Lymphatic System

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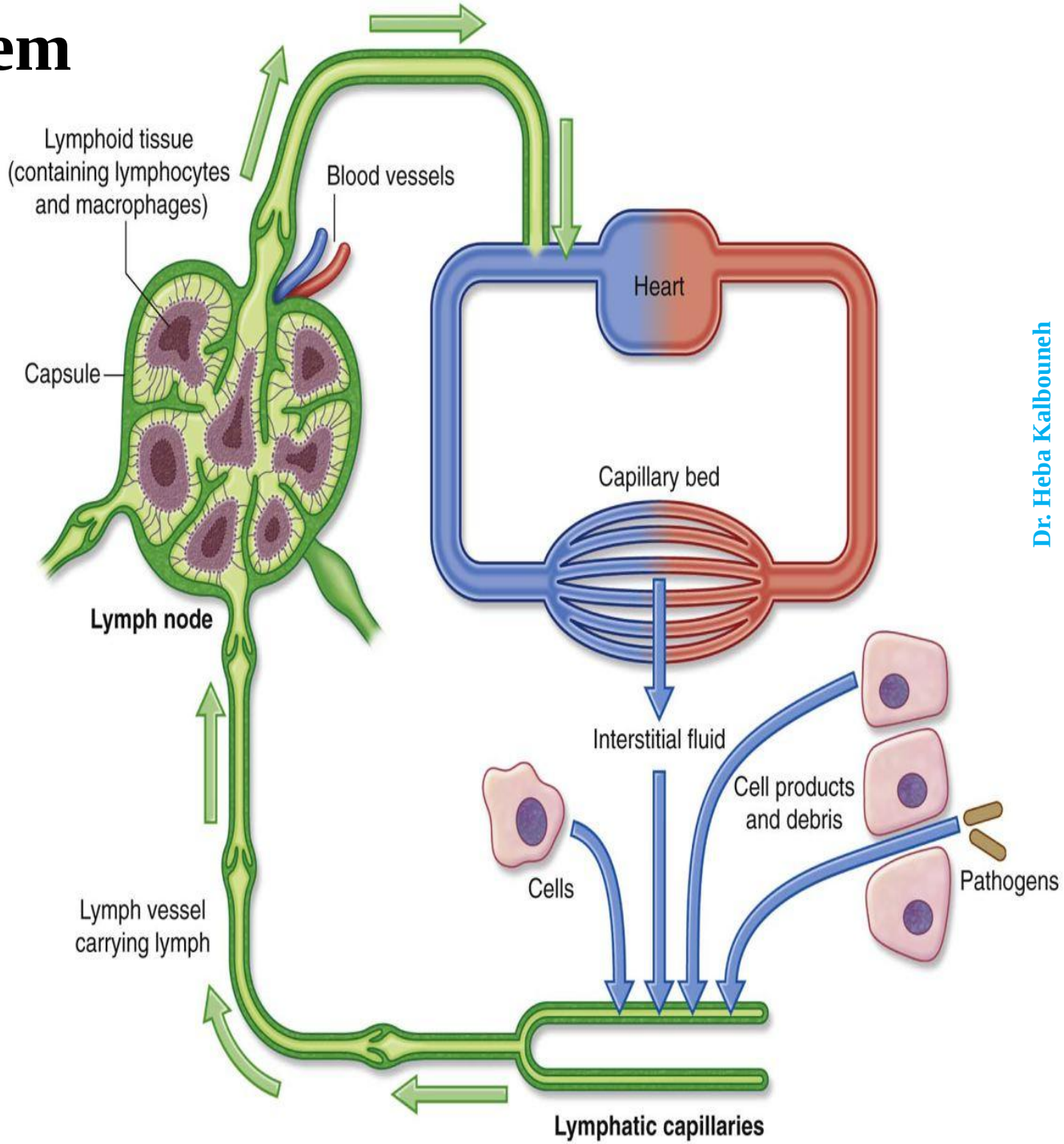
Lymphatic system

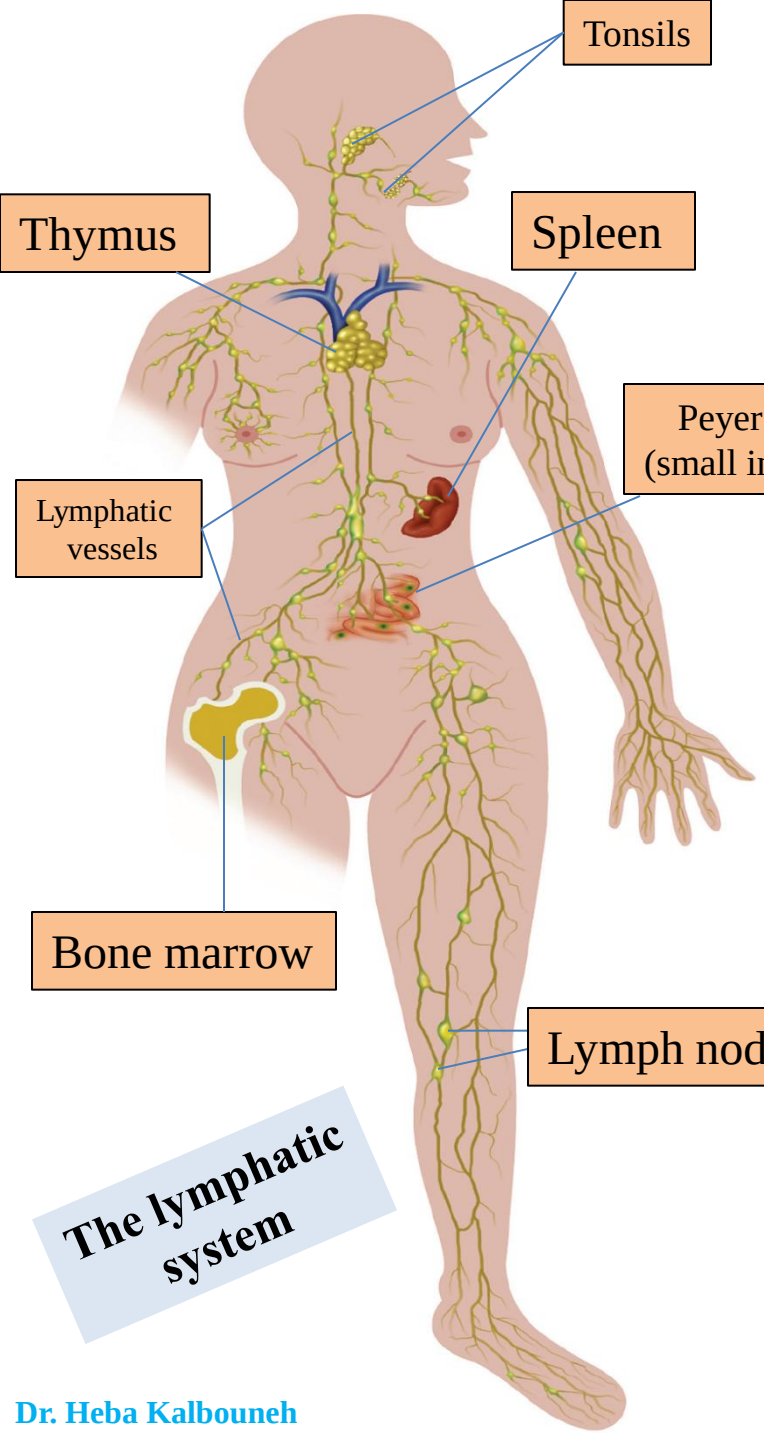
The lymphatic system consists of lymphatic fluid, lymphatic vessels, lymphatic tissue, and lymphatic organs located throughout the tissues of the body. It functions to:

1- Drain excess interstitial fluid from the tissues and return to blood stream

2- Initiate an immune response against disease by producing and transporting lymphocytes

3- Transport dietary lipids absorbed by the gastrointestinal tract into the blood.





The lymphatic system

Lymph is a colorless fluid that floats in the lymphatic vessels (lymphatics). It is similar in composition to blood plasma

Lymphatic vessels are thin vessels that accompany arteries and veins throughout the body and transport lymph.

Lymphatic tissue is a specialized form of reticular connective tissue that is composed of masses of lymphocytes. These either occur alone as lymph nodules (follicles) or are organized into various lymphatic organs.

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

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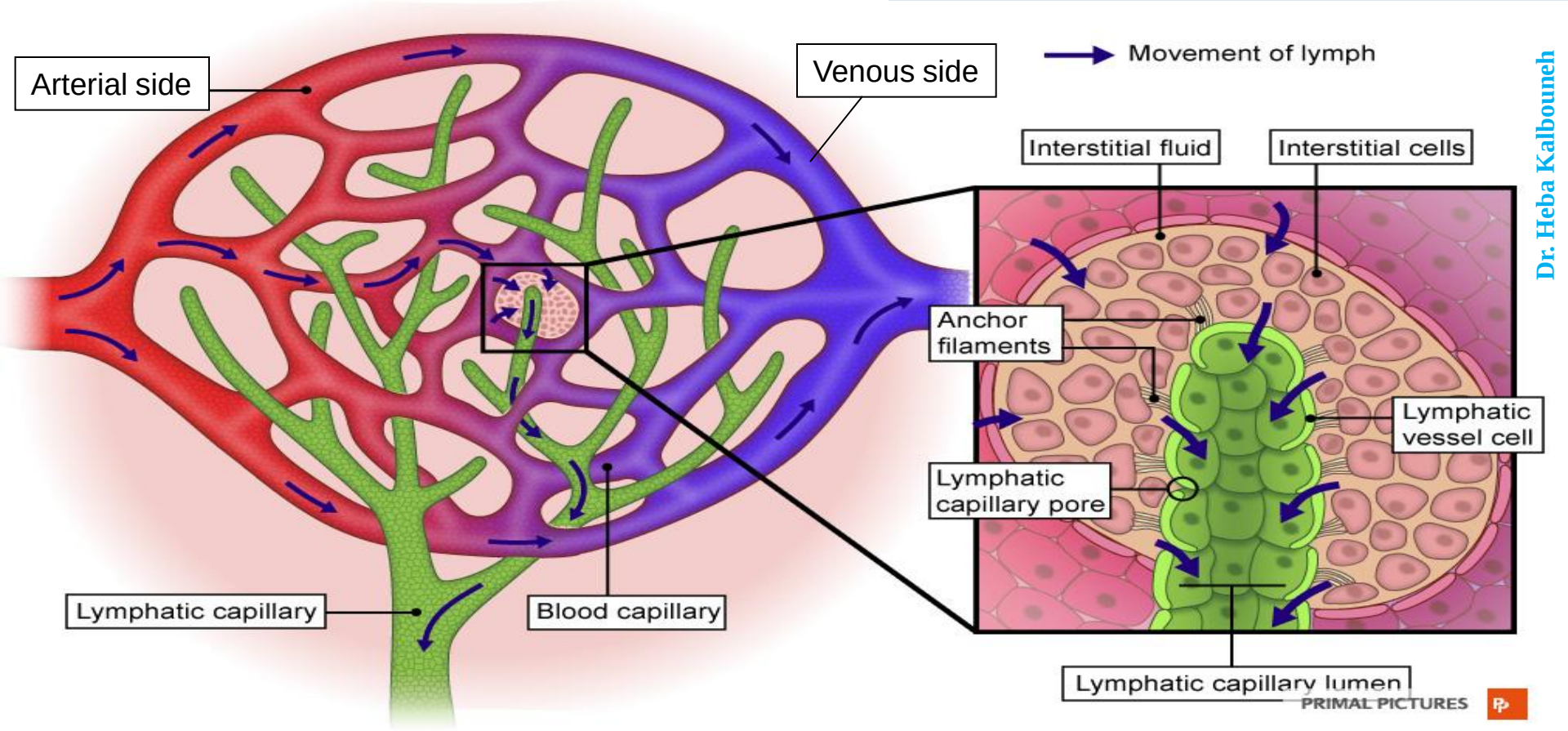
Fluid balance

The tissues of the body are supplied by blood capillaries that bring oxygen-rich blood and remove carbon dioxide-rich blood.

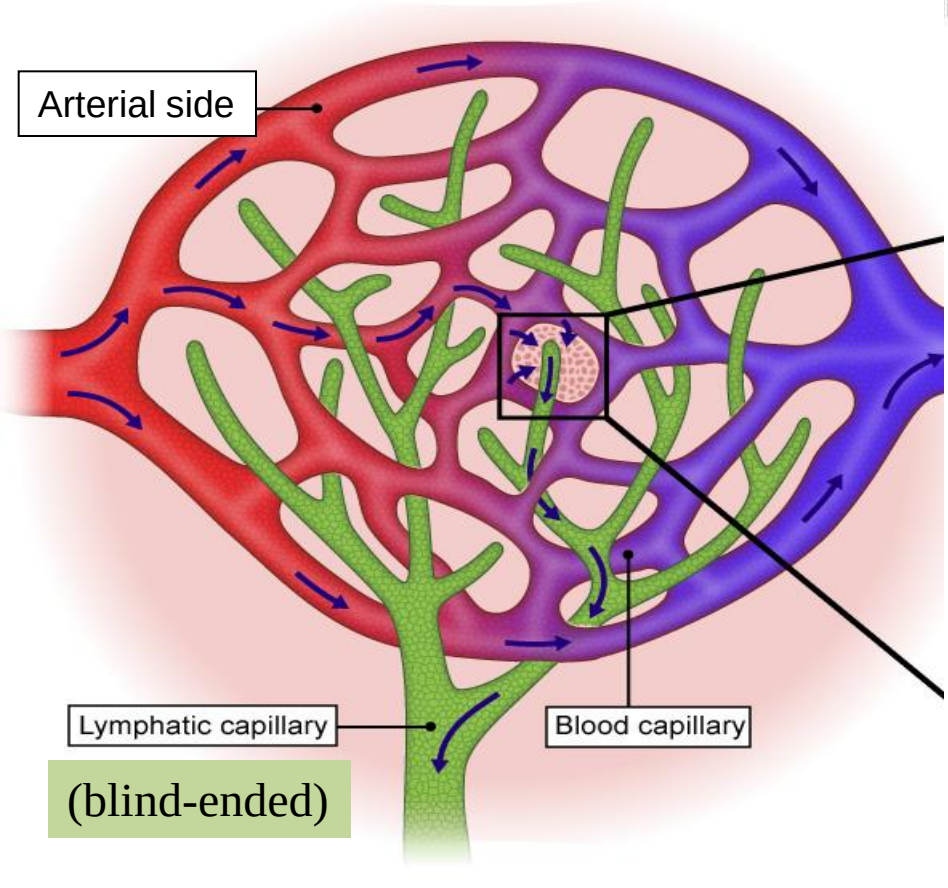
Fluid similar to blood plasma, called **interstitial fluid**, leaches from these vessels into the surrounding tissue.

Around 20 liters of fluid leaves the arterial capillaries every day, but only 17 liters of fluid returns to the venous capillaries.

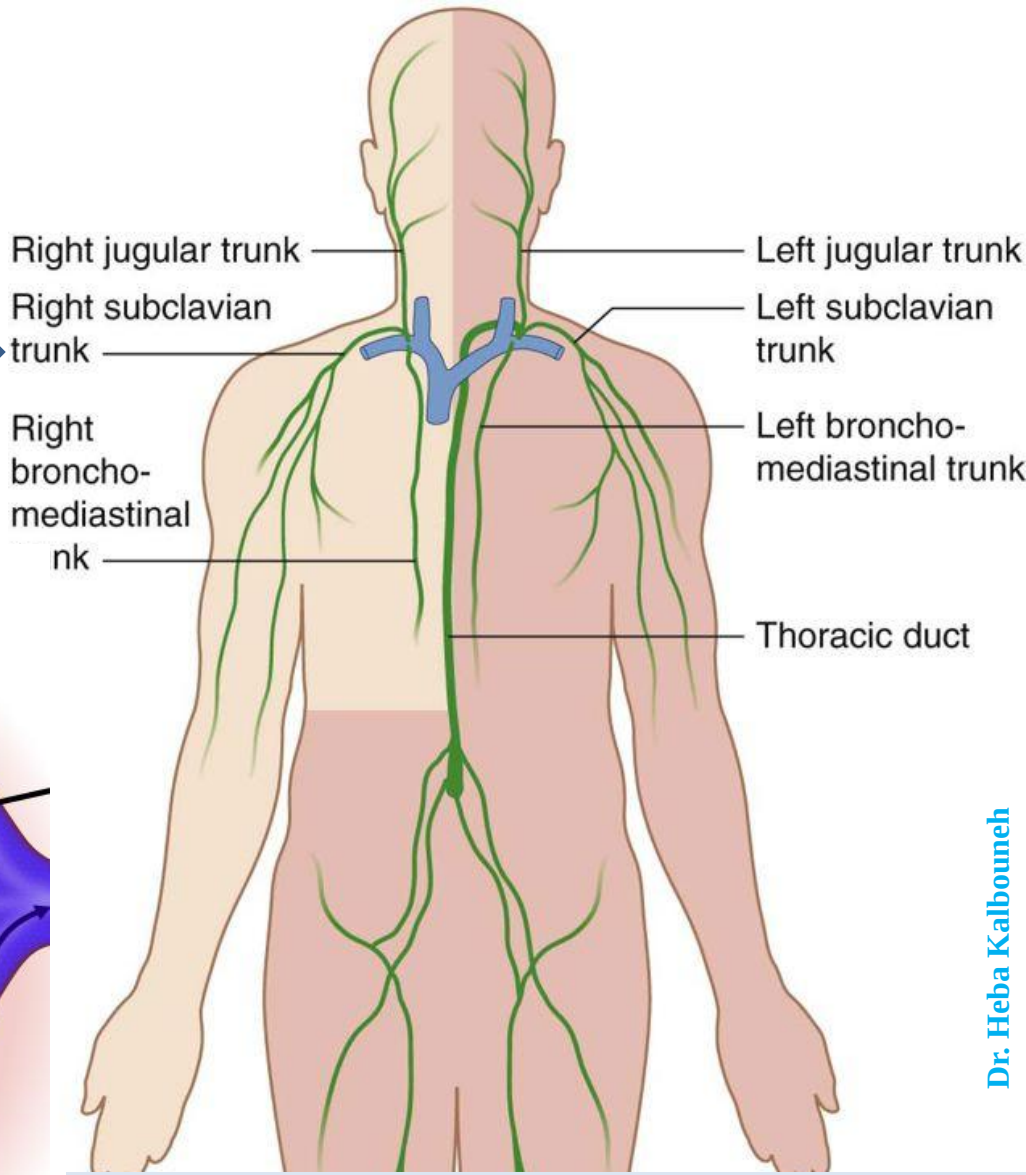
Lymphatic vessels function to drain this excess fluid from the tissues as lymph and return interstitial fluid to the blood.



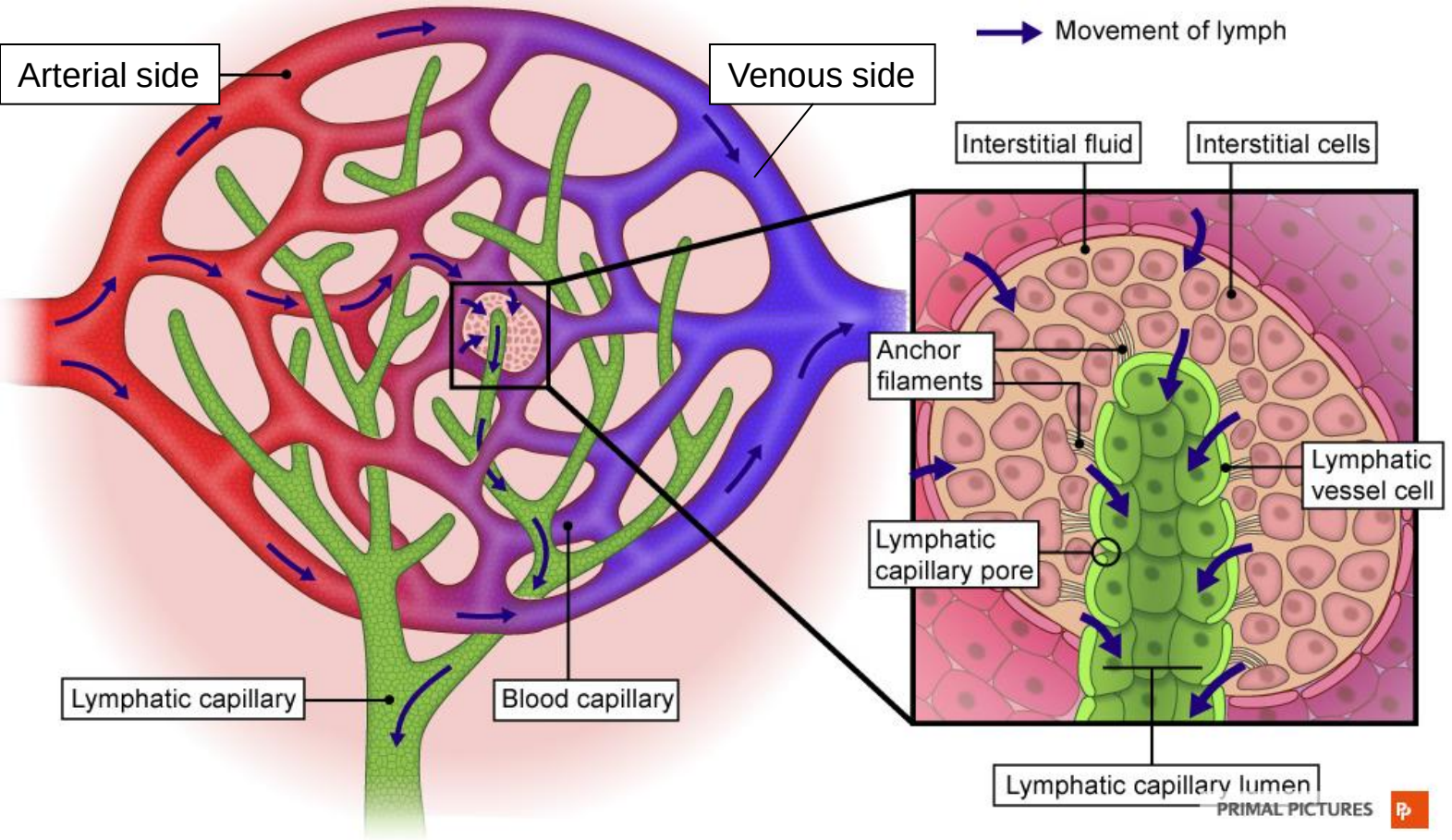
Lymphatic vessels begin as "porous" blind-ended lymphatic capillaries in tissues of the body and converge to form a number of larger vessels, which ultimately connect with large veins in the root of the neck.



(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 made of overlapping endothelial cells. The overlapping flaps function as a one-way valve.

When fluid accumulates in the tissue, interstitial pressure increases pushing the flaps inward, opening the gaps between cells, allowing fluid to flow in.

As pressure inside the capillary increases, the endothelial cells are pressed outward, closing the gaps, thus preventing backflow.

