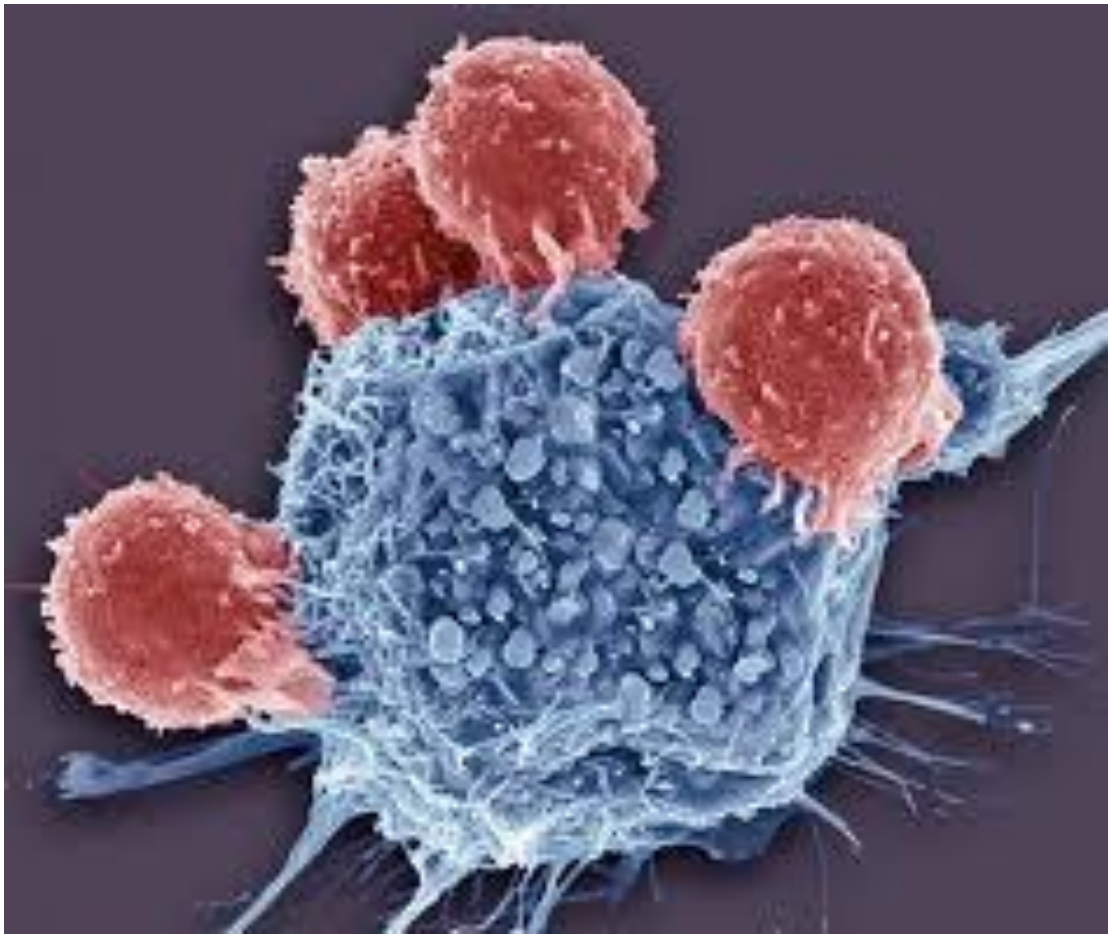
# IMMUNE SYSTEM

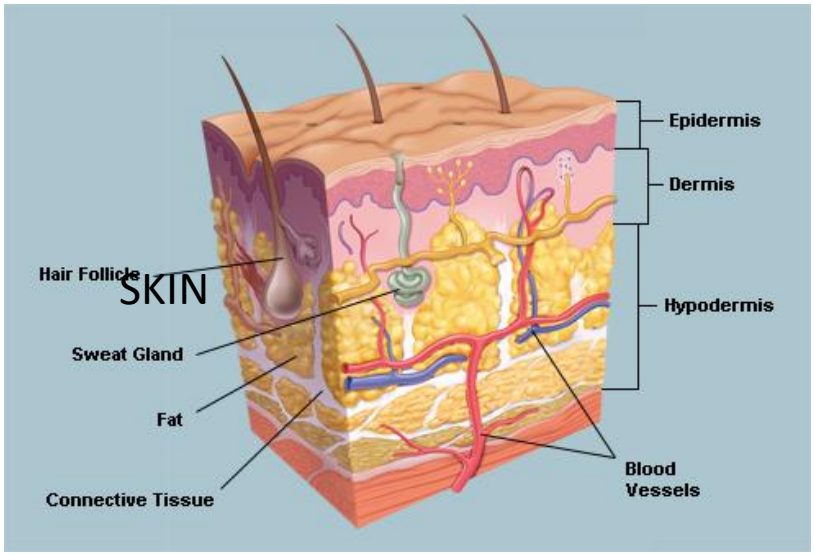
**is responsible for the immunological defense of the body.**



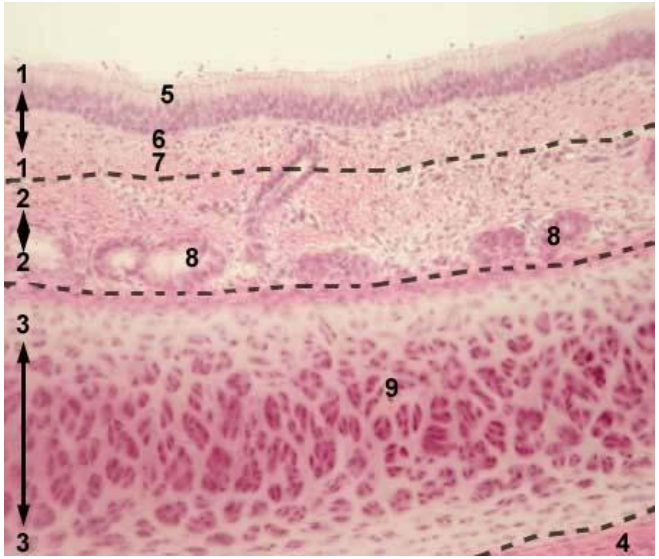
# FIRST LINE OF DEFENSE

## Mechanical barriers

SKIN

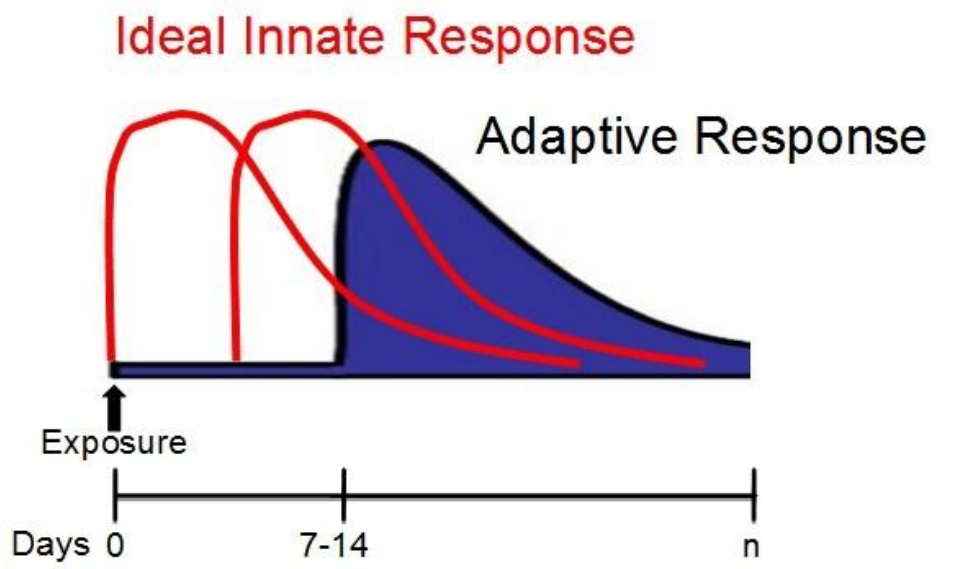



MUCOSA

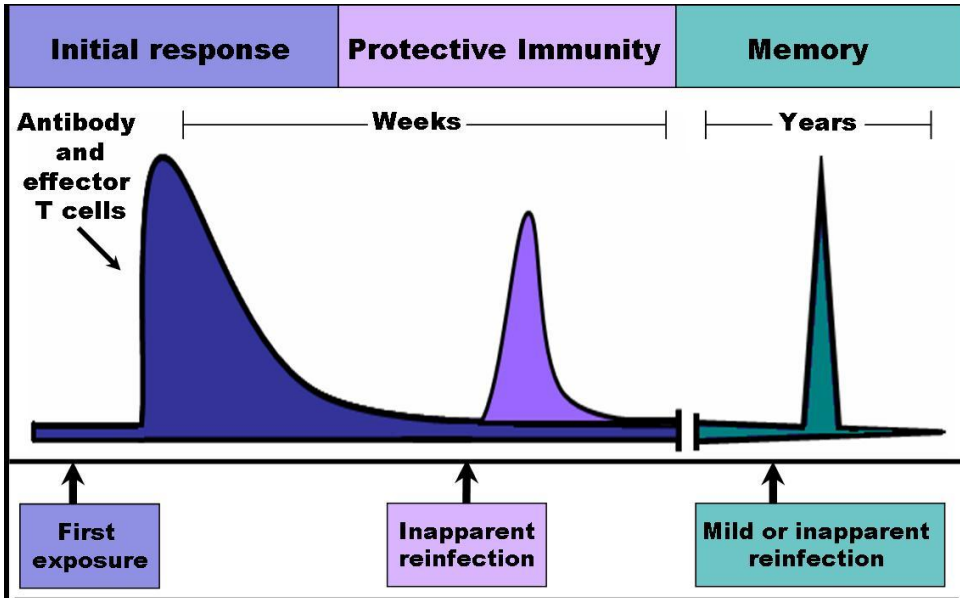


**The second and the third lines of defense:**

## INNATE IMMUNE SYSTEM
(natural immune system)
- nonspecific
- responds rapidly
- has no immunological memory




## ADAPTIVE IMMUNE SYSTEM
(acquired immune system)
- specific
- responds slowly
- has immunological memory
- depends on T and B lymphocytes



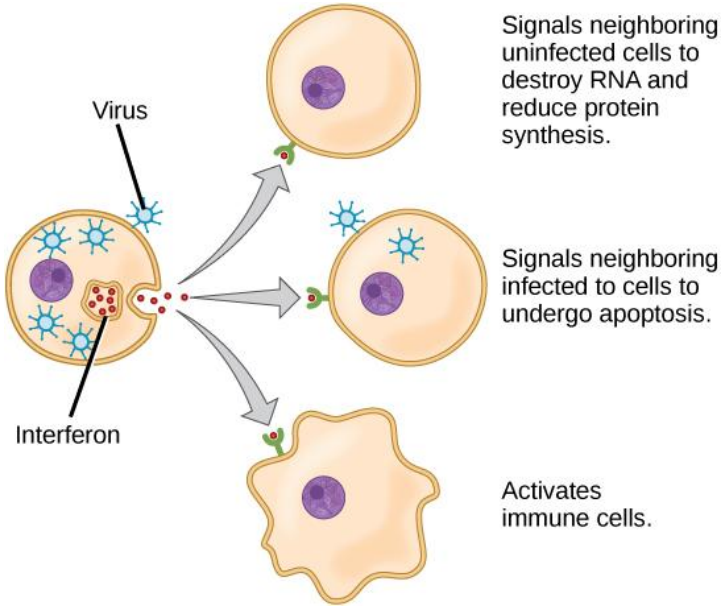
# INNATE IMMUNE SYSTEM

- **complement-** series of blood-borne proteins (form membrane attack complex on the surface of pathogens)
- **defensins** (antimicrobial peptides synthesized by epithelial cells - interact with microbial membranes)
- **lysozyme** (enzyme hydrolyzing the bacterial walls, present in secretions - tears, saliva)
- **cytokines** (signaling molecules - interleukins, chemokines, CSFs, interferons)

-**macrophages** (phagocytosis)

- **neutrophils** (phagocytosis)

- **NK cells** (recognize - using nonspecific receptors - and kill target cells)

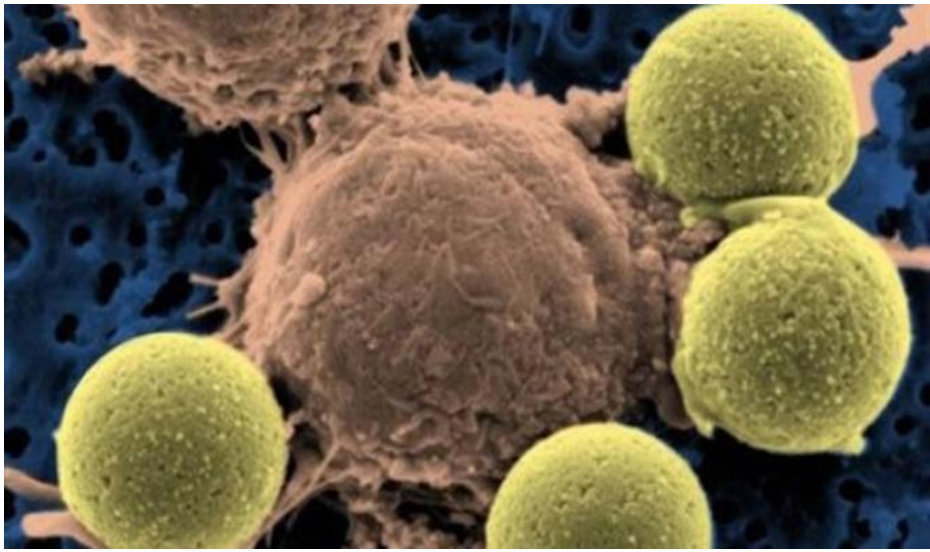


# ADAPTIVE IMMUNE SYSTEM

- has the ability to distinguish self from nonself (foreign)
- exhibits specificity, diversity, memory

The immune system destroys microorganisms, virus-infected cells and cancer cells.

It also recognizes cells of transplanted organ and can destroy them.



# CELLS OF ADAPTIVE IMMUNE SYSTEM

## T lymphocytes

cell-mediated response

**T-helper cells** – induction of immune response
**Cytotoxic T cells** – killing of target cells
**T reg cells** – suppression (modulation) of immune response

## B lymphocytes

humoral response

production of immunoglobulins (antibodies)

## Antigen-presenting cells (APC)

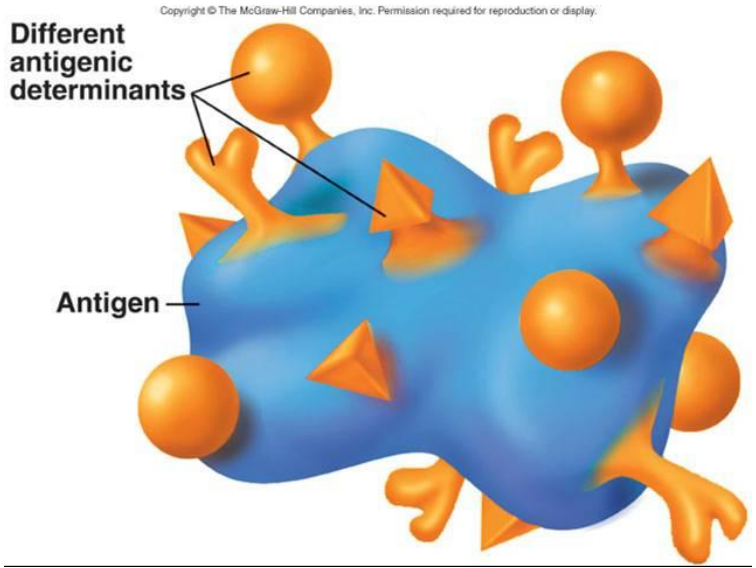
presentation of antigens

# DEFINITIONS

**Antigen** – is any substance that may be specifically bound by components of the immune system (antibody, lymphocytes).

**Immunogen** – is any antigen that is capable of inducing humoral and/or cell-mediated immune response. This ability is called immunogenicity. Sometimes the term immunogen is used interchangeably with the term antigen.

**Epitope** – antigenic determinant – is the part of an antigen that is recognized by the immune system, specifically by antibodies, B cells, or T cells.



# B LYMPHOCYTES - HUMORAL RESPONSE

**production of immunoglobulins (antibodies)**

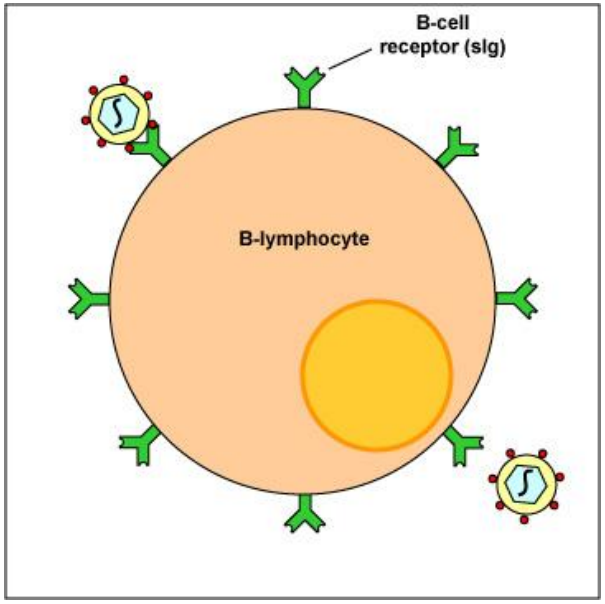
**B cells** are formed in the **bone marrow** and leave it already mature.

They possess the BCR receptors - allows a B cell to bind to a **specific** antigen.

