

## CHAPTER ONE

# INTRODUCTION TO THE IMMUNE SYSTEM



### CHAPTER OUTLINE

1. Immunology as a science has a brief history.
2. Innate immunity in vertebrates is constitutive and lacks immunologic memory; it protects through multiple mechanisms.
  - a. External innate immunity, natural barriers to infection, prevents the penetration of pathogens into tissues.
  - b. Internal innate immunity offers many forms of protection after pathogens enter the body.
3. Adaptive immunity in vertebrates that is achieved through experience because of either recovery from disease or medical intervention.
  - a. Adaptive immunity is humoral, cell-mediated, or both.
  - b. Adaptive immunity can be active or passive.
4. Clonal selection of lymphocytes explains diversity, specificity, and memory.
5. The immune system has two levels of development.
6. The architecture and mechanisms of the immune system are varied and complex: an overview.

### OBJECTIVES

The reader should be able to:

1. Begin to speak immunology by learning the vocabulary.
2. Appreciate the two functions of the immune system.
3. Gain perspective on immunology's historical foundations.
4. Distinguish between innate immunity and adaptive immunity.
5. Discuss how clonal selection explains the immune system's ability to recognize millions of antigens.
6. Follow the development of the immune system in a species and within an individual member of a species.
7. Understand the basic structural and functional components of the immune system.

The body is a citadel under relentless siege from disease-causing agents (such as bacteria or viruses) and cancer cells. The counterattack, or **immunity** (L. *immunis*, free of burden) originally denoted freedom from some kind of service to the Roman state; now, in medical terms, it denotes freedom from disease. Vertebrate animals acquire immunity against these challengers because of the cells and molecules that make up the body's defense system—the *immune system*. Successful immunity depends on the successful collaboration of these cells, which leads to many new cells and molecules that match up with and counteract each challenger. This activity constitutes the *immune response*. In an anthropomorphic sense, the immune system identifies invaders as either friends or enemies and subsequently directs its various components either “to pass in peace” or “to seek and destroy.” Our health depends on the accuracy of such decisions. Furthermore, the immune system can “remember” invaders (a characteristic that we exploit when we are vaccinated) so efficiently that there are no symptoms. Because of the protection it provides, the immune system is vital to an organism's livelihood. Vertebrate animals lacking functional immune systems are without defense and consequently perish.

However, a dark side to the immune system's behavior exists. In some instances, the efficiency of the immune system can actually be harmful to the organism it is designed to protect. Sometimes the immune system responds negatively to an innocuous substance or a life-saving organ transplant. Whether an immune response leads to protection or disease, the mechanisms of recognition and response are the same. The single-mindedness of the immune system does not allow it to distinguish between good and bad foreign substances, or foreign substances it is better off leaving alone. The immune system also can cause destruction of what is thought to be nonself tissue but is really normal self-tissue. This aberration can lead to autoimmune diseases. At the opposite end of the immune spectrum, deficiencies in the ability to mediate immune responses can lead to life-threatening infections or cancer. Fortunately, as our knowledge of immunology increases, we are learning how to safely modify or prevent undesirable or augment missing immune responses.

*The immune system has two primary functions: (1) recognition of, and defense against, foreign substances and (2) establishment of immunosurveillance. Receptor-ligand interaction, the lock-and-key complementarity mechanism, instigates the conveyance of signals called *signal transduction*; the signals follow*

a pathway of intracellular molecule interactions that ends with the consequence of the signal—activation of the immune cell and destruction of the invader. The recognition of a foreign substance protects against disease, but immunity is not restricted to pathogens (disease-causing organisms). We develop immunity against many harmless substances. In some cases, immunity also can be harmful to the host. Allergies and autoimmune diseases are the classical examples of detrimental immune responses. The second major function of the immune system is surveillance. Surveillance consists of the recognition and destruction of mutant cells that can become cancerous. The incidence of malignant diseases is much lower than predicted by the frequency of abnormal cell generation. A depressed immune surveillance system (caused by immunodeficiency diseases or by chemotherapy-induced immunosuppression) can lead to the appearance of some types of cancer.

The increase in basic immunologic information has dramatically advanced during the past century and particularly during roughly the past five decades. In addition to allergy therapy, autoimmune disorder treatments, and increased organ transplantation efficacy, the rise in knowledge has allowed the development of vaccines to prevent infectious disease and of new methods to detect and treat cancer, and somatic gene therapy for immunodeficiency diseases. The prospect of being able to bolster failing immune defenses in different clinical situations is truly epochal. Also, scientists have used immunologic discoveries in the laboratory to identify pathogens facilitating the diagnosis and prevention of disease, product or package tampering; and in fundamental studies of cell biology, such as identifying different protein substances in cell cytoplasm. Deciphering the complex molecular pathways of immune cell activation will continue to provide mechanistic understandings needed to target molecules in dysfunctional immune cells. Human genome sequencing data combined with immunologic data are being exploited through the science of bioinformatics and its subdisciplines to determine gene function on a whole-organism scale. Assigning function to immune system-associated genes will allow us to generate a key for deciphering the type and nature of immune responses—furthering our understanding of the immune system through these approaches boggles the imagination.

Keeping infectious microbes out, destroying them once they enter, and doing the same for self-infectious cells like cancer cells is the immune system's mission. This chapter introduces the complex and sensitive

system of checks and balances that permit (when provoked) the development of an immune response.

## IMMUNOLOGY AS A SCIENCE HAS A BRIEF HISTORY

**Immunology**, or the science that studies the structure and functioning of the immune system, began long before anyone knew about disease-causing microbes or even that individuals had an immune system that protected the body against disease. Immunology began through efforts to understand, and to intervene in, states of disease. The Greek historian of the Peloponnesian War, Thucydides (430 B.C.), recorded that during the plague of Athens only those persons who recovered from the disease could nurse the sick because they did not catch the disease a second time. During the 15th century, the Arabs and the Chinese translated this knowledge into a crude form of clinical practice by infecting individuals with material from the pustules of smallpox patients. The intentional infection usually gave the infected person a mild form of the disease and induced immunity. It was not risk free, between 1 and 2% of those deliberately infected died as compared to 30% who died when they contracted smallpox naturally. Furthermore, the mild form of the disease that the patient contracted could spread, causing an epidemic. This practice of using unmodified pathogen became established in Western Europe in 1718 when Lady Mary Wortley Montagu (the wife of the English ambassador in Constantinople) performed this technique, called **variola** (*L. variola*, smallpox), on her children. Variolation was modified by Edward Jenner, an English physician, in 1796 and his results on *vaccination* were published in 1798—the birth of Immunology. Although he knew nothing about the immune system, Jenner observed that dairymaids who contracted cowpox from cows rarely contracted smallpox. Jenner reasoned that the mild cowpox disease protected an individual against the killer smallpox. He tested this hypothesis by inoculating an 8-year-old boy with fluid from a dairymaid's cowpox pustule and later inoculated the boy with smallpox (variola). The experiment proved successful because the boy was protected from smallpox. Thus, Jenner is credited with the technique of **vaccination**<sup>1</sup> (*L. vacca*, cow),

<sup>1</sup>Vaccination is the process of using noninfectious substances to do harmlessly what the body does after recovering from a disease—establish resistance.

which replaced variolation. Because cowpox and smallpox viruses were structurally similar, the immune system could not differentiate between the look-alikes. The flip side would be that the immune system *does* distinguish between the two. The similar structures allowed for cross-reactive protection to smallpox with cowpox vaccine. Effective vaccination programs eradicated the smallpox virus in 1979 from the face of the earth.

A century later, Louis Pasteur formulated the germ theory of disease. This theory declared that disease is caused by microorganisms rather than by an imbalance of body humors or the position of the moon. Although Pasteur was the founder of bacteriology, he was much more interested in preventing the diseases caused by microorganisms than in studying the microorganisms themselves. To induce immunity to microbes, Pasteur used **vaccines** (he called them vaccines in honor of Jenner). These substances contain components from infectious organisms that stimulate immunity (but not disease), which protects against reinfection by those organisms. The **attenuation of virulence** (*elimination or reduction of disease-causing potential*) was achieved in two ways: aging of cultures and variation of culture temperature. Pasteur showed (accidentally at first) that the causative agents of chicken cholera and rabies lost their virulence when maintained in culture for long periods of time but still could induce immunity. Pasteur also showed that temperature attenuated *Bacillus anthracis* (the causative agent of anthrax). The vaccines against chicken cholera, rabies, and anthrax are called **attenuated vaccines**. Later, two other types of immunizing agent vaccines were introduced: **killed vaccines** (*suspensions of killed bacteria or viruses*) and **toxoids** (*attenuated bacterial toxins*) (see Chapter 17). Pasteur's many contributions to the discipline, in particular his development of the rabies and chicken cholera vaccines, marked the beginning of modern scientific immunology. There are new categories of vaccines, they include: *subunit*, *glycoconjugate*, *recombinant*, and *nucleic acid vaccines* (see Chapter 17).

At the time of Pasteur, the underlying mechanisms of adaptive immunity were unknown. Building on Pasteur's achievements, the new field of immunology began developing in two directions. Efforts continued to extend the range of diseases treated by vaccination and to find new ways of preparing these vaccines; simultaneously, bacteriologists began trying to explain the mechanisms responsible for immunity. The evolution of immunology from the 19th century to the 1930s can be summarized as follows: (1) separating immunity into two divisions, (2) identification of the principal mediators of immunity, (3) recognition

of the detrimental side of immunity, (4) description of the main human blood groups, and (5) observation that a host normally cannot induce immunity to its body constituents.

At the turn of the 20th century, immunologists were trying to answer the question “How is protection mediated?” Two camps arose: the humoralists lead by Paul Ehrlich, who pushed the idea that soluble (so-called “humoral” cell-free) molecules mediated immunity, based on the induction of antitoxin and bactericidal activity in serum, and the cellularists lead by Elie Metchnikoff, who believed innate phagocytic cells (which he called *macrophages*) mediated immunity, based on ingestion and digestion of microorganisms—the humoral (adaptive) immunity and the cell-mediated (innate) immunity camps. (Ehrlich and Metchnikoff shared the 1908 Nobel Prize, largely to call a truce in a divisive war.) A US microbiologist by the name of Wright brought the two camps together. He showed that humoral molecules (non-antibodies now known as *complement* and considered part of innate immunity) enhanced cellular phagocytic immune responses. Cell-mediated immunity as mediated by T cells, along with humoral immunity mediated by antibodies, are now both considered part of adaptive immunity, while innate immunity is mediated in part by phagocytic cells. The humoral arm of adaptive immunity dominated until the mid-1940s, when Gowens brought back cells, but they were lymphocytes. It took until the mid-1990s to integrate the adaptive and innate systems—which are jointly needed for the resolution of most infections.

The first three principal mediators described were: (1) the phagocytic cells (actively internalize foreign substances), (2) antibodies (mark foreign substances for destruction), and (3) complement (plasma proteins that “complement” antibody activity). At the same time that these mediators were identified, the hallmark of immunity, specificity, was described. Immunologically, specificity means that the antibody or immune cell that protects you from measles will not protect you from mumps. However, antibody that protects one person from a specific disease can be transferred to another and protect that person from the same disease. These early results showed that the body is capable of producing specific antibodies when invaded by infectious agents. In the 1920s, the dangers of immunity were recognized by Arthus, Dale, and others, who found that such diseases as hay fever and poison ivy are immunologically based. For example, when certain people are exposed to pollen, their bodies make a specific antibody that

overreacts and produces responses like hay fever. In the 1940s, scientists finally realized that an injured or absent immune system eliminates protection against disease-causing agents.

The discovery by Karl Landsteiner in 1900 of the three main human blood groups (A, B, and O) showed that immunologic reactions could affect tissues. Red blood cells can differ from person to person; if a wrong blood type is transfused, an immune response called a *transfusion reaction* occurs. A naturally occurring equivalent arises during childbirth when an Rh incompatibility occurs between the fetus and the mother. (Landsteiner also discovered Rh red blood cell markers.) If the mother becomes immunized to the fetus’s red blood cells, the resulting antibodies can destroy the fetus’s red cells. This disease is called *hemolytic disease of the newborn*.

Ehrlich observed another important characteristic of the immune system early in the 20th century. He noted that our bodies do not normally produce antibodies against our own tissues; he called this phenomenon *horror autotoxicus* (fear of self-poisoning). Currently, it is called *immunologic tolerance*. The maintenance of this peaceable coexistence of immune cells and other body cells, or self-tolerance, is the balancing feature of the immune system, preventing the continual initiation of autoimmune diseases.

