The term “immunity” in a biologic context has historically referred to resistance to pathogens; however, reactions to some noninfectious substances including harmless environmental molecules, tumors, and even unaltered host components are also considered forms of immunity (allergy, tumor immunity, and autoimmunity, respectively). The collection of cells, tissues, and molecules that mediate these reactions is called the immune system, and the coordinated response of these cells and molecules to pathogens and other substances comprises an immune response.

The most important physiologic function of the immune system is to prevent or eradicate infections (Fig. 1.1), and this is the principal context in which immune responses are discussed throughout this book. In addition, it prevents the growth of some tumors, and some cancers can be treated by stimulating immune responses against tumor cells. The immune system also plays a major role in the repair of damaged tissues. Because the immune system can respond to microbial and nonmicrobial substances and also can cause disease under some circumstances, a more inclusive definition of the immune response is a reaction to microbes, as well as to other molecules that are recognized as foreign, regardless of the physiologic or pathologic consequence of such a reaction. Immunology is the study of immune responses in this broader sense and of the cellular and molecular events that occur after an organism encounters microbes and other foreign molecules.

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. Conversely, stimulating immune responses against microbes through vaccination is the most effective method for protecting individuals against infections; this approach has led to the worldwide eradication of smallpox, the only disease that has been eliminated from civilization by human intervention (Fig. 1.2). The appearance of acquired immunodeficiency syndrome (AIDS) in the 1980s tragically emphasized the importance of the immune system for defending individuals against infection.
In contrast to these beneficial roles, abnormal immune responses cause many inflammatory diseases with serious morbidity and mortality. The immune response is the major barrier to the success of organ transplantation, which is often used to treat organ failure. The products of immune cells can also be of great practical use. For example, antibodies, which are proteins made by certain cells of the immune system, are used in clinical laboratory testing and in research as highly specific reagents for detecting a wide variety of molecules in the circulation and in cells and tissues. Antibodies designed to block or eliminate potentially harmful molecules and cells are used widely for the treatment of immunologic diseases, cancers, and other types of disorders. For all these reasons, the field of immunology has captured the attention of clinicians, scientists, and the lay public.

This chapter introduces the nomenclature of immunology, 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 and respond to microbes in ways that lead to their elimination?

The basic principles introduced here set the stage for more detailed discussions of immune responses in later chapters. A Glossary of the important terms used in this book is provided near the end of the book.

**INNATE AND ADAPTIVE IMMUNITY**

Host defenses are grouped under innate immunity, which provides immediate protection against microbial invasion, and adaptive immunity, which develops more slowly and provides more specialized defense against infections (Fig. 1.3). Innate immunity, also called natural immunity or native immunity, is always present in healthy individuals (hence the term innate), prepared to block the entry of microbes and to rapidly eliminate microbes that do succeed in entering host tissues. Adaptive immunity, also called specific immunity or acquired immunity, requires proliferation and differentiation of lymphocytes in response to microbes before it can provide effective defense (i.e., it adapts to the presence of microbial invaders). Innate immunity is phylogenetically older, and the more specialized and powerful adaptive immune response evolved later.
In innate immunity, the first line of defense is provided by epithelial barriers of the skin and mucosal tissues and by 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 circulation, several other components of the innate immune system defend against them, including phagocytes and innate lymphoid cells, and several plasma proteins, such as the complement system. In addition to providing early defense against infections, innate immune responses are required to initiate adaptive immune responses against the infectious agents. The components and mechanisms of innate immunity are discussed in detail in Chapter 2.

The adaptive immune system consists of lymphocytes with highly diverse and variable receptors for foreign substances, and the products of these cells, such as antibodies. Adaptive immune responses are essential for defense against infectious microbes that are pathogenic for humans (i.e., capable of causing disease) and may have evolved to resist innate immunity. The cells and molecules of innate immunity recognize structures shared by classes of microbes, whereas the lymphocytes of adaptive immunity express receptors that specifically recognize a much wider variety of molecules produced by microbes, as well as noninfectious molecules. Any molecule that is specifically recognized by lymphocytes or antibodies is called an antigen. Adaptive immune responses often use the cells and molecules of the innate immune system to eliminate microbes. For example, 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. Examples of the cooperation between innate and adaptive immunity are discussed in later chapters.

By convention, the term immune response generally refers to adaptive immunity, and that is the focus of most of this chapter.

