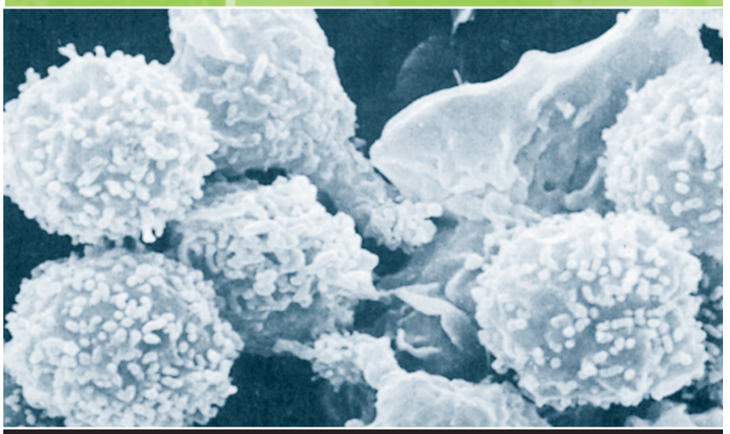
chapter 1

Overview of the Immune System



Numerous T Lymphocytes Interacting with a Single Macrophage

THE IMMUNE SYSTEM IS A REMARKABLY VERSATILE defense system that has evolved to protect animals from invading pathogenic microorganisms and cancer. It is able to generate an enormous variety of cells and molecules capable of specifically recognizing and eliminating an apparently limitless variety of foreign invaders. These cells and molecules act together in a dynamic network whose complexity rivals that of the nervous system.

Functionally, an immune response can be divided into two related activities—recognition and response. Immune recognition is remarkable for its specificity. The immune system is able to recognize subtle chemical differences that distinguish one foreign pathogen from another. Furthermore, the system is able to discriminate between foreign molecules and the body's own cells and proteins. Once a foreign organism has been recognized, the immune system recruits a variety of cells and molecules to mount an appropriate response, called an **effector response,** to eliminate or neutralize the organism. In this way the system is able to convert the initial recognition event into a variety of effector responses, each uniquely suited for eliminating a particular type of pathogen. Later exposure to the same foreign organism induces a **memory response,** characterized by a more rapid and heightened immune reaction that serves to eliminate the pathogen and prevent disease.

This chapter introduces the study of immunology from an historical perspective and presents a broad overview of the cells and molecules that compose the immune system, along with the mechanisms they use to protect the body against foreign invaders. Evidence for the presence of very simple immune systems in certain invertebrate organisms then gives an evolutionary perspective on the mammalian immune system, which is the major subject of this book. Elements of the primitive immune system persist in vertebrates as *innate immunity* along with a more highly evolved system of specific responses termed *adaptive immunity*. These two systems work in concert to provide a high degree of protection for vertebrate species. Finally, in some circumstances, the immune system fails to act as protector because of some deficiency in its components; at other times, it becomes an aggressor and turns its awesome powers against its own host. In this introductory chapter, our description of immunity is simplified to reveal the essential structures and function of the immune system. Substantive discussions, experimental approaches, and in-depth definitions are left to the chapters that follow.

Like the later chapters covering basic topics in immunology, this one includes a section called "Clinical Focus" that describes human disease and its relation to immunity. These sections investigate the causes, consequences, or treatments of diseases rooted in impaired or hyperactive immune function.

Historical Perspective

The discipline of immunology grew out of the observation that individuals who had recovered from certain infectious diseases were thereafter protected from the disease. The Latin term *immunis,* meaning "exempt," is the source of the English word immunity, meaning the state of protection from infectious disease.

Perhaps the earliest written reference to the phenomenon of immunity can be traced back to Thucydides, the great historian of the Peloponnesian War. In describing a plague in Athens, he wrote in 430 BC that only those who had recovered from the plague could nurse the sick because they would not contract the disease a second time. Although early societies recognized the phenomenon of immunity, almost

two thousand years passed before the concept was successfully converted into medically effective practice.

The first recorded attempts to induce immunity deliberately were performed by the Chinese and Turks in the fifteenth century. Various reports suggest that the dried crusts derived from smallpox pustules were either inhaled into the nostrils or inserted into small cuts in the skin (a technique called *variolation*). In 1718, Lady Mary Wortley Montagu, the wife of the British ambassador to Constantinople, observed the positive effects of variolation on the native population and had the technique performed on her own children. The method was significantly improved by the English physician Edward Jenner, in 1798. Intrigued by the fact that milkmaids who had contracted the mild disease cowpox were subsequently immune to smallpox, which is a disfiguring and often fatal disease, Jenner reasoned that introducing fluid from a cowpox pustule into people (i.e., inoculating them) might protect them from smallpox. To test this idea, he inoculated an eight-year-old boy with fluid from a cowpox pustule and later intentionally infected the child with smallpox. As predicted, the child did not develop smallpox.

Jenner's technique of inoculating with cowpox to protect against smallpox spread quickly throughout Europe. However, for many reasons, including a lack of obvious disease targets and knowledge of their causes, it was nearly a hundred years before this technique was applied to other diseases. As so often happens in science, serendipity in combination with astute observation led to the next major advance in immunology, the induction of immunity to cholera. Louis Pasteur had succeeded in growing the bacterium thought to cause fowl cholera in culture and then had shown that chickens injected with the cultured bacterium developed cholera. After returning from a summer vacation, he injected some chickens with an old culture. The chickens became ill, but, to Pasteur's surprise, they recovered. Pasteur then grew a fresh culture of the bacterium with the intention of injecting it into some fresh chickens. But, as the story goes, his supply of chickens was limited, and therefore he used the previously injected chickens. Again to his surprise, the chickens were completely protected from the disease. Pasteur hypothesized and proved that aging had weakened the virulence of the pathogen and that such an attenuated strain might be administered to protect against the disease. He called this attenuated strain a **vaccine** (from the Latin *vacca*, meaning "cow"), in honor of Jenner's work with cowpox inoculation.

Pasteur extended these findings to other diseases, demonstrating that it was possible to **attenuate,** or weaken, a pathogen and administer the attenuated strain as a vaccine. In a now classic experiment at Pouilly-le-Fort in 1881, Pasteur first vaccinated one group of sheep with heat-attenuated anthrax bacillus (*Bacillus anthracis*); he then challenged the vaccinated sheep and some unvaccinated sheep with a virulent culture of the bacillus. All the vaccinated sheep lived, and all the unvaccinated animals died. These experiments marked the beginnings of the discipline of immunology. In 1885, Pasteur administered his first vaccine to a human, a young boy who had been bitten repeatedly by a rabid dog (Figure 1-1). The boy, Joseph Meister, was inoculated with a series of attenuated rabies virus preparations. He lived and later became a custodian at the Pasteur Institute.

FIGURE 1-1 Wood engraving of Louis Pasteur watching Joseph Meister receive the rabies vaccine. [*From* Harper's Weekly ***29:****836; courtesy of the National Library of Medicine.*]

Early Studies Revealed Humoral and Cellular Components of the Immune System

Although Pasteur proved that vaccination worked, he did not understand how. The experimental work of Emil von Behring and Shibasaburo Kitasato in 1890 gave the first insights into the mechanism of immunity, earning von Behring the Nobel prize in medicine in 1901 (Table 1-1). Von Behring and Kitasato demonstrated that **serum** (the liquid, noncellular component of coagulated blood) from animals previously immunized to diphtheria could transfer the immune state to unimmunized animals. In search of the protective agent, various researchers during the next decade demonstrated that an active component from immune serum could neutralize toxins, precipitate toxins, and agglutinate (clump) bacteria. In each case, the active agent was named for the activity it exhibited: antitoxin, precipitin, and agglutinin, respectively.

TABLE 1-1 Nobel Prizes for immunologic research

Year	Recipient	Country	Research
1901	Emil von Behring	Germany	Serum antitoxins
1905	Robert Koch	Germany	Cellular immunity to tuberculosis
1908	Elie Metchnikoff Paul Ehrlich	Russia Germany	Role of phagocytosis (Metchnikoff) and antitoxins (Ehrlich) in immunity
1913	Charles Richet	France	Anaphylaxis
1919	Jules Border	Belgium	Complement-mediated bacteriolysis
1930	Karl Landsteiner	United States	Discovery of human blood groups
1951	Max Theiler	South Africa	Development of yellow fever vaccine
1957	Daniel Bovet	Switzerland	Antihistamines
1960	F. Macfarlane Burnet Peter Medawar	Australia Great Britain	Discovery of acquired immunological tolerance
1972	Rodney R. Porter Gerald M. Edelman	Great Britain United States	Chemical structure of antibodies
1977	Rosalyn R. Yalow	United States	Development of radioimmunoassay
1980	George Snell Jean Dausset Baruj Benacerraf	United States France United States	Major histocompatibility complex
1984	Cesar Milstein Georges E. Köhler	Great Britain Germany	Monoclonal antibody
	Niels K. Jerne	Denmark	Immune regulatory theories
1987	Susumu Tonegawa	Japan	Gene rearrangement in antibody production
1991	E. Donnall Thomas Joseph Murray	United States United States	Transplantation immunology
1996	Peter C. Doherty Rolf M. Zinkernagel	Australia Switzerland	Role of major histocompatibility complex in antigen recognition by by T cells

Initially, a different serum component was thought to be responsible for each activity, but during the 1930s, mainly through the efforts of Elvin Kabat, a fraction of serum first called gamma-globulin (now **immunoglobulin**) was shown to be responsible for all these activities. The active molecules in the immunoglobulin fraction are called **antibodies.** Because immunity was mediated by antibodies contained in body fluids (known at the time as humors), it was called humoral immunity.

In 1883, even before the discovery that a serum component could transfer immunity, Elie Metchnikoff demonstrated that cells also contribute to the immune state of an animal. He observed that certain white blood cells, which he termed **phagocytes,** were able to ingest (phagocytose) microorganisms and other foreign material. Noting that these phagocytic cells were more active in animals that had been immunized, Metchnikoff hypothesized that cells, rather than serum components, were the major effector of immunity. The active phagocytic cells identified by Metchnikoff were likely blood monocytes and neutrophils (see Chapter 2).

In due course, a controversy developed between those who held to the concept of humoral immunity and those who agreed with Metchnikoff's concept of **cell-mediated immunity.** It was later shown that both are correct—immunity requires both cellular and humoral responses. It was difficult to study the activities of immune cells before the development of modern tissue culture techniques, whereas studies with serum took advantage of the ready availability of blood and established biochemical techniques. Because of these technical problems, information about cellular immunity lagged behind findings that concerned humoral immunity.

In a key experiment in the 1940s, Merrill Chase succeeded in transferring immunity against the tuberculosis organism by transferring white blood cells between guinea pigs. This demonstration helped to rekindle interest in cellular immunity. With the emergence of improved cell culture techniques in the 1950s, the **lymphocyte** was identified as the cell responsible for both cellular and humoral immunity. Soon thereafter, experiments with chickens pioneered by Bruce Glick at Mississippi State University indicated that there were

two types of lymphocytes: T lymphocytes derived from the thymus mediated cellular immunity, and B lymphocytes from the bursa of Fabricius (an outgrowth of the cloaca in birds) were involved in humoral immunity. The controversy about the roles of humoral and cellular immunity was resolved when the two systems were shown to be intertwined, and that both systems were necessary for the immune response.

Early Theories Attempted to Explain the Specificity of the Antibody–Antigen Interaction

One of the greatest enigmas facing early immunologists was the specificity of the antibody molecule for foreign material, or **antigen** (the general term for a substance that binds with a specific antibody). Around 1900, Jules Bordet at the Pasteur Institute expanded the concept of immunity by demonstrating specific immune reactivity to nonpathogenic substances, such as red blood cells from other species. Serum from an animal inoculated previously with material that did not cause infection would react with this material in a specific manner, and this reactivity could be passed to other animals by transferring serum from the first. The work of Karl Landsteiner and those who followed him showed that injecting an animal with almost any organic chemical could induce production of antibodies that would bind specifically to the chemical. These studies demonstrated that antibodies have a capacity for an almost unlimited range of reactivity, including responses to compounds that had only recently been synthesized in the laboratory and had not previously existed in nature. In addition, it was shown that molecules differing in the smallest detail could be distinguished by their reactivity with different antibodies. Two major theories were proposed to account for this specificity: the selective theory and the instructional theory.