During World War II, urgent medical problems shifted emphasis from immunochemistry to immunobiology and helped to develop immunology into a major discipline of basic science that delved into problems of infectious disease, allergy, maternal-fetal interactions, immunologic tolerance, immunologic deficiency diseases, autoimmunity, transplantation, and cancer. This shift in interest is illustrated by the research on immunologic tolerance. The experimental basis for an understanding of tolerance was provided in 1946 by Ray Owen, who observed that some nonidentical twin cattle were incapable of an immune response against their nonidentical sibling. These cattle had shared a common blood supply during fetal development because of a birth defect. Because they were of differing types, the expectation had been that the components of each other’s blood would elicit immune responses. From these observations, Peter Medawar (1953) designed an experiment in which he exposed fetal animals to foreign skin cells and thus deliberately induced tolerance to foreign skin grafts. He also showed that tolerance was specific because these animals as adults still rejected unrelated skin grafts. Others helped to show that cells of the immune system are responsible for the rejection of grafts. The work of Snell and others in the 1930s on the

genetics of graft rejection showed that the problem of transplantation was partly genetic and that inherited tissue markers recognized by the immune system that distinguish self from nonself frequently lead to graft rejection. A self-arising transplant, or cancer, also was shown to have unique markers that can be recognized as foreign. This discovery of tumor-specific immune responses produced an entirely new area of medicine, immunotherapy, and opened a major subdiscipline of immunology called *tumor immunology*.

One of the most significant findings during the late 1940s involved the recognition of the importance of certain white blood cells (*lymphocytes*), which can be activated to perform many biologic functions. Most of contemporary immunology starts in the 1960s and is devoted to studies dealing with the activation, proliferation, and differentiation of lymphocytes and the functions that these lymphocytes are then able to perform and molecules lymphocytes can make; characterizing these molecules lead to the discovery of how antibody and T cell antigen receptor (TCR) diversity was generated, and the *in vitro* production of pure copies of antibody and TCRs. This knowledge of immune cells and the previous knowledge of antibodies formed the basis for the separation of adaptive aspects of immunology into its classical and current divisions—*humoral (antibodies) and cellular (immune [T] cells) immunology*. The recognition that two types of lymphocytes were responsible for this division led to an explanation of how lymphocytes recognize foreign substances and the needed “immune response” genes, their trafficking to sites of collaboration, their mechanisms of collaboration and subsequent activation pathways, and the ever increasing number of elements in this collaboration, leading to the realization that the immune system infrastructure was, and continues to be, much more varied and complex than originally appreciated.

It was not until the mid-1990s that the divisiveness of the early 1900s ended when a link between innate and adaptive immunity was discovered—the discovery of Toll-like receptors (TLRs) and their associated functions provided the connection. It suggested that innate immunity was not only a first line of defense but that it incited adaptive immunity into action, and like adaptive immunity it could be divided into humoral and cellular parts.<sup>2</sup>

<sup>2</sup>For more information on the benchmark developments in immunology see the “Pillars in Immunology” series in *The Journal of Immunology* starting in July of 2004.

## INNATE IMMUNITY IN VERTEBRATES IS CONSTITUTIVE AND LACKS IMMUNOLOGIC MEMORY; IT PROTECTS THROUGH MULTIPLE MECHANISMS

Initially, the term *immunity* only implied resistance to disease because infectious diseases were the main cause of death in humans. Early immunologists focused primarily on the development of immunity to infectious agents. Contemporary immunologists investigate all aspects of the immune response, and, as a result, immunity has acquired a much broader meaning.

Spore-forming bacteria can be considered capable of immune responses because they produce spores when confronted with hostile conditions. However, immunologists evaluate the specialized responses of vertebrate hosts. *When foreign substances such as bacteria, viruses, fungi, or parasites are introduced into a vertebrate host, the host either (1) nonspecifically clears the infectious agent using preformed components or (2) produces specific cells and molecules directed against the foreign invader. The combined responses are traditionally called an immune response.* The foreign invader that induces and reacts with immune cells and the molecules it induced (such as antibodies) is called an *antigen*. These two responses, or two kinds of immunity—innate and adaptive—are the abbreviated subject of the pages that follow. A general comparison between innate and adaptive is illustrated in Figure 1-1 and Table 1-1. *The distinction revolves around the mechanisms and receptors used for immune recognition, that is, how the immune system senses infection and how it eradicates infection while sparing self-tissues.*

**Innate immunity** (also called *natural resistance*) operates relatively nonspecifically during the early phases of an immune response without a need for prior exposure. Innate immune system recognition is mediated by *pattern recognition receptors (PRRs)*, which recognize conserved shared classes of molecules produced by pathogens called *pathogen-associated molecular patterns (PAMPs)* (detailed in Chapter 3); PAMPs are not restricted to pathogens all microbes express them. These PAMPs are not found in host tissues and cells. Pattern recognition receptor engagement with infectious agents activates nonspecific cells and molecules. This interaction signals the host that a microbial pathogen has been encountered, drives

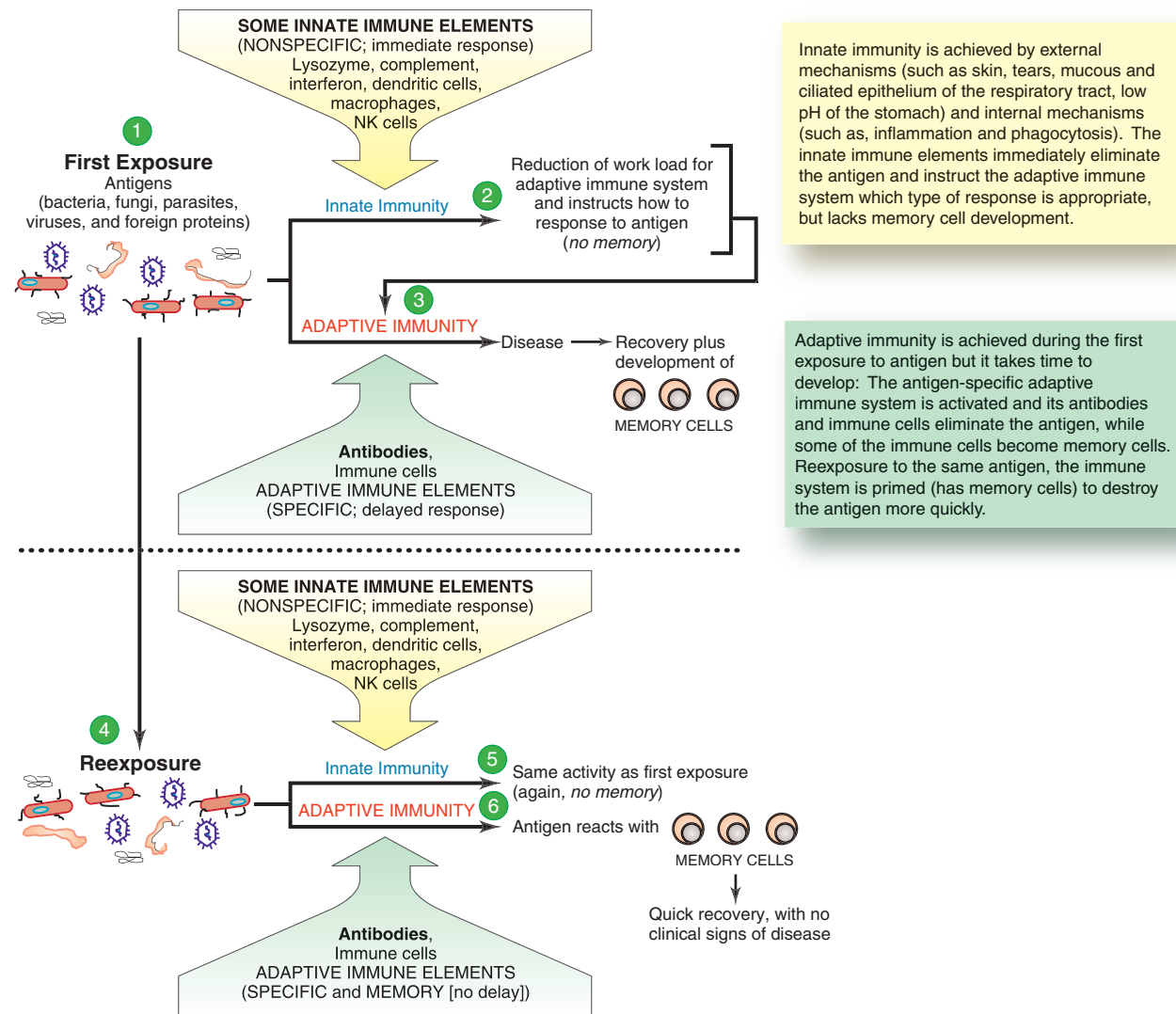


FIGURE 1-1 A general comparison between innate and adaptive immunity. (Innate immunity is detailed in Chapter 3.)

TABLE 1-1 Innate and Adaptive Immunity

Property	Innate Immune System	Adaptive Immune System
Receptors	Germline-encoded	Antigen receptors are products of somatic DNA recombination
Mechanism for recognition	Nonspecific (conserved molecular patterns: LPS, mannan, glycans)	Specific (details of molecular structure: proteins, peptides, carbohydrates)
Effector components	Preformed	Selected
Activation time of effectors	Immediate	Delayed
Immunologic memory	No	Yes
Distinguishing self from nonself components	Perfect	Imperfect (autoimmune diseases)

LPS, Lipopolysaccharides.

the maturation of these nonspecific cells, clears the pathogen, and eventually leads to the activation of the adaptive immune response. Innate immunity serves as the first line of defense and includes both external and internal constitutive responses. External defenses occur in those areas of the body exposed to the outside environment (the contact areas for pathogens). Internal defenses come into play when the pathogen has penetrated the external defenses; the host creates an inhospitable or lethal environment to microbes. The major component of these internal processes is *inflammation*. Taken together, the components of innate immunity are *performed* (the components are present before challenge), *standardized* (the response magnitude is consistent), *without memory* (the host does not realize it has been reexposed to the same invader), and relatively *nonspecific* (targets commonly shared microbe antigens). The latter antigens are unique to microorganisms and the receptors that recognize them do not recognize host molecules—a perfect system that recognizes only foreign antigens (pathogens) and ignores self components.

### External Innate Immunity, Natural Barriers to Infection, Prevents the Penetration of Pathogens into Tissues

External, innate immunity (skin, body secretions, and mucous membranes) prevents the penetration of pathogens into host tissues (see Figure 3-2). Intact skin prevents penetration of most pathogens; exceptions include *Treponema pallidum* and *Schistosoma mansoni* (the causative agents of syphilis and schistosomiasis, respectively). *T. pallidum* is acquired through sexual contact, attaches to host cells by coating itself with fibronectin, and invades intact mucous membranes or abraded skin by boring through them. *S. mansoni* can be acquired by contact with water containing the infective forms, which penetrate the skin by means of enzymes that break down the skin. Skin also secretes lactic acid and fatty acids that act as bacteriostatic agents by lowering skin pH. Tears protect the eye by providing a washing action. Tears also contain a hydrolytic enzyme against Gram-positive bacteria called *lysozyme*. If pathogens are inhaled, mucus and the ciliated epithelium of the respiratory tract act as filters. If pathogens are swallowed, mucus in the digestive tract prevents adsorption and penetration of pathogens into cells. The low pH in the stomach kills organisms, and the normal flora of the lower intestine inhibits the attachment of pathogens. Similar components and mechanisms are in place in the urogenital tract.

### Internal Innate Immunity Offers Many Forms of Protection After Pathogens Enter the Body

If a pathogen breaches the external innate defenses and invades the tissues, internal defense mechanisms provide protection. Internal, innate immunity includes three general mechanisms: (1) *physiologic barriers*, (2) *phagocytosis*, and (3) *inflammation*. Physiologic barriers offer inhospitable environments to pathogens. These barriers include body temperature and oxygen tension. For example, chickens are resistant to anthrax because of their high body temperature. If their temperature is lowered, they become susceptible. Anaerobic organisms (such as *Clostridium perfringens*, the causative agent of gangrene) cannot grow in tissues where oxygen concentrations are high. Microorganisms themselves also can activate physiologic barriers called *complement proteins* that mediate cell lysis and enhance phagocytosis. Virally infected host cells release *interferons*, which interfere with the replication of viruses that have infected neighboring cells.

