CHAPTER 5

# Cellular Adaptation, Injury, and Death



When confronted with stresses that endanger its normal structure and function, the cell undergoes adaptive changes that permit survival and maintenance of function. It is only when the stress is overwhelming or adaptation is ineffective that cell injury and death occur. This chapter focuses on cellular adaptation, injury, and death.

## Cellular Adaptation

*After you have completed this section of the chapter, you should be able to meet the following objectives:*

- Cite the general purpose of changes in cell structure and function that occur as the result of normal adaptive processes
- Describe cell changes that occur with atrophy, hypertrophy, hyperplasia, metaplasia, and dysplasia and state general conditions under which the changes occur
- Cite three sources of intracellular accumulations
- Compare the pathogenesis and effects of dystrophic and metastatic calcifications

Cells adapt to changes in the internal environment, just as the total organism adapts to changes in the external environment. Cells may adapt by undergoing changes in size, number, and type. These changes, occurring singly or in combination, may lead to atrophy, hypertrophy, hyperplasia, metaplasia, and dysplasia (Fig. 5-1). Adaptive cellular responses also include intracellular accumulations and storage of products in abnormal amounts.[1,2]

Numerous molecular mechanisms mediate cellular adaptation, including factors produced by other cells or by the cells themselves. These mechanisms depend largely on signals transmitted by chemical messengers that exert their effects by altering gene function. In general, the genes expressed in all cells fall into two categories: "housekeeping" genes that are necessary for normal function of a cell, and genes that determine the differentiating characteristics of a particular cell type. In many adaptive cellular responses, the expression of the differentiation genes is altered, whereas that of the housekeeping genes remains unaffected. Thus, a cell is able to change size or form without compromising its normal function. Once the stimulus for adaptation is removed, the effect on expression of the differentiating genes is removed, and the cell resumes its previous state of specialized function. Whether adaptive cellular changes are normal or abnormal depends on whether the response was mediated by an appropriate stimulus. Normal adaptive responses occur in response to need and an appropriate stimulus. After the need has been removed, the adaptive response ceases.

### ATROPHY

When confronted with a decrease in work demands or adverse environmental conditions, most cells are able to revert to a smaller size and a lower and more efficient level

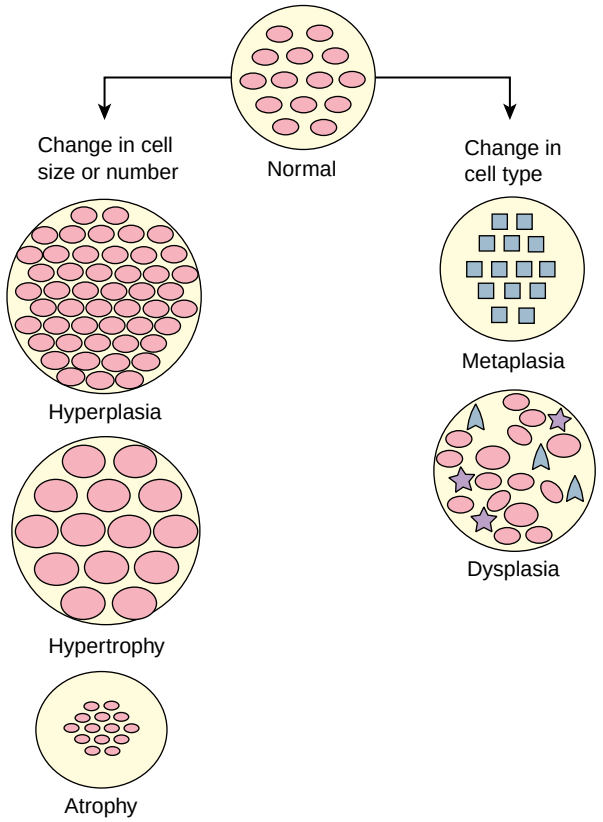


**FIGURE 5-1** Adaptive tissue (*large circles*) and cell responses involving a change in number (hyperplasia), cell size (hypertrophy and atrophy), cell type (metaplasia), or size, shape, and organization (dysplasia).

of functioning that is compatible with survival. This decrease in cell size is called *atrophy*. Cell size, particularly in muscle tissue, is related to workload. As the workload of a cell declines, oxygen consumption and protein synthesis decrease. Cells that are atrophied reduce their oxygen consumption and other cellular functions by decreasing the number and size of their organelles and other structures. There are fewer mitochondria, myofilaments, and endoplasmic reticulum structures. When a sufficient number of cells are involved, the entire tissue or muscle atrophies.

The general causes of atrophy can be grouped into five categories: (1) disuse, (2) denervation, (3) loss of endocrine stimulation, (4) inadequate nutrition, and (5) ischemia or decreased blood flow. Disuse atrophy occurs when there is a reduction in skeletal muscle use. An extreme example of disuse atrophy is seen in the muscles of extremities that have been encased in plaster casts. Because atrophy is adaptive and reversible, muscle size is restored after the cast is removed and muscle use is resumed. Denervation atrophy is a form of disuse atrophy that occurs in the muscles of paralyzed limbs. Lack of endocrine stimulation produces a form of disuse atrophy. In women, the loss of estrogen stimulation during menopause results in atrophic changes in the reproductive organs. With malnutrition and decreased blood flow, cells decrease their size and energy requirements as a means of survival.

### CELLULAR ADAPTATIONS

- Cells are able to adapt to increased work demands or threats to survival by changing their size (atrophy and hypertrophy), number (hyperplasia), and form (metaplasia).
- Normal cellular adaptation occurs in response to an appropriate stimulus and ceases once the need for adaptation has ceased.

## HYPERTROPHY

*Hypertrophy* represents an increase in cell size and with it an increase in the amount of functioning tissue mass. It results from an increased workload imposed on an organ or body part and is commonly seen in cardiac and skeletal muscle tissue, which cannot adapt to an increase in workload through mitotic division and formation of more cells. Hypertrophy involves an increase in the functional components of the cell that allows it to achieve equilibrium between demand and functional capacity. For example, as muscle cells hypertrophy, additional actin and myosin filaments, cell enzymes, and adenosine triphosphate (ATP) are synthesized.

Hypertrophy may occur as the result of normal physiologic or abnormal pathologic conditions. The increase in muscle mass associated with exercise is an example of physiologic hypertrophy. Pathologic hypertrophy occurs as the result of disease conditions and may be adaptive or compensatory. Examples of adaptive hypertrophy are the thickening of the urinary bladder from long-continued obstruction of urinary outflow and the myocardial hypertrophy that results from valvular heart disease or hypertension. Compensatory hypertrophy is the enlargement of a remaining organ or tissue after a portion has been surgically removed or rendered inactive. For instance, if one kidney is removed, the remaining kidney enlarges to compensate for the loss.

The precise signal for hypertrophy is unknown. It may be related to ATP depletion, mechanical forces such as stretching of the muscle fibers, activation of cell degradation products, or hormonal factors.[1] Whatever the mechanism, a limit is eventually reached beyond which further enlargement of the tissue mass is no longer able to compensate for the increased work demands. The limiting factors for continued hypertrophy might be related to limitations in blood flow. In hypertension, for example, the increased workload required to pump blood against an elevated arterial pressure results in a progressive increase in left ventricular muscle mass and need for coronary blood flow (Fig. 5-2).

There has been recent interest in the signaling pathways that control the arrangement of contractile elements in myocardial hypertrophy. Research suggests that certain signal molecules can alter gene expression, controlling the size and assembly of the contractile proteins in hypertrophied myocardial cells. For example, the hypertrophied

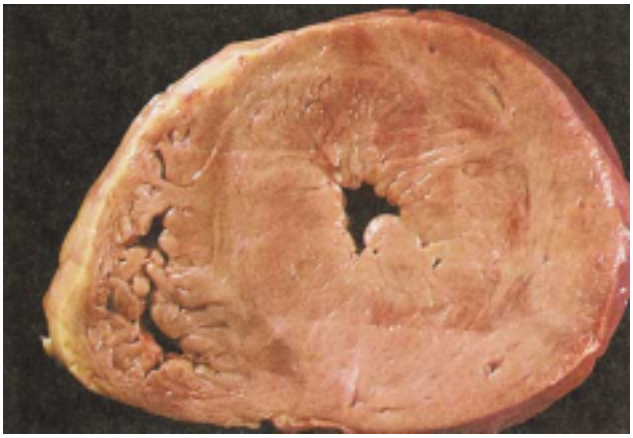

**FIGURE 5-2** Myocardial hypertrophy. Cross-section of the heart in a patient with long-standing hypertension. (From Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 9]. Philadelphia: Lippincott-Raven)

myocardial cells of well-trained athletes have proportional increases in width and length. This is in contrast to the hypertrophy that develops in dilated cardiomyopathy, in which the hypertrophied cells have a relatively greater increase in length than width. In pressure overload, as occurs with hypertension, the hypertrophied cells have greater width than length.[3] It is anticipated that further elucidation of the signal pathways that determine the adaptive and nonadaptive features of cardiac hypertrophy will lead to new targets for treatment.

