Histology - HLS

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Lymphatic System

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Lymphatic system

The lymphatic system consists of lymphatic fluid, lymphatic vessels, lymphatic tissue (**masses or aggregations of lymphocytes and other immune cells distributed throughout our body specially the mucosa –diffuse lymphatic tissues-**) , 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.

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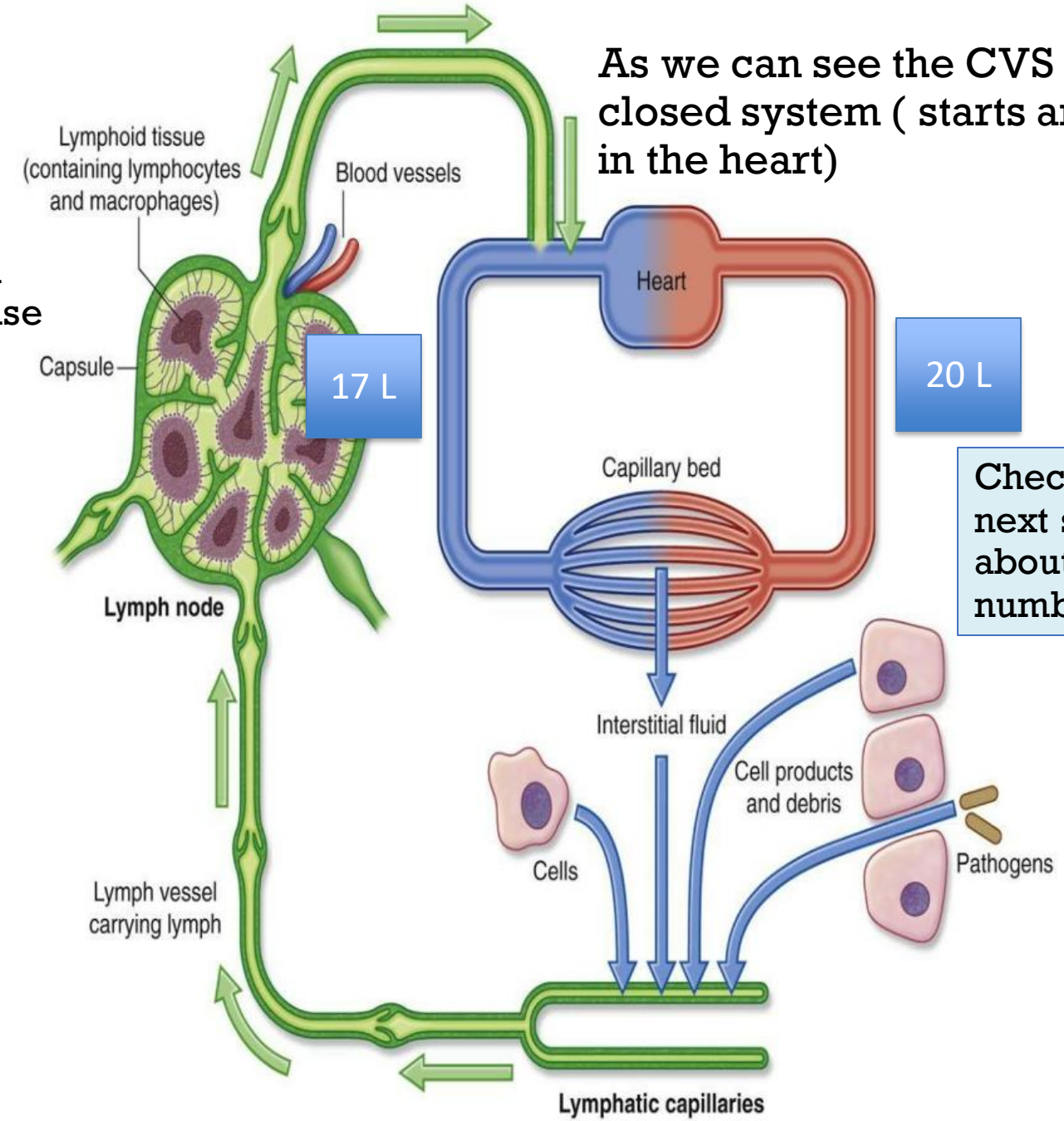


As we can see the CVS is a closed system (starts and ends in the heart)

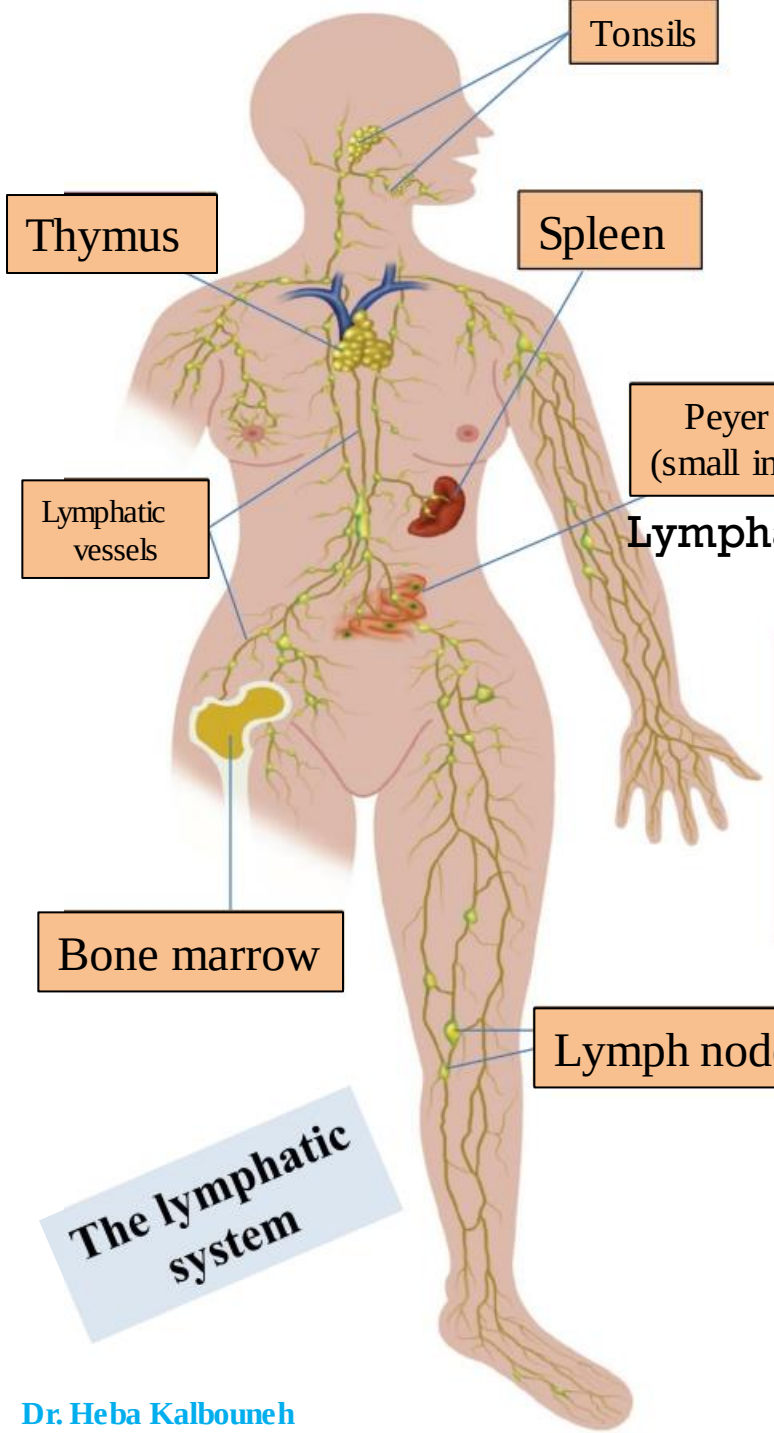
Check the next slide about the numbers

Explanation from the previous slide

From the left of the heart a large blood vessel -Aorta-originates carrying oxygenated blood with it, as it goes away from the heart it branches to small arteries until we end with arteriole then it branches to form a capillary bed where we have arterial and venous sides.
From the venous side, venules will be formed, and these venules will unit to form larger veins then the venous blood is going to drain back into the right side of the heart.

At the level of the capillary bed, we have fluid exchange between the blood and interstitial fluid, at the arterial side we have a high hydrostatic pressure results from the pumping force of the heart and the contraction of the smooth muscles inside the wall of the arteries. This hydrostatic pressure forces the fluid to leave capillaries in order to enter the interstitial fluid carrying nutrients and oxygen, and since plasma proteins remain inside blood this will create an osmotic pressure at the venous side of the capillary bed that will force fluid to return back to the blood flow carrying with it carbon dioxide and waste products then it going to be drained in the right side of the heart

There is about 3 liters of the interstitial fluid that is not drained into the venous blood –we call it lymph-, if it accumulates it will cause an edema so this extra fluid has to be drained by lymphatic system which starts at the lymphatic capillaries that unites to form lymph vessels and along the lymph vessels we have stations called lymph nodes and this extra fluid will be drained again into the venous blood and they're considered filtration stations because lymph contain pathogens, antigens, APCs, cancer cells or viral infected cells and so on



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.

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

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Fluid balance

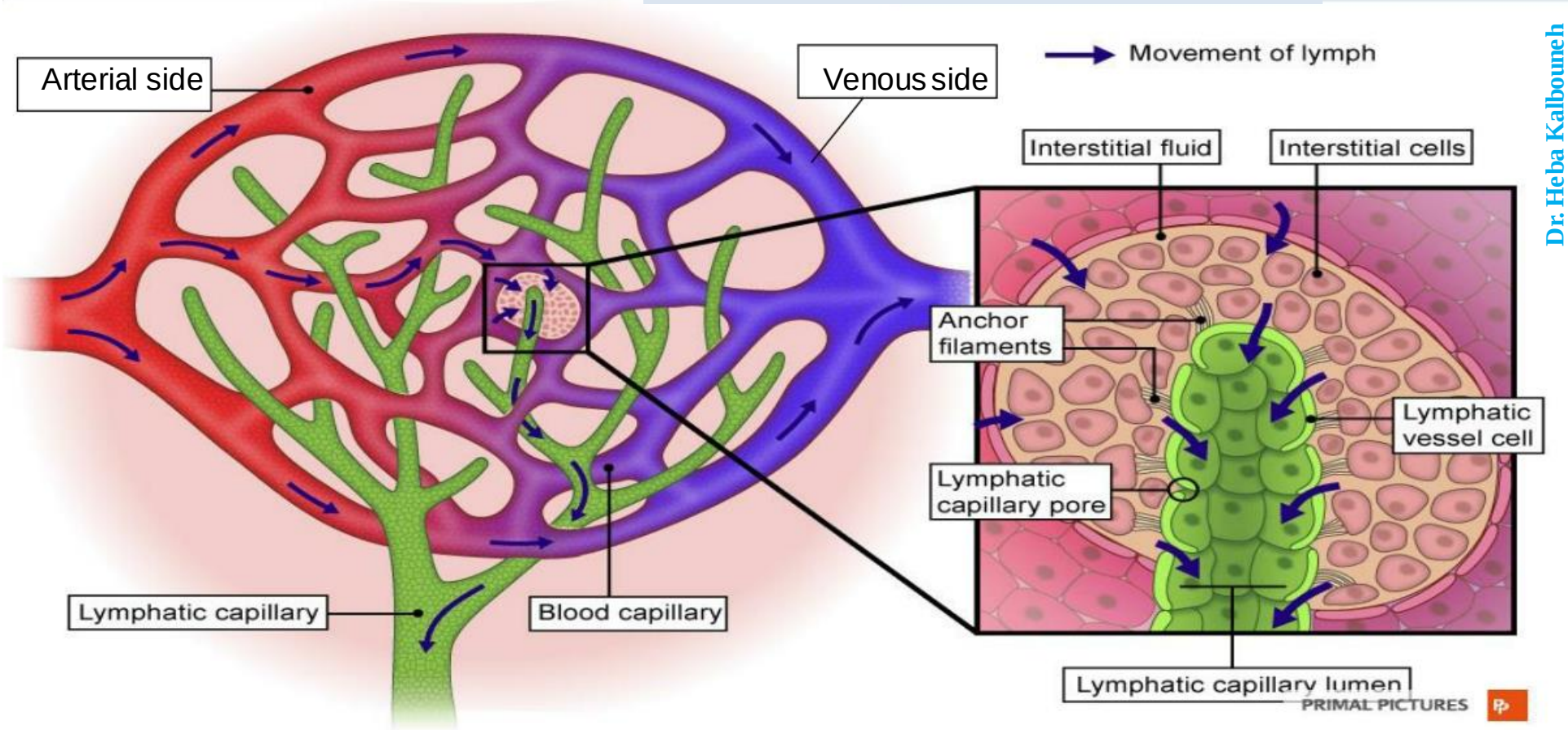
The tissues of the body are supplied by blood capillaries that bring oxygen-rich blood and remove carbon dioxide-rich blood.

