IMMUNE SYSTEM CONTINUED

PRIMARY LYMPHOID ORGANS:

Also called central lymphoid organs, these are responsible for synthesis and maturation of immunocompetant cells. These include the bone marrow and the thymus.

BONE MARROW:

All the cells of the immune system are initially derived from the bone marrow through a process called hematopoiesis. During foetal development hematopoiesis occurs initially in yolk sac and para-aortic mesenchyme and later in the liver and spleen. This function is taken over gradually by the bone marrow. During hematopoiesis, bone marrow-derived stem cells differentiate into either mature cells or into precursors of cells that migrate out of the bone marrow to continue their maturation in thymus.

The bone marrow produces B cells, natural killer cells, granulocytes and immature thymocytes, in addition to red blood cells and platelets. It is both a primary and secondary lymphoid organ. The proliferation and maturation of precursor cells in the bone marrow are stimulated by cytokines, many of which are called colony stimulating factors (CSFs). The bone marrow also contains antibody secreting plasma cells, which have migrated from the peripheral lymphoid tissue.

THYMUS:

The thymus is a gland located in the anterior mediastinum just above the heart, which reaches its greatest size just prior to birth, then atrophies with age. This lymphoepithelial organ develops from ectoderm derived from the third branchial cleft and endoderm of the third branchial pouch.

Immature lymphocytes begin to accumulate in the thymus of human embryos at about 90-100 days after fertilization. Initially most of these immature lymphocytes have come from the yolk sac and fetal liver rather than the bone marrow. Cells from the bone marrow, later migrate to the thymus as precursors and develop into mature peripheral T cells. Once the immature lymphocytes have passed the blood-thymus barrier they are called thymocytes. Mature T cells migrate from the thymus to secondary lymphoid organs such as lymph node, Peyer's patches and spleen.

Ultimately the thymus becomes an encapsulated and consists of many lobes, each divided into an outer cortical region and an inner medulla. The cortex contains mostly immature thymocytes, some of which mature and migrate to the medulla, where they learn to discriminate between self and non-self during foetal development and for a short time after birth. T cells leave the medulla to enter the peripheral blood circulation, through which they are transported to the secondary lymphoid organs. About 98% of all T cells die in the thymus.

The greatest rate of T cell production occurs before puberty. After puberty, the thymus shrinks and the production of new T cells in the adult thymus drops away. Children with no development of thymus suffer from DiGeorge syndrome that is characterized by deficiency in T cell development but normal numbers of B cells.

PERIPHERAL LYMPHOID ORGANS:

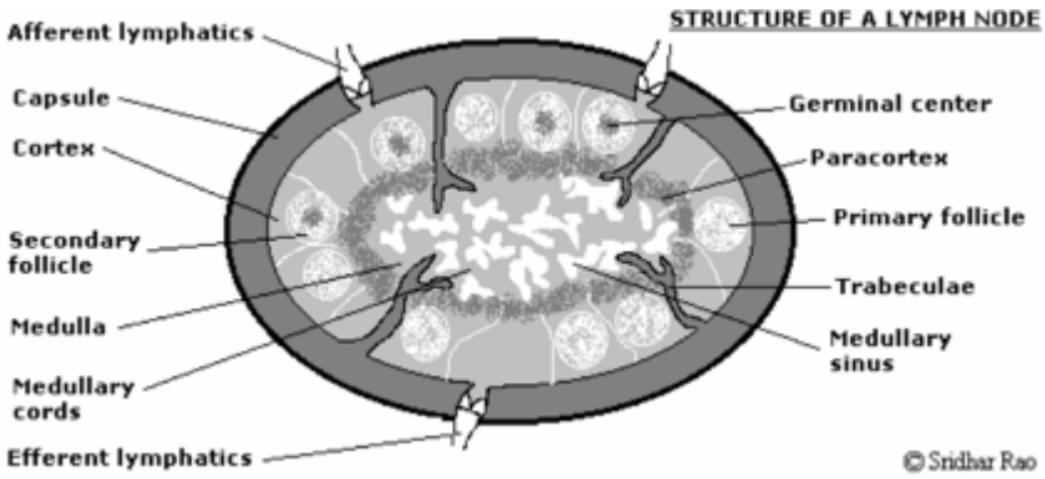
While primary lymphoid organs are concerned with production and maturation of lymphoid cells, the secondary or peripheral lymphoid organs are sites where the lymphocytes localise, recognise foreign antigen and mount response against it. These include the lymph nodes, spleen, tonsils, adenoids, appendix, and clumps of lymphoid tissue in the small intestine known as Peyer's patches. They trap and concentrate foreign substances, and they are the main sites of production of antibodies.

Some lymphoid organs are capsulated such as lymph node and spleen while others are non-capsulated, which include mostly mucosa-associated lymphoid tissue (MALT).

