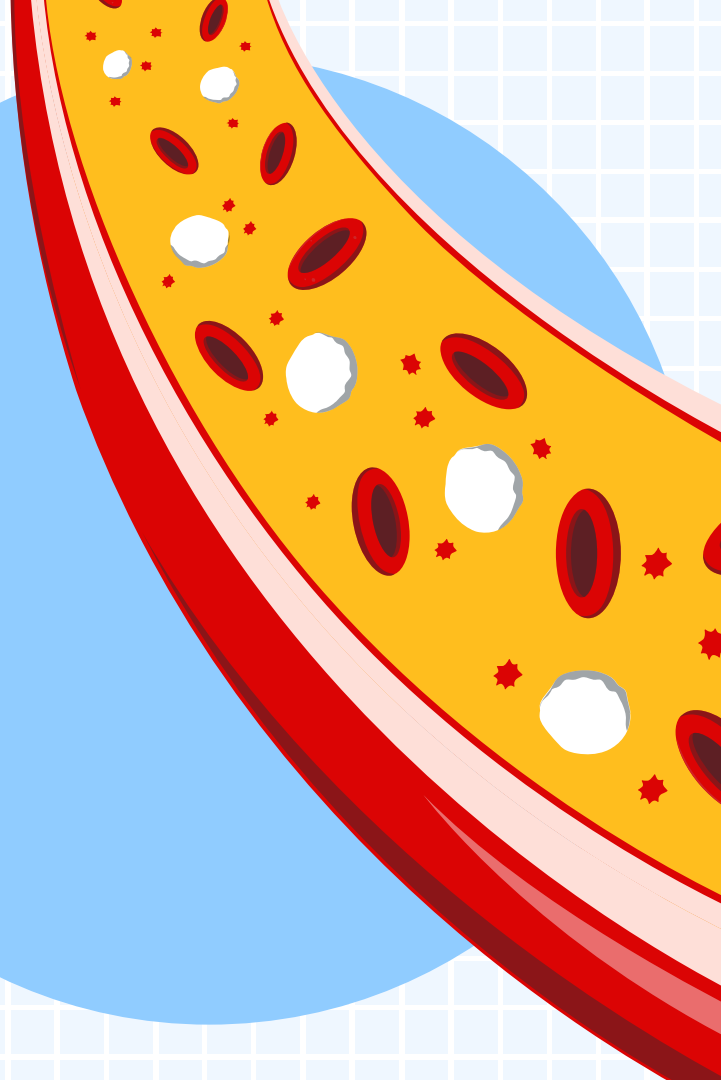
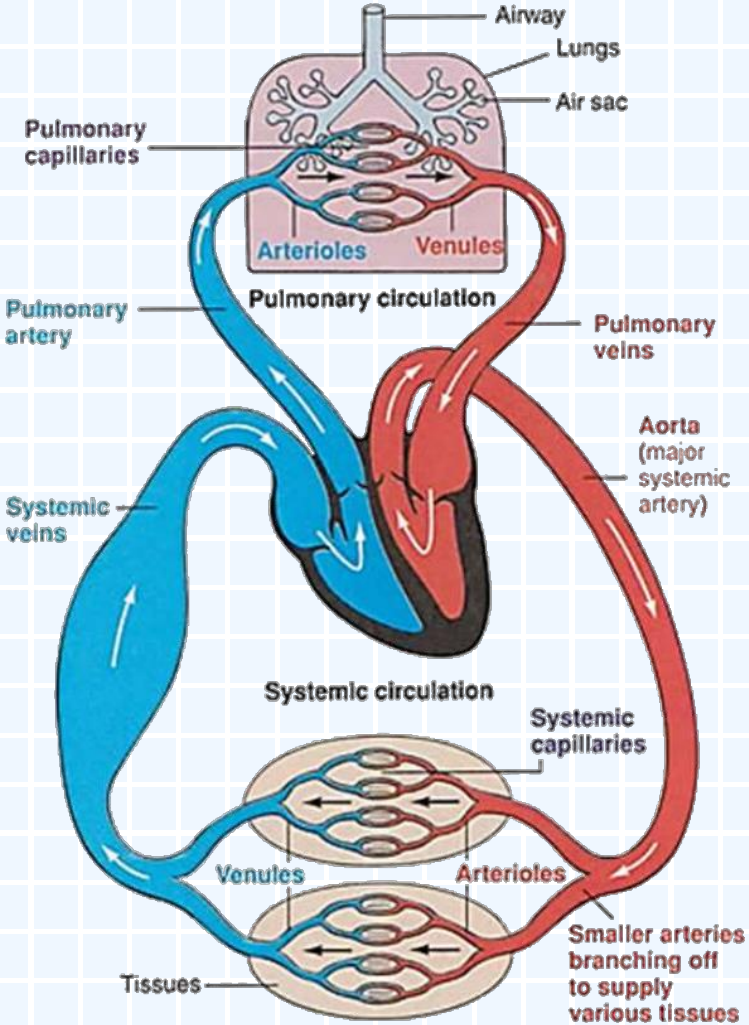
MODULE

HLS (HEMO & LYMPH)

Physiology Lectures
Lecture No. (1)
Slides By: Malek Hassan
Notes By:




Airway
Lungs
Air sac
Pulmonary capillaries
Arterioles
Venules
Pulmonary circulation
Pulmonary artery
Pulmonary veins
Aorta (major systemic artery)
Systemic veins
Systemic circulation
Systemic capillaries
Venules
Arterioles
Smaller arteries branching off to supply various tissues
Tissues

Blood

Blood is part of the extracellular fluid. It is continuously circulating in blood vessels throughout the cardiovascular system through the heart's pumping action. It is considered a part of the connective tissue. It constitutes 8% of the body weight.

Composition of Blood

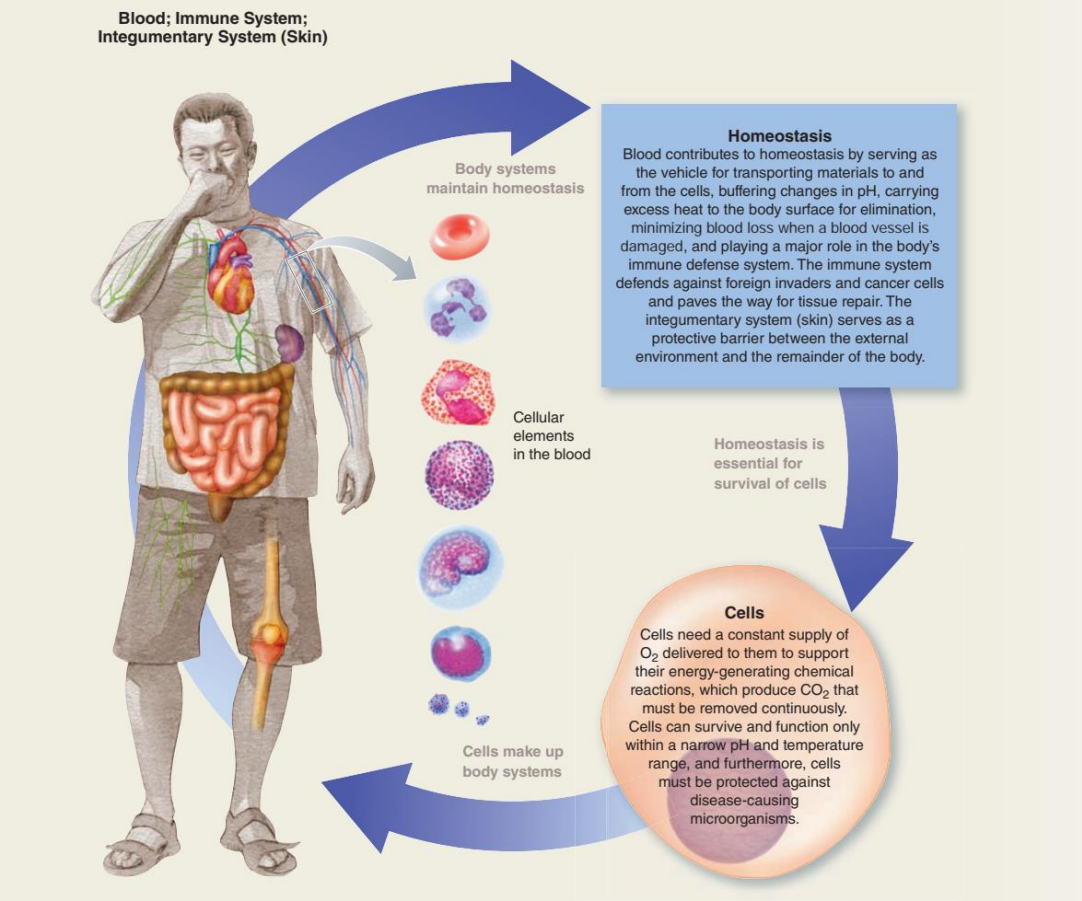
Blood is composed of two parts:

1. **Plasma:** This is the fluid part of blood. It constitutes 55% of blood.
2. **Cellular part:** includes red blood corpuscles (RBCs), white blood cells (WBCs), and platelets. It constitutes 45% of blood.

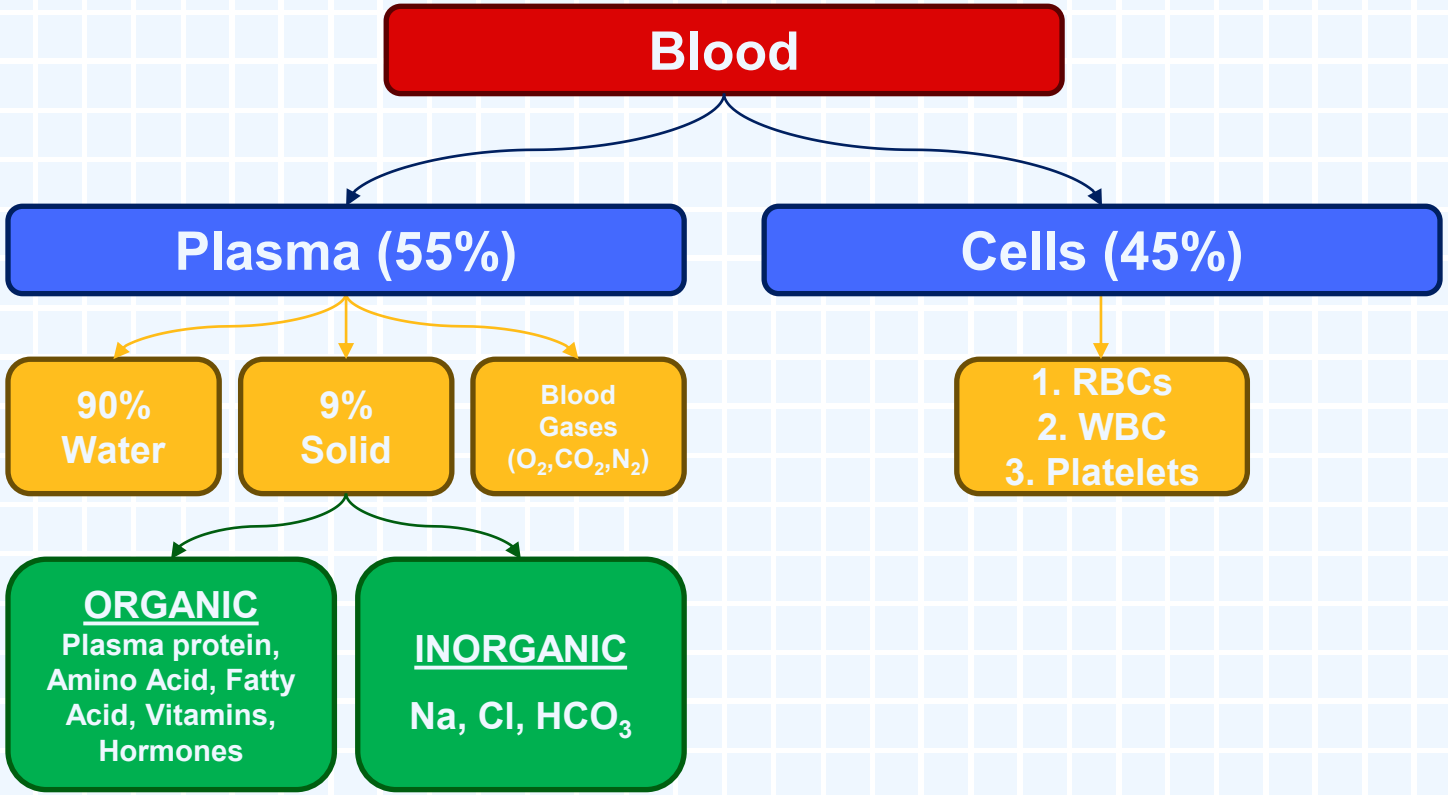
Functions of blood:

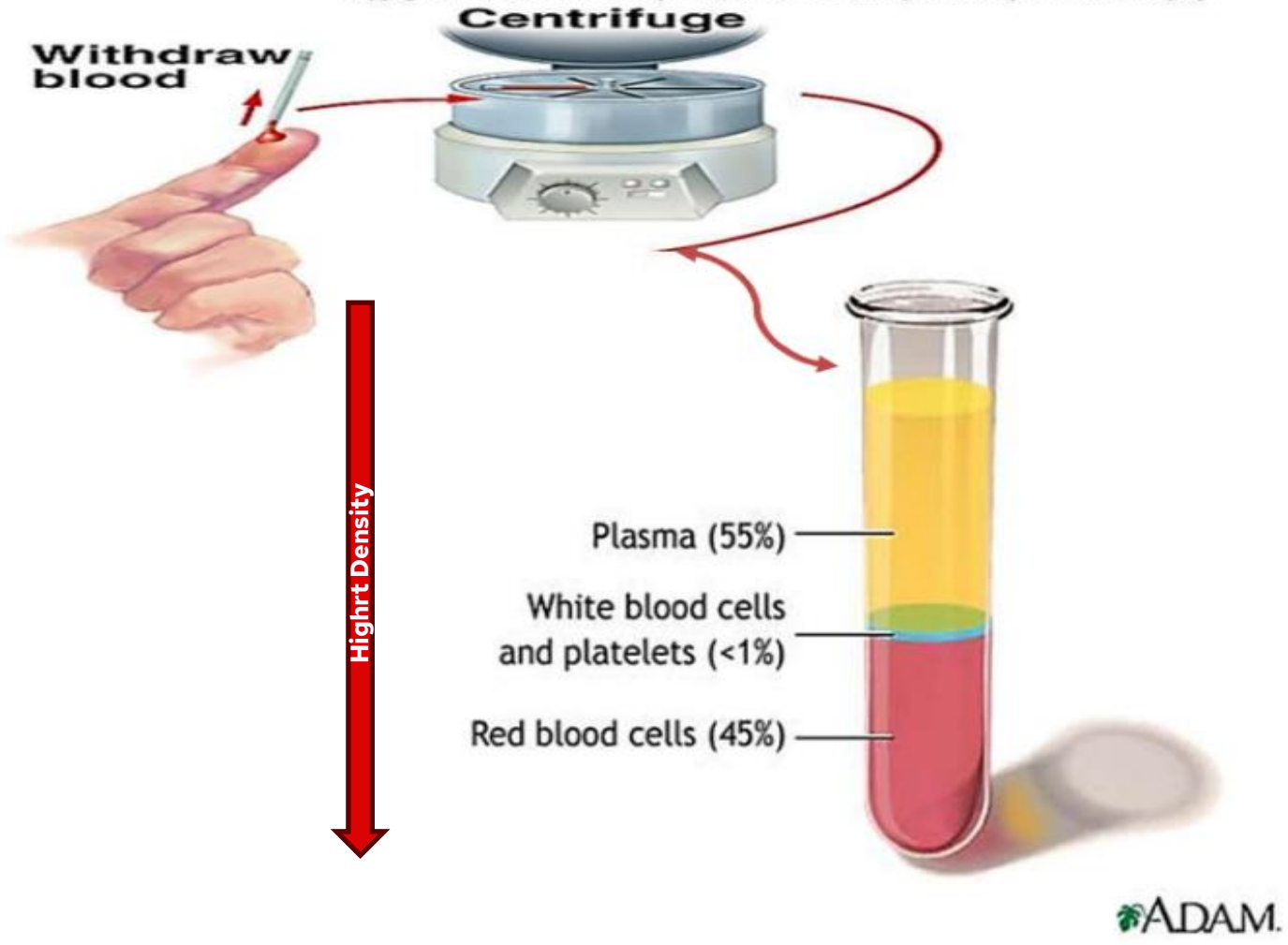
1. Transport.
2. Immune Function
3. Haemostasis [Stoppage of bleeding]
4. Homeostasis [Keeping body environment constant]

Blood


Blood; Immune System;
Integumentary System (Skin)
Body systems
maintain homeostasis
Homeostasis
Blood contributes to homeostasis by serving as the vehicle for transporting materials to and from the cells, buffering changes in pH, carrying excess heat to the body surface for elimination, minimizing blood loss when a blood vessel is damaged, and playing a major role in the body's immune defense system. The immune system defends against foreign invaders and cancer cells and paves the way for tissue repair. The integumentary system (skin) serves as a protective barrier between the external environment and the remainder of the body.
Cellular
elements
in the blood
Homeostasis is
essential for
survival of cells
Cells
Cells need a constant supply of O_2 delivered to them to support their energy-generating chemical reactions, which produce CO_2 that must be removed continuously. Cells can survive and function only within a narrow pH and temperature range, and furthermore, cells must be protected against disease-causing microorganisms.
Cells make up
body systems

Composition of Blood





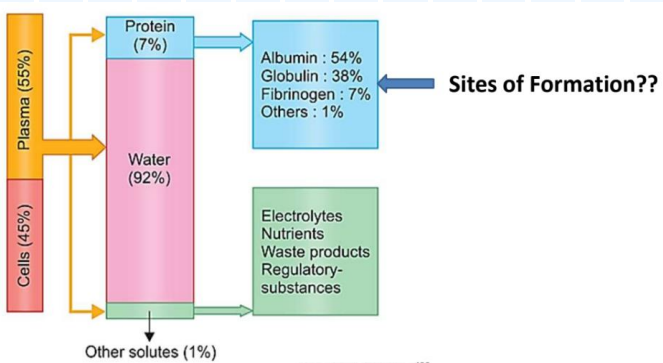
Plasma

It is a clear yellow fluid. Its volume is about 3.5 L (5% of body weight). It clots on standing. The remnant is called Serum.

