tight, such as in trabeculae (T) and the cells here are generally more stationary. X10. Silver impregnation. **(b):** Cells of typical lymphoid tissue include the fibroblast-like reticular cells (R) which produce and maintain the trabeculae (T) and reticulin framework. Many cells are loosely attached to the reticulin fibers, including macrophages (M) and many lymphocytes. X240. H&E. (With permission, from Paulo A. Abrahamsohn, Institute of Biomedical Sciences, University of São Paulo, Brazil.)

The network of reticular fibers of the lymphoid tissue may be relatively dense and thus able to hold many free lymphocytes, macrophages, and plasma cells. Areas of more loosely organized lymphoid tissue, with fewer and larger spaces, allow easy movement of these cells (Figure 14–9).

In **nodular lymphoid tissue** groups of lymphocytes are arranged as spherical masses called **lymphoid nodules** or **lymphoid follicles**, containing primarily 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 **germinal center.** After completion of the initial immune response, the germinal center may disappear. Germinal centers contain a special cell, the **follicular dendritic cell** (**FDC**, distinct from the dendritic APCs), with surfaces that have many extremely fine processes. Antigens bind surface proteins of FDCs in several ways (not including MHC proteins) but are not internalized or degraded by these cells. Rather antigen is retained by FDCs for extended periods (months to years) for interaction with B lymphocytes.

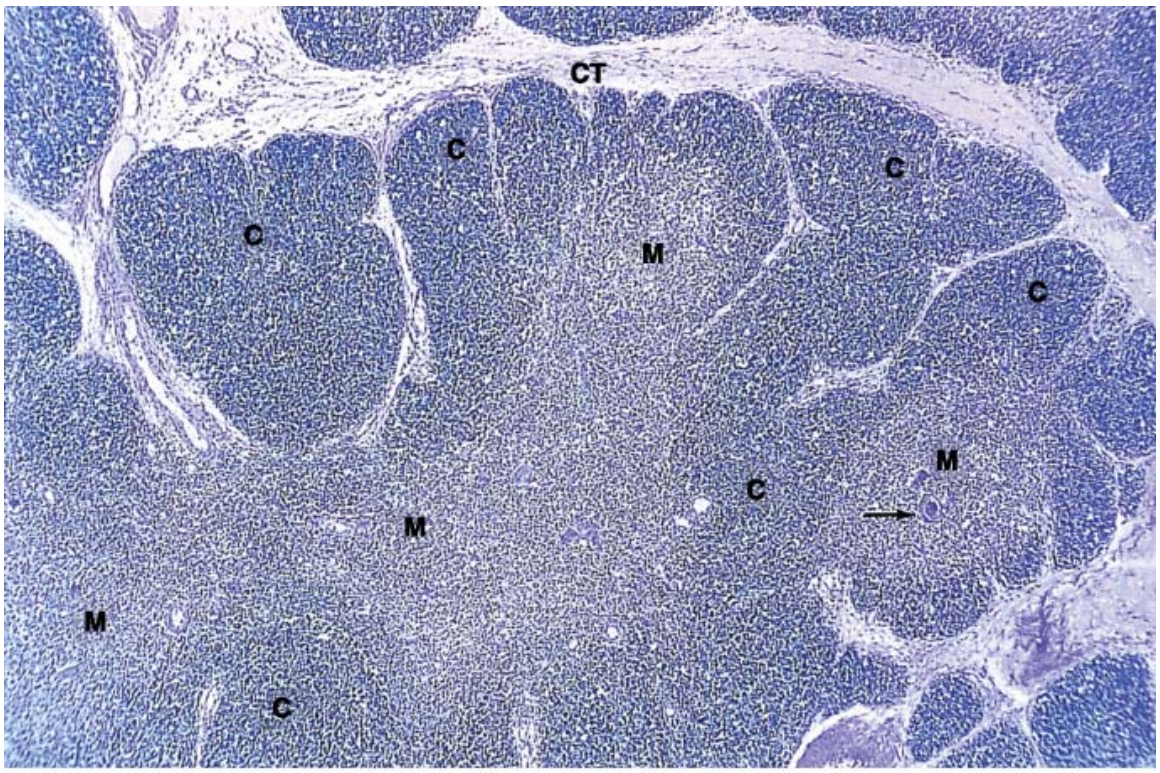
Lymphoid nodules vary widely in size, typically measuring a few hundred micrometers to one mm in diameter. They are found free in many connective tissues in the body and within lymph nodes, spleen, and tonsils, but not in the thymus which contains only T cells. Free lymphoid nodules are commonly present in the connective tissue of mucosal linings, where, together with free lymphocytes, they constitute the mucosa-associated lymphoid tissue (MALT). Individual lymphoid follicles are not encapsulated with connective tissue.

THYMUS

The thymus is a bilateral organ located in the mediastinum; it attains its peak development during youth. Like bone marrow and B cells, the thymus is considered a central or primary lymphoid organ because T lymphocytes form there. Whereas all other lymphoid organs originate exclusively from mesenchyme (mesoderm), the thymus has a dual embryonic origin. Its precursor lymphoblasts originate in the bone marrow, but then move to invade a unique epithelium that developed from the endoderm of the embryo's third and fourth pharyngeal pouches.

The thymus has a connective tissue capsule that penetrates the parenchyma and divides it into incomplete lobules, with continuity between the cortex and medulla of adjoining lobules (Figure 14–10). Each lobule has a peripheral darkly stained zone known as the **cortex** and a central light zone called the **medulla.** The cortex is richer in small lymphocytes than the medulla and therefore it stains more darkly.

Figure 14–10.



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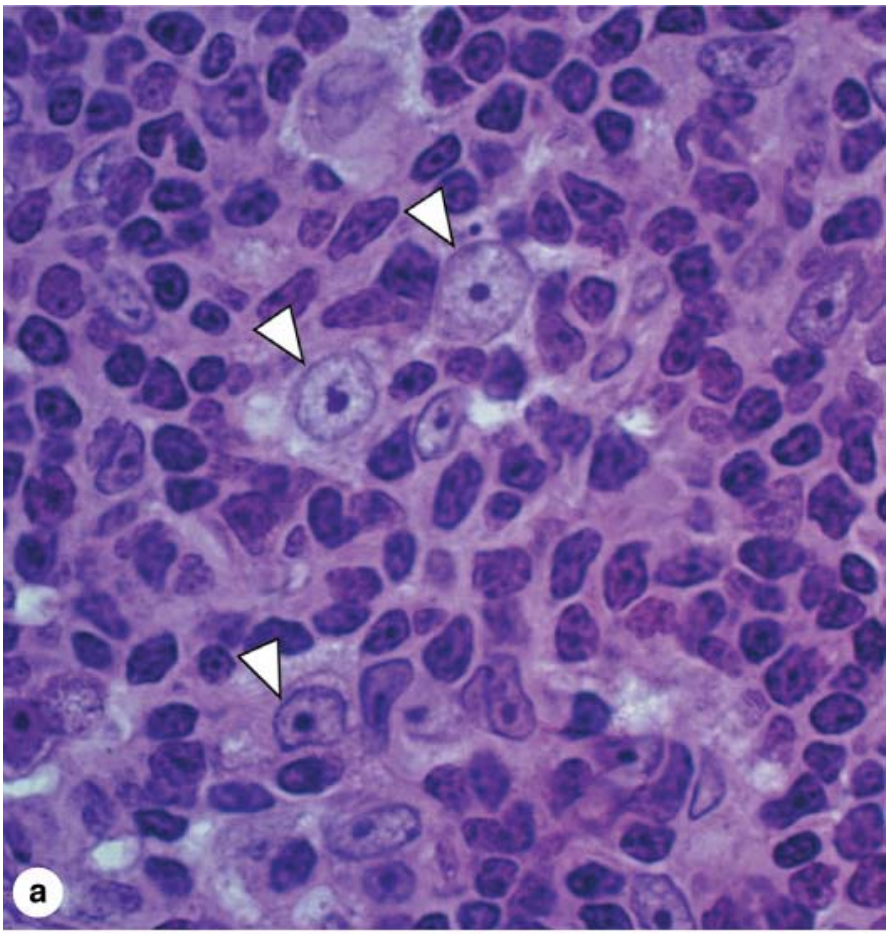
Thymus.

The thymus, an encapsulated, bilateral organ in the mediastinum, is subdivided by connective tissue (CT) septa into connected lobes. Lobes of an active thymus shown have peripheral regions of cortex (C), where basophilic lymphocytes are fairly dense, and more central medulla (M) regions with fewer lymphocytes. Besides the differences in location and cell density, the medulla region is characterized by the scattered presence of distinct thymic corpuscles (arrow). X140. H&E.

The thymic cortex is composed of an extensive population of T lymphoblasts (also called **thymocytes**) and macrophages in a stroma of **epithelial reticular cells**. The epithelial reticular cells usually have large euchromatic nuclei and are diverse morphologically, but generally either squamous or stellate with long processes. They are typically joined to similar adjacent cells by desmosomes (Figure 14–11), forming an unusual **cytoreticulum**. Cytoplasmic bundles of intermediate keratin filaments (tonofilaments) give evidence of these cells' epithelial origin. Occluding junctions between flattened epithelial reticular cells at the boundary between cortex and medulla help to separate these two regions.

Figure 14–11.



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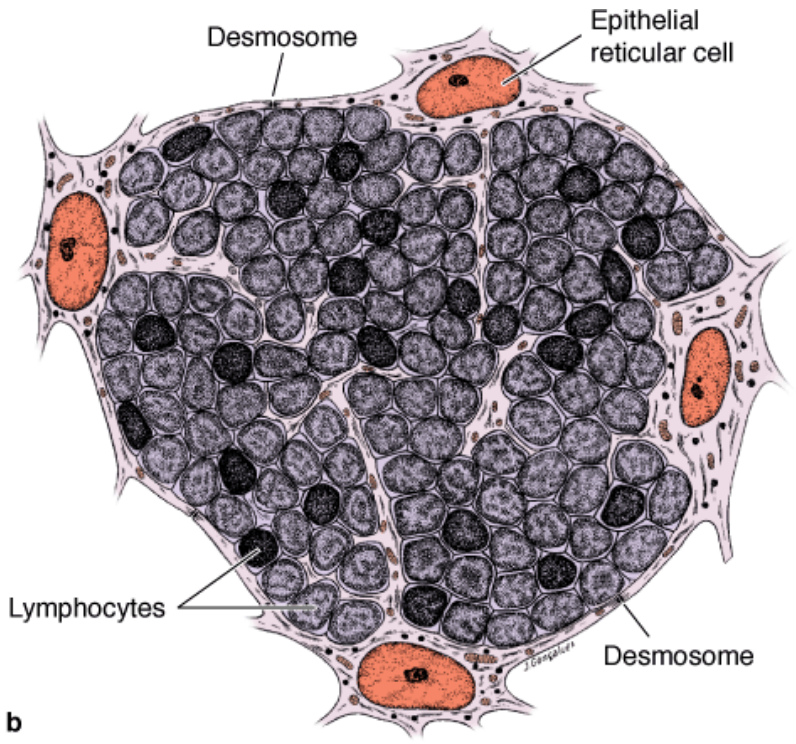

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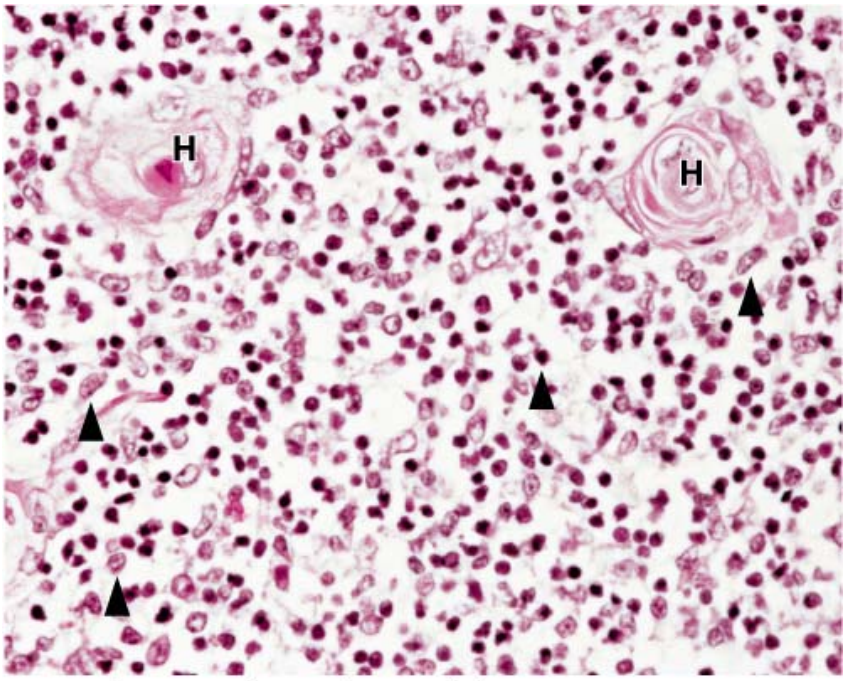
Cortex of the thymus.