**Naïve B cells** – is a B cell that has not been exposed to an antigen

**Plasma cell** - produce and secrete of antibodies

**B memory cells -** are able to live for a long time, and can respond quickly following a second exposure to the same antigen



# Antibodies

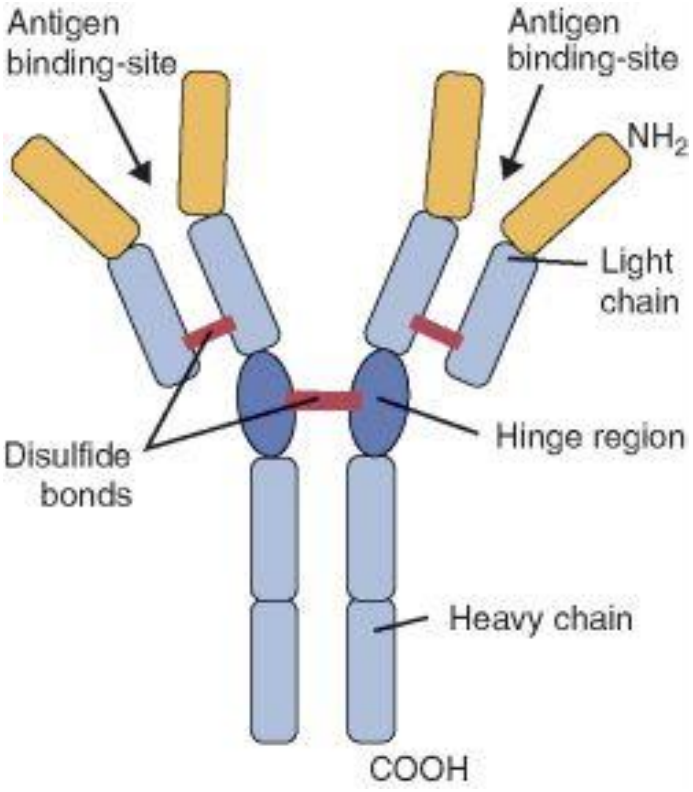
**IgD** –BCR receptors

**IgM** - BCR receptor for antigens, first antibody in primary immune response

**IgG** – most abundant, crosses the placental barrier

**IgA** - found in secretions

**IgE** – allergic reactions, defense against parasites.



# T LYMPHOCYTES

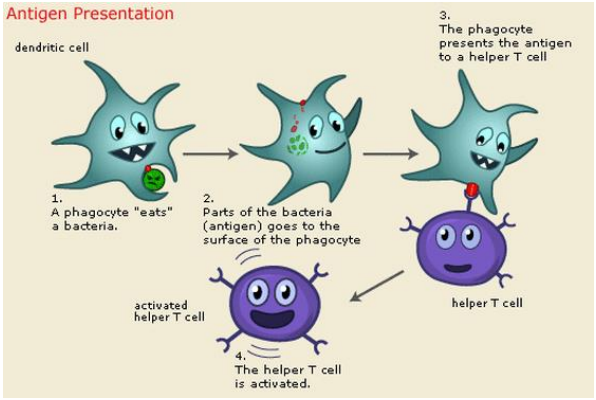
## - CELL-MEDIATED IMMUNE RESPONSE

T cells are formed in the bone marrow and migrate to the **thymus** to mature. They possess TCR receptors, **recognize only epitopes presented to them by other cells.**

Three types of T cells:

**Naive T cells** – before the first contact with antygen

**Memory T cells -** T cells that persist long-term after an infection




**Effector T cells**

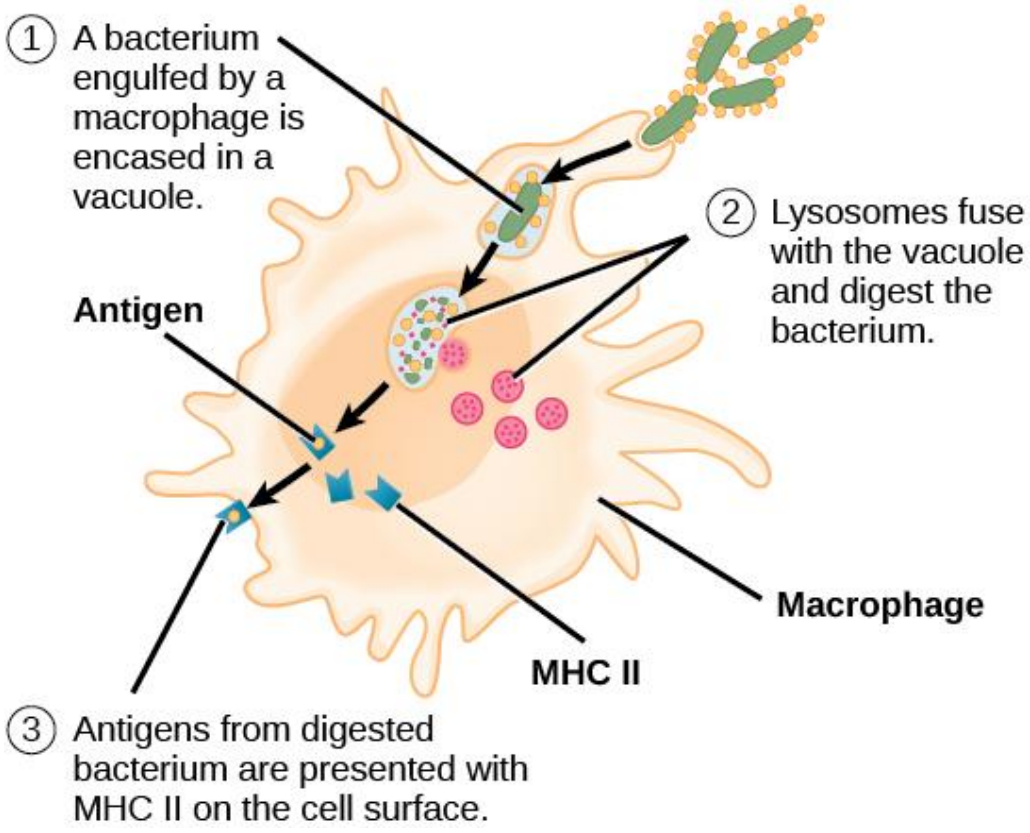
**T-helper cells – CD4** – direct the immune response

**T cytotoxic cells – CD8 (CTLs)** – killer cells (destroy virally infected cells and tumor cells)

**T regulatory cells – CD4 -** suppress immune response

# ANTIGEN-PRESENTING CELLS (APCS)

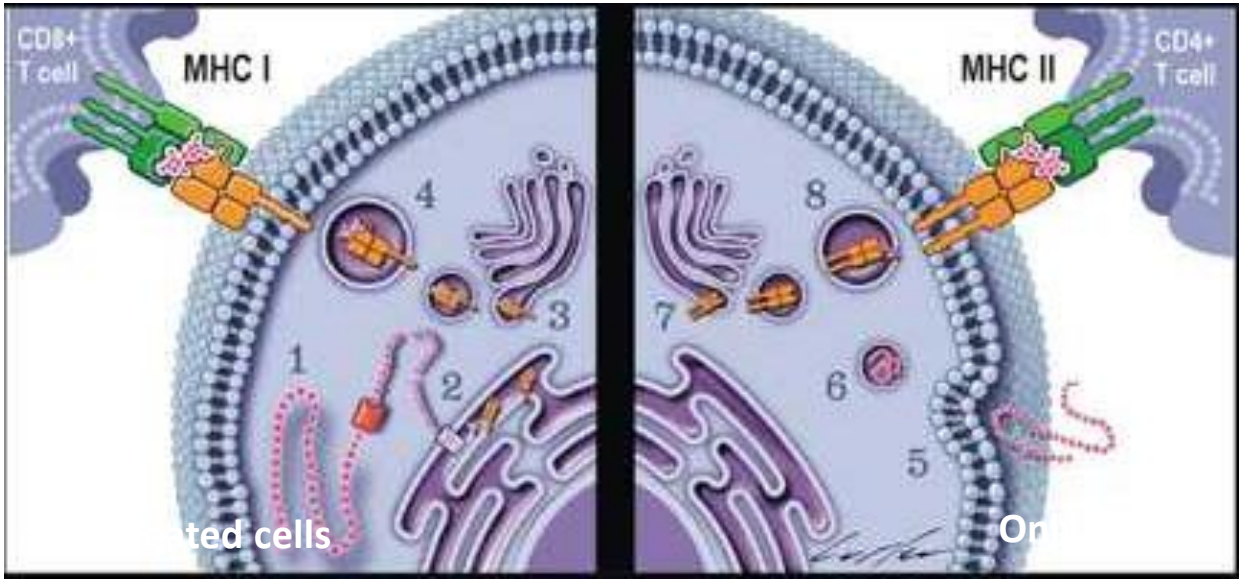
-phagocytose and process antigens
-present antigens to T cells
-express MHC I and MHC II
-release cytokines

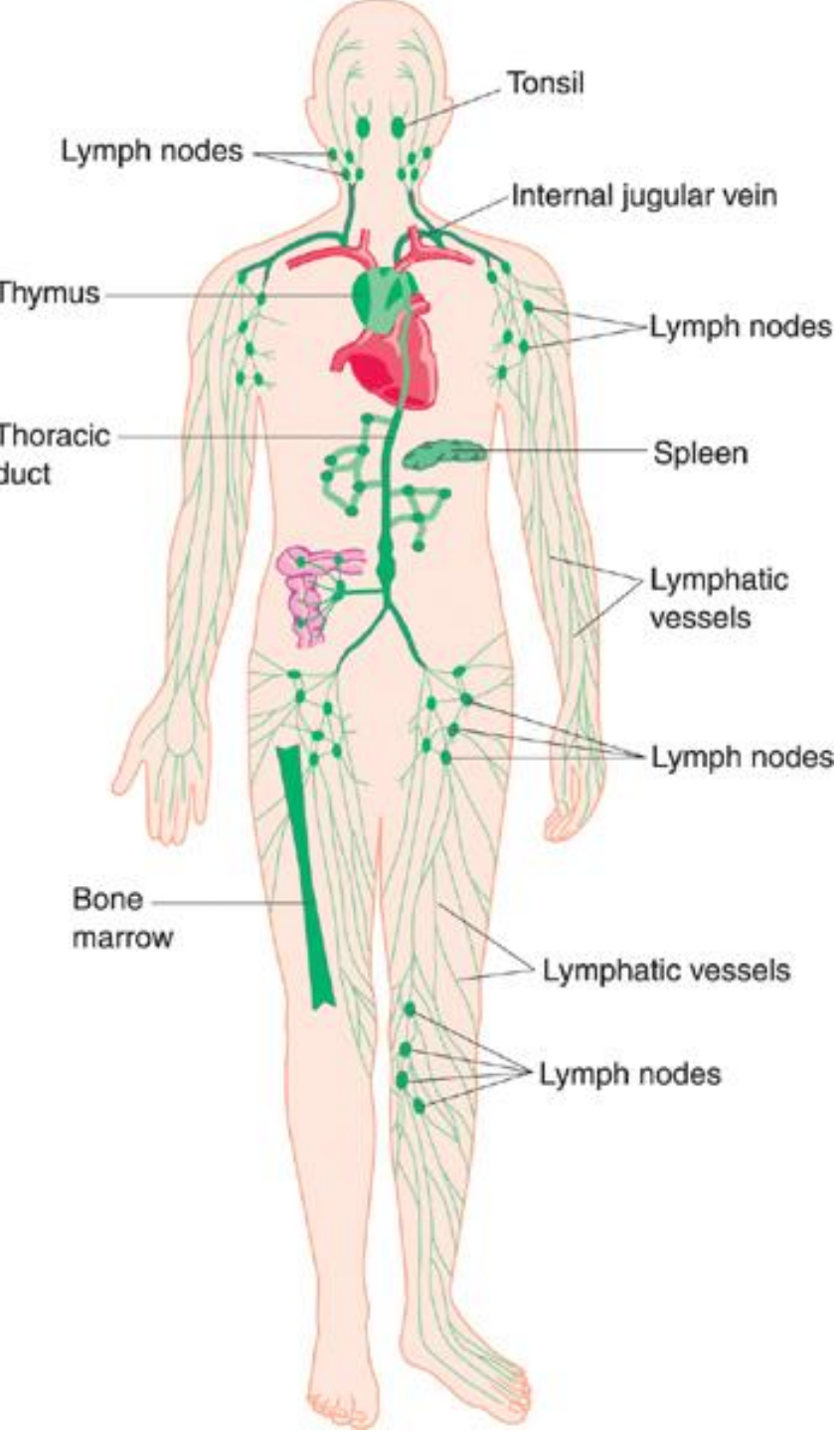


# MAJOR HISTOCOMPATIBILITY COMPLEX

**MHC I (bind CD8)**
- are present on the plasma membrane of all nucleated cells
- all cells present endogenous proteins to T CD8 cells

**MHC II (bind CD4)**
- are present only on APCs
- only APCs can present exogenous proteins to T CD4 cells






# ADAPTIVE IMMUNE SYSTEM-

## LYMPHOID ORGANS

**-primary (central) lymphoid organs**

Development and maturation of lymphocytes

**bone marrow**

**thymus**

**-secondary lymphoid organs**

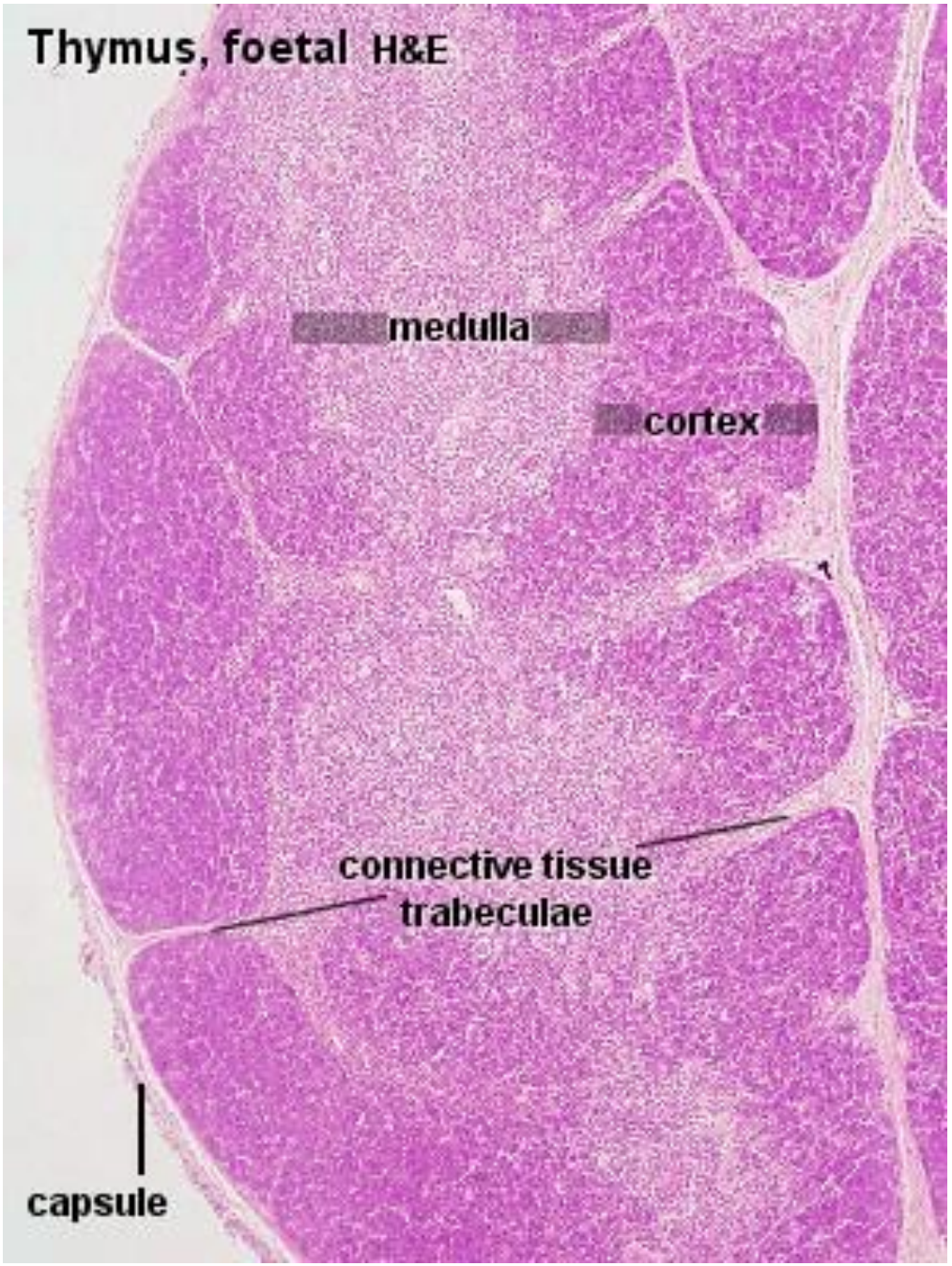
Proper environment for immunocompetent cells

