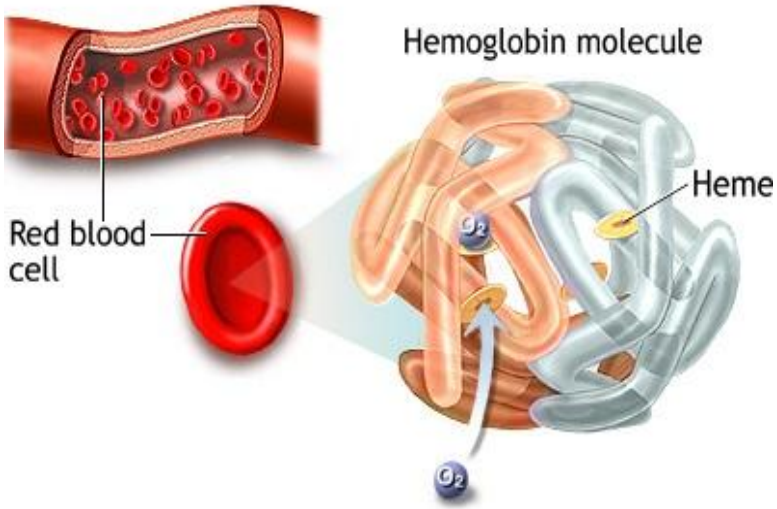
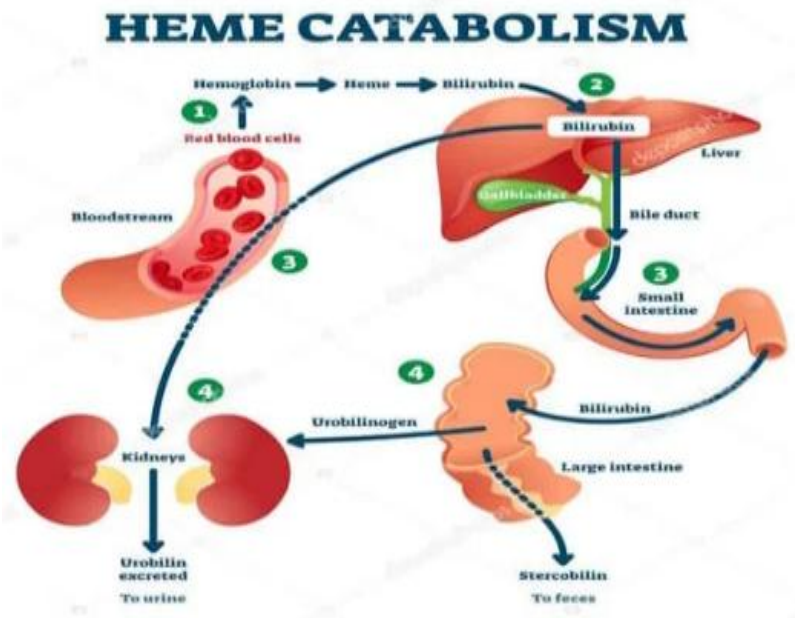
Mansoura National University
Faculty of Medicine

Level: 1

Semester: 2

Hemoglobin





By

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Agenda

- Hemoglobin and its functions.
- Hemoglobin structure.
- Types of Hemoglobin.
- Hemoglobinopathies: Thalassemias – Sickle cell disease.
- Hemoglobin degradation.
- Jaundice.

Learning Outcomes (LOs)

At the end of this session, the students should be able to:

- Understand the functions of hemoglobin.
- Describe the structure of hemoglobin and recognize the differences between hemoglobin and myoglobin.
- Identify normal and abnormal types of hemoglobin.
- Understand the biochemical basis of hemoglobinopathies, such as thalassemias and sickle cell disease.
- Describe hemoglobin degradation.
- Discuss jaundice and its different types.
- Correlate their knowledge to a clinical situation.

LO 1

Hemoglobin and its functions

Hemoglobin

❖ **Hemoglobin (Hb) is an iron-containing protein (metalloprotein), occupying about one third of the volume of the erythrocytes.**

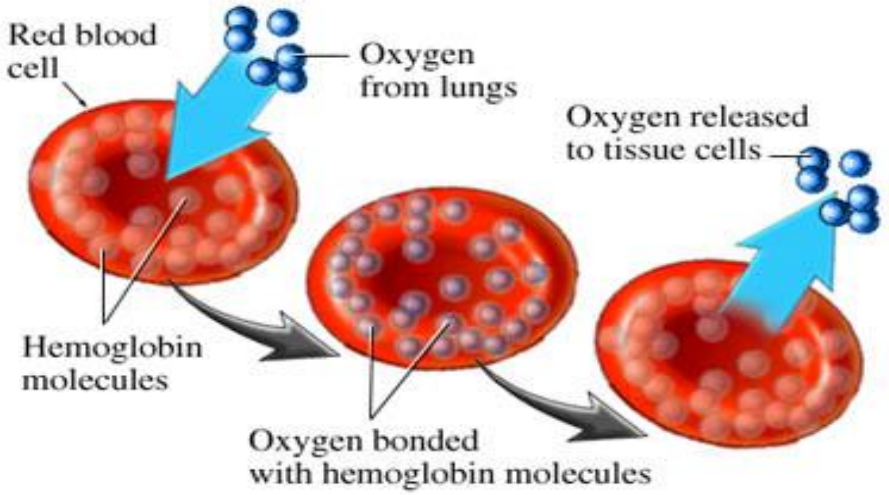
❖ **It is a red pigment (chromoprotein), gives the blood its red color.**

❖ **The normal hemoglobin level is about 14 to 18 g/dl for males and 12 to 16 g/dl for females.**

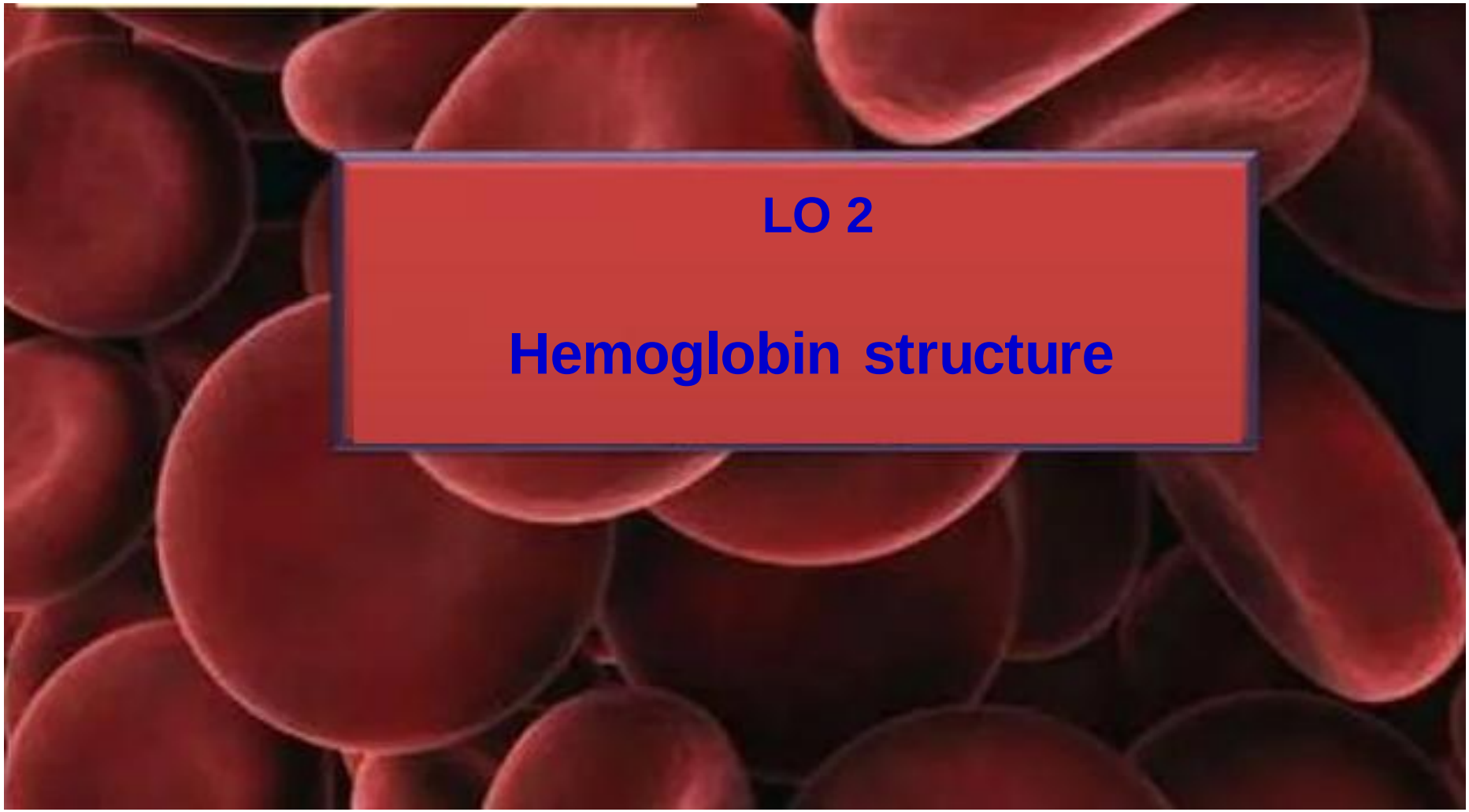
Hemoglobin

❖ **It has two primary functions:**

-**Transports oxygen from the lungs to the tissues throughout the body.**



- **Transports carbon dioxide and protons (H+) from the tissues back to the lungs so it can be expelled.**



