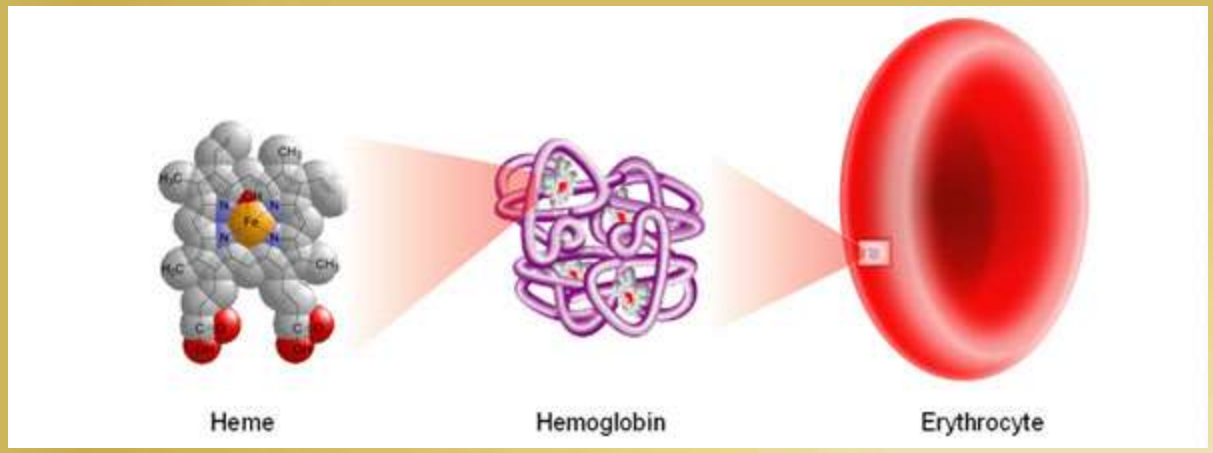
BIOSYNTHESIS & CATABOLISM OF HEMOGLOBIN



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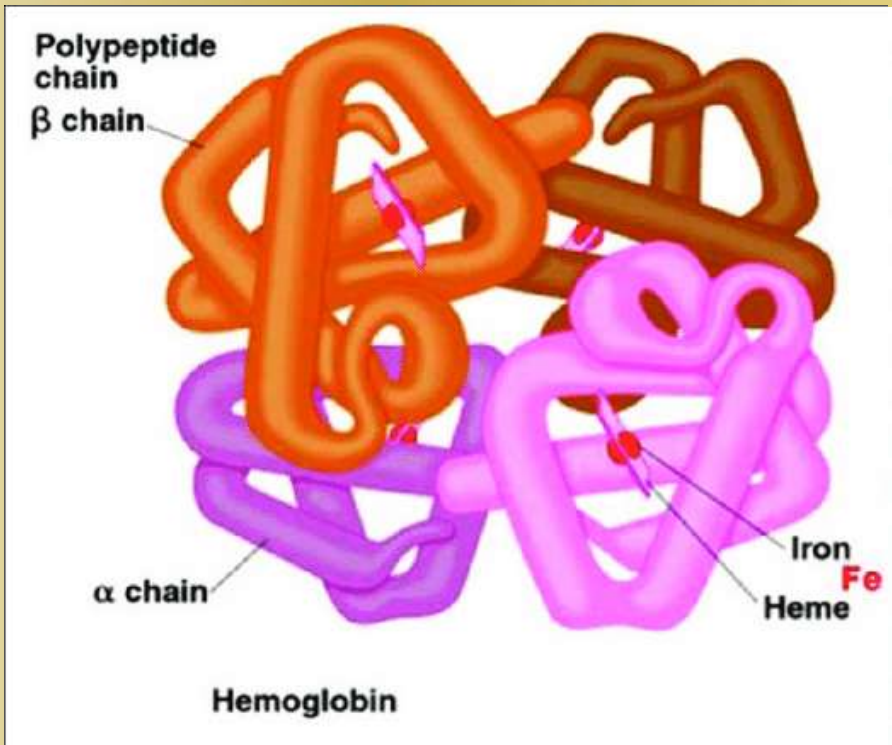
Introduction

