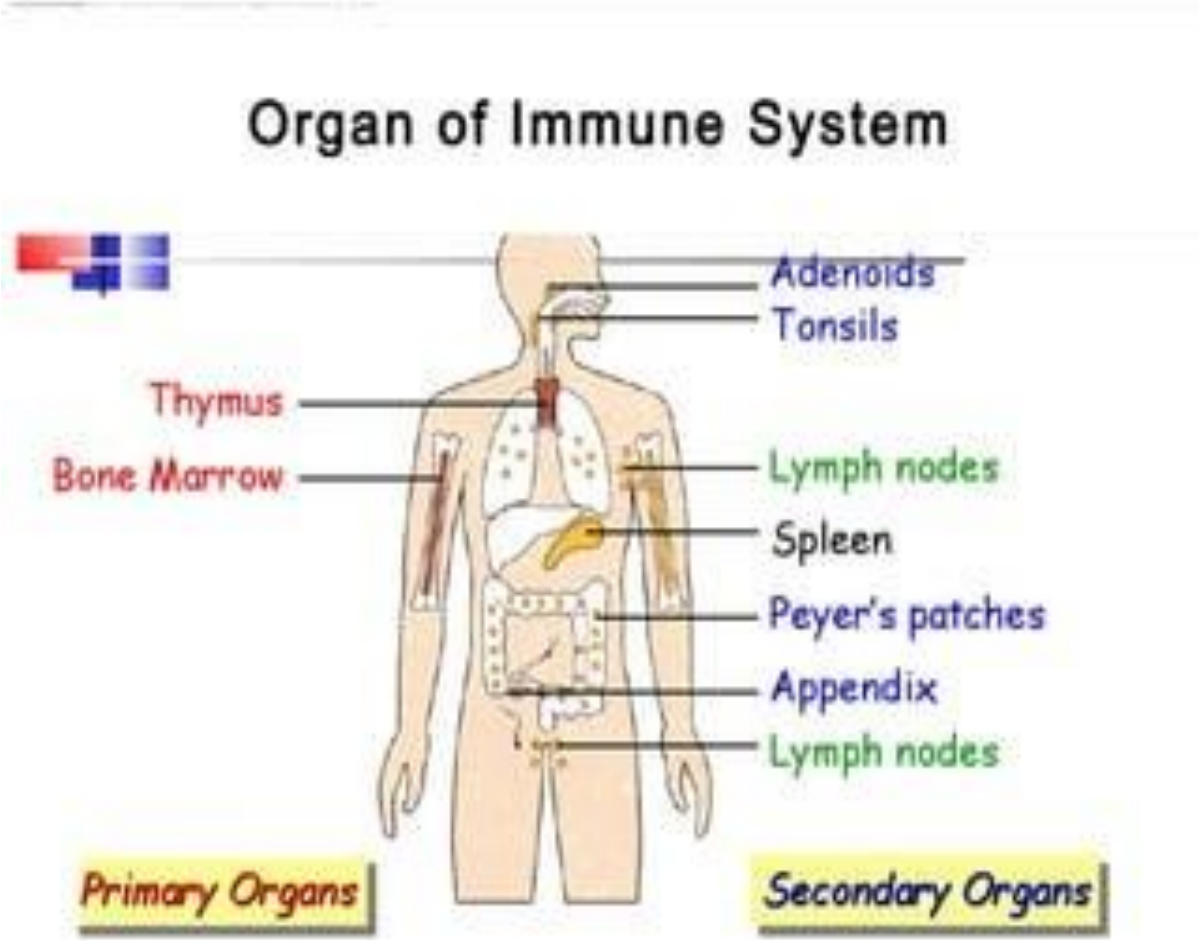
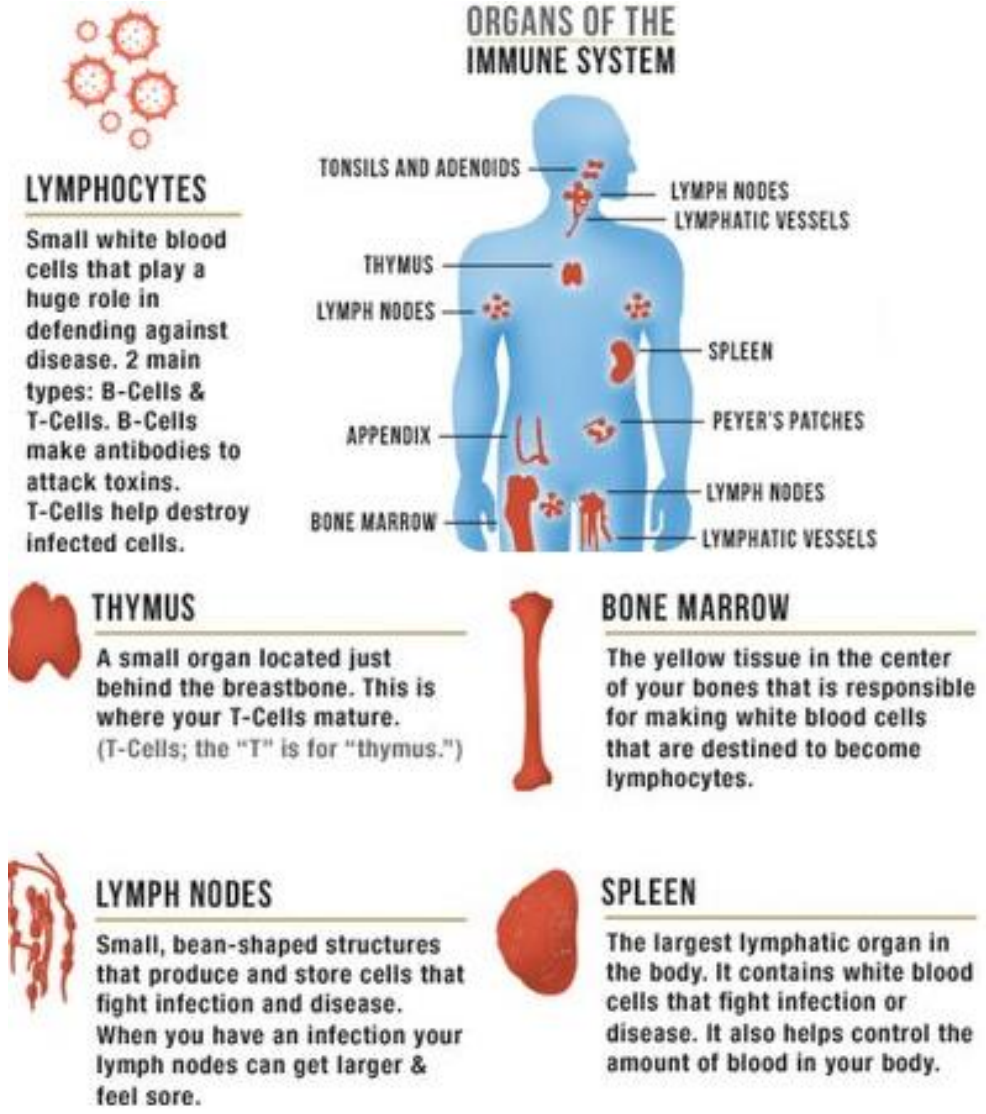
Organs of the Immune System