LO 2

Hemoglobin structure

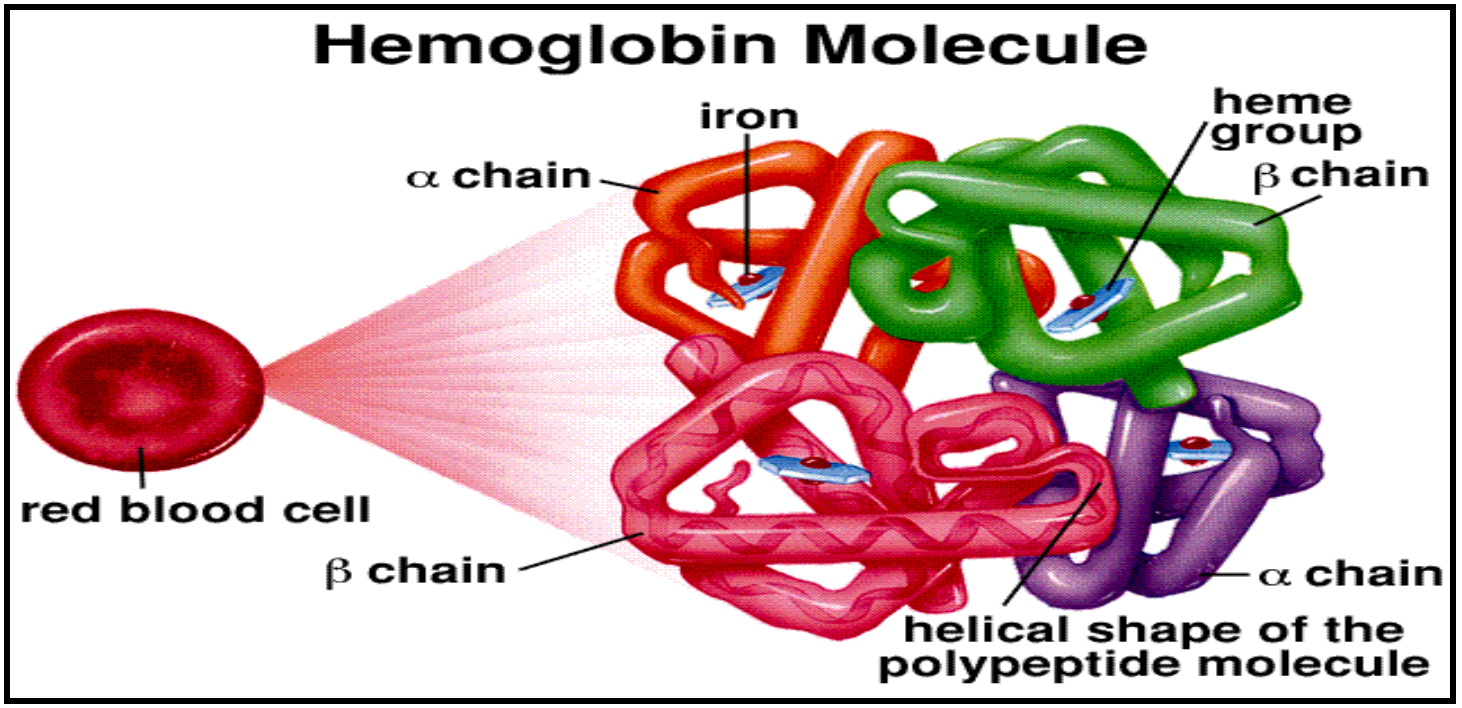
Hemoglobin structure

Hemoglobin is a conjugated protein

Protein part	**Non-protein part**
Globin	**Heme (Iron containing pigment)**

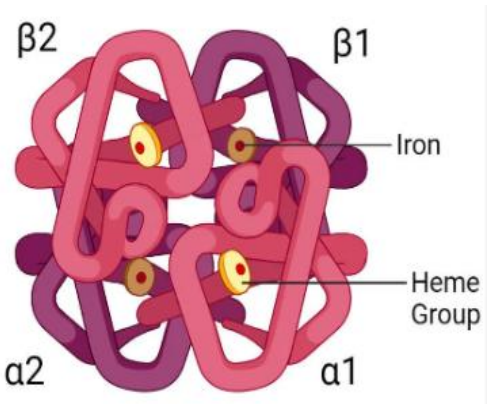
Hemoglobin structure

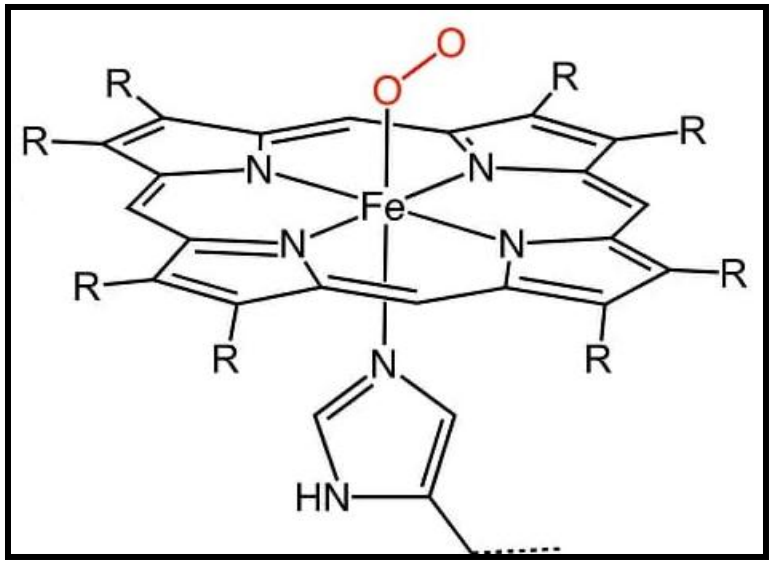
❖ **Hemoglobin is a tetramer, formed of four subunits; each subunit has one polypeptide chain and one heme group.**



Hemoglobin structure

❖ **Heme** is composed of a ring-like organic compound known as a **porphyrin**, to which an **iron atom** is attached.



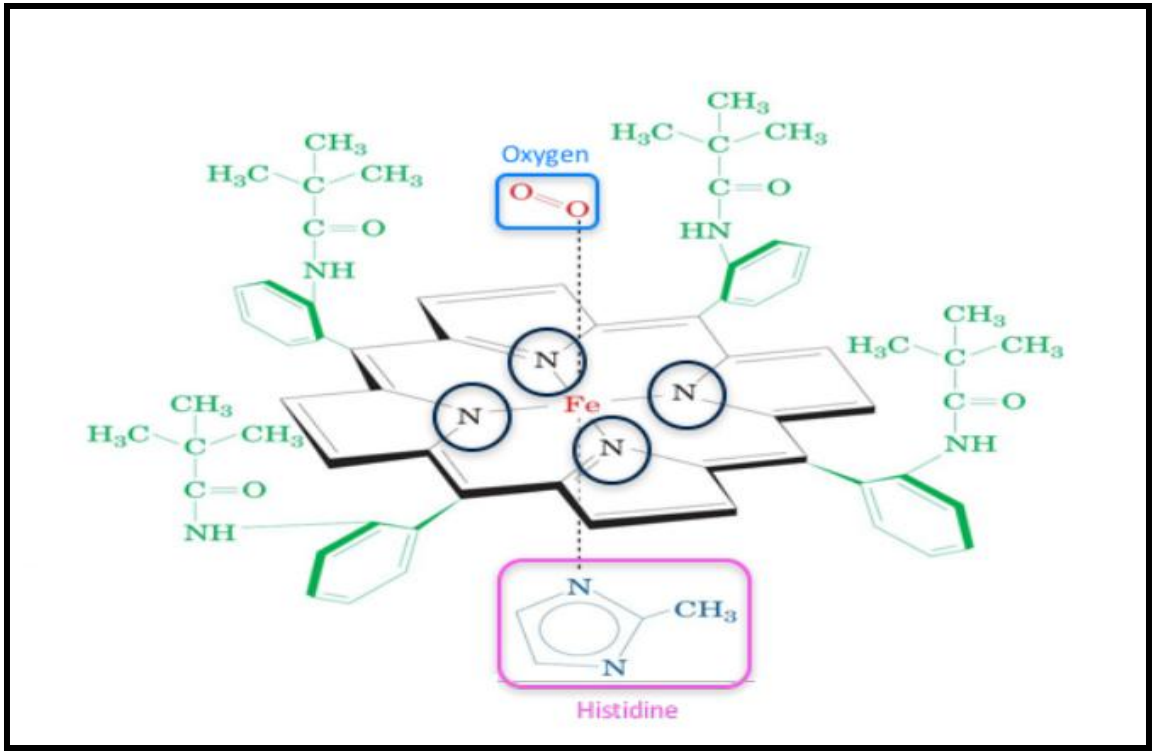


❖ The iron (Fe) is present in the **center of the heme** molecule, coordinates **six bonds**.

Hemoglobin structure

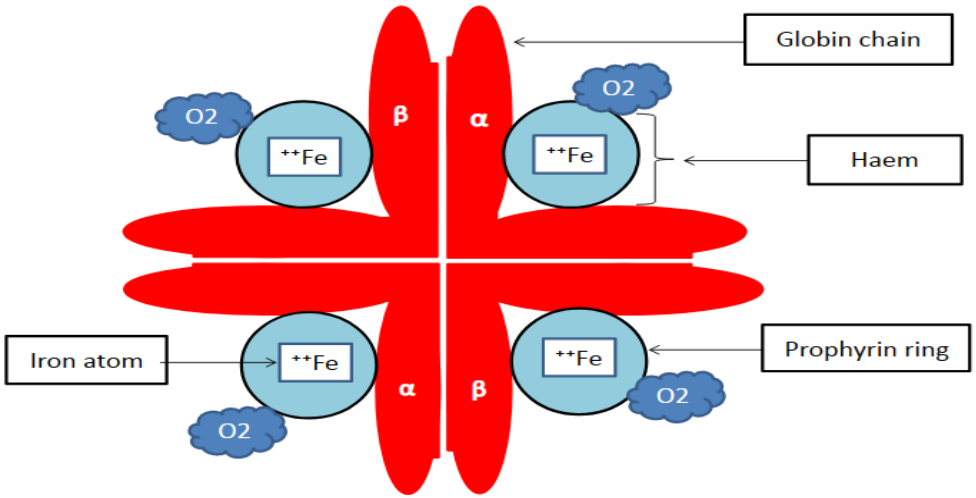
❖ The iron binds to:

- ✓ Four **nitrogen** atoms of the porphyrin ring.
- ✓ **Histidine residue** of the globin chain.
- ✓ **Oxygen** molecule.



