Immune system

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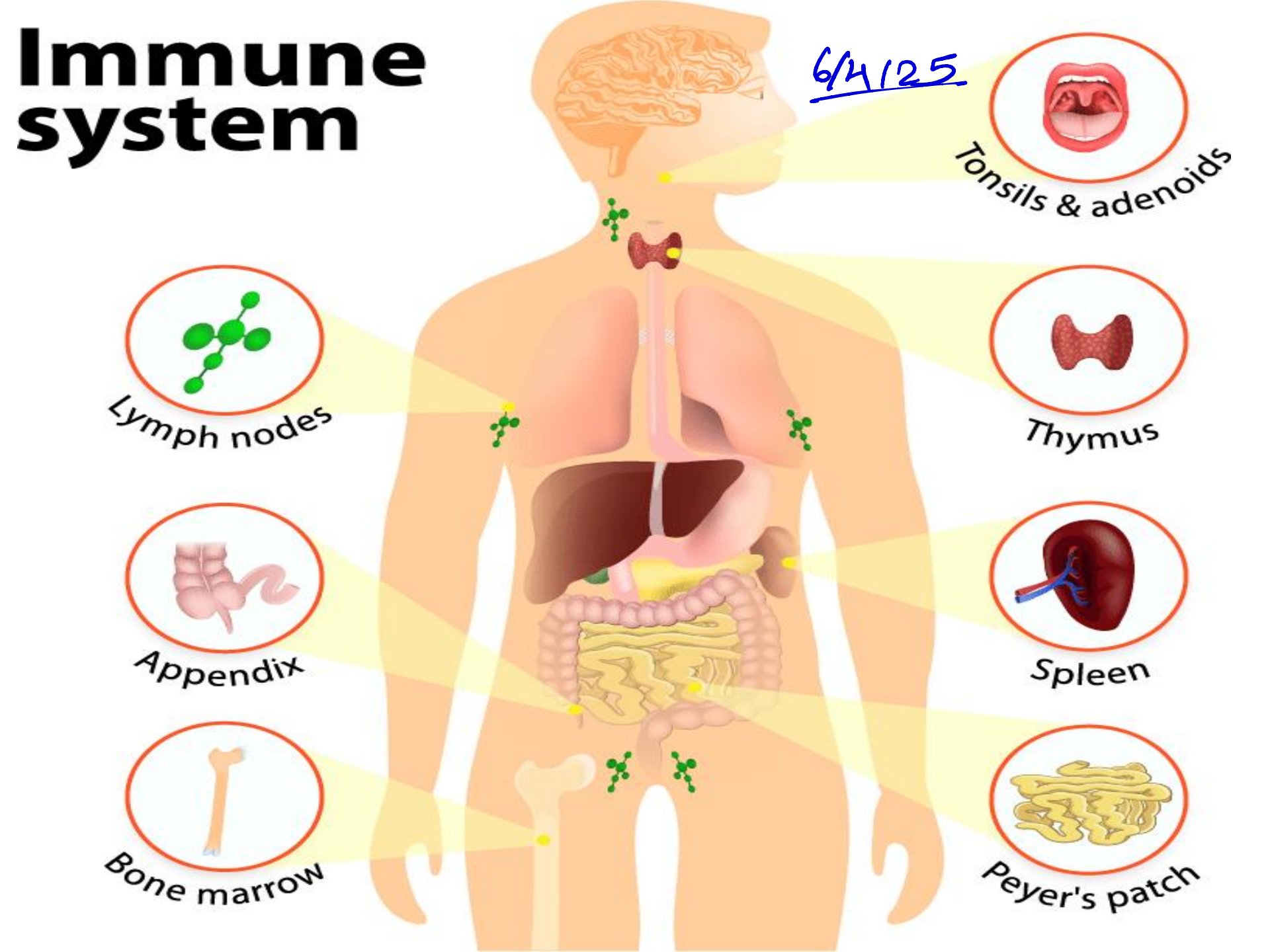

immune system

- All cells and structures distributed throughout the body that Protect the body from invasion of microorganisms or foreign substances.
- Histologically this system consists of a large, diverse population of leukocytes located within every tissue of the body and lymphoid organs interconnected only by the blood and lymphatic circulation.

except : Brain.

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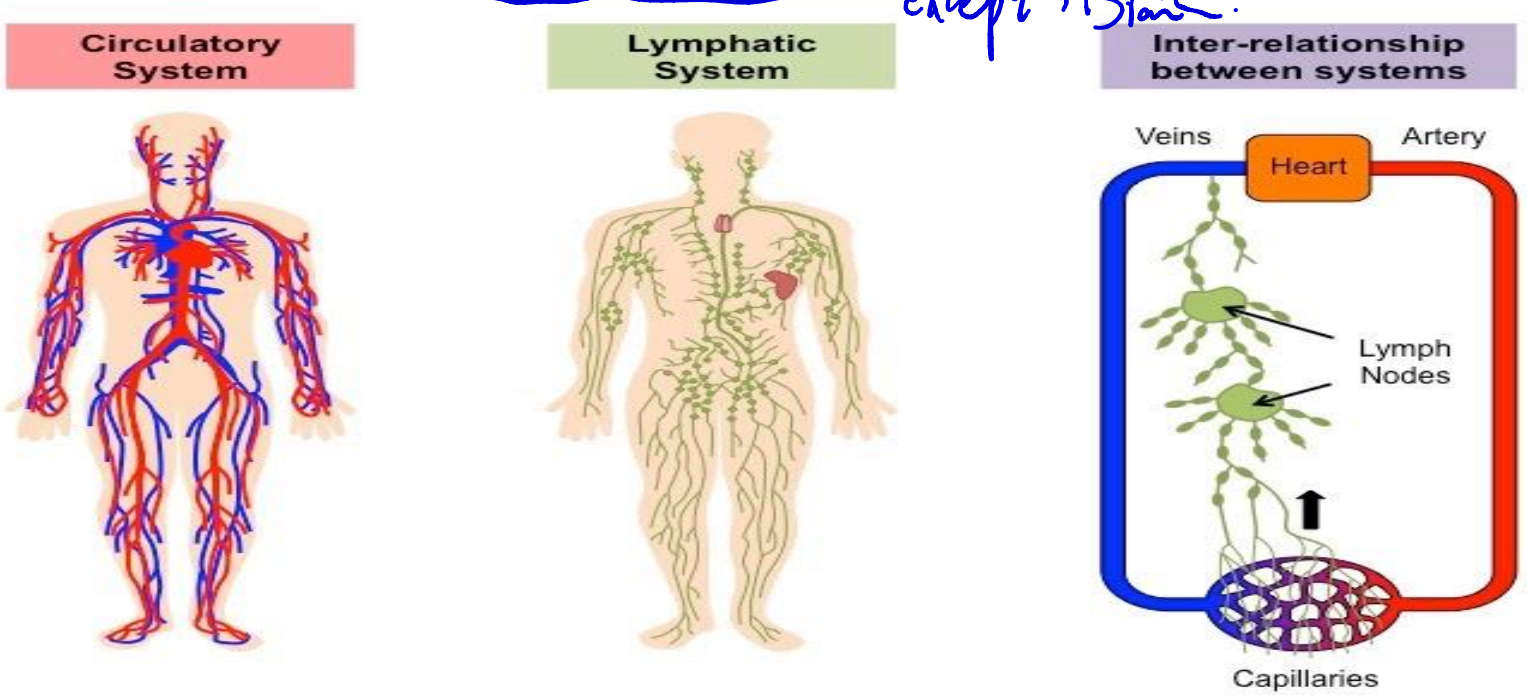


