



Lymphatic System

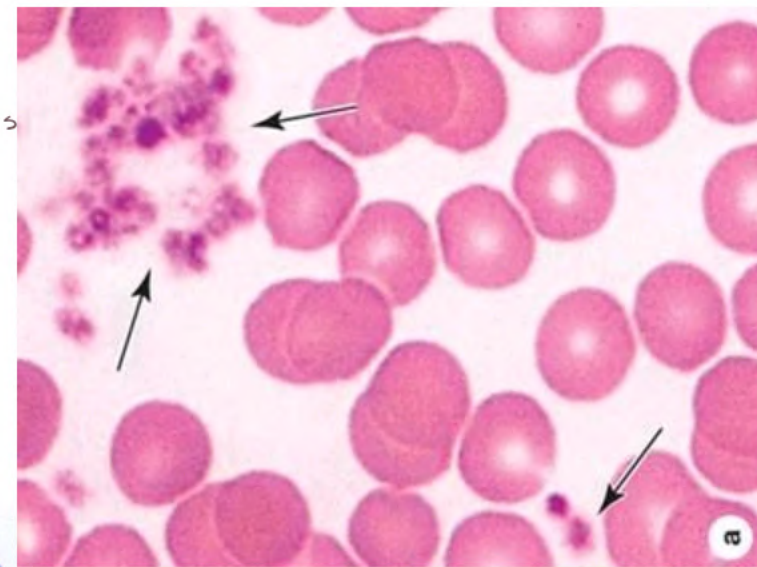


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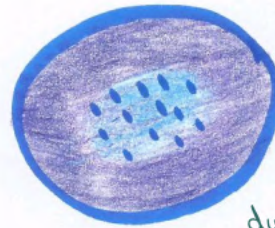
Thrombocytes (Platelets)

↳ small fragments of cells biconcave in shape & usually form aggregations

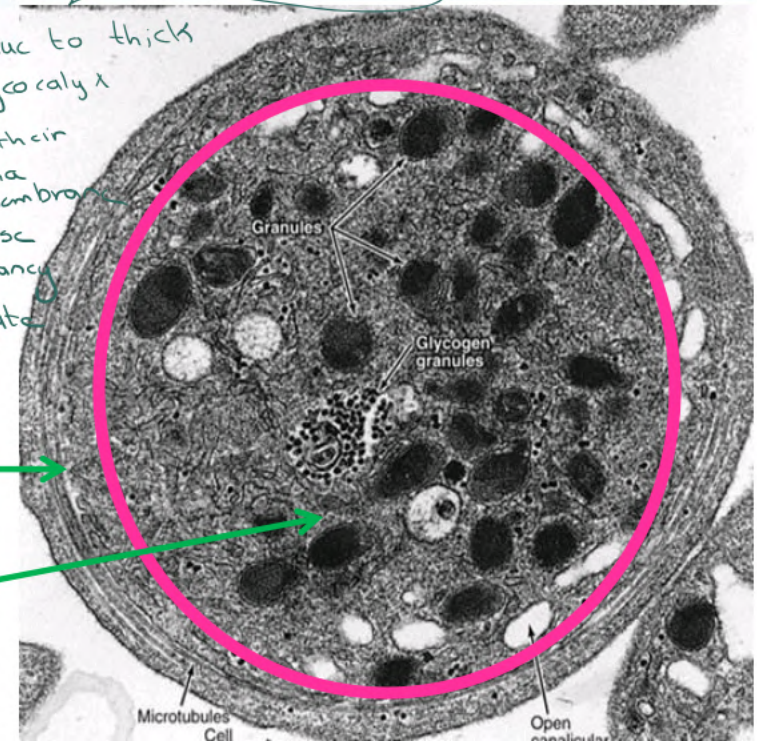
- Small non-nucleated cytoplasmic fragments
- Formed by fragmentation of the cytoplasm of **megakaryocytes** in the bone marrow
- **Number: 200,000-400,000/mm³**
- **Shape: biconvex discs**
- **Cytoplasm: purple, granular**
- **Diameter: 2-4 μ m**
- **Lifespan about 10 days**
- Control the bleeding by plugging the defects in blood vessels and activating blood clotting cascades



In stained blood smears, platelets often appear in clumps

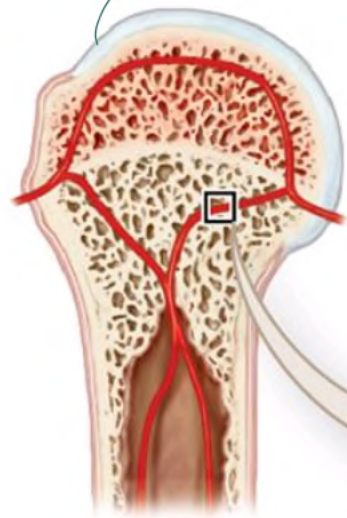


due to thick
glycocalyx
in their
plasma
membrane
which cause
high tendency
to aggregate

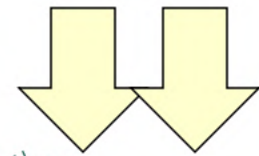


Platelet has 2 zones

- Outer pale basophilic (clear) peripheral zone: **hyalomere**
- Central dark granular zone: **granulomere**



Blood vessel inside bone marrow $\Rightarrow$ sinusoidal type of capillary with clefts or gaps between endothelial cells to permit movement of mature cells from red bone marrow to stream

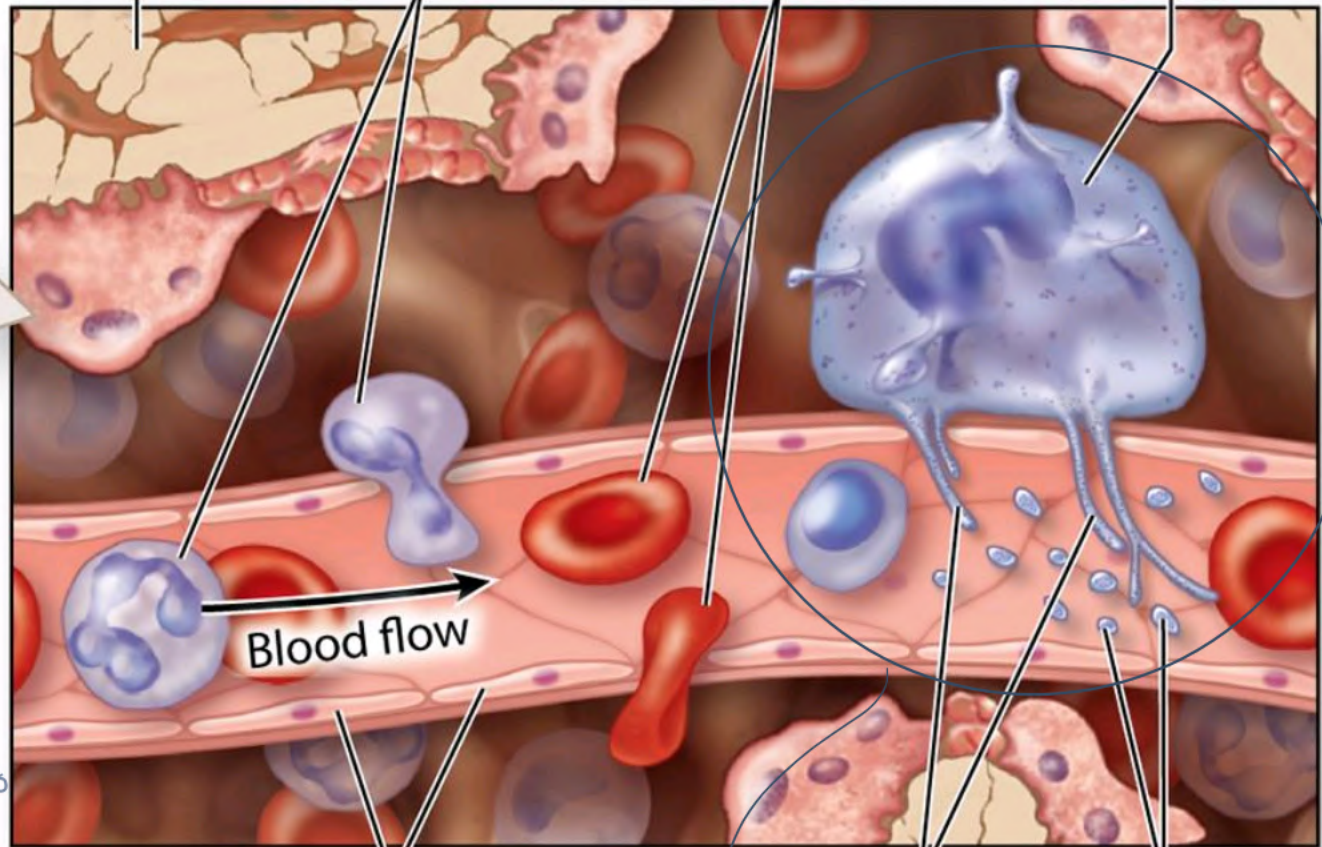


Trabecula of bone

Leucocytes

Erythrocytes

Megakaryocyte



bone marrow containing HPSCs at different stages of differentiation.

large polyploid nucleus

Blood flow

Endothelial cells

Proplatelets Platelets

larger & the nucleus undergoes many DNA duplications without nuclear division

megakaryocyte as blood flows, this will cause fragmentation of the cytoplasmic processes

* Inside bone marrow we have this large cell with cytoplasmic processes in between endothelial cells

Hyalomere: contains cytoskeleton and membranous channels
(outer area)

Cytoskeletal elements

- Microtubule
- Actin filaments ^{contractile filaments}

Maintain shape and help contractions of platelets and squeezing, clot retraction

Membrane channels

- Open canalicular system ^{Ca²⁺ needed for clot formation & exocytosis in platelets}
- Dense tubular system ^{remnants of smooth endoplasmic reticulum → store for (Ca²⁺)}

Granulomere: contains granules and organelles
(inner area)

Alpha granules: clotting factors, growth factors ^{for blood clot formation}

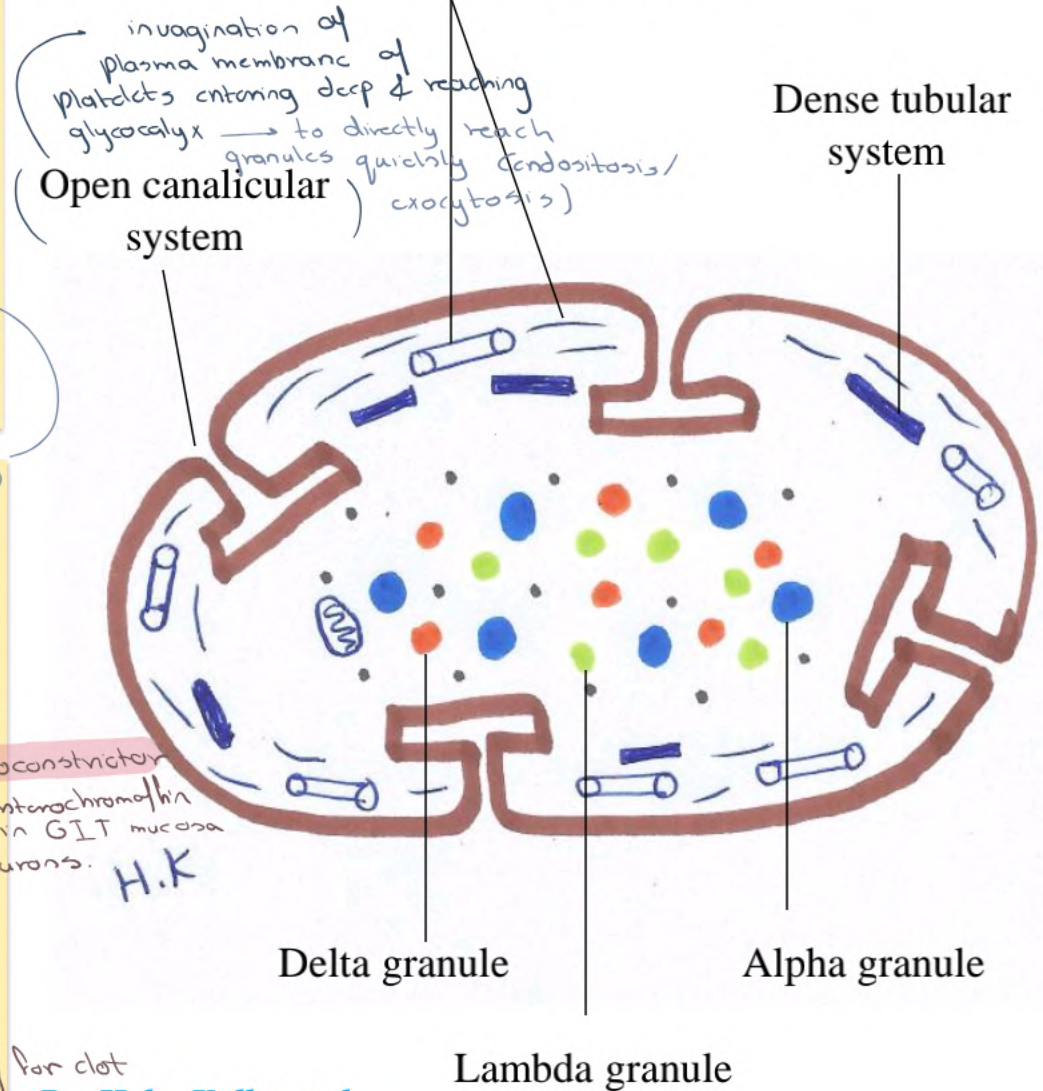
Dense (delta) granules: serotonin (absorbed from plasma), ATP, ADP ^{not synthesized in platelets rather absorbed from plasma}

Lambda granules: lysosomes (aid in clot resorption) ^{lysosomes... necessary for clot removal & retraction}

*platelets appear basophilic under light microscope

Have thick glycocalyx

Microtubule and microfilament



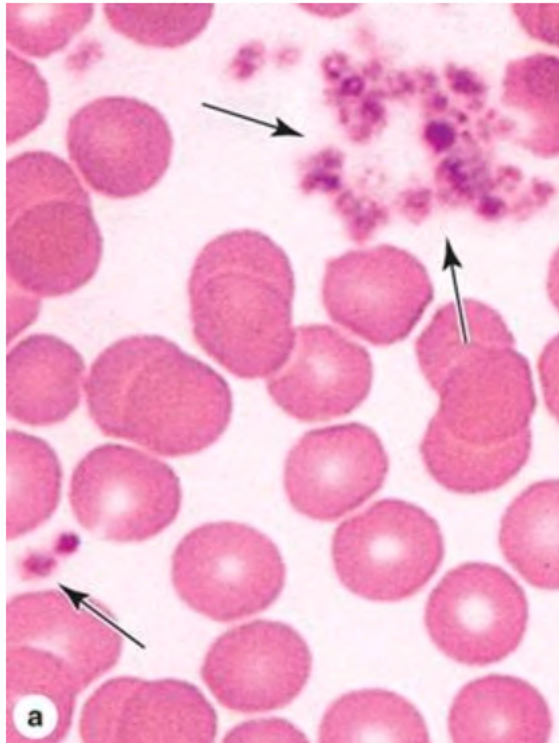
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Their main function is to continually monitor the vascular system and detect any damage to the endothelial lining of the vessels. If the endothelial lining breaks, the platelets adhere to the damaged site and initiate a highly complex chemical process that produces a **blood clot**



Thus preventing blood loss

*platelets
after their function
will get
eliminated
by macrophages
in spleen

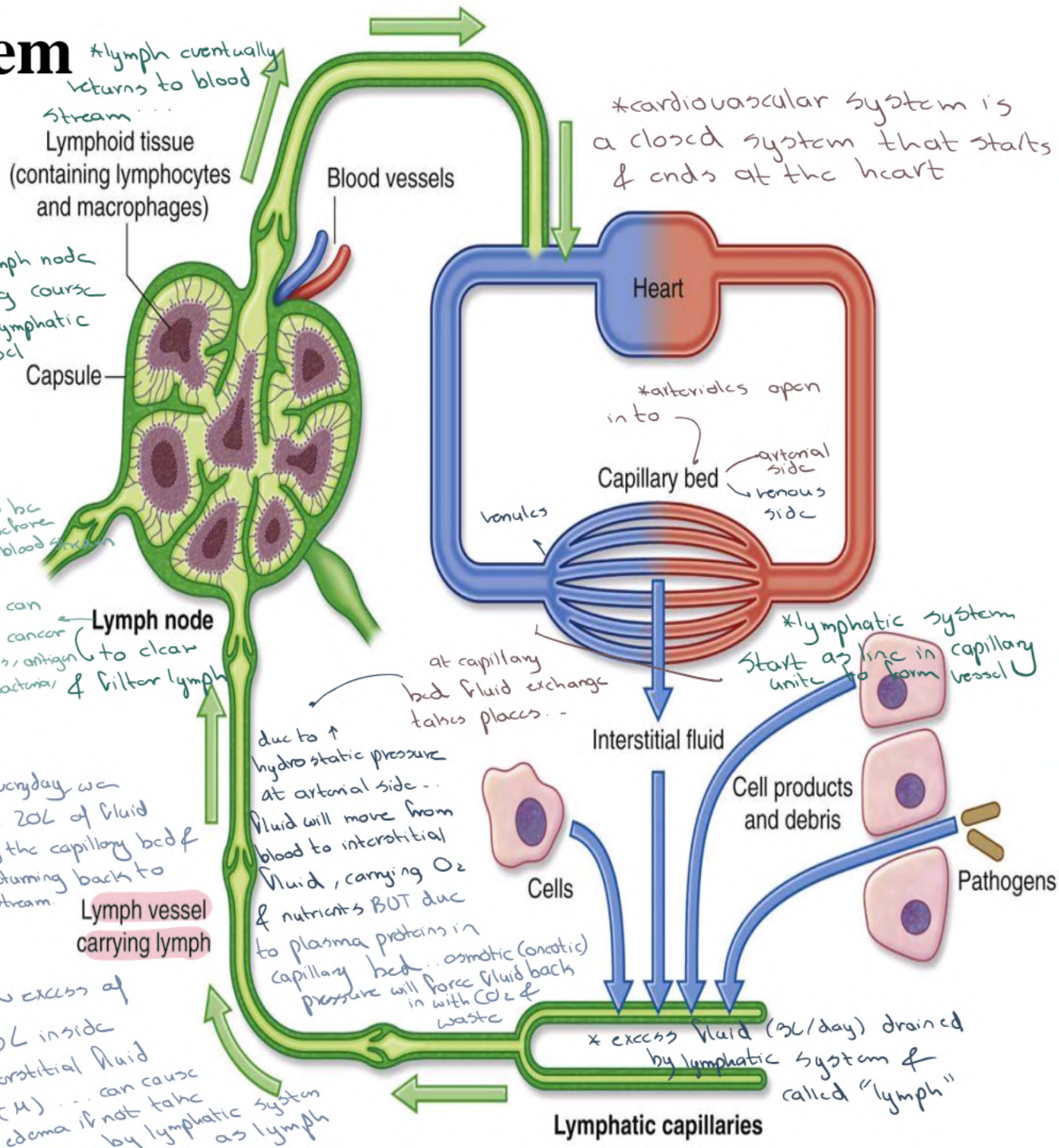


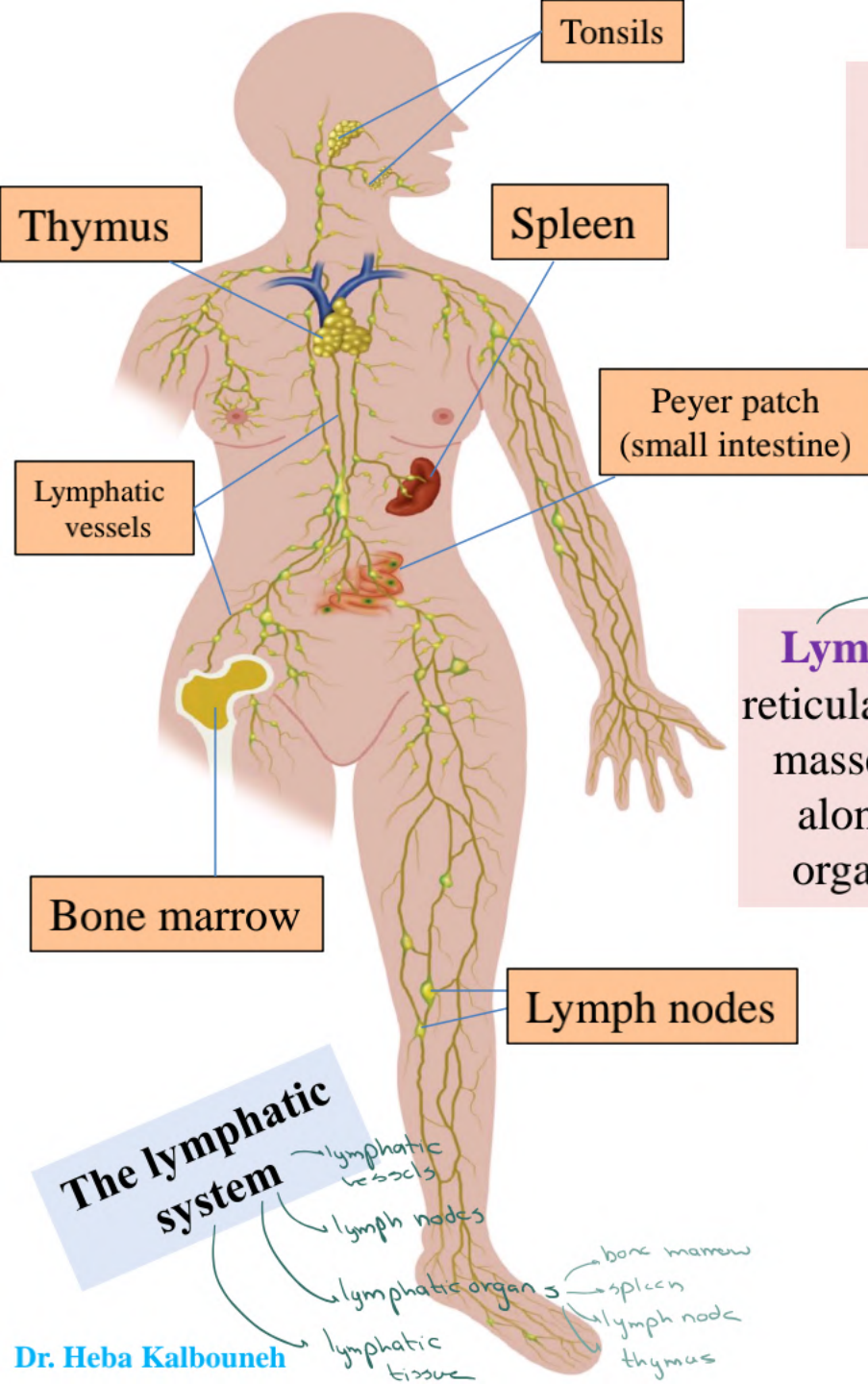
Lymphatic system

not closed system like CVS;
lymphatic system is blind ended
from one side & open in other side

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.





Lymph is a colorless fluid that floats in the lymphatic vessels. 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.

Handwritten notes:
 - aggregations of lymphatic tissue along mucous membranes (mucous + urinary tract, genital tract, GIT, respiratory etc...)
 - *collection of lymphatic tissue that is not organized into an organ "diffuse lymphatic tissue"
 - *But it can be like tonsils (MALT)
 - mucosa associated lymphatic tissue - that is more prominent HENCE was given a name.
 - Also like the prominent Peyer's patches in ileum

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

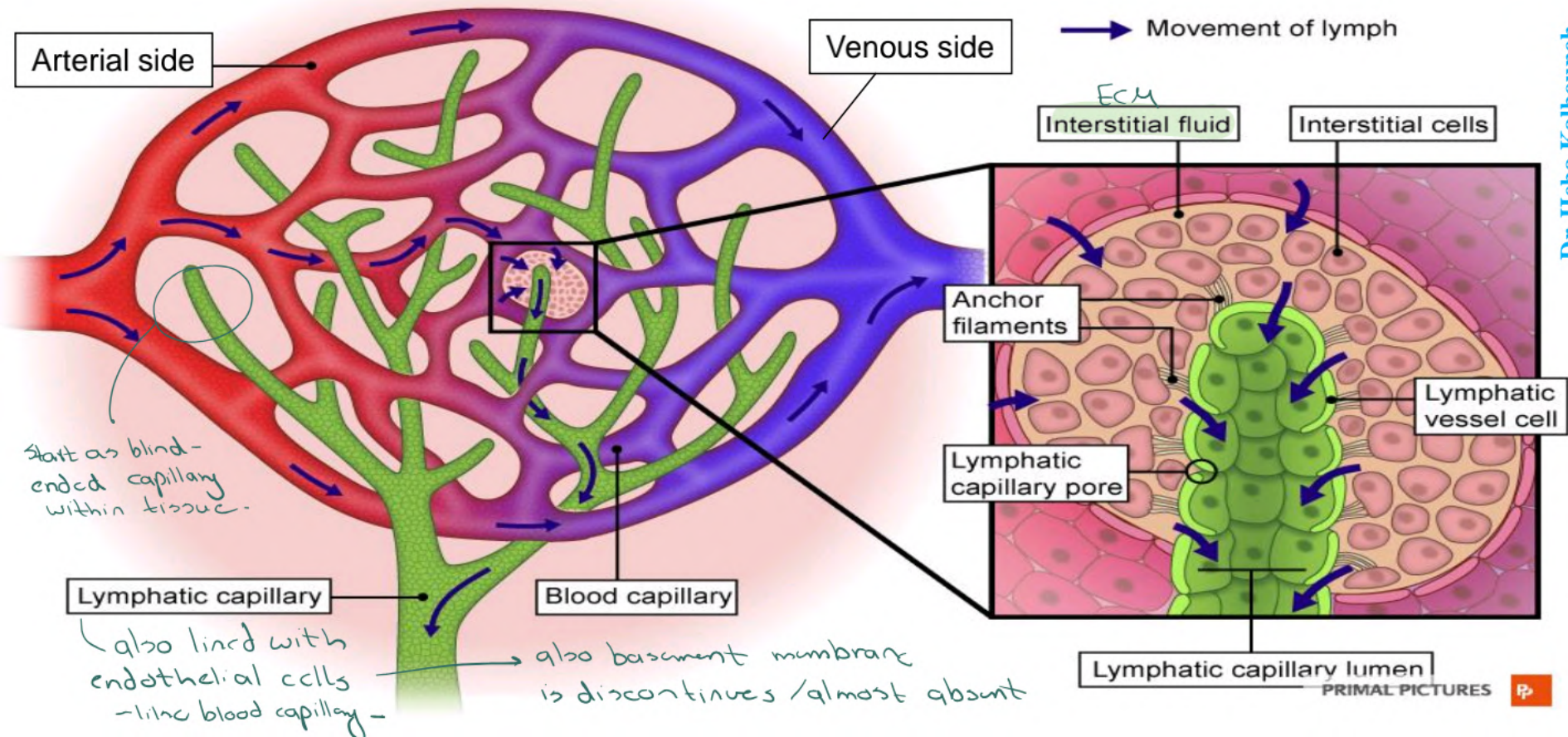
Fluid balance

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

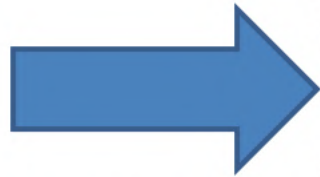
Around 20 liters of fluid leaves the arterial capillaries every day, but only 17 liters of fluid returns to the venous capillaries.

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

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



Right jugular trunk

Right subclavian trunk

Right broncho-mediastinal trunk

Left jugular trunk

Left subclavian trunk

Left broncho-mediastinal trunk

Thoracic duct

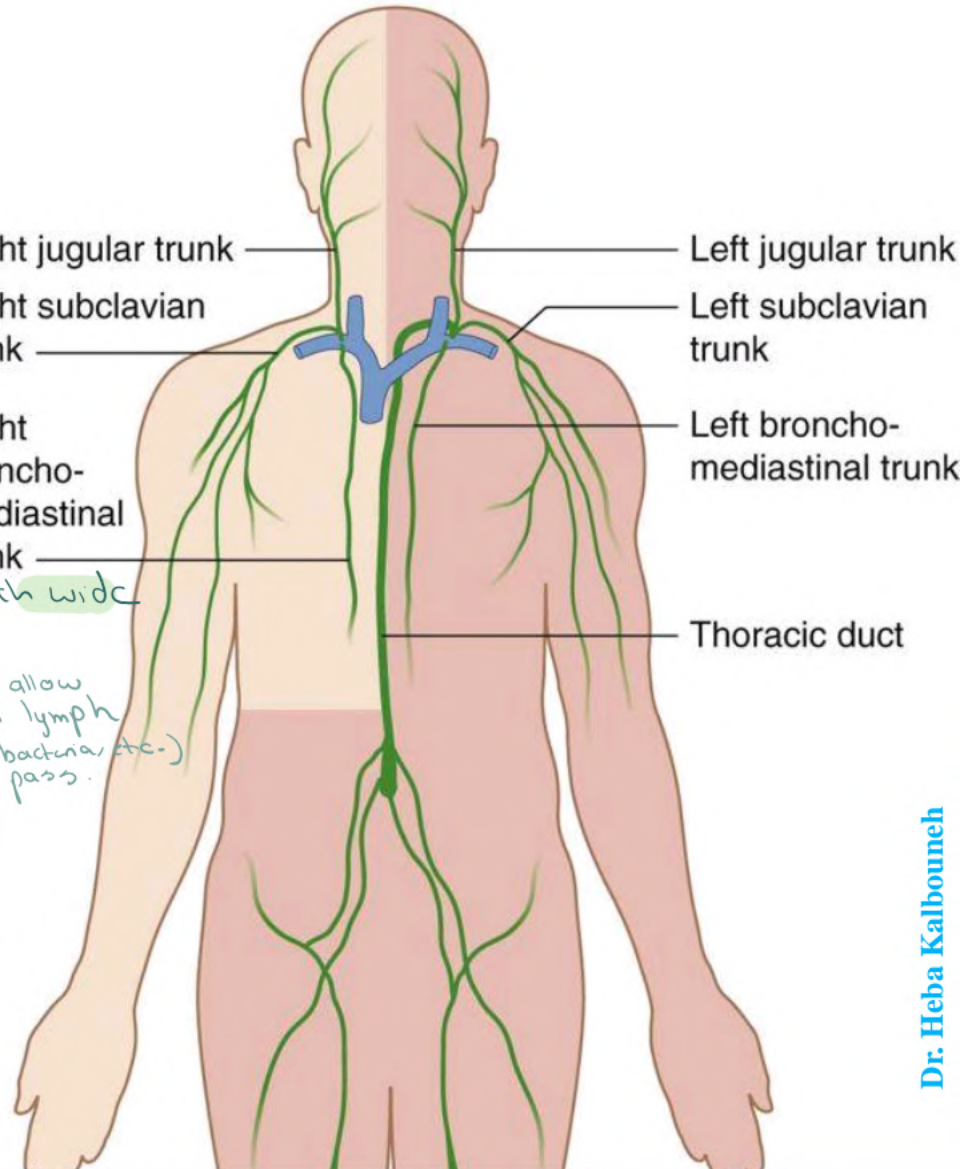
Arterial side

Lymphatic capillary

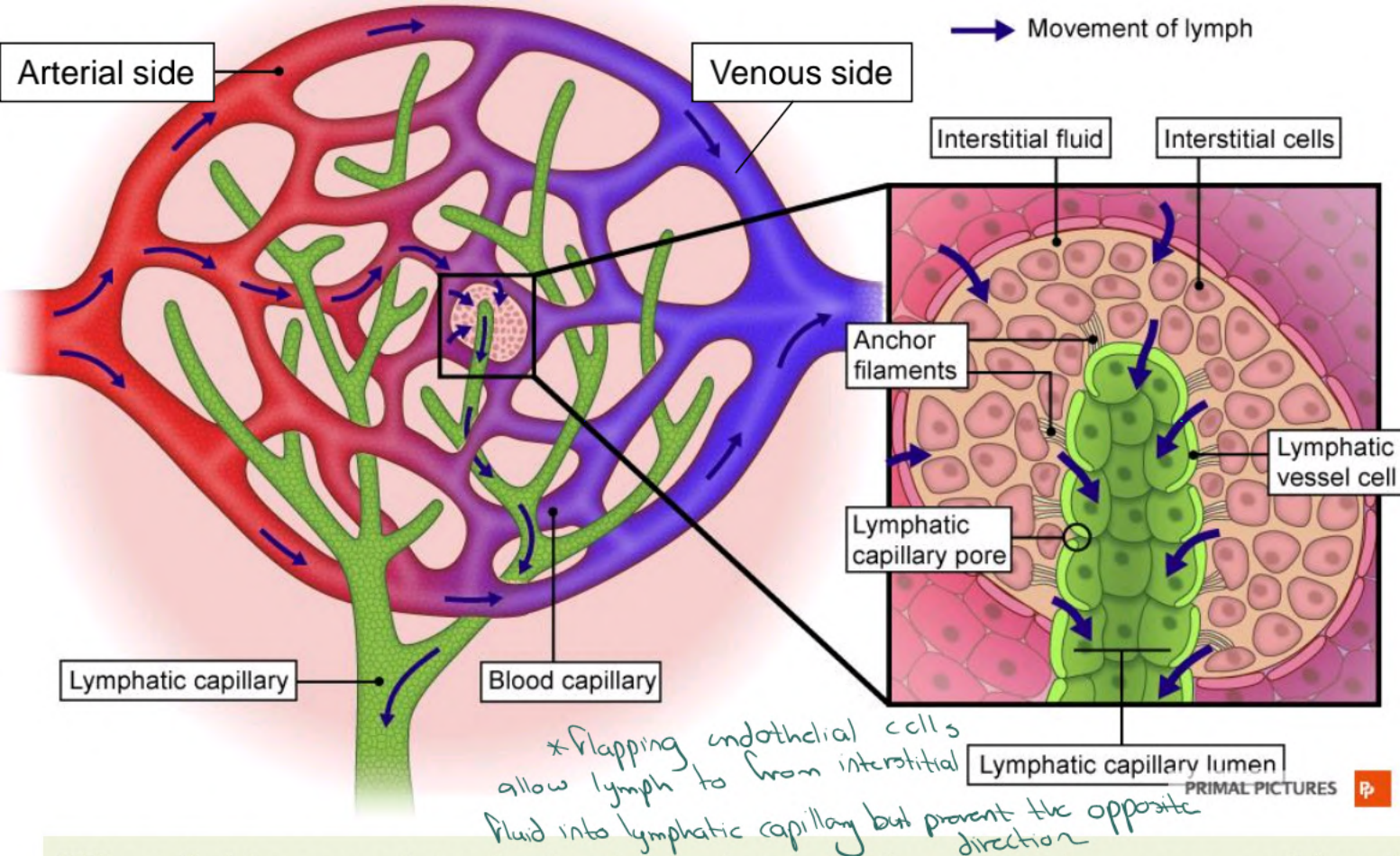
Blood capillary

(blind-ended)

endothelial cell of lymphatic capillary are overlapping cells with wide gaps to allow cells in lymph (APCs, bacteria, etc.) to pass.



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 with large gaps. 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/ dendritic cells) 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.