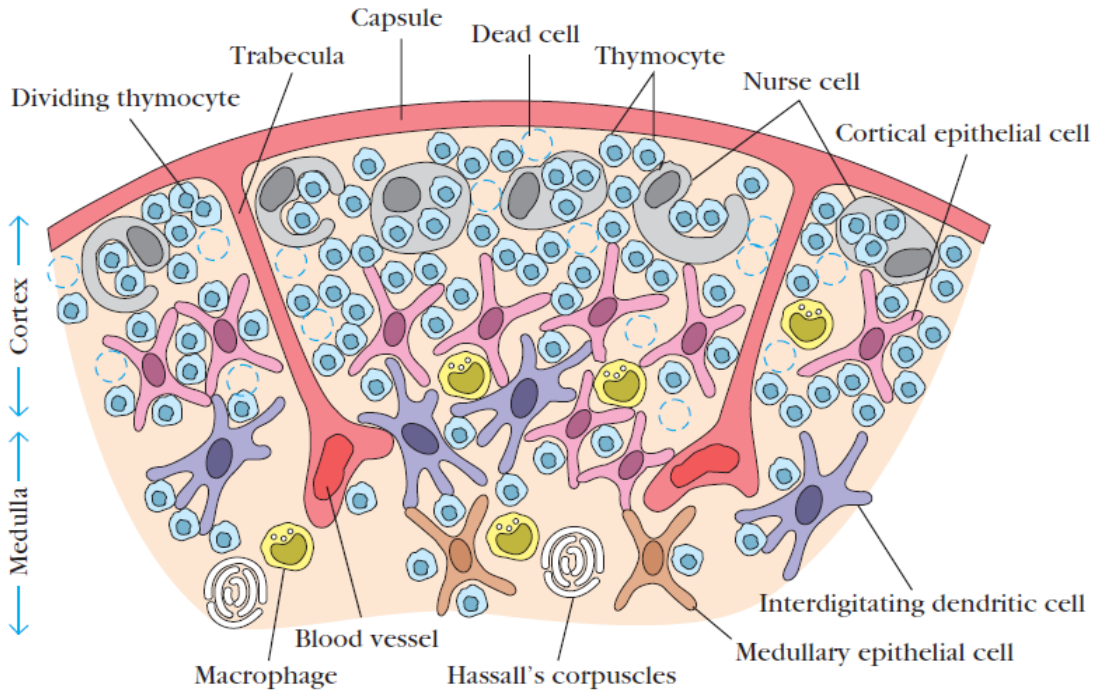




- A number of morphologically and functionally diverse organs and tissues have various functions in the development of immune responses.
- These can be distinguished by function as the **primary** and **secondary lymphoid organs**.
- The thymus and bone marrow are the primary (or central) lymphoid organs, where maturation of lymphocytes takes place.
- The lymph nodes, spleen, and various mucosal associated lymphoid tissues (MALT) such as gut-associated lymphoid tissue (GALT) are the secondary (or peripheral) lymphoid organs, which trap antigen and provide sites for mature lymphocytes to interact with that antigen.
- In addition, **tertiary lymphoid tissues,** which normally contain fewer lymphoid cells than secondary lymphoid organs, can import lymphoid cells during an inflammatory response.
- Most prominent of these are cutaneous-associated lymphoid tissues.
- Once mature lymphocytes have been generated in the primary lymphoid organs, they circulate in the blood and **lymphatic system,** a network of vessels that collect fluid that has escaped into the tissues from capillaries of the circulatory system and ultimately return it to the blood.

Primary Lymphoid Organs

THYMUS



Nurse cells in the thymus are epithelial cells that bind and internalize immature T lymphocyte progenitors in specialized vesicles to help their development, maturation and selection.

Hassall's corpuscles are a potent source of the cytokine TSLP. *In vitro*, TSLP directs the maturation of dendritic cells, and increases the ability of dendritic cells to convert naive thymocytes to a Foxp3+ regulatory T cell lineage. (**Thymic stromal lymphopoietin** (**TSLP**)

- Thymopoietin: fuels the production of T-cells and tells the pituitary gland to release hormones.
- Thymosin and thymulin: help make specialized types of T-cells.
- Thymic humoral factor: keeps your immune system working properly.

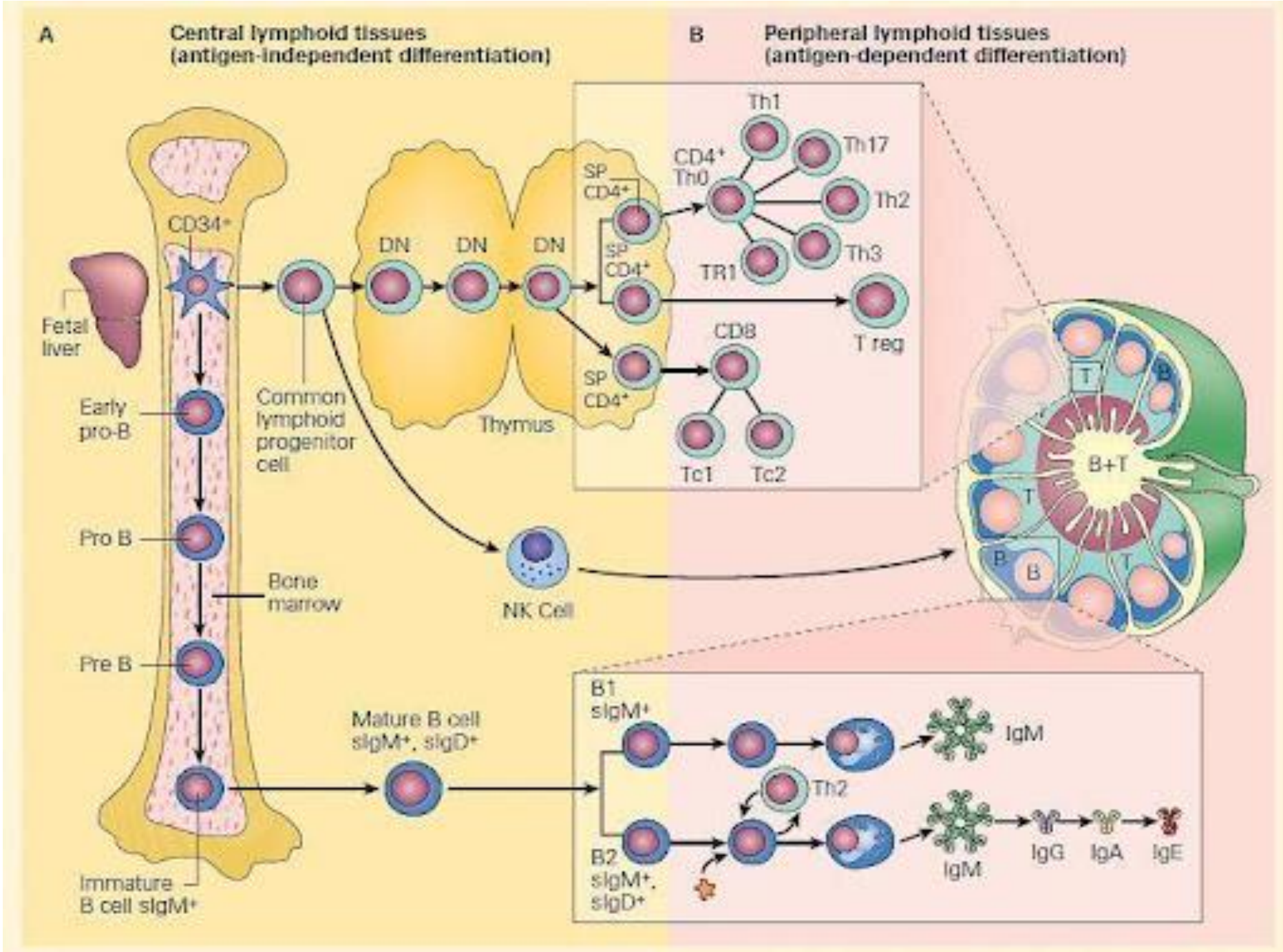
FIGURE 2-14 Diagrammatic cross section of a portion of the thymus, showing several lobules separated by connective tissue strands (trabeculae). The densely populated outer cortex is thought to contain many immature thymocytes (blue), which undergo rapid proliferation coupled with an enormous rate of cell death. Also present in the outer cortex are thymic nurse cells (gray), which are specialized epithelial cells with long membrane extensions that surround as many as 50 thymocytes. The medulla is sparsely populated and is thought to contain thymocytes that are more mature. During their stay within the thymus, thymocytes interact with various stromal cells, including cortical epithelial cells (light red), medullary epithelial cells (tan), interdigitating dendritic cells (purple), and macrophages (yellow). These cells produce thymic hormones and express high levels of class I and class II MHC molecules. Hassalls corpuscles, found in the medulla, contain concentric layers of degenerating epithelial cells. [*Adapted, with permission, from W. van Ewijk, 1991,* Annu. Rev. Immunol. ***9:****591, © 1991 by Annual Reviews.*]