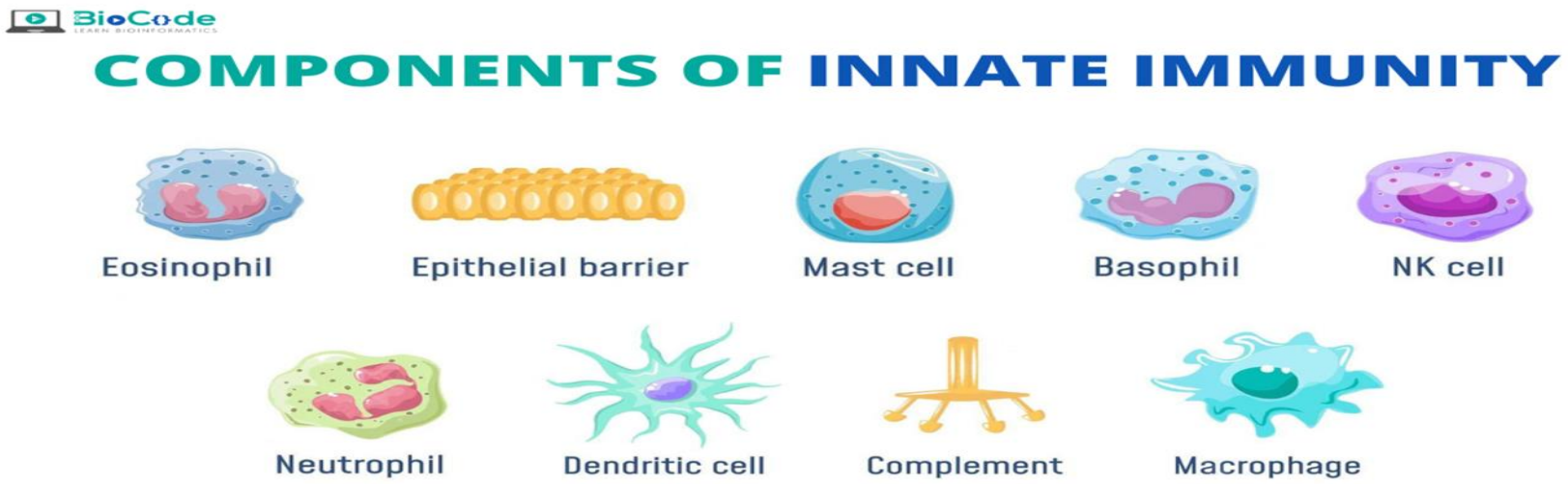
Lymph is protein rich fluid that circulates throughout the lymphatic system.

- It is formed, when the interstitial fluid (the fluid which lies between all body tissues) is collected inside lymphatic capillaries, transported through lymphatic vessels to larger lymph nodes, where it is cleaned by lymphocytes, before emptying finally into the right or the left subclavian vein, where it mixes back with the blood.

Body defense Mechanisms:

1. The innate immune system

- innate immunity involves immediate, nonspecific actions, including physical barriers such as the skin and mucous membranes of the gastrointestinal, respiratory, and urogenital tracts that prevent infections or penetration of the host body. Bacteria, fungi, and parasites that manage to penetrate these barriers are quickly removed by neutrophils and other leukocytes in the adjacent connective tissue.
- **Toll-like receptors (TLRs) on leukocytes** allow the recognition and binding of surface components of such invaders. **Natural killer (NK) cells** destroy various unhealthy host cells, including those infected with virus or bacteria, as well as certain potentially tumorigenic cells.



❖Leukocytes and specific cells of the tissue barriers also produce a wide variety of **antimicrobial chemicals** that also form a major part of innate immunity, including the following:

■ **Hydrochloric acid (HCl)** and organic acids in specific regions lower the pH locally to either kill entering microorganisms directly or inhibit their growth.

■ **Defensins,** short cationic polypeptides produced by neutrophils and various epithelial cells that kill bacteria by disrupting the cell walls.

■ **Lysozyme**, an enzyme made by neutrophils and cells of epithelial barriers, which hydrolyzes bacterial cell wall , killing those cells.

■ **Complement**, a system of proteins in blood plasma, mucus, and macrophages that react with bacterial surface components to aid removal of bacteria.

■ **Interferons**, paracrine factors from leukocytes and virus-infected cells that signal NK cells to kill such cells and adjacent cells to resist viral infection.

2. Adaptive immunity:

- acquired gradually by exposure to microorganisms, is more specific, slower to respond. The adaptive immune response involves **B and T lymphocytes** which become activated against specific invaders by being presented with specific molecules from those cells by **antigen presenting cells APCs**, which are usually derived from monocytes.

2^{nd} exposure → faster.

- Unlike innate immunity, adaptive immune responses are aimed at specific microbial invaders and involve production of memory lymphocytes so that a similar response can be mounted very rapidly if that invader ever appears again.

- ❑Humoral immunity …. Against antigens
- ❑Cell mediated immunity…. Against tumor, transplant cells, virus infected cells & microorganisms

Cells of the immune system

- **Macrophages**
- **Antigen – presenting cells**
  - Dendritic cells
  - Macrophages
  - B- lymphocytes
  - Epithelial reticular cells

Express **both MHC I &II** on their cell membrane

- **Granular** leucocytes(N,E,B(
- **Mast cell**
- **Lymphocytes (B ,T, natural killer(**

Lymphocytes

Arise in the red bone marrow, they protect the body against antigens

Types of lymphocytes

- **T-lymphocytes** (T cells): mature in the thymus, directly attack and destroy foreign cells
- **B-lymphocytes** (B cells): mature in the bone marrow, produce plasma cells that manufacture antibodies
- **NK (natural killer)** cells (non-speficic immunity) = they mature in the bone marrow

Antigenic markers of lymphocytes

The cell coat: Large no. of cell receptors.

1. **Major histocompatibility complex (MHC)**
   Glycoprotein + specific a.a. sequence.

Tissue typing & antigenic recognition.

2. subclasses:

MHC I & MHC II.

2- The cluster of differentiation antigens (CDs):

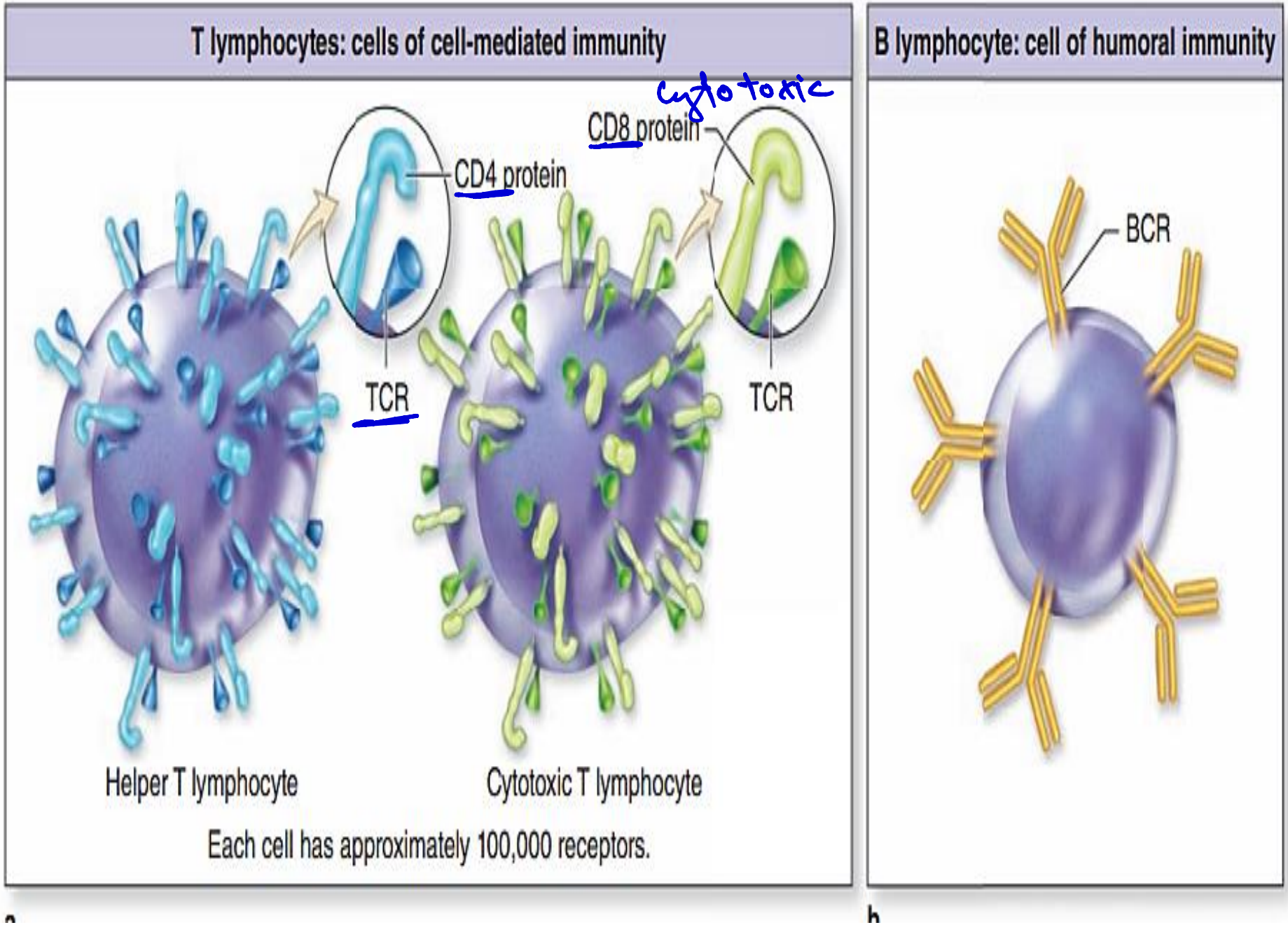
glycocalyx.