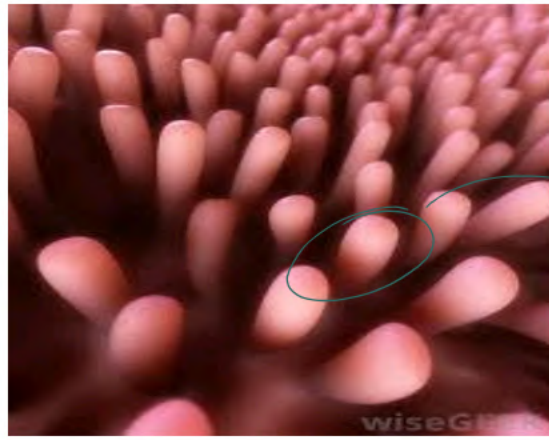


The lymphatic capillaries within the small intestine, known as **lacteals**, can absorb these large lipid molecules and transport them into the venous circulation via the thoracic duct. Lymph containing these lipids becomes a creamy white color and is referred to as

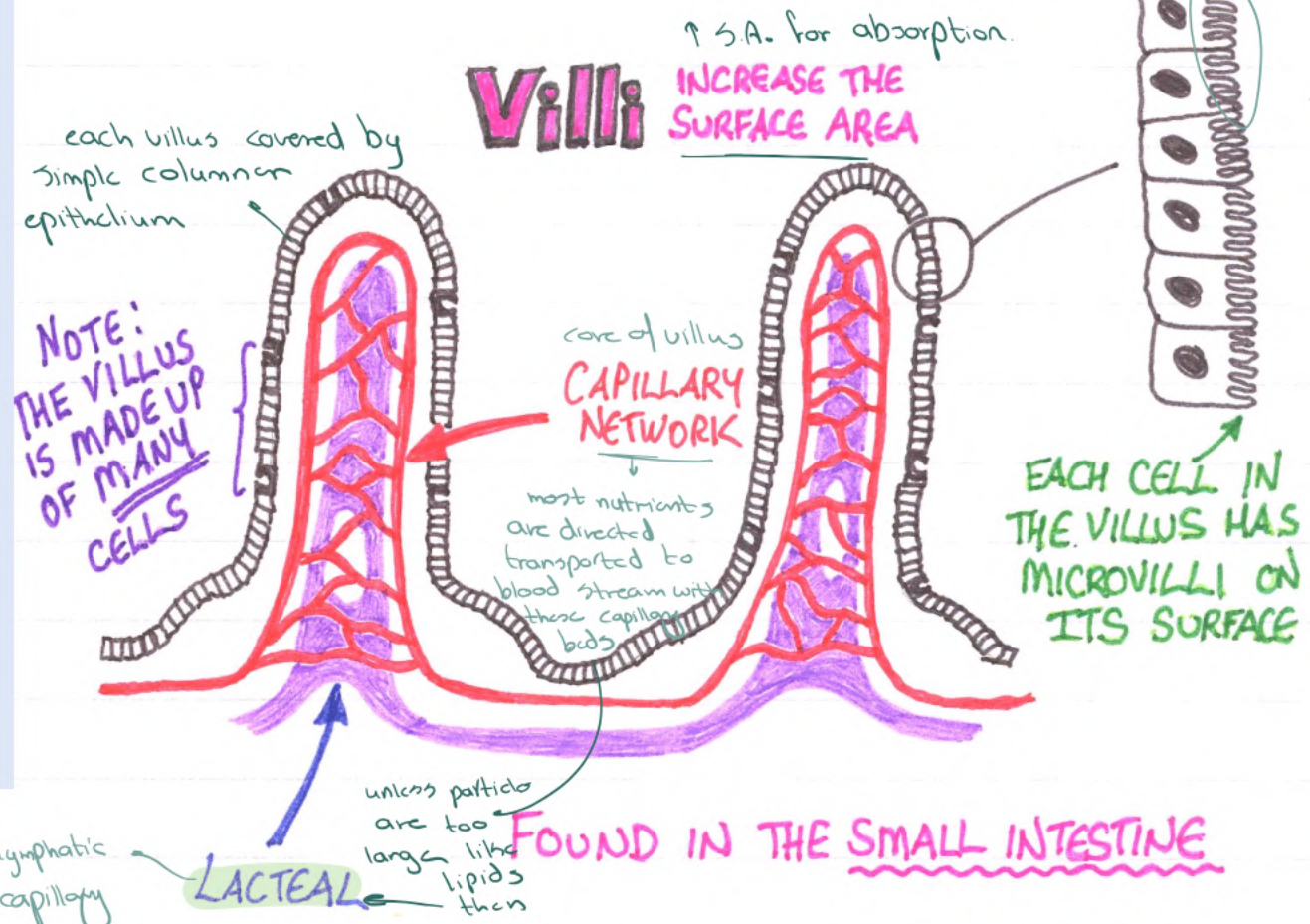
lymph formed ← **chyle**.
inside the lacteals
≈ whitish in color.
Creamy in consistency → rich in fat.

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other function of lymphatic system (transport lipid)



villi
microvilli - cytoplasmic extensions - on simple columnar epithelium apical surface -



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 tissues and organs.

Lymphatic organs are divided into:

Primary lymphatic organs (central)

Bone marrow. → lymphocytes originate from bone marrow, B cells differentiate in bone marrow, while T cells complete maturation in Thymus.

Thymus gland.

Are sites of Lymphocyte production, maturation, selection



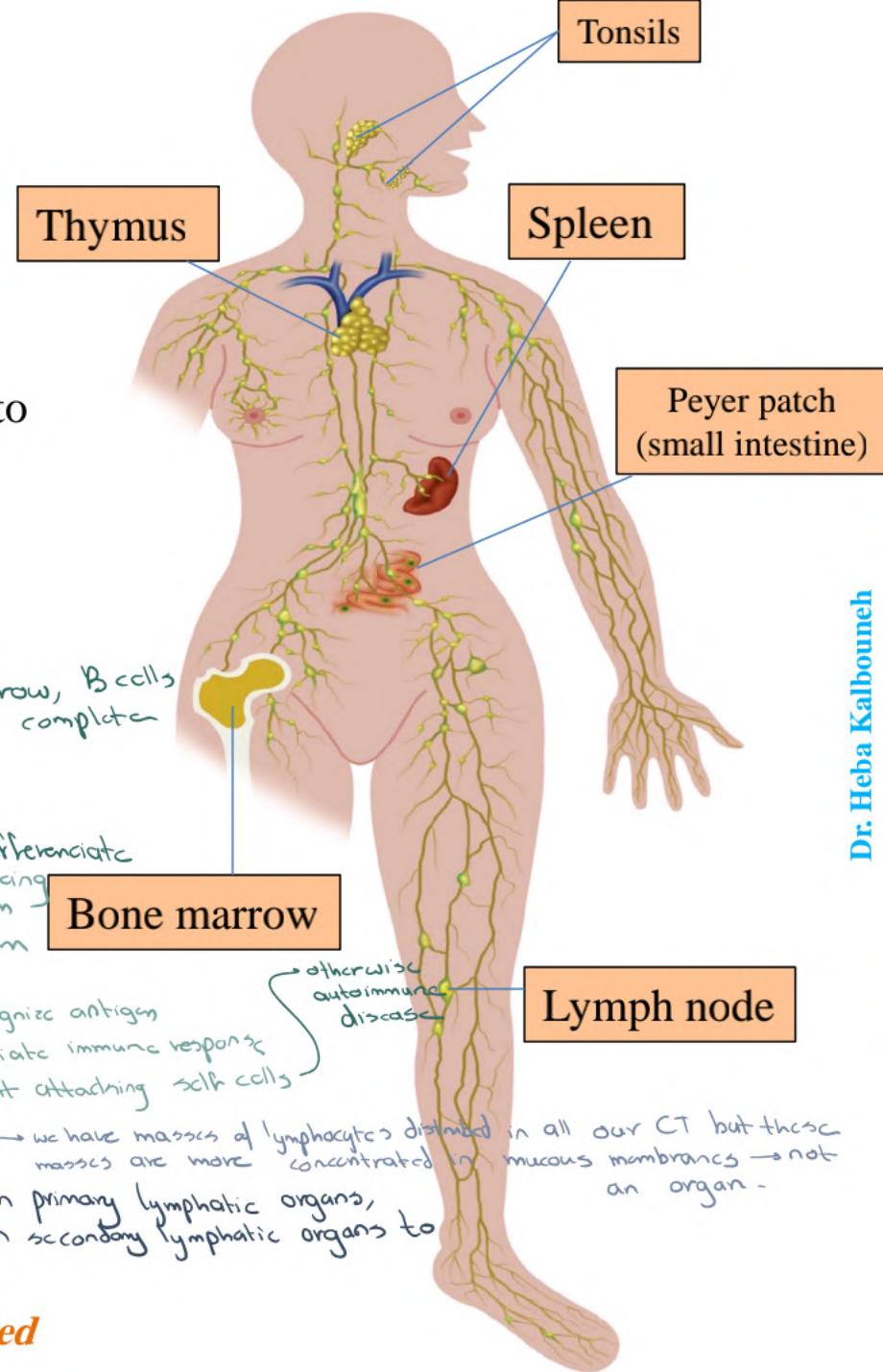
Secondary lymphatic organs (peripheral)

Diffuse lymphatic tissue (lymphatic nodules),

Spleen.

Lymph nodes.

Are sites to encounter pathogens and become activated

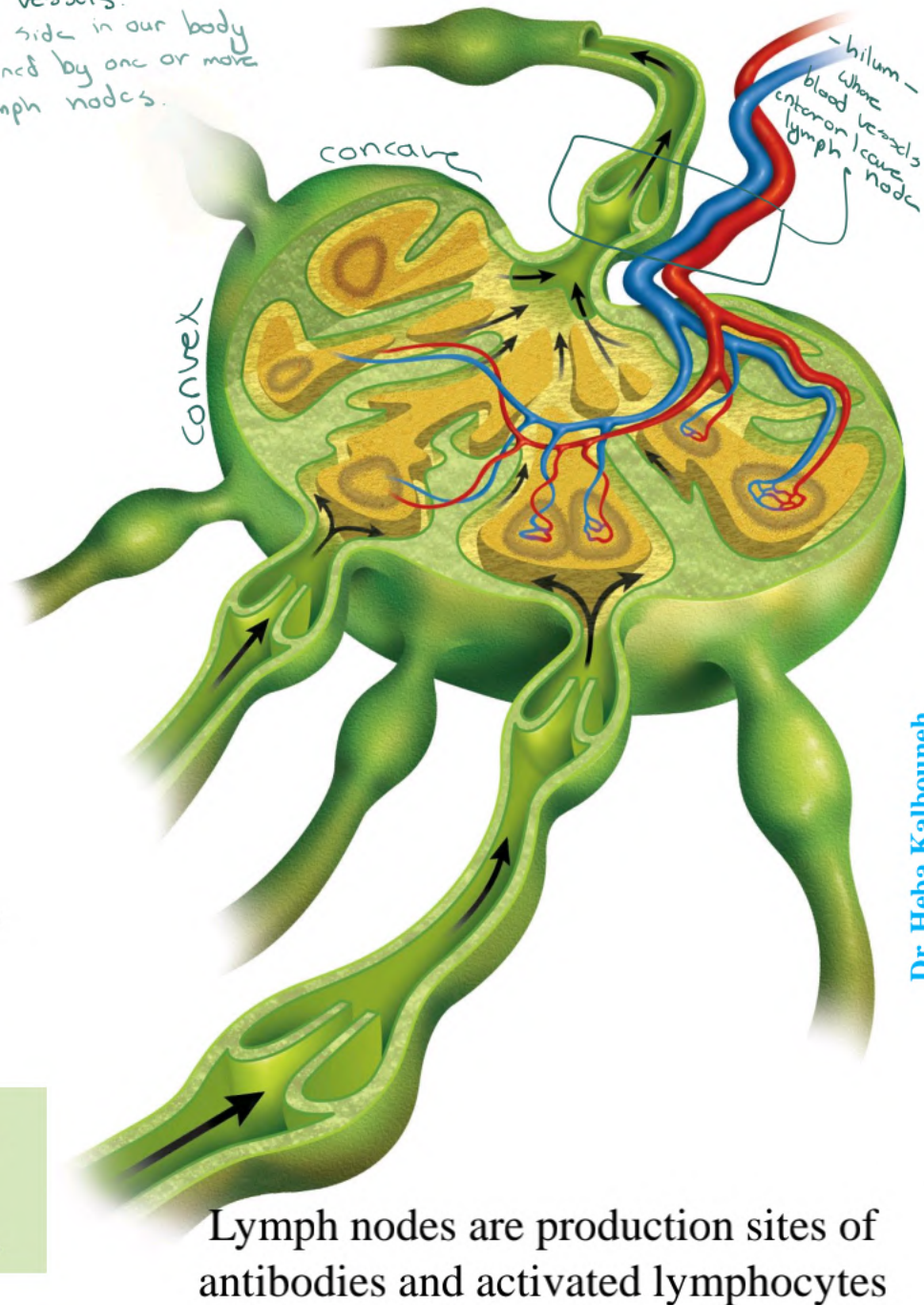


Lymph nodes → located along course of lymphatic vessels.
~ few millimeters in size → usually form groups & usually each side in our body is drained by one or more lymph nodes.

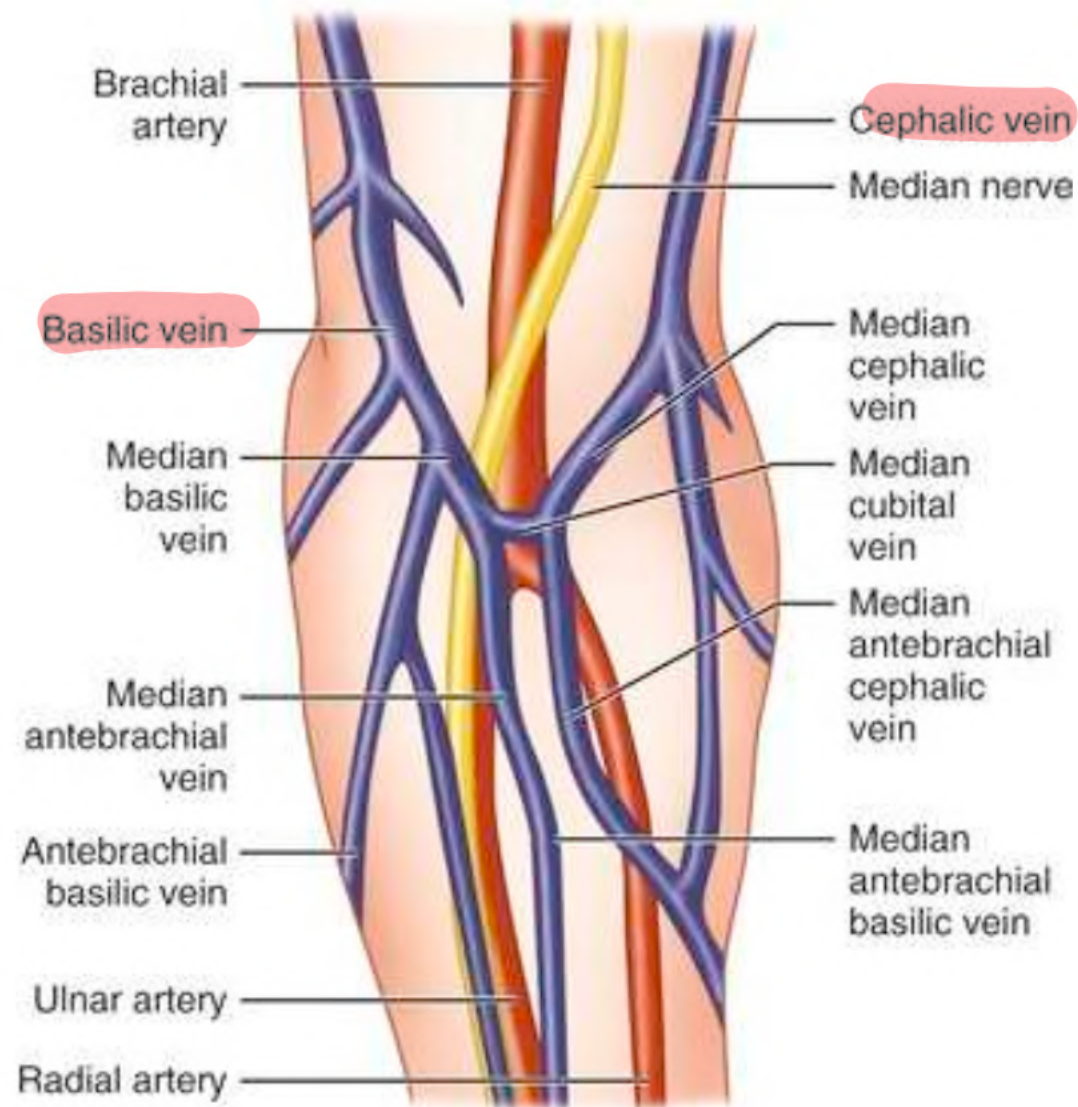
- ✓ Are kidney-shaped small encapsulated bodies located along the course of lymphatic vessels (Approximately 600 lymph nodes)
- ✓ Reticular tissue forms the stroma of the lymph node
- ✓ Immunocompetent B cells and T cells are suspended throughout the lymph node
- ✓ Nodes filter the lymph, removing foreign 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.

~ usually few millimeters

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

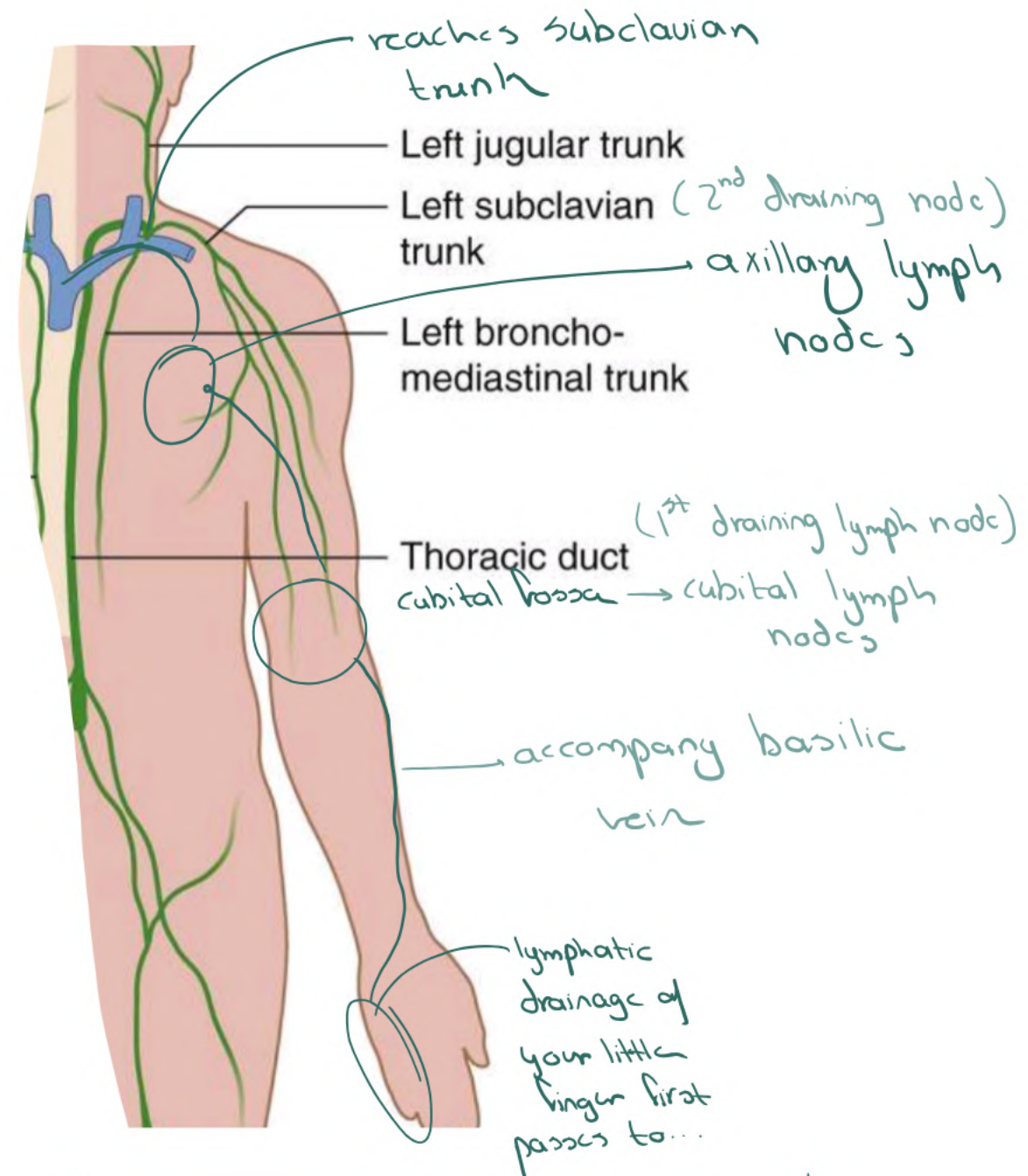


*superficial veins of upper limb



lymph from certain part of our body can be drained by single lymph node or more than one before returning to stream

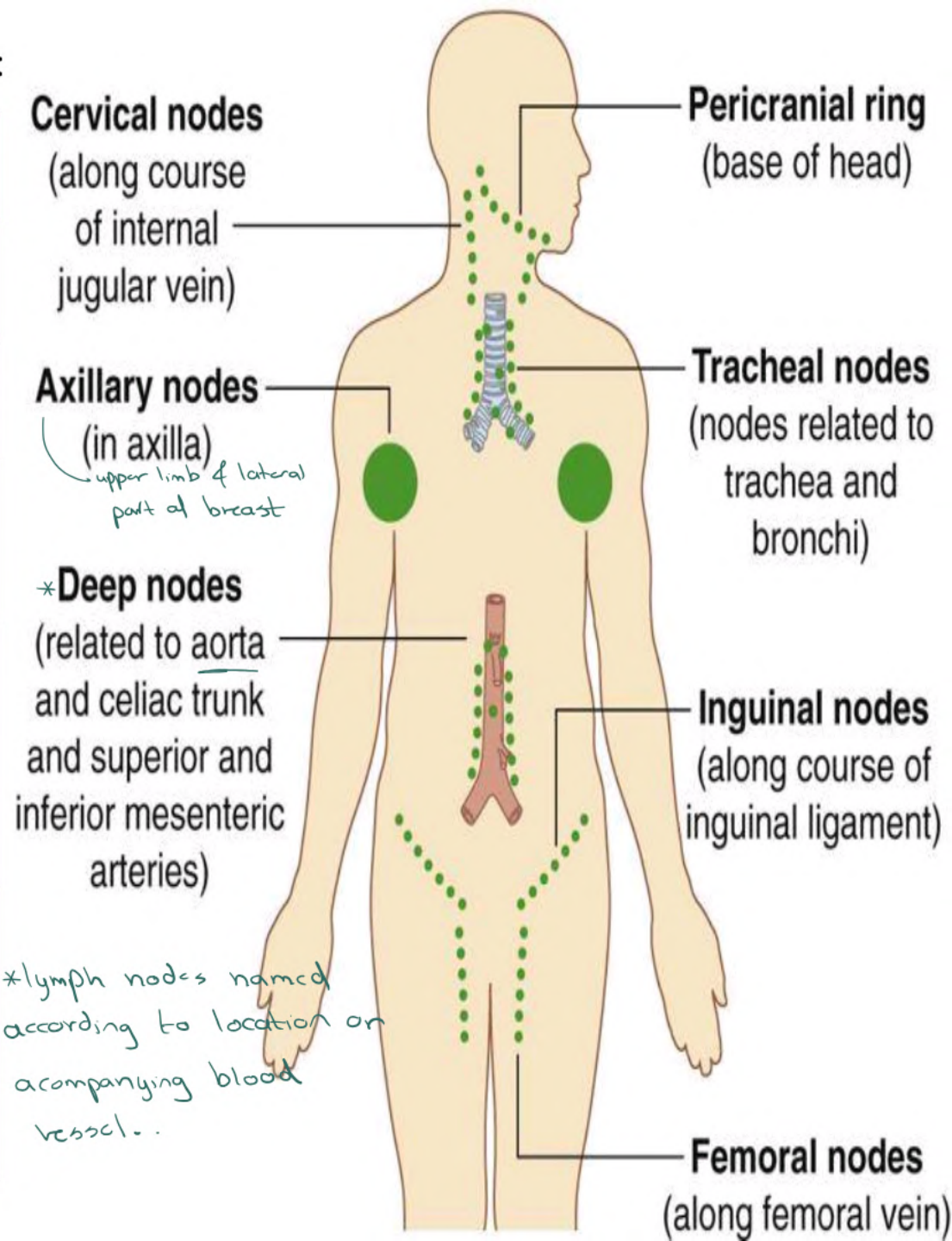
* E.g. of draining a body organ "little finger"



lymph from pinkie passes two lymph nodes before returning to blood stream.

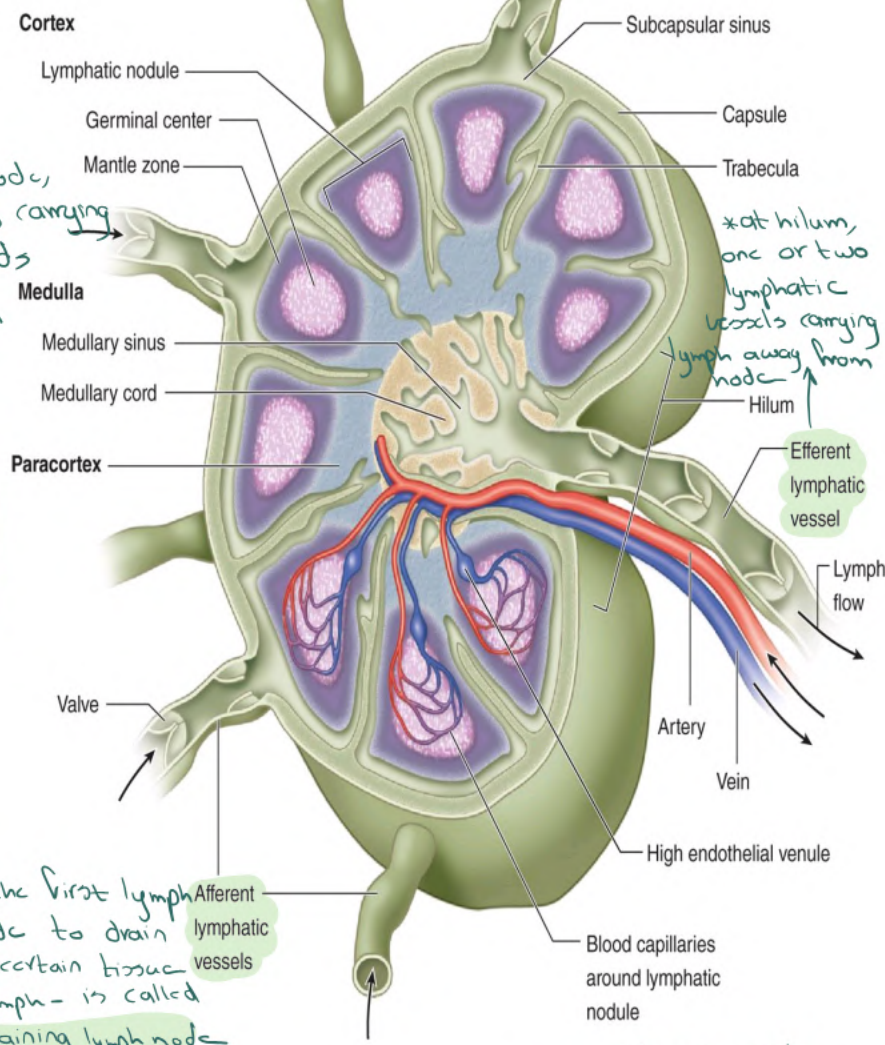
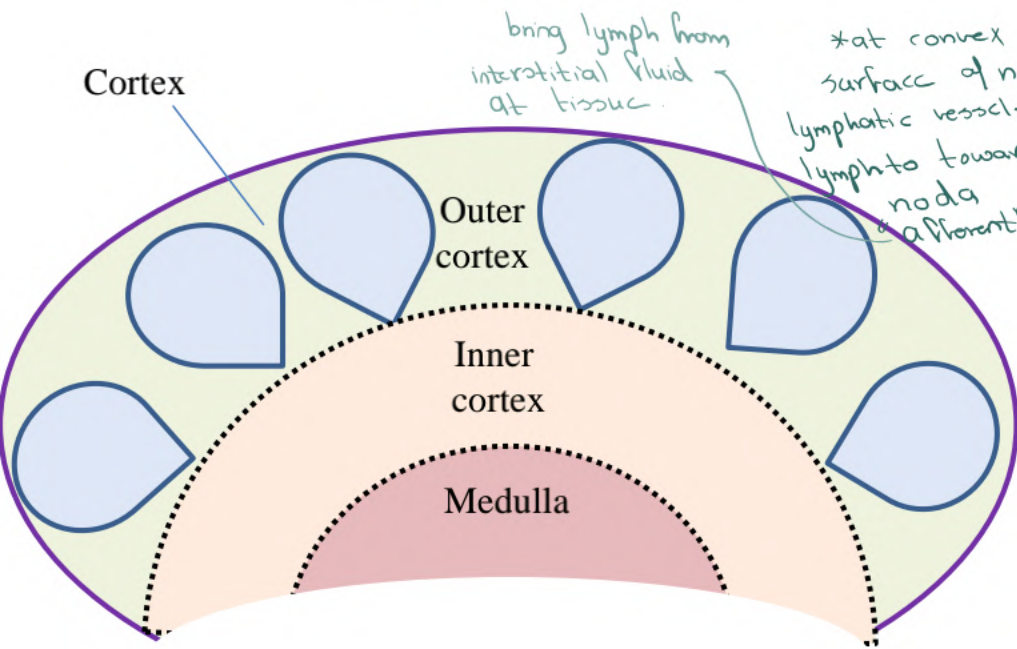
The main groups of lymph nodes include:

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



*different cellular organization between these parts

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 first lymph node to drain a certain tissue - lymph - is called draining lymph node

many afferent: vessels

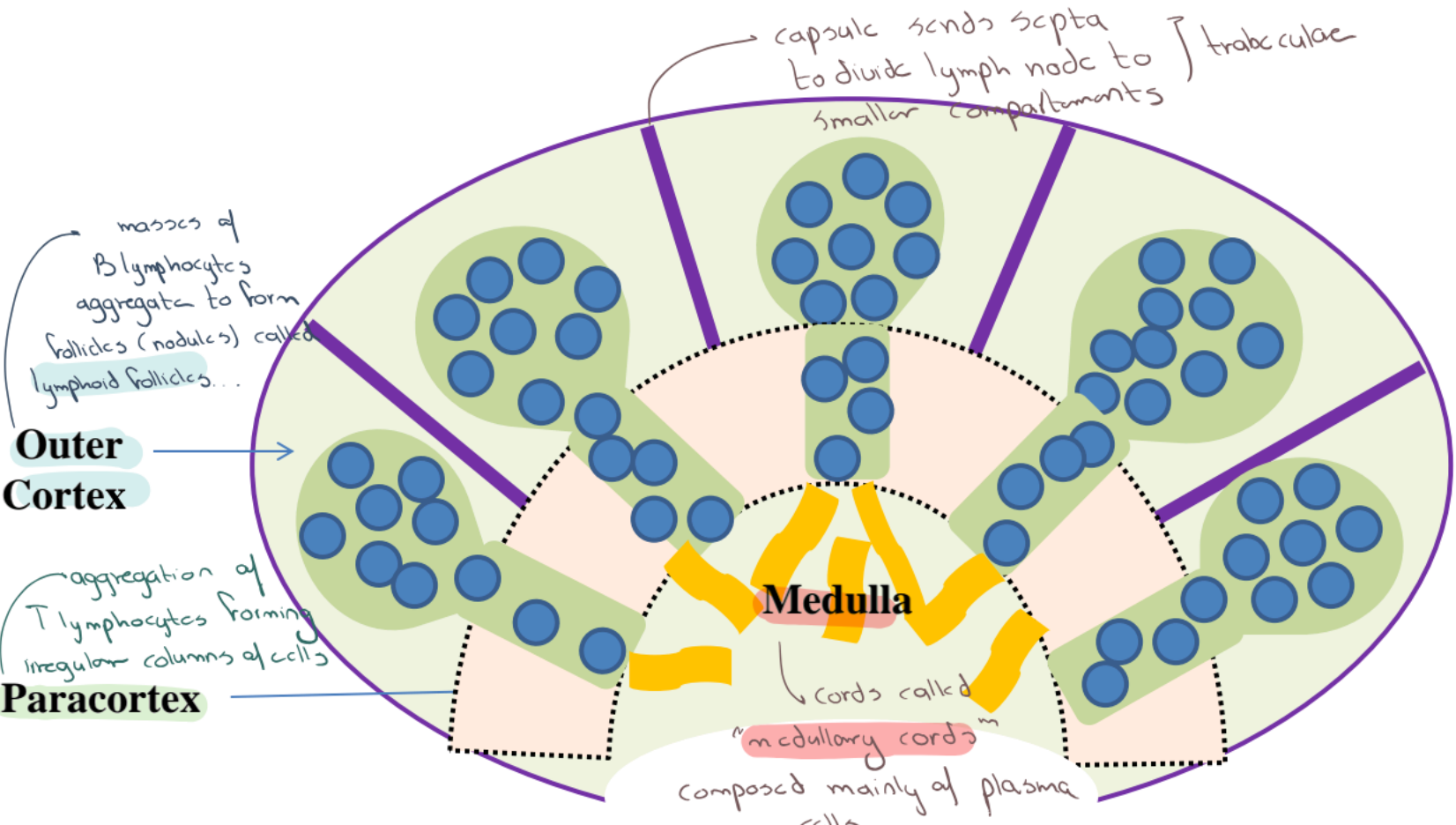
one or two efferent vessels
the efferent vessels of one lymph node can be afferent vessels of other nodes..

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.

- B lymphocytes → outer cortex
- T lymphocytes → paracortex
- plasma cells → medulla



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**.

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)

Other cells in the lymph node:

Macrophages

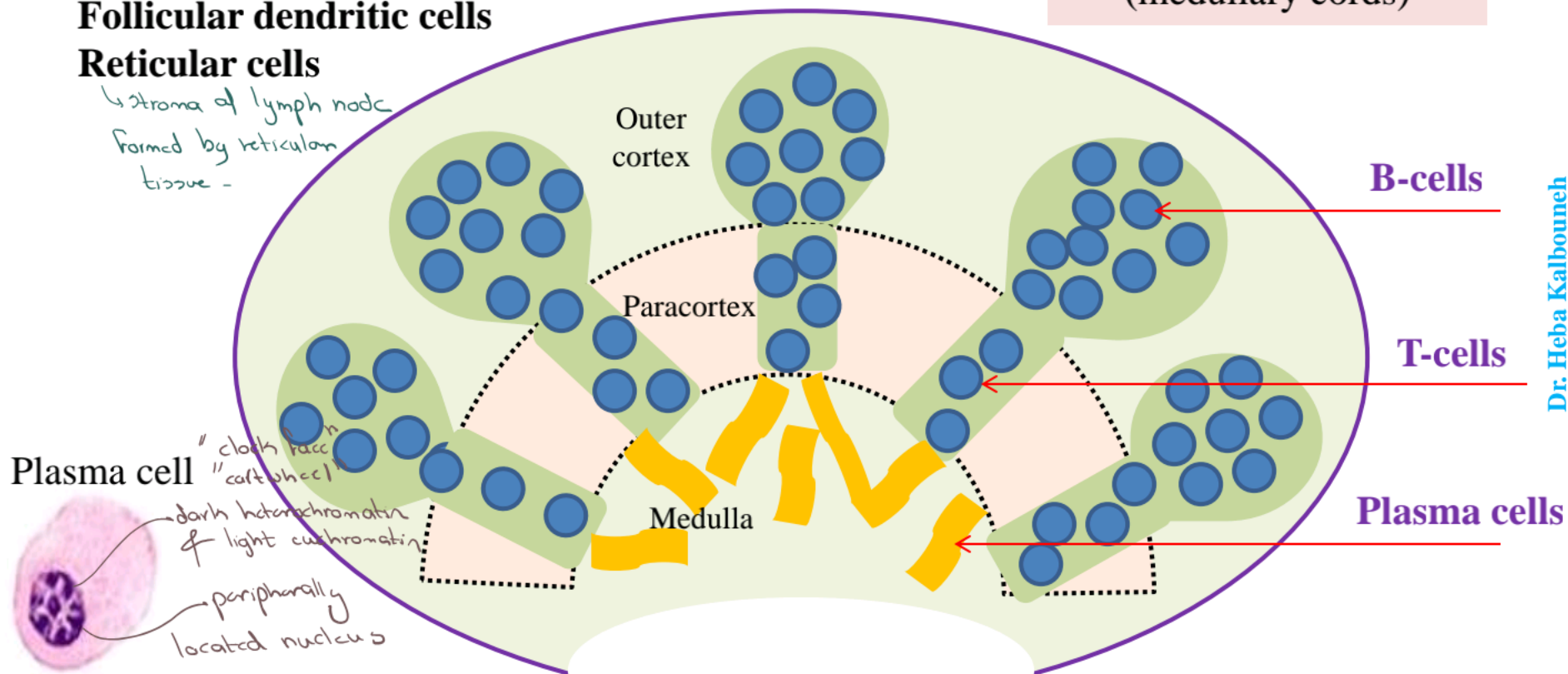
Dendritic cells

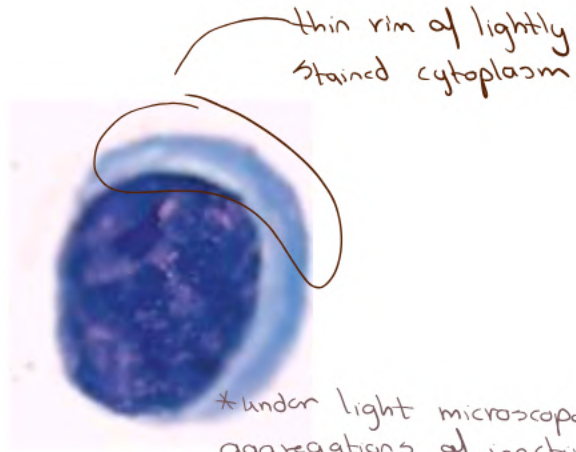
Follicular dendritic cells

Reticular cells

↳ stroma of lymph node
formed by reticular tissue -

Antigen presenting cells derived from monocytes.

