Blood physiology

Blood: is a connective tissue in fluid form. It is considered as the fluid of life because it carries oxygen from lungs to all parts of the body and carbon dioxide from all parts of the body to the lungs.

PROPERTIES OF BLOOD

1. Color: Blood is red in color. Arterial blood is scarlet red because of more O2 and venous blood is purple red because of more CO2.

2. Volume: The average volume of blood in a normal adult is 5 L. In newborn baby it is 450 ml. It increases during growth and reaches 5 L at the time of puberty. In females, it is slightly less and is about 4.5 L. It is about 8% of the body weight in a normal young healthy adult weighing about 70 kg.

3. Reaction and pH: Blood is slightly alkaline and its pH in normal conditions is 7.4.

4. Viscosity: Blood is five times more viscous than water. It is mainly due to red blood cells and plasma protein

Blood is made of two parts:
1-Plasma which makes up 55% of blood volume
2-Formed cellular elements (red and white blood cells, and platelets) which combine to make the remaining 45% of blood volume.

Functions of the blood include:

1. Nutrient Function
Nutritive substances like glucose, amino acids, lipids and vitamins derived from digested food are absorbed from gastrointestinal tract and carried by blood to different parts of the body for growth and production of energy.

2. Respiratory Function
Transport of respiratory gases is done by the blood. It carries O2 from alveoli of lungs to different tissues and CO2 from tissues to alveoli.

3. Excretory Function
Waste products formed in the tissues during various metabolic activities are removed by blood and carried to the excretory organs like kidney, skin, liver, etc. for excretion.

4. Transport of Hormones and Enzymes
Hormones which are secreted by ductless (endocrine) glands are released directly into the blood. The blood transports these hormones to their target organs/tissues. Blood also transports enzymes.

5. Regulation of Acid-base Balance the plasma proteins and hemoglobin act as buffers and help in regulation of acid-base balance.

6. Regulation of Body Temperature Because of the high specific heat of blood, it is responsible for maintaining the thermoregulatory mechanism in the body, i.e. the balance between heat loss and heat gain in the body.

7. Storage Function
Water and some important substances like proteins, glucose, sodium and potassium are constantly required by the tissues. All these substances are present in the blood are taken by the tissues during the conditions like starvation, fluid loss, electrolyte loss, etc.

8. Defensive Function
The WBCs in the blood provide the defense mechanism and protect the body from the invading organisms. Neutrophils and monocytes engulf the bacteria by phagocytosis. Lymphocytes provide cellular and humoral immunity. Eosinophils protect the body by detoxification, disintegration and removal of foreign proteins.

Plasma

Plasma is a straw-colored clear liquid part of blood. It contains 91 to 92% of water and 8 to 9% of solids. The solids are the organic and inorganic substances.

Serum

Serum is the clear straw-colored fluid that oozes out from the clot. When the blood is shed or collected in a container, it clots because of the conversion of fibrinogen into fibrin. After about 45 minutes, serum oozes out of the clot. For clinical investigations, serum is separated from blood cells by centrifuging. Volume of the serum is almost the same as that of plasma (55%). It is different from plasma only by the absence of fibrinogen, i.e., serum contains all the other constituents of plasma except fibrinogen. Fibrinogen is absent in serum because it is converted into fibrin during blood clotting. Thus, the Serum = Plasma – Fibrinogen.

PLASMA PROTEINS

The plasma proteins are:
1. Serum albumin
2. Serum globulin
3. Fibrinogen.

Globulin is of three types,
A-globulin,
β-globulin and
γ-globulin.

NORMAL VALUES
The normal values of the plasma proteins are:
Total proteins: 7.3 g/dL (6.4-8.3 g/dL)
Serum albumin: 4.7 g/dL
Serum globulin: 2.3 g/dL
Fibrinogen: 0.3 g/d
Albumin/globulin Ratio
The ratio between plasma level of albumin and globulin is called Albumin/Globulin (A/G) ratio. It is an important indicator of some liver and kidney diseases. Normal A/G ratio is 2:1.