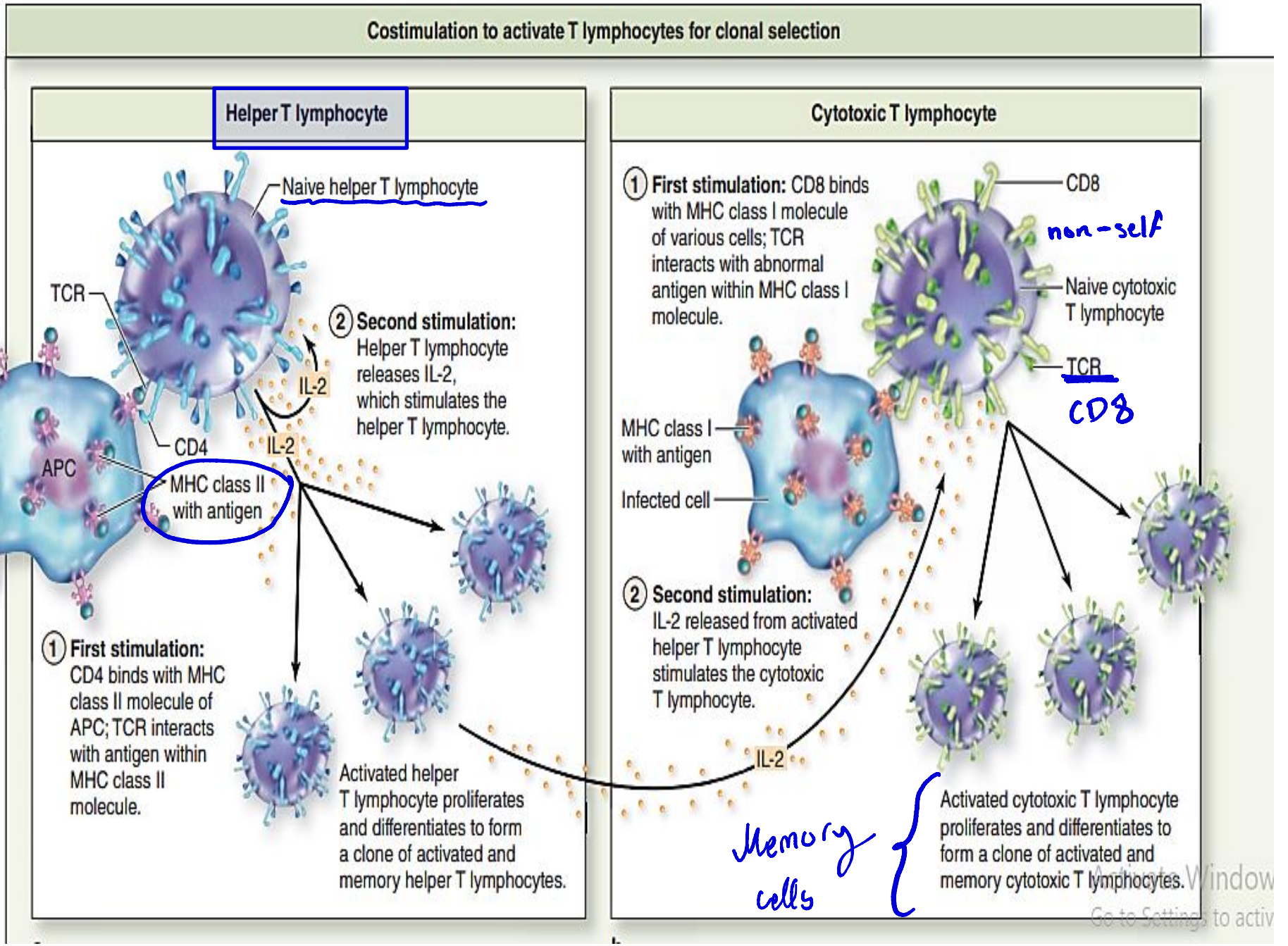
- **Cell- surface glycoprotein + specific a.a. sequence.**
- **Expressed on different types of lymphocytes**
- **Marker proteins upon which** 

Functional types of lymphocytes.

T Lymphocytes

- T cells are long-lived lymphocytes and constitute nearly 75% of the circulating lymphocytes.
- They recognize antigenic epitopes via surface protein complexes termed T-cell receptors (TCRs).
- Most TCRs include two glycoproteins called α and β chains. TCRs only recognize antigenic peptides when presented as part of MHC molecules.
- Several types of T lymphocytes exist, with various functions.


T lymphocytes: cells of cell-mediated immunity
cytotoxic
CD8 protein
CD4 protein
TCR
TCR
Helper T lymphocyte
Cytotoxic T lymphocyte
Each cell has approximately 100,000 receptors.
B lymphocyte: cell of humoral immunity
BCR


Costimulation to activate T lymphocytes for clonal selection
Helper T lymphocyte
Naive helper T lymphocyte
TCR
CD4
APC
MHC class II with antigen
IL-2
IL-2
2 Second stimulation: Helper T lymphocyte releases IL-2, which stimulates the helper T lymphocyte.
1 First stimulation: CD4 binds with MHC class II molecule of APC; TCR interacts with antigen within MHC class II molecule.
Activated helper T lymphocyte proliferates and differentiates to form a clone of activated and memory helper T lymphocytes.
Cytotoxic T lymphocyte
1 First stimulation: CD8 binds with MHC class I molecule of various cells; TCR interacts with abnormal antigen within MHC class I molecule.
CD8
non-self
Naive cytotoxic T lymphocyte
TCR
CD8
MHC class I with antigen
Infected cell
2 Second stimulation: IL-2 released from activated helper T lymphocyte stimulates the cytotoxic T lymphocyte.
IL-2
Memory cells
Activated cytotoxic T lymphocyte proliferates and differentiates to form a clone of activated and memory cytotoxic T lymphocytes.

Important subpopulations of T cells include the following:

- **Helper T cells (Th cells)** are characterized by CD4, the coreceptor with the TCR for binding MHC class II molecules and the peptides they are presenting. Activated by such binding, helper T cells greatly assist immune responses by producing cytokines.

Functions:

- promote differentiation of B cells into plasma cells,
- activate macrophages to become phagocytic,
- activate cytotoxic T lymphocytes (CTLs), and induce many parts of an inflammatory reaction.
- Some specifically activated helper T cells persist as long-lived memory helper T cells, which allow a more rapid response if the antigen appears again later.

- **Cytotoxic T lymphocytes** are CD8+. Their TCRs together with CD8 coreceptors bind specific antigens on foreign cells or virus-infected cells displayed by MHC class I molecules. In the presence of interleukin-2 (IL-2) from helper T cells, cytotoxic T cells are activated and proliferate.

- Also called killer T cells, they attach to the cell sources of the antigens and remove them by releasing perforins and granzymes, which trigger apoptosis. This represents cell-mediated immunity and its mechanism is largely similar to that of NK cells.

- Activation of cytotoxic T cells also results in a population of memory cytotoxic T cells.

- **Regulatory T cells** (Tregs or suppressor T cells) are CD4+CD25+ and serve to inhibit specific immune responses.