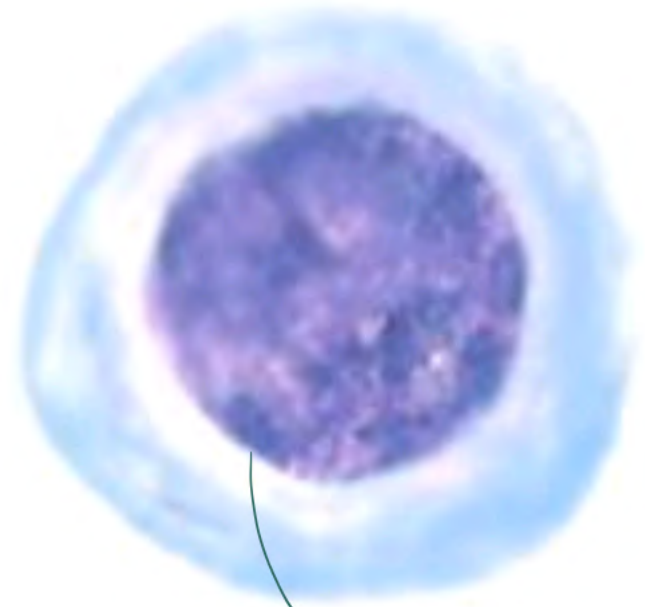




*under light microscope -
aggregations of inactive
lymphocytes appear like
basophilic dots →
because small lymphocytes
have nucleus filling most of
cytoplasm & nucleus is heterochromatic
-dark basophilic stain-

Small
(6-9 μm)
Inactive lymphocyte

Darkly stained cell

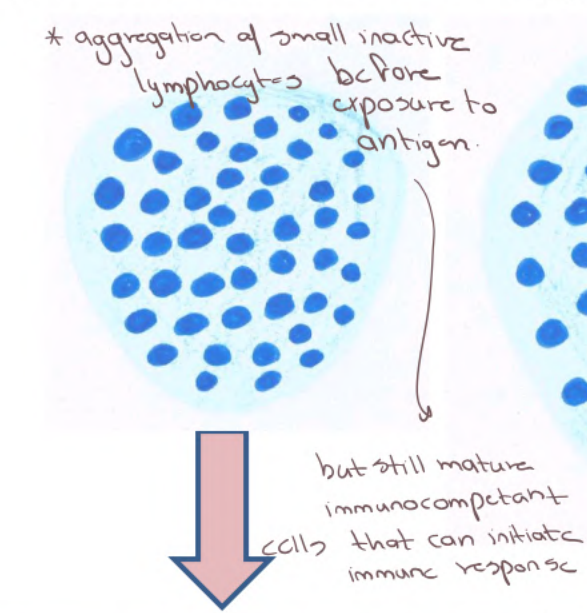


nucleus is
lightly basophilic in
color... mainly
active form of
DNA "euchromatin"
Large
(9-18 μm)
Active lymphocyte

Lightly stained cell

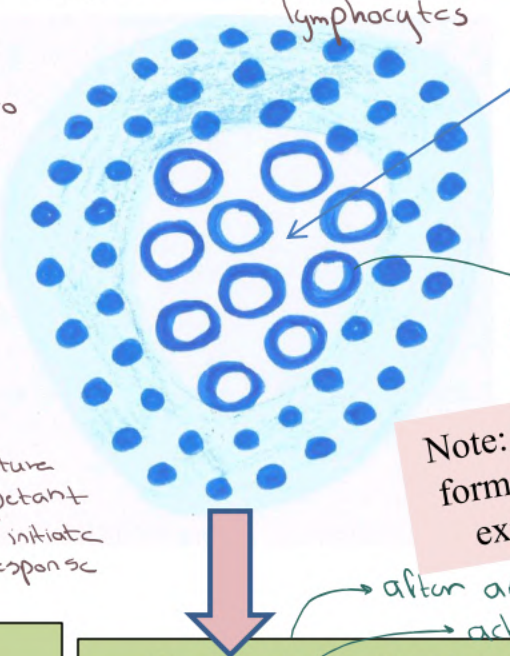
The outer cortex houses lymphatic follicles

(nodules) which are of two types:



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

not yet exposed to an antigen & activated



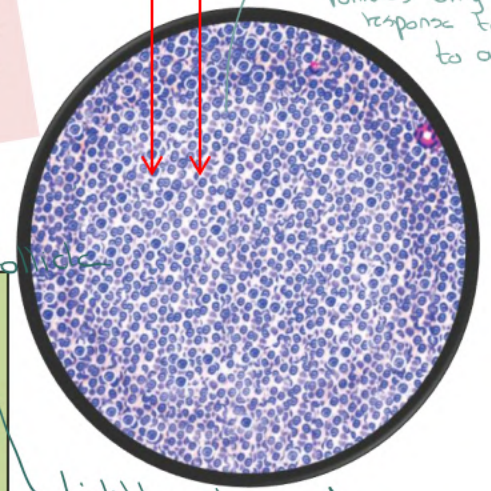
Secondary follicles: lymphoid follicles with a germinal center.
Sites for B memory cell and plasma cell generation



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

germinating proliferating B cells → large in size & lightly stained

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



secondary lymphoid follicles only form in response to exposure to antigen.

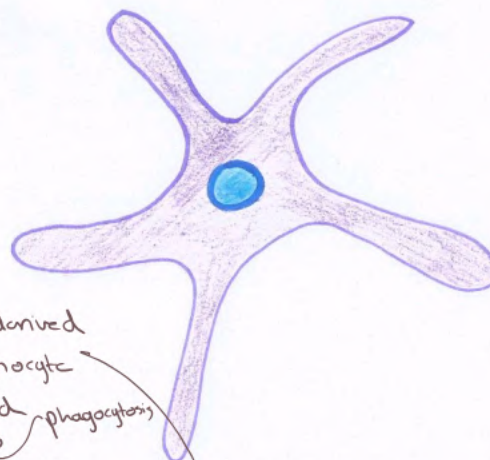
When **activated by antigens (and T helper cells)**, B cells migrate to the center of the follicle, forming a germinal center. Germinal centers are the central regions of secondary follicles where activated B cells are **proliferating** (dividing by mitosis) and **differentiating** into **plasma cells**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

antibodies reach blood & circulate to reach everywhere lymph leave lymph node through efferent vessels then secrete antibodies directly into lymph (move to medullary cords)

at infection site,
antibodies form complexes
with antigens.. & these
complexes are completely
eliminated by resident macrophages
within infected CT.. or monocyte-
derived macrophages..
after infection is eliminated
we have complete clearance
of antigens...



Macrophage



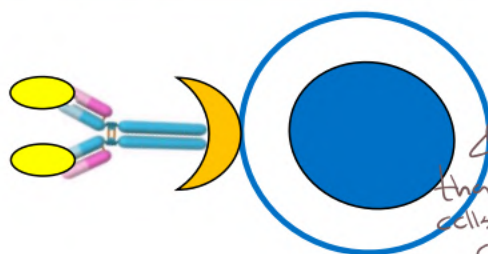
Dendritic cell

Both derived
from monocyte
*all cells derived
from monocytes
perform two
function
phagocytosis
antigen-
presentation.

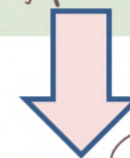
Macrophages and
Dendritic cells capture
antigen within tissues
and transport antigen
to secondary lymphoid
tissue

cells have special receptors
for antibody-antigen complex..
keep holding them

	Macrophage	Dendritic cell	Follicular dendritic cell
Phagocytosis cell able to form phagosome, degradation of antigen by lysosomal enzyme & complete clearance of antigen.	Most phagocytic	Moderately phagocytic	X <i>antigen holding</i>
Antigen presenting (via MHC-II) cell able to process antigen & present it on surface using MHC-II molecules.	Moderate Ag- presenter	Very powerful Ag- presenter	X
Location in lymph node	Cortex and medulla	Cortex and medulla	Outer cortex "lymphatic follicles"



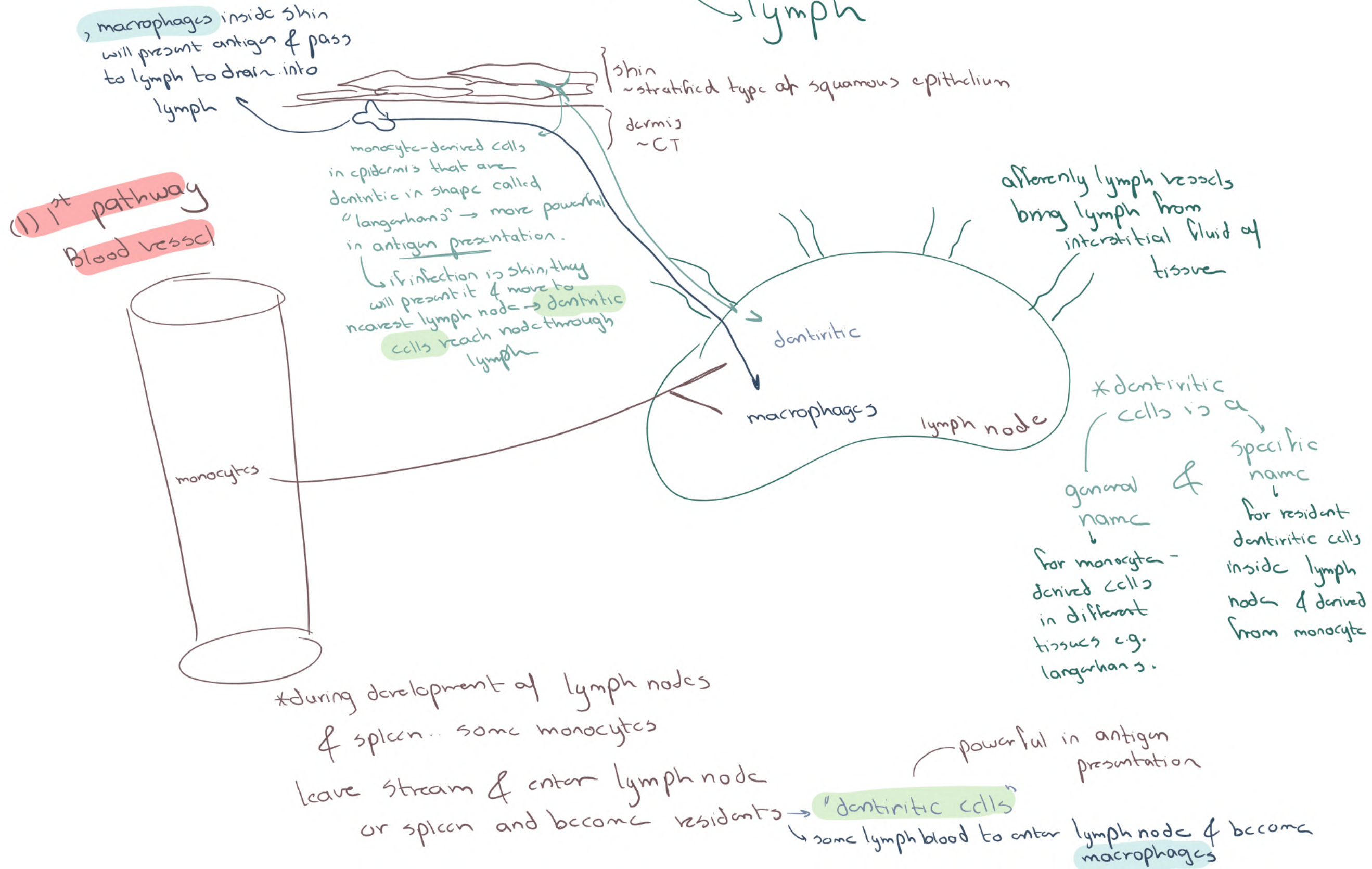
keeps immune
system in semi-
stimulated state..
& offers
them to B
cells inside
cortex



not presenting

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

*dendritic cells & macrophages reach lymph node
either through blood
lymph



The **medulla** is the deep, cavitated part of the lymph node; it is composed of **medullary cords**

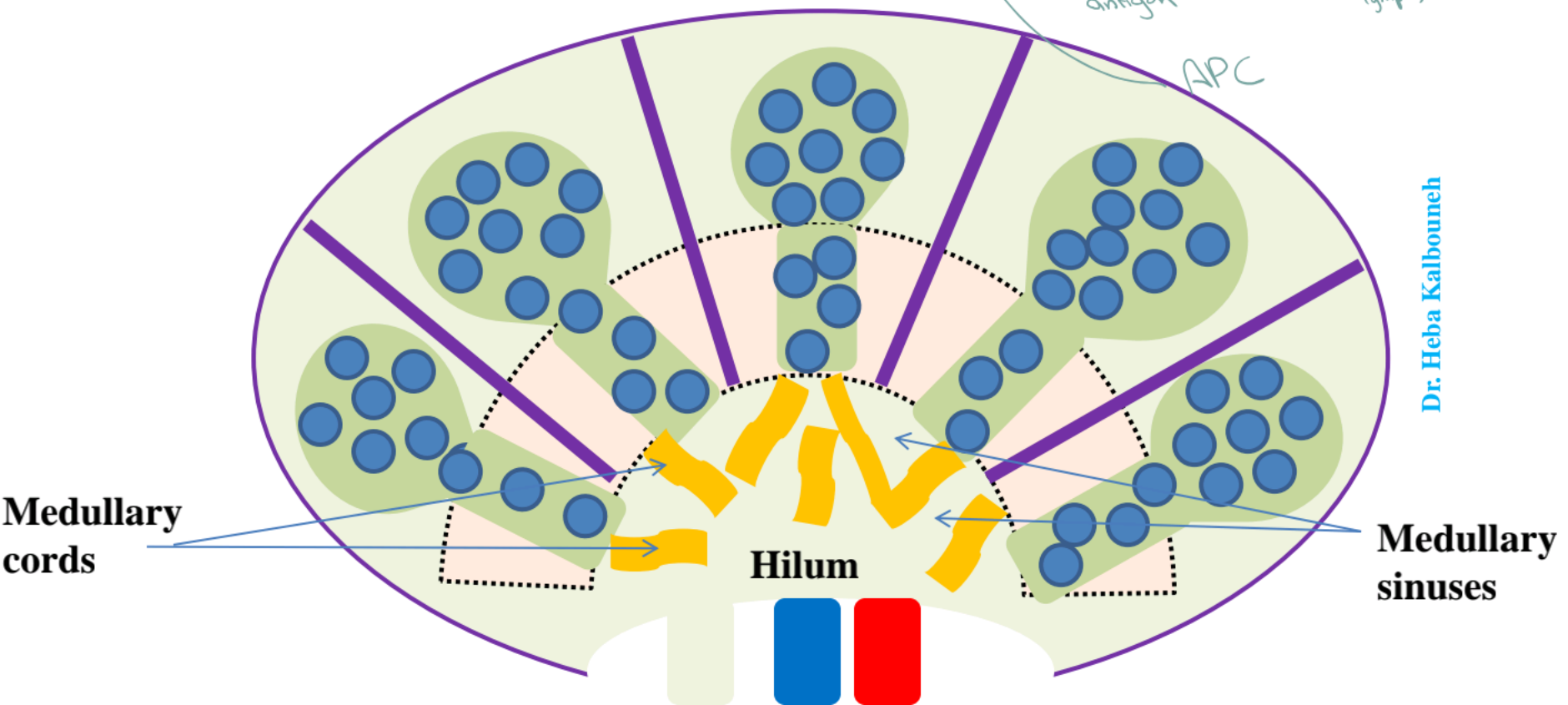
The cords are separated by spaces known as **medullary sinuses**

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.

*what can we find inside afferent lymph entering lymph node?

- cancer / virally - infected cells
- soluble antigens
- fragments of antigens
"neutrophils release fragments of antigens by exocytosis that can pass through lymph"
- intact antigen



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

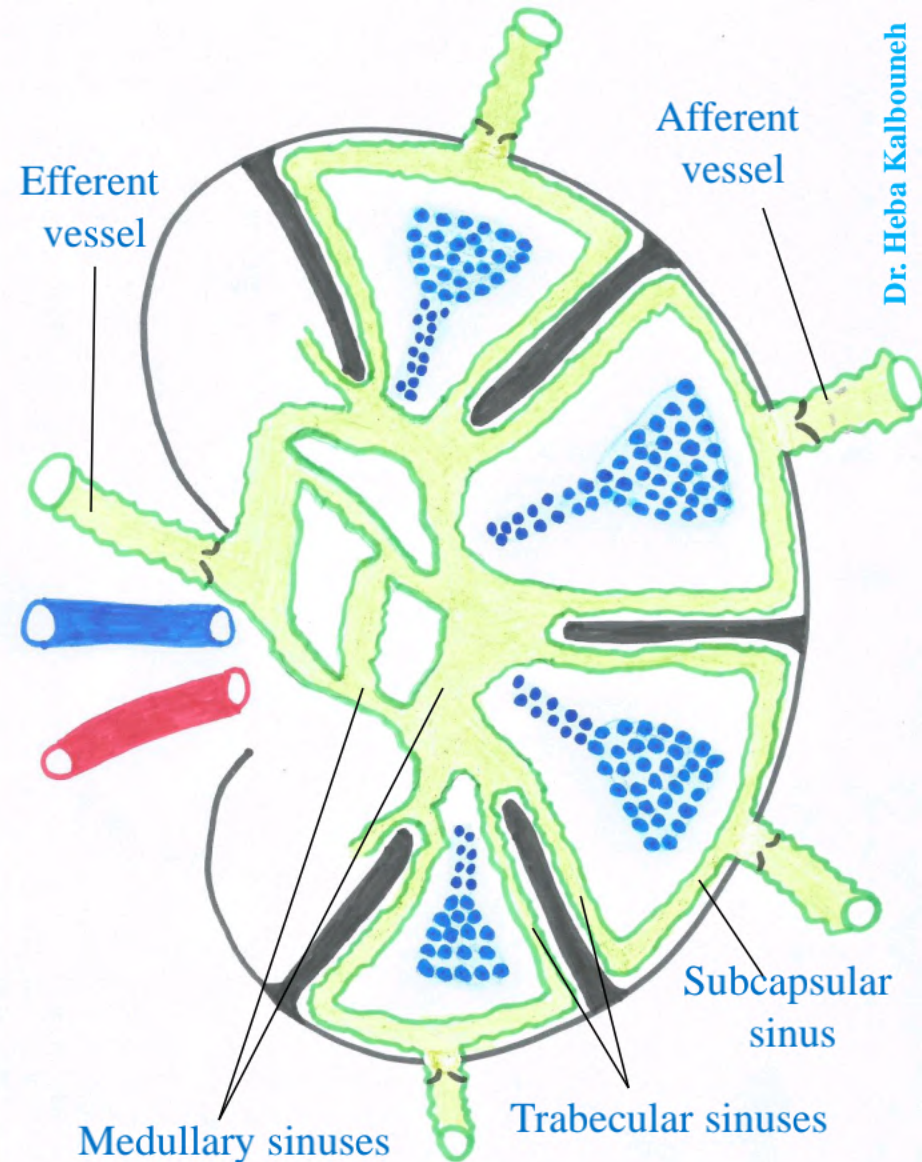
The trabecular sinuses are a continuation of the subcapsular sinuses that follow the trabeculae and drain into the medullary sinuses.

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.



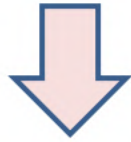
Sinuses are irregular spaces through which the lymph percolates

Lymph flow

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

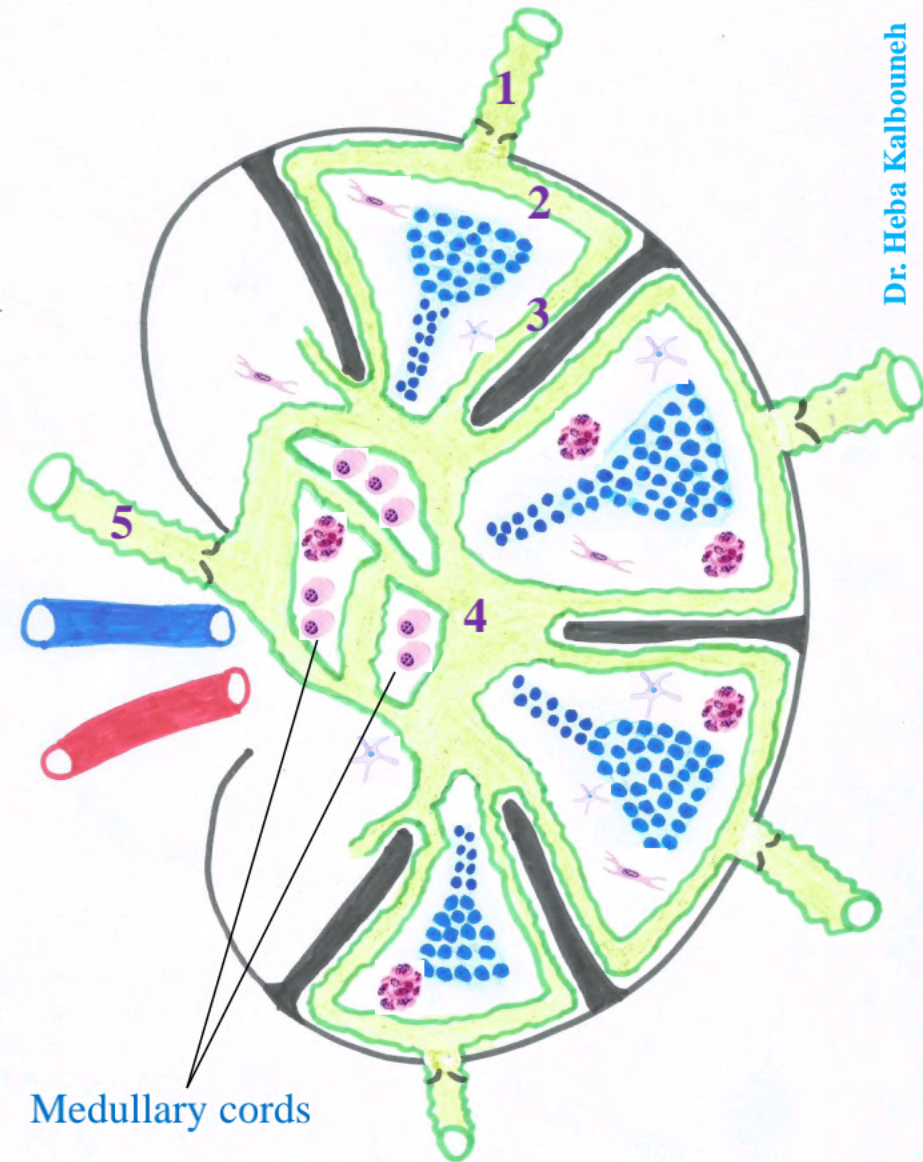
lymphatic sinus → irregular spaces filled with lymph & lined with endothelium that is discontinuous.

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**.



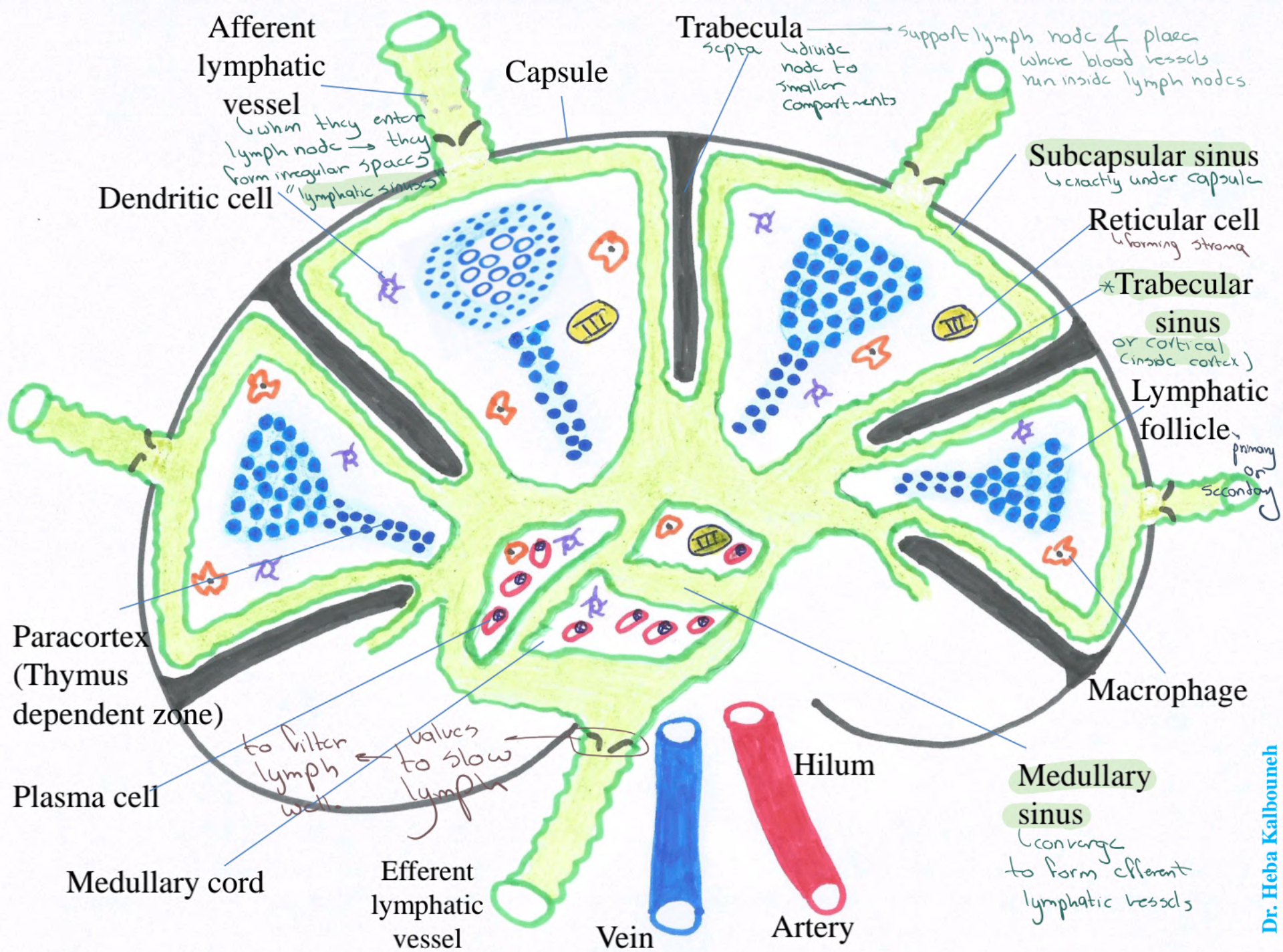
Efferent lymph contains lots of activated T-lymphocytes, activated B-lymphocytes, plasma cells and antibodies.

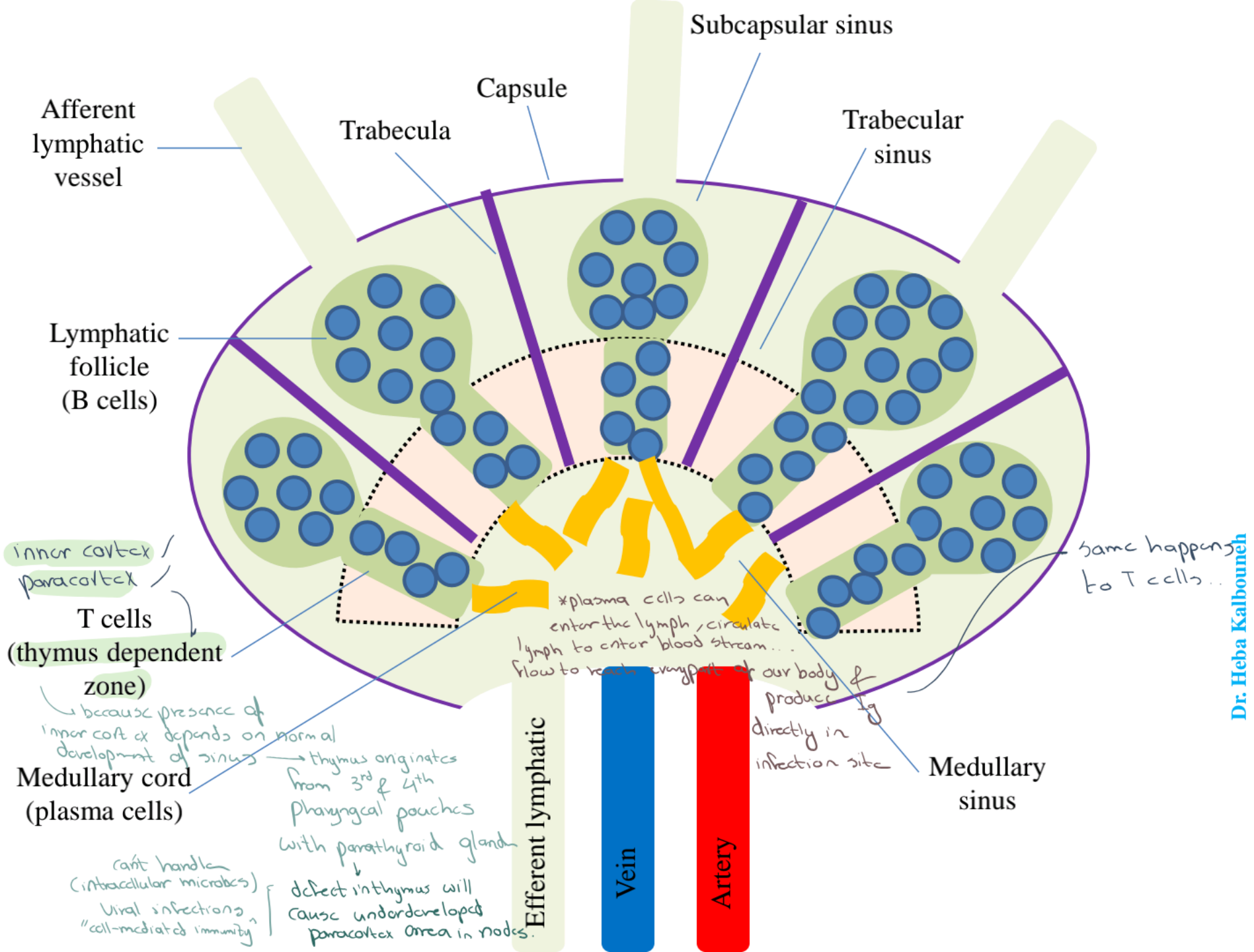
Lymph slows down when it passes in lymph nodes.



