White blood cells (WBCs)

White blood cells (WBCs) or leukocytes are the colorless and nucleated formed elements of blood (leuko = white or colorless). Compared to RBCs, the WBCs are larger in size and lesser in number. Yet functionally, these cells are as important as RBCs and play very important role in defense mechanism of body by acting like soldiers and protecting the body from invading organisms.

NORMAL LEUKOCYTE COUNT

Total WBC count (TC): 4,000 to 11,000/cu mm of blood

CLASSIFICATION

WBCs are classified into two groups depending upon the presence or absence of granules in the cytoplasm:
1. Granulocytes – with granules
2. Agranulocytes – without granules.

1. Granulocytes: Depending upon the staining property of granules, the granulocytes are classified into three types.

i. Neutrophils – granules take both acidic and basic stains
ii. Eosinophils – granules take acidic stain
iii. Basophils – granules take basic stain.

2. Agranulocytes
Agranulocytes have plain cytoplasm without granules.
Agranulocytes are of two types:

i. Monocytes
ii. Lymphocytes.

Depending upon the function, the lymphocytes are divided into two types:

i. T lymphocytes– concerned with cellular immunity
ii. B lymphocytes– concerned with humoral immunity.

PROPERTIES OF WBCs

1. Diapedesis

Diapedesis is the process by which the WBCs squeeze through the narrow blood vessels.

2. Ameboid Movement

Neutrophils, monocytes and lymphocytes show amebic movement characterized by protrusion of the cytoplasm and change in the shape.

3. Chemotaxis

Chemotaxis is the attraction of WBCs towards the injured tissues by the chemical substances released at the site of injury.

4. Phagocytosis

Neutrophils and monocytes engulf the foreign bodies by means of phagocytosis.

Genesis of the White Blood Cells

The granulocytes and monocytes are formed only in the bone marrow. Lymphocytes and plasma cells are produced mainly in the various lymphogenous tissues—especially the lymph glands, spleen, thymus, tonsils, and various pockets of lymphoid tissue elsewhere in the body, such as in the bone marrow and in so-called Peyer's patches underneath the epithelium in the gut wall. The white blood cells formed in the bone marrow are stored within the marrow until they are needed in the circulatory system.

Life Span of the White Blood Cells

The life of the granulocytes after being released from the bone marrow is normally 4 to 8 hours circulating in the blood and another 4 to 5 days in tissues where they are needed. In times of serious tissue infection, this total life span is often shortened to only a few hours because the granulocytes proceed even more rapidly to the infected area, perform their functions, and, in the process, are themselves destroyed. The monocytes also have a short transit time, 10 to 20 hours in the blood, before wandering through the capillary membranes into the tissues. Once in the tissues, they swell to much larger sizes to become tissue macrophages, and, in this form, can live for months unless destroyed while performing phagocytic functions. Lymphocytes enter the circulatory system continually, along with drainage of lymph from the lymph nodes and other lymphoid tissue. After a few hours, they pass out of the blood back into the tissues by diapedesis. Then, still later, they re-enter the lymph and return to the blood again and again; thus, there is continual circulation of lymphocytes through the body.

The lymphocytes have life spans of weeks or months; this life span depends on the body's need for these cells.

Phagocytosis

The most important function of the neutrophils and macrophages is phagocytosis, which means cellular ingestion of the offending agent. Phagocytes must be selective of the material that is phagocytized; otherwise, normal cells and structures of the body might be ingested. Whether phagocytosis will occur depends especially on three selective procedures. **First,** most natural structures in the tissues have smooth surfaces, which resist phagocytosis. But if the surface is rough, the likelihood of phagocytosis is increased. **Second**, most natural substances of the body have protective protein coats that repel the phagocytes. Conversely, most dead tissues and foreign particles have no protective coats, which makes them subject to phagocytosis. **Third,** the immune system of the body develops antibodies against infectious agents such as bacteria. The antibodies then adhere to the bacterial membranes and thereby make the bacteria especially susceptible to phagocytosis. To do this, the antibody molecule also combines with the C3 product of the complement cascade, which is an additional part of the immune system The C3 molecules, in turn, attach to receptors on the phagocyte membrane, thus initiating phagocytosis. This selection and phagocytosis process is called opsonization.