A more effective innate internal defense is phagocytosis. **Phagocytosis** involves the engulfment and destruction of pathogens and particulate matter by cells of the **mononuclear phagocyte system**. The cells that make up this network are the *mononuclear phagocytic cells* (*monocytes* and *macrophages*). These cells also provide help during adaptive immunity. Monocytes and macrophages are called *professional phagocytes*—professional in the sense that their primary role is phagocytosis. Phagocytic cells, the first line of internal defense, respond immediately and without specificity (see Figure 3-11). Macrophages ingest and digest whole bacteria and even injured and dead host cells. Macrophages constitutively express receptors for polysaccharides found on bacteria; these receptors facilitate phagocytosis. Also, during phagocytosis, macrophages release powerful chemical molecules, called *monokines* (generically called *cytokines*), such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), and IL-6 that activate many nonspecific protective effects through the inflammatory response. However, phagocytosis against soluble antigens (such as toxins) is poor.

Another important group of professional phagocytic cells, filled with granules containing potent digestive chemicals, not included in the mononuclear phagocyte system are the *polymorphonuclear neutrophilic leukocytes*, or *neutrophils* for short (so named because they exhibit large, lobed nuclei). These cells are arbitrarily excluded from the mononuclear phagocyte system because they are not participants

in normal specific immune induction reactions; they only internalize microorganisms for digestion, not for subsequent presentation to other immune cells. Along with their phagocytic activity, neutrophils are the main source for small peptides called *defensins* and *cathelicidins*. These peptides have a broad antimicrobial spectrum and exert nonspecific cytotoxic activity against a wide range of normal and malignant targets.

The third group of paraprofessional phagocytes is *dendritic cells*, which are a specialized group of cells that are inefficient at clearing infectious microbes but are highly efficient at presenting antigens to T lymphocytes—a bridge between innate and adaptive immunity.

Another set of granule-filled, lymphocyte-like cells called *natural killer (NK) cells* are not phagocytic but contribute to innate immunity through nonspecific defense against virus-infected body cells and tumor cells without need for prior exposure and clonal expansion. In addition to their killing abilities, they produce the immunoregulatory cytokines interferon- $\gamma$  and TNF- $\alpha$ , which stimulate dendritic cell maturation and activation, the activation of macrophages, and drive the development of certain adaptive immune cells. *Natural-killer T (NKT) cells*, a cross between a NK cell and a T cell, exhibit rapid cytolytic activity and cytokine production without need for priming and clonal expansion—early responders important in the initiation and regulation of immune responses.

The other component of the internal innate defenses is a complex group of reactions leading to **inflammation**. Pathogen insult and chemical mediators that are released during the host's attempt to clear the pathogen and repair the associated tissue damage initiate the inflammatory response. Inflammation (literally, “setting on fire”) of a particular body region is indicated by the suffix *-itis*; for example, inflammation of the tonsils is called *tonsillitis*, and inflammation of the appendix is called *appendicitis*. The four cardinal signs of inflammation were described by the Roman physician Celsus roughly 2000 years ago. The four distinct symptoms that always accompany short-term, or acute, inflammation are redness, swelling, heat, and pain. Two hundred years after Celsus's description, another physician, Galen, added a fifth sign, loss of function. *Inflammation collectively involves a series of vascular events that serve as a defense mechanism. Inflammation includes (1) clotting mechanism activation, (2) increased blood flow, (3) increased capillary permeability, and (4) enhanced influx of phagocytic cells* (see Chapter 3).

Innate immunity serves as a rapid response system for sensing and clearing infections caused by

pathogens. If the system fails to contain a pathogen, vertebrates use an additional immune recognition strategy called *adaptive*, or *acquired* or *specific immunity*. Adaptive immunity kicks in later and permits the host to recognize and respond to a specific invader and is marked by an enhanced response on repeated exposures to the invader. Nonetheless, both innate and adaptive immune defenses work together to enhance each other's effects. Innate mechanisms reduce the workload and set the stage for adaptive defenses, and adaptive mechanisms amplify and focus innate defenses.

#### MINI SUMMARY

The immune system has two primary functions: (1) recognition of and defense against foreign substances and (2) immunosurveillance. The components of external and internal innate immunity are preformed, standardized, without memory, and nonspecific. When external defenses such as skin, secretions, and mucous membranes fail to prevent invasion by pathogens, internal innate defenses such as temperature, oxygen tension, phagocytosis, and inflammation control infections. To accomplish this, the innate immune system depends heavily on neutrophils, macrophages, dendritic cells, NK cells, and NKT cells for host defense. Collectively, innate immunity reduces the workload for the immune system's specific defenses and sets the stage for adaptive immunity.

## ADAPTIVE IMMUNITY IN VERTEBRATES THAT IS ACHIEVED THROUGH EXPERIENCE BECAUSE OF EITHER RECOVERY FROM DISEASE OR MEDICAL INTERVENTION

**Adaptive** (also called **acquired** or **specific**) **immunity** develops during a host's lifetime and is based partly on the host's experiences, such as stimulated by tissues-invading microbes—in turn, the immune system adjusts to the microbe's presence (see Table 1-1). This exposure process is called **immunization**. Adaptive immunity is the surveillance mechanism of vertebrates that *specifically* recognizes foreign *antigens* and *selectively* eliminates them, and on reencountering the antigens

has an enhanced response. The recall response is often so efficient that no symptoms appear. This activity is organized around two classes of specialized cells, T cells and B cells, and their somatically generated, structurally unique, specific receptors. Once a host has been exposed to a specific disease, the host will develop specific immunity and will probably not catch the disease again. This section briefly describes the six major characteristics of adaptive immunity: (1) *specificity*, (2) *inducibility*, (3) *diversity*, (4) *memory*, (5) *distinguishing self from nonself*, and (6) *self-limiting*.

The persistence of a foreign antigen in a host initiates, or induces, adaptive immunity. The recognition of and response to the antigen are highly specific, each lymphocyte is endowed with a unique receptor—a lock and key complementarity, although immune specificity is not absolute. **Cross-reactions** happen when adaptive immunity to one substance gives immunity to another substance. The earlier example of cowpox exposure causing immunity to smallpox illustrates cross-reactive protection. This cross-reactivity is due to the physical similarity of the agents. If there was no immunity to a foreign substance before exposure, immunity to that substance can be induced by that substance. In fact, there is an opulence, or diversity, to the immune system's resources once the system is induced. It can recognize and mount a unique response to a seemingly endless variety ( $10^9$ ) of antigens. This diversity is the result of a matching number of antigen receptors. Two or three types of gene segments, randomly assembled during B- and T-cell development by a series of DNA-rearrangement events, encode the antigen-binding portions of these receptors. Once immunity has been acquired, re-exposure to the same antigen leads to a rapid and more effective immune response called a *secondary immune response*. The ability of the immune system to remember antigenic intrusion is called **immunologic memory** (in contrast, innate immunity lacks specificity for unique protein structures and memory). Although the immune system can respond to at least  $10^9$  different foreign antigens, it is unresponsive to, or tolerant of, self-antigens present in that individual. A breakdown in the maintenance of self-tolerance can lead to autoimmune disease. When the antigen has been brought under control, the immune response is downregulated through antigen removal, antagonistic cytokine production, limiting immune cell activity by regulatory cells, and feedback regulation of the induced response.

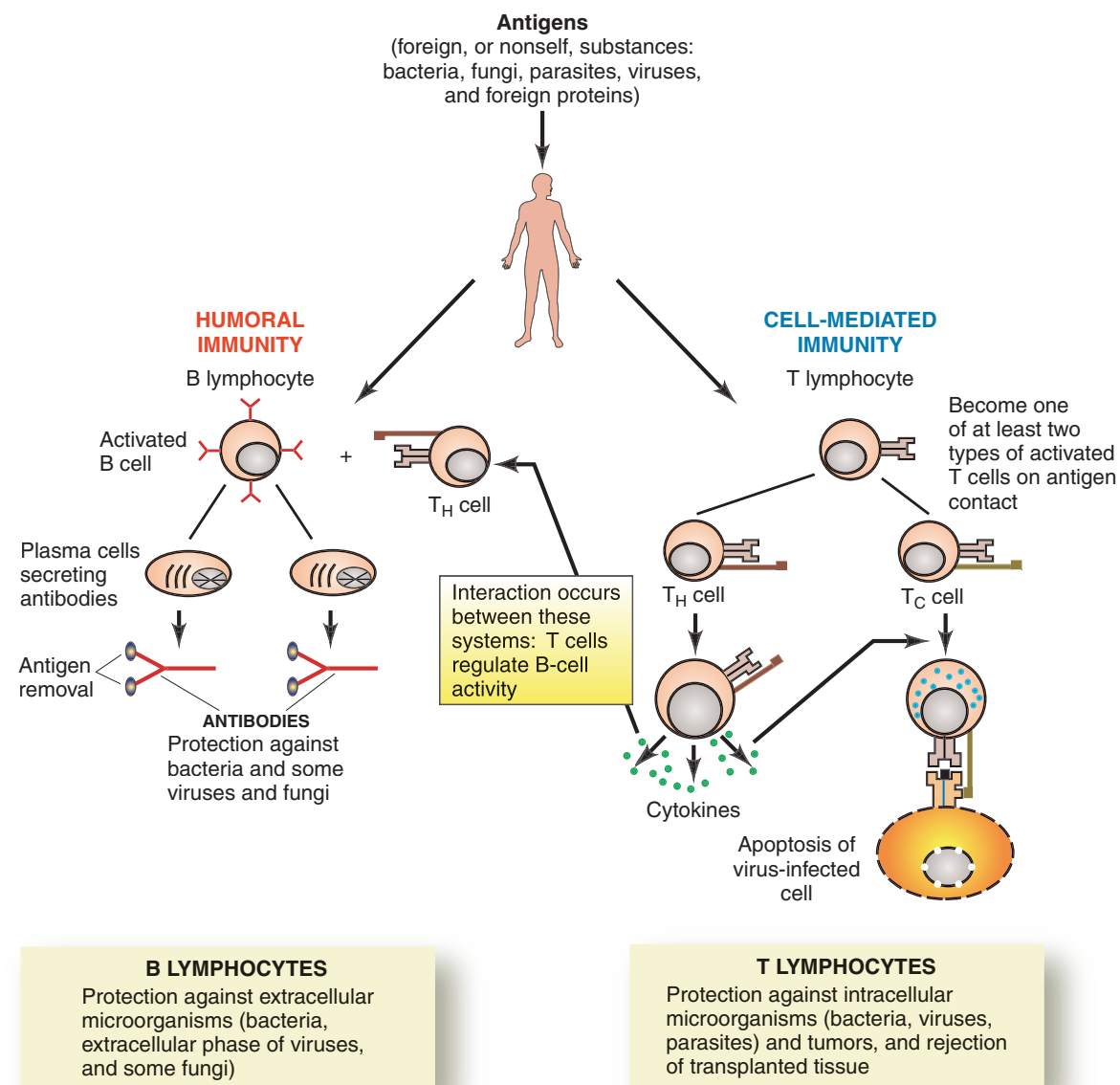
How does the immune system accomplish an adaptive immune response? It divides it into phases or functional steps: antigen recognition (the cognitive

phase), lymphocyte activation (a two signal event), and antigen elimination (effector phase). The successful completion of these phases leads to decline of the immune response (homeostasis) and memory. The antigen recognition phase requires direct contact (ensures specificity) between the antigen and the counterpart receptor on a clone of antigen-specific lymphocytes. This engagement leads to the activation phase, which requires two distinct but synergistic signals: the first signal is antigen and the second signal is a series of costimulators and cytokines. The second signal results from the interaction of innate immune system components with microbes and injured cells. The result of the activation phase events is the proliferation and differentiation of lymphocytes into effector cells, which produce effector molecules or mediate effector functions directly and memory cells. The effector molecules (antibodies) and cells (T lymphocytes) neutralize and eliminate extracellular (such as bacteria) and intracellular (such as viruses) antigens, respectively. Once antigen is removed the immune system returns to a resting state. Any remaining antigen-specific effector cells die by apoptosis.

