CHAPTER

9

Inflammation, Tissue Repair, and Fever

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The ability of the body to sustain injury, resist attack by microbial agents, and repair damaged tissue is dependent upon the inflammatory reaction, the immune system response, and tissue repair and wound healing. Although the effects of inflammation are often viewed as undesirable because they are unpleasant and cause discomfort, the process is essentially a beneficial one that allows a person to live with the effects of everyday stress. Without the inflammatory response, wounds would not heal, and minor infections would become overwhelming. Inflammation also produces undesirable effects. For example, the crippling effects of rheumatoid arthritis result from chronic inflammation.

This chapter focuses on the manifestations of acute and chronic inflammation, tissue repair and wound healing, and temperature regulation and fever. The immune response is discussed in Chapter 8.

THE INFLAMMATORY RESPONSE

Inflammation is the reaction of vascularized tissue to local injury. The causes of inflammation are many and varied. Inflammation commonly results because of an immune response to infectious microorganisms. Other causes of inflammation are trauma, surgery, caustic chemicals, extremes of heat and cold, and ischemic damage to body tissues.

Inflammatory conditions are named by adding the suffix *-itis* to the affected organ or system. For example, *appendicitis* refers to inflammation of the appendix, *pericarditis* to inflammation of the pericardium, and *neuritis* to inflammation of a nerve. More descriptive expressions of the inflammatory process might indicate whether the process was acute or chronic and what type of exudate was formed (*e.g.*, acute fibrinous pericarditis).

Acute Inflammation

Acute inflammation is the early (almost immediate) response to injury. It is nonspecific and may be evoked by any injury short of one that is immediately fatal. It is usually of short duration and typically occurs before the immune response becomes established and is aimed primarily at removing the injurious agent and limiting the extent of tissue damage.

Cardinal Signs

The classic description of acute inflammation has been handed down through the ages. In the first century AD, the Roman physician Celsus described the local reaction of injury in terms that have come to be known as the *cardinal signs* of inflammation. These signs are *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain). In the second century AD, the Greek physician Galen added a fifth cardinal sign, *functio laesa*, or loss of function. These signs and symptoms, which are apparent when inflammation occurs on the surface of body, may not be present when internal organs are involved. For example, inflammation of the lung does not usually cause pain unless the pleura, where pain receptors are located, is affected. In addition, an increase in heat is uncommon in inflammation involving internal organs, where tissues are normally maintained at core temperature.

In addition to the cardinal signs that appear at the site of injury, systemic manifestations (*e.g.*, fever) may occur as chemical mediators produced at the site of inflammation gain entrance to the circulatory system. The constellation of systemic manifestations that may occur during an acute inflammatory response is known as the *acute-phase response* (to be discussed).

The manifestation of acute inflammation can be divided into two categories: vascular and cellular responses.[1,2,3] At the biochemical level, many of the responses that occur during acute inflammation are associated with the release of chemical mediators.

The Vascular Response

The vascular, or hemodynamic, changes that occur with inflammation begin almost immediately after injury and are initiated by a momentary constriction of small blood vessels in the area. This vasoconstriction is followed rapidly by vasodilation of the arterioles and venules that supply the area (Fig. 9-1). As a result, the area becomes congested, causing the redness (erythema) and warmth associated with acute inflammation. Accompanying this hyperemic vascular response is an increase in capillary permeability, which causes fluid to move into the tissues and cause swelling, pain, and impaired function. The exudation or movement of the fluid out of the capillaries and into the tissue spaces dilutes the offending agent. As fluid moves out of the capillaries, stagnation of flow and clotting of blood in the small capillaries occurs at the site of injury. This aids in localizing the spread of infectious microorganisms.

Depending on the severity of injury, the vascular changes that occur with inflammation follow one of three patterns of response.[3] The first is an immediate transient response, which occurs with minor injury. The second is an immediate sustained response, which occurs with more serious injury and continues for several days and damages the vessels in the area. The third type of response is a delayed hemodynamic response, which involves an increase in capillary permeability that occurs 4 to 24 hours after injury. A delayed response often accompanies radiation types of injuries, such as sunburn.

KEY CONCEPTS

THE INFLAMMATORY RESPONSE

- Inflammation represents the response of body tissue to immune reactions, injury, or ischemic damage.
- The classic response to inflammation includes redness, swelling, heat, pain or discomfort, and loss of function.
- The manifestations of an acute inflammatory response can be attributed to the immediate vascular changes that occur (vasodilation and increased capillary permeability), the influx of inflammatory cells such as neutrophils, and, in some cases, the widespread effects of inflammatory mediators, which produce fever and other systemic signs and symptoms.
- The manifestations of chronic inflammation are due to infiltration with macrophages, lymphocytes, and fibroblasts, leading to persistent inflammation, fibroblast proliferation, and scar formation.

The Cellular Stage

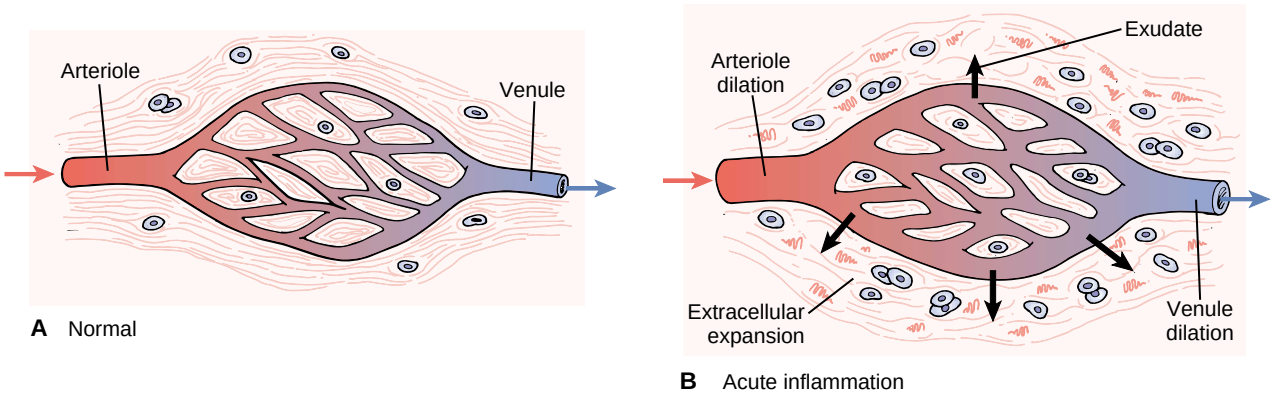
The cellular stage of acute inflammation is marked by movement of phagocytic white blood cells (leukocytes) into the area of injury. Two types of leukocytes participate in the acute inflammatory response—the granulocytes and monocytes.

Granulocytes. Granulocytes are identifiable because of their characteristic cytoplasmic granules. These white blood cells have distinctive multilobed nuclei. The granulocytes are divided into three types (*i.e.*, neutrophils, eosinophils, and basophils) according to the staining properties of the granules (Fig. 9-2).

The *neutrophil* is the primary phagocyte that arrives early at the site of inflammation, usually within 90 minutes of injury. The neutrophils' cytoplasmic granules contain enzymes and other antibacterial substances that are used in destroying and degrading the engulfed particles. They also have oxygen-dependent metabolic pathways that generate toxic oxygen (*e.g.*, hydrogen peroxide) and nitrogen (*e.g.*, nitric oxide) products. Because these white blood cells have nuclei that are divided into three to five lobes, they often are called *polymorphonuclear neutrophils (PMNs)* or *segmented neutrophils (segs)*. The neutrophil count in the blood often increases greatly during the inflammatory process, especially with bacterial infections. After being released from the bone marrow, circulating neutrophils have a life span of only approximately 10 hours and therefore must be constantly replaced if their numbers are to remain adequate. This requires an increase in circulating white blood cells, a condition called *leukocytosis*. With excessive demand for phagocytes, immature forms of neutrophils are released from the bone marrow. These immature cells often are called *bands* because of the horseshoe shape of their nuclei.

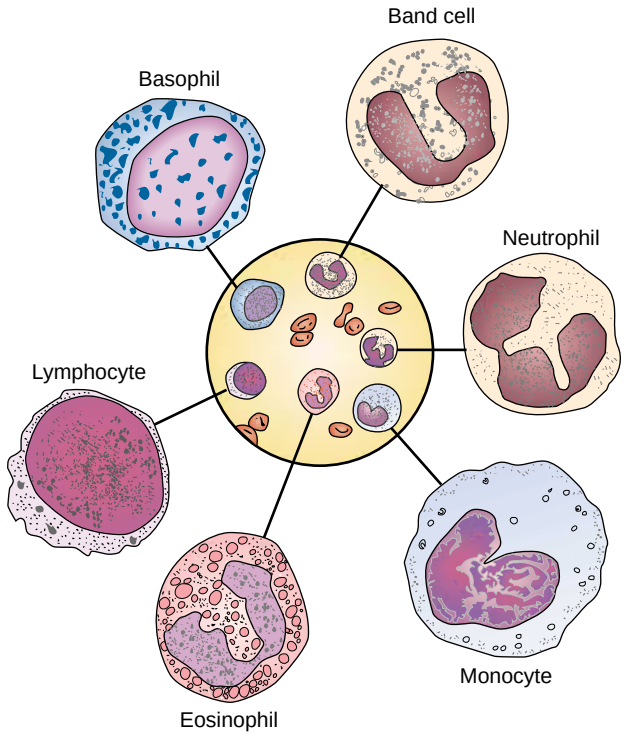
The cytoplasmic granules of the *eosinophils* stain red with the acid dye eosin. These granulocytes increase in the blood during allergic reactions and parasitic infections. The granules of eosinophils contain a protein that is highly toxic to large parasitic worms that cannot be phagocytized. They also regulate inflammation and allergic reactions by controlling the release of specific chemical mediators during these processes.

The granules of the *basophils* stain blue with a basic dye. The granules of these granulocytes contain histamine and other



■ **FIGURE 9-1** ■ Vascular phase of acute inflammation. (**A**) Normal capillary bed. (**B**) Acute inflammation with vascular dilation causing increased redness (erythema) and heat (calor), movement of fluid into the interstitial spaces (swelling), extravasation of plasma proteins into the extracellular spaces (exudate), and emigration of leukocytes.

bioactive mediators of inflammation. The basophils are involved in producing the symptoms associated with inflammation and allergic reactions. The mast cell, which is widely distributed in connective tissues throughout the body, is very similar in many of its properties to the basophil. It can participate in acute and chronic inflammatory responses.[2] Sensitized mast cells, which are "armed" with IgE, play a central role in allergic and hypersensitivity responses (see Chapter 10). They also may play a role in parasitic infections. Mast cells can also elaborate tumor necrosis factor (TNF), thereby participating in chronic inflammatory responses.