Composition of Plasma

Plasma is composed of :

1. **Water:** 92%
2. **Organic substances:** Plasma proteins, Lipids, glucose, amino acids, vitamins, enzymes, and waste products.
3. **Inorganic constituents:** (Na^+, Cl^-,HCO_3^-).
4. **Blood gases:** O_2, CO_2 and N_2.



Plasma Proteins

There are many types of plasma proteins in the blood. The most important types include:

Type	Concentration (g/dl)
Albumin	3.5 - 5
Globulin (α,β,γ)	2.5
Fibrinogen	0.4
Prothrombin	0.01

Site of Formation of Plasma Protein:

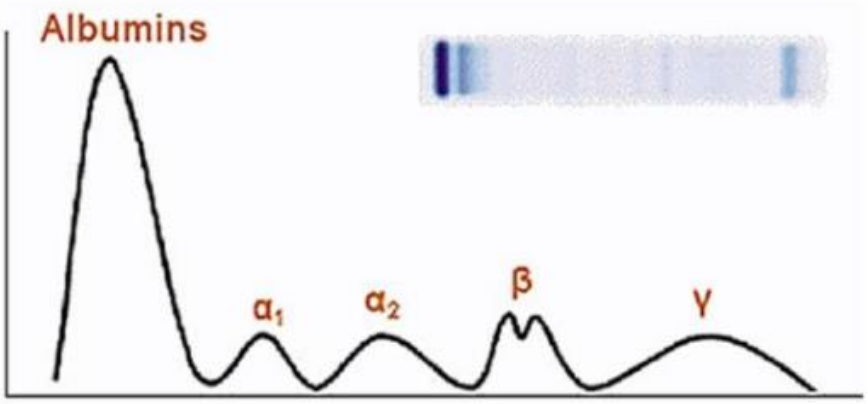
- **Albumin, fibrinogen, and prothrombin** are synthesized **in the liver.**
- **Globulins: 50% are synthesized in the liver**, and 50% (γ globulin) are synthesized in the plasma cells of the reticuloendothelial system (RES), a diffuse system of cells present in the liver, spleen, lymph nodes, and bone marrow.

Albumin/Globulin Ratio (A/G)

The Normal A/G ratio is 1.5 to 2.5 : 1

It decreases in :

1. **Liver diseases,** such as liver cirrhosis and infective hepatitis, since the liver does not produce sufficient albumin.
2. **Kidney diseases,** e.g., nephrosis, as the albumin, with its small molecular size, is lost in the urine.
3. **Infections & Inflammation:** due to increase γ globulin.

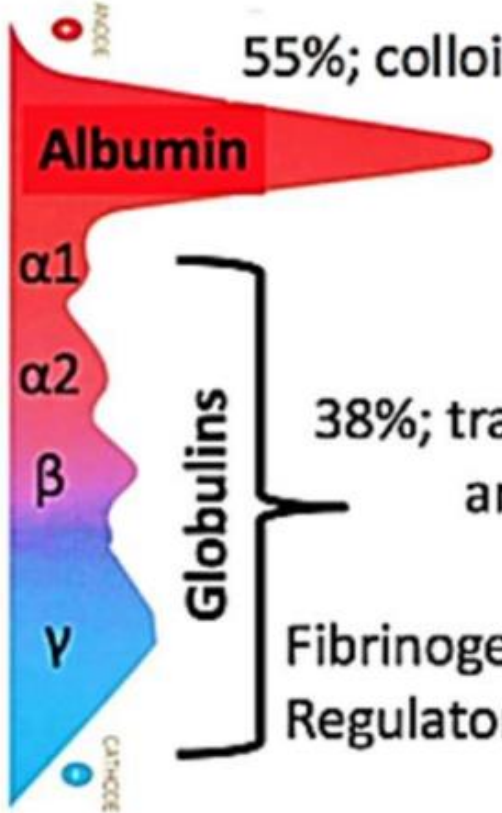


Plasma Proteins

Functions of Plasma Proteins:

1. Osmotic Function (mainly by albumin)
2. Transport function
3. Defensive function
4. Blood clotting function
5. Capillary function
6. Buffer function
7. Function as a source of tissue proteins

Plasma Proteins



55%; colloid osmotic pressure or **oncotic pressure;** lipid, steroid, and hormone transport antioxidant protein (binds metals and reacts with ROS)

38%; transport ions, hormones, and immune function (γ-globulins)

Fibrinogen (7%); clotting

Regulatory Proteins (< 1%); protease inhibitors, enzymes, hormones

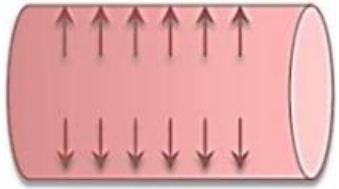
Factors controlling fluid filtration across capillary walls

Movement of fluids across capillary walls depends on the balance of starling forces acting across the capillary walls.

Starling forces
Forces that control the movement of fluid in/out of the capillary

Hydrostatic pressure P

The pressure exerted by blood (water) on the walls of the blood vessel.

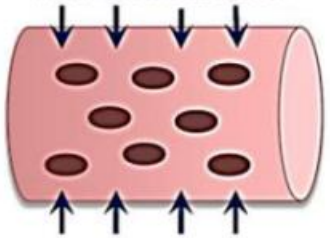


Pushes fluid OUTSIDE

Colloid osmotic(oncotic) pressure π

(especially albumin)

The osmotic pressure created by the non-diffusible plasma proteins inside the blood vessel.



Pulls fluid INSIDE

Plasma Proteins

Functions of Plasma Proteins:

1. **Osmotic Function (mainly by albumin):**

The total osmotic pressure of plasma is about 5000 mmHg:

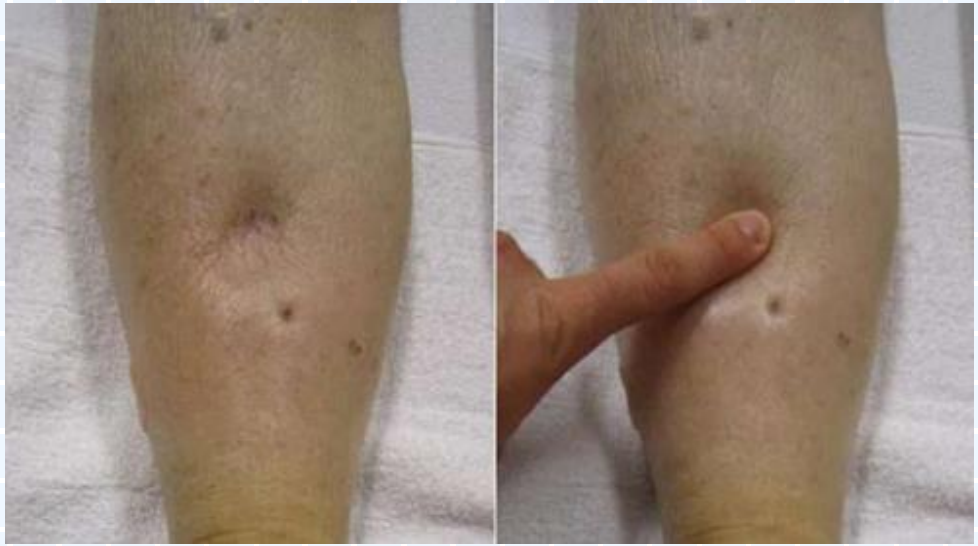
- Plasma proteins cause 25 mmHg pressure. It is known as the Colloidal Osmotic Pressure or Oncotic Pressure.

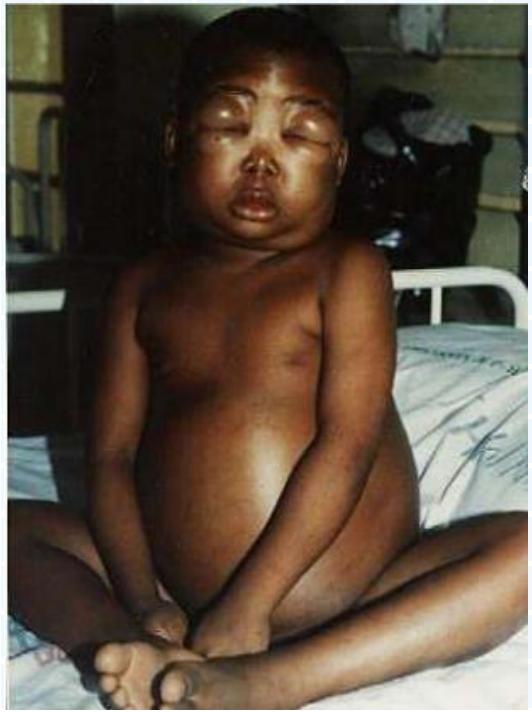
- The remaining pressure is caused by Crystalloids, e.g., Na^+, Cl^- ,HCO_3^- , and is called the Crystalloid Osmotic Pressure.

- Plasma proteins have a weaker osmotic effect, but they are more important because they cannot diffuse through the capillary membrane. Therefore, they are kept inside blood vessels and tend to draw water from interstitial fluid (ISF) into capillaries. The colloidal osmotic pressure regulates blood volume by regulating fluid exchange between ISF and blood.

Edema

Edema: It is the presence of abnormally large amounts of fluid in the intercellular tissue spaces of the body (It is excessive accumulation of fluid in the tissues). **Hypoalbuminemia** is one of the causes of edema.





Plasma Proteins

Functions of Plasma Proteins:

2. Transport function:

- Albumin and globulin (α and β) act as carriers for some substances, e.g., hormones, vitamins, lipids, and minerals. They prevent their loss of urine.

3. Defensive function :

- γ-globulins are also called immunoglobulins (antibodies). They defend the body against microorganisms and their toxins.

4. Blood clotting function :

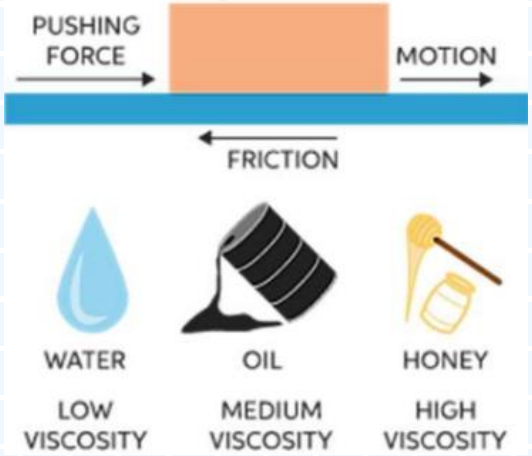
- Prothrombin and fibrinogen are essential for this process.

Plasma Proteins

Functions of Plasma Proteins:

5. Viscosity :

- Whole blood is 3-5 times as viscous as water, while plasma is 1.5 times as viscous.
- Viscosity is responsible for peripheral resistance that maintains Arterial Blood Pressure.
- Fibrinogen contributes most to plasma viscosity due to its large size and elongated shape.



Viscosity is a fluid's resistance to flow or deformation.

Determinants of Blood Pressure

$$MAP = CO \times TPR$$

$$CO = HR \times SV$$

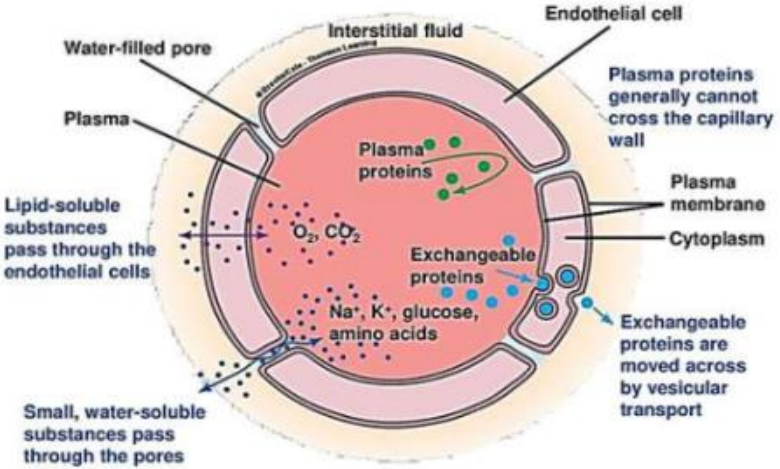
- MAP is mean Arterial pressure (normal ~100 mmHg)
- CO is Cardiac Output (normal 5 L/min)
- HR is Heart Rate (normal 72 BPM)
- SR is Stroke Volume (normal 70 L)
- TPR is Total Peripheral Resistance

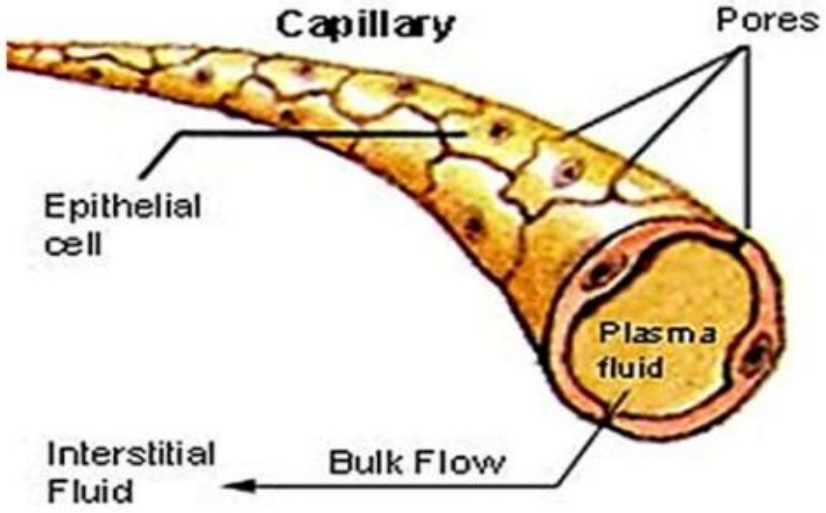
Plasma Proteins

Functions of Plasma Proteins:

6. Capillary function:

Plasma proteins are required for normal capillary permeability because they partially block capillary pores.





Plasma proteins → closes capillary pores → maintains capillary permeability.

Plasma Proteins

Functions of Plasma Proteins:

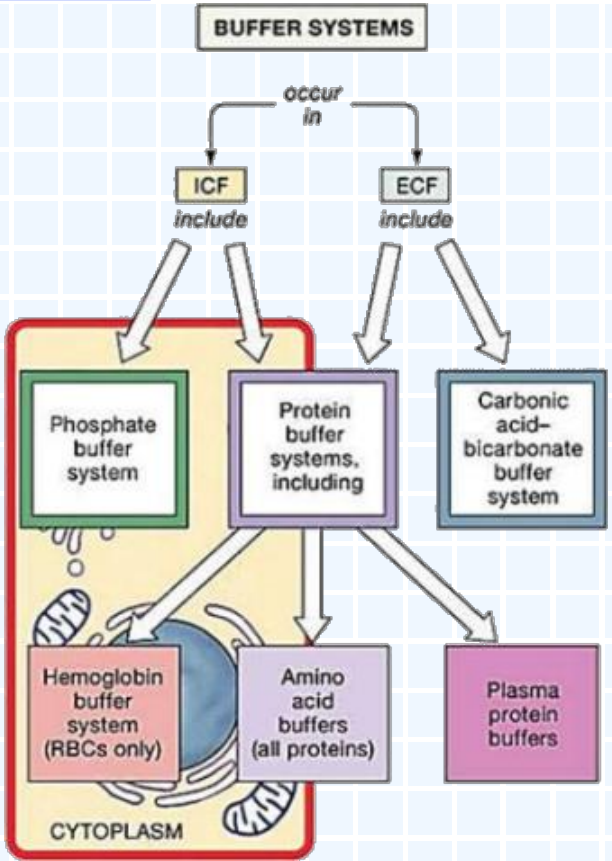
7. Buffer function:

Any buffer system consists of a Weak Acid and a Strong Base. In an alkaline medium (blood pH is alkaline: 7.4), plasma proteins form proteinic acid and sodium proteinate. So, they act as a buffer system. therefore, plasma proteins maintain the pH of blood constant at 7.4 despite the addition of acids or alkalis. They constitute 15% of the buffering power of blood.