Hemoglobin structure

❖ There are 4 iron atoms in each molecule of hemoglobin, which accordingly can bind 4 molecules of oxygen.

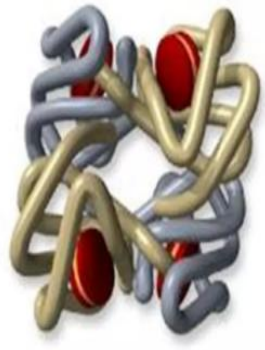


❖ The iron must exist in the ferrous (Fe2+) state to bind oxygen and form oxy Hb.

Hemoglobin structure

❖ **Globin is a histidine rich protein formed of 4 polypeptide chains, each one of them has α-helical segments and a heme-binding pocket.**

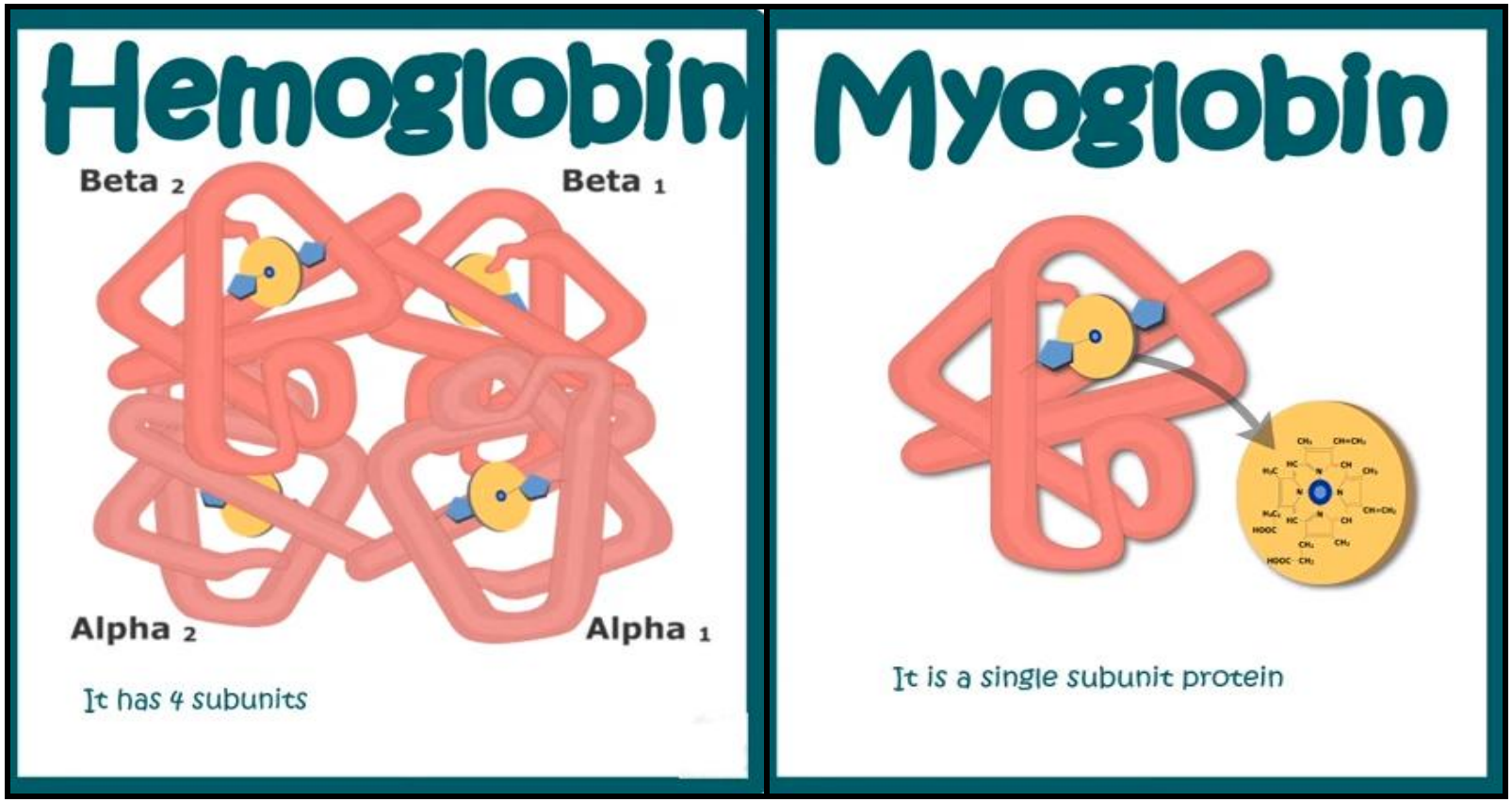
Heme is suspended in a pocket form by the folding of the poly peptide chain.



❖ **There are four types of globin chains:**

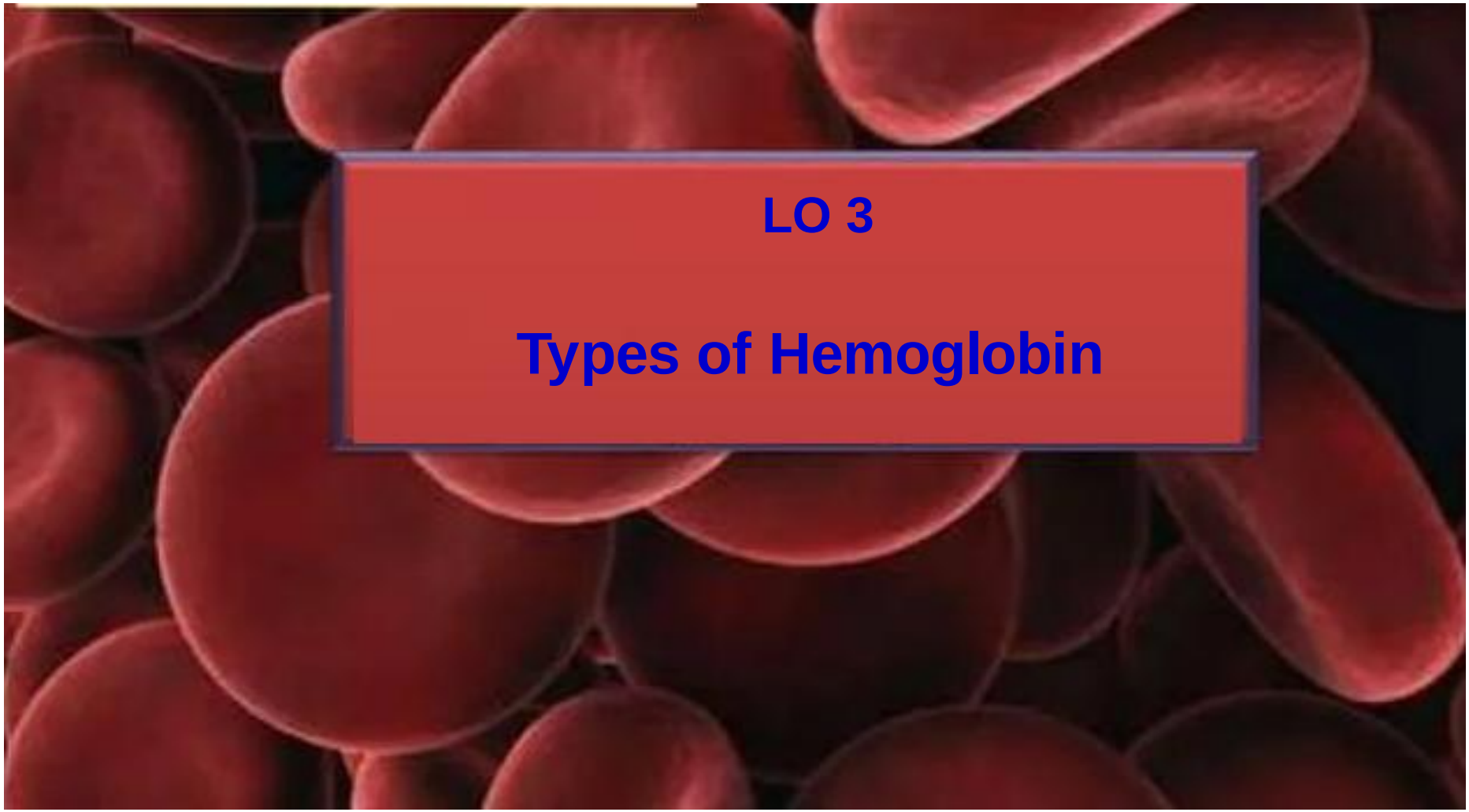
alpha (α), beta (β), gamma (γ) and delta (δ).

