The Innate Immune Response

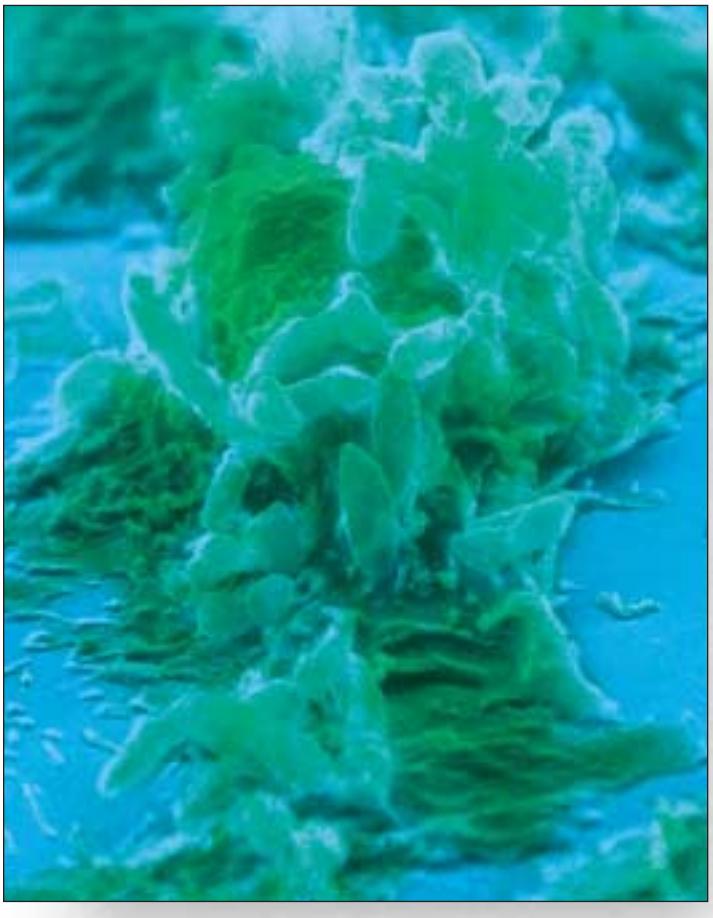
Once microorganisms were shown to cause disease, scientists worked to explain how the body defended itself against invasion by microorganisms. Elie Metchnikoff, a Russian-born scientist, theorized that there were specialized cells within the body that could destroy invading organisms. His ideas arose from observations he made while studying the transparent immature larval form of starfish in Sicily in 1882. As he looked at the larvae in the microscope, he could see ameba-like cells within the bodies. He described his observations:

> *. . . I was observing the activity of the motile cells of a transparent larva, when a new thought suddenly dawned on me. It occurred to me that similar cells must function to protect the organism against harmful intruders . . . . I thought that if my guess was correct a splinter introduced into the larva of a starfish should soon be surrounded by motile cells much as can be observed in a man with a splinter in his finger. No sooner said than done. In the small garden of our home . . . I took several rose thorns that I immediately introduced under the skin of some beautiful starfish larvae which were as transparent as water. Very nervous, I did not sleep during the night, as I was waiting for the results of my experiment. The next morning, very early, I found with joy that it had been successful.*

Metchnikoff reasoned that certain cells present in animals were responsible for ingesting and destroying foreign material. He called these cells ***phagocytes,*** *meaning "cells that eat," and he proposed that these cells were primarily responsible for the body's ability to destroy invading microorganisms.*

When Metchnikoff returned to Russia, he looked for a way to study the ingestion of materials by phagocytes, called ***phagocytosis.*** *A water flea that could be infected with a yeast provided a vehicle for such studies. He observed phagocytes ingesting and destroying invading yeast cells within the experimentally infected, transparent water fleas. In 1884, Metchnikoff published a paper that strongly supported his contention that phagocytic cells were primarily responsible for destroying disease-causing organisms. He spent the rest of his life studying phagocytosis and other biological phenomena; in 1908, he was awarded the Nobel Prize for these studies of immunity.*

—A Glimpse of History



Phagocytic cells engulfing bacteria

FROM A MICROORGANISM'S STANDPOINT, THE tissues and fluids of the human body are much like a warm culture flask filled with a nutrient-rich solution. Considering this, it may be surprising that the interior of the body—including blood, muscles, bones, and organs—is generally sterile. If this were not the case, microbes would simply degrade our tissues, just as they readily decompose the carcass of a dead animal.

How does the interior of the body remain sterile in this world full of microbes? Like other multicellular organisms,

humans have evolved several mechanisms of defense. First, we are covered with skin and mucous membranes that prevent entry of most foreign material, including microbes, into the body. Ready in case the barriers are breached are sensor systems that detect molecules associated with danger; for example, compounds that are unique to bacteria or are typically released only when tissues are damaged. These sensors can direct and assist other host defenses, facilitating the destruction of the foreign material. Also lying in wait are host cells that specialize in ingesting and digesting foreign material; if needed, additional reinforcements can be recruited to the site of breach. The protection provided by these systems is termed **innate immunity,** reflecting that we are born with it. Innate immunity differs from adaptive immunity, which will be described shortly, in that all invaders are dealt with using a limited set of weapons. Although the number of copies of the various weapons can be modulated in response to an invader, their mechanisms cannot be modified to enhance the reaction.

The components of innate immunity have been called non-specific defenses, but recent discoveries have shown that most of these components are far from unfocused; instead, they rely on the recognition of certain molecular patterns associated with invading microbes or tissue damage, a feature referred to as **pattern recognition.** Molecular patterns associated with pathogens include various compounds unique to bacterial cell walls, such as lipopolysaccharide, lipoteichoic acid, and peptidoglycan, and other molecules. Those associated with damage include various proteins that are normally intracellular and are now outside cells, and substances produced during tissue necrosis and damage. ■ **lipopolysaccharide, p. 59** ■ **lipoteichoic acid, p. 59** ■ **peptidoglycan, p. 58**

In addition to innate immunity, vertebrates have evolved a more specialized response, termed the **adaptive immune response;** this develops throughout life and substantially increases the ability of the host to defend itself. Each time the body is exposed to foreign material, the adaptive defense system first "learns" and then "remembers" the most effective response to that specific material; it then reacts accordingly if the material is encountered again. The foreign material to which the immune system responds is called an **antigen.** On first exposure to an invading microbe or other antigen, the response develops relatively slowly, during which time the microbe may cause damage if the innate defenses are unable to contain it. Successive exposures, however, lead to a swift and greater repeat response, generally eliminating the invader before it causes obvious harm.

There are two general mechanisms used by the adaptive immune response to eliminate an invader. If the antigen is within one of the body's own cells, which are referred to as either a **host cell** or a **"self" cell,** then the cell may be sacrificed as a means of destroying the invader. If the antigen is extracellular, then the body responds by making **antibodies.** These glycoprotein molecules have two functional regions; one region binds specifically to the antigen and the other functions as a "red flag," directing other host defenses to remove or destroy the antigen.

The study of the many mechanisms the body uses to defend itself against invading microbes is called **immunology.** It encompasses not only the study of protection against infectious agents, but also cancers and the acceptance or rejection of transplanted cells and organs. Immunologists also study the effects of the immune response that can damage the body, such as **autoimmunity,** which occurs when the immune response is inappropriately directed against the cells of one's own body, and **hypersensitivity,** or allergic reactions.

To simplify the description of a network as complex and intricate as the immune system, it is helpful to consider it as a series of individual parts. This chapter, for example, will focus almost exclusively on innate immunity. Bear in mind, however, that although the various parts are discussed separately, in the body their actions are intimately connected and coordinated. In fact, as you will see in chapter 16, certain components of the innate defenses are instrumental in educating the adaptive defenses, helping them to distinguish antigens that represent danger.

15.1 Overview of the Innate Defenses

First-line defenses are the barriers that separate and shield the interior of the body from the surrounding environment; they are the initial obstacles that microorganisms must overcome to invade the tissues. The anatomical barriers, which include the skin and mucous membranes, not only provide physical separation, but they are often bathed in secretions containing substances that have antimicrobial properties **(figure 15.1).** Characteristics of the components of innate immunity, including the first-line defenses, are summarized in **table 15.1.**

Sensor systems within the body recognize when the first-line barriers have been breached and then relay that information to other components of the host defenses. An important group

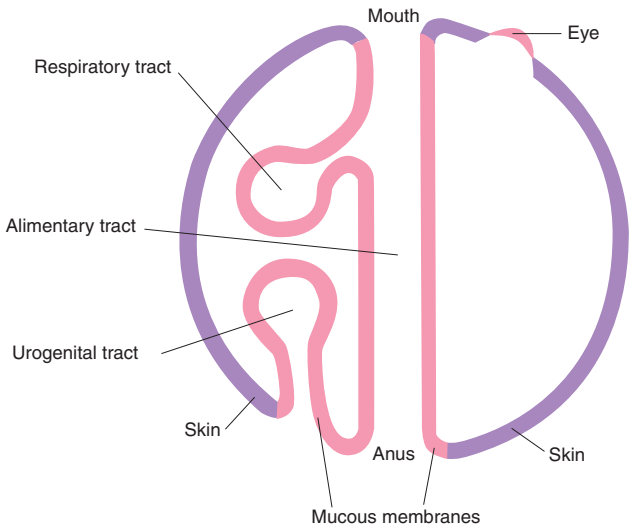


Figure 15.1 Anatomical Barriers These barriers separate the interior of the body from the surrounding environment; they are the initial obstacles microorganisms must overcome to invade tissues. The skin is shown in purple.

Table 15.1 Summary of Important Aspects of Innate Defense

Defense Component	Protective Characteristics
First-Line Defenses	Separate and shield the interior of the body from the surrounding environment.
Physical barriers	Physically prevent microbes from accessing the tissues. Skin is a tough durable border; the outermost layers of cells constantly slough off. Mucous membranes are constantly bathed with mucus and other secretions that help wash microbes from the surfaces; some mucous membranes have mechanisms that propel microbes, directing them toward areas where they can be eliminated more easily.
Antimicrobial substances	Destroy or inhibit microbes. Lysozyme degrades peptidoglycan, peroxidase enzymes produce potent oxidizing compounds, lactoferrin sequesters iron, and defensins form pores in bacterial membranes.
Normal flora	Competitively excludes pathogens by preventing adherence, consuming nutrients, and producing toxins; the normal flora also stimulates the host defenses.
Cell Communication	Enables cells to respond to trauma or invasion in a cooperative fashion.
Surface receptors	Enable the inner workings of the cell to sense and respond to signals outside of the cell. The receptors span the cell membrane, connecting the outside of the cell with the inside. Ligands bind the receptors.
Cytokines	Function as chemical messengers, allowing cells to communicate. Cytokines include interleukins, colony-stimulating factors, tumor necrosis factors, chemokines, and interferons.
Adhesion molecules	Allow cells to adhere to other cells. Endothelial cells use adhesion molecules to snare passing phagocytes that are needed in tissues. Some cells use adhesion molecules to make direct contact with other cells, enabling the targeted the delivery of certain compounds to particular cells.
Sensor Systems	Detect signs of invasion or tissue damage and then destroy the invading microbes or recruit other components of the host defense.
Toll-like receptors (TLRs)	Allow a cell to "sense" the presence of microbes and respond accordingly. TLRs on the cell surface bind directly or indirectly to molecules such as peptidoglycan and lipopolysaccharide (LPS) that are uniquely associated with microbes.
Complement System	Activated forms of the complement proteins assist phagocytes in their recognition and engulfment of foreign material, assemble themselves into membrane attack complexes, and contribute to inflammation. Antibody-antigen complexes and foreign cell surfaces both trigger the activation of the complement system.
Phagocytes	Engulf and degrade foreign material and cell debris.
Macrophages	Always in tissue to some extent, but more can be recruited to the site of injury. Activated macrophages have greater killing power.
Neutrophils	Inherently have more killing power than macrophages, but a shorter life span; rapidly recruited to a site of infection.
Inflammation (a coordinated response to invasion or damage)	Contains a site of damage, localizes the response, and ultimately restores tissue function. The inflammatory process is initiated in response to microbial products, microbes, and tissue damage. This results in dilation of blood vessels, allowing fluid and cells to exit the bloodstream and enter the site of damage.
Interferons	Induce cells to prepare to cease protein synthesis in the event that the cell becomes infected with a virus. Virally infected cells produce interferon, a cytokine, which diffuses to neighboring cells.
Fever	Elevates the temperature above the optimum growth temperature of most pathogens. Activates and accelerates other body defenses.

of sensors that has only recently been discovered is the **toll-like receptors,** which are found on the surface of a variety of different cell types. These receptors recognize families of compounds unique to microbes, enabling the cell to sense invaders and then send chemical signals to alert other components of the host's defense. Another type of sensor is a series of proteins that are always present in blood; these proteins are collectively called the **complement system** because they can "complement," or act in conjunction with, the adaptive immune defenses. In response to certain stimuli, the complement proteins become activated, setting off a chain of events that results in removal and destruction of invading microbes.

Phagocytes, cells that specialize in engulfing and digesting microbes and cell debris, act as sentries, alert for signs of invasion of the body. More can be recruited from the bloodstream, serving as reinforcements at the sites in tissues where first-line defenses have been breached.

