Lymphoid Organs

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.

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. 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**. **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. 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.

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

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).

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.**

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. In most lymphoid organs, the fibrils are produced by a fibroblastic cell called a **reticular cell,** whose many processes rest on the reticular fibrils. The thymus is an exception in so far as its cells are supported by a reticulum of epithelial cells of endodermic origin.

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.

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**, 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. 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.

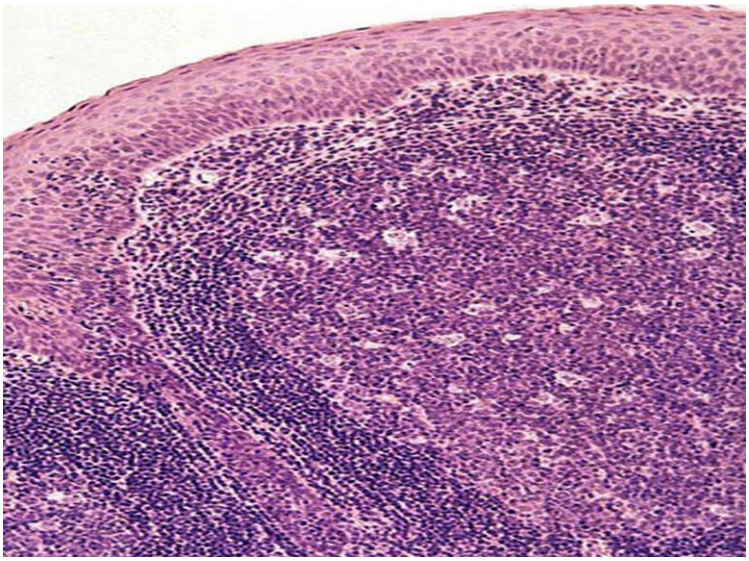
In the Peyer's patches, some of the regular surface epithelial cells may be replaced by special **M cells**. The M cells do not have microvilli as do the regular cells that line the intestine. By pinocytosis they actively capture and transport antigens from the intestinal lumen to the connective tissues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

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

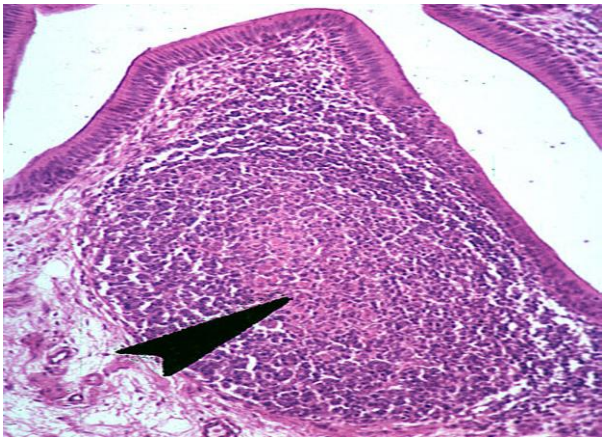
The two palatine tonsils are located in the lateral walls of the oral part of the pharynx. They are lined with a squamous stratified epithelium that often becomes so densely infiltrated by lymphocytes that it may be difficult to recognize. The lymphoid tissue in these tonsils forms a band that contains free lymphocytes and lymphoid nodules, generally with germinal centers. 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 . This capsule usually acts as a barrier against spreading tonsillar infections.



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 and are covered by stratified squamous epithelium. Each lingual tonsil has a single crypt.

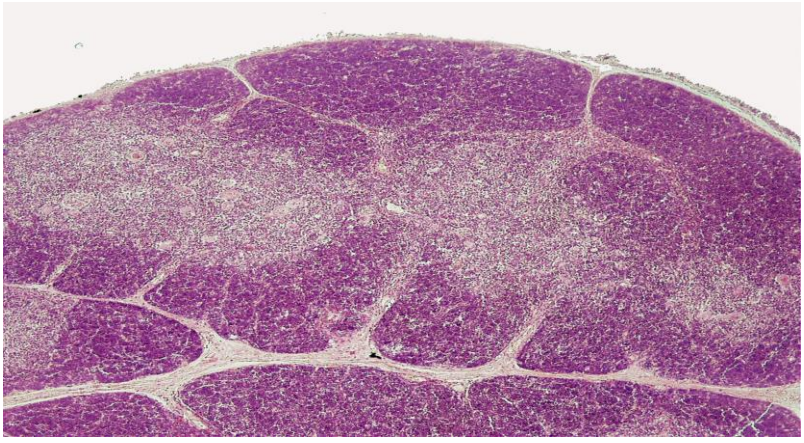
Thymus

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. Each lobule has a peripheral dark zone known as the **cortex** and a central light zone called the **medulla**.

