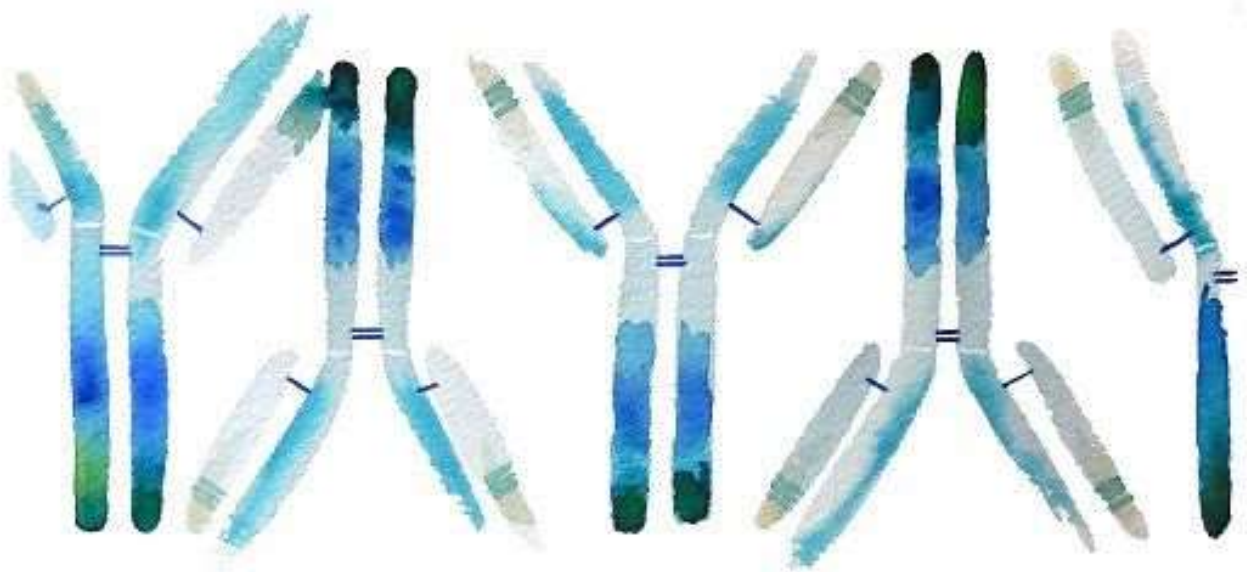
Medical Immunology



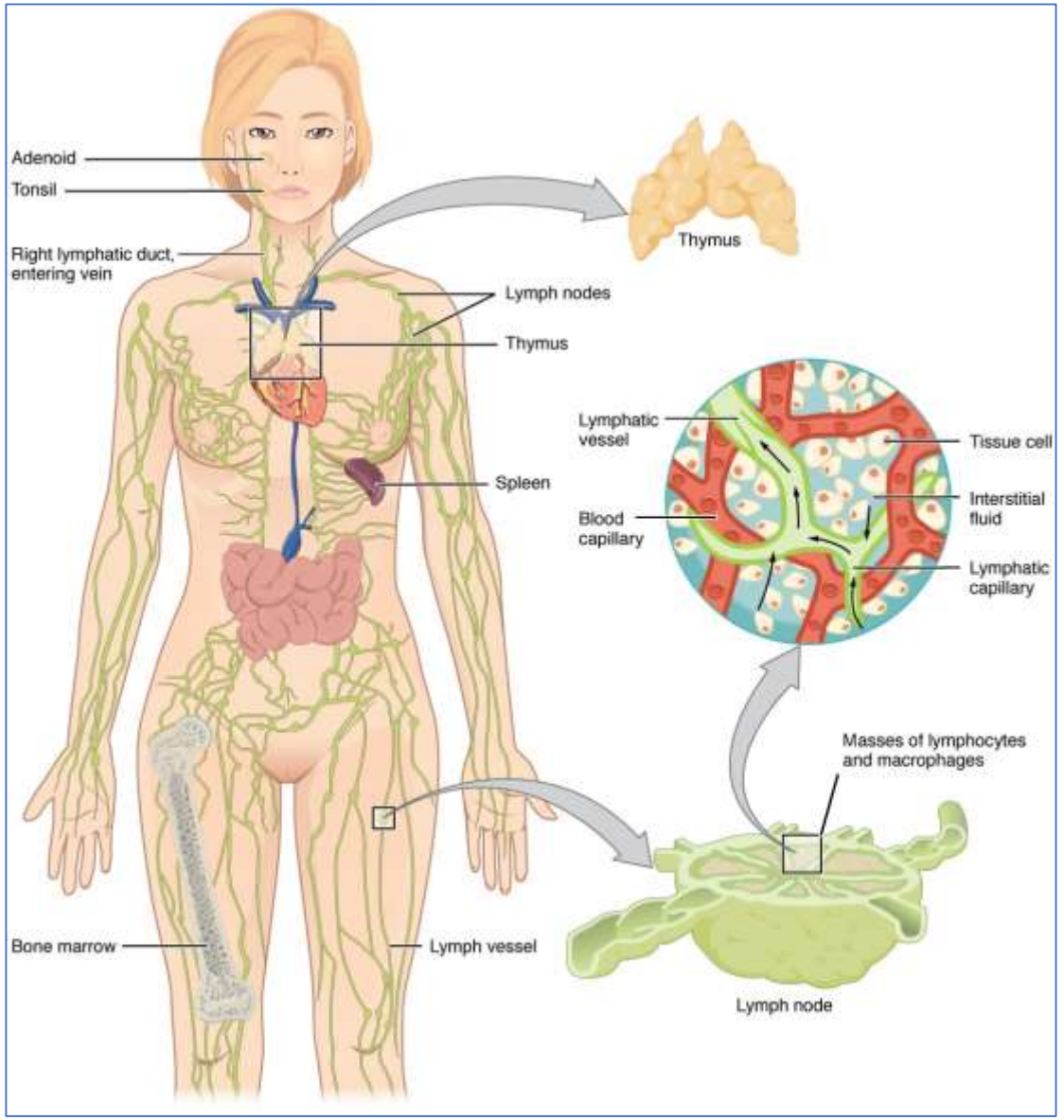
Anas Abu-Humaidan
M.D. Ph.D.

Lecture 4

Tissues of the immune system

- To **optimize the cellular interactions** necessary for antigen recognition and lymphocyte activation in adaptive immune responses, **lymphocytes and APCs are localized and concentrated in anatomically defined tissues** or organs, which are also the sites where foreign antigens are transported and concentrated

- Lymphoid tissues are classified as generative organs, also called **primary or central lymphoid organs**, where lymphocytes first express antigen receptors and attain phenotypic and functional maturity, and as peripheral organs, also called **secondary lymphoid organs**, where lymphocyte responses to foreign antigens are initiated and develop



Tissues of the immune system/ primary lymphoid tissue/ Bone Marrow

- The bone marrow is the site of generation of most mature circulating blood cells, including red cells, granulocytes, and monocytes, and the site of early events in B cell maturation.

- The generation of all blood cells, called hematopoiesis occurs initially, during fetal development, in blood islands of the yolk sac and the para-aortic mesenchyme, then shifts to the liver between the third and fourth months of gestation, and gradually shifts again to the bone marrow.

