Histology - HLS

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Lymphatic System

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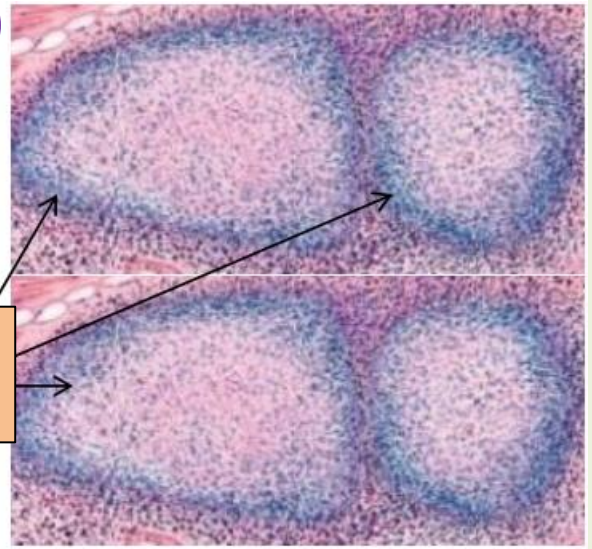
Diffuse lymphatic tissue (lymphatic nodules)

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

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



Mucus membrane: the lining of a cavity inside our body that has a connection to the outer environment . It is a layer of epithelial cells, resting on loose type of connective tissue called Lamina Propria. Inside the mucosa (lamina propria), and sometimes it can extend into the submucosa, we have aggregations of lymphatic tissue. These aggregations are lymphatic follicles/nodules, mainly formed by B cells surrounded by diffuse number of immune cells (T cells, APCs, Macrophages, Dendritic cells, plasma cells) and we call it diffuse lymphatic tissue because it does NOT form an organ.

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)

MALT is located along the whole length of the Digestive system. It starts from the pharynx and ending in the rectum, but its more concentrated in certain areas so we decided to give these areas specific names. e.x, the tonsils (masses of lymphatic tissue that are so prominent). Generally, we use MALT to refer to the diffuse lymphatic tissue but to be more specific we use GALT for the GI tract & BALT for Respiratory tract

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

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

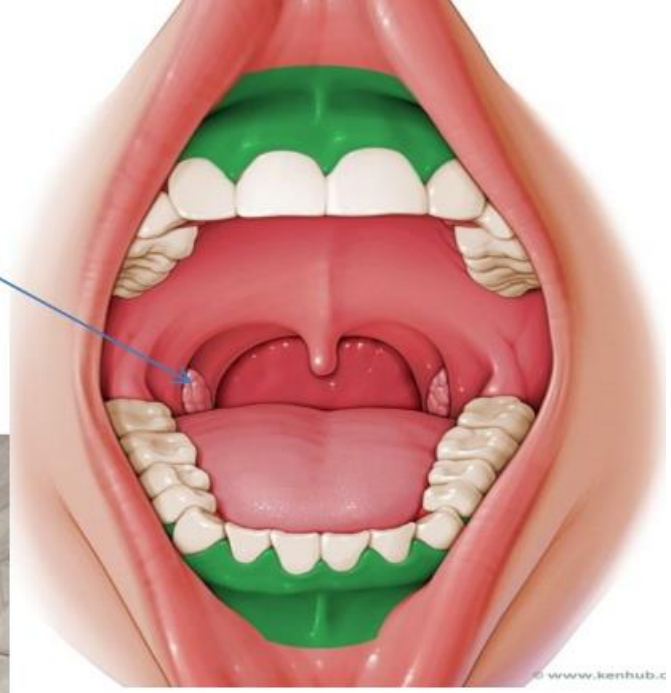
Because lymphocytes have prominent basophilic nuclei and very little cytoplasm, lymphoid tissue packed with such cells usually stains **dark blue** in H&E stained sections

Tonsils are large, irregular masses of lymphoid tissue

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

Palatine tonsils

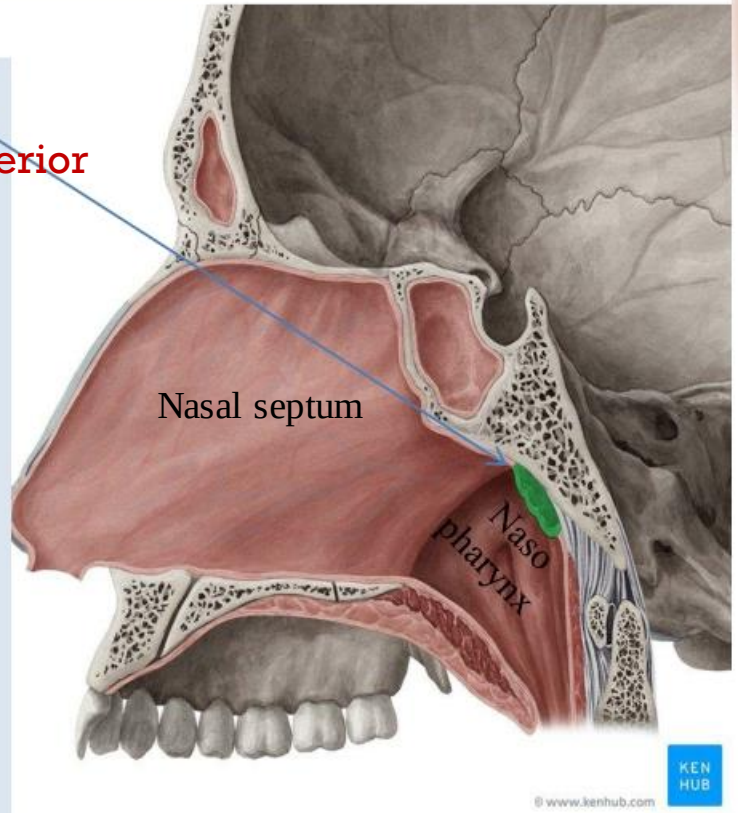
Are located at the lateral wall of oropharynx, between the glossopalatine and pharyngopalatine arches (two masses) Acuteinflammationofthesetonsilscausestonsillitis.

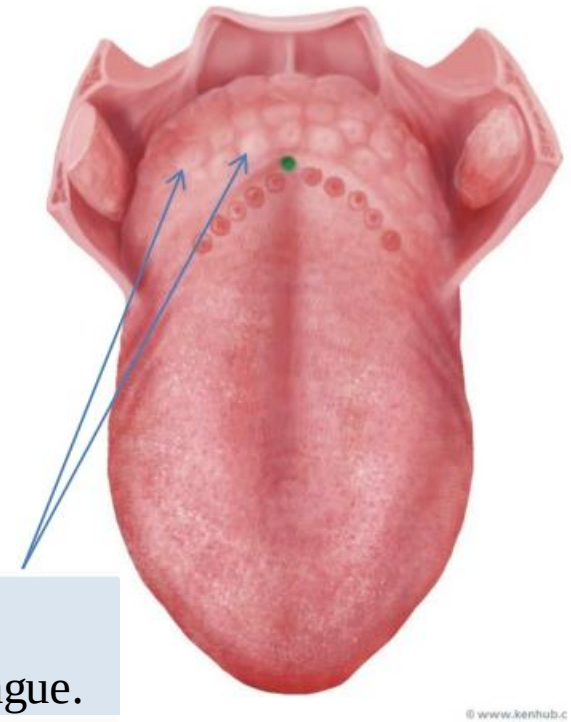


At (posterior aspect of oral cavity).

Pharyngeal tonsils

Are located in the superior & posterior wall of the nasopharynx. Itismostprominentin children,butbeginsto atrophyfromthe ageofseven. Hypertrophiedregionsof pharyngealtonsils resultingfromchronic inflammationarecalled **adenoids**.

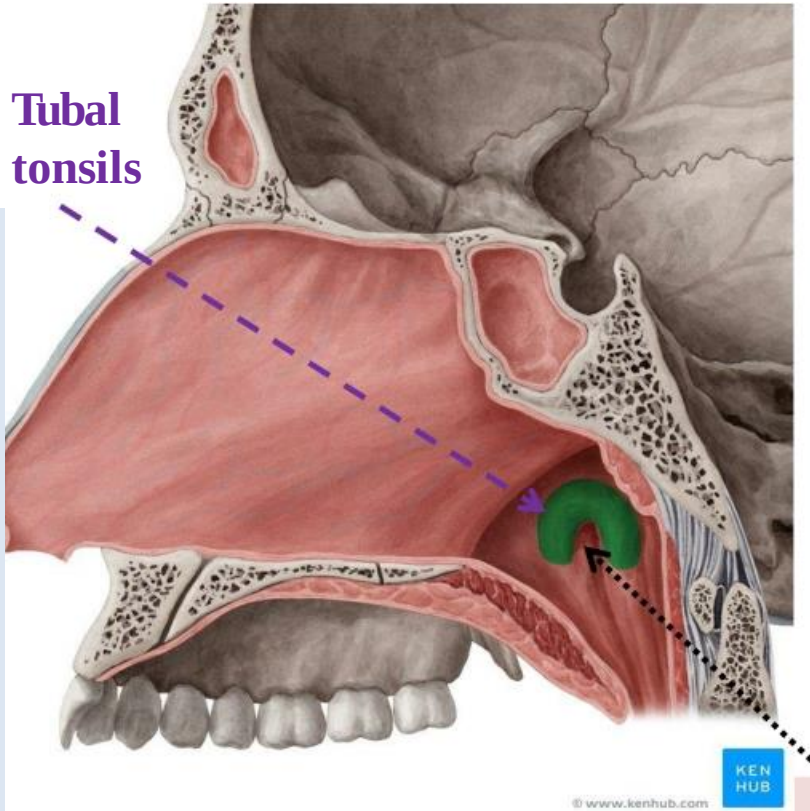


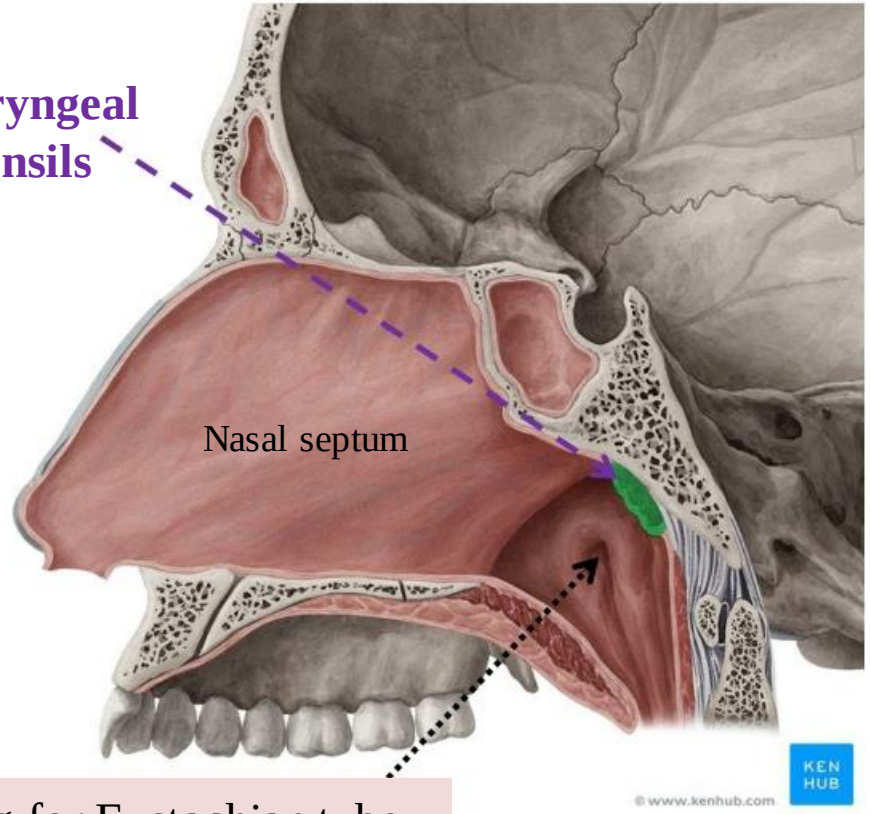


Lingual tonsils

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

On the lateral side, we have the opening for Eustachian tube. Around this opening, we have tubal tonsils (aggregation of lymphatic tissue) which are considered part of pharyngeal tonsils so they can cause middle ear infection (Otitis Media)