## HYPERPLASIA

*Hyperplasia* refers to an increase in the number of cells in an organ or tissue. It occurs in tissues with cells that are capable of mitotic division, such as the epidermis, intestinal epithelium, and glandular tissue. Nerve, skeletal, and cardiac muscle cells do not divide and therefore have no capacity for hyperplastic growth. There is evidence that hyperplasia involves activation of genes controlling cell proliferation and the presence of intracellular messengers that control cell replication and growth. As with other normal adaptive cellular responses, hyperplasia is a controlled process that occurs in response to an appropriate stimulus and ceases after the stimulus has been removed.

The stimuli that induce hyperplasia may be physiologic or nonphysiologic. There are two common types of physiologic hyperplasia: hormonal and compensatory. Breast and uterine enlargement during pregnancy are examples of a physiologic hyperplasia that results from estrogen stimulation. The regeneration of the liver that occurs after partial hepatectomy (*i.e.,* partial removal of the liver) is an example of compensatory hyperplasia. Hyperplasia is also an important response of connective tissue in wound healing, during which proliferating fibroblasts and blood vessels contribute to wound repair. Although hypertrophy and hyperplasia are two distinct processes, they may occur together and are often triggered by the same mechanism.[1] For example, the pregnant uterus undergoes both hypertrophy and hyperplasia as the result of estrogen stimulation.

Most forms of nonphysiologic hyperplasia are due to excessive hormonal stimulation or the effects of growth factors on target tissues.[2] Excessive estrogen production can cause endometrial hyperplasia and abnormal menstrual bleeding (see Chapter 47). Benign prostatic hyperplasia, which is a common disorder of men older than 50 years of age, is thought to be related to the action of androgens (see Chapter 45). Skin warts are an example of hyperplasia caused by growth factors produced by certain viruses, such as the papillomaviruses.

## METAPLASIA

Metaplasia represents a reversible change in which one adult cell type (epithelial or mesenchymal) is replaced by another adult cell type. Metaplasia is thought to involve the reprogramming of undifferentiated stem cells that are present in the tissue undergoing the metaplastic changes.

Metaplasia usually occurs in response to chronic irritation and inflammation and allows for substitution of cells that are better able to survive under circumstances in which a more fragile cell type might succumb. However, the conversion of cell types never oversteps the boundaries of the primary groups of tissue (*e.g.,* one type of epithelial cell may be converted to another type of epithelial cell, but not to a connective tissue cell). An example of metaplasia is the adaptive substitution of stratified squamous epithelial cells for the ciliated columnar epithelial cells in the trachea and large airways of a habitual cigarette smoker. Although the squamous epithelium is better able to survive in these situations, the protective function that the ciliated epithelium provides for the respiratory tract is lost. Also, continued exposure to the influences that cause metaplasia may predispose to cancerous transformation of the metaplastic epithelium.

## DYSPLASIA

Dysplasia is characterized by deranged cell growth of a specific tissue that results in cells that vary in size, shape, and organization. Minor degrees of dysplasia are associated with chronic irritation or inflammation. The pattern is most frequently encountered in areas of metaplastic squamous epithelium of the respiratory tract and uterine cervix. Although dysplasia is abnormal, it is adaptive in that it is potentially reversible after the irritating cause has been removed. Dysplasia is strongly implicated as a precursor of cancer. In cancers of the respiratory tract and the uterine cervix, dysplastic changes have been found adjacent to the foci of cancerous transformation. Through the use of the Papanicolaou (Pap) test, it has been documented that cancer of the uterine cervix develops in a series of incremental epithelial changes ranging from severe dysplasia to invasive cancer. However, dysplasia is an adaptive process and as such does not necessarily lead to cancer. In many cases, the dysplastic cells revert to their former structure and function.

## INTRACELLULAR ACCUMULATIONS

Intracellular accumulations represent the buildup of substances that cells cannot immediately use or dispose of. The substances may accumulate in the cytoplasm (frequently in the lysosomes) or in the nucleus. In some cases, the accumulation may be an abnormal substance that the cell has produced, and in other cases, the cell may be storing exogenous materials or products of pathologic processes occurring elsewhere in the body. These substances can be grouped into three categories: (1) normal body substances, such as lipids, proteins, carbohydrates, melanin, and bilirubin, that are present in abnormally large amounts; (2) abnormal endogenous products, such as those resulting from inborn errors of metabolism; and (3) exogenous products, such as environmental agents and pigments that cannot be broken down by the cell.[2] These substances may accumulate transiently or permanently, and they may be harmless or, in some cases, toxic.

The accumulation of normal cellular constituents occurs when a substance is produced at a rate that exceeds its metabolism or removal. An example of this type of process is fatty changes in the liver due to intracellular accumulation of triglycerides. Liver cells normally contain some fat, which is either oxidized and used for energy or converted to triglycerides. This fat is derived from free fatty acids released from adipose tissue. Abnormal accumulation occurs when the delivery of free fatty acids to the liver is increased, as in starvation and diabetes mellitus, or when the intrahepatic metabolism of lipids is disturbed, as in alcoholism.

Intracellular accumulation can result from genetic disorders that disrupt the metabolism of selected substances. A normal enzyme may be replaced with an abnormal one, resulting in the formation of a substance that cannot be used or eliminated from the cell, or an enzyme may be missing, so that an intermediate product accumulates in the cell. For example, there are at least 10 genetic disorders that affect glycogen metabolism, most of which lead to the accumulation of intracellular glycogen stores. In the most common form of this disorder, von Gierke's disease, large amounts of glycogen accumulate in the liver and kidneys because of a deficiency of the enzyme glucose-6-phosphatase. Without this enzyme, glycogen cannot be broken down to form glucose. The disorder leads not only to an accumulation of glycogen but also to a reduction in blood glucose levels. In Tay-Sachs disease, another genetic disorder, abnormal lipids accumulate in the brain and other tissues, causing motor and mental deterioration beginning at approximately 6 months of age, followed by death at 2 to 3 years of age. In a similar manner, other enzyme defects lead to the accumulation of other substances.

Pigments are colored substances that may accumulate in cells. They can be endogenous (*i.e.,* arising from within the body) or exogenous (*i.e.,* arising from outside the body). Icterus, also called *jaundice,* is characterized by a yellow discoloration of tissue due to the retention of bilirubin, an endogenous bile pigment. This condition may result from increased bilirubin production from red blood cell destruction, obstruction of bile passage into the intestine, or toxic diseases that affect the liver's ability to remove bilirubin from the blood. Lipofuscin is a yellow-brown pigment that results from the accumulation of the indigestible residues produced during normal turnover of cell structures (Fig. 5-3). The accumulation of lipofuscin increases with age and is sometimes referred to as the *wear-and-tear pigment.* It is more common in heart, nerve, and liver cells than other tissues and is seen more often in conditions associated with atrophy of an organ.

One of the most common exogenous pigments is carbon in the form of coal dust. In coal miners or persons exposed to heavily polluted environments, the accumulation of carbon dust blackens the lung tissue and may cause serious lung disease. The formation of a blue lead line along the margins of the gum is one of the diagnostic features of lead poisoning. Tattoos are the result of insoluble pigments introduced into the skin, where they are engulfed by macrophages and persist for a lifetime.

The significance of intracellular accumulations depends on the cause and severity of the condition. Many accumulations, such as lipofuscin and mild fatty change, have no effect on cell function. Some conditions, such as the hyperbilirubinemia that causes jaundice, are reversible. Other disorders, such as glycogen storage diseases, produce accumulations that result in organ dysfunction and other alterations in physiologic function.

## PATHOLOGIC CALCIFICATIONS

Pathologic calcification involves the abnormal tissue deposition of calcium salts, together with smaller amounts of iron, magnesium, and other minerals. It is known as *dystrophic calcification* when it occurs in dead or dying tissue and as *metastatic calcification* when it occurs in normal tissue.