The earliest conception of the *selective theory* dates to Paul Ehrlich in 1900. In an attempt to explain the origin of serum antibody, Ehrlich proposed that cells in the blood expressed a variety of receptors, which he called "side-chain receptors," that could react with infectious agents and inactivate them. Borrowing a concept used by Emil Fischer in 1894 to explain the interaction between an enzyme and its substrate, Ehrlich proposed that binding of the receptor to an infectious agent was like the fit between a lock and key. Ehrlich suggested that interaction between an infectious agent and a cell-bound receptor would induce the cell to produce and release more receptors with the same specificity. According to Ehrlich's theory, the specificity of the receptor was determined before its exposure to antigen, and the antigen selected the appropriate receptor. Ultimately all aspects of Ehrlich's theory would be proven correct with the minor exception that the "receptor" exists as both a soluble antibody molecule and as a cell-bound receptor; it is the soluble form that is secreted rather than the bound form released.

In the 1930s and 1940s, the selective theory was challenged by various *instructional theories,* in which antigen played a central role in determining the specificity of the antibody molecule. According to the instructional theories, a particular antigen would serve as a template around which antibody would fold. The antibody molecule would thereby assume a configuration complementary to that of the antigen template. This concept was first postulated by Friedrich Breinl and Felix Haurowitz about 1930 and redefined in the 1940s in terms of protein folding by Linus Pauling. The instructional theories were formally disproved in the 1960s, by which time information was emerging about the structure of DNA, RNA, and protein that would offer new insights into the vexing problem of how an individual could make antibodies against almost anything.

In the 1950s, selective theories resurfaced as a result of new experimental data and, through the insights of Niels Jerne, David Talmadge, and F. Macfarlane Burnet, were refined into a theory that came to be known as the **clonal-selection theory.** According to this theory, an individual lymphocyte expresses membrane receptors that are specific for a distinct antigen. This unique receptor specificity is determined before the lymphocyte is exposed to the antigen. Binding of antigen to its specific receptor activates the cell, causing it to proliferate into a clone of cells that have the same immunologic specificity as the parent cell. The clonal-selection theory has been further refined and is now accepted as the underlying paradigm of modern immunology.

The Immune System Includes Innate and Adaptive Components

Immunity—the state of protection from infectious disease—has both a less specific and more specific component. The less specific component, **innate immunity,** provides the first line of defense against infection. Most components of innate immunity are present before the onset of infection and constitute a set of disease-resistance mechanisms that are not specific to a particular pathogen but that include cellular and molecular components that recognize classes of molecules peculiar to frequently encountered pathogens. Phagocytic cells, such as macrophages and neutrophils, barriers such as skin, and a variety of antimicrobial compounds synthesized by the host all play important roles in innate immunity. In contrast to the broad reactivity of the innate immune system, which is uniform in all members of a species, the specific component, **adaptive immunity,** does not come into play until there is an antigenic challenge to the organism. Adaptive immunity responds to the challenge with a high degree of specificity as well as the remarkable property of "memory." Typically, there is an adaptive immune response against an antigen within five or six days after the initial exposure to that antigen. Exposure to the same antigen some time in the future results in a memory response: the immune response to the second challenge occurs more quickly than

the first, is stronger, and is often more effective in neutralizing and clearing the pathogen. The major agents of adaptive immunity are lymphocytes and the antibodies and other molecules they produce.

Because adaptive immune responses require some time to marshal, innate immunity provides the first line of defense during the critical period just after the host's exposure to a pathogen. In general, most of the microorganisms encountered by a healthy individual are readily cleared within a few days by defense mechanisms of the innate immune system before they activate the adaptive immune system.

Innate Immunity

Innate immunity can be seen to comprise four types of defensive barriers: anatomic, physiologic, phagocytic, and inflammatory (Table 1-2).

The Skin and the Mucosal Surfaces Provide Protective Barriers Against Infection

Physical and anatomic barriers that tend to prevent the entry of pathogens are an organism's first line of defense against infection. The skin and the surface of mucous membranes are included in this category because they are effective barriers to the entry of most microorganisms. The skin consists of two distinct layers: a thinner outer layer—the **epidermis**—and a thicker layer—the **dermis.** The epidermis contains several layers of tightly packed epithelial cells. The outer epidermal layer consists of dead cells and is filled with a waterproofing protein called keratin. The dermis, which is composed of connective tissue, contains blood vessels, hair follicles, sebaceous glands, and sweat glands. The sebaceous glands are associated with the hair follicles and produce an oily secretion called **sebum.** Sebum consists of lactic acid and fatty acids, which maintain the pH of the skin between 3 and 5; this pH inhibits the growth of most microorganisms. A few bacteria that metabolize sebum live as commensals on the skin and sometimes cause a severe form of acne. One acne drug, isotretinoin (Accutane), is a vitamin A derivative that prevents the formation of sebum.

Breaks in the skin resulting from scratches, wounds, or abrasion are obvious routes of infection. The skin may also be penetrated by biting insects (e.g., mosquitoes, mites, ticks, fleas, and sandflies); if these harbor pathogenic organisms, they can introduce the pathogen into the body as they feed. The protozoan that causes malaria, for example, is deposited in humans by mosquitoes when they take a blood meal. Similarly, bubonic plague is spread by the bite of fleas, and Lyme disease is spread by the bite of ticks.

The conjunctivae and the alimentary, respiratory, and urogenital tracts are lined by mucous membranes, not by the dry, protective skin that covers the exterior of the body. These

TABLE 1-2 Summary of nonspecific host defenses

Type	Mechanism
Anatomic barriers	
Skin	Mechanical barrier retards entry of microbes. Acidic environment (pH 3–5) retards growth of microbes.
Mucous membranes	Normal flora compete with microbes for attachment sites and nutrients. Mucus entraps foreign microorganisms. Cilia propel microorganisms out of body.
Physiologic barriers	
Temperature	Normal body temperature inhibits growth of some pathogens. Fever response inhibits growth of some pathogens.
Low pH	Acidity of stomach contents kills most ingested microorganisms.
Chemical mediators	Lysozyme cleaves bacterial cell wall. Interferon induces antiviral state in uninfected cells. Complement lyses microorganisms or facilitates phagocytosis. Toll-like receptors recognize microbial molecules, signal cell to secrete immunostimulatory cytokines. Collectins disrupt cell wall of pathogen.
Phagocytic/endocytic barriers	Various cells internalize (endocytose) and break down foreign macromolecules. Specialized cells (blood monocytes, neutrophils, tissue macrophages) internalize (phagocytose), kill, and digest whole microorganisms.
Inflammatory barriers	Tissue damage and infection induce leakage of vascular fluid, containing serum proteins with antibacterial activity, and influx of phagocytic cells into the affected area.

membranes consist of an outer epithelial layer and an underlying layer of connective tissue. Although many pathogens enter the body by binding to and penetrating mucous membranes, a number of nonspecific defense mechanisms tend to prevent this entry. For example, saliva, tears, and mucous secretions act to wash away potential invaders and also contain antibacterial or antiviral substances. The viscous fluid called mucus, which is secreted by epithelial cells of mucous membranes, entraps foreign microorganisms. In the lower respiratory tract, the mucous membrane is covered by **cilia,** hairlike protrusions of the epithelial-cell membranes. The synchronous movement of cilia propels mucus-entrapped microorganisms from these tracts. In addition, nonpathogenic organisms tend to colonize the epithelial cells of mucosal surfaces. These *normal flora* generally outcompete pathogens for attachment sites on the epithelial cell surface and for necessary nutrients.

Some organisms have evolved ways of escaping these defense mechanisms and thus are able to invade the body through mucous membranes. For example, influenza virus (the agent that causes flu) has a surface molecule that enables it to attach firmly to cells in mucous membranes of the respiratory tract, preventing the virus from being swept out by the ciliated epithelial cells. Similarly, the organism that causes gonorrhea has surface projections that allow it to bind to epithelial cells in the mucous membrane of the urogenital tract. Adherence of bacteria to mucous membranes is due to interactions between hairlike protrusions on a bacterium, called **fimbriae** or **pili,** and certain glycoproteins or glycolipids that are expressed only by epithelial cells of the mucous membrane of particular tissues (Figure 1-2). For this reason, some tissues are susceptible to bacterial invasion, whereas others are not.

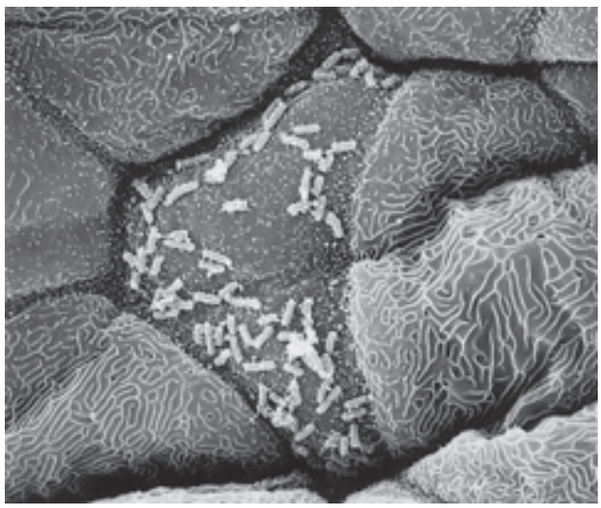


FIGURE 1-2 Electron micrograph of rod-shaped *Escherichia coli* bacteria adhering to surface of epithelial cells of the urinary tract. [*From N. Sharon and H. Lis, 1993,* Sci. Am. ***268(1):****85; photograph courtesy of K. Fujita.*]

Physiologic Barriers to Infection Include General Conditions and Specific Molecules

The physiologic barriers that contribute to innate immunity include temperature, pH, and various soluble and cell-associated molecules. Many species are not susceptible to certain diseases simply because their normal body temperature inhibits growth of the pathogens. Chickens, for example, have innate immunity to anthrax because their high body temperature inhibits the growth of the bacteria. Gastric acidity is an innate physiologic barrier to infection because very few ingested microorganisms can survive the low pH of the stomach contents. One reason newborns are susceptible to some diseases that do not afflict adults is that their stomach contents are less acid than those of adults.

A variety of soluble factors contribute to innate immunity, among them the soluble proteins lysozyme, interferon, and complement. **Lysozyme,** a hydrolytic enzyme found in mucous secretions and in tears, is able to cleave the peptidoglycan layer of the bacterial cell wall. **Interferon** comprises a group of proteins produced by virus-infected cells. Among the many functions of the interferons is the ability to bind to nearby cells and induce a generalized antiviral state. **Complement,** examined in detail in Chapter 13, is a group of serum proteins that circulate in an inactive state. A variety of specific and nonspecific immunologic mechanisms can convert the inactive forms of complement proteins into an active state with the ability to damage the membranes of pathogenic organisms, either destroying the pathogens or facilitating their clearance. Complement may function as an effector system that is triggered by binding of antibodies to certain cell surfaces, or it may be activated by reactions between complement molecules and certain components of microbial cell walls. Reactions between complement molecules or fragments of complement molecules and cellular receptors trigger activation of cells of the innate or adaptive immune systems. Recent studies on **collectins** indicate that these surfactant proteins may kill certain bacteria directly by disrupting their lipid membranes or, alternatively, by aggregating the bacteria to enhance their susceptibility to phagocytosis.