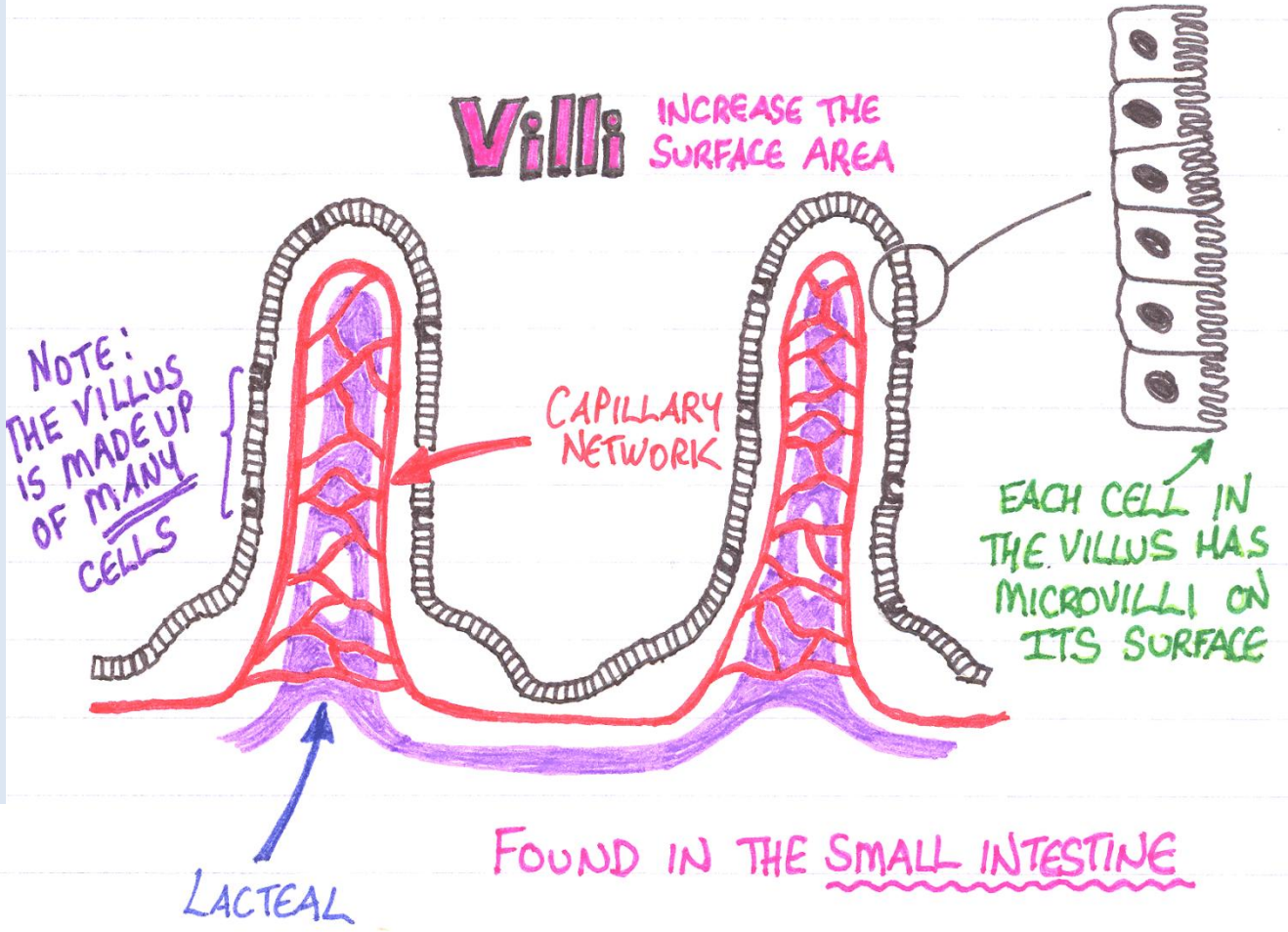
Unlike blood capillaries, the gaps in lymphatic capillaries are so large that they allow bacteria and immune cells (ex. macrophages) to enter. This makes the lymphatic system a useful way for large particles to reach the bloodstream.

Remember: lymphatic system is used, for example, for dietary fat absorption in the intestine.

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 can be found throughout the body, however, they aggregate in places where they are most likely to come into contact with pathogens.

Lymphocytes are produced within the red bone marrow and are transported via the blood vessels to lymphatic organs and tissues.

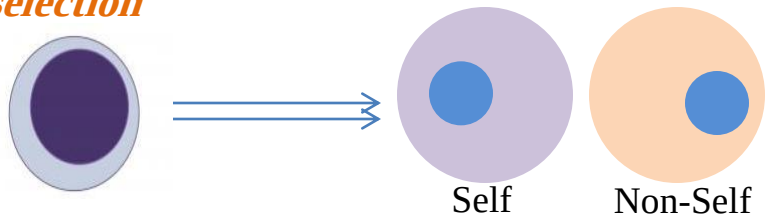
Lymphatic organs are divided into:

<u>Primary lymphatic organs</u>

Bone marrow.

Thymus gland.

Are sites of Lymphocyte production, maturation, selection



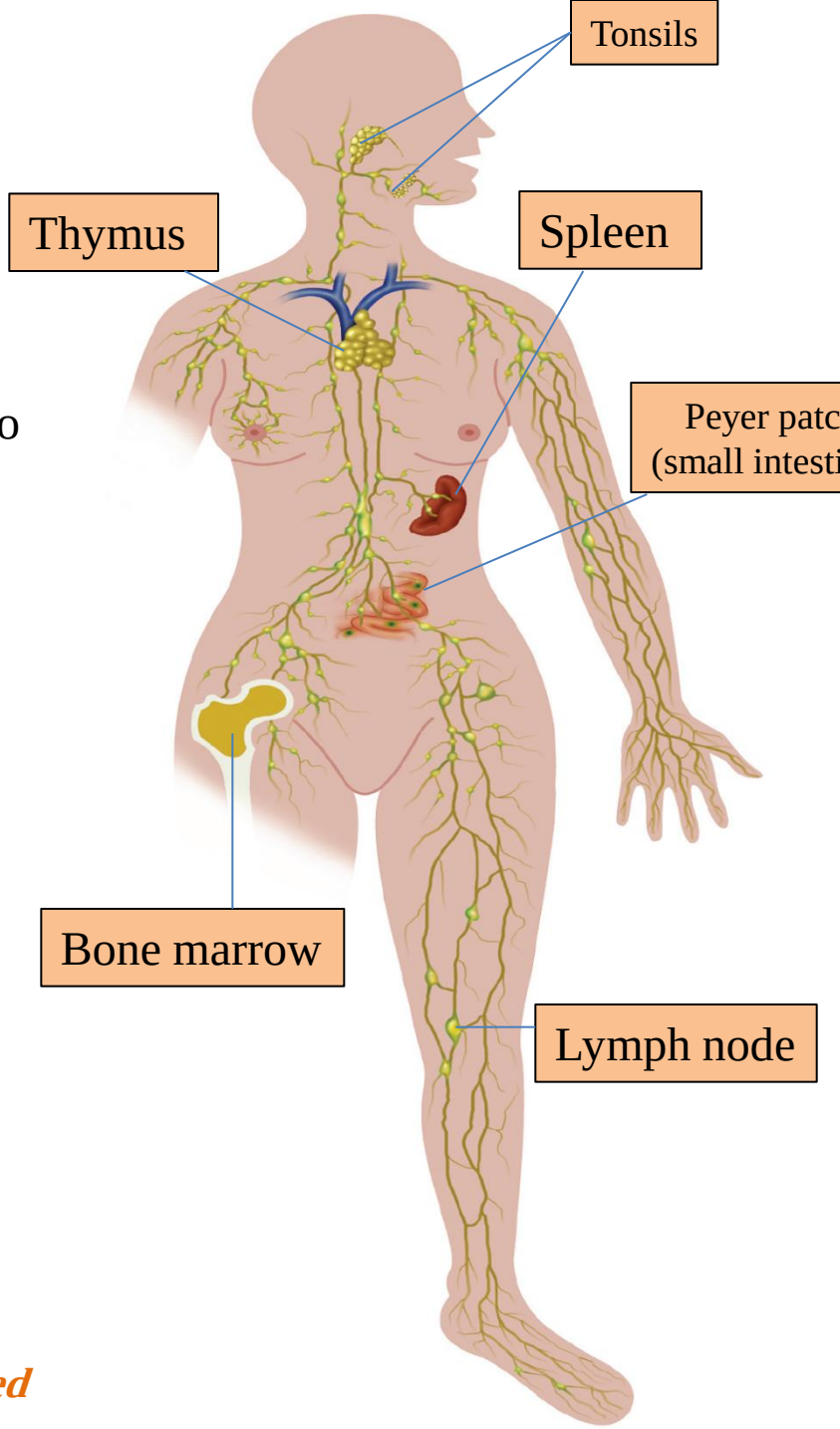
<u>Secondary lymphatic organs</u>

Diffuse lymphatic tissue (lymphatic nodule).

Spleen.

Lymph nodes.

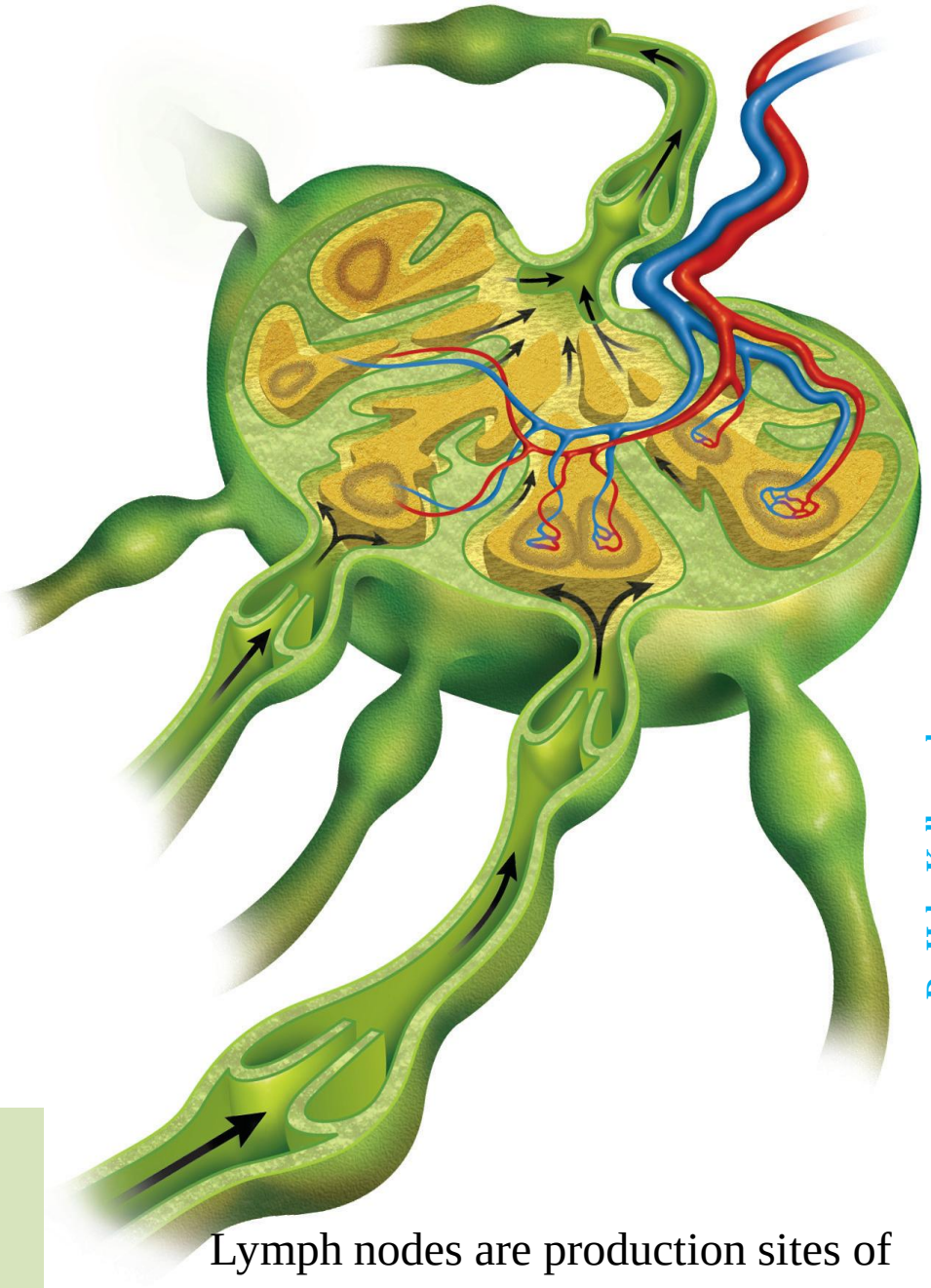
Are sites to encounter pathogens and become activated



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
✓Lymph nodes are up to 3 cm in length
✓Immunocompetent B cells and T cells are suspended throughout the lymph node
✓Nodes filter the lymph, removing foreign material and microorganisms.
✓ All lymph is filtered by at least one lymph node before it returns to the blood.
✓Antibody- mediated and cell- mediated immune responses occur in the lymph nodes
✓Lymph nodes congregate around blood vessels in clusters and are usually named according to the vessel or location that they are associated with.

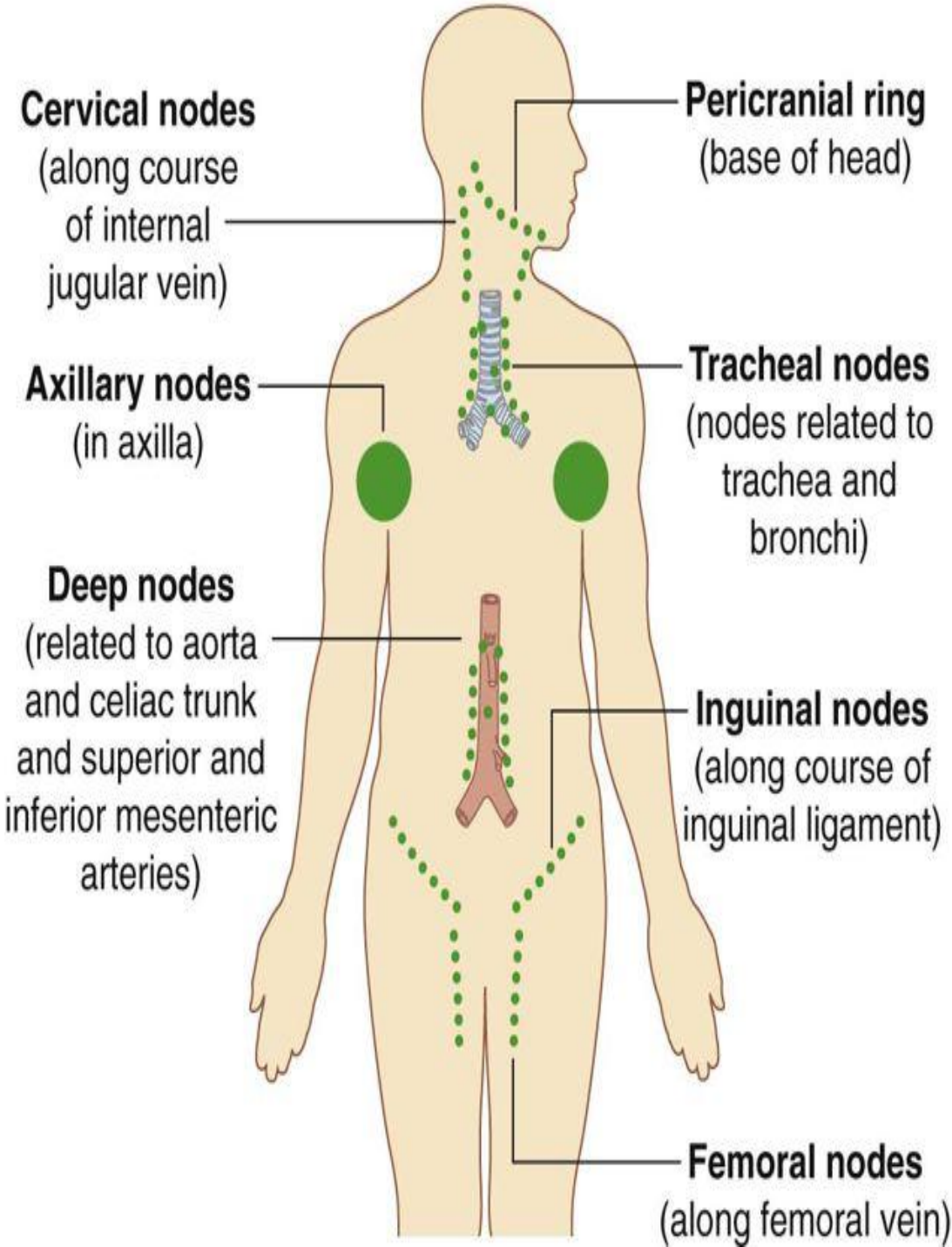
Lymph node enlargement can happen in cases of lymphoma (painless lymphadenopathy) or infection (painful).



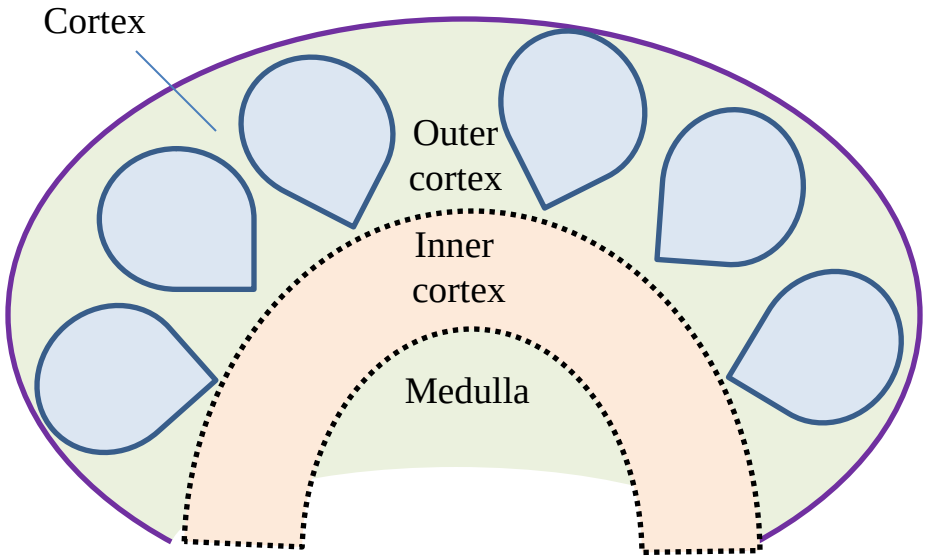
Lymph nodes are production sites of antibodies and activated lymphocytes

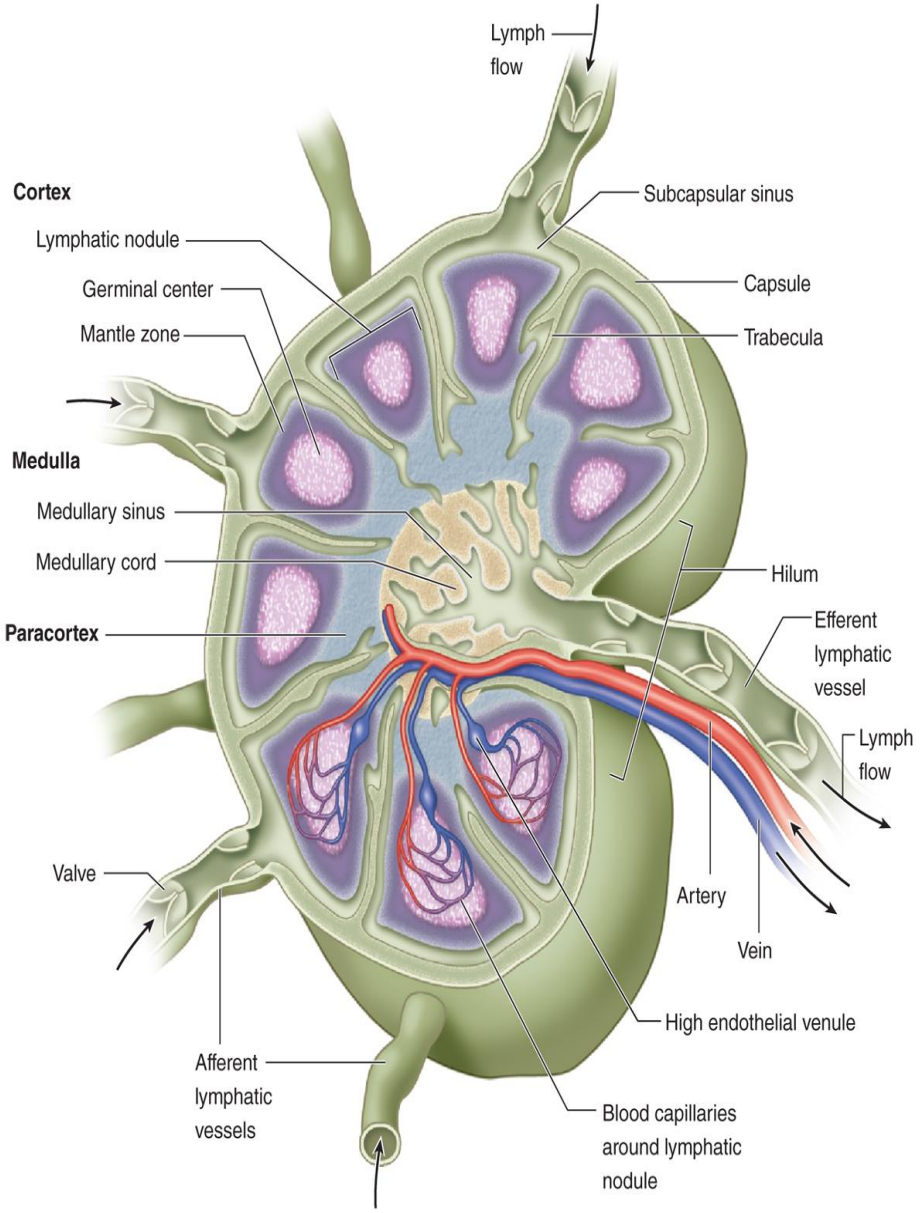
The main groups of lymph nodes include:

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



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



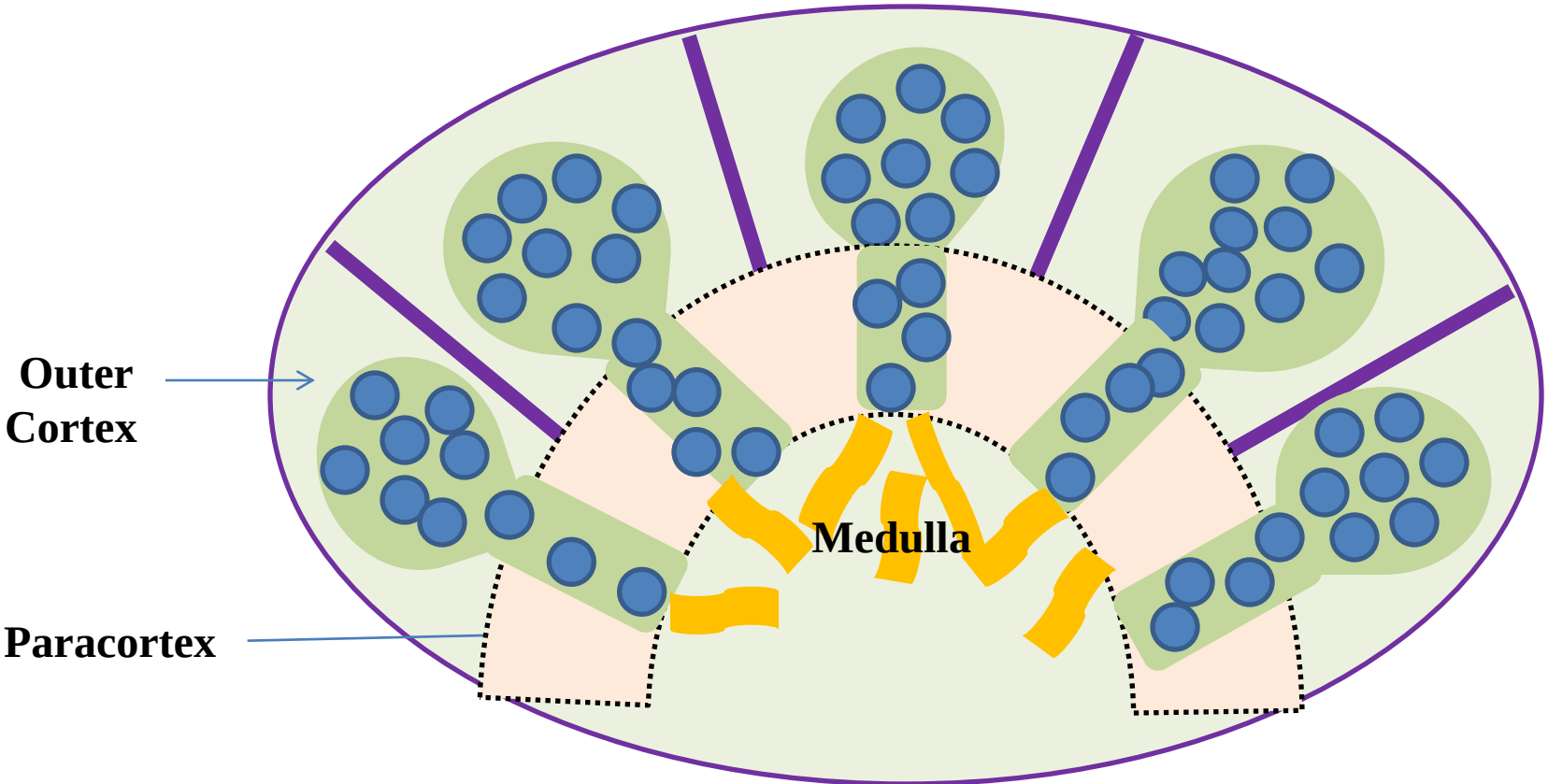


Cortex	Medulla
Contains lymphatic follicles	No follicles
Receives lymph from afferent vessels	Forms sinuses that lead to efferent vessels at the hilum

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.