(a): The cortical zone of an active thymus is packed with lymphoblasts that proliferate as well as undergo positive and negative selection in that region. The lymphoblasts are supported on a meshwork of epithelial reticular cells (arrowheads). X400. PT. **(b):** The epithelial reticular cells extend long processes bound together by desmosomes to make the framework for the lymphocytes. The epithelial reticular cells also secrete polypeptide factors that promote T cell maturation.

The thymic medulla also contains a cytoreticulum of epithelial reticular cells, many less densely packed differentiated T lymphocytes, and structures called **thymic (Hassall's) corpuscles,** which are characteristic of this region (Figure 14–12). Thymic corpuscles consist of epithelial reticular cells arranged concentrically, filled with keratin filaments, and sometimes calcified. They are absent in mice and a unique function for these structures in humans has not been established.

Figure 14–12.



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Medulla of the thymus.

The thymic medulla contains fewer lymphocytes than the cortex and the epithelial reticular cells (arrowheads) have different morphology and function. The most characteristic feature of the medulla in humans is the presence of thymic (Hassall's) corpuscles (H). These are of variable size and contain layers of epithelial reticular cells undergoing keratinization and degeneration. X200. H&E.

Arterioles and capillaries in the thymic cortex are sheathed by flattened epithelial reticular cells with tight junctions. The capillary endothelium is continuous and has a thick basal lamina. These features create a **blood-thymus barrier** and prevent most circulating antigens from leaving the microvasculature and entering the thymus cortex. No such barrier is present in the medulla and mature T lymphocytes exit the thymus via venules in this zone.

The thymus has no afferent lymphatic vessels and does not constitute a lymph filter, as do lymph nodes. The few lymphatic vessels of the thymus are in the connective tissue of the capsule, septa and blood vessel walls and are all efferent.

Role of the Thymus in T Cell Maturation

The thymus is the site of T lymphocyte differentiation and removal of T lymphocytes reactive against self-antigens, an important part of **central self-tolerance induction**.

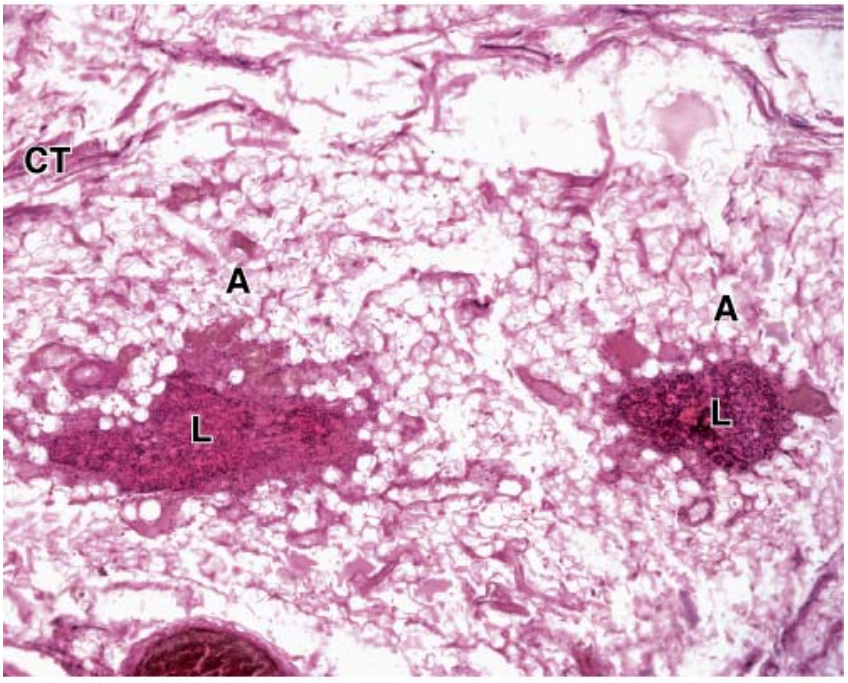
T lymphoblast surfaces do not yet exhibit the T cell receptor (TCR) or the CD4 and CD8 markers. Their progenitor cells arise in the fetal liver or bone marrow and migrate to the thymus during both fetal and postnatal life. After entering the thymus, T lymphoblasts populate the cortex where they proliferate extensively. As thymocytes mature and express T cell markers, they undergo **thymic selection**, a stringent quality control process, as they pass through a succession of microenvironments created by different mixes of the stromal epithelial reticular cells.

Differentiating thymocytes in the cortex are presented with antigens bound to class I and class II MHC proteins on the epithelial reticular cells, macrophages, and dendritic cells. Thymocytes whose TCRs cannot bind MHC molecules at all are nonfunctional and have no future as T cells; these cells (as many as 80% of the total) are induced to undergo apoptosis. Similarly, those thymocytes that strongly bind MHCs containing self-peptides are also deleted since such T cells could cause a damaging autoimmune response. Only 2–3% of the thymocytes pass both these positive and negative selection tests and survive to migrate into the thymic medulla. The others die by apoptosis and are removed by the numerous local macrophages. Movement into the medulla depends on the action of chemokines and on the interaction of thymocytes with the ECM and cytoreticulum. Mature, functional T cells enter the blood circulation by passing through the walls of venules in the medulla and are distributed throughout the body (Figure 14–4).

Besides their structural roles, the epithelial reticular cells produce a number of paracrine factors required for differentiation, selection and migration of mature T lymphocytes, notably thymopoietin and thymosins. Other polypeptides secreted by these cells, including thymulin and thymus humoral factor, also affect target cells outside the thymus.

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 14–13).

Figure 14–13.



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Adult thymus.

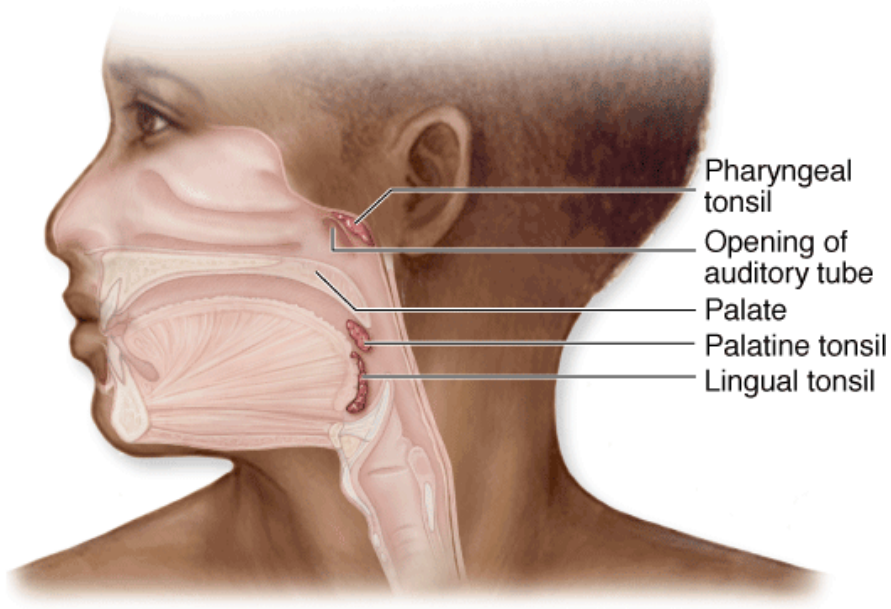
The thymus is highly active at birth and remains so through early childhood, during which time most central tolerance is established. After puberty thymic activities decline and with many fewer lymphocytes present, its structure is reduced in a process of involution. In the adult thymus shown here, cortex and medulla regions are difficult to distinguish within the connective tissue (CT) capsule and only remnants of lymphoid tissue (L) remain, surrounded by much adipose tissue (A). Compare with Figure 14–10 to contrast the functional states of the active and involuted thymus. T lymphocytes continue to be produced in thymic tissue throughout adult life, but at a greatly reduced rate. X140. H&E.

MUCOSA-ASSOCIATED LYMPHOIDTISSUE (MALT)

The digestive, respiratory, and genitourinary tracts are common sites of invasion by pathogens because their lumens are open to the external environment. To protect the organism, the mucosal connective tissue of these tracts contains large and diffuse collections of dendritic cells, lymphocytes, IgA-secreting plasma cells, APCs, and lymphoid nodules. Lymphocytes and dendritic cells are also present within the epithelia lining the lumens. Most of the lymphocytes are B cells; among T cells, CD4 helper cells predominate. In some places, these aggregates form large, conspicuous structures such as the **tonsils** and the **Peyer patches** in the ileum. Similar aggregates with lymphoid follicles are found in the **appendix**. Collectively the **mucosa-associated lymphoid tissue (MALT)** is one of the largest lymphoid organs, containing up to 70% of all the body's immune cells.

Tonsils are partially encapsulated lymphoid tissue lying beneath and in contact with the epithelium of the oral cavity and pharynx. According to their location they are called **palatine, pharyngeal,** or **lingual tonsils** (Figure 14–14).

Figure 14–14.



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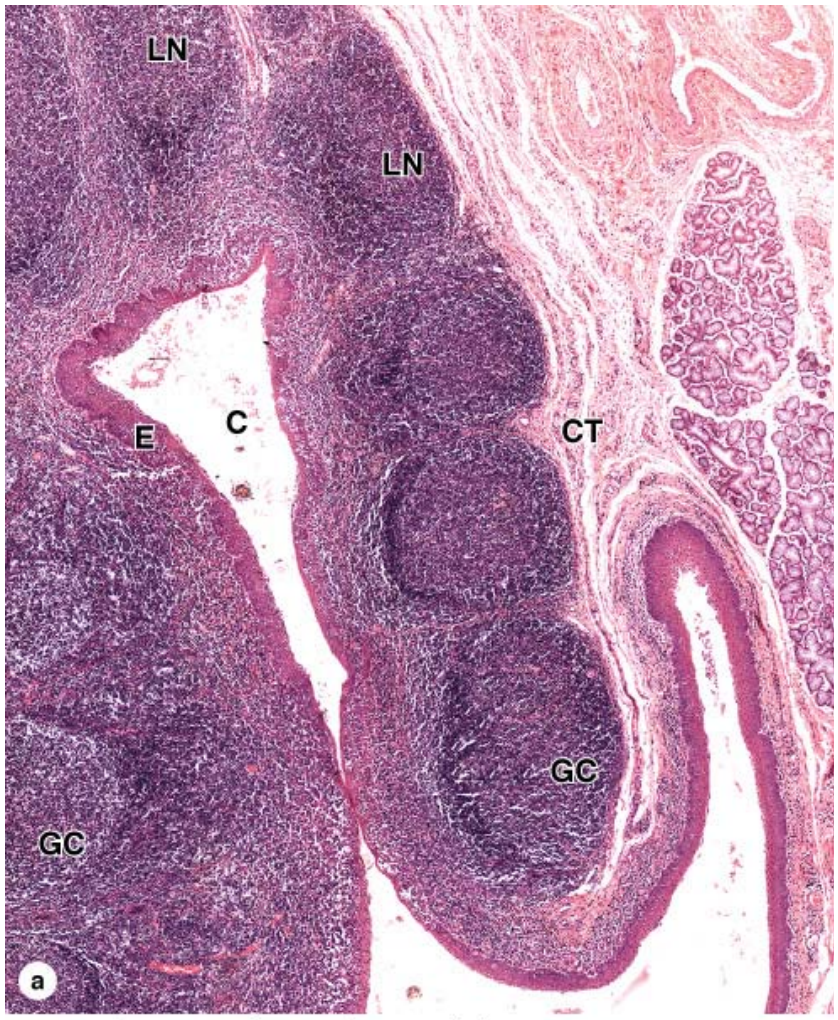
Tonsils.