Plasma Proteins

Functions of Plasma Proteins:

7. Buffer function:

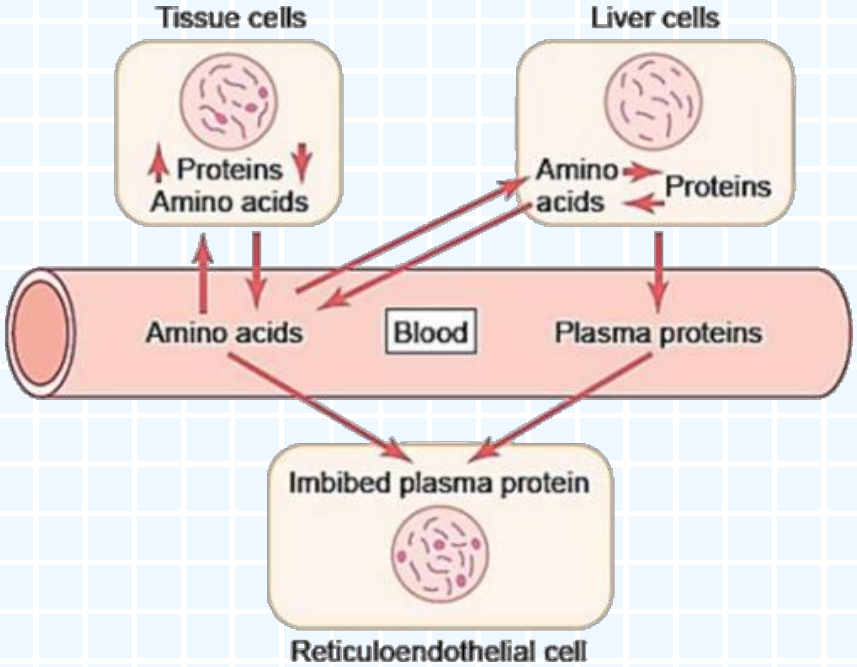


Plasma Proteins

Functions of Plasma Proteins:

8. Function as a source of tissue proteins:

Plasma proteins act as labile protein stores for tissue proteins since they are dynamic structures in continuous turnover.



RED BLOOD CORPUSCLES (RBCs) "ERYTHROCYTES"

Shape and Size of RBCs

RBCs are non-nucleated biconcave discs

Erythrocytes (RBCs) count

Adult Males: 4.5–6 million/mm3.

Adult Females: 4–5.5 millions/mm3.

Infants: higher RBCs count than adults.

Children: lower RBCs count than adults.

In Old Age: RBCs count decreases.

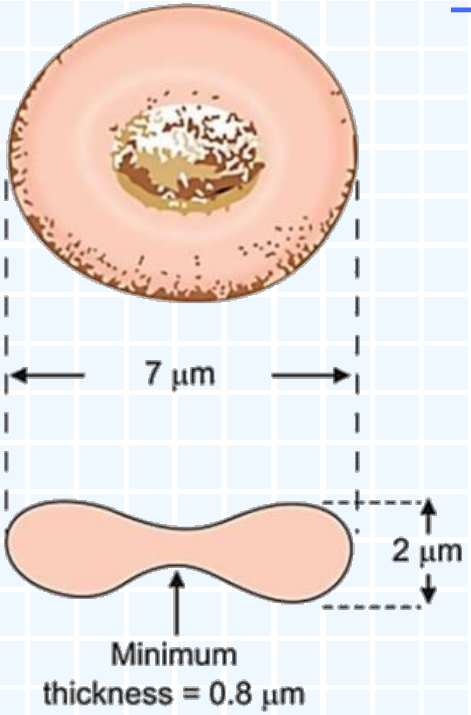
RED BLOOD CORPUSCLES (RBCs) "ERYTHROCYTES"

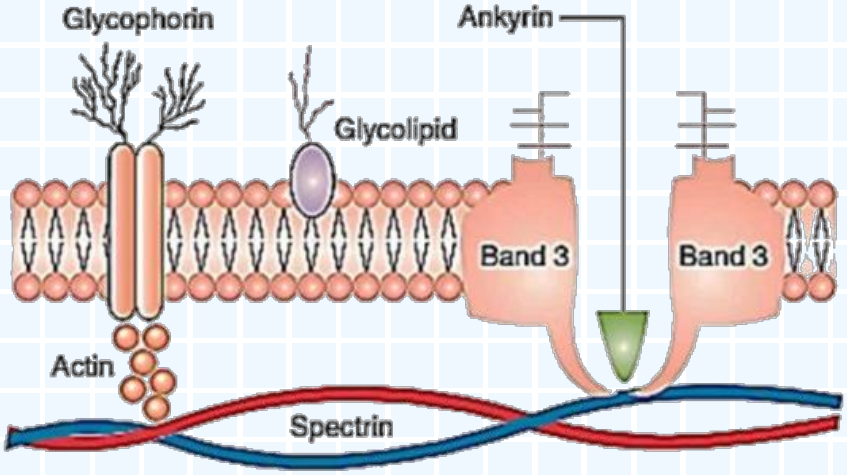
Structure of RBCs

- RBCs have no nuclei and are therefore called corpuscles. RBCs have a biconcave shape (The peripheral proteins like spectrin, ankyrin, and actin on the inner surface of the membrane help maintain the shape of the RBC). The biconcave shape has the following advantages: It has a large surface area and enhances cell flexibility allowing erythrocytes to be squeezed into tiny capillaries without rupture. Also, it results in minimal tension on the membrane when the cell volume increases in venous blood due to the transport of CO_2.
- The most important content of RBCs is Hb. K^+ is the principal intracellular cation, and Carbonic Anhydrase (CA) is an enzyme present in RBCs, which is essential for the transport of CO_2. No mitochondria exist in RBCs; therefore, they derive their energy from anaerobic glycolysis.

RED BLOOD CORPUSCLES (RBCs)
"ERYTHROCYTES"

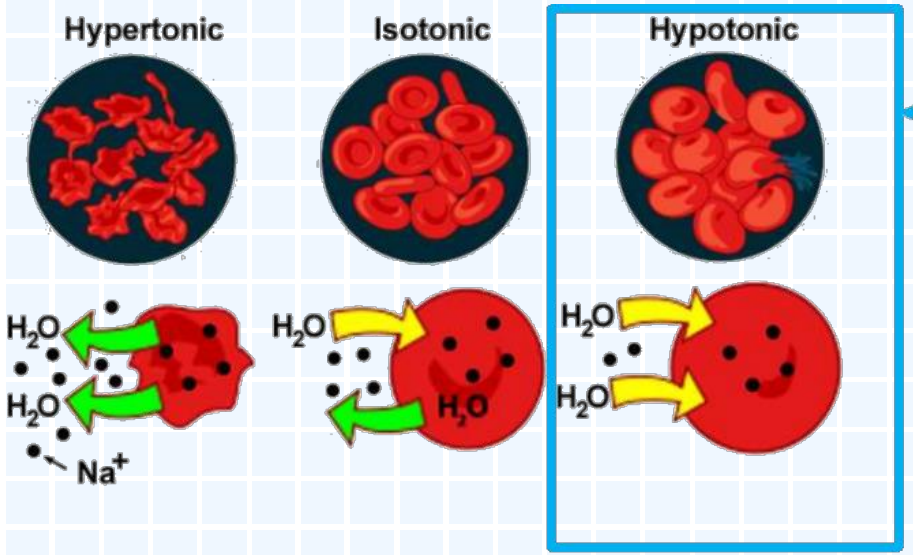
Structure of RBCs



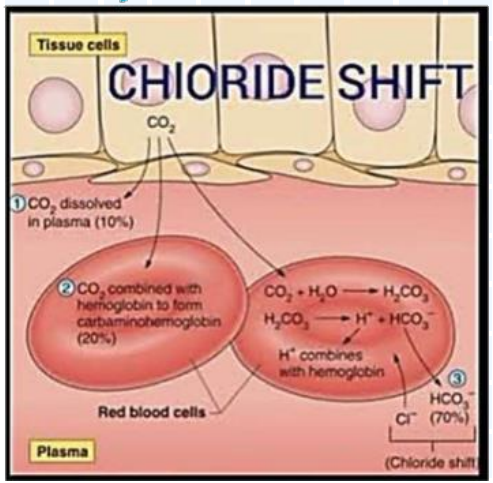


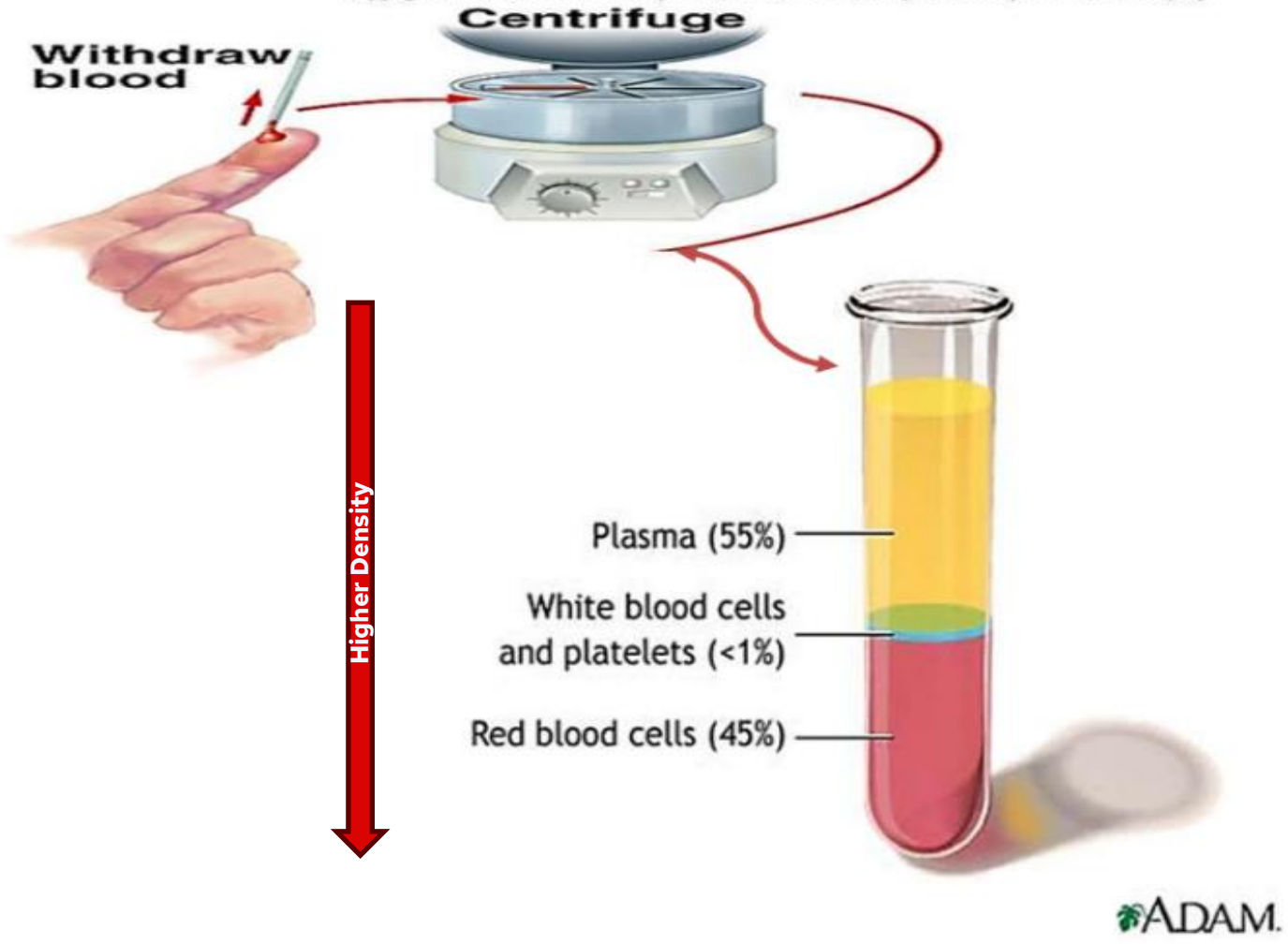
Schematic diagram showing ultra structure of red cell membrane.

RED BLOOD CORPUSCLES (RBCs)
"ERYTHROCYTES"



Venous Blood





RED BLOOD CORPUSCLES (RBCs) "ERYTHROCYTES"

Hematocrit value (Hct)=Packed cell volume (PCV)

The percentage of the blood, by volume, that is occupied by RBCs.
Hemoglobin (Hb): It is the red oxygen-carrying pigment of RBCs 46% (40–50%)for adult male and 42% (37–47%) for adult female

- **Hb content is the number of grams of hemoglobin in 100 ml (dl) of blood:**
  - **In Adult Male: 15-16 g/dl**
  - **In Adult Female: 13-14 g/dl**

RED BLOOD CORPUSCLES (RBCs)
"ERYTHROCYTES"

Characteristics of Human Red Cell

RBCs Indices (reflect the functional characteristics of RBCs)

		Male	Female
Hematocrit (Hct) (%)		47	42
Red blood cells (RBC) ($10^6/\mu L$)		5.4	4.8
Hemoglobin (Hb) (g/dL)		16	14
Mean corpuscular volume (MCV) (fL)	$= \frac{Hct \times 10}{RBC\ (10^6/\mu L)}$	87	87
Mean corpuscular hemoglobin (MCH) (pg)	$= \frac{Hb \times 10}{RBC\ (10^6/\mu L)}$	29	29
Mean corpuscular hemoglobin concentration (MCHC) (g/dL)	$= \frac{Hb \times 100}{Hct}$	34	34

RED BLOOD CORPUSCLES (RBCs) "ERYTHROCYTES"

Characteristics of Human Red Cell

- **Mean Corpuscular volume (MCV):** Average volume of single RBC.
- **Mean Corpuscular hemoglobin (MCH):** Average amount of Hb /single RBC.
- **Mean Corpuscular hemoglobin concentration (MCHC):** s the average concentration of hemoglobin in a given volume of packed red blood cells
- **Structure of Hemoglobin:** Hemoglobin is made up of 4 subunits; each is formed of a polypeptide chain and heme. The four polypeptide chains are collectively called globin. Heme is an iron protoporphyrin in which iron is in the ferrous state (Fe^{2+}).



THANK
YOU
النادي الطبي

MODULE

HLS (HEMO & LYMPH)

Physiology Lectures
Lecture No. (2)
Slides By: Malek Hassan
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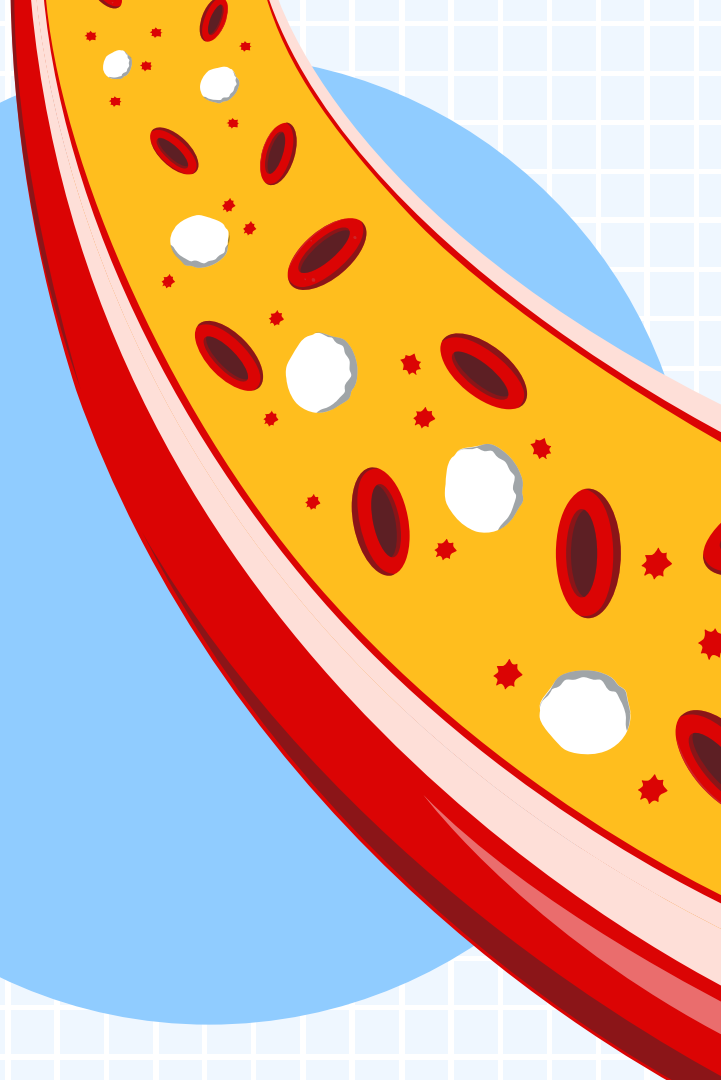
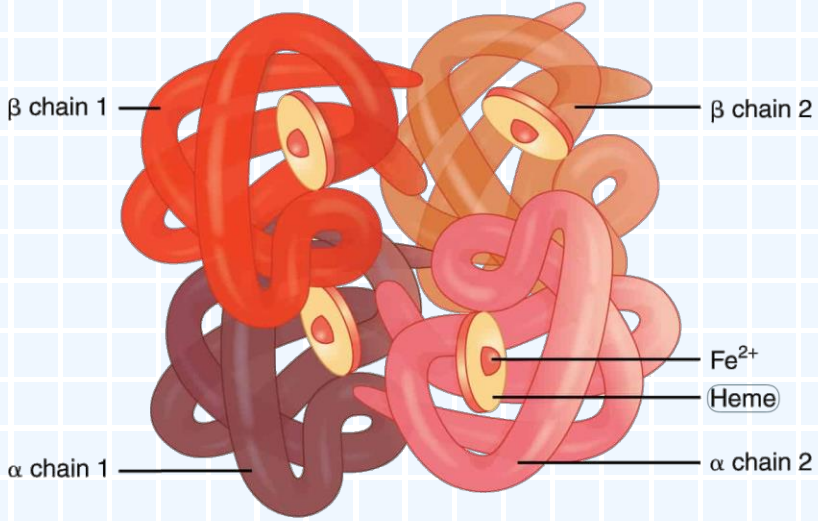


