiroshima and Nagasaki, research in radiobiology developed rapidly. Significant milestones include the development of techniques to culture single mammalian cells in vitro in 1956 and to determine survival curves in vivo in 1959. These developments ushered in a greatly enhanced effort in radiation biology to understand conventional radiation therapy and suggested new horizons for improvements in treatment. In the national laboratories on both sides of the Atlantic, radiation biology studies not related to radiation therapy were at the same time developing, involving basic studies of mutagenesis and carcinogenesis.

PHYSICAL BASIS

Types of Radiations

Radiations of concern in this book are those with the capacity to produce ionizations and excitations during the absorption of energy in biologic material. The raising of an electron in an atom or molecule to a higher energy level, without the actual ejection of that electron from the atom or molecule, is called *excitation.* If the radiation has sufficient energy to eject one or more orbital electrons from the atom or molecule, this process is referred to as *ionization,* and the radiation is said to be *ionizing radiation.* The important characteristic of ionizing radiation is the localized release of large amounts of energy. The energy dissipated by an ionizing event is approximately 33 eV, which is more than enough to break a strong chemical bond; e.g., the energy associated with a carbon-carbon bond is 4.9 eV. Ionizing radiations produce substantial biologic effects for the relatively small, total amounts of energy involved, because the energy is released locally in "packets" large enough to break chemical bonds and initiate the chain of events that leads ultimately to a biologic effect.

Electromagnetic Radiation

Electromagnetic radiations (x-rays and gamma rays), are *indirectly* ionizing. They do not themselves produce chemical and biologic damage, but when absorbed in the medium through which they pass, they give up their energy to produce fast-moving electrons by either the Compton, photoelectric, or pair production processes (Fig. 1-1). X-rays and gamma rays are forms of electromagnetic radiation that do not differ in nature or properties; the designation *x* or *gamma* reflects simply the way in which they are produced. X-rays are produced extranuclearly, which means that they are generated in an electric device that accelerates electrons to high energy and then stops them abruptly in a target, made usually of tungsten or gold. Part of the kinetic energy, or energy of motion of the electrons, is converted into photons of x-rays.

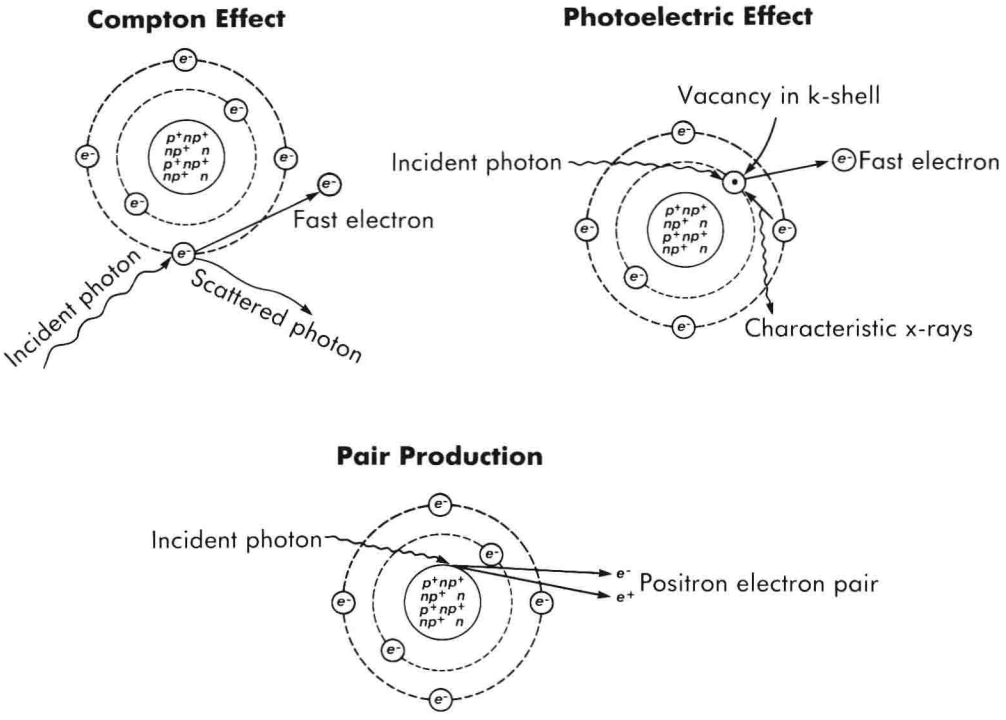

Fig. 1-1. The first step in the absorption of a photon of x-rays or gamma rays is the conversion of the energy of the photon into kinetic energy of an electron, or electron-positron pair. At higher energies, when the energy of the incident photon greatly exceeds the binding energy of the planetary electrons in the atoms of the absorber, the Compton process dominates. The photon interacts with the electron in a classic "billiard-ball" collision. Part of the photon energy is given to the electron as kinetic energy, while the photon is deflected and has reduced energy.

