IMMUNOLOGY

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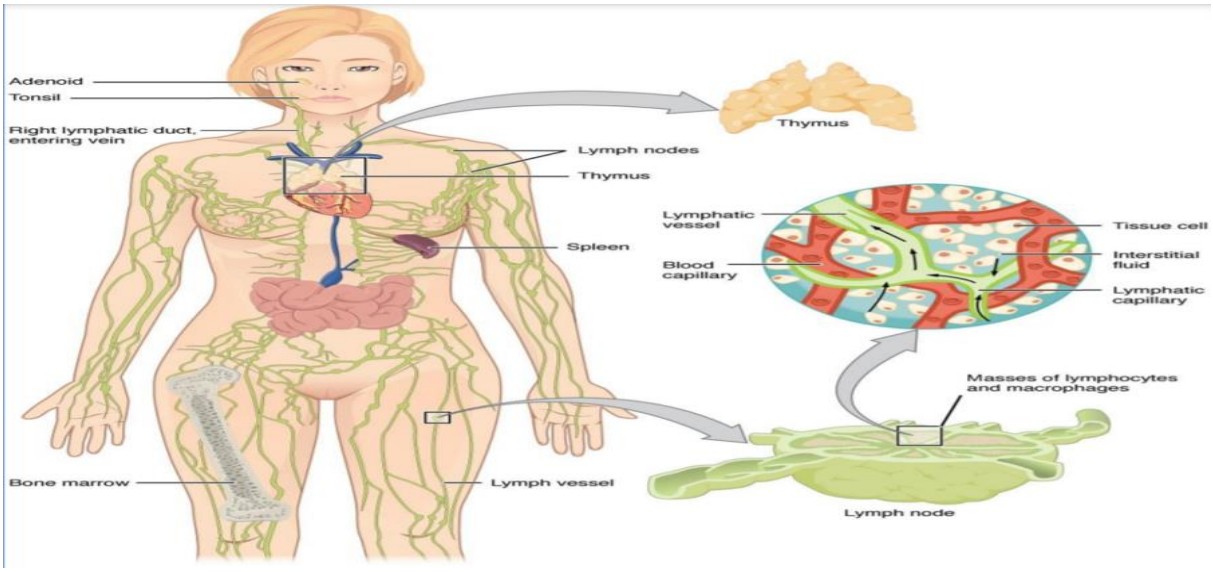
Today we will talk about tissues of the immune system.

- A **tissue** is a collection of cells in a specific organ.
  - The **Lymphatic tissue** is a collection of lymphocytes (B, T and NK cells) and APCs, all for optimizing the cellular interactions necessary for **antigen recognition** and **lymphocyte activation** in adaptive immune response. This is possible, due to them being concentrated in anatomically defined tissues or organs, which are also the spaces where foreign antigens are transported and concentrated, thus, being anatomically close to each other serves the functional purpose.



Depending on the place lymphocytes first pass through & after maturation, lymphatic tissue is classified into, **primary** and **secondary** lymphatic tissues

<u>1- Generative organs, also called primary or Central lymphoid organs</u>,

where **lymphocytes first express antigen receptors and attain phenotypic and functional maturity.** Such as,

a) <u>Bone Marrow</u>

The bone marrow is the site of **generation of most mature circulation blood cells, including red cells, granulocytes, monocytes and the site of early maturation stages of B cells**. And the **production** of T and B cells.

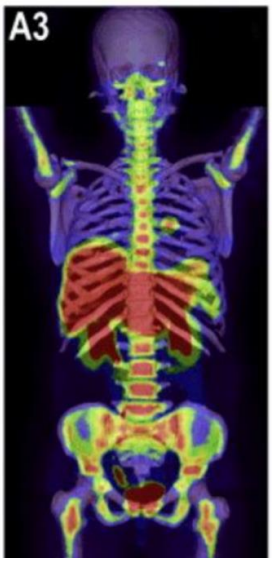
This generation of all blood cells, called **hematopoiesis**.

