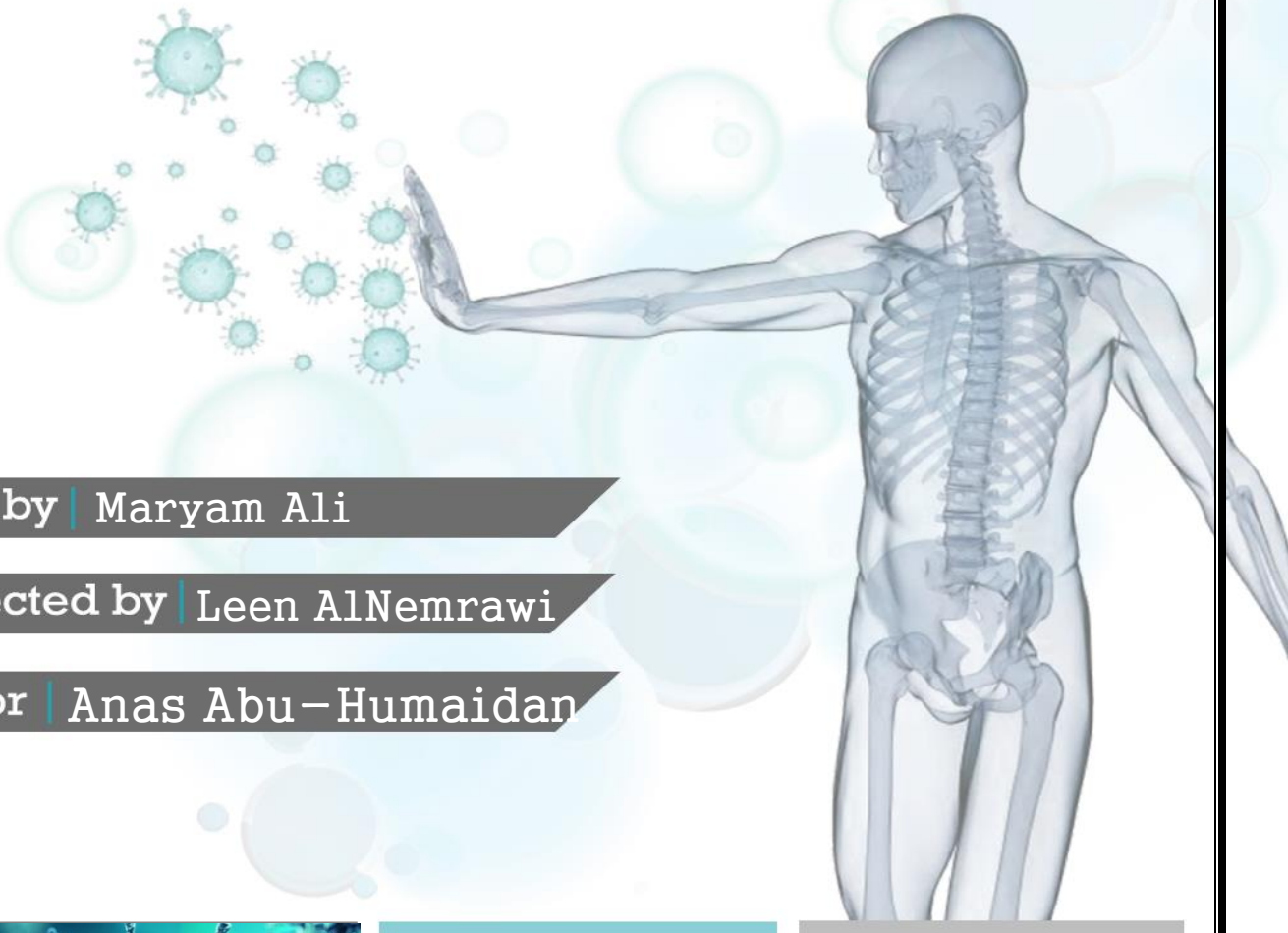
Sheet 4

Immunology



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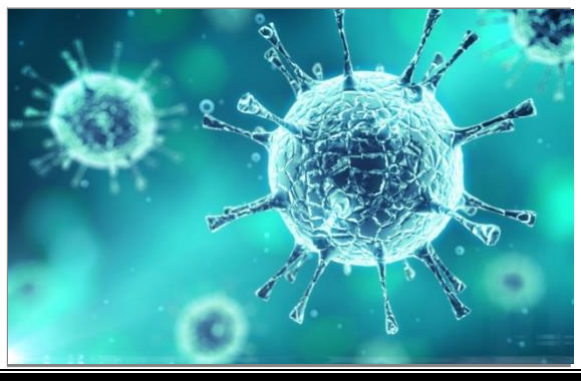


today we will talk about tissues of the immune system

A tissue is a collection of cells in a specific organ. The lymphatic tissue is a collection of T cells, B cells and APCs. 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. So, being anatomically close to each other serves a functional purpose.