Masses of lymphoid nodules comprising the tonsils are collected in three general locations in the wall of the pharynx. Palatine tonsils are located in the posterior lateral walls of the oral cavity and lingual tonsils are situated along the surface of the posterior third of the tongue. Both are covered with stratified squamous epithelium. The pharyngeal tonsil is a single tonsil situated in the posterior wall of the nasopharynx. It is usually covered by ciliated pseudostratified columnar epithelium typical of the upper respiratory tract, but areas of stratified epithelium can also be observed. Hypertrophied pharyngeal tonsils resulting from chronic inflammation are called **adenoids.**

Palatine tonsils, in the posterior parts of the soft palate, are covered by stratified squamous epithelium. Each has 10–20 epithelial invaginations that penetrate the tonsil deeply, forming **crypts** (Figure 14–15). The lymphoid tissue in these tonsils forms a band that contains free lymphocytes and lymphoid nodules, generally with germinal centers. The epithelium covering palatine tonsils can become so densely infiltrated by dendritic cells and lymphocytes that it may be difficult to recognize (Figure 14–15). Separating the lymphoid tissue from subjacent structures is a band of dense connective tissue that acts as a capsule or barrier against spreading tonsil infections.

Figure 14–15.



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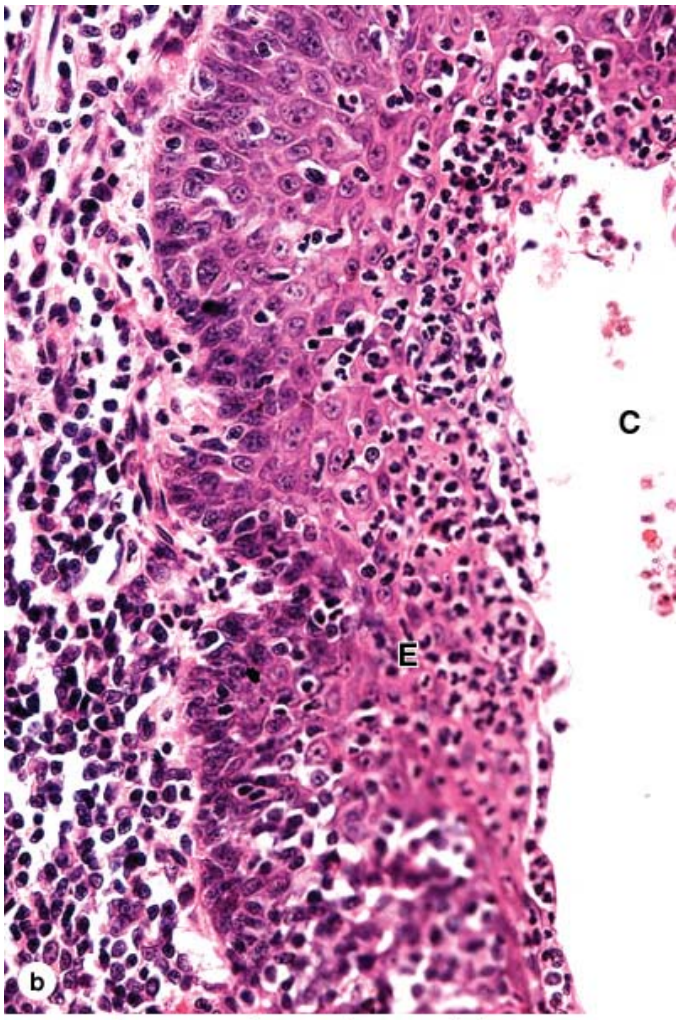

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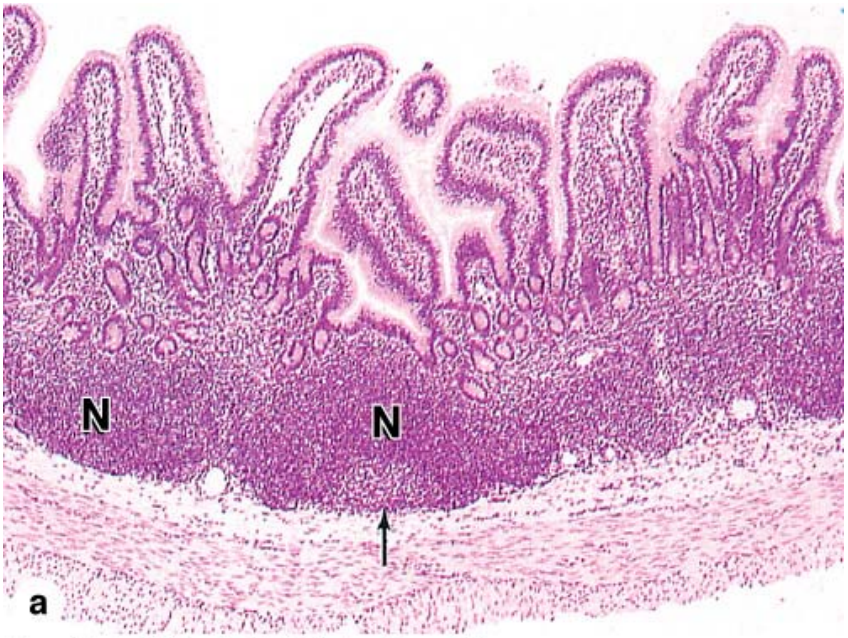
Detail of a tonsil.

Palatine tonsils are aggregates of lymphoid tissue, usually with nodules, in the mucosa of the posterior soft palate. **(a):** Micrograph showing several lymphoid nodules (LN), collectively covered by stratified squamous epithelium (E) on one side and a connective tissue capsule (CT) on the other. Some nodules show lighter staining germinal centers (GC). Infoldings of the mucosa in some tonsils form crypts (C), along which nodules are especially numerous. Lumens of crypts contain desquamated epithelial cells, live and dead lymphocytes, and bacteria. X140. H&E. **(b):** Epithelium surrounding crypts often becomes infiltrated with lymphocytes and neutrophils and can become difficult to recognize histologically. Lymphocytes abundant in the underlying connective tissue are seen on the left. X200. H&E. (Reproduced, with permission, from Paulo A. Abrahamsohn, Institute of Biomedical Sciences, University of São Paulo, Brazil.)

The pharyngeal tonsil is situated in the posterior wall of the nasopharynx (Figure 14–14) and is usually covered by ciliated pseudostratified columnar epithelium, although areas of stratified epithelium can also be observed. The pharyngeal tonsil is composed of pleated mucosa containing diffuse lymphoid tissue and lymphoid nodules and a capsule thinner than that of the palatine tonsils. The lingual tonsils are situated along the posterior surface of the tongue (Figure 14–14) and are covered by stratified squamous epithelium with crypts. The lymphoid tissue of these tonsils has many of the same basic features as that of palatine tonsils (Figure 14–15). All these epithelia contain intraepithelial lymphocytes and dendritic cells.

MALT extends along the entire gastrointestinal tract, but in the wall of the ileum are particularly large aggregates of lymphoid follicles called Peyer patches, each consisting of 10–200 nodules and bulging into the gut lumen with no connective tissue capsule (Figure 14–16). The simple follicle-associated epithelium (FAE) covering these nodules contains specialized **M cells** with apical microfolds rather than the brush border and glycocalyx typical of enterocytes. M cells continuously sample antigens and microorganisms in the intestinal lumen. Each is characterized by a large basal intraepithelial pocket open to the underlying lymphoid tissue through a porous basement membrane (Figure 14–16), discussed further in Chapter 15. Antigenic material bound to the apical surface of M cells is rapidly translocated via transcytosis from the intestinal lumen to APCs and lymphocytes located in the pocket. T helper cells and B cells derived from these lymphocytes move away from the FAE and initiate adaptive responses to the antigens. These B cells give rise to plasma cells secreting IgA, which is transported by enterocytes into the intestinal lumen to bind and neutralize potentially harmful antigens.

Figure 14–16.



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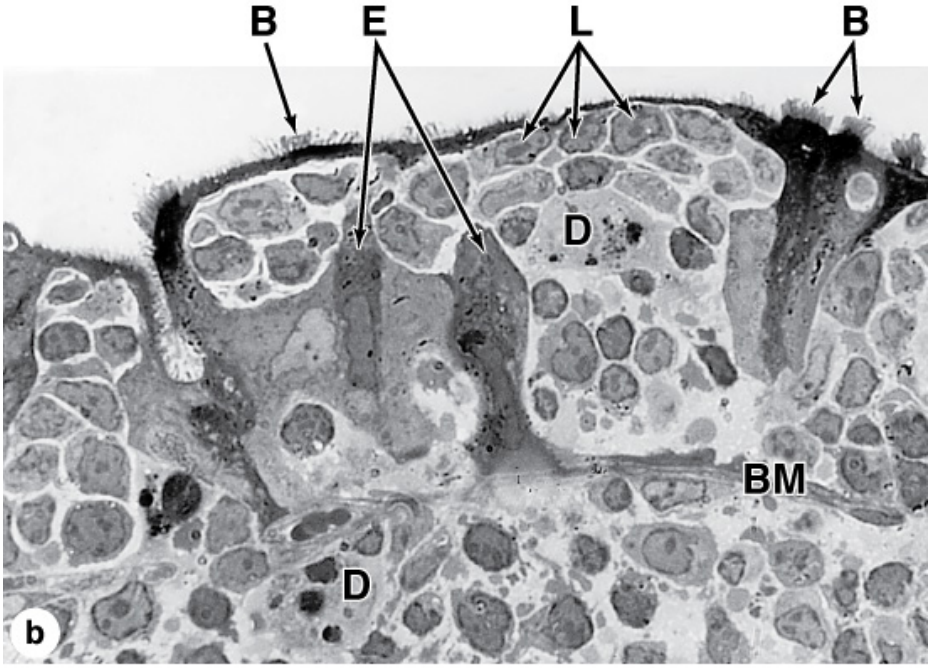

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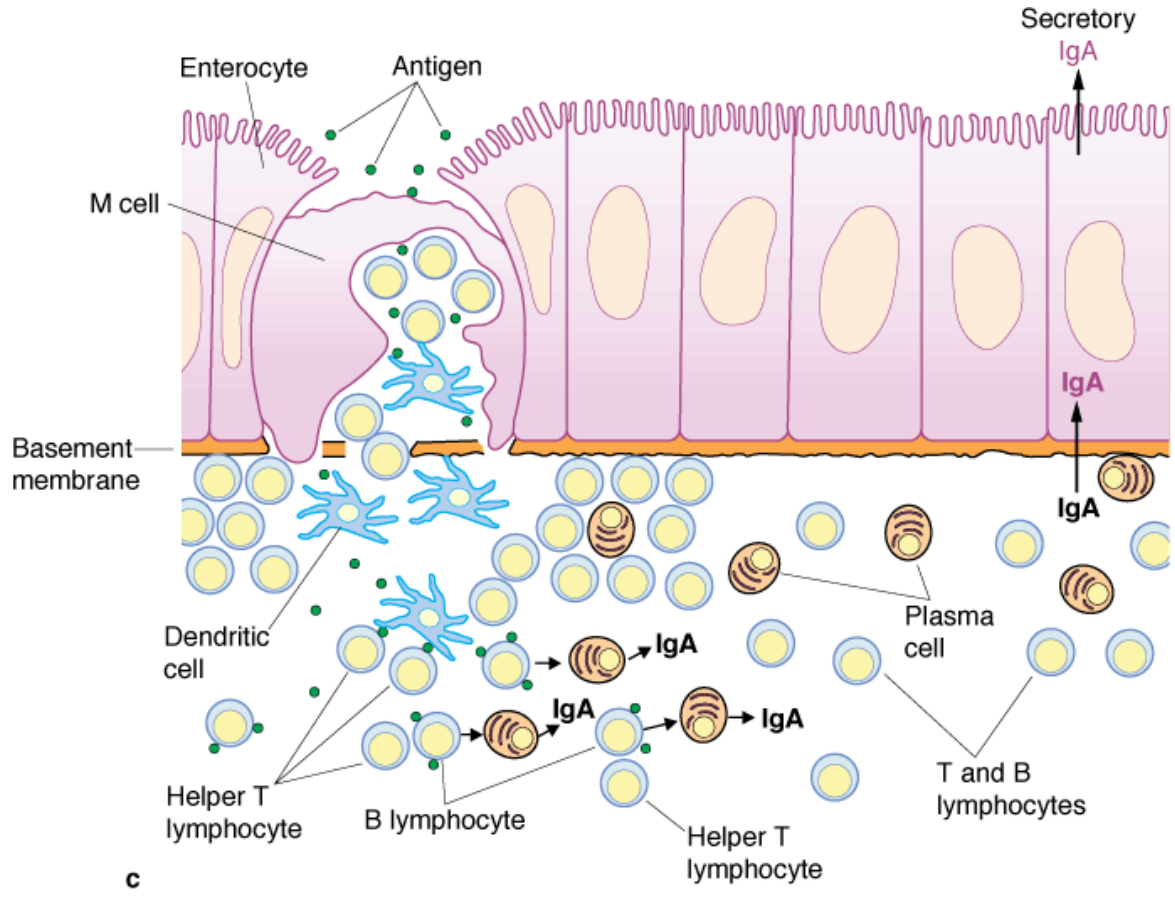

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Peyer patch and M cells.

