15 Innate Immunity

CHAPTER SUMMARY

An Overview of the Body's Defenses (p. 438)

Because the cells and certain basic physiological processes of humans are incompatible with those of most plant and animal pathogens, humans have resistance to these pathogens. Nevertheless, we are confronted every day with pathogens that do cause disease in humans. It is convenient to cluster the structures, cells, and chemicals that act against pathogens into three main lines of defense:

- 1. The first line of defense is nonspecific and part of our innate immunity. It is chiefly composed of external barriers to pathogens, especially the skin and mucous membranes.
- 2. The second line is also our innate immunity. It is internal and is composed of protective cells, blood-borne chemicals, and processes that inactivate or kill invaders.
- 3. The third line of defense is adaptive immunity, and will be examined in Chapter 16.

The Body's First Line of Defense (pp. 438–442)

The skin and mucous membranes present a formidable barrier to the entrance of microorganisms.

The Role of Skin in Nonspecific Defense

The skin is composed of an outer epidermis, which is in turn composed of multiple layers of tightly packed cells that constitute a barrier to most bacteria, fungi, and viruses. In addition, microorganisms attached to the epidermis are routinely sloughed off with the flakes of dead skin cells. The epidermis also contains phagocytic cells called **dendritic cells** or **Langerhans cells**. Their slender processes form an almost continuous network to intercept invaders.

The dermis lies beneath the epidermis, and contains hair follicles, glands, blood vessels, and nerve endings. It contains tough collagen fibers that give the skin strength and flexibility, and its blood vessels deliver defensive cells and chemicals. Its sweat glands secrete perspiration, which contains salt, antimicrobial peptides, and lysozyme, an enzyme that destroys the cell wall of bacteria. Its sebaceous glands secrete sebum, an oily substance that keeps the skin pliable and lowers the pH of the skin surface.

The Role of Mucous Membranes in Nonspecific Defense

Mucous membranes line the lumens of the respiratory, urinary, gastrointestinal, and reproductive tracts. The epithelial cells of the outermost layer are tightly packed but form only a thin layer. They play key roles in the diffusion of nutrients and

oxygen and in the elimination of wastes. Like epidermal cells, epithelial cells are continually shed and then replaced via the cytokinesis of stem cells, generative cells capable of dividing to form daughter cells of a variety of types. In the mucous membrane of the trachea, **goblet cells** secrete a sticky mucus that traps bacteria, and cilia sweep it upward for expulsion from the lungs via coughing.

The Role of Normal Microbiota in the First Line of Defense

The skin and mucous membranes are normally home to a variety of microorganisms that protect the body by competing with potential pathogens, a situation called **microbial antagonism**. Some microbiota change the pH to favor their own growth, or consume nutrients that might otherwise be available to pathogens. The presence of the normal microbiota stimulates the body's second line of defense. Finally, the normal microbiota of the intestines provide several vitamins important to human health.

Other First-Line Defenses

The lacrimal apparatus of the eye washes away pathogens in tears, which contain lysozyme to destroy bacteria. Antimicrobial peptides on the skin and in mucous membranes act against microorganisms. In addition, stomach acid prevents the growth of many potential pathogens, and saliva washes microbes from the teeth and also contains lysozyme.

An Overview of the Body's Second Line of Defense (pp. 442–445)

The second line of defense includes cells such as phagocytes, antimicrobial chemicals such as complement and interferons, and the processes of inflammation and fever.

Defense Components of Blood

Blood is composed of formed elements (cells and parts of cells) within a fluid called plasma. Plasma is mostly water containing electrolytes, dissolved gases, nutrients, and protective proteins such as clotting factors, complement proteins, and antibodies. Plasma also contains compounds that transport and store iron. These compounds can play a defensive role by sequestering iron so that it is unavailable to microorganisms. Serum is that portion of plasma without clotting factors.