- At birth, hematopoiesis takes place mainly in the bones throughout the skeleton, but it becomes restricted increasingly to the **marrow of the flat bones.**

Percentage of total bone marrow activity by bony site

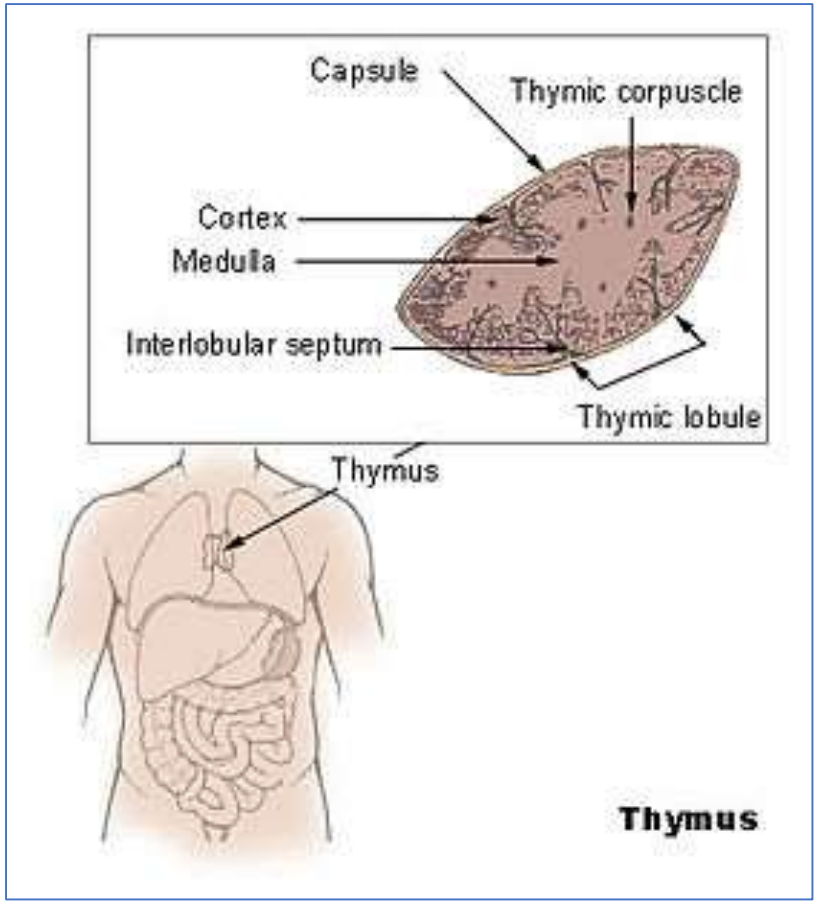
Site	Mean ± SD
Skull	2.9 ± 2.1
Proximal humeri	1.9 ± 1.2
Sternum	2.9 ± 1.3
Ribs and clavicles	8.8 ± 4.7
Scapulas	3.8 ± 0.9
Cervical spine	4.3 ± 1.6
Thoracic spine	19.9 ± 2.6
Lumbar spine	16.6 ± 2.2
Sacrum	9.2 ± 2.3
Pelvis	25.3 ± 4.9
Proximal femurs	4.5 ± 2.5

Tissues of the immune system/ primary lymphoid tissue/ Thymus غدة زعترية

- The thymus is **the site of T cell maturation**. The thymus is a bilobed organ situated in the **anterior mediastinum**. Each lobe is divided into multiple lobules by fibrous septa, and each lobule consists of an outer cortex and an inner medulla.

- A subset of these epithelial cells found only in the medulla, called **thymic medullary epithelial cells** (often abbreviated as TMEC), play a special role in **presenting self antigens to developing T cells** and causing their deletion.

- Maturation in the thymus begins in the **cortex**, and as thymocytes mature, they migrate toward the medulla, so that the medulla contains mostly mature T cells



- By the early teens, the thymus begins to atrophy and thymic stroma is mostly replaced by adipose (fat) tissue.