- During fetal development, it occurs in multiple waves throughout the developing embryo and fetus. **Blood islands of yolk sac & the para-aortic Mesenchyme → Fetal liver & Spleen** [Between 3-4 months of gestation] before eventually **homing Bone marrow** where it occurs just before birth. [**Y**ou **L**ove **S**mart **B**unny]

- At birth, hematopoiesis mainly takes place in bones throughout the skeleton → It increasingly becomes restricted to the marrow of **flat bones**. [Pelvis, sacrum, sternum, clavicles, ribs, cervical and thoracic 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



b) <u>Thymus</u>

Thymus is the site of T cell maturation. (*after if 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 → cortex**. In the cortex, cells undergo maturation and selection. As thymocytes mature, they migrate toward → medulla, so that the medulla **contains mostly mature T cells. Only fully mature T cells** or **lymphocytes** leave the **thymus** through **blood stream**.

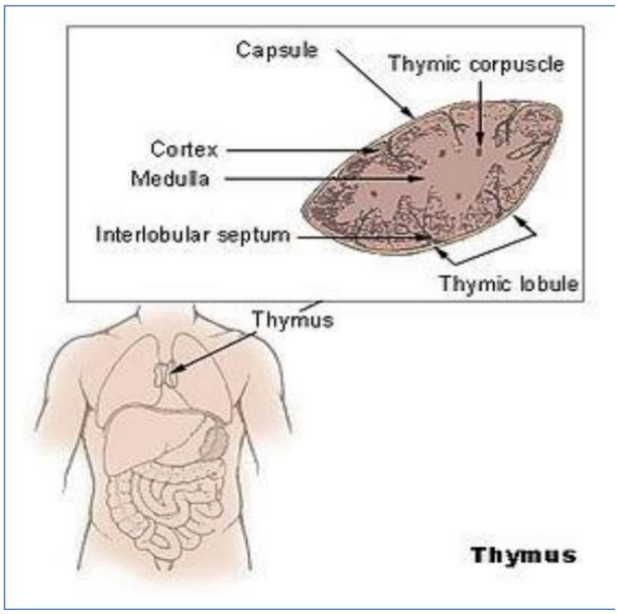
<u>TMEC</u>

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 and only if,**

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

- It is therefore strongly expected, T-cells released from the thymus wouldn't be activated by self-antigens. This is SELECTION.

❖ "**Central tolerance"** is the training T-lymphocytes take early in the thymus. Where after thymus's atrophy, it is called **"Peripheral tolerance**



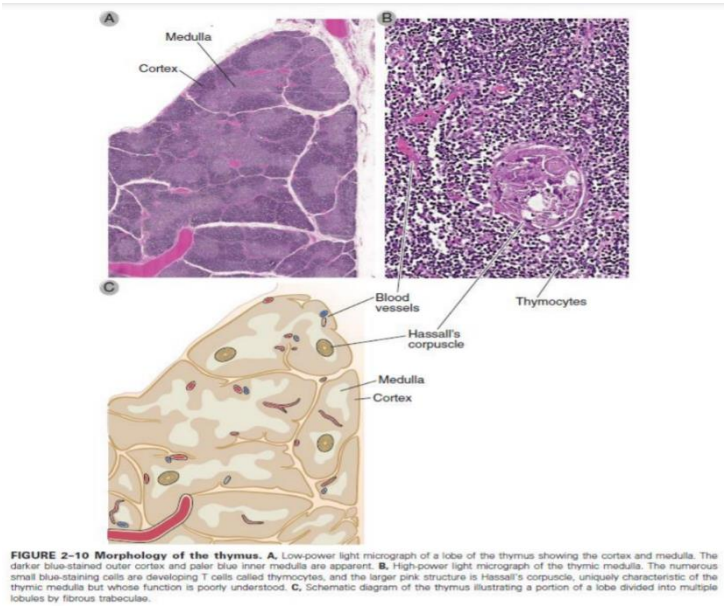


FIGURE 2–10 Morphology of the thymus. A, Low-power light micrograph of a lobe of the thymus showing the cortex and medulla. The darker blue-stained outer cortex and paler blue inner medulla are apparent. **B,** High-power light micrograph of the thymic medulla. The numerous small blue-staining cells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