Opening for Eustachian tube

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

Adenoids

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

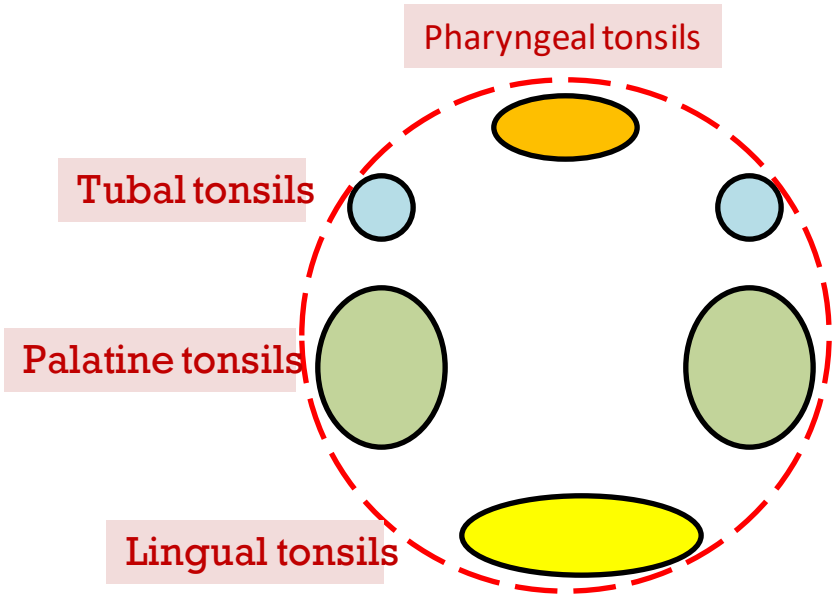
Waldeyer's tonsillar ring

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

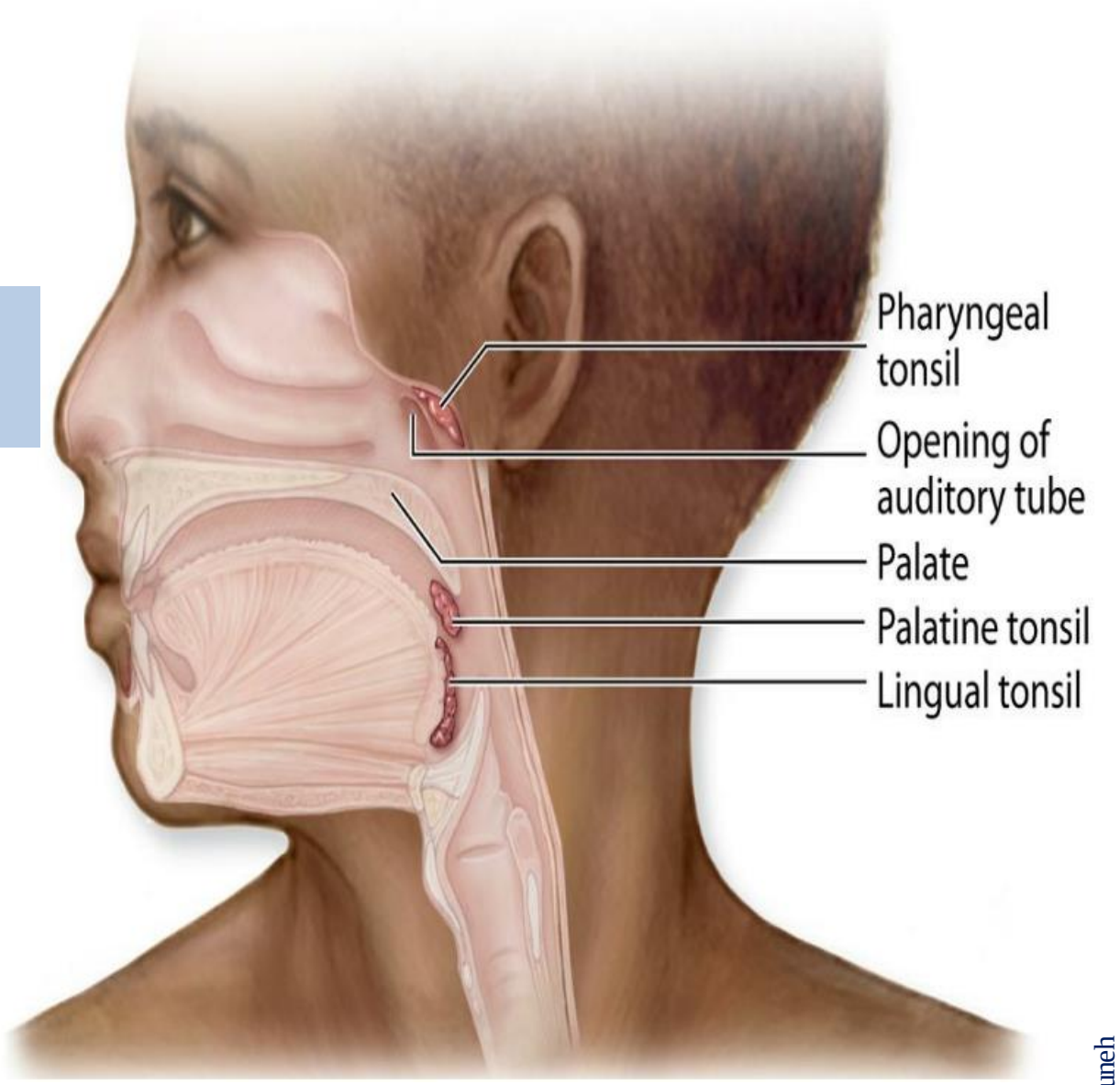
Ring of tonsils acting as a first barrier for inhaled and ingested antigens

At the beginning of the digestive tract & respiratory tract

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



Anterior view



Palatine tonsils

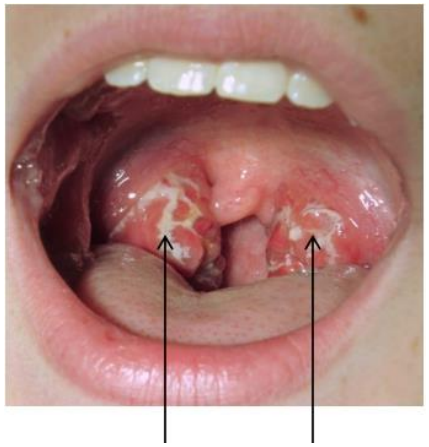
Are covered by stratified squamous epithelium.

The surface area of each is enlarged with 10-20 tonsillar crypts (deep invaginations)

Many lymphoid nodules around the crypts Germial centers surrounded by immune cell

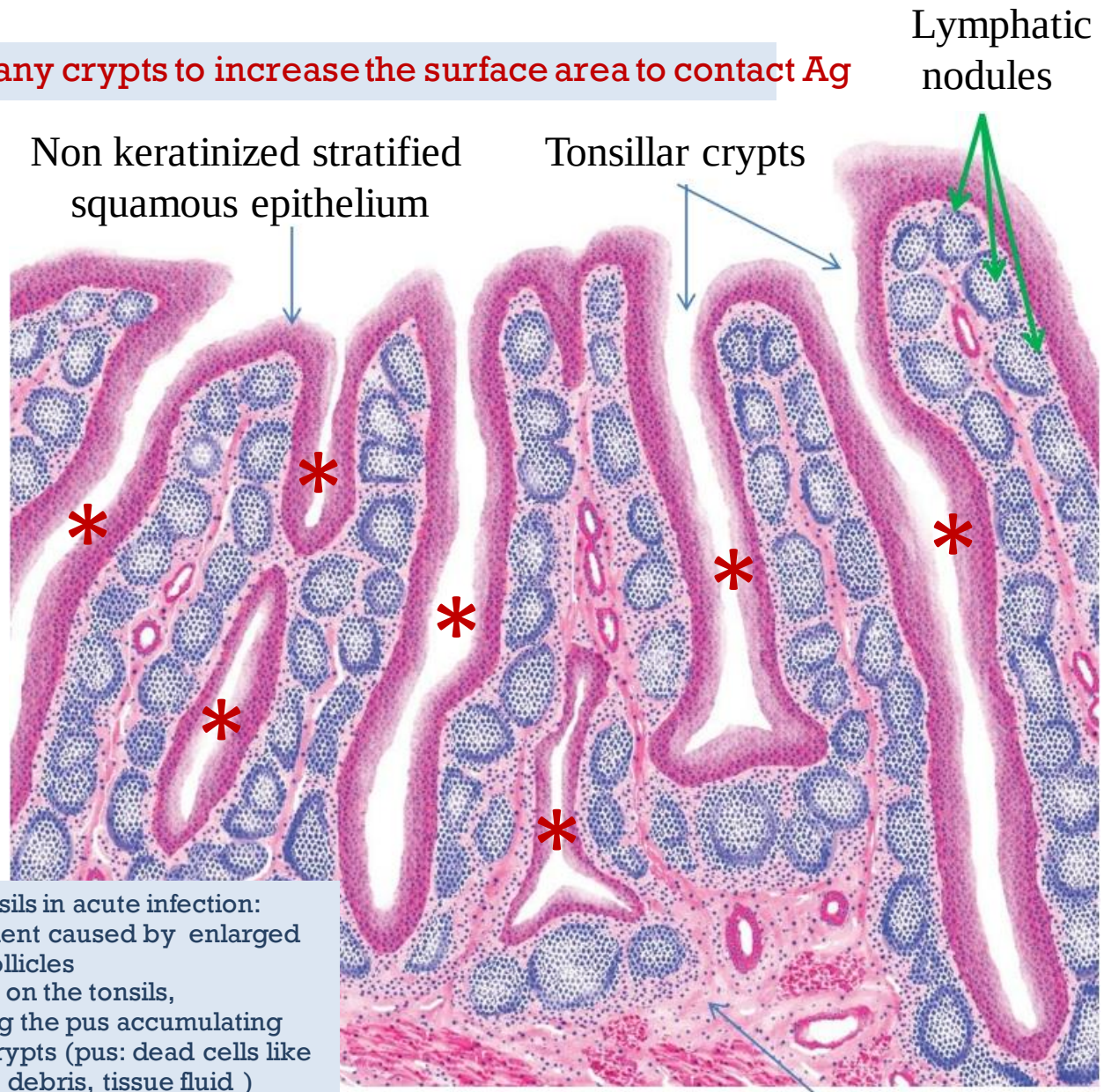
Has an underlying capsule (partial capsule)

MALT is not encapsulated and so it is not an organ. But in here, under these crypts, we have capsule so we consider the palatine tonsils PARTIALLY CAPSULATED.



Pus in tonsillar crypts

Many crypts to increase the surface area to contact Ag



Palatine tonsils in acute infection:
A)Enlargement caused by enlarged lymphatic follicles
white spots on the tonsils, representing the pus accumulating inside the crypts (pus: dead cells like neutrophils, debris, tissue fluid)
C) these tonsils are drained by Jugulodigastric lymph node so we have to check for enlargement in these lymph nodes in case of tonsillitis

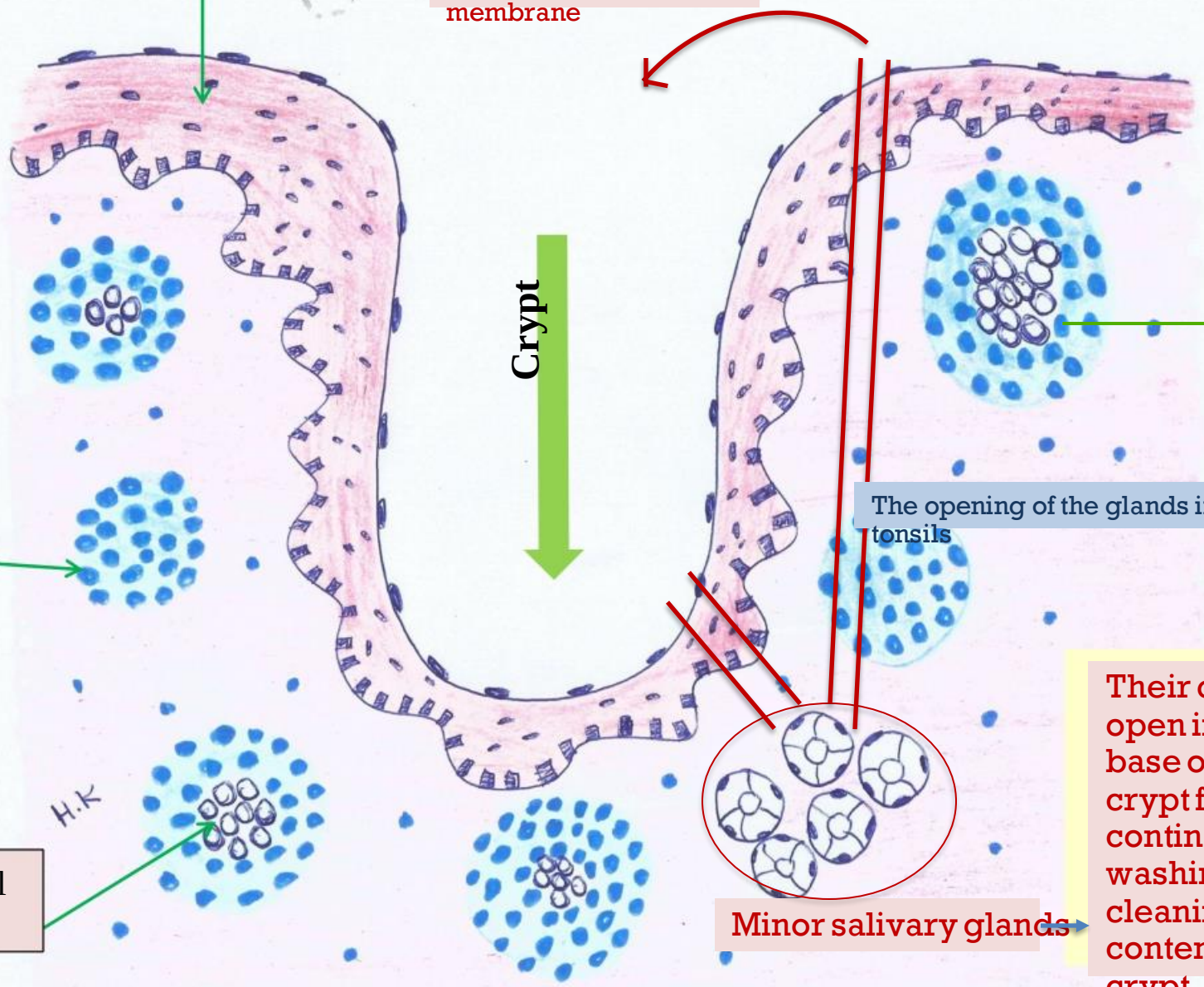
Palatine tonsils

Dr. Heba Kalbouneh

Palatine tonsils

Stratified non-keratinized squamous epithelium

(It is a wet surface so no need for keratin)
It rests on Lamina Propria and together, it is called mucous membrane



Stratified non-keratinized squamous epithelium invaginate, forming a CRYPT to increase the surface area which is surrounded by lymphatic follicles/ nodules (B cells) & these lymphatic nodules are surrounded by diffuse lymphatic cells (T cells, APCs.....)