The cells of the immune system are located in different tissues and serve different roles in host defense. Most of these cells are derived from bone marrow precursors that circulate in the blood and are called leukocytes (white blood cells). Others are present in tissues at all times. Some of these cells function mainly in innate immunity, others in adaptive immunity, and some function in both types of responses. These cells are grouped into two broad categories—lymphoid cells (most of...
CHAPTER 1 Introduction to the Immune System

which are the mediators of adaptive immune responses) and nonlymphoid cells, also called myeloid cells, which play diverse roles, including in innate immune responses.

- Tissue-resident dendritic cells, macrophages, and mast cells serve as sentinels to detect the presence of microbes in tissues and initiate immune responses. Dendritic cells (DCs), so called because of their many protruding membrane extensions, also have the specialized function of capturing microbial antigens and displaying them to T lymphocytes to initiate adaptive immune responses and are therefore called antigen-presenting cells (APCs, discussed later).

- Phagocytes ingest and destroy microbes. They are myeloid cells and include neutrophils, which are recruited from the blood, and macrophages, which can develop from circulating monocytes and live in tissues much longer than neutrophils do. Macrophages are not only sentinels and destroyers of microbes, they also help to repair damaged tissues. Because the sentinels and phagocytes are primarily cells of innate immunity, they are described in Chapter 2.

- Lymphocytes, including B and T cells, circulate through lymphoid organs and nonlymphoid tissues. They recognize foreign antigens and carry out adaptive immune responses. They are described further later in this chapter.

**TYPES OF ADAPTIVE IMMUNITY**

The two types of adaptive immunity, called humoral immunity and cell-mediated immunity, are mediated by different cells and molecules and 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. Secreted antibodies enter the circulation, extracellular tissue fluids, and the lumens of mucosal organs such as the gastrointestinal and respiratory tracts. The antibodies defend against microbes...
present in these locations by preventing them from invading tissue cells and by neutralizing toxins made by the microbes. Microbes that live and divide outside cells but are readily killed once ingested by phagocytes are called extracellular microbes, and antibodies can enhance the uptake of these microbes into phagocytes. However, many microbes, often called intracellular microbes, can live and divide inside infected cells, including phagocytes. Although antibodies can prevent such microbes from infecting tissue cells, they are not effective after the microbes have entered the cells.

- Defense against microbes that have already entered host cells is called **cell-mediated immunity** because it is mediated by cells, which are called **T lymphocytes**. Cell-mediated immunity is especially important to defend against intracellular organisms that can survive and replicate inside cells. Some T lymphocytes activate phagocytes to destroy microbes that have been ingested and live within intracellular vesicles of these phagocytes. Other T lymphocytes kill any type of host cells (including non-phagocytic cells) that harbor infectious microbes in the cytoplasm or nucleus. In both cases, the T cells recognize microbial antigens that are displayed on host cell surfaces, which indicates there is a microbe inside the cell. Some T lymphocytes also help to defend against extracellular microbes by recruiting large numbers of

---

### Table: Types of adaptive immunity

<table>
<thead>
<tr>
<th><strong>Humoral immunity</strong></th>
<th><strong>Cell-mediated immunity</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microbe</strong></td>
<td></td>
</tr>
<tr>
<td>Extracellular microbes</td>
<td>Phagocytosed microbes in macrophage</td>
</tr>
<tr>
<td><strong>Responding lymphocytes</strong></td>
<td></td>
</tr>
<tr>
<td>B lymphocyte</td>
<td>Helper T lymphocyte</td>
</tr>
<tr>
<td><strong>Effector mechanism</strong></td>
<td></td>
</tr>
<tr>
<td>Secreted antibody</td>
<td>Cytokines</td>
</tr>
<tr>
<td><strong>Functions</strong></td>
<td></td>
</tr>
<tr>
<td>Block infections and eliminate extracellular microbes</td>
<td>Activated macrophage</td>
</tr>
<tr>
<td>Elimination of phagocytosed microbes</td>
<td>Killed infected cell</td>
</tr>
</tbody>
</table>

Fig. 1.4 Types of adaptive immunity. In humoral immunity, B lymphocytes secrete antibodies that eliminate extracellular microbes. In cell-mediated immunity, some T lymphocytes secrete soluble proteins called cytokines that recruit and activate phagocytes to destroy ingested microbes, and other T lymphocytes kill infected cells.
phagocytes to sites of infection, and the phagocytes ingest and destroy the microbes.

The specificities of B and T lymphocytes differ in important respects. Most T cells recognize only peptide fragments of protein antigens presented on cell surfaces, whereas B cells and antibodies are able to recognize many different types of molecules, including proteins, carbohydrates, nucleic acids, and lipids. These and other differences are discussed in more detail later.

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).

