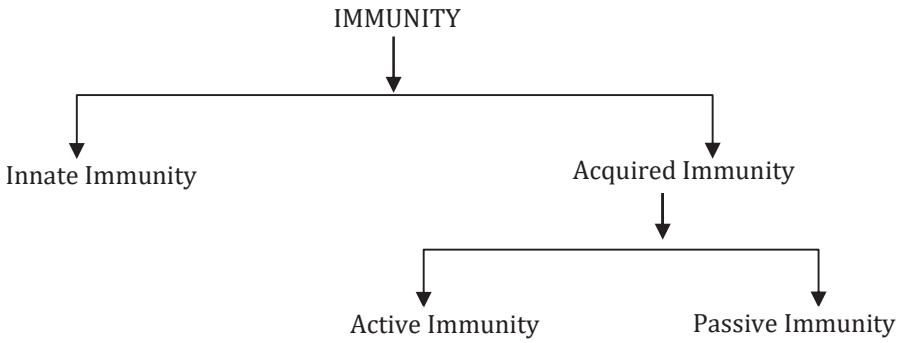
IMMUNITY

Each day, we encounter numerous infectious agents, yet only a select few of these encounters lead to illness. This is because the body possesses the capability to protect itself from the majority of these foreign agents. This collective ability of the host to combat disease-causing organisms, facilitated by the immune system, is known as immunity. Immunity manifests in two primary forms:

1. Innate Immunity
2. Acquired Immunity



1. Innate Immunity

Innate immunity operates by establishing various barriers to impede the entry of foreign agents or pathogens into our body. This form of immunity is inherent from birth; hence it is often referred to as inborn immunity. It constitutes a non-specific defense mechanism.

Innate immunity encompasses four primary types of barriers, which are:

(a) Physical Barriers

It consists of two components:

(i) Skin: The skin covering our body serves as the primary barrier against the entry of microorganisms. The outermost layer of the skin, known as the stratum corneum, is composed of dead cells, preventing the growth or penetration of bacteria. Additionally, the acidic pH of the skin (ranging from 3 to 5) aids in destroying bacteria.

(ii) Mucosa: The mucous coating present on the epithelial lining of the respiratory, gastrointestinal, and urogenital tracts also plays a role in trapping microbes attempting to enter our body. Mucosa comprises mucosal cells and cilia, where the mucosa captures microorganisms, and the cilia propel the microbes away.

(b) Physiological Barriers

Certain physiological processes within the body create unfavorable conditions for the growth of bacteria.

For instance:

(i) Stomach Acid, Saliva, and Tears: The acid present in the stomach, saliva in the mouth, and tears from the eyes all serve to inhibit microbial growth.

(ii) Fever: Elevated body temperature associated with fever acts as a deterrent for microbial growth.

(iii) Body pH: The acidic pH found in various parts of the body such as the oral cavity, stomach, and vagina helps to prevent microbial growth.

(iv) Secretions: Body secretions, including those from the eyes and sebum, contain lysozyme, an enzyme that effectively destroys microbes.

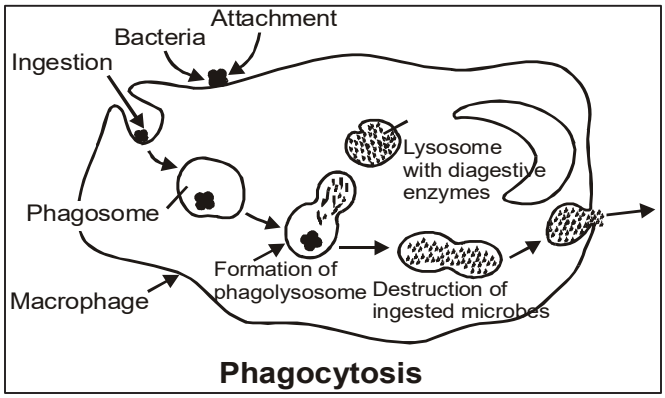
(c) Cellular Barriers

Polymorphonuclear leukocytes (PMNL-neutrophils), monocytes, and natural killer cells (a type of lymphocytes) present in the bloodstream, along with macrophages in tissues, possess the ability to phagocytose and eradicate microbes.