- Thymus is the site of T-cell development and maturation.
- It is a flat, bilobed organ situated above the heart.
- Each lobe is surrounded by a capsule and is divided into lobules, which are separated from each other by strands of connective tissue called trabeculae.
- Each lobule is organized into two compartments:
- the outer compartment, or *cortex,* is densely packed with immature T cells, called thymocytes, whereas
- the inner compartment, or *medulla,* is sparsely populated with thymocytes.
- Both the cortex and medulla of the thymus are crisscrossed by a three-dimensional stromal-cell network composed of epithelial cells, dendritic cells, and macrophages, which make up the framework of the organ and contribute to the growth and maturation of thymocytes.
- Many of these stromal cells interact physically with the developing thymocytes
- Some thymic epithelial cells in the outer cortex, called **nurse cells,** have long membrane extensions that surround as many as 50 thymocytes, forming large multicellular complexes.
- Other cortical epithelial cells have long interconnecting cytoplasmic extensions that form a network and have been shown to interact with numerous thymocytes as they traverse the cortex.
- The function of the thymus is to generate and select a repertoire of T cells that will protect the body from infection.
- As thymocytes develop, an enormous diversity of T-cell receptors is generated by a random process (see Chapter 9) that produces some T cells with receptors capable of recognizing antigen-MHC complexes.
- However, most of the T-cell receptors produced by this random process are incapable of recognizing antigen-MHC complexes and a small portion react with combinations of self antigen-MHC complexes.
- Thymus induces the death of those T cells that cannot recognize antigen- MHC complexes and those that react with self-antigen–MHC and pose a danger of causing autoimmune disease.
- More than 95% of all thymocytes die by apoptosis in the thymus without ever reaching maturity.

- **In DiGeorge's syndrome in humans** and in certain mice **(nude mice)** thymus fails to develop.
- In both cases, there is an absence of circulating T cells and in turn cell-mediated immunity and therefore an increase in infectious disease.
- Aging is accompanied by a decline in thymic function.
- This decline may play some role in the decline in immune function during aging in humans and mice.
- The thymus reaches its maximal size at puberty and then atrophies, with a significant decrease in both cortical and medullary cells and an increase in the total fat content of the organ.
- Whereas the average weight of the thymus is 70 g in infants, its age-dependent involution leaves an organ with an average weight of only 3 g in the elderly.

Bone Marrow

- In humans and mice, bone marrow is the site of B-cell origin and development.
- Immature B cells proliferate and differentiate within the bone marrow, and stromal cells within the bone marrow interact directly with the B cells and secrete various cytokines that are required for development.
- Selection process within the bone marrow eliminates B cells with self-reactive antibody receptors.
- Bone marrow is not the site of B-cell development in all species.
- In birds, bursa of Fabricius, is the primary site of B-cell maturation.
- In cattle and sheep, the **primary lymphoid tissue** hosting the maturation, proliferation, and diversification of B cells early in gestation is the **fetal spleen.**
- Later in gestation, this function is assumed by a **patch of tissue** embedded in the wall of the intestine called **the ileal Peyer's patch**, which contains a large number (10^{10}) B cells.
- The rabbit, too, uses gut-associated tissues such as the appendix as primary lymphoid tissue for important steps in the proliferation and diversification of B cells.


A
Central lymphoid tissues
(antigen-independent differentiation)
B
Peripheral lymphoid tissues
(antigen-dependent differentiation)
CD34+
Fetal liver
Early pro-B
Pro B
Bone marrow
Pre B
Immature B cell sIgM+
Common lymphoid progenitor cell
DN
DN
DN
Thymus
SP CD4+
SP CD4+
SP CD4+
CD4+ Th0
Th1
Th17
Th2
Th3
TR1
T reg
CD8
Tc1
Tc2
NK Cell
T
B
B+T
T
B
B
T
Mature B cell sIgM+, sIgD+
B1 sIgM+
B2 sIgM+, sIgD+
Th2
IgM
IgM
IgG
IgA
IgE

Lymphatic System

- As blood circulates under pressure, its fluid component **(plasma)** seeps through the thin wall of the capillaries into the surrounding tissue.
- Much of this fluid, called **interstitial fluid,** returns to the blood through the capillary membranes.
- The remainder of the interstitial fluid, now called **lymph,** flows from the spaces in connective tissue into a network of tiny open lymphatic capillaries and then into a series of progressively larger collecting vessels called **lymphatic vessels.**