Cells of the immune system communicate with one another by producing proteins that function as chemical messengers, called **cytokines.** A cytokine produced by one cell

diffuses to another and binds to the appropriate cytokine receptor of that cell. When a cytokine binds a receptor, the receptor transmits a signal to the interior of the cell, inducing certain changes in the activities of the cell. Some types of cytokines endow cells with enhanced powers; others prompt cells to migrate to specific locations within the body.

When invading microorganisms or tissue damage is detected, **inflammation** ensues; this is a coordinated response involving many aspects of the innate defenses. During inflammation, the cells that line local blood vessels near the area of invasion or damage undergo changes that allow antibodies, complement proteins, and coagulation proteins in **plasma,** the fluid portion of the blood, to leak into tissues. Other changes allow phagocytic cells in the bloodstream to adhere to the vessels and then squeeze between cells, exiting the bloodstream. Phagocytic cells then migrate to the area of infection or damage where they ingest and destroy foreign material. Some types of phagocytes play a dual role, destroying invaders while also communicating with cells of the adaptive immune system, enlisting their far more powerful effects.

The body also has physiological defense mechanisms, such as the increase in internal body temperature called **fever,** which acts in several ways to discourage infection.

MICROCHECK 15.1

First-line defenses are the initial obstacles that microbes must overcome to invade the tissues. Within the body are sensor systems such as toll-like receptors and the complement system that recognize when the barriers have been breached. Phagocytic cells engulf foreign material; they can communicate with other cells via cytokines. Inflammation is a coordinated response to invasion or tissue damage.

- How do cytokines function?
- Describe the dual roles played by some types of phagocytes.
- What types of molecules that are unique to microbes might toll-like receptors recognize?

15.2 First-Line Defenses

All exposed surfaces of the body, including the skin and the alimentary, respiratory, and genitals tracts, are lined with **epithelial cells (figure 15.2).** These cells are tightly packed together and rest on a thin layer of fibrous material, the **basement membrane.** In addition to the physical protection provided by this physical barrier against the outside world, the body's surfaces are bathed with a variety of antimicrobial substances that either kill or inhibit many microbes **(figure 15.3).** Certain microbes, however, are highly adapted to these conditions and actually grow, providing other types of additional protection.

In this chapter, we will describe the general physical and chemical aspects of the anatomical barriers. We will also discuss the protective contributions of the **normal flora,** those microbes that routinely inhabit the body surfaces. Various other first-line defense mechanisms are discussed more fully in the chapters dealing with each body system. ■ **normal flora, p. 461**

Physical Barriers

The skin is the most visible barrier, covering the majority of surfaces that are in obvious contact with the environment. **Mucous membranes** line the alimentary tract, respiratory tract, and genitourinary tract. These surfaces are often considered to be "inside" the body, but actually they are in direct contact with the external environment. For example, the alimentary tract, which begins at the mouth and ends at the anus, is simply a hollow tube that runs through the body, providing the opportunity for intestinal cells to absorb nutrients from food that passes (see figure 24.1); the respiratory tract is a cavity that allows oxygen and carbon dioxide gases to be exchanged (see figure 23.1).

Skin

The skin provides the most difficult barrier for microbes to penetrate; it is composed of two main layers—the dermis and the epidermis (see figure 22.1). The **dermis** contains tightly woven

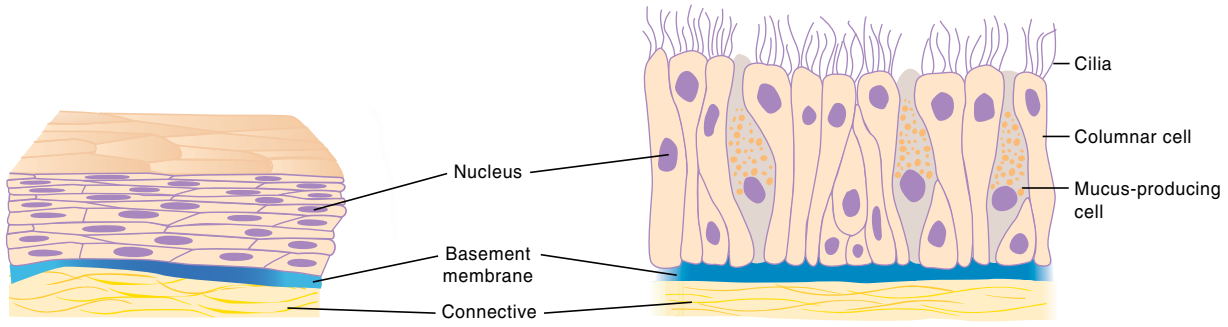


Figure 15.2 Epithelial Barriers Cells of these barriers are tightly packed together and rest on a layer of thin fibrous material, the basement membrane, helping prevent entry of materials through the barrier. Note the cilia on some epithelial cells propel material to an area where it can be eliminated.

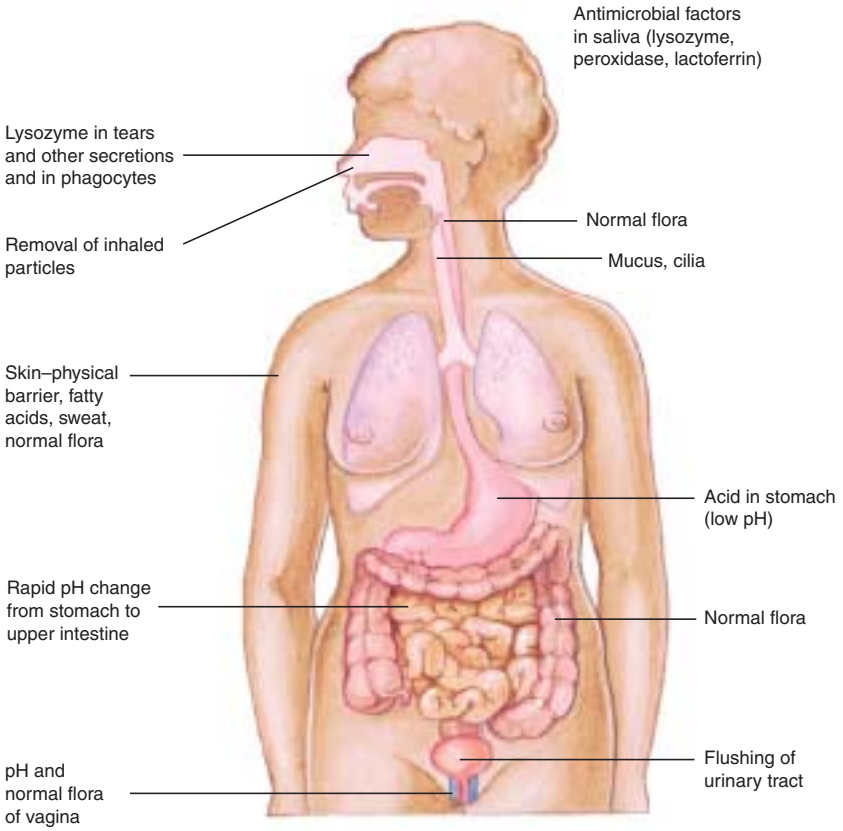


Figure 15.3 **First-Line Defense Mechanisms in Humans** Physical barriers, such as skin and mucous membranes, antimicrobial secretions, and normal flora work together to prevent entry of microorganisms into the host's tissues.

fibrous connective tissue, making it extremely tough and durable; the dermis of cows is used to make leather. The **epidermis** is composed of many layers of epithelial cells, which become more progressively flattened towards the exterior. The outermost sheets are made up of dead cells that have been embedded with a water-repelling protein called **keratin,** resulting in the skin being an arid environment. The cells continually slough off, taking with them any microbes that might be adhering. ■ **anatomy and physiology of the skin, p. 533**

Mucous Membranes

The cells of the mucous membranes, or **mucosa,** are constantly bathed with mucus and other secretions that help wash microbes from the surfaces. Some mucous membranes have mechanisms that propel microorganisms and viruses, directing them toward areas where they can be eliminated more easily. For example, **peristalsis,** the rhythmic contractions of the intestinal tract that propels food and liquid, also helps expel microbes. The respiratory tract is lined with ciliated cells; the hairlike cilia constantly beat in an upward motion, propelling material including microbes away from the lungs to the throat where they can then be swallowed. The flow of urine regularly flushes organisms from the urinary tract. ■ **cilia, p. 74**

Antimicrobial Substances

Both the skin and mucous membranes have a variety of **antimicrobial substances** that inhibit or kill microorganisms. Sweat, for example, is high in salt; as it evaporates it leaves a salty residue, inhibiting many organisms that might otherwise proliferate on the skin.

Lysozyme, the enzyme that degrades peptidoglycan, is found in tears, saliva, and in mucus that bathes mucous membranes. It is also found within the body, in phagocytic cells, blood, and the fluid that bathes tissues. Lysozyme is primarily effective against Gram-positive bacteria, whose peptidoglycan is more likely to be exposed and therefore accessible to the enzyme; recall that in Gram-negative bacteria, the peptidoglycan layer is sandwiched between the cytoplasmic and outer membranes (see figures 3.33 and 3.34). ■ **lysozyme, p. 60**

Peroxidase enzymes are found in saliva and milk; they are also found within body tissues and inside phagocytes. These enzymes break down hydrogen peroxide and, in the process, produce potent oxidizing compounds. For example, the interaction of peroxidase, hydrogen peroxide, and chlorine produces hypochlorite, the active ingredient in bleach. Bacteria that produce the enzyme catalase, however, may avoid the damaging products associated with peroxidase activity; catalase breaks down hydrogen peroxide to produce water and oxygen, potentially destroying the compound before it can interact with peroxidase. Catalase-negative organisms are more sensitive to peroxidase killing. ■ **catalase, p. 89**

Lactoferrin is an iron-binding protein found in saliva, mucus, and milk; it is also found in some types of phagocytic cells. A similar compound, **transferrin** is found in blood and tissue fluids. Iron, an important part of some enzymes, is one of the major elements required for growth (see table 4.3). By sequestering iron, the lactoferrin and transferrin effectively withhold the essential element from most microbes. Some bacteria, however, make compounds that capture iron in body fluids and secretions, thus circumventing this defense.

Defensins are short antimicrobial peptides found on mucous membranes and within phagocytic cells. They are thought to function by inserting into bacterial membranes, forming pores that disrupt the integrity of this essential barrier.

Normal Flora

The population of microorganisms routinely found growing on the body surfaces of healthy individuals is called the **normal flora.** Although these organisms are not technically part of the immune system, the protection they provide is considerable.

One protective effect of the normal flora is competitive exclusion of pathogens. For example, the normal flora prevents adherence of invading organisms to the host by covering binding sites that might otherwise be used for attachment. The population also consumes available nutrients that could otherwise

be used by less desirable organisms. Members of the normal flora also produce compounds that are toxic to other bacteria. For example, in the hair follicles of the skin, *Propionibacterium* species degrade the lipids found in body secretions, releasing fatty acids that inhibit the growth of many potential disease-producers. In the gastrointestinal tract, some strains of *E. coli* synthesize colicins, proteins that are toxic to some strains of bacteria. *Lactobacillus* species growing in the vagina produce lactic acid as a fermentation end product, resulting in an acidic pH that inhibits the growth of many potential disease-causing organisms. Disruption of the normal flora, which occurs when antibiotics are used, can predispose a person to various infections. Examples include antibiotic-associated colitis, caused by the growth of toxin-producing strains of *Clostridium difficile* in the intestine, and vulvovaginitis, caused by excessive growth of *Candida albicans* in the vagina. ■ **antibiotic-associated colitis, p. 601** ■ **vulvovaginitis, p. 640**

The normal flora also stimulates the host defenses, effectively providing a moderate amount of "exercise" to the system, thereby enhancing its function. Other aspects of the normal flora will be discussed in chapter 19.

MICROCHECK 15.2

Physical barriers that prevent entry of microorganisms into the body include the skin and mucous membranes. Various antimicrobial substances, including lysozyme, peroxidase enzymes, lactoferrin, and defensins are found on the body surfaces. The normal flora plays a protective role by excluding certain other microbes.

- What is peristalsis?
- What is the role of lactoferrin?
- How would damage to the ciliated cells of the respiratory tract predispose a person to infection?

15.3 The Cells of the Immune System

The cells of the immune system can move from one part of the body to another, traveling through the body's circulatory systems like vehicles on an extensive interstate highway system. They are always found in normal blood, but their numbers usually increase during infections, recruited from reserves of immature cells that develop in the bone marrow. Some cells play dual functions, having crucial roles in both innate and adaptive immunity.

The formation and development of blood cells is called **hematopoiesis** (Greek for "blood" and "to make"). All blood cells, including those important in the body's defenses, originate from the same type of cell, the **hematopoietic stem cell,** found in the bone marrow **(figure 15.4).** Stem cells are induced to develop into the various types of blood cells by a group of cytokines called **colony-stimulating factors.** Some of the cells of the immune system are already mature as they circulate in the bloodstream, but others **differentiate,** developing functional properties, after they leave the blood and enter the tissues.