(i) Phagocytic Cells (e.g., Monocytes, PMNL – neutrophils, Macrophages): In response to a pathogenic infection, the overall count of white blood cells (WBCs) in the body increases. Some types of WBCs exhibit phagocytosis, earning them the designation of phagocytes. The primary phagocytes include macrophages and neutrophils. Monocytes are released at the site of infection and subsequently transform into macrophages. Macrophages, characterized by their large irregular shape, engulf microbes, viruses, cellular debris, and other foreign substances in response to an infection.

Steps of Phagocytosis

- Vasodilation: Blood vessels at the site of entry widen, increasing their diameter.
- Adhesion: Leukocytes accumulate at the periphery of blood vessels due to reduced blood flow.
- Diapedesis: Leukocytes (neutrophils or monocytes) migrate from the blood vessel into the extracellular fluid (ECF) through active movements, a process known as diapedesis.
- Chemotaxis: Leukocytes move toward the pathogen through chemotactic movement.
- Phagocytosis



Attachment (adherence)

The infective agent adheres to the membrane of the phagocyte.

- Ingestion: The phagocyte engulfs the particular material into a vacuole (phagosome), which merges with a lysosome to form a phagolysosome. The lysosome contains hydrolytic enzymes and other bactericidal substances.
- Intracellular killing of bacterium: Most bacteria are destroyed within the phagolysosome by hydrolytic enzymes shortly after phagocytosis.

(ii) Non-Phagocytic Cells (e.g., Natural Killer Cell): Natural killer cells, large granular lymphocytes, play a crucial role in killing virus-infected cells and tumor cells by creating perforin-lined pores in the plasma membrane of target cells (i.e., infected cells). These pores allow water to enter, leading to swelling and bursting of the diseased cells.

(d) Cytokine Barriers

Virus-infected cells release proteins known as interferons, which shield non-infected cells from further viral invasion. Interferons, consisting of up to 270 amino acids, are antiviral proteins secreted by virus-infected cells. They prompt neighboring cells to produce Translation Inhibiting Protein (T.I.P.), thereby

curtailing viral infection. Interferons exhibit species specificity, meaning those produced by a particular species can only safeguard cells of the same species against viral intrusion. By inducing the synthesis of antiviral proteins within cells, interferons confer resistance to viral infection.

Interferons can serve both prophylactic and therapeutic purposes in managing viral infections.

They come in various types:

- Interferon-α: Generated by Leucocytes (B-lymphocytes), activates the immune system and aids in tumor destruction. It has demonstrated efficacy in inducing regression of Kaposi sarcoma in AIDS patients.
- Interferon-β: Produced by Fibroblasts.
- Interferon-γ: Synthesized by Lymphocytes (T-lymphocytes).

Inflammation denotes the local response of living mammalian tissue to injury caused by various agents. It serves as the body's defense mechanism to eradicate or contain the spread of infectious agents.

Inflammation is characterized by:

(i) Redness (Rubor/Erythema): Resulting from vasodilation.
(ii) Heat (Calor): Arising from accelerated metabolic reactions.
(iii) Swelling (Tumor): Due to heightened permeability of blood vessels.
(iv) Pain (Dolor): Stemming from neuronal injury and the release of chemicals by damaged cells (e.g., prostaglandins).

2. Acquired Immunity

Acquired immunity is developed after birth and is tailored to specific pathogens. Upon encountering a pathogen for the first time, the body initiates what is known as the primary response, characterized by a relatively low-intensity reaction that may result in illness. When a specific antigen enters the body, specialized B and T cells begin to proliferate, giving rise to effector B and T cells that combat the disease. Additionally, memory B and T cells are produced and stored in the spleen and lymph nodes throughout one's lifetime. In the event of a subsequent encounter with the same pathogen, these memory cells rapidly multiply to generate effector B and T cells, triggering what is referred to as the secondary or anamnestic response. This secondary response is markedly more intense due to the body's recollection of the initial encounter.

