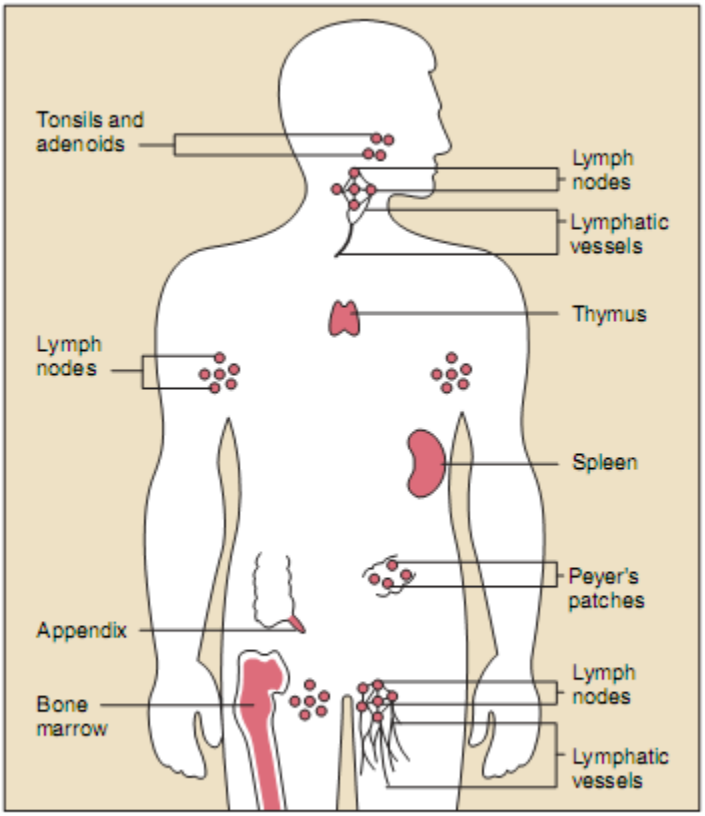
Lec.5:The Structure of the Immune System

The organs of the immune system are positioned throughout the body. They are called lymphoid organs because they are home to lymphocytes.



The organs of the immune system are positioned throughout the body.

The lymphoid tissues can be divided into primary and secondary lymphoid organs.

Primary lymphoid tissues

Primary lymphoid tissues are sites where lymphocytes develop from progenitor cells into functional and mature lymphocytes. The major primary lymphoid tissue is the marrow, the site where all lymphocyte progenitor cells reside and initially differentiate. The other primary lymphoid tissue is the thymus, the site where progenitor cells from the marrow differentiate into mature thymus-derived (T) cells.

Bone marrow

Bone marrow, the soft tissue in the hollow center of bones, is the ultimate source of all blood cells, including lymphocytes. B lymphocytes, also known as B cells, become activated and mature into plasma cells, which make and release antibodies.

Anatomical organization:

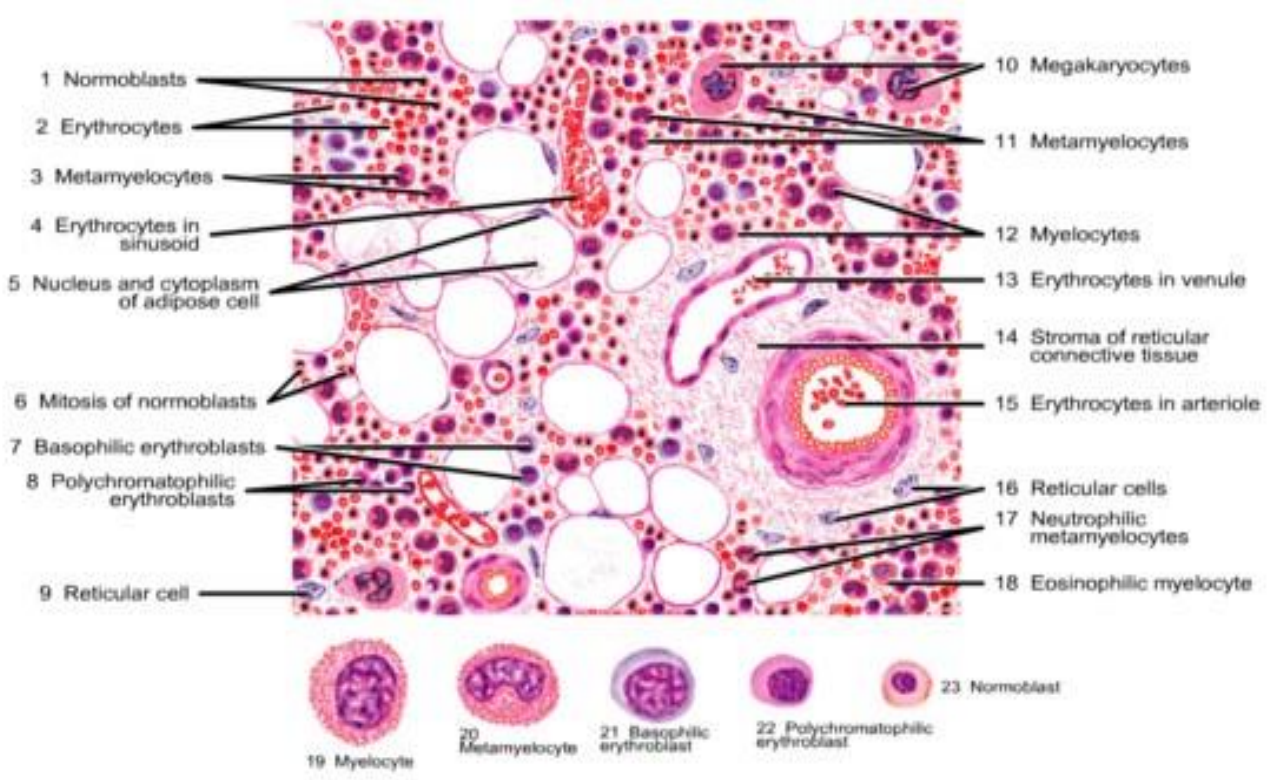
The two types of bone marrow are "red marrow", which consists mainly of hematopoietic tissue, and "yellow marrow", which is mainly made up of fat cells. Red blood cells, platelets, and most white blood cells arise in red marrow. Both types of bone marrow contain numerous blood vessels and capillaries. At birth, all bone marrow is red. With age, more and more of it is converted to the yellow type; only around half of adult bone marrow is red. Red marrow is found mainly in the flat bones, such as the pelvis , sternum, cranium, ribs, vertebrae and scapulae, and in the cancellous ("spongy") material at the epiphyseal ends of long bones such as the femur and humerus. Yellow marrow is found in the medullary cavity, the hollow interior of the middle portion of short bones. In cases of severe blood loss, the body can convert yellow marrow back to red marrow to increase blood cell production.

