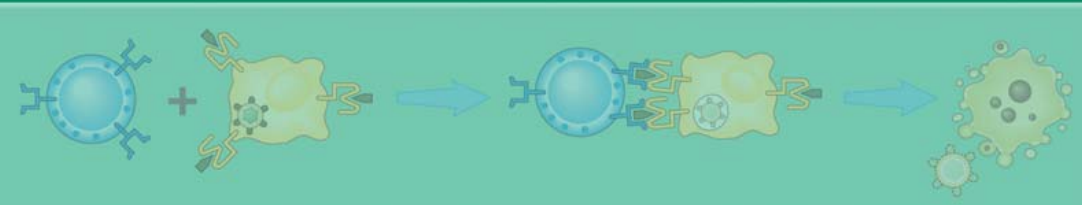
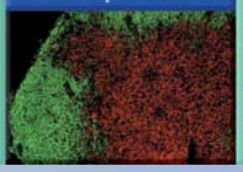


Chapter 1



INTRODUCTION TO THE IMMUNE SYSTEM

The Nomenclature, General Properties, and Components of the Immune System

Immunity is defined as resistance to disease, specifically infectious disease. The collection of cells, tissues, and molecules that mediate resistance to infections is called the **immune system,** and the coordinated reaction of these cells and molecules to infectious microbes is the **immune response.** Immunology is the study of the immune system and its responses to invading pathogens. **The physiologic function of the immune system is to prevent infections and to eradicate established infections,** and this is the principal context in which immune responses are discussed throughout this book.

The importance of the immune system for health is dramatically illustrated by the frequent observation that individuals with defective immune responses are susceptible to serious, often life-threatening infections (Fig. 1-1). Conversely, stimulating immune responses against microbes by the process of vaccination is the most effective method for protecting individuals against infections and is, for example, the approach that has led to the worldwide eradication of smallpox (Fig. 1-2). The emergence of the acquired immunodeficiency syndrome (AIDS) since the 1980s has tragically emphasized the importance of the immune system for defending individuals against infection. The impact of immunology, however, goes beyond infectious disease (see Fig. 1-1). The immune response is the major barrier to successful organ transplantation, an increasingly used therapy for organ failure. Attempts to treat cancers by stimulating immune responses against cancer cells are being tried for many

Role of the immune system	Implications
Defense against infections	Deficient immunity results in increased susceptibility to infections; exemplified by AIDS Vaccination boosts immune defenses and protects against infections
The immune system recognizes and responds to tissue grafts and newly introduced proteins	Immune responses are barriers to transplantation and gene therapy
Defense against tumors	Potential for immunotherapy of cancer

FIGURE 1-1 The importance of the immune system in health and disease. This table summarizes some of the physiologic functions of the immune system. Note that immune responses are also the causes of diseases. AIDS, acquired immunodeficiency syndrome.

human malignancies. Furthermore, abnormal immune responses are the causes of many inflammatory diseases with serious morbidity and mortality. Antibodies, one of the products of immune responses, are highly specific reagents for detecting a wide variety of molecules in the circulation and in cells and tissues and have therefore become invaluable reagents for laboratory testing in clinical medicine and research. Antibodies designed to block or eliminate potentially harmful molecules and cells are in widespread use for the treatment of immunologic diseases, cancers, and other types of disorders. For all of these reasons, the field of immunology has captured the attention of clinicians, scientists, and the lay public.

Disease	Maximum number of cases (year)	Number of cases in 2004	Percent change
Diphtheria	206,939 (1921)	0	-99.99
Measles	894,134 (1941)	37	-99.99
Mumps	152,209 (1968)	236	-99.90
Pertussis	265,269 (1934)	18,957	-96.84
Polio (paralytic)	21,269 (1952)	0	-100.0
Rubella	57,686 (1969)	12	-99.98
Tetanus	1,560 (1923)	26	-98.33
Haemophilus influenzae type b infection	~20,000 (1984)	16	-99.92
Hepatitis B	26,611 (1985)	6,632	-75.08

FIGURE 1-2 The effectiveness of vaccination for some common infectious diseases. This table illustrates the striking decrease in the incidence of selected infectious diseases for which effective vaccines have been developed. In some cases, such as with hepatitis B, a vaccine has become available recently, and the incidence of the disease is continuing to decrease. (Adapted from Orenstein WA, Hinman AR, Bart KJ, Hadler SC: Immunization. In Mandell GL, Bennett JE, Dolin R (eds): Principles and Practices of Infectious Diseases, 4th ed. New York, Churchill Livingstone, 1995; and Morbidity and Mortality Weekly Report 53:1213-1221, 2005.)

In this opening chapter of the book, we introduce the nomenclature of immunology, some of the important general properties of all immune responses, and the cells and tissues that are the principal components of the immune system. In particular, the following questions are addressed:

- What types of immune responses protect individuals from infections?
- What are the important characteristics of immunity, and what mechanisms are responsible for these characteristics?
- How are the cells and tissues of the immune system organized to find microbes and respond to them in ways that lead to their elimination?

We conclude the chapter with a brief overview of immune responses against microbes. The basic principles that are introduced in this chapter set the stage for more detailed discussions of immune responses in the remainder of the book. A glossary of the important terms used in the book is provided in Appendix I.

Innate and Adaptive Immunity

Host defense mechanisms consist of innate immunity, which mediates the initial protection against infections, and adaptive immunity, which develops more slowly and mediates the later, even more effective, defense against infections (Fig. 1-3). The term **innate immunity** (also called natural or native immunity) refers to the fact that this type of host defense is always present in healthy individuals, prepared to block the entry of microbes and to rapidly eliminate microbes that do succeed in entering host tissues. **Adaptive immunity** (also called specific or acquired immunity) is the type of host defense that is stimulated by microbes that invade tissues, that is, it adapts to the presence of microbial invaders.

The first line of defense in innate immunity is provided by epithelial barriers and by specialized cells and natural antibiotics present in epithelia, all of which function to block the entry of microbes. If microbes do breach epithelia and enter the tissues or

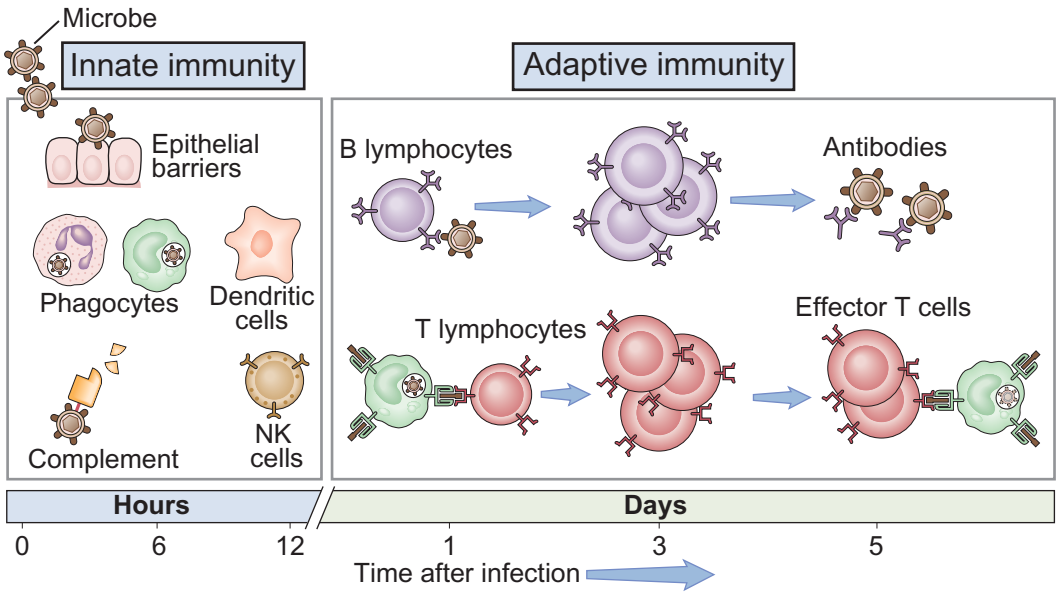


FIGURE 1-3 The principal mechanisms of innate and adaptive immunity. The mechanisms of innate immunity provide the initial defense against infections. Some of the mechanisms prevent infections (e.g., epithelial barriers) and others eliminate microbes (e.g., phagocytes, natural killer [NK] cells, the complement system). Adaptive immune responses develop later and are mediated by lymphocytes and their products. Antibodies block infections and eliminate microbes, and T lymphocytes eradicate intracellular microbes. The kinetics of the innate and adaptive immune responses are approximations and may vary in different infections.

circulation, they are attacked by phagocytes, specialized lymphocytes called natural killer cells, and several plasma proteins, including the proteins of the complement system. All of these agents of innate immunity specifically recognize and react against microbes but do not react against noninfectious foreign substances. Different components of innate immunity may be specific for molecules produced by different classes of microbes. In addition to providing early defense against infections, innate immune responses enhance adaptive immune responses against the infectious agents. The components and mechanisms of innate immunity are discussed in detail in Chapter 2.

