

Ionizing radiation is a double-edged sword: it provides an invaluable means of clinical diagnosis and for some tumors a

curative mode of therapy, but at the same time it is a potent mutagen and destroyer of cells. Cosmic radiation and emissions from naturally occurring terrestrial radionuclides (radon gas) are omnipresent; diagnostic x-ray procedures are common occurrences, as is radiotherapy for cancers. Public concern about the location of nuclear waste disposal sites and the safety of nuclear reactors reflects a widespread awareness of the potential dangers of ionizing radiation.

Ionizing radiation occurs in two forms: (1) electromagnetic waves (x-rays and gamma rays) and (2) high-energy neutrons and charged particles (alpha and beta particles and protons). All forms of ionizing radiation exert their effects on cells by displacing electrons from molecules and atoms with which they collide, causing ionization and inducing a cascade of events that may alter the cell transiently or permanently. The most important target molecule in living cells is DNA. Ionizing radiation may directly damage DNA (direct target theory), but more often it indirectly damages DNA by inducing the formation of free radicals, particularly those that form from the radiolysis of water (indirect target theory). Other cell molecules that may also be direct or indirect targets of radiant injury include lipids in cell membranes and proteins that function as critical enzymes. The transfer of energy to a target atom or molecule from the incident source of radiant energy occurs within microfractions of a second, yet its biologic effect may not become apparent for minutes or, if the effect is on DNA, even decades.

The following terms are used to express radiation dose:

- **Roentgen (R)** is a unit of x- or gamma irradiation defined by the quantity of induced ionization in air. Thus, it is a measure of exposure.
- **Radiation absorbed dose (rad)** and **grays (Gy)** are units that express the energy absorbed by target tissue from gamma and x-rays. A rad or its equivalent, the centigray (cGy), is the dose that results in absorption of 100 ergs of energy per gram of tissue.
- **Curie (Ci)** defines the disintegrations per second of a spontaneously disintegrating radionuclide (radioisotope). One Ci is equal to 3.7×10^{10} disintegrations per second.

These three measurements do not directly quantify energy transferred per unit of tissue and therefore do not predict the biologic effects of radiation. The following terms provide a better approximation of such information:

- **Linear energy transfer (LET)** expresses energy loss per unit of distance traveled as electron volts per micrometer. This value depends on the type of ionizing radiation. LET is very high for alpha particles, less so for beta particles, and even less for gamma rays and x-rays. Thus, alpha and beta particles penetrate short distances and interact with many molecules within that short distance. Gamma rays and x-rays penetrate deeply but interact with relatively few molecules per unit distance. It should be evident that if equivalent amounts of energy entered the body in the form of alpha and gamma radiation, the alpha particles would induce heavy damage in a restricted area, whereas gamma rays would dissipate energy over a longer course and produce considerably less damage per unit of tissue.
- **Relative biologic effectiveness (RBE)** is simply a ratio that represents the relationship of the LETs of various forms

of irradiation to cobalt gamma rays and megavolt x-rays, both of which have an RBE of unity (1).

Effects of Ionizing Radiation on Cells and Tissues. The primary target of ionizing radiation is DNA. Except at extremely high doses that impair DNA transcription, DNA damage is compatible with survival if the cell remains in the intermitotic phase; however, during mitosis, cells that have incurred irreparable DNA damage die, because chromosome abnormalities prevent normal division. Understandably, therefore, *tissues with a high rate of cell turnover, such as bone marrow and the mucosa of the gastrointestinal tract, are extremely vulnerable to radiation*, and the injury is manifest early after exposure. Tissues with slower turnover rates, such as liver and endothelium, are not affected immediately after irradiation but are depopulated slowly, because dividing cells cannot be replaced. Tissues with nondividing cells, such as brain and myocardium, do not demonstrate radiation effects except at doses that are so high that DNA transcription or some other molecule vital to the normal functioning of the cell is affected. In summary, within days of exposure to radiant energy, tissues containing many rapidly dividing cells show evidence of radiation injury, while tissues that contain few dividing cells show little injury.

