Immune system:
Primary & secondary lymphoid organs

MICROBIOLOGY – V

BVOC –HCT

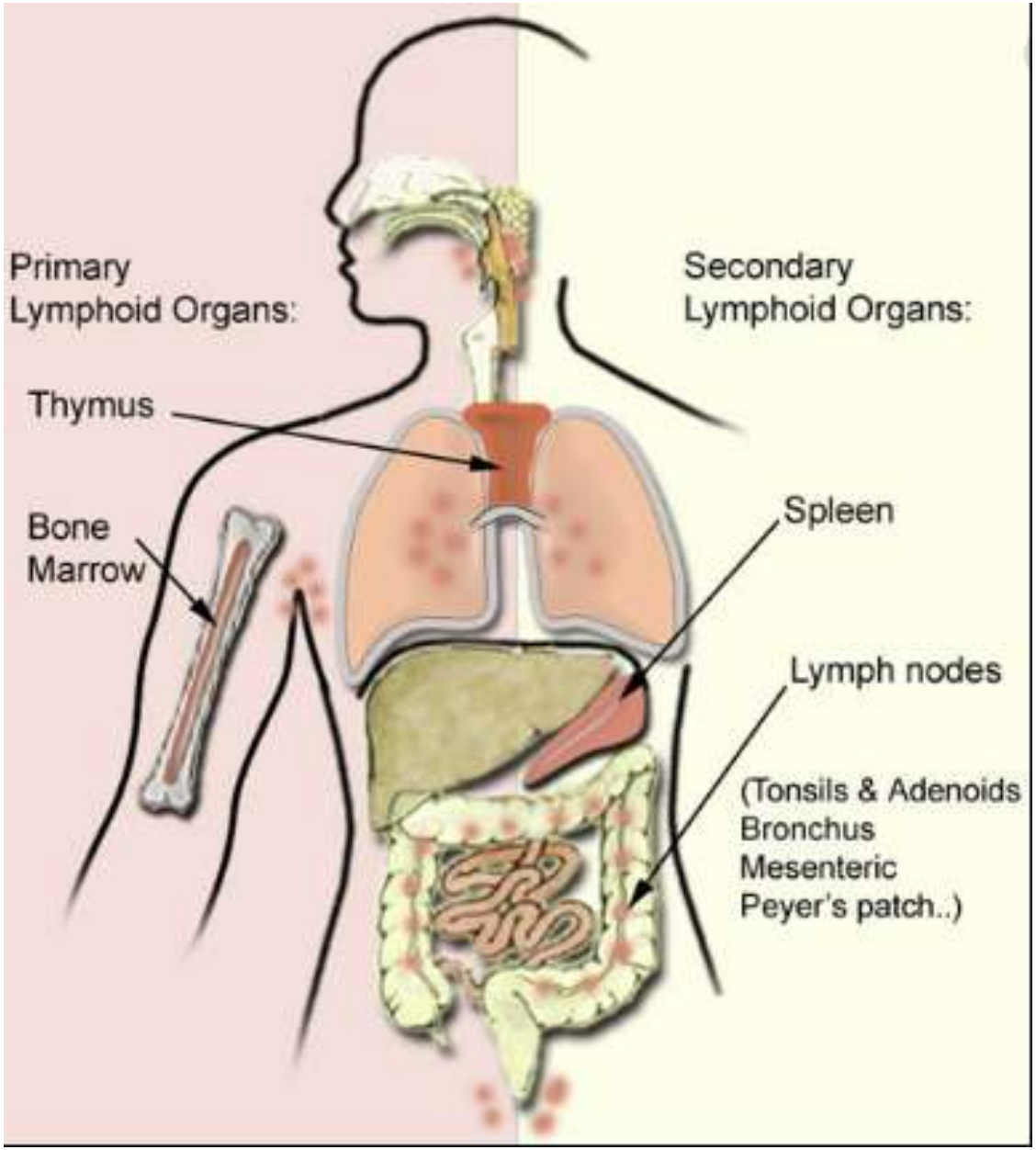
Dr. Angelina Stanley

IMMUNE SYSTEM

- Consists of many different organs & tissues that are found throughout the body
- Immune system is organized into several special tissues - collectively termed as lymphoid or immune tissues
- Tissues that have evolved to a high degree of specificity of function are termed as lymphoid organs

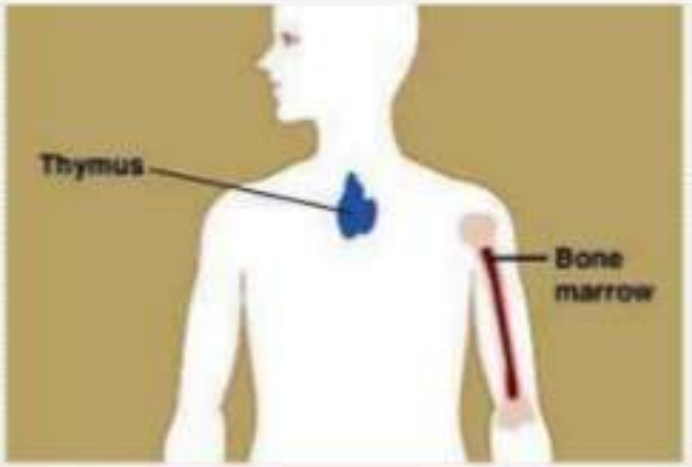
IMMUNE SYSTEM

- Based on their function - classified into
  - **Primary lymphoid organs – central**
    - Provide appropriate environment for development & maturation of ***Lymphocytes***
  - **Secondary lymphoid organs – peripheral**
    - Trap antigens from defined tissues or vascular spaces
    - Site where mature lymphocytes can interact effectively with those antigens
- Blood vessels & lymphatic systems connect these organs, & unite them as a whole to function against Ag

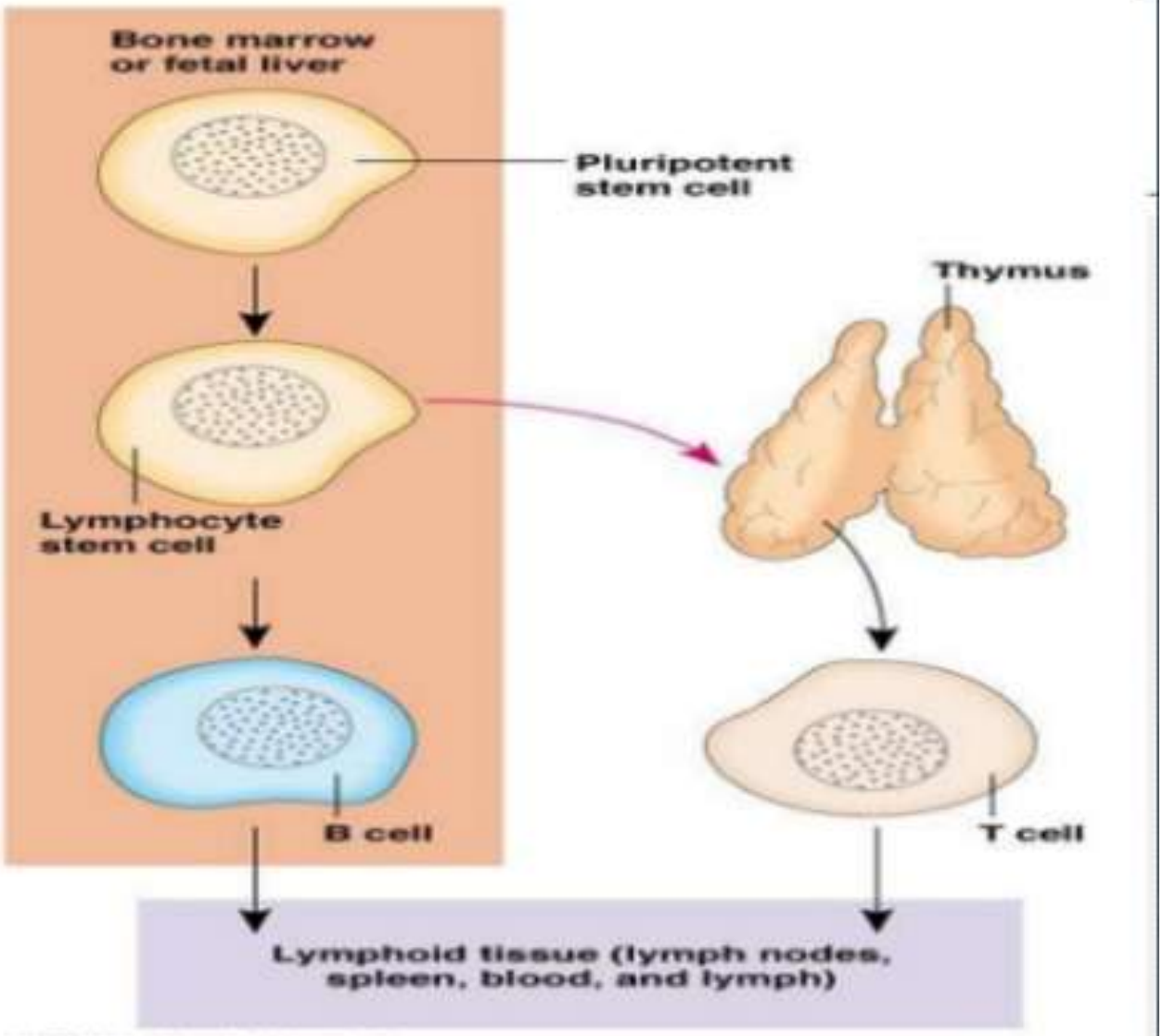

Primary
Lymphoid Organs:
Thymus
Bone
Marrow
Secondary
Lymphoid Organs:
Spleen
Lymph nodes
(Tonsils & Adenoids
Bronchus
Mesenteric
Peyer's patch..)

PRIMARY LYMPHOID ORGANS

- Major sites of ***Lymphopoiesis***
- These organs have the ability to produce the progenitor cells of the lymphocytic lineage
- Precursor lymphocytes proliferate, develop, & differentiate from lymphoid stem cells to become immunologically competent cells.
- Include
  - a) THYMUS &
  - b) BONE MARROW

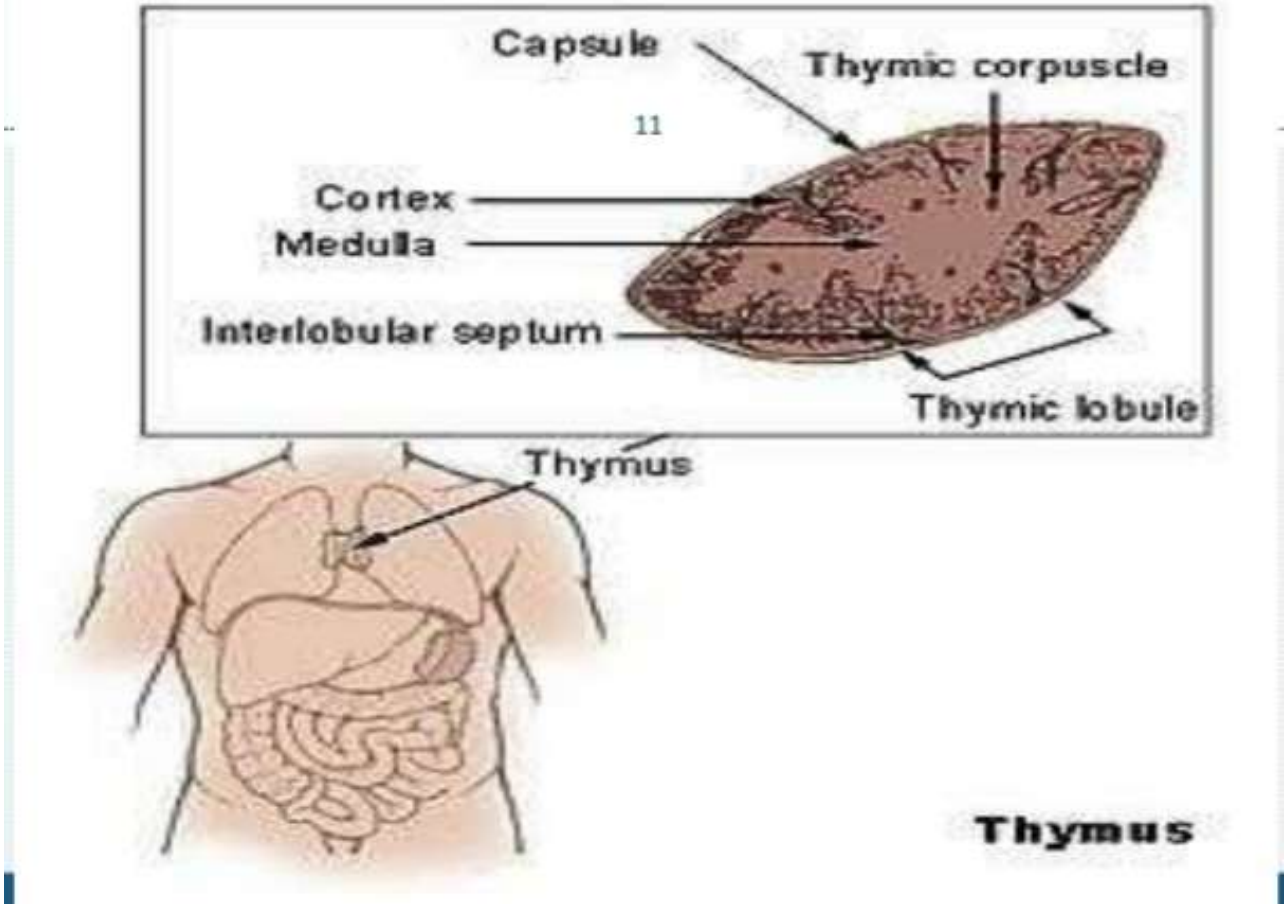


MATURATION & DIFFERENTIATION OF LYMPHOCYTES



PRIMARY LYMPHOID ORGANS – IN HUMANS

- T cells mature in thymus
- B cells mature in fetal liver & bone marrow
- After attaining immunological competency, the lymphocytes migrate to secondary lymphoid organs
- In secondary Lymphoid organs, the lymphocytes induce appropriate immune response on exposure to antigens.