Secondary Lymphoid follicle

Primary Lymphoid follicle

The opening of the glands into palatine tonsils

Germinal center

Minor salivary glands

Their ducts open into the base of the crypt for continues washing and cleaning of the contents of the crypt

Note:
Lingual tonsils are also covered by stratified squamous epithelium with crypts

Why it is more common to have palatine tonsillitis than lingual tonsillitis although they have the same histology (Stratified non-keratinized squamous epithelium)?

Because we have mucus-secreting cells called minor salivary glands that wash away microbes in the crypt by mucus secretions. In lingual tonsils, the glands open DIRECTLY into the CRYPT while in the palatine tonsils, the glands open into the EPITHELIUM so the palatine is less efficient in washing away the microbes in the crypt.

For pharyngeal tonsils, we almost have the same histology except the covering epithelium. Its epithelium is Pseudostratified Ciliated Columnar Epithelium (nasopharynx / respiratory epithelium)

Gut-associated lymphoid tissue (GALT)

Is located in the mucosa of the intestine.

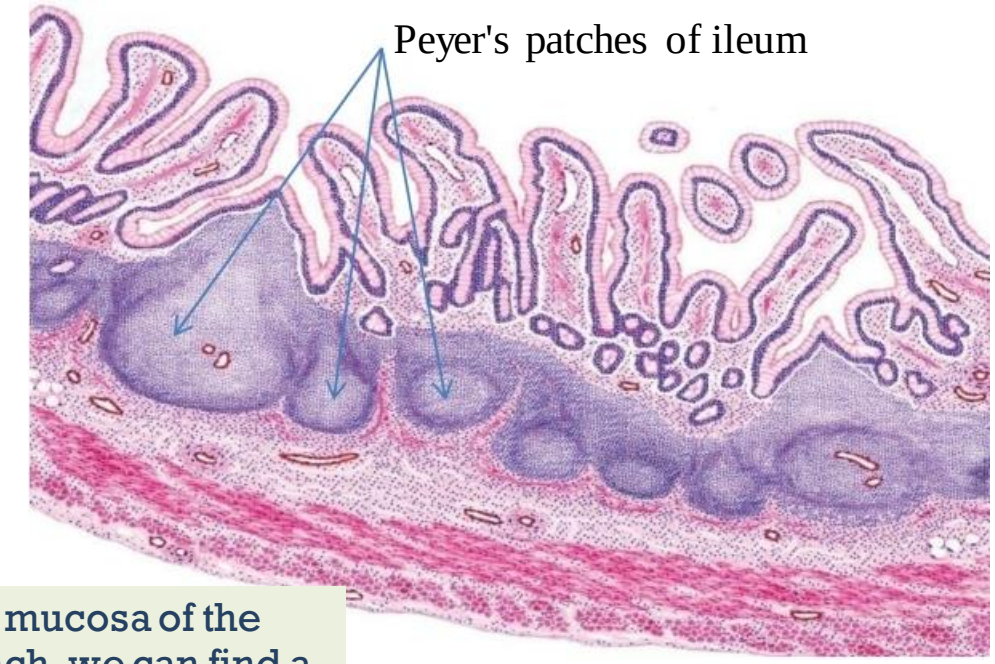
Examples:

1- Peyer's patches of ileum

2- Lymphatic nodules of appendix

Function:

Protects the body from ingested pathogens.

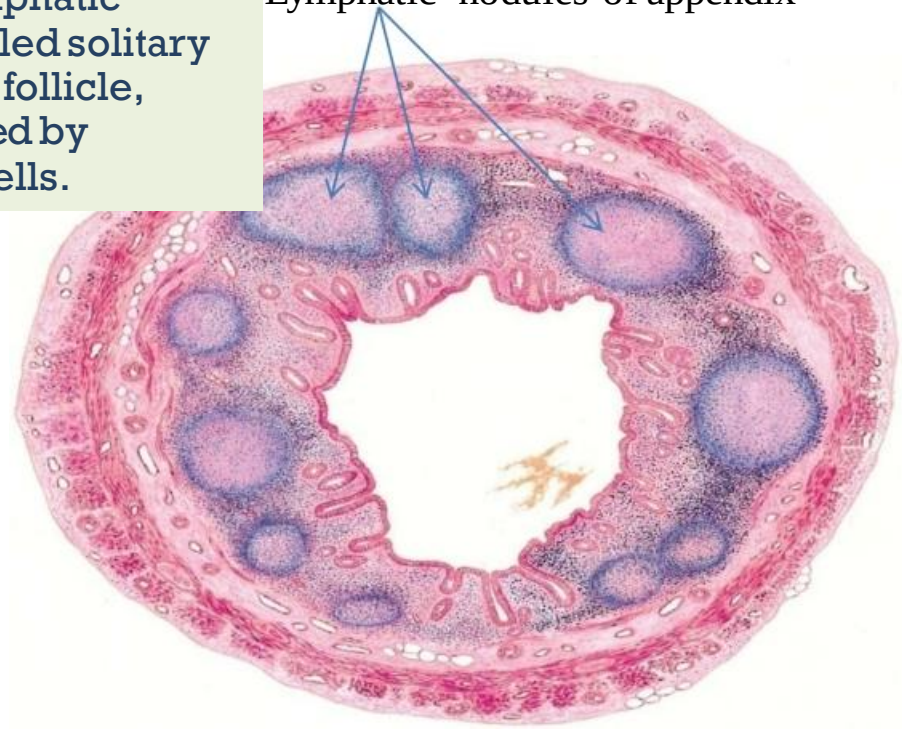


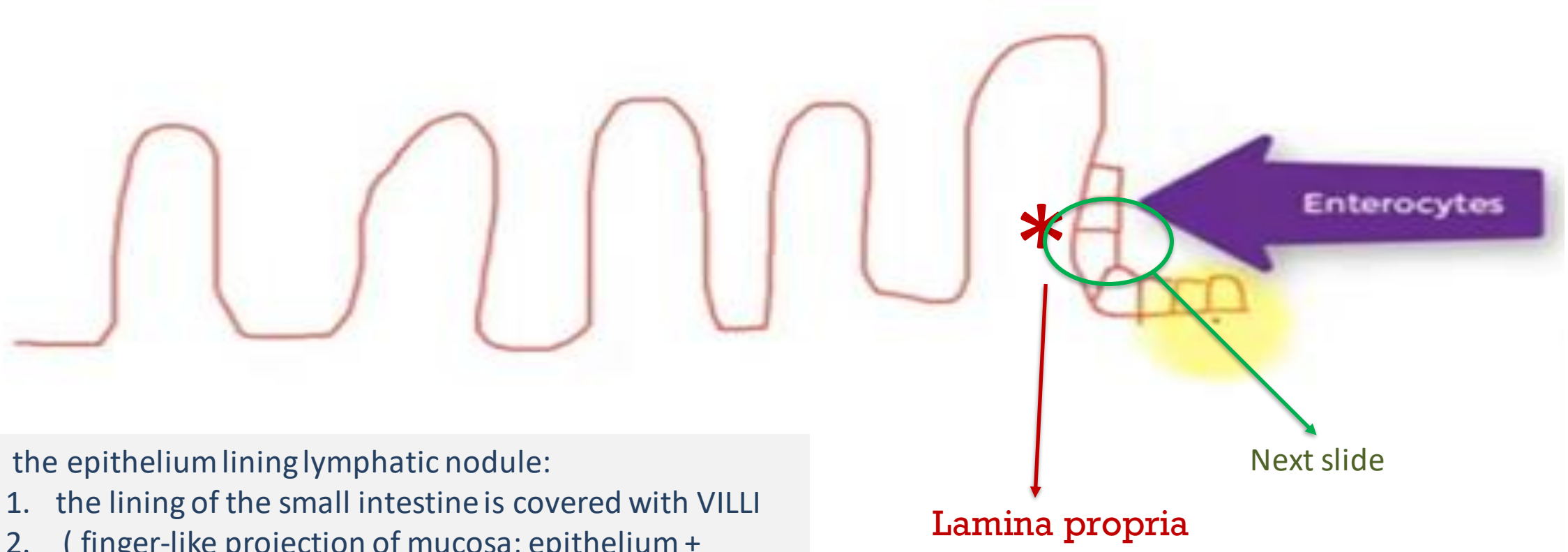
In the mucosa of the stomach, we can find a single lymphatic follicle called solitary lymphatic follicle, surrounded by immune cells.

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***

Lymphatic nodules of appendix





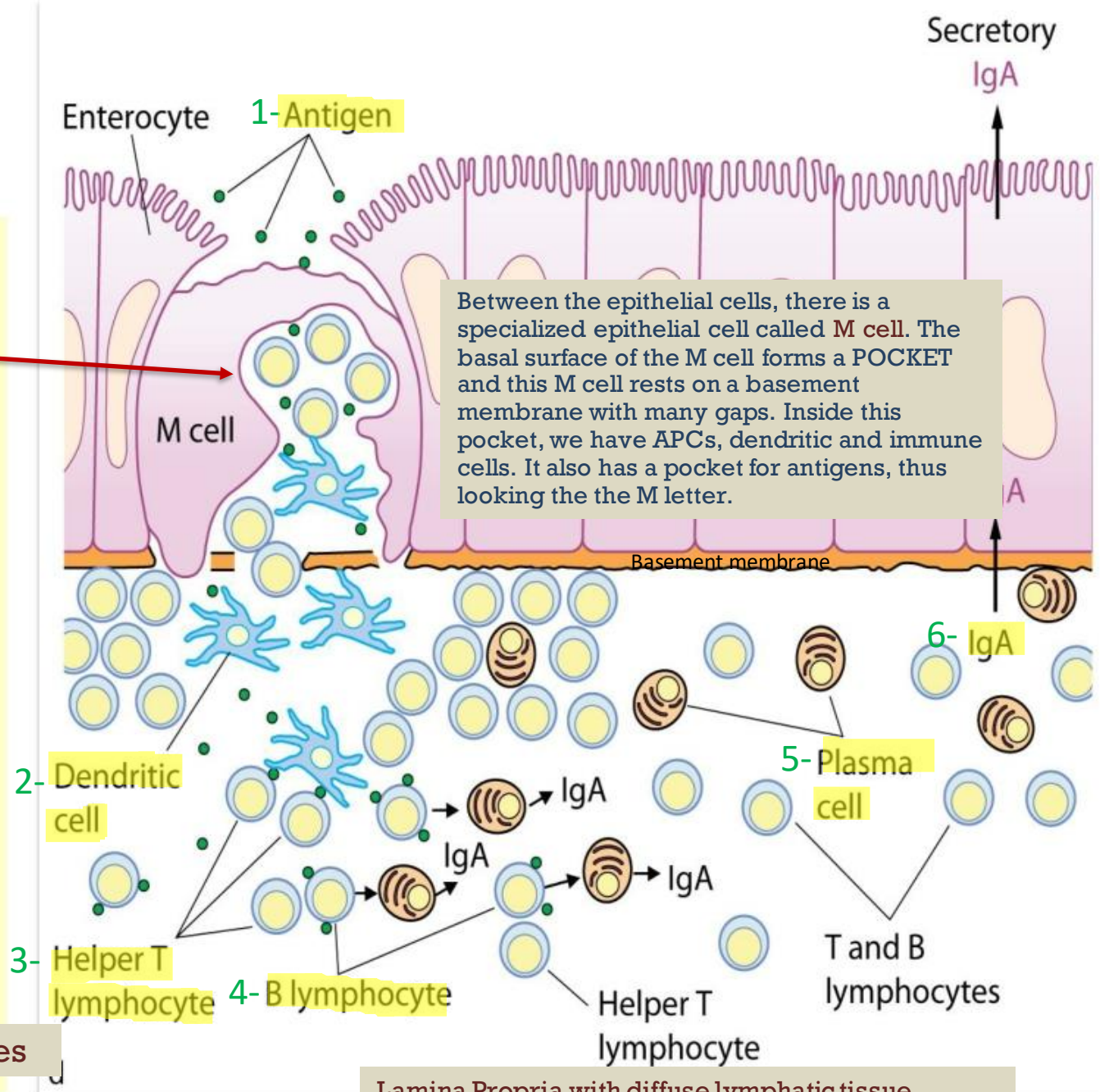
the epithelium lining lymphatic nodule:

1. the lining of the small intestine is covered with VILLI
2. (finger-like projection of mucosa; epithelium + underlying connective tissue) and the core of each villus is Lamina Propria.
3. the epithelium is simple columnar cells lined with microvilli and these cells are called enterocytes.
4. the diffuse lymphatic tissue is in the Lamina Propria and can extend down into the submucosa.

Peyer's patch and M cells

A summary diagram showing that antigens in the gut lumen are bound by **M cells** and undergo Transcytosis (without being used) 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.