ORIGIN OF PLASMA PROTEINS

In embryonic stage, the plasma proteins are synthesized by the mesenchyme cells. In adult s, the plasma proteins are synthesized mainly from reticuloendothelial cells of liver and also from spleen, bone marrow, disintegrating blood cells and general tissue cells. Gamma globulin is synthesized from B lymphocytes.

FUNCTIONS OF PLASMA PROTEINS

1. Role in Coagulation of Blood Fibrinogen is essential for the coagulation of Blood.
2. Role in Defense Mechanism of Body the gamma globulins play an important role in the defense mechanism of the body by acting as antibodies. These proteins are also called immunoglobulins.
3. Role in Transport Mechanism: Plasma proteins are essential for the transport of various substances in the blood. Albumin, alpha globulin and beta globulin are responsible for the transport of the hormones, enzymes, etc.

The alpha and beta globulins transport metals in the blood.

4. Role in Maintenance of Osmotic: Pressure in Blood Plasma proteins exert the colloidal osmotic (oncotic) pressure.

5. Role in Regulation of Acid-base Balance: Plasma proteins, particularly the albumin, play an important role in regulating the acid-base balance in the blood. This is because of the virtue of their buffering action.

6. Role in Viscosity of Blood: The plasma proteins provide viscosity to the blood, which is important to maintain the blood pressure. Albumin provides maximum viscosity than the other plasma proteins.

7. Role in Erythrocyte Sedimentation Rate (ESR): Globulin and fibrinogen accelerate the tendency of rouleaux formation by the red blood cells. Rouleaux formation is responsible for ESR, which is an important diagnostic and prognostic too.

8. Role as Reserve Proteins
During fasting, inadequate food intake or inadequate protein intake, the plasma proteins are utilized by the body tissues as the last source of energy. The plasma proteins are split into amino acids by the tissue macrophages. The amino acids are taken back by blood and distributed throughout the body to form cellular protein molecules. Because of this, the plasma proteins are called the reserve proteins.

Red blood cells (RBCs)

Red blood cells (RBCs), also known as erythrocytes are the non-nucleated formed elements in the blood. The red color of the RBC is due to the presence of hemoglobin.

NORMAL VALUE

The RBC count ranges between 4 and 5.5 millions/cu mm of blood. In adult males, it is 5 millions/cu mm and in adult females it is 4.5 millions/cu mm.

MORPHOLOGY OF RED BLOOD CELLS

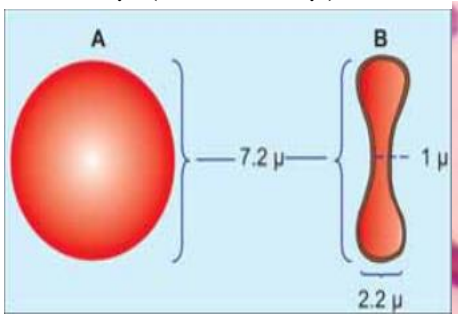
NORMAL SHAPE
Normally, the RBCs are disk-shaped and biconcave (dumbbell-shaped). The central portion is thinner and periphery is thicker. The biconcave contour of RBCs has some mechanical and functional advantages.

Advantages of Biconcave Shape of RBCs

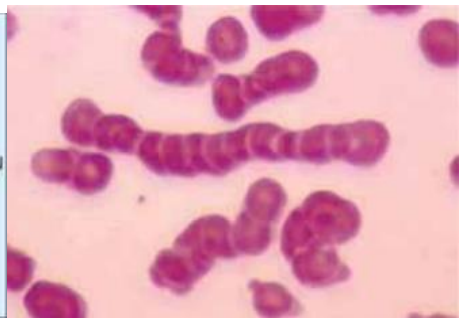
1. It helps in equal and rapid diffusion of oxygen and other substances into the interior of the cell.
2. Large surface area is provided for absorption or removal of different substances.
3. While passing through minute capillaries, RBCs can squeeze through the capillaries easily without getting damaged.

