

a leading killer in the United States. Massive brain contusions, injury to internal organs and soft tissues, and blood loss may lead to immediate mortality. Survivors may succumb to infections and multiple organ failure. Repair of injuries to soft tissue, skeletal and muscular systems, and internal organs often requires prolonged periods of rehabilitation. Penetrating trauma inflicted by a variety of weapons can result in multiple complications.

Extremes of physical agents, such as temperature, radiation, and electricity, may damage cells. Generalized increases in body temperature (hyperthermia) or reduction in body temperature (hypothermia) can lead to cell injury; high or low tissue temperatures can cause tissue injury or death. With increased temperature, the resulting morbidity and mortality are dependent on the severity of the burn and the total surface area that was burned. Markedly reduced temperatures may induce the freezing of tissue (frostbite). Ice crystals in cellular tissue rupture the cell membrane, which leads to cell death.

Irradiation for the treatment of cancer can cause injury of susceptible normal cells. Ionizing radiation causes radiolysis of water and the production of hydroxyl radicals (OH^-). These radicals will lead to membrane damage and breakdown of structural and enzymatic proteins that result in cell death. Often, arterioles that supply oxygenated blood are damaged by ionizing radiation, resulting in inadequate nutritional supply leading to ischemia and death of the irradiated tissues. Irradiation also causes damage to nucleic acids and may result in gene mutations, possibly leading to neoplasia years later.

Mechanical Factors

The *physical stress theory* may help explain mechanical factors influencing tissue adaptation and injury. The physical stress theory proposes that changes in the relative level of physical stress cause a predictable adaptive response in all biologic tissue. Typical tissue response to physical stress includes decreased stress tolerance (e.g., atrophy), maintenance, increased stress tolerance (e.g., hypertrophy), injury, and death.⁸

Failure of a tissue occurs when the applied load exceeds the failure tolerance of the tissue. Soft tissues are influenced by the history of recent physical stresses, so that the accumulation of individual stresses can cause injury. Characteristics of the load, such as rate, compression, and forces (e.g., torsion, shear), along with the properties of the affected tissue determine the type and extent of tissue damage. The time elapsed since injury and the extent of tissue damage determine the inflammatory response.^{8,90}

With repetitive and/or forceful tasks, the initiating stimuli for inflammatory responses include repeated overstretch, compression, friction, and anoxia. These insults lead to mechanical injury of cellular membranes and intracellular structures and a localized release of proteins such as collagen, fibronectin, and cytokines.⁸

A single high load or stress from a traumatic fall, car accident, or other traumatic event can cause significant injury. Bones can fracture from one episode of high-magnitude force, while workers lifting heavy boxes repeatedly can incur a slow degradation of the tissue tolerance. Decreasing tissue tolerance may explain why there are no active acute inflammatory indicators in tendons associ-

ated with tendinitis. Instead, antiinflammatory mediators and fibrotic proliferation are observed, suggesting the acute inflammatory phase has resolved. Tennis elbow or golfer's elbow is recognized in many cases as a noninflammatory condition after an inflammatory episode.⁸ In fact, research is ongoing to find ways to reinitiate the inflammatory cascade and promote healing in an otherwise degenerative process.³⁵ Low loads sustained over a long period of time, such as workers who remain in a fixed, flexed posture for prolonged periods of time, can also result in tissue injury because of decreased tissue tolerance.⁹⁸

Some soft tissues, such as ligaments, can rupture with a single high-magnitude force but can also fail from repeated bouts of moderate-magnitude stress. Likewise, as mentioned, bone can fracture from high-magnitude force but can also develop stress fractures or stress reactions from repeated episodes of moderate-magnitude force.⁷⁰ Altering mechanical stress (either increasing or decreasing forces) can be used to benefit individuals under varying circumstances. For example, reducing mechanical stress by offloading or pressure reduction is a concept used for healing ulcers and preventing their recurrence.

Controlled increase in physical stress is the underlying principle of progressive resistive exercise used to cause muscle fibers to hypertrophy and thereby able to withstand and generate greater force. Higher than normal levels of physical stress can promote remodeling in bone. Musculoskeletal tissues subjected to higher than normal levels of stress become more tolerant to subsequent physical stresses and are more resistant to injury.⁹⁸

Chemical Factors

Toxic substances cause chemical injury. These substances can be divided into two categories: those that can injure cells directly and those that require metabolic transformation into the toxic agent. Examples of chemicals that injure cells directly are heavy metals, such as mercury, that bind to and disrupt critical membrane proteins and a number of toxins and drugs, such as alkylating agents, used in chemotherapy.

Alkylating agents, such as nitrogen mustards, induce cross linking of DNA and inactivation of other essential cellular constituents. Carbon tetrachloride and acetaminophen are examples of inert substances that must be metabolized to reactive intermediates to cause cell injury. Taken in large amounts, most medications can be toxic, and many are even lethal. Suicide by drug overdose is a common example of drug-induced chemical toxicity.

Free Radical Formation. An important mechanism of cell injury and disease is the production of reactive oxygen species sometimes referred to as the formation of *free radicals*. Free radicals are an integral part of metabolism and are formed continuously in the body. They can exert positive effects (e.g., on the immune system) or negative effects (e.g., lipid, protein, or DNA oxidation). A variety of normal and pathologic reactions can lead to the activation of oxygen by the sequential addition or subtraction, respectively, of one electron at a time (Fig. 6-2).

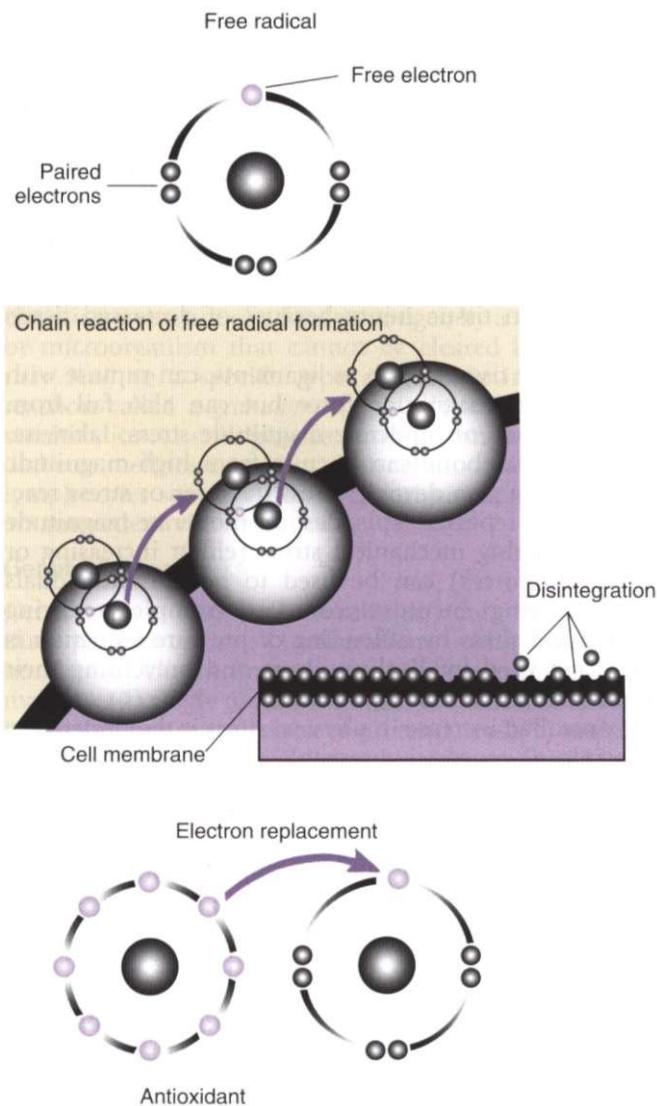


Figure 6-2

The oxidative process and formation of free radicals. Normal metabolic processes and a variety of other extrinsic factors, such as pollution, poor nutrition, and exposure to toxic chemicals, can result in the formation of free radicals when normal oxygen atoms lose one of their four paired electrons. The resulting unstable atom attempts to replace the missing electron by "stealing" an electron from a healthy cell, creating another unstable atom (free radical) and setting off a chain reaction referred to as *oxidation*. Oxidation as a by-product of metabolism damages cell membranes, leading to intrinsic cellular damage, a part of the normal aging process. Free radical damage (oxidation) is believed to alter the way cells encode genetic information in the DNA and may contribute to a variety of diseases and disorders. Antioxidant molecules freely give up an electron to stabilize the oxygen atom without becoming unstable and without initiating a chain reaction.

For example, the body's natural process of using oxygen and food to produce energy can create free radicals as a by-product of these functions. These unpaired electrons are reactive and commonly bind to oxygen for stabilization. The oxygen then binds to hydrogen for stabilization. This series of reactions generated by normal cellular metabolism results in a phenomenon referred to as *oxygen toxicity* and yields superoxide (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical ($\cdot OH$). These

forms of reactive oxygen are referred to as *oxygen radicals*, which are toxic to cells.

The cellular enzymes always scavenging the body to protect cells from this type of injury normally inactivate these radicals and convert the radical back to usable oxygen. Some unstable oxygen molecules (i.e., free radicals) enable the body to fight inflammation, kill bacteria, and help regulate the autonomic nervous system.

However, if produced in excess amounts (a situation referred to as *oxidative stress*), these radicals can become the mechanism of cell injury and subsequent cell death. Free radicals have been considered central to the damaging effects that can lead to degenerative conditions such as heart disease, cerebrovascular disease, diabetes mellitus, cataracts, Parkinson's disease, premature aging, and cancer. In fact, research has shown that oxidative stresses caused by reactive oxygen species are factors in over 90% of lifestyle-related diseases.²⁴

Reactive oxygen species or free radical formation occur as a result of many events such as prolonged exercise; exposure to high levels of oxygen, irradiation, ultraviolet or fluorescent light, pollutants, tobacco smoke, and pesticides (airborne or in food); drug overdose; heat stress; and the reperfusion injury that is induced by the restoration of normal blood flow after a period of ischemia such as occurs during organ transplantation or after MI.

Free radical toxicity may also be the underlying cause of degeneration of neurons located in the *substantia nigra* leading to the loss of dopamine necessary for the normal control of movements that produces the abnormal movements seen in Parkinson's disease.²⁴

Antioxidants. Oxygen is the most common form of free radical in the human body, but the utilization of oxygen as a life-supporting mechanism means oxidative stress is an inescapable part of the human biologic system. The simultaneous presence of antioxidants is an adaptive response to help the body ward off the potentially harmful effects of oxygen and its derivatives, including free radicals.¹⁵⁴

Antioxidants neutralize the extra free radicals and keep them from taking electrons from other molecules, resulting in cellular and DNA damage. A variety of enzymatic and nonenzymatic defense mechanisms are present within cells to perform the function of antioxidants detoxifying reactive oxygen species and protecting the cells from this type of injury. These are called *endogenous antioxidants*. Researchers are finding a variety of uses for natural antioxidants in combating the effects of aging and disease.

There are also *exogenous antioxidants* that can be taken from outside the body through our diet. Vitamin C, E, and beta-carotene are three important exogenous antioxidants. Over 200 antioxidants have been identified through food or plant substances. For example, vitamin E effectively scavenges several types of free radicals and other reactive species in lipid membranes and other lipid concentrations, making it a potentially effective antioxidant (able to neutralize the free radical before damage occurs) in preventing LDL cholesterol from adhering to the walls of arteries. In the case of the prostate, lycopene, the compound that makes tomatoes red, is a potent antiox-

dant potentially effective in promoting prostate health.^{51,79}

Adequate folate intake has been shown to reduce the risk of breast cancer associated with alcohol consumption by providing bioactive compounds to counteract the formation of oxidative compounds.^{50,155}

Multiple trials are ongoing to investigate oxidation and its effect on cellular injury, aging, and disease (e.g., cancer, heart disease, and cataracts) and the use of antioxidants found naturally in food and plants to combat oxidative stress, thereby preventing or possibly modifying diseases at the cellular level. Animal and human studies have confirmed that regular, moderate physical activity and exercise strengthen the antioxidant defense system, whereas intense or prolonged, strenuous exercise (especially in a person who has a sedentary lifestyle) constitutes an oxidative stress.^{40,116,119}

Nitric Oxide. The nitric oxide (NO) molecule is composed of one nitrogen atom and one oxygen atom. It is present in all mammals including humans and is one of the few gaseous signaling molecules known. NO should not be confused with nitrous oxide (N_2O), a general anesthetic, or with nitrogen dioxide (NO_2), which is a poisonous air pollutant.

The nitric oxide molecule is a free radical, which is relevant to understanding its high reactivity. NO is recognized as an important modulator of an enormous number of physiologic responses. Reduced NO bioavailability that is a result of oxidative stress seems to be the common molecular disorder causing many pathologic effects within the body.

NO assists in long-term memory. It also influences neuronal transmission by increasing the permeability of nerve endings, making acetylcholine transfer across the synapses easier. NO alters the ability of the gastrointestinal mucosa to resist injury induced by toxins, thereby influencing the immune system. NO inhibits virally induced cytokine and chemokine production, possibly combating the common cold.¹²⁰ It also stimulates collagen synthesis for wound healing, modulates fracture healing, and is useful in the treatment of tendonopathy.^{107,108}

NO is an antilipid that provides a nonstick coating to the lining of blood vessels, much like Teflon. These two effects have helped explain how NO might prevent heart attacks and strokes and why nitroglycerin works—nitroglycerin is converted to NO inside vascular tissue, where it relaxes smooth muscle in arteries and causes blood vessels to dilate. It also controls platelet function by preventing platelets from clumping together, thus preventing the formation of blood clots.

Researchers are studying the effect of NO on free radicals that cannot be stabilized or removed. Studies show that NO appears to play a role in exercise-induced dilation of blood vessels supplying cardiac and skeletal muscle. Exercise training enhances NO-mediated vasodilation. The exact mechanism is not clear yet, but a growing number of studies suggest that exercise training, perhaps via increased capacity for NO formation, retards atherosclerosis.⁸⁵ There is also accumulating evidence that NO is involved in skeletal muscle glucose uptake during exercise.⁸⁶

Exercise and Free Radicals. Physical activity and exercise can have positive or negative effects on oxidative stress depending on training load, training specificity, and basal level of training. Oxidative stress seems to be involved in muscular fatigue and overtraining.⁴³ Excessive exercise has been shown to induce DNA damage in peripheral leukocytes. Exhaustion of the leukocyte reactive oxygen species (ROS) may reduce the body's ability to combat microbial invasions (i.e., infections) before the system has been restored.¹⁰³ On the other hand, moderate stress in the form of regular exercise training may have protective effects against exercise-induced DNA damage.

Evidence is emerging to support a role for improved NO bioavailability with exercise training.¹²⁸ Up-regulation of endogenous antioxidant defense systems and complex regulation of repair systems are seen in response to training and exercise. Up-regulation of antioxidants and modulation of the repair response may be mechanisms by which exercise can influence our health in a positive way.⁴¹

Regular, long-term aerobic exercise has been shown to reduce migraine pain severity, frequency, and duration, possibly a result of increased NO production.¹⁰²

Psychosocial Factors

Psychosocial factors can have an impact on tissue adaptation, especially as related to tissue injury.⁸⁹ Psychosocial factors (e.g., fear, tension, or anxiety) may influence individual threshold values for tissue adaptation and injury. Many studies have investigated the role of mechanical and psychosocial factors in the onset of musculoskeletal (and other regional) acute and chronic pain.¹²¹ For example, people who are only occasionally or never satisfied in their work settings or who describe their work as "monotonous" have a higher risk of injury than those who are satisfied or completely satisfied with support from supervisors and colleagues.^{11,57,58,100}

Reversible Cell Injury

Alteration in a cell's functional environment, either acute or chronic, produces a stress to the cell's ability to attain or maintain homeostasis. The extent to which the cell is able to alter mechanisms and regain homeostasis in the altered environment is considered an adaptation by the cells or tissues. When the cell is unable to adapt, injury can occur. A sublethal or reversible injury occurs if the stress is sufficiently small in magnitude or short enough in duration that the cell is able to recover homeostasis after removal of the stress.

Cells react to injurious stimuli by changing their steady state to continue to function in a hazardous environment. Reversible (sublethal) injury caused by any of the mechanisms of cell injury listed in Box 6-1 is a transient impairment in the cell's normal structure or function. Normal cell structure and function can return after removal of the stressor or injurious stimulus (Fig. 6-3).

Acute reversible injury causes an impairment of ion homeostasis within the cell and leads to increased intracellular levels of sodium and calcium. An influx of interstitial fluid into the cell accompanies these ionic shifts and causes increased cell volume (swelling). Swelling

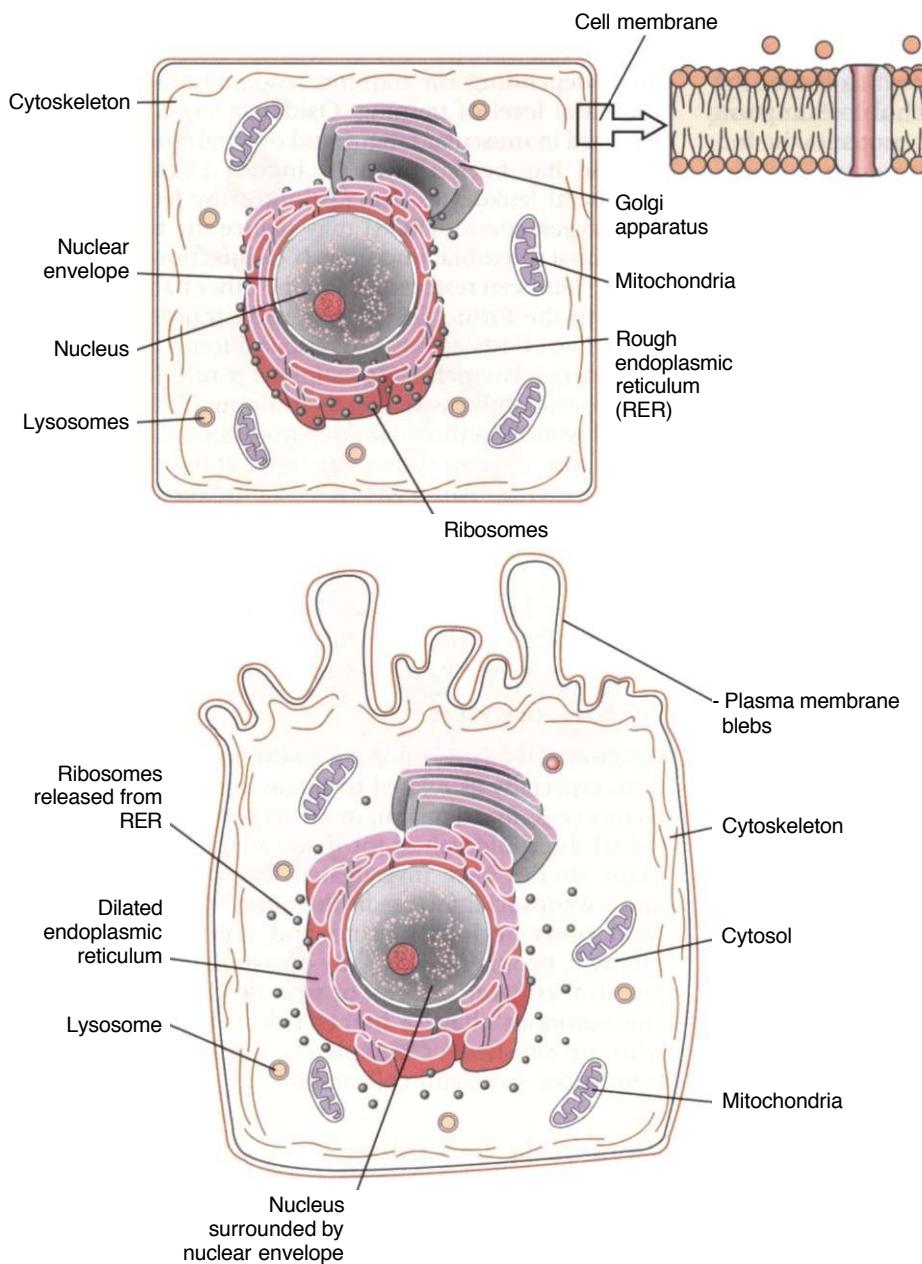


Figure 6-3

A, A normal cell with its organelles. **B**, Reversible cell injury with cellular swelling, accumulation of fluid in endoplasmic reticulum, and the release of ribosomes and formation of membrane blebs. [Courtesy SH Tepper, PhD, PT, Winchester, VA, Shenandoah University.]

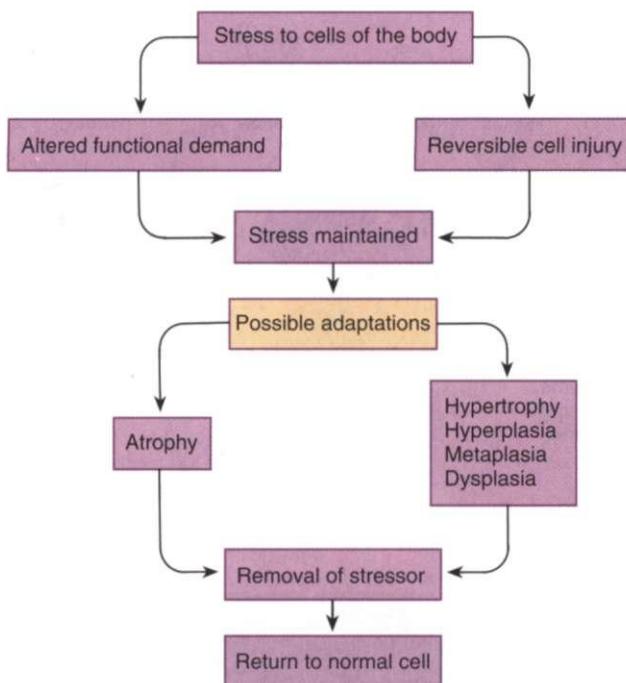
occurs within the cytosol (liquid medium of the cytoplasm) and within organelles such as mitochondria and the endoplasmic reticulum. Swollen mitochondria generate less energy. Thus, instead of oxidative ATP production, the cell reverts to less efficient anaerobic glycolysis, which results in excessive production of lactic acid. The pH of the cell becomes acidic, which slows down the cell metabolism, resulting in further cellular damage. The injured cell forms plasma membrane *blebs* that can seal off and detach from the cell surface. In severely injured cells, ribosomes detach from the rough endoplasmic reticulum (RER), and a decrease in the number of polysomes occurs. These changes lead to reduced protein synthesis by the affected cells and the cycle of damage can continue.

However, if the cell nucleus remains undamaged and the energy source is restored or the toxic injury is neutralized, the cell is able to recover and pump the ions and

excess fluid back out. The swelling disappears, and the cell is returned to the original steady state, constituting a reversible cell injury.

Cellular Adaptations in Chronic Cell Injury

When a sublethal stress remains present over a period of time, stable alterations (adaptations) take place within the affected cells, tissues, and organs. Adaptation enables the cells to function in an altered environment and thereby avoid injury. Characteristics of cell adaptation, such as change in size, number, or function, increase the cell's ability to survive. In many but not all cases, these changes benefit the function of the parent organ or structure within which the cell resides. These changes are potentially reversible; common cellular adaptations include atrophy, hypertrophy, hyperplasia, metaplasia, and dysplasia (Fig. 6-4).

**Figure 6-4**

Cellular adaptations and reversible cell injury in response to stress. When the body is under persistent stress leading to either reversible cell injury or altered functional demand, the tissues adapt. Adaptations could include atrophy, hypertrophy, hyperplasia, metaplasia, or dysplasia. All of these changes are reversible with removal of the stressor. (Courtesy SH Tepper, PhD, PT, Winchester, VA, Shenandoah University.)

Atrophy is a reduction in cell and organ size. Atrophy can occur with vascular insufficiency, reduction in hormone levels, malnutrition, immobilization, pain limiting function, and chronic inflammation. Atrophy, involving the entire body, may occur with aging and is referred to as *physiologic atrophy*. Bone loss, thymus involution, muscle wasting, and brain cell loss are examples of either tissue or organ atrophy associated with aging. Pathologic atrophy occurs as a result of some of the mechanisms of cell injury, such as ischemia, inadequate nutrition, or physical factors, listed in Box 6-1. For example, ischemia of the viscera results in atrophied organs; cancer or malnutrition can result in cachexia, a general wasting of the body; and spinal cord injury results in atrophy of the affected muscles.

Hypertrophy is an increase in the size of the cell and organ. Hypertrophy can occur when increased functional demands are placed on the cells, tissue, or organs and with increased hormonal input (e.g., exercise stress can induce skeletal muscle hypertrophy). Pure hypertrophy only occurs in the heart and striated muscles because these organs consist of cells that cannot divide. Hypertrophy of the heart is a common pathologic finding that occurs as an adaptation of heart muscle to an increased workload. Specifically, hypertrophy of the left ventricle is a typical complication of hypertension. Increased blood pressure requires that the heart produce more force to eject the blood. The additional force is produced by hypertrophy of muscle fibers in the left ventricle.

Hyperplasia is an increase in the number of cells leading to increased organ size. Tissues can divide, and in the presence of excessive functional demands, these tissues increase in cell number. Pure hyperplasia typically occurs because of hormonal stimulation (e.g., prolonged estrogen exposure causes the endometrium of the uterus to become thick) or chronic stimulation (e.g., persistent pressure on the skin induces hyperplasia and the formation of a callus). Some hyperplasia has no discernible cause and may represent early neoplasia. Hypertrophy and hyperplasia often occur together such as in the case of prostate enlargement and obstruction of the urethra and bladder. The result is an increase in size and number of smooth muscle cells in the wall of the urinary bladder.

Metaplasia is a change in cell morphology and function resulting from the conversion of one adult cell type into another. For example, in smokers, portions of the respiratory tract change from ciliated pseudostratified columnar epithelium into stratified squamous epithelium, leading to a thickening of the respiratory epithelium and loss of the functional clearance of mucus and debris along the respiratory tree.

Dysplasia is an increase in cell numbers that is accompanied by altered cell morphology and loss of histologic organization. Considered to be a preneoplastic alteration, dysplasia can be found in areas that are chronically injured and undergoing hyperplasia or metaplasia.

Intracellular Accumulations or Storage

Intracellular accumulations are increases in the storage of lipids, proteins, carbohydrates, or pigments within the cell that occur as a result of an overload of various metabolites or exogenous material. These accumulations can also be caused by metabolic disturbances altering cell function. For example, when the liver is sublethally injured, lipid (triglyceride) accumulates within the hepatocyte. This lipid accumulation occurs when a reduction in protein synthesis occurs as a result of disaggregation of the ribosomes from the rough endoplasmic reticulum as previously discussed. Hepatocytes normally produce our endogenous lipoproteins.

With sublethal damage to hepatocytes (e.g., alcohol abuse), a lack of protein shell formation occurs so that lipoproteins cannot be packaged and transported to the plasma. As a result, lipids remain within the hepatocyte, causing the characteristic "fatty liver" found in alcoholics.

Irreversible Cell Injury

If the injurious or stressful stimulus is of sufficient magnitude or duration or if the cell is unable to adapt, the cell will be irreversibly injured. Irreversible cell injury is synonymous with cell death. Hallmarks of lethally injured cells include alterations in the cell nucleus, mitochondria, and lysosomes and the rupture of the cell membrane.

Damage to the nucleus can present in three forms: pyknosis, karyorrhexis, and karyolysis. Nuclei undergo clumping or pyknosis, which is a degeneration of the cell as the nucleus shrinks in size and the chromatin con-

denses to a solid mass. The pyknotic nuclei can fragment, a process termed *karyorrhexis*, or it can undergo dissolution (*karyo lysis*).

Mitochondria lose their membrane potential and become unable to synthesize ATP, leaving the cell without the necessary energy production for cell function. Morphologically, irreversibly injured mitochondria appear swollen, contain large lipid-protein aggregates called *floculent densities*, and may also contain dense crystalline deposits of calcium (Fig. 6-5).

After cell death, lysosomes release their digestive enzymes within the cytoplasm of the cell, initiating enzymatic degradation of all cellular constituents, a process that may be aided by enzymes released from inflammatory cells. The active process of degradation of dead cells is called *necrosis*. Enzymes help dissolve the dead tissue, making it easier for phagocytic cells to remove the dead tissue in preparation for healing by repair (laying down of a collagenous tissue scar) or regeneration (regrowth of parenchymal tissue). Dead cells release their contents into the extracellular fluid, eventually making their way into the circulation, where they can be measured as clinically useful signs of cell injury. For example, levels of aspartate aminotransferase (AST), creatine kinase (CK), and lactate dehydrogenase (LDH) are typically elevated in the serum of people with myocardial infarct or viral hepatitis (see Tables 40-5, 40-15, and 40-16).

Types of Necrosis

Dead tissue becomes morphologically distinguishable from healthy tissue only after the process of necrosis begins with the dissolution of irreversibly injured cells within living tissue. Removal of this dead tissue is essential for healing to take place. Histologically, several different types of necrosis are recognized (Table 6-1) with some additional subcategories.

For example, gangrene caused by bacterial infection and associated with tissue ischemia (peripheral vascular disease) may form coagulative necrosis (dry gangrene) or liquefactive necrosis (wet gangrene). The fermentation reactions caused by certain bacterial pathogens may cause the formation of gas bubbles in the infected tissue. In muscle necrosis, one of the causative agents is *Clostridium perfringens*. The term used to describe this condition is *clostridial myonecrosis* or gas gangrene (see Chapter 8).