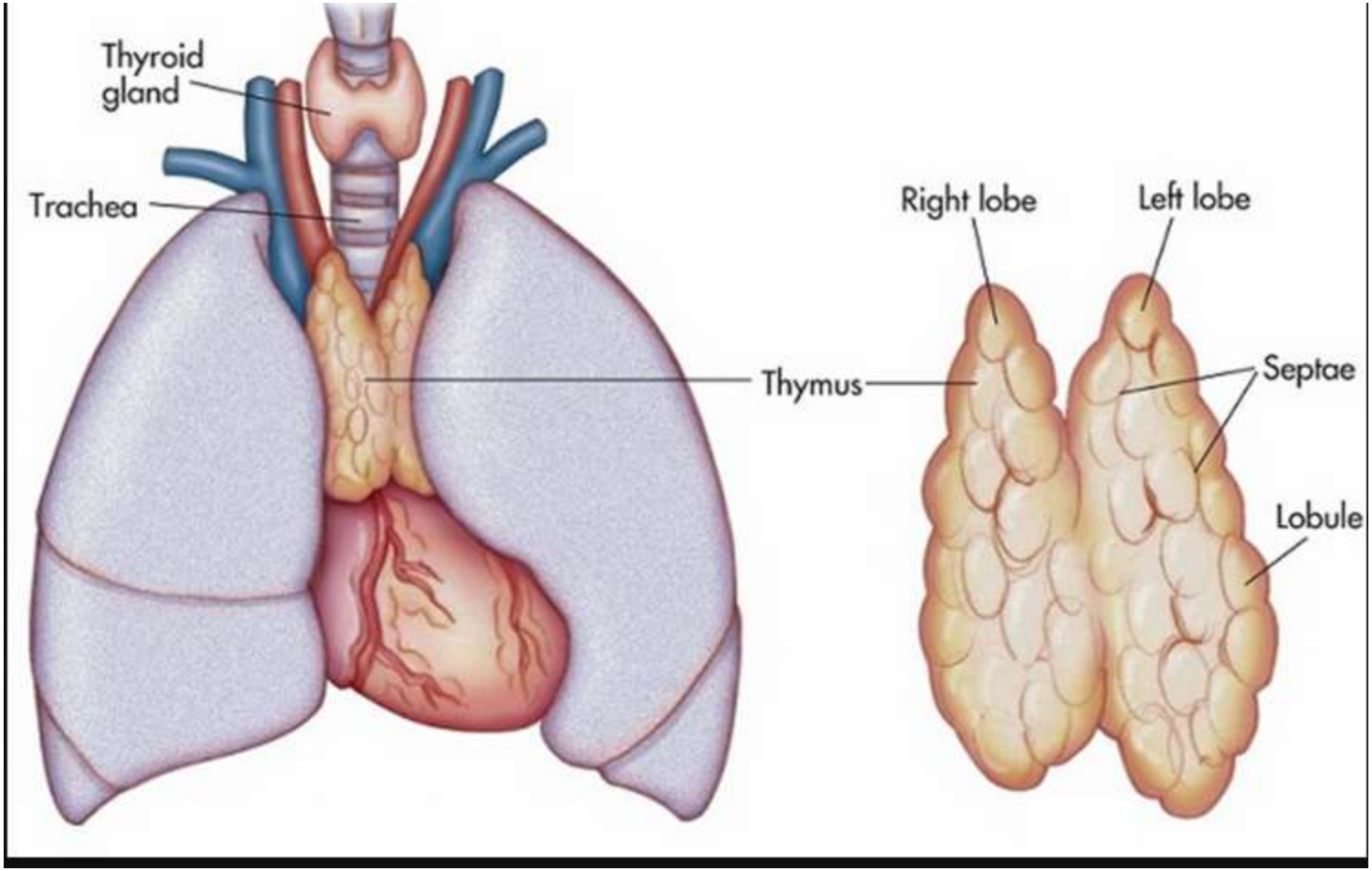

Capsule
Thymic corpuscle
Cortex
Medulla
Interlobular septum
Thymic lobule
Thymus

Thymus

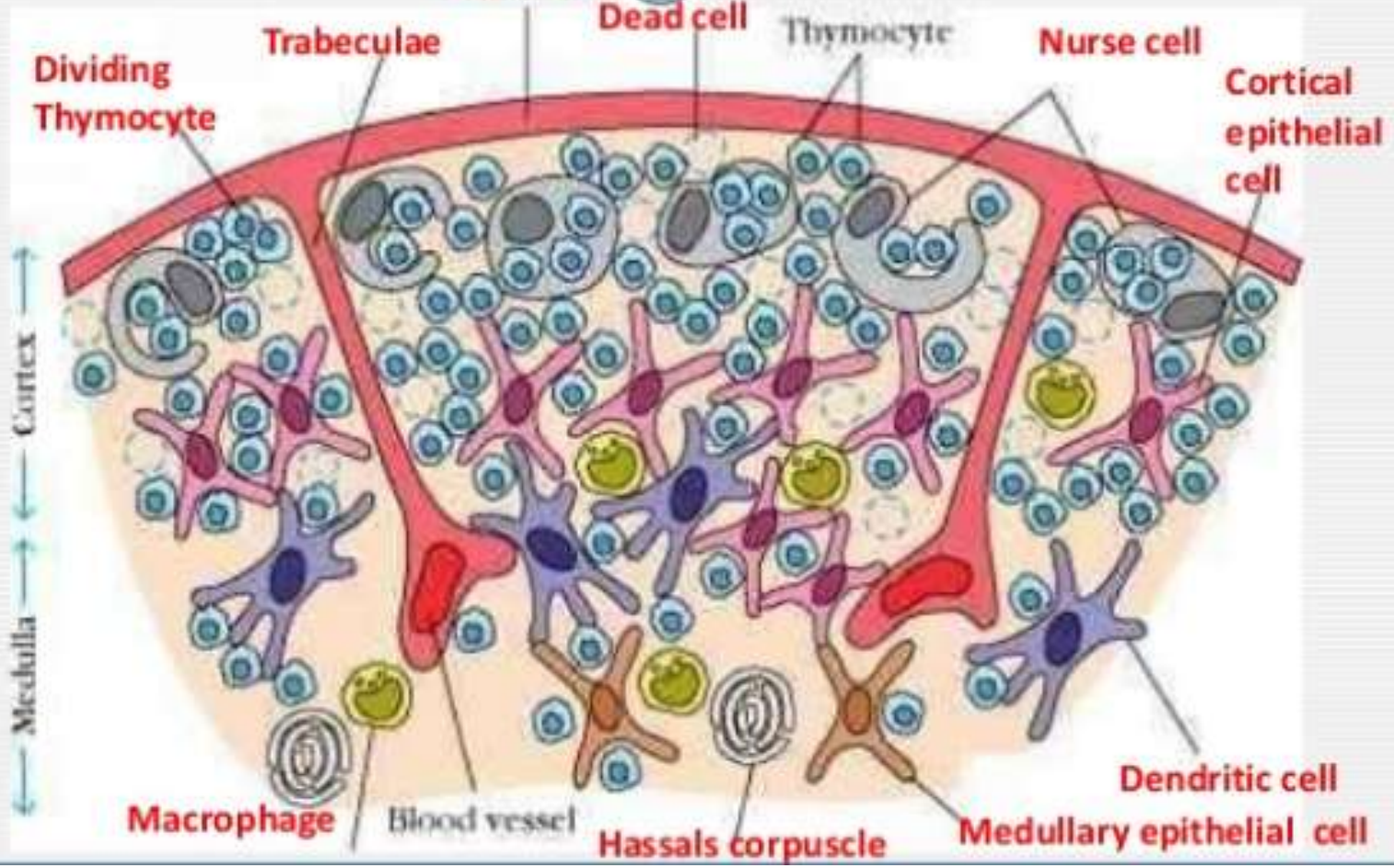
THYMUS

- The first lymphoid organ to develop
- Reaches maximal size at puberty & then atrophies. (significant decrease in both cortical & medullary cells & an increase in the total fat content of the organ)
- Flat, bilobed organ,
- Situated above heart, behind mediastinum of sternum.
- Each lobe is surrounded by capsule & divided into lobules
- Lobules are separated from each other by strands of connective tissue called as trabeculae.

THYMUS

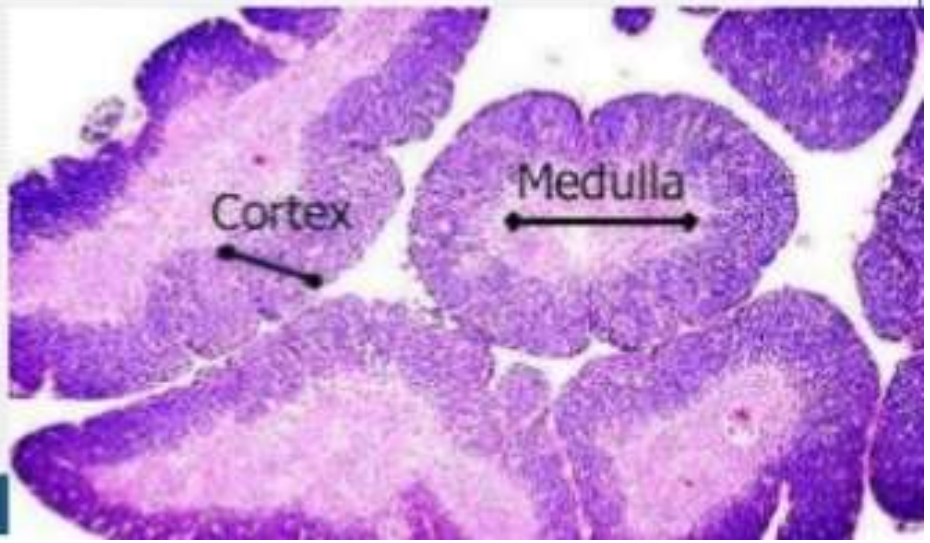

Thyroid gland
Trachea
Thymus
Right lobe
Left lobe
Septae
Lobule

CROSS-SECTION OF A PORTION OF THYMUS



THYMUS...contd...

- Each lobule is organised into two compartments
  - Cortex –
    - densely packed with immature T cells - cortical thymocytes
  - Medulla –
    - Sparesly populated with thymocytes - mature
- Stroma is composed of
  - Dendritic cells,
  - Epithelial cells, &
  - Macrophages.



CORTEX OF THYMUS

- Consists mainly of cortical thymocytes (immunologically immature T lymphocytes),
- Macrophages & plasma cells are also present in cortex but in small number
- In addition contains 2 subpopulations of epithelial cells,
  - the epithelial nurse cells &
  - the cortical epithelial cells,
    - which form a network within the cortex

MEDULLA OF THYMUS

- Contains predominantly mature T lymphocytes
- Has a larger epithelial cell to lymphocyte ratio than cortex.
- **Hassals corpuscles:-**
  - found extensively in the medulla
  - Concentric rings of squamous epithelial cells.