NORMAL SIZE

Diameter: 7.2 μ (6.9 to 7.4 μ).



Dimensions of RBC. A: Surface view. B. Sectioned view



Rouleaux formation

FUNCTIONS OF RED BLOOD CELLS

1. Transport of O2 from the Lungs to the tissues Hemoglobin combines with oxygen to form oxyhemoglobin.
2. Transport CO2 from the Tissues to the Lungs Hemoglobin combines with carbon dioxide and form carbhemoglobin.
3. Buffering Action in Blood: Hemoglobin functions as a good buffer. By this action, it regulates the hydrogen ion concentration and thereby plays a role in the maintenance of acid-base balance.
4. In Blood Group Determination: RBCs carry the blood group antigens like A antigen, B antigen and Rh factor. This helps in determination of blood group and enables to prevent the reactions due to incompatible blood transfusion.

Erythropoiesis

Erythropoiesis is the process of the origin, development and maturation of erythrocytes.

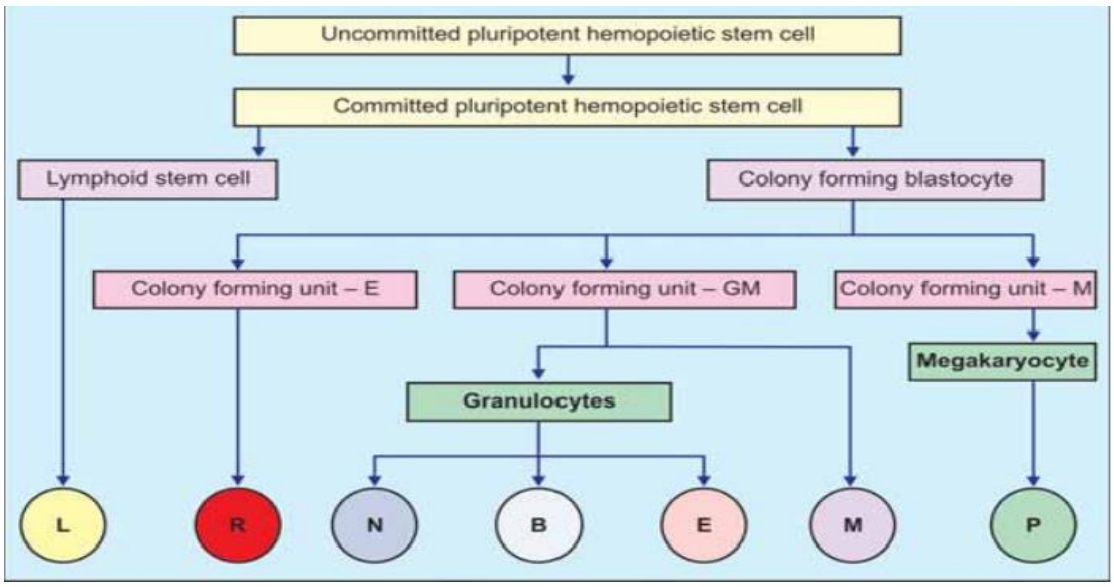
Hemopoiesis is the process of origin, development and maturation of all the blood cells.

SITE OF ERYTHROPOIESIS

IN FETAL LIFE
In fetal life, the erythropoiesis occurs in different sites in different periods:

Fetus 0-2 months (yolk sac)
2-7 months (liver, spleen)
5-9 months (bone marrow)

Infants bone marrow (practically all bones)



Stem cells. L – Lymphocyte, R – Red blood cells, N – Neutrophil, B – Basophil, E – Eosinophil, M – Monocyte, P – Platelets

PROCESS OF ERYTHROPOIESIS

STEM CELLS
RBCs develop from the hemopoietic stem cells in the bone marrow. These cells are called uncommitted pluripotent hemopoietic stem cells (PHSC). PHSC are not designed to form a particular type of blood cell; hence the name uncommitted PHSC. When the cells are designed to form a particular type of blood cell, the uncommitted PHSCs are called committed.