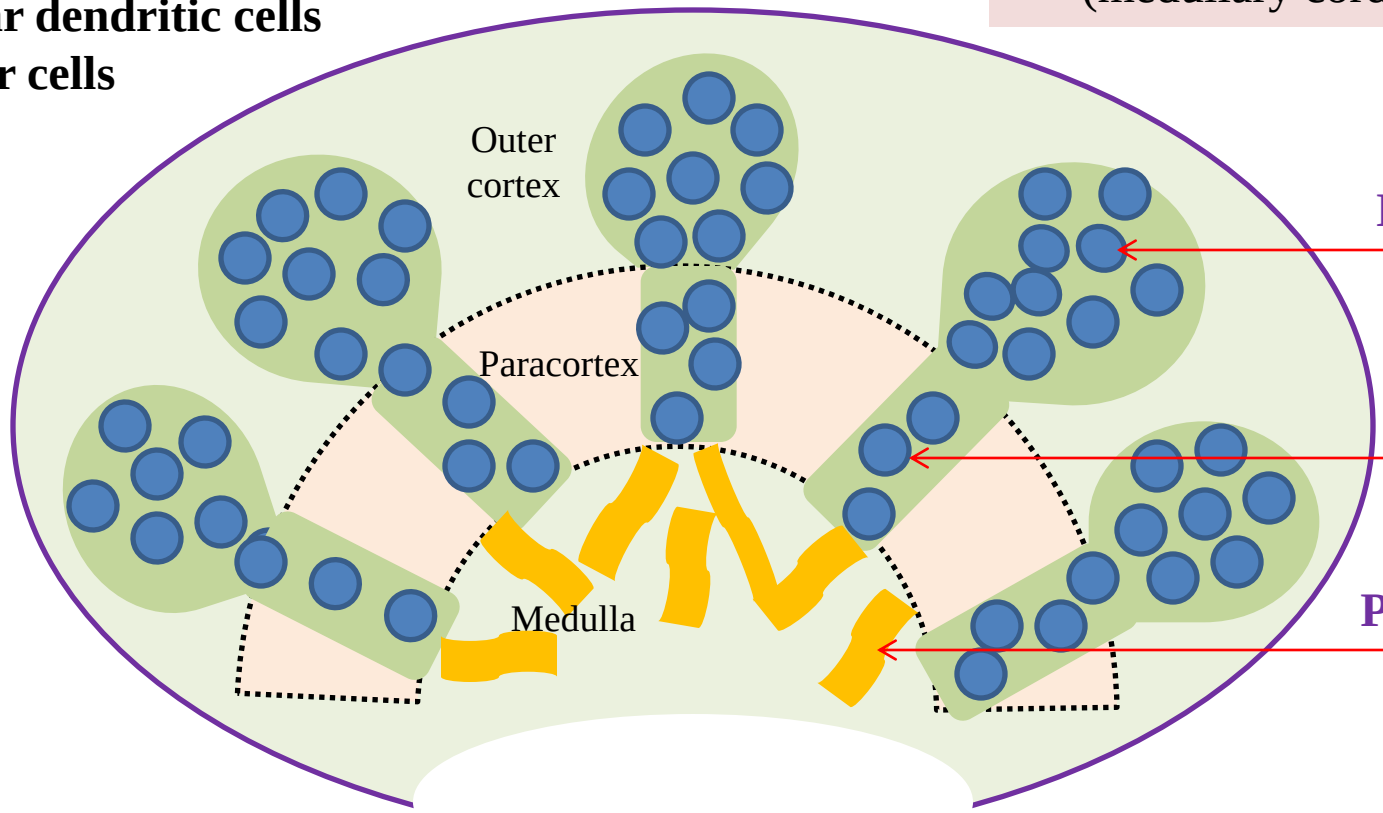


The **outer cortex** has lymphatic follicles that mostly contain **B-cells.**
The **inner cortex (paracortex)** contains mostly **T-cells.**
The **medullary cords** contain mostly **plasma cells.**

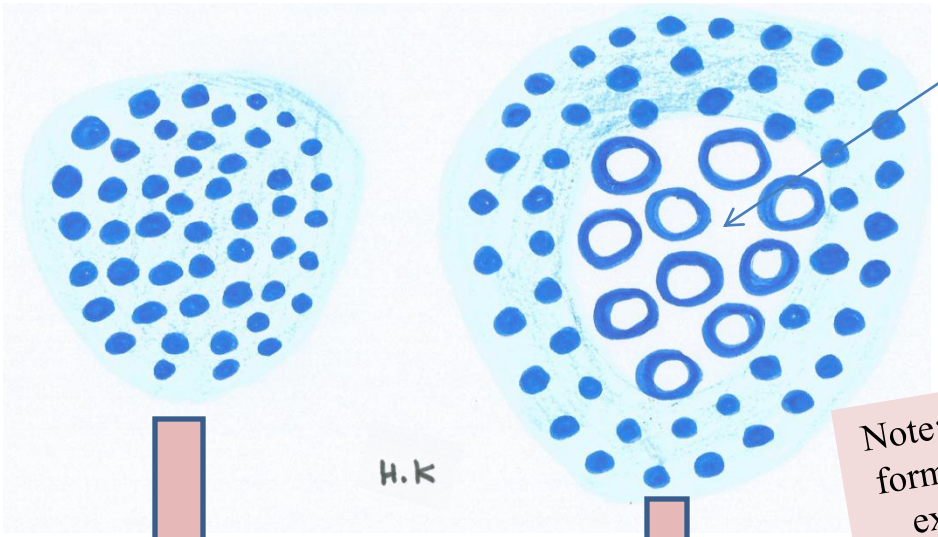
Other cells in the lymph node:
Macrophages
Dendritic cells
Follicular dendritic cells
Reticular cells

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

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

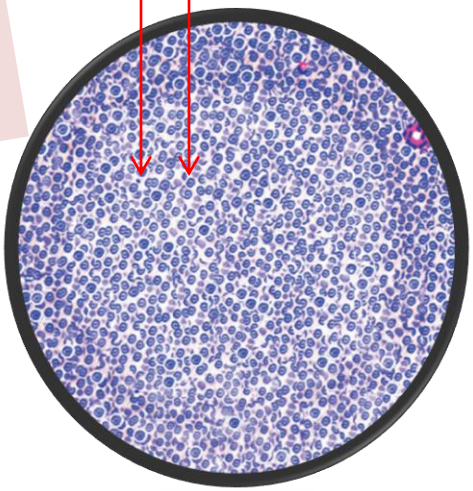


The outer cortex houses lymphatic follicles (nodules) which are of two types:



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

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

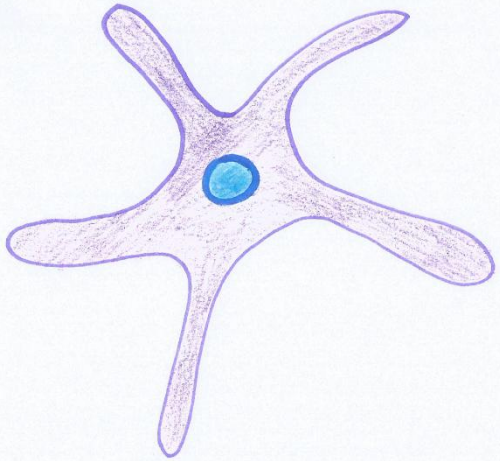


Primary follicles: lymphoid follicles without a germinal center. (virgin B cells)

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

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

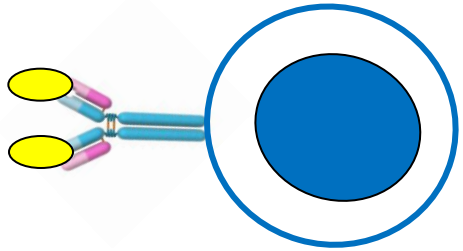
Macrophage



Dendritic cell

Macrophages and Dendritic cells capture antigen within tissues and transport antigen to secondary lymphoid 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
Location in lymph node	Cortex and medulla	Cortex and medulla	Outer cortex



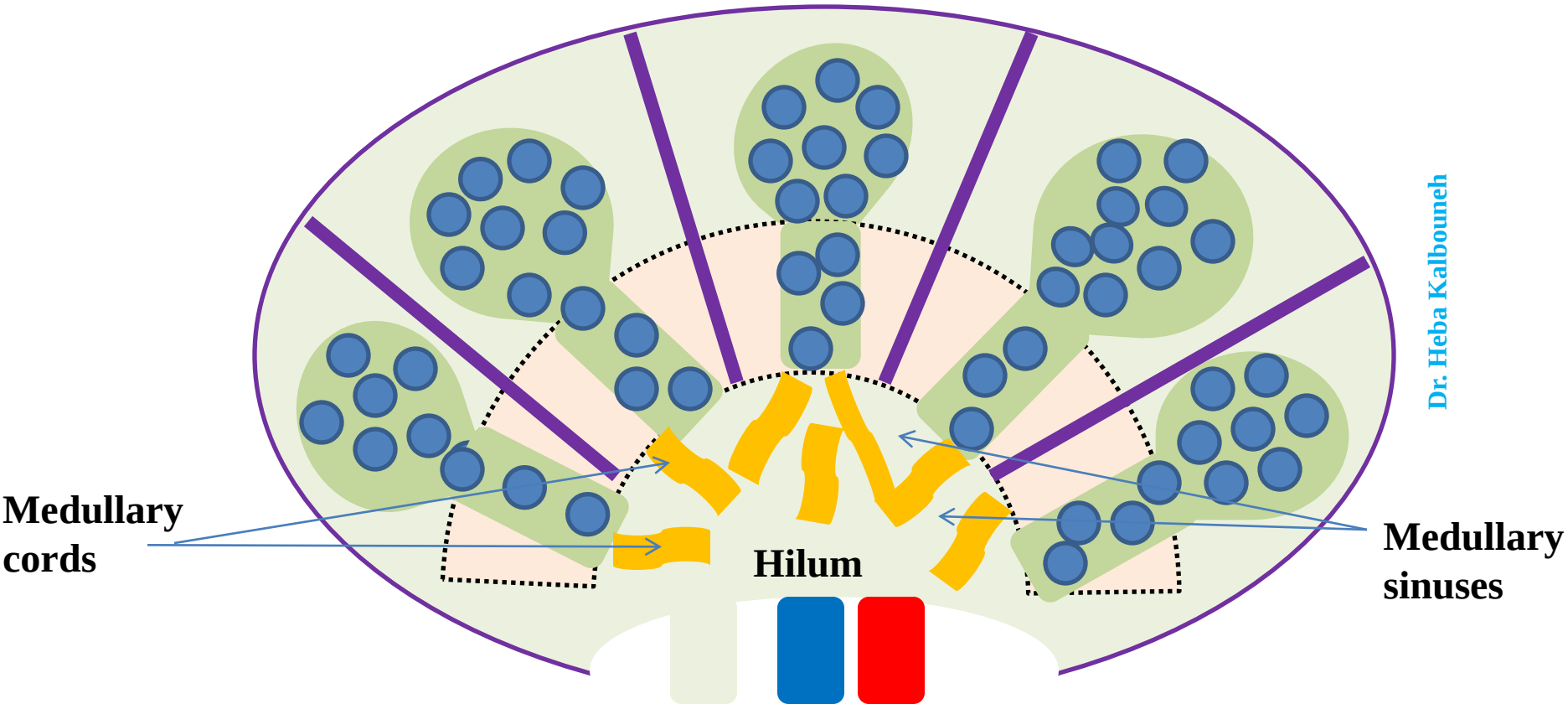
Are antigen **HOLDING** cells
Holds the Ag for long time

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 surface, each containing valves to prevent backflow of lymph.

Subcapsular sinuses

Each afferent vessel empties into the subcapsular sinus.

Trabecular sinuses

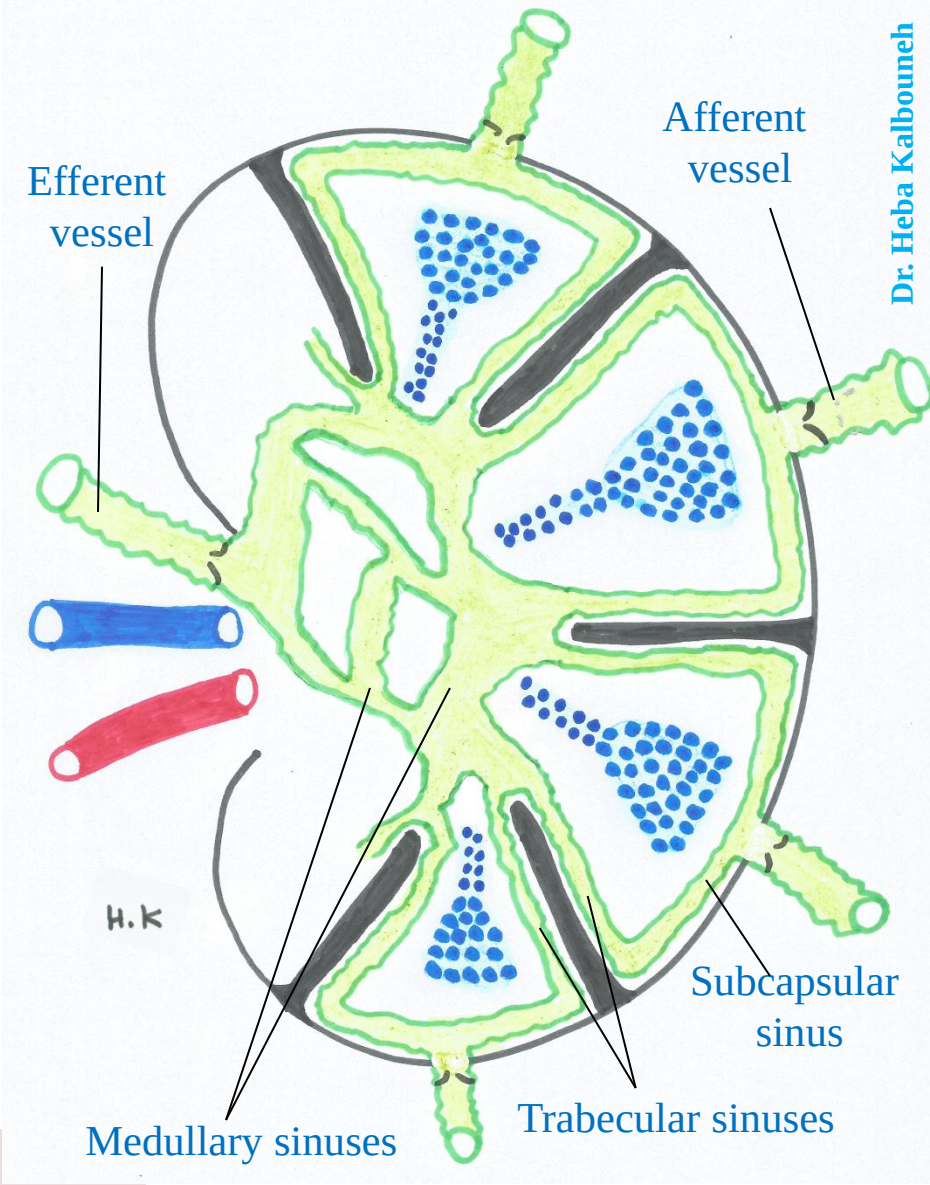
The trabecular sinuses are a continuation of the subcapsular sinuses that follow the trabeculae and drain into the medullary sinuses.

Medullary sinuses

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

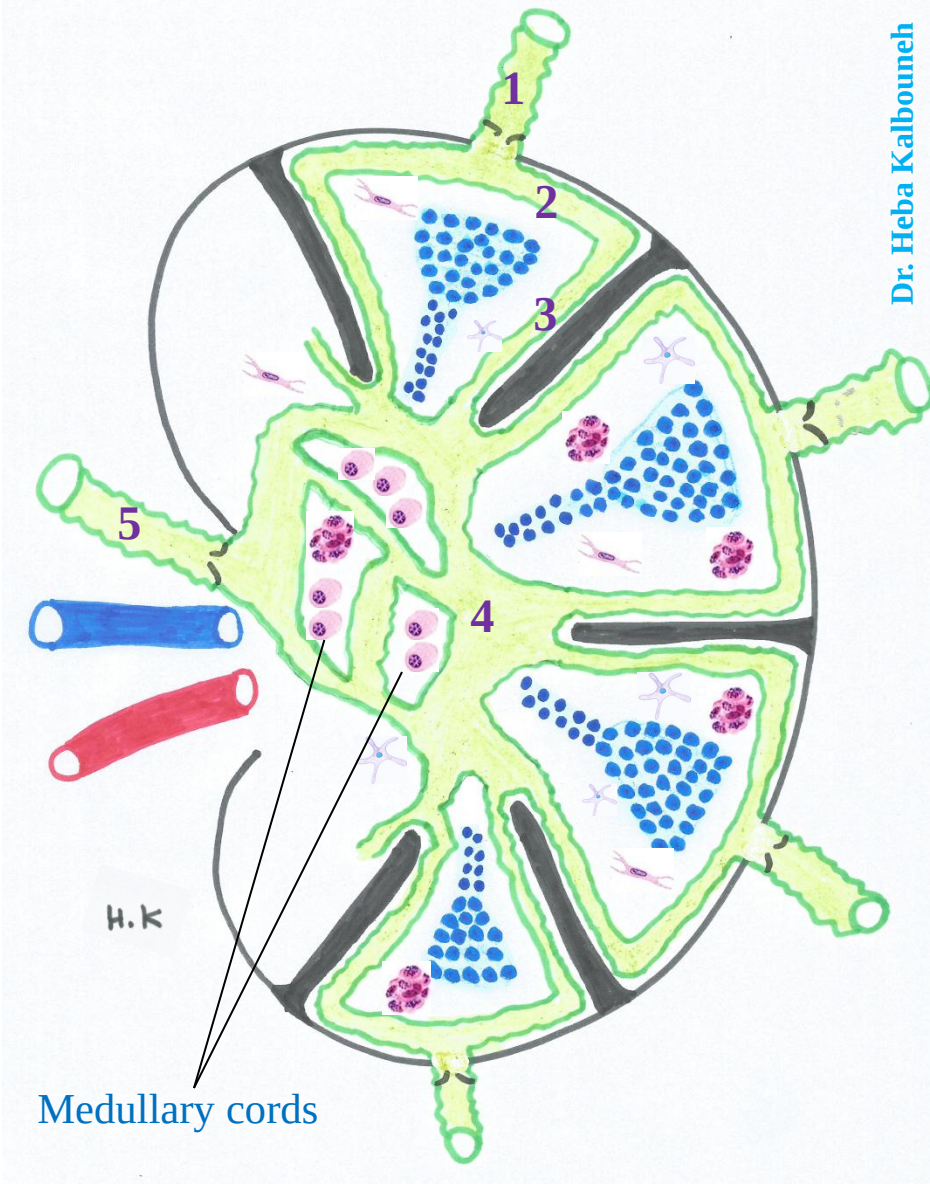
Lymph flow

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

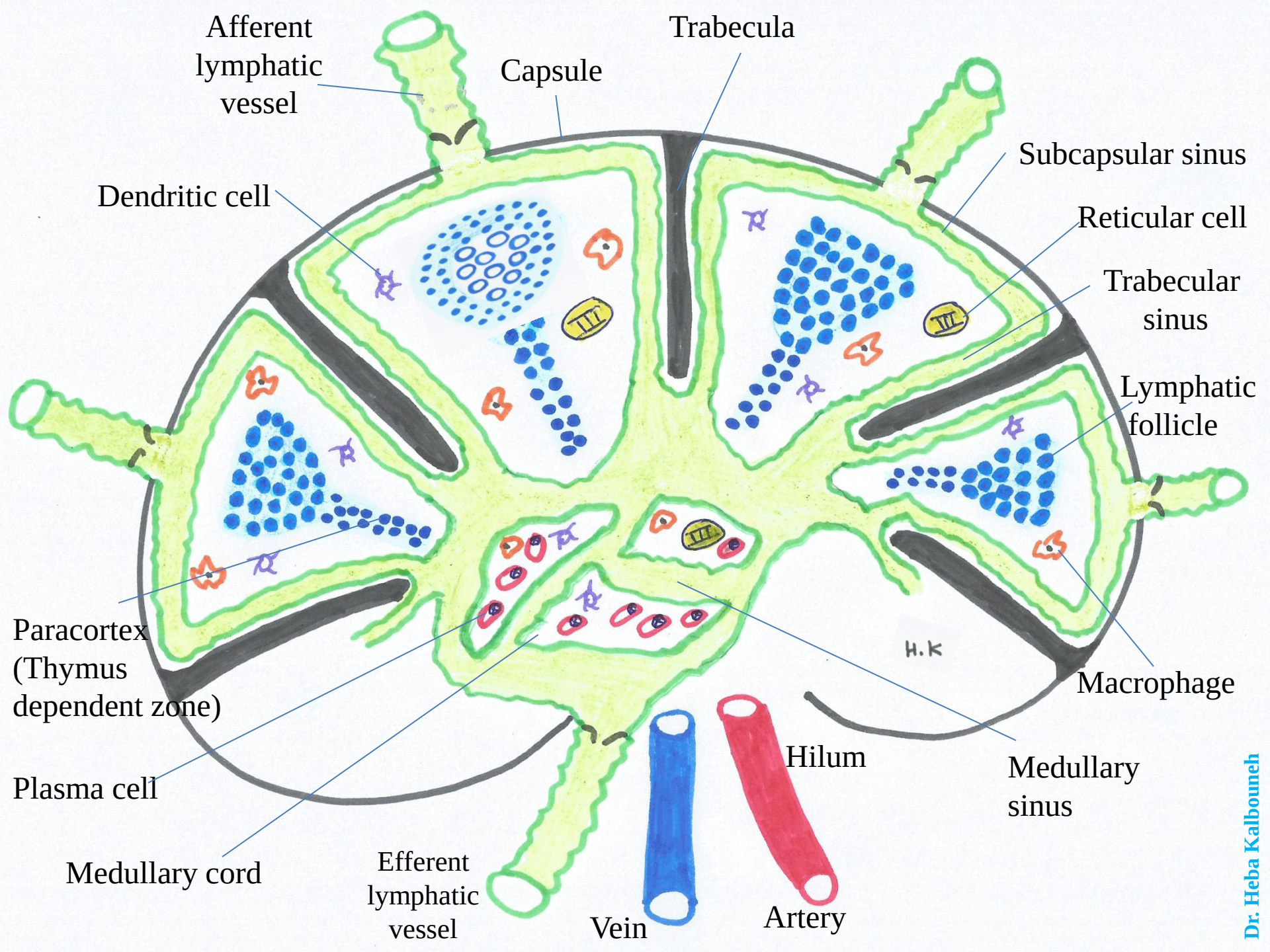
Lymph, containing micro-organisms, soluble antigens and antigen presenting cells, enters the lymph node via **afferent lymphatic** vessels **(1)** which enter the **subcapsular sinus (2)**. It then runs through **trabecular** (**cortical) sinuses (3)** into **medullary sinuses (4)** and leaves through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

Efferent lymph contains lots of activated T-lymphocytes, activated B-lymphocytes, plasma cells and antibodies.

Lymph slows down when it passes in lymph nodes.