THYMUS CONTD...

- Thymus is the site where a **large diversity of T cells** is produced – (so they can recognize and act against a large number of antigen – MHCs)
- Thymus induces the **death** of those T cells that cannot recognize antigen – MHCs.
- Also induces death of those T cells **that react with self-Ag –MHC** (which pose a danger of causing autoimmune dis)
- More than 90% of all thymocytes **die by apoptosis** in the thymus without ever reaching maturity.

FUNCTIONS OF THYMUS

- Only clearly individualized 1^{o} lymphoid organ
- **Primary function**:- production of thymic lymphocytes
- A **major organ** for proliferation of lymphocytes in body.
- Plays key role in determining the differentiation of T cell

FUNCTIONS OF THYMUS

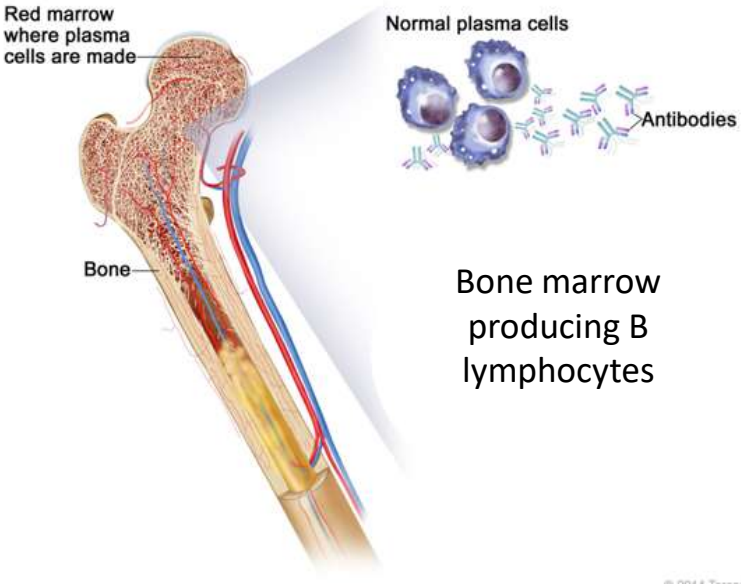
- Lymphocytes during maturation acquire new surface antigens (*Thy Ag*)& are called as **T lymphocytes or T cells (thymus dependent)**
- Confers **immunological competence on T cells** during their stay in the organ
- Lymphocyte proliferation in thymus is **not dependent on antigenic stimulus** (unlike in peripheral lymphoid organs)

FUNCTIONS OF THYMUS

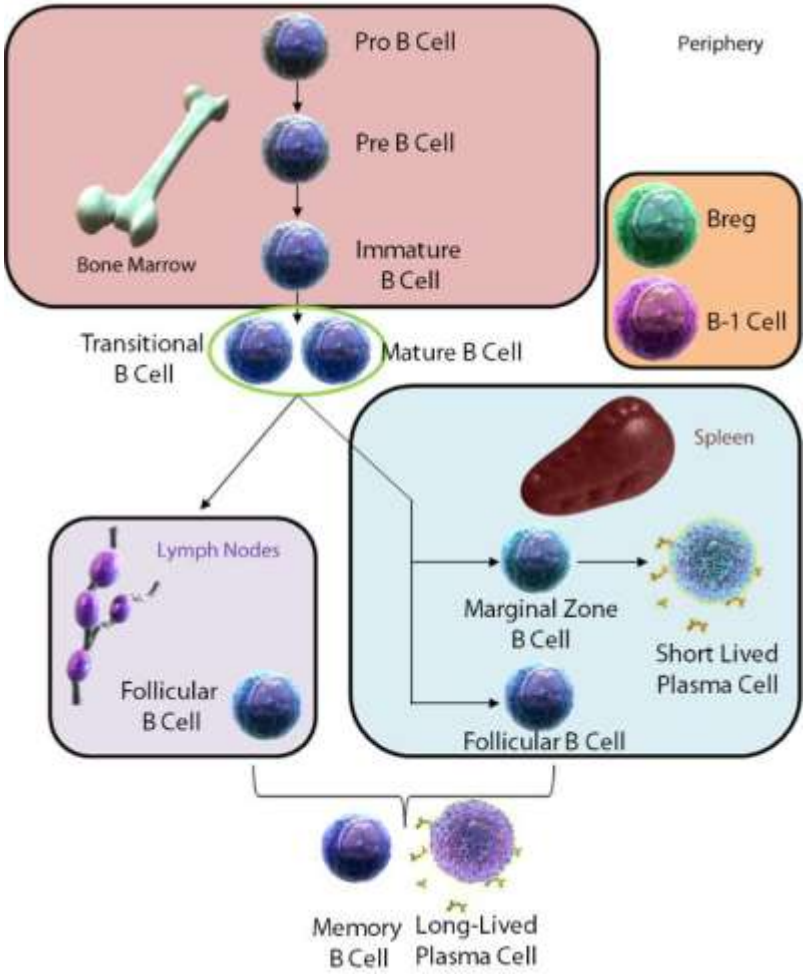
- T lymphocytes –primarily responsible for CMI
- Absence of thymus in neonatally thymectomized mice is associated with gross deficiency of the CMI →
  - lymphopenia,
  - deficient graft rejection, &
  - unting disease
- Congenital aplasia of thymus (Di-George synd)
  - another example of deficiency of CMI due to the absence of thymus

BONE MARROW

- Some lymphocytes originate, develop, & mature within the bone marrow – B cells..
- B for **Bursa Of Fabricus In Birds** – equivalent to bonemarrow in humans
- Site for proliferation of stem cells
- Site for the origin of pre-B cells & their maturation to become immunoglobulin producing lymphocytes (PLASMA CELL)



Bone marrow producing B lymphocytes

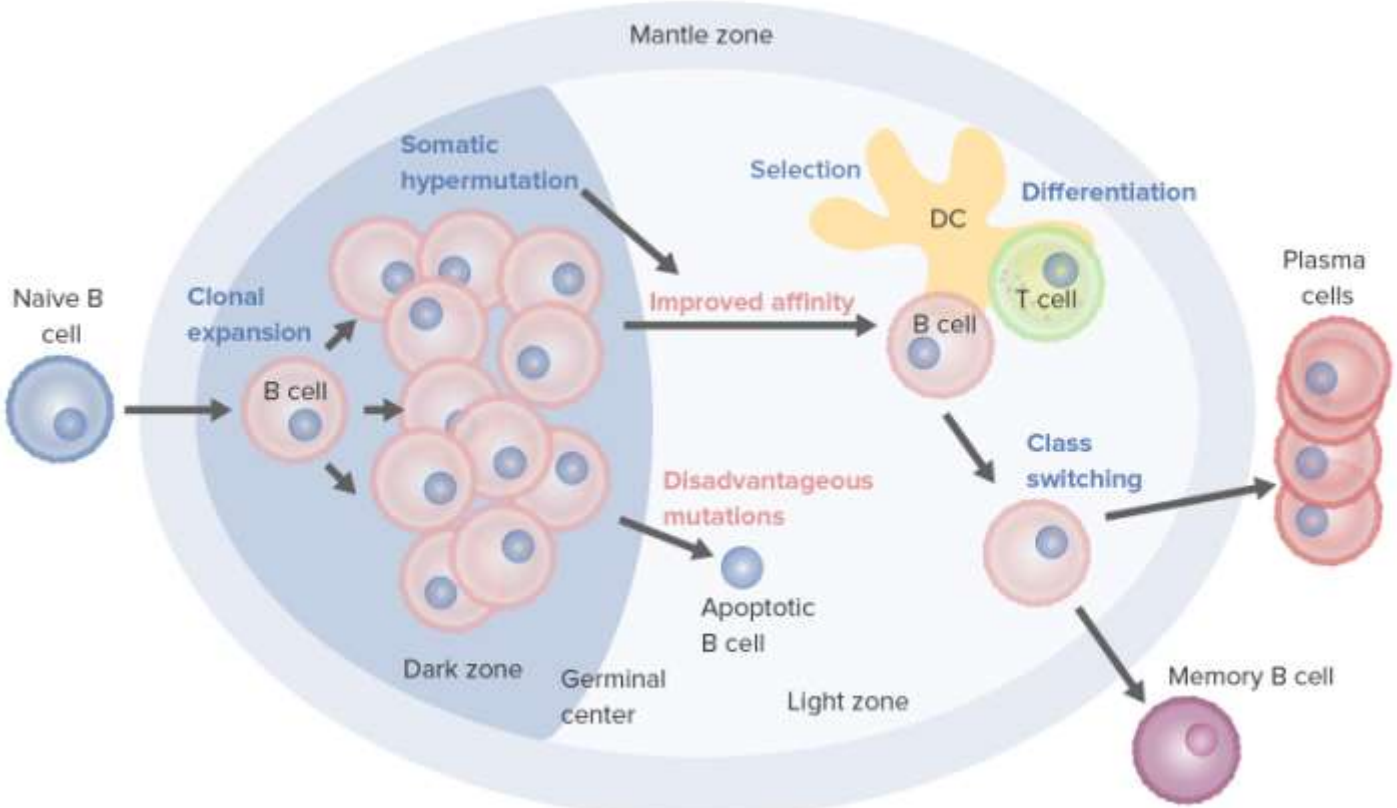


BONE MARROW

- Immature B-cells proliferate & differentiate within the bone marrow.

- Stromal cells within bonemarrow interact directly with B-cells & secrete various cytokines →that are required for development of B cells

B - cell development:



BONE MARROW

- A selection process within the bone marrow **eliminates B-cells with self-reactive antibody receptors** (like thymic selection during T-cell maturation)

- B-cells develop their B-cell receptors (BCRs) by DNA rearrangement.

- B cells express auxillary molecules such as Ig□ & Igβ, & they begin to express IgM on their surfaces before leaving bone marrow.

BONE MARROW

- Mature B-cells also acquire C3 & Fc receptors on their surfaces.
- B- cells on their surfaces either bear IgM alone or in association with IgG or IgA depending upon the production of particular class of immunoglobulin
- B lymphocytes are transformed into plasma cells & secrete antibodies, & are primarily responsible for antibody-mediated immunity.

