2 Ionizing Radiation: Biologic Effects and Essential Cell Biology

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2.1 Introduction

Ionizing radiation can ionize matter directly or indirectly when its quantum energy exceeds the ionization potential of atoms, thus introducing a reactive and potentially damaging ion into the environment of the irradiated medium. Examples of ionizing radiations are X-rays, γ-rays, energetic neutrons, electrons, protons, and heavier particles (such as α-particles). Radiation used in diagnostic imaging and treatment of diseases like cancer consists mainly of high energy photons such as X-rays and γ-rays. Biologic effects of radiation result principally from damage to deoxyribonucleic acid (DNA). DNA damage is considered the principal target in cells (Fig. 2.1). DNA double-strand break (DSB) constitutes the leading and most dangerous type of DNA damage by radiation. In response, three intimately related cellular processes intervene DNA repair, recombination, and replication. Alternatively, inaccurately repaired or unrepaired DNA lesions can lead to mutagenesis and cell death (Fig. 2.1). The biological effects of IR depend on several factors, such as the received dose and the area of the body exposed, making them variable and inconsistent. These effects can be early or delayed, somatic or hereditary, and stochastic or deterministic. Stochastic effects refer to random and unpredictable effects usually following chronic exposure to low-dose radiation. Genetic effects and carcinogenesis following diagnostic imaging are examples of stochastic effects. Deterministic (non-stochastic) effects are non-random effects and have a highly predictable response to radiation. Some of the known deterministic effects are radiation-induced lung fibrosis and cataract. Thus, radiation users need to be familiar with its biological effects and their pathophysiological basis.

2.2 Overview of the Genetic Material

To understand how ionizing radiation can affect cells in in the body, overview the structure of the Genetic material is presented.

2.2.1 DNA and Gene Expression

The ability of cells to maintain a high degree of order depends on the hereditary information that is stored in the genetic material, the DNA. The total genetic information stored in the chromosomes of an organism is said to constitute its genome. The human genome consists of 23 pairs of chromosomes. A chromosome is formed from a single, enormously long DNA molecule that

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A. H. Elgazzar (ed.), *The Pathophysiologic Basis of Nuclear Medicine*,
https://doi.org/10.1007/978-3-030-96252-4_2

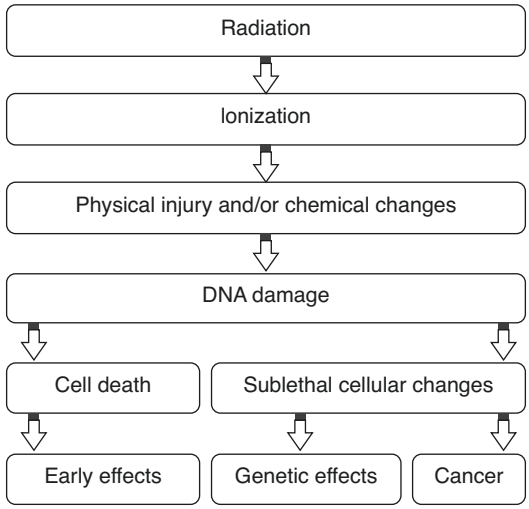

Fig. 2.1 Effects of ionizing radiation

consists of many small subsets called genes; these represent a specific combination of DNA sequence designed for a specific cellular function. There are approximately 100,000 genes per human genome, and only 15% of the genome is actively expressed in any specific cell type. The genetic information is transcribed into ribonucleic acid (RNA), which subsequently is translated into a specific protein on the ribosome. The three most important events in the existence of a DNA molecule are replication, repair, and expression.

2.2.2 DNA Structure

The most widespread DNA structure, discovered by Watson and Crick in 1953, represents DNA as a double helix containing two polynucleotide strands that are antiparallel and following an intrinsic directionality (5′–3′ direction) (Fig. 2.2). The "backbone" of the DNA molecule is composed of the deoxyribose sugars joined by phosphodiester bonds to a phosphate group, while the bases are linked in the middle of the molecule by hydrogen bonds. Two of the bases, thymine (T) and cytosine (C), are called pyrimidines, while the other two, adenine (A) and guanine (G), are called purines (Fig. 2.2). These bases link together through weak hydrogen bonds, and form base pairs. Adenine always pairs with thymine, A and T. Cytosine with guanine, C and G.

2.2.3 DNA Replication and Transcription

To serve as the primary genetic material, all the nuclei chromosomes duplicate their DNA before every cell division. The principle of complementary base pairing dictates that the process of replication proceeds by a mechanism in which a new DNA strand is synthesized that matches each of the original strands serving as a template [2]. Replication is semiconservative, in the sense that at the end of each round of replication, one of the parental strands is maintained intact, and it combines with one newly synthesized complementary strand (Fig. 2.2). At the end of replication, a repair process known as DNA proofreading is catalyzed by DNA ligase and DNA polymerase enzymes, which cut out the inappropriate or mismatched nucleotides from the new strand and replace these with the appropriate complementary nucleotides (Fig. 2.2). The replication process is almost errorless, and the DNA sequences are maintained with very high fidelity. The essence of heredity is the ability of the cell to use the information in its DNA to control and direct the synthesis of all proteins in the body.

2.2.4 DNA Repair, Recombination and Replication

For each type of DNA damage, the cell has evolved a specific method of repairing the damage or eliminating the damaging compound [3–6]. Genetic lesions include DNA base damage or base misincorporation, DNA crosslinks, and DNA strand breaks. These are repaired by (1) direct reversal, (2) base excision repair (BER), (3) nucleotide excision repair, (4) mismatch repair, (5) homologous recombination (HR), (6) nonhomologous end-joining (NHEJ) and (7) translesion DNA synthesis.

DNA single strand breaks (SSBs) are of little biologic consequence as far as cell killing is con-

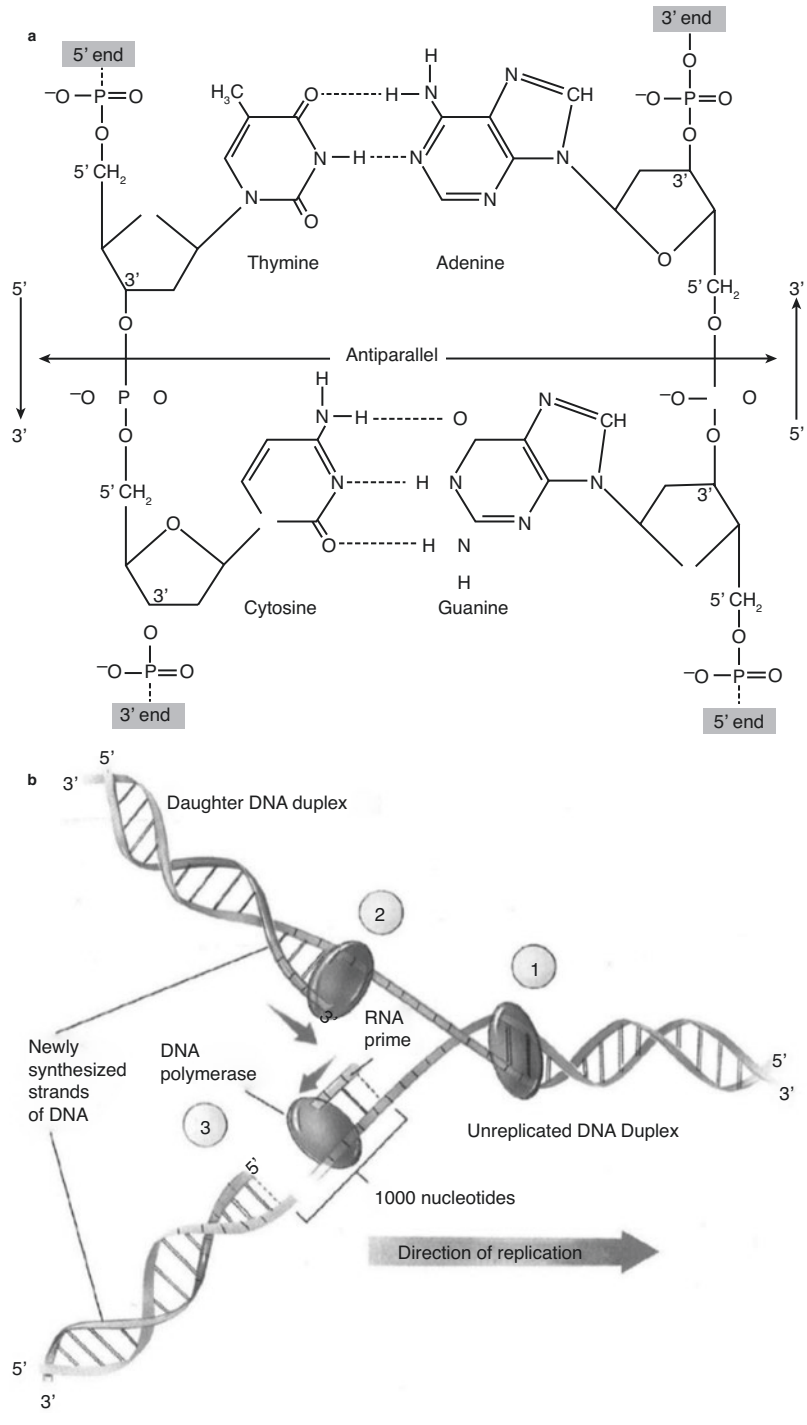

Fig. 2.2 DNA structure and replication. (**a**) The double-stranded DNA molecule consists of four bases (thymine, cytosine, adenine, and guanine), deoxyribose sugar, and phosphate. The antiparallel nature of DNA strands shows the opposite direction of the two strands of a double helix. Note the hydrogen bonds between the two strands of DNA molecules (Reprinted with permission from Devin). (**b**) DNA replication fork. Replication occurs in three stages: special proteins separate and stabilize the strands of the double helix, creating a fork (*1*). During continuous synthesis of a new DNA strand, DNA polymerase adds nucleotides to the 3′ end of a leading strand (*2*). In discontinuous synthesis, a short RNA primer is added 1000 nucleotides ahead of the end of lagging strand. DNA polymerase then adds nucleotides to the primer until the gap is filled (*3*) [1]

cerned because they are repaired readily using the excision repair mechanism. The damaged DNA polynucleotide chain is cleaved by enzymes on either side of the damage. The short segment resulting gap is then filled by a DNA polymerase using the opposite (complementary) undamaged strand as a template to guide the repair process. If just one nucleotide is damaged, it can be fixed by

a process called base excision repair. Here, the damaged base is snipped out and replaced with a new one.