LYMPH NODE:

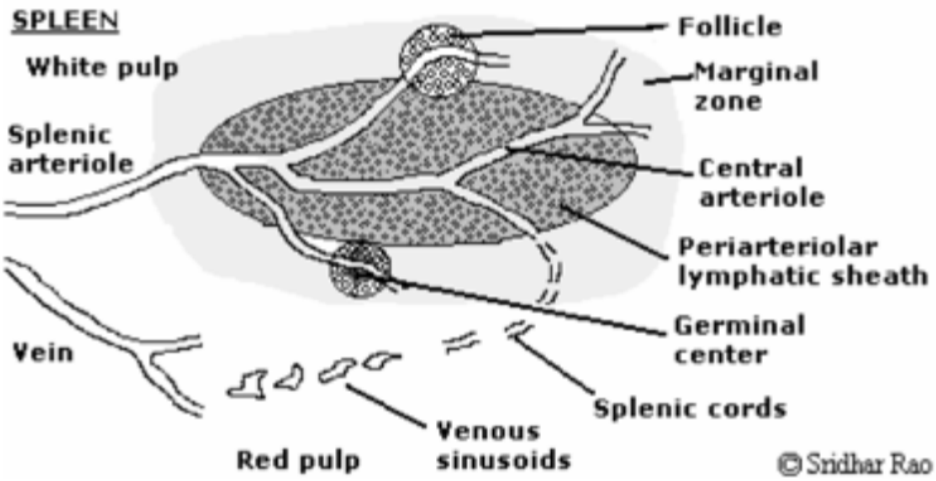
Clusters of lymph nodes are strategically placed in the neck, axillae, groin, mediastinum and abdominal cavity, where they filter antigens from the interstitial tissue fluid and the lymph during its passage from the periphery to the thoracic duct. The key lymph nodes are the axillary lymph nodes, the inguinal lymph nodes, the mesenteric lymph nodes and the cervical lymph nodes. Lymph nodes that protect the skin are termed somatic nodes, while deep lymph nodes protecting the respiratory, digestive and genitourinary tracts are termed visceral nodes.

Each lymph node is surrounded by a fibrous capsule that is pierced by numerous afferent lymphatics that drain lymph into marginal sinus. The lymph flows through the medullary sinus and leaves through efferent lymphatics. Each lymph node is divided into an outer cortex, inner medulla and intervening paracortical region. The cortex is also referred as B cell area, which mainly consists of B cells. The cortex is a high traffic zone where recirculating T- and B lymphocytes enter from the blood. Aggregates of cells called follicles are present in the cortex, which in turn may have central areas called germinal centers. Follicles without germinal centers are called primary follicles and those with germinal centers are called secondary follicles. Primary follicles are rich in mature but resting B cells. Germinal centers develop in response to antigenic stimulation and consist of follicular dendritic cells and reactive B cells. The medulla contains a mixture of B cells, T cells, plasma cells and macrophages. The medulla consists of medullary cords that lead to the medullary sinus. The cords are populated by plasma cells and macrophages. Between these two zones, lie the paracotex (T cell area) that contains T lymphocytes, dendritic cells and mononuclear phagocytes. Most of the T cells (70%) located there are CD4+ helper cells.



SPLEEN:

Situated in the left upper quadrant of the abdomen and weighing about 150 grams, spleen is the largest single lymphoid organ in the body. It has a dense fibrous capsule with muscular trabeculae extending inward to subdivide the spleen into lobules. It filters blood and is the major organ in which antibodies are synthesized and released into circulation. In addition to capturing foreign antigens from the blood that passes through the spleen, migratory macrophages and dendritic cells also bring antigens to the spleen via the bloodstream. Persons lacking spleen (eg. splenectomy) are highly susceptible to infections with capsulated bacteria such as pneumococci and meningococci. Spleen is the major site for phagocytosis of antibody coated bacteria and destruction of aged RBCs.



It is supplied by splenic artery, which pierces the capsule at hilum and divides into smaller branches that are surrounded by fibrous trabeculae. The spleen is composed of two types of tissue, the red pulp and the white pulp. The red pulp contains vascular sinusoids, large number of erythrocytes, resident macrophages, dendritic cells, granulocytes, few plasma cells and lymphocytes. It is the site where aged platelets and erythrocytes are destroyed. The white pulp contains the lymphoid tissue clustered around small arterioles and is known as a periarteriolar

lymphoid sheath (PALS). PALS contain mainly T lymphocytes, about 75% of which are CD4+ helper T cells. Attached to this are lymphoid follicles, some of which contain germinal centers. Follicles and germinal center predominantly contain B cells. The PALS and follicles are surrounded by rim of lymphocytes and macrophages, called marginal zone. Marginal zone is composed of macrophages, B cells, and CD4+ helper T cells. The arterioles end in vascular sinusoids in the red pulp, which in turn end in venules that drain into splenic vein. Antigens and lymphocytes enter the spleen through vascular sinusoids. Activation of B cells occurs at the juncton between follicle and PALS. Activated B cells then migrate to the germinal centers or into the red pulp.

MUCOSA ASSOCIATED LYMPHOID TISSUE (MALT):

Approximately >50% of lymphoid tissue in the body is found associated with the mucosal system. MALT is composed of gut-associated lymphoid tissues (GALT) lining the intestinal tract, bronchus-associated lymphoid tissue (BALT) lining the respiratory tract, and lymphoid tissue lining the genitourinary tract. The respiratory, alimentary and genitourinary tracts are guarded by subepithelial accumulations of lymphoid tissue that are not covered by connective tissue capsule. They may occur as diffuse collections of lymphocytes, plasma cells and phagocytes throughout the lung and lamina propria of intestine or as clearly organised tissue with well-formed lymphoid follicles. The well-formed follicles include the tonsils (lingual, palatine and pharyngeal), Peyer's patches in the intestine and appendix. The major function of these organs is to provide local immunity by way of sIgA (also IgE) production. Diffuse accumulations of lymphoid tissue are seen in the lamina propria of the intestinal wall. The intestinal epithelium overlying the Peyer's patches is specialized to allow the transport of antigens into the lymphoid tissue. This function is carried out by cuboidal absorptive epithelial cells termed "M" cells, so called because they have numerous microfolds on their luminal surface. M cells endocytose, transport and present antigens to subepithelial lymphoid cells.