Inflammation:

Role of Neutrophils and Macrophages Inflammation

When tissue injury occurs, whether caused by bacteria, trauma, chemicals, heat, or any other phenomenon, multiple substances are released by the injured tissues and cause dramatic secondary changes in the surrounding uninjured tissues. This entire complex of tissue changes is called inflammation. Inflammation is characterized by

(1) vasodilation of the local blood vessels, with consequent excess local blood flow;

(2) increased permeability of the capillaries, allowing leakage of large quantities of fluid into the interstitial spaces;

(3) often clotting of the fluid in the interstitial spaces because of excessive amounts of fibrinogen and other proteins leaking from the capillaries;

(4) migration of large numbers of granulocytes and monocytes into the tissue; and

(5) swelling of the tissue cells. Some of the many tissue products that cause these reactions are histamine, bradykinin, serotonin, prostaglandins, several different reaction products of the complement system, reaction products of the blood clotting system, and multiple substances called lymphokines that are released by sensitized T cells. Several of these substances strongly activate the macrophage system, and within a few hours, the macrophages begin to devour the destroyed tissues. But at times, the macrophages also further injure the still-living tissue cells.

The Leukemias

Uncontrolled production of white blood cells can be caused by cancerous mutation of a myelogenous or lymphogenous cell. This causes leukemia, which is usually characterized by greatly increased numbers of abnormal white blood cells in the circulating blood.

Types of Leukemia.

Leukemias are divided into two general types:

1- lymphocytic leukemias: The lymphocytic leukemias are caused by cancerous production of lymphoid cells, usually beginning in a lymph node or other lymphocytic tissue and spreading to other areas of the body.

2- myelogenous leukemias:The myelogenous leukemia, begins by cancerous production of young myelogenous cells in the bone marrow and then spreads throughout the body so that white blood cells are produced in many extramedullary tissues—especially in the lymph nodes, spleen, and liver.

In myelogenous leukemia, the cancerous process occasionally produces partially differentiated cells, resulting in what might be called neutrophilic leukemia, eosinophilic leukemia, basophilic leukemia, or monocytic leukemia. More frequently, however, the leukemia cells are bizarre and undifferentiated and not identical to any of the normal white blood cells. Usually, the more undifferentiated the cell, the more acute is the leukemia, often leading to death within a few months if untreated. With some of the more differentiated cells, the process can be chronic, sometimes developing slowly over 10 to 20 years. Leukemic cells, especially the very undifferentiated cells, are usually nonfunctional for providing the normal protection against infection

Leukopenia or Agranulocytosis: A clinical condition known as leukopenia occurs in which the bone marrow stops producing W.B.C.

leaving the body unprotected against bacteria and other agents that might invade 7 the tissues. Without treatment, death often is less than a week after acute total leukopenia begins. This result from different cases:
1. Irradiation of the body by gamma rays caused by a nuclear explosion.
2. Exposure to drugs and chemical that contain benzene or other is likely to cause aplasia of the bone marrow.

Immunity
Ability to resist microorganisms or toxins

A- Nonspecific (innate)
Rapid
No special recognition
No previous exposure

1- Mechanical and chemical barriers
a. Epithelial covering of skin, GIT, respiratory tract.
b. Mucous secretion of respiratory tract.
c. Acid secretion of stomach and vagina.

2- Nonspecific cellular mechanisms
a. Microphages neutrophil and eosinophils
b. Macrophages monocytes macrophage
c. Natural killer cells (NK cells) …large cell, non B.cell , non T.cell , destroy malignant cells.
Virus infected cells. first line of defense
Activated α interferons, Interlukine-2, Antigen -Antibody reaction.

3- Non specific humoral mechanisms
a. Lysosomes Mucopolysacrides dissolve bacteria
b. B. Interferons p realeased by virus infected cell
α, β, δ, IFN

Functions
1.Interfere (inhibit)virus replication by other cells
2.α IFN has activity of NK cells
3.β IFN has antiviral effects
4.δ IFN has activity of macrophage
c. Properdin proteins system
Activated complement (Alternative system)

d. Acute phase protein Ant inflammatory proteins
e.g C. reactive proteins
Formed by liver in acute inflammation.
complement system: 30 plasma proteins enzymes
-These enzymes are activated in a cascade sequence
-They complete effect of antibodies and Lymphocyte
-It is activated in 2 ways
1-Classical Pathway Antigen Antibody reaction
2-Alternative pathway properdin system.