SECONDARY LYMPHOID ORGANS

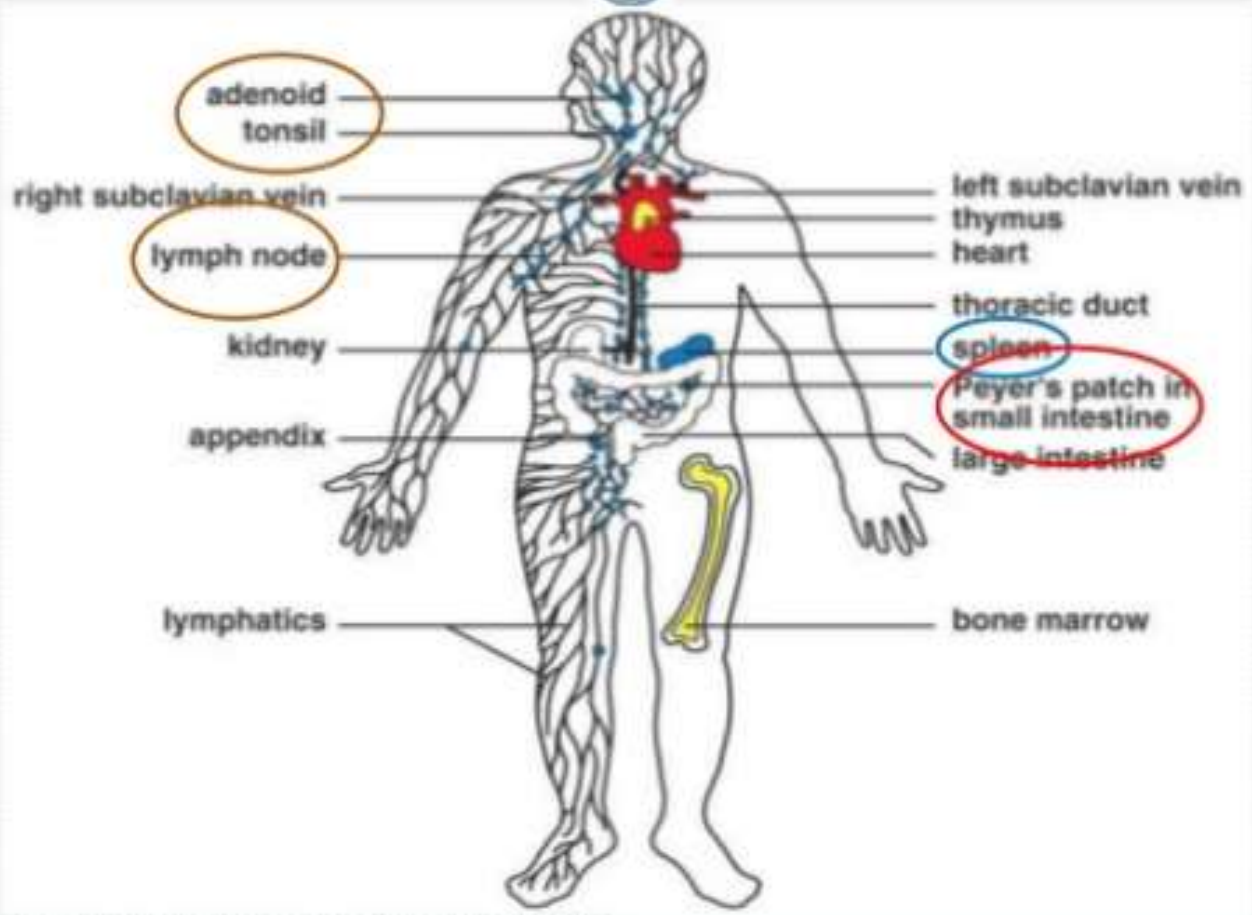
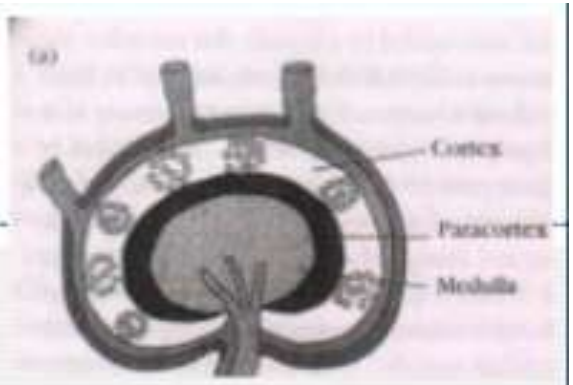


Figure 1-7 Immunobiology, 6/e. (© Garland Science 2005)

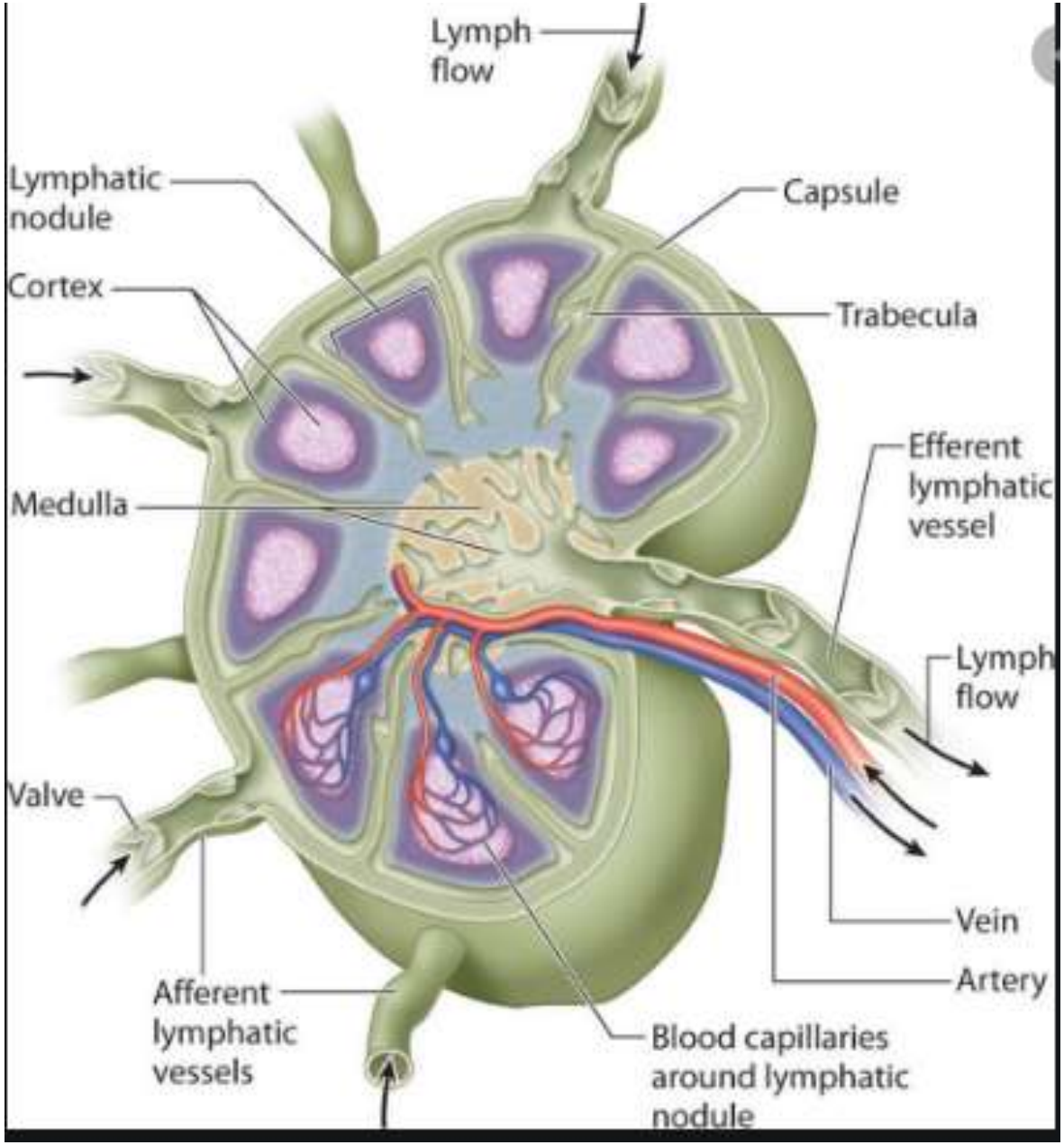
SECONDARY LYMPHOID ORGANS

- Peripheral lymphoid organs
- Consists of
  - Well encapsulated organs –
    - LYMPH NODES &
    - SPLEEN
  - Non-encapsulated organs –
    - Mucosa – Associated Lymphoid Tissues (MALT)
- These organs serve as sites for the interaction of the mature lymphocytes with the antigens.

LYMPH NODES

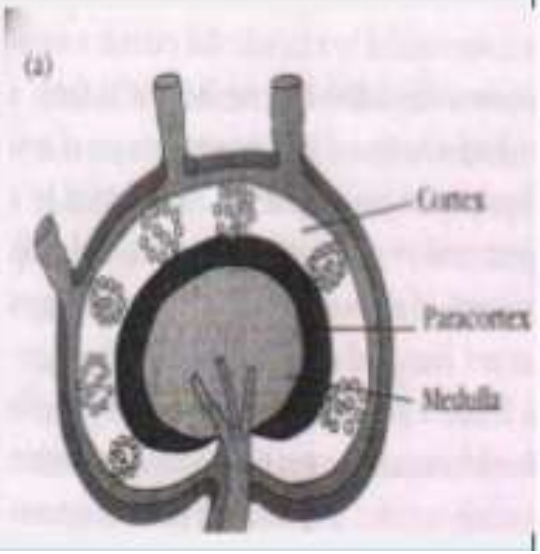


- Disseminated all over the body
- Extremely numerous
- Plays an impt role in initial phases of immune response
- Measures 1-25mm in diameter
- Surrounded by a connective tissue capsule
- Two main parts :- cortex & medulla
- Reticulum of lymph node – composed of phagocytes & specialized types of reticular or dendritic cells


Lymph flow
Lymphatic nodule
Capsule
Cortex
Trabecula
Efferent lymphatic vessel
Medulla
Lymph flow
Valve
Vein
Artery
Afferent lymphatic vessels
Blood capillaries around lymphatic nodule

CORTEX OF LYMPH NODE

- Densely populated by lymphocytes
- B & T lymphocytes seen in different areas of cortex
- Contains **Primary Lymphoid Follicles/ Nodules** – spherical areas containing densely packed lymphocytes
  - Predominantly contain **B lymphocytes**
  - Also contain macrophages, dendritic cells, & some T-lymp – to trap antigen
  - Very densely packed with **small lymphocytes** –which are not actively involved in immune response



Lymph nodes – showing regions of B and T cells

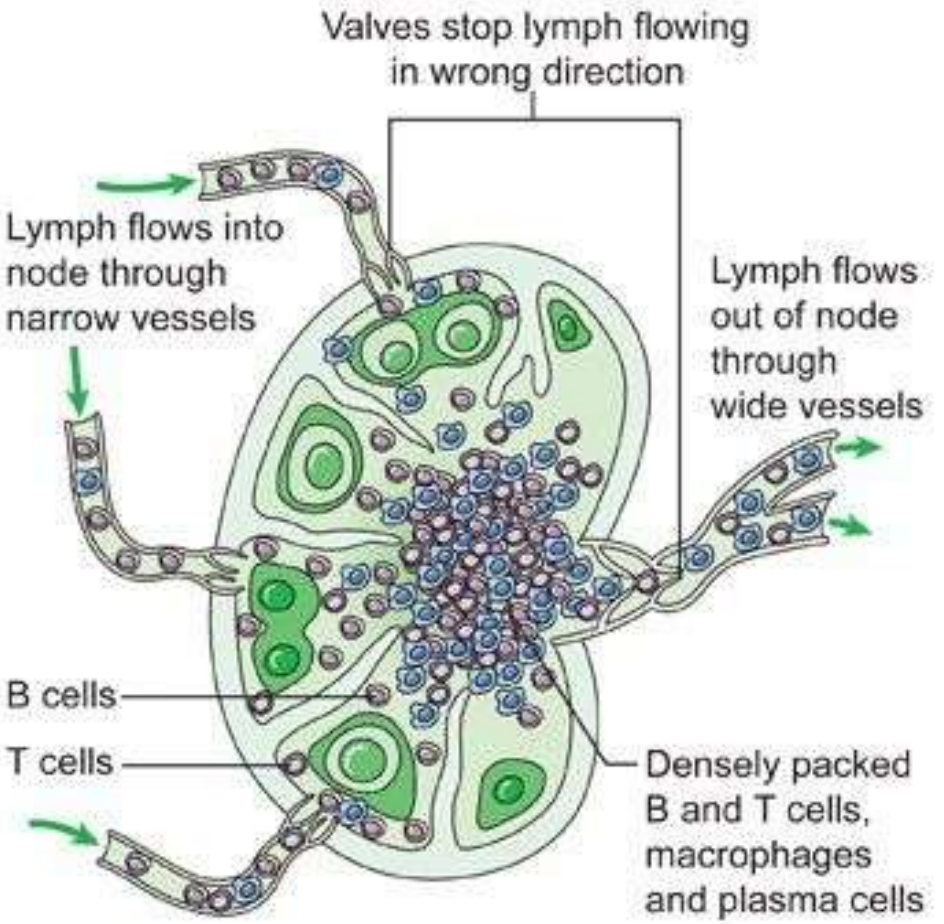
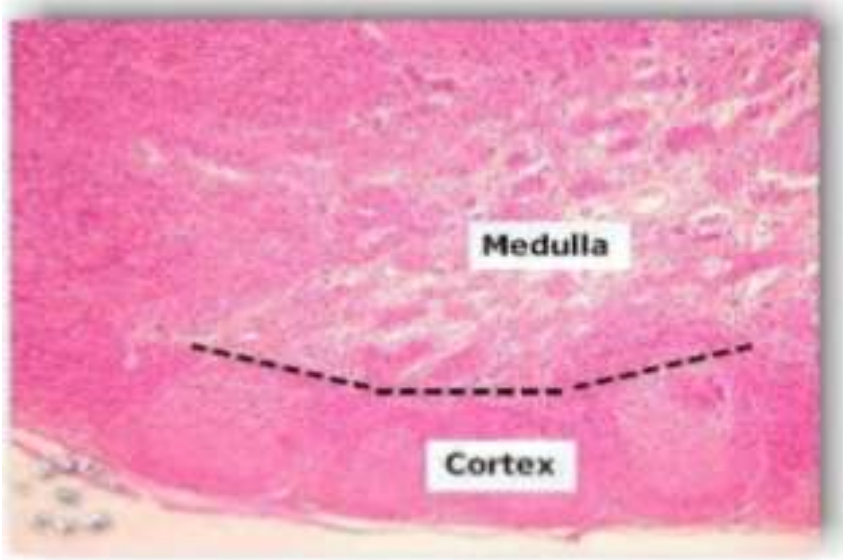
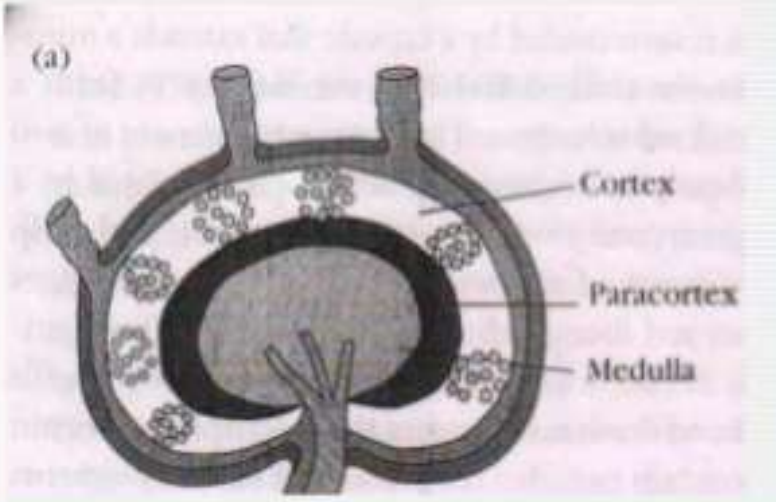