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

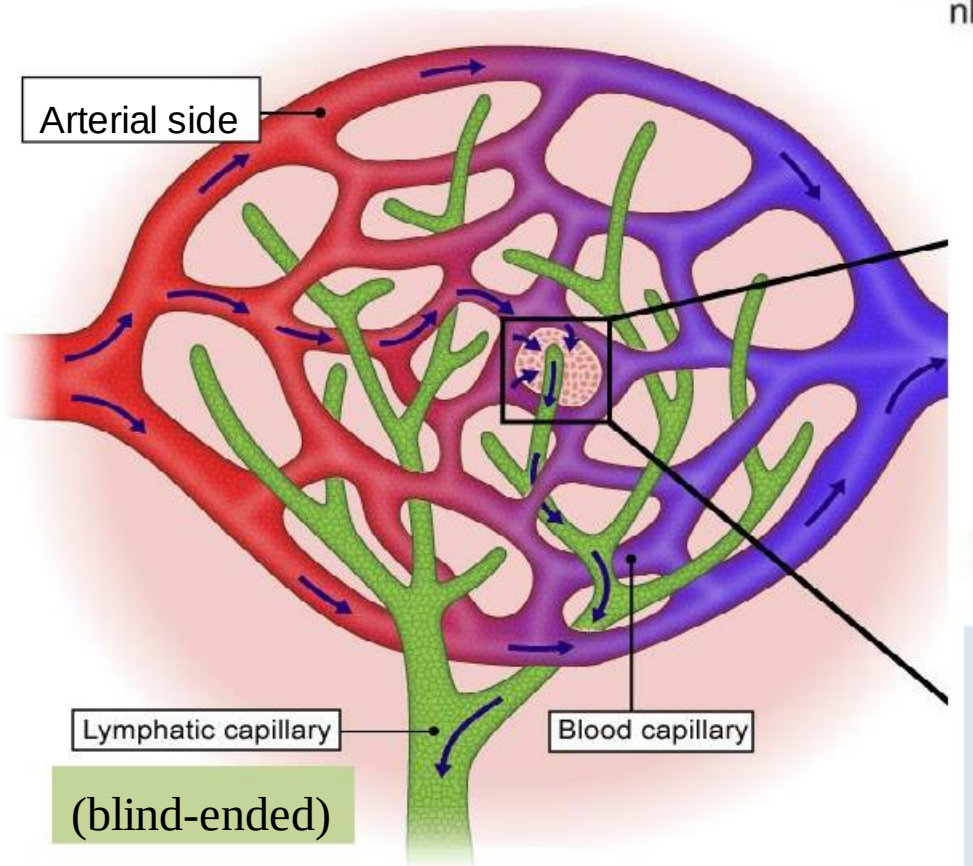
Around 20 liters of fluid leaves the arterial capillaries every day, but only 17 liters of fluid returns to the venous capillaries.

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

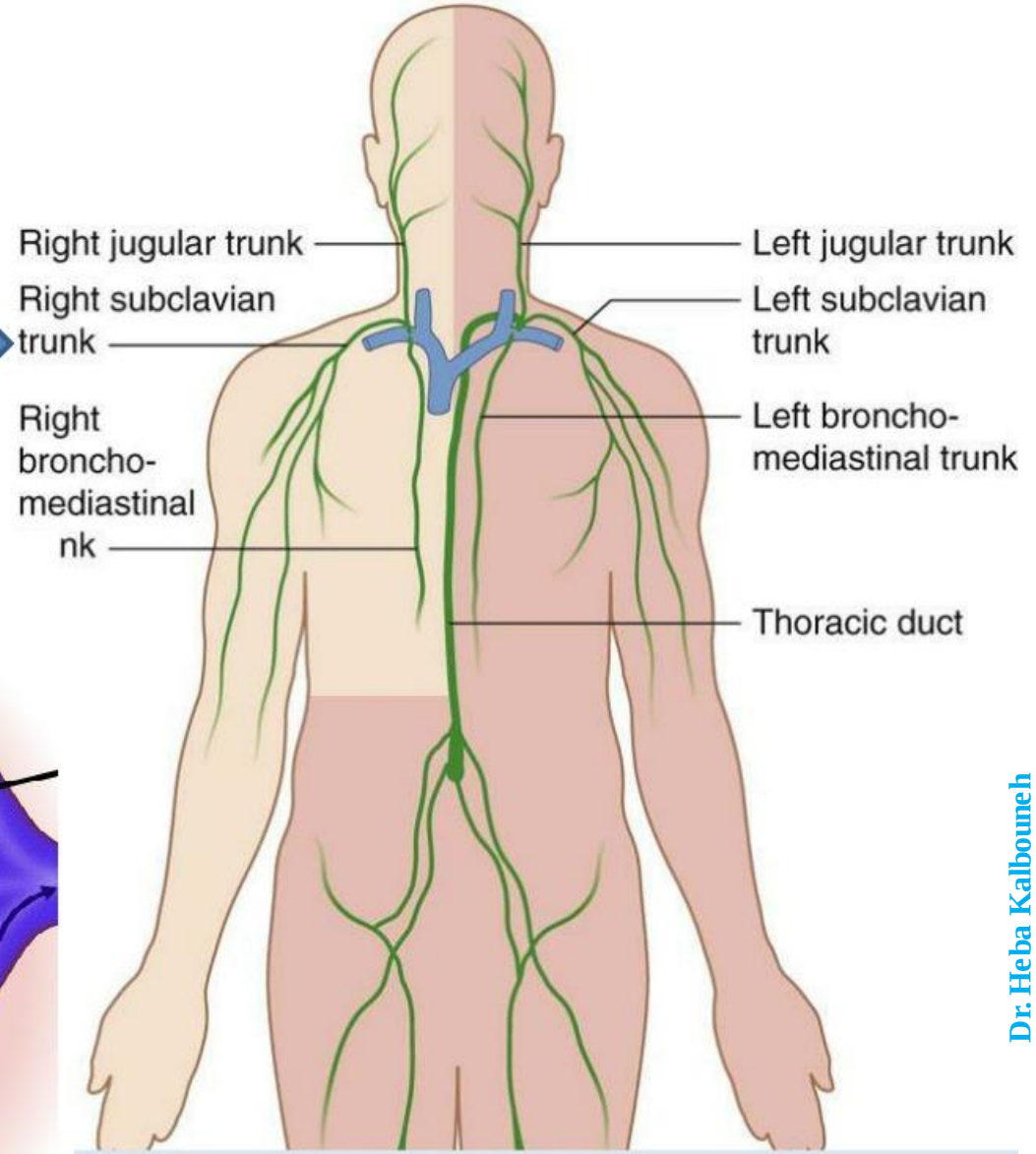
Lymphatic vessels start as blind-ended lymphatic capillaries that are lined with simple squamous epithelial endothelial cells, overlapping with large gaps in between >> to allow viral, cancer and AP cells to enter it.



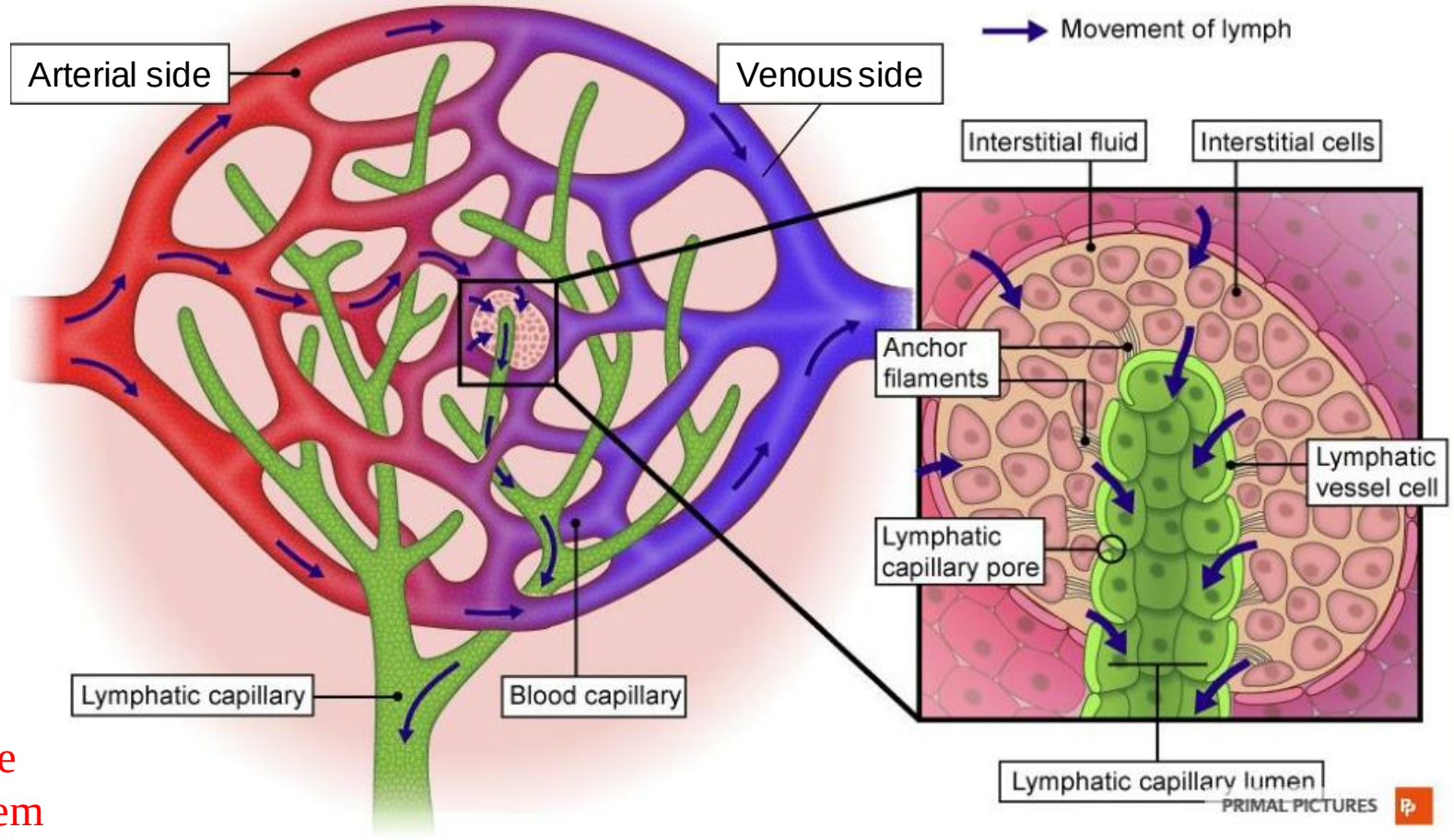
Lymphatic vessels begin as "porous" blind-ended lymphatic capillaries in tissues of the body and converge to form a number of larger vessels, which ultimately connect with large veins in the root of the neck.



(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 with large gaps. The overlapping flaps function as a one-way Valve

They prevent the back flow of lymph from capillary to interstitial fluid

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

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.