Pathologic Tissue Calcification

Calcification is the deposition of calcium salts, primarily calcium phosphate, in body tissues. Normally, 99% of all calcium is deposited in the teeth and bone matrix to ensure stability and strength; the remaining 1% is dissolved in body fluids, such as blood, or within skeletal muscle. Two types of pathologic calcification are evident. The first type is *dystrophic calcification*, the deposition of calcium salts in an area of damaged tissue. Classic examples of dystrophic calcification include tuberculosis and atherosclerosis. With tuberculosis, calcification occurs in the granulomas (accumulations of macrophages and connective tissue) that may be found in lymph nodes or in the lung parenchyma and may be seen on radiograph. In the case of atherosclerosis, vessels damaged by the deposition of cholesterol may become calcified. Calcifications

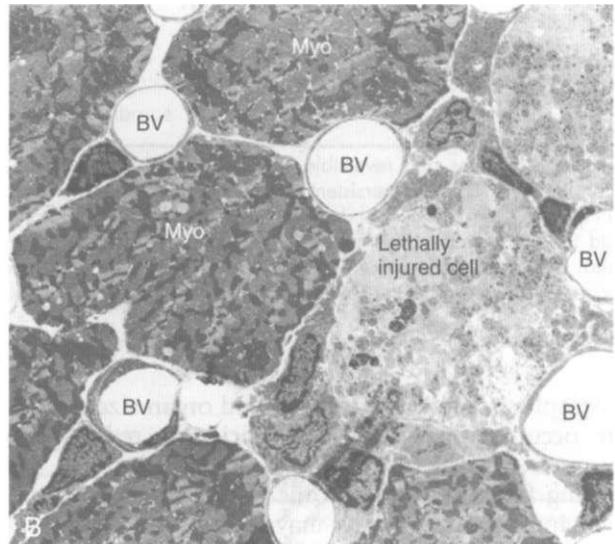
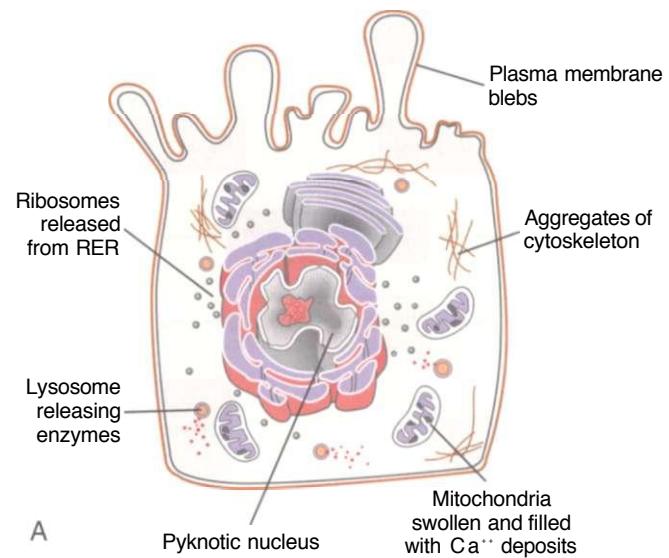


Figure 6-5

Irreversible cell injury: ultrastructural alterations in an irreversibly killed cell. A, Mitochondria are nonfunctional and filled with floculent densities. Lysosomes are releasing their digestive enzymes. The nucleus is condensing upon itself (pyknosis). Membrane breakdown allows intracellular enzymes to be released into the interstitial area. B, Electron micrograph of lethally injured cardiomyocytes next to healthy viable cardiomyocytes (Myo). Note lethally injured cells to the right of the Myo are swollen, mitochondria are filled with floculent densities, there is a loss of myofilaments, and mononuclear phagocytic cells are beginning to remove these dead cells. BV, Blood vessel. Original magnification $\times 1500$. (A, Courtesy SH Tepper, PhD, PT, Winchester, VA, Shenandoah University; B, From Tepper SH, Anderson PA, Mergner WJ: Recovery of the heart following focal injury induced by dietary restriction of potassium, *Path Res Pract* 186(2):265-285, 1990.)

within the vessel wall lead to a reduction in elasticity of the vessel.

Dystrophic calcification can occur in soft tissues such as the tendons. Calcifying tendinitis occurs in up to 20% of the adult population but is mostly asymptomatic. Women between the ages of 30 and 60 years old are affected most often but men can be affected, too. The

Table 6-1 Types of Necrosis

Type	Cause	Effects	Area of Involvement
Coagulative	Ischemia (lack of blood supply)	Cell membrane is preserved; nucleus undergoes pyknosis and karyolysis (dissolution), organelles dissolve.	Solid internal organs (e.g., heart, liver, kidneys)
Caseous ("cheesy")	<i>Mycobacterium tuberculosis</i> (TB); seen with other fungal infections	Cell membrane is destroyed; debris appears cheeselike and does not disappear by lysis but persists indefinitely; damaged area is walled off in a fibrous calcified area forming a granuloma.	Dry gangrene (extremities) Lungs, bronchopulmonary lymph nodes, skeletal bone (extrapulmonary TB)
Liquefactive	Pyogenic bacteria (e.g., <i>Staphylococcus aureus</i>)	Death of neurons releases lysosomes that liquefy the area, leaving pockets of liquid and cellular debris (abscess or fluid-filled cavity); shapeless, amorphous debris remains.	Brain tissue (e.g., brain infarct); skin, wound, joint infections Wet gangrene (extremities)
Fatty necrosis	Acute pancreatitis, abdominal trauma	Formation of calcium soaps by the release of pancreatic lipases.	Abdominal area
Fibrinoid	Trauma in blood vessel wall	Plasma proteins accumulate; cellular debris and serum proteins form pink deposits.	Blood vessels (tunica media, smooth muscle cells)

TB, Tuberculosis.

shoulder is the primary site involved; calcific tendinitis is bilateral in approximately 25% to 30% of all cases. The etiopathology remains unknown but hydroxyapatite crystals are the main component of the calcifications within the tendons. Iontophoresis remains a common treatment for this condition along with antiinflammatory medications. Extracorporeal shockwave therapy has been used; surgery is a rare treatment approach.⁸¹

The second type of calcification is *metastatic calcification*. This type occurs with hypercalcemia (increased blood calcium levels) in living tissue. The normal absorption of calcium is facilitated by parathyroid hormone and vitamin D. When there are increased levels of parathyroid hormone in the blood (e.g., hyperparathyroidism), an increased accumulation of calcium in the pulmonary alveoli, renal tubules, thyroid gland, gastric mucosa, and arterial walls interferes with normal organ function.

during the healing process by understanding these concepts of injury and recovery.

TBI often occurs during motor vehicle accidents. With direct trauma to the head, brain tissue can be lethally damaged by two means (primary and secondary injury). Depending on the nature, direction, and magnitude of forces applied to the skull, primary injury to the brain may be of any or all of the following types: (1) local brain damage occurs at the site where the brain impacts the skull (coup injury) and the site opposite impact (contrecoup injury); (2) polar brain damage occurs at the tips (poles) of the frontal, temporal, and occipital lobes and the undersurface of the frontal and temporal lobes when the brain moves inside the skull; or (3) diffuse axonal injury (DAI) occurs throughout the subcortical white matter (and brainstem if the magnitude of force is great enough) with sufficient shear force to injure axons.

Secondary injury is usually the result of hypoxic-ischemic injury (HII) caused by cerebral edema. Because the soft and pliable brain is enclosed within the rigid skull, abnormal brain fluid dynamics caused by cerebral edema result in increased intracranial pressure (ICP). Signs and symptoms of increased ICP include headache, loss of sense of smell, obtunded consciousness, and loss of consciousness. Even a mild increase in ICP is sufficient to cause death of neural tissue caused by inadequate perfusion. Moderate and severe increases in ICP can cause brain tissue to shift position or herniate from one chamber into another. Intracranial hematomas (epidural, subdural, and intracerebral) are another source of secondary brain damage.

Passive imaging techniques (e.g., computed tomography [CT] and magnetic resonance imaging [MRI])

Continued.

SPECIAL IMPLICATIONS FOR THE THERAPIST

6-1

Cell Injury: Multiple Cell Injuries

The concepts discussed in this first section on cell (tissue) injury are essential for understanding the pathogenesis of a variety of acute illnesses and injuries the therapist may see in a primary practice pattern. Often, multiple episodes of care with complex cases involving comorbidities occur in clinical practice. For example, the victim of a motor vehicle accident experiencing a traumatic brain injury (TBI) and concomitant pelvic fracture may develop pneumonia and pulmonary compromise and subsequently experience MI. The therapy staff following this client from the intensive care unit (ICU) through rehabilitation to a home health service setting and possibly as an outpatient can better meet the needs of such an individual

are useful to visualize the structural changes that occur with TBI, whereas active imaging techniques (e.g., electroencephalogram [EEG], positron emission tomography [PET], and evoked potentials) are useful to visualize physiologic changes that occur with TBI.

Open wounds and fracture are common sequelae associated with motor vehicle accidents. In this case the pelvic fracture resulted from the mechanical force distributed through the pelvis during a motor vehicle accident. Fractures are often diagnosed by radiograph. When a bone is fractured, its normal blood supply is disrupted. Osteocytes (bone cells) die from the trauma and the resulting ischemia. Bone macrophages remove the dead bone cells and damaged bone.

A precursor fibrocartilaginous growth of tissue occurs before the laying down of primary bone, eventually followed by the laying down and remodeling on normal adult bone. This process from fracture to full restoration of the bone will take weeks to months depending on the type of fracture, location, vascular supply, health, and age of the individual.

In this example, if the myocardium is subjected to ischemia for a sufficient duration, the myocytes become irreversibly injured. A cascade of physiologic and anatomic changes leads to the death of myocardial cells. Coagulative necrosis ensues, followed by acute inflammation and finally repair by scar tissue formation (Fig. 6-6).

Coagulative necrosis begins with the release of lysosomal enzymes that cause dissolution of the normal structural relationships found within myocytes. The dead cells attract acute inflammatory cells that phagocytize the necrotic debris and release growth factors. The growth factors initiate the proliferation of blood vessels (angiogenesis) and fibroblasts, resulting in the eventual production of a collagenous scar.

Signs and symptoms correlate with the different stages of lethal cell injury and differ according to the organ or structure(s) involved. During acute MI, the individual often experiences angina, shortness of breath, sweating, and nausea. These symptoms of physiologic stress are caused by the release of histamines, bradykinins, and prostaglandins such as substance P from the lethally injured myocytes.

An electrocardiogram (ECG) reveals ST segment elevation and Q waves over the affected area. The person is also at an increased risk for life-threatening dysrhythmias due to the loss of electrical conductivity of lethally injured myocytes and disrupted conductivity (irritability) of the adjacent cells. If a significant percentage of the myocardium is infarcted, cardiogenic shock or congestive heart failure may ensue.

Cytoplasmic enzymes or proteins (e.g., CK-MB) are released from the dead cells. Normally, the plasmalemma is impermeable to these large molecules and contains them within the confines of the cytoplasm. After lethal injury the plasmalemma is broken down by the actions of phospholipases, and these molecules are released from inside the cell. A number of cytoplasmic proteins are released into the interstitial area and are taken up by adjacent lymphatic vessels and finally enter the bloodstream. LDH, CK-MB, and troponin

(see Tables 40-15 and 40-16) are clinically relevant for diagnosis and assessment of the severity of a MI.

The therapist must understand the process of injury and repair to the brain, pelvic bones, and myocardium (or other involved organs and/or structures) as appropriate client care is determined by the different stages of this process. For example, recovery from TBI tends to follow the progression outlined by the Rancho Los Amigos Levels of Cognitive Function (LOCF) (see Table 33-2).

In general, intervention is directed by the person's current LOCF level. During LOCF levels I to III, primary goals involve increasing tolerance of activities, including intervention, tolerating upright posture, and increasing interaction with the environment. During levels IV to VI the emphasis shifts to increasing physical and cognitive endurance. During levels VII and VIII intervention focuses on the skills necessary to reenter the community.

After fracture of bone, a period of immobilization usually occurs to remove longitudinal stress. This period allows for the phagocytic removal of necrotic bone tissue and the initial deposition of the fibrocartilaginous callus. As the fracture heals as revealed by radiograph, gradual progression of stress is applied. Mobilization of this individual will occur depending on the type of fixation used on the pelvis. For example, if an external fixation is applied for fracture stabilization, mobilization can occur almost immediately within tolerance of the person's symptoms.

The highest risk of death during the first hours after MI stems from dysrhythmias. Rupture of the myocardium is possible during days 3 to 10 after a transmural MI (from outside epicardium to inside endocardium). The risk of these events dictates that exercise during this time must not subject damaged cells to excessive stress. Proper mobilization of the individual soon after infarction may decrease the likelihood of succumbing to the negative effects of bedrest but may be complicated by variables such as pelvic fracture, pneumonia, and the TBI in this case.

TISSUE HEALING

The process of tissue healing begins soon after tissue injury or death and occurs either by regeneration (regrowth of original tissue) or by repair (formation of a connective tissue scar). The inflammatory cells that are recruited from the blood circulation begin the healing process by breaking down and removing the necrotic tissue. This is accomplished primarily by phagocytes that secrete degradative enzymes and also phagocytose the cellular debris, connective tissue fragments, and plasma proteins present in the dead tissue.

The healing process is complex and influenced by many components such as fibronectin, proteoglycans and elastin, collagen, and parenchymal and endothelial cells. In addition, there is a wide range of factors that affect tissue healing and must be taken into account during

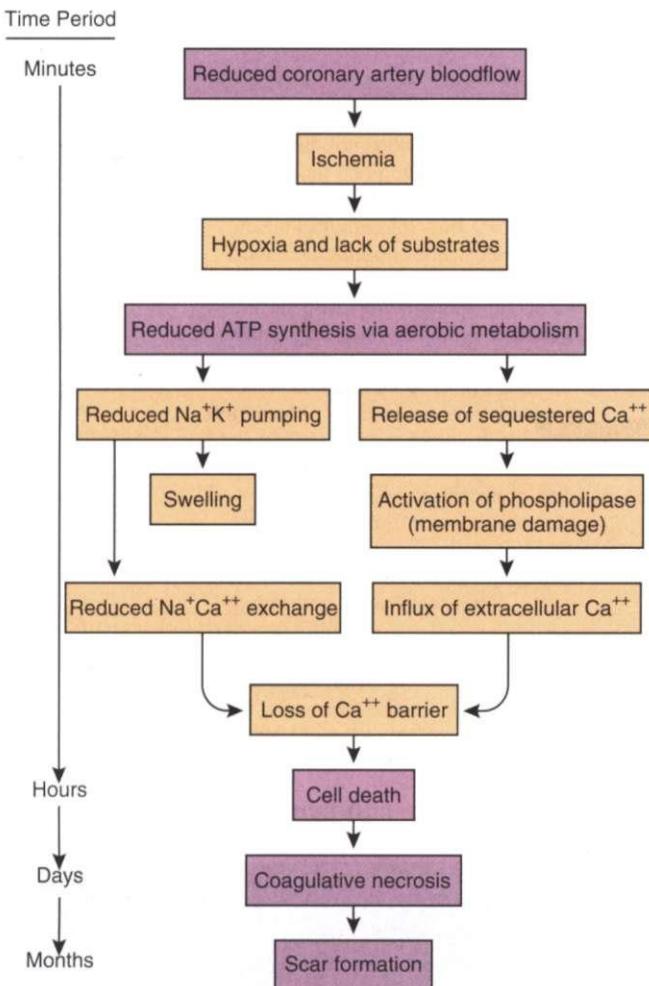


Figure 6-6

Pathogenesis of myocardial infarction (MI). With reduction in coronary artery blood flow (CABF) caused by a thrombus formation, ischemia results in a reduction of aerobic metabolism. Irreversible cell injury occurs, followed by necrosis of the heart tissue. Release of intracellular enzymes (CK-MB, troponin) from the dead heart tissue serve as biochemical markers in the early diagnosis of MI (see Tables 40-15 and 40-16). In the following weeks, healing occurs by repair, the formation of a connective tissue scar. (Courtesy SH Tepper, PhD, PT, Winchester, VA, Shenandoah University.)

recovery and rehabilitation. Both the components and the factors that affect tissue healing are presented in this section, followed by a discussion of the multiphasic process of tissue healing and recovery.

Components of Tissue Healing

Fibronectin

Fibronectin has numerous functions in wound healing, the most important of which are the formation of scaffold, the provision of tensile strength, and the ability to "glue" other substances and cells together. It is one of the earliest proteins to provide the structural support that stabilizes the healing tissue. Plasma proteins that leak from inflamed vessels are the first source of fibronectin for the healing tissue. Plasma-derived fibronectin binds

to and stabilizes fibrin, a protein that makes up the blood clots that are present in the injured tissue.

Fibronectin binds together several types of proteins present in the extracellular matrix and can also bind to debris, such as DNA material derived from necrotic cells, thereby acting as an opsonin (molecule that acts as a binding enhancer to facilitate phagocytosis) during the breakdown of necrotic tissue. Fibronectin is also responsible for attracting fibroblasts and macrophages by chemotaxis to the healing tissue. The stimulated fibroblasts, in turn, secrete more fibronectin. Fibronectin binds to proteoglycans and collagens and this binding further stabilizes the healing tissue.

The importance of fibronectin can be seen as researchers seek to explain the lack of a functional healing response in the anterior cruciate ligament (ACL) after injury.¹⁵⁴ Studies focusing on the signaling pathways and on binding to fibronectin for specific tissues, such as the ACL, may yield improved prevention and intervention strategies in the future.^{91,138,153}

Proteoglycans and Elastin

Proteoglycans, proteins containing carbohydrate chains and sugars, are secreted in abundance by fibroblasts early during the tissue repair reaction. Proteoglycans bind to fibronectin and to collagen and help stabilize the tissue that is undergoing repair. Proteoglycans also retain water and aid in the hydration of the tissue being repaired. Once the tissue is healed, proteoglycans contribute to the organization and stability of collagen and create an electrical charge that gives basement membranes the property of functioning like molecular sieves. Fibroblasts also synthesize and secrete elastin, a protein that becomes cross-linked to form fibrils or long sheets that provide tissues with elasticity.

Collagen

Collagen is the most important protein to provide structural support and tensile strength for almost all tissues and organs of the body. The different types of collagen give stability to healing tissue; the word collagen is derived from the Greek and means *glue producer*. Collagen is a fibrous protein molecule consisting of three chains of amino acid coiled around each other in a triple helix (Fig. 6-7). Improved technology has made it possible to identify collagen types and measure protein turnover. It is the most abundant protein in the body; at least 27 collagen types have been identified.

We know that exercise is a potent stimulus for protein synthesis in skeletal muscle. Collagen in the extracellular matrix of muscle and tendon is also sensitive to mechanical stimuli. Collagen does not appear to be nutritionally sensitive, which may contribute to the loss of muscle during aging. It is possible that the tissue is unable to respond adequately to increased availability of nutrients.¹⁵⁰

Organization of Collagen. Each collagen type has a specialized function (Table 6-2). The amino acid makeup of the collagen molecule and the manner in which the molecules are assembled together vary for each one of the collagen types. The differences in organization and composition account for the structural properties of each

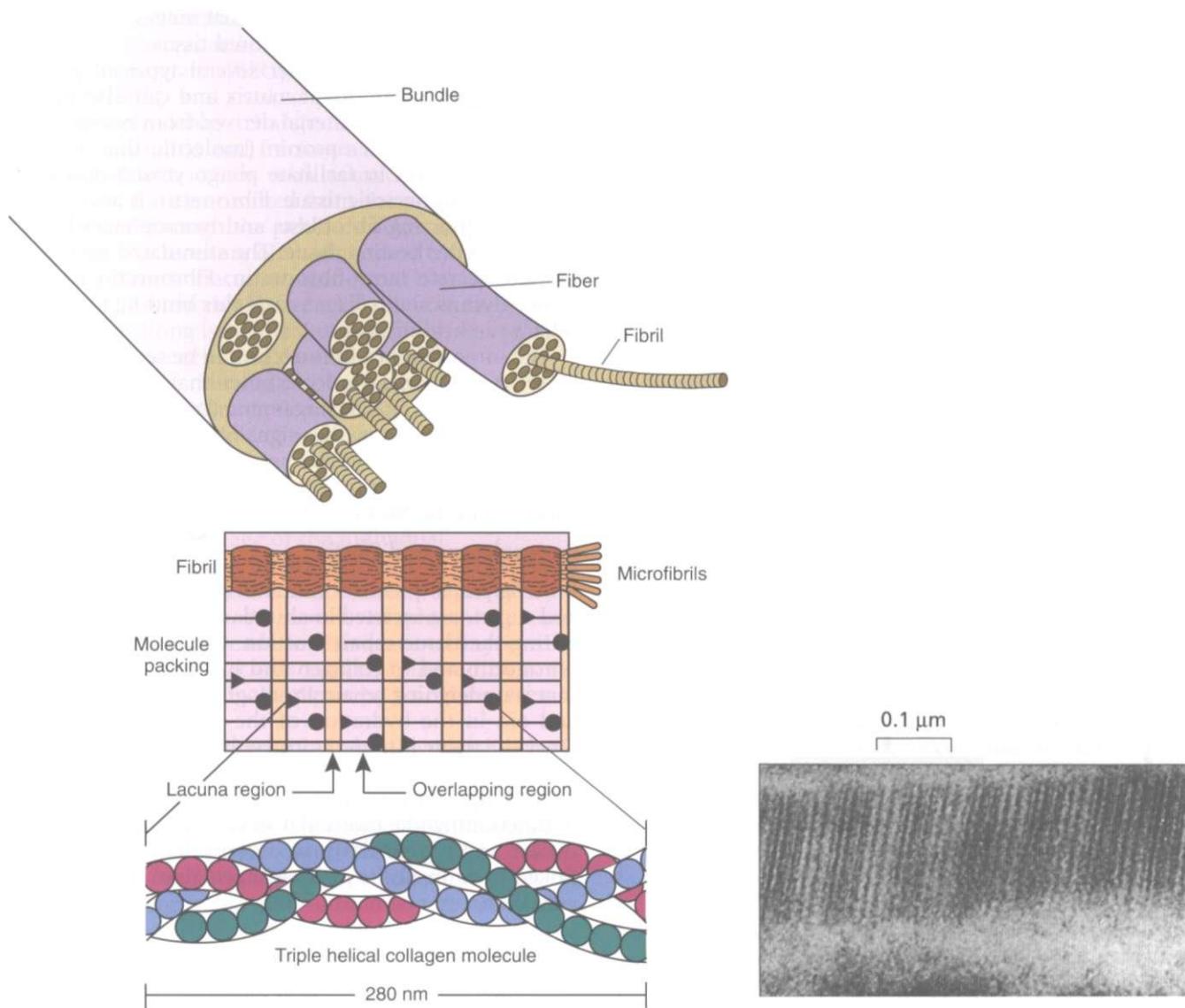


Figure 6-7

Structure of collagen. A, The collagen fiber is composed of fibrils, each of which is composed of microfibrils. B, The molecule itself consists of three polypeptide chains called *alpha chains* that wrap around each other in a triple helix. The helix is made possible because each third amino acid in the polypeptide chain is glycine. The molecules are quarter-staggered one to another, which ensures that no weak points occur across the fibril to prevent overload and slippage. C, Visualized by transmission electron microscopy, the individual collagen fibrils are seen to have two orders of banding. The larger bands result from the gaps between the individual molecules of collagen, which then overlap the adjacent molecules to form a strong bond. (From Bullough PG: *Bullough and Vigorita's orthopaedic pathology*, ed 3, St Louis, 1997, Mosby.)

collagen type. For example, collagen organized in unidirectional or parallel bundles contributes to the strength of tendons. Collagen is the principal extracellular component of normal tendon.

Collagen in random arrangement provides flexibility of the skin and rigidity of bone. When organized at right angles, collagen allows transmission of light in the cornea and vitreous. Collagen laid down in a tubular fashion contributes to the elasticity of the blood vessels.

Some collagen molecules are assembled into progressively thicker and stronger filamentous structures, allowing the molecules to become cross-linked. These cross-links impart tensile strength to collagen fibers and prevent slippage of molecules past one another when

under tension. The structural stability of the extracellular matrix is primarily a consequence of collagen and the extent of cross-linking.²³

Types of Collagen. Type I collagen, the most common form, is assembled as a thick bundle that is structurally very strong and can be found in all body tissues, where it forms bundles together with other collagen types. Type I collagen is the main component of mature scars and is also predominant in strong tissues such as tendons and bones.

Type II collagen is assembled into thin supporting filaments and is the predominant collagen type found in cartilaginous tissue. Type II fibers of the external annulus have a half-life of about 3 months. This allows

Table 6-2 Types of Collagen

Type	Location
Type I	Predominant structural collagen of the body; constitutes 80% to 85% of dermal collagen; prominent in mature scars, tendon, bone, and dentin; joints
Type II	Predominant component of hyaline cartilage (e.g., outer ear, end of nose, joint); not present in skin; found in nucleus pulposus external annulus
Type III	Prominent in vascular and visceral structures (e.g., blood vessels, gastrointestinal tract, liver, uterus) but absent in bone and tendon, constitutes 15% to 20% of dermal collagen, abundant in embryonic tissues, first collagen deposited in wound healing (granulation tissue)
Type IV	Found in basement membranes (base of epithelial, endothelial, and mesenchymal cells found in developing fetus), glomeruli of kidney nephron
Type V	Present in most tissues but never as a major component; prominent in fetal membrane, cornea, heart valve; minor component of skin; synovial membranes
Type VI	Prevalent in most connective tissues
Type VII	May be involved in matrix and bone disorders, anchoring filaments of lymphatic vessels and at dermal-epidermal junctions
Type VIII	Secreted by rapidly proliferating cells; found in basement membranes; may provide a molecular bridge between different types of matrix molecules
Type IX	Minor component in hyaline cartilage; vitreous humor (fluid of the eye)
Type X	Only formed in the epiphyseal growth plate cartilage; may have a role in angiogenesis; may be involved in matrix and bone disorders
Type XI	Hyaline cartilage
Type XII	Embryonic skin and tendon, periodontal ligament
Type XIII	Endothelial cells
Type XIV	Fetal skin and tendons; similar to type I
Types XV-XXVII	Identified but not clearly understood

maintenance of the nutritive exchanges between degenerative external annulus and any healthy remaining tissue, possibly delaying or avoiding further degeneration.⁴⁸

Type III collagen is assembled into thin filaments that make tissues strong but supple and elastic. It contains interchain disulfide bonds or bridges not found in type I or II and is the collagen type first deposited in wound healing (i.e., fresh scars). This type of highly soluble collagen accounts in part for the plasticity of skin and blood vessels. Overexposure to the sun speeds up the breakdown of collagen and elastin, two proteins that give skin its strength and resilience, thus contributing to the development of skin wrinkling.

Type III collagen is more prevalent in newborns; with each passing decade, collagen-producing cells make less soluble collagen and progressively convert to synthesizing an insoluble, more stable type I collagen. The changing ratio of collagen types I and III throughout the body is so reliable that chronologic age can be determined by analyzing the collagen type III content of a skin sample.⁷

During the initial stages of tissue repair, fibroblasts secrete large amounts of type III collagen, which provides support for the developing capillaries. Within a few days after the tissue injury, type III collagen is degraded by enzymes secreted by fibroblasts and other cells and is replaced by newly synthesized type I collagen. Type I collagen enhances wound tensile strength and is the main component of the scar tissue that remains after repair is completed. Type IV collagen is not assembled into fibers. Together with other proteins, it forms the basement membrane to which epithelial, endothelial, and certain mesenchymal cells are anchored.

Mutations in the genes for collagen cause a wide spectrum of diseases of bone, cartilage, and blood vessels,

including osteogenesis imperfecta, a variety of chondrodysplasias, Alport syndrome, the Ehlers-Danlos syndrome, and more rarely, some forms of osteoporosis, osteoarthritis, and familial aneurysms. Scientists are finding that aberrant collagen cross-linking and increased collagen synthesis are present in some malignancies,¹² whereas the presence of free radical scavengers inhibits the rate of collagen formation.⁹³

When either collagen or elastin becomes resorbed, elements are released into blood and concentrate in urine. Determining the presence of these components in tissues and body fluids provides important markers in the clinical investigation of various diseases.¹³³ Methods to quantify the number of collagen cross-links in tissue are also being further developed at this time.^{112,131,147}

Differences in collagen fibril diameter have been demonstrated in people with unidirectional (anterior) shoulder instability versus multidirectional instability. Smaller collagen diameters in the multidirectional instability group suggest the possibility of an underlying connective tissue abnormality.¹²⁷

SPECIAL IMPLICATIONS FOR THE THERAPIST

6-2

Collagen

Much debate has been directed toward the role of the therapist in using myofascial techniques or soft tissue mobilization techniques (including friction massage) to change collagen structures and improve mobility, increase joint range of motion, or alter scar tissue. Whether these techniques can break the collagen cross-links and allow slippage to lengthen or realign the collagen fibers remains unproven at this time. Clinical

Continued.

research and determination of evidence-based intervention in this area are needed.

It has been found that regular mobility of affected tissues helps maintain lubrication and critical fiber distance.^{1,44,152} Immobilization is associated with excessive deposition of connective tissue in associated areas. This is accompanied by a loss of water and subsequent dehydration. The result is an increase in intermolecular cross-linking, which further restricts normal connective tissue flexibility and extensibility.

Ultrasound

The use of ultrasound to increase collagen tissue extensibility, increase enzymatic activity at the site of wound healing, absorb joint adhesions, and reduce fibrous tissue volume and density in scar tissue has been widely accepted, although some of these effects remain to be definitively proved. Ultrasound has been shown to facilitate the development of stronger and better-aligned scar tissue¹⁹; the first study to examine the ability of ultrasound to heat human tendon has been published.²⁰ Ultrasound as a therapeutic intervention in the treatment of human tendinopathy remains under investigation.^{34,49,151}

In the physiologic response of injury or wound healing, the key to growth or replacement tissue at sites of injury is stimulation of protein synthesis in fibroblasts. Exposure of injured tissue to ultrasound at clinically practical doses seems to provide this stimulation.⁸⁷ Continuous ultrasound during the first week of wound healing may hinder repair, but pulsed ultrasound at the lower ranges of intensity may be used during the acute phase to stimulate the release of vasodilator amine histamine from mast cells.⁴⁵ Other research has shown that 0.1 w/cm² continuous ultrasound provides the same total amount of ultrasound as 0.5 w/cm² pulsed, but the pulsed ultrasound was more effective in its nonthermal wound healing effects.³³

It is thought that the nonthermal effects of ultrasound increase cellular diffusion, membrane permeability, and fibroblastic activities such as protein synthesis, which speeds up tissue regeneration during the proliferative phase.^{20,122}

After 3 weeks, collagen synthesis continues to occur for remodeling during the subacute stage of healing, and ultrasound can be used as an adjunct to other interventions to promote this collagen synthesis and to minimize adhesions. Reducing adhesions occurs by raising the tissue temperature to increase viscoelastic properties during the proliferation to remodeling stage.^{38,39} Combining ultrasound with other interventions, such as electrical stimulation or laser photo stimulation, may not be as effective as ultrasound alone.⁵⁵

Ultrasound aids in reabsorption of joint adhesions by depolymerization of mucopolysaccharides, mucoproteins, or glycoproteins and may reduce the viscosity of hyaluronic acid in joints, thereby reducing joint adhesions. Slow, static stretching after ultrasound is important in increasing viscoelastic properties and maintaining length of the structure.^{54,125}

Tight capsular tissue, tendon, and mature scar tissue can also obtain increased extensibility when ultrasound is properly applied and followed immediately by slow, static stretching. This increased extensibility occurs as the mechanical effects of ultrasound disrupt the glucoside bonds forming scar tissue and the thermal effects increase the viscoelastic properties of the connective tissue.

Again, ultrasound must be accompanied or immediately followed by a slow, controlled stretching and then active motion through the full available range of motion to assist in restoring mobility in tissue and between the tissue interfaces.^{20,64} The stretch must be held until the collagen reaches a deformation phase. Without these follow-up techniques, the bond will re-form in its original position.^{54,76}

The therapist is advised to make careful assessment of the phase of injury and clinical results in the use of ultrasound and discontinue its use if there are increases in pain or edema or decreases in range of motion or function. Continuous ultrasound at low intensities may be used for nonthermal or thermal effects during the subacute and proliferative phase (fibroblastic infiltration and collagen formation) and early into the remodeling phase.

Factors That Affect Tissue Healing

Many variables regulate or affect the healing process and either facilitate, inhibit, or delay wound healing (Box 6-4). Since local blood supply is vital to the delivery of the materials necessary for wound healing, factors that impede local circulation or depletion of the necessary materials could delay rehabilitation. Certain tissues (e.g., tendons, ligaments, cartilage, disk) have a decreased blood supply, thus the healing process may require additional time.

Growth Factors

The cells involved in the tissue repair response produce proteins called *growth factors* that regulate a number of cellular reactions involved in healing. Growth factors regulate cell proliferation, differentiation, and migration; biosynthesis and degradation of proteins; and angiogenesis. Through all of these varying functions, growth factors integrate the inflammatory events with the reparative processes. When these complex mechanisms are disturbed, the result can be delayed healing and an inferior scar (hypotrophic) or elevated levels of growth factor, resulting in hypertrophic scarring such as occurs after a burn injury or in the formation of keloids.^{117,144}

Growth factors act by binding to receptors on the plasma membranes of specific cells and have a stimulatory or inhibitory effect on these cells. This binding initiates a process of transmembrane signaling that results in the phosphorylation of proteins (the process of attaching a phosphate group to the protein). These steps lead to the activation of gene expression and DNA synthesis in the cell.

