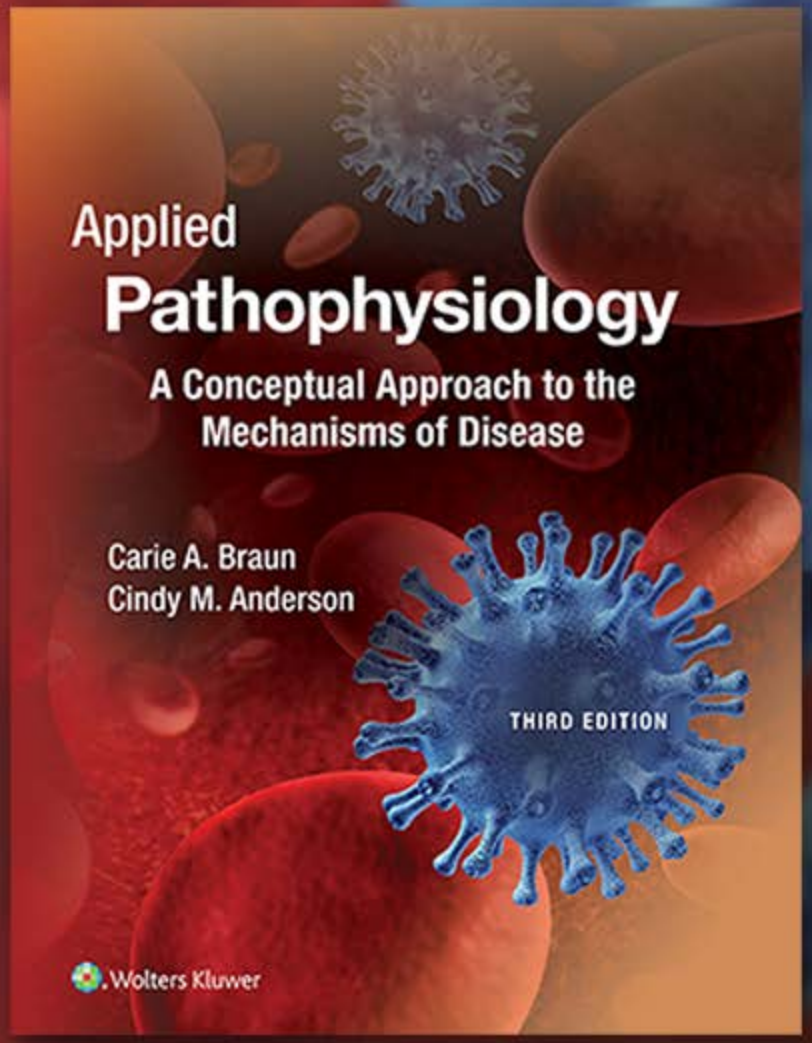

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CASE STUDY 3.1

A friend has disclosed that she has been having problems with heartburn. She has been told that she has gastroesophageal reflux disease (GERD), in which stomach acid backs up into the esophagus causing esophagitis. Think about which clinical model is most related to this process. From your reading related to cellular injury and adaptations as well as inflammation, answer the following questions:

1. **What anatomic problem most likely leads to gastroesophageal reflux?**
2. **What is the injury in gastroesophageal reflux?**
3. **What would the acute inflammatory response look like?**
4. **Why might this condition become a chronic problem?**
5. **What pathophysiologic changes would mo**

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formation as discussed above. Other systemic manifestations associated with chronic inflammation may include fever, malaise, anemia, fatigue, anorexia, weight loss, or weakness. Remission of the chronic inflammation can occur in some conditions; during these times the patient will have no symptoms.

See video, Tight Pectoralis Minor

TREATMENT

The treatment of chronic inflammation is aimed at removing the source of injury if possible and managing symptoms. Long-term use of antiinflammatory, analgesic, or immune-modifying drugs are often

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ment has been employed resolution may improve with the application of warmth/heat and increased movement. As with all health conditions, optimal fluid and nutritional intake is needed to facilitate healing.

Stop and Consider

The RICE (rest, ice, compression, elevation) protocol is employed frequently in acute injury to minimize the effects of inflammation. How does each of these components reduce inflammation?

Resolution of Acute Inflammation

The acute inflammatory response is self-limited. Once the offending agent has been destroyed and removed, feedback systems regulated by the three plasma protein systems (clotting, complement, and kinin), along with the relevant inflammator

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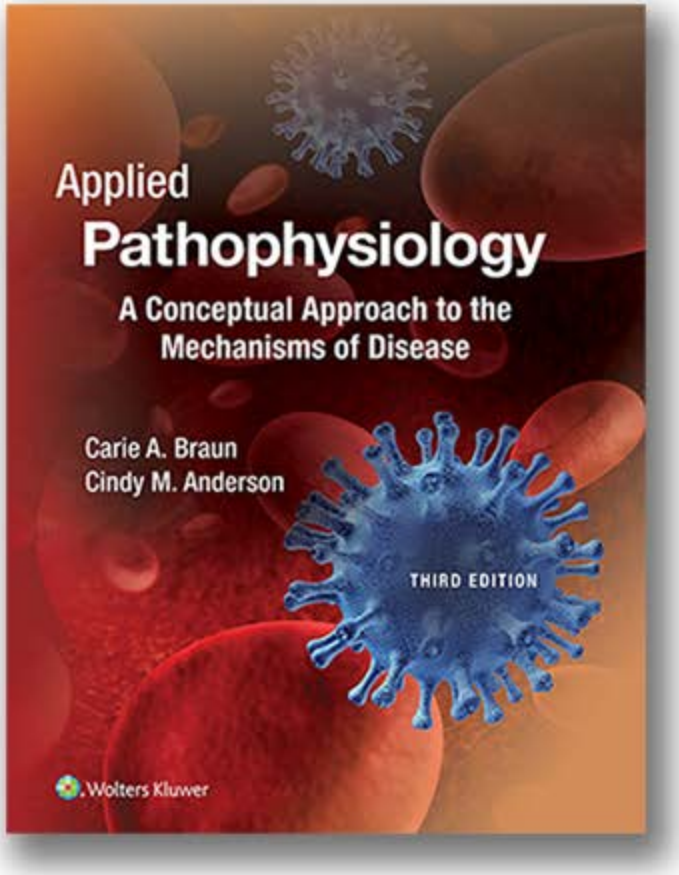

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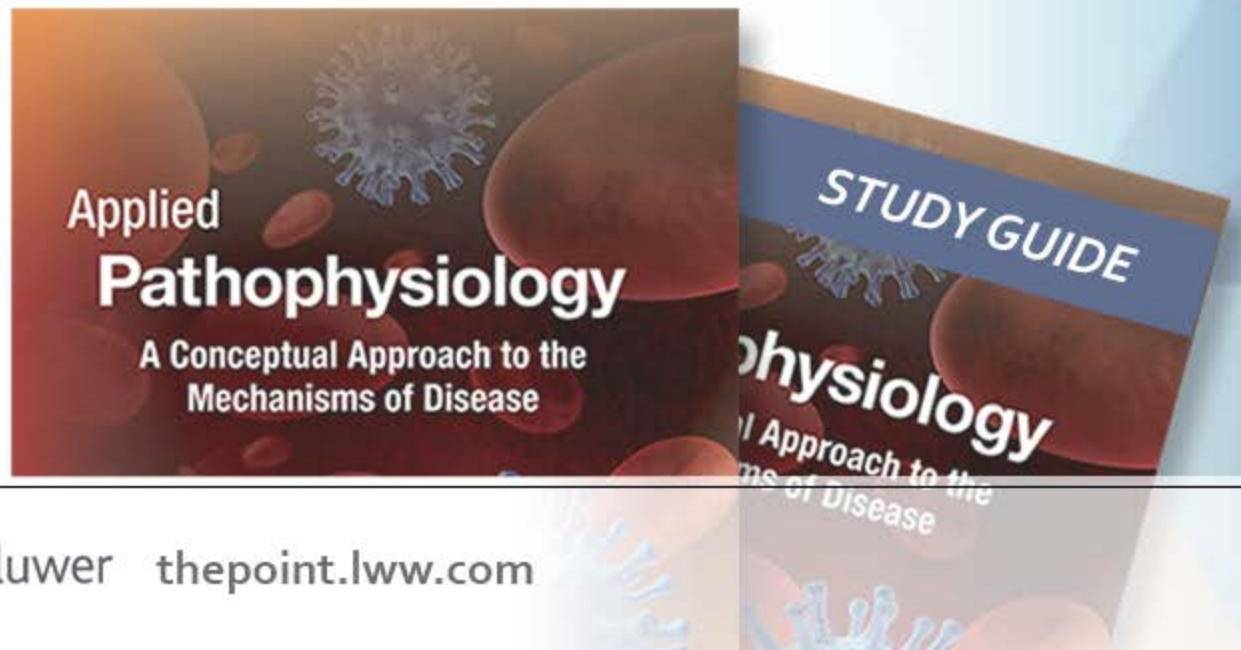

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Chapter

3

Inflammation and Tissue Repair

LEARNING OUTCOMES

1. Define and use the key terms listed in this chapter.
2. Differentiate the three lines of defense.
3. Outline the process of acute inflammation, including the role of chemical mediators.
4. Describe the process of healing and repair after tissue injury.
5. Differentiate acute and chronic inflammation.
6. Identify the cardinal signs of inflammation.
7. Discuss treatment methods used for acute and chronic inflammation.
8. Apply concepts of acute and chronic inflammation to select clinical models.

INTRODUCTION

Think back to all of the injuries, even minor ones, that you have sustained in your lifetime. When did you last burn the roof of your mouth on hot pizza, get a paper cut, or sprain your ankle? All of these activities, and many others, cause tissue trauma that requires healing. This chapter focuses on the inflammatory response, which occurs with any type of injury. Inflammation is critical for you to understand as a student in the health professions. All disease processes cause injury, and healing can occur only with an effective inflammatory response. The *acute* inflammatory response is considered an expected body response to injury; *chronic* inflammation is presented as an altered inflammatory response because of unrelenting injury. The stages of tissue repair and complications that can occur during the healing process are also detailed in this chapter.

Review of Body Defense Mechanisms

Protection of the body depends on three major lines of defense, as depicted in Figure 3.1:

- The first line of defense relies on the protection of the skin and mucous membranes.
- The second line of defense is waged through an effective inflammatory response.
- The third line of defense is activated through the immune response.

The skin and mucous membranes comprise a physical and chemical barrier to invasion and are considered the first line of defense. Skin allows a protective

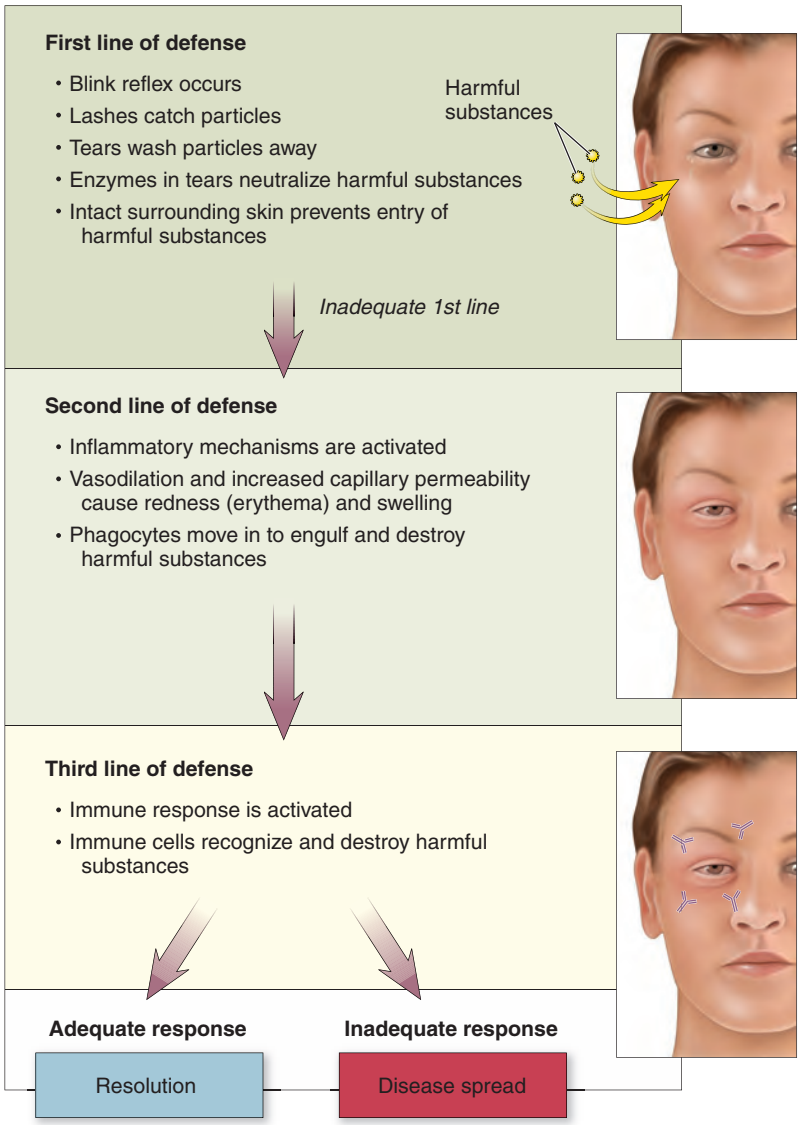


Figure 3.1. Lines of defense.

physical barrier against harmful substances in the external environment. Areas not covered by skin are protected by chemically coated mucous membranes that help to neutralize or destroy many harmful invaders. Tears and saliva are examples of enzyme-filled fluids that bathe mucous membranes and offer essential protection to the eyes and oral cavity. Breaks in the skin and mucous membranes or loss of protective fluids allow microorganisms and other harmful agents to enter the body and threaten homeostasis.

Stop and Consider
What can you do to improve or strengthen your first line of defense?

The second line of defense, or inflammatory response, is activated when the first line of defense is inadequate. The inflammatory response is nonspecific; that is, the process of waging an inflammatory response is identical regardless of the cause of injury. The **immune response** is considered to be the third line of defense. The immune response wages a specific defense depending on the type of invader; this is the focus of Chapter 4.

Stop and Consider
What lines of defense are you enhancing by putting on an antibiotic ointment and covering a laceration with a Band-Aid?

Module 1 Acute Inflammation

Acute inflammation is triggered by tissue injury and is essential for healing. **Injury** is defined in the broadest sense to include any form of damage or alteration to cells or tissues. Injury can include invasion by microorganisms, cellular mutations, hypoxia or anoxia, nutritional deficiencies, and physical or chemical damage. The acute inflammatory response has three major goals:

1. To increase blood flow to the site of an injury, which is referred to as the **vascular response**
2. To alert the products of healing to attend to the site of injury, which is referred to as the **cellular response**
3. To remove injured tissue and prepare the site for repair and healing

The process of inflammation requires the ability to recognize the injury, activate a response, and appropriately shut down the response when the injury has passed. The result is tissue repair, regeneration, or the formation of scar tissue.

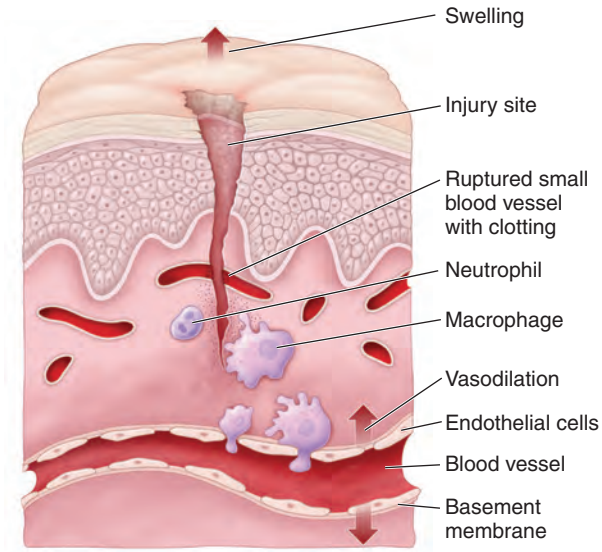


Figure 3.2. Vascular response. Inflammation causes widening of endothelial cell junctions and vasodilation. (Modified from Werner R, Benjamin BE. *A Massage Therapist's Guide to Pathology*. 3rd ed. Baltimore, MD: Lippincott Williams & Wilkins; 2005, with permission.)

Vascular Response

Tissue injury requires a response at the level of the blood vessel near the site of the injury. Put simply, clotting must occur. If the blood vessels are considered roads, injury requires that the roads be widened and expanded to allow for emergency vehicles to get to the scene of the accident. The objective is to attract sufficient products of clotting and healing to the site of injury and to prevent infection.

Anatomically, the structure of the blood vessels must change to accommodate this increase in emergency vehicle traffic.

- The blood vessels **dilate**, or widen, to accommodate increased blood flow to the site of injury.
- The lining of the blood vessel becomes more **permeable**, or loosens to allow cells to easily move from the vessel into the injured tissue.

Loosening of the blood vessel must occur with the basement membrane of the blood vessel and adjacent endothelial cells (Fig. 3.2). **Endothelial cells** form a tight junction within the inner lining of the blood and lymphatic vessels and the heart. Endothelial cells are connected to the basement membrane. The **basement membrane** is the outer membrane of the vessels, which separates the vessel from the tissues of the body. The vessel walls are needed to confine blood cells and plasma, but with injury, they must be loosened to allow for movement of healing fluids and cells into damaged tissues.

Increased blood and fluid are needed at the site of the injury for two reasons:

1. Blood is composed of cells active in **phagocytosis**, the process of engulfing and removing harmful agents, as well as cells essential in promoting healing and developing an immune response.
2. Increased fluid dilutes harmful substances at the site of the injury.

Inspection of a scraped knee after a bike accident will show a layer of watery fluid that seeps from the wound. **Exudate**, the watery fluid that accumulates at the site of injury, has a high protein and leukocyte concentration. This is a sure sign that the vessels have become more permeable and that cells active in phagocytosis are present and ready to fend off microorganisms. Healing can then begin.

This whole process is orchestrated through the work of potent chemicals, referred to as inflammatory mediators. **Inflammatory mediators**, specifically vasoactive inflammatory mediators, facilitate the process of widening and loosening the blood vessels at the site of injury. Inflammatory mediators are located in the blood plasma and in many cells, including platelets, mast cells, basophils, neutrophils,

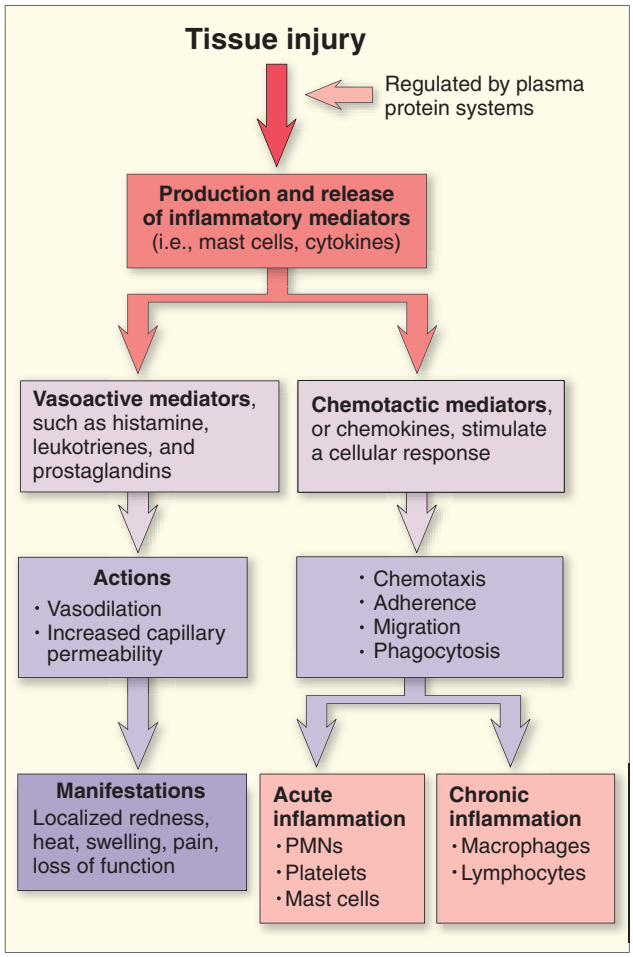


Figure 3.3. Concept map. An overview of the importance of chemical mediators in the vascular and cellular responses of inflammation. PMNs, polymorphonuclear neutrophils. (Modified from Rubin E, Farber JL. *Pathology*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005, with permission.)

endothelial cells, monocytes, and macrophages. The location of inflammatory mediators is important; these substances must be constantly ready to respond to injury anywhere in the body. Figure 3.3 illustrates the major roles of the inflammatory mediators in the inflammatory process. Refer to this figure frequently as you move through this chapter.