### Dystrophic Calcification

Dystrophic calcification represents the macroscopic deposition of calcium salts in injured tissue. It is often visible to the naked eye as deposits that range from gritty sandlike grains to firm, hard, rock material. The pathogenesis of

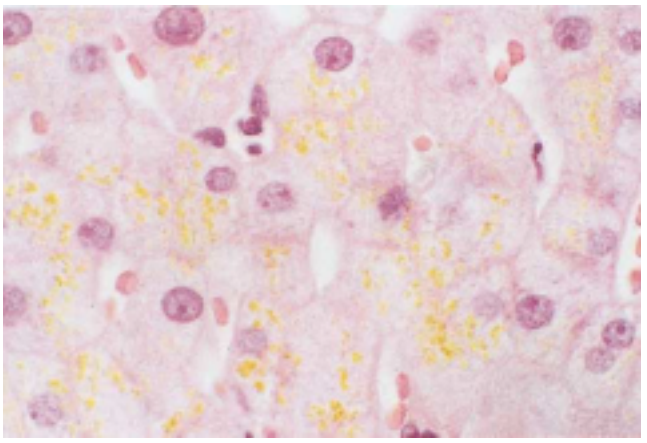

**FIGURE 5-3** Accumulation of intracellular lipofuscin. A photomicrograph of the liver of an 80-year-old man shows golden cytoplasmic granules, which represent lysosomal storage of lipofuscin. (From Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 13]. Philadelphia: Lippincott-Raven)

dystrophic calcification involves the intracellular or extracellular formation of crystalline calcium phosphate. The components of the calcium deposits are derived from the bodies of dead or dying cells as well as from the circulation and interstitial fluid.

Dystrophic calcification is commonly seen in atheromatous lesions of advanced atherosclerosis, areas of injury in the aorta and large blood vessels, and damaged heart valves. Although the presence of calcification may only indicate the presence of previous cell injury, as in healed tuberculosis lesions, it is also a frequent cause of organ dysfunction. For example, calcification of the aortic valve is a frequent cause of aortic stenosis in elderly people (Fig. 5-4).

### Metastatic Calcification

In contrast to dystrophic calcification, which occurs in injured tissues, metastatic calcification occurs in normal tissues as the result of increased serum calcium levels (hypercalcemia). Almost any condition that increases the serum calcium level can lead to calcification in inappropriate sites, such as the lung, renal tubules, and blood vessels. The major causes of hypercalcemia are hyperparathyroidism, either primary or secondary to phosphate retention in renal failure; increased mobilization of calcium from bone, as in Paget disease, cancer with metastatic bone lesions, or immobilization; and vitamin D intoxication.

**In summary,** cells adapt to changes in their environment and in their work demands by changing their size, number, and characteristics. These adaptive changes are consistent with the needs of the cell and occur in response to an appropriate stimulus. The changes are usually reversed after the stimulus has been withdrawn.

When confronted with a decrease in work demands or adverse environmental conditions, cells atrophy or reduce their size and revert to a lower and more efficient level of functioning. Hypertrophy results from an increase in work demands and is characterized by an increase in tissue size brought about by an increase in cell size and functional components in the cell. An increase in the number of cells in an organ or tissue that is still capable of mitotic division is called hyperplasia. Metaplasia occurs in response to chronic irritation and represents the substitution of cells of a type that are better able to survive under circumstances in which a more fragile cell type might succumb. Dysplasia is characterized by deranged cell growth of a specific tissue that results in cells that vary in size, shape, and appearance. It is a precursor of cancer.

Under some circumstances, cells may accumulate abnormal amounts of various substances. If the accumulation reflects a correctable systemic disorder, such as the hyperbilirubinemia that causes jaundice, the accumulation is reversible. If the disorder cannot be corrected, as often occurs in many inborn errors of metabolism, the cells become overloaded, causing cell injury and death.

Pathologic calcification involves the abnormal tissue deposition of calcium salts. Dystrophic calcification occurs in dead or dying tissue. Although the presence of dystrophic calcification may only indicate the presence of previous cell injury, it is also a frequent cause of organ dysfunction (*e.g.,* when it affects the heart valves). Metastatic calcification occurs in normal tissues as the result of elevated serum calcium levels. Almost any condition that increases the serum calcium level can lead to calcification in inappropriate sites such as the lung, renal tubules, and blood vessels.

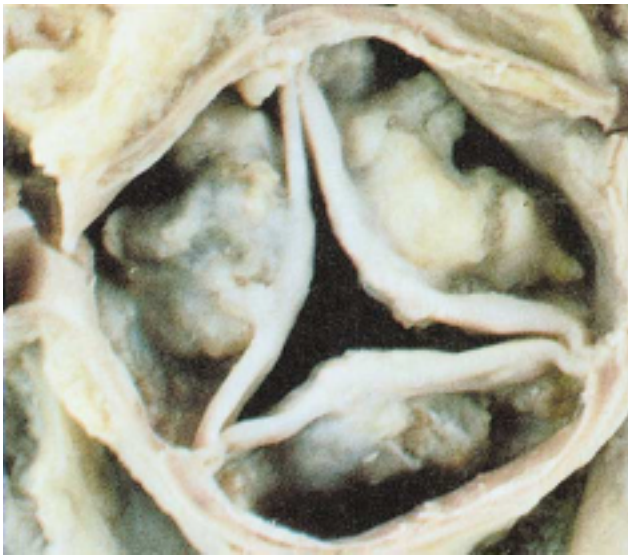

**FIGURE 5-4** Calcific aortic stenosis. Large deposits of calcium salts are evident in the cusps and free margins of the thickened aortic valve as viewed from above. (From Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 28]. Philadelphia: Lippincott-Raven)

## Cell Injury and Death

*After you have completed this section of the chapter, you should be able to meet the following objectives:*

- Describe the mechanisms whereby physical agents such as blunt trauma, electrical forces, and extremes of temperature produce cell injury
- Differentiate between the effects of ionizing and nonionizing radiation in terms of their ability to cause cell injury
- Explain how the injurious effects of biologic agents differ from those produced by physical and chemical agents
- State the mechanisms and manifestations of cell injury associated with lead poisoning
- State how nutritional imbalances contribute to cell injury
- Describe three types of reversible cell changes that can occur with cell injury
- Define *free radical* and relate free radical formation to cell injury and death
- Describe cell changes that occur with ischemic and hypoxic cell injury
- Relate the effects of impaired calcium homeostasis to cell injury and death
- Differentiate cell death associated with necrosis and apoptosis
- Cite the reasons for the changes that occur with the wet and dry forms of gangrene

Cells can be injured in many ways. The extent to which any injurious agent can cause cell injury and death depends in large measure on the intensity and duration of the injury and the type of cell that is involved. Cell injury is usually reversible up to a certain point, after which irreversible cell injury and death occur. Whether a specific stress causes irreversible or reversible cell injury depends on the severity of the insult and on variables such as blood supply, nutritional status, and regenerative capacity. Cell injury and death are ongoing processes, and in the healthy state, they are balanced by cell renewal.

## CAUSES OF CELL INJURY

Cell damage can occur in many ways. For purposes of discussion, the ways by which cells are injured have been grouped into five categories: (1) injury from physical agents, (2) radiation injury, (3) chemical injury, (4) injury from biologic agents, and (5) injury from nutritional imbalances.

### Injury From Physical Agents

Physical agents responsible for cell and tissue injury include mechanical forces, extremes of temperature, and electrical forces. They are common causes of injuries due to environmental exposure, occupational and transportation accidents, and physical violence and assault.

***Mechanical Forces.*** Injury or trauma due to mechanical forces occurs as the result of body impact with another object. The body or the mass can be in motion, or as sometimes happens, both can be in motion at the time of impact. These types of injuries split and tear tissue, fracture bones, injure blood vessels, and disrupt blood flow.

***Extremes of Temperature.*** Extremes of heat and cold cause damage to the cell, its organelles, and its enzyme systems. Exposure to low-intensity heat (43° to 46°C), such as occurs with partial-thickness burns and severe heat stroke, causes cell injury by inducing vascular injury, accelerating cell metabolism, inactivating temperature-sensitive enzymes, and disrupting the cell membrane. With more intense heat, coagulation of blood vessels and tissue proteins occurs. Exposure to cold increases blood viscosity and induces vasoconstriction by direct action on blood vessels and through reflex activity of the sympathetic nervous system. The resultant decrease in blood flow may lead to hypoxic tissue injury, depending on the degree and duration of cold exposure. Injury from freezing probably results from a combination of ice crystal formation and vasoconstriction. The decreased blood flow leads to capillary stasis and arteriolar and capillary thrombosis. Edema results from increased capillary permeability.

