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Lymphoid Organs: Introduction

The body has a system of cells—**the immune system**—that has the ability to distinguish "self" (the organism's own molecules) from "nonself" (foreign substances). This system has the ability to neutralize or inactivate foreign molecules (such as soluble molecules as well as molecules present in viruses, bacteria, and parasites) and to destroy microorganisms or other cells (such as virus-infected cells, cells of transplanted organs, and cancer cells). On occasion, the immune system of an individual reacts against its own normal body tissues or molecules, causing **autoimmune diseases.**

The cells of the immune system (1) are distributed throughout the body in the blood, lymph, and epithelial and connective tissues; (2) are arranged in small spherical nodules called **lymphoid nodules** found in connective tissues and inside several organs; and (3) are organized as differently sized organs called **lymphoid organs**—the lymph nodes, the spleen, the thymus, and the bone marrow. Lymphoid nodules and isolated cells of the immune system found in the mucosa of the digestive system (tonsils, Peyer's patches, and appendix), the respiratory system, the reproductive system, and the urinary system are collectively known as mucosa-associated lymphoid tissue **(MALT)** and may be considered a lymphoid organ. The wide distribution of immune system cells and the constant traffic of lymphocytes through the blood, lymph, connective tissues, and lymphoid organs provide the body with an elaborate and efficient system of surveillance and defense (Figure 14–1).

Figure 14–1.

The lymphoid organs and lymphatic vessels are widely distributed in the body. The lymphatic vessels collect lymph from most parts of the body and deliver it to the blood circulation primarily through the thoracic duct.

Antigens

A molecule that is recognized by cells of the immune system is called an **antigen** and may elicit a response from these cells. Antigens may consist of soluble molecules (such

as proteins, polysaccharides, and nucleoproteins) or molecules belonging to whole cells (bacteria, protozoa, tumor cells, or virus-infected cells). The cells of the immune system do not recognize and react to the whole antigen molecule but instead react to small molecular domains of the antigen known as **antigenic determinants** or **epitopes.** The response of the organism to antigens may be called cellular (in which lymphocytes are primarily in charge of eliminating the antigen) or humoral (in which molecules secreted by plasma cells, called antibodies, are primarily responsible for the response). Some epitopes (eg, polysaccharides of bacterial walls or lipids) usually elicit a humoral response whereas proteins elicit both a cellular and humoral response. More details on cellular and humoral immune responses are provided below.

Antibodies

An **antibody** is a glycoprotein that interacts specifically with an antigenic determinant. Antibodies belong to the **immunoglobulin (Ig)** protein family. Free molecules of antibodies are secreted by plasma cells that arise by proliferation and terminal differentiation of clones of B lymphocytes whose receptors recognize and bind specific epitopes. These secreted antibodies either circulate in the plasma and may leave the blood vessels reaching the tissues or are present in the secretion of some epithelia (eg, of the mammary gland and salivary glands). Other antibodies are not free molecules, but are integral membrane proteins of the surface of lymphocytes. In any case, each antibody combines with the epitope that it specifically recognizes.

There are several classes of antibody molecules but all have a common design: they consist of two identical light chains and two identical heavy chains bound by disulfide bonds and noncovalent forces (Figure 14–2). The isolated carboxyl-terminal portion of the heavy chain molecules is called the **Fc region.** The Fc regions of some immunoglobulins are recognized by receptors present on the membrane of several cell types and for this reason antibodies may bind to the surface of these cells. The first 110 amino acids near the amino-terminal part of the light and heavy chains are very variable among different antibody molecules. Therefore, this region of the molecule is called the **variable region.** The **antigen-binding site** of an antibody consists of the variable regions of one heavy and one light chain. Thus, each antibody molecule has two binding sites for antigens, both for the same antigen. The molecules of some of the immunoglobulin classes may form dimers, trimers, or pentamers.

Figure 14–2.

Two light chains and two heavy chains form an antibody molecule. The chains are linked by disulfide bonds. The variable portions near the NH_2 end of the light and heavy chains bind the antigen. The Fc region of the molecule may bind to surface receptors of several cell types.

Classes of Antibodies

The main classes of immunoglobulins in humans are immunoglobulin G (IgG), IgA, IgM, IgE, and IgD (Table 14–1).

Table 14–1. Summary of Classes of Antibodies.

	lgG	**lgM**	**lgA**	**lgD**	**lgE**
Structure	Monomer	Pentamer	Dimer or trimer with secretory component	Monomer	Monomer
Antibody percentage in the serum	80%	5–10%	10–15%	0.2%	0.002%
Presence in sites other than blood, connective tissue, and lymphoid organs	Fetal circulation in pregnant women	B lymphocyte surface (as a monomer)	Secretions (saliva, milk, tears, etc)	Surface of B lymphocytes	Bound to the surface of mast cells and basophils
Known functions	Activates phagocytosis, neutralizes antigens, protects newborn	First antibodies to be produced in an initial immune response; activates complement	Protects the surfaces of mucosas	Functions as a receptor to antigens triggering initial B cell activation	Participates in allergy and destruction of parasitic worms

IgG is the most abundant class representing 75% of serum immunoglobulins. It is produced in large amounts during immune responses. IgG is the only immunoglobulin that crosses the placental barrier and is transported to the circulatory system of the fetus, protecting the newborn against infections for a certain period of time.

IgA is the main immunoglobulin found in secretions, such as nasal, bronchial, intestinal, and prostatic, as well as in tears, colostrum, saliva, and vaginal fluid. It is present in secretions as a dimer or trimer called **secretory IgA,** composed of two or three molecules of monomeric IgA united by a polypeptide chain called **protein J** and combined with another protein, the **secretory,** or **transport,component.** Because it is resistant to several enzymes, secretory IgA subsists in the secretions where it provides protection against the proliferation of microorganisms. IgA monomers and protein J are secreted by plasma cells in the lamina propria of the epithelium of the digestive,

respiratory, and urinary passages; the secretory component is synthesized by the mucosal epithelial cells and is added to the IgA polymer as it is transported through the epithelial cells.

IgM constitutes about 10% of blood immunoglobulins and usually exists as a pentamer. Together with IgD, it is the major immunoglobulin found on the surface of B lymphocytes. These two classes of immunoglobulins have both membrane-bound and circulating forms. IgM bound to the membrane of a B lymphocyte functions as its specific receptor for antigens. The result of this interaction is the proliferation and further differentiation of B lymphocytes into antibody-secreting plasma cells. Secreted IgM, when bound to antigen, is very effective in activating the **complement system.**

IgE usually exists as a monomer. As its Fc region has a great affinity for receptors present on the surfaces of mast cells and basophils, it attaches to these cells after being secreted by plasma cells and only small amounts are found in the blood. When IgE molecules present on the surface of mast cells or basophils encounter the antigen that elicited the production of this specific IgE, the antigen–antibody complex triggers the liberation of several biologically active substances, such as histamine, heparin, leukotrienes, and eosinophil-chemotactic factor of anaphylaxis. This characterizes an **allergic reaction,** which is thus mediated by the binding of cell-bound IgE with the antigens **(allergens)** that stimulated its production (see Mast Cells in Chapter 5: Connective Tissue).

The properties and activities of **IgD** are not completely understood. It has a molecular mass of 180 kDa, and its concentration in blood plasma constitutes only 0.2% of the immunoglobulins. IgD is found on the plasma membranes of B lymphocytes.

