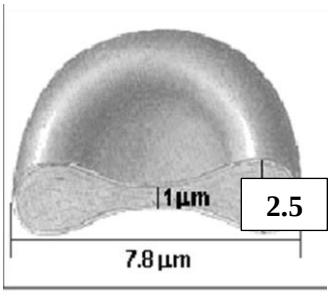
BLOOD PHYSIOLOGY

BLOOD: is a fluid that transports oxygen and nutrients to the cells and carries away carbon dioxide and other waste products. Blood is a connective tissue. Blood is composed of plasma and three types of cells: red blood cells, white blood cells and platelets.

PLASMA: it is the liquid portion of the blood. It is a complex solution containing more than 90% water. Blood cells are suspended in plasma. Electrolytes, proteins such as albumin, globulins and clotting factors, lipids, and lipoproteins are found in plasma. Plasma acts as a vehicle for nutrient transport and the immune system and plays a key role in coagulation and hemostasis. Plasma is clear, slightly sticky, yellowish liquid.

RED BLOOD CELLS (ERYTHROCYTES): RBCs contain no nucleus or other organelles, but they are enriched with hemoglobin (Hb).



Shape: Normal RBCs are thin biconcave discs having a mean diameter of about 7.8 micrometers and a thickness of 2.5 micrometers at the thickest point and 1 micrometer or less in the center. The shapes of RBCs can change remarkably as the cells squeeze through capillaries.
Actually, the RBC resembles a bag that can be deformed into almost any shape.

Functions:

1. A major function of RBCs is to transport hemoglobin, which, in turn, carries oxygen from the lungs to the tissues.
2. They contain a large quantity of *carbonic anhydrase*, an enzyme that catalyzes the reversible reaction between carbon dioxide (CO_2) and water to form carbonic acid (H_2CO_3), increasing the rate of this reaction several thousand fold. The rapidity of this reaction makes it possible for the water of the blood to transport enormous quantities of CO_2 in the form of bicarbonate ion (HCO_3^-) from the tissues to the lungs, where it is reconverted to CO_2 and expelled into the atmosphere as a body waste product.
3. The hemoglobin in the cells is an excellent *acid-base buffer* (as is true of most proteins), so the RBCs are responsible for most of the acid-base buffering power of whole blood.

Production RBCs:

- In the early weeks of embryonic life primitive nucleated RBCs are produced in the *yolk sac*.
- During the middle trimester of gestation, the *liver* is the main organ for RBC production but reasonable numbers are also produced in the *spleen* and *lymph nodes*.
- Then, during the last month or so of gestation and after birth, the bone marrow is the main site of erythrogenesis. During early years all bones are filled up with blood forming red marrow, but by the age of 20 years almost all the long bones are replaced with inactive yellow marrow and RBC formation in this location stops. Only the upper ends of femur and

humerus contain red marrow and continue to form red cells throughout life. In addition to this, the vertebrae, the ribs and the flat bones produce red cells continuously.

RBC production takes about a week. The single most important influence is hypoxia, which stimulates RBC production through hypoxia-inducible factor 1 (HIF-1) activation and release of erythropoietin (EPO) from the kidney. Erythropoietin stimulates the bone marrow and increases the rate and maturation of RBCs formation.
The production of all blood cells begins with:

1. A multipotent hematopoietic stem cell found in the bone marrow → differentiate into

2. proerythroblasts → differentiate into

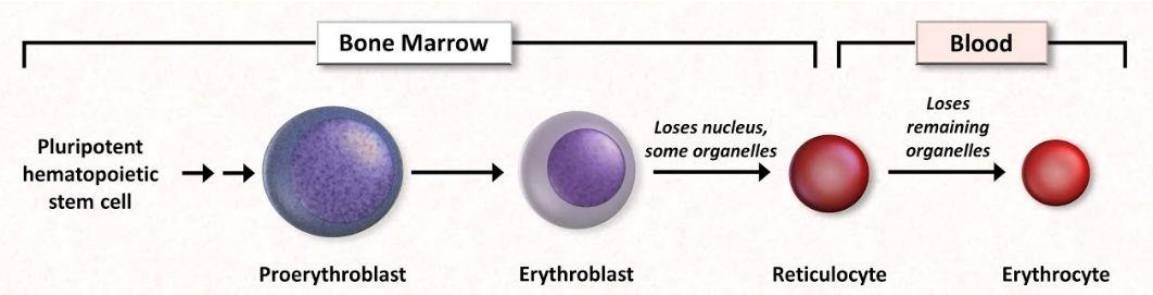
3. erythroblasts →

4. immature RBC begin synthesizing and storing Hb→ differentiate into

5. reticulocyte and eject organelles and nucleus→

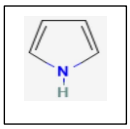
6. mature into erythrocyte and

7. enter circulation by diapedesis (squeezing through the pores of the capillary membrane).

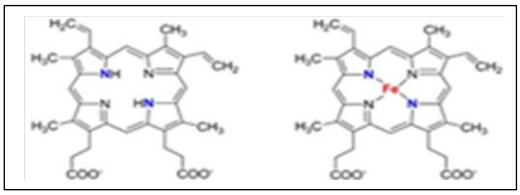


Hemoglobin Formation:

1. Succinyl-CoA (from Krebs cycle in the mitochondria) binds with glycine to form a pyrrole molecule.



2. Four pyrroles combine to form protoporphyrin IX.
3. The protoporphyrin IX combines with iron to form the heme molecule.



4. Finally, each heme molecule combines with a long polypeptide chain called globin (which is synthesized by ribosomes) forming a subunit of Hb called hemoglobin chain.
5. Four of these chains, in turn, bind together loosely to form the whole Hb molecule.

There are different types of hemoglobin chains, depending on the amino acid composition of the polypeptide portion. The different types of chains are designated as:

- ✓ alpha (α) chains,
- ✓ beta (β)chains,
- ✓ gamma (γ) chains,
- ✓ delta (δ) chains.

Types of Hb (in normal conditions):

1. Hemoglobin A (HbA) also known as adult hemoglobin or HbA1: it is the most common form of hemoglobin in adults (97%). It is a combination of two alpha chains and two beta chains.
2. Hemoglobin A2: presents in normal adults but in small amounts(2.5%). It is composed of two alpha chains and two delta chains.
3. Fetal hemoglobin (HbF): it is dominant during fetal life. its production ceases in the period just after the child is born. It is composed of two alpha and two gamma chains.

Destruction of RBCs:

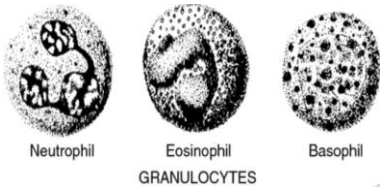
When RBCs are delivered from the bone marrow into the circulatory system, they normally circulate an average of 120 days before being destroyed. Once the RBC membrane becomes fragile, the cell ruptures during passage through some tight spot of the circulation. Many of the RBCs self-destruct in the spleen. When RBCs burst and release their hemoglobin, the hemoglobin is phagocytized almost immediately by macrophages in many parts of the body, but especially by the Kupffer cells of the liver and macrophages of the spleen and bone marrow. During the next few hours to days, the macrophages release iron from the hemoglobin and pass it back into the blood to be carried by transferrin either to the bone marrow for production of new RBCs or to the liver and other tissues for storage in the form of ferritin. The porphyrin portion of the hemoglobin molecule is converted by the macrophages, through a series of stages, into the bile pigment *bilirubin,* which is released into the blood and later removed from the body by secretion through the liver into the bile.

LEUKOCYTES (WHITE BLOOD CELLS)

The leukocytes, also called white blood cells or WBCs, are the mobile units of the body's protective system.