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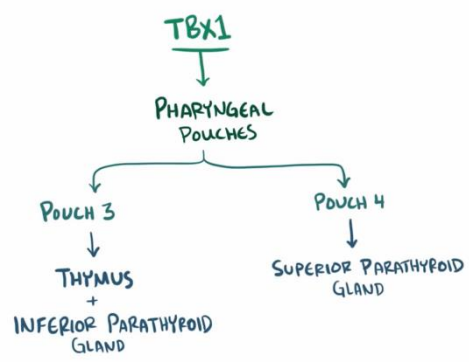
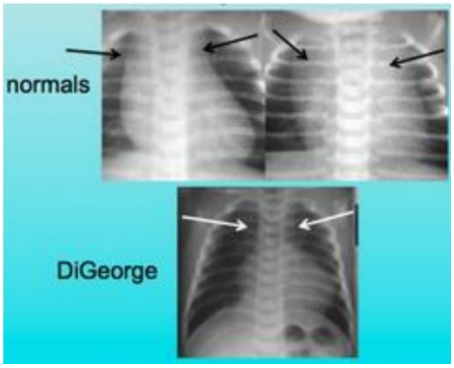
DiGeorge syndrome : more accurately known by a broader term — 22q11.2 deletion syndrome — is a disorder caused when a **small part of chromosome *22* is missing(microdeletion).** Consequently, resulting in the poor development of several body systems.

❖ One of the key missing genes is TBX1, which encodes for the rise of **thymus** and **parathyroid** gland. Thus, without it, both of them would either end up underdeveloped (*Hypoplasia*) or in complete absence and ultimately, their dysfunctionality. Many consequences would happen,





- The pathway of T-cells of **bone marrow → Thymus** is broken, thus, a deficiency of mature T-cells → Immunodeficiency.
- Parathyroid hypoplasia → Less PTH → Less Ca^{2+} (*Hypocalcemia*) → increased neuromuscular excitability → More and more involuntary contractions of muscles → Tetany/Neonatal seizures

DiGeorge Syndrome

CATCH-22

Cardiac abnormalities
Abnormal facies
Thymic absence/abnormality, **T** cell abnormality
Cleft palate
Hypocalcemia
Chromosome **22**

Cardiac Abnormalities. Facial abnormalities, such as, cleft palate.

We often see a "nude" mouse be the favourite of researchers….but why?

- A mutation in the gene encoding a transcription factor causes a failure of differentiation of certain types of epithelial cells that are required for normal development of the **thymus** and hair **follicles**. Consequently, these mice **lack T cells and hair.** Which means, mouses being the perfect tool for
  - Studying the function of T cells (*What would be absent in their absence*), human-tumors without the disruption of Immune cells (*Xenografts*).

2- **<u>Peripheral organs, also called Secondary lymphoid organs</u>**, where **lymphocyte responses to foreign antigens are initiates and develop**. They are the places a mature T cell go to after being in the Thymus (*Primary lymphoid organs*) such as: **Lymph nodes, spleen, adenoid, tonsils and payers patches in the intestine**.

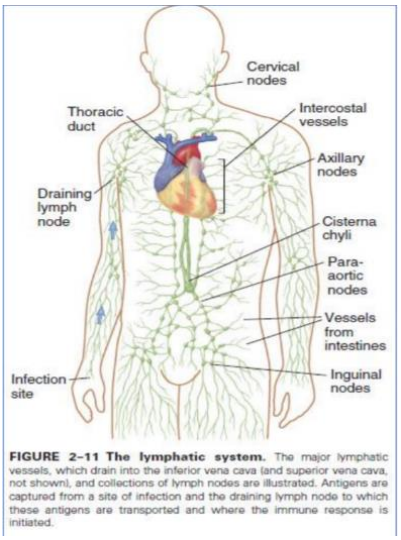


FIGURE 2–11 The lymphatic system. The major lymphatic vessels, which drain into the inferior vena cava (and superior vena cava, not shown), and collections of lymph nodes are illustrated. Antigens are captured from a site of infection and the draining lymph node to which these antigens are transported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

a) **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**
  - **<u>Lymph nodes</u>**

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.