Hemoglobin:

Structure of Hemoglobin:



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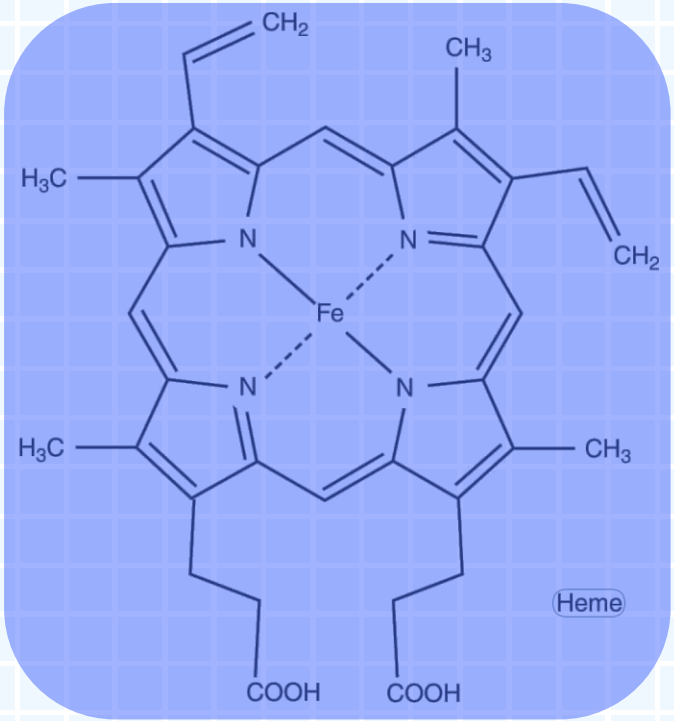


(b)

Hemoglobin:

Reactions of Hemoglobin:

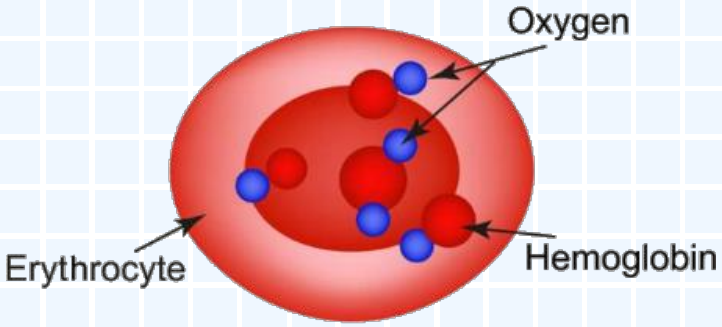
1. **Oxygenation**

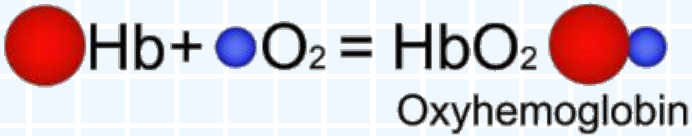
The dynamics of the reaction of hemoglobin with O_2 make it a particularly suitable O_2 carrier. Hemoglobin is a protein comprised of four subunits, each containing a heme moiety attached to a polypeptide chain. In normal adults, most hemoglobin molecules contain two α and two β chains. Heme is a porphyrin ring complex that includes one atom of ferrous iron (Fe^{2+}). Each of the four iron atoms in hemoglobin can reversibly bind one O_2 molecule. The iron stays in the ferrous state, so the reaction is oxygenation (not oxidation). It has been customary to write the reaction of hemoglobin with O_2 as $Hb + O_2 \rightleftarrows HbO_2$. Because it contains four deoxyhemoglobin (Hb) units, the hemoglobin molecule can also be represented as Hb_4, and it actually reacts with four molecules of O_2 to form Hb_4O_8.

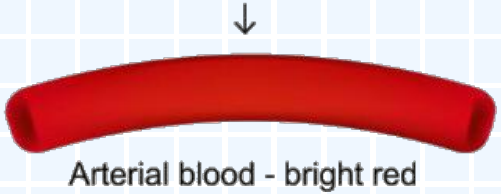
Hemoglobin:

Reactions of Hemoglobin:

1. **Oxygenation**







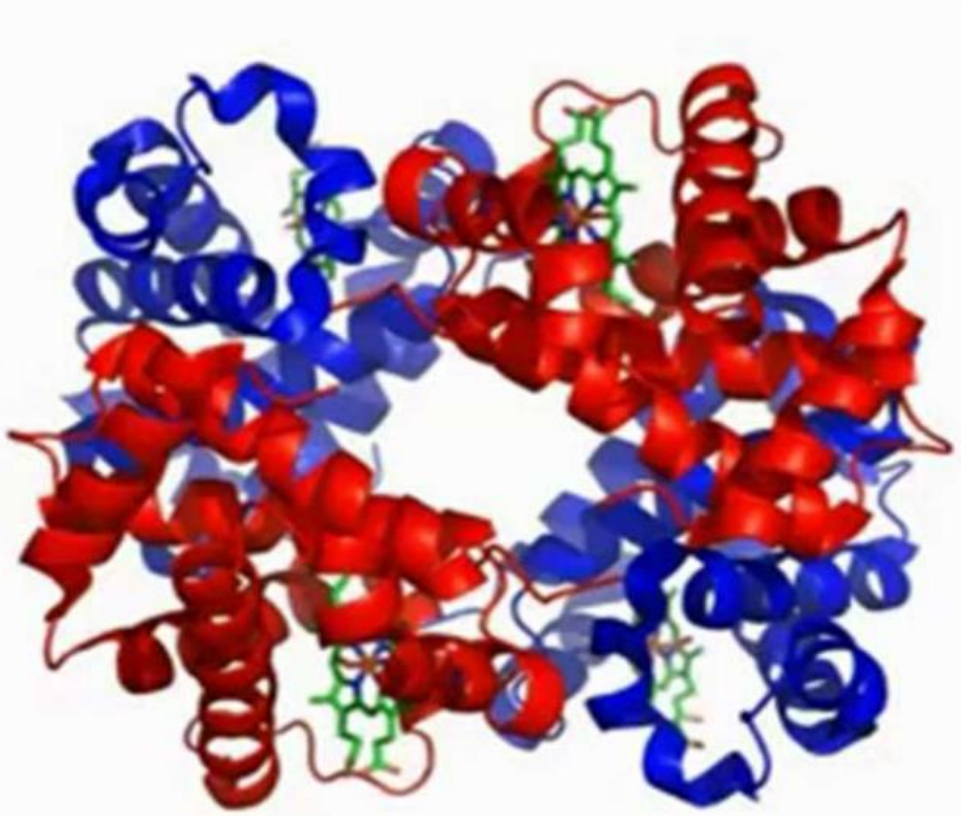
$$Hb_4 + O_2 \rightleftarrows Hb_4O_2$$

$$Hb_4O_2 + O_2 \rightleftarrows Hb_4O_4$$

$$Hb_4O_4 + O_2 \rightleftarrows Hb_4O_6$$

$$Hb_4O_6 + O_2 \rightleftarrows Hb_4O_8$$

Hemoglobin:



https://www.youtube.com/watch?v=XxElVpgNUF0&ab_channel=JamesMoss

Hemoglobin:

Reactions of Hemoglobin:

1. **Oxygenation**

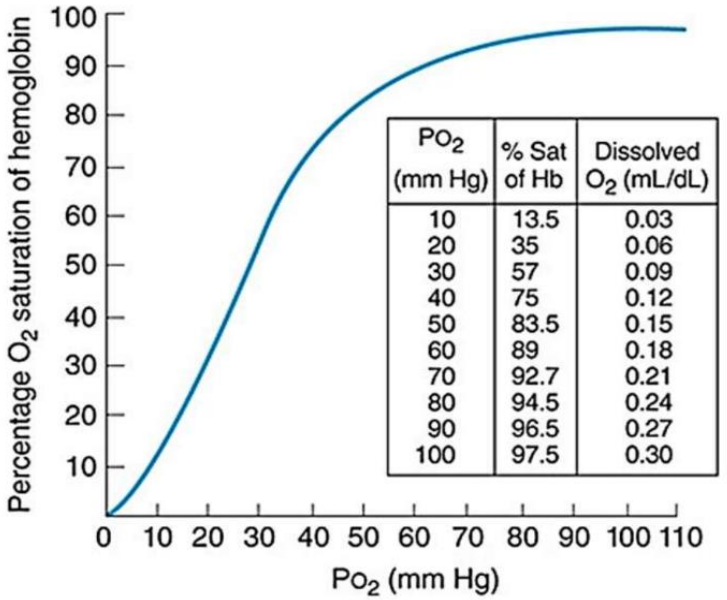
The Oxygen–Hemoglobin dissociation curve relates the percentage saturation of the O_2-carrying power of hemoglobin (abbreviated as SaO_2) to the PO_2. Due to the T–R configuration interconversion, the curve has a characteristic sigmoid shape. Combination of the first heme in the Hb molecule with O_2 increases the affinity of the second heme for O_2, and oxygenation of the second increases the affinity of the third, and so on, so that the affinity of Hb for the fourth O_2 molecule is many times that for the first.

Hemoglobin:

Reactions of Hemoglobin:

1. **Oxygenation**

The Oxygen–Hemoglobin dissociation curve



PO_2 (mm Hg)	% Sat of Hb	Dissolved O_2 (mL/dL)
10	13.5	0.03
20	35	0.06
30	57	0.09
40	75	0.12
50	83.5	0.15
60	89	0.18
70	92.7	0.21
80	94.5	0.24
90	96.5	0.27
100	97.5	0.30

-1 **Oxygen–hemoglobin dissociation curve.** pH 7.40, temperature

Hemoglobin:

Reactions of Hemoglobin:

1. **Oxygenation**

   Factors that decrease the affinity between Oxygen & Hb shift the curve to the Right, while factors that increase the affinity between Oxygen & Hb cause a curve shift to the Left. The affinity of Hb for oxygen is decreased by (Release of oxygen = Shift to the Right):

   A. **Hydrogen ions, as they compete with oxygen for deoxygenated Hb.**

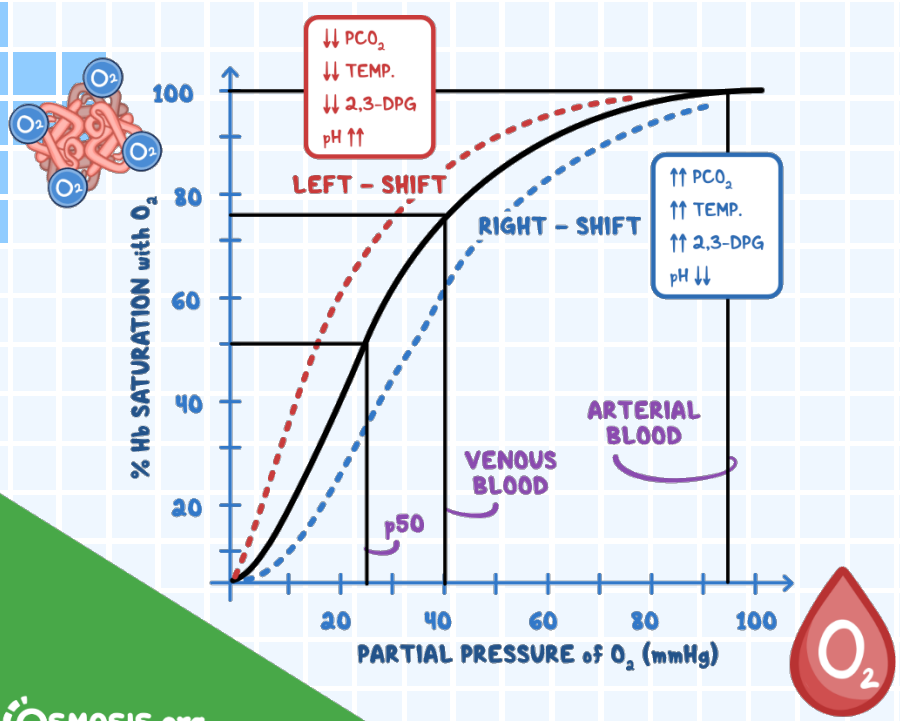
   B. **Rise of temperature.**

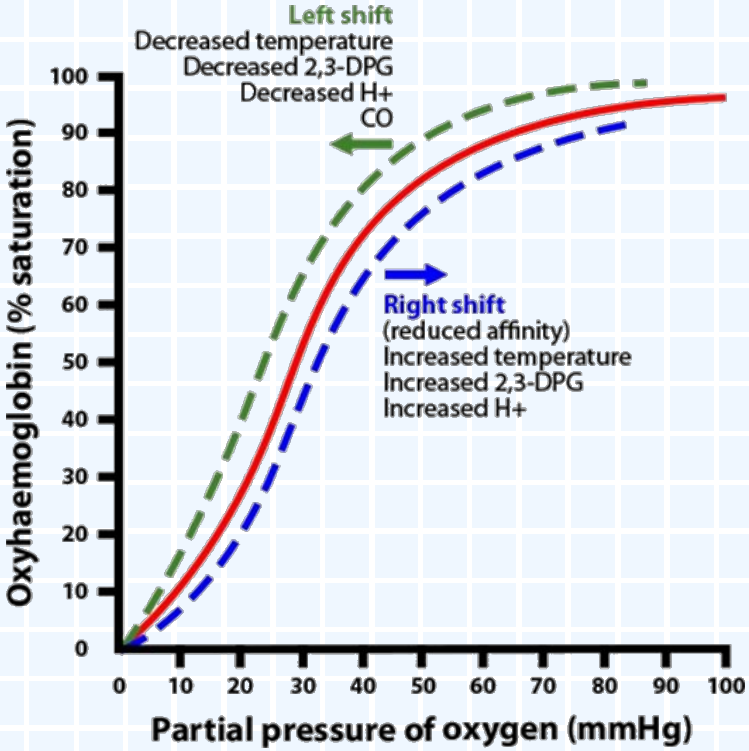
   C. **2, 3-diphosphoglycerate (2, 3-DPG) concentration (2,3-DPG is very plentiful in red cells. It is formed from 3- phosphoglyceraldehyde, a glycolysis product via the Embden–Meyerhof pathway. It is a highly charged anion that binds to the β chains of deoxyhemoglobin.**

Hemoglobin:

Reactions of Hemoglobin:

1. **Oxygenation**



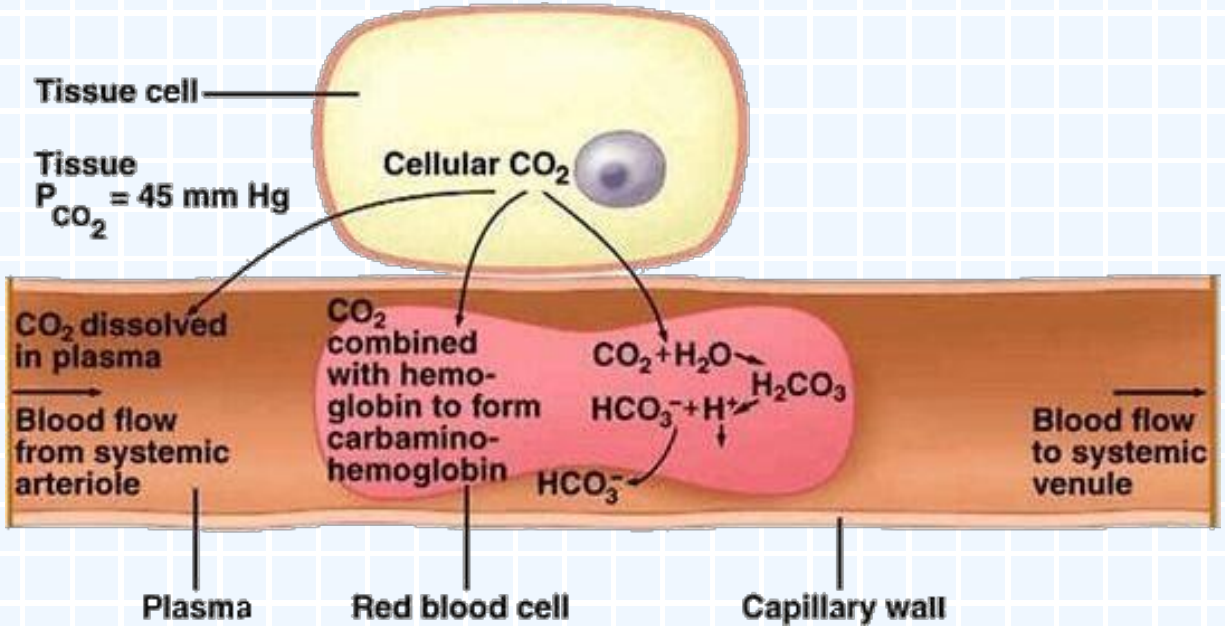


Hemoglobin:

Reactions of Hemoglobin:

2. With Carbon dioxide

Hemoglobin combines with carbon dioxide to form Carbaminohemoglobin. This is one of the ways by which the carbon dioxide added to the blood at the tissues is transported to the lungs.