- In **active immunity**, an individual exposed to the antigens of a microbe mounts a response to 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 who has not previously been exposed to that microbe's antigens.

- In **passive immunity**, a naive individual receives antibodies or cells (e.g., lymphocytes) from another individual already immune to an infection or protective antibodies that have been synthesized using modern bioengineering techniques. The recipient acquires the ability to combat the infection for as long as the transferred antibodies or cells last. 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. The only physiologic 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 during fetal life from their mothers through the placenta and in the neonatal period from breast milk. Clinically, passive immunity is useful for treating some immunodeficiency diseases with antibodies pooled from multiple donors and for emergency treatment of some viral infections and snakebites using serum from immunized donors. Antibodies and T cells designed to recognize tumors are now widely used for passive immunotherapy of cancers.

## 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).

<table>
<thead>
<tr>
<th>Feature</th>
<th>Functional significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
<td>Ensures that immune responses are precisely targeted to microbial pathogens</td>
</tr>
<tr>
<td>Diversity</td>
<td>Enables immune system to respond to a large variety of antigens</td>
</tr>
<tr>
<td>Memory</td>
<td>Leads to enhanced responses to repeated exposures to the same antigens</td>
</tr>
<tr>
<td>Clonal expansion</td>
<td>Increases number of antigen-specific lymphocytes from a small number of naive lymphocytes</td>
</tr>
<tr>
<td>Specialization</td>
<td>Generates responses that are optimal for defense against different types of microbes</td>
</tr>
<tr>
<td>Contraction and homeostasis</td>
<td>Allows immune system to respond to newly encountered antigens</td>
</tr>
<tr>
<td>Nonreactivity to self</td>
<td>Prevents injury to the host during responses to foreign antigens</td>
</tr>
</tbody>
</table>

**Fig. 1.5 Properties of adaptive immune responses.** This table summarizes the important properties of adaptive immune responses and how each feature contributes to host defense against microbes.

### Specificity and Diversity

The adaptive immune system is capable of distinguishing millions of different antigens or portions of antigens, a feature that is referred to as specificity. It implies that the total collection of lymphocyte specificities, sometimes called the lymphocyte repertoire, is extremely diverse. The total population of B and T lymphocytes consists of many different clones (each clone made up of cells all derived from one lymphocyte), and all the cells of one clone express identical antigen receptors, which are different from the receptors of all other clones. We now know the molecular basis for the generation of this remarkable diversity of lymphocytes (see Chapter 4). The **clonal selection hypothesis**, formulated in the 1950s, correctly predicted that clones of lymphocytes specific for different antigens develop before an encounter with these antigens, and each antigen elicits an immune response by selecting and activating the lymphocytes of a specific clone (Fig. 1.6).
The diversity of the lymphocyte repertoire, which enables the immune system to respond to a vast number and variety of antigens, also means that before exposure to any one antigen, very few cells, perhaps as few as 1 in 100,000 or 1 in 1,000,000 lymphocytes, are specific for that antigen. Thus, the total number of lymphocytes that can recognize and react against any one antigen ranges from approximately 1,000 to 10,000 cells. To mount an effective defense against microbes, these few cells have to give rise to a large number of lymphocytes capable of destroying the microbes. Each unique lymphocyte that recognizes a single antigen and its progeny constitute an antigen-specific clone. The effectiveness of immune responses is attributable to several features of adaptive immunity, including the marked expansion of the clone of lymphocytes specific for any antigen upon exposure to that antigen, the selection and preservation of the most potent lymphocytes, and numerous positive feedback loops that amplify immune responses. These characteristics of the adaptive immune system are described in later chapters.

**Memory**

The adaptive immune system mounts faster, larger and more effective responses to repeated exposure to the same antigen. This feature of adaptive immune responses implies that the immune system remembers every encounter with antigen, and this property of adaptive immunity is therefore called immunologic memory. The response to the first exposure to antigen, called
the primary immune response, is initiated by lymphocytes called naive lymphocytes that are seeing antigen for the first time (Fig. 1.7). The term naive refers to these cells being immunologically inexperienced, not having previously 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 primary responses. 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 exposure to a microbe generates more memory cells and activates previously generated memory cells. Immunologic memory is one mechanism by which 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 naive or memory lymphocytes are activated by antigens, they undergo proliferation, generating many thousands of cells, all with the same antigen receptors and specificity. This process, called clonal expansion, rapidly increases the number of cells specific for the antigen encountered and ensures that adaptive immunity keeps pace with rapidly proliferating microbes.
- Immune responses are specialized, and different responses are designed to defend best against different types of microbes.
- All immune responses are self-limited and decline as the infection is eliminated, allowing the system to return to a resting state (homeostasis), prepared to respond to another infection.

