



Lymphatic System

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*Prepared and adapted for teaching by Prof. Dr. Heba Kalbounieh.
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Lymphatic system

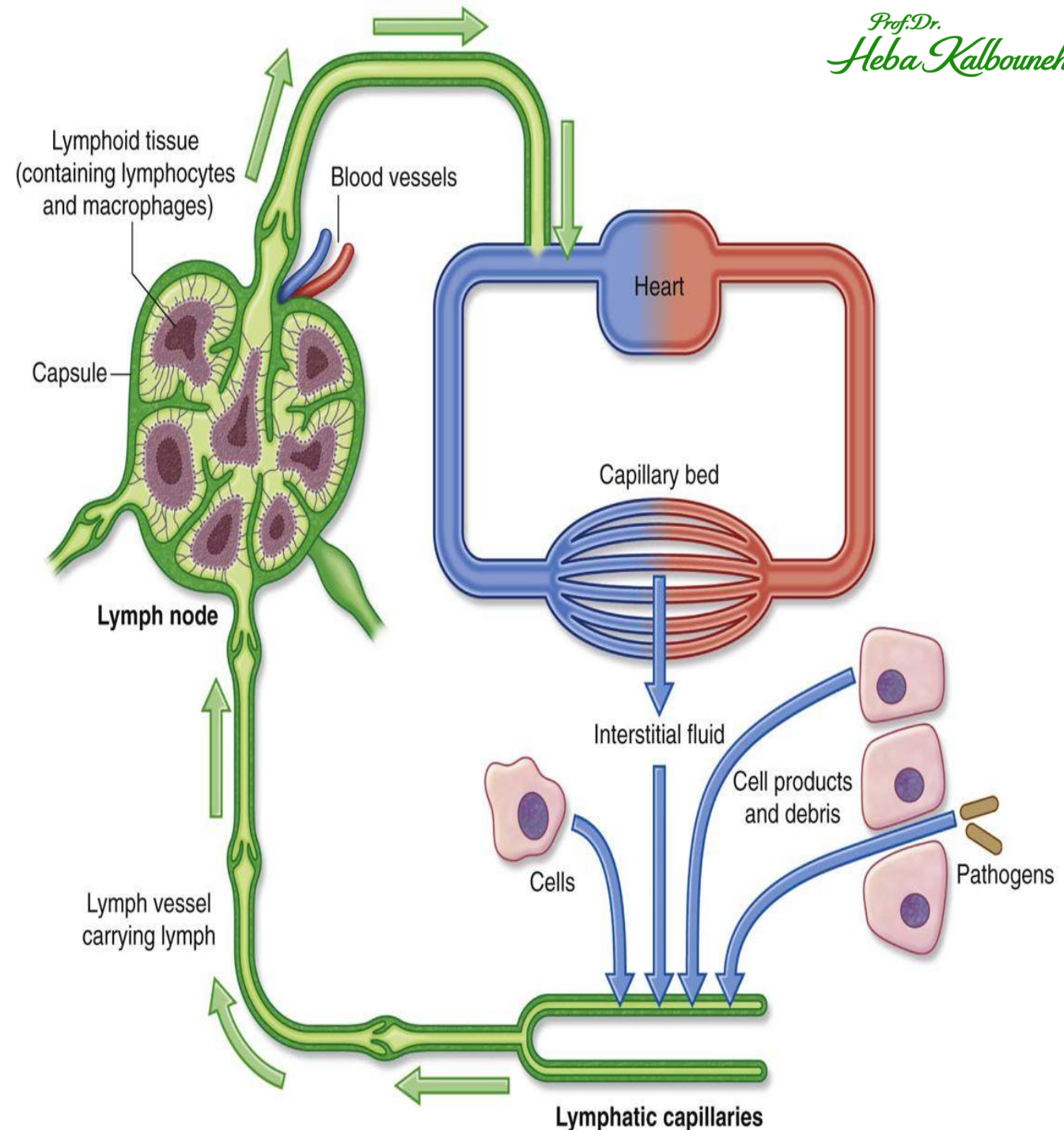
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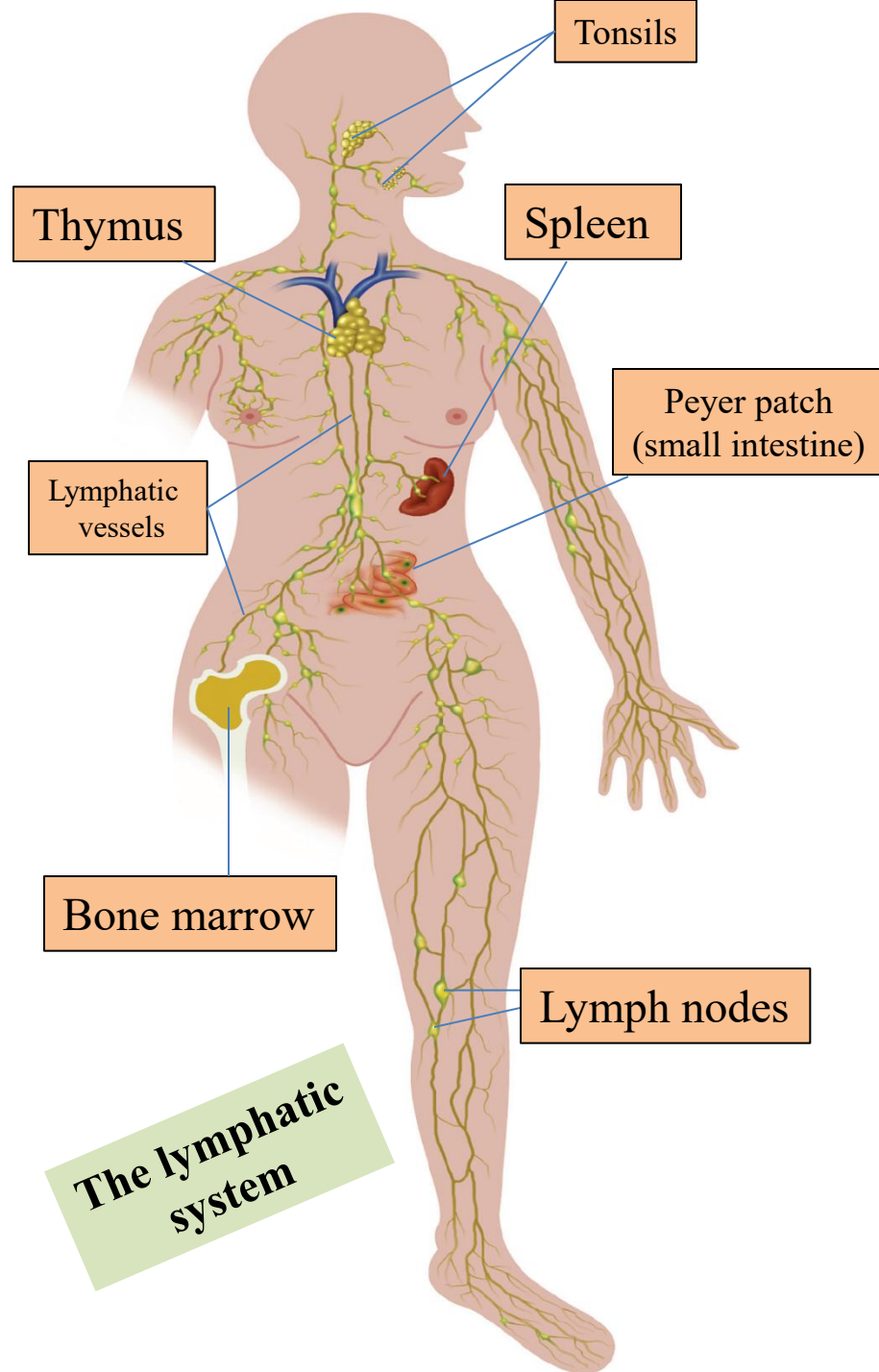
The lymphatic system consists of lymph, lymphatic vessels, lymphatic tissues, and lymphatic organs distributed throughout the body.

It has three major functions:

1. **Fluid balance:** Drains excess interstitial fluid from the tissues and returns it to the bloodstream.
2. **Immune defense:** Initiates immune responses against foreign antigens by housing, producing/maturing, and transporting lymphocytes and other immune cells.
3. **Lipid absorption:** Transports dietary lipids and fat-soluble vitamins absorbed from the small intestine into the bloodstream.

The lymphatic system is a drainage system that removes excess interstitial fluid from body tissues and returns it to the bloodstream. It is an important component of both the circulatory and immune systems.





Lymph is a clear, colorless fluid that flows through lymphatic vessels. It is derived from interstitial fluid and is similar in composition to blood plasma, but generally contains less protein.

Lymphatic vessels are thin-walled vessels that begin as blind-ended lymphatic capillaries in tissues, collect excess interstitial fluid, and transport it as lymph toward the venous circulation.

Lymphatic tissue consists mainly of lymphocytes and other immune cells supported by a framework of reticular connective tissue. It may occur as lymphatic nodules (follicles) or be organized into lymphatic organs.

Lymphatic organs include the lymph nodes, spleen, thymus, and red bone marrow

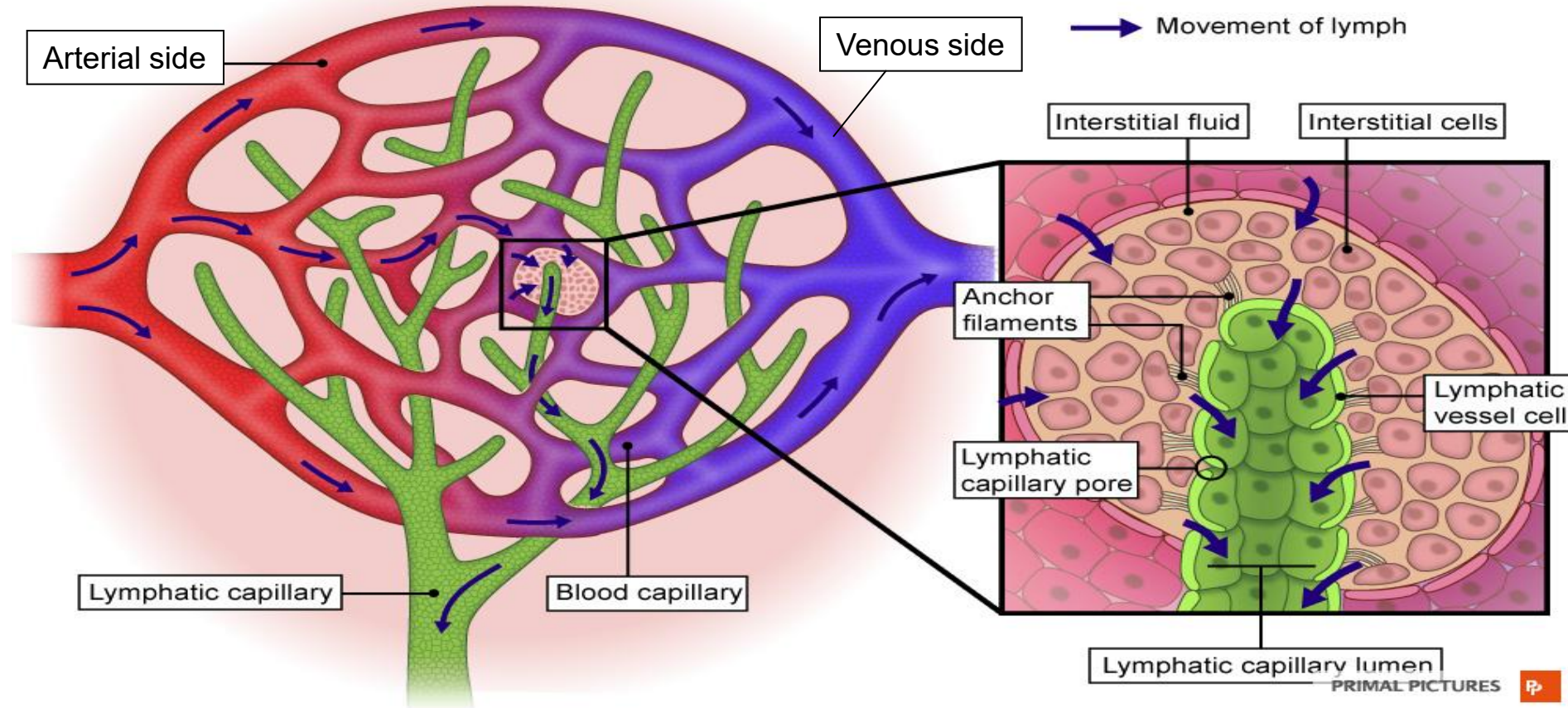
Fluid balance

Body tissues are supplied by blood capillaries, where oxygen and nutrients are delivered to the tissues and carbon dioxide and metabolic wastes are taken up from them.

Approximately 20 L of fluid is filtered from the blood capillaries into the tissues each day. About 17 L returns to the bloodstream, while the remaining ~3 L enters lymphatic capillaries and becomes lymph.

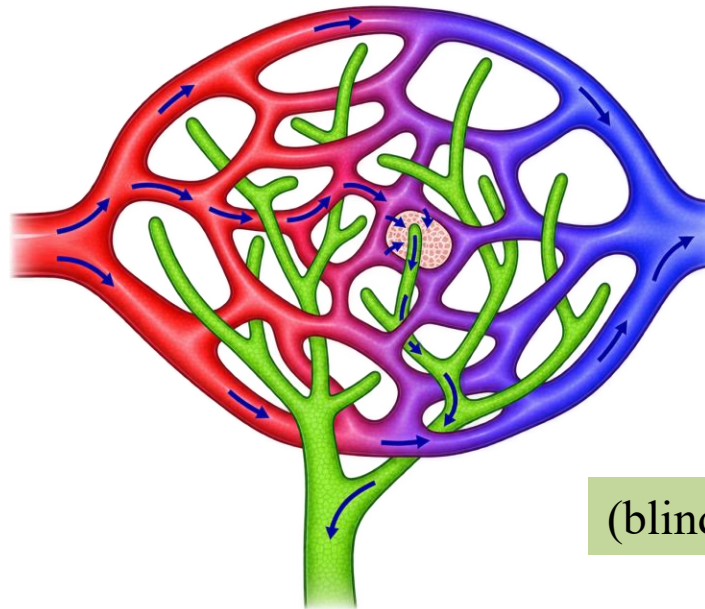
Fluid similar in composition to blood plasma, called interstitial fluid, is filtered from blood capillaries into the surrounding tissues.

Lymphatic vessels drain excess interstitial fluid from the tissues. Once this fluid enters the lymphatic vessels, it is called lymph and is eventually returned to the bloodstream.

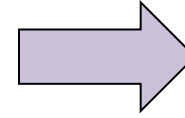
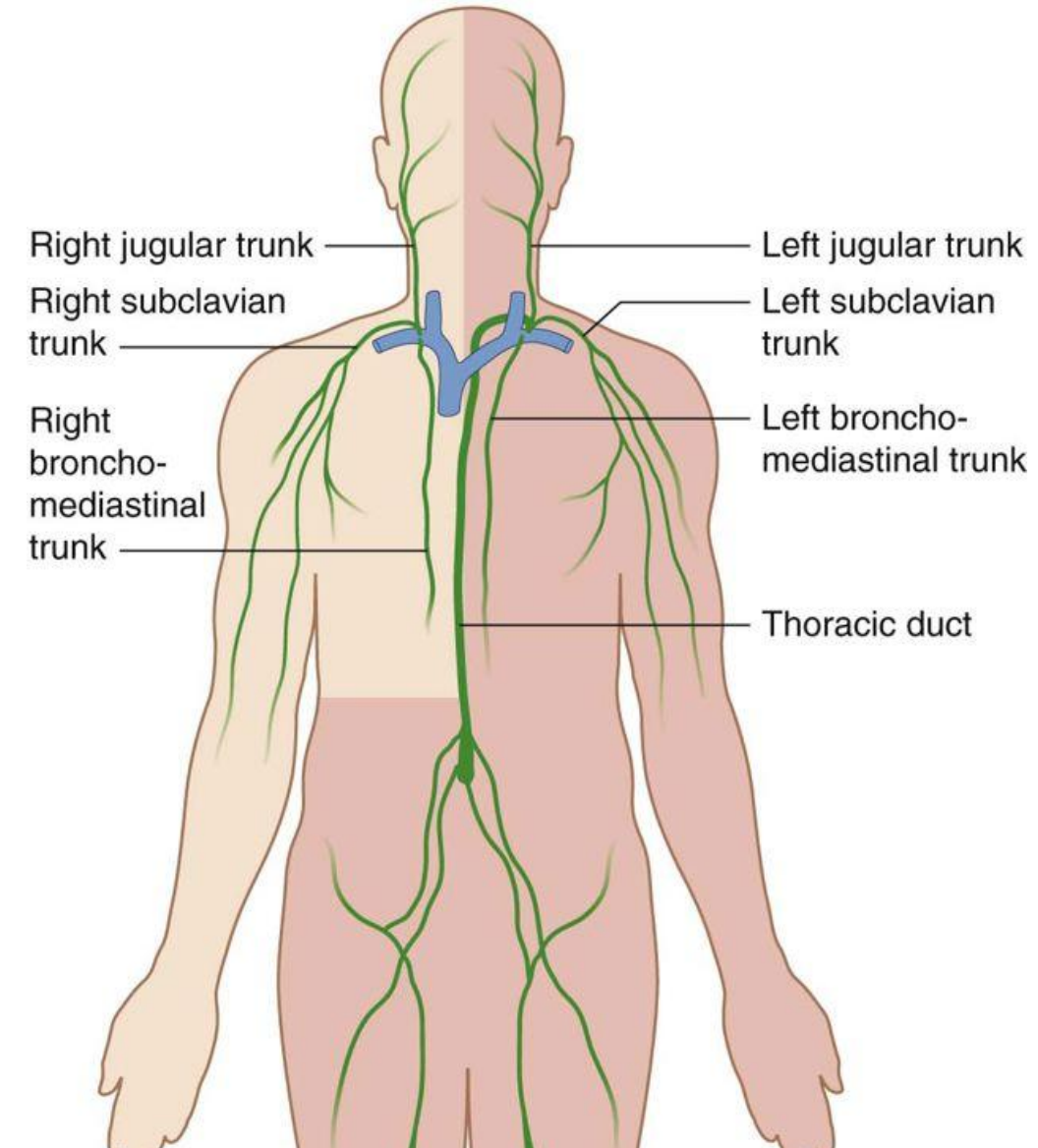


Lymphatic vessels begin as highly permeable, blind-ended lymphatic capillaries in the tissues. These capillaries converge to form progressively larger lymphatic vessels, which ultimately drain into large veins at the root of the neck.

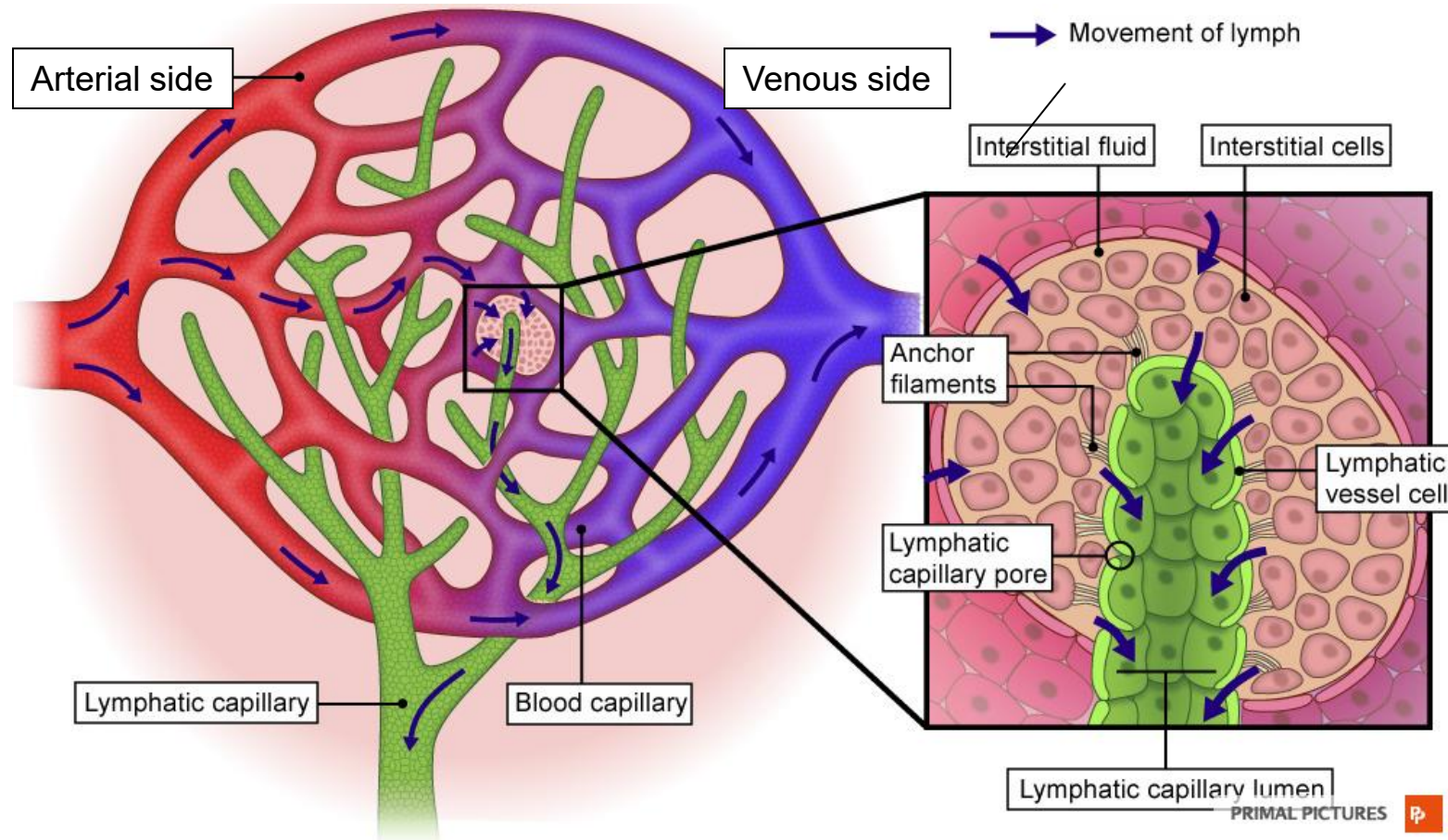
Lymph flow is facilitated by skeletal muscle contraction, respiratory movements, and contraction of smooth muscle in the walls of larger lymphatic vessels. Valves prevent backflow, ensuring unidirectional flow. Lymph flows from lymphatic capillaries into progressively larger lymphatic vessels and eventually returns to the bloodstream. Along its course, lymph passes through lymph nodes, where it is filtered and exposed to immune cells, allowing foreign antigens and pathogens to be detected and an immune response to be initiated..



(blind-ended)



Lymph returns back to the big veins (**venous angle**): the junction between subclavian and internal jugular veins) through the Thoracic duct and Right lymphatic duct.



Lymphatic capillaries are composed of a single layer of overlapping endothelial cells. The overlapping edges form flap-like minivalves that open when interstitial pressure increases, allowing interstitial fluid to enter, and close to prevent backflow.

This allows large molecules, antigens, and immune cells that cannot readily enter blood capillaries to be transported from peripheral tissues to lymph nodes.

When fluid accumulates in the tissues, interstitial fluid pressure increases, pushing the overlapping endothelial flaps inward and opening the spaces between endothelial cells, allowing fluid to enter the lymphatic capillary.

When pressure inside the lymphatic capillary becomes greater than the surrounding interstitial pressure, the endothelial flaps are pushed against each other, closing the openings and preventing backflow.

Lymphatic capillaries are much more permeable than blood capillaries, allowing the entry of large molecules, cellular debris, microorganisms, and migrating immune cells such as dendritic cells. These materials are transported in lymph to regional lymph nodes, where lymph is filtered and antigens can be presented to lymphocytes.

Transport

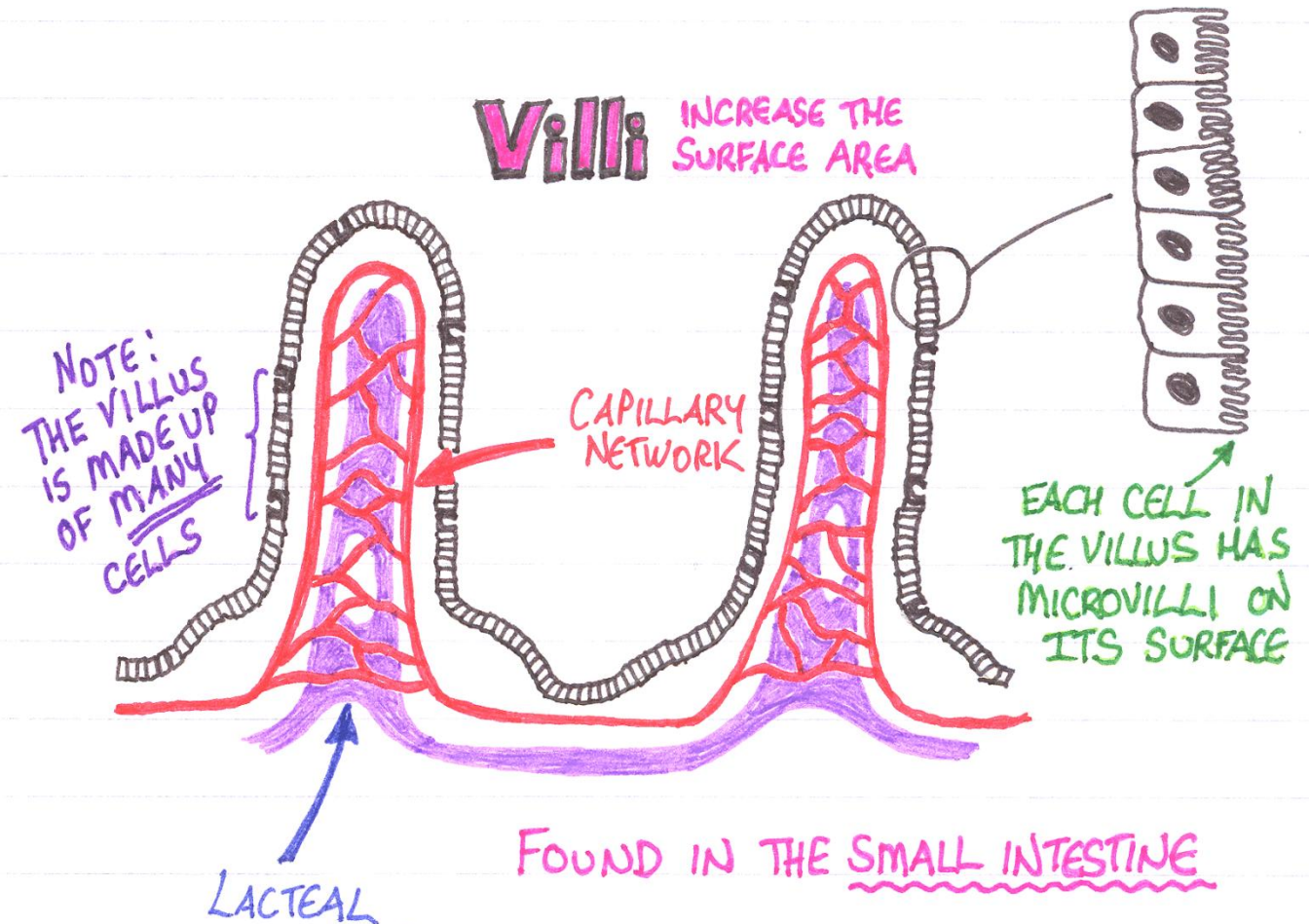
Some lipids are too large to pass through the capillary walls of the small intestine and therefore cannot be absorbed.



The lymphatic capillaries within the small intestine, known as **lacteals**, can absorb these large lipid molecules and transport them into the venous circulation via the thoracic duct. Lymph containing these lipids becomes a creamy white color and is referred to as **chyle**.



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Lymphatic Organs and Tissues

Lymphocytes are distributed throughout the body but are concentrated in lymphatic tissues and organs, particularly at sites where they are likely to encounter foreign antigens.

All lymphocytes originate from hematopoietic stem cells in the red bone marrow. B lymphocytes mature in the bone marrow, whereas T lymphocytes migrate to the thymus to mature. Mature lymphocytes then circulate between the blood, lymph, and lymphatic tissues and organs.

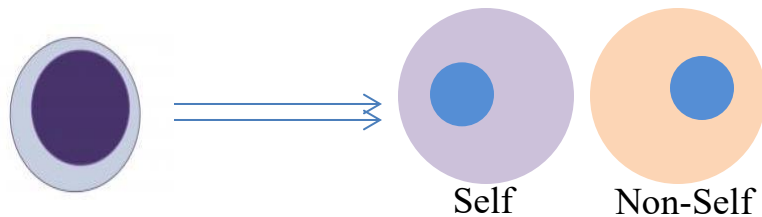
Lymphatic organs are divided into:

Primary lymphoid organs

Bone marrow.

Thymus gland.

Are sites of Lymphocyte production, maturation, selection



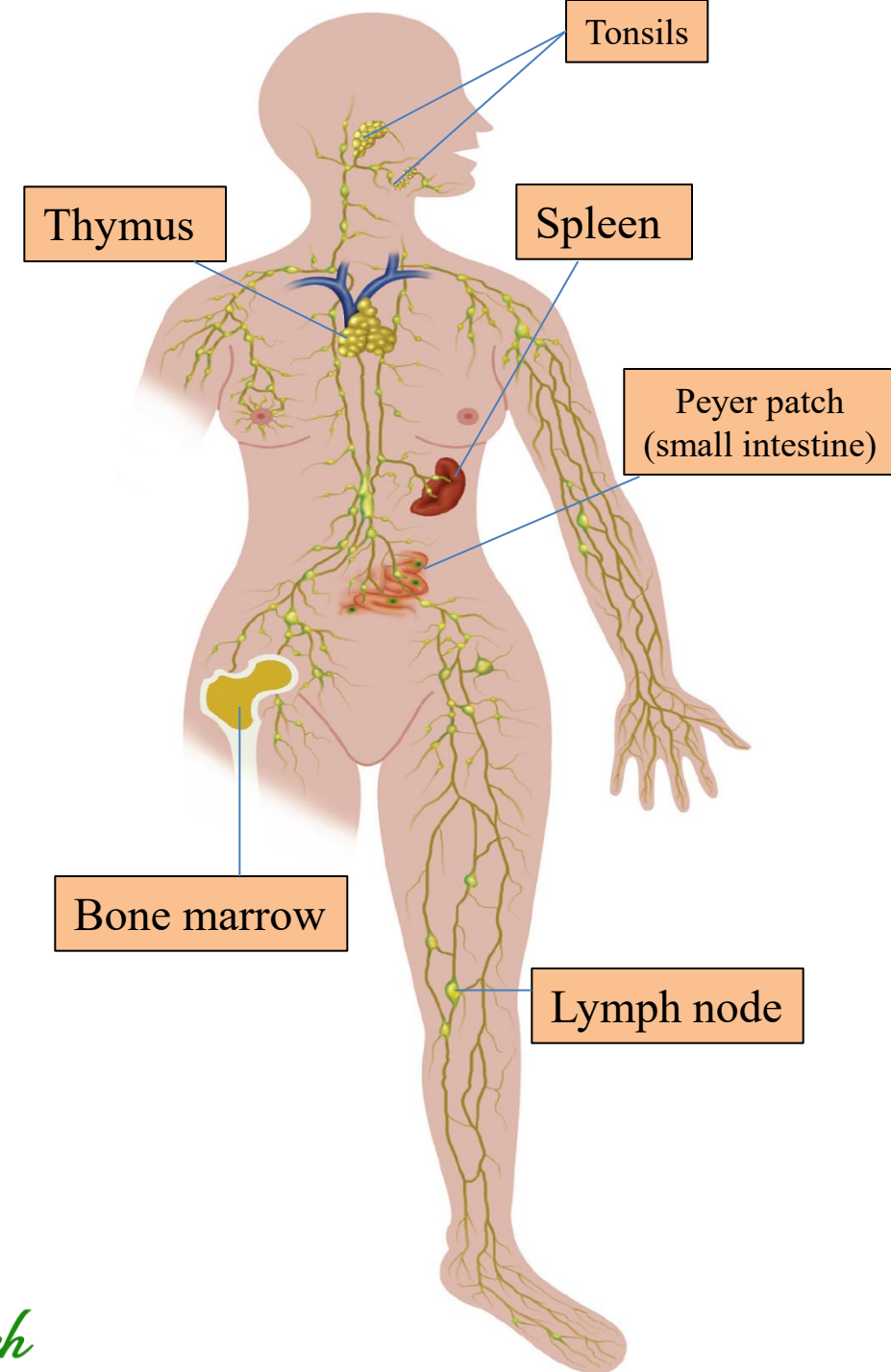
Secondary lymphoid organs

Diffuse lymphoid tissue (lymphoid follicles/ nodules).

Spleen.

Lymph nodes.

