IMMUNE SYSTEM:

The immune system protects the organism against invading pathogens or antigens (bacteria, parasites, and viruses). The immune response occurs as soon as the pathogens enter the organism. The lymphoid system includes all cells, tissues, and organs that contain aggregates (accumulations) of immune cells called lymphocytes. Cells of the immune system, especially lymphocytes, are distributed throughout the body as single cells; as isolated accumulations of cells; as distinct nonencapsulated lymphatic nodules in the loose connective tissue of the digestive, respiratory, and reproductive systems; or as encapsulated individual lymphoid organs.

Lymphoid organs can be divided into two major categories:
The primary lymphoid organs include the bone marrow and the thymus. In these organs, the cells of immune system, the lymphocytes, are formed, differentiate, and become mature.
The secondary lymphoid organs include the lymph nodes, spleen, tonsils, and the mucosa-associated lymphoid tissue (MALT) such as the diffuse lymphoid tissue in the mucosa of the digestive tract (gut-associated lymphoid tissue [GALT]), respiratory tract (bronchial-associated lymphoid tissue [BALT]), and Peyer patches. In the secondary lymphoid organs, most of the lymphocytes encounter foreign antigens, become activated, and produce an immune response to the invading pathogens.

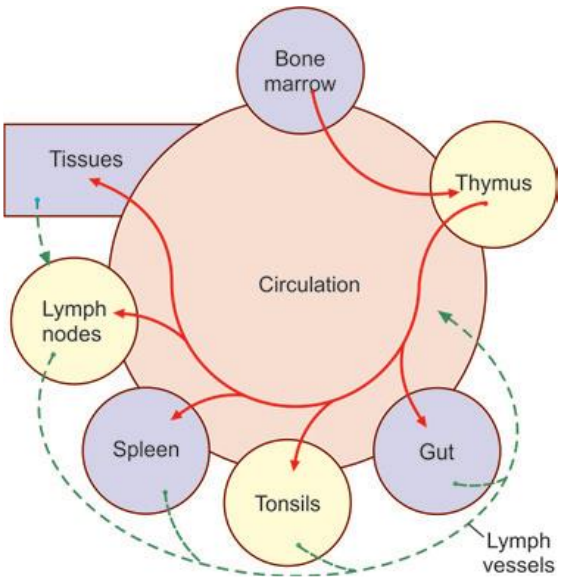
IMMUNE SYSTEM CELLS

Different types of lymphocytes are found in blood, lymph, lymphoid tissues, and lymphoid organs. lymphocytes originate from precursor hematopoietic stem cells in the bone marrow and then enter the bloodstream. Morphologically, all lymphocytes appear similar, but, functionally, they are different. Lymphocytes can be distinguished on the basis of where they differentiate, reside, and mature into immunocompetent cells and on the types of surface receptors or markers present on their cell membranes. These criteria allow the lymphocytes to be distinguished into two functionally distinct types, the B lymphocytes (B cells) and subcategories of T lymphocytes (T cells).

Three major types of lymphocytes are recognized. These are T lymphocytes (T cells), B lymphocytes (B cells), and natural killer (NK) cells.

T lymphocytes (T cells)

T cells originate from lymphocytes that were carried from the bone marrow to the thymus gland where they mature, differentiate, and acquire surface receptors and immunocompetence before migrating to peripheral lymphoid tissues and organs. The thymus gland produces mature T cells early in life, after which the T cells are distributed throughout the body via the blood and populate lymph nodes, the spleen, and lymphoid aggregates or nodules in connective tissue of the mucosa in the digestive tract (GALT), respiratory tract (BALT), and Peyer patches. On encountering an antigen, T cells destroy the antigen either by cytotoxic action or by activating B cells. There are four main subtypes of differentiated T cells: helper T cells, cytotoxic T cells, regulatory (suppressor) T cells, and memory T cells.



Circulation of T-lymphocytes (Schematic representation)

helper T cells assist other lymphocytes by secreting immune chemicals called cytokines or interleukins. Cytokines are protein hormones that stimulate the proliferation, secretion, differentiation, and maturation of B cells into plasma cells, which then produce antibodies, or immunoglobulins. The immunoglobulins then bind to antigens either to neutralize them or to cause their elimination by macrophage actions. The helper T cells also activate macrophages to become phagocytic and activate cytotoxic T cells.

Cytotoxic T cells recognize antigenically different cells, such as virusinfected cells, foreign cells, or malignant tumor cells, and destroy them. These lymphocytes are activated in the presence of APCs containing antigens that react with their receptors. The cytotoxic T cells then release lysosomes with lytic granules that contain pore-forming protein called perforin that creates pores in the membrane of the targeted cell causing apoptosis, or cell death.