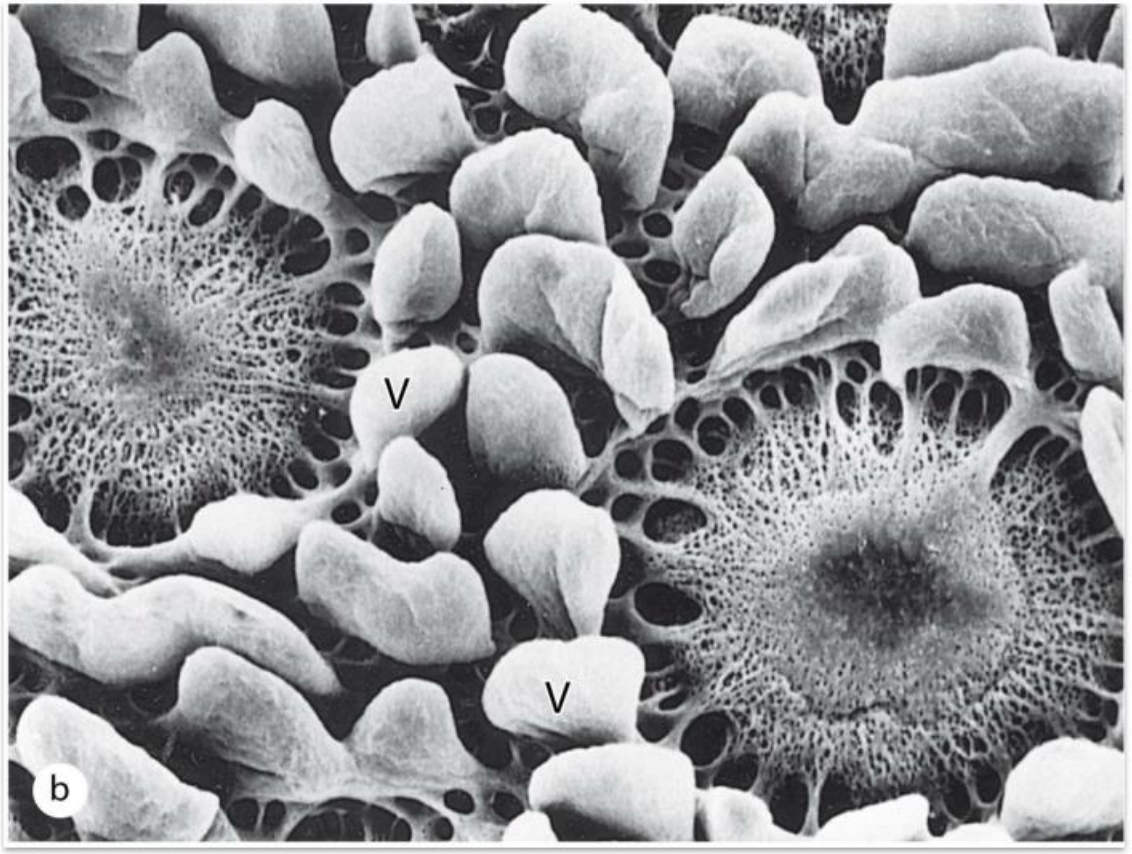
IgA antibodies are found in the mucous membranes



Lamina Propria with diffuse lymphatic tissue (lymphatic follicles surrounded by immune cells)

Figure 14-13

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.



Peyer's patch and M cells

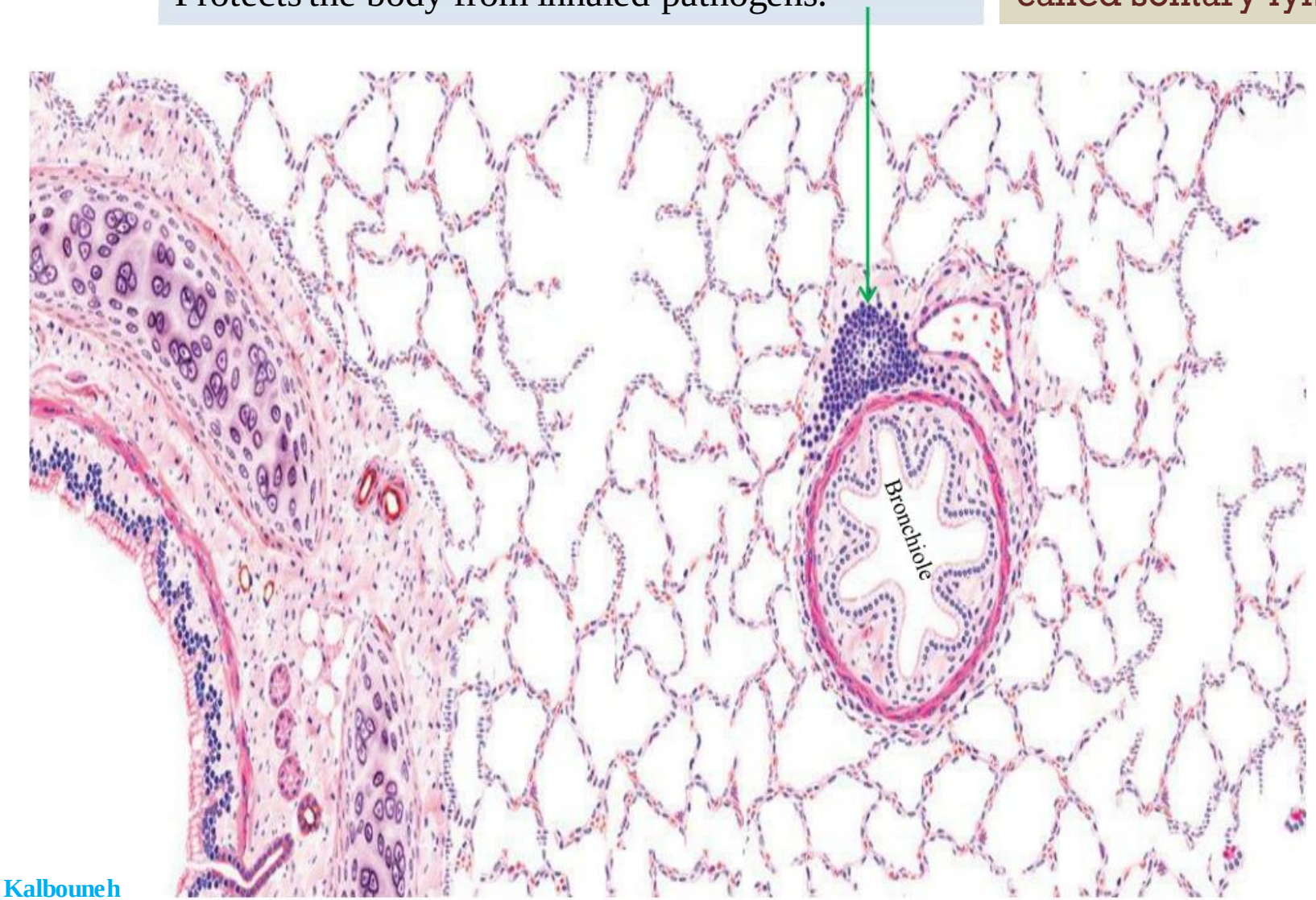
This sieve-like basement membrane facilitates interactions between immune cells and M cells in the epithelium over the nodules.

Figure 14-13

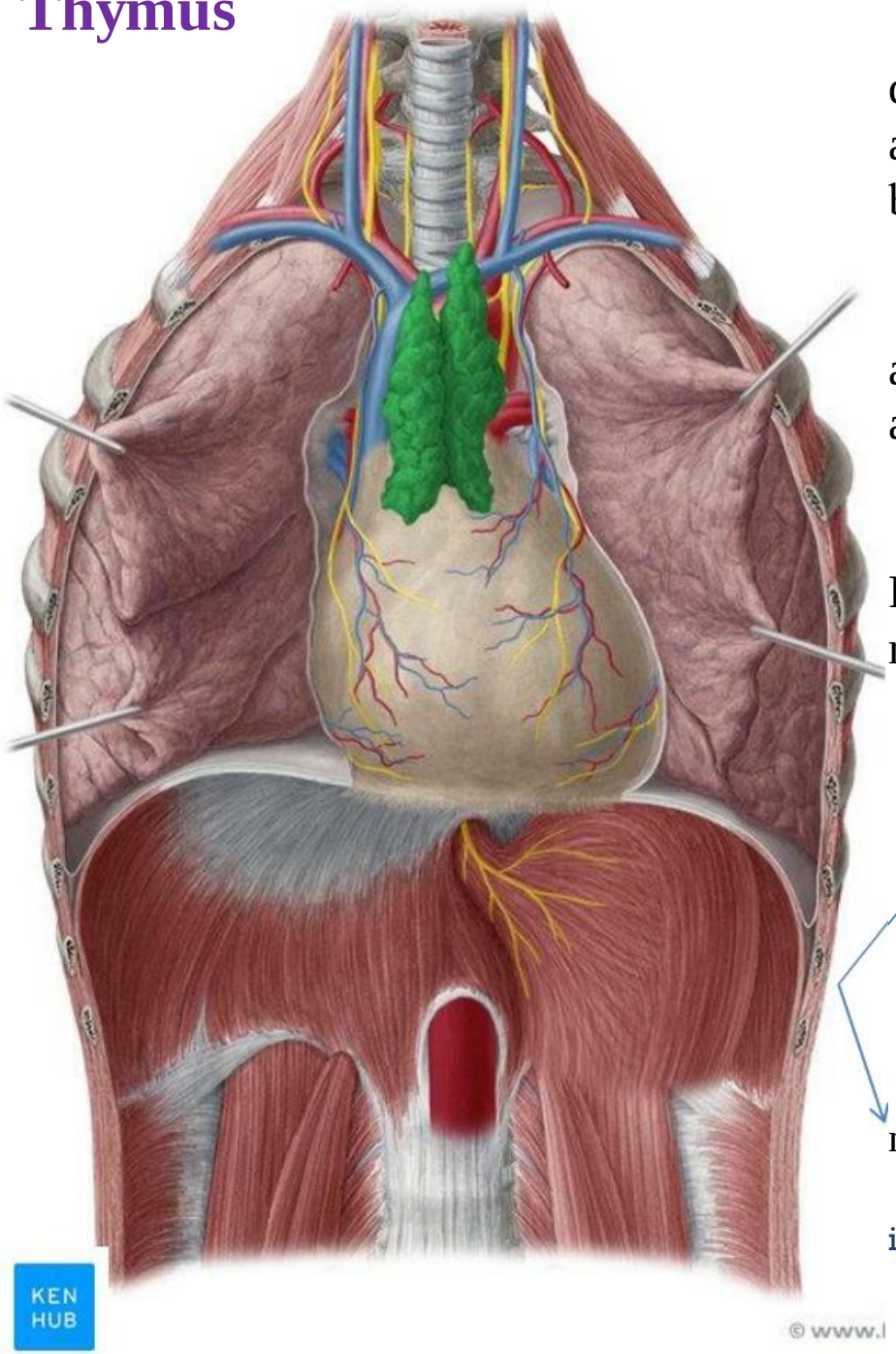
Bronchus-associated lymphatic tissue (BALT)
Is located in the mucosa of the bronchioles.

Function:
Protects the body from inhaled pathogens.

Lymphatic follicle surrounded by immune cells (T cells, APCs and plasma cells). This single lymphatic follicle in the mucosa is called solitary lymphatic follicle



Thymus



Within the thymus, immature T-cells develop, differentiate, and multiply, as well as gaining their antigen specificity and immune tolerance to the body's own tissues.

The thymus is a bi-lobed gland located in the anterior mediastinum, posterior to the sternum and anterior to the trachea.

Has 2 Functions:
endocrine function- secrete hormones
Lymphatic function- T cell differentiation

It is large in the newborn and young child
From puberty onwards, it gradually becomes replaced by fat.

Thymic involution

Fullyformedandfunctionalatbirth,the thymusremainslargeandveryactiveinT-cellproductionuntilpubertyduringwhichit normallyundergoesinvolution,with decreasinglymphoidtissuemassand cellularityandreducedTcelloutput

may be involved with the decline of immune function in the elderly cell- mediated immunity

The thymus is also part of the endocrine system.

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The thymus has a double embryonic origin: Endoderm and Mesoderms. In order to understand more, let's revise the pharyngeal arches.

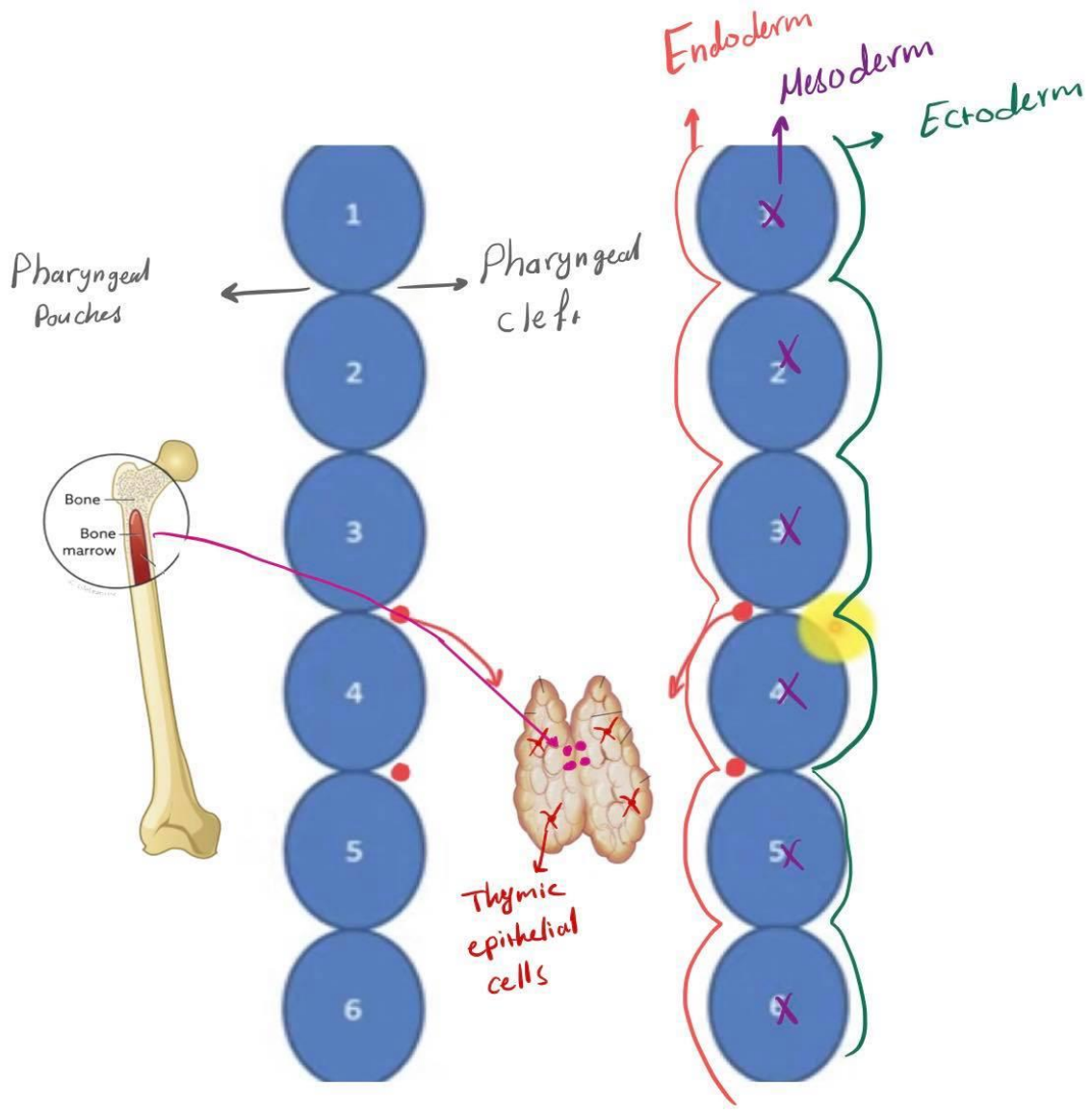
A) the thymus and parathyroid gland originate from the 3rd and 4th pharyngeal pouches

the thymus MAINLY originate from the ENDODERM of the 3rd pharyngeal pouch (it will form the EPITHELIUM part of the thymus)