The primary and secondary immune responses are facilitated by two types of lymphocytes circulating in our bloodstream: B-lymphocytes and T-lymphocytes.

which confer two types of acquired immunity:

(i) Humoral Immunity or Antibody-Mediated Immunity (AMI)
(ii) Cell-Mediated Immunity (CMI)

(i) Humoral Immunity

In response to pathogens, B-lymphocytes produce an array of proteins. Upon entry of any pathogen into the bloodstream, B-lymphocytes become activated and differentiate into plasma cells. These plasma cells secrete numerous antibodies into the bloodstream to combat the pathogens. Meanwhile, undifferentiated B-lymphocytes remain as memory cells.

Antigens:

Antigens are molecules that stimulate the production of antibodies when introduced into the body. These molecules, often large in size, trigger the immune response. Antigens are typically composed of proteins or polysaccharides found on the cell walls of bacteria, viruses, and other cells. However, not all antigens originate from microorganisms; substances like pollen grains, egg whites, shellfish, certain fruits and vegetables, poultry, bird feathers, blood cells from other organisms, drugs, and chemicals can also elicit antibody production from the immune system.

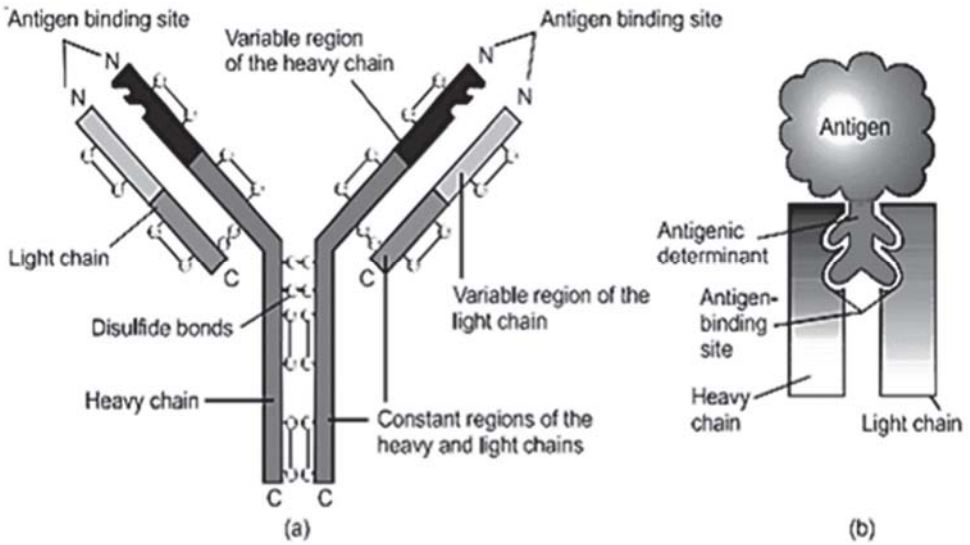


Fig.: Immunoglobulin: (a) Structure, (b) Antigen binding site

Self-antigens, also known as antigens related to blood groups, are those present on the body's own cells.

Antibodies, also called immunoglobulins (Ig), are produced in response to antigenic stimulation. Each antibody molecule comprises four peptide chains: two long chains referred to as heavy or H chains, each with a molecular weight of approximately 50,000 Da, and two short chains known as light or L chains, each with an approximate molecular weight of 25,000 Da. Therefore, an antibody is denoted as H_2L_2. The heavy and light chains are composed of sequences of amino acids. In the regions responsible for binding to antigens, these regions exhibit extreme variability, whereas in other regions of the molecule, they remain relatively constant. Consequently, each heavy and light chain possesses a variable and a constant region. The isotype of an immunoglobulin is determined by the constant region. Both chains are connected by disulfide bonds.