Medullary cords

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





Lymphocytes can enter lymphoid tissues in two ways:

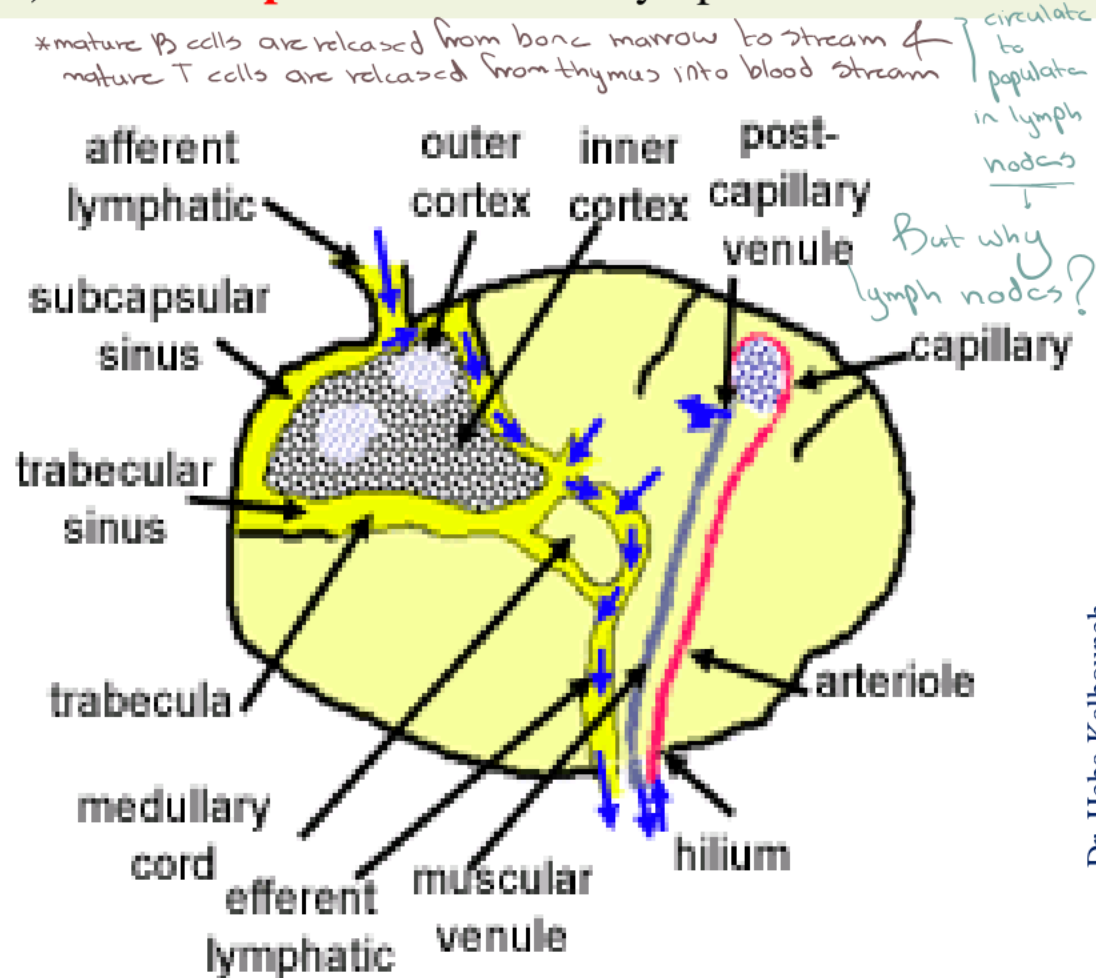
- 1) Direct entry into lymph nodes via afferent lymphatics
- 2) Entry from blood capillaries across specialized endothelial cells present in the postcapillary venules (High Endothelial Venules= HEV) within the **paracortex** of the lymph node

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



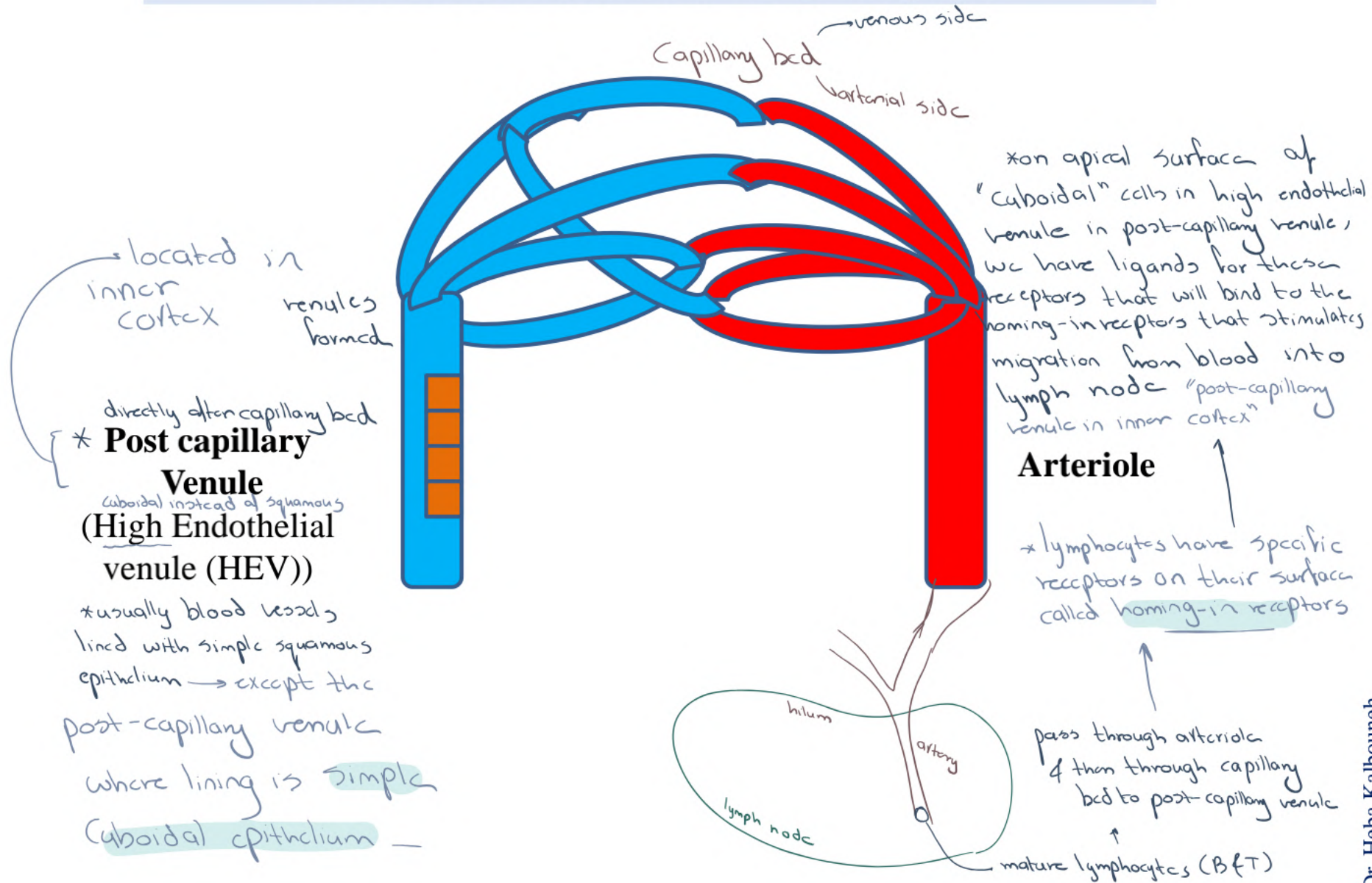
The structure of the post-capillary venule, in the paracortex is unusual in that it is not lined by simple squamous epithelium, but by a **simple cuboidal epithelium**. These are called high endothelial venules (HEVs). Lymphocytes recognize and adhere to these endothelial cells, and squeeze through them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

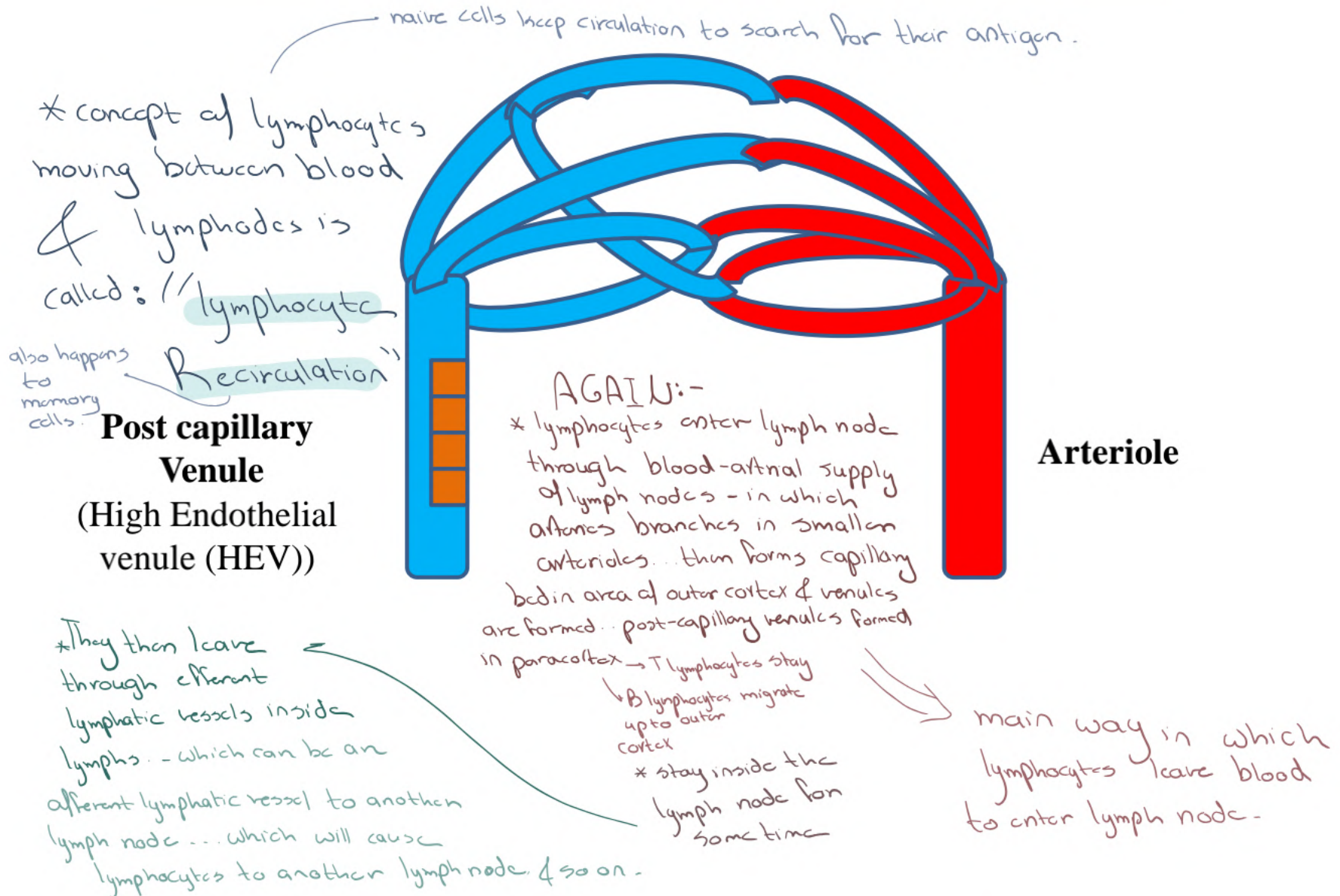


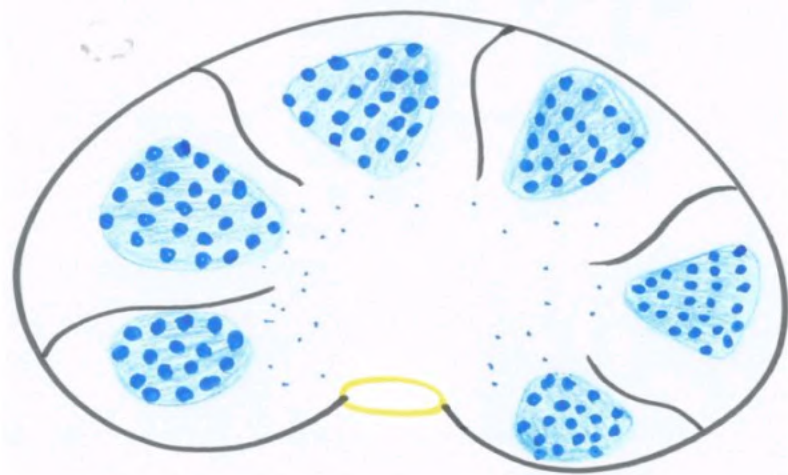
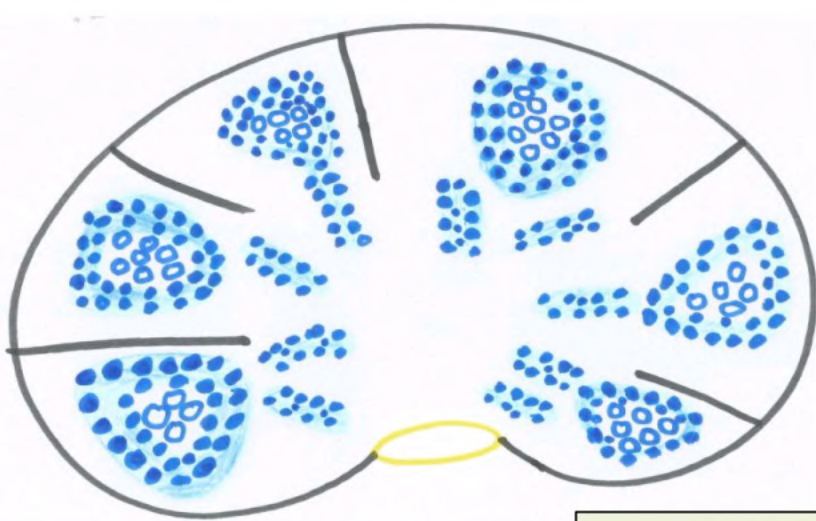
This diagram of a lymph node shows the pathways that lymphocytes can take, in and out of the lymph node.

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

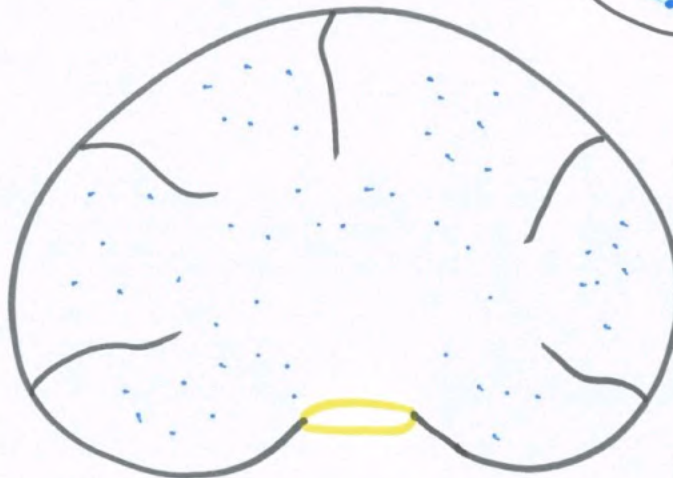
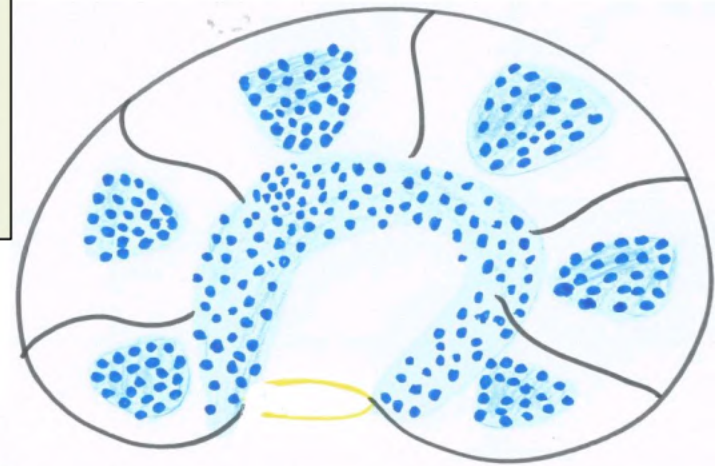
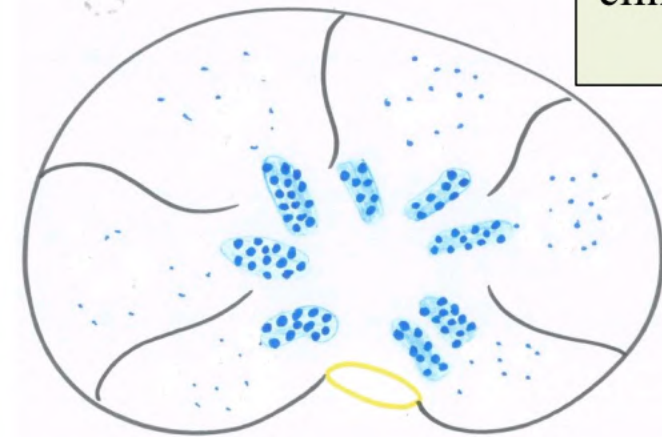


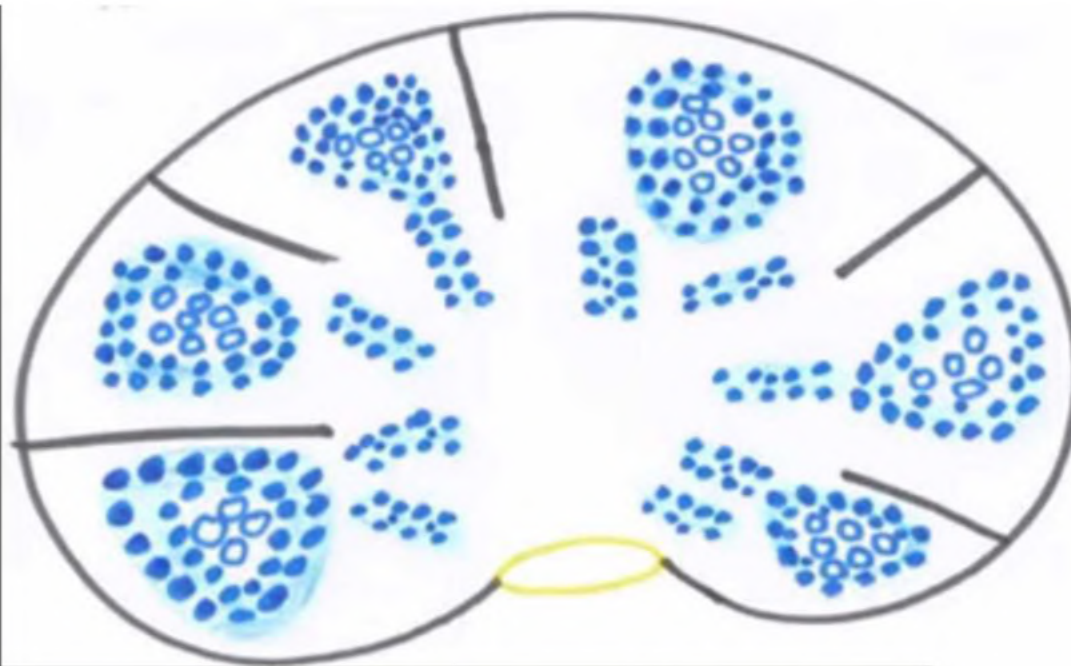
Note: Most of the lymphocytes enter the lymph nodes via blood vessels, and about 10% enter through the lymph.





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





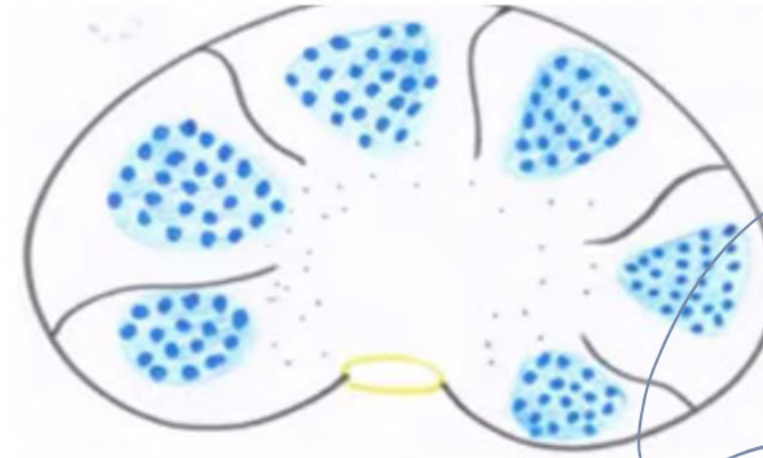
Germinal centers, enlarged follicles: bacterial infection

we usually fight bacteria by antibodies



Agammaglobulinemia
Underdeveloped outer cortex:
Bruton's immunodeficiency
(rare) disease

* can't produce antibodies or handle bacterial infections



* Underdeveloped paracortex:
DiGeorge syndrome

abnormal / absence of thymus

thymus originates from 3rd & 4th pharyngeal pouches with parathyroid gland which will also be absent → hypocalcemia

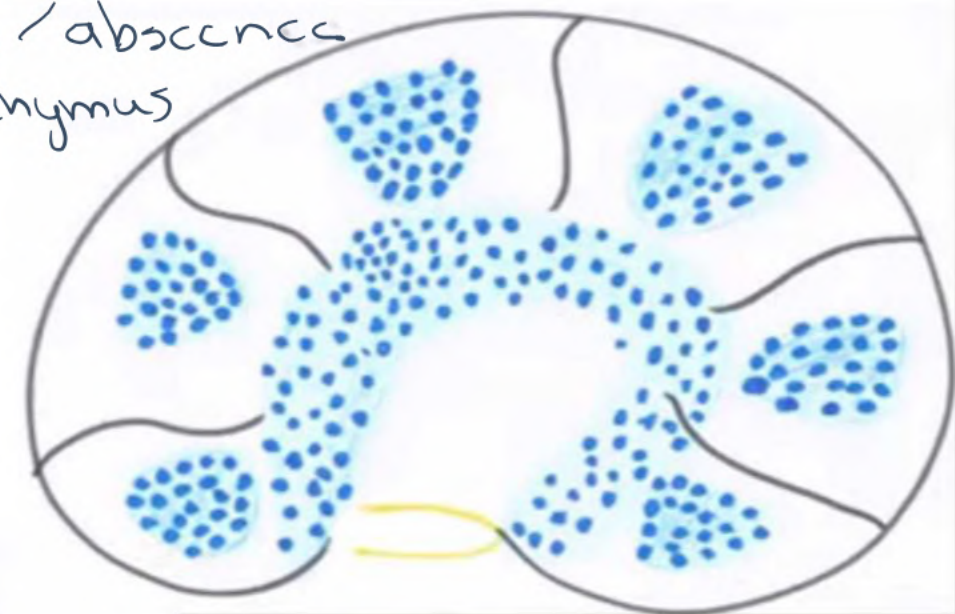
problems in cell mediated immunity

- SCID is caused by mutations in different genes that affect the development of immune cells.
- It is most often inherited in an autosomal recessive pattern, meaning a child must inherit a defective gene from both parents to have the condition.
- A form of SCID is X-linked, occurring almost exclusively in males.
- In one form, a deficiency in the enzyme adenosine deaminase leads to a buildup of a toxic substance that kills white blood cells.

SCID (rare)
severe combined
immunodeficiency
syndrome



Both B and T areas are underdeveloped



Enlarged paracortex: ex.
Viral infection

~ intracellular microorganism

- cell-mediated organism -

can be bacteria or parasites if they are intracellular microbes

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

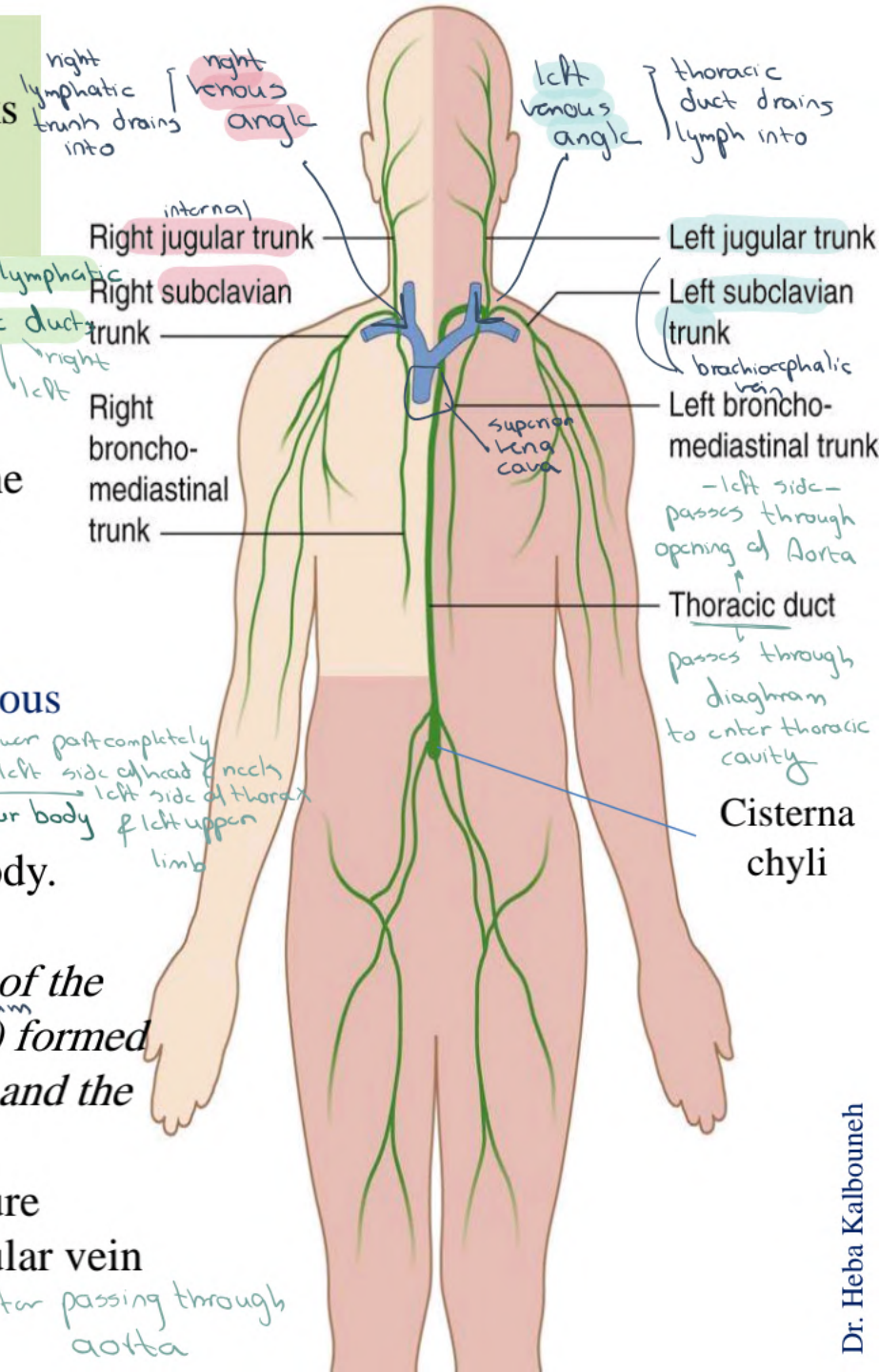
- ✓ Is formed by right jugular and right subclavian trunks
- ✓ Drains lymph from the upper right quadrant of the body (the right side of the head and neck, the right side of the thorax and the right upper limb)
- ✓ Empties into the junction where right internal jugular vein joins the right subclavian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

Functions related to lymphatic system
related to blood

✓ **Filtration of blood**

(defense against blood-borne antigens) will initiate immune response of activated immunocytes and antibodies

✓ The main site of old **RBCs destruction**.

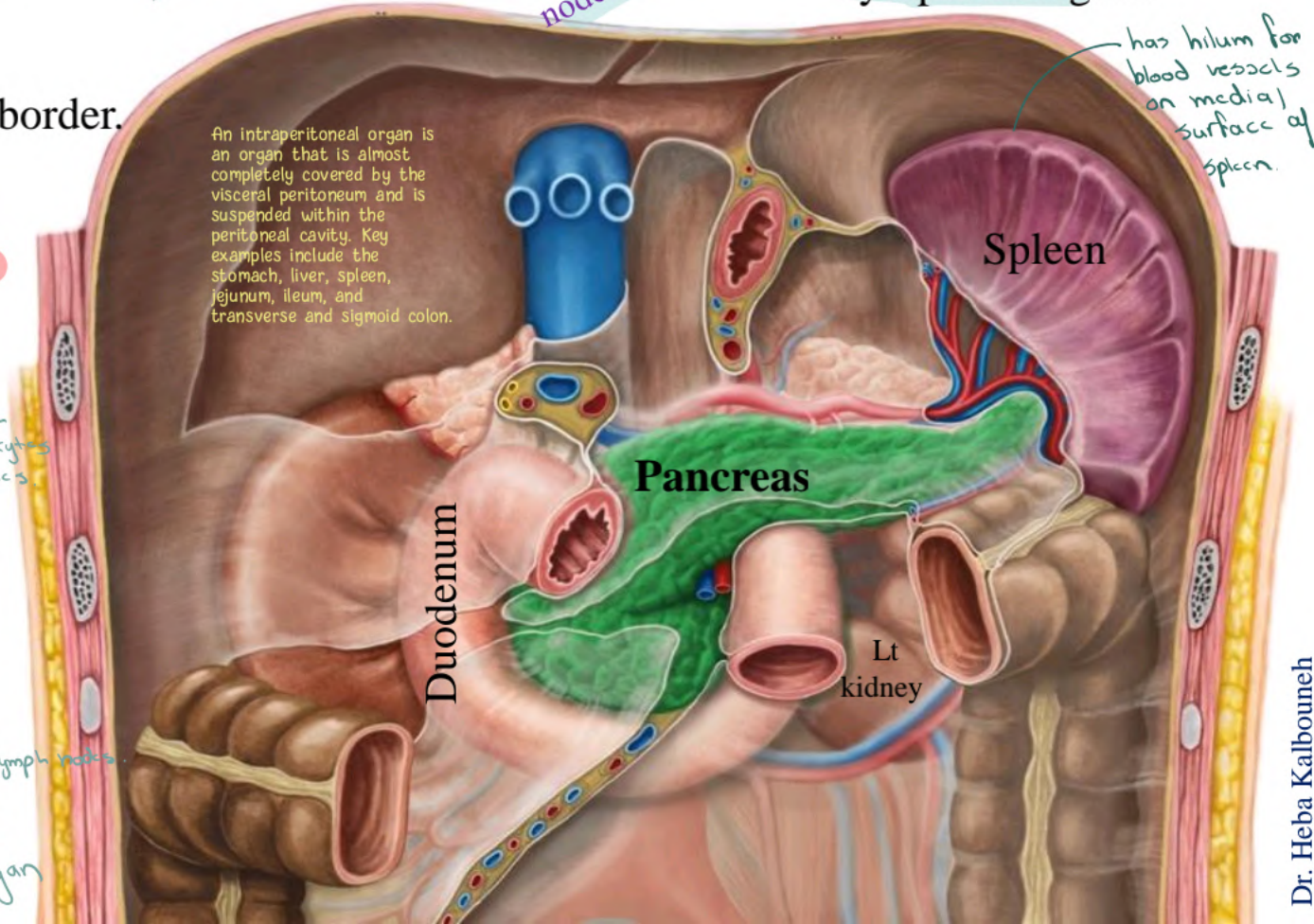
✓ Production site of antibodies and activated lymphocytes (which are delivered directly into the blood) acts as lymph node
secondary lymphatic organ

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

has no afferent lymphatic vessels - only efferent -
The spleen resembles a large lymph node
* The spleen filters the blood while lymph nodes filter the lymph

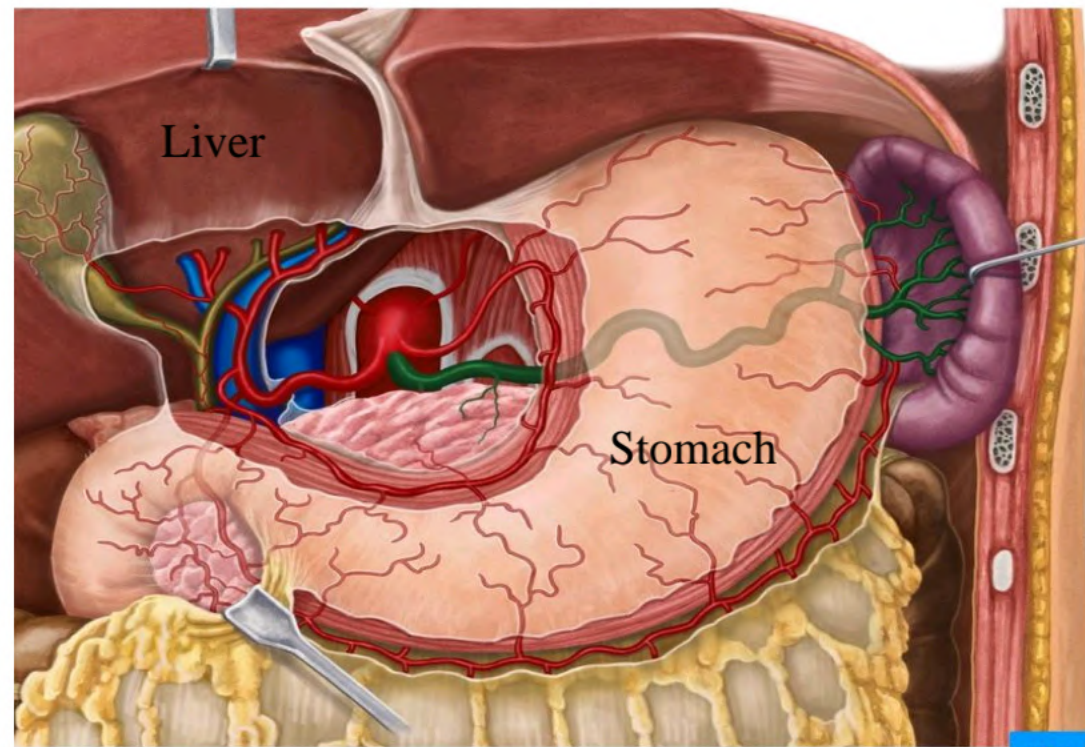
✓ It lies high on the upper left portion of the abdomen, just beneath the diaphragm, behind the stomach and above the left kidney.

✓ It is the largest of the lymphoid organs



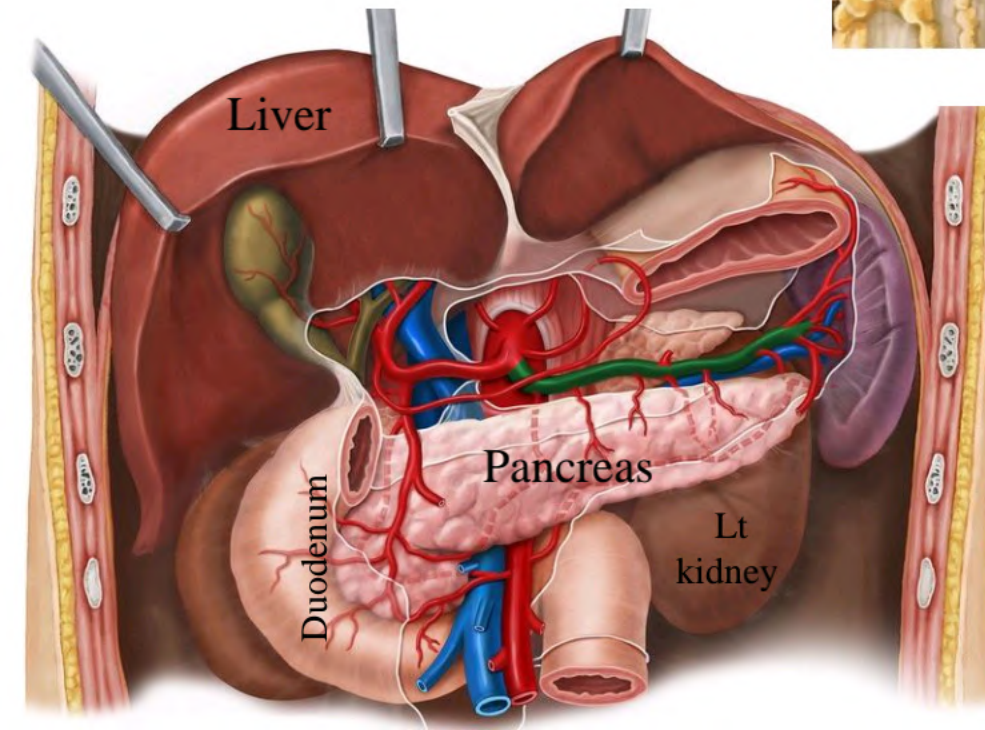
The **splenic artery** is the largest branch of the celiac artery. It has a tortuous course as it runs along the upper border of the pancreas. The splenic artery then divides into about six branches, which enter the spleen at the hilum

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



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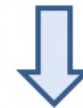
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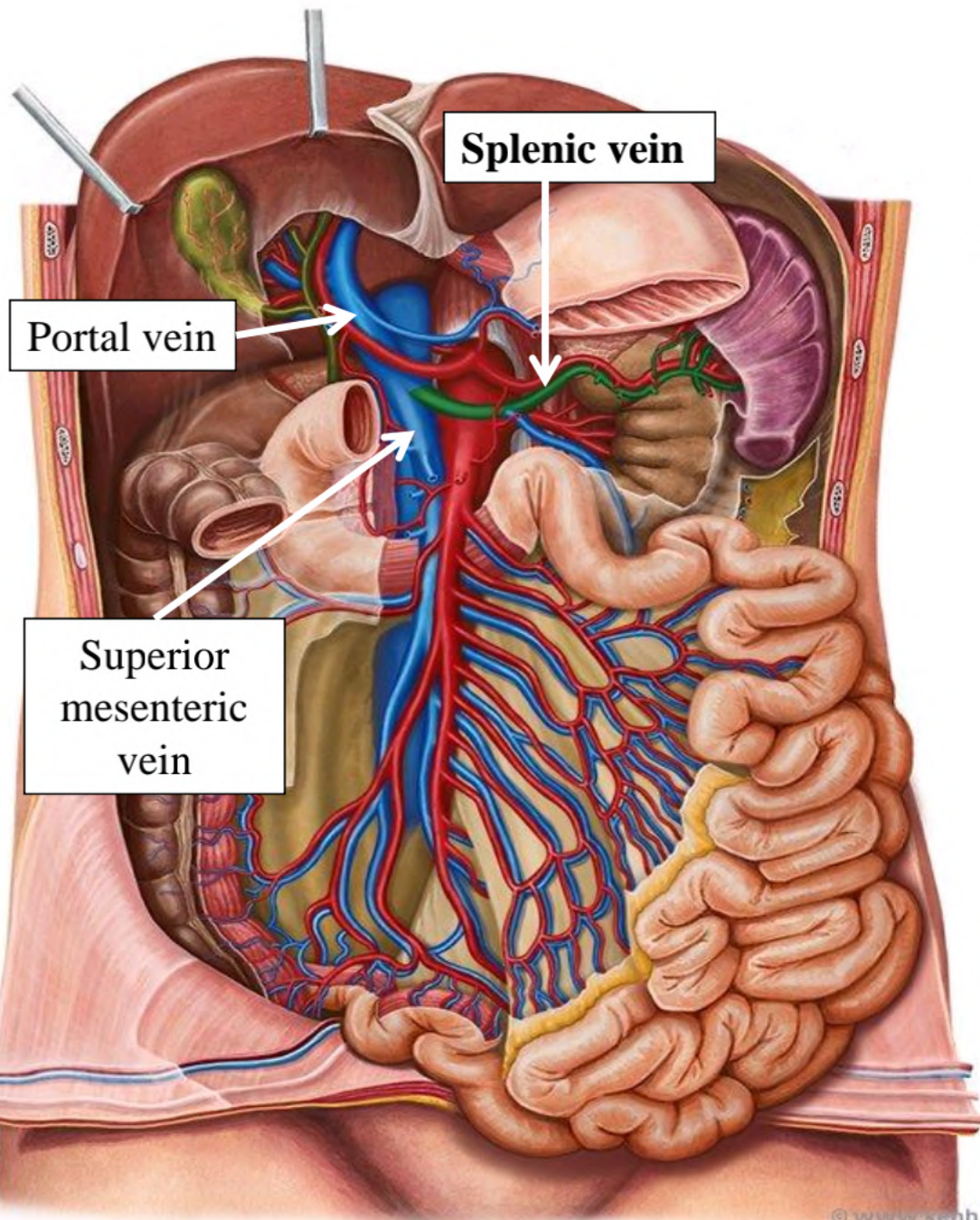
Abdominal Aorta



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**



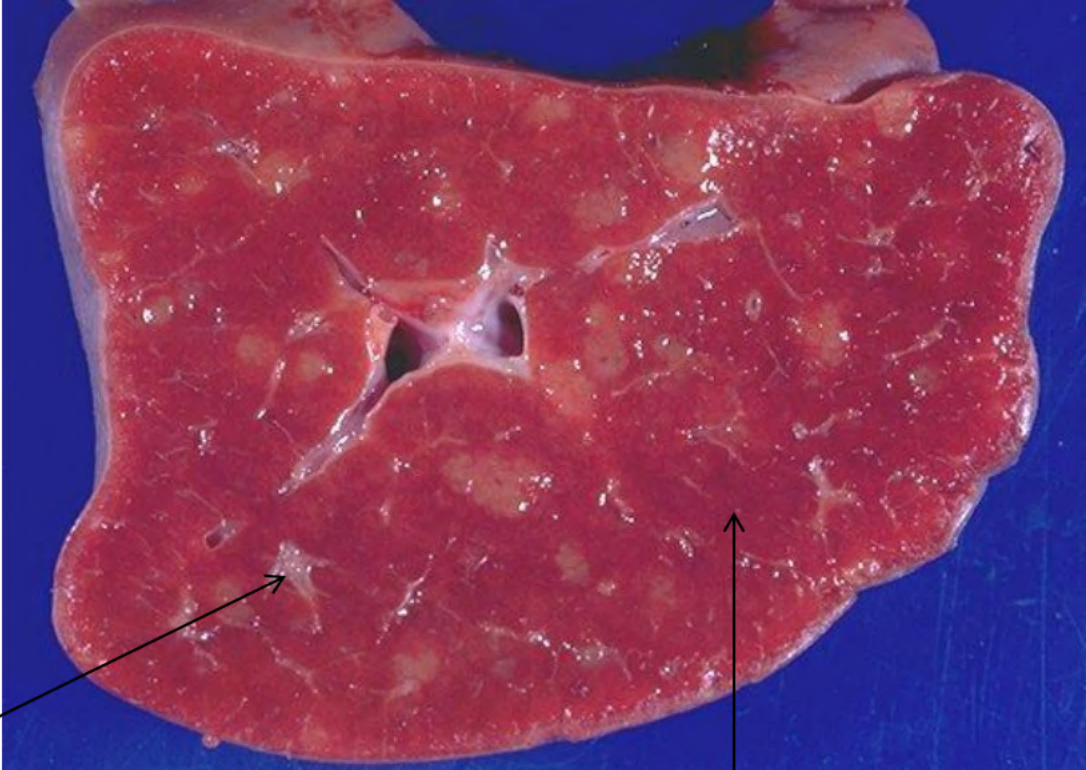
In cases of portal hypertension, spleen often enlarges from venous congestion.

