Sanoop KS
Mridul GS
Nishanth PS

Foreword
N Geetha

SECOND EDITION

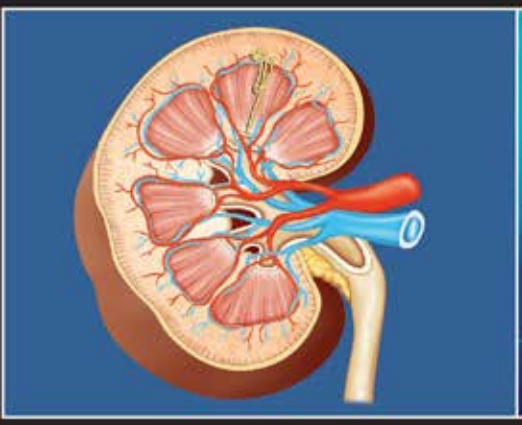
PHYSICON

The Reliable Icon in PHYSIOLOGY

Exam Preparatory Manual for Undergraduates

Highlights

- Concise, yet comprehensive manual on Physiology
- Most simplified book for exam preparation and revision
- Structured presentations, abundant diagrams and flowcharts
- Clinical boxes and clinical questions added
- First and only of its kind – Theory + Practicals + Question bank + MCQs



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CHAPTER

2

Circulating Body Fluids

BLOOD

The circulating system is the transport system that supplies O_2 and substances absorbed from the tissues, returns CO_2 to the lungs and products of metabolism to the kidney, functions in the regulation of body temperature, distributes hormones and other agents that regulate cell function. The blood is the carrier of these substances.

The cellular elements of the blood represents 45% of the total blood volume. It includes white blood cells, red blood cells, platelets and are suspended in the plasma. Plasma is a clear, straw colored fluid portion of the blood and represents 55% of the total blood volume. It contains 91–92% water, 8–9% solids. The solids comprise both organic [8%; plasma proteins, carbohydrates, enzymes, fats, hormones, nonprotein nitrogenous (NPN) substances] and inorganic (1%; sodium, calcium, potassium, magnesium, bicarbonate, chloride, phosphate, copper, iron). The thin middle layer that separates the upper plasma and lower red cell mass after centrifugation of blood is the buffy coat (Fig. 2.1).

The normal total circulating volume is 5600 ml in a 70 kg man (about 8% of body weight). The pH is 7.35–7.45 (average 7.4) and the specific gravity is 1055–1062. Blood is five times more viscous than water. Salinity of blood is 0.9 N.

Functions of Blood

- *Respiratory*: Helps in the transport of O_2 and CO_2
- *Nutritive:* Distribute various nutrients to all parts of the body
- *Excretory:* Transports waste materials to the organs of excretion
- *Defense mechanism:* Due to the presence of antibody.
- *Storage function:* Acts as storehouse for different materials like nutrients, water, electrolytes, etc.
- Regulation of body temperature (due to high specific heat of blood).
- *Regulation of acid-base balance:* Plasma proteins and Hb acts as buffers.
- Plays a major role in homeostasis.

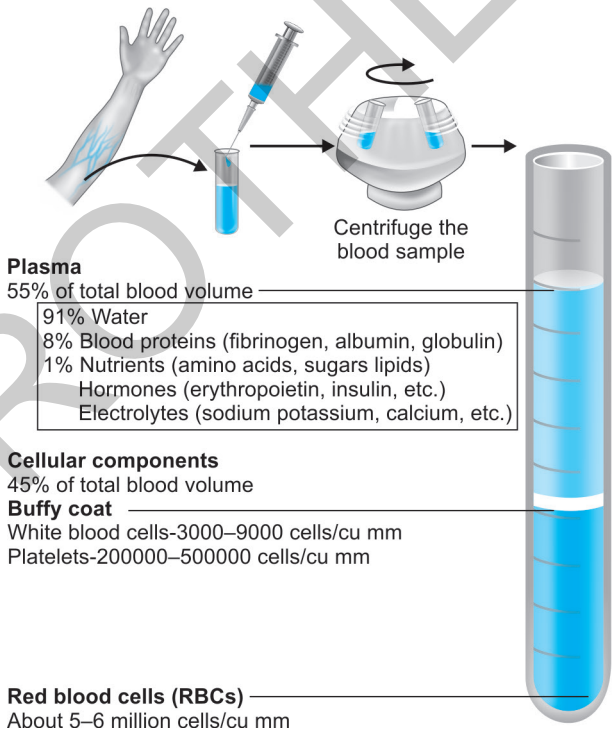


Fig. 2.1: Appearance of centrifuged blood and its constituents

PLASMA PROTEINS

The plasma proteins include albumin, globulin, fibrinogen, prothrombin. The total amount of plasma proteins in the blood is 6.4–8.3 gm %. The further details about each of them are given in Table 2.1. Normal A/G (albumin–globulin) ratio is 1.7:1. It is reversed in liver disorders. Plasmapheresis/ Whipple's experiment is an experimental procedure done in animals to demonstrate the importance of plasma proteins.

Functions of Plasma Proteins

- *Coagulation of blood:* Due to the presence of fibrinogen, prothrombin and clotting factors.
- *Defense mechanism of body:* Gamma-globulins produce antibodies.
- *Maintain colloidal osmotic pressure (COP):* Eighty-percent of COP is due to albumin (COP is inversely proportional

Table 2.1: Types of plasma proteins and functions

Type	Molecular weight	Normal plasma level	Site of production	Function
Albumin	69000	3.5–5 gm%	Liver	Binding and carrier protein, osmotic regulation
Globulin	90000–156000	2–3 gm%	Recticuloendothelial cells, plasma cells	Mediates immunity, transport proteins like transferin, ceruloplasmin, hemopexin are different forms of globulin
Fibrinogen	350000	0.2–0.4 gm%	Liver	Important for clotting of blood, responsible for major part of viscosity
Prothrombin	68000	0.1 gm%	Liver	Important for clotting of blood

to molecular size and directly related to concentration of molecule).