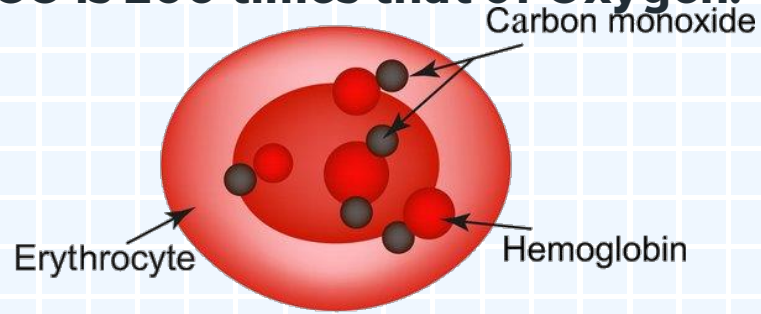


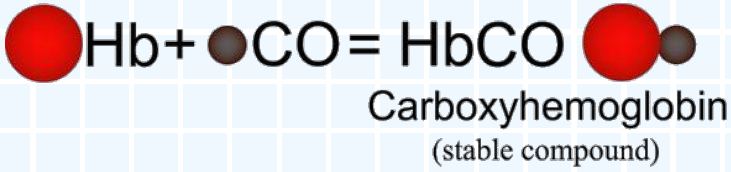
Hemoglobin:

Reactions of Hemoglobin:

3. With Carbon monoxide

Hemoglobin reacts with carbon monoxide (CO) to form Carboxyhemoglobin. CO combines with iron and displaces oxygen; thus, it prevents hemoglobin from carrying oxygen. The affinity of hemoglobin for CO is 200 times that of Oxygen.





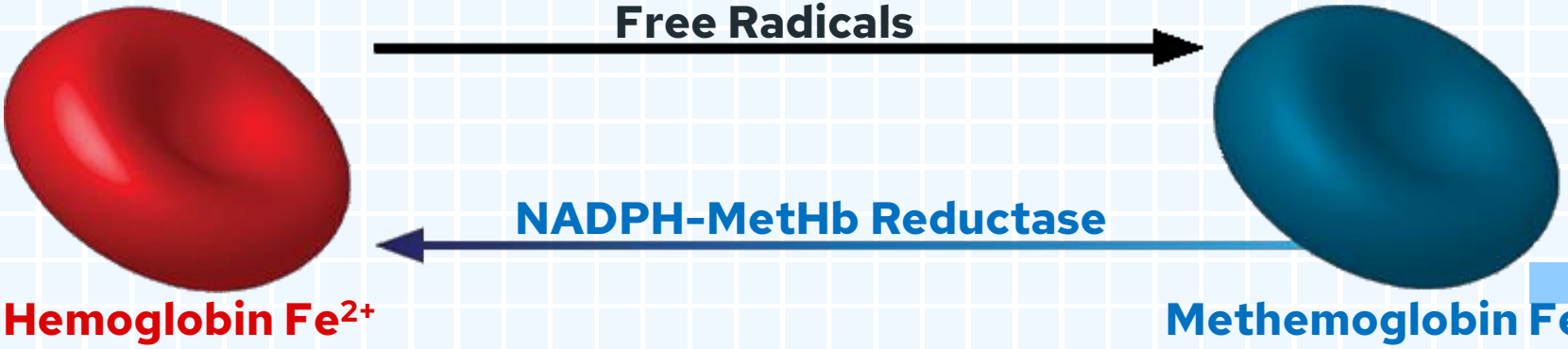
Carboxyhemoglobin cannot carry oxygen and carbon dioxide

Hemoglobin:

Reactions of Hemoglobin:

4. With Strong Oxidizing Agents

When hemoglobin is exposed to strong oxidizing agents, the Fe^{2+} iron is changed to Ferric Iron (Fe^{3+}), and the Hemoglobin is changed to dark-colored Methemoglobin, which cannot carry oxygen.
Small amounts of methemoglobin are normally formed but are reduced by NADH-MetHb Reductase back to hemoglobin.



Hemoglobin:

Types of Hemoglobin :

1. **Adult hemoglobin (HbA):**

   In Normal Adult Human hemoglobin (hemoglobin A), the two polypeptides are α chains and β chains. Thus, hemoglobin A is designated α2β2. Not all the hemoglobin in the blood of normal adults is hemoglobin A. less than 3% of the total Hb is HbA2, in which β chains are replaced by δ chains (α2δ2).

   Small amounts of hemoglobin A derivatives closely associated with hemoglobin A represent glycated hemoglobin. One of these, hemoglobin A1c (HbA1c), has glucose attached to the terminal valine in each β chain and is of particular interest because it increases in the blood of patients with poorly controlled diabetes mellitus and is measured clinically as a marker of the progression of that disease and the effectiveness of treatment.

2. **Fetal hemoglobin (HbF):**
3. **Other:**

Hemoglobin:

Types of Hemoglobin :

1. **Adult hemoglobin (HbA):**
2. **Fetal hemoglobin (HbF):**

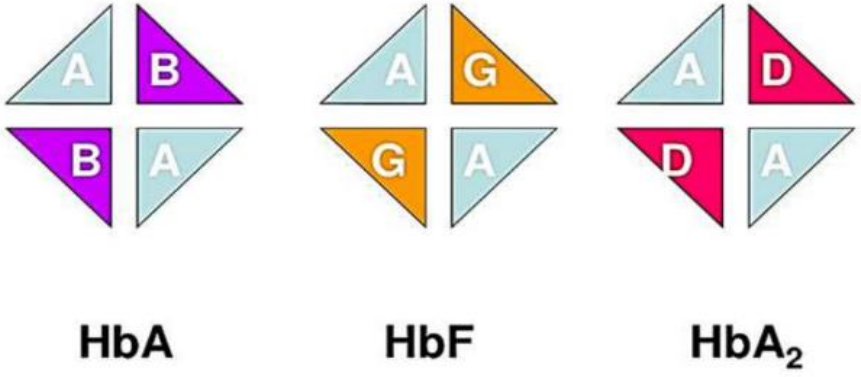
   The blood of the Human Fetus normally contains fetal hemoglobin (Hemoglobin F). Its structure is like that of hemoglobin A except that γ chains replace the β chains; that is, hemoglobin F is α2γ2. The cause of this greater affinity is the poor binding of 2,3-DPG by the γpolypeptide chains that replace β-chains in fetal hemoglobin. Fetal hemoglobin is normally replaced by adult hemoglobin soon after birth. Hemoglobin F is, therefore, critical to facilitate the movement of O_2 from the maternal to the fetal circulation.

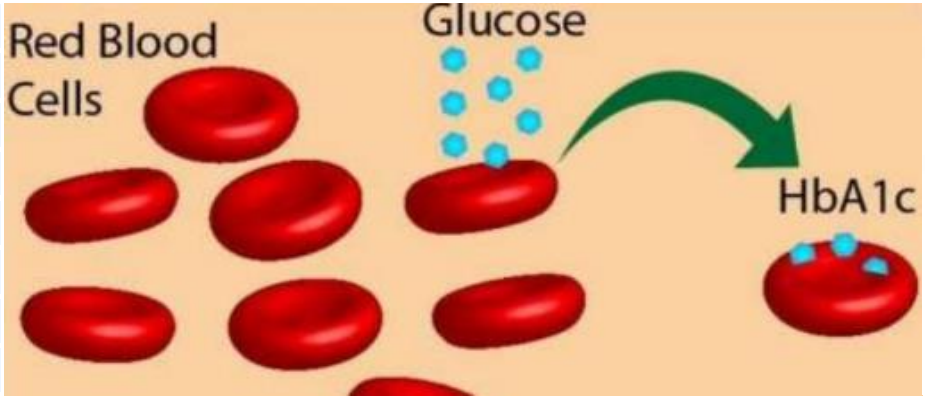
3. **Other:**

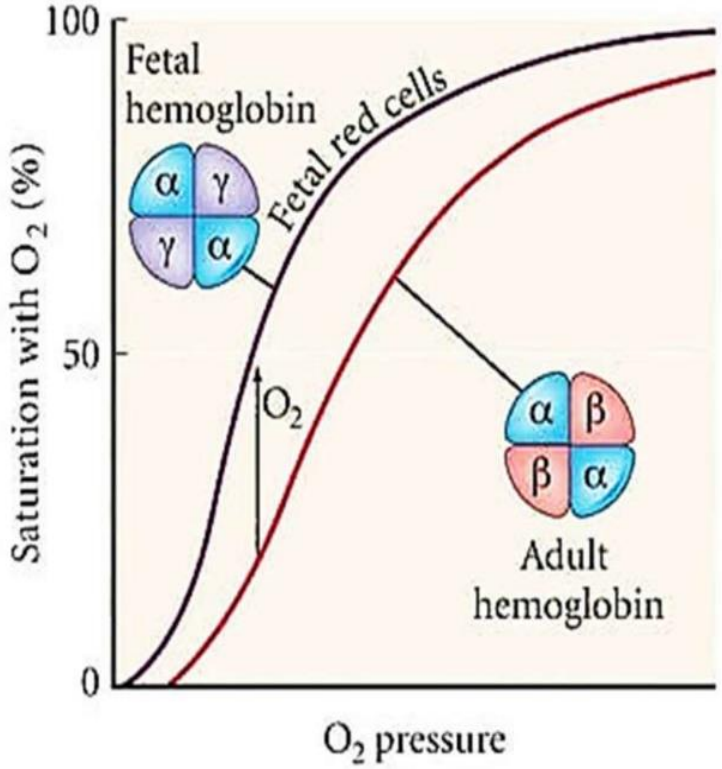
   In Young Embryos, there are Gower 1 hemoglobin and Gower 2 hemoglobin. Switching from one form of hemoglobin to another during the development

Hemoglobin:

Types of Hemoglobin :

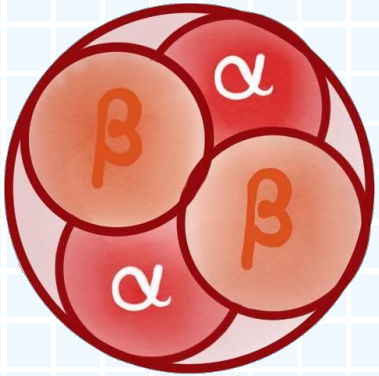






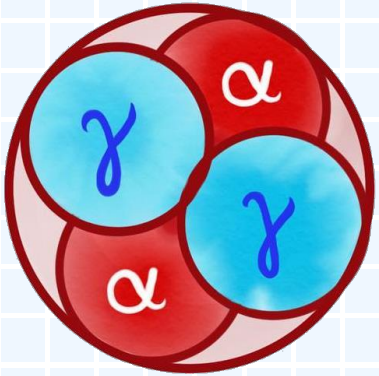
Hemoglobin:

Types of Hemoglobin :



Adult Haemoglobin
Hb A

2 x Beta chains
2 x Alpha chains



Fetal Haemoglobin
Hb F

2 x Gamma chains
2 x Alpha chains

Functions of RBCs

Functions of Hemoglobin :

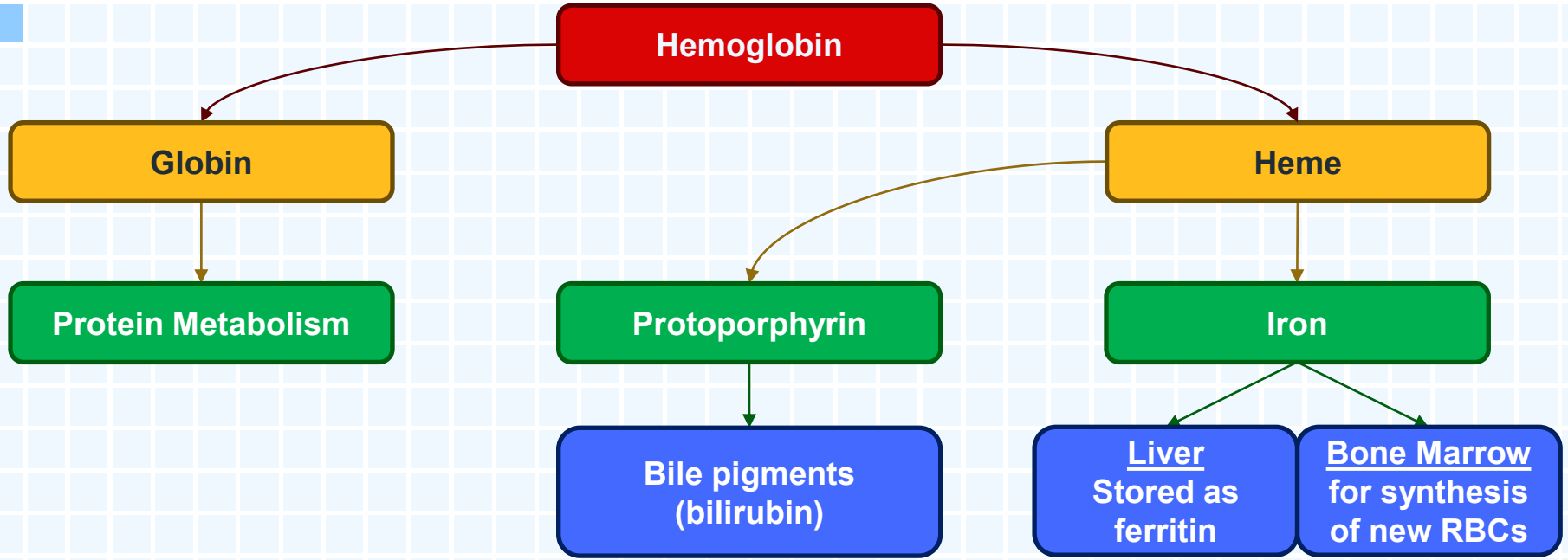
1. **The transport of Oxygen from lungs to tissues & Carbon dioxide** (involving CA enzyme reaction) from tissues to lungs is the most important function of RBCs. Carbonic Anhydrase in RBCs converts the carbon dioxide taken up by them:

2. **Hemoglobin is an important buffer.**
   It has Six Times more buffering power than plasma proteins. Therefore, it can buffer H^+ inside RBCs (formed during CO_2 transport) and can carry CO_2 with minimal change in pH. Hemoglobin-Carrying CO_2 (deoxyHb) is a stronger buffer than Hemoglobin-Carrying O_2 since deoxyHb dissociates less (i.e., it forms a Weaker Acid = a Stronger Buffer).

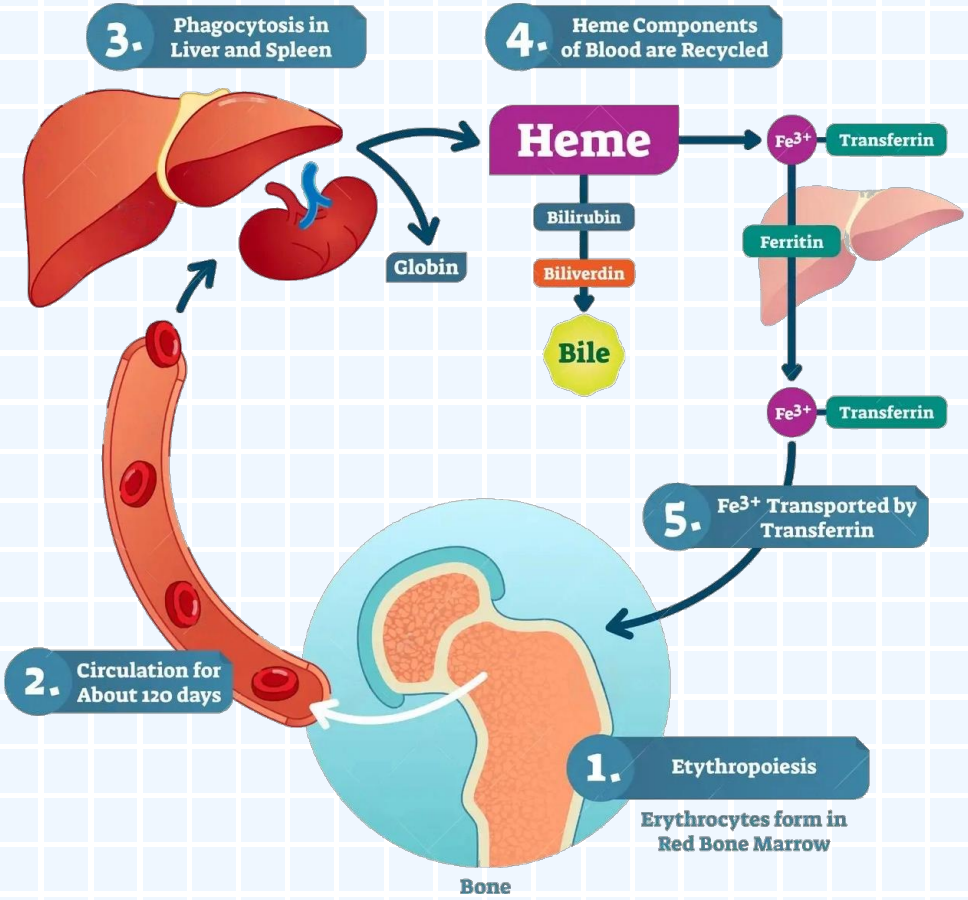
Life Span and Fate of RBCs

The life span of RBCs is 120 days. Old RBCs have fragile walls, which rupture easily when RBCs pass through very narrow blood vessels, especially in the spleen.

