Chapter 9

LATE AND LOW-LEVEL EFFECTS OF IONIZING RADIATION

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INTRODUCTION

Ionizing radiation damages biological tissues by exciting or ionizing their atoms and molecules. Depending on the radiation dose and the biochemical processes altered, damage may be prompt (expressed minutes to weeks after exposure) or delayed (expressed several months to years later; Figure 9-1).

The exposure dose of gamma or X-rays in air is expressed in roentgens. The dose of any type of radiation absorbed by the tissues was at one time expressed by the rad, which is equivalent to 100 ergs of energy per gram of tissue. The international measure of absorbed dose is the gray, which is equal to 100 rads (conversely, 1 rad equals 1 cGy). Because the biological responses to radiation exposure may vary with the type of radiation, dose equivalents are expressed by the roentgen equivalents mammal (rem), which equal 1 joule per kilogram, or by the sievert, which is an international unit equaling 100 rem. The sievert allows effects from radiations with differing linear energy transfer (LET) values to be compared because 1 Sv of neutron radiation has the same biological effects as 1 Sv of low-LET gamma or X-radiation. Comparisons cannot be made among absorbed-dose measures of different kinds of radiation (for example, 1 Gy of neutron radiation will not have the same effect as 1 Gy of gamma or X-radiation).

Low-level radiation exposure is generally considered to be less than the dose that produces immediate or short-term observable biological effects. In humans, low-LET gamma or X-radiation doses of less than 0.5 Gy do not produce prodromal symptoms or the hematopoietic subsyndrome; however, recent studies suggest that low-level radiation exposure does increase the probability that delayed effects will occur.[1–3] Therefore low-level and delayed radiation effects are frequently discussed together.

There are four types of delayed radiation effects: (1) somatic, (2) genetic, (3) teratogenic, and (4) transgenerational. Irradiation enhances the naturally occurring frequency of the specific effect, and in some cases produces the observable endpoint by a process different than that of a natural process. Certain biological responses have such low thresholds that they are statistically indistinguishable, in many cases, from normal incidence.[3] Even so, current radioprotection guidelines state that all exposures to radiation should be avoided if possible and that exposure should be kept as low as is reasonably achievable.

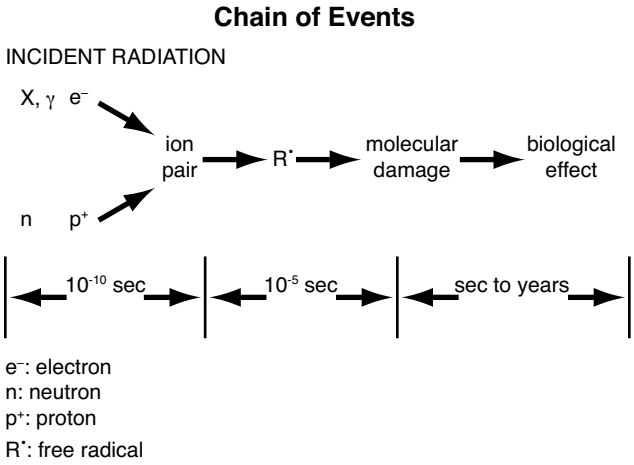

Figure 9-1. Chain of events in radiation exposure. The chain of events involved in radiation exposure is initiated with the exposure. First, an ion pair forms within 10^{-10} seconds. Free radicals are formed after 10^{-5} seconds. Molecular damage occurs within seconds but can take up to years to manifest. Similarly, biological damage occurs within many seconds postradiation but can also take years to manifest.

Background Radiation

Living organisms are continually exposed to ionizing radiation in nature as well as from nuclear weapons testing, occupations, consumer products, and medical procedures. The radiation from all of these sources together is called natural background radiation and is estimated to measure 180 to 200 mrem/person/y. Medical procedures contribute most whole-body background radiation (Figure 9-2).[1,2] In addition, large doses of partial-body radiation may be delivered to the lungs by radon gas (radon-222 and radon-220) produced from the natural decay of radium and thorium.[4] High concentrations of radon gas escape from soil and are released from marble and granite, accumulating in buildings with poor air circulation.[4] Radon exposure is a health concern because its solid daughter products, polonium-214 and polonium-218, decay by alpha particle emission in the human body near the lung tissue and may increase the incidence of lung cancer.[4]

Extraterrestrial radiation includes solar-flare and cosmic radiation. Most cosmic radiation is absorbed by the dense atmosphere before it reaches the earth's surface. A person's exposure to cosmic radiation increases at higher latitudes or altitudes as the atmosphere becomes less dense. For example, a resident of the higher altitude city of Denver receives approximately 100 mrem/y more radiation exposure than does a resident of Washington, DC. A cross-country

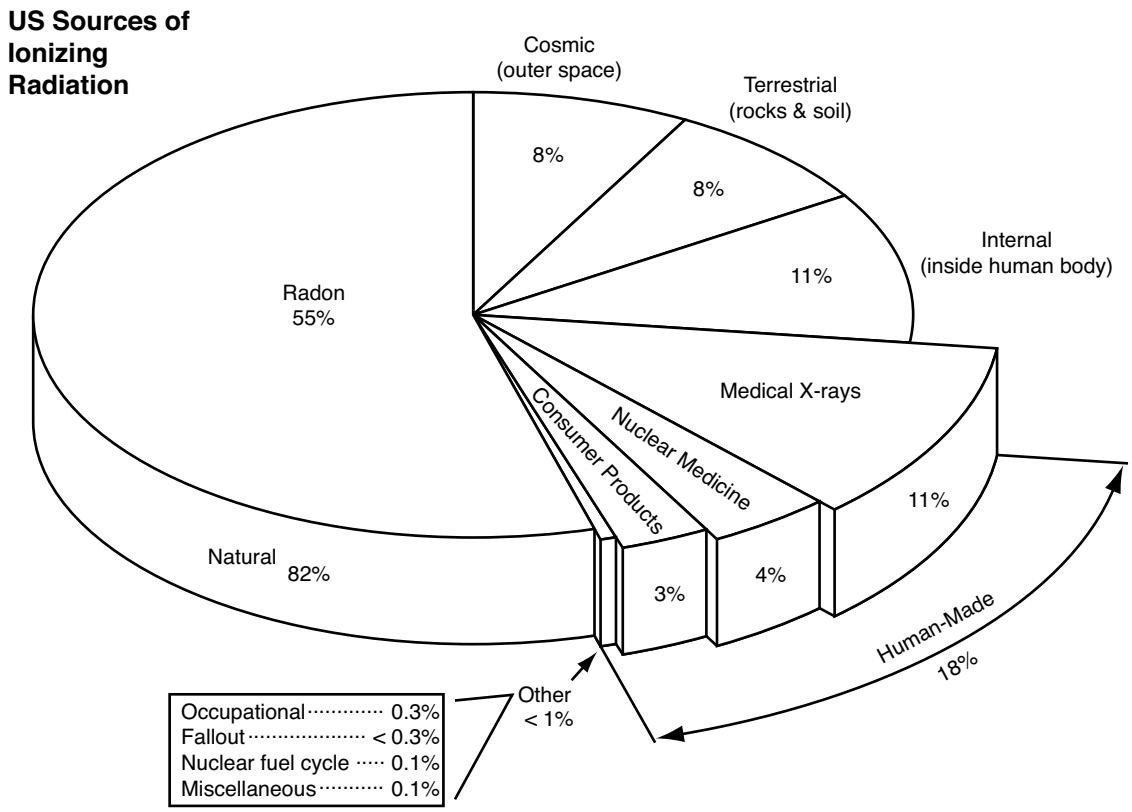

Figure 9-2. US sources of ionizing radiation. There are many sources of radiation to which an individual may be exposed. The majority of exposure is from natural sources (82%); the remaining exposure is from artificial sources (18%).

airplane flight increases individual exposure by 0.2 mrem/h because the level of cosmic radiation is greater at 36,000 feet than at sea level.[2] As humans venture farther from the protective atmosphere in extremely high-altitude flights, their background occupational exposures to cosmic radiation will increase as well. Spaceflight increases exposure to solar and cosmic radiations; for example, *Apollo* astronauts traveling to the moon received an average of 275 mrem over 19.5 days. Shuttle astronauts receive a similar level of exposure to radiation during spaceflight and may receive a much higher dose during a space walk.[3]

On earth, naturally occurring radioactive elements contribute to background radiation.[1–3] External exposure sources include potassium-40, which may be concentrated in concrete, and radon gas. Internal radiation comes primarily from radioactive isotopes of naturally occurring elements in biological systems, such as potassium-40 and sodium-24. In some areas of Brazil and India, large concentrations of monazite, a mineral containing thorium, are present in the soil or sand. Background radiation exposures there range from 0.008 to 0. 17 Gy/y.[3]

Fallout from nuclear weapons testing peaked in 1964, after 77 atmospheric detonations occurred in 1962. Of the total fallout, 69% was from carbon-14, 4% was from cesium-137, and 3% was from strontium-90. The remaining 24% was from radioactive isotopes of plutonium, rubidium, barium, iodine, iron, manganese, krypton, americium, tritium, and zinc.[4] Carbon-14 will be a long-term contributor to background radiation because it has a half-life of 5,700 years.