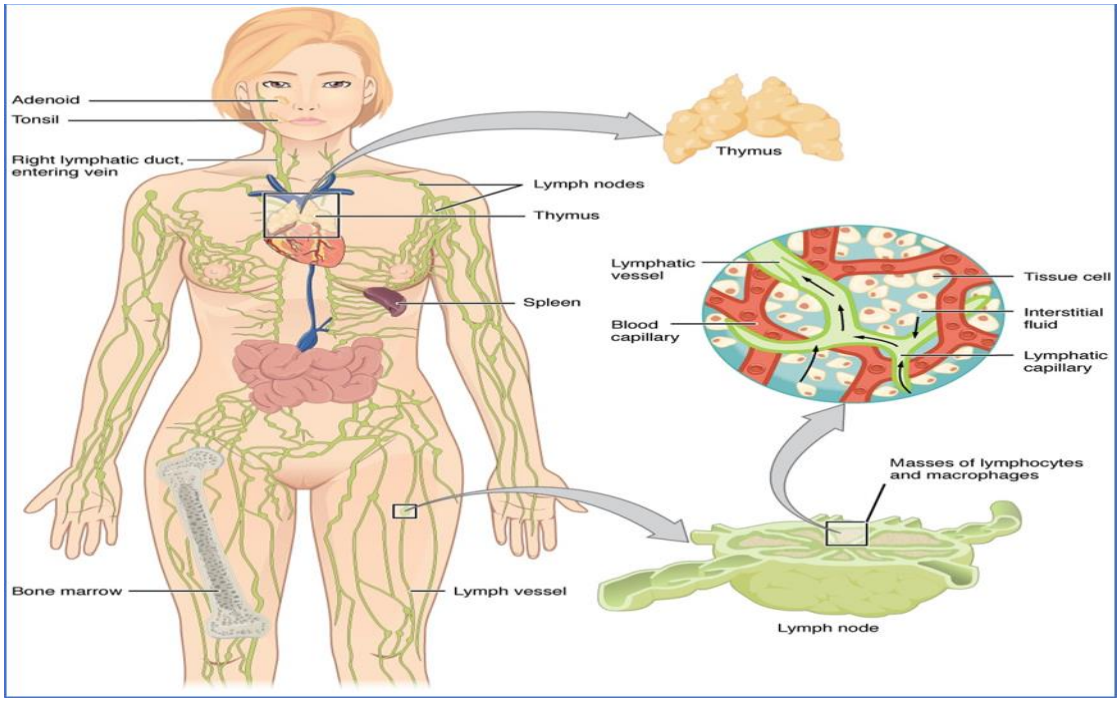
Lymphoid tissues are classified as

1- **Generative organs, also called Primary or Central lymphoid organs,**

where **lymphocytes first express antigen receptors** and attain **phenotypic and functional maturity**. (*the place where they come from)* such as; bone marrow which has the progenitor cells for T and B cells, and thymus which is where T cells mature.

2- **Peripheral organs, also called Secondary lymphoid organs,**

where **lymphocyte responses to foreign antigens are initiated and develop.** *(The place they go to when they get out of primary lymphoid organs)* such as: lymph nodes , spleen , adenoid , tonsils and payers patches in the in the intestine**.**



Primary Lymphoid Tissue

1- Bone marrow

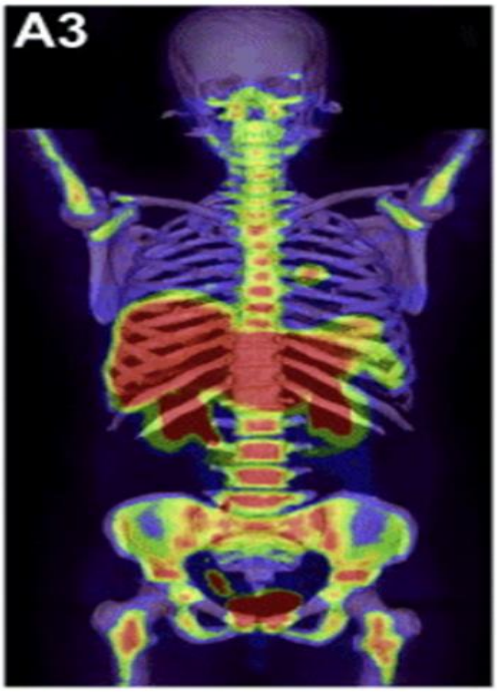
The bone marrow is the site **of generation of most mature circulating blood cells, including red cells, granulocytes, and monocytes, and the site of early events in B cell maturation.**

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 and spleen 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. **(pelvis , sacrum , sternum , clavicles , ribs , cervical and thoracic spine)**

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



2- Thymus

Thymus is the site of T cell maturation. *(after it gets out from the bone marrow)*. It is situated in the **anterior mediastinum,** posterior to sternum and anterior to trachea. The thymus is a bilobed organ ,right and left lobes, each lobe is divided into multiple lobules by fibrous septa, and each lobule consists of an outer cortex and an inner medulla.

Unlike other organs, the thymus grows only until a certain stage. By the early teens, after educating T cells and thymocytes to a large extent, it begins to atrophy and thymic stroma is mostly replaced by **adipose** *(fat)* tissue.