Many of the molecules involved in innate immunity have the property of **pattern recognition,** the ability to recognize a given class of molecules. Because there are certain types of molecules that are unique to microbes and never found in multicellular organisms, the ability to immediately recognize and combat invaders displaying such molecules is a strong feature of innate immunity. Molecules with pattern recognition ability may be soluble, like lysozyme and the complement components described above, or they may be cell-associated receptors. Among the class of receptors designated the **toll-like receptors (TLRs),** TLR2 recognizes the lipopolysaccharide (LPS) found on Gram-negative bacteria. It has long been recognized that

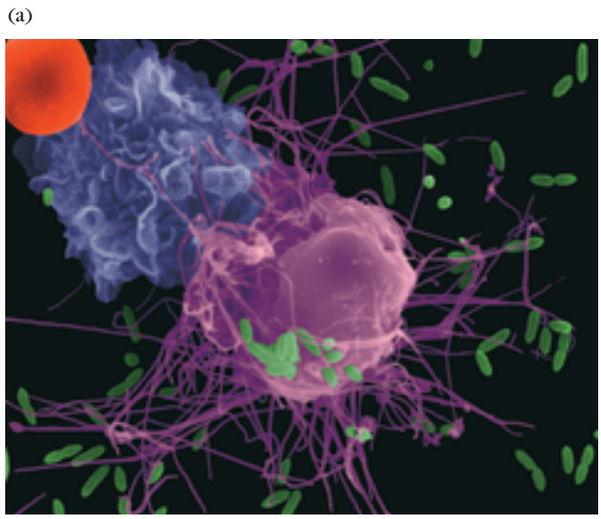


FIGURE 1-3 (a) Electronmicrograph of macrophage (pink) attacking *Escherichia coli* (green). The bacteria are phagocytized as described in part b and breakdown products secreted. The monocyte (purple) has been recruited to the vicinity of the encounter by soluble factors secreted by the macrophage. The red sphere is an erythrocyte. (b) Schematic diagram of the steps in phagocytosis of a bacterium. [*Part a, Dennis Kunkel Microscopy, Inc./Dennis Kunkel.*]

systemic exposure of mammals to relatively small quantities of purified LPS leads to an acute inflammatory response (see below). The mechanism for this response is via a TLR on macrophages that recognizes LPS and elicits a variety of molecules in the inflammatory response upon exposure. When the TLR is exposed to the LPS upon local invasion by a Gram-negative bacterium, the contained response results in elimination of the bacterial challenge.

Cells That Ingest and Destroy Pathogens Make Up a Phagocytic Barrier to Infection

Another important innate defense mechanism is the ingestion of extracellular particulate material by **phagocytosis.** Phagocytosis is one type of **endocytosis,** the general term for the uptake by a cell of material from its environment. In phagocytosis, a cell's plasma membrane expands around the particulate material, which may include whole pathogenic microorganisms, to form large vesicles called **phagosomes** (Figure 1-3). Most phagocytosis is conducted by specialized cells, such as blood monocytes, neutrophils, and tissue macrophages (see Chapter 2). Most cell types are capable of other forms of endocytosis, such as *receptor-mediated endocytosis,* in which extracellular molecules are internalized after binding by specific cellular receptors, and *pinocytosis,* the process by which cells take up fluid from the surrounding medium along with any molecules contained in it.

Inflammation Represents a Complex Sequence of Events That Stimulates Immune Responses

Tissue damage caused by a wound or by an invading pathogenic microorganism induces a complex sequence of events collectively known as the **inflammatory response.** As described above, a molecular component of a microbe, such as LPS, may trigger an inflammatory response via interaction with cell surface receptors. The end result of inflammation may be the marshalling of a specific immune response to the invasion or clearance of the invader by components of the innate immune system. Many of the classic features of the inflammatory response were described as early as 1600 BC, in Egyptian papyrus writings. In the first century AD, the Roman physician Celsus described the "four cardinal signs of inflammation" as *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain). In the second century AD, another physician, Galen, added a fifth sign: *functio laesa* (loss of function). The cardinal signs of inflammation reflect the three major events of an inflammatory response (Figure 1-4):

1. *Vasodilation*—an increase in the diameter of blood vessels—of nearby capillaries occurs as the vessels that carry blood away from the affected area constrict, resulting in engorgement of the capillary network. The engorged capillaries are responsible for tissue redness (*erythema*) and an increase in tissue temperature.

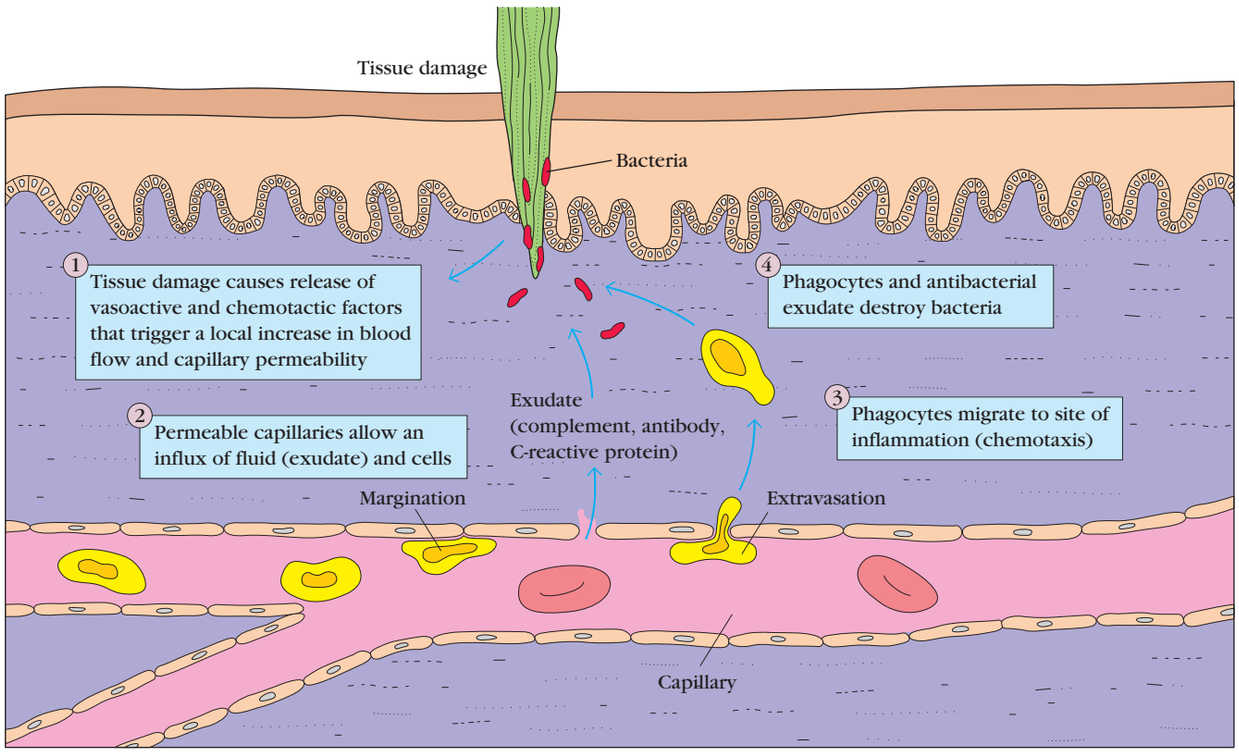


FIGURE 1-4 Major events in the inflammatory response. A bacterial infection causes tissue damage with release of various vasoactive and chemotactic factors. These factors induce increased blood flow to the area, increased capillary permeability, and an influx of white blood cells, including phagocytes and lymphocytes, from the blood into the tissues. The serum proteins contained in the exudate have antibacterial properties, and the phagocytes begin to engulf the bacteria, as illustrated in Figure 1-3.

2. An *increase in capillary permeability* facilitates an influx of fluid and cells from the engorged capillaries into the tissue. The fluid that accumulates (**exudate**) has a much higher protein content than fluid normally released from the vasculature. Accumulation of exudate contributes to tissue swelling (**edema**).
3. *Influx of phagocytes* from the capillaries into the tissues is facilitated by the increased permeability of the capillaries. The emigration of phagocytes is a multistep process that includes adherence of the cells to the endothelial wall of the blood vessels (**margination**), followed by their emigration between the capillary-endothelial cells into the tissue (**diapedesis** or **extravasation**), and, finally, their migration through the tissue to the site of the invasion (**chemotaxis**). As phagocytic cells accumulate at the site and begin to phagocytose bacteria, they release lytic enzymes, which can damage nearby healthy cells. The accumulation of dead cells, digested material, and fluid forms a substance called pus.

The events in the inflammatory response are initiated by a complex series of events involving a variety of chemical mediators whose interactions are only partly understood. Some of these mediators are derived from invading microorganisms, some are released from damaged cells in response to tissue injury, some are generated by several plasma enzyme systems, and some are products of various white blood cells participating in the inflammatory response.

Among the chemical mediators released in response to tissue damage are various serum proteins called **acute-phase proteins.** The concentrations of these proteins increase dramatically in tissue-damaging infections. C-reactive protein is a major acute-phase protein produced by the liver in response to tissue damage. Its name derives from its pattern-recognition activity: C-reactive protein binds to the C-polysaccharide cell-wall component found on a variety of bacteria and fungi. This binding activates the complement system, resulting in increased clearance of the pathogen either by complement-mediated lysis or by a complement-mediated increase in phagocytosis.

One of the principal mediators of the inflammatory response is **histamine,** a chemical released by a variety of cells in response to tissue injury. Histamine binds to receptors on nearby capillaries and venules, causing vasodilation and increased permeability. Another important group of inflammatory mediators, small peptides called **kinins,** are normally present in blood plasma in an inactive form. Tissue injury activates these peptides, which then cause vasodilation and in-

creased permeability of capillaries. A particular kinin, called bradykinin, also stimulates pain receptors in the skin. This effect probably serves a protective role, because pain normally causes an individual to protect the injured area.

Vasodilation and the increase in capillary permeability in an injured tissue also enable enzymes of the blood-clotting system to enter the tissue. These enzymes activate an enzyme cascade that results in the deposition of insoluble strands of **fibrin,** which is the main component of a blood clot. The fibrin strands wall off the injured area from the rest of the body and serve to prevent the spread of infection.

Once the inflammatory response has subsided and most of the debris has been cleared away by phagocytic cells, tissue repair and regeneration of new tissue begins. Capillaries grow into the fibrin of a blood clot. New connective tissue cells, called fibroblasts, replace the fibrin as the clot dissolves. As fibroblasts and capillaries accumulate, scar tissue forms. The inflammatory response is described in more detail in Chapter 15.

Adaptive Immunity

Adaptive immunity is capable of recognizing and selectively eliminating specific foreign microorganisms and molecules (i.e., foreign antigens). Unlike innate immune responses, adaptive immune responses are not the same in all members of a species but are reactions to specific antigenic challenges. Adaptive immunity displays four characteristic attributes:

- Antigenic specificity
- Diversity
- Immunologic memory
- Self/nonself recognition

The **antigenic specificity** of the immune system permits it to distinguish subtle differences among antigens. Antibodies can distinguish between two protein molecules that differ in only a single amino acid. The immune system is capable of generating tremendous *diversity* in its recognition molecules, allowing it to recognize billions of unique structures on foreign antigens. Once the immune system has recognized and responded to an antigen, it exhibits *immunologic memory;* that is, a second encounter with the same antigen induces a heightened state of immune reactivity. Because of this attribute, the immune system can confer life-long immunity to many infectious agents after an initial encounter. Finally, the immune system normally responds only to foreign antigens, indicating that it is capable of *self/nonself recognition.* The ability of the immune system to distinguish self from nonself and respond only to nonself molecules is essential, for, as described below, the outcome of an inappropriate response to self molecules can be fatal.