In contrast, DNA double-strand breaks (DSBs) are much more difficult to repair and also much more dangerous. They represent the principal lesion that, if not adequately repaired, can lead to cell death via the generation of lethal chromosomal aberrations or the direct induction of apoptosis [7]. Alternatively, an inaccurately repaired or unrepaired DSB may result in mutations or genomic rearrangements in a surviving cell, which in turn can lead to genomic instability and subsequently result in malignant cell transformation. The cell can repair and/or restart replication forks by multiple mechanisms. For DSBs, there are two principal recombinational repair pathways: the homologous recombination (HR) and the nonhomologous end-joining (NHEJ) that employ entirely separate protein complexes [4, 8, 9].

HR reparation pathway requires an undamaged template molecule that contains a homologous DNA sequence at the time of the radiation damage. This repair by homologous recombination utilizes sequence homology with an identical or highly similar copy of the broken region. It typically operates on the sister chromatid in the late S and G_2 phases of the cell cycle. Undamaged DNA from both strands is used as a template to repair the break. This process is accurate, considered error-free and does not usually cause mutations. However, mutations in genes acting in HR can lead to both impaired DNA replication and increased radiation sensitivity [8, 10].

On the other hand, NHEJ repair pathway of the two double-stranded DNA ends, does not require an undamaged template and does not rely on extensive homologies between the recombinant ends and can possibly occur in all cell-cycle phases. NHEJ is suggested to be the dominant DSB repair pathway. This repairing process involves the repair proteins recognizing lesion termini, cleaning up the broken ends of the DNA molecule, and the final ligation of the broken ends. The process is inherently error-prone and mutagenic because it does not rely on sequence homology and can introduce sequence changes during repair with the loss or addition of nucleotides at the break site [11]. And, mutations in NHEJ genes lead to greater radiation hypersensitivity than mutations in HR genes, suggesting that NHEJ is the dominant pathway for the removal of IR-induced DSBs [8].

2.2.5 Outcomes for DNA Damage Repair

There are essentially four possible outcomes for DNA damage repair. One option is that the cell is able to completely repair the damage, function normally and survive. Another possible option, is that the DNA damage is severe enough and cannot be replaced, and this unfortunately leads to the apoptosis or self-destruction of the cell. It is also possible that the unrepaired mutation prior to mitosis, is passed to the daughter cells with three possible resulting responses:

1. Critical life-sustaining components are missing; the daughter cell may become apoptotic. Sufficient DNA damage may trigger an apoptotic signaling cascade, forcing the cell into programmed cell death.
2. The daughter cell survives the permanent genetic mutation to pass on its damaged DNA and may become senescent, i.e., irreversibly dormant. A gene mutation is any inherited change in the genetic material involving irreversible alterations in the sequence of DNA nucleotides. It may be classified into two categories: base substitutions and frameshift mutations. These mutations may be phenotypically silent (hidden) or expressed (visible). Research show that radiation increases the rate of mutation [12].
3. The daughter cell survives the mutation and may become malignant. If enough mutated cells survive, they can undergo rapid cell division and form a new growth called a neoplasm or a new growth called a tumor. Tumors are an abnormal mass of tissue. Sometimes these neoplasms can be benign, in other words, not harmful to our health. But in other times, they can be malignant, what we call cancerous [13].

2.2.6 Tumor Suppressor Genes

Many genes are activated in our body's repair pathway. Tumor suppressor genes, for instance, is a class of genes that encode proteins to control cell division and block cancerous cells from proliferating. However, if a tumor suppressor gene is lost or mutated with loss of its activity, uncontrollable mitosis is initiated, leading to cancer development. So the inactivation of tumor suppressor genes is one type of genetic alteration that contributes to tumor genesis. There are many different cancer suppressor genes, but an essential one is the p53 gene. Mutations of the gene p53 could play a role in up to 50% of all cancers, including leukemia, brain tumors, breast and colon, and lung carcinomas.

Mutations of tumour suppressor genes can also be inherited. BRCA1 and BRCA2 are two cancer suppressor genes associated with inherited or familial breast cancer. All cells contain two copies of BRCA1 and BRCA2 genes. Some individuals are born with a specific mutation or different mutations in these genes, and they develop an increased incidence of breast cancer. Individuals who inherit mutations have usually one copy of the gene that is not working. If the other copy is lost, DNA repair is not possible. Moreover, when the cell replicates its DNA during cell division, more mistakes enter into that replicate. Those mistakes make it more likely that the cell will become cancerous.

2.3 Basic Cell and Tissue Biology

The human body contains trillions of cells generated by repeated division from a single precursor cell. They constitute clones. With proliferation, some cells become specialized with a different structure, chemistry, and function.

More than 200 distinct cell types assemble into various tissue types such as epithelial, connective tissue, muscle, and nervous tissue. Different cells assemble to form each organ in the body. Although these cells often differ markedly, they all have similar essential characteristics.

2.3.1 Cell Types

The human body contains approximately 200 different cell types that represent, for the most part, discrete and distinctly different categories based on histological and morphological characteristics and cellular function. Recent subtler techniques involving immuno-histology and mRNA expression reveal new subdivisions of cell types within the traditional classification. Different cell types, such as neurons and lymphocytes, have the same genome, but the structural and functional differences are so extreme that it is difficult to imagine coming from the same cell. Different cell types synthesize different sets of proteins.

Differentiated cells have unique proteins with specific functions absent in other cells. The genome of a cell contains the essential information to produce thousands of different proteins and RNA molecules in its DNA sequence. A cell typically expresses a fraction of these genes, and the different types of cells in a human body arise from the expression of different sets of genes. Moreover, cells can change the genes they express in response to signals from other cells or the environment.

Different cells perform different functions. The most important cellular functions are movement, conductivity, metabolic absorption, secretion, excretion, respiration, and reproduction.

2.3.2 Tissue Types

In the human body, specialized cells of one or more types organize into cooperative assemblies, the tissues that perform unique functions. Different types of tissue compose organs, and organs, in turn, are integrated to perform complex functions.

The four major tissue types are epithelial, muscle, connective, and nervous. Some tissues do not exist as isolated units but rather in association with one another and variable proportions, forming different organs and systems in the body such as blood and lymphoid tissues. Such tissue cells are in contact with a network of extracellular

macromolecules known as the extracellular matrix, which holds cells and tissues together, that provides an organized latticework within which cells can migrate and interact with one another.

All tissues are further divided into many subtypes (Table 2.1).

2.3.3 Normal and Neoplastic Growth of Cells

Cellular reproduction is usually a tightly controlled process. Social control genes regulate cell division, proliferation, and differentiation under normal conditions. Certain stimuli and growth factors, both physiological and pathological, can influence a cell's reproduction rate. An uncontrolled cellular division that serves no purpose is called neoplasia. The uncontrolled growth of an abnormal cell that serves no purpose will give rise to a tumor or neoplasm that can be benign or malignant. Transformation is the process by which a normal cell becomes a cancer cell.

The common characteristics of cancerous tissue include a local increase in the cell population, loss of typical arrangement of cells, variation of cell shape and size, increase in nuclear size and density of staining, increase in mitotic activity, and abnormal mitoses and chromosomes.

Cancer cells produce many substances referred to as tumor cell markers. These can be hormones, enzymes, gene products, or antigens found on tumor cell plasma membrane or in the blood, spinal fluid, or urine. Regarding the tissue origin of cancer, in children up to 10 years of age, most tumors develop from hematopoietic organs, nerve tissues, connective tissues, and epithelial tissues (in decreasing order). This proportion gradually changes with age so that after 45 years of age, more than 90% of all tumors are of epithelial origin.

2.3.4 Cell Death

Cell death is essential in maintaining tissue homeostasis, embryonic development, immune self-tolerance, killing by immune effector cells, and regulation of cell viability by hormones and growth factors [14, 15].

Deregulation of cell death, however, is a feature of disease including cancer, myocardial infarction, cerebral stroke, and autoimmunity [14].

Based on the new recommendations of the nomenclature committee for cell death, it can be regulated and nonregulated. The regulated type is represented predominantly by apoptosis but also includes other types (Table 2.2).

2.4 Sources, Types, and Effects of Ionizing Radiation

2.4.1 Sources of Ionizing Radiation

Our bodies are exposed to radiation in two different ways depending on the location of the radiation-emitting source. For "external exposure," radiation comes from a radiation-emitting source present outside the body, such as radioactive materials existing on the ground, suspended in the air, or attached to clothes or the body's surface. Conversely, for internal exposure to radiation, radioactive material is present inside our bodies. Internal exposure to ionizing radiation can come from sources (1) ingested from food or drink; (2) inhaled from the air; (3) absorbed through the skin (percutaneous absorption); (4) from wound contamination, and (5) administered of radiopharmaceuticals for medical diagnostic imaging or therapeutic purposes. Once radioactive materials enter the body, the body will continuously be exposed to radiation until the radioactive materials are excreted biologically in the urine or feces (biological half-life) or as the radioactivity weakens over time. The difference between internal and external exposure lies in whether the radiation source is inside or outside the body. The body is equally exposed to radiation in both cases.