### Adaptive Immunity Is Humoral, Cell-Mediated, or Both

Vertebrates possess two types of adaptive immunity based on the components the immune system uses to mediate immunity (Figure 1-2). **Humoral immunity**<sup>3</sup> is mediated by antigen-specific blood proteins called *antibodies* (see Chapter 4). Antibodies are secreted only by plasma cells (the daughter cells of *bone marrow-derived B lymphocytes*). This immunity protects against circulating extracellular antigens such as bacteria, microbial exotoxins, and viruses in their extracellular phase; that is, antibodies normally interact with circulating antigens but are unable to penetrate living cells. Humoral immunity's concomitant counterpart during an immune response is **cell-mediated immunity**. This immunity is mediated by antigen-specific cells called *thymus-derived, or T, lymphocytes*; there are at least two main subpopulations of T cells: *T helper (T<sub>H</sub>) cells* and *T cytotoxic (T<sub>C</sub>) cells* (see Chapter 2). Cell-mediated immunity protects against intracellular parasites, such as viruses, and is important in the rejection of organ transplants and tumor cells. Because activated, antigen-specific B and T lymphocytes eliminate antigen, they are called *effector*

<sup>3</sup>The word *humoral* is used because plasma cells secrete antibodies into the body's fluids, or humors.

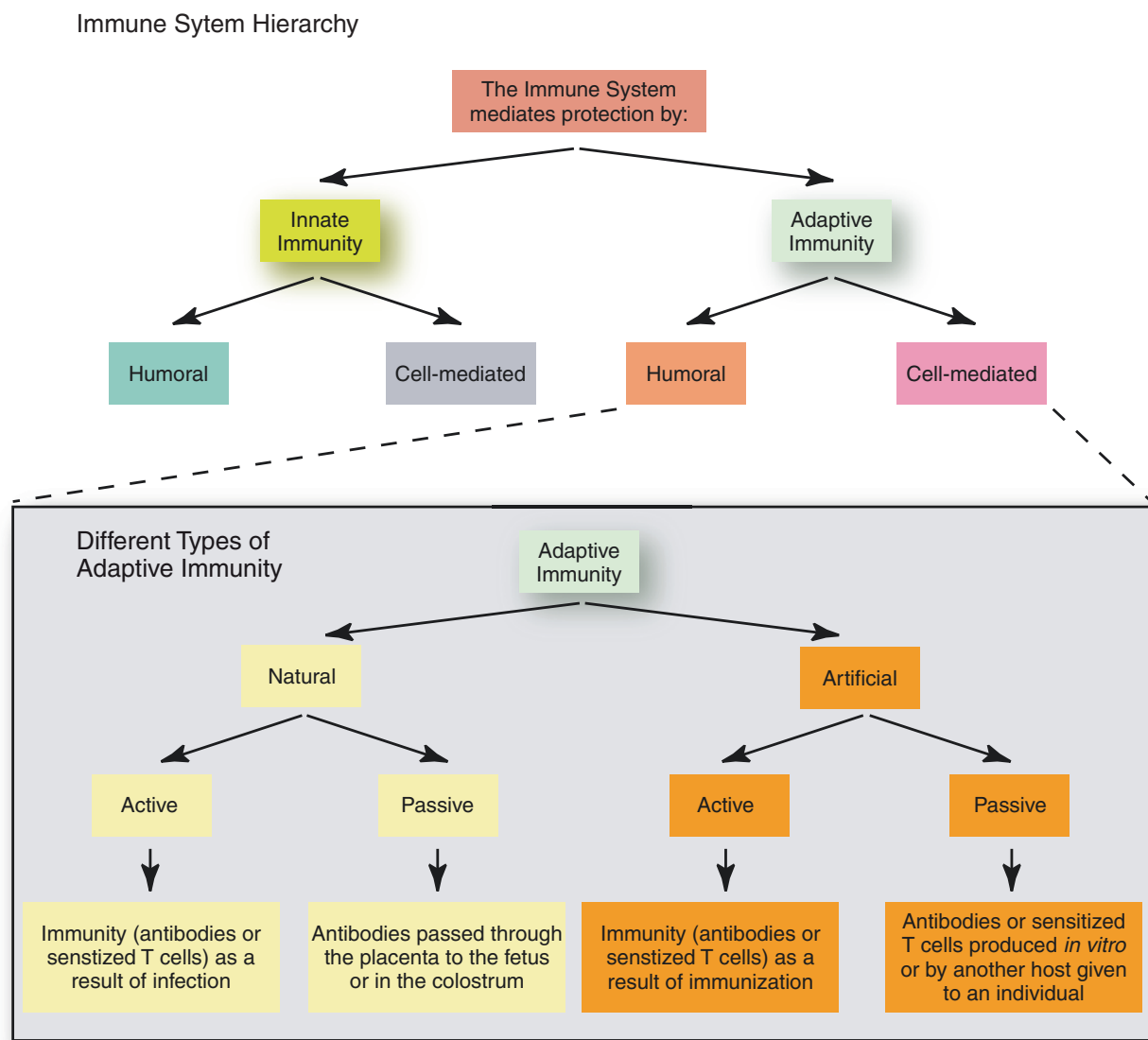


**FIGURE 1-2** The two types of adaptive immunity—humoral and cell-mediated. When antigens such as bacteria or some viruses are introduced into a host, the host responds by producing antibodies that bind the introduced antigens and lead to their elimination. This response to antigens constitutes the *humoral immune response*. When an antigen is unreachable by antibodies or a virus-infected cell, the host can rally cytotoxic T ( $T_C$ ) cells that can specifically react with and destroy the virus-infected cell; this response is known as the *cell-mediated immune response*. To develop into plasma cells or  $T_C$  cells, these cells need help from helper T ( $T_H$ ) cells and their cytokines.

cells. B cell–derived plasma cells act as effector cells by releasing antibodies, while  $T_H$  cells release communication molecules (*cytokines*) and  $T_C$  cells kill target cells. Both humoral and cellular immune responses are evoked during antigen insult, although one of these two responses predominates based on the type of challenge.

### Adaptive Immunity Can Be Active or Passive

Humoral and cell-mediated adaptive immunity can each be divided into **active** and **passive immunity** (Figure 1-3). Active immunity is acquired gradually (5 to 14 days after antigen exposure), lasts for years,



**FIGURE 1-3** A flow chart of the different types of immunity.

and is highly protective. Passive immunity is immediate, lasts for days to months, has low to moderate protective effectiveness, and does not develop memory in the recipient. Some diseases, such as tetanus, often kill a person before immunity can be established. To avoid such a drastic result, the person can be given immediate protection by the infusion of antibodies, but the effect is short-lived and there is no immunologic memory. Both active and passive immunity can be further subdivided into *natural* and *artificial* forms. In active immunity, an individual has adaptive immunity mediated by antibodies or sensitized T lymphocytes (T cells) *formed by that individual*. If an individual is exposed to foreign

substances naturally through the environment, rather than by immunization with a vaccine, that individual acquires the *natural* rather than the *artificial* form of active immunity. In passive immunity, an individual has adaptive immunity mediated by antibodies (or sensitized T cells) *formed in another individual*. Antibodies are transferred from one host to another to confer immunity. The passage of antibodies between individuals is called *passive transfer*. *Adoptive transfer* is the passage of T cells (or any immune cells) between inbred animals of the same strain or in human bone marrow transplants to grant immunity. The passage of antibodies from the mother to the fetus across the placenta or to the infant through the colostrum

is a form of natural, passive adaptive immunity. Artificial, passive adaptive immunity occurs when preformed antibodies or immune cells are given to a nonimmune individual (such as gamma globulin injections for hepatitis).

## CLONAL SELECTION OF LYMPHOCYTES EXPLAINS DIVERSITY, SPECIFICITY, AND MEMORY

As mentioned earlier, adaptive immunity revolves around two groups of lymphocytes that bind antigen using antigen-specific membrane receptors. To set the stage for clonal selection let's answer the following question: how do these receptors originate? Genetic rearrangement recombines linearly arranged groups of germline gene segments into a single, contiguous DNA sequence that encodes the antigen-binding part of B or T cell antigen receptor chains. This process occurs as B cells develop in the bone marrow and T cells develop in the thymus. The unsuccessful production of functional receptors for either cell type leads to their death in these organs. This mixing-and-matching process, the random recombination of different gene segments, leads to the huge diversity of functional genes that encode the antigen-binding domains of antigen-receptors—thus shaping our adaptive immune system to recognize and react with all antigens. This huge number of different antigen specificities is called the *immune repertoire*. Since this repertoire is randomly generated, some lymphocytes express self-antigen-reactive receptors; when these cells bind to antigen in the bone marrow or thymus, they are eliminated (*clonal deletion*) before they mature. If they escape this process, they are inhibited in the periphery (see Chapter 13).

The specificity and memory associated with adaptive immunity fall within the framework of *clonal selection*. This paradigm of immune cell origin and development is the central integrating concept in modern immunology. Clonal selection of lymphocytes provides the framework to explain the hallmarks of the immune response, which comprise (1) *diversity*, (2) *specificity*, and (3) *immunologic memory*. *Each immune cell can recognize and respond to only one antigen and the specificity of these cells is developed before the antigen is introduced.* An antigen does not induce the appearance of immune cells; rather, it *selects* preexisting antigen-specific immune cells by interacting with the cells' receptors. Thus a host exists in a

preimmune state against antigens that have yet to be encountered. The group of immune cells specific for an antigen is called a *clone* of cells. Clones are derived from the same mother cell and so are identical; clones are activated after antigen selectively stimulates their antigen-specific receptors. Thus diversity and specificity result from having millions of different clones that each demonstrate unique antigen specificity, and both diversity and specificity exist before any antigen exposure. However, memory develops during clonal expansion and differentiation. *Memory cells* represent an enlarged clone of long-lived cells B or T cells that are committed to respond rapidly, or by their clonal expansion, on reexposure to the same antigen. Immunologic memory results from having more cells and cells that can immediately be directed against a previously encountered antigen; it permits a secondary immune response on reexposure to the antigen.

Many years of research led to the development of the concept known as *clonal selection*. Immunologists now know, for example, that the B cell is a "parent" cell that expresses antibody on its surface. The binding of specific antigen by surface antibodies induces the B cell to proliferate and differentiate into an antibody-secreting "daughter" cell called a *plasma cell*. The antibody secreted has the same antigen-binding specificity as when the antibody acted as a receptor molecule.

B cells are selected when antigen binds to membrane-bound antibody receptors specific for that antigen. This interaction, plus signals from other immune cells, causes B cells to differentiate into plasma cells that secrete antibody with the same specificity as their membrane-bound counterpart. This scenario for interaction is one of the basic tenets of **clonal selection** in antibody formation. It is called *selective* because antibody receptors are selected for specifically by the right antigen. B cells that bind antigens are found in an individual before the individual has been exposed to those antigens.

Realization that DNA determined protein structure changed the thinking of immunologists. If every antigen receptor specificity means a different protein molecule and each protein molecule has a unique gene, the genetic information that encodes these receptors must exist in a person's DNA before exposure to the antigen. Within a few years of the discovery of DNA structure, immunologists, particularly Burnet, outlined the **clonal selection theory** of antibody formation. Burnet's contemporized basic tenets for the clonal selection theory are summarized as follows:

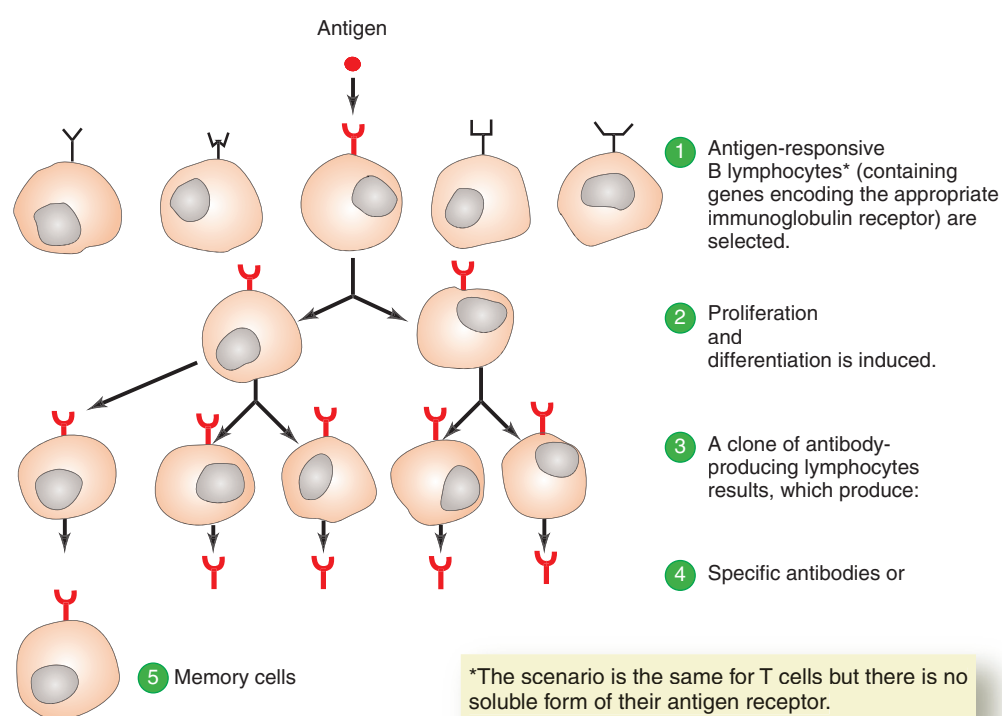
1. Early in embryogenesis and throughout adult life, a host develops a large repertoire of

antibody[receptor]-forming cell precursors, or *clones* (can be B cell or T cell clones). Each clone can recognize and respond to only one unique antigen. The number of progenitor cells in each clone is small (each lymphocyte expresses a single type of receptor with a unique specificity, so at the single-cell level there is no diversity), but the collective clonal repertoire can respond to any antigen.