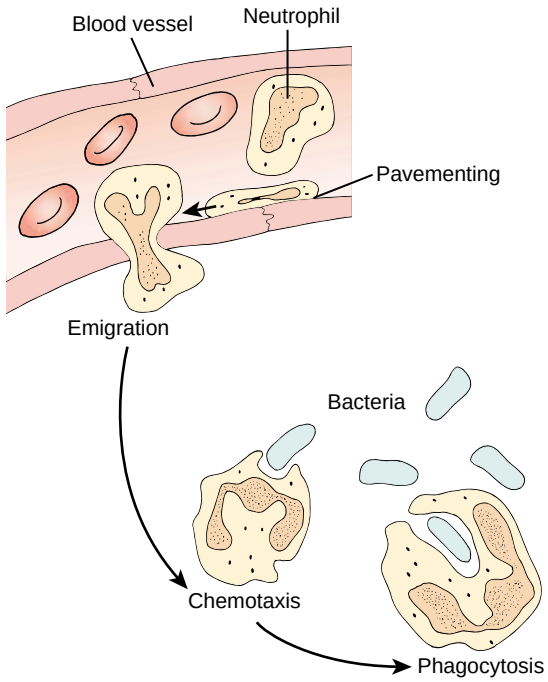
■ **FIGURE 9-2** ■ White blood cells.

Mononuclear Phagocytes. The monocytes are the largest of the white blood cells and constitute 3% to 8% of the total blood leukocytes. The circulating life span of the monocyte is three to four times longer than that of the granulocytes, and these cells survive for a longer time in the tissues. These longer-lived phagocytes help to destroy the causative agent, aid in the signaling processes of specific immunity, and serve to resolve the inflammatory process.

The monocytes, which migrate in increased numbers into the tissues in response to inflammatory stimuli, mature into macrophages. Within 24 hours, mononuclear cells arrive at the inflammatory site, and by 48 hours, monocytes and macrophages are the predominant cell types. The macrophages engulf larger and greater quantities of foreign material than do the neutrophils. They also migrate to the local lymph nodes to prime specific immunity. These leukocytes play an important role in chronic inflammation, where they can surround and wall off foreign material that cannot be digested.

Cellular Response. The sequence of events in the cellular response to inflammation includes: (1) pavementing, (2) emigration, (3) chemotaxis, and (4) phagocytosis (Fig. 9-3). During the early stages of the inflammatory response, fluid leaves the capillaries, causing blood viscosity to increase. The release of chemical mediators (*i.e.*, histamine, leukotrienes, and kinins) and cytokines affects the endothelial cells of the capillaries and causes the leukocytes to increase their expression of adhesion molecules. As this occurs, the leukocytes slow their migration and begin to marginate, or move to and along the periphery of the blood vessels.

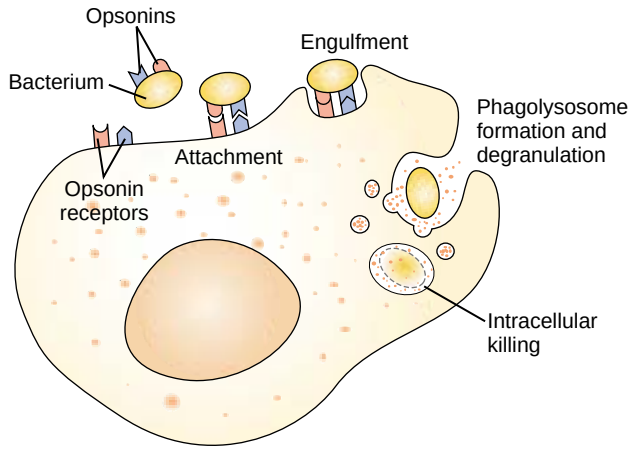
Emigration is a mechanism by which the leukocytes extend pseudopodia, pass through the capillary walls by ameboid movement, and migrate into the tissue spaces. The emigration of leukocytes also may be accompanied by an escape of red blood cells. Once they have exited the capillary, the leukocytes wander through the tissue guided by secreted cytokines (chemokines; interleukin [IL]-8), bacterial and cellular debris, and complement fragments (C3a, C5a). The process by which leukocytes migrate in response to a chemical signal is called *chemotaxis*. The positive movement up the



■ **FIGURE 9-3** ■ Cellular phase of acute inflammation. Neutrophil margination, pavementing, chemotaxis, and phagocytosis.

concentration gradient of chemical mediators to the site of injury increases the probability of a sufficiently localized cellular response.

During the next and final stage of the cellular response, the neutrophils and macrophages engulf and degrade the bacteria and cellular debris in a process called *phagocytosis*. Phagocytosis involves three distinct steps: (1) adherence plus opsonization, (2) engulfment, and (3) intracellular killing (see Fig. 9-4). Contact of the bacteria or antigen with the phagocyte cell membrane is essential for trapping the agent and triggering the final steps of phagocytosis. If the antigen is coated with antibody or complement, its adherence is increased because of binding to complement. This process of enhanced binding of an antigen caused by antibody or complement is called *opsonization* (Chapter 8). Engulfment follows the recognition of the agent as foreign. Cytoplasmic extensions (pseudopods) surround and enclose the particle in a membrane-bounded phagocytic vesicle or phagosome. In the cell cytoplasm, the phagosome merges with a lysosome containing antibacterial molecules and enzymes that can digest the microbe.



■ **FIGURE 9-4** ■ Phagocytosis of a particle (*e.g.*, bacterium): opsonization, attachment, engulfment, and intracellular killing.

Intracellular killing of pathogens is accomplished through several mechanisms, including enzymes, defensins, and toxic oxygen and nitrogen products produced by oxygen-dependent metabolic pathways. The metabolic burst pathways that generate toxic oxygen and nitrogen products (*i.e.*, nitric oxide, peroxyonitrites, hydrogen peroxide, and hypochlorous acid) require oxygen and metabolic enzymes such as myeloperoxidase, NADPH oxidase, and nitric oxide synthetase. Individuals born with genetic defects in some of these enzymes have immunodeficiency conditions that make them susceptible to repeated bacterial infection.

Inflammatory Mediators

Although inflammation is precipitated by injury, its signs and symptoms are produced by chemical mediators. Mediators can be classified by function: those with vasoactive and smooth muscle-constricting properties such as histamine, prostaglandins, leukotrienes, and platelet-activating factor; chemotactic factors such as complement fragments and cytokines; plasma proteases that can activate complement and components of the clotting system; and reactive molecules and cytokines liberated from leukocytes, which when released into the extracellular environment can damage the surrounding tissue. Table 9-1 describes some chemical mediators and their major impact on inflammation.

Histamine. Histamine is widely distributed throughout the body. It is found in high concentration in platelets, basophils, and mast cells. Histamine causes dilation and increased permeability of capillaries. It is one of the first mediators of an inflammatory response. Antihistamine drugs inhibit this immediate, transient response.

Plasma Proteases. The plasma proteases consist of the kinins, activated complement proteins, and clotting factors. One kinin, bradykinin, causes increased capillary permeability and pain. The clotting system (see Chapter 12) contributes to the vascular phase of inflammation, mainly through fibrinopeptides that are formed during the final steps of the clotting process.

Prostaglandins. The prostaglandins are ubiquitous, lipid-soluble molecules derived from arachidonic acid, a fatty acid liberated from cell membrane phospholipids. Several prostaglandins are synthesized from arachidonic acid through the cyclooxygenase metabolic pathway (Fig. 9-5). Prostaglandins contribute to vasodilation, capillary permeability, and the pain and fever that accompany inflammation. The stable prostaglandins (PGE_1 and PGE_2) induce inflammation and potentiate the effects of histamine and other inflammatory mediators. The prostaglandin thromboxane A_2 promotes platelet aggregation and vasoconstriction. Aspirin and the nonsteroidal

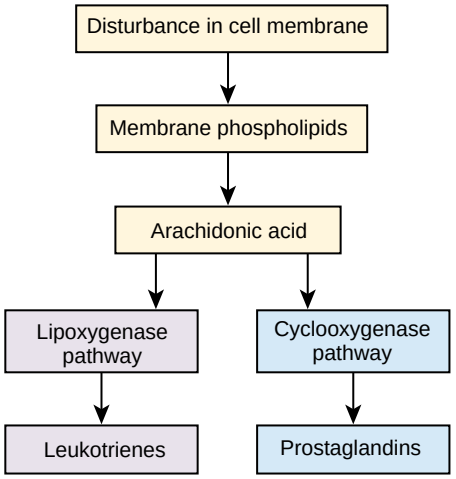
TABLE 9-1 Signs of Inflammation and Corresponding Chemical Mediator

Inflammatory Response	Chemical Mediator
Swelling, redness, and tissue warmth (vasodilation and increased capillary permeability)	Histamine, prostaglandins, leukotrienes, bradykinin, platelet-activating factor
Tissue damage	Lysosomal enzymes and products released from neutrophils, macrophages, and other inflammatory cells
Chemotaxis	Complement fragments
Pain	Prostaglandins Bradykinin
Fever	Interleukin-1 and interleukin-6
Leukocytosis	Tumor necrosis factor and interleukin-8

anti-inflammatory drugs (NSAIDs) reduce inflammation by inactivating the first enzyme in the cyclooxygenase pathway for prostaglandin synthesis.

Leukotrienes. Like the prostaglandins, the leukotrienes are formed from arachidonic acid, but through the lipoxygenase pathway (see Fig. 9-5). Histamine and leukotrienes are complementary in action in that they have similar functions. Histamine is produced rapidly and transiently while the more potent leukotrienes are being synthesized. Leukotrienes C4 and D4 are recognized as the primary components of the *slow-reacting substance of anaphylaxis* (SRS-A) that causes slow and sustained constriction of the bronchioles and is an important inflammatory mediator in bronchial asthma and anaphylaxis. The leukotrienes also have been reported to affect the permeability of the postcapillary venules, the adhesion properties of endothelial cells, and the chemotaxis and extravascularization of neutrophils, eosinophils, and monocytes.

Platelet-Activating Factor. Platelet-activating factor (PAF), which is generated from a complex lipid stored in cell membranes, affects a variety of cell types and induces platelet aggregation. It activates neutrophils and is a potent eosinophil chemoattractant. When injected into the skin, PAF causes a wheal-and-flare reaction and the leukocyte infiltrate characteristic of immediate hypersensitivity reactions. When inhaled, PAF causes bronchospasm, eosinophil infiltration, and nonspecific bronchial hyperreactivity.