Majority of intra-epithelial lymphocytes are T cells, and most often CD8+ lymphocytes. The intestinal lamina propria contains CD4+ lymphocytes, large number of B cells, plasma cells, macrophages, dendritic cells, eosinophils and mast cells. Peyer's patches contain both B cells and CD4+ T cells.

LYMPHOCYTES:

Lymphocytes are stem cells derived cells that mature either in the bone marrow or thymus. Together, the thymus and marrow bone marrow produce approximately 109 mature lymphocytes each day and the adult human body contains approximately 1012 lymphocytes. Lymphocytes comprise 20-40% (1000 - 4000 cells/µl) of all leukocytes. The lymphocytes are distributed to blood, lymph and lymphoid organs.

Typically, lymphocyte is small, round, cell with diameter of 5-10µm, spherical nucleus, densely compacted nuclear chromatin and scanty cytoplasm. Though the cytoplasm contains mitochondria and ribosomes, other organelles are not detectable. Such mature but resting lymphocytes are known as naïve cells. They are mitotically inactive but when stimulated can undergo cell division. Naïve lymphocytes have a short life span and die in few days after leaving bone marrow or thymus unless they are stimulated. Once the lymphocyte is activated (stimulated), they become large (10-12µm), have more cytoplasm and more organelles. Activated lymphocytes may undergo several successive rounds of cell division over a period of several days. Some of the progeny cells revert to the resting stage and become memory cells, but can survive for several years in the absence of any antigenic stimulus.

There are three major types of lymphocyte, B lymphocyte, T lymphocyte and NK cells. Different lymphocytes are identified by certain protein markers on their surface called "cluster of differentiation" or "CD" system. One marker that all leukocytes have in common is CD45. The presence of the markers can be detected using specific monoclonal antibodies.

Distribution of lymphocytes

	Approximate %		
Tissue	**T-Cells**	**B-Cells**	**NK Cells**
Peripheral blood	70-80	10-15	10-15
Bone marrow	5-10	80-90	5-10
Thymus	99	<1	<1
Lymph node	70-80	20-30	<1
Spleen	30-40	50-60	1-5

B LYMPHOCYTE:

Also called B-cells, they are so called because in birds they were found to mature in bursa of fabricius. Humans don't have an anatomical equivalent to bursa, but the development and maturation of these cells occur in bone marrow.

Ontogeny:

In mammals, the early stages of B cell maturation occur in the fetal liver and bone marrow. B cell development begins in the fetal liver and continues in the bone marrow throughout life.

The stages in B cell development in the bone marrow are:

Stem cell > pro-B cell > pre-B cell > small pre-B cell > immature B cell > mature B cell.

Distribution:

They account for 5-15% of lymphocytes (250 cells/µl) in circulation and 80-90% in bone marrow, 20-30% in lymph node and 50-60% in spleen.

Surface markers:

The most important surface marker on the surface of mature B cell is the surface immunoglobulin. The surface immunoglobulins are of IgM and IgD type. A B cell will have approximately 109 immunoglubulins of single specificity on its surface. Markers/Receptors on B cells are Surface Immunoglobulin (IgM and IgD), CD40, B7, ICAM-1, LFA-1, MHC II, CD32 (Ig Fc receptor), CD35 (Receptor for complement component) and additional markers that distinguish B cells such as CD19, CD20, CD21 and CD22.

Demonstration of B cells:

EAC (Erythrocyte Amboceptor Complement) Rosettes: When sheep RBCs coated with antibody and treated with complement and B cells, a rosette is formed due to the presence of complement receptor on B cells. B cells can be demonstrated by immunofluorescence with fluorescent-labelled monoclonal antibodies against surface markers such as surface immunoglobulin.

On stimulation by pokeweed mitogen, they undergo blast transformation.