**lymph nodes**

**spleen**

**tonsils**

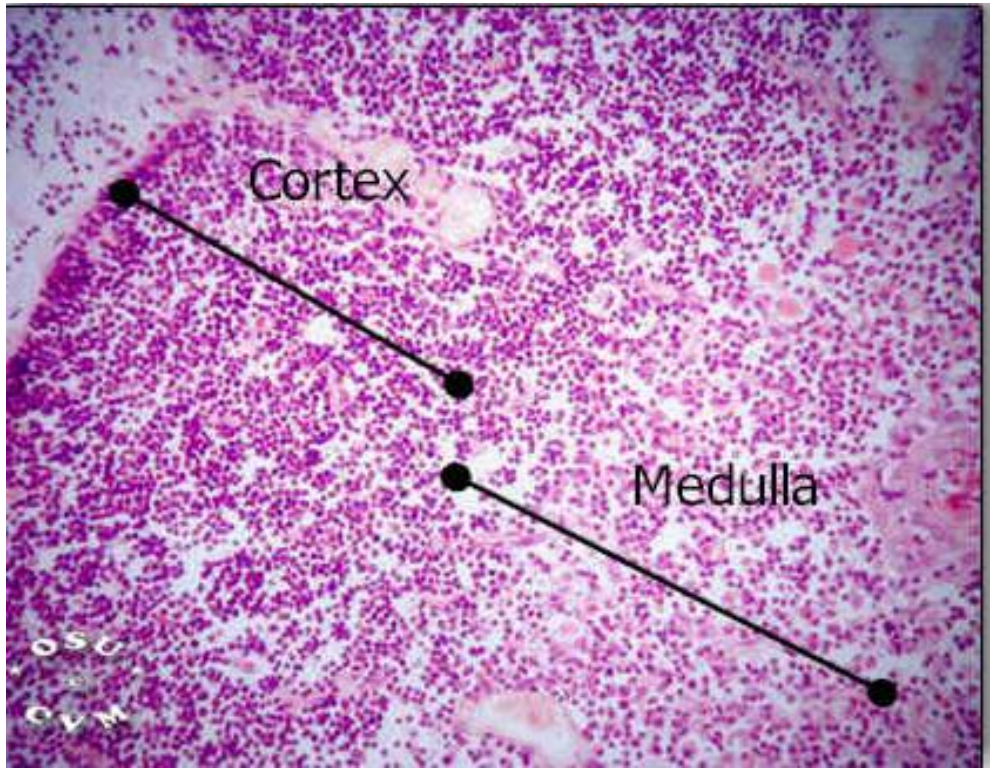
**Peyer's patches**

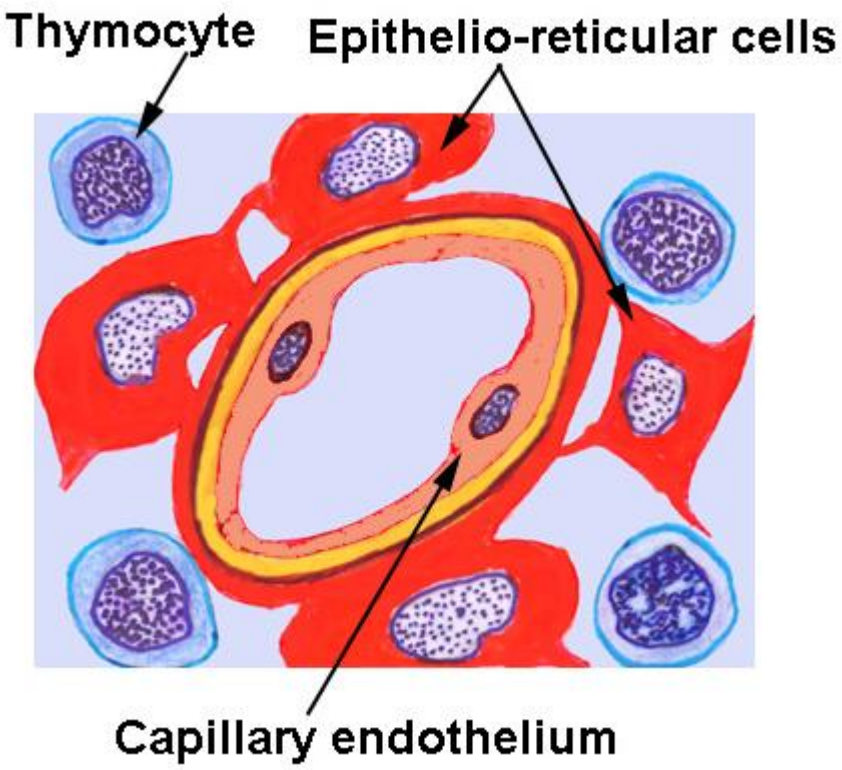


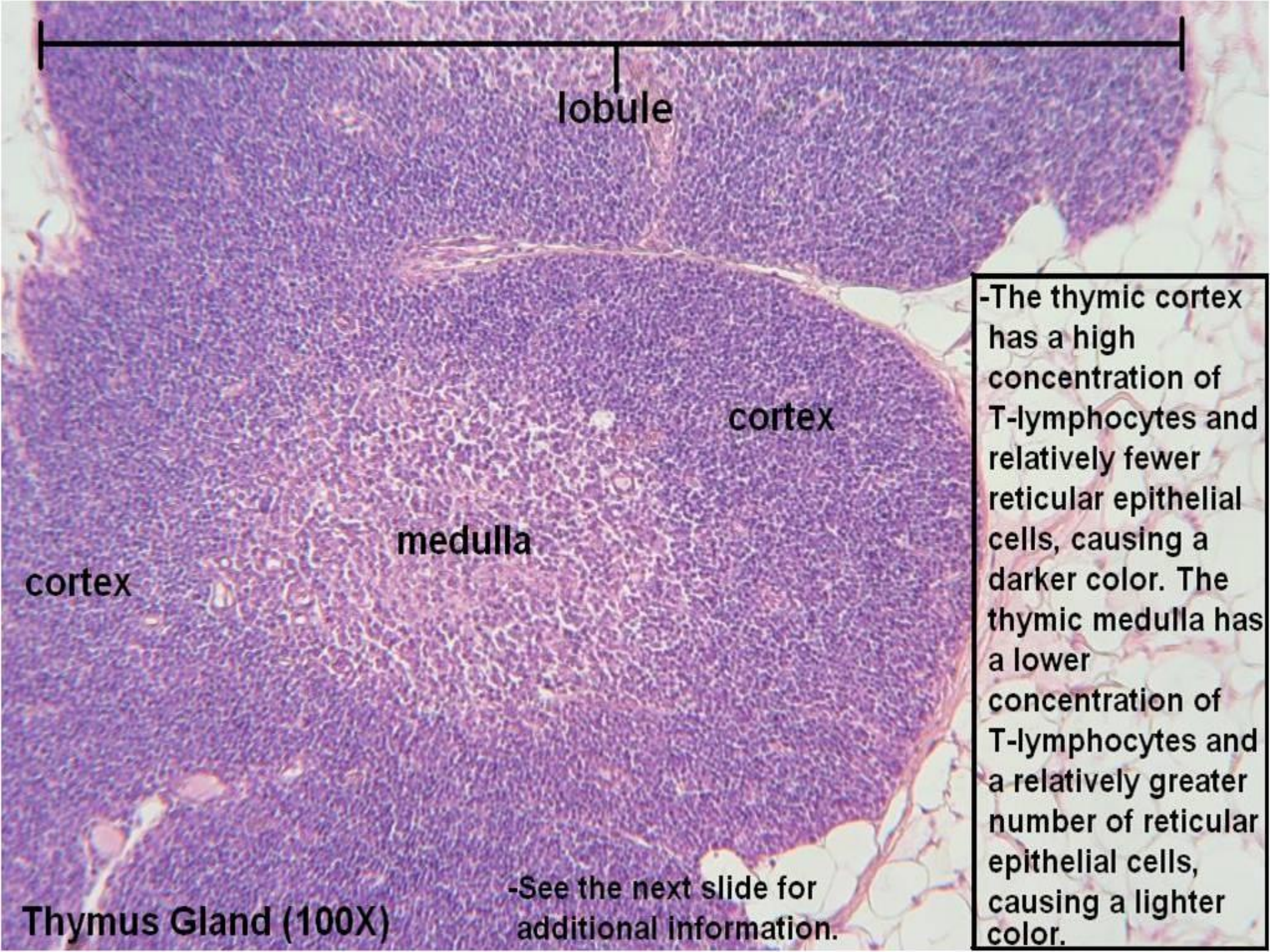

**the site of maturation of T lymphocytes**

1. capsule composed of dense, irregular connective tissue.
2. 2. Numerous septae subdivide lobes into lobules.
3. Each lobulus is divided into **cortex, and medulla**.

Stroma of the organ is formed by **epithelial reticular cells** (derived from endoderm). Main cells in thymus are lymphocytes T (thymocytes) but macrophages are present also.



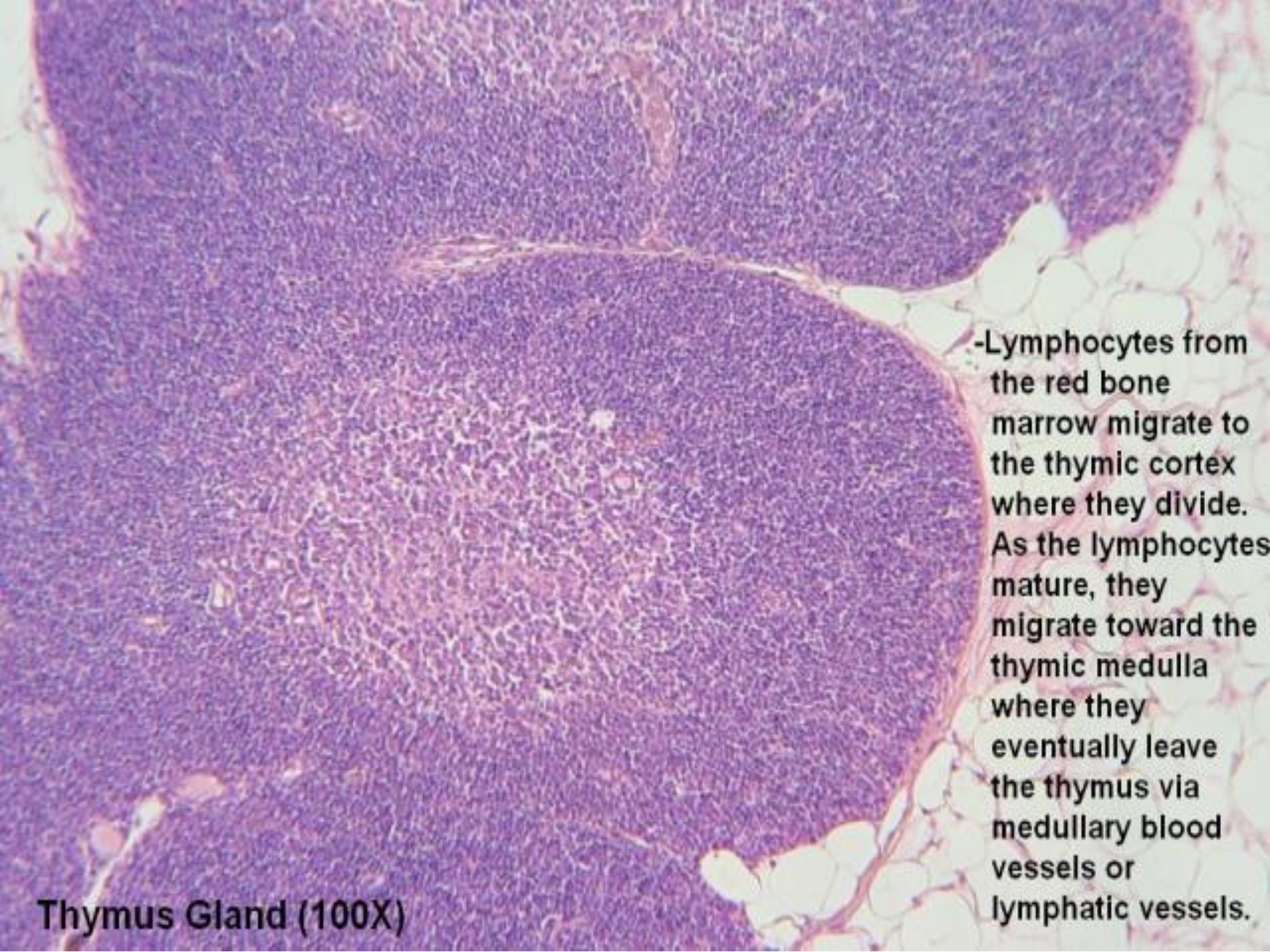






-The thymic cortex has a high concentration of T-lymphocytes and relatively fewer reticular epithelial cells, causing a darker color. The thymic medulla has a lower concentration of T-lymphocytes and a relatively greater number of reticular epithelial cells, causing a lighter color.

Thymus Gland (100X)

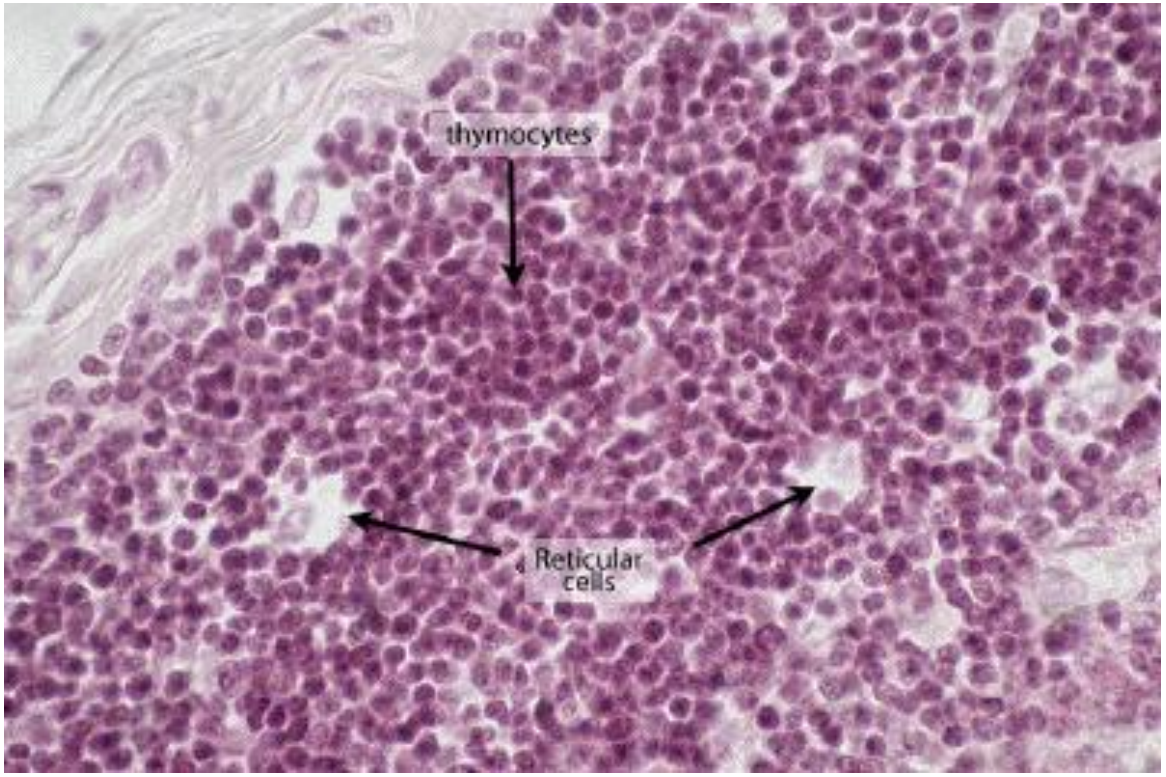
-See the next slide for additional information.



-Lymphocytes from the red bone marrow migrate to the thymic cortex where they divide. As the lymphocytes mature, they migrate toward the thymic medulla where they eventually leave the thymus via medullary blood vessels or lymphatic vessels.

Thymus Gland (100X)

# THYMUS CORTICAL ZONE



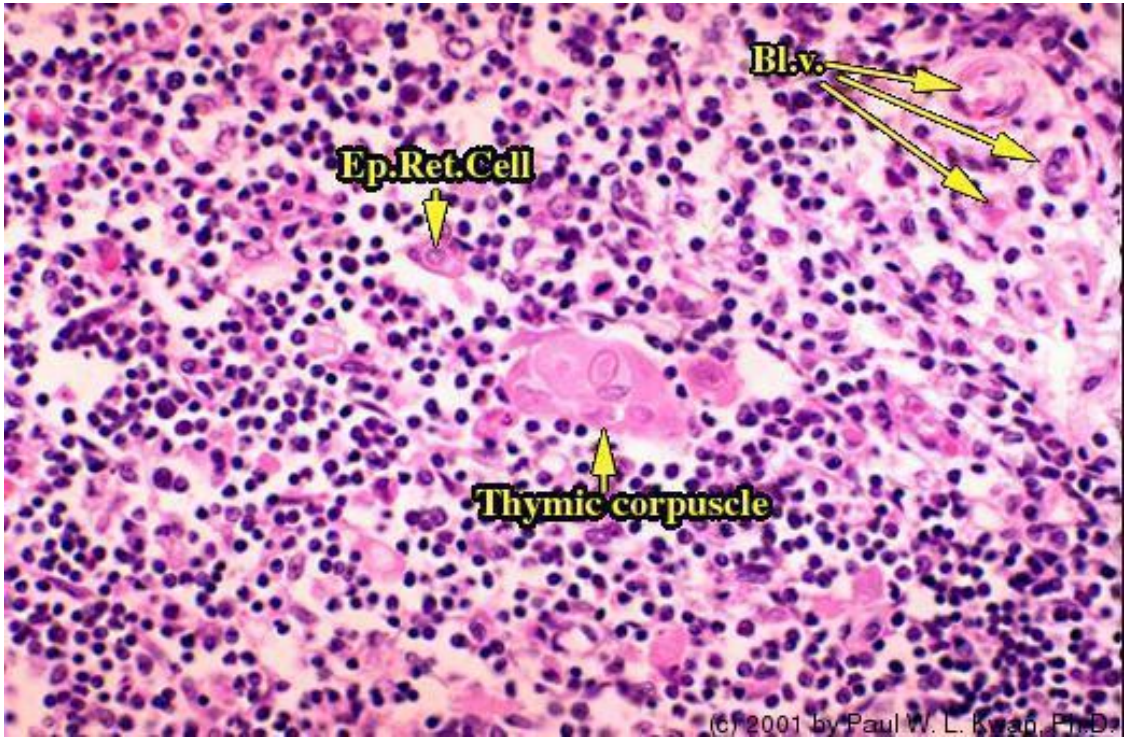

**Epithelial reticular cells** surrounded by T lymphocytes

**Type I** – in outer cortex, isolation of thymic cortex from the remainder of the body - **thymus-blood barrier** – contains also continuous blood capillaries -prevents the immature T cells from contacting foreign antigens