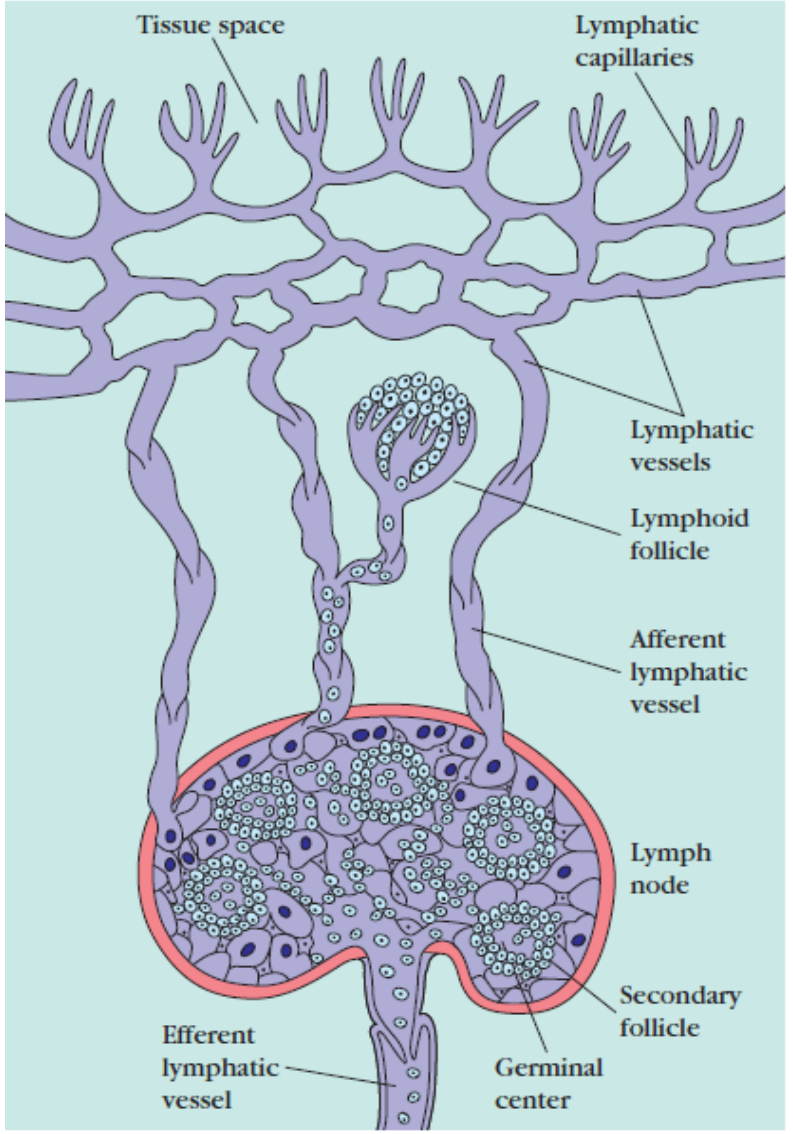


FIGURE 2-16 Lymphatic vessels. Small lymphatic capillaries opening into the tissue spaces pick up interstitial tissue fluid and carry it into progressively larger lymphatic vessels, which carry the fluid, now called lymph, into regional lymph nodes. As lymph leaves the nodes, it is carried through larger efferent lymphatic vessels, which eventually drain into the circulatory system at the thoracic duct or right lymph duct (see Figure 2-13).

- The largest lymphatic vessel, the **thoracic duct,** empties into the left subclavian vein near the heart.
- In this way, the lymphatic system captures fluid lost from the blood and returns it to the blood, thus ensuring steady-state levels of fluid within the circulatory system.
- The heart does not pump the lymph through the lymphatic system; instead the flow of lymph is achieved as the lymph vessels are squeezed by movements of the body's muscles.
- A series of one-way valves along the lymphatic vessels ensures that lymph flows only in one direction.
- When a foreign antigen gains entrance to the tissues, it is picked up by the lymphatic system and is carried to various organized lymphoid tissues such as lymph nodes, which trap the foreign antigen.
- As lymph passes from the tissues to lymphatic vessels, it becomes progressively enriched in lymphocytes.
- Thus, the lymphatic system also serves as a means of transporting lymphocytes and antigen from the connective tissues to organized lymphoid tissues where the lymphocytes may interact with the trapped antigen and undergo activation.

Secondary Lymphoid Organs

- Various types of organized lymphoid tissues are located along the vessels of the lymphatic system.
- Some lymphoid tissue in the lung and lamina propria of the intestinal wall consists of diffuse collections of lymphocytes and macrophages.
- Other lymphoid tissue is organized into structures called lymphoid follicles, which consist of aggregates of lymphoid and nonlymphoid cells surrounded by a network of draining lymphatic capillaries.
- Until it is activated by antigen, a lymphoid follicle—called a **primary follicle**—comprises a network of follicular dendritic cells and small resting B cells.
- After an antigenic challenge, a primary follicle becomes a larger **secondary follicle**—a ring of concentrically packed B lymphocytes surrounding a center (the **germinal center**) in which one finds a focus of proliferating B lymphocytes and an area that contains nondividing B cells, and some helper T cells interspersed with macrophages and follicular dendritic cells.

Primary follicle
- Naïve Lymphocytes
- No germinal center

Secondary follicle
- **Germinal Center**
- Antigen has been encountered
- Looks pale! - because of plasmablasts

- Most antigen-activated B cells divide and differentiate into antibody-producing plasma cells in lymphoid follicles, but only a few B cells in the antigen-activated population find their way into germinal centers.
- Those that do undergo one or more rounds of cell division, during which the genes that encode their antibodies mutate at an unusually high rate.
- Following the period of division and mutation, there is a rigorous selection process in which more than 90% of these B cells die by apoptosis.
- In general, those B cells producing antibodies that bind antigen more strongly have a much better chance of surviving than do their weaker companions.
- The small number of B cells that survive the germinal center's rigorous selection differentiate into plasma cells or memory cells and emerge.
- **Lymph nodes** and the **spleen** are the most highly organized of the secondary lymphoid organs; they comprise not only lymphoid follicles, but additional distinct regions of T-cell and B-cell activity, and they are surrounded by a fibrous capsule.
- Less-organized lymphoid tissue, collectively called mucosal-associated lymphoid tissue (MALT), is found in various body sites.
- MALT includes Peyer's patches (in the small intestine), the tonsils, and the appendix, as well as numerous lymphoid follicles within the lamina propria of the intestines and in the mucous membranes lining the upper airways, bronchi, and genital tract.

Lymph Nodes

- Lymph nodes are the sites where immune responses are mounted to antigens in lymph.
- They are encapsulated bean shaped structures containing a reticular network packed with lymphocytes, macrophages, and dendritic cells.
- lymph nodes are the first organized lymphoid structure to encounter antigens that enter the tissue spaces.
- As lymph percolates through a node, any particulate antigen that is brought in with the lymph will be trapped by the cellular network of phagocytic cells and dendritic cells (follicular and interdigitating).
- The overall architecture of a lymph node supports an ideal microenvironment for lymphocytes to effectively encounter and respond to trapped antigens.