Tissues of the immune system/ primary lymphoid tissue/ Thymus

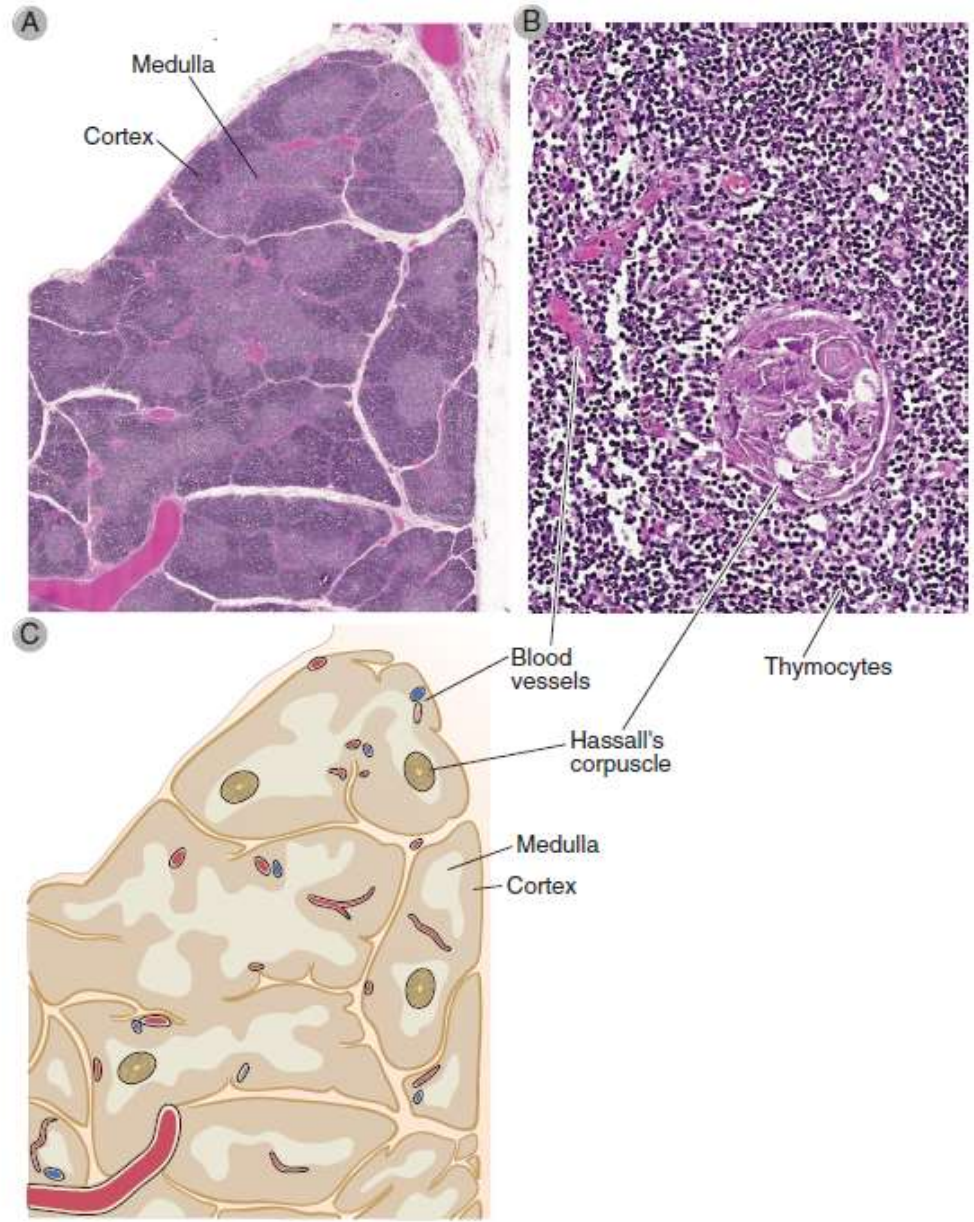


FIGURE 2–10 Morphology of the thymus. A, Low-power light micrograph of a lobe of the thymus showing the cortex and medulla. The darker blue-stained outer cortex and paler blue inner medulla are apparent. **B,** High-power light micrograph of the thymic medulla. The numerous small blue-staining cells are developing T cells called thymocytes, and the larger pink structure is Hassall's corpuscle, uniquely characteristic of the thymic medulla but whose function is poorly understood. **C,** Schematic diagram of the thymus illustrating a portion of a lobe divided into multiple lobules by fibrous trabeculae.

- The lymphatic system, which consists of specialized vessels that drain fluid from tissues into and out of lymph nodes and then into the blood, is essential for **tissue fluid homeostasis** and **immune responses**.

- The lymphatic system **collects microbial antigens** from their portals of entry and **delivers them to lymph nodes**, where they can stimulate adaptive immune responses.

- **Microbes/ antigens**, **Dendritic cells**, and **inflammatory mediators** reach **lymph nodes** from the tissue.

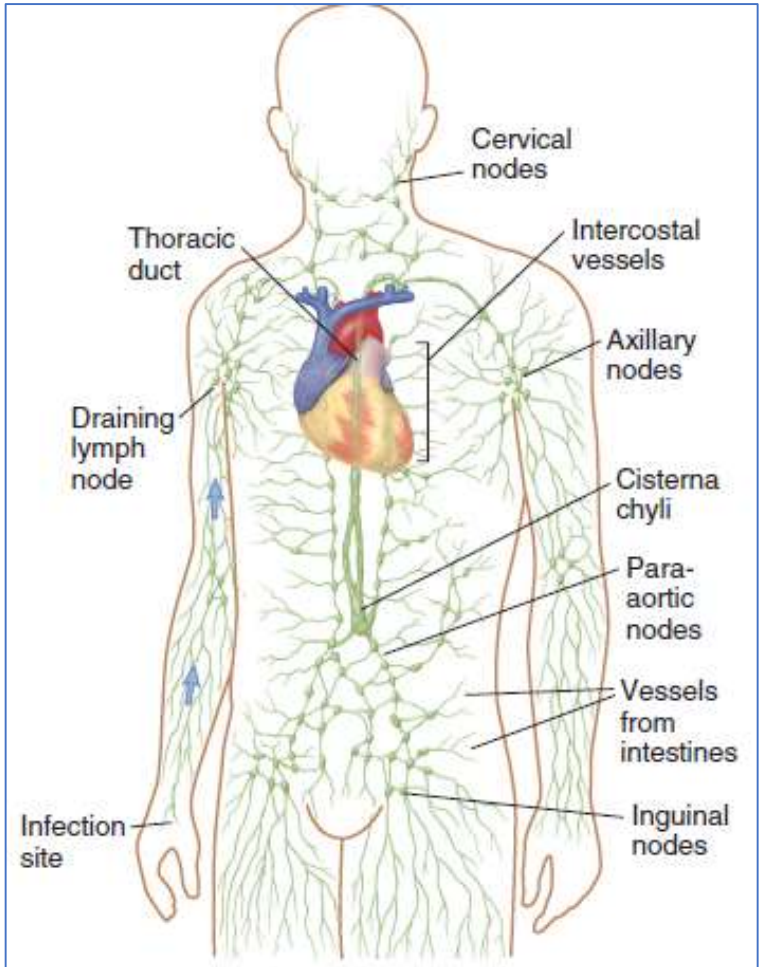


FIGURE 2–11 The lymphatic system. The major lymphatic vessels, which drain into the inferior vena cava (and superior vena cava, not shown), and collections of lymph nodes are illustrated. Antigens are captured from a site of infection and the draining lymph node to which these antigens are transported and where the immune response is initiated.

Tissues of the immune system/ Secondary lymphoid tissue/ lymph nodes

- Lymph nodes are **encapsulated, vascularized secondary lymphoid organs** with anatomic features that favor the initiation of adaptive immune responses to antigens carried from tissues by lymphatics.

- **Follicles are the B cell zones**. They are located in the lymph node cortex and are organized around FDCs, which have processes that interdigitate to form a dense reticular network. While T-cells in the parafollicular cortex.

- The anatomic segregation of B and T lymphocytes in distinct areas of the node is dependent on cytokines that are secreted by lymph node stromal cells in each area and that direct the migration of the lymphocytes