Physiological role:

1- B cell development : B cell development occurs through several stages, each stage representing a change in the genome content at the antibody loci.

When the B cell fails in any step of the maturation process, it will die by a mechanism called apoptosis, or specifically, clonal deletion. B cells are continuously produced in the bone marrow. When the B cell receptor, on the surface of the cell matches the detected antigens present in the body, the B cell proliferates and secretes a free form of those receptors (antibodies) with identical binding sites as the ones on the original cell surface.
Like their fellow lymphocytes, the T cells, immature B cells are tested for auto-reactivity by the immune system before leaving the bone marrow. In the bone marrow (the central lymphoid organ), central tolerance is produced. The immature B cells whose B-cell receptors (BCRs) bind too strongly to self antigens will not be allowed to mature. If B cells are found to be highly reactive to self, three mechanisms can occur.

2- production and development of hematopoietic cells



Thymus Gland

The thymus is a lymphoid organ that lies behind the breastbone. Lymphocytes known as T lymphocytes or T cells ("T" stands for "thymus") mature in the thymus and then migrate to other tissues.

The thymus is the only clearly individualized primary lymphoid organ in mammals. It is believed to play a key role in determining the differentiation of T lymphocytes.

Anatomical organization: The thymus is located in the superior mediastinum, anterior to the great vessels. It has a connective tissue capsule from which emerge the trabeculae, which divide the organ into lobules. Each lobule has a cortex and medulla, and the trabeculae are coated with epithelial cells.

a. Cortex. Lymphocyte aggregates, composed mainly of immunologically immature T lymphocytes, are located in the cortex, an area of intense cell proliferation. A small number of macrophages and plasma cells are also present. In addition, the cortex contains two subpopulations of epithelial cells, the epithelial nurse cells and the cortical epithelial cells which form a network within the cortex.

b. Medulla. Not as densely populated as the cortex, the medulla contains predominantly mature T lymphocytes, and has a larger epithelial cell-to-lymphocyte ratio than the cortex. Macrophage and dendritic cells (DC) found almost in the medulla. Unique to the medulla are concentric rings of squamous epithelial cells known as Hassall's corpuscles.

Physiological role:

a. T-lymphocyte differentiation. The thymus is believed to be the organ where T lymphocytes differentiate during embryonic life. The thymic cortex is an area of intense cell proliferation and death (only 5% of the cells generated in the thymus eventually mature and migrate to the peripheral tissues). The mechanism whereby the thymus determines T-lymphocyte differentiation is believed to involve the interaction of T-lymphocyte precursors with thymus epithelial cells. These interactions result in the elimination or inactivation of self-reactive T-cell clones and in the differentiation of two separate lymphocyte subpopulations with different membrane antigens and different functions. Most T-lymphocyte precursors appear to reach full maturity in the medulla.

T-cell precursors, which still retain the ability to give rise to multiple hematopoietic cell types, travel via the blood from the bone marrow to the thymus. Immature T cells, known as **thymocytes (thymus cells)** because of their site of maturation, pass through defined developmental stages in specific thymic microenvironments as they mature into functional T cells. The thymus is a specialized environment where immature T cells generate unique antigen receptors **(T cell receptors, or TCRs)** and are then selected on the basis of their reactivity to self MHC-peptide complexes expressed on the surface of thymic stromal cells. Those thymocytes whose T-cell receptors bind self MHC-peptide complexes with too high affinity are induced to die **(negative selection),** and those thymocytes that

bind self MHC-peptides with an intermediate affinity undergo **positive selection**, resulting in their survival, maturation, and migration to the thymic medulla.

Most thymocytes do not navigate the journey through the thymus successfully; in fact, it is estimated that 95% of thymocytes die in transit. The majority of cells die because they have too low an affinity for the self-antigen- MHC combinations that they encounter on the surface of thymic epithelial cells and fail to undergo positive selection.

These developmental events take place in several distinct thymic microenvironments . T-cell precursors enter the thymus in blood vessels at the corticomedullary junction between the thymic cortex, the outer portion of the organ, and the thymic medulla, the inner portion of the organ. At this stage thymocytes express neither CD4 nor CD8, markers associated with mature T cells. They are therefore called double negative (DN) cells.