2. During *in utero* development and throughout adult life, a host takes inventory of self-antigen reactive cells, and these cells (Burnet called them *forbidden clones*) are deleted or functionally inhibited. "Forbidden clones" are the precursor cells capable of responding against the host's tissue antigens and therefore absent from the repertoire of mature lymphocytes. (If absent, why do we still have autoimmune diseases? This question will be answered in later chapters.)
3. Foreign antigen reacts selectively with the right high-affinity receptor-expressing, pre-existing clones and activates them. Clonal

expansion occurs, leading to differentiation into antibody[receptor]-forming cells and memory cells; all of these daughter cells will bear receptors of identical antigen specificity to the parental cells.

Clonal selection supports genetic control of the immune response (Figure 1-4) and suggests that discrete, separate genes control the tertiary structure of antibody. It also supports that the interaction of antigen with antibody receptors starts the clonal proliferation of a group of B cells genetically restricted to one antibody specificity. These cells differentiate into either memory cells or antibody-forming plasma cells. However, both antigen-independent and antigen-dependent phases of B-cell development exist. The generation of diversity that leads to antigenically committed B cells, which then can be "selected," is antigen-independent (see Chapter 6). The antigen-dependent phase of B-cell development (clonal selection) occurs only when specific antigen *chooses* the appropriate preexisting B cell (see Chapter 10).



**FIGURE 1-4 Model of clonal selection.** A host exists in a preimmune state because each B lymphocyte has genes that encode one specific antibody. Specific antibodies that are secreted are at first found on the surface of lymphocytes as receptors. The antigen selects the right cell and induces it to proliferate and differentiate. These activities lead to a clone of antibody-producing cells (plasma cells) that secrete specific antibody. The released antibody is an accurate reflection of its receptor counterpart. Memory cells with receptors of the same specificity also are generated.

Although discussions of clonal selection mention antibodies, this paradigm also applies to cellular immunity. T cells are selected for specific antigen by TCR interaction, inducing proliferation and differentiation of a clone of T cells into regulators of humoral immunity and regulators/effectors of cell-mediated immunity and innate immunity (see Chapter 10). Clonal selection remains the pivotal integrating concept in modern immunology and provides explanations for immunologic diversity, specificity, and memory.

## THE IMMUNE SYSTEM HAS TWO LEVELS OF DEVELOPMENT

Immune system development occurs at two levels: (1) the species level and (2) the individual level. *The developmental history of the immune system during evolution is called phylogeny, and the developmental history of the immune system in an individual within a species is called ontogeny.* The first antibody to appear in phylogeny is also the first to appear during immunologic development in an individual. Thus, “ontogeny recapitulates phylogeny” and vice versa.

Phagocytosis and inflammatory reactions are the most primitive signs of an immune-like system. These forms of nonspecific (innate) immunity are present in invertebrates (such as porifera [sponges], annelids [earthworms], and arthropods [insects, crustaceans]). The anti-microbial peptides and pattern recognition receptors start in arthropods. The first evidence of a vertebrate-like immune system (also called the *lymphoid system*) appears in the primitive vertebrates cyclostomes (hagfish and lamprey) that possess a diffuse system and lack distinct higher vertebrate immune structures. Hagfish and lampreys produce a high-molecular-weight antibody on exposure to foreign substances and reject foreign transplanted tissues. This antibody is comparable to a class of human antibody known as *immunoglobulin M (IgM)*. The earliest immune organ to appear in phylogeny is the thymus. The thymus is present in most primitive vertebrates such as the elasmobranchs (dogfish and shark). Amphibians, reptiles, and birds produce at least two of the five classes of antibodies found in humans, mediate graft rejection, and possess B and T cells and the immune organs typical of mammals, such as the thymus, lymph nodes, and spleen.

Throughout the fetal, newborn, and young adult stages of life, the individual undergoes progressive immunologic maturation (ontogeny). The human fetus starts to develop an immune system during

the first trimester of pregnancy, and serum antibody (IgM) can be detected during the second trimester. Cells responsible for nonspecific and specific immunity arise from descendants of hematopoietic stem cells. These cells are initially found in the yolk sac, but later appear in the fetal liver and finally in the bone marrow (see Chapter 2).

Because the immune system is poorly developed both in the fetus and in the newborn, the mother’s antibodies provide protection. Maternal antibodies are transmitted to the fetus through the placenta during prenatal development in the womb and to the newborn through the colostrum during breast-feeding. A human newborn’s lymphocytes are fully competent for cell-mediated immune responses.

In summary, the immune system develops early within species (phylogeny) and becomes progressively more sophisticated. Immune development in individuals within a species (ontogeny) occurs shortly after conception, with final maturity being reached at puberty.

### MINI SUMMARY

Adaptive immunity, whether humoral or cellular, permits the destruction of all substances (living and nonliving) within the body that are not recognized as self. The six major characteristics of adaptive immunity are (1) specificity, (2) inducibility, (3) diversity, (4) memory, (5) distinguishing self from nonself, and (6) downregulation of itself. The main cells of the adaptive immune system are B cells and T cells (and dendritic cells and macrophages). B cells are responsible for humoral immunity, and T cells confer cellular immunity. Unlike the lymphocytes, phagocytic cells (such as dendritic cells and macrophages) do not respond specifically to foreign substances but instead play required auxiliary roles. Adaptive immune responses develop in three phases: antigen recognition, lymphocyte activation, and antigen elimination. Adaptive immunity can be divided into active and passive immunity, each of which is further subdivided into natural and artificial forms. Clonal selection explains how the vertebrate immune system specifically recognizes millions of different antigens. It applies to both B and T cells and accounts for immunologic diversity, memory, and specificity. The developmental history of host immunity can be divided into phylogeny and ontogeny—innate immunity is found in all multicellular plants and animals, while adaptive immunity is found only in vertebrates.

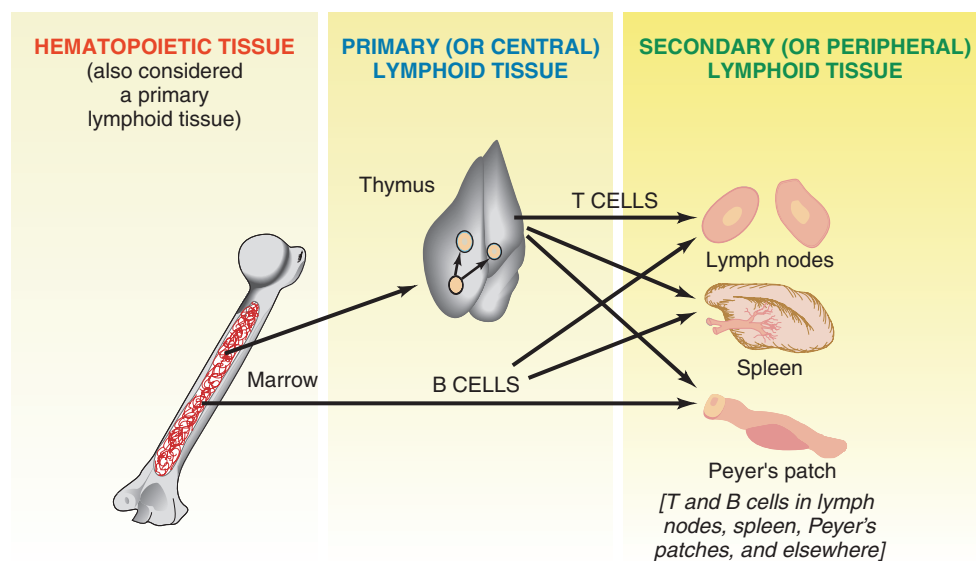
## THE ARCHITECTURE AND MECHANISMS OF THE IMMUNE SYSTEM ARE VARIED AND COMPLEX: AN OVERVIEW

The immune system is a complex functional system consisting of diverse organs, tissues, and cells distributed throughout most of the body (Figure 1-5). Despite the system's complexity, its components are interrelated and act in a highly coordinated and specific manner when they recognize, eliminate, and remember foreign macromolecules and cells (Figure 1-6). To accomplish this task, the immune system must distinguish between *self* and *nonself* materials.

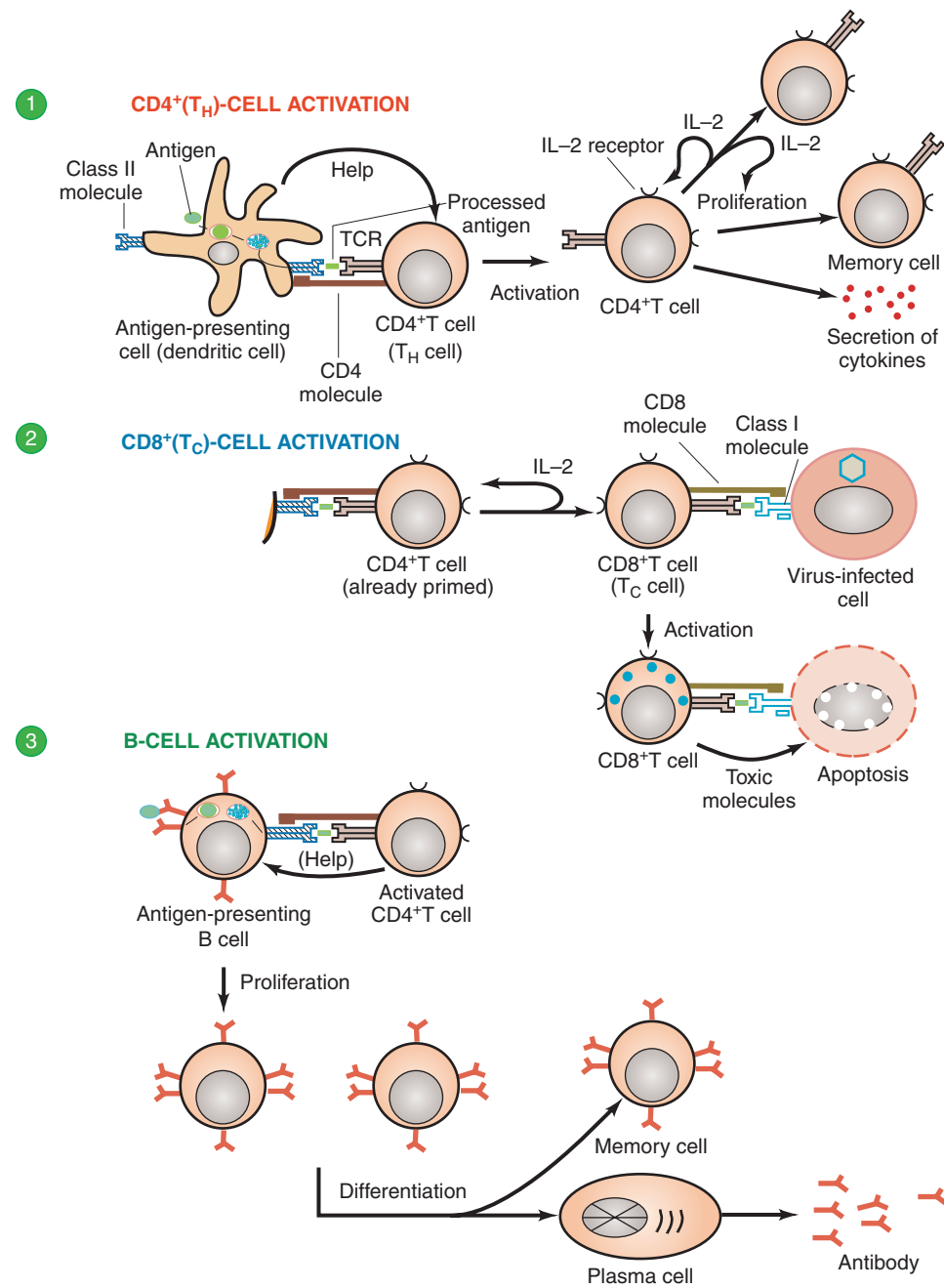
Any foreign substance (living or nonliving) that induces an immune response when introduced into a host is called an *immunogen*, or more generally, an *antigen*. Most antigens are large, complex macromolecules not recognized as self. Only small parts of antigens, called *antigenic determinants* or *epitopes*, induce and react with immune elements such as antibodies or antigen receptors on lymphocytes. Antibodies recognize antigens through their surface characteristics, particularly by the antigen's pattern or shape and

charge. The binding sites of the antibody are precisely complementary, or *specific*, for the right antigenic determinant. When antigen enters the body, it usually induces the production of antibodies that react only with that particular antigen. The immune system also has pre-existing lymphocytes expressing receptors capable of reacting with the specific antigen. The first time we are exposed to an antigen, the result is a *primary immune response*. The second exposure to the same antigen leads to a *secondary immune response*, which is much faster and stronger. This phenomenon is mediated by *immunologic memory cells* and accounts for a person's long-term immunity against infectious diseases.