- *Transport:* Albumin and globulin transports various hormones, enzymes, bilirubin and metals like Cu, Fe, etc.
- *Acid-base regulation:* Due to buffering action.
- *Provides stability to blood:* This is due to the presence of globulin and fibrinogen. If blood loose viscosity RBC will pile upon each other and leads to *Rouleaux formation.*
- *Maintains systemic arterial BP constant:* Viscosity of the blood is mostly due to fibrinogen. Arterial BP depends on viscosity of the blood.
- Acts as protein store.

Hyperproteinemia

Increase in level of plasma proteins and is seen in conditions which causes hemoconcentration (diabetes insipidus).

Hypoproteinemia

Decrease in level of plasma proteins. It is seen in malnutrition, burns, malabsorbtion, hemorrhages. This causes decrease in COP; therefore increase in filtration occurs at arterial end and decrease in absorption at venous end, resulting in edema.

In Liver Disorders, A/G Ratio Reverses

When body tissues are damaged, though plasma albumin falls, plasma immunoglobulin increases as a result of plasma cell hyperplasia causing A/G ratio reversal.

Multiple Myeloma

Increase in the level of globulin due to malignant growth of plasma cells.

Clinical Box

Plasma is separated by centrifuging anticoagulated blood. The serum separated from blood by allowing the blood to coagulate. (serum = blood-fibrinogen and other clotting factors)

HEMOGLOBIN

Hemoglobin (Hb) is the most important red cell constituent. Major function of hemoglobin is uptake of oxygen in lung and delivery of it to tissues. Hemoglobin starts appearing in developing RBC at intermediate normoblastic stage. The hemoglobin molecule is an assembly of four subunits.

Structure of Hb (Fig. 2.2)

Each subunit is composed of a protein (polypeptide) part, i.e. globin and a nonprotein part, i.e. heme. Heme is an iron containing porphyrin derivative. Each hemoglobin molecule contains four heme units and two pairs of similar polypeptides (globin). The heme part of globular protein is same in all types of hemoglobin. The protein part vary in different hemoglobin. For example, Hb A consists of two identical α chains and two identical β chains, Hb F consists of two identical α chains and two identical γ chains. The iron atom in each subunit of heme is in ferrous form (Fe^{2+}) and has a bond available for loose union with oxygen molecule. So, one Hb molecule can combine with four molecules of O_2 (Fig. 2.2A).

Normal Values

Males: 14 –18 gm% (avg -15.5 gm%)
Females: 12–15.5 gm% (avg -14 gm%)

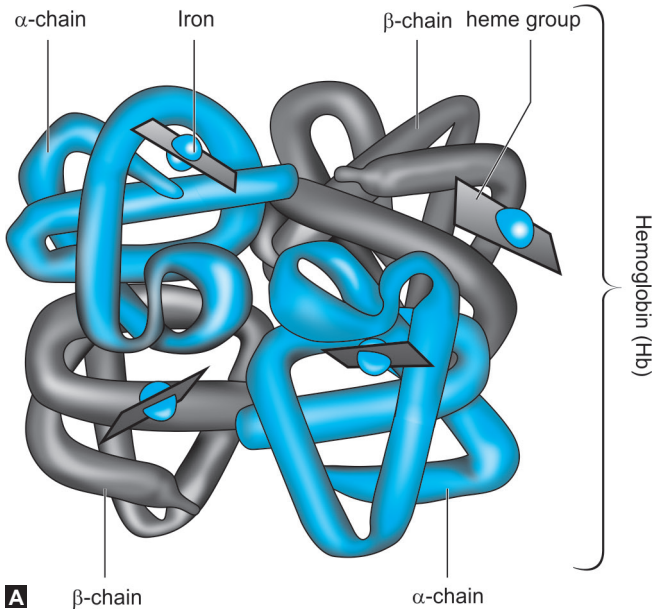
Types of Hb

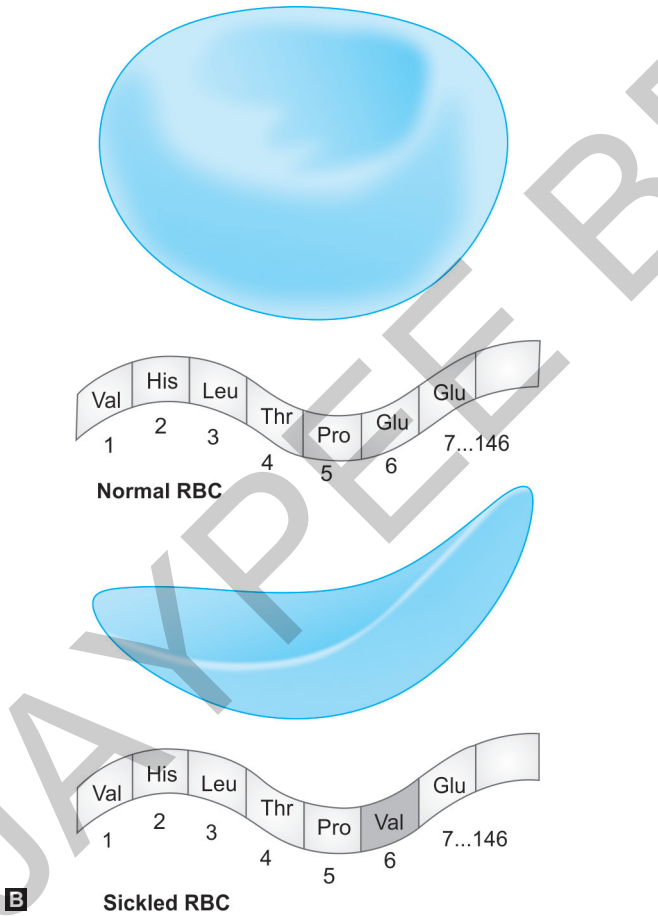
Normal Varieties

- Adult Hb are of two types:
  1. Hemoglobin A ($\alpha_2\beta_2$)
  2. Hemoglobin A2 ($\alpha_2\delta_2$)
- Fetal Hb ($\alpha_2\gamma_2$)