■ **FIGURE 9-5** ■ The cyclooxygenase and lipoxygenase pathways.

Chronic Inflammation

Acute infections usually are self-limiting and rapidly controlled by the host defenses. In contrast, chronic inflammation is self-perpetuating and may last for weeks, months, or even years. It may develop during a recurrent or progressive acute inflammatory process or from low-grade, smoldering responses that fail to evoke an acute response.

Characteristic of chronic inflammation is an infiltration by mononuclear cells (macrophages) and lymphocytes, instead of the influx of neutrophils commonly seen in acute inflammation. Chronic inflammation also involves the proliferation of fibroblasts instead of exudates. As a result, the risk of scarring and deformity usually is considered greater than in acute inflammation. Agents that evoke chronic inflammation typically are low-grade, persistent irritants that are unable to penetrate deeply or spread rapidly. Among the causes of chronic inflammation are foreign bodies such as talc, silica, asbestos, and surgical suture materials. Many viruses provoke chronic inflammatory responses, as do certain bacteria, fungi, and larger parasites of moderate to low virulence. Examples are the tubercle bacillus, the treponema of syphilis, and the actinomyces. The presence of injured tissue such as that surrounding a healing fracture also may incite chronic inflammation. Immunologic mechanisms are thought to play an important role in chronic inflammation. The two patterns of chronic inflammation are a nonspecific chronic inflammation and granulomatous inflammation.

Nonspecific Chronic Inflammation

Nonspecific chronic inflammation involves a diffuse accumulation of macrophages and lymphocytes at the site of injury. Ongoing chemotaxis causes macrophages to infiltrate the inflamed site, where they accumulate because of prolonged survival and immobilization. These mechanisms lead to fibroblast proliferation, with subsequent scar formation that in many cases replaces the normal connective tissue or the functional parenchymal tissues of the involved structures. For example, scar tissue resulting from chronic inflammation of the bowel causes narrowing of the bowel lumen.

Granulomatous Lesions

A granulomatous lesion results from chronic inflammation. A *granuloma* typically is a small, 1- to 2-mm lesion in which there is a massing of macrophages surrounded by lymphocytes. These modified macrophages resemble epithelial cells and sometimes are called *epithelioid cells.* Like other macrophages, these epithelioid cells are derived originally from blood monocytes. Granulomatous inflammation is associated with foreign bodies such as splinters, sutures, silica, and asbestos and with microorganisms that cause tuberculosis, syphilis, sarcoidosis, deep fungal infections, and brucellosis. These types of agents have one thing in common: they are poorly digested and usually are not easily controlled by other inflammatory mechanisms. The epithelioid cells in granulomatous inflammation may clump in a mass (granuloma) or coalesce, forming a large, multinucleated giant cell that attempts to surround the foreign agent (Fig. 9-6). A dense membrane of connective tissue eventually encapsulates the lesion and isolates it.

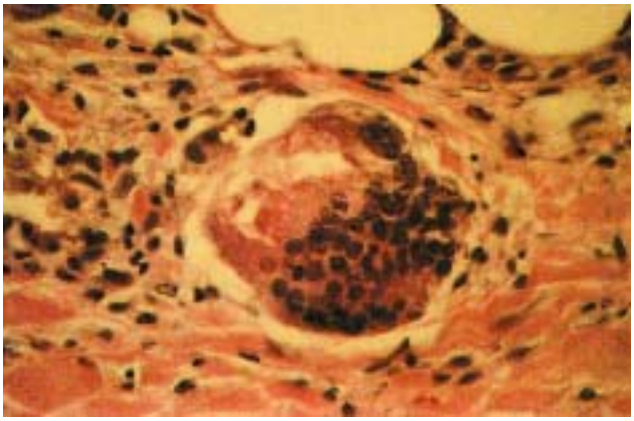
A *tubercle* is a granulomatous inflammatory response to *Mycobacterium tuberculosis* infection. Peculiar to the tuberculosis granuloma is the presence of a caseous (cheesy) necrotic center.

Local Manifestations of Inflammation

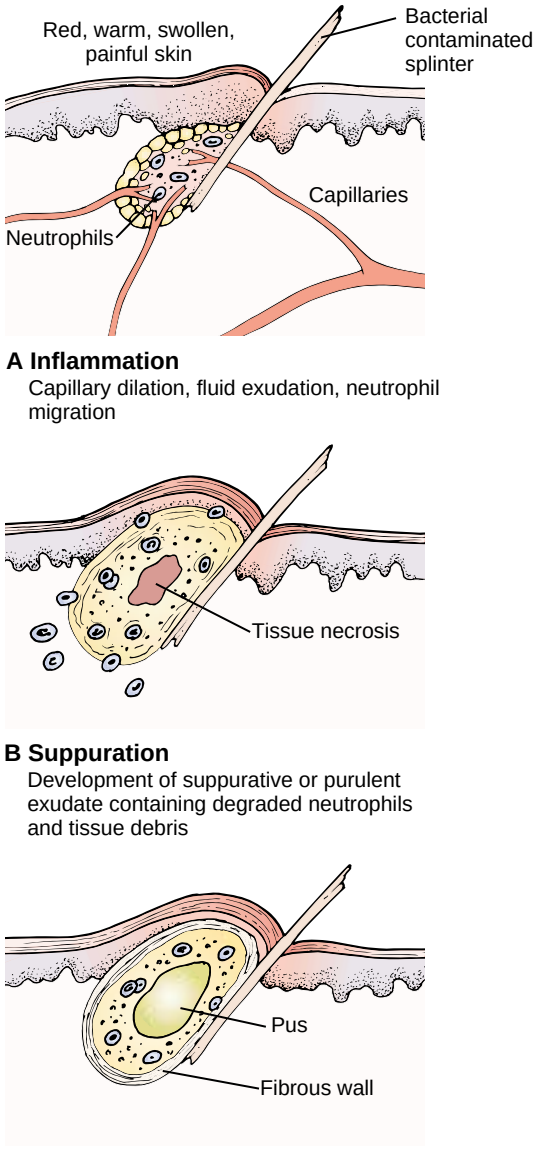
The local manifestations of acute and chronic inflammation are dependent upon its cause and the particular tissue involved. These manifestations can range from swelling and the formation of exudates to abscess formation or ulceration.

Characteristically, the acute inflammatory response involves production of exudates. These exudates vary in terms of fluid, plasma proteins, and cell count. Acute inflammation can produce serous, hemorrhagic, fibrinous, membranous, or purulent exudates. Inflammatory exudates often are composed of a combination of these types. *Serous exudates* are watery fluids low in protein content that result from plasma entering the inflammatory site. *Hemorrhagic exudates* occur when there is severe tissue injury that causes damage to blood vessels or when there is significant leakage of red cells from the capillaries. *Fibrinous exudates* contain large amounts of fibrinogen and form a thick and sticky meshwork, much like the fibers of a blood clot. *Membranous* or *pseudomembranous exudates* develop on mucous membrane surfaces and are composed of necrotic cells enmeshed in a fibropurulent exudate.

A *purulent* or *suppurative exudate* contains pus, which is composed of degraded white blood cells, proteins, and tissue debris (Fig. 9-7). An abscess is a localized area of inflammation containing a purulent exudate. Certain microorganisms (*e.g.,* staphylococcus) are more likely to induce localized suppurative inflammation and are referred to as *pyogenic.* Abscesses typically have a central necrotic core containing purulent



■ **FIGURE 9-6** ■ Foreign body giant cell. The numerous nuclei are randomly arranged in the cytoplasm. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p 40]. Philadelphia: Lippincott-Raven)



A Inflammation
Capillary dilation, fluid exudation, neutrophil migration

B Suppuration
Development of suppurative or purulent exudate containing degraded neutrophils and tissue debris

C Abscess formation
Walling off of the area of purulent (pus) exudate to form an abscess

■ **FIGURE 9-7** ■ Abscess formation. (**A**) Bacterial invasion and development of inflammation. (**B**) Continued bacterial growth, neutrophil migration, liquefaction tissue necrosis, and development of a purulent exudate. (**C**) Walling off of the inflamed area with its purulent exudate to form an abscess.

exudates surrounded by a layer of neutrophils.[2] Fibroblasts may eventually enter the area and wall of the abscess. Because antimicrobial agents cannot penetrate the abscess wall, surgical incision and drainage may be required to effect a cure.

An *ulceration* refers to a site of inflammation where an epithelial surface (*e.g.*, skin or gastrointestinal epithelium) has become necrotic and eroded, often with associated subepithelial inflammation. Ulceration may occur as the result of traumatic injury to the epithelial surface (*e.g.*, peptic ulcer) or because of vascular compromise (foot ulcers associated with diabetes). In chronic lesions where there is repeated insult, the area surrounding the ulcer develops fibroblastic proliferation, scarring, and accumulation of chronic inflammatory cells.[2]

Systemic Manifestations of Inflammation

Under optimal conditions, the inflammatory response remains confined to a localized area. However, in some cases local injury can result in prominent systemic manifestations as inflammatory mediators are released into the circulation. The most prominent systemic manifestations of inflammation are the acute phase response, alterations in white blood cell count (leukocytosis or leukopenia), and fever. Sepsis and septic shock, also called the *systemic inflammatory response,* represent the severe systemic manifestations of inflammation (see Chapter 18).

Acute-Phase Response

Along with the cellular responses that occur during the inflammatory response, a constellation of systemic effects called the *acute-phase response* occurs. The acute-phase response, which usually begins within hours or days of the onset of inflammation or infection, includes changes in the concentrations of plasma proteins, increased erythrocyte sedimentation rate (ESR), fever, increased numbers of leukocytes, skeletal muscle catabolism, and negative nitrogen balance. These responses are generated after the release of the cytokines, IL-1, IL-6, and TNF-α. These cytokines affect the thermoregulatory center in the hypothalamus to produce fever, the most obvious sign of the acute-phase response. IL-1 and other cytokines induce an increase in the number and immaturity of circulating neutrophils by stimulating their production in the bone marrow. Lethargy, a common feature of the acute-phase response, results from the effects of IL-1 and TNF-α on the central nervous system.

During the acute-phase response, the liver dramatically increases the synthesis of acute-phase proteins such as fibrinogen and C-reactive protein that serve several different nonspecific host defense functions. The change in the types of plasma proteins contributes to the increased ESR. The metabolic changes, including skeletal muscle catabolism, provide amino acids that can be used in the immune response and for tissue repair. The total systemic process coordinates various activities in the body to enable an optimum host response.