Diagram of a lymph node

CORTEX OF LYMPH NODE

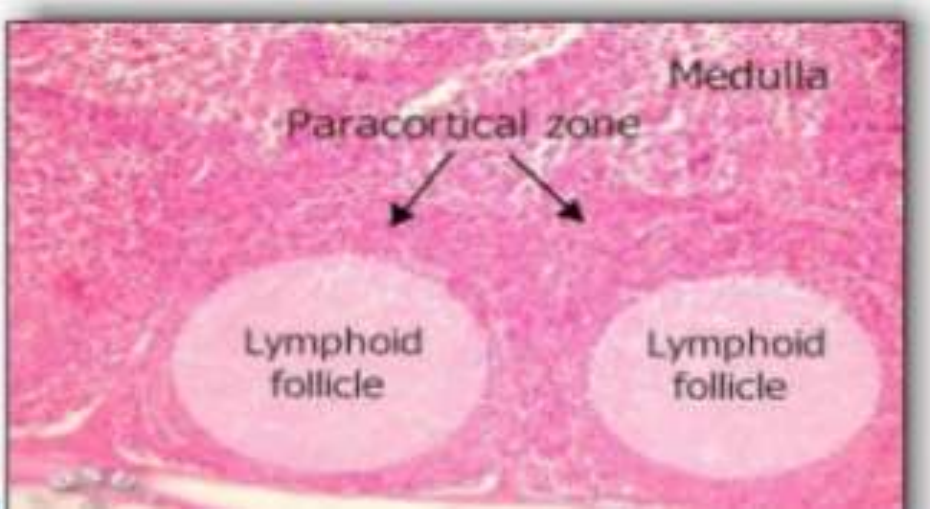
- Secondary lymphoid follicles –
  - Larger, less dense, follicles found in cortex,
  - drain an area in which an infection has taken place
  - Contain clear **Germinal Centres** where B lymphocytes actively divide as a result of antigenic stimulation.

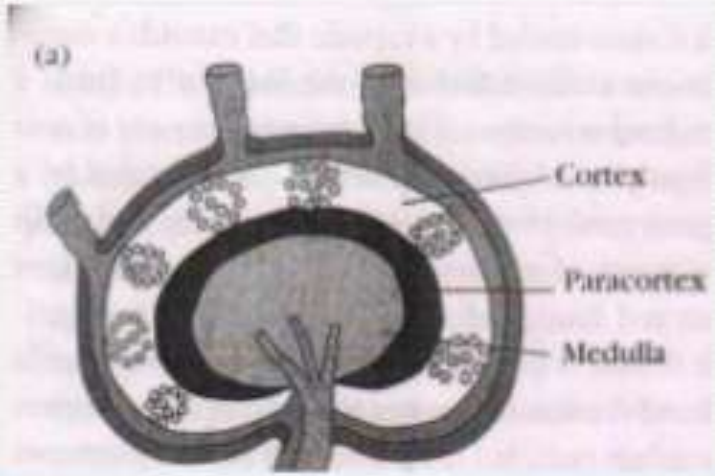


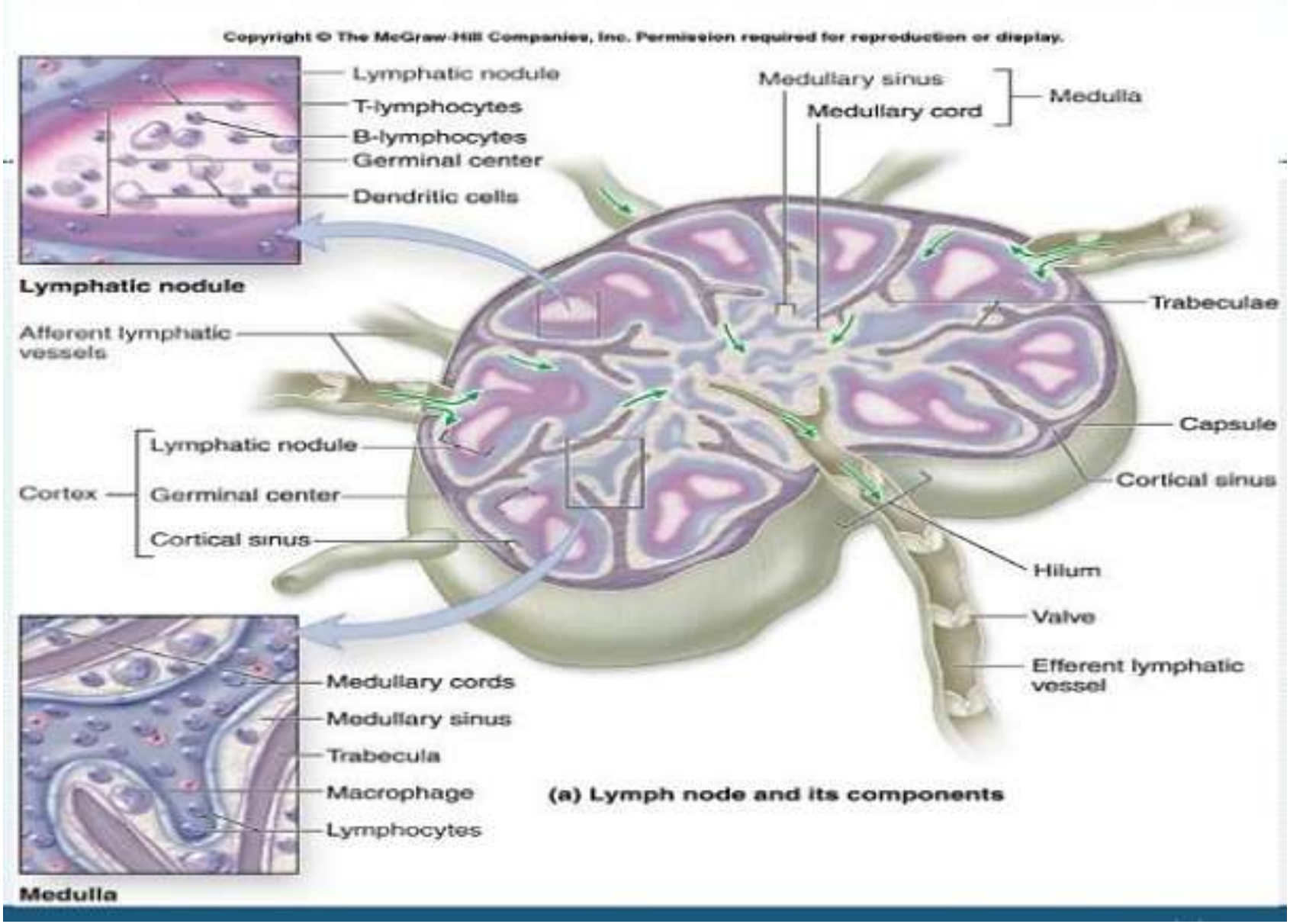


LYMPH NODES - PARA CORTICAL AREA

- Also known as Deep cortex
- T – lymphocytes are found predominantly - hence designated as T-dependent area
- Interdigitating cells are also present in this area – they present antigen to T- lymphocytes.

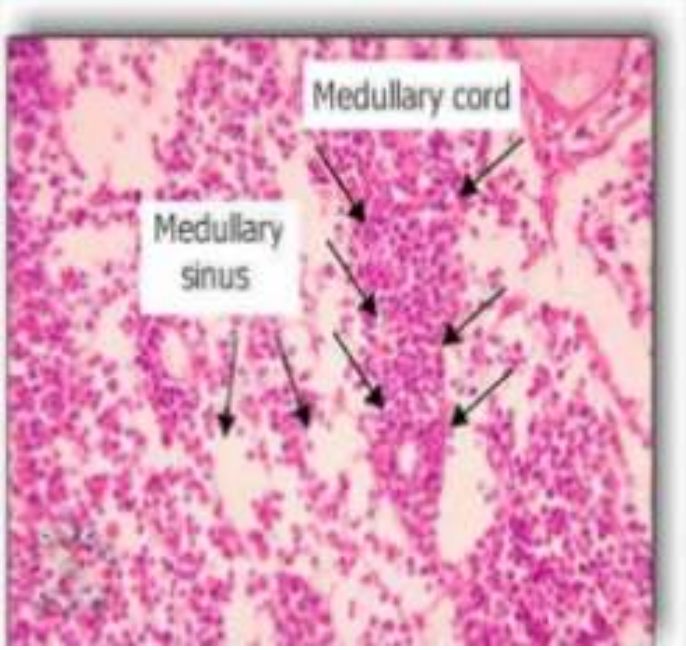






LYMPH NODES - MEDULLA

- Less densely populated
- Composed mainly of **Medullary Cords** –
  - Elongated branching bands of lymphocytes, plasma cells & macrophages
- Antibody producing Plasma cells are more populated
- Drain into the hilar efferent lymphatic vessels.



LYMPH NODES - MEDULLA

- Following the period of division & maturation,
  - there is a rigorous selection process in which more than 90% of these B cells die by apoptosis or cell death.
- As antigen is carried into a regional node by lymph,
  - it is trapped, processed, & presented together with class II MHC molecules by interdigitating dendritic cells in the paracortex, resulting in the activation of helper T cells.

LYMPH NODES - MEDULLA

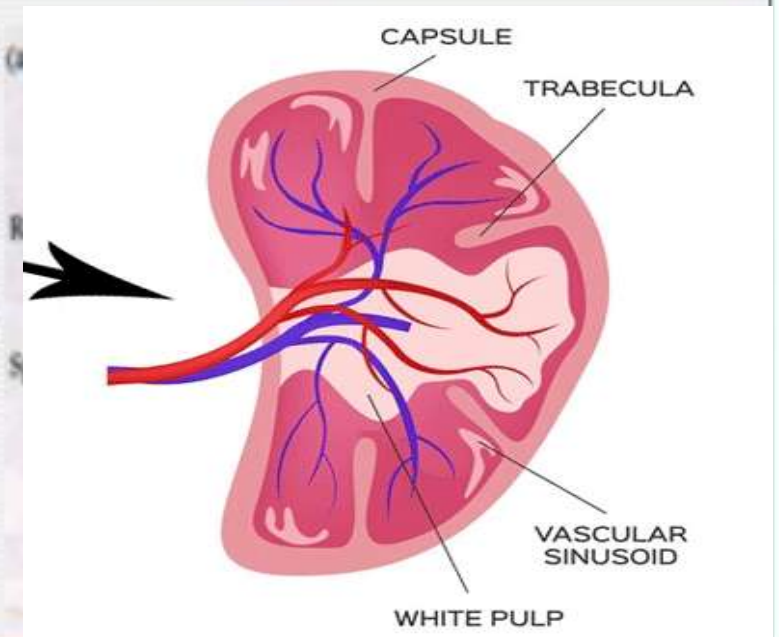
- Initial activation of B cells is also thought to take place within the T cell rich Paracortex
- Once activated, helper T cells & B cells form small foci consisting largely of proliferating B cells at edges of paracortex
- Some B cells within the foci differentiate into plasma cells secreting IgM & IgG.