Abnormal Varieties

- *Hemoglobinopathies;* here abnormal polypeptides are produced.
  - HbS: In the β chain, glutamine at the 6th position is replaced by valine. When HbS is reduced, it precipitates into crystals within RBCs leading to sickling of RBCs. Sickle shaped RBCs are more fragile resulting in sickle cell anemia (Fig. 2.2B).
  - HbC
  - HbE
  - HbI, etc.

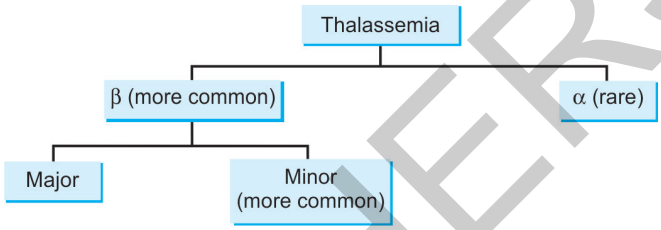




Figs 2.2A and B: **A.** Structure of hemoglobin; **B.** Comparison of normal erythrocyte to a sickled erythrocyte. Part of its hemoglobin sequence is shown

- *Thalassemias (Flowchart 2.1):* Both α and β chains are present and are normal in structure, but produced in decreased amounts or absent.

Flowchart 2.1: Types of thalassemia



Major β thalassemia (Cooley's anemia or Mediterranean anemia):

- Less common
- Total absence of chain synthesis
- Homozygous transmission
- Victim usually dies.

Minor β thalassemia

- More common
- Partial synthesis of β chain
- Heterozygous transmission.

Heme-Heme Interaction

In the initial phase of oxygenation the combination of heme and O_2 is a bit slow. But once a little of O_2 has combined with heme further interactions are facilitated. This is called heme-heme interaction and this explains the sigmoid shape of O_2 dissociation curve *(See Chapter 3)*.

Catabolism of Hb (Flowchart 2.2)

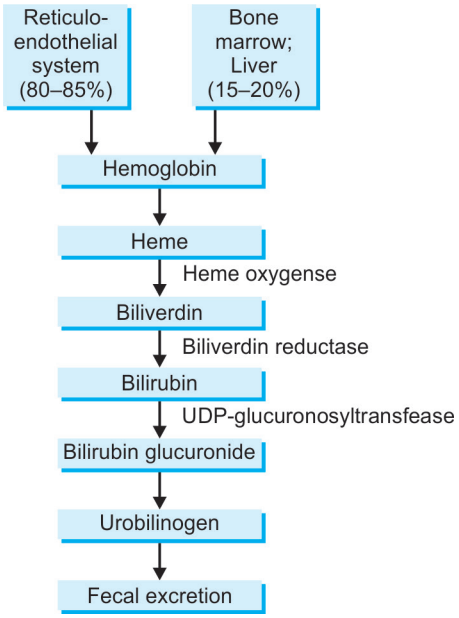
When the RBCs become old their walls become weak and their shape changes and finally the RBC are broken down. RBCs are destroyed mainly in the spleen by the reticuloendothelial cells. Hb is then released from RBC, which splits into heme and globin.

The end products of heme catabolism are bile pigments. Bilirubin has no function in the body so excreted through bile. Globin is broken into amino acids within the RE (reticuloendothelial) cells, which will be later utilized for synthesis of body proteins. Iron is then released into plasma and is transported by transferrin to the storage sites. The porphyrin ring is broken down in RE cells of liver, spleen and bone marrow where it gets converted into biliverdin (green pigment).

Bilirubin metabolism can be discussed under the following headings (Fig. 2.3).

- Normal sources of bilirubin
- Transport of bilirubin

Flowchart 2.2: Catabolism of hemoglobin



- Hepatic metabolism
- Intestinal phase of bilirubin metabolism
- Renal excretion of bilirubin

Normal Sources of Bilirubin

- 80–85% of bilirubin is derived from catabolism of hemoglobin of senescent red blood cells.
- 15–20% is derived from bone marrow due to destruction of maturing cells and from liver due to turnover of heme and heme containing precursors (cytochromes, myoglobin, etc.).
- In plasma, Hb binds with haptoglobin. The Hb-haptoglobin complex is transported to liver, where heme of Hb is oxidized to biliverdin by enzyme heme oxygenase to iron and biliverdin. Heme liberated from other sources are also oxidized to biliverdin by enzyme heme oxygenase.
- Biliverdin is then reduced to bilirubin by the enzyme biliverdin reductase.

Transport of Bilirubin

Unconjugated bilirubin is liberated into plasma. This unconjugated bilirubin is tightly bound to albumin in a fully reversible manner. Thus, unconjugated bilirubin is transported in the plasma and bound to albumin. Unbound unconjugated bilirubin can cross blood brain barrier and cause kernicterus in neonates with hyperbilirubinemia. Conjugated bilirubin is also bound to albumin, but both in reversible and irreversible manner.

Hepatic Metabolism

It has three distinct phases: Hepatic uptake, conjugation, excretion into bile.

Hepatic Uptake

Unconjugated bilirubin—albumin complex is subjected to the liver cell, i.e. hepatocyte. Albumin dissociates and the unconjugated bilirubin enters the cell. In the cell, unconjugated bilirubin gets bound to several of the glutathione-S-transferases. This binding prevents the efflux of unconjugated bilirubin back into plasma.