INFLAMMATORY MEDIATORS WITHIN CELLS

As mentioned, some inflammatory mediators are formed within the blood plasma and some are formed within cells. Within cells, most of these inflammatory mediators are generated in the cell plasma membrane or are made up of proteins within the cell. Most commonly, it is the white blood cells (WBCs) that produce and release inflammatory mediators; platelets, endothelial cells, and injured tissue cells are also potential sources. The generation and activation of inflammatory mediators is a complex process. Try not to get overwhelmed. In this section, focus on the key inflammatory cells, where they are located, examples of inflammatory mediators released from those cells, and what their role is in the inflammatory process.

Inflammatory Mediators Within White Blood Cells

The **mast cell** is an important inflammatory mediator. Mast cells are leukocytes (WBCs) that are housed throughout the connective tissues of the body and near all blood vessels. The placement of the mast cell allows for a rapid response directly at the site of the injury. Mast cells are similar to having emergency first responders trained in all neighborhoods. They are right there on the scene. The mast cell is responsible for the production and immediate release of inflammatory mediators through a process of **degranulation**, the mast cell breaks apart and releases inflammatory mediators in the form of extracellular granules (grain-like particles). The **basophil**, a WBC that also contains granules, functions in the same manner. Examples of inflammatory mediators released by mast cells include histamine, leukotrienes, and prostaglandins.

Stop and Consider

Where have you heard the names of the various inflammatory mediators listed above? What do you already know about these inflammatory mediators?

Signals to trigger, enhance, and discontinue the inflammatory response are also generated within other WBCs, such as lymphocytes and monocytes/macrophages. For example, **cytokines** are more than a hundred distinct cell proteins most often found within WBCs that have a vital role in regulating inflammation; they are active from the onset of vasodilation and increased vascular permeability to the resolution of the inflammatory response. Each of the different cytokines is released from a specific cell and serves a specific purpose. For example, cytokines released from lymphocytes are called lymphokines. Those released from monocytes or macrophages are called monokines. Other examples of cytokines include interleukins, growth factors, interferons, and chemokines. Now try not to hyperventilate here. The main point is that potent inflammatory mediators are released from a variety of WBCs in order to effectively orchestrate the inflammatory process.

Inflammatory Mediators Within Platelets

Platelets are also active in generating and releasing inflammatory mediators to promote vasodilation,

clotting, attraction of WBCs, and healing of injured tissues. Serotonin is one example of an inflammatory mediator found in platelets. Serotonin causes vasodilation and increased vascular permeability, allowing cells of healing to arrive quickly to the site of injury. Histamine, which functions similarly to serotonin, is found in both WBCs and platelets.

Inflammatory Mediators Within Endothelial or Injured Tissue Cells

Inflammatory mediators can also be released from endothelial cells or injured tissue cells. For example, **platelet-activating factor** is a complex lipid stored in cell membranes, including those of endothelial cells that line blood vessels, and in many other types of cells that can become injured. Platelet-activating factor is a potent inflammatory mediator that has a key role in promoting vessel vasodilation, clotting, and attracting infection-fighting WBCs to the site of injury.

Another example is arachidonic acid. **Arachidonic acid** is a substance derived from the plasma membrane of an injured cell, which generates various inflammatory mediators through a complex chemical conversion. Inflammatory mediators associated with arachidonic acid include prostaglandins, lipoxins, leukotrienes, and thromboxane. These inflammatory mediators are active in the processes of vasodilation and vasoconstriction, increasing vascular permeability, bronchodilation and bronchoconstriction, and attraction of leukocytes. Corticosteroids are a highly effective group of anti-inflammatory drugs that work to block the production of arachidonic acid, thereby decreasing the inflammatory response. Corticosteroids also have a role on inhibiting the immune response, as discussed in Chapter 4.

Stop and Consider
Why would you want to block the production of arachidonic acid and inhibit the work of the inflammatory mediators?

INFLAMMATORY MEDIATORS WITHIN PLASMA

Inflammatory mediators can also circulate continuously within blood plasma. This is usually accomplished through the work of three major interrelated pathways. These pathways are responsible for the activation and deactivation of inflammatory mediators that circulate in the plasma. Table 3.1 summarizes these three pathways.

Multiple sources and pathways to induce and suppress inflammation are necessary because the inflammatory response *must occur* to heal tissues, and the inflammatory mediators are so *potent and powerful* that multiple pathways are needed to regulate these substances. Impaired activation of inflammation can lead to inadequate blood flow to the injured area. This will impair healing by limiting phagocytosis, clot formation, and repair of injured tissues. Impaired inhibition of inflammation can lead to an uncontrolled inflammatory response, the depletion of proteins needed within the three pathways (complement, clotting, and kinin). Loss of the ability to shut down the inflammatory response effectively can also lead to **autoimmunity**, a self-attack against body tissues.

To summarize, the initial steps in the inflammatory response influenced by vasoactive inflammatory mediators include:

- Tissue injury
- Blood vessel vasodilation
- Increased vascular permeability
- Clotting cascade activated
- Continued release and circulation of vasoactive inflammatory mediators

Cellular Response

After the vessels are dilated and permeable, the cells essential for healing are needed at the site of injury. As with the vascular response, the cellular response

Table 3.1 Continuously Circulating and Interrelated Plasma Systems That Regulate Inflammation

System	Key Characteristics
Complement	Several proteins that comprise 10%–15% of plasma; produced in liver
	Triggered by the presence of microorganisms
	Once triggered, activates a cascade of inflammatory mediators
	Primary role to destroy and remove microorganisms to prevent infection through **opsonization** (making bacteria vulnerable to phagocytosis) and cell **lysis** (destruction)
Clotting	Promotes coagulation through a cascade of clotting factors
	Suppresses coagulation when clotting is complete
	Various clotting factors produce and release inflammatory mediators
Kinin	Source of highly potent vasoactive inflammatory mediators
	Amplify the inflammatory response by triggering other inflammatory mediators

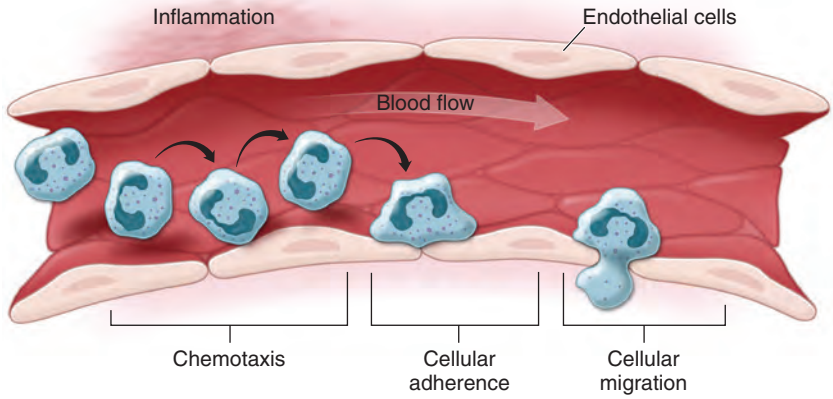


Figure 3.4. Cellular response: chemotaxis, adherence, and migration. (Modified from Rubin E, Farber JL. *Pathology*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005, with permission.)

is regulated by inflammatory mediators. Three steps are needed for a successful cellular response: (1) chemotaxis, (2) cellular adherence, and (3) cellular migration (Fig. 3.4).

Chemotaxis is a process of moving certain cells to the site of injury. Specific inflammatory mediators, referred to as **chemotactic factors**, are activated, which attract specific types of cells. The neutrophil chemotactic factor attracts neutrophils. The eosinophil chemotactic factor attracts eosinophils, and so forth.

Table 3.2 Cells Active in the Cellular Response

Cell	Role
Leukocytes (WBCs)	Phagocytosis; removal of dead tissue
Neutrophils	A type of WBC; earliest phagocytic responders
Macrophages	A type of WBC; large, long-lived phagocytes associated with a prolonged (chronic) inflammatory response; monocytes are immature macrophages
Erythrocyte (red blood cells)	Carry oxygen to tissues
Platelets	Trap harmful substances; stop bleeding; form structural origin of repair

WBC, white blood cell.

Blood cells are constantly moving through the vascular system. Attraction and binding, or cellular **adherence**, is another step essential for effective phagocytosis. Cellular adherence is regulated by:

- Inflammatory mediators, specifically, chemotactic factors released by endothelial cells
- Receptors that bind leukocytes to the surface of endothelial cells near the site of injury

Cellular migration is the third essential step in the cellular response. The cellular response depends on the ability of cells, primarily leukocytes, erythrocytes, and platelets, to migrate, or move across, endothelial cells and get to the exact site of the injury. In the process of **diapedesis**, cells can move between and through endothelial junctions. The role of the major cells activated in the cellular response is summarized in Table 3.2. Leukocyte is a global term for many different types of WBCs, including neutrophils, monocytes, macrophages, mast cells, basophils, and T and B lymphocytes. Because there is extensive crossover of cellular activity between the inflammatory response, immune response, and the subsequent development of infection, this discussion of the cells will continue into the next two chapters and beyond.

During phagocytosis, inflammatory cells release inflammatory mediators to attract more neutrophils. The neutrophil itself also releases potent inflammatory mediators as it works to engulf and digest impaired tissue. During this aggressive process, unaffected, healthy tissue is also destroyed. Tissue destruction is minimized by the work of inhibitor proteins in the plasma-derived complement, clotting, and kinin systems.

GENERAL MANIFESTATIONS

The local manifestations of acute inflammation are often referred to as the **cardinal signs**. These signs include **erythema** (redness), heat, swelling, pain, and loss of function. **Lymphadenitis**, or enlargement and inflammation of the nearby lymph nodes, can occur as a function of filtering or draining

harmful substances at the injury site. Local manifestations with rationales are presented in Table 3.3. These manifestations are primarily related to vasodilation and fluid accumulation in the tissues as a result of the activation of inflammatory mediators.

Table 3.3 Local Manifestations of Acute Inflammation

Manifestation	Rationale
Redness (erythema)	Vasodilation; increased blood flow to the injured area
Heat	Vasodilation; increased blood flow to the injured area
Incapacitation	Loss of function is related to tissue damage from injury, pain, and swelling at the site
Pain	Increased vascular permeability and accumulation of fluid causes compression in the tissues; inflammatory mediators can also directly elicit a pain response
Exudate and edema	Extracellular fluid accumulation often in tissues because of increased vascular permeability

Systemic manifestations related to the inflammatory response include fever, leukocytosis, and a higher percentage of circulating plasma proteins. **Pyrexia**, or fever (an elevated core body temperature), is a result of inflammatory mediators acting directly on the hypothalamus. The hypothalamus is responsible for controlling body temperature. An elevated body temperature stimulates phagocytosis and can also inhibit the growth of certain microorganisms. **Leukocytosis** is an elevation in WBCs, or leukocytes, with a count usually above 10,000/mm^3. Typically, the individual has a WBC count of 5,000 to 10,000/mm^3. All laboratory information is approximate because variability in laboratory ranges exists among various populations and sources. Leukocytosis demonstrates the increased circulation of WBCs to aid in healing. Plasma proteins are also increased as a result of the three plasma protein systems discussed previously. These proteins are called acute-phase reactants and can be measured through the use of laboratory tests, such as C-reactive protein (CRP). Common blood tests used to detect inflammation are presented in Table 3.4.

Stop and Consider

What does an elevation in leukocytes, erythrocyte sedimentation rate (ESR), or CRP levels tell you about the *location* of acute or chronic inflammation?

TREATMENT

The inflammatory response has multiple components and is often considered "overzealous," which explains the efforts of the booming pharmaceutical industry to find effective anti-inflammatory drugs. Damage to healthy surrounding tissue is a common occurrence in the acute inflammatory response. Therefore, the initial treatment principles for acute inflammation are to:

1. Reduce blood flow to the local area
2. Decrease swelling
3. Block the action of various inflammatory mediators
4. Decrease pain

RESEARCH NOTES

In a recent issue of Inflammation Research, scientists are uncovering new ways of thinking about pharmacologic treatment for inflammation. Current therapy targets one aspect of the inflammatory process (e.g., blocking the production of arachidonic acid). Emerging research is demonstrating a significant value of designer drugs created to target several aspects of tissue repair. Such drugs combine actions of multiple cells and chemicals to regulate the complex metabolic and immune pathways underlying inflammation. The authors note, "addressing multiple targets of inflammation holistically, in moderation, is probably a more evolutionarily viable strategy, as compared to current therapy, which addresses drug targets in isolation."[1]

FROM THE LAB

CRP and the erythrocyte sedimentation rate (ESR) are two nonspecific tests of inflammation. Elevations in either test will signify inflammation is present, but neither will identify the exact source or location of the inflammation. CRP is often the preferred test for acute inflammation. CRP signifies the presence of a specific protein triggered by plasma protein systems during the inflammatory process. The erythrocyte sedimentation rate (also referred to as a sed rate) is a nonspecific method of testing for inflammation. During the inflammatory process, the coagulation cascade results in increased circulating levels of fibrinogen, which causes cells to stick together. When measured in a tube in the lab, red blood cells (RBCs) exposed to the inflammatory process will fall faster and will clump together. The ESR test then measures (in mm/hr) the level of RBC stacking.[2]

Table 3.4 Common Blood Tests Used to Detect Acute Inflammation

Blood Test	Reference Values	Changes With Inflammation
White blood cell count	5,000–10,000 cells/mm^3	Circulating white blood cells are increased, often above 10,000/mm^3
White blood cell differential	Neutrophils, 45%–75% Bands (immature neutrophils), 0%–5% Eosinophils, 0%–8% Basophils, 0%–3% Lymphocytes, 16%–46% Monocytes, 4%–11%	Measures proportion of each of the five types of white blood cells; the proportion of immature neutrophils (bands) is increased in comparison to other white blood cell types
Erythrocyte sedimentation rate	0–17 mm/hr for men 1–25 mm/hr for women 44–114 mm/hr in pregnancy 1–13 mm/hr for children	Detects red blood cell clumping or stacking as a result of increased fibrinogen levels; levels increase, often above 100 mm/hr for those with inflammation
C-reactive protein	Routine CRP <10 mg/L High sensitivity CRP, 0.1–3.8 mg/L	>10 mg/L indicates significant inflammatory disease
Complement activity	Total complement, 63–145 U/mL C3 (comprises 70% of total protein in the complement system), 80–184 mg/dL	Elevated in inflammation signifying the activation of complement; over time may decrease, indicating that complement factors are exhausted
Prothrombin time	Measured in time to coagulate, approximately 11.2–13.2 seconds	Increased prothrombin levels result in a reduced time to coagulate
Fibrinogen	175–400 mg/dL	Elevated during inflammation to promote coagulation

CRP, C-reactive protein.

The goal of treatment is to minimize damage to healthy, unaffected tissue and promote rapid healing. Pharmacologic, or drug treatments for inflammation most commonly block the action of inflammatory mediators, thereby reducing the swelling, pain, redness, and warmth typical of inflammation. Table 3.5 illustrates the actions of common pharmacologic treatments for inflammation. Nonpharmacologic treatments for inflammation initially include rest, ice, compression, and elevation. Once the initial treatment has been employed, resolution may improve with the application of warmth/heat and increased movement. As with all health conditions, optimal fluid and nutritional intake is needed to facilitate healing.

Stop and Consider

The RICE (rest, ice, compression, elevation) protocol is employed frequently in acute injury to minimize the effects of inflammation. How does each of these components reduce inflammation?

RESOLUTION OF ACUTE INFLAMMATION

The acute inflammatory response is self-limited. Once the offending agent has been destroyed and removed, feedback systems regulated by the three plasma protein systems (clotting, complement, and kinin), along with the relevant inflammatory mediators, deactivate the inflammatory response, allowing the tissue to heal.

Table 3.5 Common Pharmacologic Agents Used to Treat Inflammation

Pharmacologic Agent	Action
Aspirin	Inhibits the conversion of arachidonic acid to prostaglandins to suppress inflammation, reduce pain, and reduce fever
Nonsteroidal anti-inflammatory drugs	Similar to aspirin; inhibit the anti-inflammatory conversion of arachidonic acid to prostaglandins (NSAIDs) Examples: ibuprofen, naproxen
Glucocorticoids	Act through several mechanisms to interrupt the inflammatory process: inhibit synthesis of chemical mediators and reduce swelling, warmth, redness, and pain; suppress infiltration of phagocytes and avert tissue damage from release of lytic (cell-destroying) enzymes; suppress lymphocyte proliferation; and reduce immune component of inflammation. Example: prednisone

NSAIDs, nonsteroidal anti-inflammatory drugs.

Module 2 Healing and Tissue Repair

Tissue repair is similar to home repair. If a home is damaged, the destroyed area needs to be sealed off to prevent further exposure to the external environment. Then a process can begin to clear the debris, rebuild the walls and roof, and restore the interior working contents of the home, such as the electrical system, appliances, or heating system. Likewise, the goal of tissue healing and repair is to seal the wound, clear the debris, and restore the structural and functional integrity of the injured area. This process is often divided into three phases: the inflammatory phase, the proliferative phase, and the remodeling phase. Within these phases, structural supports must be rebuilt and functional cells and tissues regenerated or replaced (Fig. 3.5).

The construction workers of tissue repair fit into the following categories:

- Clotting (coagulation) factors to stop bleeding and form a fibrin clot
- Inflammatory mediators to promote chemotaxis to the affected area
- Proteinases (enzymes) to degrade dead tissue
- Proteinase inhibitors to prevent healthy tissue breakdown
- Matrix, or structural, proteins to rebuild architectural supports
- Molecule receptors to attract cells needed to form a structural matrix
- Adhesion molecules to provide "stickiness" to these cells
- Growth factors to promote regeneration of new cells and tissues

Sealing the Wound

Inflammatory mediators released from platelets and other cells constrict blood vessels and form a clot at the site. A protective scab is formed from dried blood and exudate. This protective clot and subsequent scab is also called a **thrombus**. The role of the thrombus is to form a physical barrier to prevent additional harmful substances from entering the wound. This covering also prevents the loss of plasma. Epithelial (skin) cells regenerate under the thrombus. Once reepithelialization is complete, enzymes degrade the scab.

Stop and Consider

Why is it not a good idea to pick off a scab before a wound has healed?

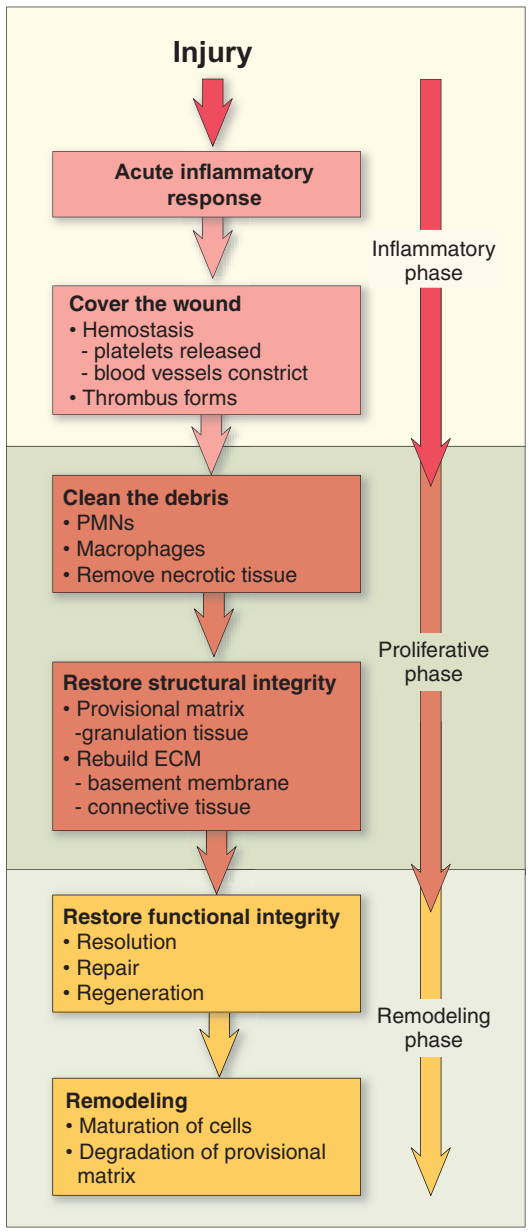


Figure 3.5. Concept map. Phases of healing and tissue repair. ECM, extracellular matrix; PMNs, polymorphonuclear neutrophils.