Box 6-4**FACTORS INFLUENCING HEALING**

- Physiologic variables (e.g., age, growth factors, vascular sufficiency)
- General health of the individual; immunocompetency; psychologic/emotional/spiritual well-being
- Presence of comorbidities (examples):
 - Diabetes mellitus
 - Decreased oxygen perfusion (e.g., COPD, CHF, CAD, pneumonia)
 - Hematologic disorders (e.g., neutropenia)
 - Cancer (local and systemic effects)
 - Incontinence
 - Alzheimer's disease
 - Neurologic impairment
 - Immobility
- Tobacco, alcohol, caffeine, other substance use/abuse
- Nutrition (especially presence of protein, vitamins, and heavy metal depletion)
- Local or systemic infection; presence of foreign bodies
- Type of tissue
- Medical treatment (e.g., prednisone, chemotherapy, radiation therapy)

COPD, Chronic obstructive pulmonary disease; CHF, chronic heart failure; CAD, coronary artery disease.

The signals that turn on proliferation of normal cells and cause tissue healing are also responsible for turning on proliferation of cancer cells. With continued growth of neoplastic cells, a neoplasm or tumor may occur. The significant difference between the healing process and cancer is that the growth of the cancer cells goes on unchecked. These analogies have led to the designation of cancers as wounds that do not heal.

Platelets, endothelial cells, fibroblasts, macrophages, and cytokines are important sources of growth factors. Two important growth factors are platelet-derived growth factor (PDGF), which activates fibroblasts and macrophages, and fibroblast growth factor (FGF), which stimulates endothelial cells to form new blood vessels. An example of a growth factor that inhibits cell growth and inactivates macrophages is transforming growth factor- β (TGF- β).

Several growth factors (e.g., recombinant human PDGF-BB and granulocyte colony-stimulating factor) are being tested clinically to establish if these can boost the healing process in people who have deficiencies in wound healing (e.g., diabetic lower extremity ulcers).^{36,99}

PDGF-BB has been approved by the FDA for the treatment of neuropathic ulcers when there is adequate blood supply.¹¹⁰ Wound dressings of the future may include several growth factors, each with a specific function. The application of topically active growth factors to chronic ulcers remains in the experimental phase.^{31,149} Efforts to improve methods of delivering growth factors are also under investigation.¹¹⁰

Finally, it should be mentioned that cytokines, such as IL-1, IL-2, IL-15, and TNF, can also regulate some aspects of the healing response. Some ILs have been identified as T-cell growth factors with proinflammatory properties or the transforming growth factor associated

with hypertrophic scarring. Further studies are necessary to clarify the mechanism of cytokine release in normal postoperative wounds before therapeutic use can be developed.⁶⁷

Nutrition

Nutrition is an important factor influencing healing. Adequate nutritional intake is necessary to support the active metabolism of cells involved in repair. Trauma, including surgery, infections, or large draining wounds, often increases the systemic rate of protein catabolism (loss). This has adverse effects on the synthesis of proteins required for healing. Inadequate intake of specific nutritional factors can specifically affect collagen production and remodeling. Examples are vitamin C deficiency, which causes defective collagen molecules to form, and deficiency of zinc.

Zinc is essential for the activity of enzymes that degrade collagen and of enzymes that are responsible ultimately for the induction of protein synthesis. Zinc deficiency therefore impairs healing. People with cancer often manifest delayed healing because of poor nutritional status often associated with the cancer process or the medical treatment (e.g., chemotherapy); particularly notable is the poor healing in tissues that have been subjected to radiation therapy. For an excellent source of information related to nutrition and healing in the therapist's practice, see *Nutrition Applied to Injury Rehabilitation and Sports Medicine*.¹⁶

Other Factors

Other factors that influence healing include vascular supply, presence of infection, immune reaction, client's age, and the presence of other medical conditions referred to as *comorbidities*. Healing is often adversely affected in people who smoke, who are immunosuppressed, or who have other compromising medical conditions. For example, incontinence, peripheral vascular disease, confusion associated with dementia or Alzheimer's disease, or other neurologic impairment can contribute to delayed wound healing.

Diseases associated with decreased oxygen (tissue) perfusion (e.g., anemia, congestive heart failure, chronic obstructive pulmonary disease [COPD], or diabetes mellitus) can also delay healing. Diabetes mellitus is associated with poor healing; one of the causes appears to be impaired function of phagocytic cells and another is a defect in granulation tissue formation.²⁷

Medications can directly affect healing, especially the prolonged use of corticosteroids, or undergoing chemotherapy or radiation treatment. Anyone taking prednisone or other corticosteroids may be at risk, as steroids are well known to impair the healing process by inhibiting the inflammatory response necessary for tissue regeneration or repair.

An adequate vascular supply is critical to provide oxygen and nutrients to support healing. Vascular insufficiency, particularly in the lower limbs, is an important cause of slow-healing or nonhealing wounds. When blood return is not normal, a buildup of fluid can occur, reducing the body's ability to supply nutrients and oxygen to the wound site.

Infection interferes with healing by inciting a severe and prolonged inflammatory reaction that can increase tissue damage. Certain microorganisms can also release toxins that directly cause tissue necrosis and lysis. Foreign bodies may retard healing by inducing a chronic inflammatory reaction, by interfering with closure of a tissue defect, and by providing a site protected from leukocytes and antibiotics where bacteria can multiply.

It may be necessary to offload weight-bearing surfaces to relieve pressure on the wound and surrounding area. Immobility, lack of desire to exercise or follow a plan of care, and refusal to change dietary or other lifestyle behaviors contributing to poor wound healing must also be considered.

Healing may be delayed or inhibited for individuals who are in a constant state of survival or sympathetic nervous system (SNS) stimulation. When the SNS is locked in a hyperactive mode, exaggerated responses to relatively minor stimuli cause the body to work against itself for healing and recovery. Concepts discussed in Chapter 3 can be applied with these individuals to "reset" the system and facilitate forward movement in the healing process.

SPECIAL IMPLICATIONS FOR THE THERAPIST 6-3

Tissue Healing

Tissue Injury

The therapist is often involved with individuals who have chronic tissue injury, often caused by stresses of moderate magnitude that are repeated many times a day. Injuries from this mechanism range from cervical and back pain to patellofemoral dysfunction, tendinitis, impingement syndromes, stress fractures, and carpal tunnel syndrome.⁹⁸ The therapist must identify and modify all factors that may contribute to excessive stress on injured tissues. This includes movement and alignment (e.g., motor control, posture, and muscle length), extrinsic factors (e.g., footwear, gravity, and ergonomic environment), psychosocial factors, medications, age, obesity, or other comorbidities.⁹⁸

After sources of excessive stress have been addressed, injured tissues are still less tolerant of stress than before the injury. Once pain and inflammation have subsided, previously injured tissue must be exposed gradually to higher levels of physical stress. This progression will help restore the tissues' ability to tolerate greater levels of stress. Once healing occurs and tissue integrity is restored, activity tolerance can be increased.⁹⁸

Mueller and Maluf offer a good example of how to think about our clients in this way. An older adult has asked the therapist to help her stand independently from a sitting position. The examining therapist identifies the primary modifiable factors limiting this activity as being lower extremity muscle atrophy resulting in poor force production, decreased ankle dorsiflexion, poor motor control (movement and alignment factors), and a low seat surface (extrinsic factor).⁹⁸

A plan of care that considers her age as an important physiologic factor includes a progressive resistive

exercise program for lower extremity extensor muscles with at least 70% of maximum effort, 2 to 3 times a week to increase muscle force production. At the same time, the client is instructed in stretching exercises to increase ankle range of motion and appropriate movement strategies with good alignment to practice going from a seated to a standing position. Finally, the client was advised to use a higher chair to lower muscle force needed to meet her goal of independently standing from a seated position.⁹⁸

Delayed Wound Healing

Understanding the interaction of the wound, wound microorganisms, and the immune response is central to developing successful therapeutic interventions for wound care and management. This chapter has carefully explained how wounding of normal tissue initiates an inflammatory response that ordinarily contributes to the healing process orchestrated by specific and nonspecific immune responses. Inflammatory cells provide growth factors and stimulate the deposition of matrix proteins and phagocytose debris. However, the maturation and resolution of a wound may be complicated by the presence of microorganisms. The effects of microorganisms on oxygen consumption and pH or toxin production may interrupt the natural course of wound healing.

Besides ineffective medications, numerous other factors may delay or inhibit wound healing. Box 6-4 lists factors that could delay recovery from an injury. Since local blood supply is vital to the delivery of the materials necessary for wound healing, factors that impede local circulation or a depletion of the necessary materials could delay rehabilitation. Certain tissues (e.g., tendons, cartilage, and disks) have a decreased blood supply, thus the healing process may require additional time.

Therapists should screen a client's medical history for the presence of conditions, such as diabetes, chemical dependency (alcoholism), cigarette smoking, and so on, to identify factors that could delay recovery.

Finally, local infection delays healing. If an abscess is present, the expected fever, chills, and sweats associated with infection may not be present in someone who is taking steroid medications. A sudden worsening of symptoms; the presence of a hot, acutely inflamed joint; or the onset of fever should warn the therapist that something more serious may exist. In general, the more compromised the host, the greater the chance of a slow or incomplete recovery.

The wound may not progress from the acute phase but may become a nonhealing chronic or recalcitrant wound as long as the antigens from microorganisms or underlying pathology remain, leading to wound infection. Even so, most chronic wounds progress toward healing, depending on the wound care strategy employed.¹⁴³ For example, a venous leg ulcer will heal once the proper compression and support have been provided to counteract the underlying venous hypertension and appropriate wound care has been provided. Similarly, diabetic neuropathic foot ulcers do not heal until the disordered glucose metabolism is

controlled, adequacy of the vascular supply is ensured, and causative pressure on the foot is offloaded.

Successful healing of chronic wounds involves intervention to address the underlying causes and clinical wound management that provides an environment to tip the balance in favor of healing. The therapist is more likely to select appropriate intervention measures if the evaluation and assessment process takes into consideration the physiology of tissue repair along with the many factors that can affect wound healing. Investigating the status of these other factors (e.g., nutritional status; mobility status; turning schedule for the immobile; continence status; use of substances such as tobacco, alcohol, or caffeine; and medication schedule) requires collaboration with other health care specialists and with the family.¹³⁹

Laboratory values, such as prealbumin levels, indicating nutritional status 48 hours before may be helpful (see Table 40-5). Glucose levels, hemoglobin, and hematocrit (see Table 40-8) provide the therapist with necessary information to monitor wound healing when setting up and carrying out an appropriate intervention plan.

Specific techniques for wound management are beyond the scope of this text. The reader is referred to other texts for this information.

PHASES OF HEALING

Acute wounds caused by trauma or surgery usually heal according to a well-defined process that has the following four phases that overlap each other and can take months to years to complete⁶:

- Hemostasis and degeneration
- Inflammation
- Proliferation and migration
- Remodeling and maturation

Hemostasis and Degeneration

When tissue injury occurs, hemostasis is the first step. Hemostasis occurs immediately after an acute injury as the body tries to stop the bleeding by initiating coagulation. Blood fills the gap, and the coagulation cascade commences immediately, clumping platelets together to form a loose clot. Platelets release chemical messengers, including growth factors that summon inflammatory cells to the wounded tissue. Growth factors stimulate proliferation and migration of epithelial cells, fibroblasts, and vascular endothelial cells. Growth factors also regulate the differentiation of cells such as expression of extracellular matrix proteins.⁶

The inflammatory process described in detail in the next section begins right away, bringing fluid to the area to dilute harmful substances and support infection-fighting and scavenger cells (neutrophils and macrophages). Some sources describe this first phase as degeneration and inflammation.

The degeneration phase is characterized by the formation of a hematoma, necrosis of dead cells, and as mentioned, the start of the inflammatory cell response. After the removal of the dead tissue, the healing process undertakes the repair of the tissue defect that remains. Tissue repair begins within 24 hours of the injury with the migration of fibroblasts from the margins of the viable tissue into the defect caused by the injury. The fibroblasts proliferate and synthesize and secrete proteins such as fibronectin, various proteoglycans and elastin, and several types of collagen. The function of these proteins is to reconstitute the extracellular matrix and provide a scaffolding-like framework for the developing endothelial and parenchymal cells.

It is at this point that proliferation and migration occur as epidermal skin cells in the top layer move down the sides of the wound to help fill in the gap. Fibroblasts move in from the dermis, and new blood vessels form to create granulation tissue, which later becomes scar tissue. The next phase of remodeling eventually progresses into the final maturation phase as the regenerated tissue reorganizes into healthy scar tissue.

But we have just jumped ahead to tell you the "rest of the story" by discussing proliferation and migration before describing the inflammatory process. Since the phases of tissues healing overlap, it is difficult to describe the process from start to finish without interrupting the discussion.

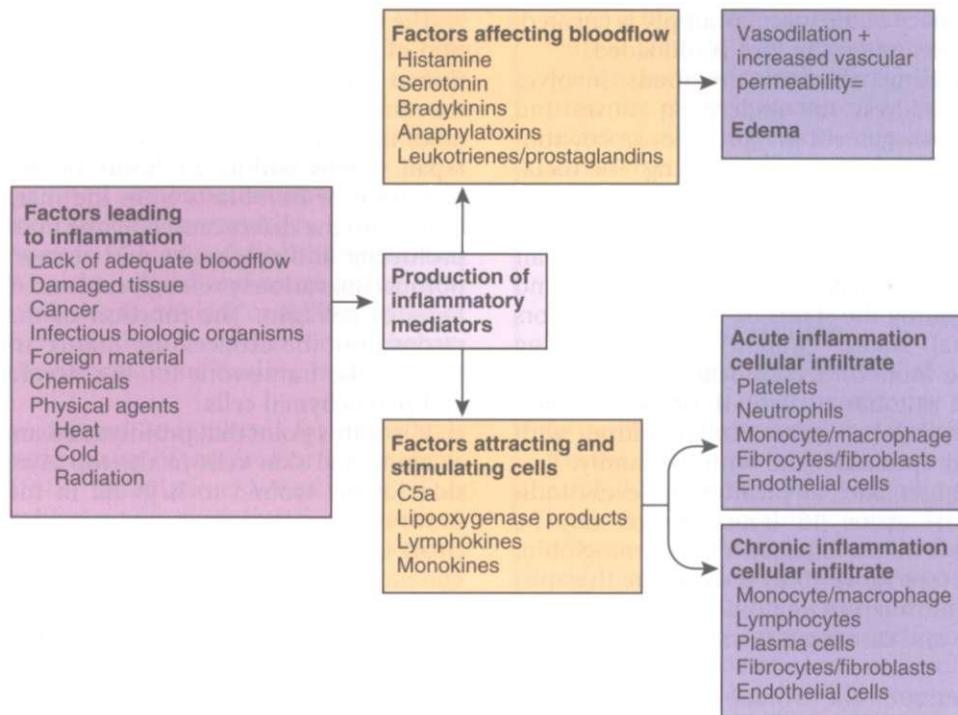
Inflammation Overview and Definition

Inflammation serves a vital role in the healing process. Inflammation has both protective and curative features. Every step serves a specific purpose and is necessary as the body responds to tissue injury or damage. The ultimate goal of the inflammatory process is to replace injured tissue with healthy regenerated tissue, a fibrous scar, or both.⁸

The inflammatory phase begins once the blood clot forms. Vasodilation and increased capillary permeability activate the movement of various cells, such as polymorphonuclear leukocytes and macrophages, to the wound site. These cells destroy bacteria; release proteases, such as elastase and collagenase; and secrete additional growth factors.

Growth factors, cytokines, and chemokines are the key molecular bioregulators of the inflammatory phase of tissue healing. The functions of these three bioregulators overlap considerably. About 5 days after injury, fibroblasts, epithelial cells, and vascular endothelial cells move into the wound to form granulation tissue. This newly developing tissue is not strong, so there is a higher risk of wound dehiscence during this time.⁶

In contrast to cell injury, which occurs at the level of single cells, inflammation is the coordinated reaction of body tissues to cell injury and cell death that involves vascular, humoral, neurologic, and cellular responses. Regardless of the type of cell injury or death, the inflammatory response follows a basically similar pattern. As a result of all of these factors, inflammation occurs only in living organisms.

**Figure 6-8**

Contributing factors and components of inflammation. Note the vascular alterations associated with factors affecting blood flow (vasoactive mediators) leading to edema and the factors attracting and stimulating cellular alterations (chemotactic factors) resulting in acute (and sometimes) chronic inflammation. (Courtesy SH Tepper, PhD, PT, Winchester, VA, Shenandoah University.)

The functions of the inflammatory reaction are to inactivate the injurious agent, to break down and remove the dead cells, and to initiate the healing of tissue. The key components of the inflammatory reaction are as follows:

- Blood vessels
- Circulating blood cells
- Connective or interstitial tissue cells (fibroblasts, mast cells, and resident macrophages)
- Chemical mediators derived from inflammatory cells or plasma cells
- Specific extracellular matrix constituents, primarily collagen and basement membranes

Basement membranes are thin, sheetlike structures deposited by endothelial (cells that line the heart, blood vessels, lymph vessels, and serous body cavities) and epithelial cells (cells that cover the body and viscera) but are also found surrounding nerve and muscle cells. They provide mechanical support for resident cells and function as a scaffold for accurate regeneration of preexisting structures of tissue. Basement membrane tissue also serves as a semipermeable filtration barrier for macromolecules in organs, such as the kidney and the placenta, and act as regulators of cell attachment, migration, and differentiation. The major constituents are collagen type IV and proteoglycans.

Inflammation of sudden onset and short duration is referred to as *acute inflammation*, whereas inflammation that does not resolve but persists over time is called *chronic inflammation*. Although inflammation has been linked with many other conditions (e.g., Alzheimer's,

cardiovascular disease, cancer, diabetes, insulin resistance syndrome, and obesity), the focus of this chapter is inflammation and the musculoskeletal system.

Acute Inflammation

Normally, inflammation has a protective role and is generally beneficial to the body. However, inflammation, whether in the acute or chronic stage (and with all of its components), can be detrimental, causing damage and even death to adjacent healthy tissue.

In the acute stage, the inflammatory stimulus acts on blood cells and plasma constituents. Chemical mediators are produced that alter vascular tone and permeability. These mediators also cause the accumulation of plasma proteins, fluid (edema), and blood cells in the injured site (Fig. 6-8).

The clinical manifestations of this inflammatory reaction are redness, swelling, increased temperature, pain, and decreased function of the affected site (Table 6-3). Arteriolar constriction followed by vasodilation gives rise to the redness and heat. The exudation and leukocyte infiltration give rise to the swelling. Pain and loss of function occur as a result of the increased pressure from the edema on the peripheral nerves.⁸

Accompanying clinical findings include increased muscle tone or spasm and loss of motion or function. Cyriax describes two components of passive movement testing that also suggest acute inflammation: a spasm end feel and pain reported before resistance is noted by the practitioner as the limb is moved passively.²⁵ If movement testing suggestive of acute inflammation persists,

inflammation can become chronic with proliferation of blood vessels and connective tissue components.

In the normal, healthy individual, symptoms may be more intense because the body is vital and capable of healing quickly. Conversely, immunocompromised individuals and especially older adults with multiple comorbidities often require much longer time to heal. The symptoms may be less in intensity, but healing and repair are often delayed and chronic inflammation may occur.

There are three primary outcomes of acute inflammation: (1) complete resolution with restoration of normal tissue structure, (2) healing with scar formation, and (3) chronic fibrosis. Complete resolution usually occurs after mild trauma and minimal tissue damage. Healing with scar formation occurs after substantial tissue destruction in tissues with little capacity for regeneration or after prolonged edema. The soft tissue structures of the musculoskeletal system are often characterized by this result.

Chronic Inflammation

As described, acute inflammation follows injury. Once the injurious agent is removed, acute inflammation subsides. If little necrosis is present and replacement of lost

parenchymal cells is possible, restitution of normal structure and function of the tissue occurs. In the presence of extensive necrosis or if regeneration of parenchymal cells is not possible (e.g., heart, CNS, or peripheral nervous system cells), the inflammatory reaction can become chronic. Chronic inflammation also develops if the underlying cause is not addressed and the injurious agent persists for a prolonged period. Repeated episodes of acute inflammation in the same tissue over time or low-grade, persistent immune reactions can also result in a chronic inflammatory response (Fig. 6-9).

The hallmark of chronic inflammation in a tissue is the accumulation of macrophages, lymphocytes, and plasma cells (see Fig. 6-8). The macrophage accumulation is the result of chemotaxis of monocytes (precursors to macrophages) to the area of injury. Macrophages modulate lymphocyte functions and promote growth of endothelial cells and fibroblasts by the release of growth factors. Eosinophils may also be present, particularly if allergic reactions or parasite invasions are involved.

Granulation tissue made up of proliferating endothelial cells and fibroblasts is also seen in areas of chronic inflammation. Granulation tissue can be seen in well-healing, open wounds. Inspection of the wound site reveals red "beefy" tissue with pinpoint red dots (new capillaries) and a granular surface composed of newly formed collagen.

Certain diseases cause the formation of a specific type of chronic inflammation called a *granuloma*. The granuloma is a microscopic (less than 2 mm in diameter) aggregate of macrophages often surrounded by lymphocytes. Most of the macrophages are flattened "epithelioid" in appearance and some may fuse together, giving rise to large cells with multiple nuclei (Langerhans and foreign body giant cells).

The presence of granulomatous inflammation is clinically important because it aids in the diagnosis of the injurious stimulus. Tuberculosis, a disease caused by *Mycobacterium tuberculosis*, classically causes granulomas

Table 6-3 Four Cardinal Signs/Symptoms of Inflammation

Sign	Precipitating Events
Erythema	Vasodilation and increased blood flow
Heat	Vasodilation and increased blood flow
Edema	Fluid and cells leaking from local blood vessels into the extravascular spaces
Pain	Direct trauma; chemical mediation by bradykinins, histamines, serotonin; internal pressure secondary to edema; swelling of the nerve endings

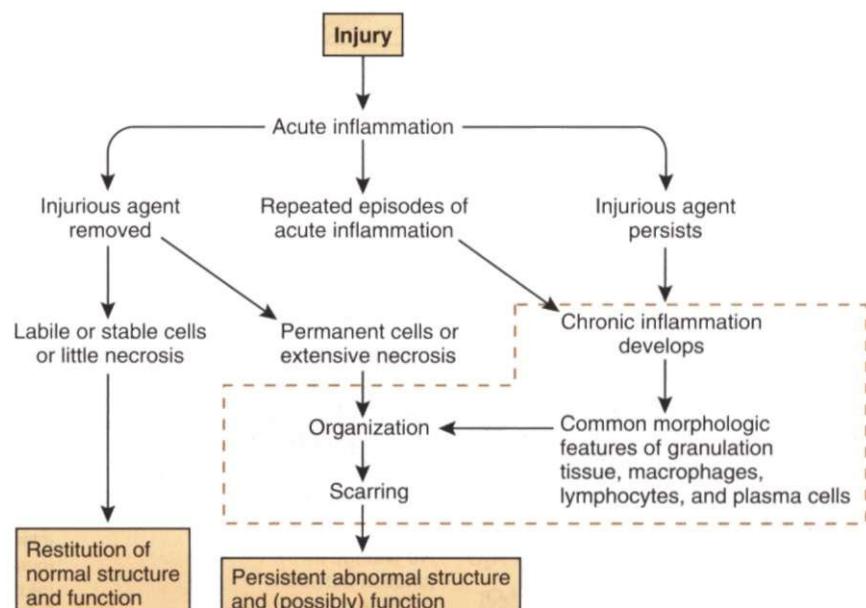


Figure 6-9

Overview after tissue injury: acute inflammation, chronic inflammation, and the likely healing process.
(Courtesy SH Tepper, PhD, PT, Winchester, VA, Shenandoah University.)

or tubercles in this condition with a central focus of caseous necrosis. The presence of a foreign body (e.g., a suture) is another common cause of granulomatous inflammation.

Chronic inflammation can contribute to the healing of injured tissue but usually without a full return of function. The proliferation of endothelial cells reconstitutes the vasculature in the injured tissue, whereas proliferation of fibroblasts and the production of collagens and proteoglycans (polymers that form the gel between collagen fibrils) reconstitute the extracellular matrix. Together, these constituents make up the granulation tissue and lead to the formation of a connective tissue scar. This process is regulated by growth factors derived from macrophages, platelets, and plasma.

Components of the Inflammatory Reaction

Vascular Alterations. Acute inflammation can last from a few minutes (e.g., redness and swelling from scratching your skin) to a few days (e.g., after an open cut on the finger), during which time a series of vascular events occurs. After an injury that disrupts the integrity of a vessel wall, the small arteries supplying blood to the area undergo vasoconstriction. This is mediated by a neural reflex and results in a slowing down of blood flow to the affected area.

At the same time, the blood flowing into the surrounding tissue exerts pressure on the damaged vessels, compressing them from outside. The slowdown of the blood flow promotes aggregation of platelets, which leads to the formation of a blood clot, resulting in a reduction in the amount of blood loss.

In the case of an injury that does not disrupt the integrity of the blood vessel wall but does cause tissue injury, the temporary neurally mediated constriction of arterioles is followed by a more sustained and overriding vasodilation, resulting in an increased blood flow to the affected area. The increased blood volume raises hydrostatic pressure, and an increased loss of protein-poor fluid occurs from the vasculature into the injured tissue.

At this stage, clinical manifestations include redness (erythema) and warmth of the injured area due to the increased blood flow. The leakage of protein-poor fluid (transudate) from the vasculature into the interstitial spaces is called *transudation* and causes the affected area to appear swollen (Fig. 6-10).

Transudation, the passage of fluid through a membrane or tissue surface, occurs as a result of a difference in hydrostatic pressure, primarily in conditions in which there is protein loss and low protein content (e.g., left ventricular failure, cirrhosis, nephrosis). Typically, transudate is thin and watery, containing few blood vessels or other large proteins. The terms *transudate*, *exudate*, *effusion*, and *edema* are often used interchangeably, although each of these has its own clinical significance. When fluid transudates or leaks from blood vessels and accumulates inside an anatomic space, such as the pleural, pericardial, or peritoneal cavities or the joint space, these accumulations are called effusions.

Effusion is a more general term referring to the escape of a fluid and can either be a transudate or an exudate. Exudates occur when an increase in capillary permeability allows proteinaceous fluid and/or cells to leak out

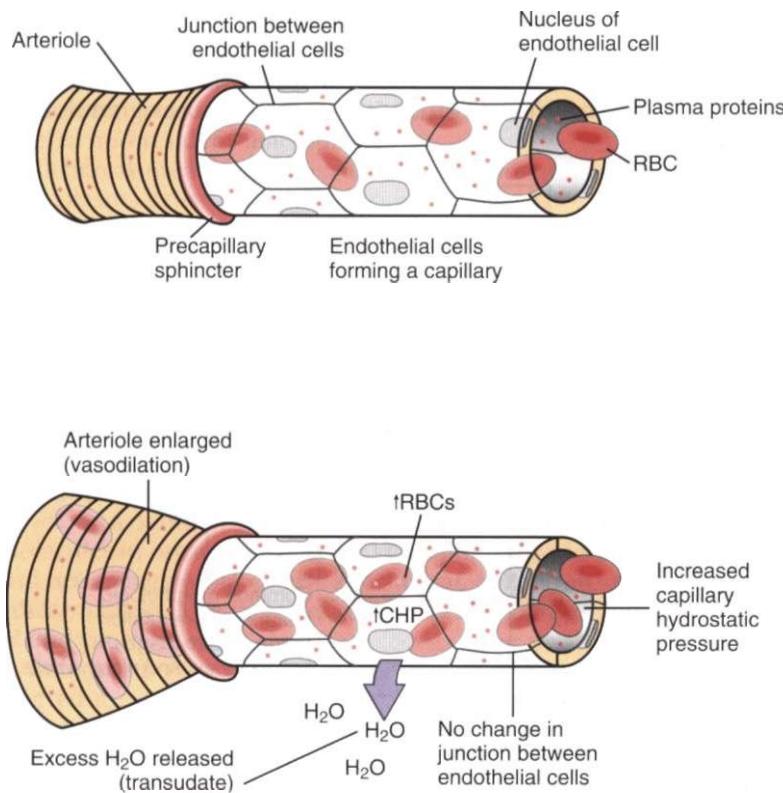


Figure 6-10

Normal capillary (A) reveals endothelial cells connected by tight junctions limiting flow of plasma proteins into the interstitium. With mild injury (B) vasodilation results in increased capillary hydrostatic pressure pushing more water into the interstitial area (transudate). (Courtesy SH Tepper, PhD, PT, Winchester, VA, Shenandoah University.)

primarily through openings created between adjacent endothelial cells in the capillaries or venules (Fig. 6-11).

Exudate contains much more protein than transudate. Exudate may also contain inflammatory phagocytic cells that occur in response to necrotic tissue and/or an infection. Protein-rich fibrinous (stringy) material found within some blisters or pus are sometimes identified as exudates. Various types of exudate are evident, depending on the stage of inflammation and its cause (Table 6-4).

Removal of the fluid for analysis is required when differentiating between transudates and exudates and helps establish a specific diagnosis. Sometimes exudates are described by visual appearance (e.g., serosanguineous exudate, a fluid containing erythrocytes or red blood cells [RBCs]).

The time of onset of the vascular reaction to injury varies. Mild injuries may induce an increase in vascular permeability that occurs very soon after injury and resolves in a few minutes. In this case, the anatomic site responsible for the leak is the capillary/venule.²³ The leak occurs because endothelial cells lining the lumen of the capillary/venules actively contract and open up their intercellular junctions. This increase in vascular permeability allows proteins to shift from the plasma into the interstitium, causing a greater attraction and retention of fluid in this area.

The increase in vascular permeability caused by the injury may be delayed for some time and may persist for days such as the delayed reaction seen in tissue injury

caused by ultraviolet light (sunburn) or irradiation (radiation therapy); typically, the vascular leak begins a few hours after exposure to the sun. In severely injured tissues (e.g., trauma or extensive burns), all vascular structures may be directly injured and become leaky instantly.

Leukocyte Accumulations. An important consequence of the exudation of protein and fluid from the vasculature is the engorgement of vessels with blood cells. This causes a slowing or cessation of blood flow in the affected vessels, a phenomenon called *stasis*. During stasis, the leukocytes (white blood cells [WBCs]) accumulate and adhere to the endothelial cells of blood vessel walls at the site of injury in a process called *margination*. Inflammatory mediators cause an increased expression of specific glycoproteins called *adhesion molecules* on the surface membrane of leukocytes and endothelial cells. These adhesion glycoproteins, by adhering to each other, function as receptors and counterreceptors. The adhesion glycoproteins are the glue that binds the leukocytes to each other and to the endothelium of venules and capillaries.

The binding of leukocytes to receptors on endothelial cells of venules is the first step in the migration of leukocytes from the vasculature to the interstitial tissues. This process initiates the circulation of leukocytes through the extravascular space in normal conditions and the infiltration of leukocytes into the site of inflammation.