The parenchyma of the spleen appears in fresh specimen as:
two different areas:-

White pulp which appears white on gross examination (collection of both B and T lymphocytes) → condensation of WBCs appear white.

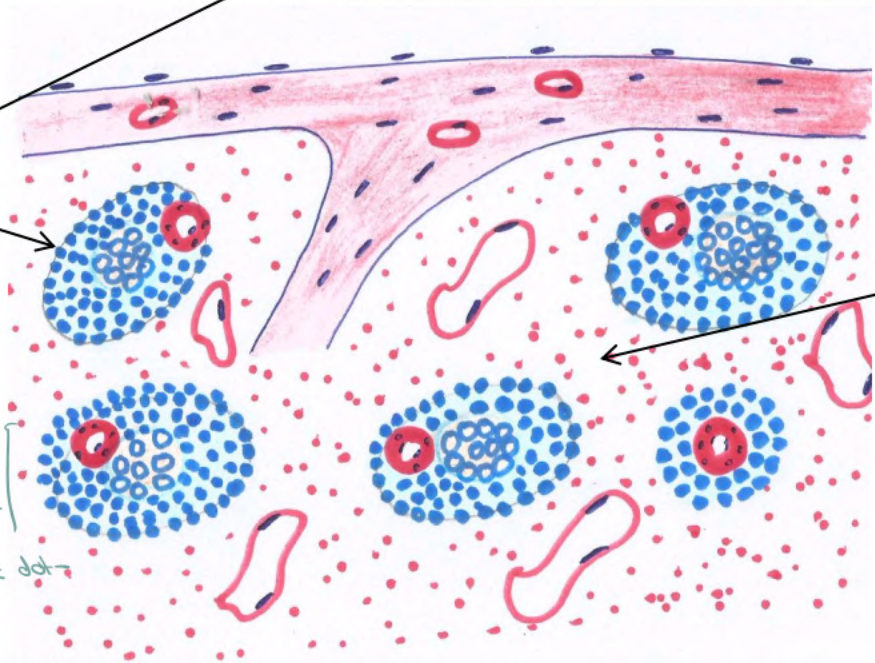
→ mainly present in parenchyma
Red pulp which appears red on gross examination (blood filled) → mainly RBCs.

many organ has stroma & parenchyma
of spleen is reticular tissue



White pulp

aggregation of lymphocytes
- has large heterochromatic basophilic nucleus that appears as blue dot -



Red pulp
↳ RBCs

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

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:

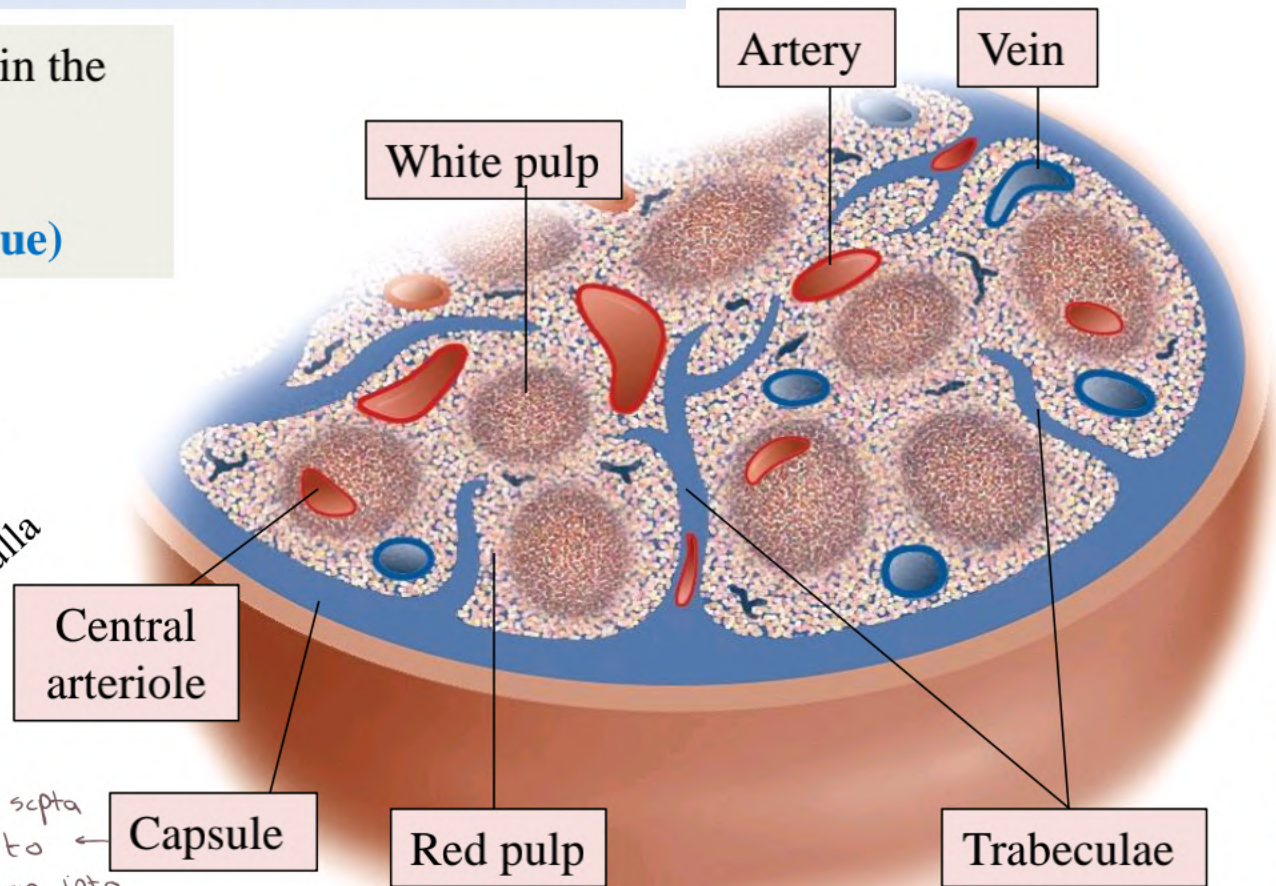
Red pulp (rich in blood)

White pulp (lymphatic tissue)

Unlike lymph nodes, the spleen:

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

sends septa
(trabeculae) to
divide spleen into
smaller compartments.



*the periarteriolar lymphatic sheath (PALS) is equivalent to paracortex of lymph node $\Rightarrow$ can be called thymus dependant zone

presence of mature immunocompetent T cells depends on thymus.

PALS will be underdeveloped if thymus defected.

blood have to return to vascular system by passing between endothelial cells.

spaces between these splenic sinusoids are called "splenic cords"

(2) open circulation:

where blood falls in spaces between splenic sinusoids many are present-

blood flow inside spleen then has two options:

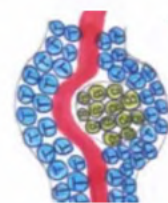
(1) closed circulation

opens into sinusoid & venous blood collected & drained into trabecular vein then at hilum.

trabecular veins unite to form splenic vein

splenic sinusoid

a special capillary that has large lumen lined with endothelial cells with many spaces inbetween.



area of aggregations of T lymphocytes & lymphatic follicles is called "white pulp"

PALP + lymphatic follicles + central arteriole

- blood here screened for any microbe -

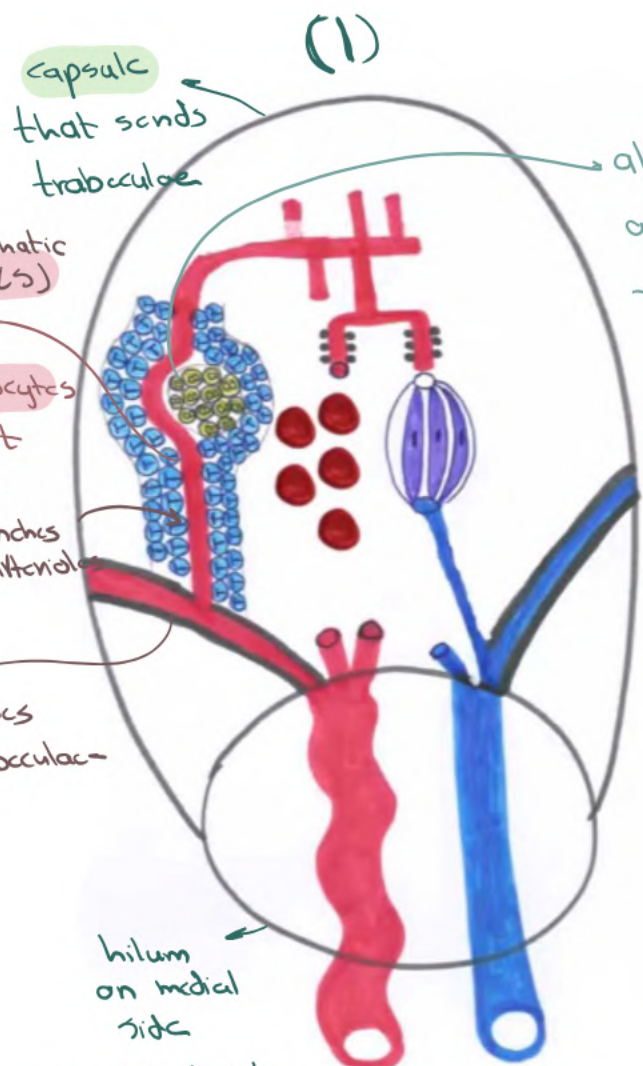
central arteriole leaves white pulp to enter red pulp then divides into smaller branches - straight & short - called penicillar arterioles

(2)

penicillar arterioles divide to form terminal capillaries - some of them sheathed by macrophages - HENCE also called "sheathed capillaries"

trabecular vein

splenic vein



hilum on medial side

- most trabeculae originate here -

splenic artery

- divides at hilum to many branches called trabecular arteries -

capsule that sends trabeculae

along pathway of central arteriole, a lymphatic follicle - aggregations of B cells - appears that displace central arteriole into a peripheral location --- some books call it "follicular arteriole" But still surrounded by PALS

called periarteriolar lymphatic sheath (PALS)
*the central arteriole is surrounded by aggregations of T lymphocytes & form sheath around it HENCE called "central".

gives many branches called central arterioles

trabecular artery - passes inside trabeculae

"Spleen"

Magnification of Splenic Sinusoid.

*the endothelial cells are supported by a discontinuous layer of basement membrane forming bars.

Macrophage
extend cytoplasmic process into lumen of sinusoid to sense foreign antigen in blood

Endothelial Cell (stave cell)

Splenic sinusoid

Splenic cords

Again, large space filled with blood lined with endothelial cells - that are arranged with long axis of splenic sinusoid. No cell junctions inbetween endothelial cells... - no desmosomes, no tight junction, etc - & has large intercellular clefts..

Also called "stave cells"



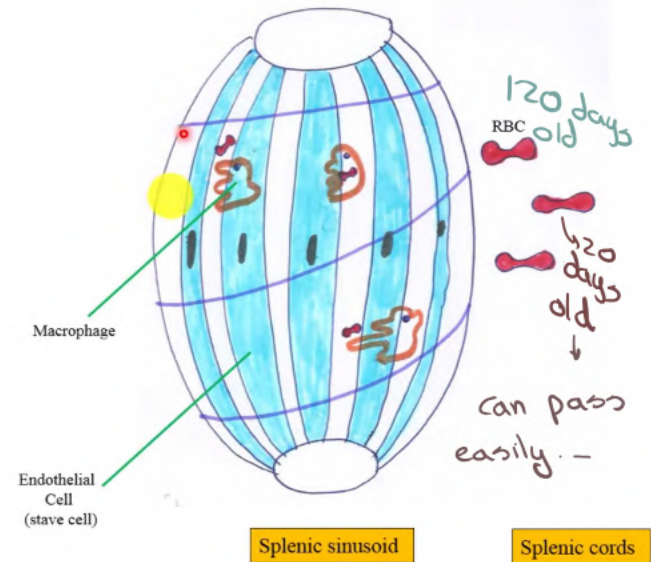
if one is old RBC & other is young & they reached the sinusoidal cord & need to squeeze through endothelial cells to reenter circulation.

test in which RBCs pass between endothelial cells to enter venous blood is called "twisting test or flexibility test"

so when it passes.. it will be slow & will cause membranous fragmentation.. macrophages will identify these old RBCs & get rid of it.

when RBCs loose submembranous proteins, cells become less flexible & has ↓ ability to squeeze bc endothelial cells.

*as RBC gets older → we will have protein denaturation - can't regenerate them without organelles -



can pass easily..

*another concept of aged RBC: glycolipid glycoprotein → glycocalyx protrudes from plasma membrane of RBCs.. it is covered with sialic acids..

lost with old age in RBCs that exposes the underlying sugar.. makes old RBCs easily recognized by macrophages.

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.



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

**most blood passes through open circulation.*

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)

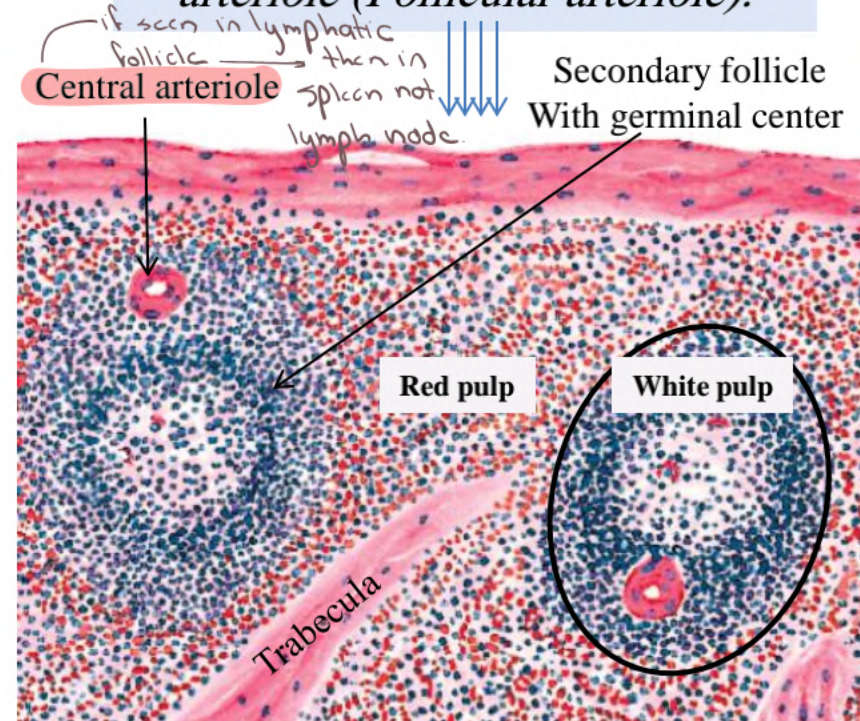
(lymphatic nodule = lymphatic follicle)

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

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



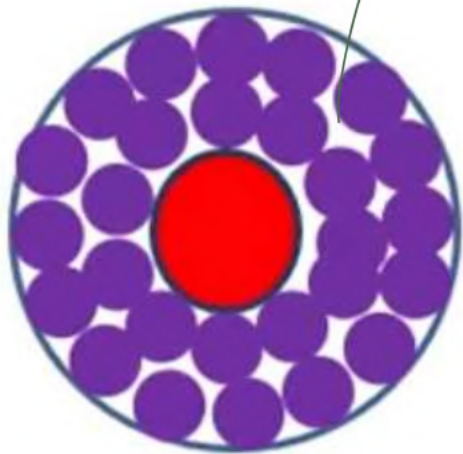
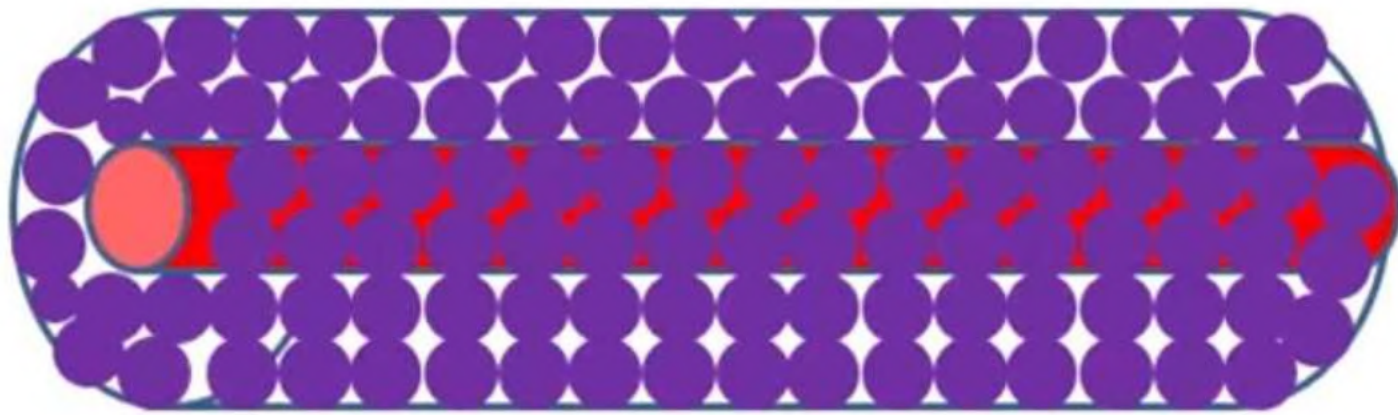
When the lymphatic sheath expands to incorporate the follicles, the central arteriole is displaced to one side and acquires an eccentric position in the follicle but is still called the central arteriole (Follicular arteriole).



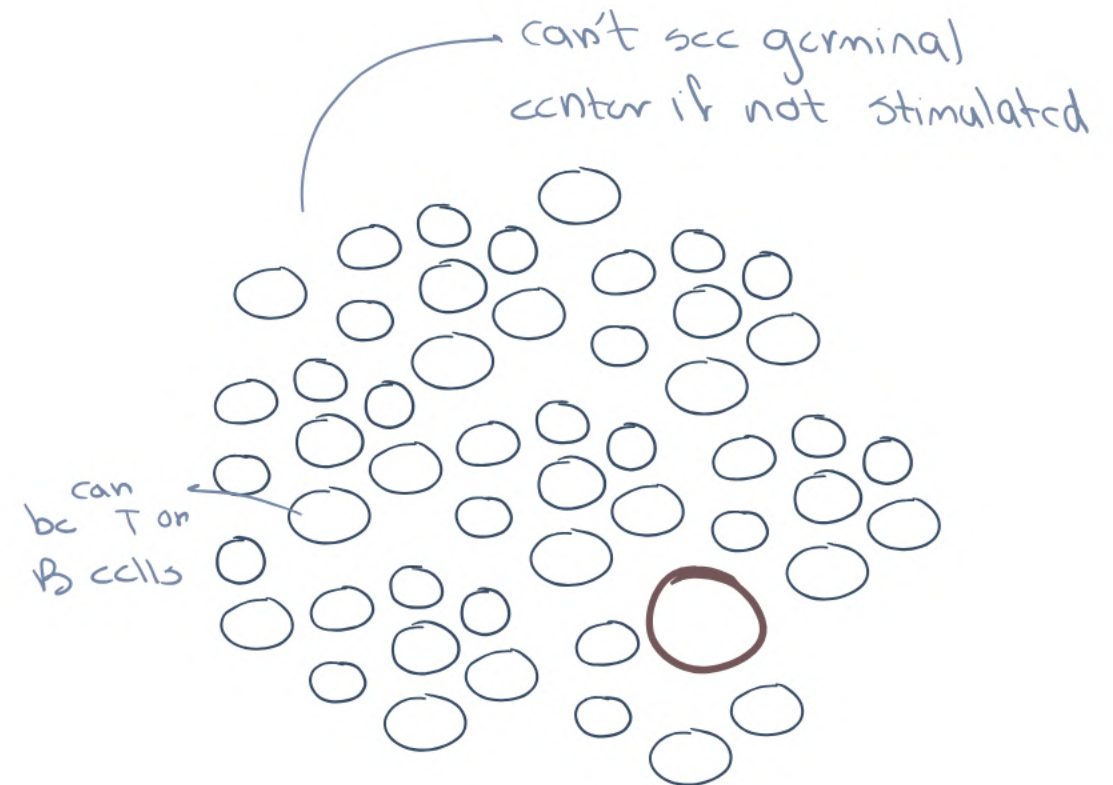
*if all lymphatic follicles in spleen are stimulated $\Rightarrow$ blood-borne infection like capsulated bacteria.

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

*to differentiate between PALS area & lymphoid follicle area under light microscope:
→ remember both T & B lymphocytes appear the same under LM.



central arteriole
in the center
surrounded by
many basophilic
nuclei
"PALS Area"



*but if you see
many lymphocytes
-aggregations- with peripherally
located arteriole:
"Lymphatic follicle of White
Pulp"

Red pulp (blood filled) *splenic sinusoids + splenic cords*

✓ 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)

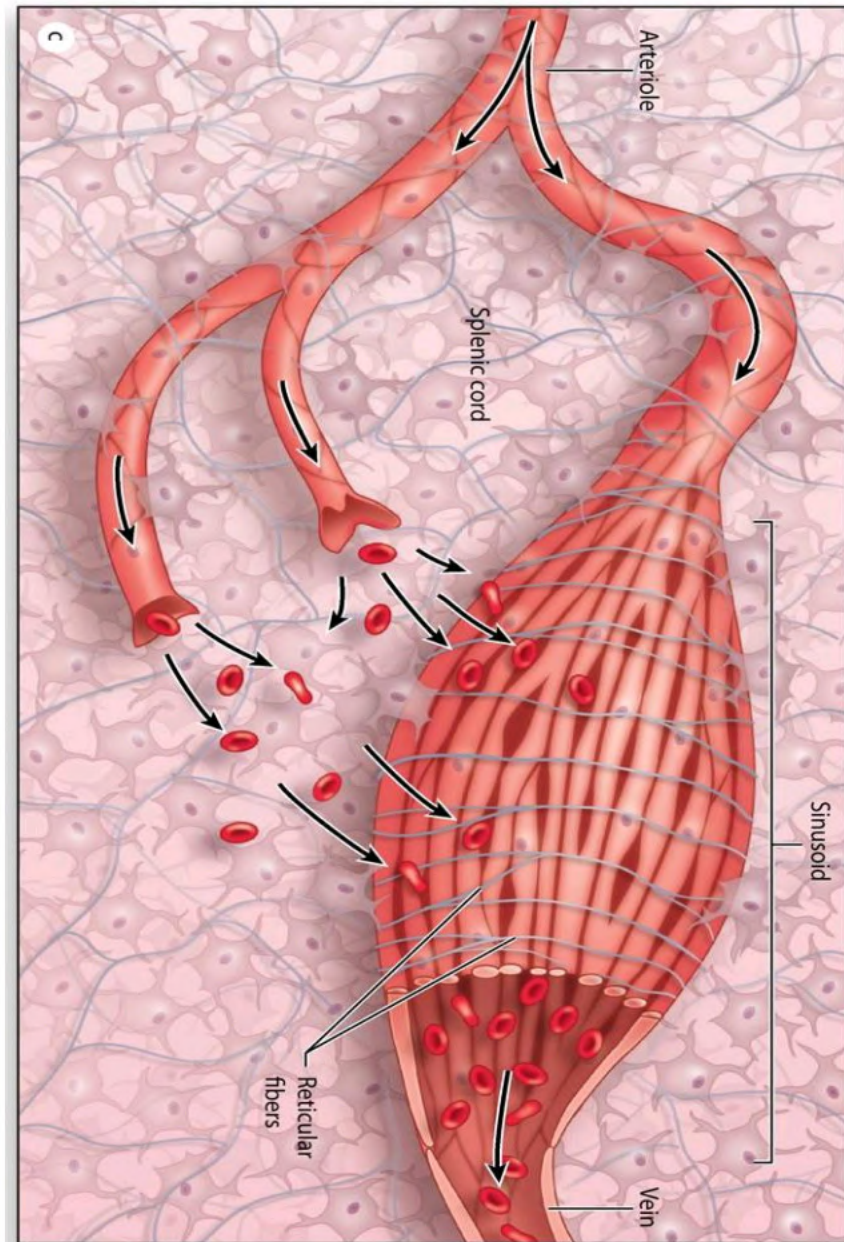
Splenic sinusoids: are blood- filled spaces located throughout the red pulp. They have large, dilated, irregular lumens and large pores (spaces between the endothelial cells)

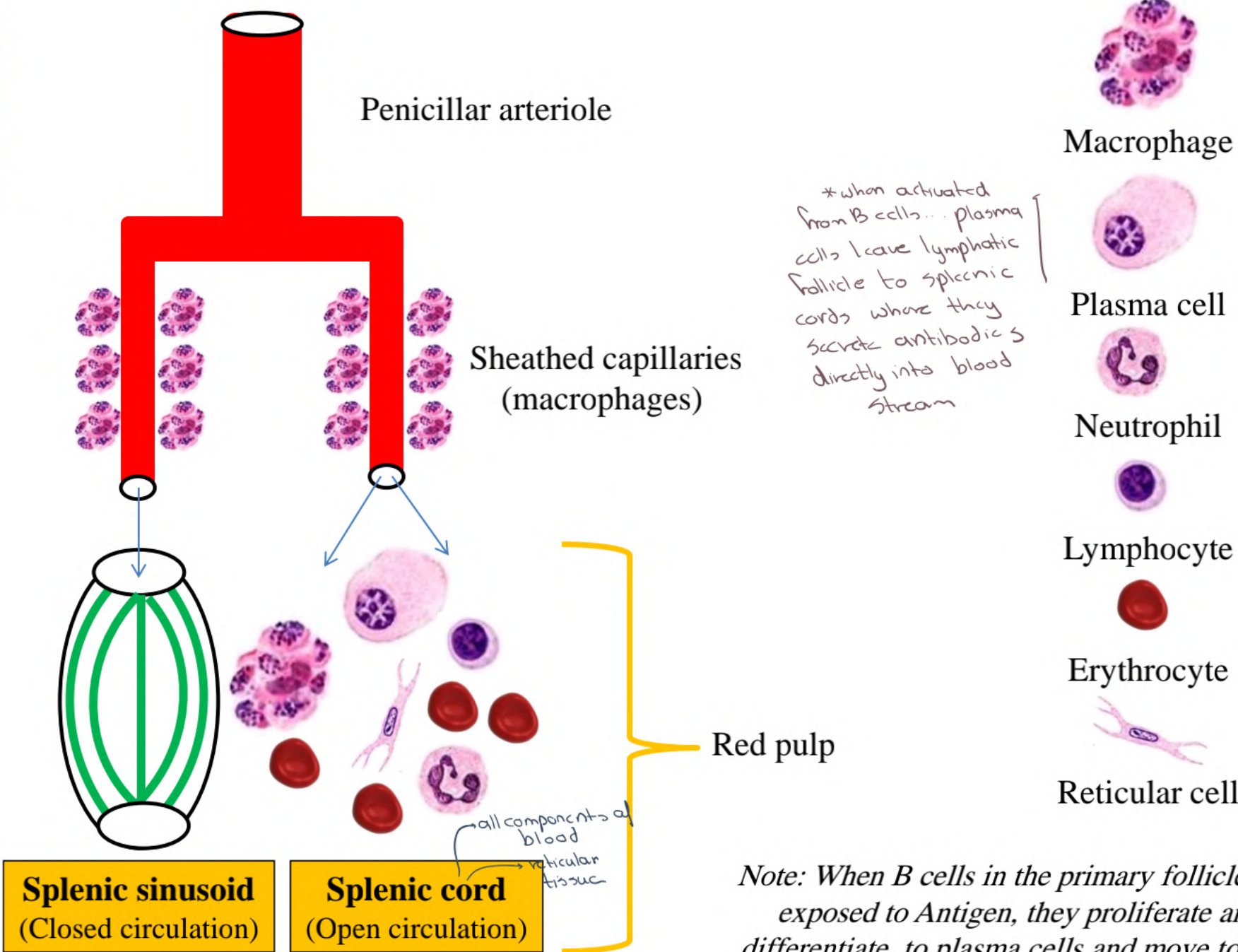


1. The endothelial cells (**stave cells**) are elongated, fusiform cells that lie parallel to the long axis of the vessel
2. The cells lie side by side around the vessel but not joined by any type of intercellular junctions
3. The endothelial cells are supported by highly discontinuous basal lamina (forms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

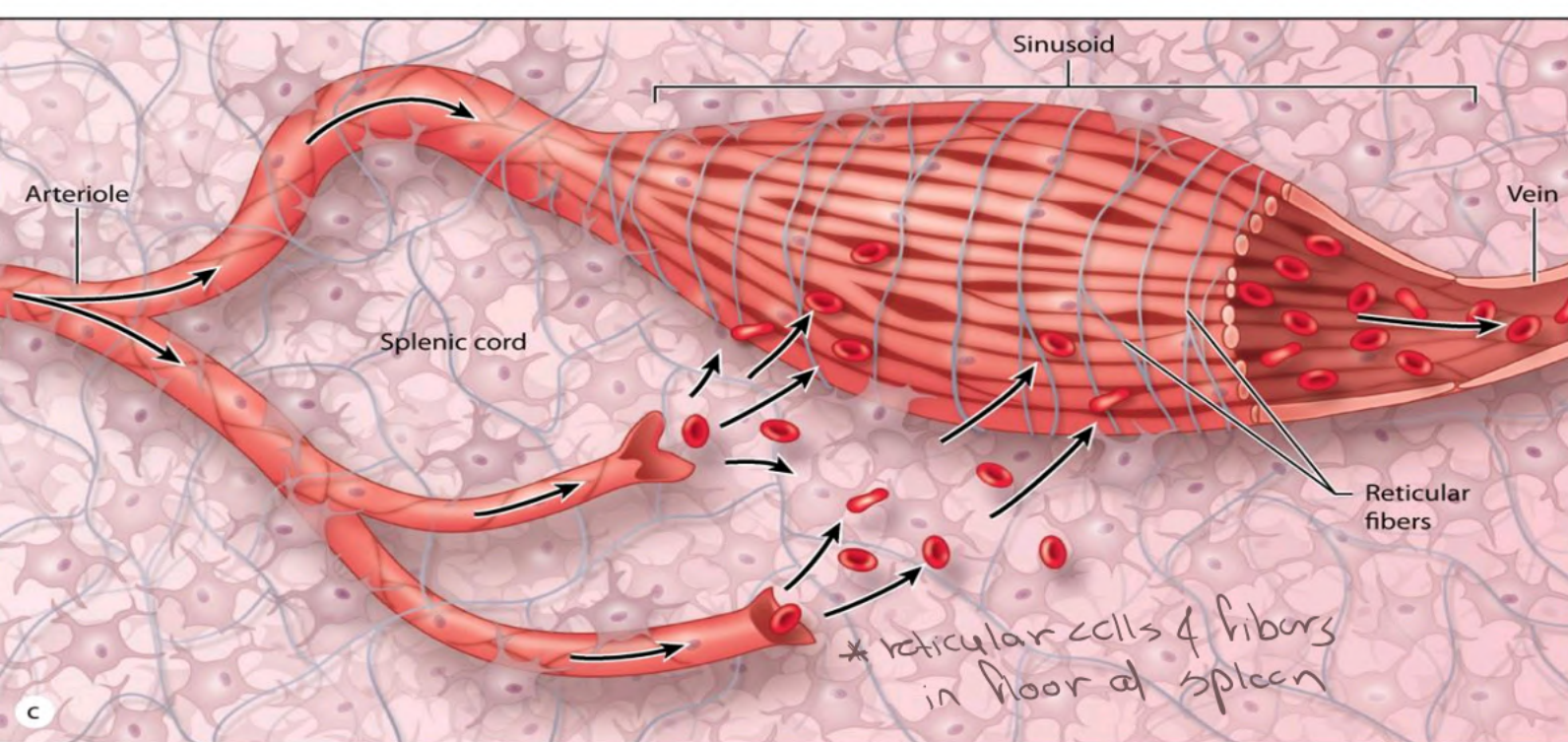
Function: Destruction of worn-out RBCs and platelets

↓↓ Red pulp





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.