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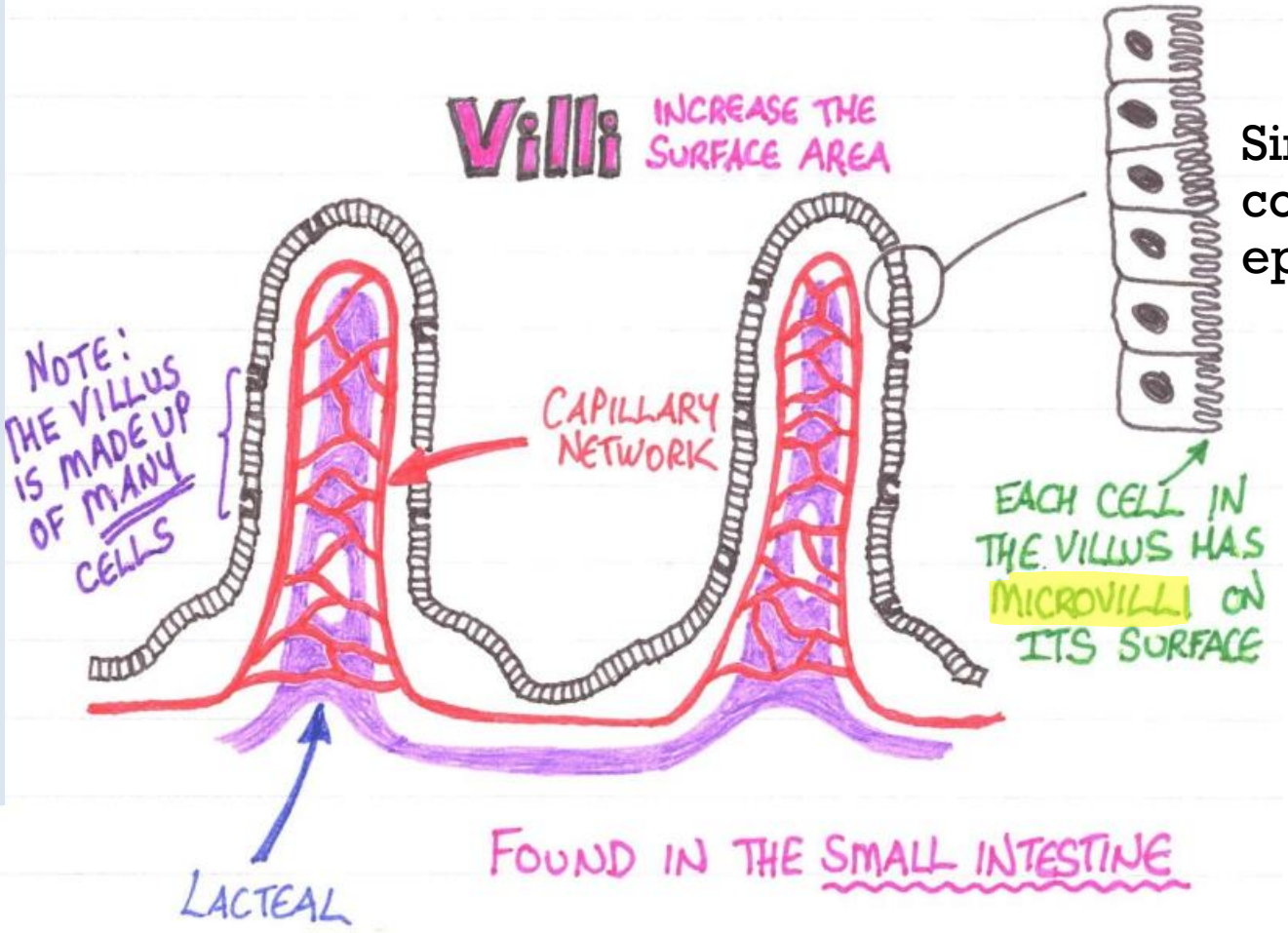
The 2nd function of LS –the first was filtering the fluid and bringing it back to the circulation-

Transport lipid

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**.

Finger like projections in small intestine to increase the surface area for absorption



Simple columnar epithelium

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.

B cells : originate and maturate in BM
T cells: originate from BM and maturate in Thymus.

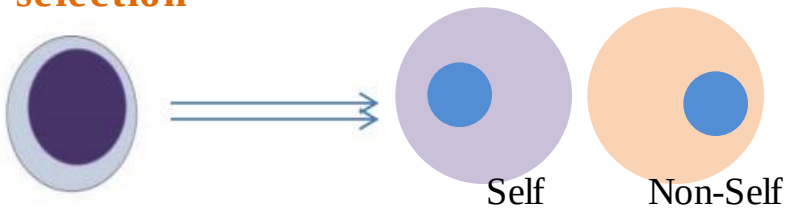
Lymphatic organs are divided into:

Primary lymphatic organs(central)

Bone marrow.

Thymus gland.

Are sites of Lymphocyte production, maturation, selection



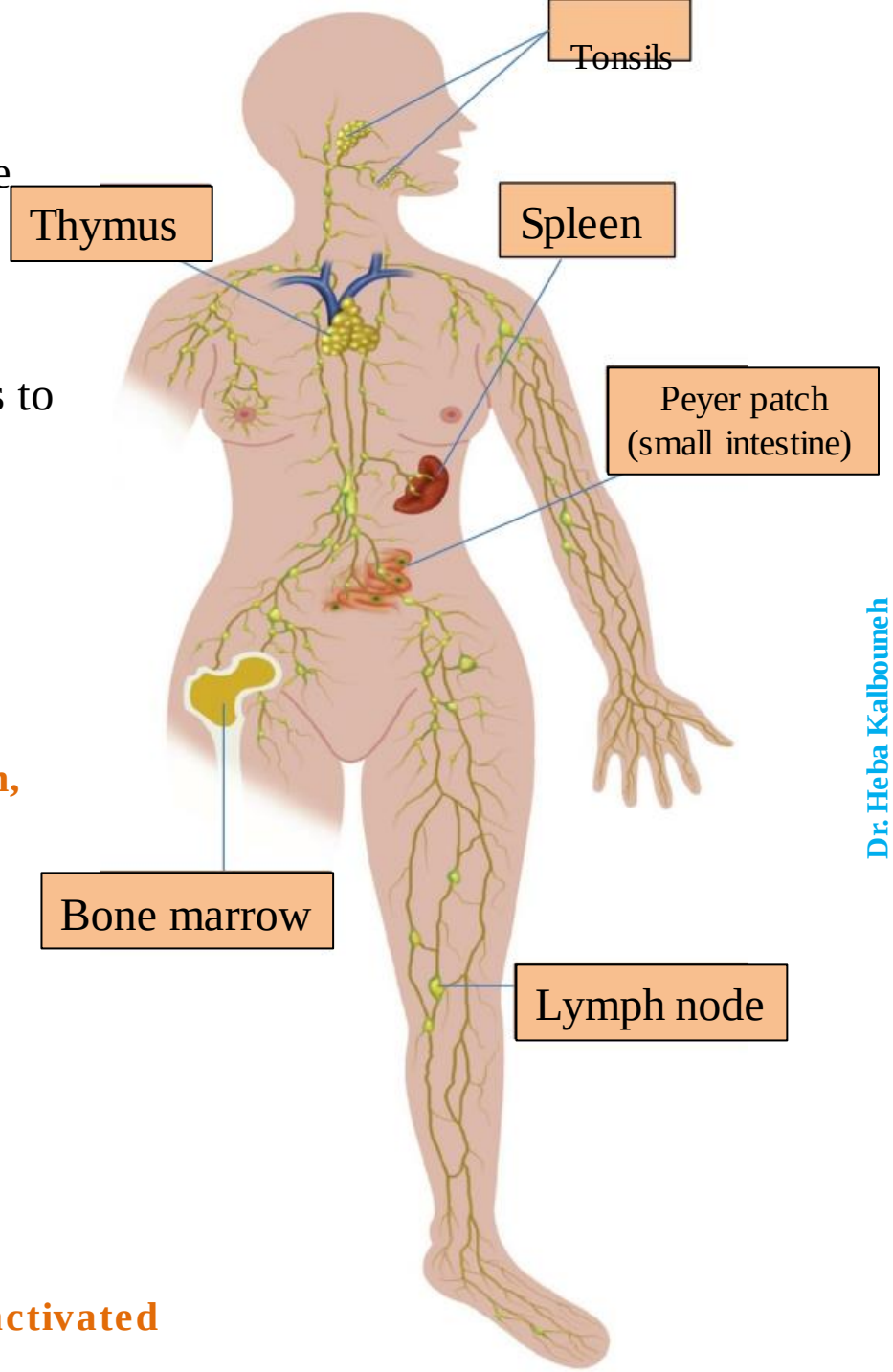
Secondary lymphatic organs(peripheral)

Diffuse lymphatic tissue (lymphatic nodules).

Spleen.

Lymph nodes.

Are sites to encounter pathogens and become activated



Cont..

What is "selection" that occurs in primary lymphoid organs ?

The process where lymphocytes learn to differentiate between self and non-self-antigens, before being released into the blood stream.

The lymphocytes that are selected to be released from the primary lymphoid organs in the blood stream are the immunocompetent mature cells, and if these cells are released from center organs and attack the body itself, this means that we have an autoimmune disease.

- These immunocompetent cells are produced in primary lymphatic organs and released in the blood stream, circulate inside blood and then settle down inside secondary lymphatic organs in order to search for their antigens.

Lymph nodes

Are kidney-shaped small encapsulated bodies located along the course of lymphatic vessels (Approximately 600 lymph nodes)

It has concave –hilum- and convex surfaces

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

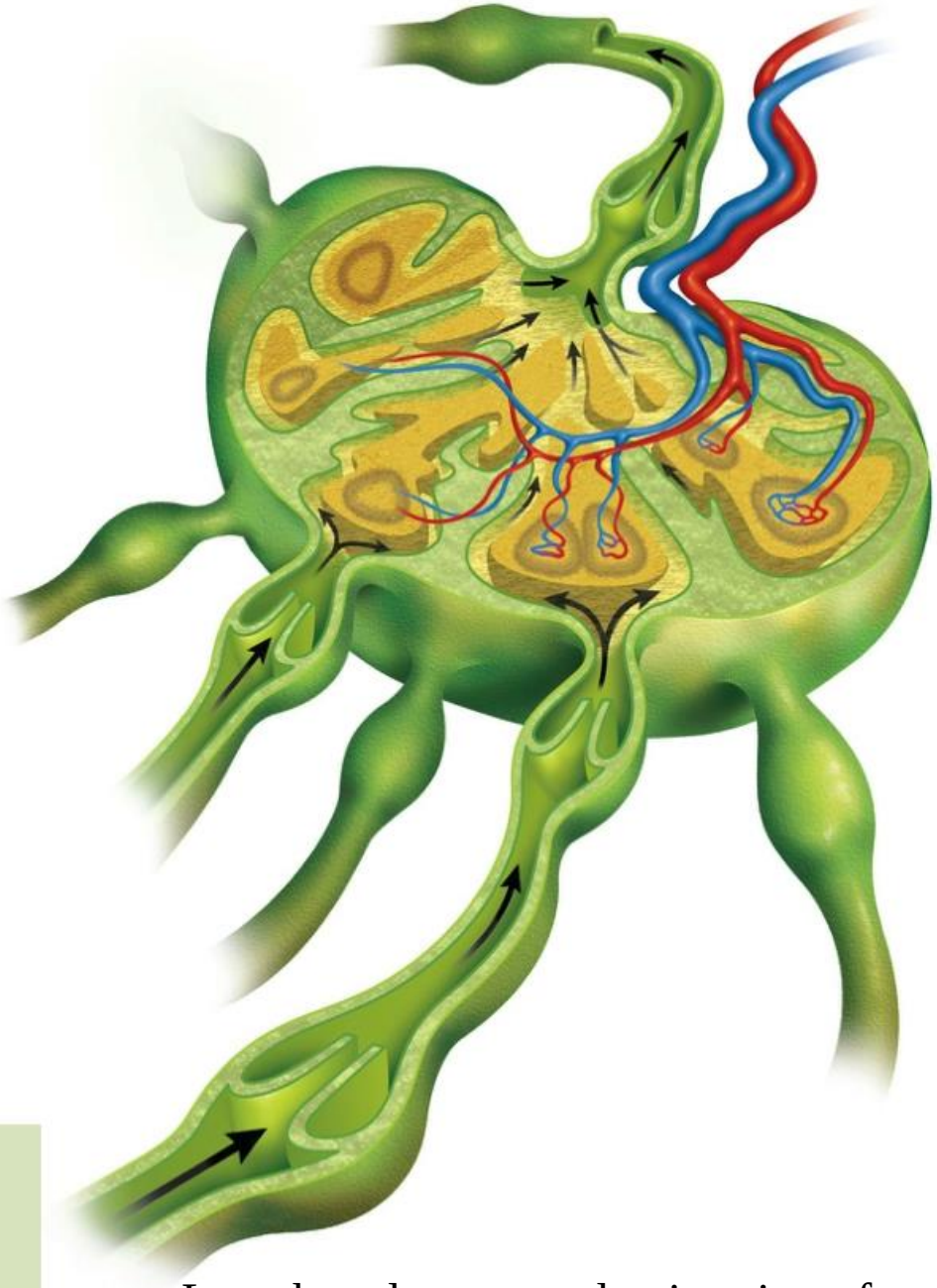
Nodes filter the lymph, removing foreign material and microorganisms.