***Electrical Injuries.*** Electrical injuries can affect the body through extensive tissue injury and disruption of neural and cardiac impulses. The effect of electricity on the body is mainly determined by its voltage, the type of current (*i.e.,* direct or alternating), its amperage, the resistance of the intervening tissue, the pathway of the current, and the duration of exposure.[4]

Lightning and high-voltage wires that carry several thousand volts produce the most severe damage.[2] Alternating current (AC) is usually more dangerous than direct current (DC) because it causes violent muscle contractions, preventing the person from releasing the electrical source and sometimes resulting in fractures and dislocations. In electrical injuries, the body acts as a conductor of the electrical current. The current enters the body from an electrical source, such as an exposed wire, and passes through the body and exits to another conductor, such as the moisture on the ground or a piece of metal the person is holding. The pathway that a current takes is critical because the electrical energy disrupts impulses in excitable tissues. Current flow through the brain may interrupt impulses from respiratory centers in the brain stem, and current flow through the chest may cause fatal cardiac arrhythmias.

The resistance to the flow of current in electrical circuits transforms electrical energy into heat. This is why the elements in electrical heating devices are made of highly resistive metals. Much of the tissue damage produced by electrical injuries is caused by heat production in tissues that have the highest electrical resistance. Resistance to electrical current varies from the greatest to the least in bone, fat, tendons, skin, muscles, blood, and nerves. The most severe tissue injury usually occurs at the skin sites where the current enters and leaves the body. After electricity has penetrated the skin, it passes rapidly through the body along the lines of least resistance—through body fluids and nerves. Degeneration of vessel walls may occur, and thrombi may form as current flows along the blood vessels. This can cause extensive muscle and deep tissue injury. Thick, dry skin is more resistant to the flow of electricity than thin, wet skin. It is generally believed that the greater the skin resistance, the greater is the amount of local skin burn, and the less the resistance, the greater are the deep and systemic effects.

### Radiation Injury

Electromagnetic radiation comprises a wide spectrum of wave-propagated energy, ranging from ionizing gamma rays to radiofrequency waves (Fig. 5-5). A photon is a par-

### CELL INJURY

- Cells can be damaged in a number of ways, including physical trauma, extremes of temperature, electrical injury, exposure to damaging chemicals, radiation damage, injury from biologic agents, and nutritional factors.
- Most injurious agents exert their damaging effects through uncontrolled free radical production, impaired oxygen delivery or utilization, or the destructive effects of uncontrolled intracellular calcium release.
- Cell injury can be reversible, allowing the cell to recover, or it can be irreversible, causing cell death and necrosis.
- In contrast to necrosis, which results from tissue injury, apoptosis is a normal physiologic process designed to remove injured or worn-out cells.

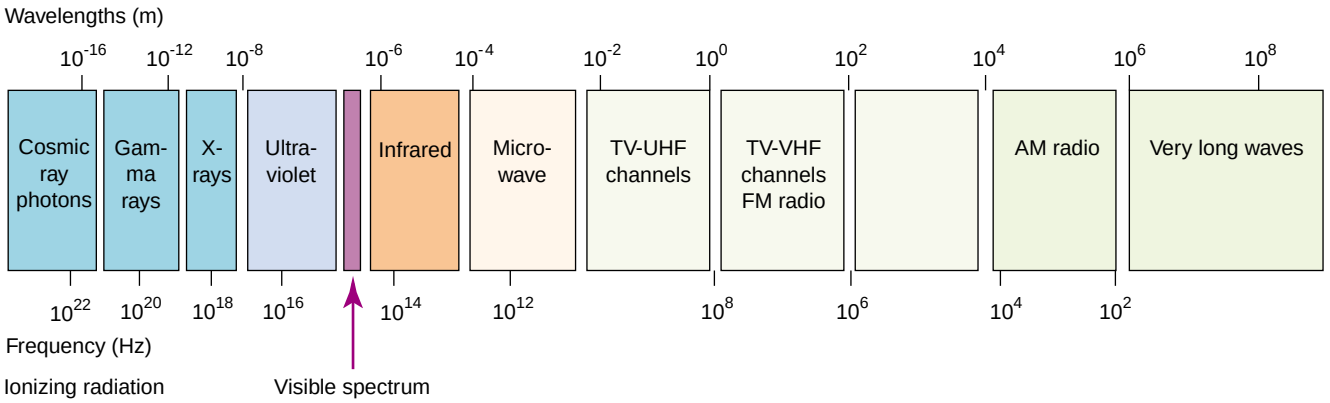


**FIGURE 5-5** Spectrum of electromagnetic radiation.

ticle of radiation energy. Radiation energy above the ultraviolet (UV) range is called *ionizing radiation* because the photons have enough energy to knock electrons off atoms and molecules. *Nonionizing radiation* refers to radiation energy at frequencies below that of visible light. *UV radiation* represents the portion of the spectrum of electromagnetic radiation just above the visible range. It contains increasingly energetic rays that are powerful enough to disrupt intracellular bonds and cause sunburn.

***Ionizing Radiation.*** Ionizing radiation affects cells by causing ionization of molecules and atoms in the cell, by directly hitting the target molecules in the cell, or by producing free radicals that interact with critical cell components.[1,2,5] It can immediately kill cells, interrupt cell replication, or cause a variety of genetic mutations, which may or may not be lethal. Most radiation injury is caused by localized irradiation that is used in treatment of cancer (see Chapter 8). Except for unusual circumstances such as the use of high-dose irradiation that precedes bone marrow transplantation, exposure to whole-body irradiation is rare.

The injurious effects of ionizing radiation vary with the dose, dose rate (a single dose can cause greater injury than divided or fractionated doses), and the differential sensitivity of the exposed tissue to radiation injury. Because of the effect on DNA synthesis and interference with mitosis, rapidly dividing cells of the bone marrow and intestine are much more vulnerable to radiation injury than tissues such as bone and skeletal muscle. Over time, occupational and accidental exposure to ionizing radiation can result in increased risk for the development of various types of cancers, including skin cancers, leukemia, osteogenic sarcomas, and lung cancer.

Many of the clinical manifestations of radiation injury result from acute cell injury, dose-dependent changes in the blood vessels that supply the irradiated tissues, and fibrotic tissue replacement. The cell's initial response to radiation injury involves swelling, disruption of the mitochondria and other organelles, alterations in the cell membrane, and marked changes in the nucleus. The endothelial cells in blood vessels are particularly sensitive to irradiation. During the immediate postirradiation period, only vessel dilation takes place (*e.g.,* the initial erythema of the skin after radiation therapy). Later or with higher levels of radiation, destructive changes occur in small blood vessels such as the capillaries and venules. Acute reversible necrosis is represented by such disorders as radiation cystitis, dermatitis, and diarrhea from enteritis. More persistent damage can be attributed to acute necrosis of tissue cells that are not capable of regeneration and chronic ischemia. Chronic effects of radiation damage are characterized by fibrosis and scarring of tissues and organs in the irradiated area (*e.g.,* interstitial fibrosis of the heart and lungs after irradiation of the chest). Because the radiation delivered in radiation therapy inevitably travels through the skin, radiation dermatitis is common. There may be necrosis of the skin, impaired wound healing, and chronic radiation dermatitis.

***Ultraviolet Radiation.*** Ultraviolet radiation causes sunburn and increases the risk for skin cancers (see Chapter 61). The degree of risk depends on the type of UV rays, the intensity of exposure, and the amount of protective melanin pigment in the skin. Skin damage induced by UV radiation is thought to be caused by reactive oxygen species and by damage to melanin-producing processes in the skin. UV radiation also damages DNA, resulting in the formation of pyrimidine dimers (*i.e.,* the insertion of two identical pyrimidine bases into replicating DNA instead of one). Other forms of DNA damage include the production of single-stranded breaks and formation of DNA–protein cross-links. Normally, errors that occur during DNA replication are repaired by enzymes that remove the faulty section of DNA and repair the damage. The importance of the DNA repair process in protecting against UV radiation injury is evidenced by the vulnerability of persons who lack the enzymes needed to repair UV-induced DNA damage. In a genetic disorder called *xeroderma pigmentosum,* an enzyme needed to repair sunlight-induced DNA damage is lacking. This autosomal recessive disorder is characterized by extreme photosensitivity and a 2000-fold increased risk for skin cancer in sun-exposed skin.[2]

***Nonionizing Radiation.*** Nonionizing radiation includes infrared light, ultrasound, microwaves, and laser energy. Unlike ionizing radiation, which can directly break chemical bonds, nonionizing radiation exerts its effects by causing

vibration and rotation of atoms and molecules. All of this vibrational and rotational energy is eventually converted to thermal energy. Low-frequency nonionizing radiation is used widely in radar, television, industrial operations (*e.g.,* heating, welding, melting of metals, processing of wood and plastic), household appliances (*e.g.,* microwave ovens), and medical applications (*e.g.,* diathermy). Isolated cases of skin burns and thermal injury to deeper tissues have occurred in industrial settings and from improperly used household microwave ovens. Injury from these sources is mainly thermal and, because of the deep penetration of the infrared or microwave rays, tends to involve dermal and subcutaneous tissue injury.