C) these epithelial cells are called thymic epithelial cells and these cells represent the ENDOCRINE portion of the thymus (secrete the hormones)

D) Also, during the development of the thymus, there will be production of precursor T cells and these cells will leave the Bone Marrow and populate in the Thymus

E) these immature T cells will represent the MESODERMAL origin of the thymus (hematopoietic origin of the thymus)



The thymus has a double embryonic origin

Endoderm and Mesoderm

Originates from the embryo's third pair of pharyngeal pouches

↓

unique thymic epithelial cells

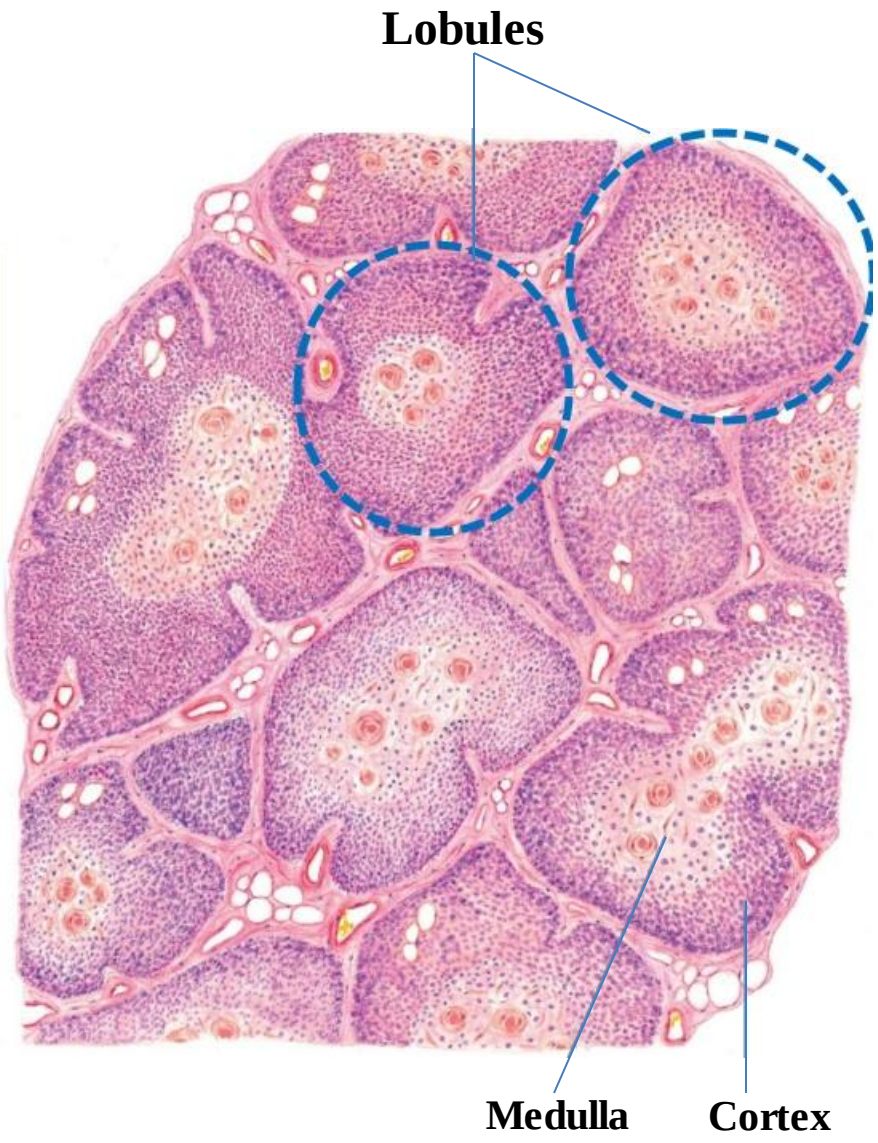
Hematopoietic origin
Immature T lymphocytes (T lymphoblasts) circulating from the bone marrow to invade and proliferate in thymus during its development.

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**.

↓↓↓

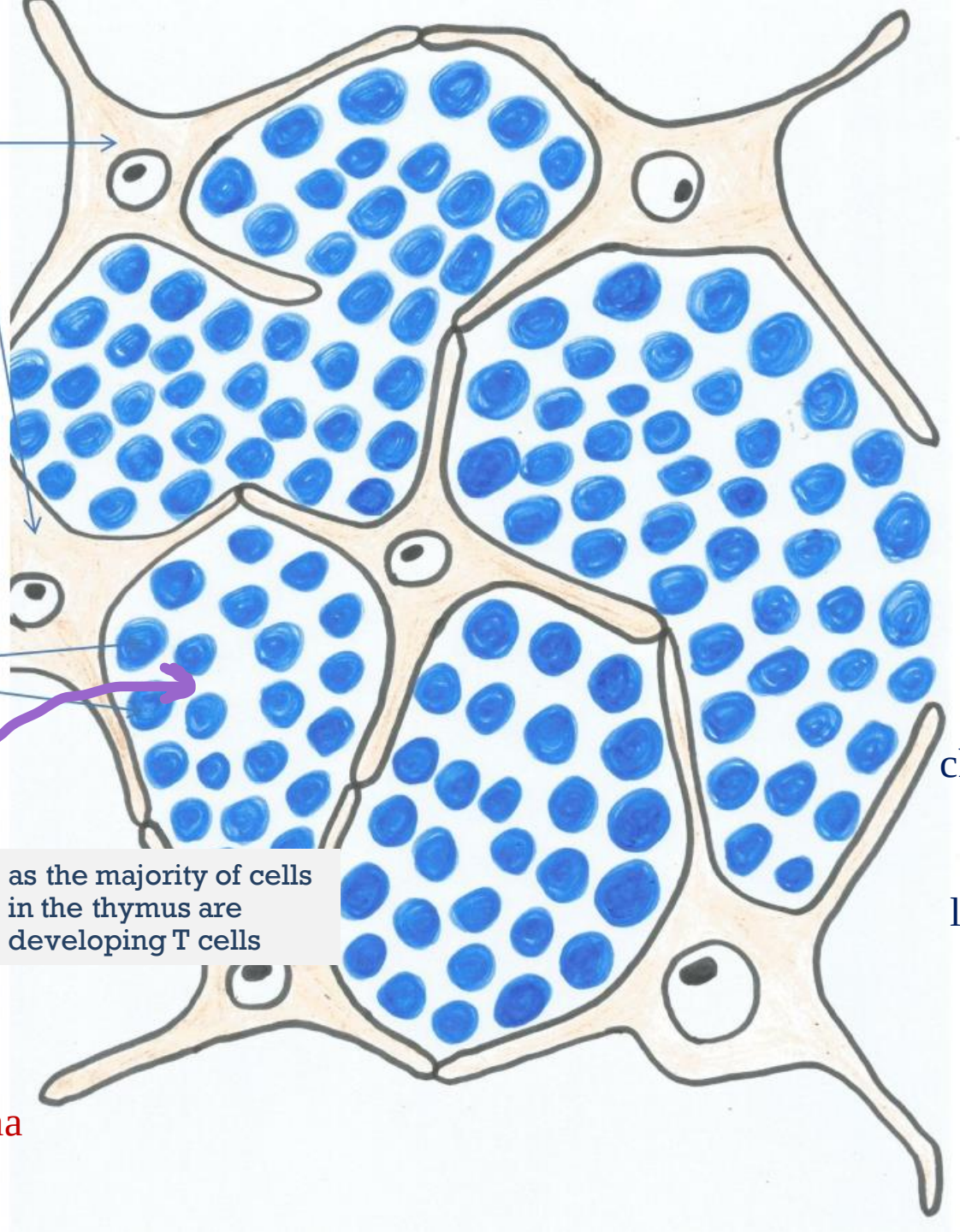
Thestainingdifferencesreflectthemuchgreater densityoflymphocytesinthecortexthanthe medulla



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

Thymic Epithelial Cells (TECs) (Epithelial reticular cells)

Have many processes and these processes are connected by desmosomes and they form the stroma of the thymus, so the stroma of the thymus is NOT formed of reticular tissue. Since these cells appear reticular in shape, we can call these cells Epithelial reticular cells



immature T cells (T lymphoblasts, pre T cells, thymocytes) (invariousstagesof differentiation and maturation)

Forms the parenchyma

as the majority of cells in the thymus are developing T cells

Thymotaxin
Thymosin
Thymopoietin

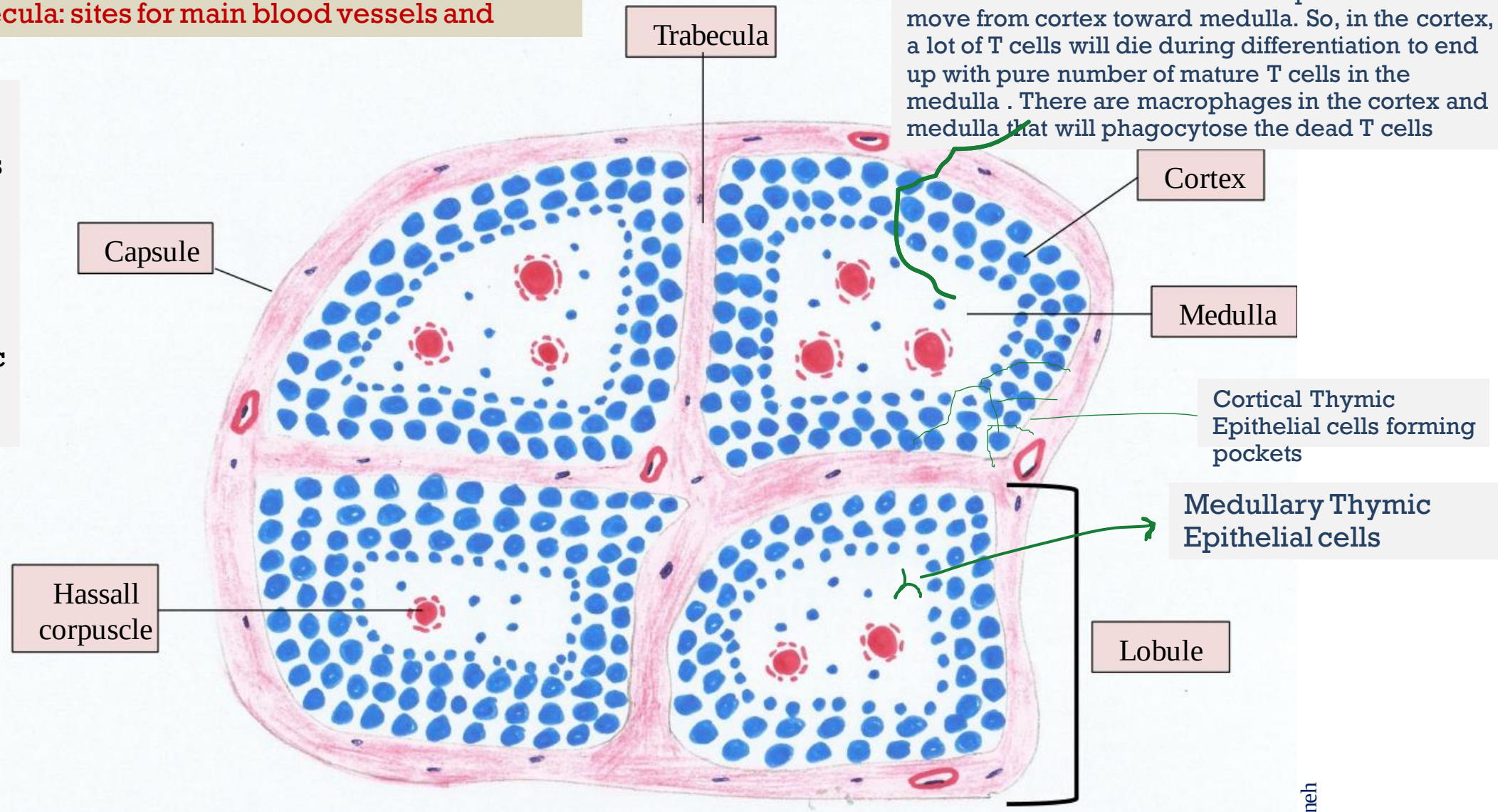
Thymic Epithelial Cells functions :
1) form the stroma
2) Endocrine hormones (Thymosin and Thymopoitin) to promote differentiation and development of T cells inside thymus. 3)Thymopoeitin

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

Capsule and Trabecula: sites for main blood vessels and nerve supply

What are the cells in the Thymus ? Developing T cells Thymic epithelial cells (in the cortex and medulla) Macrophages (in the cortex and medulla) Dendritic cells inside the medulla