The general categories of blood cells and their derivatives include red blood cells, platelets, and white blood cells. Red blood cells, or **erythrocytes,** carry oxygen in the blood. **Platelets,** which are actually fragments arising from large cells called **megakaryocytes,** are important for blood clotting. White blood cells, or **leukocytes,** are important in all immune defenses. Leukocytes can be divided into three broad groups—granulocytes, mononuclear phagocytes, and lymphocytes **(table 15.2).**

Granulocytes

Granulocytes all contain prominent cytoplasmic granules, filled with biologically active chemicals that are important in their function. There are three types of granulocytes—neutrophils, basophils, and eosinophils; their names reflect the staining properties of their cytoplasmic granules. Characteristics of granulocytes are described here:

- **Neutrophils** are the most abundant and important granulocytes of the innate responses and are by far the best understood; they are sometimes called **polymorphonuclear neutrophilic leukocytes, polys,** or **PMNs,** names that reflect the appearance of multiple lobes of their single nucleus. They normally account for over 50% of circulating leukocytes, and their numbers increase during most acute bacterial infections. There are generally few in tissues except during inflammation and in reserve locations. Neutrophils are **professional phagocytes;** they are highly efficient at phagocytizing and destroying foreign material, particularly bacteria, and damaged cells. The contents of their granules, which stain poorly, include many antimicrobial substances and degradative enzymes essential for destruction of materials that the cell engulfs. Because of the importance of neutrophils in innate immunity, they will be described in more detail later in the chapter. ■ **specialized attributes of neutrophils, p. 385**
- **Basophils** are blood cells involved in allergic reactions and inflammation. Their granules, which are stained dark purplish-blue by the basic dye methylene blue, contain histamine and other chemicals that increase capillary permeability during inflammation. **Mast cells** are similar in appearance and function to basophils but they are found in virtually all tissues, rather than in blood. They do not come from the same precursor cells as basophils. Mast cells are important in the inflammatory response and are responsible for many allergic reactions.
- **Eosinophils** are thought to be primarily important in expelling parasitic worms from the body. They seem to be involved in allergic reactions, causing some of the symptoms associated with allergies, but reducing others. Relatively few eosinophils are found in blood, because most leave the bloodstream, ultimately entering local secretions. The granules of eosinophils, which are stained red by the acidic dye eosin, contain antimicrobial substances and also histaminase, an enzyme that breaks down histamine.

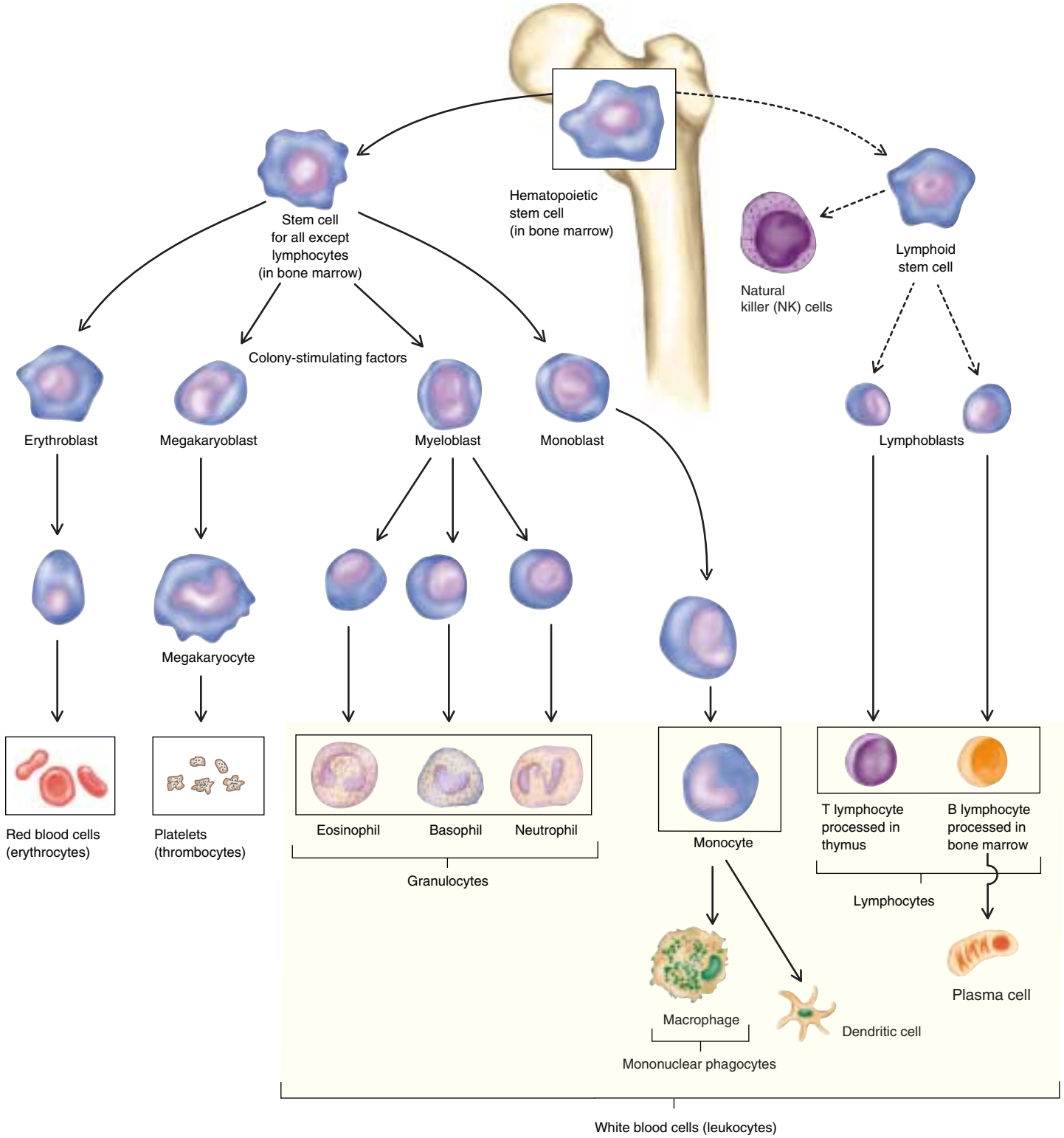


Figure 15.4 **Blood and Lymphoid Cells** All these types of cells are derived from precursor stem cells found in the bone marrow. Some of the steps not yet clearly defined are indicated by dotted arrows. Multiple steps occur between the stem cell and the final cells produced. The role of these cells in the immune response will be explained in this chapter and chapter 16.

Mononuclear Phagocytes

Two functional types of mononuclear phagocytes, macrophages and dendritic cells, arise from the same precursor, the monocyte. Characteristics of mononuclear phagocytes are described here:

- **Monocytes** circulate in blood after leaving the bone marrow. When they migrate into tissues they develop into either macrophages or dendritic cells.
- **Macrophages,** like neutrophils, are professional phagocytes. Although macrophages are present in

Table 15.2 Human Leukocytes

Cell Type (% of Blood Leukocytes)	Morphology	Location in body	Functions
Granulocytes			
Neutrophils (polymorphonuclear neutrophilic leukocytes or PMNs, often called polys; 55%–65%)	Lobed nucleus; granules in cytoplasm; ameboid appearance	Account for most of the circulating leukocytes; few in tissues except during inflammation and in reserve locations	Phagocytize and digest engulfed materials
Eosinophils (2%–4%)	Large eosinophilic granules; non-segmented or bilobed nucleus	Few in tissues except in certain types of inflammation and allergies	Participate in inflammatory reaction and immunity to some parasites
Basophils (0%–1%), Mast cells	Lobed nucleus; large basophilic granules	Basophils in circulation; mast cells present in most tissues	Release histamine and other inflammation-causing chemicals from the granules
Mononuclear Phagocytes			
Monocytes (3%–8%),	Single nucleus; abundant cytoplasm	In circulation; they differentiate into either macrophages or dendritic cells when they migrate into tissue	Phagocytize and digest engulfed materials
Macrophages	Single nucleus, abundant cytoplasm	Present in virtually all tissues; given various names based on the tissue in which they are found	Phagocytize and digest engulfed materials
Dendritic cells	Branched	Initially in tissues, but they migrate to lymph nodes and other secondary lymphoid organs	Gather antigen from the tissues and then present it to the lymphocytes that congregate in the secondary lymphoid organs
Lymphocytes			
Several types (25%–35%)	Single nucleus; little cytoplasm before differentiation	In lymphoid organs (such as lymph nodes, spleen, thymus, appendix, tonsils); also in circulation	Participate in adaptive immune responses

virtually all tissues, they are particularly abundant in liver, spleen, lymph nodes, lungs, and the peritoneal (abdominal) cavity; they are given various names based on the tissue in which they are found. This widespread collection of phagocytic cells, along with monocytes, constitutes the **mononuclear phagocyte system (MPS)**, formerly called the reticuloendothelial system (RES) **(figure 15.5).** The role of macrophages in phagocytosis and other aspects of host defense will be discussed in more detail later in the chapter. ■ **specialized attributes of macrophages, p. 385**

- **Dendritic cells** are mobile, branched cells that are highly phagocytic early in their life. They are intimately involved in adaptive immunity, functioning as scouts in various tissues throughout the body. Initially, they continually engulf antigens, gathering them from the tissues; eventually, however, they migrate to lymph nodes and other secondary lymphoid organs, which are regions where various cells of the immune system congregate. There they show fragments of the proteins they have collected to lymphocytes, a process called **antigen presentation.** Details of antigen presentation by dendritic cells with be discussed in chapter 16. ■ **the role of dendritic cells in T-cell activation, p. 410** ■ **secondary lymphoid organs, p. 396**

Lymphocytes

Lymphocytes are involved in adaptive immunity. In contrast to the generic pattern recognition of antigens by cells of the innate defenses, individual cells of the two major groups of lymphocytes, B cells and T cells, show remarkable molecular specificity in their recognition of antigen. Relatively few of the millions of different B and T cells can respond to a given antigen. When these cells encounter that antigen, they must multiply in order to amass sufficient numbers of cells to mount an effective response. The role of lymphocytes is the primary topic in chapter 16. Characteristics of lymphocytes are described here:

- **B cells** are responsible for producing antibodies.

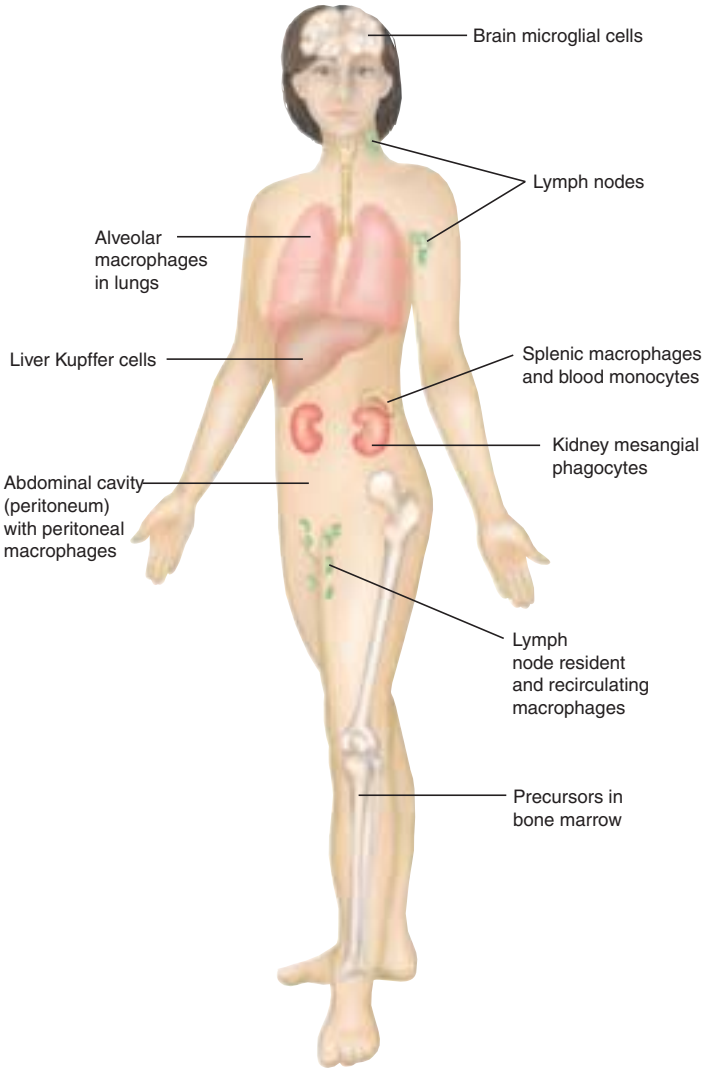


Figure 15.5 Mononuclear Phagocyte System This system of monocytes and macrophages was formerly known as the reticuloendothelial system. Many of these cells have special names to denote their location—for example, Kupffer cells (in the liver) and alveolar macrophages (in the lung).

- **T cells** can be divided into two main functional types. T-cytotoxic cells are responsible for destroying infected or abnormal host cells; T-helper cells coordinate the immune response.
- **Natural killer (NK) cells** kill cells, but they do not specifically recognize that the target is an invader; instead, NK cells destroy cells that have been bound by antibody or that exhibit certain abnormal traits.

