Radiation Biology and Medicine Therapeutic radiation is ionizing; it damages any tissue in its path. The selectivity of radiation for causing cancer cell death may be due to defects in a cancer cell's ability to repair sublethal DNA and other damage. Ionizing radiation causes breaks in DNA and generates free radicals from cell water that may damage cell membranes, proteins, and organelles. Radiation damage is augmented by oxygen; hypoxic cells are more resistant. Augmentation of oxygen presence is one basis for radiation sensitization. Sulfhydryl compounds interfere with free radical generation and may act as radiation protectors. X-rays and gamma rays are the forms of ionizing radiation most commonly used to treat cancer. They are both electromagnetic, nonparticulate waves that cause the ejection of an orbital electron when absorbed. This orbital electron ejection is called *ionization*. X-rays are generated by linear accelerators; gamma rays are generated from decay of atomic nuclei in radioisotopes such as cobalt and radium. These waves behave biologically as packets of energy, called *photons*. Particulate ionizing radiation using protons has also become available. Most radiation-induced cell damage is due to the formation of hydroxyl radicals from tissue water:

$$\text{Ionizing radiation} + H_2O \rightarrow H_2O^+ + e^-$$
$$H_2O^+ + H_2O \rightarrow H_3O^+ + OH^\bullet$$
$$OH^\bullet \rightarrow \text{cell damage}$$

Radiation is quantitated based on the amount of radiation absorbed by the tumor in the patient; it is not based on the amount of radiation generated by the machine. The International System (SI) unit for radiation absorbed is the Gray (Gy): 1 Gy refers to 1 J/kg of tissue; 1 Gy equals 100 centigrays (cGy) of absorbed dose. A historically used unit appearing in the oncology literature, the *rad* (*r*adiation *a*bsorbed *d*ose), is defined as 100 ergs of energy absorbed per gram of tissue and is equivalent to 1 cGy. Radiation dosage is defined by the energy absorbed per mass of tissue. Radiation dose is measured by placing detectors at the body surface or based on radiating phantoms that resemble human form and substance, containing internal detectors. The features that make a particular cell more sensitive or more resistant to the biologic effects of radiation are not completely defined and critically involve DNA repair proteins that, in their physiologic role, protect against environmentally related DNA damage.

Localized Radiation Therapy Radiation effect is influenced by three determinants: total absorbed dose, number of fractions, and time of treatment. A frequent error is to omit the number of fractions and the duration of treatment. This is analogous to saying that a runner completed a race in 20 s; without knowing how far he or she ran, the result is difficult to interpret. The time could be very good for a 200-m race or very poor for a 100-m race. Thus, a typical course of radiation therapy should be described as 4500 cGy delivered to a particular target (e.g., mediastinum) over 5 weeks in 180-cGy fractions. Most curative radiation treatment programs are delivered once a day, 5 days a week, in 150- to 200-cGy fractions.

A number of parameters influence the damage done to tissue (normal and tumor) by radiation. Hypoxic cells are relatively resistant. Nondividing cells are more resistant than dividing cells, and this is one rationale for delivering radiation in repeated fractions, to ultimately expose a larger number of tumor cells that have entered the division cycle. In addition to these biologic parameters, physical parameters of the radiation are also crucial. The energy of the radiation determines its ability to penetrate tissue. Low-energy orthovoltage beams (150–400 kV) scatter when they strike the body, much like light diffuses when it strikes particles in the air. Such beams result in more damage to adjacent normal tissues and less radiation delivered to the tumor. Megavoltage radiation (>1 MeV) has very low lateral scatter; this produces a skin-sparing effect, more homogeneous distribution of the radiation energy, and greater deposit of the energy in the tumor, or *target volume*. The tissues that the beam passes through to get to the tumor are called the *transit volume*. The maximum dose in the target volume is often the cause of complications to tissues in the transit volume, and the minimum dose in the target volume influences the likelihood of tumor recurrence. Dose homogeneity in the target volume is the goal. Computational approaches and delivery of many beams to converge on a target lesion are the basis for "gamma knife" and related approaches to deliver high doses to small volumes of tumor, sparing normal tissue.

Therapeutic radiation is delivered in three ways: (1) *teletherapy*, with focused beams of radiation generated at a distance and aimed at the tumor within the patient; (2) *brachytherapy*, with encapsulated sources of radiation implanted directly into or adjacent to tumor tissues; and (3) *systemic therapy*, with radionuclides administered, for example, intravenously but targeted by some means to a tumor site. Teletherapy with x-ray or gamma-ray photons is the most commonly used form of radiation therapy. Particulate forms of radiation are also used in certain circumstances, such as the use of proton beams. The difference between photons and protons relates to the volume in which the greatest delivery of energy occurs. Typically protons have a much narrower range of energy deposition, theoretically resulting in more precise delivery of radiation with improvement in the degree to which adjacent structures may be affected, in comparison to photons. Electron beams are a particulate form of radiation that, in contrast to photons and protons, have a very low tissue penetrance and are used to treat cutaneous tumors. Apart from sparing adjacent structures, particulate forms of radiation are in most applications not superior to x-rays or gamma rays in clinical studies reported thus far, but this is an active area of investigation.

Certain drugs used in cancer treatment may also act as radiation sensitizers. For example, compounds that incorporate into DNA and alter its stereochemistry (e.g., halogenated pyrimidines, cisplatin) augment radiation effects at local sites, as does hydroxyurea, another DNA synthesis inhibitor. These are important adjuncts to the local treatment of certain tumors, such as squamous head and neck, uterine cervix, and rectal cancers.

Toxicity of Radiation Therapy Although radiation therapy is most often administered to a local region, systemic effects, including fatigue, anorexia, nausea, and vomiting, may develop that are related in part to the volume of tissue irradiated, dose fractionation, radiation fields, and individual susceptibility. Injured tissues release cytokines that act systemically to produce these effects. Bone is among the most radioresistant organs, with radiation effects being manifested mainly in children through premature fusion of the epiphyseal growth plate. By contrast, the male testis, female ovary, and bone marrow are the most sensitive organs. Any bone marrow in a radiation field will be eradicated by therapeutic irradiation. Organs with less need for cell renewal, such as heart, skeletal muscle, and nerves, are more resistant to radiation effects. In radiation-resistant organs, the vascular endothelium is the most sensitive component. Organs with more self-renewal as a part of normal homeostasis, such as the hematopoietic system and mucosal lining of the intestinal tract, are more sensitive. Acute toxicities include mucositis, skin erythema (ulceration in severe cases), and bone marrow toxicity. Often these can be alleviated by interruption of treatment.

Chronic toxicities are more serious. Radiation of the head and neck region often produces thyroid failure. Cataracts and retinal damage can lead to blindness. Salivary glands stop making saliva, which leads to dental caries and poor dentition. Taste and smell can be affected. Mediastinal irradiation leads to a threefold increased risk of fatal myocardial infarction. Other late vascular effects include chronic constrictive pericarditis, lung fibrosis, viscus stricture, spinal cord transection, and radiation enteritis. A serious late toxicity is the development of second solid tumors in or adjacent to the radiation fields. Such tumors can develop in any organ or tissue and occur at a rate of about 1% per year beginning in the second decade after treatment. Some organs vary in susceptibility to radiation carcinogenesis. A woman who receives mantle field radiation therapy for Hodgkin's disease at age 25 years has a 30% risk of developing breast cancer by age 55 years. This is comparable in magnitude to genetic breast cancer syndromes. Women treated after age 30 years have little or no increased risk of breast cancer. No data suggest that a threshold dose of therapeutic radiation exists below which the incidence of second