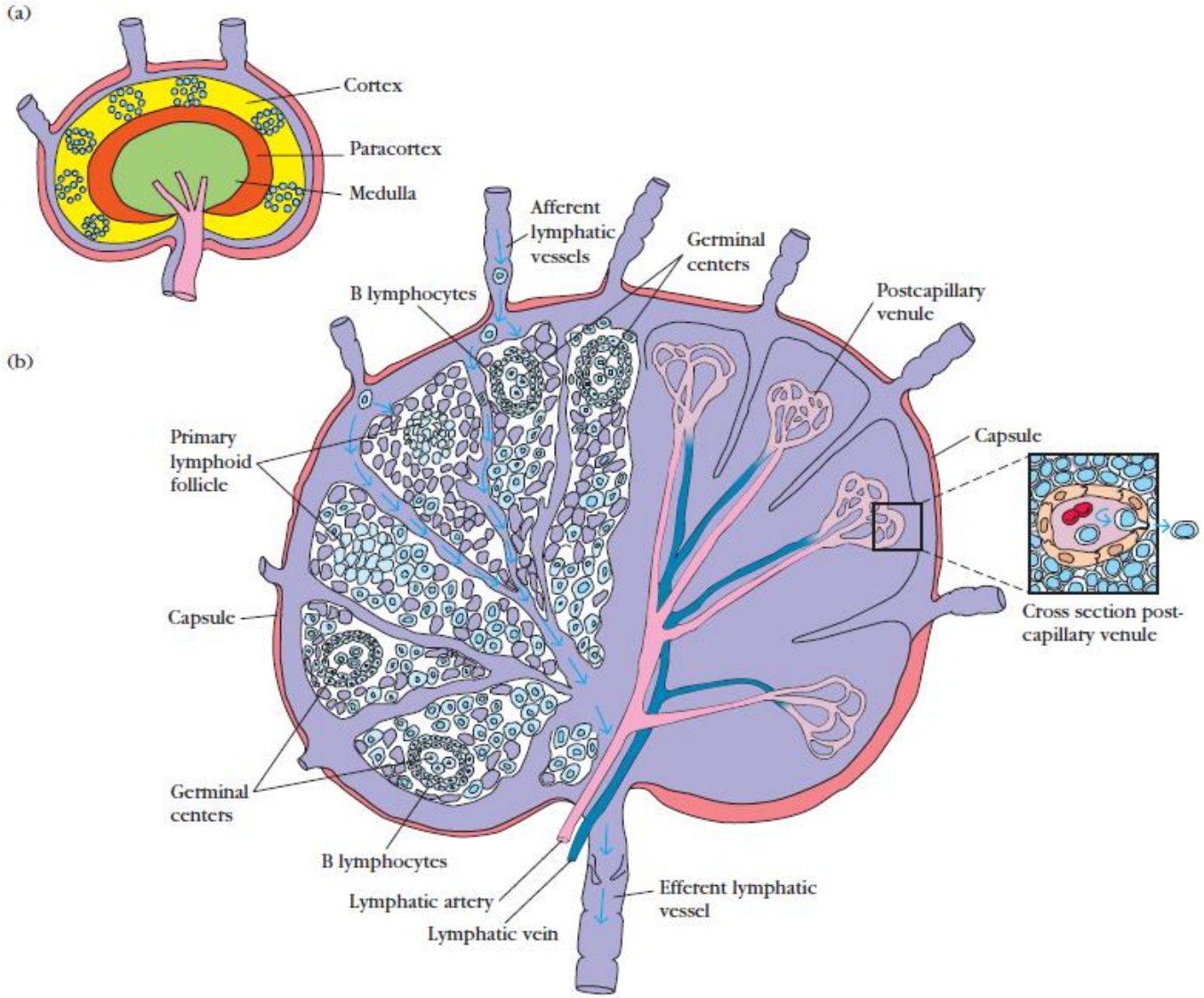


FIGURE 2-18 Structure of a lymph node. (a) The three layers of a lymph node support distinct microenvironments. (b) The left side depicts the arrangement of reticulum and lymphocytes within the various regions of a lymph node. Macrophages and dendritic cells, which trap antigen, are present in the cortex and paracortex. T_H cells are concentrated in the paracortex; B cells are located primarily in the cortex, within follicles and germinal centers. The medulla is populated largely by antibody-producing plasma cells. Lymphocytes circulating in the lymph are carried into the node by afferent lymphatic vessels; they either enter the reticular matrix of the node or pass through it and leave by the efferent lymphatic vessel. The right side of (b) depicts the lymphatic artery and vein and the postcapillary venules. Lymphocytes in the circulation can pass into the node from the postcapillary venules by a process called extravasation (*inset*).

- Lymph node can be divided into three roughly concentric regions:
    - Cortex,
    - Paracortex, and
    - Medulla, each of which supports a distinct microenvironment.

- **Cortex,** contains Macrophages, dendritic cells and B-lymphocytes.
- **Paracortex,** contains Macrophages, dendritic cells and TH-lymphocytes.
- **Medulla is** populated by antibody producing plasma cells.

- After antigenic challenge, the primary follicles enlarge into secondary follicles, each containing a germinal center.
- These interdigitating dendritic cells express high levels of class II MHC molecules, which are necessary for presenting antigen to TH cells.

- As antigen is carried into a regional node by the lymph, it is trapped, processed, and presented together with class II MHC molecules by interdigitating dendritic cells in the paracortex, resulting in the activation of TH cells.
- The initial activation of B cells is also thought to take place within the T-cell-rich paracortex.
- Once activated, TH and B cells form small foci consisting largely of proliferating B cells at the edges of the paracortex.
- Some B cells within the foci differentiate into plasma cells secreting IgM and IgG.
- These foci reach maximum size within 4–6 days of antigen challenge.
- Within 4–7 days of antigen challenge, a few B cells and TH cells migrate to the primary follicles of the cortex.
- Within a primary follicle, cellular interactions between follicular dendritic cells, B cells, and TH cells take place, leading to development of a secondary follicle with a central germinal center.
- Some of the plasma cells generated in the germinal center move to the medullary areas of the lymph node, and many migrate to bone marrow.

- Afferent lymphatic vessels pierce the capsule of a lymph node at **numerous sites** and empty lymph into the subcapsular sinus.

- Lymph coming from the tissues percolates slowly inward through the cortex, paracortex, and medulla, allowing phagocytic cells and dendritic cells to trap any bacteria or particulate material (e.g., antigen-antibody complexes) carried by the lymph.

- After infection or the introduction of other antigens into the body, the lymph leaving a node through its single efferent lymphatic vessel is enriched with antibodies newly secreted by medullary plasma cells and also has a **50 fold higher** concentration of lymphocytes than the afferent lymph.

- The increase in lymphocytes in lymph is because lymphocyte proliferation within the node in response to antigen.

Spleen

- The spleen plays a major role in mounting immune responses to antigens in the blood stream. It is a large, secondary lymphoid organ situated high in the left abdominal cavity.
- While lymph nodes are specialized for trapping antigen from local tissues, the spleen specializes in filtering blood and trapping blood-borne antigens; thus, it can respond to systemic infections. Unlike the lymph nodes, the spleen is not supplied by lymphatic vessels. Instead, bloodborne antigens and lymphocytes are carried into the spleen through the splenic artery.
- More recirculating lymphocytes pass daily through the spleen than through all the lymph nodes combined.
- The spleen is surrounded by a capsule that extends a number of projections (trabeculae) into the interior to form compartment.
- The compartments are of two types, the red pulp and white pulp, which are separated by a diffuse marginal zone.
- The splenic **red pulp** consists of a network of sinusoids populated by macrophages and numerous RBCs and few lymphocytes; it is the site where old and defective RBCs are destroyed and removed.
- Many of the macrophages within the red pulp contain engulfed RBCs or iron pigments from degraded hemoglobin.
- The splenic **white pulp** surrounds the branches of the splenic artery, forming a **periarteriolar lymphoid sheath (PALS)** populated mainly by T lymphocytes.