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 lymphatic nodes are small in size, usually they form groups and a certain part of our body is drained by one or more lymph nodes

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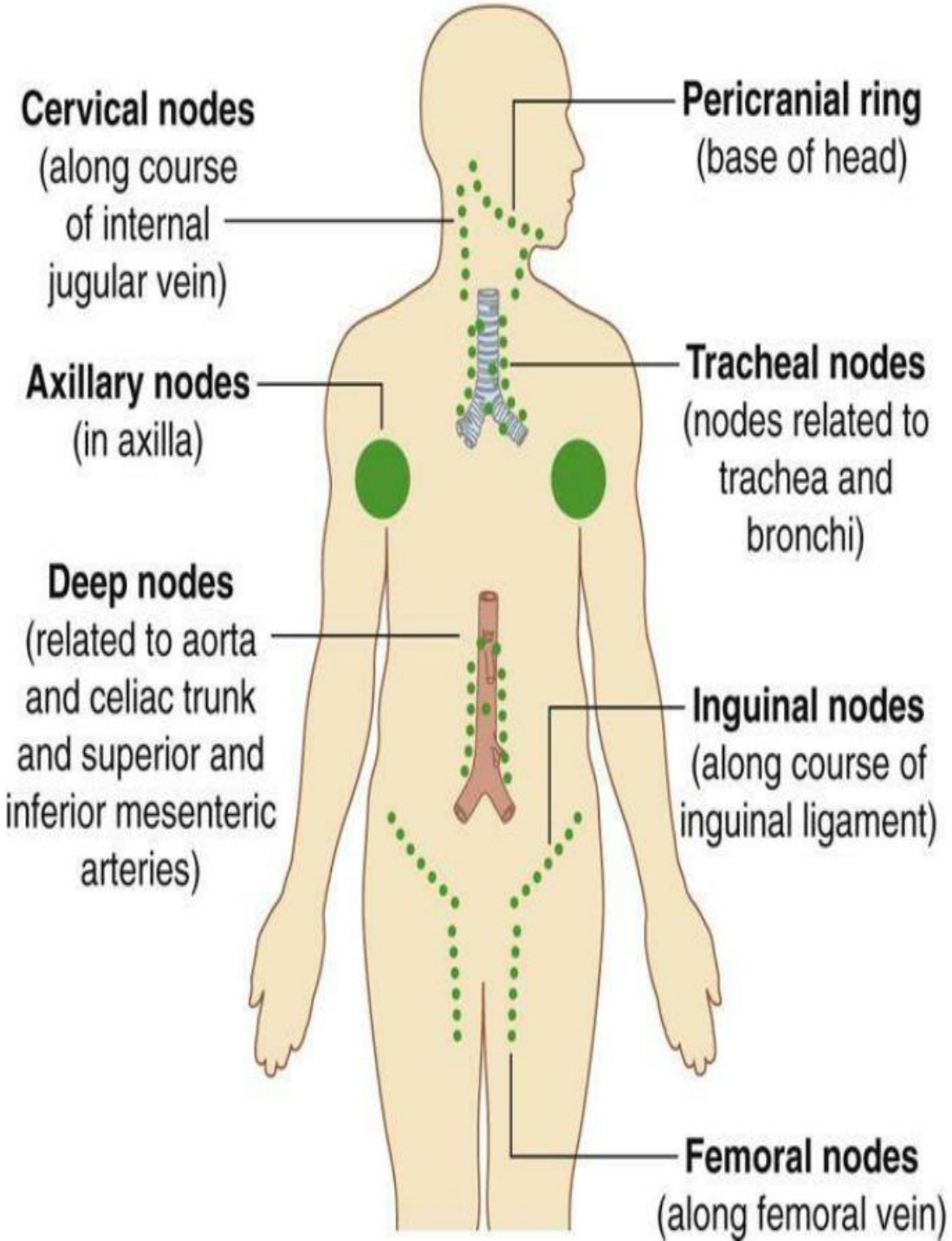
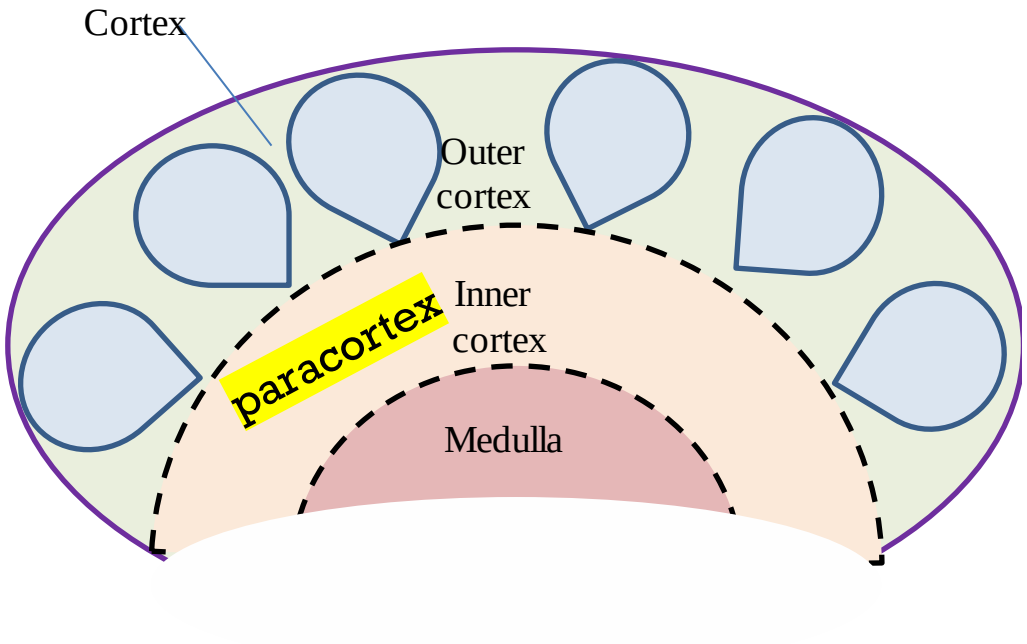
We name this lymph nodes according to their location or the blood vessels they run with

The main groups of lymph nodes include:

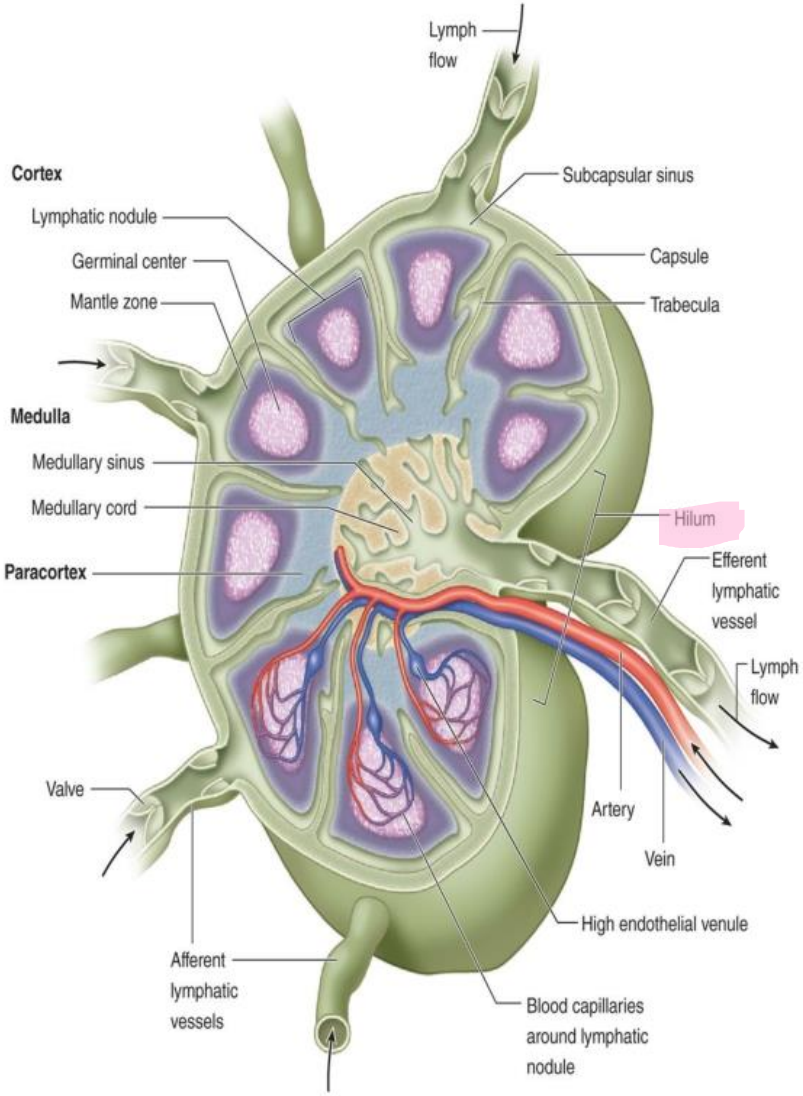
Name	Location	Associated vessel
Axillary nodes	Armpit	Axillary vein
Cubital nodes	Elbow	Basilic vein
Popliteal nodes	Posterior knee	Popliteal vein
Inguinal nodes (superficial and deep)	Groin	Great Saphenous vein Femoral vein
Cervical lymph nodes (superficial and deep)	Neck	Internal jugular vein External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



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



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



The hilum where the blood enter or leave the lymph node

-The efferent could be an afferent to another lymph node.

Afferent lymphatic vessels : many vessels that bring the lymph from the interstitial fluid

Efferent :In the hilum there are one or 2 lymphatic vessels carrying the lymph away from the lymph node

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NOTE: In the tissues, Afferent lymphatic vessels are formed for draining the lymph into a certain lymph node from its convex surface. Efferent lymph vessels originate from the lymph nodes carrying the lymph away from the lymph node with them, it could drain into the blood stream directly or into another lymph node (being an Afferent vessel itself.)

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 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.