Radiation is also emitted from consumer products, such as color television sets (averaging 0.3–1.0 rem/h of use), video screens, smoke detectors (which contain an alpha emitter, usually americium-241), and dinnerware that uses uranium for an orange color.[4–6] Ophthalmic glass, used in prescription lenses, contains trace impurities of thorium-232, and uranium is added to dental porcelain to give dentures a natural fluorescent quality. The latter may result in an alpha radiation dose of 60 rem/y to the gums.

Deterministic Versus Stochastic Events

Radiation effects on the human body are generally divided into two categories: deterministic and stochastic effects. Deterministic effects are those whose

severity increases as dose increases. Below a certain level, known as the threshold, the effect is absent. The level of damage particularly depends on the radiation dose received. Deterministic effects depend on the killing of many cells over a relatively short period of time. Examples of this type of damage include organ damage, cataracts, erythema, and infertility.[5–8]

Stochastic effects are independent of absorbed dose and, under certain exposure conditions, the effects may or may not occur. There is no threshold and the probability of having the effects is not proportional to the dose absorbed. Curability of the effect has little to do with the radiation dose received. Stochastic effects modify a limited number of cells following irradiation. Examples of this type of damage include radiation-induced cancer and genetic damage.

Somatic Cells Versus Germ Cells

All cells in the body (except germ cells) are somatic. Germ cells are reproductive cells that pass their genetic material, including mutations, on to the organism's offspring. Somatic cells, on the other hand, do not pass on genetic material.

SOMATIC CELL EFFECTS

Delayed somatic effects of ionizing radiation result from somatic mutations and accumulated damage, and include impaired circulation, necrosis, fibrosis of skin and muscle tissue, loss of hair, loss of taste, impaired bone growth, susceptibility to disease, immunodeficiency, aplastic anemia, cataracts, and increased incidence of cancer. Some organs are more radioresistant than others. Radiation doses exceeding 15 to 50 Gy must be received before damage to the liver or heart is detected.[2] In contrast, other tissues, such as the lens and the sperm, show some detriment from doses as low as 0.15 to 0.30 Gy.[3] Delayed somatic effects of intermediate- or high-level exposures include cataract formation, skin abnormalities, and sterility.

Cataract Formation

The lens tissue of the eye is particularly radiosensitive and radiation exposure can increase its opacity. Radiation cataractogenesis is the most common delayed radiation injury and is thought to result from damage to the anterior equatorial cells of the lens's epithelial tissue.[6,7] These cells normally divide and migrate to the posterior portion of the lens, where they gradually lose their nuclei and become lens fibers.[3] The lens tissue, like that of the testes and the brain, is separated from the rest of the body by a barrier system.[4] As a result, it has no direct blood supply, no macrophages for phagocytosis, and no way to remove accumulated damage. In a study of 446 survivors of the Nagasaki atomic bomb, 45% of the 395 individuals who were 0.1 to 2.0 km from the hypocenter developed cataracts by 1959, whereas only 0.5% (or 2 out of 395) sustained severe visual impairment.[1] Four of the remaining 51 individuals (7.8%) who were 2 to 4 km from the hypocenter developed mild cataract impairment. Even survivors exposed to small doses of radiation were at increased risk for cataract formation. By 1964, the incidence of cataract formation among bomb survivors who received 0.01 to 0.99 Gy of radiation was 1.5% in Hiroshima compared to 1.0% in the control population, and 2.0% in Nagasaki compared to 0.9% in controls.[3] Higher doses tend to increase the degree of opacity and shorten the latency period.[1] Studies have shown that there is a 10% risk of developing a severely imperiling cataract following a single exposure to 2.4 Gy of low-LET radiation, and a 50% risk for a dose of 3.1 Gy. The latency period for cataract formation in humans has been estimated to be 6 months to 35 years; however, fractionation or protracted exposure lowers the incidence and prolongs the latency.[2]

Small radiation doses may increase the lens's opacity, but visually impairing cataract formation results from an accumulation of dead or injured cells and therefore has a threshold. For low-LET radiation, this threshold is 2 Gy, while high-LET neutrons have thresholds of less than 0.2 Gy. The International Commission on Radiological Protection (ICRP) has recommended an occupational exposure limit of 0.15 Sv for the eye.[1,6]

Tissue Fibrosis

Radiation-induced fibrosis (RIF) is one of the most predominant long-term adverse effects of ionizing radiation.[8–14] Typically, fibrotic response occurs due to the progressive onset of extra cellular matrix (ECM) deposition from stromal tissue such as lung, liver, kidney, and intestine.[8] Chronic deposition leads to loss of elasticity and muscular dysfunction or atrophy in extreme cases. The severity of fibrosis depends on radiation dose, quality of radiation, and dose rate.[9,10] Fibrosis may be accompanied by epilation, loss of vascularity, and even necrosis of the tissue.[8] Radiation-induced mutations are also responsible for fibrosis.[11] Cellular response in fibrosis manifestation primarily involves sustained elevation of growth factors or cytokines that trigger a proinflammatory response in

fibroblasts, transform epithelial and endothelial cells into ECM-producing myofibroblasts, and infiltrate immune cells into the interstitial spaces.[12] The term "ECM" collectively describes aggregates of fibrous proteins such as fibronectin, collagen, and smooth muscle actin. These aggregates are formed by upregulation of matrix metalloproteinases in myofibroblasts. Severe fibrosis of the lungs can lead to loss of function and, sometimes, mortality.

The mechanism involved in RIF is fairly complicated. Radiation-induced cellular response involves activation of various stress-related signaling pathways, which includes acute responses such as apoptosis, necrosis, and chronic response, such as proinflammatory pathways. Leukocyte infiltration and adhesion into the vessel wall of the irradiated tissue is one of the key factors of progressive inflammatory response. Chronic alteration in signaling pathways can lead to tissue remodeling and fibrosis.[13] One of the key mediators of RIF is transforming growth factor β (TGF-β).[14–17] Early alterations in ECM and TGF-β-gene expression in mouse lungs are indicative of radiation fibrosis.[15] TGF-β signaling involves attachment of peptide to the TGF-I, II, and III receptors. The I and III receptors either homodimerize or heterodimerize and lead to a cascade of events, such as the TGF-β signaling family, S-mothers against decapentaplegic homolog 2 (SMAD2) phosphorylation, nuclear translocation, and transcriptional upregulation of profibrotic proteins.[18] Even though the role of TGF-β in the development of fibrosis is well established, very few studies have attempted to inhibit TGF-β in amelioration of fibrosis. Different strategies developed to reduce fibrosis include systemic administration of superoxide dismutase mimetics, and pentoxyfylline (alone and in combination with alpha tocopherol). Clinical trials have shown beneficial effects of superoxide dismutase in radiation-induced fibrosis.[19–21] Clinical trials using a combination of paclitaxel and arsenic trioxide have somewhat promising results.[21–23] Unfortunately, the US Food and Drug Administration has not yet approved any drug to treat RIF.