In the next stage, the leukocytes actively migrate out of the vessels, passing through the vascular walls without

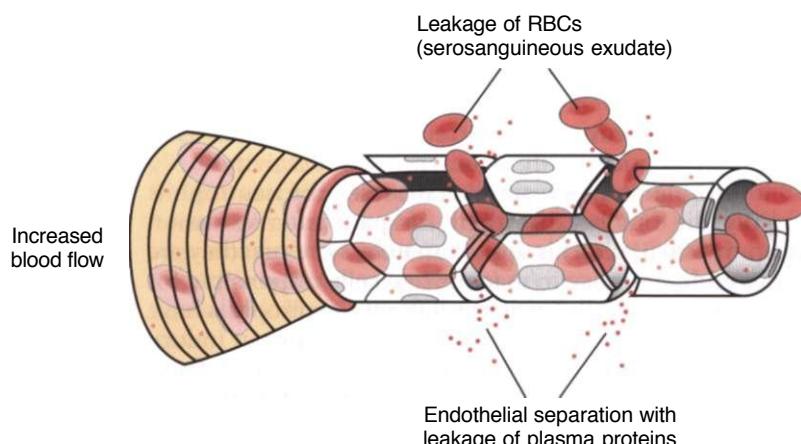
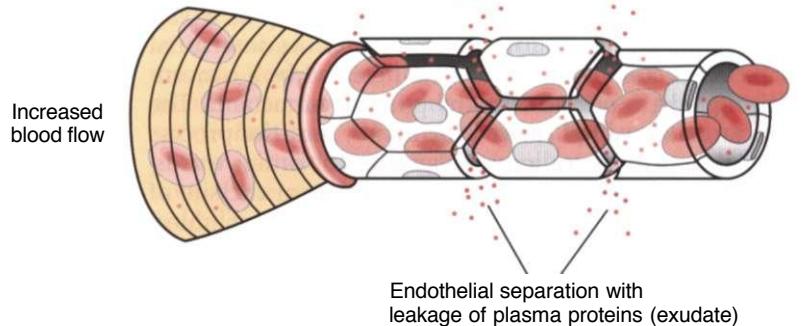


Figure 6-11

A, With a more severe inflammatory response, endothelial cells separate, causing leakage of plasma proteins into the interstitium (exudate). This accentuates the edema. B, With damage to the endothelial cells, the separation between the damaged cells may allow even erythrocytes to extravasate (serosanguineous exudate). (Courtesy SH Tepper, PhD, PT, Winchester, VA, Shenandoah University.)

Table 6-4 Inflammatory Exudates

Type	Appearance	Significance
Hemorrhagic; sanguineous	Bright red or bloody; presence of RBCs	Small amounts expected after surgery or trauma. Large amounts may indicate hemorrhage. Sudden large amounts of dark red blood may indicate a draining hematoma.
Serosanguineous	Blood-tinged yellow or pink; presence of RBCs	Expected for 48 to 72 hours after injury or trauma to the microvasculature. A sudden increase may precede wound dehiscence (rupture or separation).
Serous	Thin, clear yellow, or straw-colored; contains albumin and immunoglobulins	Occurs in the early stages of most inflammations; common with blisters, joint effusion with rheumatoid arthritis, viral infections (e.g., skin vesicles caused by herpesvirus); expected for up to 1 week after trauma or surgery. A sudden increase may indicate a draining seroma (pocket of serum within tissue or organ).
Purulent	Viscous, cloudy, pus; cellular debris from necrotic cells and dying neutrophils (PMNs)	Usually caused by pus-forming bacteria (streptococci, staphylococci) and indicates infection. May drain suddenly from an abscess (boil).
Catarrhal	Thin, clear mucus	Seen with inflammatory process within mucous membranes (e.g., upper respiratory infection).
Fibrinous	Thin, usually clear; may be yellow or pink, tinged, or cloudy	Occurs with severe inflammation or bacterial infections (e.g., strep throat, pneumonia); does not resolve easily; can cause fibrous scarring and restriction (e.g., constrictive pericarditis).

Modified from Black J: Wound healing. In Black JM, Matassarin-Jacobs E, eds: *Luckmann and Sorensen's medical-surgical nursing*, ed 5, Philadelphia, 2000, WB Saunders.

RBCs, Red blood cells; PMNs, polymorphonuclear neutrophils.

damaging the blood vessels and entering the interstitial space in a process called *diapedesis*, or oozing (Fig. 6-12). The continued migration of leukocytes in interstitial space is directed by a chemical trail created by a concentration gradient of one of many possible attractants. The attractants are called *chemotactic agents*, and the process of locomotion is called *chemotaxis*. In other words, leukocytes are attracted to and accumulate at the site of an inflammatory reaction in response to a chemical stimulus.

The presence of leukocyte accumulations in tissue or fluid specimens is diagnostic of an inflammatory process. The predominant cell type found in a specimen identifies the type of inflammation and/or its duration and original stimulus (see Table 40-11). Typically, during acute inflammation, neutrophils predominate (neutrophilia). Neutrophils inhibit bacterial growth by releasing lactoferrin, a protein that binds with iron, thus preventing microorganisms from using iron for growth and development. Neutrophils also demonstrate direct cytotoxic activity toward viruses, fungi, and bacteria by releasing defensin, which are peptides with natural antibiotic activity.

If the inflammatory stimulus subsides, the neutrophils rapidly die out because their lifespan (after extrusion from the circulation) is approximately 24 hours; they are replaced by monocytic/macrophage cells responsible for cleaning up the cellular debris left after neutrophils have done their job. Certain inflammatory stimuli can induce a sustained neutrophil response (e.g., first defense against pyogenic bacteria), a predominantly lymphocytic response (e.g., fight tumor cells or respond to viruses), or

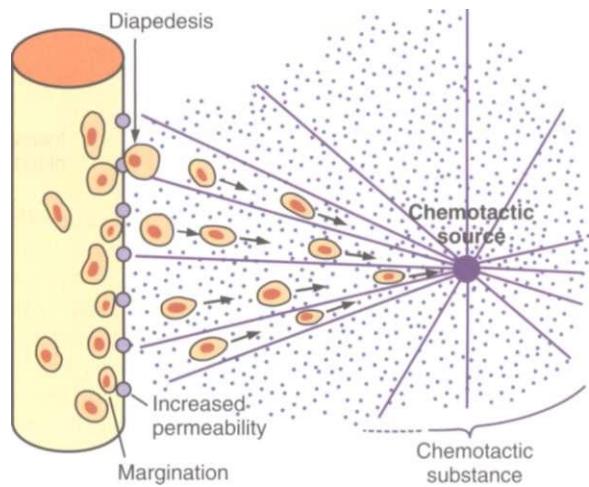


Figure 6-12

Many different chemical substances in the tissues cause both neutrophils and macrophages to move through the capillary pores in a process called *diapedesis* and toward the area of tissue damage by *chemotaxis*. *Chemotaxis* depends on the concentration gradient of the chemotactic substance. The concentration is greatest near the source, which directs the unidirectional movement of the white blood cells. *Chemotaxis* is effective up to 100 μm away from an inflamed tissue. Since almost no tissue area is more than 50 μm away from a capillary, the chemotactic signal can easily move vast numbers of WBCs from the capillaries into the inflamed area. (From Guyton AC, Hall JE: *Textbook of medical physiology*, ed 11, Philadelphia, 2006, WB Saunders.)

an eosinophilic response (e.g., plays a role in asthma and allergies or attacks parasites).

In addition to the types of WBCs present, the total and differential counts of the leukocytes in the circulating blood are also very important diagnostic tools (see Table 40-11). An increased number of circulating leukocytes (leukocytosis) is often an indication of an active inflammatory reaction (typically to an infection or tissue injury). A decreased WBC count (leukopenia) can, for example, be seen in certain types of infections and is an indicator of grave prognosis in severe systemic infections (sepsis).

The main function of the leukocytes recruited to the affected tissue is to remove or eliminate the injurious stimulus. Leukocytes achieve this function by releasing enzymes and toxic substances that kill, inactivate, and degrade microbial agents, foreign antigens, or necrotic tissue. Leukocytes also take up these materials by phagocytosis and release growth factors necessary for healing or regeneration (see Fig. 6-17).

In addition to the role played by blood vessels in inflammation, a contribution is made from a system of thin-walled channels formed by endothelial cells with loose junctions. These channels are called the *lymphatics* and ultimately drain into the subclavian vein via the thoracic duct (see Fig. 13-8). These channels in physiologic conditions help drain fluid and protein from the interstitium, thereby reducing edema. They also serve as a conduit for the removal of certain leukocytes and inflammatory stimuli.¹⁴¹

The movement of the phagocytic cells into the lymphatic vessels allows presentation of the engulfed material to immunocompetent cells located in the lymph nodes. Hyperplasia of immunocompetent cells (T and B lymphocytes) in the lymph nodes leads to an enlargement of the nodes called lymphadenopathy. During the process of removing infectious agents, lymphatics and their lymph nodes may become actively inflamed. Clinically, the inflamed lymphatics may appear as red streaks under the epidermis and may be painful to palpation; this condition is called *lymphangitis* (see Chapter 13).

Chemical Mediators of Inflammation. A large number of chemical mediators are responsible for the vascular and leukocyte responses generated by the cells involved in an acute inflammatory response. These mediators are either released from inflammatory cells (cell-derived) or are generated by the action of plasma protease (plasma-derived). Mediators of inflammation are multifunctional and have numerous effects on blood vessels, inflammatory cells, and other cells in the body. Some of their primary effects in the inflammatory response include vasodilation or vasoconstriction, modulation of vascular permeability, activation of inflammatory cells, chemotaxis, cytotoxicity, degradation of tissue, pain, and fever. These mediators include histamine, serotonin, bradykinin, the complement system, platelet-activating factors, arachidonic acid derivatives (e.g., prostaglandins, leukotrienes), and cytokines (Table 6-5).

Histamine. Histamine is synthesized and stored in granules (for quick availability and release) of mast cells, basophils, and platelets. Histamine causes endothelial contraction leading to the formation of gaps, which increase blood vessel permeability and allow fluids and

Table 6-5 Mediators of Inflammation

Cell-Derived Sources	Plasma Cell-Derived Sources
Circulating platelets (PAF, histamine, serotonin)	Blood coagulation cascade
Tissue mast cells (histamine)	Fibrinolytic system
Basophils (histamine)	Kinin enzymatic system:
Polymorphonuclear leukocytes (neutrophils)	• Bradykinin
Endothelial cells	• Hageman factor
Monocytes/macrophages	Complement system: C3a, C3b, C5a, C5b
Injured tissue itself	MAC
Arachidonic acid derivatives (prostaglandins, leukotrienes)	
Cytokines (TNF, IL-1)	

PAF, Platelet-activating factor; MAC, membrane attack complex; TNF, tumor necrosis factor; IL-1, interleukin-1.

blood cells to exit into the interstitial spaces (vascular leak). Histamine's effect occurs quickly but is short lived because it is inactivated in less than 30 minutes. Histamine is also a potent vasodilator and bronchoconstrictor. Serotonin is another mediator released from platelets; it induces vasoconstriction, but its effect is usually overridden by the vasodilator action of histamine.

Platelet-Activating Factor. Leukocytes and other cells on stimulation also synthesize three classes of inflammatory mediators that are derived from phospholipids (the major lipids present in cell membranes). The first of these mediators is an acetylated lysophospholipid named *platelet-activating factor* (PAF). The other two classes of mediators are derived from a fatty acid (arachidonic acid) of membrane phospholipids and are called *prostaglandins* and *leukotrienes*. All three of these lipid mediators have potent and wide-ranging inflammatory activities. In addition, these mediators have hormonelike functions that modulate physiologic responses and induce pathology in a variety of organ systems.

PAF was so-named because it was first found to induce platelet activation and secretion. PAF is now known to be a potent activator of cells, such as smooth muscle cells, endothelial cells, and leukocytes, by receptor binding and intracellular signaling mechanisms. As a consequence, PAF can induce the aggregation of leukocytes and leukocyte infiltration in tissues and can profoundly affect vasomotor tone and permeability.¹³⁵ PAF can potentiate (increase or strengthen) the activity of other inflammatory mediators.

Arachidonic Acid Derivatives. The synthesis of prostaglandins and leukotrienes begins with the cleavage (splitting) of arachidonic acid from membrane phospholipids by the action of the phospholipase (Fig. 6-13). Once this step is completed, either a cyclooxygenase (COX) enzyme or a lipoxygenase enzyme further metabolizes the arachidonic acid. The COX pathway leads to the production of several types of prostaglandins that modulate vasomotor tone and platelet aggregation (e.g., thromboxane is a strong platelet aggregator and vasoconstrictor, whereas prostacyclin [PGI₂] is a strong platelet inhibitor and vaso-

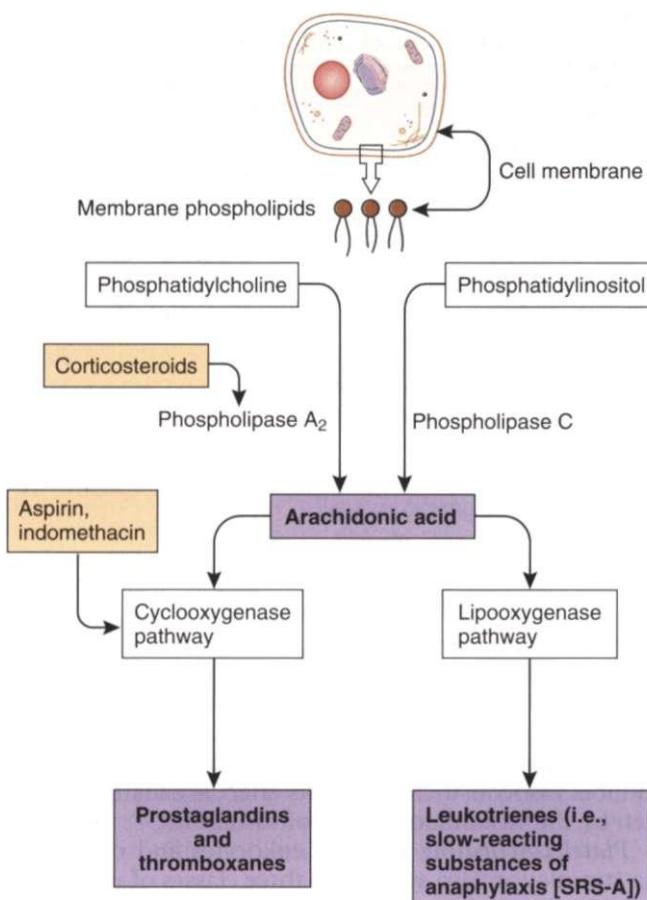


Figure 6-13

Production of prostaglandins and leukotrienes from damaged cell membranes. Note sites for pharmacologic (aspirin and prednisone) interventions. (Courtesy SH Tepper, PhD, PT, Winchester, VA, Shenandoah University.)

dilator). Clinically, prostaglandins are also important because they are mediators of the fever and pain responses associated with inflammation.²⁴

The lipoxygenase pathway leads to the production of leukotrienes. Leukotrienes occur naturally in leukocytes and produce allergic and inflammatory reactions similar to those of histamine. They are extremely potent mediators of immediate hypersensitivity reactions and inflammation, producing smooth muscle contraction, especially bronchoconstriction; increased vascular permeability; and migration of leukocytes to areas of inflammation. They are thought to play a role in the development of allergic and autoimmune disease such as asthma and rheumatoid arthritis. Certain leukotrienes (C₄, D₄, and E₄) are collectively known as a slow-reacting substance of anaphylaxis (SRS-A), which is the name given when their potent bronchoconstrictor activity was discovered; they also cause leakage of fluid and proteins from the microvasculature.

The importance of the arachidonic acid metabolites in the inflammatory process is made evident by the excellent clinical response to treatment of acute and chronic inflammatory conditions with drugs that block the production of arachidonic acid (corticosteroids) or inhibit

Box 6-5

ACTIONS OF CYTOKINES: INTERLEUKIN-1 AND TUMOR NECROSIS FACTOR

Local

- Stimulates leukocyte adhesion to endothelium
- Modulates the coagulation cascade
- Stimulates production and/or secretion of inflammatory mediators, including interleukin-1 (IL-1)
- Activates fibroblasts, chondrocytes, osteoclasts

Systemic

Metabolic

- Induces fever
- Increases body metabolism
- Decreases appetite
- Induces sleep
- Induces adrenocorticotrophic hormone (ACTH) release to secrete corticosteroids
- Nonspecific resistance to infection

Hemodynamic

- Causes hypotension
- Hypovolemia (sepsis)

Hematologic

- Changes blood chemistry (see text)
- Activates endothelial, macrophage, and resting T cells
- Increases neutrophils in circulation
- Decreases lymphocytes in circulation
- Stimulates synthesis of collagen and collagenases

the enzyme and block the production of prostaglandins and cyclooxygenase (nonsteroidal antiinflammatory drugs [NSAIDs] such as aspirin or the newer COX-2 inhibitors). These antiinflammatory medications are commonly used for people with somatic pain or inflammatory conditions, especially rheumatoid arthritis.

Cytokines. Leukocytes also produce polypeptide substances called *cytokines* (see Chapter 7) that have a wide range of inflammatory actions affecting either the cytokine-producing cells themselves (autocrine effects) or adjacent cells (paracrine effects). Cytokines also have a number of systemic "hormonal" inflammatory effects.

Two important cytokines with overlapping functions are IL-1 and TNF. As many as fifteen ILs are now identified. Most ILs direct other cells to divide and differentiate, each interleukin acting on a particular group of cells that have receptors specific for that interleukin. TNF is thought to be capable of inducing most of the actions of IL-1 with the exception of activation of lymphocytes.

IL-1 has a number of local actions that promote the inflammatory reaction and a number of systemic actions that induce metabolic, hemodynamic, and hematologic alterations (Box 6-5). These alterations are discussed in some detail because of their importance in the clinical and laboratory diagnosis of inflammation. IL-1 causes fever by raising the production of prostaglandins in the hypothalamus and thereby resetting the threshold of temperature-sensitive neurons.

Fever in turn raises the systemic metabolism and increases the systemic consumption of oxygen by approximately 10% for each degree Celsius of body temperature elevation. As a result, a decrease in systemic vascular resistance occurs, thereby producing hypotension and an increase in cardiac output to increase the flow of blood and the delivery of oxygen to various organs. These hemodynamic changes are characteristic of severe systemic infections and a febrile condition.

IL-1 also causes characteristic changes in blood chemistry. Albumin and transferrin levels are decreased, while levels of coagulation factors, complement components, C-reactive protein, and serum amyloid A increase. These changes occur because IL-1 alters the rate of synthesis of these proteins by the liver. IL-1 also increases the number of neutrophils and decreases the number of lymphocytes in the circulation.

The Blood Coagulation, Fibrinolytic, and Complement Systems. Plasma proteins produce chemical inflammatory mediators by the enzymatic activity of proteases on plasma proteins. Plasma proteases are enzymes that act as a catalyst in the breakdown of proteins. These plasma protein systems are the blood coagulation and fibrinolytic, kinin enzymatic, and complement systems.

All of these systems can become activated by contact with by-products of cell injury or foreign materials. Examples include contact with components of denuded vascular endothelial cells revealing their underlying basement membrane, which occurs with trauma to the vessel wall and contact with bacterial endotoxins. The key plasma protein in the activation sequence of these systems is clotting factor XII, also known as *Hageman factor*.

The blood coagulation system (Fig. 6-14) is formed in part by plasma proteins. The design is to bandage injuries with clots (coagulation), then disassemble (lyse) the clots when the job is done. The system protects against both hemorrhage and catastrophic clotting. To maintain homeostasis, these two processes must remain in balance.

Platelets circulating throughout the bloodstream are always ready to seal any damage to blood vessels with a hemostatic plug. When there is no need for the platelets, the smooth vascular walls prevent platelets from adhering and aggregating. At the same time, endothelial cells in the walls of the blood vessels make tissue plasminogen activator to prevent fibrin deposits from forming and for breaking down existing clots.

More specifically, when injury or bleeding occurs, a series of enzymes are activated sequentially to generate the enzyme thrombin, which converts the plasma protein fibrinogen to fibrin, the essential component of a blood clot. Fibrin forms a meshwork at bleeding sites to stop the bleeding and trap exudate, microorganisms, and foreign materials and keep this content contained in an area where eventually the greatest number of phagocytes will be found. This localizing effect prevents the spread of infection to other sites and begins the process of healing and tissue repair.

The fibrinolytic system (designed to dissolve these clots) is activated by the conversion of plasminogen to the enzyme plasmin (also known as *fibrinolysin*, which means "to loosen"). Plasmin splits or divides fibrin and

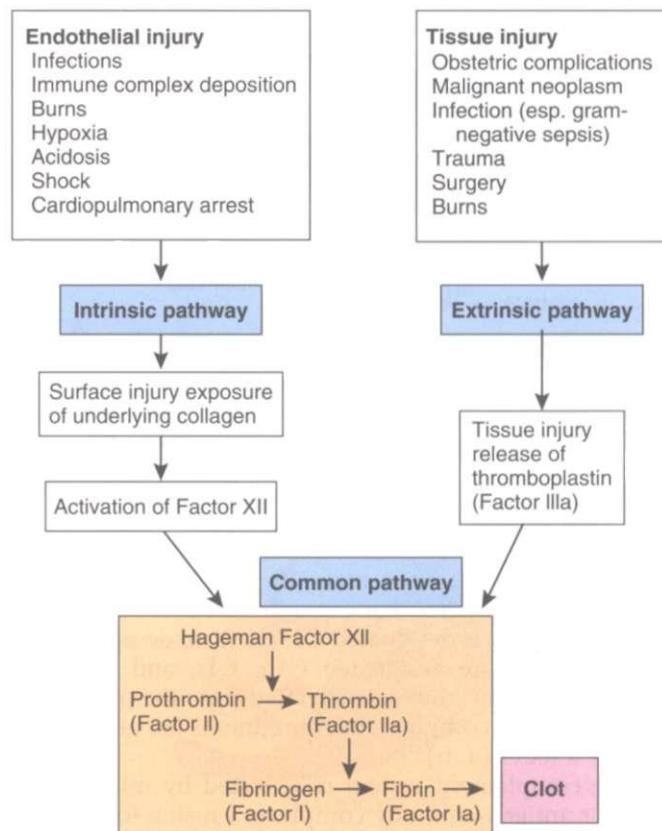


Figure 6-14

Clinical causes of the activation of a clotting cascade, intrinsic and extrinsic pathways of activation, and the mechanism by which both pathways lead to the formation of fibrin threads, or clot. In the chain reaction, inactive proenzymes (represented by Roman numerals followed by the letter "a") are converted into active enzymes (represented by Roman numerals followed by the letter "a"). The clotting cascade can follow two pathways: intrinsic and extrinsic. The intrinsic pathway is activated within the vascular compartment. The extrinsic pathway is activated outside the vascular compartment, when blood comes in contact with any tissue other than blood vessels. In the case of internal bleeding, both pathways are activated. (Courtesy SH Tepper, PhD, PT, Winchester, VA, Shenandoah University.)

lyses the blood clots. Both the coagulation and the fibrinolytic systems are activated in inflammation and function together in a system of checks and balances to preserve vascular function.

The products of fibrin degradation are chemotactic for leukocytes and increase vascular permeability. The kinin enzymatic system is also activated by Hageman factor and functions to produce bradykinin. Bradykinin is a mediator that causes dilatation and leakage of blood vessels and induces pain.

The complement system is composed of a group of plasma proteins that normally lie dormant in the blood, interstitial fluid, and mucosal surfaces. Then, through a series of enzymatic reactions, several plasma protein fragments (C3a, C3b, C5a, and C5b) are formed that are potent inflammatory mediators. These components are also active in immunologic processes. In the nomenclature used for the complement system, each complement component (C) is designated by a number (1 to 9). The

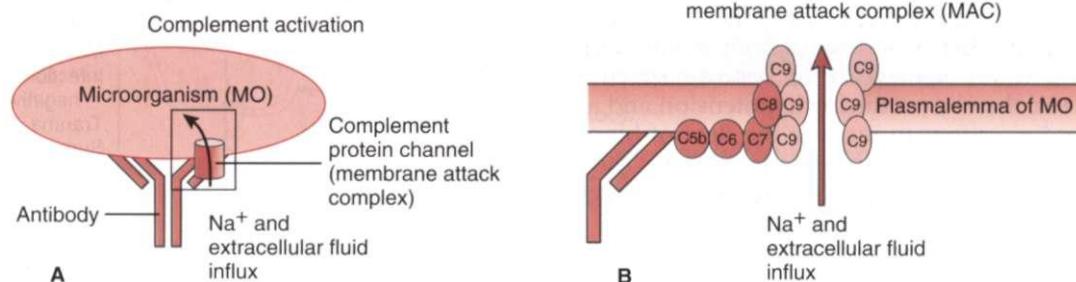


Figure 6-15

A. When an antibody attaches to an antigen (foreign protein) on a microorganism (MO), the antibody-antigen stimulates plasma-derived complement proteins to attach and form the membrane attack complex (MAC). **B.** This MAC forms a channel through the membrane of the invading cell and allows ions and extracellular fluid to enter, causing cytolysis (death of the microorganism). (Courtesy SH Tepper, PhD, PT, Winchester, VA, Shenandoah University.)

individual subunits that make up each component are designated by a letter. For example, the first component of complement is designated C1. C1 is made up of three subunits that are designated C1q, C1r, and C1s. The protein fragments that are generated from the proteolytic degradation of complement components are also identified by a letter (a, b).

The complement system is activated by microorganisms or antigen-antibody complexes causing four events to occur that promote inflammation: (1) vasodilates the capillaries, which increases blood flow to the area, (2) facilitates the movement of leukocytes into the area by chemotaxis, (3) coats the surfaces of microbes to make them vulnerable to phagocytosis, and (4) formation of a membrane attack complex (MAC).

Complement activation can follow one of two pathways, the classic or the alternate pathway; each pathway produces the same active complement components. The products of the complement system bind to particles of foreign material, microorganisms, or other antigens, coating them to make them vulnerable to phagocytosis by leukocytes, a process called *opsonization*. Activation of the complement cascade by either pathway also results in the formation of the MAC. The MAC is inserted in cell membranes of the microorganism where it creates an opening (pore or channel) in the cell membrane, leading to influx of sodium and extracellular fluid, eventually leading to its lysis (Fig. 6-15). For example, in hemolytic anemia, MAC bores holes in the cell membrane of RBCs, causing their destruction.

The plasma protease systems (blood coagulation, fibrinolytic, kinin enzymatic, and complement systems) are interconnected at several steps. This arrangement serves to amplify the stimulus for the inflammatory reaction as a balance mechanism. For example, the activation of the plasma protein Hageman factor can initiate both the coagulation (blood clotting) and the kinin systems (produces bradykinin causing dilation and vascular leakage).

The kinin system can in turn activate the fibrinolytic system by producing plasmin (splits or divides fibrin and lyses blood clots). Plasmin then can activate the complement system and further amplify these protease loops by

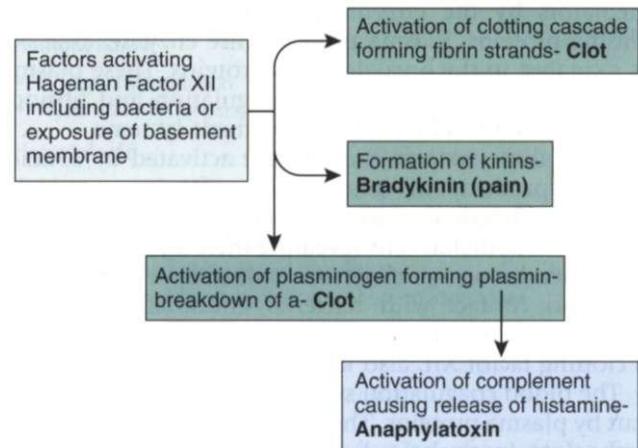


Figure 6-16

Clot formation. Revealed in this figure are the mechanisms for activating both the intrinsic and the extrinsic pathways for clot formation. Either of the above pathways leads to activation of the Hageman factor XII that results in the formation of a fibrin clot. (Courtesy SH Tepper, PhD, PT, Winchester, VA, Shenandoah University.)

activating Hageman factor, once again starting the cycle (Fig. 6-16).

PHAGOCYTOSIS. One of the most important functions of the inflammatory reaction is to inactivate and remove the inflammatory stimulus and to begin the process of healing. The process of ingestion (phagocytosis) of microorganisms, other foreign substances, necrotic cells, and connective tissue constituents by specialized cells (phagocytes) is important in achieving this goal.

Although phagocytosis could be considered the next step in the process of acute inflammation (as a separate section after the section on Chemical Mediators of Inflammation), it is included here as part of the section on Chemical Mediators because the chemical mediators are what attract phagocytic cells to the area for removal of the dead tissue or microorganisms. After ingestion by phagocytic cells, microorganisms are killed or inactivated, and necrotic debris is removed to allow tissue healing to proceed.

The most important phagocytes involved in the inflammatory and healing reactions are neutrophils, monocytes, or when found in tissues of the body, macrophages. Macrophages have different names depending on their location (e.g., histiocytes in the skin, osteoclasts in bone, and microglial cells in the CNS).

The mechanism of phagocytosis is well understood. Phagocytosis is facilitated by the coating (opsonization) of particles to be ingested by immunoglobulin G (IgG) antibody or by the C3b component of complement. These opsonins bind to specific receptor sites located on the cell surface of neutrophils and macrophages. This receptor binding initiates a process of transmembrane signaling allowing calcium influx that activates cytoskeletal proteins within the cell. These cytoskeletal structures allow the movement of cell membranes that is necessary for phagocytosis.

The internalization of the opsonized particle begins by the enfolding of the cell surface membrane (Figs. 6-17 and 6-18). The membrane folds surround the particle to be ingested and seal it within a pouch that separates it from the cell surface and becomes an intracellular vacuole called the *phagosome*. The phagosomes fuse with lysosomes (containing digestive materials and bactericidal components) and acquire enzymes and other substances that allow the killing and degradation of microorganisms and other ingested materials. Many neutrophils (e.g., polymorphonuclear neutrophils [PMNs]) die in their battle with bacteria. Dead and dying leukocytes, mixed with tissue debris and lytic enzymes, form a viscous yellow fluid known as *pus*. Inflammations identified by their pus formations are called *purulent* or *suppurative* (see Table 6-4).

SPECIAL IMPLICATIONS FOR THE THERAPIST 6-4

Inflammation

Inflammation, which involves all of the processes described in this section, is a normal, healthy response to tissue injury, but it can also damage adjacent healthy tissue. Chronic activation of inflammatory cells can cause tissue injury such as occurs with rheumatoid arthritis. The role of the therapist is important in supporting the healing process and when appropriate, to limit inflammation and its consequences. The therapist must remember that finding and correcting the cause of inflammation is the key, not just addressing the inflammatory process. Poor lifestyle choices including poor nutrition, improper posture and body mechanics, and poor breathing habits can contribute to the chronicity of this condition.