Are sites to encounter pathogens and become activated



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Lymph nodes

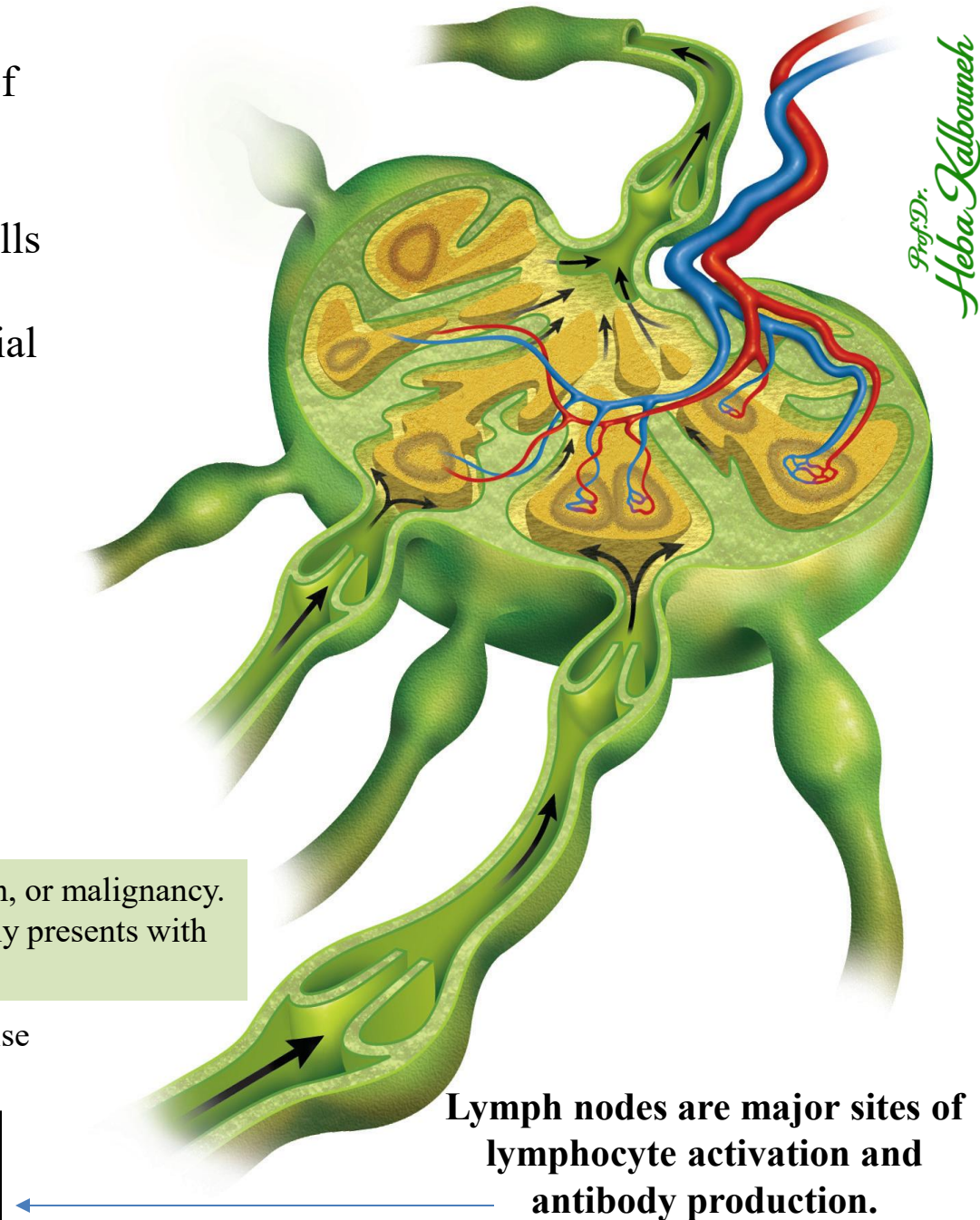
- ✓ Are kidney-shaped small encapsulated bodies located along the course of lymphatic vessels (Approximately 600 lymph nodes)
- ✓ Reticular tissue forms the stroma of the lymph node
- ✓ Immunocompetent B and T lymphocytes, together with other immune cells such as macrophages and dendritic cells, are distributed within specific regions of the lymph node. Nodes filter the lymph, removing foreign material and microorganisms.
- ✓ Antibody- mediated and cell- mediated immune responses occur in the lymph nodes
- ✓ Lymph nodes commonly occur in clusters along major lymphatic vessels and are usually named according to their anatomical location or associated region/vessels.

Most lymph passes through one or more lymph nodes before returning to the bloodstream.

Lymph node enlargement (lymphadenopathy) may occur in response to infection, inflammation, or malignancy. Infections commonly cause tender or painful lymphadenopathy, whereas lymphoma classically presents with painless lymphadenopathy.

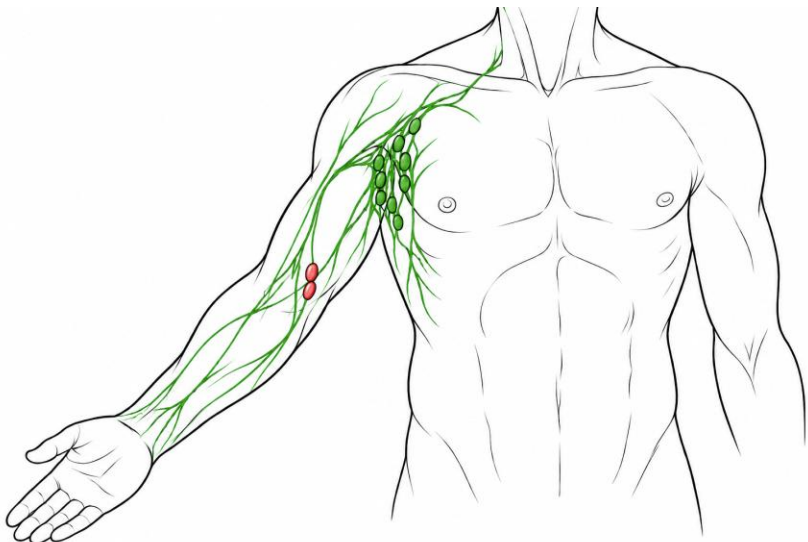
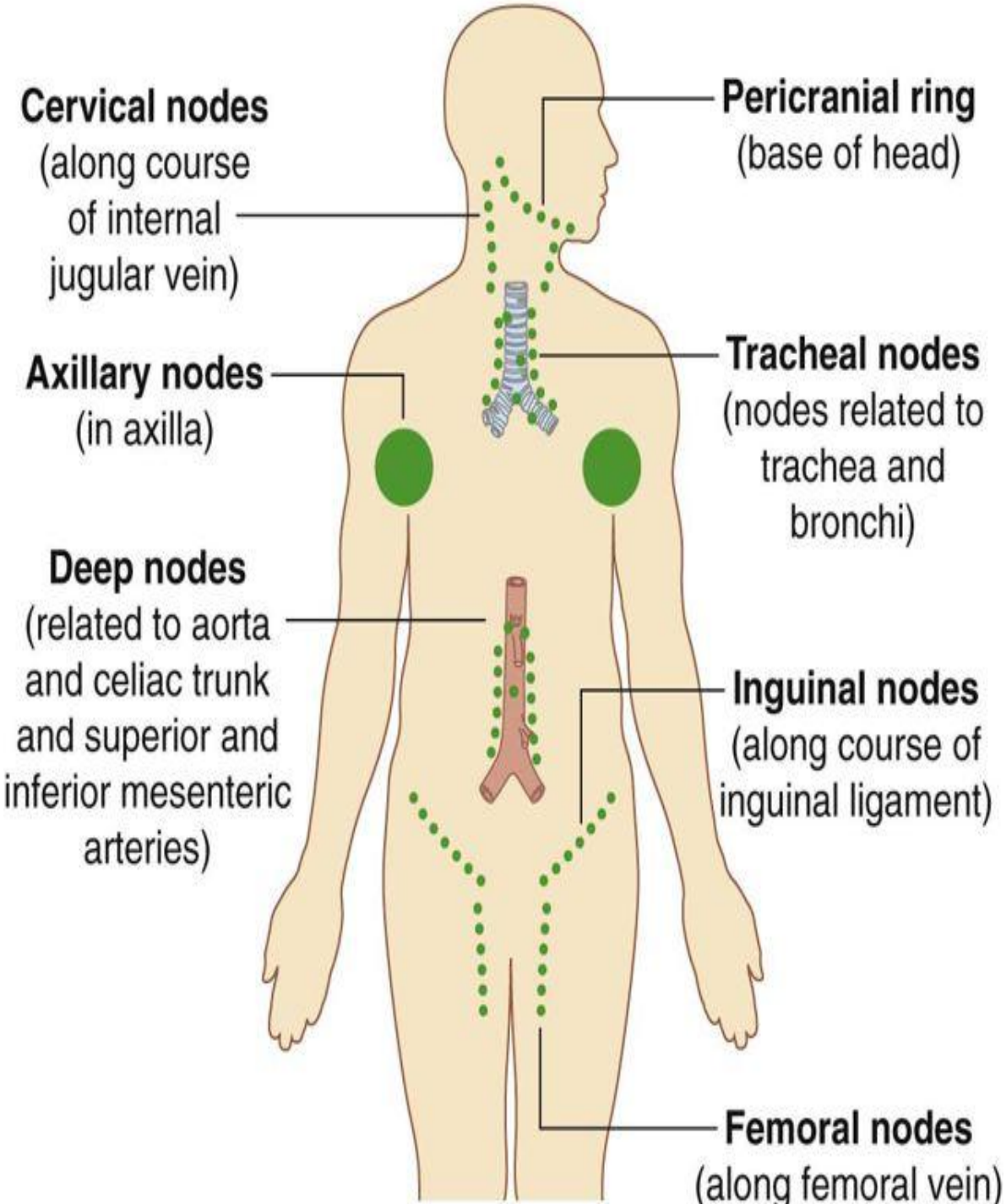
Lymph nodes measuring >1 cm in short-axis diameter may be considered enlarged and raise suspicion for pathology, depending on their anatomical location and clinical context.

Antigen enters lymph node → B/T lymphocyte activation → clonal proliferation → effector cells
B cells → plasma cells → antibodies
T cells → activated effector T cells

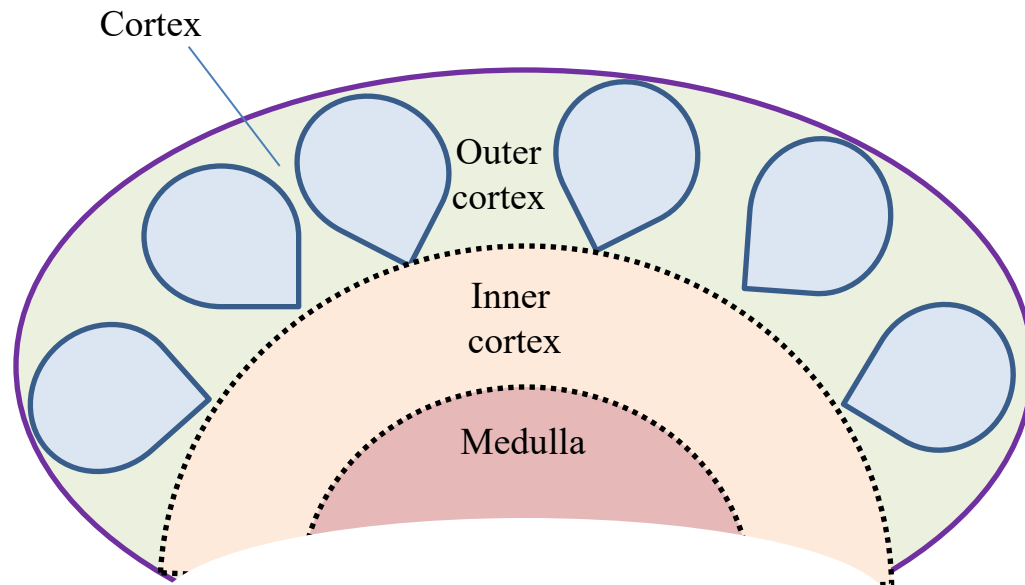
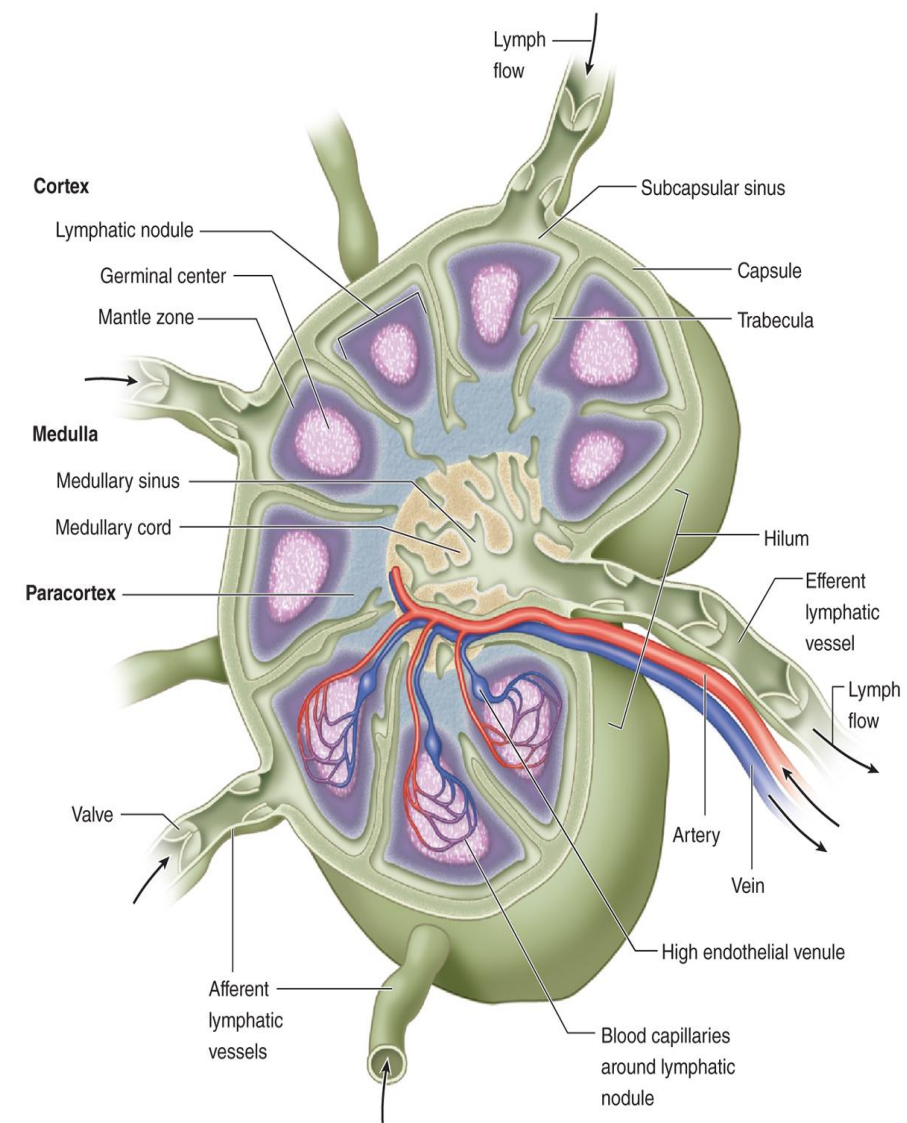


The main groups of lymph nodes include:

Name	Location	Associated vessel
Axillary nodes	Armpit	Axillary vein
Cubital nodes	Elbow	Basilic vein
Popliteal nodes	Posterior knee	Popliteal vein
Inguinal nodes (superficial and deep)	Groin	Great saphenous vein Femoral vein
Cervical lymph nodes (superficial and deep)	Neck	Internal jugular vein External jugular vein



The lymph node consists of an outer cortex and an inner medulla



Cortex

Contains lymphoid follicles

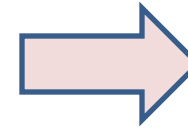
Receives lymph from afferent vessels

Medulla

No follicles

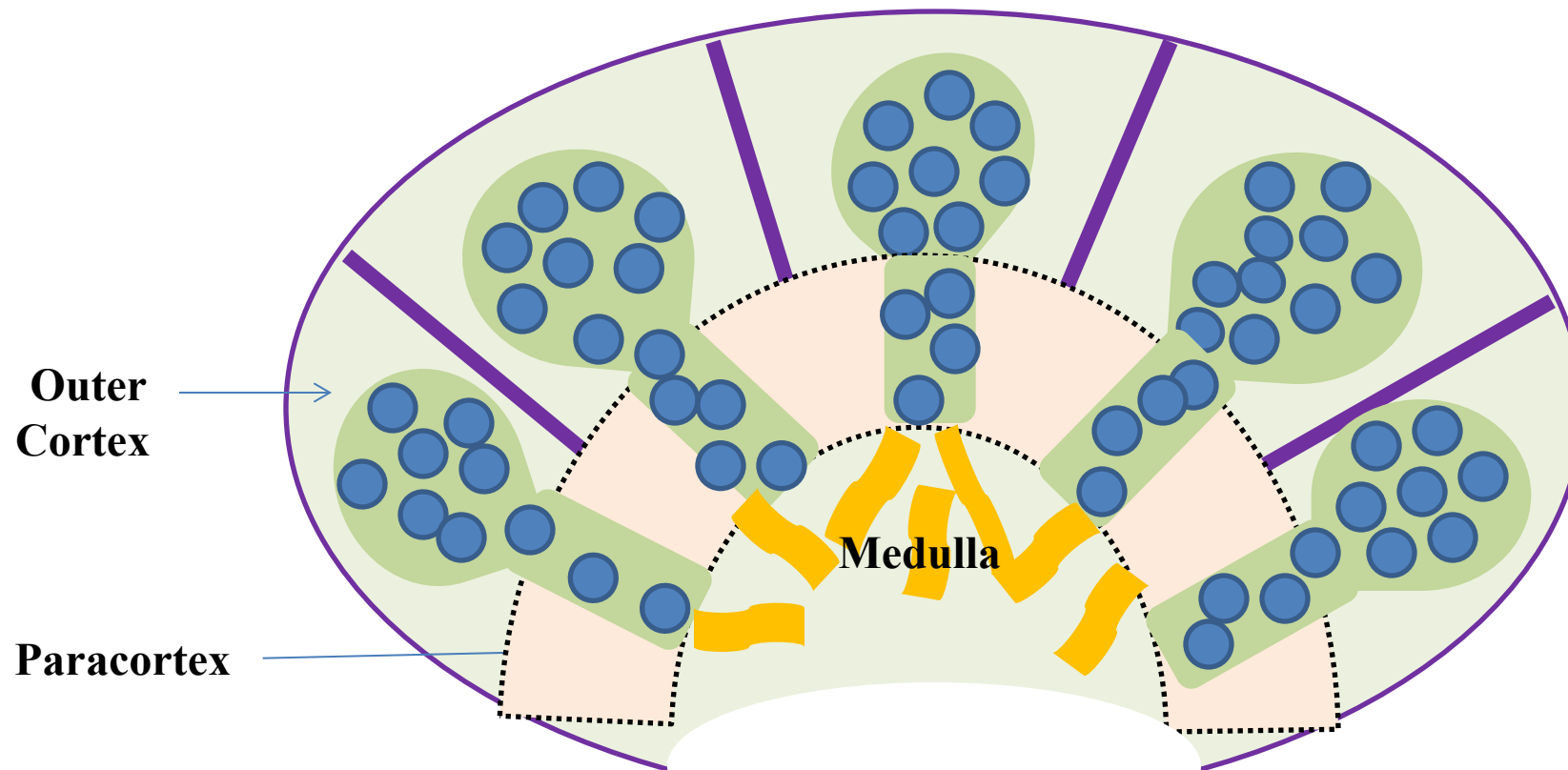
Forms sinuses that lead to efferent vessels at the hilum

The nodes are covered by a **capsule** of dense connective tissue, and have capsular extensions called the **trabeculae**, which provide support for blood vessels entering into the nodes.



When lymph nodes become enlarged, the capsule is stretched and becomes painful

The cortex is the outer, highly cellular part of the lymph node; it can be divided into an outer cortex and inner paracortex.



The **outer cortex** has lymphoid follicles that mostly contain **B-cells**.

The **inner cortex (paracortex)** contains mostly **T-cells**.

The **medullary cords** contain mostly **plasma cells**.

Other cells in the lymph node:

Macrophages

Dendritic cells

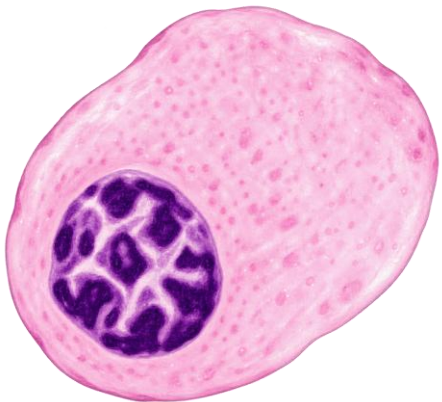
Follicular dendritic cells

Reticular cells

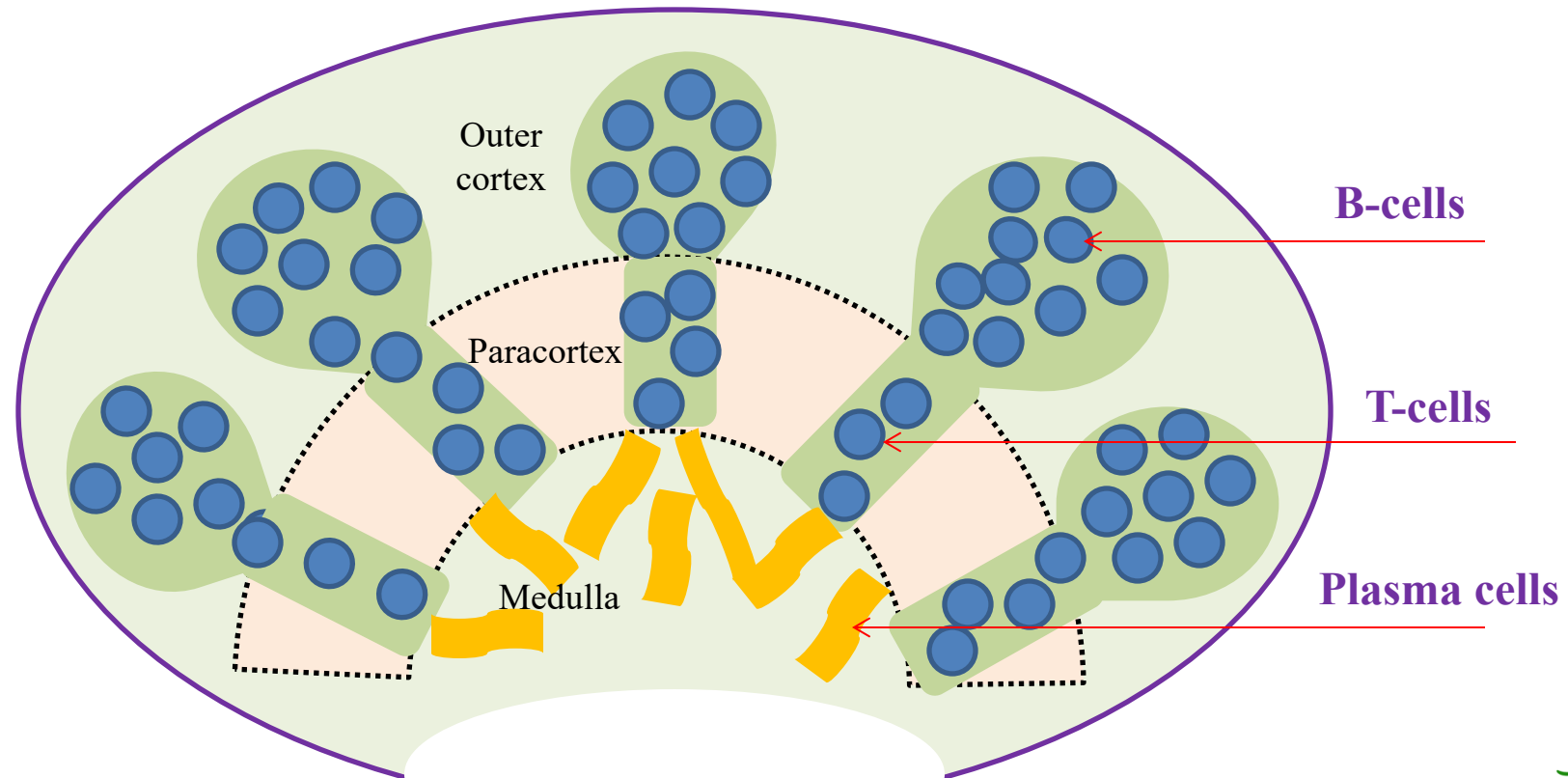
Both the macrophages, and the dendritic cells trap antigens and present them on their surfaces

As B cells in lymphoid follicle are stimulated, they differentiate into plasma cells. Plasma cells move to medulla (medullary cords)

Note: the nucleus of plasma cell is eccentrically placed, round or oval with *cartwheel (clock-face)* chromatin pattern.

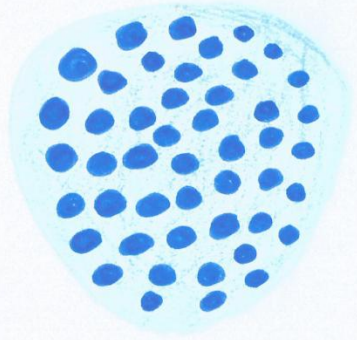


Plasma cell

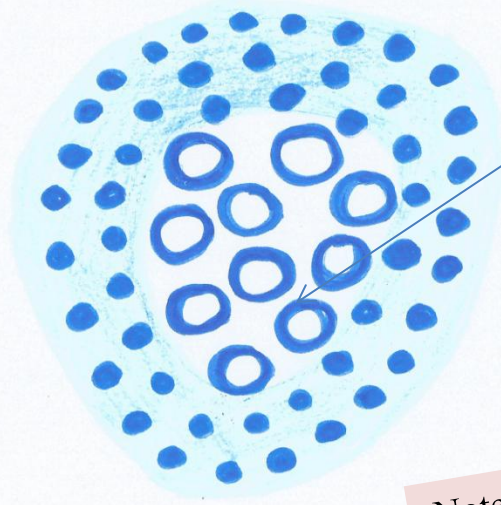


The outer cortex houses lymphatic follicles (nodules) which are of two types:

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Primary follicles:
lymphoid follicles
without a germinal center.
(virgin B cells)

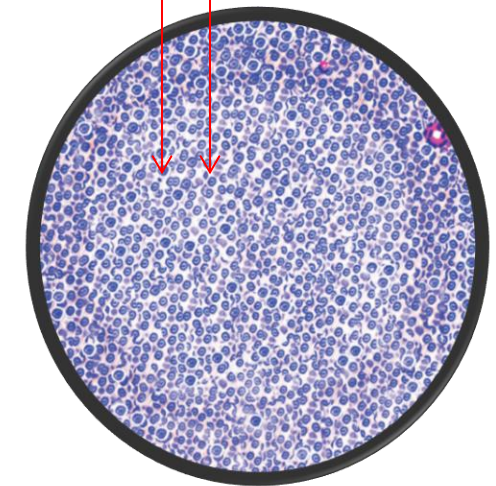


Secondary follicles: lymphoid
follicles with a germinal center.
Sites for B memory cell and plasma
cell generation

Note: Secondary follicles
form **only** in response to
exposure to antigens

The lighter staining areas are
germinal centers, where the **B-cells**
proliferate and activate into
antibody secreting plasma cells and
B memory cells

Centroblasts are large,
activated B lymphocytes
found in the germinal
centers of secondary
lymphoid follicles



When activated by antigens (and T helper cells), B cells migrate to the center of the follicle, forming a germinal center. Germinal centers are the central regions of secondary follicles where activated B cells are proliferating (dividing by mitosis) and differentiating into plasma cells and memory B cells. When stimulated by antigens, lymph nodes enlarge due to the formation of germinal centers and B cell proliferation

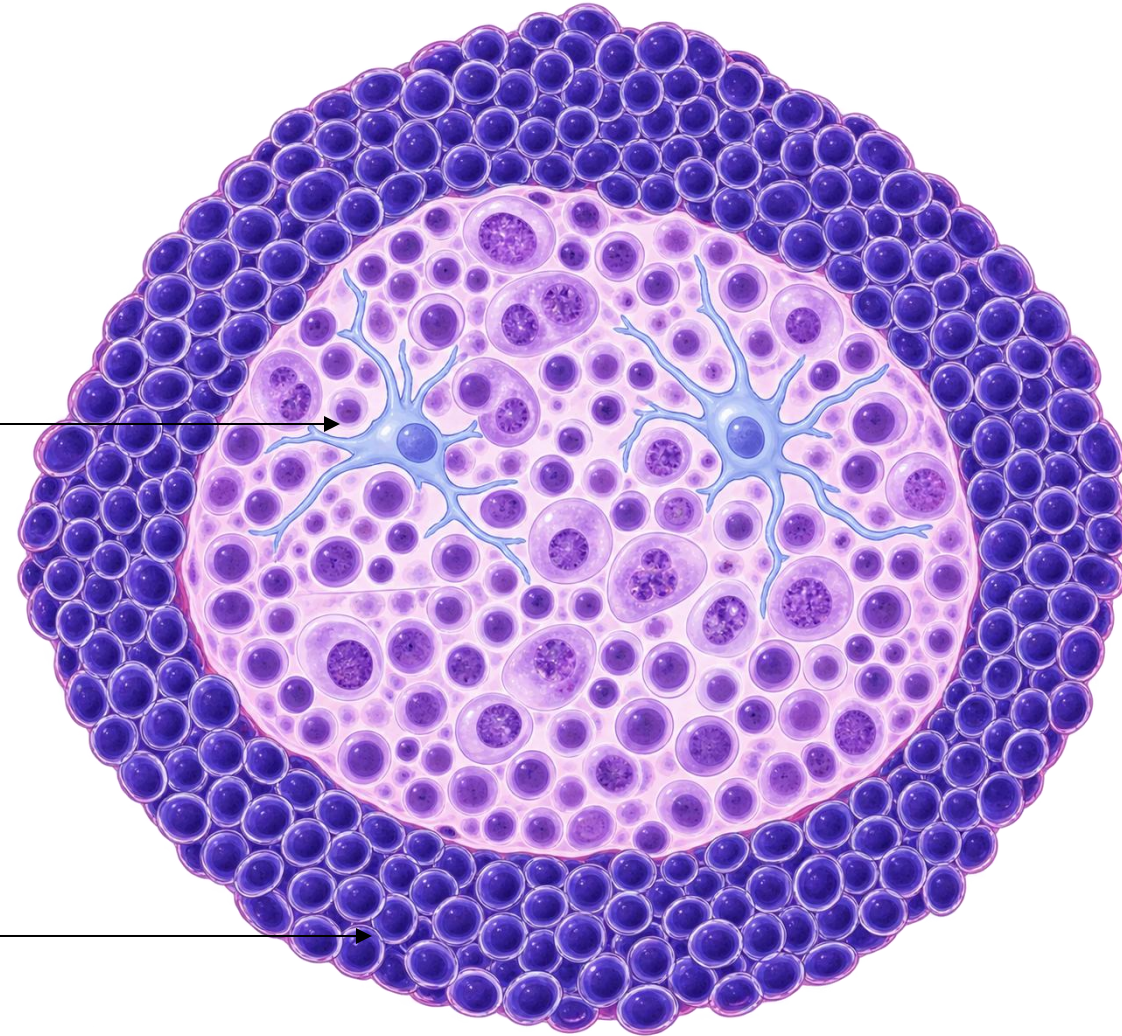
Note: Splenic lymphatic follicles are additionally surrounded by a marginal zone, which contains specialized B lymphocytes and macrophages involved in trapping blood-borne antigens and initiating immune responses.

Germinal Center:

- ✓ Pale central region of a secondary lymphatic follicle.
- ✓ Contains **proliferating B lymphocytes** (centroblasts), follicular dendritic cells, and helper T cells.
- ✓ Site of B-cell proliferation and differentiation into plasma cells and memory B cells.

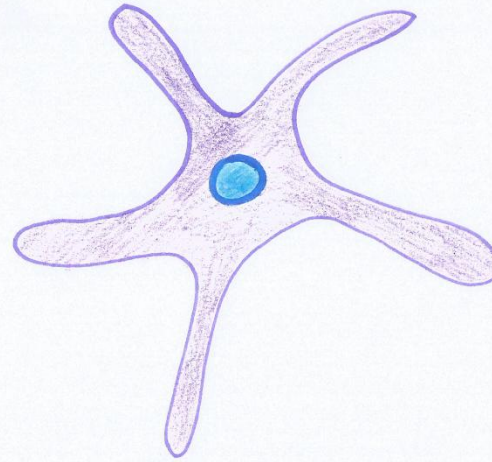
Mantle Zone (Corona):

- ✓ Dark-staining outer region surrounding the germinal center.
- ✓ Consists mainly of densely packed, small, resting B lymphocytes.
- ✓ Appears darker due to the high density of lymphocyte nuclei.