- **<u>Follicles</u>** 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.

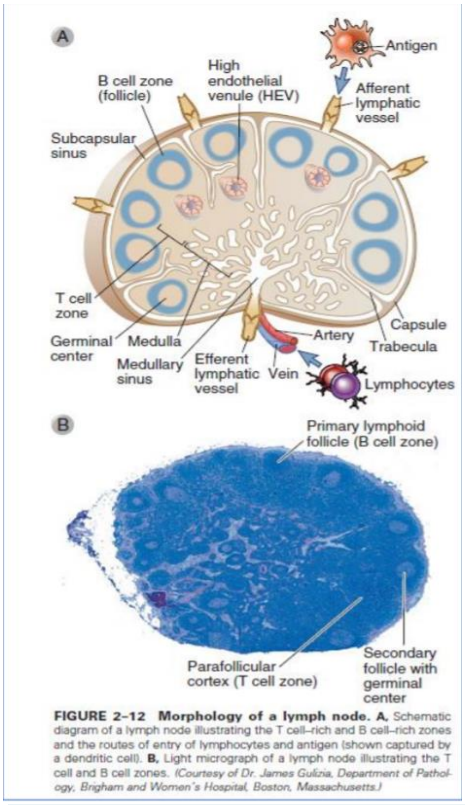
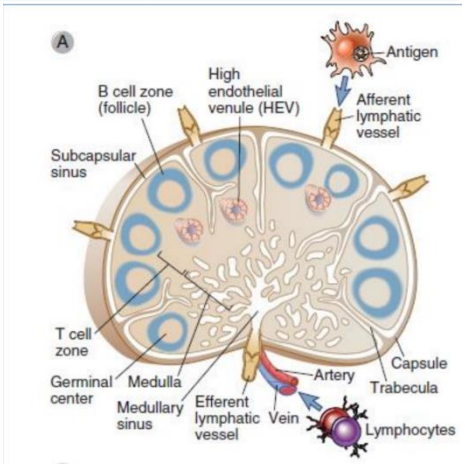


FIGURE 2–12 Morphology of a lymph node. A, Schematic diagram of a lymph node illustrating the T cell–rich and B cell–rich zones and the routes of entry of lymphocytes and antigen (shown captured by a dendritic cell). **B,** Light micrograph of a lymph node illustrating the T cell and B cell zones. *(Courtesy 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 Lymph Node

B cells → B cells **follicle** which has follicular dendritic cells.

T cells → Parafollicular area which has mobile APCs (*Macrophages and dendritic cells*)



- Now, they will keep recirculating between LNs until they find a SPECIFIC antigen 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 (الحدود) by immunofluorescent microscopy.

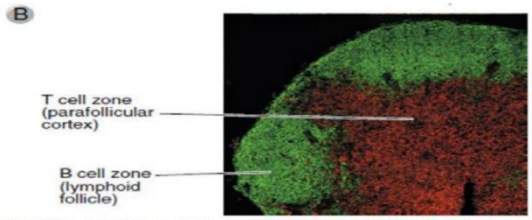


FIGURE 2–13 Segregation of B cells and T cells in a lymph node. A, The schematic diagram illustrates the path by which naive T and B lymphocytes migrate to different areas of a lymph node. The lymphocytes enter through an artery and reach a high endothelial venule, shown in cross section, from where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