Types and Functions of WBCs:

Granulocytes:



1. Neutrophils: are most numerous of the granulocytes, making up 50-80 % of all WBCs. They are often one of the first cell types to arrive at a site of infection, where they engulf and destroy the infectious microorganisms through a process called phagocytosis.

2. Basophils: accounts for less than 1% of WBCs. The granules of basophils contain a number of chemicals, including histamine and leukotrienes, that are important in inducing allergic inflammatory responses.
3. Eosinophils: destroy parasites and also help to modulate inflammatory responses.

Monocytes: constitute 4-8% of the total number of white blood cells in the blood, move from the blood to sites of infection, where they differentiate further into macrophages. These are present when the body fights off chronic infections. These cells are scavengers that phagocytose whole or killed microorganisms and are therefore effective at direct destruction of pathogens and cleanup of cellular debris from sites of infection. Neutrophils and macrophages are the main phagocytic cells of the body, but macrophages are much larger and longer-lived than neutrophils. Some macrophages are important as antigen-presenting cells, cells that phagocytose and degrade microbes and present portions of these organisms to T lymphocytes, thereby activating the specific acquired immune response.

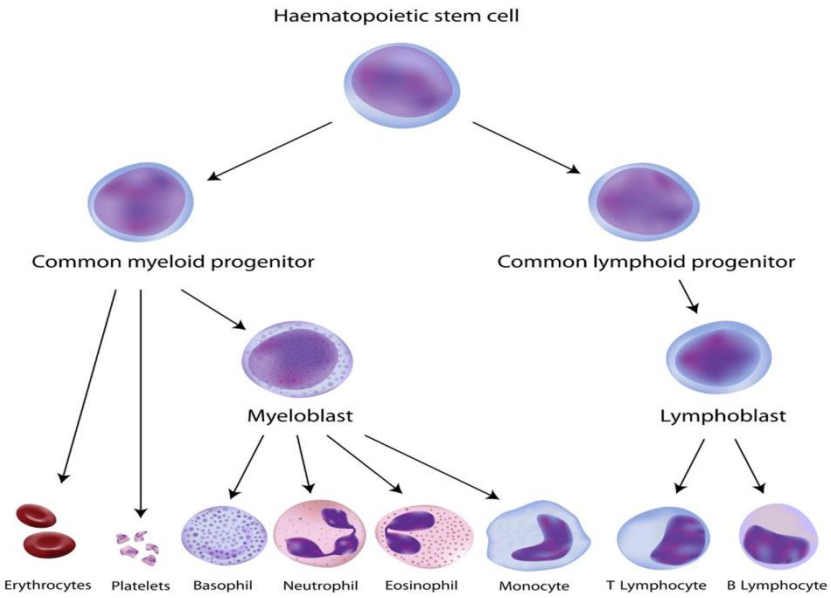
Lymphocytes: 25-33 % of all WBCs are lymphocytes. These include

- B cells: Also known as B-lymphocytes, these cells produce antibodies to help the immune system mount a response to infection.
- T cells: Also known as T-lymphocytes, these white blood cells help recognize and remove infection-causing cells.
- Natural killer cells: These cells are responsible for attacking and killing viral cells, as well as cancer cell

Genesis of WBCs:

Two major lineages of WBCs are formed,

- *Myelocytic lineage*, begins with the *myeloblast:* The granulocytes and monocytes are formed only in the bone marrow. The WBCs formed in the bone marrow are stored in the marrow until they are needed in the circulatory system. Then, when the need arises, various factors cause them to be released.
- *Lymphocytic lineage*, begins with the *lymphoblast*: 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 *Peyer's patches* underneath the epithelium in the gut wall.
  The lymphocytes are mostly stored in the various lymphoid tissues, except for a small number that are temporarily being transported in the blood.



Life Span of WBCs:

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.