White Blood Cell Response (Leukocytosis and Leukopenia)

Leukocytosis is common feature of the inflammatory response, especially those caused by bacterial infection. The white blood cell count usually increases to 15,000 to 20,000 cells/μL (normal 4000 to 10,000 cells/μL). After being released from the bone marrow, circulating neutrophils have a life span of only about 10 hours and therefore must be constantly replaced if their numbers are to be adequate. With excessive demand for phagocytes, immature forms of neutrophils (bands) are released from the bone marrow. The phase, which is referred to as a "shift to the left" in a white blood cell differential count, refers to the increase in immature neutrophils seen in severe infections.

Bacterial infections produce a relatively selective increase in neutrophils (neutrophilia), whereas parasitic and allergic responses induce eosinophilia. Viral infections tend to produce neutropenia (decreased numbers of neutrophils) and lymphocytosis.[3] Leukopenia is also encountered in infections that overwhelm persons with other debilitating diseases such as cancer.

Lymphadenitis

Localized acute and chronic inflammation may lead to a reaction in the lymph nodes that drain the affected area. This response represents a nonspecific response to mediators released from the injured tissue or an immunologic response to a specific antigen. Painful palpable nodes are more commonly associated with inflammatory processes, whereas nonpainful lymph nodes are more characteristic of neoplasms.[1]

In summary, inflammation describes a local response to tissue injury and can present as an acute or chronic condition. The classic signs of inflammation are redness, swelling, local heat, pain, and loss of function. It involves a hemodynamic phase during which blood flow and capillary permeability are increased, and a cellular phase during which phagocytic white blood cells move into the area to engulf and degrade the inciting agent. The inflammatory response is orchestrated by chemical mediators such as histamine, prostaglandins, PAF, complement fragments, and reactive molecules that are liberated by leukocytes.

In contrast to acute inflammation, which is self-limiting, chronic inflammation is prolonged and usually is caused by persistent irritants, most of which are insoluble and resistant to phagocytosis and other inflammatory mechanisms. Chronic inflammation involves the presence of mononuclear cells (lymphocytes and macrophages), rather than granulocytes.

The local manifestations of acute and chronic inflammation depend upon the agent and extent of injury. Acute inflammation may involve the production of exudates containing serous fluid (serous exudate), red blood cells (hemorrhagic exudate), fibrinogen (fibrinous exudate), or tissue debris and white blood cell breakdown products (purulent exudate). *Ulceration* occurs at the site of inflammation where an epithelial surface (skin or mucous membranes) has become necrotic and eroded. In chronic lesions where there is repeated insult, the area surrounding the ulcer develops fibroblastic proliferation, scarring, and the accumulation of chronic inflammatory cells.

The systemic manifestations of inflammation include an increased ESR, fever, and leukocytosis (or in some cases, leukopenia). These responses are mediated by release of the cytokines, IL-1, TNF-α, and IL-6. Localized acute and chronic inflammation may lead to a reaction in the lymph nodes and enlargement of the lymph nodes that drain the affected area.

TISSUE REPAIR AND WOUND HEALING

Body organs and structures contain two types of tissues: parenchymal and stromal. The parenchymal tissues contain the functioning cells of an organ or body part (*e.g.*, hepatocytes, renal tubular cells). The stromal tissues consist of the supporting connective tissues, blood vessels, and nerve fibers.

Injured tissues are repaired by regeneration of parenchymal cells or by connective tissue repair in which scar tissue is substituted for the parenchymal cells of the injured tissue. The primary objective of the healing process is to fill the gap created by tissue destruction and to restore the structural continuity of the injured part. When regeneration cannot occur, healing by replacement with connective scar tissue provides the means for maintaining this continuity. Although scar tissue fills the gap created by tissue death, it does not repair the structure with functioning parenchymal cells. Because the regenerative capabilities of most tissues are limited, wound healing usually involves some connective tissue repair.

Considerable research has contributed to the understanding of chemical mediators and growth factors that orchestrate the healing process.[4,5] These chemical mediators and growth factors are released in an orderly manner from many of the cells that participate in the healing process. Some growth factors act as chemoattractants, enhancing the migration of white blood cells and fibroblasts to the wound site, and others act as mitogens, causing increased proliferation of cells that participate in the healing process.[6] For example, platelet-derived growth factor, which is released from activated platelets, attracts white blood cells and acts as a growth factor for blood vessels and fibroblasts. Many of the cytokines discussed in Chapter 8 function as growth factors that are involved in wound healing.

Regeneration

Regeneration involves replacement of the injured tissue with cells of the same parenchymal type, leaving little or no evidence of the previous injury. The ability to regenerate varies with the tissue and cell type. Body cells are divided into three types according to their ability to undergo regeneration: labile, stable, or permanent cells.[4]

Labile cells are those that continue to divide and replicate throughout life, replacing cells that are continually being destroyed. Labile cells can be found in tissues that have a daily turnover of cells. They include the surface epithelial cells of the skin, the oral cavity, vagina, and cervix; the columnar epithelium of the gastrointestinal tract, uterus, and fallopian tubes; the transitional epithelium of the urinary tract; and bone marrow cells.

Stable cells are those that normally stop dividing when growth ceases. However, these cells are capable of undergoing regeneration when confronted with an appropriate stimulus. For stable cells to regenerate and restore tissues to their original state, the supporting stromal framework must be present. When this framework has been destroyed, the replacement of tissues is haphazard. The hepatocytes of the liver are one form of stable cell, and the importance of the supporting framework to regeneration is evidenced by two forms of liver disease. For example, in some types of viral hepatitis there is selective destruction of the parenchymal liver cells, while the cells of the supporting tissue remain unharmed. After the disease has subsided, the injured cells regenerate, and liver function returns to normal. In cirrhosis of the liver, fibrous bands of tissue form and replace the normal supporting tissues of the liver, causing disordered replacement of liver cells and disturbance of hepatic blood flow and liver function.

Permanent or *fixed cells* cannot undergo mitotic division. The fixed cells include nerve cells, skeletal muscle cells, and cardiac muscle cells. These cells cannot regenerate; once destroyed, they are replaced with fibrous scar tissue that lacks the functional characteristics of the destroyed tissue. For example, the scar tissue that develops in the heart after a heart attack (Fig. 9-8) cannot conduct impulses or contract to pump blood.

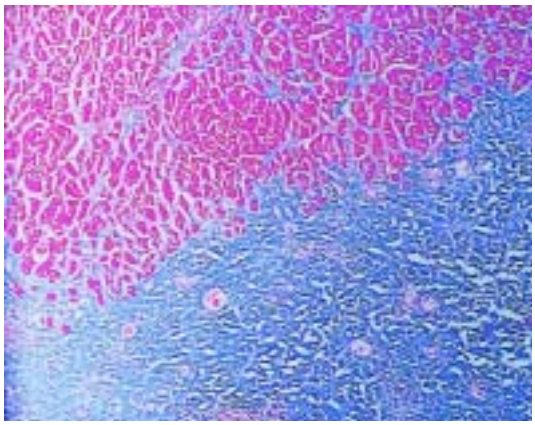
Connective Tissue Repair

Connective tissue replacement is an important process in the repair of tissue. It allows replacement of nonregenerated parenchymal cells by a connective tissue scar. Depending on the extent of tissue loss, wound closure and healing occur by *primary* or *secondary* intention. A sutured surgical incision is an example of healing by primary intention. Larger wounds (*e.g.*, burns and large surface wounds) that have a greater loss of tissue and contamination, heal by secondary intention. Healing by secondary intention is slower than healing by primary intention and results in the formation of larger amounts of scar tissue. A wound that might otherwise have healed by primary intention may become infected and heal by secondary intention.

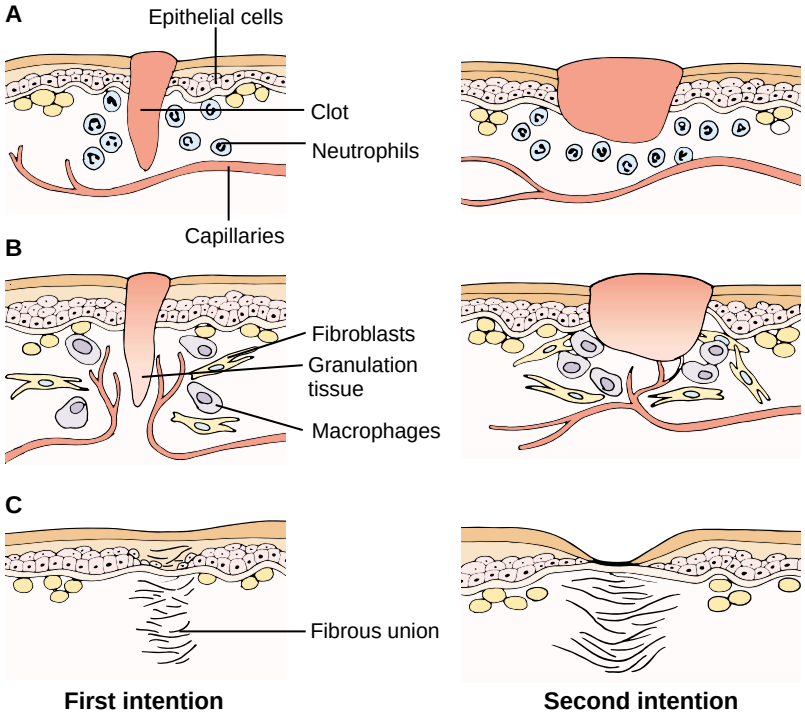
Wound healing is commonly divided into three phases: the inflammatory phase, the proliferative phase, and the maturational or remodeling phase (Fig. 9-9).[6,7] In wounds healing by primary intention, the duration of the phases is fairly predictable. In wounds healing by secondary intention, the process depends on the extent of injury and the healing environment.

Inflammatory Phase

The inflammatory phase of wound healing begins at the time of injury and is a critical period because it prepares the wound environment for healing. It includes hemostasis and the



■ **FIGURE 9-8** ■ Healed myocardial infarct. Tissues with permanent cells are replaced with scar tissue only. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 102]. Philadelphia: Lippincott Williams & Wilkins)



■ **FIGURE 9-9** ■ Healing of a skin wound by primary and secondary intention. (**A**) The inflammatory phase with formation of a blood clot and migration of neutrophils. (**B**) The proliferative phase with migration of macrophages and fibroblasts, proliferation of vascular endothelial cells, and development of granulation tissue. (**C**) Remodeling stage with development of the fibrous scar, disappearance of increased vascularity, and exit of inflammatory cells.

vascular and cellular phases of inflammation. Hemostatic processes are activated immediately at the time of injury. There is constriction of injured blood vessels and initiation of blood clotting by way of platelet activation and aggregation (see Chapter 12). After a brief period of constriction, these same vessels dilate and capillaries increase their permeability, allowing plasma and blood components to leak into the injured area. In small surface wounds, the clot loses fluid and becomes a hard, desiccated scab that protects the area.