**Fig. 1.7 Primary and secondary immune responses.** The properties of memory and specificity can be demonstrated by repeated immunizations with defined antigens in animal experiments. 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. The level of antibody produced is shown as arbitrary values and varies with the type of antigen exposure. Only B cells are shown, but the same features are seen with T cell responses to antigens. The time after immunization may be 1 to 3 weeks for a primary response and 2 to 7 days for a secondary response, but the kinetics vary, depending on the antigen and the nature of immunization.
• 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. This unresponsiveness to self is called immunological tolerance, referring to the ability of the immune system to coexist with (tolerate) potentially antigenic self molecules, cells, and tissues.

**CELLS OF THE ADAPTIVE IMMUNE SYSTEM**

This section of the chapter describes the important properties of the major cell populations of adaptive immunity—namely, lymphocytes and antigen-presenting cells. Phagocytes and other cells of innate immunity are described in Chapter 2.

**Lymphocytes**

Lymphocytes are the only cells that produce clonally distributed receptors specific for diverse antigens and are the key mediators of adaptive immunity. A healthy adult contains 0.5 to $1 \times 10^{12}$ lymphocytes. Although all lymphocytes are morphologically similar and rather unremarkable in appearance, they are heterogeneous in lineage, function, and phenotype and are capable of complex biologic responses and activities (Fig. 1.9). These cells often are distinguished by the expression of surface proteins that may be identified using panels of monoclonal antibodies. The standard nomenclature for these proteins is the CD (cluster of differentiation).

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Principal function(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lymphocytes:</strong></td>
<td>Specific recognition of antigens and generation of adaptive immune responses:</td>
</tr>
<tr>
<td>B lymphocytes;</td>
<td>• B lymphocytes: mediators of humoral immunity</td>
</tr>
<tr>
<td>T lymphocytes</td>
<td>• T lymphocytes: mediators of cell-mediated immunity</td>
</tr>
<tr>
<td><strong>Antigen-presenting cells:</strong></td>
<td>Capture of antigens for display to lymphocytes:</td>
</tr>
<tr>
<td>dendritic cells;</td>
<td>• Dendritic cells: initiation of T cell responses</td>
</tr>
<tr>
<td>macrophages;</td>
<td>• Macrophages: effector phase of cell-mediated immunity</td>
</tr>
<tr>
<td>B cells; follicular dendritic cells</td>
<td>• Follicular dendritic cells: display of antigens to B lymphocytes in humoral immune responses</td>
</tr>
<tr>
<td><strong>Effector cells:</strong></td>
<td>Elimination of antigens:</td>
</tr>
<tr>
<td>T lymphocytes;</td>
<td>• T lymphocytes: activation of phagocytes, killing infected cells</td>
</tr>
<tr>
<td>macrophages;</td>
<td>• Macrophages: phagocytosis and killing of microbes</td>
</tr>
<tr>
<td>granulocytes</td>
<td>• Granulocytes: killing microbes</td>
</tr>
</tbody>
</table>

**Fig. 1.8** Principal cells of the adaptive immune system. Micrographs illustrate the morphology of some cells of each type. The major functions of these cell types are listed.
**Fig. 1.9** Classes of lymphocytes. 

A, Different classes of lymphocytes in the adaptive immune system recognize distinct types of antigens and differentiate into effector cells whose function is to eliminate the antigens. B lymphocytes recognize soluble or microbial surface antigens and differentiate into antibody-secreting cells called plasma cells. Both helper T cells and cytotoxic T lymphocytes recognize peptides derived from intracellular microbial proteins displayed on the cell surface by MHC molecules, described in Chapter 3. Helper T cells recognize these peptides displayed on the surface of macrophages or other antigen presenting cells, and secrete cytokines that stimulate different mechanisms of immunity and inflammation. Cytotoxic T lymphocytes recognize peptides displayed by any type of infected cell type (or tumor cell), and kill these cells. Regulatory T cells limit the activation of other lymphocytes, especially of T cells, and prevent autoimmunity.
### B Lymphocytes