Result of complement activation

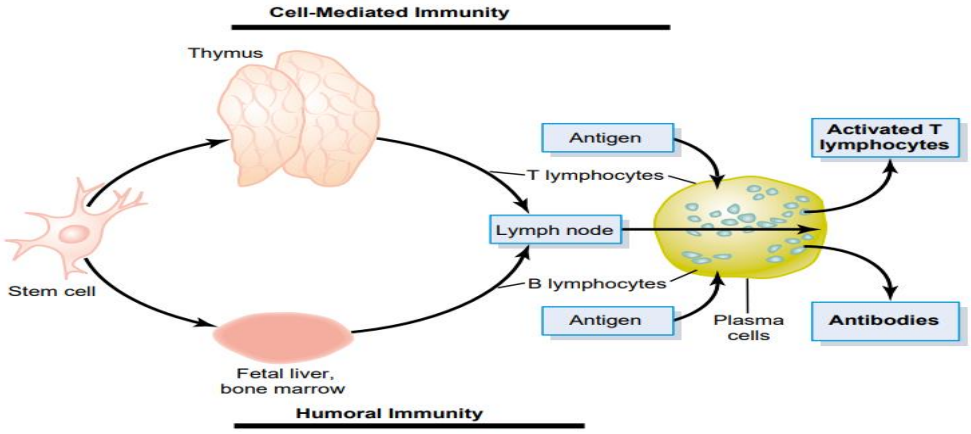
1- Agglutination: invading organisms adhere to each other
2- Neutralization: Toxic sites of virus
3- Insertion of perforin (pore forming molecules) in cell wall
4- Chemotaxis attraction of WBCs
5- Opsonization : stimulation of phagocytosis
6- Formation of fragment that release histamine vasodilation capillary permeability.

Specific (aquired) immunity
Different from nonspecific (innate)immunity

1- Specificity must recognize antigen.
2- Discriminate self and non self
3- Memory cell second exposure faster and stronger.

Two types via 2 types of small lymphocytes

Humoral immunity	Cell mediated immunity
Antibody by B lymphocyte	Lymphocyte (activated lymphocyte)
Against bacteria	TB, virus and fungus.
IgE causes allergy	Tumor (cancer cells).
	Delayed allergic reaction.

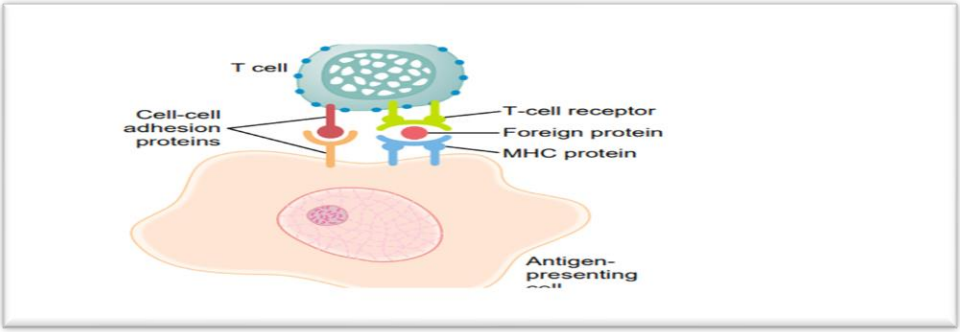


Formation of antibodies and sensitized lymphocytes by a lymph node in response to antigens. This figure also shows the origin of thymic (T) and bursal (B) lymphocytes that respectively are responsible for the cell-mediated and humoral immune processes

Antigen
1-stimulation specific (acquired) immunity -immune response
2-Forergner
3-High molecular weight protein or polysaccharides
4-Determinate group
5-Usually attached to cell membrane except best toxins.

Hapten Antigen at low molecular weight +body proteins – immune response e.g. antibiotics like penicillin.

Antigen presentation
Antigen is phagocytosed by antigen presenting cells APCS. then partially digested to expose determinate group. APC are macrophages, B-lymphocytes, dendritic cells in lymph nodes and spleen.



Specific (aquired) immunity includes 4 steps

1- Development (processing)
   Time: Fetal and early neonatal life
   Location: Lymphocytic committed stem cells in bone marrow migrate to be processed in
   a. Thymus: In case T. lymphocytes
   b. Bursa (in birds) or Bursa equivalent
      Bone marrow in case of B. lymphocyte

Mechanism: After processing B and T lymphocytes will have specific antigen.

Recognition of antigens
a. B lymphocyte direct binding of their receptor antigen
b. T lymphocyte indirect by help of APCS
Differentiation
B lymphocyte enlarge, proliferate and differentiate into
1.Plasma cells: they have well developed rough reticulum which produce antibodies Ig MAGED at rapid rate
2.Memory cells: Strong and rapid response on second exposure to same antigen (secondary response).