Because tissues are made up of many cell types, the effects of radiation are complex. For example, vascular injury can result in changes that interfere with repair, and therefore parenchymal cells may reveal manifestations of radiation injury months to years later. Endothelial cells, which are moderately sensitive to irradiation, may be damaged, and the resultant narrowing or occlusion of the blood vessels may lead to impaired healing of parenchymal cells or chronic ischemic atrophy. Vascular changes in the central nervous system after irradiation can lead to late manifestations of radiation damage, although nerve cells were not directly affected by the ionizing radiation.

In addition to the number of replicating cells in a tissue, several other important parameters determine whether injury will occur in irradiated tissue. These include (1) the rate of the dose delivered, (2) the capacity of the cells to repair themselves, and (3) the effect of oxygen. An important practical application of this knowledge is in designing strategies for radiation treatment of cancer.

The rate of delivery significantly modifies the biologic effect. Although the effect of radiant energy is cumulative, delivery in divided doses may allow cells to repair some of the damage in the intervals. Thus, fractional doses of radiant energy have a cumulative effect only to the extent that repair during the intervals is incomplete. Radiotherapy of tumors exploits the fact that, in general, normal cells are capable of more rapid repair and recovery and so do not sustain as much cumulative radiation injury as do tumor cells. Oxygenation amplifies radiation damage to cells and tissues. Radiant energy may interact with molecular oxygen to induce free radicals, such as superoxide, which can then interact with atoms and molecules to compound the cellular injury. The oxygen effect is significant in the radiotherapy of neoplasms. The center of rapidly growing tumors may be poorly vascularized and therefore somewhat hypoxic, making radiotherapy less effective. A summary of the biologic effects of ionizing radiation is provided in Figure 8-13.

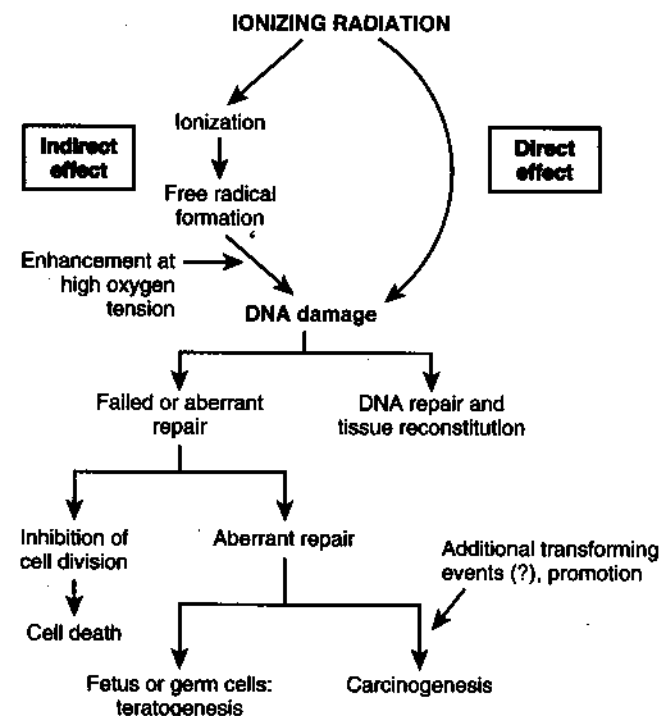


Figure 8-13

Effects of ionizing radiation on DNA. The major effect is indirect, via free radical formation.

MORPHOLOGY. At the molecular level, the DNA sustains a variety of alterations. These include the formation of pyrimidine dimers, cross-links, single-strand or double-strand breaks, and various rearrangements. Most single-strand breaks are rapidly repaired, often within minutes; double-strand breaks are more often irreparable. These alterations lead to a wide range of structural changes in chromosomes, including deletions, breaks, translocations, and fragmentation. The mitotic spindle often becomes disorderly, and polyploidy and aneuploidy may be encountered. At the cellular level, nuclear swelling and condensation and clumping of chromatin may appear; sometimes the nuclear membrane breaks. All forms of abnormal nuclear morphology may be produced. Giant cells with pleomorphic nuclei or more than one nucleus may appear and persist for years after exposure. At extremely high dose levels of radiant energy, nuclear pyknosis or lysis appears quickly as a marker of cell death.