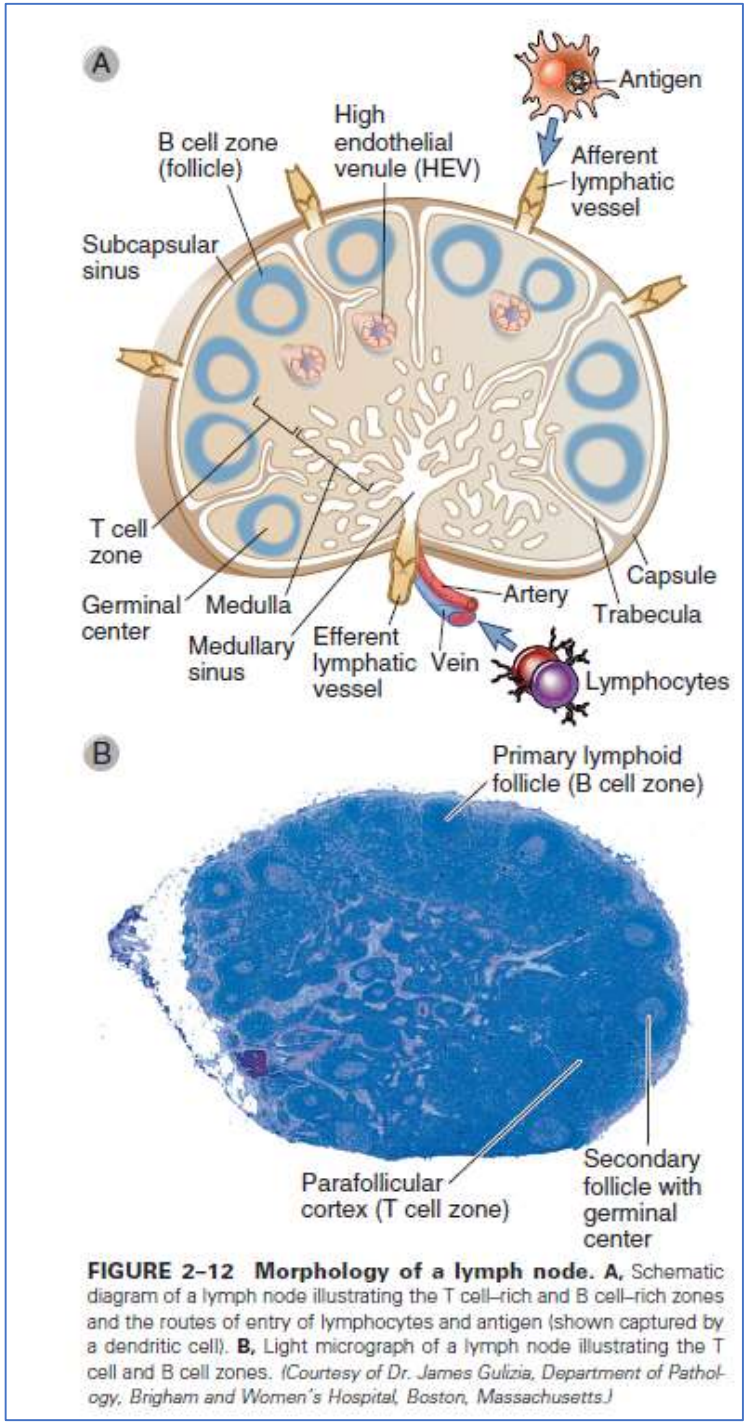
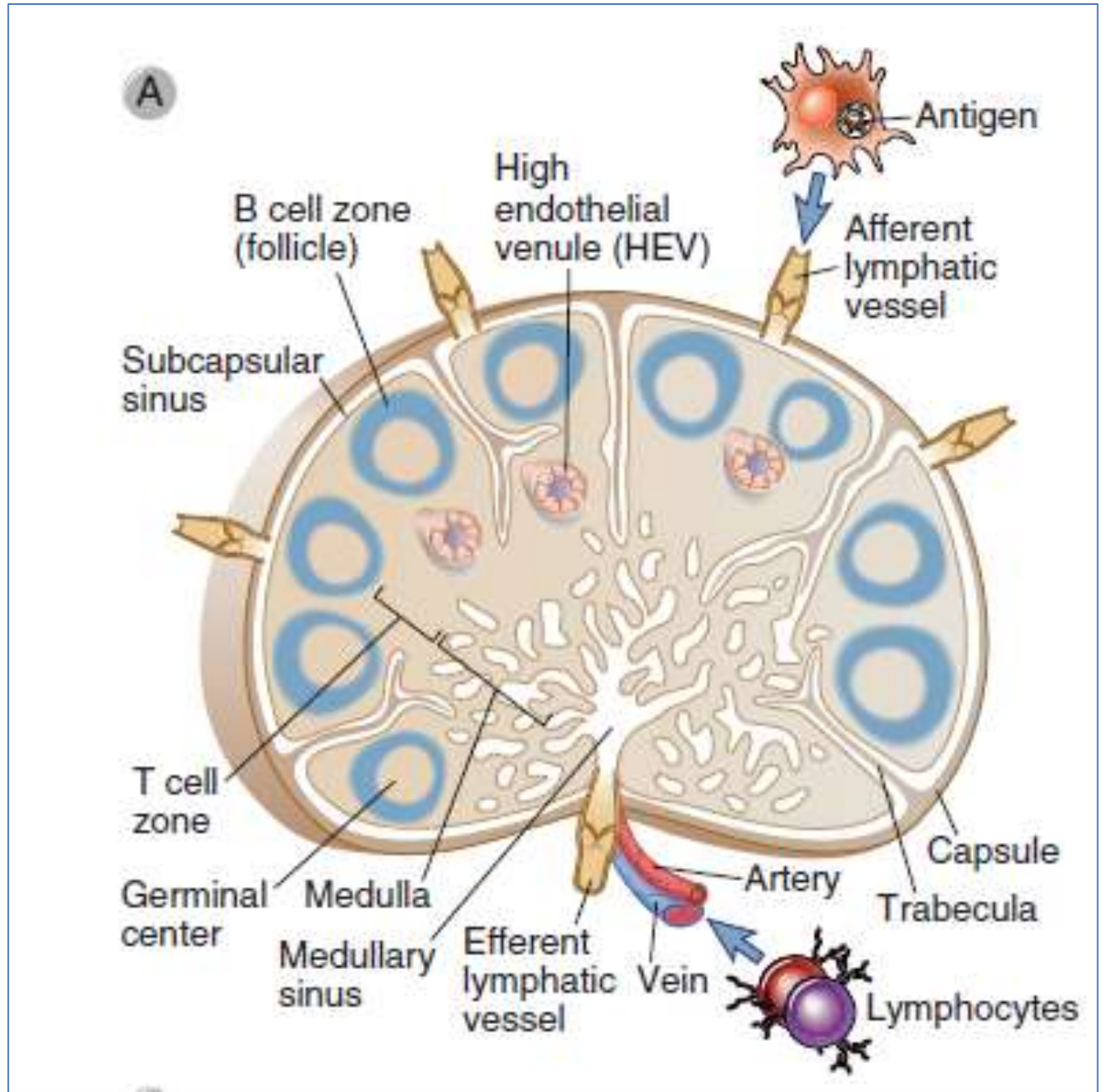


FIGURE 2–12 Morphology of a lymph node. A, Schematic diagram of a lymph node illustrating the T cell–rich and B cell–rich zones and the routes of entry of lymphocytes and antigen (shown captured by a dendritic cell). **B,** Light micrograph of a lymph node illustrating the T cell and B cell zones. *(Courtesy of Dr. James Gulizia, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts.)*

Tissues of the immune system/ Secondary lymphoid tissue/ lymph nodes



Tissues of the immune system/ Secondary lymphoid tissue/ lymph nodes

- The type of cytokines that determine where B and T cells reside in the node are called **chemokines** (chemoattractant cytokines), which bind to chemokine receptors on the lymphocytes.

- The anatomic segregation of T and B cells ensures that each lymphocyte population is in **close contact with the appropriate APCs**, that is, **T cells with dendritic cells and B cells with FDCs.**