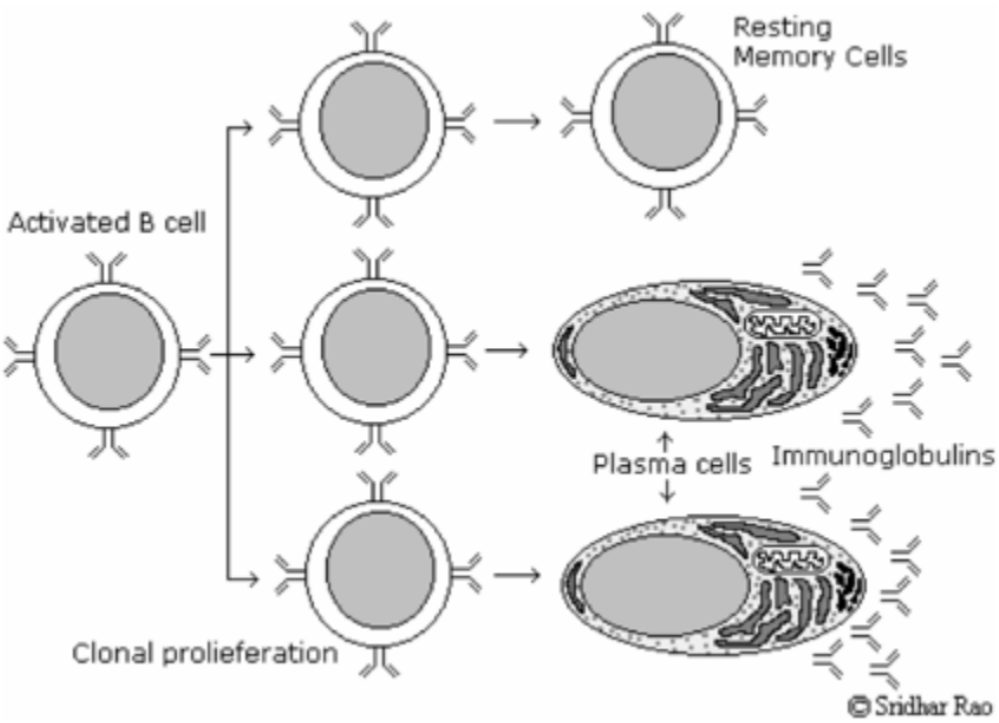
Functions of B-cells:

Direct antigen recognition and Antigen presentation

B cells may differentiate into plasma cells (which secrete large amounts of antibodies) or into memory B cells. Memory cells can survive 20 years or more.

Plasma cells:

These are the effector cells of the B-cell lineage and are specialised in secreting immunoglobulins. When activated B cells divide, some of its progeny become memory cells and the reminder become immunoglobulin-secreting plasma cells. Plasma cells are oval or egg shaped, have eccentrically placed nuclei, have abundant cytoplasm containing dense rough endoplasmic reticulum (the site of antibody production), perinuclear Golgi body (where immunoglobulins are converted to final form and packaged). Unlike B cells, immunoglobulins are not present on the surface of plasma cells. They have a short life span of few days to few weeks.



T LYMPHOCYTE:

Ontogeny:

The name "T-cell" is an abbreviation of "thymus dependent lymphocyte". T lymphocytes arise in the bone marrow as T-cell precursors, then migrate to and mature in the thymus. After entry into the thymus T-cell precursors are also referred to as "thymocytes".

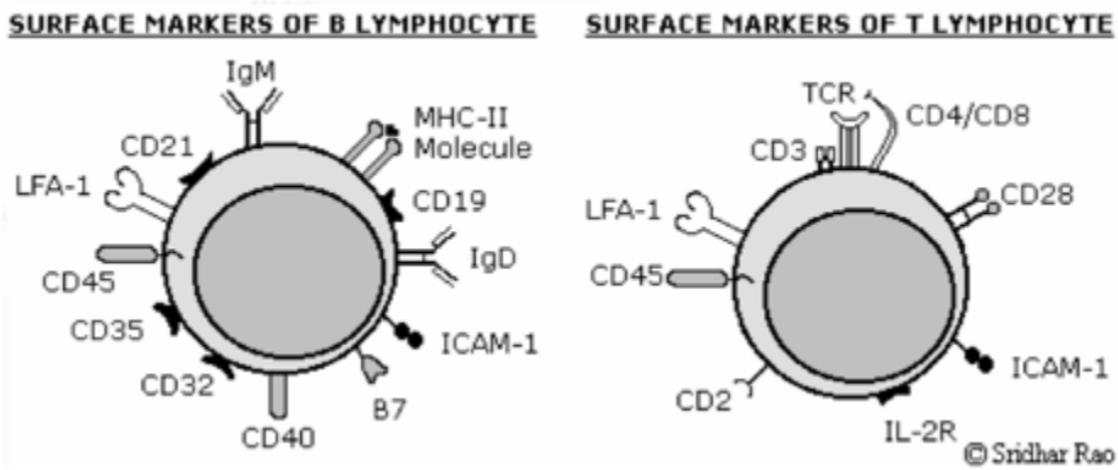
In the thymus there are rearrangements at gene segments coding for the variable part of the TCR (T Cell Receptor) resulting in generation of diversity. T Cell Receptors are then expressed on the surface, which is followed by expression of either CD8 or CD4 surface molecules. Those cells expressing receptors that can interact with self MHC molecules are positively selected while those cells that express receptors that recognize peptides derived from self protein in association with self MHC are negatively selected. Such cells undergo clonal deletion or anergy.

Distribution:

T cell accounts for 70-80% (1500 cells/µl) lymphocytes in peripheral blood, 5-10% in bone marrow, 70-80% in lymph node and 30-40% in spleen.

Surface markers:

The most important surface receptor is TCR. TCR are polypeptides that belong to the immunoglobulin superfamily. There are two kinds of TCR, one composed of a α-β heterodimer (TCR2) and the other composed of a γ-δ heterodimer (TCR1). An individual T cell can express either α-β or γ-δ as its receptor but never both. 95% of T cells express the α-β heterodimer. The other markers/receptors present on the surface are IL-2R, IL-1R, CD2, CD3, CD4/CD8, CD28, ICAM-1 and LFA-1. Nearly all the mature T lymphocytes express both CD2 and CD3 on their surface. CD3, which is always found closely associated with TCR, is necessary for signal transduction following antigen recognition by the TCR.