The **cortex** 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.

The **medulla** 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. These corpuscles contain flattened epithelial reticular cells that are arranged concentrically and are filled with keratin filaments. They sometimes calcify.



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

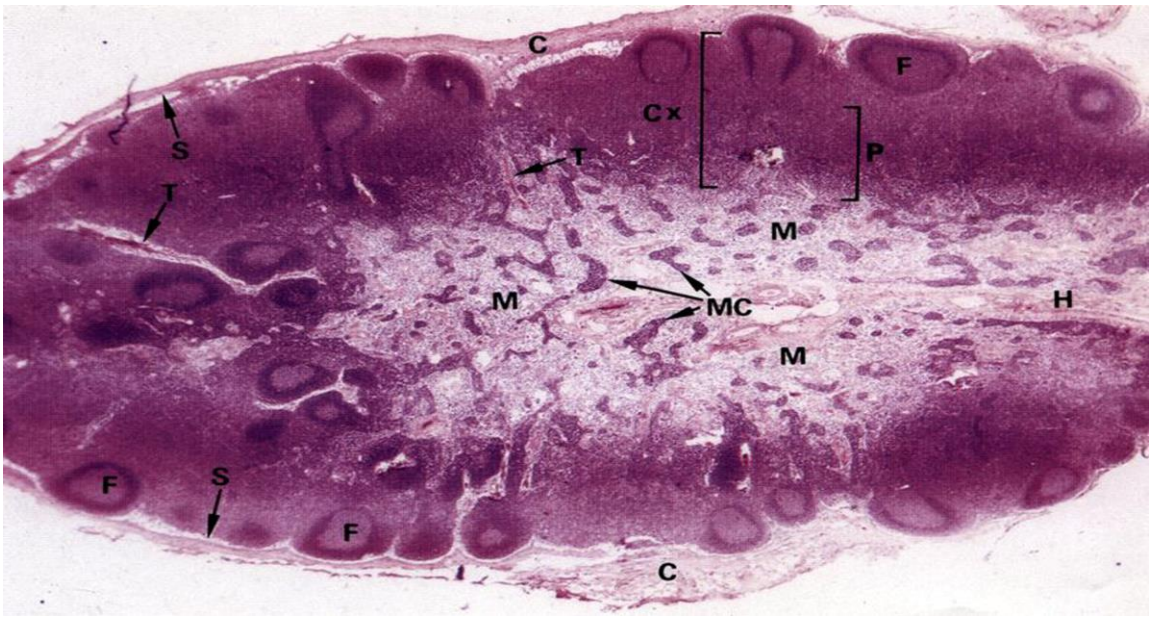
prevents most circulating antigens from reaching the thymus cortex, thus creating the so-called **thymic–blood barrier.**

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.

Lymph Nodes

Lymph nodes are distributed throughout the body along the course of the lymphatic vessels. 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. A connective tissue **capsule** surrounds the lymph node, sending trabeculae into its interior.

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**. The cortex can be subdivided into an **outer cortex** and an **inner cortex** or **paracortical region.**



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; 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.
3. Areas of loose lymphoid tissue (whose reticular fibril meshes are wide) situated immediately beneath the capsule, called the **subcapsular sinuses**. 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.

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.

Medulla

The medulla has two components:

1. The **medullary cords** 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.
2. The medullary cords are separated by dilated spaces, frequently bridged by reticular cells and fibers, called the **medullary sinuses**. 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.

Lymph Circulation

Afferent lymphatic vessels cross the capsule and pour lymph into the subcapsular sinus . 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.

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. 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.

In humans, the connective tissue of the capsule and trabeculae contains only a few smooth muscle cells.

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**. 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. 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. 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. In these nodules the artery, which has now turned into an arteriole, occupies an eccentric position but is still called the central artery. During its passage through the white pulp, the artery also divides into numerous radial branches that supply the surrounding lymphoid tissue.

Surrounding the lymphoid nodules is a **marginal zone** consisting of many blood sinuses and loose lymphoid tissue. 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.