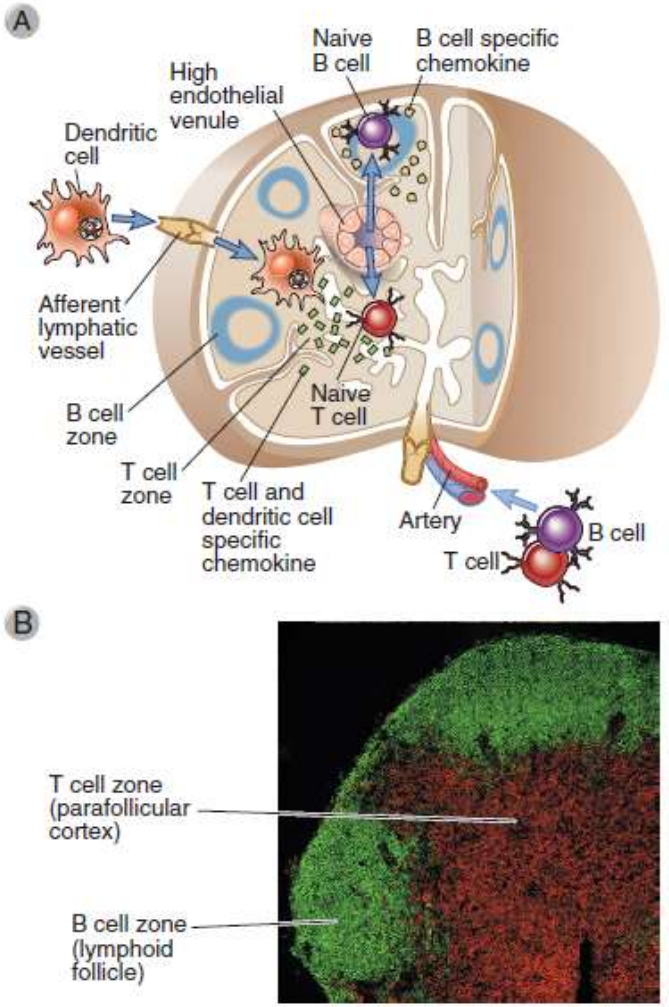
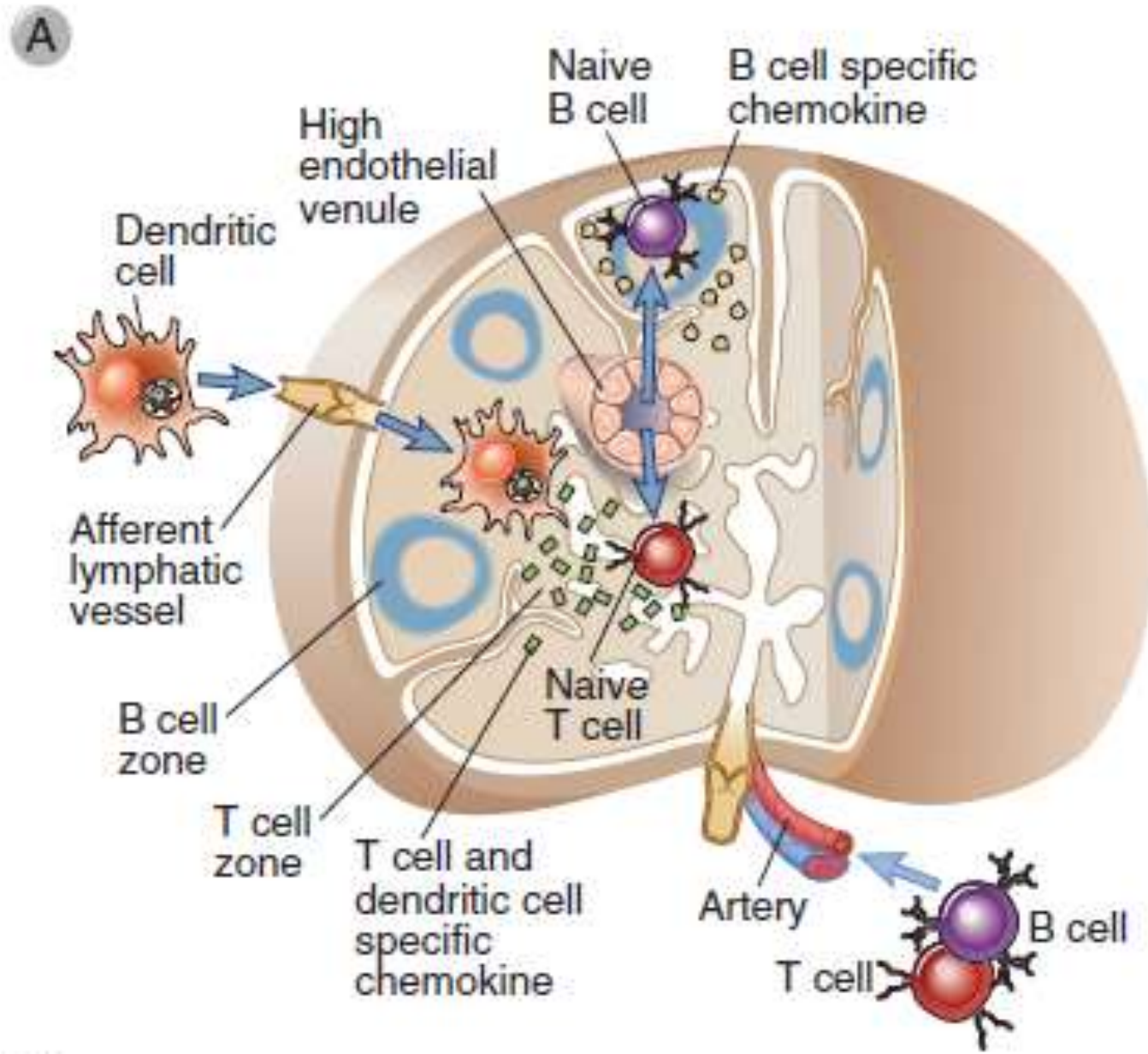


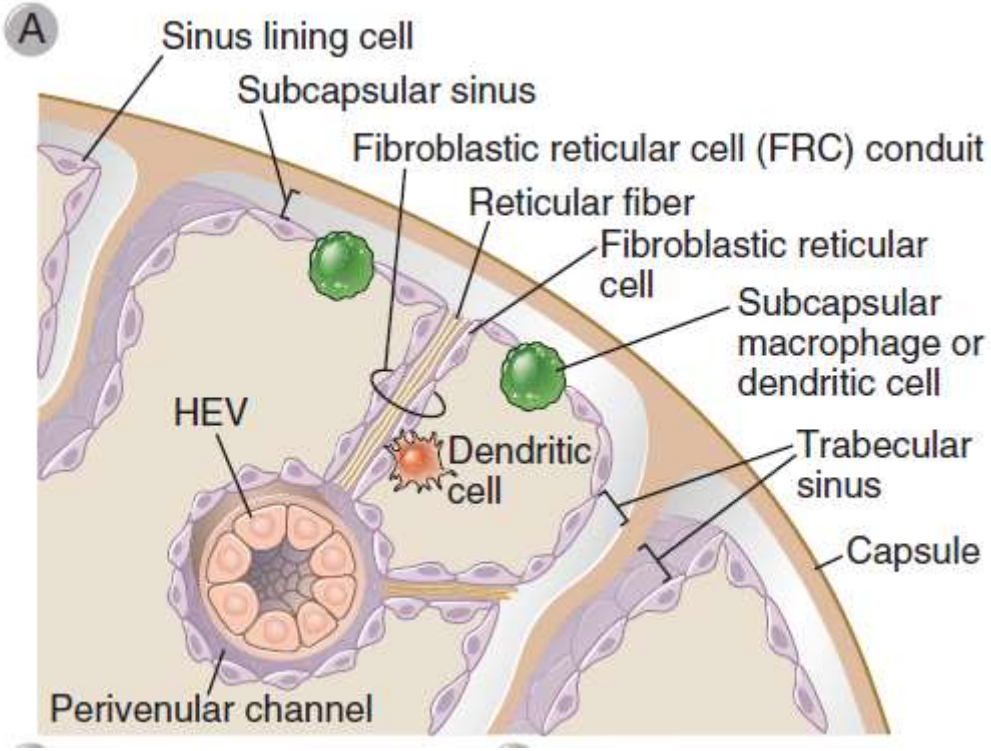
FIGURE 2–13 Segregation of B cells and T cells in a lymph node. A, The schematic diagram illustrates the path by which naive T and B lymphocytes migrate to different areas of a lymph node. The lymphocytes enter through an artery and reach a high endothelial venule, shown in cross section, from where naive lymphocytes are drawn to different areas of the node by chemokines that are produced in these areas and bind selectively to either cell type. Also shown is the migration of dendritic cells, which pick up antigens from the sites of antigen entry, enter through afferent lymphatic vessels, and migrate to the T cell–rich areas of the node. **B,** In this section of a lymph node, the B lymphocytes, located in the follicles, are stained green; the T cells, in the parafollicular cortex, are red. The method used to stain these cells is called immunofluorescence (see Appendix IV for details). *(Courtesy of Drs. Kathryn Pape and Jennifer Walter, University of Minnesota School of Medicine, Minneapolis.)* The anatomic segregation of T and B cells is also seen in the spleen (see Fig. 2-15).