One end of the antibody, known as the Fab portion (fragment antigen binding), binds to the antigen. The other end, termed Fc (crystallizable fragment), is responsible for effector function.

Various types of antibodies are generated within our bodies, namely IgA, IgM, IgE, IgG, and IgD.

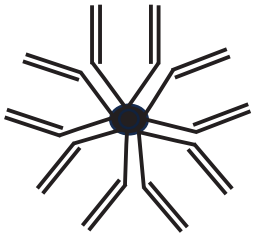
(a) IgA constitutes approximately 15% of the overall antibody count. It is primarily found in mucous secretions lining the respiratory tract, upper digestive tract, and the vagina. Additionally, IgA is present in colostrum, a yellowish liquid that a lactating mother excretes from her breasts within 24-48 hours after childbirth. Colostrum, produced before the onset of milk production, plays a crucial role in transferring antibodies to the newborn, providing protection for approximately six months.

(b) IgD comprises less than 1% of the total antibodies and appears to play a role in both activating and suppressing lymphocyte activity. It is abundant in the cell membrane of many B-cells and possesses two paratopes.

(c) IgE, constituting less than 1% of total antibodies, acts as a mediator in allergic responses. It notably triggers the secretion of histamine and is implicated in combating parasitic infections.

(d) IgG constitutes approximately 75% of our immunoglobulin pool. It stimulates phagocytic cells, activates the complement system, binds to neutrophils, opsonizes pathogens, and possesses the ability to neutralize toxins. Importantly, IgG is the sole antibody capable of crossing the placenta, thereby conferring immunity to the fetus.

(e) IgM accounts for 7-10% of our total antibodies. As the predominant early antibody, it is the first to activate during an initial encounter with antigens (primary response). IgM is also the largest antibody in size.



IgM

As all these antibodies are present in the bloodstream, the resulting reaction is referred to as the humoral (fluid) immune response.

Antigens possess determinants known as epitopes, which are molecular structures recognized by antibodies. Antibodies specifically target individual epitopes rather than the entire antigen. Antigens can be comprised of proteins, lipids, or carbohydrates, and may contain numerous distinct epitopes, or multiple repeated epitopes.

Under the influence of T cell-released cytokines, B-lymphocytes undergo maturation into plasma cells. Plasma cells, situated in lymphoid tissues rather than the bloodstream, produce antibodies in significant quantities without undergoing division. Meanwhile, other B cells circulate as memory cells. Upon encountering antigens again, these memory cells divide, generating both plasma cells and additional B memory cells.

Plasma cells continuously generate and release between 2000 and 20,000 antibody molecules per second into the bloodstream for approximately four to five days. Conversely, B memory cells have a prolonged lifespan, enduring for months or even years, thus contributing to the immune memory system.

(ii) Cell-mediated immunity (CMI)

also known as T-lymphocyte mediated immunity, relies on T-cells. Unlike B cells, T cells do not directly secrete antibodies but play a crucial role in aiding B cells in their antibody production process.

Immature lymphocytes originate from the bone marrow and subsequently migrate to the thymus through the bloodstream. Within the thymus, these cells undergo maturation into T-lymphocytes or T-cells before dispersing to various lymphoid tissues throughout the body, where they undergo differentiation into different types:

(a) **Helper T cells:** These cells stimulate B cells to initiate antibody production and activate killer T cells to eliminate foreign cells.

(b) **Cytotoxic/Killer T cells:** This subset of T cells releases perforins, which puncture the membranes of invading cells, causing them to swell and eventually rupture.

(c) **Suppressor T cells:** Functioning to modulate the immune response, suppressor T cells inhibit the activity of cytotoxic and helper T cells, thereby preventing the immune system from targeting the body's own cells.