Conjugation

In the hepatocyte, the unconjugated bilirubin is conjugated by the enzyme bilirubin UDP-glucuronosyl-transferase. The cosubstrate for bilirubin conjugation is UDP-glucuronic acid, ubiquitous intracellular substance derived from glucose. Conjugation is a two-step reaction resulting first in the formation of bilirubin monoglucuronide and then bilirubin diglucuronide. *Why conjugate?* Unconjugated bilirubin is water insoluble and so not excreted into bile. So, it must be converted to a water soluble derivative (i.e. conjugated bilirubin or bilirubin glucuronide) in order to be excreted by liver cell into bile.

Excretion or Secretion into Bile

This is the rate limiting step of bilirubin metabolism. This step is the one that is most susceptible to impairment when liver cell is damaged. The secretion across the plasma membrane is by ATP dependent transport process mediated by a membrane protein. So conjugated bilirubin is secreted into bile. Normal bile contains 90% of bilirubin diglucuronide and 7% of bilirubin monoglucuronide with remaining 2–3% as unconjugated bilirubin. When this step is comprised two consequences occur: 1) Decreased excretion of bilirubin into bile, and 2) Regurgitation or reentry of conjugated into the blood-stream (conjugated hyperbilirubinemia).

Intestinal Phase of Bilirubin Metabolism

Conjugated bilirubin (bilirubin diglucuronide and bilirubin monoglucuronide) reaches the intestinal lumen through bile. Conjugated bilirubin as such is not reabsorbed by intestinal mucosa. This conjugated bilirubin has got two fates:

1. Part of this conjugated bilirubin is excreted in the stool as such, i.e. bilirubin diglucuronide and bilirubin monoglucuronide.
2. Rest of the conjugated bilirubin is metabolized in the lumen to urobilinogen by the action of intestinal bacteria. This urobilinogen has three fates:
   a. Part of this urobilinogen is reabsorbed from small intestine into portal circulation, thus reaching liver (enterohepatic circulation). The liver reexcretes this urobilinogen into bile.

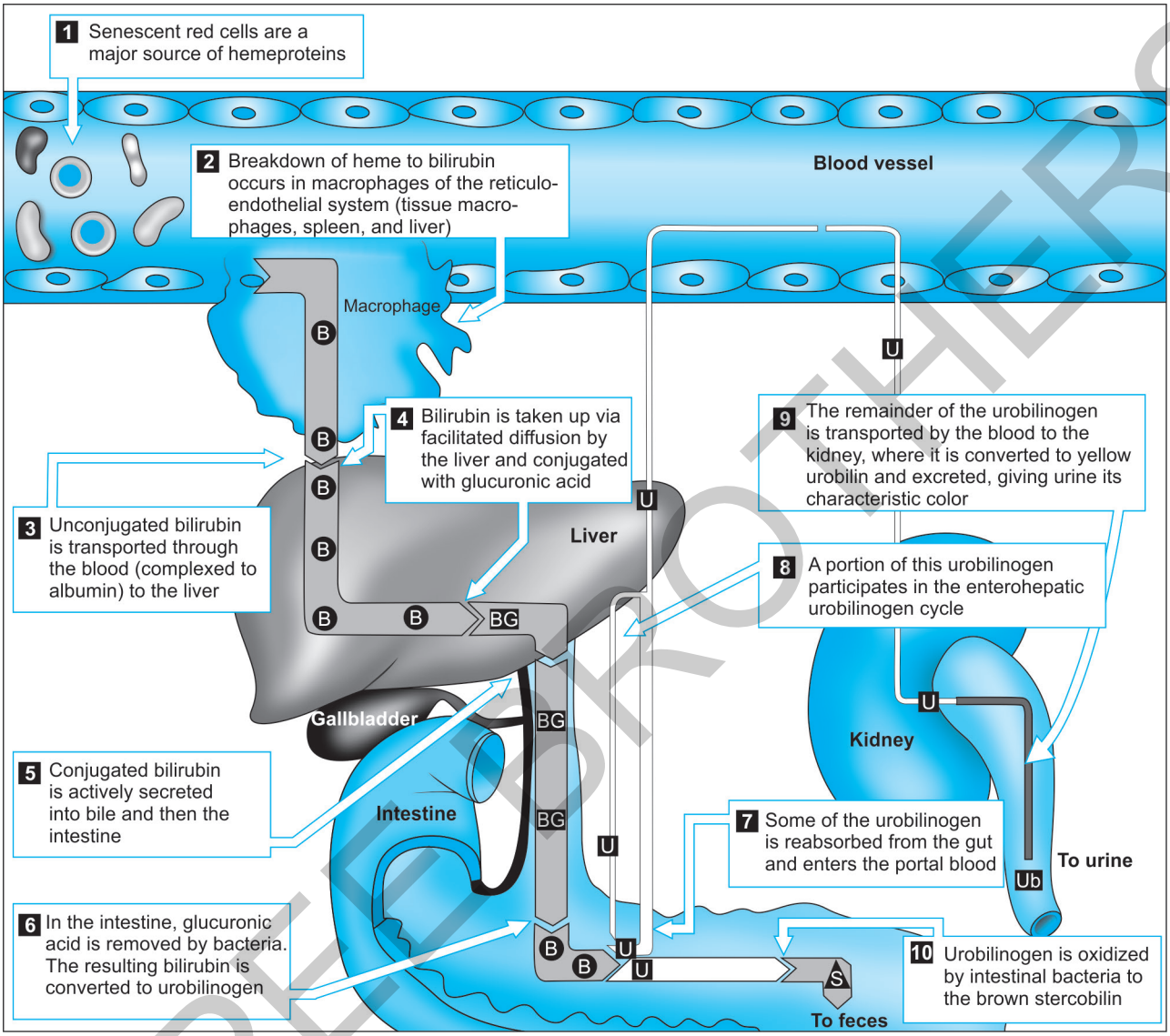


Fig. 2.3: Summary of catabolism of heme. B = bilirubin, BG = bilirubin diglucoronide, U = urobilinogen, Ub = urobilin, S = stercobilin