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


Afferent lymphatic vessel
Capsule
Trabecula
Subcapsular sinus
Dendritic cell
Reticular cell
Trabecular sinus
Lymphatic follicle
Paracortex (Thymus dependent zone)
Macrophage
Plasma cell
Medullary sinus
Hilum
Medullary cord
Efferent lymphatic vessel
Vein
Artery
H.K
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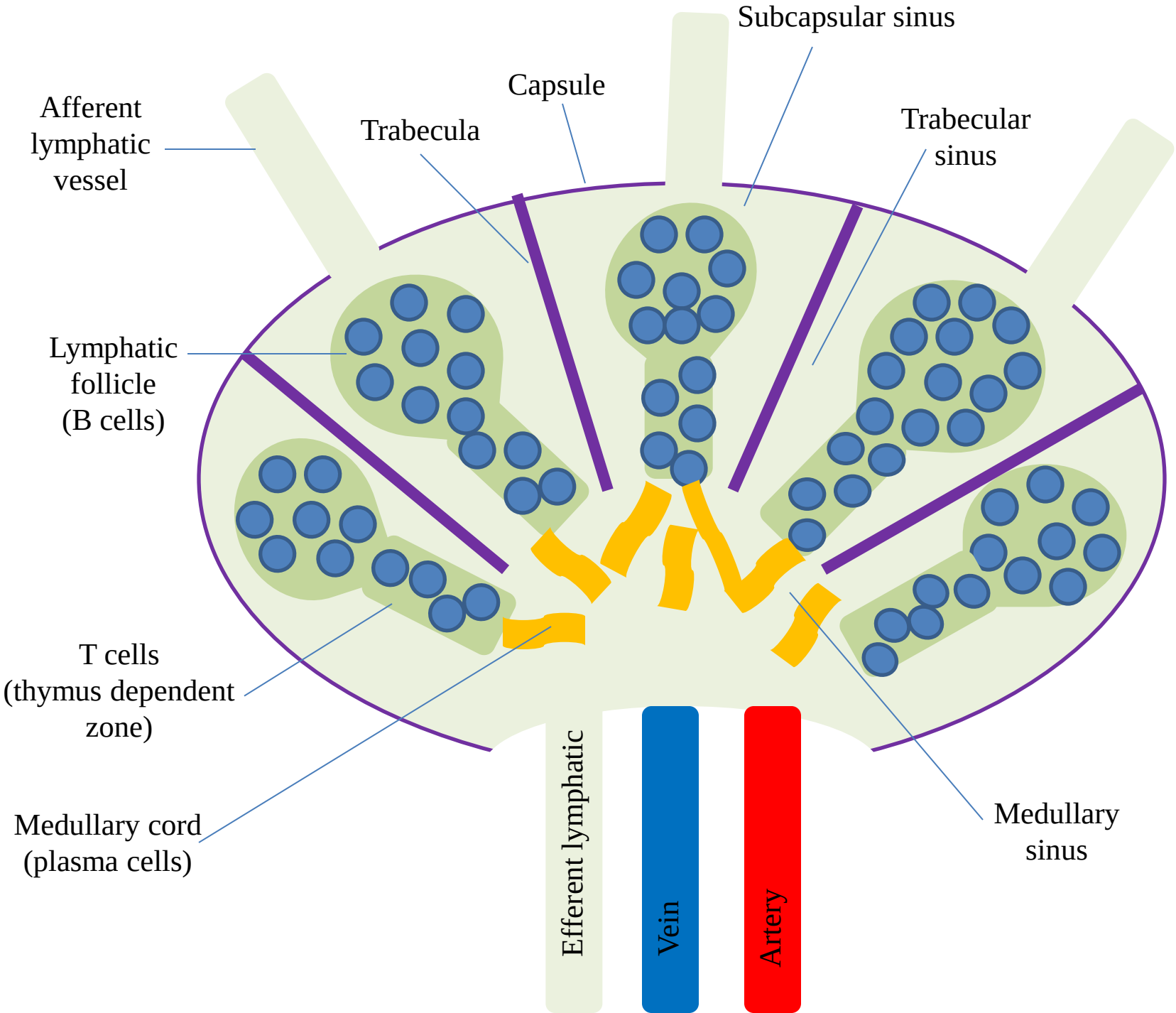


Lymphocytes can enter lymphoid tissues in two ways:

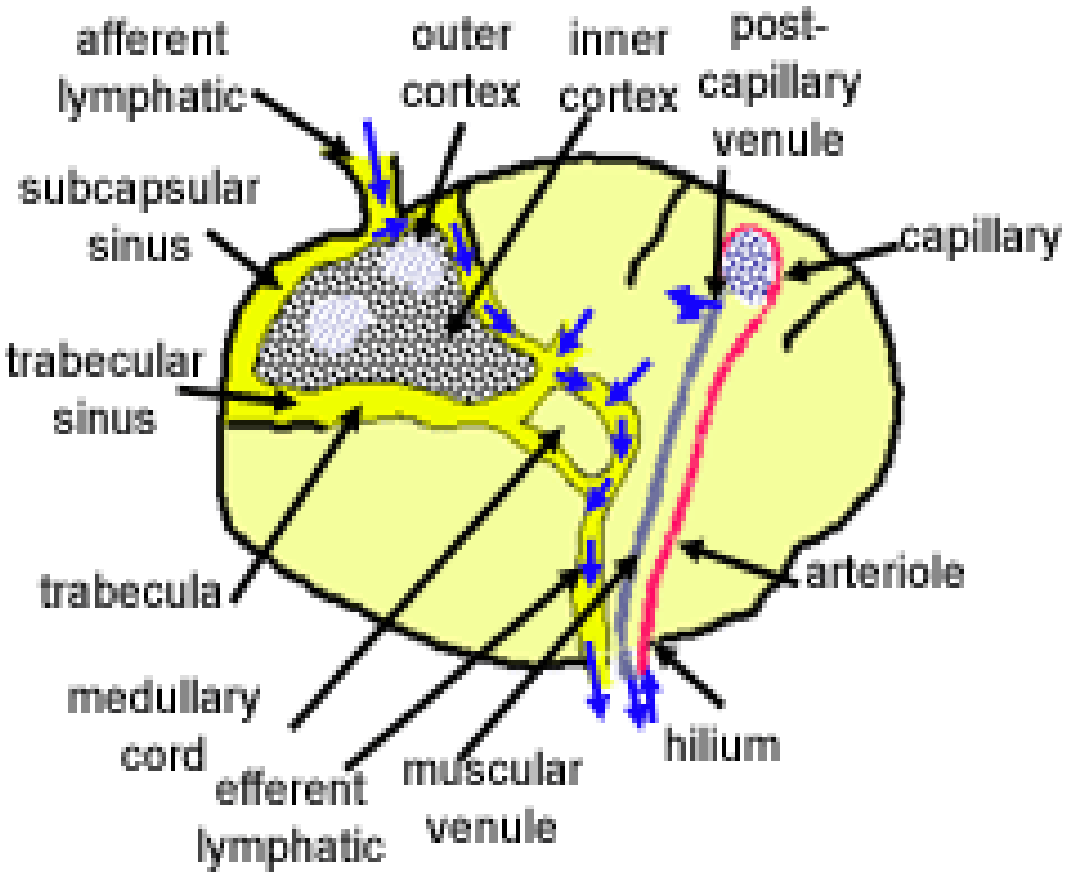
1) Direct entry into lymph nodes via afferent lymphatics

2) Entry from blood capillaries across specialized endothelial cells present in the postcapillary venules (High Endothelial Venules= HEV) within the **paracortex** of the lymph node

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

The structure of the post-capillary venule, in the paracortex is unusual in that it is not lined by simple squamous epithelium, but by a **simple cuboidal epithelium.** These are called high endothelial venules (HEVs) Lymphocytes recognise and adhere to these endothelial cells, and squeeze through them into the paracortex

The process of lymphocyte recirculation is regulated by adhesion molecules on lymphocytes called **Homing receptors** and their ligands on vascular endothelial cells called **Adressins**



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

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)

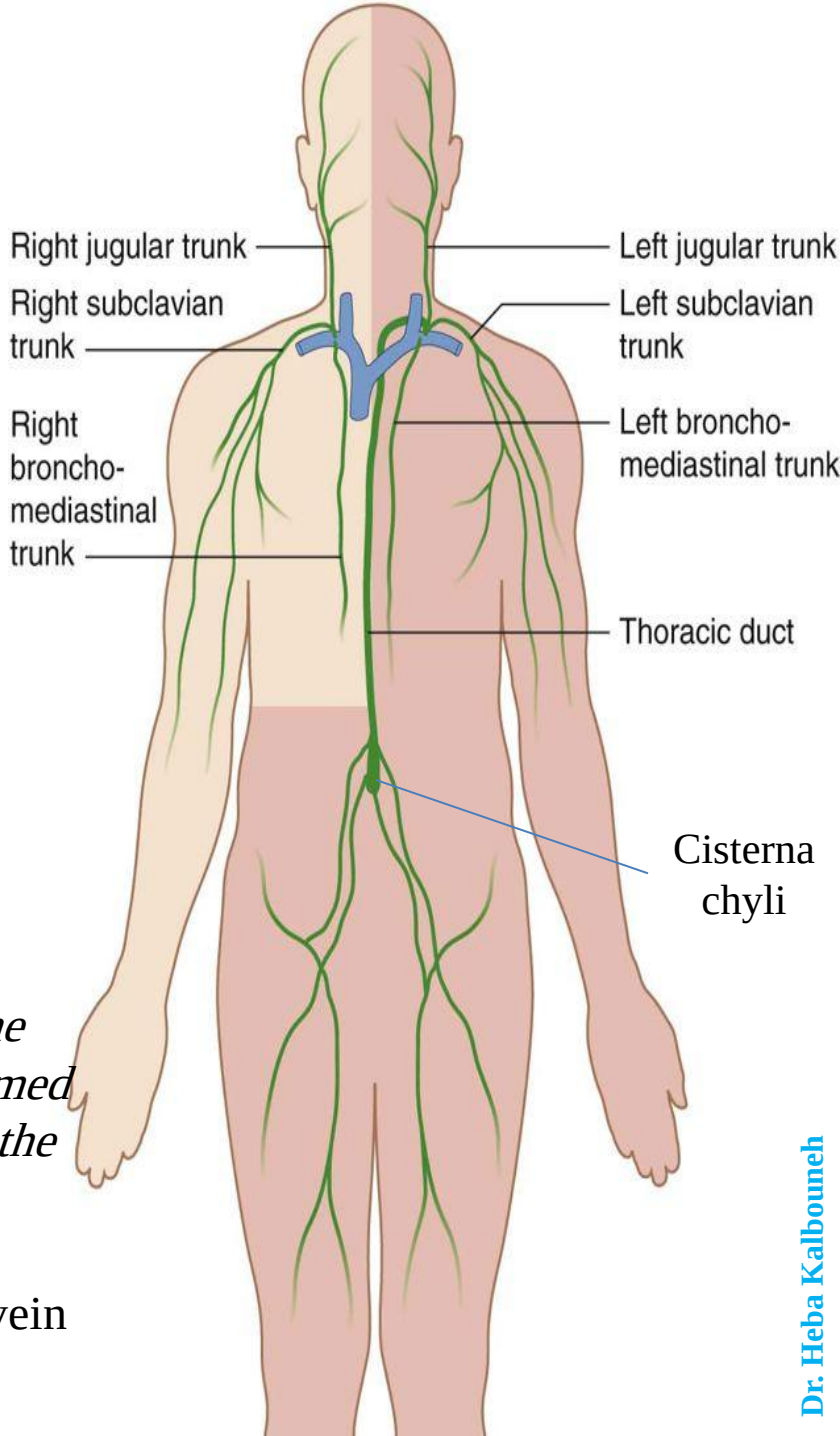
✓Is larger and drains lymph from the rest of the body.

✓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)

Weighs **7** ounces (200gm)

Lies under ribs **9** to **11**

✓ Has a notched anterior border.

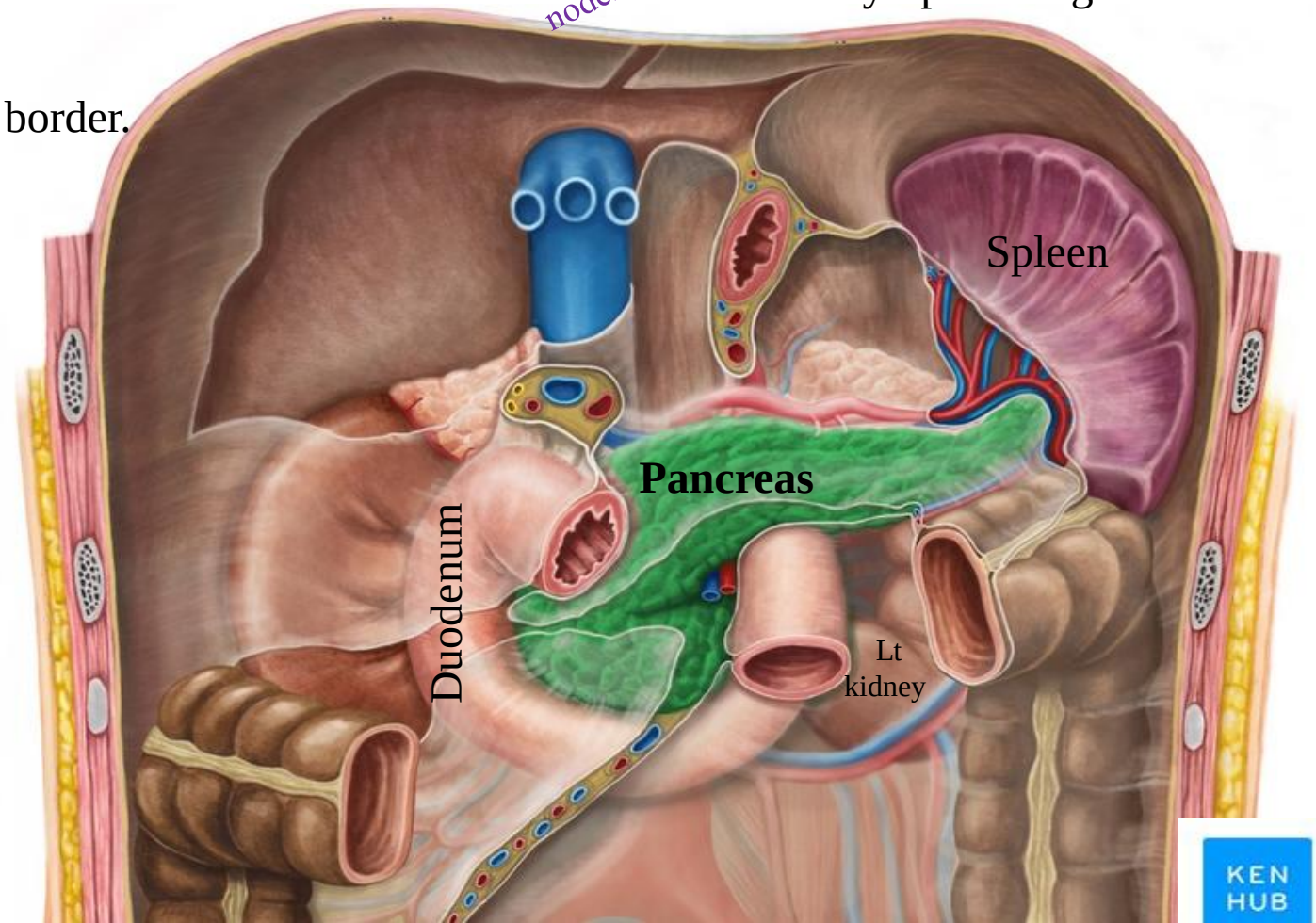
The spleen is the organ of odds number 1, 3, 5, 7, 9 , and11

The spleen resembles a large lymph node

The spleen filters the blood while lymph nodes filter the lymph

✓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



Functions

✓Filtration of blood (defense against blood-borne antigens)

✓ The main site of old RBCs destruction.

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

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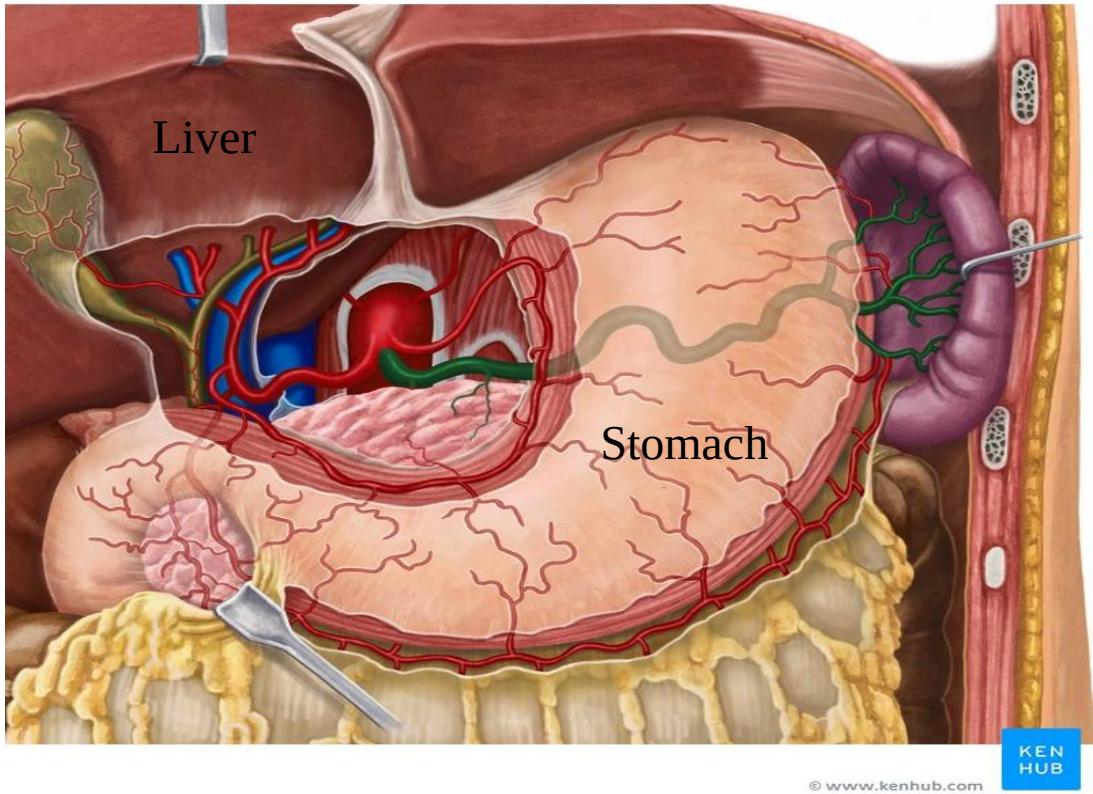
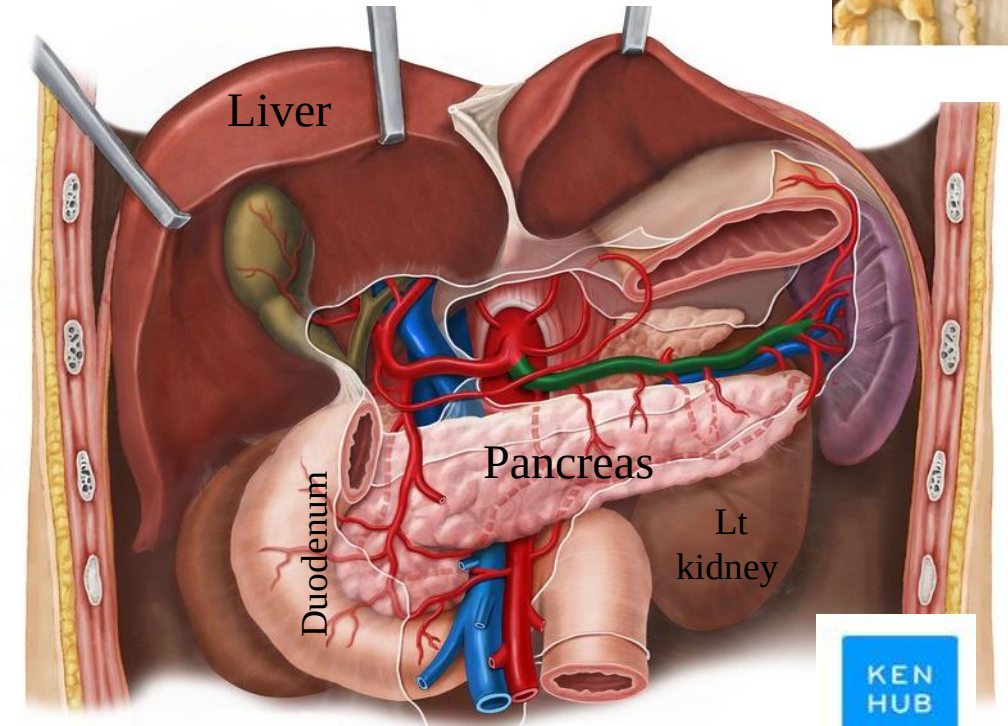
The **splenic artery** is the largest branch of the celiac artery. It has a tortuous course as it runs along the upper border of the pancreas. The splenic artery then divides into about six branches, which enter the spleen at the hilum

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





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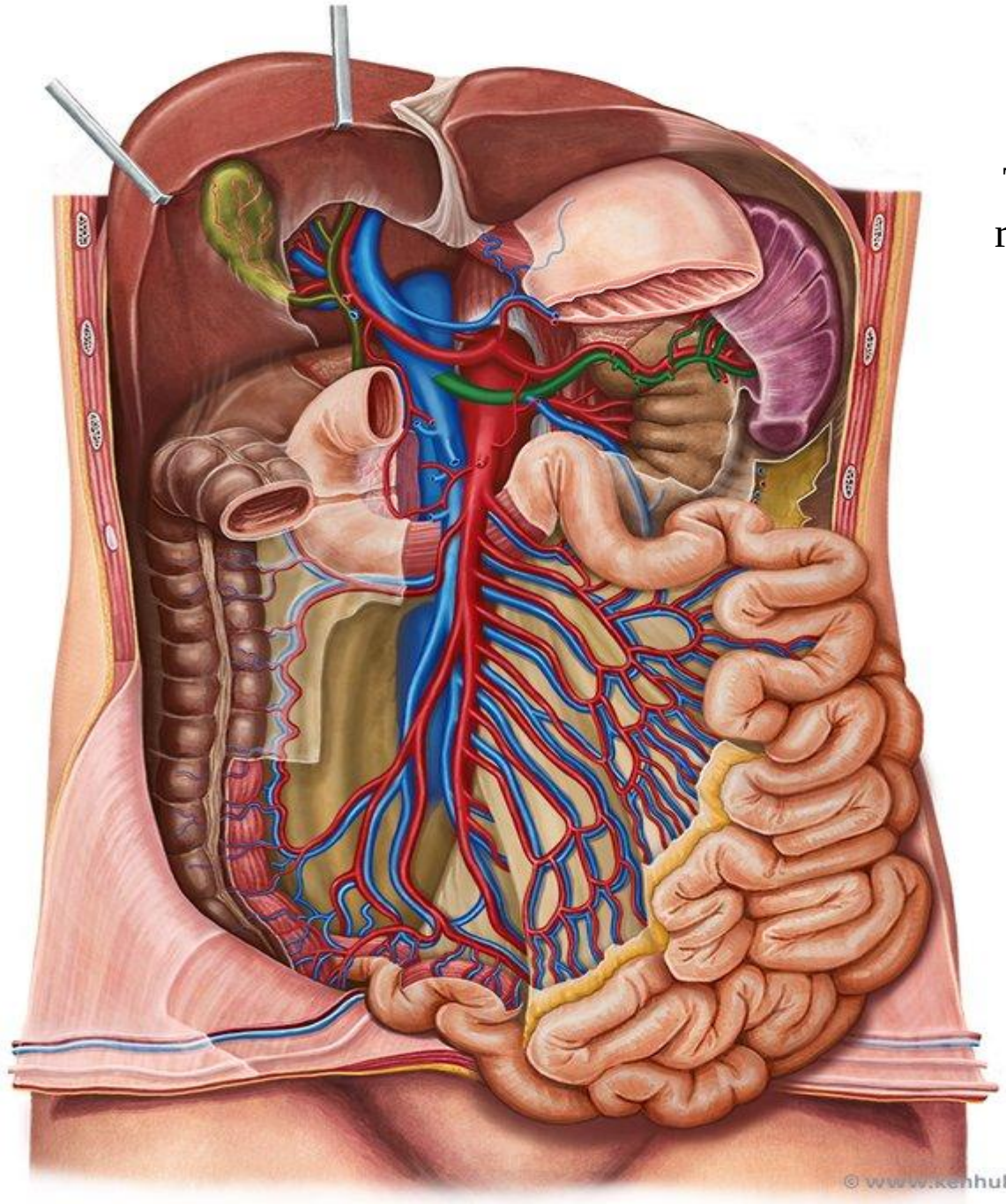