Regulatory (suppressor) T cells may regulate (moderate or inhibit) specific functions of helper T cells and cytotoxic T cells and, thus, can functionally suppress immune response by influencing the activities of other cells in the immune system.

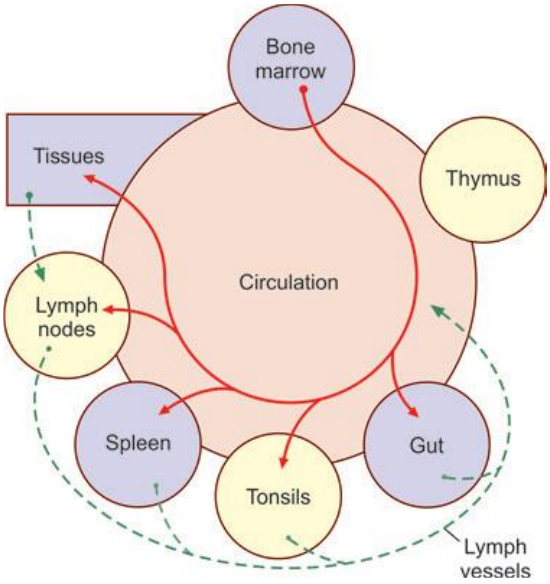
Memory T cells are the long-living progeny of T cells. They respond rapidly to the same antigens in the body and stimulate the immediate production of cytotoxic T cells. Memory T cells are the counterparts of memory B cells. Memory T cells activate the immune system and directly attack pathogens, whereas B cells produce antibodies that disable or kill the pathogens.

B lymphocytes (B cells)

B cells mature and become immunocompetent in bone marrow. After maturation, blood carries B cells to such nonthymic lymphoid organs or tissues as the lymph nodes, spleen, and connective tissue. B cells recognize particular type of antigen due to antigen receptor complex on the surface of their cell membrane. Immunocompetent B cells become activated when a specific antigen is encountered that binds to the surface antigen receptor complex of the B cell.

The activated B cells enlarge, divide, proliferate, and differentiate into plasma cells that secrete antibodies specific to the antigen that triggered plasma cell formation. Antibodies react with the antigens and initiate a process that destroys the foreign substance that activated the immune response.

Other activated B cells do not become plasma cells but persist in lymphoid organs as memory B cells. These memory cells produce a more rapid and longer-lasting immunologic response should the same antigen reappear.



Circulation of B-lymphocytes (Schematic representation)

Natural killer (NK) cells

NK cells develop from the same precursor cells as B and T cells and are the third type of lymphocytes that are genetically programmed to recognize and destroy altered cells. NK cells attack virally infected cells and cancer cells and destroy them in a fashion similar to cytotoxic T cells by releasing perforins and inducing apoptosis (cell death).

Approximate percentages of B and T cells in lymphoid organs

Lymphoid Organ	B Lymphocytes (%)	T Lymphocytes (%)
Thymus	0	100
Bone marrow	90	10
Spleen	55	45
Lymph nodes	40	60
Blood	30	70

Supporting or accessory cells are those that interact with lymphocytes and are antigen-presenting cells (APCs) to lymphocytes for activation and immune response. APCs are important in immune responses, and they are found in most tissues. These cells phagocytose and process antigens and then present the antigen to T cells, inducing their activation. These include cells from the mononuclear phagocyte system, the connective tissue macrophages, perisinusoidal macrophages in the liver (Kupffer cells), Langerhans cells (also called dendritic cells in the skin), and macrophages within the lymphoid organs.

TYPES OF IMMUNE RESPONSES

The immune responses to invading foreign organisms can be divided into two main types:

Innate immune response

is the first line of defense that limits the spread of infection. Its response to antigen invasion involves phagocytic functions that are rapid and involve neutrophils, mast cells, macrophages, dendritic cells, and NK cells. The response of the innate immune system is fast and but nonspecific and does not produce memory cells. Stimulation of macrophages and dendritic cells in an innate response produces cytokines (interleukins) that start the inflammatory response.

Adaptive immune response

The adaptive immune response targets specific invading foreign organisms and provides specific, or adaptive, defenses. This response is slower than the innate immune response, but it produces and retains numerous memory cells that can respond to the second encounter with the particular antigen that is faster, stronger, and longer lasting. Production of long-lived memory cells is the main feature of adaptive immunity.