**Type II** in midcortex – long processes, presentation of self antigens.

**Type III** – in deep cortex – isolation of cortex from the medulla, presentation of self antigens.

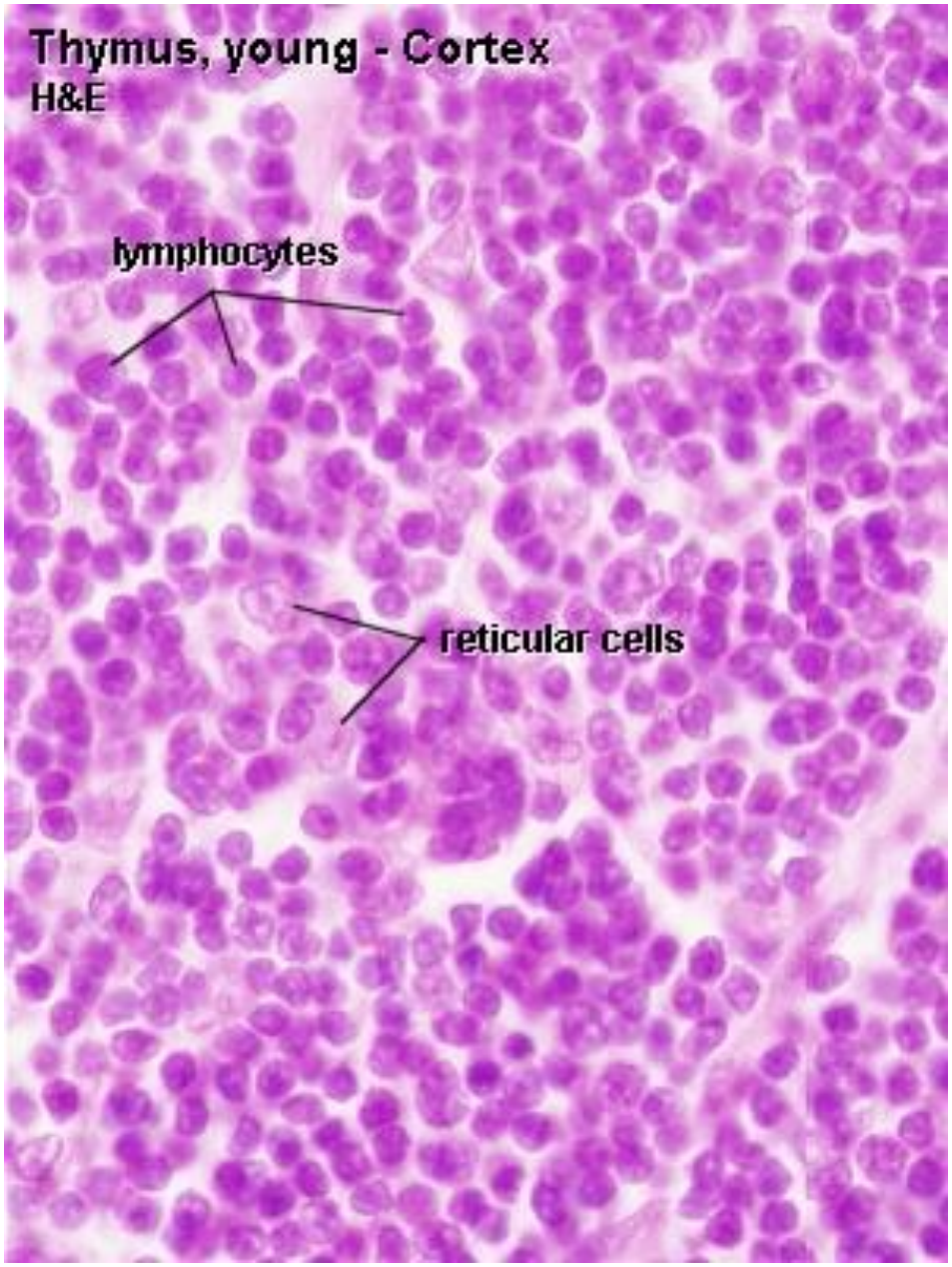
# MEDULLARY ZONE OF THE THYMUS

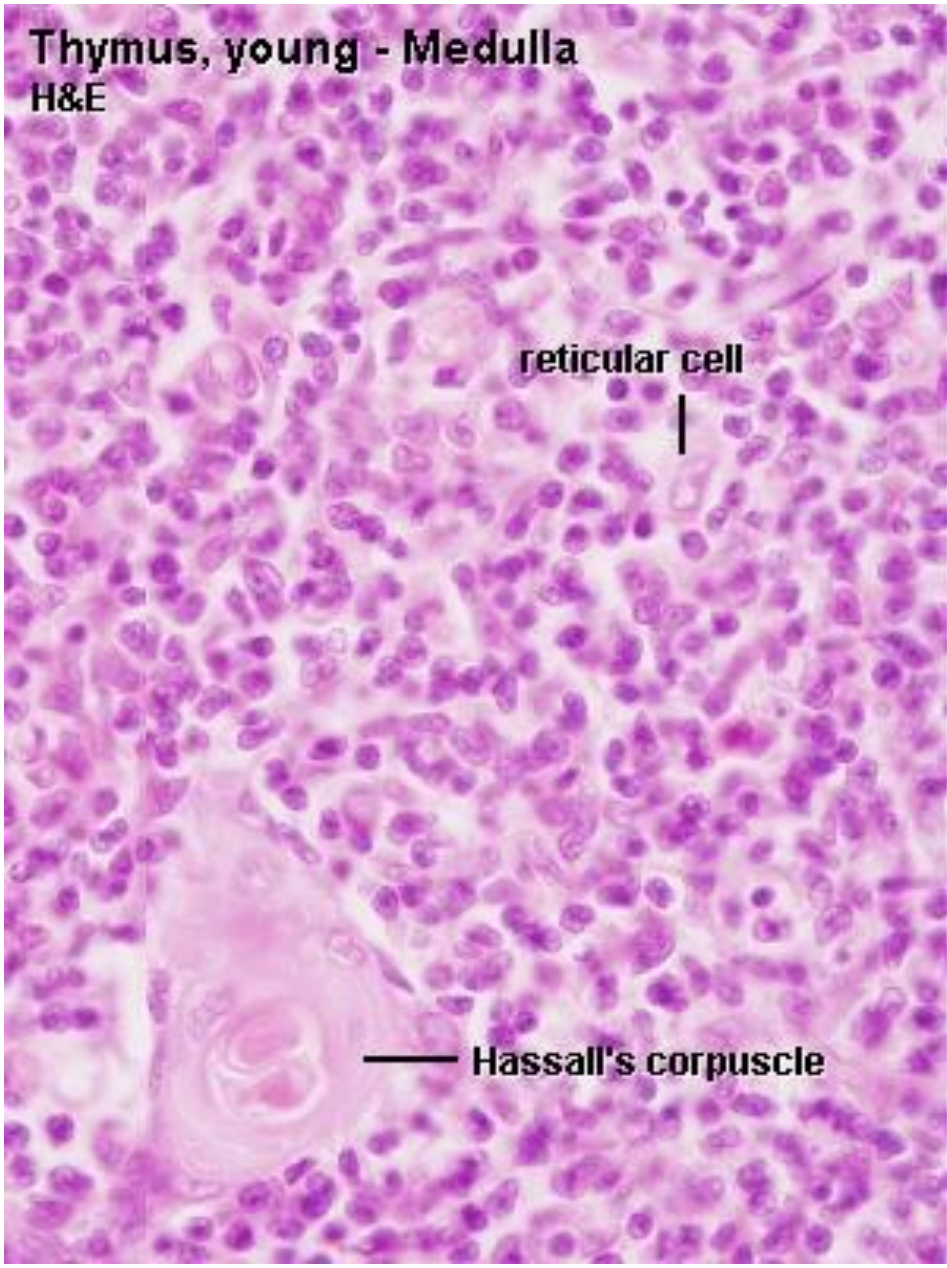


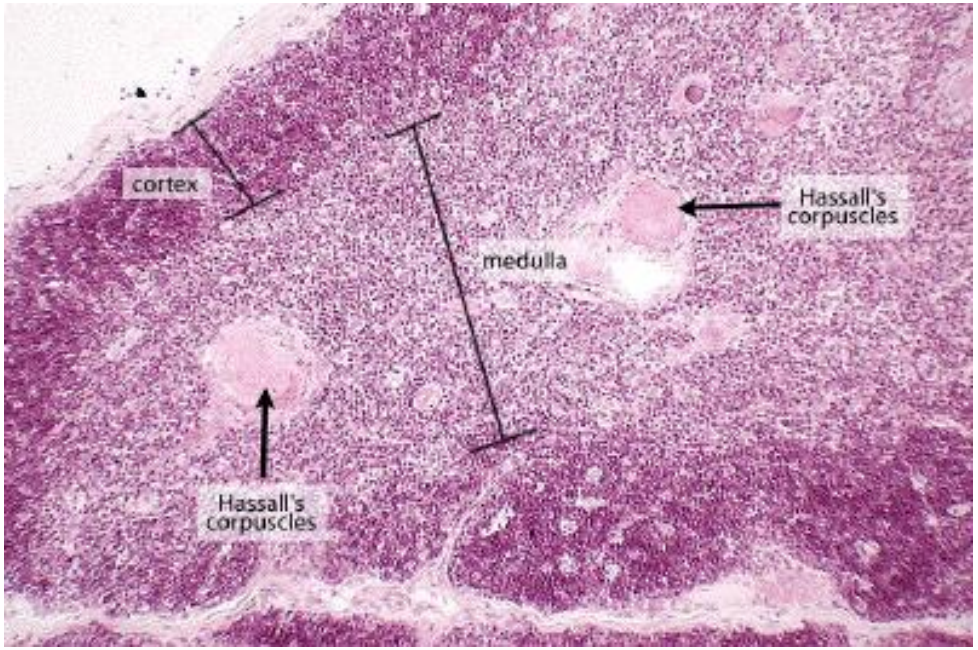

Contains large number of epithelial reticular cells with large and light stained nuclei and mature T cells.

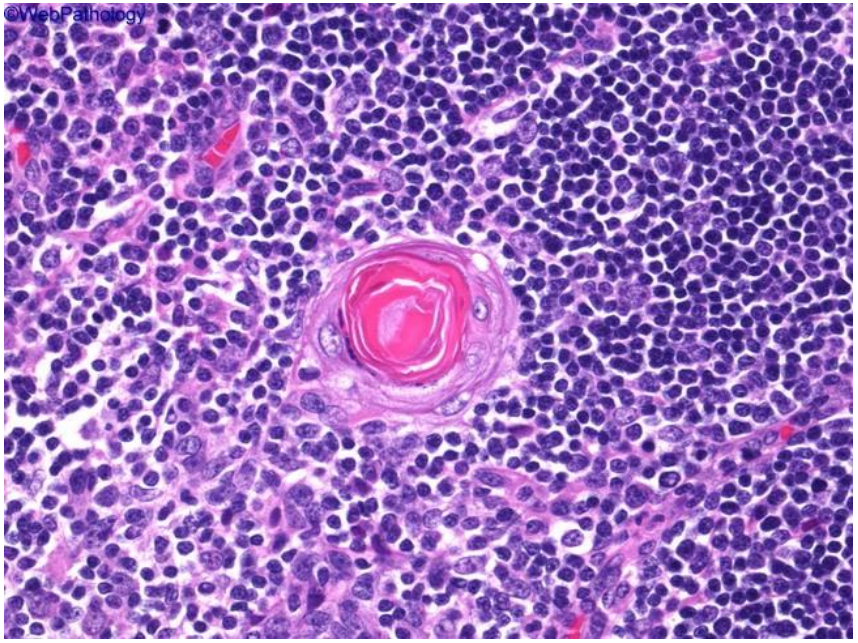
Medulla contains three types of epithelial reticular cells: **Type IV, Type and Type VI** – form **thymic corpuscles (Hassal's corpuscles)**.

**HASSALL corpuscles** – present only in the medulla.


Thymus, young - Cortex
H&E
lymphocytes
reticular cells


Thymus, young - Medulla
H&E
reticular cell
Hassall's corpuscle

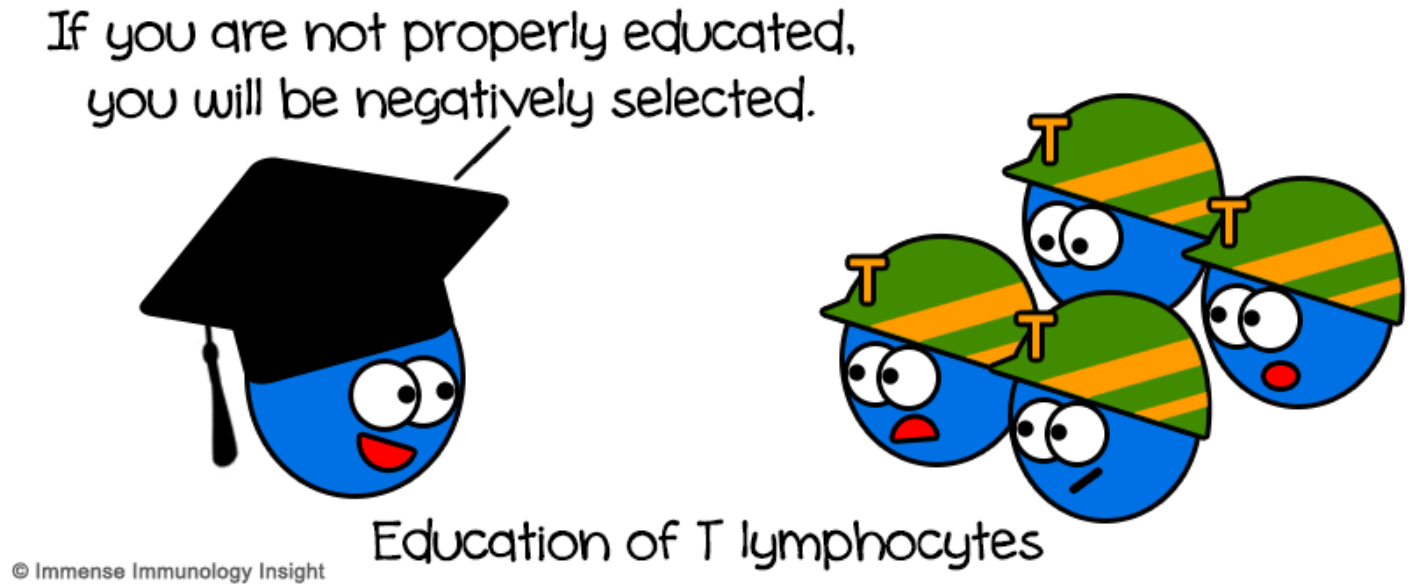



The function of Hassall's corpuscles is unclear. They are a potent source of the cytokines which direct the maturation of thymocytes and dendritic cells.

# Thymus - function

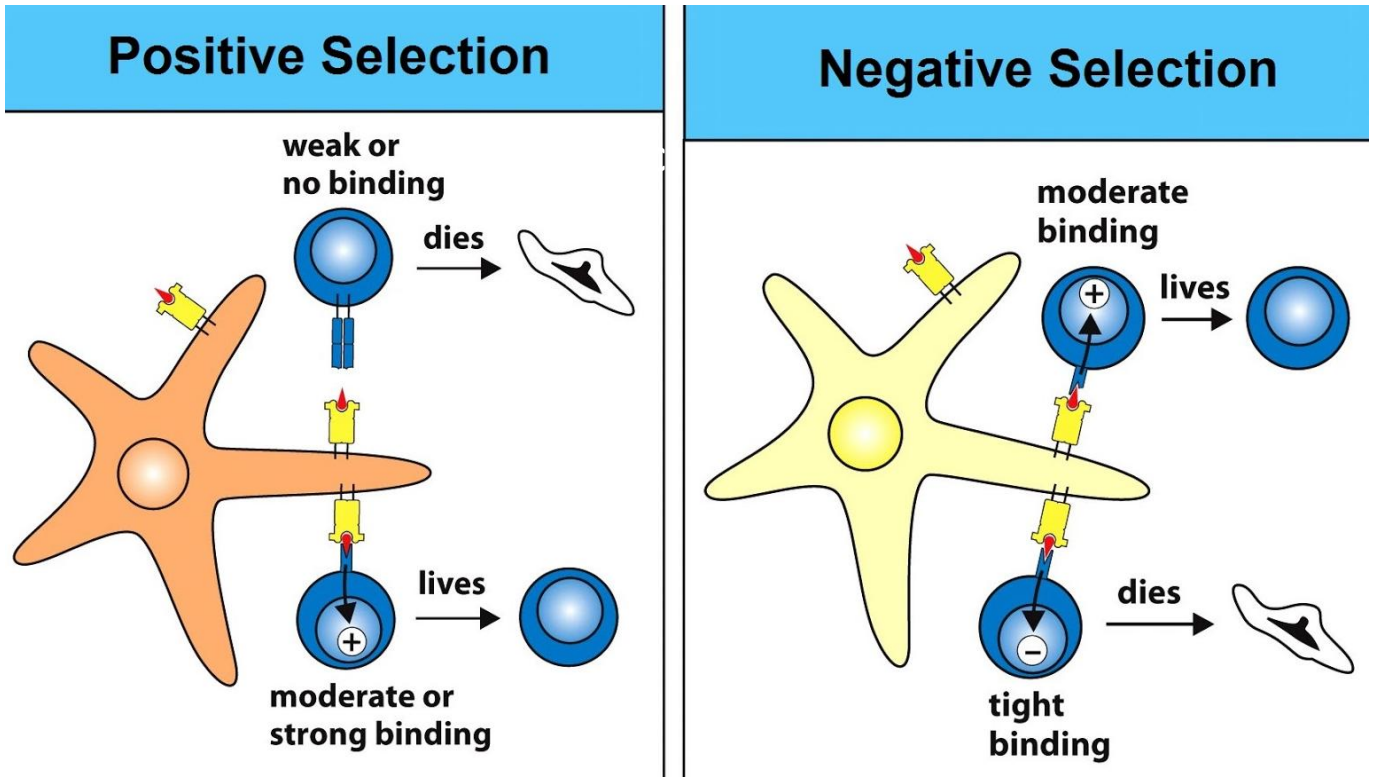
- precursors of T lymphocytes from the bone-marrow (thymocytes), mature into T-cells
- T cells that attack the body's own proteins are eliminated in the thymus
- Thymocytes in thymus are subject to two processes: POSITIVE SELECTION and NEGATIVE SELECTION



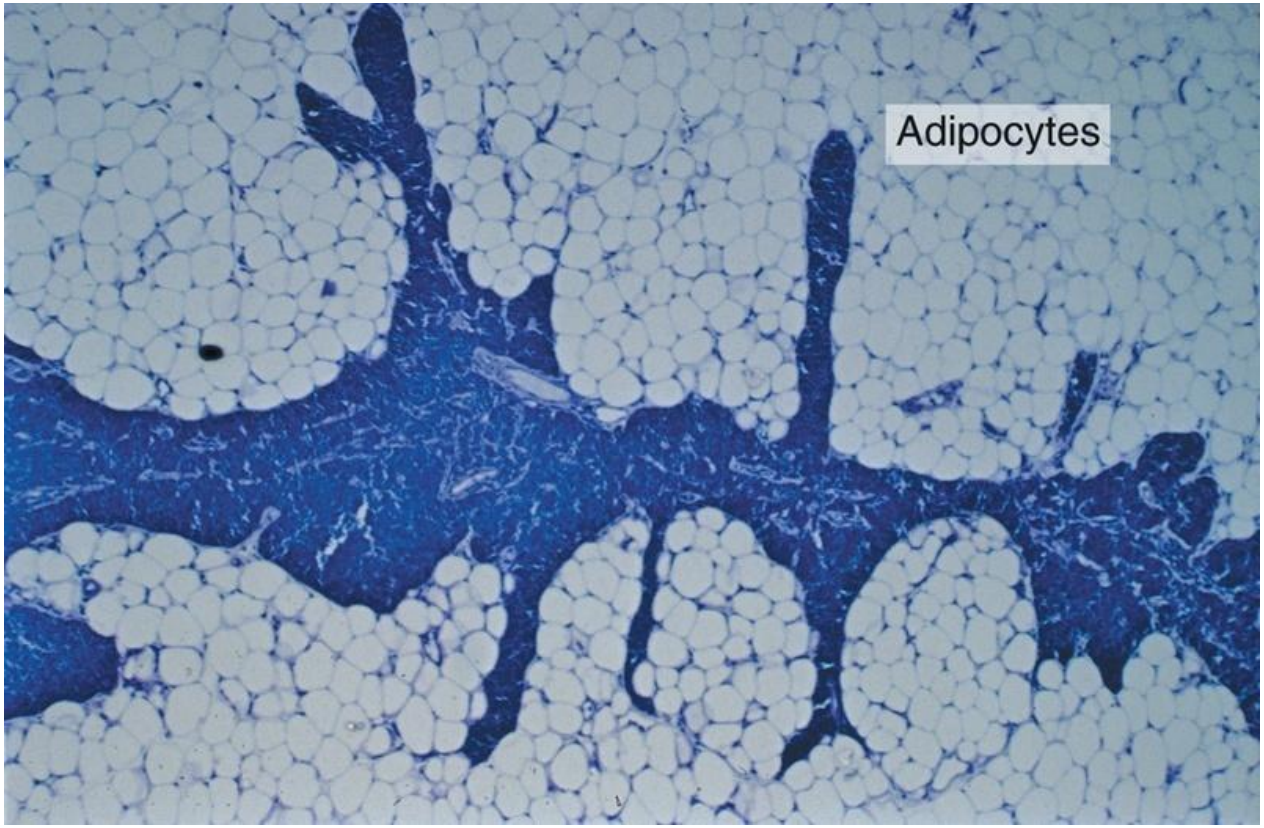

Education of T lymphocytes

In order to be positively-selected, thymocytes have to bind with MHC I or MHC II (connected with self antigens) present on the surface of epithelial cells, macrophages and dendritic cells. Thymocytes which can bind MHC divide, these which cannot interact undergo apoptosis **(POSITIVE SELECTION)**

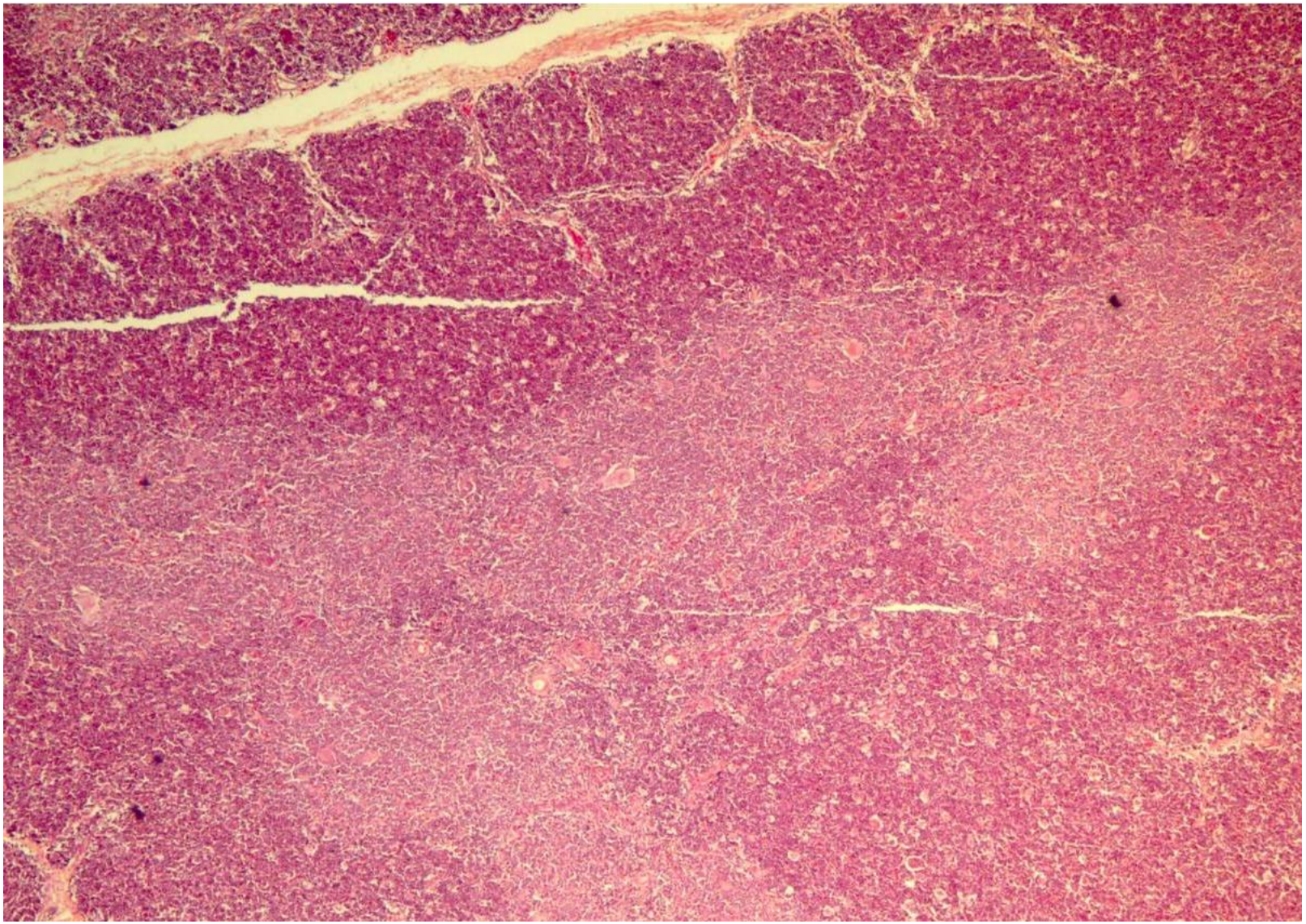
These thymocytes which would direct immune response towards self-proteins undergo apoptosis and  are removed by macrophages. The survivors migrate to the medulla **(NEGATIVE SELECTION)**