Rheumatoid arthritis illustrates how the inflammatory mediators discussed are activated and how this process leads to clinical manifestations observed in a therapy practice. Inflammatory activity can be detected by the erythrocyte sedimentation rate (ESR). The therapist can review laboratory values (see Table 40-7) to assess systemic factors; in general, as the inflammation improves, the ESR decreases. Systemic

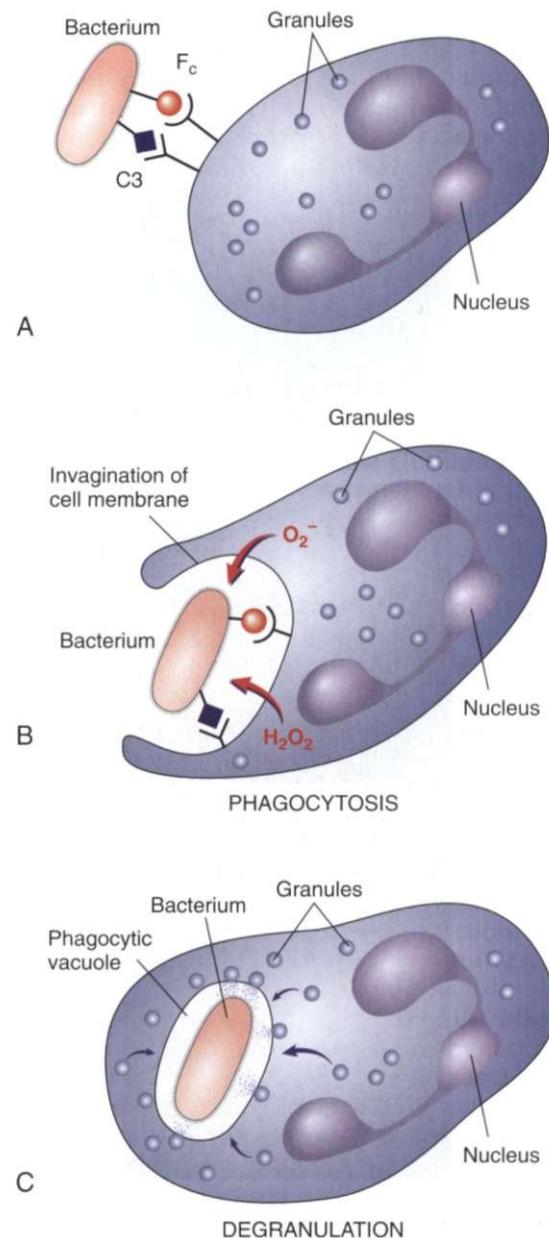


Figure 6-17

Phagocytosis of bacteria. A, The bacterium that was opsonized (coated with IgG and complement [C3b]) binds to the Fc and complement receptors on the surface of the leukocytes. B, Engulfment of the bacterium into an invagination of surface membrane is associated with an oxygen burst and formation of oxygen radicals that are bactericidal and thus kill the bacterium. C, Inclusion of the bacterium into a phagocytic vacuole is associated with the fusion of the vacuole with lysosomes and specific granules of the leukocyte. The contents of the lysosomes and specific granules are bactericidal and contribute to final inactivation and degradation of the bacterium. The cytoplasm of the leukocyte becomes devoid of granules in a process referred to as degranulation of leukocytes. (From Damjanov I: Pathology for the health-related professions, ed 3, Philadelphia, 2006, WB Saunders.)

Continued.

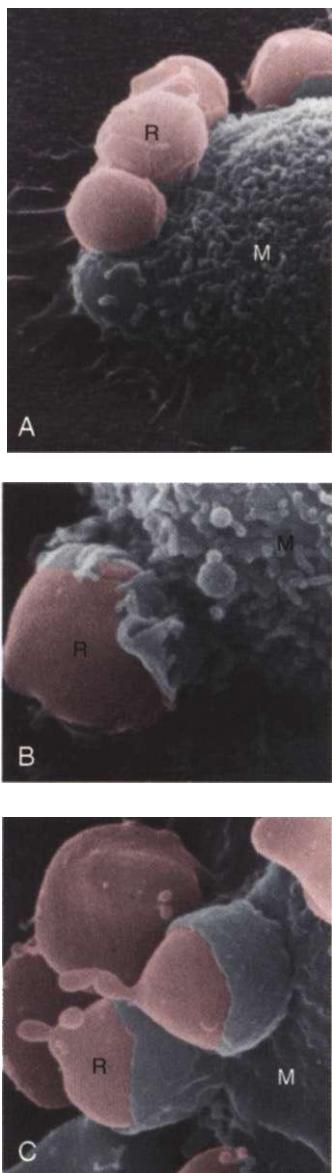


Figure 6-18

Phagocytosis. This series of scanning electron micrographs shows the progressive steps in phagocytosis of damaged red blood cells (RBCs) by a macrophage. A, RBCs (*R*) attach to the macrophage (*M*). B, Plasma membrane of the macrophage begins to enclose the RBC. C, The RBCs are almost totally ingested by the macrophage. (From Thibodeau GA, Patton KT: *The human body in health and disease*, ed 4, St. Louis, 2005, Mosby. Courtesy Emma Shelton.)

effects of acute and chronic inflammation are discussed in Chapter 5.

Clinical Example

The majority of people with rheumatoid arthritis produce rheumatoid factor, an antibody that is made against the person's own antibodies of the IgG class. In this case the IgG antibody actually functions as an antigen (Ag) capable of inducing an immune response.

This antibody-to-antibody attachment can occur in the joint space where it leads to the formation of large

antibody-antigen (Ig-Ag) aggregates. Ig-Ag complexes stimulate complement activation by the classic pathway and to the formation of the strongly chemotactic cleavage products C3a and C5a. These products attract neutrophils, which then release free radicals (see Fig. 6-2) and enzymes that degrade the joint cartilage, prostaglandins, and leukotrienes that amplify the inflammatory reaction. The Ig-Ag complex is phagocytosed by synovial-lining cells that are stimulated to release collagen-degrading enzymes, prostaglandins, and IL-1.

Lymphocytes contribute to the acute reaction by the production of rheumatoid factor and are responsible for the evolution of a chronic inflammatory reaction by producing cytokines that attract and activate macrophages. The macrophages produce cytokines, such as IL-1, that further amplify the inflammatory reaction by attracting more neutrophils and lymphocytes and by stimulating the synthesis and release from fibroblasts, chondrocytes, and osteoclasts of enzymes that degrade cartilage and bone.

Clinically, the joints affected by the inflammatory process appear red and swollen and are painful; a low-grade fever may also be present. A prominent symptom is joint stiffness that is relieved by activity. With disease progression, damage to the joints occurs; with loss of cartilage, narrowing of the joint space occurs, and resorption of bone is evident on radiograph. These changes are associated with a decrease in the range of motion of the affected joints. In later stages, obvious joint deformities develop that are accompanied by muscle wasting. Antiinflammatory agents, such as aspirin and corticosteroids, are effective in providing symptomatic relief and in slowing the progression of the disease.

The inflammatory process associated with rheumatoid arthritis may also affect other organ systems (see Box 27-9). Foci of chronic inflammation can develop in muscles, tendons, blood vessels, nerves, and various organs of the body (e.g., heart and lungs). In the skin, these foci cause the deposition of connective tissue called *subcutaneous nodules*.

Exercise and Inflammation

Exercise and physical training definitely influence the concentration of immunocompetent cells in the circulating pool, the proportional distribution of lymphocyte subpopulations, and the function of these cells in relation to tissue injury and infection. However, the extent of these changes and their clinical significance remains a topic for intense study at this time.¹¹³ The mechanisms of exercise-associated muscle damage and the initiation of the inflammatory cytokine cascade are further discussed in Chapter 7 (see the section on Exercise and the Immune System).

Proliferation and Migration Phase

Within 2 days after a skin wound or injury, endothelial cells from viable blood vessels near the edge of the necrotic tissue begin to proliferate. The purpose of the endothelial cell proliferation is to establish a vascular

network that can transport oxygen and nutrients and support the metabolism of the healing tissue. The endothelial cells bud out from the vessels and form new capillary channels that merge with each other as they develop and grow toward the tissue defect caused by the injury. This process of formation of new blood vessels is called *neovascularization* or *angiogenesis*.

The rich network of developing blood vessels with its connective tissue matrix can be seen with the naked eye in healing wounds. As described previously, the appearance of a reddish granular layer of tissue was therefore given the name "granulation tissue." Histologically, the main cellular components of granulation tissue are the endothelial cells and the fibroblasts, although some inflammatory cells are also commonly present.

Initially, the newly formed vessels are leaky, and this leak contributes to the edematous appearance of tissue undergoing repair. As tissue healing is completed, blood flow to the newly formed vasculature shuts down, and the nonfunctional vessels are degraded, leaving few blood vessels in mature scar tissue.

Tissue gaps are replaced during the proliferation phase when the number of inflammatory cells decreases and fibroblasts, endothelial cells, and keratinocytes take over synthesis of growth factors. The result is the continued promotion of cell migration, proliferation, and formation of new capillaries and synthesis of extracellular matrix components.⁶ The next step is the removal of damaged matrix as new matrix builds up to fill the wound. The wound initially fills with provisional wound matrix, which consists primarily of fibrin and fibronectin. As fibroblasts are drawn into the matrix, they synthesize new collagen, elastin, and proteoglycan molecules, which cross-link the collagen of the matrix and produce the initial scar.⁶

Damaged proteins in the matrix have to be removed before the newly synthesized matrix components can be properly integrated. This process is facilitated by proteases secreted by neutrophils, macrophages, fibroblasts, epithelial cells, and endothelial cells. Epithelial cells are at the front of the wound edge, traveling across the highly vascularized extracellular matrix, forming granulation tissue to re-form the epidermal layer. This process can take several weeks.⁶

Remodeling and Maturation Phase

In the maturation phase of healing, the scar tissue is reduced and remodeled, leaving tissue smoother, stronger, less dense, and less red in color (in Caucasians) as the concentration of blood vessels in the area decreases. In all skin colors, the scar tissue becomes more like the natural skin tones of the person. The density of fibroblasts and capillaries needed in the early phase of healing but no longer needed now declines, primarily through apoptosis or programmed cell death.⁶ The remodeling phase can take years as the skin first produces collagen fibers, which are broken down and rearranged to withstand stress. Over time, scar tissue grows stronger, relaxes, and then lightens.

Tissue Contraction and Contracture

As the healing process proceeds, the newly formed extracellular matrix draws together, causing a shrinkage (contraction) of the healing tissue. In this manner the size of the tissue defect caused by the injury is diminished. Some fibroblasts within the healing tissue differentiate and acquire some of the morphologic and functional characteristics of smooth muscle cells (myocytes). These specialized fibroblasts are called *myofibroblasts*. Myofibroblasts contain abundant contractile proteins and apparently contract and contribute to the shrinkage of the healing tissue.

Tissue contraction is a normal process that contributes to tissue repair by approximating the margins of the healing tissue and speeding up the closure of wounds. In some cases, excessive shrinkage of the healing tissue occurs. This condition is called *contracture*. Contracture is an undesirable outcome of healing because it can be disfiguring and can impair movement or organ function. For example, people with severe burns often develop skin contractures because of the process of "hypertrophic scarring" that can result in significant movement impairments and subsequent disability.

Contracted tissue with excessive arthrofibrosis can occur in the joints (most often the shoulder and knee) after either injury or surgery. Postoperative or posttraumatic arthrofibrosis is characterized by local or global periartricular scarring that can restrict, and in some cases a thickened, fibrotic capsule inhibits motion. Arthrofibrosis can be caused by a variety of factors including prolonged immobilization, infection, or graft malposition after ligament reconstruction (e.g., ACL reconstruction).⁹⁴

Studies have not been done to identify when scar tissue can be broken up by manual therapy techniques, but anecdotal evidence indicates that immature scar tissue can be successfully treated conservatively (e.g., analgesia and antiinflammatory medications, early motion, bracing, strengthening, electrical stimulation, or manual therapy techniques).

Exactly when scar tissue becomes mature is variable and remains a topic of debate. Some estimate an open window of 3 to 4 months after which time surgical (arthroscopic) manipulation is required. Forceful manipulation of the stiff joint is never advised as this can create excessive joint compression leading to articular cartilage damage and even fracture.⁹⁵

Tissue Regeneration

Within a few hours after lethal injury to skin, epithelial cells, the viable cells that surround the necrotic tissue, detach from their extracellular matrix anchorage sites and separate from the other epithelial cells. The remaining epithelial cells flatten out to cover the area left bare by the necrotic cells. These epithelial cells also divide and migrate into the tissue using the extracellular matrix support provided by the proteins secreted by the fibroblasts. This process of replacement of dead parenchymal cells by new cells is called *regeneration*. Regeneration is a very desirable healing process because it restores normal tissue structure and function. In most cases, healing of

tissue is achieved by both cell regeneration and replacement by connective tissue (scarring) called *repair*. In the case of skin, for example, this type of healing occurs after wounds that involve both the epidermis and dermis. In some instances, tissue healing occurs almost exclusively by the progress of regeneration (regrowth of original tissue).

Regeneration can only occur if the parenchymal cells can undergo mitosis. Cells are classified as *permanent*, *stable*, and *labile* based on their ability to divide. Regeneration does not occur in permanent tissues that cannot divide (e.g., cardiac myocytes or central or peripheral neurons); they are long-lived and irreplaceable. Regeneration can also only occur in labile or stable tissues and only if the inflammatory reaction that follows injury is short-lived and does not disrupt the basement membranes, other extracellular components, and vascular structures of labile or stable parenchymal cells. Labile cells, such as epithelial cells of the skin and gastrointestinal (GI) system, and bone marrow divide continuously. Hematopoietic (blood cell-forming) stem cells continuously divide, giving rise to specialized cells, such as erythrocytes and neutrophils, with finite life spans (see Fig. 21-6).

Under these conditions the regenerating parenchymal cells can use the existing connective tissue scaffolding to reconstitute the normal structure and function of the organ. This type of tissue healing can be seen after superficial mechanical injury to epithelia. An example is a superficial abrasion of the skin that causes only necrosis of the epidermis. In this case, regeneration occurs with little or no scarring.

Stable cells, such as hepatocytes, skeletal muscle fibers, and kidney cells, normally do not divide but can be induced to undergo mitosis by an appropriate stimulus. For example, if a portion of the liver is removed by surgery or if liver cells are killed by a viral infection (hepatitis), the remaining hepatocytes divide and sometimes can fully replace the missing liver tissue.

Studies have revealed some capability of neurons to regenerate (neurogenesis) but only in certain areas of the brain (e.g., hippocampus or olfactory bulb).¹⁰ The reasons for the restriction of neurogenesis to a few regions of the brain in mammals compared to a more widespread neurogenesis in other vertebrates remain unknown.¹⁰⁴ It may be that neuronal stem cells persist in these areas throughout the lifespan but why they do not persist in all areas is still a mystery.³ What we do know is that neural stem cells residing in specific niches are able to proliferate and differentiate, giving rise to migrating neuroblasts, which in turn mature into functional neurons. These new neurons integrate into the existing circuits and contribute to the structural plasticity of certain brain areas.¹¹¹ Scientific evidence suggests that the process could become more general under pathologic conditions. For example, adult neurogenesis increases under acute and chronic brain diseases. Neuronal precursors are directed to the lesions where they contribute to tissue repair. Investigations are underway to find ways to manipulate and direct the neurogenic process toward the amelioration of neurodegenerative diseases.^{111,137}

Tissue Repair (Formation of Scar Tissue)

Skin has the remarkable ability to heal, often without scarring. Growth factors, blood components, and epithelial (skin) cells mobilize to seal off wounds and protect the body. Scarring does not occur unless the cut, incision, damage, or trauma extends beneath the surface layer (epidermis).

Tissue repair, including the formation of a connective tissue scar, requires removal of the connective tissue matrix. Without this matrix, labile cells do not regenerate or else they regenerate in an incomplete fashion. Therefore the structural integrity of the parenchymal tissue depends on the formation of this connective tissue scar (dense, irregular laying down of collagen). In many cases, however, healing of tissue is achieved by both cell regeneration and replacement by connective tissue (which is what constitutes scarring). In the case of skin, for example, both types of healing occur in wounds that involve both the epidermis and dermis.

Minimizing tissue scarring is important not only for cosmetic reasons, as is the case in skin, but also because excessive scarring can interfere with organ function. Very large tissue defects may require the use of grafts or flaps of tissue to achieve optimal healing. It is possible to minimize scarring by surgical obliteration of the tissue defect caused by injury and cell necrosis. For example, treatment of skin wounds begins with careful cleansing of the wound to remove foreign materials and bacterial contamination, which interfere with healing. This is followed by debridement to remove nonviable tissue that normally would be broken down by the inflammatory reaction.

Careful attention to hemostasis minimizes the deposition of blood into the wound. During closure, the wound margins are closely apposed under the right amount of tension by surgical sutures. A clean, closed wound is free of infectious and other foreign material, fibrin, and necrotic debris. As a result, the duration and intensity of the inflammatory reaction are minimized. Little granulation tissue forms, and the epithelial cell surface is readily reconstituted.

The healing that occurs in the type of wound described is called *primary union* or *healing by first intention* and results in a small scar (Fig. 6-19). In the presence of large tissue defects or infections, and in other conditions where surgical closure is not possible or desirable, healing occurs by *secondary union*. In this situation the time required for healing is longer and the amount of scarring is greater. There is a distinction between closure and healing; the wound or skin may close but healing takes much longer, as much as two years in some situations.

Even after wound closure is complete, degradation and resynthesis of collagen continue. This is a response at least in part to shifts in the stress forces to which the tissue is subjected. Cross-linking of collagen fibers continues for a period of several weeks, providing progressive strengthening of scar tissue. However, even under optimal conditions, the repaired tissue never fully regains its original stability. In the case of skin, a fully mature fibrous scar requires 12 to 18 months and is about 20% to 30% weaker than normal skin.

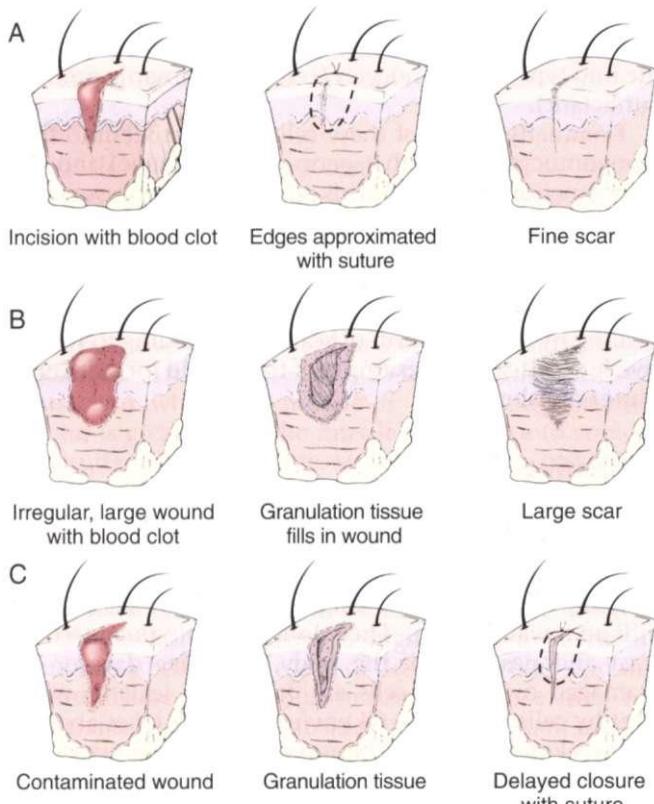


Figure 6-19

A, Healing by primary intention is the initial union of the edges of a wound, progressing to complete healing without granulation. **B**, Healing by secondary intention is wound closure in which the edges are separated, granulation tissue develops to fill the gap, and epithelium grows in over the granulations, producing a scar. **C**, Healing by tertiary intention is wound closure in which granulation tissue fills the gap between the edges of the wound, with epithelium growing over the granulation at a slower rate and producing a larger scar than results from healing from second intention. Suppuration is also usually found in tertiary wound closure. (From Lewis SL, Heitkemper MM, Dirksen SR: *Medical surgical nursing: assessment and management of surgical problems*, ed 7, St. Louis, 2007, Mosby.)

In some people, especially people of African or Asian descent, there is an inherited tendency to produce excessive amounts of collagen during the healing process, causing large amounts of collagen arranged in thick bundles to accumulate in the tissue. These collagenous masses are called *keloids* and can be seen protruding from the skin surface (Fig. 6-20). Keloids are more than just raised, hypertrophic scar tissue. Both keloid and hypertrophic scar tissue result from excess collagen formation, but hypertrophic scars generally calm down in 12 to 24 months, whereas keloids tend to grow larger and appear worse, often invading surrounding tissue.

Several methods are used to treat keloids, although none of them are 100% successful. Surgical keloid excision followed by high-dose rate brachytherapy, form-pressure garments, and pulsed dye lasers have some reported success.^{14,30}

Necrosis of heart tissue (myocardial infarct) results in a fibrous scar because cardiac myocytes do not replicate to any great extent. Outcomes that can result from tissue

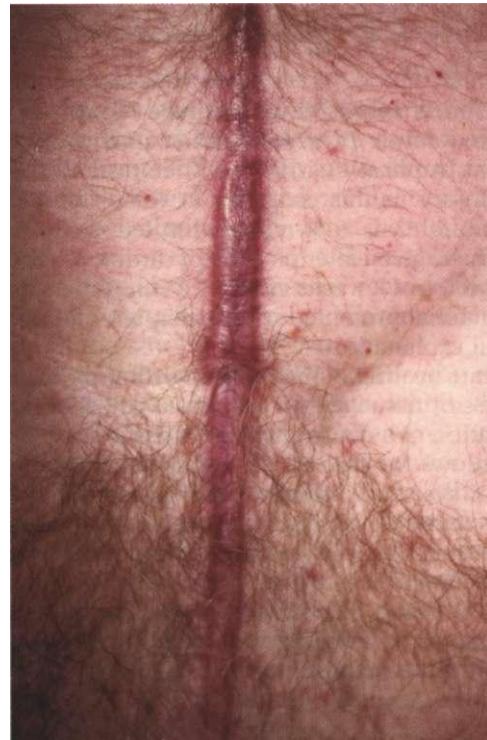


Figure 6-20

Keloid (hypertrophic) scar composed predominantly of type III collagen, rather than type I collagen. Keloids result from defective remodeling of scar tissue and the persistence of type III collagen, which is typical of immature scar. Epidermis is elevated by excess scar tissue, which may continue to increase long after healing occurs. Looks smooth, rubbery, "clawlike." Young women, black people, and people of Mediterranean descent are particularly susceptible to keloid formation. (From Rakel RE: *Textbook of family medicine*, ed 7, Philadelphia, 2007, Saunders.)

repair in various tissue and conditions are summarized in Fig. 6-9. The CNS differs in its healing process because neurons are permanent cells and do not replicate.

After tissue necrosis neither regeneration nor tissue scarring occurs. No fibroblasts are present in the brain parenchyma, and no collagen is produced. After a brain infarct (stroke), the inflammatory cells arrive from the blood circulation and clear away the necrotic tissue, leaving behind an empty cavity (cyst). Specialized CNS cells called *astrocytes (glial cells)* proliferate, forming dense aggregates around the necrotic area called *glial scars* or *gliosis*.

Chronic Wounds. When a wound fails to heal normally, reepithelialization and closure do not occur. Chronic wounds can occur when the wrong biochemicals are present in the wrong amounts at the wrong times and fail to function effectively. There may be a deficiency in endogenous growth factors, which have the primary role of stimulating cell migration, proliferation, and extracellular matrix deposition. Chronic wounds remain in the inflammatory and proliferative phases.³¹ Understanding the normal repair process and factors that affect tissue healing can help guide the therapist in removing barriers to healing. Preparing the wound bed appropriately changes the wound's biochemical environment back to an acute wound, thus re-initiating the healing cascade.

Scar Tissue

The clinical implications of tissue repair can be seen in the example presented earlier in this chapter (see Special Implications for the Therapist: Collagen and Cell Injury in this chapter). In this example, after a transmural MI, a symptom-limited stress test will usually be given after phase II of cardiac rehabilitation, around 8 to 12 weeks after MI. With understanding of the material presented in this chapter, one can see the logical explanation.

Heart healing, which occurs primarily through the process of tissue repair, requires 8 to 12 weeks for the formation of a dense connective tissue scar. This dense scar allows for structural integrity and force transduction of the viable myocardium, leading to a complete heart contraction. Since the connective tissue scar is not contractile, this area of the heart will never return to full function. Of great importance is the fact that after MI (heart attack), a person's aerobic fitness can improve (or exceed) to the level before his or her pre-morbid state with proper exercise.

SPECIFIC TISSUE OR ORGAN REPAIR

Throughout this chapter, examples of cell types and healing processes within various organs and systems of the body have been discussed. Some organs are composed of cells that cannot regenerate (e.g., heart, CNS, or peripheral nervous system cells), whereas other organs such as the liver and epithelial cells of the integumentary and CI systems can replace missing tissue through cell division (mitosis). Some cells, such as skeletal muscle cells and renal cells, do not divide but can be induced to undergo mitosis. The extent to which cells can regenerate depends on the type of cell (e.g., permanent, stable, labile), the cell's ability to divide, the type of damage incurred (e.g., lethal, sublethal), and other factors discussed (e.g., nutrition, age, immunocompetency, vascular supply, or presence of microorganisms leading to infection). The proliferation and migration of cells, including parenchymal cells, have been discussed; regeneration can only occur if the parenchymal cells can undergo mitosis. When regeneration of parenchymal cells is not possible, the inflammatory reaction can become chronic.

Using an example of a person with TBI, who also experiences MI (see Special Implications for the Therapist: Cell Injury: Multiple Cell Injuries), healing of brain and myocardial tissue was discussed earlier in this chapter. In this final section, only those tissues not specifically included in the main body of this chapter are presented further.

Lung

After lethal injury to alveolar cells (type I and II pneumocytes), regeneration can occur only when the basement membrane remains intact. After the phagocytic removal

of the necrotic cells, adjacent living epithelial cells migrate onto the remaining basement membrane and differentiate into type II pneumocytes (cells that primarily produce surfactant).

Eventually, some of these cells differentiate into type I pneumocytes (cells that permit gas exchange) and full lung function is restored. This regeneration process occurs after a bout of pneumonia. If the damage to the lung disrupts the basement membrane, incomplete and inadequate regeneration occurs and healing must be achieved by repair. Also, certain injurious agents induce lung healing by the formation of scar tissue, leading to restrictive lung disease. An example of this would include inhalation of asbestos.

Digestive Tract

The healthy gut is lined with multiple rows of villi structures. These fingerlike projections are responsible for nutrient absorption and the production of digestive enzymes. Gut cells grow single file from the base of the villi up toward the top. They slough off into the intestinal tract and pass out of the body every five days or so. Damaged or injured cells are constantly leaving, while healthy cells renew the GI environment. It takes about 3 to 4 weeks for a complete turnover of all gut cells throughout the digestive tract. A mildly to moderately impaired gut takes 3 to 6 months to heal and 12 to 18 months for a more severe intestinal injury.²⁹

Since two-thirds of all immune system function and 90% of serotonin function take place in the gut, healing the gut can assist in bringing both of these functions back into balance. Serotonin is needed to produce melatonin, which is an essential component for good, restful sleep; the proper amount of circulating and functioning serotonin is also needed to stabilize mood.²⁹

Peripheral Nerves

When a nerve is cut, the peripheral portion rapidly undergoes a myelin degeneration and axonal fragmentation. The lipid debris is removed by macrophages mobilized from the surrounding tissues in a process referred to as *Wallerian degeneration*. However, within 24 hours of section, new axonal sprouts from the central stump are observed with proliferation of Schwann cells from both the central and peripheral stumps.

Careful microsurgical approximation of the nerve may result in reinnervation. The most important factor in achieving successful nerve regeneration after repair is the maintenance of the neurotubules (basement membrane and connective tissue endoneurium), along which the new axonal sprouts can pass.¹⁷

Skeletal Muscle

Skeletal muscle is composed of contractile and connective tissue elements. Actin and myosin myofilaments make up the sarcomere units of muscle fibers. Each individual myofiber is surrounded by a delicate sheath called the *endomysium* (basement membrane) and then arranged in bundles. Satellite cells surround the muscle fibers and

stiffness include increased collagen fibers from reduced collagen turnover, increased cross-links of aged collagen fibers, changes in the mechanical properties of connective tissues, and structural and functional changes in the collagen protein. Tendons and ligaments also have less water content, resulting in increased stiffness.¹¹⁸

In the athlete, prolonged exercise can result in fatigue or damage as a result of muscle membrane leakage lasting several days after the exercise event. Research studies suggest initiation of degenerative processes in muscles after severe exercise may be the result of changes in sodium, potassium, and calcium ion content.^{52,106}

Release of muscle enzymes, such as LDH and CK, has also been reported as an indicator of muscle damage associated with intense exercise. These enzymes are found within 6 to 24 hours of muscle injury and remain elevated up to 4 days postinjury.^{21,22}

Motor Control and Muscle Inhibition

Neurophysiologic adaptation to chronic pain appears to result in changes in motor control and muscle recruitment strategies. Three important motor control issues seem to be part of musculoskeletal dysfunction and human movement impairment observed: feedforward mechanisms, cortical plasticity, and task-specificity.^{32,148} For example, studies of low back pain are reporting muscle inhibition after injury, a state in which there is no activation seen in the muscle on electromyography (EMG) even when the particular muscle under surveillance is expected to serve as the prime mover. Inhibition can be task-specific (i.e., related only to one task) or global (i.e., as if the brain has forgotten that muscle altogether).⁶⁰

Task-specific inhibition shows a muscle recruitment pattern that is perfectly normal in one motion or direction but absent in another. With global inhibition, the muscle is inactive throughout most (but not all) motions and tasks involving that muscle. The presence of global inhibition signals that a different approach is required in intervention. Pain management and muscle strengthening must be done in conjunction with treatment to restore normal motor recruitment patterns.^{60,61}

New information in the areas of motor control and muscle inhibition as these topics relate to muscle injury and repair is being reported. We may expect to see more information in the near future. Greater knowledge and understanding in these areas may help direct treatment interventions in the future.

Bone

Bone is comprised of two types of tissue: cortical and cancellous (trabecular). Cortical bone accounts for approximately 80% of skeletal tissue. It is the tough outer layer of bone, densely packed, and surrounds trabecular or cancellous bone. The remaining 20% is cancellous bone, which consists of spongy, intermeshing thin plates (trabeculae) that are in contact with the bone marrow. Bone has two surfaces referred to as *periosteal* (external) and *endosteal* (internal).

Bone must be light enough to allow locomotion but strong enough to protect internal organs and to with-

stand fracture while providing a readily available store of calcium and phosphorus. Skeletal shape and mass is influenced by two major factors: mechanical loading placed on it and mineral homeostasis, which is controlled by systemic and hormonal factors. Bone's response to mechanical stress is modulated by hormones and is under genetic control, although it can also be influenced by drugs, toxins, and diseases.

Loss of bone occurs when there is an imbalance between destruction and production of bone cells or when there is a defective mineralization of bone matrix. An increase in osteoclasts or failure of osteoblasts to assemble can result in bone resorption faster than bone is being built up.

A variety of conditions can affect bone and require a reparative process, including fracture, infection, inflammation (e.g., tuberculosis or sarcoidosis), metabolic disturbances (e.g., Paget's disease, osteoporosis, or osteogenesis imperfecta), tumors, response to implanted prostheses, bone infarction, and any other systemic diseases that have skeletal manifestations (e.g., sickle cell disease, amyloidosis, or hemochromatosis). For a discussion of these specific conditions and their impact on bone, the reader is referred to each individual chapter that includes those diseases. Only the bone response to injury and the reparative process (specifically fracture) will be discussed in this chapter.