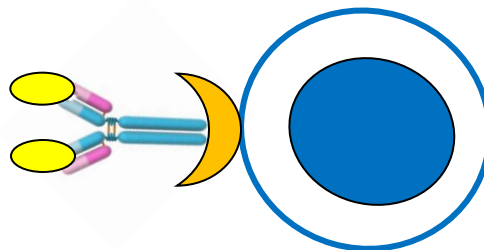
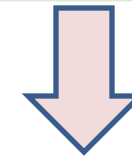
Macrophage



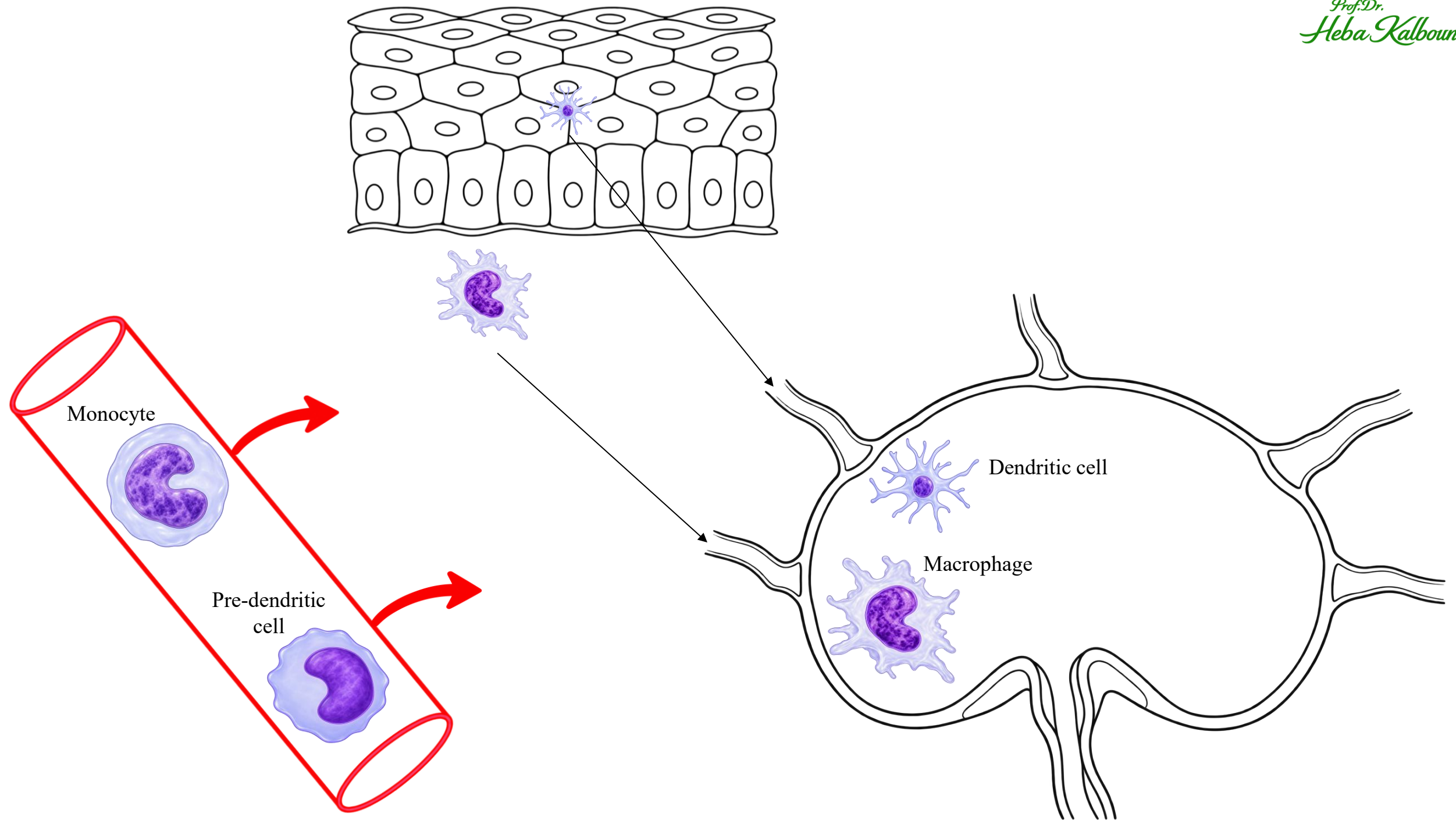
Dendritic cell

Macrophages and Dendritic cells capture antigen within tissues and transport antigen to secondary lymphatic tissue

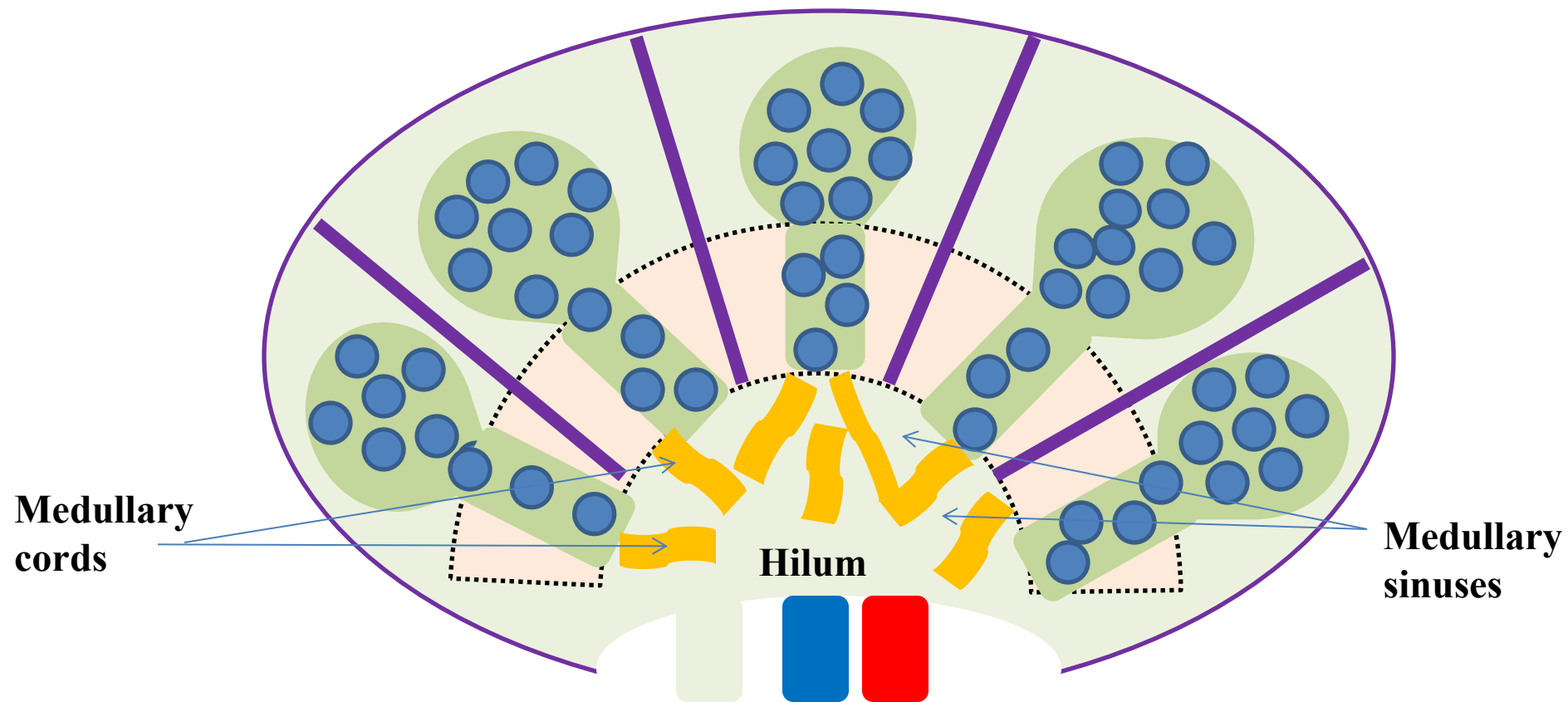
	Macrophage	Dendritic cell	Follicular dendritic cell
Phagocytosis	Most phagocytic	Moderately phagocytic	X
Antigen presenting (via MHC-II)	Moderate Ag- presenter	Very powerful Ag- presenter	X <i>Non-classical antigen presentation to B cells</i>
Location in lymph node	Cortex and medulla	Cortex and medulla	Outer cortex



Are antigen **HOLDING** cells
Holds the Ag for long time



- ✓ The **medulla** is the deep, cavitated part of the lymph node; it is composed of **medullary cords**
- ✓ The cords are separated by spaces known as **medullary sinuses**
- ✓ The medullary sinuses converge at the **hilum**.
- ✓ The hilum is a slight indentation on one side of the node. Here, an artery, vein, and an efferent lymphatic vessel enter and leave the node.



Afferent vessels

Many afferent lymphatic vessels enter the lymph node at different points over its convex surface, each containing valves to prevent backflow of lymph.

Subcapsular sinuses

Each afferent vessel empties into the subcapsular sinus.

Trabecular sinuses

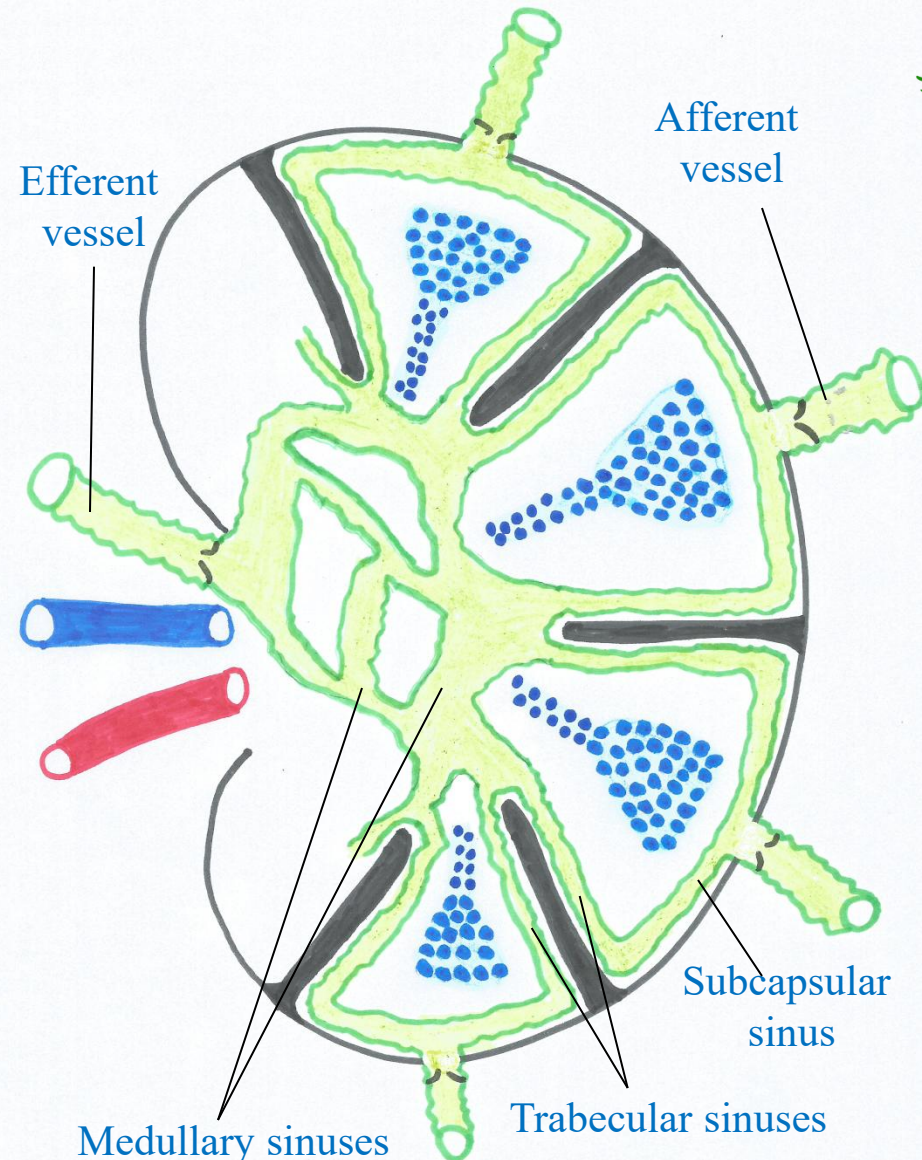
The trabecular sinuses are a continuation of the subcapsular sinuses that follow the trabeculae and drain into the medullary sinuses.

Medullary sinuses

Found separating the cords. The medullary sinuses converge at the hilum into the efferent lymphatic vessel.

Efferent vessels

The lymph is removed from the medullary sinus via one or two efferent lymphatic vessels that leave the lymph node at the hilum. Valves in the vessels prevent lymph from flowing in the wrong direction.



Sinuses are irregular spaces through which the lymph percolates

Lymph flow

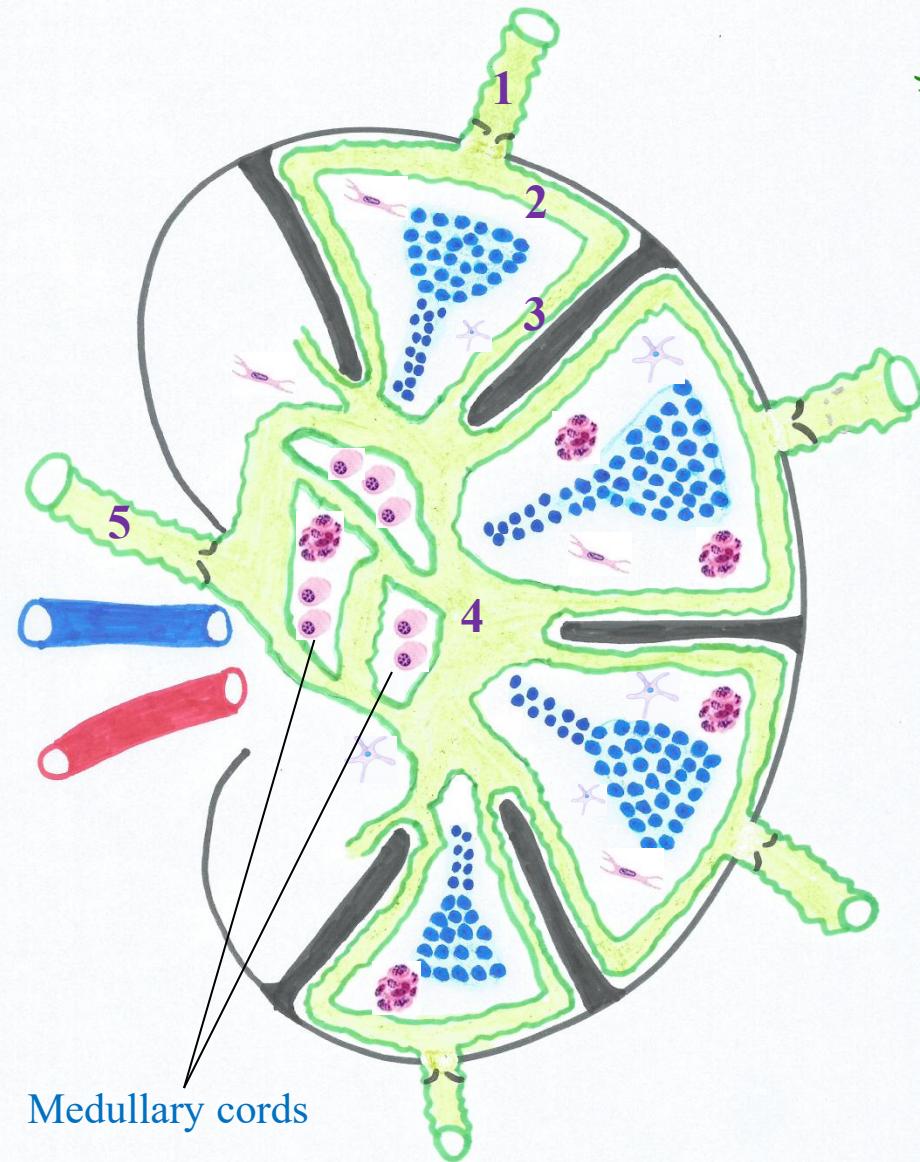
Lymph nodes are linked together by lymphatic vessels. Lymph flows through a lymph node via a series of sinuses and lymphatic tissue

Lymph, containing micro-organisms, soluble antigens and antigen presenting cells, enters the lymph node via **afferent lymphatic vessels (1)** which enter the **subcapsular sinus (2)**. It then runs through **trabecular (cortical) sinuses (3)** then into **medullary sinuses (4)** and leaves through the **efferent lymphatic vessels (5)**, at the **Hilum** as **efferent lymph**.

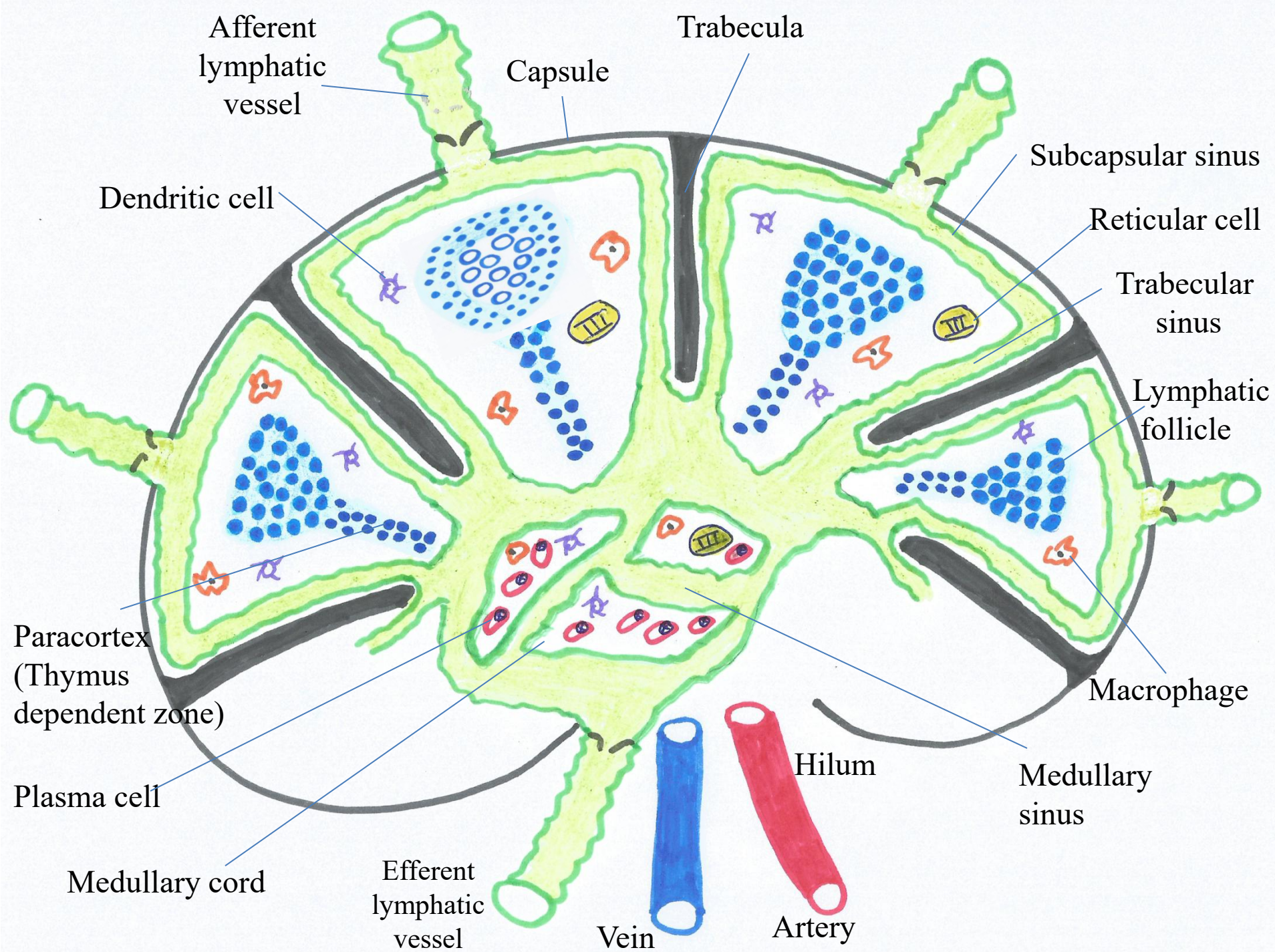


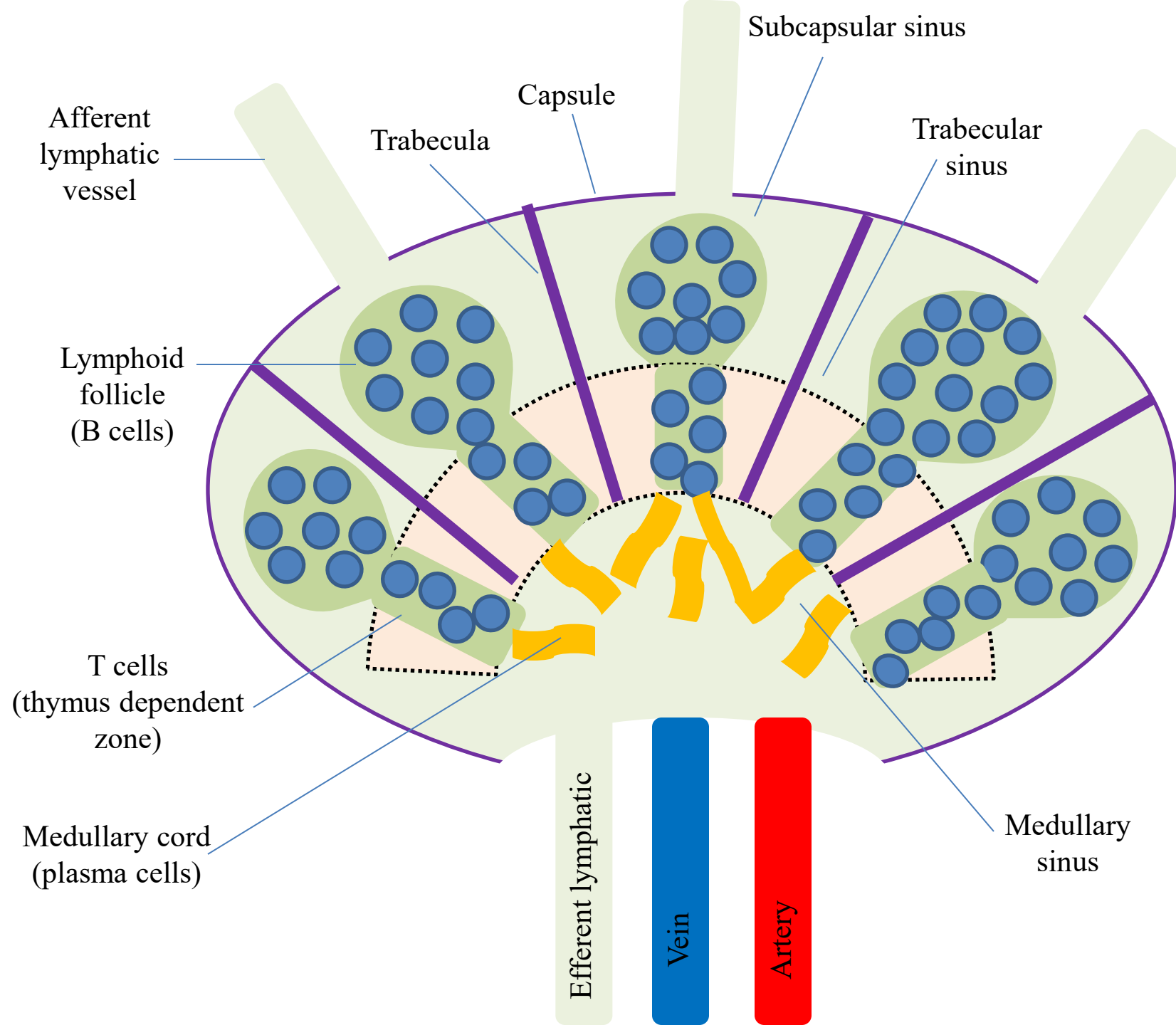
Efferent lymph contains lots of activated T-lymphocytes, activated B-lymphocytes and antibodies produced during immune responses

Lymph slows down when it passes in lymph nodes.



All the **lymphatic sinuses** are lined by a discontinuous layer of simple squamous endothelium





Lymphocytes can enter lymphoid tissues in two ways:

- 1) Direct entry into lymph nodes via afferent lymphatics
- 2) Entry from blood capillaries across specialized endothelial cells present in the postcapillary venules (High Endothelial Venules= HEV) within the **paracortex** of the lymph

→ major route by which naïve B and T lymphocytes enter lymph nodes.

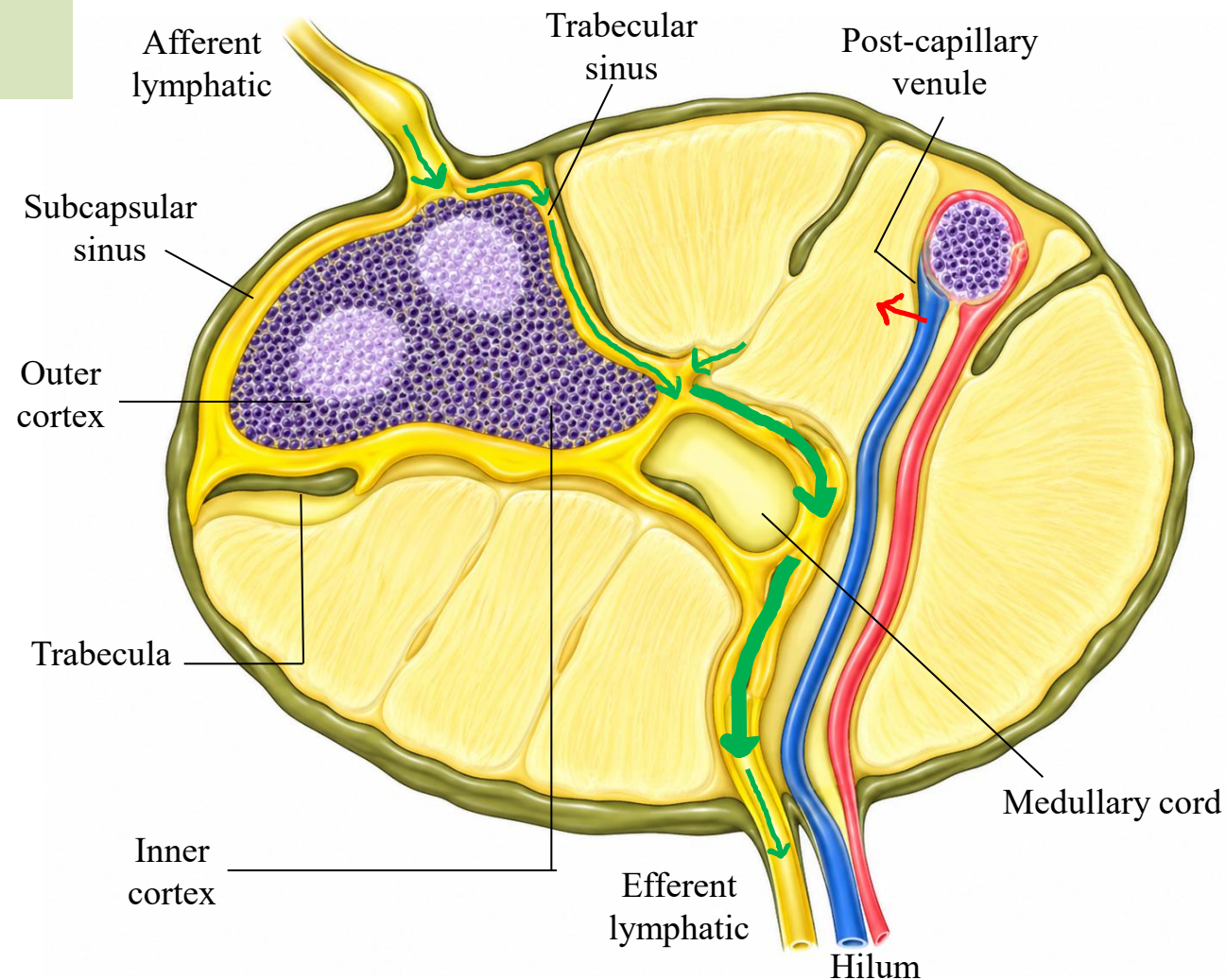
Why naïve lymphocytes migrate preferentially to lymph node?????



Postcapillary venules in the paracortex of lymph nodes have an unusual endothelium composed of cuboidal endothelial cells, rather than the usual flattened endothelial cells. These specialized vessels are called High Endothelial Venules (HEVs).

Circulating lymphocytes recognize and adhere to the endothelial cells of HEVs and then migrate across the vessel wall (diapedesis) into the lymph node parenchyma.

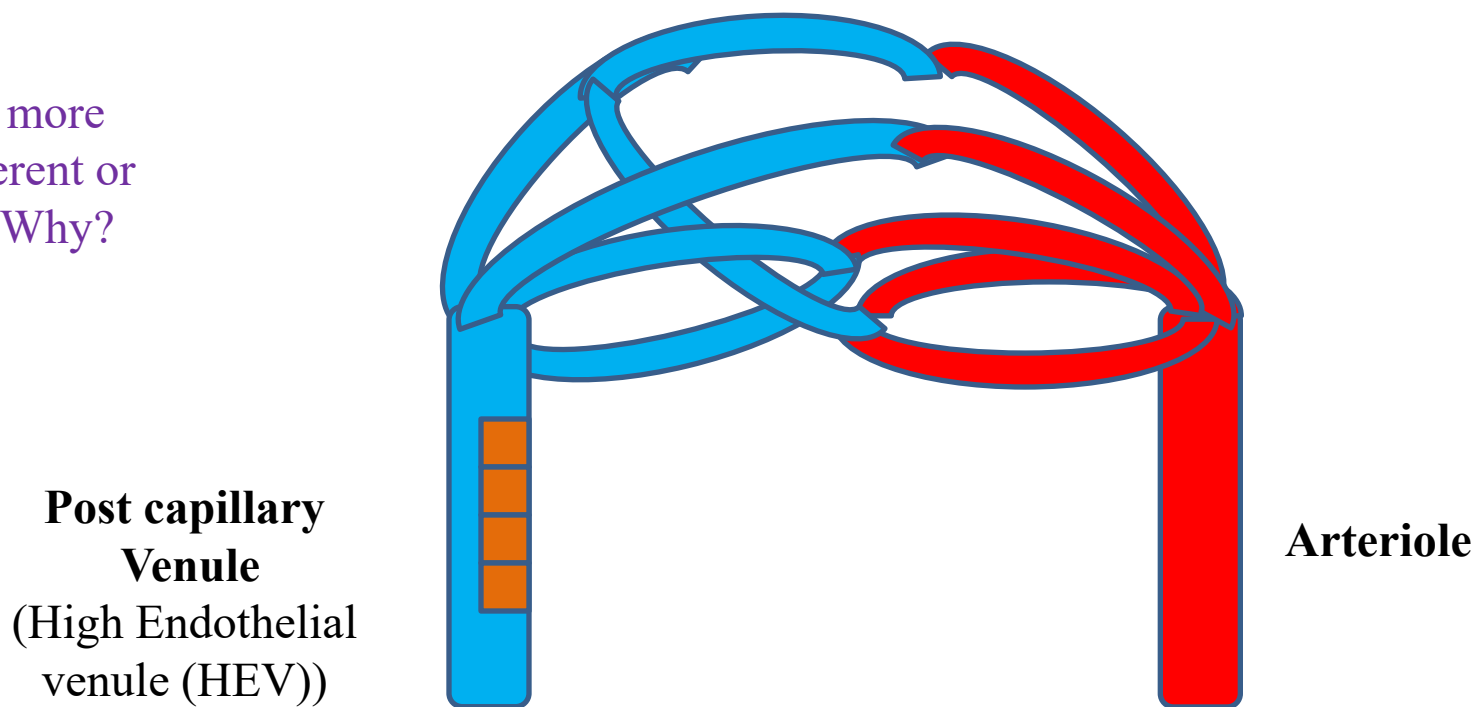
Lymphocyte homing and recirculation are regulated by adhesion molecules on lymphocytes called homing receptors and complementary ligands on endothelial cells called addressins.



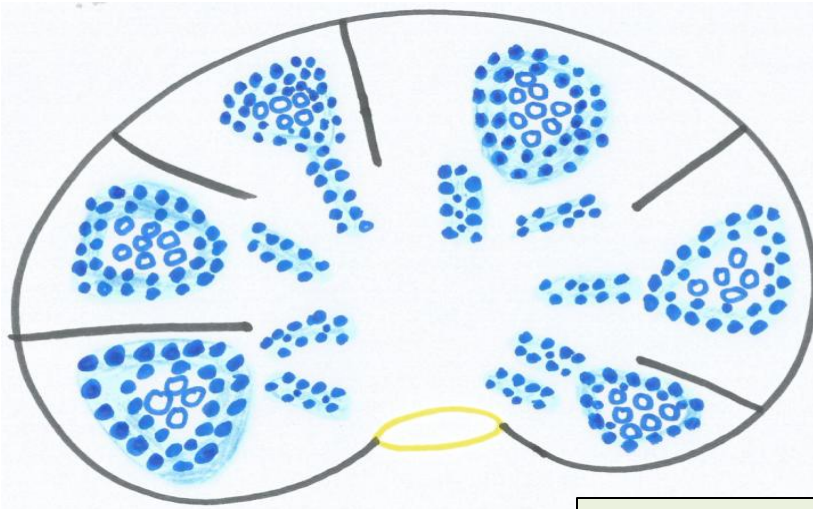
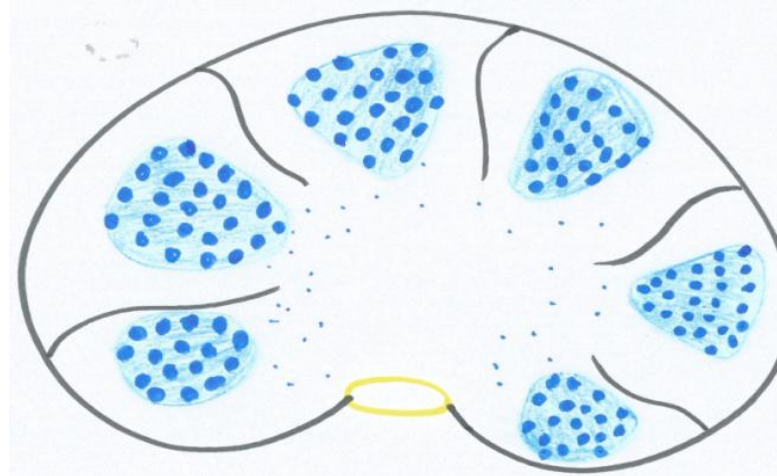
This diagram of a lymph node shows the pathways that lymphocytes can take, in and out of the lymph node.