Exposure to ionizing radiation comes from several natural and man-made sources (Table 2.3). Whether the radiation source is natural or artificial, and independently of the dose of radiation, there will be some biological effects. The nuclear medicine professional should provide informa-

Table 2.1 Tissue types

Tissue	Tissue type	Location	Function
Epithelial	Simple squamous	Lines major organs	Absorption, filtration, secretion
	Simple cuboidal	Lines tubules and ducts of glands	Absorption and secretion
	Simple columnar	Lines GI tract	Secretion and absorption
	Stratified squamous	Lines interior of mouth, tongue, vagina	Protection
	Transitional	Lines urinary bladder	Permits stretching
Connective	Loose connective	Deep layers of skin, blood vessels, organs	Support, elasticity
	Dense connective	Tendons, ligaments	Attaches structures together, provides strength
	Elastic connective	Lungs, arteries, trachea, vocal cards	Provides elasticity
	Reticular connective	Spleen, liver, lymph nodes	Provides internal scaffold for soft organs
	Cartilage	Ends of long bones, trachea, tip of nose	Provides flexibility and support
	Bone	Bones	Protection, support, muscle attachment
	Vascular connective tissue	Within blood vessels	Transport of gases, blood clotting
	Adipose tissue	Deep layers of skin, surrounds heart, kidney	Support, protection, heat conservation
Muscle	Smooth muscle	GI tract, uterus, blood vessels, and bladder	Propulsion of materials
	Cardiac muscle	Heart	Contraction
	Skeletal muscle	Attached to bones	Movement
Neural	Different types of neurons	Brain and spinal cord	Conduction of electrical impulse, neurotransmission

Table 2.2 Cell death classification

1. Regulated (programmed, noninflammatory)
Apoptosis
Autophagy
Necroptosis
Mitotic catastrophe
Lysosomal-mediated programmed cell death
2. Nonregulated (inflammatory, accidental)
Necrosis

Table 2.3 Sources of ionizing radiation

Natural sources	Man-made sources
External radiation	Medical
Cosmic rays	Occupational
Terrestrial radiation	Nuclear power
Internal radiation	Nuclear explosions
Inhalation (radon gas)	Nuclear accidents
Ingestion	

tion to the patient and the public about the radiation risks from these sources and compare exposure from medical procedures to natural sources.

2.4.2 Types of Ionizing Radiation

Incident electromagnetic radiation (X-rays and γ-rays) or charged particulate radiation (α-particles, β-particles, and neutrons) interact with orbital electrons within the cellular atoms and molecules to cause their excitation or ionization. α-particles are helium nuclei made of two protons and two neutrons ejected at high speed, while β-particles are electrons ejected from a nucleus. Particle beams also include neutron beams and proton beams. γ-ray photons are types of electromagnetic waves. While α-particles, β-particles, and γ-ray photons originate within the nucleus, X-ray photons are generated outside the nucleus. X-ray photons include Bremsstrahlung (braking) X-rays and characteristic X-rays. Exciting radiations involve raising a bound electron to a higher energy state. A low-energy particle transfers sufficient energy to bump an electron from the atom's inner to the outer shell without removing it from its orbit.

The atom is in a higher energy state and is thus, called excited. The displaced electron promptly returns to the lower-energy shell, releasing its recently acquired energy as characteristic X-ray in a process called de-excitation. Ionizing radiations can create an ion pair following the electron ejection process. Ionization occurs when the radiation has sufficient energy to overcome the electron's binding energy and completely eject it from its orbit. The ejected electron may be sufficiently energetic to cause secondary ionizations on its own. Such an electron is called a delta γ-ray. The vacancy or positive electric charge in the host atom makes it very reactive. It will be easily attracted and interact with atoms having an excess negative charge. The irradiation of cellular material with such ionizing radiation gives rise to a flux of energetic secondary particles (electrons). These unbound secondary electrons migrate away from their production site and perturb the surrounding medium by giving up their energy through a series of interactions with other atoms and molecules.

Charged particles have high kinetic energy and can ionize matter directly. They deposit energy in the medium through direct Coulomb interactions with the orbital electrons of atoms in the absorber. In particular, α-particles have a high ionization density, causing ionization at a density hundred times as high as that of β-particles.

Indirectly ionizing radiation consists of uncharged, neutral particles such as X-ray or γ-ray photons which ionize matter indirectly using secondary electrons generated through their interaction with the substances. They deposit energy in the absorber through a two-step process. The neutral particle releases a charged particle in the absorber. Furthermore, the produced particle deposits partially or completely its kinetic energy in the absorber through Coulomb interactions with the orbital electrons. Energy transfer from the primary radiation beam to biological targets is constantly via the flux of secondary electrons produced, irrespectively of the nature of the primary radiation (charged particles and electromagnetic waves). These unbound and energetic secondary electrons can migrate away

from their production site and perturb the surrounding medium by giving up their energy through a series of interactions with other atoms and molecules. This energy absorption process gives rise to free highly reactive and unstable radicals, and it is the subsequent chemical interaction involving these are the true causative of radiation damage.

The energy from ionizing radiations is not deposited uniformly in the absorbing medium. When α- and β-particles or X- and γ-rays interact with matter, they transfer their energy heterogeneously and generate thus, clusters of ionization within a few nanometers diameter range, i.e., high-density ionization [16]. For energy deposition below 100 eV, spurs are produced. They involve, on average, three ion pairs within a diameter of about 4 nm. For an energy level ranging between 100 to 500 eV, blobs with 12 ion pairs within a diameter of about 7 nm are produced. Blobs are groups of overlapping spurs. For X-rays and γ-rays, 95% of the energy deposition events are spurs, whereas blobs remain less frequent [16]. These ionization clusters have dimensions similar to the DNA double helix diameter (about 2.5 nm) and can cause multiple radical attacks if they overlap the DNA helix. Thus, these locally multiplied damage sites could lead to considerable local damage, including DSBs, SSBs, and base damage.

External exposure to α-particles does not cause harmful effects on the body. α-particles cannot penetrate the skin layer because their penetrating distance is about several tens of micrometers. However, internal exposure to radioactive material that emits α-particles causes large amounts of ionization clusters within tissues, providing concentrated energy.

Ionization clusters can significantly damage DNA and have strong biological effects. β-particles cause direct ionization, but because of their low ionization density, their biological effects are less catastrophic than those of α-particles. β-particles have a penetrating distance of about several millimeters and could affect the skin and subcutaneous tissues. β-particles can cause burn-like symptoms when doses are very high, but they do not reach deep into the body. γ-rays and X-rays reach deep organs and tissues because of their high penetrating power. Nevertheless, because of their low ionization density, their biological effects are similar to those of β-particles.

On the other hand, in the case of internal exposure, all radioactive materials emitting α-particles, β-particles, or γ-rays could strongly affect cells within the body. Given the distance α-particles travel, their effects are visible on tissues containing the radioactive materials. However, due to their significant biological effects, caution is required with internal exposure.

2.4.3 Biochemical Effects of Exposure to Ionizing Radiation

Biological damage occurs due to chemical changes caused by ionization at the cellular level. Cell materials can be affected by ionizing radiation either directly or indirectly [16] (Fig. 2.3).

The two mechanisms of ionizing radiation effects on DNA: the direct, or target, mechanism and the indirect, through the production of free radicals that consequently cause damage.

2.4.3.1 Direct Effect

Direct effects of ionizing radiation occur when radiation ionizes atoms in DNA molecules or some other parts of the cell critical to its survival. The direct effect of ionizing radiation acts by direct collisions with target atoms. All atoms or molecules within the cells, such as enzymatic and structural proteins and RNA, are vulnerable to ionizing radiation injury. DNA, however, is the principal target [16]. If enough atoms are affected such that the chromosomes do not replicate properly, or if there is a significant alteration in the information carried by the DNA molecule, then the cell may be destroyed by "direct" interference with its life-sustaining system.

Charged particles with sufficient energy, e.g., electrons, interact directly with cellular components (atoms, molecules) without an intermedi-

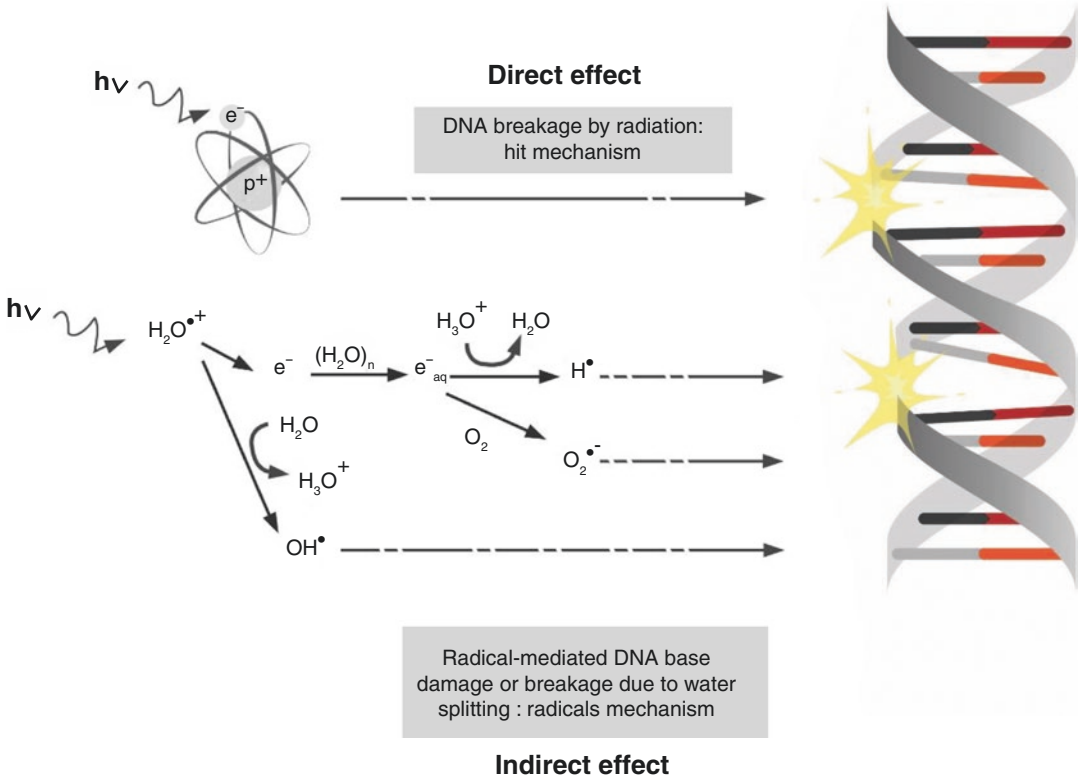

Fig. 2.3 Direct and indirect effects of radiation on DNA

ary step. The charged particle can continue interacting with other cellular atoms or molecules until all its kinetic energy is lost. Such interaction may ionize or excite the atoms and initiate a chain of events leading to a biological change and affecting the ability of the cell to reproduce and, thus, survive. The recoil electron directly ionizes the target molecule by creating ions that can physically break either the sugar–phosphate backbone of the DNA or its base pairs, thus affecting the ability of the cell to reproduce and ultimately survive. Luckily, ionizing radiation rarely interacts directly with DNA molecules as they occupy only a tiny fraction of the cell. In typically oxygenated cells, the direct effect of ionizing radiation accounts for about one-third of the damage for low LET radiations (such as electrons and photons).