Clearing the Debris

Chemical mediators activate neutrophils to move into the injured area and begin the work of healing. The inflammatory response activates neutrophils and later macrophages to engulf, digest, and remove harmful substances and debris. The process of healing cannot begin until the necrotic cells and tissues are removed.

Restoring Structural Integrity

Restoring structural integrity depends on the delicate balance of tissue destruction and construction. Tissue lysis, or breakdown and removal, is accomplished through the work of enzymes that are needed to rid the body of the damaged tissue. Growth factors and matrix proteins are responsible for rebuilding the **extracellular matrix** (ECM), the layers of architectural structures that support the cells.

Extracellular matrices include the basement membrane and connective tissue layers. The basement membrane serves to:

1. Provide a supportive architectural structure
2. Support **reepithelialization**, or the movement of epithelial cells to form a covering over the wound
3. Store growth factors
4. Restore neuromuscular function
5. Support the development of **parenchymal** tissues, that is, those tissues made up of cells with a specific function (such as neurons, myocardial cells, and epithelial cells)

The basement membrane is reproduced by endothelial, epithelial, muscle, adipose (fat), and Schwann (nerve fiber) cells. The basement membrane must be restored before reepithelialization can occur. Extensive damage to the basement membrane is a hindrance to reepithelialization because the basement membrane must be replaced first.

Another structural ECM is connective tissue (Fig. 3.6). The connective tissue layer is composed primarily of collagen, elastin, and glycoproteins. This layer is also referred to as stromal or interstitial tissue. The connective tissue layer provides storage of proteins, an exchange medium between proteins and other cells, and architectural support and physical protection from trauma by resisting stretching or compressing of tissues. Cells such as fibroblasts, adipose cells, endothelial cells, osteocytes, and chondrocytes stimulate the replacement of connective tissue.

Fibroblasts are important cells that produce and replace the connective tissue layer. Fibroblasts are stimulated by macrophages. The fibroblast moves into the area to support the constructive phase of wound healing. Fibroblasts actively manufacture and secrete collagen. **Collagen** helps to fill in the gaps left after the removal of damaged tissues. Excess collagen production leads to tissue fibrosis and can result in scarring at the site of injury.

The connective tissue layer is also composed of elastin and glycoproteins. **Elastin** allows stretching and recoil of tissue. Elastin is resistant to damage, but is also slow and difficult to replace. Damaged

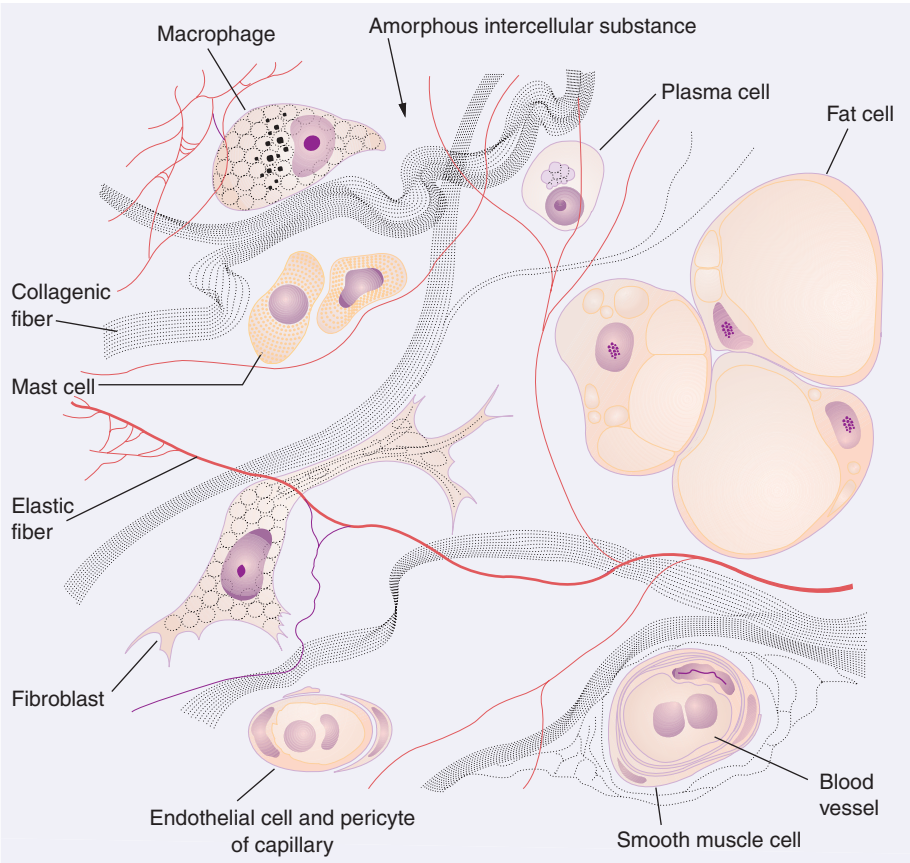


Figure 3.6. Diagram of cells that may be seen in loose connective tissue. The cells lie in the extracellular matrix that is bathed in tissue fluid that originates in capillaries. (From Cormack DH. *Ham's Histology*. 9th ed. Philadelphia, PA: J. B. Lippincott; 1987, with permission.)

tissue is often less flexible after injury. Glycoproteins are essential within the basement membrane and connective tissue layer. **Glycoproteins** regulate cell movement across the matrix, provide a place for attachment of the cells to the matrix, and prompt the cells to function.

Basement membranes and connective tissue layers are continuously present and must be replaced to support architectural structure and tissue function. A third, temporary ECM also forms in response to injury. This temporary matrix, called a **provisional matrix**, promotes healing by decreasing blood and fluid loss at the site and attracting and supporting fibroblasts, endothelial cells, and epidermal (skin) cells. When an injury occurs, increased vascular permeability allows proteins from the plasma to move to the site and form this provisional protective layer.

Macrophage activity converts this provisional matrix into **granulation tissue** (Fig. 3.7). Granulation tissue is connective tissue characterized by extensive macrophages and fibroblasts, and the promotion of **angiogenesis**, or the generation of new blood vessels, at the site. The generation of blood vessels, particularly capillaries, at the site is needed for oxygen/carbon dioxide exchange and to provide other nutrients to the newly developing tissue. Granulation tissue is most noted for the presence of an extensive network of capillaries. As the wound heals, granulation tissue loses the excessive capillary network and retains only that needed to support the final connective tissue matrix. The provisional matrix and specialized granulation tissue are no longer needed and are reabsorbed once the wound is healed and the final connective tissue matrix is in place.

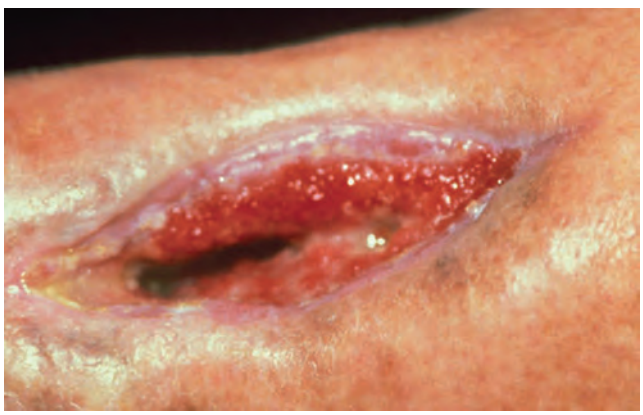


Figure 3.7. Epithelial resurfacing. Note epithelial resurfacing at superior aspect of wound, where there is healthy granulation tissue. At the inferior aspect, there is minimal epithelial resurfacing because of poor quality granulation. At the left side of the wound, there is no epithelial resurfacing because there is no granulation tissue.

Restoring Functional Integrity

A major goal in healing is to restore the functional integrity of parenchymal tissues. Parenchymal tissues are those that perform a specific body function, such as neuronal (brain) tissue, epithelial (skin) tissue, cardiac myocyte (heart) tissue, or hepatocyte (liver) tissue. Without restoring functional integrity, even minor injuries would be problematic. Restoring functional integrity can be accomplished by one of three processes:

1. Resolution
2. Regeneration
3. Replacement

Resolution is healing in response to mild injury with minimal disruption to cells, such as with a small superficial scratch or mild sunburn. The epithelial cells basically slough and regenerate without incident. Resolution is like "business as usual." Healing is rapid.

Regeneration of parenchymal tissues can occur only in those cells that undergo mitotic division. This is accomplished through (1) **proliferation** (growth and reproduction), (2) **differentiation** (cells mature and become more specialized), or (3) **diapedesis** (migration of nearby cells). Some cells constantly regenerate through mitosis, particularly epithelial cells of the skin, gastrointestinal tract, and urinary tract, and blood cells in the bone marrow. These cells are often referred to as **labile cells**. The skin is a common tissue that requires regeneration after injury. Basal epithelial cells (the bottom, or deepest, layer) are reestablished through mitosis in a process called reepithelialization. Once this continuous basal layer is reestablished, the cells mature and are shed off and regenerated every few days. A prerequisite for epithelial cell replacement is the presence of the basement membrane. In the process of reepithelialization, the skin cells at the periphery of the wound undergo mitosis and migrate inward until the process is complete (Fig. 3.8). Multiple substances, including growth factors, adhesion molecules, and receptor molecules, direct this activity.

Other cells stop regenerating when growth is complete but can resume regeneration if injured. These cells are referred to as **stable cells**. Hepatocytes in the liver are one example. Similar to epithelial cell regeneration, an intact ECM is needed to support cell division. The liver has tremendous capacity to regenerate with the support of the matrix.

Replacement through the production of scar tissue occurs in extensive wounds and when regeneration is not possible (Fig. 3.9). **Permanent cells**, such as neurons, cardiac myocytes, and the lens of the eye, do not undergo mitosis and are unable to regenerate. When permanent cells are damaged,

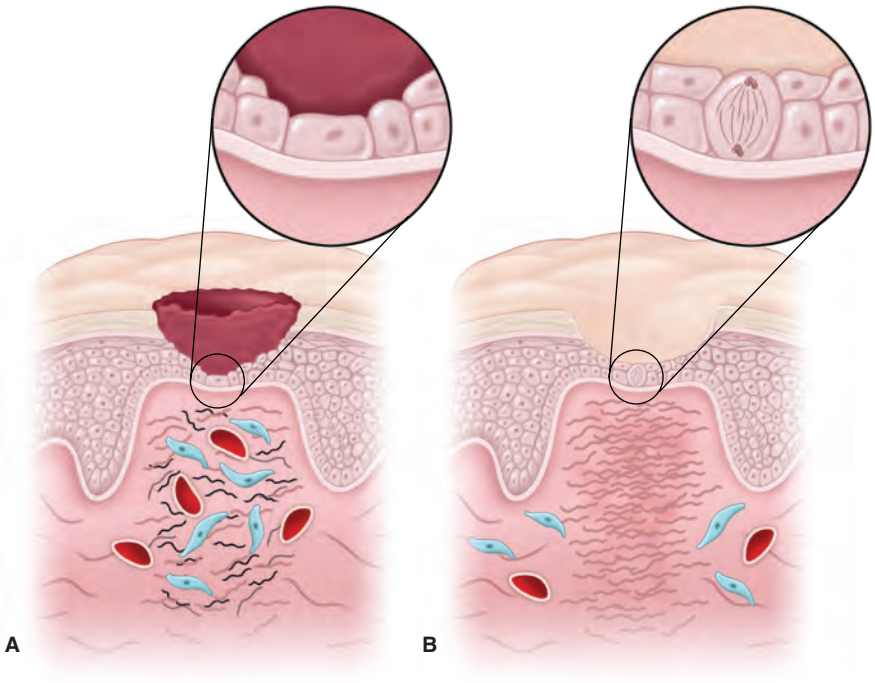


Figure 3.8. Regeneration and migration of epidermal cells. **A:** The migration of epidermal cells, sustained by the mitotic activity of neighboring cells, fills the wound gap and displaces the scab. **B:** The gap created by the wound has been repaired. The mitotic activity of the epidermal cells will restore the epidermal thickness. (Modified from Rubin E, Farber JL. *Pathology*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005, with permission.)

the functional tissue is replaced with connective tissue. For example, if neuronal tissue of the brain is destroyed by a brain tumor, the neurons do not regenerate, and the damaged area of the brain does not function as it had prior to the injury. Connective tissue, or scar tissue, can also replace labile or stable cells if the injury and subsequent damage is extensive. For example, in a severe burn that covers a large area of the body, connective scar tissue will replace the epithelial tissues of the skin. The scar tissue fills in the gap but does not function as the parenchymal tissue.

Conditions That Promote Wound Healing

Wound healing requires certain conditions. Promotion of wound healing depends primarily on adequacy of the vascular and cellular inflammatory responses, reformation of the ECM (including collagen deposition), and regeneration of those cells capable of mitosis.

These processes are enhanced and supported by an adequate dietary intake of water, proteins, carbohydrates, fats, vitamins, and minerals. The most beneficial of these nutrients are proteins and vitamins, particularly vitamins A and C. Proteins are needed during every phase of repair, including ECM regeneration and angiogenesis. Vitamins A and C are needed for reepithelialization and collagen synthesis. Adequate blood flow is also needed to transport inflammatory cells and products of healing to the injured site and to oxygenate cells and tissues.

Stop and Consider
What did you eat and drink yesterday? What nutrients did you consume that would promote wound healing?

Healing by Intention

Wounds that are smaller with approximated wound edges will heal much more quickly and easily than wounds that are large and craterlike. Approximated wound edges are those that are "lined up" or close together, such as that which occurs with a paper cut or a surgical incision. These wounds heal by **primary intention**. When healing occurs by primary intention, the wound is basically closed with all areas of the wound connecting and healing simultaneously. The risk for infection is reduced and scarring is minimal.

Larger, open, craterlike wounds must heal by **secondary intention**. These wounds heal from the bottom up. The process is much slower and more involved than the primary intention process. Healing by secondary intention results in a greater risk for infection and scarring. Figure 3.10 compares healing by primary intention with healing by secondary intention.

Stop and Consider
How does the concept of healing by primary or secondary intention compare to the body's three lines of defense?

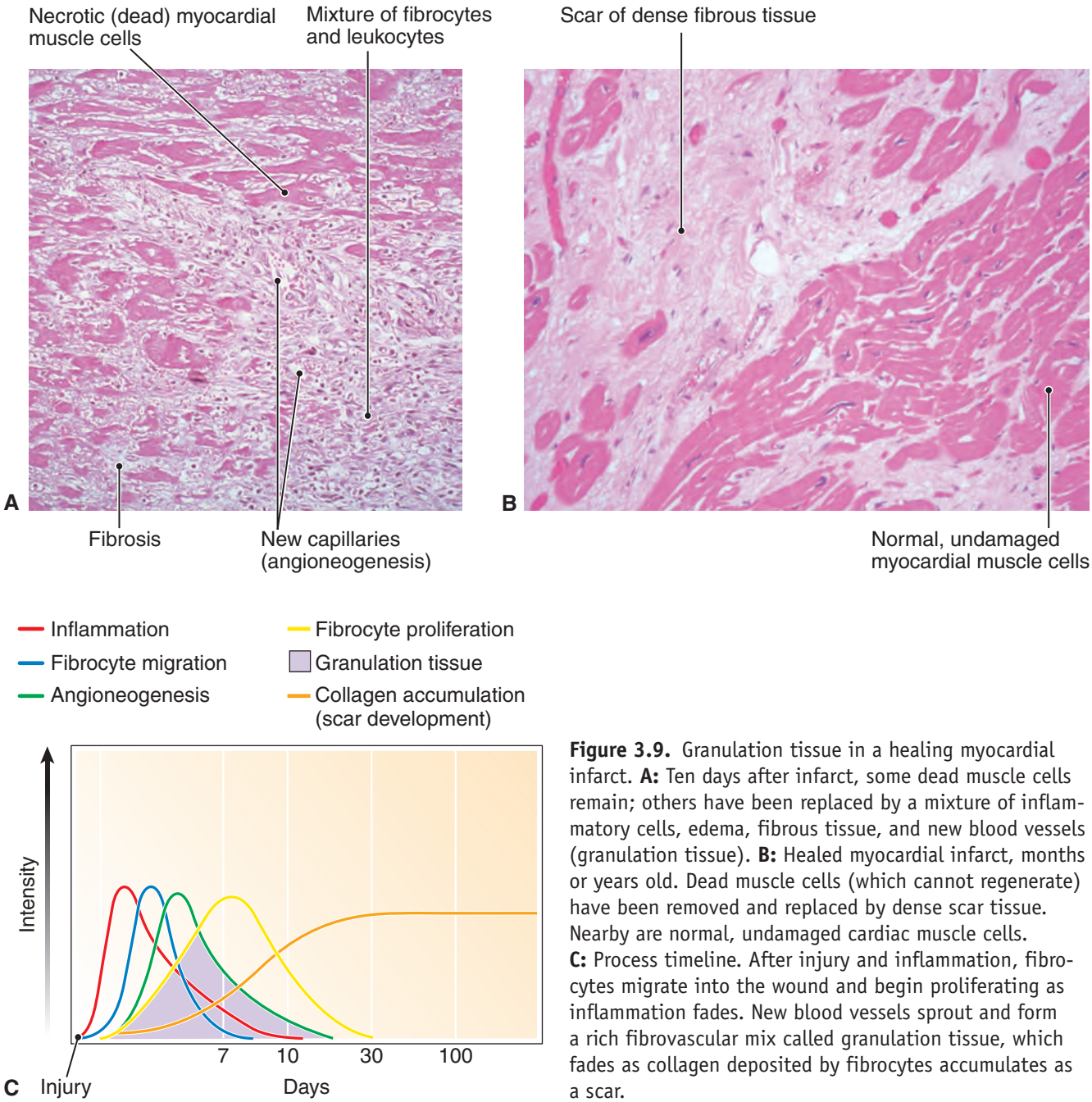


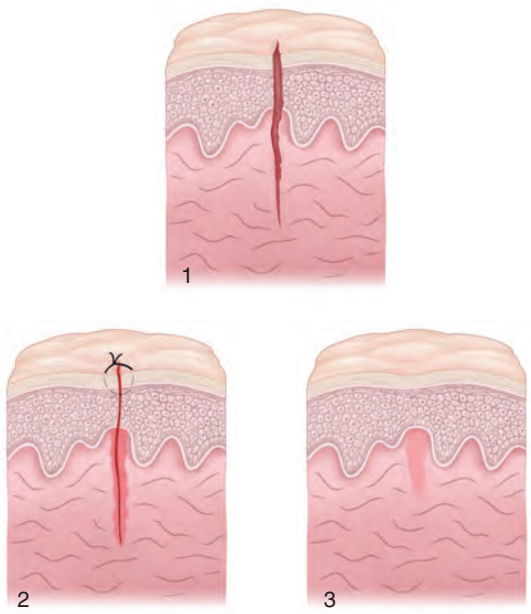
Figure 3.9. Granulation tissue in a healing myocardial infarct. **A:** Ten days after infarct, some dead muscle cells remain; others have been replaced by a mixture of inflammatory cells, edema, fibrous tissue, and new blood vessels (granulation tissue). **B:** Healed myocardial infarct, months or years old. Dead muscle cells (which cannot regenerate) have been removed and replaced by dense scar tissue. Nearby are normal, undamaged cardiac muscle cells. **C:** Process timeline. After injury and inflammation, fibrocytes migrate into the wound and begin proliferating as inflammation fades. New blood vessels sprout and form a rich fibrovascular mix called granulation tissue, which fades as collagen deposited by fibrocytes accumulates as a scar.