Note: Most of the lymphocytes enter the lymph nodes via blood vessels, and about 10% enter through the lymph.

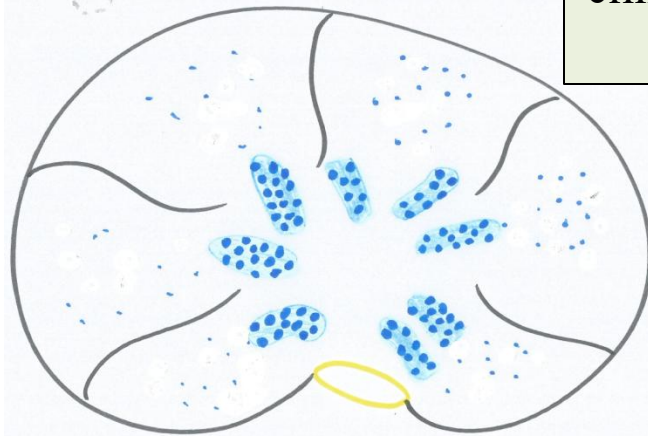
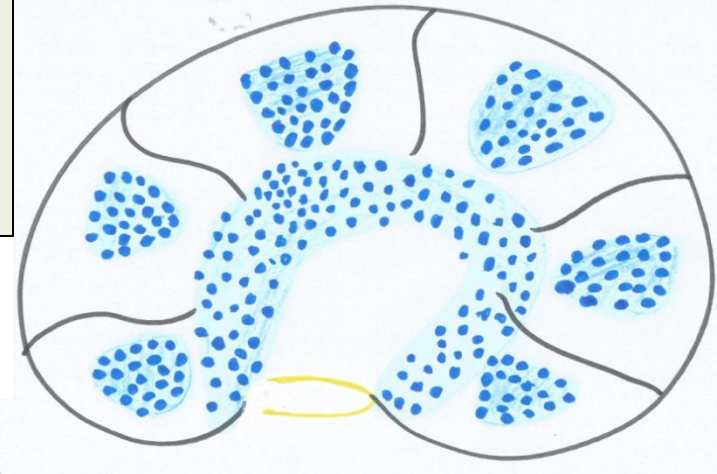
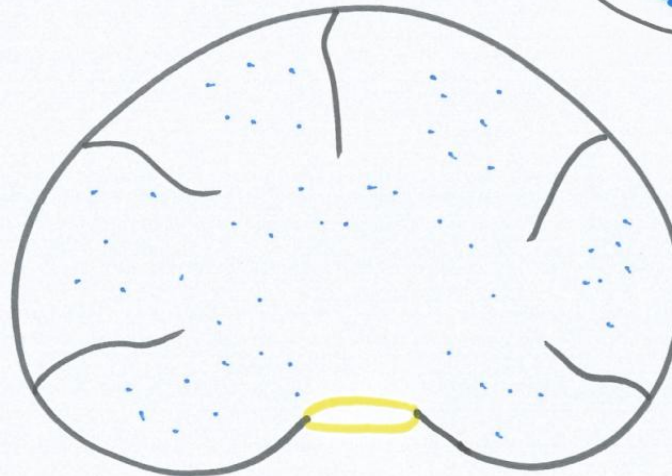
Which contains more lymphocytes: afferent or efferent lymph? Why?



High endothelial venules (HEVs) are specialized postcapillary venules lined by cuboidal endothelial cells. Their endothelial cells express adhesion molecules (addressins) and chemokines that facilitate the homing, adhesion, and extravasation of circulating lymphocytes through the vessel wall into the lymph node.



Try to describe these
histological sections and the
clinical picture a patient would
have in each case



Lymphatic trunks and ducts

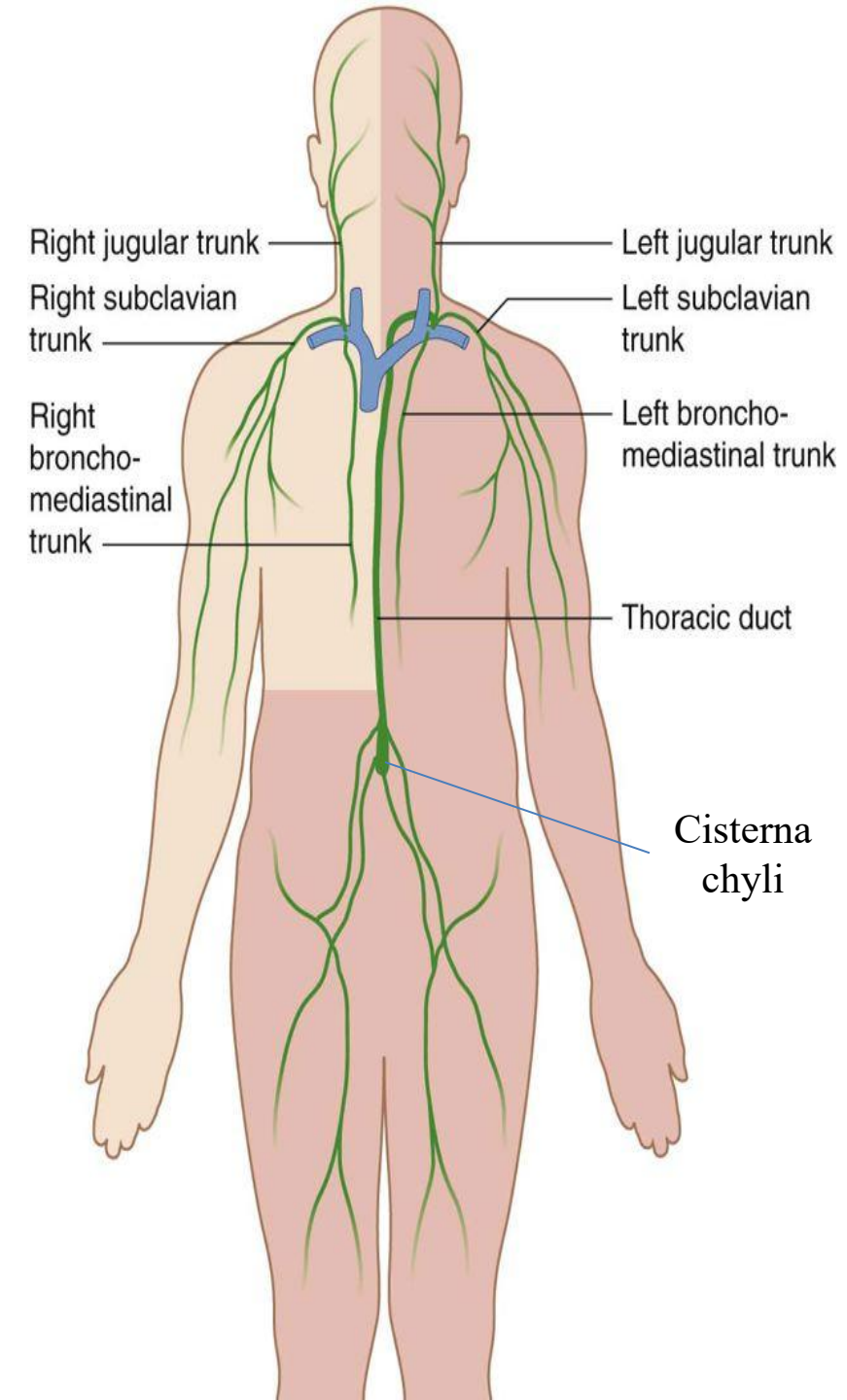
All lymphatic vessels coalesce to form larger trunks which eventually converge to form the right lymphatic duct and the thoracic duct

Right lymphatic duct

- ✓ Is formed by right jugular and right subclavian trunks
- ✓ Drains lymph from the upper right quadrant of the body (the right side of the head and neck, the right side of the thorax and the right upper limb)
- ✓ Empties into the junction where right internal jugular vein joins the right subclavian vein (**Rt venous angle**)

Thoracic duct (Left lymphatic duct)

- ✓ Is larger and drains lymph from the rest of the body.
- ✓ Originates in the abdomen as cisterna chyli
 - Cisterna chyli is a dilated sac at the lower end of the thoracic duct (anterior to the bodies of L1 and L2) formed by confluence of the right and left lumbar trunks and the intestinal trunk*
- ✓ Passes through the diaphragm at the aortic aperture
- ✓ Empties into the junction where left internal jugular vein joins the left subclavian vein (**Lt venous angle**)



Spleen

- ✓ The spleen is an oval-shaped **intraperitoneal** organ
- ✓ Approximately
 - 5** inches in height (12-13 cm)
 - 3** inches in width (7-8 cm)
 - 1** inch in thickness (2.5 cm)
- Weights **7** ounces (200gm)
- Lies under ribs **9** to **11**
- ✓ Has a notched anterior border.

The spleen is the organ
of odds number
1, 3, 5, 7, 9, and 11

Functions of the spleen

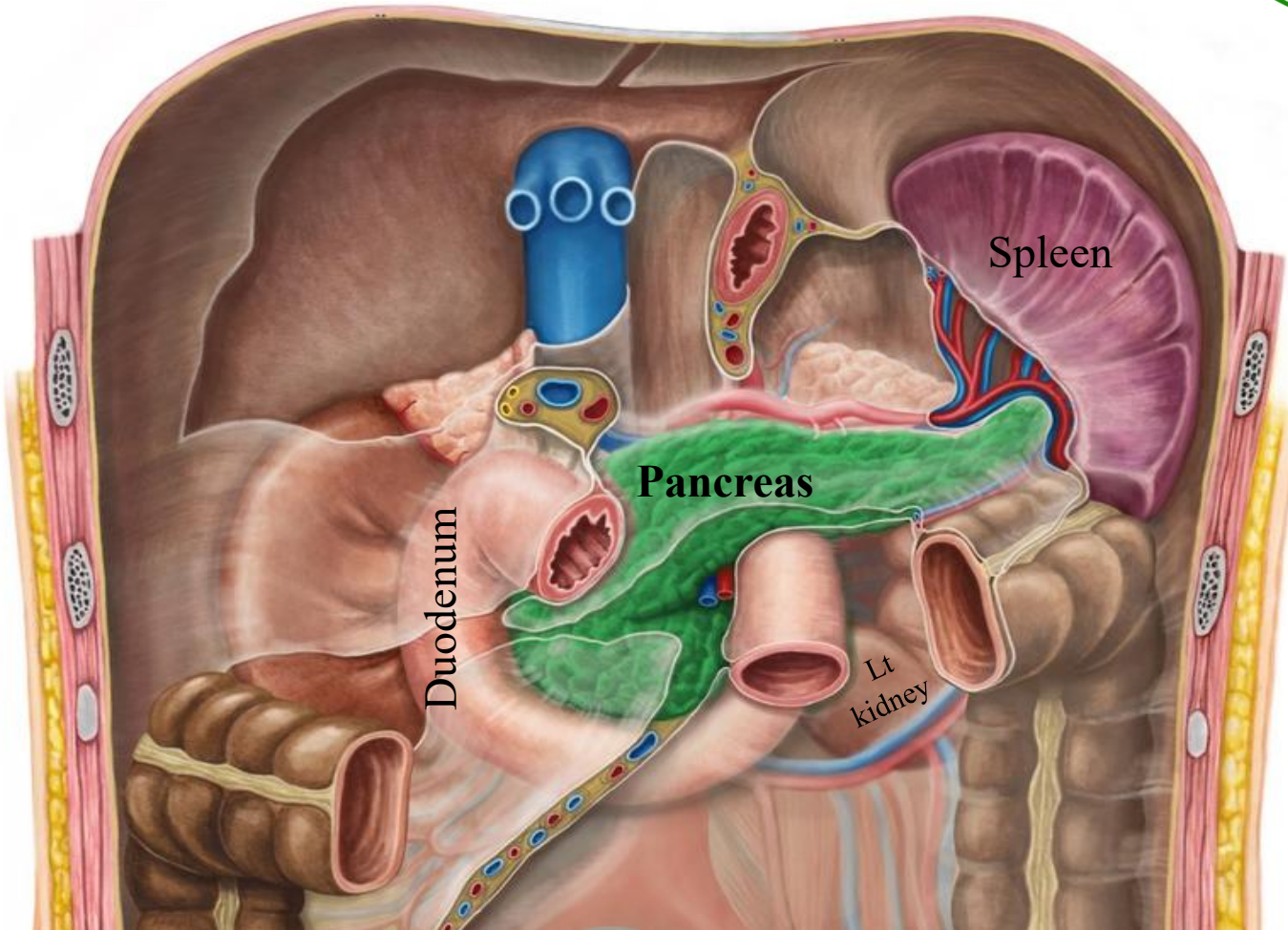
Filtration of blood: removes blood-borne microorganisms, foreign antigens, cellular debris, and abnormal or damaged blood cells, contributing to immune defense against blood-borne antigens.

Removal of aged or damaged erythrocytes: splenic macrophages recognize and phagocytose senescent or abnormal RBCs.

Immune responses: the spleen is an important site for activation and proliferation of lymphocytes in response to blood-borne antigens and for antibody production by plasma cells. Activated lymphocytes and antibodies enter the blood circulation.

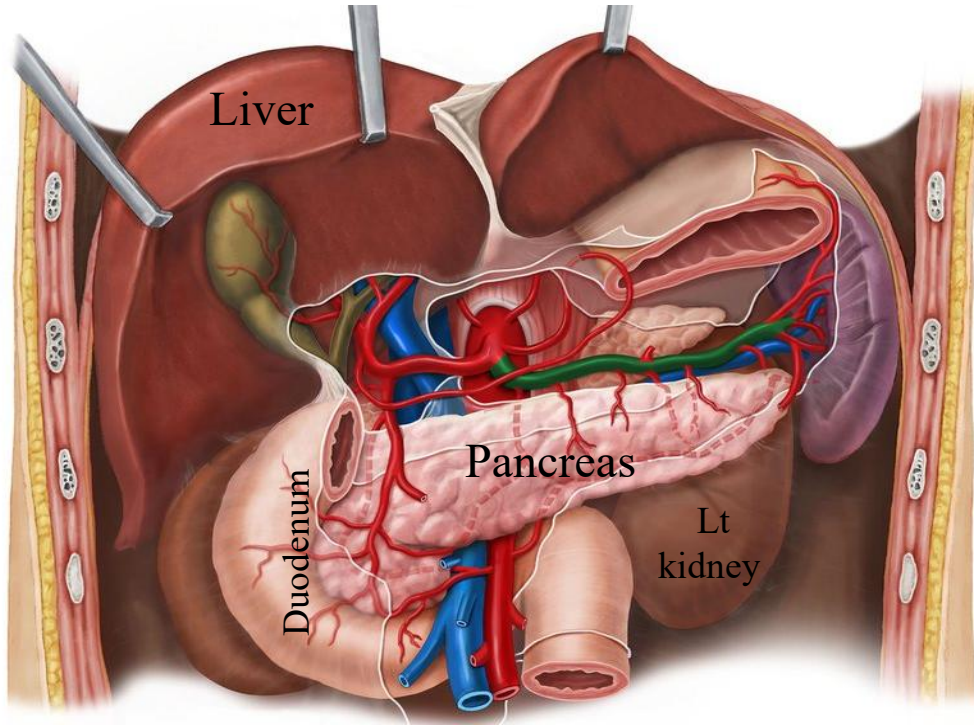
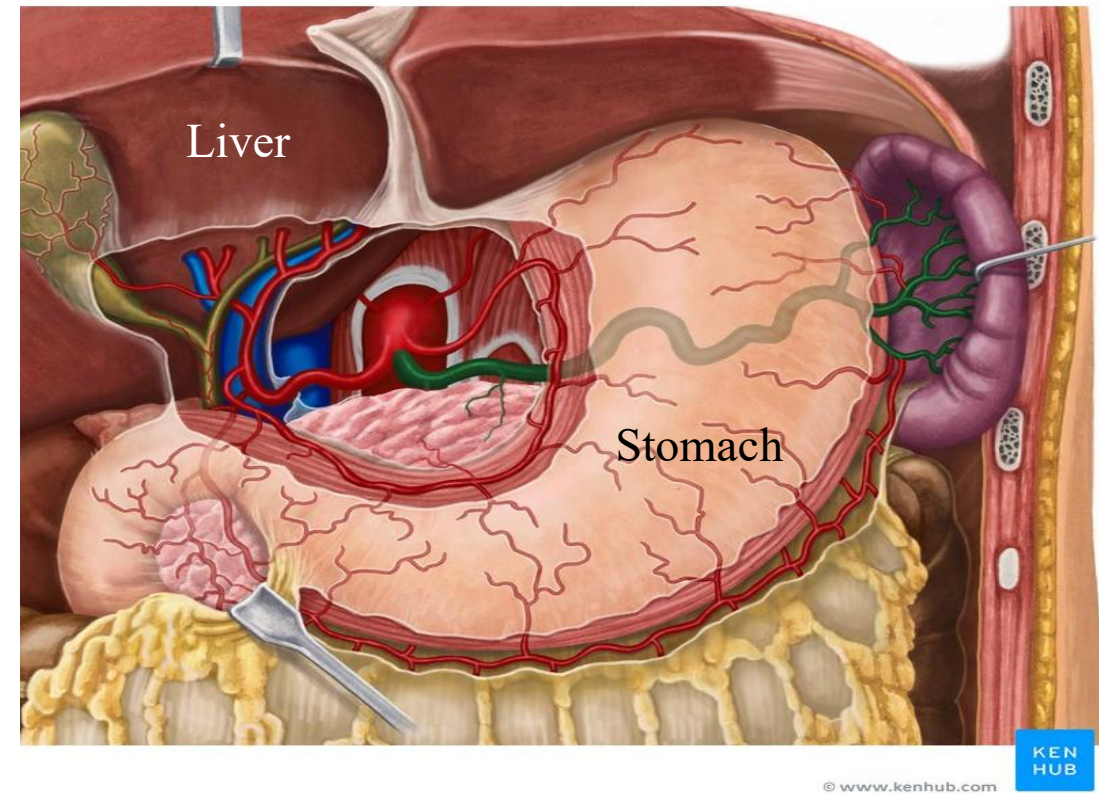
- ✓ It lies high on the upper left portion of the abdomen, just beneath the diaphragm, behind the stomach and above the left kidney.
- ✓ It is the largest of the lymphoid organs

The spleen resembles a large lymph node
The spleen filters the blood while lymph nodes filter the lymph



The **splenic artery** is the largest branch of the celiac artery. It has a tortuous course as it runs along the upper border of the pancreas. The splenic artery then divides into about six branches, which enter the spleen at the hilum

The **splenic artery** supplies the spleen as well as large parts of the stomach and pancreas



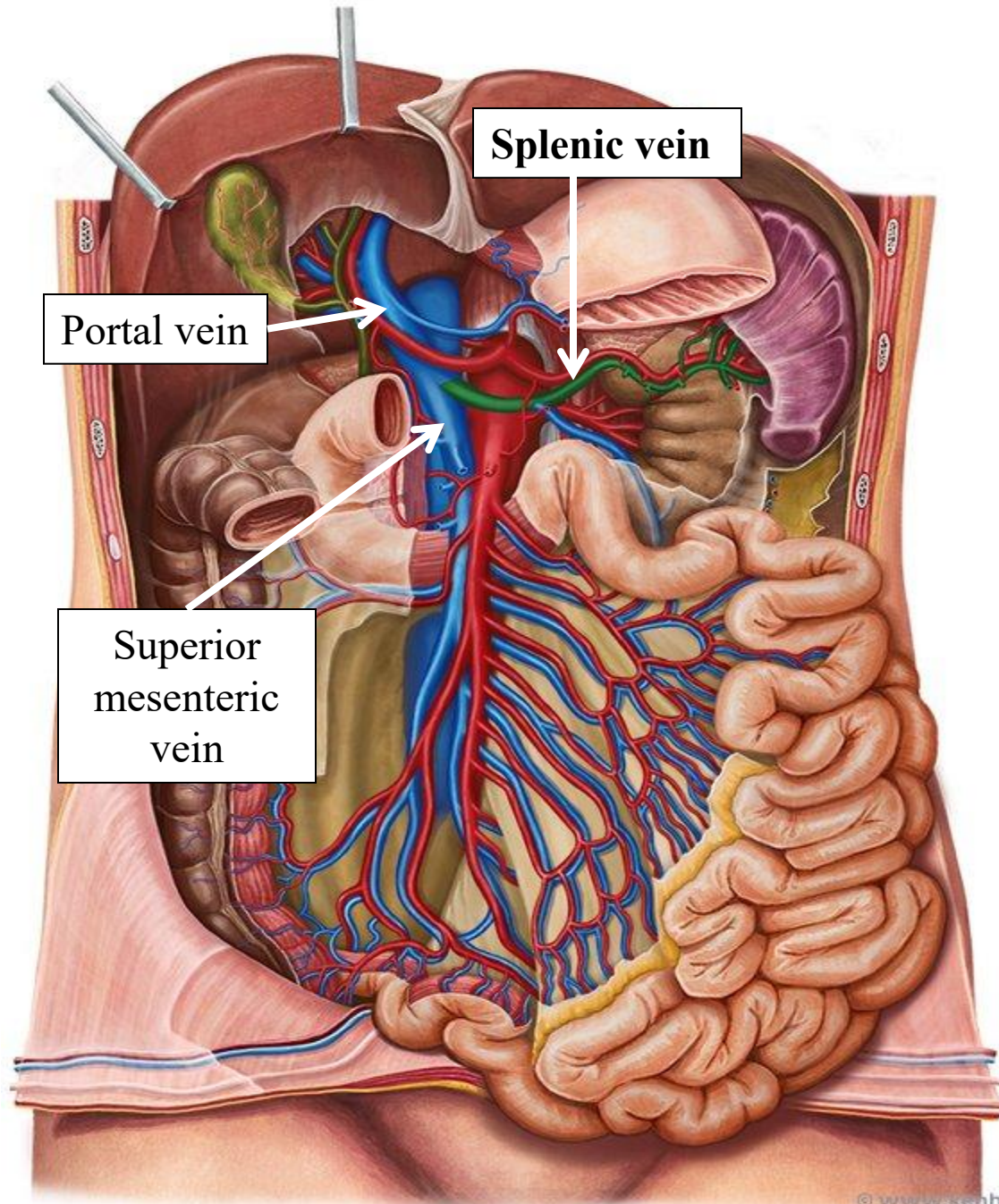
Abdominal Aorta



Celiac Trunk



Splenic artery



The **splenic vein** leaves the hilum and runs behind the tail and the body of the pancreas. Behind the neck of the pancreas, the splenic vein joins the superior mesenteric vein to form the portal vein

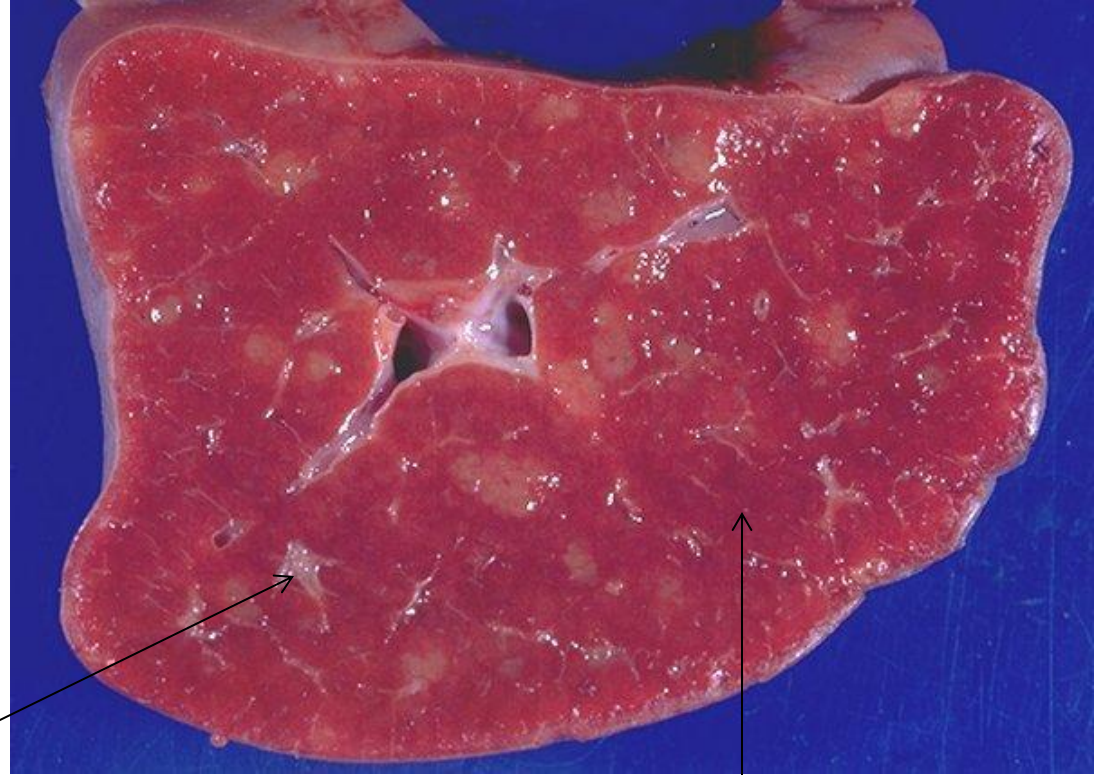


In cases of portal hypertension, spleen often enlarges from venous congestion.

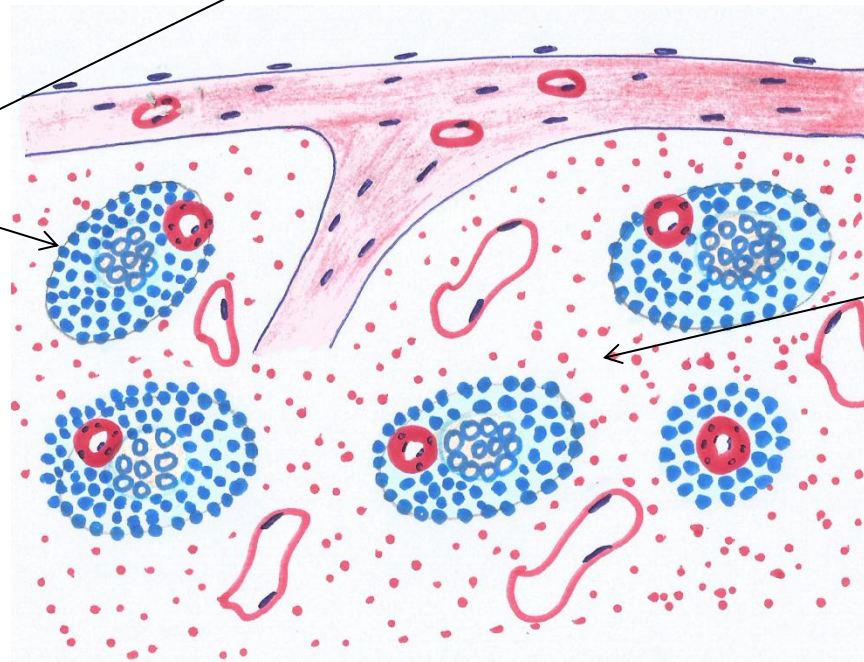
The parenchyma of the spleen appears in fresh specimen as:

White pulp which appears white on gross examination (collection of both B and T lymphocytes)

Red pulp which appears red on gross examination (blood filled)



White pulp



Red pulp

The spleen is covered by a **capsule** of dense connective tissue, and have capsular extensions called the **trabeculae**. Large trabeculae originate at the hilum, on the medial surface of the spleen, and carry branches of the splenic artery, vein, lymphatics, and nerves into the spleen.

The spleen is composed of parenchyma and stroma:

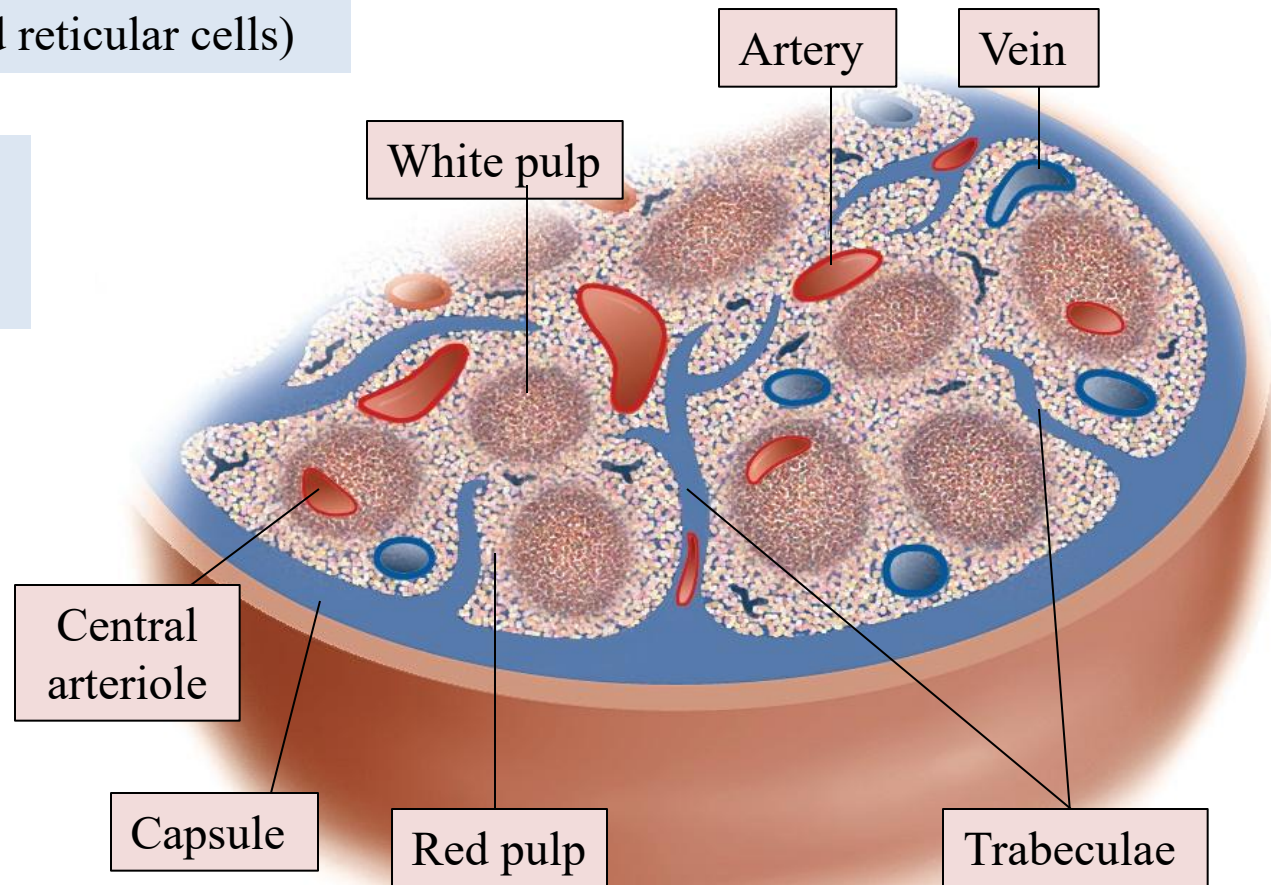
Parenchyma: Splenic pulps

Stroma: Reticular tissue (reticular fibers and reticular cells)

There are two types of pulp in the spleen:

Red pulp (rich in blood)

White pulp (lymphatic tissue)



Unlike lymph nodes, the spleen:

- 1- Has no afferent lymphatics
- 2- Has no lymphatic sinus system
- 3- Its lymphoid tissue is not arranged into cortex and medulla

Splenic artery

Divides into trabecular arteries as it enters the hilum

Trabecular arteries

Follow the course of trabeculae

Central arterioles

Are branches of trabecular arteries entering the white pulp. They are surrounded by a sheath of lymphocytes.

Penicillar arterioles

Each central arteriole eventually leaves the white pulp and enters the red pulp, losing its sheath of lymphocytes and branching as several short straight penicillar arterioles that continue as terminal capillaries.