The committed PHSCs are of two types:

1. Lymphoid stem cells (LSC) which give rise to lymphocytes and natural killer (NK) cell

2. Colony forming blastocytes, which give rise to all the other blood cells except lympho-cytes. When grown in cultures, these cells form colonies hence the name colony forming blastocytes.

The different units of colony forming cells are:

i. Colony forming Unit – Erythrocytes (CFU-E) from which RBCs develop.

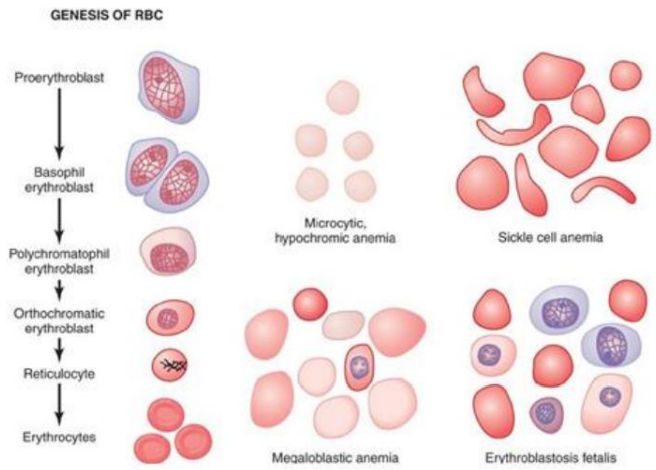
ii. Colony forming Unit – Granulocytes/Monocytes (CFU-GM) from which granulocytes (neutrophils, basophils and eosinophils) and monocytes develop.

iii. Colony forming Unit – Megakaryocytes (CFU-M) from which platelets develop.

Genesis of RBC

The first cell that can be identified as belonging to the red blood cell series is the proerythroblast,

under appropriate stimulation, large numbers of these cells are formed from the CFU-E stem cells. Once the proerythroblast has been formed, it divides multiple times, eventually forming many mature red blood cells. The first-generation cells are called basophil erythroblasts because they stain with basic dyes; the cell at this time has accumulated very little hemoglobin. In the succeeding generations, the cells become filled with hemoglobin to a concentration of about 34 per cent, the nucleus condenses to a small size, and its final remnant is absorbed or extruded from the cell. At the same time, the endoplasmic reticulum is also reabsorbed. The cell at this stage is called a reticulocyte because it still contains a small amount of basophilic material, consisting of remnants of the Golgi apparatus, mitochondria, and a few other cytoplasmic organelles. During this reticulocyte stage, the cells pass from the bone marrow into the blood capillaries by diapedesis (squeezing through the pores of the capillary membrane). The remaining basophilic material in the reticulocyte normally disappears within 1 to 2 days, and the cell is then a mature erythrocyte. Because of the short life of the reticulocytes, their concentration among all the red cells of the blood is normally slightly less than 1 per cent.



Genesis of normal red blood cells (RBCs) and characteristics of RBCs in different types of anemias.

FACTORS NECESSARY FOR ERYTHROPOIESIS

Development and maturation of erythrocytes require many factors which are classified into 3 categories:

I. General factors

II. Maturation factors

III. Factors necessary for hemoglobin formation.

GENERAL FACTORS

1. Erythropoietin

Erythropoietin is a hormone secreted mainly by peritubular capillaries in the kidney and a small quantity is also secreted from the liver and the brain. Hypoxia is the stimulant for the secretion of erythropoietin.

Erythropoietin promotes the following processes:

i. Production of proerythroblasts from CFU-E of the bone marrow.

ii. Development of proerythroblasts into matured RBCs through the several stages

iii. Release of matured erythrocytes into blood. Some reticulocytes are also released along with matured RBCs.