<table>
<thead>
<tr>
<th>Class</th>
<th>Functions</th>
<th>Antigen receptor and specificity</th>
<th>Selected phenotypic markers</th>
<th>Percentage of total lymphocytes*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>αβ T Lymphocytes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4⁺ helper T lymphocytes</td>
<td>B cell activation (humoral immunity)</td>
<td>αβ heterodimers Diverse specificities for peptide–class II MHC complexes</td>
<td>CD3⁺ CD4⁺ CD8⁻</td>
<td>Blood 35–60, Lymph node 50–60, Spleen 50–60</td>
</tr>
<tr>
<td></td>
<td>Macrophage activation (cell-mediated immunity)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stimulation of inflammation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD8⁺ cytotoxic T lymphocytes</td>
<td>Killing of cells infected with intracellular microbes, tumor cells</td>
<td>αβ heterodimers Diverse specificities for peptide–class I MHC complexes</td>
<td>CD3⁺ CD4⁻ CD8⁺</td>
<td>15–40 Blood, 15–20 Lymph node, 10–15 Spleen</td>
</tr>
<tr>
<td>Regulatory T cells</td>
<td>Suppress function of other T cells (regulation of immune responses, maintenance of self-tolerance)</td>
<td>αβ heterodimers Specific for self and some foreign antigens (peptide–class II MHC complexes)</td>
<td>CD3⁺ CD4⁺ CD25⁺ FoxP3⁺ (most common)</td>
<td>0.5–2 Blood, 5–10 Lymph node, 5–10 Spleen</td>
</tr>
</tbody>
</table>

**Fig. 1.9, cont’d** B, The table summarizes the major properties of the lymphocytes of the adaptive immune system. Not included are γδ T cells, natural killer cells and other innate lymphoid cells, which are discussed in Chapter 2. *The percentages are approximations, based on data from human peripheral blood and mouse lymphoid organs. Ig, Immunoglobulin; MHC, major histocompatibility complex.

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-bound 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, resulting in the proliferation and differentiation of the antigen-specific B cells. This leads to the secretion of soluble forms of antibodies with the same antigen specificity as the membrane receptors.
T lymphocytes are responsible for cell-mediated immunity. The antigen receptors of most T lymphocytes recognize only peptide fragments of protein antigens that are bound to specialized peptide display molecules, called major histocompatibility complex (MHC) molecules, on the surface of specialized cells, called antigen-presenting cells (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. CD8+ T lymphocytes are called cytotoxic T lymphocytes (CTLs) because they kill cells harboring intracellular microbes. Some CD4+ T cells belong to a special subset that functions to prevent or limit immune responses; these are called regulatory T lymphocytes.

All lymphocytes arise from common lymphoid precursor 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 lymphocytes are produced (generated) are called the generative (or central) lymphoid organs. Mature lymphocytes leave the generative lymphoid organs and enter the circulation and peripheral (secondary) lymphoid organs, which are the major site of immune responses where lymphocytes encounter antigens and are activated.

When naive lymphocytes recognize microbial antigens and also receive additional signals induced by microbes, the antigen-specific lymphocytes proliferate and then 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 months up to a few years, 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. 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 that is recognized.

- **Effector lymphocytes** 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. Plasma cells develop in response to antigenic stimulation in the peripheral organs.
### Table 1.11 Stages in the life history of lymphocytes

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Stage</th>
<th>Naive cell</th>
<th>Activated or effector lymphocyte</th>
<th>Memory lymphocyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>B lymphocytes</td>
<td>Antigen recognition</td>
<td>Preferentially to peripheral lymph nodes</td>
<td>Preferentially to inflamed tissues</td>
<td>Heterogenous: different subsets to lymph nodes, mucosa and other tissues</td>
</tr>
<tr>
<td></td>
<td>Proliferation</td>
<td>Very low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Differentiation</td>
<td>None</td>
<td>Cytokine secretion; cytotoxic activity</td>
<td>None</td>
</tr>
<tr>
<td>T lymphocytes</td>
<td>Antigen recognition</td>
<td>Very low</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td></td>
<td>Proliferation</td>
<td>None</td>
<td>Cytokine secretion; cytotoxic activity</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Differentiation</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

**T lymphocytes**

- **Migration**
  - Preferentially to peripheral lymph nodes
  - Preferentially to inflamed tissues
  - Heterogenous: different subsets to lymph nodes, mucosa and other tissues

- **Frequency of cells responsive to particular antigen**
  - Very low
  - High
  - Low

- **Effector functions**
  - None
  - Cytokine secretion; cytotoxic activity
  - None

**B lymphocytes**

- **Membrane immunoglobulin (Ig) isotype**
  - IgM and IgD
  - Frequently IgG, IgA, and IgE (low level in plasma cells)
  - Frequently IgG, IgA, and IgE

- **Affinity of Ig produced**
  - Relatively low
  - Increases during immune response
  - Relatively high

- **Effector functions**
  - None
  - Antibody secretion
  - None

---

**Fig. 1.11** Stages in the life history of lymphocytes. A, Naive lymphocytes recognize foreign antigens to initiate adaptive immune responses. Naive lymphocytes need signals in addition to antigens to proliferate and differentiate into effector cells; these additional signals are not shown. Effector cells, which develop from naive cells, function 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 generation and functions of effector cells, including changes in migration patterns and types of immunoglobulin produced, are described in later chapters.
lymphoid organs, where they may stay and produce antibodies. Small numbers of antibody-secreting cells are also found in the blood; these are called plasma blasts. Some of these migrate to the bone marrow, where they mature into long-lived plasma cells and continue to produce antibody years after the infection is eradicated, providing immediate protection in case the infection recurs.