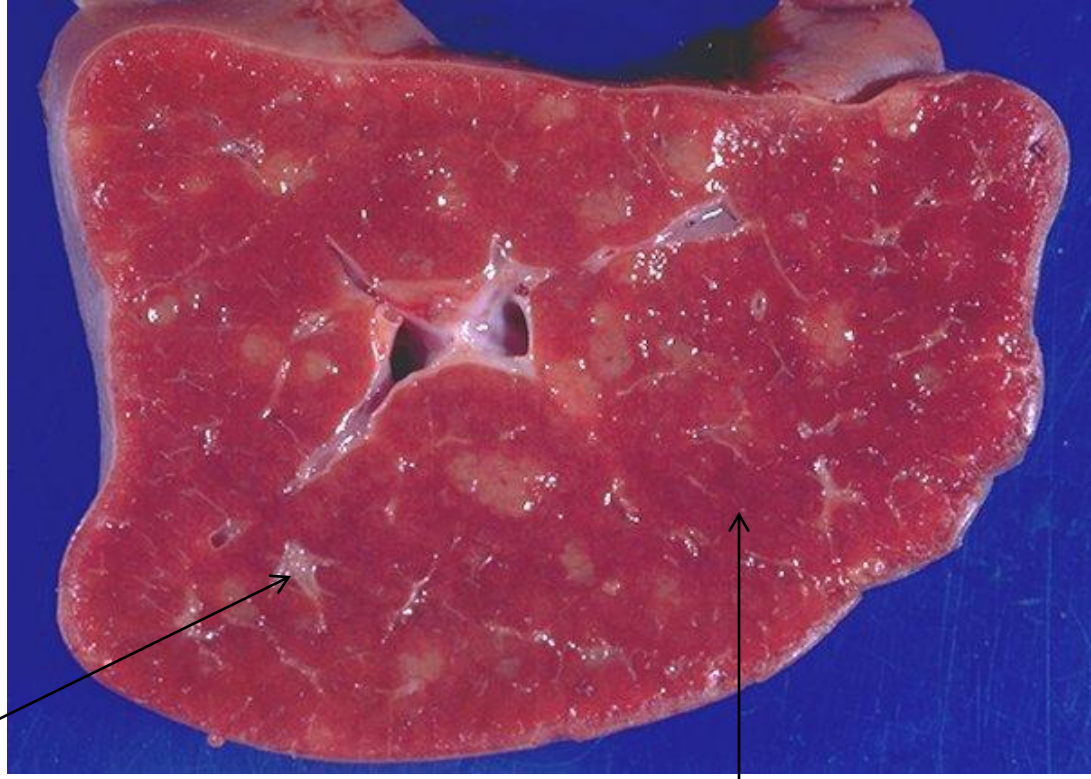
The **splenic vein** leaves the hilum and runs behind the tail and the body of the pancreas. Behind the neck of the pancreas, the splenic vein joins the superior mesenteric vein to form the portal vein

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

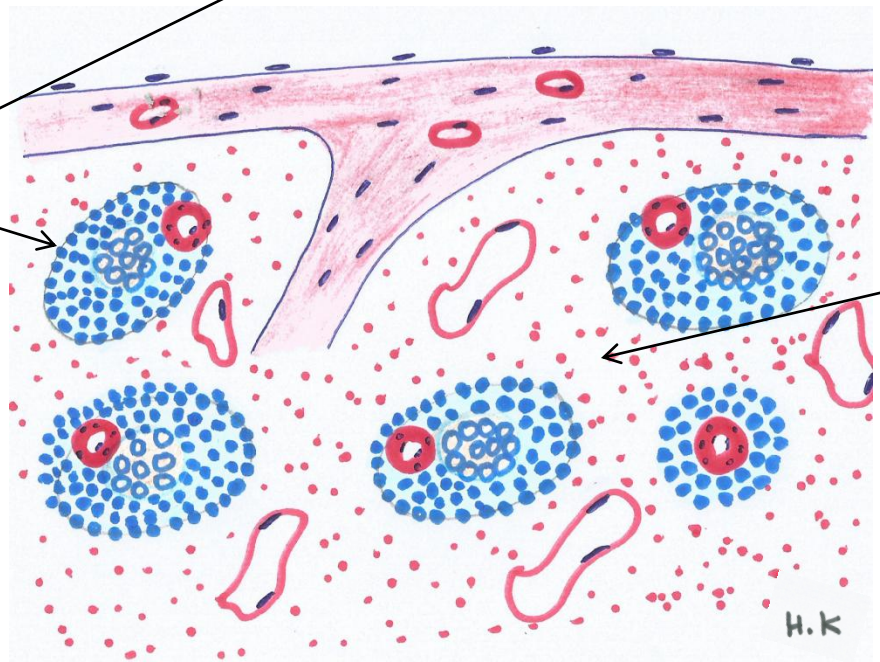
The parenchyma of the spleen appears in fresh specimen as:

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

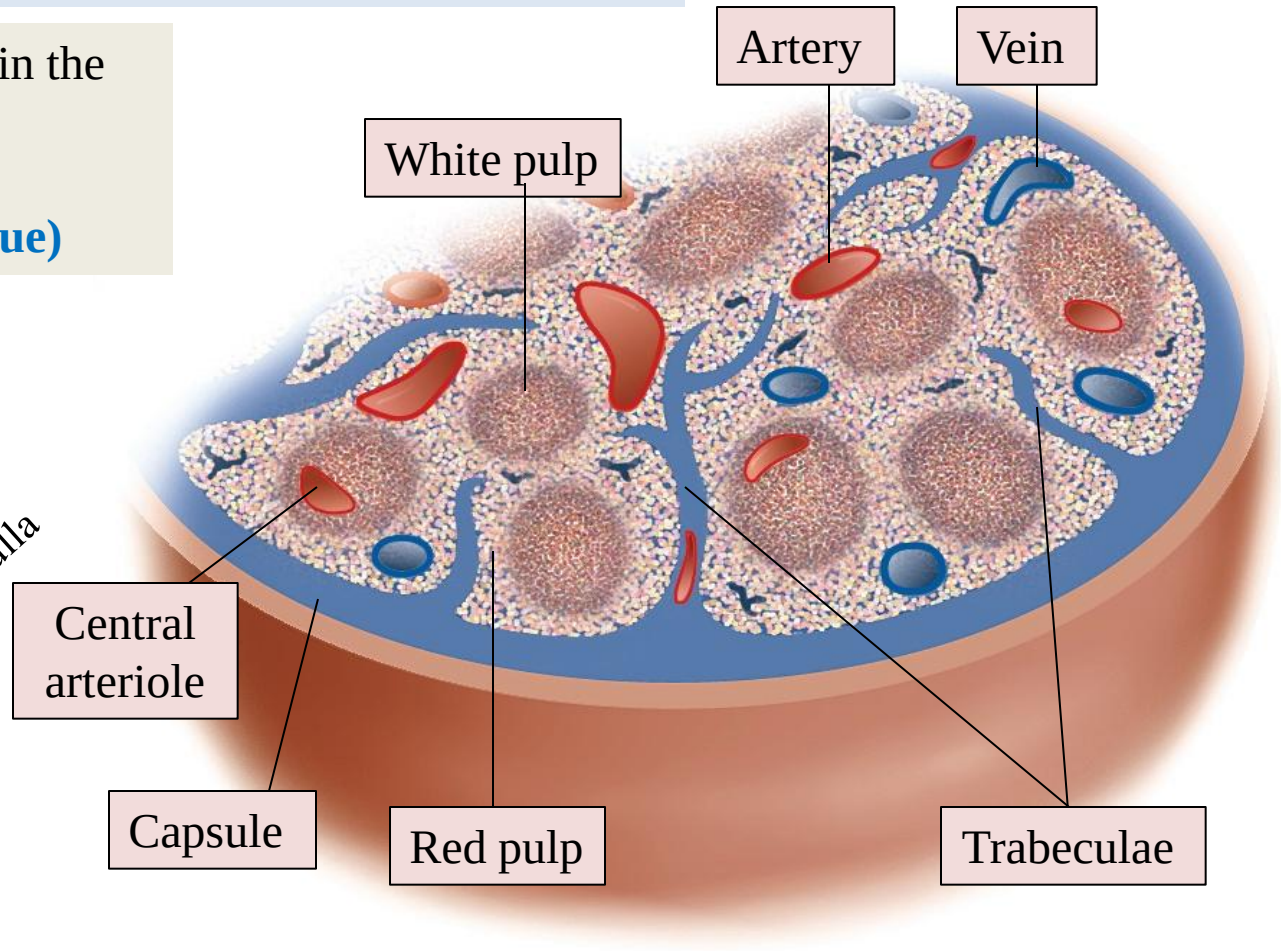
The spleen is covered by a **capsule** of dense connective tissue, and have capsular extensions called the **trabeculae**

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 pulp
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 lymphatic 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 *The morphology is like penicillus*
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.

Sheathed 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)

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 lymphatic 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

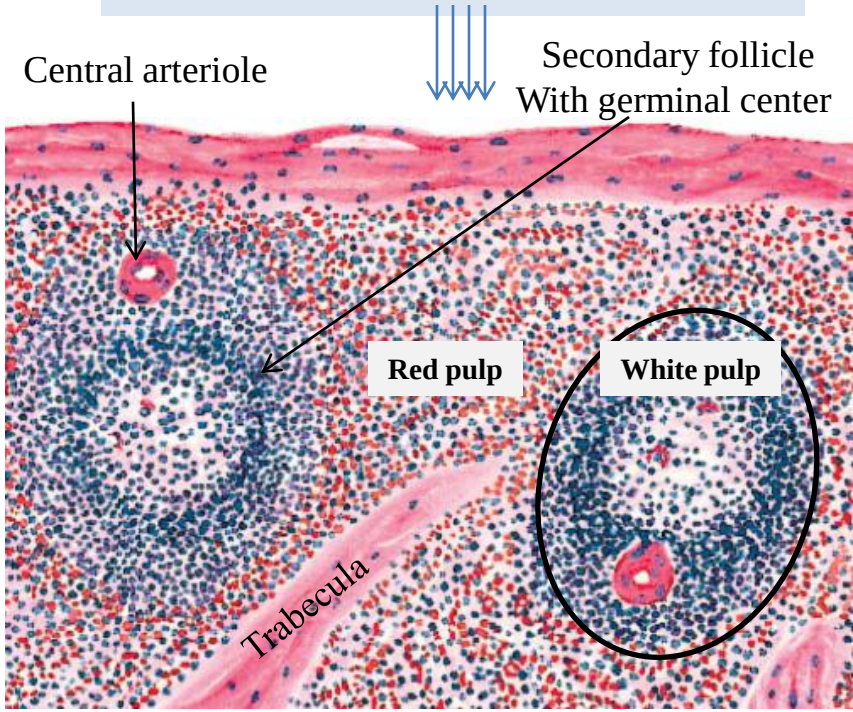
Secondary (stimulated) follicles contain activated B cells in a central region (germinal center)

Splenic nodules (Malpighian corpuscles)

Note: These follicles have the same structural organization as those found in lymph nodes

Function: The lymphocytes and phagocytes 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.



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

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 :

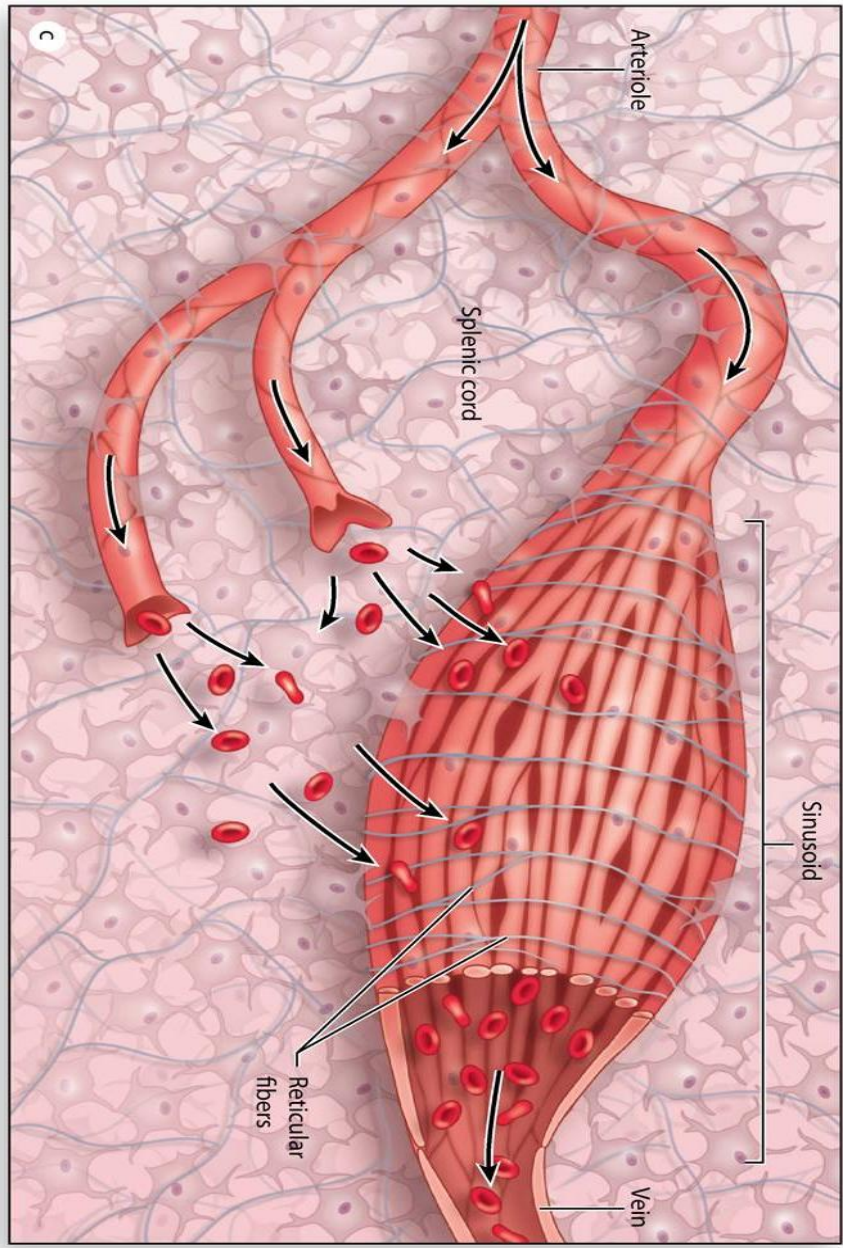
Splenic cords (Billroth's cords): consist of all cells between the sinusoids in the red pulp (reticular cells, macrophages, plasma cells, lymphocytes, RBCs, platelets, other leukocytes)

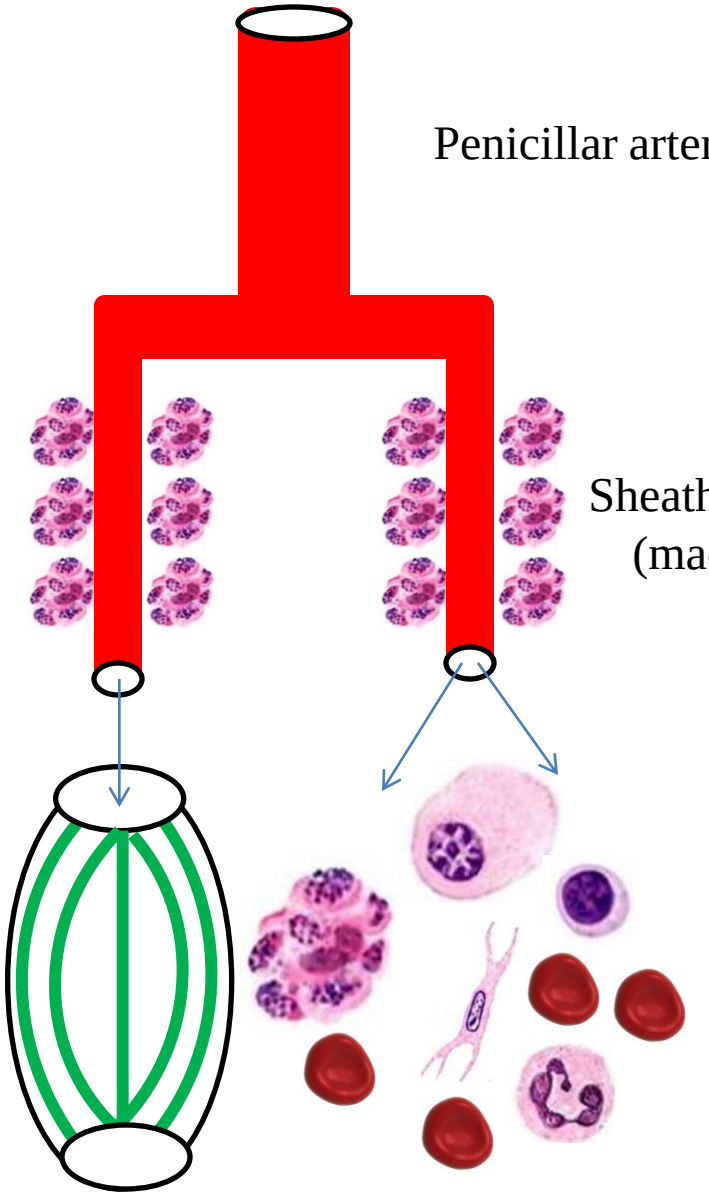
Splenic sinusoids: are blood- filled spaces located throughout the red pulp. They have large, dilated, irregular lumens and large pores (spaces between the endothelial cells)

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

↓↓**Red pulp**





Penicillar arteriole

Sheathed capillaries
(macrophages)

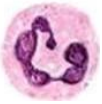
Splenic sinusoid
(Closed circulation)

Splenic cord
(Open circulation)

Red pulp

Macrophage

Plasma cell



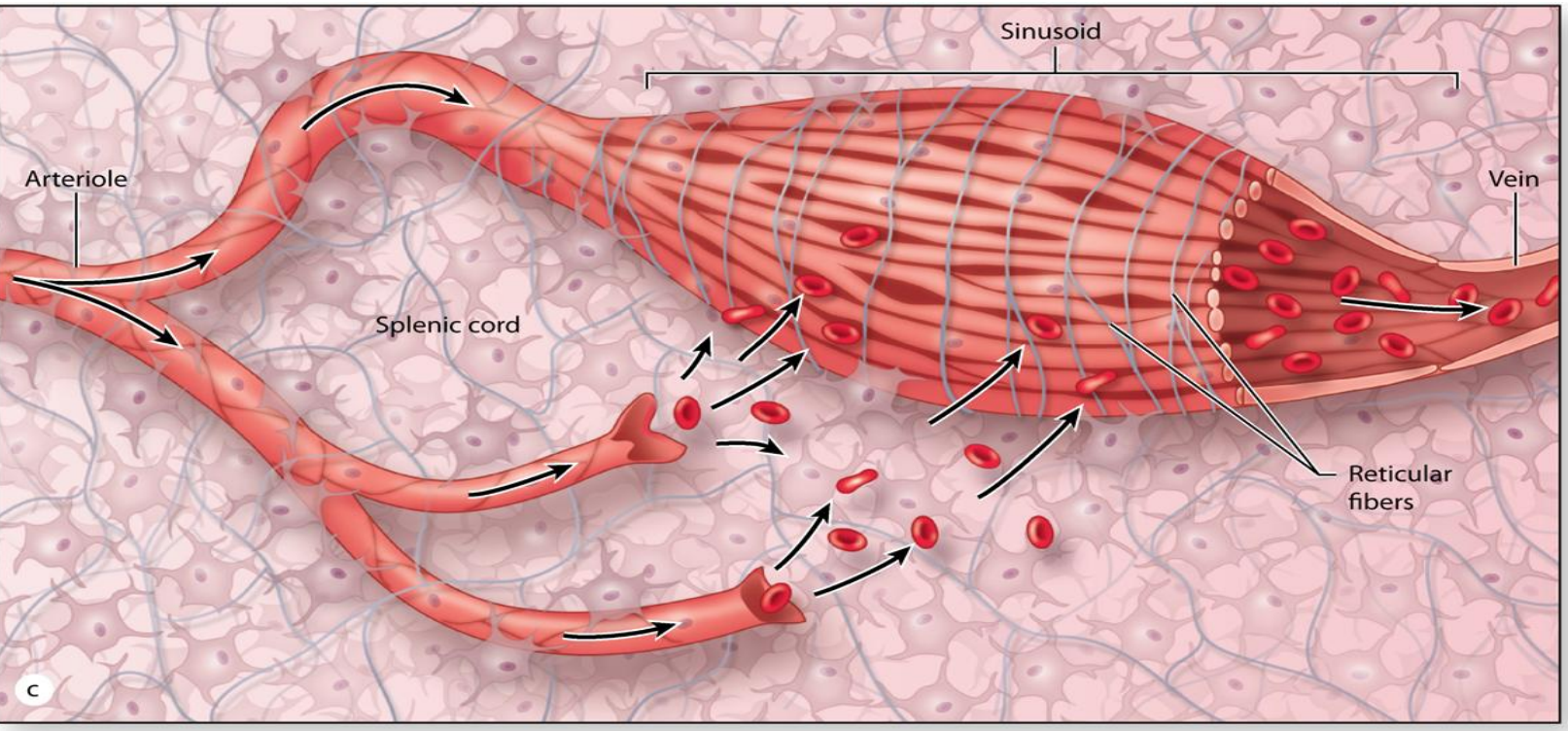
Neutrophil

Lymphocyte

Erythrocyte

Reticular cell

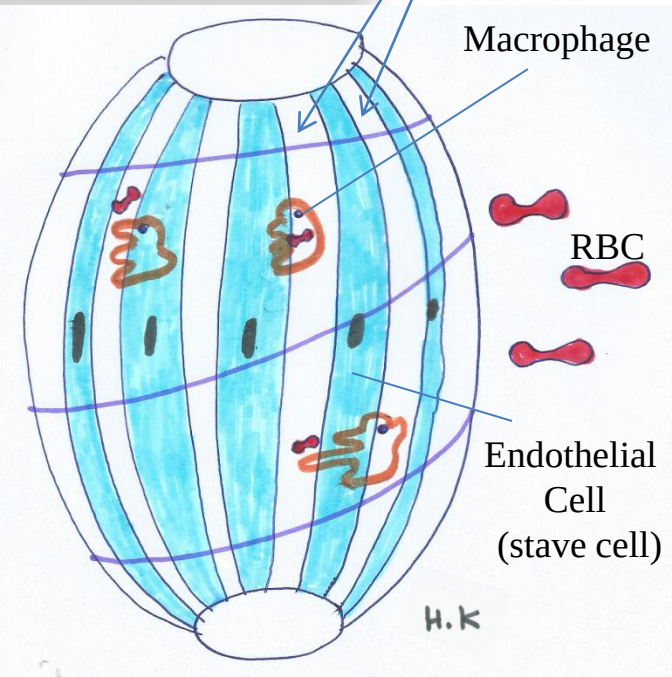
Note: When B cells in the primary follicles are exposed to Antigen, they proliferate and differentiate to plasma cells and move toward the red pulp.



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

Old erythrocytes **lose their flexibility**

They cannot penetrate the spaces between the endothelial cells and are phagocytosed by macrophages

Old erythrocytes lose sialic acid from their cell membranes

Galactose exposed

Induce phagocytosis of RBCs

Hemoglobin is broken into **Heme** and **Globin**

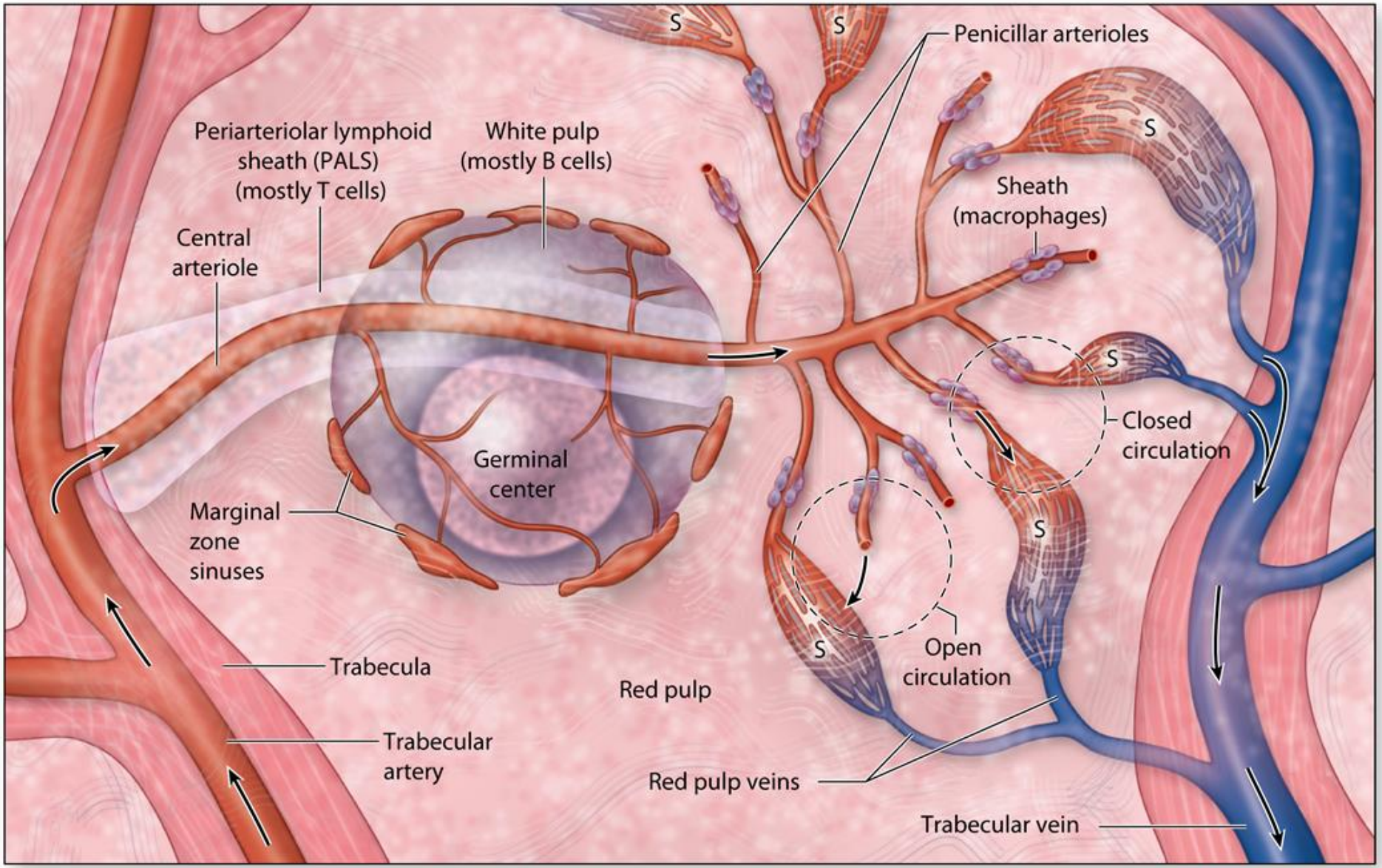
amino acids pool of blood

Iron: carried by transferrin to bone marrow (used again)

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.