2.4.3.2 Indirect Effect

Indirect effects of ionizing radiation are more frequent to occur. The indirect effect remains the leading cause of radiation damage, with about two-thirds of the biological damage. It is predominant with low linear energy transfer (LET) radiation, e.g., X-rays and γ-rays. At the same time, direct action is dominant with high LET radiation, e.g., charged particles (α- and β-particles) and neutrons. Indirect action of ionizing radiation involves radiation effects on atoms or molecules which are not constituent parts of the biological target. The probability of radiation interaction with DNA is minimal since it only represents a small cell fraction. As water is the main component of cells, there is a much higher probability that the recoil electron will interact with the water molecules.

The indirect effect of ionizing radiation occurs when an uncharged particle, e.g., photons, forms a free radical through water radiolysis of the cellular water molecule. When ionizing radiation interacts with a water molecule, the energy absorbed by the water molecule results in the breakage of the bonds holding the molecule together and in the formation of ion pairs such as hydrogen (H) and reactive oxygen metabolites such as hydroxyl radicals (OH) (Fig. 2.3). If oxygen atoms are present in the medium, other more aggressive free radicals such as hydroperoxyl and hydrogen peroxide can form. Free radicals are uncharged molecules carrying an unpaired valence electron in the outer shell. This state is associated with a high degree of chemical instability and makes them highly chemically reactive. Free radicals may recombine or interact with other fragments or ions to form compounds, such as water, without harming the cell. Free radicals would also quickly bond to other atoms or molecules, creating toxic substances like hydrogen peroxide (H_2O_2), contributing to apoptosis. Free radicals can also diffuse far enough to reach the critical target and produce chemical modifications and harmful effects. For the indirect action of X-rays, for example, the chain of events, from the absorption of the incident X-ray photon to the final observed biologic effect, may be described as follows:

1. When X-ray photons interact with water, two types of free radicals can be formed:

$$H^{\cdot} \rightarrow H^{\cdot}\left(\text{hydrogen}\right) + OH^{\cdot}\left(\text{hydroxy}\right).$$

2. The presence of an excess of oxygen during cells irradiation allows the formation of additional free radicals and increase biological damage:

$$R^{\cdot} + O_2 \rightarrow RO_2^{\cdot}\left(\text{highly toxic}\right).$$

$$H^{\cdot} + O_2 \rightarrow HO_2^{\cdot}\left(\text{hydroxyperoxy free radicals}\right).$$

$$HO_2^{\cdot} + HO_2^{\cdot} = H_2O_2\left(\text{highly toxic}\right) + O_2.$$

It is worth noting that antioxidants block hydroxyl-peroxy free radical combination into the highly unstable hydrogen peroxide.

3. Those highly toxic free radicals will induce chemical changes in the DNA structure from breaking its bonds, leading to severe biologic damages.

2.5 Cellular Effects of Exposure to Ionizing Radiation

To understand the biological effects of radiation exposure, it is thus essential, to begin with, a description of the different cellular lesions such as DNA damages (i.e., breaks) (Fig. 2.4) which will lead to cellular injury if not repaired as well as genomic instability and cancer.

2.5.1 Radiation-Induced DNA Strand Breaks

Ionizing radiation induces many DNA lesions, most of which are repaired successfully by the cell. Ionizing radiation can cause DNA lesions directly (the recoil electron directly ionizes the target molecule) or indirectly (the recoil electron interacts with water to produce an OH. free radical, which diffuses and interacts with the target molecule, here DNA). A dose of radiation causing one lethal event per cell (on average) leaves 37% of irradiated cells still viable; this is called the D0 dose. For mammalian cells, the X-ray D0 dose usually lies between 1 and 2 Gy. The number of DNA lesions per cell detected immediately after exposure to 1 mGy of X-rays (the equivalent of 1 mSv) is on average equal to 1 single-strand break at one location per cell. Double-strand breaks occur less frequently, at 0.04 locations per cell, which means that if 100 cells are evenly exposed to 1 mGy of X-rays, double-strand breaks occur in four cells (Table 2.4) [17].

Irradiated cells with a modest dose of X-rays, many breaks of a single-strand occur. By contrast, if the breaks in the two strands are opposite

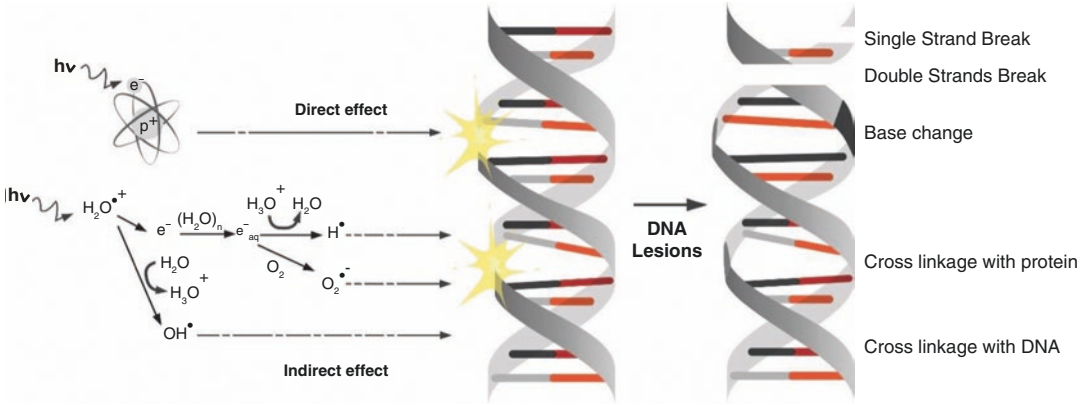

Fig. 2.4 DNA lesions: DNA strand breaks and base loss

Table 2.4 Radiation-induced DNA damages

Damage per 1 mGy of X-rays (per cell)	Averaged number of DNA lesions
Base damage	2.5
Single-strand breaks	1.0
Double-strand breaks	0.04
DNA–DNA crosslinks	0.03

one another or separated by only a few base pairs, this may lead to a DSB (double-strand break), resulting in chromatin cleavage into two pieces. DSBs are believed to be the principal lesions produced in chromosomes by radiation [18].

The interaction of two DSBs can cause cell killing, carcinogenesis, mutations, or genetic effects. There are many kinds of DSBs. They vary in the distance between the breaks on the two DNA strands and the types of end groups formed. The DSB yield in irradiated cells is about 0.04 times that of SSBs, and they are induced linearly with dose, indicating that single tracks of ionizing radiation form them. And, if breaks from both free radicals and direct ionizations occur in both directly opposed strands or separated by only a few base pairs, this could induce a double-strand break in which the chromatin snaps into pieces.

While the number of DNA lesions generated by irradiation is large, there are several mechanisms for DNA damage repairing or eliminating the damaging compound. As a result of cells tremendous ability to repair the damage, not all radiation effects are irreversible, and the percentage of lesions evolving into cell apoptosis is low. Multiple enzymatic mechanisms for detecting and repairing radiation-induced DNA lesions are triggered. They play an essential role in the recovery of cells from radiation and other damaging agents. SSBs have little biologic consequence as far as cell killing is concerned because they are repaired readily using the excision repair mechanism.

On the other hand, DSBs are much more difficult to repair and also much more dangerous. They represent the principal lesion that, if not adequately repaired, can generate lethal chromosomal aberration and lead to cell death. The homologous recombination (HR) and the nonhomologous end-joining (NHEJ) are the two primary repair pathways for DSBs [4, 8, 9].

Alternatively, inaccurately repaired DSB may result in mutations or genomic rearrangements in a surviving cell. In turn, it can lead to genomic instability and subsequently result in malignant cell transformation [19].

2.5.2 Radiation Induced Cell Injury

In general, an injury with a high chance of repair is sublethal, repaired with treatment is potentially lethal, and permanent is considered lethal. The nucleus is relatively more radiosensitive than the

cytoplasmic structures. Nuclear changes after radiation include swelling of the nuclear membrane and disruption of chromatin materials. Cytoplasmic changes include swelling, vacuolization, mitochondria disintegration and endoplasmic reticulum disintegration, and reduction in the number of polysomes [20, 21].

Depending on the radiation dose and the subcellular changes, along with the previously described factors, the potential effects on the cell may vary [20] (Table 2.5). Radiation dose is expressed as the absorbed energy by the irradiated tissue. After exposure to ionizing, cellular injury occurs in one of the following forms [22]:

1. Division delay: After exposure to 0.5–3 Gy of radiation, delayed mitosis is observed; however, near-normal restoration of mitotic activity is achieved following several generations.
2. Reproductive failure: The failed mitotic activity is permanent, and eventually, cell death follows. This is observed linearly after exposure to more than 1.5 Gy. Below this level, the reproductive failure is random in nature and nonlinear.
3. Interphase death: Apoptosis, or programmed cell death, is defined as a particular set of microscopic changes associated with cell death. Radiation-induced apoptosis is highly related to the type of involved cell. Lymphocytes, for example, are highly susceptible to radiation by this mechanism.

Table 2.5 Types of cellular damage in relation to approximate radiation dose

Dose grays (rads)	Type of damage	Comments
0.01–0.05 (10–50)	Mutation (chromosomal aberration, gene damage)	Irreversible chromosome breaks, may repair
1 (100)	Mitotic delay, impaired cell function	Reversible
3 (300)	Permanent mitotic inhibition, impaired cell function, activation and deactivation of cellular genes and oncogenes	Certain functions may repair; one or more divisions may occur
>4–10 (>400–1000)	Interphase death	No division
500 (50,000)	Instant death	No division
		Proteins coagulate

2.5.3 The Bystander Effect and Genomic Instability

Radiation effects have been observed to an extent beyond that explained by effects exerted on directly irradiated cells. Cells in temporal or spatial distance from the initial radiation insult have been shown to have delayed effects of radiation. Two phenomena are described: The Bystander Effect and the Genomic Instability.