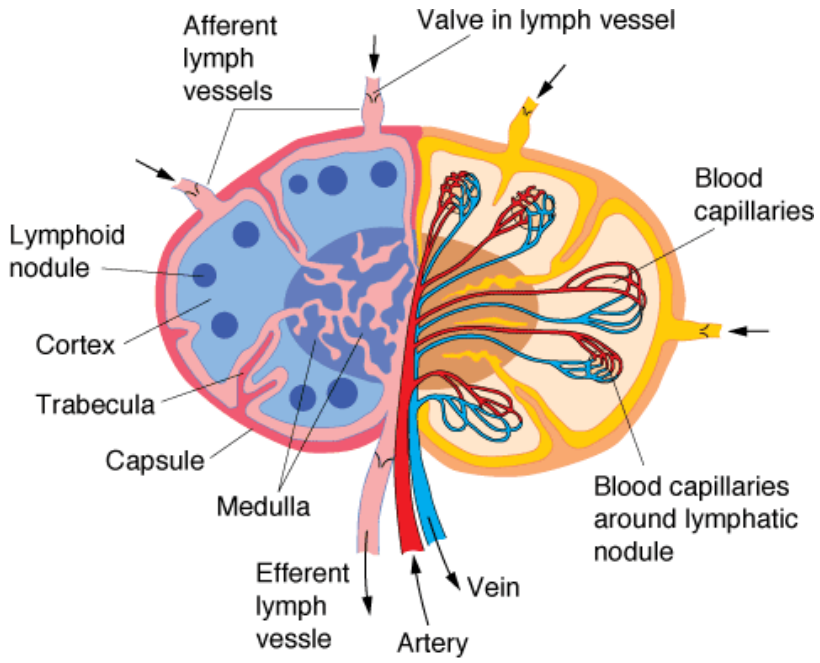
The mucosa of the entire digestive tract is rich in diffuse lymphocytes and scattered follicles, which make up the gut-associated lymphoid tissue (GALT). Particularly large clusters of lymphoid follicles in the ileum of the small intestine are called Peyer patches, where microorganisms of the gut are continuously monitored by specialized sampling stations. **(a):** Section of Peyer patch shows a few of the typical lymphoid nodules (N), some with germinal centers (arrow), in these aggregates. The ileum is lined by an absorptive simple columnar epithelium and intraepithelial lymphocytes are frequently present between the columnar cells. X20. H&E. **(b):** Micrograph shows that the follicle-associated epithelium or FAE directly over each lymphoid follicle/nodule has other epithelial cells called M cells. M cells have distinctive short apical microfolds but lack the brush border and thick glycocalyx typical of enterocytes. The basal surface of M cells forms a unique large intraepithelial pocket harboring a transient population of T and B lymphocytes (L) and antigen-presenting dendritic cells (D) which pass through openings in the basement membrane (BM). Lymphocytes and phagocytic cells fill the lamina propria and the intraepithelial pockets of four large M cells shown in section here. Also seen are the brush border (B) and darker cytoplasm of enterocytes (E) within the FAE. These enterocytes release chemokines that attract dendritic cells and lymphocytes to the FAE and M cell intraepithelial pockets. X500.

(c): Diagram shows luminal antigens that are bound by M cells and transported by transcytosis directly to their intraepithelial pockets containing dendritic cells, helper T cells, and B cells. Dendritic cells then take up the antigen, process it, and present it to lymphocytes and induce adaptive immune responses. B lymphocytes are stimulated by T helper cells to differentiate into IgA-secreting plasma cells. These IgA molecules are coupled with secretory protein and transported into the intestinal lumen by enterocytes adjacent to the FAE. This IgA binds eliciting antigens, helping to neutralize potentially harmful microorganisms in the lumen, and binds the apical surfaces of M cells to promote antigen uptake and induction of immune responses. (Figure 14–16b reproduced, with permission, from Marian R. Neutra, Children's Hospital, Harvard Medical School.)

LYMPH NODES

Lymph nodes are bean-shaped, encapsulated structures, generally 2–10 mm in diameter, distributed throughout the body along the course of the lymphatic vessels (Figure 14–1). The nodes are found in the axillae (armpits) and 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. These kidney-shaped organs 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 lymphatics leave the organ (Figure 14–17). A connective tissue **capsule** surrounds the lymph node, sending trabeculae into its interior.

Figure 14–17.



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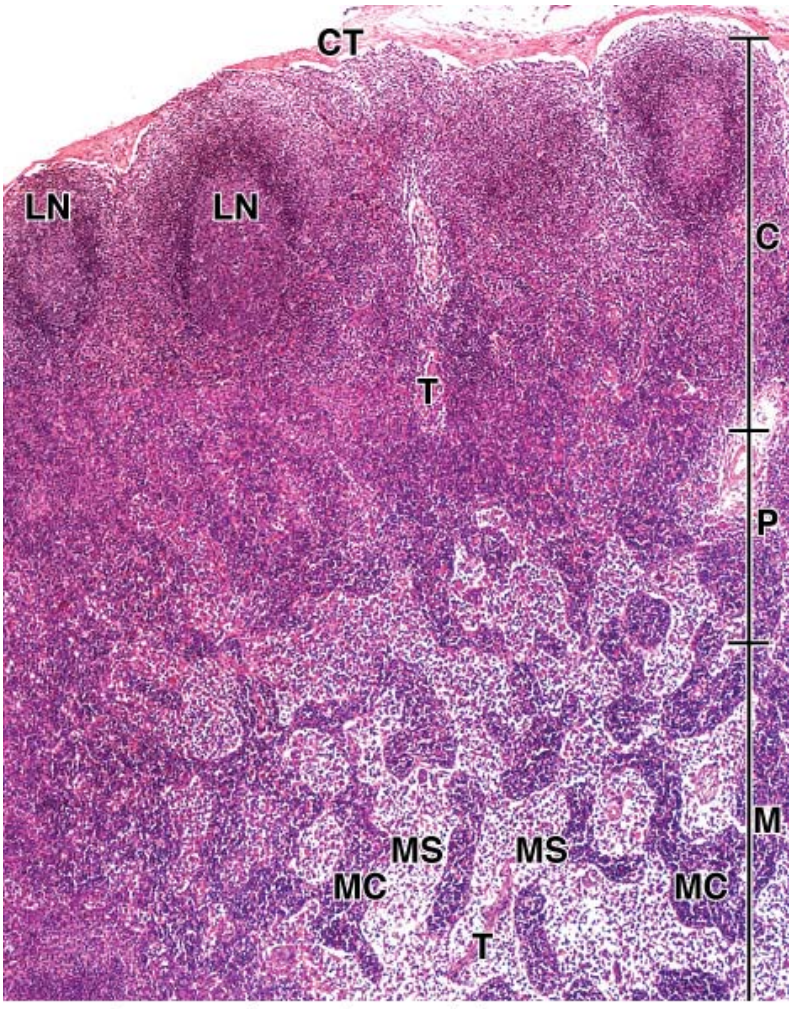
Schematic structure of a lymph node.

The left half of the figure shows the major regions and structural components of a lymph node and the flow of lymph within these organs, entering via afferent lymphatics on the convex side of the node, passing through unlined sinuses (shown in pink) in the lymphoid tissue, and leaving through an efferent lymphatic at the hilum. Valves in the lymphatic vessels assure the one-way flow of lymph. The right half depicts part of the blood circulation, with a small artery and vein both entering and leaving at the hilum.

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 fiber stroma supporting the cells creates a **cortex**, a **medulla**, and an intervening **paracortex** (Figures 14–17, 14–18, 14–19).

Figure 14–18.



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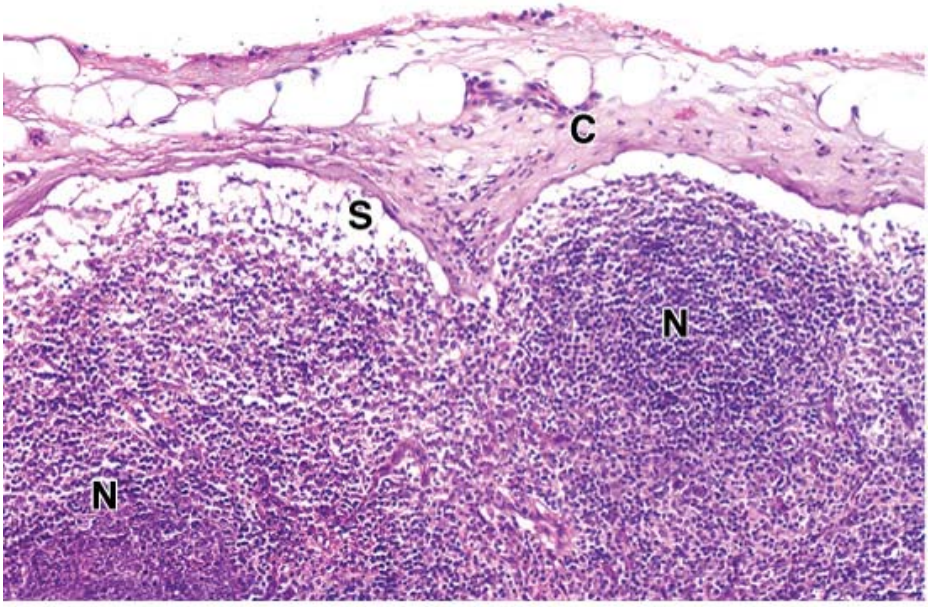
Regions of a lymph node.

A low-magnification section of a lymph node showing the three functional regions: the cortex (C), the paracortex (P), and the medulla (M). Connective tissue of the capsule (CT) completely surrounds each lymph node and extends as several trabeculae (T) throughout the lymphoid tissue. Major spaces for lymph flow are present in this tissue under the capsule and along the trabeculae. A changing population of immune cells is suspended on reticular fibers throughout the cortex, paracortex, and medulla. Lymphoid nodules (LN) are normally restricted to the cortex and the medulla is characterized by sinuses (MS) and cords (MC) of lymphoid tissue. X40. H&E. (With permission, from Paulo A. Abrahamsohn, Institute of Biomedical Sciences, University of São Paulo, Brazil.)

Figure 14–19.