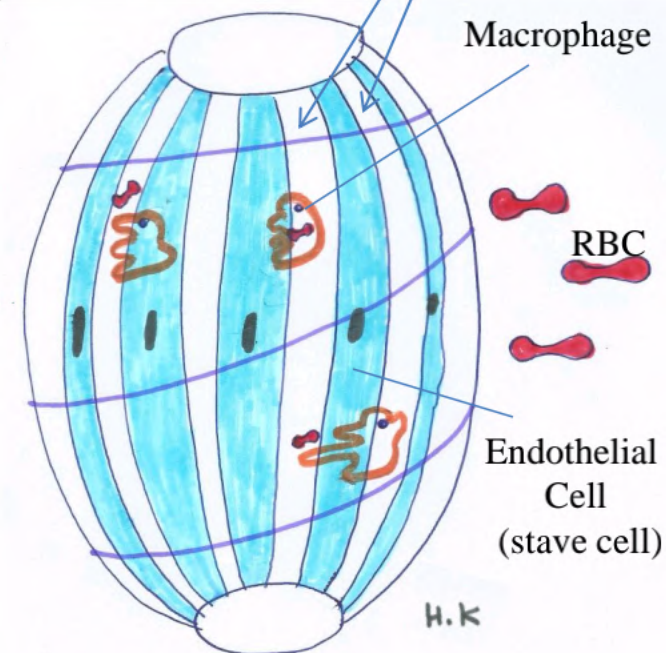


Note the wide gaps between endothelial cells which allow for movement of entire cells from cords to sinuses

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**

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.

more prone to septicemia especially in children

amino acids

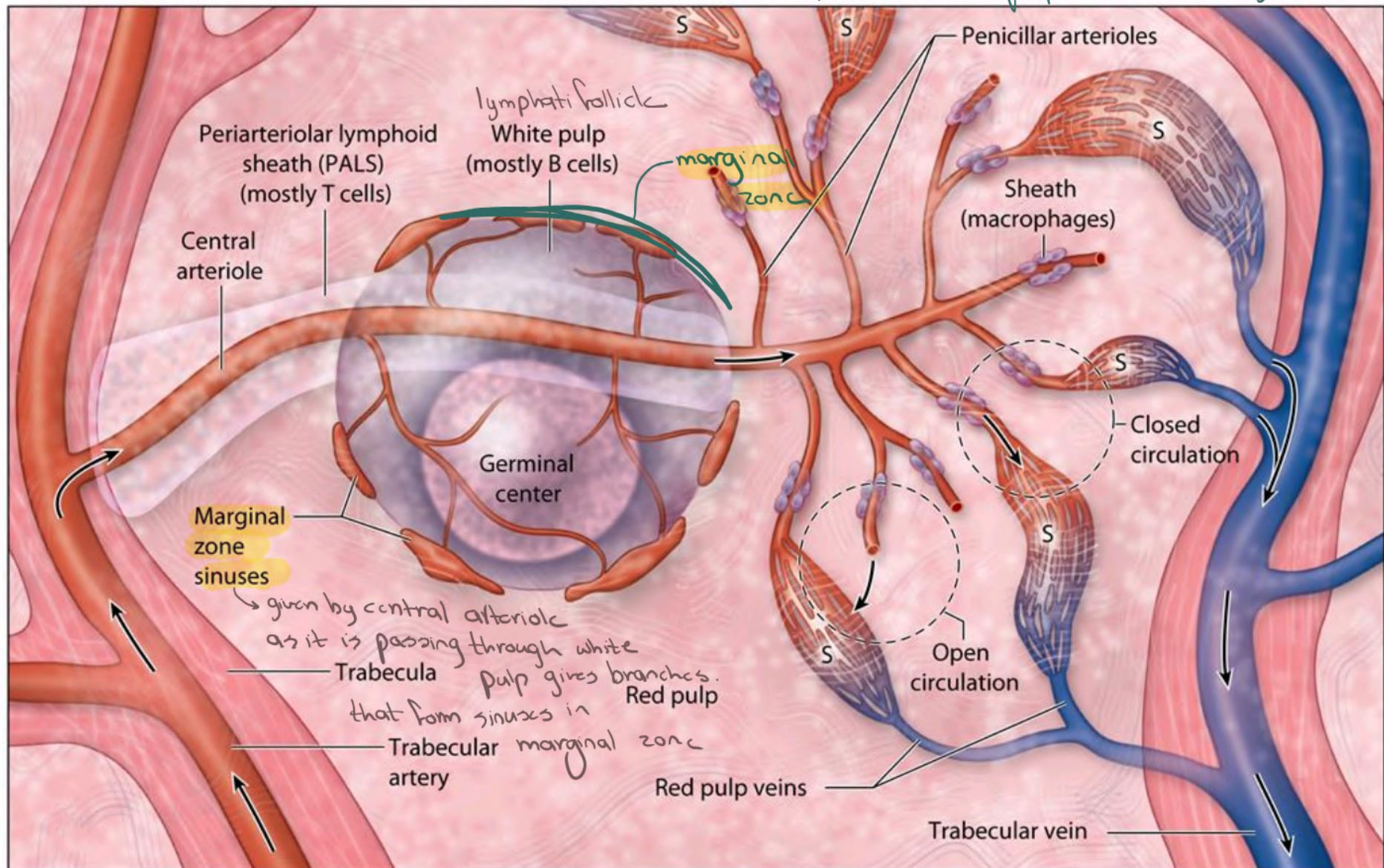
pool of blood

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

Bilirubin: excreted by liver bile

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

*area located between Red pulp & white pulp is called: "marginal zone"



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

*rich in APCs
so site of initiation
of immune responses.* ← 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

lymphocytes leave central arteriole to marginal zone sinus then white pulp in spleen parenchyma.

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

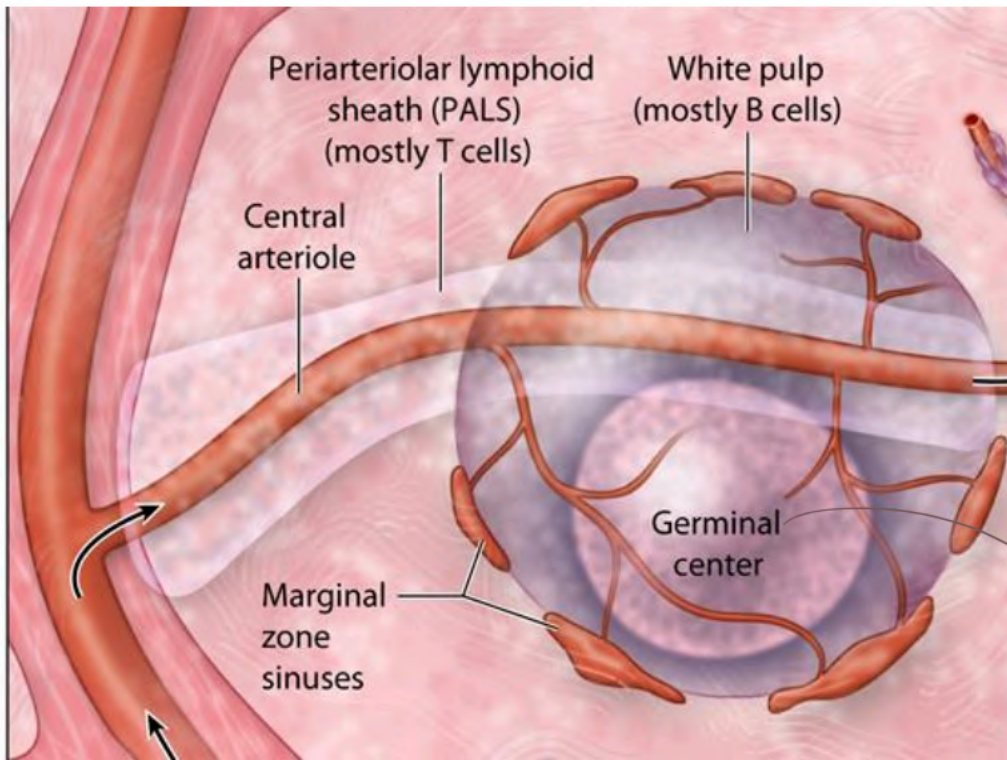
* **T cells: PALS**

* **B cells: lymphatic follicles**

equivalent to high endothelial venules inside lymph nodes.

can be seen in splenic cord

activated B cells form plasma cells that move from germinal center from white pulp to populate inside red pulp.



To summarize

↑ volume of blood

During contraction causes movement of blood from splenic cords into splenic sinusoids

quantity
sinusoids
capsule of spleen & inside
there is smooth muscle
Central

cells are (some in low). They are macrophages

size
demonstrated the
blood
residing in
immune

*and activated lymphocytes
directly into the blood)*

Penicillar arterioles

Sheathed capillary

Splenic sinusoid

Red pulp vein

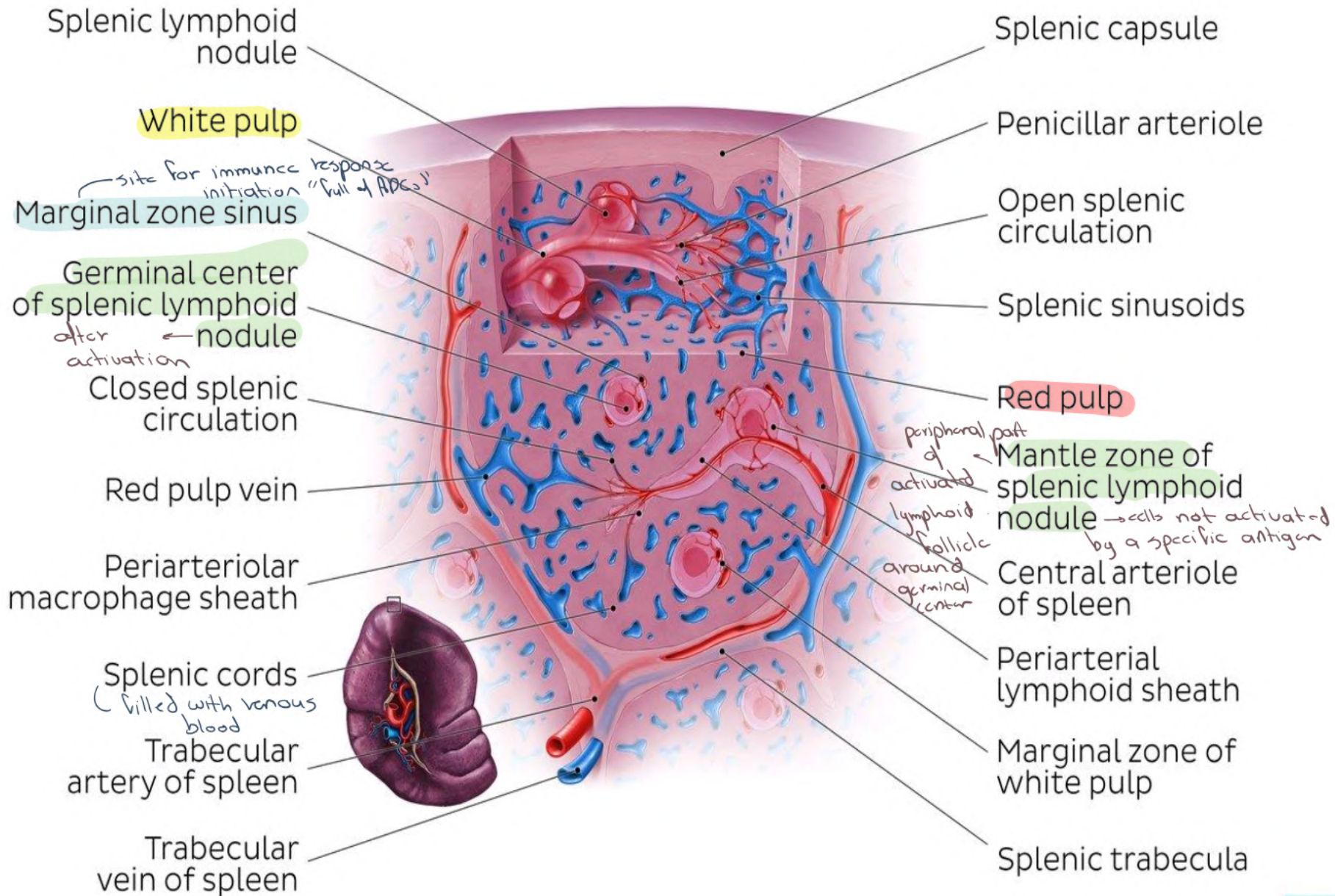
Trabecular vein

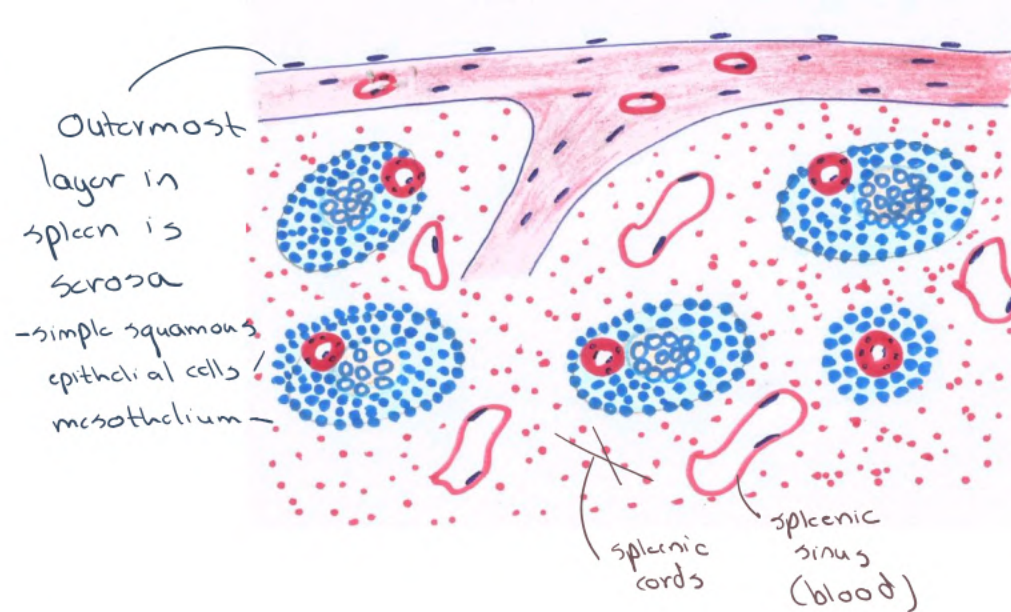
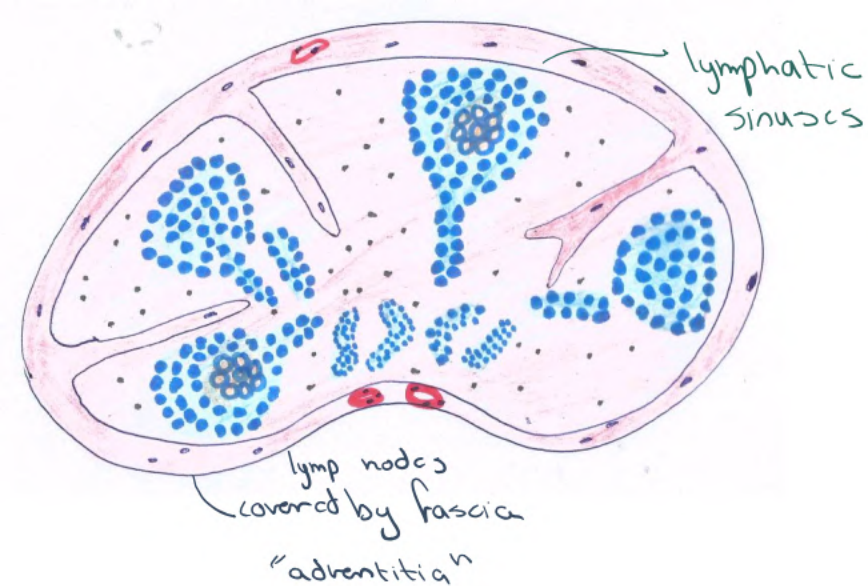
H.K.

Splenic artery

Splenic vein

Dr. Heba Kalbouneh





Lymph node	Spleen
Multiple, small	Single, large
Along the course of lymphatic vessels	Intra-abdominal upper-left quadrant of abdomen
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

aggregations of lymphocytes & other immune cells distributed along whole length of our mucus membranes

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.

*mucosa: any lining membrane of any cavity inside our body that has communication with outer environment

- ✓ 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)



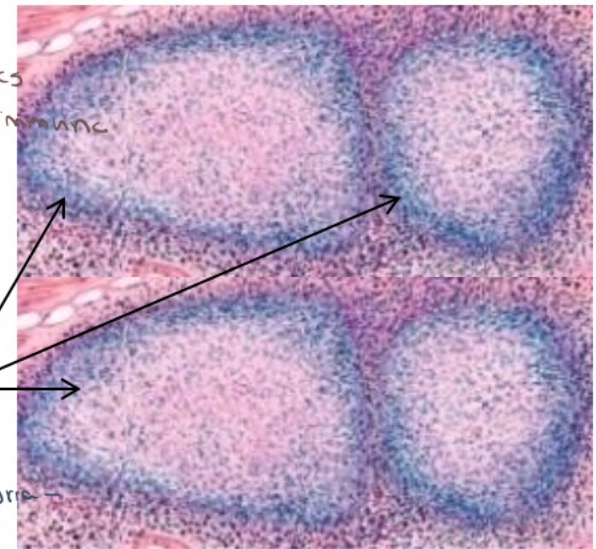
*largest lymphatic organ is spleen

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

* lymphatic follicles surrounded by immune cells

Lymphatic nodules

loose CT
- lamina propria -
epithelium
- different types based on area -



Dr. Heba Kalbounch

* any mucosa has lymphatic tissue → 1st barrier for inhaled / ingested antigens.

* some places have highly prominent & concentrated diffuse lymphatic tissue → they were given a name.

eg. tonsils & Peyer's patches of ileum.

MALT is populated by:

T cells

B cells

Plasma cells

APCs

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

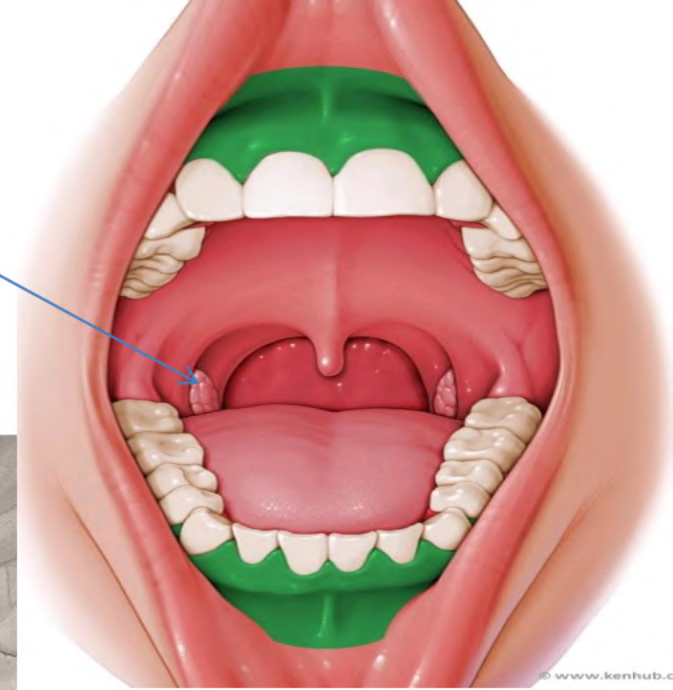
Tonsils are large, irregular masses of lymphoid tissue

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

Palatine tonsils (لوز)

Are located at the lateral wall of oropharynx, between the palatoglossus & palatopharyngeal arches. *behind oral cavity*

Acute inflammation of these tonsils causes tonsillitis.

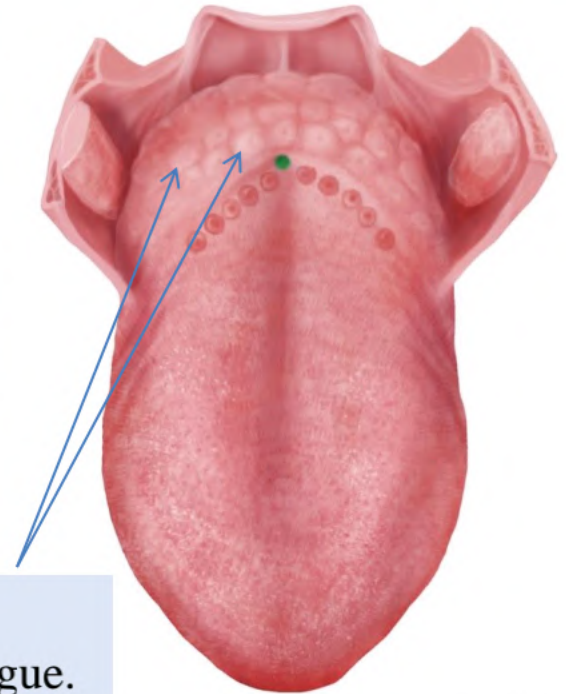
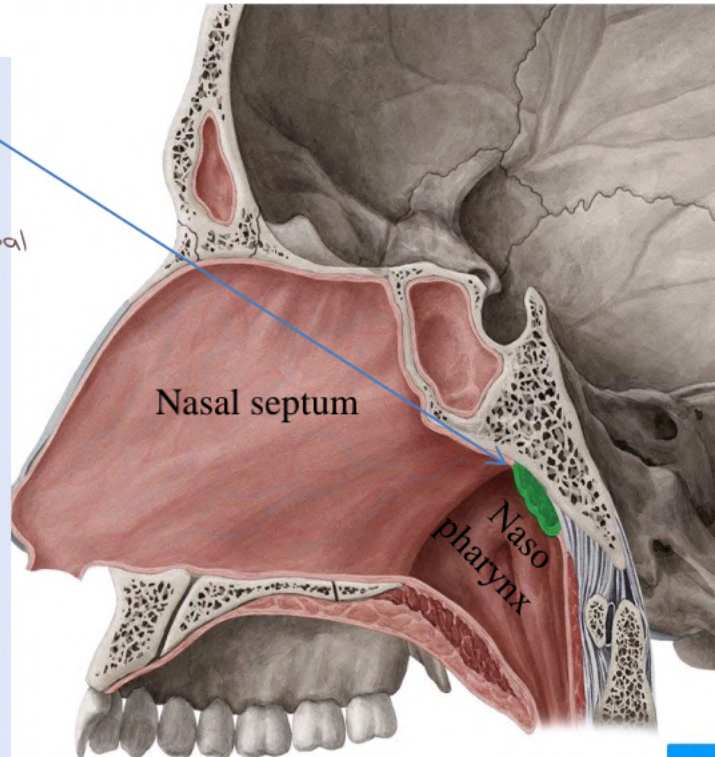


Pharyngeal tonsils

Are located in the *-roof-* posterior wall of the nasopharynx. *behind nasal cavity*

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.

Tubal tonsils

Pharyngeal tonsils

tubal tonsils considered part of pharyngeal tonsils.

Nasal septum

Opening for Eustachian tube

connects nasopharynx with middle ear.

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

Adenoids (لحمية)

* recurrent infection

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.

* causes middle ear infection

ring of tonsils

Waldeyer's tonsillar ring

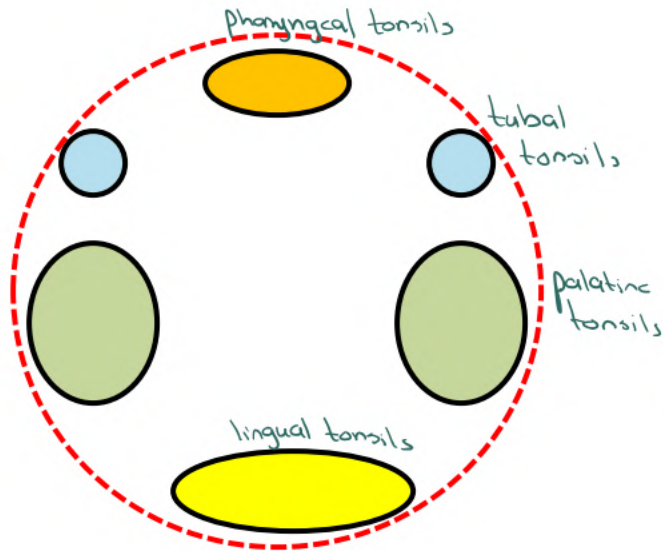
(Waldeyer's lymphatic ring) is a ringed arrangement of lymphoid

tissue

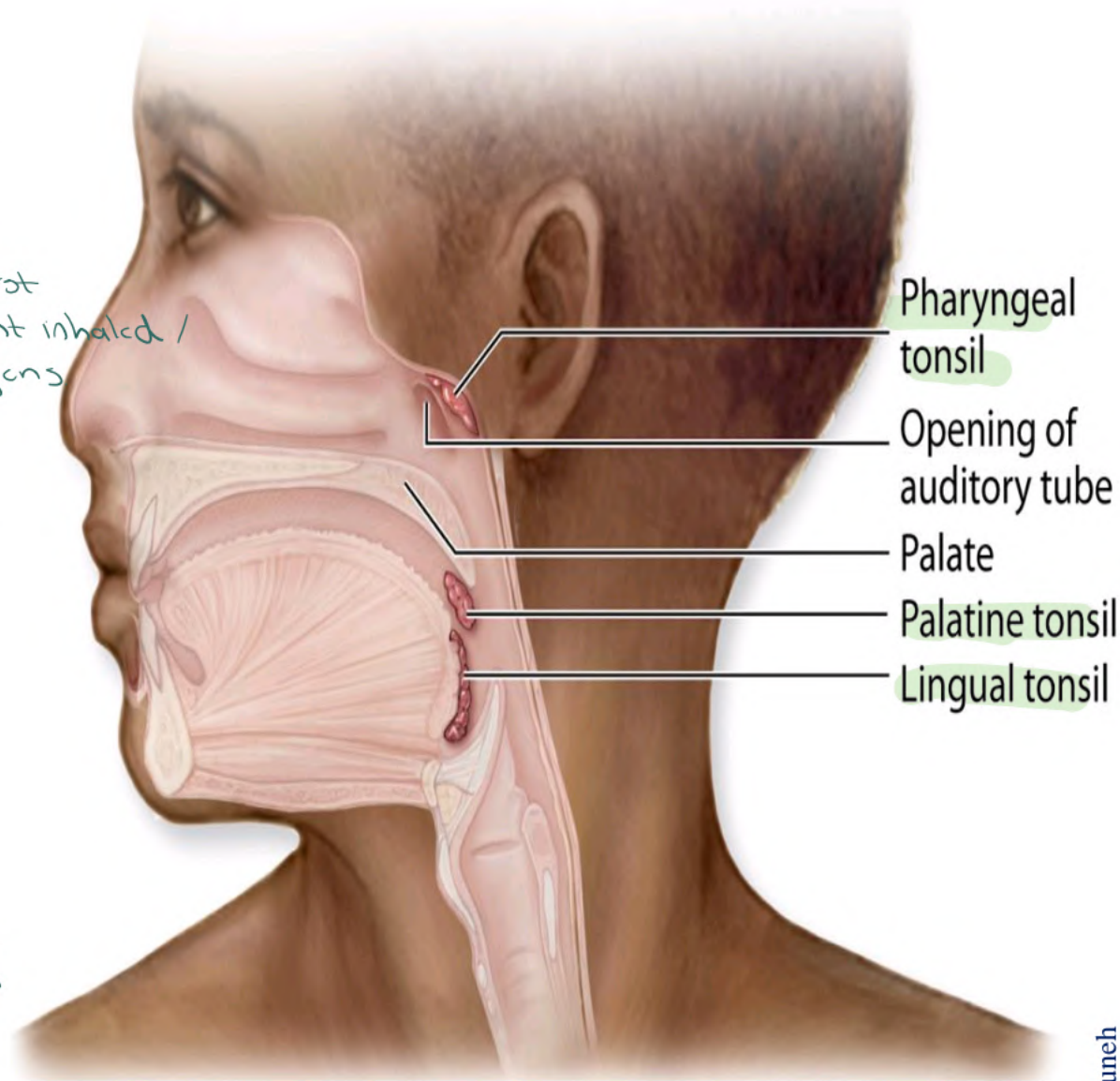


↳ represents first
barrier to fight inhaled /
ingested antigens

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



Anterior view



Palatine tonsils

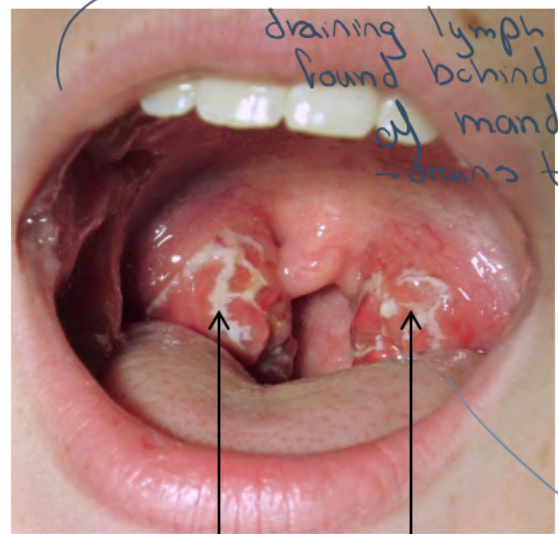
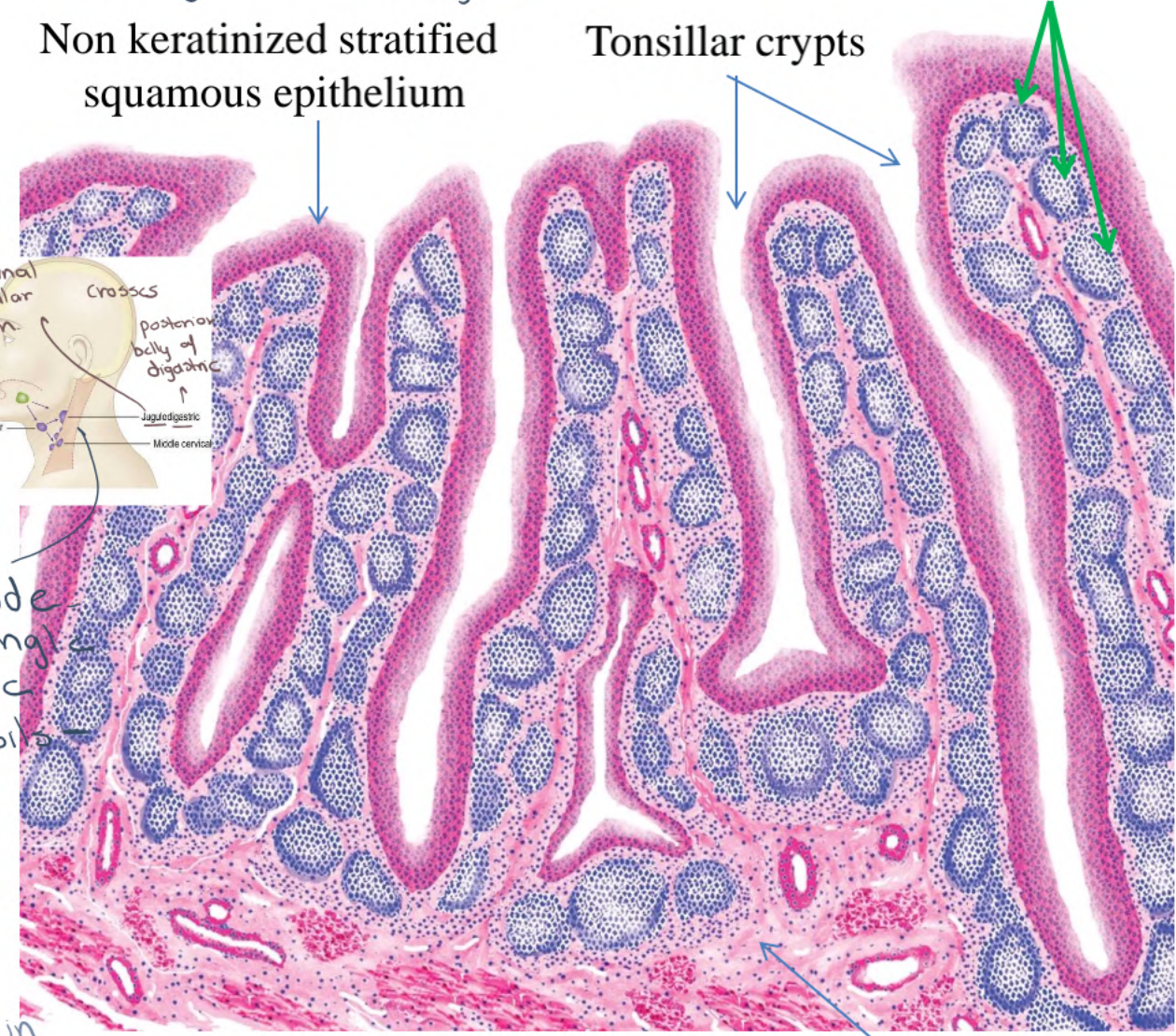
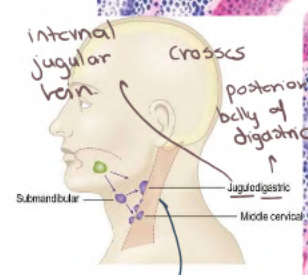
except in palatine tonsils; partially capsulated underlining the crypts.
**diffuse lymphatic is not capsulated - not organized in an organ -*

- ✓ 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)

Lymphatic nodules

Non keratinized stratified squamous epithelium

Tonsillar crypts



need to check draining lymph node - found behind angle of mandible - drains tonsils -

inside crypts.
Pus in tonsillar crypts

*in bacterial tonsillitis
crypts swollen from tissue fluids
enlargement of follicles & diffuse immune cells surrounding*

Palatine tonsils

Capsule

Stratified non-keratinized
squamous epithelium

oropharynx

*all types of
tonsils have same
histology with
slight differences

Palatine tonsils

epithelium
lamina propria
- where lymphatic tissue is located -

Crypt

invagination

surrounded by
lymphatic nodules/
follicles formed
mainly by
B cells -
these are
surrounded
by immune
cells.

Secondary
Lymphoid
follicle

Primary
Lymphoid
follicle

Germinal
center

H.K

their
ducts open
directly to oral
pharynx

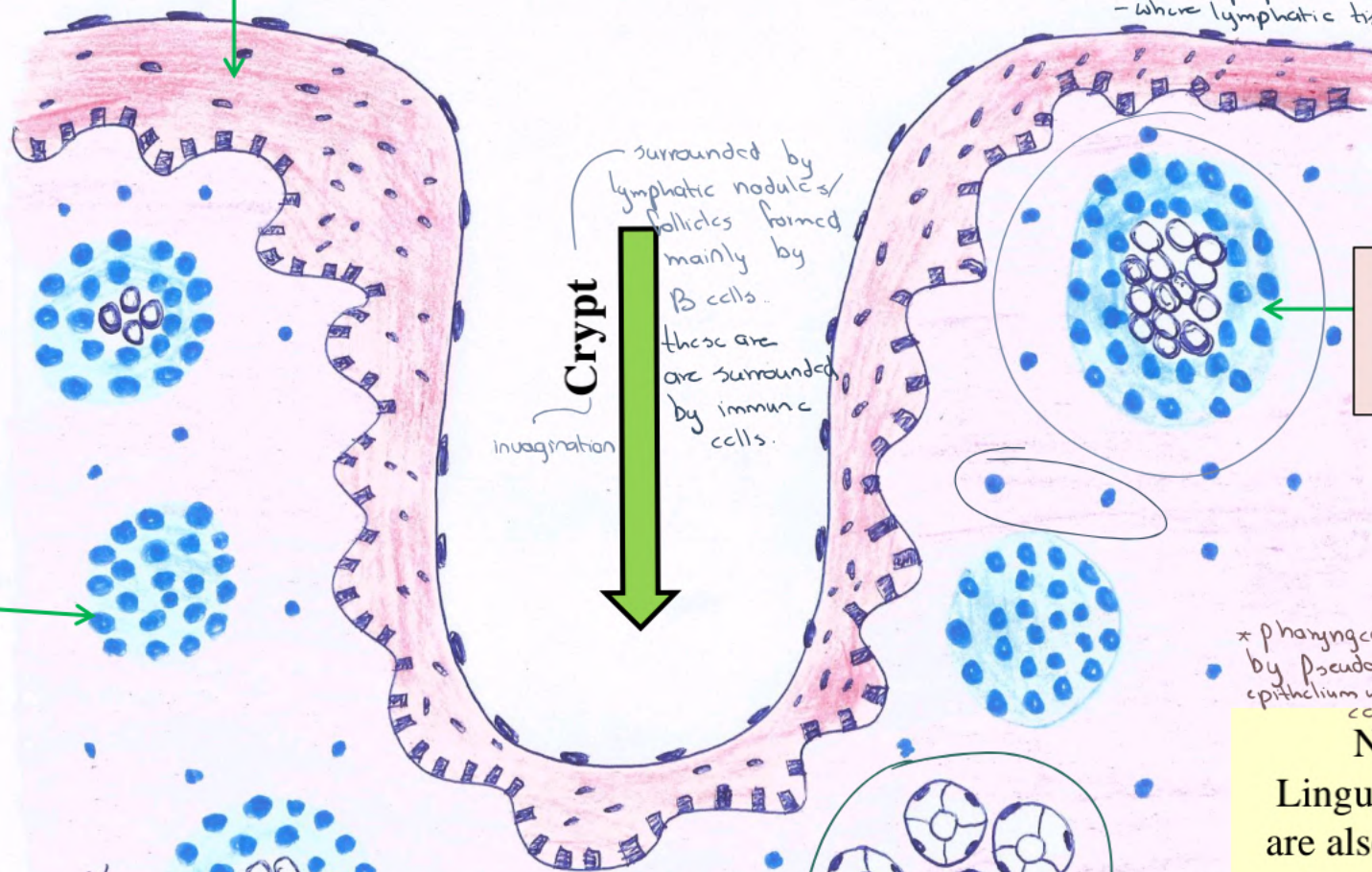
Alveoli:
minor salivary glands

inside lamina propria
- we have collection of mucus-secreting cells -

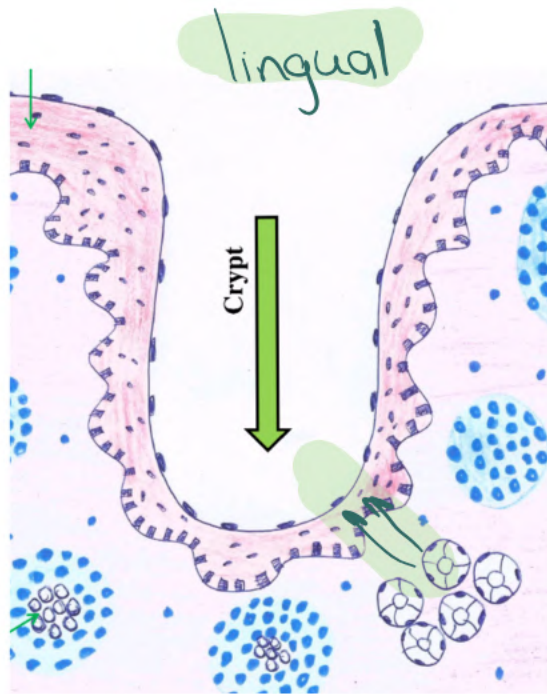
* pharyngeal covered
by pseudostratified ciliated
epithelium with goblet
cells

Note:

Lingual tonsils
are also covered
by stratified
squamous
epithelium with
crypts

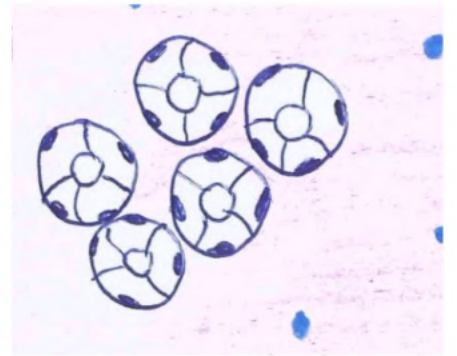


* usually when we have tonsillitis - - - } very rare to hear
 we refer to palatine tonsils } lingual tonsillitis..
 why?