Adoptive immunity involves two types of specific responses. These are the humoral immune response and the cellmediated immune response. These responses produce antibodies that bind to the antigens or stimulate cells that destroy foreign matter.

IMMUNE SYSTEM ORGANS:

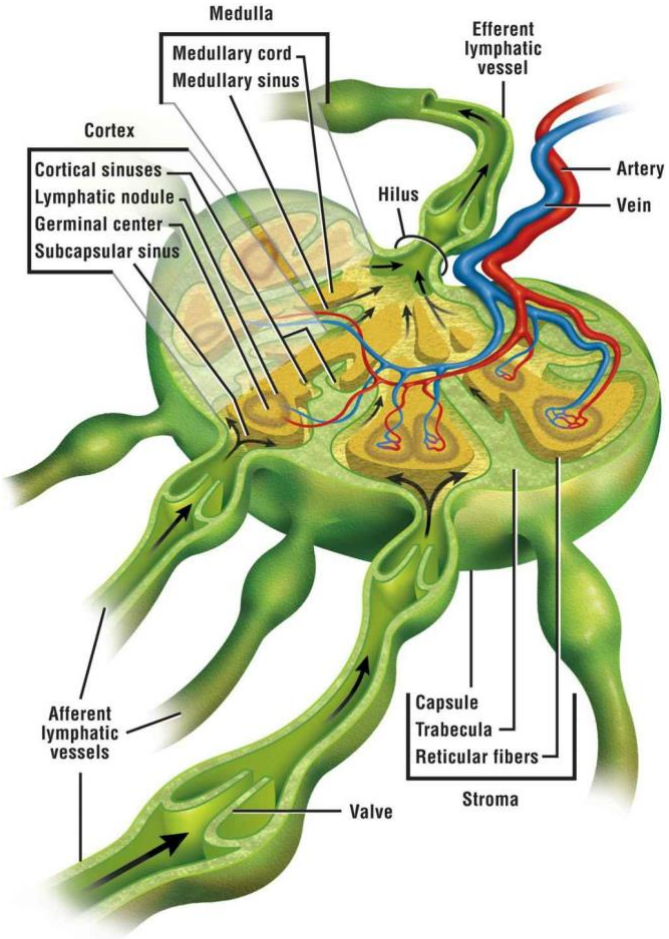
LYMPH NODES

The lymph nodes are widely distributed and are primarily found along the paths of lymphatic vessels that are prominent in inguinal and axillary regions. The lymph node consists of lymphocyte aggregations intermixed with dilated lymphatic sinuses that contain lymph and are supported by a framework of fine reticular fibers.

Lymph node is a bean-shaped organ with a fibrocollagenous capsule from which fibrous trabeculae extend into the node to form a supporting framework. The convex surface of the gland is penetrated by a number of afferent lymphatic vessels, which drain into the node, whereas at the hilum there is an efferent lymphatic vessel that transports lymph toward larger collecting lymphatic vessels. In turn these vessels drain into more proximal nodes or chains of nodes, before entering the blood via either the thoracic duct or the right lymphatic duct.

Afferent lymphatic vessels with valves course in the connective tissue capsule of the lymph node and, at intervals, penetrate the capsule to enter a narrow subcapsular sinus. From here, the sinuses (cortical sinuses) extend along the trabeculae into the medullary sinuses.

Efferent lymphatic vessels drain the lymph from the medullary sinuses and exit the lymph node in the hilus. Nerves, blood vessels, and veins that supply and drain the lymph node are located in the hilus.



The lymph node is surrounded by a pericapsular adipose tissue with numerous blood vessels. A dense connective tissue capsule surrounds the lymph node. From the capsule, connective tissue trabeculae extend into the node, initially between the lymphatic nodules and then throughout the medulla. The trabecular connective tissue also exhibits the major blood vessels.

The most abundant cells of lymph nodes are lymphocytes of all types, plasma cells, dendritic cells, macrophages, and other APCs.

Histologically, a lymph node is subdivided into three regions: cortex, paracortex, and medulla. All three regions have a rich supply of sinusoids, enlarged endothelially lined spaces through which lymph percolates.