Sterility

Males

Germ cells of the human testes are very radiosensitive. Temporary sterility may occur after 1 Gy whole-body or local irradiation, with 50% incidence following exposure to 0.7 Gy. Sperm cells become more resistant as they develop; spermatogonia are more radiosensitive than spermatocytes, which are in turn more radiosensitive than spermatids.[5,24]

Radiogenic aspermia is caused by a maturation depletion process similar to that observed for hematopoietic cells after irradiation. Radiation kills stem cells or delays mitosis so that differentiating cells continue to divide without being replaced. The latency period for aspermia after radiation exposure is approximately 2 months,[1,2] and the time for recovery is several months to years. Chronic and protracted exposures produce greater testicular damage than do acute large exposures. This damage is reflected in the duration of aspermia (approximately 25 wk) and is thought to result from cycling of the radioresistant type-A spermatogonia to the more radiosensitive type-B spermatogonia. A dose of about 0.35 Gy, protracted over 1 to 10 days, produces a 50% incidence of aspermia. At low dose rates, the recovery period depends on the total dose received and can vary significantly. At higher total doses, following the onset of aspermia, it may take up to 3 years for recovery from a 2 to 3 Gy exposure and up to 5 years for 6 Gy exposure.[4]

Females

The ovary is not as sensitive to radiation as are the male testes.[1,2] Temporary sterility may be induced in females by acute radiation doses of 1.5 to 6.4 Gy radiation. Permanent sterility can result from doses of 2 to 10 Gy and depends on the woman's age at the time of irradiation. Older women, particularly those close to menopause, are particularly radiosensitive for sterilization. Permanent sterility may result in 50% of the exposed female population over 40 years of age after 2 Gy of low-LET radiation, compared to an estimated 3.5 Gy for women under 40.[1,6] This is due to the numbers of oocytes present at the time of irradiation. Women have about a half million oocytes at puberty; by menopause, these are almost all depleted through atresia.

Shortly before birth, the oogonia stop multiplying and proceed to prophase I of meiosis. After puberty, meiosis resumes for individual cells by ovulation. Oocytes lose the ability to renew after birth and are unable to replace stem cells that have been damaged or killed by radiation. The oocyte is most radiosensitive as a proliferative stem cell during the fetal stage of gestation, prior to ceasing mitosis and entering meiosis. For fractionated radiation exposure, higher radiation doses of 3.6 to 20.0 Gy are required for sterilization.[1,2]

Radiation Effects on Skin

The acute effects of radiation exposure on skin are well known and result in severe skin burns.[1–6] However, low levels of chronic radiation to skin have been observed as well. Soon after Roentgen's

discovery of X-rays, researchers and radiologists became aware of the skin's sensitivity to radiation damage. Eight months after the discovery of X-rays in 1896, a German scientist reported a case of dermatitis and alopecia on the face and back of a 17-year-old male who had been exposed to these rays for 10 to 20 minutes a day for 4 weeks during a scientific investigation.[7] The accompanying erythema, which resembled a burn, was painless; however, chronic radiation dermatitis following repeated exposure is usually extremely painful. Several other anecdotal cases have been noted. In another 1896 case, a man received an hour-long X-ray exposure during an examination for a kidney stone. The patient experienced nausea (a prodromal symptom) 3 hours after irradiation. Following a second exposure lasting 1.5 hours, the patient developed a radiation sequela leading to ulcer formation at the site of exposure, which was not responsive to skin grafting.[7] From 1897 through 1928, additional evidence was collected that demonstrated that low-level radiation exposure caused radiation dermatitis.

Before the introduction of the roentgen in 1928 as a unit to measure exposure dose, the skin erythema dose (SED) was commonly used.[1,2] The SED is the radiation dose required to produce a given degree of erythema and it depends on the quality, energy, and exposure time of the radiation. For X-radiation, the SED is about 8.5 Gy. In 1925, it was proposed that the exposure of radiologists and X-ray machine operators not exceed 1/100th of the SED in a 30-day period.

During a radiation incident, skin may be exposed either by direct blast irradiation or by beta rays from the direct deposition of particulate fallout.[5] The degree of radiation-induced skin damage depends on a number of factors, including the type of radiation, the dose and dose rate, the area of skin irradiated, and skin-quality characteristics, such as texture, age, color, thickness, and location.[5,6] The neck is the most radiosensitive area because its skin is thin and usually not protected by clothing. Additional trauma through burn, abrasion, exposure to ultraviolet light, or extreme temperature variations increase the damage. Environmental factors and inadequate clothing may contribute to hyperthermia, and wool or other coarse fabrics may further abrade the damaged skin. An illness like diabetes or a genetic disease like ataxia telangiectasia may also make the skin more radiosensitive.

In terms of radiation quality, alpha radiation is of little concern for skin damage because the average penetrated dose is usually absorbed by the dead corneocytes of the stratum corneum.[1,6] However, it may present a problem at sites where the skin is thinner and the radiation can penetrate to the basal level. Therefore, depleted uranium exposure to the skin could not cause significant skin erythema. In contrast, beta particulates in fallout may contain extremely high radiation dose rates (tens of grays per hour). When they land on the skin, their energy may penetrate to the germinal basal cells. This radiation damage (known as a beta burn) was observed in the atomic bomb survivors and the Marshall Islanders who had been exposed to nuclear fallout. The threshold dose of beta radiation for skin damage depends on the average energy of the beta particle, the total absorbed dose, and the dose rate. The average penetrating range of a beta particle is proportional to its energy; thus, higher-energy beta emitters, such as strontium-90 (0.61 MeV average), require lower surface doses to produce wet desquamation than do lower-energy beta particles, such as those from cobalt-60 (0.31 MeV average). Lower-energy beta particles, like sulfur-35 (0.17 MeV energy), are not capable of penetrating to the dermis and cannot induce chronic radiation dermatitis. Most importantly, beta injuries from fallout can be minimized by decontamination and washing.

Five progressive categories of radiation damage are observed in skin: (1) erythema, (2) transepithelial injury (moist desquamation), (3) ulceration, (4) necrosis, and (5) skin cancer.[1–3] Radiation-induced erythema occurs in two stages: (1) mild initial erythema, usually appearing within minutes or hours on the first day after irradiation (occurring earlier with higher doses), and (2) the main erythema, appearing at 2 to 3 weeks and persisting for longer periods. In some cases, a third erythema may occur at 6 weeks. Radiation-induced erythema is a threshold phenomenon. For example, a dose of 6 Gy of low-LET radiation (eg, X-rays) received in less than 1 day, or 10 Gy in 10 days, will induce erythema in 50% of exposed individuals.[3] In contrast, the threshold for neutron radiation is 2 Gy. Because of these variables, and the fact that the threshold dose decreases with an increase in the surface area exposed, erythema is not a good biological dosimeter.

Early erythema arises from the release of mediators and from increased capillary dilation and permeability.[3] Early erythema is equivalent to a first-degree burn or mild sunburn, subsiding within 2 or 3 days. Although indomethacin and other prostaglandin-synthesis inhibitors have been used topically to prevent or reduce erythema caused by sunburn or ultraviolet light, they have not been widely used to treat radiation-induced erythema.

The second onset of erythema is attributed to impaired circulation in the arterioles, producing inflammation and edemas and accompanied by dry desquamation of the epidermal corneocytes. Upper cells are sloughed or abraded off, exposing cells that

are not completely keratinized. Cell death and moist desquamation ensue. Both dry and wet desquamation occur about 1 to 4 weeks after irradiation. Regeneration of the stratum corneum requires 2 months to 4 years, and this regenerated tissue will be more sensitive to other skin-damaging agents. The new skin may be thinner than the original, with greater sensitivity to touch and pain. Reduction or loss of the dermal ridges making up the fingerprint has occurred from large or chronic exposures.

Epidermal basal cells are thought to be the targets of early radiation damage.[1–3] Further damage to the surrounding vasculature is an important factor in late radiation injury and necrosis. The blood vessel damage may lead to telangiectasia, and fibrosis and alterations in connective tissue may appear. Hyper- or hypopigmentation may occur after radiation exposure; low doses activate melanocytes and produce hyperpigmentation, and higher doses may result in death of melanocytes and cause hypopigmentation. These biological changes play a role in tissue necrosis and skin cancer development.