Actions of Antibodies

Some antibodies are able to agglutinate cells and to precipitate soluble antigens, thus neutralizing their harmful effects on the body (Figure 14–3). Although phagocytosis of microorganisms and other particles occurs spontaneously, this event is greatly stimulated when they are covered by antibodies produced against them, a phenomenon called **opsonization** (Figure 14–3). Opsonization occurs because macrophages, neutrophils, and eosinophils have receptors for the Fc region of IgG on their surfaces.

Figure 14–3.

Mechanisms of antigen inactivation. (**1**) Agglutination, in which antibodies bind to antigens, forming aggregates and reducing the amount of free antigens; aggregates may be ingested by phagocytes; (**2**) opsonization of antigens by complement stimulates their phagocytosis; (**3**) opsonization of antigens by antibodies stimulates phagocytosis; (**4**) neutralization, in which the binding of antibody to microorganisms blocks their adhesion to cells and inactivates toxins; (**5**) cytotoxicity mediated by cells, which involves antibodies adhering to the surface of worms activating cells of

the immune system (macrophages and eosinophils) and inducing them to liberate molecules that attack the surface of the animal; (**6**) complement activation, in which the binding of antibodies to the initial protein of the complement system triggers the complement cascade and causes cell lysis.

Antigen–antibody complexes and some antigens activate the **complement system,** a group of around 20 plasma proteins produced mainly in the liver and activated through a cascade of reactions. One of the most important proteins of this system is the component called **C3**. To defend the body against foreign molecules or cells, the complement system may (1) stimulate phagocytosis of bacteria or other microorganisms because of opsonization due to the binding of C3 fragments to specific C3 receptors present on the surface of phagocytic cells (Figure 14–3) and (2) induce lysis of microorganisms by acting on their cell membranes (Figure 14–3).

Cytokines

The function of the immune system is regulated by a large number of molecules, mainly **cytokines,** which are peptides or glycoproteins with low molecular masses (between 8 and 80 kDa). They influence both the cellular and humoral immune responses (Table 14–2). Cytokines act on many cells that have receptors for them—not only cells of the immune system, but also cells of other systems, such as the nervous system and endocrine system. They are primarily produced by cells of the immune system, mainly lymphocytes, macrophages, and leukocytes, but may also be synthesized by other cell types, such as endothelial cells and fibroblasts. **Chemotaxins,** or **chemokines,** are cytokines that induce the attraction of leukocytes to sites of inflammation.

Table 14–2. Examples of Cytokines, Grouped According to Their Main Function.

Cytokine[1]	**Main Function**
GM-CSF, M-CSF	Growth and differentiation factors for bone marrow cells
TNF- , IL-1, IL-6	Inflammation and fever
IL-12	Stimulation of innate and specific response
IL-2, IL-4, IL-3	Growth factors for T and B cells
IL-5	Eosinophil differentiation and activation
Interferon-	Activation of macrophages
IL-10, TGF-	Regulation of the immune response

Interferon- , Interferon-	Antiviral activity

[1]GM-CSF, granulocyte–macrophage colony-stimulating factor; M-CSF, macrophage colony-stimulating factor; TNF, tumor necrosis factor; IL, interleukin; TGF, transforming growth factor.

Cells of the Immune System

The primary cells that participate in the immune response are lymphocytes, plasma cells, mast cells, neutrophils, eosinophils, and cells of the mononuclear phagocyte system. Antigen-presenting cells, a group of very diverse cell types, assist other cells in the immune response. This group includes, among other cells, lymphocytes, macrophages, and dendritic cells.

Lymphocytes

Lymphocytes are classified as **B,T,** or **natural killer (NK) cells.** The B and T cells are the only cells that have the ability to selectively recognize a specific epitope among a vast number of different epitopes (of the order of 10^{18}). B and T cells differ based on their life history, surface receptors, and behavior during an immune response. Although B and T cells are morphologically indistinguishable in either the light or electron microscope, they can be distinguished by immunocytochemical methods because they have different surface proteins (markers). The precursors of all lymphocyte types originate in the bone marrow; some lymphocytes mature and become functional in the bone marrow, and after leaving the bone marrow enter the blood circulation to colonize connective tissues, epithelia, lymphoid nodules, and lymphoid organs. These are the **B lymphocytes** (Figure 14–4). **T lymphocyte precursors,** on the other hand, leave the bone marrow, and through the blood circulation reach the thymus where they undergo intense proliferation and differentiation or die by apoptosis. After their final maturation, T cells leave the thymus and are distributed throughout the body in connective tissues and lymphoid organs (Figure 14–4). Because of their function in lymphocyte production and maturation, the bone marrow and the thymus are called the **primary** or **central lymphoid organs.** The other lymphoid structures are the **secondary** or **peripheral lymphoid** organs (spleen, lymph nodes, solitary lymphoid nodules, tonsils, appendix, and Peyer's patches of the ileum). B and T cells are not anchored in the lymphoid organs; instead, they continuously move from one location to another, a process known as **lymphocyte recirculation.** B and T cells are not uniformly distributed in the lymphoid system but occupy preferential sites in these organs (Table 14–3).

Figure 14–4.

Origin of the main types of lymphocytes. B lymphocytes and natural killer lymphocytes are formed in the bone marrow and leave the bone marrow already mature, to seed the secondary lymphoid organs and transit through the blood, epithelia, and connective tissues. Immature $CD4^-$ and $CD8^-$ T lymphocyte precursors are transported by the blood circulation from the bone marrow to the thymus, where they complete their maturation and leave as either $CD4^+$ or $CD8^+$ cells.

Table 14–3. Approximate Percentage of B and T Lymphocytes in Lymphoid Organs.

Lymphoid Organ	**T Lymphocytes, (%)**	**B Lymphocytes, (%)**
Thymus	100	0
Bone marrow	10	90
Spleen	45	55
Lymph nodes	60	40
Blood	75	35

A very important feature of B and T lymphocytes involves the receptors they have on their surface. These receptors are fundamental for recognition of antigen epitopes and, thus, for triggering an immune response. T cells recognize a linear sequence of amino acids whereas in B cells the spatial arrangement (ie, the molecular conformation) of proteins, nucleic acids, polysaccharides, or lipids is also important. Each B lymphocyte that leaves the bone marrow or each T lymphocyte that leaves the thymus has just one type of surface receptor that recognizes a specific epitope. As a result of gene rearrangement during the maturation of B and T cells, many millions (10^{13} to 10^{18}) of different cells, each carrying identical surface receptors able to recognize one specific epitope, are produced. Thus, each lymphocyte recognizes only one epitope.

In an organism not yet exposed to antigens, very few individual lymphocytes are able to recognize each of the millions of epitopes that exist. The exact number is not known, but may vary from one to a few hundred. Soon after a lymphocyte is first exposed to the epitope it recognizes, a stimulus to cell proliferation occurs, leading to an amplification of that particular lymphocyte population, and thereby producing an expanded clone of lymphocytes able to recognize that epitope.

B Lymphocytes

In B lymphocytes, the surface receptors able to recognize antigens are monomeric molecules of IgM; each B cell is covered by about 150,000 molecules of IgM. The encounter of a B lymphocyte with the epitope it recognizes leads to several cycles of cell proliferation, followed by a redifferentiation of most of these lymphocytes into **plasma cells.** This population of plasma cells secretes antibodies against the same epitope as that of the B cell that originated them. In most cases, the activation of B cells requires the assistance of a subclass of T lymphocytes known as **T-helper**

lymphocytes. Not all activated B cells, however, become plasma cells; some remain **B memory lymphocytes,** which react rapidly to a second exposure to the same epitope.