## Chemical Injury

Chemicals capable of damaging cells are everywhere around us. Air and water pollution contain chemicals capable of tissue injury, as does tobacco smoke and some processed or preserved foods. Some of the most damaging chemicals exist in our environment, including gases such as carbon monoxide, insecticides, and trace metals such as lead.

Chemical agents can injure the cell membrane and other cell structures, block enzymatic pathways, coagulate cell proteins, and disrupt the osmotic and ionic balance of the cell. Corrosive substances such as strong acids and bases destroy cells as the substances come into contact with the body. Other chemicals may injure cells in the process of metabolism or elimination. Carbon tetrachloride ($CCl_4$), for example, causes little damage until it is metabolized by liver enzymes to a highly reactive free radical ($CCl_3^{\bullet}$). Carbon tetrachloride is extremely toxic to liver cells.

***Drugs.*** Many drugs—alcohol, prescription drugs, over-the-counter drugs, and street drugs—are capable of directly or indirectly damaging tissues. Ethyl alcohol can harm the gastric mucosa, liver (see Chapter 40), developing fetus (see Chapter 7), and other organs. Antineoplastic (anticancer) and immunosuppressant drugs can directly injure cells. Other drugs produce metabolic end products that are toxic to cells. Acetaminophen, a commonly used over-the-counter analgesic drug, is detoxified in the liver, where small amounts of the drug are converted to a highly toxic metabolite. This metabolite is detoxified by a metabolic pathway that uses a substance (*i.e.,* glutathione) normally present in the liver. When large amounts of the drug are ingested, this pathway becomes overwhelmed, and toxic metabolites accumulate, causing massive liver necrosis.

***Lead Toxicity.*** Lead is a particularly toxic metal. Small amounts accumulate to reach toxic levels. There are innumerable sources of lead in the environment, including flaking paint, lead-contaminated dust and soil, lead-contaminated root vegetables, lead water pipes or soldered joints, pottery glazes, and newsprint. Adults often encounter lead through occupational exposure. Lead and other metal smelters, miners, welders, storage battery workers, and pottery makers are particularly at risk.[1,6] Children are exposed to lead through ingestion of peeling lead paint, by breathing dust from lead paint (*e.g.,* during remodeling), or from playing in contaminated soil. There has been a substantial decline in blood lead levels of the entire population since the removal of lead from gasoline and from soldered food cans.[7] However, high lead blood levels continue to be a problem, particularly among children. In the Third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1991), blood lead levels were highest in 1- to 2-year-old children and lowest in 12- to 19-year-olds.[7] The prevalence of elevated blood lead levels is higher for children living in more urbanized areas. By race or ethnicity, non-Hispanic black children residing in central cities with a population of 1 million or more have the highest proportion of elevated blood lead levels. A high percentage of Mexican-American children living in the most urbanized areas also had elevated lead levels.[8]

Lead is absorbed through the gastrointestinal tract or the lungs into the blood. A deficiency in calcium, iron, or zinc increases lead absorption. In children, most lead is absorbed through the lungs. Although children may have the same or a lower intake of lead, the absorption in infants and children is greater; thus, they are more vulnerable to lead toxicity.[2] Lead crosses the placenta, exposing the fetus to levels of lead that are comparable with those of the mother. Lead is stored in bone and eliminated by the kidneys. Approximately 85% of absorbed lead is stored in bone (and teeth of young children), 5% to 10% remains in the blood, and the remainder accumulates in soft tissue deposits. Although the half-life of lead is hours to days, bone deposits serve as a repository from which blood levels are maintained. In a sense, bone protects other tissues, but the slow turnover maintains blood levels for months to years.

The toxicity of lead is related to its multiple biochemical effects.[2] It has the ability to inactivate enzymes, compete with calcium for incorporation into bone, and interfere with nerve transmission and brain development. The major targets of lead toxicity are the red blood cells, the gastrointestinal tract, the kidneys, and the nervous system.

Anemia is a cardinal sign of lead toxicity. Lead competes with the enzymes required for hemoglobin synthesis and with the membrane-associated enzymes that prevent hemolysis of red blood cells. The resulting red cells are microscopic and hypochromic, resembling those seen in iron-deficiency anemia. The life span of the red cell is also decreased. The gastrointestinal tract is the main source of symptoms in the adult. This is characterized by "lead colic," a severe and poorly localized form of acute abdominal pain. A lead line formed by precipitated lead sulfite may appear along the gingival margins. The lead line is seldom seen in children. The kidneys are the major route for excretion of lead. Lead can cause diffuse kidney damage, eventually leading to renal failure. Even without overt signs of kidney damage, lead toxicity leads to hypertension.

In the nervous system, lead toxicity is characterized by demyelination of cerebral and cerebellar white matter and death of cortical cells. When this occurs in early childhood, it can affect neurobehavioral development and result in lower IQ levels and poorer classroom performance.[9] Peripheral demyelinating neuropathy may occur in adults. The most serious manifestation of lead poisoning is acute encephalopathy. It is manifested by persistent vomiting,

ataxia, seizures, papilledema, impaired consciousness, and coma. Acute encephalopathy may manifest suddenly, or it may be preceded by other signs of lead toxicity such as behavioral changes or abdominal complaints.

Because of the long-term neurobehavioral and cognitive deficits that occur in children with even moderately elevated lead levels, the Centers for Disease Control and Prevention and the American Academy of Pediatrics have issued recommendations for childhood lead screening.[10–12] A safe blood level of lead is still uncertain. At one time, 25 µg/dL was considered safe. Surveys have shown abnormally low IQs in children with levels as low as 10 to 15 µg/dL; in 1991, the safe level was lowered to 10 µg/dL.[13] Recent research suggests that even levels below 10 µg/dL are associated with declines in children's IQ at 3 to 5 years of age.[14]

Screening for lead toxicity involves use of capillary blood obtained from a finger stick to measure free erythrocyte protoporphyrin (EP). Elevated levels of EP result from the inhibition by lead of the enzymes required for heme synthesis in red blood cells. The EP test is useful in detecting high lead levels but usually does not detect levels below 20 to 25 µg/dL. Thus, capillary screening test values greater than 10 µg/dL should be confirmed with those from a venous blood sample. This test also reflects the effects of iron deficiency, a condition that increases lead absorption.[13]

Because the symptoms of lead toxicity usually are vague, diagnosis is often delayed. Anemia may provide the first clues to the disorder. Laboratory tests are necessary to establish a diagnosis. Measurement of lead levels in venous blood is usually used. Treatment involves removal of the lead source and, in cases of severe toxicity, administration of a chelating agent. Asymptomatic children with blood levels of 45 to 69 µg/dL usually are treated. A public health team should evaluate the source of lead because meticulous removal is needed.

### Injury From Biologic Agents

Biologic agents differ from other injurious agents in that they are able to replicate and can continue to produce their injurious effects. These agents range from submicroscopic viruses to the larger parasites. Biologic agents injure cells by diverse mechanisms. Viruses enter the cell and become incorporated into its DNA synthetic machinery. Certain bacteria elaborate exotoxins that interfere with cellular production of ATP. Other bacteria, such as the gram-negative bacilli, release endotoxins that cause cell injury and increased capillary permeability.

### Injury From Nutritional Imbalances

Nutritional excesses and nutritional deficiencies predispose cells to injury. Obesity and diets high in saturated fats are thought to predispose persons to atherosclerosis. The body requires more than 60 organic and inorganic substances in amounts ranging from micrograms to grams. These nutrients include minerals, vitamins, certain fatty acids, and specific amino acids. Dietary deficiencies can occur in the form of starvation, in which there is a deficiency of all nutrients and vitamins, or because of a selective deficiency of a single nutrient or vitamin. Iron-deficiency anemia, scurvy, beriberi, and pellagra are examples of injury caused by the lack of specific vitamins or minerals. The protein and calorie deficiencies that occur with starvation cause widespread tissue damage.