The Bystander effect refers to the radiation damage induced in cells within an organ or the whole body that have not been directly exposed to radiation. In other words, a cell that a charged particle has not traversed is damaged as a result of radiation interactions occurring in neighboring cells [23–25]. A possible explanation is that, through cell-to-cell interaction, the directly irradiated cells communicate with adjacent cells (local level), which may elicit a response from the latter and spread the effect of radiation to a more significant number of cells and distant organs (long-range abscopal level). The mechanism is not clearly understood, and the overall relevance is currently difficult to gauge; however, gap junctional intercellular communication [26] or release of soluble factors (such as cytokines) [27] from irradiated cells is presented.

The Bystander effect has been mainly described for densely ionizing radiation such as charged α-particles [28, 29]. However, it has also been observed in low LET radiation (such as X-rays or γ-rays). Low LET radiation amplifies the overall radiation effect, making the overall radiation risk higher than expected from considerations of the gross response exhibited by those cells that have been directly irradiated. Bystander (nontargeted) and directly irradiated cells show a similar type of DNA damage, mutation and carcinogenesis [24].

Maximal radiation-induced genetic damage is formed shortly (minutes to hours) after radiation exposure. Nevertheless, it has been observed that the irradiated cells and descendants may show delayed effects. Cells that sustain nonlethal DNA damage show an increased mutation rate in descendants several generations after the initial exposure [30]. Delayed effects include delayed reproductive death up to six generations following the primary insult [31].

2.6 Factors Affecting Radiation Hazards

2.6.1 Factors Related to Ionizing Radiation

Radiation injury is a function of the ionizing radiation type and the target tissue. Specific factors related to radiation itself determine the various effects of the same radiation dose on biological organs.

1. Type of Radiation
   Electromagnetic and particulate (charged and uncharged) ionizing radiation have different ionizing properties. They differ in penetrability based on their LET, which expresses energy loss per unit distance traveled (kilo electron volts per micrometer). The linear energy transfer (LET) is high for α-particles, lower for β-particles, and less for γ-rays and X-rays. α-particles are the least penetrating but induce severe cellular damage. β-particles travel a longer distance, and γ-rays are the most penetrating type of ionizing radiation.
2. Mode of Administration
   The radiation dose is an essential factor. In addition, a single dose of radiation causes more damage than the same dose being divided (fractionated). Collectively these two factors are expressed as dose per fraction.
3. Dose Rate
   Dose rate expresses the time for which dose is administered. If the same total dose is administered over a more extended period, the cellular repair is improved, and cellular damage becomes negligible.

2.6.2 Factors Related to Biological Target

Certain properties of tissues and cells can significantly modify the biological effects of ionizing radiation.

2.6.2.1 Cell-Cycle Phase

Normal cells are cycled through five physiological phases: the pre-DNA synthetic phase (G1), the DNA synthetic phase (S), the post-DNA synthetic phase (G2), mitosis (M), and the more recently identified phase of no growth (G0), corresponding to the time after mitosis to the start of the G1 phase [32].

- The G0 phase is a latent phase. Cells are prepared to be recruited into the reproductive cycle, the G1 phase.
- The G1 phase is the first active phase of the reproductive cycle. In this phase, the cells synthesize RNA, enzymes, and proteins in anticipation of entering subsequent phases of the reproductive cycle.
- The S phase follows the G1 phase. The predominant event in this phase is the synthesis of DNA. At the end of the S phase, the cells contain twice the original amount of DNA.
- The G2 phase follows the S phase. During the G2 phase, the mitotic spindle essential for cell division is created. In the mitotic phase, the M phase, cell division takes place.

Ionizing radiation can affect all phases of the cell cycle with different radiosensitivity. Cells are most radiosensitive in the G1, G2, and M phases, respectively. They are most radioresistant in the S phase. Irradiation during the G2 phase retards the onset of cytokinesis. Irradiation during mitosis induces chromosomal aberrations. For a given cell cycle, radiation injury also differs from one cell type to another by altering radiation injury. For example, the reproductive cells have higher radiation sensitivity during the M phase, whereas

DNA synthesis and chromosome lesions occur during the G2 phase.

Recovery from sublethal injury happens in all phases of the cell cycle. However, this is more important in the S phase, which is also the most radioresistant phase. Exposed cells to radiation in the G0\G1 phase of the cell cycle tend to cease their progression into the G2\M phase. G2 synchronization produces a cluster of radiosensitive cells. A second hit within a time frame of 5–12 h leads to a higher proportion of deleterious effects [33]. The latter happens for radioisotopes with sequential α or β decay as in 90Sr\90Y [33].

2.6.2.2 Cell Radiosensitivity

The degree of cell sensitivity is directly related to the reproductive capacity of cells and tissues, thus stem cells (germ cells are more radiosensitive than mature differentiated cells. In 1906, one of radiology's most important discoveries was made: the law of Bergonié and Tribondeau, which states that "the Radiosensitivity of a tissue is directly proportional to its reproductive capacity and inversely proportional to its degree of differentiation" [34]. Although all cells can be affected by ionizing radiation, normal cells and their tumors vary in their sensitivity to radiation.

Radiosensitivity varies in function of the mitosis rate and cellular maturity. Rapidly dividing cells are more radiosensitive than cells that do not divide. And, undifferentiated cells are more radiosensitive than the mature cells that have specialized in function (Fig. 2.5). For example, undifferentiated hematopoietic cells in bone marrow proliferating from stem cells and differentiating into various blood cells are susceptible to radiation. They die after exposure to a small

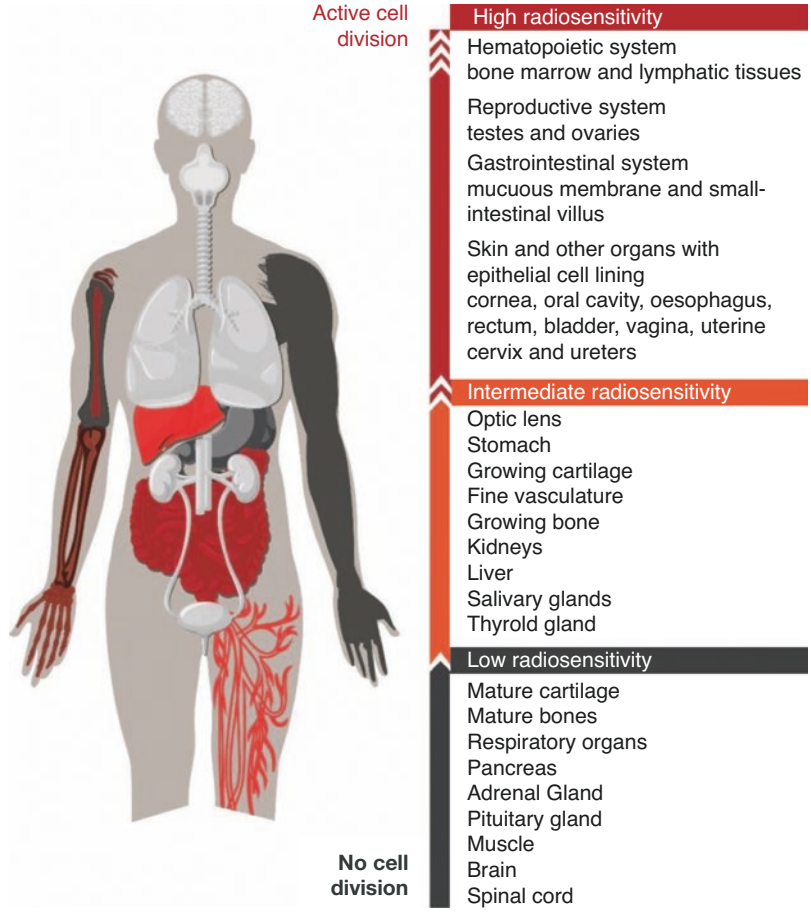

Fig. 2.5 Organs and tissues radiosensitivity

amount of radiation. As a result, the supply of blood cells is suspended, and the number of various types of cells in the blood decreases. In addition, the epithelium of the digestive tract is constantly metabolized and is also highly sensitive to radiation. On the other hand, nerve tissues, muscle tissues, and parathyroid cells are highly radioresistant. They no longer undergo cell division at the adult stage and are known to be resistant to radiation (Fig. 2.5).

2.6.2.3 Effect of Radiation Dose on Cell Dynamics

Exposure of highly dividing cells to high dose radiation would severely delay cell division activity. The mitotic rate is affected for an extended period before going back to normal. Exposure of highly dividing cells to moderate doses of radiation would delay mitotic activity on average for an intermediate period. Subsequently, the mitotic activity is moderately increased shortly before returning to normal. Moreover, exposure of highly dividing cells to low dose radiation would lead initially to a mild delay in cells mitotic activity followed by a short period of increased mitosis before the mitotic rate returns to normal.

2.6.2.4 Repair Capacity of Cells

Some cells have a higher capacity than others to repair the damage caused by ionizing radiation. Thus, the biological effects of the same radiation dose differ from one cell to the other. A significant repair occurs quickly, within 3 h. However, malignant cells have a decreased capacity to repair radiation damage.

2.6.2.5 Degree of Tissue Oxygenation

Molecular oxygen potentiates radiation response; this is called the oxygen effect. The amount of present molecular oxygen rather than the rate of oxygen utilization by the cells is the most critical factor to increase cellular radiation sensitivity. The probable mechanism is the allowance of additional free radicals, which enhance the damage of cells [21]. The free radicals produced due to direct or indirect effects of ionizing radiation are highly reactive will interact with other molecules to share electrons. Molecular oxygen (O_2) has two unpaired electrons and can thus directly interact with free radicals, leading to DNA damage by the indirect chain of reactions.

2.7 Biological Effects of Exposure to Ionizing Radiation

The effects of ionizing radiation on the human body depend on several factors, such as the nature of the effect and the timing after exposure. Biological effects due to exposure to ionizing radiation are variable and inconsistent. They can appear early (short term) or delayed (long term), be somatic or hereditary, and stochastic or deterministic types of effects (Fig. 2.6). Effects symptoms that appear within several weeks are acute (early) effects, while effects that develop after a relatively long time are called late effects. In particular, it takes several years to decades until a person develops cancer. Radiation effects can also be classified in the difference in mechanisms of how radiation effects appear, i.e., deterministic effects and stochastic effects.