DN cells first travel to the region under the thymic capsule, a region referred to as the subcapsular cortex, where they proliferate and begin to generate their T-cell receptors. Thymocytes that successfully express TCRs begin to express both CD4 and CD8, becoming double positive (DP) cells, and populate the cortex, the site where most (85% or more) immature T cells are found. The cortex features a distinct set of stromal cells, cortical thymic epithelial cells (cTECs), whose long processes are perused by thymocytes testing the ability of their T-cell receptors to bind MHC-peptide complexes. Thymocytes that survive selection move to the thymic medulla, where positively selected thymocytes encounter specialized stromal cells, medullary thymic epithelial cells (mTECs). Not only do mTECs support the fi nal steps of thymocyte maturation, but they also have a unique ability to express proteins that are otherwise found exclusively in other organs. This allows them to negatively select a group of potentially very damaging, autoreactive T cells that could not be deleted in the cortex.

Mature thymocytes, which express only CD4 or CD8 and are referred to as single positive (SP), leave the thymus as they entered: via the blood vessels of the corticomedullary junction. Maturation is finalized in the periphery, where these new T cells (recent thymic emigrants) explore antigens presented in secondary lymphoid tissue, including spleen and lymph nodes.

b. Hormone synthesis. The thymic epithelial cells are believed to produce hormonal factors (e.g., thymosin and thymopoietin), which may play an important role in the differentiation of T lymphocytes.

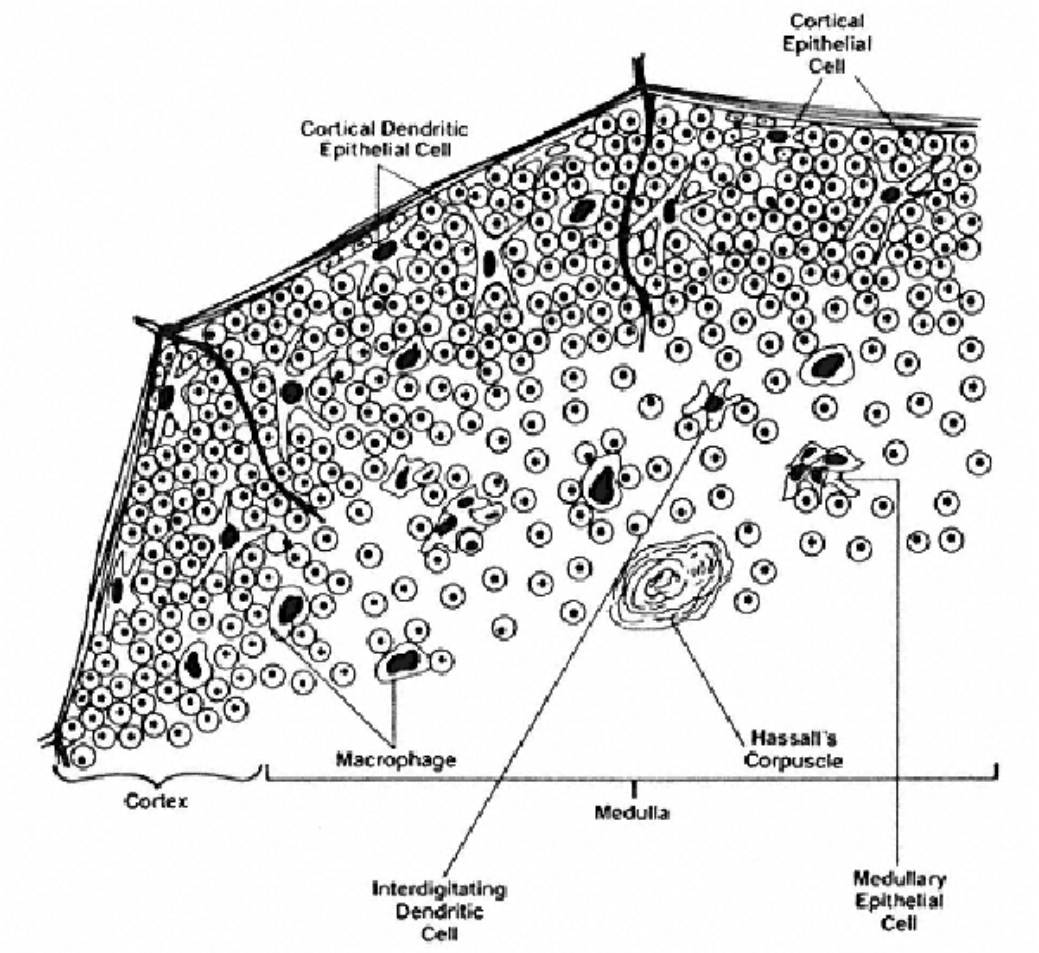
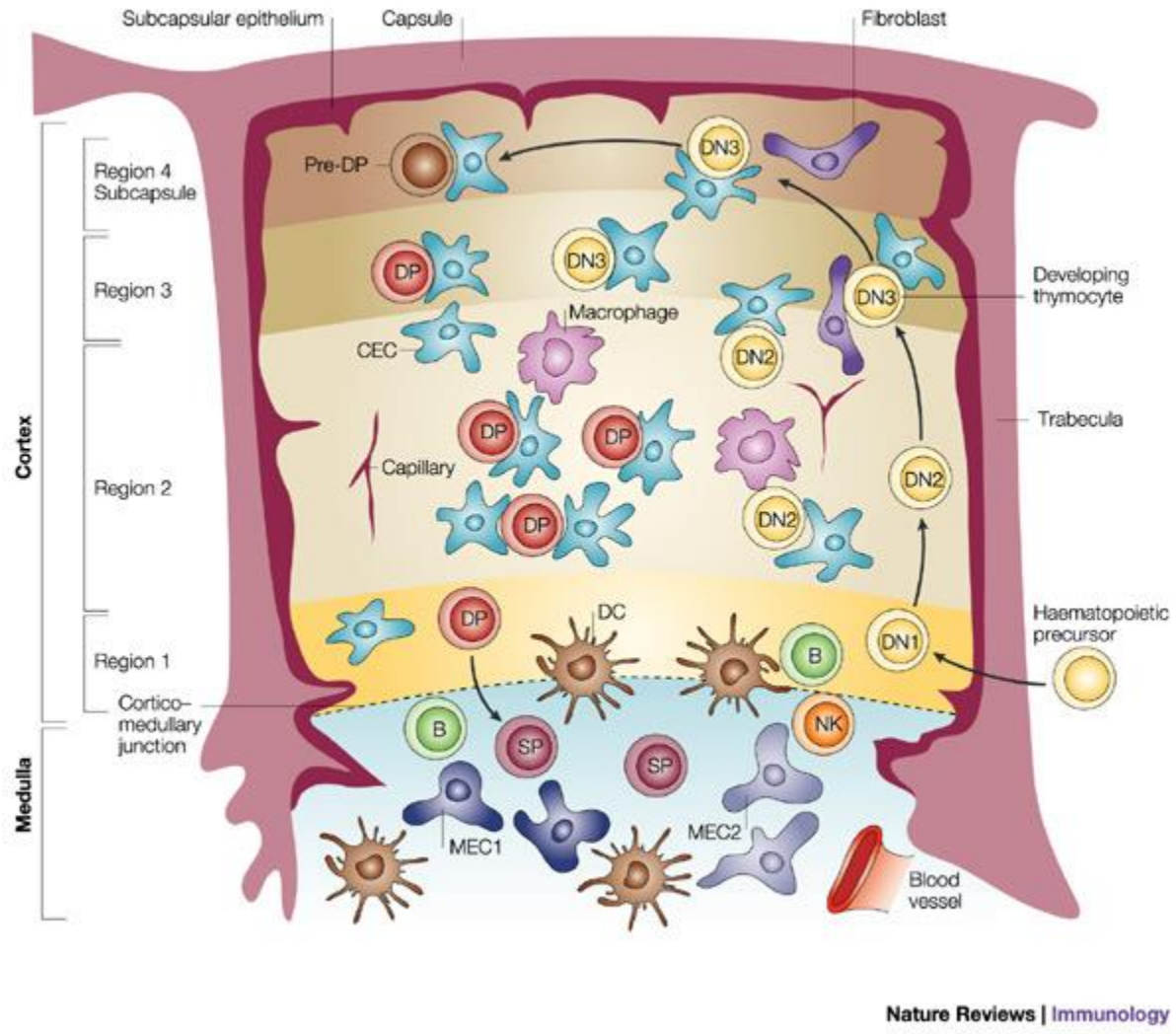