FUNCTIONS OF LYMPH NODE

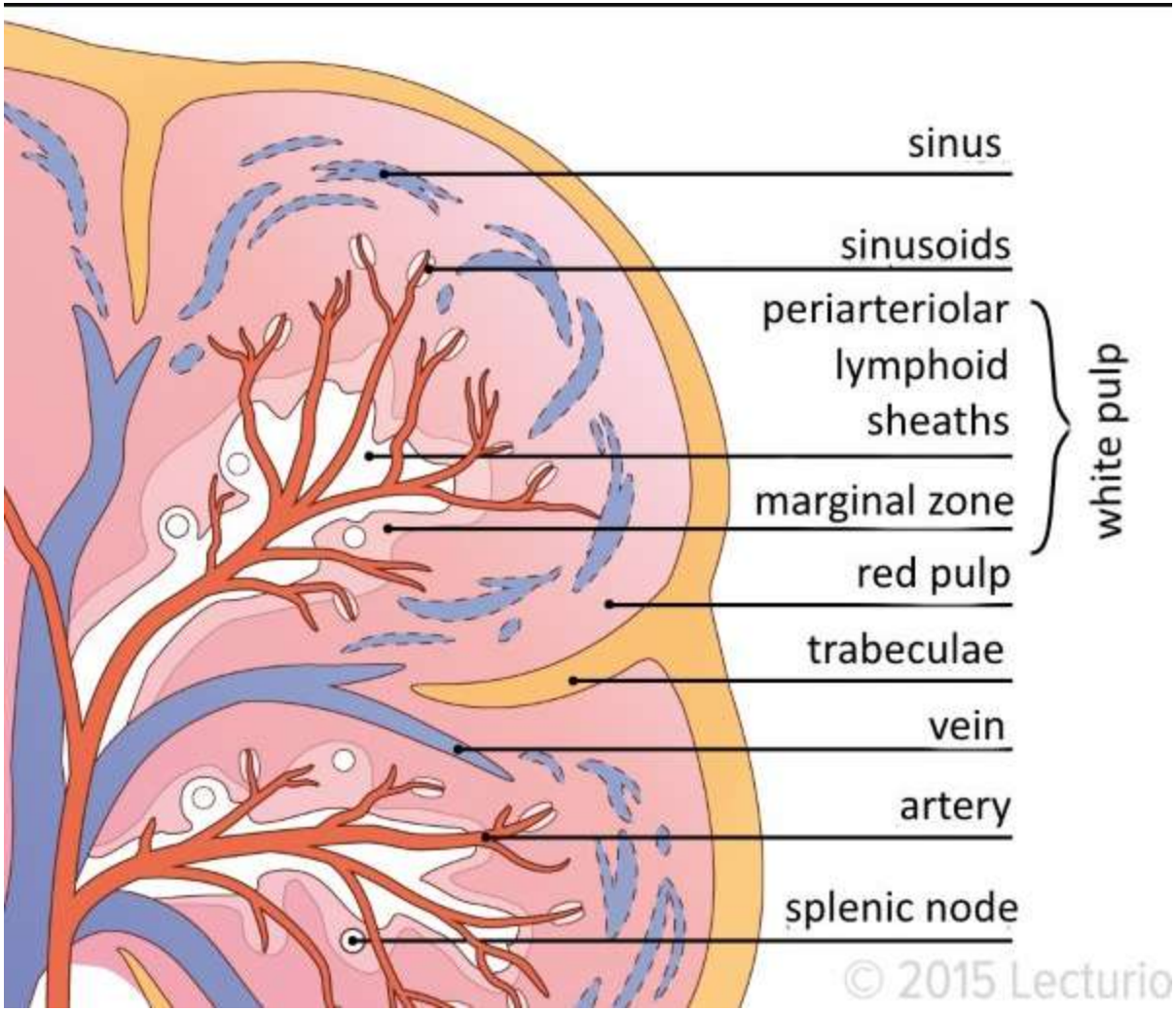
- Act as filter for lymph (fluid & cellular content of the lymphocytic circular system)
- Provide sites for mingling of lymphocytes, monocytes, & dendritic cells for initiation of immune response
- Phagocytose microbial pathogens & other foreign substances.

SPLEEN

- Largest lymphoid organ
- Large ovoid secondary lymphoid organ situated in the left abdominal cavity
- Parenchyma is heterogeneous
  - composed of white & red pulp
- Surounded by
  connective tissue capsule
- Specialized for trapping
  blood borne Ag

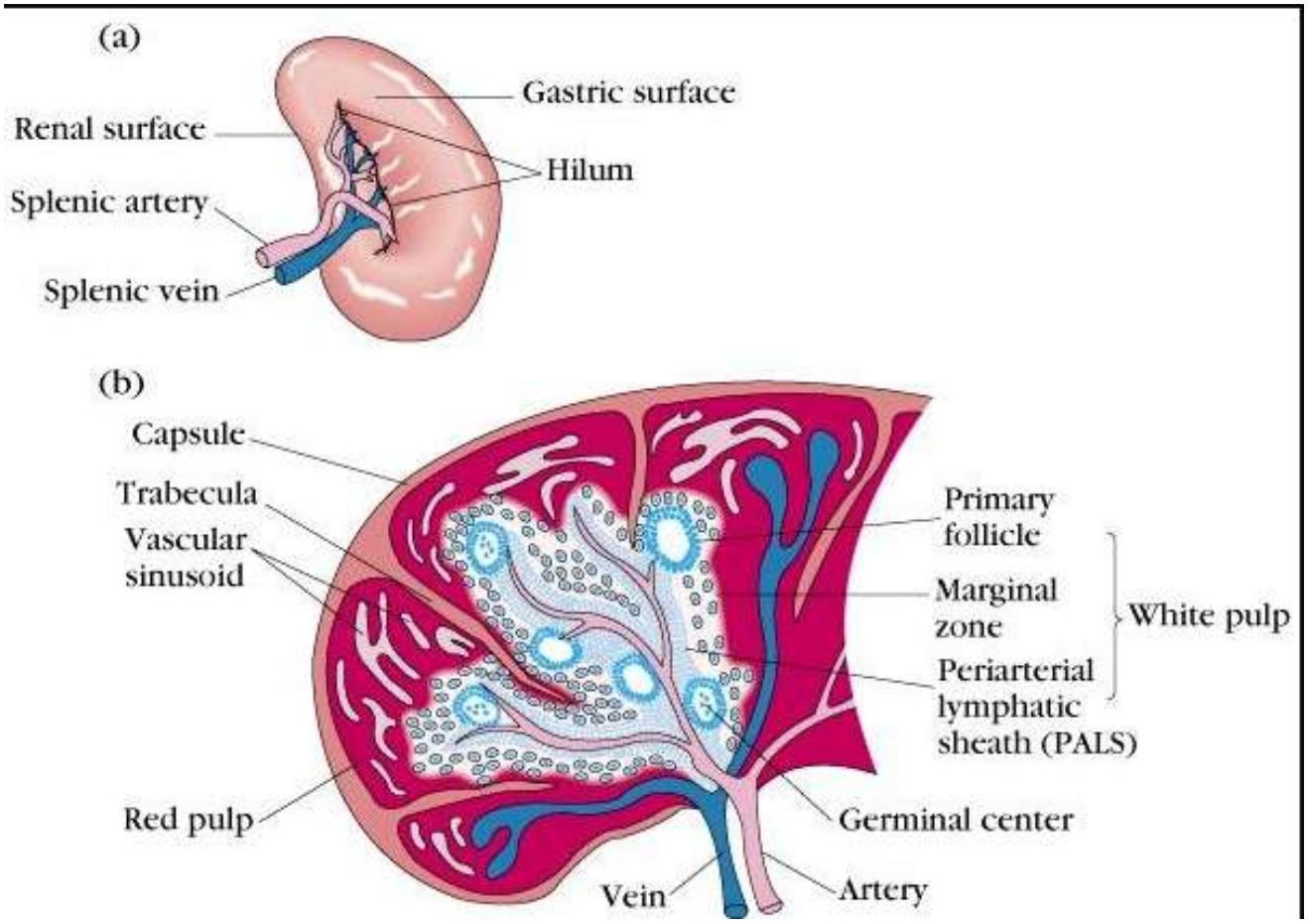


Cross section of spleen



SPLEEN

- Not supplied by lymphatic vessels (unlike lymph node)
  - But bld-borne Ag & lymphocytes carried to spleen - splenic artery
- Narrow central arterioles (derived from splenic artery after multiple branchings) are surrounded by lymphoid tissue called as peri-arteriolar lymphatic sheath (PALS)
- PALS contains numerous T cells
- Marginal zone – closely asso with PALS
  - An area rich in B cells that contain lymphoid follicles which can develop into secondary follicles containing germinal centre
- Red pulp is filled with erythrocytes


(a)
Gastric surface
Renal surface
Hilum
Splenic artery
Splenic vein
(b)
Capsule
Trabecula
Vascular sinusoid
Primary follicle
Marginal zone
White pulp
Periarterial lymphatic sheath (PALS)
Red pulp
Germinal center
Vein
Artery

SPLEEN

- In the white – pulp, T lymphocytes are found in the lymphatic sheath immediately surrounding the arteriole

- B lymphocytes are primarily found in
  - Perifolicular area
  - Germinal center &
  - Mantle layer –
    - which lie more peripherally relative to the arterioles

Functions of the spleen

- Filtering or clearing of
  - Infectious organism
  - Aged or defectively formed elements (spherocytes / ovalocytes)
  - Particulate matter from peripheral blood
- Traps blood borne antigen & microbes
- Plays major role in mounting immune responses to antigens present in blood stream
- Major filtering function →performed by macrophages lining up the splenic cords – trap the circulating Ag & processes them & sends them to white pulp
- Initiate immune response by interacting with T & B cells

EFFECT OF SPLENECTOMY ON IMMUNE RESPONSE

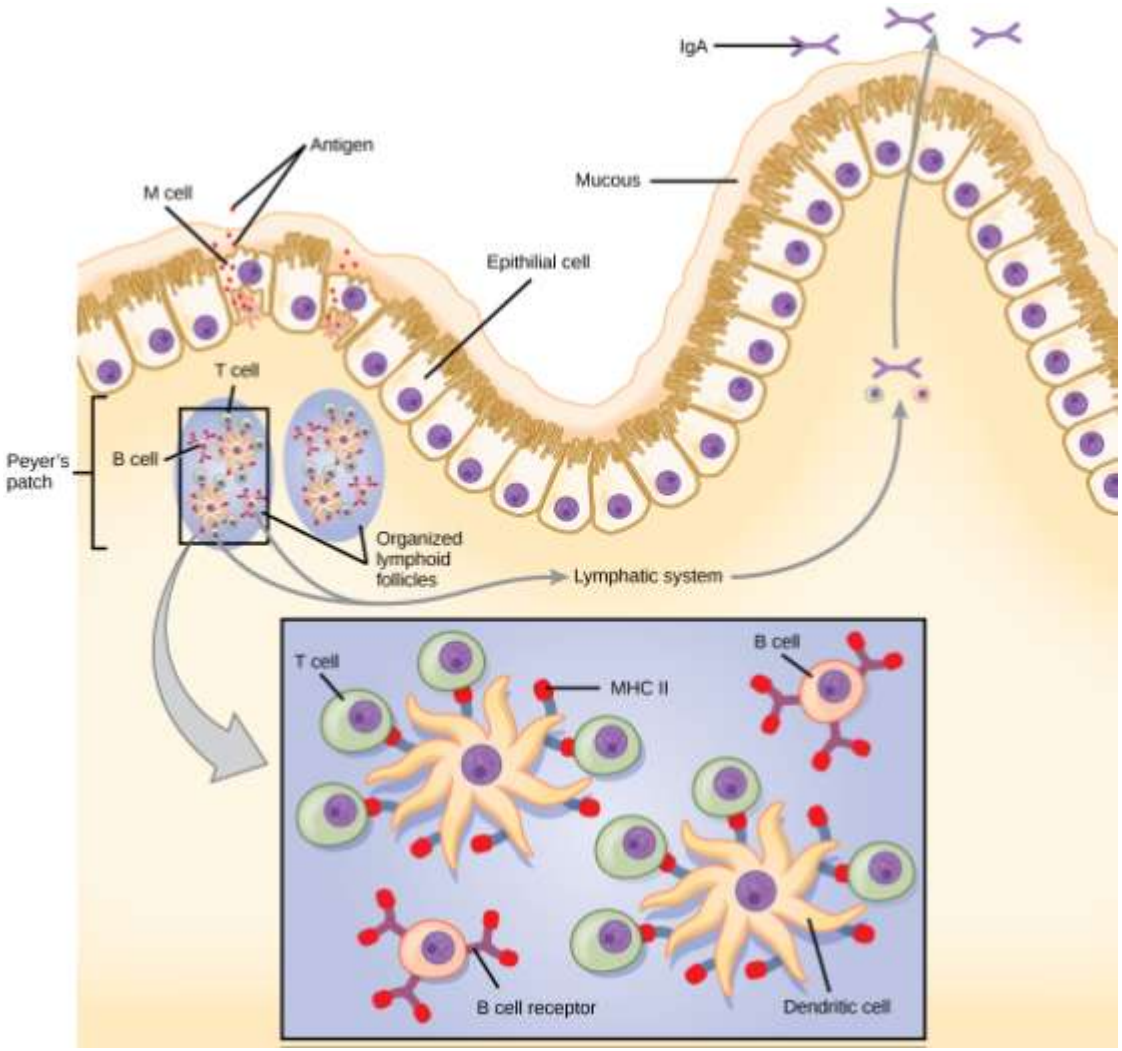
- Depends on the age at which the spleen is removed
- In children
  - Leads to an increased incidence of bacterial sepsis caused by
    - Pneumococci
    - Meningococci
    - H. Influenzae
- In adults - have lesser adverse effects
  - Makes the host most susceptible to blood borne bacterial infections