Tissues of the immune system/ Secondary lymphoid tissue/ lymph nodes



- Viruses and other high molecular- weight antigens are taken up by **sinus macrophages** and **presented to cortical B lymphocytes.**

- Low-molecular-weight soluble antigens are transported to **resident dendritic cells** that extend processes and capture and pinocytose soluble antigens. The contribution of this pathway of antigen delivery may be important for **initial T cell immune responses** to some microbial antigens, but larger and sustained responses require delivery of antigens to the node by **tissue dendritic cells**



Tissues of the immune system/ Secondary lymphoid tissue/ lymph nodes

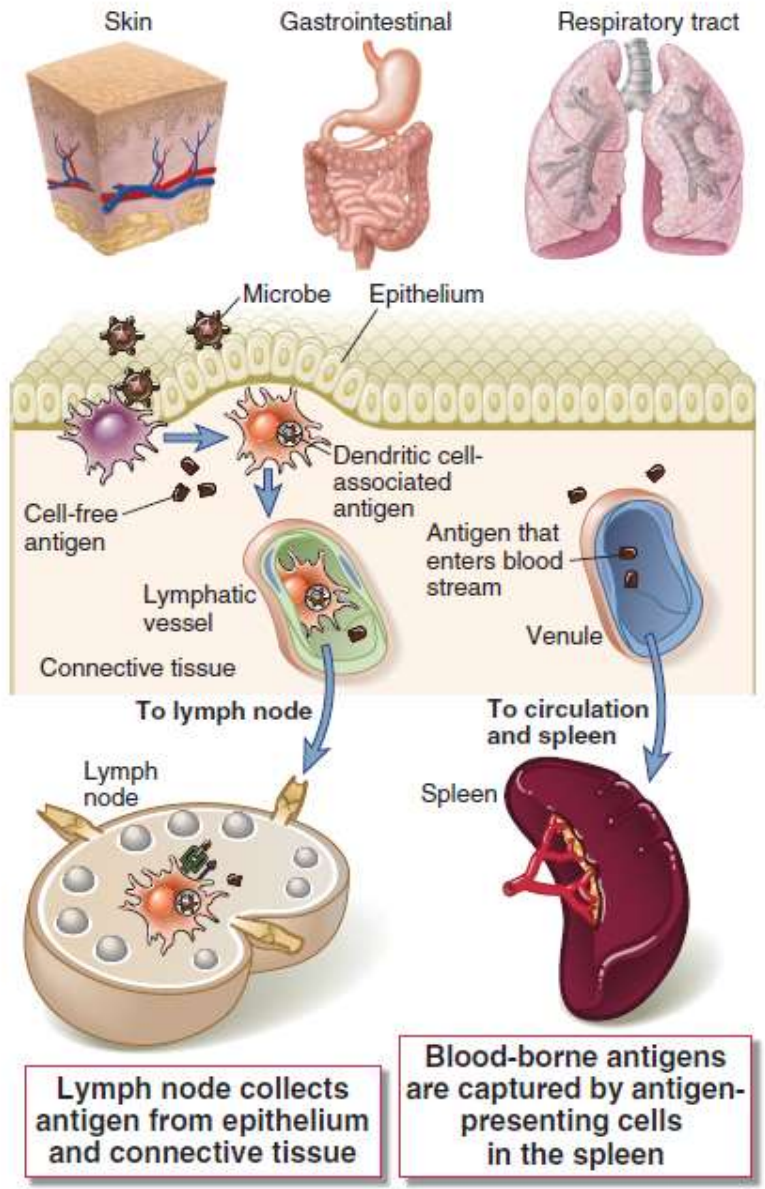


FIGURE 6–3 Routes of antigen entry. Microbial antigens commonly enter through the skin and gastrointestinal and respiratory tracts, where they are captured by dendritic cells and transported to regional lymph nodes. Antigens that enter the blood stream are captured by APCs in the spleen.

Tissues of the immune system/ Secondary lymphoid tissue/ Spleen

- The spleen is a highly vascularized organ whose major functions are to **remove aging and damaged blood cells** and **particles** (such as **immune complexes and opsonized microbes**) from the circulation and to **initiate adaptive immune responses** to **blood-borne antigens.**

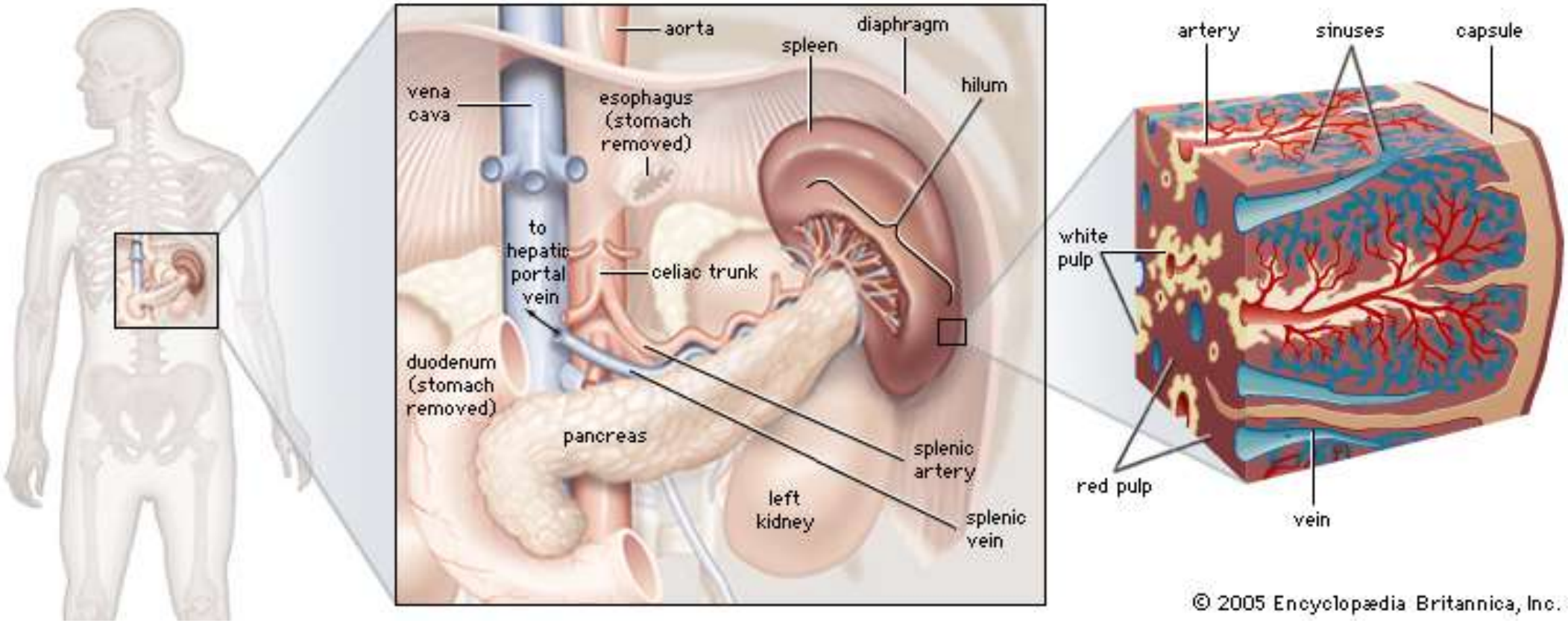
- The splenic parenchyma is anatomically and functionally divided into the **red pulp**, composed **mainly of blood-filled vascular sinusoids**, and the **lymphocyte-rich white pulp.**