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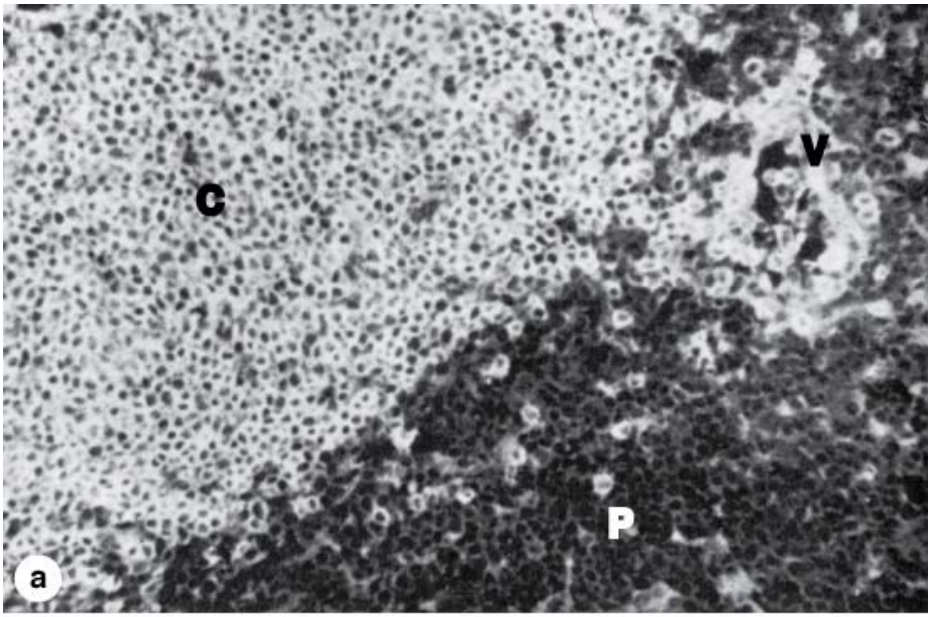
Lymph node cortex.

The outer regions on the convex sides of a lymph node include the capsule (C), subcapsular sinuses (S), and diffuse lymphoid tissue with lymphoid nodules (N). Afferent lymphatic vessels (which are only rarely shown well in sections) penetrate this capsule, dumping lymph into the sinus where its contents are processed by lymphocytes and APCs. X140. H&E. (With permission, from Paulo A. Abrahamsohn, Institute of Biomedical Sciences, University of São Paulo, Brazil.)

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

- Many reticular cells, macrophages, APCs, and lymphocytes (Figure 14–18).
- Lymphoid nodules, with or without germinal centers, formed mainly of B lymphocytes, embedded within the diffuse population of other cells (Figure 14–18).
- Areas immediately beneath the capsule, called the **subcapsular sinuses**, where the lymphoid tissue has wide reticular fiber meshes (Figures 14–18 and 14–19). Lymph containing antigens, lymphocytes, and APCs circulates around the wide spaces of these sinuses after being delivered there by the afferent lymphatic vessels.
- **Cortical sinuses**, running between the lymphoid nodules, which arise from and share the structural features of the subcapsular sinuses. They communicate with the subcapsular sinuses through spaces similar to those present in the medulla (Figures 14–17, 14–18, 14–19, and 14–20).

Figure 14–20.



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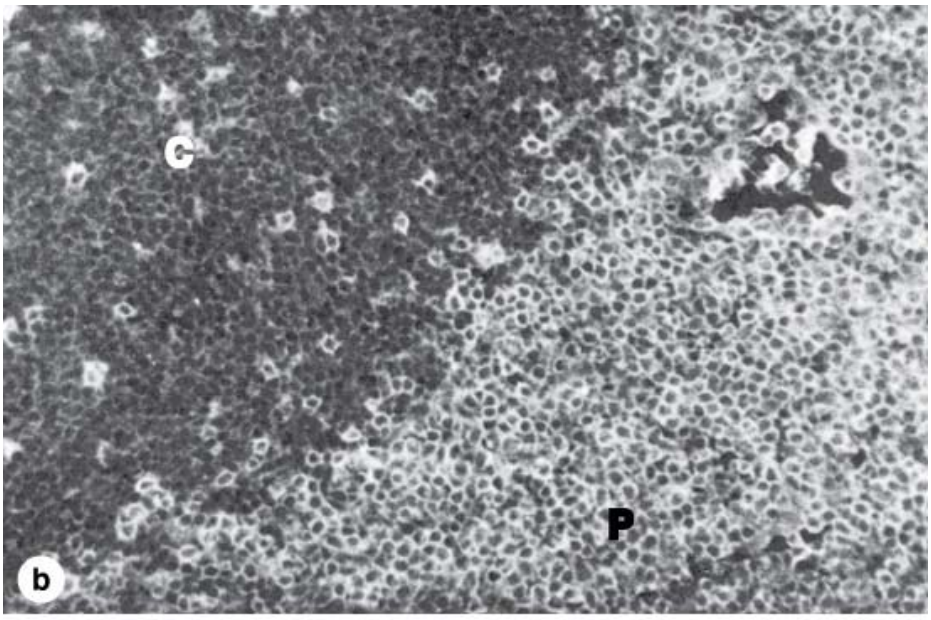

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Lymph node cortex and paracortex.

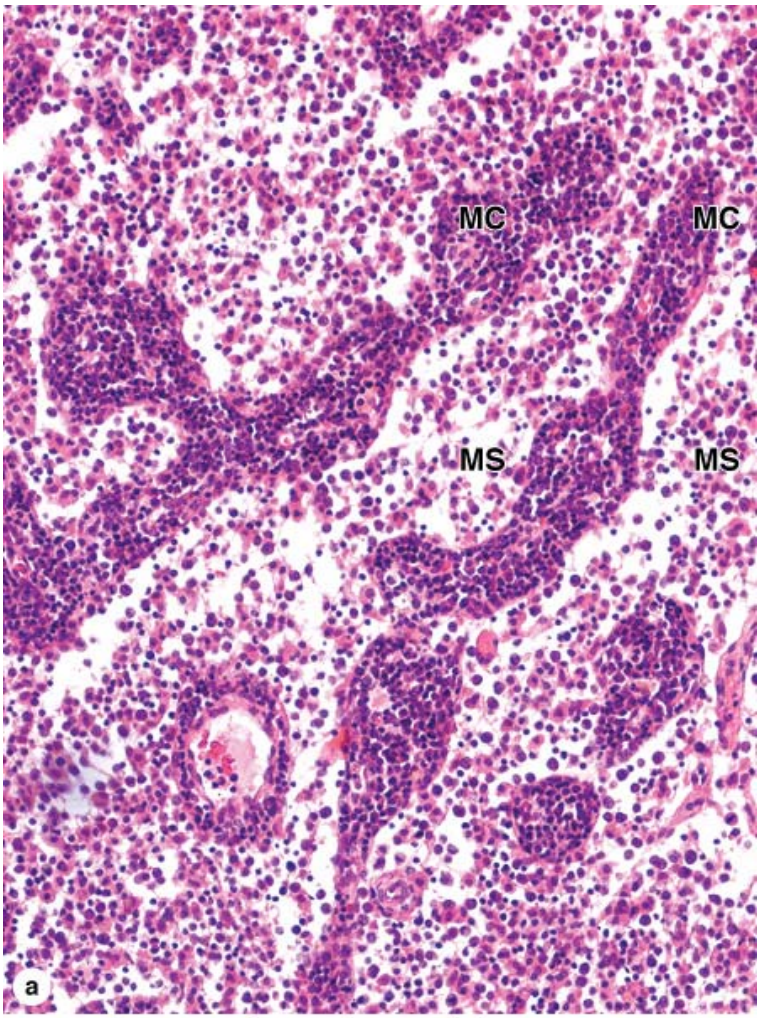
The region just inside the cortex is called the paracortex. Although most lymphocytes in the cortex are B cells, many located in nodules, the lymphocytes of the paracortex are largely T cells. This separation is indicated in the fluorescence micrographs here using immunohistochemistry on adjacent sections of lymph node. **(a):** Antibody against a B cell surface marker labels nearly all the lymphocytes in the cortex (C), as well as many cells around a high endothelial venule (V) in the paracortex, but few cells in the paracortex proper (P). **(b):** Stained with an antibody against a T cell marker, the paracortex is heavily labeled, but only a few cells in the cortex are stained, possibly T helper cells. X200. (Reproduced and modified, with permission, from IL Weissman: *Transplant Rev.* 1975;24:159.)

The **paracortex** does not have precise boundaries with the cortex and medulla. It can be distinguished from the outer cortex by its lack of B cell lymphoid nodules (Figure 14–18) and its accumulation of T cells, which can be determined by immunohistochemistry (Figure 14–20). Venules in the paracortex comprise an important entry point for lymphocytes moving from blood into lymph nodes.

The lymph node **medulla** has two major components:

- **Medullary cords** (Figure 14–21) are branched cordlike extensions of lymphoid tissue arising from the paracortex. They contain primarily B lymphocytes and often plasma cells and macrophages (Figures 14–19 and 14–21).
- Medullary cords are separated by dilated spaces, frequently bridged by reticular cells and fibers, called **medullary sinuses** (Figure 14–21). They contain lymph, lymphocytes, often many macrophages, and sometimes even granulocytes if the lymph node is draining an infected region. These sinuses are continuous with the cortical sinuses and join at the hilum to deliver lymph to the efferent lymph vessel of the lymph node (Figure 14–17).

Figure 14–21.



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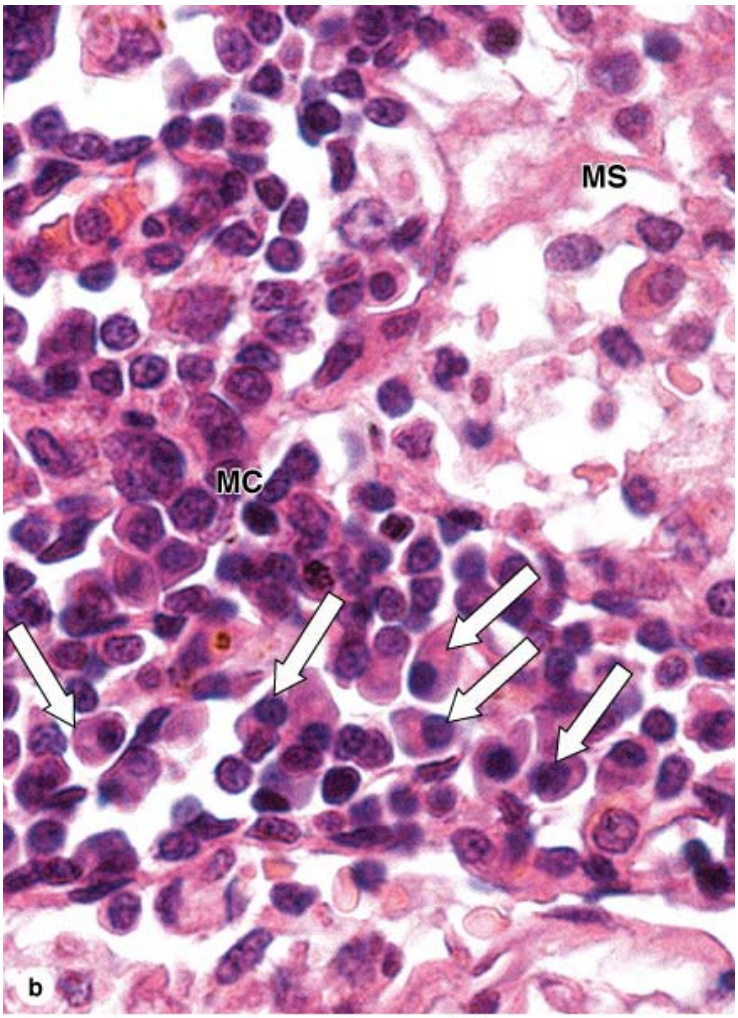

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Lymph node medulla.

(a): The medulla of a lymph node consists mainly of the medullary sinuses (MS) separated by intervening medullary cords (MC). Lymphocytes and plasma are abundant and predominate in number over other cell types. A blood vessel within a medullary cord is also seen. X200. H&E. **(b):** Higher magnification of a medullary cord (MC) shows plasma cells (arrows) with spherical, eccentric nuclei and much more cytoplasm than lymphocytes. Efferent lymph is rich in newly synthesized antibodies. A medullary sinus (MS) is also seen. X400. H&E. (With permission, from Paulo A. Abrahamsohn, Institute of Biomedical Sciences, University of São Paulo, Brazil.)