CARCINOGENESIS: THE HUMAN DATABASE

Cancer induction is the most important somatic late effect of low-dose radiation exposure. In contrast to other types of late effects, like genetic effects, cancer risk estimates are based on the human experience. There is an association between low-dose radiation exposure and cancer.[1–6] Early reports of this association were anecdotal. Both Marie Curie and her daughter Irene died from leukemia that was thought to have resulted from radiation exposure. One of the earliest reports of radiation-induced cancers occurred in Thomas Edison's laboratory. Edison's assistant died in 1904 from skin cancer contracted while developing a fluorescent light using an X-ray tube.[5] Many early radiologists, researchers, and workers experienced chronic radiodermatitis, increased cancer incidence, and other damage before the dangers of radiation were clarified and protective measures were initiated. Currently, the National Academy of Sciences considers cancer induction to be the most important somatic effect of low-dose ionizing radiation.[1,5]

Cancer development is thought to be a multistep process in which the initial damage leads to a preneoplastic stage, followed by selection and proliferation of the neoplastic cell.[1,2,4] Chromosomal and enzymatic analyses indicate that all of the cancer cells of a tumor and its metastases are derivatives or clones of a single cell. However the multistage theory of cancer development is now believed to involve tumor suppressor genes, oncogenes, and epigenetic effects as well.

Previously the simplistic view of cancer formation involved the three stages in cancer formation: initiation, promotion, and latency (Figure 9-3).[1,2,4] During initiation, fixation of the somatic mutational event occurs, which leads to the development of a neoplasm. Damage can be initiated by various agents, including exposure to radiation or another environmental or chemical carcinogen. During the promotion stage, the preneoplastic cell is stimulated to divide or is given preferential selection. A promoter is an agent that by itself does not cause cancer, but once the initiating carcinogenic event has occurred, it promotes or stimulates the proliferation of the neoplastic cell. Chromosomal and enzymatic analyses indicate that all of the cancer cells of a tumor and its metastases are derivatives or clones of a single cell. During the promotion stage, the preneoplastic cell is stimulated to divide or is given preferential selection.

The mechanism of carcinogenesis is more complicated than a simple initiation-and-promotion model.[1–4] Tissue homeostasis depends on the regulated cell division and self-elimination of each of its constituent members, excluding stem cells. A tumor arises because of uncontrolled cell division and failure for self-elimination. Alterations in genes are responsible for dysregulated growth and self-elimination.

Carcinogenesis appears to be a multistep process with multiple genetic alterations occurring over an extended period of time.[1,2,11] Most genetic alterations that lead to cancer are acquired in the form of somatic mutations (eg, chromosomal translocations, deletions, inversions, amplifications, and point mutations). While the deregulated growth signals by oncogenes are critical to cancer development, other recent findings suggest additional gene alterations. Many cancers seem to possess diminished apoptotic or cell-death programs. The loss of cell cycle control has led to the concept that mutations in protooncogenes and tumor suppressor genes that inhibit apoptosis provide a selective growth advantage to a premalignant cell that allows it to clonally expand. Additionally, mutations in deoxyribonucleic acid (DNA) stability genes increase the rate of acquiring mutations that will result in a malignant tumor. Although tumor cells are considered clonal in origin, most tumors contain heterogeneous populations of cells that differ in their ability to populate the tumor mass or form metastases.

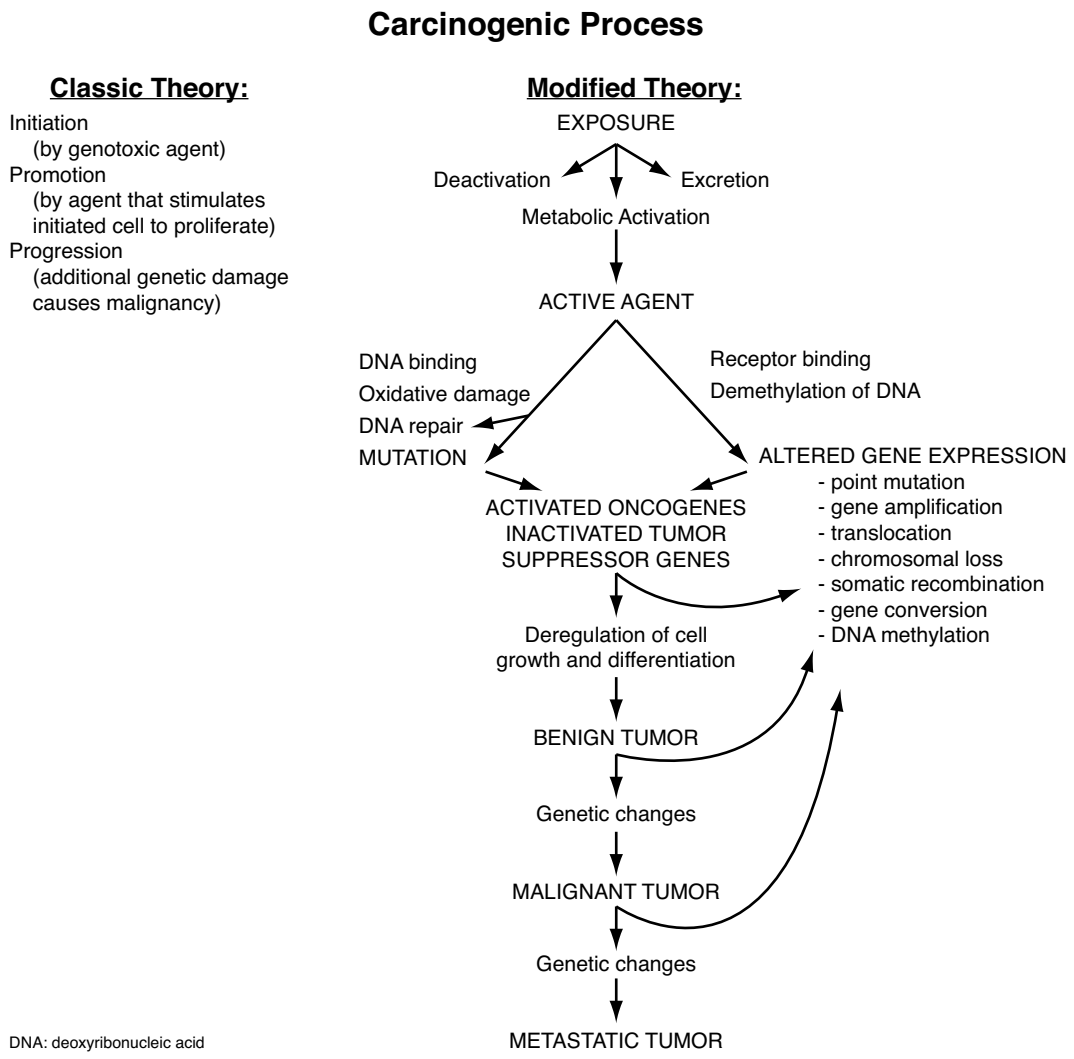

Figure 9-3. Carcinogenic process. Carcinogenisis is a multistep process. The classic theory was characterized by initiation, promotion, and progression. In contrast, the modified theory details the involvement of multiple types of molecular DNA (deoxyribonucleic acid) damage (genetic) coupled with alterations in the expression of oncogenes and tumor suppressor genes. Altered gene expression can also occur via an epigenetic process in which the DNA is not damaged.

The Human Database

Information regarding the human experience with radiation-induced cancer comes from four sources (Table 9-1): (1) atomic bomb survivors, (2) medical exposures, (3) occupational exposures, and (4) epidemiological comparisons of geographic areas containing high background radiation.[1–3,5]

The 92,231 survivors of the atomic detonations in Hiroshima and Nagasaki are being monitored by the Radiation Effects Research Foundation for possible radiation-induced health effects.[1,2,5] Of the 37,000 deaths in this population through 2002, 9,110 were attributable to radiogenic and nonradiogenic cancers.[1,2,5] The foundation is also following 27,000 children of the survivors who were conceived after the detonations to determine if genetic damage induced in their parents and passed on to them resulted in any adverse health effects.[1,2,5] Radiation doses received by a majority of the survivors were initially determined in 1965 and were revised in 1986 after more information on the explosions became available. Revisions in which radiation type (neutrons or gamma radiation) caused the most damage have led to the conclusion that gamma radiation plays a greater role than earlier thought.[5] Therefore, risk estimates for low-LET radiation exposure must be revised, and potential risk estimates may be increased by 50%.