MICROCHECK 15.3

Granulocytes include neutrophils, basophils, and eosinophils. Mononuclear phagocytes include monocytes, which mature to become macrophages, and dendritic cells. Lymphocytes are involved in adaptive immunity.

- Which cell types are professional phagocytes?
- What cell types constitute the mononuclear phagocyte system (MPS)?
- Why can stem cell transplants be used to replace defective lymphocytes?

15.4 Cell Communication

In order for the various cells of the immune system to respond to trauma or invasion in a cooperative fashion, cells must communicate both with their immediate environment and with each other. Cells receive signals from their external environment by producing surface receptors that are able to bind specific chemical messengers; these surface receptors can be considered the "eyes" and "ears" of a cell. The "voices" of a cell are the cytokines, or chemical messengers, that a cell can make. In addition, some cells can make adhesion molecules; these function as "hands," enabling one cell to directly contact another.

Surface Receptors

Surface receptors are integral membrane proteins to which certain signal molecules bind. They generally span the cell membrane, connecting the outside of the cell with the inside, enabling the inner workings of the cell to sense and respond to signals outside of the cell. Each surface receptor is specific with respect to the compound or compounds it will bind; a molecule that can bind to a given receptor is called a **ligand** for that receptor. When a ligand binds to its surface receptor, the internal portion of the receptor becomes modified in some manner, effectively communicating to the cell that the ligand is present. This then elicits some type of response, such as chemotaxis.

■ chemotaxis, p. 65

Cells can alter the types of surface molecules they make, enabling them to respond only to signals that are relevant when the cell is in a certain location or developmental stage. For example, a dendritic cell in the tissues would respond differently to certain stimuli than one that has migrated to a secondary lymphoid organ.

Cytokines

Cytokines are low molecular weight proteins made by certain cells as a mechanism to communicate with other cells. Cytokines produced by lymphocytes are also called **lymphokines.** Cytokines bind to certain surface receptors, **cytokine receptors,** found on the cells they regulate, inducing a change such as growth, differentiation, movement, or cell death. Although cytokines are short-lived, they are very powerful, acting at extremely low concentrations. They can act locally, regionally, or systemically. Often, they act together or in sequence, in a complex fashion. The source and effects of representative cytokines are summarized in **table 15.3.** General characteristics of the various groups are briefly described here:

- **Chemokines** are cytokines important in chemotaxis of immune cells; more than 50 different varieties have been identified by their structure. Certain types of cells of the

Table 15.3 Some Important Cytokines

Cytokine	Source	Effects
Chemokines	Various cells	Chemotaxis
Colony-Stimulating Factors (CSFs)	Fibroblasts, endothelium, other cells	Stimulation of growth and differentiation of different kinds of leukocytes
Interferons		
Interferon alpha	Leukocytes	Antiviral; induces fever; contributes to inflammation
Interferon beta	Fibroblasts	Antiviral
Interferon gamma	T lymphocytes	Antiviral; macrophage activation; development and regulation of adaptive immune responses
Interleukins (ILs)		
IL–1	Macrophages, epithelial cells	Proliferation of lymphocytes; macrophage production of cytokines, induce adhesion molecules for PMNs on blood vessel cells; induce fever
IL–2 (T-cell growth factor)	T lymphocytes	Changes in growth of lymphocytes; activation of natural killer cells; promote adaptive cell-mediated immune responses
IL–3	T lymphocytes, mast cells	Changes in growth of precursors of blood cells and also of mast cells
IL–4, IL–5, IL–10, IL–14	T lymphocytes, mast cells, other cells	Promote antibody responses
IL–6	T lymphocytes, macrophages	T- and B-cell growth; production of acute-phase proteins; fever
Tumor Necrosis Factors (TNFs)		
Alpha	Macrophages, T lymphocytes, other cell types, mast cell granules	Initiation of inflammatory response; cytotoxicity for some tumor cells; regulation of certain immune functions; induce fever; chemotactic for granulocytes
Beta	T lymphocytes	Killing of target cells by T cytotoxic cells and natural killer (NK) cells

host defenses have receptors for chemokines, thereby enhancing their ability to migrate to the appropriate region of the body, such as an area of inflammation. Two chemokine receptors, CCR5 and CXCR4, play a critical role in HIV infection; they serve as co-receptors for the virus, influencing which cell types are most likely to become infected. ■ **chemotaxis, p. 65** ■ **HIV co-receptors, p. 745**

- **Colony-stimulating factors (CSFs)** are important in the multiplication and differentiation of leukocytes (see figure 15.4). During the immune response when more leukocytes are needed, a variety of colony-stimulating factors direct immature cells into the appropriate maturation pathways.
- **Interferons (IFNs)** are glycoproteins important in the control of viral infections. In addition to being antiviral, IFN-gamma helps regulate the function of cells involved in the inflammatory response, particularly mononuclear phagocytes, and modulates certain responses of adaptive immunity. The role of interferons in the containment of viral infections will be described in more detail later in the chapter. ■ **glycoproteins, p. 29**
- **Interleukins (ILs)** are produced by leukocytes; at least 18 interleukins with various functions have been studied. As a group, interleukins are important in both innate immunity, including the inflammatory response, and in adaptive immunity. Their activities often overlap.
- **Tumor necrosis factors (TNFs)** were discovered because of their activities in killing tumor cells, which is how they acquired their name, but they actually have multiple roles. TNF-alpha, which is produced by macrophages and other cell types, plays an instrumental role in initiating the inflammatory response. Tumor necrosis factors can also initiate the process of programmed cell death, or apoptosis. ■ **apoptosis, p. 387**

Groups of cytokines often act together to facilitate a particular response by the host defenses. For example, cytokines referred to as **pro-inflammatory cytokines** contribute to inflammation (TNF-alpha, IL-1, IL-6, and others). Others are especially involved in promoting antibody responses (IL-4, IL-5, IL-10, and IL-14). A different group promotes responses that involve certain groups of T cells (IL-2, and IFN-gamma, and others).

Adhesion Molecules

Adhesion molecules on the surface of cells allow those cells to adhere to other cells. Some cells use adhesion molecules to "grab" other cells as they pass by. For example, when phagocytic cells in the blood are needed in tissues, the **endothelial cells,** which are the cells that line the blood vessels, synthesize adhesion molecules, snaring passing phagocytic cells. This slows down the rapidly moving phagocytic cells, and provides them with the opportunity to exit the bloodstream. Other types of adhesion molecules allow cells to make direct contact with one another, thereby enabling cells to target the delivery of cytokines or other compounds to a particular cell.

MICROCHECK 15.4

Surface receptors allow a cell to detect molecules that are present outside of that cell. Cytokines provide cells with a mechanism of communication. Adhesion molecules allow a cell to adhere to other cells.

- What is a ligand?
- What is the function of colony-stimulating factors?
- How could colony-stimulating factors be used as a therapy?

15.5 Sensor Systems

Sensor systems within the blood and tissues lie ready to detect signs of either tissue damage or microbial invasion. They respond to patterns associated with danger, such as bacterial cell wall components, by directly destroying the invading microbe or by recruiting other components of the host defenses.

Toll-Like Receptors

Toll-like receptors (TLRs) are surface receptors that enable certain cells to "see" molecules that signify the presence of microorganisms or viruses **(figure 15.6).** The name indicates they are part of a family of receptors called Toll receptors, first identified in *Drosophila* species (fruit flies). They have only recently been discovered and much is still being learned about them, but already they have caused a tremendous resurgence of interest in innate immunity, which many scientists had thought was well understood. At least 10 TLRs have been described so far, and each recognizes a distinct compound or group of compounds associated with "danger." For example, TLR-2 recognizes peptidoglycan and TLR-4 is triggered by lipopolysaccharide. Other bacterial compounds that activate the receptors include flagellin and specific nucleotide sequences that typify bacterial DNA. When a compound activates a toll-like receptor, which appears to occur by either direct or indirect binding, a signal is transmitted to the nucleus of the host cell, inducing that cell to alter the expression of certain genes. For example, lipopolysaccharide triggers a toll-like receptor of monocytes and macrophages, causing the cells to begin producing chemokines that attract additional phagocytes to the area. Engagement of toll-like receptors on endothelial cells, which line blood vessels, causes those cells to produce pro-inflammatory cytokines.

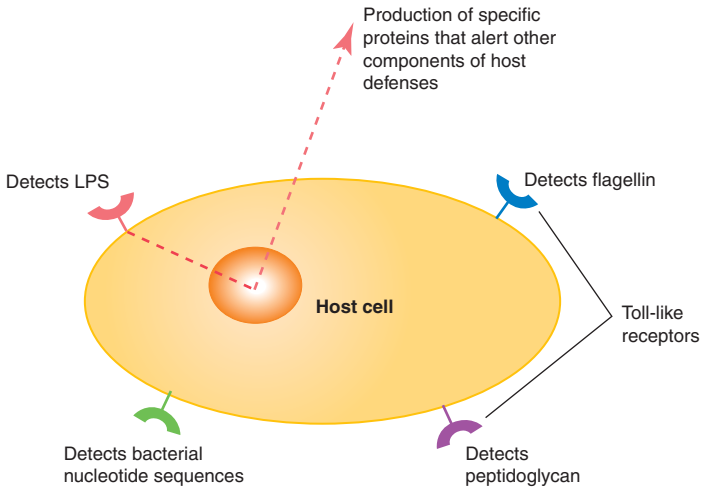


Figure 15.6 Toll-Like Receptors These surface receptors are used by host cells to detect the presence of pathogen-associated molecular patterns. Engagement of a toll-like receptor transmits a signal to the cell's nucleus, inducing the cell to begin producing certain proteins such as cytokines, alerting other components of host defenses.

The discovery of toll-like receptors has led to some intriguing ideas about how they function. Perhaps the specific combination of toll-like receptors that have been triggered helps the cell identify the invader. If this is true, cells of the innate defenses might be tailoring their responses to fit specific groups of disease-causing microbes, such as Gram-positive bacteria.

The Complement System

The **complement system** is a series of proteins that constantly circulate in the blood and the fluid that bathes the tissues. Early studies showed that these proteins augment the activities of the adaptive immune response; in fact, their name is derived from observations that they "complement" the activities of antibodies. They routinely circulate in an inactive form, but in response to certain stimuli indicating the presence of foreign material, a cascade of reactions occurs. This results in the rapid activation of critical complement components. These activated forms have specialized functions that cooperate with other aspects of the host defenses to quickly remove and destroy the offending material.

Three pathways lead to the activation of the complement system **(figure 15.7):**

- **Classical pathway.** Activation by the classical pathway requires antibodies, a component of adaptive immunity. When antibodies bind to antigen, forming **antigen-antibody complexes,** the "red flag" portion of the antibody can then interact with a complement component, activating it. This, in turn, leads to the activation of other complement proteins.
- **Lectin pathway.** Activation by the lectin pathway requires **mannan-binding lectins (MBLs);** these are pattern-recognition molecules the body uses to detect

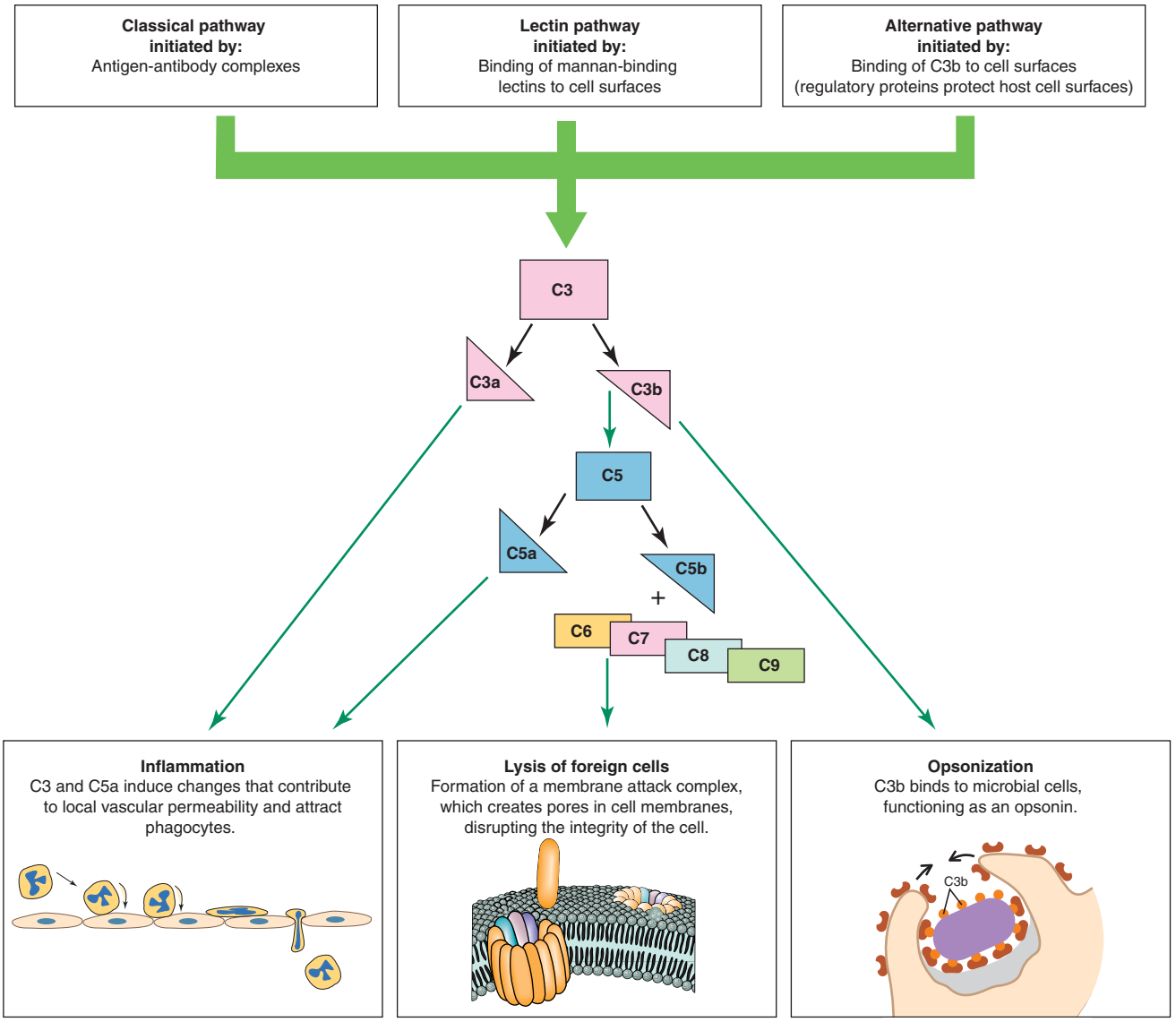


Figure 15.7 Complement System Activation of the complement system leads to inflammation, lysis of foreign cells, and opsonization. The three mechanisms that trigger the cascade include the classical pathway, the lectin pathway, and the alternative pathway. Not all of the steps in these pathways are shown.

mannan, a polymer of mannose typically found on microbial but not mammalian cells. When MBL binds to a surface, it can then interact with the complement component involved in initiating the classical pathway.