## MECHANISMS OF CELL INJURY

The mechanisms by which injurious agents cause cell injury and death are complex. Some agents, such as heat, produce direct cell injury; other factors, such as genetic derangements, produce their effects indirectly through metabolic disturbances and altered immune responses. There seem to be at least three major mechanisms whereby most injurious agents exert their effects: free radical formation, hypoxia and ATP depletion, and disruption of intracellular calcium homeostasis.

### Free Radical Injury

Many injurious agents exert their damaging effects through a reactive chemical species called a *free radical*.[1,2,15–17] Free radical injury is rapidly emerging as a final common pathway for tissue damage by many injurious agents.

In most atoms, the outer electron orbits are filled with paired electrons moving in opposite directions to balance their spins. A free radical is a highly reactive chemical species arising from an atom that has a single unpaired electron in an outer orbit (Fig. 5-6). In this state, the radical is highly unstable and can enter into reactions with cellular constituents, particularly key molecules in cell membranes and nucleic acids. Moreover, free radicals can establish chain reactions, sometimes thousands of events long, as the molecules they react with in turn form free radicals. Chain reactions may branch, causing even greater damage. Uncontrolled free radical production causes damage to cell membranes, cross-linking of cell proteins, inactivation of enzyme systems, or damage to the nucleic acids that make up DNA.

Free radical formation is a byproduct of many normal cellular reactions in the body, including energy generation, breakdown of lipids and proteins, and inflammatory processes. For example, free radical generation is the main mechanism for killing microbes by phagocytic white blood cells. Molecular oxygen ($O_2$), with its two unpaired outer electrons, is the main source of free radicals. During the course of normal cellular respiration, molecular oxygen is sequentially reduced in the mitochondria by the addition of four electrons to produce water. During the process, small amounts of partially reduced intermediate species are converted to free radicals. These reactive species include the superoxide radicals (one electron), hydrogen peroxide (two electrons), and the hydroxyl radical (three electrons). Transition metals, such as copper and iron, which can accept or donate free electrons during intracellular reactions, are also a source of free radicals. Nitric oxide (NO), an important mediator that is normally synthesized by a variety of cell types, can act as a free radical or be converted into a highly reactive nitrite species.

FIGURE 5-6 Generation of free radicals.

Although the effects of these reactive species are wide-ranging, three types of effects are particularly important in cell injury: lipid peroxidation, oxidative modification of proteins, and DNA effects (Fig. 5-7). Destruction of the phospholipids in cell membranes, including the outer plasma membrane and those of the intracellular organelles, results in loss of membrane integrity. Free radical attack on cell proteins, particularly those of critical enzymes, can interrupt vital processes throughout the cell. DNA is an important target of the hydroxyl free radical. Damage can involve single-stranded breaks in DNA, modification of base pairs, and cross-links between strands. In most cases, various DNA repair pathways can repair the damage. However, if the damage is extensive, the cell dies. The effects of free radical–mediated DNA changes have also been implicated in aging and malignant transformation of cells.

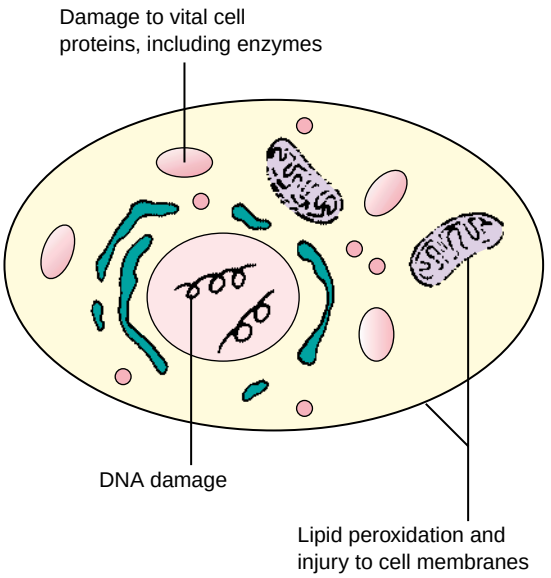


FIGURE 5-7 Mechanisms of free radical cell damage.

Under normal conditions, most cells have chemical mechanisms that protect them from the injurious effects of free radicals. These mechanisms commonly break down when the cell is deprived of oxygen or exposed to certain chemical agents, radiation, or other injurious agents. Free radical formation is a particular threat to tissues in which the blood flow has been interrupted and then restored. During the period of interrupted flow, the intracellular mechanisms that control free radicals are inactivated or damaged. When blood flow is restored, the cell is suddenly confronted with an excess of free radicals that it cannot control.

Scientists continue to investigate the use of free radical scavengers to protect against cell injury during periods when protective cellular mechanisms are impaired. Defenses against free radicals include vitamins E and C.[17,18] Vitamin E is the major lipid-soluble antioxidant present in all cellular membranes. Vitamin C is an important water-soluble cytosolic chain-breaking antioxidant; it acts directly with superoxide and singlet oxygen radicals. β-carotene, a pigment found in most plants, reacts with singlet oxygen and can also function as an antioxidant.[19]

## Hypoxic Cell Injury

Hypoxia deprives the cell of oxygen and interrupts oxidative metabolism and the generation of ATP. The actual time necessary to produce irreversible cell damage depends on the degree of oxygen deprivation and the metabolic needs of the cell. Well-differentiated cells, such as those in the heart, brain, and kidneys, require large amounts of oxygen to provide energy for their special functions. Brain

cells, for example, begin to undergo permanent damage after 4 to 6 minutes of oxygen deprivation. A thin margin can exist between the time involved in reversible and irreversible cell damage. One study found that the epithelial cells of the proximal tubule of the kidney in the rat could survive 20 but not 30 minutes of ischemia.[20]

Hypoxia can result from an inadequate amount of oxygen in the air, respiratory disease, ischemia (*i.e.,* decreased blood flow due to circulatory disorders), anemia, edema, or inability of the cells to use oxygen. Ischemia is characterized by impaired oxygen delivery and impaired removal of metabolic end products such as lactic acid. In contrast to pure hypoxia, which affects the oxygen content of the blood and affects all of the cells in the body, ischemia commonly affects blood flow through small numbers of blood vessels and produces local tissue injury. In cases of edema, the distance for diffusion of oxygen may become a limiting factor. In hypermetabolic states, the cells may require more oxygen than can be supplied by normal respiratory function and oxygen transport. Hypoxia also serves as the ultimate cause of cell death in other injuries. For example, toxins from certain microorganisms can interfere with cellular use of oxygen, and a physical agent such as cold can cause severe vasoconstriction and impair blood flow.

Hypoxia literally causes a power failure in the cell, with widespread effects on the cell's functional and structural components. As oxygen tension in the cell falls, oxidative metabolism ceases, and the cell reverts to anaerobic metabolism, using its limited glycogen stores in an attempt to maintain vital cell functions. Cellular pH falls as lactic acid accumulates in the cell. This reduction in pH can have profound effects on intracellular structures. The nuclear chromatin clumps and myelin figures, which derive from destructive changes in cell membranes and intracellular structures, are seen in the cytoplasm and extracellular spaces.

One of the earliest effects of reduced ATP is acute cellular swelling caused by failure of the energy-dependent sodium/potassium ($Na^+/K^+$)-ATPase membrane pump, which extrudes sodium from and returns potassium to the cell. With impaired function of this pump, intracellular potassium levels decrease, and sodium and water accumulate in the cell. The movement of fluid and ions into the cell is associated with dilation of the endoplasmic reticulum, increased membrane permeability, and decreased mitochondrial function.[2] To this point, the cellular changes due to ischemia are reversible if oxygenation is restored. If the oxygen supply is not restored, however, there is a continued loss of essential enzymes, proteins, and ribonucleic acid through the hyperpermeable membrane of the cell. Injury to the lysosomal membranes results in leakage of destructive lysosomal enzymes into the cytoplasm and enzymatic digestion of cell components. Leakage of intracellular enzymes through the permeable cell membrane into the extracellular fluid is used as an important clinical indicator of cell injury and death. These enzymes enter the blood and can be measured by laboratory tests.