TABLE 9-1

SOURCES OF DATA ON RADIATION EXPOSURE IN HUMANS

Type of Exposure	Population Affected
Atomic bomb	Survivors Offspring of survivors
Medical	Treatment of tinea capitis X-ray treatment of ankylosing spondylitis Prenatal diagnostic X-rays X-ray therapy for enlarged thymus gland Fluoroscopy treatment for tuberculosis Thorotrast treatment
Occupational	Radium dial painters Uranium miners and millers Nuclear dockyard workers Nuclear materials workers Participants in nuclear weapons testing Construction workers Industrial workers Reactor personnel Civilian aviation personnel Astronauts Scientific researchers Diagnostic and therapeutic radiation personnel

The second group used in human risk estimates is the medically irradiated population for which dosimetry is available: the 14,111 patients in the United Kingdom who received spinal irradiation for treatment of ankylosing spondylitis between 1935 and 1944. Ankylosing spondylitis is a rheumatoid disease primarily affecting the spine and characterized by destruction of the cartilage and ossification of the vertebral joints. An increased incidence of leukemia has been observed in this population. Other medically irradiated groups that are used for risk estimation and who demonstrated increased cancer incidence are children who received head radiation for treatment of tinea capitis and patients who received routine fluoroscopy examinations for postpartum mastitis or during treatment of tuberculosis.

The third category used for determining human risk estimates includes occupational groups who receive very low radiation doses averaging less than 1 rem/y (medical, scientific, and industrial professions). However, depending on the type of radiation, other groups are also sometimes used in determining cancer risk estimates.

The risk of radiation-induced cancer varies considerably with age, with a younger age being associated with increased cancer risk and susceptibility. The exceptions to this are leukemia, which appears to be constant throughout all ages, and respiratory cancers, which increase with age.

Leukemia

Leukemia is one of the most frequently observed radiation-induced cancers.[1–5] It accounts for one sixth of the mortality associated with radiocarcinogenesis, with equal numbers of cancers of the lung, breast, and gastrointestinal tract. Leukemia may be acute or chronic and may take a lymphocytic or myeloid form. With the exception of chronic lymphocytic leukemia, increases in all forms of leukemia have been detected in humans exposed to radiation and in irradiated laboratory animals. More acute than chronic leukemias are induced, although the latencies are roughly equal. Characteristic chromosomal aberrations and alterations in gene expression induced by radiation have been identified in patients with a variety of leukemias.

Leukemia first appeared in the atomic bomb survivors 2 to 3 years after the nuclear detonations and reached a peak incidence 10 to 15 years after irradiation. The average latency period for leukemia is thought to be 2 to 20 years. This estimate is derived from the ankylosing spondylitis patients (6 y) and the atomic bomb survivors (13.7 y). The difference between the two groups may reflect the larger radiation dose (averaging 3.21 Gy) received by the bone marrow of the ankylosing spondylitis patients, compared to an average dose of 0.27 Gy in the atomic bomb survivors.[1,2,5]

Thorotrast exposure has also been linked to leukemia induction. Thorotrast is a contrast medium that contains thorium-22 and decays by alpha particle emission. It was used in diagnostic radiological procedures between 1928 and 1955. An increased incidence of leukemia and liver cancer was observed in patients in whom thorium had concentrated in the liver and bone. The mean radiation dose to the bone marrow from thorotrast ingestion was 3.5 Gy. These data demonstrate that alpha particle exposure, like neutron and gamma radiation exposure, can also induce leukemia.

The incidence of radiation leukemia is influenced by age at the time of exposure. The younger the person at the time of exposure, the shorter the latency and the risk period for developing leukemia. The incidence of leukemia decreases with increasing age at the time of exposure; however, this older individual is at increased risk for a greater period of time. Conversely, as the leukemia risk decreases, the risk of developing a solid tumor increases. There is no apparent difference in the

incidences of leukemia in females and males at any age or at any dose.

In terms of military exposure and leukemia risk, over 200,000 US military and civilian personnel have been involved in the testing of nuclear weapons since 1945. This number includes military personnel and civilians who were permitted to view a nuclear detonation from a safe distance, such as those who witnessed testing at the Nevada Test Site and the Pacific Proving Grounds in the Marshall Islands. The average doses received by the participants in those tests were 0.5 rem of gamma radiation and 0.005 rem of neutron radiation. These doses are now considered to be safe; Nuclear Regulatory Commission regulations permit persons in occupations with radiation exposures to receive 3 rem in any calendar quarter, or 5 rem per year. At the request of the Department of Defense, the National Research Council conducted a study of mortality among participants of nuclear weapons tests. The study concluded that "there is no consistent or statistically significant evidence for an increase in leukemia or other malignant disease in nuclear test participants."[5]

Thyroid Cancer

Thyroid cancer is also a concern for low-level exposure and late radiation effects, possibly accounting for 6% to 12% of the mortality attributed to radiation-induced cancers.[1–5] Radiation-induced thyroid cancer is 2.0 to 3.5 times more prevalent in women than in men. This is based on information showing that female atomic bomb survivors sustained thyroid cancer 3.5 times more frequently than male survivors, and as much as 5 times more frequently in one clinical study.[1,2,5] The difference in thyroid tumor inductions in males and females is most likely due to hormonal influences on thyroid function. Variations in thyroid cancer induction also exist for ethnic groups. One study examined thyroid neoplasms in Jewish and gentile women who received radiotherapy (approximately 3.99 Gy) during infancy for enlarged thymus glands.[5] The risk of thyroid cancer in women of Jewish background was four times greater than in gentile women. Both the atom bomb survivor studies and those involving Israelis irradiated for tinea capitis indicate that the incidence of thyroid cancer following radiation is also affected by the age at exposure. The risk is generally greater during the first two decades of life.[5]

Breast Cancer

Breast cancer is the major concern for women exposed to low-level radiation because of its high incidence in the unexposed population.[5] In the United States, one in eleven women will develop breast cancer (the incidence of mortality from breast cancer is almost nonexistent in men). Because of their increased normal incidences of thyroid and breast cancer, women are also at greater risk of developing these cancers as a result of radiation exposure.[1,2,5]

It is important to note that in most cases, radiation exposure increases the incidence of the cancer but does not affect the histology of the tumor nor the prognosis. The risk of breast cancer associated with radiation exposure is age dependent. In female adolescents, breast cancer does not manifest until after puberty. However, studies have shown an increased incidence of breast cancer in atomic bomb survivors who were younger than 10 years old at the time of exposure.[1,2,5] Increases in breast cancer have also been observed in women who received radiotherapy during infancy to treat enlarged thymus glands. The latency period for breast cancer following radiation exposure ranges from 5 to 40 years.[5] Estrogen may promote breast cancer because a woman's age at exposure is associated with increased risk, and because few breast cancers occur before age 30. This is supported by the fact that breast cancer incidence does not increase in men following irradiation. Several investigators have proposed that the actual period in which estrogen is present as a promoter is the important factor in determining cancer incidence and latency. Women irradiated after menopause are less likely to develop radiation-induced breast cancer. A decreased incidence of breast cancer was seen in women who received X-radiotherapy to the ovaries for metropathia hemorrhagica, although the incidence of radiation-induced leukemia did increase, as expected. The radiotherapy induced an artificial menopause, with a corresponding decrease in estrogen production.[1,2]

In terms of dose estimates, the estimated dose of radiation required to double the naturally occurring incidence of breast cancer is 0.8 Gy. Dose fractionation does not appear to reduce the incidence of breast cancer. Damage in breast tissue tends to accumulate rather than to be repaired, so the risk from acute exposure (such as atomic bomb radiation) is the same as the risk from chronic exposure (such as small daily doses from fluoroscopy or treatment for postpartum mastitis).

Other Systemic Cancers

Cancers of the stomach, colon, liver, pancreas, salivary glands, and kidneys are also induced by radiation.[1–3,5] However, these neoplasms are fairly rare. Most radiation-induced solid tumors have a latency of 10 to 30 years and no difference exists in the absolute risks for males and females.