The differentiation of T cells takes place as the cells move from cortex toward medulla. So, in the cortex, a lot of T cells will die during differentiation to end up with pure number of mature T cells in the medulla . There are macrophages in the cortex and medulla that will phagocytose the dead T cells



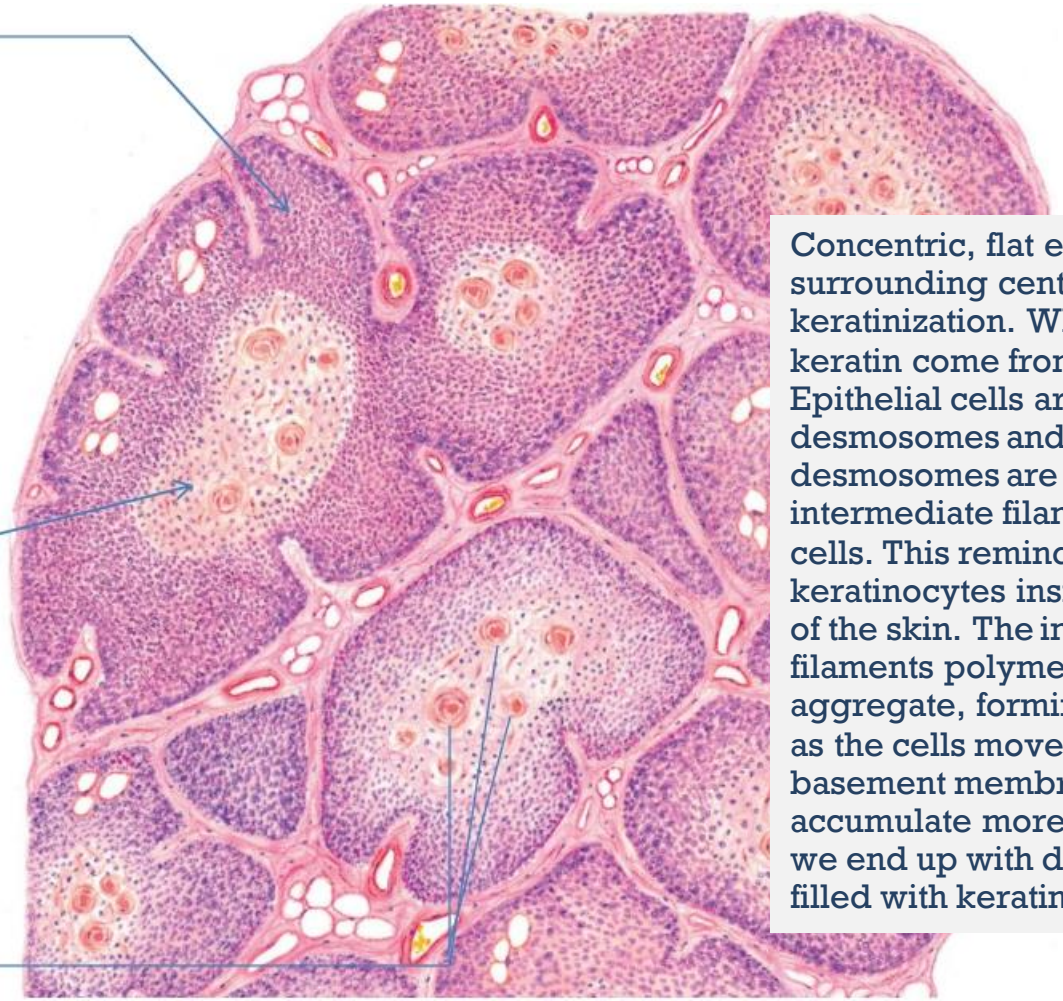
The cortex contains:

1. Immature T cells (T lymphoblasts, thymocytes) (invariousstagesof differentiationandmaturation)
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**



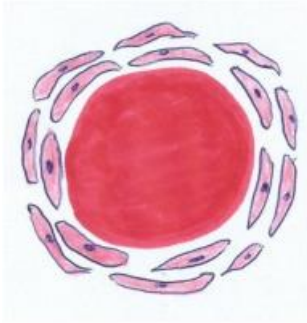
Concentric, flat epithelial cells surrounding central keratinization. Where did the keratin come from? The Thymic Epithelial cells are connected by desmosomes and the desmosomes are connected to intermediate filaments inside the cells. This reminds us with the keratinocytes inside the epidermis of the skin. The intermediate filaments polymerize and aggregate, forming keratin, and as the cells move away from the basement membrane, the keratin accumulate more and more until we end up with dead flat cells filled with keratin.

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



Unknown function. Some say it is a graveyard for thymic epithelial cells. These cells accumulate more and more with keratin until we end up with dead cells completely filled with keratin, resulting in this central keratinization. These cells start to appear after puberty and their number increase with age. Others say it secretes factors necessary for the function of Dendritic cells inside the medulla.

Thymic Epithelial Cells (TECs) (Epithelial reticular cells)

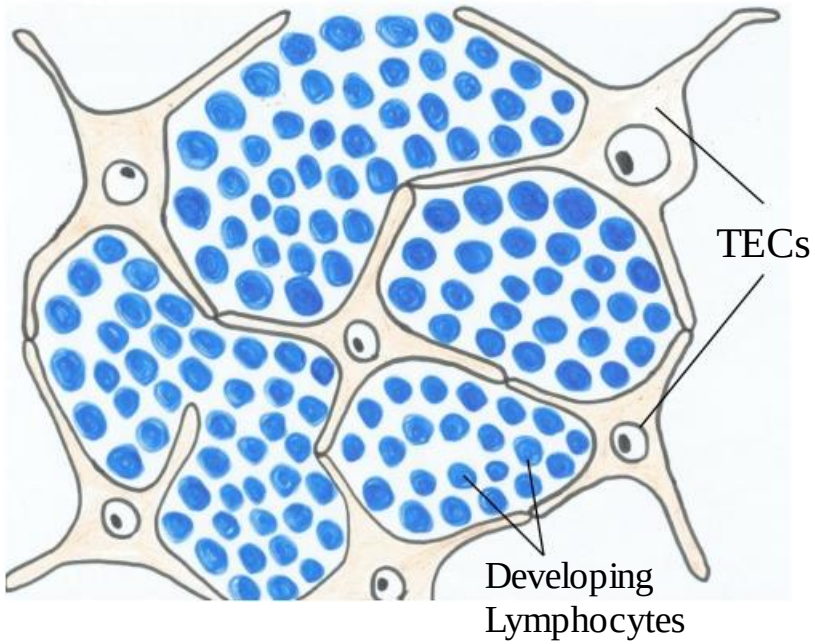
Developfromendoderm

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

Form a network of cells bound together by desmosomes

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

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



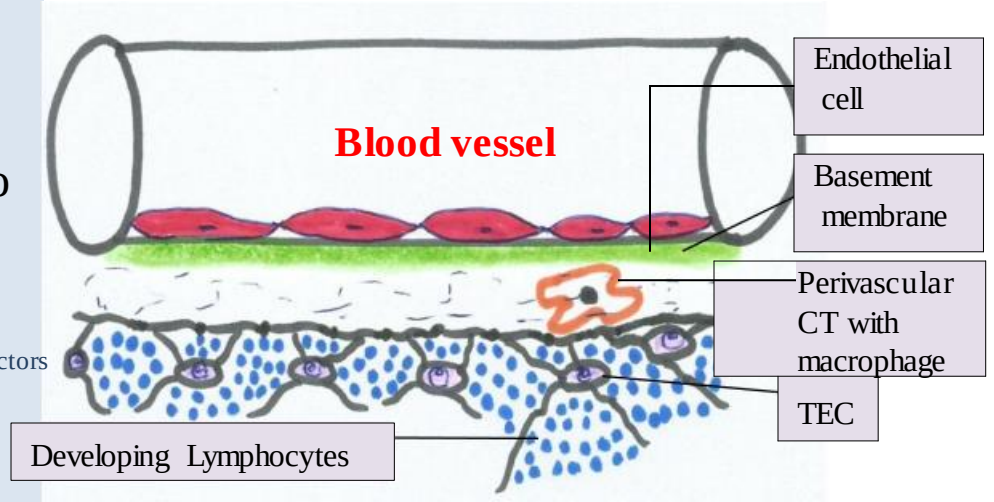
3- Envelop groups of T cells that are multiplying and maturing **(in cortex)**

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, tissuespecificantigens**(in medulla)**

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

Thymosin, Thymopoietin



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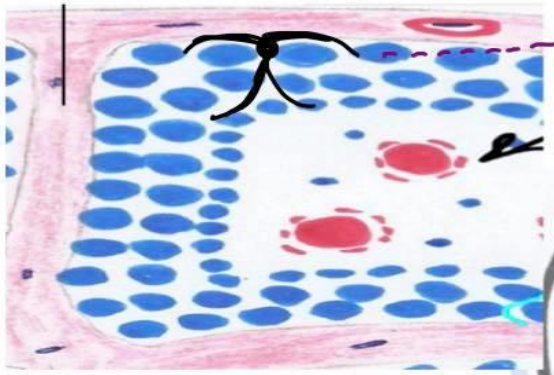
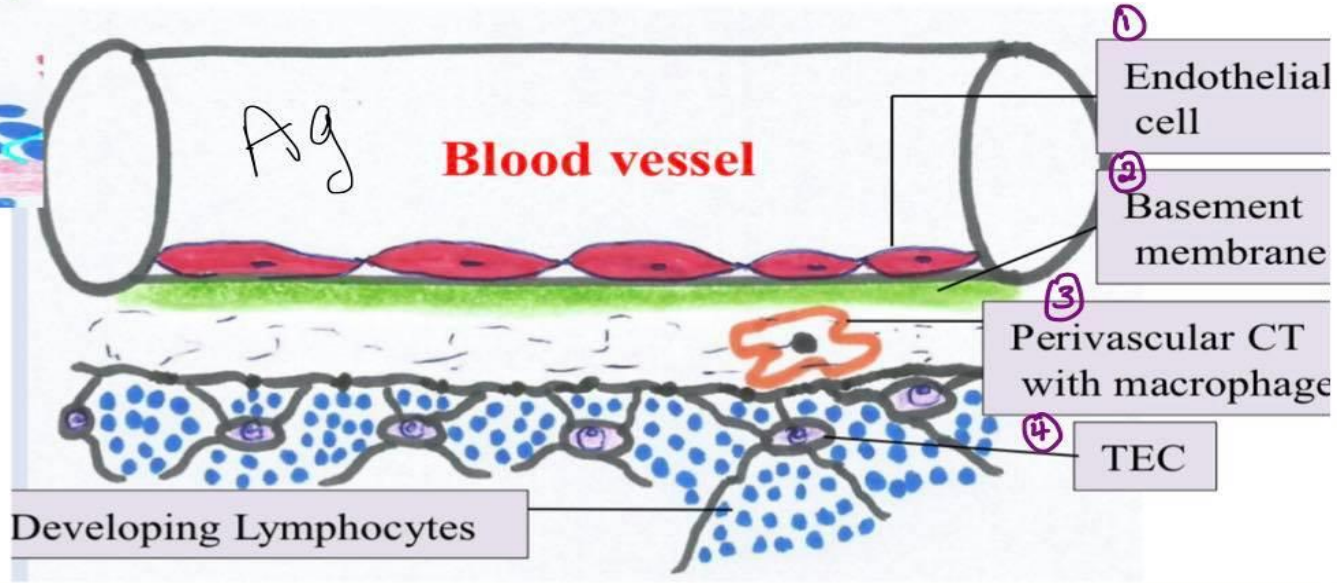


The Thymic Epithelial cells form the stroma in the Thymus and these cells are mainly concentrated under the capsule and along trabecula. Also, concentrated around any blood vessel in the Thymus. Why? To understand why, see the figure below