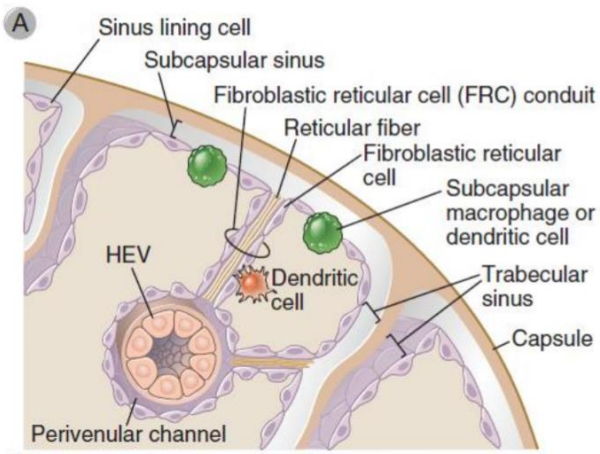
- B and T cells don't recognize free antigens, the must be presented on APCs. Therefore, right **below the capsule of the lymph nodes** there are (*refer to figure below*):

  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}



- **Infiltrated Lymph nodes**,
  - Non-cancerous

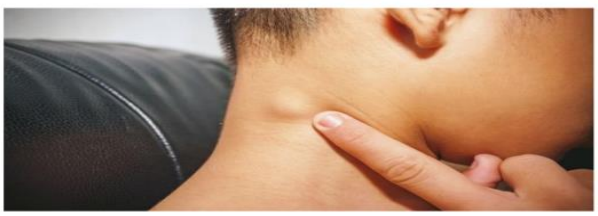
In the cases of infections, like when cervical lymph nodes drain the fluid of an upper respiratory tract in the midst of infection. It basically 'swallows' **inflammatory mediators + Dendritic cells + Lymphocytes that PROLIFERATE**(*Get activated*), of course the end result would be a swollen enlarged LN.

  - Cancerous

In **metastasis**, where malignant cells escapes to the blood stream → Lymph vessels → Lymph nodes where they proliferate → **Enlarging the node**. Because of us having other hundreds of lymph nodes, removing the cancerous node may be the best choice.

Table 1 Causes of cervical lymph node enlargement

Inflammatory	Infective	Local	Bacterial	Local infections in the head and neck
			Viral	Viral respiratory infections Herpes simplex Herpes zoster Herpangina
		Systemic	Bacterial	Syphilis Tuberculosis Atypical mycobacterioses Cat scratch fever Brucellosis
			Viral	Glandular fever syndromes (EBV, CMV, HIV, HHV-6) Rubella
			Protozoal	Toxoplasmosis
			Others	Mucocutaneous lymph node syndrome (Kawasaki disease)
	Non-infective	Sarcoidosis Crohn's disease Orofacial granulomatosis Connective tissue diseases		
Malignancy	Primary	Leukaemias Lymphomas		
	Secondary	Metastases		



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;

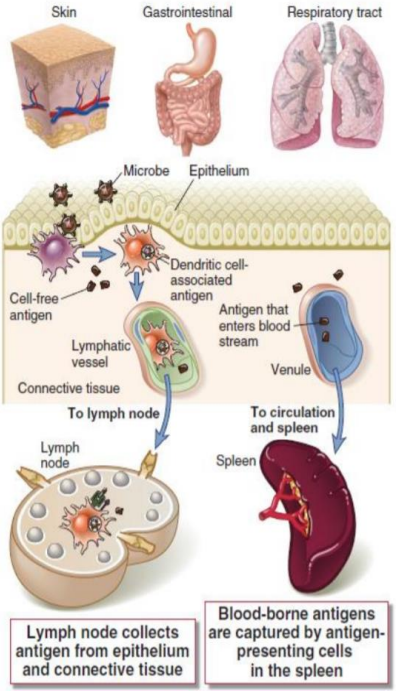
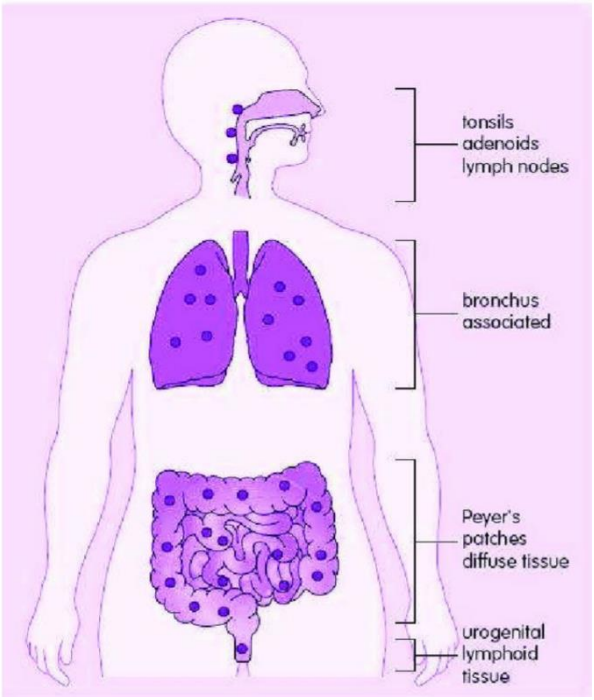