Although innate immunity can effectively combat infections, many microbes that are pathogenic for humans (i.e., capable of causing disease) have evolved to resist innate immunity. Defense against these infectious agents is the task of the adaptive immune response, and this is why defects in the adaptive immune system result in increased susceptibility to infections. **The adaptive immune system consists of lymphocytes and their products, such as antibodies.** Whereas the mechanisms of innate immunity recognize structures shared by classes of microbes, the cells of adaptive immunity, namely, lymphocytes, express receptors that specifically recognize different substances produced by microbes as well as noninfectious molecules. These substances are called **antigens.** Adaptive immune responses are triggered only if microbes or their antigens pass through epithelial barriers and are delivered to lymphoid organs where they can be recognized by lymphocytes. Adaptive immune responses are specialized to combat different types of infections. For example, antibodies function to eliminate microbes in extracellular fluids, and activated T lymphocytes eliminate microbes living inside cells. These specialized mechanisms of adaptive immunity are described throughout the book. Adaptive immune responses often use the cells and molecules of the innate immune system to eliminate microbes, and adaptive immunity functions to greatly enhance these antimicrobial mechanisms of innate immunity. For instance, antibodies (a component of adaptive immunity) bind to microbes, and these coated microbes avidly bind to and activate phagocytes (a component of innate immunity), which ingest and destroy the microbes. Many similar examples of the cooperation between innate and adaptive immunity are referred to in later chapters. By convention, the terms ***immune system*** and ***immune response*** refer to adaptive immunity, unless stated otherwise.

Types of Adaptive Immunity

The two types of adaptive immunity, *humoral immunity* and *cell-mediated immunity*, are mediated by different cells and molecules and are designed to provide defense against extracellular microbes and intracellular microbes, respectively (Fig. 1-4). Humoral immunity is mediated by proteins called **antibodies,** which are produced by cells called **B lymphocytes.** Antibodies are secreted into the circulation and mucosal fluids, and they neutralize and eliminate microbes and microbial toxins that are present outside of host cells, in the blood and in the lumens of mucosal organs, such as the gastrointestinal and respiratory tracts. One of the most important functions of antibodies is to stop microbes that are present at mucosal surfaces and in the blood from gaining access to and colonizing host cells and connective tissues. In this way, antibodies prevent infections from ever getting established. Antibodies cannot gain access to microbes that live and divide inside infected cells. Defense against such intracellular microbes is called cell-mediated immunity because it is mediated by cells called **T lymphocytes.** Some T lymphocytes activate phagocytes to destroy microbes that have been ingested by the phagocytes into intracellular vesicles. Other T lymphocytes kill any type of host cells that are harboring infectious microbes in the cytoplasm. Thus, the antibodies produced by B lymphocytes recognize extracellular microbial antigens, whereas T lymphocytes recognize antigens produced by intracellular microbes. Another important difference between B and T lymphocytes is that most T cells recognize only protein antigens, whereas antibodies are able to recognize many different types of molecules, including proteins, carbohydrates, and lipids.

Immunity may be induced in an individual by infection or vaccination (*active immunity*) or conferred on an individual by transfer of antibodies or lymphocytes from an actively immunized individual (*passive immunity*). An individual exposed to the antigens of a microbe mounts an active response to

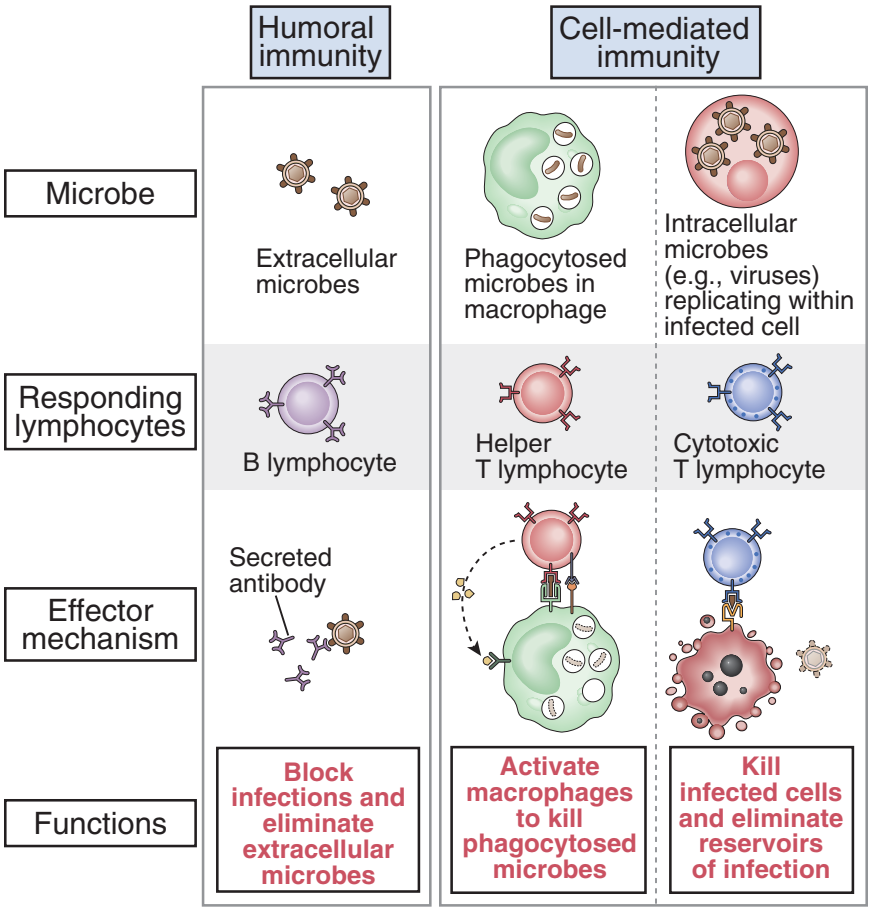


FIGURE 1-4 Types of adaptive immunity. In humoral immunity, B lymphocytes secrete antibodies that eliminate extracellular microbes. In cell-mediated immunity, T lymphocytes either activate macrophages to destroy phagocytosed microbes or kill infected cells.

eradicate the infection and develops resistance to later infection by that microbe. Such an individual is said to be *immune* to that microbe, in contrast with a *naive* individual, not previously exposed to that microbe's antigens. We shall be concerned mainly with the mechanisms of active immunity. In passive immunity, a naive individual receives cells (e.g., lymphocytes, feasible only in genetically identical [inbred] animals) or molecules (e.g., antibodies) from another individual already immune to an infection; for the lifetime of the transferred antibodies or cells, the recipient is able to combat the infection. Passive immunity is therefore useful for rapidly conferring immunity even before the individual is able to mount an active response, but it does not induce long-lived resistance to the infection. An excellent example of passive immunity is seen in newborns, whose immune systems are not mature enough to respond to many pathogens but who are protected against infections by acquiring antibodies from their mothers through the placenta and in milk.

Properties of Adaptive Immune Responses

Several properties of adaptive immune responses are crucial for the effectiveness of these responses in combating infections (Fig. 1-5).

Feature	Functional significance
Specificity	Ensures that distinct antigens elicit specific responses
Diversity	Enables immune system to respond to a large variety of antigens
Memory	Leads to enhanced responses to repeated exposures to the same antigens
Clonal expansion	Increases number of antigen-specific lymphocytes to keep pace with microbes
Specialization	Generates responses that are optimal for defense against different types of microbes
Contraction and homeostasis	Allows immune system to respond to newly encountered antigens
Nonreactivity to self	Prevents injury to the host during responses to foreign antigens

FIGURE 1-5 Properties of adaptive immune responses. The important properties of adaptive immune responses, and how each feature contributes to host defense against microbes, are summarized.

SPECIFICITY AND DIVERSITY

The adaptive immune system is capable of distinguishing among millions of different antigens or portions of antigens. Specificity for many different antigens implies that the total collection of lymphocyte specificities, sometimes called the lymphocyte repertoire, is extremely diverse. The basis of this remarkable specificity and diversity is that lymphocytes express clonally distributed receptors for antigens, meaning that the total population of lymphocytes consists of many different clones (each of which is made up of one cell and its progeny), and each clone expresses an antigen receptor that is different from the receptors of all other clones. The clonal selection hypothesis, formulated in the 1950s, correctly predicted that clones of lymphocytes specific for different antigens arise before encounter with these antigens, and each antigen elicits an immune response by selecting and activating the lymphocytes of a specific clone (Fig. 1-6). We now know how the specificity and diversity of lymphocytes are generated (see Chapter 4).

The diversity of lymphocyte means that very few cells, perhaps as few as one in 100,000 lymphocytes, are specific for any one antigen. In order to mount effective defense against microbes, these few cells have to proliferate to generate a large number of cells capable of combating the microbes. The remarkable effectiveness of immune responses is possible because of several features of adaptive immunity–marked expansion of the pool of lymphocytes specific for any antigen subsequent to exposure to that antigen, positive feedback loops that amplify immune responses, and selection mechanisms that preserve the most useful lymphocytes. We will describe these characteristics of the adaptive immune system in later chapters.