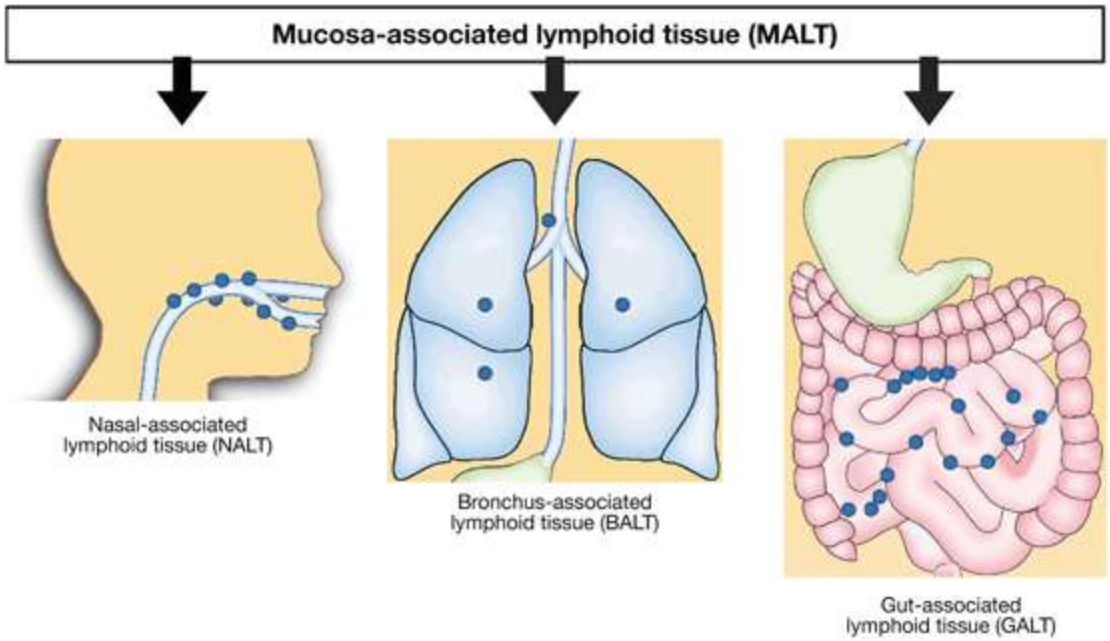
MUCOSA ASSOCIATED LYMPHOID TISSUE - MALT

- Consists of lymphoid tissues of the
  - Intestinal tract
  - Genitourinary tract
  - Tracheobronchial tree
  - Mammary glands
- Un-encapsulated organs
- Contain both T & B lymphocytes (B predominating)
- Structurally these tissues include clusters of lymphoid cells in the lamina propria of Intestinal Villi, Tonsils, Appendix, & Peyer's Patches.

MUCOSA ASSOCIATED LYMPHOID TISSUE (MALT)

Intestinal lining





MALT is found in different regions:

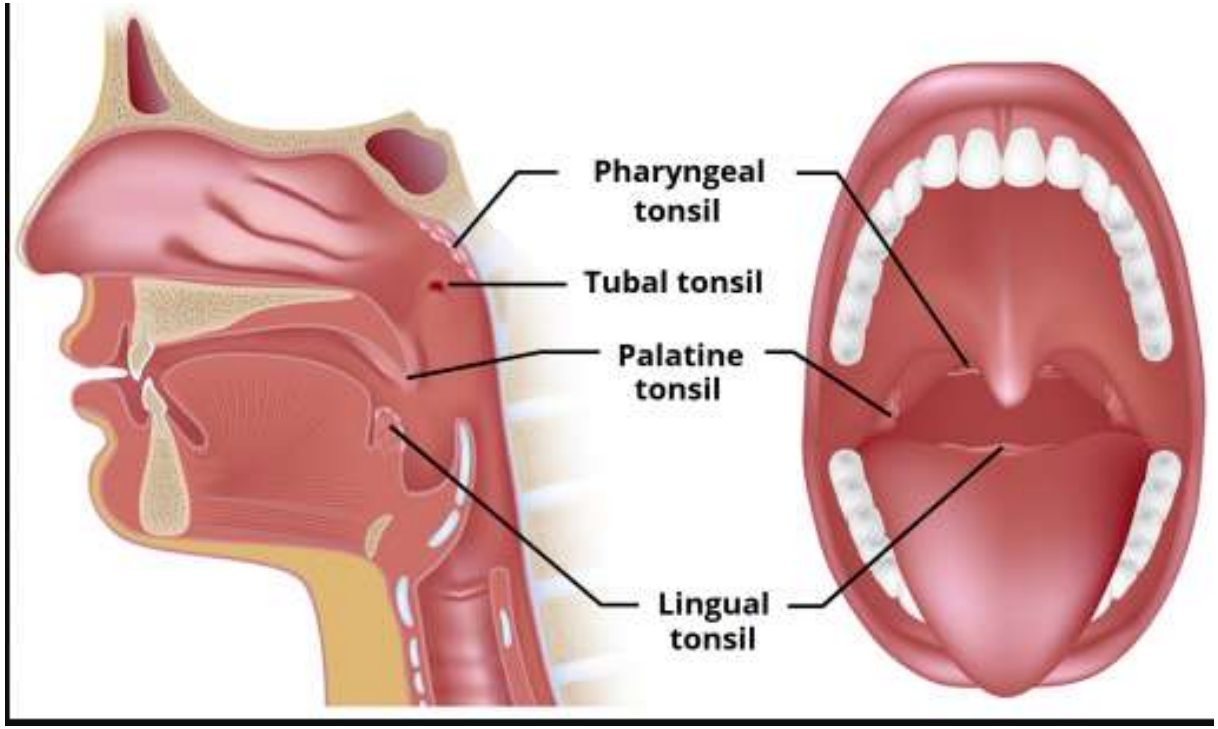
1. Nasal associated lymphoid tissue – **NALT**
2. Bronchus associated lymphoid tissue – **BALT**
3. Gut associated lymphoid tissue – **GALT**

Tonsils

- Found in 3 locations –
  - lingual,
  - palatine, &
  - pharyngeal (adenoids)

- Nodular structures consisting of meshwork of reticular cells & fibers interspersed with lymphocytes, macrophages, granulocytes and mast cells.

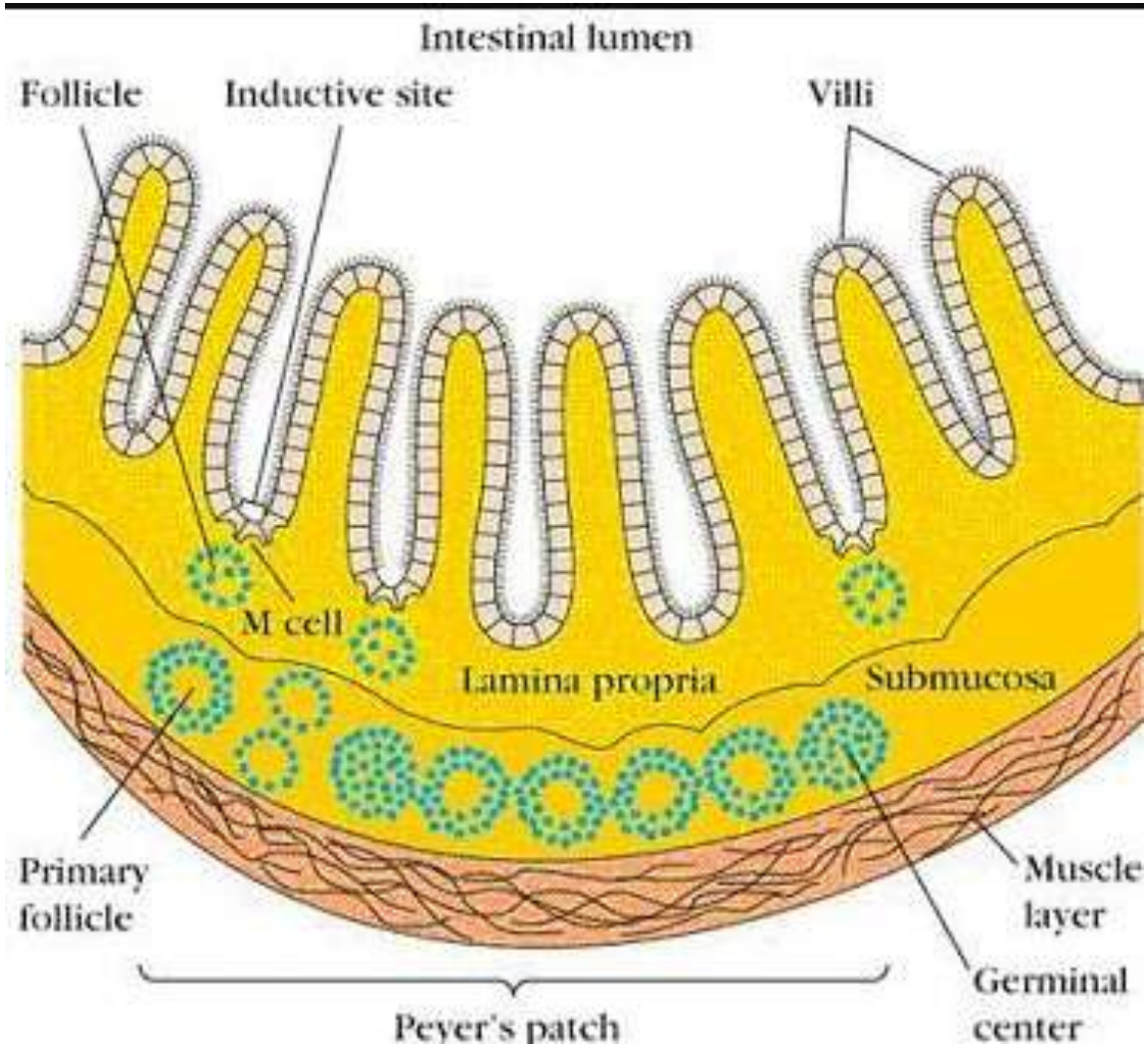
THREE TYPES OF TONSIL



Tonsils

- Predominantly B lymphocytes – organized into follicles & germinal centres – surrounded by regions showing T cell activity
- Defends against antigens entering through nasal & oral epithelial routes
- Site of intense antigenic stimulation,
  - shown by presence of numerous secondary follicles with germinal centres in the tonsillar crypts