Afferent lymphatic vessels cross the capsule and pour lymph into the subcapsular sinus (Figure 14–17). From there, lymph passes through the cortical sinuses and then into the medullary sinuses. During this passage, the lymph infiltrates the cortex and the medullary cords and is filtered and modified by immune cells. The lymph is collected by **efferent lymphatics** at the hilum and valves in both lymphatics assure the unidirectional flow of lymph.

Role of Lymph Nodes in the Immune Response

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

The lymph node is an important site of lymphocyte proliferation (especially of B cells in the germinal 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. When the lymph is returned to the blood circulation, these antibodies will be delivered to the entire body.

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 **metastasis**.

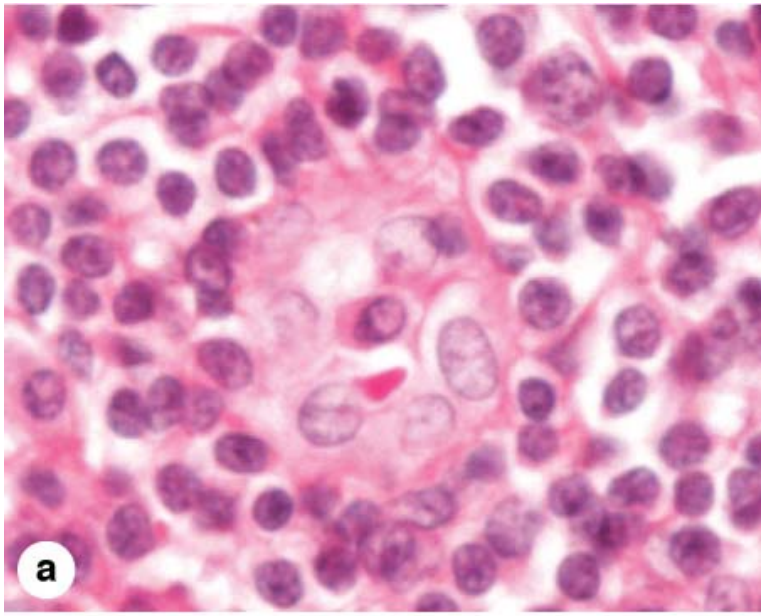
Infection and antigenic stimulation often cause lymph nodes to enlarge. These swollen nodules, which may be palpated

under the skin as indicators of inflammation, 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 normally drains back into the blood, lymphocytes that leave the lymph nodes by efferent lymphatics eventually reach the bloodstream. These lymphocytes may then leave the blood vessels by entering the tissues and return with other lymph to another lymph node. However, most (90%) lymphocytes return to a lymph node by crossing the walls of specific postcapillary venules in the paracortex, the **high endothelial venules (HEVs)** (Figure 14–22). These vessels have an unusual endothelial lining of tall cuboidal cells, whose apical surface glycoproteins and integrins facilitate rapid diapedesis of lymphocytes out of the blood into the paracortex of the lymph node. High endothelial venules are also present in other lymphoid organs, such as the tonsils, Peyer patches, and appendix, but not in the spleen.

Figure 14–22.



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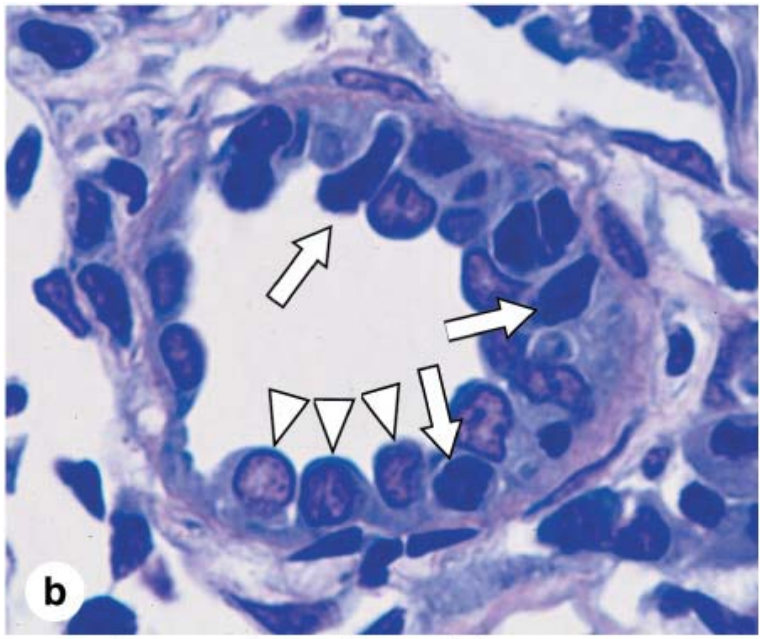

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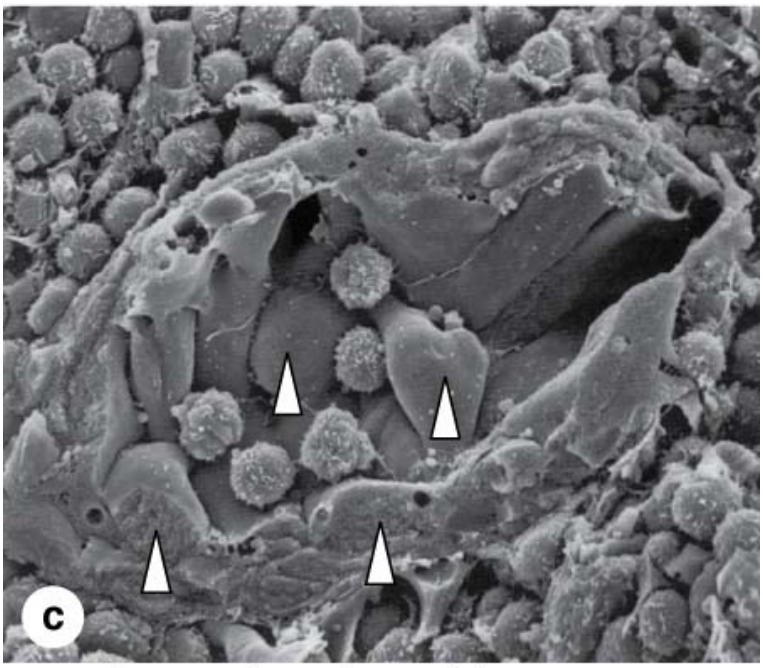

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High endothelial venules (HEV).

(a): High endothelial venules are found in the paracortex of lymph nodes, as shown, as well as in tonsils and Peyer patches. Their endothelial cells are unusually shaped but generally cuboidal and facilitate rapid translocation of lymphocytes into the lymphoid tissue. L-selectin on the lymphocytes recognizes sugar-rich ligands on the surfaces of these endothelial cells and as a consequence the lymphocytes stop there. Integrins promote adhesion between lymphocytes and the endothelial cells and the lymphocytes cross the vessel wall into the lymph node parenchyma. HEVs can be difficult to identify in H&E-stained paraffin sections. X400. H&E. **(b):** Plastic sections more clearly reveal the high endothelial cells (arrowheads) and the lymphocytes passing between them (arrows). X400. PT. **(c):** SEM of a sectioned HEV showing five typical lymphocytes adhering to endothelial cells (arrowheads) prior to migrating between them and joining other lymphocytes in the surrounding paracortex. X500. (Figure 14–22c reproduced, with permission from Fujita, T., 1989, *Prog. Clin. Biol. Res.*, 295:493.)

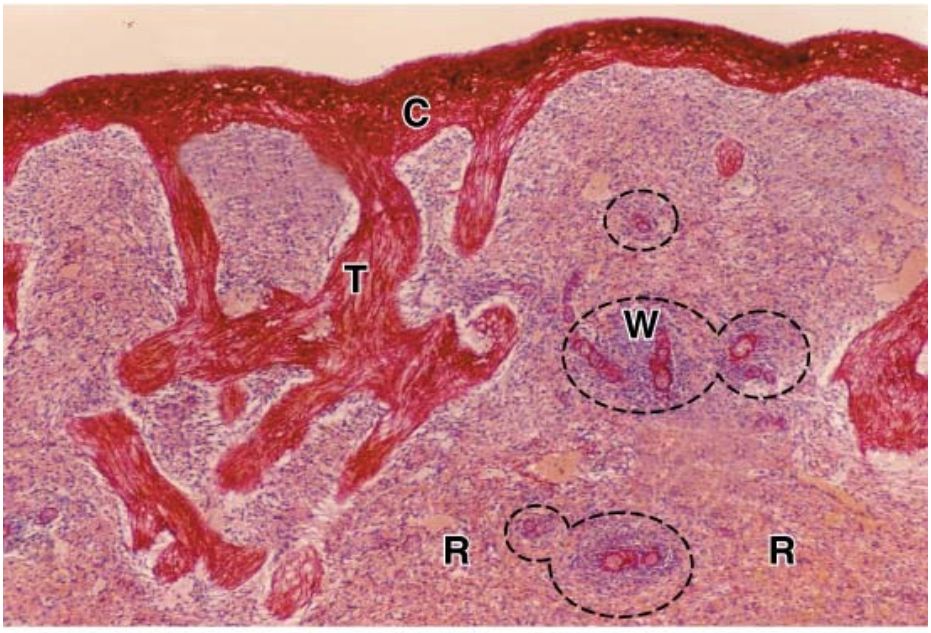
The continuous recirculation of lymphocytes enables most parts of the body to be constantly monitored, increasing the opportunity for lymphocytes to encounter activated APCs that have migrated to lymph nodes.

SPLEEN

The spleen is the largest single accumulation of lymphoid tissue in the body and the only one involved in filtration of blood, making it an important organ in defense against blood-borne antigens. It is also the main site of destruction of aged erythrocytes. As is true of other secondary lymphoid organs, the spleen is a production site of antibodies and activated lymphocytes, which are delivered to the blood. Any inert particles in blood are actively phagocytosed by spleen macrophages.

The spleen is surrounded by a **capsule** of dense connective tissue from which emerge **trabeculae**, which partially subdivide the parenchyma or **splenic pulp** (Figure 14–23). 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 14–23.



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Spleen.

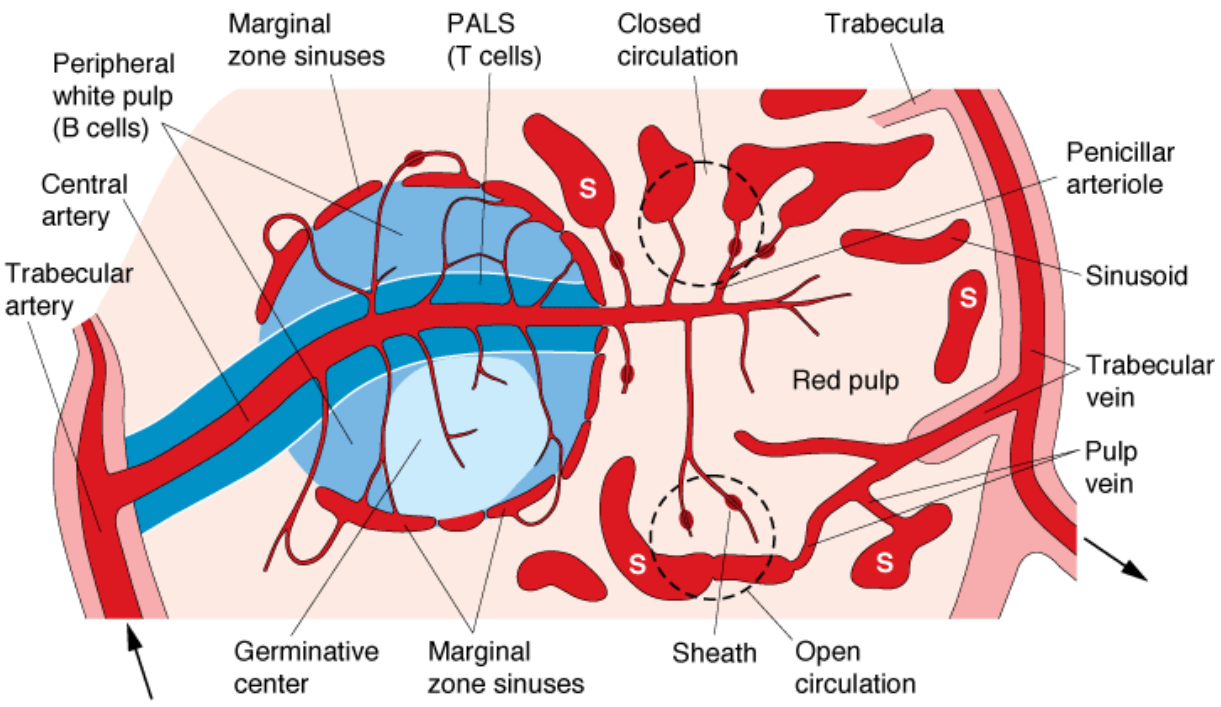
The capsule (C) of the spleen connects to trabeculae (T) which partially subdivide the pulp-like interior of the organ. The red pulp (R) occupies most of the parenchyma, with white pulp (W) restricted to smaller areas, mainly around the central arterioles. Names of these splenic areas refer to their color in the fresh state: red pulp is filled with blood cells of all types, located both in cords and sinuses; white pulp is lymphoid tissue. Large blood vessels and lymphatics enter and leave the spleen at a hilum. X20. PSH.