Terminal capillaries

Some of these terminal capillaries are sheathed with APCs for additional immune surveillance of blood

Blood flow through the splenic red pulp can take either of two routes:

→ **Open circulation:** the capillaries open into the spaces of the red pulp (splenic cords) and then the blood returns to the venous system through the wall of the splenic sinusoids

→ **Closed circulation:** the capillaries open directly into the splenic sinusoids (blood is enclosed by endothelium)



The morphology is like penicillus

Splenic sinusoids



Trabecular veins



Splenic vein

White pulp (lymphoid tissue)

- ✓ Constituting 25% of the spleen, the white pulp is responsible for the immunological (lymphatic) function of the spleen.
- ✓ The white pulp contains:

Periarteriolar lymphoid sheaths (PALS):

tightly packed T cells arranged in cylindrical sheaths around central arterioles

Lymphoid follicles: spherical aggregations of B cells scattered throughout the PALS

Primary (unstimulated) follicles contain resting (inactive) B cells

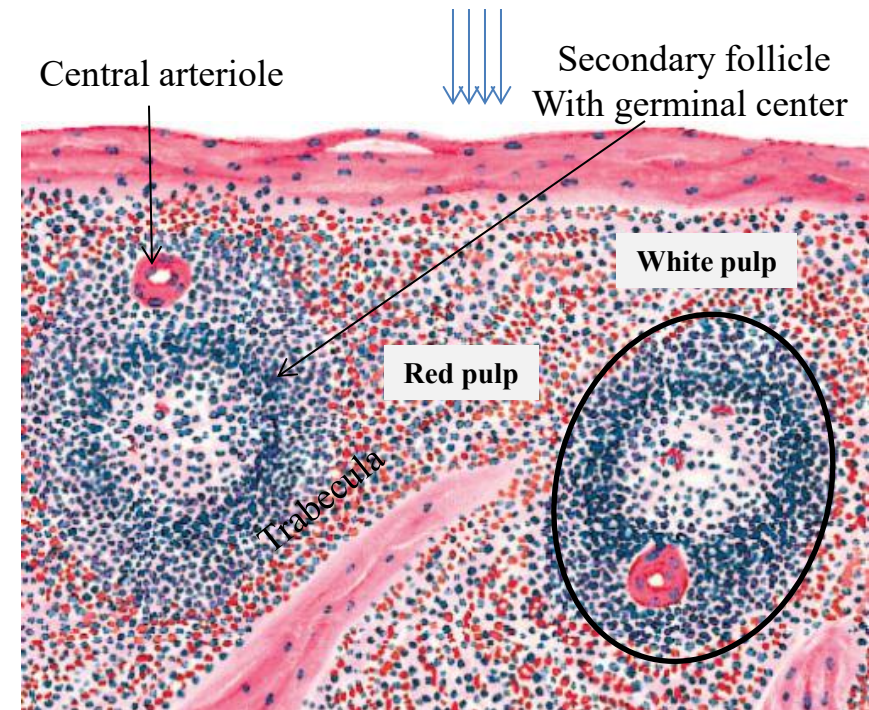
Secondary (stimulated) follicles contain activated B cells in a central region (germinal center)

Splenic nodules (Malpighian corpuscles)

Note: These follicles have the same structural organization as those found in lymph nodes. However, splenic follicles are associated with the central arteriole and are surrounded by an additional marginal zone.

Function: The lymphocytes and APCs monitor the blood for foreign antigens and respond in a similar way to those in the lymph nodes.

When the lymphatic sheath expands to incorporate the follicles, the central arteriole is displaced to one side and acquires an eccentric position in the follicle but is still called the central arteriole (Follicular arteriole).



Production of antibodies and activated lymphocytes (which are delivered directly into the blood)

↓↓ Red pulp

Red pulp (blood filled)

✓ Constituting 75% of the spleen, the red pulp is responsible for the hematological (circulatory) function of the spleen.

✓ The red pulp contains :

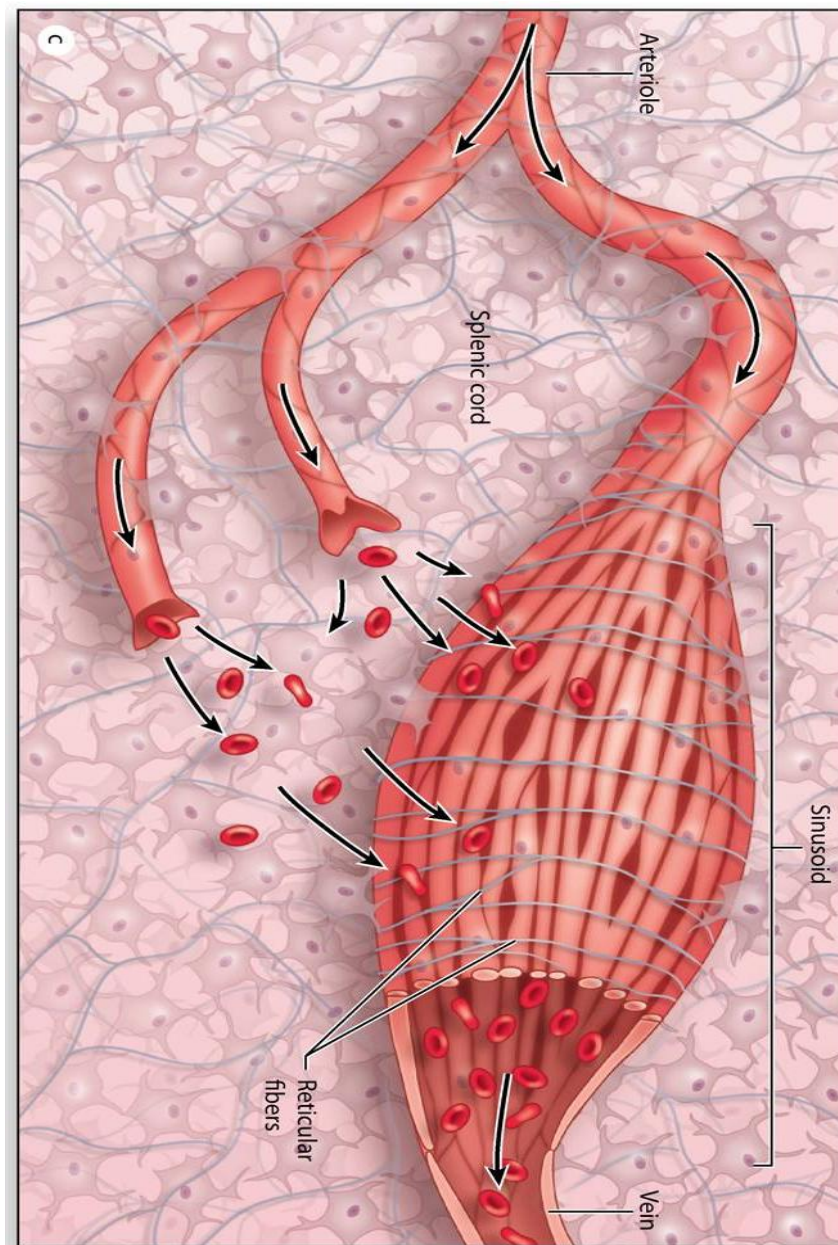
Splenic cords (Billroth's cords): consist of all cells between the sinusoids in the red pulp (reticular cells, macrophages, plasma cells, lymphocytes, RBCs, platelets, other leukocytes)

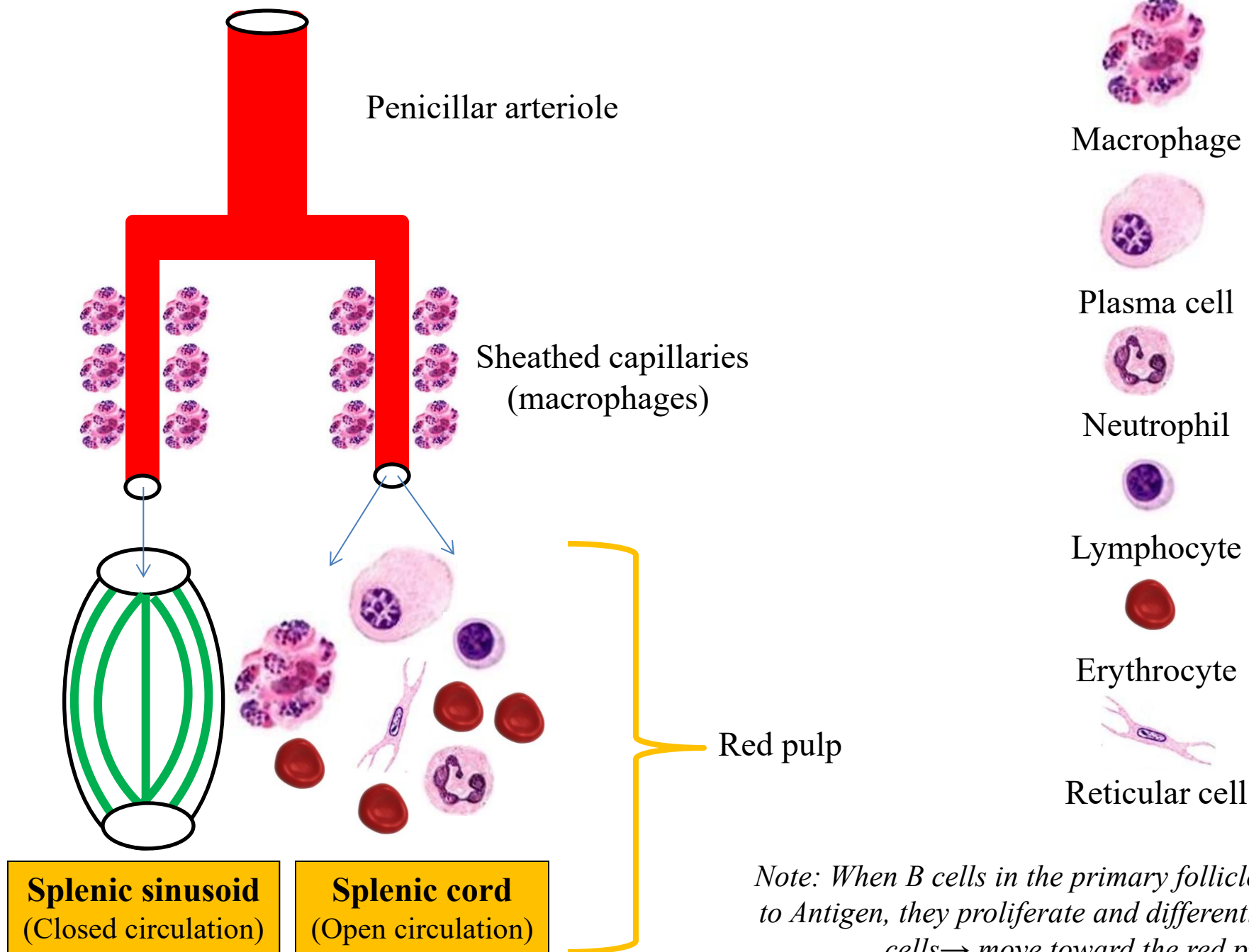
Splenic sinusoids: are blood- filled spaces located throughout the red pulp. They have large, dilated, irregular lumens and large pores (spaces between the endothelial cells)



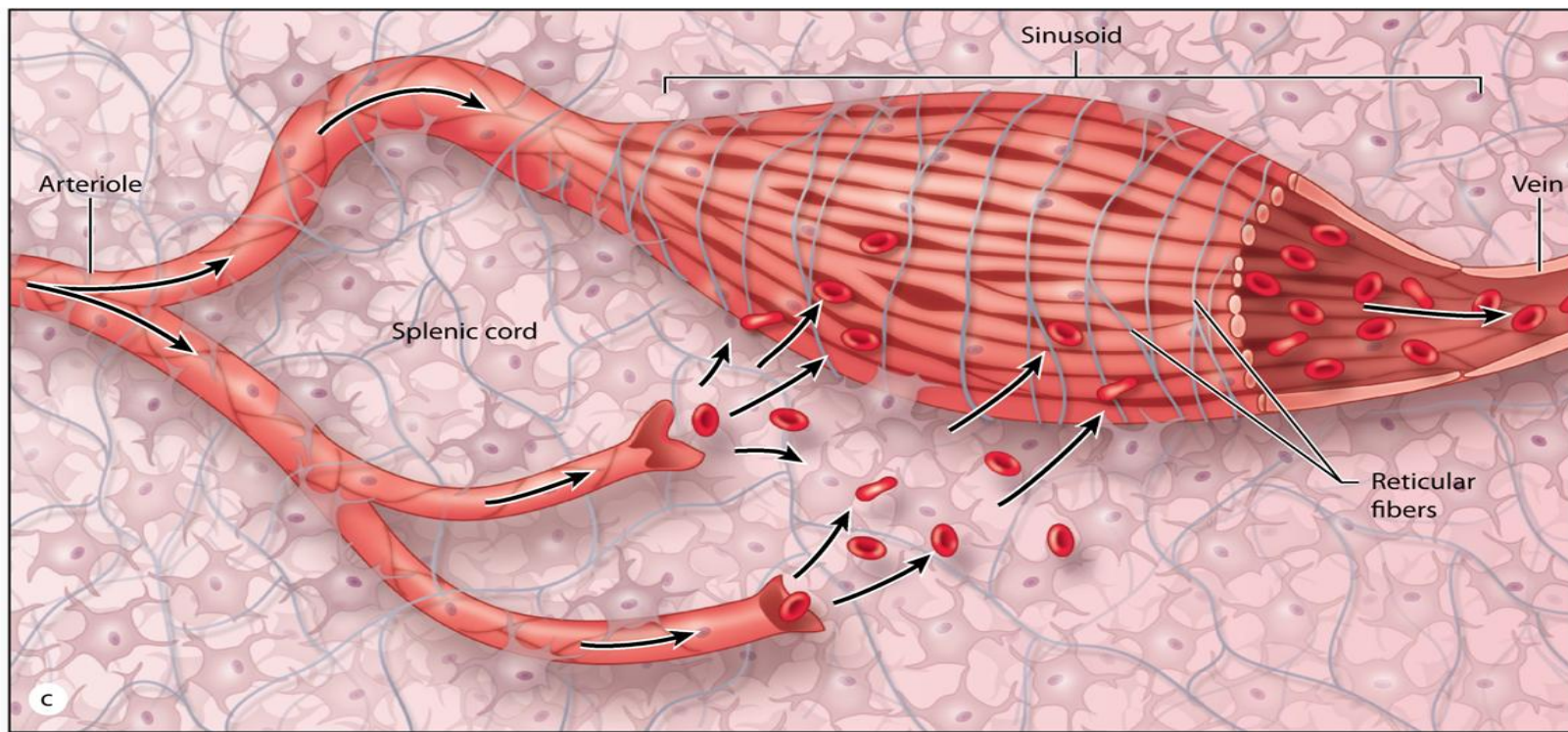
1. The endothelial cells (**stave cells**) are elongated, fusiform cells that lie parallel to the long axis of the vessel
2. The cells lie side by side around the vessel but not joined by any type of intercellular junctions
3. The endothelial cells are supported by highly discontinuous basal lamina (forms bars and encircles the sinusoid)

Function: Destruction of worn-out RBCs and platelets





Note: When B cells in the primary follicles are exposed to Antigen, they proliferate and differentiate to plasma cells → move toward the red pulp.

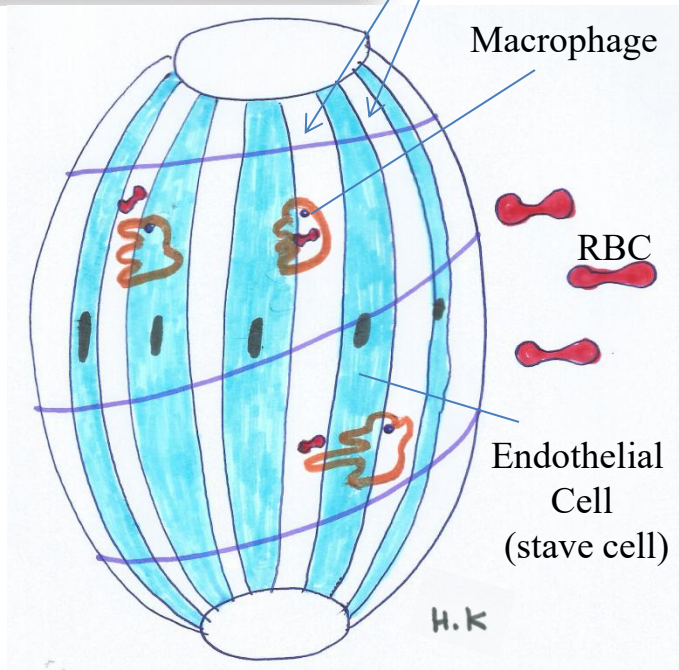


Note the wide gaps between endothelial cells which allow for movement of entire cells from cords to sinuses

In this route plasma and all the formed elements of blood must reenter the vasculature by passing through narrow slits between the stave cells into the sinusoids. These small openings present no obstacle to platelets, to the motile leukocytes, or to thin flexible erythrocytes. However stiff or swollen RBCs at their normal life span of 120 days are blocked from passing between the stave cells and undergo selective removal by macrophages



Deformed or less pliable RBCs cannot squeeze effectively from the cord into the sinus and upon their mechanical fragmentation are removed by resident macrophages (lie just next to the sinusoids)



Macrophages monitor erythrocytes as they migrate from splenic cords between the endothelial cells into the splenic sinusoids

Aging RBCs lose deformability and undergo membrane alterations.



Less deformable RBCs become trapped in the splenic cords.



Splenic macrophages recognize and phagocytose these RBCs.
Hemoglobin is degraded into heme and globin.

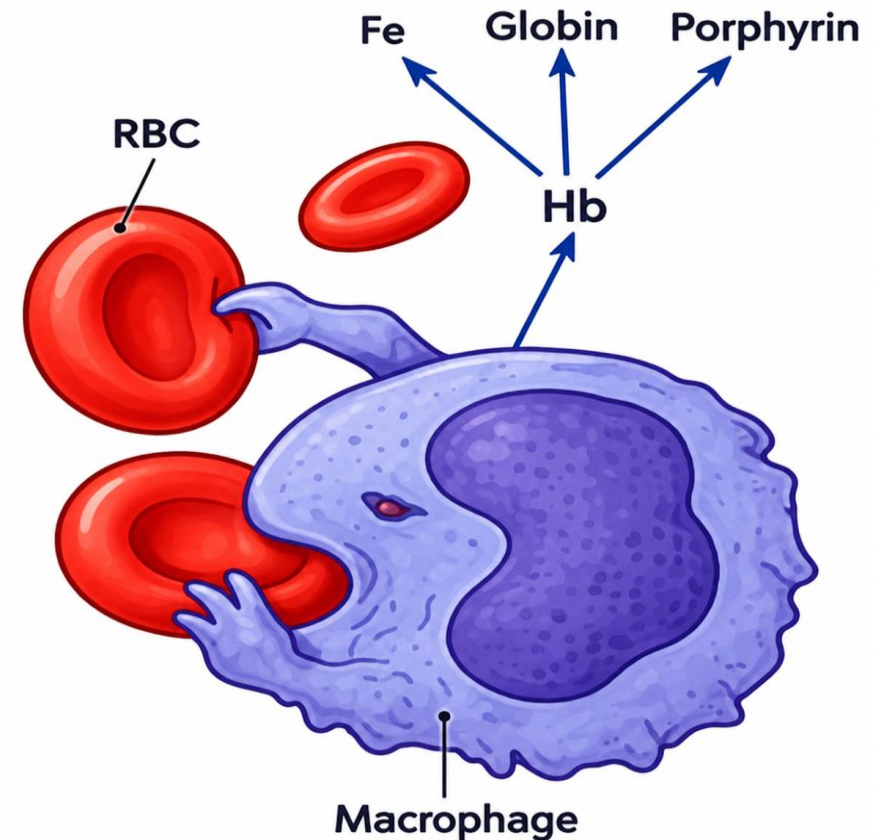


Globin is broken down into reusable **amino acids**.
Heme is degraded, releasing **iron** and producing **biliverdin**, which is converted into **bilirubin**.

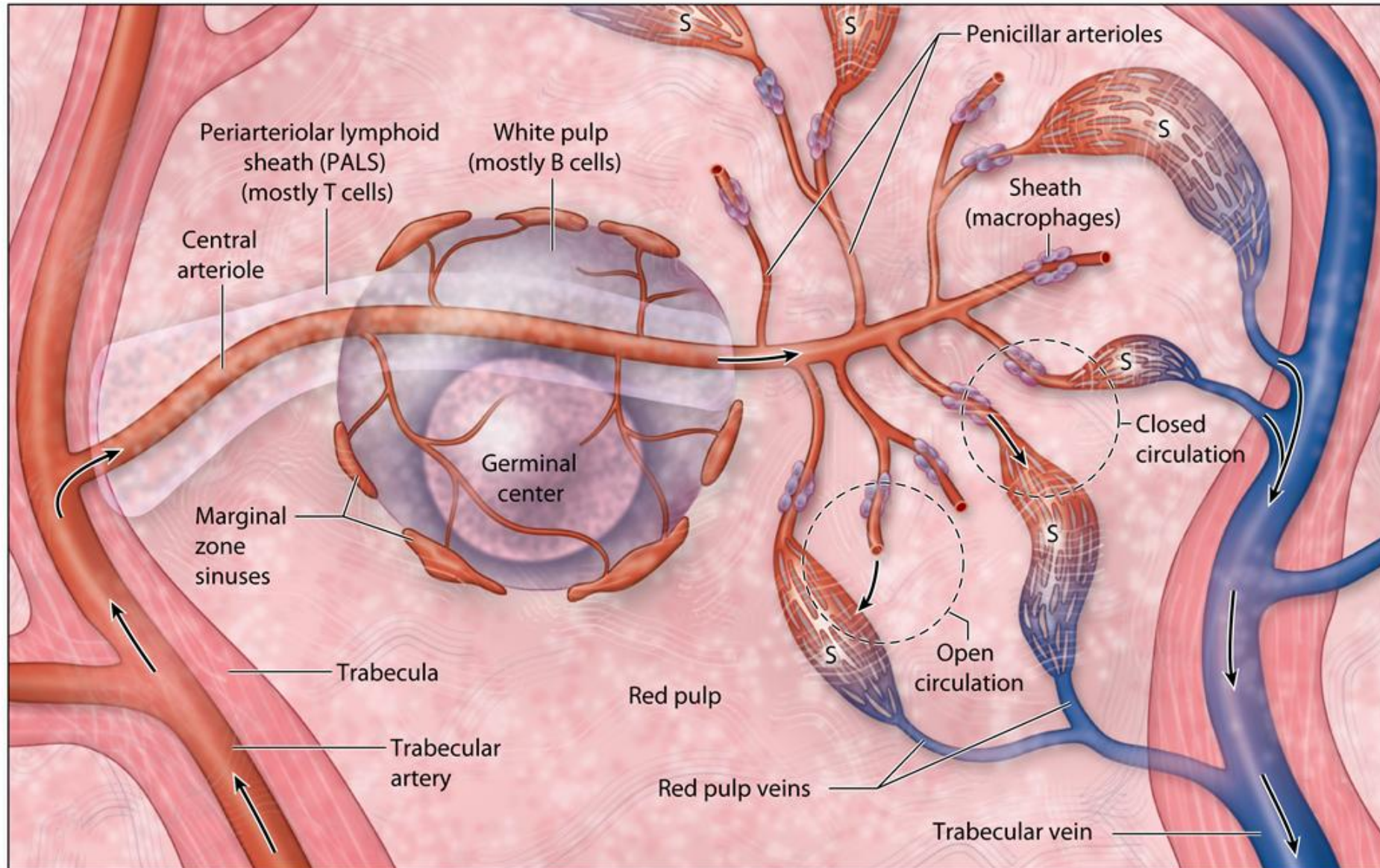
Iron: carried by transferrin to bone marrow for hemoglobin synthesis or stored as ferritin

Bilirubin: excreted by liver bile

After surgical removal of the spleen (splenectomy), the number of abnormal erythrocytes in the circulation increases although most such cells are then removed by macrophages in sinusoids of the bone marrow and liver.



Schematic view of the blood circulation and the structure of the spleen, from the trabecular artery to the trabecular vein.

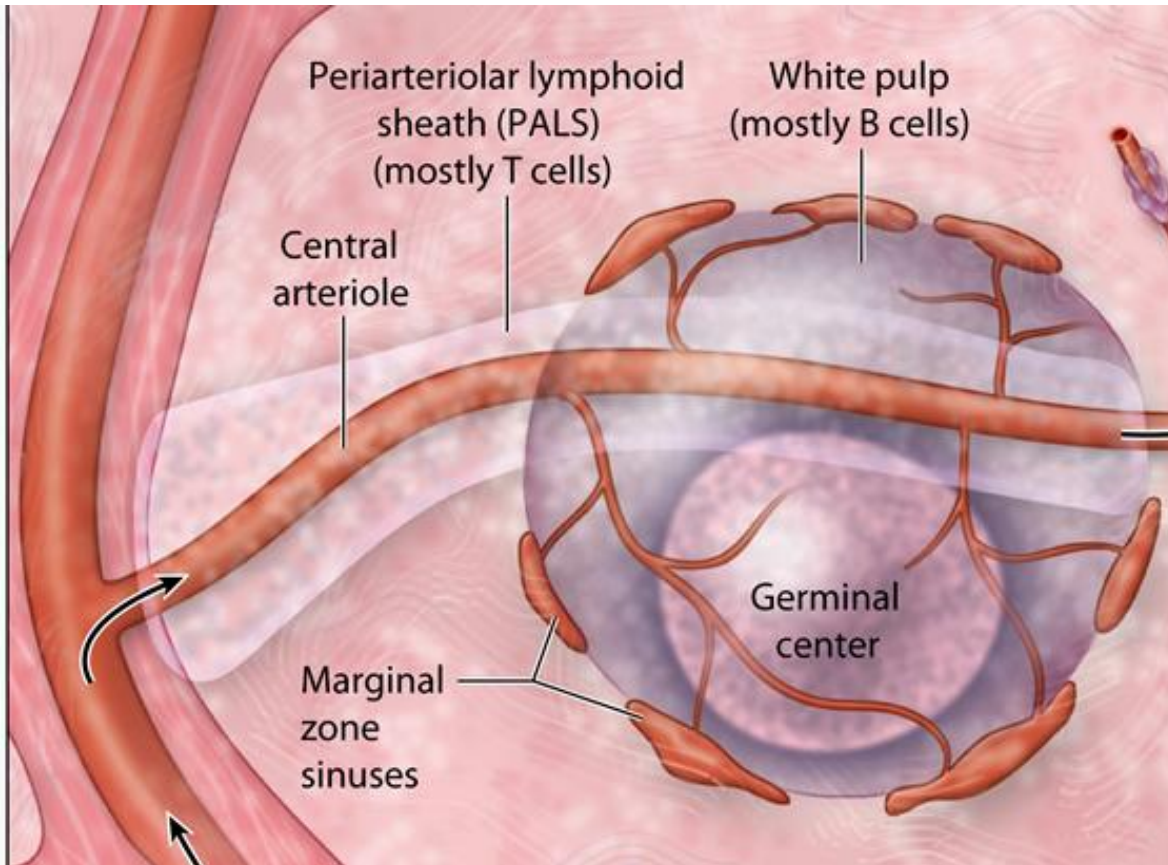


Marginal zone sinuses

- ✓ Located between the white and the red pulp
- ✓ The spaces between these sinuses are wide (2-3µm)



It is here the blood-borne antigens and particulate matter have their first free access to the parenchyma of the spleen



The following events occur at the marginal zone:

- 1- APCs sample the material travelling in blood searching for antigens
- 2- Macrophages engulf and destroy blood-borne microorganisms.

Lymphocytes come into contact with APCs, if they recognize their Ag-MHC complex, the lymphocytes initiate immune response within the white pulp

- 3- The circulating B and T cells leave the blood stream to enter the preferred location within the white pulp

T cells: PALS

B cells: lymphoid follicles

To summarize

Functions of the spleen

The spleen has both hematological and immune functions.

Blood cell production:

During fetal life, the spleen functions as a site of hematopoiesis. In healthy adults, hematopoiesis normally occurs in the bone marrow, although extramedullary hematopoiesis may occur in the spleen under certain pathological conditions.

Blood storage:

A small volume of blood is contained within the red pulp. The human spleen can therefore serve as a limited blood reservoir, although this function is much less significant in humans than in some other mammals.

Removal of aged and damaged RBCs:

The spleen is a major site for the removal of aged, damaged, or abnormal erythrocytes. These cells are trapped and phagocytosed by macrophages of the red pulp. The liver and bone marrow also contribute to RBC removal.

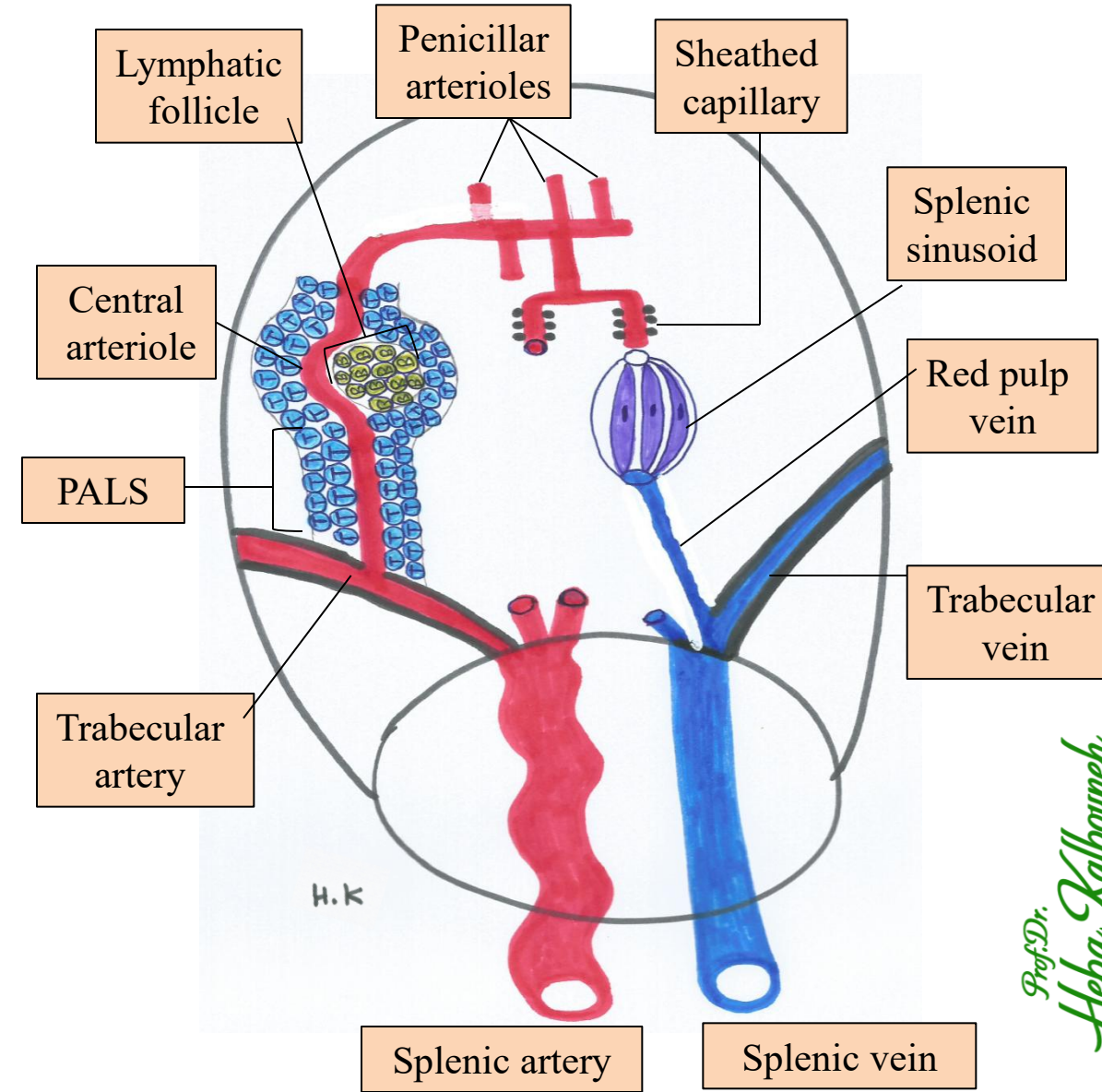
Immune defense:

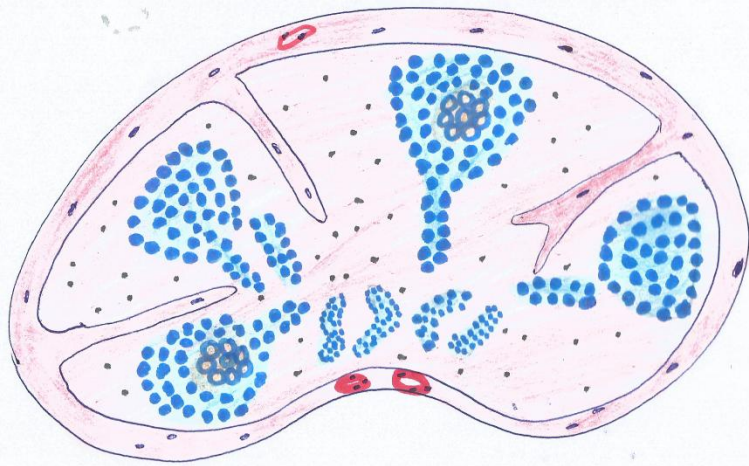
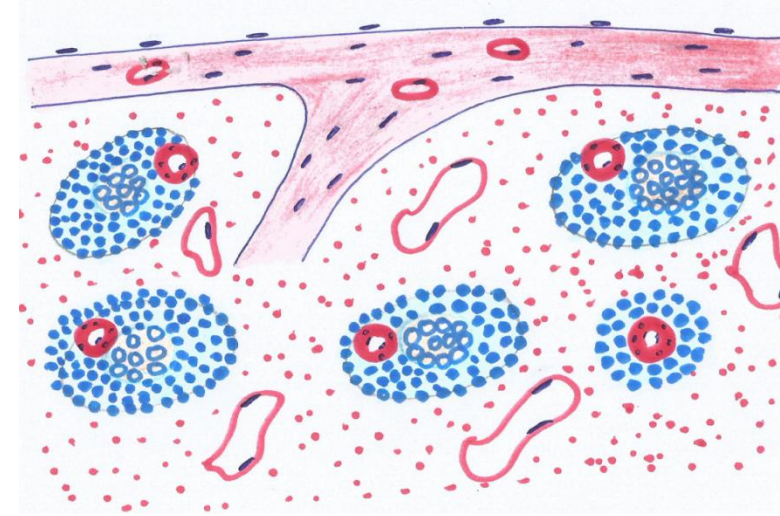
Splenic macrophages remove microorganisms and particulate material from the blood. Blood-borne antigens also activate B and T lymphocytes in the white pulp, initiating immune responses, including the formation of antibody-producing plasma cells and effector T lymphocytes.