b. Part of the urobilinogen is transported by blood to kidneys, where it is reabsorbed and oxidized to yellow urobilin and excreted in the urine giving the urine its color.
c. Part of the urobilinogen in the intestine is oxidized by intestinal bacteria to excrete in the stool as stercobilinogen. Stercobilinogen gives the stool its normal color. In obstructive jaundice stercobilinogen is absent in the stool, and hence stools are pale or clay colored.

Renal Excretion of Bilirubin

In normal individuals, there is no bilirubin in urine since unconjugated bilirubin is tightly bound to albumin and hence not filtered by glomeruli. But with regard to conjugated bilirubin, a small fraction (5%) is less tightly bound to albumin and another small fraction is unbound. This unbound fraction is filtered and appears in the urine as bilirubin. So in contrast to unconjugated hyperbilirubinemia, bilirubin appears in the urine in conjugated hyperbilirubinemia.

Clinical Box

Plasma haptoglobin indicates hemolysis. In intravascular hemolysis, Hb-haptoglobin complex clears haptoglobin from plasma. Therefore, haptoglobin content of the plasma is decreased in hemolysis and the degree of decrease is apparently proportionate to the rate of hemolysis. Therefore, estimation of plasma haptoglobin level is an index of hemolysis.

ERYTHROCYTES (RBC)

Normal count	:	*Males*—5–6 million cells/mm^3 (average 5.4 million cells/mm^3) *Females*—4.5–5.5 million cells/mm^3 (average 4.8 million cells/mm^3)
Diameter	:	7.2 μm (avg)
Thickness	:	2 μm (avg)
Volume	:	78 – 94 μm^3
Hematocrit (PCV)	:	Males 47% and Females 42%
Lifespan	:	120 days
Site of production	:	Bone marrow
Site of destruction	:	Tissue macrophage system.

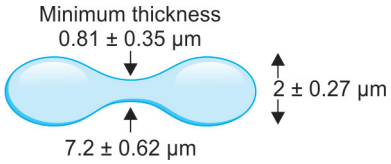


Fig. 2.4: RBC

Advantages of Biconcave Shape

- Can squeeze through capillaries very easily
- Can withstand endosmosis
- Large surface area is provided which help in quick exchange of gases.

Functions

- Gas transport
- Acid-base balance
- Formation of bilirubin
- Responsible for major portion of viscosity of whole blood
- Helps in identifying blood groups as it contains antigen on its surface.

Red Cell Fragility

Red blood cells shrink in solutions with an osmotic pressure > normal plasma (0.9N). In solutions with a lower osmotic pressure they swell, becoming spherical and lose their Hb (hemolysis). The tendency to hemolyze is called fragility. In hereditary spherocytosis (congenital hemolytic icterus) cells hemolyze more readily than normal cells in hypotonic NaCl solutions. Fragility is high in G6PD deficiency. Red cells can also be lysed by drugs and infections.

Hereditary Spherocytosis

Common cause of hereditary hemolytic anemia. The membrane of RBC is made of spectrin and is anchored to transmembrane protein band 3 by the protein ankyrin. Hereditary spherocytosis is caused by defects in band 3, spectrin and ankyrin.

RBC Indices

The number, shape, volume and color of RBCs indicate the quality of blood. Blood indices have got a diagnostic value in determining the type of anemia. These are:

Mean Corpuscular Volume (MCV)

It is the volume of a single RBC in cubic microns.

$$\text{MCV} = \frac{\text{PCV per 100 ml blood} \times 10\ \mu m^3}{\text{RBC count in million/cu mm}}$$

Normal value: 87 μm^3

Mean Corpuscular Hemoglobin (MCH)

It is the average amount of Hb in a single RBC in pictogram.

$$\text{MCH} = \frac{\text{Hb in gm\%} \times 10\ \text{pg}}{\text{RBC count in million/cu mm}}$$

Normal value: 29 pg

Mean Corpuscular Hemoglobin Concentration (MCHC)

It is the Hb concentration in a single RBC or it is the amount of Hb expressed as % of the volume of a RBC.

$$\text{MCHC} = \frac{\text{Hb in gm\%} \times 100}{\text{PCV per 100 ml blood}}$$

Normal value: 34%

Color Index

It denotes the ratio of Hb to RBC.

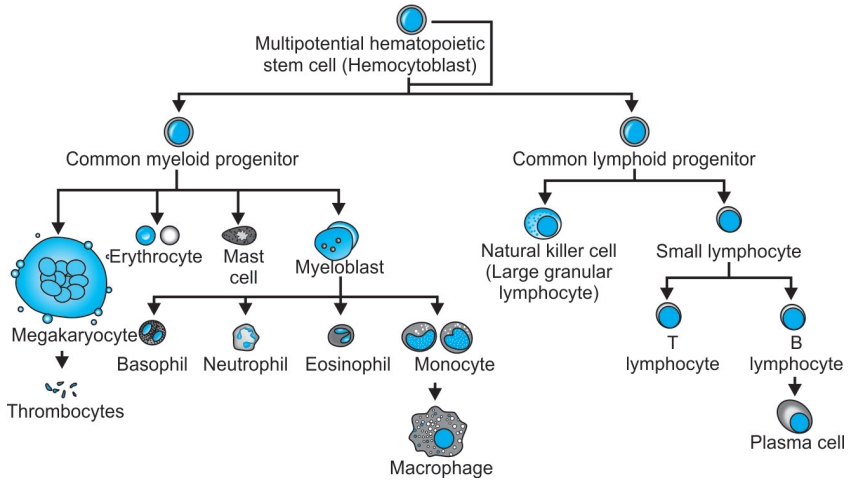
$$\text{Color index} = \frac{\text{Hb\%}}{\text{RBC\%}}$$

Normal value: 1

Packed cell volume (hematocrit), erythrocyte sedimentation rate (ESR) are discussed in practical section.