Figure: Diagrammatic representation of the structure of a thymic lobe. The densely packed cortex is mostly populated by T lymphocytes and by some cortical dendritic epithelial cells and cortical epithelial cells. The more sparsely populated medulla contains epithelial and dendritic cells, macrophages, T lymphocytes, and Hassall's corpuscles.



The thymus is broadly divided into two histologically defined regions, the cortex and the medulla, each of which contains several different thymic epithelial cell (TEC) subtypes. In adults, T-cell precursors enter the thymus at the cortico–medullary junction, and then begin a highly ordered differentiation programme, which is linked to migration through the thymic stroma. Different thymocyte subsets are therefore found in spatially restricted regions of the thymus. The thymic cortex has been separated into four regions by Lind and colleagues[8]: region 1, the cortico–medullary junction, is the site of entry into the thymus and contains uncommitted progenitors, $CD4^-CD8^-$ double-negative 1 (DN1) cells; in region 2, cells differentiate to the DN2 stage, undergo a proliferative clonal expansion, and lose B- and natural killer (NK)-cell potential; T-cell lineage commitment and the onset of T-cell receptor (TCR) β-chain rearrangement occurs in DN3 cells in region 3; and the transition from DN to $CD4^+CD8^+$ double-positive (DP) status occurs in region 4. DP cells then migrate back through the cortex and, having differentiated into either $CD4^+$ or $CD8^+$ single-positive (SP) cells, into the medulla. Positive selection occurs mainly in the cortex, and requires cortical TECs, whereas negative selection occurs mainly in the medulla, and is mediated by medullary TECs and thymic dendritic cells (DCs). SP cells that have completed the differentiation programme egress from the medulla to the periphery. CEC, cortical epithelial cell; MEC, medullary epithelial cell.

Secondary lymphoid tissues

Secondary lymphoid tissues are sites where lymphocytes interact with each other and non lymphoid cells to generate immune responses to antigens. These include the spleen, lymph nodes, and mucosa-associated lymphoid tissues (MALT). The structure of these tissues provides insight into how the immune system discriminates between self-antigens and foreign antigens and develops the capacity to orchestrate a variety of specific and nonspecific defenses against invading pathogens.