- play crucial roles in allowing immune tolerance, maintaining unresponsiveness to self-antigens and suppressing excessive immune responses.

innate immune

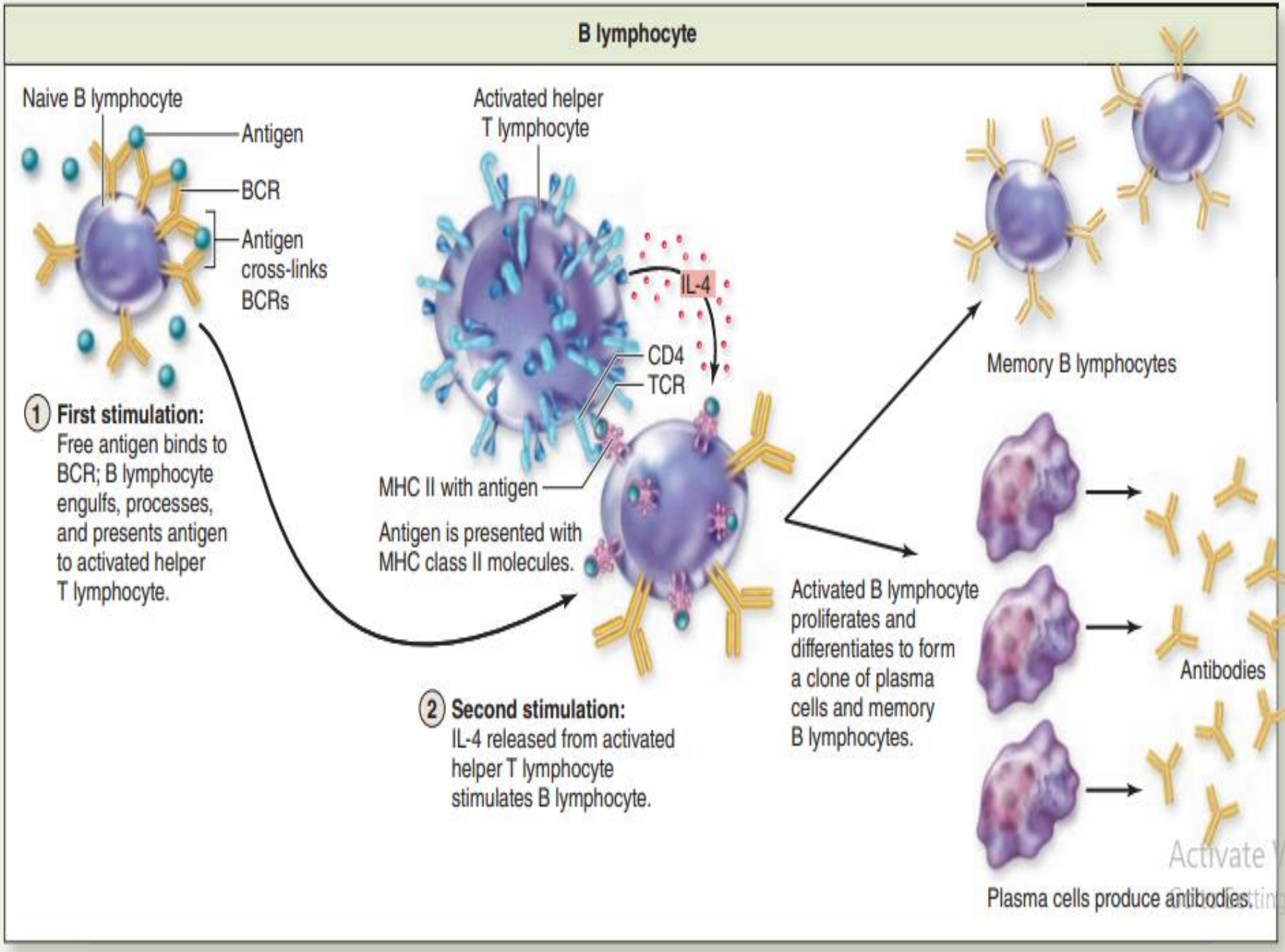
Not in circulation/lymphoid org.

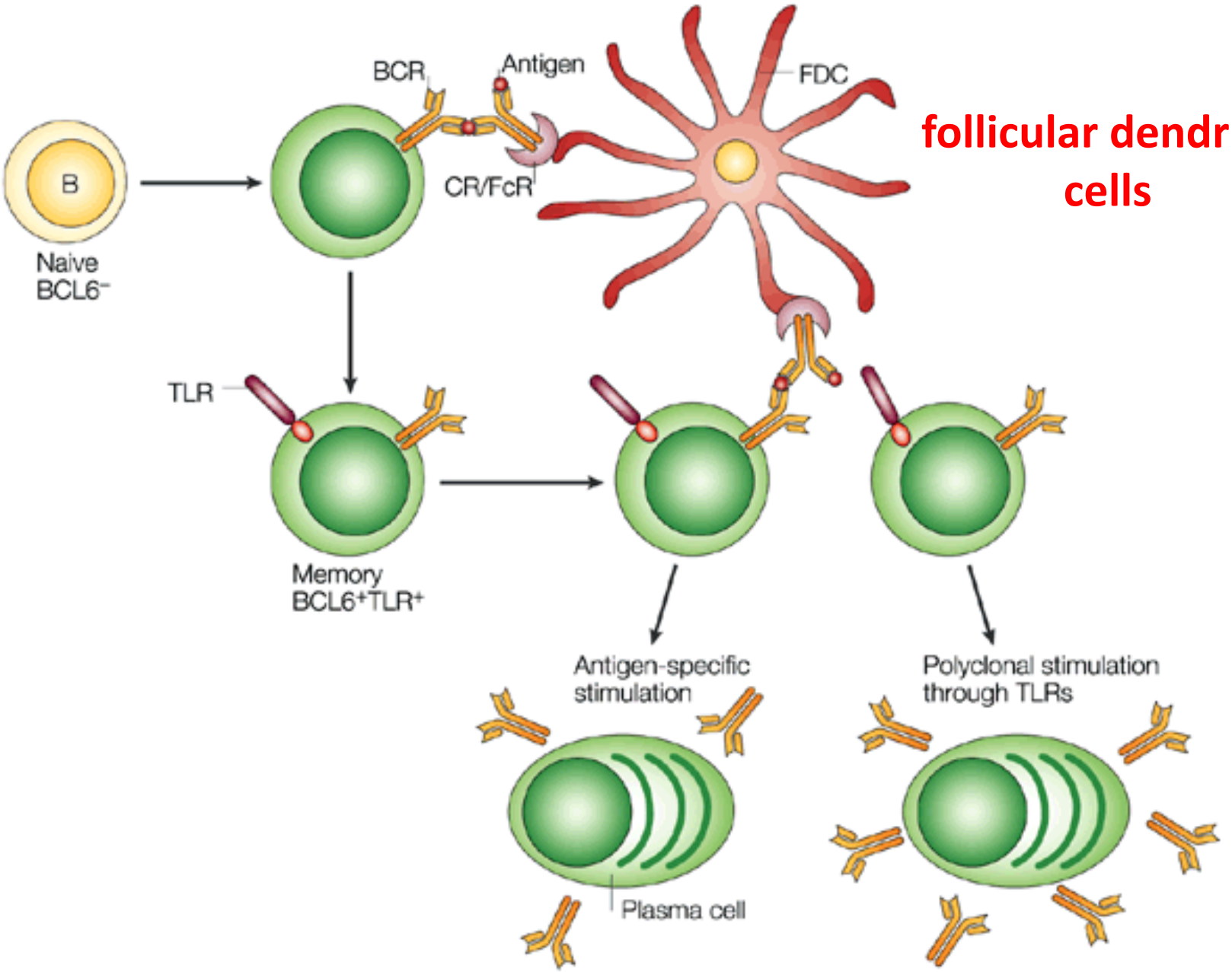
- **γδ T lymphocytes** represent a smaller subpopulation whose TCRs contain γ (gamma) and δ (delta) chains instead of α and β chains. The γδ T cells migrate to the epidermis and mucosal epithelia, becoming largely intraepithelial, and do not recirculate to secondary lymphoid organs. They function in like cells of innate immunity

B Lymphocytes

Direct surface of other.