HEMOPOIESIS

Formation of blood cells is termed as hemopoiesis or hematopoiesis. In children, blood formation occurs in the marrow cavities of most of the bones. The well marked cellularity gives the red color to the marrow when seen with a naked eye. Red bone marrow contains various developing stages of red cells, white cells and platelets as well as some adipose tissue and connective tissue cells. By 21 years of age, the red bone marrow is limited to the axial skeleton (skull, vertebrae, ribs, sternum and pelvis) and the proximal ends of the femur and the humerus. In the remaining parts of long bones, the marrow consists of adipose tissue and some blood capillaries. Such marrow is known as yellow bone marrow. When the rate



Age	Site of hematopoiesis
3 weeks–3 months	Yolk sac
3–5 months	Liver, spleen
5–9 months	Red bone marrow in long and flat bones
After birth till 20 years of age	Red bone marrow in long and flat bones
>20 years	Only in flat bones like ilia

Fig. 2.5: Hemopoiesis

of formation of red cells (erythropoiesis) is to be markedly accelerated (e.g. after severe hemorrhage or in hemolytic anemia), the yellow marrow is converted to red marrow. Thus yellow marrow acts as a reserve for increased blood formation in case of situations requiring rapid erythropoiesis.

The red marrow contains pluripotent/multipotent stem cells (hemocytoblast) which give rise to all types of blood cells (Fig. 2.5). Certain humoral substances like erythropoietin, colony stimulating factors, thrombopoietin push the stem cells into respective line of development. Pluripotent stem cells give rise to two specialized stem cells. The myeloid cell gives rise to still other cells, which become red blood cells, platelets, and all the whole blood cells except lymphocytes. The lymphatic stem cells gives rise to lymphoblasts, which become lymphocytes. The process of differentiation from stem cell to mature erythrocyte is called **erythropoiesis**, to mature leukocyte is called **leukopoiesis** and development of platelets is called **thrombopoiesis**. The rates at which the blood cells produced are regulated in healthy individuals to match the rates at which they leave the circulation. The balance between production and elimination is disturbed in pathological condition.

Erythropoiesis

Formation of red blood cells is called erythropoiesis. In normal adult human, the site of production is bone marrow (red bone marrow). In the first-three months of intrauterine life, blood cells develop from mesoderm of yolk sac or area vasculosa (mesoblastic stage). After 3 months, up to 5 months of fetal life red blood cells are developed from liver and spleen (hepatic stage). From 5th month onwards up to birth and up to adulthood from red bone marrow (myeloid stage).

In children erythropoiesis occurs in:

- All bones with red marrow (mainly)
- Liver and spleen

In adults erythropoieses occurs in red bone marrow which includes:

- Ends of long bones (shaft is converted to yellow marrow)
- Flat bones (skull, vertebrae, ribs, sternum, pelvis).

Stages of Erythropoiesis (Fig. 2.6)

Hemocytoblast

- It is considered as a pleuripotent stem cell (noncommitted)
- Diameter: 18–20 μm
- Nucleated with thin rim of basophilic cytoplasm
- Nucleus may contain two or more nucleoli with open chromatin.
- They proliferate extensively and give rise to committed stem cell.

Committed Stem Cells

- Develop from pleuripotent stem cells.
- Two types—myeloid and lymphoid.
- They have become committed to give rise to a particular line of cells (either erythrocytes, platelets, monocytes, etc.).
- Committed stem cells of myeloid series gives rise to all types of blood cells except lymphocytes.

Progenitor Cells

- Develop from committed stem cells
- Progenitor cells are of two types:
  - BFU-E (burst forming unit of erythrocyte series)
  - CFU-E (colony forming unit of erythrocyte series)
- BFU-E give rise to CFU-E cells.

Proerythroblast

- The first blast cell (immature cells) belonging to red blood series

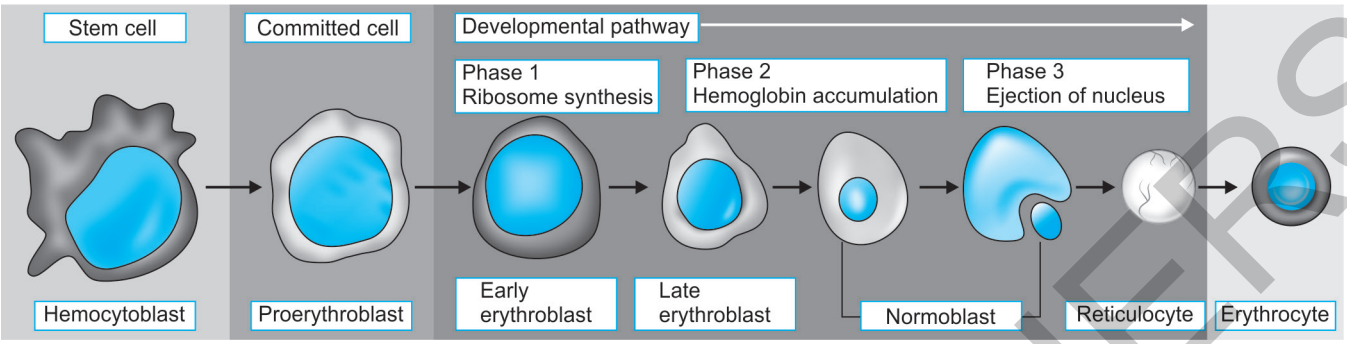


Fig. 2.6: Phases of erthrocyte differentiation

- They are formed from CFU-E stem cells
- Large nucleus, distinct nucleoli, open chromatin
- Basophilic cytoplasm
- Shows active mitosis.