Adaptive immunity is not independent of innate immunity. The phagocytic cells crucial to nonspecific immune responses are intimately involved in activating the specific immune response. Conversely, various soluble factors produced by a specific immune response have been shown to augment the activity of these phagocytic cells. As an inflammatory response develops, for example, soluble mediators are produced that attract cells of the immune system. The immune response will, in turn, serve to regulate the intensity of the inflammatory response. Through the carefully regulated interplay of adaptive and innate immunity, the two systems work together to eliminate a foreign invader.

The Adaptive Immune System Requires Cooperation Between Lymphocytes and Antigen-Presenting Cells

An effective immune response involves two major groups of cells: *T lymphocytes* and *antigen-presenting cells.* Lymphocytes are one of many types of white blood cells produced in the bone marrow by the process of hematopoiesis (see Chapter 2). Lymphocytes leave the bone marrow, circulate in the blood and lymphatic systems, and reside in various lymphoid organs. Because they produce and display antigen-binding cell-surface receptors, lymphocytes mediate the defining immunologic attributes of specificity, diversity, memory, and self/nonself recognition. The two major populations of lymphocytes—**B lymphocytes (B cells)** and **T lymphocytes (T cells)**—are described briefly here and in greater detail in later chapters.

B LYMPHOCYTES

B lymphocytes mature within the bone marrow; when they leave it, each expresses a unique antigen-binding receptor on its membrane (Figure 1-5a). This antigen-binding or B-cell receptor is a membrane-bound **antibody molecule.** Antibodies are glycoproteins that consist of two identical heavy polypeptide chains and two identical light polypeptide chains. Each heavy chain is joined with a light chain by disulfide bonds, and additional disulfide bonds hold the two pairs together. The amino-terminal ends of the pairs of heavy and light chains form a cleft within which antigen binds. When a naive B cell (one that has not previously encountered antigen) first encounters the antigen that matches its membrane-bound antibody, the binding of the antigen to the antibody causes the cell to divide rapidly; its progeny differentiate into **memory B cells** and **effector B cells** called **plasma cells.** Memory B cells have a longer life span than naive cells, and they express the same membrane-bound antibody as their parent B cell. Plasma cells produce the antibody in a form that can be secreted and have little or no membrane-bound antibody. Although plasma cells live for only a few days, they secrete enormous amounts of antibody during this time. It has been estimated that a single plasma cell can secrete more than 2000 molecules of antibody per second. Secreted antibodies are the major effector molecules of humoral immunity.

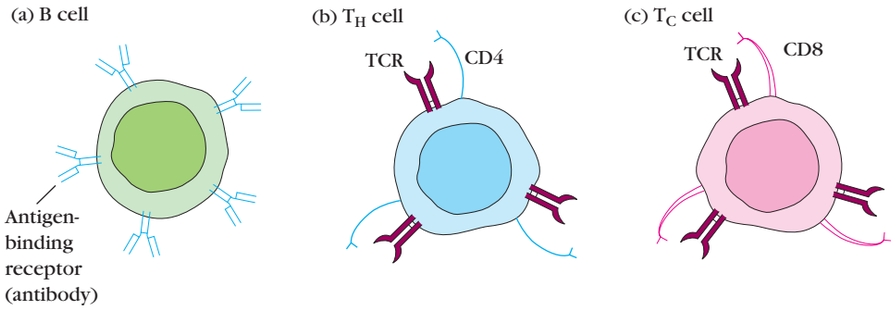


FIGURE 1-5 Distinctive membrane molecules on lymphocytes. (a) B cells have about 10^5 molecules of membrane-bound antibody per cell. All the antibody molecules on a given B cell have the same antigenic specificity and can interact directly with antigen. (b) T cells bearing CD4 ($CD4^+$ cells) recognize only antigen bound to class II MHC molecules. (c) T cells bearing CD8 ($CD8^+$ cells) recognize only antigen associated with class I MHC molecules. In general, $CD4^+$ cells act as helper cells and $CD8^+$ cells act as cytotoxic cells. Both types of T cells express about 10^5 identical molecules of the antigen-binding T-cell receptor (TCR) per cell, all with the same antigenic specificity.

T LYMPHOCYTES

T lymphocytes also arise in the bone marrow. Unlike B cells, which mature within the bone marrow, T cells migrate to the thymus gland to mature. During its maturation within the thymus, the T cell comes to express a unique antigen-binding molecule, called the **T-cell receptor,** on its membrane. Unlike membrane-bound antibodies on B cells, which can recognize antigen alone, T-cell receptors can recognize only antigen that is bound to cell-membrane proteins called **major histocompatibility complex (MHC) molecules.** MHC molecules that function in this recognition event, which is termed "antigen presentation," are polymorphic (genetically diverse) glycoproteins found on cell membranes (see Chapter 7). There are two major types of MHC molecules: Class I MHC molecules, which are expressed by nearly all nucleated cells of vertebrate species, consist of a heavy chain linked to a small invariant protein called β_2-microglobulin. Class II MHC molecules, which consist of an alpha and a beta glycoprotein chain, are expressed only by antigen-presenting cells. When a naive T cell encounters antigen combined with a MHC molecule on a cell, the T cell proliferates and differentiates into memory T cells and various effector T cells.

There are two well-defined subpopulations of T cells: **T helper (T_H)** and **T cytotoxic (T_C) cells.** Although a third type of T cell, called a T suppressor (T_S) cell, has been postulated, recent evidence suggests that it may not be distinct from T_H and T_C subpopulations. T helper and T cytotoxic cells can be distinguished from one another by the presence of either **CD4** or **CD8** membrane glycoproteins on their surfaces (Figure 1-5b,c). T cells displaying CD4 generally function as T_H cells, whereas those displaying CD8 generally function as T_C cells (see Chapter 2).

After a T_H cell recognizes and interacts with an antigen–MHC class II molecule complex, the cell is activated—it becomes an effector cell that secretes various growth factors known collectively as **cytokines.** The secreted cytokines play an important role in activating B cells, T_C cells, macrophages, and various other cells that participate in the immune response. Differences in the pattern of cytokines produced by activated T_H cells result in different types of immune response.

Under the influence of T_H-derived cytokines, a T_C cell that recognizes an antigen–MHC class I molecule complex proliferates and differentiates into an effector cell called a **cytotoxic T lymphocyte (CTL).** In contrast to the T_C cell, the CTL generally does not secrete many cytokines and instead exhibits cell-killing or cytotoxic activity. The CTL has a vital function in monitoring the cells of the body and eliminating any that display antigen, such as virus-infected cells, tumor cells, and cells of a foreign tissue graft. Cells that display foreign antigen complexed with a class I MHC molecule are called *altered self-cells*; these are targets of CTLs.

ANTIGEN-PRESENTING CELLS

Activation of both the humoral and cell-mediated branches of the immune system requires cytokines produced by T_H cells. It is essential that activation of T_H cells themselves be carefully regulated, because an inappropriate T-cell response to self-components can have fatal autoimmune consequences. To ensure carefully regulated activation of T_H cells, they can recognize only antigen that is displayed together with class MHC II molecules on the surface of antigen-presenting cells (APCs). These specialized cells, which include macrophages, B lymphocytes, and dendritic cells, are distinguished by two properties: (1) they express class II MHC molecules on their membranes, and (2) they are able to deliver a co-stimulatory signal that is necessary for T_H-cell activation.

Antigen-presenting cells first internalize antigen, either by phagocytosis or by endocytosis, and then display a part of that antigen on their membrane bound to a class II MHC molecule. The T_H cell recognizes and interacts with the

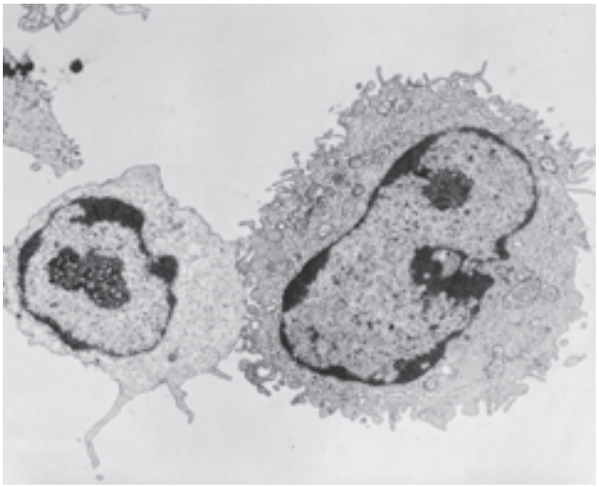


FIGURE 1-6 Electron micrograph of an antigen-presenting macrophage (*right*) associating with a T lymphocyte. [*From A. S. Rosenthal et al., 1982, in* Phagocytosis—Past and Future, *Academic Press, p. 239.*]

antigen–class II MHC molecule complex on the membrane of the antigen-presenting cell (Figure 1-6). An additional costimulatory signal is then produced by the antigen-presenting cell, leading to activation of the T_H cell.

Humoral Immunity But Not Cellular Immunity Is Transferred with Antibody

As mentioned earlier, immune responses can be divided into humoral and cell-mediated responses. Humoral immunity refers to immunity that can be conferred upon a nonimmune individual by administration of serum antibodies from an immune individual. In contrast, cell-mediated immunity can be transferred only by administration of T cells from an immune individual.

The humoral branch of the immune system is at work in the interaction of B cells with antigen and their subsequent proliferation and differentiation into antibody-secreting plasma cells (Figure 1-7). Antibody functions as the effector of the humoral response by binding to antigen and neutralizing it or facilitating its elimination. When an antigen is coated with antibody, it can be eliminated in several ways. For example, antibody can cross-link several antigens, forming clusters that are more readily ingested by phagocytic cells. Binding of antibody to antigen on a microorganism can also activate the complement system, resulting in lysis of the foreign organism. Antibody can also neutralize toxins or viral particles by coating them, which prevents them from binding to host cells.

Effector T cells generated in response to antigen are responsible for cell-mediated immunity (see Figure 1-7). Both activated T_H cells and cytotoxic T lymphocytes (CTLs) serve as effector cells in cell-mediated immune reactions. Cytokines secreted by T_H cells can activate various phagocytic cells, enabling them to phagocytose and kill microorganisms more effectively. This type of cell-mediated immune response is especially important in ridding the host of bacteria and protozoa contained by infected host cells. CTLs participate in cell-mediated immune reactions by killing altered self-cells; they play an important role in the killing of virus-infected cells and tumor cells.

Antigen Is Recognized Differently by B and T Lymphocytes

Antigens, which are generally very large and complex, are not recognized in their entirety by lymphocytes. Instead, both B and T lymphocytes recognize discrete sites on the antigen called **antigenic determinants,** or **epitopes.** Epitopes are the immunologically active regions on a complex antigen, the regions that actually bind to B-cell or T-cell receptors.

Although B cells can recognize an epitope alone, T cells can recognize an epitope only when it is associated with an MHC molecule on the surface of a self-cell (either an antigen-presenting cell or an altered self-cell). Each branch of the immune system is therefore uniquely suited to recognize antigen in a different milieu. The humoral branch (B cells) recognizes an enormous variety of epitopes: those displayed on the surfaces of bacteria or viral particles, as well as those displayed on soluble proteins, glycoproteins, polysaccharides, or lipopolysaccharides that have been released from invading pathogens. The cell-mediated branch (T cells) recognizes protein epitopes displayed together with MHC molecules on self-cells, including altered self-cells such as virus-infected self-cells and cancerous cells.

Thus, four related but distinct cell-membrane molecules are responsible for antigen recognition by the immune system:

- Membrane-bound antibodies on B cells
- T-cell receptors
- Class I MHC molecules
- Class II MHC molecules

Each of these molecules plays a unique role in antigen recognition, ensuring that the immune system can recognize and respond to the different types of antigen that it encounters.