Hemoglobin and myoglobin



Hemoglobin and myoglobin

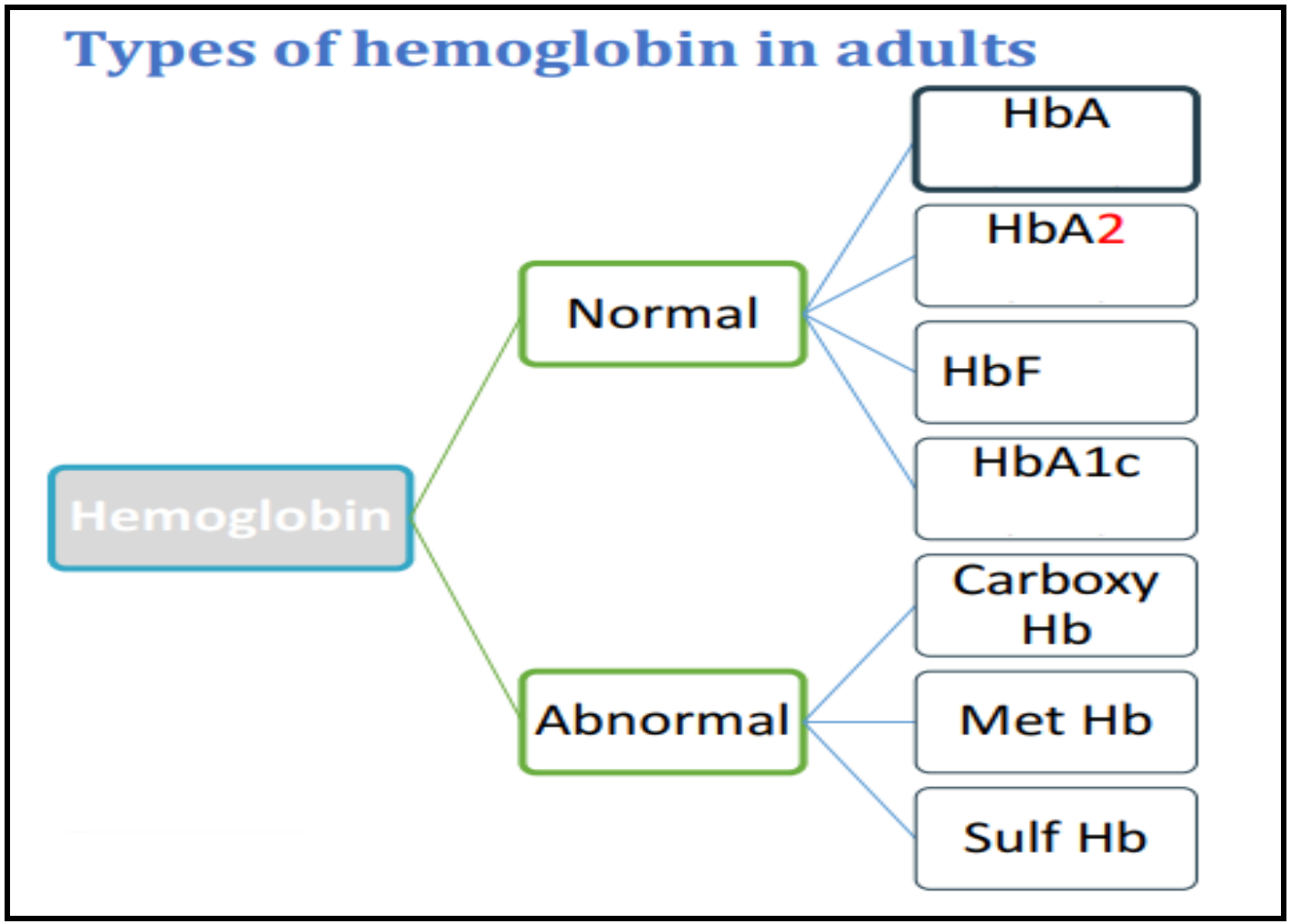
	Hemoglobin "Hemo" = blood	Myoglobin "Myo" = muscle
Site	RBCs	Mainly in muscle cells
Protein type	Oxygen transport protein	oxygen storage protein
Function	It takes O2 from the lungs to the tissues (including muscles)	It stores O2 in the muscle cells
Structure	-Heterotetramer -Quaternary structure -Four polypeptide chains	-Monomer -Tertiary structure -Single polypeptide chain
Oxygen binding	Four oxygen molecules	Single oxygen molecule
Affinity for oxygen	Lower	Higher



LO 3

Types of Hemoglobin

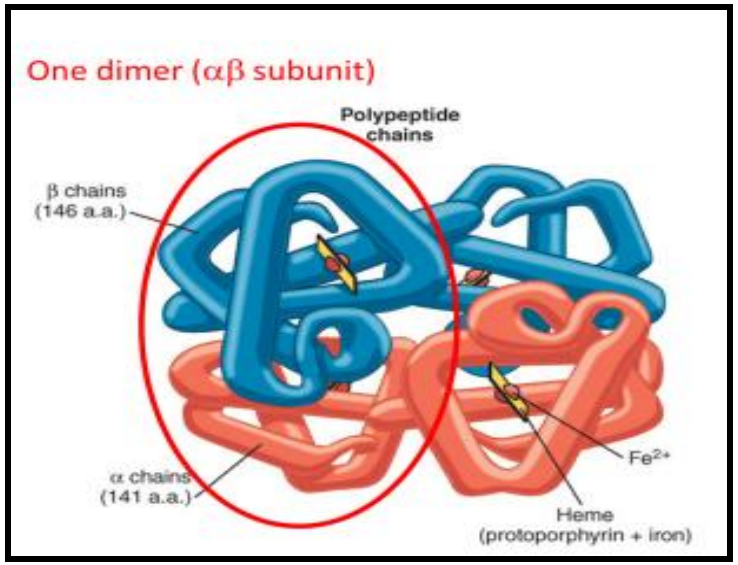
Types of Hemoglobin



Form	Chain composition
HbA	$\alpha_2\beta_2$
HbF	$\alpha_2\gamma_2$
HbA_2	$\alpha_2\delta_2$
HbA_{1c}	$\alpha_2\beta_2$-glucose

Types of Hemoglobin

❖ **In adult humans, the most common hemoglobin type is hemoglobin A (A1), consisting of 2 α and 2 β subunits, each made of 141 and 146 amino acid residues, respectively (α2β2).**



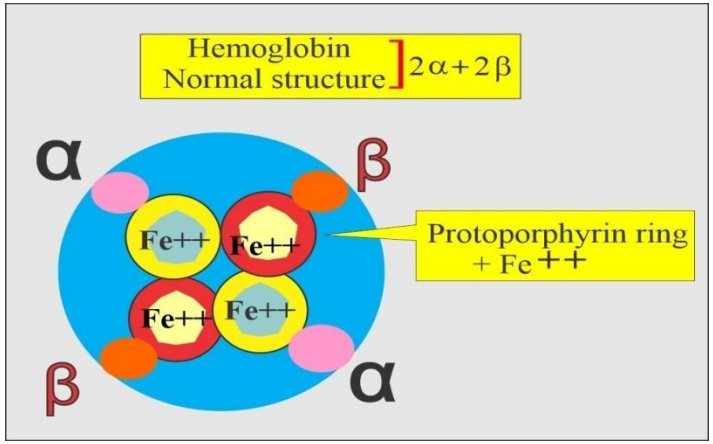
Types of Hemoglobin

❖ **Normal hemoglobin types include:**

○ **Hemoglobin A1 (Hb A1 or Hb A):**

• About 95%-98% of hemoglobin found in adults.

• It contains 2 α and 2 β protein chains held together by non-covalent (hydrophobic) interactions.



○ **Hemoglobin A2 (Hb A_2):**

• About 2%-3% of hemoglobin found in adults.

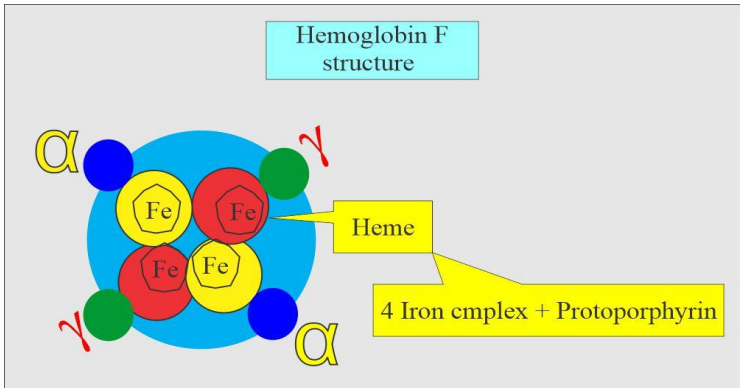
• It has 2 α and 2 δ protein chains.

Types of Hemoglobin

❖ Normal hemoglobin types include:

○ Hemoglobin F (Hb F, fetal hemoglobin):

- Up to 1%-2% of hemoglobin found in adults.
- It has 2 α and 2 γ protein chains.
- It is the primary hemoglobin produced by the fetus during pregnancy.
- At birth, approximately **80%** of the hemoglobin in cord blood is HbF (the rest is HbA1).



Types of Hemoglobin

❖ **Normal hemoglobin types include:**

○ **Hemoglobin F (Hb F, fetal hemoglobin):**

• It binds oxygen more strongly than Hb A and this enables the fetus to take oxygen from the mother's bloodstream through the placenta.

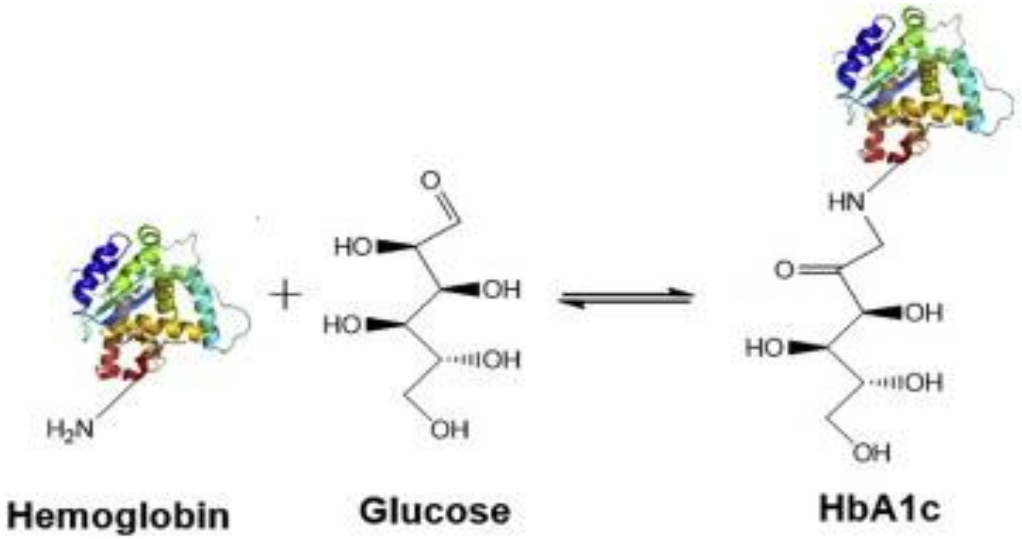
• Its production usually ↓↓ shortly after birth and reaches adult level within 1-2 years.