MEMORY

The immune system mounts larger and more effective responses to repeated exposures to the same antigen. The response to the first exposure to antigen, called the **primary immune response,** is mediated by lymphocytes, called **naive lymphocytes,** that are seeing antigen for the first time (Fig. 1-7). The term *naive* refers to the fact that these cells are "immunologically inexperienced," not having previously recognized and responded to antigens. Subsequent encounters with the same antigen lead to responses, called **secondary immune responses,** that usually are more rapid, larger, and better able to eliminate the antigen than are the primary responses (see Fig. 1-7). Secondary responses are the result of the activation of **memory lymphocytes,** which are long-lived cells that were induced during the primary immune response. Immunologic memory optimizes the ability of the immune system to combat persistent and recurrent infections, because each encounter with a microbe generates more memory cells and activates previously generated memory cells. Memory also is one of the reasons

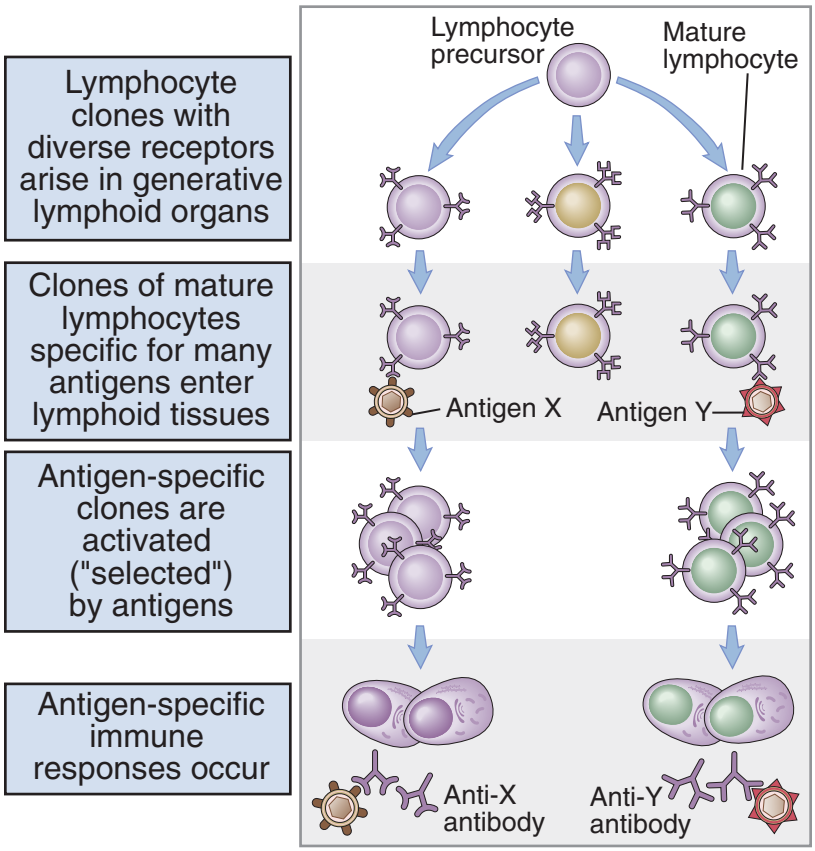


FIGURE 1-6 Clonal selection. Mature lymphocytes with receptors for many antigens develop before encounter with these antigens. A clone refers to a population of lymphocytes with identical antigen receptors and, therefore, specificities; all these cells are presumably derived from one precursor cell. Each antigen (e.g., the examples X and Y) selects a preexisting clone of specific lymphocytes and stimulates the proliferation and differentiation of that clone. The diagram shows only B lymphocytes giving rise to antibody-secreting effector cells, but the same principle applies to T lymphocytes. The antigens shown are surface molecules of microbes, but clonal selection also is true for soluble antigens.

why vaccines confer long-lasting protection against infections.

OTHER FEATURES OF ADAPTIVE IMMUNITY

Adaptive immune responses have other characteristics that are important for their functions (see Fig. 1-5). When lymphocytes are activated by antigens, they undergo proliferation, generating many thousands of clonal progeny cells, all with the same antigen specificity. This process, called **clonal expansion,** ensures that adaptive immunity keeps pace with rapidly proliferating microbes. Immune responses are specialized, and different responses are designed to best defend against different classes of microbes. All immune responses are self-limited and decline as the infection is eliminated, allowing the system to return to a resting state, prepared to respond to another infection. The immune system is able to react against an enormous number and variety of microbes and other foreign antigens, but it normally does not react against the host's own potentially antigenic substances—so-called self antigens.

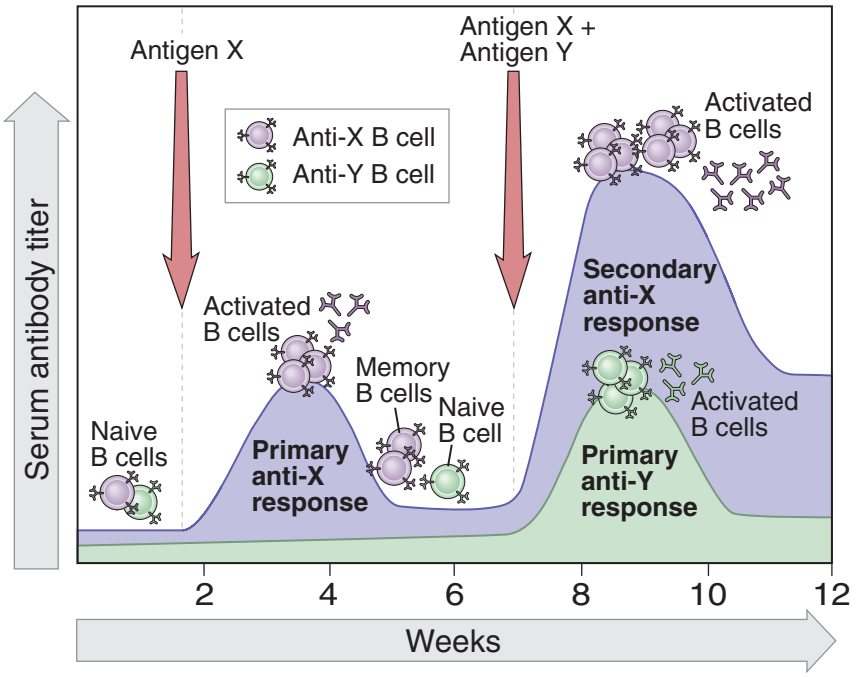


FIGURE 1-7 Primary and secondary immune responses. Antigens X and Y induce the production of different antibodies (a reflection of specificity). The secondary response to antigen X is more rapid and larger than the primary response (illustrating memory) and is different from the primary response to antigen Y (again reflecting specificity). Antibody levels decline with time after each immunization.

Cells of the Immune System

The cells of the immune system consist of lymphocytes, specialized cells that capture and display microbial antigens, and effector cells that eliminate microbes (Fig. 1-8). In the following section the important functional properties of the major cell populations are discussed; the details of the morphology of these cells may be found in histology textbooks.

LYMPHOCYTES

Lymphocytes are the only cells that produce specific receptors for antigens and are thus the key mediators of adaptive immunity. Although all lymphocytes are morphologically similar and rather unremarkable in appearance, they are extremely heterogeneous in lineage, function, and phenotype and are capable of complex biologic responses and activities (Fig. 1-9). These cells often are distinguishable by surface proteins that may be identified using panels of monoclonal antibodies. The standard nomenclature for these proteins is the *CD* (cluster of differentiation) numerical designation, which is used to delineate surface proteins that define a particular cell type or stage of cell differentiation and are recognized by a cluster or group of antibodies. (A list of CD molecules mentioned in the book is provided in Appendix II.)

As alluded to earlier, B lymphocytes are the only cells capable of producing antibodies; therefore, they are the cells that mediate humoral immunity. B cells express membrane forms of antibodies that serve as the receptors that recognize antigens and initiate the process of activation of the cells. Soluble antigens and antigens on the surface of microbes and other cells may bind to these B lymphocyte antigen receptors and elicit humoral immune responses. T lymphocytes are the cells of cell-mediated immunity. The antigen receptors of most T lymphocytes only recognize peptide fragments of protein antigens that are bound to specialized peptide display molecules

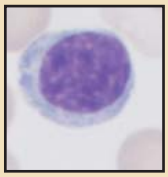
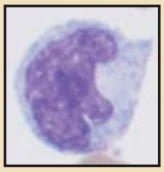
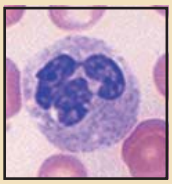
Cell type	Principal function(s)
Lymphocytes: B lymphocytes; T lymphocytes; natural killer cells  *Blood lymphocyte*	Specific recognition of antigens: B lymphocytes: mediators of humoral immunity T lymphocytes: mediators of cell-mediated immunity Natural killer cells: cells of innate immunity
Antigen-presenting cells: dendritic cells; macrophages; follicular dendritic cells  *Dendritic cell*  *Blood monocyte*	Capture of antigens for display to lymphocytes: Dendritic cells: initiation of T cell responses Macrophages: initiation and effector phase of cell-mediated immunity Follicular dendritic cells: display of antigens to B lymphocytes in humoral immune responses
Effector cells: T lymphocytes; macrophages; granulocytes  *Neutrophil*	Elimination of antigens: T lymphocytes: helper T cells and cytotoxic T lymphocytes Macrophages and monocytes: cells of the mononuclear-phagocyte system Granulocytes: neutrophils, eosinophils

FIGURE 1-8 The principal cells of the immune system. The major cell types involved in immune responses, and their functions, are shown. Micrographs in the *left panels* illustrate the morphology of some of the cells of each type. Note that tissue macrophages are derived from blood monocytes.

called major histocompatibility complex (MHC) molecules, on the surface of specialized cells called antigen-presenting cells (APCs) (see Chapter 3). Among T lymphocytes, $CD4^+$ T cells are called **helper T cells** because they help B lymphocytes to produce antibodies and help phagocytes to destroy ingested microbes. Some $CD4^+$ T cells belong to a special subset that functions to prevent or limit immune responses; these are called **regulatory T lymphocytes.** $CD8^+$ T lymphocytes are called **cytotoxic, or cytolytic, T lymphocytes (CTLs)** because they kill ("lyse") cells harboring intracellular microbes. A third class of lymphocytes is called **natural killer (NK) cells;** these cells also kill infected host cells, but they do not express the kinds of clonally distributed antigen receptors that B cells and T cells do and are components of innate immunity, capable of rapidly attacking infected cells.