T Lymphocytes

T cells constitute 65–75% of blood lymphocytes. To recognize epitopes, all T cells have on their surfaces a molecule called a **T cell receptor (TCR).** In contrast to B cells, which recognize soluble antigens or antigens present on cell surfaces, T lymphocytes recognize only epitopes (mostly small peptides) that form complexes with special proteins of the cell surface of other cells (proteins of the major histocompatibility complex, see below).

The two main subpopulations of T cells are **helper** and **cytotoxic lymphocytes (CTLs).** Helper cells play very important roles in the immune response, being responsible for cytokine production, interaction with B cells to promote their differentiation into plasma cells, activation of macrophages to phagocytose, activation of cytotoxic lymphocytes, and induction of an inflammatory reaction. Many of these actions are mediated by cytokines. Helper cells have a marker called CD4 on their surfaces and are, hence, called **$CD4^+$ T cells.** Cytotoxic, or **$CD8^+$ T cells,** can act against foreign cells or virus-infected cells by means of two main mechanisms. In one, they attach to the cells to be killed and release proteins called **perforins** that create holes in the cell membrane of the target cell, with consequent cell lysis. In the other, they attach to a cell and kill it by triggering mechanisms that induce programmed cell death, or **apoptosis.** The first encounter of a $CD4^+$ or $CD8^+$ T cell with its specific epitope is followed by amplification of that clone; some of the cells of this increased population become effector cells and some remain memory helper or memory cytotoxic T cells, reacting rapidly to the next presentation of the same epitope.

Natural Killer Cells

The **natural killer** lymphocytes lack the marker molecules characteristic of B and T cells. They comprise about 10–15% of the lymphocytes of circulating blood. Their name derives from the fact that they attack virus-infected cells, transplanted cells, and cancer cells without previous stimulation; for this reason they are involved in what is called an **innate immune response.**

MEDICAL APPLICATION

One of the primary causes of the immunodeficiency syndrome known as AIDS involves the killing of helper T cells by the infecting retrovirus. This cripples patients' immune systems rendering them susceptible to opportunistic infections by microorganisms that usually do not cause disease in immunocompetent individuals.

Major Histocompatibility Complex & Antigen Presentation

The major histocompatibility complex (MHC) is a complex of chromosome loci that encodes several proteins known as class I MHC molecules and class II MHC molecules. Because a great many alleles exist for each of the loci, there is great

variation of these molecules among the general population. One individual, however, expresses only one set of class I proteins and one set of class II proteins; these proteins are unique to this individual. All nucleated cells have class I proteins; class II proteins, however, exist in only a small group of cells operationally denominated **antigen-presenting cells.**

MHC molecules are integral membrane proteins present on the cell surface. They are synthesized by polyribosomes and are inserted in the membrane of the rough endoplasmic reticulum, as a regular membrane protein. However, on their way to the cell surface, they couple with small peptides of 10–30 amino acids whose origin differs depending on whether class I or class II molecules are involved.

In most cases, class I molecules form complexes with peptides derived from cytosolic proteins synthesized by the same cell. Proteins synthesized under the direction of virus nucleic acid (in a virus-infected cell) are a good example of this kind of cytosolic protein. The proteins are targeted by ubiquitin to be degraded by proteasomes, resulting in the production of small peptides. These peptides are transported to membranes of the endoplasmic reticulum where they join class I molecules; the resulting complex migrates to the cell surface, exposing the peptides to the extracellular space (Figure 14–5).

Figure 14–5.

Binding of class I and class II MHC molecules to antigens. **Left:** The sequence of events by which antigens present in a cell (eg, in a virus-infected cell) are processed, bound to class I MHC molecules, and displayed at the cell surface. (**1**) Proteins of the cell are digested by proteasomes and are transferred to the rough endoplasmic reticulum (RER) where they associate with class I MHC molecules synthesized at the RER. (**2**) The class I MHC–antigen complex is transferred to the Golgi region. (**3**) Golgi vesicles transport the complex to the cell membrane presenting the antigen at the outer surface. **Right:** Formation of complexes between class II MHC molecules and antigens internalized by the cell. (**1**) Synthesis of class II MHC molecules. (**2**) Transfer of class II MHC molecules to the Golgi region and formation of a Golgi vesicle. Fusion of the Golgi vesicle to an endolysosome that contains antigens processed after endocytosis and digestion of antigens by lysosomic enzymes **(a, b, c)**. (**3**) Antigens form complexes with class II MHC molecules. (**4**) The class II MHC–antigen complex is exposed at the cell surface.

The peptides that join class II MHC molecules result mostly from endocytosis and digestion in endolysosomes. The vesicles that contain these peptides fuse with Golgi-derived vesicles that have class II MHC embedded in their membranes. The peptides form complexes with the MHC proteins and, as in the case of class I molecules, the complex is transported to the cell surface exposing the peptides to the exterior of the cell (Figure 14–5).

Contrary to B cells, which recognize soluble antigens or antigens present on cell surfaces, T lymphocytes recognize only small peptides displayed by MHC molecules. However, the T cell receptor does not interact only with the peptide; instead it interacts with the complex formed by the peptide and the portion of the MHC protein exposed on the surface of the antigen-presenting cell. Moreover, T cells from an individual recognize this complex only if the MHC molecule belongs to the same individual (self MHC molecules). This happens because during T cell development in the thymus, the T cell precursors whose receptors did not recognize self MHC molecules were induced to die. The display of peptides on the surface of antigen-presenting cells is known as **antigen presentation.**

Because different individuals express different MHC molecules, cell or organ transplantation between genetically distinct individuals induces an intense immune reaction that leads to the rejection of the graft.

The cytosolic peptides displayed by class I molecules may derive from (1) the cells' own proteins, in which case the T cell will recognize them as self-proteins, or (2) foreign proteins produced by cells infected by viruses, tumor cells, or transplanted cells and organs. The peptides displayed by class II molecules are mostly foreign proteins internalized by the cells through phagocytosis.

MEDICAL APPLICATION

Organ Transplantation

Tissue grafts and organ transplants are classified as **autografts** when the transplanted tissues or organs are taken from the individual receiving them, **isografts** when taken from an identical twin, **homografts** or **allografts** when taken from an individual (related or unrelated) of the same species, and **heterografts** or **xenografts** when taken from an animal of a different species.

The body readily accepts autografts and isografts as long as an efficient blood supply is established for the organ. There is no rejection in such cases, because the transplanted cells are genetically identical to those of the host and present the same MHC on their surfaces. The organism recognizes the grafted cells as self (same MHC) and does not react with an immune response.

Homografts and heterografts, on the other hand, contain cells whose membranes have class I and class II MHC molecules that are foreign to the host; they are therefore recognized and treated as such. Transplant rejection is a complex process due to the activity of T lymphocytes and antibodies that react to and destroy the transplanted cells.

Antigen-Presenting Cells (APCs)

APCs are found in many tissues and constitute a heterogeneous cell population that includes B lymphocytes, macrophages, and dendritic cells. The dendritic cells (not to be confused with cells of the nervous tissue) are present within the epidermis (where they are called **Langerhans cells**), within other epithelia, and within lymphoid organs.

A common feature of APCs is the presence of class II MHC molecules on their surfaces. $CD4^+$ T (helper) cells interact with complexes formed by peptides and class II MHC molecules on APCs, whereas $CD8^+$ T (cytotoxic) cells interact with complexes of peptides with class I MHC molecules that can be presented by any nucleated cell. APCs, being recognized by helper lymphocytes, are, thus, essential for the triggering and development of a complex immune response.

The Langerhans cells of the epidermis constitute a very efficient system for trapping antigens that happen to enter the epidermis. These cells have many processes and upon capturing antigens, they retract the processes, move toward the dermis, and may enter a lymphatic vessel.