Bone Cancer

The risk of radiation-induced bone, lung, and skin cancers is higher than other systemic cancers.[1,2,5] In the 1920s, workers who hand-painted the fluorescent dials on wristwatches with radium-based paint achieved the necessary fine detail by moistening the tip of the brush into a point with their tongues; in so doing, they ingested small amounts of radium. Because radium is a bone-seeking element with a half-life of 1,600 years, these workers had a higher incidence of bone sarcomas. Increased incidences of breast cancer were also observed.[6]

Lung Cancer

Radiation is one of several carcinogens known to be associated with lung cancer.[1–3,5] Risk estimates have been obtained from atomic bomb survivors, patients with ankylosing spondylitis, and underground miners exposed to uranium and radon.[1,5] In each case an excess was found, even when smoking is considered as a confounder. There is a clear excess of lung cancer in the uranium mine workers of Colorado, the Czech Republic, Sweden, and Newfoundland.[1–3,5] It is difficult to separate the contributory effects of radon, uranium, and smoking in causing the observed lung cancers. There is also some evidence of an excess of lung cancer from domestic radon exposure and it has been estimated that 10% of 150,000 lung cancer deaths are associated with radon exposure.[1,6]

Skin Cancer

Skin cancers are common in those using radiation equipment, although the incidence has decreased due to increased safety standards.[1,5] In general, radiation skin cancers are readily diagnosed and treated at any early stage of development and maintain a high rate of curability.

Dose and Dose-Rate Effectiveness

From the human data that has been collected and evaluated, it seems that high-dose and high-dose-rate radiation exposures are associated with an increased risk of cancer development. The human data from low-dose and low-dose-rate exposures are sparse, and therefore the excess rate is not well defined for humans under these exposure circumstances.

RADIATION EFFECTS IN UTERO

Prenatal exposure to ionizing radiation can interfere with embryonic and fetal development, depending on dose and the gestational age in which exposure occurs.[24] Documented reports show instances of children with severe intellectual disability and microencephaly, as well as other physiological malformations, born to mothers exposed to radiotherapy.[24] Further, experimental data from small mammals are available that indicate that relatively low doses of 0.05 or 0.1 Gy are sufficient to induce sensitivity in the developing embryo. The main factors that determine the outcome of in-utero exposure are the dose, dose rate, and the gestational stage at which exposure occurs.

Developmental Stages

Radiation is highly damaging to rapidly proliferating cells. The biological systems with high cell proliferation rates are extremely radiosensitive. To demarcate the radiation effects at different embryonic/fetal stages, the gestation can be divided into three periods: (1) preimplantation (the period extending from cell fertilization to the time when the embryo attaches to the uterine wall), (2) major organogenesis (the period when the major organs are formed), and (3) fetal stage (from growth of organs to birth).

Preimplantation Stage: In-Vivo Studies

The duration of the preimplantation period is 5 days for mice, 7 days for rats, and 8 days for humans.[25] It is also the stage in which cells are most sensitive to the lethal effects of radiation, resulting in increased prenatal deaths and resorption of the embryo.[26,27] There are no human data (because pregnancy would not have been established at this time), but experimental data in mice, rats, rabbits, and dogs have been collected.[24-32] All animal studies indicate that if the irradiated embryo did not die, it survived without malformation, leading to the "all-or-none" term coined by Russell in 1956 for radiation effects on the conceptus.[1, 26–31] Structural as well as numerical chromosomal aberrations have been implicated in both preimplantation lethality and in subsequent genomic instability. Recent studies on genomic instability in rodents indicate that irradiation at the preimplantation stage resulted in a surprising increase in chromosomal aberrations several cell divisions after the initial exposure.[32] This is of some concern because of reports that genomic instability is inherited by the next generation,[33] which indicates heritable stable mutations.

Organogenesis: In-Vivo Studies

The principal effect of radiation in rodents during this period is the production of congenital abnormalities, growth retardation, and, if the dose is sufficiently high, embryonic or neonatal death. The consequences of exposure depend on the dose, radiation quality, gestational age of the conceptus, oxygen tension, relative biologic effectiveness (RBE), close interactions between cells in the rapidly dividing fetus, and maternal and environmental factors.[34]

Teratogenesis

By far the most common effect of irradiation during organogenesis in rodents is congenital anomalies (Table 9-2). These frequent and highly varied aberrations are intimately related to the developmental stage during exposure, radiation dose and quality, and other compounding factors. Due to the complexities arising from phase-dependent, biological, and other experimental variations, there are discrepancies in the assessment of the lowest or threshold dose at which various malformations have been observed.[35] Neutrons and beta particles are more damaging to the in-utero fetus than low-LET, radiation-like gamma or X-rays.[1,34] Effects of fractionating the radiation dose depend on the critical period. If the critical period has a narrow window, fractionating the dose over that short period of time increases malformations resulting from cell destruction.

TABLE 9-2

TERATOGENIC EFFECTS OF RADIATION ON RODENTS

Species	Gestational Age (days pc)	Exposure (R)	Effects Observed
Mouse	0.5	5	Increase in resorption
	0.5–1.5	15–20	Exencephaly
	7.5	5	Skeletal malformations
	7.5	5	Decreased litter weight
	8.0	25	Hydrocephalus
	8.5	50	Eye defects
Rat	0.5	5	Growth disturbances
	8.0–9.5	36–40	Ocular and cerebral malformations
	9.0	50	Increase in resorption frequency
	9.0	100	Aortic and urinary malformations
	9.0	50	Brain and spinal malformations
	16–22	10–50	Permanent nerve damage

pc: postconception

The Fetal Stage

The fetal stage extends from the end of major organogenesis until birth (from days 14–20 of gestation in mice and 45–266 in humans). This stage is relatively resistant to radiation lethality and externally detectable malformation at doses below 3 Gy.[32–34] However, anomalies of the central nervous system and sense organs are especially sensitive to the deleterious effects of ionizing radiations. This is accompanied by significant and permanent growth retardation at moderate doses of exposure (~1 Gy). Hematological consequences of fetal irradiation arise from damage to the liver and spleen and manifest as hematological disorders in adults.[35]

Human Studies

Lethality

There are no convincing data in humans regarding lethality of the embryo at the preimplantation period due to the difficulty in determining pregnancy at the initial stages (Table 9-3). However, very few atomic bomb survivors less than 4 weeks of gestational age at the time of the bombing survived, which is an indirect indication of high fetal loss or resorption in the early stages of pregnancies. Higher numbers of stillbirths and neonatal infant deaths were reported for survivors in Nagasaki. Fetal, neonatal, and infant mortality was higher in women who demonstrated radiation sickness and those that were closer to the epicenter of the explosion.[36] Findings following the Chernobyl accident are highly inconsistent; Sweden reported an increase in neonatal mortality, while surrounding Germany, Norway, Finland, and the highly contaminated Kiev region of the former Union of Soviet Socialist Republics showed no changes in perinatal mortality after the accident.[37–40] Studies have focused on stillbirths in 18 European countries and found elevated stillbirths following Chernobyl in the eastern countries of Europe (Poland, Hungary, Sweden, and Greece). In West Germany in May of 1986, mortality among infants within the first 7 days of life was increased, which the authors attributed to Chernobyl fallout in southern Germany.[40,41]

TABLE 9–3

TERATOGENIC EFFECTS OF RADIATION ON HUMANS

	Postconception Time (wk)				
Effects	**Pre-implantation**	**Organogenesis**	**Early Fetal**	**Mid Fetal**	**Late Fetal**
	1	2–7	8–15	16–25	> 25
Lethality	+++	+	+	—	—
Gross malformation	—	+++	+	+	—
Growth retardation	—	+++	++	+	+
Mental retardation	—	—	+++	+	—
Sterility	—	+	++	+	+
Cataracts	—	+	+	+	+
Other neurology	—	+++	+	+	+
Malignant diseases	—	+	+	+	+

—: no observed effect
+: demonstrated
++: moderate incidence
+++: high incidence

Growth Retardation

In 1980, the committee for the Biological Effects of Ionizing Radiation compared the average growth pattern over 17 years of 1,613 children exposed in utero at Hiroshima who were closer to the blast center (< 1,500 m) to those who were farther away (> 3,000 m) and thus received lower doses. Children exposed closer to the hypocenter demonstrated significant growth retardation, averaging 2.25 cm shorter, 3 kg lighter, and head diameters 1.1 cm smaller in circumference. Interestingly, the small head circumference did not alter with age, with most children showing no compensatory growth.[42,43]