Lymph Nodes

The lymph nodes are extremely numerous and disseminated all over the body. They measure 1 to 25 mm in diameter and play a very important and dynamic role in the initial or inductive states of the immune response.

Lymph nodes, which are located in many parts of the body, are lymphoid tissues that contain numerous specialized structures.

- T cells from the thymus concentrate in the paracortex.
- B cells develop in and around the germinal centers.
- Plasma cells occur in the medulla.

Anatomical organization:

The lymph nodes are circumscribed by a connective tissue capsule. Afferent lymphatics draining peripheral interstitial spaces enter the capsule of the node and open into the subcapsular sinus. The lymph node also receives blood from the systemic circulation through the hilar arteriole. Two main regions can be distinguished in a lymph node: the cortex and the medulla.

The cortex and the deep cortex (also known as paracortical area) are densely populated by lymphocytes, in constant traffic between the lymphatic and systemic circulation. In the cortex, at low magnification, one can distinguish roughly spherical areas containing densely packed lymphocytes, termed follicles or nodules

T and B lymphocytes occupy different areas in the cortex. B lymphocytes predominate in the follicles (hence, the follicles are designated as T-independent areas), which also contain macrophages, dendritic cells, and some T lymphocytes. The follicles can assume two different morphologies:

i. The primary follicles are very densely packed with small lymphocytes in lymph nodes not actively involved in an immune response.

ii. In a lymph node draining in an area in which an infection has taken place, one will find larger, less dense follicles, termed secondary follicles, containing clear germinal centers where B lymphocytes are actively dividing as a result of antigenic stimulation.

In the deep cortex or paracortical area, which is not as densely populated as the follicles, T lymphocytes are the predominant cell population and, for this reason, the paracortical area is designated as T-dependent. Interdigitating cells are also present in this area, where they present antigen to T lymphocytes.

The medulla, less densely populated, is organized into medullary cords draining into the hilar efferent lymphatic vessels. Plasma cells can be identified in the medullary cords.

Physiological role: The lymph nodes can be compared to a network of filtration and communication stations where antigens are trapped and messages are interchanged between the different cells involved in the immune response.

The dual circulation in the lymph nodes. Lymph nodes receive both lymph and arterial blood flow. The afferent lymph, with its cellular elements, percolates from the subcapsular sinus to the efferent lymphatics via cortical and medullary sinuses, and the cellular elements of the lymph have ample opportunity to migrate into the lymphocyte-rich cortical structures during their transit through the nodes. The artery that penetrates through the hilus brings peripheral blood lymphocytes into the lymph node; these lymphocytes can leave the vascular bed at the level of the high endothelial venules located in the paracortical area.

Lymph nodes as the anatomical fulcrum of the immune response.

Soluble or particulate antigens reach the lymph nodes primarily through the lymphatic circulation. Once in the lymph nodes, antigen is concentrated on a network formed by the dendritic cells, designated as antigen-retaining reticulum. The antigen is retained by these cells in its unprocessed form, often associated with antibody (particularly during secondary immune responses), and is efficiently presented to B lymphocytes. The B lymphocytes recognize specific epitopes, but are also able to internalize and process the antigen, presenting antigen-derived peptides associated to MHC-II molecules to helper T lymphocytes, whose "help" is essential for the proper activation and differentiation of the B cells presenting the antigen .

Antigens can also reach the lymph nodes in association with trafficking cells, particularly the Langerhans cells of the dermis. Those cells express MHC-II molecules, and therefore can function as APC. From the dermis they migrate to the paracortical areas, where they assume the morphology of interdigitating cells and interact with the T lymphocytes that abound in that region. The close contact between the interdigitating cells presenting antigen-derived peptides on their MHC-II molecules and helper T lymphocytes able to specifically recognize those MHC-associated peptides is essential for proper initiation of the immune response .