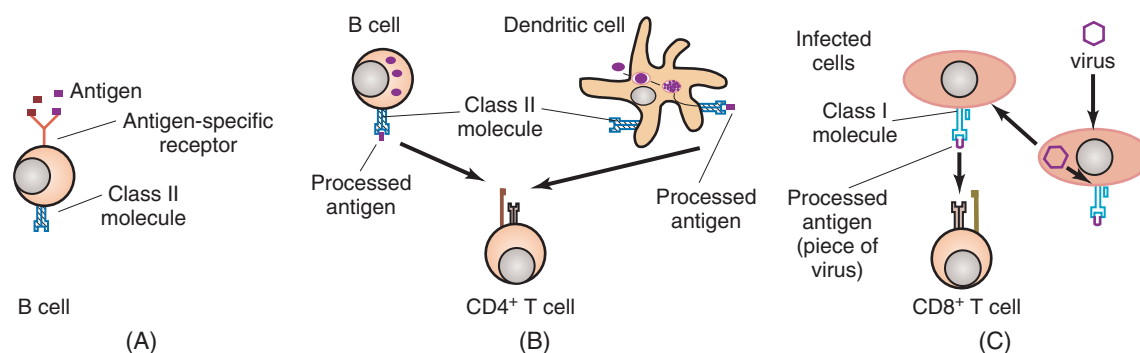
Among the first cells to interact with antigen are *macrophages* ("big eaters"). As their name implies a defining feature of macrophages is their ability to internalize antigen; they are janitorial cells. These phagocytic cells internalize (called *phagocytosis*) and digest the whole antigen, displaying a small peptide portion on its surface in association with membrane self-markers. This series of events, known as *antigen processing and presentation*, manipulates the antigen into a form that can be recognized as nonself by the T lymphocyte. Thus macrophages, along with their star-shaped cousins dendritic cells, are called *antigen-presenting cells (APCs)*. Dendritic cells also



**FIGURE 1-5** Principal tissues, organs, and cells of the immune system. Cells destined to become immune cells are produced in the bone marrow. Some of the descendants of stem cells can become lymphocytes. The classes of lymphocytes are T cells and B cells. The pre-T cells migrate to the thymus, where they multiply and mature into T cells capable of mediating an immune response. In humans, B cells complete most of their maturation in the bone marrow. Once both T and B cells are mature physically and functionally, they populate the secondary lymphoid organs.



**FIGURE 1-6 Development of the immune response.** The details of this response will be discussed in subsequent chapters. When an antigen [■] is introduced into a host, antigen-presenting cells (mainly dendritic cells) process and present the antigen to CD4<sup>+</sup> T cells (usually considered T<sub>H</sub> cells). This process and the release of interleukin-1 (IL-1), a helper cytokine, and other cytokines, activate the CD4<sup>+</sup> T cells. Activated CD4<sup>+</sup> T cells help themselves and CD8<sup>+</sup> T cells (usually considered T<sub>C</sub> cells) by releasing IL-2 and interferon- $\gamma$ . Activated CD8<sup>+</sup> T cells respond in cell-mediated immunity reactions by their direct participation as effector cells. Antigen-activated B cells, after processing and presenting antigen to activated CD4<sup>+</sup> T cells and by cytokines like IL-4 and IL-5. The plasma cells secrete specific antibodies against the inducing agent and thereby provide humoral immunity. Some cells become memory cells and react more rapidly to rechallenge by the same antigen. The T cell receptors (TCR) of CD4<sup>+</sup> and CD8<sup>+</sup> T cells recognize antigen only when associated with class II or I MHC molecules, respectively.



**FIGURE 1-7 Receptors for antigen recognition.** Membrane-bound antibodies, T cell antigen receptors, and MHC molecules are the three kinds of molecules used by the immune system to recognize antigen. **(A)** The B cell's antigen-specific receptor is an antibody anchored in its surface that recognizes antigen in its natural state. B cells can internalize and process antigens similar to the method used by macrophages and dendritic cells and eventually present the antigen using class II MHC molecules. MHC molecules serve as self-labels and identify a cell as belonging to that individual; these molecules permit processed antigen presentation to the appropriate T cell. **(B)** The CD4<sup>+</sup> T cell's antigen-specific receptor cannot recognize antigen in its natural state; the antigen must be processed and presented by APCs such as dendritic cells and macrophages. **(C)** The CD8<sup>+</sup> T cell's antigen-specific receptor is like that of the CD4<sup>+</sup> T cell, but it recognizes antigen bound to a class I MHC molecule, which is found on all nucleated body cells.

communicate with T cells during antigen invasion through soluble factors. The *T* and *B lymphocytes* are the only immunologically specific cellular components of the immune system (Figure 1-7).

T and B lymphocytes are antigen-specific thereby the mediators of adaptive immunity, but their function is under the control of innate immunity cells, *dendritic cells*—the premier APCs of which there are many types. While macrophages, in addition to being APCs, execute a wide array of functions, the related dendritic cells have developed as specialized APCs. In contrast to macrophages, dendritic cells do not use phagocytosis as a scavenger function, but as a means to process and present antigen-derived peptides to specific T cells. Dendritic cells establish themselves in an immature form in tissues, such as Langerhans' cells in the skin, where they are highly phagocytic but cannot present antigen. Upon encountering an infectious microbe in the periphery, they capture it, process it, express lymphocyte co-stimulatory molecules, migrate to lymphoid organs where they arrive as mature dendritic cells with antigen-presenting capacity—they lose their phagocytic ability and shift to APCs that can activate T cells, the initiation of primary adaptive immunity. They are more than initiators; dendritic cells are also crucial regulators of innate immune activities, in particular natural killer (NK) cell function. In turn, NK cells can influence dendritic cell activity.

A third group of lymphocytes, *NK cells*, do not recognize antigen in the same way as T and B cells

and therefore are nonspecific killer cells and part of innate immunity. Unlike T and B cells, whose receptors undergo random DNA recombination or sequence diversification in somatic cells, NK cell receptors are hard-wired. NK cells use a two-receptor (killer-activating and killer-inhibitory receptors) recognition strategy, they recognize normal cells and cells that lack major histocompatibility complex (MHC) class I surface molecules, which are normally expressed on all nucleated cells. Cells can sometimes lose the ability to express these MHC molecules due to either microbial interference with the expression mechanism or malignant transformation making them "abnormal." Killer-activating receptors recognize some ubiquitous surface molecules present on normal, nucleated cells, and in the absence of a blocking signal from their counterpart killer-inhibitory receptors, which recognize MHC class I molecules, the killer-activating receptors instruct NK cells to attack and kill the target cell. NK cells mediate killing by cellular cytotoxicity and production of cytokines and chemokines. They are important in attacking virus-infected cells, during the early phases of an infection. They are also efficient killers of tumor cells and thereby involved in tumor surveillance. NK cells are more than killing cells, they also can exert an immunoregulatory effect, particularly on dendritic cells.

Another group of lymphocytes with innate-like antimicrobial functions, *natural killer T (NKT) cells* are a heterogeneous subset of T cells that expresses

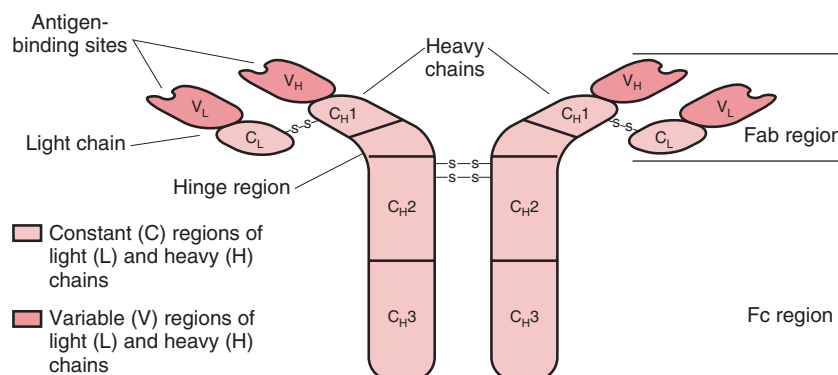
both NK cell markers and semi-invariant  $\alpha\beta$  TCRs. As NK cells, there is interplay between dendritic cells and NKT cells. Some NKT cells recognize lipid antigens, which are presented to NKT cells by dendritic cell-expressed MHC-like CD1d molecules. Selective presentation of lipids by dendritic cells induces a stronger and more prolonged NKT-cell response. Reciprocally, NKT cells can promote dendritic cell maturation. After TCR stimulation, NKT cells rapidly produce copious amounts of interferon- $\gamma$  and IL-4. In contrast to T and B cells but like NK cells, NKT cells exhibit rapid effector functions without need for priming and clonal expansion.

Cells of the immune system communicate by *cytokines*, small, “messenger” molecules that can determine the fate of an immune response. The cytokines produced by lymphocytes are called *lymphokines*, whereas macrophage-derived signals are called *monokines*. *Interleukins*, as the name implies, act as messengers between *leukocytes* (the general name for lymphocytes and APCs). Interleukins are a major group of cytokines. Another group of cytokines are called *chemokines*. They are a large group of low-molecular-weight molecules that mediate leukocyte chemotaxis (soluble signposts that help immune cells find their way in the body) and control the expression of leukocyte adhesion molecules (once they arrive, they stick to the surrounding cells). Chemokines play a major role in inflammatory reactions.

Although T lymphocytes originate in the bone marrow, maturation in the absence of antigen occurs in the *thymus*. Because their differentiation occurs during their residence within the thymus, these cells are called *thymus-derived (T) lymphocytes* or *T cells*. The vast majority of mature T cells express antigen receptors (abbreviated TCR) on their surfaces that are composed of an  $\alpha$  chain and a  $\beta$  chain, the remaining 1–5% of T cells express a  $\gamma$  chain and a  $\delta$  chain. Each T cell reacts only with the antigen for which its receptor is specific; the level of receptor diversity, the type of antigen, and how it is recognized differs between  $\alpha\beta^+$  and  $\gamma\delta^+$  T cells. T cells expressing the  $\alpha\beta$  receptor cannot react against free, undigested protein antigen like B cells and their antibodies can;  $\alpha\beta^+$  T cells recognize antigen-derived peptides only when they are associated with self-major histocompatibility complex (MHC) molecules on the surface of an APC or some other target cell. This interaction stimulates the T cells to proliferate and produce progeny with the same antigen specificity. Two major T cell populations exist that differ both phenotypically and functionally. One population of T cells expresses the surface molecule CD8, usually is called *cytotoxic T*

(*T<sub>C</sub>*) cells, and recognizes antigen on the target cell surface associated with class I MHC molecules. These MHC molecules are present on all nucleated cells and permit the CD8<sup>+</sup> T cells to recognize and destroy virally infected (any intracellular parasite-infected) cells, foreign tissues, or tumor cells. The other population of T cells expresses CD4, usually is called *helper T (T<sub>H</sub>) cells*, and acts as the commander-in-chief of the immune system by providing direct and indirect help to various cellular components. CD4<sup>+</sup> T cells recognize antigen presented on the surface of APCs in association with class II MHC molecules. Unlike class I MHC molecules, class II MHC molecules are expressed only on APCs such as macrophages, dendritic cells, and B cells. Based on cytokine profiles, naïve T<sub>H</sub> cells can differentiate into at least two functional subsets during an immune response: T<sub>H</sub>1 cells, which secrete interferon- $\gamma$ , and T<sub>H</sub>2 cells, which secrete interleukin-4. T<sub>H</sub>1 and T<sub>H</sub>2 cells are generally responsible for cell-mediated and humoral immunity, respectively. Recent evidence suggests that the twins may be triplets; a new T<sub>H</sub> cell subset producing interleukin-17, a previously unknown lineage of CD4<sup>+</sup> T cells, has emerged—the T<sub>H</sub>17 cell. It seems to regulate tissue inflammation and, in some animal models, the development of autoimmune disease. There also are CD4<sup>+</sup> regulatory T cells