Effector CD4+ T cells (helper T cells) produce proteins called cytokines that activate B cells, macrophages, and other cell types, thereby mediating the helper function of this lineage. The properties of cytokines are listed in Appendix II and will be discussed in later chapters. Effector CD8+ T cells (CTLs) have the machinery to kill infected host cells. The development and functions of these effector cells are also discussed in later chapters. Effector T lymphocytes are short lived and die as the antigen is eliminated.

- Memory cells, also generated from the progeny of antigen-stimulated lymphocytes, can survive for long periods 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 (Fig. 1.12). As individuals age, the gradual accumulation of memory cells compensates for the reduced output of new, naive T cells from the thymus, which involutes after puberty (see Chapter 4). 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 initiate secondary immune responses. The signals that generate and maintain memory cells are not well understood but include cytokines.

### Antigen-Presenting Cells

The common portals of entry for microbes—the skin and gastrointestinal, respiratory, and genitourinary tracts—contain specialized cells located in the epithelium that capture antigens, transport them to peripheral lymphoid tissues, and display (present) them to lymphocytes. These are the first steps in the development of adaptive immune responses against antigens. This function of antigen capture and presentation is best understood for dendritic cells, the most specialized antigen-presenting cells (APCs) in the immune system. Dendritic cells capture protein antigens of microbes that cross epithelial barriers and transport these antigens to regional lymph nodes, where they display fragments of the proteins for recognition by T lymphocytes. If a microbe has invaded through the epithelium, it may be phagocytosed and presented by tissue macrophages. Microbes or their antigens that enter lymphoid organs may be captured by dendritic cells or macrophages that reside in these organs and presented to lymphocytes. The process of antigen presentation to T cells is described in Chapter 3.

Dendritic cells have another important feature that gives them the ability to stimulate T cell responses. These specialized cells respond to microbes by producing surface proteins, called costimulators, which are required, together with antigen, to activate naive T lymphocytes to proliferate and differentiate into effector cells. Dendritic cells express higher levels of these costimulatory proteins than do other cell types and are thus the most potent stimulators of naive T cells and the most efficient initiators of T cell responses. Other antigen-presenting cells, such as macrophages and B cells, present antigens to differentiated effector T cells in various immune responses.

B lymphocytes may directly recognize the antigens of microbes (either released or on the surface of the microbes), and macrophages and dendritic cells in peripheral lymphoid organs may also capture antigens and display them to B cells. A distinct type of 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 (see Chapter 7). FDCs do not present antigens to T cells and differ from the dendritic cells described earlier that function as APCs for T lymphocytes.

**TISSUES OF THE IMMUNE SYSTEM**

The tissues of the immune system consist of the generative lymphoid organs, in which T and B lymphocytes mature and become competent to respond to antigens, and the peripheral lymphoid organs, in which adaptive immune responses to microbes are initiated (see Fig. 1.10). Most of the lymphocytes in a healthy human are found in lymphoid organs and other tissues (Fig. 1.13). However, as we discuss later, lymphocytes are unique among the cells of the body because of their ability to recirculate, repeatedly going through the blood to visit every secondary lymphoid organ in the body. The generative (also called primary or central) lymphoid organs are described in Chapter 4, when we discuss the process of lymphocyte maturation. The following section highlights some of the features of peripheral (or secondary) lymphoid organs that are important for the development of adaptive immunity.

**Peripheral (Secondary) Lymphoid Organs and Tissues**

The peripheral lymphoid organs and tissues, which consist of the lymph nodes, the spleen, and the mucosal and cutaneous immune systems, are organized in a way that promotes the development of adaptive immune responses. T and B lymphocytes must locate microbes that enter at any site in the body, then respond to these microbes and eliminate them. 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 peripheral lymphoid organs and tissues, in which antigen is concentrated, whereas most effector cells go to sites of infection where microbes must be eliminated. Furthermore, different types of lymphocytes often need to communicate to generate effective immune responses. For example, within peripheral lymphoid organs, 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 after stimulation by antigen so they interact when they need to.