In addition to affecting DNA and nuclei, radiant energy may induce a variety of cytoplasmic changes, including cytoplasmic swelling, mitochondrial distortion, and degeneration of the endoplasmic reticulum. Plasma membrane breaks and focal defects may appear. The histologic constellation of cellular pleomorphism, giant cell formation, conformational changes in nuclei, and

mitotic figures creates a more than passing similarity between radiation-injured cells and cancer cells, a problem that plagues the pathologist evaluating postirradiation tissues for the possible persistence of tumor cells.

At the light microscopic level, vascular changes are prominent in irradiated tissues. During the immediate postirradiation period, vessels may show only dilation. Later, or with higher doses, a variety of degenerative changes appear, including endothelial cell swelling and vacuolation, or even dissolution with total necrosis of the walls of small vessels such as capillaries and venules. Affected vessels may rupture or thrombose. Still later, endothelial cell proliferation and collagenous hyalinization with thickening of the media are seen in irradiated vessels, resulting in marked narrowing or even obliteration of the vascular lumina.

Effects on Organ Systems. Figure 8-14 depicts the organs that are particularly radiosensitive, together with common early and late manifestations.

The hematopoietic and lymphoid systems are extremely susceptible to radiant injury and deserve special mention here. With high dose levels and large exposure fields, severe lymphopenia may appear within hours of radiation, along with shrinkage of the lymph nodes and spleen. Radiation directly destroys lymphocytes, both in the circulating blood and in tissues (nodes, spleen, thymus, gut). With sublethal doses of irradiation, regeneration from viable precursors is prompt, leading to restoration of a normal lymphocyte count in the blood within weeks to months. The circulating granulocyte count may first rise but begins to fall toward the end of the first week. Levels near zero may be reached during the second week. If the patient survives, recovery of the normal granulocyte count may require 2 to 3 months. Platelets are similarly affected, with the nadir of the count occurring somewhat later than that of granulocytes; recovery is similarly delayed. Hematopoietic cells in the bone marrow, including red cell precursors, are also quite sensitive to radiant energy. Erythrocytes are radioresistant, but anemia may nonetheless appear after 2 to 3 weeks and persist for months because of marrow damage.

Another effect of irradiation on organ systems that deserves special mention relates to *malignant transformation* (see Fig. 8-13 and Chapter 6). Any cell capable of division that has sustained a mutation has the potential to become cancerous. Thus, an increased incidence of neoplasms may occur in any organ after radiation. The level of radiation required to increase the risk of cancer development is difficult if not impossible to determine. Radiation in very large doses kills cells and therefore is not associated with occurrence of tumors. Sublethal but relatively high doses are clearly associated with an increased risk. This is documented by the increased incidence of neoplasms in survivors of the atomic bombing of Hiroshima and Nagasaki, in radiologists of bygone years, and in miners of uranium ores. Exposure to low-dose irradiation has its risks as well, as will be evident from the following discussion of the relationship of radon to bronchogenic carcinoma.