B and T Lymphocytes Utilize Similar Mechanisms To Generate Diversity in Antigen Receptors

The antigenic specificity of each B cell is determined by the membrane-bound antigen-binding receptor (i.e., antibody) expressed by the cell. As a B cell matures in the bone marrow, its specificity is created by random rearrangements of a series

VISUALIZING CONCEPTS

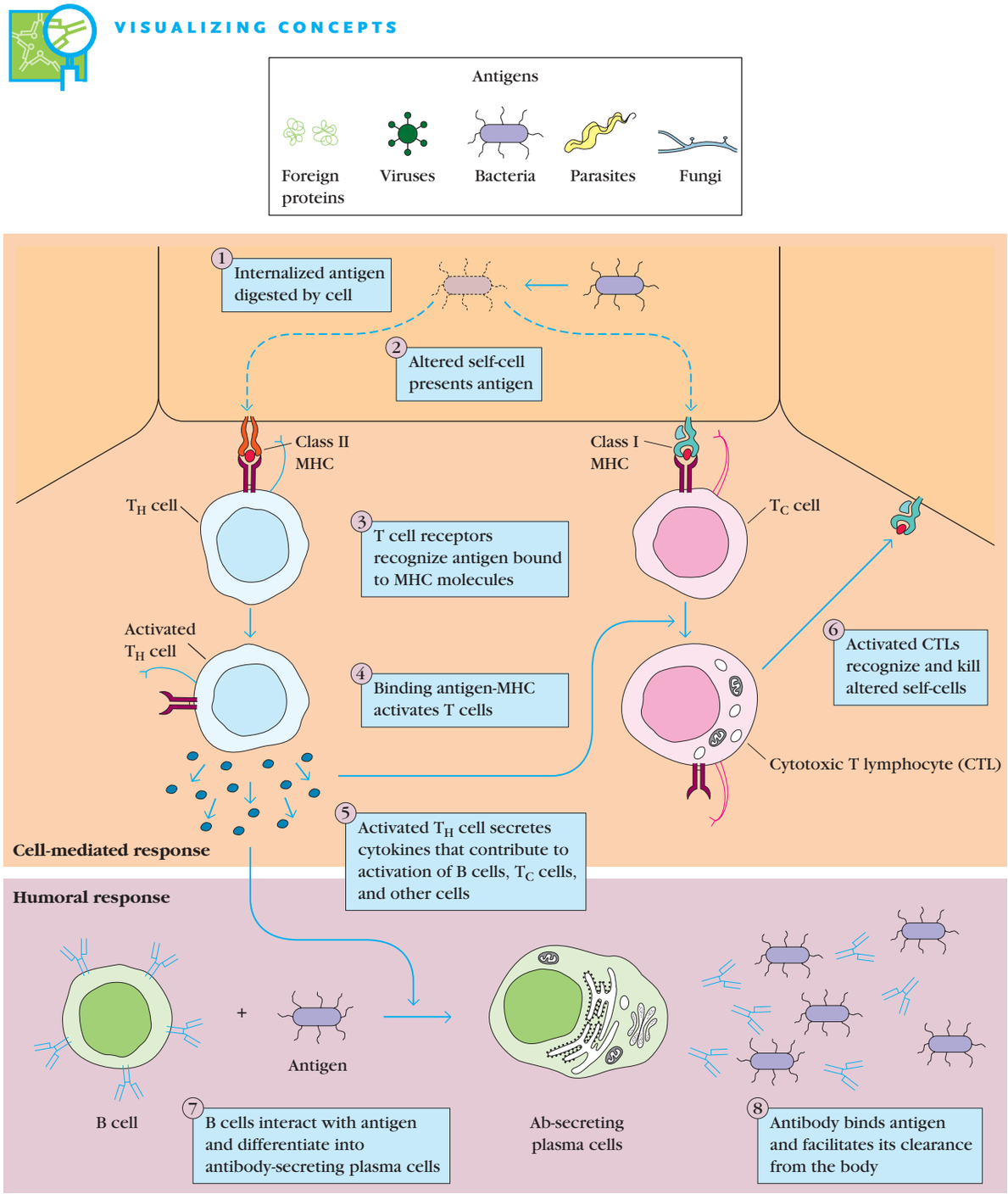


FIGURE 1-7 Overview of the humoral and cell-mediated branches of the immune system. In the humoral response, B cells interact with antigen and then differentiate into antibody-secreting plasma cells. The secreted antibody binds to the antigen and facilitates its clearance from the body. In the cell-mediated response, various subpopulations of T cells recognize antigen presented on self-cells. T_H cells respond to antigen by producing cytokines. T_C cells respond to antigen by developing into cytotoxic T lymphocytes (CTLs), which mediate killing of altered self-cells (e.g., virus-infected cells).

of gene segments that encode the antibody molecule (see Chapter 5). As a result of this process, each mature B cell possesses a single functional gene encoding the antibody heavy chain and a single functional gene encoding the antibody light chain; the cell therefore synthesizes and displays antibody with one specificity on its membrane. All antibody molecules on a given B lymphocyte have identical specificity, giving each B lymphocyte, and the clone of daughter cells to which it gives rise, a distinct specificity for a single epitope on an antigen. The mature B lymphocyte is therefore said to be **antigenically committed.**

The random gene rearrangements during B-cell maturation in the bone marrow generate an enormous number of different antigenic specificities. The resulting B-cell population, which consists of individual B cells each expressing a unique antibody, is estimated to exhibit collectively more than 10^{10} different antigenic specificities. The enormous diversity in the mature B-cell population is later reduced by a selection process in the bone marrow that eliminates any B cells with membrane-bound antibody that recognizes self-components. The selection process helps to ensure that self-reactive antibodies (auto-antibodies) are not produced.

The attributes of specificity and diversity also characterize the antigen-binding T-cell receptor (TCR) on T cells. As in B-cell maturation, the process of T-cell maturation includes random rearrangements of a series of gene segments that encode the cell's antigen-binding receptor (see Chapter 9). Each T lymphocyte cell expresses about 10^5 receptors, and all of the receptors on the cell and its clonal progeny have identical specificity for antigen. The random rearrangement of the TCR genes is capable of generating on the order of 10^9 unique antigenic specificities. This enormous potential diversity is later diminished through a selection process in the thymus that eliminates any T cell with self-reactive receptors and ensures that only T cells with receptors capable of recognizing antigen associated with MHC molecules will be able to mature (see Chapter 10).

The Major Histocompatibility Molecules Bind Antigenic Peptides

The major histocompatibility complex (MHC) is a large genetic complex with multiple loci. The MHC loci encode two major classes of membrane-bound glycoproteins: **class I** and **class II MHC molecules.** As noted above, T_H cells generally recognize antigen combined with class II molecules, whereas T_C cells generally recognize antigen combined with class I molecules (Figure 1-8).

MHC molecules function as antigen-recognition molecules, but they do not possess the fine specificity for antigen characteristic of antibodies and T-cell receptors. Rather, each MHC molecule can bind to a spectrum of **antigenic peptides** derived from the intracellular degradation of antigen molecules. In both class I and class II MHC molecules the distal regions (farthest from the membrane) of different alleles display wide variation in their amino acid sequences. These variable regions form a cleft within which the antigenic peptide sits and is presented to T lymphocytes (see Figure 1-8). Different allelic forms of the genes encoding class I and class

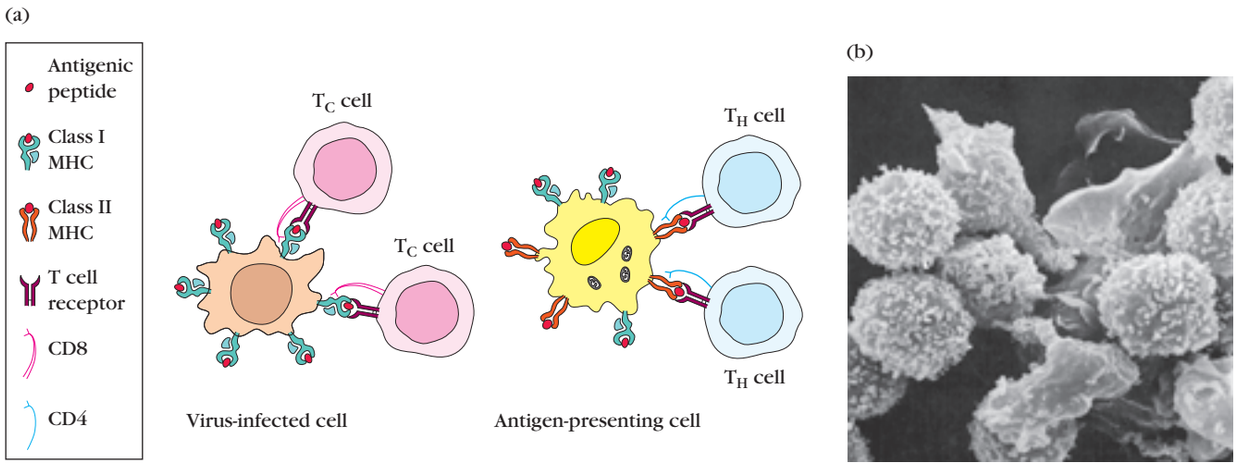


FIGURE 1-8 The role of MHC molecules in antigen recognition by T cells. (a) Class I MHC molecules are expressed on nearly all nucleated cells. Class II MHC molecules are expressed only on antigen-presenting cells. T cells that recognize only antigenic peptides displayed with a class II MHC molecule generally function as T helper (T_H) cells. T cells that recognize only antigenic peptides displayed with a class I MHC molecule generally function as T cytotoxic (T_C) cells. (b) This scanning electron micrograph reveals numerous T lymphocytes interacting with a single macrophage. The macrophage presents processed antigen combined with class II MHC molecules to the T cells. [*Photograph from W. E. Paul (ed.), 1991,* Immunology: Recognition and Response, *W. H. Freeman and Company, New York; micrograph courtesy of M. H. Nielsen and O. Werdelin.*]

II molecules confer different structures on the antigen-binding cleft with different specificity. Thus the ability to present an antigen to T lymphocytes is influenced by the particular set of alleles that an individual inherits.

Complex Antigens Are Degraded (Processed) and Displayed (Presented) with MHC Molecules on the Cell Surface

In order for a foreign protein antigen to be recognized by a T cell, it must be degraded into small antigenic peptides that form complexes with class I or class II MHC molecules. This conversion of proteins into MHC-associated peptide fragments is called *antigen processing and presentation*. Whether a particular antigen will be processed and presented together with class I MHC or class II MHC molecules appears to be determined by the route that the antigen takes to enter a cell (Figure 1-9).

Exogenous antigen is produced outside of the host cell and enters the cell by endocytosis or phagocytosis. Antigen-presenting cells (macrophages, dendritic cells, and B cells) degrade ingested exogenous antigen into peptide fragments within the endocytic processing pathway. Experiments suggest that class II MHC molecules are expressed within the endocytic processing pathway and that peptides produced by degradation of antigen in this pathway bind to the cleft within the class II MHC molecules. The MHC molecules bearing the peptide are then exported to the cell surface. Since expression of class II MHC molecules is limited to antigen-presenting cells, presentation of exogenous peptide–class II MHC complexes is limited to these cells. T cells displaying CD4 recognize antigen combined with class II MHC molecules and thus are said to be *class II MHC restricted*. These cells generally function as T helper cells.

Endogenous antigen is produced within the host cell itself. Two common examples are viral proteins synthesized within virus-infected host cells and unique proteins synthesized by cancerous cells. Endogenous antigens are degraded into peptide fragments that bind to class I MHC molecules within the endoplasmic reticulum. The peptide–class I MHC complex is then transported to the cell membrane. Since all nucleated cells express class I MHC molecules, all cells producing endogenous antigen use this route to process the antigen. T cells displaying CD8 recognize antigen associated with class I MHC molecules and thus are said to be *class I MHC restricted*. These cytotoxic T cells attack and kill cells displaying the antigen–MHC class I complexes for which their receptors are specific.