Deterministic effects manifest themselves with a severity that is dose-related. They do not appear unless exposed to radiation exceeding a certain level of radiation dose after which the response is dose-related: a threshold value. Most of the deterministic effects represent acute disorders whose symptoms appear within several weeks after exposure. And, mostly known deterministic effects are radiation-induced lung fibrosis and cataract.

On the other hand, stochastic effects refer to random and unpredictable effects usually following chronic exposure to low-dose radiation. Their incidence cannot be denied entirely, even with low-dose exposure. Stochastic effects are dose-related, but the severity of the resultant condition is not related to the received dose. Thus, their management is generally on the safe side under

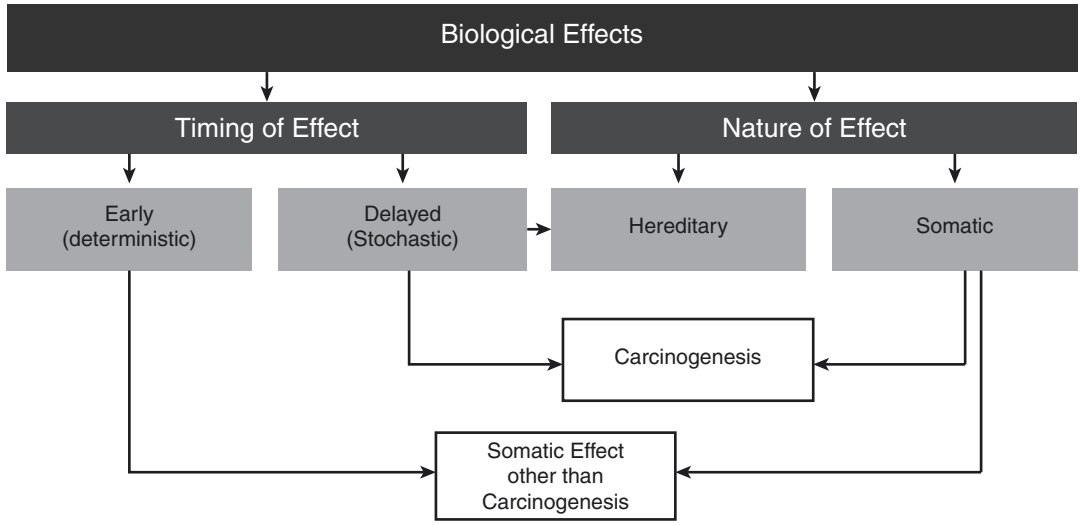

Fig. 2.6 The various biological effects of ionizing radiation

the assumption that there is no threshold value. Genetic effects and carcinogenesis following diagnostic imaging are stochastic.

Effects can be classified into early or deterministic, which have a threshold, and delayed or stochastic, with no threshold. Effects are also classified into somatic and hereditary. The somatic include early and delayed effects (cancer).

Table 2.6 The timescales of radiation effects

Action	Approximative timescale
Initial ionizing event	10^{-18} s
Transit of secondary electrons	10^{-15} s
Production of ion radicals	10^{-10} s
Production of free radicals	10^{-9} s
Chemical changes	10^{-5} s
Individual cell death	Hours–months
Gross, biological effects	Hours–years

2.7.1 Timescales of Radiation Effects

At the cellular scale, the initial ionization events are the precursors to a chain of subsequent events that may eventually lead to the biological and clinical, at the macroscopic scale, manifestation of radiation damage. Although the chemical changes may appear to operate over a short time, about 10^{-5} s, this period is a factor of 10^{-18} longer than the time taken for the original particle to traverse the cell nucleus. Thus, there is a relatively long period during which chemical damage is inflicted (Table 2.6). Cell death in individual lethally damaged cells takes place later, within an hour to 1 day, usually at the point when the cell subsequent attempts to enter mitosis. Clinically observable radiation effects result from the wholesale functional impairment that follows from lethal damage being inflicted on many cells or critical substructures. It takes some time until the reaction occurring at the cellular level develops into clinical symptoms at an individual level, and the timescale of the whole process may extend to months or years. This period is called the incubation period. Thus, in clinical studies, any deleterious health effects of a radiation procedure may not be seen until long after the diagnostic test or treatment has been completed (Table 2.6) [35].

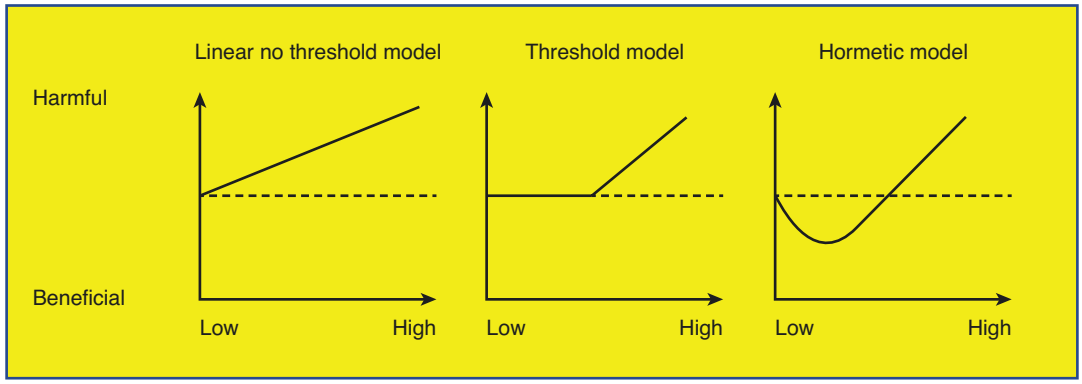

Fig. 2.7 Comparison between three different dose–response models. The *dashed line* represents health effects in the absence of radiation. *Y*- and *X*-axes represent health effects and radiation dose, respectively. (Reproduced from Ernst et al. [36] with permission)

2.7.2 Dose–Response Models

Many models predict relationships between the radiation dose and the effect of radiation exposure to a biological target. However, these models differ due to different underlying assumptions. Figure 2.7 illustrates three models describing the response of a biological system to various radiation doses.

1. Linear No-Threshold Model
   This model assumes that any level of radiation is harmful and that the risk increases linearly with increments of dose. It is applied for radiation protection purposes to limit the risk to workers in radiation fields.
2. Threshold Model
   This model assumes that radiation risk is linearly related to the dose; however, this occurs if the received dose is above the threshold level. There is no risk expected below the threshold level. The theory behind the threshold level is that some degree of cellular damage should accumulate and produce cell damage.
3. Hormesis Model
   In this model, there is a bimodal effect of radiation. Below a certain threshold level, radiation is protective. Harmful effects happen only when above the threshold dose level. The rationale is that radiation at low levels induces protective cellular mechanisms which prevent DNA damage from occurring spontaneously or due to other stresses [37, 38]. Figure 2.8 presents the scheme of the dose–response function (Reproduced with permission from Feinendegen [39]).

2.7.2.1 Deterministic Radiation Effects

Deterministic effects are nonrandom and have a highly predictable response to radiation. Even if some cells die due to exposure to a small amount of radiation, clinical symptoms do not appear if tissues and organs can fully function with the remaining cells. When the radiation increases and more cells die, relevant tissues and organs suffer temporary dysfunction, and some clinical symptoms may appear. However, such symptoms improve when normal cells proliferate and increase in number.

When cells in tissues or organs are damaged severely due to a large amount of radiation, this may lead to permanent cell damage or morphological defects. In this manner, there is a specific exposure dose above which symptoms appear and under which no symptoms appear for deterministic effects due to cell deaths. Such dose is called the threshold dose.

Acute Disorders

Clinically observed radiation effects in whole tissues or organs reflect the damage inflicted to

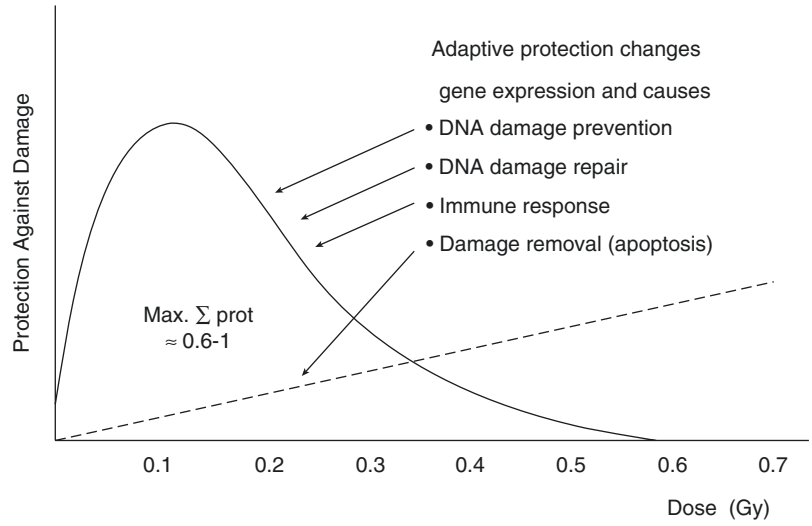

Fig. 2.8 Low-dose (low LET)-induced adaptive protection changes

large numbers of constituent cells and, thus, appear on a timescale which is mainly governed by the underlying proliferation rates of those cells. Early (or acute) effects appear within days, weeks or months of irradiation. They are associated with fast-proliferating, i.e., undifferentiated cells of irradiated tissues or organs. They are acute with transient disruption of the integrity and function of affected tissues or organs. If the doses are relatively low, the stems cells will be able to differentiate shortly after exposure. Damaged tissues and organs will heal with a re-established function at least partially.

Local Exposure Effects

When enough radiation is delivered locally to a particular tissue or organ, as in the case of radiation therapy, which focuses on a specific field, acute effects can appear in the exposed area. Examples include skin erythema and gastrointestinal edema, and ulceration.

Whole-Body Exposure Effects

Following exposure to a large, single, short-term whole-body dose of ionizing radiation, the resulting injury is a rapid whole-body response called the Acute Radiation Syndrome (ARS) and is expressed as a series of clinical symptoms. Radiation exposure at levels exceeding 1 Gy at one time may cause effects on the human body due to cell deaths. Organs susceptible to radiation are more likely to be affected by a small amount of radiation. This series of disorders in organs is called Acute Radiation Syndrome (ARS). The sequence of events can be generally divided into four clinical periods (Fig. 2.9).