Types of Immune Responses

The two basic types of immune responses are the **innate response** and the **adaptive response.** The innate response, which occurs through the action of neutrophils, macrophages, mast cells, and natural killer cells, is fast, nonspecific, and older from an evolutionary point of view. It does not produce memory cells. The adaptive response, which depends on the initial recognition of antigens by B and T cells, is much more complex, is slower and specific, produces memory cells, and is a more recent evolutionary development.

The adaptive mechanisms that lead to the elimination of antigens are classified as **humoral** or **cellular responses.** Humoral immunity is accomplished by antibodies produced by plasma cells derived from clones of activated B lymphocytes. Cellular immunity is mediated by T lymphocytes that (1) secrete cytokines that act on B lymphocytes, on other T cells, and on inflammatory cells such as macrophages and neutrophils, and (2) attack foreign cells or cells that exhibit foreign epitopes on their surfaces, such as cells infected by viruses or parasites, and tumor cells. With few exceptions, both types of immune response are activated when foreign epitopes are recognized by lymphocytes.

Antigens (such as a microorganism or molecules) that reach the skin or a mucosa (or the connective tissue in the case of an injected vaccine) have two main fates. In the first, the antigen is phagocytosed either by a macrophage or by a dendritic cell and is transported by these cells through the lymphatic vessels to the lymph node that drains that region of the body (**satellite lymph node**). In the second, the molecules, the whole microorganism, or its debris are transported by the lymph to the satellite lymph node where macrophages or other APCs phagocytose them. Antigens that reach the lymph node are recognized by B lymphocytes. APCs that arrived from the skin or mucosa as well as APCs that processed antigens within the lymph node display the antigens to helper T lymphocytes as complexes with class II MHC molecules (Figure 14–6). B lymphocytes that recognize antigens are activated by helper cells to enter several cycles of cell division. Many of the daughter cells of B lymphocytes differentiate into plasma cells that secrete antibodies against the antigen recognized by the first B lymphocyte. The plasma cells secrete most of the antibodies into the lymph and the antibodies eventually reach the blood circulation and act on antigens in different ways (Figure 14–3). B cells that are not transformed into plasma cells remain B memory cells.

Figure 14–6.

Basic events of the immune response of an organism to a microorganism. B lymphocytes recognize antigens as well as helper T lymphocytes after presentation by antigen-presenting cells. Helper cells stimulate B cells to enter several cycles of cell division followed by differentiation of many daughter cells into plasma cells that secrete antibodies to the antigen recognized by the first B lymphocyte. In practice, several different B cells recognize different epitopes, so that several different antibodies are produced. After the microorganism has been eliminated, some of the lymphocytes remain as long-lived memory cells.

Intracellular antigens, such as those synthesized in the cytosol of virus-infected cells, tumor cells, or transplanted cells, are presented to cytotoxic T lymphocytes bound to class I MHC molecules (Figure 14–7). Concurrently, APCs that phagocytose fragments of viruses, tumor cells, or transplanted cells display the antigens to helper T lymphocytes, bound to class II MHC molecules. Cytotoxic T cells, activated by helper cells, enter several cycles of proliferation and some of these cells become effector cytotoxic T cells that will destroy the cells that hold the antigens (Figure 14-7). Some cells, instead of becoming effector cells, remain memory cytotoxic T cells. A humoral response resulting from recognition of antigens by B lymphocytes generally occurs simultaneously.

Figure 14–7.

Basic events of the immune response of an organism to a virus infection. Virus-infected cells present antigens as complexes with class I MHC cells. The complexes are recognized by cytotoxic T lymphocytes that are stimulated by helper T lymphocytes to enter several cycles of cell division. Many daughter cytotoxic cells turn into effector cells that kill the infected cells. A population of helper and cytotoxic cells remains as memory cells. A simultaneous humoral response is usually launched by B lymphocytes that recognized the antigen.

MEDICAL APPLICATION

Diseases of the Immune System

The diseases of immune system can be broadly grouped into three types:

1. Some individuals develop abnormal and intense reactions in an attempt to neutralize the effects of some antigens. This exaggerated intolerance produces the numerous processes called **allergic reactions.**

2. The immune response can be impaired, a condition generally called **immunodeficiency**; this may have several causes, such as genetic or infectious (eg, by measles and human immunodeficiency virus). Immunodeficiencies of genetic origin may be caused by mutations or deletions in genes that codify for molecules that participate in effector immune mechanisms or that are involved in the differentiation of T, B, and APC cell populations. As such, immunodeficiencies may affect the complement system, phagocytic activity, and the development and function of B and T lymphocytes.

3. Autoimmune diseases are caused by T or B cell responses directed to self molecules. Tissues are affected or even destroyed by cytotoxic T lymphocytes or by autoantibodies.

Lymphoid Tissue

Lymphoid tissue is a type of connective tissue characterized by a rich supply of lymphocytes. It exists free within the regular connective tissue or is surrounded by capsules, forming the lymphoid organs. Because lymphocytes have very little cytoplasm, lymphoid tissue stains dark blue in hematoxylin and eosin-stained sections. Lymphoid tissues are basically made up of free cells; as a result, they typically have a rich network of reticular fibrils (made principally of type III collagen) that supports the cells (Figure 14–8). In most lymphoid organs, the fibrils are produced by a fibroblastic cell called a **reticular cell,** whose many processes rest on the reticular fibrils (Figures 5–46 and 14–25). The thymus is an exception in so far as its cells are supported by a reticulum of epithelial cells of endodermic origin.

Figure 14–8.

A three-dimensional skeleton of reticular fibers supports the cells of most lymphoid tissues and organs (except the thymus). Areas with larger meshes offer more mobility to cells than areas in which the meshes are tight (darker parts of the figure) and the cells are more stationary. Silver impregnation. Medium magnification. (Courtesy of PA Abrahamsohn.)

Figure 14–25.

Medullary sinus of a lymph node containing reticular cells with long processes and elongated nuclei, macrophages, and many lymphocytes. (**1**) Macrophage; (**2**) reticular cell; (**3**) trabecula. H&E stain. High magnification. (Courtesy of PA Abrahamsohn.)

The network of reticular fibrils of the lymphoid tissue may be relatively closed (**dense lymphoid tissue**) and is, thus, able to hold many free cells (mostly lymphocytes, macrophages, and plasma cells). Another type is **loose lymphoid** tissue, whose network has fewer but larger spaces, providing means for easy movement of the free cells (Figure 14–8).

In the **nodular lymphoid tissue,** groups of lymphocytes are arranged as spheres, called **lymphoid nodules** or **lymphoid follicles,** that primarily contain B lymphocytes. When lymphoid nodules become activated as a result of the arrival of antigen-carrying APCs and recognition of the antigens by B lymphocytes, these lymphocytes proliferate in the central portion of the nodule, which then stains lighter and is called a **germinative center.** After completion of the immune response, the germinative center may disappear. The germinative centers contain a special cell, the **follicular dendritic cell** (distinct from the epithelial dendritic APCs), that has many processes that bind antigen on their surfaces, to be presented to B lymphocytes.

Lymphoid nodules vary widely in size, typically measuring a few hundred micrometers to 1 mm in diameter. They are found free in connective tissues anywhere in the body or within lymphoid organs (lymph nodes, spleen, tonsils, but not in the thymus). They are, however, never covered by a capsule. Free lymphoid nodules are commonly present in the lamina propria of several mucosal linings, where, together with free lymphocytes, they constitute the mucosa-associated lymphoid tissue (MALT).