Antigen Selection of Lymphocytes Causes Clonal Expansion

A mature immunocompetent animal contains a large number of antigen-reactive clones of T and B lymphocytes; the antigenic specificity of each of these clones is determined by the specificity of the antigen-binding receptor on the mem-

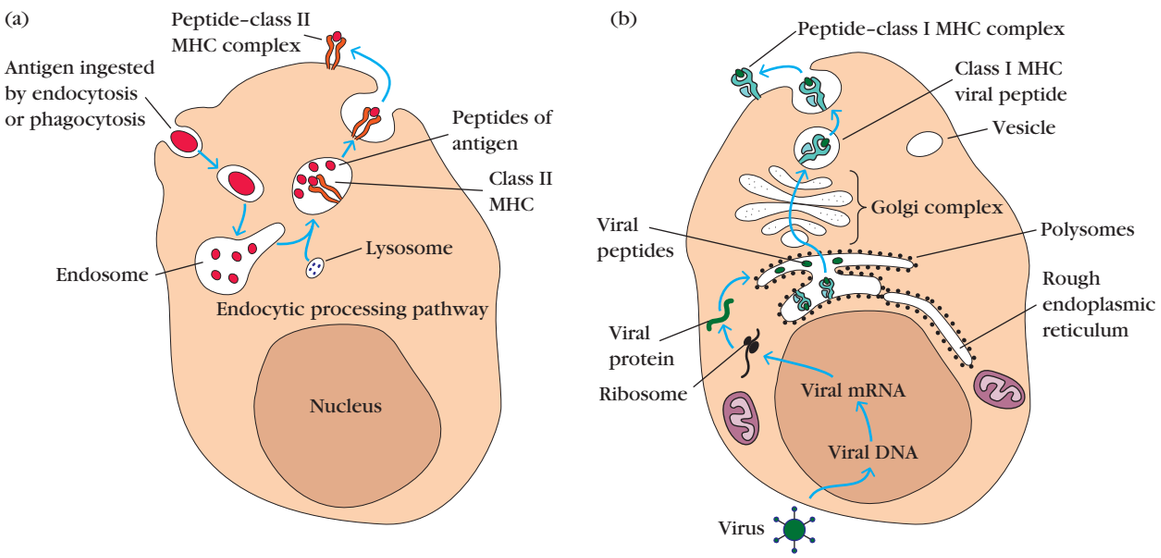


FIGURE 1-9 Processing and presentation of exogenous and endogenous antigens. (a) Exogenous antigen is ingested by endocytosis or phagocytosis and then enters the endocytic processing pathway. Here, within an acidic environment, the antigen is degraded into small peptides, which then are presented with class II MHC molecules on the membrane of the antigen-presenting cell. (b) Endogenous antigen, which is produced within the cell itself (e.g., in a virus-infected cell), is degraded within the cytoplasm into peptides, which move into the endoplasmic reticulum, where they bind to class I MHC molecules. The peptide–class I MHC complexes then move through the Golgi complex to the cell surface.

brane of the clone's lymphocytes. As noted above, the specificity of each T and B lymphocyte is determined before its contact with antigen by random gene rearrangements during maturation in the thymus or bone marrow.

The role of antigen becomes critical when it interacts with and activates mature, antigenically committed T and B lymphocytes, bringing about expansion of the population of cells with a given antigenic specificity. In this process of **clonal selection,** an antigen binds to a particular T or B cell and stimulates it to divide repeatedly into a clone of cells with the same antigenic specificity as the original parent cell (Figure 1-10).

Clonal selection provides a framework for understanding the specificity and self/nonself recognition that is characteristic of adaptive immunity. Specificity is shown because only lymphocytes whose receptors are specific for a given epitope on an antigen will be clonally expanded and thus mobilized for an immune response. Self/nonself discrimination is accomplished by the elimination, during development, of lymphocytes bearing self-reactive receptors or by the functional suppression of these cells in adults.

Immunologic memory also is a consequence of clonal selection. During clonal selection, the number of lymphocytes specific for a given antigen is greatly amplified. Moreover, many of these lymphocytes, referred to as memory cells, appear to have a longer life span than the naive lymphocytes from which they arise. The initial encounter of a naive immunocompetent lymphocyte with an antigen induces a

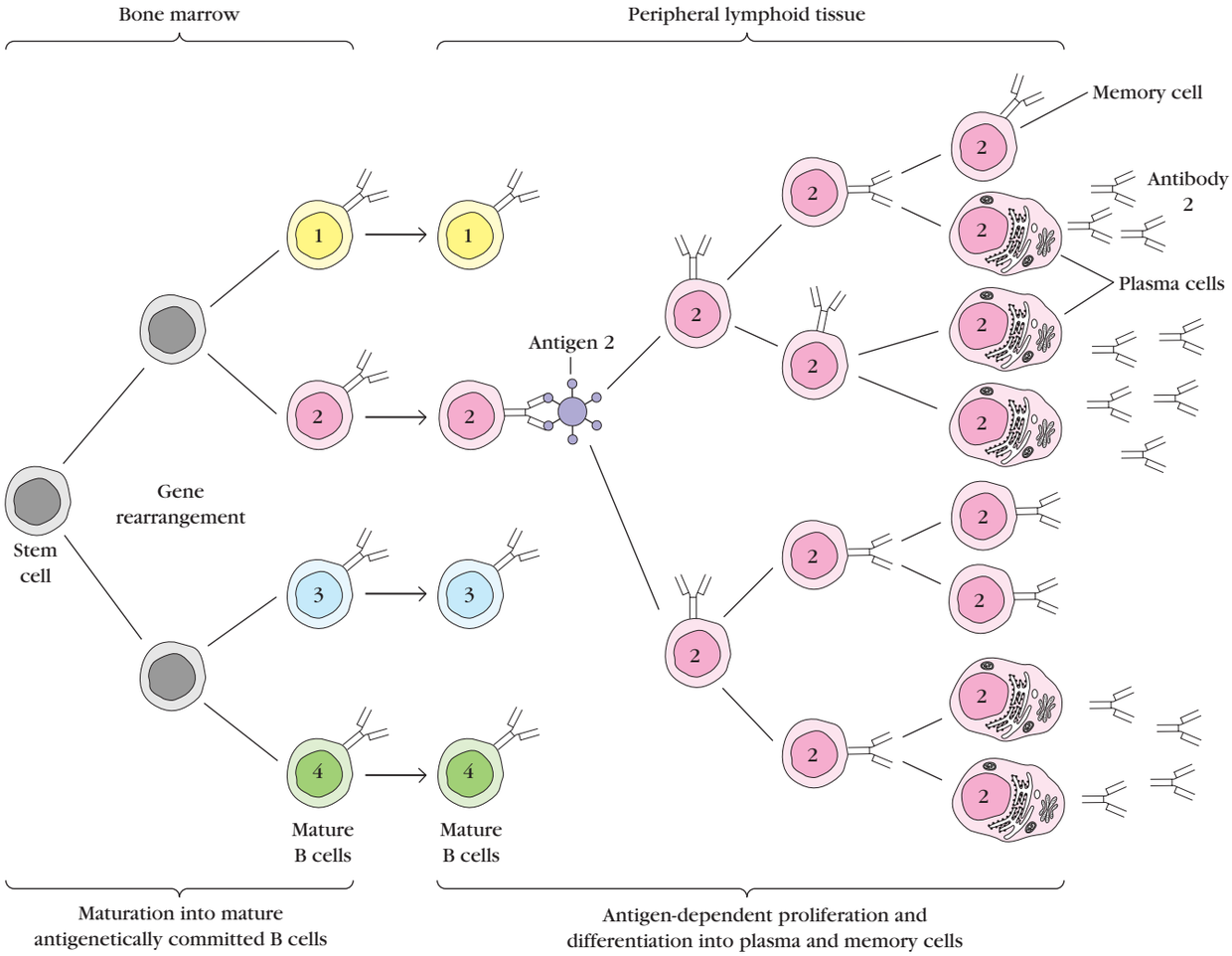


FIGURE 1-10 Maturation and clonal selection of B lymphocytes. Maturation, which occurs in the absence of antigen, produces antigenically committed B cells, each of which expresses antibody with a single antigenic specificity (indicated by 1, 2, 3, and 4). Clonal selection occurs when an antigen binds to a B cell whose membrane-bound antibody molecules are specific for epitopes on that antigen. Clonal expansion of an antigen-activated B cell (number 2 in this example) leads to a clone of memory B cells and effector B cells, called plasma cells; all cells in the expanded clone are specific for the original antigen. The plasma cells secrete antibody reactive with the activating antigen. Similar processes take place in the T-lymphocyte population, resulting in clones of memory T cells and effector T cells; the latter include activated T_H cells, which secrete cytokines, and cytotoxic T lymphocytes (CTLs).

primary response; a later contact of the host with antigen will induce a more rapid and heightened **secondary response.** The amplified population of memory cells accounts for the rapidity and intensity that distinguishes a secondary response from the primary response.

In the humoral branch of the immune system, antigen induces the clonal proliferation of B lymphocytes into antibody-secreting plasma cells and memory B cells. As seen in Figure 1-11a, the primary response has a lag of approximately 5–7 days before antibody levels start to rise. This lag is the time required for activation of naive B cells by antigen and T_H cells and for the subsequent proliferation and differentiation of the activated B cells into plasma cells. Antibody levels peak in the primary response at about day 14 and then begin to drop off as the plasma cells begin to die. In the secondary response, the lag is much shorter (only 1–2 days), antibody levels are much higher, and they are sustained for much longer. The secondary response reflects the activity of the clonally expanded population of memory B cells. These memory cells respond to the antigen more rapidly than naive B cells; in addition, because there are many more memory cells than there were naive B cells for the primary response, more plasma cells are generated in the secondary response, and antibody levels are consequently 100- to 1000-fold higher.

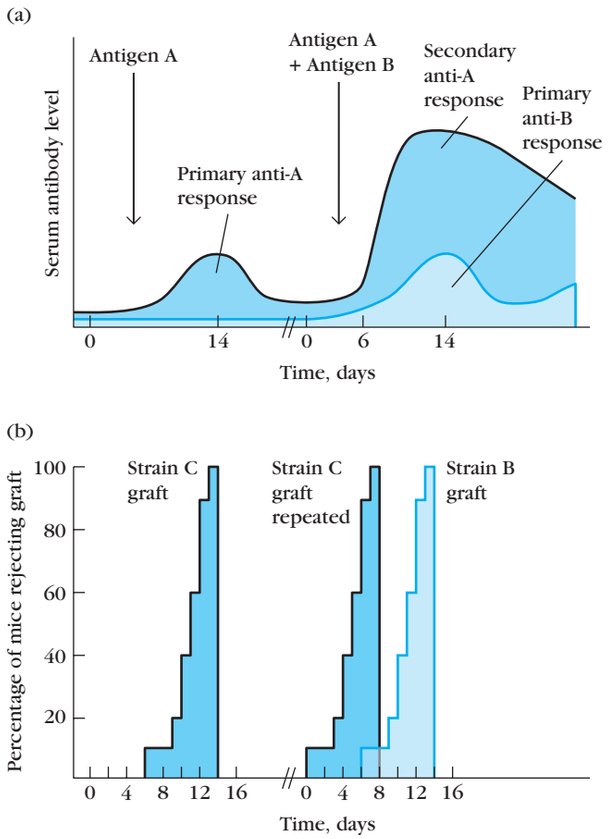


FIGURE 1-11 Differences in the primary and secondary response to injected antigen (humoral response) and to a skin graft (cell-mediated response) reflect the phenomenon of immunologic memory. (a) When an animal is injected with an antigen, it produces a primary serum antibody response of low magnitude and short duration, peaking at about 10–17 days. A second immunization with the same antigen results in a secondary response that is greater in magnitude, peaks in less time (2–7 days), and lasts longer (months to years) than the primary response. Compare the secondary response to antigen A with the primary response to antigen B administered to the same mice. (b) Results from a hypothetical experiment in which skin grafts from strain C mice are transplanted to 20 mice of strain A; the grafts are rejected in about 10–14 days. The 20 mice are rested for 2 months and then 10 are given strain C grafts and the other 10 are given skin from strain B. Mice previously exposed to strain C skin reject C grafts much more vigorously and rapidly than the grafts from strain B. Note that the rejection of the B graft follows a time course similar to that of the first strain C graft.