- Blood enters the spleen through a single splenic artery, which pierces the capsule at the hilum and divides into progressively smaller branches that remain surrounded by protective and supporting fibrous trabeculae

- The **red pulp** macrophages serve as an important **filter for the blood**, removing microbes, damaged cells.

- Individuals lacking a spleen **are highly susceptible to infections with encapsulated bacteria**

Tissues of the immune system/ Secondary lymphoid tissue/ Spleen



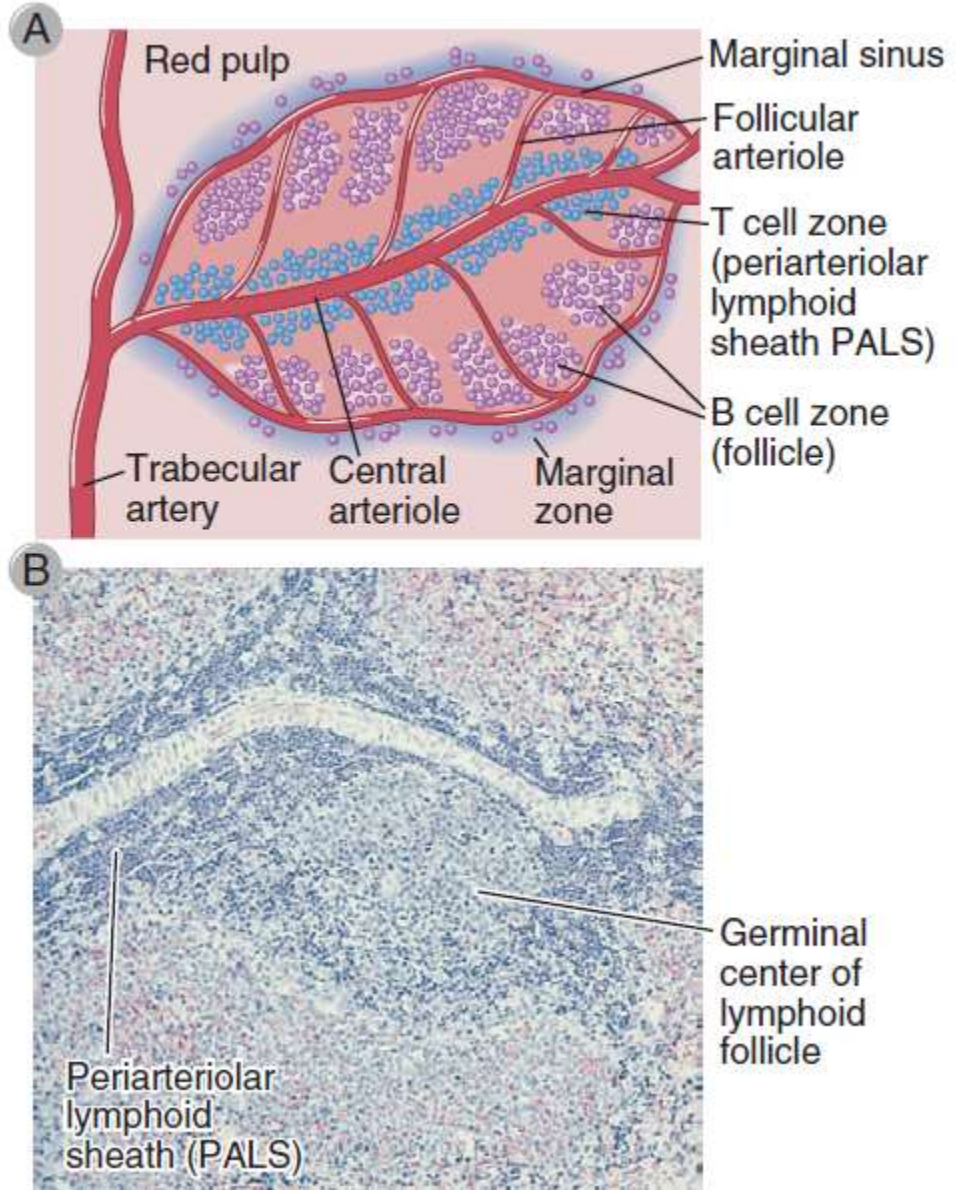
The spleen weighs about 150 g in adults and is located in the **left upper quadrant of the abdomen**.

Tissues of the immune system/ Secondary lymphoid tissue/ Spleen

- The function of the **white pulp** is to promote adaptive immune responses to blood-borne antigens.

- The white pulp is organized around central arteries, which are branches of the splenic artery distinct from the branches that form the vascular sinusoids. Several smaller branches of each central artery pass through the lymphocyte-rich area and drain into a marginal sinus.