2. Thyroxine
Being a general metabolic hormone, thyroxine accelerates the process of erythropoiesis at many levels.
3. Hemopoietic Growth Factors Hemopoietic growth factors or growth inducers are the interleukins – 3, 6 and 11 and stem cell factor (steel factor). Generally, these factors induce the proliferation of PHSCs.
4. Vitamins
The vitamins A, B, C, D and E are necessary for erythropoiesis. Deficiency of these vitamins causes anemia.

MATURATION FACTORS

Vitamin B12, intrinsic factor and folic acid are necessary for the maturation of RBCs.
1. Vitamin B12 (Cyanocobalamin). Vitamin B12 is essential for synthesis of DNA, cell division and maturation in RBCs. It is also called extrinsic factor as it is obtained mostly from diet. It is also produced in the large intestine by the intestinal flora. It is absorbed from the small intestine in the presence of intrinsic factor of Castle. Vitamin B12
is stored mostly in liver and in small quantity in muscle. Its deficiency causes pernicious anemia (macrocyticanemia) in which the cells remain larger with fragile and weak cell membrane.

2. Intrinsic Factor of Castle
It is produced in gastric mucosa by the parietal cells of the gastric glands. It is essential for the absorption of vitamin B12 from intestine. Absence of intrinsic factor also leads to pernicious anemia because of failure of vitamin B12 absorption. The deficiency of intrinsic factor occurs in conditions like severe gastritis, ulcer and gastrectomy.

3. Folic Acid
Folic acid is also essential for the synthesis of DNA. Deficiency of folic acid decreases the DNA synthesis causing maturation failure. Here the cells are larger and remain in megaloblastic (proerythroblastic) stage which leads to
megaloblastic anemia.

FACTORS NECESSARY FOR HEMOGLOBIN FORMATION

Various materials are essential for the formation of hemoglobin in the RBCs such as:

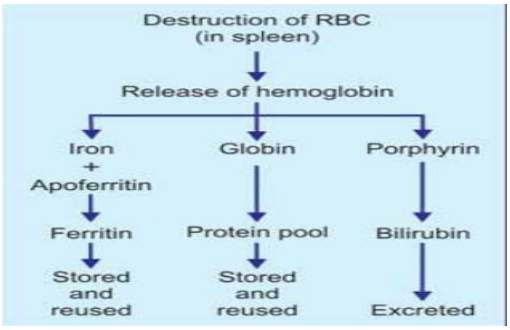
1.First class proteins and amino acids of high biological value — for the formation of globin.
2.Iron — for the formation of heme part of the hemoglobin.
3.Copper — for the absorption of iron from GI tract.
4.Cobalt and nickel — for the utilization of iron during hemoglobin synthesis.
5.Vitamins: Vitamin C, riboflavin, nicotinic acid and pyridoxine — for hemoglobin synthesis.

LIFE SPAN OF RED BLOOD CELLS

Average lifespan of RBC is about 120 days. After the lifetime, the senile (old) RBCs are destroyed in reticuloendothelial system.

FATE OF RED BLOOD CELLS

When the RBCs become older (120 days), the cell membrane becomes very fragile. So, these cells are destroyed while trying to squeeze through the capillaries which have lesser or equal diameter as that of RBC. The destruction occurs mainly in the capillaries of spleen because these capillaries are very much narrow. So, the spleen is called graveyard of RBCs. The destroyed RBCs are fragmented and hemoglobin is released from the fragmented parts. Hemoglobin is degraded into iron, globin and porphyrin. Iron combines with the protein called apoferritin to form ferritin, which is stored in the body and reused later. Globin enters the protein depot for later use .The porphyrin is degraded into bilirubin which is excreted by liver through bile. Daily 10% of senile RBCs are destroyed in normal young healthy adults. It causes release of about 0.6 g/dL of hemoglobin into the plasma.
From this 0.9 to 1.5 mg/dL bilirubin is formed.