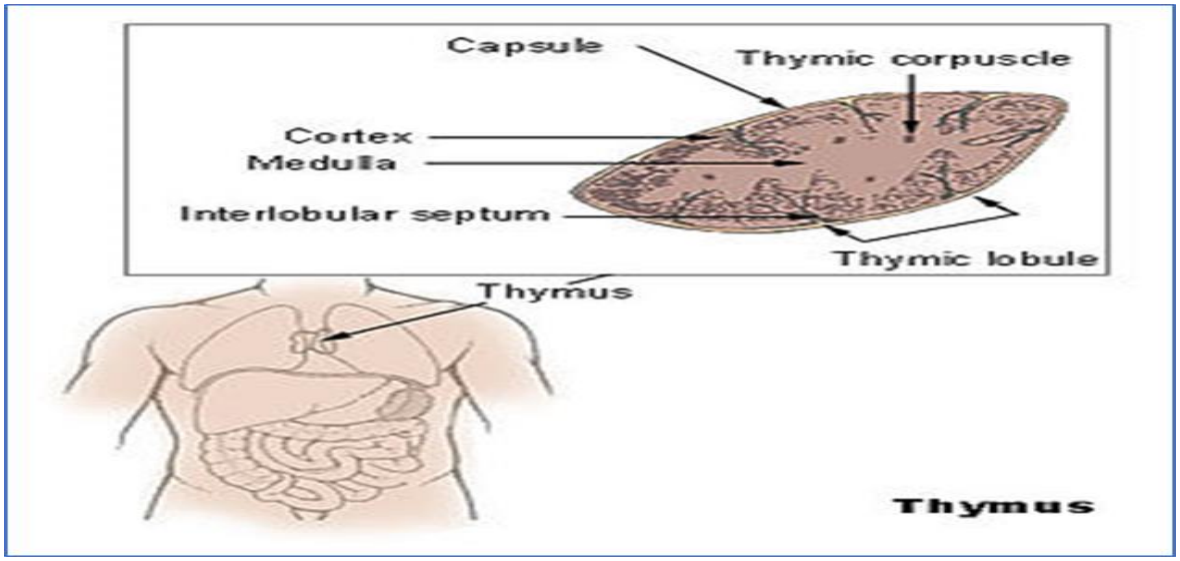
The T lymphocytes (*called **thymocytes** when inside the thymus)* reach the thymus through blood vessels as immature cells. **At first, they will enter the cortex.** Within the cortex, cells undergo maturation and selection. As thymocytes mature, they migrate toward the medulla, so that the medulla contains **mostly mature T cells**. Only **fully mature T cells or lymphocytes leave the thymus** through blood stream.

TMEC

A subset of 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 all developing T cells** and causing their deletion.

→ if a T lymphocyte binds the self-antigens and is strongly activated by them, the TMECs will eliminate it by apoptosis.

→ **Due to the role of TMEC**, cells released from the thymus are not expected to react against *(be activated by)* self-antigens.



Notes:

- maturation begins in the cortex.
- Most of the training of T lymphocytes occurs early in the thymus **"central tolarence"**. The education of new T lymphocytes that arise after atrophy of thymus is called **"peripheral tolarence"**.

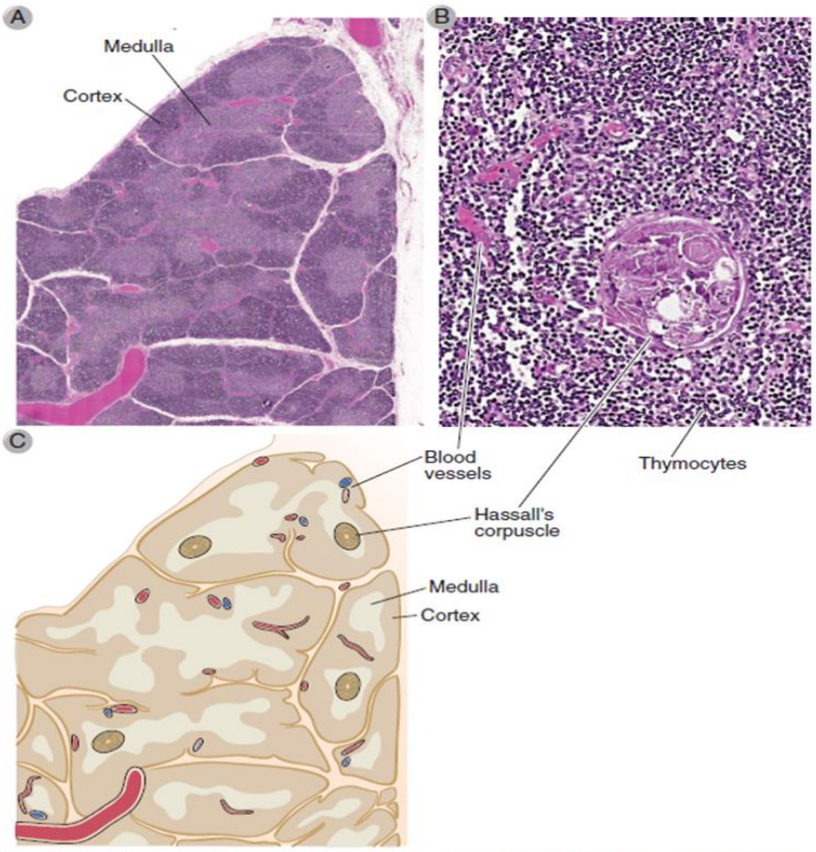


FIGURE 2–10 Morphology of the thymus. A, Low-power light micrograph of a lobe of the thymus showing the cortex and medulla. The darker blue-stained outer cortex and paler blue inner medulla are apparent. **B,** High-power light micrograph of the thymic medulla. The numerous small blue-staining cells 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.