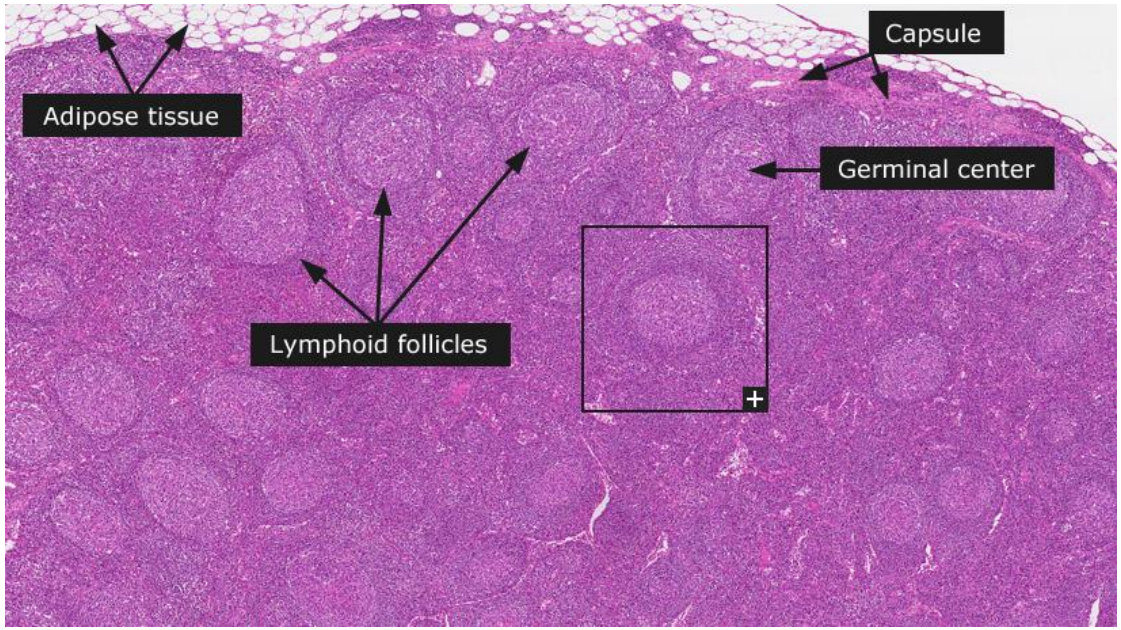
# THYMUS OF AN ELDERLY ADULT

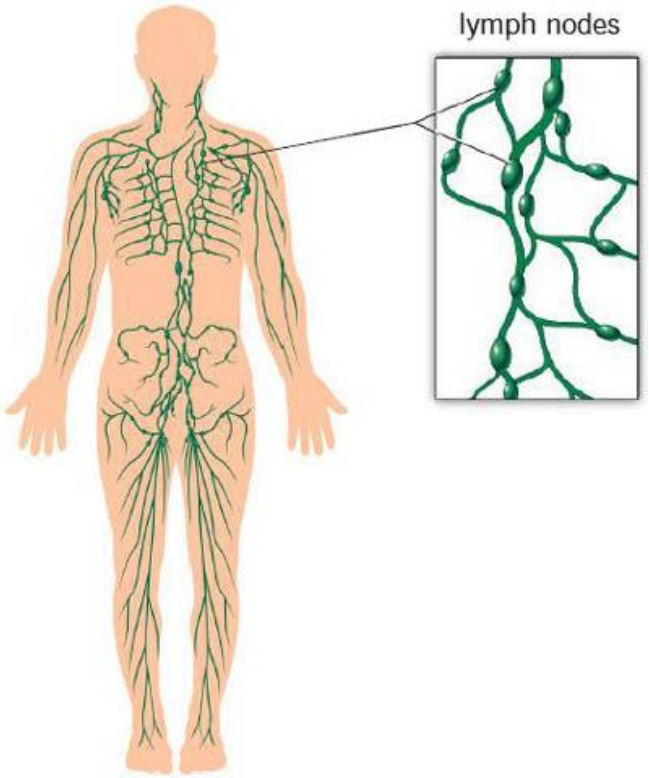



The thymus originates in the embryo and grows until puberty, later begins to involute and becomes infiltrate by adipose cells.



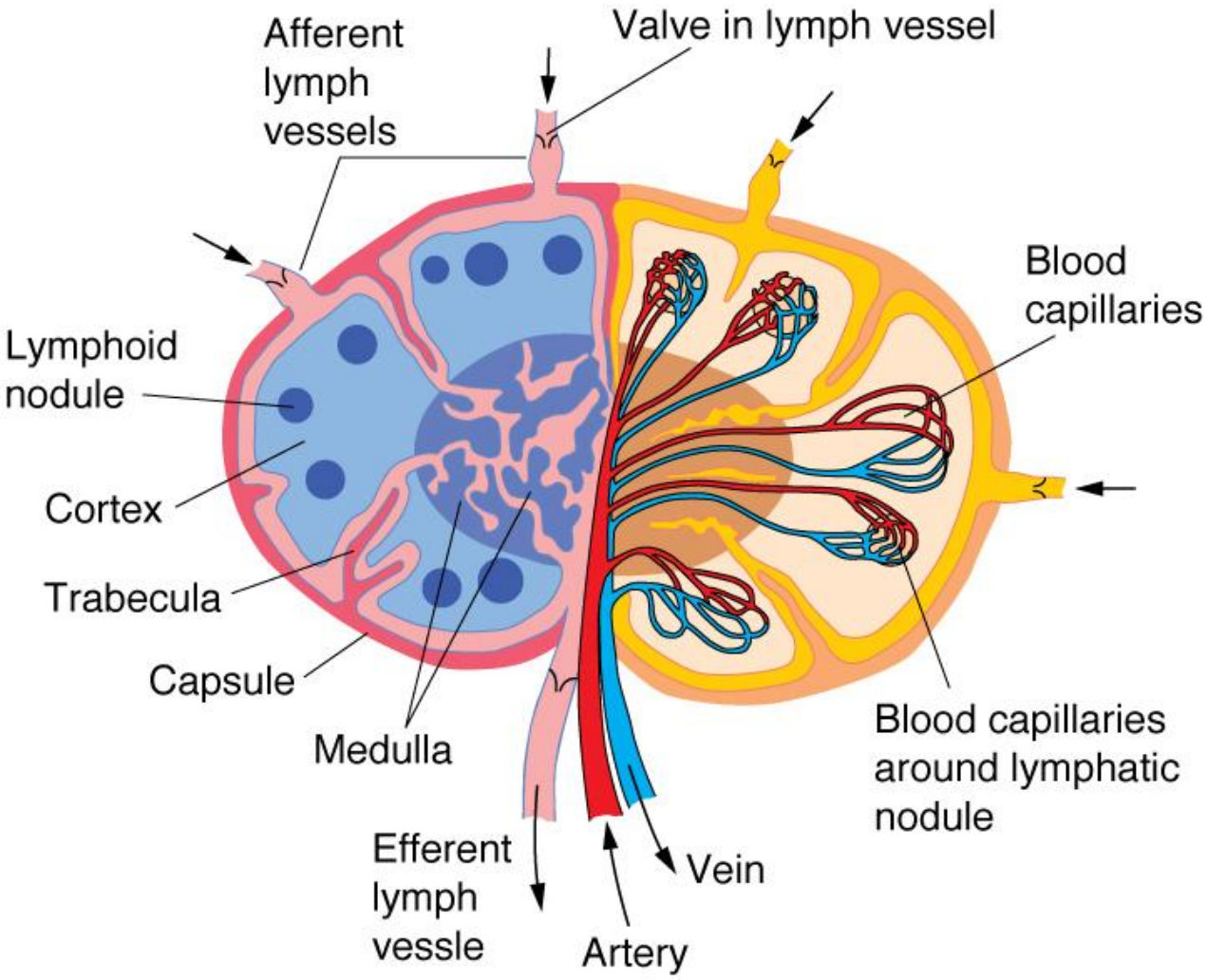
# Lymph Nodes



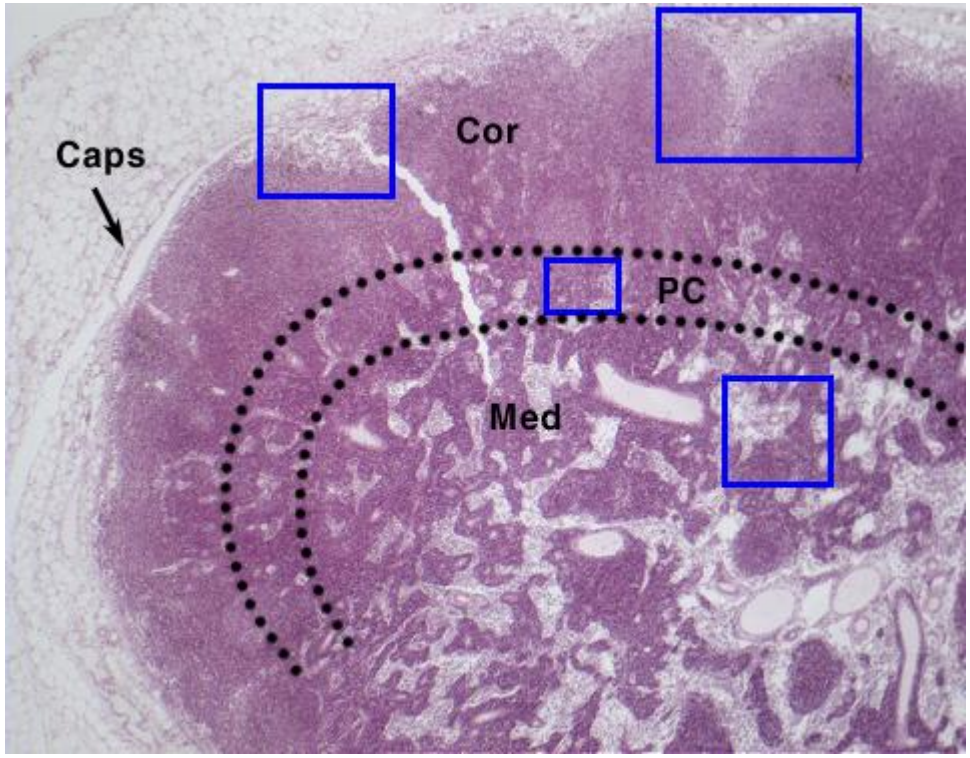

- small, oval structures located in the path of lymph vessels
- surrouded with a dense, irregular connective tissue capsule usually surrounded by adipose tissue,
- serve as filters for the removal of bacteria and other foreign substances, act as sites for antigen recognition and mounting the immune response.

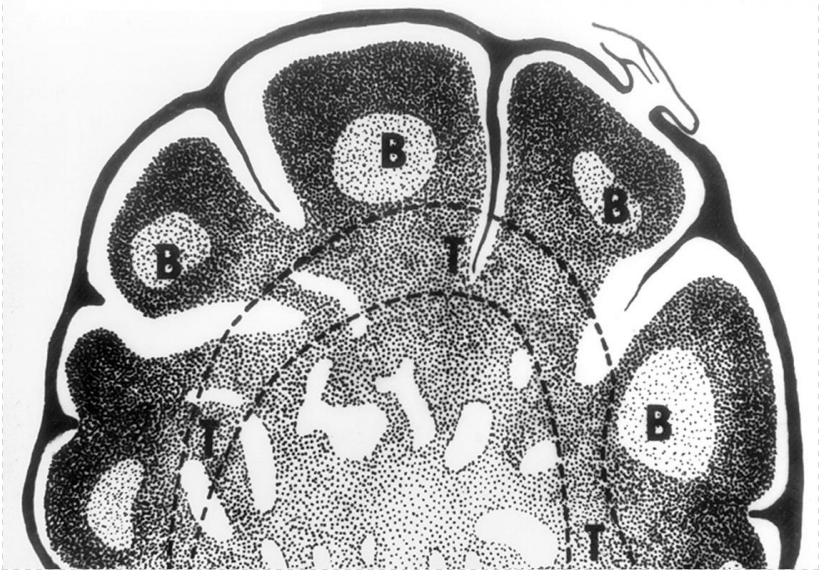
# LYMPH NODES




**Afferent lymph vessels** bring lymph into the substance of the node at its convex surface. At the concave surface of the node, the **hilum,** arteries and veins enter and exit the node. Lymph leaves the node via the **efferent lymph vessels** at the hilum.

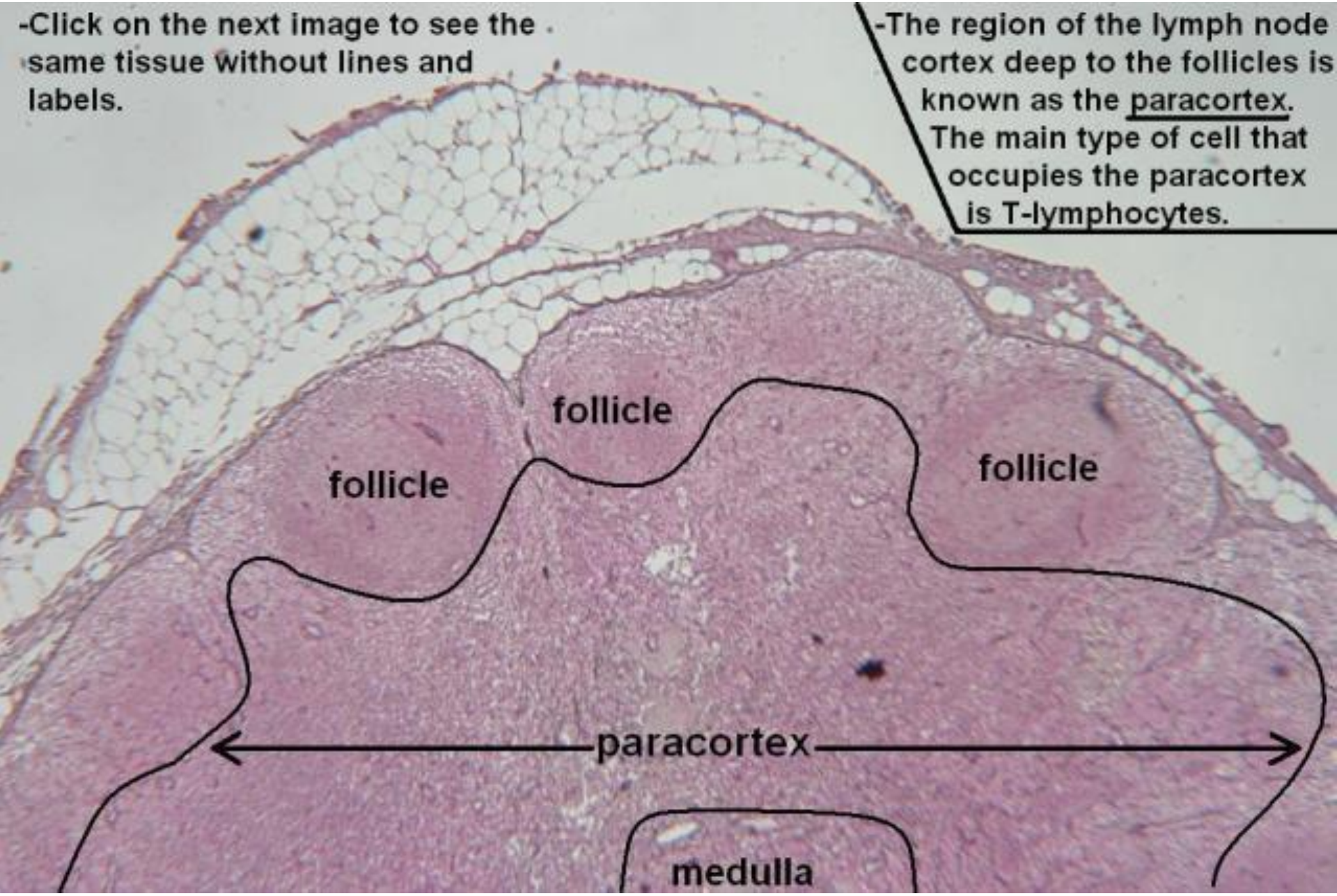
# Lymph Nodes



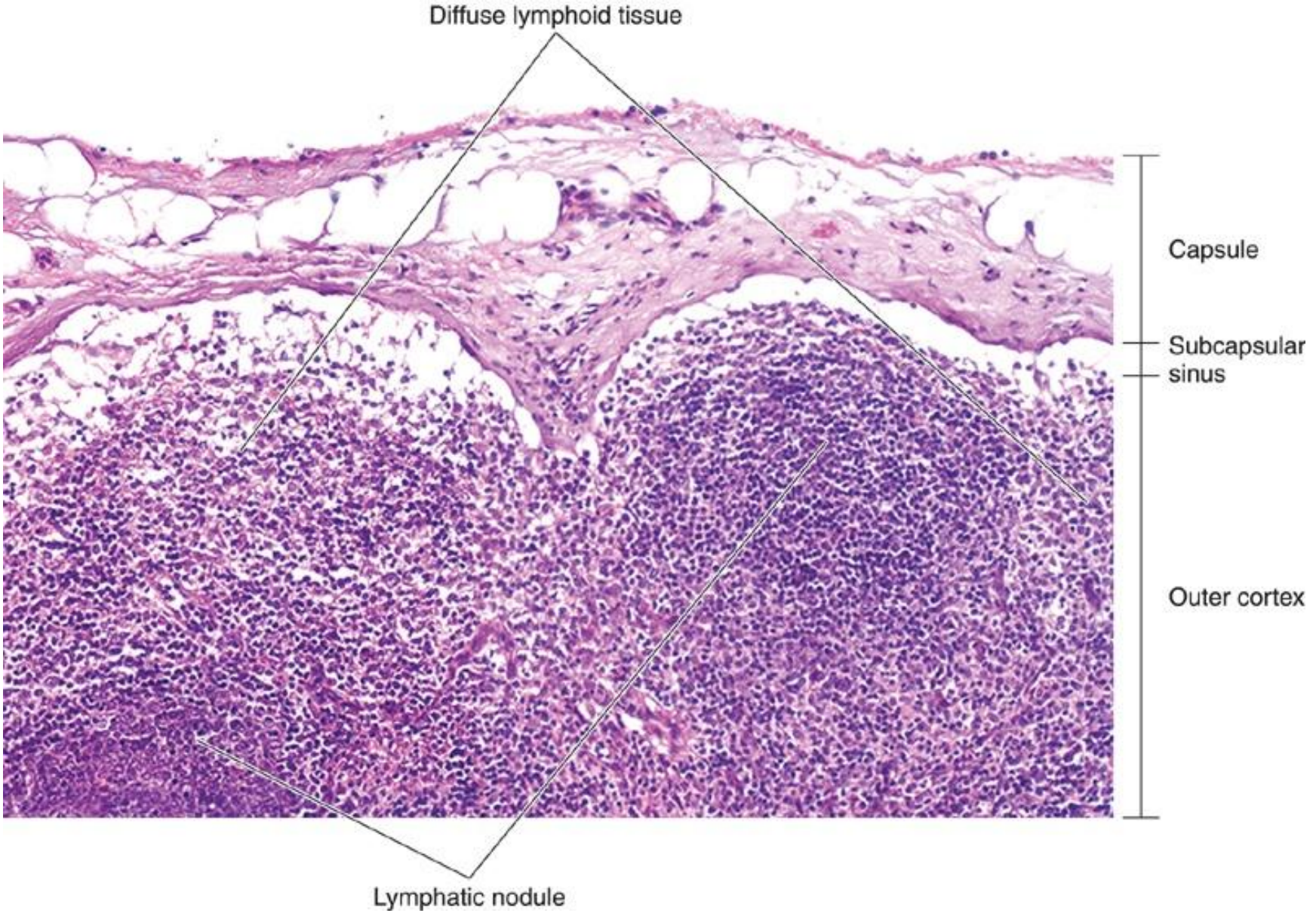




Three regions:

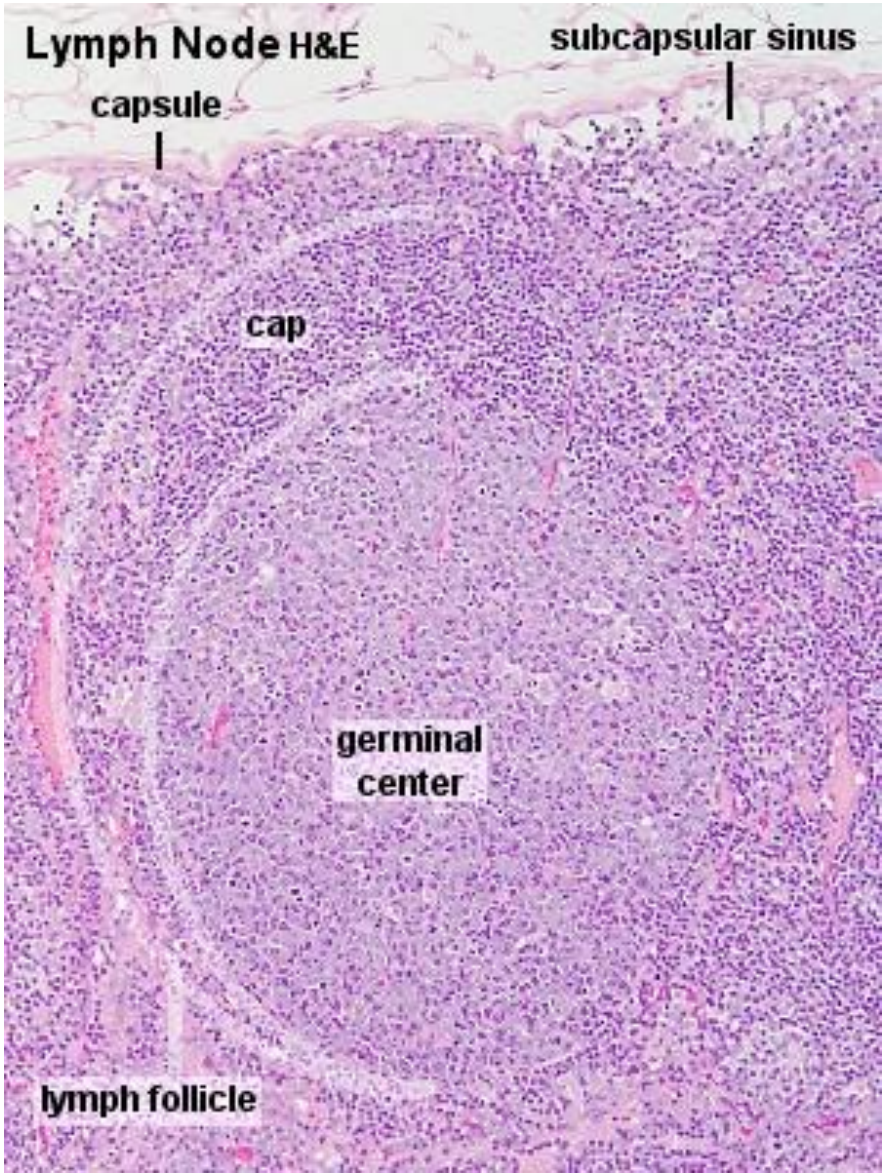
**CORTEX -** subdivided by trabeculae into incomplete compartments. Conains lymphoid nodules –aggregates of B lymhocytes, subcapsular sinus and cortical sinuses.
**PARACORTEX -** thymus-dependent zone. It houses mostly T cells (also APCs)
**MEDULLA** - houses large, medullary sinuses and lymphoid cells organized in medullary cords.


-Click on the next image to see the same tissue without lines and labels.
-The region of the lymph node cortex deep to the follicles is known as the paracortex. The main type of cell that occupies the paracortex is T-lymphocytes.
follicle
follicle
follicle
paracortex
medulla

# LYMPH NODE - CORTEX



# LYMPH NODE - CORTEX

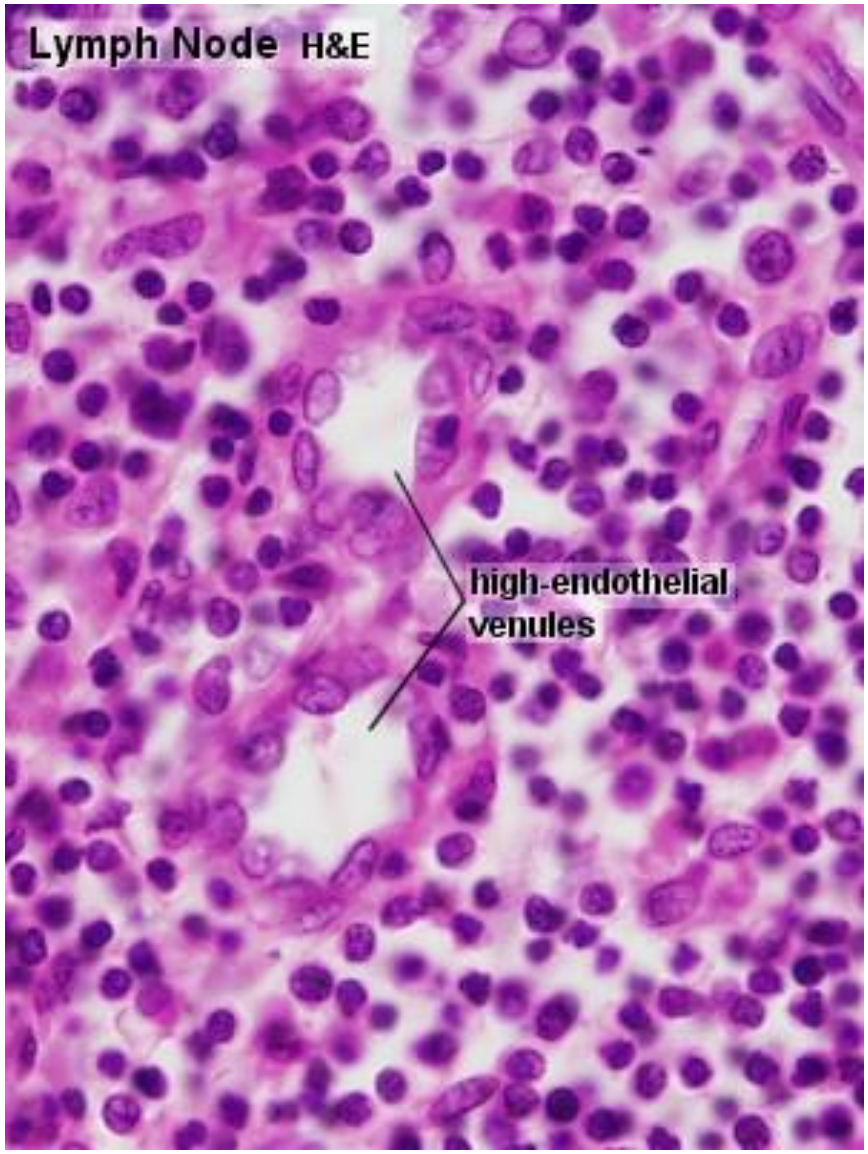



- an **aggregates of B lymphocytes**

- **germinal center** and **peripheral corona (mantle).** The germinal center is the place of antigen presentation (dendritic cells), B cells proliferation, maturation (plasma cells, memory cells) and also apoptosis of inappropriate B cells

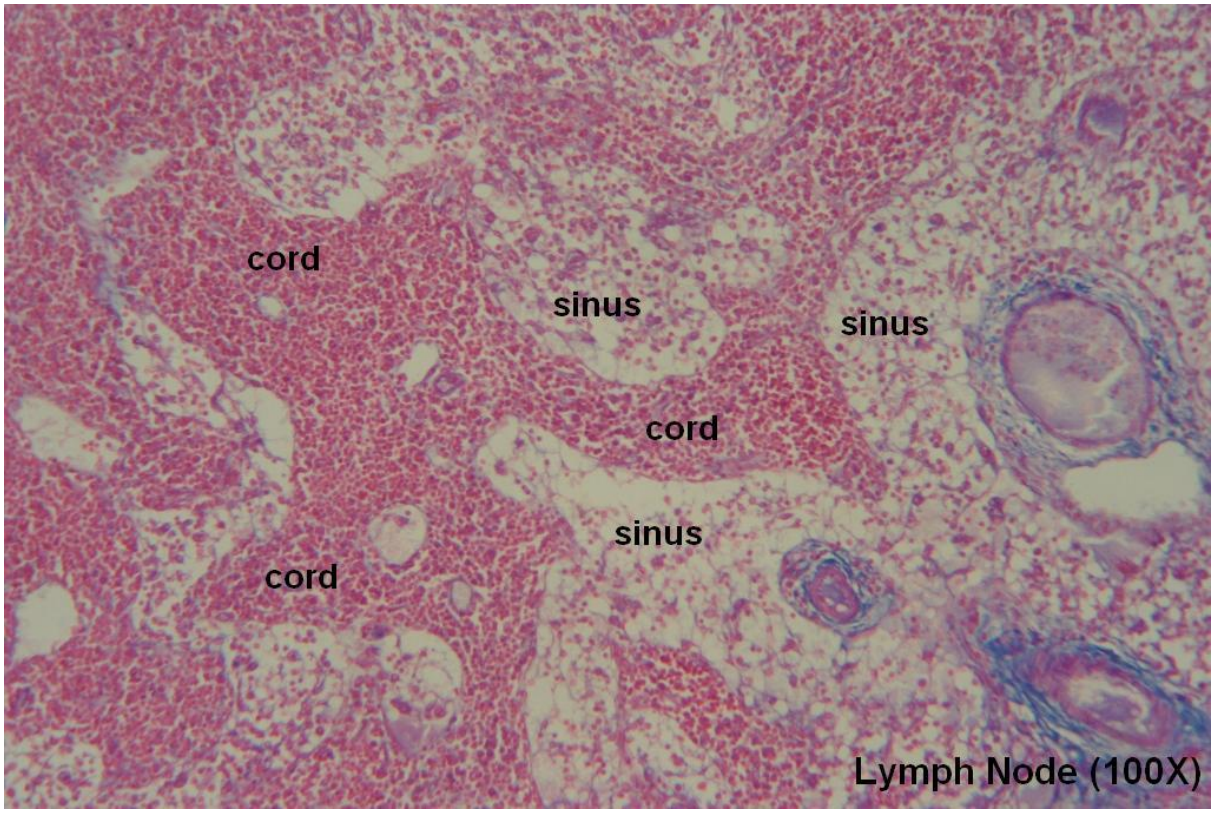
- later lymphocytes migrate from germinal center to corona.

# LYMPH NODE - PARACORTEX

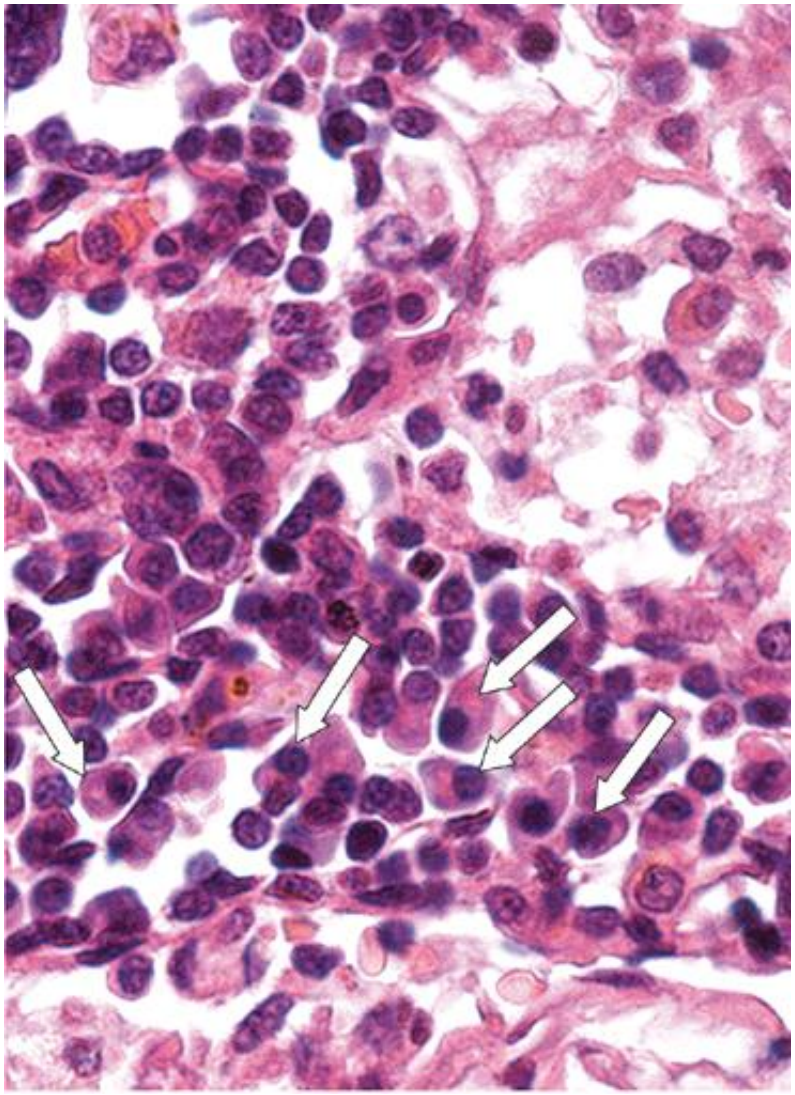



**Thymus-dependent zone**.
- houses mostly **T cells**, but also APCs. APCs- migrate to paracortex to present antigen to Th cells. As a result T cells proliferate, migrate to the medullary sinuses and leave the lymph node.
**High endothelial venules (HEV)** – the sites of entering of lymphocytes from cardiovascular system into lymph node. The B cells migrate to cortex, T cells remain in paracortex.

# LYMPH NODE - MEDULLA



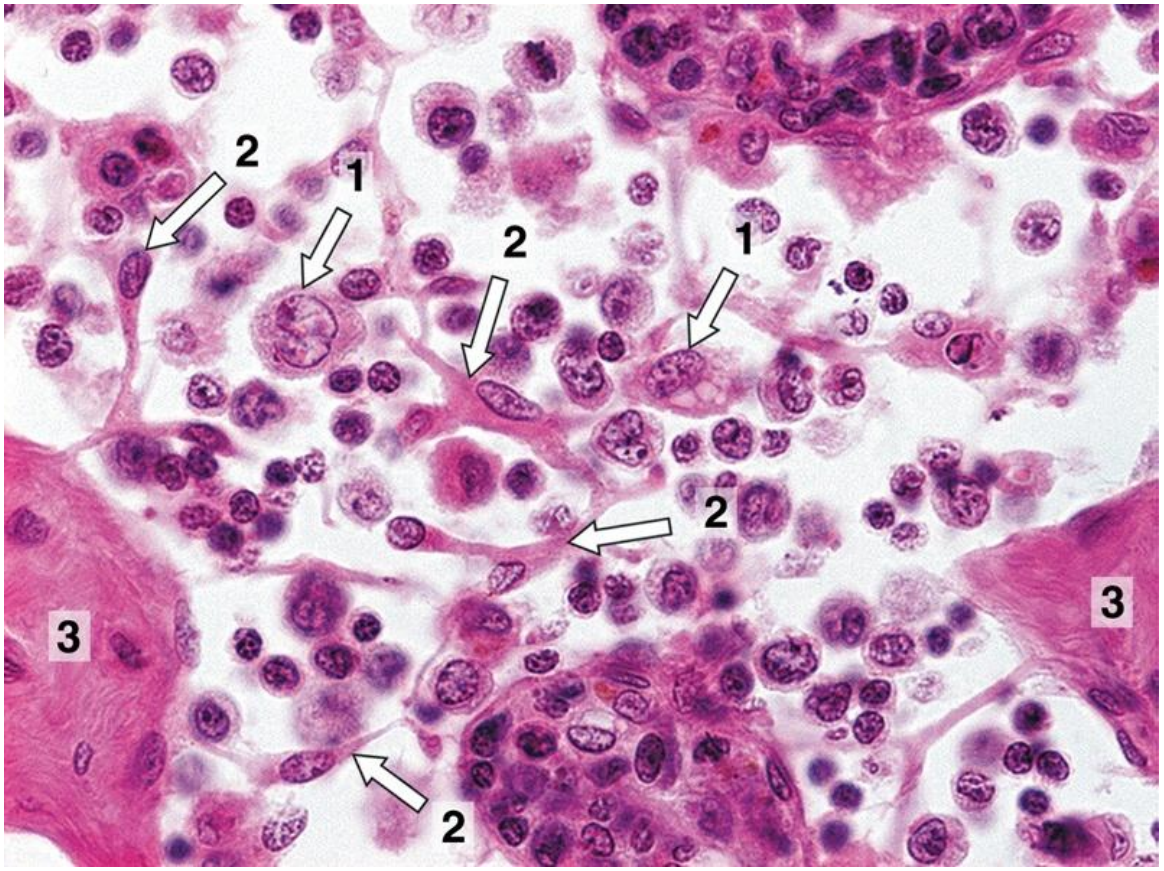

- composed of **medullary cor**ds (clusters of lymphoid cells – lymphocytes, plasma cells and macrophages) and **lymph sinuses**
- from medullary sinuses lymphocytes enter the efferent lymphatic vessels to leave the lymph node



# MEDULLARY CORD

Lymhocytes  T, B (plasma cells) and macrophages in reticular fibers and reticular cells network.

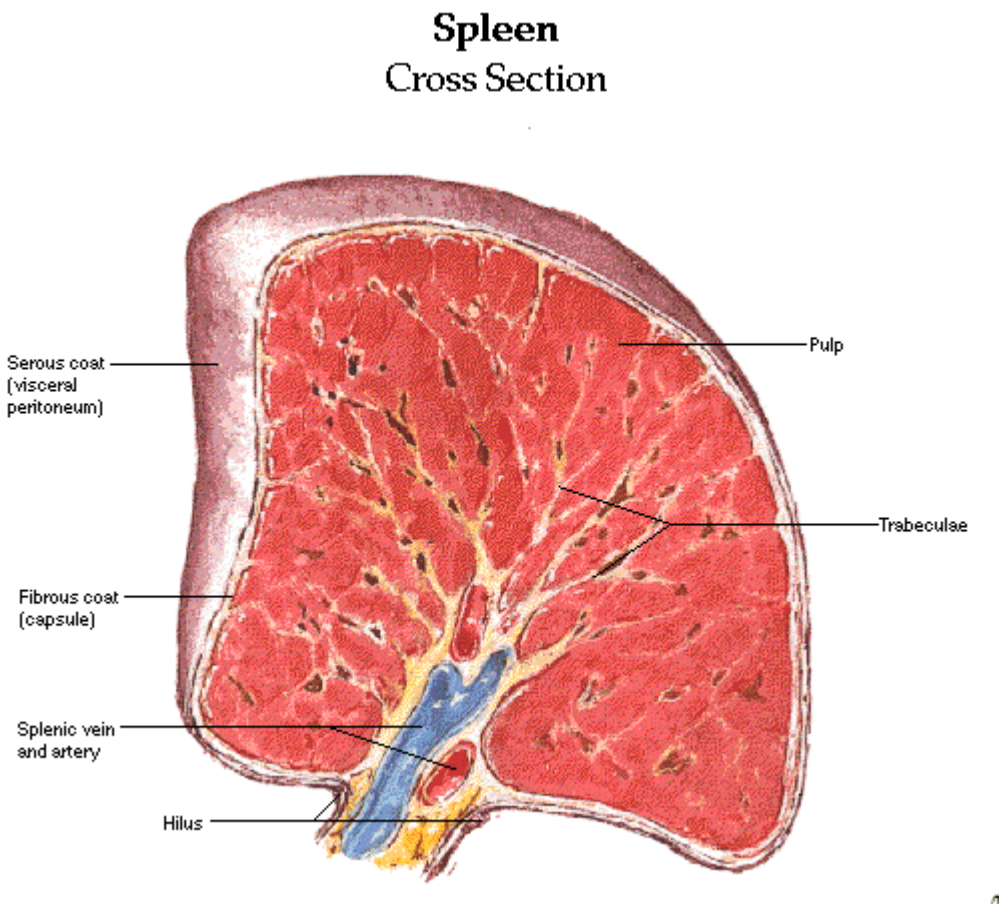
# MEDULLARY SINUS OF A LYMPH NODE




Lymphocytes migrate from the cortex and paracortex to the medullary sinuses and later to the efferent lymphatic vessels to leave the lymph node.