The formed elements are erythrocytes (red blood cells), leukocytes (white blood cells), and platelets (cell fragments involved in blood clotting). Leukocytes are divided into two groups according to their appearance in stained blood smears:

- Granulocytes have large granules that stain different colors. Of these, basophils stain blue with basic dye, eosinophils stain red to orange with the acidic dye eosin, and neutrophils stain lilac with a mixture of basic and acidic dyes. Basophils function to release histamine during inflammation, whereas eosinophils and neutrophils phagocytize pathogens. They exit capillaries by squeezing between the cells in a process called diapedesis or emigration.
- Agranulocytes do not appear to have granules when viewed via light microscopy; however, granules become visible with electron microscopy. They are of two types: lymphocytes are the smallest leukocytes and have nuclei which nearly fill the cell, whereas monocytes are large with slightly lobed nuclei. The latter leave the blood and mature into macrophages, which are the phagocytic cells

of the second line of defense. Wandering macrophages perform their scavenger function while traveling throughout the body, whereas fixed macrophages do not wander. For example, alveolar macrophages remain in the lungs, microglia in the central nervous system, and Küppfer cells in the liver. A special group of phagocytes, the dendritic cells, are located throughout the body, particularly the skin and mucous membranes.

Macrophages plus monocytes attached to cells of the heart chambers, blood vessels, and lymphatic vessels together constitute a system called the mononuclear phagocytic system.

Analysis of blood is a key tool of medical diagnosis. The proportions of leukocytes, as determined in a differential white blood cell count, can serve as a sign of disease.

The Body's Second Line of Defense (pp. 445–457)

The key components of the second line of defense are phagocytosis, extracellular killing by leukocytes, nonspecific chemical defenses, inflammation, and fever.

Phagocytosis

Cells of the body capable of phagocytosis are called **phagocytes**. Phagocytosis is a continuous process that can be divided into five steps:

- 1. Chemotaxis is movement of a cell either toward or away from a chemical stimulus. Chemotactic factors include chemicals called chemokines and peptides derived from complement. They attract phagocytic leukocytes to the site of damage or invasion.
- 2. The phagocytes attach to pathogens via a process called **adherence**, in which complementary chemicals such as membrane glycoproteins bind together. Pathogens are more readily phagocytized if they are coated with antibodies or the antimicrobial proteins of complement (discussed later). This coating process is called **opsonization** and the proteins are called **opsonins**.
- 3. After phagocytes adhere to pathogens, they extend pseudopodia to surround the microbe. The encompassed microbe is internalized as the pseudopodia fuse to form a food vesicle called a **phagosome**.
- 4. Killing occurs when lysosomes within the phagocyte fuse with newly formed phagosomes to form **phagolysosomes**, or digestive vesicles. Lysosomes contain digestive enzymes and other antimicrobial substances in an environment with a pH of about 5.5 due to the active pumping of H⁺ from the cytosol. Most pathogens are dead within 30 minutes. In the end, the phagolysosome is known as a *residual body*.
- 5. Phagocytes eliminate remains of microorganisms via exocytosis.

Extracellular Killing by Leukocytes

Eosinophils, **natural killer lymphocytes** (or NK cells), and neutrophils can accomplish extracellular killing. Eosinophils primarily attack parasitic helminths by attaching to their surface and secreting toxins. *Eosinophilia*, an abnormally high number of eosinophils in the blood, is often indicative of helminth infestation. NK cells secrete toxins onto the surfaces of virally infected cells and cancerous tumors. Neutrophils can destroy nearby microbial cells without phagocytosis by creating chemicals that kill nearby invaders or by producing extracellular fibers that bind to and kill bacteria.

Nonspecific Chemical Defenses Against Pathogens

Chemicals assist phagocytic cells either by directly attacking pathogens or by enhancing other features of innate immunity. In addition to lysozyme (discussed earlier), they include complement, interferons, and defensins.

Complement (the complement system) is a set of proteins that acts as chemotactic attractants, indirectly triggers inflammation and fever, and ultimately affects the destruction of foreign cells via the formation of membrane attack complexes (MAC), which puncture multiple fatal holes in pathogens' membranes. Complement is activated by a classical pathway involving antibodies and by an alternate pathway that occurs independent of antibodies.