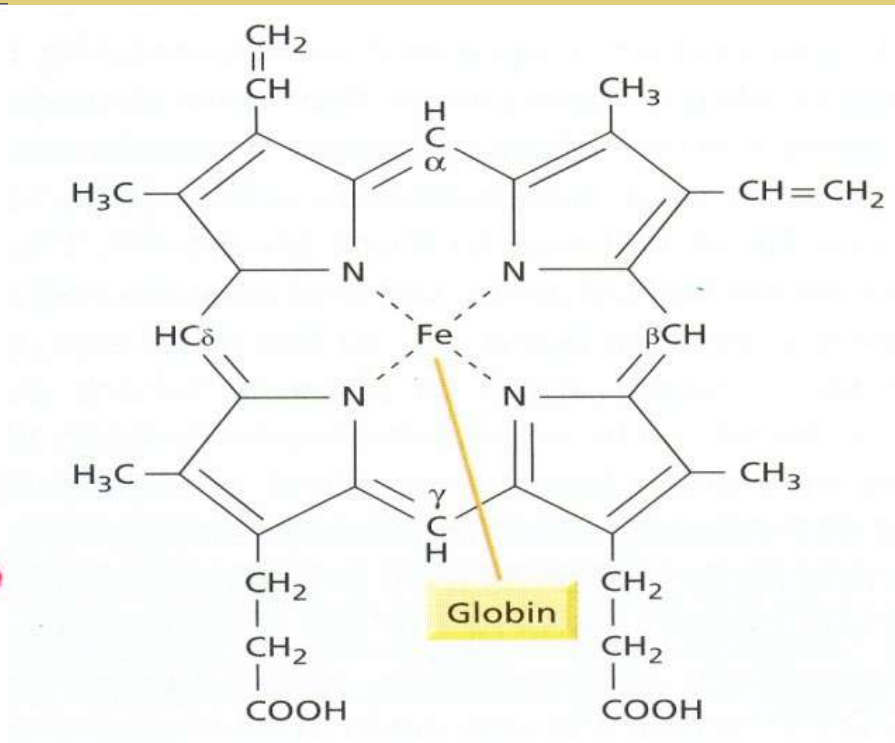
- Hemoglobin (Hb) is the red blood pigment, exclusively found in **erythrocytes** **(Greek:** erythrose—red; kytos—a hollow vessel).
- The normal concentration of Hb in blood in males is 14–16 g/dl, and in females 13–15 g/dl.
- Hemoglobin performs two important biological functions concerned with respiration

1. Delivery of O2 from the lungs to the tissues.
2. Transport of CO2 and protons from tissues to lungs for excretion.

Structure of Hb

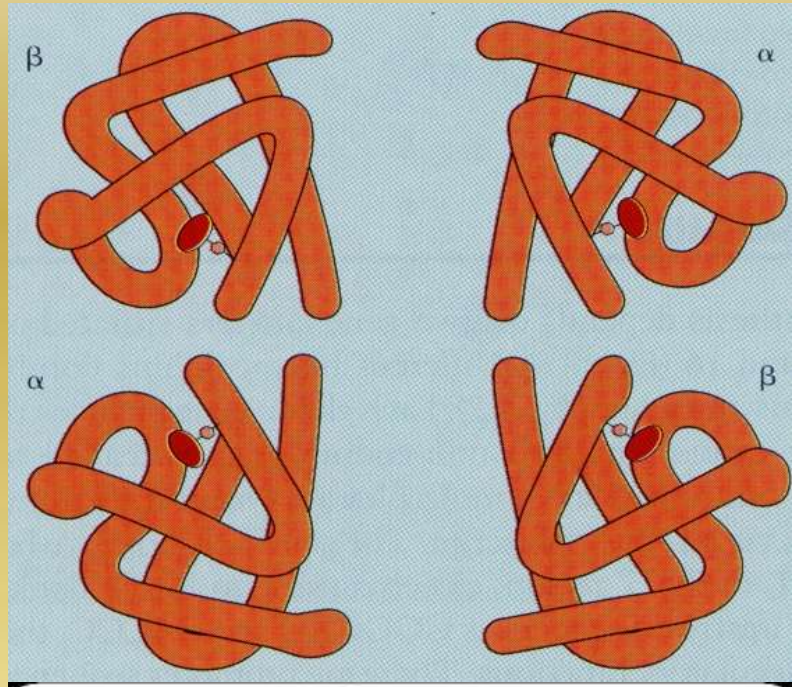
- Hemoglobin (mol. wt. 64,450) is a conjugated protein, containing **globin—the apoprotein** part—and the **heme—the non-protein part** (prosthetic group).
- Hemoglobin is a **tetrameric allosteric protein**

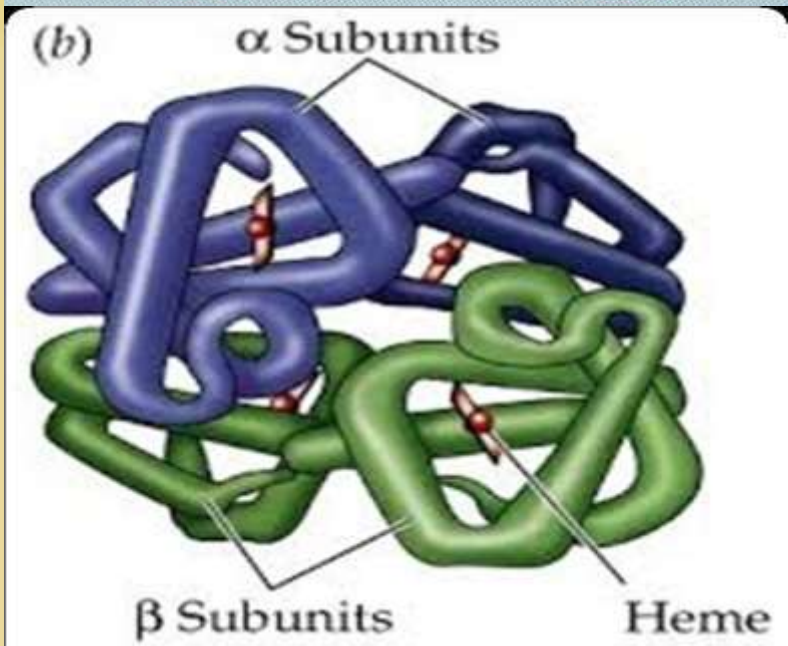




Structure of Globin:

- Globin consists of four polypeptide chains.
- Adult hemoglobin (HbA1) contains two α-chains and two β-chains (**α 2 β 2**).
- **α-chain** contains 141 amino acids.
- **β-chain** contains 146 amino acids.