All lymphocytes arise from stem cells in the bone marrow (Fig. 1-10). **B lymphocytes mature in the bone marrow, and T lymphocytes mature in an organ called the thymus;** these sites in which mature

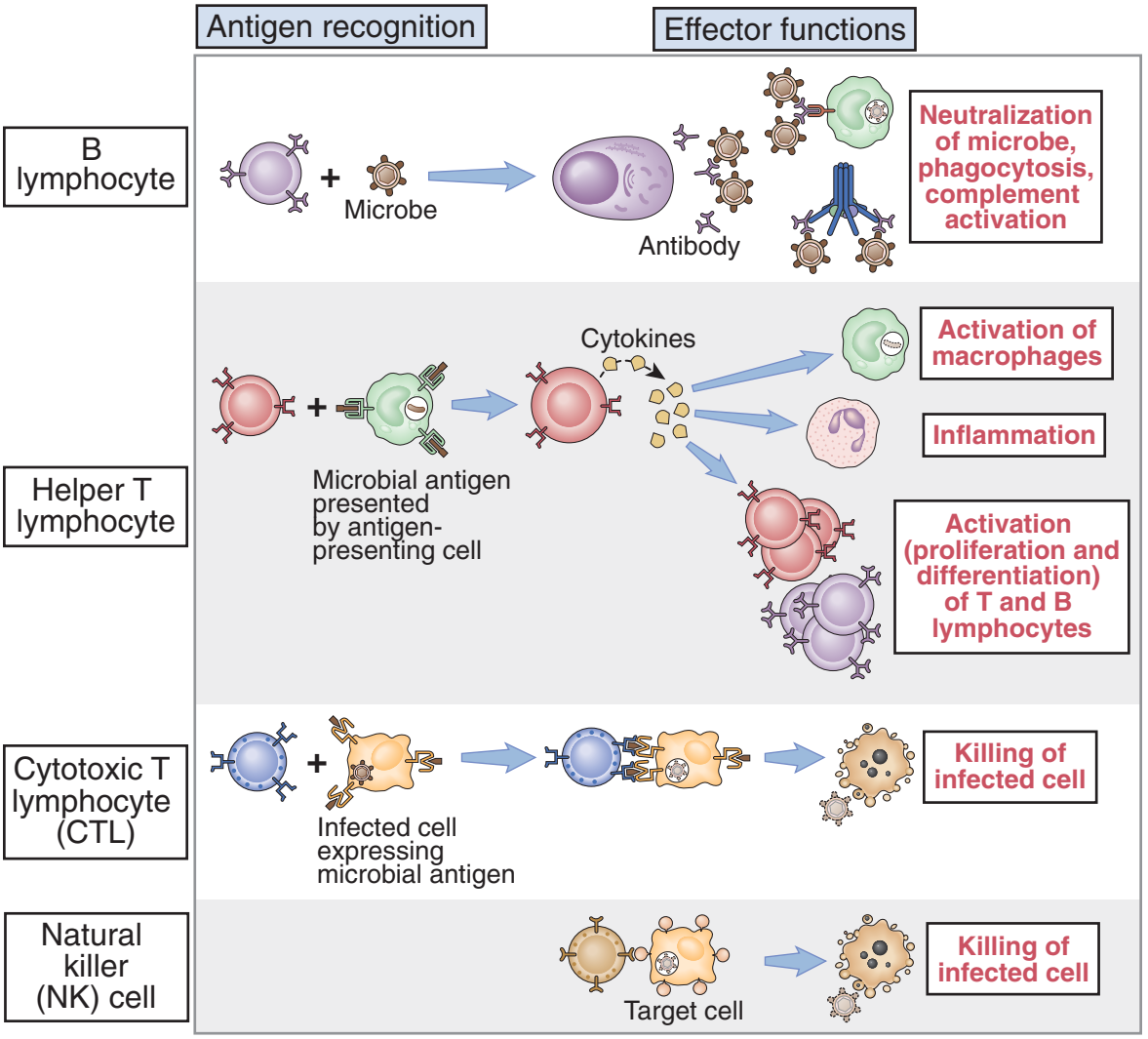


FIGURE 1-9 Classes of lymphocytes. Different classes of lymphocytes recognize distinct types of antigens and differentiate into effector cells whose function is to eliminate the antigens. B lymphocytes recognize soluble or cell surface antigens and differentiate into antibody-secreting cells. Helper T lymphocytes recognize antigens on the surfaces of antigen-presenting cells and secrete cytokines, which stimulate different mechanisms of immunity and inflammation. Cytotoxic (cytolytic) T lymphocytes recognize antigens on infected cells and kill these cells. (Note that T lymphocytes recognize peptides that are displayed by major histocompatibility complex (MHC) molecules; this process is discussed in Chapter 3.) Natural killer cells recognize changes on the surface of infected cells and kill these cells. Regulatory T cells are not shown in the figure.

lymphocytes are produced are called the generative lymphoid organs. Mature lymphocytes leave the generative lymphoid organs and enter the circulation and the peripheral lymphoid organs, where they may encounter antigen for which they express specific receptors. A normal adult contains approximately 10^{12} lymphocytes in the circulation and lymphoid tissues.

When naive lymphocytes recognize microbial antigens and also receive additional signals

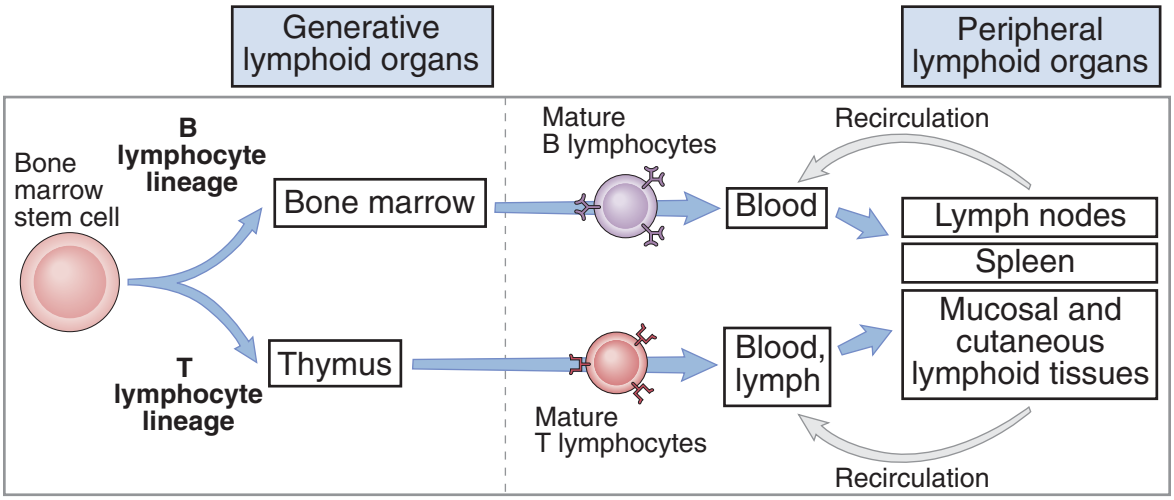
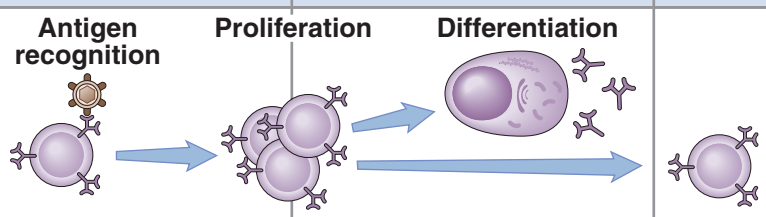
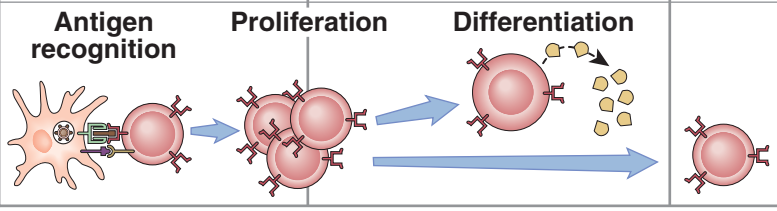


FIGURE 1-10 Maturation of lymphocytes. Lymphocytes develop from precursors in the generative lymphoid organs (the bone marrow and thymus). Mature lymphocytes enter the peripheral lymphoid organs, where they respond to foreign antigens and from where they recirculate in the blood and lymph.

induced by microbes, the antigen-specific lymphocytes proliferate and differentiate into effector cells and memory cells (Fig. 1-11). **Naive lymphocytes** express receptors for antigens but do not perform the functions that are required to eliminate antigens. These cells reside in and circulate between peripheral lymphoid organs and survive for several weeks or months, waiting to find and respond to antigen. If they are not activated by antigen, naive lymphocytes die by the process of apoptosis and are replaced by new cells that have arisen in the generative lymphoid organs. This cycle of cell loss and replacement maintains a stable number of lymphocytes, a phenomenon called **homeostasis.** The differentiation of naive lymphocytes into effector cells and memory cells is initiated by antigen recognition, thus ensuring that the immune response that develops is specific for the antigen. **Effector cells** are the differentiated progeny of naive cells that have the ability to produce molecules that function to eliminate antigens. The effector cells in the B lymphocyte lineage are antibody-secreting cells, called **plasma cells.** Effector $CD4^+$ T cells (helper T cells) produce proteins called cytokines that activate B cells and macrophages, thereby mediating the helper function of this lineage, and effector $CD8^+$ T cells (CTLs) have the machinery to kill infected host cells. The development and functions of these effector cells are discussed in later chapters. Most effector lymphocytes are short-lived and die as the antigen is eliminated, but some may migrate to special anatomic sites and live for long periods. This prolonged survival of effector cells is best documented for antibody-producing plasma cells, which develop in response to microbes in the peripheral lymphoid organs but may then migrate to the bone marrow and continue to produce small amounts of antibody long after the infection is eradicated. **Memory cells,** which also are generated from the progeny of antigen-stimulated lymphocytes, do survive for long periods of time in the absence of antigen. Therefore, the frequency of memory cells increases with age, presumably because of exposure to environmental microbes. In fact, memory cells make up less than 5% of peripheral blood T cells in a newborn, but 50% or more in an adult. Memory cells are functionally inactive—they do not perform effector functions unless stimulated by antigen. When memory cells encounter the same antigen that induced their development, the cells rapidly respond to give rise to secondary immune responses. Very little is known about the signals that generate memory cells, the factors that determine whether the progeny of