- In B lymphocytes the surface receptors for antigens are monomers of IgM or IgD, with each B cell covered by about 150,000 receptors (BCRs).
- BCRs bind an antigen, which may be free in solution, on an exposed part of an infectious agent, or already bound to antibodies, and the surface complexes then undergo endocytosis. Degraded in endosomes, peptides from the antigens are presented on MHC class II molecules of the B cell.
- A helper T cell then binds this B cell and activates it further with a cytokine, stimulating several cycles of cell proliferation


B lymphocyte
Naive B lymphocyte
Antigen
BCR
Antigen cross-links BCRs
1 First stimulation:
Free antigen binds to BCR; B lymphocyte engulfs, processes, and presents antigen to activated helper T lymphocyte.
Activated helper T lymphocyte
IL-4
CD4
TCR
MHC II with antigen
Antigen is presented with MHC class II molecules.
2 Second stimulation:
IL-4 released from activated helper T lymphocyte stimulates B lymphocyte.
Memory B lymphocytes
Activated B lymphocyte proliferates and differentiates to form a clone of plasma cells and memory B lymphocytes.
Antibodies
Plasma cells produce antibodies.



follicular dendritic cells

- In all secondary lymphoid tissues, B lymphocytes interact with scattered follicular dendritic cells (FDCs), which have long filamentous processes. These cells causing B cells to attach, become activated, and aggregate as a small **primary lymphoid nodule** (or follicle). With the help of adjacent T-helper cells, these B cells now form a much larger and more prominent **secondary lymphoid nodule.**

- Secondary nodules are characterized by a lightly stained germinal center. Growth of activated B cells in germinal centers is very rapid, causing naive, non proliferating B cells to be pushed aside and produce the more darkly stained **peripheral mantle**.

- Most of these new, specific B lymphocytes differentiate into **plasma cells** secreting antibodies that will bind the same epitope recognized by the activated B cell. Some of the newly formed B cells remain as long-lived memory B cells.

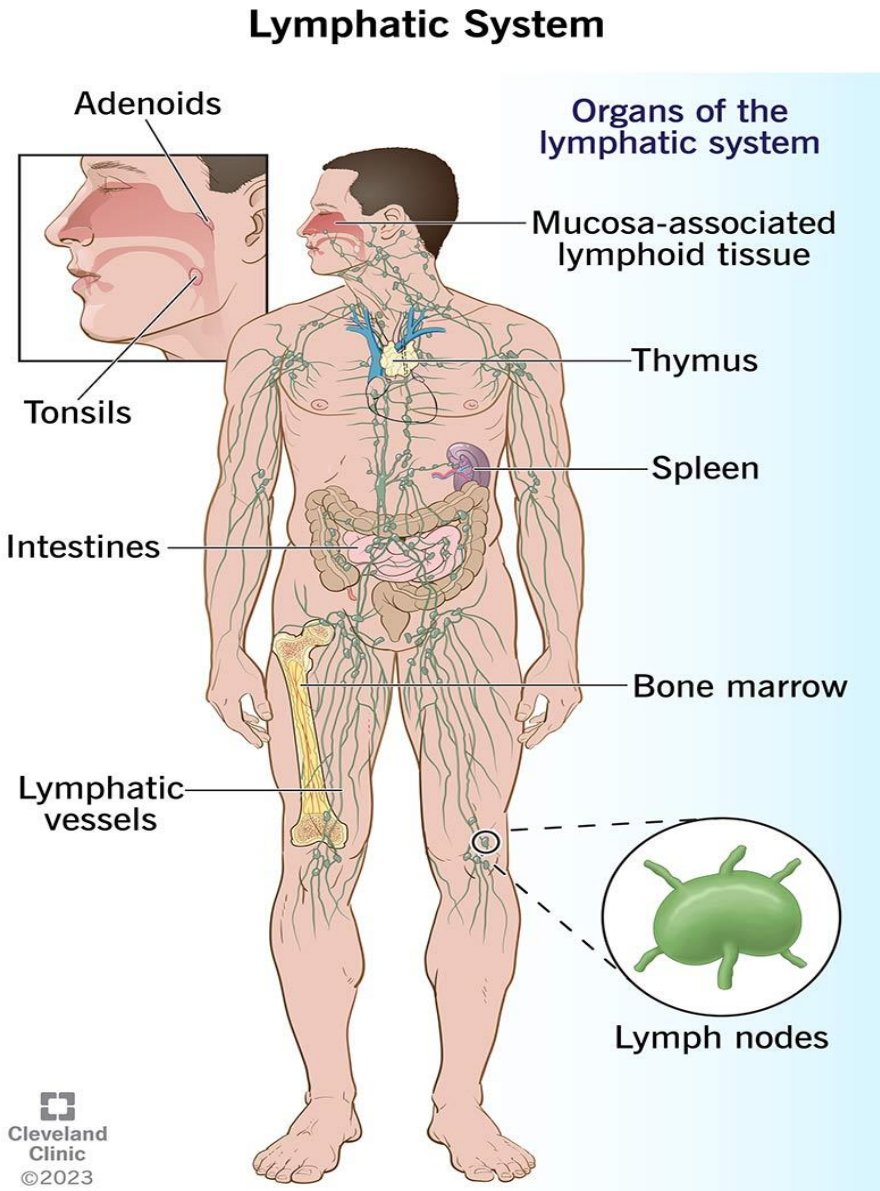
- After 2 to 3 weeks of proliferation, most cells of the germinal center and mantle are dispersed and the structure of the secondary lymphoid nodule is gradually lost.

Lymphoid organs

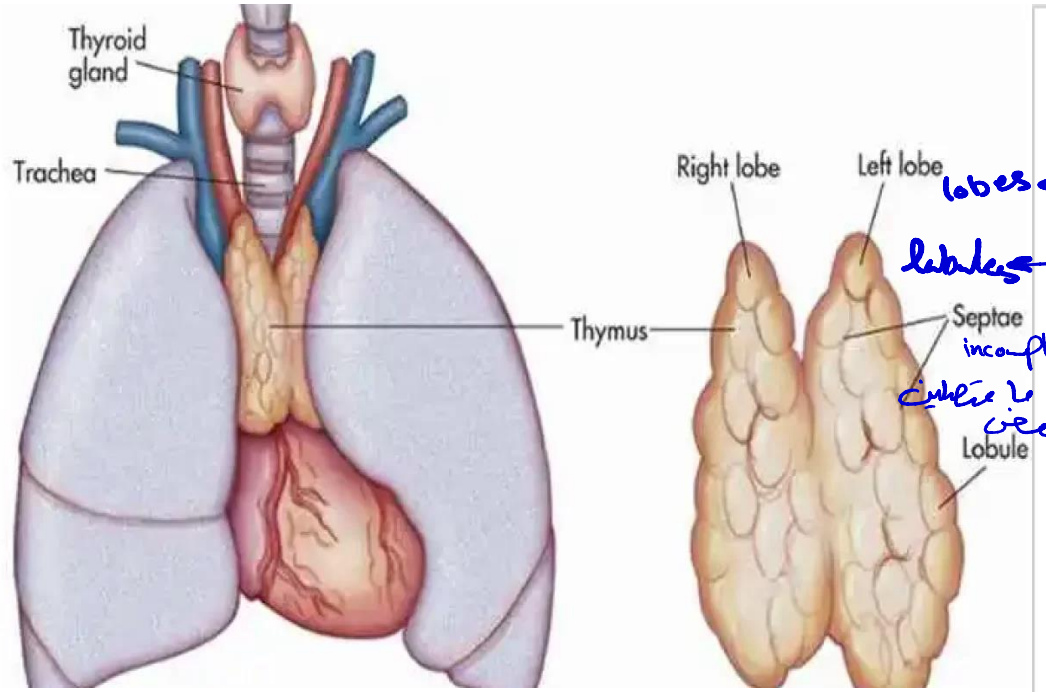
- Encapsulated (spleen, thymus, lymph nodes).
- Uncapsulated (tonsils, Peyers patches, nodules in tracts).