Early Normoblast

- Size further decreases
- No nucleoli, condensed chromatin threads
- Cytoplasm is basophilic
- Shows active mitosis.

Intermediate Normoblast

- Cell size reduces
- Chromatin thread further condenses
- Hb starts appearing
- Cytoplasm becomes polychromatic
- In the later part mitosis stops.

Late Normoblast

- Further reduction in cell size
- Nucleus moves to periphery
- Further condensation of chromatin threads
- In the later part nucleus becomes pyknotic
- Further increase in concentration of Hb
- Cytoplasm is mostly eosinophilic (acidic).

Reticulocyte

- Cell size reduces and almost same size of matured RBC (7–9 μm)
- No nucleus
- When stained with dyes like brilliant cresyl blue, cytoplasm shows a small reticulum (due to the presence of RNA) and hence the name
- Cytoplasm is eosinophilic.

Erythrocyte

- Fully eosinophilic
- Non-nucleated, biconcave
- *Diameter*: 7.2 μm.

Factors Affecting Erythropoiesis

General Factors

Erythropoietins

- Glycoprotein in nature, also called hemopoietin or erythrocyte stimulating factor.
- It is secreted by interstitial cells in peritubular capillaries of kidney and by hepatocytes in the liver. In adults 85% of secretion comes from kidney, 15% from liver.
- It acts from the stage committed stem cell. It causes early differentiation of erythropoietin sensitive stem cells to proerythroblast and subsequently to mature RBCs. It prevents apoptosis of red cells. It increases synthesis of RNA, DNA, globin, ferritin which increases heme synthesis. It increases the release of reticulocytes from bone marrow.
- Stimulants for secretion includes hypoxia (most important), androgens, cobalt salts, catecholamines, alkalosis.
- Estrogen decreases the production of erythropoietin. This is the reason for decreased red cell count in females.

Lack of O_2

The role of hypoxia on erythropoietin is in Flowchart 2.3.

Hormones

Testosterone, thyroxine, corticosteroids, growth hormone favors and estrogen inhibits erythropoiesis.

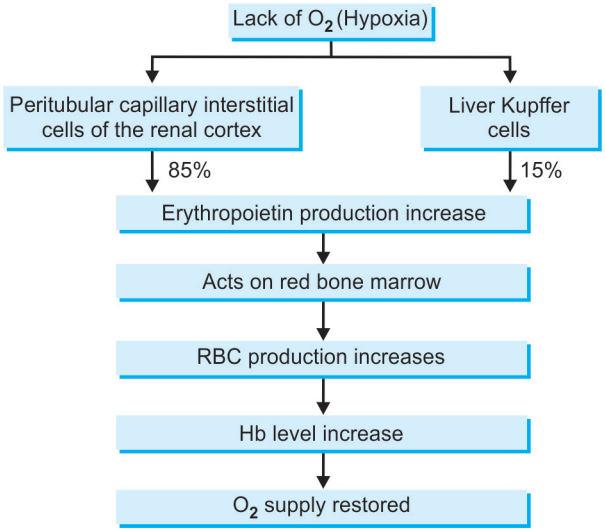
Hemopoietic Growth Factors

These are interleukins and stem cell factor. Generally these factors induce the proliferation of pleuripotent stem cells.

Maturation Factors

- *Vitamin B_{12} and folic acid:* They are called extrinsic factors and are necessary for DNA synthesis. Erythroblast need them before every mitosis and deficiency leads to failure in maturation and reduction in cell divisions.
- *Iron:* It is necessary for Hb synthesis.

Flowchart 2.3: Role of hypoxia on erythropoiesis



- *Castle's intrinsic factor:* It is produced by parietal cells of the stomach. It is essential for the absorption of vitamin B_{12}.
- *Dietary factors:* Proteins help in globin formation. Fe, Mn, Cu, Co helps in heme formation. Vitamin C and Ca increases iron absorption from gut.

Note: Androgens has stimulating effect on erythropoietin. Estrogen decreases hepatic synthesis of globulin. They also depress the erythropoietic response to hypoxia. That is why in females, RBC count is less as compared to males.

Clinical Box

Reticulocyte indicate bone marrow activity. Reticulocytes are the immediate precursors of red cells. Therefore, when the demand for red cells in the body is increased, the reticulocyte formation and release are also increased.

Anemia

Anemia is a clinical condition characterized by decrease in O_2 carrying capacity of blood due to either decrease in the number of RBCs or their content of Hb or both.

Grading

Mild anemia: Hb 8–12 gm%
Moderate anemia: Hb 5–8 gm%
Severe anemia: Hb < 5 gm%

General Clinical Features of Anemia

- Generalized weakness, tenderness and fatigability.
- Pallor of skin and mucous membrane.
- Respiratory symptoms like breathlessness.
- CVS manifestations like palpitation, tachycardia and cardiac murmurs.
- CNS features due to cerebral hypoxia like lethargy, headache, tinnitus and confusion.
- Ocular manifestations like visual disturbances, retinal hemorrhage.
- Gastrointestinal symptoms like anorexia, nausea, constipation.
- Reproductive system: Menstrual disturbances like amenorrhea, menorrhagia in females.
- Renal system involvement.
- BMR increases in severe anemia.

Classification

Morphological/Wintrobe's classification

Based on the size and color of RBC (i.e. based on MCV and MCHC):

- Normocytic normochromic
- Normocytic hypochromic
- Macrocytic normochromic
- Macrocytic hypochromic
- Microcytic normochromic
- Microcytic hypochromic.