A

Cell type	Stage		
	Naive cells	Effector cells	Memory cells
B lymphocytes			
Helper T lymphocytes			

B

Property	Stage		
	Naive cells	Effector cells	Memory cells
Antigen receptor	Yes	B cells: reduced T cells: Yes	Yes
Lifespan	Weeks or months	Usually short (days)	Long (years)
Effector function	None	Yes B cells: antibody secretion Helper T cells: cytokine secretion CTLs: cell killing	None
Special characteristics			
B cells			
Affinity of Ig	Low	Variable	High (affinity maturation)
Isotype of Ig	Membrane-associated IgM, IgD	Membrane-associated and secreted IgM, IgG, IgA, IgE (class switching)	Various
T cells			
Migration	To lymph nodes	To peripheral tissues (sites of infection)	To lymph nodes and mucosal and other tissues

FIGURE 1-11 Stages in the life history of lymphocytes. A, Naive lymphocytes recognize foreign antigens to initiate adaptive immune responses. Some of the progeny of these lymphocytes differentiate into effector cells, whose function is to eliminate antigens. The effector cells of the B lymphocyte lineage are antibody-secreting plasma cells (some of which are long-lived). The effector cells of the $CD4^+$ T lymphocyte lineage produce cytokines. (The effector cells of the $CD8^+$ lineage are CTLs; these are not shown.) Other progeny of the antigen-stimulated lymphocytes differentiate into long-lived memory cells. **B,** The important characteristics of naive, effector, and memory cells in the B and T lymphocyte lineages are summarized. The processes of affinity maturation and class switching in B cells are described in Chapter 7. Ig, immunoglobulin.

antigen-stimulated lymphocytes will develop into effector or memory cells, or the mechanisms that keep memory cells alive in the absence of antigen or innate immunity.

ANTIGEN-PRESENTING CELLS

The common portals of entry for microbes—the skin, gastrointestinal tract, and respiratory tract—contain specialized antigen-presenting cells (APCs) located in the epithelium that capture antigens, transport them to peripheral lymphoid tissues, and display them to lymphocytes. This function of antigen capture and presentation is best understood for a cell type called **dendritic cells** because of their long processes. Dendritic cells capture protein antigens of microbes that enter through the epithelia and transport the antigens to regional lymph nodes. Here the antigen-bearing dendritic cells display portions of the antigens for recognition by T lymphocytes. If a microbe has invaded through the epithelium, it may be phagocytosed by macrophages that live in tissues and in various organs. Macrophages are also capable of presenting protein antigens to T cells. The process of antigen presentation to T cells is described in Chapter 3.

Cells that are specialized to display antigens to T lymphocytes have another important feature that gives them the ability to trigger T cell responses. These specialized cells respond to microbes by producing surface and secreted proteins that are required, together with antigen, to activate naive T lymphocytes to proliferate and differentiate into effector cells. Specialized cells that display antigens to T cells and provide additional activating signals sometimes are called "professional APCs." The prototypical professional APCs are dendritic cells, but macrophages and a few other cell types may serve the same function.

Less is known about cells that may capture antigens for display to B lymphocytes. B lymphocytes may directly recognize the antigens of microbes (either released or on the surface of the microbes), or macrophages lining lymphatic channels may capture antigens and display them to B cells. A type of dendritic cell called the follicular dendritic cell (FDC) resides in the germinal centers of lymphoid follicles in the peripheral lymphoid organs and displays antigens that stimulate the differentiation of B cells in the follicles. The role of FDCs is described in more detail in Chapter 7. FDCs do not present antigens to T cells and are quite different from the dendritic cells described earlier that function as APCs for T lymphocytes.

EFFECTOR CELLS

The cells that eliminate microbes are called effector cells and consist of lymphocytes and other leukocytes. The effector cells of the B and T lymphocyte lineages were mentioned earlier. The elimination of microbes often requires the participation of other, nonlymphoid leukocytes, such as granulocytes and macrophages. These leukocytes may function as effector cells in both innate immunity and adaptive immunity. In innate immunity, macrophages and some granulocytes directly recognize microbes and eliminate them (see Chapter 2). In adaptive immunity, the products of B and T lymphocytes call in other leukocytes and activate them to kill microbes.

Tissues of the Immune System

The tissues of the immune system consist of the generative (also called primary, or central) lymphoid organs, in which T and B lymphocytes mature and become competent to respond to antigens, and the peripheral (or secondary) lymphoid organs, in which adaptive immune responses to microbes are initiated (see Fig. 1-10). The generative lymphoid organs are described in Chapter 4, when we discuss the process of lymphocyte maturation. In the

following section, we highlight some of the features of peripheral lymphoid organs that are important for the development of adaptive immunity.

PERIPHERAL LYMPHOID ORGANS

The peripheral lymphoid organs, which consist of the lymph nodes, the spleen, and the mucosal and cutaneous immune systems, are organized to optimize interactions of antigens, APCs, and lymphocytes in a way that promotes the development of adaptive immune responses. The immune system has to locate microbes that enter at any site in the body and then respond to these microbes and eliminate them. In addition, as we have mentioned earlier, in the normal immune system very few T and B lymphocytes are specific for any one antigen—perhaps as few as 1 in 100,000 cells. The anatomic organization of peripheral lymphoid organs enables APCs to concentrate antigens in these organs and lymphocytes to locate and respond to the antigens. This organization is complemented by a remarkable ability of lymphocytes to circulate throughout the body in such a way that naive lymphocytes preferentially go to the specialized organs in which antigen is concentrated and effector cells go to sites of infection, from where microbes have to be eliminated. Furthermore, different types of lymphocytes often need to communicate to generate effective immune responses. For instance, helper T cells specific for an antigen interact with and help B lymphocytes specific for the same antigen, resulting in antibody production. An important function of lymphoid organs is to bring these rare cells together in a way that will enable them to interact productively.

Lymph nodes are nodular aggregates of lymphoid tissues located along lymphatic channels throughout the body (Fig. 1-12). Fluid from all epithelia and connective tissues and most parenchymal organs is drained by lymphatics, which transport this fluid, called lymph, from the tissues to the lymph nodes. Therefore, the lymph contains a mixture of substances that are absorbed from epithelia and tissues. As the lymph passes through lymph nodes, APCs in the nodes are able to sample the antigens of microbes that may enter through epithelia into tissues. In addition, dendritic cells pick up antigens of microbes from epithelia and transport these antigens to the lymph nodes. The net result of these processes of antigen capture and trans-

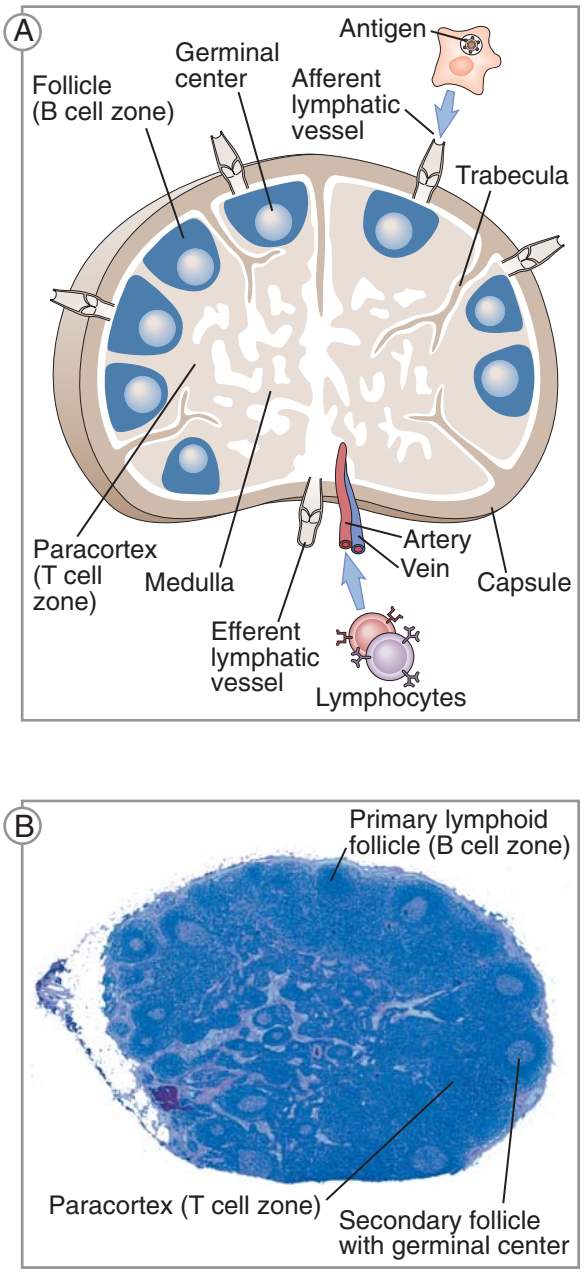


FIGURE 1-12 **The morphology of lymph nodes. A,** This schematic diagram shows the structural organization and blood flow in a lymph node. **B,** This light micrograph shows a cross section of a lymph node with numerous follicles in the cortex, some of which contain lightly stained central areas (germinal centers), and the central medulla.

port is that the antigens of microbes that enter through epithelia or colonize tissues become concentrated in draining lymph nodes.