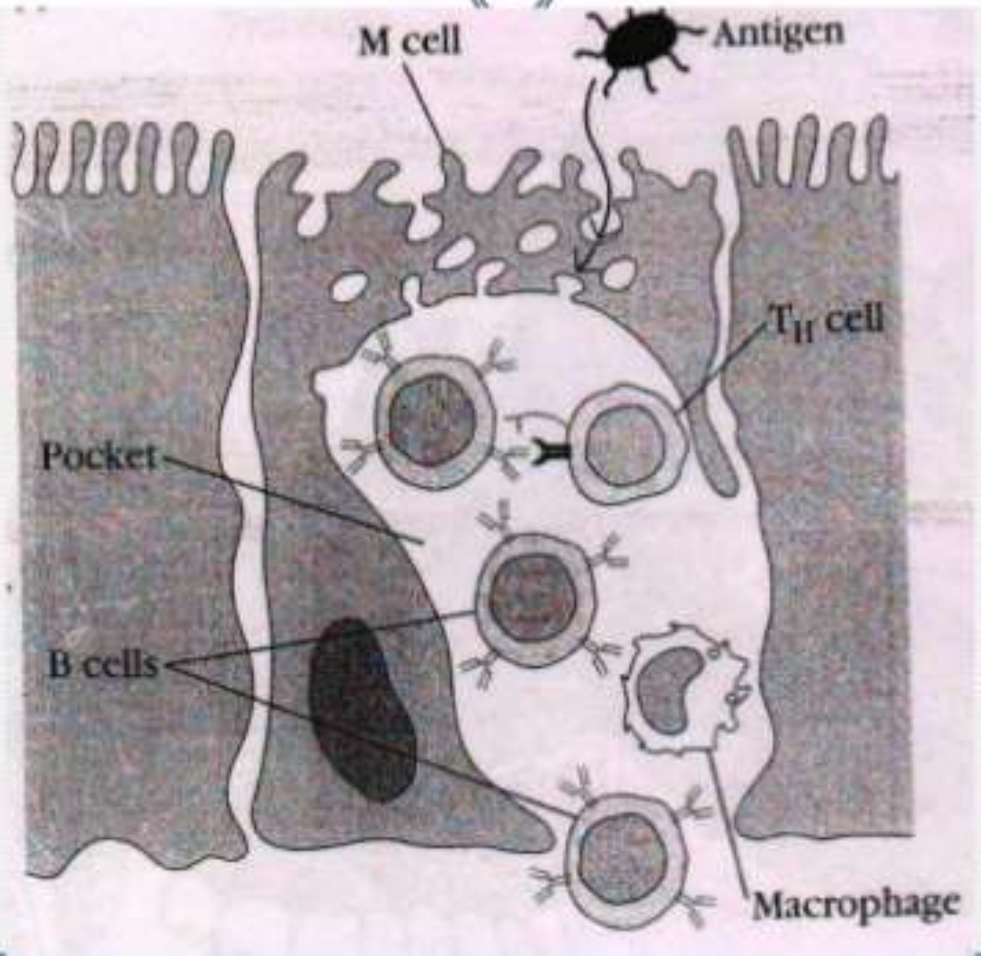
PEYER'S PATCHES



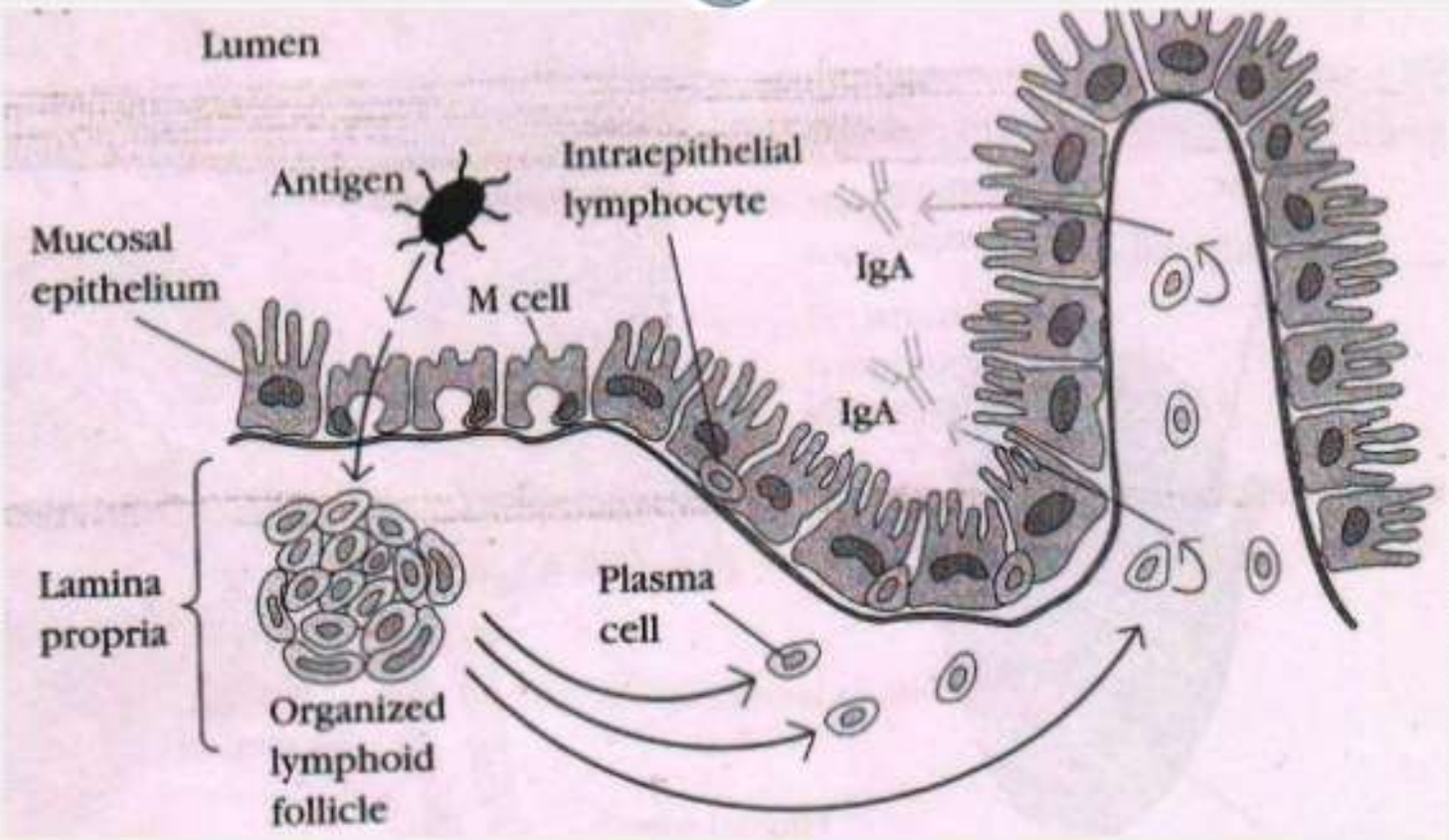
PEYER'S PATCHES

- Lymphoid structures found within the submucosal layer of the intestinal lining
- Follicles are extremely rich in B cells → differentiates into IgA – producing plasma cells.
- M cells:- specialised epithelial cells found abundantly in dome epithelia of Peyer's patches (mainly ileum).
  - Takeup small particles, viruses, bacteria & deliver to submucosal macrophages → these macrophages process the engulfed material & presents them to the T & B cells.

STRUCTURE OF 'M' CELLS



PRODUCTION OF IgA



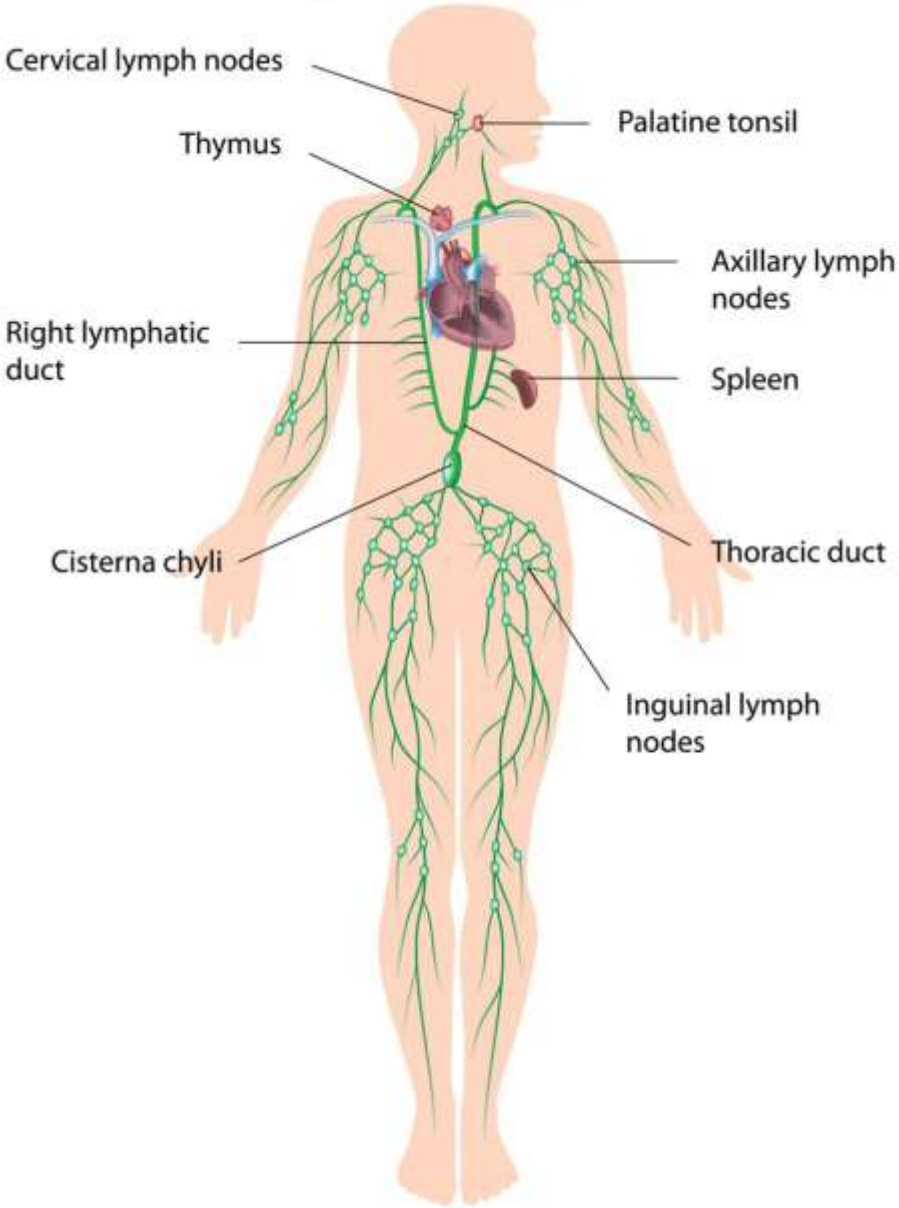
ROLE OF MALT

- Important role in defense system of human host
  - Demonstrated by large population of antibody-producing plasma cells in MALT (number far exceeds that of plasma cells in the spleen, lymph node, & bone marrow, when combined together)
- Facilitates interaction among circulating leucocytes – in addition to spleen and lymphnodes

LYMPHATIC CIRCULATORY SYSTEM

- Leukocytes & their products use 2 circulatory system
  - Cardiovascular system
  - Lymphatic circulatory system (LCS)
- LCS - An extensive capillary network which collects lymph
- Lymph = a clear watery fluid containing leucocytes & cellular debris, from various organs & tissues.

The Lymphatic System



LYMPHATIC CIRCULATORY SYSTEM

- Cleared lymph from
  - Below the diaphragm & the upper left half of the body → drains via efferent lymphatics into the thoracic duct → subsequent drainage into the left innominate vein
  - Right side above the diaphragm → drains into the right lymphatic duct → subsequent drainage into the origin of right innominate vein
- Same routes are followed by the lymphocytes stimulated and produced in the lymph nodes, or peripheral lymphoid tissues, which eventually reach the systemic circulation.

LYMPHATIC CIRCULATORY SYSTEM

- Peripheral blood is filtered by the spleen & liver
- Macrophage derived phagocytes are present in
  - Spleen - as organized lymphoid areas
  - Liver – as kupffer cells,
- Organisms & antigens that enter directly into the systemic circulation are trapped in these two organs – spleen plays the most impt role as a lymphoid organ

PRIMARY LYMPHOID ORGANS VERSUS SECONDARY LYMPHOID ORGANS

PRIMARY LYMPHOID ORGANS	SECONDARY LYMPHOID ORGANS
Organs of the immune system where lymphocytes are formed and mature	Organs of the immune system which maintain mature naive lymphocytes and initiate an adaptive immune response
Allow lymphoid stem cells to proliferate, differentiate, and mature	Allow lymphoid cells to become functional
Contain either T cells or B cells	Contain both T cells and B cells
Have no contact with antigens	Have contact with antigens
Undergo atrophy with age	Increase size with age