COMPLICATIONS OF HEALING AND TISSUE REPAIR

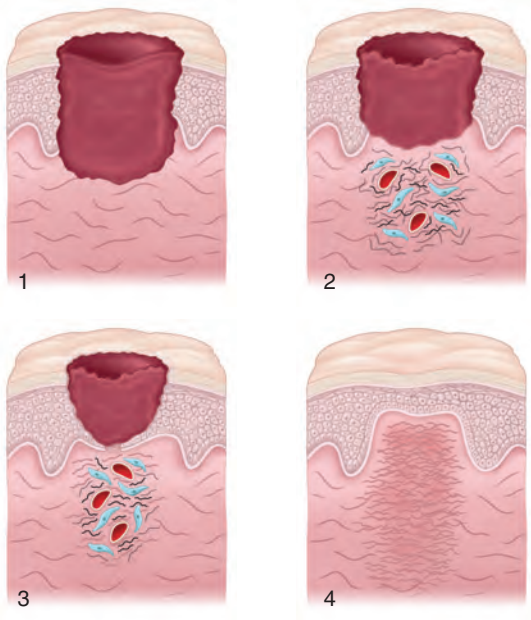
Impaired wound healing can occur at any point in the process of closing the wound, clearing the debris, and restoring structural and functional integrity. Primary factors that impact wound healing are an ineffective inflammatory response, inadequate immune response, inadequate nutritional status, and poor tissue perfusion. Common complications of wound healing include:

- Infection
- Ulceration
- Dehiscence
- Keloid development
- Adhesions

Infection (Chapter 5) refers to invasion by microorganisms. Destroying the first line of defense, along with many other factors, such as a poor inflammatory and immune response, will promote infection and ultimately impair wound healing. As mentioned, tissue healing also requires adequate **perfusion** (passage of oxygenated blood) to the site. Poor perfusion can lead to ulceration. **Ulcers** are circumscribed, open, craterlike lesion of the skin or mucous membranes. These areas are necrotic and



A Healing by primary intention (wounds with approximated edges)



B Healing by secondary intention (wounds with separated edges)

Figure 3.10. Comparison of healing by primary versus secondary intention. **A:** Healing by primary intention. **A1:** A wound with closely approximated edges and minimal tissue loss. **A2:** Such a wound requires minimal cell proliferation and neovascularization to heal. **A3:** The result is a small scar. **B:** Healing by secondary intention. **B1:** A wound in which the edges are far apart with substantial tissue loss. **B2:** This wound requires extensive cell proliferation and granulation tissue to heal. **B3:** The wound is reepithelialized from the margins, and collagen fibers are deposited into the granulation tissue. **B4:** Granulation tissue is eventually reabsorbed and replaced by a large scar. (Modified from Rubin E, Farber JL. *Pathology*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005, with permission.)

open to further invasion by microorganisms. Ulcers are often resistant to healing because of the lack of perfusion to the site and persistent habitation by microorganisms. Ulcers are a common complication of gastritis, one of the clinical models in this chapter.

Wound **dehiscence** is a problem of deficient scar formation, in which the wound splits or bursts open, often at a suture line. Wound separation, like ulceration, opens the area to invasion by microorganisms. This is a possible complication early after surgery because of mechanical stresses put on the wound during movement or coughing. Poor development of the ECM and ineffective or inadequate collagen is often the cause of wound dehiscence later in the recovery period.

Keloid development is the opposite of dehiscence. **Keloids** are hypertrophic scars that result from excessive collagen production at the site of injury (Fig. 3.11). Keloids occur with higher frequency in those with deeply pigmented skin and tend to develop in those between the ages of 10 and 30 years with a familial disposition to developing keloids. Keloids are often seen only as a cosmetic problem, but these large areas of scarring represent ineffective healing at the site. Attempts at removal of the keloid often result in another keloid forming in the same location.

Adhesions are also a problem with collagen deposition. Collagen fibers can develop and form adhesions with injuries located in or nearby serous (watery) body cavities, such as the peritoneum (inner lining of the abdomen). **Adhesions** are fibrous connections between serous cavities and nearby tissues, which do not allow the surrounding tissues to move freely. Abdominal surgery presents an increased risk for adhesion development. The collagen fibers connect to organs within the peritoneum, such as the bowel, bladder, and ovaries. Adhesions restrict free movement of the organ and cause pain and loss of organ function.

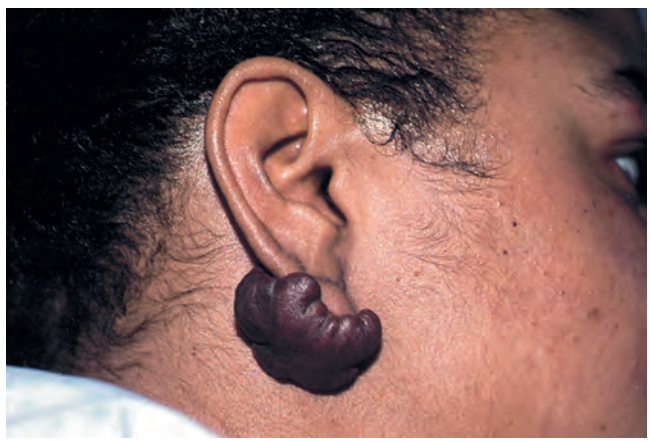


Figure 3.11. Keloid. This woman developed a keloid as a reaction to having her earlobe pierced. (Modified from Rubin E, Farber JL. *Pathology*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005, with permission.)

Module 3 Chronic Inflammation

Chronic inflammation represents a persistent or recurrent state of inflammation lasting several weeks or longer. This state occurs when the acute inflammatory and immune responses are unsuccessful. Chronic inflammation can be related to an unrelenting injury, persistent infectious process, or an autoimmune condition. Autoimmunity occurs when the immune system identifies self-cells as "foreign" and attacks these cells (Chapter 4). Often, injuries or infections that cause chronic inflammation are subtle and slow-growing. Chronic inflammation differs from acute inflammation in many ways, as illustrated in Table 3.6.

Table 3.6 Comparison of Acute and Chronic Inflammation

Characteristic	Acute Inflammation	Chronic Inflammation
Time	Resolution within a few weeks	Present for a prolonged period of time, usually greater than 6 months
Chief phagocytic cells	Neutrophils	Monocytes Macrophages Lymphocytes
Restoration	Minimal scarring	Marked by fibrosis, scarring, or granuloma formation

Cells of Chronic Inflammation

Cellular activity is notably different between acute and chronic inflammation. The longer-lasting activity of monocytes, macrophages, and lymphocytes is more prominent in chronic inflammation. Monocytes circulate in the blood to the site of injury and mature into macrophages in the tissues. As monocytes mature into macrophages, they produce **proteinases** and fibroblasts. Proteinases are enzymes that destroy elastin and other tissue components. These enzymes help to break down dead tissue; unfortunately, these enzymes do not discriminate. Proteinase activity is responsible for ongoing tissue destruction at and surrounding the site of the persistent injury. Fibroblasts are also active in chronic inflammation. Fibroblasts are responsible for collagen development, which contributes to the extensive scarring characteristic of chronic inflammation. Scarring leads to permanent loss of function and deformity of the tissue or organ.

Granuloma Formation

In some cases, chronic inflammation results in **granuloma** formation (Fig. 3.12). Granulomas are nodular inflammatory lesions that encase harmful substances. Granuloma formation is also regulated by macrophages. Granulomas typically form when the injury is too difficult to control by the usual inflammatory and immune mechanisms, such as with foreign bodies or certain microorganisms. One classic example of a microorganism that results in granuloma formation is *Mycobacterium tuberculosis*, the bacteria responsible for tuberculosis infection (Chapter 5).

By forming granulomas, macrophages protect healthy, unaffected surrounding tissue from further damage. Macrophages adapt into **giant cells** or **epithelioid cells**. Giant cells are phagocytes that can engulf particles much larger than the typical macrophage. Epithelioid cells gather and contain smaller substances by forming a wall, or fibrotic granuloma, around the affected area. Inside the wall, macrophages are busy phagocytizing harmful substances. As a result, necrosis fills the inside of the granuloma. Gradually, the necrosis diffuses through the granuloma wall and a fibrotic capsule remains.

GENERAL MANIFESTATIONS

The general manifestations of chronic inflammation can be similar to those of acute inflammation during a flare-up of symptoms, such as redness, heat, pain, swelling, and loss of function. These symptoms may lead to scarring in the affected area or granuloma formation, as discussed earlier. Other systemic manifestations associated with chronic inflammation may include fever, malaise, anemia, fatigue, anorexia, weight loss, or weakness. Remission of the chronic inflammation can occur in some conditions; during these times, the patient will have no symptoms.

TREATMENT

The treatment of chronic inflammation is aimed at removing the source of injury if possible and managing symptoms. Long-term use of anti-inflammatory, analgesic, or immune-modifying

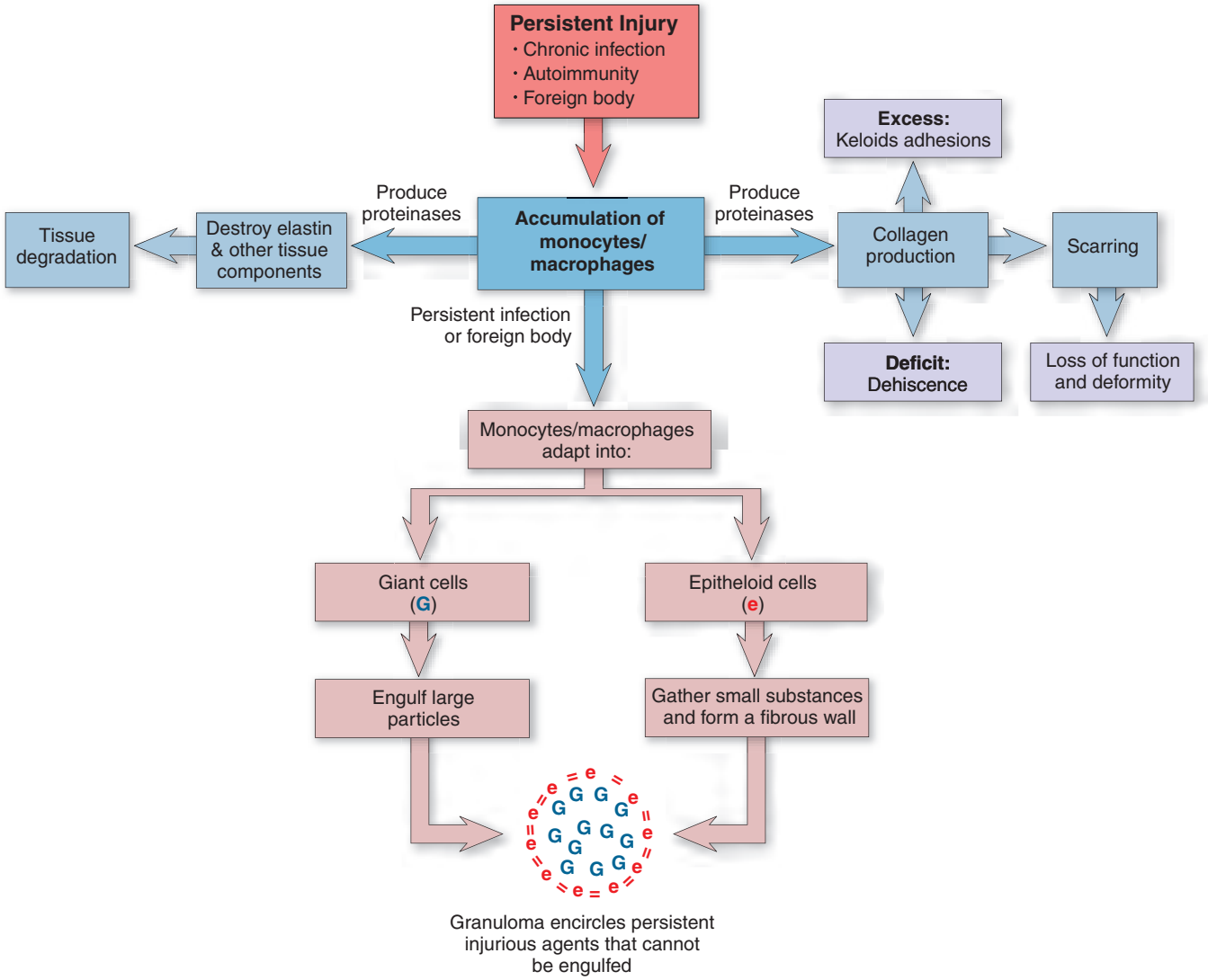


Figure 3.12. Concept map. The process of chronic inflammation leading to granuloma formation.

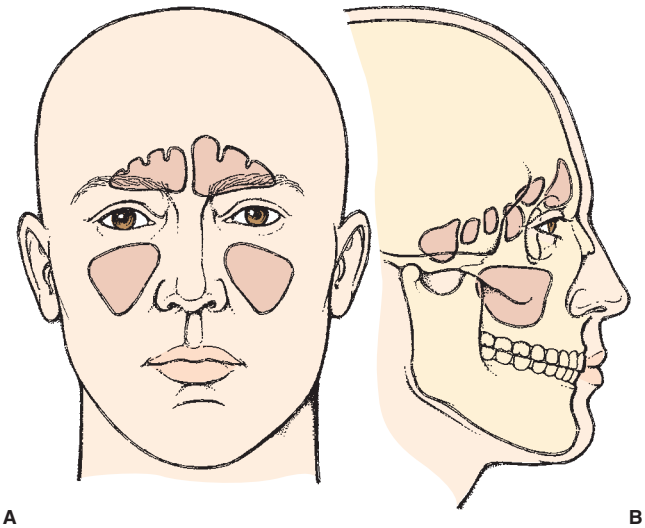
drugs is often needed. Chronic infections as a source of chronic inflammation would be treated with antimicrobial drugs (Chapter 5). Nonpharmacologic treatments are important as well, such as the use of heat or cold, immobilization, dietary changes, exercise/physical therapy, and rest. Complementary therapies, such as homeopathic preparations, acupuncture, and guided imagery, should also be explored with patients and monitored for safety and effectiveness.

Module 4 Applied Pathophysiology Clinical Models

The following clinical models have been selected to aid in the understanding and application of inflammatory processes. When reading about the clinical models, visualize the process of acute versus chronic inflammation and healing and note the commonalities and unique features of each model.

Sinusitis

Sinusitis, also known as rhinosinusitis, refers to symptomatic inflammation of the paranasal sinuses and nasal cavity. About 1 in 8 US adults have sinusitis, resulting in more than 20% of antibiotic



A B

Figure 3.13. Paranasal sinuses: anterior **(A)** and lateral **(B)** views of head.

prescriptions.[3] Children average around 6 to 8 upper respiratory tract infections (the common cold) per year, with around 10% of these further complicated by acute bacterial sinusitis. Sinusitis can be either acute or chronic.

FUNCTIONS OF THE SINUSES

Figure 3.13 depicts the paranasal sinuses, open spaces lined with protective mucosa, composed of ciliated, pseudostratified columnar epithelial cells interspersed with goblet cells. Goblet cells are responsible for secreting mucins, which is the main component of mucus. The main function of sinuses is to produce mucus that moisturizes and protects the inside of the nose. Although the nasal cavity is usually colonized with bacteria, the sinuses are most often sterile.

ACUTE SINUSITIS

Acute sinusitis is inflammation of the lining of the paranasal sinuses lasting 4 to 8 weeks. Subacute sinusitis lasts 8 to 12 weeks. Recurrent acute sinusitis occurs when the patient has up to four episodes per year, with the sinus inflammation resolving completely between episodes.

Pathophysiology

Sinuses produce secretions, which normally flow in one direction toward the ostia. The ostia provide outflow of the drainage and prevent backflow and contamination of the sinuses. If the ostia and outflow of mucus are blocked, most often because of allergy, viruses, or some other form of irritation, this can result in sinusitis. Secondly, as the nasal cavity is not sterile, impaired clearance of the mucus by protective cilia or altered mucus quality or quantity can also lead to sinusitis. Patients with cystic fibrosis and chronic respiratory allergies are at higher risk for sinusitis because of chronic nasal inflammation, changes in mucus, and mucociliary clearance issues.

The primary etiology for acute sinusitis is viral infections transmitted via respiratory droplets from person to person. The most frequently implicated viruses are rhinovirus, adenovirus, coronaviruses, parainfluenza, and the influenza A and B viruses. The presence of bacterial sinusitis is often a complication of overwhelming viral infection, which has caused increased mucus secretion, obstruction, and impaired mucociliary clearance. Other conditions that predispose to bacterial infection include respiratory allergy, facial injury, dental infections, or immunodeficiency/immunosuppression. On rare occasions, sinusitis can be the result of fungal invasion.

Clinical Manifestations

Clinical manifestations for acute sinusitis are related to the congestion of sinuses with excessive, obstructed mucus and inflammation. These clinical manifestations include:

- Facial pain over the sinus regions of the face increasing with straining or bending down (can be unilateral)
- Fever
- Nasal congestion and/or excessive nasal discharge and postnasal drainage
- Persistent cough
- Fatigue

Diagnostic Criteria

The diagnosis of acute sinusitis is often made through physical examination, revealing the clinical manifestations above, following an upper respiratory infection that has lasted greater than 10 days. General laboratory tests for inflammation or infection, such as ESR, CRP, and WBC counts, can be used, but are nonspecific.

Sinus radiographs may be helpful when the diagnosis is in question. X-rays reveal opaque, mucus-filled, thickened sinuses (Fig. 3.14).

Treatment

The primary goal of treatment is to eliminate the infection and care for the symptoms of sinusitis. Approximately 40% of acute sinusitis cases resolve spontaneously without antibiotics.[3] However, for patients without spontaneous resolution, appropriate antibiotics are needed for 14 to 21 days. Antihistamine (in respiratory allergy) and decongestant medications may be helpful. Nasal sprays that promote

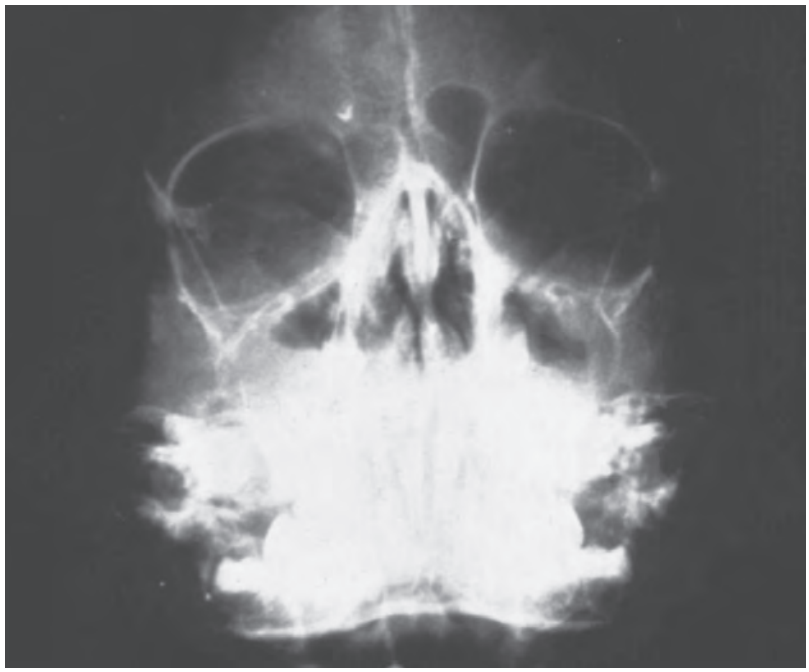


Figure 3.14. Maxillary sinusitis. This radiograph demonstrates bilateral maxillary sinusitis. There is an air–fluid level present in the right maxillary sinus and an example of mucosal swelling demonstrated in the left maxillary sinus.

vasoconstriction, such as oxymetazoline hydrochloride, should be used only up to 5 days. Otherwise, the patient could experience rebound nasal congestion and swelling.