Fate of RBC

PROPERTIES OF RED BLOOD CELLS

1. ROULEAUX FORMATION
When blood is taken out of the blood vessel, the RBCs pile up one above another like the pile of coins.
This property of the RBCs is called rouleaux (pleural = rouleau) formation. It is accelerated by plasma proteins, namely globulin and fibrinogen.

2. SPECIFIC GRAVITY
The specific gravity of RBC is 1.092 to 1.101.

3. PACKED CELL VOLUME
Packed cell volume (PCV) is the volume of the RBSc expressed in percent age. It is also called hematocrit value. It is 45% of the blood and the plasma volume is 55% .

4. SUSPENSION STABILITY: During circulation, the RBCs remain suspended or dispersed uniformly in the blood. This property of the RBCs is called the suspension stability.

VARIATIONS IN NUMBER OF RED BLOOD CELLS

PHYSIOLOGICAL VARIATIONS

A-Increase in RBC Count — Polycythemia:
Increase in the RBC count is known as polycythemia. It occurs in both physiological and pathological conditions. When it occurs in physiological conditions it is called physiological polycythemia. The increase in number during this condition is marginal and temporary. It occurs in the following conditions:

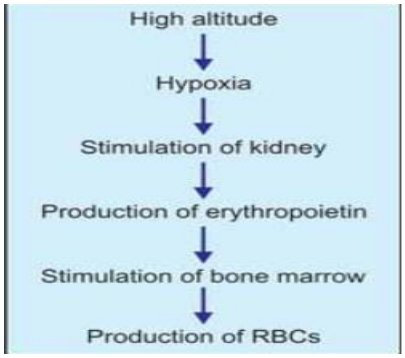
1. Age
At birth, the RBC count is 8 to 10 millions/cu mm of blood. The count decreases within 10 days after birth due to destruction of RBCs. This may cause physiological jaundice in some newborn babies. In infants and growing children, the RBC count is more than in the adults.

2. Sex

Before puberty and after menopause, in females the RBC count is similar to that in males. During reproductive period of females, the count is less than that of males (4.5 millions/cu mm).

3. High altitude

In people living in mountains (above 10,000 feet from mean sea level), the RBC count is more than 7 millions/cu mm. It is due to hypoxia (decreased oxygen supply to tissues) in high altitude. Hypoxia stimulates kidney to secrete a hormone called erythropoietin which stimulates the bone marrow to produce more RBCs.



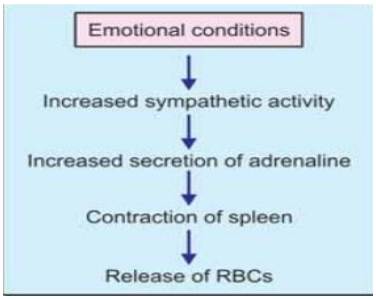
Physiological polycythemia in high altitude

4. Muscular exercise

RBC count increases after muscular exercise. It is because of mild hypoxia which increases the sympathetic activity and secretion of adrenaline from adrenal medulla. Adrenaline contracts spleen and RBCs are released into blood. Hypoxia causes secretion of erythropoietin which stimulates the bone marrow to produce more RBCs.

5. Emotional Conditions

The RBC count increases during the emotional conditions such as anxiety. It is because of increase in the sympathetic activity and contraction of spleen .



RBC count in emotional conditio

6. Increased environmental temperature generally increased temperature increases all the activities in the body including production of RBCs.

7. After meals
There is a slight increase in the RBC count after taking meals. It is because of need for more oxygen for metabolic activities.

Pathological Polycythemia

Pathological polycythemia is the abnormal increase in the RBC count. The count increases above 7 millions/cu mm of the blood. Polycythemia is of two types, the primary polycythemia and secondary polycythemia.
Primary Polycythemia — Polycythemia Vera Primary polycythemia is otherwise known as polycythemia vera. It is a disease characterized by persistent increase in RBC count above 14 millions/cu mm of blood. This is always associated with increased WBC count above 24,000/cu mm of blood. Polycythemia vera occurs because of red bone marrow malignancy.