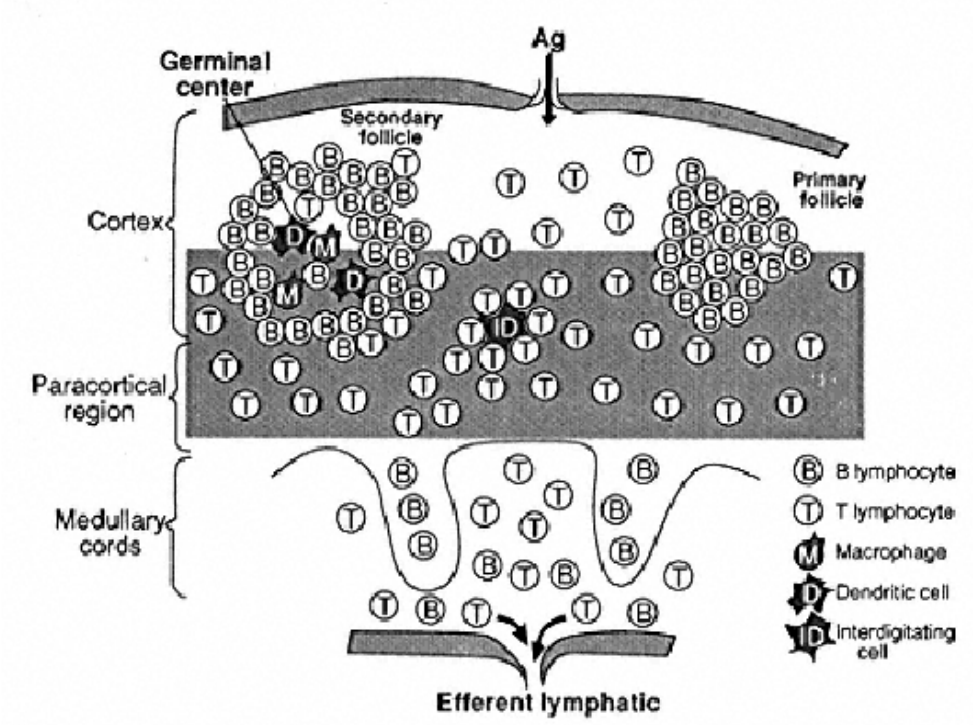
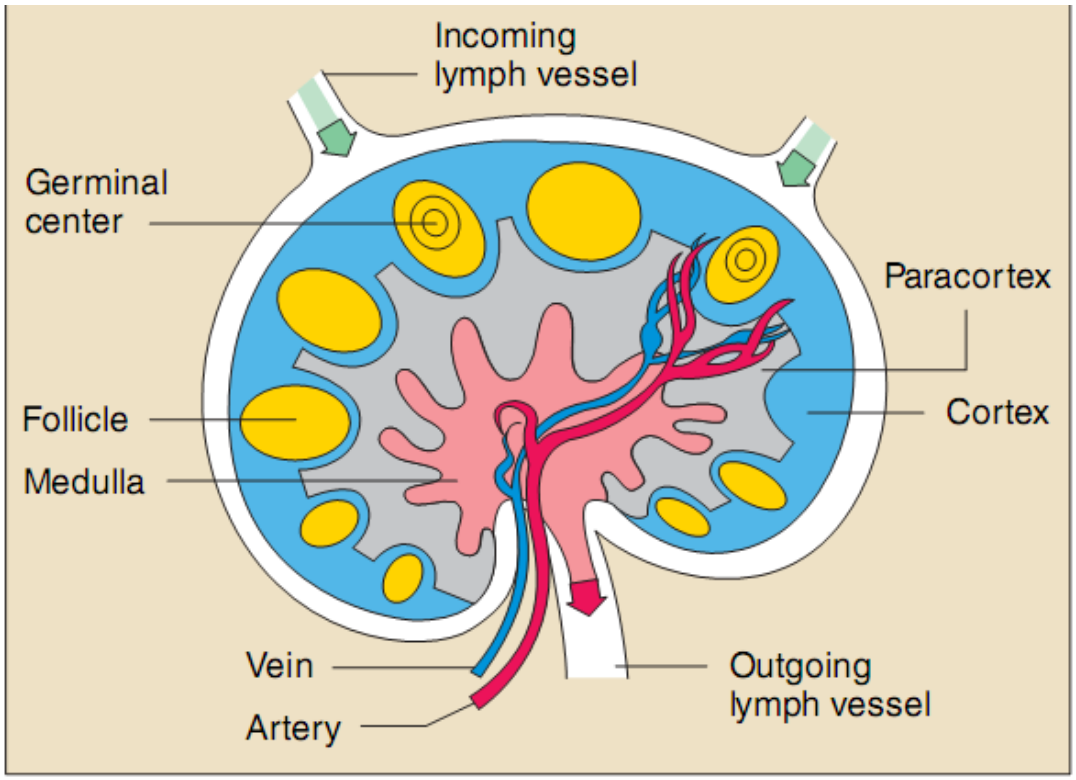
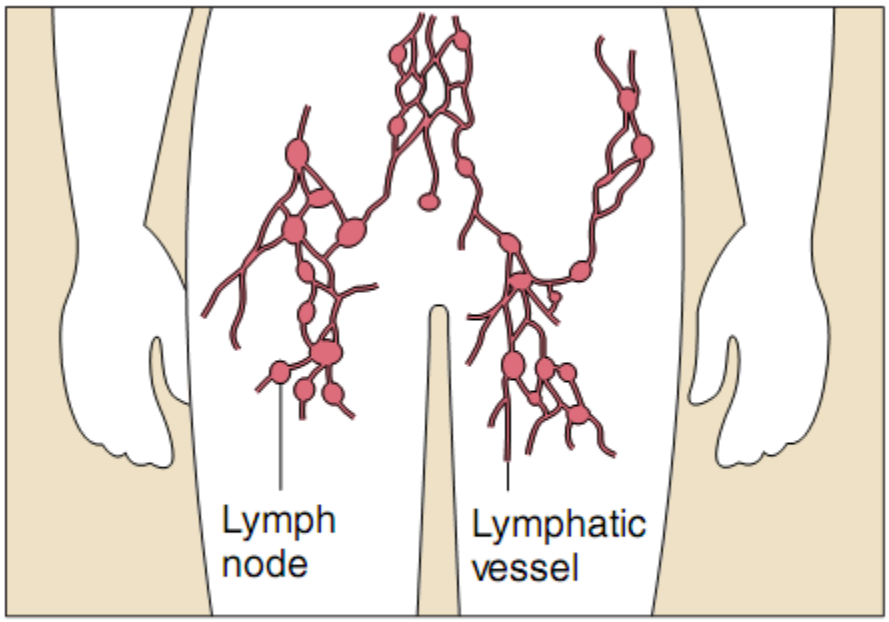


Figure:Diagrammatic representation of the lymph node structure. B lymphocytes are predominantly located on the lymphoid follicles and medullary cords (B-dependent areas), while T lymphocytes are mostly found in the paracortical area (T-dependent area).