■ **mannose, p. 384**

- **Alternative pathway.** The alternative pathway is quite unlike the other pathways in how it is initiated; nearly any cell surface automatically triggers the pathway unless regulatory proteins specifically halt the process. This occurs because one of the complement proteins, C3b, readily binds cell surfaces. Unless regulatory proteins quickly inactivate C3b, a stabilizing protein will bind to it, allowing a subsequent cascade of reactions to occur. Host cell membranes contain molecules that bind those regulatory proteins, facilitating the inactivation of C3b before the alternative pathway is triggered. Those regulatory proteins are generally not associated with microbial surfaces, however, leading to complement activation by the alternative pathway. As we will discuss in chapter 19, some disease-causing bacteria have developed mechanisms to thwart complement activation by this pathway.

The nature of the complement system allows an exceedingly rapid and powerful response. Its activation occurs by a cascade of reactions; once a specific protein becomes activated, it functions as an enzyme, cleaving and therefore activating millions of molecules of the next protein in the cascade. In turn, each of those molecules activates multiple molecules of the next

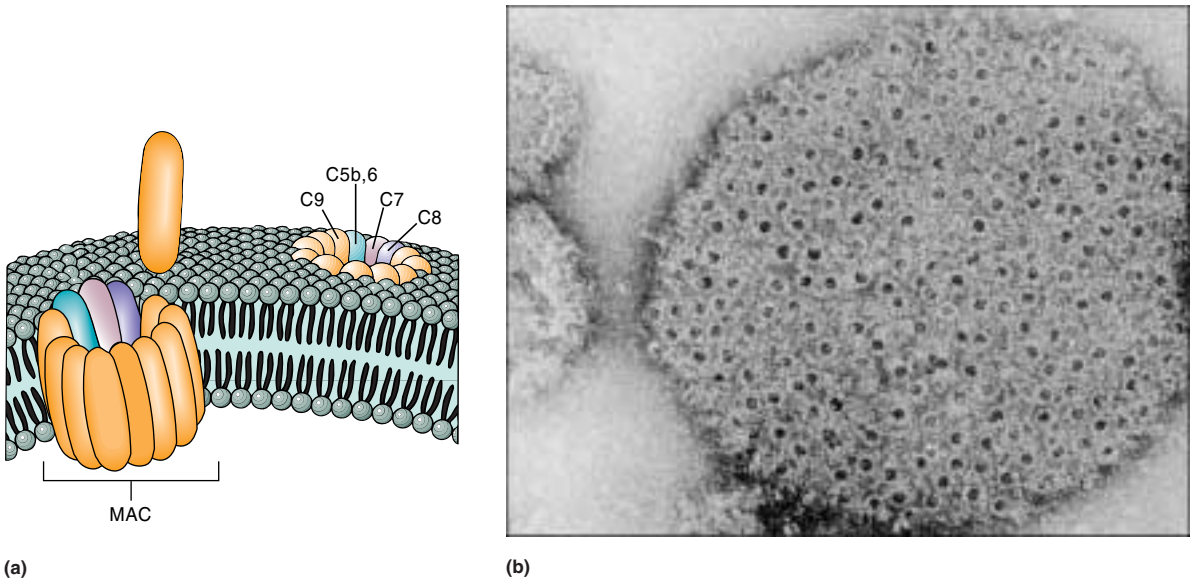


Figure 15.8 Membrane Attack Complex of Complement (MAC) **(a)** The MAC is formed after C5b, C6, and C7 combine into a complex on the cell surface of bacteria or other foreign cells. This complex, together with C8, causes changes in C9, allowing it to polymerize with the complex and form a MAC. The MAC forms a pore in the membrane, resulting in lysis of the cell. **(b)** An electron micrograph of MACs; each dark dot is a MAC.

protein in the cascade, and so on. Generally, activation involves splitting the protein into two parts, each of which then carries out a specific function. Stringent mechanisms operate to control the complement system at various points.

The major complement components have each been given a number along with the letter C, for complement. The nine major components, C1 through C9, were numbered in the order in which they were discovered and not the order in which they react. When one of these components is split into two molecules, a lowercase letter is added to the name. For example, the activation of C3 splits it into C3a and C3b. Note that C3 spontaneously splits into C3a and C3b even when the complement system has not been activated, but does so at a very low rate; this spontaneous hydrolysis allows enough C3b to be present to potentially trigger the alternative pathway of complement activation. ■ hydrolysis, p. 25

Activation of the complement system eventually leads to three major protective outcomes:

- **Inflammation.** The complement components **C3a** and **C5a** induce changes in endothelial cells, which line the blood vessels, and in mast cells. These effects contribute to the vascular permeability associated with inflammation. C5a is a potent chemoattractant, drawing phagocytes into the area where complement was activated.
- **Lysis of foreign cells.** Complexes of **C5b, C6, C7, C8,** and multiple **C9** molecules, spontaneously assemble in the membranes of cells, forming doughnut-shaped structures each called a **membrane attack complex (MAC) (figure 15.8).** This creates pores in that membrane, disrupting the integrity of the cell. Note that the membrane attack complex has little effect on Gram-positive bacteria because their peptidoglycan layer prevents the complement components from reaching their cytoplasmic membrane. The outer membrane of Gram-negative bacteria, however, renders them susceptible.
- **Opsonization.** The complement protein **C3b** binds to foreign material; phagocytes more easily "grab" particles coated with C3b because phagocytic cells have receptors for the molecule on their surface. The material that C3b has coated is said to be **opsonized** (which means "prepared for eating"); compounds such as C3b that can opsonize material are called **opsonins.** Opsonized material may be viewed as carrying a giant "eat me" sign that can be read by phagocytes. Our own cells are protected from the effects of C3b because our membranes contain regulatory molecules, leading to the inactivation of C3b when it binds. **C3a** and **C5a** cause phagocytes to produce more receptors for C3b on their surfaces. They also directly stimulate metabolic activity of phagocytes.

MICROCHECK 15.5

Toll-like receptors enable cells to detect molecules that signify the presence of a microbe. Complement proteins can be activated by three mechanisms, leading to opsonization, lysis of foreign cells, and inflammation.

- What is the role of C3b in opsonization?
- What is the role of C3b in complement activation?
- Why would the discovery of toll-like receptors alter the view that innate immunity is non-specific?

15.6 Phagocytosis

Phagocytes are cells that routinely engulf and digest material, including invading organisms. Yet, with the multitude of different particles in the body, how do those cells determine which ones to engulf? The answer lies in the various pattern recognition receptors that stud the phagocyte surface, binding to certain molecular configurations often found on cell debris and foreign material. Binding of a substance to certain pattern recognition receptors induces the phagocytic cell to engulf that material. A receptor called the **scavenger receptor,** for example, facilitates the engulfment of various materials that have charged molecules on their surface.

In routine situations, such as when organisms are introduced through a minor skin wound, macrophages that reside in the tissues readily destroy the relatively few bacteria that have entered. If the invading microbes are not rapidly cleared, however, macrophages can produce cytokines to recruit additional phagocytes, particularly neutrophils, for extra help. It is the toll-like receptors on macrophages that enable them to sense that the material is microbial in origin, and must therefore be eliminated quickly.

The Process of Phagocytosis

Phagocytosis involves a series of complex steps by which phagocytes engulf and kill invading microorganisms **(figure 15.9).** The steps are particularly relevant medically, because most disease-causing organisms have evolved the ability to evade one or more of the steps. Chapter 19 will describe some of the mechanisms microorganisms have developed to circumvent this important aspect of innate immunity. The steps of phagocytosis include:

- **Chemotaxis.** The phagocytic cells are recruited to the site of infection or tissue damage by certain chemical stimuli that act as chemoattractants. Compounds that promote chemotaxis of phagocytes include products of microorganisms, phospholipids released by injured mammalian cells, and the complement component C5a.
- **Recognition and attachment.** Phagocytic cells use various receptors to bind invading microbes either directly or indirectly. Direct binding occurs through receptors that bind patterns associated with compounds found on microbes. For example, one type of receptor on phagocytic cells binds mannose, a type of sugar found on the surface of some types of bacteria and yeasts. Indirect binding occurs when a particle has first been opsonized, dramatically enhancing the phagocytes' ability to attach and subsequently engulf the material. Opsonins include the complement component C3b and certain classes of antibody molecules; phagocytes have receptors for specific parts of these molecules.

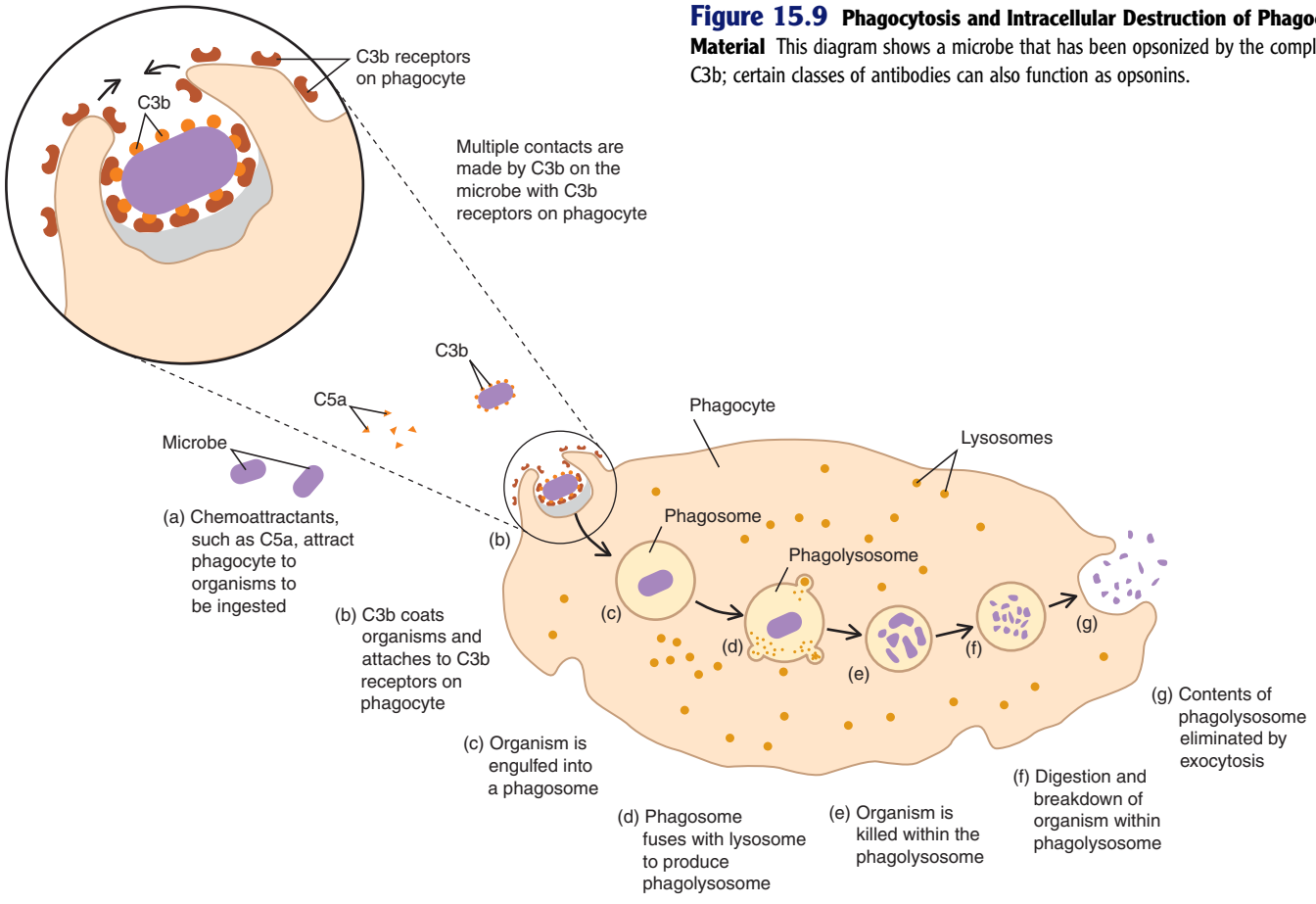


Figure 15.9 Phagocytosis and Intracellular Destruction of Phagocytized Material This diagram shows a microbe that has been opsonized by the complement protein C3b; certain classes of antibodies can also function as opsonins.