(d) **Memory T cells:** Formed from activated T cells, memory T cells reside within lymphatic tissues, retaining the ability to recognize the original invading antigen or pathogen even after prolonged periods since the initial encounter.

Graft rejection

In instances where vital human organs such as the heart, eyes, liver, and kidneys fail to function adequately, transplantation emerges as the sole recourse enabling patients to regain a semblance of

normalcy in their lives. The organs or tissues utilized for transplantation, commonly referred to as grafts, must be carefully sourced to mitigate the risk of eventual rejection. Grafts obtained from various sources such as animals, other primates, or different human donors are subject to rejection over time. Prior to any graft or transplant procedure, meticulous tissue and blood group matching are imperative. Despite these precautions, transplantation carries the risk of organ rejection, as the immune system perceives the proteins present in transplanted tissues or organs as foreign entities, thus initiating cellular immunity. To counteract this immune response during transplantation, histocompatibility antigens and immunosuppressants play pivotal roles.

(i) Histocompatibility pertains to the property of possessing identical or predominantly identical alleles of a specific set of genes known as the major histocompatibility complex (MHC). The MHC, consisting of molecules displayed on cell surfaces responsible for lymphocyte recognition and antigen presentation, is encoded by multiple genes situated on human chromosome 6. Often referred to as the Human Leucocyte Antigen (HLA) System in humans, the major histocompatibility complex plays a crucial role in transplantation compatibility.

(ii) Immunosuppressive drugs are administered to forestall rejection. While kidney transplantation from an identical twin invariably yields success, similar outcomes can be achieved when the kidney is sourced from a non-twin individual, provided immunosuppressive medications are utilized. Cyclosporin, a potent immunosuppressant, is particularly effective in preventing rejection. By selectively targeting T-cell mediated immune responses while preserving humoral antibody responses, cyclosporin safeguards against rejection in kidney, heart, and liver transplants, as graft rejection is primarily mediated by the cell-mediated immune response.

Active and Passive Immunity

Acquired immunity can be further categorized into:

(i) Active immunity

This type of immunity occurs when a host is exposed to antigens, which may take the form of living or dead microbes or other proteins, leading to the production of antibodies within the host's body. Active immunity is characterized by its gradual onset and can be either natural or artificial.

(a) Natural active immunity: This form of immunity is acquired when antigens enter the body during a natural infection. For instance, individuals who have recovered from illnesses such as smallpox, measles, or mumps develop natural active immunity.

(b) Artificial active immunity: Resistance is induced through vaccines, prompting the body to generate an immune response.

(ii) Passive immunity

In passive immunity, pre-formed antibodies are directly administered to protect the body against foreign agents.

(a) Natural passive immunity: During the initial days of lactation, the yellowish fluid known as colostrum, secreted by the mother, contains abundant antibodies (IgA) to safeguard the infant. Additionally, the fetus receives some antibodies (IgG) from the mother through the placenta during pregnancy.

(b) Artificial passive immunity: Pre-formed antibodies are directly injected into the body to confer immunity. Examples include the administration of anti-venom following a snake bite or anti-tetanus serum (ATS).

Difference between active and passive immunity

S. No.	Active immunity	Passive immunity
1.	Produced actively by the immune system of host.	Received passively by the host and the host's immune system does not participate.
2.	Induced by infection or by contacts with immunogen, e.g. vaccines.	Conferred by introduction of ready-made antibodies.
3.	Immune response-durable and effective.	Immune response-short lived and less effective.
4.	Immunity develops only after a lag period.	Immunity effective immediately.
5.	Immunological memory present.	No immunological memory.
6.	Serves no purpose in immunodeficient host.	Applicable in immunodeficient host.
7.	Used for prophylaxis to increase body resistance.	Used for treatment of acute infection.

Vaccination and Immunization

The concept of immunization or vaccination revolves around the immune system's ability to remember pathogens it has encountered before.