The major peripheral lymphoid organs share many characteristics but also have some unique features.

- **Lymph nodes** are encapsulated nodular aggregates of lymphoid tissues located along lymphatic channels throughout the body (Fig. 1.14). Fluid constantly leaks out of small blood vessels in all epithelia and connective tissues and most parenchymal organs. This fluid, called **lymph**, is drained by lymphatic vessels from the tissues to the lymph nodes and eventually back into the blood circulation. Therefore the lymph contains a mixture of substances 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 other tissues and transport these antigens to the lymph nodes. The net result of these processes of antigen capture and transport is that the antigens of microbes entering through epithelia or colonizing tissues become concentrated in draining lymph nodes.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Number of lymphocytes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen</td>
<td>$70 \times 10^9$</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>$190 \times 10^9$</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>$50 \times 10^9$</td>
</tr>
<tr>
<td>Blood</td>
<td>$10 \times 10^9$</td>
</tr>
<tr>
<td>Skin</td>
<td>$20 \times 10^9$</td>
</tr>
<tr>
<td>Intestines</td>
<td>$50 \times 10^9$</td>
</tr>
<tr>
<td>Liver</td>
<td>$10 \times 10^9$</td>
</tr>
<tr>
<td>Lungs</td>
<td>$30 \times 10^9$</td>
</tr>
</tbody>
</table>

*Fig. 1.13* Distribution of lymphocytes in lymphoid organs and other tissues. Approximate numbers of lymphocytes in different organs of healthy adults are shown.
The spleen is a highly vascularized 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 (Fig. 1.15). Blood entering the spleen flows through a network of channels (sinusoids). Blood-borne antigens are captured and concentrated by dendritic cells and macrophages in the spleen. The spleen contains abundant phagocytes that line the sinusoids, which ingest and destroy microbes in the blood. These macrophages also ingest and destroy old red blood cells.
• The **cutaneous immune system** and **mucosal immune system** are specialized collections of lymphoid tissues and APCs located in and under the epithelia of the skin and the gastrointestinal and respiratory tracts, respectively. Although most of the immune cells in these tissues are diffusely scattered beneath the epithelial barriers, there are discrete collections of lymphocytes and APCs organized in a similar way as in lymph nodes. For example, tonsils in the pharynx and Peyer patches in the intestine are two anatomically defined mucosal lymphoid tissues (Fig. 1.16). The immune system of the skin consists of most of the cells of innate and adaptive immunity, but without any anatomically defined structures (Fig. 1.17). At any time, at least a quarter of the body’s lymphocytes are in the mucosal tissues and skin (reflecting the large size of these tissues) (see Fig. 1.13), and many
of these are memory cells. Cutaneous and mucosal lymphoid tissues are sites of immune responses to antigens that breach epithelia. A remarkable property of the cutaneous and mucosal immune systems is that they are able to respond to pathogens but do not react to the enormous numbers of usually harmless commensal microbes present at the epithelial barriers. This is accomplished by several mechanisms, including the action of regulatory T cells and other cells that suppress rather than activate T lymphocytes.

Within the peripheral lymphoid organs, T lymphocytes and B lymphocytes are segregated into different anatomic compartments (Fig. 1.18). 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 a protein antigen and received signals from helper T cells, this follicle may contain a central lightly staining region called a germinal center. The germinal center has an important role in the production of highly effective antibodies and is described in Chapter 7. The T lymphocytes are concentrated outside but adjacent to the follicles, in the paracortex. The follicles contain the FDCs described earlier that are involved in the activation of B cells, and the paracortex contains 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 after stimulation by antigens. B lymphocytes are attracted to and retained in the follicles because of the action of a class of cytokines called chemokines (chemoattractant cytokines; chemokines and other cytokines are discussed in more detail in later chapters). FDCs in the follicles secrete a particular chemokine for which naive B cells express a receptor, called CXCR5.
The chemokine that binds to CXCR5 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 CCR7, which recognizes chemokines that are produced in these regions of the lymph nodes and spleen. When the lymphocytes are activated by antigens, they alter their expression of chemokine receptors. As a result, the antigen-activated 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). Thus, these lymphocyte populations are kept apart from each other until it is useful for them to interact, after exposure to an antigen. This is an excellent example of how the structure of lymphoid organs ensures that the cells that have recognized and responded to an antigen interact and communicate with one another only when necessary.

Many of the effector T cells 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.