Splenic Pulp

The spleen is composed of reticular tissue containing 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 14–23). The small masses of white pulp consist of **lymphoid nodules** and the **periarteriolar lymphoid sheathes**, while the red pulp consists of blood-filled **sinusoids** and **splenic cords** (of Bilroth).

As expected of an organ specialized to process blood, the microvasculature of the spleen is important, although much about it remains to be learned. The splenic artery divides inside the hilum, branching into small **trabecular arteries** following this connective tissue. They leave the trabeculae and enter the parenchyma as arterioles enveloped by a sheath of T lymphocytes, the periarteriolar lymphoid sheath **(PALS)**, which is part of the white pulp (Figure 14–24). Surrounded by the PALS, these vessels are known as **central arterioles** (Figure 14–25). After coursing through the parenchyma for variable stretches, the PALS receive large numbers of lymphocytes, mostly B cells, and may form lymphoid nodules (Figure 14–25). In these nodules the arteriole occupies an eccentric position but is still called the central arteriole. During its passage through the white pulp, this arteriole sends off smaller branches that supply the surrounding lymphoid tissue (Figure 14–24).

Figure 14–24.



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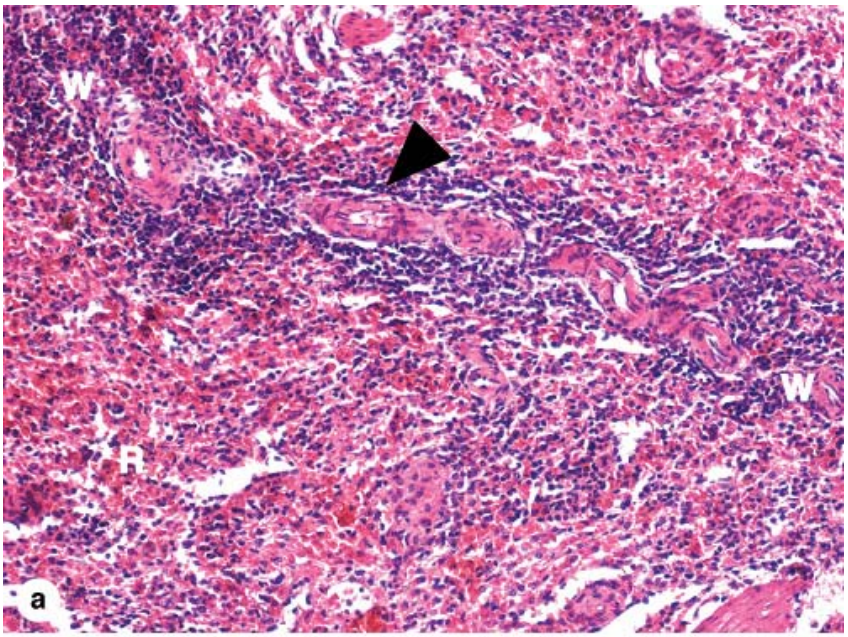
Blood flow in the spleen.

Schematic view of the blood circulation and the structure of the spleen, from the trabecular artery to the trabecular vein. Small branches of these arteries are called central arteries and become enclosed within a sheath of lymphoid cells, the periarteriolar lymphoid sheath (PALS) in white pulp. B cells in these sheathes can form nodules as the largest masses of white pulp, and around these nodules are located the marginal sinuses. Emerging from the white pulp, the central arteriole branches as the penicillar arterioles, which lead to sheathed capillaries. From these, blood flows into either a closed circulation passing directly into splenic sinuses (S) or an open circulation, being dumped from the vasculature into the lymphoid tissue of the red pulp's splenic cords.

Figure 14–25.



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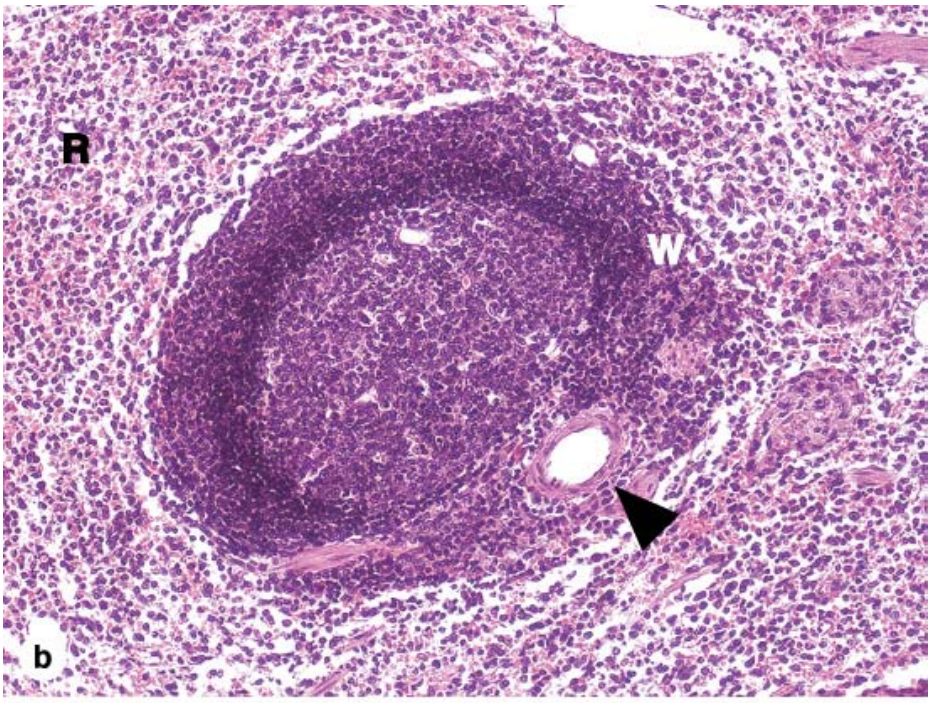

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White pulp of the spleen.

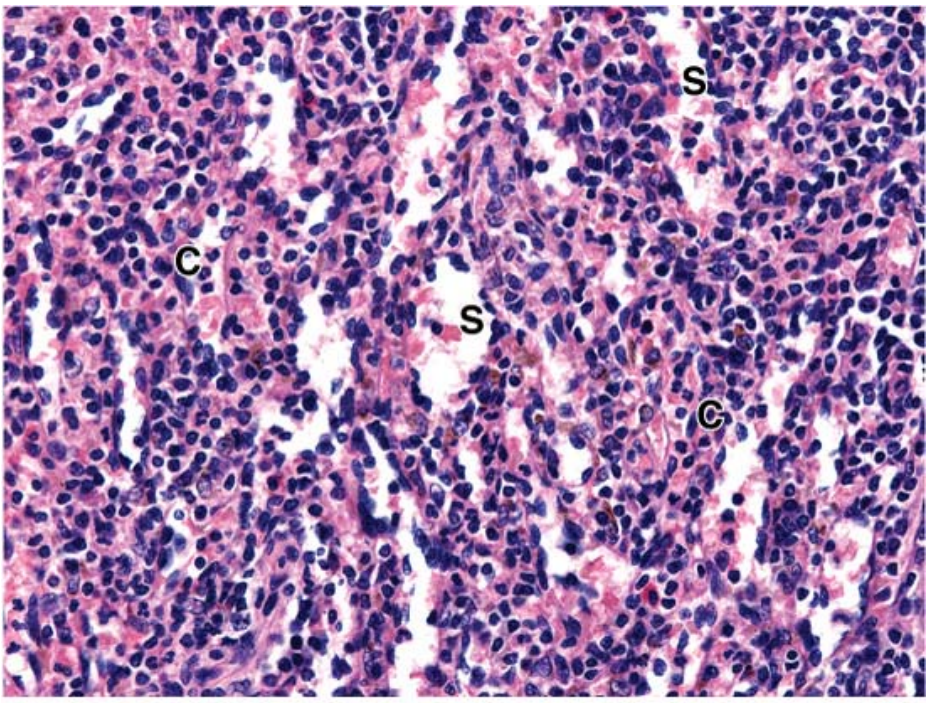
The splenic white pulp consists of lymphoid tissue surrounding the central arterioles as the periarteriolar lymphoid sheath (PALS) and the nodules of proliferating B cells in this sheath. **(a):** Longitudinal section of white pulp (W) in a PALS and the central arteriole (arrowhead) it surrounds. Surrounding the PALS is much red pulp (R). **(b):** A large nodule with a germinal center forms in the PALS. and the central arteriole (arrowhead) is displaced to the nodule's periphery. Small sinuses can be seen at the margin between white and red pulp. Both X20. H&E. (With permission, from Paulo A. Abrahamsohn, Institute of Biomedical Sciences, University of São Paulo, Brazil.)

Surrounding the lymphoid nodules is a **marginal zone** consisting of many blood sinuses and lymphoid tissue (Figures 14–24 and 14–25b). The marginal zone contains lymphocytes, many macrophages, and an abundance of blood antigens and thus plays an important role in the immunological activities of the spleen.

After leaving the white pulp, the sheath of lymphocytes slowly thins and the central arteriole subdivides to form straight **penicillar arterioles** (Figure 14–24). Some of the capillaries that emerge from these penicillar arterioles are sheathed with reticular cells, macrophages and lymphocytes, whose functional significance is not clear.

The red pulp is composed almost entirely of splenic cords and venous sinusoids (Figure 14–26). The splenic cords contain a network of reticular cells or reticular fibers that support T and B lymphocytes, macrophages, plasma cells, and many blood cells (erythrocytes, platelets, and granulocytes). The splenic cords are separated by wide, irregularly shaped sinusoids (Figures 14–26 and 14–27). Unusual elongated endothelial cells, called **stave cells**, line the splenic sinusoids, oriented in parallel with the sinusoid's blood flow. These cells are sparsely wrapped in reticular fibers set in a transverse direction, much like the hoops surrounding the staves of a wooden keg (Figure 14–28).

Figure 14–26.