The **spleen** (Fig. 1-13) is an abdominal organ that serves the same role in immune responses to blood-borne antigens as that of lymph nodes in responses to lymph-borne antigens. Blood entering the spleen flows through a network of channels (sinusoids). Blood-borne antigens are trapped and concentrated by dendritic cells and macrophages in the spleen. The spleen contains abundant phagocytes, which ingest and destroy microbes in the blood.

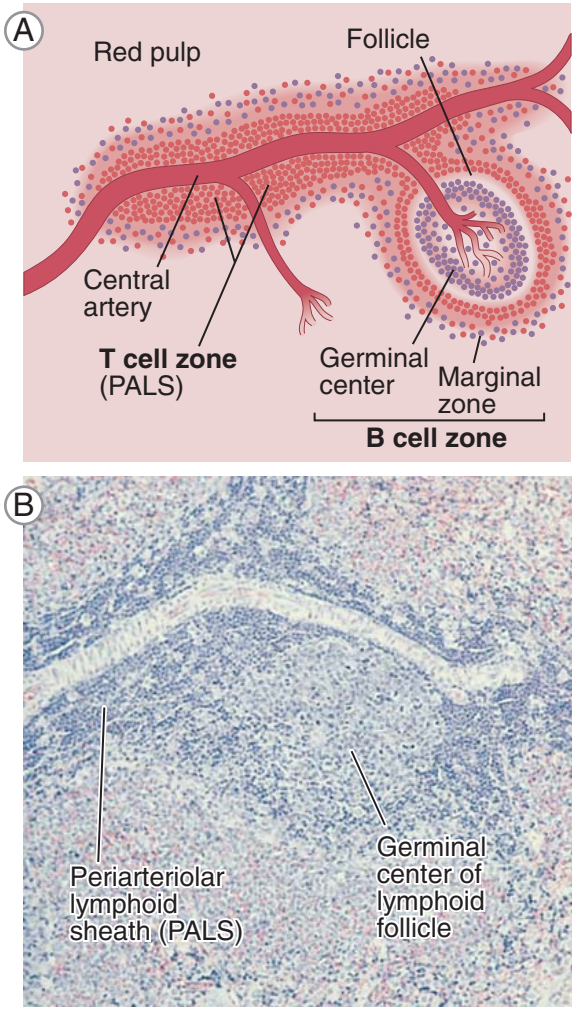


FIGURE 1-13 **The morphology of the spleen. A,** This schematic diagram shows a splenic arteriole surrounded by the periarteriolar lymphoid sheath (PALS) and attached follicle containing a prominent germinal center. The PALS and lymphoid follicles together constitute the white pulp. **B,** This light micrograph of a section of a spleen shows an arteriole with the PALS and a secondary follicle. These are surrounded by the red pulp, which is rich in vascular sinusoids.

The cutaneous and mucosal lymphoid systems are located under the epithelia of the skin and the gastrointestinal and respiratory tracts, respectively. Pharyngeal tonsils and Peyer's patches of the intestine are two anatomically defined mucosal lymphoid tissues. At any time, more than half of the body's lymphocytes are in the mucosal tissues (reflecting the large size of these tissues), and many of these are memory cells. Cutaneous and mucosal lymphoid tissues are sites of immune responses to antigens that breach epithelia.

Within the peripheral lymphoid organs, T lymphocytes and B lymphocytes are segregated into different anatomic compartments (Fig. 1-14). In lymph nodes, the B cells are concentrated in discrete structures, called **follicles**, located around the periphery, or cortex, of each node. If the B cells in a follicle have recently responded to an antigen, this follicle may contain a central region called a **germinal center**. The role of germinal centers in the production of antibodies is described in Chapter 7. The T lymphocytes are concentrated outside, but adjacent to, the follicles, in the paracortex. The follicles contain the FDCs that are involved in the activation of B cells, and the paracortex contains the dendritic cells that present antigens to T lymphocytes. In the spleen, T lymphocytes are concentrated in periarteriolar lymphoid sheaths surrounding small arterioles, and B cells reside in the follicles.

The anatomic organization of peripheral lymphoid organs is tightly regulated to allow immune responses to develop. B lymphocytes are located in the follicles because FDCs secrete a protein that belongs to a class of cytokines called chemokines ("chemoattractant cytokines"), for which naive B cells express a receptor. (Chemokines and other cytokines are discussed in more detail in later chapters.) This chemokine is produced all the time, and it attracts B cells from the blood into the follicles of lymphoid organs. Similarly, T cells are segregated in the paracortex of lymph nodes and the periarteriolar lymphoid sheaths of the spleen, because naive T lymphocytes express a receptor, called

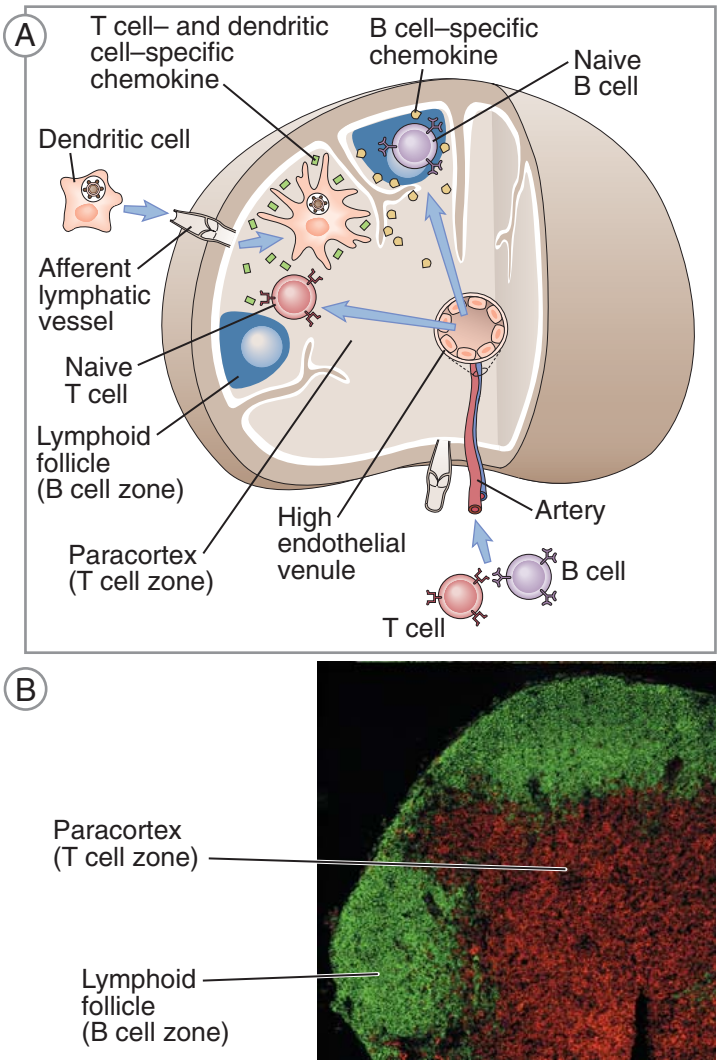


FIGURE 1-14 Segregation of T and B lymphocytes in different regions of peripheral lymphoid organs. A, This schematic diagram illustrates the path by which naive T and B lymphocytes migrate to different areas of a lymph node. The lymphocytes enter through a high endothelial venule (HEV), shown in cross section, and are drawn to different areas of the node by chemokines that are produced in these areas and bind selectively to either cell type. Also shown is the migration of dendritic cells, which pick up antigens from epithelia, enter through afferent lymphatic vessels, and migrate to the T cell–rich areas of the node. **B,** In this section of a lymph node, the B lymphocytes, located in the follicles, are stained green, and the T cells, in the parafollicular cortex, are red. The method used to stain these cells is called immunofluorescence. In this technique, a section of the tissue is stained with antibodies specific for T or B cells that are coupled to fluorochromes that emit different colors when excited at the appropriate wavelengths. The anatomic segregation of T and B cells also occurs in the spleen (not shown). (Courtesy of Drs. Kathryn Pape and Jennifer Walter, University of Minnesota Medical School, Minneapolis.)

CCR7, that recognizes chemokines that are produced in these regions of the lymph nodes and spleen. As a result, T lymphocytes are recruited from the blood into the parafollicular cortex region of the lymph node and the periarteriolar lymphoid sheaths of the spleen. When the lymphocytes are activated by microbial antigens, they alter their expression of the chemokine receptors. As a result, the B cells and T cells migrate toward each other and meet at the edge of follicles, where helper T cells interact with and help B cells to differentiate into antibody-producing cells (see Chapter 7). The activated lymphocytes ultimately exit the node through efferent lymphatic vessels and leave the spleen through veins. These activated lymphocytes end up in the circulation and can go to distant sites of infection.