Reticular cells with long processes and elongated nuclei, macrophages and many lymphocytes. (1) Macrophage; (2) Reticular cell; (3) Trabecula

# SPLEEN

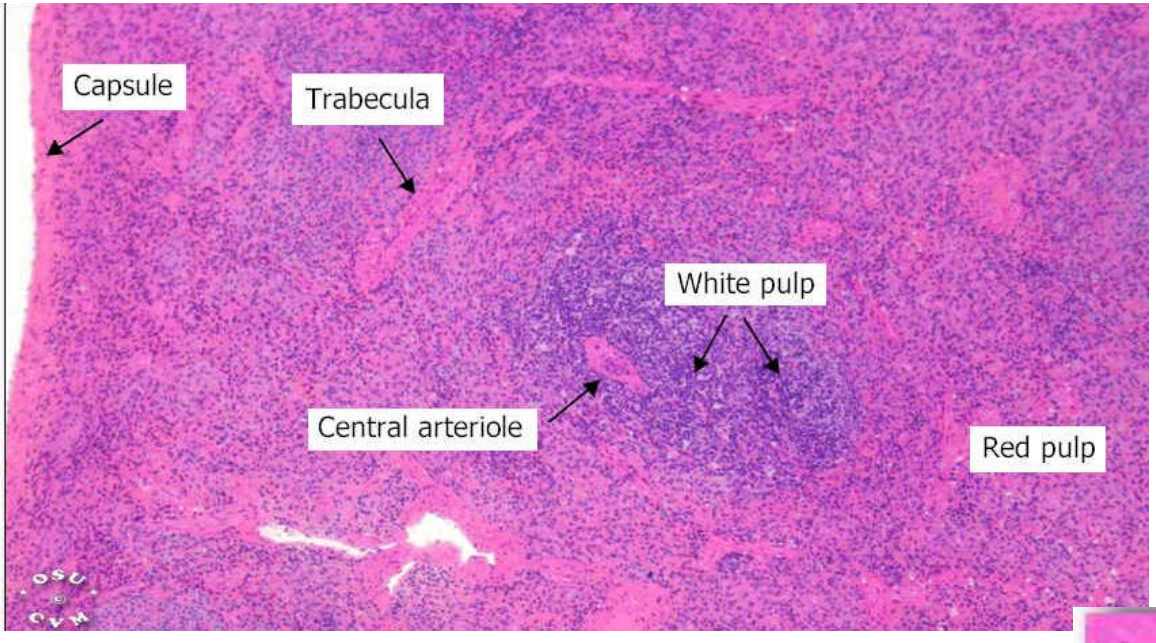



- the largest lymphoid organ in the body,

- functions as a site of antibody formation, T-cell and B-cell proliferation and as a filter of the blood
- is also a place of senescent erythrocytes elimination.

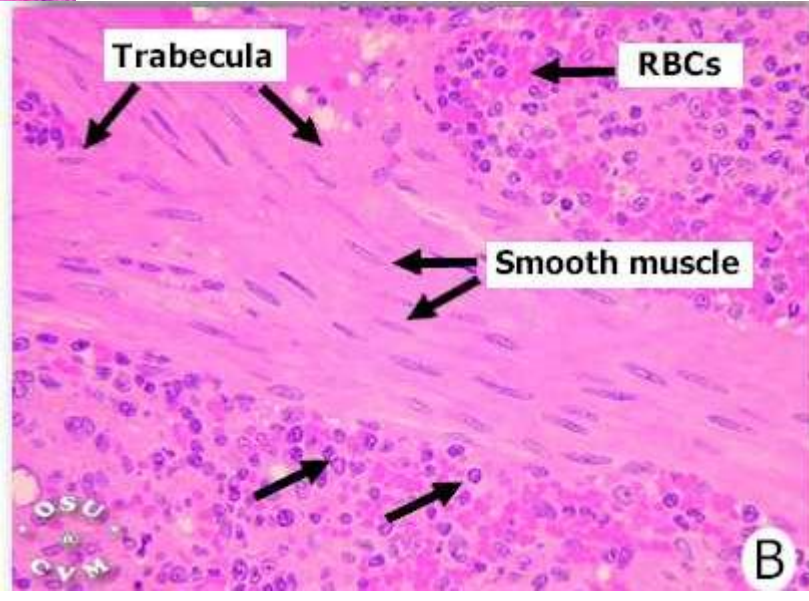
The spleen has convex surface and concave hilum – the site of penetration of blood vessels (splenic artery and splenic vein).

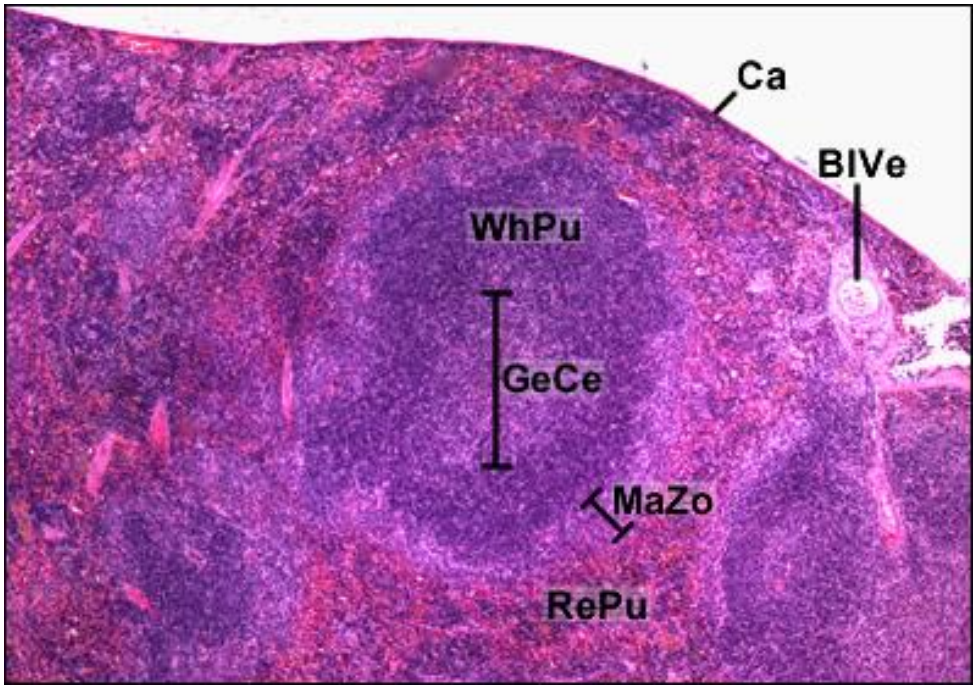
# SPLEEN




- surrounded with a dense, irregular, connective tissue capsule with smooth muscle cells,
- trabeculae – arise from the capsule
- is composed of red pulp and white pulp

The **red pulp** occupies most of the microscopic field.
**White pulp** contains central arteries.
Trabeculae from the capsule run into the interior of the spleen, carry blood vessels into and out of the spleen. ,






## WHITE PULP

1.Periarterial lymphatic sheath (PALS) containing T lymphocytes

2.Lymphoid nodules housing B cells

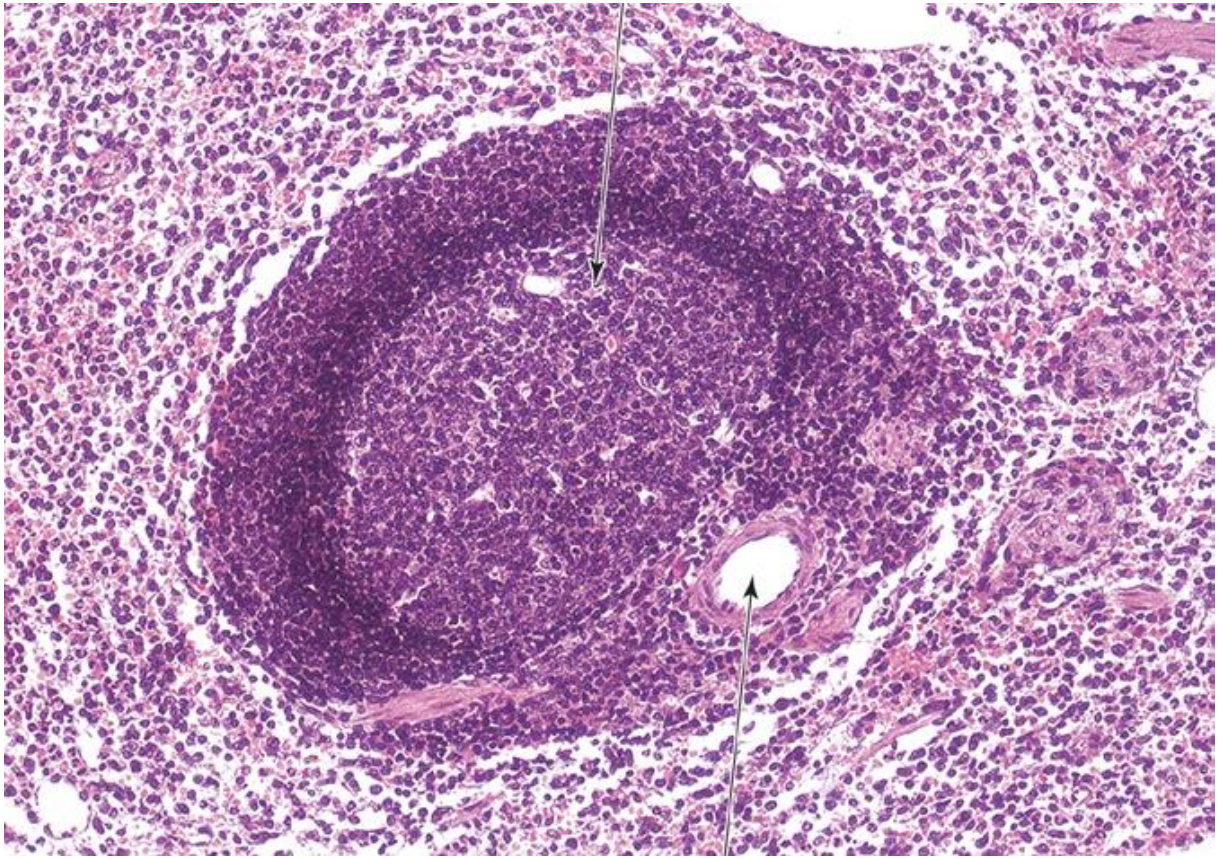
**MARGINAL ZONE** separates white pulp from red pulp; houses B and T lymphocytes, macrophages, dendritic cells and marginal sinuses surrounding lymphoid nodules.

## RED PULP

1.Splenic sinuses

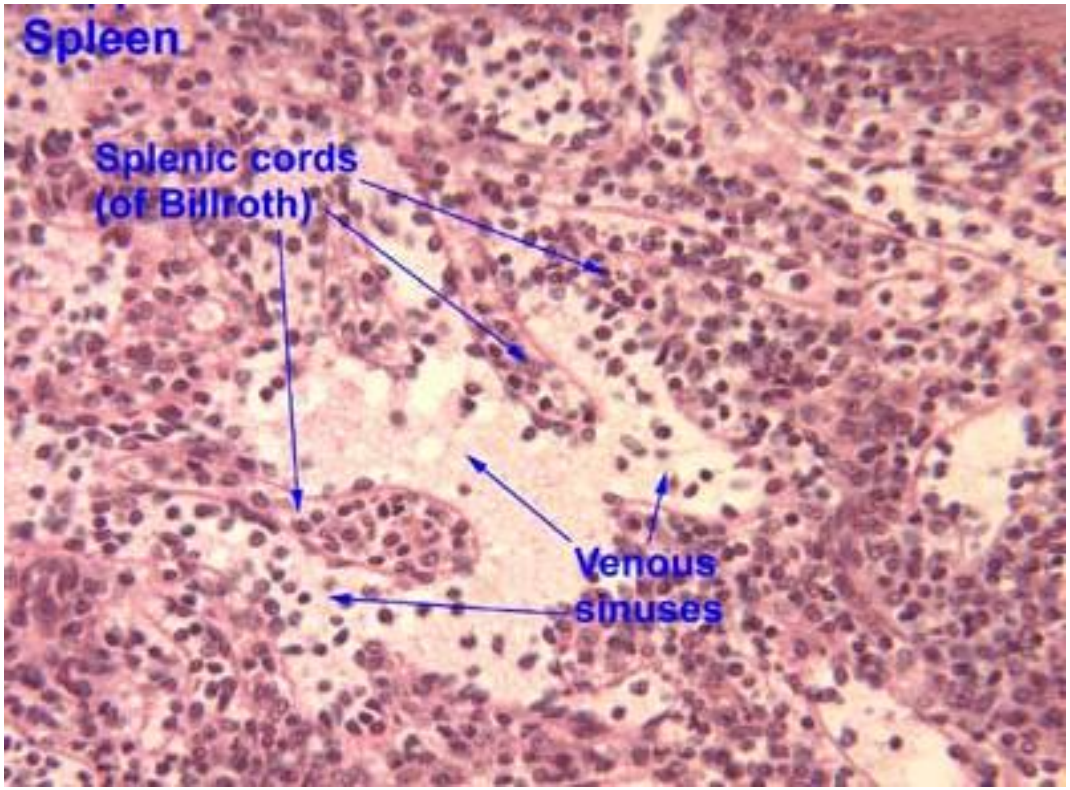
2.Splenic cords (of Billroth) housing reticular fibers, stellate reticular cells and macrophages.

# WHITE PULP



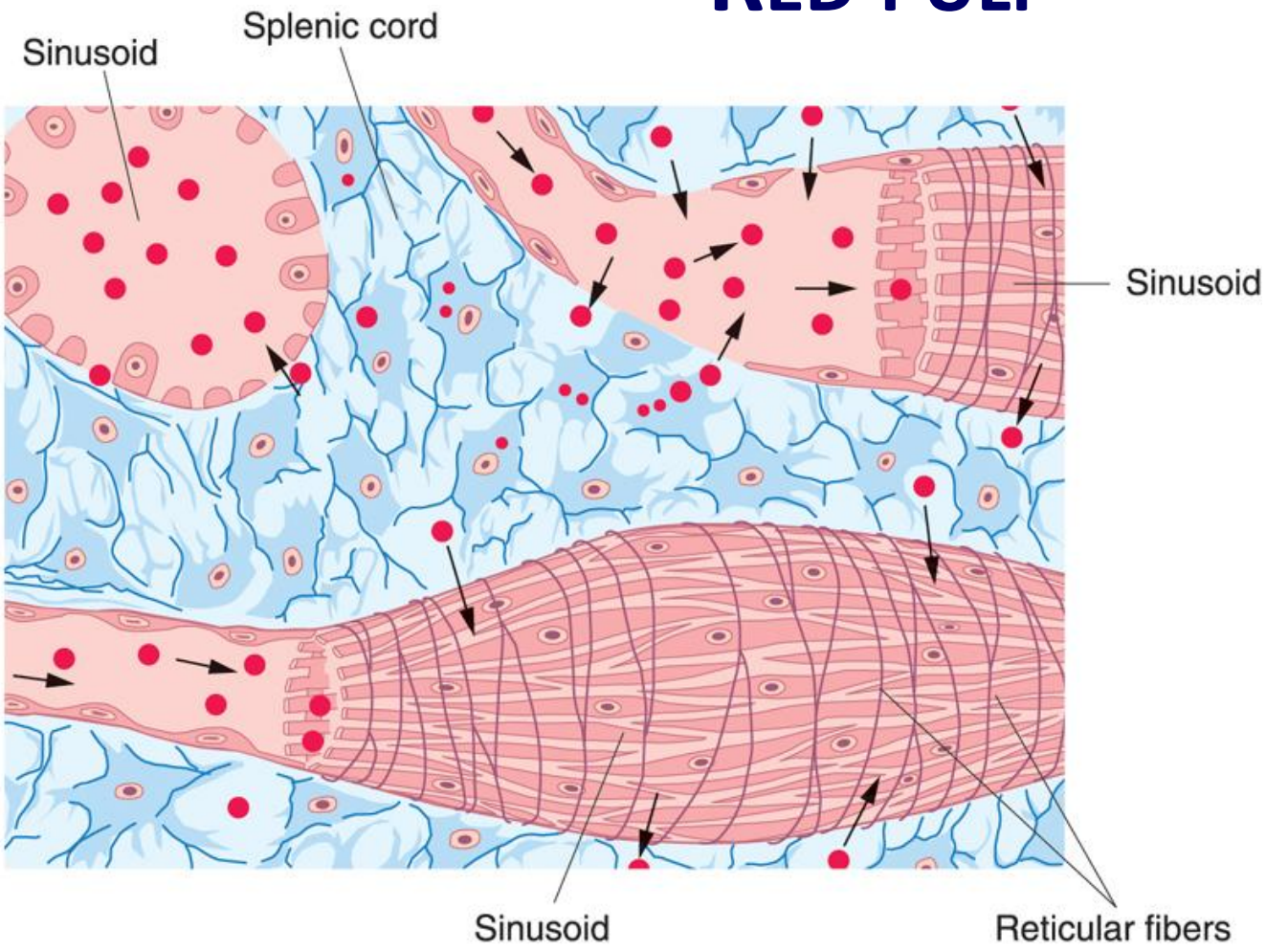
**Periarterial lymphatic sheath (PALS)** - T lymphocytes, central artery
**Lymphoid nodules with germinal center** - B cells, marginal zone with marginal sinuses

# RED PULP




The **red pulp** of the spleen is composed of splenic sinuses and splenic cords (of Billroth). In these sinusoids blood is filtered and old RBCs are destroyed.

# RED PULP

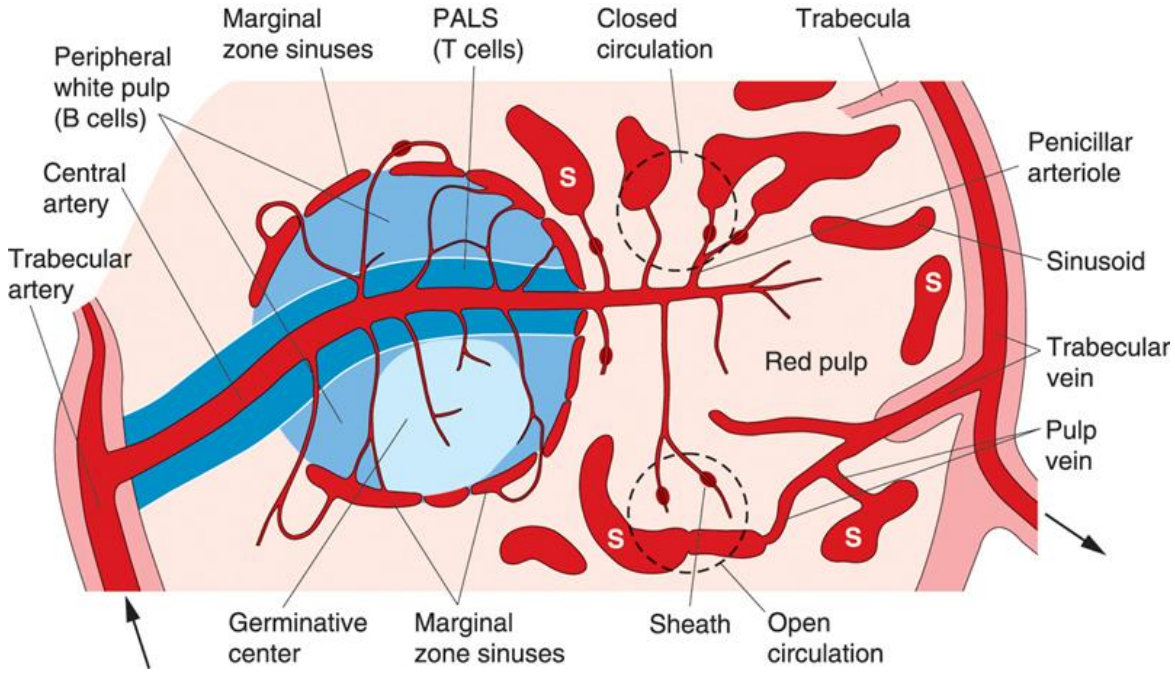



Splenic sinusoids, splenic cords
Reticular fibers surround sinusoids. Spaces between endothelial cells of the sinusoids allow movement of blood cells to the cords and back (arrows).