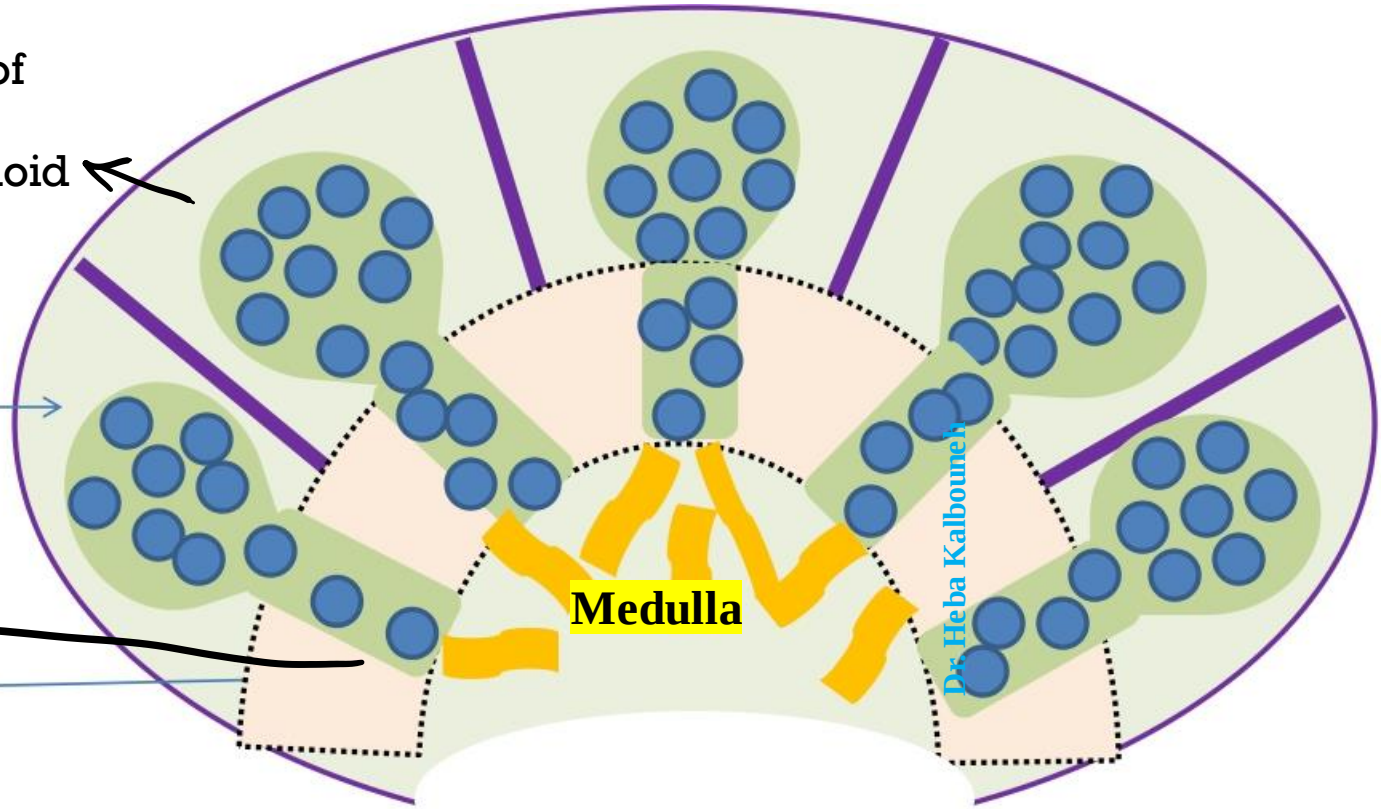
Masses of B cells In lymphoid follicles

Outer Cortex

Medulla

Paracortex

T cells forming Irregular columns of T cells in 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(they secrete antibodies directly in lymph ,then the lymph leaves through the effernet lymphatic vessels ,then to blood and reach every site of the body including the site of infection where antigen-antibody complex form and eliminated by macrophages).**

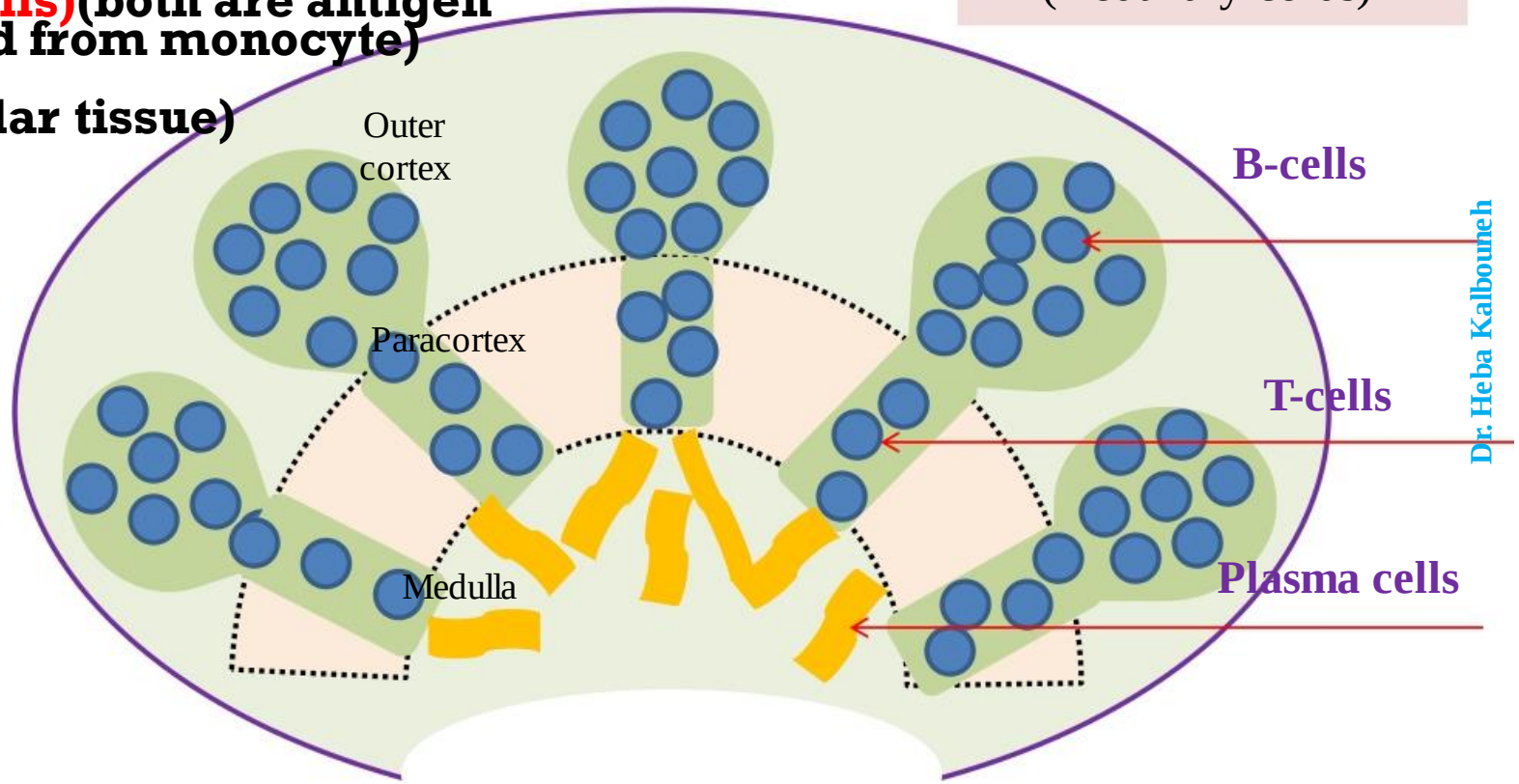
Other cells in the lymph node:
(Macrophages/Dendritic cells)(both are antigen presenting cells and derived from monocyte)
Follicular dendritic cells
Reticular cells(forms reticular tissue)

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)

Plasma cell

Periphral located nucleous with cartwheel or clock face apperance because of the dark heterochromatin



- Important note:

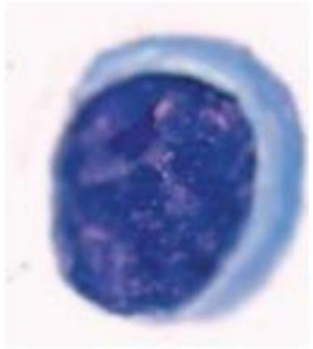
➢ If you take a section through a lymph node and you find that all lymphatic follicles in the outer cortex are secondary type of follicles with germinal centers ,you know that this patient has an infection ,especially bacterial infection because we fight them by producing antibodies.

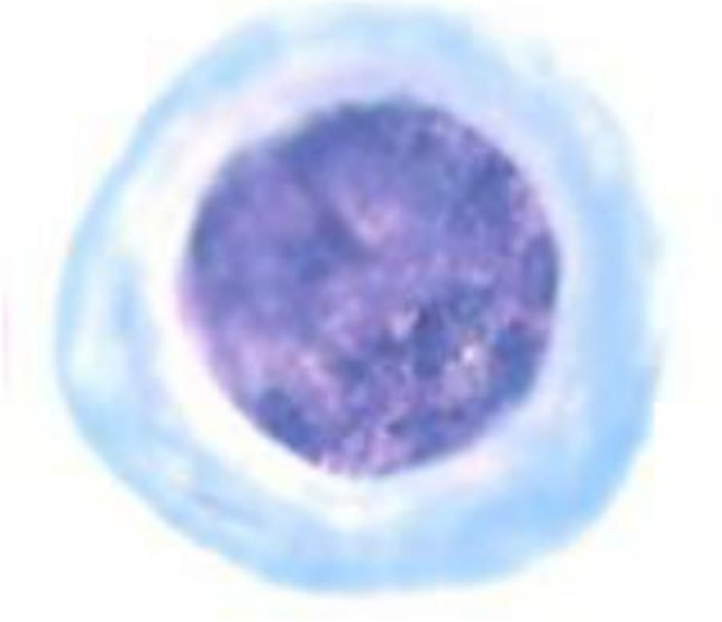
❑ What could be found inside the afferent lymph entering the lymph vessels??

We could find:

1-soluble antigen (fragments of antigens), remember when nutrophils finish their work, they exocytose these fragments that can pass through lymph to the lymph nodes.

2-intact antigen like: viruses,bacteria. Also, we could find antigen presenting cells(dendritic cells and macrophages)as well as cancer cells and viraly infected cells.





Small
(6-9 µm)
Inactive lymphocyte

Large
(9-18 µm)
Active lymphocyte

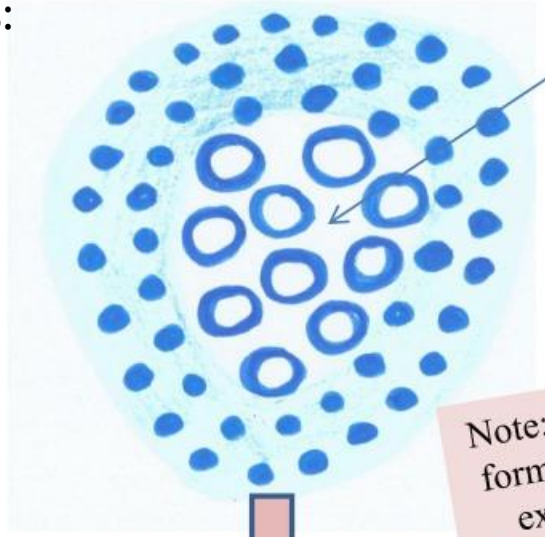
Darkly stained cell

Lightly stained cell

Aggregation of these cells under microscope appear like basophilic dots because of the heterochromatin nucleus and thin cytoplasm that lightly stained

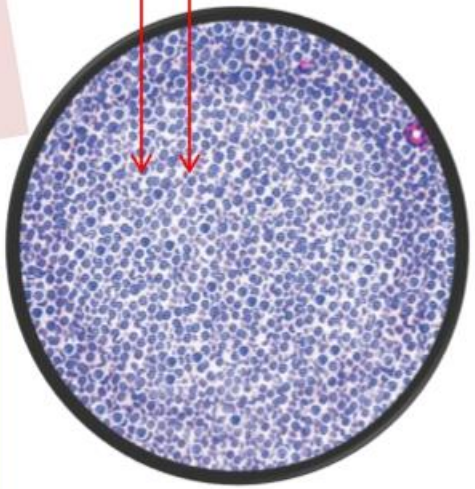
Because of the euchromatin nucleus so it lightly stained

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



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

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



Primary(inactive)follicles: lymphoid follicles without a germinal center (virgin B cells/before exposure to antigen)

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

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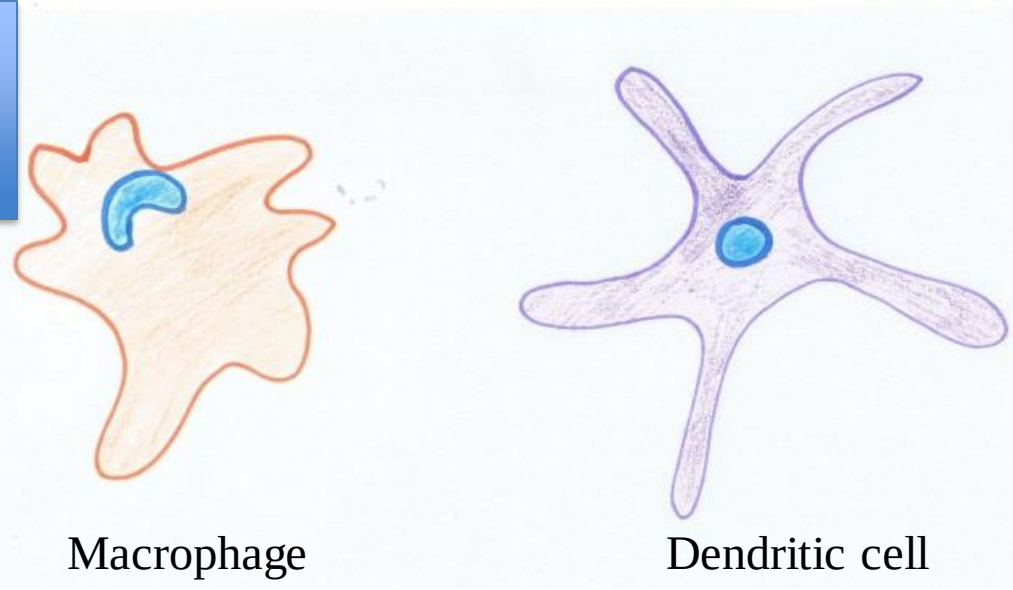
When virgin B cells (the small inactive cells that are mature, immunocompetent and able to produce immune response when exposed to an antigen) are activated by antigens (and T helper cells), B cells migrate to the center of the follicle, forming a germinal center. Germinal centers are the central regions 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