Subsets of T Cells:

There are two major types of T cells, Helper (CD4) and Cytotoxic/Suppressor (CD8) T cells. CD4 cells account for 45% (900/µl) of lymphocytes while CD8 cells account for 30% (600/µl).

Helper T cells (TH) secrete cytokines that promote the proliferation and differentiation of cytotoxic T cells, B cells and macrophages and activation of inflammatory leukocytes. TH cells are identified by the presence of the CD4 marker. They recognize antigen when presented along with Class II

MHC molecules. TH cells are further subdivided into the TH1 and TH2 subsets on the basis of the kinds of cytokines they produce. TH1 cells produce interleukin-2 (IL-2), interferon-gamma (IFNγ), and tumour necrosis factor-beta (TNF-β) while TH2 cells produce IL-4, IL-5, IL-6, IL-10 and TGF-β.

Cytotoxic T cells (TC) lyse cells with foreign antigens, e.g. tumour cells, virus-infected cells, and foreign tissue grafts. TC cells are identified by the presence of the CD8 marker. They recognize antigen presented when presented along with Class I MHC molecules. The suppressor T cells have a role in downregulation of immune response.

Demonstration of T cells:

T cells can be demonstrated by immunofluorescence using fluorescent-labelled monoclonal antibodies against TCR or other surface markers.

E-Rosette/ SRBC rosette: T cells bind to sheep RBCs at 37oC forming rosettes.

They undergo blast transformation on treatment with mitogens such as phytohemagglutinin (PHA) or Concanavalin A.

Functions of Helper T-cells (TH):

Promotes differentiation of B-cells and cytotoxic T-cells Activates macrophages

Functions of Cytotoxic/Suppressor T-cells (CTL): Kills cells expressing appropriate antigen Downregulates the activities of other cells

NK CELLS (LARGE GRANULAR LYMPHOCYTES):

Also called Large Granular Lymphocytes (LGLs), these are large lymphocytes containing azurophilic granules in the cytoplasm. NK cells derive form bone marrow but don't require thymus for development. NK cells are so called because they kill variety of target cells (such as tumour cells, virus-infected cells, transplanted cells) without the participation of MHC molecules. They can kill target cell without a need for activation unlike cytotoxic T lymphocytes. Hence they mediate a form of natural (innate) immunity.

Distribution:

They account for 10-15% of blood lymphocytes. They are rare in lymph nodes and don't circulate through lymph.

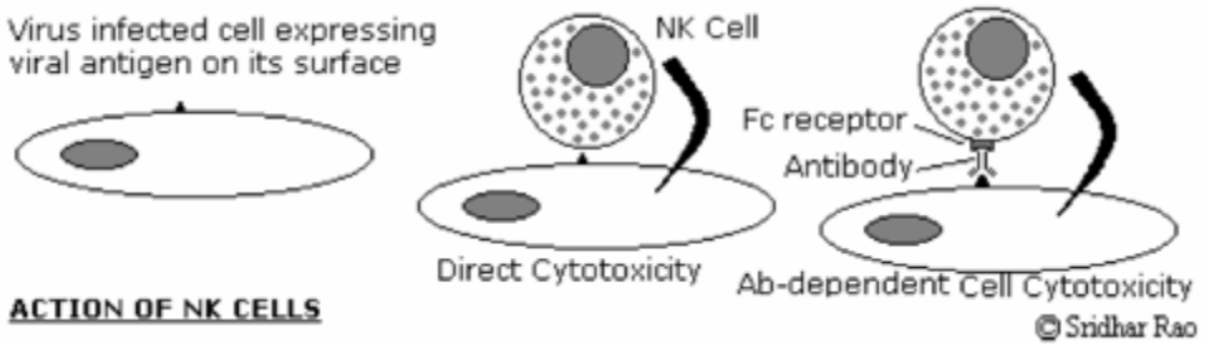
Surface markers:

NK cells lack any surface immunoglobulins, TCR or CD4 makers; instead they have CD16 (Immunoglobulin Fc receptor) and CD56. Approximately 50% of human NK cells express only one form of CD8. Other receptors include IL-2R, CD2, ICAM-1 and LFA-1.

Functions:

NK cells are activated by recognition of antibody-coated cells, virus infected cell, cell infected with intracellular bacteria and cells lacking MHC I proteins. Activation of NK cell results in cytolysis of target and cytokine secretion but no clonal expansion. Interestingly, NK cells are inhibited on contact with MHC I proteins.