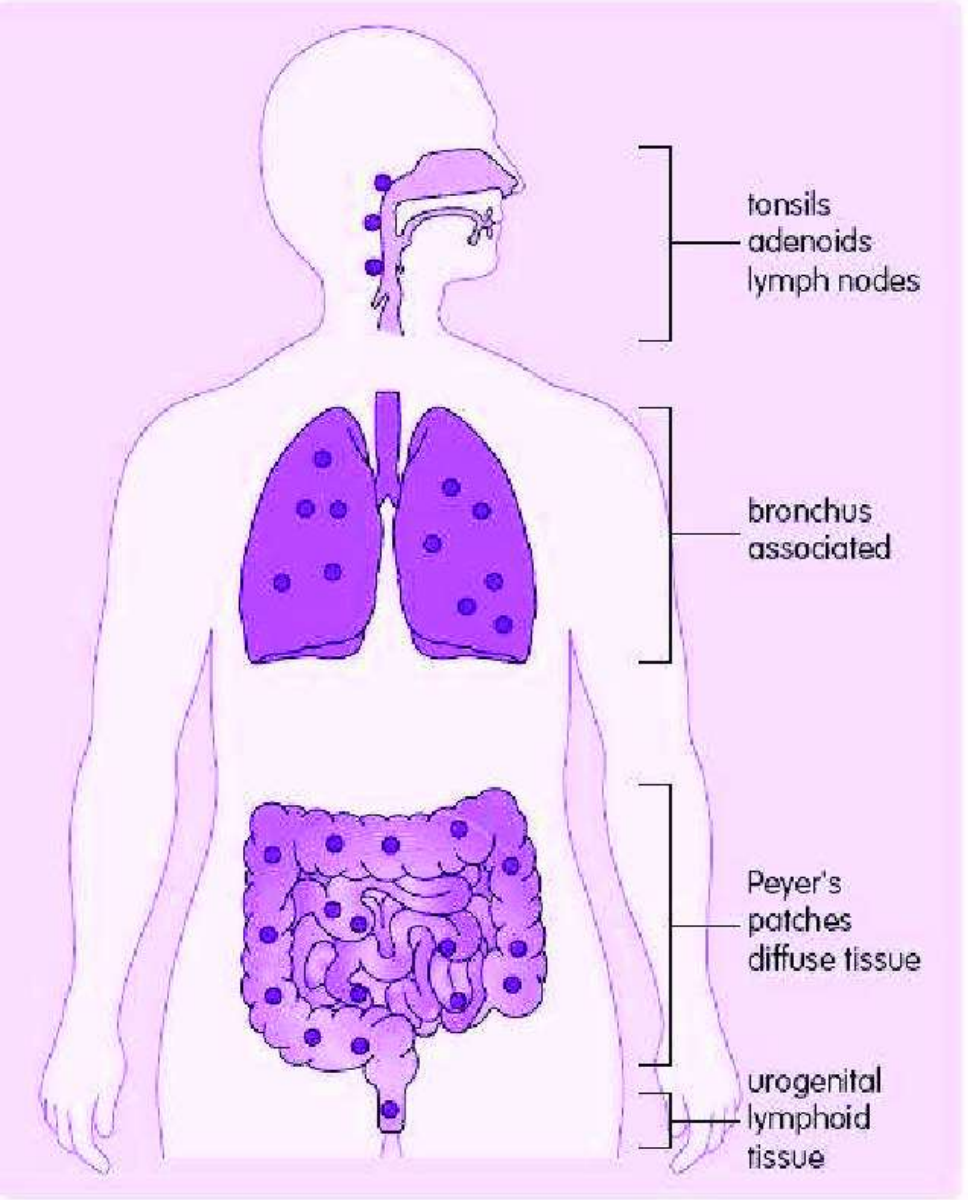
- A region of specialized cells surrounding the marginal sinus, called the marginal zone, forms the boundary between the red and white pulp.



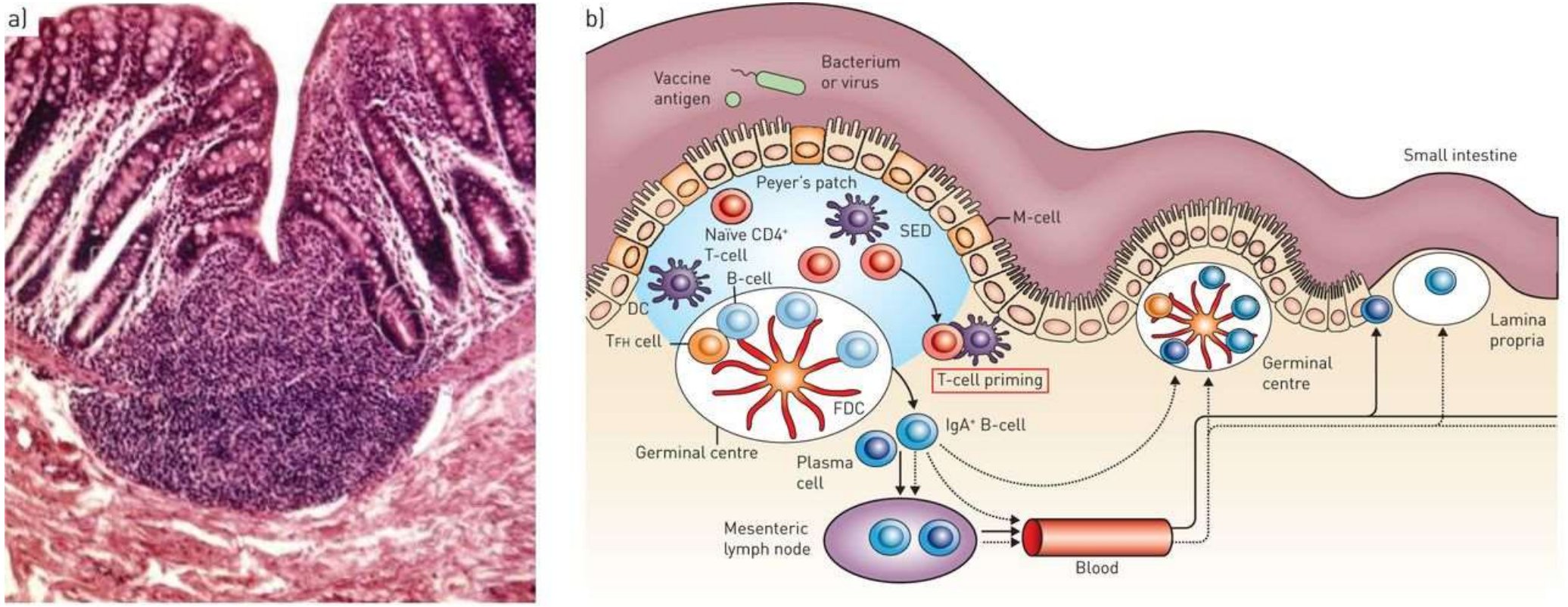
Tissues of the immune system/ Regional Immune Systems

- Each major epithelial barrier of the body, including the **skin**, **gastrointestinal mucosa**, and **bronchial mucosa**, has its own system of lymph nodes, **non encapsulated lymphoid structures**, and diffusely distributed immune cells, which work in coordinated ways to provide specialized immune responses against the pathogens that enter at those barriers.

- Mucosa-associated lymphoid tissue (MALT) and are involved in immune responses to ingested and inhaled antigens and microbes.



Tissues of the immune system/ Regional Immune Systems



Normal small intestine histology with Peyer's patches. b) Initiation of the immune response in the gut: antigens are taken up by microfold (M)-cells and process to the resident dendritic cells (DCs) in Peyer's patches. T-follicular helper (T_{FH}) cells interact with B-cells and follicular dendritic cell (FDC) thus forming a germinal centre. Antigen specific plasma cells and memory B-cells are generated and migrate through the blood and mesenteric lymph nodes

Further reading:

- Cellular and Molecular Immunology. 7th Edition..

Chapter 2. Cells and tissues of the immune system

- Secondary lymphoid organs: responding to genetic and environmental cues in ontogeny and the immune response. Journal of Immunology 183:2205-2212, 2009.