The cellular phase of inflammation follows and is evidenced by the migration of phagocytic white blood cells that digest and remove invading organisms, fibrin, extracellular debris, and other foreign matter. The neutrophils or PMNs are the first cells to arrive and are usually gone by day 3 or 4. They ingest bacteria and cellular debris. Approximately 24 hours after the arrival of the PMNs, a larger and less specific phagocytic cell, the macrophage, which is an essential cell in the healing process, enters the wound area and remains for an extended period. Its functions include phagocytosis and release of growth factors that stimulate epithelial cell growth, angiogenesis (*i.e.*, growth of new blood vessels), and attraction of fibroblasts. When a large defect occurs in deeper tissues, PMNs and macrophages are required to remove the debris and facilitate wound closure. Although a wound may heal in the absence of PMNs, it cannot heal in the absence of macrophages.

Proliferative Phase

The proliferative phase of healing usually begins within 2 to 3 days of injury and may last as long as 3 weeks in wounds healing by primary intention. The primary processes during this time focus on the building of new tissue to fill the wound space. The key cell during this phase is the *fibroblast.* The fibroblast is a connective tissue cell that synthesizes and secretes collagen and other intercellular elements needed for wound healing. Fibroblasts also produce a family of growth factors that induce the growth of blood vessels (angiogenesis) and endothelial cell proliferation and migration.

As early as 24 to 48 hours after injury, fibroblasts and vascular endothelial cells begin proliferating to form a specialized type of soft, pink granular tissue, called *granulation tissue,* that

KEY CONCEPTS

TISSUE REPAIR AND WOUND HEALING

- Injured tissues can be repaired by regeneration of the injured tissue cells with cells of the same tissue or parenchymal type, or by connective repair processes in which scar tissue is used to effect healing.
- Regeneration is limited to tissues with cells that are able to undergo mitosis.
- Connective tissue repair occurs by primary or secondary intention and involves the inflammatory phase, the proliferative phase, and remodeling phases of the wound healing process.
- Wound healing is impaired by conditions that diminish blood flow and oxygen delivery, restrict nutrients and other materials needed for healing, and depress the inflammatory and immune responses; and by infection, wound separation, and the presence of foreign bodies.

serves as the foundation for scar tissue development. This tissue is fragile and bleeds easily because of the numerous, newly developed capillary buds. Wounds that heal by secondary intention have more necrotic debris and exudate that must be removed, and they involve larger amounts of granulation tissue. The newly formed blood vessels are leaky and allow plasma proteins and white blood cells to leak into the tissues. At approximately the same time, epithelial cells at the margin of the wound begin to regenerate and move toward the center of the wound, forming a new surface layer that is similar to that destroyed by the injury. In wounds that heal by primary intention, these epidermal cells proliferate and seal the wound within 24 to 48 hours.[8] When a scab has formed on the wound, the epithelial cells migrate between it and the underlying viable tissue; when a significant portion of the wound has been covered with epithelial tissue, the scab can be easily removed. At times, excessive granulation tissue, sometimes referred to as *proud flesh*, may form and extend above the edges of wound, preventing re-epithelialization. Surgical removal or chemical cauterization of the defect allows healing to proceed.

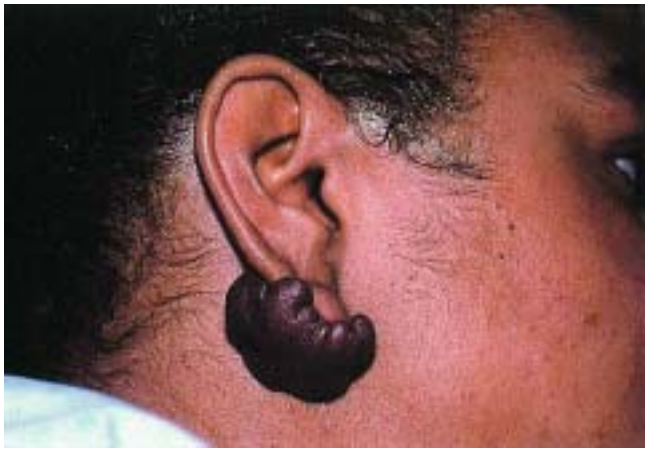
As the proliferative phase progresses, there is continued accumulation of collagen and proliferation of fibroblasts. Collagen synthesis reaches a peak within 5 to 7 days and continues for several weeks, depending on wound size. By the second week, the white blood cells have largely left the area, the edema has diminished, and the wound begins to blanch as the small blood vessels become thrombosed and degenerate.

Remodeling Phase

The third or remodeling phase of wound healing begins approximately 3 weeks after injury and can continue for 6 months or longer, depending on the extent of the wound. As the term implies, there is continued remodeling of scar tissue by simultaneous synthesis of collagen by fibroblasts and lysis by collagenase enzymes. As a result of these two processes, the architecture of the scar becomes reoriented to increase the tensile strength of the wound.

Most wounds do not regain the full tensile strength of unwounded skin after healing is completed. Carefully sutured wounds immediately after surgery have approximately 70% of the strength of unwounded skin, largely because of the placement of the sutures. This allows persons to move about freely after surgery without fear of wound separation. When the sutures are removed, usually at the end of the first week, wound strength is approximately 10%. It increases rapidly during the next 4 weeks and then slows, reaching a plateau of approximately 70% to 80% of the tensile strength of unwounded skin at the end of 3 months.[5] An injury that heals by secondary intention undergoes wound contraction during the proliferative and remodeling phases. As a result, the scar that forms is considerably smaller than the original wound. Cosmetically, this may be desirable because it reduces the size of the visible defect. However, contraction of scar tissue over joints and other body structures tends to limit movement and cause deformities. As a result of loss of elasticity, scar tissue that is stretched fails to return to its original length.

An abnormality in healing by scar tissue repair is *keloid* formation (Fig. 9-10). Keloids are tumorlike masses caused by excess production of scar tissue. The tendency toward development of keloids is more common in African Americans and seems to have a genetic basis.



■ **FIGURE 9-10** ■ Keloid. A light-skinned black woman with keloid that developed following ear piercing. (Rubin E., Farber J.L. [1999]. *Pathology* [3rd ed., p. 90]. Philadelphia: Lippincott Williams & Wilkins)

Factors That Affect Wound Healing

Many local and systemic factors influence wound healing. Although there are many factors that impair healing, science has found a few ways to hasten the normal process of wound repair. Among the causes of impaired wound healing are malnutrition; impaired blood flow and oxygen delivery; impaired inflammatory and immune responses; infection, wound separation, and foreign bodies; and age effects.

Malnutrition

Successful wound healing depends in part on adequate stores of proteins, carbohydrates, fats, vitamins, and minerals. It is well recognized that malnutrition slows the healing process, causing wounds to heal inadequately or incompletely.[9] Protein deficiencies prolong the inflammatory phase of healing and impair fibroblast proliferation, collagen and protein matrix synthesis, angiogenesis, and wound remodeling. Carbohydrates are needed as an energy source for white blood cells. Carbohydrates also have a protein-sparing effect and help to prevent the use of amino acids for fuel when they are needed for the healing process. Fats are essential constituents of cell membranes and are needed for the synthesis of new cells.

Although most vitamins are essential cofactors for the daily functions of the body, only vitamins A and C have been shown to play an essential role in the healing process. Vitamin C is needed for collagen synthesis. In vitamin C deficiency, improper sequencing of amino acids occurs, proper linking of amino acids does not take place, the by-products of collagen synthesis are not removed from the cell, and new wounds do not heal properly. Vitamin A functions in stimulating and supporting epithelialization, capillary formation, and collagen synthesis. The B vitamins are important cofactors in enzymatic reactions that contribute to the wound-healing process. All are water soluble, and with the exception of vitamin B_{12}, which is stored in the liver, almost all must be replaced daily. Vitamin K plays an indirect role in wound healing by preventing bleeding disorders that contribute to hematoma formation and subsequent infection.

The role of minerals in wound healing is less clearly defined. The macrominerals, including sodium, potassium, calcium, and phosphorus, as well as the microminerals, such as copper and zinc, must be present for normal cell function. Zinc is a cofactor in a variety of enzyme systems responsible for cell proliferation. In animal studies, zinc has been found to aid in re-epithelialization.

Blood Flow and Oxygen Delivery

For healing to occur, wounds must have adequate blood flow to supply the necessary nutrients and to remove the resulting waste, local toxins, bacteria, and other debris. Impaired wound healing caused by poor blood flow may occur as a result of wound conditions (*e.g.*, swelling) or pre-existing health problems. Arterial disease and venous pathology are well-documented causes of impaired wound healing. In situations of trauma, a decrease in blood volume may cause a reduction in blood flow to injured tissues.

Molecular oxygen is required for collagen synthesis. It has been shown that even a temporary lack of oxygen can result in the formation of less stable collagen.[10] Wounds in ischemic tissue become infected more frequently than do wounds in well-vascularized tissue. PMNs and macrophages require oxygen for destruction of microorganisms that have invaded the area. Although these cells can accomplish phagocytosis in a relatively anoxic environment, they cannot digest bacteria.

Impaired Inflammatory and Immune Responses

Inflammatory and immune mechanisms function in wound healing. Inflammation is essential to the first phase of wound healing, and immune mechanisms prevent infections that impair wound healing. Among the conditions that impair inflammation and immune function are disorders of phagocytic function, diabetes mellitus, and therapeutic administration of corticosteroid drugs.

Phagocytic disorders may be divided into extrinsic and intrinsic defects. Extrinsic disorders are those that impair attraction of phagocytic cells to the wound site, prevent engulfment of bacteria and foreign agents by the phagocytic cells (*i.e.*, opsonization), or cause suppression of the total number of phagocytic cells (*e.g.*, immunosuppressive agents). Intrinsic phagocytic disorders are the result of enzymatic deficiencies in the metabolic pathway for destroying the ingested bacteria by the phagocytic cell (see Chapter 10).