- Effector B cells = Plasma cells (antibody secretion).
- Effector T cells = Activated T lymphocytes that perform immune functions, such as cytotoxic killing or cytokine secretion.

The blood flow in the spleen goes from splenic artery to trabecular artery to central arteriole, and upon leaving the white pulp, the blood flows through penicillar arterioles and terminal capillaries to the splenic sinusoids, and back to veins of the pulp, trabecular veins and the splenic vein





Lymph node	Spleen
Multiple, small	Single, large
Along the course of lymphatic vessels	Intra-abdominal
Filters lymph	Filters blood
Covered by fascia	Covered by peritoneum
Has afferent vessels	No afferent vessels
Cortex and medulla	White pulp and red pulp
Contains Lymphatic sinuses	Contains Blood sinuses

Mucosa-Associated Lymphoid Tissue (MALT)

✓ MALT consists of *unencapsulated* lymphoid tissue located in the mucosa (and submucosa), particularly at sites exposed to antigens from the external environment.

✓ MALT may occur as:

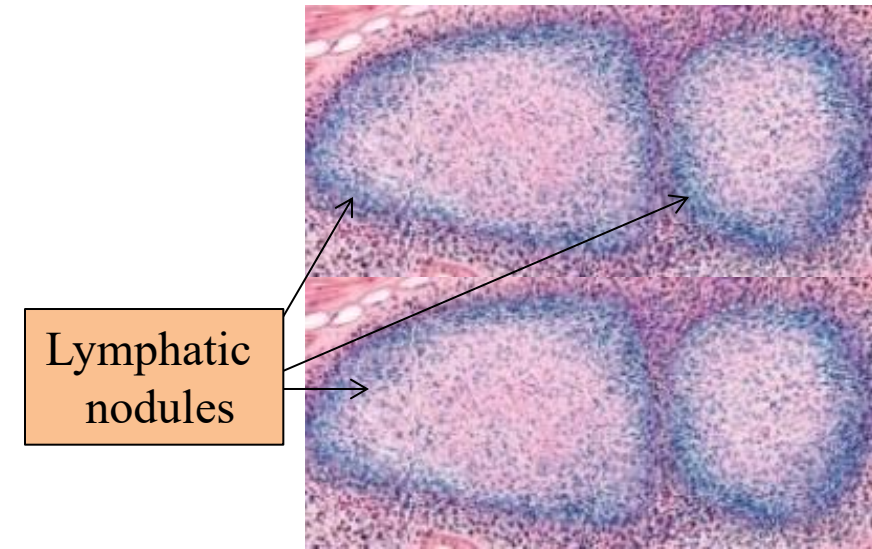
Diffuse lymphoid tissue — scattered lymphocytes and other immune cells without a distinct boundary.

Lymphoid nodules (follicles) — localized, more densely organized aggregates of lymphocytes.

The mucosa or inner lining of the digestive, respiratory, and genitourinary tracts is a common site of invasion by pathogens because their lumens open to the external environment.

✓ MALT includes:

1. Palatine tonsils
2. Lingual tonsils
3. Pharyngeal tonsil
4. Gut-associated lymphoid tissue (GALT) — including Peyer's patches and lymphoid tissue of the appendix
5. Bronchus-associated lymphoid tissue (BALT)



MALT is populated by:

T cells

B cells

Plasma cells

APCs

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Each of which is well situated to encounter antigens passing through the mucosal epithelium



Because lymphocytes have prominent basophilic nuclei and very little cytoplasm, lymphoid tissue packed with such cells usually stains **dark blue** in H&E stained sections

Tonsils are large, irregular masses of lymphoid tissue

Function of tonsils: Protect the body from inhaled and ingested pathogens.

Palatine tonsils

Are located at the lateral wall of oropharynx, between the glossopalatine and pharyngopalatine arches (two masses)

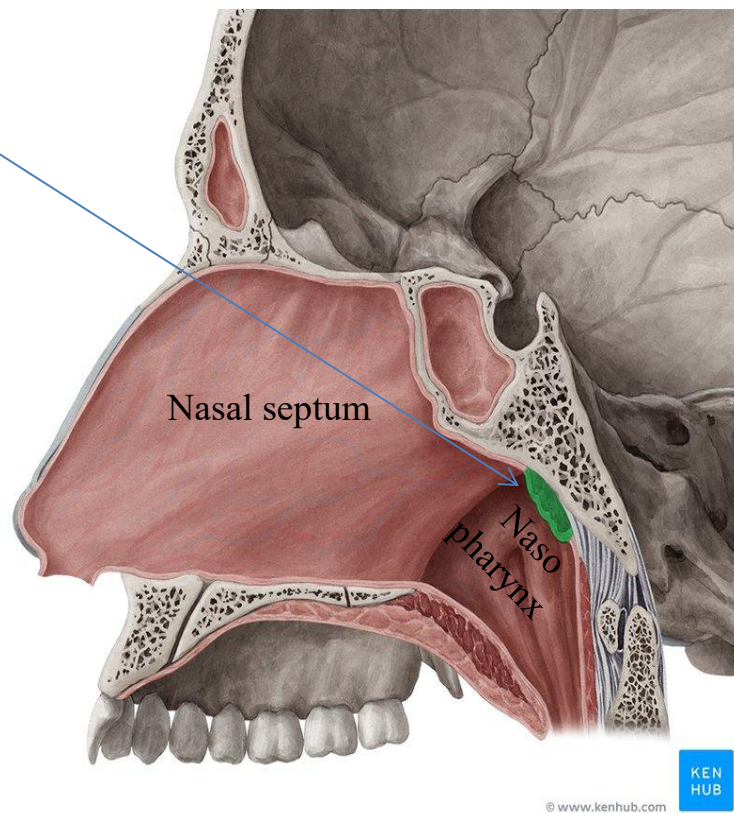
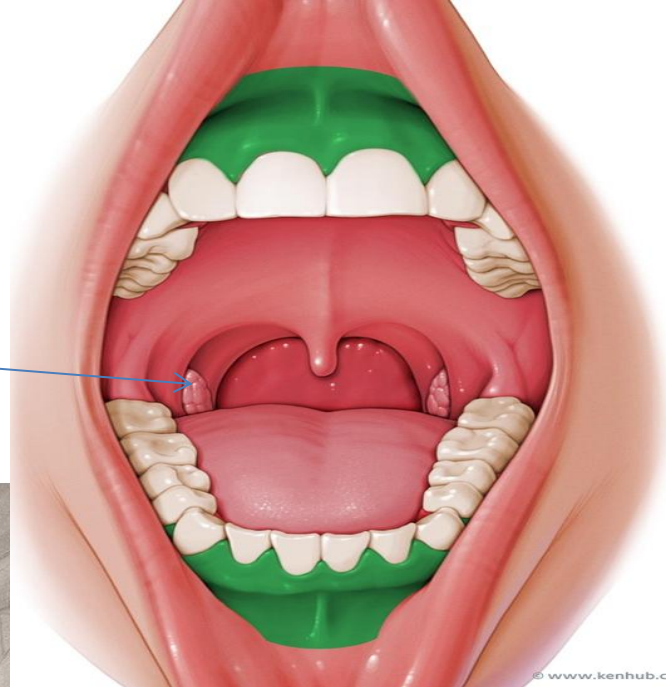
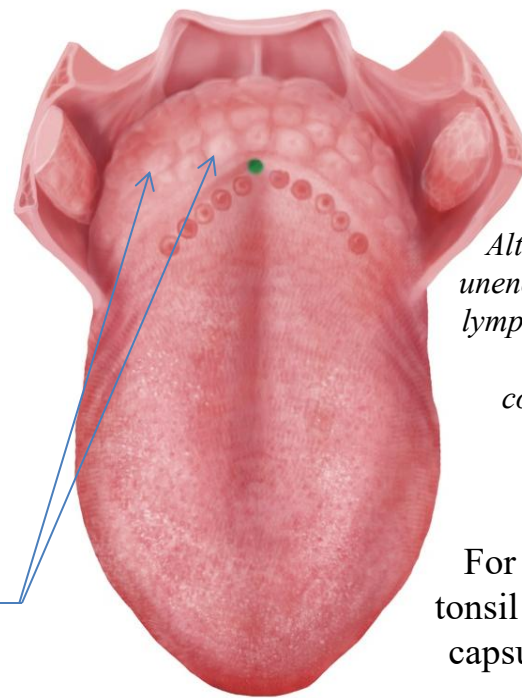
Acute inflammation of these tonsils causes tonsillitis.

Pharyngeal tonsils

Are located in the posterior wall of the nasopharynx.

It is most prominent in children, but begins to atrophy from the age of seven.

*Hypertrophied regions of pharyngeal tonsils resulting from chronic inflammation are called **adenoids**.*



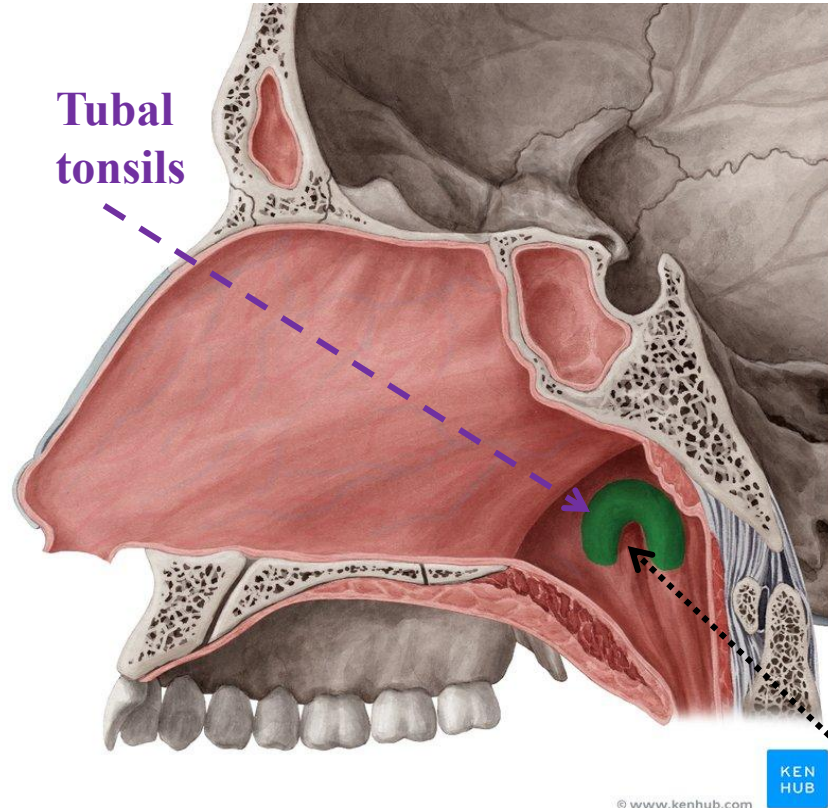
Although MALT is generally unencapsulated, some organized lymphoid structures, such as the tonsils, have a partial connective tissue capsule.



For example, the palatine tonsil has a connective-tissue capsule on its deep surface.

Lingual tonsils

Are located on the posterior 1/3 of the tongue.



Pharyngeal
tonsils

Nasal septum

Opening for Eustachian tube

Note:
Pharyngeal tonsils are
covered by ciliated
pseudostratified
columnar epithelium
(respiratory epithelium)

Adenoids

Excessive hypertrophy of the lymphoid tissue, usually associated with infection, causes the pharyngeal tonsils to become enlarged; they are then commonly referred to as adenoids. Marked hypertrophy blocks the posterior nasal openings and causes the patient to snore loudly at night and to breathe through the open mouth. The close relationship of the infected lymphoid tissue to the auditory tube may be the cause of recurrent otitis media. Adenoidectomy is the treatment of choice for hypertrophied adenoids with infection.

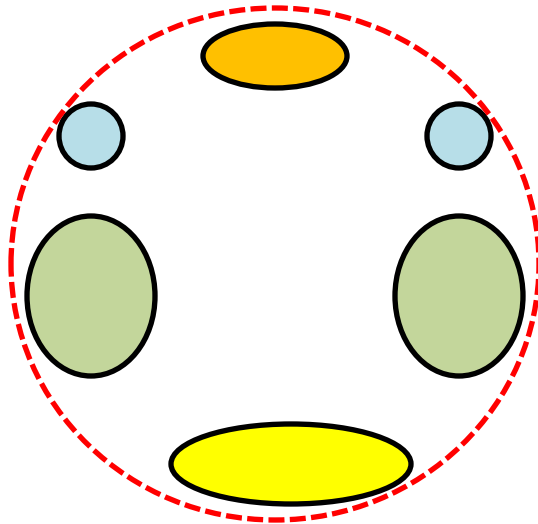
Waldeyer's tonsillar ring

(Waldeyer's lymphatic ring)

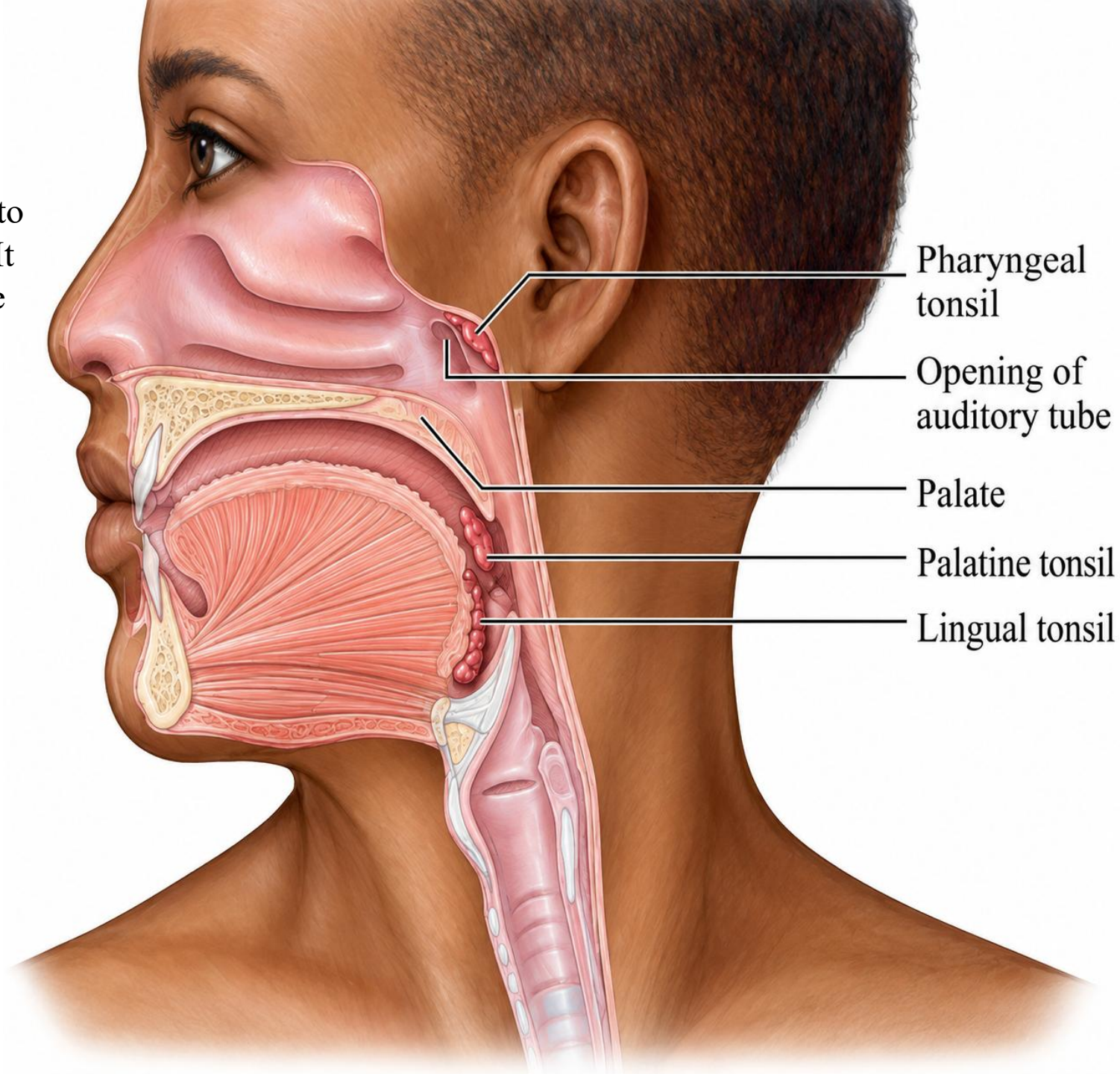
A ring of lymphoid tissue surrounding the entrance to the respiratory and digestive tracts in the pharynx. It forms part of MALT and provides immune defense against inhaled and ingested antigens.



In the nasopharynx, oropharynx, and base of the tongue.



Anterior view



Pharyngeal tonsil

Opening of auditory tube

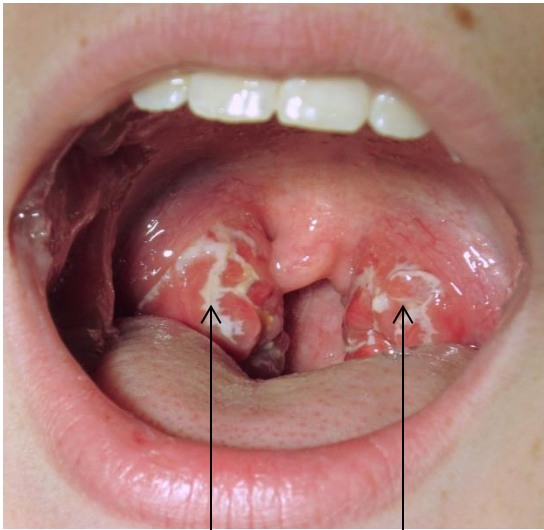
Palate

Palatine tonsil

Lingual tonsil

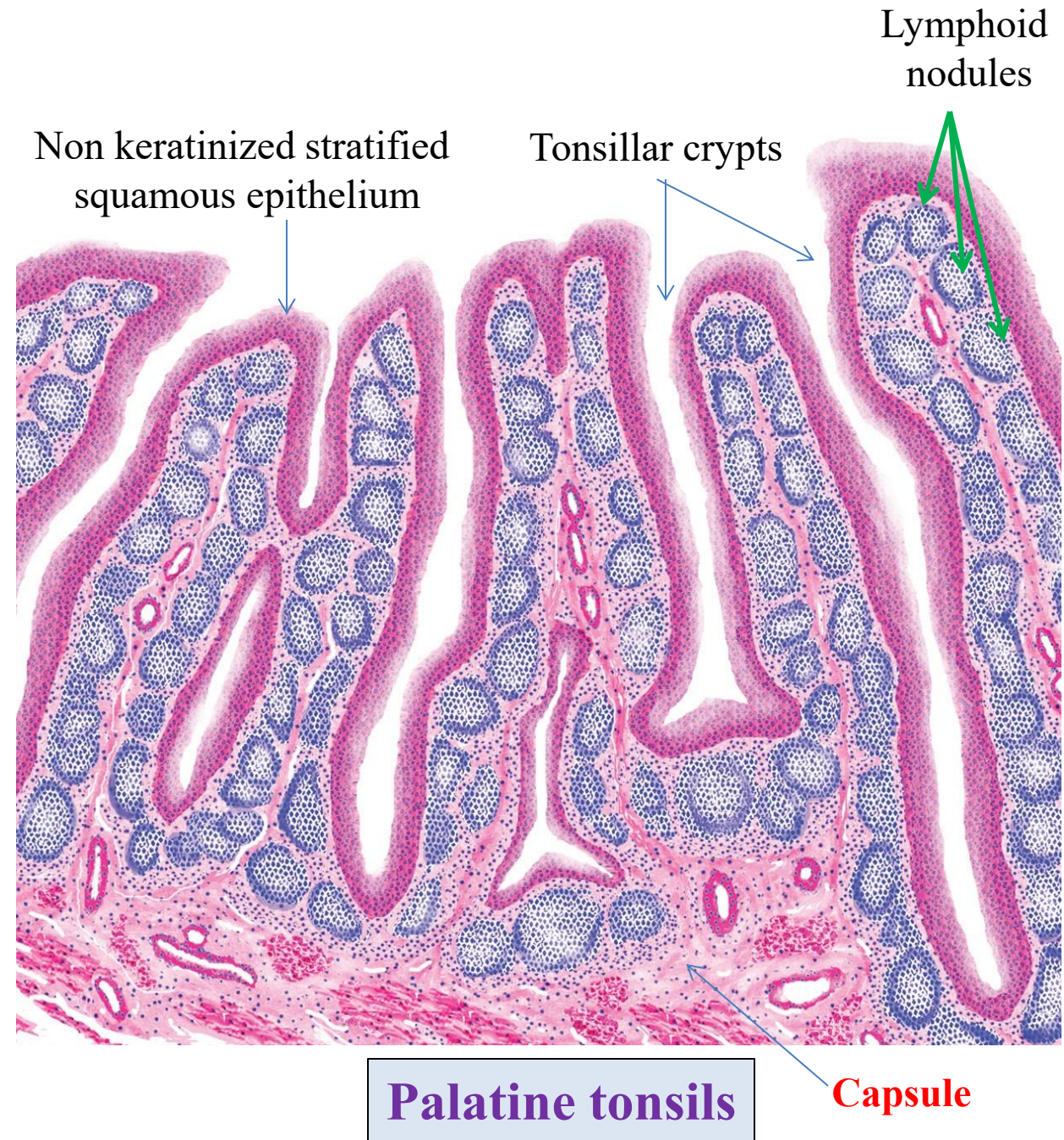
Palatine tonsils

- ✓ Are covered by stratified squamous epithelium.
- ✓ The surface area of each is enlarged with 10-20 tonsillar crypts (deep invaginations)
- ✓ Many lymphoid follicles around the crypts
- ✓ Has an underlying capsule (partial capsule)

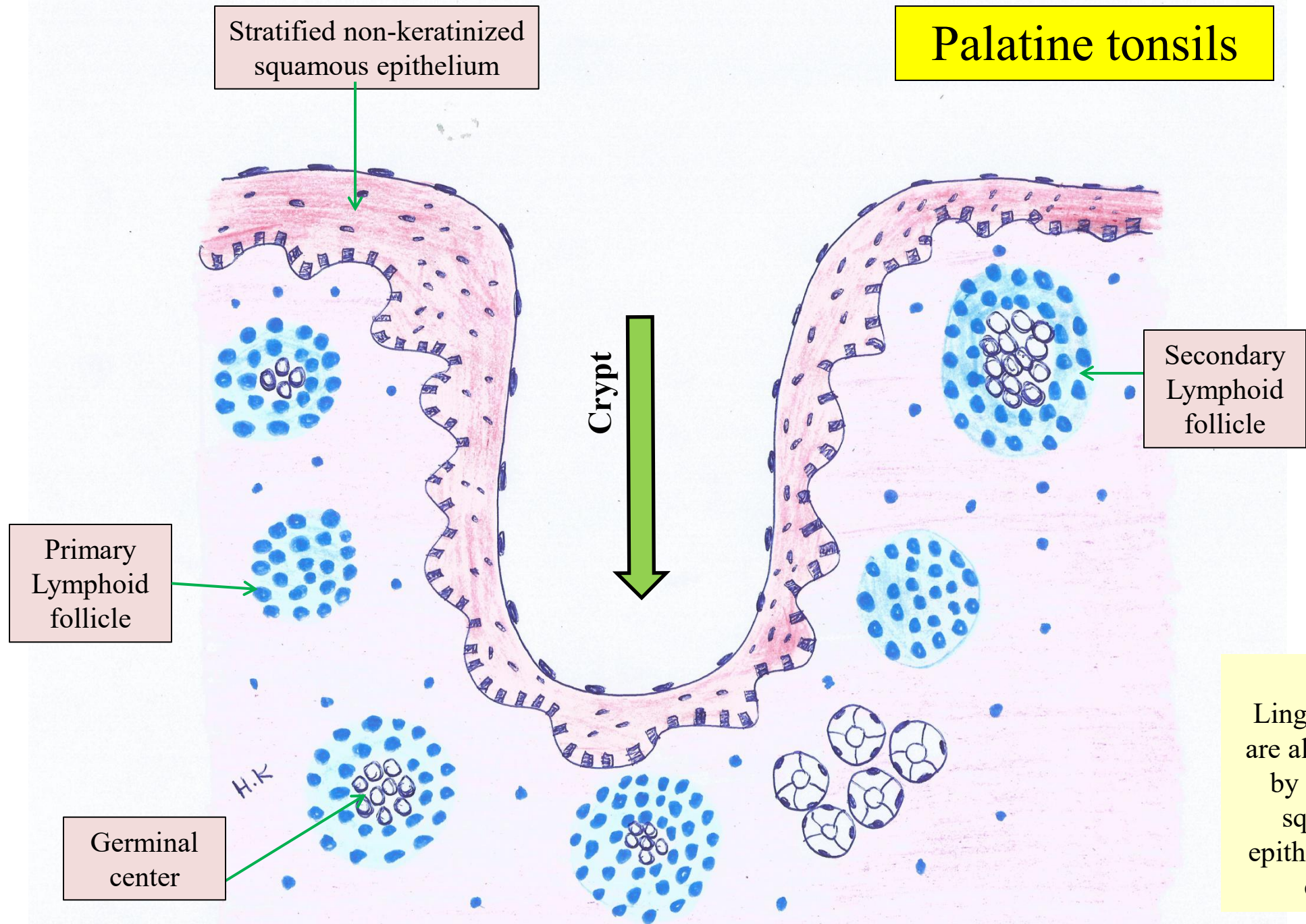


Pus in tonsillar crypts

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Heba Kalbouneh*



Palatine tonsils



Gut-associated lymphoid tissue (GALT)

Is located in the mucosa of the intestine.

Examples:

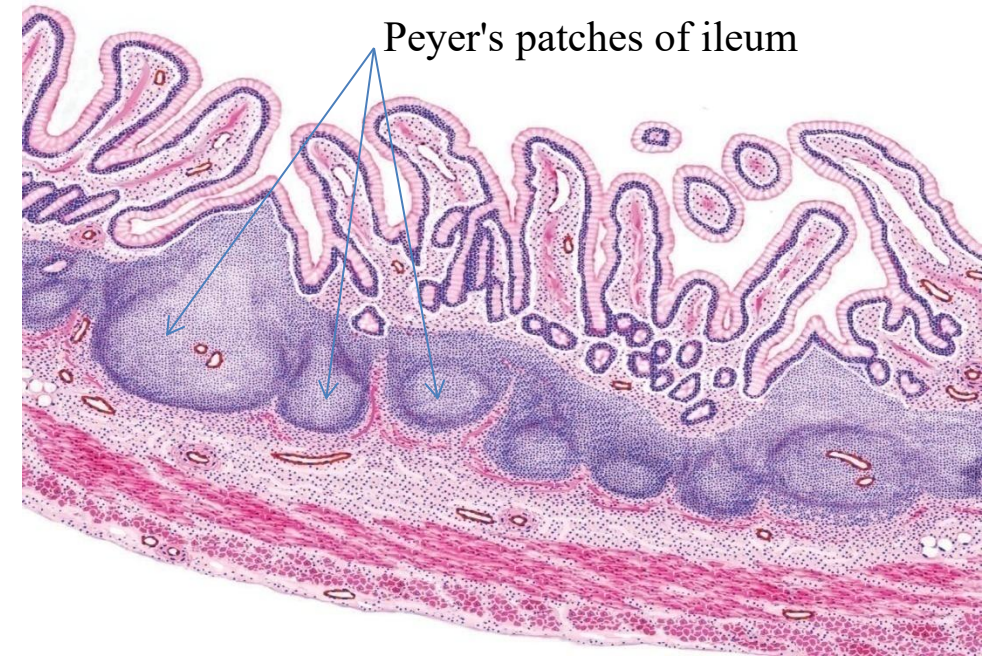
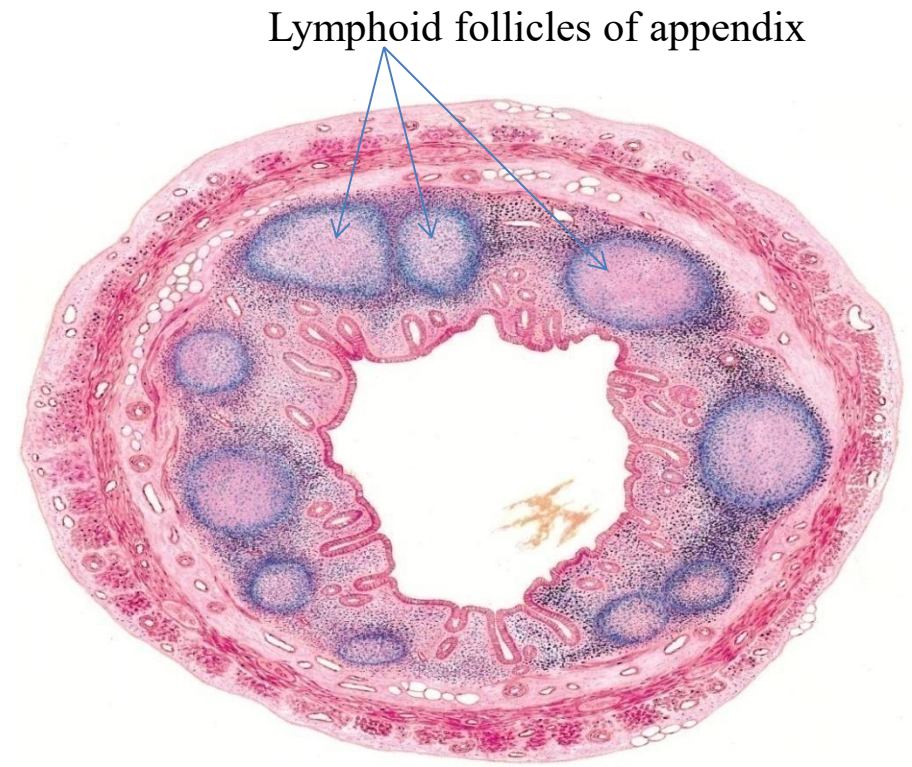
- 1- Peyer's patches of ileum
- 2- Lymphoid follicles of appendix

Function:

Protects the body from ingested pathogens.

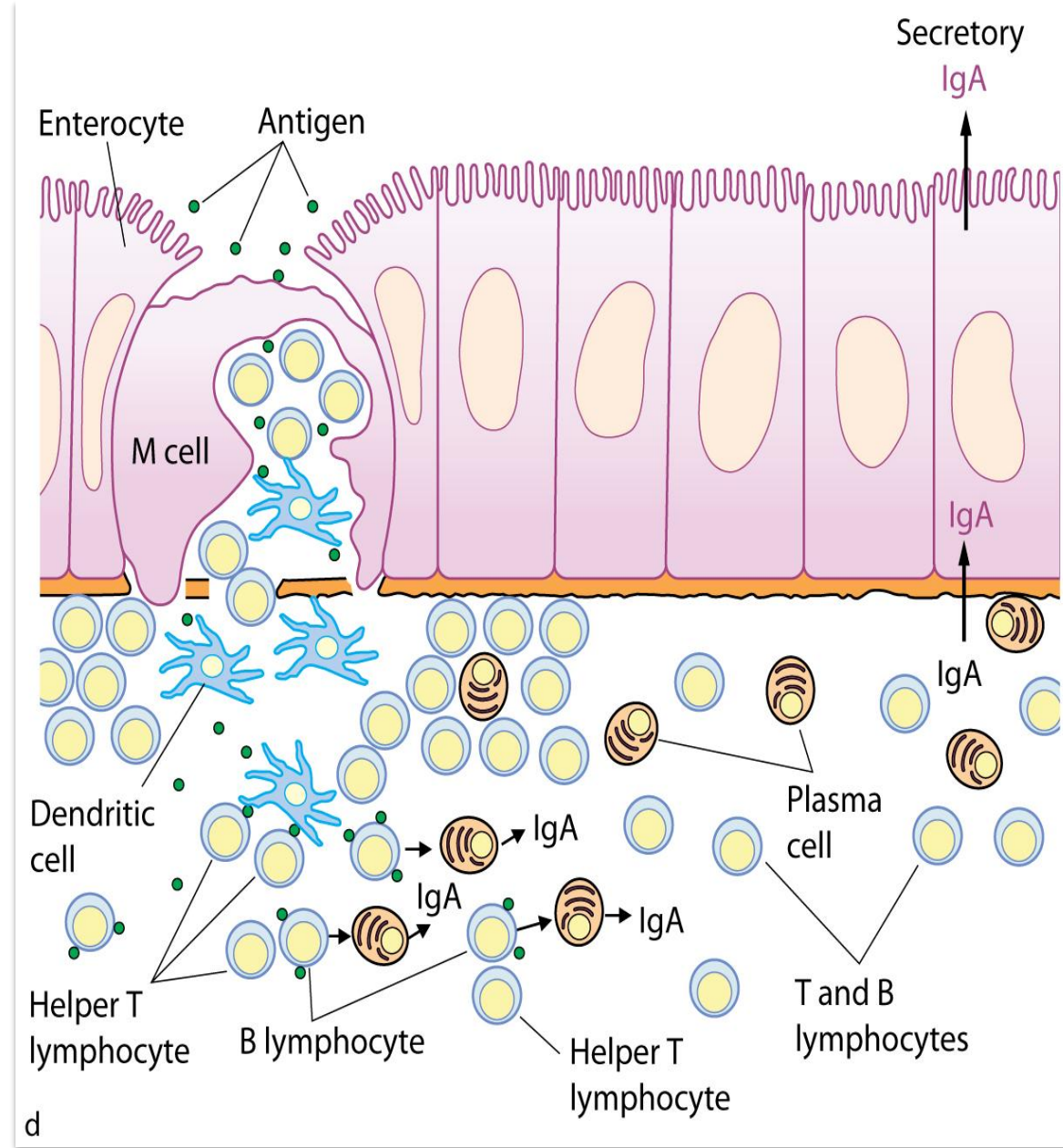
By their ability to transport luminal antigens and bacteria, Peyer's patches can be considered as the **immune sensors** of the intestine.