Fig. 1.18 Segregation of T and B lymphocytes in different regions of peripheral lymphoid organs. A, Schematic diagram illustrates the path by which naive T and B lymphocytes migrate to different areas of a lymph node. Naive B and T 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 (see Chapter 3). B, In this histologic section of a lymph node, the B lymphocytes, located in the follicles, are stained green, and the T cells, in the parafollicular cortex, are stained red using immunofluorescence. In this technique, a section of the tissue is stained with antibodies specific for T or B cells 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 Drs. Kathryn Pape and Jennifer Walter, University of Minnesota Medical School, Minneapolis, MN.)
Some activated T cells remain in the lymphoid organ where they were generated and migrate into lymphoid follicles, where they help B cells to make high-affinity antibodies.

**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 from lymphoid tissues to sites of infection, where microbes are eliminated (Fig. 1.19). Thus, lymphocytes at distinct stages of their lives migrate to the different sites where they are needed for their functions. Migration of effector lymphocytes to sites of infection is most relevant for T cells because effector T cells have to locate and eliminate microbes at these sites. By contrast, plasma cells do not need to migrate to sites of infection; instead, they secrete antibodies, and the antibodies enter the blood. These antibodies bind pathogens or toxins in the blood, or in tissues into which the antibodies enter. Plasma cells in mucosal organs secrete antibodies that enter the lumens of these organs, where they bind to and combat ingested and inhaled microbes.

The migration of different lymphocyte populations has distinct features and is controlled by different molecular interactions.

- Naive T lymphocytes that have matured in the thymus and entered the circulation migrate to lymph nodes, where they can find antigens that are brought to the lymph nodes 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). The adhesion molecules used by the T cells to bind to the endothelium are described in Chapter 5. Chemokines produced in the T cell zones of the lymph nodes and displayed on HEV surfaces bind to the chemokine receptor CCR7 expressed on naive T cells, which causes the T cells to bind tightly to HEVs. The naive T cells then migrate into the T cell zone, where antigens are displayed by dendritic cells. Naive B cells also enter lymphoid tissues but then migrate to follicles in response to chemokines that bind CXCR5, the chemokine receptor expressed on these B cells.

- In the lymph node, T cells move around rapidly, scanning the surfaces of dendritic cells for antigens. If a T cell specifically recognizes an antigen on a dendritic cell, that T cell forms stable conjugates with
the dendritic cell 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 mentioned earlier and described further 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. Thus, T cells find the antigen they can recognize, and these T cells are activated to proliferate and differentiate. Naive cells that have not encountered specific antigens leave the lymph nodes and reenter the circulation.

- The effector cells that are generated upon T cell activation preferentially migrate into the tissues infected by microbes, where the T lymphocytes perform their function of eradicating the infection. Specific signals control these precise patterns of migration of naive and activated T cells (see Chapter 6).
- B lymphocytes that recognize and respond to antigen in lymph node follicles differentiate into antibody-secreting plasma cells, most of which migrate to the bone marrow or mucosal tissues (see Chapter 7).
- Memory T cells consist of different populations (see Chapter 6); some cells recirculate through lymph nodes, where they can mount secondary responses to captured antigens, and other cells migrate to sites of infection, where they can respond rapidly to eliminate the infection. Yet other memory cells permanently reside in epithelial tissues, such as mucosal tissues and the skin.

We know less about lymphocyte circulation through the spleen or other lymphoid tissues. The spleen does not contain HEVs, but the general pattern of naive lymphocyte migration through this organ probably is similar to migration through lymph nodes.

**SUMMARY**

- The physiologic function of the immune system is to protect individuals against infections and cancers.
- 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 mediated by lymphocytes stimulated by microbial antigens, which leads to the proliferation and differentiation of the lymphocytes and generation of effector cells, 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 specific for different 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 surface expression of particular membrane molecules.

- B lymphocytes are the only cells that produce antibodies. B lymphocytes express membrane antibodies that recognize antigens, and the progeny of activated B cells, called plasma 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 produce cytokines that activate phagocytes to destroy ingested microbes, recruit leukocytes, and activate B lymphocytes to produce antibodies. Cytotoxic T lymphocytes (CTLs) kill infected cells harboring microbes in the cytoplasm.
- Antigen-presenting cells (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 (secondary) lymphoid organs, where immune responses are initiated and develop.
- Naive lymphocytes circulate through peripheral lymphoid organs, searching for foreign antigens. Effector T lymphocytes migrate to peripheral sites of infection, where they function to eliminate infectious microbes. Plasma cells remain in lymphoid organs and the bone marrow, 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, and how do they differ in function?
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?

Answers to and discussion of the Review Questions are available at Student Consult.