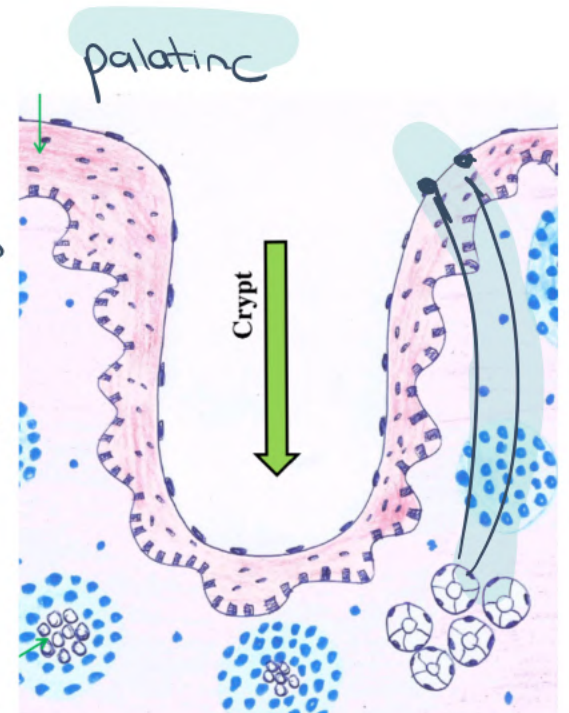
Due to the
 mucus-secreting
 cells.. AKA
 minor salivary glands
 in lingual tonsils have
 ducts that open to
 base of crypt.

* This causes continuous
 washing, cleaning of content
 of crypt - - (crypts contain
 saliva, food debris, microbes,
 desquamated cells of epithelium, etc.)



* But in palatine
 tonsils, ducts open
 into surface epithelium
 not base of crypt.
 & are able to partially
 clean crypt but less
 efficient than lingual
 tonsils..

More common to have
 palatine tonsillitis..



Gut-associated lymphoid tissue (GALT)

Is located in the mucosa of the intestine.

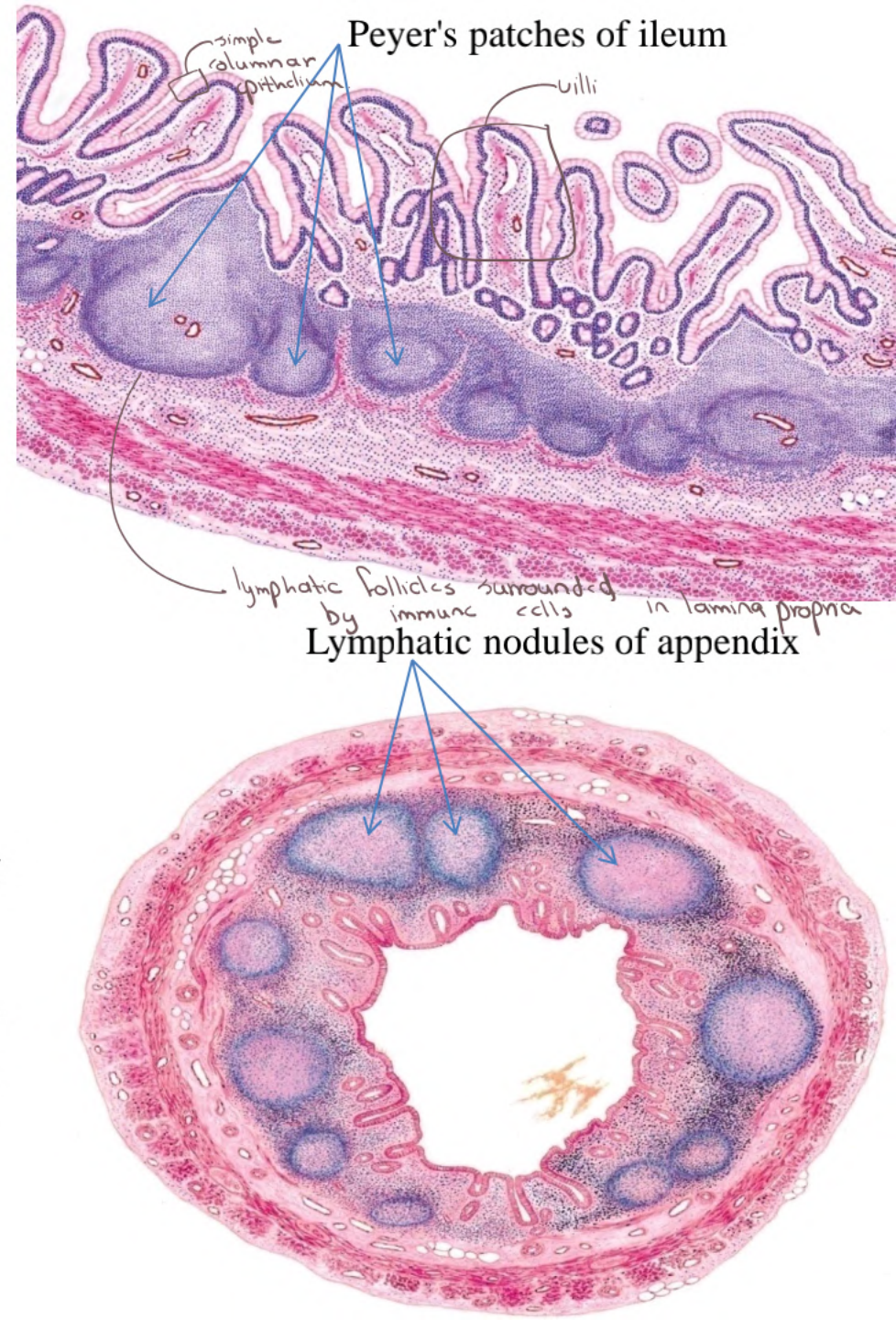
Examples:

- 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**



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.

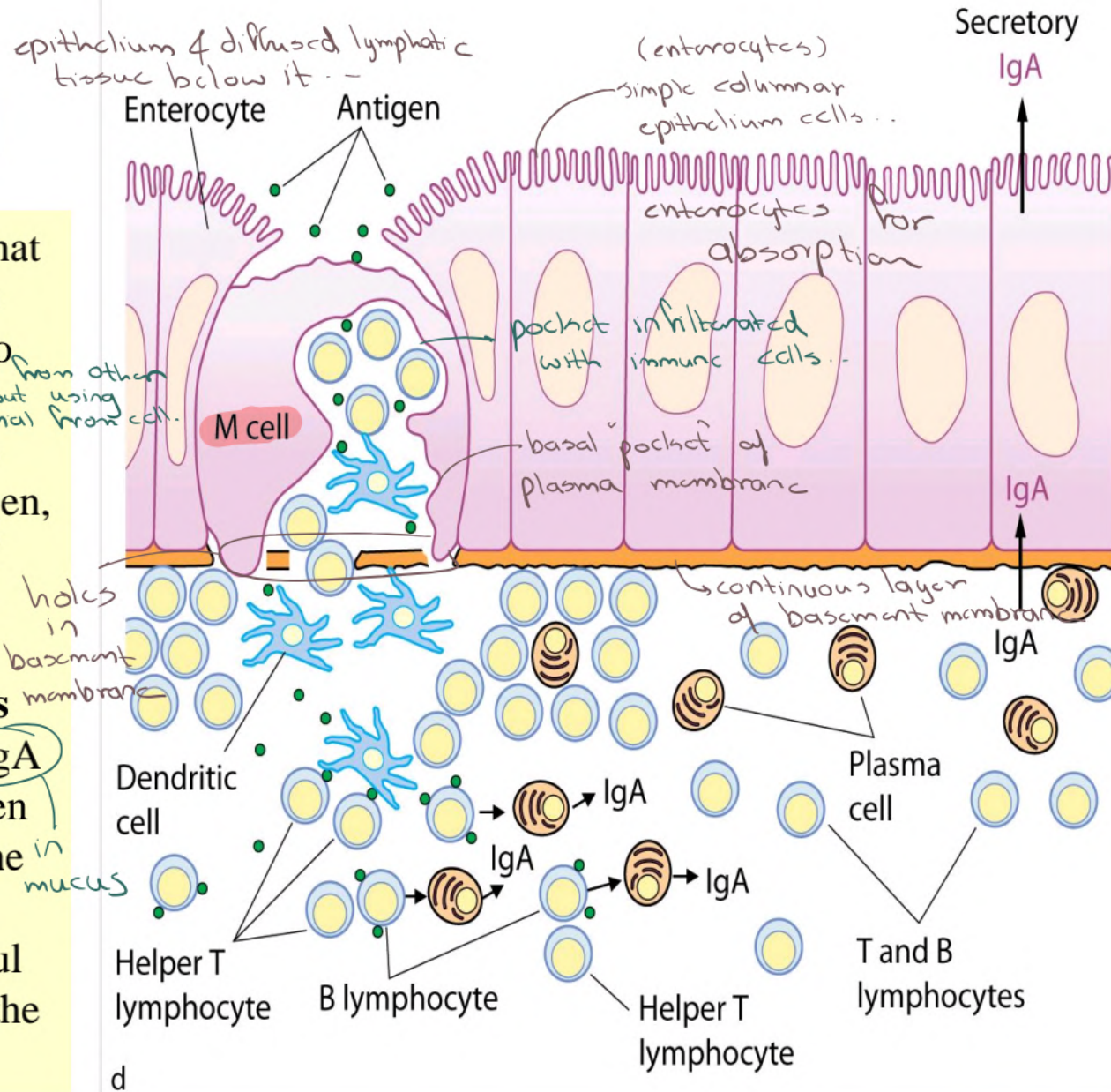
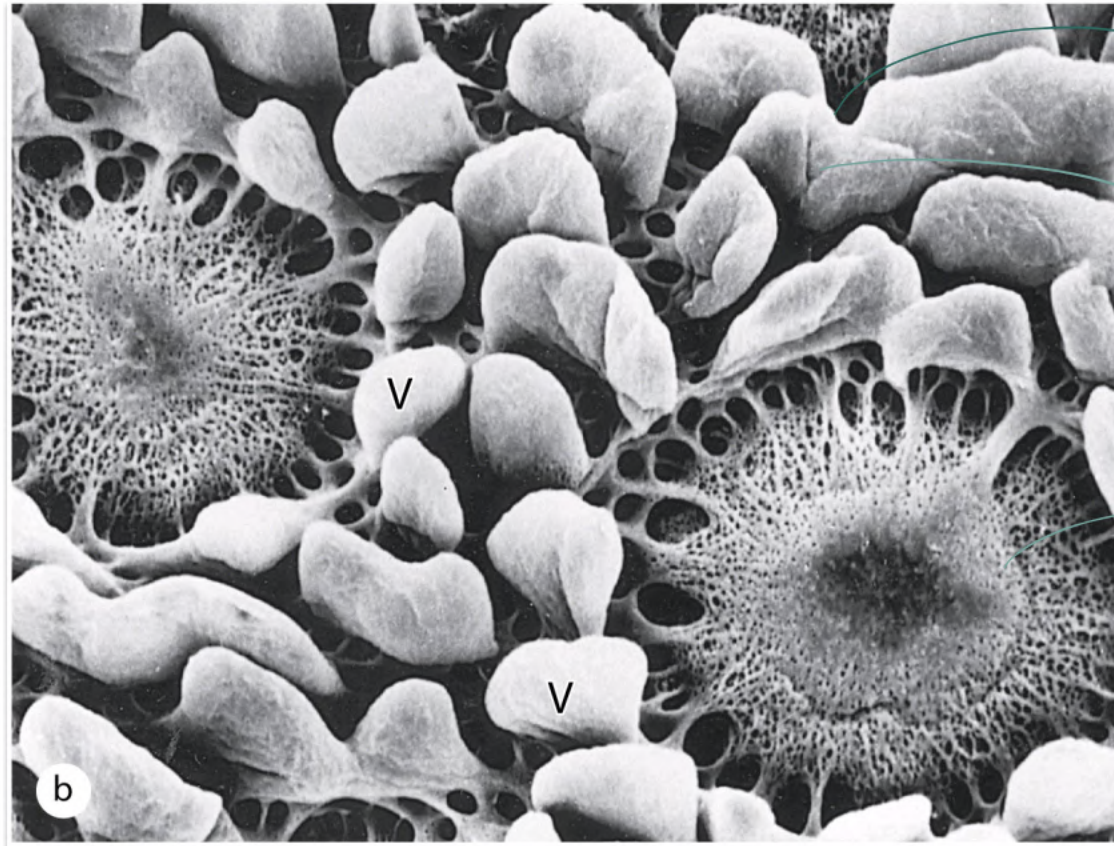


Figure 14-13

enterocytes & M cells removed

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 nodules of the Peyer patch.



villi... usually covered by enterocytes & M cells.

continuous layer of basement membranes

Peyer's patch and M cells

M cells... Basement membrane has wholes.

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

Bronchus-associated lymphatic tissue (BALT)

Is located in the mucosa of the bronchioles.

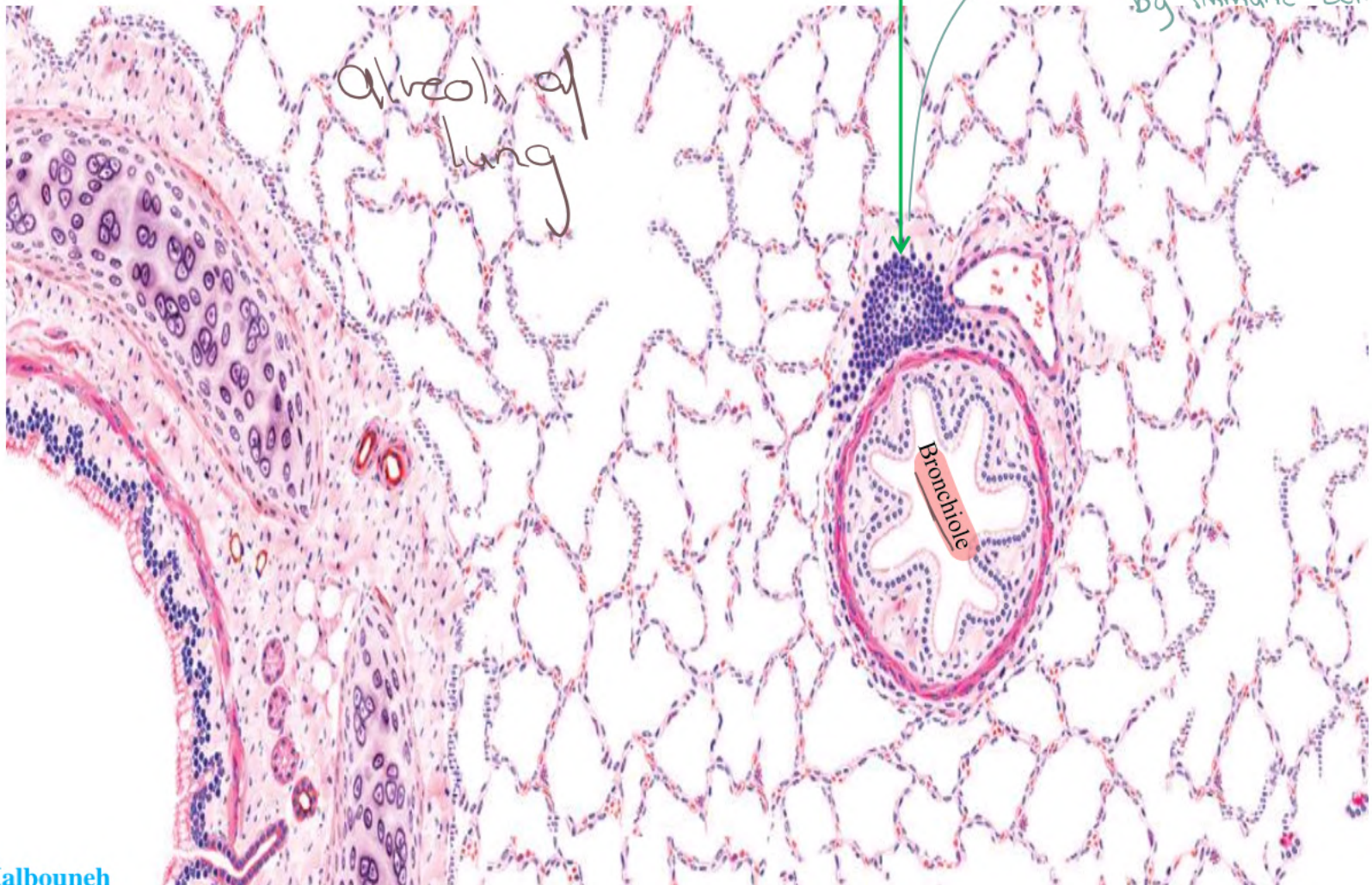
Function:

Protects the body from inhaled pathogens.

over
whole length
of mucus
membranes.

Solitary lymphatic
follicle/nodules.

single lymphatic
follicle surrounded
by immune cells.



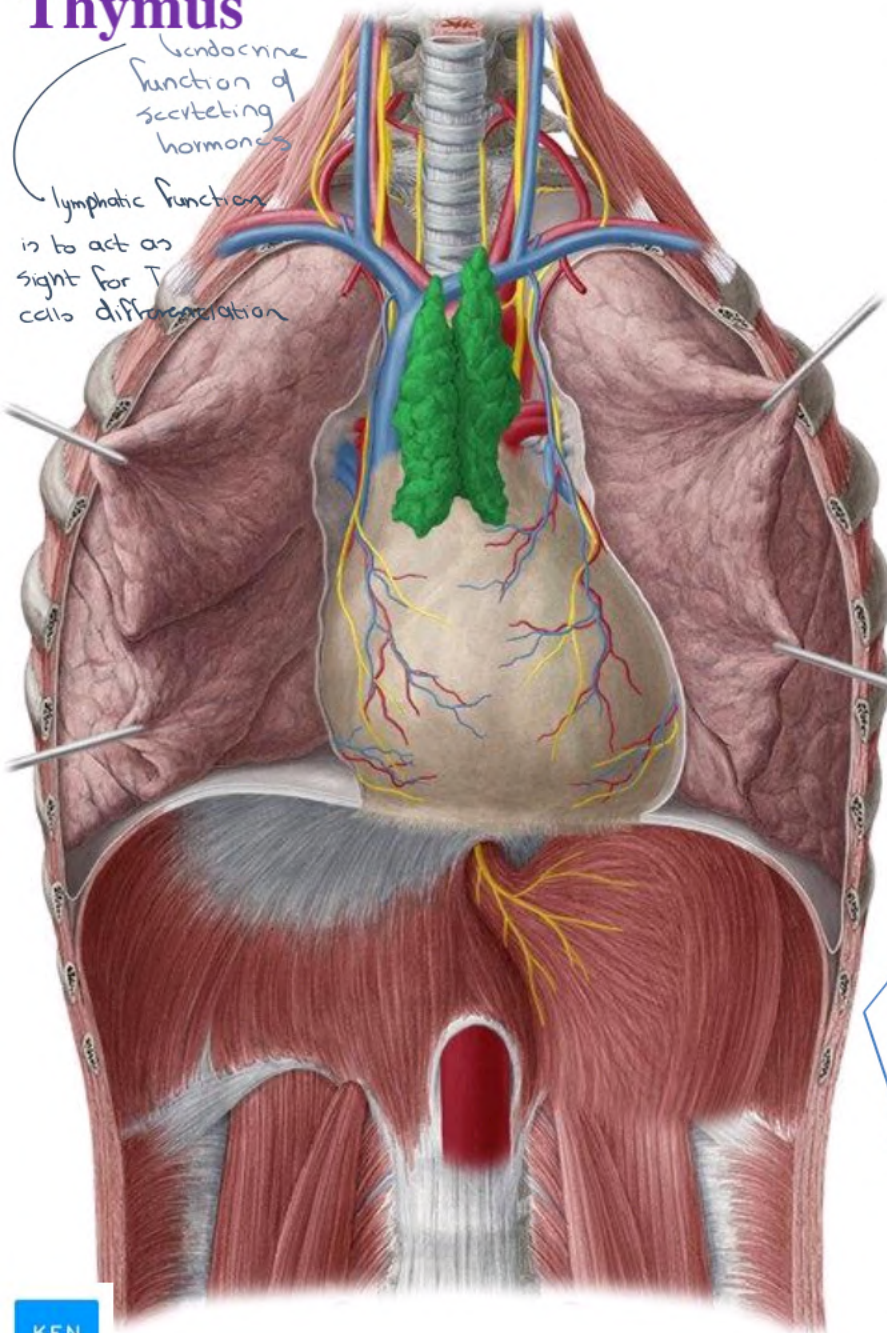
بَاقِي التَّزْوِيلِ مِنَ مُحَاضَرَةٍ
ال e-learning

وَسَارِعُوا إِلَى مَغْفِرَةٍ مِنْ رَبِّكُمْ وَجَنَّةٍ عَرْضُهَا السَّمَاوَاتُ وَالْأَرْضُ أُعِدَّتْ لِلْمُتَّقِينَ {آل عمران:133}

لا تَزُولُ قَدَمًا عَبْدٌ يَوْمَ الْقِيَامَةِ، حَتَّى يُسْأَلَ عَنْ عُمْرِهِ؛ فِيمَ أَفْنَاهُ؟ وَعَنْ عِلْمِهِ؛ فِيمَ
فَعَلَ فِيهِ؟ وَعَنْ مَالِهِ؛ مِنْ أَيْنَ اكْتَسَبَهُ؟ وَفِيمَ أَنْفَقَهُ؟ وَعَنْ جِسْمِهِ؛ فِيمَ أَبْلَاهُ؟
خلاصة حكم المحدث : صحيح

Thymus

Endocrine function of secreting hormones
Lymphatic function
is to act as sight for T cells differentiation



✓ 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 ^{shrinks} gradually becomes replaced by fat.



less cellular & ↑ fat
= called thymic involution

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 → thymus small in size & less cellular → less efficient in producing T cells

✓ The thymus is also part of the endocrine system.

The thymus has a double embryonic origin

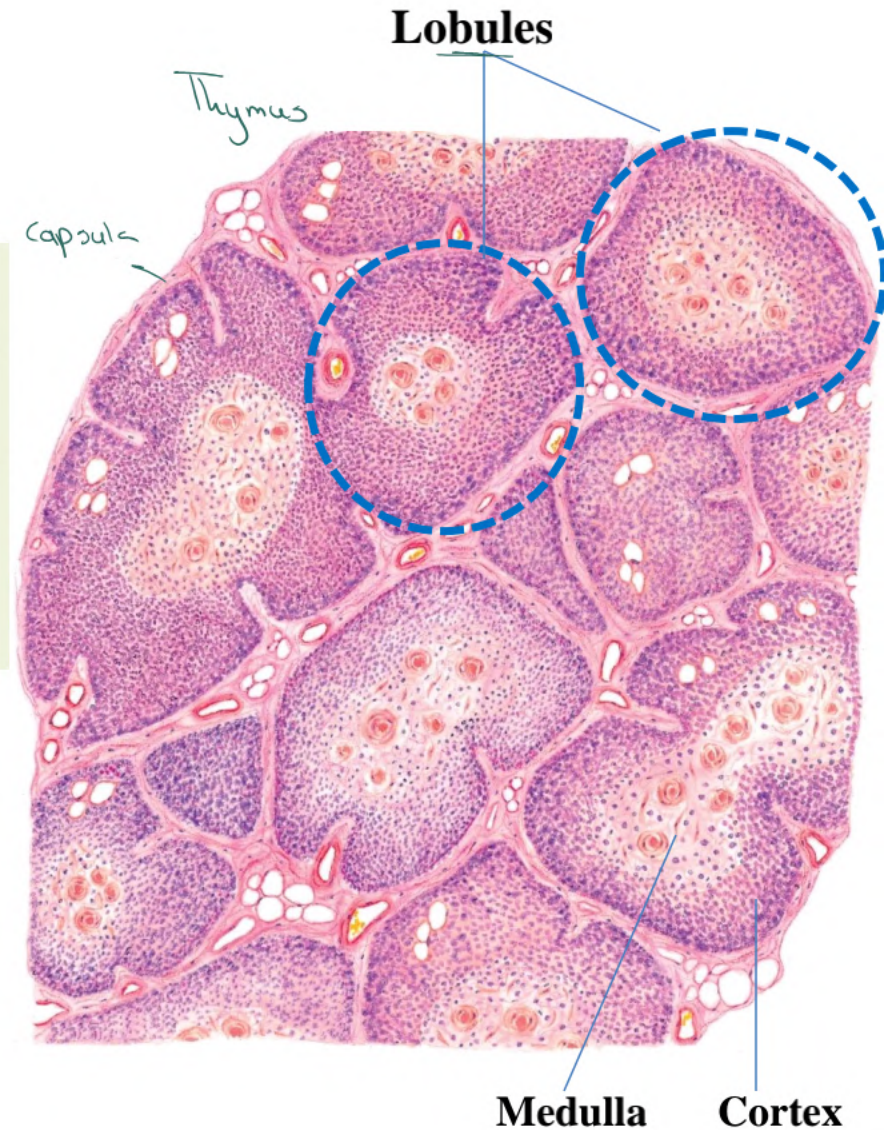
Endoderm and Mesoderm

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

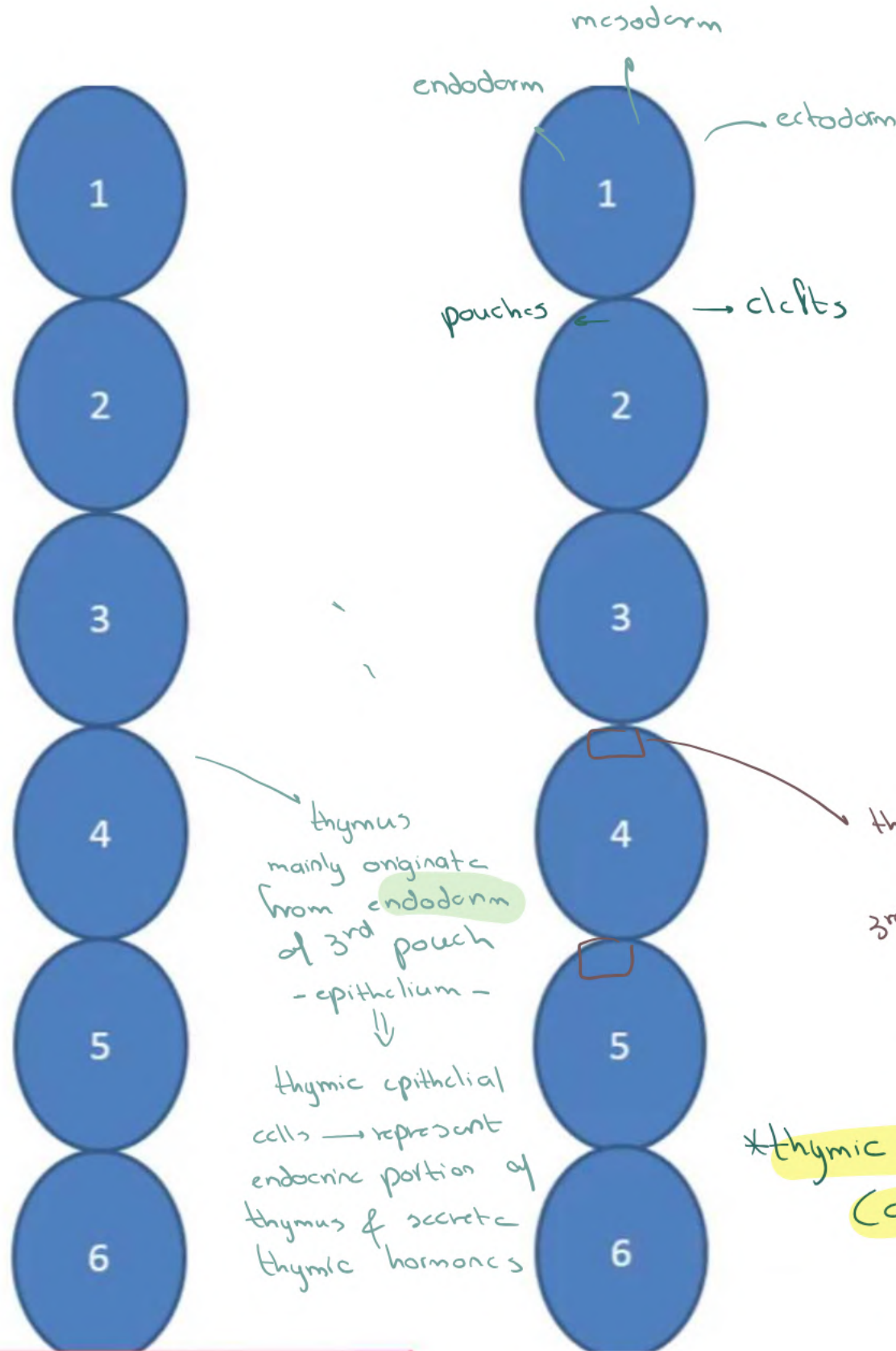
* Pharyngeal arches

Double Origin

→ inside red bone marrow we have precursor T cells - immature T cells - that migrate from bone marrow to thymus during development of thymus

↓ represent

mesodermal (hematopoietic) origin of thymus.



*thymic epithelial cells

→ release chemotactic factor to attract immature T cells to enter thymus

→ secrete hormones to promote differentiation & development of T cells

originate from endoderm
Thymic Epithelial Cells (TECs)
(Epithelial reticular cells)

many processes that are connected by desmosomes & form thymus stroma.
- epithelial cells form stroma -

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

mesodermal origin of thymus

*parenchyma of thymus is formed by developing T cells at different stages of differentiation.

to promote differentiation & development of T cells inside thymus
Thymotaxin
Thymosin
Thymopoietin

thymic epithelial cells form pockets to accommodate & protect T cells during development

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

* Capsule & Trabeculae act as
sights for main blood vessels
& nerve supply

Trabecula

thymic epithelial cells
- that form stroma - are concentrated
under capsule & along trabeculae.
Also more concentrated around
blood vessels inside
thymus.

Cortex

Medulla

~ less no.
of cells.
& more
mature cells
than cortex

Capsule

blood vessel
in capsule

Dendritic cells
only in medulla

Hassall
corpuscle

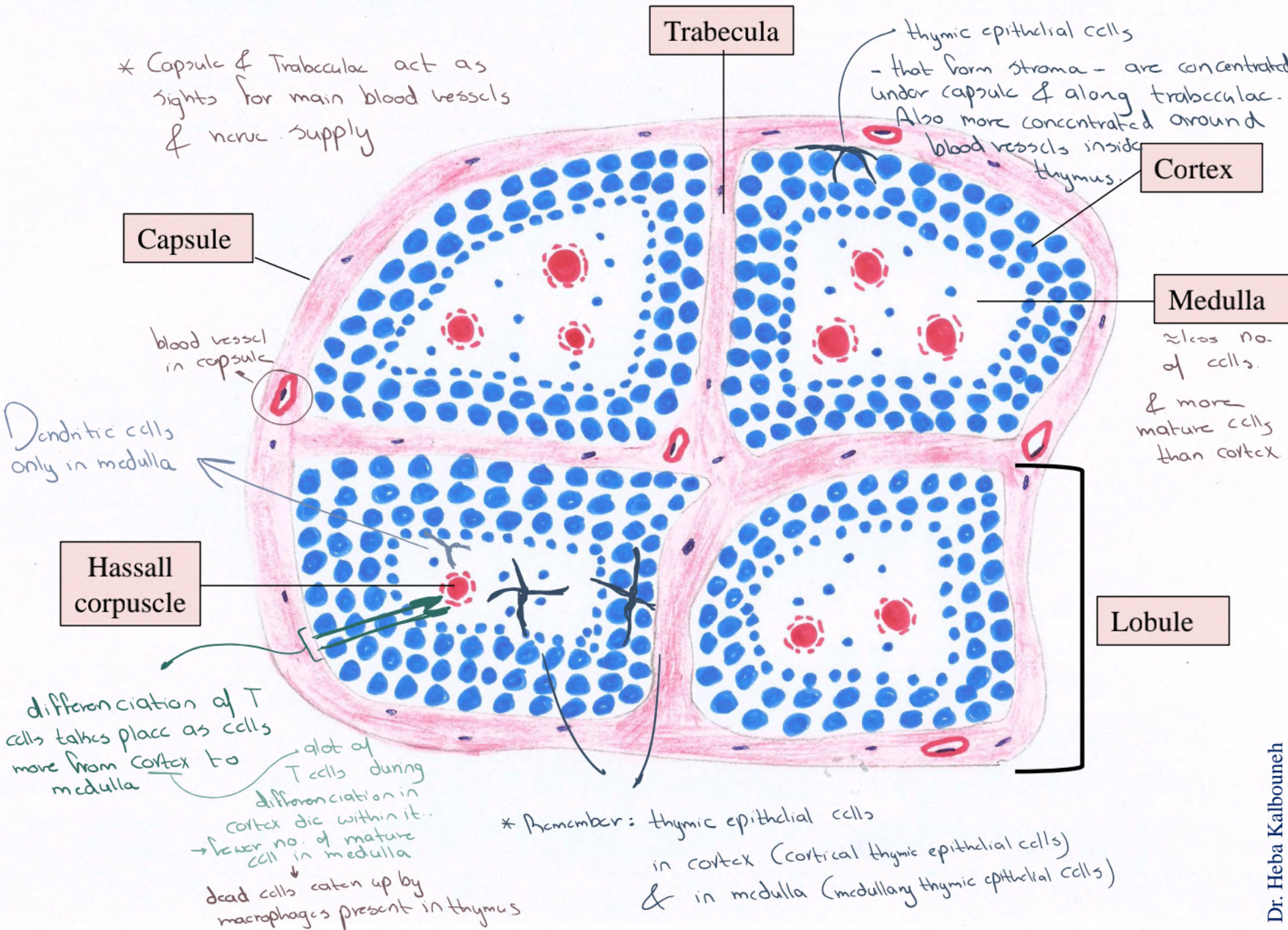
differentiation of T
cells takes place as cells
move from cortex to
medulla

alot of
T cells during
differentiation in
cortex die within it.
→ fewer no. of mature
cell in medulla

dead cells eaten up by
macrophages present in thymus

* Remember: thymic epithelial cells
in cortex (cortical thymic epithelial cells)
& in medulla (medullary thymic epithelial cells)

Lobule



* Hassall corpuscles:-

function: ?