T lymphocyte differentiate into
1.Memory cells
2. CD4 T cell (T help) Th
3. CD8 T cells (cytotoxic cell) Tc
4. Suppresser T cell

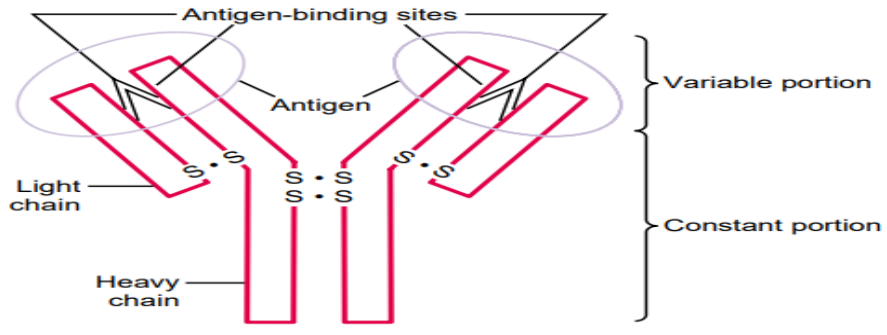
CYTOKINES

Cytokines are the hormone like small proteins acting as intercellular messengers (cell signaling molecules) by binding to specific receptors of target cells. These non-antibody proteins are secreted by WBCs and some other types of cells. Their major function is the activation and regulation of general immune system of the body.
Cytokines are distinct from the other cell signaling molecules such as growth factors and hormones. Cytokines are classified into several types:
1. Interleukins
2. Interferons

3. Tumor necrosis factors
4. Chemokines
5. Defensins
6. Cathelicidins
7. Platelet activating factor

Nature of the Antibodies

The antibodies are gamma globulins called immunoglobulins (abbreviated as Ig), and they have molecular weights between 160,000 and 970,000. They usually constitute about 20 per cent of all the plasma proteins. All the immunoglobulins are composed of combinations of light and heavy polypeptide chains. Most are a combination of two light and two heavy chains. However, some of the immunoglobulins have combinations of as many as 10 heavy and 10 light chains, which gives rise to high-molecular-weight immunoglobulins. Yet, in all immunoglobulins, each heavy chain is paralleled by a light chain at one of its ends, thus forming a heavy-light pair, and there are always at least 2 and as many as 10 such pairs in each immunoglobulin molecule. The circled area a designated end of each light and heavy chain, called the variable portion; the remainder of each chain is called the constant portion. The variable portion is different for each specificity of antibody, and it is this portion that attaches specifically to a particular type of antigen. The constant portion of the antibody determines other properties of the antibody, establishing such factors as diffusivity of the antibody in the tissues, adherence of the antibody to specific structures within the tissues, attachment to the complement complex, the ease with which the antibodies pass through membranes, and other biological properties of the antibody.



Structure of the typical IgG antibody, showing it to be composed of two heavy polypeptide chains and two light polypeptide chains. The antigen binds at two different sites on the variable portions of the chains.

ACQUIRED IMMUNE DEFICIENCY DISEASES

Acquired immune deficiency diseases occur due to infection by some organisms. The most common disease of this type is acquired immune deficiency syndrome (AIDS).
Acquired Immune Deficiency Syndrome (AIDS)

It is an infectious disease caused by immune deficiency virus (HIV). AIDS is the most common problem throughout the world because of rapid increase in the number of victims. Infection occurs when a glycoprotein from HIV binds to surface receptors of T lymphocytes, monocytes, macrophages and dendritic cells leading to destruction of these cells. It causes slow progressive decrease in immune function resulting in opportunistic infections of various types. The common opportunistic infections, which kill the AIDS patient, are pneumonia and skin cancer.

AUTOIMMUNE DISEASES

Autoimmune disease is defined as condition in which the immune system mistakenly attacks body's own cells and tissues. Normally, an antigen induces the immune response in the body. The condition in which the immune system fails to give response to an antigen is called tolerance. This is true with respect to body's own antigens that are called self antigens or autoantigens. Normally, body has the tolerance against self antigen. However, in some occasions, the tolerance fails or becomes incomplete against self antigen. This state is called autoimmunity and it leads to the activation of T lymphocytes or production of autoantibodies from B lymphocytes. The T lymphocytes (cytotoxic T cells) or autoantibodies attack the body's normal cells whose surface contains the self antigen or autoantigen.

Common Autoimmune Diseases
1. Diabetes mellitus
2. Myasthenia gravis
3. Hashimoto's thyroiditis
4. Graves' disease
5. Rheumatoid arthritis.