A network of reticular fibers and spherical, nonencapsulated aggregations of lymphocytes called lymphoid nodules characterize the cortex. The cortex consists of B cell–rich lymphatic nodules situated adjacent to each other but separated by internodular connective tissue trabeculae and trabecular (cortical) sinuses. Some nodules exhibit a lighter-stained area in their center. These are the germinal centers of the lymphatic nodules and represent the sites of active lymphocyte proliferation. In the germinal centers, the cells are loosely aggregated with the developing lymphocytes showing larger and lighter-staining nuclei with more cytoplasm. The germinal center of the lymphatic nodule contains medium-sized lymphocytes characterized by larger, lighter nuclei and more cytoplasm than in the small lymphocytes. The nuclei of medium-sized lymphocytes exhibit variations in the size and density of the chromatin. The largest cells, with less condensed chromatin, are the lymphoblasts visible in the germinal center as large cells with a broad band of cytoplasm and a large vesicular nucleus with one or more nucleoli. Lymphoblasts produce other lymphoblasts and medium-sized lymphocytes. With mitotic divisions of lymphoblasts, the chromatin condenses and the cells decrease in size, producing small lymphocytes.

The dense peripheral zone of the lymphatic nodule contains an aggregation of small lymphocytes, characterized by dark-staining nuclei, condensed chromatin, and little or no cytoplasm.

The deeper portion of the lymph node cortex is the paracortex, it houses mostly T cells and fibroblastic reticular cells and is the thymus-dependent zone of the lymph node. This area represents the transition from the lymphatic nodules to the medullary cords of the lymph node medulla. The paracortex of lymph nodes contains postcapillary venules with an unusual morphology to facilitate the migration of lymphocytes from the blood into the lymph node. the postcapillary venules are called high endothelial venules because they are lined by tall cuboidal endothelium, instead of the usual squamous endothelium. These specialized venules are also present in Peyer patches in the small intestine, tonsils, appendix, and cortex of the thymus; but are absent from the spleen. Several migrating lymphocytes are seen moving through the venule wall between the high endothelium into the paracortex. Surrounding the high endothelial venule are lymphocytes of the paracortex, a medullary sinus, and a venule with blood cells.

The cell population of the paracortex consists of lymphocytes and accessory cells. T cells dominate the paracortex, dendritic APC and Macrophages are also found in the paracortex.

The medulla of the lymph node contains mainly:

• Cell-rich medullary cords

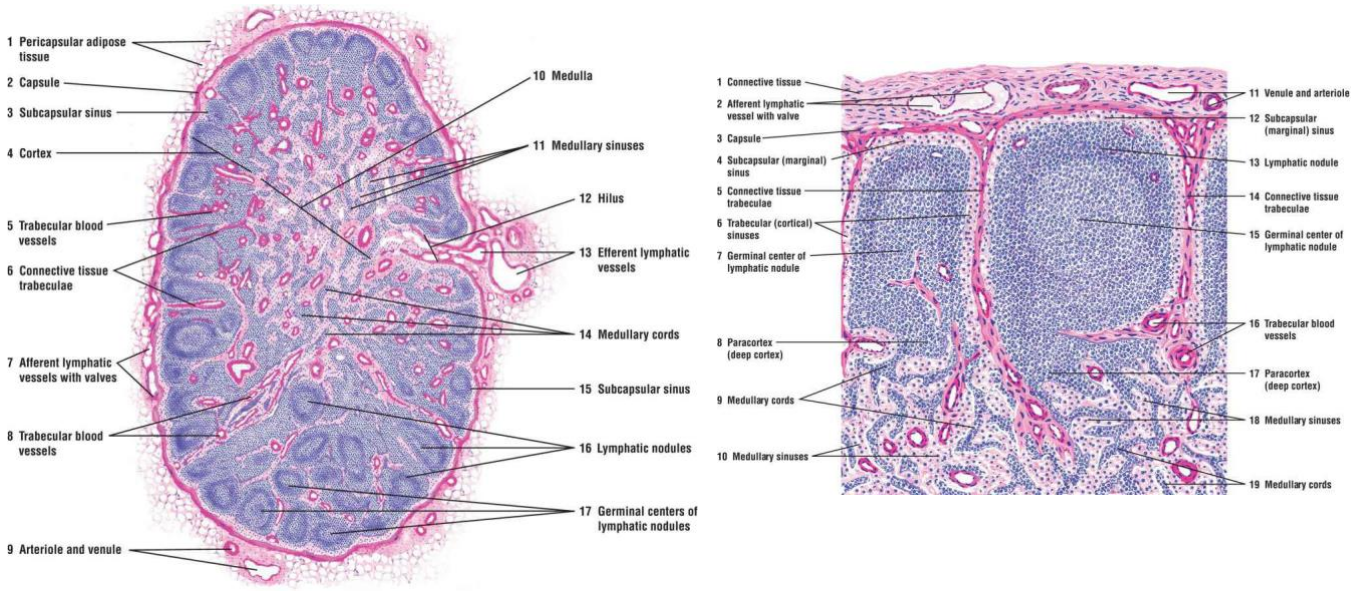
• Wide medullary sinuses (separating the medullary cords) through which lymph percolates toward the hilum from the cortex

• Larger blood vessels and their supporting trabeculae.