Secondary Lymphoid Tissue

1- Lymphatic system

Consists of specialized vessels that drain fluid (lymph) from tissues into and out of lymph nodes and then into the blood. It has two functions:

a) **essential for tissue fluid homeostasis**
b) **immune responses, performed by the lymph nodes**

As the blood passes by tissues, some of the fluid leaks out to the interstitial spaces. This fluid is the lymph. The lymph collects **microbes/ antigens, dendritic cells and inflammatory mediators** present in the tissue and **delivers them to lymph nodes**. The lymphatic system also carries **microbial antigens** from their portals of entry to lymph nodes, where they can **stimulate adaptive immune responses.**

Lymph Nodes

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 (non-mobile APCs for B cells and help in the maturation of B cells)** which have processes that interdigitate to form a dense reticular network. While T-cells reside in the parafollicular cortex.

The anatomic segregation of B and T lymphocytes in distinct areas of the node is dependent on cytokines -specifically chemokines or "chemoattractant cytokines"- that are secreted by lymph node stromal cells in each area and that direct the migration of the lymphocytes. These chemokines bind to chemokine receptors on the lymphocytes.

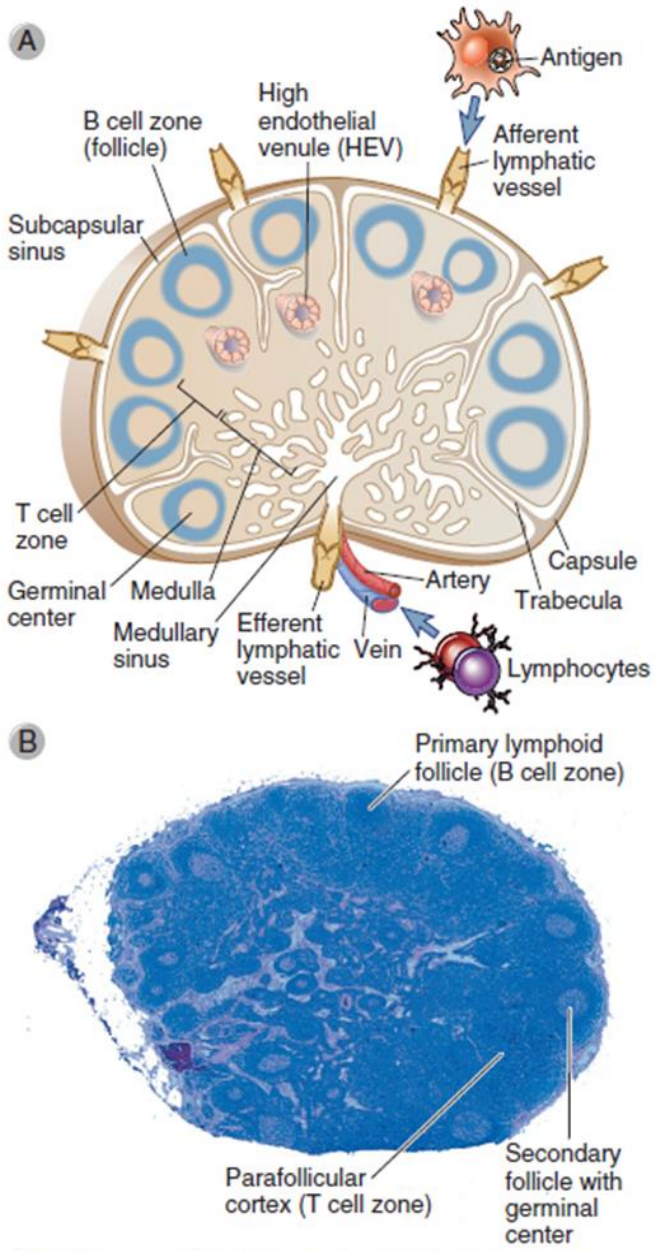


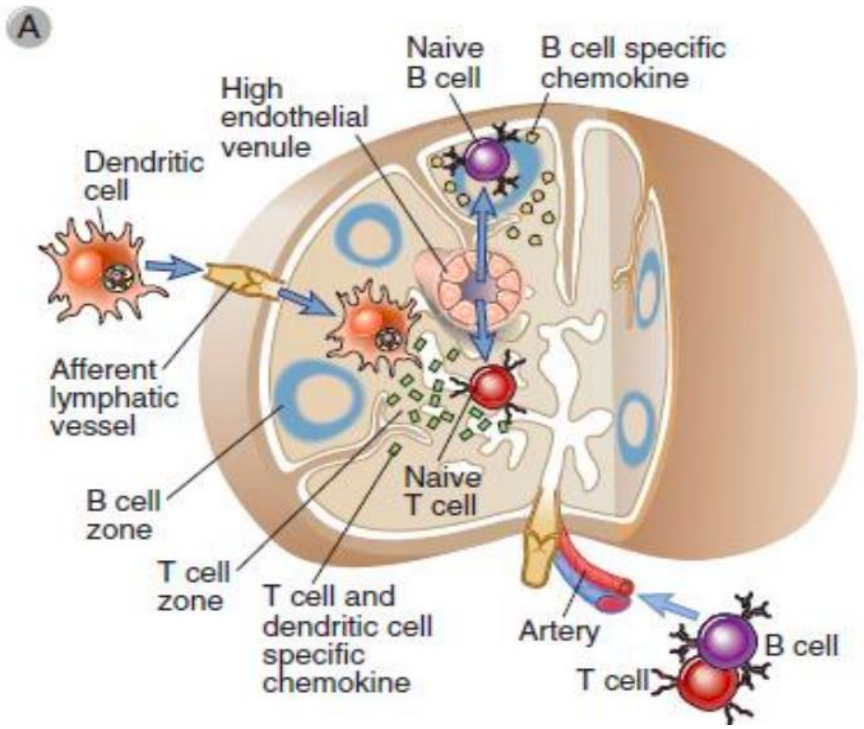
FIGURE 2–12 Morphology of a lymph node. A, Schematic diagram of a lymph node illustrating the T cell–rich and B cell–rich zones and the routes of entry of lymphocytes and antigen (shown captured by a dendritic cell). **B,** Light micrograph of a lymph node illustrating the T cell and B cell zones. *(Courtesy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