Further evaluation is warranted if the clinical manifestations of sinusitis persist beyond antibiotic treatment or if there are episodes of recurrence. If antibiotic therapy has failed and thick, purulent sinus secretions persist, sinuses can be more aggressively treated surgically.

Chronic Sinusitis

Chronic sinusitis is a persistent low-grade inflammation of the paranasal sinuses lasting over 12 weeks with or without flares of acute sinusitis. Chronic sinusitis can occur with or without nasal polyps or as an allergic or fungal disease. Risk factors include[4]:

- Anatomic abnormalities of the ostiomeatal complex (e.g., septal deviation)
- Allergic rhinitis
- Aspirin sensitivity
- Asthma
- Nasal polyps
- Nonallergic rhinitis (e.g., vasomotor rhinitis, cocaine abuse)
- Defects in mucociliary clearance
- Nasotracheal intubation
- Nasogastric intubation
- Hormonal (e.g., puberty, pregnancy, oral contraception)
- Obstruction by tumor
- Immunodeficiency
- Cystic fibrosis
- Primary ciliary dyskinesia, Kartagener syndrome
- Wegener granulomatosis
- Repeated viral upper respiratory tract infections
- Smoking
- Environmental irritants and pollutants
- Periodontitis/significant dental disease

Similar to acute sinusitis, chronic sinusitis often begins as stasis of secretions inside the sinuses, which can be triggered by obstruction of the ostia or mucosal edema. Most cases of chronic sinusitis are due to acute sinusitis that either is untreated or does not respond to treatment.

PATHOPHYSIOLOGY

Currently, chronic sinusitis is thought to be a multifactorial inflammatory disease combining environmental factors, such as persistent infection or allergens, with genetic factors, such as metabolic abnormalities or immune deficiencies. These multifactorial triggers or risk factors, when present, disrupt mucociliary clearance and result in mucus stagnation, creating an environment conducive to bacterial growth and chronic inflammation in the sinuses.

CLINICAL MANIFESTATIONS

In contrast to acute sinusitis where facial pain and fever are common manifestations, chronic sinusitis

is much more insidious in its onset. The common clinical manifestations include:

- Nasal congestion
- Nasal and postnasal discharge
- Sore throat
- Foul breath, unpleasant taste
- Low-grade fever
- Fatigue, anorexia
- Chronic cough
- **Hyposmia**, the reduced ability to smell
- Facial fullness, discomfort, pain, and headache (with polyps)

DIAGNOSTIC CRITERIA

Diagnosis is based on a persistence of obstructed and mucus-filled sinuses over 12 weeks or longer. At least two of the following symptoms must be present:

- Anterior or posterior mucopurulent drainage
- Nasal obstruction
- Facial pain, pressure, fullness
- Hyposmia

These must be accompanied by the presence of chronic inflammation, resulting in at least one of the following:

- Purulent mucus or edema in the middle meatus or ethmoid region
- Polyps in the nasal cavity or middle meatus

The above findings are confirmed by the presence of mucosal thickening, changes to the surrounding bones, and/or changes in air–fluid levels visualized via CT scan.

TREATMENT

The goals of treatment are to reduce mucosal swelling, promote sinus drainage, and clear any infections that may be present. This often means that the patient will need a combination of glucocorticoids (oral or topical through a nasal spray), antibiotics, and nasal saline irrigation. If these treatments are ineffective, a referral to an otolaryngologist for consideration of sinus surgery is warranted. If the chronic disease is severe, if there are orbital or intracranial complications, or if the patient is immunocompromised, hospitalization is required.

CLINICAL PRACTICE
When to Seek Medical Care

Clinicians should advise patients to call a doctor when experiencing pain or pressure in the upper face accompanied by nasal congestion or discharge, postnasal drip, fever for several days, or ongoing bad breath unrelated to dental problems. If left untreated, complications of sinusitis can occur that may lead to severe medical conditions. If you have the following symptoms, you may have a medical emergency and should seek immediate evaluation in a hospital's emergency department:

- Headache and fever with soft tissue swelling over the frontal sinus may indicate an infection of the frontal bone.
- Severe pain when moving the eye, fever, eyelid swelling or drooping, or vision changes due to infection in the eye socket as a result of ethmoid sinusitis; permanent blindness can result.
- Severe pain in the eye, one or both dilated pupils, fever, eyelid swelling, or vision changes can also be related to a blood clot in the sinuses.
- Personality changes, headache, neck stiffness, high fever, altered consciousness, visual problems, or seizures are signs that the sinusitis has penetrated the meninges of the central nervous systems (meningitis), which is a medical emergency.

Burn Injuries

Every year in the United States, burns cause 2 million injuries, with over 5,000 of these resulting in death.[5] The most common causes include fire/flame exposure (46%), scalding (32%), hot object contact (8%), electrical burns (4%), and chemical burns (3%). Burn injuries cause an inflammatory response locally and can have major systematic effects as well.

FUNCTIONS OF THE SKIN

The skin serves as an important barrier between the body and the external environment. It is composed of the dermis, which is a dense, irregular connective tissue, and the epidermis, a layer of epithelial tissue. The epidermis and dermis are separated by the basement membrane. The skin protects internal structures from invasion by infectious or harmful agents and mechanical damage. The skin prevents dehydration, regulates body temperature, and produces vitamin D. Understanding the vital function of the skin is important because loss of function is a critical manifestation of inflammatory processes.

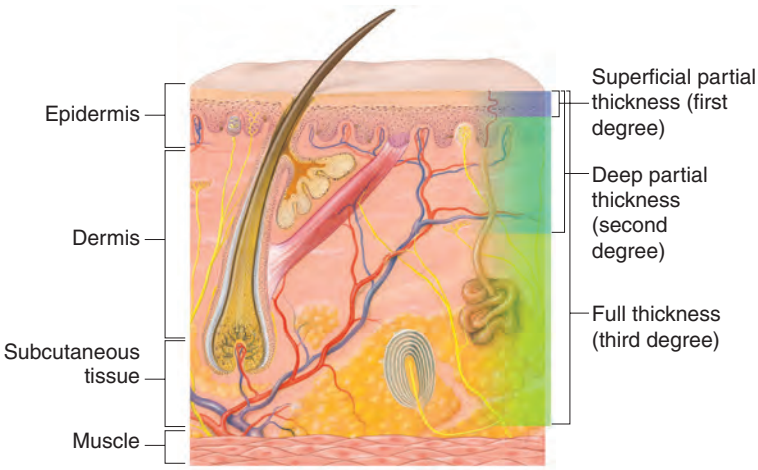


Figure 3.15. Classification of burns by depth of injury. Superficial partial-thickness burns enter the epidermis. Deep partial-thickness burns penetrate the epidermis and dermal layers. Full-thickness burns penetrate all skin layers and can progress to underlying structures as well. (Courtesy Anatomical Chart Company.)

BURNS

Pathophysiology

Burns can result from thermal injury, electrical injury, caustic chemical injury, radiation exposure, or inhalation of noxious fumes. In thermal injuries, higher temperature and increased length of heat exposure increase the severity of the burn. Temperatures above 45°C (113°F) cause proteins to denature, and irreversible cellular damage occurs. The extent of damage from chemical injuries depends on the toxicity of the chemical, location of exposure (particularly in the eyes, respiratory tract, or gastrointestinal tract), and length of exposure. Electrical injuries follow the path of least resistance in the body, that is, along tissue, fluids, blood vessels, and nerves. Serious electrical trauma results from the electrical current passing through vital organs, nerves, and blood vessels. Electrical currents can disrupt cardiac conduction and cause immediate death.

With all burns, the injury triggers an acute inflammatory response. The extent and nature of the inflammation, along with corresponding clinical manifestations, diagnostic criteria, and treatment, primarily depend on the surface area that is affected as well as the depth of the burn injury (Fig. 3.15).

Superficial partial-thickness burns, also known as first-degree burns, damage the epidermis. Mild sunburn is one example. This radiation-induced injury triggers vasodilation of the dermal blood vessels and increased capillary permeability, causing erythema, pain, and swelling of affected areas. Superficial partial-thickness burns do not result in cell necrosis or scarring. The ECM generally remains intact, allowing uneventful healing of superficial partial-thickness burns as endothelial and epithelial cells rapidly regenerate. Healing occurs within a week.

Deep partial-thickness burns, also known as second-degree burns, damage epidermal skin layers and penetrate some dermal skin layers. Scalding with hot liquids, more severe sunburn, mild to moderate chemical burns, or flash flame exposure can lead to deep partial-thickness burns. Epidermal and dermal layers separate, fluid accumulates between these layers, and blisters form (Fig. 3.16). A loss of function of the skin as the first line of defense allows microorganisms to invade the tissue. If necrosis occurs in the upper epidermal cell layers but the basal cell layer remains intact, scarring is avoided. More commonly, however, necrosis results in both epidermal and upper dermal layers. Collagen fills in the gaps left after the removal of damaged tissues. Excess collagen production often leads to tissue fibrosis and scarring at the burn site. The process of healing occurs within approximately 2 to 4 weeks.

Full-thickness burns, also known as third-degree burns, damage the epidermis and dermis and can penetrate subcutaneous layers as well. Contact

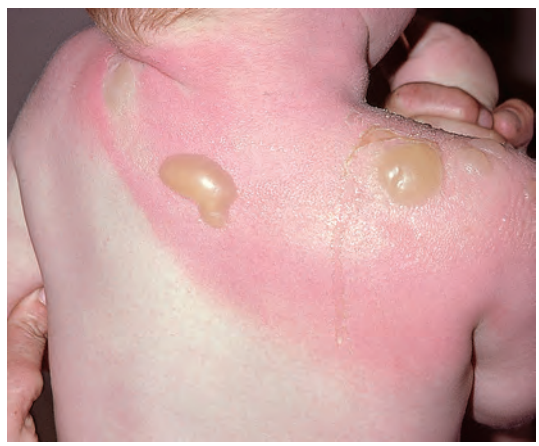


Figure 3.16. Deep partial-thickness (second-degree) sunburn. Epidermal and dermal layers separate, fluid accumulates between the layers, and blisters form. (From Fleisher GR, Ludwig S, Baskin MN. *Atlas of Pediatric Emergency Medicine*. Philadelphia, PA: Lippincott Williams & Wilkins; 2004, with permission.)

with extremely hot objects, exposure to a flame, electrical exposures, and caustic chemicals are likely to result in full-thickness burns. The severity depends on the temperature or type of chemical and the length of exposure. Destruction of blood vessels is also common as heat cauterizes the vessels. The healing of full-thickness burns is challenged by extensive loss of elastin, replacement of skin cells with collagen, and invasion by microorganisms. Regeneration of epithelial cells is impaired because of destruction of the ECM. Scarring is often extensive. Loss of elasticity is evidenced by **contractures**, areas of thick, shortened, and rigid tissue.

Stop and Consider

Hematocrit is a laboratory test that indicates the percentage of RBCs in a designated volume of blood. Would an individual with partial-thickness and full-thickness burns covering 20% body surface area have a decrease or increase in this laboratory value? What would be the impact of this change?

The loss of skin function results in multiple potential complications, particularly in severe burn injuries, defined as full-thickness burns covering greater than 20% of the adult body surface area, including:

1. Body fluid shifts that cause impaired blood circulation, edema, and dehydration
2. Microorganism invasion that leads to infection
3. Overwhelming metabolic demands that increase the risk for malnutrition
4. Problems with temperature regulation

In widespread inflammation, impaired blood circulation and cellular dehydration can result as fluids shift from cells and blood vessels into the tissues (edema). This is due to massive capillary permeability and direct damage to blood vessels at the site of the burn injury (Fig. 3.17). In patients with full-thickness burns, water loss is extensive: Approximately 0.3 mL of body water per square centimeter is lost per day. When full-thickness burns cover 70% of the body, extensive fluid shifts out of the blood vessels and swells into the tissues, resulting in severe hypovolemia (low fluid volume in the blood vessels). The blood becomes viscous (thick), heat converts RBCs from a concave to a spherical shape, and the flow of blood is altered. At the local site of the burn, **thrombi**, or clots, can develop, oxygenated blood flow is restricted, and necrosis can develop as the burned tissue becomes hypoxic. An inadequate amount of blood in the circulation leads to **shock**, a state of inadequate perfusion (oxygenated blood flow) to peripheral tissues. Poor perfusion is particularly problematic in vital organs, which require a constant flow of oxygen to survive. In partial-thickness burns, capillary permeability is restored after 24 to 48 hours and interstitial fluid shifts decrease after this time. This allows the volume of fluid in the blood vessels needed for optimal circulation.

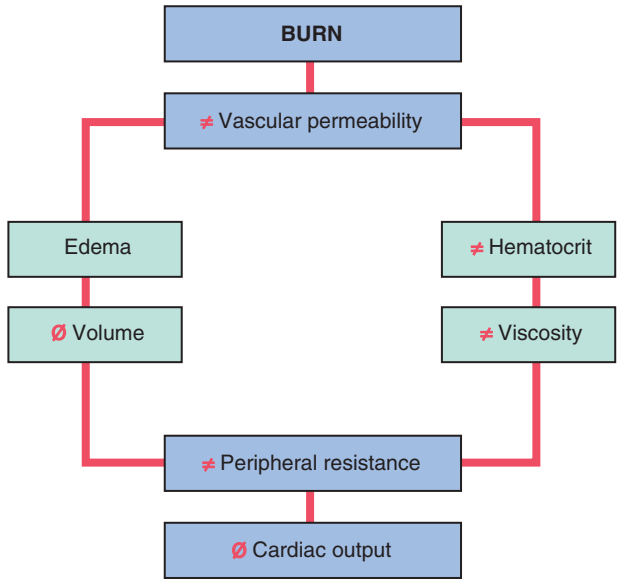


Figure 3.17. Hemodynamic changes in burn injury. (From Nettina S. *The Lippincott Manual of Nursing Practice*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001, with permission.)

The loss of skin function as a result of burn injuries also allows for ready access for microorganisms and stresses the metabolic and reparative processes of the body. Burns covering a larger surface area pose a greater risk for the development of **sepsis**, which is a bacterial infection of the blood, and septic shock. In full-thickness burns, dead tissue and exudate convert into an **eschar**, which is a thick, coagulated crust. The eschar must be surgically removed to prevent extensive microorganism growth. Energy, protein, and oxygen use are also increased because of the extensive reparative processes required in substantial burn injuries. If these increasing needs are not met, tissue hypoxia, tissue wasting, and infection are the potential results.

CLINICAL MANIFESTATIONS

Clinical manifestations primarily depend on the depth of the burn injury. Superficial partial-thickness burns result in erythema, warmth, pain, swelling, and loss of function of affected areas. Deep partial-thickness burns lead to blistering, along with erythema, warmth, pain, edema, and **serous exudate**, which is a clear fluid that seeps out of the tissues. Erythema, eschar formation, edema, and exudate characterize full-thickness burns. Full-thickness burns destroy nerve endings, sweat glands, and hair follicles. Destruction of nerve endings

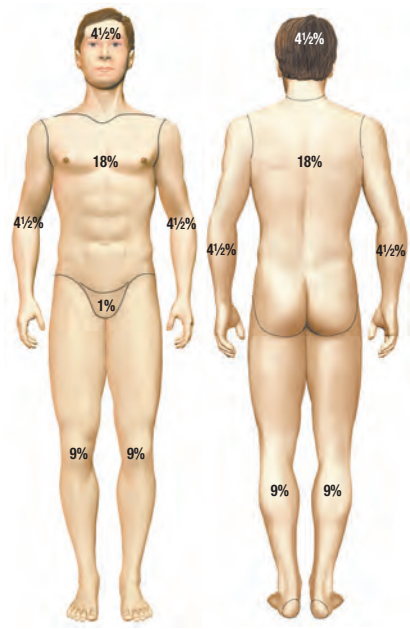


Figure 3.18. Rule of nines. Estimating the extent of burns in adults. (Courtesy Anatomical Chart Company.)

inhibits the pain response in areas where the burn has penetrated all skin layers. The individual with a full-thickness burn is not pain free, however. Areas of deep and superficial thickness burns, like a bull's eye, often surround full-thickness burns. Pain is notable in these surrounding tissues.

DIAGNOSTIC CRITERIA

Wound depths (superficial, deep partial, or full thickness) are classified according to the affected tissue layers. Surface area is also a significant variable in determining the diagnosis and treatment of a burn injury. Calculation of adult body surface area is aided using the "rule of nines" depicted in Figure 3.18. For children under 5 years, body proportions do not match that of the adult. For example, although the trunk and arms are similar in proportion to the adult, the infant's head and neck make up 18% of total body surface area, and each lower extremity accounts for 14%. Health care professionals who treat childhood burns should refer to a "modified rule of nines" appropriate for the specific age of the child.

Estimation of the rule of nines, along with a determination of the thickness of the burn, allows the health professional to determine the severity of the injury and direct treatment. The American Burn Association has published criteria for distinguishing minor, moderate, and major burns (Table 3.7).

TREATMENT

Initial treatment for minor and moderate burns requires removing the source of injury and stopping the burning process. Chemical burns should be flushed with copious amounts of water. In minor burns, the wound is cleansed with tepid sterile saline (cool but not cold) or water. In some cases, the wound is covered with an antimicrobial ointment and dressed with fine-mesh gauze. Dressings are usually changed every 1 to 2 days. Frequent (daily) dressing changes aid in **debridement**, which is a process of mechanically removing debris, including necrotic tissue, from the wound. Analgesics can be used to treat pain.

Moderate and major burns require emergency medical attention. Also, burns larger than the palm of the hand or those that involve the face, hands, feet, or genital areas require specialized intervention in a burn treatment center. Treatment for moderate and major burns, as with other emergencies, focuses on the airway, breathing, and circulation. Once these are stabilized, administration of intravenous fluids is instituted to replace water and sodium losses. Administering fluids helps to restore the circulating blood volume and improves perfusion of vital organs. Because metabolic demands increase significantly with the stress of a burn injury, nutrition support in the form of increased calories and protein is needed. Analgesics and antibiotics are also used to treat pain and infection. Protective isolation measures are often instituted to protect the patient from contact with microorganisms as much as possible.

Wound management for major burns involves cleansing with sterile saline while wearing powder-free gloves (powder will irritate the burn wound), removing blisters or necrotic tissue as appropriate, covering the wound with a sterile

Table 3.7 American Burn Association (ABA) Burn Severity Grading Scale

	Minor[a]	Moderate	Major
Partial-thickness	<10% TBSA	10%–20% TBSA	>20% TBSA
Full-thickness			All
Treatment	Usually treated at home	Admission to hospital; may require specialized burn center treatment	Admission to specialized burn center

[a]Minor burns exclude any burn involving the face, hands, feet, and perineum; also exclude electrical burns, inhalation injuries, or other trauma.
ALL, acute lymphocytic leukemia; TBSA, total body surface area.
http://www.ameriburn.org/BurnCenterReferralCriteria.pdf

dressing, and preventing infection. Hydrotherapy, which involves soaking in a tub or showering once or twice per day, is used to cleanse the wound by removing dead tissue and exudate. Full-thickness burns are unable to undergo reepithelialization and require surgical excision and grafting to close the wound. Skin grafting is a process of using self or donor tissue to cover and protect the exposed area. This transplanted epithelial tissue supports cellular regeneration, decreases invasion by microorganisms, and minimizes scarring. Long-term rehabilitation (tertiary prevention) involves prevention of complications such as scar formation, contractures, deformity, and chronic pain. Treatment may also involve psychosocial support because those with burn injuries may experience depression or other psychologic sequelae.

Arthritis

Arthritis is a general term for degeneration or inflammation of the joints and refers to a group of diseases of varying pathogenesis. Inflammatory arthritis is usually a result of chronic infections, autoimmune conditions, or other chronic irritants in the joint capsule. Rheumatoid arthritis, a systemic autoimmune disease leading to chronic inflammation of synovial tissue, is the selected clinical model.

FUNCTIONS OF SYNOVIAL JOINTS

The primary function of joints is skeletal stability and mobility. Synovial joints, particularly those in the knees, wrists, hands, fingers, and feet, are highly mobile and common targets for inflammation. Synovial joints are also highly vascular. The two-layer synovial membrane lines the joint capsule. One layer is composed of connective tissue, elastin, adipocytes, fibroblasts, macrophages, and mast cells. The second layer is a row of synovial cells, which are capable of phagocytosis and secreting synovial fluid. Synovial fluid nourishes, cushions, and protects the joint from microorganisms. Synovial cells are labile cells, which can quickly regenerate.