They can reach the lymph node either by blood or through lymph

FD cells have specific receptors for the antibody antigen complexes, after these complexes are eliminated by macrophages at the end of infection - complete clearance of antigen from the tissue-, FD cells keep **holding** the complexes and offering them to B cells inside the outer cortex **for long time** and this is important to keep our immune system in a semi stimulated state tuned up for the next infection



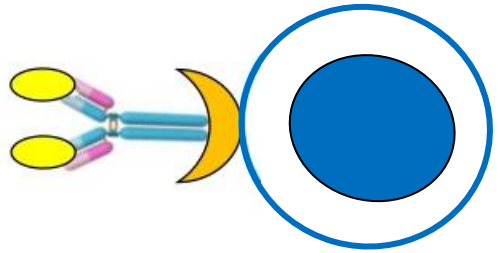
Macrophage

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

They are only located in the outer cortex and cannot p hagocyte the antigen and present it



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

- Further explanation:
- Dendritic cells and macrophages are present in the lymph nodes by one of the following processes:

1- During the development of lymph nodes and spleen, some of the monocytes leave the blood stream and enter the spleen or the lymph node and become resident within the lymph node and we call these monocytes derived cells "dendritic cells"(most powerful cells in antigen presentation)

Monocytes also leave the blood to lymph nodes to differentiate into macrophages (the big eaters)

2- through afferent lymphatic vessels which bring lymph from interstitial fluid to the lymph nodes.

Inside the epidermis of the skin, there are monocyte-derived cells that are dendritic in shape called Langerhans cells(dendritic cells), which means that these cells are more powerful in antigen presentation. So, if we have an infection inside the skin, these cells will present the antigen of the infectious agent on a special molecule called MHC-II, then it will drain through the afferent vessels to the nearest lymphatic vessel.

Inside the dermis, we have macrophages that are going to present the antigens of the infectious agent and drain into lymph nodes through afferent vessels.

➢ Important note:

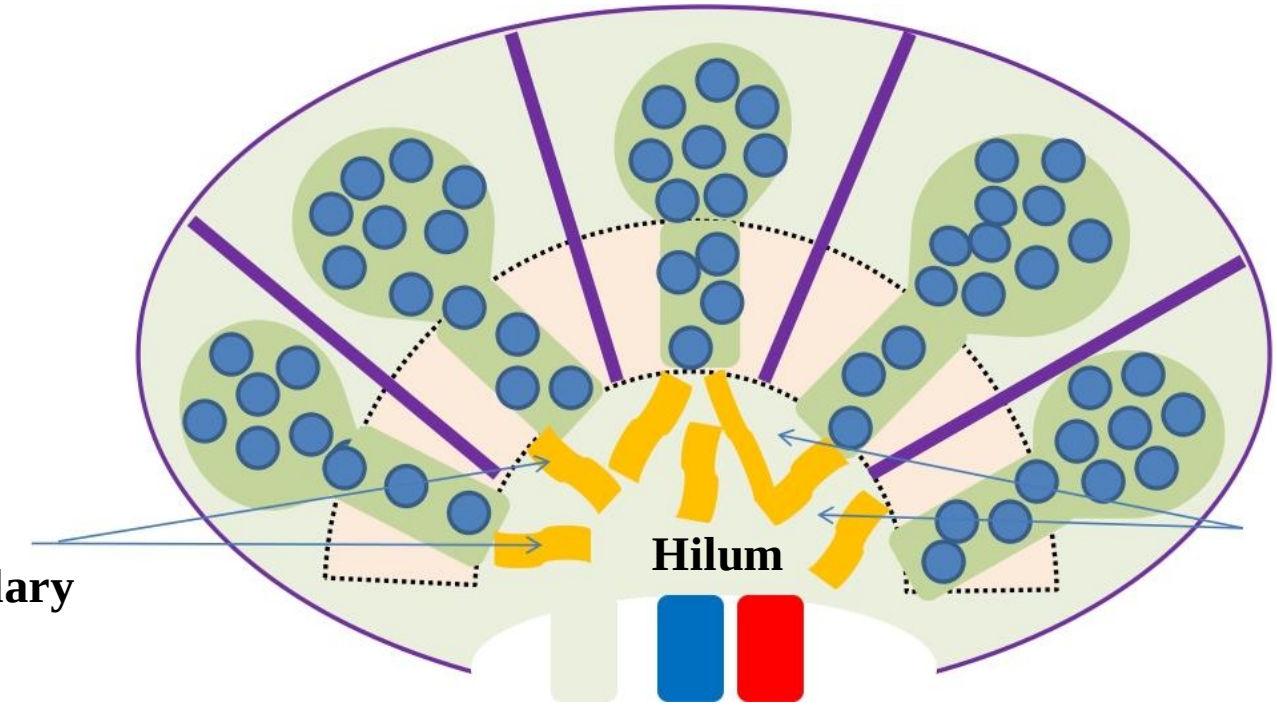
Dendritic cells can have a specific name and a general name, specific for the resident dendritic cells inside the lymph nodes that are derived from monocytes. And a general name for monocyte-derived cells in different tissues.

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.



Medullary cords

Medullary sinuses

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(cortical) sinuses

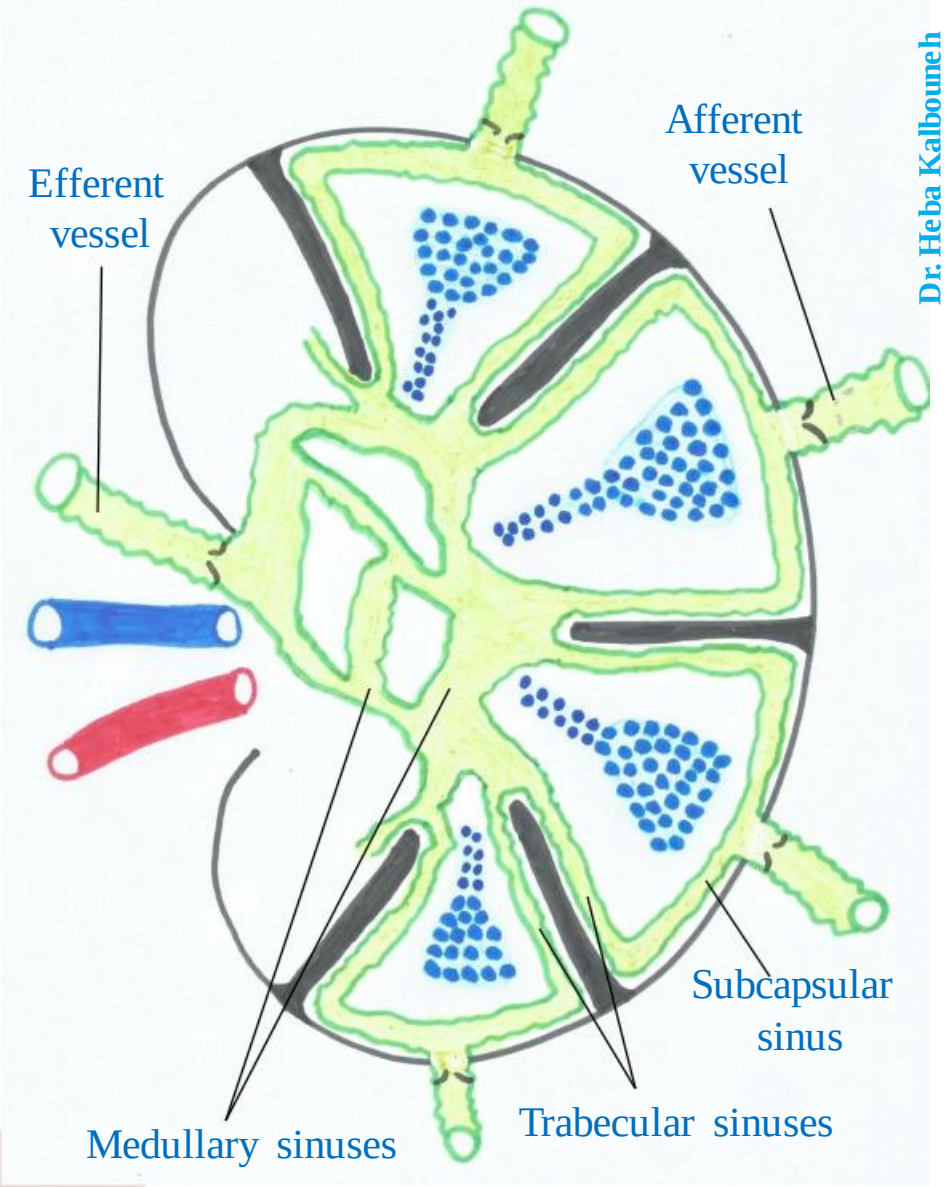
The trabecular sinuses are a continuation of the subcapsular sinuses that follow the trabeculae and drain into the medullary sinuses.

Medullary sinuses

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

Efferent vessels

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



Sinuses are irregular spaces through which the lymph percolates

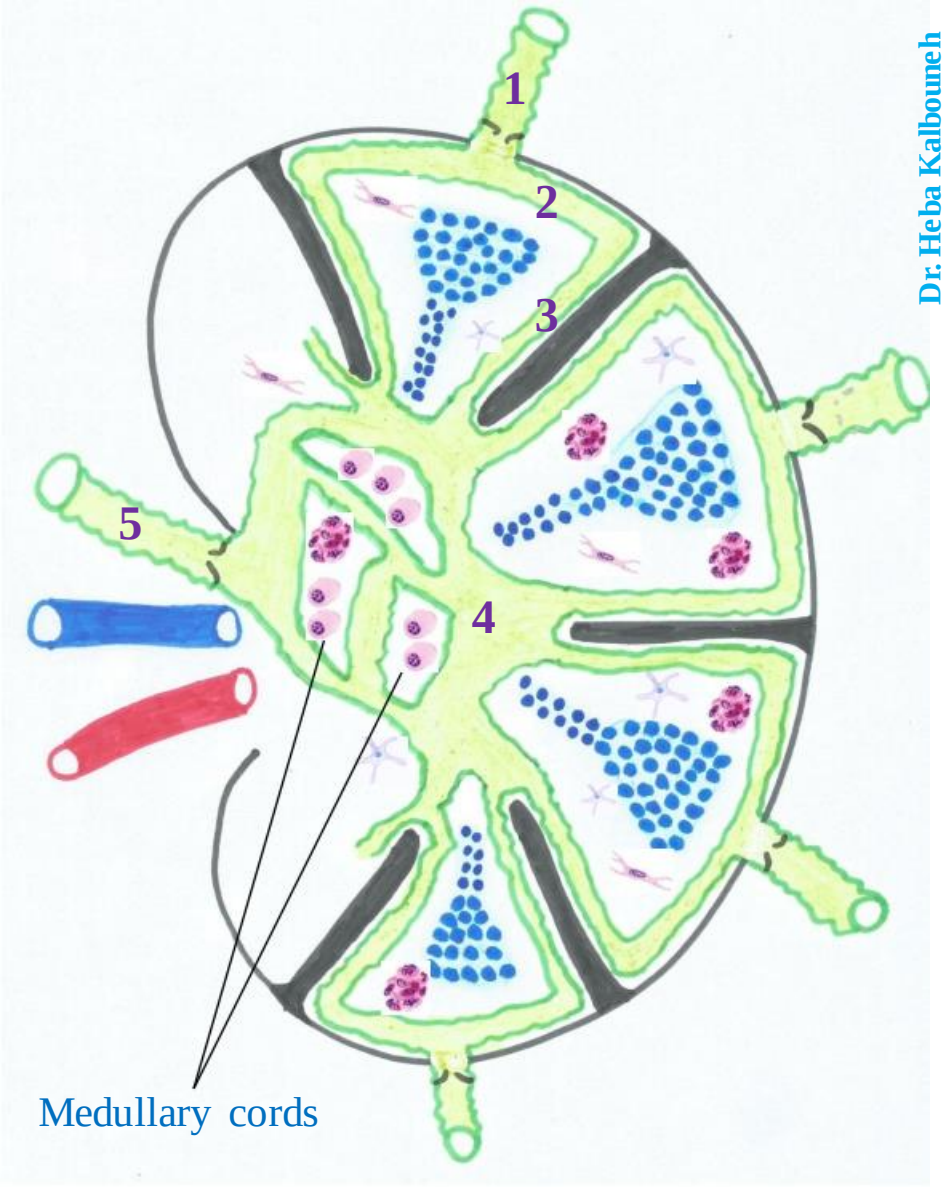
Lymph flow

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

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

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

Lymph slows down when it passes in lymph nodes.