Secondary Polycythemia

It is the pathological condition in which poly-cythemia occurs because of diseases in some other system such as:
1. Respiratory disorders like emphysema
2. Congenital heart disease
3. Ayerza's disease — condition associated with hypertrophy of right ventricle and obstruction of blood flow to lungs.
4. Chronic carbon monoxide poisoning.
5. Poisoning by chemicals like phosphorus and arsenic
6. Repeated mild hemorrhages.
All these conditions lead to hypoxia which stimulates the release of erythropoietin.
Erythropoietin stimulates the bone marrow resulting in increased RBC count.

B. Decrease in RBC Count

Decrease in RBC count occurs in the following physiological conditions:

1. High Barometric Pressures
At high barometric pressures as in deep sea, where the oxygen tension of blood is higher, the RBC count decreases.

2. During Sleep
Generally, all the activities of the body are decreased during sleep including production of RBCs.

3. Pregnancy
In pregnancy, the RBC count decreases. It is because of increase in ECF volume. Increase in ECF volume, increases the plasma volume also resulting in hemodilution. So, there is a relative reduction in the RBC count.

Anemia
The abnormal decrease in RBC count is called anemia.

VARIATIONS IN SIZE OF RED BLOOD CELLS

Under physiological conditions, the size of RBCs in venous blood is slightly larger than those in arterial blood. In pathological conditions, the variations in size of RBCs are:

1. Microcytes —smaller cells
2. Macrocytes — larger cells
3. Anisocytosis —cells of different sizes.

Anemia is the blood disorder characterized by the reduction in:
1. Red blood cell count
2. Hemoglobin content
3. Packed cell volume.

CLASSIFICATION OF ANEMIA
Anemia is classified by two methods:
A. Morphological classification
B. Etiological classification.

MORPHOLOGICAL CLASSIFICATION

Morphological classification depends upon the size and color of RBC.
Size of RBC is expressed as mean corpuscular volume (MCV) and the color is expressed as mean corpuscular hemoglobin concentration (MCHC). By this method, the anemia is classified into four types as given

Morphological classification of anemia

Type of anemia	Size of RBC (MCV)	Color of RBC (MCHC)
Normocytic normochromic	Normal	Normal
Normocytic hypochromic	Normal	Less
Macrocytic hypochromic	Large	Less
Microcytic hypochromic	Small	Less

ETIOLOGICAL CLASSIFICATION

On the basis of the etiology (study of cause or origin), the anemia is divided into five types:

1-Hemorrhagic Anemia

Hemorrhage refers to excessive loss of blood anemia due to hemorrhage is known as hemorrhagic anemia or blood loss anemia. It occurs both in acute and chronic hemorrhagic conditions.

Acute Hemorrhage

Acute hemorrhage means sudden loss of large quantity of blood as in case of accidents. The RBCs are normocytic and normochromic.

Chronic Hemorrhage

It refers to loss of blood over a long period of time by internal or external bleeding as in conditions like peptic ulcer, purpura, hemophilia and menorrhagia. The RBCs are microcytic and hypochromic . It is because of decrease in iron content.

2. Hemolytic Anemia

Hemolysis means destruction of RBCs. Anemia due to excessive destruction of RBCs is called hemolytic anemia. Hemolysis occurs because of the following reasons:

i. Liver failure
ii. Renal disorder
iii. Hypersplenism
iv. Burns

v. Infections like hepatitis, malaria and septicemia
vi. Drugs such as penicillin, antimalarial drugs and sulfa drugs
vii. Poisoning by chemical substances like lead, coal and tar
viii. Presence of isoagglutinins like anti-Rh
ix. Autoimmune diseases such as rheumatoid arthritis and ulcerative colitis.
x. Hereditary factors

Hereditary Disorders

Sickle cell anemia

Sickle cell anemia is an inherited blood disorder characterized by sickle shaped RBCs. It occurs when a person inherit s two abnormal genes (one from each parent). It is also called hemoglobin SS disease or sickle cell disease. It is common in people of African origin.