FIGURE 6–3 Routes of antigen entry. Microbial antigens commonly enter through the skin and gastrointestinal and respiratory tracts, where they are captured by dendritic cells and transported to regional lymph nodes. Antigens that enter the blood stream are captured by APCs in the spleen.



2- The spleen

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

- **Remove aging and damaged blood cells and particles** by **red pulp**

immune complexes and **pathogens** which are usually **opsonized** are removed from the circulation. (*Opsonization is the process of attaching Opsonins that induces the phagocytosis of the cells or substances they bound to.*)

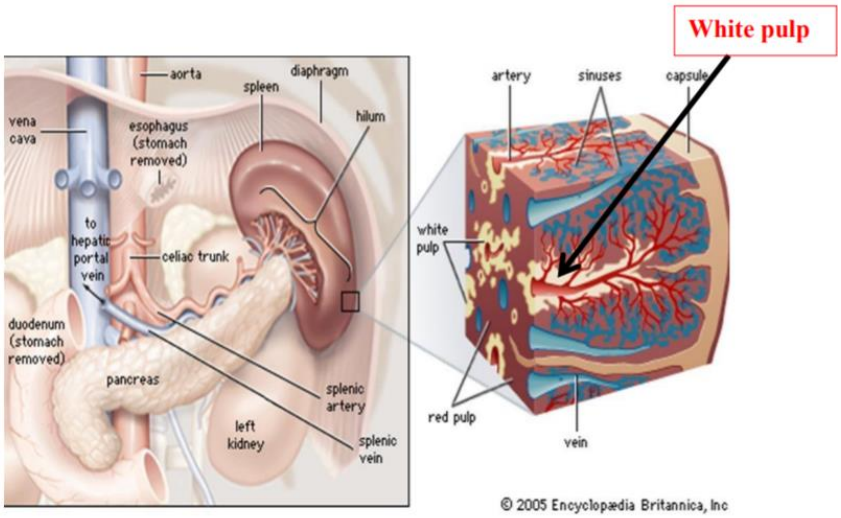
- **Initiate adaptive immune responses to blood-borne antigens** by **white pulp**

The splenic parenchyma is anatomically and functionally divided into:

- Red pulp, composed mainly of **blood-filled vascular sinusoids(channels)**

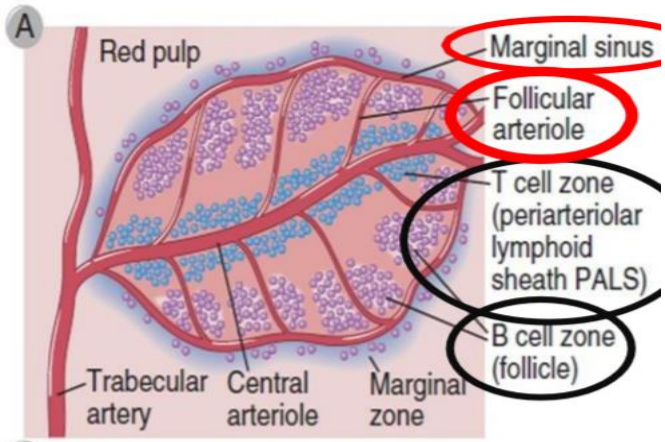
- The lymphocyte-rich White pulp. [Immune-response-inducers]