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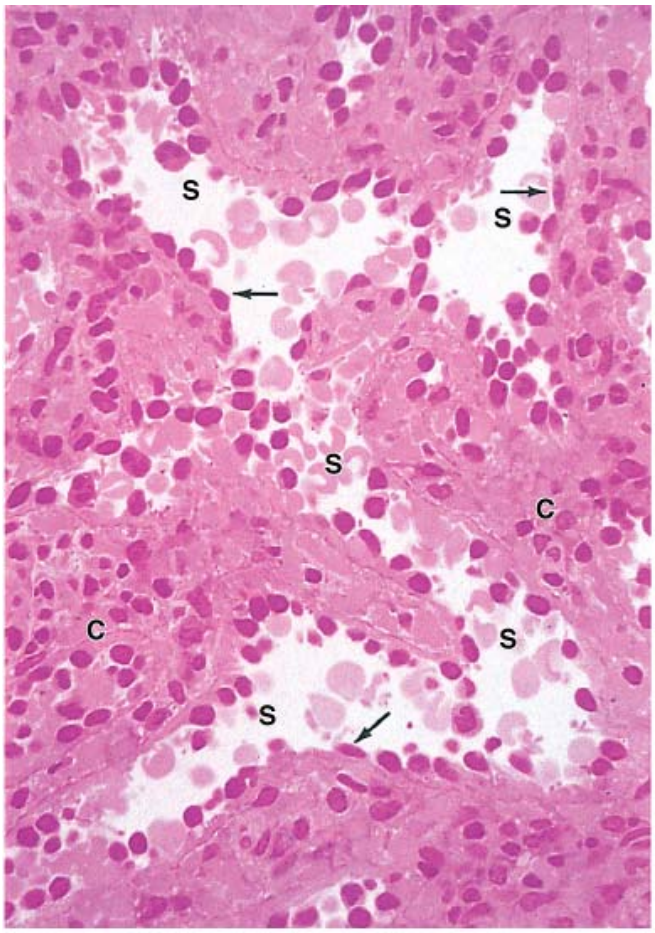
Red pulp of the spleen.

The splenic red pulp is composed of splenic venous sinusoids (S) and splenic cords (C), both of which contain blood cells of all types. The cords, often called cords of Bilroth, are reticular tissue rich in lymphocytes. The sinuses are lined by unusual, nonsquamous endothelial cells. X40.H&E. (With permission, from Paulo A. Abrahamsohn, Institute of Biomedical Sciences, University of São Paulo, Brazil.)

Figure 14–27.



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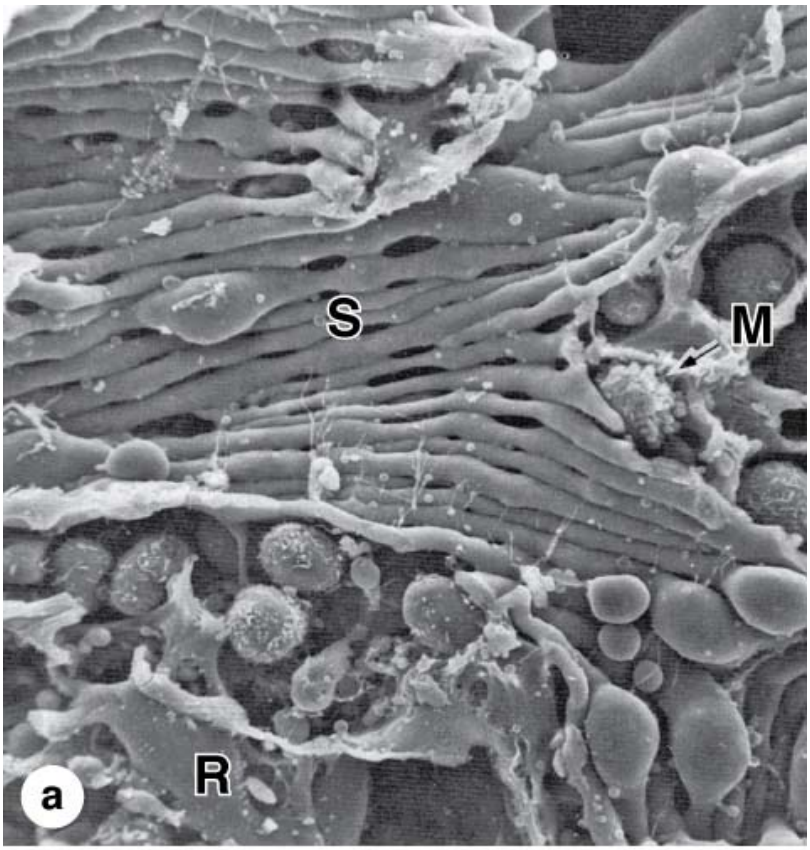
Splenic venous sinuses and stave cells.

Higher magnification of splenic red pulp shows that the venous sinuses (S) are lined by endothelial cells (arrows) with large nuclei bulging into the sinusoidal lumens. The unusual endothelial cells are called stave cells and have special properties that allow selection of healthy red blood cells in the splenic cords (C). X100. H&E. (With permission, from Paulo A. Abrahamsohn, Institute of Biomedical Sciences, University of São Paulo, Brazil.)

Figure 14–28.



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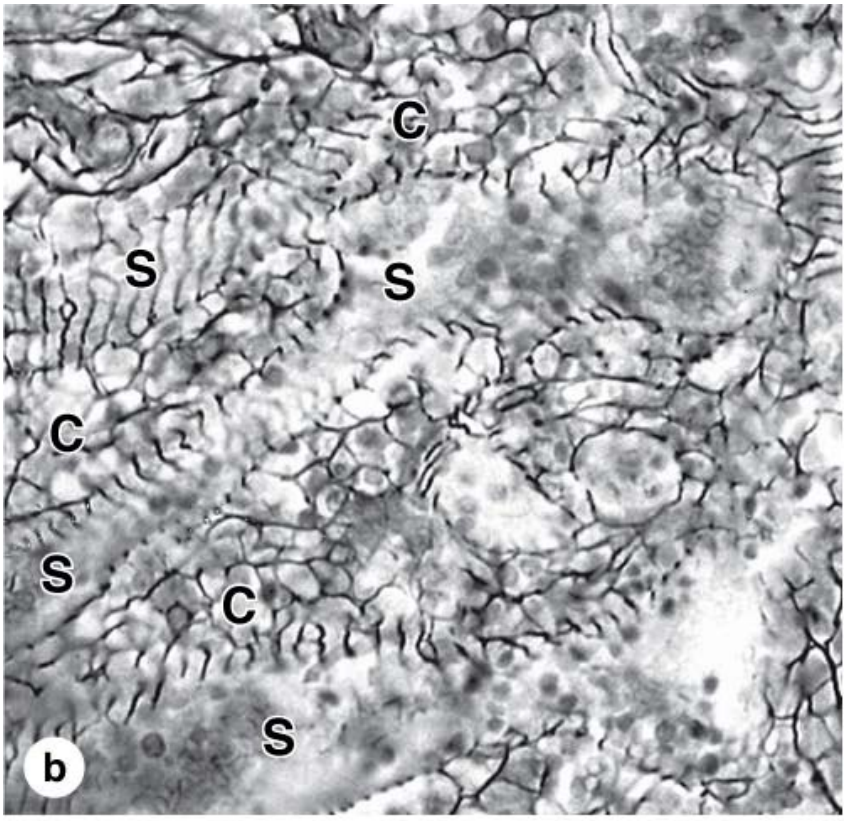

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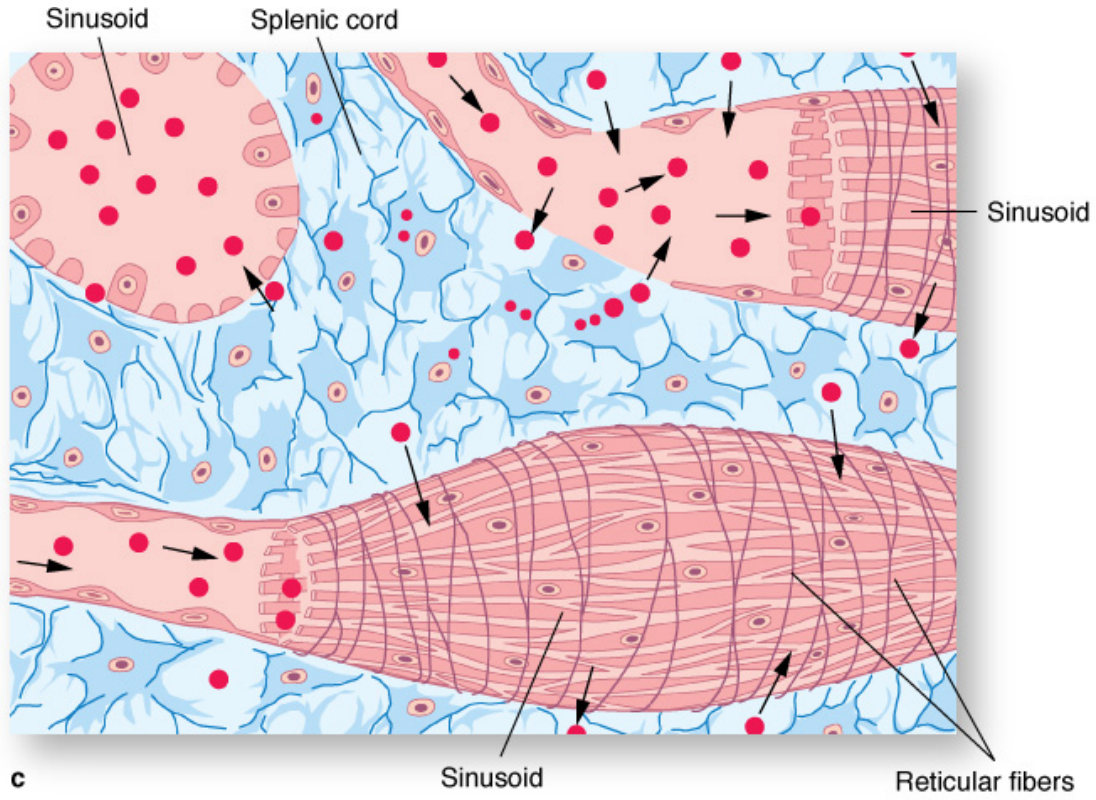

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Structure and function of splenic sinusoids.

The endothelial stave cells that line venous sinuses in red pulp are long cells oriented lengthwise along the sinuses. The elongated shape of the cells is difficult to appreciate from light micrographs (see Figure 14–26). **(a):** SEM clearly shows the parallel alignment of the stave cells (S), as well as many macrophages (M) in the surrounding red pulp (R). X500. **(b):** Silver-stained sections of spleen show black reticular fibers surrounding the sinuses, oriented 90 degrees to the long axis of the sinuses (S). These fibers appear similar to those in the surrounding splenic cords (C). The basement membrane of the stave cells is incomplete and open to the passage of cells. X400. Silver. **(c):** Diagram showing these components of splenic sinuses schematically, with the structures resembling a loosely organized wooden barrel. In the open circulation mode of blood flow, blood cells dumped into the cords of the red pulp move under pressure or by their own activity through the spaces between stave cells, reentering the vasculature and soon leaving the spleen via the splenic vein. Cells that cannot squeeze between the stave cells, mainly effete erythrocytes, are removed by macrophages. (Figure 14-28a reproduced, with permission, from Fujita T:, 1989, *Prog. Clin. Biol. Res. 1989;*295:493)

The highly permeable splenic sinusoids are surrounded by very incomplete basal laminae. The spaces between the endothelial cells of the splenic sinusoids are 2–3 μm or smaller and only flexible cells are able to pass easily from the red pulp cords into the lumen of the sinusoids. Because the lumen of splenic sinusoids is often blood-filled and very small and because the splenic cords are infiltrated with red blood cells, microscopic distinctions between splenic cords and sinusoids may be difficult.

Blood Flow in the Red Pulp

Blood flow through the splenic red pulp can take two routes (Figure 14–24). In the **closed circulation**, the penicillar arterioles or capillaries branching from them connect directly to the sinusoids, so that blood is always enclosed by the vascular endothelium. Alternatively, other penicillar arterioles are open-ended, dumping blood into the stroma of the splenic cords in a unique example of **open circulation**. In this route plasma and formed elements of blood reenter the vasculature by passing between the stave cells of sinusoids, which presents no problem for platelets, leukocytes, and healthy flexible erythrocytes. However, after their normal lifespan of 120 days effete erythrocytes undergo membrane changes, becoming swollen and less flexible, signalling their selective engulfment by macrophages in the splenic cords (Figure 14–29). From the sinusoids, blood proceeds to the red pulp veins that join together and enter the trabeculae, forming the **trabecular veins** (Figure 14–24). The splenic vein originates from these vessels and emerges from the hilum of the spleen. The trabecular veins do not have muscle in their wall and resemble channels hollowed out in the trabecular connective tissue and lined by endothelium.

Figure 14–29.