LYMPHOCYTE RECIRCULATION AND MIGRATION INTO TISSUES

Naive lymphocytes constantly recirculate between the blood and peripheral lymphoid organs, where they may be activated by antigens to become effector cells, and the effector lymphocytes migrate to sites of infection, where microbes are eliminated

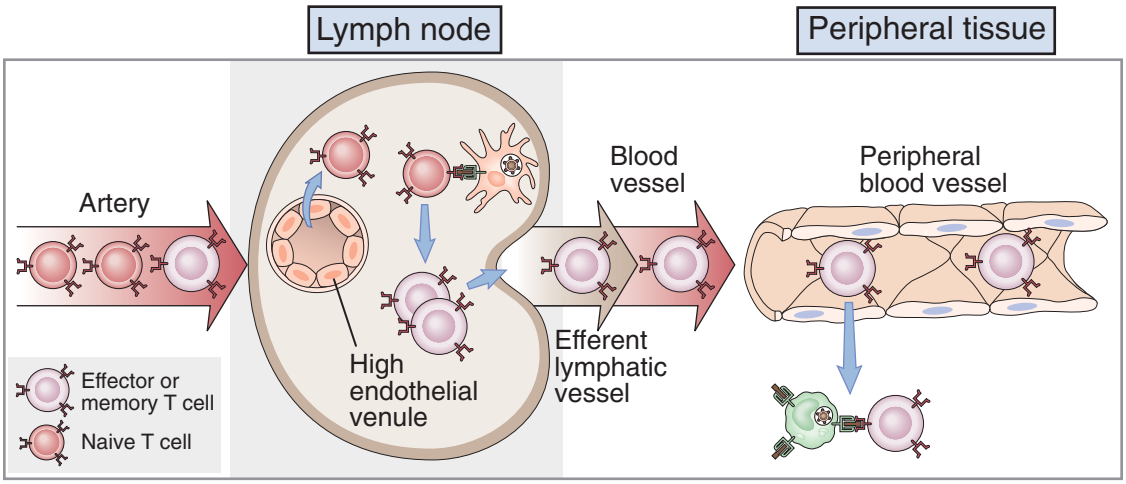


FIGURE 1-15 Migration of T lymphocytes. Naive T lymphocytes migrate from the blood through high endothelial venules (HEVs) into the T cell zones of lymph nodes, where the cells are activated by antigens. Activated T cells exit the nodes, enter the bloodstream, and migrate preferentially to peripheral tissues at sites of infection and inflammation. The adhesion molecules involved in the attachment of T cells to endothelial cells are described in Chapter 6.

(Fig. 1-15). Thus, lymphocytes at distinct stages of their lives migrate to the different sites where they are needed for their functions. This process of lymphocyte recirculation is best described for T lymphocytes. It also is most relevant for T cells, because effector T cells have to locate and eliminate microbes at any site of infection. By contrast, effector B lymphocytes remain in lymphoid organs and do not need to migrate to sites of infection. Instead, B cells secrete antibodies, and the antibodies enter the blood and find microbes and microbial toxins in the circulation or distant tissues. Therefore, we will largely limit our discussion of lymphocyte recirculation to T lymphocytes.

Naive T lymphocytes that have matured in the thymus and entered the circulation migrate to lymph nodes where they can find antigens that enter through lymphatic vessels that drain epithelia and parenchymal organs. These naive T cells enter lymph nodes through specialized postcapillary venules, called **high endothelial venules** (HEVs), that are present in lymph nodes. Naive T cells express a surface receptor called L-selectin that binds to carbohydrate ligands that are expressed only on the endothelial cells of HEVs. (Selectins are a family of proteins involved in cell-cell adhesion that contain conserved structural features, including a lectin, or carbohydrate-binding, domain. More information about these proteins is in Chapter 6.) Because of the interaction of L-selectin with its ligand, naive T cells bind loosely to HEVs. In response to chemokines produced in the T cell zones of the lymph nodes, the naive T cells bind strongly to HEVs and then migrate through the HEVs into this region, where antigens are displayed by dendritic cells.

In the lymph node, naive T cells move around rapidly, scanning the surfaces of dendritic cells searching for antigens. If a T cell specifically recognizes an antigen, that T cell is transiently arrested on the antigen-presenting dendritic cell, forms stable conjugates with the APCs, and is activated. Such an encounter between an antigen and a specific lymphocyte is likely to be a random event, but most T cells in the body circulate through some lymph nodes at least once a day. As a result, some of the cells in the total population of T lymphocytes have an excellent chance of encountering antigens for which these cells express specific receptors. As we mentioned earlier and will describe in more detail in Chapter 3, the likelihood of the correct T cell finding its antigen is increased in peripheral lymphoid organs, particularly lymph nodes, because microbial antigens are concentrated in the same regions of these organs through which naive T cells circulate. In response to the microbial antigen, the naive T cells are activated to proliferate and differentiate. During this process, the cells reduce expression of adhesion molecules and chemokine receptors that keep naive cells in the lymph nodes. At the same time, T cells increase their expression of receptors for a phospholipid called sphingosine

1-phosphate, and since the concentration of this phospholipid is higher in the blood than in lymph nodes, activated cells are drawn out of the nodes into the circulation. The net result of these changes is that differentiated effector T cells leave the lymph nodes and enter the circulation. These effector cells preferentially migrate into the tissues that are colonized by infectious microbes, where the T lymphocytes perform their function of eradicating the infection. This process is described in more detail in Chapter 6, where cell-mediated immune reactions are discussed.

Memory T cell populations appear to consist of some cells that recirculate through lymph nodes, where they can mount secondary responses to captured antigens, and other cells that migrate to sites of infection, where they can respond rapidly to eliminate the infection.

We do not know much about lymphocyte circulation through the spleen or other lymphoid tissues or about the circulation pathways of naive and activated B lymphocytes. The spleen does not contain HEVs, but the general pattern of lymphocyte migration through this organ probably is similar to migration through lymph nodes. B lymphocytes appear to enter lymph nodes through HEVs, but after they respond to antigen, their differentiated progeny either remain in the lymph nodes or migrate mainly to the bone marrow.

Overview of Immune Responses to Microbes

Now that we have described the major components of the immune system, it is useful to summarize the key features of immune responses to microbes. The focus here is on the physiologic function of the immune system—defense against infections. In subsequent chapters, each of these features is discussed in more detail.

THE EARLY INNATE IMMUNE RESPONSE TO MICROBES

The principal barriers between the host and the environment are the epithelia of the skin and the gastrointestinal and respiratory tracts. Infectious microbes usually enter through these routes and attempt to colonize the host. Epithelia serve as physical and functional barriers to infections, simultaneously impeding the entry of microbes and interfering with their growth through production of natural antimicrobial agents. If microbes are able to traverse these epithelia and enter tissues and the circulation, they encounter the defense mechanisms of innate immunity, which are designed to react rapidly against microbes and their products. Phagocytes, including neutrophils and macrophages, ingest microbes into vesicles and destroy them by producing microbicidal substances in these vesicles; macrophages and dendritic cells also secrete soluble proteins called **cytokines,** which stimulate inflammation and lymphocyte responses. NK cells kill virus-infected cells and produce the macrophage-activating cytokine interferon-γ (IFN-γ). Many plasma proteins are involved in host defense, including the proteins of the complement system, which are activated by microbes, and whose products kill microbes and coat (opsonize) them for phagocytosis by macrophages and neutrophils. In addition to combating infections, innate immune responses stimulate subsequent adaptive immunity, providing signals that are essential for initiating the responses of antigen-specific T and B lymphocytes. The combined actions of the mechanisms of innate immunity can eradicate some infections and keep other pathogens in check until the more powerful adaptive immune response kicks in.

THE ADAPTIVE IMMUNE RESPONSE

The adaptive immune system uses three main strategies to combat most microbes.

- Secreted antibodies bind to extracellular microbes, block their ability to infect host cells, and promote their ingestion and subsequent destruction by phagocytes.
- Phagocytes ingest microbes and kill them, and helper T cells enhance the microbicidal abilities of the phagocytes.
- Cytotoxic T lymphocytes destroy cells infected by microbes that are inaccessible to antibodies.

The goal of the adaptive response is to activate these defense mechanisms against microbes that are in different anatomic locations, such as intestinal lumens, the circulation, or inside cells. All adaptive immune responses develop in steps, each of which corresponds to particular reactions of lymphocytes (Fig. 1-16). We start this overview of adaptive immunity with the first step, which is the recognition of antigens.