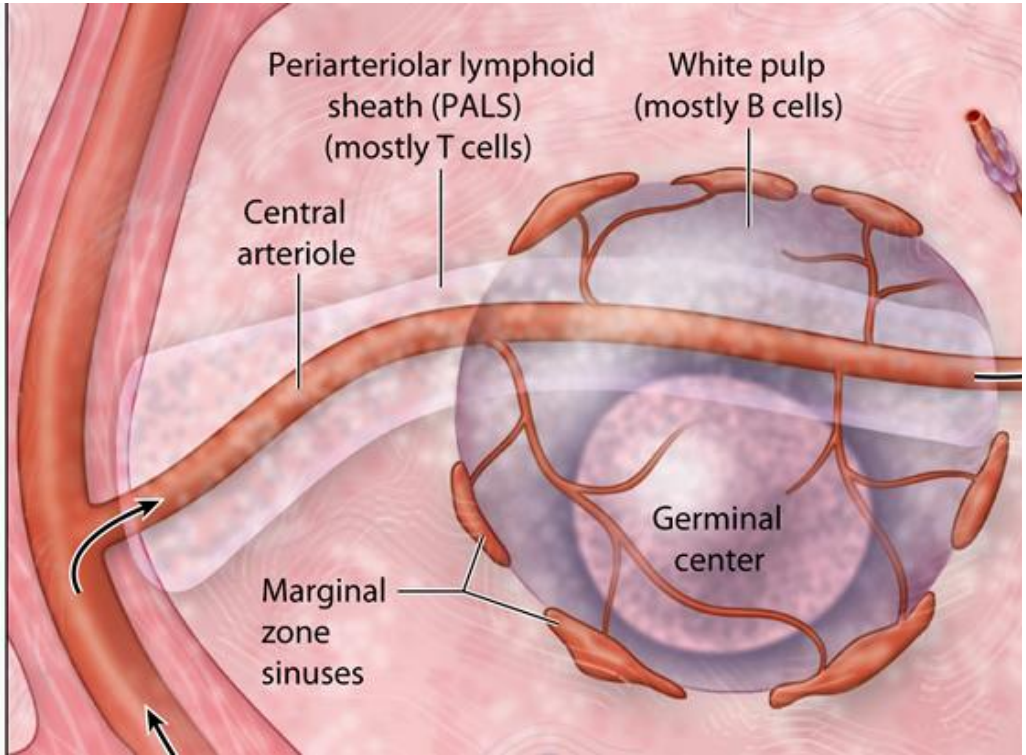


Marginal zone sinuses

✓ Located between the white and the red pulp

✓The spaces between these sinuses are wide (2-3um)

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 attack microorganisms present in the blood

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: lymphatic follicles

Functions of the spleen:

To summarize

It has circulatory as well as lymphatic functions

Blood cell production: During the fetal life, blood cells are produced in the spleen

Blood storage: a small quantity of blood is stored in the sinusoids of the red pulp

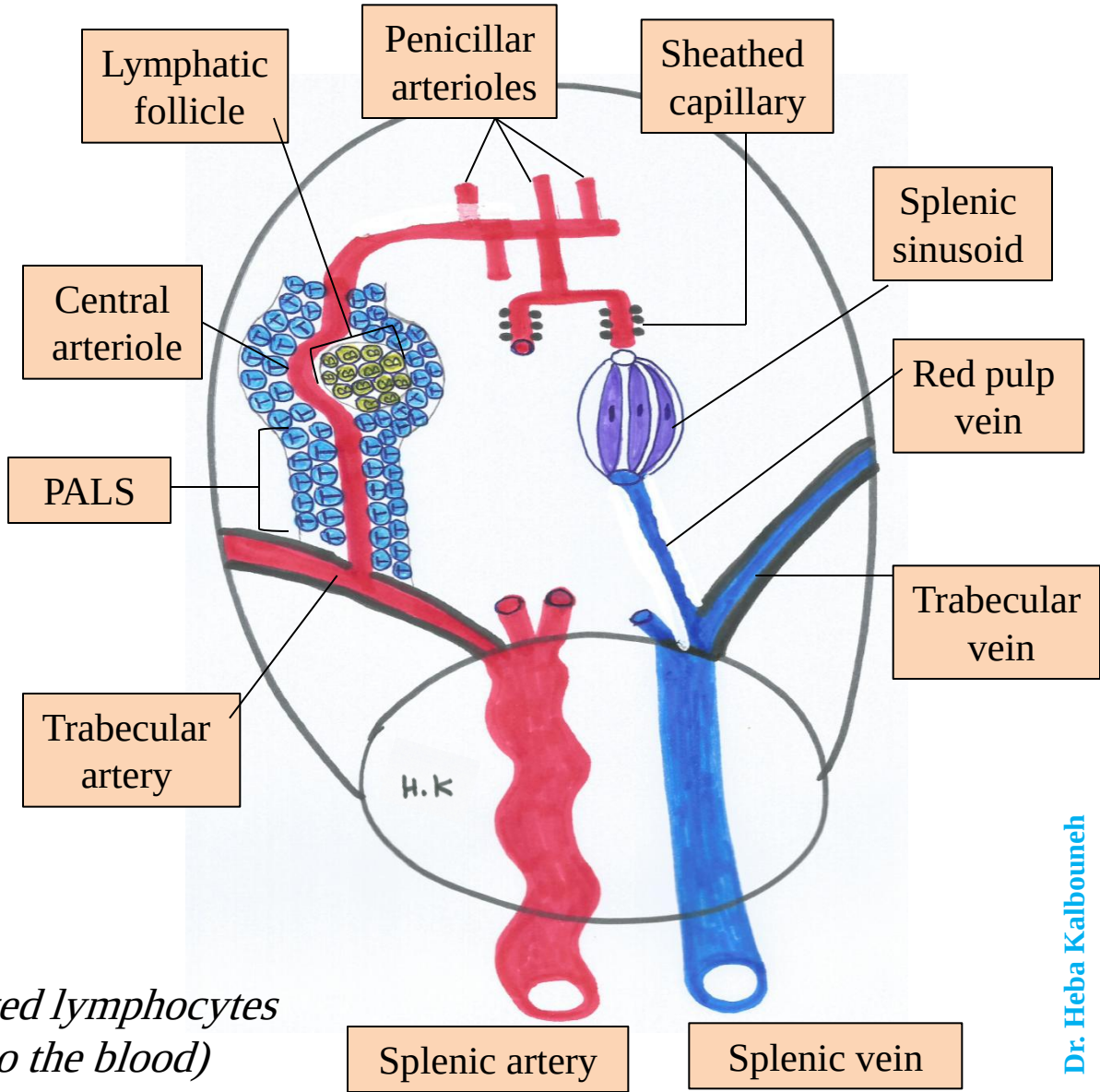
RBC destruction: most worn-out or damaged red blood cells are destroyed in the spleen (some in the liver and bone marrow). They are phagocytized by macrophages

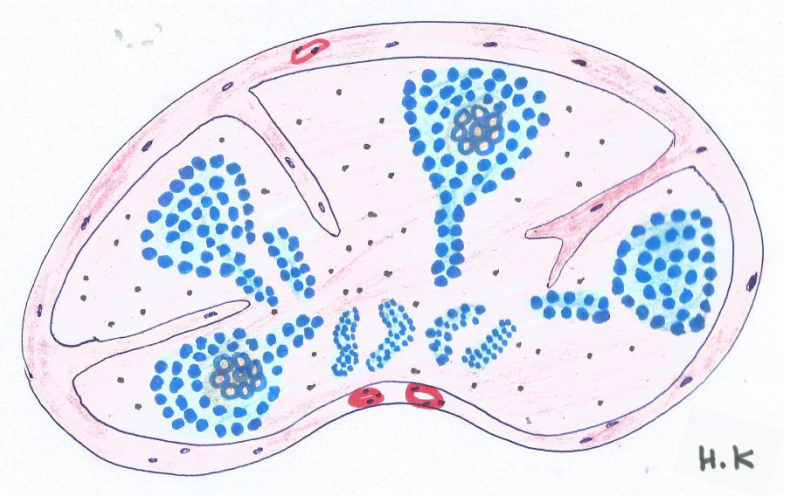
Defense mechanism: macrophages phagocytize microbes that have penetrated the blood. Antigens in the blood activate B and T cells residing in the spleen, triggering immune response

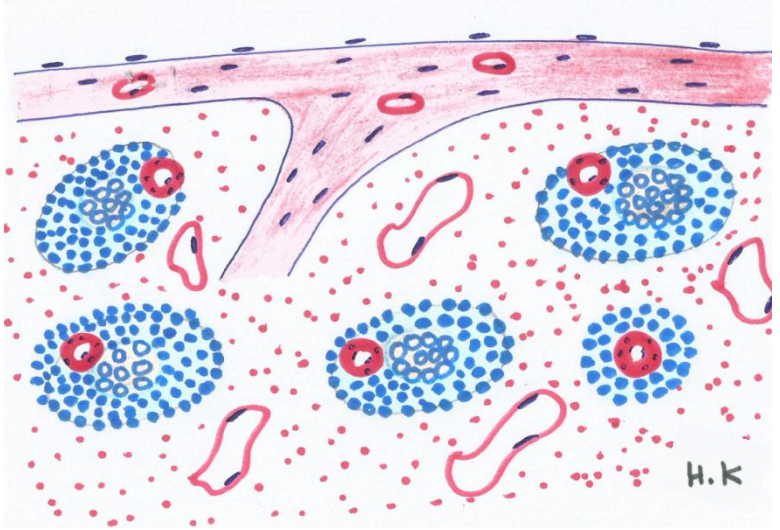
⇓⇓

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

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 sheathed capillaries to the splenic sinusoids, and back to veins of the pulp, trabecular veins and the splenic vein





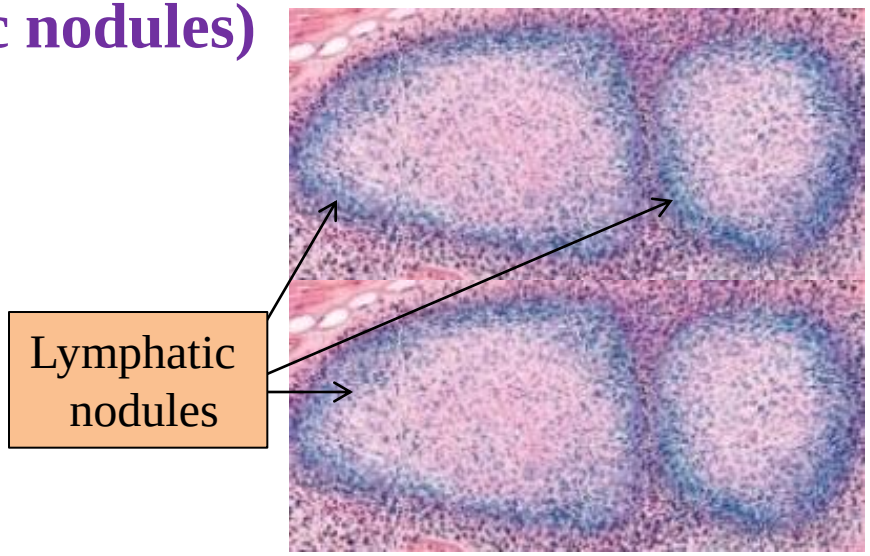


Lymph node	Spleen
Multiple, small	Single, large
Along the course of lymphatic vessels	Intra-abdominal
Filters lymph	Filters blood
Covered by fascia	Covered by peritoneum
Has afferent vessels	No afferent vessels
Cortex and medulla	White pulp and red pulp
Contains Lymphatic sinuses	Contains Blood sinuses

Diffuse lymphatic tissue (lymphatic nodules)

✓ Is formed by aggregations of lymphatic tissue
✓ Is found in various mucosal sites of the body

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.



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✓ It can therefore be referred to as:

Mucosa-Associated Lymphatic Tissue (MALT)

✓ These aggregations are **not encapsulated**
✓ MALT can be found in the following locations:

Palatine tonsils
Lingual tonsils
Pharyngeal tonsils
Gut-associated lymphoid tissue (GALT)
Bronchus-associated lymphatic tissue (BALT)

Collectively the MALT is one of the largest lymphoid organs, containing up to 70% of all the body's immune cells.

MALT is populated by:
T cells
B cells
Plasma cells
Macrophages

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

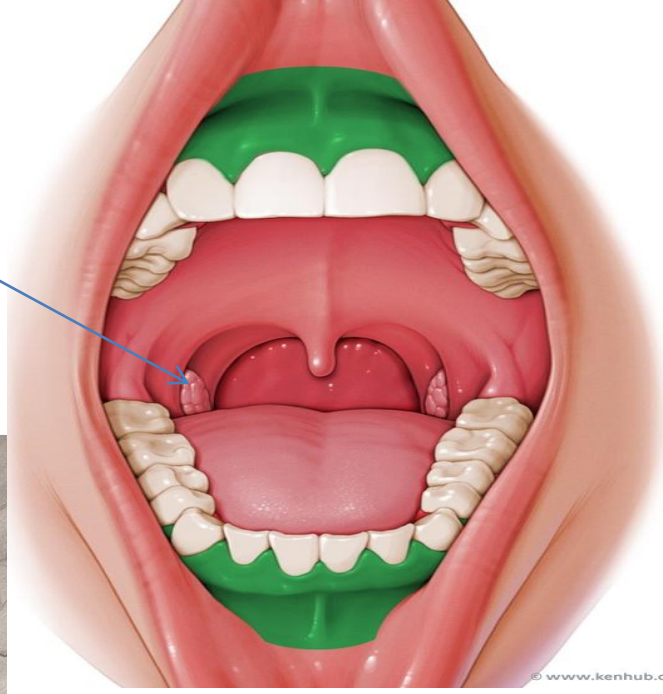
Tonsils are large, irregular masses of lymphoid tissue

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.

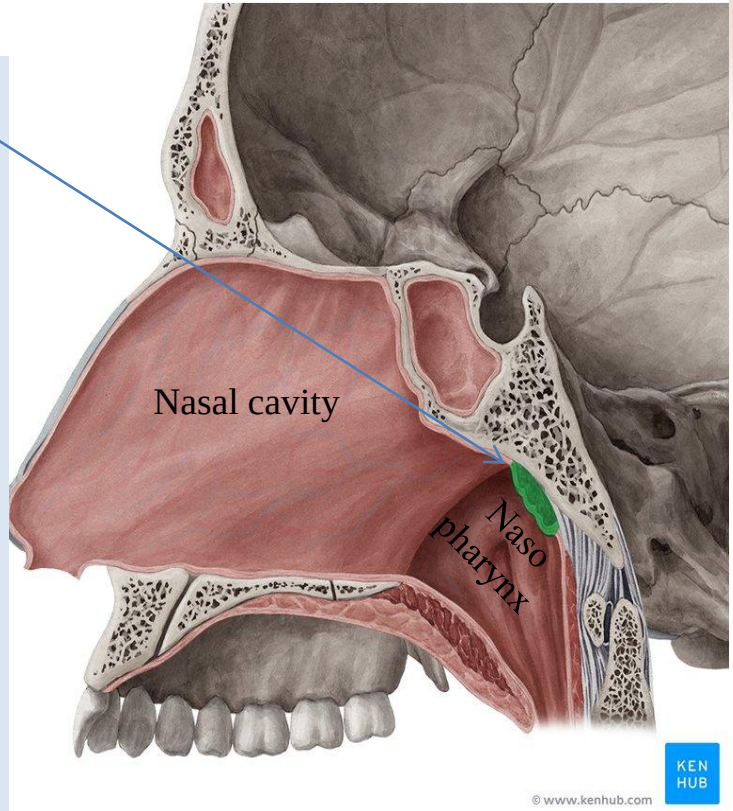


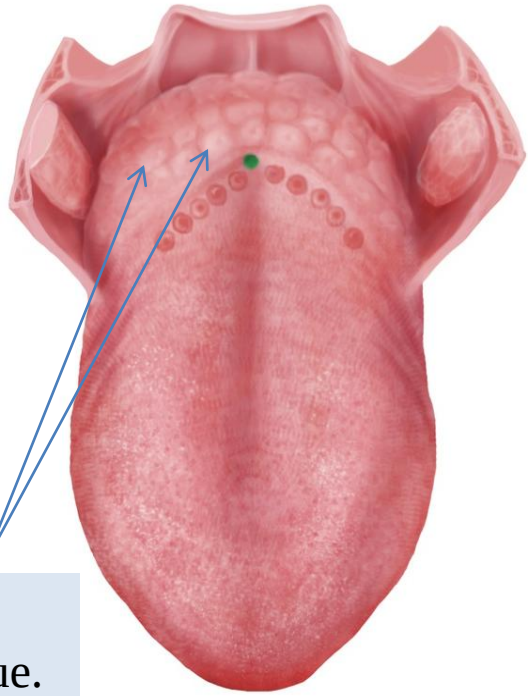
Pharyngeal tonsils

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***.





Lingual tonsils

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

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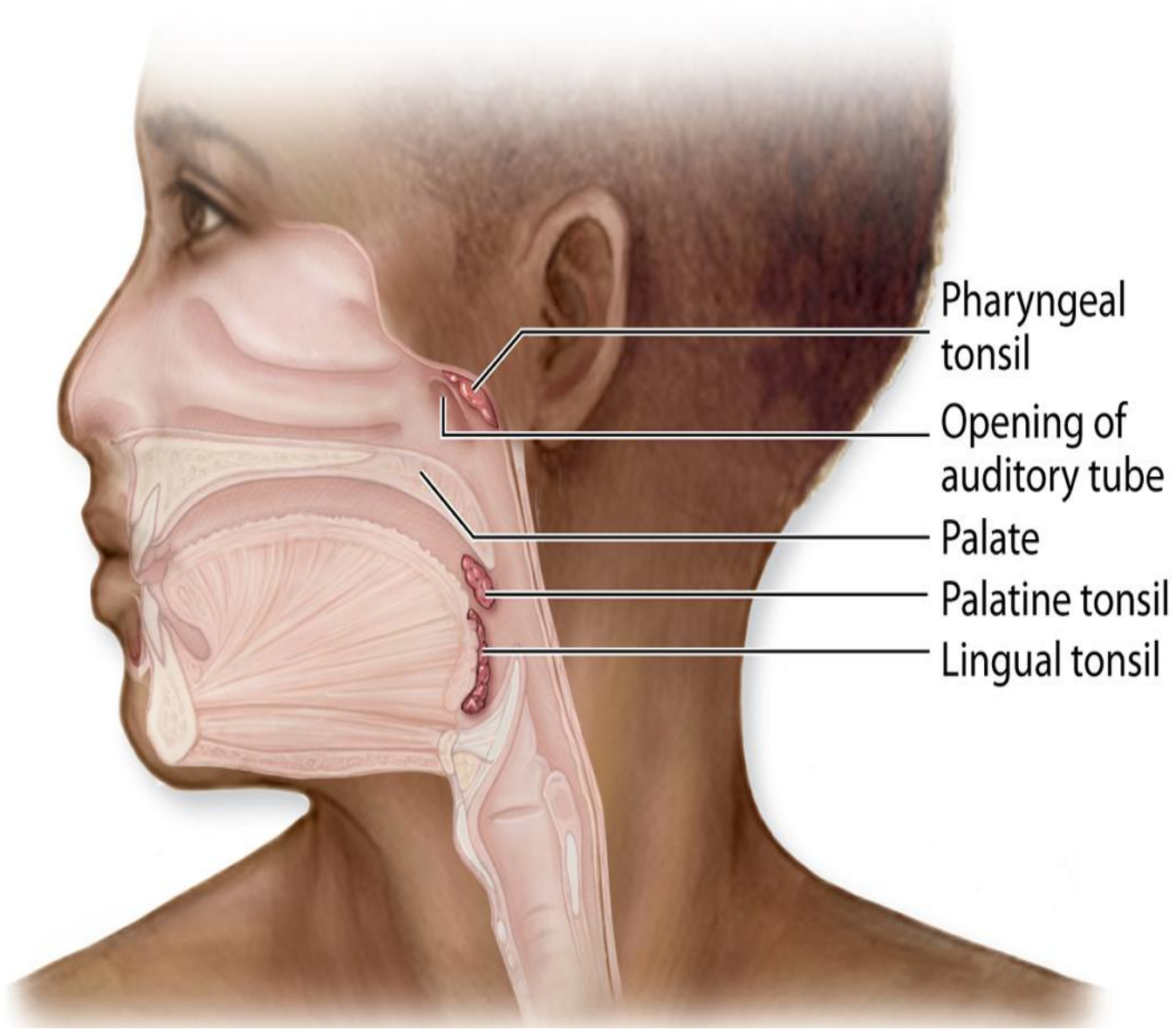
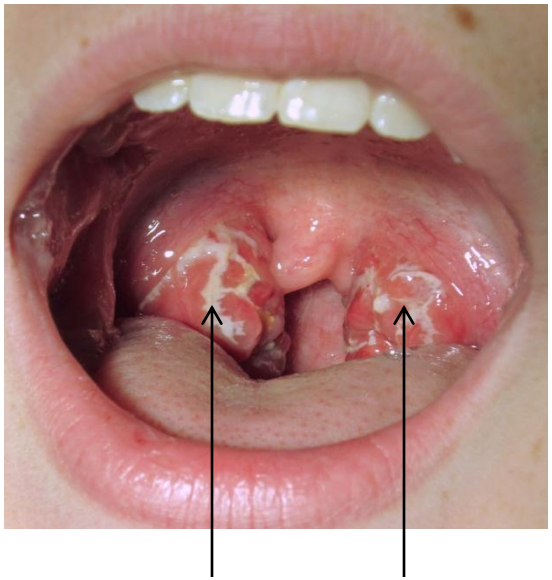
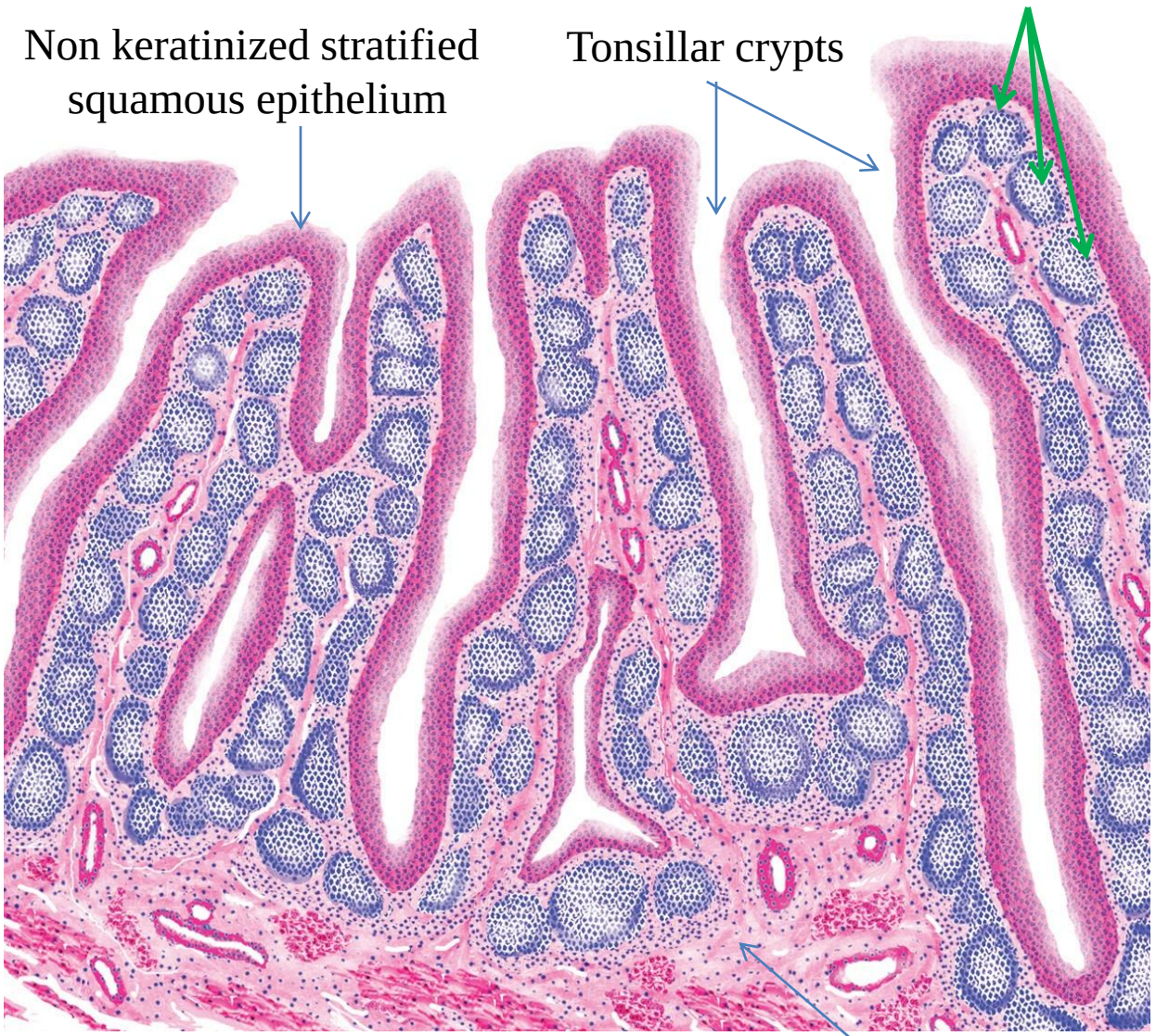

Pharyngeal tonsil
Opening of auditory tube
Palate
Palatine tonsil
Lingual tonsil

Palatine tonsils

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



Pus in tonsillar crypts



Palatine tonsils

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Gut-associated lymphoid tissue (GALT)

Is located in the mucosa of the intestine.