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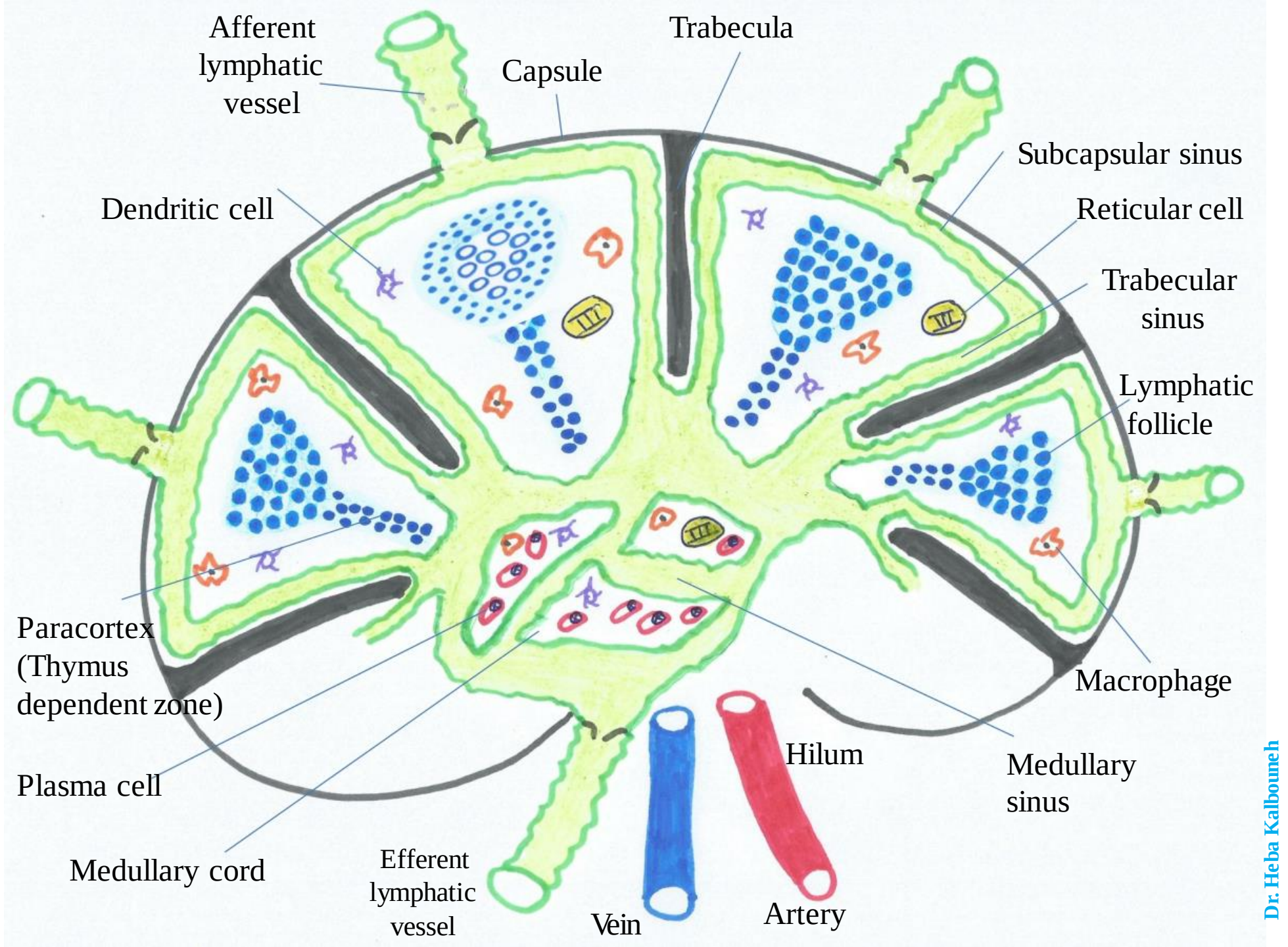
All the **lymphatic sinuses** are lined by a discontinuous layer of simple squamous endothelium

This picture is very important



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- # Further explanation of the previous slide:

1- Capsule: dense type of connective tissue, this structure sends septa called trabeculae.

2- Trabeculae: divide the lymph node into smaller compartments.

Trabeculae support the lymph nodes. Also, these are the places where blood vessels run inside the lymph nodes.

3- Afferent lymphatic vessels: present along the convex surface of the node.

4- Efferent lymphatic vessels and blood vessels: present on the concave surface of the node (hilum).

Note that efferent vessels can be an afferent vessels for another lymph nodes.

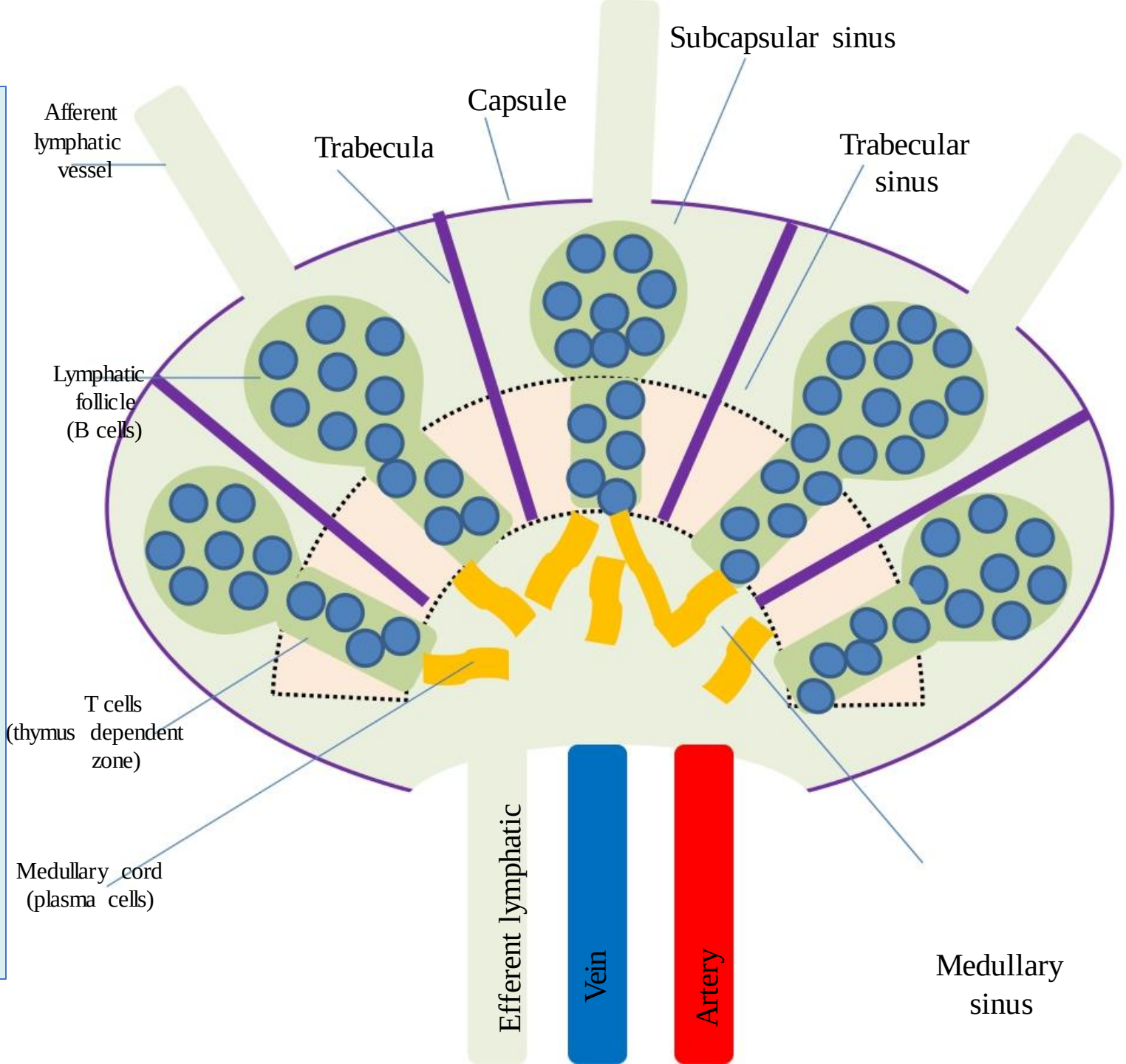
5- Inside the lymph node we have irregular spaces filled with lymph and lined with endothelium (which is discontinous) called lymphatic sinuses.

6- In the area of the paracortex, we have irregular aggregation of T lymphocytes. This area is called (Thymus dependent) because the presence of this area depends on the development of thymus.

Remember: thymus originates from third and fourth pharyngeal pouches along with parathyroid gland, so if there is a defect in the formation of the thymus, we can't find this zone under microscope, because the presence of mature T lymphocytes depends on the presence of the thymus. So, this patinet can't handle viral infections as well as intracellular microbes such as parasites and certain types of bacteria because there is a defect in the cell mediated immunity.

7- At the entry and exit points of the lymphatic vessels, we have valves. These valves slow the flow of the lymph to the node so the immune cells can act on the current lymph.

1. **The plasma (activated) cells** themselves can enter the lymph then to the blood to flow with it and reach every part of the body and produce Antibodies directly inside the site of infection
2. Production of activated **T cells** that leave lymph node through the efferent lymph and enter the blood to reach every part in our body including the site of infection



3. After the activation of **B cells**, they will become plasma cells that move to reside in the medullary cords and start producing antibodies into lymph that leaves lymph node through efferent lymphatic vessels that reache the blood and while circulating inside the blood, antibodies reach every part in our body including the site of infection to form antibody-antigen complexes

- ## Further explanation of the previous slide:

Lymphocytes enter the lymph node through the arterial supply of the node, then the artery divides into smaller arterioles and forms a capillary bed in the area of the outer cortex then venules will be formed .postcapillary venules located in the paracortex. Lymphocytes leaves these venules and enter the paracortex region.

If we are talking about T lymphocytes, they will stay in the paracortex region while B lymphocytes migrates to the outer cortex. this way represents the main way where lymphocytes leave the blood to the lymph node.

The other way of circulation is through the lymph. after the lymphocytes spend a period in the lymph node, they will leave it through an efferent lymphatic vessel which could be an afferent vessel for the next lymph node.

The concept that lymphocytes keep moving between blood and lymph nodes is called lymphocytes circulation.

Mature Lymphocytes keep moving between lymphoid tissues and lymph nodes in order to find their antigens, because we only have a specific number of mature lymphocytes that are specific to their antigens

- The concept of lymphocytes recirculation also applies to memory cells.