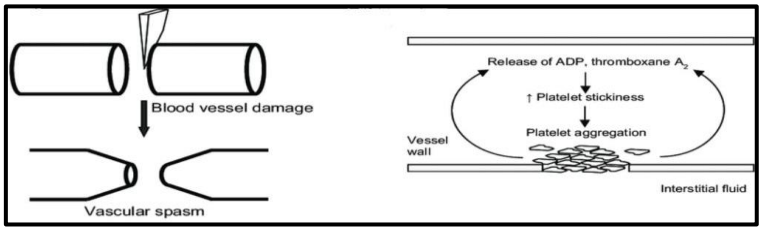
The monocytes also have a short transit time, 10 to 20 hours in the blood, before wandering through the capillary membranes into the tissues where they swell to much larger sizes to become tissue macrophages and, in this form, they can live for months unless destroyed while performing phagocytic functions. These tissue macrophages are the basis of the tissue macrophage system which provides continuing defense against infection.

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/extravasation. Then, they re-enter the lymph and return to the blood again and again; thus, there is continual circulation of lymphocytes through the body. Lymphocytes have life spans of weeks or months, depending on the body's need for these cells.

PLATELETS (*THROMBOCYTES*) : Platelets are non-nucleated round or oval, biconvex discs 1 to 4 micrometers in diameter . They are very important in the initiation of blood clotting. They are formed by fragmentation of megakaryocytes (giant cells in the bone marrow). The life span of platelets is about 10 days. They are destroyed in the spleen and other reticulo-endothelial macrophages.

HEMOSTASIS EVENTS

The term *hemostasis* means prevention of blood loss. Whenever a vessel is severed or ruptured, hemostasis is achieved by several mechanisms:



1. **Vascular Constriction:** Immediately after a blood vessel has been cut or ruptured, the trauma to the vessel wall causes smooth muscle in the wall to contract; this instantaneously reduces the flow of blood from the ruptured vessel.
2. **Formation of a platelet plug:** If the cut in the blood vessel is very small, the cut is often sealed by a *platelet plug* rather than by a blood clot. Endothelial injury and exposure of the vascular extracellular matrix facilitates platelet adhesions and activation, which changes their shape (begin to swell and assume irregular forms) and causes release of adenosine diphosphate (ADP), thromboxane A2 (TXA2), and platelet-activating factor (PAF). These platelet-secreted factors recruit additional platelets (aggregation) to form a hemostatic plug. Von Willebrand factor (vWF) serves as an adhesion bridge between subendothelial collagen and the glycoprotein Ib (GpIb) platelet receptor. This plug is loose at first but is usually successful in blocking blood loss if the vascular opening is small. Then, during the subsequent process of blood coagulation, fibrin threads form. These threads attach tightly to the platelets, thus constructing an unyielding plug.
3. **Formation of a blood clot as a result of blood coagulation:** The clot begins to develop in 15 to 20 seconds if the trauma to the vascular wall is severe and in 1 to 2 minutes if the trauma is minor. Activator substances from the traumatized vascular wall, from platelets, and from blood proteins adhering to the traumatized vascular wall initiate the clotting process. Within 3 to 6 minutes after rupture of a vessel, the entire opening or broken end of the vessel is filled with clot if the vessel opening is not too large. After 20 to 60 minutes, the clot retracts. As the clot retracts, the edges of the broken blood vessel are pulled together, thus contributing still further to hemostasis.
4. **Fibrous organization or dissolution of blood clots:** Once a blood clot has formed, it can follow one of two courses:

   (1) it can become invaded by fibroblasts, which subsequently form connective tissue all through the clot; or

   (2) it can dissolve.

   The usual course for a clot that forms in a small hole of a vessel wall is invasion by fibroblasts, beginning within a few hours after the clot is formed, which is promoted at least partially by *growth factor* secreted by platelets. This process continues to complete organization of the clot into fibrous tissue within about 1 to 2 weeks.

   Conversely, when excess blood has leaked into the tissues, and tissue clots have formed where they are not needed, special substances in the clot usually become activated. These substances function as enzymes to dissolve the clot .