In sickle cell anemia, hemoglobin becomes abnormal with normal α chains and abnormal β chains. Because of this, RBCs attain sickle (crescent) shape and become more fragile leading to hemolysis.

Thalassemia

Thalassemia is an inherited disorder characterized by abnormal hemoglobin. In normal hemoglobin, the number of α and β chains is equal. In thalassemia the number of these chains is not equal. This causes the precipitation of the polypeptide chains leading to defective formation of RBCs or hemolysis of the matured RBCs.

It is also known as Cooley's anemia or Mediterranean anemia. It is more common in Thailand and to some extent in Mediterranean countries.

Thalassemia is of two types:
i. α thalassemia
ii. β thalassemia. The β thalassemia is very common among these two.

3. Nutrition Deficiency Anemia

Anemia that occurs due to deficiency of a nutritive substance necessary for erythropoiesis is called nutrition deficiency anemia. Such substances are iron, proteins and vitamins like C, B12 and folic acid. The types of nutrition deficiency anemia are:

Iron deficiency anemia
Iron deficiency anemia is the most common type of anemia. It develops due to inadequate availability of iron for hemoglobin synthesis. The RBCs are microcytic and hypochromic.

Protein deficiency anemia
Protein deficiency decreases the hemoglobin synthesis and the RBCs become macrocytic and hypochromic in nature.
Vitamin B12 deficiency — Pernicious anemia Vitamin B12 is a maturation factor for RBC and deficiency of this causes pernicious anemia which is also called Addison's anemia. It occurs because of less intake of vitamin B12 or poor absorption of vitamin B12. Vitamin B12 is absorbed from the stomach with the help of intrinsic factor of Castle which is secreted in the gastric mucosa. Decrease in the production of intrinsic factor causes poor absorption of vitamin B12.

RBCs are macrocytic and normochromic/hypochromic.

Folic acid deficiency — Megaloblastic anemia
Folic acid is necessary for the maturation of RBC.
Deficiency of this leads to defective DNA synthesis making the nucleus to remain immature. The RBCs are megaloblastic and hypochromic .

4. Aplastic Anemia
Aplastic anemia is due to the bone marrow disorder. The red bone marrow is reduced and replaced by fatty tissues. In this condition, the RBCs are normocytic and normochromic. It occurs in conditions such as repeated exposure to X-ray or gamma ray radiation, tuberculosis and viral infections like hepatitis and HIV infections.

5. Anemia due to Chronic Diseases
Anemia occurs due to some chronic diseases such as rheumatoid arthritis, normochromic.

Etiological classification of anemia

Type of anemia	Causes	Morphology of RBC
Hemorrhagic anemia	1. Acute hemorrhage — acute loss of blood	Normocytic, normochromic
	2. Chronic hemorrhage — chronic loss of blood	Microcytic, hypochromic
Hemolytic anemia	1. Liver failure 2. Renal disorder 3. Hypersplenism 4. Burns 5. Infections — malaria and septicemia 6. Drugs like penicillin, antimalarial drugs and sulfa drugs 7. Poisoning by lead, coal and tar 8. Isoagglutinins — anti-Rh	Normocytic normochromic
	9. Hereditary disorders	Sickle cell anemia: Sickle shape and hypochromic Thalassemia: Small, irregular and hypochromic
Nutrition deficiency anemia	1. Iron deficiency	Microcytic, hypochromic
	2. Protein deficiency	Macrocytic, hypochromic
	3. Vitamin B_{12} deficiency	Macrocytic, normochromic / hypochromic
	4. Folic acid deficiency	Megaloblastic, hypochromic
Aplastic anemia	Bone marrow disorder	Normocytic, normochromic
Anemia of chronic diseases	1. Rheumatoid arthritis 2. Tuberculosis 3. Chronic renal failure	Normocytic, normochromic