Teratogenic Effects

Microencephaly and intellectual disability were the main effects observed in the children of the atom bomb survivors. Microencephaly was phase dependent and observed only in those exposed at 0 to 7 and 8 to 15 weeks of gestation, but not among those exposed at 16 weeks or more.[40,41] Studies on children irradiated during medical exposures revealed several kinds of malformations, including eye anomalies, hydrocephaly, ossification of the cranial bones, deformities, alopecia, divergent squint, blindness, and spina bifida (incomplete closure of the spinal column).[38] The gestational age of 8 to 15 weeks is the most sensitive to radiation injury to the central nervous system, followed by the 16- to 25-week period. This is when the highest incidence of intellectual disability was observed in the Hiroshima-Nagasaki cohort, with a threshold of 0.12 to 0.2 Gy.[1,3,5] Studies on cohorts of children exposed in utero to the Chernobyl fallout validates the earlier findings that radiation can impair cognitive ability at doses lower than projected.[40,41] The decline in intelligence quotient could be seen with doses as low as 0.1 Gy at certain sensitive periods. Further, there was increased frequency of a number of congenital malformations, including cleft lip and/or palate ("hare lip"), doubling of the kidneys, polydactyly (extra fingers or toes), anomalies in the development of the nervous and blood systems, amelia (limb reduction defects), anencephaly (defective development of the brain), spina bifida, Down syndrome, abnormal openings in the esophagus and anus, and multiple malformations occurring simultaneously.[40,41]

Cancer Risk and In-Utero Exposure

Data on the effect of postnatal age at irradiation from follow-up studies of the Japanese survivors of the atomic bombings show that relative cancer risks are greatest for younger ages for a number of cancer types, including carcinoma of the colon and stomach.[38,39] Information on cancer risk following in-utero irradiation is available from studies of prenatal diagnostic X-ray exposures, as well as studies of the Japanese survivors. The largest study of the effects of prenatal diagnostic X-irradiation is the Oxford Survey of Childhood Cancers, a national case-control study of childhood cancer mortality carried out in the United Kingdom. Reviewing the available data from the Oxford Survey and other studies, Doll and Wakeford concluded that there is strong evidence that low-dose irradiation of

the fetus (about 10 mGy), particularly during the last trimester of pregnancy, causes an increased risk of cancer in childhood (< 15 years of age).[40,41,44–47] However, in 2003, the ICRP drew attention to differences between studies in the relative risks estimated for leukemia and solid cancers and concluded that the data provide an insufficient basis for the specification of risks of in-utero irradiation of individual organs and tissues.[40,47]

GENETIC EFFECTS

A complete discussion of the genetic effects of radiation are beyond the scope of this chapter. However, a summary is provided here as a means to assist the clinician caring for an irradiated individual. Exposure to radiation can cause adverse health effects in descendents as a consequence of mutations in the germ cells of irradiated individuals.[1–5] Hereditary or genetic diseases can result when mutations occurring in the germ cells of irradiated parents are transmitted to progeny. Most cancers occur from mutations in somatic cells.

Although it is a common belief that radiation causes bizarre mutations, radiation exposure does not result in effects that are new or unique but rather it increases the frequency of the same mutations that occur naturally or spontaneously in the general population. Hereditary effects are classified into three categories: (1) Mendelian, (2) chromosomal, or (3) multifactorial (Table 9-4). The frequency of these diseases ranges from 0.15 to 7.1 per million in the general population.

Information of the hereditary effects of radiation comes almost entirely from animal and insect studies. These studies have led to the description of the "doubling dose." The doubling dose is the dose required to double the spontaneous mutation incidence. Based on the mouse studies, the doubling dose in humans is estimated to be 1 Gy. The ICRP has estimated that the hereditary risk of radiation is approximately 0.2% per sievert for the general population, and 0.1% per sievert for occupational exposures based on data derived from rodents and insects.[1,2,5]

Children of the atomic bomb survivors have been studied for a number of adverse health indicators, including congenital defects, gender ratio, physical development, survival, cytogenetic damage, malignant diseases, and oncogenic proteins in blood, as described in the section above. The doubling dose was estimated to be 2 Sv, with a lower limit of 1 Sv.

TABLE 9-4

BASELINE FREQUENCY OF GENETIC DISEASES IN HUMAN POPULATIONS

Disease Class	Frequency (per million)
Mendelian	24,000
Autosomal dominant	15,000
X-linked	1,500
Autosomal recessive	7,500
Chromosomal	4,000
Multifactorial	710,000
Congenital abnormalities	879,200

Data sources: (1) Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation; Board on Radiation Effects Research; Division on Earth and Life Studies; National Research Council of the National Academies. *Health Risks From Exposure to Low Levels of Ionizing Radiation*. Washington, DC: National Academies Press; 2006. (2) Sankaranarayanan K. Ionizing radiation and genetic risks IX. Estimates of the frequencies of mendelian diseases and spontaneous mutation rates in human populations: a 1998 perspective. *Mutat Res.* 1998;411(2):129–178.

TRANSGENERATIONAL EFFECTS

While it is well known that maternal exposure to radiation while pregnant can cause birth defects in children, the effects of paternal exposure prior to conception have only recently been studied. Paternal exposure to radiation has been implicated in the etiology of childhood cancer and seems like a possible factor in the occurrence of clusters of childhood leukemias near some nuclear installations. One interpretation of this phenomenon is that genomic instability has been induced in offspring of irradiated male parents. In a case-control study of leukemia and non-Hodgkin's lymphoma, a higher-than-normal incidence of the diseases occurred in children whose fathers worked at the Sellafield reprocessing plant in West Cumbria, UK.[44] This study demonstrated that children of men who had been exposed to penetrating ionizing radiation prior to conception were at an increased risk of leukemia, and the authors speculated that cumulative occupational exposure caused a mutation in a father's spermatozoa that could cause the offspring to develop leukemia.[44] A study of children in other health districts of the United Kingdom, whose fathers also worked in the nuclear industry (atomic weapons establishments at Aldermaston and Burghfield, UK), showed a similar elevation in leukemia development.[45,46] However, several retrospective studies were unable to confirm the observations reported in the Gardner study.[47] Taken together, the results of these studies are inconsistent and

the cause of the leukemia clusters remains unknown at present. Birth defects and leukemia have not been reported in the offspring of service members exposed to fragments of depleted uranium (an internal emitter used in military munitions).

Several in-vitro studies have demonstrated a mechanism by which radiation induces transmissible genomic instability at the cellular level, expressed in the form of chromosomal aberrations.[48] Using an in-vitro bone marrow assay, the authors observed a high incidence of offspring cells containing chromosomal aberrations after exposure of the parental bone-marrow stem cells to alpha particles from plutonium. Several other studies have demonstrated that chromosomal instability in parental bone-marrow cells can be passed on to offspring cells in the bone marrow.[49,50] Exposure to depleted uranium has also been shown to induce genomic instability in unexposed offspring cells.[51]

Transgenerational mouse studies continue to confirm the hypothesis that paternal radiation exposure can cause genomic instability in unexposed offspring. These studies support the hypothesis that preconceptional parental irradiation of mice can cause transgenerational transmission of factors leading to genomic instability and increased mutations in F1 offspring. Recent studies with depleted uranium using a similar transgenic mouse system have demonstrated that preconceptional, paternal depleted uranium exposure can increase gene mutation frequency in unexposed offspring.[52] The studies with depleted uranium are complicated by the fact that it is not only an alpha-particle emitter but is a toxic heavy metal, so no definite conclusions can be drawn as to whether the offspring effects were due to radiation or chemical toxicity because data support the roles of both radiation and heavy metal effects.

While the epidemiological data are controversial regarding preconceptional paternal radiation effects, numerous studies support both the observation and genomic instability mechanism as being involved in rodent and cellular models. Although the results in animal studies were not obtained at the low-dose level to the male parents (100 mSv) in the epidemiological studies,[44] those data with radiation[53] and depleted uranium[52] suggest that there is evidence for transgenerational transmission of factors leading to genomic instability and increased mutations in F1 offspring. A more definitive answer awaits further studies.