1. The prodromal period: symptoms appear within 48 h after the exposure. Exposure to radiation exceeding 1 Gy may cause loss of appetite, nausea and vomiting, and exposure to radiation exceeding 4 Gy may cause headaches. When exposure doses exceed 6 Gy, such symptoms as diarrhea and fever may appear.
2. The incubation period, from 48 h to 2–3 weeks after exposure, when the patient becomes asymptomatic.
3. The manifest or onset phase, from week 6 to week 8 after exposure, when variable symptoms appear based on the radiation dose. Disorders appear in the hematopoietic organ, gastrointestinal tract, and nerves and blood vessels, in this order, as doses increase. Disorders mainly appear in organs and tissues susceptible to radiation. In general, the larger the exposure dose, the shorter the incubation phase.
4. The recovery period: If the patient survives, recovery occurs from 6 weeks to several months after exposure.

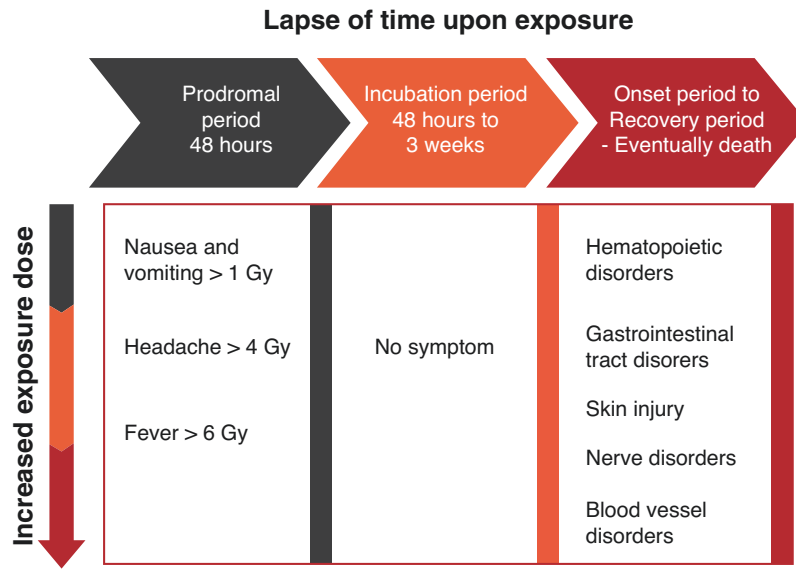

Fig. 2.9 Acute radiation syndrome effects upon exposure to radiation

The presentation of these periods and their duration depend on the amount of radiation exposure. In general, about half of those who receive doses of 2 Gy suffer vomiting within 3 h, and symptoms are rare after doses below 1 Gy. With a sufficiently high radiation dose, acute radiation sickness may result. Additional symptoms related to specific organ injury may occur, based on the dose, and are divided according to the known acute radiation syndromes:

1. Radiation Sickness

   The symptoms can be mild, such as loss of appetite and mild fatigue, or evident only on laboratory tests with mild lymphopenia (subclinical), or maybe severe, appearing as early as 5 min after exposure to very high doses of 10 Gy or more and also include fatigue, sweating, fever, apathy, and low blood pressure. Lower doses delay the onset of symptoms and produce less severe symptoms or a subclinical syndrome that can occur with doses of less than 2 Gy to the whole body, and recovery is complete with 100% survival.
2. Hematopoietic (Bone Marrow) Syndrome

   A blood cells number decrease due to deterioration of hematopoietic capacity may occur at higher doses of more than 1.5–2 Gy to the whole body. With doses up to 4 Gy, a radiation prodrome is seen, followed by a latent period of up to 3 weeks. The clinical effects are not seen for several weeks after the radiation dose when anemia, petechiae, increased blood pressure, fatigue, ulceration in the mouth, epilation, purpura, or infection appear. At doses on the order of 4–8 Gy, a modified bone marrow syndrome occurs. The latest period is shortened, and the manifest illness is aggravated. Death is possible due to bleeding with exposure in this dose range.
3. Gastrointestinal Syndrome

   This syndrome occurs with still higher doses of 6–10 Gy, which can cause manifestations related to the gastrointestinal tract in addition to those of the bone marrow syndrome. Initially, loss of appetite, apathy, nausea, and vomiting occur for 2–8 h. These effects may subside rapidly. Malaise, anorexia, nausea, vomiting, high fever, persistent diarrhea, abdominal distention, and infections appear several days later. During the second week of irradiation, severe dehydration, hemoconcentration, and circulatory collapse may be seen, eventually leading to death.
4. Central Nervous System Syndrome

   The central nervous system is generally resistant to radiation effects. A dose higher than 10 Gy is required to cause substantial

effects on the brain and the nervous system. Symptoms include intractable nausea and vomiting, confusion, convulsions, coma, and absent lymphocytes. The prognosis is poor, with death in a few days.

In most types of radiotherapy, the late effects are considered to be most critical and generally limit the total dose that may be delivered to the tumor. If the radiation tolerance of the late-responding tissues is exceeded, then the subsequent reactions, depending on the tissues in which they arise, may seriously affect mobility and quality of life and may even be life-threatening. Such problems arise long after the completion of treatment and are, thus, impossible to correct. Although they may be unpleasant, acute reactions in radiotherapy are usually transient and easier to control by adjusting the treatment dose delivery pattern and simple medication. In radionuclide therapies, it is possible to circumvent acute radiation toxicities once they begin to occur, such as by accelerating clearance of the radiopharmaceutical.

Delayed Effects

Fetal Disorders

Deterministic effects include fetal effects with a shallow threshold dose. Radiation exposure during pregnancy passes through the womb to the unborn child, who may also be exposed. The embryonic stage is one of the most radiosensitive stages in the life of any organism, and the incidence of effects has time specificity.

The classical triad of effects of radiation on the embryo is growth retardation, embryonic, fetal, or neonatal death, and congenital malformation. The probability of finding one or more of these effects depends upon radiation dose, the dose rate, and the stage of gestation at exposure. The stage of development is critical since the differentiated organ will be most vulnerable; this determines the type of abnormality or malformation observed. The effect of exposure to radiation exceeding 0.1 Gy during the germinal stage or pre-implantation period, first 2 weeks of conception, is an all-or-none effect leading to embryo abortion. Following this period and up to 8 weeks, the possibility of miscarriage decreases, but the embryo is very vulnerable to dysplasia (malformations). Radiation exposure above 0.1 Gy during the embryonic period (or organogenesis period) when the cerebrum is actively growing (early fetal period) poses risks of mental retardation, congenital malformation, as well as organ-specific effects. For example, radioactive iodine administered to a pregnant mother who passed 10–13 weeks of gestation will cross the placenta and accumulate in the already formed fetal thyroid. A summary of the possible effects of irradiation at various stages of gestation is shown in Table 2.7. The development of cancer at an early age is controversial. Risks of stochastic effects such as cancer or hereditary disorders also increase depending on exposure dose levels. Studies have suggested an increased risk of hematopoietic and solid tumors at an early age [40].

Table 2.7 Effects of radiation on the unborn child

Stage of gestation (days)	Possible effects
1–9	Death of embryo is most likely, with little chance of malformation
10–12	Reduced lethal effect with still little chance of malformation
13–56	Production of congenital malformation and retarded growth
57–112	Extreme mental retardation (time of most severe effect on CNS)
113–175	Less frequent effect on CNS
After 175	Very low frequency of CNS effects (no reported case of severe retardation)

However, a comparison between individuals whose parents were exposed to radiation during the atomic bombing of Hiroshima and Nagasaki and those whose parents were not showed any significant differences in a large number of variables, including congenital effects, stillbirths, and cancer at an early age.

Leukemia and Cancer

Cancer is an essential concern of radiation. It has been recognized for more than 90 years that ionizing radiation causes cancers. Highly proliferating

tissues are more prone to radiation tumor induction. Cancer becomes evident only long after the first damage is done, following a period of latency. First leukemia appearance is at least 2–5 years after exposure, while solid tumors appear after at least 10 years, often several decades. The tumors associated with radiation include leukemia, multiple myeloma, and cancers of the breast, colon, thyroid, ovary, lung, urinary bladder, stomach, CNS (other than the brain), and esophagus.

There is no clear evidence that low-level radiation causes cancer. Khamwan et al. [41] studied 6000 patients given a diagnostic dose of I-131. There was no increase in the incidence of thyroid cancer in this population, including a subset of 2000 children [41]. Brix et al. [42] also studied 2000 patients treated with I-131 in doses of up to several hundreds of MBq with 20 years' follow-up. The incidences of thyroid cancer and leukemia were identical to those among patients treated surgically for the same conditions. To complicate the issue further, recently acquired data minimize the effects of low-level radiation in the induction of cancer and even suggest that such levels of radiation exposure may be helpful [43]. DNA mutations unrelated to radiation appear continuously. Each day the intrinsic human metabolism produces on average 240,000 DNA mutations in each body cell [44]. During youth, in general, cancer infrequently occurs thanks to mutations repair. With old age, the capability to repair may decrease, and cancer appears more frequently. A high dose of 2 Gy adds 4000 (20 mutations/cGy) to the daily 240,000 mutations. Ward [21] determined that a low radiation dose of 0.2 Gy stimulates repair by 50–100% and adds only 400 mutations to the intrinsic 240,000 mutations. Our repair mechanism's reduced ability to correct the very high background of intrinsic mutations increases the risk of developing cancer. Genetic impairment of DNA repair capacity results in death from cancer at an early age. Loss of DNA repair capacity with age increases the risk of cancer. Exposure to high doses of radiation similarly reduces the repair capacity of cellular DNA and increases the risk of cancer [45, 46].

Genetic Effects

Genetic effects may include changes in the number and structure of chromosomes and gene mutations, dominant or recessive. They depend on the following factors:

1. The stage of germ cell development

   Immature germ cells appear to be capable of repair, while in mature germ cells, there is little or no repair (Table 2.1).
2. The dose rate

   The repair process starts simultaneously with radiation damage. The damage with a high dose rate is corresponding; lower dose rates produce minor mutations. At a low-intermediate dose rate, time is an essential factor in the outcome of radiation injuries. However, this does not hold in the case of a high radiation rate, where the repair process is minimal due to the direct action of injury.
3. The dose fractionation

   The time interval between fractions is significant for the frequency of mutations. Dose fractionation reduces the number of translocations; however, the incidence of mutations will not be affected by increasing the time interval between fractions.
4. The interval between exposure and conception

   The mutation frequency is shallow if conception occurs after 7 weeks, but it is high when radiation exposure and conception interval is 7 weeks or less.