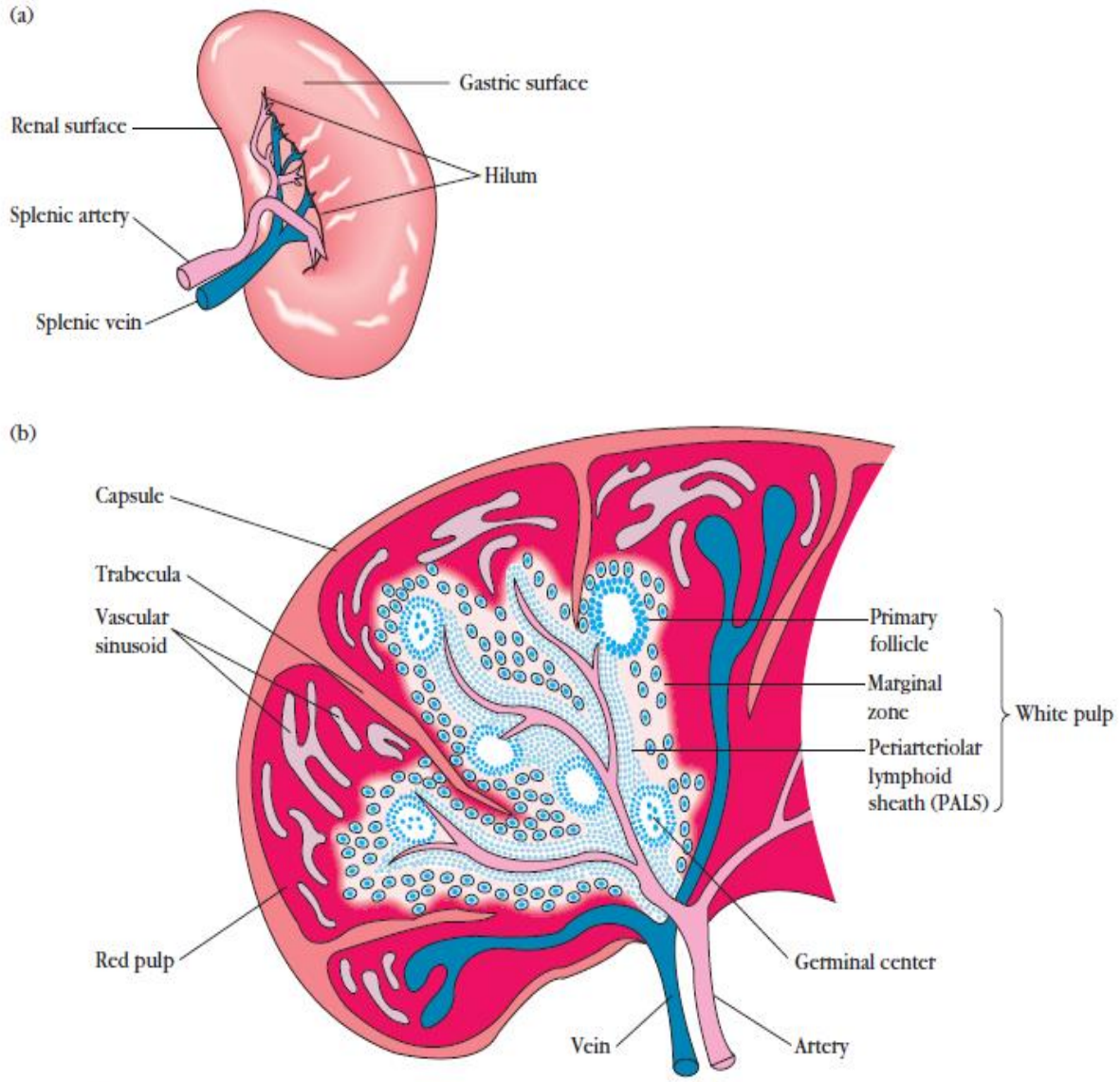
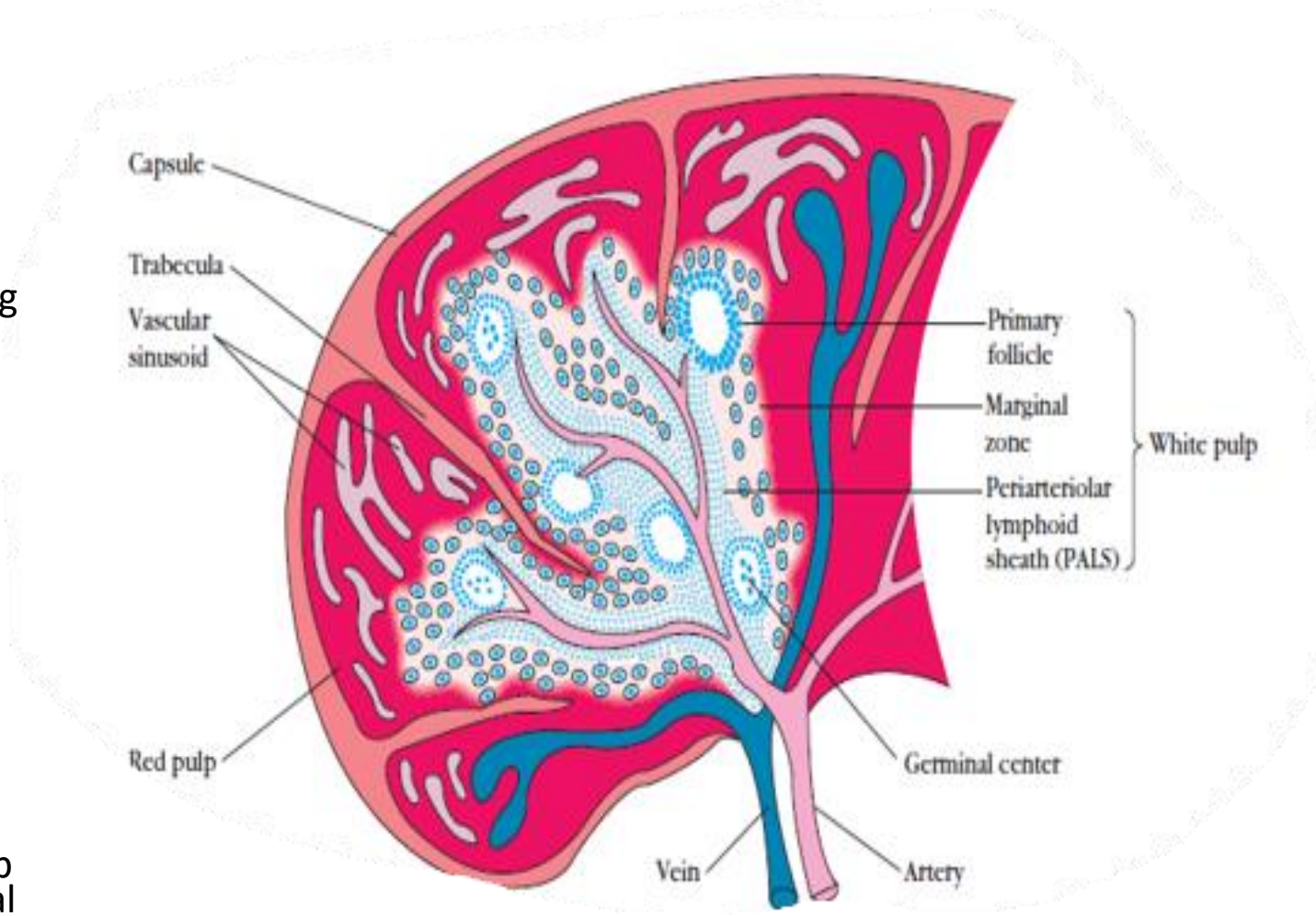