Between the bone and synovial membrane is cartilage. Cartilage is composed of chondrocytes, collagen, water, and protein glycans. Collagen forms an ECM, which attaches bone to the cartilage. Cartilage is needed to distribute body weight and to decrease joint friction. Cartilage must be replaced by collagen if damaged; chondrocytes do not regenerate.

RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation and hyperplasia of the synovial membranes with increased synovial exudate, leading to swelling and thickening of the synovial membranes, joint erosion, and pain. The onset of disease occurs typically between the ages of 36 and 50 years. RA affects 0.8% of adults worldwide. Females are affected three times more often than males, and the rate of comorbidities is high with depression, asthma, and cardiovascular problems being the most common comorbid conditions.[6]

Pathophysiology

Although the exact cause of RA is unknown, the etiology is likely a combination of:

- Genetic susceptibility
- An immune triggering event
- The subsequent development of autoimmunity against synovial cells

The triggering injury in RA that leads to inflammation is difficult to pinpoint and is often never determined. Despite the lack of an identifiable trigger, autoimmunity plays a key role. $CD4^+$ helper T cells have been implicated as activating the inflammatory response along with the release of cytokines. Lymphocytes and plasma cells then form antibodies in the synovial membrane and cartilage. The antibodies are formed against specific antigens. The antibodies actually see other antibodies within the body as foreign (see From the Lab).

In RA, the antigens and antibodies form complexes, called immune complexes. These immune complexes are found in the synovium of most individuals diagnosed with RA. These antigen–antibody complexes trigger the complement system, thereby stimulating an exaggerated inflammatory response.

The inflammatory response is marked by excess production and release of inflammatory mediators. These inflammatory mediators act on the vasculature of the joints to cause increased vasodilation and capillary permeability. The joint becomes erythematous, warm, swollen, painful, and difficult to move. Exudate accumulates in the synovium. Neutrophils

FROM THE LAB

Rheumatoid factor (RF), a substance that can be found in the blood, synovial fluid, and synovial membranes, signifies that antibodies (IgM, IgG, or IgA) are acting against other antibodies (mainly IgG). RF is present in the vast majority of patients who have RA and can also be found in a variety of other conditions. The presence of RF in RA often signifies more severe disease.

and macrophages move into the site to defend against harmful substances. This process, while necessary, also promotes the production of destructive tissue enzymes. Synovial cells adapt by rapidly regenerating. The synovium, after the initial bout of inflammation, is altered and causes the following changes:

1. Mild edema
2. Accumulation of the cells of chronic inflammation (macrophages, plasma cells, and lymphocytes)
3. Acceleration of angiogenesis
4. Accumulation of fibrin
5. Synovial cells continue to undergo reactive hyperplasia

These initial synovial changes usually demonstrate minimal damage to the joints.

Exacerbations of the disease progressively damage affected joints through pannus formation, cartilage erosion, fibrosis, and joint fixation and deformity (Fig. 3.19). **Pannus** is granulation tissue that forms over the inflamed synovium and cartilage as a result of accelerated angiogenesis. Pannus is filled with synovial cells, which undergo hyperplasia and migrate, along with the pannus, over the cartilage. The pannus and synovial cells are joined by mast cells, lymphocytes, and macrophage giant cells. These cells further exacerbate inflammation and tissue destruction. Pannus separates the cartilage from synovium, thereby depriving the cartilage of nutrients. The pannus also produces enzymes that break down the cartilage and can erode the adjacent bone as well. These erosions are irreversible. Fibroblasts work to form and replace the connective tissue layer by producing and secreting collagen. Collagen fills in the gaps that remain after tissue damage. As a result, fibrosis forms in the joint capsule. Fibrosis impairs joint mobility and can result in a debilitating fixation of the joint, a condition termed **ankylosis**. Limited joint movement decreases the workload of surrounding muscle tissue, leading to muscle tissue atrophy. Inflammatory cells can also irritate surrounding muscle tissue, resulting in muscle spasms.

CLINICAL MANIFESTATIONS

The severity of RA can range from mild to debilitating. Involvement is characteristically symmetric and can involve any number of joints, producing erythema, pain, swelling, warmth, and decreased mobility. Malalignment or deviation of symmetrical joints is a common clinical manifestation of long-standing RA (Fig. 3.20). Malalignment is caused by a combination of cartilage and bone erosion, fibrosis, ankylosis, muscle spasms, and muscle atrophy. Pain and stiffness is often most notable upon rising in the morning and after periods of immobility.

Common systemic manifestations during disease exacerbations are low-grade fever, fatigue, anorexia, weight loss, and weakness. Chronic pain can also lead to isolation and depression. Manifestations of long-standing RA can also be found outside of the joint capsule. Granulomas, called nodules, can form on blood vessels throughout the body. Vasculitis, an inflammatory condition involving small- and medium-sized arteries, may also occur in those with long-standing disease.

DIAGNOSTIC CRITERIA

No definitive test exists to diagnose RA. Diagnosis is based on history and physical examination (during which stiffness and pain in symmetrical joints is

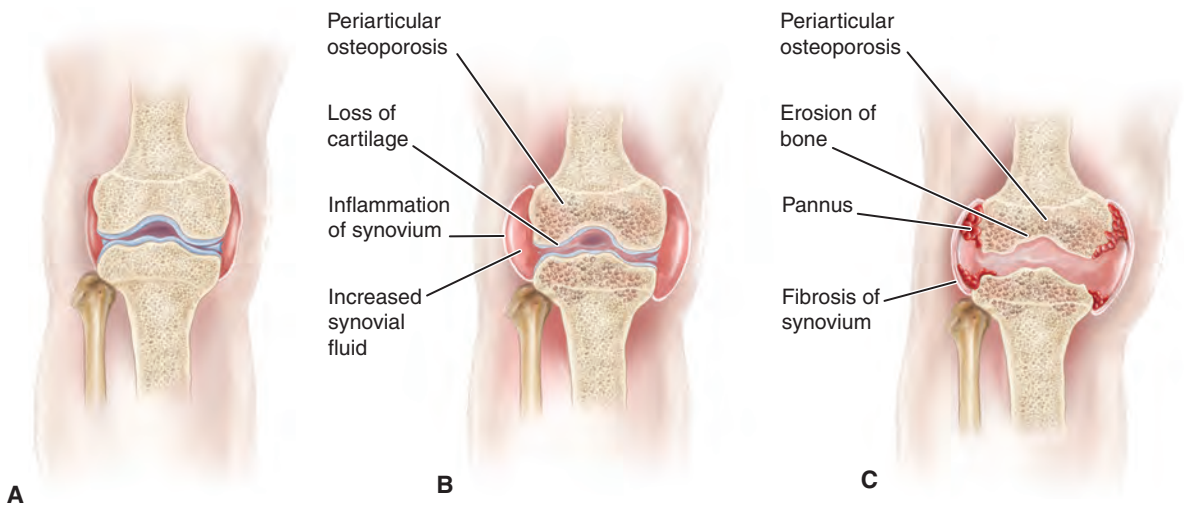


Figure 3.19. Normal joint **(A)**; early rheumatoid arthritis with fluid accumulation and synovial swelling **(B)**; late rheumatoid arthritis with pannus formation, eroded articular cartilage, and joint space narrowing **(C)**.

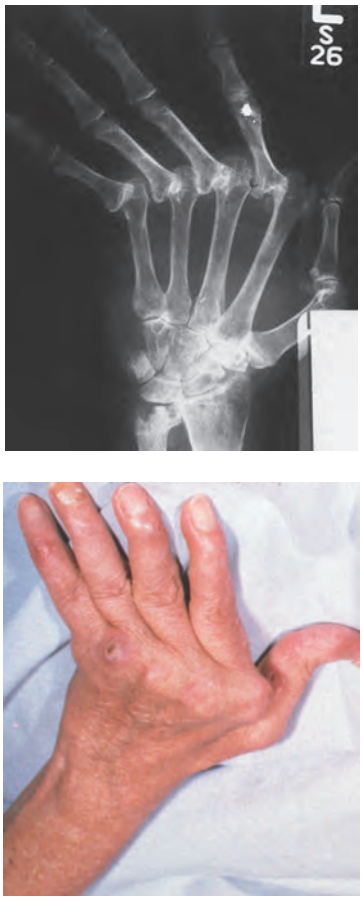


Figure 3.20. Deviation of joints in rheumatoid arthritis, as shown in a radiograph **(A)** and a photograph **(B)**. (**A:** Reprinted with permission from Harris JH Jr, Harris WH, Novelline RA. *The Radiology of Emergency Medicine*. 3rd ed. Baltimore, MD: Williams & Wilkins; 1993:440; **B:** Reprinted with permission from Smeltzer SC, Bare BG. *Textbook of Medical–Surgical Nursing*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003, with permission.)

demonstrated), and it may involve several diagnostic tests. Test results that increase the likelihood of RA as the diagnosis include:

1. An elevated serum ESR
2. An elevated serum CRP level
3. The presence of RF significant for antibodies against IgG
4. A positive antinuclear antibody (ANA) assay indicating suspected autoimmune disease
5. The presence of inflammatory products in a synovial joint fluid analysis
6. Visualization with a radiograph demonstrating joint damage

RA presents a diagnostic challenge because multiple autoantibodies are known to be associated with this disease. Many of these tests are nonspecific and indicate the presence of an inflammatory or autoimmune process but do not directly point to RA as the cause. Each test also has a risk of false-positive (positive result without the disease) or false-negative (negative result with the disease) results. RF appears to have the greatest advantage in diagnosing early RA compared with multiple other autoantibody tests; however, it is unlikely that a single antigen is involved in the development of RA. The diagnostic challenge can lead to frustration for the patient and health care professional and may lead to a delay in treatment.

TREATMENT

Treatment of RA involves a careful balance of pharmacologic and nonpharmacologic treatment strategies. Medications employed include anti-inflammatory drugs, immunosuppressive drugs, and medications that otherwise induce remission. Nonpharmacologic strategies involve the balance of activity and rest, physical therapy exercises to promote joint mobility, and the use of splints and other devices that allow the joints to rest and help to prevent deformities. Heat or cold therapy can be helpful. In some cases, synovectomy or total joint replacement surgery may be needed to reduce pain and deformity.

Gastritis

Gastritis refers to inflammation of the lining of the stomach, or gastric mucosa, thereby impairing gastric function. Gastritis can be both acute and chronic.

RESEARCH NOTES

Current research is uncovering connections between RA and a number of other chronic conditions, such as cancer, cardiovascular disease, and diabetes. In a recent study, a significant increase in cardiovascular disease was noted in patients with RA who had more acute flares than those who spent more time in remission. The researchers concluded that tight inflammation control and improved flare management are critical to decreasing the cumulative cardiovascular burden of RA.[7]

FUNCTIONS OF THE STOMACH

The stomach functions as an organ of protection, digestion, and absorption, primarily absorbing water and alcohol. Stomach acid forms a first line of defense by destroying many types of microorganisms and other harmful substances on contact. During the digestive process, foods and liquids are mixed

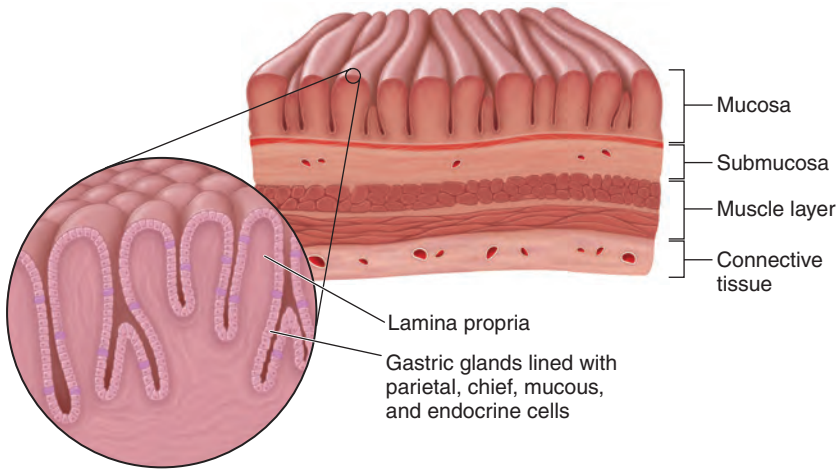


Figure 3.21. Gastric lining. The lining of the stomach contains four types of glandular epithelial cells: mucous, parietal, chief, and endocrine.

with gastric secretions, composed of mucus, acid, enzymes, hormones, and intrinsic factor (IF). Secretion of these substances is accomplished through the work of gastric glands lined by specialized epithelial cells (Fig. 3.21).

Epithelial cells form a tight connection. This connection is an important source of protection from the corrosive effects of gastric acid. Prostaglandins also play a key role in maintaining the integrity of the gastric mucosa through the stimulation of a protective mucus barrier.

Stop and Consider
Explain how anti-inflammatory drugs that inhibit prostaglandins can cause or further exacerbate gastritis.

The surface mucus barrier is highly vascular and dependent on a rich blood supply to support gastric function. Restriction or loss of perfusion to this layer can be a cause of gastritis. For example, altered perfusion can occur in the case of shock when blood is shunted to vital organs and not to the stomach, causing the protective mucus barrier to form ulcers and perforate.

Acute Gastritis

Acute gastritis refers to inflammation in the gastric mucosa most often caused by the ingestion of irritants such as aspirin, alcohol, or certain microorganisms. Acute gastritis typically occurs over a short period and is considered reversible when the causative agent is removed. Although gastritis is often associated with having too much stomach acid, the role of gastric acid hypersecretion is unclear.

PATHOPHYSIOLOGY

The gastric mucosa is accustomed to and functions best in the acidic environment of the stomach. Exposure to gastric irritants inhibits the production of gastric mucosa and makes the mucosa more vulnerable to acidic stomach contents. This leads to an acute inflammatory response ranging from mild erythema to erosion and gastric perforation (Fig. 3.22). Epithelial cells become necrotic. The underlying gastric tissue is eroded. Hemorrhaging often occurs. Gastric acid is allowed to escape the confines of the gastric mucosa and corrode nearby tissues. Perforation may occur in severe cases.

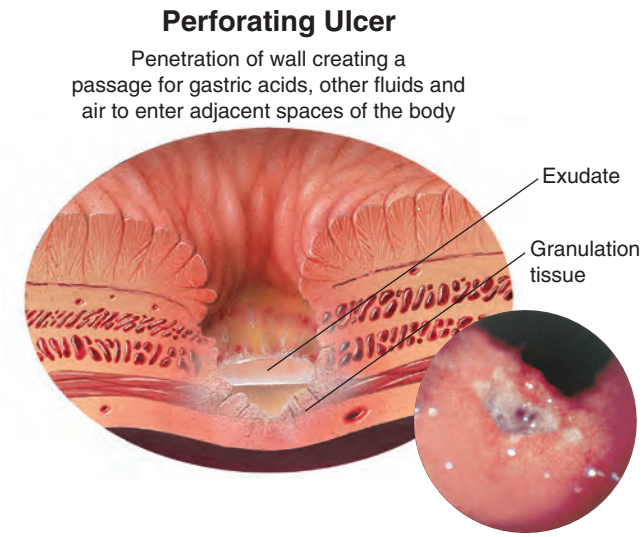


Figure 3.22. Gastric perforation as a result of acute gastritis.

CLINICAL MANIFESTATIONS

Clinical manifestations are dependent on the severity and range from mild to severe abdominal pain, which can be accompanied by indigestion (heartburn), loss of appetite, nausea, vomiting, and hiccups. **Hematemesis**, or vomiting blood, can occur. Anemia may result from mild gastric hemorrhage. Severe hemorrhage and perforation is quickly followed by shock and is a medical emergency.

DIAGNOSTIC CRITERIA

The patient history often reveals aspirin or other nonsteroidal anti-inflammatory drug use, excessive alcohol intake, recent contaminated food intake, or conditions causing ischemia of the gastric mucosa. The physical examination may reveal abdominal tenderness. Direct visualization of the stomach with an endoscope is needed to visualize ulcers in the mucosa, and a stool analysis may show occult blood in the fecal material. Hemoglobin or hematocrit levels provide information about anemia.

TREATMENT

Treatment begins with removal of the gastric irritant. Medications are then needed temporarily to buffer gastric acid or decrease gastric acid production. The healing of gastritis and gastric ulceration depends on regeneration of the epithelial cells that line the gastric mucosa. Most acute gastritis improves rapidly when the irritant is removed and treatment is initiated.

Chronic Gastritis: Infection

Chronic gastritis is related to an unrelenting injury, such as with chronic infection or autoimmunity. Chronic gastritis due to *Helicobacter pylori* is an example caused by chronic infection. *H. pylori* infection is most prevalent in Asia and in developing countries with poor sanitation. About half of the world's population is infected.

PATHOPHYSIOLOGY

H. pylori is a gram-negative proteobacterium that is passed from person to person through infected saliva and stool. The microorganism is ingested and multiplies on the epithelial surface cells and mucus barrier. *H. pylori* produces enzymes that neutralize gastric acid, and the microorganism is able to survive. The microorganisms then produce toxins that can destroy the mucosal barrier (Fig. 3.23).

In response to the microorganism-induced injury, inflammatory mediators trigger an intense inflammatory response. Phagocytes work to engulf, destroy, and remove these aggressive microorganisms. Neutrophils migrate to the lamina propria and gastric epithelium to phagocytize the bacteria. As the infection becomes chronic, macrophages and T and B lymphocytes move in an attempt to rid the body of the offending bacteria. *H. pylori* tends to remain contained within the mucosal barrier and surface epithelial cells, and unlike acute gastritis, there are no erosions of the gastric mucosa. Instead, epithelial cells and mucosal glands atrophy. Eventually, the chronic inflammatory response wanes. The mucosal lining of the stomach remains thin, and gastric acid production and secretion is impaired.

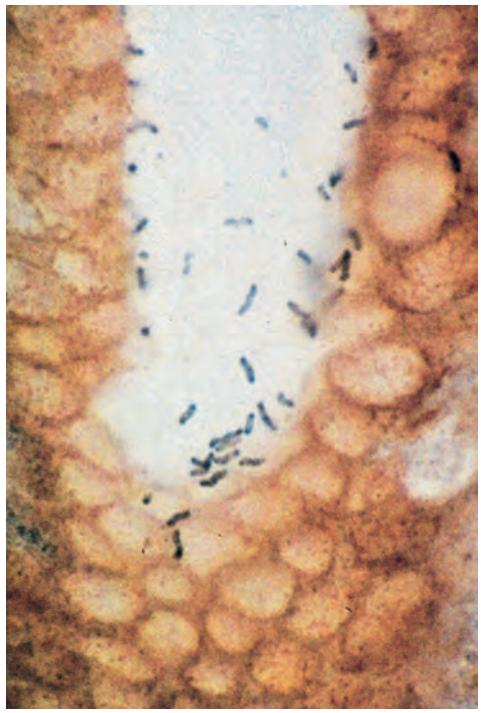


Figure 3.23. Infective gastritis. *H. pylori* appears as small curved rods on the surface of the gastric mucosa. (From Rubin E, Farber JL. *Pathology*. 3rd ed. Philadelphia, PA: Lippincott-Raven; 1999:687, with permission.)

CLINICAL MANIFESTATIONS

Dyspepsia, a vague epigastric discomfort associated with nausea and heartburn, is a possible clinical manifestation. Some patients may experience a loss of appetite or vomiting. Most infected people, however, are asymptomatic carriers.

DIAGNOSTIC CRITERIA

Diagnosis of chronic gastritis caused by *H. pylori* infection is accomplished through direct endoscopic visualization and biopsy of gastric tissue. A breath test

can be used to measure the presence of an enzyme given off when the bacterium converts urea to carbon dioxide in the lungs. Protein antibodies against *H. pylori* may also be detected in the blood, indicating past or present infection with the bacteria.

TREATMENT

Because *H. pylori* is buried deep in the stomach mucosa, multiple antibiotics are needed to treat this infection along with proton pump inhibitors or bismuth, which have antimicrobial properties and raise gastric pH. Over time, certain strains of *H. pylori* can lead to chronic ulcers and gastric cancer.