Types of Hemoglobin

❖ **Normal hemoglobin types include:**

○ **Hemoglobin A1c (HbA1c) or glycated Hb:**

- < 5.7 % of hemoglobin found in adults.
- Glucose reacts spontaneously and non-enzymatically with free amino group on proteins to form covalent **glycated proteins**.



Types of Hemoglobin

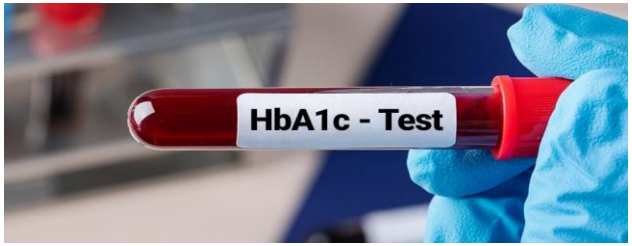
❖ **Normal hemoglobin types include:**

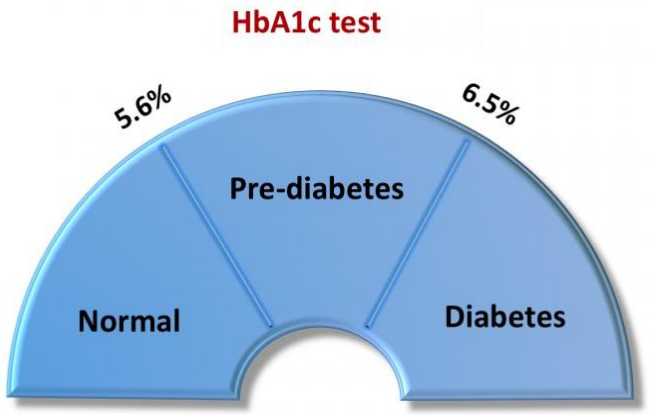
○ **Hemoglobin A1c (HbA1c) or glycated Hb:**

• The extent of protein glycation depends on the average glucose to which the protein is exposed and the half-life of the protein.

• Since RBCs life span is about **120 days**, so HbA1c reflects glycemic control over **2 months**

(HbA1c ≥ 6.5% = diabetes).



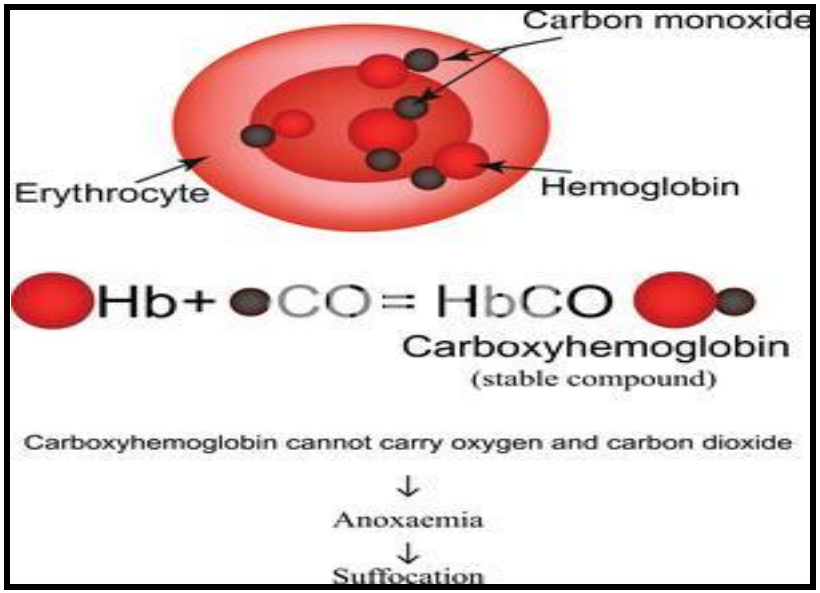


Types of Hemoglobin

❖ Abnormal hemoglobin types include:

Carboxyhemoglobin

- Produced by the binding of **carbon monoxide (CO) to hemoglobin**.
- CO is generated during **incomplete combustion of organic products** and has toxic effect because it **competes with oxygen** for the same binding site in the Fe2+ of Hb.



Types of Hemoglobin

❖ Abnormal hemoglobin types include:

Carboxyhemoglobin

• Hemoglobin has a **210-fold greater affinity for CO** than for oxygen, which explains the extraordinary toxicity of CO even when its concentration in the inspired air is relatively low.

• Carboxyhemoglobin has a **cherry red color**, so subjects intoxicated with CO show apparently healthy **reddish lips and cheeks**.

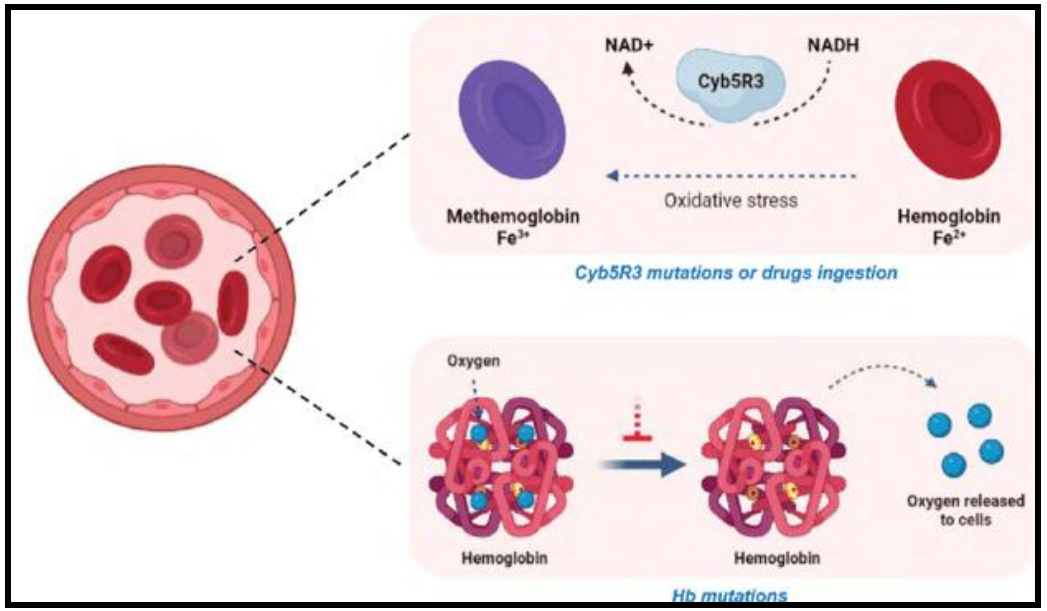

Cherry-red skin color produced by CO poisoning.

Types of Hemoglobin

❖ Abnormal hemoglobin types include:

Methemoglobin

- **A type of Hb that has hematin or ferriheme (Fe3+) as a prosthetic group instead of ferrous heme (Fe2+).**
- **The conversion of Fe2+ to Fe3+ prevents hemoglobin from transporting oxygen.**



Types of Hemoglobin

❖ **Abnormal hemoglobin types include:**

Methemoglobin

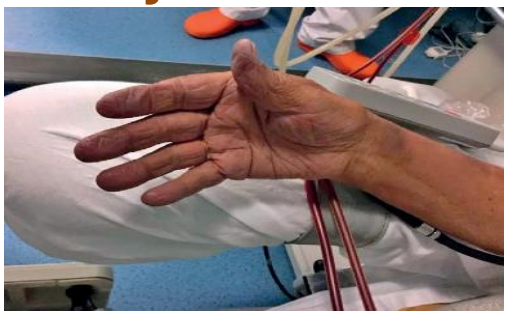
- **Genetic defects can produce changes in the heme or affect the reducing system enzymes, generating methemoglobinemia (inherited methemoglobinemia).**
- **The inherited form most commonly results from mutations that result in a deficiency in the quantity or activity of cytochrome b5 methemoglobin reductase.**

Types of Hemoglobin

❖ Abnormal hemoglobin types include:

Methemoglobin

- **Moreover, agents, such as nitrophenols, aniline, sulfonamides or other drugs can cause acquired methemoglobinemia and variable degrees of tissue hypoxia.**
- **Methemoglobin has a *dark brown color*.**
- **Its increase in blood is clinically apparent by the presence of brownish cyanosis.**