Etiological/Whitby's classification (Table 2.2)

Based on the cause of anemia:

- Hemorrhagic: Due to blood loss
- Hemolytic: Due to destruction
- Nutritional deficiency
- Aplastic due to decreased formation.

Pernicious Anemia/Addison's Anemia

(Pernicious Means Destructive or Injurious)

Causes

This is due to lack of intrinsic factor. Consequently there will be failure in the absorption of vitamin B_{12}. Production of intrinsic factor is affected due to atrophy of gastric mucosa.

RBCs are macrocytic normochromic. Excessive destruction of RBCs produces mild hemolytic jaundice. Bone marrow becomes hyperplasic due to increased hypoxic stimulation for erythropoiesis. Neurological disorders are seen in extreme conditions.

Reticulocyte Response

Increase in number of reticulocytes after vitamin B_{12} therapy. This is due to proliferation of bone marrow and numerous young RBC pass into circulation.

Folic Acid Deficiency Anemia

Anemia is megaloblastic as seen with vitamin B_{12} deficiency. But neurological disorders may not develop.

Net outward force (at arterial end) 13 mm Hg. Thus, the forces at the arterial end of the capillary shows net filtration of 13 mm Hg, tending to move fluid outward through the capillary pores.

Factors causing reabsorption of fluid at the venous end of capillaries: The low blood pressure at the venous end of the capillary changes the balance of forces in favor of absorption. Forces tending to move fluid inward:

a. *Plasma colloid osmotic pressure (π_c):* 28 mm Hg
b. *Interstitial fluid colloid osmotic pressure (π_i):* 8 mm Hg

Total inward force (π_c - π_i) = [28 – 8] = 20 mm Hg

Forces tending to move fluid outward are:

a. *Capillary hydrostatic pressure (P_c):* 10 mm Hg
b. *Negative interstitial fluid hydrostatic pressure (π_i):* –3 mm Hg

Total outward force (P_c – P_i) = [10 – (–3)] = 13 mm Hg

So, net filtering force [(P_c - P_i) - (π_c - π_i)] = 13 – 20 = -7 mm Hg.

Net inward force is 7 mm Hg which causes reabsorption. The reabsorption pressure at venous end is less than the filtration pressure at the arterial ends of capillaries but venous capillaries are more numerous and more permeable than the arterial capillaries, so less pressure is required to cause inward movement. About nine-tenths of filtered fluid is absorbed at the venous end.

Starling's Equilibrium

EH starling pointed out that under normal condition a state of near equilibrium exists at capillary membrane. The amount of fluid filtering out from capillaries equals almost exactly the quantity of fluid that is returned to the circulation by absorption. The slight disequilibrium that occurs accounts for small amount of fluid that is eventually returned by way of the lymphatics.

Edema

It means presence of excess fluid in the tissues of the body mainly in the extracellular fluid compartment. It is due to:

- Abnormal leakage of fluid from the capillaries. This in turn is due to:
  - Increased capillary pressure
  - Decreased plasma proteins
  - Increased capillary permeability.
- Failure of lymphatic system to return the fluid from extracellular compartment back to circulation.
- Retention of water and salt by the kidneys.

Causes

1. Cardiac edema
2. Mechanical obstruction to veins
3. Renal disease
4. Inflammatory area (increased capillary permeability)
5. Malnutrition (lack of proteins)
6. Toxic substances (increased capillary permeability).

Clinical Box

Hypoproteinemia causes decrease in COP, therefore increased filtration occurs at arterial end and decrease in absorption of fluid at venous end, resulting in abnormal collection of fluid in interstitial spaces called edema.

CLINICAL QUESTIONS

1. **A RBC was placed in a saline (NaCl) solution and the cell volume increased to 1.5 times its original volume.**
   a. What is the nature of the saline solution? (isotonic/hypotonic/hypertonic)
   b. Define the transport mechanism responsible for the above effect.
   c. Name other mechanisms for transport across the cell membrane.
2. **A patient after receiving blood transfusion developed deep jaundice and hemoglobinuria within 48 hours.**
   a. Identify the condition.
   b. What is the cause of jaundice and hemoglobinuria?
   c. What is the preventive line of treatment?
3. **A patient came with the complaint of brownish spots under skin. On examination spleen was found to be enlarged. Investigations showed:**
   - **Bleeding time—10 min**
   - **Clotting time—6 min**
   - **Platelet count—30,000/mm^3**

   a. Identify the condition and give probable cause.
   b. Explain the features.
   c. Outline the physiological basis of treatment?
4. **A 16-year-old boy from Himachal Pradesh is found to have hemoglobin of 22 gm%. His physical examination and other routine investigations are within normal limits.**
   a. Identify the condition.
   b. What is the cause?
   c. Does he need treatment for this?

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Sanoop KS MBBS MD (Internal Medicine), **Mridul GS** MBBS MS (General Surgery), **Nishanth PS** MBBS MD (Pulmonary Medicine) completed their MBBS from Kannur Medical College Hospital and Research Centre, Kannur, Kerala, India and PG from JSS Medical College, Mysore, Bangalore Medical College and Research Centre, Bengaluru, and Government Medical College, Amritsar, Punjab, respectively. The difficulties faced during their first year MBBS in learning and understanding the concepts of Physiology inspired them in bringing up this student-friendly concise book for Physiology, that too immediately after their first MBBS. Having sold numerous copies gave ample proof of the popularity of this book among medical students particularly in Kerala, even before M/s Jaypee Brothers Medical Publishers started publishing and distributing all over India. The trio have been actively involved in undergraduate teaching. They have national level presentations and publications in different journals to their credit.

Sanoop KS

Mridul GS

Nishanth PS

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