### Impaired Calcium Homeostasis

Calcium functions as a messenger for the release of many intracellular enzymes. Normally, intracellular calcium levels are kept extremely low compared with extracellular levels. These low intracellular levels are maintained by energy-dependent membrane-associated calcium/magnesium ($Ca^{2+}/Mg^{2+}$)-ATPase exchange systems.[2] Ischemia and certain toxins lead to an increase in cytosolic calcium because of increased influx across the cell membrane and the release of calcium stored in the mitochondria and endoplasmic reticulum. The increased calcium level activates a number of enzymes with potentially damaging effects. The enzymes include the phospholipases responsible for damaging the cell membrane, proteases that damage the cytoskeleton and membrane proteins, ATPases that break down ATP and hasten its depletion, and endonucleases that fragment chromatin. Although it is known that injured cells accumulate calcium, it is unknown whether this is the ultimate cause of irreversible cell injury.

## REVERSIBLE CELL INJURY AND CELL DEATH

The mechanisms of cell injury can produce sublethal and reversible cellular damage or lead to irreversible injury with cell destruction or death (Fig. 5-8). Cell destruction and removal can involve one of two mechanisms: apoptosis,

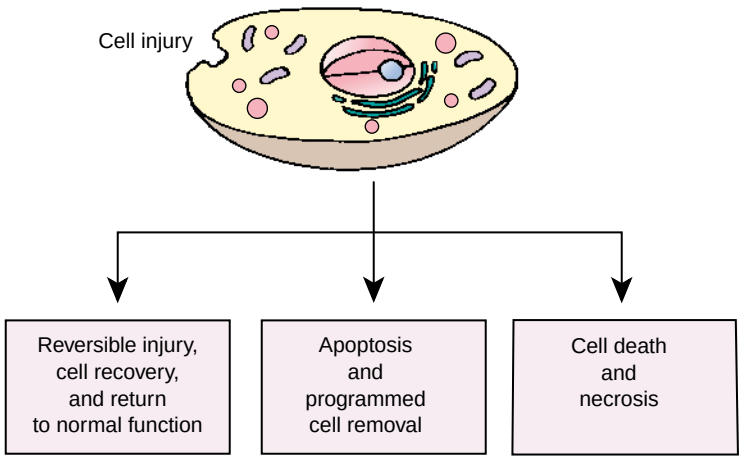


**FIGURE 5-8** Outcomes of cell injury: reversible cell injury, apoptosis and programmed cell removal, cell death and necrosis.

which is designed to remove injured or worn-out cells, or cell death and necrosis, which occurs in irreversibly damaged cells.

## Reversible Cell Injury

Reversible cell injury, although impairing cell function, does not result in cell death. Two patterns of reversible cell injury can be observed under the microscope: cellular swelling and fatty change. Cellular swelling occurs with impairment of the energy-dependent $Na^+/K^+$-ATPase membrane pump, usually as the result of hypoxic cell injury.

Fatty changes are linked to intracellular accumulation of fat. When fatty changes occur, small vacuoles of fat disperse throughout the cytoplasm. The process is usually more ominous than cellular swelling, and although it is reversible, it usually indicates severe injury. These fatty changes may occur because normal cells are presented with an increased fat load or because injured cells are unable to metabolize the fat properly. In obese persons, fatty infiltrates often occur within and between the cells of the liver and heart because of an increased fat load. Pathways for fat metabolism may be impaired during cell injury, and fat may accumulate in the cell as production exceeds use and export. The liver, where most fats are synthesized and metabolized, is particularly susceptible to fatty change, but fatty changes may also occur in the kidney, the heart, and other organs.

## Programmed Cell Death

In each cell line, the control of cell number is regulated by a balance of cell proliferation and cell death. Cell death can involve apoptosis or necrosis. Apoptotic cell death involves controlled cell destruction and is involved in normal cell deletion and renewal. For example, blood cells that undergo constant renewal from progenitor cells in the bone marrow are removed by apoptotic cell death.

*Apoptosis,* from Greek *apo* for "apart" and *ptosis* for "fallen," means *fallen apart.* Apoptotic cell death, which is equated with cell suicide, eliminates cells that are worn out, have been produced in excess, have developed improperly, or have genetic damage. In normal cell turnover, this process provides the space needed for cell replacement. The process, which was first described in 1972, has become one of the most vigorously investigated processes in biology.[21] Apoptosis is thought to be involved in several physiologic and pathologic processes. Current research is focusing on the control mechanisms of apoptosis in an attempt to understand the pathogenesis of many disease states, such as cancer and autoimmune disease.

Apoptotic cell death is characterized by controlled autodigestion of cell components. Cells appear to initiate their own death through the activation of endogenous enzymes. This results in cell shrinkage brought about by disruption of the cytoskeleton, condensation of the cytoplasmic organelles, disruption and clumping of nuclear DNA, and a distinctive wrinkling of the cell membrane.[2] As the cell shrinks, the nucleus breaks into spheres, and the cell eventually divides into membrane-covered fragments. Membrane changes occur during the process, signaling surrounding phagocytic cells to engulf the apoptotic cell parts and complete the degradation process (Fig. 5-9).

Apoptosis is thought to be responsible for several normal physiologic processes, including programmed destruction of cells during embryonic development, hormone-dependent involution of tissues, death of immune cells, cell death by cytotoxic T cells, and cell death in proliferating cell populations. During embryogenesis, in the development of a number of organs such as the heart, which begins as a single pulsating tube and is gradually modified to become a four-chambered pump, apoptotic cell death allows for the next stage of organ development. It also separates the webbed fingers and toes of the developing embryo (Fig. 5-10). Apoptotic cell death occurs in the hormone-dependent involution of endometrial cells during the menstrual cycle and in the regression of breast tissue after weaning from breast-feeding. The control of immune cell numbers and destruction of autoreactive T cells in the thymus have been credited to apoptosis. Cytotoxic T cells and natural killer cells are thought to destroy target cells by inducing apoptotic cell death.

Apoptosis appears to be linked to several pathologic processes. For example, suppression of apoptosis may be a determinant in the growth of cancers. Apoptosis is also thought to be involved in the cell death associated with certain viral infections, such as hepatitis B and C, and in cell death caused by a variety of injurious agents, such as mild thermal injury and radiation injury. Apoptosis may also be involved in neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). The loss of cells in these disorders does not induce inflammation; although the initiating event is unknown, apoptosis appears to be the mechanism of cell death.[22]

Several mechanisms appear to be involved in initiating cell death by apoptosis. As in the case of endometrial changes that occur during the menstrual cycle, the process

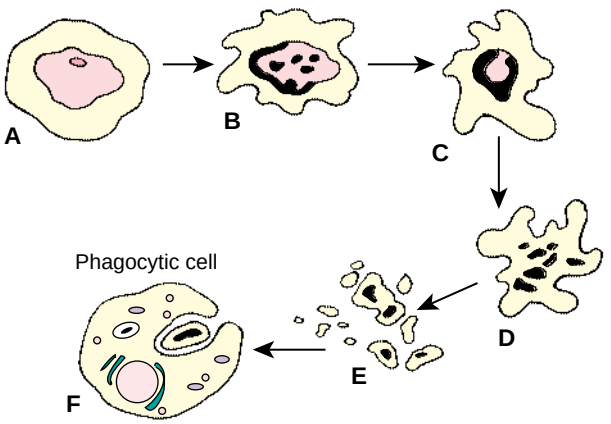


**FIGURE 5-9** Apoptotic cell removal: (**A**) shrinking of the cell structures, (**B** and **C**) condensation and fragmentation of the nuclear chromatin, (**D** and **E**) separation of nuclear fragments and cytoplasmic organelles into apoptotic bodies, and (**F**) engulfment of apoptotic fragments by phagocytic cell.