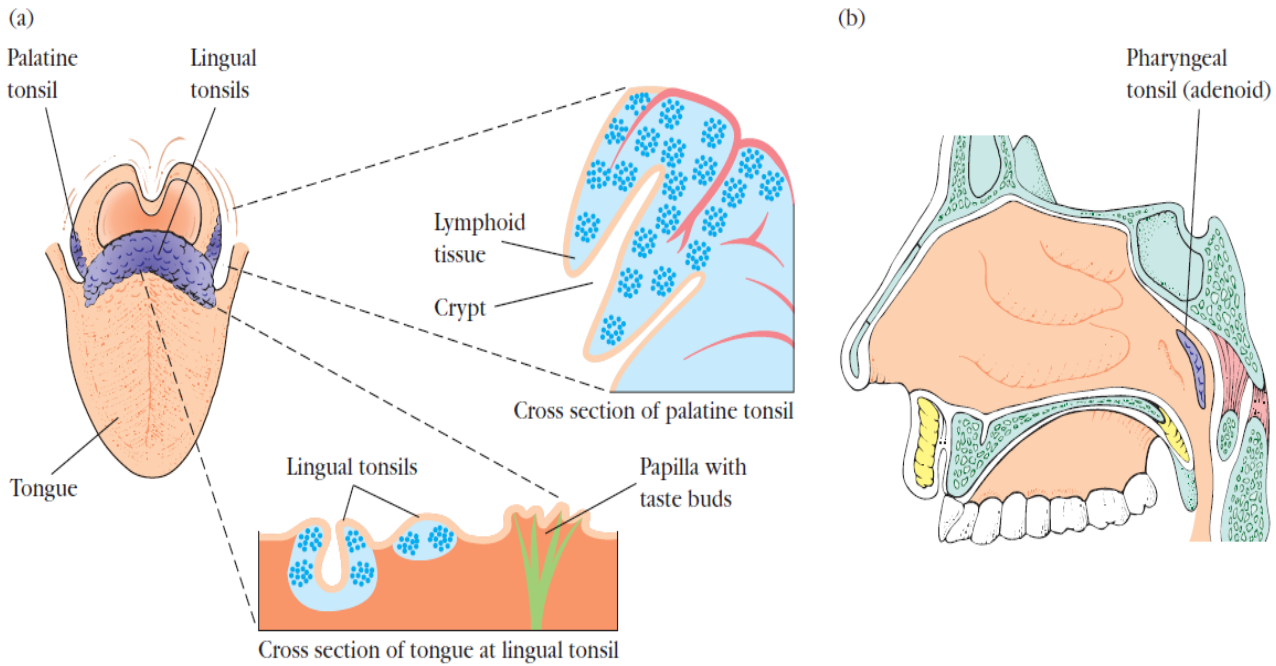
FIGURE 2-19 Structure of the spleen. (a) The spleen, which is about 5 inches long in adults, is the largest secondary lymphoid organ. It is specialized for trapping blood-borne antigens. (b) Diagrammatic cross section of the spleen. The splenic artery pierces the capsule and divides into progressively smaller arterioles, ending in vascular sinusoids that drain back into the splenic vein. The erythrocyte-filled red pulp surrounds the sinusoids. The white pulp forms a sleeve, the periarteriolar lymphoid sheath (PALS), around the arterioles; this sheath contains numerous T cells. Closely associated with the PALS is the marginal zone, an area rich in B cells that contains lymphoid follicles that can develop into secondary follicles containing germinal centers.

- Primary lymphoid follicles are attached to the PALS.
- These follicles are rich in B cells.
- The **marginal zone,** located peripheral to the PALS, is populated by lymphocytes and macrophages.
- Blood-borne antigens and lymphocytes enter the spleen through the splenic artery, which empties into the marginal zone.
- In the marginal zone, antigen is trapped by interdigitating dendritic cells, which carry it to the PALS.
- Lymphocytes in the blood also enter sinuses in the marginal zone and migrate to the PALS.
- The initial activation of B and T cells takes place in the T cell-rich PALS.
- Here interdigitating dendritic cells capture antigen and present it combined with class II MHC molecules to TH cells.
- Once activated, these TH cells can then activate B cells.
- Activated B cells, together with some TH cells, then migrate to primary follicles in the marginal zone.
- Upon antigenic challenge, these primary follicles develop into characteristic secondary follicles containing germinal centers, where rapidly dividing B cells (centroblasts) and plasma cells are surrounded by dense clusters of concentrically arranged lymphocytes.