Interferons are protein molecules released by host cells to nonspecifically inhibit the spread of viral infections. They also cause the malaise, muscle aches, and fever typical of viral infections. Virally infected monocytes, macrophages, and some lymphocytes secrete interferon alpha, and fibroblasts secrete interferon beta, both of which are released within hours of infection. These interferons trigger antiviral proteins to prevent viral replication. T lymphocytes and NK cells produce interferon gamma several days after initial infection, which activates macrophages and can stimulate phagocytic activity.

Inflammation

Inflammation is a general, nonspecific response to tissue damage resulting from a variety of causes, including infection with pathogens. Acute inflammation develops quickly and is short-lived. It is typically beneficial, resulting in destruction of pathogens. Chronic inflammation develops slowly and can cause bodily damage that can lead to disease. Signs and symptoms of inflammation include rubor (redness), calor (heat), tumor (swelling), and dolor (pain).

Acute inflammation results in dilation and increased permeability of blood vessels. Macrophages that have phagocytized pathogens release inflammatory chemicals. Damaged cells also release various chemicals, including histamine, which triggers vasodilation, and prostaglandins and leukotrienes, which increase permeability of small veins. In addition, basophils, platelets, and specialized cells located in connective tissue (mast cells) release histamine when they are exposed to complement fragments.

Increased blood flow delivers monocytes and neutrophils to a site of infection. As they arrive, these leukocytes stick to the walls of blood vessels in a process called **margination**. They then squeeze between the cells of the vessel's wall (diapedesis) and enter the site of infection, usually within an hour of the tissue damage, to destroy the pathogens via phagocytosis.

The final stage of inflammation is *tissue repair*, which in part involves the delivery of extra nutrients and oxygen to the site. If cells called *fibroblasts* are involved in the damage, scar tissue is formed, inhibiting normal function. Cardiac muscle and certain brain tissues cannot be repaired.

Fever

Fever is a body temperature above 37°C. It results when pyrogens, chemicals such as interleukin-1, trigger the hypothalamic "thermostat" to reset at a higher temperature. Fever augments the beneficial effects of inflammation by enhancing the effects of interferons and inhibiting the growth of some microorganisms. It probably enhances the performance of phagocytes, the activity of cells of specific immunity, and the process of tissue repair as well. However, it has unpleasant side effects, including malaise, body aches, and tiredness, and if the fever rises too high, critical proteins are denatured and nerve impulses are inhibited, resulting in seizures and even death.

KEY THEMES

Before a microbe can cause disease, it first has to adhere to a host and establish an infection. This is not an easy process. Our bodies are built to resist this invasion and we have many lines of defense to protect us. So long as these lines hold, health is maintained. When they fail or are breached, however, microbes can take over. As you read this chapter, concentrate on the following:

• First and second lines of defense are the mechanisms by which most invaders are repelled: The barriers of the first line of defense are the first things encountered by a microbe and must be the first overcome. Second line defenses catch the majority of what bypasses the first line. The reason we are generally as healthy as we are is that very few organisms make it past the second line.

QUESTIONS FOR FURTHER REVIEW

Answers to these questions can be found in the answer section at the back of this study guide. Refer to the answers only after you have attempted to solve the questions on your own.

Multiple Choice

- 1. Skin is one of your best primary defenses because:
 - a. It is a tightly packed physical barrier
 - b. The outer layers shed and thus remove any adhered microbes
 - c. It is completely incapable of harboring any microbial life
 - d. Both a and b
- 2. Which of the following is not one of the first lines of defense against infection?

c. Macrophages

- a. Skin
 - b. Mucous membranes d. Normal flora
- 3. Which of the following statements is true regarding mucous membranes?
 - a. Mucous membranes are as physically protective as the skin
 - b. Mucous membranes are dead, just as the outer layers of the skin are dead
 - c. The outer layers of mucous membranes are shed just as the outer layers of the skin are shed
 - d. All of the above are true
- 4. Saliva contributes to first line defense against infections by:
 - a. Washing microbes from teeth
 - b. Destroying microbes through the action of lysozyme
 - c. Presenting a physical barrier to adhesion
 - d. Both a and b
- 5. The cells in the blood that are actively involved in defense against infection are called:
 - a. Erythrocytes
 - b. Platelets