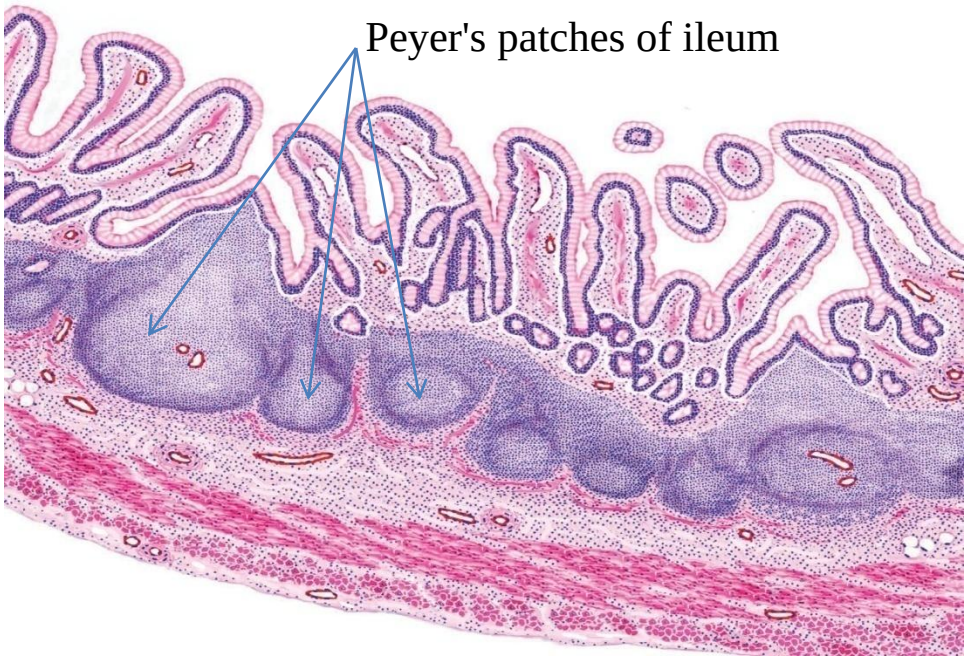
Examples:

1- Peyer's patches of ileum

2- Lymphatic nodules of appendix

Function:

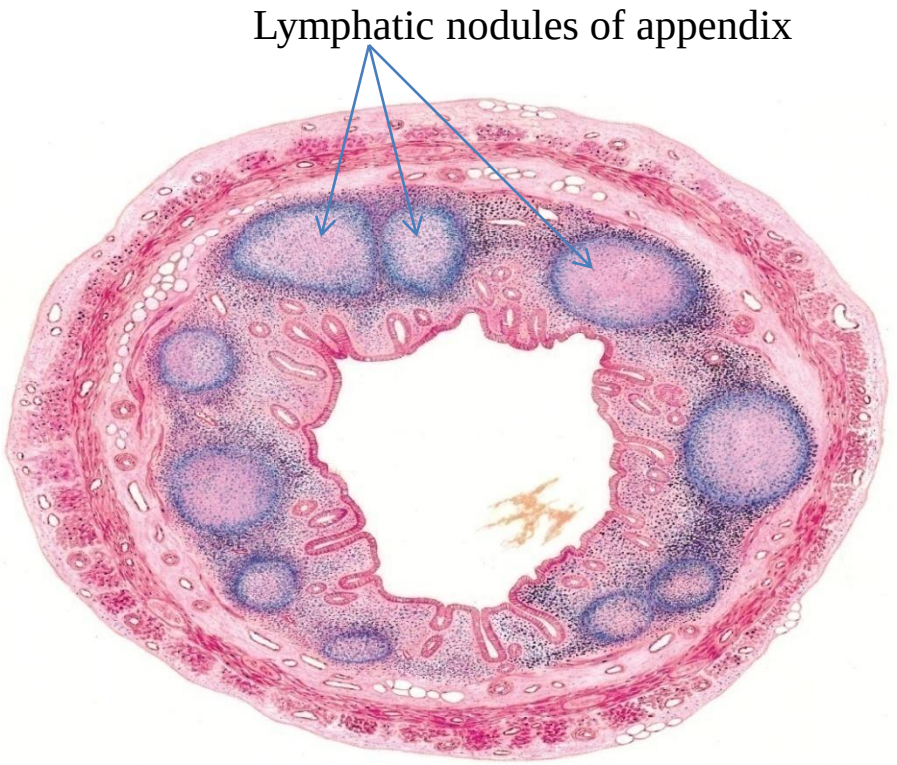
Protects the body from ingested pathogens.



Remember:

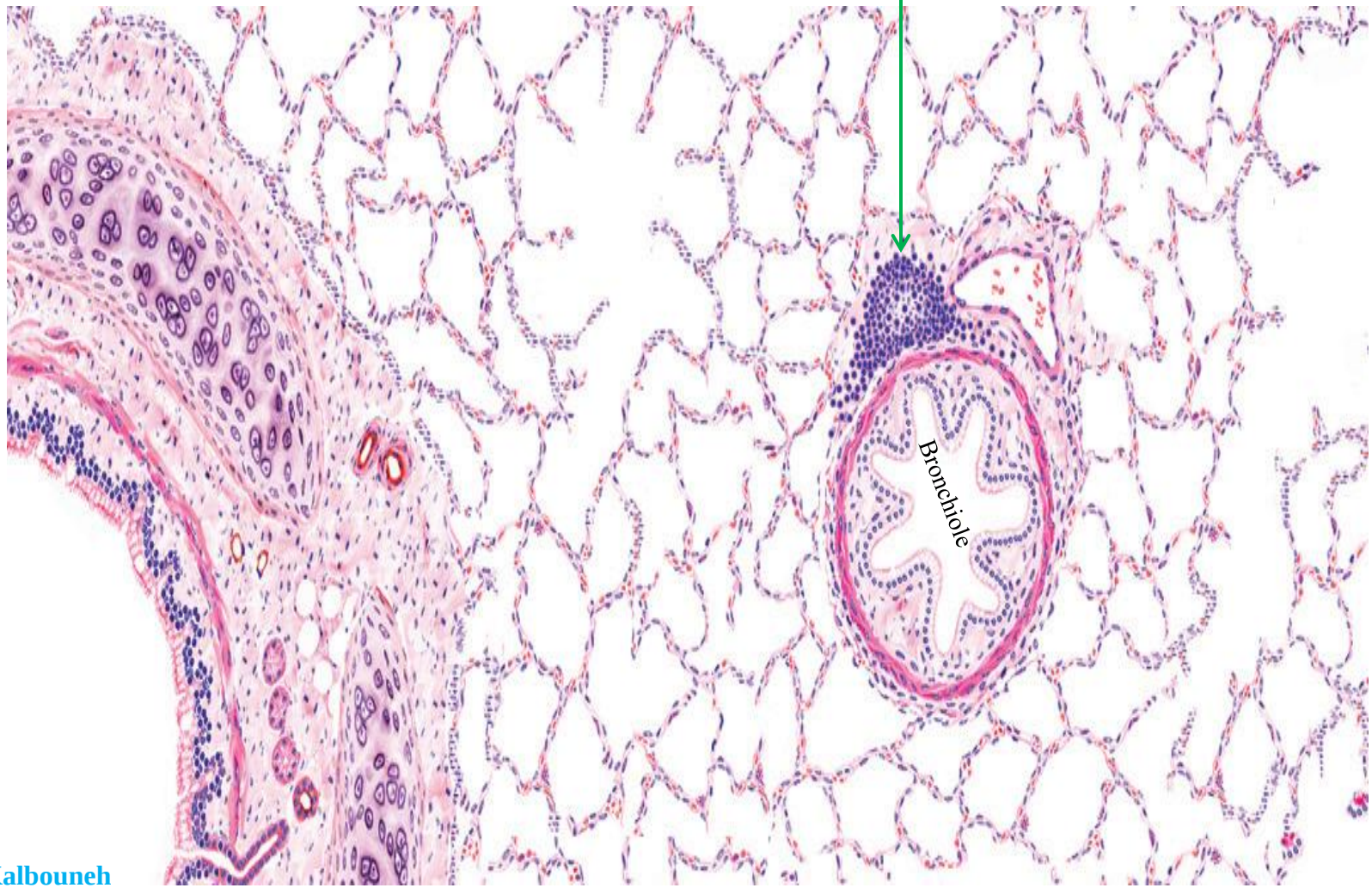
Diffuse MALT extends from the pharynx along the entire gastrointestinal tract but becomes very well-developed again in the mucosa and submucosa of the ***ileum.*** *Here large aggregates of lymphoid nodules comprise the Peyer patches, each containing dozens of nodules with no underlying connective tissue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

Another significant collection of MALT occurs in the mucosa of the ***appendix***

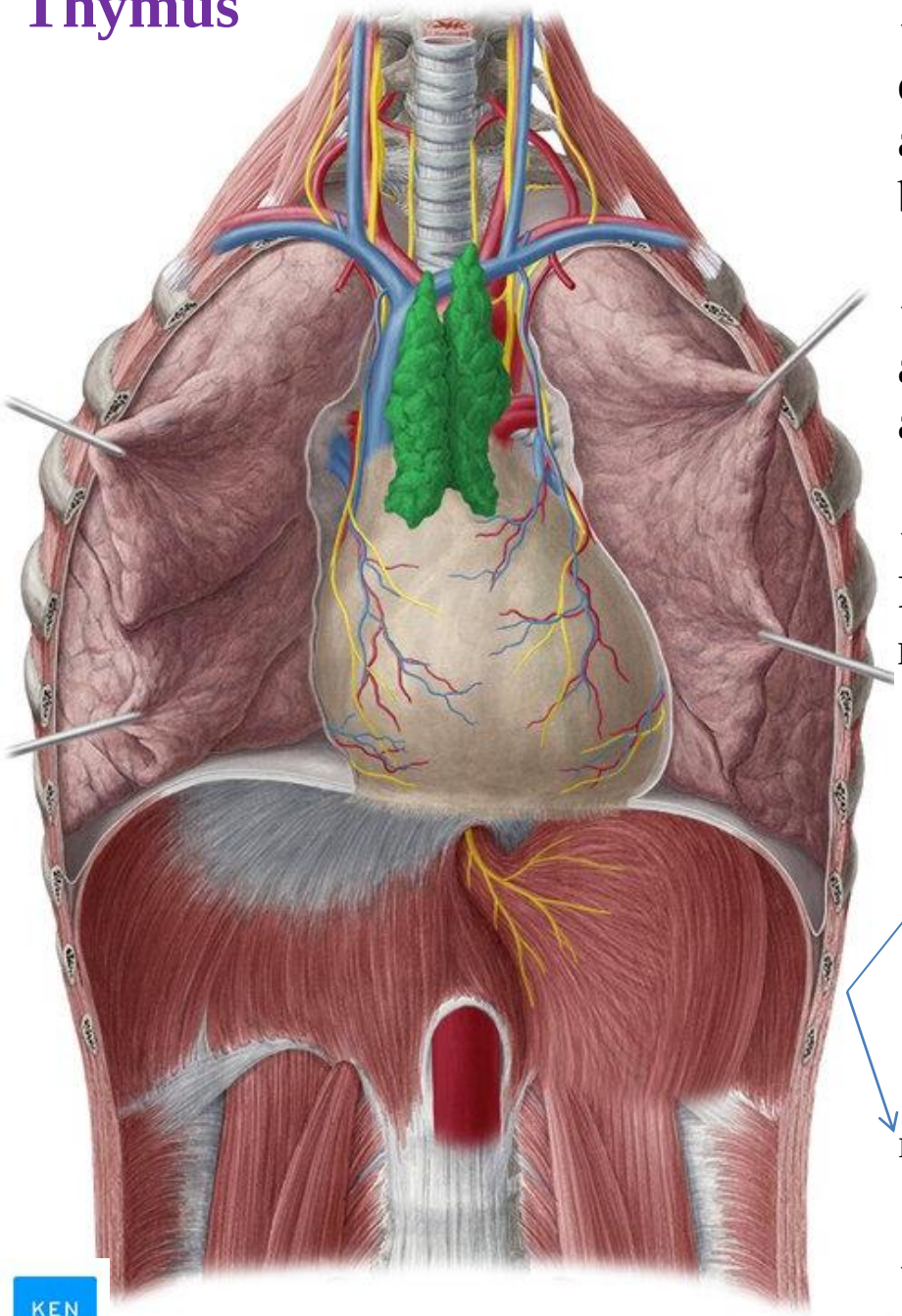


Bronchus-associated lymphatic tissue (BALT)
Is located in the mucosa of the bronchioles.

Function:
Protects the body from inhaled pathogens.



Thymus



✓ 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 formed and functional at birth, the thymus remains large and very active in T-cell production until puberty during which it normally undergoes involution, with decreasing lymphoid tissue mass and cellularity and reduced T cell output

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

✓The thymus is also part of the endocrine system.

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The thymus has a double embryonic origin

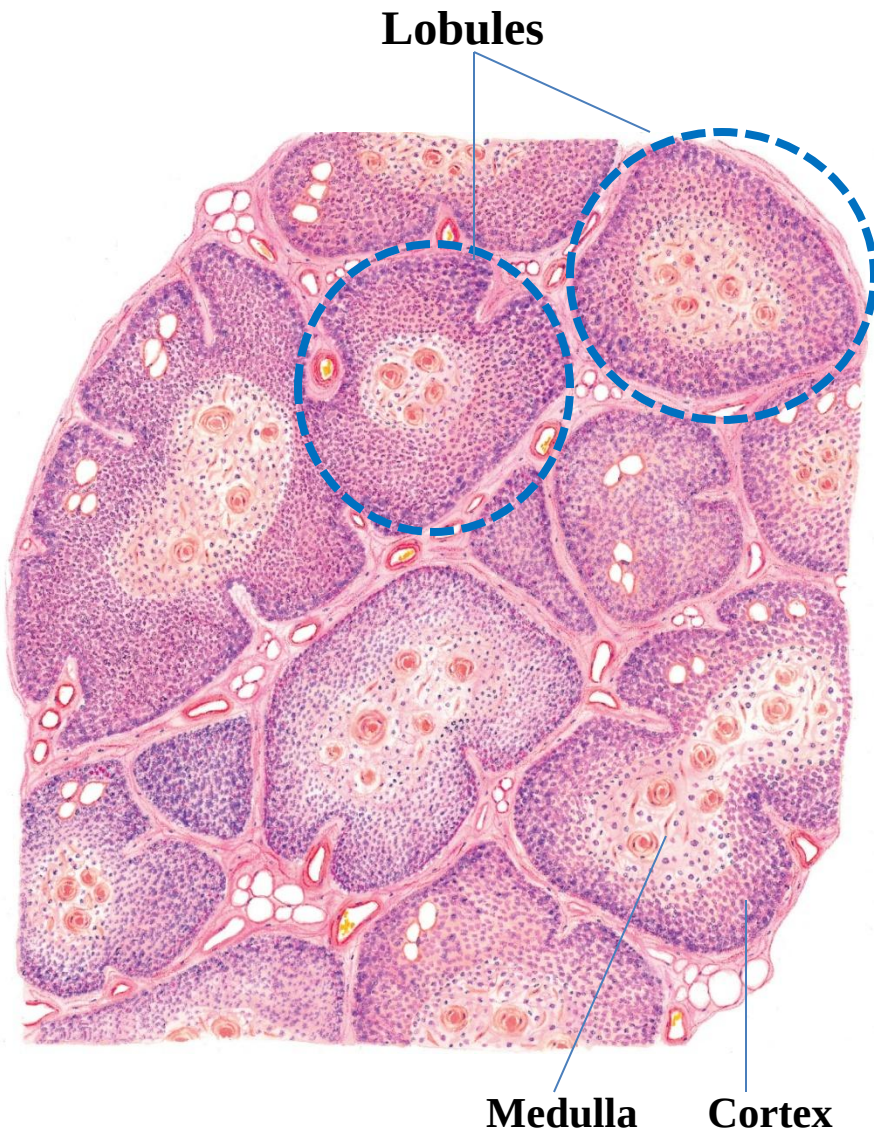
Endoderm and Mesoderm

Originates from the embryo's third pair of pharyngeal pouches

↓

unique thymic epithelial cells

Hematopoitic 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

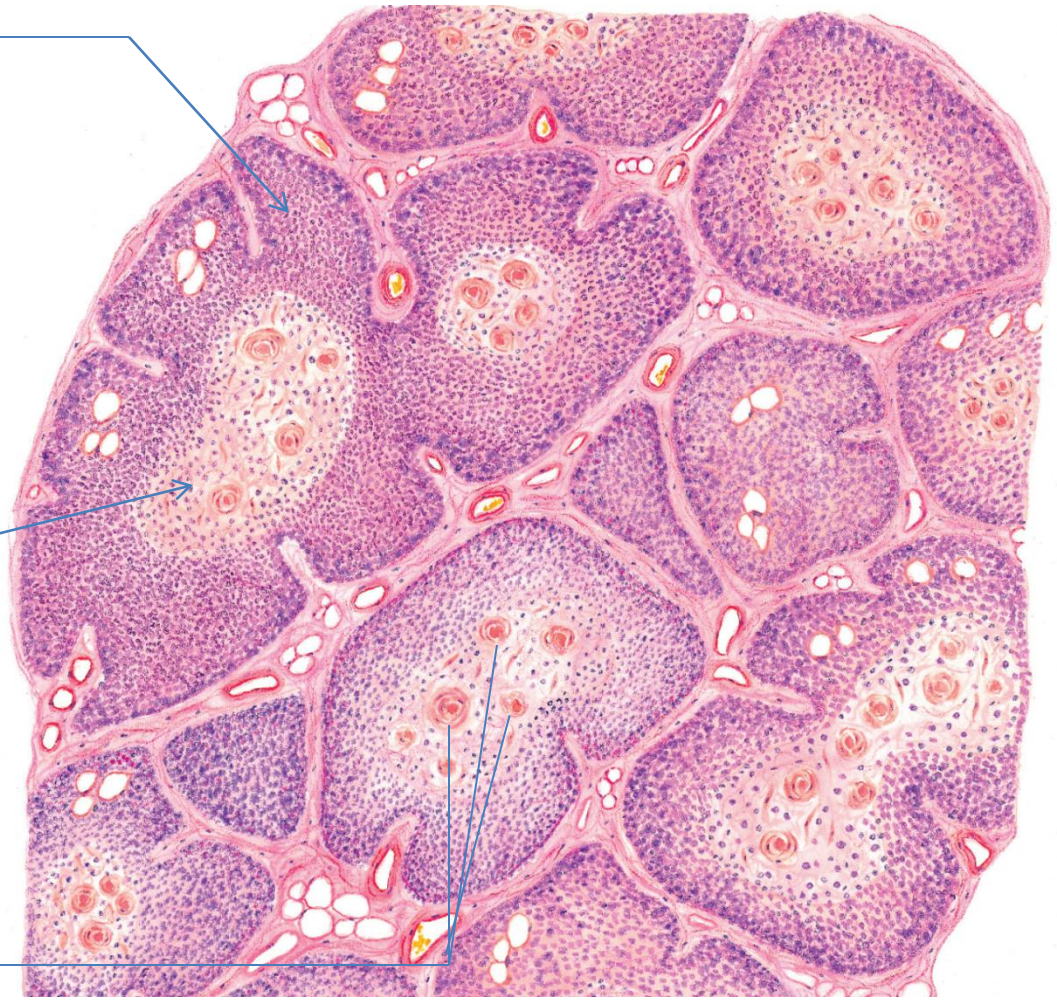
The cortex contains:

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**

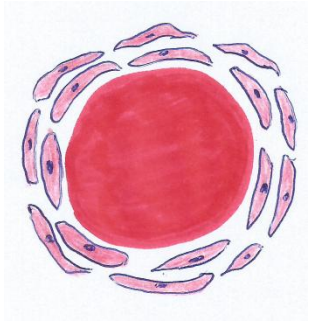


Hassall corpuscles are unique to the thymic medulla

✓Up to 100 μm in diameter

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

✓Tend to grow larger with age



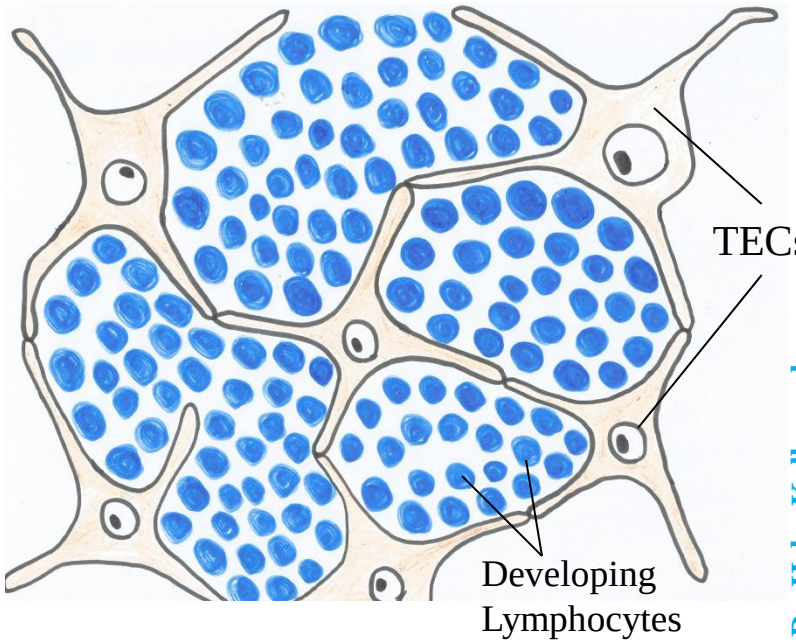
Thymic Epithelial Cells (TECs) (Epithelial reticular cells)

Develop from endoderm

1- Form a stroma to which macrophages and developing lymphocytes attach instead of reticular fibers ⟹ Form a network of cells bound together by desmosomes