Vaccination involves the introduction of either inactivated or weakened pathogens, or antigenic proteins derived from pathogens, into the body. The antibodies generated in response to these antigens work to neutralize the pathogenic agents during a real infection. Additionally, vaccines stimulate the production of memory B and T-cells, which rapidly recognize the pathogen upon subsequent exposure. This quick response enables the immune system to mount a robust defense, overwhelming the invaders with a surge of antibody production.

Passive Immunization

Passive immunization occurs when pre-formed antibodies are directly injected to induce a rapid immune response. For instance, if an individual requires immediate protection against dangerous microbes, such as in the case of tetanus, pre-formed antibodies or antitoxins are directly administered. Similarly, in the event of snake bites, injections containing pre-formed antibodies against snake venom are administered to patients. This form of immunization is termed passive immunization.

In 1891, a significant breakthrough in immunology occurred, adding to our understanding of immune responses. A young girl was gravely ill with diphtheria. Her physician, Emil von Behring, conducted an experiment where he infected sheep with diphtheria-causing bacteria and allowed some time to pass. He then extracted blood from the sheep and separated the serum by clotting. This serum was then injected into the patient. Remarkably, within a few hours, the girl began to recover dramatically. This innovative treatment approach marked the discovery of passive immunity. Von Behring's groundbreaking work earned him the Nobel Prize.

Disorders of the Immune System

(i) Allergy or Hypersensitivity/Allergies

Allergy, also known as hypersensitivity, refers to an individual's heightened sensitivity to certain foreign substances, known as allergens, upon contact or entry into the body. It represents an exaggerated response of the immune system to specific antigens present in the environment. Allergens encompass a wide range of substances including mites, dust, pollens, animal dander, fabrics, feathers, molds, as well as environmental factors such as heat, cold, and sunlight.

Cause: Allergic reactions typically involve the production of IgE antibodies against these allergens. The onset of allergic reactions is attributed to the release of chemicals like histamine and serotonin from

mast cells. During an allergic reaction, there is an increased release of histamine, resulting in significant dilation of peripheral blood vessels and heightened capillary permeability. This leads to a substantial leakage of fluid from the blood into the surrounding tissues, causing a drastic decrease in blood pressure that can potentially result in fatal outcomes. Identifying the specific substance to which an individual is hypersensitive is crucial for effective treatment.

Types of Allergies

(a) Hay fever: Characterized by swollen, reddened, and runny eyes and nose, hay fever often necessitates treatment with antihistamines.

(b) Asthma: This condition involves sudden spasms of the tissues surrounding the respiratory tract, leading to narrowed airways and breathing difficulties.

(c) Anaphylactic shock: A severe allergic reaction affecting multiple tissues in the body, anaphylactic shock can occur within minutes of exposure to an antigen, such as penicillin. It is characterized by a drastic drop in blood pressure due to widespread arterial dilation, leading to unconsciousness and potentially fatal outcomes.

(d) Eczema: Eczema manifests as redness of the skin followed by the appearance of tiny blisters.
Symptoms: Symptoms of allergic reactions may include sneezing, watery eyes, runny nose, and difficulty in breathing.
Treatment: Determining the cause of allergy often involves exposing or injecting the patient with minute doses of potential allergens, followed by the observation of resulting reactions. Treatment typically involves the use of medications such as antihistamines, adrenaline, and steroids to alleviate symptoms rapidly.

(ii) Auto Immunity

In higher vertebrates, acquired immunity operates on a memory-based system. One of the remarkable features of the immune system is its ability to distinguish between foreign particles or proteins and the body's own proteins. Normally, the immune system targets and eliminates foreign organisms, such as pathogens, while leaving self-cells untouched. However, under certain circumstances, which may involve genetic factors or other unknown triggers, the body may erroneously attack its own cells. This phenomenon results in damage to the body and is termed an Autoimmune Disease.