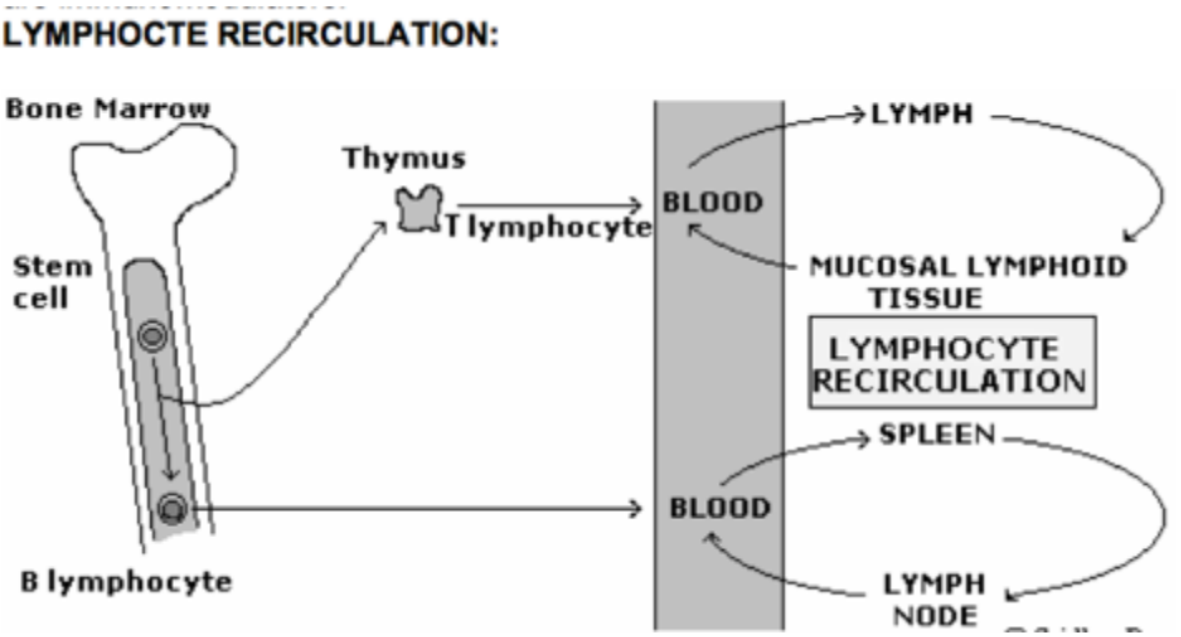
NK cells can kill antibody-coated target cells, which is mediated through Fc receptor present on its surface. This is called antibody-dependent cell cytotoxicity (ADCC).



NK cells also participate in Graft vs Host reaction in recipient of bone marrow transplants. NK cells can be activated by IL-2 so that their cytotoxic capacity is enhanced. Such cells are called Lymphokine Activated Killer cells (LAK) and have

been used clinically to treat tumours. LAK cells have enhanced cytolytic activity and are effective against wide range of tumour cells. Activated NK cells produce cytokines such as IFN-γ, TNFα, GM-CSF and CSF-1 all of which are immunomodulators.

LYMPHOCTE RECIRCULATION:



The movement of lymphocytes via the blood stream and lymphatics from peripheral tissue to another is called lymphocyte recirculation. Lymphocytes are migratory cells; mature lymphocytes continually migrate in and out of all peripheral lymphoid tissue. At an average each cell changes location once or twice each day. At any given point of time 1-2% of lymphocytes will be in transit. In most lymphoid organs, they enter through blood and exit

through lymphatics, but in spleen they enter and leave directly through blood. As lymphocytes migrate, they can survey the body for foci of infection or presence of foreign antigens. Such a movement also helps to maintain a balance in distribution of lymphocytes in the body.

Dualities in the Immune System

In biology, **immunity** is the balanced state of having adequate biological defenses to fight infection, disease, or other unwanted biological invasion, while having adequate tolerance to avoid allergy, and autoimmune diseases.

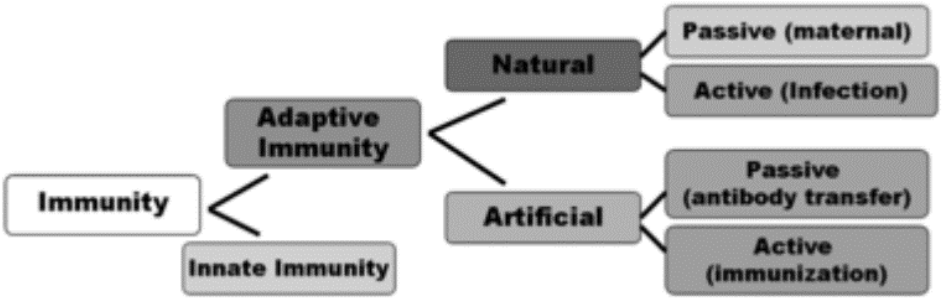
Innate and adaptive immunity

It is the capability of the body to resist harmful microorganisms or viruses from entering it. Immunity involves both specific and nonspecific components. The nonspecific components act either as barriers or as eliminators of wide range of pathogens irrespective of antigenic specificity. Other components of the immune system adapt themselves to each new disease encountered and are able to generate pathogen-specific immunity.

The basic premise for the division of the immune system into innate and adaptive components comes down to the innate system being composed of primitive bone marrow cells that are programmed to recognise *foreign* substances and *react*, versus the adaptive system being composed of more advanced lymphatic cells that are programmed to recognise *self* substances and *don't react*. The reaction to foreign substances is etymologically described as inflammation, meaning *to set on fire*, while the non-reaction to self substances is etymologically described as immunity, meaning *to exempt*. The interaction of these two components of the immune system creates a dynamic biological environment where "Health" can be seen as an active physical state where what is self is immunologically spared, and what is foreign is inflammatorily and immunologically eliminated. Extending this concept, "Disease" then can arise when what is foreign cannot be eliminated, or what is self cannot be spared.