- **Engulfment.** The phagocytic cell engulfs the invader, forming a membrane-bound vacuole called a **phagosome.** This process involves rearrangement of the phagocyte's cytoskeleton, forming armlike extensions called pseudopods that surround the material being engulfed. Engulfment itself does not destroy the microbe. ■ **cytoskeleton, p. 73** ■ **pseudopod, p. 73**
- **Fusion of the phagosome with the lysosome.** Within the phagocyte, the phagosome is transported along the cytoskeleton to a point where it can fuse with a **lysosome,** a membrane-bound body filled with various digestive enzymes, including lysozyme and proteases. The fusion results in the formation of a **phagolysosome.** In neutrophils, the membrane-bound bodies are referred to as **granules.**
- **Destruction and digestion.** Within the fusion product, oxygen consumption increases enormously as sugars are oxidized via the TCA cycle, with the production of highly toxic oxygen products such as superoxide, hydrogen peroxide, singlet oxygen and hydroxyl radicals. As the available oxygen in the phagolysosome is consumed, the metabolic pathway switches to fermentation with the production of lactic acid, lowering the pH. Various enzymes degrade the peptidoglycan of the bacterial cell walls, and other components of the cell. ■ **TCA cycle, pp. 137, 144** ■ **superoxide, p. 89** ■ **hydrogen peroxide, p. 89**
- **Exocytosis.** Following the digestion of the microorganisms, the membrane-bound vesicle containing the digested material fuses with the plasma membrane. This expels the material to the external environment. ■ **exocytosis, p. 72**

Specialized Attributes of Macrophages

Macrophages can be viewed as the scavengers and sentries—routinely phagocytizing dead cells and debris, but always on the lookout, ready to destroy invaders, and able to call in reinforcements when needed. They are always present in tissues to at least some extent, where they either slowly wander or remain stationary. Macrophages that remain fixed in tissues are often referred to by different names according to the type of tissue in which they reside (see figure 15.5). These phagocytic cells play an essential role in every major tissue in the body.

Macrophages live for weeks to months, and maintain their killing power by continually regenerating their lysosomes. As macrophages die they are continually replaced by circulating monocytes that leave the blood and migrate to the tissues; recall that monocytes can differentiate into macrophages. Migration of monocytes is enhanced by certain stimuli associated with invasion and tissue damage.

Macrophages have several important characteristics that enable them to accomplish their diverse tasks. Various toll-like receptors enable them to sense material that signifies danger. When these receptors are triggered, the macrophage produces pro-inflammatory cytokines to alert and stimulate various other cells of the immune system. A macrophage can increase its otherwise limited killing power with the assistance of a subset of T-helper cells to become an **activated macrophage.** This is an example of the cooperation between the innate and adaptive host defenses. Activation of macrophages induces the production of nitric oxide (NO) and oxygen radicals, which more effectively destroy microbes. These products also damage tissues when they are released, a reason why it would be detrimental for macrophages to continually maintain an activated state. Details of the activation process, including the roles of T-helper cells, will be discussed in chapter 16. ■ **macrophage activation, p. 409**

If activated macrophages fail to destroy microbes and chronic infection ensues, large numbers of macrophages can fuse together to form **giant cells.** Macrophages, giant cells, and T-helper cells form concentrated groups of cells called **granulomas** that wall off and retain organisms or other material that cannot be destroyed by the cells; again, this is an example of the cooperation between defense systems. This prevents the microbes from escaping to infect other cells (see figure 23.18). Granulomas are part of the disease process in tuberculosis, histoplasmosis, and other illnesses. ■ **tuberculosis, p. 580** ■ **histoplasmosis, p. 592**

Specialized Attributes of Neutrophils

Neutrophils can be viewed as the rapid response team—quick to move into an area of trouble so that the offending invaders can be removed. They play a critical role during the early stages of inflammation, being the first cell type recruited from the bloodstream to the site of damage. They inherently have more killing power than macrophages, including those that have been activated. The cost for their effectiveness, however, is a relatively short life span of only 1 to 2 days in the tissues; once they have expended their granules, they die. Many more are in reserve, however, for it is estimated that for every neutrophil in the circulatory system, 100 more are waiting in the bone marrow, ready to be mobilized when needed.

MICROCHECK 15.6

The process of phagocytosis includes chemotaxis, recognition and attachment, engulfment, fusion of the phagosome with the lysosome, destruction and digestion of the ingested material, and exocytosis. Macrophages are long-lived phagocytic cells that are always present in tissues; they can be activated to enhance their killing power. Neutrophils are highly active, short-lived phagocytic cells that must be recruited to the site of damage.

- How does a phagolysosome differ from a phagosome?
- What is a granuloma?
- What could a microorganism do to avoid engulfment?

15.7 Inflammation—A Coordinated Response to Invasion or Damage

When tissues have been damaged, such as when an object penetrates the skin or when microbes produce toxic compounds, a coordinated response called the **inflammatory response,** or **inflammation** occurs. Everyone has experienced the signs of

inflammation; in fact, the Roman physician Celsus described these four cardinal signs of inflammation in the first century A.D. They are swelling, redness, heat, and pain. A fifth sign, loss of function, is sometimes present.

The vital role of inflammation is to contain a site of damage, localize the response, and restore tissue function. Early inflammatory activation quickly recruits neutrophils, followed by monocytes and other cells, to assist the local macrophages and eosinophils at the site of damage.

Factors that Initiate the Inflammatory Response

Inflammation is initiated in response to invading microbes or tissue damage. In the case of a surface wound, the action that caused the tissue damage is likely to also introduce microbes either residing on the offending instrument or on the skin's surface. Therefore, both factors are often involved in eliciting the response. Events that initiate inflammation include, either singly or in combination:

- Microbial products such as LPS, flagellin, and bacterial DNA trigger the toll-like receptors of macrophages, causing these cells to produce pro-inflammatory cytokines. One of these, tumor necrosis factor alpha, induces the liver to synthesize a group of proteins, termed **acute-phase proteins,** that facilitate phagocytosis and complement activation.
- Microbial cell surfaces can trigger the complement cascade, leading to the production of the C3a and C5a, both of which stimulate changes associated with inflammation. The complement components also induce mast cells to release various pro-inflammatory cytokines, including tumor necrosis factor alpha, and other substances.
- Tissue damage results in the activation of two enzymatic cascades. One is the coagulation cascade, which results in blood clotting, and the other produces several molecules such as bradykinin that elicit changes involved in inflammation. Current research is seeking to determine if some of the substances released during tissue damage are recognized by toll-like receptors, causing the production of pro-inflammatory cytokines.

The Inflammatory Process

Initiation of the inflammatory process leads to a cascade of events that result in dilation of small blood vessels, leakage of fluids from those vessels, and the migration of leukocytes out of the bloodstream and into the tissues **(figure 15.10).**

The diameter of local blood vessels increases during inflammation due to the action of certain pro-inflammatory chemicals. This results in an increase in blood flow to the area, causing the heat and redness associated with inflammation, accompanied by a decrease in the velocity of blood flow in the capillaries. Because of the dilation, normally tight junctions between endothelial cells are disrupted, allowing fluid to leak from the vessels and into the tissue. This fluid contains various substances such as transferrin, complement proteins, and antibodies, and thus helps to counteract invading microbes. The increase of fluids in the tissues causes the swelling and pain associated with inflammation. The direct effects of chemicals on sensory nerve endings also cause pain.

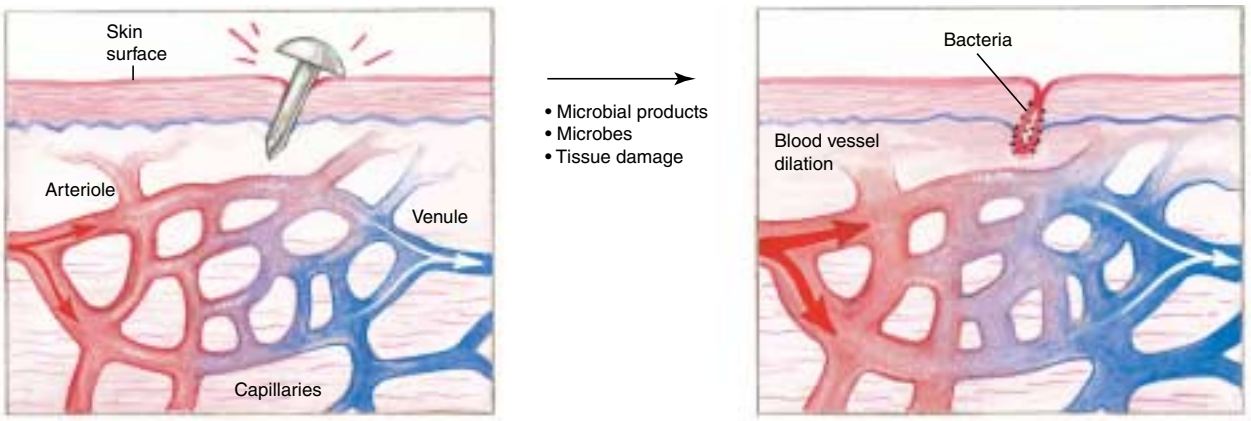
Some of the pro-inflammatory cytokines cause endothelial cells in the local area to produce adhesion molecules that loosely adhere to phagocytes. The phagocytes normally flow rapidly through the vessels, but slowly tumble to a halt as they attach to the adhesion molecules. The phagocytic cells themselves then begin producing a different type of adhesion molecule that strengthens the attachment. Then, in response to other cytokines and complement components that function as chemoattractants, phagocytes migrate from the blood vessels into the area. They do this by squeezing between the cells of the dilated permeable vessel, the process of **diapedesis.** Neutrophils (PMNs) are the first type of phagocyte to be lured from the circulation, and soon they predominate in the area of inflammation. After the influx of neutrophils to the area, monocytes and lymphocytes accumulate. Both neutrophils and monocytes, which mature into macrophages at the site of infection, actively phagocytize foreign material. Clotting factors, which are in the fluid that leaks into the tissues, initiate clotting reactions. This helps prevent further bleeding and halts spread of invading microbes, which get caught in the clot. As the inflammatory process continues, large quantities of dead neutrophils accumulate. Along with tissue debris, these dead cells make up **pus.** A large amount of pus constitutes a **boil** or **abscess** (see figure 22.3). ■ boil, p. 537

The extent of inflammation varies, depending on the nature of the injury, but the response is localized, begins immediately upon injury, and increases over a short period of time. This short-term inflammatory response is called **acute inflammation** and is marked by a prevalence of neutrophils. Then, as inflammation subsides, healing occurs. During healing, new capillary blood vessels grow into the area and destroyed tissues are replaced; eventually, scar tissue is formed. If acute inflammation cannot limit the infection, **chronic inflammation** occurs. This is a long-term inflammatory process that can last for years. Chronic inflammation is characterized by the prevalence of macrophages, giant cells, and granulomas. ■ giant cells, p. 409 ■ granulomas, p. 409

Outcomes of Inflammation

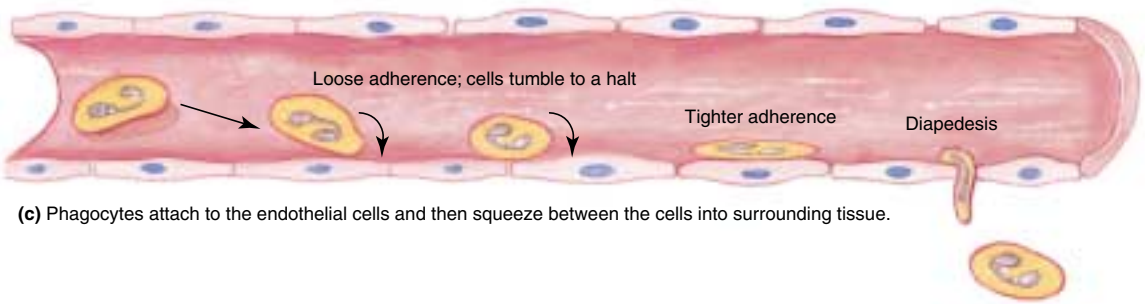
The inflammatory process can be likened to a sprinkler system that prevents fire from spreading in a building. While the intention of the process—to limit damage and restore function—is positive, the response itself can cause significant harm. One undesirable consequence of inflammation, for example, is that some of the enzymes and toxic products contained within phagocytic cells are inevitably released, damaging tissues.