The other main class of lymphocytes is the *bone marrow- or bursa-derived (B) lymphocytes* or B cells. Like T cells, there are B cell subsets. B cells both originate and mature in the bone marrow (except in birds) and the spleen. Mature B cells express antibodies (the abbreviation for these antigen receptors is BCR) on their surfaces and bind free antigen with them. When the antigen is processed by its specific B cell and presented to T<sub>H</sub> cells, the B cells proliferate and differentiate. The end cells, the sole producers of antibodies, are *plasma cells* that develop elaborate internal machinery and produce large quantities of antibody also referred to as *immunoglobulins* because they are globular proteins that confer immunologic protection. A typical plasma cell can secrete antibodies at the rate of 2000 to 10,000 molecules per second for 4 or 5 days before it dies. These antibody molecules have the same binding specificity as when they were BCRs. Secreted antibodies act as circulating forms of receptors and “red flags” that mark foreign antigen for destruction. Antibodies also “butter up” antigens, thereby enhancing phagocytosis—adaptive immunity helping innate immunity. The prototype antibody is made of four chains, containing about 1300 amino acids. Two of the chains are about twice as long as the other two; they are called *heavy chains*, and the smaller ones are called *light chains*. The heavy



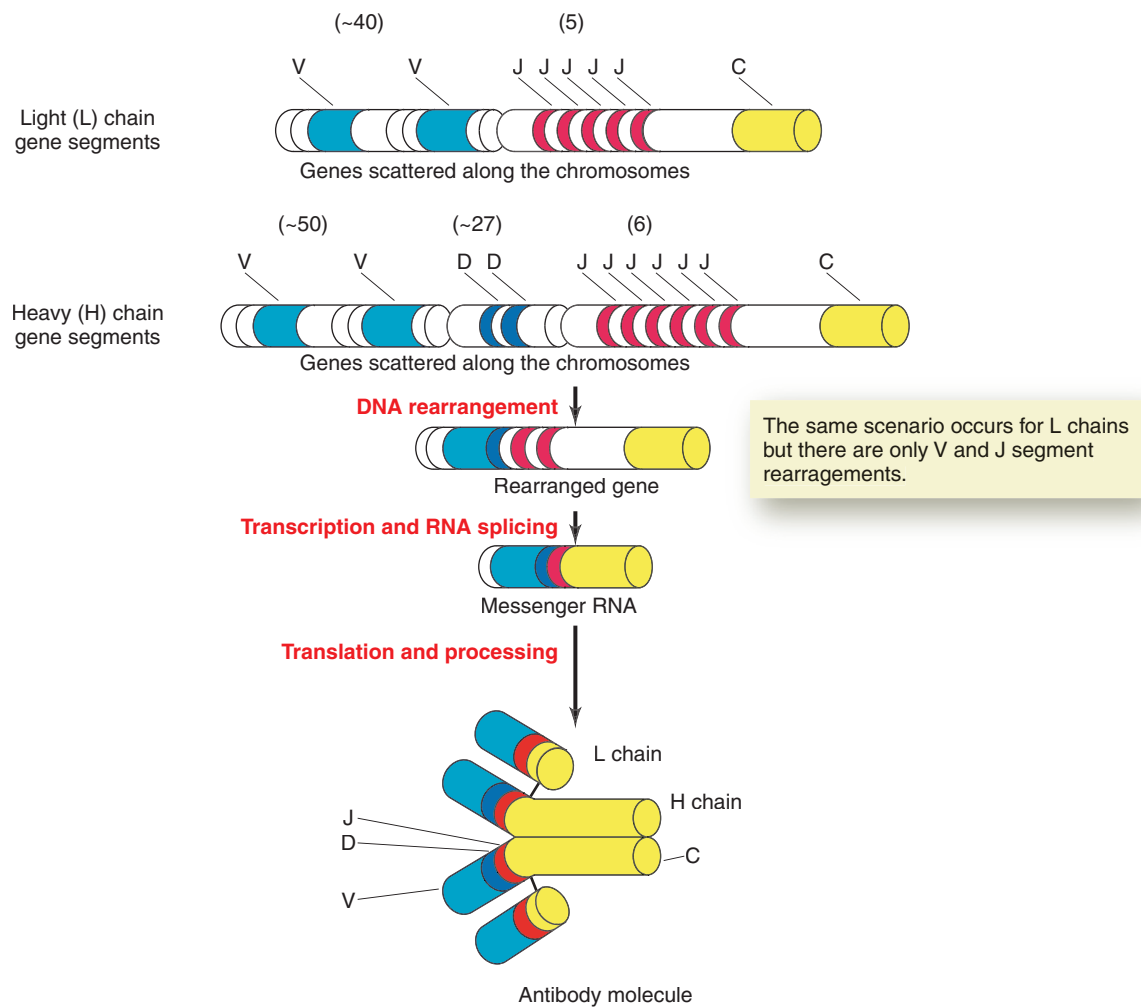
**FIGURE 1-8** Prototype structure of an antibody or immunoglobulin. The different regions of antibodies perform different functions. The corresponding ends of each pair of adjacent light (L) and heavy (H) chains represent the two antigen-binding parts of the antibody molecule; they are called *variable*, or *V*, *regions*. These regions vary greatly in amino acid sequence among antibodies responding to different antigens and account for the *diversity of antibodies*. The other regions have constant amino acid sequences that are characteristic for each antibody class; therefore, they are called *constant*, or *C*, *regions*. They determine the class and biological function of antibodies. Light chains and  $V_H$  and  $C_{H1}$  make up the fragment for the antigen-binding (Fab) region. Other common regions of the H chain make up the fragment of the crystallization (Fc) region.

and light chains are held together by disulfide bonds, forming a Y (Figure 1-8). The ends of the Y arms are the antigen-binding sites.

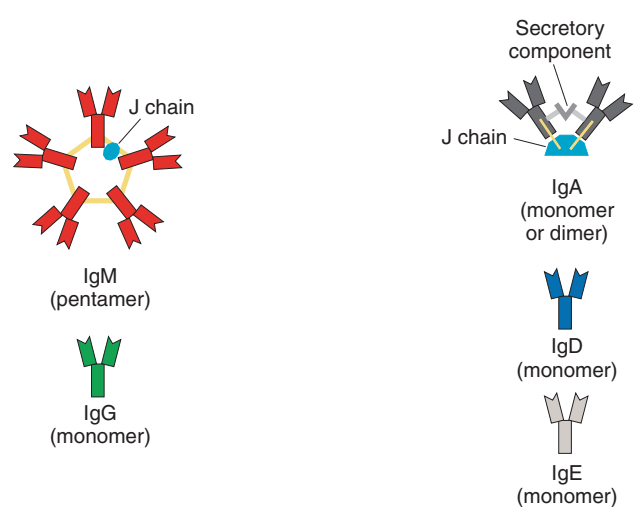
Antibodies and TCRs are primary gene products. The light- and heavy-chain and TCR gene pools contain one or more constant-region genes and sets of variable gene segments (see Figure 1-9). *The variable sequences form the antigen-binding site and determine specificity.* To make a receptor molecule, light-chain and heavy-chain and TCR gene segments are selected and assembled. Because people and animals can respond to any antigen, immunologists once thought that individuals must have between 10 million and 100 million different receptor genes. However, this number is unreasonably large because human chromosomes possess only a few hundred genes that encode receptors. For example, how can a person have so few genes yet unlimited antibody diversity? Two possibilities were initially proposed; the *germline* and *somatic* mechanisms. Germline mechanisms proposed that *all* antibody genes are inherited from our parents, while the somatic mechanisms proposed that during development to a mature B cell a *few* germline antibody genes undergo some sort of somatic variation. It turns out that both mechanisms are largely correct. The important point is that the genes encoding antibodies and TCRs do not exist as one sequence of nucleotides, even though the genes encoding all other proteins are inherited intact. Rather than harboring a complete or functional set

of antibody or TCR genes, embryonic cells contain several hundred genetic bits and pieces that can be thought of as an “erector set” of antibody or TCR genes. Segments are randomly selected and by DNA recombination placed together on the DNA in each B and T cell as it becomes immunocompetent. This mixing and matching of gene segments allows each B or T cell to reassemble the parts to form its functional *composite gene* that encodes an antibody light or heavy chain (Figure 1-9) or  $\alpha$  and  $\beta$  (or  $\gamma$  and  $\delta$ ) TCR chains.

Human *Immunoglobulins* can be divided into five classes (*IgG*, *IgM*, *IgA*, *IgD*, and *IgE*), which differ from each other in one portion of their heavy chains (Figure 1-10). Two (*IgM* and *IgA*) of the five antibody classes consist of multiples of the two light-chain and two heavy-chain structures of the prototype antibody molecule. All of the five antibody classes except *IgD* have distinctive and important biological functions as soluble molecules. *IgG* can coat microbes to promote phagocytosis and killing by immune cells. *IgG* is also the only class of antibody that can cross the placental barrier. *IgM* is known as an “early” antibody because it is the first antibody to be formed in an immune response. *IgM* is the largest antibody and consists of five monomeric forms of the prototype antibody. *IgG* and *IgM*, on reacting with specific antigen, activate a blood protein system (the *complement system*, which “complements” the work of antibodies) that amplifies the inflammatory and



**FIGURE 1-9 Antibody (receptor) diversity.** A host can make antibodies to millions of antigens because antibody genes (listed as *rearranged gene*) that encode antibody chains are pieced together from scattered bits of DNA called *variable (V)*, *diversity (D)*, *joining (J)*, and *constant (C)* segments. (The same scenario occurs for the development of T cell receptor chain diversity.)



**FIGURE 1-10 Antibody classes.**

immune responses and can cause the lysis of some types of bacteria. IgA is the predominant antibody class present in the body's secretions (including those of the respiratory and gastrointestinal tracts). IgA acts as the first line of defense at the mucosal linings against invading organisms. IgE, from a human's perspective, seems to have only negative activities because its production is responsible for an overzealous response against pollen, animal dander, and dust. Such reactions against "harmless" intruders lead to the common immune disorder known as *allergy*. A positive activity of IgE is its role in immunity to certain parasites. The fifth class, IgD, is found in large quantities on the surfaces of antigen-naïve mature B cells. The function or importance of IgD in the immune response is unclear, but it is relevant during antigen-triggered B cell growth.

The humoral immune system mediates protection by several methods. Antibodies enhance phagocytosis (called *opsonization*) and can prevent a virus or toxin from attaching to a target cell (called *neutralization*). Antibodies also regulate certain nonspecific defense mechanisms, the most important of which is the *complement system*. There are three pathways of complement activation, one pathway uses antibodies, and microbes or their products activate the other two pathways. This system consists of several serum proteins that work in a sequential cascade and ultimately puncture the targeted microbes. The breakdown products of the intermediate complement components have powerful effects on blood vessels and leukocytes. The result is an amplification of the immune response.

As described in the previous paragraphs, all vertebrates possess an important genetic region called the *major histocompatibility complex (MHC)* that regulates many immunologic functions and interactions. In humans, the MHC is called the *human leukocyte antigen (HLA) complex*; in mice it is called the *H-2 complex*. The MHC contains genes that encode both *class I molecules* that are expressed on all nucleated cells, including immune cells, and *class II molecules* that are found on APCs (macrophages, dendritic cells, and B cells). Class I and class II MHC molecules exist in each species in many different genetic forms and are required by TCRs to distinguish between self and nonself cells. Specific T-cell activation occurs only when digested antigen is presented by some cell in the context of class I or II MHC molecules to a T cell that has a receptor specific for that antigen-MHC complex. This focused, or restricted, interaction is called *MHC restriction*. MHC genes also encode components of the complement system, cytokines, and molecules needed for antigen processing. Thus, the genes of the MHC help determine susceptibility to many diseases in humans and animals.