Medullary cords (the dark-staining) are networks of reticular fibers filled with plasma cells, macrophages, and lymphocytes separated by capillary-like channels called medullary sinuses (the light-staining). The dilated medullary sinuses drain the lymph from the cortical region of the lymph node and course between the medullary cords toward the concavity of the lymph node, the hilus.

Fine reticular connective tissue provides support for the lymph node and forms the core of the lymphatic nodules in the cortex, the medullary cords, and all medullary sinuses in the medulla.

Because few lymphocytes are seen in the medullary sinuses, it is possible to distinguish the reticular framework in the lymphatic nodules and the medullary cords.



LYMPH CIRCULATION

Continuous lymphocyte circulation between blood and lymph takes place in the lymph nodes, tonsils, Peyer patches, and spleen. B cells and T cells enter the lymph nodes through the incoming arteries. Lymph formed in the body eventually reaches the blood, and lymphocytes that leave the lymph nodes via the efferent lymph vessels also return to the bloodstream. The arteries supplying lymph nodes branch into capillaries in the cortex and paracortex, which provide an entryway for lymphocytes into the lymph nodes. Most lymphocytes enter the lymph nodes through the postcapillary venules in the paracortex. Here, the postcapillary venules are called high endothelial venules because they are lined by tall cuboidal or columnar endothelium and are the sites of entry by diapedesis of lymphocytes into the lymph node. B cells and T cells recognize special adhesion molecules on the high endothelial cells in these venules and leave the bloodstream to enter the lymph node. This pathway allows the movement of lymphocytes to travel in lymph to other lymph nodes, eventually entering the systemic circulation. Movement of B cells and T cells across the high endothelial venules into lymph nodes is considered homing.

FUNCTIONAL CORRELATIONS OF LYMPH NODES

Lymph nodes are important components of the defense mechanism. They have a strategic location along the paths of lymphatic vessels and are most prominent in the inguinal and axillary regions. Their major functions are lymph filtration and the phagocytosis of bacteria or foreign substances from the filtered lymph, preventing them from reaching the general circulation.

Trapped within the reticular fiber network of each lymph node are fixed or free macrophages that destroy foreign substances. Thus, as lymph is filtered, the nodes localize and prevent the spread of infection into the general circulation and other organs.

Lymph nodes produce, store, and activate B cells and T cells. Here the lymphocytes proliferate, and the B cells can transform into plasma cells. As a result, lymph that leaves the lymph nodes via the efferent vessels may contain antibodies that can be distributed to the entire body.

In the lymph node, the B cells congregate in the lymphatic nodules in the outer cortex, whereas the T cells concentrate below the lymphatic nodules in the deep cortical or paracortical (paracortex) regions.

Lymph nodes are the sites of antigenic recognition and antigenic activation of B cells, giving rise to plasma cells and memory B cells. When B cells are activated by the APCs, these lymphocytes proliferate in the central region of the lymphatic nodule and form lighter-staining germinal centers surrounded by darker-staining lymphocytes. Lymphatic nodules that lack the light-staining germinal centers and only exhibit the dense aggregations of lymphocytes are considered as inactive primary lymphatic nodules. After antigenic stimulation, primary lymphatic nodules become secondary lymphatic nodules with a lighter-staining germinal centers surrounded by dense staining lymphocytes. Germinal centers become the major sites for various B-cell proliferation and differentiation, whereas the T cells undergo the same process in the paracortex of the lymph node beneath and between the lymphatic nodules.

CLINICAL CORRELATIONS

- In the presence of antigens or bacteria, lymphocytes of the lymph node rapidly proliferate, and the node may increase to several times its normal size, becoming hard and palpable and at times painful to the touch.
- Neoplastic proliferation of lymphocytes, producing a malignant lymphoma, may occur diffusely but is often located in one or more lymph nodes. Such growth can completely obliterate the normal architecture of the node and convert it to an enlarged, encapsulated structure filled with lymphocytes, a condition called lymphadenopathy.
- Lymph nodes are located along the paths of lymph vessels and form a chain of lymph nodes so that lymph flows from one node to the next. For this reason, infection can spread, and malignant cells may metastasize through a chain of nodes to remote regions of the body.