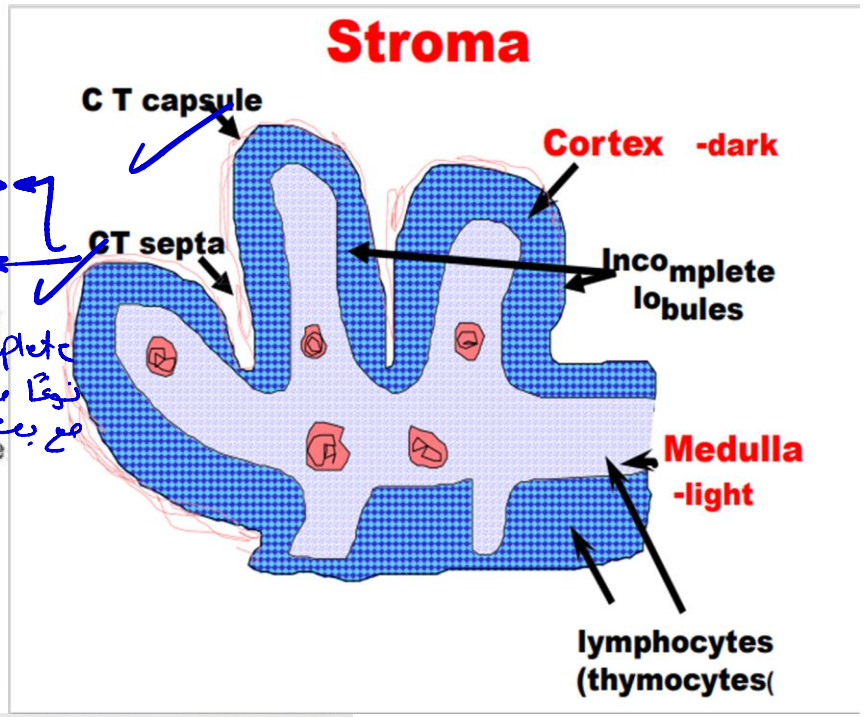
ilium.

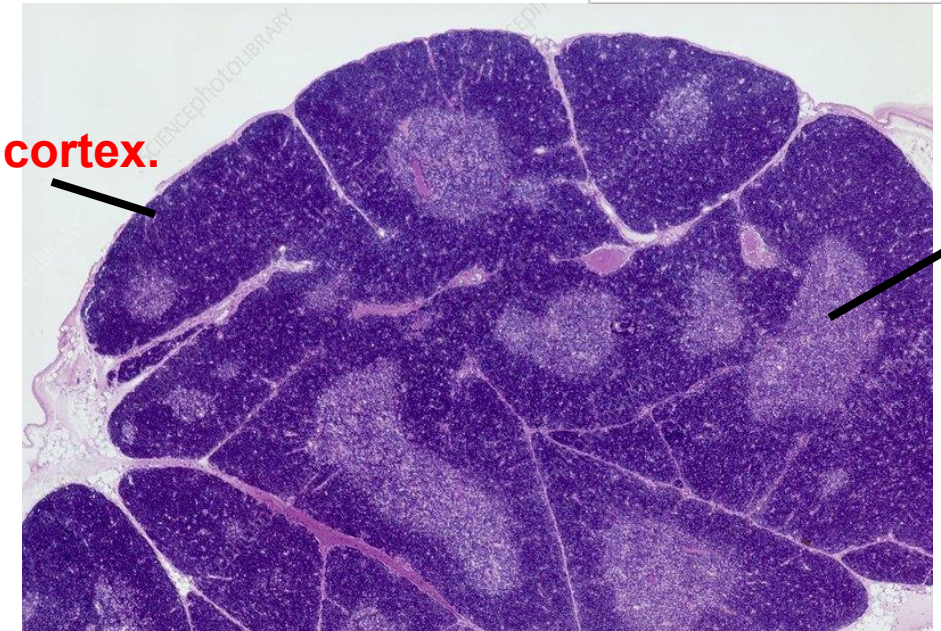
- **Central** (Thymus, bone marrow)
- **Peripheral** (spleen, lymph nodes).



Thymus gland







Thymus gland

Structure:

1. Stroma: C.T component (capsule, trabeculae (septa).....lobes & lobules

No reticular fibers

*From the capsule, connective tissue septa containing blood vessels

penetrate the substance of the organ, forming lobes.

*Thin septa divide the lobes into incomplete lobules

2. Parenchyma: (functioning component) Lobules of thymus continuous with each other.

* Each lobe has dark cortex and pale medulla.

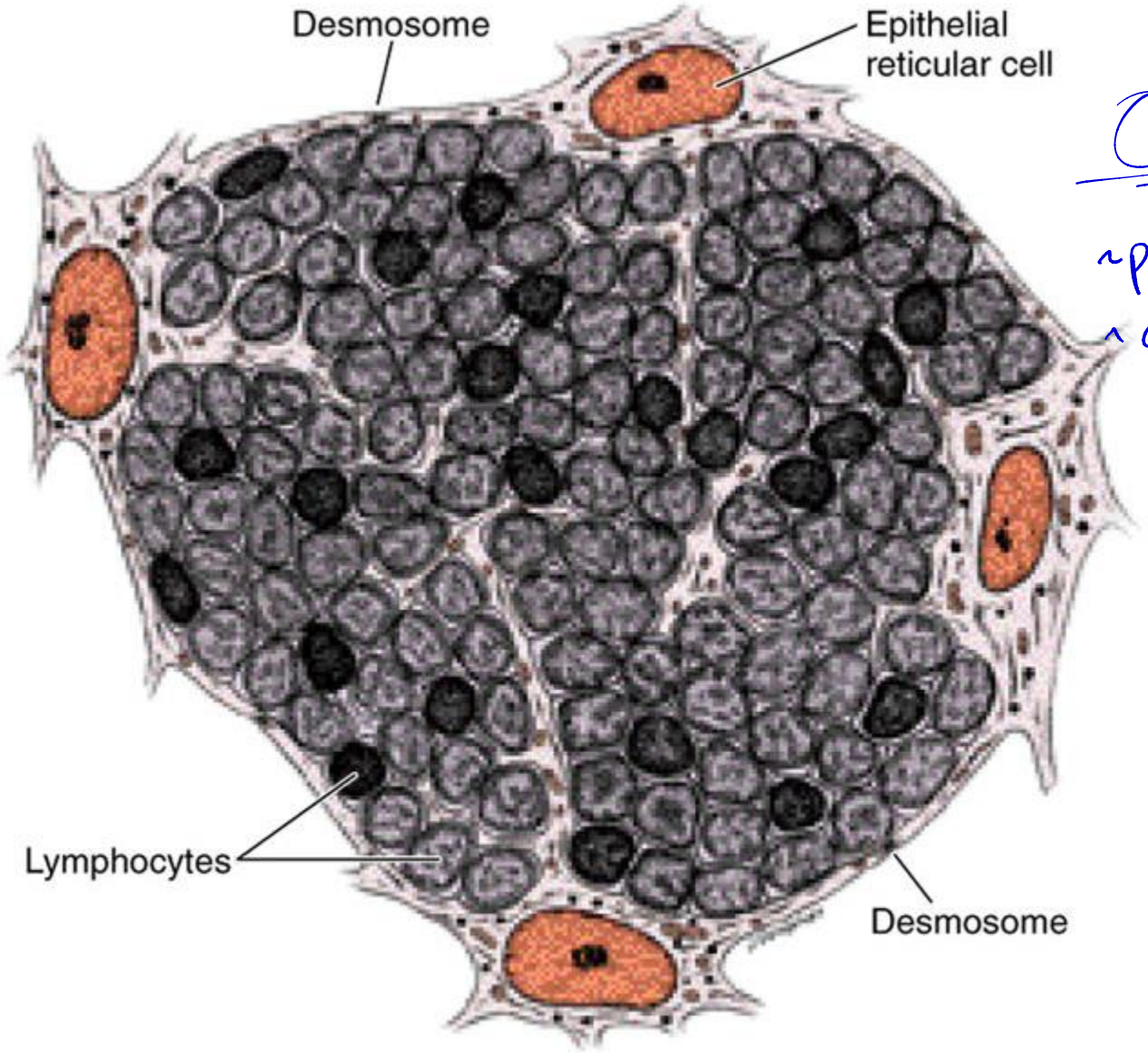
Cortex

1- Small T-lymphocytes (predominant cells).

2- Epithelial reticular cells:
- Nucleus: oval pale (extended chromatin).
- Cytoplasm: cytokeratin filaments.
- Branched:
  - processes joined together by desmosomes.
  - extend around lymphocytes.
  - form sheath around blood capillaries.

3- Macrophages.

4- Large lymphocytes.