The lymph node contains numerous specialized structures. T cells concentrate in the paracortex, B cells in and around the germinal centers, and plasma cells in the medulla.



Immune cells and foreign particles enter the lymph nodes via incoming lymphatic vessels or the lymph nodes' tiny blood vessels.

Spleen

The spleen is a flattened organ at the upper left of the abdomen.

Anatomical organization: Surrounded by a connective tissue capsule, the parenchyma of this organ is heterogeneous, constituted by the white and the red pulp.

a. White pulp: The spleen receives blood from the splenic artery. The narrow central arterioles, derived fromthe splenic artery after multiple branchings, are surrounded by lymphoid tissue (periarteriolar lymphatic sheath). In the white pulp, T lymphocytes are in close proximity to the arteriole, whereas B lymphocytes areconcentrated in follicles, which lie more peripherally relative to the arterioles , and which may or may not show germinal centers depending on the state of activation of the resident cells.

b. The red pulp surrounds the white pulp. Blood leaving the white pulp through the central arterioles flows into the penicillar arteries and from there flows directly into the venous sinuses. The red pulp is formed by these venous sinuses which are bordered by the splenic cords (cords of Billroth) and venous sinuses, where

macrophages abound. From the sinuses, blood reenters the systemic circulation through the splenic vein.

c. Between the white and the red pulp lies an area known as the marginal zone, more sparsely cellular than the white pulp, but very rich in macrophages and B lymphocytes.

Physiological role: The spleen is the lymphoid organ associated with filtering or clearing of particulate matter, infectious organisms, and aged or defectively formed elements (e.g., spherocytes, ovalocytes) from the peripheral blood. The main filtering function is performed by the macrophages lining up the splenic cords. In the marginal zone, circulating antigens are trapped by the macrophages which will then be able to process the antigen, migrate deeper into the white pulp, and initiate the immune response by interacting with T and B lymphocytes.

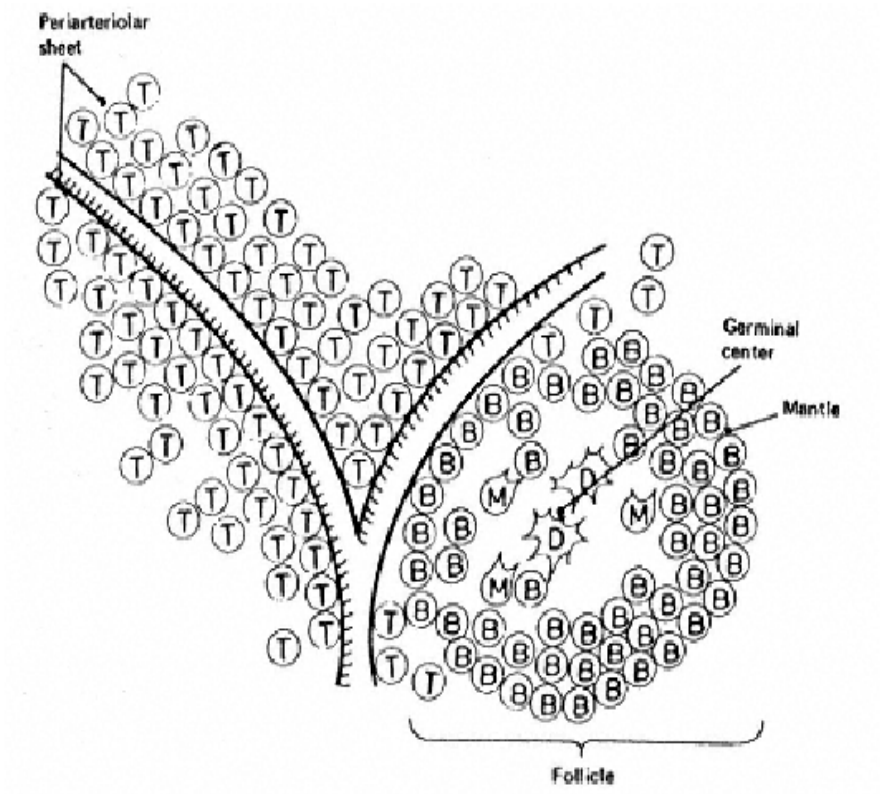


Figure :Diagrammatic representation of the topography of the splenic lymphoid tissue. The lymphocytic periarteriolar sheet is a T-dependent area, while the B lymphocytes are localized on lymphoid follicles (B-dependent areas).

Mucosa-Associated Lymphoid Tissues (MALT)

MALT encompass the lymphoid tissues of the intestinal tract, genitourinary tract, tracheobronchial tree, and mammary glands. All of the mucosa-associated lymphoid tissues are unencapsulated and contain both T and B lymphocytes, the latter predominating.

Gut-Associated Lymphoid Tissue

Gut-Associated Lymphoid Tissue is the designation proposed for all lymphatic tissues found along the digestive tract. Three major areas of GALT that can be identified are the tonsils, the Peyer's patches, located on the submucosa of the small intestine, and the appendix. In addition, scanty lymphoid tissue is present in the lamina propria of the gastrointestinal tract.

1. Tonsils, located in the oropharynx, are predominantly populated by B lymphocytes and are the site of intense antigenic stimulation, as reflected by the presence of numerous secondary follicles with germinal centers in the tonsilar crypts .