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.**



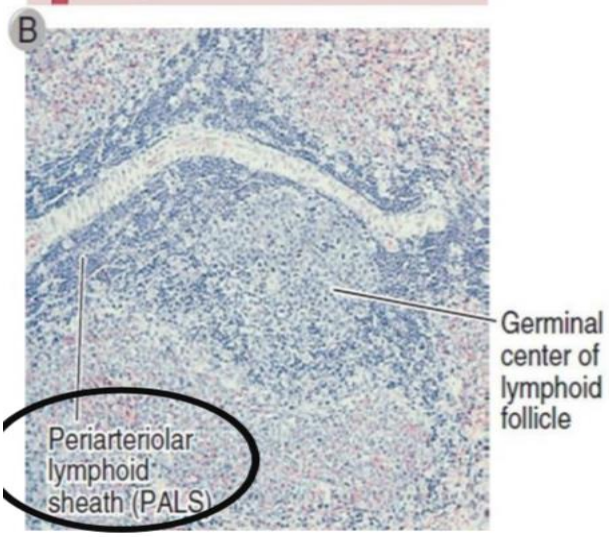
Red Pulp

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 (Splenectomy, due to injury through an accident, autoimmune diseases, or a tumor) are highly susceptible to infections with encapsulated bacteria such as; Streptococcus pneumoniae and Neisseri meningitidis **because they lack macrophages that filter the blood which are found in RED PULP**, such individuals must be given **prophylactic(وقائي)vaccines.**

Marginal Zone

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

[[[These videos could be proven helpful for the topic,

https://www.youtube.com/watch?v=RezL2xWFCe8

https://www.youtube.com/watch?v=waLd8Lf41kc

]]]

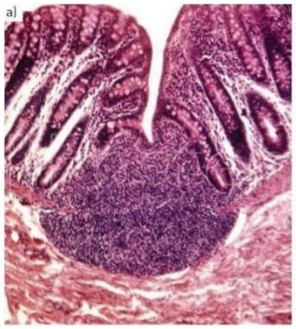
3- Regional Immune Systems (MALT)

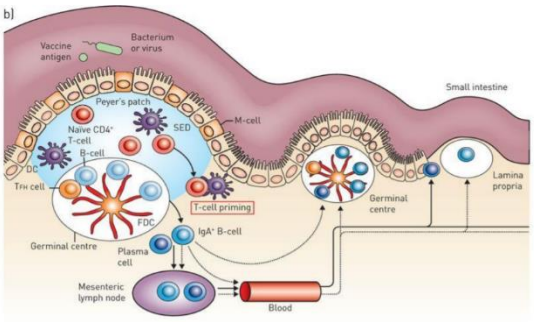
Each major epithelial barrier of the body, including the **skin**, **gastrointestinal mucosa**, and **bronchial mucosa**, has its own system of lymph nodes, **non-encapsulated lymphoid structures**, and diffusely distributed immune cells, which work in coordinated ways to provide specialized immune responses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

- **Mucosa-associated lymphoid tissue (MALT) [*Non-Encapsulated*]**

These collections found in the mucosa and are involved in immune responses to ingested and inhaled antigens and microbes. Examples include tonsils, **the Peyer patches within the small intestine,** and the vermiform appendix. (*refer to figure in page 8*)

• Peyer's Patches are groupings of lymphoid follicles in the mucus membrane that lines your small intestine and are found under the villi of the small intestine. also, **they have high amount of lymphocytes and APCs.**





• There are also **microfold (M)-cells** (specialized epithelial cells in PPs in the GI tract) **feed luminal antigens to the macrophages and resident dendritic cells** (*subepithelial cells* ***SED***)of your Peyer's patches. → They show them to Follicular T helper cell and B cell → Potential immune response.

- [[[T-follicular helper (TFH) cells interact with B-cells and follicular dendritic cell (FDC) thus forming a **germinal center(B-cells machinery). Antigen specific plasma cells** and **memory B-cells** are generated and migrate through the blood and mesenteric lymph nodes. It's generally found in, **lymph nodes, intestines** (PPs) and **spleen.**]]]