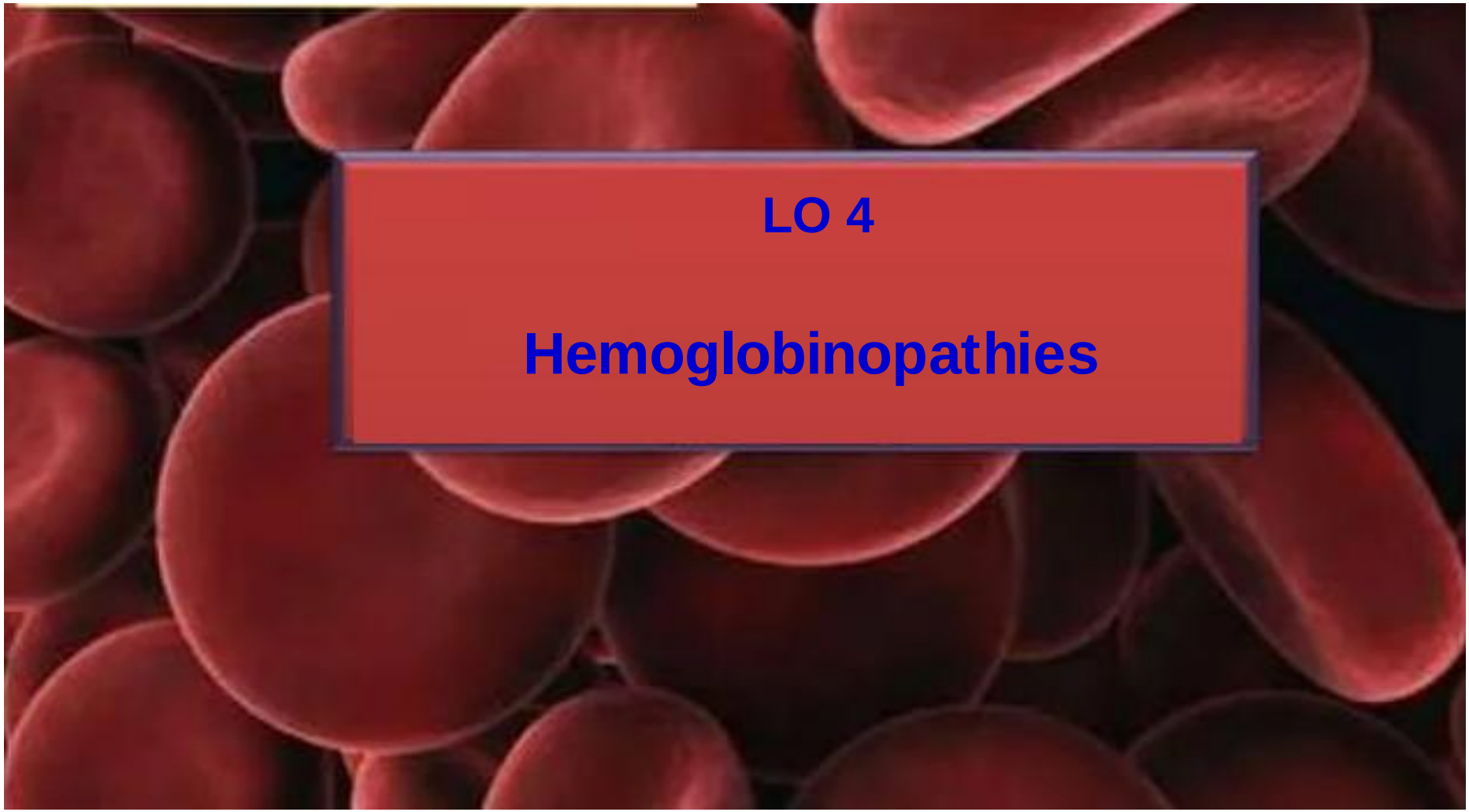


Types of Hemoglobin

❖ Abnormal hemoglobin types include:

Sulfhemoglobin

- **A green-pigmented molecule, which is not normally present in the body and cannot carry oxygen.**
- **It is formed by irreversible oxidation of the iron in hemoglobin to a ferric state by drugs (such as sulfanilamides, nitrites, and phenylhydrazine) or exposure to sulfur chemicals in industrial or environmental settings.**



LO 4

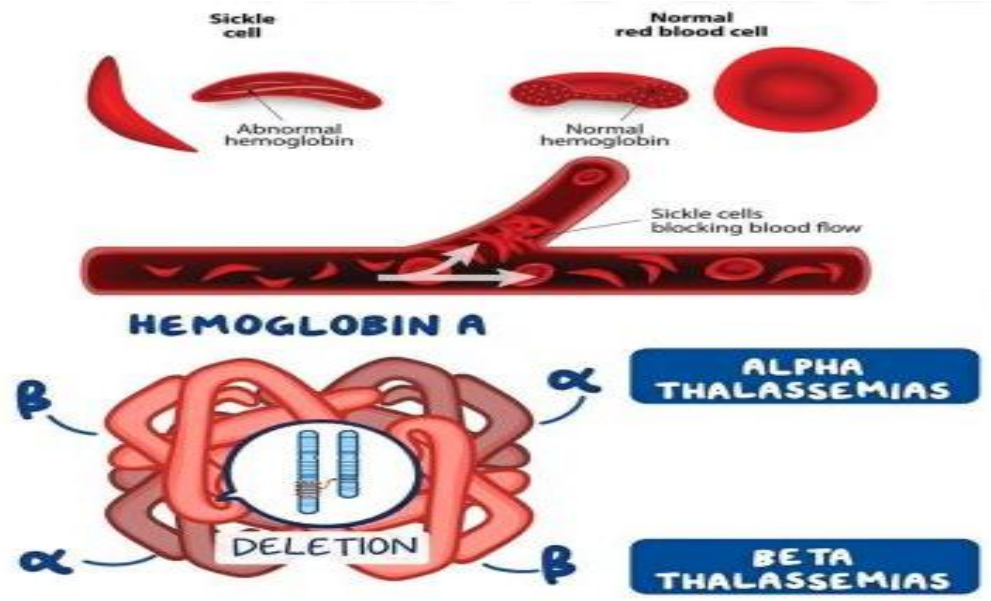
Hemoglobinopathies

Hemoglobinopathies

- **Hemoglobinopathies are genetic disorders affecting the structure or the production of the hemoglobin molecule.**
- **There are two main groups:**

1) Thalassemias: low production of normal hemoglobin molecules.

2) Structural hemoglobin variants (abnormal hemoglobins): as HbS, HbE and HbC.



(1) Thalassemias

- Group of inherited **hemolytic anemias** characterized by **defective hemoglobin synthesis**.
- **Ineffective production of α or β globin chains**

→ ineffective erythropoiesis, premature red blood cell destruction and anemia.

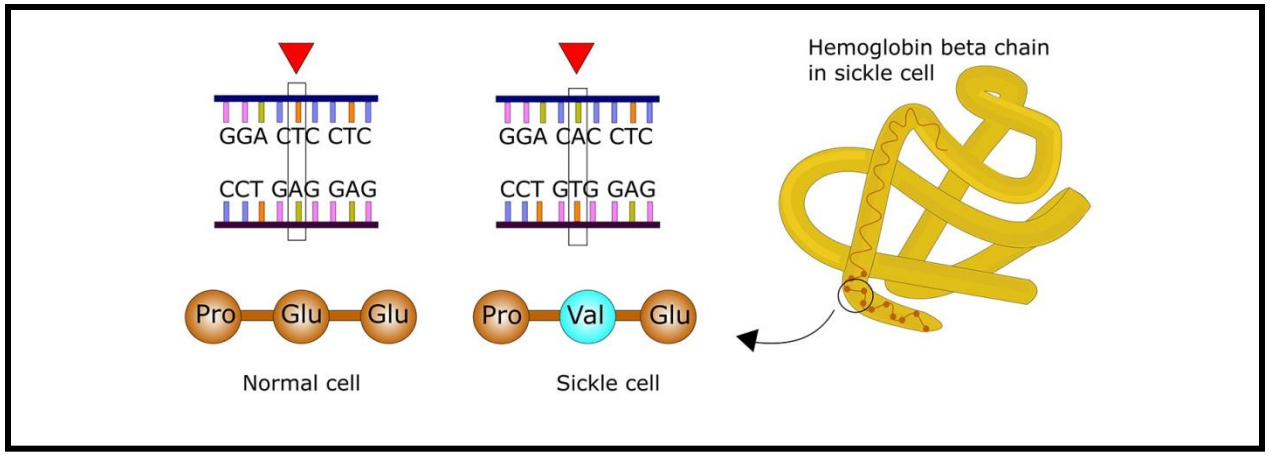
- According to which chain of the hemoglobin molecule is affected:

Thalassemias

α-thalassemia	β-thalassemia
the production of the α-globin chain is affected due to mutations in the α-globin genes.	the production of the β-globin chain is affected due to mutations in the β-globin gene.

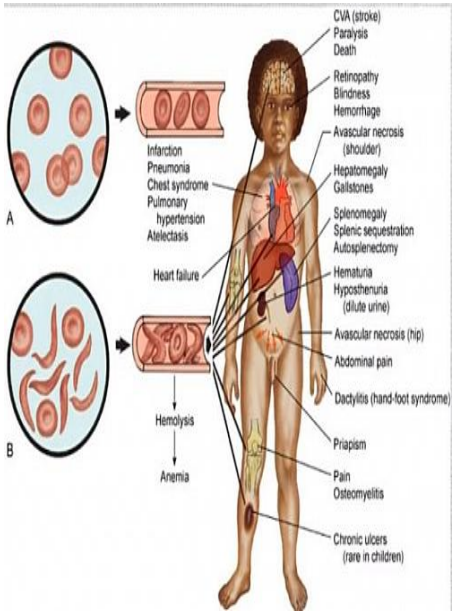
(2) Sickle cell disease (SCD) (HbS disease)

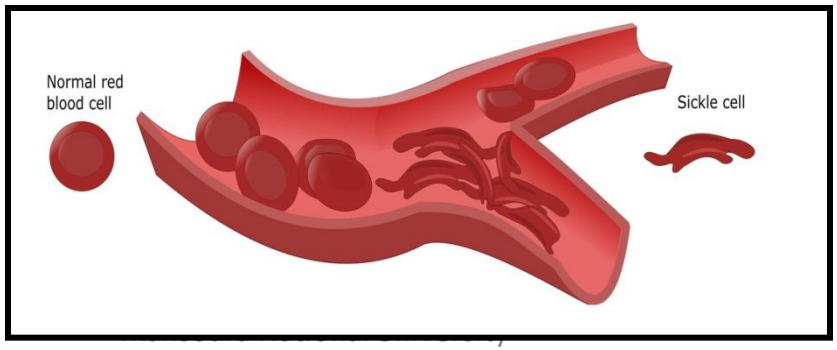
- **HbS** is an example of a **genetic variant** of human hemoglobin where a **point mutation in the β globin gene** results in **substitution of glutamic acid to valine at the 6th position of the β** globin chain.
- Valine residues aggregate together by hydrophobic interactions leading to **precipitation of HbS within RBCs** (Oxygenated Hb S is much less soluble than oxygenated Hb A) → formation of **sickle-shaped RBCs.**