In the cell-mediated branch of the immune system, the recognition of an antigen-MHC complex by a specific mature T lymphocyte induces clonal proliferation into various T cells with effector functions (T_H cells and CTLs) and into memory T cells. The cell-mediated response to a skin graft is illustrated in Figure 1-11b by a hypothetical transplantation experiment. When skin from strain C mice is grafted onto strain A mice, a primary response develops and all the grafts are rejected in about 10–14 days. If these same mice are again grafted with strain C skin, it is rejected much more vigorously and rapidly than the first grafts. However, if animals previously engrafted with strain C skin are next given skin from an unrelated strain, strain B, the response to strain B is typical of the primary response and is rejected in 10–14 days. That is, graft rejection is a specific immune response. The same mice that showed a secondary response to graft C will show a primary response to graft B. The increased speed of rejection of graft C reflects the presence of a clonally expanded population of memory T_H and T_C cells specific for the antigens of the foreign graft. This expanded memory population generates more effector cells, resulting in faster graft rejection.

The Innate and Adaptive Immune Systems Collaborate, Increasing the Efficiency of Immune Responsiveness

It is important to appreciate that adaptive and innate immunity do not operate independently—they function as a highly interactive and cooperative system, producing a combined response more effective than either branch could produce by itself. Certain immune components play important roles in both types of immunity.

An example of cooperation is seen in the encounter between macrophages and microbes. Interactions between receptors on macrophages and microbial components generate soluble proteins that stimulate and direct adaptive immune responses, facilitating the participation of the adap-

TABLE 1-3 Comparison of adaptive and innate immunity

	Innate	Adaptive
Response time	Hours	Days
Specificity	Limited and fixed	Highly diverse, improves during the course of immune response
Response to repeat infection	Identical to primary response	Much more rapid than primary response

tive immune system in the elimination of the pathogen. Stimulated macrophages also secrete cytokines that can direct adaptive immune responses against particular intracellular pathogens.

Just as important, the adaptive immune system produces signals and components that stimulate and increase the effectiveness of innate responses. Some T cells, when they encounter appropriately presented antigen, synthesize and secrete cytokines that increase the ability of macrophages to kill the microbes they have ingested. Also, antibodies produced against an invader bind to the pathogen, marking it as a target for attack by complement and serving as a potent activator of the attack.

A major difference between adaptive and innate immunity is the rapidity of the innate immune response, which utilizes a pre-existing but limited repertoire of responding components. Adaptive immunity compensates for its slower onset by its ability to recognize a much wider repertoire of foreign substances, and also by its ability to improve during a response, whereas innate immunity remains constant. It may also be noted that secondary adaptive responses are considerably faster than primary responses. Principle characteristics of the innate and adaptive immune systems are compared in Table 1-3. With overlapping roles, the two systems together form a highly effective barrier to infection.

Comparative Immunity

The field of immunology is concerned mostly with how innate and adaptive mechanisms collaborate to protect vertebrates from infection. Although many cellular and molecular actors have important roles, antibodies and lymphocytes are considered to be the principal players. Yet despite their prominence in vertebrate immune systems, it would be a mistake to conclude that these extraordinary molecules and versatile cells are essential for immunity. In fact, a determined search for antibodies, T cells, and B cells in organisms of the nonvertebrate phyla has failed to find them. The interior spaces of organisms as diverse as fruit flies, cockroaches, and plants do not contain unchecked microbial populations, however, which implies that some sort of immunity exists in most, possibly all, multicellular organisms, including those with no components of adaptive immunity.

Insects and plants provide particularly clear and dramatic examples of innate immunity that is not based on lymphocytes. The invasion of the interior body cavity of the fruit fly, *Drosophila melanogaster,* by bacteria or molds triggers the synthesis of small peptides that have strong antibacterial or antifungal activity. The effectiveness of these antimicrobial peptides is demonstrated by the fate of mutants that are unable to produce them. For example, a fungal infection overwhelms a mutant fruit fly that is unable to trigger the synthesis of drosomycin, an antifungal peptide (Figure 1-12). Further evidence for immunity in the fruit fly is given by the recent findings that cell receptors recognizing various classes of microbial molecules (the toll-like receptors) were first found in *Drosophila.*

Plants respond to infection by producing a wide variety of antimicrobial proteins and peptides, as well as small

FIGURE 1-12 Severe fungal infection in a fruit fly (*Drosophila melanogaster*) with a disabling mutation in a signal-transduction pathway required for the synthesis of the antifungal peptide drosomycin. [*From B. Lemaitre et al., 1996,* Cell ***86:****973; courtesy of J. A. Hoffman, University of Strasbourg.*]

nonpeptide organic molecules that have antibiotic activity. Among these agents are enzymes that digest microbial cell walls, peptides and a protein that damages microbial membranes, and the small organic molecules phytoalexins. The importance of the phytoalexins is shown by the fact that mutations that alter their biosynthetic pathways result in loss of resistance to many plant pathogens. In some cases, the response of plants to pathogens goes beyond this chemical assault to include an architectural response, in which the plant isolates cells in the infected area by strengthening the walls of surrounding cells. Table 1-4 compares the capabilities of immune systems in a wide range of multicellular organisms, both animals and plants.

Immune Dysfunction and Its Consequences

The above overview of innate and adaptive immunity depicts a multicomponent interactive system that protects the host from infectious diseases and from cancer. This overview would not be complete without mentioning that the immune system can function improperly. Sometimes the immune system fails to protect the host adequately or misdirects its activities to cause discomfort, debilitating disease, or even death. There are several common manifestations of immune dysfunction:

- Allergy and asthma
- Graft rejection and graft-versus-host disease
- Autoimmune disease
- Immunodeficiency

Allergy and asthma are results of inappropriate immune responses, often to common antigens such as plant pollen, food, or animal dander. The possibility that certain substances increased sensitivity rather than protection was recognized in about 1902 by Charles Richet, who attempted to immunize dogs against the toxins of a type of jellyfish, *Physalia.* He and his colleague Paul Portier observed that dogs exposed to sublethal doses of the toxin reacted almost instantly, and fatally, to subsequent challenge with minute amounts of the toxin. Richet concluded that a successful immunization or vaccination results in *phylaxis,* or protection, and that an opposite result may occur—**anaphylaxis**—in which exposure to antigen can result in a potentially lethal sensitivity to the antigen if the exposure is repeated. Richet received the Nobel Prize in 1913 for his discovery of the anaphylactic response.

Fortunately, most allergic reactions in humans are not rapidly fatal. A specific allergic or anaphylactic response usually involves one antibody type, called IgE. Binding of IgE to its specific antigen (allergen) releases substances that cause irritation and inflammation. When an allergic individual is exposed to an allergen, symptoms may include sneezing, wheezing, and difficulty in breathing (asthma); dermatitis or skin eruptions (hives); and, in more extreme cases, strangulation due to blockage of airways by inflammation. A significant fraction of our health resources is expended to care for those suffering from allergy and asthma. The frequency of allergy and asthma in the United States place these complaints among the most common reasons for a visit to the doctor's office or to the hospital emergency room (see Clinical Focus).

When the immune system encounters foreign cells or tissue, it responds strongly to rid the host of the invaders. However, in some cases, the transplantation of cells or an organ from another individual, although viewed by the immune system as a foreign invasion, may be the only possible treatment for disease. For example, it is estimated that more than 60,000 persons in the United States alone could benefit from a kidney transplant. Because the immune system will attack and reject any transplanted organ that it does not recognize as self, it is a serious barrier to this potentially life-saving treatment. An additional danger in transplantation is that any transplanted cells with immune function may view the new host as nonself and react against it. This reaction, which is termed graft-versus-host disease, can be fatal. The rejection reaction and graft-versus-host disease can be suppressed by drugs, but this type of treatment suppresses all immune function, so that the host is no longer protected by its immune system and becomes susceptible to infectious diseases. Transplantation studies have played a major role in the development of immunology. A Nobel prize was awarded to Karl Landsteiner, in 1930, for the discovery of human blood groups, a finding that allowed blood transfusions to be carried out safely. In 1980, G. Snell, J. Dausset, and B. Benacerraf were recognized for discovery of the major histocompatibility complex, and, in 1991, E. D. Thomas and J. Murray were awarded Nobel Prizes for advances in transplantation immunity. To enable a foreign organ to be accepted without suppressing immunity to all antigens remains a challenge for immunologists today.

In certain individuals, the immune system malfunctions by losing its sense of self and nonself, which permits an immune attack upon the host. This condition, **autoimmunity,** can cause a number of chronic debilitating diseases. The symptoms of autoimmunity differ depending on which tissues and organs are under attack. For example, multiple sclerosis is due to an autoimmune attack on the brain and central nervous system, Crohn's disease is an attack on the tissues in the gut, and rheumatoid arthritis is an attack on joints of the arms and legs. The genetic and environmental factors that trigger and sustain autoimmune disease are very active areas of immunologic research, as is the search for improved treatments.

If any of the many components of innate or specific immunity is defective because of genetic abnormality, or if any immune function is lost because of damage by chemical, physical, or biological agents, the host suffers from **immunodeficiency.** The severity of the immunodeficiency disease

TABLE 1-4 Immunity in multicellular organisms

Taxonomic group	Innate immunity (nonspecific)	Adaptive immunity (specific)	Invasion-induced protective enzymes and enzyme cascades	Phagocytosis	Antimicrobial peptides	Pattern-recognition receptors	Graft rejection	T and B cells	Antibodies
Higher plants	+	−	+	−	+	+	−	−	−
Invertebrate animals									
Porifera (sponges)	+	−	?	+	?	?	+	−	−
Annelids (earthworms)	+	−	?	+	?	?	+	−	−
Arthropods (insects, crustaceans)	+	−	+	+	+	+	?	−	−
Vertebrate animals									
Elasmobranchs (cartilaginous fish; e.g., sharks, rays)	+	+	+	+	equivalent agents	+	+	+	+
Teleost fish and bony fish (e.g., salmon, tuna)	+	+	+	+	probable	+	+	+	+
Amphibians	+	+	+	+	+	+	+	+	+
Reptiles	+	+	+	+	?	+	+	+	+
Birds	+	+	+	+	?	+	+	+	+
Mammals	+	+	+	+	+	+	+	+	+

KEY: + = definitive demonstration; − = failure to demonstrate thus far; ? = presence or absence remains to be established.

SOURCES: L. Du Pasquier and M. Flajnik, 1999, "Origin and Evolution of the Vertebrate Immune System," in *Fundamental Immunology*, 4th ed. W. E. Paul (ed.), Lippincott, Philadelphia; B. Fritig, T. Heitz, and M. Legrand, 1998, *Curr. Opin. Immunol.* **10:**16; K. Soderhall and L. Cerenius, 1998, *Curr. Opin. Immunol.* **10:**23.

CLINICAL FOCUS

Allergy and Asthma as Serious Public Health Problems

Although the immune system serves to protect the host from infection and cancer, inappropriate responses of this system can lead to disease. Common among the results of immune dysfunction are allergies and asthma, both serious public health problems. Details of the mechanisms that underlie allergic and asthmatic responses to environmental antigens (or allergens) will be considered in Chapter 16. Simply stated, allergic reactions are responses to antigenic stimuli that result in immunity based mainly on the IgE class of immunoglobulin. Exposure to the antigen (or allergen) triggers an IgE-mediated release of molecules that cause symptoms ranging from sneezing and dermatitis to inflammation of the lungs in an asthmatic attack. The sequence of events in an allergic response is depicted in the accompanying figure.