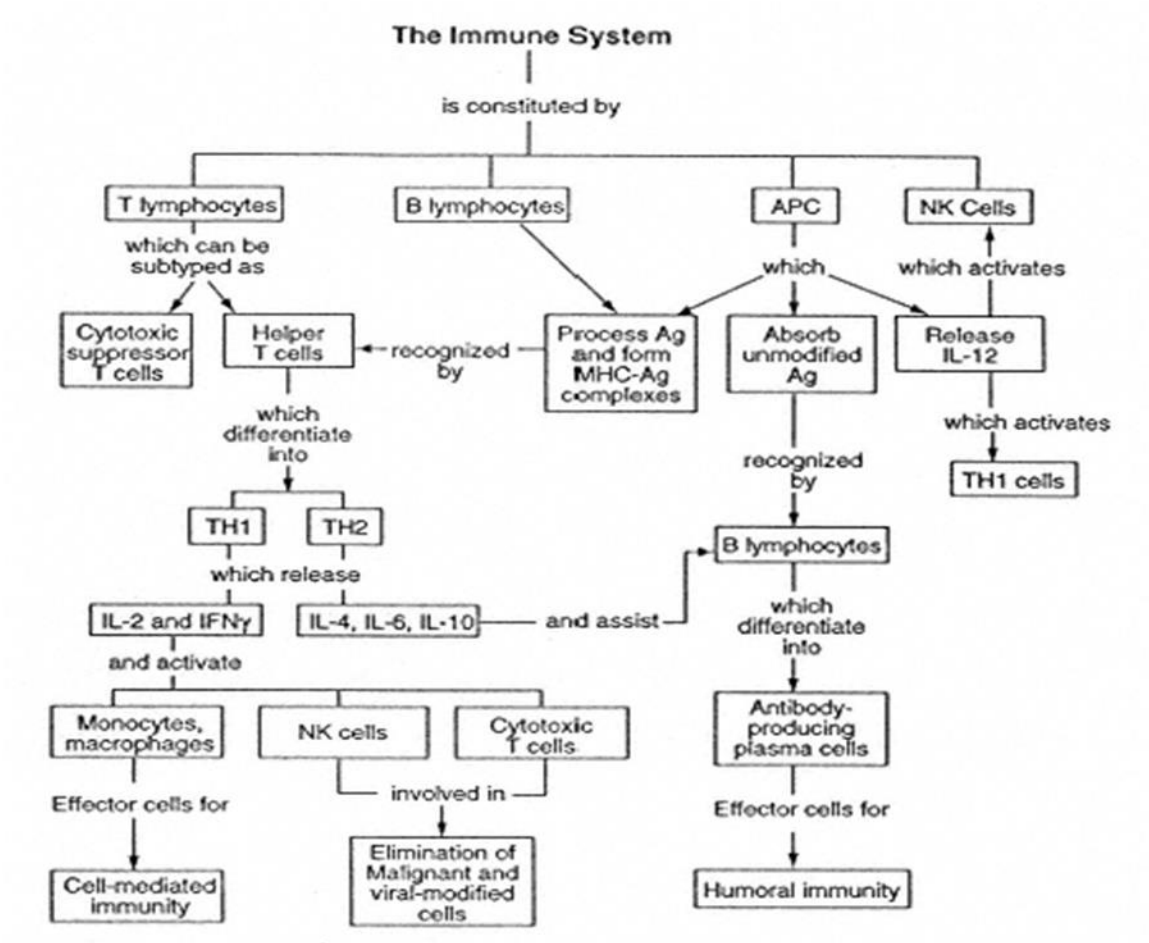
2. Peyer's patches are lymphoid structures disseminated through the submucosal space of the small intestine.

- The follicles of the intestinal Peyer's patches are extremely rich in B cells, which differentiate into IgA-producing plasma cells.
- Specialized epithelial cells, known as M cells abound in the dome epithelia of Peyer's patches, particularly at the ileum. These cells take up small particles, virus, bacteria, etc., and deliver them to submucosal macrophages, where the engulfed material will be processed and presented to T and B lymphocytes.
- T lymphocytes are also present in the intestinal mucosa, the most abundant of them expressing membrane markers that are considered typical of memory helper T cells. This population appears to be critically involved in the induction of humoral immune responses.
- A special subset of T cells, with a different type of T-cell receptor (g/d T lymphocytes) is well represented on the small intestine mucosa.

These lymphocytes appear to recognize and destroy infected epithelial cells by a non immunological mechanism (i.e., not involving the T-cell receptors).

Table 2.1 Distribution of T and B Lymphocytes in Humans

	Lymphocyte distribution (%)[a]	
Immune tissue	T lymphocyte	B lymphocyte
Peripheral blood	80	10[b]
Thoracic duct	90	10
Lymph node	75	25
Spleen	50	50
Thymus	100	<5
Bone marrow	<25	>75
Peyer's patch	10–20	70


The Immune System
is constituted by
T lymphocytes
B lymphocytes
APC
NK Cells
which can be subtyped as
which
which activates
Cytotoxic suppressor T cells
Helper T cells
recognized by
Process Ag and form MHC-Ag complexes
Absorb unmodified Ag
Release IL-12
which differentiate into
which activates
recognized by
TH1 cells
TH1
TH2
B lymphocytes
which release
IL-2 and IFNγ
IL-4, IL-6, IL-10
and assist
which differentiate into
and activate
Monocytes, macrophages
NK cells
Cytotoxic T cells
Antibody-producing plasma cells
Effector cells for
involved in
Effector cells for
Elimination of Malignant and viral-modified cells
Cell-mediated immunity
Humoral immunity