Autoimmune diseases arise when the body's immune system fails to properly differentiate between 'self' and 'non-self', leading to the destruction of the body's own cells. For instance, if the autoantigens targeted are red blood cells (RBCs), the body may inadvertently destroy its own RBCs, leading to chronic anemia. Similarly, if the autoantigens are muscle cells, it can result in the destruction of muscle tissue, leading to severe weakness, as seen in conditions like Myasthenia gravis. Autoimmune attacks on liver cells may lead to chronic hepatitis, while other autoimmune diseases include insulin-dependent diabetes, Addison's disease, ulcerative colitis, rheumatoid arthritis, and Hashimoto's disease.

The Immune System in the Human Body

The human immune system comprises lymphoid organs, tissues, cells, and soluble molecules such as antibodies. It is responsible for identifying and responding to foreign antigens while retaining a memory of encountered threats. Additionally, the immune system plays a crucial role in regulating allergic reactions, managing autoimmune diseases, and facilitating organ transplantation.

Lymphoid Organs

Lymphoid organs serve as sites for the origin, maturation, and proliferation of lymphocytes, with two main types identified:

(i) Primary lymphoid organs (ii) Secondary lymphoid organs

(i) Primary lymphoid organs

These organs facilitate the differentiation of immature lymphocytes into antigen-specific lymphocytes. Examples include the bone marrow and thymus.

The bone marrow serves as a vital primary lymphoid organ where all blood cells, including lymphocytes, are produced. It is considered equivalent to the Avian Bursa of Fabricius and serves as the primary site for B-lymphocyte maturation.

The thymus, located adjacent to the heart and beneath the sternum, is a lobed organ. While relatively large at birth, it gradually diminishes in size with age, reaching a significantly reduced state by the time puberty is attained. The thymus serves as the site for T-lymphocyte maturation.

Primary lymphoid organs, encompassing the bone marrow and thymus, provide specialized microenvironments conducive to the development and maturation of lymphocytes.

(ii) Secondary Lymphoid Organs

Following maturation, B-lymphocytes and T-lymphocytes traverse through the bloodstream and lymphatic system to reach secondary lymphoid organs. These organs serve as sites for the interaction between lymphocytes and antigens, where they undergo proliferation and differentiation to become effector cells. Secondary lymphoid organs include the spleen, lymph nodes, tonsils, Peyer's patches of the small intestine, and the appendix.

Spleen: This large, bean-shaped organ primarily comprises lymphocytes, phagocytes, and a significant number of erythrocytes. Functionally, the spleen acts as a blood filter, capturing blood-borne microorganisms. It also serves as a major reservoir for red blood cells and is often referred to as the "Graveyard of RBCs."

Lymph Nodes: These small, solid structures are situated at various points along the lymphatic system. Lymph nodes function to capture microorganisms or other antigens present in lymph and tissue fluid. Antigens trapped within lymph nodes activate the lymphocytes present therein, eliciting an immune response.

MALT (Mucosa-Associated Lymphoid Tissue): MALT refers to lymphoid tissue located within the mucosal lining of major tracts such as the respiratory, digestive, and urogenital tracts. Comprising approximately 50 percent of the lymphoid tissue in the human body, MALT serves as a crucial component of the immune system's defense mechanism.

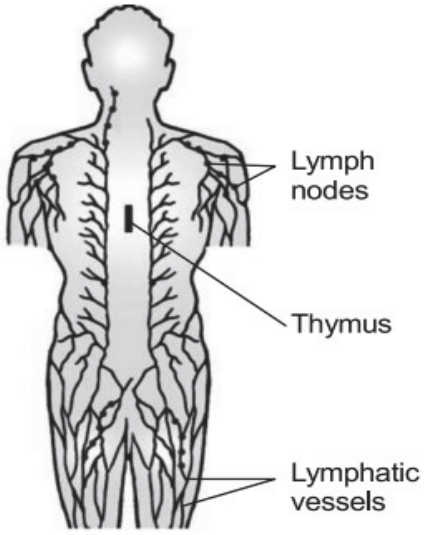


Fig. : Diagrammatic representation of lymph nodes