Remember:
Diffuse MALT extends from the pharynx along the entire gastrointestinal tract but becomes very well-developed again in the mucosa and submucosa of the **ileum**. Here large aggregates of lymphoid follicles comprise the Peyer patches, each containing dozens of follicles with no underlying connective tissue capsule.
Another significant collection of MALT occurs in the mucosa of the **appendix**

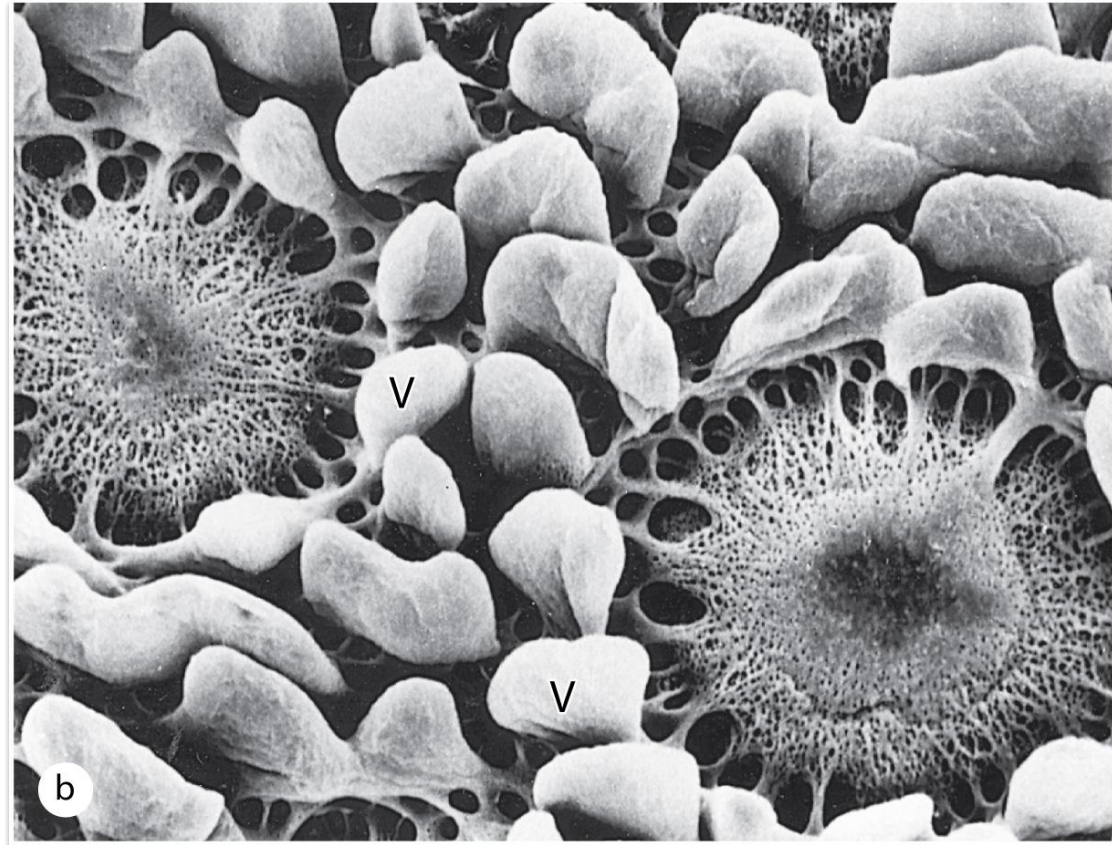


Peyer's patch and M cells

A summary diagram showing that antigens in the gut lumen are bound by **M cells** and undergo transcytosis into their intraepithelial pockets where **dendritic cells** take up the antigen, process it, and present it to **T helper cells**. B lymphocytes stimulated by the Th cells differentiate into **plasma cells** secreting IgA antibodies. The IgA is transported into the gut lumen where it binds its antigen on the surface of microorganisms, neutralizing potentially harmful invaders before they penetrate the mucosa.



With the surface epithelial cells removed, scanning electron microscopy (SEM) shows typical basement membrane over the villi (V) but reveals a highly porous covering over lymphoid follicles of the Peyer patch.



**Peyer's patch
and M cells**

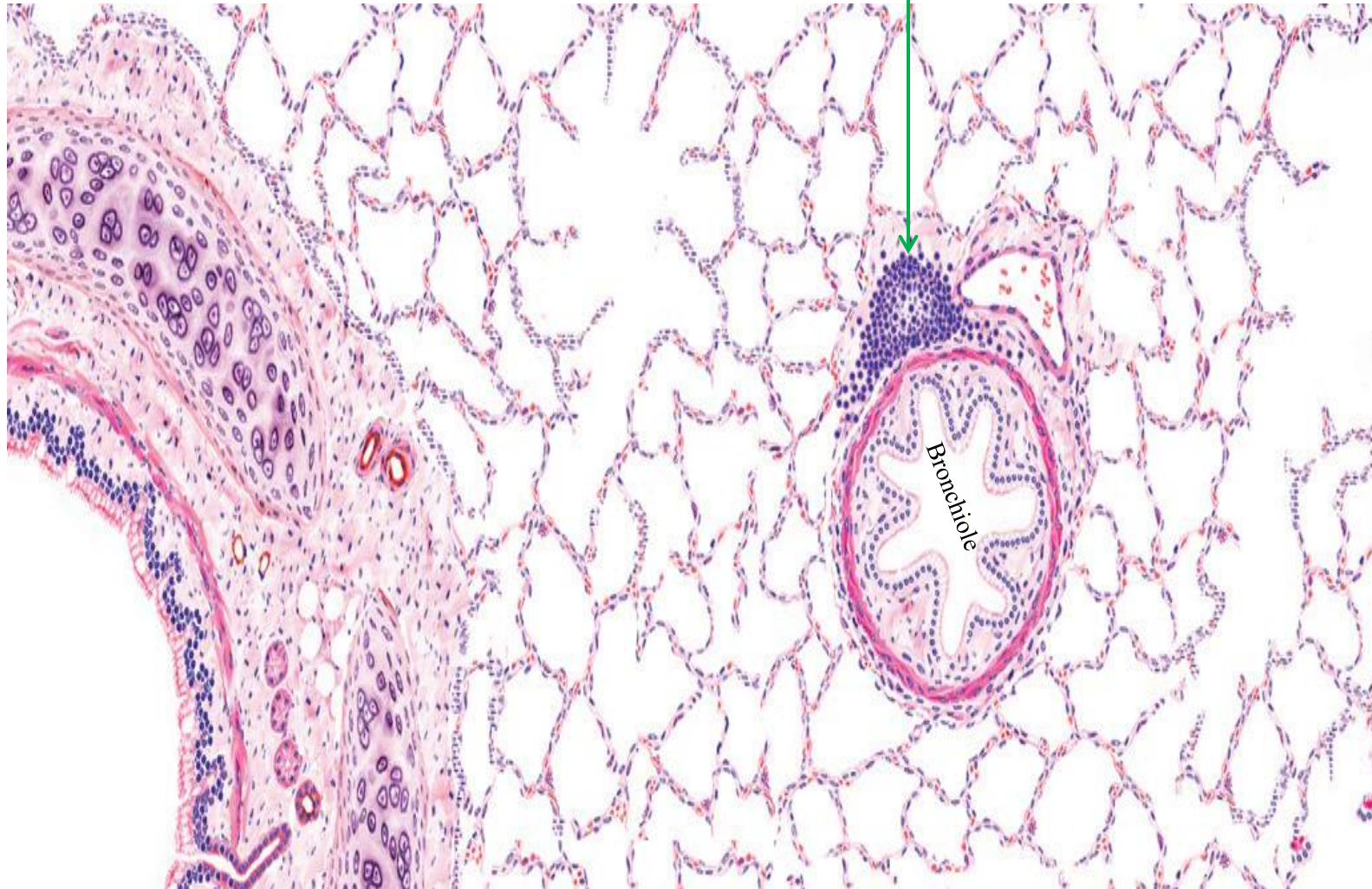
This sieve-like basement membrane facilitates interactions between immune cells and M cells in the epithelium over the follicles.

Bronchus-associated lymphatic tissue (BALT)

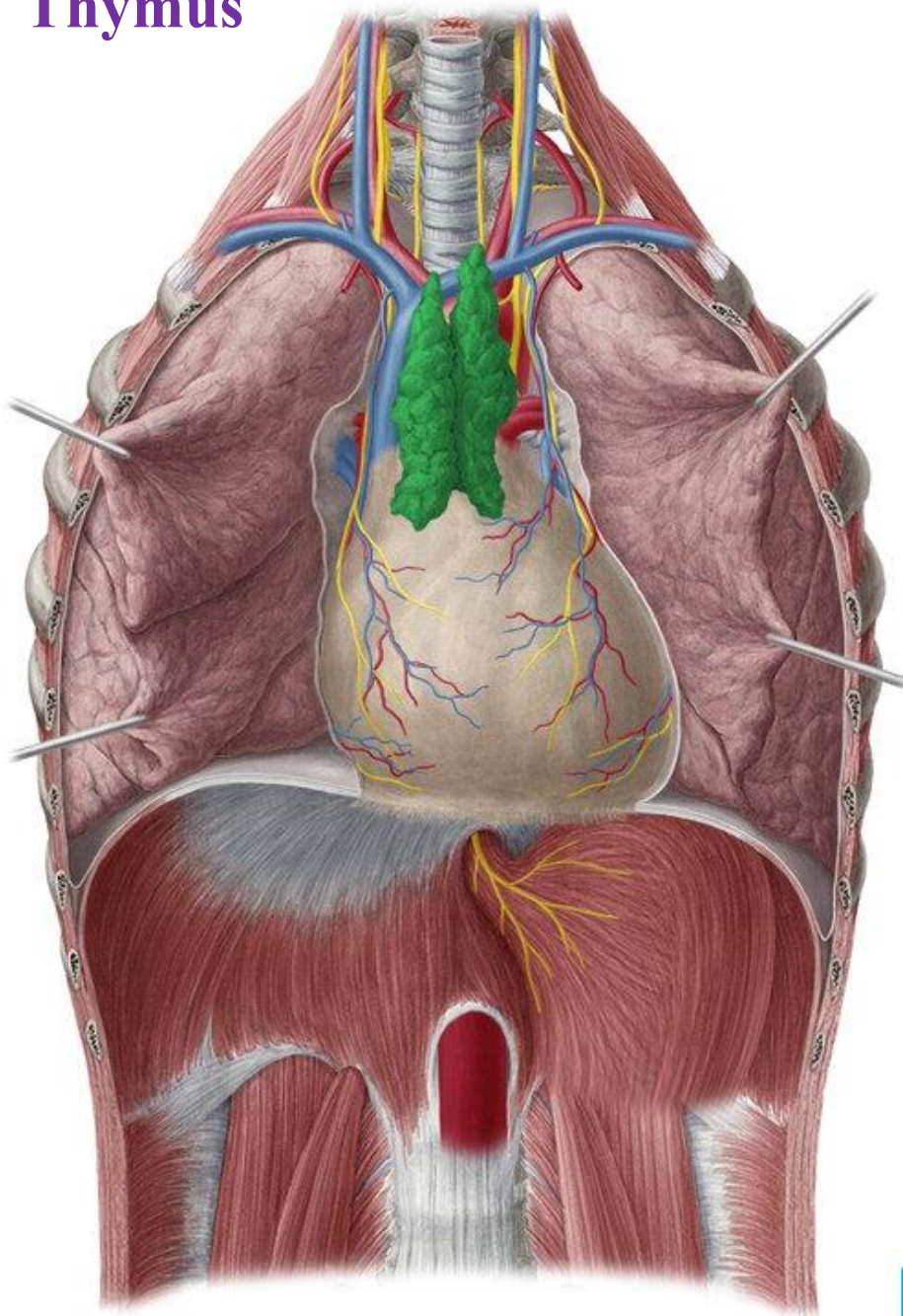
Is located in the mucosa of the bronchioles.

Function:

Protects the body from inhaled pathogens.



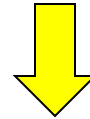
Thymus



© www

KEN
HUB

- ✓ Within the thymus, immature T-cells develop, differentiate, and multiply, as well as gaining their antigen specificity and immune tolerance to the body's own tissues.
- ✓ The thymus is a bi-lobed gland located in the anterior mediastinum, posterior to the sternum and anterior to the trachea.
- ✓ It is large in the newborn and young child
From puberty onwards, it gradually becomes replaced by fat.



Fully developed and functional at birth, the thymus remains highly active in T-cell production throughout childhood. Beginning around puberty, it undergoes progressive thymic involution, characterized by a reduction in lymphoid tissue mass and cellularity, gradual replacement by adipose tissue, and decreased T-cell output.

may be involved with the decline of immune function in the elderly

- ✓ The thymus is also part of the endocrine system.

The thymus has a double embryonic origin

Endoderm and Mesoderm

Originates from the embryo's third pair of pharyngeal pouches



unique thymic epithelial cells

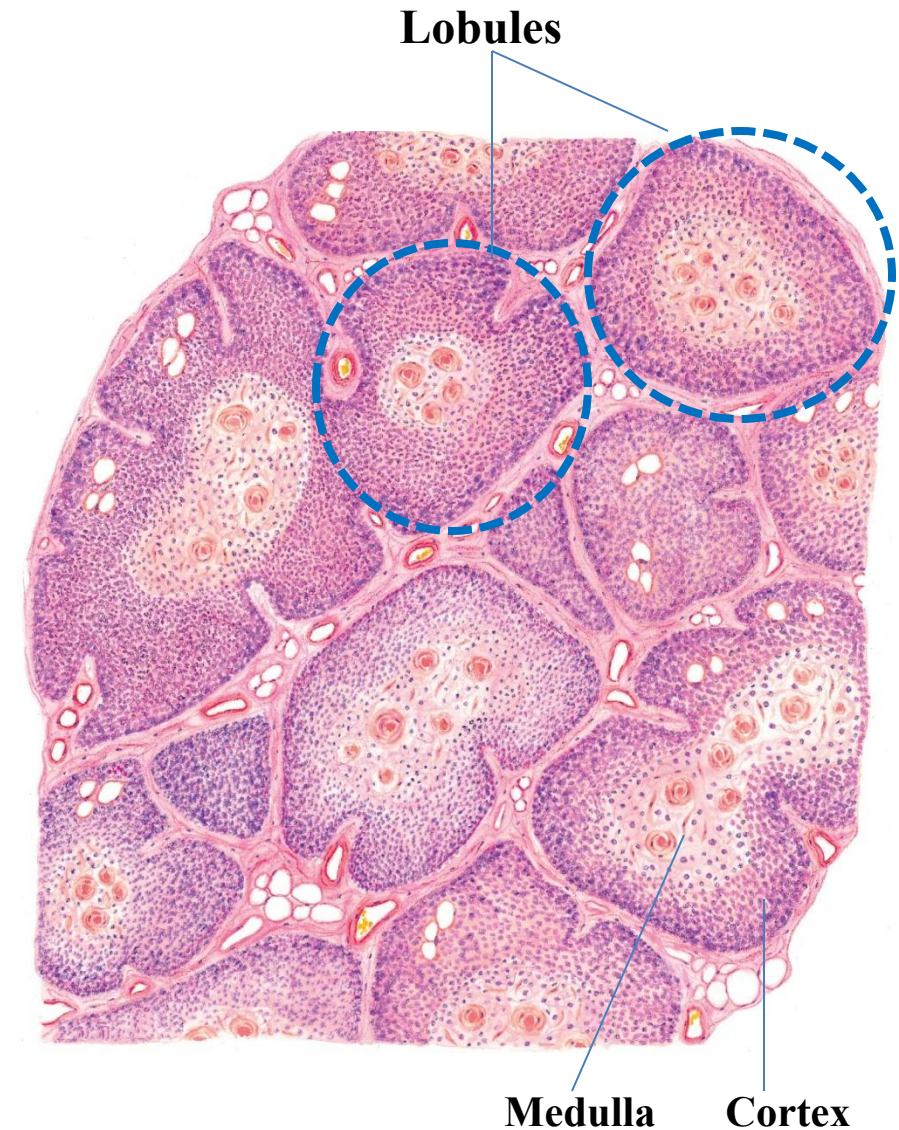
Hematopoietic origin
Immature T lymphocytes (T lymphoblasts) circulating from the bone marrow to invade and proliferate in thymus during its development.

The thymus has a connective tissue capsule that extends septa, dividing the organ into many incomplete **lobules**.

Each lobule has an outer **darkly basophilic cortex** surrounding a more **lightly stained medulla**.



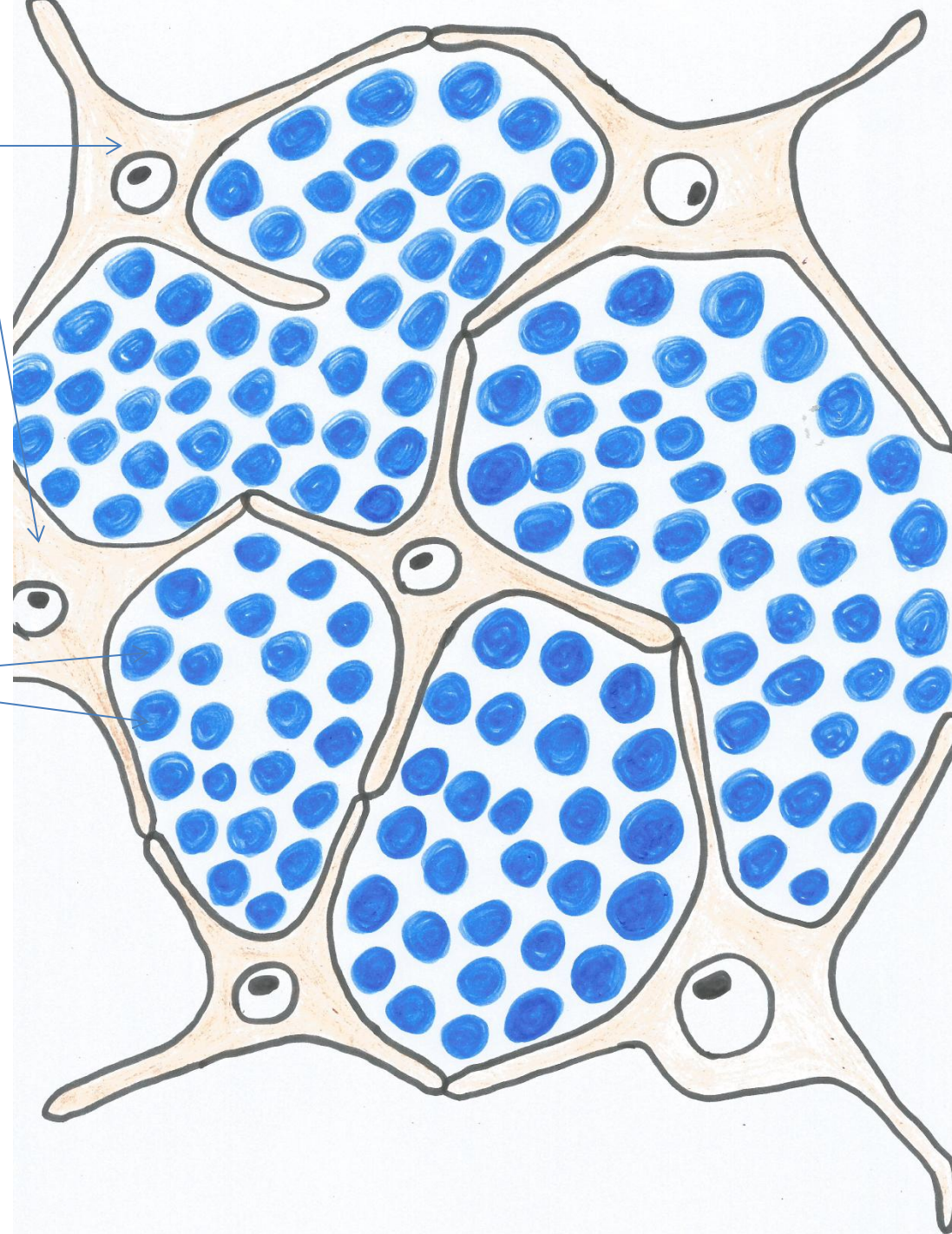
The staining differences reflect the much greater density of lymphocytes in the cortex than the medulla



Note: Cells of the medulla are less densely packed than in the cortex

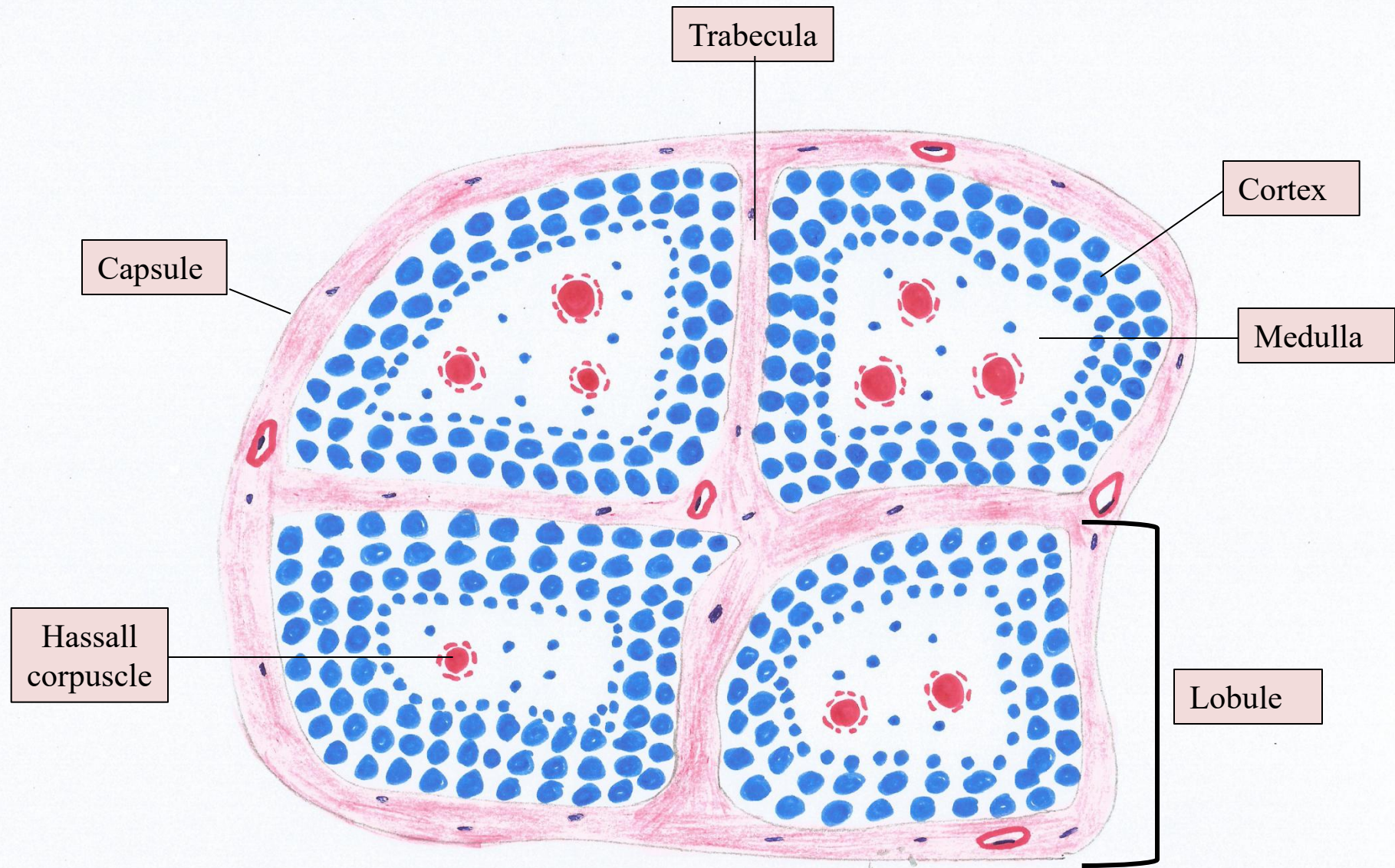
**Thymic Epithelial Cells
(TECs)**
(Epithelial reticular cells)

Immature T cells (T lymphoblasts,
pre T cells, thymocytes)
*(in various stages of differentiation
and maturation)*



Thymotaxin
Thymosin
Thymopoietin

Thymotaxin: is a chemotactic
peptide that attracts the
migration of T lymphoblasts
from bone marrow to thymus



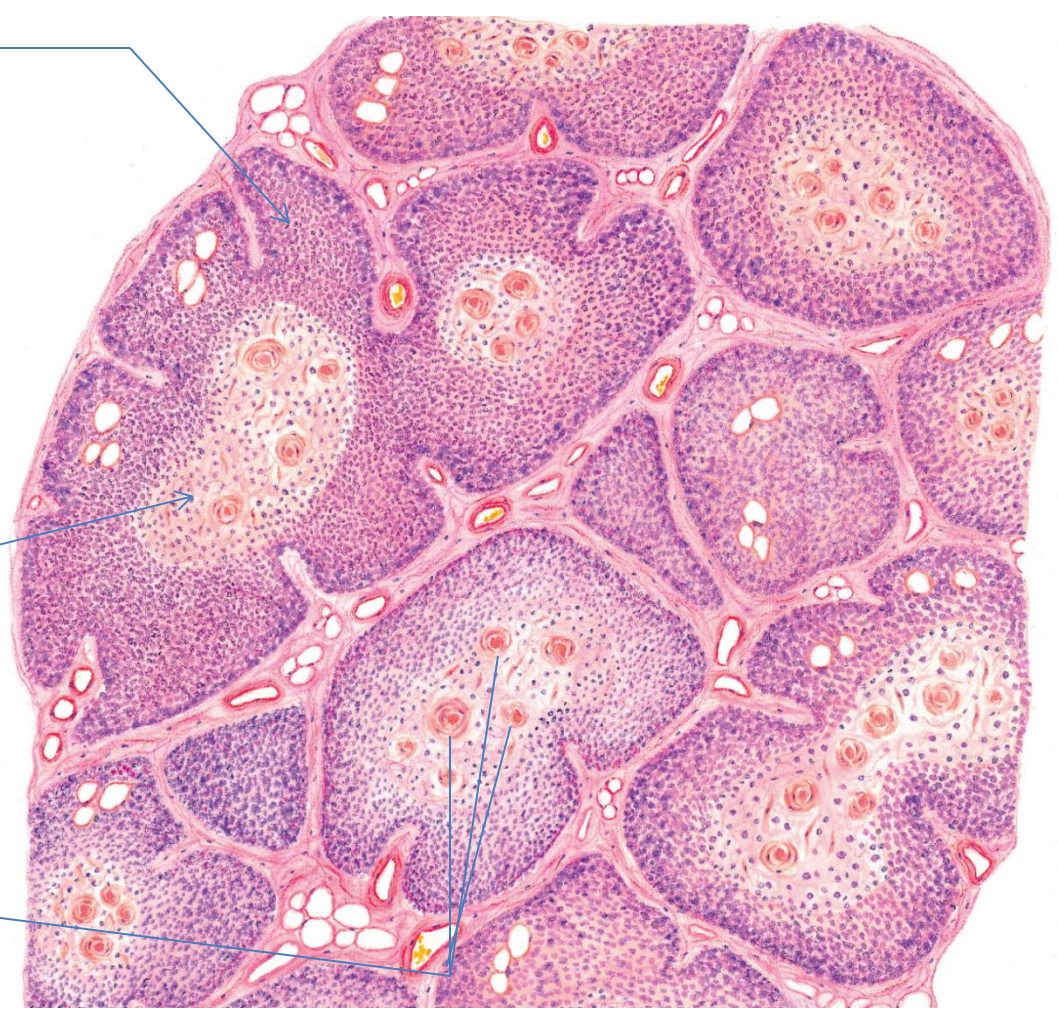
The cortex contains:

1. Immature T cells (T lymphoblasts, thymocytes) (*in various stages of differentiation and maturation*)
2. Macrophages
3. Unique thymic epithelial cells (TECs)

As T cells mature, they migrate to the medulla

The medulla contains:

1. Fewer and more mature lymphocytes.
2. Macrophages
3. Dendritic cells (APCs)
4. Unique thymic epithelial cells (TECs)
5. Large aggregates of TECs called **Hassall corpuscles**

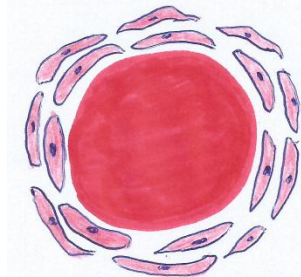


Hassall corpuscles are unique to the thymic medulla

✓ Up to 100 μm in diameter

✓ Are concentric aggregates of squamous cells with central keratinization (**acidophilic**)

✓ Tend to grow larger with age



Thymic Epithelial Cells (TECs) (Epithelial reticular cells)

1- Form a stroma to which macrophages and developing lymphocytes attach instead of reticular fibers

2- Line the capsule and septa and surround all blood vessels in the cortex



Form a **blood-thymus barrier** preventing antigens in the blood from making contact with the developing T cells (**in cortex**)

3- Envelop groups of T cells that are multiplying and maturing (**in cortex**)

4- Act as APCs, expressing MHC class II and MHC class I molecules (**in cortex**)

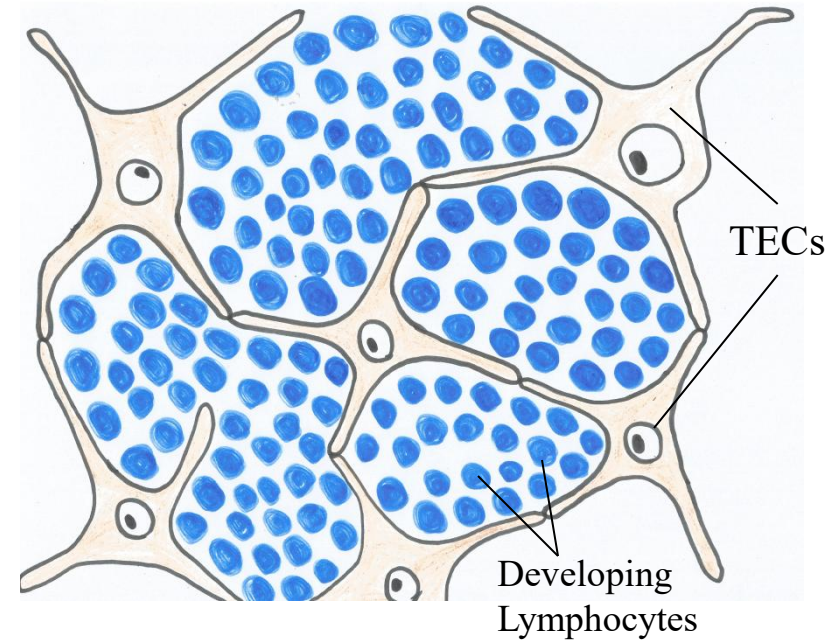
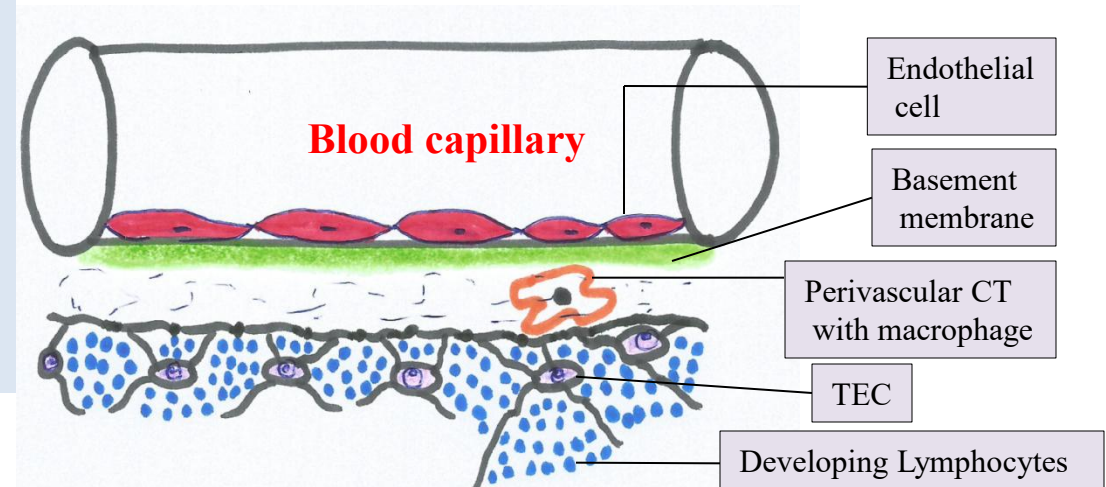
5- Express many specialized proteins specific to cells of other organs, *tissue specific antigens* (**in medulla**)