Fracture Healing

Fracture repair is a healing process by regeneration and remodeling (i.e., without a scar) and with the potential for a return of optimal function in many cases. After an uncomplicated fracture, bone heals in similar overlapping phases previously discussed in this chapter (Fig. 6-21). At the moment of fracture, tiny blood vessels through the haversian systems are torn at the fracture site. A brief period of local internal bleeding occurs, resulting in a hematoma around the fracture site called a fracture hematoma. Bleeding from the fracture site delivers fibroblasts, platelets, and osteoprogenitor cells, which secrete numerous growth factors and cytokines. They stimulate transformation of the initial hematoma into a more organized granulation tissue, eventually promoting callus formation.

The *inflammatory phase* occurs as inflammatory cells arrive at the injured site accompanied by the vascular response and cellular proliferation. Clinical evidence of this phase include pain, swelling, and heat.

Clotting factors from the blood initiate the formation of a fibrin meshwork. This meshwork is the scaffolding for the ingrowth of fibroblasts and capillary buds around and between the bony ends. By the end of the first week, phagocytic cells have removed a majority of the hematoma, and neovascularization and initial fibrosis are occurring.

The *reparative phase* begins during the next few weeks and includes the formation of the soft callus seen on x-rays around 2 weeks after the injury, which is eventually replaced by a hard callus. During this phase, osteoclasts (bone macrophages) clear away the necrotic bone while the periosteum and endosteum regenerate and begin to differentiate into formation of hyaline cartilage (soft

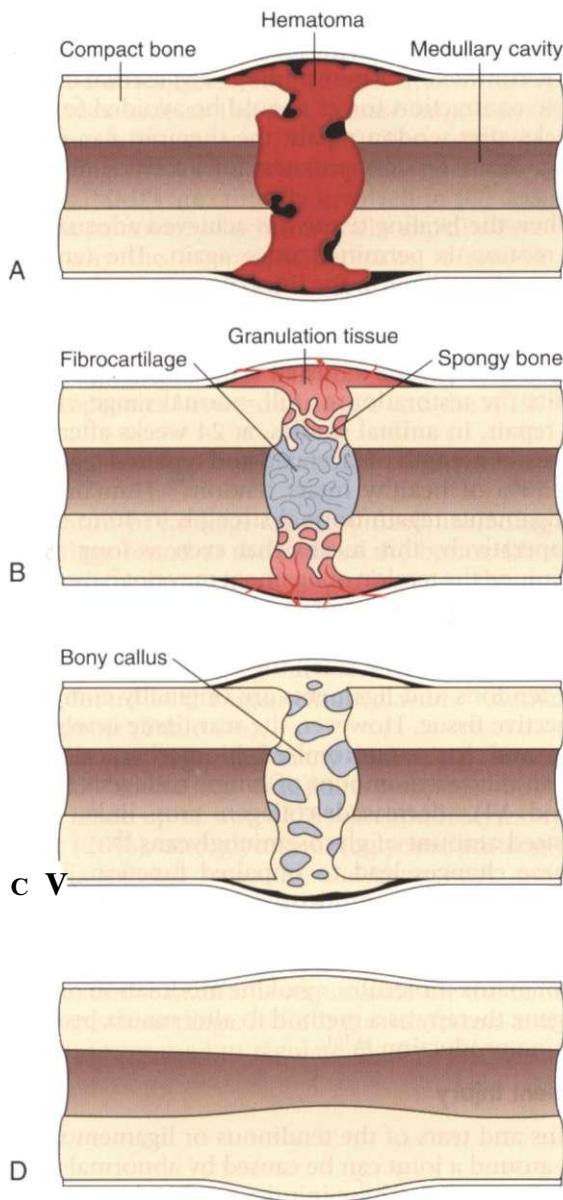


Figure 6-21

Fracture healing occurs in overlapping stages or phases. A, Immediate vascular response with hematoma formation and inflammatory response. B, Granulation tissue and fibrocartilage formation during early reparative phase. C, Fibrocartilaginous union (soft callus) is replaced by a fibroosseous union (hard callus). D, Remodeling phase with complete restoration of the medullary canal. (From Damjanov I: Pathology for the health-related professions, ed 3, Philadelphia, 2006, WB Saunders.)

callus) and primary bony spicules (hard callus). Bone growth factors, including bone morphogenetic proteins, TGF- β , PDGF, insulin-like growth factors I and II, and acid and basic fibroblast growth factors, are powerful components of the fracture healing (reparative) phase.⁷⁷

Once the callus is sufficient to immobilize the fracture site, repair occurs between the fractured cortical and medullary bones when the fibrocartilaginous union (soft callus) is replaced by a fibroosseous union (hard callus). The process is called enchondral ossification. Delayed union and nonunion fractures result from errors in this phase of bone healing. The completion of the reparative

phase (usually occurring between 6 and 12 weeks) is indicated by fracture stability. Radiographically, the fracture line begins to disappear.⁶⁸

The *remodeling phase* begins with clinical and roentgenographs union (no movement occurs at the fracture site) and persists until the bone is returned to normal, including restoration of the medullary canal. During this phase, which may take months to years, the immature, disorganized woven bone is replaced with a mature organized lamellar bone that adds further stability to the fracture site. The excessive bony callus is resorbed, and the bone remodels in response to the mechanical stresses placed on it.

In the normal adult skeleton, approximately 10% to 30% of the bone is replaced or remodeled to replace microfractures from stress and maintain mineral balance. Bone remodeling is carried out by bone cells, including osteoblasts, osteoclasts, and osteocytes. Osteoblasts produce the bone matrix and initial bone mineralization while osteoclasts resorb bone. Osteocytes detect local mechanical loading and send signals to the surface osteoblasts to initiate bone remodeling.²

The time for overall bone healing varies depending on the bone involved, the fracture site and type, treatment required (e.g., immobilization versus surgical repair, the need for bone grafting or use of bone graft substitutes), degree of soft tissue injury, treatment complications, and other factors mentioned previously (e.g., age, vascular supply, nutritional status, or immunocompetency). Specific types of fractures, their treatment, and special implications for the therapist are discussed in greater detail in Chapter 27.

Tendons and Ligaments

Tendons and ligaments are dense bands of fibrous connective tissue composed of 78% water, 20% collagen, and 2% glycosaminoglycans. This composition allows them to sustain high unidirectional tensile loads, transfer forces, provide strong flexible support, and help the tissue respond to normal loads while resisting excessive mechanical or shearing forces and deformation. The viscoelastic characteristics of these tissues make them capable of undergoing deformation under tensile or compressive force, yet still capable of returning to their original state after removal of the force.

Tendons attach muscles to their osseous origins and insertions, whereas ligaments provide support to joints through bone-to-bone attachments. Both are made up of parallel fibers of type I collagen produced by fibroblasts/fibrocytes, glycosaminoglycans/proteoglycans, a small vascular supply, and sensory innervation. The mechanical properties of tendons and ligaments are dependent not only on the architecture and properties of the collagen fibers but also on the proportion of elastin that these structures contain (e.g., minimal elastin in tendons and ligaments of the extremities, substantial elastin in the ligamentum flavum).

Tendon Injury

Tendons may heal either as a result of proliferation of the tenoblasts from the cut ends of the tendon or more likely

as a result of vascular ingrowth and proliferation of fibroblasts derived from the surrounding tissues that were injured at the time of the tendon injury. Because the surrounding tissues contribute so much to the healing of a tendon, adhesions are very common. With rupture of the Achilles tendon, rotator cuff tendons, or cruciate ligament(s), functional restoration requires surgical repair to appose and suture the cut ends.¹⁷ Tendon healing progresses through the same overlapping phases as other tissues: hemostasis and inflammation, cellular proliferation and matrix deposition, and long-term remodeling. Hemostasis begins immediately followed by the inflammatory process, which begins during the first 72 hours (3 to 5 days) after injury and/or surgical intervention.

Hemostasis occurs as platelets from blood plasma enter the tear to initiate clot formation. Fibrin and fibronectin form cross-links with collagen fibers to form a fragile bond, which helps reduce hemorrhage. The activity of phagocytic cells clears away the debris in the area from damaged and devitalized tissue. Chemotactic mediators attract inflammatory white blood cells to the area, including polymorphonuclear leukocytes and monocytes. The release of histamine and bradykinin increases vascular permeability.⁹⁵

The *inflammatory phase* overlaps and transforms into the *proliferative phase*, which usually occurs 2 to 3 weeks after tendon injury or repair but can begin as early as 48 hours after injury.¹⁸ Granulation tissue is formed by the migration and proliferation of fibroblasts and vascular buds from the surrounding connective tissue. Capillary sprouts grow out of blood vessels around the edges of the wound-forming loops by joining with each other or with capillaries already carrying blood. The new blood vessels enhance delivery of nutrients to the healing tissue.

While this is occurring, the fibroblasts are secreting soluble type III collagen molecules, which form fibrils. A new extracellular matrix is formed. In this step, the original fibrin clot and scaffolding are replaced with more permanent repair tissue.

Approximately 2 weeks into the healing process, the collagen fibrils are oriented and rearranged into thick bundles, providing the tissue with greater strength. During this period, the affected area remains immobilized to relieve stress from the healing tissue and prevent rupture recurrence. The lack of stress causes the newly forming collagen to be deposited in random alignment without the formation of cross-links. The immature collagen is randomly oriented and has limited strength.

Now the transition from the proliferative phase to the *maturity phase* takes place. The maturation and remodeling phase begins around week 3 after the initial injury. The immature type III collagen is replaced by mature type I collagen; the latter aligns along tensile forces. The collagen is continually remodeled until permanent repair tissue is formed that is oriented along the lines of stress and organized to provide increasing resistance to stretch and tearing.⁸⁰ Based on animal models, we know that tendon healing takes at least 12 to 16 weeks to reach a level at which the tendon can be stressed.⁹⁵

Aggressive early motion that stresses the repair and exceeds the mechanical strength of the repair should be avoided. During the early weeks of the remodeling phase,

the force required to rupture a lacerated and repaired tendon can be less than the force generated by a maximum muscle contraction. These findings suggest that maximum muscle contraction forces should be avoided for at least 8 weeks after tendon repair; the therapist can expect to see significant tendon weakness for a considerable period afterward.^{18,66}

When the healing tissue has achieved adequate integrity, motion is permitted once again. The remodeling collagen then aligns to the lines of stress produced by the motion, thereby permitting the healed tendons and ligaments to provide support in line with the stress. Realignment of collagen to its usual parallel arrangement also permits the restoration of full, normal range of motion after repair. In animal studies, at 24 weeks after surgery, the tensile strength of lacerated and repaired tendons was only 50% of healthy intact tendon.⁶⁶ Human tendons and ligaments regain normal strength in 40 to 50 weeks postoperatively; this means that even as long as a year after injury, the tendon or ligament may not have achieved premorbid tensile strength.

Although the process of healing is by repair (formation of a connective tissue scar), this constitutes regeneration since tendons and ligaments are originally composed of connective tissue. However, the scar tissue is weaker and larger and has compromised biomechanical integrity with an increased amount of minor collagens (types III, V, and VI), decreased collagen cross-links, and an increased amount of glycosaminoglycans.⁶⁵

These changes lead to impaired function, increased risk of reinjury, and increased risk of osteoarthritis. Research on ligament healing includes studies on low-load and failure-load properties, alterations in the expression of matrix molecules, cytokine modulation of healing, and gene therapy as a method to alter matrix protein and cytokine production.^{84,101}

Ligament Injury

Sprains and tears of the tendinous or ligamentous structures around a joint can be caused by abnormal or excessive joint motion. These injuries can be classified as first, second, or third degree, depending on the changes in structural or biomechanical integrity (ranging from injury of a few fibers without loss of integrity to a complete tear).

Common sites for this type of injury include the ankle, knee, and fingers with clinical manifestations of local pain, edema, increased local tissue temperature, ecchymosis, hypermobility or instability, and loss of motion and/or function. If, after injury, the therapist notes quick onset of joint effusion, and the joint feels hot to the touch with extremely painful and limited movement, the joint needs to be examined by a physician to rule out hemarthrosis.

In many extraarticular ligaments (e.g., medial collateral ligament), healing occurs by the same basic phases described in the previous section. However, there is variation in the manner in which ligaments heal; some intraarticular ligaments (e.g., anterior cruciate ligament) have a poor healing response. After the ligament ruptures, the thin synovial sheath is disrupted and blood dissipates, preventing clot and hematoma formation. Healing cannot

take place without a foundation for repair or localization of chemotactic cytokines and growth factors.¹¹⁴

Recent studies have revealed that after injuries, ligament tissues such as the ACL release large amounts of matrix metalloproteinases (MMPs). These enzymes have a devastating effect on the healing process of the injured ligaments. MMPs are critically involved in the extracellular matrix turnover, which may help explain one of the reasons why the injured ACL repairs minimally. The higher levels of active MMP-2 seen in ACL injuries may disrupt the delicate balance of extracellular matrix remodeling. MMP activity is less in the medial collateral ligament (MCL), which may account for the difference in healing capacities between the MCL and the ACL.¹⁵⁶

Cartilage

Several forms of cartilage are recognized, including articular cartilage found at the ends of the bones; fibrocartilage found in the menisci of the knee, at the annulus fibrosus, at the insertions of the ligaments and tendons into the bone, and on the inner side of tendons as they angle around pulleys (e.g., at the malleoli); and elastic cartilage found in the ligamentum flavum, external ear, and epiglottis (Table 6-6).

Articular cartilage has many individual zones that make up the whole (Fig. 6-22). It is composed of hyaline cartilage made up of water (75%), chondrocytes, type II collagen (20%), and glycosaminoglycans/proteoglycans (5%). It is avascular, avascular, and alymphatic and does not appear to regenerate well after adolescence, most likely because of its avascularity and low cell-to-matrix ratio. Proteoglycan, produced by the chondrocytes and secreted into the matrix, is responsible for the compressive strength of cartilage. It binds growth factors and traps and holds water used to regulate matrix hydration.

Cartilage Healing

Ideal conditions for healing of articular cartilage require a source of cells, provision of matrix, removal of stress concentration, and intact subchondral bone plate with some mechanical stimulation. The exact nature of this healing process is not understood at this time. Microfracture techniques to enhance chondral resurfacing have made it possible to stimulate the formation of a durable repair cartilage cap over the lesion.^{123,136}

In adults without intervention, the healing of articular cartilage occurs by fibrous scar tissue or fails to heal at all. This replacement tissue does not function as well as the original, and the adjacent joint surface can be affected. Fibrous scarring of the articular cartilage leads to local degenerative arthritis (Fig. 6-23).

In people with rheumatoid arthritis, stiffness and pain are common. Researchers are still investigating the underlying mechanisms contributing to mechanical stiffness. One hypothesis is that chronic pain leads to CNS plasticity. Chronic pain may elicit joint, ligament, and capsule mechanoreceptor sensitivity alterations at the spinal level,

Table 6-6 Types of Cartilage

Types	Location
Articular (hyaline)	Joint surfaces, bone apophyses, epiphyseal plates, costal cartilage (ribs), fetal skeleton
Fibrocartilage	Tendon and ligament insertion, meniscus, disk
Elastic	Trachea (epiglottis), earlobe, ligamentum flavum
Fibroelastic	Meniscus

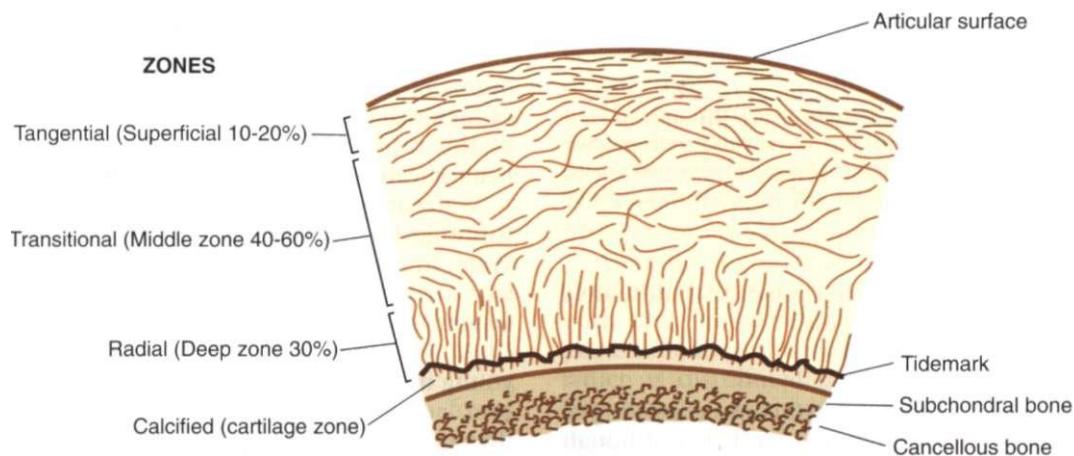


Figure 6-22

Zones of cellular distribution in adult articular cartilage. A, Superficial tangential zone: type II collagen fibers are oriented tangentially to the surface providing the greatest ability to resist shear stresses. B, Transitional (middle) zone: composed primarily of proteoglycans but collagen fibers present are arranged obliquely to provide a transition between the shearing forces of the surface layer and the compression forces in the cartilage layer. C, Radial (deep) zone: collagen fibers are attached vertically (radial) into the tidemark; distributes loads and resists compression. D, Tidemark layer is located in the calcified zone; the Tidemark is the line that straddles the boundary between calcified and uncalcified cartilage; it separates hyaline cartilage from subchondral bone. E, Calcified zone: layer just above subchondral bone containing type X collagen. F, Subchondral bone. G, Cancellous bone.

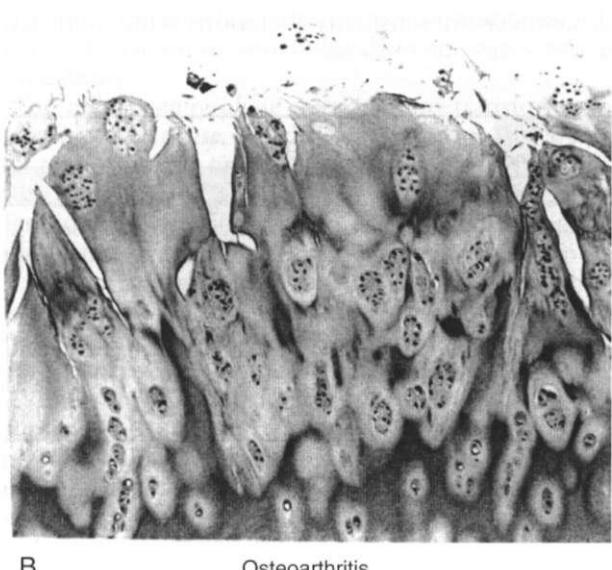
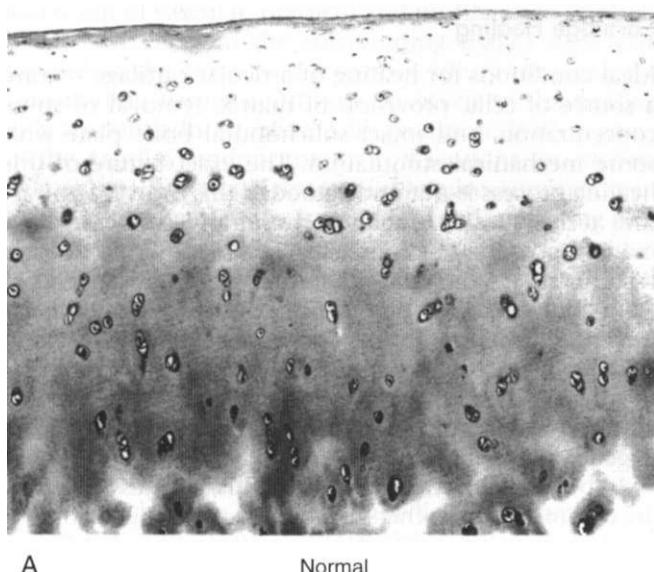


Figure 6-23

Histologic sections of normal (A) and osteoarthritic (B) articular cartilage obtained from the femoral head. The osteoarthritic cartilage demonstrates surface irregularities, with clefts to the radial zone and cloning of chondrocytes. (From Harris ED: *Kelley's textbook of rheumatology*, ed 7, Philadelphia, 2005, WB Saunders.)

impairing proprioceptive joint responses and ultimately resulting in perceived joint stiffness.^{56,62}

Menisci (Knee)

The menisci are fibrocartilaginous structures consisting of cartilage bundles composed mainly of collagen, although some proteoglycan is also present. The amount of proteoglycan increases dramatically in the injured, degenerate meniscus. The cells of the meniscus sometimes are called fibrochondrocytes because of their appearance and the fact that they synthesize a fibrocartilaginous matrix.⁵³ The principal orientation of collagen fibers in the menisci is circumferential, designed to disperse compressive load, resist shear, aid in shock absorption, and withstand the

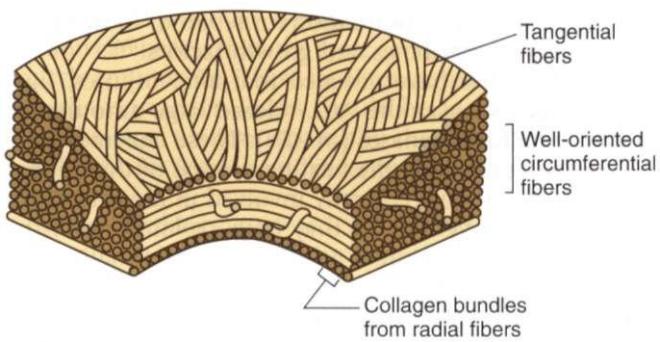


Figure 6-24

Diagrammatic representation of the distribution of collagen fibers in the meniscus of a knee. Collagen is oriented throughout the connective tissues in such a way as to maximally resist the forces placed upon these tissues. The majority of the fibers in the meniscus are circumferentially arranged, with a few fibers on or near the tibial surface placed in a radial pattern. This structural arrangement enables the meniscus to resist the lateral spread that occurs during high loads generated during weight bearing. Longitudinally arranged collagen fibers facilitate shock absorption and sustain the tension generated between the anterior and posterior attachments. (From Bullough PG: *Bullough and Vigorita's orthopaedic pathology*, ed 3, St. Louis, 1997, Mosby.)

circumferential tension within the meniscus during normal loading (Fig. 6-24). A few small, radially oriented fibers present on the tibial surface probably act as ties to resist lateral splitting of the menisci from undue compression.

At birth, the entire meniscus is vascular; by age 9 months, the inner one-third has become avascular. By adulthood, only the outer 10% to 30% of vascularity remains, with blood supplied via the perimeniscal capillary plexus off the superior and inferior medial and lateral genicular arteries.¹²³ Blood supply to the meniscus flows from the peripheral to the central meniscus principally through diffusion or mechanical pumping (movement).⁴ Meniscal tears heal by migration of cells from the synovial membrane adjacent to the meniscus. The remodeling events of the healing process remain unknown. Healing of meniscal tears may be inhibited based on the location of the tear; less vascular locations have less vigorous healing capability.

Water accounts for 70% of meniscal composition, contributing to the meniscal function of joint lubrication. Water in the menisci also provides resistance to compressive loads. Collagen makes up 60% to 70% of the dry weight; 90% of it is type I collagen fibers with types II, III, V, and VI present in much smaller amounts.⁵³ In the young individual, the menisci are usually white, translucent, and supple on palpation. In the older individual, the menisci lose their translucency, become more opaque and yellow in color, and become less supple.

Injury and degeneration leading to laceration are the two most common causes of symptoms that require surgical intervention.¹⁷ The presence of clinical symptoms of pain, swelling, locking and catching, and loss of motion often require surgical intervention. Proper management depends on the type of tear and its location (Fig. 6-25).⁵³

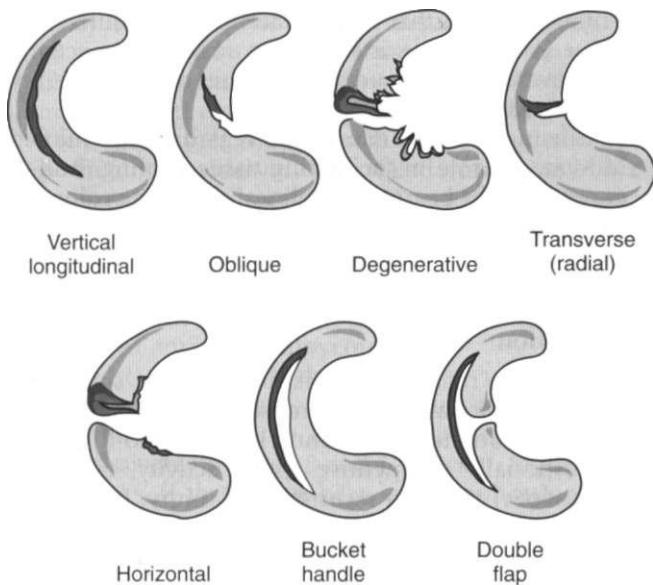


Figure 6-25

Classification of most common meniscal tears.

Synovial Membrane

The synovial membrane lines the inner surface of the joint capsule and all other intraarticular structures (e.g., subcutaneous and subtendinous bursae sacs, tendon sheaths), with the exception of articular cartilage and the meniscus. Synovial membrane consists of two components: the intimal (cellular layer or synoviocytes) layer next to the joint space and the subintimal or supportive layer made of fibrous and adipose tissue.

The synovial membrane has three principal functions: secretion of synovial fluid hyaluronate, phagocytosis of waste material, and regulation of the movement of solutes, electrolytes, and proteins from the capillaries into the synovial fluid. This latter function provides a regulatory mechanism for maintenance of the matrix through various chemical mediators such as ILs.

Injury to any of the joint structures affects the synovium and results in hemorrhage, hypertrophy, and hyperplasia of the synovial lining cells and mild chronic inflammation.¹⁷ In the case of prolonged, chronic synovitis, such as occurs in hemophilia, abnormal synovial fluid, joint immobilization, and fibrous adhesions, a progressive destructive condition in the joint can result.

Any type of immobilization leads to contraction of the capsule. Loss of glycosaminoglycans with the associated water loss further increases capsule stiffness and results in decreased joint motion. The synovial membrane lining the inside of the capsule hypertrophies and forms adhesions between itself and the adjacent articular cartilage.⁹⁷

Disk

The intervertebral disk sits between each pair of vertebrae and is made of connective tissue (collagen fibers) that help the disk withstand tension and pressure (Fig. 6-26). The disk is made of three zones: (1) the outer annulus

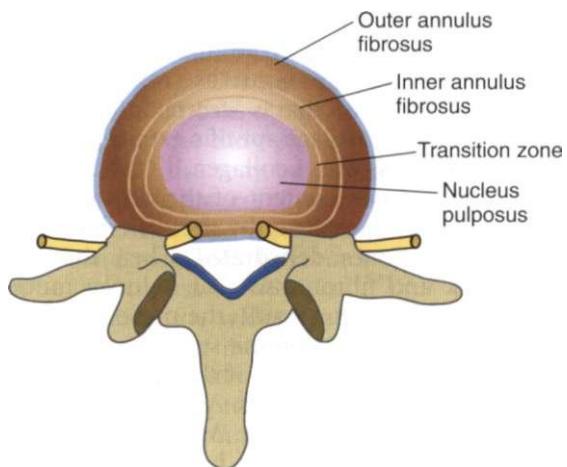


Figure 6-26

Zones of the adult human lumbar intervertebral disk.

fibrosus, a lamellated ring of alternately obliquely oriented, densely packed type I collagen fibers that insert onto the vertebral bodies; (2) the fibrocartilaginous inner annulus fibrosus, consisting of a type II collagen fibrous matrix; and (3) the viscoelastic central nucleus pulposus with type II collagen fibers along with various mucopolysaccharides and a high concentration of proteoglycans.¹ This composition supports the high water content of the nucleus, which behaves biomechanically as a fluid cushion that transmits loading forces to the outer annulus fibrosus, as well as to the vertebral endplate.¹¹⁵

The nucleus is held in place by the *annulus*, a series of strong ligament rings surrounding it. The annulus is primarily composed of type I collagen arranged in multiple concentric layers. This fiber arrangement allows the annulus to resist tensile, radial, and torsional forces. With acute trauma or degenerative changes and microtrauma over time, the fibers of the annulus may be disrupted.¹¹⁵ The normal disk's blood supply is restricted to the peripheral outer annulus. The vertebral body's blood vessels lie directly against the endplates but do not enter the disk itself. The nutrition of the more centrally located disk cells is derived from diffusional and convection transport of nutrients and wastes through the porous solid matrix.¹ The metabolism of the avascular disk is so slow that the turnover of proteoglycans takes 500 days.¹⁴⁵

Although the nucleus has no nerve supply, the outer third of the annulus is innervated, receiving supply from both the sinuvertebral nerve, which innervates the posterior and posterolateral regions, and the gray ramus, which is distributed primarily anteriorly and laterally. The annulus may have a role in neuromodulation of pain.¹¹⁵

Aging and Disk Degeneration

Our intervertebral disks change with age and demonstrate degenerative changes relatively early in life. Cell senescence in the disk has been linked with degenerative disease, with more senescence of cells in the nucleus pulposus compared to the annulus fibrosus in individuals with herniated disks.¹²⁶

Disk degeneration follows a predictable pattern. First, the nucleus in the center of the disk begins to lose its ability to absorb water. This occurs as a result of a decrease in cell density in the disk that is accompanied by a reduction in synthesis of cartilage-specific extracellular matrix components such as type II collagen.⁴⁷

As the proteoglycan content of the disk decreases, a loss of water-binding capacity by the disk matrix occurs and the disk becomes dehydrated. Then the nucleus becomes thick and fibrous, so that it looks much the same as the annulus. As a result, the nucleus is not able to absorb shock as well. Routine stress and strain begin to take a toll on the structures of the spine. Tears called *fissures* form around the annulus. Annulus injury is sufficient to cause disk degeneration. As the disk weakens, it starts to collapse, and the bones of the spine compress.¹⁴⁵

Along with the pathology of degeneration, changes in the extracellular matrix content affecting collagen fibers can reduce the disk's load-bearing capacity. Calcification of the vertebral endplates is another factor thought to contribute to disk degeneration. Alterations in permeability adversely affect chondrocyte metabolism. The passage of nutrients and waste products across the endplate depends on fluid flowing into the disk during the night while resting and flowing out during the day when we move about.⁴⁷

Injury to the disk (herniation) is more likely in the morning soon after waking when the nucleus pulposus is maximally hydrated after a prolonged period of rest. Vigorous early morning activities increase the vertical load beyond the strength of the collagen in the annulus. Other proposed risk factors for lumbar disk herniation include lifting heavy loads, torsional stress, strenuous physical activity, and occupational driving of motor vehicles.⁵

Conditions, such as a major back injury or fracture, can affect how the spine works, making the changes happen even faster. Daily wear and tear and certain types of vibration can also speed up degeneration in the spine. In addition, strong evidence suggests that smoking speeds up degeneration of the spine. Scientists have also found links among family members, showing that genetics play a role in how fast these changes occur.

SPECIAL IMPLICATIONS FOR THE THERAPIST

6-6

Specific Tissue or Organ Repair

Therapists have an important role in the rehabilitation of acute injuries. Certain components of the inflammatory process must be controlled quickly for recovery to proceed. For example, if edema is a component of a joint injury, it must be controlled as quickly as possible. Studies have demonstrated that joint edema can inhibit or hinder local muscle activity, which could result in altered joint mechanics and further irritation.^{28,134} The anticipated goals are to facilitate wound healing and maintain the normal function of noninjured tissue and body regions. The overall goal of the rehabilitation program is to return the person to normal activity as soon as possible, yet not so fast that

irritation and further inflammation of the injured area occur. A fine line exists between maximizing activity and overdoing the activity to the point of injury aggravation.