Mucosa-Associated Lymphoid Tissue & Tonsils

The digestive, respiratory, and genitourinary tracts are common sites of microbial invasion because their lumens are open to the external environment. To protect the organism, the mucosa and submucosa of these tracts contain a large amount of diffuse collections of lymphocytes, IgA-secreting plasma cells, APCs, and lymphoid nodules (Figure 14–9). Most of the lymphocytes are B cells; among T cells, $CD4^+$ helper cells predominate. In some places, these aggregates form conspicuous structures such as the tonsils and the Peyer's patches in the ileum. Similar aggregates are found in the appendix.

Figure 14–9.

Section of lung showing a collection of lymphocytes in the connective tissue of the bronchiolar mucosa, an example of mucosa-associated lymphoid tissue (MALT). Pararosaniline–toluidine blue (PT) stain. Low magnification.

In the Peyer's patches, some of the regular surface epithelial cells may be replaced by special **M cells** (Figure 14–10). The M cells do not have microvilli as do the regular cells that line the intestine. By pinocytosis they actively capture and transport antigens from the intestinal lumen to the connective tissues where APCs and B lymphocytes are usually present (Figure 14–11). The plasma cells derived from these lymphocytes secrete mostly IgA, which is transported through the epithelium toward the intestinal cavity.

Figure 14–10.

Section of Peyer's patch of the small intestine showing the epithelial covering of enterocytes and goblet cells (**right**), the intestinal lumen (**center**), and the covering of the patch with a row of M cells and groups of lymphocytes (**left**). The small dark nuclei belong to lymphocytes, and the large pale-stained nuclei belong to M cells. PT stain. Medium magnification.

Figure 14–11.

General view of the mucosa immunity in the intestine. Luminal antigens are captured by dome-shaped M cells present in the covering of Peyer's patches and transported to the subjacent region. Antigens are recognized by B lymphocytes and displayed to helper T lymphocytes by antigen-presenting cells (macrophages and dendritic cells). B lymphocytes are stimulated by helper cells to differentiate into IgA-secreting plasma cells. Many IgA molecules are transported to the intestinal lumen coupled with the secretory piece.

Tonsils

Tonsils belong to the MALT, but because they are incompletely encapsulated, they are considered organs and will be studied apart from the MALT. The tonsils constitute a lymphoid tissue that lies beneath, and in contact with, the epithelium of the initial portion of the digestive tract. Depending on their location, tonsils in the mouth and pharynx are called **palatine, pharyngeal,** or **lingual.**

Palatine Tonsils

The two palatine tonsils are located in the lateral walls of the oral part of the pharynx (Figure 14–12). They are lined with a squamous stratified epithelium that often becomes so densely infiltrated by lymphocytes that it may be difficult to recognize (Figure 14–13). The lymphoid tissue in these tonsils forms a band that contains free

lymphocytes and lymphoid nodules, generally with germinal centers (Figure 14–12). Each tonsil has 10–20 epithelial invaginations that penetrate the tonsil deeply, forming **crypts,** whose lumens contain desquamated epithelial cells, live and dead lymphocytes, and bacteria. Crypts may appear as purulent spots in tonsillitis. Separating the lymphoid tissue from subjacent structures is a band of dense connective tissue, the **capsule** of the tonsil (Figure 14–12). This capsule usually acts as a barrier against spreading tonsillar infections.

Figure 14–12.

A: The palatine tonsil consists of diffuse lymphocytes and lymphoid nodules disposed under a stratified squamous epithelium. One of the crypts of the tonsil is shown; the crypts often contain dead epithelial and inflammatory cells. **B:** (**1**) Crypt; (**2**) stratified squamous epithelium; (**3**) lymphoid nodules; (**4**) diffuse lymphoid tissue; (**5**) germinative center; (**6**) capsule; (**7**) mucous glands. Hematoxylin and eosin (H&E) stain. Low magnification. (Courtesy of PA Abrahamsohn.)

Figure 14–13.

Stratified squamous epithelium of the palatine tonsil. This epithelium contains a few lymphocytes and neutrophils but often becomes so infiltrated that its recognition is difficult. Free cells are seen within the crypt on the right. H&E stain. High magnification. (Courtesy of PA Abrahamsohn.)

Pharyngeal Tonsil

The pharyngeal tonsil is a single tonsil situated in the superior— posterior portion of the pharynx. It is covered by ciliated pseudostratified columnar epithelium typical of the respiratory tract, although areas of stratified epithelium can also be observed.

The pharyngeal tonsil is composed of pleats of mucosa and contains diffuse lymphoid tissue and lymphoid nodules. It has no crypts, and its capsule is thinner than the capsule of the palatine tonsils. Hypertrophied pharyngeal tonsils resulting from chronic inflammation are called **adenoids.**

Lingual Tonsils

The lingual tonsils are smaller and more numerous than the palatine and pharyngeal tonsils. They are situated at the base of the tongue (see Chapter 15: Digestive Tract) and are covered by stratified squamous epithelium. Each lingual tonsil has a single crypt.

Thymus

The thymus is a lymphoepithelial organ located in the mediastinum; it attains its peak development during youth. Whereas the other lymphoid organs originate exclusively from mesenchyme (mesoderm), the thymus has a dual embryonic origin. Its lymphocytes arise in the bone marrow from cells of mesenchymal origin that invade an epithelial primordium that has developed from the endoderm of the third and fourth pharyngeal pouches.

The thymus has a connective tissue capsule that penetrates the parenchyma and divides it into incomplete lobules, so that there is continuity between the cortex and medulla of adjoining lobules (Figure 14–14). Each lobule has a peripheral dark zone known as the **cortex** and a central light zone called the **medulla** (L. *medius*, middle).

Figure 14–14.

Photomicrograph of a section of thymus showing the lobules. Two lobules show the dark cortical and the light medullary zones. PT stain. Low magnification.

The **cortex** (Figure 14–15) is composed of an extensive population of T cell precursors (also called **thymocytes**), dispersed epithelial reticular cells, and macrophages. Because the cortex is richer in small lymphocytes than the medulla, it stains more darkly. The epithelial reticular cells are stellate cells with light-staining oval nuclei. They are usually joined to similar adjacent cells by desmosomes (Figure 14–16). Bundles of intermediate keratin filaments (tonofibrils) in their cytoplasm are evidence of the epithelial origin of these cells. A subpopulation of epithelial reticular cells present in the cortex consists of **thymic nurse cells** (**TNCs**), which contain many (20–100) maturing lymphocytes in their cytoplasm.

Figure 14–15.

Thymus cortical zone showing epithelial reticular cells with visible nucleoli (arrowheads) surrounded by dark-stained T lymphocytes. PT stain. Medium magnification.

Figure 14–16.

The relationship between epithelial reticular cells and thymus lymphocytes. Note the desmosomes and the long processes of epithelial reticular cells extending among the lymphocytes.

The **medulla** (Figure 14–17) contains epithelial reticular cells, many differentiated T lymphocytes, and structures called **thymic corpuscles** or **Hassall corpuscles,** which are characteristic of this region, although their function is unknown (Figure 14–18). These corpuscles contain flattened epithelial reticular cells that are arranged concentrically and are filled with keratin filaments. They sometimes calcify.

Figure 14–17.

Photomicrograph of the medullary zone of the thymus. Large numbers of epithelial reticular cells with their large and light-stained nuclei are responsible for the light color of the thymus medulla. This zone also contains mature T lymphocytes. PT stain. Medium magnification.

Figure 14–18.

Photomicrograph of a portion of the cortical zone, identified by its dark staining, and a portion of medulla, identified by its lighter staining and a Hassall corpuscle. These corpuscles exist only in the medulla. PT stain. Medium magnification.