Wound healing is a problem in persons with diabetes mellitus, particularly those who have poorly controlled blood glucose levels. Studies have shown delayed wound healing, poor collagen formation, and poor tensile strength in diabetic animals. Of particular importance is the effect of hyperglycemia on the phagocytic function of white blood cells. For example, neutrophils have diminished chemotactic and phagocytic function, including engulfment and intracellular killing of bacteria, when exposed to elevated glucose levels. Small blood vessel disease is also common among persons with diabetes, impairing the delivery of inflammatory cells, oxygen, and nutrients to the wound site.[11]

The therapeutic administration of corticosteroid drugs decreases the inflammatory process and may delay the healing process. These hormones decrease capillary permeability during the early stages of inflammation, impair the phagocytic property of the leukocytes, and inhibit fibroblast proliferation and function.

Infection, Wound Separation, and Foreign Bodies

Wound contamination, wound separation, and foreign bodies delay wound healing. Infection impairs all dimensions of wound healing. It prolongs the inflammatory phase, impairs the formation of granulation tissue, and inhibits proliferation of fibroblasts and deposition of collagen fibers. All wounds are contaminated at the time of injury. Although body defenses can handle the invasion of microorganisms at the time of wounding, badly contaminated wounds can overwhelm host defenses. Trauma and existing impairment of host defenses also can contribute to the development of wound infections.

Approximation of the wound edges (*i.e.*, suturing of an incision type of wound) greatly enhances healing and prevents infection. Epithelialization of a wound with closely approximated edges occurs within 1 to 2 days. Large, gaping wounds tend to heal more slowly because it is often impossible to effect wound closure with this type of wound. Foreign bodies tend to invite bacterial contamination and delay healing. Fragments of wood, steel, glass, and other compounds may have entered the wound at the site of injury and can be difficult to locate when the wound is treated. Sutures are also foreign bodies, and although needed for the closure of surgical wounds, they are an impediment to healing. This is why sutures are removed as soon as possible after surgery. Wound infections are of special concern in persons with implantation of foreign bodies such as orthopedic devices (*e.g.*, pins, stabilization devices), cardiac pacemakers, and shunt catheters. These infections are difficult to treat and may require removal of the device.

In summary, the ability of tissues to repair damage caused by injury depends on the body's ability to replace the parenchymal cells and to organize them as they were originally. Regeneration describes the process by which tissue is replaced with cells of a similar type and function. Healing by regeneration is limited to tissue with cells that are able to divide and replace the injured cells. Body cells are divided into types according to their ability to regenerate: labile cells, such as the epithelial cells of the skin and gastrointestinal tract, which continue to regenerate throughout life; stable cells, such as those in the liver, which normally do not divide but are capable of regeneration when confronted with an appropriate stimulus; and permanent or fixed cells, such as nerve cells, which are unable to regenerate. Scar tissue repair involves the substitution of fibrous connective tissue for injured tissue that cannot be repaired by regeneration.

Wound healing occurs by primary and secondary intention and is commonly divided into three phases: the inflammatory phase, the proliferative phase, and the maturational or remodeling phase. In wounds healing by primary intention, the duration of the phases is fairly predictable. In wounds healing by secondary intention, the process depends on the extent of injury and the healing environment. Wound healing can be impaired or complicated by factors such as malnutrition; restricted blood flow and oxygen delivery; diminished inflammatory and immune responses; and infection, wound separation, and the presence of foreign bodies.

TEMPERATURE REGULATION AND FEVER

Fever is a clinical hallmark of infection and inflammation. This section of the chapter focuses on regulation of body temperature and fever caused by infectious and noninfectious conditions.

Body Temperature Regulation

The temperature within the deep tissues of the body (core temperature) is normally maintained within a range of 36.0°C to 37.5°C (97.0°F to 99.5°F).[12] Within this range, there are individual differences and diurnal variations; internal core temperatures reach their highest point in late afternoon and evening and their lowest point in the early morning hours (Fig. 9-11). Virtually all biochemical processes in the body are affected by changes in temperature. Metabolic processes speed up or slow down, depending on whether body temperature is rising or falling.

Body temperature reflects the difference between heat production and heat loss. Body heat is generated in the tissues of the body, transferred to the skin surface by the blood, and then released into the environment surrounding the body. The thermoregulatory center in the hypothalamus functions to modify heat production and heat losses as a means of regulating body temperature.

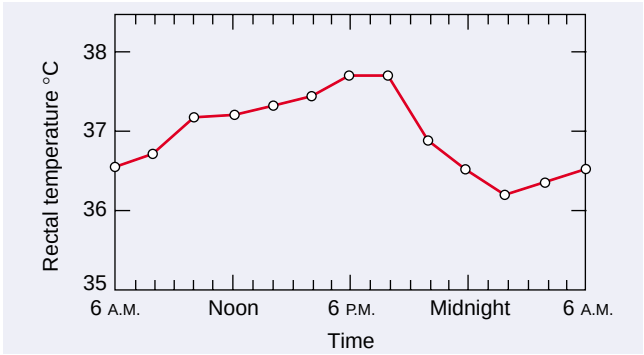
It is the core body temperature, rather than the surface temperature, that is regulated by the thermoregulatory center in the hypothalamus. This center integrates input from cold and warm thermal receptors located throughout the body and generates output responses that conserve body heat or increase its dissipation. The *thermostatic set point* of the thermoregulatory center is set so that the core temperature is regulated within the normal range. When body temperature begins to rise above the normal range, heat-dissipating behaviors are initiated; when the temperature falls below the normal range, heat production is increased. A core temperature greater than 41°C (105.8°F) or less than 34°C (93.2°F) usually indicates that the body's ability to thermoregulate is impaired (Fig. 9-12). Body responses that produce, conserve, and dissipate heat are described in Table 9-2. Spinal cord injuries that transect the cord at T6 or above can seriously impair temperature regulation because the hypothalamus can no longer control skin blood flow or sweating.

In addition to physiological thermoregulatory mechanisms, humans engage in voluntary behaviors to help regulate body temperature. These behaviors include the selection of proper clothing and regulation of environmental temperature through heating systems and air conditioning. Body positions that hold the extremities close to the body (*e.g.*, huddling or holding the extremities close to the body) prevent heat loss and are commonly assumed in cold weather.

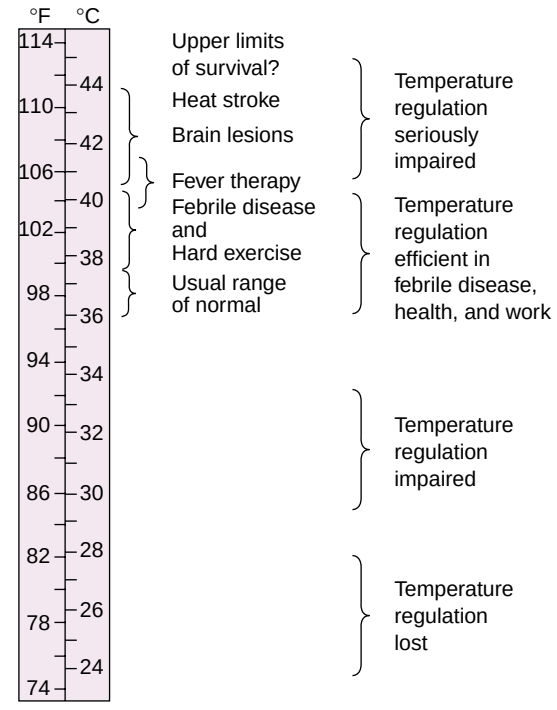
KEY CONCEPTS

FEVER

- Fever represents an increase in body temperature due to resetting of the hypothalamic thermoregulatory set point as the result of endogenous pyrogens released from host macrophages or endothelial cells.
- In response to the increase in set point, the hypothalamus initiates physiologic responses to increase core temperature to match the new set point.
- Fever is an adaptive response to bacterial and viral infections or to tissue injury. The growth rate of microorganisms is inhibited, and immune function is enhanced.



■ **FIGURE 9-11** ■ Normal diurnal variations in body temperature.



■ **FIGURE 9-12** ■ Body temperatures under different conditions. (Dubois, E.F. [1948]. *Fever and the regulation of body temperature.* Courtesy of Charles C. Thomas, Publisher, Ltd., Springfield, IL)

TABLE 9-2 Heat Gain and Heat Loss Responses Used in Regulation of Body Temperature

Heat Gain		Heat Loss	
Body Response	*Mechanism of Action*	*Body Response*	*Mechanism of Action*
Vasoconstriction of the superficial blood vessels	Confines blood flow to the inner core of the body, with the skin and subcutaneous tissues acting as insulation to prevent loss of core heat	Dilatation of the superficial blood vessels	Delivers blood containing core heat to the periphery where it is dissipated through radiation, conduction, and convection
Contraction of the pilomotor muscles that surround the hairs on the skin	Reduces the heat loss surface of the skin	Sweating	Increases heat loss through evaporation
Assumption of the huddle position with the extremities held close to the body	Reduces the area for heat loss		
Shivering	Increases heat production by the muscles		
Increased production of epinephrine	Increases the heat production associated with metabolism		
Increased production of thyroid hormone	Is a long-term mechanism that increases metabolism and heat production		

Mechanisms of Heat Production

Metabolism is the body's main source of heat production. The sympathetic neurotransmitters, epinephrine and norepinephrine, which are released when an increase in body temperature is needed, act at the cellular level to shift metabolism so energy production is reduced and heat production is increased. This may be one of the reasons fever tends to produce feelings of weakness and fatigue. Thyroid hormone increases cellular metabolism, but this response usually requires several weeks to reach maximal effectiveness.

Fine involuntary actions such as shivering and chattering of the teeth can produce a threefold to fivefold increase in body temperature. *Shivering* is initiated by impulses from the hypothalamus. The first muscle change that occurs with shivering is a general increase in muscle tone, followed by an oscillating rhythmic tremor involving the spinal-level reflex that controls muscle tone. Because no external work is performed, all of the energy liberated by the metabolic processes from shivering is in the form of heat.

Physical exertion increases body temperature. With strenuous exercise, more than three quarters of the increased metabolism resulting from muscle activity appears as heat within the body, and the remainder appears as external work.

Mechanisms of Heat Loss

Most of the body's heat is produced by the deeper core tissues (*i.e.*, muscles and viscera), which are insulated from the environment and protected against heat loss by the subcutaneous tissues. Adipose tissue is a particularly good insulator, conducting heat only one third as effectively as other tissues.

Heat is lost from the body through radiation and conduction from the skin surface; through the evaporation of sweat and insensible perspiration; through the exhalation of air that has been warmed and humidified; and through heat lost in urine and feces. Contraction of the *pilomotor muscles* of the skin, which raises the skin hair and produces goose bumps, reduces the surface area available for heat loss. Of these mechanisms, only heat losses that occur at the skin surface are directly under hypothalamic control.