- c. Leukocytes
- d. Goblet cells

- 6. The digestive vesicles of phagocytes are formed by the fusion of:
 - a. Antibodies and pathogens c. Phagosomes and lysozyme
 - b. Phagosomes and lysozomes
- d. Complement and antibodies
- 7. Which type of cells are known to directly and specifically kill virally infected cells and neoplastic cells?
 - a. Eosinophils

- c. Wandering macrophages
- b. NK cells
- d. Erythrocytes
- 8. Which organism(s) below would be most susceptible to lysis by MACs produced following initiation of the classical complement pathway?
 - a. Gram-negative bacteria c. Fungi
 - b. Gram-positive bacteria d. Viruses
- 9. The alternate complement pathway is not dependent on which of the following for functionality?
 - a. C3b
 - b. Properdin factors
 - c. Microbial endotoxins or lipopolysaccharides
 - d. Antibodies bound to antigens
- 10. Which of the following is not a function of inflammation?
 - a. Increased permeability of blood vessels
 - b. Migration of phagocytes
 - c. Tissue repair
 - d. All are functions of inflammation

Fill in the Blanks

1. Skin is a ______ (specific/nonspecific) line of defense

against infectious agents; it is, in fact, part of your _____

(first/second/third) line of defense.

2. Fever is an example of one of the body's _____ lines of

defense. It is a ______ (specific/nonspecific) response to

invading pathogens.

3. The three types of proteins found in blood plasma that aid in protecting the

body from infection are _____, ____,

and _____.

4. Phagocytic granulocytes, specifically ______ and

_____, have the ability to leave the blood and enter

tissues through a process called ______ or

5. ______ is the process where proteins called

______ are used to cover pathogens to make them more susceptible to phagocytosis.

6. Four categories of defensive chemicals used as part of second line defenses

are _____, _____,

_____, and ______.

7. Phagocytic cells such as macrophages are capable of producing interferon

_____ in response to viral infections. Furthermore, fibroblasts produce

interferon _____ and T lymphocytes produce interferon _____.

8. Fever results from the presence of chemicals called ______.

Short-Answer Questions for Thought and Review

- 1. Explain the concept of innate resistance.
- 2. Describe the main difference between nonspecific and specific lines of defense.
- 3. Create a flow chart showing leukocyte lineages: what cells are considered leukocytes, how are they divided into groups, and what are the specific functions of each cell type?
- 4. Summarize the process by which inflammation allows for diapedesis of macrophages to occur.

Critical Thinking

1. Use the information in the chapter regarding skin and mucous membrane structure and function to explain why, for essentially healthy individuals, most respiratory tract, digestive tract, and skin rashes are rarely fatal (infections remain local and usually do not spread and cause massive body-wide damage).

- 2. Other than physical structure or components, what is the primary difference between first line defenses and second line defenses?
- 3. Briefly summarize the key differences between the modes of action of complement and interferon.
- 4. A person is exposed to a pathogenic bacterium from a puncture wound and becomes infected. List all of the first and second line defenses that failed to stop the infection once the skin was broken.

Concept Building Questions

- 1. Describe the similarities and differences between the chemotaxis displayed by macrophages vs. the chemotaxis displayed by bacteria. Then, discuss how each cell can differentially respond to attractants. Bacteria, for example, respond to attractants such as nutrients but macrophages respond to cytokines and other factors, not nutrients. Based on what you have learned in previous chapters, how does each cell type know what is in the environment and know whether to respond to it or not?
- 2. Epidemiology is concerned with the spread of diseases in populations (and, ultimately, with controlling that spread). First and second line defenses influence, on an individual level, the ability to combat infections that directly affects the ability to transmit pathogens.
 - a. First line defenses are essentially barriers. If a pathogen is stopped here, what happens to the spread of a pathogen in a population?
 - b. Second line defenses are active methods of cell- and chemical-based death. What can activation of second line defenses in individuals tell an epidemiologist about the spread of disease in a population?
 - c. What does self-administration of over-the-counter medicines to suppress fever, inflammation, pain, etc. do to an epidemiologist's ability to track disease within a population?
 - d. Why aren't first and second line defenses enough to stop the spread of diseases in a population, even if they protect us most of the time from initiation of the infection process?