RADIATION-INDUCED IMMUNOSUPPRESSION

Radiation-induced immunosuppression is a critical concern in populations exposed to sublethal to lethal doses of ionizing radiation. Radiation results in a dramatic decrease in peripheral blood cell population, especially granulocytes, lymphocytes, and platelets, due to depletion in hematopoietic stem and progenitor cells.[54,55] However, depletion is often followed by delayed repopulation and recovery as the surviving stem cells reconstitute the hematopoietic system. The delay in repopulation can be correlated to the extent of damage to the stem and progenitor cells, which further depends on the absorbed dose.[56] During this delay, individuals are susceptible to opportunistic infections; thus, accelerated recovery is essential to prevent bone-marrow–related injury and mortality. Radiation-induced stem cell damage was first illustrated in a mouse model by Till and McCulloch; the team demonstrated that bone-marrow stem cells from mice exposed to significant doses of ionizing radiation exhibited lower numbers of stem cell colonies in the spleen and poor capacity to reconstitute the hematopoietic system in recipient animals.[56] Reduction in the reconstitutive capacity of hematopoietic stem cells (HSCs) depended on absorbed dose. Since then, this assay is routinely used to assess stem cell function in animal models and is considered an index of the reconstitutive capacity of HSCs.[57–59]

Bone marrow suppression can be prevented by stimulating hematopoiesis and rapid recovery. In clinical and animal models, such recovery is routinely stimulated by use of various cytokines, cytokine mimetics, and hematopoietic growth factors.[60–64] However, it has become increasingly evident that growth-factor–mediated recovery is not entirely a complete hematopoietic recovery. Radiation-induced damage, such as genotoxic stress, in stem cells is not alleviated by cytokines and growth factors.[65] In contrast, replicative stress is induced upon proliferative stimuli in damaged stem cells that may potentially accumulate genomic instability. Indeed, several studies report higher incidences of malignancies in hematopoietic system in response to ionizing radiation.[66]

Prevalence of long-term immunosuppression is also concerning in patients treated with radio- or chemotherapy years after treatment. It was believed that HSCs have finite capacity to replicate, thus mitotic overload in HSCs potentially leads to accelerated aging and exhaustion of the stem cell pool. However, serial bone-marrow transplant experiments suggest that long-term colony-forming units increased upon serial transplantation in mice, showing practically infinite replicative capacity.[67] Also an increase in telomere length did not increase HSC expansion any further compared to control animals.[68] In some

studies involving the effect of oxidative damage in ataxia telangiectasia mutated mice ($ATM^{-/-}$ mice), HSC replicative capacity was inversely correlated to oxidative stress-related DNA damage.[69] Ionizing radiation was also shown to induce expression of senescence markers, such as protein 21 in HSCs in murine models. These studies clearly indicate that preventing DNA damage was the key determining factor in preserving stem cell function.[70,71]

Early onset of leukemogenesis and stem cell aging are major drawbacks of current hematopoietic injury treatments in radiation exposure. More emphasis is required to address the long-term effects of radiation on the hematopoietic system. Current understanding of molecular pathology and more advancement in the regulatory mechanisms of stem cells can help design better drug targets to reduce genomic instability and long-term damage.

REGULATORY GUIDES FOR EXPOSURE

Based on the scientific evidence, the US government (through the National Council on Radiation Protection [NCRP]) has set regulatory guidelines for the occupational exposure of workers and for the general public (Table 9-5). The permissible concentrations for the occupational exposure to radiation workers are 10-fold higher than exposure levels for the general public. It is thought that the presumed detrimental effects on health from exposures at these limits are negligible. Scientific bodies continually reevaluate these risk estimates as additional information becomes available on radiation effects in human populations.

The NCRP has defined a dose of 0.01 mSv/y, equivalent to 10 Gy or 1 mrad of low-LET radiation, as the negligible individual risk level.[1,3,5] This implies that almost every dose of radiation carries potential risk; in some cases, the risk is extremely small and difficult to identify. The goal is to keep exposures as low as is reasonably achievable in daily life and in emergency situations.

SUMMARY

The late effects of ionizing radiation can be divided into three major groups: (1) somatic, (2) genetic, and (3) teratogenic. Somatic damage ranges from fibrosis and necrosis of individual organs to cataracts and cancer (Table 9-6). Most somatic effects require high-threshold doses of radiation; cancer is the main health concern after exposure to low-level radiation. The three most common radiation-induced malignancies

TABLE 9-5

SUMMARY OF RECOMMENDED DOSE LIMITS

Type of Exposure	Dose Limit
Occupational	
Stochastic effects	
Cumulative	10 mSv x age
Annual	50 mSv/y
Deterministic effects (annual dose equivalent limits for tissues and organs)	
Lens of eye	150 mSv/y
Skin, hands, and feet	500 mSv/y
Embryonic/Fetal (effective dose limit after pregnancy declared)	0.5 mSv/mo
Public	
Effective dose limit, continuous or frequent exposure	1 mSv/y
Effective dose limit, infrequent exposure	5 mSv/y
Dose equivalent limits of lens of eye, skin, and extremities	50 mSv/y
Education and Training (annual)	
Effective dose limit	1 mSv/y
Dose equivalent limit for lens of eye	15 mSv/y
Dose equivalent limit for skin and extremities	50 mSv/y
Negligible Individual Dose (annual)	0.01 mSv/y

Data source: National Council on Radiation Protection and Measurements. *Recommendations on Limits for Exposure to Ionizing Radiation.* Bethesda, MD: NCRP; 1993. NCRP Report 116.

are leukemia, breast cancer, and thyroid cancer. The latency periods for the detection of cancer after radiation exposure range from 2 years for leukemia to 30 to 40 years for some solid tumors.

Mathematical models predicting cancer risks based on observations from high radiation exposures imply that 120 to 180 additional cancer deaths will occur for every million individuals receiving 1 cGy of radiation.[1,3,5] This estimate range includes the incidence of all cancers and presumes that no thresholds for induction exist. Some evidence indicates that thresholds for radiation-induced cancer do exist, ranging from 0.01 Gy for breast cancer to 0.2 Gy for leukemia.

Genetic or hereditary effects are the second category of low-level or late effects of radiation. It is estimated that 5 to 65 additional genetic disorders will occur in the next generation for every million individuals receiving 0.01 Gy of gamma or low-LET radiation.[1,3,5] These disorders will be mainly autosomal dominant and gender linked. If each succeeding generation were to receive an additional 0.01 Gy of radiation, equilibrium would be reached in the gene pool, and an average increase of 60 to 1,100 genetic disorders per million individuals would be observed in the population. This would result in a 1.5% increase in the overall incidence of genetic disorders. The normal incidence of genetic disorders in the population is 1 in 10.

The third category of late radiation damage is teratogenic effects. The primary teratogenic somatic effects seen in humans exposed in utero are microencephaly, intellectual disability, and growth retardation. These effects have been observed with an increased incidence in the atomic bomb survivors exposed in utero to doses of less than 0.10 Gy, although a neutron component may have enhanced the radiation effectiveness. In general, thresholds exist for the induction of birth defects by radiation, and effects below 0.10 Gy are negligible. The normal incidence of birth defects is 1 in 10 live births. One concern for low-level exposure to ionizing radiation in utero is the increased incidence of cancer in childhood. An estimated 25 additional cancer deaths are predicted for every million children receiving 1 cGy of radiation in utero.

Preconceptional parental exposures leading to transgenerational effects have recently become a concern. The human data are inconclusive and controversial, so no risk estimates have been established. Further studies in epidemiology and with animal models will provide guidance.

TABLE 9-6

SUMMARY OF DELETERIOUS EFFECTS OF RADIATION*

Endpoint	Risk Estimate
Carcinogenesis (general population; low dose, low dose rate)	5%/Sv
Hereditary effects (general population)	0.2%/Sv
Severe intellectual disability (exposure of embryo/fetus, 8–15 wk)	40%/Sv

*Radiation risk estimates are based upon the human database of radiation-exposed individuals. The relative risk model assumes that radiation increases the spontaneous incidence by a factor. Since the natural cancer incidence increases with age, this model predicts a large number of excess cancers appearing late in life after irradiation. The most recent reassessment of radiation-induced cancer risks by the BEIR V committee was based on a time-related relative risk model. Excess cancer mortality was assumed to depend on dose, age at exposure, time since exposure, and, for some cancers, sex.[1] For example, a 5% risk/Sv means that there is an increased probability of 5 additional cancers per 1,000 individuals exposed per sievert of radiation.

(1) Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation; Board on Radiation Effects Research; Division on Earth and Life Studies; National Research Council of the National Academies. *Health Risks From Exposure to Low Levels of Ionizing Radiation*. Washington, DC: National Academies Press; 1990.

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