Chronic Gastritis: Autoimmune

Chronic gastritis can also result from autoimmune processes. Although more rare than other forms of chronic gastritis, antibodies are produced against gastric parietal cells or IF.

PATHOPHYSIOLOGY

Parietal cells secrete hydrochloric acid. When antibodies are formed against parietal cells, gastric acid secretion is impaired. Intrinsic factor is needed for intestinal absorption of B_{12}. When antibodies are formed against IF, absorption of B_{12} is impaired. B_{12} is a critical vitamin that promotes DNA synthesis in RBCs. Impaired DNA synthesis in RBCs leads to a marked decrease in RBCs and low hemoglobin levels. This condition is known as pernicious anemia. Chronic inflammation related to autoimmunity allows T cells to infiltrate the gastric mucosa, destroying epithelial cells and causing gastric atrophy.

CLINICAL MANIFESTATIONS

Autoimmune gastritis can be asymptomatic. The presence of pernicious anemia may be the first clue that chronic gastritis is present. Manifestations of anemia include weakness, light-headedness, pale mucous membranes, and fatigue. Clinical manifestations can also include dyspepsia, vague abdominal pain, nausea, vomiting, and anorexia.

DIAGNOSTIC CRITERIA

Diagnosis of autoimmune gastritis can be determined only with histologic examination of the gastric mucosa. Several biopsy samples are obtained and analyzed for atrophic changes in the cells. Antiparietal or anti-IF antibodies may present in a blood sample, which indicate an autoimmune process against the parietal cells or IF. Because autoimmunity against IF impairs B_{12} absorption, a low B_{12} level will be noted in the blood.

TREATMENT

Treatment is aimed at blocking the autoimmune attack against the parietal cells. The administration of B_{12} intramuscular injections monthly is needed to facilitate absorption of this important vitamin. Similar to *H. pylori*, autoimmune gastritis can lead to gastric cancer.

Pancreatitis

Pancreatitis refers to inflammation of the pancreas, resulting in destruction of the pancreas by pancreatic enzymes. Pancreatitis can be both acute and chronic.

FUNCTIONS OF THE PANCREAS

The pancreas is both an endocrine and exocrine gland located in the upper posterior abdomen on the patient's left side. The endocrine pancreas (about 20% of the gland) produces insulin; the exocrine pancreas (80% of the gland) produces and secretes digestive enzymes. These digestive enzymes are essential for the metabolism of carbohydrates, fats, and proteins.

Digestive enzymes are produced within the acinar cells of the pancreas, are stored in zymogens, and are released into the pancreatic duct and to the small intestine, where digestion can then occur. In a process of negative feedback, the secretion of pancreatic enzymes is reduced when digestion is complete. Disruption of this protective process triggers pancreatic enzymes to become activated and self-destruct through autodigestion.

Acute Pancreatitis

PATHOPHYSIOLOGY

Acute pancreatitis may occur when there is an injury to the acinar cells, zymogen, pancreatic duct, or protective digestive feedback mechanisms in the exocrine pancreas. Common causes include duct blockage by gallstones or excessive alcohol use (Fig. 3.24). In about 10% of cases, the cause is unknown.[8] Alcohol is a major cause of pancreatic autodigestion by triggering:

- Intracellular accumulation of digestive enzymes
- Premature enzyme activation and release
- Increased permeability of ductules and easy passage of enzymes to the parenchyma
- Increased protein content of pancreatic secretions and creation of protein plugs

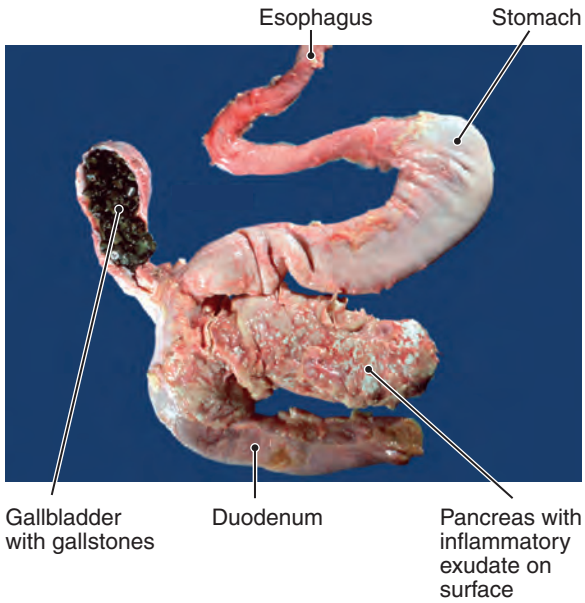


Figure 3.24. Acute pancreatitis as a result of gall stone obstruction.

The injury triggers blockage of enzymatic pathways, the activation of trypsin and the zymogen, spilling of secretory enzymes, and ultimately inflammation. Neutrophils, tumor necrosis factor, and interleukins (early responders) and macrophages (later) mediate the inflammatory response. Consistent with the inflammatory cascade, there is increased vascular permeability in the pancreas, leading to edema. This condition is referred to as acute edematous pancreatitis. Later, hemorrhage and necrosis ensue, leading to a state of hemorrhagic or necrotizing pancreatitis with eventual granuloma or abscess formation. In severe cases, necrosis is widespread, and there is organ dysfunction and potentially systemic multiorgan failure.

CLINICAL MANIFESTATIONS

Clinical manifestations are related to the inflammatory response occurring in the pancreas and its resulting pain and digestive impact. These manifestations include:

- Upper abdominal pain of sudden onset, growing in intensity, and leading to a dull, steady ache often radiating to the back
- Nausea, vomiting, anorexia, and/or diarrhea

DIAGNOSTIC CRITERIA

Diagnosing acute pancreatitis is generally achieved through the history and physical examination, noting the presence of clinical manifestations above. Laboratory testing is implemented to aid in the diagnosis. Tests for complete blood count, ESR, and CRP levels may give clues to the presence of inflammation. Specific laboratory tests include measuring:

- **Serum amylase and lipase:** Levels of these enzymes are typically elevated in acute pancreatitis. Both are digestive enzymes (amylase breaks down carbohydrates and lipase breaks down fats) that are excessively released with inflammation of the pancreas.
- **Serum alkaline phosphatase, total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT):** These are liver enzymes, which are likely to be elevated in cases of pancreatitis caused by gallstones.

When the diagnosis is in doubt or the symptoms are severe, imaging studies, such as ultrasound, CT, or MRI, are needed to aid in determining the location and potentially the cause of the pancreatic injury.

TREATMENT

Treatment aims to eliminate the cause of pancreatic injury if at all possible and to care for the symptoms. Patients should receive aggressive IV hydration in the first 24 hours. In mild pancreatitis with no nausea or vomiting, patients can continue oral feeding. Otherwise, all patients must be NPO (nothing by mouth). Analgesics should be administered to manage pain. Surgical removal of gallstones is warranted if they are present.

Patients with severe pancreatitis, often defined as a CRP level above 10 mg/dL along with severe symptoms and potential for negative sequelae, should be hospitalized in the intensive care unit to prevent complications of shock, renal failure, or systemic multiorgan failure. Ranson's Criteria for Pancreatitis Mortality[9] is a tool that helps to determine the patient's prognosis based on WBC count, age, AST level, hematocrit, blood urea nitrogen level, fluid requirements, and other indicators. Intensive treatment is successful if the patient has no pain, is able to take in adequate nutrition, and has experienced no complications.

Chronic Pancreatitis

Chronic pancreatitis is an ongoing inflammatory process of the pancreas, characterized by irreversible cellular and tissue changes. Chronic pancreatitis differs from acute pancreatitis in duration, and its impact on both the endocrine and exocrine functions of the pancreas. The most common causes are chronic alcohol abuse (60% to 70%), autoimmune or hereditary disease (10%), and in 20% of cases the cause is unknown.[10]

PATHOPHYSIOLOGY

As described above, alcohol has an effect on the pancreas, whereas enzymes and protein accumulation cause the pancreatic ducts to become obstructed. Obstruction leads to ischemia. The acinar cells become atrophic and fibrotic, leading to loss of function. When alcohol abuse is chronic, the demands of metabolizing alcohol lead to oxidative stress, which promotes further cellular injury and organ damage.

Autoimmunity (Chapter 4) can occur against the pancreas, resulting in chronic pancreatitis. The etiology is often undetermined; however, as a result of high levels of circulating autoantibodies, there is diffuse enlargement of the pancreas and narrowing of the ducts. Certain autoimmune disorders, which disrupt metabolic processes, have also been associated with chronic pancreatitis. One major example is renal tubular acidosis (Chapter 9), a condition of excess acid accumulation in the body due to a failure of the kidneys to appropriately acidify urine. Cystic fibrosis (Chapter 15) is an example of a genetic condition that can promote chronic pancreatic inflammation. Recurrent acute pancreatitis can also promote a state of fibrosis and necrosis characteristic of chronic pancreatitis. Whatever the etiology, the pathophysiology is based on the fibrotic changes of the pancreas due to the presence of chronic inflammatory cells and fibroblast proliferation.

CLINICAL MANIFESTATIONS

Typically, a patient with chronic pancreatitis has severe intermittent episodes of abdominal pain (mid or upper right-sided, radiating to the back) lasting several hours and at unpredictable intervals. The development of disease has likely begun several months to years before the onset of symptoms. Diarrhea, steatorrhea (fatty stools), and weight loss can also occur as a result of damage to the digestive functions of the exocrine pancreas; however, this occurs only after 90% of the pancreas has been destroyed.

DIAGNOSTIC CRITERIA

Endoscopic retrograde cholangiopancreatography (ERCP) is considered the gold standard for diagnosing chronic pancreatitis (Fig. 3.25). In ERCP, the stomach and duodenum are visualized through an endoscope and then a radiographic contrast dye is injected into the ducts of the biliary tree and pancreas so that the obstructed pancreatic pathways can be seen on radiographs. Serum amylase and lipase (described above) may be elevated in acute exacerbations of disease, but over time the levels are normal to low because of fibrotic changes in the pancreas and loss of function, whereas enzymes can no longer be concentrated. Although expensive and invasive, direct aspiration of the pancreatic duct or the duodenum, where the pancreas deposits enzymes, can be tested to determine levels of pancreatic bicarbonate and enzymes that have been secreted.

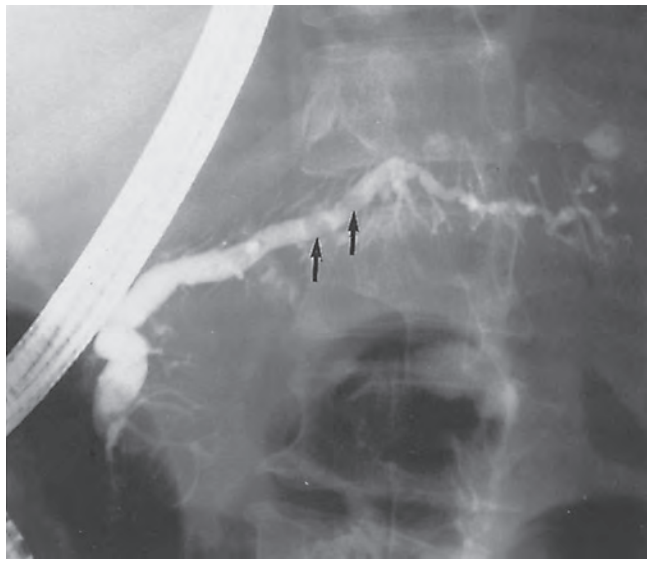


Figure 3.25. Endoscopic retrograde cholangiopancreatography (ERCP) illustrates moderate dilation of the main pancreatic duct and ectasia of the secondary ducts associated with moderately advanced chronic pancreatitis. Arrows indicate intraductal pancreatic stones.

TREATMENT

Treatment for chronic pancreatitis is based on the cause and focused on healing:

- Pain management
- Behavior modification to promote a healthy lifestyle: alcohol cessation, smoking cessation, exercise, quality nutrition
- Surgical intervention to correct cyst, abscess, obstruction, or fistula formation

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) refers to chronic inflammatory processes most commonly in the small and large intestine, but it can occur anywhere along the gastrointestinal tract from the mouth to the anus. The most common forms of IBD include Crohn disease and ulcerative colitis.

The incidence of IBD is highest in developed countries, where persons in colder climates and urban areas have an increased risk. The American Jewish population has a four to five times greater prevalence than in other groups. Among those of European descent in the United States, the

prevalence of ulcerative colitis is estimated at 116 per 100,000 people, and this is slightly increased at 133 per 100,000 people for Crohn disease. The risk appears similar for African Americans but is lower for Asian Americans and Hispanic Americans. Males and females are equally affected.[11]

FUNCTIONS OF THE SMALL INTESTINE

The small intestine is composed of several layers (Fig. 3.26). From inner to outer, these layers consist of the mucosa, submucosa, muscularis, and serosa. The innermost mucosal tissue is composed of three sublayers: mucous columnar epithelium, lamina propria (connective tissue), and the thin muscularis layer. The mucous epithelium layer lines the villi, which provide a large surface area. These villi are lined with columnar cells, which secrete mucus, enzymes, and hormones. The submucosa is a thick connective tissue layer that houses nerves, small glands, and blood vessels.

The primary functions of the small intestine are digestion and absorption. Enzymes secreted by villi promote digestion. Vitamins, minerals, fats, carbohydrates, proteins, water, and electrolytes, such as sodium and potassium, are absorbed through columnar epithelium of the intestinal mucosa. The lamina propria houses infection-fighting macrophages, plasma cells, and lymphocytes. Replacement of columnar epithelial cells is rapid, primarily because of the presence of the crypts of Lieberkühn. These pit-like depressions store cells that can quickly differentiate into replacement cells. The rate of production and differentiation of epithelial cells is increased with injury, thereby promoting healing and repair.

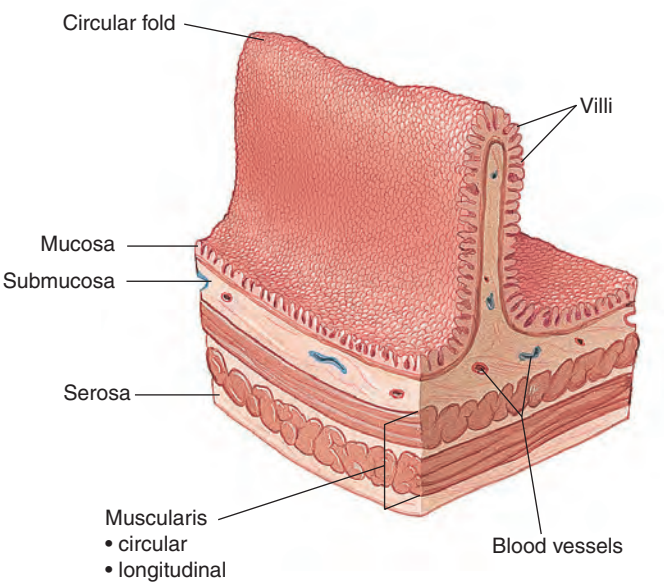


Figure 3.26. Wall of small intestine.

Crohn Disease

Crohn disease is selected as a clinical model to demonstrate chronic inflammatory process in the small intestine. It is recurrent and characterized by a granulomatous inflammatory process. Although Crohn disease can be found anywhere along the gastrointestinal tract, the small intestine and ascending colon, particularly the submucosal layers, are most often affected.

PATHOPHYSIOLOGY

The exact cause of Crohn disease is unknown. Consistent with many other chronic inflammatory conditions, autoimmunity and genetic etiologies have been suggested. Family history does play a role: Those with a family history of bowel inflammation are more likely to develop Crohn disease. Environmental factors, such as smoking, diet, or microorganisms, may trigger the condition as well. As with all conditions, Crohn disease has varying levels of disease severity.

As mentioned, chronic inflammation occurs in patchy segments (called "skip lesion") of the intestine and penetrates all layers of those segments. Between affected areas of intestine is unaffected, noninflamed bowel tissue. Inflammation begins in the mucosa and submucosa. Increased permeability and vascularity contributes to edema and fibrosis. Macrophages, plasma cells, and lymphocytes are released in response to inflammatory mediators. Granulomas develop to wall off affected areas.

As the affected bowel segments become further inflamed, interior surfaces thicken because of excessive edema, fibrosis, and granuloma formation (Fig. 3.27). The thickening of the bowel can lead to total bowel obstruction. Ingested food is unable to move through the digestive tract, which is a life-threatening emergency. Although thickening and granuloma formation are most characteristic of Crohn disease, ulcers can form in the intestinal mucosa. These ulcers can become deep and penetrate through bowel layers, forming a fistula. A **fistula** is an abnormal track or passage that forms between two segments of bowel or other epithelial tissue. At the base of a fistula, an **abscess**, or pocket of purulent (containing pus) exudate, is likely to develop. External surfaces can also be affected by the chronic inflammatory response. Outer surfaces can stick to other sections of bowel and form adhesions, further limiting bowel function.

Destruction of the mucosa and submucosa leads to damage to the villi and crypts. This damage impairs absorptive and epithelial regenerative functions within the affected areas. Malnutrition from the inability to properly absorb nutrients further

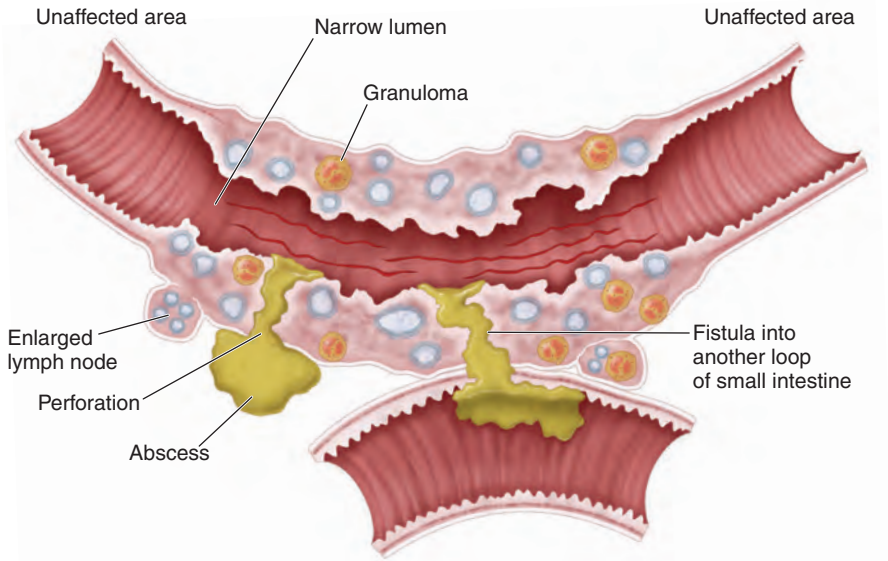


Figure 3.27. Major features of Crohn disease. (Modified from Rubin E, Farber JL. *Pathology*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005, with permission.)

exacerbates problems with healing. The most severe complication is massive infection and shock from total bowel obstruction and perforation.

CLINICAL MANIFESTATIONS

Clinical manifestations are related to rapid stool transit time, intestinal edema and fibrosis, and loss of absorptive function that results from bowel inflammation during periods of exacerbation. Symptoms depend on the location of the affected areas. Abdominal pain, intermittent nonbloody diarrhea, malnutrition, and **occult**, or hidden, blood in the stool are possible clinical manifestations. Nonbloody diarrhea often indicates greater involvement in the submucosal layer as compared to the mucosal layers. If the colon mucosal layer is involved, diarrhea may contain mucus, blood, or pus. Abdominal pain is often relieved with defecation. Systemic manifestations are also common with Crohn disease and can include fever, weight loss, and fatigue. Anemia is often present when there is chronic blood loss through the gastrointestinal tract.

DIAGNOSTIC CRITERIA

Diagnosis of Crohn disease is based on the patient history, physical examination, and diagnostic tests. Direct visualization with an endoscope (sigmoidoscopy) or with radiographs shows a cobblestone pattern to the mucosa with alternating affected and unaffected areas of inflammation. Complications, such as abscesses or fistulas, can also be detected through radiographs or CT scan. Stool cultures may be needed to rule out infectious processes.