Most of the body's heat losses occur at the skin surface as heat from the blood moves to the skin and from there into the surrounding environment. There are numerous *arteriovenous (AV) shunts* under the skin surface that allow blood to move directly from the arterial to the venous system (Fig. 9-13). These AV shunts are much like the radiators in a heating system. When the shunts are open, body heat is freely dissipated to the skin and surrounding environment; when the shunts are closed, heat is retained in the body. The blood flow in the AV shunts is controlled almost exclusively by the sympathetic ner-

vous system in response to changes in core temperature and environmental temperature. The transfer of heat from the skin to the environment occurs by means of radiation, conduction, convection, and evaporation.

Radiation. Radiation involves the transfer of heat through the air or a vacuum. Heat from the sun is carried by radiation. The human body radiates heat in all directions. The ability to dissipate body heat by radiation depends on the temperature of the environment. Environmental temperature must be less than that of the body for heat loss to occur.

Conduction. Conduction involves the direct transfer of heat from one molecule to another. Blood carries, or conducts, heat from the inner core of the body to the skin surface. Normally, only a small amount of body heat is lost through conduction to a cooler surface. However, loss of heat by conduction to air represents a sizable proportion of the body's heat loss.

The conduction of heat to the body's surface is influenced by blood volume. In hot weather, the body compensates by increasing blood volume as a means of dissipating heat. Exposure to cold produces a cold diuresis and a reduction in blood volume as a means of controlling the transfer of heat to the body's surface.

Convection. Convection refers to heat transfer through the circulation of air currents. Normally, a layer of warm air tends to remain near the body's surface; convection causes continual removal of the warm layer and replacement with air from the surrounding environment. The wind-chill factor that often is included in the weather report combines the effect of convection caused by wind with the still-air temperature.

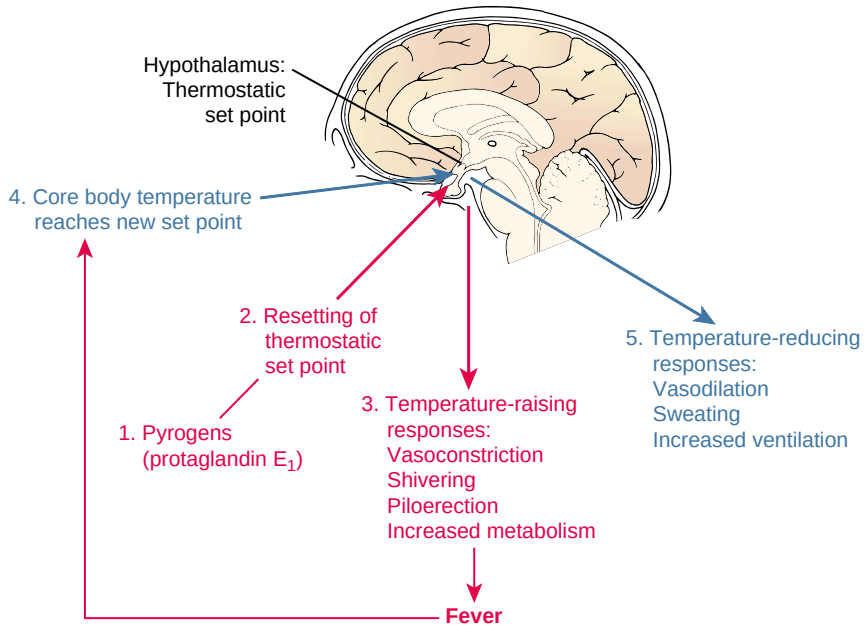
Evaporation. Evaporation involves the use of body heat to convert water on the skin to water vapor. Water that diffuses through the skin independent of sweating is called *insensible perspiration.* Insensible perspiration losses are greatest in a dry environment. Sweating occurs through the sweat glands and is controlled by the sympathetic nervous system. In contrast to other sympathetically mediated functions, sweating relies on acetylcholine, rather that the catecholamines, as a neurotransmitter. This means that anticholinergic drugs, such as atropine, can interfere with heat loss by interrupting sweating.

Evaporative heat losses involve insensible perspiration and sweating, with 0.58 calories being lost for each gram of water that is evaporated.[12] As long as body temperature is greater than the atmospheric temperature, heat is lost through radiation. However, when the temperature of the surrounding environment becomes greater than skin temperature, evaporation is the only way the body can rid itself of heat. Any condition that prevents evaporative heat losses causes the body temperature to rise.

Fever

Fever, or *pyrexia,* describes an elevation in body temperature that is caused by a cytokine-induced upward displacement of the set point of the hypothalamic thermoregulatory center. Fever is resolved or "broken" when the factor that caused the increase in the set point is removed. Fevers that are regulated by the hypothalamus usually do not rise above 41°C (105.8°F), suggesting a built-in thermostatic safety mechanism. Temperatures above that level are usually the result of superimposed activity, such as convulsions, hyperthermic states, or direct impairment of the temperature control center.

Fever can be caused by a number of microorganisms and substances that are collectively called pyrogens (Fig. 9-14). Many proteins, breakdown products of proteins, and certain other substances, including lipopolysaccharide toxins released from bacterial cell membranes, can cause the set point of the hypothalamic thermostat to increase. Some pyrogens can act directly and immediately on the hypothalamic thermoregulatory center to increase its set point. Other pyrogens, sometimes called *exogenous pyrogens,* act indirectly and may require several hours to produce their effect.[12]



■ **FIGURE 9-14** ■ Mechanisms of fever. (1) Release of endogenous pyrogen from inflammatory cells, (2) resetting of hypothalamus thermostatic set point to a higher level (prodrome), (3) generation of hypothalamic-mediated responses that raise body temperature (chill), (4) development of fever with elevation of body to new thermostatic set point, and (5) production of temperature-lowering responses (flush and defervescence) and return of body temperature to a lower level.

Exogenous pyrogens induce host cells, such as blood leukocytes and tissue macrophages, to produce fever-producing mediators called *endogenous pyrogens* (*e.g.*, interleukin-1). For example, the phagocytosis of bacteria and breakdown products of bacteria that are present in the blood lead to the release of endogenous pyrogens into the circulation. The endogenous pyrogens are thought to increase the set point of the hypothalamic thermoregulatory center through the action of prostaglandin E_2.[12] In response to the sudden increase in set point, the hypothalamus initiates heat production behaviors (shivering and vasoconstriction) that increase the core body temperature to the new set point, and fever is established. In addition to their fever-producing actions, the endogenous pyrogens mediate a number of other responses. For example, interleukin-1 is an inflammatory mediator that produces other signs of inflammation, such as leukocytosis, anorexia, and malaise.

Many noninfectious disorders, such as myocardial infarction, pulmonary emboli, and neoplasms, produce fever. In these conditions, the injured or abnormal cells incite the production of pyrogen. For example, trauma and surgery can be associated with several days of fever. Some malignant cells, such as those of leukemia and Hodgkin's disease, secrete pyrogen.

A fever that has its origin in the central nervous system is sometimes referred to as a *neurogenic fever*.[13] It usually is caused by damage to the hypothalamus caused by central nervous system trauma, intracerebral bleeding, or an increase in intracranial pressure. Neurogenic fevers are characterized by a high temperature that is resistant to antipyretic therapy and is not associated with sweating.

The purpose of fever is not completely understood. However, from a purely practical standpoint, fever is a valuable index to health status. For many, fever signals the presence of an infection and may legitimize the need for medical treatment. In ancient times, fever was thought to "cook" the poisons that caused the illness. With the availability of antipyretic drugs in the late 19th century, the belief that fever was useful began to wane, probably because most antipyretic drugs also had analgesic effects.

There is little research to support the belief that fever is harmful unless the temperature is greater than 40°C (104°F). Animal studies have demonstrated a clear survival advantage in infected members with fever compared with animals that were unable to produce a fever.[14] It has been shown that small elevations in temperature, such as those that occur with fever, enhance immune function. There is increased motility and activity of the white blood cells, stimulation of interferon production, and activation of T cells.[15,16] Many of the microbial agents that cause infection grow best at normal body temperatures, and their growth is inhibited by temperatures in the fever range. For example, the rhinoviruses responsible for the common cold are cultured best at 33°C (91.4°F), which is close to the temperature in the nasopharynx. Temperature-sensitive mutants of the virus that cannot grow at temperatures greater than 37.5°C (99.5°F), produce fewer signs and symptoms.[17]

Patterns

The patterns of temperature change in persons with fever vary and may provide information about the nature of the causative agent.[18] These patterns can be described as intermittent, remittent, sustained, or relapsing. An *intermittent fever* is one in which temperature returns to normal at least once every 24 hours. Intermittent fevers are commonly associated with conditions such as gram-negative/positive sepsis, abscesses, and acute bacterial endocarditis. In a *remittent fever*, the temperature does not return to normal and varies a few degrees in either direction. It is associated with viral upper respiratory tract, legionella, and mycoplasma infections. In a *sustained* or *continuous* fever, the temperature remains above normal with minimal variations (usually less than 0.55°C or 1°F). Sustained fevers are seen in persons with drug fever. A *recurrent* or *relapsing fever* is one in which there is one or more episodes of fever, each as long as several days, with one or more days of normal temperature between episodes. Relapsing fevers may be caused by a variety of infectious diseases, including tuberculosis, fungal infections, Lyme disease, and malaria.

Critical to the analysis of a fever pattern is the relation of heart rate to the level of temperature elevation. Normally, a 1°C rise in temperature produces a 15-bpm (beats per minute) increase in heart rate (1°F, 10 bpm).[19] Most persons respond to an increase in temperature with an appropriate increase in heart rate. The observation that a rise in temperature is not accompanied by the anticipated change in heart rate can provide useful information about the cause of the fever. For example, a heart rate that is slower than would be anticipated can occur with Legionnaires' disease and drug fever, and a heart rate that is more rapid than anticipated can be symptomatic of hyperthyroidism and pulmonary emboli.