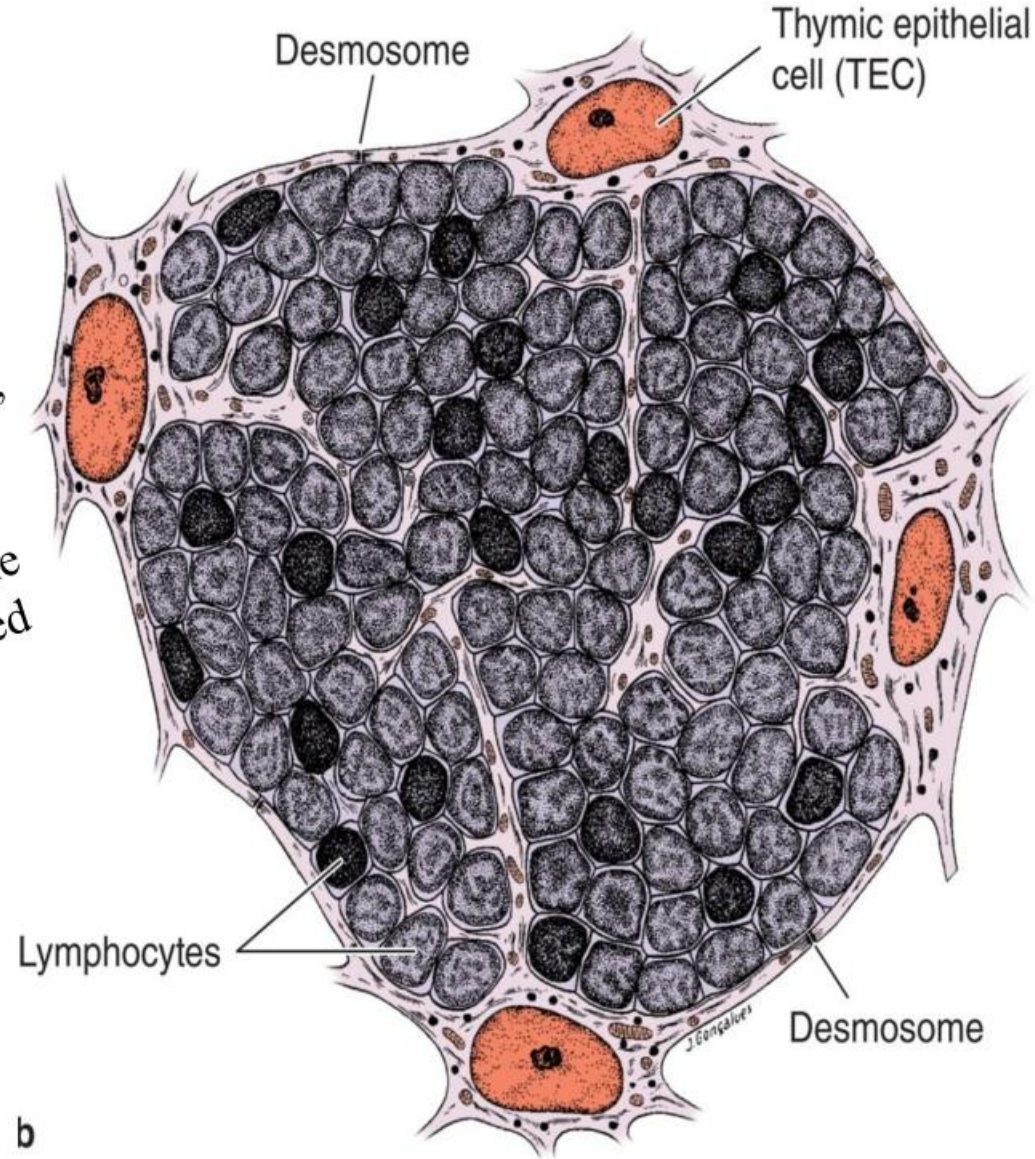
Here we have a blood vessel inside the capsule lined with simple squamous epithelial cells, connected by tight junctions and this endothelium rests on a thick basement membrane. Below the BM, a loose type of CT, perivascular CT, rich in macrophages. Beneath that, the Thymic Epithelial cells forming stroma of thymus. Notice how the TEC extend their cytoplasmic processes to form a SHEILD to protect the developing T cells during their differentiation as these cells should NOT be exposed to the blood. These layers form the BLOOD-THYMUS BARRIER, preventing ANTIGENS in the blood from making contact with the developing T cells (in cortex)

Blood-thymus barrier:

1) Endothelium (tight junctions)
2) Basement membrane (thick)
3) Perivascular CT with macrophages (the macrophages will phagocytose the antigens)
4) TEC (cytoplasmic processes)

Thymic epithelial cells are also called
Nursing Cells

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



Cortex

Double negative

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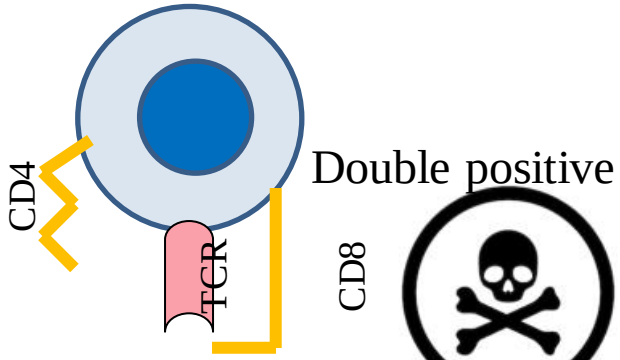
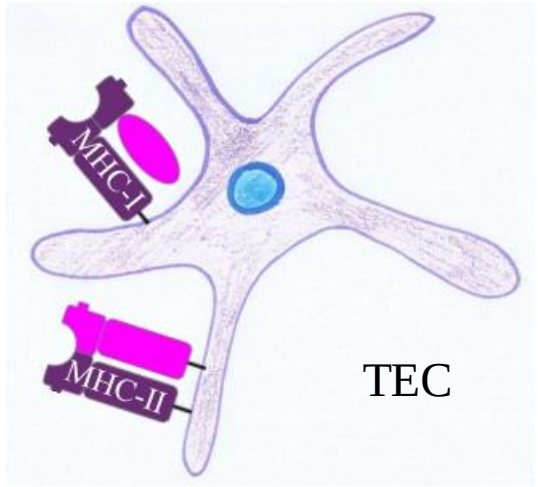


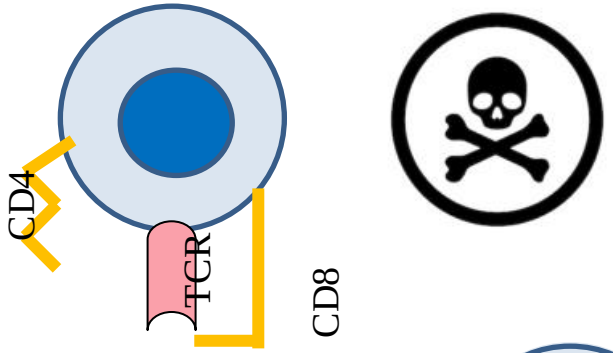
Double positive

CD8

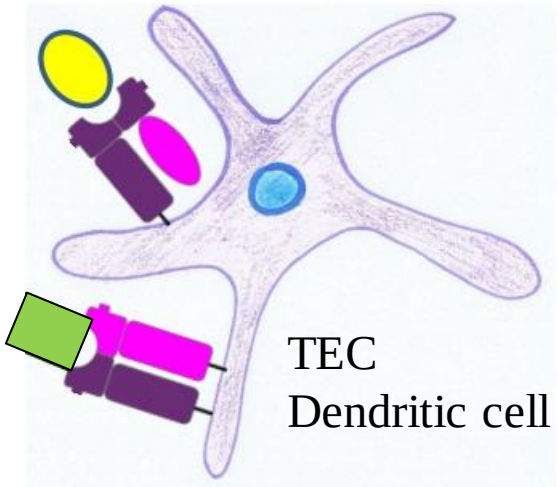


TEC

Medulla



CD8



TEC
Dendritic cell

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THYMIC EDUCATION IN THE CORTEX:

1- we start with immature T cell that have arrived from the BM to enter Thymus. Notice this cell has NO CD4 or CD8 on its surface and that's why we call it Double negative cell. Also, it has NO TCR.
2- Once this cell enters Thymus, and under the influence of the hormones released by TECs, we will have upregulation of genes for CD4, CD8 AND TCR (specific to recognize a certain antigen) and all 3 will be expressed on its surface. Both CD4 and CD8 expressed —> Double positive cell
3- Now, we are going to test the TCR to see if it binds to MHC I or MHC II (functional or not). Inside the cortex, we have TEC that expresses both MCH I and II. If the TCR binds to MHC I or II, then it receives SURVIVAL signal from TEC and it moves to the medulla. If it didn't bind to MHC I or II, then it DIES by neglect (within 3-4 days) and it's eliminated by macrophages. (Note: 80% of developing T cells die in the cortex. This test is called POSITIVE SELECTION.

Thymic education in the OUTER PART of the medulla, next to cortico-medullary junction:

1- Inside the medulla, we have Double positive cell that we are sure the TCR is functional.
2- TEC and Dendritic cells present MHC I and II coupled to SELF- PEPTIDES. TEC and Dendritic cells have a gene, called Autoimmune regulator, that is able to produce MANY self-peptides. These peptides could be liver peptides, lung peptides, stomach peptides and so on, and that's why they are cell called Tissue specific peptides.
3- the TCR should NOT RECOGNIZE self-antigens. So, if it binds to MHC I and II, this cell should DIE here in the medulla (if it is released into the bloodstream, it will produce autoimmune disease and we call it Autoreactive T cell). The TEC and Dendritic cells secrete death molecules to induce apoptosis
4- if the TCR didn't recognize the self- peptides, these cells will be selected and released into the bloodstream. This test is called NEGATIVE SELECTION.

Why we have millions of cells with TCR inside the cortex and each TCR is made to recognize a certain type of Ag that we may or may not be exposed to?

A) The TCR gene has 2 parts : a CONSTANT part and a VARIABLE part

B) we have DNA Recombinases that produce shuffling of the VARIABLE part of the TCR gene, randomly, producing each time different TCR.

At the end, we should have CD8+ or CD4+ and this is determined in the cortex according to which MHC molecule the TCR binds to in POSITIVE SELECTION.

A) If the TCR binds to MHC I -- CD8 will be upregulated and CD4 will be downregulated giving - CYTOTOXIC T CELL

if the TCR binds to MHC II -- CD4 will be upregulated and CD8 will be downregulated - HELPER T CELL

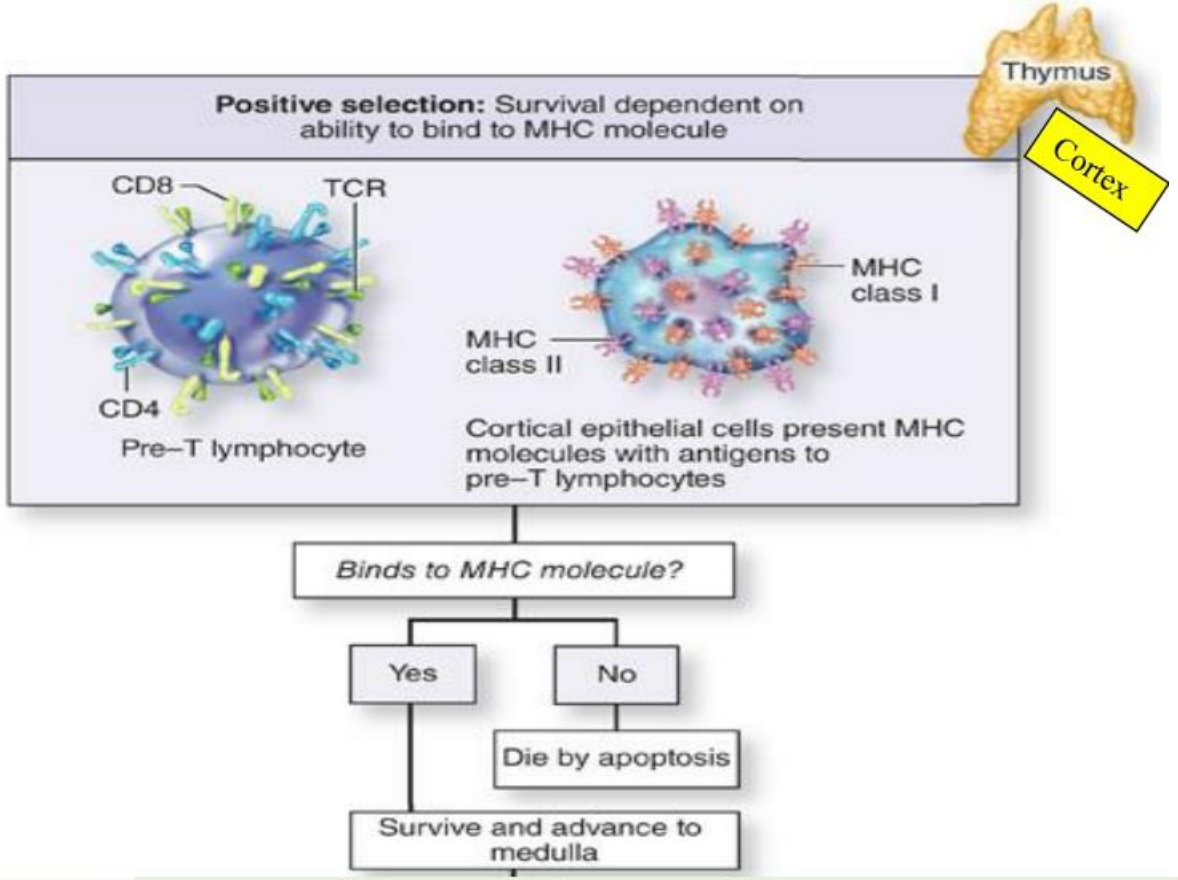
And this up regulation or down regulation of surface molecules is under the influence of TEC

TECs are called **DEATH CELLS** --- TECs & Dendritic cells are called DEATH CELLS bc. They secrete death molecules to induce apoptosis in AUTOREACTIVE T 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

Thisinteractiondetermineswhetherthenewlymade TCRproteinsofthesecellsarefunctional.