The discomfort from common allergies such as plant pollen allergy (often called ragweed allergy) consists of a week or two of sneezing and runny nose, which may seem trivial compared with health problems such as cancer, cardiac arrest, or life-threatening infections. A more serious allergic reaction is asthma,

(continued)

CLINICAL FOCUS *(continued)*

Allergy and Asthma as Serious Public Health Problems

a chronic disease of the lungs in which inflammation, mediated by environmental antigens or infections, causes severe difficulty in breathing. Approximately 15 million persons in the United States suffer from asthma, and it causes about 5000 deaths per year. In the past twenty years, the prevalence of asthma in the Western World has doubled.*

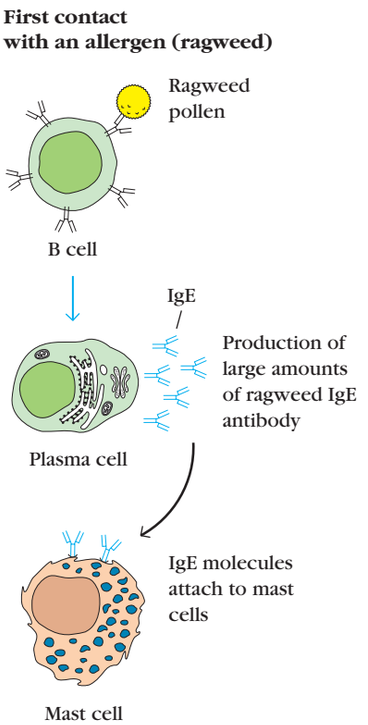
Data on the frequency of care sought for the most common medical complaints in the United States show that asthma and allergy together resulted in more than 28 million visits to the doctor in 1995. The importance of allergy as a public health problem is underscored by the fact that the annual number of doctor visits for hypertension, routine medical examinations, or normal pregnancy, are each fewer than the number of visits for allergic conditions. In fact, the most common reason for a visit to a hospital emergency room is an asthma attack, accounting for one third of all visits. In addition to those treated in the ER, there were about 160,000 hospitalizations for asthma in the past year, with an average stay of 3 to 4 days.

Although all ages and races are affected, deaths from asthma are 3.5 times more common among African-American children. The reasons for the increases in number of asthma cases and for the higher death rate in African-American children remain unknown, although some clues may have been uncovered by recent studies of genetic factors in allergic disease (see Clinical Focus in Chapter 16).

An increasingly serious health problem is food allergy, especially to peanuts and tree nuts (almonds, cashews, and walnuts).† Approximately 3 million Americans are allergic to these foods and they are the leading causes of fatal and near-fatal food allergic (anaphylactic) reactions. While avoidance of these foods can prevent harmful consequences, the ubiquitous use of peanut protein and other nut products in a variety of foods makes this very difficult for the allergic individual. At least 50% of serious reactions are caused by accidental exposures to peanuts, tree nuts, or their products. This has led to controversial movements to ban peanuts from schools and airplanes.

Anaphylaxis generally occurs within an hour of ingesting the food allergen and the most effective treatment is injection of the drug epinephrine. Those prone to anaphylactic attacks often carry injectable epinephrine to be used in case of exposure.

In addition to the suffering and anxiety caused by inappropriate immune responses or allergies to environmental antigens, there is a staggering cost in terms of lost work time for those affected and for caregivers. These costs well justify the extensive efforts by basic and clinical immunologists and allergists to relieve the suffering caused by these disorders.



Sequence of events leading to an allergic response. When the antibody produced upon contact with an allergen is IgE, this class of antibody reacts via its constant region with a mast cell. Subsequent reaction of the antibody binding site with the allergen triggers the mast cell to which the IgE is bound to secrete molecules that cause the allergic symptoms.

*Holgate, S. T. 1999. The epidemic of allergy and asthma, *Nature* Supp. to vol. 402, B2.

†Hughes, D. A., and C. Mills. 2001. Food allergy: A problem on the rise. *Biologist* (London) **48:**201.

depends on the number of affected components. A common type of immunodeficiency in North America is a selective immunodeficiency in which only one type of immunoglobulin, IgA, is lacking; the symptoms may be minor or even go unnoticed. In contrast, a rarer immunodeficiency called severe combined immunodeficiency (SCID), which affects both B and T cells, if untreated, results in death from infection at an early age. Since the 1980s, the most common form of immunodeficiency has been acquired immune deficiency syndrome, or AIDS, which results from infection with the

retrovirus human immunodeficiency virus, or HIV. In AIDS, T helper cells are infected and destroyed by HIV, causing a collapse of the immune system. It is estimated that 35 million persons worldwide suffer from this disease, which is usually fatal within 8 to 10 years after infection. Although certain treatments can prolong the life of AIDS patients, there is no known cure for this disease.

This chapter has been a brief introduction to the immune system, and it has given a thumbnail sketch of how this complex system functions to protect the host from disease. The following chapters will concern the structure and function of the individual cells, organs, and molecules that make up this system. They will describe our current understanding of how the components of immunity interact and the experiments that allowed discovery of these mechanisms. Specific areas of applied immunology, such as immunity to infectious diseases, cancer, and current vaccination practices are the subject matter of later chapters. Finally, to complete the description of the immune system in all of its activities, a chapter addresses each of the major types of immune dysfunction.

SUMMARY

- Immunity is the state of protection against foreign organisms or substances (antigens). Vertebrates have two types of immunity, innate and adaptive.
- Innate immunity is not specific to any one pathogen but rather constitutes a first line of defense, which includes anatomic, physiologic, endocytic and phagocytic, and inflammatory barriers.
- Innate and adaptive immunity operate in cooperative and interdependent ways. The activation of innate immune responses produces signals that stimulate and direct subsequent adaptive immune responses.
- Adaptive immune responses exhibit four immunologic attributes: specificity, diversity, memory, and self/nonself recognition.
- The high degree of specificity in adaptive immunity arises from the activities of molecules (antibodies and T-cell receptors) that recognize and bind specific antigens.
- Antibodies recognize and interact directly with antigen. T-cell receptors recognize only antigen that is combined with either class I or class II major histocompatibility complex (MHC) molecules.
- The two major subpopulations of T lymphocytes are the $CD4^+$ T helper (T_H) cells and $CD8^+$ T cytotoxic (T_C) cells. T_H cells secrete cytokines that regulate immune response upon recognizing antigen combined with class II MHC. T_C cells recognize antigen combined with class I MHC and give rise to cytotoxic T cells (CTLs), which display cytotoxic ability.
- Exogenous (extracellular) antigens are internalized and degraded by antigen-presenting cells (macrophages, B cells, and dendritic cells); the resulting antigenic peptides complexed with class II MHC molecules are then displayed on the cell surface.
- Endogenous (intracellular) antigens (e.g., viral and tumor proteins produced in altered self-cells) are degraded in the cytoplasm and then displayed with class I MHC molecules on the cell surface.
- The immune system produces both humoral and cell-mediated responses. The humoral response is best suited for elimination of exogenous antigens; the cell-mediated response, for elimination of endogenous antigens.
- While an adaptive immune system is found only in vertebrates, innate immunity has been demonstrated in organisms as different as insects, earthworms, and higher plants.
- Dysfunctions of the immune system include common maladies such as allergy or asthma. Loss of immune function leaves the host susceptible to infection; in autoimmunity, the immune system attacks host cells or tissues,

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USEFUL WEB SITES

http://www.aaaai.org/

The American Academy of Allergy Asthma and Immunology site includes an extensive library of information about allergic diseases.

http://12.17.12.70/aai/default.asp

The Web site of the American Association of Immunologists contains a good deal of information of interest to immunologists.

http://www.ncbi.nlm.nih.gov/PubMed/

PubMed, the National Library of Medicine database of more than 9 million publications, is the world's most comprehensive bibliographic database for biological and biomedical literature. It is also a highly user-friendly site.

Study Questions

CLINICAL FOCUS QUESTION You have a young nephew who has developed a severe allergy to tree nuts. What precautions would you advise for him and for his parents? Should school officials be aware of this condition?

1. Indicate to which branch(es) of the immune system the following statements apply, using **H** for the humoral branch and **CM** for the cell-mediated branch. Some statements may apply to both branches.

   a. _____ Involves class I MHC molecules
   b. _____ Responds to viral infection
   c. _____ Involves T helper cells
   d. _____ Involves processed antigen
   e. _____ Most likely responds following an organ transplant
   f. _____ Involves T cytotoxic cells
   g. _____ Involves B cells
   h. _____ Involves T cells
   i. _____ Responds to extracellular bacterial infection
   j. _____ Involves secreted antibody
   k. _____ Kills virus-infected self-cells

2. Specific immunity exhibits four characteristic attributes, which are mediated by lymphocytes. List these four attributes and briefly explain how they arise.

3. Name three features of a secondary immune response that distinguish it from a primary immune response.

4. Compare and contrast the four types of antigen-binding molecules used by the immune system—antibodies, T-cell receptors, class I MHC molecules, and class II MHC molecules—in terms of the following characteristics:

   a. Specificity for antigen
   b. Cellular expression
   c. Types of antigen recognized

5. Fill in the blanks in the following statements with the most appropriate terms:

   a. _____, _____, and _____ all function as antigen-presenting cells.
   b. Antigen-presenting cells deliver a _____ signal to _____ cells.
   c. Only antigen-presenting cells express class _____ MHC molecules, whereas nearly all cells express class _____ MHC molecules.
   d. _____ antigens are internalized by antigen-presenting cells, degraded in the _____, and displayed with class _____ MHC molecules on the cell surface.
   e. _____ antigens are produced in altered self-cells, degraded in the _____, and displayed with class _____ MHC molecules on the cell surface.

6. Briefly describe the three major events in the inflammatory response.

7. The T cell is said to be class I restricted. What does this mean?

8. Match each term related to innate immunity (a–p) with the most appropriate description listed below (1–19). Each description may be used once, more than once, or not at all.

Terms

a. _____ Fimbriae or pili
b. _____ Exudate
c. _____ Sebum
d. _____ Margination
e. _____ Dermis
f. _____ Lysosome
g. _____ Histamine
h. _____ Macrophage
i. _____ Lysozyme
j. _____ Bradykinin
k. _____ Interferon
l. _____ Edema
m. _____ Complement
n. _____ Extravasation
o. _____ C-reactive protein
p. _____ Phagosome

Descriptions

(1) Thin outer layer of skin
(2) Layer of skin containing blood vessels and sebaceous glands
(3) One of several acute-phase proteins
(4) Hydrolytic enzyme found in mucous secretions
(5) Migration of a phagocyte through the endothelial wall into the tissues
(6) Acidic antibacterial secretion found on the skin
(7) Has antiviral activity
(8) Induces vasodilation
(9) Accumulation of fluid in intercellular space, resulting in swelling
(10) Large vesicle containing ingested particulate material
(11) Accumulation of dead cells, digested material, and fluid
(12) Adherence of phagocytic cells to the endothelial wall

Go to www.whfreeman.com/immunology Self-Test
Review and quiz of key terms

(13) Structures involved in microbial adherence to mucous membranes
(14) Stimulates pain receptors in the skin
(15) Phagocytic cell found in the tissues
(16) Phagocytic cell found in the blood
(17) Group of serum proteins involved in cell lysis and clearance of antigen
(18) Cytoplasmic vesicle containing degradative enzymes
(19) Protein-rich fluid that leaks from the capillaries into the tissues

9. Innate and adaptive immunity act in cooperative and interdependent ways to protect the host. Discuss the collaboration of these two forms of immunity.

10. How might an arthropod, such as a cockroach or beetle, protect itself from infection? In what ways might the innate immune responses of an arthropod be similar to those of a plant and how might they differ?

11. Give examples of mild and severe consequences of immune dysfunction. What is the most common cause of immunodeficiency throughout the world today?

12. Adaptive immunity has evolved in vertebrates but they have also retained innate immunity. What would be the disadvantages of having only an adaptive immune system? Comment on how possession of both types of immunity enhances protection against infection.