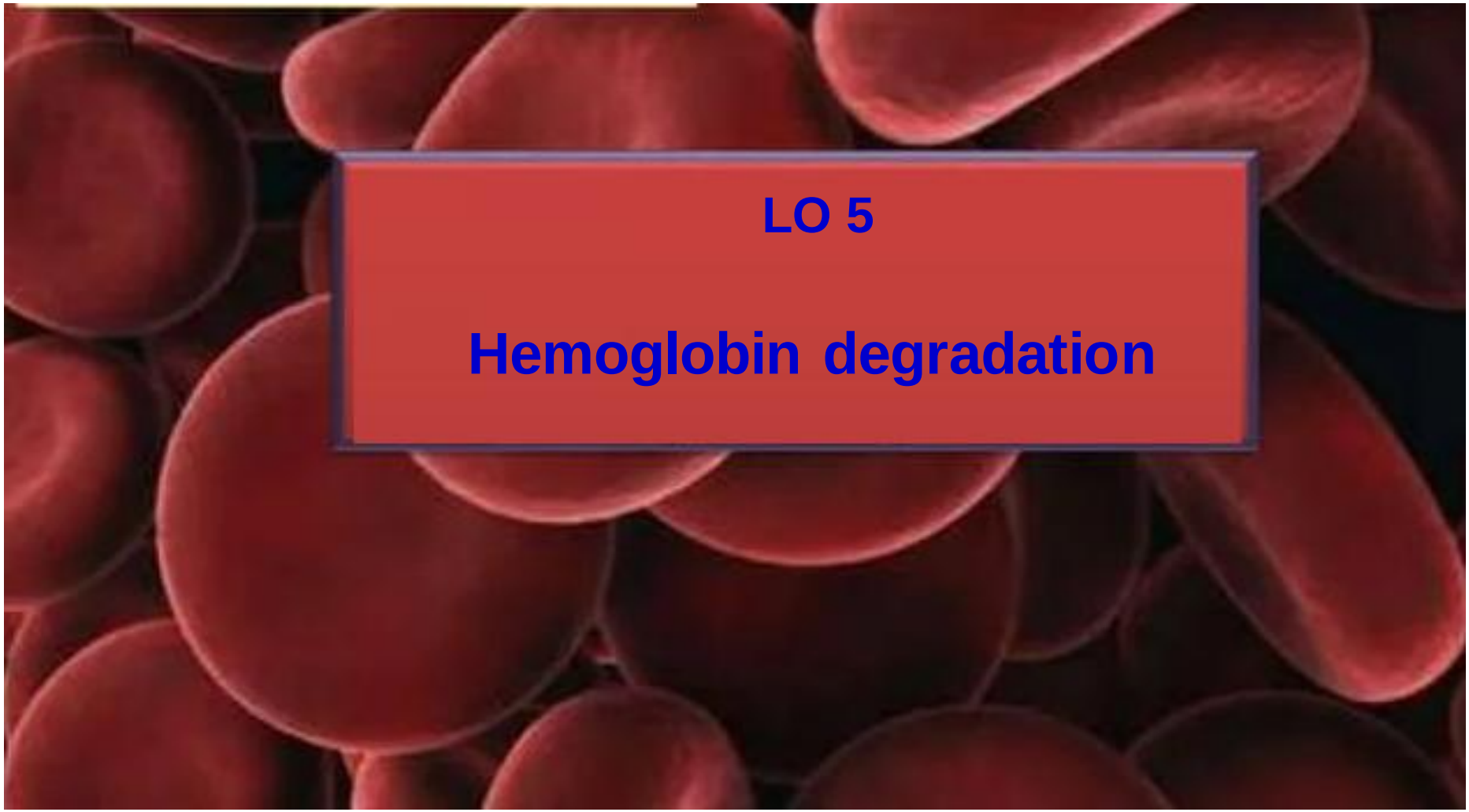


(2) Sickle cell disease (SCD) (HbS disease)

- Sickled RBCs are **fragile** → high rate of **hemolysis → sickle cell anemia.**
- Distorted, inflexible sickle-shaped RBCs adhere to vascular endothelium and plug small arterioles and capillaries → **vaso-occlusion → restrict blood flow to an organ**, resulting in **ischemia, severe pain crises, necrosis and often organ damage**.
- Vaso-occlusion also causes endothelial injury, which results in **inflammation and can lead to thrombosis**.






LO 5
Hemoglobin degradation

Hemoglobin degradation

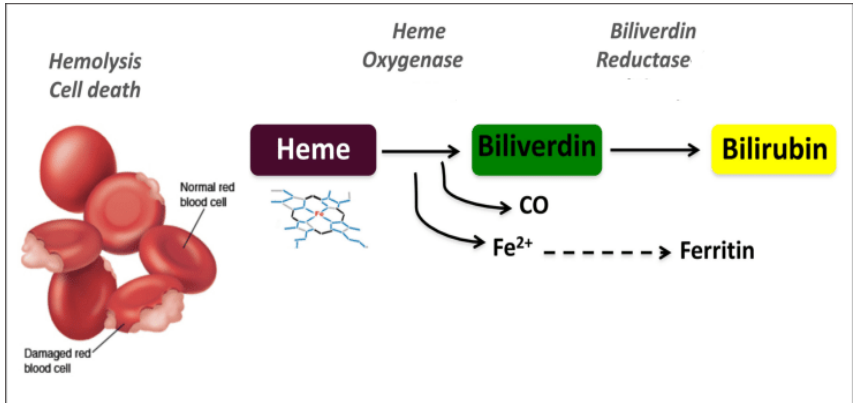
- After approximately **120 days** (RBCS life span), old RBCs are taken up and degraded by the reticuloendothelial system (RES) particularly in the **liver, spleen and bone marrow**.
- Hb is degraded to:

Heme

- Oxidized by **heme oxygenase** enzyme, producing **biliverdin (green pigment)** and **iron** (returned to the body's iron stores).
- Biliverdin is reduced by **biliverdin reductase**, producing **bilirubin (yellow pigment)**.

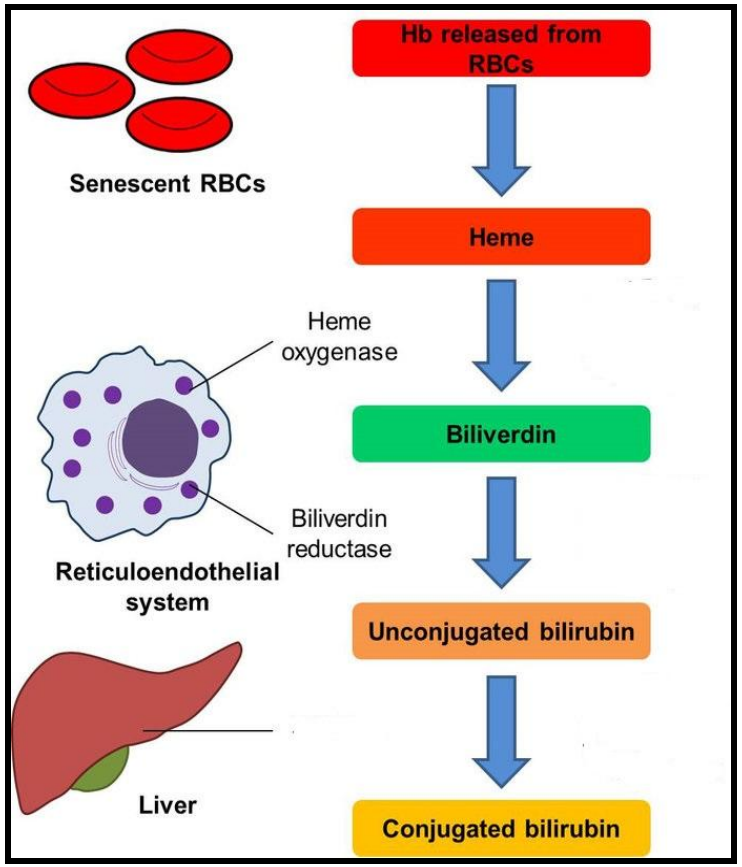
Globin

- Degraded to amino acids (reutilized in the body).



Hemoglobin degradation

- The released bilirubin is carried by **albumin** in blood **(Indirect, unconjugated bilirubin)**