Innate immunity, or nonspecific immunity, is the natural resistances with which a person is born. It provides resistances through several physical, chemical and cellular approaches. Microbes first encounter the epithelial layers, physical barriers that line skin and mucous membranes. Subsequent general defences include secreted chemical signals (cytokines), antimicrobial substances, fever, and phagocytic activity associated with the inflammatory responses. The phagocytes express cell surface receptors that can bind and respond to common molecular patterns expressed on the surface of invading microbes. Through these approaches, innate immunity can prevent the colonization, entry and spread of microbes.

Adaptive immunity is often sub-divided into two major types depending on how the immunity was introduced. 'Naturally acquired immunity' occurs through contact with a disease causing agent, when the contact was not deliberate, whereas 'artificially acquired immunity' develops only through deliberate actions such as vaccination. Both naturally and artificially acquired immunity can be further subdivided depending on whether immunity is induced in the host or passively transferred from an immune host. 'Passive immunity' is acquired through transfer of antibodies or activated T-cells from an immune host, and is short lived—usually lasting only a few months—whereas 'active immunity' is induced in the host itself by antigen and lasts much longer, sometimes lifelong. The diagram below summarizes these divisions of immunity.



A further subdivision of adaptive immunity is characterized by the cells involved; humoral immunity is the aspect of immunity that is mediated by secreted antibodies, whereas the protection provided by cell mediated immunity involves T-lymphocytes alone. Humoral immunity is active when the organism generates its own antibodies, and passive when antibodies are transferred between individuals. Similarly, cell mediated immunity is active when the organisms' own T-cells are stimulated and passive when T cells come from another organism.

Passive & Active Immunity

Passive immunity is the transfer of active immunity, in the form of readymade antibodies, from one individual to another. Passive immunity can occur naturally, when maternal antibodies are transferred to the fetus through the placenta, and can also be induced artificially, when high levels of human (or horse) antibodies specific for a pathogen or toxin are transferred to non-immune individuals. Passive immunization is used when there is a high risk of infection and insufficient time for the body to develop its own immune response, or to reduce the symptoms of ongoing or immunosuppressive diseases.[7] Passive immunity provides immediate protection, but the body does not develop memory, therefore the patient is at risk of being infected by the same pathogen later.

Naturally acquired passive immunity

Maternal passive immunity is a type of naturally acquired passive immunity, and refers to antibody-mediated immunity conveyed to a fetus by its mother during pregnancy. Maternal antibodies (MatAb) are passed through the placenta to the fetus by an FcRn receptor on placental cells. This occurs around the third month of gestation. IgG is the only antibody isotype that can pass through the placenta. Passive immunity is also provided through the transfer of IgA antibodies found in breast milk that are transferred to the gut of the infant, protecting against bacterial infections, until the newborn can synthesize its own antibodies.

Artificially acquired passive immunity

Artificially acquired passive immunity is a short-term immunization induced by the transfer of antibodies, which can be administered in several forms; as human or animal blood plasma, as pooled human immunoglobulin for intravenous (IVIG) or intramuscular (IG) use, and in the form of monoclonal antibodies (MAb). Passive transfer is used prophylactically in the case of immunodeficiency diseases, such as hypogammaglobulinemia.[10] It is also used in the treatment of several types of acute infection, and to treat poisoning. Immunity derived from passive immunization lasts for only a short period of time, and there is also a potential risk for hypersensitivity reactions, and serum sickness, especially from gamma globulin of non-human origin.

The artificial induction of passive immunity has been used for over a century to treat infectious disease, and prior to the advent of antibiotics, was often the only specific treatment for certain infections. Immunoglobulin therapy continued to be a first line therapy in the treatment of severe respiratory diseases until the 1930s, even after sulfonamide lot antibiotics were introduced.

Passive transfer of cell-mediated immunity

Passive or "adoptive transfer" of cell-mediated immunity, is conferred by the transfer of "sensitized" or activated T-cells from one individual into another. It is rarely used in humans because it requires histocompatible (matched) donors, which are often difficult to find. In unmatched donors this type of transfer carries severe risks of graft versus host disease. It has, however, been used to treat certain diseases including some types of cancer and immunodeficiency. This type of transfer differs from a bone marrow transplant, in which (undifferentiated) hematopoietic stem cells are transferred.

Active immunity

When B cells and T cells are activated by a pathogen, memory B-cells and T- cells develop, and the *primary* immune response results. Throughout the lifetime of an animal these memory cells will "remember" each specific pathogen encountered, and are able to mount a strong *secondary* response, if the pathogen is detected again. The primary and secondary responses were first described in 1921 by English immunologist Alexander Glenny. although the mechanism involved was not discovered until later.This type of immunity is both *active* and *adaptive* because the body's immune system prepares itself for future challenges. Active immunity often involves both the cell-mediated and humoral aspects of immunity as well as input from the innate immune system. The *innate system* is present from birth and protects an individual from pathogens regardless of experiences, where as adaptive immunity arises only after an infection or immunization and hence is "acquired" during life.

Naturally acquired active immunity
Naturally acquired active immunity occurs when a person is exposed to a live pathogen, and develops a primary immune response, which leads to immunological memory.[7] This type of immunity is "natural" because it is not induced by deliberate exposure. Many disorders of immune system function can affect the formation of active immunity such as immunodeficiency (both acquired and congenital forms) and immunosuppression.