Vascularization of the Thymus

Arterioles and capillaries in the thymus are surrounded by processes of epithelial reticular cells.

Thymus capillaries have a nonfenestrated endothelium and a very thick basal lamina, making these blood vessels particularly impermeable to proteins. This prevents most circulating antigens from reaching the thymus cortex, thus creating the so-called **thymic–blood barrier.**

The thymus has no afferent lymphatic vessels and does not constitute a filter for the lymph, as do lymph nodes. The few lymphatic vessels encountered in the thymus are

all efferent; they are located in the walls of blood vessels and in the connective tissue of the septa and the capsule.

Role of the Thymus in T Cell Differentiation

The thymus is the site of the terminal differentiation and selection of T lymphocytes. The thymus reaches its maximum development in relation to body weight immediately after birth; it undergoes involution after attaining its greatest size in puberty, but continues to produce lymphocytes until old age (Figure 14–19).

Figure 14–19.

Section of the thymus of an elderly adult. Severe atrophy of the parenchyma, which was partially replaced by adipose tissue, can be seen. PT stain. Low magnification.

T cell precursors, committed to produce T lymphocytes, do not exhibit the T cell receptor on their surfaces and are $CD4^-$ and $CD8^-$. They arise in the fetal liver in early fetal life and later migrate from the bone marrow to the thymus during both fetal and adult life. After penetrating the thymus, the T cell precursors populate the cortex where they divide by mitosis. In the cortex they are presented to self-antigens bound to class I and class II MHC molecules present on the surface of the epithelial cells, macrophages, and dendritic cells. The maturation and selection of T lymphocytes within the thymus are very complex processes that include positive and negative selection of T cells. Part of these processes is supposed to occur within nurse cells. In brief, thymocytes whose T cell receptors are unable to bind or, in contrast, that bind too avidly to self-antigens (about 95% of the total) are induced to die by apoptosis and are removed by macrophages. The remaining T cells survive and migrate to the medulla. Migration depends on the action of chemokines and on the interaction of thymocytes with the thymic extracellular matrix. Mature $CD4^+$ or $CD8^+$ T cells with T cell receptors on their surfaces leave the thymus, enter the blood circulation passing through the walls of medullary veins, and are distributed throughout the body (Figure 14–4).

Secretion by the Thymus

The thymus produces several proteins that act as growth factors to stimulate proliferation and differentiation of T lymphocytes. They seem to be paracrine secretions, acting in the thymus. At least four hormones have been identified:

thymosin- , thymopoietin, thymulin, and thymus humoral factor.

Lymph Nodes

Lymph nodes are distributed throughout the body along the course of the lymphatic vessels (Figure 14–1). The nodes are found in the axilla and the groin, along the great vessels of the neck, and in large numbers in the thorax and abdomen, especially in mesenteries. Lymph nodes constitute a series of in-line filters that are important in the

body's defense against microorganisms and the spread of tumor cells. All this lymph, derived from tissue fluid, is filtered by at least one node before returning to the circulation. Lymph nodes are elongated or kidney-shaped organs that have a convex surface that is the entrance site of lymphatic vessels and a concave depression, the **hilum**, through which arteries and nerves enter and veins and lymphatic vessels leave the organ (Figure 14–20). A connective tissue **capsule** surrounds the lymph node, sending trabeculae into its interior.

Figure 14–20.

Schematic representation of the structure of a lymph node. The left half of the figure shows the primary components of the organ and the circulation of lymph within a lymph node, entering through the convex side of the node and leaving through the hilum. The right half depicts part of the blood circulation.

The most common cells of lymph nodes are lymphocytes, macrophages and other APCs, plasma cells, and reticular cells; follicular dendritic cells are present within the lymphoid nodules. The different arrangement of the cells and of the reticular fibril skeleton that supports the cells creates two regions, a cortex and a **medulla** (Figures 14–20 and 14–21). The cortex can be subdivided into an **outer cortex** and an **inner cortex** or **paracortical region.**

Figure 14–21.

A: Section of a lymph node showing the cortex and the medulla and their primary components. **B:** (**1**) Capsule; (**2**) lymphoid nodule with germinative center; (**3**) subcapsular sinus; (**4**) intermediate sinus; (**5**) medullary cords; (**6**) medullary sinus; (**7**) trabecula. H&E stain. Low magnification. (Courtesy of PA Abrahamsohn.)

Cortex

The outer cortex, situated under the capsule, consists of the following components:

1. A diffuse population of cells composed mainly of T lymphocytes and reticular cells (Figure 14–21); macrophages and APCs are also present in this area.
2. Lymphoid nodules, with or without germinative centers, formed mainly by B lymphocytes, embedded in the diffuse population of cortical cells (Figures 14–20 and 14–21).

3. Areas of loose lymphoid tissue (whose reticular fibril meshes are wide) situated immediately beneath the capsule, called the **subcapsular sinuses** (Figures 14–20, 14–21, and 14–22). They are composed of a loose network of reticular cells and fibers. Lymph, containing antigens, lymphocytes, and APCs, circulates around the wide spaces of these sinuses after being delivered into these channels by the afferent lymphatic vessels.
4. **Intermediate** or **radial sinuses** that run between lymphoid nodules. These sinuses arise from and share the same structure with the subcapsular sinuses. They communicate with the subcapsular sinuses through spaces similar to those present in the medulla (Figures 14–20 and 14–21).

The inner cortex or paracortical region does not have precise boundaries with the outer cortex and contains few, if any, nodules but many T lymphocytes (Figures 14–20 and 14–21).

Figure 14–22.

Section of a portion of the outer cortex of a lymph node showing the capsule, subcapsular sinuses, diffuse lymphoid tissue, and lymphatic nodules. H&E stain. Medium magnification. (Courtesy of PA Abrahamsohn.)

Medulla

The medulla has two components:

1. The **medullary cords** (Figure 14–23) are branched cordlike extensions of dense lymphoid tissue that arise in the inner cortex. They contain primarily B lymphocytes and often plasma cells and macrophages (Figure 14–24).
2. The medullary cords are separated by dilated spaces, frequently bridged by reticular cells and fibers, called the **medullary sinuses** (Figure 14–23 and 14–25). They contain lymph, lymphocytes, often many macrophages, and sometimes even granulocytes if the lymph node is draining an infected region. These sinuses (which arise from the intermediate sinuses) join at the hilum delivering the lymph to the efferent lymph vessel of the lymph node (Figure 14–21).

Lymph Circulation

Afferent lymphatic vessels cross the capsule and pour lymph into the subcapsular sinus (Figure 14–21). From there, lymph passes through the intermediate sinuses and, finally, into the medullary sinuses. During this passage, the lymph infiltrates the cortex and the medullary cords. The lymph is finally collected by efferent lymphatic vessels at the hilum. Valves in both the afferent and efferent vessels aid the unidirectional flow of lymph (Figure 14–21).

Figure 14–23.

A: Photomicrograph of the medulla of a lymph node; the medullary sinuses are separated by medullary cords. Lymphocytes clearly predominate in number over other cell types. A blood vessel within a medullary cord is also seen. **B:** (**1**) Medullary cords; (**2**) medullary sinuses. H&E stain. Medium magnification. (Courtesy of PA Abrahamsohn.)

Figure 14–24.

A: Medullary cord of a lymphoid nodule. In addition to lymphocytes, this area contains many plasma cells (arrows). **B:** (**1**) Medullary sinus; (**2**) medullary cord. H&E stain. High magnification. (Courtesy of PA Abrahamsohn.)