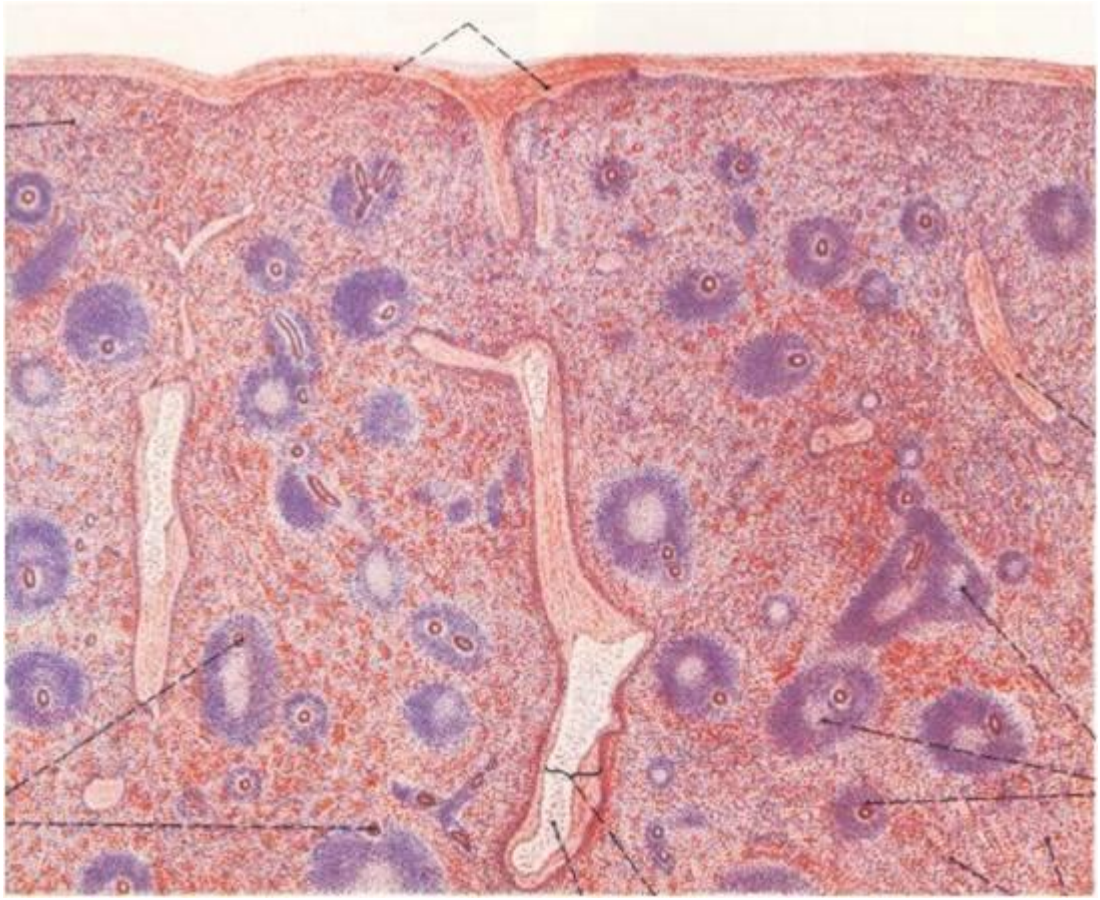
# VASCULAR SUPPLY OF THE SPLEEN

When **trabecular arteries** are reduced to 0.2 mm, they leave trabeculae. Their tunica adventitia is infiltrated by lymphocytes T - the periarterial lymphatic sheath (PALS) - **central arteries**. Frequently, enclosed within the PALS are lymphoid nodules - B cells. PALS and lymphoid nodules form WHITE PULP.

- central arteries loses PALS and subdivide into several branches - **penicillar arterioles**, which enter the red pulp. They delivered blood into **sinuses**. The sinuses are drained by small **pulp veins**, which merge and form **splenic vein**.



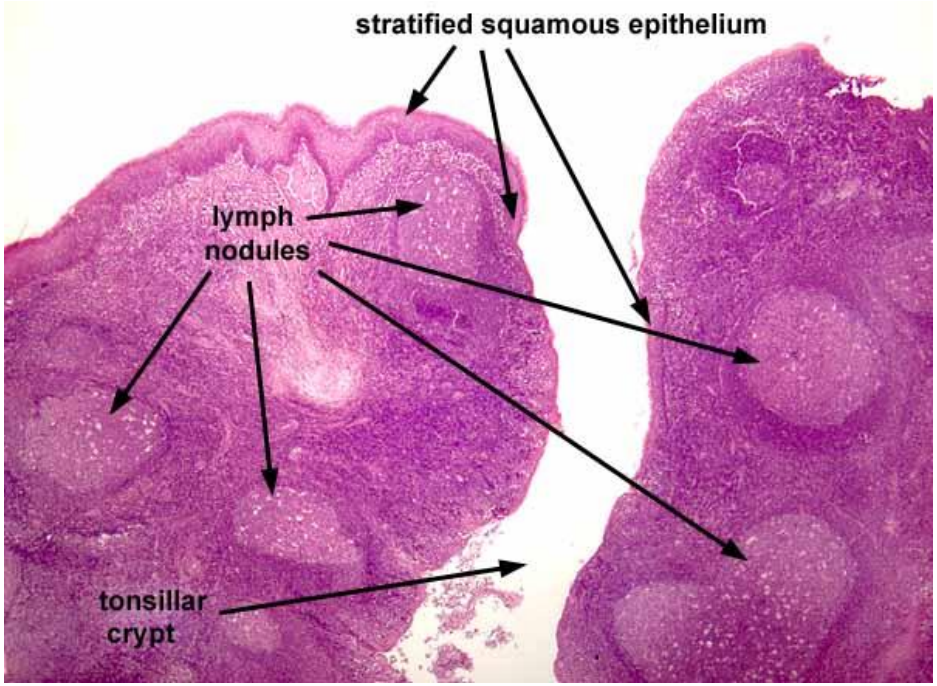
capsule

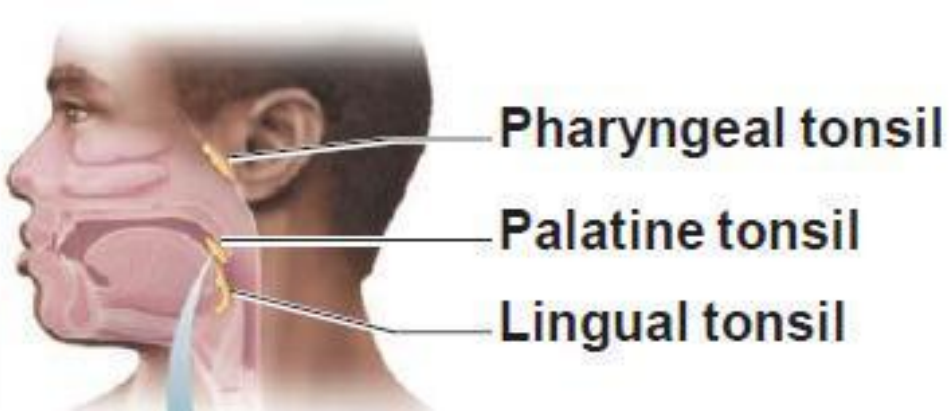


white pulp
(PALS + LN +
central artery)

trabecula with blood vessel

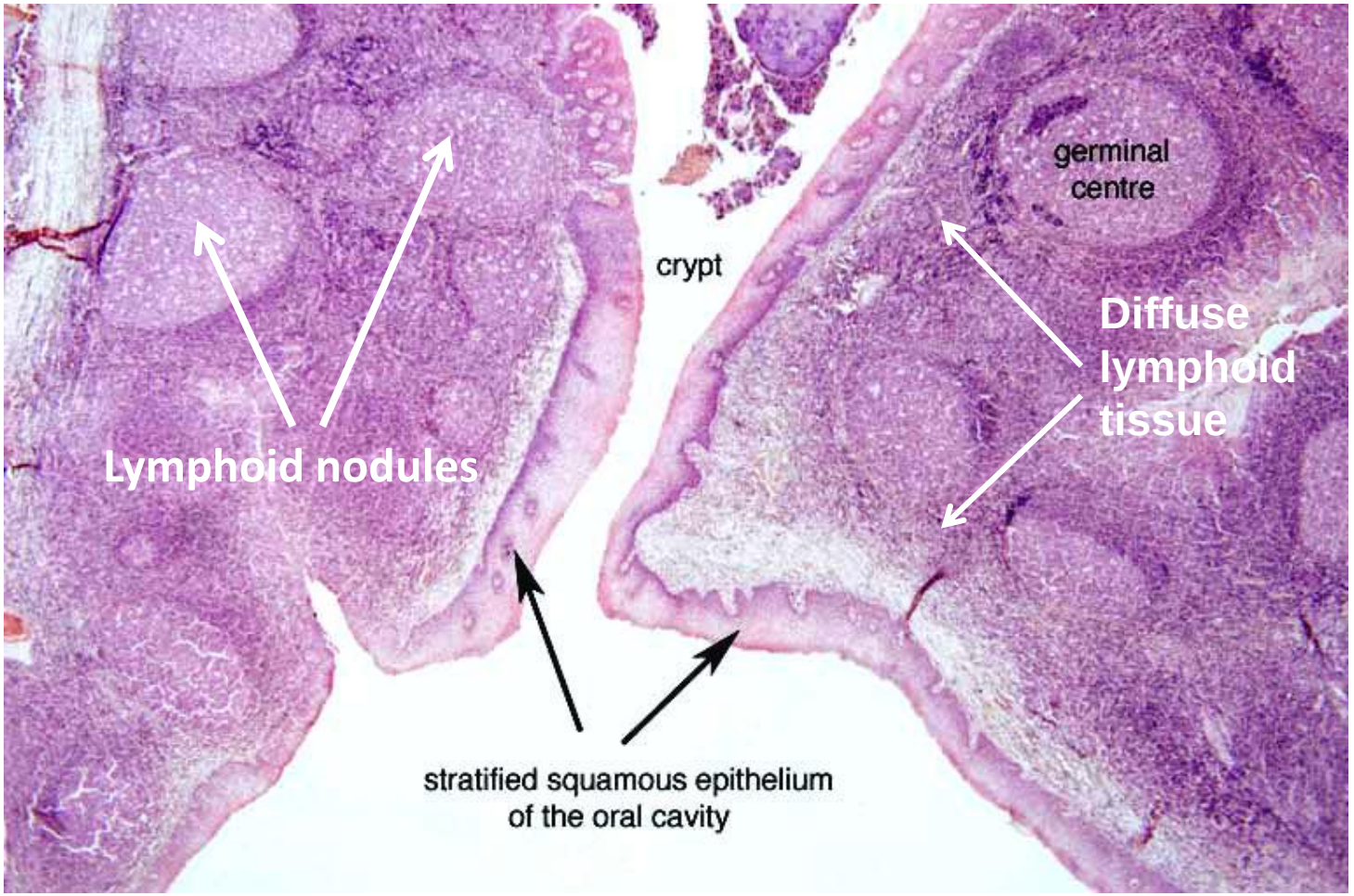
# TONSILS



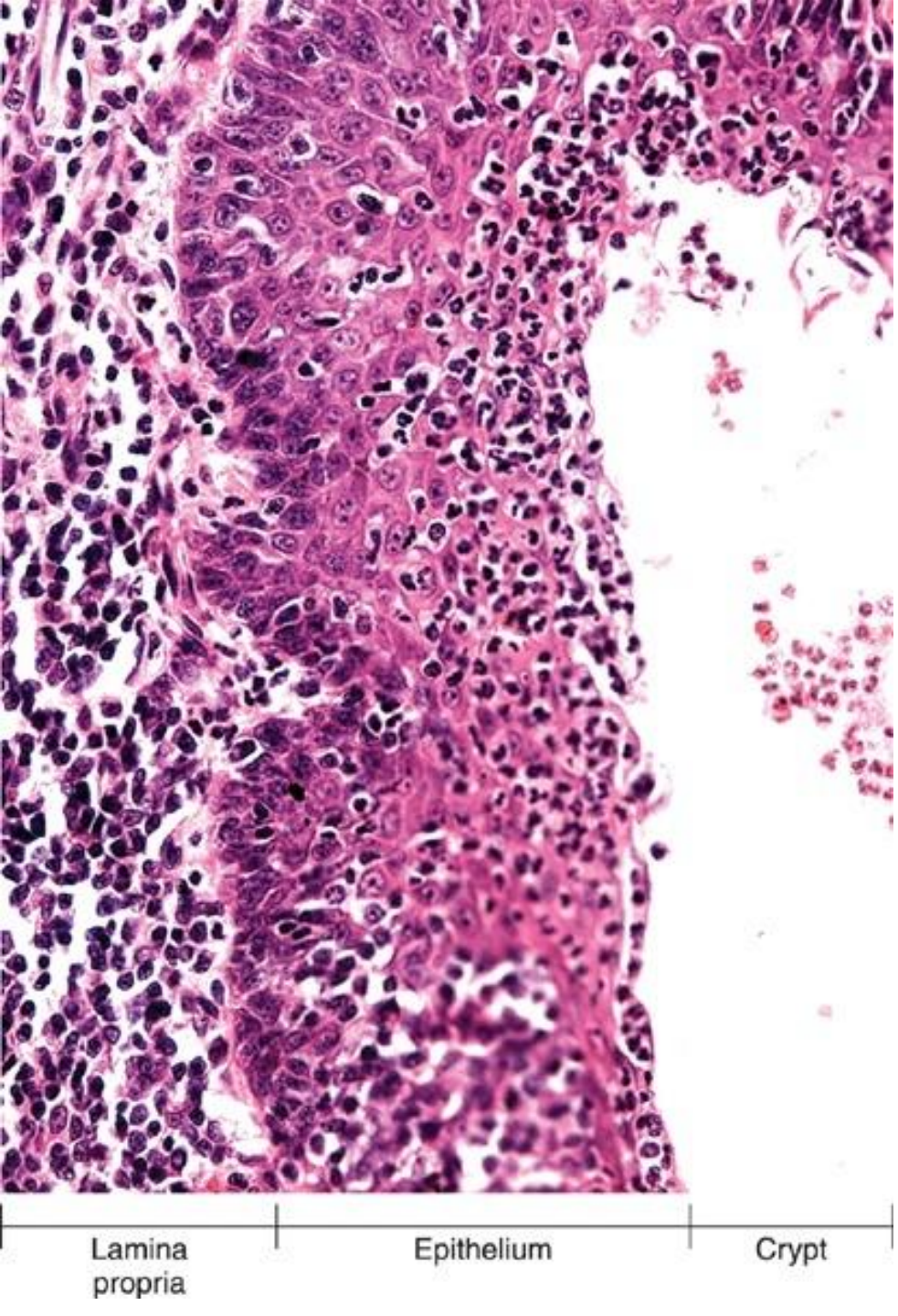




**Palatine (2), pharyngeal, and lingual tonsils** are aggregates of lymphoid nodules in mucosa that guard the entrance of the oral pharynx.
They are interposed into the path of airborne and ingested pathogens.

# PALATINE TONSIL




The palatine tonsil consists of diffuse lymphocytes and lymphoid nodules disposed under a stratified squamous epithelium. Palatine tonsils contain crypts lined with epithelium infiltrated by lymphocytes.

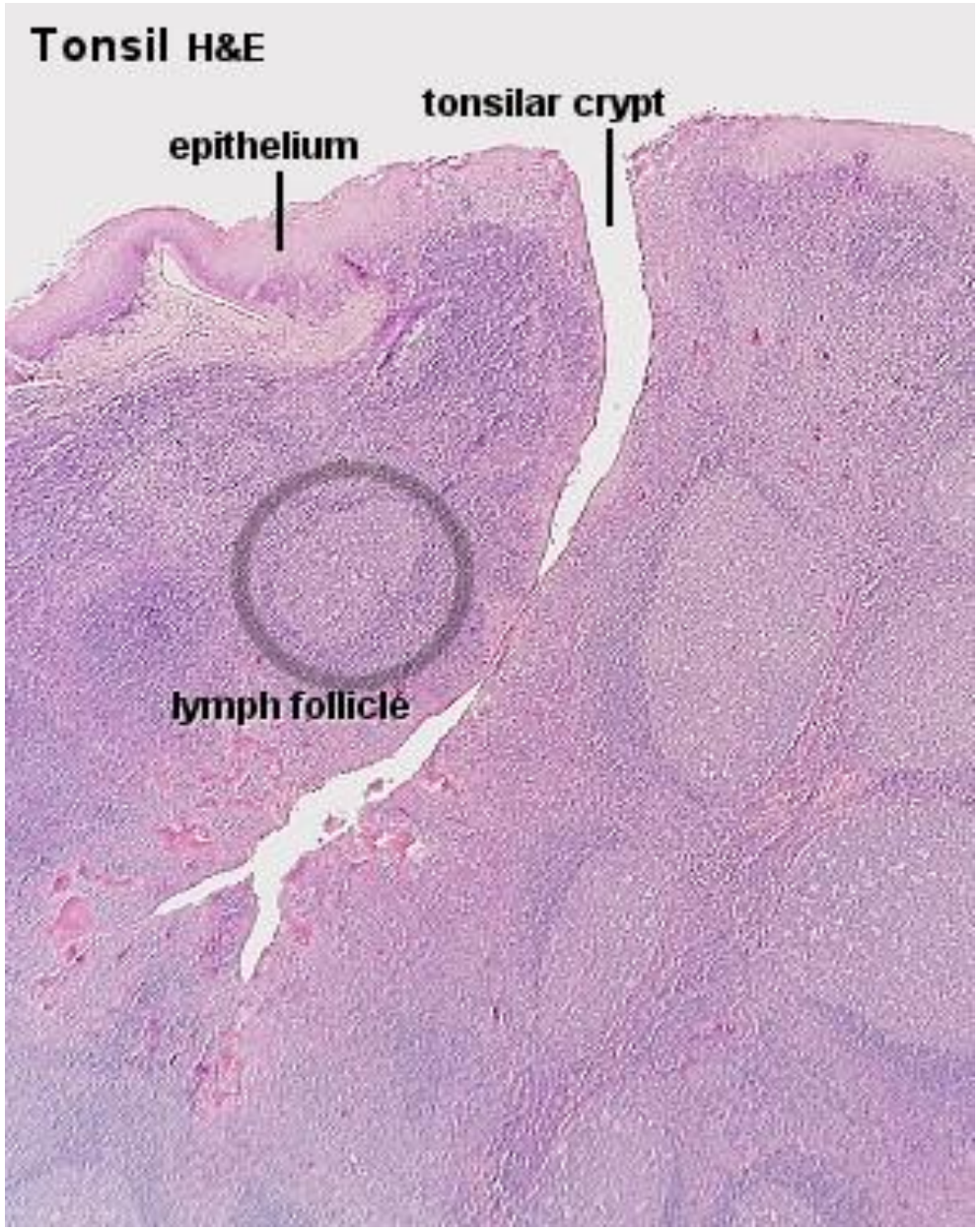



**Stratified squamous epithelium of the palatine tonsil.**

This epithelium is often heavily infiltrated by lymphocytes. The crypts often contain free lymphocytes and cell debris.

In this epithelium are present M (microfold) cells. They transport organisms and particles from the lumen to immune cells (APC) across the epithelial barrier, and thus are important in stimulating mucosal immunity.

# Palatine tonsil – slide no. 46



# Palatine tonsil – slide no.46