Client education is essential regarding the injured individual's role in facilitating tissue healing. Adherence to weight-bearing guidelines, avoiding prolonged sitting or flexion of the trunk, applying ice appropriately, and performing the prescribed exercises are key to the recovery process.

Prevention

Appropriate rehabilitation is necessary for soft tissue injuries, especially severe muscle strains and frank rupture of any tendon or muscle. Return to full activity, especially competitive sports activity, can (and often does) result in recurrence of injury. Injury prevention should include addressing issues such as muscle fatigue, weakness, and inflexibility. Stronger muscles are better able to absorb energy and thereby limit the magnitude of tissue stretch. In other words, muscle strengthening is an important way to avoid muscle strain. Recent studies have questioned the need to stretch before activity. Other studies show that increased muscle flexibility is linked with fewer injuries.⁵⁹ An appropriate warm-up before activity may also reduce strain injuries. Warm muscles may be more flexible and failure-resistant.¹⁰⁵

Rehabilitation of Repaired Soft Tissues

Careful monitoring of the timeline for tissue recovery and observing presenting signs and symptoms guide the therapist in deciding when and how to progress intervention and activity level. The type of tissue involved also makes a difference since tendon tear/repair requires prolonged rest to avoid disrupting the healing process and subsequent reinjury, whereas prolonged rest and immobilization after muscle strain can result in prevent permanent stiffness. This monitoring can also be taught so the client understands the limits of his or her condition.

The process is somewhat more difficult with acute back or neck injuries than with peripheral injuries. Owing to the depth of the tissues of the spine, increased temperature and erythema are not always present or palpable if present. The therapist must rely more on muscle tone and the degree of pain with movement changes in deciding when the program can be progressed.

As a general guideline for tissue healing, during the inflammatory phase after injury or surgery (first 3 to 5 days), the soft tissue's (e.g., tendon, ligament, or muscle) ability to hold sutures is at an all-time low. Protected rest is imperative during this stage. Gradually increasing tensile force on the healing tissue comes next. An incremental approach that is slow enough to allow and promote the stages of proliferation, maturation, and fiber realignment is required.

TENDON OR MUSCLE RUPTURE

During the proliferative phase (usually 5 to 28 days after tendon injury/repair), controlled passive move-

ment is allowed. The repaired tissue is kept protected to avoid excessive force. Passive range of motion is continued as healing progresses and until the tissue moves into the remodeling phase of healing (around 4 to 8 weeks after injury/repair). Active range of motion is then initiated with controlled movements (e.g., gravity-eliminated positions). The idea is to prevent excessive resistance from the weight of the limb while still working on gradually increasing the force of the muscle contraction. As the repair strengthens, the therapist can allow increased muscle force through increased antigravity movements.¹⁸

Resistance with weights, rubber tubing, elastic bands, and so on is not started until at least 8 weeks after the repair. Once again, resistance is increased progressively (between 8 and 12 weeks). At the end of 12 weeks, if there have been no complications (e.g., infection, wound dehiscence) and there are no comorbidities to delay healing (e.g., tobacco use, diabetes, peripheral vascular disease), then full force muscle contraction can be tolerated.

MUSCLE STRAIN

Recovery from severe muscle strain may begin with a short period of immobilization to provide pain relief and protect the tissue during the initial phase of healing. Immobilization followed by mobilization of muscle may help muscle fiber regeneration and fiber orientation with reduced scar formation.⁷⁴ As soon as pain and swelling subside, a program can be initiated to recover range of motion, strength, and endurance. Return to sports is considered safe when there is 80% return of strength compared to the noninvolved side. Surgical repair of a complete muscle tear has its own protocol. Repair is difficult as the muscle fibers do not hold sutures well.¹⁵

Modalities

Physical therapy modalities, such as transcutaneous electrical nerve stimulation (TENS), iontophoresis, and ultrasound, may be used to manage pain and limited motion, but their impact on the underlying tear and healing tissue is not known. Cryotherapy helps control postoperative pain, decreases swelling and muscle spasm, suppresses inflammation, and decreases metabolism. Transverse friction massage in the treatment of tendinitis/tendinosis is based on the soft tissue work of Cyriax.²⁵ However, there are no scientific data to support the use of this technique.

Guidelines for nonsurgical and postoperative rehabilitation for ligament, tendon, and muscle tear/repair vary based on geographical regions and physician preferences and protocols and are reported widely in the literature. The plan of care should always be based on an understanding of the healing stages of injured tissue. The goal is to restore motion and strength without subjecting the healing tissue to excessive forces that may hinder healing or rupture the repair.

Medications

A significant percentage of those coming to outpatient therapy clinics are taking salicylates or NSAIDs.¹³ These

medications can play a key role in recovery from an acute injury, facilitating the therapist's role and clinical decision making. The common clinical practice to administer NSAIDs should be limited to early symptom control during the early phases of tissue healing. Prolonged NSAID use may be counterproductive for the biologic healing process since complete tissue recovery involves delicate and finely coordinated elements of cellular and metabolic inflammatory reactions, which can be interrupted by NSAIDs.^{92,109}

Considering the widespread use of salicylates and NSAIDs, therapists must also be aware of potential side effects that would warrant communication with a physician (see Chapter 5). Irritation of the GI system is the most common potential side effect. The risk of developing peptic ulcer disease increases significantly if someone is taking more than one of these types of drugs. This pattern of drug use exists in the therapy population, in which significant numbers of subjects are taking one or more over-the-counter (OTC) anti-inflammatory agents along with a prescribed NSAID.¹³ See Chapter 16 for a description of peptic ulcer disease.

Tissue Response to Immobilization

In addition to having an important role in the rehabilitation of acute injuries, therapists often deal with clinical problems secondary to the effects of immobilization. Although not traumatic in the classic sense, immobilization of a limb or joint can result in significant impairment and functional limitations.

Immobilization takes a variety of forms, including bed rest, casting or splinting of a body part, or non-weight-bearing status of a lower extremity. On a tissue level, significant changes can occur with immobilization (Table 6-7). Besides the inert joint structures, changes also occur in muscle, particularly a loss of strength. Such changes can occur without injury, which magnifies the importance of maintaining function in noninjured tissue and body areas. A rehabilitation program should be designed to address the needs of each of the tissues.

DEEP VENOUS THROMBOSIS

While initiating rehabilitation after immobilization, the therapist must remain vigilant for the possible presence of deep vein thrombosis (DVT). A potential complication of DVT is pulmonary embolus, which represents one of the leading causes of morbidity and mortality after orthopedic surgical procedures.⁴² Although a large percentage of clients with DVT are asymptomatic, severe local pain and edema, fever, chills, and malaise are all possible manifestations. The types of immobilization that carry the risk of DVT include bed rest, a limb being placed in a cast or splint, and non-weight-bearing status following a lower extremity injury, a surgical procedure, or a long car or plane ride. (See Chapter 12 for more information about DVT.)

Continued.

Table 6-7 Effects of Prolonged Immobilization

Tissue	Results of Immobilization
Muscle	Atrophy, decreased strength, contracture, reduced capillary to muscle fiber ratio, reduced mitochondrial density, reduced endurance
Bone	Generalized osteopenia of cancellous and cortical bone
Tendons and ligaments	Disorganization of parallel arrays of fibrils and cells; increased deformation with a standard load or compressive force
Ligament insertion site	Destruction of ligament fibers attaching to bone, reduced load to failure
Cartilage	Adherence of fibrofatty connective tissue to cartilage surfaces; loss of cartilage thickness; pressure necrosis at points of contact where compression has been applied
Synovium	Proliferation of fibrofatty connective tissue into joint space
Menisci	Adhesions of synovium villi; decreased synovial intima length; decreased synovial fluid hyaluronic acid concentrations; decreased synovial intima macrophages
Joint	0-12 weeks: Impaired range of motion; increased intraarticular pressure during movements; decreased filling volume of joint cavity After 12 weeks: Force required for the first flexion-extension cycle is increased more than twelvefold
Heart	Reduced strength of contraction (SV), reduced maximal cardiac output, reduced endurance, increased work of the heart for a submaximal load
Lung	Reduced airway clearance of mucus, increased likelihood of pneumonia, reduced maximal ventilatory volume
Blood	Reduced hematocrit and plasma volume, reduced endurance and temperature regulation

STIFFNESS

Joint or muscular stiffness is not uncommon after immobilization and in conjunction with conditions such as arthritis that are accompanied by pain and stiffness contributing to movement dysfunction and causing mobility impairments. Affected individuals often use the term "stiffness" to generally describe various joint sensations that may be unrelated to mechanical stiffness (increased resistance to motion). It may be necessary for the therapist to concentrate on disrupting the pain cycle to relieve "stiffness" when pain sensations are misinterpreted or poorly described as stiffness.^{56,63}

When muscular stiffness occurs as a result of aging, increased physical activity and movement can reduce associated muscular pain. As part of the diagnostic evaluation, consider a general conditioning program for the older adult reporting generalized muscle pain. Even 10 minutes a day on a stationary bike or treadmill or in an aquatics program can bring dramatic and fast relief of painful symptoms when caused by muscle deficiency.

CARTILAGE

Immobility or immobilization causes marked changes in articular cartilage. The collagen content remains unchanged, but there is a loss of glycosaminoglycans and water from the matrix, which leads to weakening and deterioration of the cartilage. Damage to the cartilage results in impairment of cartilage nutrition.⁵⁷ Normally, synovial fluid accumulates in the peripheral part of the joint where the cartilage is not in contact with its opposing cartilage, and nutrition from the synovial fluid takes place there. Proliferation of the synovial membrane from immobilization causes a loss

to this space and thus a reduction in cartilage nutrition. These types of alteration in the structure, quality, and nutrition of cartilage can lead to changes similar to those seen with osteoarthritis.⁵⁷

Cartilage degeneration results from both loss of normal loading and loss of motion. The adverse effects of immobilization are seen in both the internal and external surfaces of cartilage. Lack of normal use also leads to loss of smoothness and the presence of fibrillation of the outer surface, potentially leading to arthritic joint changes.⁵⁷

Current research is examining the effects of replacing damaged cartilage with cartilage harvested from the individual, grown in culture, and reinjected into the area of damaged cartilage to avoid this postoperative or postinjury sequela. This technology may allow the individual to regenerate a smooth, weight-bearing surface and avoid the rough, degenerative fibrocartilage formation that leads to osteoarthritis.

Advances in the fields of biotechnology and biomaterials are providing new techniques for regeneration or repair of tissue lost to injury, disease, or aging. Bioengineered tissues, including skin, bone, articular cartilage, ligaments, and tendons, are under investigation for clinical use (see the section on Tissue Engineering in Chapter 21).^{72,73}

References

To enhance this text and add value for the reader, all references are included on the companion Evolve site that accompanies this textbook. The reader can view the reference source and access it on-line whenever possible. There are a total of 156 cited references and other general references for this chapter.

SECTION 2 CLINICAL MEDICINE

CHAPTER 7

The Immune System

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Immunology is the study of the physiologic mechanisms that allow the body to recognize materials as foreign and to neutralize or eliminate them. When the immune system is working properly, it protects the organism from infection and disease; when it is not, the failure of the immune system can result in localized or systemic infection or disease. In fact, the significance of a healthy immune system is apparent in states or diseases characterized by immunodeficiency, such as occurs in human immunodeficiency virus (HIV) infection or in people on immunosuppressive medication.

Without an effective immune system, an individual is at risk for the development of overwhelming infection, malignant disease, or both. Not all immune system responses are helpful, as in the case of organ or tissue transplant rejection.

Additionally, excessive or inappropriate activity of the immune system can result in hypersensitivity states, immune complex disease, or autoimmune disease. For a complete understanding of the immune system as it relates to injury, inflammation, and healing, the reader is encouraged to read this chapter along with Chapter 6.

TYPES OF IMMUNITY

Innate and Acquired Immunity

Two types of immunity are recognized: innate (natural or native immunity) and acquired immunity (adaptive or specific immunity). *Innate immunity* acts as the body's first line of defense to prevent the entry of pathogens.

Two nonspecific, nonadaptive lines of defense are involved in innate immunity. Nonspecific refers to the fact that this part of the immune system does not distinguish between different types of invaders (e.g., bacteria, fungus, virus) and is nonadaptive; that is, it does not remember the encounter with specific invaders for future encounters. Each time that potential pathogen is introduced, the innate immune system reacts in the same predictable manner.

The first line of defense is the skin and its mucosal barriers, and the second is a nonspecific inflammatory response to all forms of cellular injury or death. Innate responses occur to the same extent no matter how many times the infectious agent is encountered (Fig. 7-1).

Acquired immunity is characterized by specificity and memory. The primary role of the immune system as a more specific line of defense (acquired immunity) is to recognize and destroy foreign substances such as bacteria, viruses, fungi, and parasites and to prevent the proliferation of mutant cells such as those involved in malignant transformation.

This type of immunity results when a pathogen gains entry to the body and the body produces a specific response to the invader. Acquired immunity has a memory so that when the same organism is encountered again, the body can respond even more rapidly to it and with a stronger reaction. The two components to acquired immunity (humoral immunity and cell-mediated immunity) are discussed in greater detail later in this section.

Acquired Immunity: Active or Passive Immunity

Acquired immune responses can occur as a result of active or passive immunity. Active immunity includes natural immunity and artificial immunity, which is intended or deliberate (Table 7-1).

Active acquired immunity refers to protection acquired by introduction (either naturally from environmental exposure or artificially by vaccination) of an antigen (microscopic component of pathogen that causes an immune response) into a responsive host.

The concept of vaccination is based on the fact that deliberate exposure to a harmless version of a pathogen generates memory cells but not the pathologic sequelae of the infectious agent itself. In this way, the immune system is primed to mount a secondary immune response with strong and immediate protection should the pathogenic version of the microorganism be encountered in the future.⁶⁰ This type of immunity is expected to last a lifetime, but there are occasional exceptions.

Researchers are developing a new generation of vaccines to fight a variety of diseases. One of the most promising is the deoxyribonucleic acid (DNA) vaccine that allows DNA from a pathogen to be injected into the body, where cells accept the added DNA instructions and make antigens that the body can recognize and fight. Genetic manipulation allows researchers to overcome the

greatest deterrent to vaccination—the ability of common pathogens such as influenza and pneumococcal bacteria to mutate too rapidly for a vaccine to match the latest version.

Some of the most promising new techniques are being investigated against malaria, cancer, ear infections, acquired immune deficiency syndrome (AIDS), sexually

transmitted diseases (STDs), asthma, influenza, strep throat, diabetes, and hepatitis C. Improved administration of the vaccine with the use of mucosal sprays, skin patches, time-released pills, and genetically engineered foods to replace needle injections also is under development.

Passive acquired immunity occurs when antibodies or sensitized lymphocytes produced by one person are transferred to another. Preformed antibodies made in a laboratory or made by someone else are another form of passive immunity.

For example, the transplacental transfer of antibodies from mother to fetus, the transfer of antibodies to an infant through breast milk, or the administration of immune serum globulin (γ -globulin) provides immediate protection but does not result in the formation of memory cells and therefore provides only temporary immunity. This type of immunity (passively acquired) lasts only until the antibodies are degraded, which may be only a few weeks to months.

THE IMMUNE RESPONSE

See Table 7-2.

Antigens

Any foreign substance in the body that does not have the characteristic cell surface markers of that individual and is capable of eliciting an immune response is referred to as an *antigen* (from antibody generator). Bacteria, viruses, parasites, foreign tissue cells, and even large protein molecules that are recognized as antigens are called *antigenic*. On encountering an antigen, the immune system recognizes it as nonself, and the appropriate immune response is mounted against the antigen. A single bacterium contains hundreds of antigenic sites and therefore has multiple sites capable of stimulating an immune response.

The subunits of an antigen that elicit an immune response are called *epitopes*. These molecules protrude from the surface of an antigen and actually combine with an antibody (Fig. 7-2). Each antigen may display hundreds of epitopes. The more epitopes that are present, the greater is the antigenicity of a substance and the greater

Figure 7-1

Natural protective mechanisms of the human body. (Reprinted from Damjanov I: *Pathology for the health professions*, ed 3, Philadelphia, 2006, Saunders.)

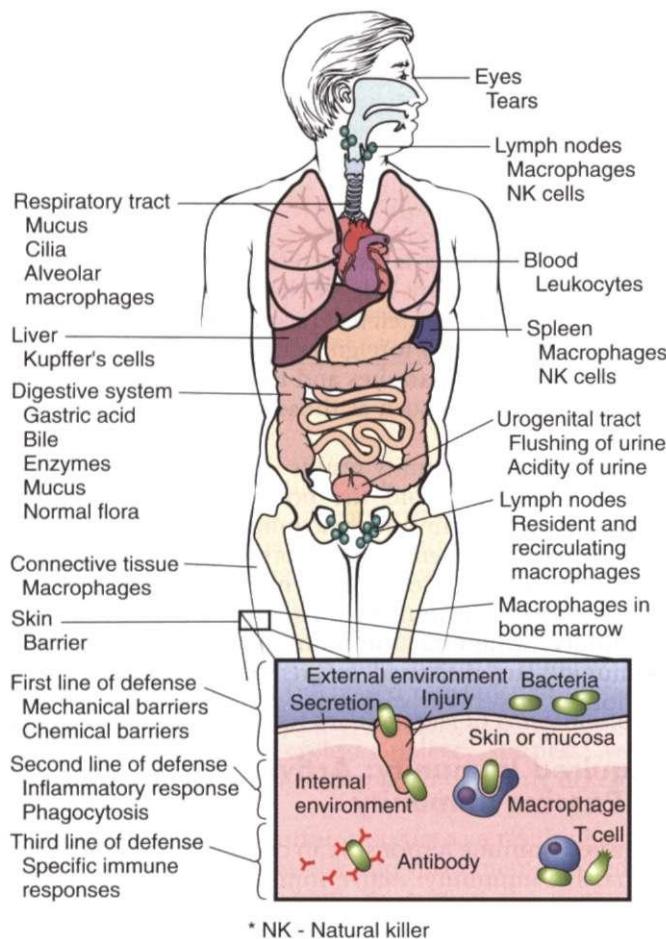


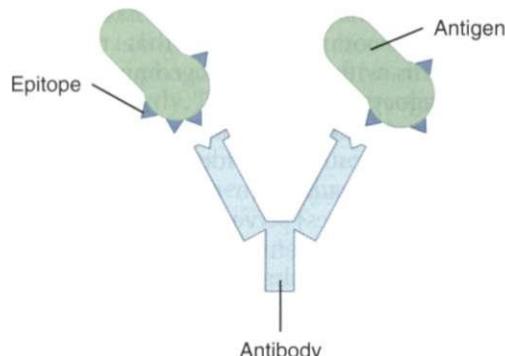
Table 7-1 Types of Acquired Immunity

Type*	Method Acquired	Length of Resistance
Active		
Natural	Natural contact and infection with the antigen (environmental exposure)	Usually permanent but may be temporary
Artificial	Inoculation of antigen (vaccination)	Usually permanent but may be temporary (occasional exceptions)
Passive		
Natural	Natural contact with antibody transplacentally (mother to fetus) or through colostrum and breast milk	Temporary
Artificial	Inoculation of antibody or antitoxin; immune serum globulin	Temporary

*Active immunity occurs when a person produces his or her own antibodies to the infecting organism; passive immunity occurs when the antibody is formed in another host and transferred to an individual.

Table 7-2 The Immune System and Its Response

Innate Immunity	Humoral	ACQUIRED IMMUNITY Cell Mediated
Nonspecific interaction with different antigens; lacks immunologic memory Exterior defenses: skin, mucosa, secretions, nasal hair, earwax Phagocytes (leukocytes): neutrophils (PMNs), monocytes/macrophages, eosinophils, basophils, mast cells, and platelets (inflammation) Soluble mediators: complement and IFNs (see Table 6-5); NK cells or large granular lymphocytes	Specific interaction with different antigens Mediated by antibody, present as serum globulins Antibodies are produced by plasma cells (differentiated form of B lymphocytes) Primary and secondary (memory) antibody response	Specific interaction with different antigens Mediated by T lymphocytes Secretion of lymphokines Production of helper T cells (CD4+), cytotoxic T cells (CD8+), and regulatory/suppressor T cells (CD+CD25+) Primary and secondary (memory) T-cell response

**Figure 7-2**

An antigen is recognized on the basis of shape. Epitopes protrude from the surface of an antigen and combine with the appropriate receptor of an antibody, much as a key fits a lock. For small antigens, the binding site on the antibody may be a pocket or cleft, but in most cases it more closely resembles an undulating surface.²³² (Reprinted from Black JM, Hawks JH, Keene AM: *Medical-surgical nursing: clinical management for positive outcomes*, ed 7, Philadelphia, 2005, Saunders.)

the immune response. Antibodies produced in response to an antigen are protein molecules structured in such a way that they only interact with the antigen that induced their synthesis, much as a key is made to fit a lock.

The Major Histocompatibility Complex

Since the basis of immunity depends on the immune cells' ability to distinguish self from nonself, all cells of the body contain specific cell surface markers or molecules that are as unique to that person as a fingerprint.

The immune system recognizes these cell markers and tolerates them as self; in other words, it produces self-tolerance. These cell markers are present on the surface of all body cells and are known as the major histocompatibility complex proteins. They were originally discovered on leukocytes and are commonly called *human leukocytic antigens (HLAs)*. The six specific HLAs within the major histocompatibility complex markers are HLA-A, HLA-B, and HLA-C, referred to as *class I antigens*, and HLA-DP, HLA-DQ, and HLA-DR, referred to as *class II antigens*.¹³⁶

Class 1 antigens are found on nucleated cells and platelets; class II antigens are found on monocytes, macrophages, B cells, activated T cells, vascular endothelial cells, Langerhans' (skin) cells, and dendritic (nerve) cells. There is a third class of antigens (class III) including certain complement proteins (C2, C4, and factor B).

Cell markers are essential for immune function. They not only determine which antigens an individual responds to and how strongly, but they also allow immune system cells to recognize and communicate with one another.

HLAs are inherited and can predispose or increase an individual's susceptibility to certain diseases (usually autoimmune) (see Table 40-20). Such diseases encompass many that affect the joints, endocrine glands, and skin, including rheumatoid arthritis, Graves' disease, psoriasis, and many others. Not all people with a certain HLA pattern develop the disease, but they have a greater probability for its development than does the general population.

Innate Immunity

The innate immune system consists of all the immune defenses that lack immunologic memory. A characteristic of innate responses is that they remain unchanged no matter how often the antigen is encountered. Innate immune responses use phagocytic cells (neutrophils, monocytes, and macrophages); cells that release inflammatory mediators (basophils, mast cells, and eosinophils); and natural killer (NK) cells. The molecular components of innate responses include complement, acute-phase proteins, and cytokines such as the interferons.⁶⁰

The innate immune response does not recognize every possible antigen but rather focuses on a few structures present in large groups of microorganisms. These structures are referred to as pathogen-recognition receptors.¹⁶⁸

A key cellular component of innate immunity and one of the most intensely studied components in the last decade is the interdigitating dendritic cell. Cells of this type (e.g., Langerhans' cells in skin) constantly but quietly endocytose extracellular antigens. Pattern recognition

receptors on these dendritic cells are a part of the innate immune response to differentiate between potentially harmful microorganisms and self-constituents and include toll-like receptors that sense a broad range of microbial products.⁶⁰

These types of receptors are specific for structures found exclusively in microbial pathogens (pathogen-associated molecular pattern). This differs from the adaptive immune system, which has a tremendous capacity to recognize almost any antigenic structure, but because antigen receptors are generated at random, they bind to antigens regardless of their origin—bacterial, environmental, or self.¹⁶⁸

Exterior Defenses

As a covering for the entire body (with the exception of any openings), the skin offers the first and best line of protection (see Fig. 7-1), which is clearly demonstrated in cases of significant burns when infection becomes a major problem. The body openings also offer their own unique protection such as lysozyme in tears that can kill bacteria, waxy secretions in the ear canal to prevent bacteria from advancing inside, nasal hair, stomach acid, and unfavorable rapid pH change at the gastro-duodenal junction for ingested organisms, protective low pH vaginal secretions, acidic urine, and so on.

When organisms enter the body by penetrating the epithelial surface of the respiratory, gastrointestinal (GI), or genitourinary tract, biochemical defenses offer additional protection in the form of soluble mediators such as complement and cytokines (particularly interferons), phagocytes that engulf and destroy foreign particles, and NK cells that attack and destroy virus-infected cells and tumor cells.

Phagocytes. Phagocytes are involved in nonspecific or innate immunity. These cells readily eat (ingest) microorganisms such as bacteria or fungi and kill them as a means of protecting the body against infection.

The two principal phagocytes are neutrophils and monocytes and are part of white blood cells (WBCs), or leukocytes. The five types of leukocytes are neutrophils, eosinophils, basophils, monocytes, and lymphocytes. Because of their granular appearance, neutrophils, eosinophils, and basophils are collectively referred to as *granulocytes*. Granulocytes are short lived (2 to 3 days) compared with monocytes and macrophages, which may live for months or years.

Phagocytes emigrate out of the blood and into the tissues in which an infection has developed, and each of these cell types has a specific phagocytic function in the immune system (see the section on Disorders of Leukocytes in Chapter 14). Neutrophils, eosinophils, basophils, and monocytes are classified as phagocytic leukocytes that function in nonspecific or innate immunity. A severe decrease in the blood level of these cells is the principal cause of susceptibility to infection in people treated with intensive radiotherapy or chemotherapy. These treatments suppress blood cell production in the marrow, resulting in deficiencies of these phagocytic cells.

Neutrophils, also referred to as polymorphonuclear cells (PMNs), derive from bone marrow and increase dramatically in number in response to infection and

inflammation. Neutrophils can directly kill invading organisms but may also damage host tissues. In the process of phagocytosis, bacteria or debris is engulfed and then digested by enzymes contained within the neutrophils (see Fig. 6-18; see also discussion of phagocytosis in Chapter 6 and Fig. 6-17). Neutrophils die after phagocytosis; the accumulation of dead neutrophils and phagocytosed bacteria contributes to the formation of pus.

Monocytes circulate in the blood, but when they migrate to tissues they mature into *macrophages*, which means "large eaters." The engulfment of a pathogen by a macrophage is an essential first step leading to a specific immune response. After neutrophils kill the invading organism and the process of phagocytosis has begun, macrophages appear to clear up the debris produced by the neutrophils and to kill any damaged but not dead bacteria or bacteria that are too large for neutrophils. Neutrophils and macrophages both have receptors for antibodies and complement so that the coating of microorganisms with antibodies, complement, or both enhances phagocytosis.³

After phagocytes digest the pathogens, antigenic material appears on their surface to identify them more specifically as foreign invaders. In this process, phagocytes (primarily macrophages) serve as antigen-presenting cells to introduce the pathogen to lymphocytes. The macrophage or antigen-presenting cell processes the pathogen and presents a small part of it, the epitope (see Fig. 7-2), to a specific cell of the immune system known as the *helper* or *inducer lymphocyte*, or T4 lymphocyte (also referred to as *CD4 lymphocyte*).

Microscopically, T lymphocytes appear identical, but they can be distinguished by means of distinctive molecules called *cluster designations* (*CDs*) located on their cell surface. For example, all mature T cells carry markers known as T2, T3, T5, and T7 (or CD2, CD3, CD5, and CD7). T4 (CD4) are the helper T cells, and T8 (CD8) are cytotoxic T cells. Another group of T lymphocytes are identified as NK cells for their ability to kill certain tumor cells and virus-infected cells without prior sensitization or activation.

To prompt the T4 lymphocyte to recognize the processed pathogen, the macrophage releases interleukin-1 (IL-1), a chemical messenger with many roles. In this way the macrophage processes the antigen and then signals the lymphocytes to stimulate the specific immune response.

Interleukins are one type of cytokine, a protein released by macrophages to trigger the immune response (see Cytokines later in this section). Some of the multiple functions of IL-1 include increasing the temperature set point in the hypothalamus; increasing serotonin in the brainstem and duodenum, causing sleep and nausea, respectively; stimulating the production of prostaglandins, leading to a decrease in the pain threshold, resulting in myalgias and arthralgias; increasing the synthesis of collagenases, resulting in the destruction of cartilage; and most importantly, kicking the T4 cells into action.

Macrophages also participate in the defense against tumor cells and secrete numerous molecules called *monokines* that assist in the immune and inflammatory

response. Stimulation of macrophages can boost the immune response.

Eosinophils are the next group of leukocytes that participate in the innate immunity process. Eosinophils are derived from bone marrow and multiply in both allergic disorders and parasitic infestations. When organisms are too large for neutrophils and macrophages, eosinophils get within close proximity of the invading organisms and release the contents of their granules to kill them.

Basophils are WBCs (leukocytes) that circulate in peripheral blood and function similarly to mast cells in allergic disorders. Basophils and mast cells are located close to blood vessels throughout the body and have similar functional characteristics; *mast cells* contain histamine that dilates blood vessels when released.

Mast cells are derived from stem cells and travel in the blood in such small numbers they are not recognized as blood cells. Arriving basophils and mast cells cause an increase in blood supply in the area where the bacteria or viral antigen is located. This increase in circulation also helps bring more phagocytes to the area, thus counteracting bacteria indirectly. The increased circulation is accompanied by the feeling of congestion during an allergic reaction; antihistamines work by neutralizing the histamines and reducing the excessive immune (allergic) response.

The role of erythrocytes and *platelets* in immune responses is sometimes overlooked, but because they have complement receptors, they play an important part in the clearance of immune complexes consisting of antigen, antibody, and components of the complement system.⁶⁰

Soluble (Inflammatory) Mediators

The complement system and interferons act as soluble inflammatory mediators along with phagocytes to destroy organisms that breach the first line of defense. The complement system consists of 20 serum proteins, which are key components in the acute inflammatory response designed to enhance immune function.

When activated, these proteins interact in a cascade-like process to assist immune cells by coating microorganisms so they can be more easily phagocytosed and to participate in bacterial lysis. In some cases the invading organisms are eliminated from the body. Sometimes the inflammation produced by the complement cascade (immune response) walls off the microorganism by forming, for example, a cyst or tubercle that protects the rest of the body from infection. (See the section on The Complement System in Chapter 6; also see Table 6-5.)

The second group of soluble mediators is the cytokines, especially interferons sometimes referred to as *biologic response modifiers*. They act as messengers, both within the immune system and between the immune system and other systems of the body, forming an integrated network that is highly involved in the regulation of immune responses.¹⁷¹

In addition to acting as messengers, some cytokines have a direct role in defense, such as the interferons. Interferons are produced by virally infected cells early in infection to limit the spread of the infection by protecting surrounding (noninfected) cells (interferons also inhibit

tumor growth). Once a cell becomes infected by a virus, certain genes are turned on in the cell that will produce these interferons that coat the surrounding cells and make them viral resistant.

Natural Killer Cells

NK cells are large granular lymphocytes that are neither T nor B lymphocytes. The function of NK cells is to kill viruses, other intracellular microbe-infected cells, and tumor cells. NK cells recognize targets by first binding to potential target cells followed by interaction between activating and inhibitory receptors with ligands available on the target, and then integrating signals transmitted by these receptors, which determines whether the NK cells will detach and move on or stay and respond. NK cells respond by releasing cytotoxic granules and by secreting cytokines (Fig. 7-3).¹⁴⁶

Acquired Immunity

To establish an infection, the pathogen must first overcome numerous surface barriers and the innate immune responses (see Fig. 7-1). In these cases, acquired immunity is tailored to recognize each different type of organism and kill it.