Role of Lymph Nodes in the Immune Response

Because lymph nodes are distributed throughout the body, lymph formed in tissues must cross at least one node before entering the bloodstream. The lymph that arrives at a lymph node may contain antigens, either soluble molecules, portions of semidestroyed microorganisms, or antigens already internalized and being transported by macrophages and other APCs. It may also contain cytokines and other cells (such as neutrophils and eosinophils), particularly if it is coming from a region undergoing inflammation. The antigens that had not been phagocytosed before may be internalized by APCs of the lymph nodes. All antigens have the opportunity to be presented to B lymphocytes and to T helper and T cytotoxic lymphocytes, to initiate an immune response.

The lymph node is an important site of lymphocyte proliferation (for instance, of B cells in the germinative centers) as well as of transformation of B lymphocytes into plasma cells. Because of this, the lymph that leaves a lymph node may be enriched in antibodies. As the lymph is transported to veins, these antibodies will ultimately be delivered to the entire body by the blood circulation.

MEDICAL APPLICATION

As each satellite node receives lymph from a limited region of the body, malignant tumor cells often reach lymph nodes and are distributed to other parts of the body via the efferent lymph vessels and blood vessels, a process known as metastasization.

Infection and antigenic stimulation often cause satellite lymph nodes to enlarge. These swollen and painful nodules, which may be palpated under the skin, signal an inflammation. Inflamed nodules have multiple germinal centers with active cell proliferation. Although plasma cells constitute only 1–3% of the cell population in resting nodes, their numbers increase greatly in stimulated lymph nodes.

Recirculation of Lymphocytes

Because all lymph formed in the body drains back into the blood, lymphocytes that leave the lymph nodes by efferent lymphatic vessels eventually reach the bloodstream. They may then leave the blood vessels by entering the tissues and return to another lymph node by a lymph vessel. They may also return to a lymph node (a process called **homing**) by crossing the walls of specific blood vessels, the **high endothelial venules (HEVs)**, present in lymph nodes (Figure 14–26). These venules have an unusual endothelial lining of tall cuboidal cells. L-selectin present on the lymphocyte surface recognizes sugar-rich ligands of the endothelial cell surface, and as a consequence, the lymphocyte stops in the internal wall of the vein. Integrins are probably important for the adhesion of the lymphocytes to the endothelial cells and the lymphocytes eventually cross the vessel wall into the lymph node parenchyma. High endothelial venules are also present in other lymphoid organs, such as the appendix, tonsils, and Peyer's patches, but not in the spleen.

Figure 14–26.

Photomicrograph of a high endothelial venule in a lymph node. Arrowheads indicate high endothelial cells. The venule wall is crossed by lymphocytes (arrows). PT stain. High magnification.

The continuous recirculation of lymphocytes enables most parts of the body to be constantly monitored, increasing the opportunity for lymphocytes to encounter APCs and antigens that have migrated to lymph nodes.

Spleen

The spleen is the largest accumulation of lymphoid tissue in the body and the only one interposed in the blood circulation. Because of its abundance of phagocytic cells, the spleen is an important defense against antigens that reach the blood circulation. It is also the site of destruction of aged erythrocytes. As is true of all other lymphoid organs, the spleen is a production site of activated lymphocytes, which are delivered to the blood. The spleen reacts promptly to antigens carried in the blood and is, thus, an important blood filter and antibody-forming organ.

General Structure

The spleen is surrounded by a **capsule** of dense connective tissue from which emerge **trabeculae**, which divide the parenchyma, or **splenic pulp**, into incomplete

compartments (Figure 14–27). Large trabeculae originate at the hilum, on the medial surface of the spleen; these trabeculae carry nerves and arteries into the splenic pulp as well as veins that bring blood back into the circulation. Lymphatic vessels that arise in the splenic pulp also leave through the hilum via the trabeculae.

Figure 14–27.

Section of spleen. The capsule is seen sending trabeculae to the interior of the organ. The red pulp occupies most of the microscopic field. Note the white pulp with its arterioles. Picrosirius stain. Low magnification.

In humans, the connective tissue of the capsule and trabeculae contains only a few smooth muscle cells, contrary to what occurs in several animals (eg, horses, dogs, and cats).

Splenic Pulp

The spleen is composed of a network of reticular tissue that contains reticular cells, many lymphocytes and other blood cells, macrophages, and APCs. The splenic pulp has two components, the **white pulp** and the **red pulp** (Figure 14–27). These names derive from the fact that on the surface of a cut through an unfixed spleen, white spots (lymphoid nodules) are observed within a dark red tissue that is rich in blood. The white pulp consists of the **periarterial lymphatic sheath** and the **lymphoid nodules,** whereas the red pulp consists of **splenic cords (Billroth's cords)** and blood **sinusoids.**

White Pulp

The splenic artery divides as it penetrates the hilum, branching into **trabecular arteries** of various sizes that follow the course of the connective tissue trabeculae (Figure 14–28). When they leave the trabeculae to enter the parenchyma, the arteries are immediately enveloped by a sheath of T lymphocytes, the periarterial lymphatic sheath **(PALS)**, which is part of the white pulp (Figure 14–29). These vessels are known as **central arteries** or **white pulp arteries.** After coursing through the parenchyma for variable stretches, the PALS receive large collections of lymphocytes – –mostly B cells—forming lymphoid nodules (Figure 14–28). In these nodules the artery, which has now turned into an arteriole, occupies an eccentric position but is still called the central artery (Figure 14–30). During its passage through the white pulp, the artery also divides into numerous radial branches that supply the surrounding lymphoid tissue (Figure 14–28).

Figure 14–28.

Schematic view of the blood circulation and the structure of the spleen. To understand the structure of the white and red pulp follow the flow of the blood from the trabecular artery to the trabecular vein. Theories of open and closed circulation are represented. Splenic sinuses (S) are indicated. PALS, periarterial lymphatic sheath. (Redrawn and reproduced, with permission, from Greep RO, Weiss L: *Histology,* 3rd ed. McGraw-Hill, 1973.)

Figure 14–29.

A: Section of spleen showing the red pulp (most of the microscopic field) and a component of the white pulp—a periarterial lymphatic sheath (PALS) surrounding a central artery. Small sections of trabeculae are present in the red pulp. **B:** (**1**) PALS; (**2**) central artery; (**3**) red pulp; (**4**) sinusoids. H&E stain. Low magnification. (Courtesy of PA Abrahamsohn.)

Figure 14–30.

Lymphoid nodule of the spleen surrounded by red pulp. A germinative center (**1**) and the (eccentric) central artery (**2**), which is characteristic of the spleen, are clearly visible. Two small sections of sheathed arteries are seen to the right of the nodule. H&E stain. Medium magnification. (Courtesy of PA Abrahamsohn.)

Surrounding the lymphoid nodules is a **marginal zone** consisting of many blood sinuses and loose lymphoid tissue (Figure 14–28). A few lymphocytes but many active macrophages can be found there. The marginal zone contains an abundance of blood antigens and thus plays a major role in the immunological activities of the spleen.

After leaving the white pulp, the sheath of lymphocytes slowly thins and the central artery (arteriole) subdivides to form straight **penicillar arterioles** with an outside

diameter of approximately 24 m (Figure 14–28). Near their termination, some of the penicillar arterioles are surrounded by a thick sheath of reticular cells, lymphoid cells, and macrophages. How the blood is delivered to the trabecular veins is not exactly known and will be discussed later.