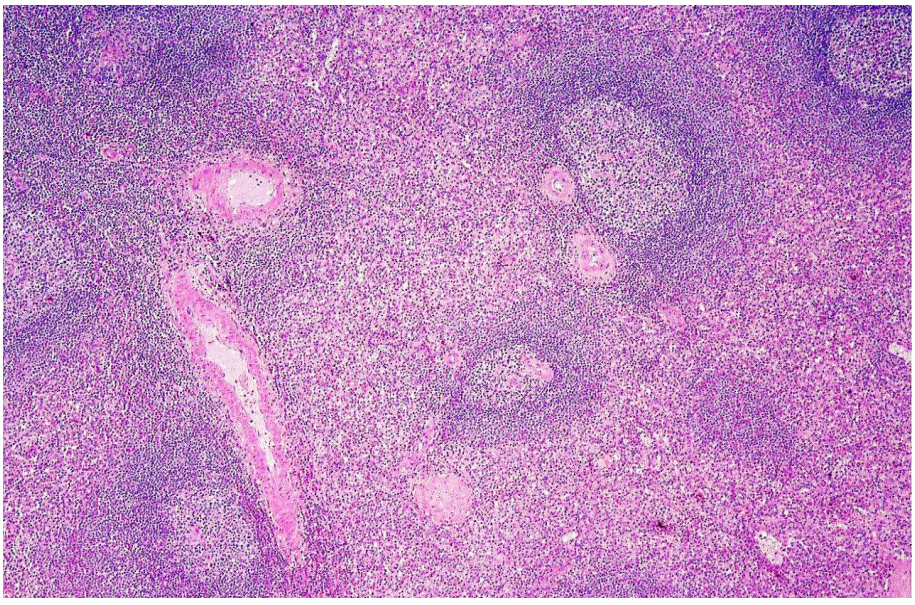
After leaving the white pulp, the sheath of lymphocytes slowly thins and the central artery (arteriole) subdivides to form straight **penicillar arterioles**. Near their termination, some of the penicillar arterioles are surrounded by a thick sheath of reticular cells, lymphoid cells, and macrophages. 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. 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).

The splenic cords are separated by irregularly shaped wide sinusoids. 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.

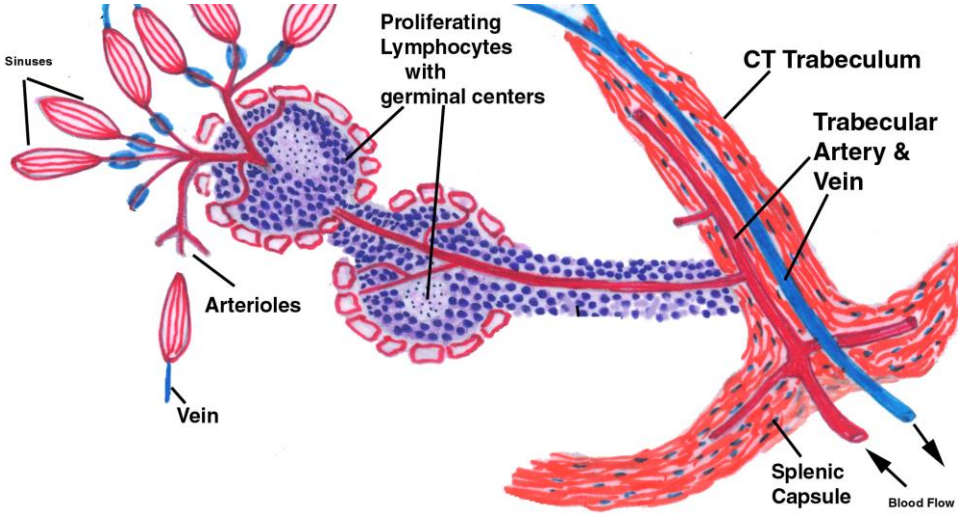
Surrounding the sinusoid is an incomplete basal lamina. Because the spaces between the endothelial cells of the splenic sinusoids are smaller, only flexible cells are able to pass easily from the red pulp cords to the lumen of the sinusoids. Unfortunately, because the lumen of sinusoids in the red pulp 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. 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)**.

From the sinusoids, blood proceeds to the red pulp veins that join together and enter the trabeculae, forming the **trabecular veins**. 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.

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. 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.