Hemoglobin is rapidly captured by the cells of the RES and broken into:



Life Span and Fate of RBCs

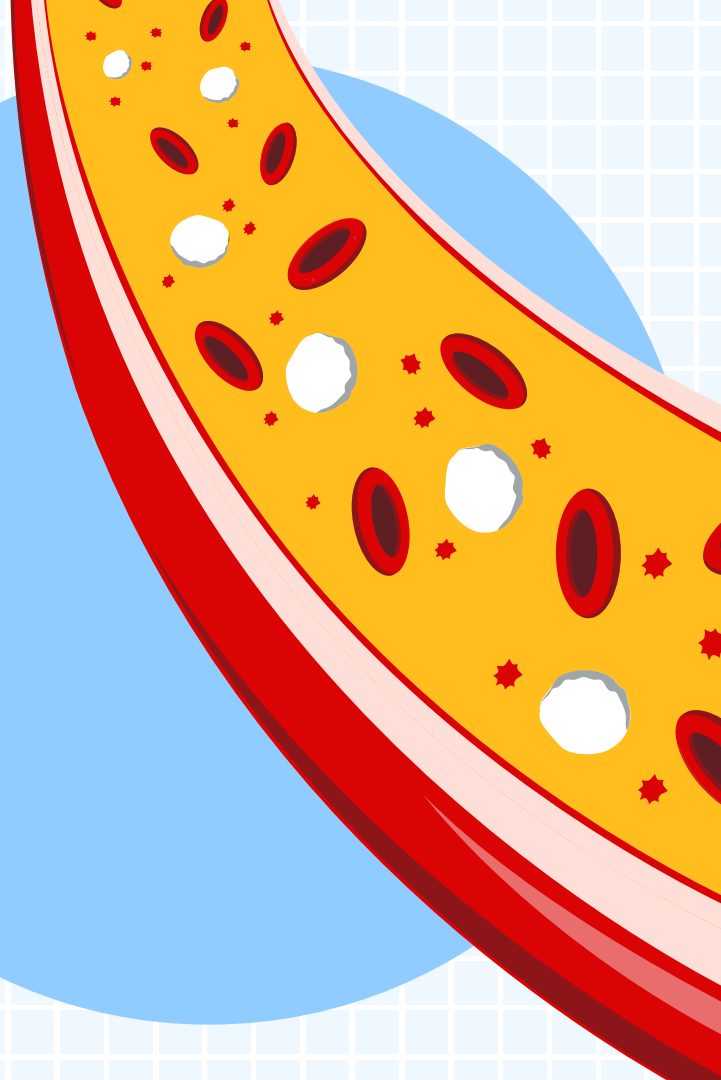




THANK
YOU
النادي الطبي

MODULE
HLS (HEMO & LYMPH)

Physiology Lectures
Lecture No. (3)
Slides By: Malek Hassan
Notes By:



ERYTHROPOIESIS

Definition: It is the process of formation of new RBCs.

Sites of Erythropoiesis:

- **In the Fetus:** RBCs are formed in the liver and spleen.
- **After Birth:** RBCs are formed in the red bone marrow of long bones.
- **By the age of 20:** The red bone marrow in long bones becomes replaced by fatty tissue and cannot produce RBCs.
- **After the age of 20:** The bone marrow of flat membranous bones, such as ribs, vertebrae, pelvis, sternum, and skull, produce RBCs.

ERYTHROPOIESIS

Middle Trimester of Gestation

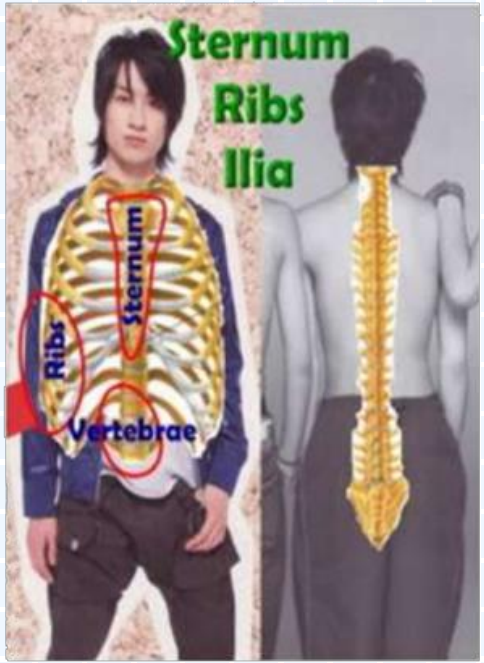
Liver
Spleen
Lymph Nodes

Last Trimester After Birth

Red bone marrow
(Bone marrow of all bones)

After 20

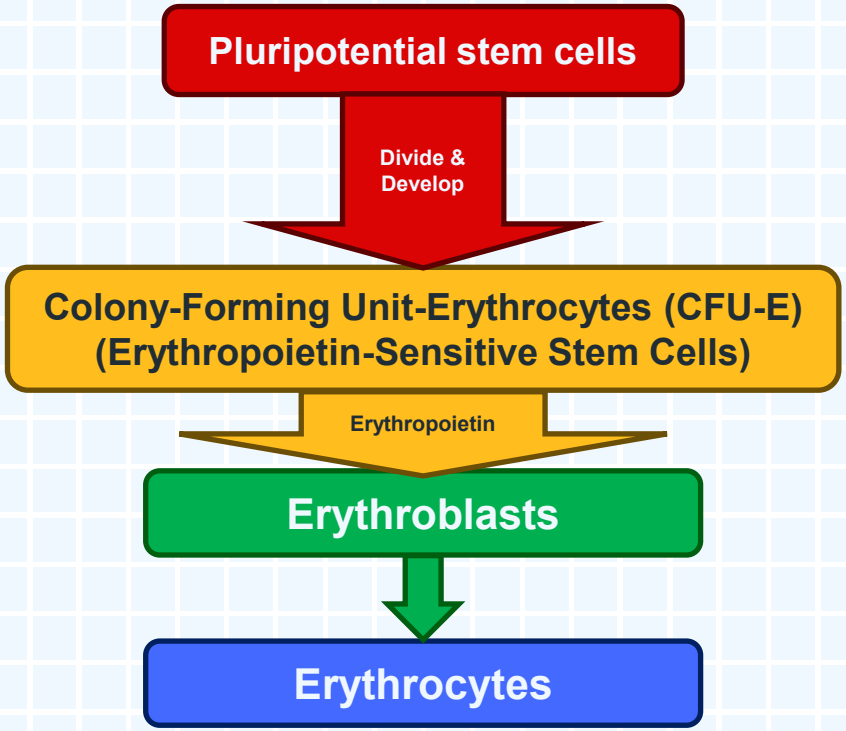
Membranous bones:
Vertebrae
Sternum
Ribs
Ilia



ERYTHROPOIESIS

Stages of Differentiation of RBCs:

Pluripotential stem cells in the bone marrow can develop into any blood cells.



ERYTHROPOIESIS

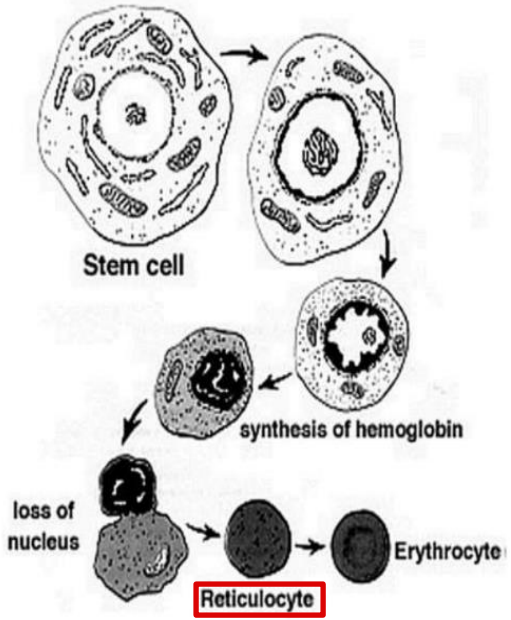
In Adult Male	4.5-6 (average 5.2) millions per cu mm of blood
In Adult Female	4-5.5 (average 4.7) millions per cu mm of blood
In Newborn	6-8 millions per cu mm of blood
In Children	3-5 millions per cu mm of blood

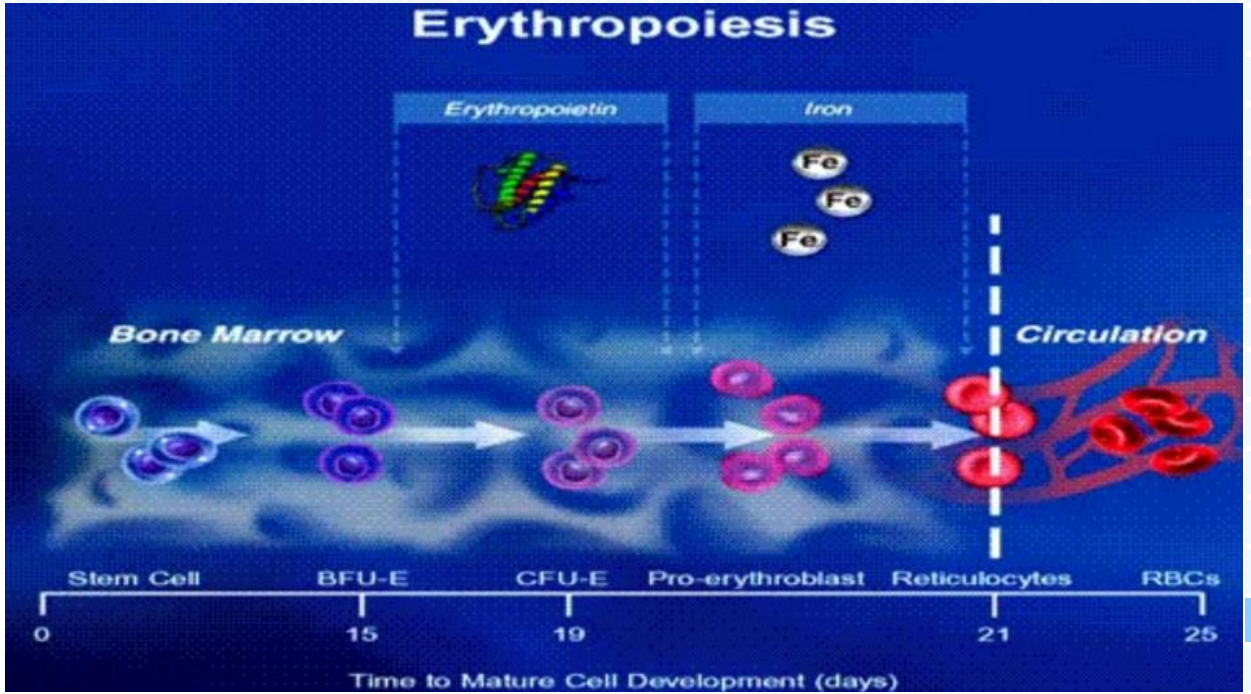
ERYTHROPOIESIS

Reticulocytes : are the immediate precursor of RBCs, following their release to the blood stream they mature within 1-2 days into RBCs. Contain a small amount of basophilic material, mainly remnants of the Golgi apparatus & mitochondria. They normally make less than 1-2% of all RBCs. Used to estimate the degree of effective erythropoiesis. Their number increases in cases of bleeding and RBC hemolysis and decreases in cases of bone marrow failure.

ERYTHROPOIESIS

Stages of Differentiation of RBCs:





ERYTHROPOIESIS

Hematopoietic growth factors

GM-CSF (granulocyte monocytes colony stimulating factor)

IL-1
IL-3

G-CSF

M-CSF

EPO

Other factors:

- Interferon «.ß, and y
- Leukemia inhibiting factor
- Oncostatin
- Transforming growth
- factor
- Insulin-like growth factor
- Fik ligand. vascular
- endothelial factor

ERYTHROPOIESIS

Factors Affecting Erythropoiesis:

I. Role of Erythropoietin and Oxygen Supply to the Tissues :

There is an increased rate of production of RBCs in conditions associated with hypoxia, such as:

1. **Hemorrhage:** hypoxia is due to the loss of RBCs.
2. **High Altitude:** hypoxia is due to decreased O_2 tension in atmospheric air.
3. **Athletes:** athletes have a relative oxygen deficiency since they have higher oxygen requirements than normal.
4. **Heart Failure:** hypoxia is due to decreased blood flow in peripheral vessels.
5. **Lung Diseases:** hypoxia is due to decreased oxygen diffusion from the lungs to the blood. Tissue hypoxia stimulates the release of a hormone called “erythropoietin“.

ERYTHROPOIESIS

Erythropoietin Hormone:

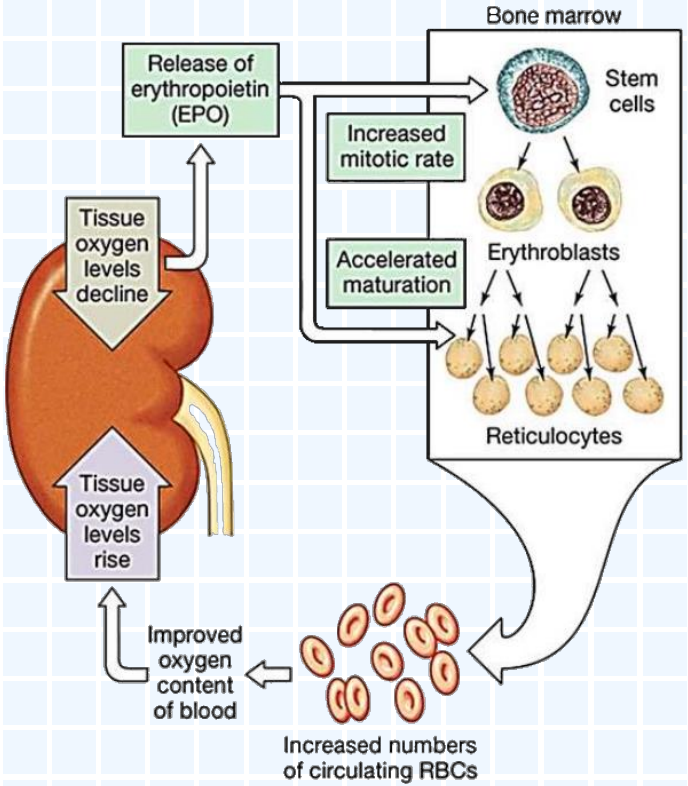
Sources:

In Adults: 85% are produced in the kidneys and 15% in the liver. Therefore, anemia develops in kidney diseases and nephrectomy, as the liver cannot compensate for the erythropoietin deficiency.

ERYTHROPOIESIS

Factors Affecting Erythropoiesis:

I. Role of Erythropoietin and Oxygen Supply to the Tissues :



ERYTHROPOIESIS

Mechanism of action of Erythropoietin :

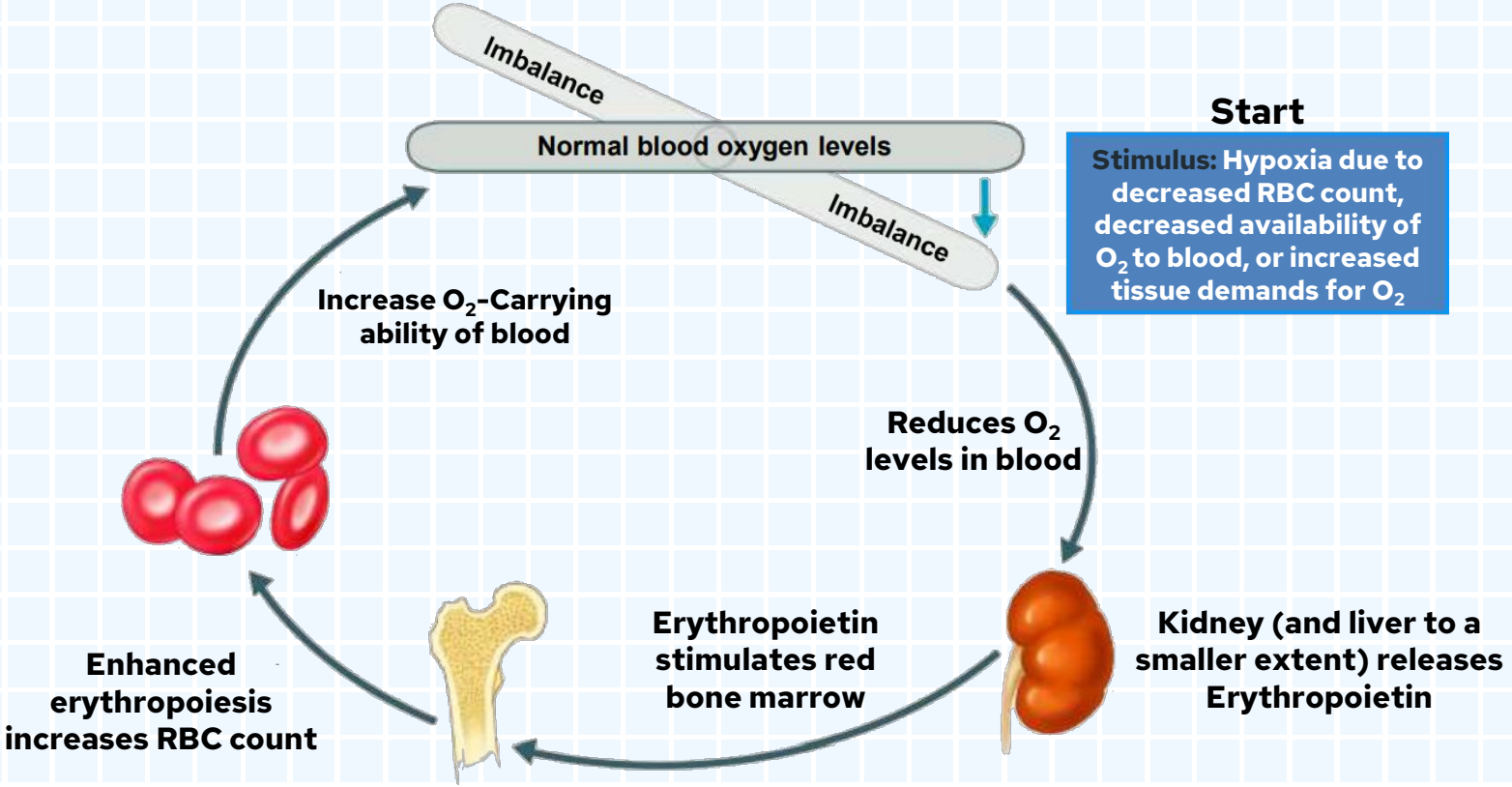
- It accelerates all steps of erythropoiesis as it Stimulates mRNA synthesis. It also Shortens the maturation time of RBCs in the bone marrow.