Red Pulp

The red pulp is composed of splenic cords and sinusoids (Figure 14–31). The splenic cords contain a network of reticular cells supported by reticular fibers. The splenic cords contain T and B lymphocytes, macrophages, plasma cells, and many blood cells (erythrocytes, platelets, and granulocytes).

Figure 14–31.

Structure of the red pulp of the spleen, showing splenic sinusoids (**1**) and splenic cords (**2**). Lining endothelial cells can be seen in many sinusoids. Lymphocytes predominate in the splenic cords. H&E stain. Medium magnification. (Courtesy of PA Abrahamsohn.)

The splenic cords are separated by irregularly shaped wide sinusoids (Figures 14–31, 14–32, and 14–33). Elongated endothelial cells line the sinusoids of the spleen with the long axes parallel to the long axes of the sinusoids. These cells are enveloped in reticular fibers set primarily in a transverse direction, much like the hoops on a barrel (Figure 14–34).

Figure 14–32.

General view of splenic red pulp with a scanning electron microscope. Note the sinusoids (S) and the splenic cords (C). x360. (Reproduced, with permission, from Miyoshi M, Fujita T: Stereo-fine structure of the splenic red pulp. A combined scanning and transmission electron microscope study on dog and rat spleen. Arch Histol Jpn 1971;33:225.)

Figure 14–33.

Scanning electron micrograph of the red pulp of the spleen showing sinusoids, red pulp cords, and macrophages (M). Note the multiple fenestrations in the endothelial cells of the sinusoids. x1600. (Reproduced, with permission, from Miyoshi M, Fujita T: Stereo-fine structure of the splenic red pulp. A combined scanning and transmission electron microscope study on dog and rat spleen. Arch Histol Jpn 1971;33:225.)

Figure 14–34.

Structure of the red pulp of the spleen, showing splenic sinusoids and splenic cords with reticular cells and macrophages, some of which contain ingested material. The reticular fibers, which form a three-dimensional network in the splenic pulp, surround the sinusoids, where they are mainly perpendicular to the long axis of the blood vessel. Spaces between endothelial cells of the sinusoids allow movement of blood cells to the cords and back, indicated by arrows.

Surrounding the sinusoid is an incomplete basal lamina. Because the spaces between

the endothelial cells of the splenic sinusoids are 2–3 m in diameter or smaller, only flexible cells are able to pass easily from the red pulp cords to the lumen of the sinusoids. Unfortunately, because the lumen of sinusoids in the red pulp may be very narrow and the splenic cords are infiltrated with red blood cells, microscopic observation of a spleen section is not always easy; observation of PALS may also be difficult.

Closed and Open Blood Circulation in the Spleen

The manner in which blood flows from the arterial capillaries of the red pulp to the interior of the sinusoids has not yet been completely explained. Some investigators suggest that the capillaries open directly into the sinusoids, forming a **closed circulation** in which the blood always remains inside the vessels (Figure 14–28). Others maintain that the prolongations of the penicillar arteries open into the splenic cords, and the blood passes through the space between the cells to reach the sinusoids **(open circulation)** (Figure 14–28).

From the sinusoids, blood proceeds to the red pulp veins that join together and enter the trabeculae, forming the **trabecular veins** (Figure 14–28). The splenic vein originates from these vessels and emerges from the hilum of the spleen. The trabecular veins do not have individual muscle walls. They can be considered channels hollowed out in the trabecular connective tissue and lined by endothelium.

Functions of the Spleen

Phagocytosis and Immunological Defense

Because of its strategic position in the blood circulation, the spleen is able to filter, phagocytose, and mount immunological responses against blood-borne antigens. The spleen contains all the components (B and T lymphocytes, APCs, and phagocytic cells) necessary for this function.

The white pulp of the spleen is an important production site of lymphocytes, which then migrate to the red pulp and reach the lumen of the sinusoids, where they enter the

blood circulation. Inert particles are also intensely phagocytosed by spleen macrophages.

MEDICAL APPLICATION

In certain pathological conditions (eg, leukemia), the spleen may reinitiate the production of granulocytes and erythrocytes, a function present during fetal life, and undergo a process known as **myeloid metaplasia** (the occurrence of myeloid tissues in extramedullary sites).

Destruction of Erythrocytes

Erythrocytes have an average life span of around 120 days, after which they are destroyed, mainly in the spleen. A reduction in their flexibility and changes in their membrane seem to be the signals for their destruction. Degenerating erythrocytes are also removed in the bone marrow.

Macrophages in the splenic cords engulf and digest the erythrocytes that frequently fragment in the extracellular space (Figure 14–35). The hemoglobin they contain is broken down into several parts. The protein, globin, is hydrolyzed to amino acids that are reused in protein synthesis. Iron is released from heme and, joined to transferrin, is transported in the blood to the bone marrow, where it is reused in erythropoiesis. Iron-free heme is metabolized to **bilirubin,** which is excreted in the bile by liver cells. After surgical removal of the spleen (splenectomy), there is an increase in abnormal erythrocytes, seen to have deformed shapes in blood smears. There is also an increase in the number of blood platelets, indicating that the spleen normally removes aged platelets.

Figure 14–35.

Photomicrograph of five spleen macrophages in active phagocytosis of erythrocytes. PT stain. High magnification.

MEDICAL APPLICATION

Although the spleen has numerous important functions in the body, it is not essential to life. In some situations the spleen must be removed (eg, an abdominal injury that results in rupture of the spleen capsule, certain anemias, and platelet disorders). In this case other organs (eg, the liver) take over some of the functions of the spleen. The risk of infection may be higher in a splenectomized individual.
References

Abbas AK et al: *Cellular and Molecular Immunology*, 2nd ed. Saunders, 2000.

Alberts B et al: The immune system. In: *Molecular Biology of the Cell*, 3rd ed. Garland, 1994.

Austyn JM, Wood KJ: *Principles of Cellular and Molecular Immunology*. Oxford University Press, 1993.

Bistrup A et al: Detection of a sulfotransferase (HEC-GlcNAc6ST) in high endothelial venules of lymph nodes and in high endothelial venule-like vessels within ectopic lymphoid aggregates: relationship to the MECA-79 epitope. Am J Pathol 2004;164:1635. [PMID: 15111310]

Cella M et al: Origin, maturation and antigen presenting function of dendritic cells. Curr Opin Immunol 1997;9:10. [PMID: 9039784]

Kanda H et al: Endomucin, a sialomucin expressed in high endothelial venules, supports L-selectin-mediated rolling. Int Immunol 2004 (on line).

Parslow TG et al: *Medical Immunology*, 10th ed. McGraw-Hill, 2001.

Rajewsky K: B-cell differentiation: clonal selection and learning in the antibody system. Nature 1996;381:751. [PMID: 8657279]

Sainte-Marie G, Peng FS: High endothelial venules of the rat lymph node, a review and a question: is their activity antigen specific Anat Rec 1996; 245:593.

Savino W et al: Intrathymic T-cell migration: a combinatorial interplay of extracellular matrix and chemokines Trends Immunol 2002;23:305. [PMID: 12072370]

Savino W et al: Molecular mechanisms governing thymocyte migration: combined role of chemokines and extracellular matrix. J Leukoc Biol 2004; 75:951.

Tough DF, Sprent J: Lifespan of lymphocytes. Immunol Res 1995;14:252.

Uchimura K et al: N-Acetylglucosamine 6-O-sulfotransferase-1 regulates expression of L-selectin ligands and lymphocyte homing. J Biol Chem 2004;279:35001. [PMID: 15175329]

van Zante A et al: Lymphocyte-HEV interactions in lymph nodes of a sulfotransferase-deficient mouse. J Exp Med 2003;198:1289.