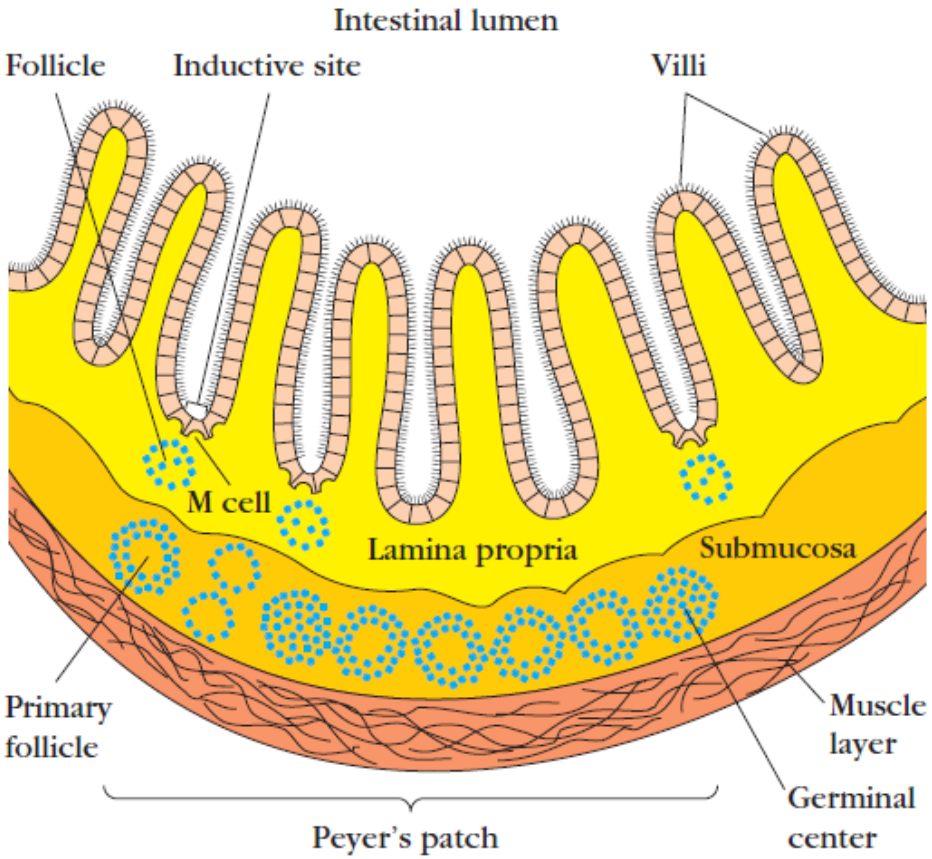


MUCOSAL-ASSOCIATED LYMPHOID TISSUE

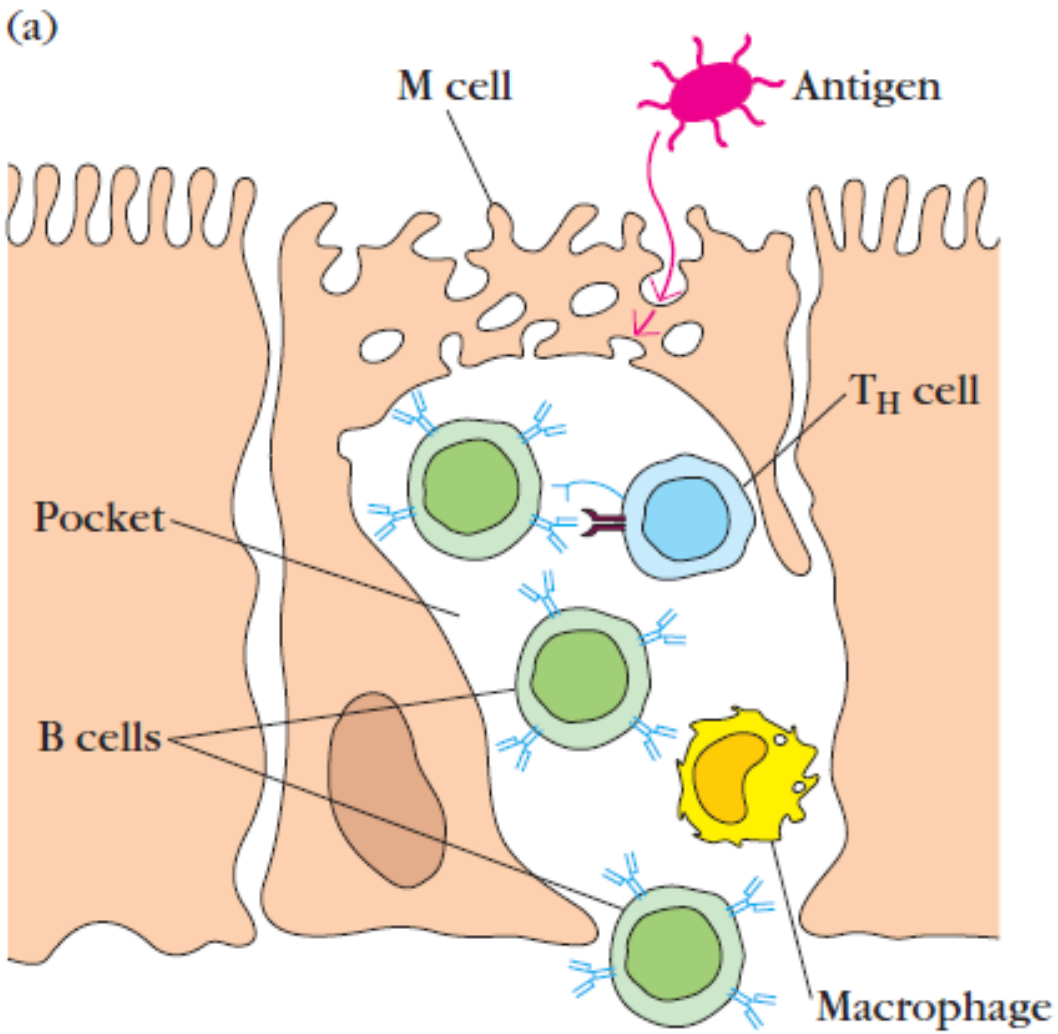
- The mucous membranes lining the digestive, respiratory, and urogenital systems have a combined surface area of about 400 m^2 and are the major sites of entry for most pathogens.
- These vulnerable membrane surfaces are defended by a group of organized lymphoid tissues known collectively as **mucosal-associated lymphoid tissue (MALT).**
- Structurally, unorganized lamina propria of intestinal villi to well-organized structures like tonsils and appendix.
- The number of plasma cells in MALT far exceeds that of in the spleen, lymph nodes, and bone marrow combined.
- The **tonsils** are found in three locations:
    - lingual at the base of the tongue;
    - palatine at the sides of the back of the mouth; and
    - pharyngeal (adenoids) in the roof of the nasopharynx
- All three tonsil groups are nodular structures consisting of a meshwork of reticular cells and fibers interspersed with lymphocytes, macrophages, granulocytes, and mast cells.
- The B cells are organized into follicles and germinal centers; the latter are surrounded by regions showing T-cell activity.
- The tonsils defend against antigens entering through the nasal and oral epithelial routes.



- The best studied of the mucous membranes is the one that lines the gastrointestinal tract.
- This tissue, like that of the respiratory and urogenital tracts, has the capacity to endocytose antigen from the lumen.
- Immune reactions are initiated against pathogens and antibody can be generated and exported to the lumen to combat the invading organisms.
- The lamina propria, which lies under the epithelial layer, contains large numbers of B cells, plasma cells, activated TH cells, and macrophages in loose clusters.
- The submucosal layer has nodules of 30–40 lymphoid follicles that can develop into secondary follicles with germinal centres.



- The epithelial cells of mucous membranes play an important role in promoting the immune response by delivering small samples of foreign antigen from the lumina of the respiratory, digestive, and urogenital tracts to the underlying mucosal-associated lymphoid tissue.
- This antigen transport is carried out by specialized M cells.
- The structure of the M cell is striking: these are flattened epithelial cells lacking the microvilli that characterize the rest of the mucous epithelium.
- In addition, M cells have a deep invagination, or pocket, in the basolateral plasma membrane; this pocket is filled with a cluster of B cells, T cells, and macrophages.
- Luminal antigens are endocytosed into vesicles that are transported from the luminal membrane to the underlying pocket membrane.
- The vesicles then fuse with the pocket membrane, delivering the potentially response-activating antigens to the clusters of lymphocytes contained within the pocket.



- M cells are located in so-called **inductive sites**—small regions of a mucous membrane that lie over organized lymphoid follicles.
- Antigens transported across the mucous membrane by M cells can activate B cells within these lymphoid follicles.
- The activated B cells differentiate into plasma cells, which leave the follicles and secrete the IgA class of antibodies.
- These antibodies then are transported across the epithelial cells and released as **secretory IgA** into the lumen, where they can interact with antigens.