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)**



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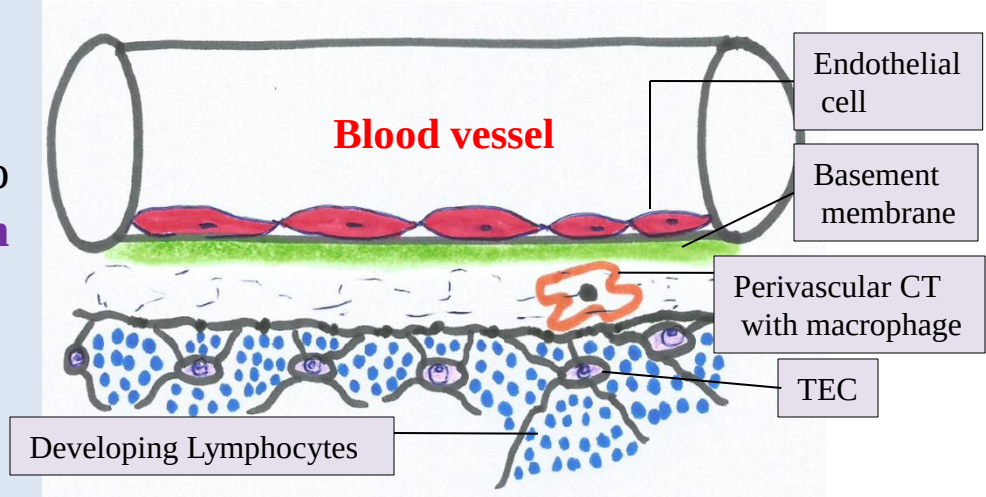
3- Envelop groups of T cells that are multiplying and maturing **(in cortex)**

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)

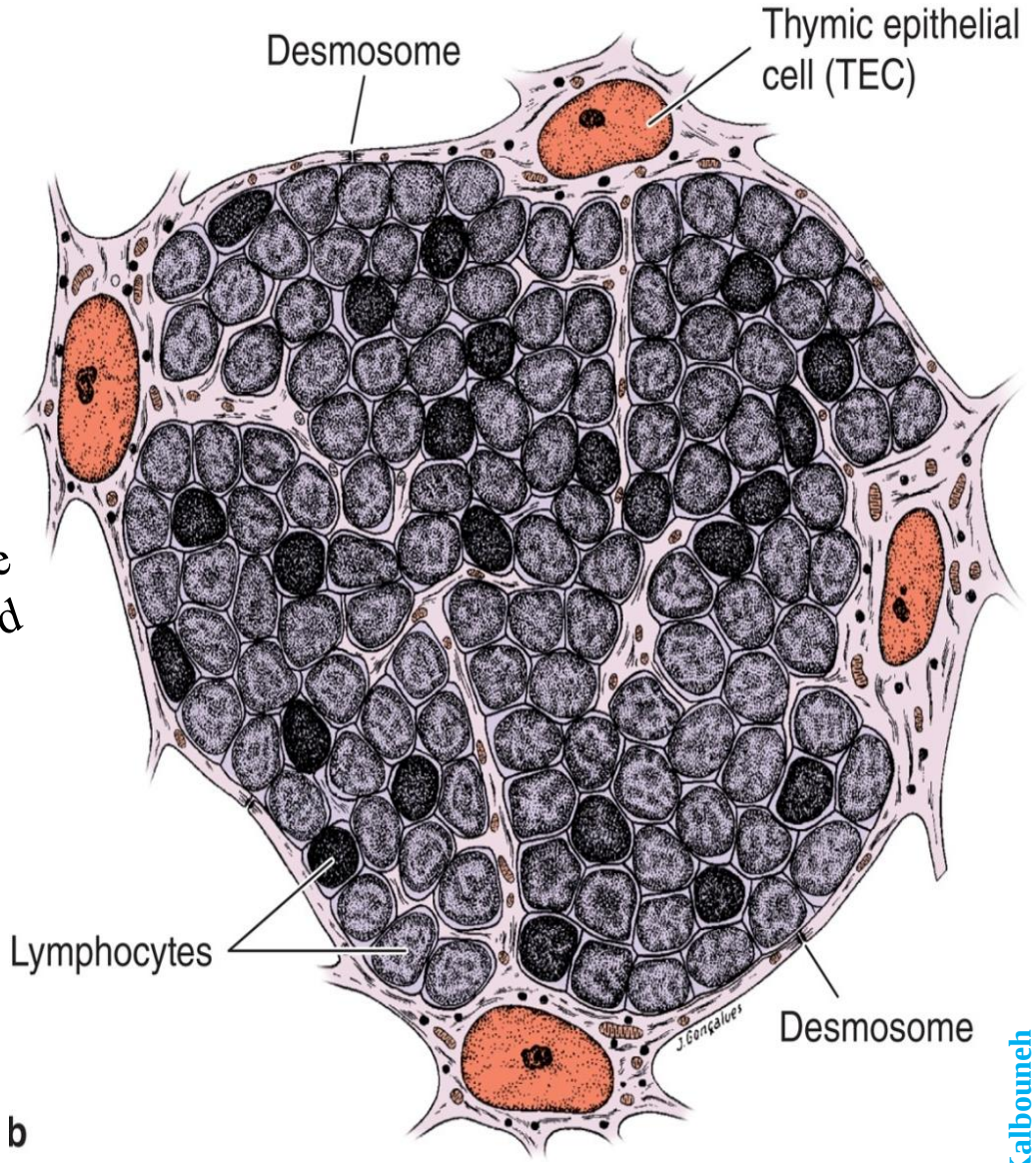
Thymosin, Thymopoietin



Thymic epithelial cells are also called

Nursing Cells

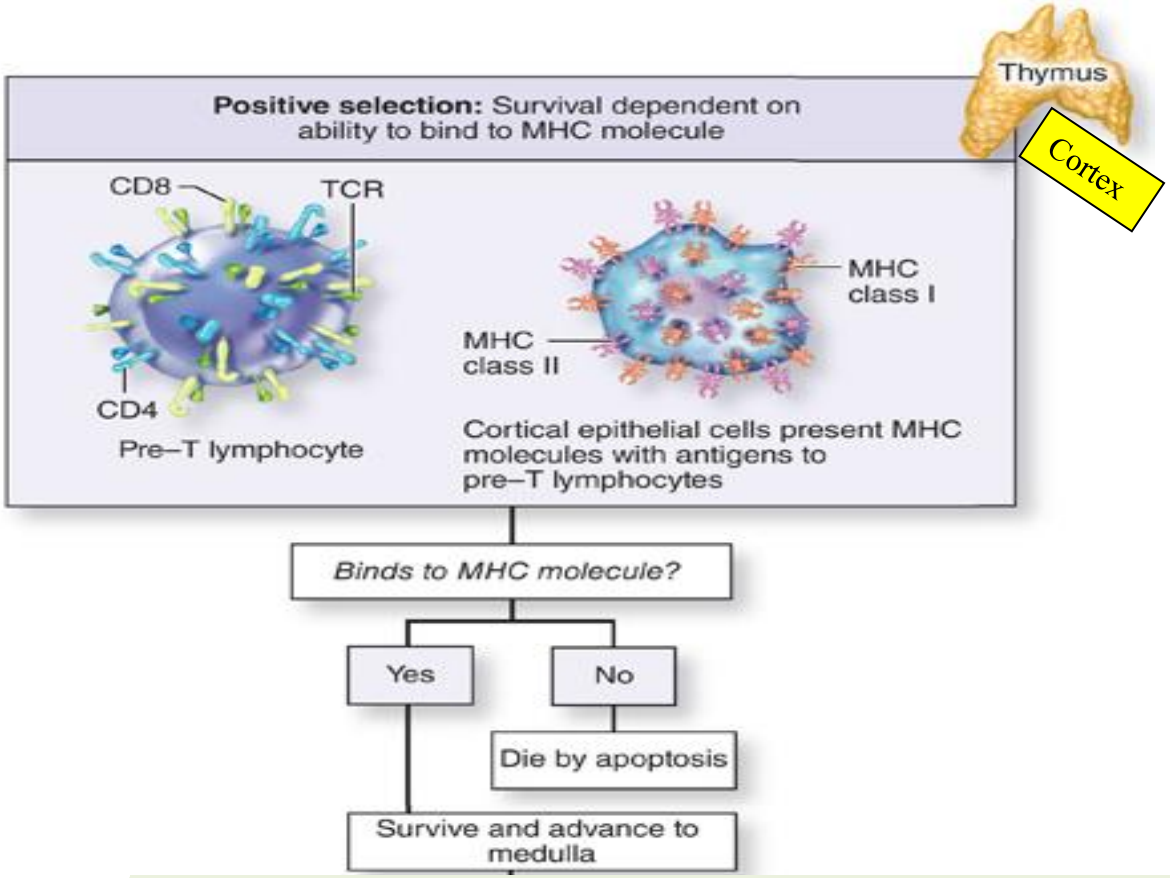
They form sheets for cells deep to the capsule, around septa and blood vessels, to isolate developing T lymphocytes in the cortex from contact with antigens (present in the blood), while they are programmed



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



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.

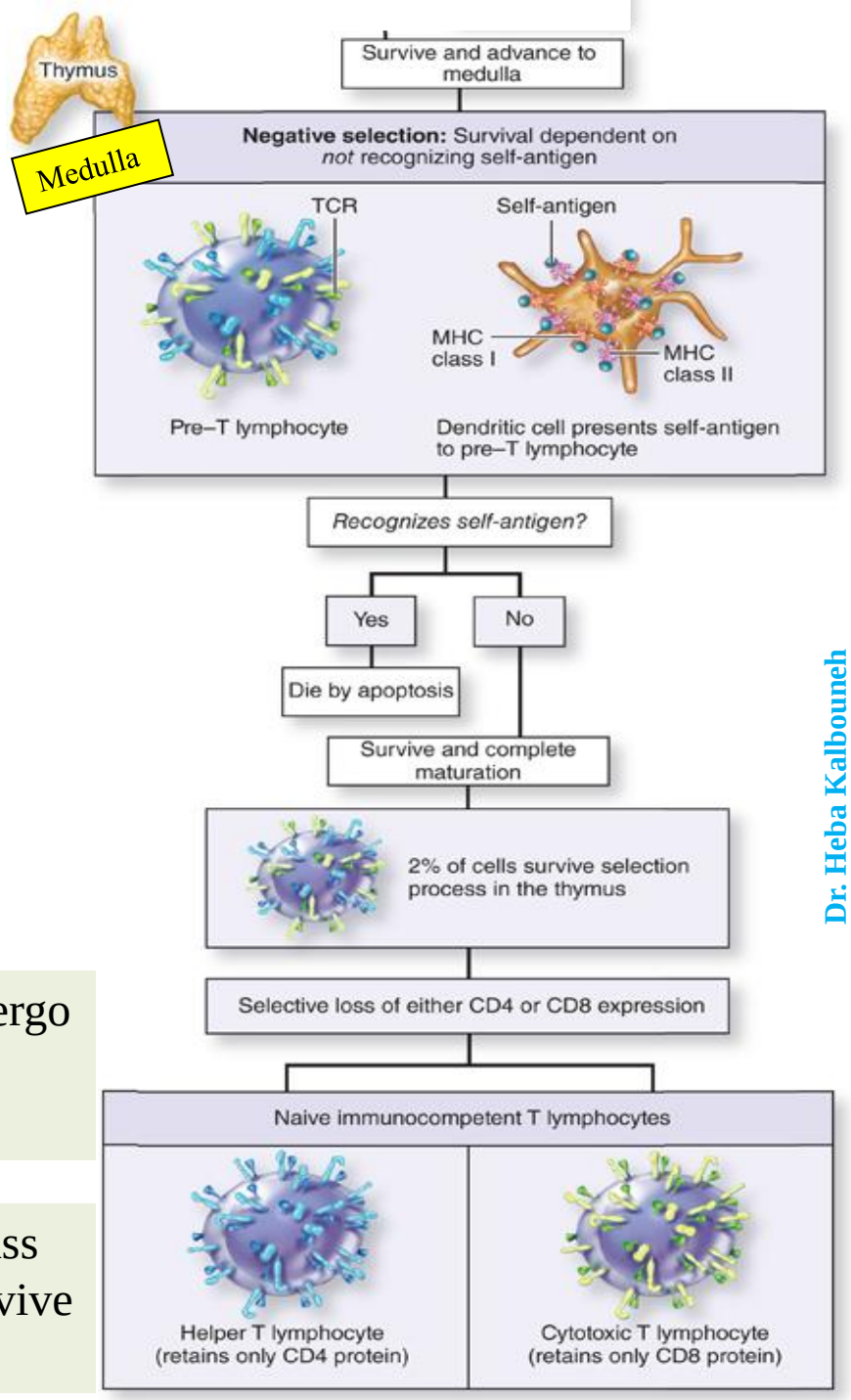
Here the focus is on removing T cells whose TCRs bind self-antigens

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!!!)**

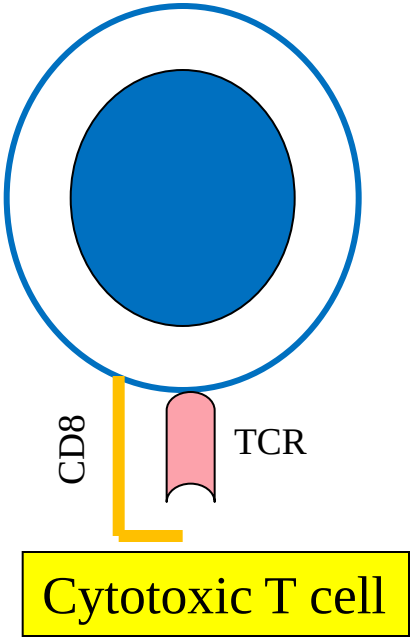
Only about 2% of all developing T lymphocytes pass both the positive and negative selection tests and survive to exit the thymus as immunocompetent T cells.



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.*

Why?

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

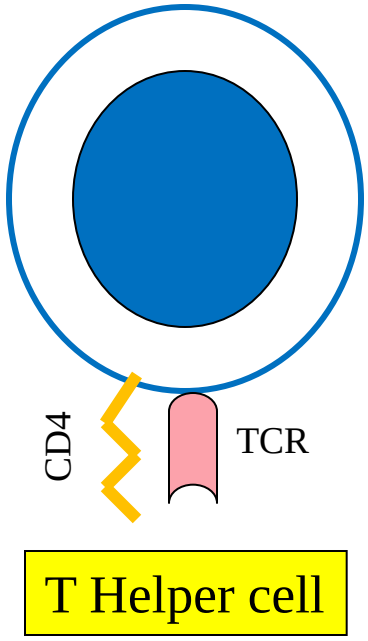


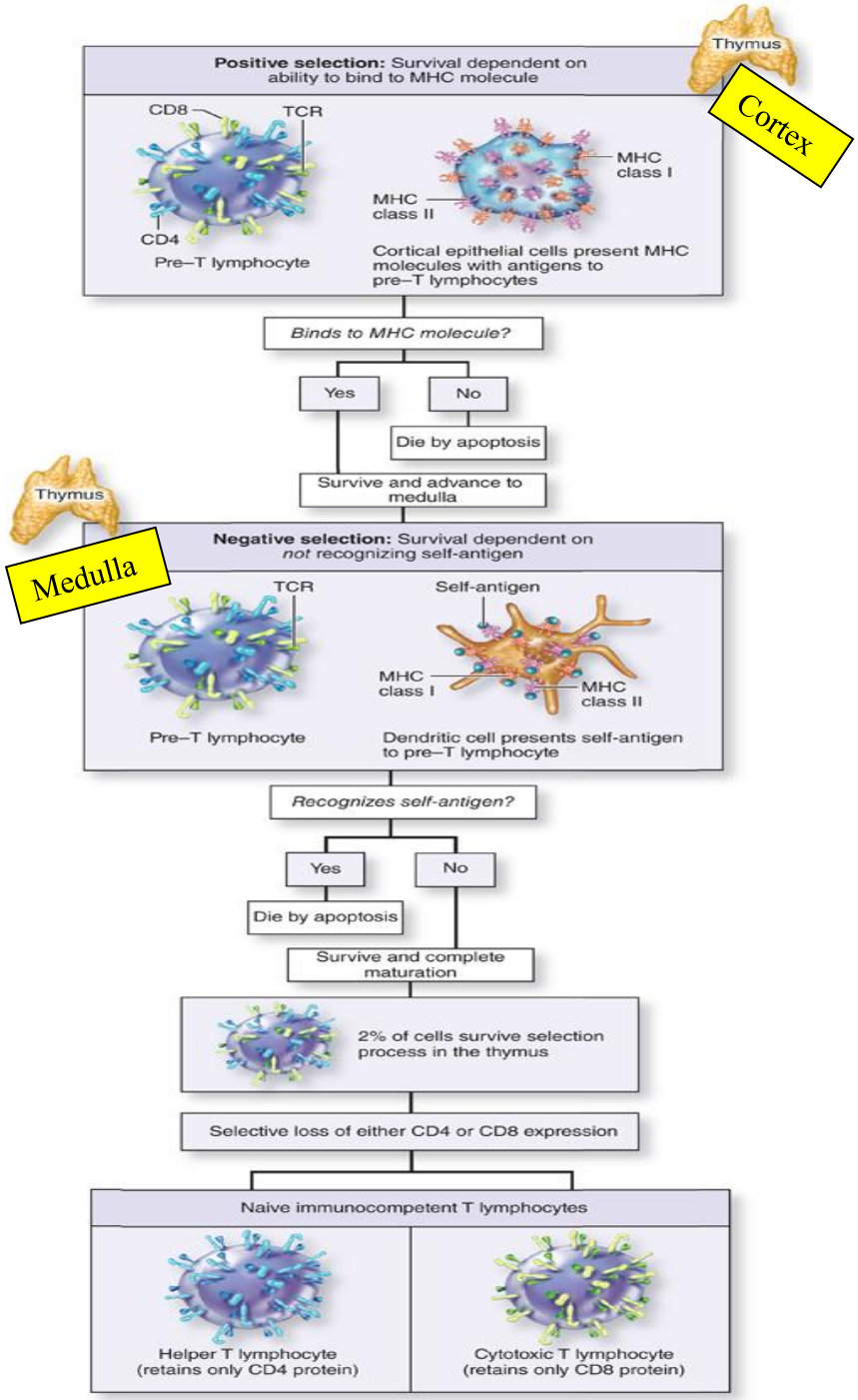
Depending on which class of MHC they interacted with, most of these lymphocytes will have stopped expressing either CD8 or CD4, and become either helper T cell or cytotoxic T cell

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

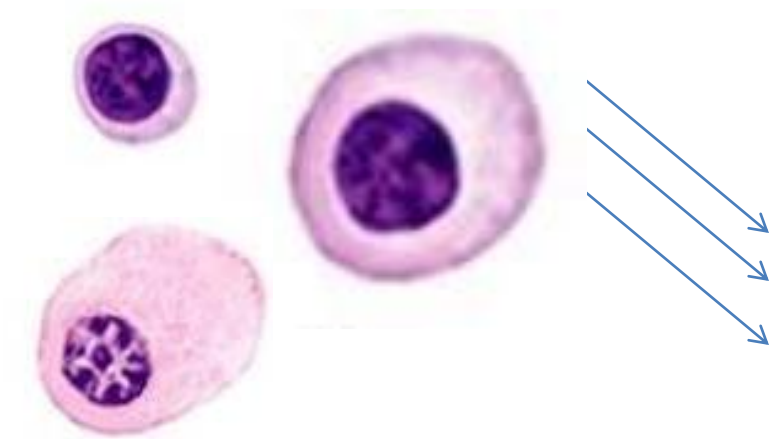
Then..

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**




Thymus
Cortex
Positive selection: Survival dependent on ability to bind to MHC molecule
CD8
TCR
CD4
Pre–T lymphocyte
MHC class I
MHC class II
Cortical epithelial cells present MHC molecules with antigens to pre–T lymphocytes
Binds to MHC molecule?
Yes
No
Die by apoptosis
Survive and advance to medulla
Thymus
Medulla
Negative selection: Survival dependent on not recognizing self-antigen
TCR
Pre–T lymphocyte
Self-antigen
MHC class I
MHC class II
Dendritic cell presents self-antigen to pre–T lymphocyte
Recognizes self-antigen?
Yes
No
Die by apoptosis
Survive and complete maturation
2% of cells survive selection process in the thymus
Selective loss of either CD4 or CD8 expression
Naive immunocompetent T lymphocytes
Helper T lymphocyte (retains only CD4 protein)
Cytotoxic T lymphocyte (retains only CD8 protein)

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

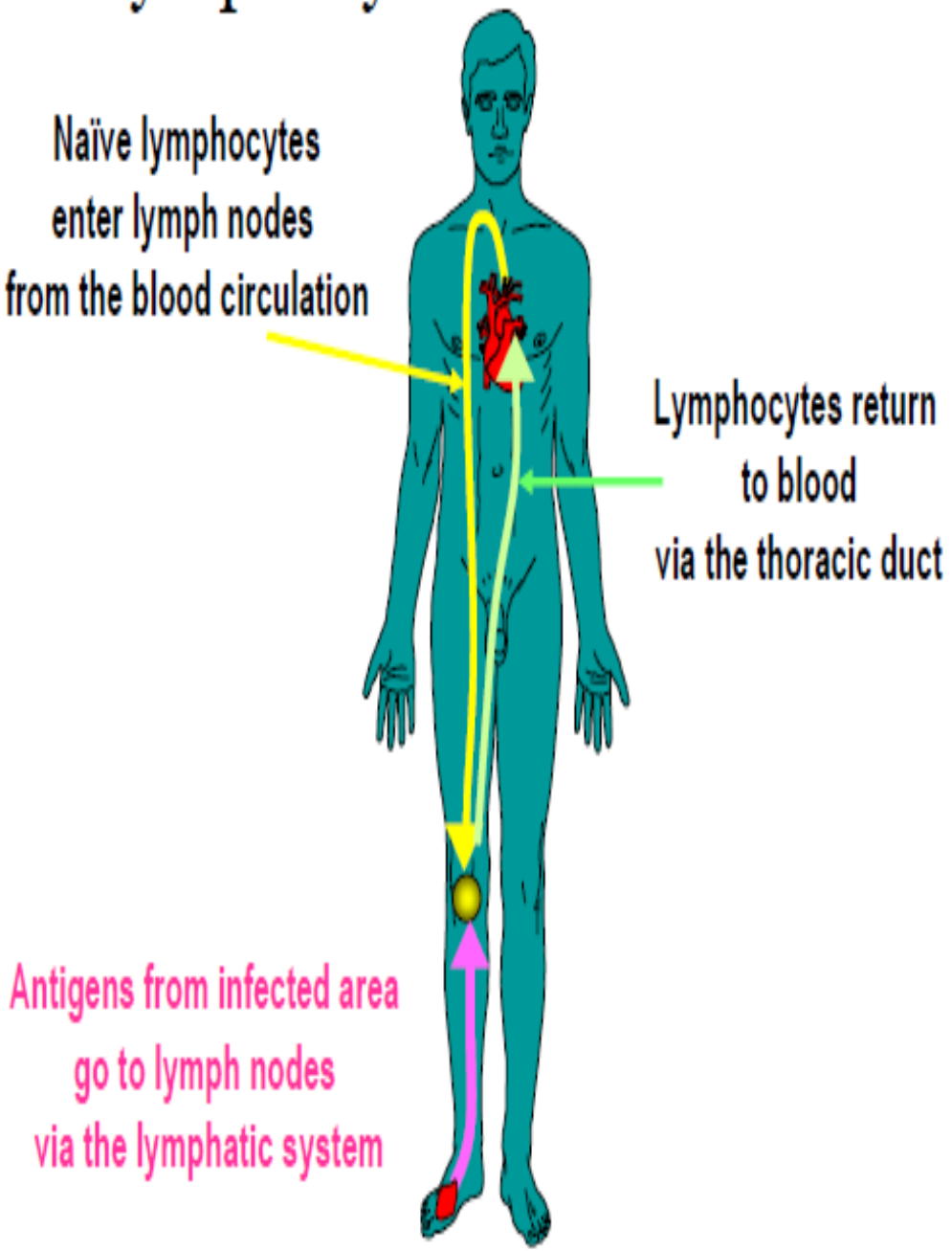
2- If antigen enters the secondary lymphoid tissue: Lymphocyte proliferation in response to antigen occurs within the lymphoid tissue.

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 and unable to recognize 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



Advantage sof 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

<u>Recirculation of naïve lymphocytes:</u>
recirculate through secondary lymphoid organs

<u>Recirculation of activated lymphocytes:</u>
migrate to peripheral tissues at sites of infection