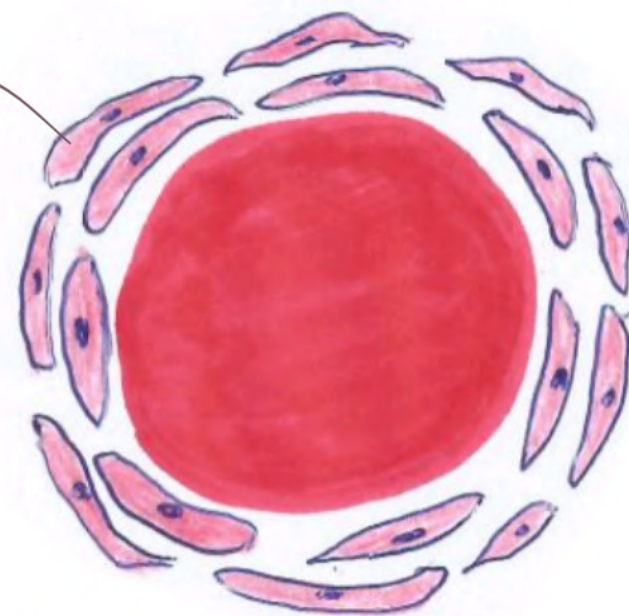
others say they secrete factors necessary for function of dendritic cells inside medulla

... perhaps a graveyard for thymic epithelial cells after performing their function
- claim that that these corpuscles appear after puberty & increase with age

* same concept of keratinization ~

intermediate filaments in the flat cells form tonofilaments then aggregate to form keratin until central keratinization inside corpuscle happens.

* flat epithelial cells surrounding central keratinization.



Remember - thymic epithelial cells are connected by desmosomes that are connected to intermediate filaments inside cell...
- like keratinocytes inside epidermis of skin -



as cells move away from cell membrane, they accumulate more & more keratin until we end up with dead flat cells full of keratin

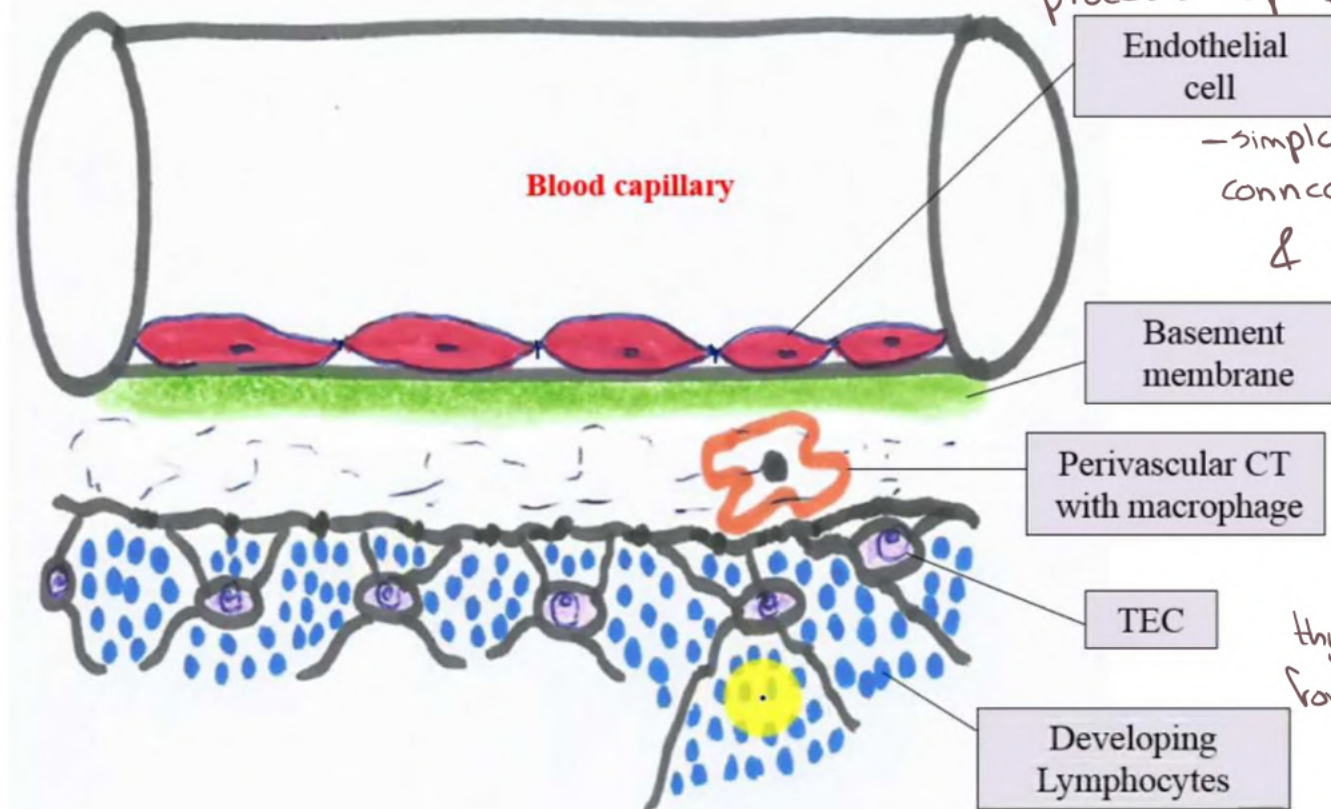
thymic epithelial cells
 - that form stroma - are concentrated under capsule & along trabeculae.
 Also more concentrated around blood vessels inside thymus.

⇒ Why?

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

formed from endothelium connected with tight junctions, thick basement membrane, perivascular CT rich in macrophages & cytoplasmic process of thymic epithelial cells

⇒ to protect differentiating cells inside thymus from any antigen inside blood



- simple squamous cells connected by tight junctions & rests on BM -

→ thick & surrounded by loose type of CT

thymic epithelial cells forming stroma of thymus

their cytoplasmic processes extend to protect developing T cells during their differentiation

↓
 not exposed to content of blood during thymic education

→ **Blood-thymus barrier**

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

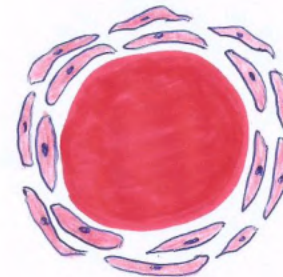
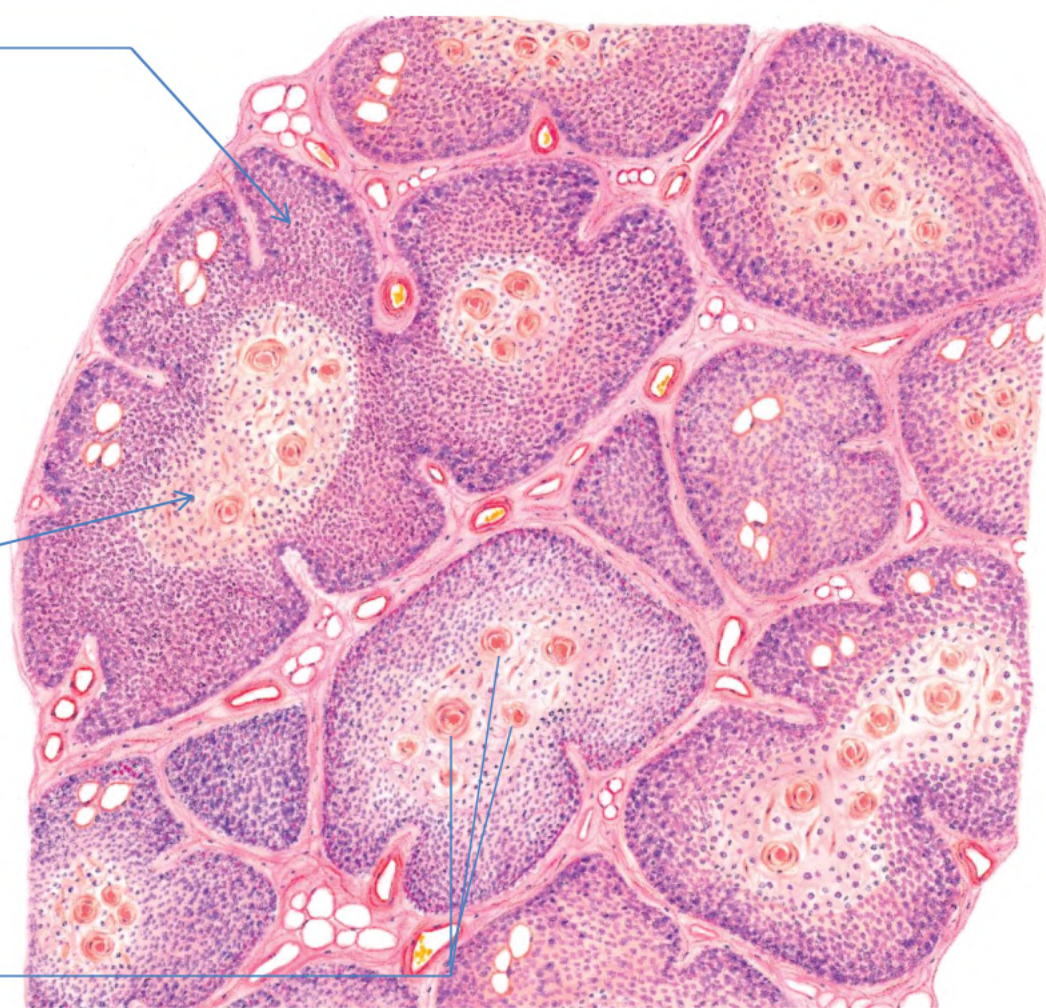
Hassall corpuscles

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

stroma of thymus is not formed by reticular or connective tissue → formed by epithelial cells

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**)

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

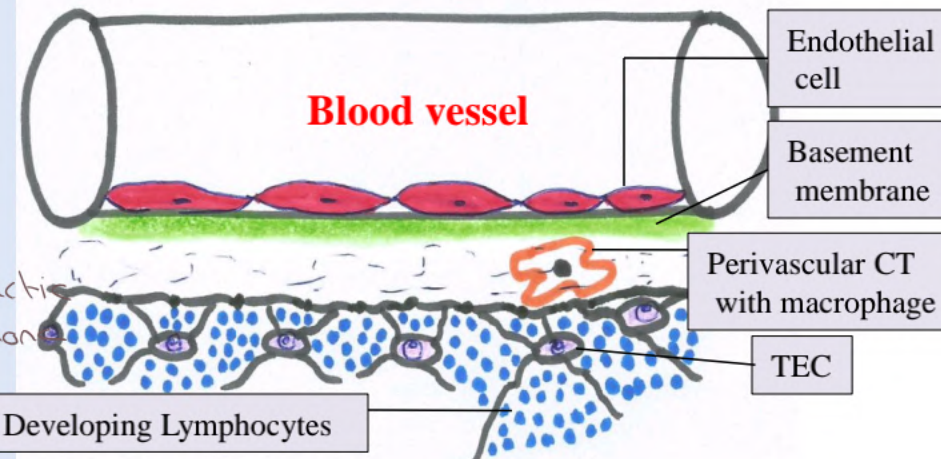
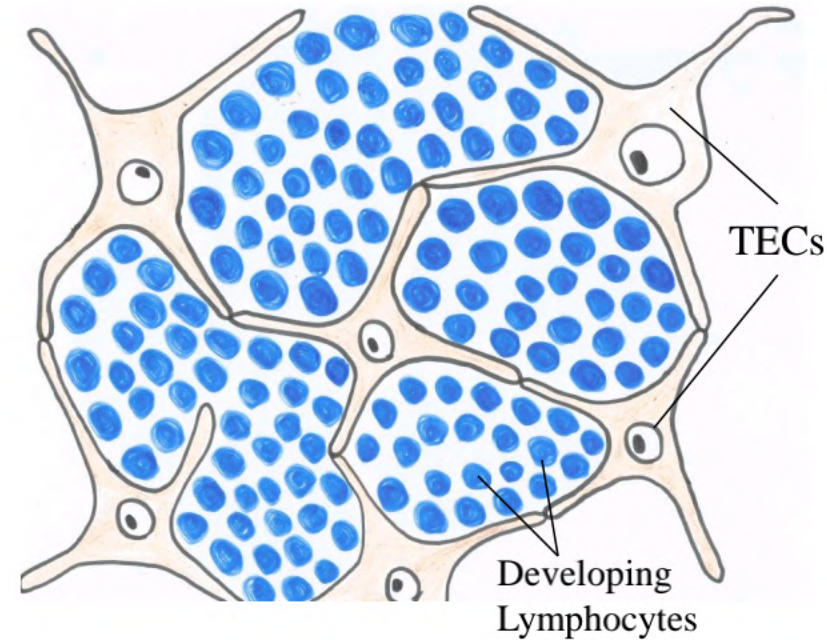
4- Act as APCs, expressing MHC class II and MHC class I molecules (**in cortex**)

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

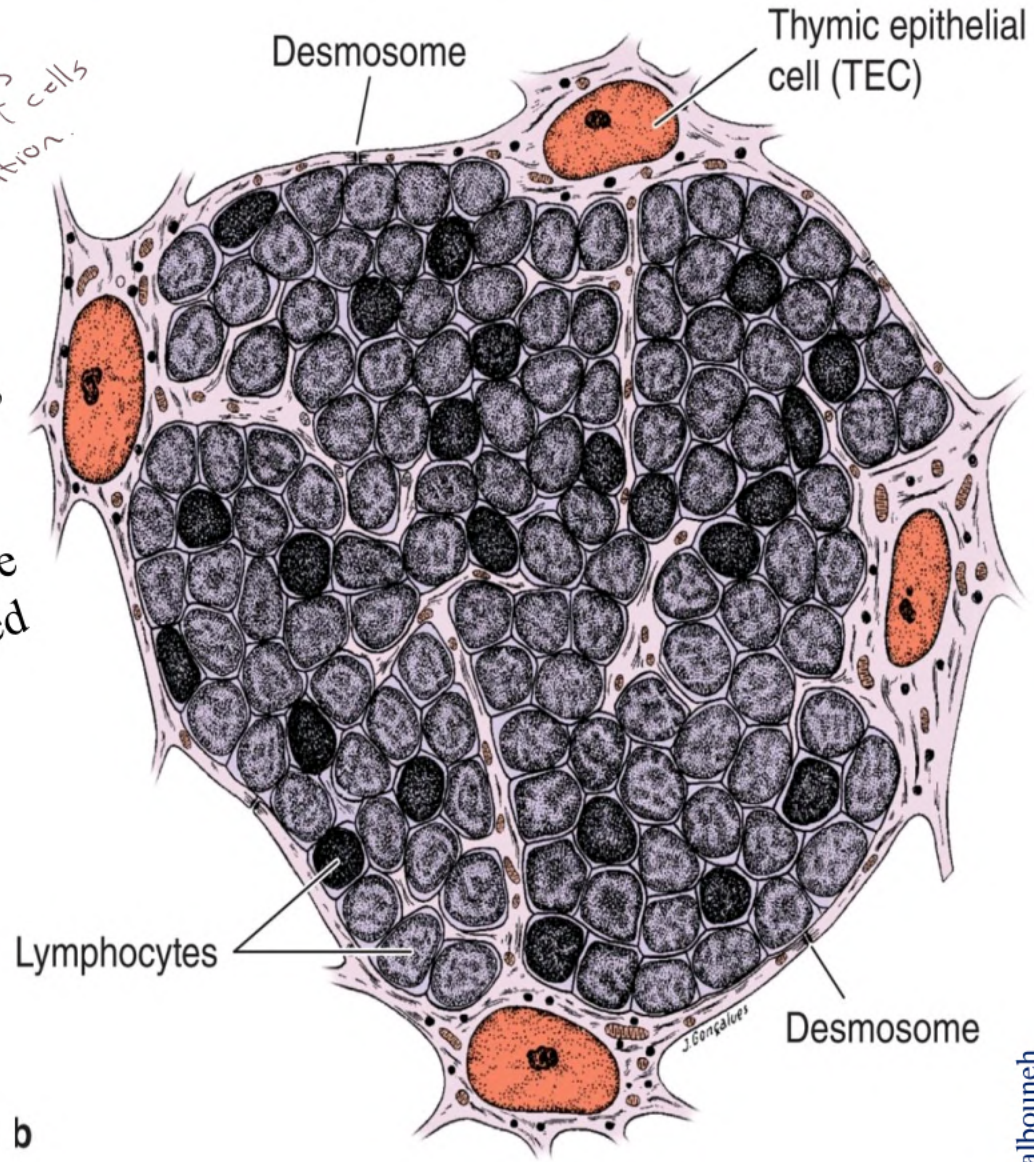
Dr. Heba Kalbouneh



Thymic epithelial cells are also called **Nursing Cells** → because they secrete hormones that promote T cells differentiation.



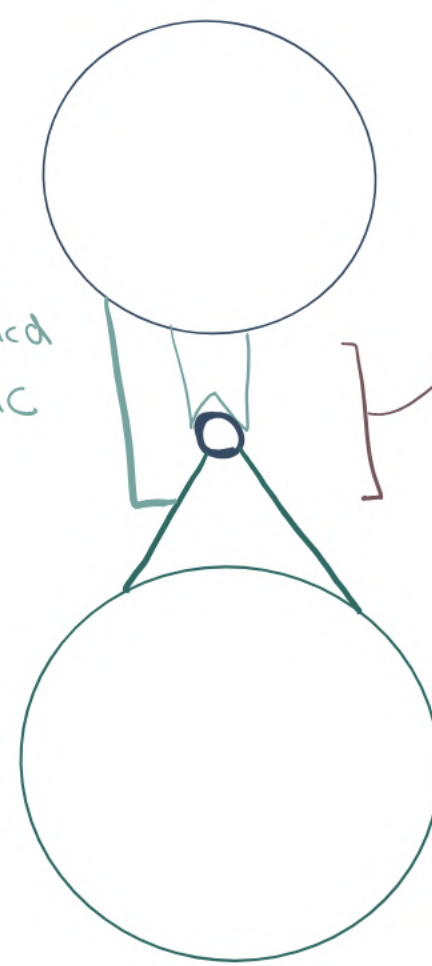
They form sheets for cells deep to the capsule, around septa and blood vessels, to isolate developing T lymphocytes in the cortex from contact with antigens (present in the blood), while they are programmed



b

T cells: Cytotoxic $CD8^+$ & Helper $CD4^+$

X TCR receptors recognizes the non self peptides coupled to class I / II MHC molecules...



binding not only between TCR receptor & antigen but also between TCR receptor & class I / II MHC molecule.

Virally-infected cell, dendritic cell, or APC... with MHC I or MHC II coupled to peptide

TCR receptor gene

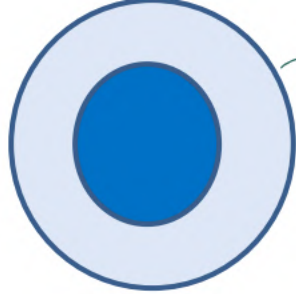
- variable part
- constant part



DNA recombinases produce shuffling inside variable portion of TCR gene - randomly -

Producing different TCR receptor each time

we will test if these newly formed TCR receptors can bind to class I & II MHC molecule... (functional or not?)



Double negative

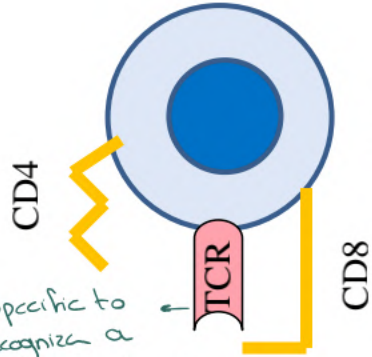
no TCR either → once they enter thymus & under influence from hormones released by thymic epithelial cell
 - immature T cells, precursor T cells or T lymphoblasts that arrived from red bone marrow to thymus -

no CD4 or CD8 on its surface

upregulation of genes (CD4, CD8, TCR)

double positive

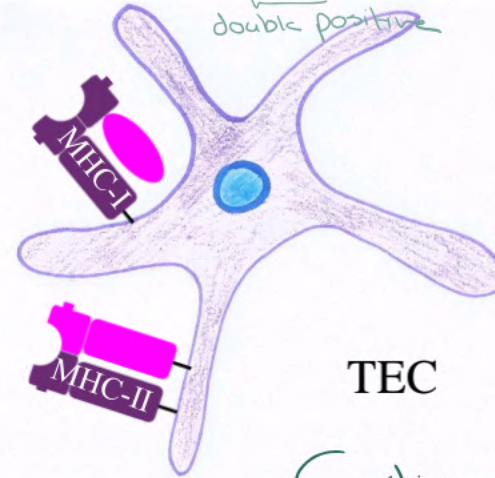
Thymic education
 → medulla & cortex



Double positive



specific to recognize a certain antigen

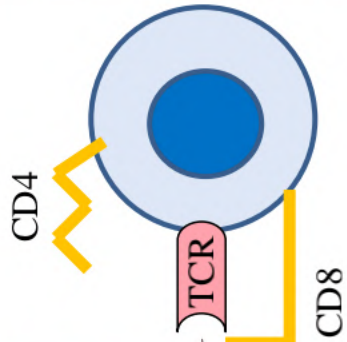


TEC

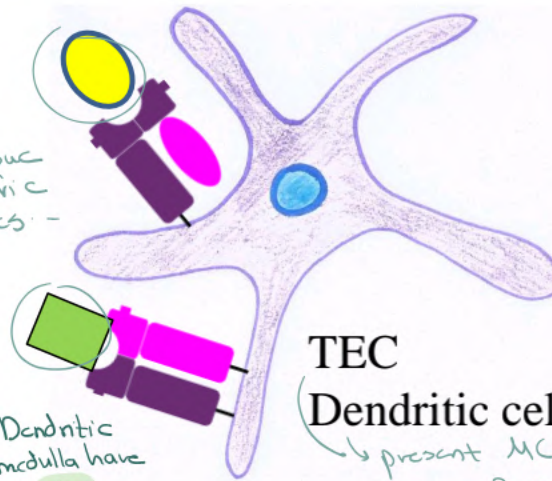
Cortex

millions of T cells with different TCR made to recognize a certain antigen... you may be exposed to the antigen in the future or not.

Cortico-medullary Junction



liver or stomach or lung etc. → tissue specific peptides -



TEC

Dendritic cell

present MHC-I & II with self peptides

Medulla

- in outer part of medulla

in medulla, we are sure this TCR is functional after (+) selection.

TEC & Dendritic cells inside medulla have a gene called auto-immune regulator that can produce many self peptides representing proteins in our cells

But they are not thymic self-peptides.

Double negative

if TCR receptor is defective - remember is formed from random process - if the cell will not receive survival signal from TEC & dies in Cortex by "neglect" within 3/4 days & eliminated by macrophages

(2) if it is able to bind to Class I or II MHC molecules - will receive survival signals from TEC - moves to medulla

Double positive

CD4

CD8



presented to

Called "positive selection"

Cortex

cells selected if they bind to MHC I or II

(1) Thymic epithelial cell TEC has both MHC I & II

Cortico-medullary junction
under influence of TEC

* According to MHC molecules recognized by cell in (+) selection; we will have upregulation of CD4⁺ or CD8⁺ & the other not recognized downregulated.

CD4

CD8



presented to tissue self peptides (1)

(3) cells that don't recognize self antigens are released to blood stream

Medulla

TEC Dendritic cell

present Class I & II MHC molecules but this time coupled to self peptides

"negative selection"

* should not recognize self antigens!

called autoreactive T cell * if it does, should die in medulla otherwise autoimmune disease.

direct death by death molecules to induce apoptosis from TEC & dendritic cells

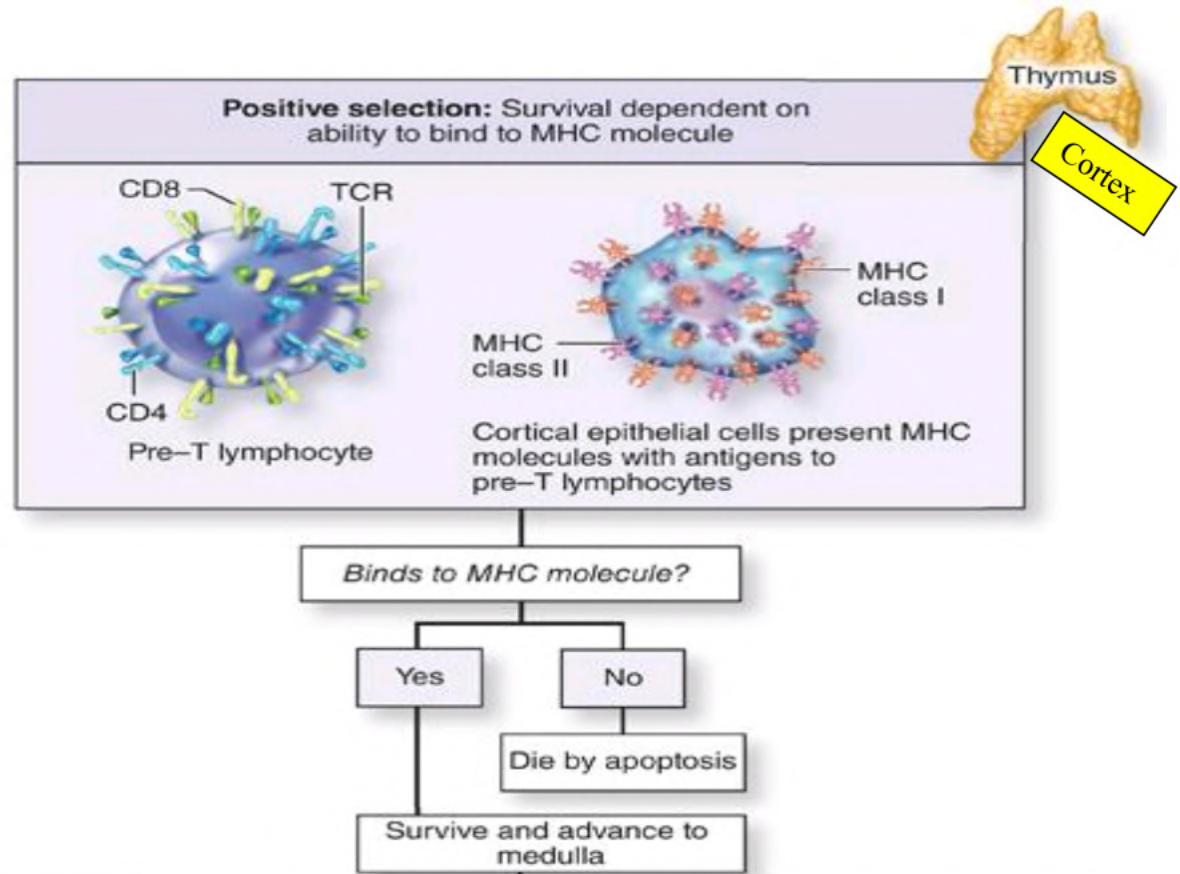
Immature T cells arriving in the thymus do not yet express CD4, CD8, or a TCR.



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**)



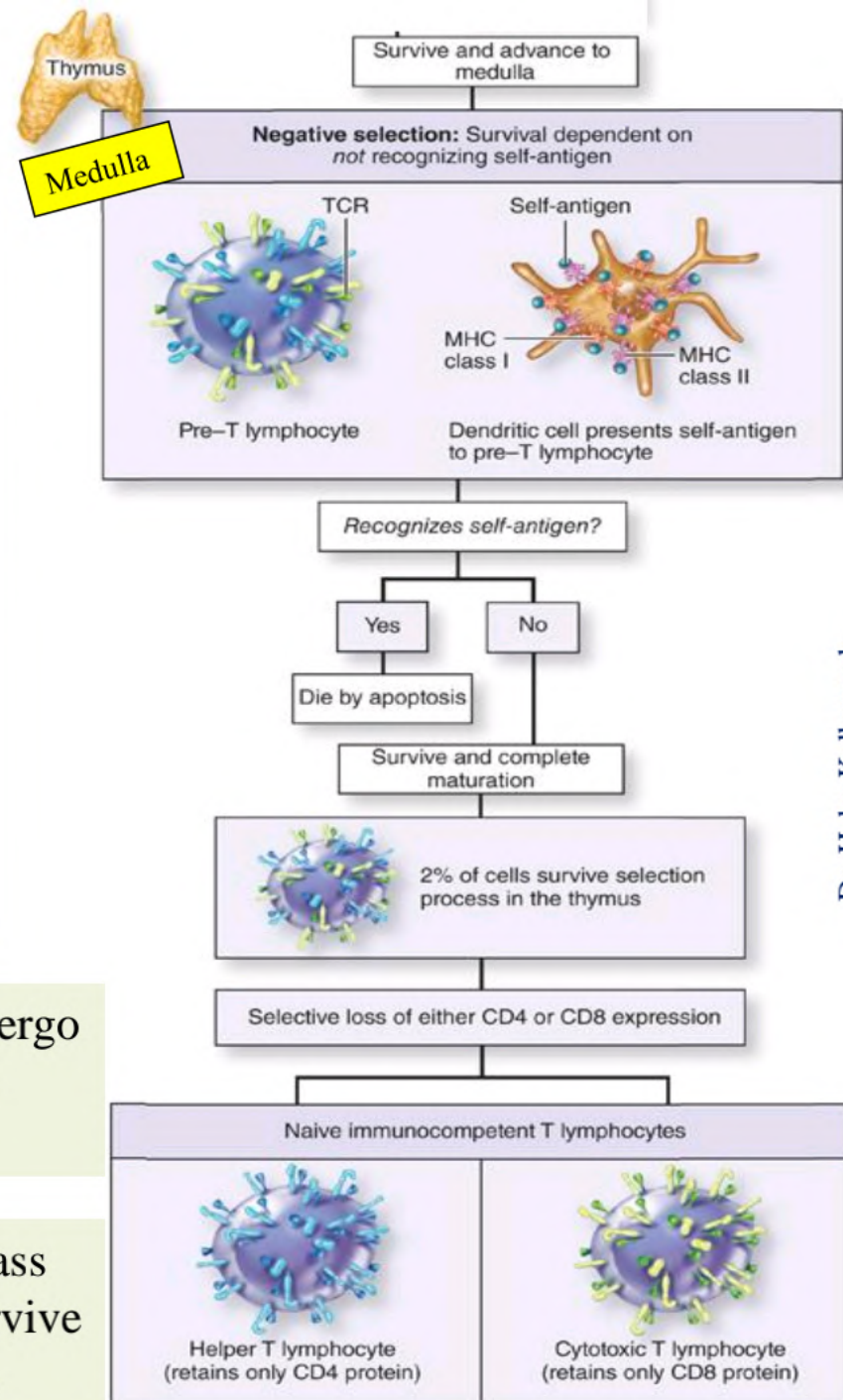
Self-antigens presented here are those from proteins specific for many tissues other than the thymus (tissue specific antigens)



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.



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

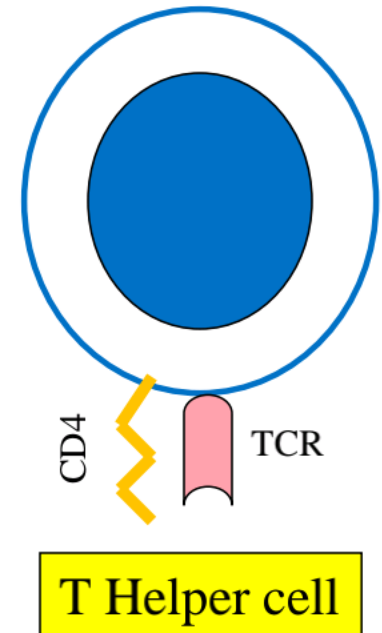
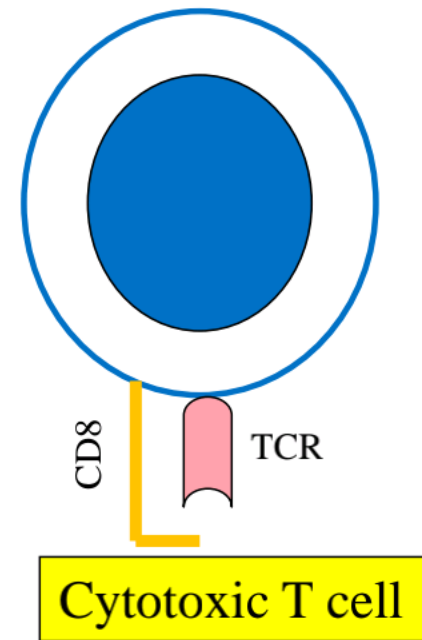
Depending on which class of MHC they interacted with, most of these lymphocytes will have stopped expressing either CD8 or CD4, and become either helper T cell or cytotoxic T cell

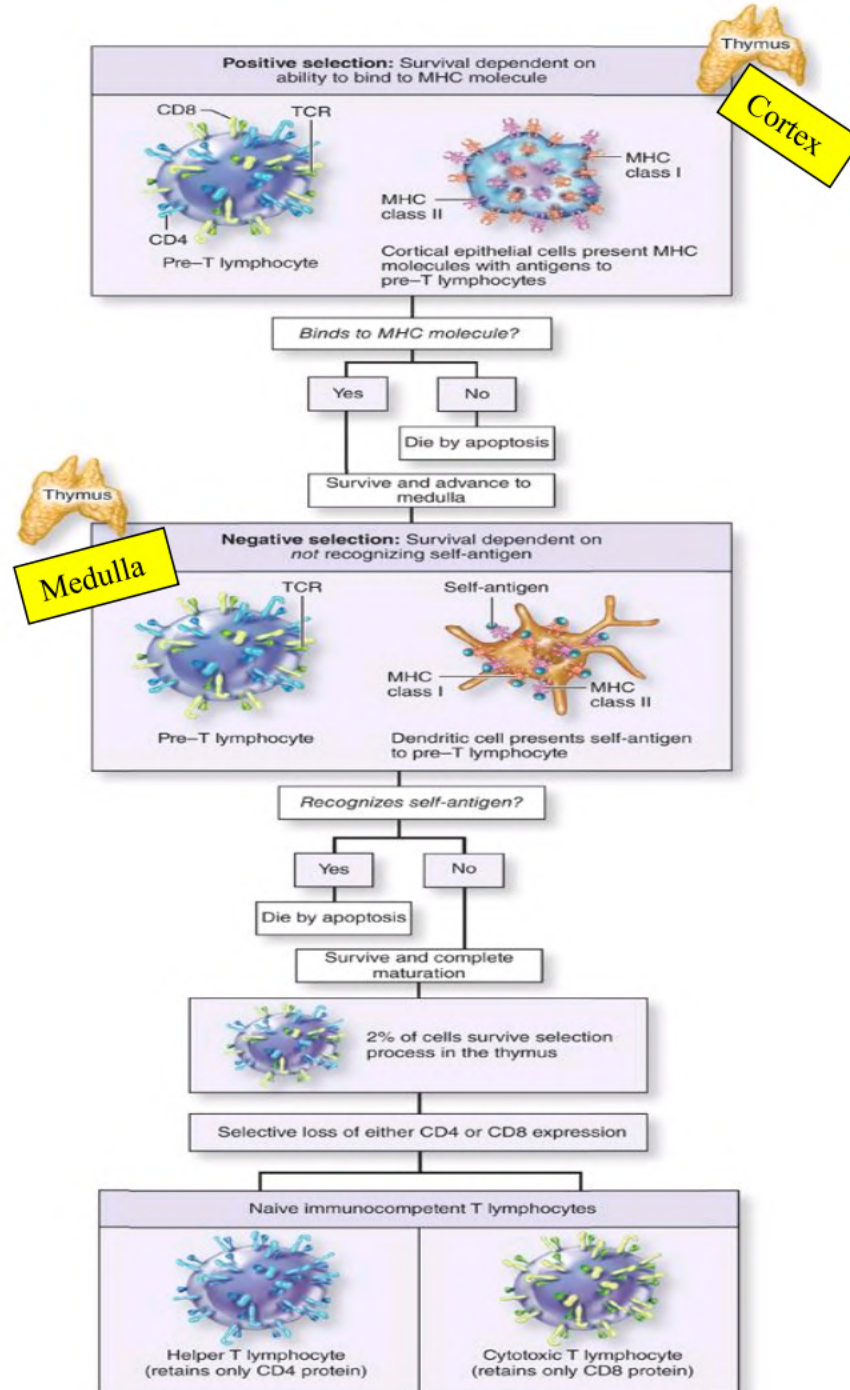
Fully mature T cells (immunocompetent T-cells) leave the medulla via venules and efferent lymphatic vessels

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.

but still are naive not yet exposed to antigen
 *after thymic education → we will have mature T cells that are immunocompetent → able to initiate immune response from 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.

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

lymphocyte recirculation: important due to limited no. of T mature cells

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

Advantage 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