TREATMENT

Treatment is symptomatic. Medications that suppress the inflammatory and immune responses are most often used. Dietary changes are required, and foods that irritate the bowel, such as spicy foods, should be avoided. Individuals with Crohn disease need a diet high in calories and protein, and low in fat and fiber during exacerbations. Surgical intervention may be needed to remove damaged bowel or to repair fistulas. Those with Crohn disease are at increased risk of small intestine and colorectal cancer.

FUNCTIONS OF THE LARGE INTESTINE

The anatomy of the large intestine is similar to the small intestine, with the notable absence of villi in the large intestine. Columnar epithelial cells and mucus-secreting cells make up the mucosa of the large intestine. The major function of the large intestine is to absorb water and electrolytes.

Ulcerative Colitis

Ulcerative colitis is selected as a chronic inflammatory condition of the colon. Ulcerative colitis is found exclusively in the large intestine and does not affect other areas of the gastrointestinal tract (Fig. 3.28). It most often affects the mucosal layer but can extend into the submucosa.

PATHOPHYSIOLOGY

The exact cause of ulcerative colitis is not known. Autoimmunity has been implicated because antibodies

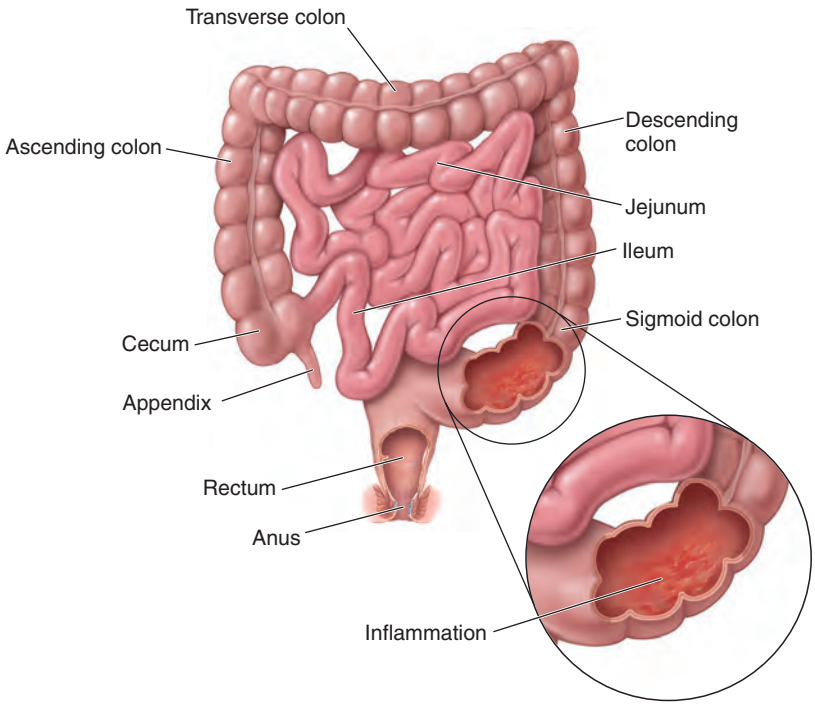


Figure 3.28. Ulcerative colitis. Chronic inflammation associated with ulcerative colitis is found exclusively in the large intestine.

to epithelial cells in the colon have been found in some individuals with ulcerative colitis. Ulcerative colitis typically begins in the distal region of the rectum and extends up the descending colon. The area of inflammation often remains on the surface of the mucosa and is continuous; ulcerative colitis does not skip any areas of the colon along the way (Fig. 3.29).

With ulcerative colitis, inflammation invades the superficial mucosa and causes **friability**, a state where tissue readily bleeds. The mucosa becomes erythematous and granular. Hemorrhagic lesions in the crypts of Lieberkühn, highly characteristic of ulcerative colitis, can form into abscesses. Extensive exudate is present early in the process, and necrosis and ulceration are common. Inflammatory processes promote the development of pseudopolyps. Over time, epithelial cells of the mucosa begin to atrophy. Metaplasia can occur. Those with long-standing ulcerative colitis demonstrate a higher risk for colorectal cancer than those with Crohn disease. Other potential complications include obstruction, perforation, and massive hemorrhage. Table 3.8 and Figure 3.30 compare pathophysiologic differences with Crohn disease and ulcerative colitis.

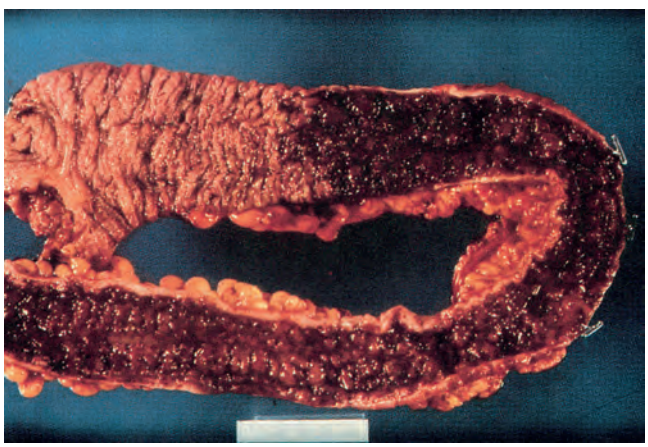


Figure 3.29. Ulcerative colitis. Prominent erythema and ulceration of the colon begin in the ascending colon and are most severe in the rectosigmoid area. (From Ruben E, Farber JL. *Pathology*. 3rd ed. Philadelphia, PA: Lippincott-Raven; 1999:731, with permission.)

CLINICAL MANIFESTATIONS

Clinical manifestations are related to large intestine irritability and friability. Diarrhea, often with rectal bleeding, is the most common clinical manifestation. Abdominal pain, fever, weakness, fatigue, and anemia can also occur. Functional losses with ulcerative colitis are related to the extent of inflammation; impaired water and electrolyte absorption are notable with extensive disease.

DIAGNOSTIC CRITERIA

Ulcerative colitis is diagnosed through endoscopy, which shows mucosal erythema. Radiographs can detect colonic dilation, ulcers, perforation, or

Table 3.8 Comparison of Crohn Disease and Ulcerative Colitis

	Crohn Disease	Ulcerative Colitis
Location	Small intestine and ascending colon	Descending colon
Pattern	Skip lesions	Continuous
Depth	Primarily submucosal	Primarily mucosal
Diarrhea	Watery	Bloody
Abdominal pain	Yes	Yes
Bowel obstruction	Common	Uncommon
Cancer risk	Increased	Higher risk than with Crohn's

obstruction. Severity is based on the number of bowel movements with rectal bleeding and the presence of systemic manifestations:

- Mild = fewer than four bowel movements per day; no systemic manifestations
- Moderate = greater than four bowel movements per day; no systemic manifestations
- Severe = greater than four bowel movements per day with systemic manifestations and low blood albumin (protein) levels

TREATMENT

Treatment is symptomatic. Anti-inflammatory, antidiarrheal, and immunosuppressive medications are sometimes used. A healthy diet and adequate fluid intake are recommended. Avoidance of certain foods such as milk, caffeine, or spicy foods may be recommended. Surgery may be needed if medical therapies are ineffective, or if perforation or obstruction occurs.

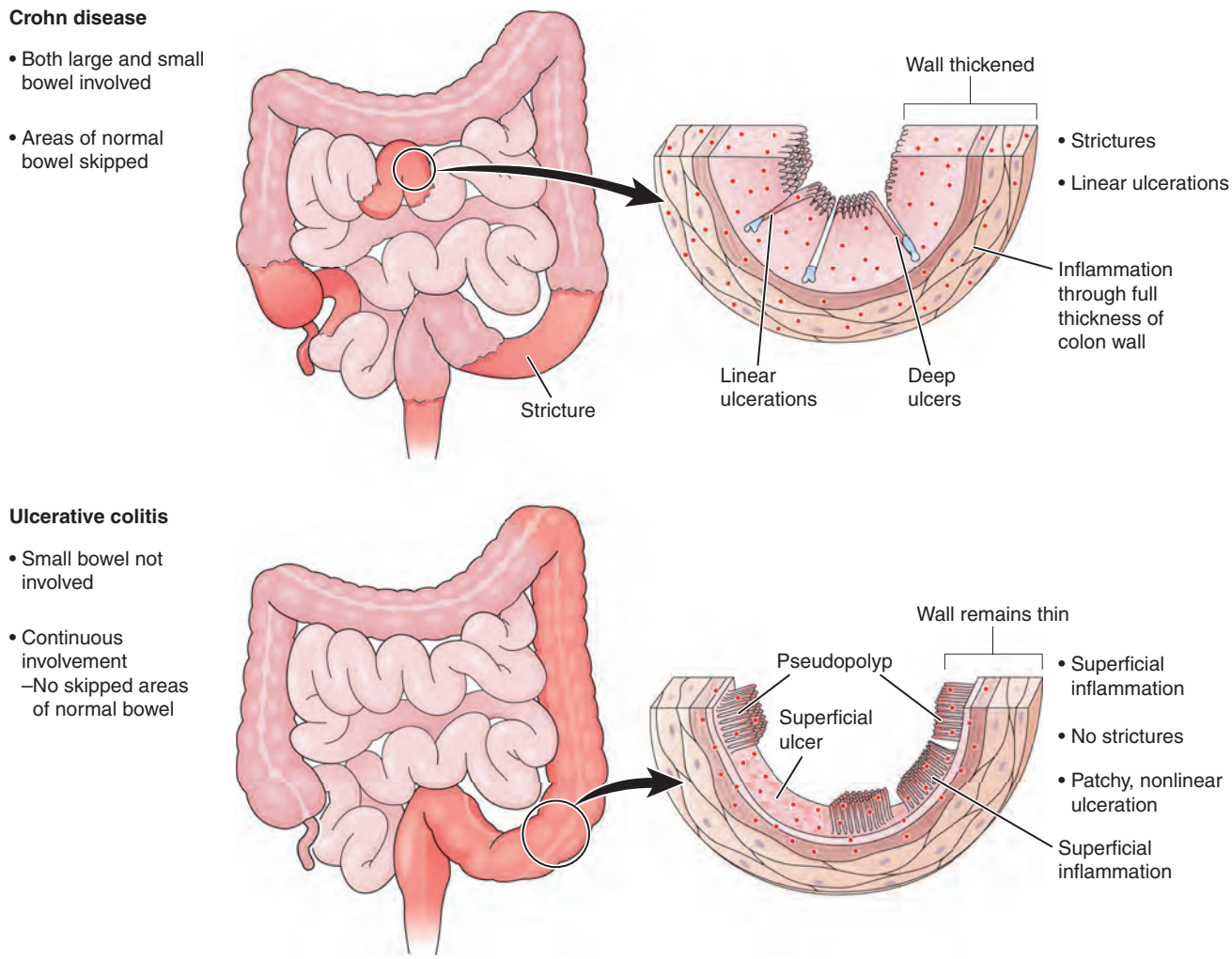


Figure 3.30. Crohn disease and ulcerative colitis. The two drawings illustrate critical differences in how the two diseases affect the gastrointestinal tract.

SUMMARY

- Inflammation is required for tissue healing and occurs in response to tissue injury.
- Inflammatory mediators, under the direction of the three plasma protein systems, regulate the inflammatory response.
- Inflammatory mediators elicit vascular and cellular responses characterized by vasodilation, increased capillary permeability, chemotaxis, cellular adherence, and cellular migration.
- Phagocytic cells (neutrophils and later macrophages) taxi to the site to engulf and destroy harmful substances.
- Removal of the injury will direct resolution of the acute inflammatory response.
- Tissue healing is a multistep process that involves covering the wound, clearing the debris, and restoring structural and functional integrity.
- The results of the inflammatory response are to repair, regenerate, or replace damaged tissue.
- Persistent injury, such as with chronic infection or autoimmune conditions, results in chronic inflammation.
- Chronic inflammation differs from acute inflammation in the types of prominent cells and in the tissue repair process. Macrophages and fibroblasts are much more prominent, resulting in increased tissue destruction, fibrosis, scarring, and granuloma formation.
- Chronic inflammatory outcomes contribute to poor wound healing. Other complications of wound healing include infection, ulcers, wound dehiscence, keloid formation, and adhesions.

CASE STUDY 3.1

A friend has disclosed that she has been having problems with heartburn. She has been told that she has gastroesophageal reflux disease (GERD), in which stomach acid backs up into the esophagus, causing esophagitis. Think about which clinical model is most related to this process. From your reading related to cellular injury and adaptations as well as inflammation, answer the following questions:

1. What anatomic problem most likely leads to gastroesophageal reflux?
2. What is the injury in gastroesophageal reflux?
3. What would the acute inflammatory response look like?
4. Why might this condition become a chronic problem?
5. What pathophysiologic changes would most likely occur with chronic gastroesophageal reflux?
6. What would you expect for clinical manifestations?
7. What diagnostic tests might be used?
8. What treatment measures would you anticipate?

Log on to the Internet, using the search words "gastroesophageal reflux." Search for relevant journal articles or Web sites that detail this condition, and confirm your predictions.

CASE STUDY 3.2

Jason is a long-distance runner. He is in the clinic today complaining of heel pain and tightness along the back of his foot and ankle. He has been recently running indoors on the treadmill as the weather has been too cold to run outside. He is diagnosed with Achilles tendonitis. From your reading related to cellular injury and adaptations as well as inflammation, answer the following questions:

1. What anatomic problem most likely leads to tendonitis?
2. What is the injury in tendonitis?
3. What would the acute inflammatory response look like?
4. Why might this condition become a chronic problem?
5. What pathophysiologic changes would most likely occur with tendonitis?
6. What would you expect for clinical manifestations?
7. What diagnostic tests might be used?
8. What treatment measures would you anticipate?

Log on to the Internet, using the search words "tendonitis." Search for relevant journal articles or Web sites that detail this condition, and confirm your predictions.

CASE STUDY 3.3

Melanie has had a recent cold with symptoms of runny nose, sneezing, coughing, congestion, and malaise. Today, she is concerned that she has a sharp pain in her chest. She goes to see her health care provider, and is diagnosed with costochondritis, an inflammation in the cartilage between the ribs. From your reading related to cellular injury and adaptations as well as inflammation, answer the following questions:

1. What anatomic problem most likely leads to costochondritis?
2. What is the injury in costochondritis?
3. What would the acute inflammatory response look like?
4. Why might this condition become a chronic problem?

5. What pathophysiologic changes would most likely occur with costochondritis?
6. What would you expect for clinical manifestations?
7. What diagnostic tests might be used?
8. What treatment measures would you anticipate?

Log on to the Internet, using the search words "costochondritis." Search for relevant journal articles or Web sites that detail this condition, and confirm your predictions.

PRACTICE EXAM QUESTIONS

1. You get a paper cut and experience pain at the site. This response is related to:
a. Increased perfusion at the site
b. Increased exudate and chemical mediators at the site
c. Bacteria that have entered the wound
d. Vasoconstriction at the site

2. Inflammation is ultimately needed to:
a. Increase inflammatory mediators at the site to vasoconstrict the area
b. Increase platelets at the site for clotting
c. Restore functional cells
d. Prepare the site for healing

3. A wound is 6 cm × 6 cm × 4 cm. A wound with these dimensions needs to heal through:
a. Secondary intention
b. Primary intention
c. Tertiary intention
d. Scar tissue formation

4. A major difference between the acute and chronic inflammatory response is that in chronic inflammation:
a. Inflammatory mediators are released
b. Neutrophils are much more prominent
c. Granulomas form around certain invaders
d. Granulation tissue is present

5. Which is not a local manifestation of acute inflammation?
a. Edema
b. Redness
c. Loss of function
d. Leukocytosis

6. Depth of injury is important to determine with burns. You are in the sun too long without sunscreen and develop redness and blistering on your face, chest, and back. What depth of burn did you experience?
a. Superficial partial-thickness burn
b. Deep partial-thickness burn
c. Full-thickness burn
d. Dermal thickness burn

7. The hospitalized burn patient wants to know why you need to remove his dressings every day. It is painful and he wants to avoid uncovering his burn injury. You explain that removing the dressings promotes:
a. Debridement
b. Infection
c. Skin function
d. Drying the exudate

8. What is the one definitive test to diagnose rheumatoid arthritis?
a. A positive rheumatoid factor (RF)
b. An elevated erythrocyte sedimentation rate (ESR)
c. A positive antinuclear antibody (ANA)
d. One test is not definitive

9. Which of the following is the most common cause of acute gastritis?
a. Poor gastric perfusion
b. Too much stomach acid
c. Ingestion of aspirin, alcohol, or other chemicals
d. H. pylori infection

10. Why is Crohn disease more likely to cause intestinal obstruction than ulcerative colitis?
a. Crohn disease is located in the small intestine.
b. Crohn disease causes granulomas to form in the submucosal layer.
c. Crohn disease causes abdominal pain and watery diarrhea.
d. Crohn disease is exacerbated by certain foods, such as spicy foods.

11. A patient is taking an anti-inflammatory drug for rheumatoid arthritis. What is the most likely action for this drug?
a. Blocks the chemical mediators of inflammation
b. Enhances the body's immune system
c. Increases blood flow to the tissues
d. Decreases scar formation

12. Which of the following is the most common cause of acute pancreatitis?
a. Cancer
b. Autoimmunity
c. Excess alcohol intake
d. Cystic fibrosis

13. Rheumatoid arthritis results in joint immobility as a result of:
   a. Synovial fluid loss
   b. Pannus formation
   c. Rheumatoid factor
   d. Joint deviation

14. Which of the following meals would you recommend to a patient with a wound to promote healing?
   a. Eggs and orange juice
   b. Spaghetti and garlic toast
   c. Steak and potatoes
   d. Tomato soup and grilled cheese

DISCUSSION AND APPLICATION

1. What did I know about inflammation and tissue repair prior to today?
2. What body processes are affected by inflammation? What are the expected functions of those processes? How does inflammation impact those processes?
3. What are the potential etiologies for inflammation? How does inflammation develop?
4. Who is most at risk for developing inflammation? How can inflammation be prevented?
5. What are the human differences that affect the etiology, risk, or course of inflammation?
6. What clinical manifestations are expected during inflammation?
7. What special diagnostic tests are useful in determining the diagnosis and course of inflammation?
8. What are the goals of care for individuals with inflammation?
9. How does the concept of inflammation build on what I have learned in the previous chapters and in previous courses?
10. How can I use what I have learned?

RESOURCES

Inflammation Research Foundation:
http://www.inflammationresearchfoundation.org/

American Burn Association:
http://www.ameriburn.org/

E-medicine:
http://emedicine.medscape.com/

References

1. Geetha M, Unnikrishnan M. Multi-target drugs to address multiple checkpoints in complex inflammatory pathologies: evolutionary cues for novel "first in class" anti-inflammatory drug candidates. *Inflamm Res*. 2015;64:747–752.
2. Corbett J. *Laboratory Tests and Diagnostic Procedures With Nursing Diagnoses*. 8th ed. Upper Saddle River, NJ: Prentice Hall; 2012.
3. Brook I. Acute sinusitis. 2015. http://emedicine.medscape.com/article/232670-overview
4. Brook I. Chronic sinusitis. 2015. http://emedicine.medscape.com/article/232791-overview
5. American Burn Association. Burn incident fact sheet. http://www.ameriburn.org/resources_factsheet.php. Accessed January 10, 2015.
6. Dougados M, Soubrier M, Antunez A, et al. Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross-sectional study (COMORA). *Ann Rheum Dis*. 2014;73:62–68.
7. Myasoedova E, Chandran A, Ilhan B, et al. The role of rheumatoid arthritis (RA) flare and cumulative burden of RA severity in the risk of cardiovascular disease. *Ann Rheum Dis*. doi:10.1136/annrheumdis-2014-206411.
8. Gardner T. Acute pancreatitis. 2015. http://emedicine.medscape.com/article/181364-overview
9. Ranson JH. Etiological and prognostic factors in human acute pancreatitis: a review. *Am J Gastroenterol*. 1982;77:633–638.
10. Huffman JL. Chronic pancreatitis. 2015. http://emedicine.medscape.com/article/181554-overview
11. Rowe WA. Inflammatory bowel disease. 2015. http://emedicine.medscape.com/article/179037-overview