→ The B and T lymphocytes came from the bone marrow and thymus respectively via blood vessels and reach the cortex through HEV (high endothelial vessel). Depending on specific chemokines, they will reside in their anatomical locations within the LN: B cells ---> B cells follicle which has follicular dendritic cells

T cells ---> Parafollicular area

(See figure in the next page)

Now, they will keep recirculating between LNs until they find a SPECIFIC ag and become activated.



- 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.** The diagram below shows this demarcation by immunofluorescent microscopy.

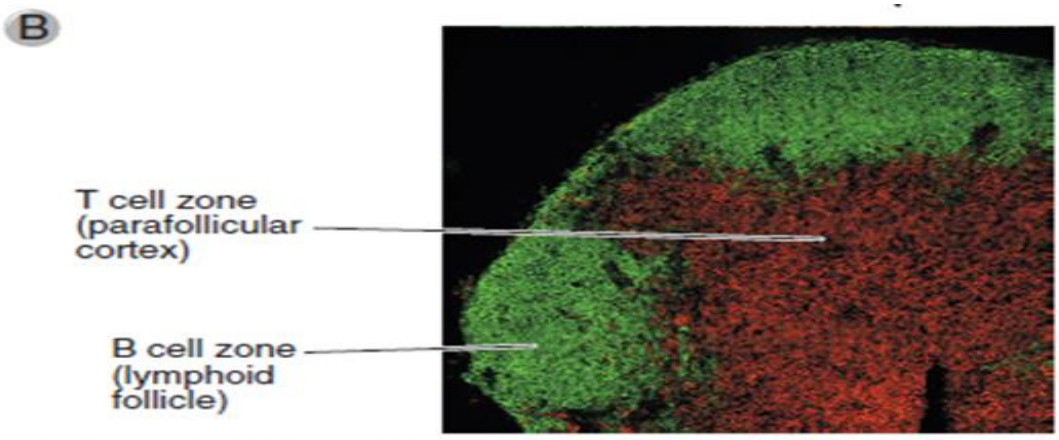


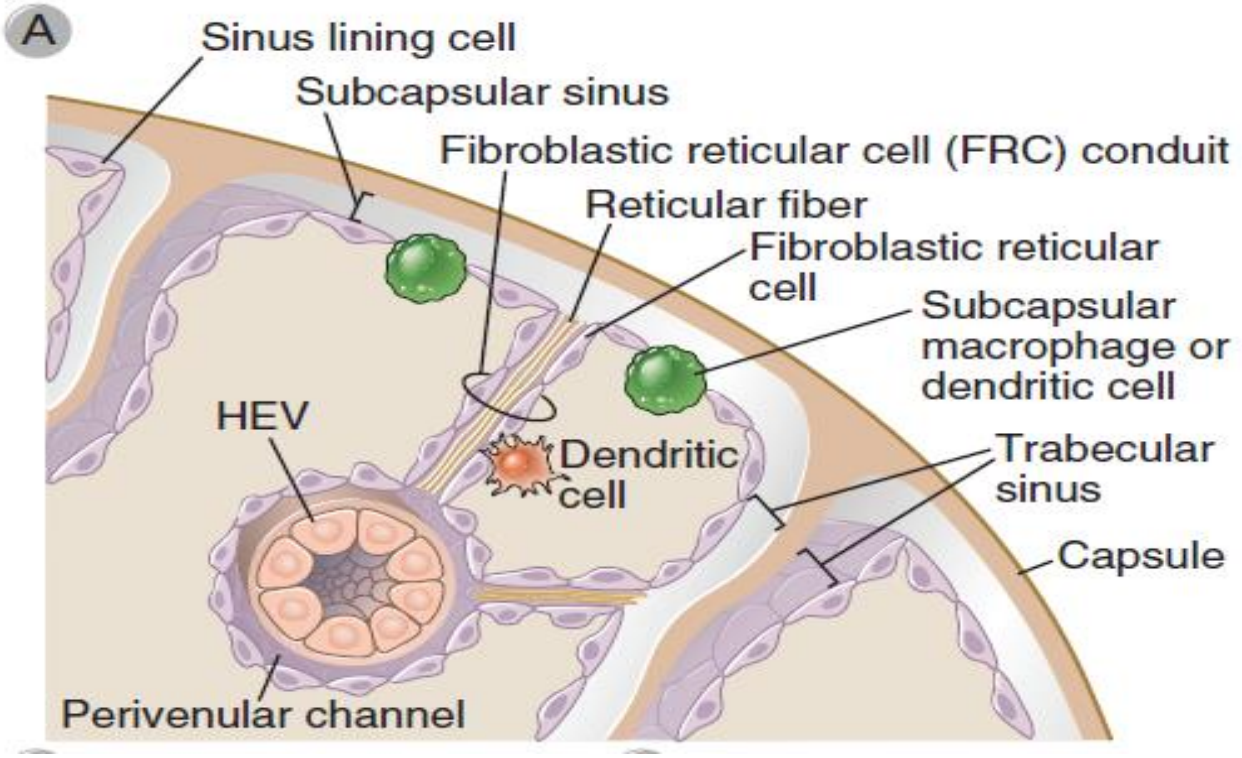
FIGURE 2–13 Segregation of B cells and T cells in a lymph node. A, The schematic diagram illustrates the path by which naive T and B lymphocytes migrate to different areas of a lymph node. The lymphocytes enter through an artery and reach a high endothelial venule, shown in cross section, from where 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).