6- Secrete hormones that promote the differentiation of T cells (endocrine thymus)

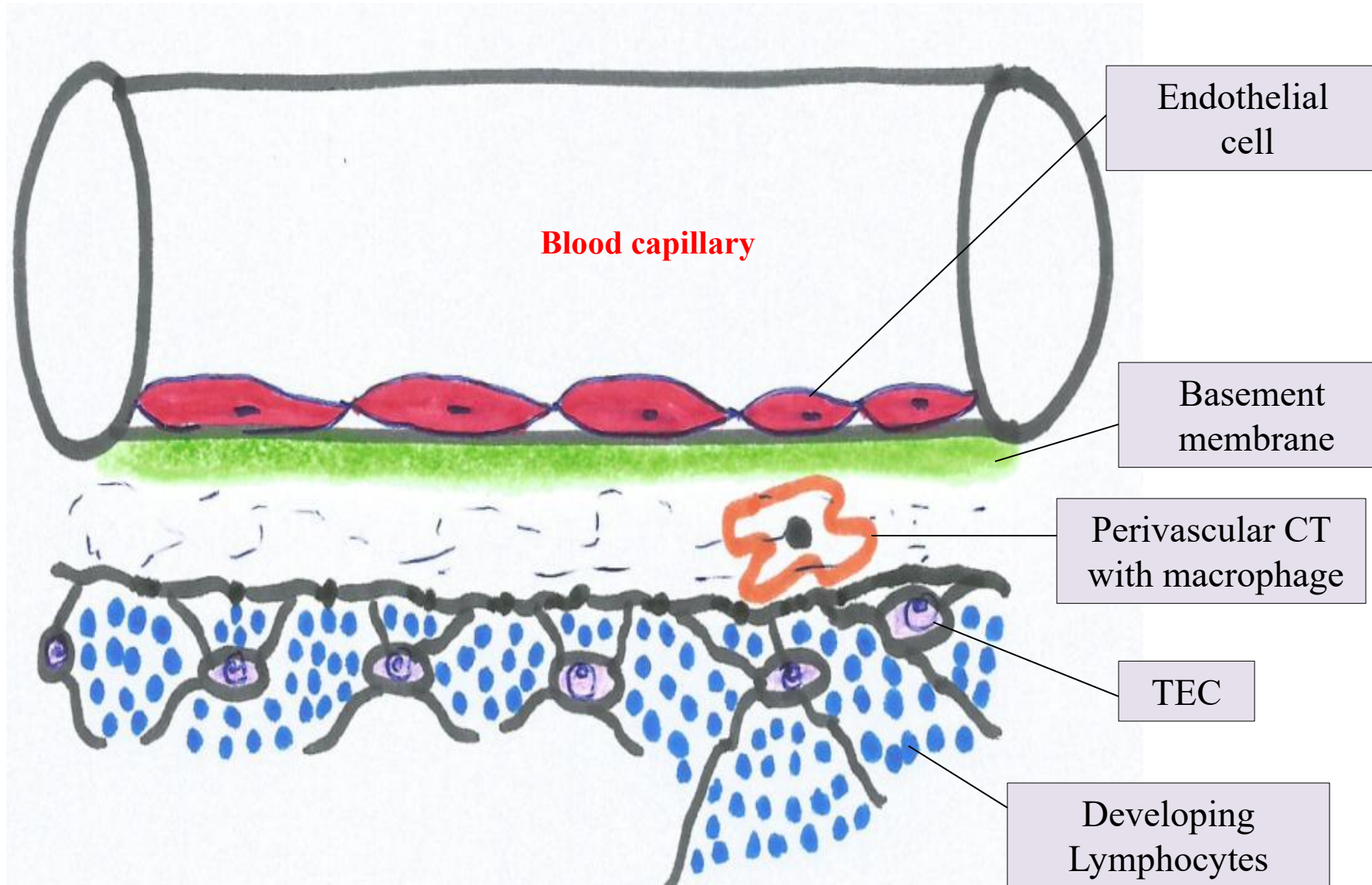
Thymosin, Thymopoietin

Develop from endoderm

Form a network of cells bound together by desmosomes



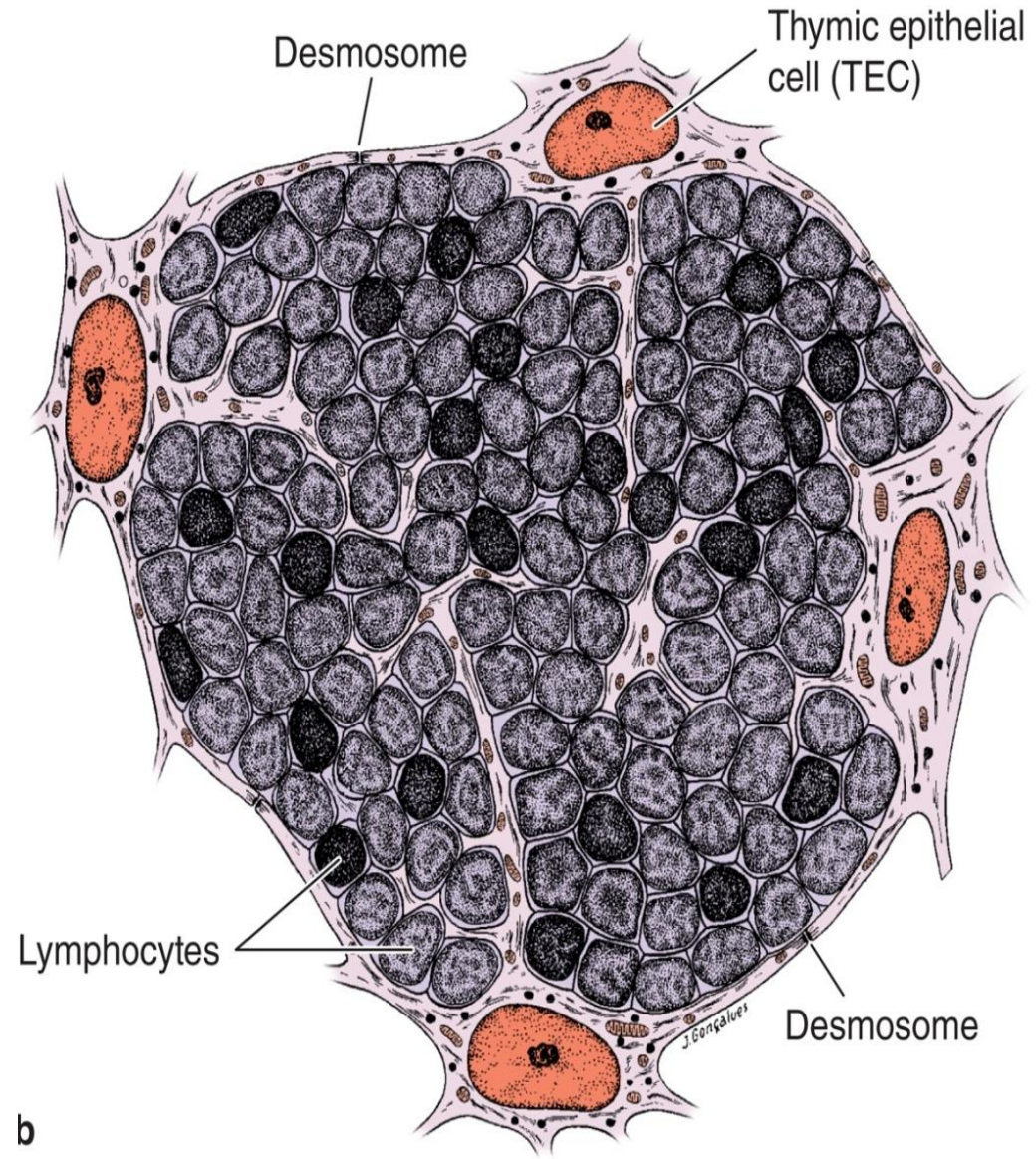
blood-thymus barrier preventing antigens in the blood from making contact with the developing T cells (**in cortex**)



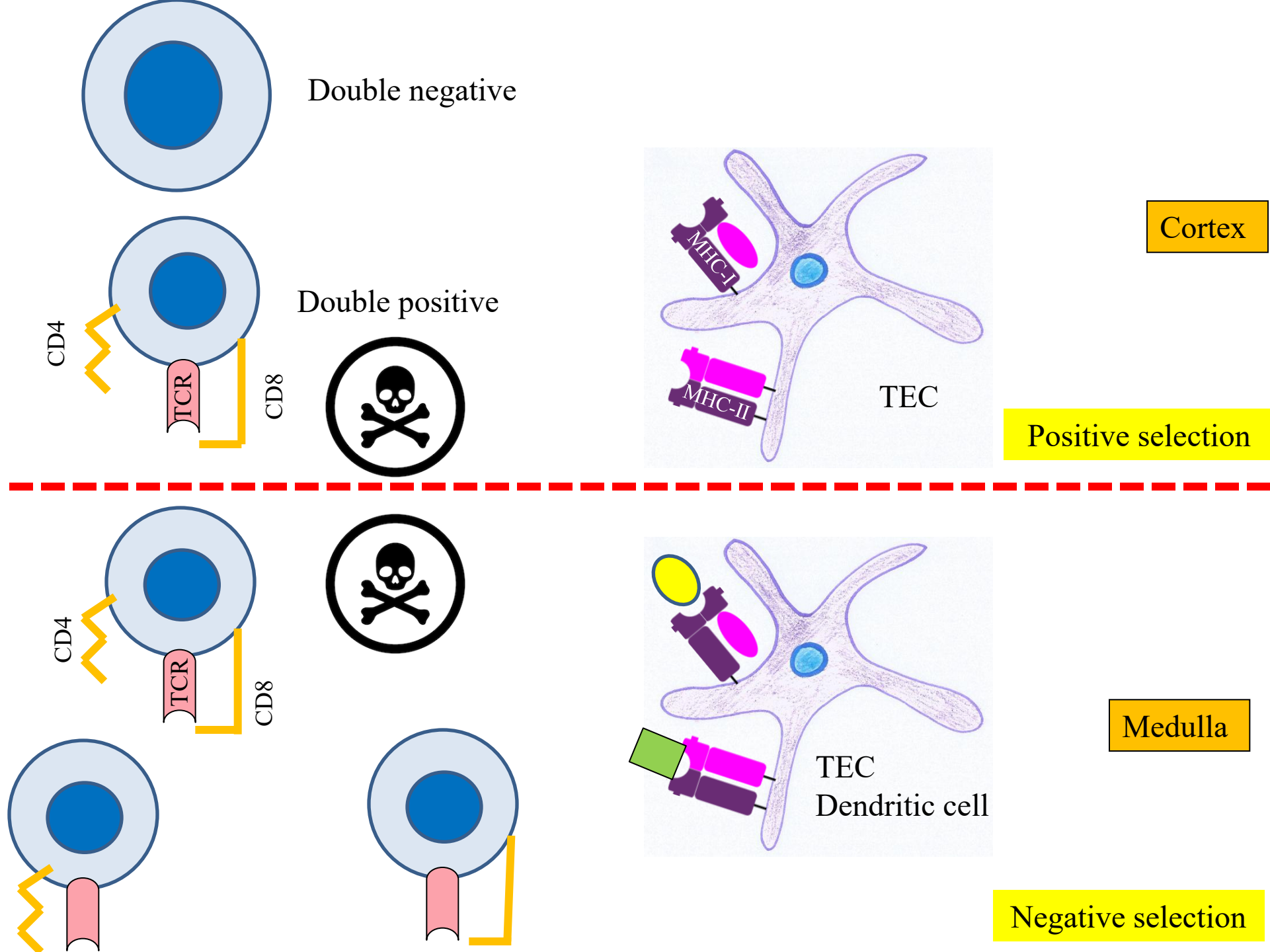
Thymic epithelial cells are also called
Nursing Cells



They form sheets for cells deep to the capsule, around septa and blood vessels, to isolate developing T lymphocytes in the cortex from contact with antigens (present in the blood), while they are programmed



b



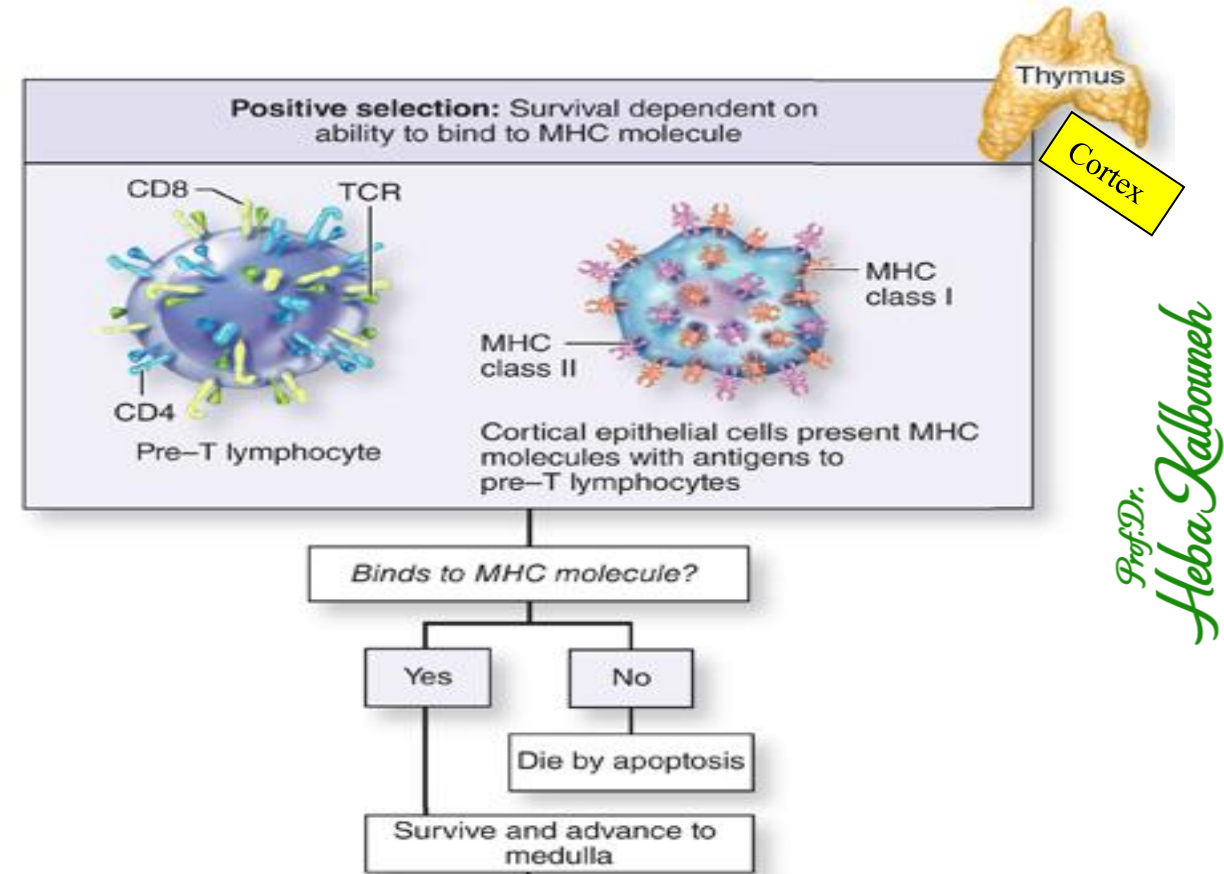
Immature T cells arriving in the thymus do not yet express CD4, CD8, or a TCR.



These cells populate the cortex and begin to proliferate and express TCR proteins, CD4 and CD8



TECs in the cortex present the developing T cells with peptides on both MHC class I and class II molecules



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Developing T cells whose TCRs or whose CD4 or CD8 cannot recognize MHC molecules undergo apoptosis before they leave the cortex

This interaction determines whether the newly made TCR proteins of these cells are functional.



A cell's survival depends on whether its TCRs can recognize and bind MHC molecules properly (**positive selection**)



80% of the developing T cells die in the cortex (undergo apoptosis) and are removed by the macrophages

The surviving cells (T cells with functional TCRs) enter medulla

In the medulla, T cells encounter antigens presented on both TECs and dendritic cells.



Here the focus is on removing T cells whose TCRs bind self-antigens

A cell's survival depends on a cell **not** binding to MHC molecules with self-antigens
(**negative selection**)



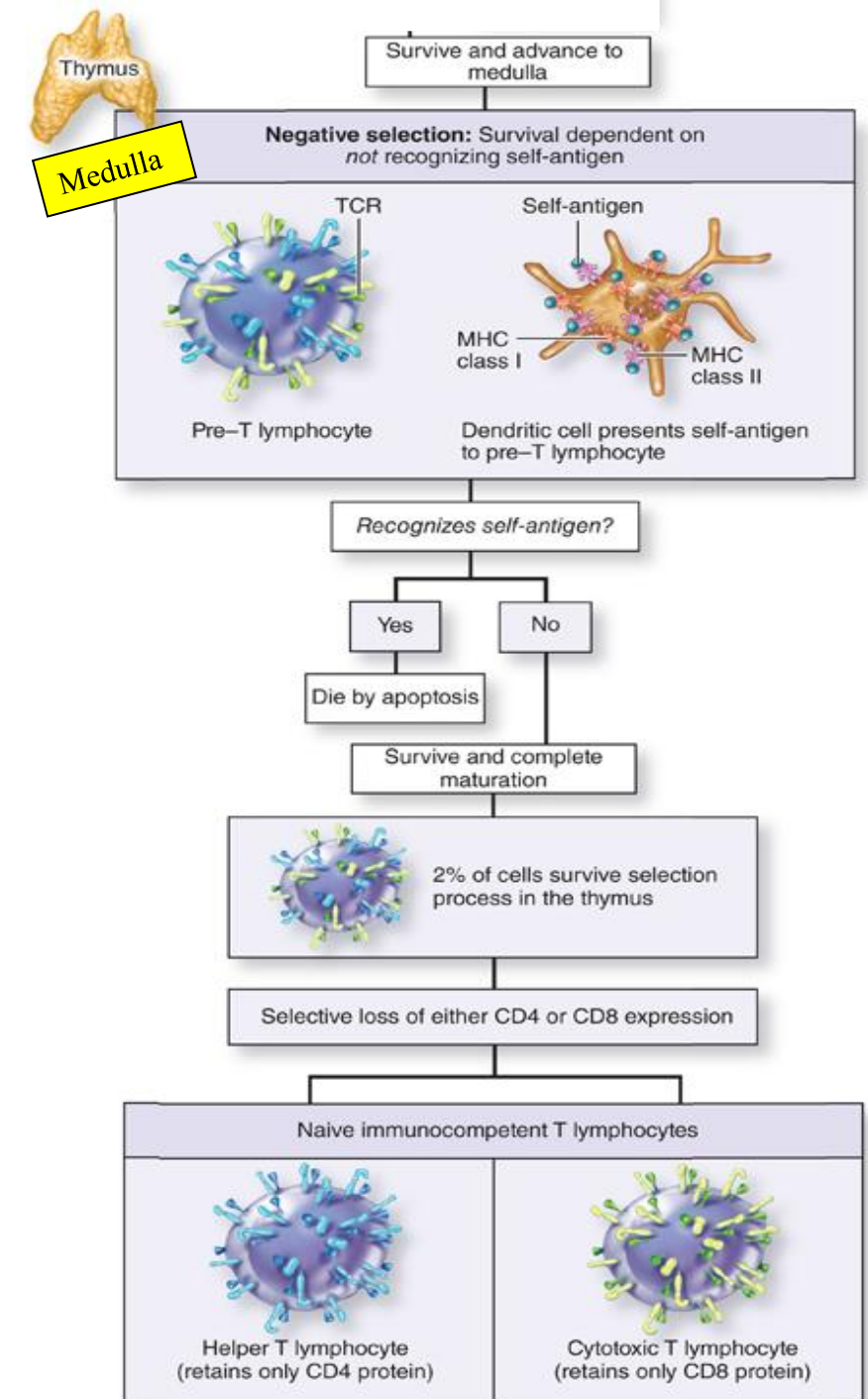
Self-antigens presented here are those from proteins specific for many tissues other than the thymus (tissue specific antigens)



T cells that bind MHCs containing self antigens undergo apoptosis and are removed by the macrophages (**if survive autoimmune response!!!**)



Only about 2% of all developing T lymphocytes pass both the positive and negative selection tests and survive to exit the thymus as immunocompetent T cells.



To summarize:

Positive selection occurs in the cortex and allows survival only of T cells with functional TCRs that recognize MHC class I and class II molecules. **Negative selection** occurs in the medulla and allows survival only of T cells that do **not** bind self-antigens presented on dendritic cells and TECs there.



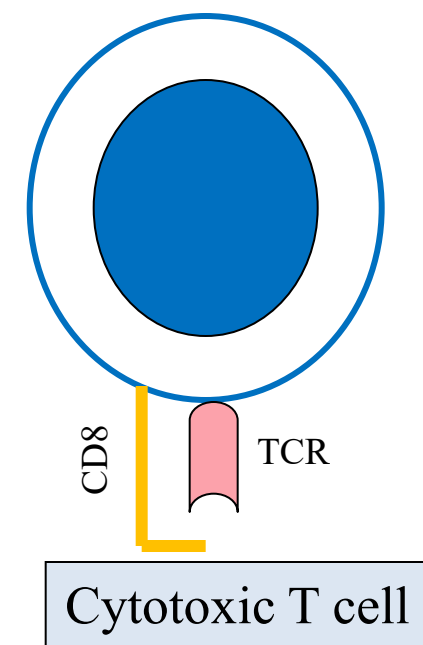
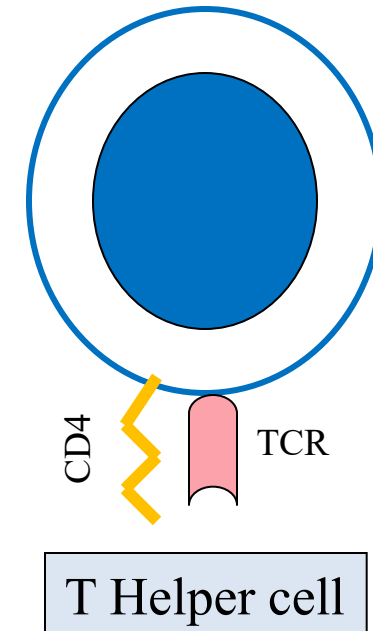
T cells undergo positive and negative selection processes to ensure that they will not react with healthy cells of the body.

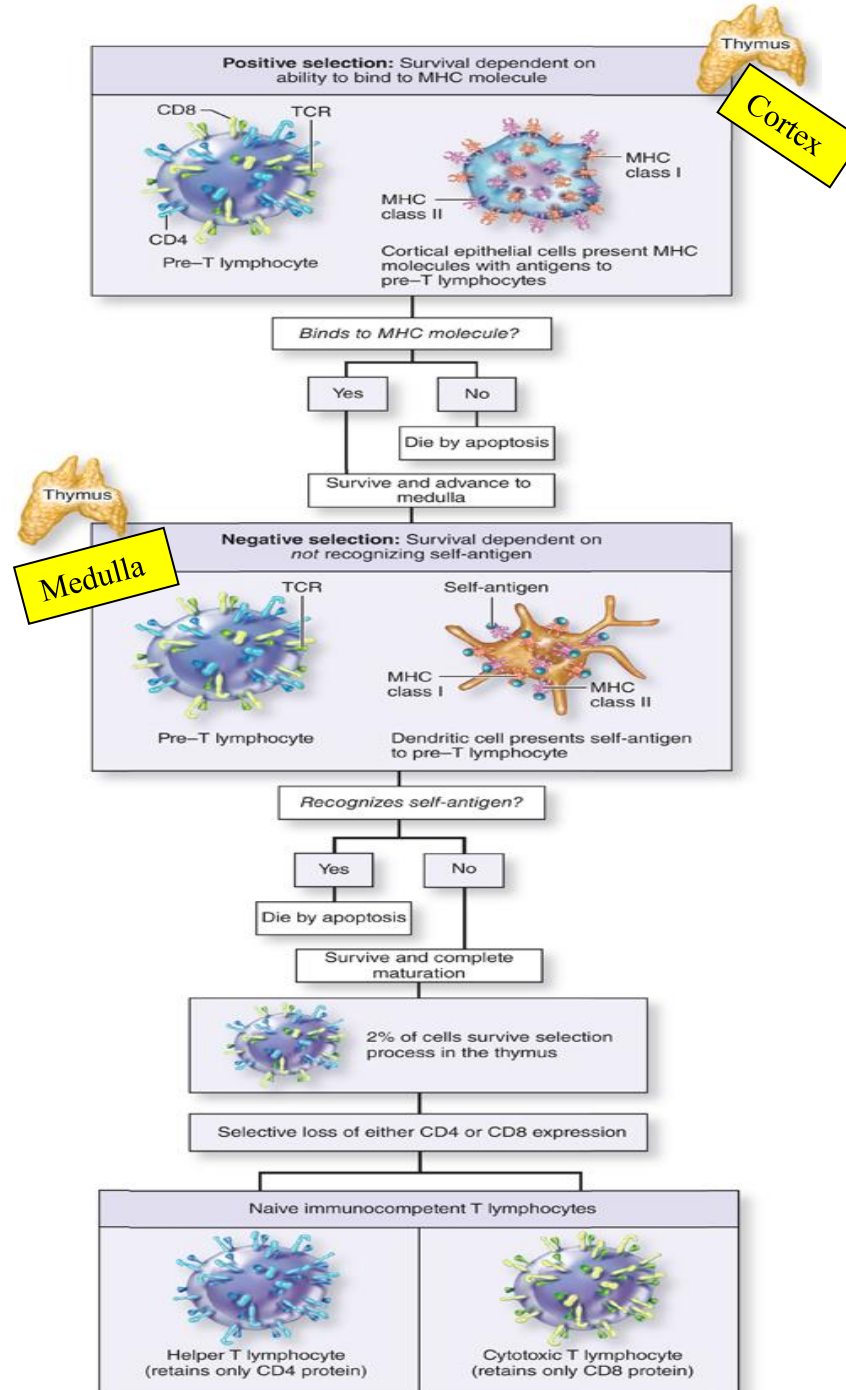
Depending on which class of MHC they interacted with, most of these lymphocytes will have stopped expressing either CD8 or CD4, and become either helper T cell or cytotoxic T cell

Fully mature T cells (immunocompetent T-cells) leave the medulla via venules and efferent lymphatic vessels

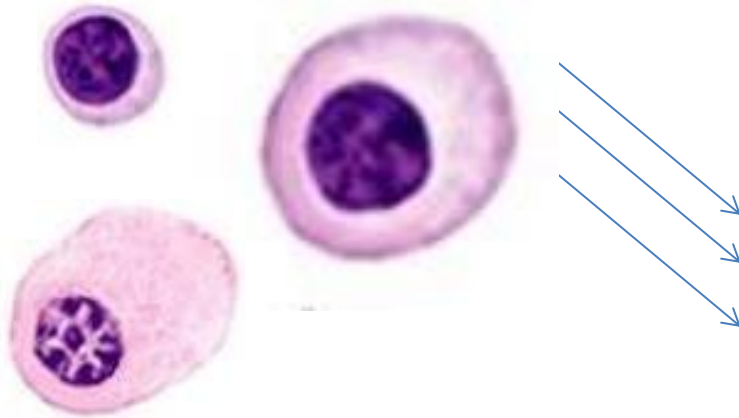
Then..

They migrate from the thymus to specific regions in the lymph nodes (paracortex), the spleen (PALS), and diffuse lymphatic tissues, where they reside and are responsible for **cell-mediated immune responses**





After maturation in primary lymphoid organs, B and T cells circulate to the peripheral secondary lymphoid organs (the MALT, the lymph nodes, and the spleen). Lymphocytes do not stay long in the lymphoid organs; they continuously recirculate through the body in connective tissues, blood, and lymph.



*Lymphocytes continuously **circulate** between the lymph and blood until they encounter their antigen*

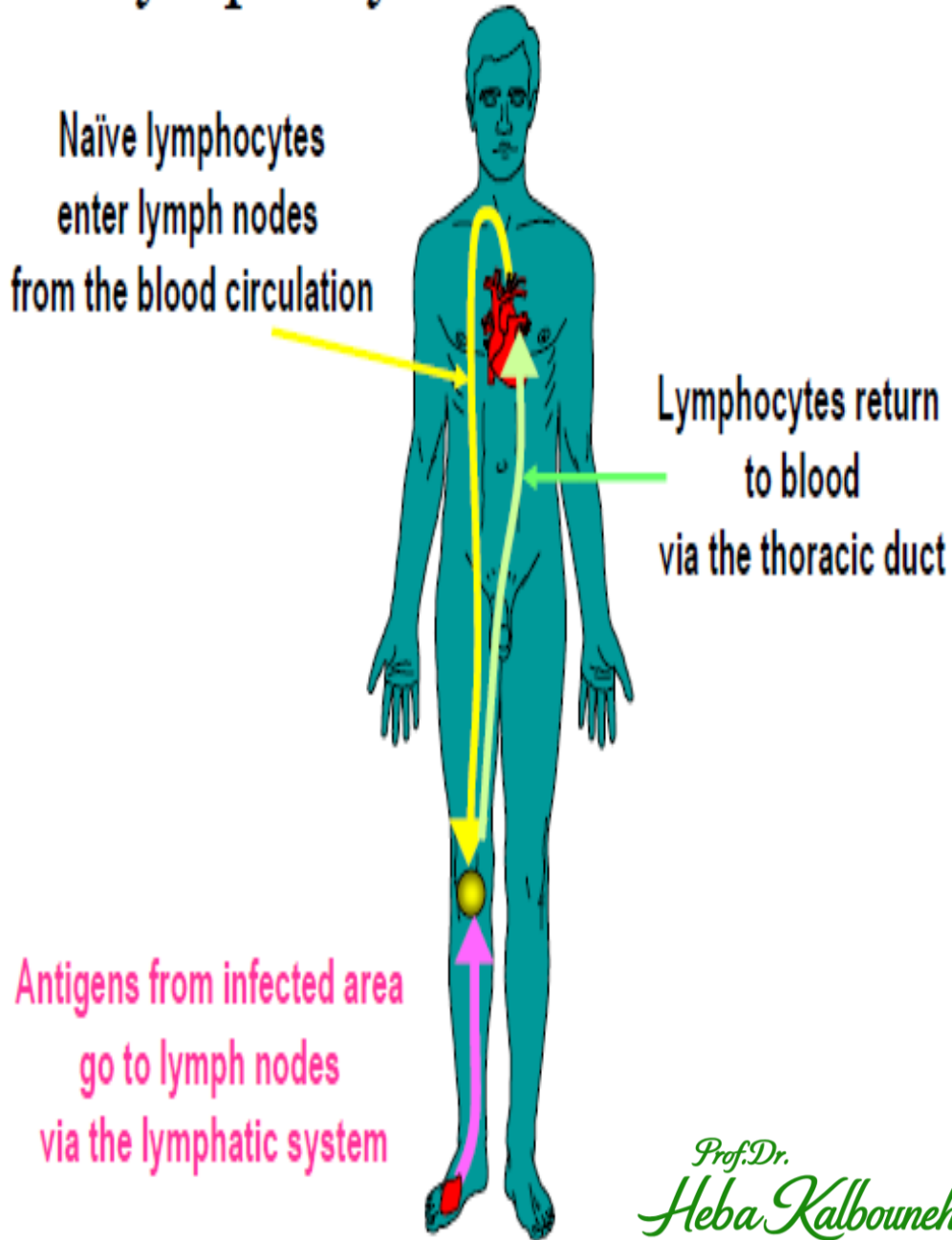
Choices of lymphocytes:

- 1- If no antigen is present:** lymphocytes routinely enter and leave secondary lymphoid tissues
- 2- If antigen enters the secondary lymphoid tissue:** Lymphocyte proliferation in response to antigen occurs within the lymphoid tissue. After several days, antigen-activated lymphocytes begin leaving the lymphoid tissue.

Because of the constant mobility of lymphocytes and APCs, the cellular locations and microscopic details of lymphoid organs differ from one day to the next. However, the relative percentages of T and B lymphocytes in these compartments are relatively steady

Lymphocytes in the marrow and thymus of a newborn infant not yet exposed to antigens are immunocompetent but naive (not yet exposed to antigens). After circulating to the various secondary lymphoid structures, lymphocytes are exposed to antigens on APCs and become activated, proliferating to produce a clone of lymphocytes all able to recognize that antigen

Lymphocyte Recirculation



Advantages of lymphocyte recirculation:

Lymphocyte recirculation enables the limited number of naïve lymphocytes in an individual that are specific for a particular antigen to search for that antigen throughout the body

It ensures that particular lymphocytes are delivered to particular tissue



Recirculation of naïve lymphocytes: recirculate through secondary lymphoid organs

Recirculation of activated lymphocytes: migrate to peripheral tissues at sites of infection

If you have a viral infection in your oral cavity, this infection spreads to lymph nodes draining the oral cavity, and lymphocytes in these lymph nodes develop an immune response against this virus.

Then the activated lymphocytes leave the lymph node and circulate in the lymph and then blood..

They will go to every lymph node in your body and settle there

The whole body is prepared against this virus,, the whole body is tuned up for the next infection with the same virus

*Prof.Dr.
Heba Kalbouneh*