At lower energies, when the binding energy of the planetary electrons of the atoms of the absorber is not small compared with the photon energy, the photoelectric effect is most important. The photon disappears completely as it interacts with a bound electron. The electron is ejected with kinetic energy equal to the photon energy, less the energy required to overcome the electron bond. The vacancy caused by the removal of the electron must be filled by an electron dropping from an outer orbit, giving rise to a photon of characteristic radiation.

At sufficiently high photon energies, the photon may interact with the powerful nuclear forces to produce an electron-positron pair. The first 1.02 MeV of photon energy is utilized to create the rest mass of the pair, and the remainder is distributed equally between them as kinetic energy.

Gamma rays, on the other hand, are produced intranuclearly, i.e., they are emitted by radioactive isotopes; they represent excess energy that is given off as the unstable nucleus breaks up and decays in its efforts to reach a stable form.

Particulate Radiation

Other forms of radiation used experimentally and that are used or contemplated for radiation therapy include electrons, protons, alpha particles, neutrons, negative pi-mesons, and high-energy heavy ions.

Electrons are light, negatively charged particles that can be accelerated to high energy and to a speed close to that of light, by means of an electrical device such as a betatron or linear accelerator.

Protons are positively charged particles and are relatively massive, having a mass

nearly 2000 times greater than an electron. They require more complex and expensive equipment to accelerate them to useful energies. For example, 160 MeV protons have a range of about 12 cm in tissue.

Alpha particles are nuclei of helium atoms, each consisting of two protons and two neutrons in close association. They have a net positive charge, and therefore can be accelerated in large electrical devices similar to those used for protons. Alpha particles are also emitted during the decay of some radioactive isotopes.

Neutrons are particles having a mass similar to that of protons, but they carry no electrical charge. Because they are electrically neutral, they cannot be accelerated in an electrical device, but are produced when a charged particle, such as a deuteron or proton, is accelerated to high energy and then made to impinge on a suitable target material. Neutrons are also emitted as a byproduct when heavy radioactive atoms undergo fission, i.e., split up to form two smaller atoms. Neutrons are indirectly ionizing, since the first step in their absorption is for them to collide with nuclei of the atoms of the absorbing material and produce recoil protons, alpha particles, or heavier nuclear fragments. It is these charged particles that are responsible for the biologic effects.

Negative pi-mesons are negatively charged particles with a mass 273 times larger than the electron. They are produced by a complex process that necessitates a huge linear accelerator or synchrocyclotron capable of accelerating protons to energies of 400 to 800 MeV. When pi-mesons are absorbed in biologic material, they behave like overweight electrons as long as they are relativistic, i.e., as long as their velocity is close to that of light. However, when they slow down, they spiral down the energy levels of an absorbing atom and are finally absorbed by the nucleus of that atom, which then explodes to produce a number of fragments consisting of neutrons, alpha particles, and larger nuclear fragments.

Heavy ions are nuclei of elements such as nitrogen, carbon, neon, argon, or silicon that are positively charged, since some, or all, of their planetary electrons have been stripped from them. To be useful, they must be accelerated to energies of thousands of millions of volts and can therefore be produced in only a very limited number of laboratories in the world.

Production of Radiation for Therapeutic Applications

When x-rays or gamma rays enter biologic material, energy is converted into chemical damage and heat. At the energy levels of most x-ray and gamma-ray sources currently in use, the primary events are the interactions of photons with electrons in the outer shells, resulting in scattering of both the photons and the electrons (Compton scattering). With higher energy photons, scatter of secondary electrons is more in the forward direction, i.e., in the direction of the primary beam. It takes some distance for the interactions to summate and reach a maximum, after which the energy of the beam dissipates by a constant fraction per unit depth. Fig. 1-2 compares depth-dose characteristics of radiation beams commonly used in radiation therapy. The insert in this figure demonstrates the physical basis for skin sparing; the maximum dose occurs below the skin surface, unlike conventional x-rays.

The most commonly used sources for external irradiation are listed in Table 1-1. Although it is not readily apparent, there is a great deal of overlap among the teletherapy sources. For example, there is relatively little difference in depth doses between the gamma rays from ^{60}Co and 2 to 6 MV x-rays. The edge of the beam produced by a linear accelerator is much sharper than that from cobalt units, which may be an important factor when irradiating close to critical structures, such as the lens of the eye.

The sources most widely employed for intracavitary or interstitial therapy are listed in Table 1-2. Again, the various brachytherapy sources have overlapping capabilities, but some have specific advantages. For example, ^{192}Ir is the only isotope listed that has been widely used satisfactorily with an afterloading technique for interstitial therapy. Radium and cesium can be used in afterloading intracavitary applicators. Gold and iodine can be used for permanent interstitial implants.

When utilized appropriately and meticulously, both teletherapy units and brachy-