- B and T cells don't recognize free antigens, the must be presented on APCs. Therefore, right **below the capsule of the lymph nodes** there are *(refer to figure below)*:

1- Subcapsular Macrophage to stimulates B cells
2- Subcapsular Dendritic cells to stimulate T cells

Where the antigen goes depends on its **molecular weight**;
→ **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 to capture and pinocytose soluble antigens and present them to **T lymphocytes.** 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 Dells {more potent than resident DCs}**.



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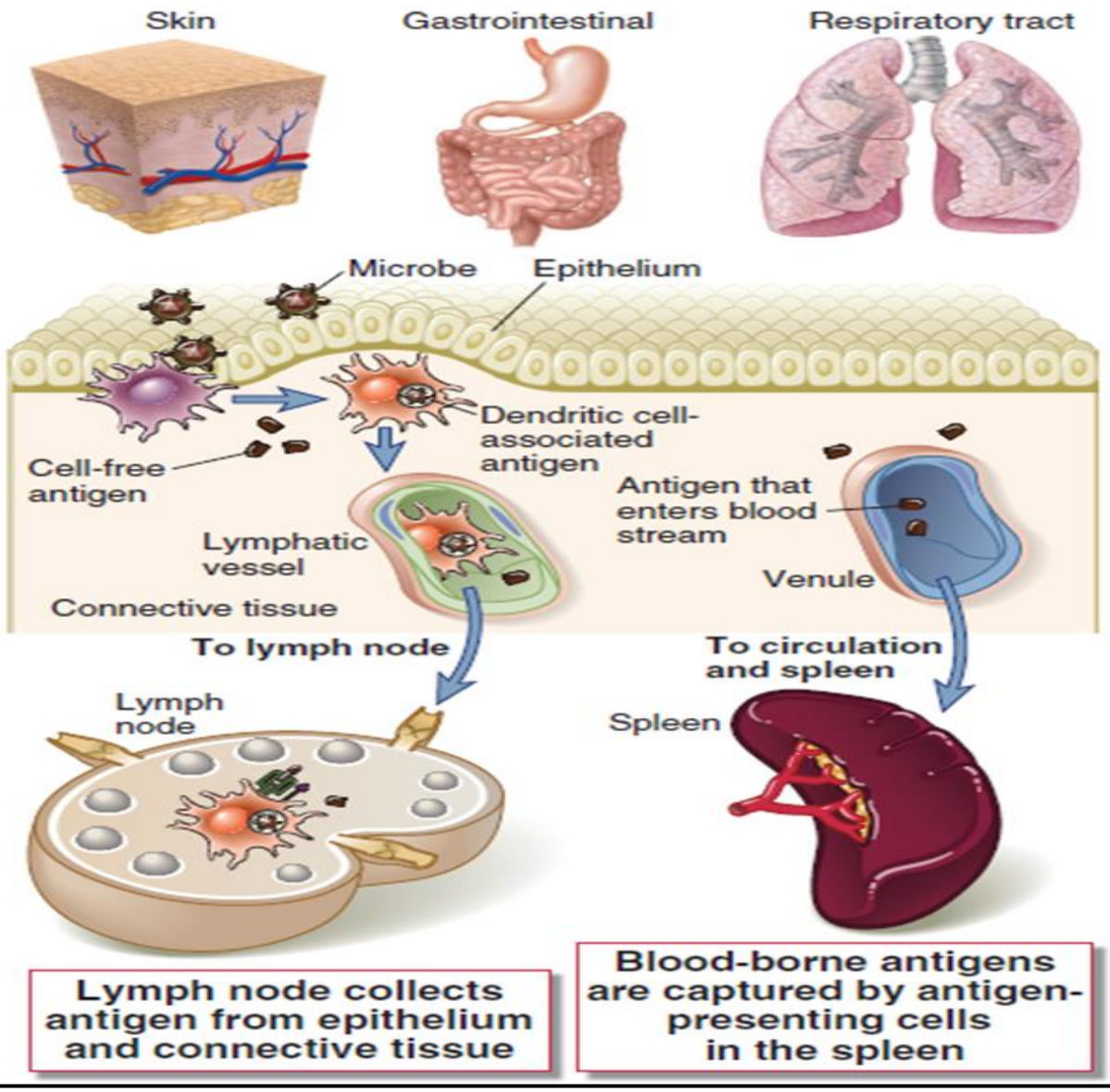
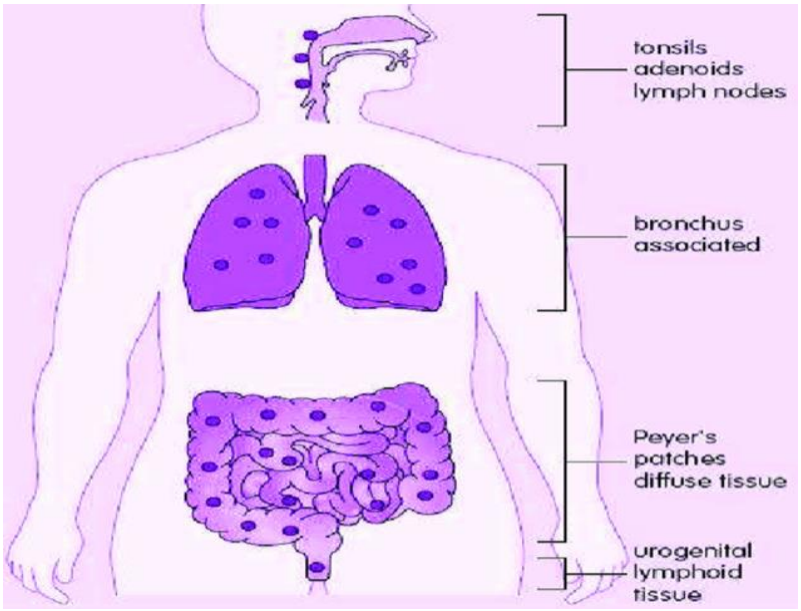