Manifestations

The physiologic behaviors that occur during the development of fever can be divided into four successive stages: a prodrome; a chill, during which the temperature rises; a flush; and defervescence. During the *first* or *prodromal* period, there are nonspecific complaints, such as mild headache and fatigue, general malaise, and fleeting aches and pains. During the *second stage* or *chill*, there is the uncomfortable sensation of being chilled and the onset of generalized shaking, although the temperature is rising. Vasoconstriction and piloerection usually precede the onset of shivering. At this point the skin is pale and covered with goose flesh. There is a feeling of being cold and an urge to put on more clothing or covering and to curl up in a position that conserves body heat. When the shivering has caused the body temperature to reach the new set point of the temperature control center, the shivering ceases, and a sensation of warmth develops. At this point, the *third stage* or *flush* begins, during which cutaneous vasodilation occurs and the skin becomes warm and flushed. The *fourth*, or *defervescence*, stage of the febrile response is marked by the initiation of sweating. Not all persons proceed through the four stages of fever development. Sweating may be absent, and fever may develop gradually, with no indication of a chill or shivering.

Common manifestations of fever are anorexia, myalgia, arthralgia, and fatigue. These discomforts are worse when the temperature rises rapidly or exceeds 39.5°C (103.1°F). Respiration is increased, and the heart rate usually is elevated. Dehydration occurs because of sweating and the increased vapor losses caused by the rapid respiratory rate. The occurrence of chills commonly coincides with the introduction of pyrogen into the circulation. This is one of the reasons that blood cultures to identify the organism causing the fever are usually drawn during the first signs of a chill.

Many of the manifestations of fever are related to the increases in the metabolic rate, increased need for oxygen, and use of body proteins as an energy source. During fever, the body switches from using glucose (an excellent medium for bacterial growth) to metabolism based on protein and fat breakdown. With prolonged fever, there is increased breakdown of endogenous fat stores. If fat breakdown is rapid, metabolic acidosis may result (see Chapter 6).

Headache is a common accompaniment of fever and is thought to result from the vasodilation of cerebral vessels occurring with fever. Delirium is possible when the temperature exceeds 40°C (104°F). In the elderly, confusion and delirium may follow moderate elevations in temperature. Because of the increasingly poor oxygen uptake by the aging lung, pulmonary function may prove to be a limiting factor in the hypermetabolism that accompanies fever in older persons. Confusion, incoordination, and agitation commonly reflect cerebral hypoxemia. Febrile seizures can occur in some children.[20] They usually occur with rapidly rising temperatures or at a threshold temperature that differs with each child.

The herpetic lesions, or fever blisters, that develop in some persons during fever are caused by a separate infection by the type 1 herpes simplex virus that established latency in the regional ganglia and is reactivated by a rise in body temperature.

Diagnosis and Treatment

Fever usually is a manifestation of a disease state, and as such, determining the cause of a fever is an important aspect of its treatment. For example, fevers caused by infectious diseases usually are treated with antibiotics, whereas other fevers, such as those resulting from a noninfectious inflammatory condition, may be treated symptomatically.

Sometimes it is difficult to establish the cause of a fever. A prolonged fever for which the cause is difficult to ascertain is often referred to as *fever of unknown origin* (FUO). FUO is defined as a temperature elevation of 38.3°C (101°F) or higher that is present for 3 weeks or longer.[21] Among the causes of FUO are malignancies (*i.e.*, lymphomas, metastases to the liver and central nervous system); infections such as human immunodeficiency virus or tuberculosis, or abscessed infections; and drug fever. Malignancies, particularly non-Hodgkin's lymphoma, are important causes of FUO in the elderly. Cirrhosis of the liver is another cause of FUO.

The methods of fever treatment focus on modifications of the external environment intended to increase heat transfer from the internal to the external environment, support of the hypermetabolic state that accompanies fever, protection of vulnerable body organs and systems, and treatment of the infection or condition causing the fever. Because fever is a disease symptom, its manifestation suggests the need for treatment of the primary cause.

Modification of the environment ensures that the environmental temperature facilitates heat transfer away from the body. Sponge baths with cool water or an alcohol solution can be used to increase evaporative heat losses. More profound cooling can be accomplished through the use of a cooling mattress, which facilitates the conduction of heat from the body into the coolant solution that circulates through the mattress. Care must be taken so that cooling methods do not produce vasoconstriction and shivering that decrease heat loss and increase heat production.

Adequate fluids and sufficient amounts of simple carbohydrates are needed to support the hypermetabolic state and prevent the tissue breakdown that is characteristic of fever. Additional fluids are needed for sweating and to balance the insensible water losses from the lungs that accompany an increase in respiratory rate. Fluids also are needed to maintain an adequate vascular volume for heat transport to the skin surface.

Antipyretic drugs, such as aspirin and acetaminophen, often are used to alleviate the discomforts of fever and protect vulnerable organs, such as the brain, from extreme elevations in body temperature. These drugs act by resetting the hypothalamic temperature control center to a lower level, presumably by blocking the activity of cyclooxygenase, an enzyme that is required for the conversion of arachidonic acid to prostaglandin E_2.[22]

Fever in Children

The mechanisms for controlling temperature are not well developed in the infant. In infants younger than 3 months, a mild elevation in temperature (*i.e.*, rectal temperature of 38°C [100.4°F]) can indicate serious infection that requires immediate medical attention.[23,24] Fever without a source occurs frequently in infants and children and is a common reason for visits to the clinic or emergency department.

Both minor and life-threatening infections are common in the infant to 3-year age group.[23,24] The most common causes of fever in children are minor or more serious infections of the respiratory system, urinary system, gastrointestinal tract, or central nervous system. Occult bacteremia and meningitis also occur in this age group and should be excluded as diagnoses. The Agency for Health Care Policy and Research Expert Panel has developed clinical guidelines for use in the treatment of infants and children 0 to 36 months of age with fever without a source.[25] The guidelines define fever in this age group as a rectal temperature of at least 38°C (100.4°F). The guidelines also point out that fever may result from overbundling or a vaccine reaction. When overbundling is suspected, it is suggested that the infant be unbundled and the temperature retaken after 15 to 30 minutes.

Fever in infants and children can be classified as low risk or high risk, depending on the probability of the infection progressing to bacteremia or meningitis. Infants usually are considered at low risk if they were delivered at term and sent home with their mother without complications and have been healthy with no previous hospitalizations or previous antimicrobial therapy. A white blood cell count and urinalysis are recommended as a means of confirming low-risk status. Signs of toxicity (and high risk) include lethargy, poor feeding, hypoventilation, poor tissue oxygenation, and cyanosis. Blood and urine cultures, chest radiographs, and lumbar puncture usually are done in high-risk infants and children to determine the cause of fever.

Infants with fever who are considered to be at low risk usually are managed on an outpatient basis providing the parents or caregivers are deemed reliable. Older children with fever without source also may be treated on an outpatient basis. Parents or caregivers require full instructions, preferably in writing, regarding assessment of the febrile child. They should be instructed to contact their health care provider should

their child show signs suggesting sepsis. Infants younger than 3 months are evaluated carefully. Infants and children with signs of toxicity and/or petechiae (a sign of meningitis) usually are hospitalized for evaluation and treatment.[26] Parenteral antimicrobial therapy usually is initiated after samples for blood, urine, and spinal fluid cultures have been taken.

Fever in the Elderly

In the elderly, even slight elevations in temperature may indicate serious infection or disease. This is because the elderly often have a lower baseline temperature, and although they increase their temperature during an infection, it may fail to reach a level that is equated with significant fever.[27,28]

Normal body temperature and the circadian pattern of temperature variation often are altered in the elderly. Elderly persons are reported to have a lower basal temperature (36.4°C [97.6°F] in one study) than do younger persons.[29] It has been recommended that the definition of fever in the elderly be expanded to include an elevation of temperature of at least 1.1°C (2°F) above baseline values.[28]

It has been suggested that 20% to 30% of elders with serious infections present with an absent or blunted febrile response.[28] When fever is present in the elderly, it usually indicates the presence of serious infection, most often caused by bacteria. The absence of fever may delay diagnosis and initiation of antimicrobial treatment. Unexplained changes in functional capacity, worsening of mental status, weakness and fatigue, and weight loss are signs of infection in the elderly. They should be viewed as possible signs of infection and sepsis when fever is absent. The probable mechanisms for the blunted fever response include a disturbance in sensing of temperature by the thermoregulatory center in the hypothalamus, alterations in release of endogenous pyrogens, and the failure to elicit responses such as vasoconstriction of skin vessels, increased heat production, and shivering that increase body temperature during a febrile response.

Another factor that may delay recognition of fever in the elderly is the method of temperature measurement. Oral temperature remains the most commonly used method for measuring temperature in the elderly. It has been suggested that rectal and tympanic membrane methods are more effective in detecting fever in the elderly. This is because conditions such as mouth breathing, tongue tremors, and agitation often make it difficult to obtain accurate oral temperatures in the elderly.

In summary, body temperature is normally maintained within a range of 36.0°C to 37.4°C. Body heat is produced by metabolic processes that occur within deeper core structures of the body and is lost at the body's surface when core heat is transported to the skin by the circulating blood. The transfer of heat from the skin to the environment occurs through radiation, conduction, convection, and evaporation. The thermoregulatory center in the hypothalamus functions to modify heat production and heat losses as a means of regulating body temperature.

Fever represents an increase in body temperature outside the normal range. Fever can be caused by a number of factors, including microorganisms, trauma, and drugs or chemicals, all of which incite the release of endogenous pyrogens and subsequent resetting of the hypothalamic thermoregulatory center. The reactions that occur during fever consist of four stages: a prodrome, a chill, a flush, and defervescence. Many of the manifestations of fever are related to the increases in the metabolic rate, increased need for oxygen, and use of body proteins as an energy source.

Fever in infants and children can be classified as low risk or high risk, depending upon the probability of the infection progressing to bacteremia or meningitis. Infants younger than 28 days and those at high risk usually are hospitalized for evaluation of their fever and treatment. In the elderly, even slight elevations in temperature may indicate serious infection or disease. The elderly often have a lower baseline temperature, so serious infections may go unrecognized because of the perceived lack of a significant fever.

REVIEW QUESTIONS

- State the five cardinal signs of acute inflammation and describe the physiologic mechanisms and mediators involved in production of these signs.
- Describe the systemic manifestations associated with an acute inflammatory response.
- Compare the etiology and pathogenesis of acute and chronic inflammation.
- Trace the wound-healing process through the inflammatory, proliferative, and remodeling phases.
- Explain the effect of malnutrition; ischemia and oxygen deprivation; impaired immune and inflammatory responses; and infection, wound separation, and foreign bodies on wound healing.
- Apply the physiologic mechanisms involved in body temperature regulation to describe the four stages of fever.
- Describe the criteria used when determining the seriousness of fever without source in children younger than 36 months.
- State the definition for fever in the elderly and cite possible mechanisms for altered febrile responses in the elderly.

connection

Visit the Connection site at connection.lww.com/go/porth for links to chapter-related resources on the Internet.

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