Stimulation of Secretion :

- Hypoxia is the main stimulus.
- Conditions that increase Oxygen hemoglobin affinity increase Erythropoietin secretion like Alkalosis or other causes of Oxy-Hb dissociation curve to be shifted to the left.
- Cobalt salts and androgens.
- Beta-Adrenergic agonists and adenosine.

ERYTHROPOIESIS

Mechanism of action of Erythropoietin :



ERYTHROPOIESIS

Factors Affecting Erythropoiesis:

II. Diet :

A. Proteins:

B. IRON:

C. Vitamin B12

D. Folic Acid

E. Vitamin C

F. Copper & Cobalt

ERYTHROPOIESIS

Factors Affecting Erythropoiesis:

II. Diet :

A. Proteins:

High-biological value proteins (containing all essential amino acids) of animal origin are needed for normal erythropoiesis.

B. IRON:

Functions of Iron :

1. Formation of Hb in RBCs and myoglobin in muscles.
2. Co-factor for some oxidation enzymes, e.g., catalase, peroxidase, and cytochrome oxidase.

Total body Iron : about 4 g.

ERYTHROPOIESIS

Factors Affecting Erythropoiesis:

II. Diet :

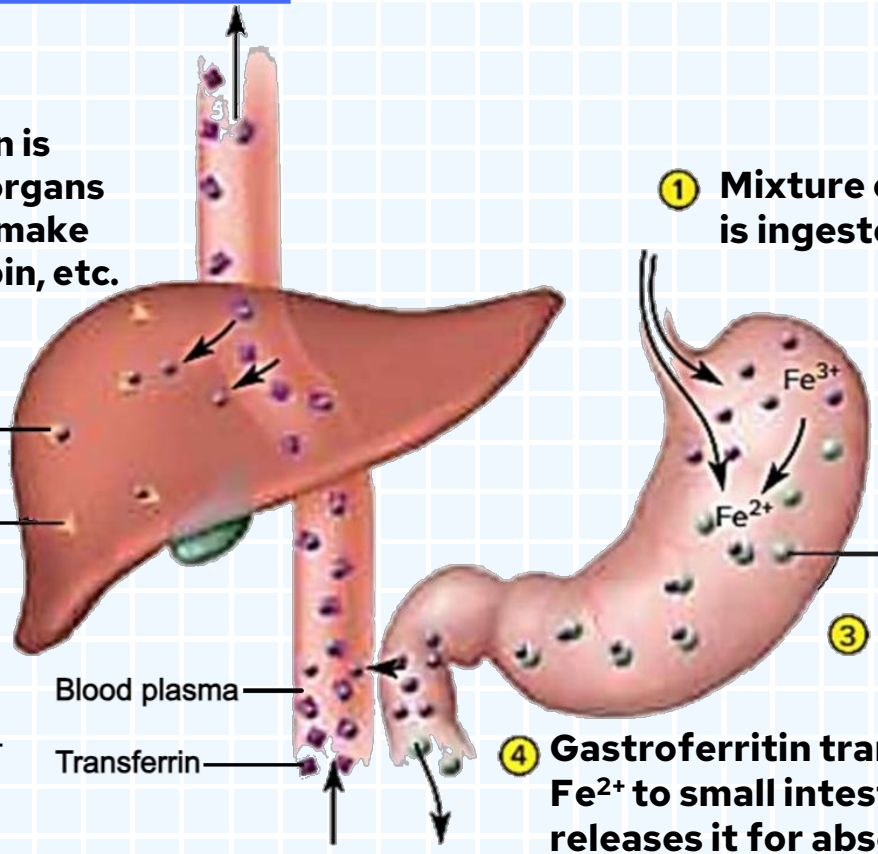
B. IRON

⑧ Remaining transferrin is distributed to other organs where Fe^{2+} is used to make hemoglobin, myoglobin, etc.

⑦ Fe^{2+} binds to Apoferritin to be stored as Ferritin

⑥ In liver, some transferrin releases Fe^{2+} for storage

⑤ In Blood plasma, Fe^{2+} binds to transferrin



① Mixture of Fe^{2+} & Fe^{3+} is ingested

② Stomach Acid converts Fe^{3+} to Fe^{2+}

③ Fe^{2+} binds to Gastroferritin

④ Gastroferritin transports Fe^{2+} to small intestine & releases it for absorption

ERYTHROPOIESIS

Iron Absorption, Transport, and Storage:

- Most dietary iron is Ferric (Fe^{3+}), which is reduced by **Stomach HCl** & **Vitamin C** (**Ascorbic Acid**) to Ferrous (Fe^{2+}) → more readily absorbed.
- **Phytic Acid** (in cereals), **Oxalates**, & **Phosphates** prevent iron absorption as they form insoluble complexes.
- Iron absorption occurs in the **Upper part of the Small Intestine** by an **active process** → carried by **Transferrin** in blood and transported to the bone marrow to form Hb and to the muscles to form myoglobin.
- Excess iron is stored in the **liver** & **spleen** as **Ferritin.**
- Ferrous iron (Fe^{3+}) is transported into the **Enterocytes** by **divalent metal transporter 1** (**DMT1**) present at the apical membrane of these cells. The iron that is not reduced in the stomach and reaches the duodenum in the Fe^{3+} form will still be reduced by a reductase enzyme associated with **DMT1** before it can be transported by **DMT1** into the enterocyte.

ERYTHROPOIESIS

Iron Absorption, Transport, and Storage:

- **Heme** can be **transported into the enterocytes** by the specific **Heme Carrier Protein** (**HCP1**) present **in the apical membrane of the enterocytes**. Iron is released from heme by the action of the **Heme Oxygenase Enzyme** inside the enterocytes.

- **Inside the enterocyte**, iron transported by **DMT1** and **HCP1** has **one of two fates, Depending on body Requirements:** If the body stores of iron are replete, and there is **no increased rate of erythropoiesis**, most of the iron inside the enterocytes is **stored in the form of Ferritin**. Because duodenal enterocytes' lifespan is very short (approximately 3-4 days), this **intracellular Ferritin iron is quickly lost into the intestinal lumen as the aging enterocytes are sloughed off and excreted in stools.** If, on the other hand, there is increased demand by the body, then **most of the iron inside the enterocytes is transported out of the cells at their basolateral border to reach the bloodstream.** The **export of iron out of the enterocytes at the basolateral border occurs through an iron export protein called** (**Ferroportin**) While **Fe^{2+} is transported out of the enterocytes**, it is **oxidized to Fe^{3+} form by the action of the** (**Ferrioxidase Enzyme**) This enzyme is **present on the basolateral border of the enterocytes in association with Ferroportin.**

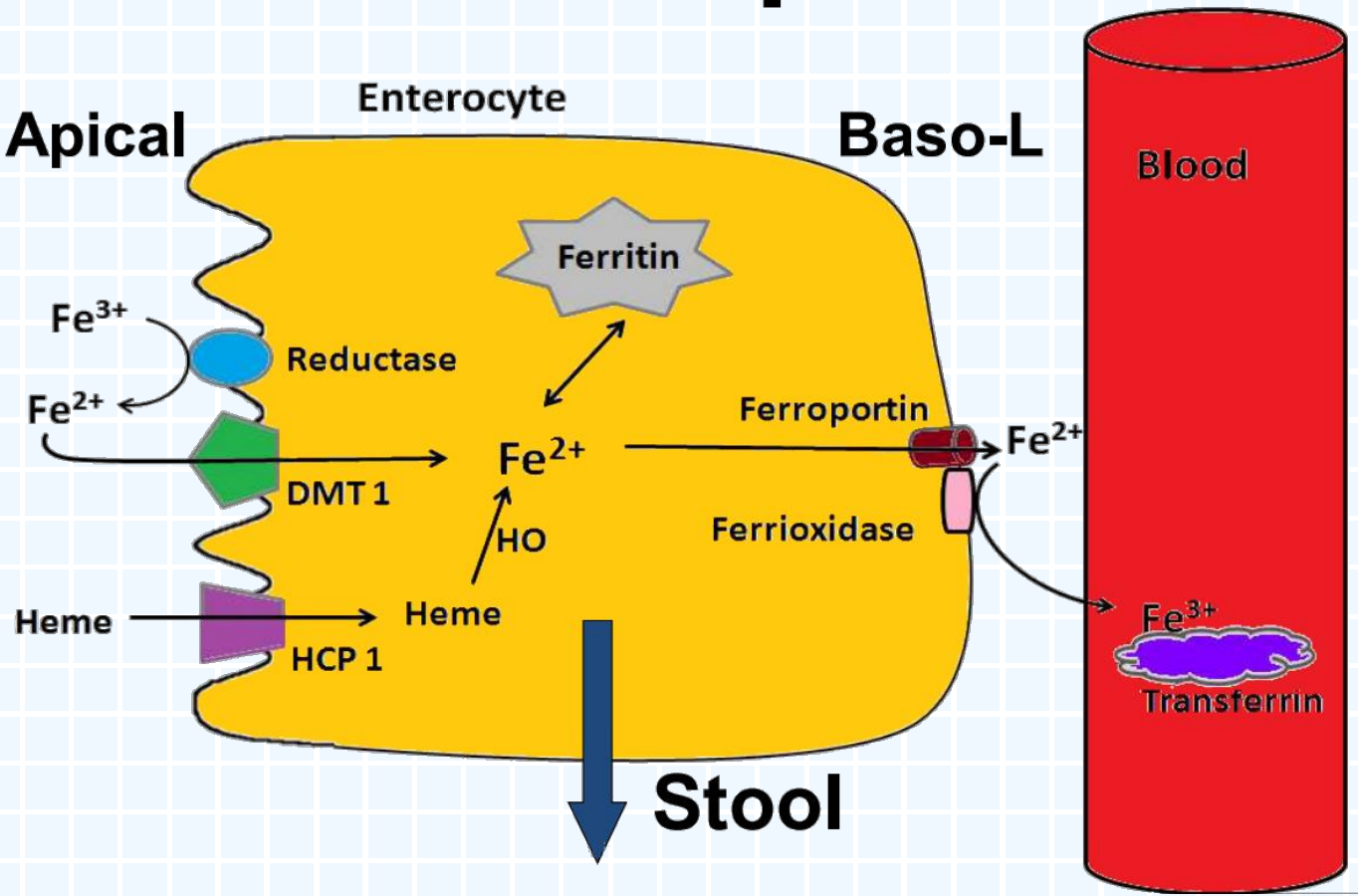
ERYTHROPOIESIS

Iron Absorption, Transport, and Storage:

- **Iron** (Fe^{3+}) **delivered by the enterocytes to plasma binds to a plasma transport protein called Transferrin. Transferrin molecule has two binding sites for iron. Normally, transferrin in plasma is 35% saturated with iron.**

- **Transferrin delivers iron to different cells in the body.**

Iron absorption

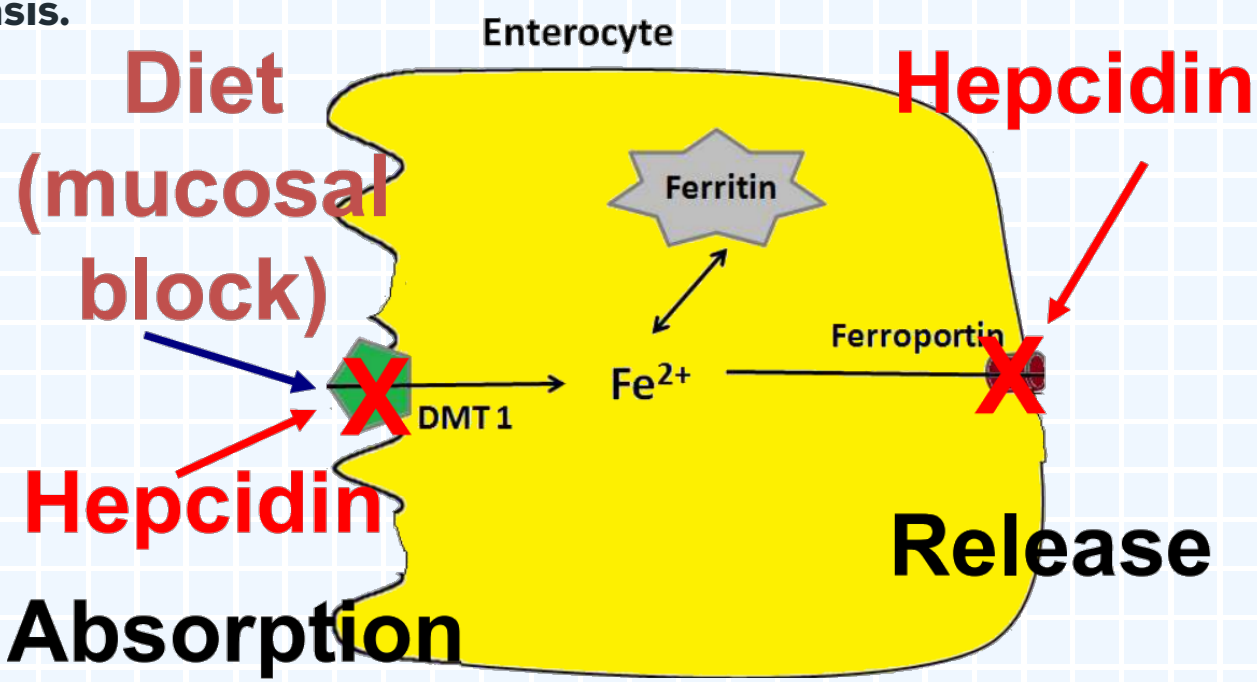


ERYTHROPOIESIS

Regulation of Iron Absorption :

Human body does not have mechanisms to regulate iron excretion.

Therefore, We depend on mechanisms that regulate iron absorption and regulate the release of recycled iron from macrophages to maintain iron homeostasis.



ERYTHROPOIESIS

These regulatory mechanisms for iron absorption and recycling involve the following:

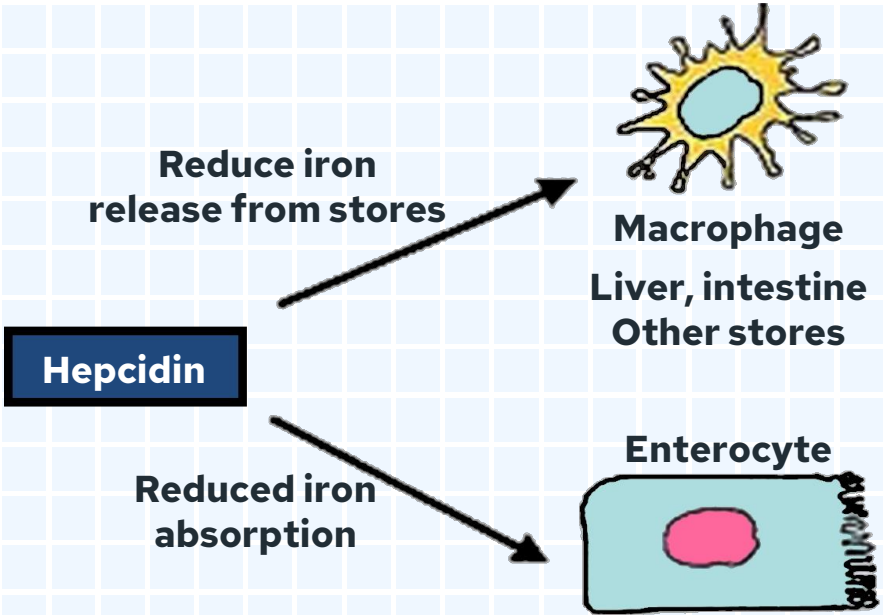
Role of dietary iron: Excess iron in food decreases the DMT1 on enterocytes, thus decreasing iron absorption. This is sometimes referred to as "the mucosal block".

Role of Hepcidin: Hepcidin is a 25-amino acid hormone secreted by the liver. Hepcidin is a major regulator of intestinal iron absorption and iron release by macrophages.

ERYTHROPOIESIS

Actions of Hepcidin :

Hepcidin binds to iron export protein Ferroportin in duodenal enterocytes, macrophages, and liver cells. The degradation of Ferroportin molecules follows such binding. This leads to the Inhibition of intestinal absorption of iron, the Inhibition of the release of recycled iron from macrophages, and the Inhibition of the release of iron from the liver and other store sites.