→ **MALT** *(page 11)*

All antigens in TISSUES have been presented to lymph nodes. However, some antigens still manage to enter directly to the blood stream. Eliminating them is the role of;

2- the spleen

The spleen is a **highly vascularized** organ that weighs about 150 g in adults and is located in the left **upper quadrant of the abdomen.** its major functions are:

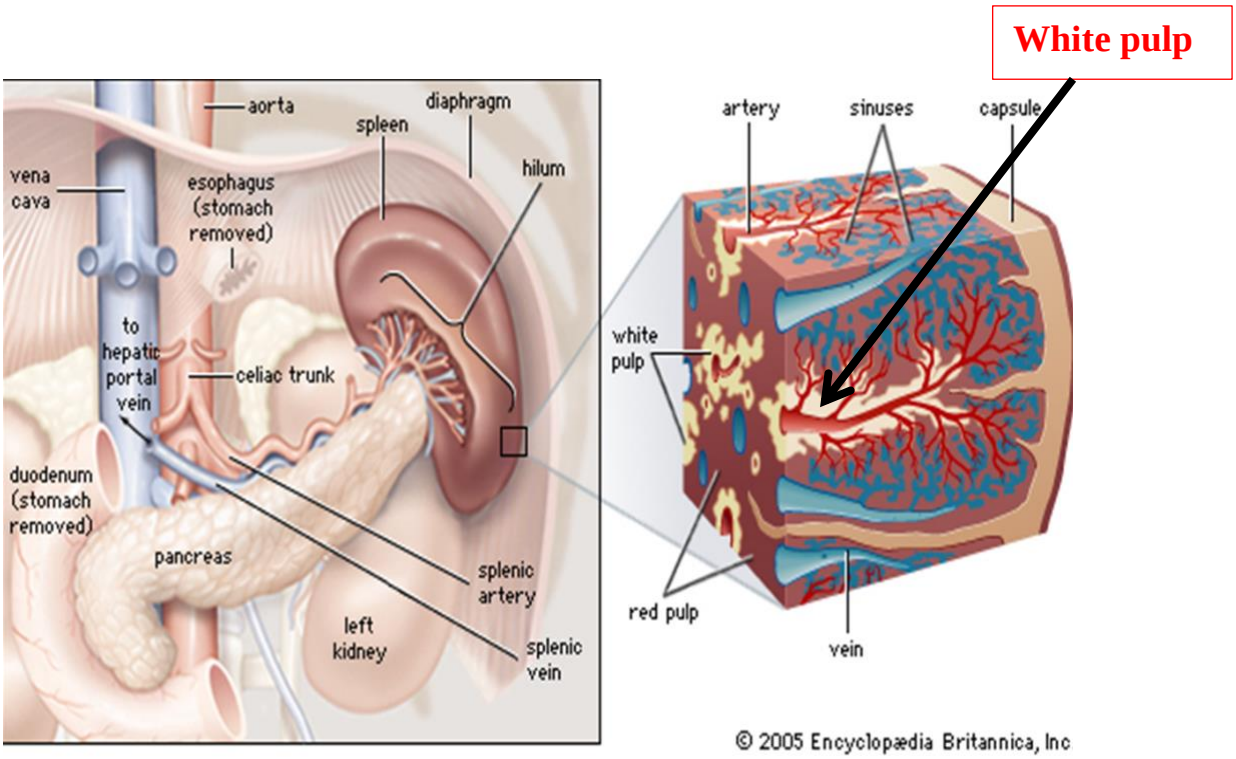
a) **remove aging and damaged blood cells and particles** →*by red pulp*
immune complexes and pathogens which are usually **opsonized** are removed from the circulation. *(opsonizaton is the process off attaching opsonis: proteins like C3b -part of the complement system- or antibodies to antigens in order facilitate phagocytosis by macrophages)*

b) **initiate adaptive immune responses to blood-borne antigens** →*by white pulp*