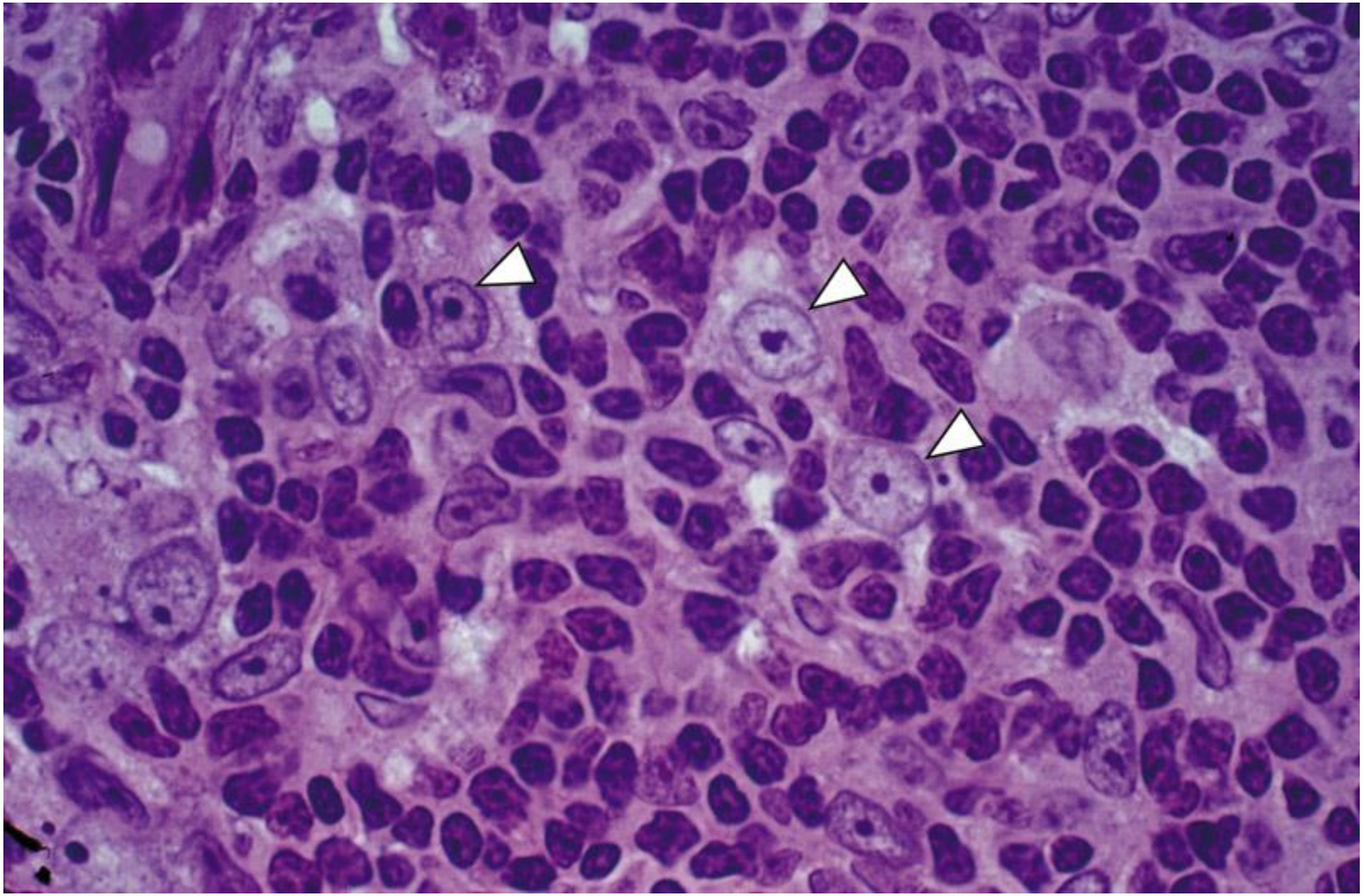


Only Cortex

- Processes.
- desmosomes.

Epithelial reticular cells processes extend among lymphocytes.

وبيتجمعوا بـ junction
Desmosomes



Cortex: Epithelial reticular cells (arrowheads) surrounded by dark-stained T lymphocytes.

B- Medulla

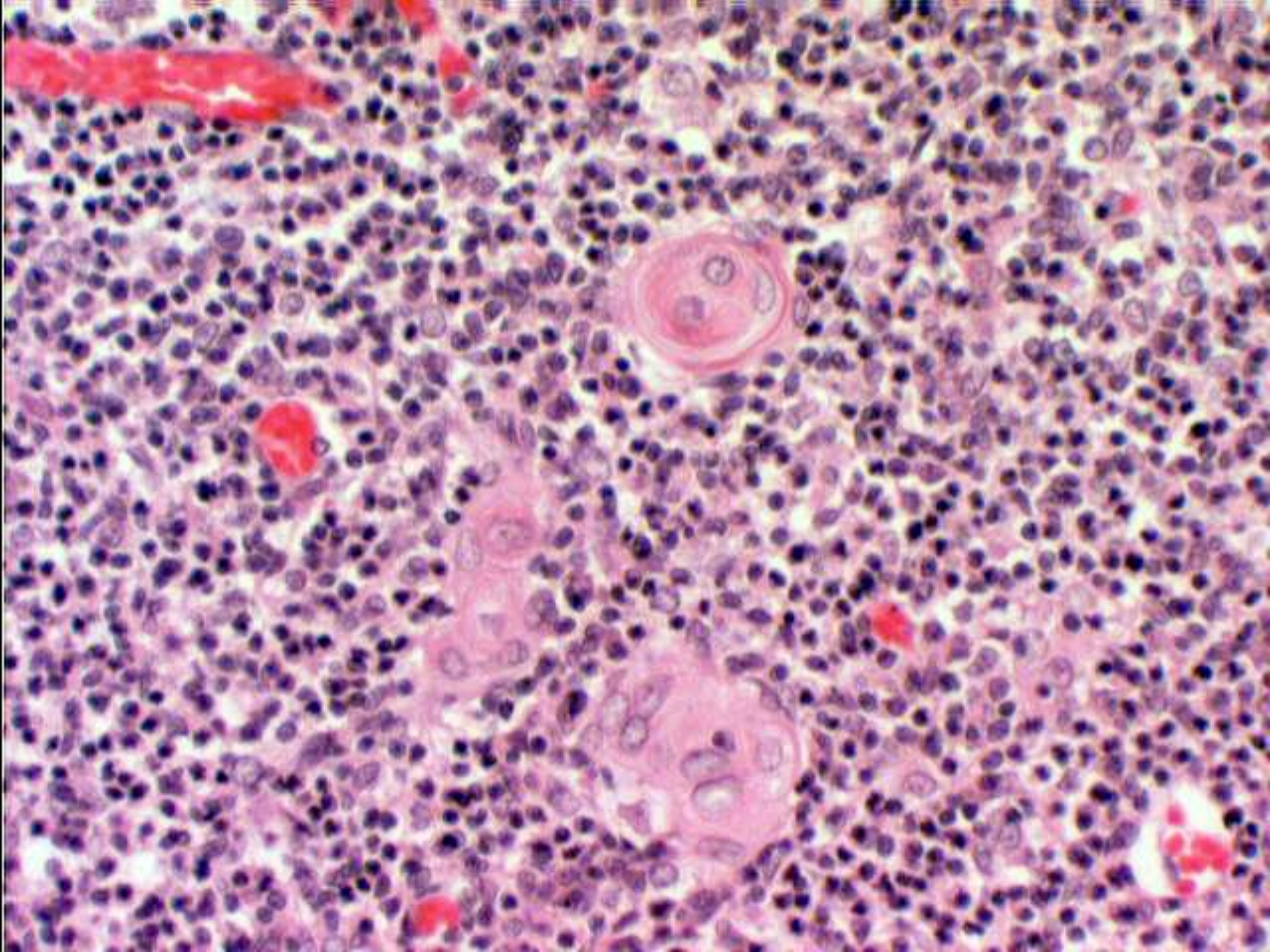
- Lightly stained due to epithelial reticular cells and large lymphocytes with abundant cytoplasm and pale nuclei.

Why its light? Because

- Fewer small T- lymphocytes than in cortex.

- Contains Hassle's corpuscles:
  - concentric layers of epithelial reticular cells.
  - Innermost cells degenerate.
  - filled with kertohyaline granules and cytokeratin filaments.

- No blood–thymic barrier in medulla as epithelial reticular cell layer is incomplete.