Other Late-Onset Somatic Disorders

1. Cataract

   Chronic and acute exposure to the eyes can lead to cataracts secondary to inducing lens fiber disorganization. Not all radiation is equally effective in producing cataracts; neutrons are much more efficient than other types of radiation. In man, the cataractogenic threshold is estimated at 2–5 Gy as a single dose or 10 Gy as a fractionated dose. The period between exposure and the appearance of the lens opacities averages 2–3 years, ranging from 10 months to more than 30 years.

2. Hypothyroidism

   The thyroid gland is exposed to radiation during radiation therapy of malignant head and neck tumors or treating hyperthyroidism with I-131. Patients who received doses 10–40 Gy to the thyroid to treat other malignant diseases developed hypothyroidism a few months to years following exposure. A lower moderate dose of (10–20 Gy) can result in hypothyroidism, while 500 Gy or more is required to eradicate the thyroid.

3. Aplastic Anemia

   Human radiation exposure can cause aplastic anemia, depending upon the dose and fractionation. Death may be the result of aplastic anemia. Permanent anemia could result from the reduced capability of cellular proliferation due to the accumulation of residual injury in stem cells. It is essential to realize that when part of the body is irradiated, the bone marrow that survives unimpaired will replace what is damaged. If only 10% of active bone marrow escapes irradiation, mortality can be decreased from 50% to zero, based on animal studies.

Psychological and Psychiatric Effects of Ionizing Radiation Exposure

In addition to noticeable CNS effects discussed earlier, exposure to radiation has other vital side effects that cannot be ignored; the psychological effects. Exposure to ionizing radiation whether due to environmental contamination such as radiation accidents, radiotherapy and diagnostics, occupational roles and space travel is a possible risk-factor for cognitive dysfunction [47]. Which can be early or late effect. This effect is not only due to high level exposure but also low levels [48]. Molecular studies described the various inflammatory and signaling mechanisms involved in cellular damage and repair which consequently drive physiological alterations that may lead to functional alterations [49].

Studies researched these topics decades ago till the present. Perceptions and memories were explored in atomic veterans and patients treated for brain tumors. Findings suggest that side effects involve emotional and cognitive processing of a new perspective that contradicts prior beliefs, trouble with memories and memory loss [50]. Cognitive deficits are related to certain factors that must be considered, including the human life span, as effects might differ with age at exposure and outcome assessment. Family members' health conditions, which may exacerbate distress, is another factor to be considered.

A case study of men who were exposed to non-background ionizing radiation while participating in atmospheric nuclear tests showed that the subjects has developed a virtually identical complex of debilitating psychiatric symptoms resulted from almost entirely focused upon the health effects of the radiation to which the subjects were exposed to. This symptom complex appears to comprise a syndrome [51].

Another recent study recently published, researched the potential psychological issues faced by British nuclear weapons testing program veterans. The study assessed the prevalence of clinically relevant anxiety and aimed to explore experiences of worry and the broader potential psychological impact and effects. The results of this qualitative study showed the following: More than third (33.7%) of the participants met the criteria for clinically relevant anxiety, the interviewers generated from (21.3%) of the participants three interconnected themes giving a rich description of the verbal data in relation to the psychological impact, namely "worry, responsibility, and guilt" and "change across the life course." Frustration and anger toward authorities resulting from perceived negligence and deception were also there. In addition; the participants showed some instances of worry regarding their family members' health [49]. Data suggest that guilt toward family members' health must be considered in potentially exposed individuals and transparency from authorities of medical personnel when dealing with any radiological exposure are of importance to reduce potential distress and anxiety [49].

Needless to say that the psychological and psychiatric effects of ionizing radiation exposure area need more research to develop some clearer interventions to deal with it.

2.7.2.2 Stochastic Radiation Effects

The effects of low-level radiation are considerably in debate. At one end, several theories and reports describe the harmful effects of low-level radiation and how underestimated the risks are. There are theories and reports of harmless and even potentially valuable effects of exposure to such radiation levels at the other extreme.

The theories describing the effects of low-level radiation and the projected risk estimates of cancer development or genetic effects in humans are purely mathematical and not actual observations. The data from populations exposed to high-level radiation were extrapolated to determine the likelihood of these events at low-level radiation exposure. Such events occur at meager rates in any given population and further complicate the issue after long latency periods. Therefore, reliable epidemiological data are challenging to obtain.

2.8 Exposure from Medical Procedures

For medical radiation, the chest X-ray delivers 0.1 mSv to the chest wall (Table 2.8). The average nuclear medicine procedure delivers 3 mSv to the whole body. The absorbed dose from the C-14 urea breath test is equivalent to that received during a 1 h flight. These values compared with those of natural sources of radiation, particularly cosmic rays, which deliver an average of 3.6 mSv per year in the United States and are higher in certain areas, the actual magnitude of the low level of radiation can be appreciated.

These levels of exposure from diagnostic medical procedures have no detectable biological effects. Less than 0.006% of those undergoing nuclear medicine procedures in the United States might be affected annually. PET studies deliver higher doses to the patient to compensate for the short half-life of positron-emitting radioisotopes. Because these radioisotopes are of high energy and prepared in high initial dosing to account for the rapid decay, PET technologist, radio pharmacists, and workers at cyclotrons are usually exposed to higher doses than other workers in the nuclear medicine field.

Therapeutic applications of radioisotopes involve not only malignant but also benign conditions, such as hyperthyroidism and arthroplasty, and are widely expanding. In the treatment of thyroid cancer, large doses of I-131 may cause depression of the bone marrow. It is essential to mention that the level of exposure from medical exposure has globally increased according to recent surveys [52]. The global exposure per capita has increased from 0.4 mSv in 2000 to 0.62 mSv in 2008 (Table 2.9).

Although globally the exposure of medical exposure is still around 20% of the total exposure per caput since the exposure from natural sources contributes to slightly less than 80%, the exposure from medical exposure in certain groups of countries with high physician-to-population ratios has dramatically increased to be almost equal to the dose from natural exposure as illustrated in the United States. This increase has been attributed mainly to the increase in the utilization of CT scans.

Positive health effects are observed from low-dose radiation exposure, i.e., decreased mortality and decreased cancer rates, in human populations exposed to low-level radiation and reported in extensive studies [43]. Several studies compared areas of high background to those with low radiation.

Lower cancer incidence or mortality rates in the former were the findings in many such studies in China [44], India [45], Iran [46], and the United States [53]. However, this epidemiological study does not compare an individual's radiation exposure to cancer rate; therefore, a strong conclusion cannot be solely based on such studies. On the other hand, none of these studies had shown a higher cancer incidence in high background radiation zones. An epidemiological study [43] comparing cancer mortality in Canada's nuclear industry workers to non-radiation workers has found similar favorable effects for low radiation exposure. The former group of workers had cancer mortality of 58% of the national average compared to 97 % of that in

Table 2.8 Radiation dose from common natural and medical sources

Diagnostic X-ray procedures	Effective dose per scan Based dose based on ICRP 103 (mSv)
X-ray CT of the head and neck	1.2
X-ray CT of the chest	6.2
Panoramic dental radiography	0.026
Intravenous urography (IVU)	3
Barium enema (lower GI X-ray)	6
Chest X-ray	0.1
Mammography	0.36

Diagnostic nuclear medicine (+A10:C20 procedures)	Effective dose per scan Based dose based on ICRP 103 (mSv)
Tc-99m-MAA lung perfusion study	0.017 (mSv/MBq)
Tc-99m-DTPA lung ventilation study (ventilation can be evaluated with the ^{99m}Tc-labeled aerosols, DTPA and Technegas)	0.015 (mSv/MBq)
Tc-99m-MDP bone scan (20 mCi)	4
Effective doses from CT component of PET/CT (diagnostic)	2.60–21.45
Effective doses from FDG-PET/CT (total)	8–26.85
Effective doses from FDG-PET (5–15 mCi)	3.515–10.545
CT component of PET/CT (attenuation only)	0.5–1.0
One-day Tl-201 stress (3.5 mCi)/redistribution protocol	15.3
Tl-201 stress (3.0 mCi) / redistribution with optional additional imaging protocols (re-injection of Tl-201 (1.5 mCi) after redistribution imaging)	19.7

Exposure from "Natural Radiation"	Effective dose per scan Based dose based on ICRP 103 (mSv)
2-h flight at altitude of approximately 6100 m	0.004
World Health Organization recommended reference level per year for intake of radionuclides in water (IAEA 2001)	0.1
Ingestion (food and drinking-water)	0.3
Terrestrial sources	0.5
Inhalation of natural gas at home (mainly radon)	1.2
Cosmic radiation (at sea level)	0.4
Total background radiation level	2.4

Table 2.9 Changes in exposure from medical sources

Year	Annual per caput dose (mSv)
1988	0.35
1993	0.30
2000	0.40
2008	0.62

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the latter. Cohen [43] studied the relationship between lung cancer death rates and residential radon gas in the United States. He found that lung cancer decreased for increments in radon levels. These findings were consistent even after reanalysis and correcting for confounding factors such as smoking. To date, there is considerable debate regarding this study.

2.9 Summary

Several biological effects can result from ionizing radiation. These can be due to direct or indirect mechanisms, and they can be acute or delayed. Acute effects occur with exposure to

high-level radiation. Delayed effects may appear after a long time and include cancer, genetic effects, effects on the unborn child, and others such as cataracts and hypothyroidism. Based on our current knowledge, no level of radiation exposure is considered safe, and no level is uniformly dangerous. Radiation doses have to reach a certain level to produce acute injury but not cause cancer or genetic damage. Absorbed doses from nuclear medicine procedures are very low, and no biological effects in individuals due to ionizing radiation were seen. Fears of radiation must not be permitted to undermine the great value of radiation in clinical practice. However, safe handling of all levels of radiation is vital to prevent or minimize possible biological effects.

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