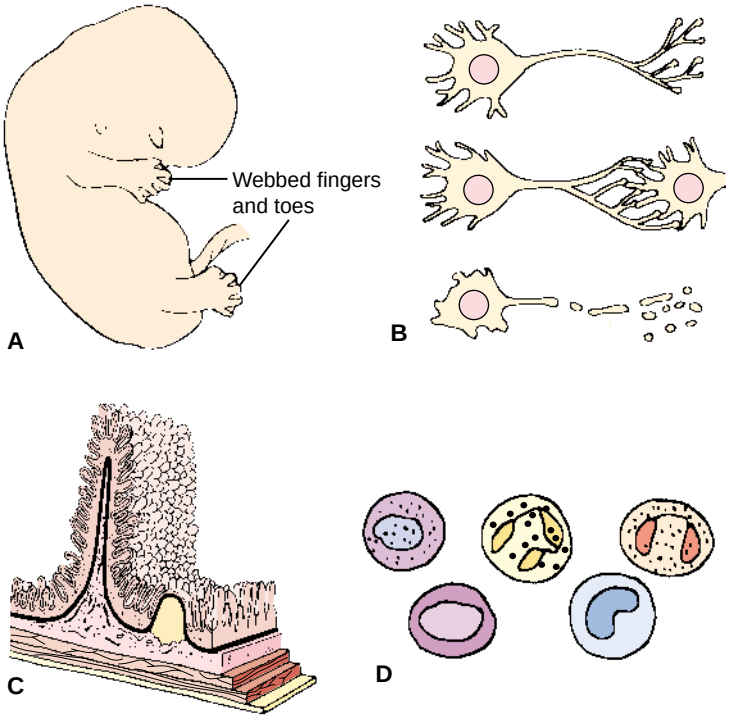


**FIGURE 5-10** Examples of apoptosis: (**A**) separation of webbed fingers and toes in embryo, (**B**) development of neural-appropriate connections, (**C**) removal of cells from intestinal villa, and (**D**) removal of senescent blood cells.

can be triggered by the addition or withdrawal of hormones. In hepatitis B and C, the virus seems to sensitize the hepatocytes to apoptosis.[23] Certain oncogenes and suppressor genes involved in the development of cancer seem to play an active role in stimulation or suppression of apoptosis. Injured cells may induce apoptotic cell death through increased cytoplasmic calcium, which leads to activation of nuclear enzymes that break down DNA. In some instances, gene transcription and protein synthesis, the events that produce new cells, may be the initiating factors. In other cases, cell surface signaling or receptor activation appears to be the influencing force.

## Necrosis

Necrosis refers to cell death in an organ or tissue that is still part of a living person.[24] Necrosis differs from apoptosis in that it involves unregulated enzymatic digestion of cell components, loss of cell membrane integrity with uncontrolled release of the products of cell death into the intracellular space, and initiation of the inflammatory response.[25] In contrast to apoptosis, which functions in removing cells so that new cells can replace them, necrosis often interferes with cell replacement and tissue regeneration.

With necrotic cell death, there are marked changes in the appearance of the cytoplasmic contents and the nucleus. These changes often are not visible, even under the microscope, for hours after cell death. The dissolution of the necrotic cell or tissue can follow several paths. The cell can undergo liquefaction (*i.e.,* liquefaction necrosis); it can be transformed to a gray, firm mass (*i.e.,* coagulation necrosis); or it can be converted to a cheesy material by infiltration of fatlike substances (*i.e.,* caseous necrosis). *Liquefaction necrosis* occurs when some of the cells die but their catalytic enzymes are not destroyed. An example of liquefaction necrosis is the softening of the center of an abscess with discharge of its contents. During *coagulation necrosis,* acidosis develops and denatures the enzymatic and structural proteins of the cell. This type of necrosis is characteristic of hypoxic injury and is seen in infarcted areas. *Infarction* (*i.e.,* tissue death) occurs when an artery supplying an organ or part of the body becomes occluded and no other source of blood supply exists. As a rule, the infarct's shape is conical and corresponds to the distribution of the artery and its branches. An artery may be occluded by an embolus, a thrombus, disease of the arterial wall, or pressure from outside the vessel.

*Caseous necrosis* is a distinctive form of coagulation necrosis in which the dead cells persist indefinitely as soft, cheeselike debris.[1] It is most commonly found in the center of tuberculosis granulomas, or tubercles, and is thought to result from immune mechanisms (see Chapter 20).

***Gangrene.*** The term *gangrene* is applied when a considerable mass of tissue undergoes necrosis. Gangrene may be classified as dry or moist. In dry gangrene, the part becomes dry and shrinks, the skin wrinkles, and its color changes to dark brown or black. The spread of dry gangrene is slow, and its symptoms are not as marked as those of wet gangrene. The irritation caused by the dead tissue produces a line of inflammatory reaction (*i.e.,* line of demarcation) between the dead tissue of the gangrenous area and the healthy tissue (Fig. 5-11). Dry gangrene

**FIGURE 5-11** Gangrenous toes. (Biomedical Communications Group, Southern Illinois University School of Medicine, Springfield, IL)

usually results from interference with arterial blood supply to a part without interference with venous return and is a form of coagulation necrosis.

In moist or wet gangrene, the area is cold, swollen, and pulseless. The skin is moist, black, and under tension. Blebs form on the surface, liquefaction occurs, and a foul odor is caused by bacterial action. There is no line of demarcation between the normal and diseased tissues, and the spread of tissue damage is rapid. Systemic symptoms are usually severe, and death may occur unless the condition can be arrested. Moist or wet gangrene primarily results from interference with venous return from the part. Bacterial invasion plays an important role in the development of wet gangrene and is responsible for many of its prominent symptoms. Dry gangrene is confined almost exclusively to the extremities, whereas moist gangrene may affect the internal organs or the extremities. If bacteria invade the necrotic tissue, dry gangrene may be converted to wet gangrene.

*Gas gangrene* is a special type of gangrene that results from infection of devitalized tissues by one of several *Clostridium* bacteria, most commonly *Clostridium perfringens*. These anaerobic and spore-forming organisms are widespread in nature, particularly in soil; gas gangrene is prone to occur in trauma and compound fractures in which dirt and debris are embedded. Some species have been isolated in the stomach, gallbladder, intestine, vagina, and skin of healthy persons. The bacteria produce toxins that dissolve cell membranes, causing death of muscle cells, massive spreading edema, hemolysis of red blood cells, hemolytic anemia, hemoglobinuria, and renal failure.[25] Characteristic of this disorder are the bubbles of hydrogen sulfide gas that form in the muscle. Gas gangrene is a serious and potentially fatal disease. Antibiotics are used to treat the infection, and surgical methods are used to remove the infected tissue. Amputation may be required to prevent spreading infection involving a limb. Hyperbaric oxygen therapy has been used, but clinical data supporting its efficacy have not been rigorously assessed.

**In summary,** cell injury can be caused by a number of agents, including physical agents, chemicals, biologic agents, and nutritional factors. Among the physical agents that generate cell injury are mechanical forces that produce tissue trauma, extremes of temperature, electricity, radiation, and nutritional disorders. Chemical agents can cause cell injury through several mechanisms: they can block enzymatic pathways, cause coagulation of tissues, or disrupt the osmotic or ionic balance of the cell. Biologic agents differ from other injurious agents in that they are able to replicate and continue to produce injury. Among the nutritional factors that contribute to cell injury are excesses and deficiencies of nutrients, vitamins, and minerals.

Injurious agents exert their effects largely through generation of free radicals, production of cell hypoxia, or unregulated intracellular calcium levels. Partially reduced oxygen species called *free radicals* are important mediators of cell injury in many pathologic conditions. They are an important cause of cell injury in hypoxia and after exposure to radiation and certain chemical agents. Lack of oxygen underlies the pathogenesis of cell injury in hypoxia and ischemia. Hypoxia can result from inadequate oxygen in the air, cardiorespiratory disease, anemia, or the inability of the cells to use oxygen. Increased intracellular calcium activates a number of enzymes with potentially damaging effects.

Injurious agents may produce sublethal and reversible cellular damage or may lead to irreversible cell injury and death. Cell death can involve two mechanisms: apoptosis and necrosis. Apoptosis involves controlled cell destruction and is the means by which the body removes and replaces cells that have been produced in excess, developed improperly, have genetic damage, or are worn out. Necrosis refers to cell death that is characterized by cell swelling, rupture of the cell membrane, and inflammation.

## REVIEW EXERCISES

A 30-year-old man sustained a fracture of his leg 2 months ago. The leg had been encased in a cast, which was just removed. The patient is amazed at the degree to which the muscles in his leg have shrunk.

**A.** Would you consider the changes in the patient's muscles to be a normal adaptive response? Explain.

**B.** Will these changes have an immediate or long-term effect on the function of the leg?

**C.** What type of measures can be taken to restore full function to the leg?

A 45-year-old woman has been receiving radiation therapy for breast cancer.

**A.** Explain the effects of ionizing radiation in eradicating the tumor cells.

**B.** Why is the radiation treatment given in small divided or fractionated doses, rather than as a single large dose?

**C.** Part way through the treatment schedule, the woman notices that her skin over the irradiated area has become reddened and irritated. What is the reason for this?

People who have had a heart attack may experience additional damage once blood flow has been restored, a phenomenon referred to *reperfusion injury*.

**A.** What is the proposed mechanism underlying reperfusion injury?

**B.** What factors might influence this mechanism?

Every day, blood cells in our body become senescent and die without producing signs of inflammation, and yet, massive injury or destruction of tissue, such as occurs with a heart attack, produces significant signs of inflammation.

**A.** Explain.

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