Radon is a ubiquitous alpha particle-emitting product of

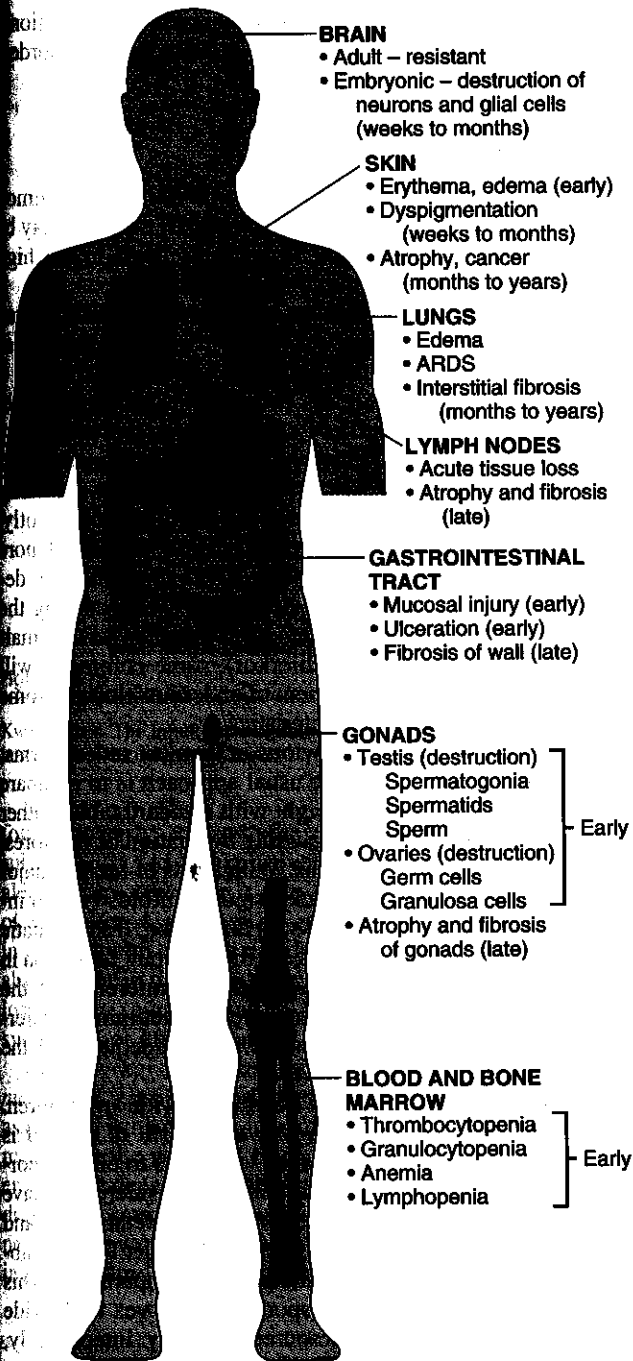


Figure 8-14

Overview of the major morphologic consequences of radiation injury. Early changes occur in hours to weeks; late changes occur in months to years. ARDS, adult respiratory distress syndrome.

the spontaneous decay of uranium. Because radon is a gas, it moves freely in and out of the lungs and generally does not accumulate in tissues, nor does it cause damage because, as previously discussed, alpha emitters penetrate tissues very poorly. In contrast, two radon decay by-products (or radon "daughters") are alpha particle-emitting particulates. These particulates are more readily deposited in lung tissue and can accumulate, producing short-range DNA damage. Over a pe-



Syndrome	Dose (rad)	Clinical Manifestations
Hematopoietic	200–500	Nausea and vomiting, lymphopenia, thrombocytopenia, neutropenia, later anemia
Gastrointestinal	500–1000	Severe gastrointestinal symptoms, including diarrhea, hemorrhage, emaciation; at higher doses, death within days; at lower doses, hematopoietic system manifestations
Cerebral	>5000	Listlessness and drowsiness, followed by convulsions, coma, and death within hours

riod of time, cells that suffer sufficient unrepaired DNA damage may become neoplastic and give rise to lung carcinomas. It is not currently known what levels of radon might be safe, but the question is of considerable importance, because radon is ubiquitous and may accumulate in buildings, particularly where ventilation is poor. Fortunately, the levels of radon currently thought to be safe are only uncommonly exceeded, except in those regions of the United States where uranium is closer to the surface and home construction practices facilitate leakage and entrapment of gases from the soil in basements.

Total Body Radiation. Exposure of large areas of the body to even very small doses of radiation may have devastating effects. Although 10 to 50 rad of gamma or x-ray exposure may exert no discernible effects, 50 to 100 rad may cause as many as 10% of exposed individuals to manifest nausea and vomiting, fatigue, and transient decreases in lymphocytes and granulocytes. As little as 100 to 300 rad of radiant energy in total body exposure delivered in one dose may induce an "acute radiation syndrome." To place this radiation level in context, it must be appreciated that doses of 4000 rad or more are often used in carefully shielded patients for radiotherapy of tumors. The lethal range in humans for total body radiation begins at about 200 rad, and at 700 rad, death is certain without medical intervention. Three often fatal acute radiation syndromes have been identified: (1) hematopoietic, (2) gastrointestinal, and (3) cerebral (Table 8–7).

NUTRITIONAL DISEASES

Adequate nutrition continues to be one of the most important concerns of humankind. In third world countries, undernutrition or protein-energy malnutrition (PEM) continues to be common, and in industrialized societies the most frequent diseases (atherosclerosis, cancer, diabetes, and hypertension) have all been linked to some form of dietary impropriety.

An adequate diet should provide (1) energy, in the form of carbohydrates, fats, and proteins; (2) essential (as well as non-essential) amino acids and fatty acids to be utilized as building blocks for synthesis of structural and functional proteins and