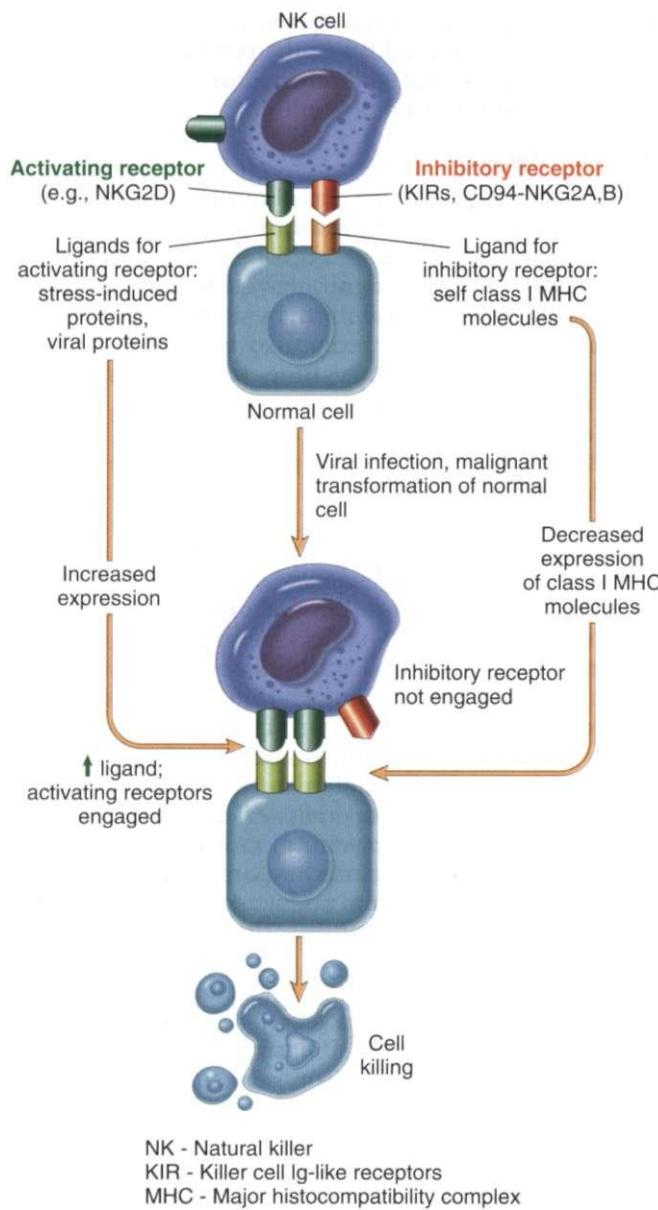
The two types of acquired immune responses that occur are *humoral immunity* (also called immunoglobulin-related immunity) and *cell-mediated immunity* (also referred to as T-cell immunity). Although these two responses are often discussed separately, they are two arms of the immune system and work together; failure in one can alter the effectiveness of the other. These two types of responses overlap and interact considerably, but the distinction is useful in understanding how the immune system is activated (Fig. 7-4).

The complexity of the cellular interactions that occur during acquired immune responses requires specialized microenvironments in which the relevant cells can collaborate efficiently. Because only a few lymphocytes are specific for any given antigen, T cells and B cells need to migrate throughout the body to increase the probability that they will encounter that particular antigen. In their travels, lymphocytes spend only about 30 minutes in the blood during each trip around the body.¹⁸² More specific information about T-cell function and migration is available.²⁵⁸

Acquired responses involve the proliferation of antigen-specific B and T cells, which occurs when the surface receptors of these cells bind to antigen and initiate the immune response involving immunoglobulins, antibodies, regulatory and suppressor T cells, and cytokines. The acquired immune system generates a highly diverse group of antigen receptors that allows the adaptive immune system to recognize virtually any antigen. However, the price for this diversity is the inability to distinguish foreign antigens from self-antigens.¹⁶⁸

Humoral Immunity

The humoral immune response is mediated by antibodies present in different body fluids or secretions, such as saliva, blood, or vaginal secretions. Antibodies produced by B lymphocytes are very effective against organisms that

**Figure 7-3**

Schematic representation of NK cell receptors and cell killing. NK cells express activating and inhibitory receptors; some examples of each are indicated. Normal cells are not killed because inhibitory signals from normal major histocompatibility complex class I molecules override activating signals. In tumor cells or virus-infected cells, there is increased expression of ligands for activating receptors and reduced expression or alteration of major histocompatibility complex molecules, which interrupts the inhibitory signals, allowing activation of NK cells and lysis of target cells. (Reprinted from Kumar V: *Robbins and Cotran: pathologic basis of disease*, ed 7, Philadelphia, 2005, Saunders.)

are free floating in the body that can be easily reached and neutralized. *B lymphocytes*, or B cells, are called such because they originate in the bone marrow and then circulate throughout the extracellular fluid.

The surface of B lymphocytes is coated with immunoglobulin, and each B cell has a receptor (an antibody) that can recognize a specific foreign substance or antigen. When this happens, B cells change into protein-synthesizing cells known as *plasma cells* and *memory B cells*.

Box 7-1**MAJOR FUNCTIONS OF IMMUNOGLOBULINS**

- Immunoglobulins directly attack antigens, destroying or neutralizing them through the processes of agglutination, precipitating the toxins out of solution, neutralizing antigenic substances, and lysing the organism's cell wall.
- Immunoglobulins activate the complement system.
- Immunoglobulins activate anaphylaxis by releasing histamine in tissue and blood.
- Immunoglobulins stimulate antibody-mediated hypersensitivity.

Globulins with antibody activity are referred to as *immunoglobulins*. Reprinted from Thompson JM, et al: *Mosby's clinical nursing*, ed 3, St Louis, 1993, Mosby.

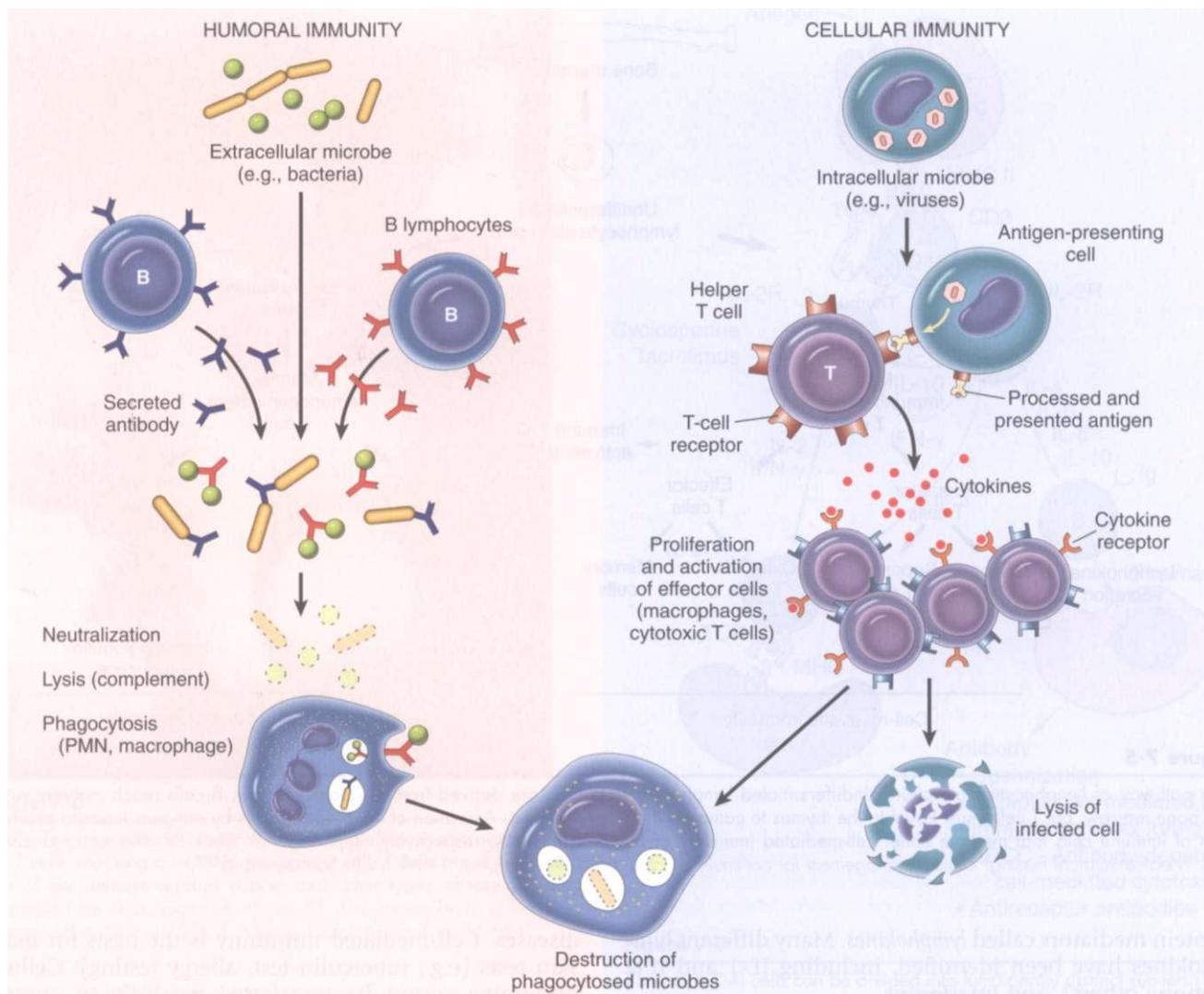
The plasma cell produces and secretes into body fluids a specific antibody to that antigen. Memory cells produced in connection with humoral immunity circulate among the blood, lymphoid system, and tissues for about 1 year or even longer. They are responsible for the more rapid and sustained (stronger) immune response that occurs with repeated exposure to the same antigen. This humoral response is particularly useful in fighting bacterial infections.

The B lymphocyte-plasma cell interaction is capable of producing five types of antibodies, or immunoglobulin (Ig), in response to specific antigens. Because of these antibodies the humoral immune response may be referred to as the *antibody immune response*. The five types of antibodies are IgG, IgM, IgA, IgD, and IgE; major functions of immunoglobulins are listed in Box 7-1.

IgM predominates in the primary or initial immune response and is the largest immunoglobulin; because of its size, it is found almost exclusively in the intravascular compartment. IgG is the major antibacterial and antiviral antibody and is the predominant immunoglobulin in blood; it is responsible for the protection of the newborn during the first 6 months of life and is the only immunoglobulin to cross the placenta. It is the major immunoglobulin synthesized during the secondary immune response (after IgM initially responds to foreign pathogens), conferring long-term or permanent immunity.

IgA defends external body surfaces, is the predominant immunoglobulin on mucous membrane surfaces, and is found in secretions such as saliva; breast milk (colostrum); urine; seminal fluid; tears; nasal fluids; and respiratory, GI, and genitourinary secretions.

IgD is the predominant antibody found on the surface of B lymphocytes, serves mainly as an antigen receptor, and may function in controlling lymphocyte activation or suppression. IgE is a primary factor in eliminating parasitic infections such as roundworms and is therefore significant in the immune responses of people in developing countries where adequate nutrition, hygiene, and primary medical care are lacking. IgE also functions during allergic reactions by activating the mast cells and releasing histamine in association with allergies, anaphylaxis, extrinsic asthma, and urticaria (hives). This response of IgE is a normal reaction but becomes excessive in people with allergies.

**Figure 7-4**

Humoral and cell-mediated immunity. (Reprinted from Kumar V: *Robbins and Cotran: pathologic basis of disease*, ed 7, Philadelphia, 2005, Saunders.)

The type of antibody produced depends on genetic variability, the specific antigenic stimulus, and whether it is a first or subsequent exposure to that antigen. The humoral immune response is more rapid than the cell-mediated response and is more often a factor in resistance to acute bacterial infections. Humoral immunity can be transmitted to another person, either by inoculation or by maternal transfer via placenta or breast milk. This transfer is called *passive immunity* (see Table 7-1).

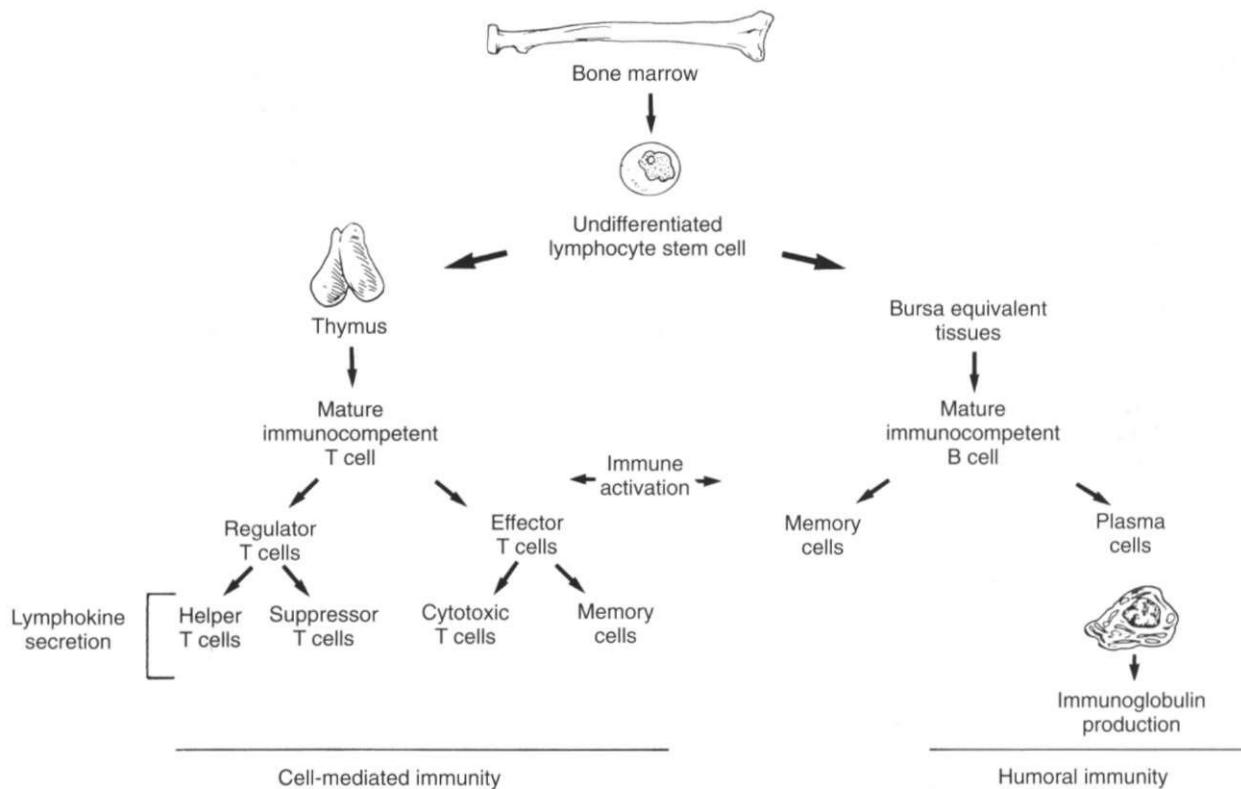
Cell-Mediated Immunity

Some organisms (all viruses and some bacteria) actually hide inside the cells where the antibodies cannot reach them. A second arm of the immune system (cell-mediated immunity or cellular immunity) with more specific cells (T lymphocytes) can recognize these hidden organisms, search them out, and destroy them on a cell-to-cell basis.

Lymphocytes originate from stem cells in the bone marrow and differentiate or mature into either B or T cells (Fig. 7-5; see also Fig. 21-6). The B cell (humoral immunity) is thought to mature and become immunocompetent in the bone marrow.

T lymphocytes, or T cells (cell-mediated immunity), are called such because the precursors of these cells start from the bone marrow but then mature in the thymus, located right behind the sternum, where it learns to discriminate self from nonself (see Fig. 7-8). Both T and B lymphocytes continuously circulate through blood, lymph, and lymph nodes.

After interaction with a specific antigen, the activated lymphocyte produces numerous additional lymphocytes called *sensitized T cells*. This T-cell subpopulation has three primary functions. The most numerous of the T cells, *helper T cells*, constituting 75% of all T cells, assist the B cells to mature and produce antibody by secreting

**Figure 7-5**

The pathway of lymphocyte maturation. Undifferentiated lymphocyte stem cells are derived from the bone marrow. B cells reach maturity within the bone marrow, but T cells must travel to the thymus to complete their development. Activation of either T or B cells by antigens leads to proliferation of immune cells that mediate either cell-mediated immunity or humoral immunity, respectively. (Reprinted from Black JM, Matassarin-Jacobs E, eds: *Medical-surgical nursing: clinical management for continuity of care*, ed 5, Philadelphia, 1997, W.B. Saunders, p 597.)

protein mediators called *lymphokines*. Many different lymphokines have been identified, including IL-1 and IL-2 (among others), and interferons.

Some of their functions include (1) helping B cells augment the production of antibodies, (2) activating macrophages and helping them destroy large bacteria, (3) helping other T lymphocytes (called *cytotoxic T cells*, or CD8 T cells) recognize and destroy virally infected cells, and (4) helping NK cells kill infected cells (Fig. 7-6).

Helper T cells (CD4 T cells) themselves can be categorized on the basis of their cytokinetic profiles into T-helper type 1 (T_h1) or T-helper type 2 (T_h2) cells. T_h1 produce interferon (IFN)- γ and tumor necrosis factor (TNF)- α and are important in assisting CD8 T-cell activation. T_h2 cells produce IL-4, IL-5, and IL-13 and drive B-cell activation and antibody generation (Fig. 7-7). HIV destroys or inactivates these helper T cells and leaves the body at risk for infectious agents such as cytomegalovirus (CMV).

The immune system also consists of regulatory/suppressor T cells (CD4+CD25+) that suppress activation of the immune system and prevent pathologic self-reactivity, or autoimmune disease. Immunosuppressive cytokines tumor growth factor- β and IL-10 have been implicated in regulatory T-cell function.²³³

Cell-mediated immunity is responsible for the rejection of transplanted tissue, delayed hypersensitivity reactions (e.g., contact dermatitis), and some autoimmune

diseases. Cell-mediated immunity is the basis for many skin tests (e.g., tuberculin test, allergy testing). Cellular immunity cannot be transferred passively to another person.

Clinical conditions that compromise the cell-mediated T-lymphocyte function include HIV infection and AIDS, with a progressive reduction in T_4 lymphocytes over the duration of the illness. Other conditions known to affect T-cell number or responsiveness include stress, malignancy, general anesthesia, thermal injury, surgery, diabetes, and immunosuppressive drugs (including corticosteroids). Older adults (aged 65 years and older) show reduced numbers of circulating lymphocytes, and malnourished people show defects in most tests of T-cell function.

Summary of the Immune Response

Immune responses are initiated according to the type of antigen presented. Adaptive immune responses are generated in the lymph nodes, spleen, and mucosa-associated tissue, referred to as the *secondary lymphoid tissues*. For example, blood-borne antigens usually initiate responses in the spleen, whereas responses to microorganisms in tissues are generated in local lymph nodes.

Most pathogens are encountered after they are inhaled or ingested. Antigens entering the body through mucosal surfaces activate cells in the mucosa-associated lymphoid

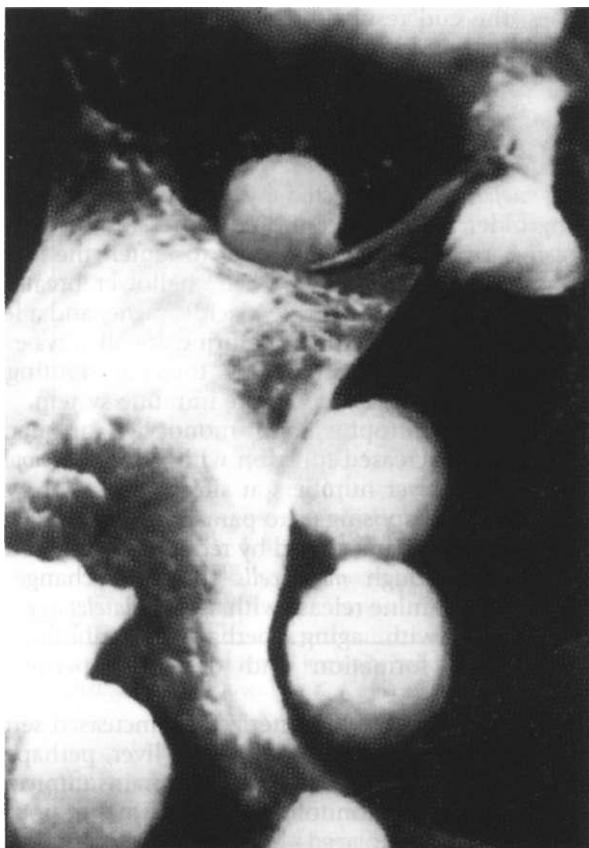


Figure 7-6

T cells. The blue spheres seen in this scanning electron microscope view are T cells attacking a much larger cancer cell. T cells are a significant part of our defense against cancer and other types of foreign cells. [Reprinted from Thibodeau GA, Patton KT: *The human body in health & disease*, ed 4, St Louis, 2005, Mosby. Courtesy James T. Barrett.]

tissues, including the tonsils, adenoids, and Peyer's patches (Fig. 7-8).⁶¹

Keeping in mind that innate immunity and acquired immunity function in tandem together (Fig. 7-9), and that within the acquired immune system humoral immunity and cellular immunity are also working simultaneously, a variety of immune responses can occur when an extracellular pathogen attempts to invade the body.

If the pathogenic organism gets past the first line of defense (innate immunity) and is presented to the body, the following can happen: (1) a B lymphocyte recognizes it as a bacteria and produces antibodies that bind to it and neutralize it (humoral response); (2) a T lymphocyte recognizes it as a bacteria and produces cytokines to help the macrophages lyse and phagocytose the bacteria (cell-mediated response); (3) in the case of a virus, a cytotoxic T lymphocyte can recognize the cell and destroy it (cell-mediated response); and (4) the complement system can recognize the invading organism and destroy it (innate immunity).

In some instances, innate and acquired immunity interact with each other, such as when bacteria enter the body and the B lymphocyte recognizes it and produces specific antibodies (acquired immunity). Examples of this interaction include (1) antibodies (acquired immu-

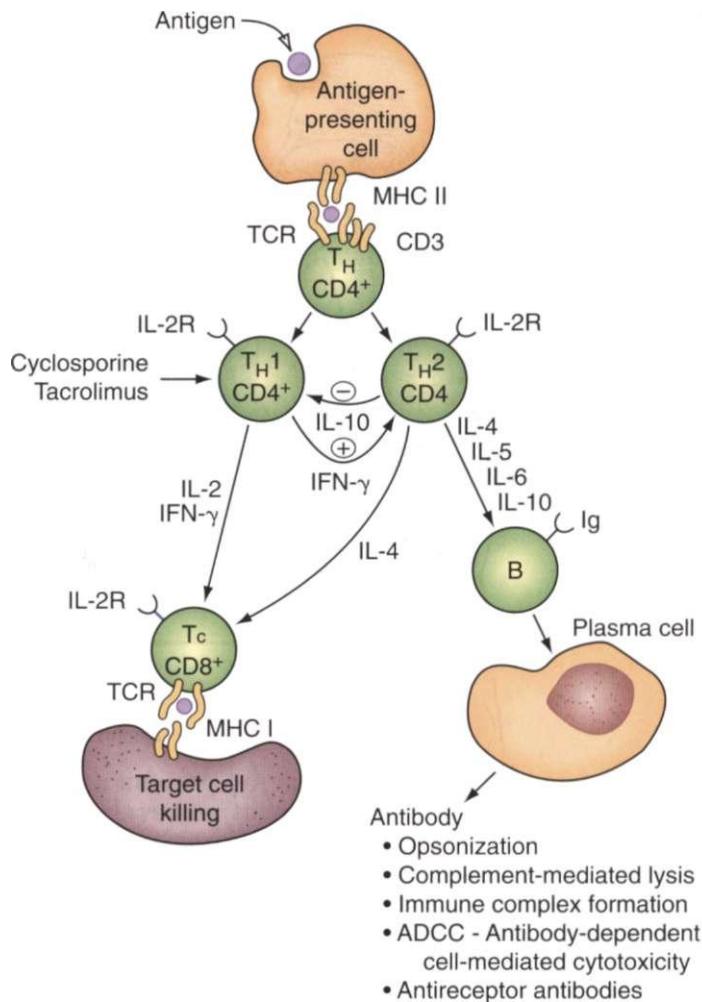


Figure 7-7

T-helper (CD4+) cells can be divided into functionally distinct subsets (T_{H1} and T_{H2}) based on their cytokine secretion profiles. Cytokines secreted by T_{H1} cells play a key role in cell-mediated immunity, whereas those produced by T_{H2} cells are important in B-cell stimulation and antibody production. An important feature of the T_{H1}/T_{H2} cell paradigm is that cross-regulation of function between T_{H1} and T_{H2} cells occurs. Thus, for example, IFN- γ stimulates T_{H2} cells, whereas IL-10 inhibits T_{H1} cells. Cyclosporine and tacrolimus (FK-506) are potent inhibitors of IL-2 and IFN- γ production by T_{H1} cells. There is evidence, however, that they may spare IL-10 (cytokine synthesis inhibitory factor) production by T_{H2} cells. (Reprinted from Townsend CM: *Sabiston textbook of surgery*, ed 17, Philadelphia, 2005, Saunders.)

nity) binding to the bacteria, coating it, and making it available for phagocytosis by the phagocytes of the innate immune system; (2) bacteria being recognized by the B lymphocyte (acquired immunity) and coated with the antibody produced by the lymphocyte, with the complement (innate immunity) recognizing it and destroying it; (3) activation of cytotoxic T lymphocytes (acquired immunity) and NK cells (innate immunity), resulting in a direct attack on cells that have been transformed by a virus or a malignant process; and (4) the foreign invader being recognized by a T lymphocyte (from the acquired immune system), which then produces hormones (lymphokines) that help the macrophage (from the innate immune system) to destroy it.

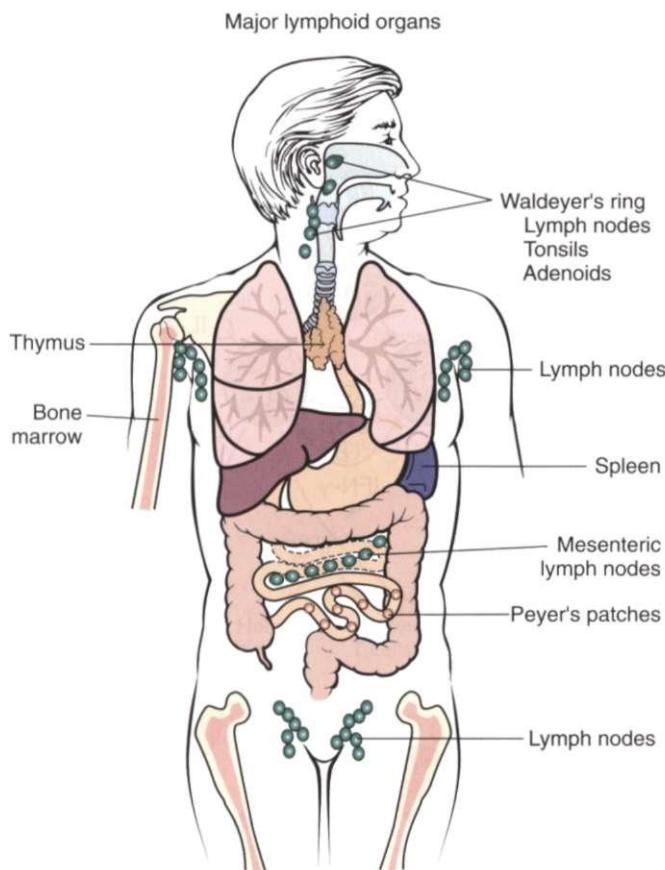


Figure 7-8

Immune system. Organs of the immune system are referred to as *lymphoid tissues*. The bone marrow and thymus are referred to as primary lymphoid organs since these organs are the central sites of all cells of the immune system and B- and T-cell differentiation, respectively. Immature lymphocytes migrate through the central lymphoid tissues and later reside as mature lymphocytes in the peripheral or secondary lymphoid tissues (e.g., lymph nodes, Peyer's patches, tonsils, spleen, mucosa-associated lymphoid tissue, or MALT from the mouth to the rectum). (Reprinted from Damjanov I: *Pathology for the health professions*, ed 3, Philadelphia, 2006, Saunders.)

Dysfunction of the immune system can contribute to diseases. For example, two general types of genetic alterations could lead to immunologic abnormalities: mutations that inactivate the receptors or signaling molecules involved in innate immune recognition and mutations that render them active all the time. The first type of mutation would be expected to result in various types of immunodeficiencies. The second type of mutation triggers antiinflammatory reactions and thereby contributes to a variety of conditions with an inflammatory component (e.g., asthma, allergy, arthritis, autoimmune diseases).¹⁶⁸

AGING AND THE IMMUNE SYSTEM

Aging is accompanied by immune dysregulation as immune function declines with increasing age; this is described as the *oxidative (free radical) theory of aging* (see the section Cellular Aging in Chapter 6). Changes are observed in both the innate and acquired immunity

defenses; the end result is reduced resistance to pathogens and increased incidence of tumors and autoimmune disorders.

Changes in Innate Immunity

Exterior defenses are affected by thinning of the skin, making older adults more prone to pressure ulcers and increasing openings for bacteria to enter the body. Decreased acidity of the GI tract, shallower breathing with decreased air exchange, less-acidic urine, and a less-elastic bladder that retains more urine are all ways exterior defenses are affected by aging, thus contributing to reduced effectiveness of the innate immune system.

Phagocytes (neutrophils and monocytes or macrophages) show decreased function with aging. *Eosinophils* accumulate in fewer numbers at sites of infection with age, perhaps predisposing us to parasitic infections as we age. *Basophils* are characterized by reduced degranulation with aging, although *mast cells* show no change in numbers or histamine release with aging. *Platelet aggregation* increases with aging, perhaps contributing to increased clot formation and decreased peripheral circulation.

Soluble mediators are characterized by increased serum levels of complement produced by the liver, perhaps as a compensatory mechanism, but this remains unproved. A decreased production of interferons by monocytes occurs with increasing age.

NK cell (large granular lymphocytes) cytotoxicity is impaired, as well as production of cytokines by activated NK cells.⁹⁴

Changes in Acquired Immunity

Decline in humoral and cell-mediated immunity occurs with aging. Older adults have particular difficulty in mounting protective immune responses to newly encountered antigens, such as West Nile virus. Such responses depend on naive T and B cells, and aging is associated with a decline in their production.

Thymic involution and T- and B-lineage-specific defects in early lymphoid development in the bone marrow appear to explain this decline. However, it cannot be assumed that changes in the lymphoid compartment are entirely responsible for the poor quality of immune responses in the older adult.

The quality of the immune response may be associated with other cellular changes, such as defective cytoskeletal assembly and hyperglycosylation of proteins, telomerase shortening, replicative senescence, and failed susceptibility to apoptosis.

In human beings, CD8 T-cell expansions are often accompanied by loss of CD28, an important receptor of accessory signals during T-cell activation. Similar changes are seen in CD4 T-cell population with dysregulation of cytokine production.³¹

Although B-cell function appears relatively intact, there is a decline in antibody production that may be due to inappropriate or insufficient T-cell help. While this change in antibody is reflected in a decline in the level of antibody upon immunization, there may also be decreases