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

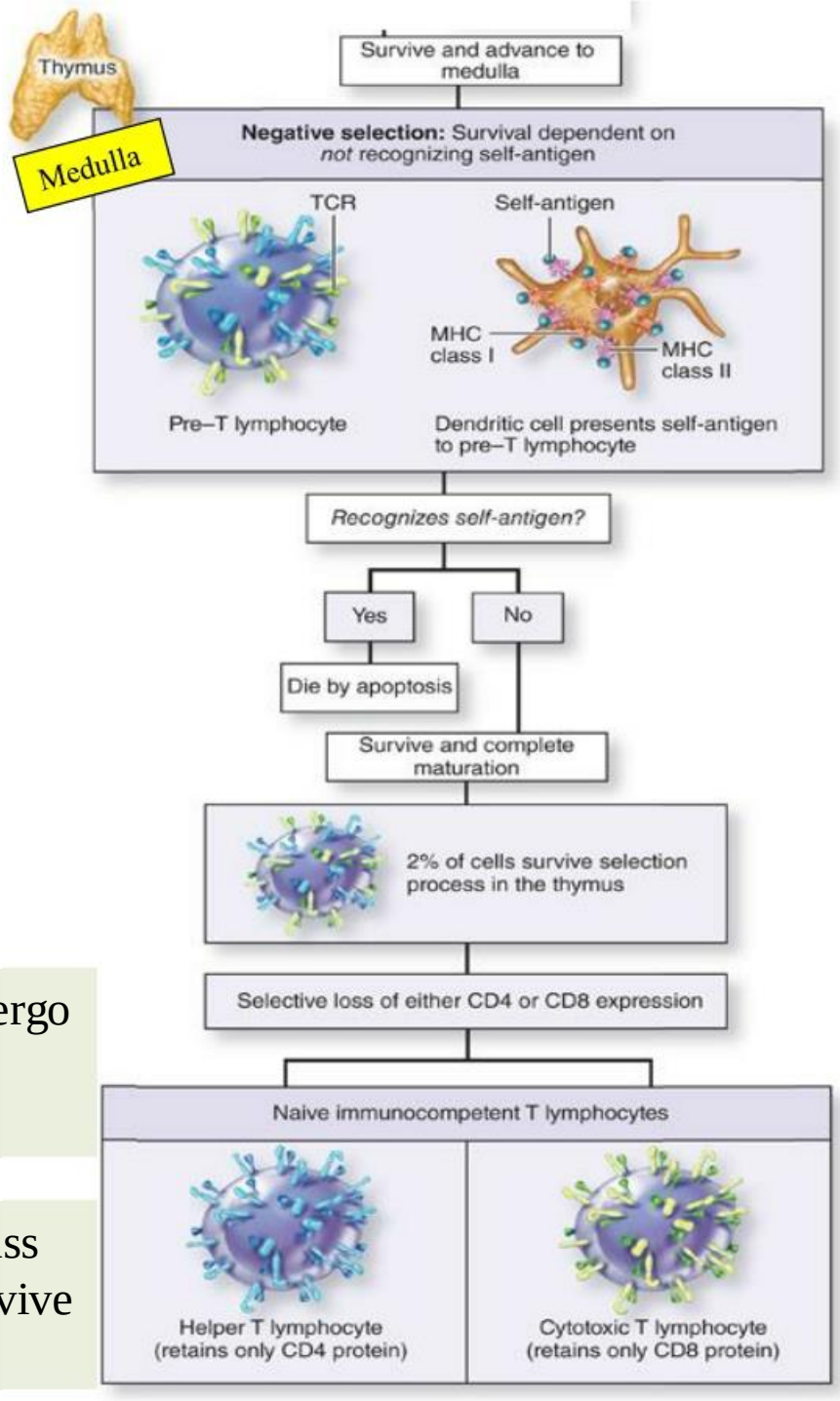
A cell's survival depends on a cell **not** binding to MHC molecules with self-antigens (**negative selection**)

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.



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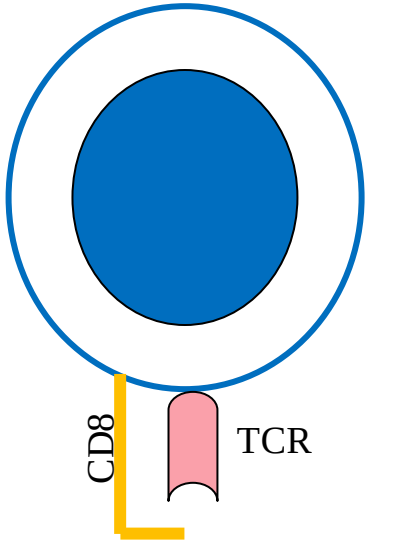
To summarize:

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

Why?

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



Cytotoxic T cell

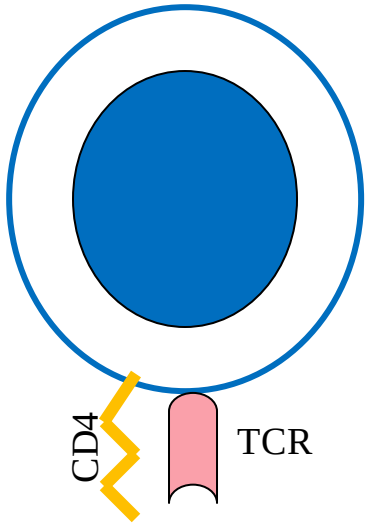
Depending on which class of MHC they interacted with, most of these lymphocytes will have stopped expressing either CD8 or CD4, and become either helper T cell or cytotoxic T cell

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

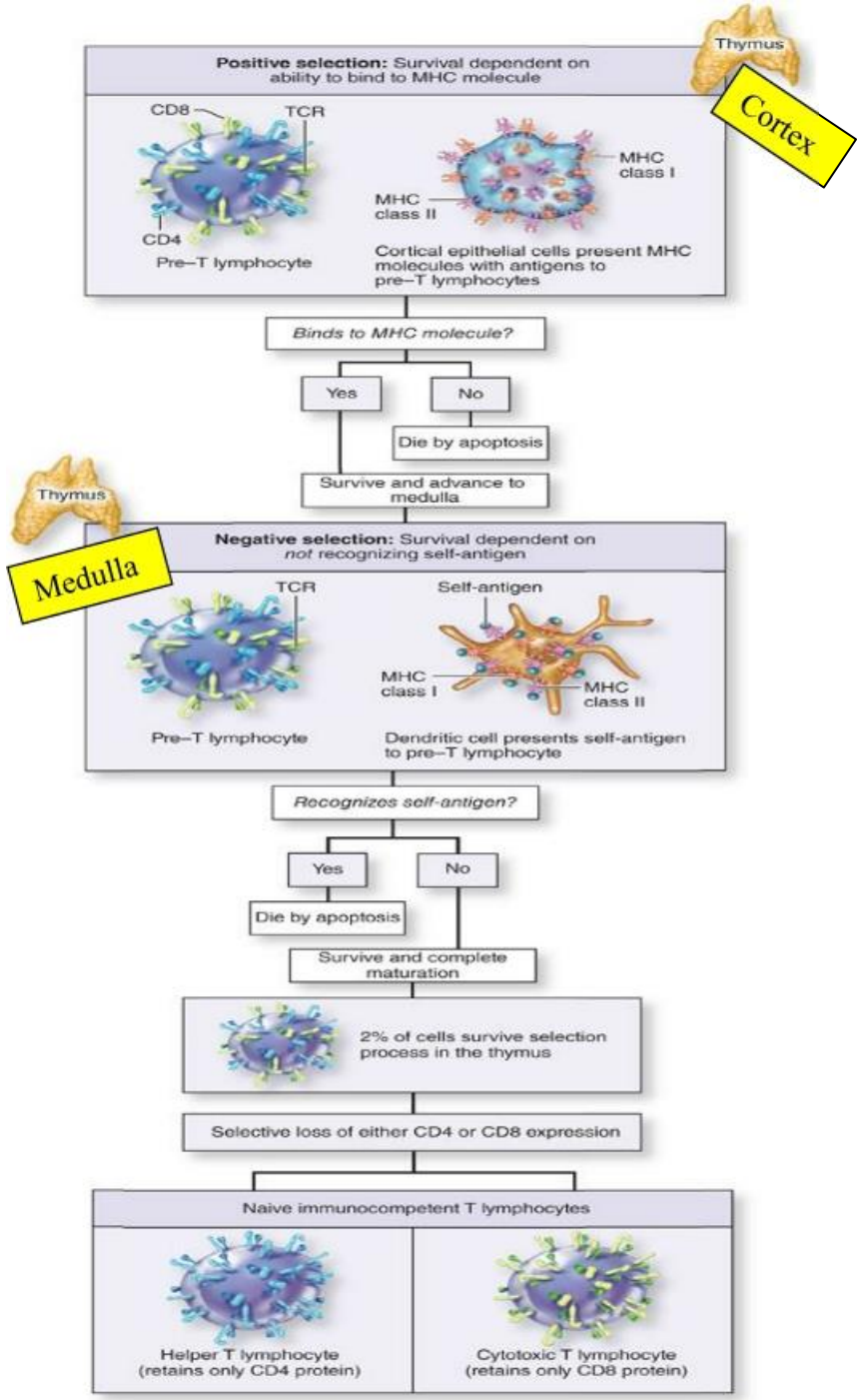
Then..

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

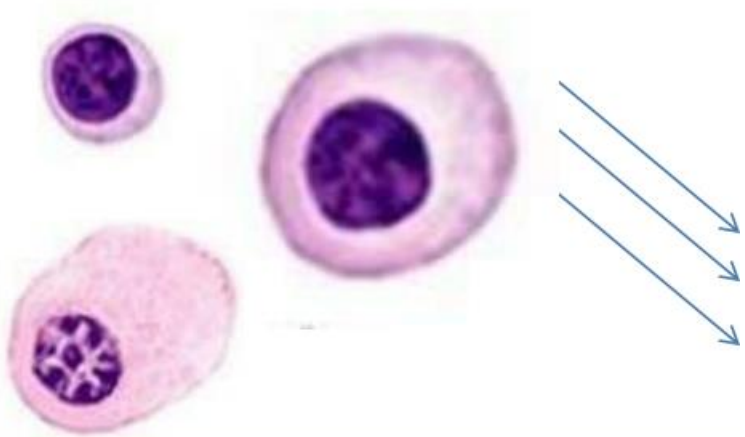


T Helper cell


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

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

This continuous movement of naive, mature T cells between the blood and secondary lymphoid organs is called LYMPHOCYTE RECIRCULATION. This concept is VERY important as we have a limited number of these mature T cells



Lymphocytescontinuously**circulate** betweenthelymphandblooduntilthey encountertheirantigen

Choices of lymphocytes:

1- If no antigen is present: lymphocytes routinely enter and leave secondary lymphoid tissues

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

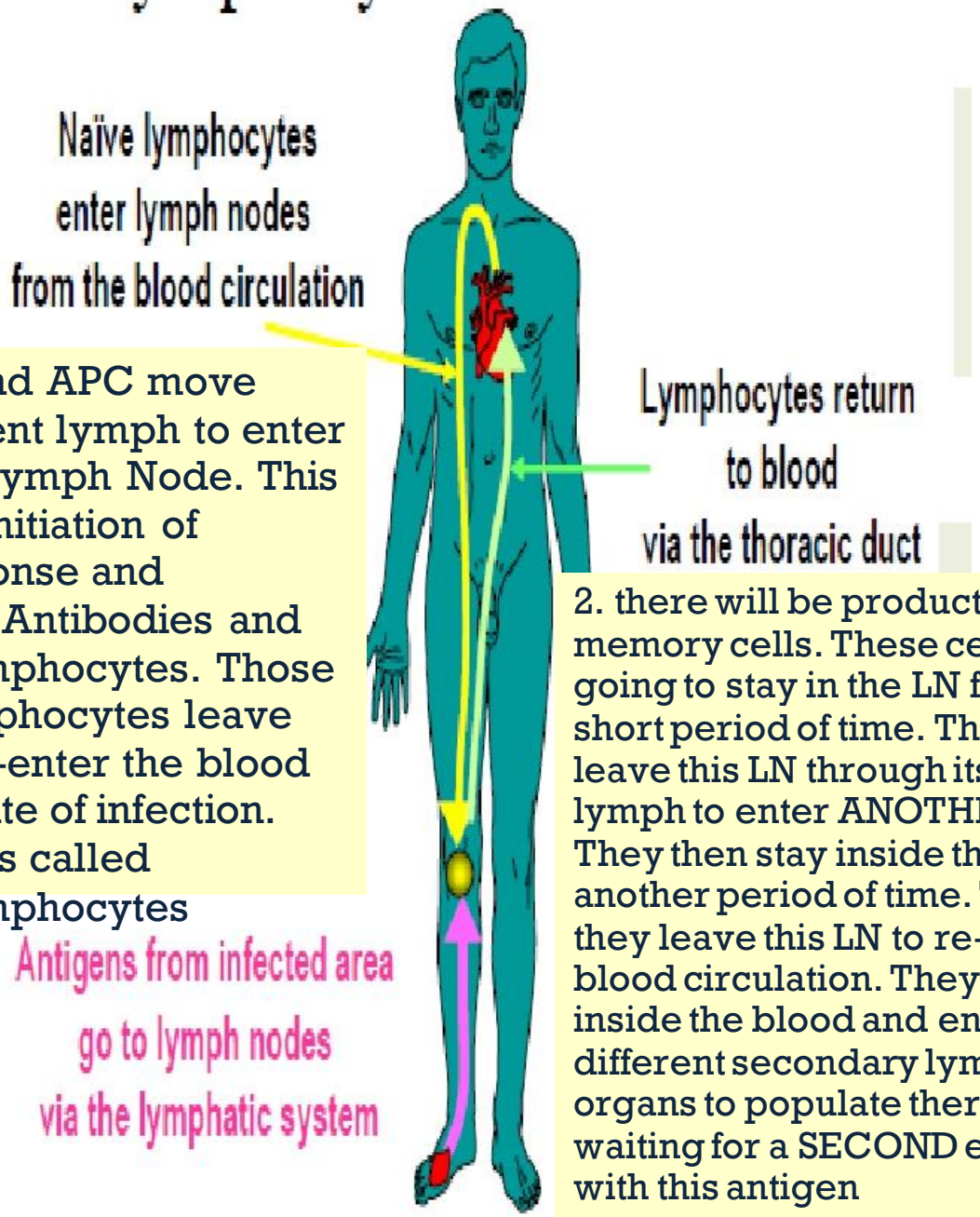
After several days, antigen-activated lymphocytes begin leaving the lymphoid tissue**.**

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

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

Dr. Heba Kalbouneh

Lymphocyte Recirculation



1. Antigens and APC move through afferent lymph to enter the draining Lymph Node. This will result in initiation of immune response and production of Antibodies and Activated Lymphocytes. Those activated lymphocytes leave the LN and re-enter the blood to reach the site of infection. This concept is called Activated Lymphocytes Recirculation.

2. there will be production of memory cells. These cells are going to stay in the LN for a short period of time. Then, they leave this LN through its efferent lymph to enter ANOTHER LN. They then stay inside this LN for another period of time. Then, they leave this LN to re-enter the blood circulation. They circulate inside the blood and enter different secondary lymphoid organs to populate there, waiting for a SECOND exposure with this antigen

Advantagesoflymphocyterecirculation:

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