If inflammation is limited, such as in a response to a cut finger, the damage caused by the process is normally minimal. If the process occurs in a delicate system, however, such as the membranes that surrounds the brain and spinal cord, the consequences can be much more severe, even life threatening. Another serious situation occurs in the response to bloodstream infections, particularly those caused by Gram-negative bacteria. The lipopolysaccharide component of their outer membrane, referred to as **endotoxin,** causes a number of responses, includ-

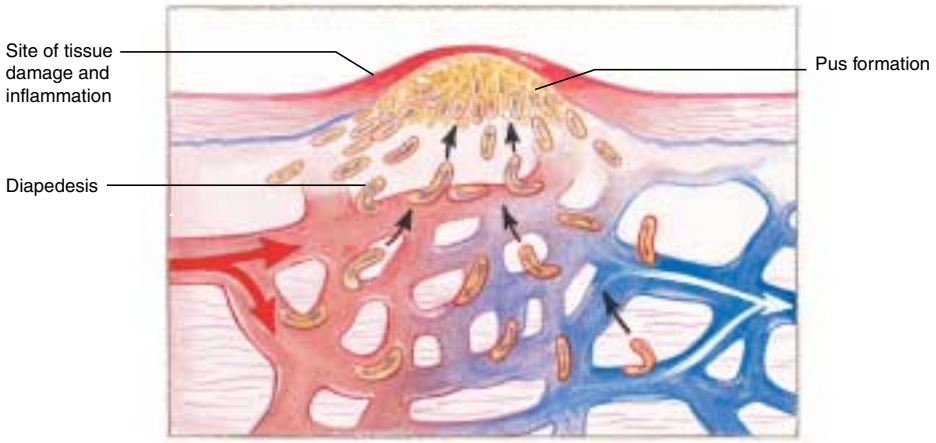


(a) Normal blood flow in the tissues as injury occurs.

(b) Substances released cause dilation of small blood vessels and increased blood flow in the immediate area.



(c) Phagocytes attach to the endothelial cells and then squeeze between the cells into surrounding tissue.



(d) The attraction of phagocytes causes them to move to the site of damage and inflammation. Collections of dead phagocytes and tissue debris make up the pus often found at sites of an active inflammatory response.

Figure 15.10 The Inflammatory Process This coordinated response to microbial invasion or tissue damage brings phagocytes and other leukocytes to the site. The role of inflammation is to contain a site of damage, localize the response, and restore tissue function.

ing the release of pro-inflammatory cytokines by monocytes, activation of the complement cascade and activation of the clotting cascade. The net result is a rapid loss in blood pressure, leading to shock, extensive tissue damage, and widespread formation of clots that plug the capillaries, cutting off the blood supply; this manifestation of a bloodstream infection (sepsis) is called **septic shock** (see figure 28.3). The cell wall components of Gram-positive bacteria can also elicit septic shock. ■ **meninges, p. 664** ■ **endotoxin, p. 59** ■ **Gram-negative sepsis, p. 719**

Apoptosis—Controlled Cell Death that Circumvents the Inflammatory Process

The inflammatory response represents a potential problem for the host; that is, how to distinguish cell death caused by abnormal

PERSPECTIVE 15.1 For *Schistosoma*, the Inflammatory Response Delivers

Just as our immune system has evolved to protect us from new and different invasions, it is not surprising that in the opportunistic and adaptable world of microbes, some would find ways to use our defenses to their advantage. The parasitic flatworms that cause schistosomiasis do not shy from the immune response when it comes to procreation; instead they appear to use it to deliver their ova to an environment where they might hatch. Adult females of *Schistosoma* species, which live in the bloodstream of infected hosts, lay their ova in veins near the intestine or bladder; they seem to rely on a robust inflammatory response to expel the ova, completing one portion of a complex life cycle. The ova released in feces or urine can hatch to form a larval form called a *miracidium* if untreated sewage reaches water. The miracidium then infects a specific freshwater snail host and undergoes asexual multiplication. The infected snail then releases large numbers of another larval form, cercariae, which swim about in search of a human host.

The parasite is acquired when a person wades or swims in contaminated water. The cercariae penetrate the skin by burrowing through it with the aid of digestive enzymes; schistosomes are rare among pathogens because they can actually penetrate intact skin. The larvae then proceed to enter the circulatory system where they can live for over a quarter of a century. *Schisotosoma* species have separate sexes and, remarkably, the male and female worms locate one another in the bloodstream. The male's body has a deep longitudinal groove in which he clasps his female partner to live in copulatory embrace (*shisto-soma* means "split-body," referring to the long slit). The adult worms effectively mask themselves from the immune system by adsorbing various blood proteins; this provides them with a primitive stealth "cloaking device."

Depending on the species, the female worm migrates to the veins of either the intestine or bladder to lay hundreds of ova per day. The body responds vigorously to the highly antigenic eggs, ejecting them in manner that appears similar to what is experienced as a sliver in the skin works its way to the surface. Over half of the ova are not expelled, however, and many of these are instead swept away by the bloodstream to the liver. The inflammatory process and granuloma formation there gradually destroys liver cells, replacing the cells with scar tissue. Malfunction of the liver results in malnutrition and a buildup of pressure in the esophagus. Fluid accumulates in the abdominal cavity and hemorrhage occurs if the engorged esophageal veins rupture.

Despite their complex life cycle, *Schistosoma* species are highly successful. Not only are they adept at avoiding certain immune responses that would otherwise lead to their destruction, they have learned to exploit inflammation for their own dissemination. Over 200 million people worldwide are infected with these parasites, resulting in the death of over 500,000 people each year.

events, such as injury, from that caused by normal events such as tissue remodeling that render certain cells unnecessary or potentially harmful. The former merits an inflammatory response whereas the latter does not and, in fact, would be unnecessarily destructive to normal tissue. **Apoptosis** (Greek, *apo* for "falling"; *ptosis* for "off"), or programmed cell death, is a process that destroys self-cells without eliciting inflammation. During apoptosis, the dying cells undergo certain changes. For example, the shape of the cell changes, enzymes cut the DNA, and portions of the cell bud off, effectively shrinking the cell. Some changes appear to signal to macrophages that the remains of the cell are to be engulfed without the commotion associated with inflammation. For example, some parts of the membrane invert, exposing molecules that are generally restricted to the inner leaflet.

The mechanisms and events connected to apoptosis are currently the focus of a great deal of research. It is now recognized that the process is used to eliminate a wide range of cells from the body, including virally infected cells, as well as those lymphocytes whose function is rendered obsolete by the successful elimination of an antigen.

MICROCHECK 15.7

Inflammation is a cascade of events initiated in response to invading microbes or tissue damage. The outcome is dilation of small blood vessels, leakage of fluids from those vessels, and migration of leukocytes out of the bloodstream and into the tissue. Inflammation can help contain an infection, but the response itself can cause damage. Apoptosis provides a mechanism for the destruction of self-cells without initiating inflammation.

- Describe three general events that can initiate inflammation.
- Describe the changes that characterize cells that are undergoing apoptosis.
- How could infection of the fallopian tubes lead to sterility and ectopic pregnancy?

15.8 Interferons

Interferons are a group of glycoproteins important in the control of viral infections as well as other immune responses. One of their most important functions is to prepare cells in the vicinity of a virally infected cell to cease protein synthesis in the event they become infected with a virus themselves. This prevents viral replication within those neighboring cells, limiting the spread of the virus.

Cells use the presence of double-stranded RNA to indicate they have been infected with a virus. Eukaryotic cells typically do not contain double-stranded RNA because only one strand of DNA in a gene is used as a template for RNA synthesis. Replication of RNA viruses other than retroviruses, however, routinely generates double-stranded RNA. Even DNA viruses often give rise to double-stranded RNA as a consequence of their efficient use of their relatively small genomes; in some regions, both strands of DNA are transcribed into mRNA.

Double-stranded RNA in an animal cell induces the synthesis and subsequent secretion of interferon **(figure 15.11).** The interferon molecules then attach to a specific receptor on both the infected cell and neighboring cells, causing them to activate genes encoding enzymes capable of directing the degradation of mRNA and inhibition of protein synthesis. The action of these enzymes requires the presence of double-stranded RNA, preventing viral replication in infected cells without impacting uninfected cells. This process essentially sacrifices an infected host cell in order to prevent viral spread. Interferons provide some protection against most types of viruses.

Three types of interferon are known. One type, **interferon alpha,** is a family of closely related proteins produced by various white blood cells. In addition to its antiviral activity, it also contributes to fever production. A second type, **interferon beta,** is made by fibroblasts, which are cells of fibrous supporting tissue.

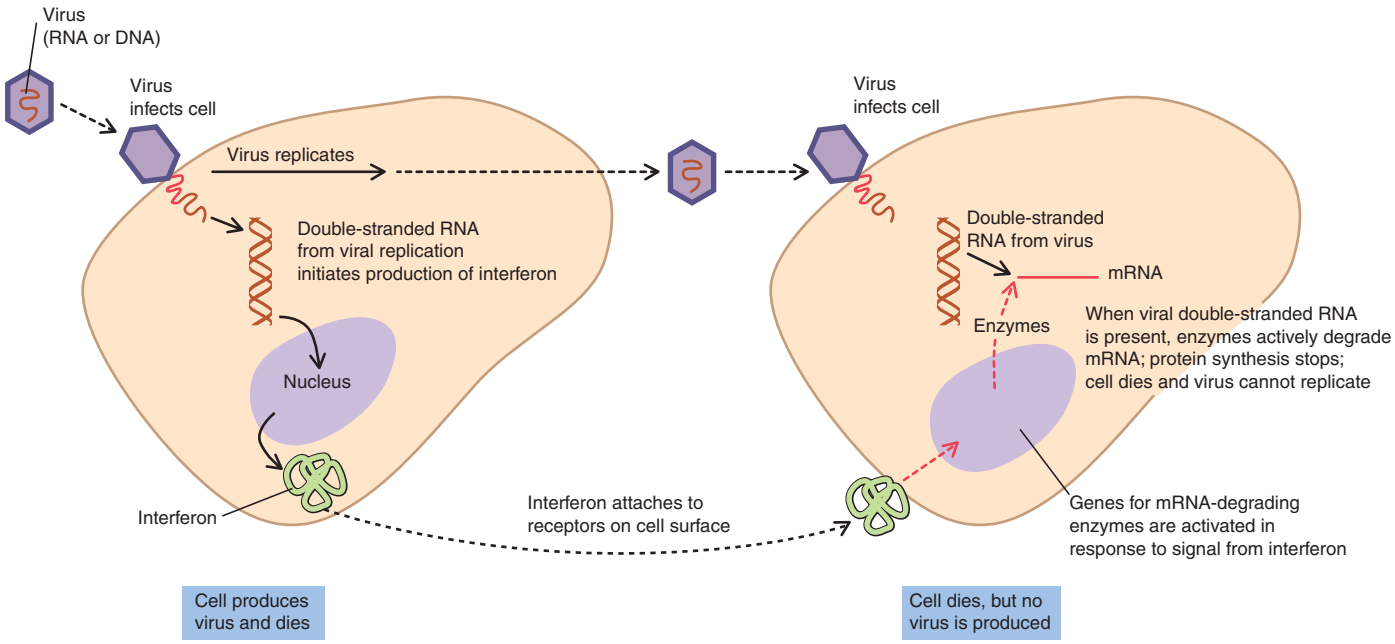


Figure 15.11 Mechanism of the Antiviral Activity of Interferons Interferons are small glycoproteins made by virus-infected cells that act on nearby cells, causing them to produce antiviral proteins. These proteins are enzymes that inhibit virus replication in various ways.

Both alpha and beta interferons are made by many cell types when infected with viruses. A third type, **inteferon gamma,** is made by lymphocytes; unlike the other interferons, its synthesis is not directly related to viral infection. In addition to being antiviral, interferon gamma is very important in enhancing the killing power of macrophages, and also functions in the development and regulation of the adaptive immune response.

Interferons are quite species specific with regard to host, which initially prevented their widespread therapeutic use; interferon from other animals is not effective in humans. Microorganisms, however, have now been genetically engineered to produce human interferons. Interferon alpha has been approved in the United States for treatment of Kaposi's sarcoma in AIDS patients, chronic hepatitis B and hepatitis C infections, and several other diseases. Interferon beta is used to slow the progression of multiple sclerosis (MS), but the mechanisms of its beneficial effects are unclear. ■ **genetic engineering, pp. 220, 230**

MICROCHECK 15.8

Interferons induce cells in the vicinity of a virally infected cell to prepare to cease protein synthesis should they become infected with virus. Double-stranded RNA functions as the signal to a cell that it is infected with a virus.

- What activities does interferon gamma have that interferons alpha and beta do not?
- What is the source of interferon that is used therapeutically?
- Considering that retroviruses have an RNA genome, why would their replication not generate double-stranded RNA?