enter the liver

conjugation

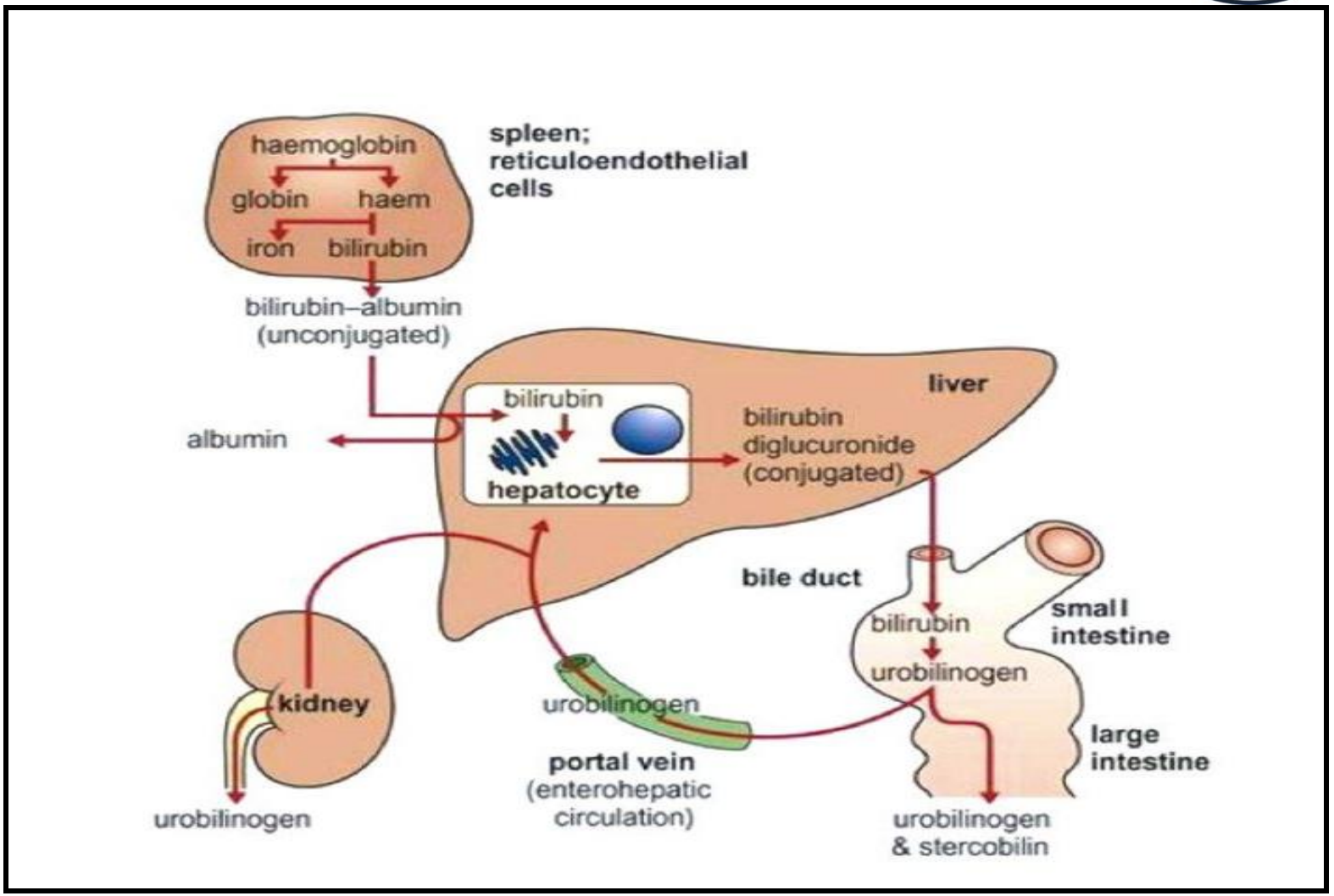
Direct (conjugated) bilirubin

excreted in bile

Hemoglobin degradation

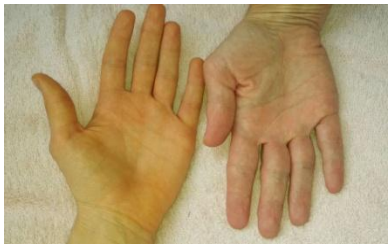
- When the conjugated bilirubin reaches the colon, it is rapidly **deconjugated by colonic bacteria** to **urobilinogen**.
- Around **80%** of this urobilinogen is converted to colorless **stercobilinogen**, which is then oxidized to **stercobilin** → **giving stool its characteristic color.**
- The remaining urobilinogen is reabsorbed into the bloodstream as part of the **enterohepatic circulation**. It is carried to the liver where some is recycled for bile production, while a small percentage reaches the kidneys.
- The urobilinogen in the kidney is further oxidized into **urobilin** and then excreted into the urine → **giving urine its characteristic color**.

Bilirubin metabolism




LO 6
Jaundice

Jaundice (icterus)



❖ It is a **yellowish discoloration** of the skin, sclera and mucous membranes due to **increase the blood bilirubin level (hyperbilirubinemia)** beyond the normal level.

❖ **Normal total bilirubin level** in blood: **up to 1-1.2 mg/dl**.

❖ **Normal direct bilirubin level** in blood**: up to 0.3 mg/dl**.

❖ **Total bilirubin level > 2.5–3 mg/dl** typically result in **jaundice**.

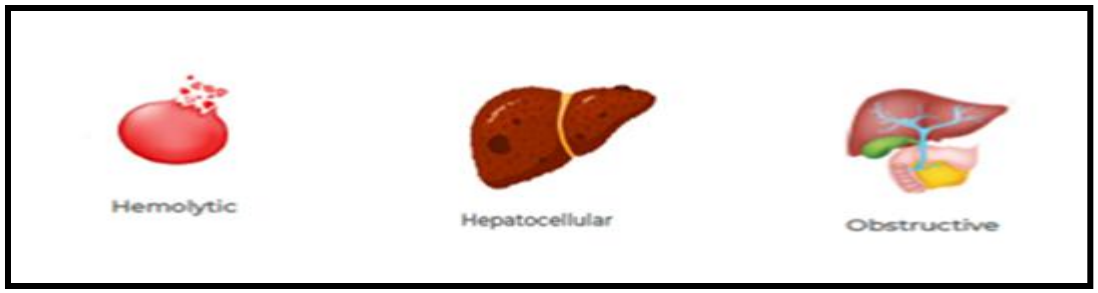
❖ Jaundice is **not a disease but it is a sign** of other diseases.

Jaundice (icterus)

Types of jaundice:

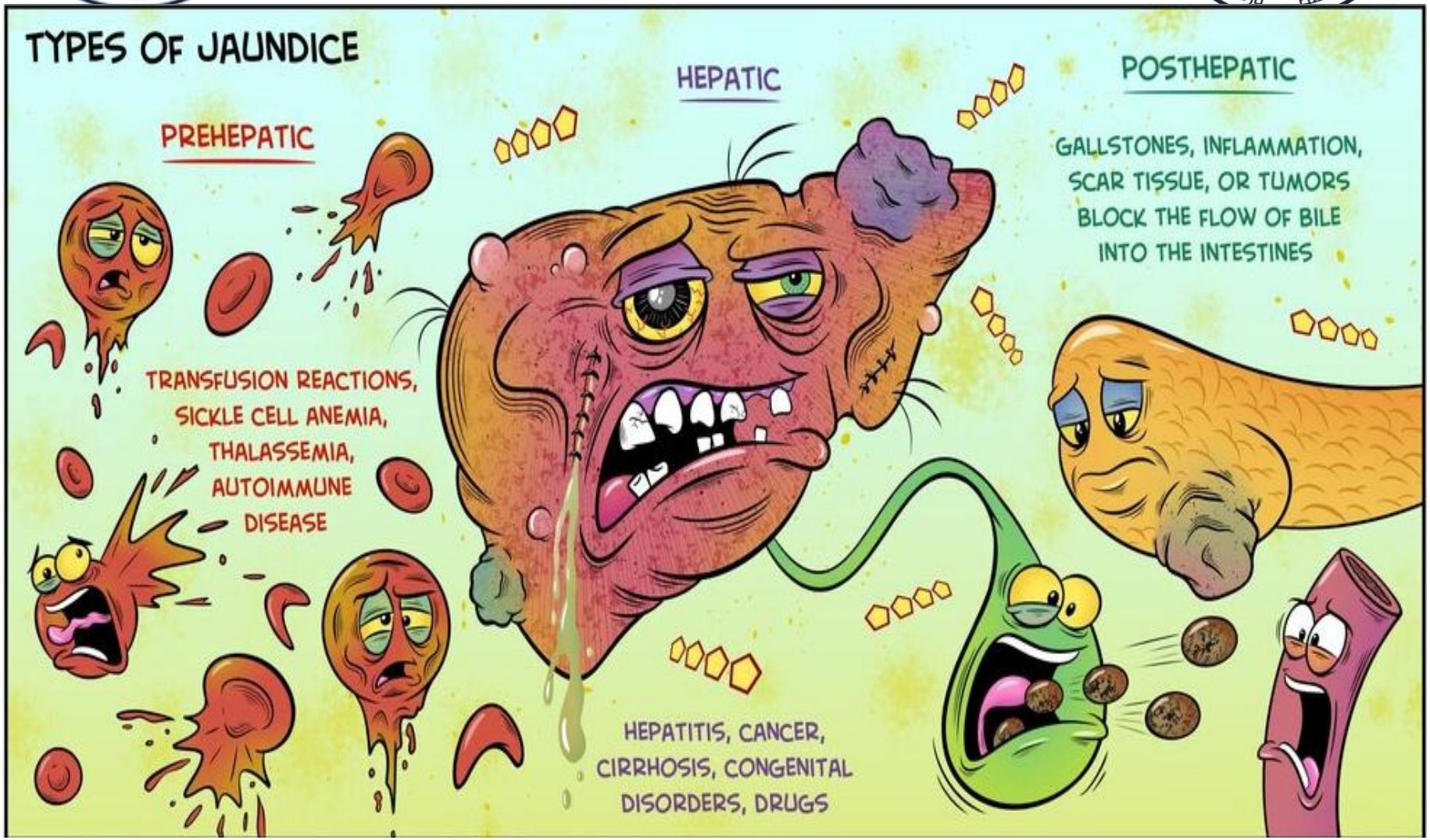
There are 3 main types of jaundice:

- Hemolytic (Prehepatic) jaundice
- Hepatocellular (Hepatic) jaundice
- Obstructive (Posthepatic) jaundice



	Hemolytic (Prehepatic) jaundice	Hepatocellular (Hepatic) jaundice	Obstructive (Posthepatic) jaundice
Biochemical basis (mechanism)	↑↑ Production of bilirubin exceeding the capacity of hepatocytes for uptake, conjugation and excretion.	Hepatocyte dysfunction → impaired hepatic uptake, conjugation or secretion of bilirubin.	Obstruction in the passage of conjugated bilirubin from the liver to the intestine → regurgitation of bilirubin to blood.
Causes	• Sickle cell anemia. • Spherocytosis. • G-6-P-D deficiency. • Incompatible blood transfusion.	• Infection (viral hepatitis). • Liver cirrhosis. • Alcoholic liver disease.	• Bile stones (common bile duct gallstones is the most common cause of obstructive jaundice). • Tumor (cancer of pancreatic head).
Type of bilirubin increased	Unconjugated (indirect)	Both unconjugated & conjugated (direct & indirect)	Conjugated (direct)

Jaundice (icterus)



References

- **Blanco, A., & Blanco, G. (2017). *Medical biochemistry*. Academic Press.**
- **Harper's Illustrated Biochemistry. 31e, Chapter 31, Rodwell & and Murray, eds.**
- Hemoglobin Structure; What's In Your Red Blood Cell? - YouTube
- Bilirubin Metabolism Simplified - YouTube
- Jaundice | definition, types, clinical picture, diagnosis, bilirubin metabolism عربي – YouTube
- **Lane, T. R., Williamson, W. J., & Brostoff, J. M. (2008). Carbon monoxide poisoning in a patient with carbon dioxide retention: a therapeutic challenge. Cases Journal, 1(1), 1-2.**
- Carbon monoxide poisoning – UpToDate


Thank
You