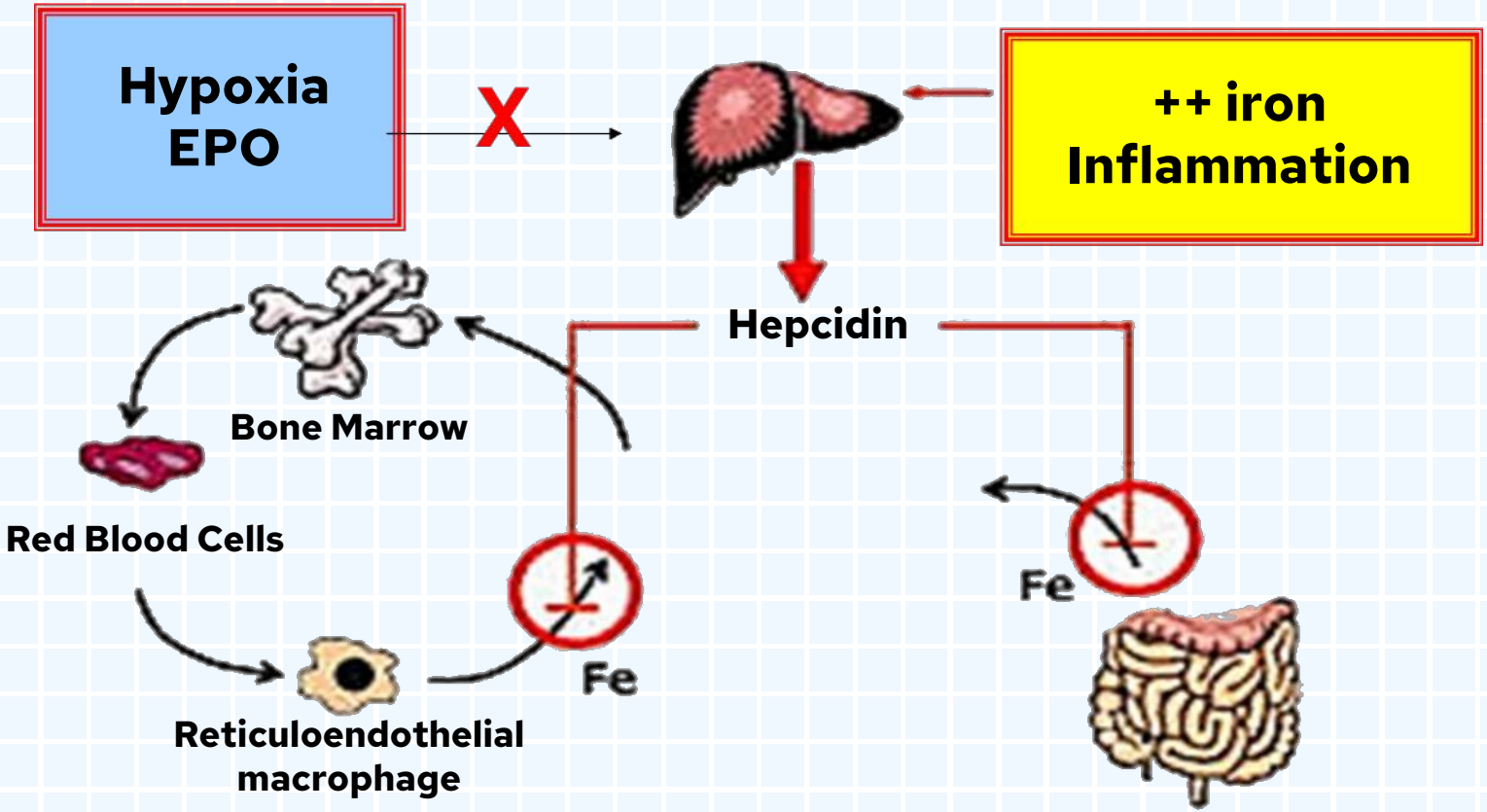
ERYTHROPOIESIS

Factors affecting hepcidin secretion :

- **Hypoxia and erythropoietin hormone decrease hepcidin secretion. In this way, iron absorption and release are increased to supply the increased demand by accelerated erythropoiesis for iron.**
- **Iron loading increases hepcidin secretion by the liver.**
- **Inflammation increases hepcidin secretion. This explains why anemia is a common complication of many inflammatory diseases.**

ERYTHROPOIESIS

Factors affecting hepcidin secretion :



ERYTHROPOIESIS

Effect of iron deficiency:

Iron deficiency anemia.

Causes of iron deficiency:

1. **Decreased iron intake in the diet**
2. **Failure of iron absorption,** which may be due to:
   - Partial gastrectomy (insufficient HCl secretion)
   - Diseases of the upper small intestine
   - Vitamin C deficiency
   - Too much Phytic acid, oxalates, and phosphates in the diet
3. **Chronic blood loss:** It results in iron deficiency, as the iron stores are insufficient and dietary iron cannot compensate for the amount of iron lost. It occurs in:
   - Excessive bleeding during menstruation in females
   - Bleeding peptic ulcer and piles.
   - Parasitic infestation.

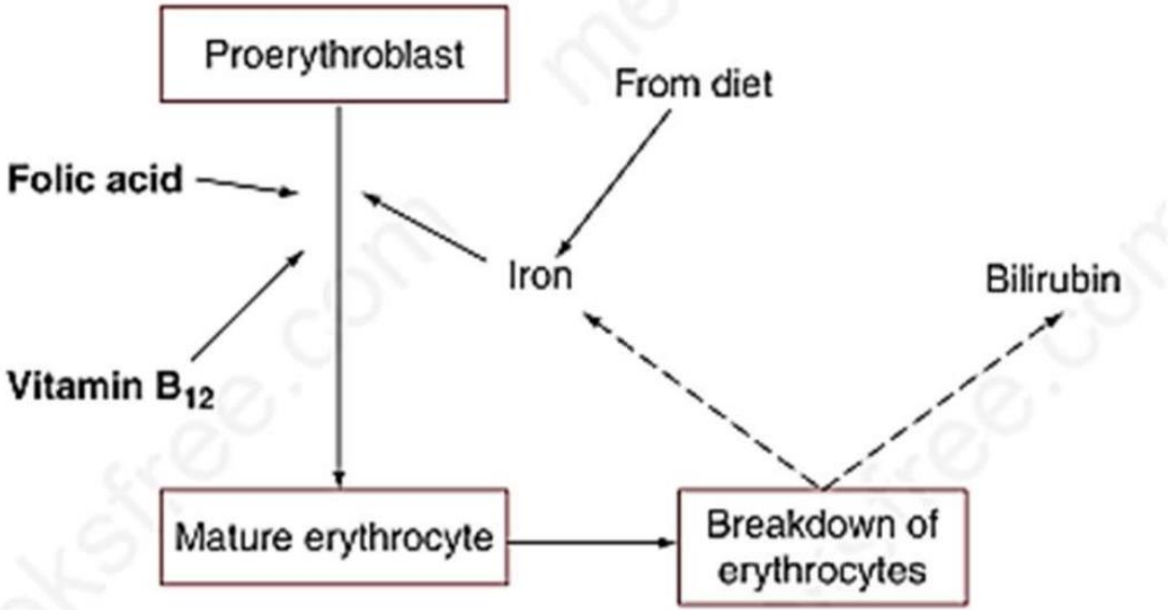
ERYTHROPOIESIS

Causes of iron deficiency:

Cause	Disease or Condition
Increased demand	Infancy and childhood Pregnancy
Inadequate intake	Dietary deficiency
Impaired absorption	Sprue Diarrhea Gastrectomy
Increased loss	Gastrointestinal bleeding Heavy menstrual bleeding Aspirin intake

ERYTHROPOIESIS

Causes of iron deficiency:



ERYTHROPOIESIS

Factors Affecting Erythropoiesis:

II. Diet :

C. Vitamins :

All vitamins are essential for erythropoiesis, especially Vitamin C, B12 & folic Acid.

Vitamin B12 (Cyanocobalamine = Extrinsic Factor)

1. Vitamin B12

Functions of Vitamin B12 :

A. Vitamin B12 is essential for transforming mRNA into DNA, i.e., for the Synthesis of DNA and Nuclear Maturation in RBCs. Therefore, Vitamin B12 is also known as the Maturation Factor.

B. It is also essential for the Metabolism of the Myelin Sheath of Nerves.

Absorption of Vitamin B12 :

- The parietal cells of the fundus of the stomach secrete a glycoprotein known as intrinsic factor. It unites with vitamin B12 (extrinsic factor) to be protected from digestion by the GIT enzymes.
- It is absorbed from the terminal ileum and passes to blood.

Failure of Absorption (Not Diet) Except in Vegetarians.

ERYTHROPOIESIS

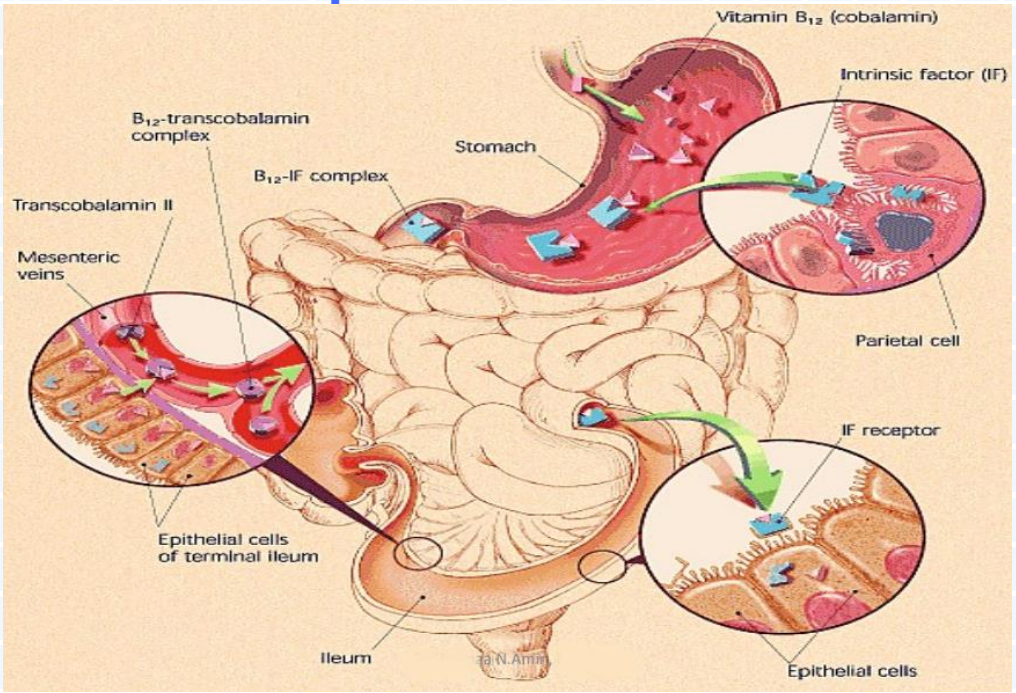
Factors Affecting Erythropoiesis:

II. Diet :

C. Vitamins :

1. Vitamin B12

Absorption of Vitamin B12 :



ERYTHROPOIESIS

C. Vitamins :

Causes of vitamin B12 deficiency :

A. **Absence of intrinsic factor** due to atrophy of the gastric mucosa. The anemia, which develops due to the absence of intrinsic factors, is known as pernicious anemia.

B. **Liver diseases:** as they result in defective storage of the vitamin.

C. **Disease or surgical resection of the terminal ileum.**

D. Very rarely, **there is deficient Vitamin B12 in the diet.**

Effect of vitamin B12 deficiency:

A. **Failure of nuclear maturation and division of erythroblasts in the bone marrow.** Therefore, erythroblasts increase in size and develop into **Megaloblasts** and **Megalocytes**. They are larger in size, contain a larger amount of hemoglobin, and have a shorter life span than erythrocytes. Therefore, the anemia, which develops due to vitamin B12 deficiency, is also called **Megaloblastic or Macrocytic Anemia.**

B. **Neurological symptoms:** Since vitamin B12 is essential for the metabolism of the myelin sheath of nerves, its deficiency causes neurological manifestations.

ERYTHROPOIESIS

Factors Affecting Erythropoiesis:

II. Diet :

C. Vitamins :

2. Folic Acid :

Folic acid is needed for DNA synthesis. Therefore, it is required for the division and maturation of RBCs.

Effect of Folic Acid deficiency:

Folic acid deficiency causes failure of maturation of RBCs and the development of macrocytes, resulting in Macrocytic anemia.

Causes of folic acid deficiency:

A. **Dietary deficiency** of folic acid
B. **GIT Diseases** interfere with folic acid absorption.
C. **Cytotoxic Drugs** (antifolates) used in the treatment of cancer.

ERYTHROPOIESIS

Factors Affecting Erythropoiesis:

II. Diet :

D. Trace Elements:

Copper is a co-factor for Hb synthesis but does not enter into its formation.

Cobalt: It stimulates erythropoiesis and enters in vitamin B12 formation.

E. Hormones:

Several hormones increase the rate of erythropoiesis, including **Thyroxin, Androgens and Glucocorticoids.**

F. Healthy Bone Marrow:

- Since the bone marrow is the site of erythropoiesis, it must be healthy for normal RBCs production.
- Bone marrow may be destroyed by: X-rays, atomic radiation, drugs and malignant tumors.
- Bone marrow destruction leads to a decrease in all types of blood cells, i.e., RBCs, WBCs, and platelets. This condition is called aplastic anemia.

ERYTHROPOIESIS

Factors Affecting Erythropoiesis:

II. Diet :

G. Healthy Liver:

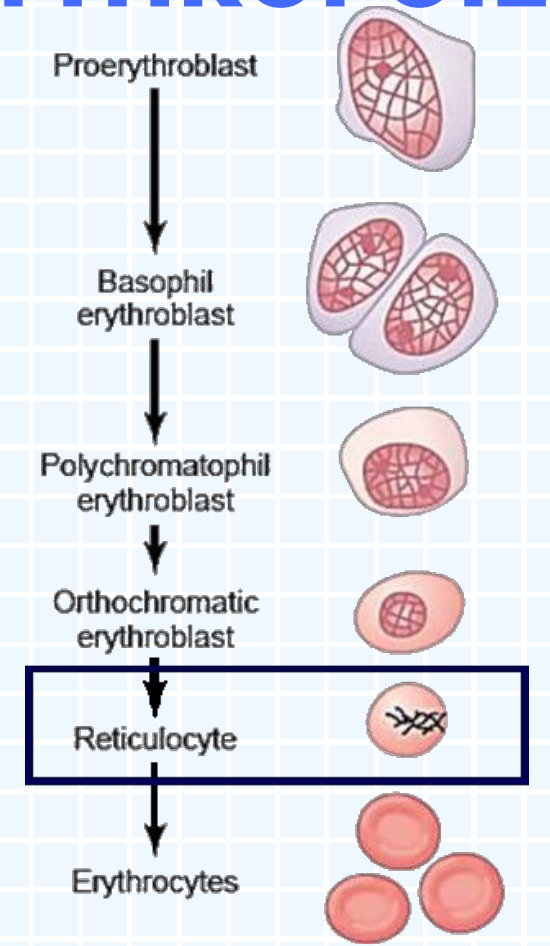
The liver is important for Erythropoiesis because:

- It forms the globin part of hemoglobin

- It stores vitamin B12 and iron, which are essential for erythropoiesis

- It produces 15% of erythropoietin.

ERYTHROPOIESIS



ERYTHROPOIESIS

Table 1 Age-specific blood cell indexes

Age	Hemoglobin g/dL (g/L)	Hematocrit (%)	MCV, μm³ (fL)	MCHC, g/dL (g/L)	Reticulocytes
• 26–30 weeks' gestation*	13.4 (134)	41.5 (0.42)	118.2 (118.2)	37.9 (379)	–
• 28 weeks' gestation	14.5 (145)	45 (0.45)	120 (120)	31.0 (310)	(5 to 10)
• 32 weeks' gestation	15.0 (150)	47 (0.47)	118 (118)	32.0 (320)	(3 to 10)
• Term† (cord)	16.5 (165)	51 (0.51)	108 (108)	33.0 (330)	(3 to 7)
• 1–3 days	18.5 (185)	56 (0.56)	108 (108)	33.0 (330)	(1.8–4.6)
• 2 weeks	16.6 (166)	53 (0.53)	105 (105)	31.4 (314)	
• 1 month	13.9 (139)	44 (0.44)	101 (101)	31.8 (318)	(0.1–1.7)
• 2 months	11.2 (112)	35 (0.35)	95 (95)	31.8 (318)	
• 6 months	12.6 (126)	36 (0.36)	76 (76)	35.0 (350)	(0.7–2.3)
• 6 months–2 years	12.0 (120)	36 (0.36)	78 (78)	33.0 (330)	
• 2–6 years	12.5 (125)	37 (0.37)	81 (81)	34.0 (340)	(0.5–1.0)
• 6–12 years	13.5 (135)	40 (0.40)	86 (86)	34.0 (340)	(0.5–1.0)
• 12–18 years					
– Male	14.5 (145)	43 (0.43)	88 (88)	34.0 (340)	(0.5–1.0)
– Female	14.0 (140)	41 (0.41)	90 (90)	34.0 (340)	(0.5–1.0)
• Adult					
– Male	15.5 (155)	47 (0.47)	90 (90)	34.0 (340)	(0.8–2.5)
– Female	14.0 (140)	41 (0.41)	90 (90)	34.0 (340)	(0.8–4.1)

Abbreviations:
MCV: Mean corpuscular volume; MCHC: Mean corpuscular hemoglobin concentration.
* Values are from fetal samplings.
† Less than one month, capillary hemoglobin exceeds venous: 1 hour—3.6 gm difference; 5 days—2.2 gm difference; 3 weeks—1.1 gm difference. Adapted with permission from Siberry GK, Lannone R, Eds. The Harriet Lane handbook: a manual for pediatric house officers, 15th edn. St Louis: Mosby, 2000.



THANK
YOU
النادي الطبي