15.9 Fever

Fever is one of the strongest indications of infectious disease, especially those of bacterial origin, although significant infections can occur without it. There is abundant evidence that fever is an important host defense mechanism in a number of vertebrates, including humans. Within the human body, the temperature is normally kept within a narrow range, around 37°C, by a temperature-regulation center in the hypothalamus of the brain. The hypothalamus controls temperature by regulating blood flow to the skin, and the amount of sweating and respiration. In this way, the heat produced by metabolism is conserved or lost in order to maintain a fairly constant temperature. During an infection, the regulating center continues to function but the body's thermostat is "set" at higher levels. An oral temperature above 37.8°C is regarded as fever.

A higher temperature setting occurs as a result of certain pro-inflammatory cytokines released by macrophages when their toll-like receptors detect microbial products. The cytokines are carried in the bloodstream to the hypothalamus, where they act as messages that microorganisms have invaded the body. These cytokines and other fever-inducing substances are **pyrogens.** Fever-inducing cytokines are called **endogeneous pyrogens,** indicating that the body makes them, whereas microbial products, such as bacterial endotoxins, are called **exogenous pyrogens,** indicating that they are introduced from external sources. The temperature-regulating center responds to pyrogens by raising body temperature. The resulting fever inhibits the growth of many pathogens by at least two mechanisms: (1) elevating the temperature above the optimum

growth temperature of the pathogen, and (2) activating and speeding up a number of other body defenses.

The adverse effects of fever on pathogens correlates in part with their ideal growth temperature. Bacteria that grow best at 37°C are less likely to cause disease in people with fever. The growth rate of bacteria often declines sharply as the temperature rises above their optimum growth temperature. A slower growth rate allows more time for other defenses to destroy the invaders. ■ **temperature requirements, p. 86**

A moderate rise in temperature increases the rate of enzymatic reactions. It is thus not surprising that fever has been shown to enhance the inflammatory response, phagocytic killing by leukocytes, the multiplication of lymphocytes, the release of substances that attract neutrophils, and the production of interferons and antibodies. Release of leukocytes into the blood from the bone marrow is also enhanced. For all these reasons, it is wise to consult a physician before taking drugs to reduce the fever of infectious disease.

MICROCHECK 15.9

Fever results when macrophages release pro-inflammatory cytokines; this occurs when the toll-like receptors on the macrophages are engaged by microbial products.

- What is an endogenous pyrogen? What is an exogenous pyrogen?
- How does fever inhibit the growth of pathogens?
- Syphilis was once treated by intentionally infecting the patient with the parasite that causes malaria, a disease characterized by repeated bouts of fever, shaking, and chills. Why would this treatment cure syphilis?

FUTURE CHALLENGES

Polishing the Magic Bullet

Very early in the twentieth century, Paul Ehrlich looked for a "magic bullet," a drug that could affect only invading microorganisms and not host cells, one that could be delivered directly to the area of infection or inflammation. In spite of extensive investigations, Ehrlich did not find a magic bullet, but others carried on the search. Through the years many attempts have been made to attach drugs to various molecules, such as specific antibodies, that could home to the area where the drugs were needed.

Currently, a promising approach to finding the elusive magic bullet is based on ongoing investigations of the mechanisms of inflammation. Early during the inflammatory response, a family of adhesion molecules called ***selectins*** *is expressed on cells of small blood vessels in the area of injury. Selectins bind to carbohydrate molecules on circulating leukocytes. As the leukocytes roll rapidly through the blood vessels, selectin molecules bind them, stopping them in their tracks. The leukocytes are held captive in the region of inflammation. Other molecules in that area attract the captured white blood cells across the vessel wall and into the injured tissue. Selectin activity is a marker for tissue damage and, therefore, a logical target for delivery of drugs into areas of inflammation resulting from infections. The drugs could be antimicrobials to act against invading microorganisms, or anti-inflammatory agents to lessen the symptoms caused by inflammation.*

In some diseases, such as arthritis and other autoimmune diseases, the tissue damage caused by inflammation is the major factor in the disease process. In addition to delivering anti-inflammatory drugs to the area, blocking the actions of selectins by a selectin inhibitor might prevent the development of inflammatory damage.

Scientists working in this area are studying the exact structure of the various selectin molecules and their characteristics. One selectin is stored in cells of the blood vessel and is expressed on the cell surface within minutes of tissue injury. Another is synthesized after injury and expressed on cell surfaces after about 4 hours. The structure of leukocyte surface molecules that will bind to selectins has also been determined. It should be possible to attach antimicrobial or anti-inflammatory drugs to the small portions of binding molecules that actually bind to the selectin. This combination would then be selectively removed from the circulation in the areas of inflammation, the only areas where selectin is produced. It is estimated that preparations of selectin-binding antimicrobials or anti-inflammatory drugs could be available within several years, making Ehrlich's long-ago dream a reality.

SUMMARY

15.1 Overview of the Innate Defenses (Table 15.1)

1. The innate defense system is composed of **first-line defenses,** sensor systems such as **toll-like receptors** and **complement,** and **phagocytes. Inflammation** is a coordinated response that involves many aspects of the innate defenses.

15.2 First-Line Defenses (Figures 15.2, 15.3)

Physical Barriers

1. The skin provides the most difficult barrier for microbes to penetrate; it is composed of two main layers—the **dermis** and the **epidermis.**
2. The cells of the **mucous membranes** are constantly bathed with mucus and other secretions that help wash microbes from the surfaces. Some mucous membranes have mechanisms that propel microbes, directing them toward areas where they can be eliminated more easily.

Antimicrobial Substances

1. **Lysozyme, peroxidase enzymes, lactoferrin,** and **defensins** are antimicrobial substances that inhibit or kill microorganisms.

Normal Flora

1. Members of the **normal flora** competitively exclude pathogens and stimulate the host defenses.

15.3 The Cells of the Immune System (Figure 15.4, Table 15.2)

Granulocytes

1. There are three types of **granulocytes—neutrophils, basophils,** and **eonsinophils.**

Mononuclear Phagocytes

1. **Monocytes** differentiate into either **macrophages** or **dendritic cells.** (Figure 15.5)

Lymphocytes

1. **Lymphocytes,** which include **B cells, T cells,** and **natural killer (NK) cells,** are involved in adaptive immunity.

15.4 Cell Communication

Surface Receptors

1. Surface receptors bind ligands that are on the outside of the cell, enabling the cell to detect that the ligand is present.

Cytokines (Table 15.3)

1. **Cytokines** include **interleukins (ILs), colony-stimulating factors (CSFs), tumor necrosis factors (TNFs), chemokines,** and **interferons.**

Adhesion Molecules

1. **Adhesion molecules** allow cells to adhere to other cells.

15.5 Sensor Systems

Toll-Like Receptors (Figure 15.6)

1. Toll-like receptors enable cells to detect molecules that signify the presence of an invading microbe.

The Complement System (Figure 15.7)

1. **Complement** proteins circulate in the blood and the fluid that bathes tissues; in response to certain stimuli that indicate the presence of foreign material, they become activated.
2. The major protective outcomes of complement activation include **opsonization,** lysis of foreign cells, and initiation of **inflammation.**

15.6 Phagocytosis

The Process of Phagocytosis (Figure 15.9)

1. The steps of phagocytosis include chemotaxis, recognition and attachment, engulfment, destruction and digestion, and exocytosis.

Specialized Attributes of Macrophages

1. Macrophages are always present in tissues to some extent, but are able to call in reinforcements when needed.
2. A macrophage can increase its killing power, becoming an **activated macrophage.**
3. Macrophages, **giant cells,** and T-helper cells form concentrated groups called **granulomas** that wall off and retain organisms or other material that cannot be destroyed by macrophages.

Specialized Attributes of Neutrophils

1. Neutrophils play a critical role during the early stages of inflammation, being the first cell type recruited from the bloodstream to the site of damage.

15.7 Inflammation—A Coordinated Response to Invasion or Damage (Figure 15.10)

1. Swelling, redness, heat, and pain are the signs of inflammation, the attempt by the body to contain a site of damage, localize the response, and restore tissue function.

Factors that Initiate the Inflammatory Response

1. Inflammation is initiated when pro-inflammatory cytokines or other inflammatory mediators are released as a result of the engagement of toll-like receptors or activation of complement by invading microbes, or when tissue damage occurs.

The Inflammatory Process

1. The inflammatory process leads to a cascade of events that result in dilation of small blood vessels, leakage of fluids from those vessels, and the migration of leukocytes out of the bloodstream and into the tissues.
2. **Acute inflammation** is marked by a preponderance of neutrophils; **chronic inflammation** is characterized by the prevalence of macrophages, giant cells, and granulomas.

Outcomes of Inflammation

1. Inflammation can contain an infection, but the process itself can cause damage; a systemic response can be life threatening.

Apoptosis—Controlled Cell Death that Circumvents the Inflammatory Process

1. Apoptosis is a mechanism of eliminating self-cells without evoking an inflammatory response.

15.8 Interferons (Figure 15.11)

1. One of the roles of **interferons** is to induce cells in the vicinity of a virally infected cell to prepare to cease protein synthesis in the event they become infected with a virus; double-stranded RNA signifies to the cell that it has been infected.

15.9 Fever

1. Fever occurs as a result of certain pro-inflammatory cytokines released by macrophages when their toll-like receptors bind microbial products.
2. Fever inhibits the growth of many pathogens and increases the rate of various body defenses.

REVIEW QUESTIONS

Short Answer

1. Why is iron metabolism important in body defenses?
2. How do phagocytes get into tissues during an inflammatory response?
3. Describe how the skin protects against infection.
4. What are the benefits of saliva in protection against infection? What factors found in saliva aid in protection?
5. Name two categories of cytokines and give their effects.
6. Contrast the classical and alternative pathways of complement activation.
7. How does the activation of a few molecules in early stages of the complement cascade result in the cleavage of millions of molecules of later ones?
8. How do complement proteins cause foreign cell lysis?
9. Describe three mechanisms of triggering inflammation.
10. Describe the purpose of apoptosis.

Multiple Choice

1. Lysozyme does which of the following:
   A. disrupts cell membranes
   B. hydrolyzes peptidoglycan
   C. waterproofs skin
   D. propels gastrointestinal contents
   E. propels the cilia of the respiratory tract
2. The hematopoietic stem cells in the bone marrow can become which of the following cell types?
   1. red blood cell 2. T cell 3. B cell
   4. monocyte 5. macrophage
   A. 2, 3 **B.** 2, 4 **C.** 2, 3, 4, 5 **D.** 1, 4, 5 **E.** 1, 2, 3, 4, 5
3. All of the following refer to the same type of cell *except*
   A. macrophage **B.** neutrophil
   C. poly **D.** PMN
4. Toll-like receptors are triggered by all of the following compounds *except*
   A. peptidoglycan **B.** glycolysis enzymes **C.** lipopolysaccharide
   D. flagellin **E.** certain nucleotide sequences
5. A pathogen that can avoid the complement component C3b would directly protect itself from
   A. opsonization **B.** triggering inflammation **C.** lysis
   D. inducing interferon **E.** antibodies
6. Which of the following statements about phagocytosis is *false?*
   A. Phagocytes move toward an area of infection by a process called chemotaxis.
   B. The vacuole in which bacteria are exposed to degradative enzymes is called a phagolysosome.
   C. Phagocytes have receptors that recognize complement proteins bound to bacteria.
   D. Phagocytes have receptors that recognize antibodies bound to bacteria.
   E. Macrophages die after phagocytizing bacteria but neutrophils regenerate their lysosomes and survive.
7. All of the following cell types are found in a granuloma *except*
   A. neutrophils **B.** macrophages
   C. giant cells **D.** T cells
8. All of the following trigger inflammation *except*
   A. engagement of toll-like receptors.
   B. activation of complement.
   C. interferon induction of antiviral protein synthesis.
   D. tissue damage.
9. Which of the following statements about inflammation is *false?*
   A. Vasodilation results in leakage of blood components.
   B. The process can cause damage to host tissue.
   C. Neutrophils predominate at the site during the early stages of acute inflammation.
   D. Apoptosis induces inflammation.
   E. The cardinal signs of inflammation are redness, swelling, heat, and pain.
10. The direct/immediate action of interferon on a cell is to
    A. interfere with the replication of the virus.
    B. prevent the virus from entering the cell.
    C. stimulate synthesis of antiviral proteins.
    D. stimulate the immune response.
    E. stop the cell from dividing.

Applications

1. Physicians regularly have to treat recurrent urinary tract infections in paralyzed paraplegic patients. What explanation would the physician provide to a patient who asked why the condition keeps coming back in spite of repeated treatment?
2. A cattle farmer sees a sore on the leg of one of his cows. The farmer feels the sore and notices that the area just around the sore is warm to the touch. A veterinarian examines the wound and explains that the warmth may be due to inflammation. The farmer wants an explanation of the difference between the localized warmth and fever. What would be the vet's explanation to the farmer?

Critical Thinking

1. A student argues that phagocytosis is a wasteful process because after engulfed organisms are digested and destroyed, the remaining material is excreted from the cell (see figure 15.9). A more efficient process would be to release the digested material *inside* the cell. This way, the material and enzymes could be reused by the cell. Does the student have a valid argument? Why or why not?
2. According to figure 15.11 *any* cell infected by viruses may die due to the action of interferons. This strategy, however, seems counterproductive. The same result would occur without interferon—any cell infected by a virus might die directly from the virus. Is there any apparent benefit from the interferon action?