Artificially acquired active immunity
Artificially acquired active immunity can be induced by a vaccine, a substance that contains antigen. A vaccine stimulates a primary response against the antigen without causing symptoms of the disease. The term *vaccination* was coined by Richard Dunning, a colleague of Edward Jenner, and adapted by Louis Pasteur for his pioneering work in vaccination. The method Pasteur used entailed treating the infectious agents for those diseases so they lost the ability to cause serious disease. Pasteur adopted the name vaccine as a generic term in honor of Jenner's discovery, which Pasteur's work built upon.

There are four types of traditional vaccines:

- Inactivated vaccines are composed of micro-organisms that have been killed with chemicals and/or heat and are no longer infectious. Examples are vaccines against flu, cholera, plague, and hepatitis A. Most vaccines of this type are likely to require booster shots.
- Live, attenuated vaccines are composed of micro-organisms that have been cultivated under conditions which disable their ability to induce disease. These responses are more durable and do not generally require booster shots. Examples include yellow fever, measles, rubella, and mumps.
- Toxoids are inactivated toxic compounds from micro-organisms in cases where these (rather than the micro-organism itself) cause illness, used prior to an encounter with the toxin of the micro-organism. Examples of toxoid-based vaccines include tetanus and diphtheria.
- Subunit vaccines are composed of small fragments of disease causing organisms. A characteristic example is the subunit vaccine against Hepatitis B virus.

Most vaccines are given by hypodermic or intramuscular injection as they are not absorbed reliably through the gut. Live attenuated polio and some typhoid and cholera vaccines are given orally in order to produce immunity based in the bowel.

Duality of Immune Function: Nonspecific and Specific Immunity
The immune system consists of nonspecific or innate immunity and specific or acquired immunity (Figure 12.7).

Nonspecific Immunity

Table 12.3 summarizes nonspecific immunity. These physiological defense mechanisms are innate (present since the time of birth). They act against microbe types. **Phagocytosis** is an important defense mechanism by which monocytes and neutrophils phagocytose foreign cells and antigens (Figure 12.8). A wound displays the four cardinal signs of **inflammation**: redness (rubor), heat (calor), swelling or edema (tumor), and pain (dolor). The discovery of phagocytosis by Elie Metchnicoff resulted in a Nobel Prize in 1908 (Figure 12.9). A variety of phagocytic cells are strategically located throughout the body. **Macrophages** are monocytes that have migrated out of the blood. Collectively, monocytes, neutrophils, and macrophages are referred to as "**professional phagocytes**."

Specific Immunity

The specific immune system is divided into two categories: **humoral (antibody-mediated) immunity** and **cell-mediated immunity (CMI)**. Most antigens are large protein molecules associated with microbes, tumor cells, damaged cells, pollens, dust, and foods. They trigger the production of antibodies specific for that antigen (humoral immunity) or bring about the production of T lymphocytes directed against that antigen (CMI). **T lymphocytes** have a role in both humoral immunity and CMI. There are several T cell types, or sub-sets (Table 12.4); each has a specific role and is identifiable by the **cluster of differentiation (CD)** molecules acquired in the thymus during the T-cell maturation process. **Cytotoxic T** ($\mathbf{T_C}$) cells are the effectors of CMI (Figure 12.10); they are **CD8⁺**. **T helper** ($\mathbf{T_H}$) cells are **CD4⁺**; they secrete molecules, known as **cytokines**, that activate B and T cells.

Antibody-Mediated (Humoral) Immunity

Humoral immunity is mediated by antibodies, products of **B cells** (with the aid of T_H cells) in response to antigens. Each antibody is constructed from two heavy (H) and two light (L) protein chains, the H and L chains combine to form a specific antigen binding site (Figure 12.11). The binding of antibodies to antigens has several outcomes (Figure 12.12), each of which facilitates destruction of the antigen-bearing microbe. Antibody secreting cells are called **plasma cells**. There are five categories of antibodies, or **immunoglobulins (Igs)**, termed **IgG**, **IgA**, **IgD**, **IgE**, and **IgM**. IgG accounts for approximately 80% of the antibody molecules and is the best characterized. T_H cells are required to help B cells produce antibodies; they do so by releasing molecules called cytokines (Figure 12.13). B cells exist since birth for every possible antigen; the **clonal selection theory** explains how antigens select the appropriate B cells for activation and clonal expansion as plasma cells (Figure 12.14). In response to antigen, some B cells develop into long-lived **memory B cells**; these cells frequently provide life-long immunity to a microbe- or vaccine-antigen encountered earlier in life.

Cell Mediated Immunity

Antibodies play little role in protection against intracellular microbes. CMI is the major adaptive defense against tumor cells and **intracellular microbes**: viruses, bacteria, and protozoans. CMI is mediated by $CD8^+$ T_C cells. Antigens of intracellular microbes and tumor cells are digested into small peptides. T_C cells can only recognize these peptide antigens if they are carried to the cell surface and displayed on **MHC** (major histo-compatability) molecules. T_C cells, like B cells, are clonally expanded from preexisting T_C cells in response to specific antigen displayed on MHC receptors. Activated T_C cells produce **perforin**, a pore-forming protein that lyses the target tumor or infected cell.

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