These genes and ones for antigen receptors occasionally allow for immune responses against self-antigens. *Autoimmunity* is a disease state in which the host has a destructive immune response against its own tissues. Some familiar diseases caused by autoimmunity are type I diabetes and rheumatoid arthritis. In both of these conditions, MHC genes appear to influence susceptibility. A related immunologic response, at least in the sense of reacting against tissues, is rejection of an organ transplant. The host's body recognizes the genetic differences (class I MHC molecules) on the organ transplant as foreign and eliminates the antigen by rejection and destruction.

When autoimmunity occurs, like "friendly-fire," the immune system mistakenly kills healthy body

cells. When cancer occurs, body cells malfunction and replace healthy cells. Membranes of cancerous cells change slightly and subsequently appear to the immune system as nonself. If this "alien from within" eludes detection, full-blown cancer results. *Tumor immunology* investigates how the immune system handles these homegrown assailants and how to treat cancer. Because of the exquisite specificity of the immune response, one would expect that a tumor could be destroyed without changing normal tissue. Many tumors bear unique antigenic determinants, yet most human tumors elicit an ineffective antitumor immune response. Nonetheless, evidence suggests that the immune system acts as a surveillance mechanism, recognizing and destroying clinically inapparent cancers through these antigenic determinants. Tumor immunologists are trying to understand the mechanisms of the immune system's response to tumor-specific antigens through assessment of these antigens' molecular nature and cellular structure. Tumor immunologists also will have to understand the molecular basis of the immune response and of effector mechanisms in simple and highly defined antigenic systems.

The glare of the more exotic diseases of autoimmunity and cancer is dimmed when we realize we are bathed in a sea of predatory microbes, which are bent on destroying us. The immune system, an organization of cells and molecules with specialized roles in defending against infection, stands in the breach. There are two conjoined types of responses to invading microbes; innate (or natural) immune responses that are repeated irrespective of the number of times the infectious agent is encountered, whereas acquired (adaptive) responses improve on rechallenge to a given infection. To establish an infection, the pathogen must first overcome numerous surface barriers that either are directly antimicrobial or inhibit attachment of the microbe. Because the surface of skin or the mucus-lined body cavities are sparse habitats for most organisms, microbes must breach these levels of innate defenses. Any organism that breaks through this first barrier encounters formidable additional defenses, the cellular and soluble components of innate and adaptive immune responses. Innate immunity is more than a stopgap against pathogens, because after their recognition, release of phagocytic effector cells and microbicidal molecules, and perfectly ignoring host self-tissues, it provides the necessary signals to instruct the adaptive immune system to initiate a response. In turn, the adaptive response supplies molecules that augment the innate immune response. The innate encounter and recognition of

pathogens usually comes with a price; it triggers an acute inflammatory response. In the short-term, inflammation is a beneficial response to foreign challenge and associated tissue damage because it leads to the restoration of tissue structure and function. Conversely, prolonged inflammation is not a beneficial event and it contributes to the pathogenesis of many disease states. The challenge (avoiding the Jekyll and Hyde effect) remains in the development of antimicrobial treatments that harness inflammatory responses, leading to successful removal of the pathogen with limited inflammatory and autoimmune disease costs.

Despite all its specialized machinery for identifying and fighting off the continuous onslaught of microbes, the immune system occasionally fails to provide the required protection; this defect is defined as an *immunodeficiency*—a decrease in the number and function of immune cells. An immunodeficiency can be inherited, leading to primary immune deficiency diseases, or acquired through an infection (such as HIV), or it can result as a side effect of some immunosuppressive medical treatments. Irrespective of source, it leads to increased susceptibility to infections and occurrence of cancers and compromised immunotherapies such as vaccination. There are more than 120 known inherited primary immunodeficiency diseases and many of the associated genetic defects have been identified. In fact, these deficiencies have contributed greatly to our understanding of the immune system, for example, children born without a thymus, called *DiGeorge's syndrome*, provided evidence of thymic involvement in immune function long before its importance in T-cell development was known. The identification of the molecular defects that trigger immunodeficiencies and the implementation of new therapeutic modalities to correct these genetic defects are being vigorously pursued.

The crux of the immune system is to provide protection. So as we began the chapter, stating that we are continuously surrounded by invaders—microorganisms—we end the chapter and the text with how the immune system deals with pathogens. Infectious diseases are the largest single cause of illness in the world. These diseases range from annoying, the common cold, to life threatening, AIDS. Moreover, infectious diseases are a common complication associated with therapies such as transplant immunosuppression and cancer chemotherapy, and primary or secondary immunodeficient patients. Despite the success of antibiotics and anti-microbial drugs, they have not, nor are they likely, to eliminate infectious diseases as a major health problem.

However, using the power of the immune system as a tool to control infectious disease is unmistakably obvious by the success of vaccines—the complete and near elimination of smallpox, poliomyelitis, diphtheria, pertussis, and tetanus to name a few. The continuance and expansion of vaccine prophylaxis provides promise to controlling many other infectious diseases. Whether a disease condition occurs depends on the outcome of the interaction of the microbe and its host. Anything we can do to shift the balance in favor of the host's immune system will surely lead to consequent savings in cost of medical care but more importantly reduction in human misery and death.

## SUMMARY

*Immunity* is concerned with the recognition and disposal of nonself substances from a host; *immunology* is the study of the *immune response*, or the reaction that creates immunity. Immunology involves the study of the cells, soluble molecules, and organs responsible for this recognition and disposal; these responses, interactions, and other activities; their desirable or undesirable consequences; and the ways in which they can be augmented or dampened.

Early scientists manipulated immunity by *variolation* and *vaccination*. A *vaccine* is administered for the prevention of disease and contains either *killed* or *attenuated* microorganisms or a solution of altered toxins (*toxoids*). Genetic engineering has led to new categories of vaccines.

The integrity of the body is maintained by multiple defense systems, including immune responses. Protection against infection can be *innate* (inborn and unchanging) or *adaptive* (developed and adjusting to antigen during the lifetime of the host). Innate immunity is achieved by external mechanisms (skin, tears, mucous and ciliated epithelium of the respiratory tract, low pH of the stomach) or internal mechanisms (*inflammation* and *phagocytosis*). Inflammation involves increased blood flow to the site of injury and increased permeability of the vascular endothelium to allow access of white blood cells and serum components to the tissues. Phagocytosis, which can trigger inflammation, uses “professional” phagocytes (neutrophils, monocytes, macrophages, and dendritic cells) to remove foreign materials that have been introduced into the body. Phagocytes show no specificity, and the kind of protection they provide is different from adaptive immunity. Dendritic cells and macrophages are more than janitorial cells; they also prod the adaptive immune

response into action. Nonphagocytic cells, such as NK cells and NKT cells also contribute to innate immunity.

Adaptive immunity is attributable to T and B cells that can respond *selectively* and *specifically* to a seemingly infinite number of different nonself materials; this selective specific response leads to a specific *immunologic memory*. Adaptive immunity is divided into three phases: antigen recognition, lymphocyte activation, and antigen elimination. Functionally, T cells are responsible for *cell-mediated immunity* and regulation of the immune response, while B cells are responsible for *humoral immunity*. Adaptive immunity can be divided into *active* and *passive immunity*.

“How are antigen receptors formed?” or “Do antigens *select* or *instruct* cells to produce receptors against the right antigen?” The first theory proposed to answer this question was the *selective theory*. It stated that an individual has all the immune cells capable of responding to any antigen and that the introduced antigen *selects* the correct cell by interacting with specific receptors (membrane antibodies or TCRs). The interaction stimulates the cell to proliferate and differentiate and eventually to produce either specific antibody or more identical T cells. The host has preexisting immune cells for all antigens. These activities now are included in the framework of the *clonal selection*. The crux of the clonal selection is that each B- or T-cell clone synthesizes an antibody or daughter cell with a unique antigen-binding site. Before encountering an antigen, the receptor molecules are inserted into the plasma membrane, where the antibodies or TCRs serve as *membrane-bound receptors*. When antigen binds them, it stimulates the B cells to divide and differentiate into plasma cells that secrete soluble antibodies with the same antigen-binding site as the receptor form of the antibodies. The soluble antibody can react with the stimulating antigen. For T cells, it leads to clones of cells with identical TCRs.

Only nonspecific innate immune mechanisms (phagocytosis) are evident among invertebrates. Primitive fishes make only IgM-like antibodies; more classes of immunoglobulins appear in advanced vertebrates. Immune cells become progressively more specialized and interactive in higher vertebrates. In this way, phylogeny repeats ontogeny; that is, the first antibody to appear in the development of a species (*phylogeny*) is also the first to appear in the development of an individual (*ontogeny*).

## SELF-EVALUATION

### RECALLING KEY TERMS

Active immunity  
 Adaptive immunity  
 Attenuation of virulence  
 Cell-mediated immunity  
 Clonal selection  
 Cross-reactions  
 Humoral immunity  
 Immune response  
 Immunity  
 Immunization  
 Immunologic memory  
 Immunology  
 Inflammation  
 Innate immunity  
 Mononuclear phagocyte system  
 Ontogeny  
 Passive immunity  
 Phagocytosis  
 Phylogeny  
 Vaccination  
 Vaccines  
   Attenuated  
   Killed  
   Toxoids  
 Variolation

### MULTIPLE-CHOICE QUESTIONS

(An answer key is not provided, but the page[s] location of the answer is.)

1. Cowpox infection provides protection against smallpox because of (a) passive protection, (b) innate immunity, (c) cross-reactivity of causative agents, (d) similar appearance of disease, (e) none of these. (See pages 3 and 9)
2. A toxoid (a) reduces the toxic activity of a toxin, (b) enhances the toxic activity of a toxin, (c) does not induce immunity, (d) is not used as a form of vaccination, (e) is none of these. (See page 3)
3. Innate immunity is characterized by (a) a memory component, (b) an absence of specificity to commonly shared microbial antigens, (c) a primary involvement of lymphocytes, (d) no phagocytic cell involvement, (e) none of these. (See pages 5–7)
4. Attenuated vaccines were introduced by (a) Jenner, (b) Pasteur, (c) Metchnikoff, (d) Ehrlich, (e) Landsteiner, (f) none of these. (See page 3)

5. Injection of human gamma globulin to protect against hepatitis infection is an example of (a) natural, active adaptive immunity, (b) natural, passive adaptive immunity, (c) artificial, active adaptive immunity, (d) artificial, passive adaptive immunity, (e) none of these. (See page 12)
6. Which of the following is not a direct part of innate immunity? (a) Macrophages, (b) lysozyme, (c) antibodies, (d) mucus, (e) neutrophils, (f) none of these. (See pages 7 and 8)
7. Which of the following is an example of innate immunity? (a) a memory response to cowpox virus, (b) plasma cell antibody production, (c) antigen removal by respiratory tract cilia, (d) cytotoxic T cell-mediated killing of virus-infected cells, (e) antibody-induced complement activation, (f) none of these. (See page 7)
8. Which of the following is an example of active immunization? (a) immunization with cowpox virus vaccine, (b) immunization with anti-tetanus antibodies, (c) transfer of antibody through the mother's milk, (d) transfer of antibody across the placenta from mother to fetus, (e) none of these. (See pages 10–12)
9. Ontogeny recapitulates phylogeny because (a) the first antibody to appear during immunologic development in an individual is also the first to appear during immunologic development in a species, (b) the first antibody in phylogeny is IgG, (c) the fetus has passive immunity provided by the mother, (d) cell-mediated immunity is not present in the newborn, (e) of none of these. (See page 14)
10. The modern concept of clonal selection (a) was proposed by Ehrlich, (b) is unable to explain fetal tolerance, (c) holds that forbidden clones are suppressed by T cells, (d) violates the central dogma of molecular biology, (e) none of these. (See pages 12–14)
5. What are three important characteristics that set adaptive immunity apart from innate immunity? Briefly discuss each.
6. Differentiate between humoral and cell-mediated immunity.
7. Why is active immunity better than passive immunity?
8. How does clonal selection explain receptor diversity, receptor specificity, and immunologic memory?
9. Why was the discovery of DNA structure important in describing the development of antibody-mediated immunity?
10. We exist in a preimmune state. Explain.
11. What do we mean, in an immunologic sense, when we say, "ontogeny recapitulates phylogeny"?

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#### SHORT-ANSWER ESSAY QUESTIONS

1. One of the functions of the immune system is surveillance. If surveillance is naturally or artificially suppressed, what can happen to the host?
2. Differentiate between variolation and vaccination.
3. Define vaccine and name two types of vaccines and give examples of each.
4. Discuss external and internal innate defenses.

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