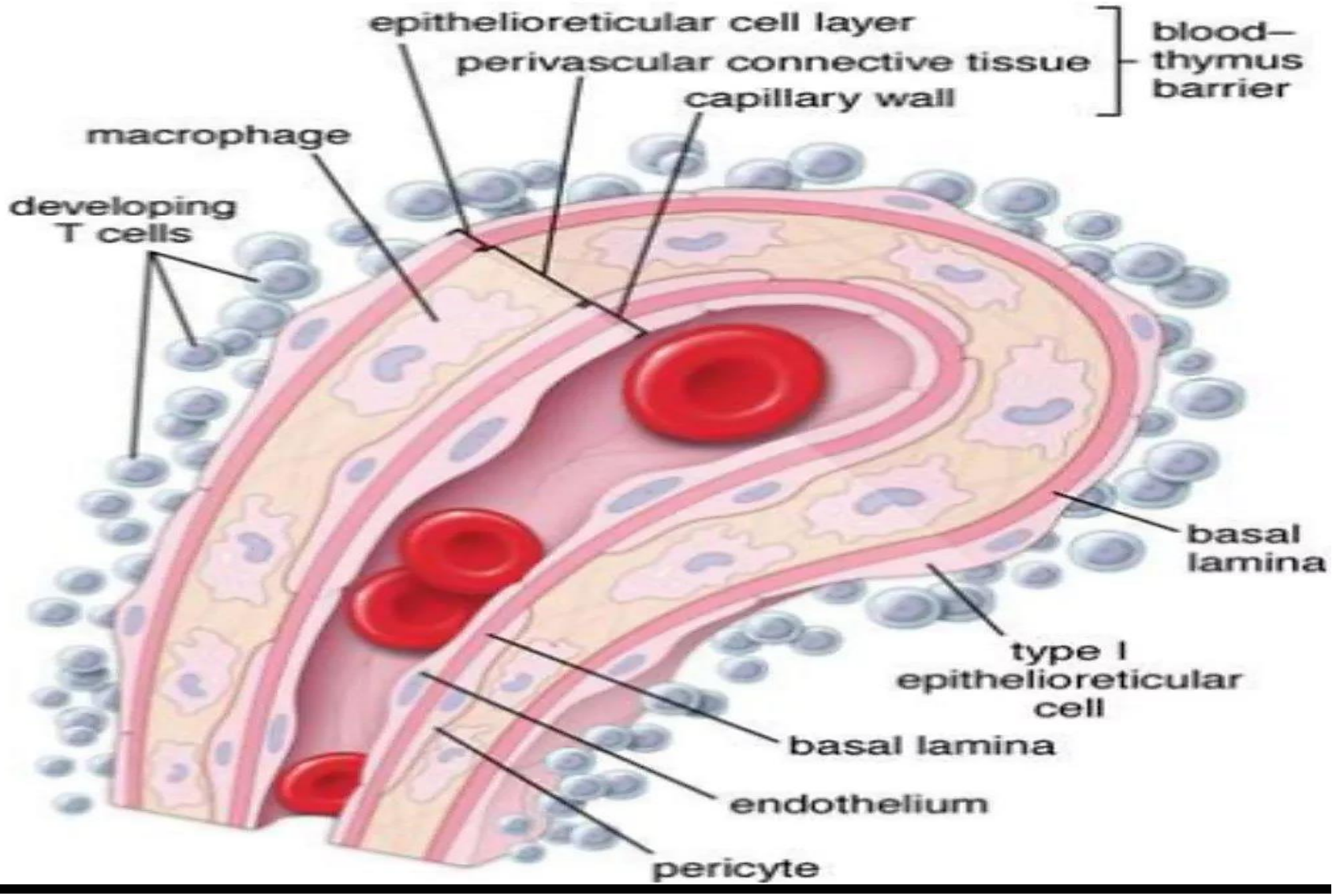
T-lymphocytes

- Proliferation and programming occur in cortex of thymus.
- Those reacting to self molecules are phagocytosed by macrophages.
- Others:
  - migrate to medulla.
  - pass through medullary venules to circulation to peripheral lymphoid organs (lymph nodes, spleen).
  - occupy thymus dependant areas to perform their function.

Vascularization

- Arteries enter capsule, follow septa → arterioles.
- Arterioles pass between cortex and medulla → capillaries.
- Capillaries → medullary venules.
- Veins → septa → capsule.

Blood- thymic barrier



Blood- thymic barrier

- Lymphocytes proliferate in cortex producing immature T-cells.

- During programming of T-cells they are protected from foreign Ag in lymph and blood as follows:

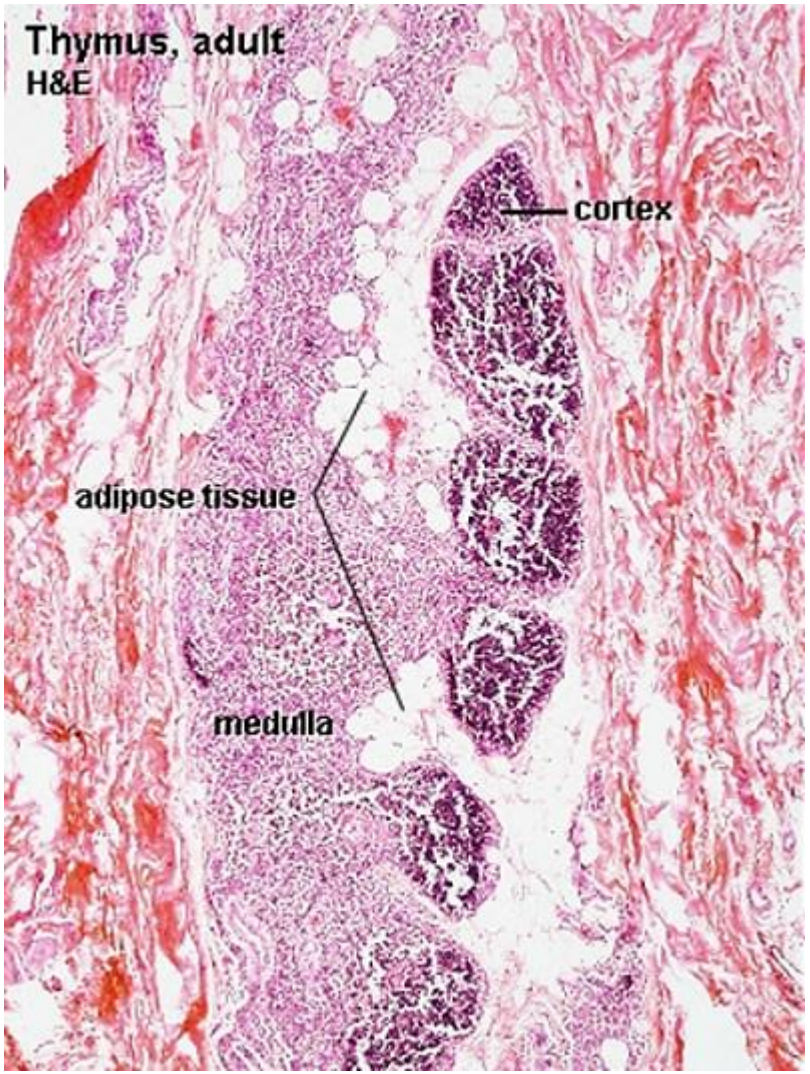
للحافظة على

  - No afferent lymphatics, only few efferents.

  - Blood–thymic barrier, present only in cortex.
    1. Continuous endothelium of blood capillaries
    2. Thick basal lamina of endothelium of blood capillaries
    3. Pericyte
    4. Small CT space: macrophages.
    5. Basal lamina of epithelial reticular cells
    6. Epithelial reticular cells processes which joined by desmosomes forming sheath around cortical blood capillaries.

Thymus gland of adult:

- Replaced by Fibrous & adipose tissue.
- Few lymphocytes, epithelial reticular cells
- Increase Hassall's corpuscles.



Effect of Hormones

- Sex hormones, ACTH and corticosteroids → stimulate involution.
- Growth hormone → stimulate development.

Functions of thymus

- Produce T-cells responsible for cellular immunity.

- Produce Thymic factors by epithelial reticular cells (thymosin, thymopoeitin, thymulin), that stimulate T- cell proliferation and differentiation.