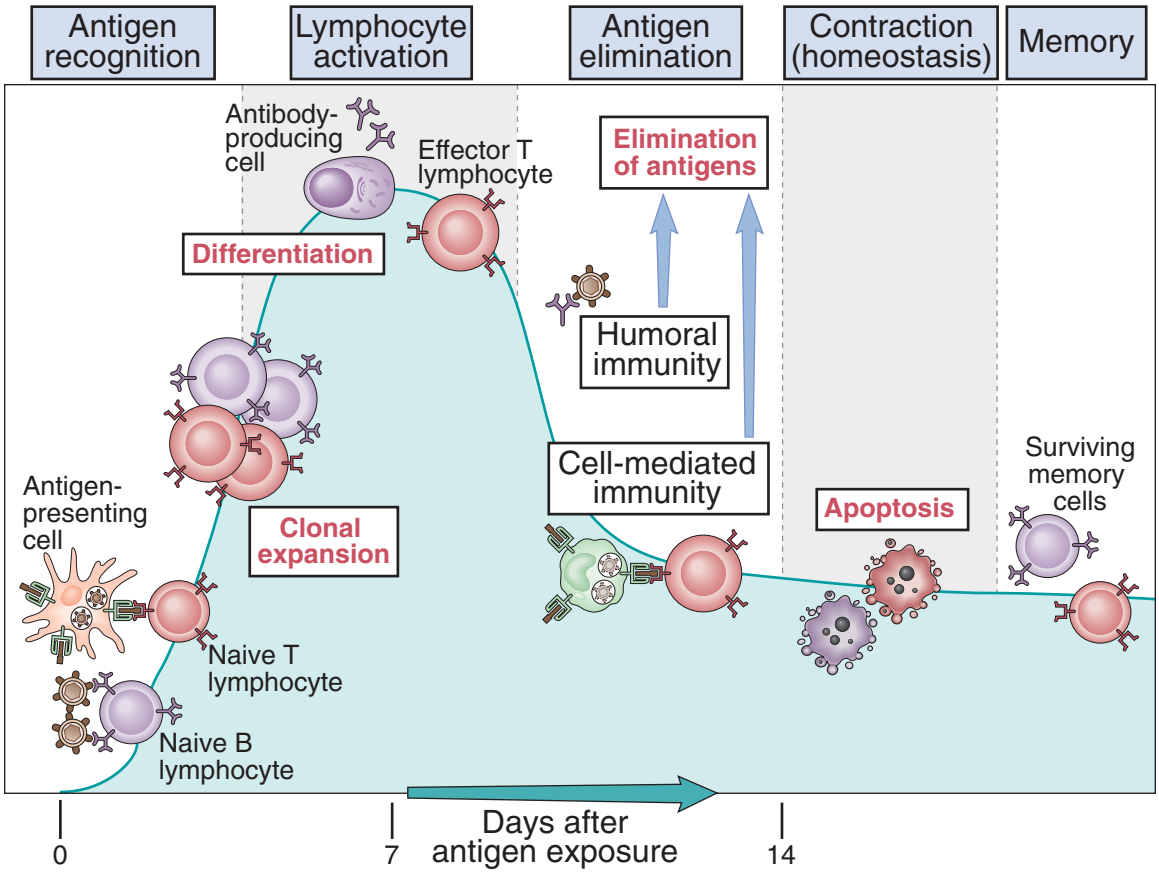


FIGURE 1-16 **Phases of an adaptive immune response.** An adaptive immune response consists of distinct phases, the first three being the recognition of antigen, the activation of lymphocytes, and elimination of antigen (the effector phase). The response declines as antigen-stimulated lymphocytes die by apoptosis, restoring homeostasis, and the antigen-specific cells that survive are responsible for memory. The duration of each phase may vary in different immune responses. The *y*-axis represents an arbitrary measure of the magnitude of the response. These principles apply to both humoral immunity (mediated by B lymphocytes) and cell-mediated immunity (mediated by T lymphocytes).

The Capture and Display of Microbial Antigens

Microbes that enter through epithelia, and their protein antigens, are captured by dendritic cells that are resident in these epithelia, and the cell-bound antigens are transported to draining lymph nodes. Protein antigens are processed in the dendritic cells to generate peptides that are displayed on the surface of the APCs bound to MHC molecules. Naive T cells recognize these peptide-MHC complexes—this is how T cell responses are initiated. Protein antigens also are recognized by B lymphocytes in the lymphoid follicles of the peripheral lymphoid organs. Polysaccharides and other nonprotein antigens are captured in the lymphoid organs and are recognized by B lymphocytes but not by T cells.

As part of the innate immune response, the dendritic cells that present the antigen to naive T cells are activated to express molecules called costimulators and to secrete cytokines, both of which are needed, in addition to the antigen, to stimulate the proliferation and differentiation of T lymphocytes. The innate immune

response to some microbes and polysaccharide antigens also results in the activation of complement, generating cleavage products of complement proteins that enhance the proliferation and differentiation of B lymphocytes. Thus, antigen (often referred to as "signal 1") and molecules produced during innate immune responses ("signal 2") function cooperatively to activate antigen-specific lymphocytes. The requirement for microbe-triggered signal 2 ensures that the adaptive immune response is induced by microbes and not by harmless substances. Signals generated in lymphocytes by the engagement of antigen receptors and receptors for costimulators lead to the transcription of various genes, which encode cytokines, cytokine receptors, effector molecules, and proteins that control cell cycling. All of these molecules are involved in the responses of the lymphocytes.

Cell-Mediated Immunity: Activation of T Lymphocytes and Elimination of Cell-Associated Microbes

When naive T cells are activated by antigen and costimulators in lymphoid organs, they secrete cytokine growth factors and respond to other cytokines secreted by APCs. The combination of signals (antigen, costimulation and cytokines) stimulates the proliferation of the T cells and their differentiation into effector T cells. Different subsets of T cells differentiate into effector cells with distinct functional properties. Naive $CD4^+$ T cells become helper T cells, and naive $CD8^+$ T cells become CTLs. The helper T cells and CTLs that are generated in the lymphoid organ may migrate back into the blood and then into any site where the antigen (microbe) is present. The effector T cells are reactivated by antigen at sites of infection and perform the functions that are responsible for elimination of the microbes. Helper T cells produce cytokines and express cell surface molecules that bind to receptors on B cells and macrophages and thereby promote antibody production or macrophage killing of ingested microbes. Some helper T cells function to recruit and activate neutrophils, which then phagocytose and destroy microbes. CTLs directly kill cells harboring microbes in the cytoplasm. These microbes may be viruses that infect many cell types or bacteria that are ingested by macrophages but have learned to escape from phagocytic vesicles into the cytoplasm (where they are inaccessible to the killing machinery of phagocytes, which is largely confined to vesicles). By destroying the infected cells, CTLs eliminate the reservoirs of infection.

Humoral Immunity: Activation of B Lymphocytes and Elimination of Extracellular Microbes

On activation, B lymphocytes proliferate and then differentiate into plasma cells that secrete different classes of antibodies with distinct functions. Many polysaccharide and lipid antigens have multiple identical antigenic determinants (epitopes) that are able to engage many antigen receptor molecules on each B cell and initiate the process of B cell activation. Typical globular protein antigens are not able to bind to many antigen receptors, and the full response of B cells to protein antigens requires help from $CD4^+$ T cells. B cells ingest protein antigens, degrade them, and display peptides bound to MHC molecules for recognition by helper T cells. The helper T cells express cytokines and cell surface proteins, which work together to activate the B cells.

Some of the progeny of the expanded B cell clones differentiate into antibody-secreting cells. Each B cell secretes antibodies that have the same antigen binding site as the cell surface antibodies (B cell receptors) that first recognized the antigen. Polysaccharides and lipids stimulate secretion mainly of a class of antibody called immunoglobulin M (IgM). Protein antigens stimulate helper T cells, which induce the production of antibodies of different classes (IgG, IgA, and IgE). This production of different antibodies, all with the same specificity, is called **heavy chain class (isotype) switching;** it provides plasticity in the antibody response, enabling antibodies to serve many functions. Helper T cells also stimulate the production of antibodies with higher and higher affinity for the antigen. This process, called **affinity maturation,** improves the quality of the humoral immune response.

The humoral immune response combats microbes in many ways. Antibodies bind to microbes and prevent them from infecting cells, thereby neutralizing the microbes. Antibodies coat (opsonize) microbes and target them for phagocytosis, because phagocytes

(neutrophils and macrophages) express receptors for the antibodies. Additionally, antibodies activate a system of serum proteases called complement, and complement products promote phagocytosis and destruction of microbes. Specialized types of antibodies and specialized transport mechanisms for antibodies serve distinct roles at particular anatomic sites, including the lumens of the respiratory and gastrointestinal tracts or the placenta and fetus.

DECLINE OF IMMUNE RESPONSES AND IMMUNOLOGICAL MEMORY

A majority of effector lymphocytes induced by an infectious pathogen die by apoptosis after the microbe is eliminated, thus returning the immune system to its basal resting state. This return to a stable or steady state is called homeostasis. It occurs because microbes provide essential stimuli for lymphocyte survival and activation and effector cells are short-lived. Therefore, as the stimuli are eliminated, the activated lymphocytes are no longer kept alive.

The initial activation of lymphocytes generates long-lived memory cells, which may survive for years after the infection. Memory cells are an expanded pool of antigen-specific lymphocytes (more numerous than the naive cells specific for any antigen that are present before encounter with that antigen), and memory cells respond faster and more effectively against the antigen than do naive cells. This is why the generation of memory cells is an important goal of vaccination.

SUMMARY

- The physiologic function of the immune system is to protect individuals against infections.
- Innate immunity is the early line of defense, mediated by cells and molecules that are always present and ready to eliminate infectious microbes. Adaptive immunity is the form of immunity that is stimulated by microbes, has a fine specificity for foreign substances, and responds more effectively against each successive exposure to a microbe.
- Lymphocytes are the cells of adaptive immunity and are the only cells with clonally distributed receptors for antigens.
- Adaptive immunity consists of humoral immunity, in which antibodies neutralize and eradicate extracellular microbes and toxins, and cell-mediated immunity, in which T lymphocytes eradicate intracellular microbes.
- Adaptive immune responses consist of sequential phases: antigen recognition by lymphocytes, activation of the lymphocytes to proliferate and to differentiate into effector and memory cells, elimination of the microbes, decline of the immune response, and long-lived memory.
- Different populations of lymphocytes serve distinct functions and may be distinguished by the expression of particular membrane molecules.
- B lymphocytes are the only cells that produce antibodies. B lymphocytes express membrane antibodies that recognize antigens, and effector B cells secrete the antibodies that neutralize and eliminate the antigen.
- T lymphocytes recognize peptide fragments of protein antigens displayed on other cells. Helper T lymphocytes activate phagocytes to destroy ingested microbes and activate B lymphocytes to produce antibodies. CTLs are cytotoxic: They kill infected cells harboring microbes in the cytoplasm.
- APCs capture antigens of microbes that enter through epithelia, concentrate these antigens in lymphoid organs, and display the antigens for recognition by T cells.
- Lymphocytes and APCs are organized in peripheral lymphoid organs, where immune responses are initiated and develop.
- Naive lymphocytes circulate through the peripheral lymphoid organs searching for foreign antigens. Effector T lymphocytes migrate to peripheral sites of infection, where they function to eliminate infectious microbes. Effector B lymphocytes remain in lymphoid organs and the bone marrow, from where they secrete antibodies that enter the circulation and find and eliminate microbes.

REVIEW QUESTIONS

1. *What are the two types of adaptive immunity, and what types of microbes do these adaptive immune responses combat?*
2. *What are the principal classes of lymphocytes, how do they differ in function, and how may they be identified and distinguished?*
3. *What are the important differences among naive, effector, and memory T and B lymphocytes?*
4. *Where are T and B lymphocytes located in lymph nodes, and how is their anatomic separation maintained?*
5. *How do naive and effector T lymphocytes differ in their patterns of migration?*