Lymphocytes can enter lymphoid tissues in two ways:

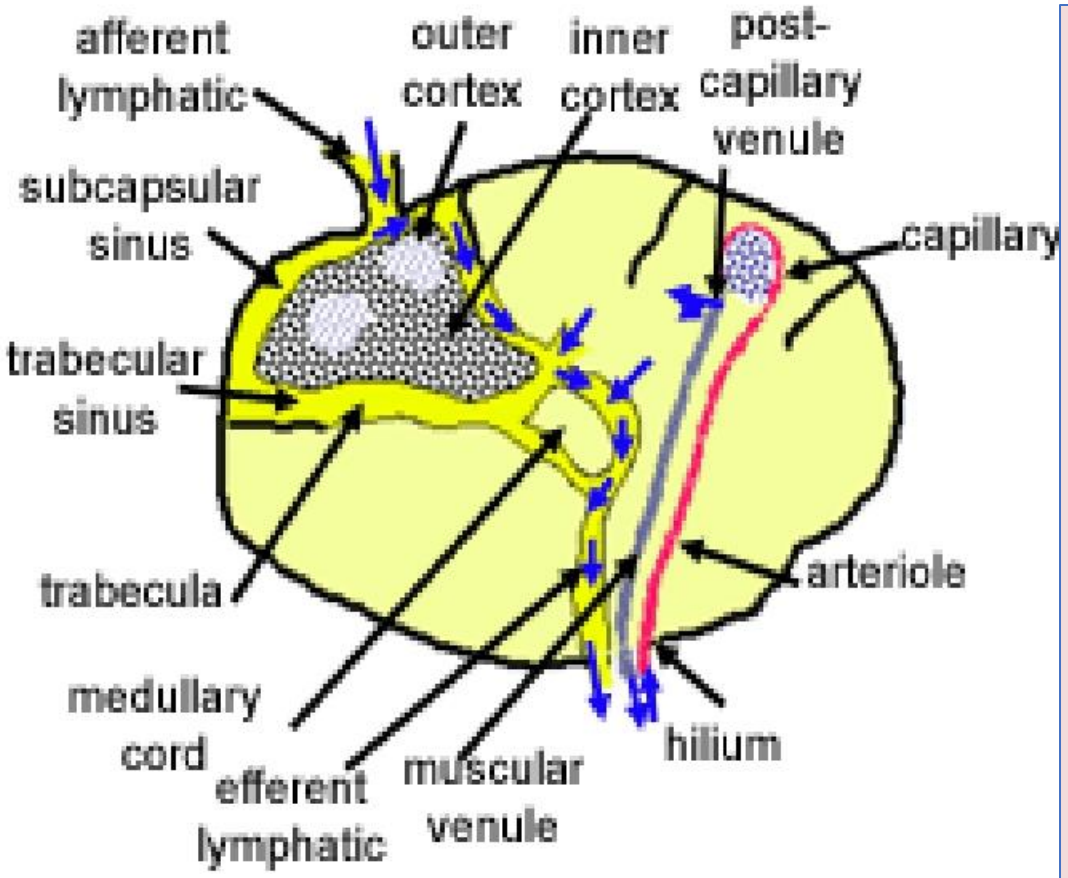
1) Direct entry into lymph nodes via afferent lymphatics

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

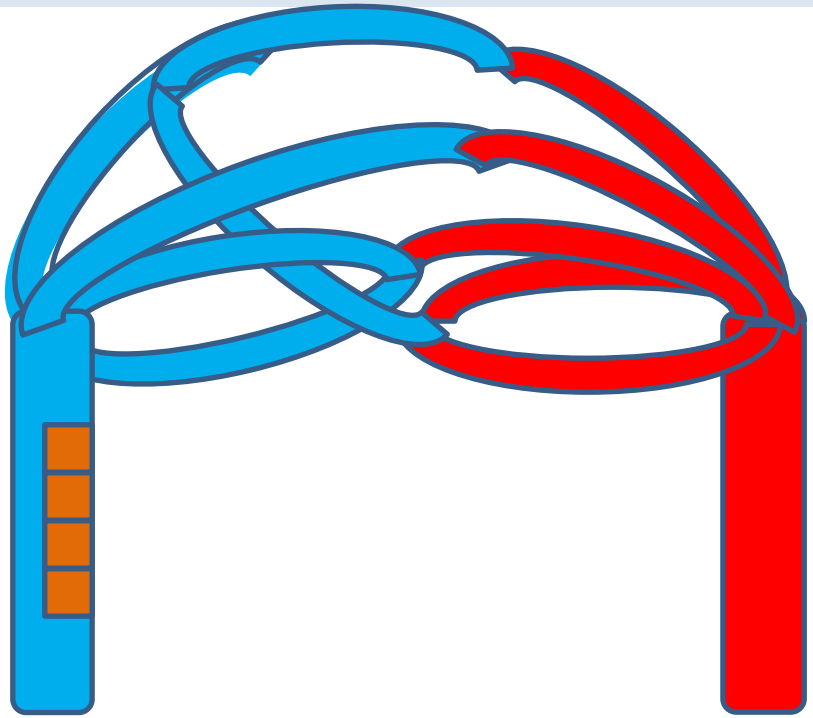
The process of lymphocyte recirculation is regulated by adhesion molecules on lymphocytes called **Homing receptors** and their ligands on vascular endothelial cells called **Adressins**



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

Mature B cells are released from BM into the blood, and the mature T cells are released from the thymus into the blood stream and circulate inside the blood to populate inside the lymph nodes (B cells in outer cortex and T cells in inner cortex)

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



Post capillary Venule (High Endothelial venule (HEV))

Arteriole

We have an artery at the hilum of lymph node supplying the lymph node with oxygenated blood and nutrients, this artery is divided into smaller branches into arterioles that branch to form a capillary bed which has arterial and venous sides. At the venous side, venules will be formed. The venule which located directly after the capillary bed is called **post capillary venule.**

When lymphocytes (that have homing-in receptors) pass through the arteriole to the capillary bed and to the post capillary venule, they bind to the ligands that on apical surfaces of endothelial cells of post capillary venule, this stimulates their migration from the blood into lymph node (this area of the post capillary venule in located in the inner cortex), so T cells stay in the inner cortex while B cells migrate to the outer cortex in order to form lymphoid follicles

The lining epithelium of blood vessels is simple squamous epithelial cells except in POST CAPILLARY VENULE, the lining epithelium is simple cuboidal epithelium and that's why we can call it high endothelial venule - it has high endothelial cells instead of simple squamous epithelial cells-

Dr. Heba Kalbouneh

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)

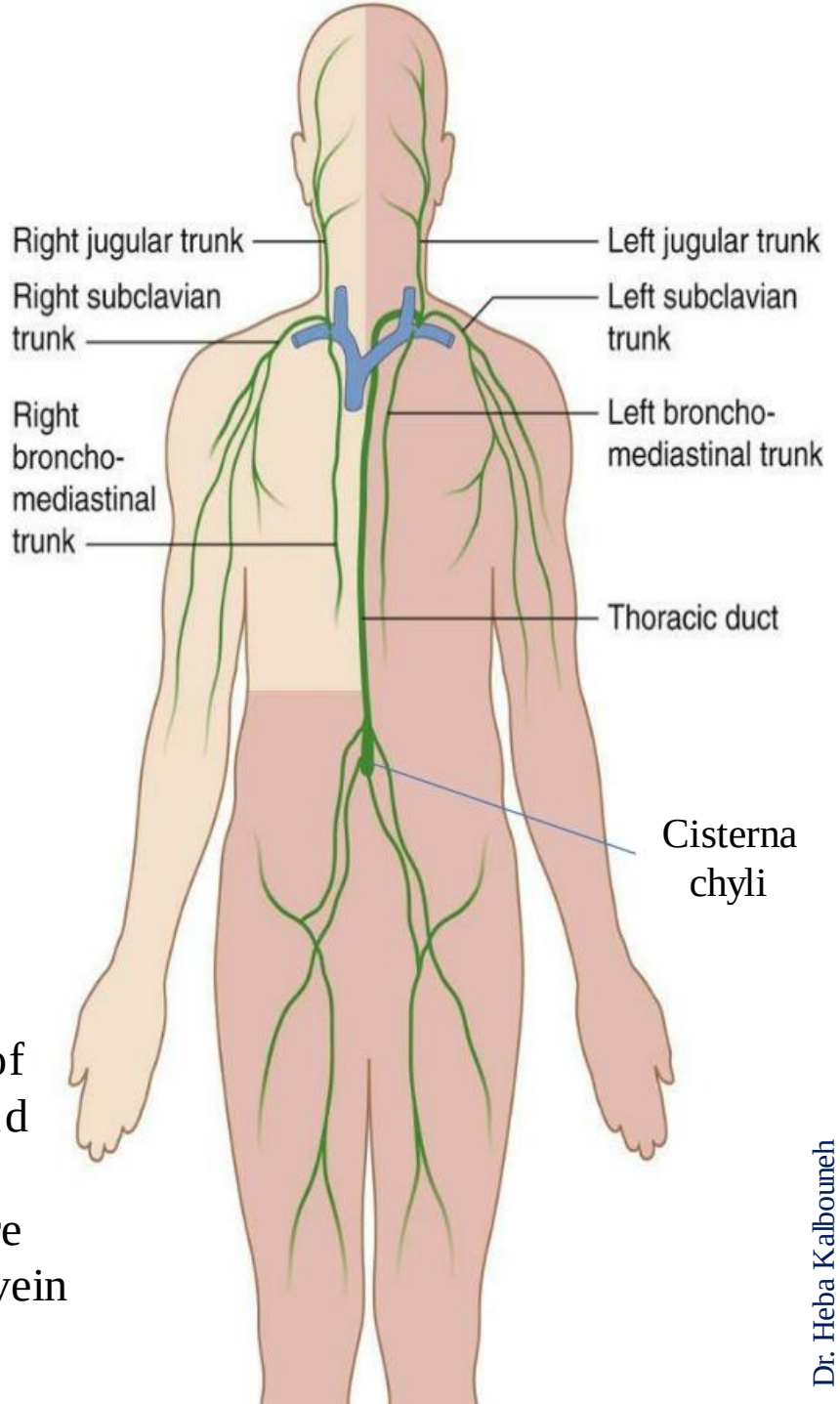
Is larger and drains lymph from the rest of the body.

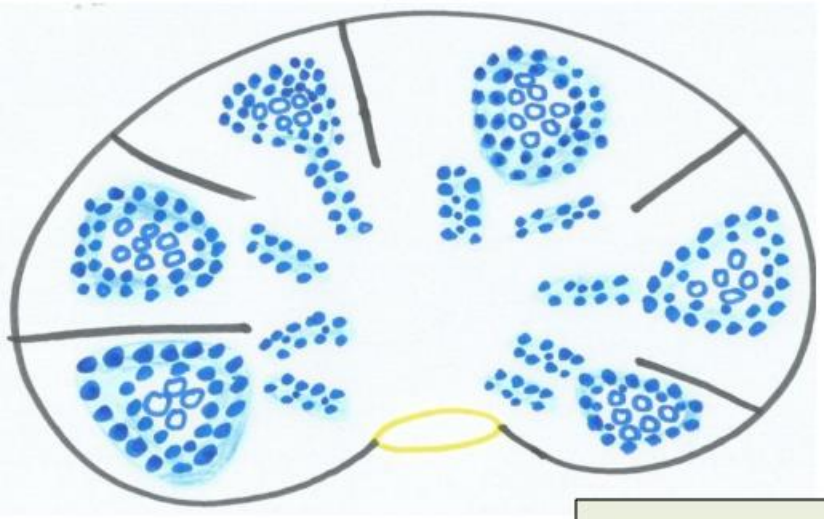
Originates in the abdomen as cisterna chyli

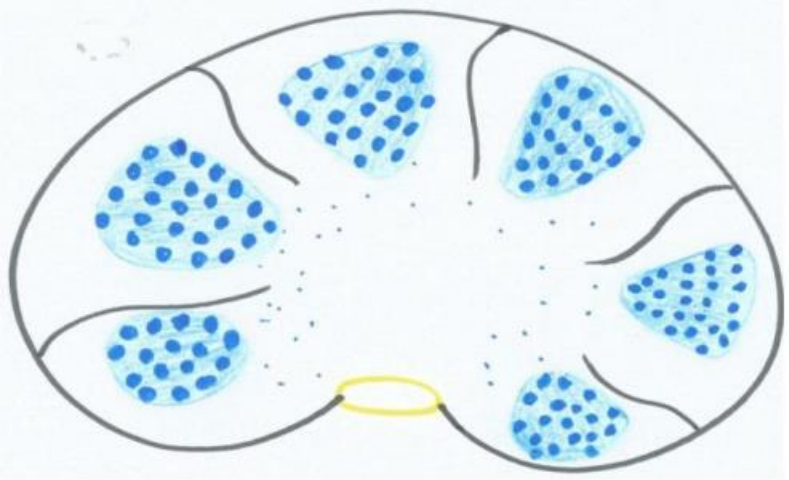
Cisterna chyli is a dilated sac at the lower end of the thoracic duct (anterior to the bodies of L1 and L2)formed by confluence of the right and left lumbar trunks and the intestinal trunk

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)







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