The splenic parenchyma is anatomically and functionally divided into:

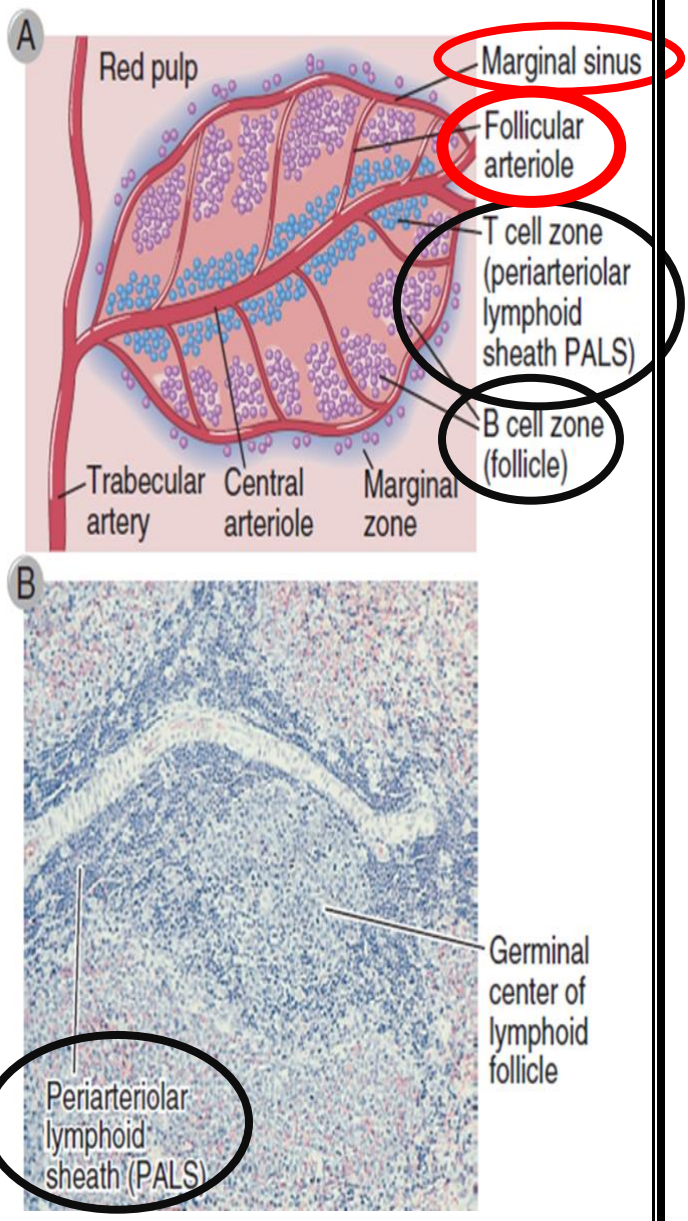
- **Red pulp,** composed mainly of **blood-filled vascular sinusoids**
- **The lymphocyte-rich White pulp**.

Blood enters the spleen through a single **splenic artery (starts from the red pulp and ends at the white pulp)** which pierces the capsule at the hilum and divides into progressively smaller branches that remain **surrounded by protective and supporting fibrous trabeculae.**



Red Pulp

The red pulp macrophages serve as an important filter for the blood, removing microbes, damaged cells. In addition, **old RBCs are phagocytosed** by macrophages.



White Pulp

The function of the white pulp is to promote adaptive immune responses to blood-borne antigens**. *(Acts similar to lymph nodes:*** *blood with ag / APC / presentation to then activation of B and T cells****)***

The white pulp is organized in PALS: (*periarteriolar lymphoid sheaths*) 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.

→ **Individuals lacking a spleen** (splectomy due to injury through an accident , autoimmune diseases , or a tumor) are highly susceptible to infections with **encapsulated bacteria such as; Streptococcus pneumoniae and Neisseria meningitidis** because they lack macrophages that filter the blood which are found in **RED PULP.**

Marginal Zone

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

3- Regional Immune Systems (MALT)

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) → these collections found in the mucosa** and are involved in immune responses to ingested and inhaled antigens and microbes. Such as peyer's patches in the small intestine. *(refer to figure in **page 8**)*

- **Peyer's Patches** found under the villi of the small intestine. also, they have high amount of lymphocytes and APCs

  if you remember how **Shigella** caused its infection → there is cell called **M cell** in the GI tract that plays immunological role against the antigens → from the lumen of the intestine the bacteria will enter → facing dendritic cells *(called subepithelial dendritic cells **SED**)* to present the antigen → then there will be either activation of B or T cell.