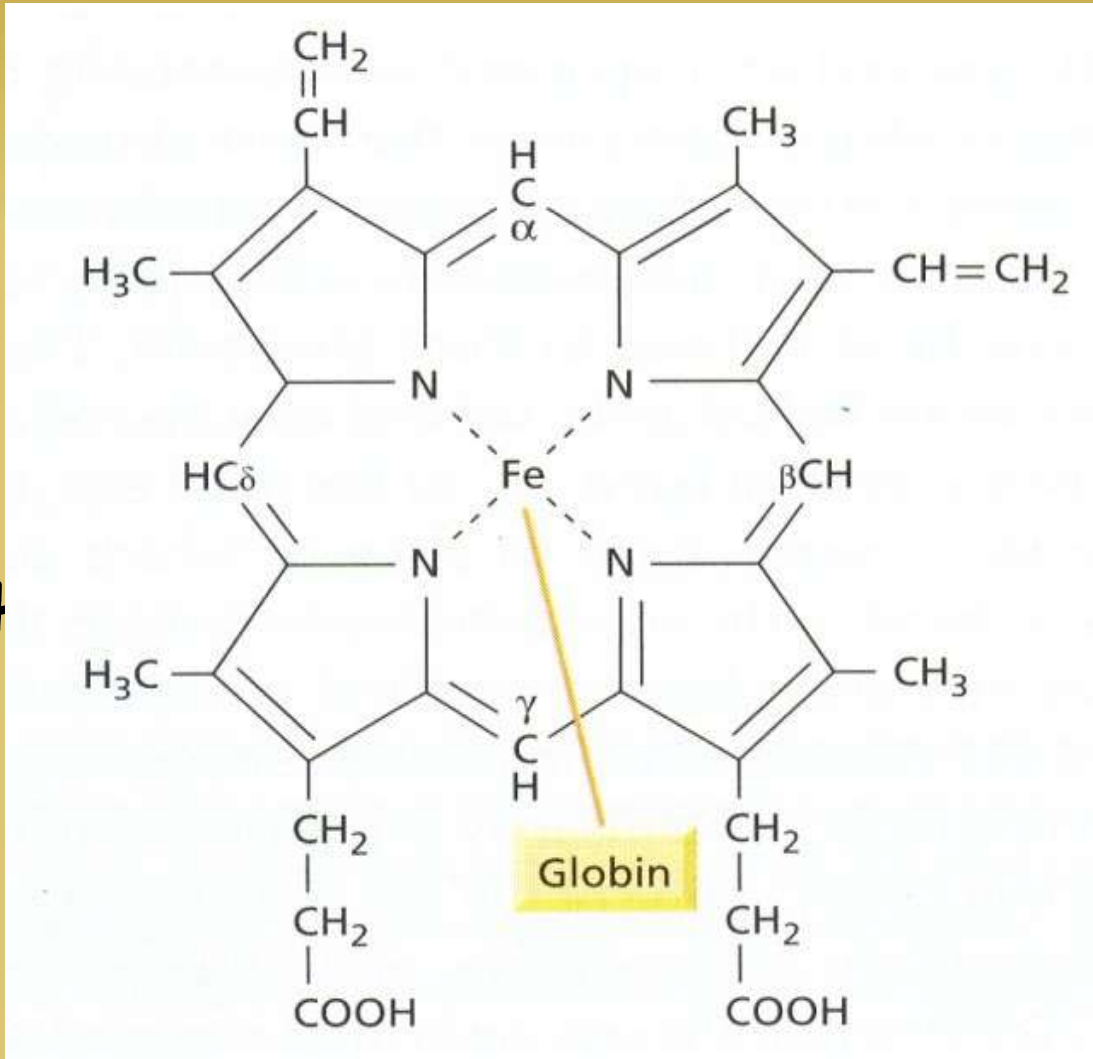
Structure of heme:

IRON

- Ferrous form (Fe2+).
- Iron attached to nitrogen atom of each pyrrole ring.
- On iron loose bond for
  - Oxygen
  - Carbon monoxide.

PORPHYRIN NUCLEUS

- 4 Pyrrole Rings
- (Tetrapyrrole)
- Bridges – Methine (CH
- Side chains – 8
  - Methyl (CH3) - 4
  - Vinyl (CH.CH2) - 2
  - Propionic acid – 2
  - (CH2.CH2.COOH)



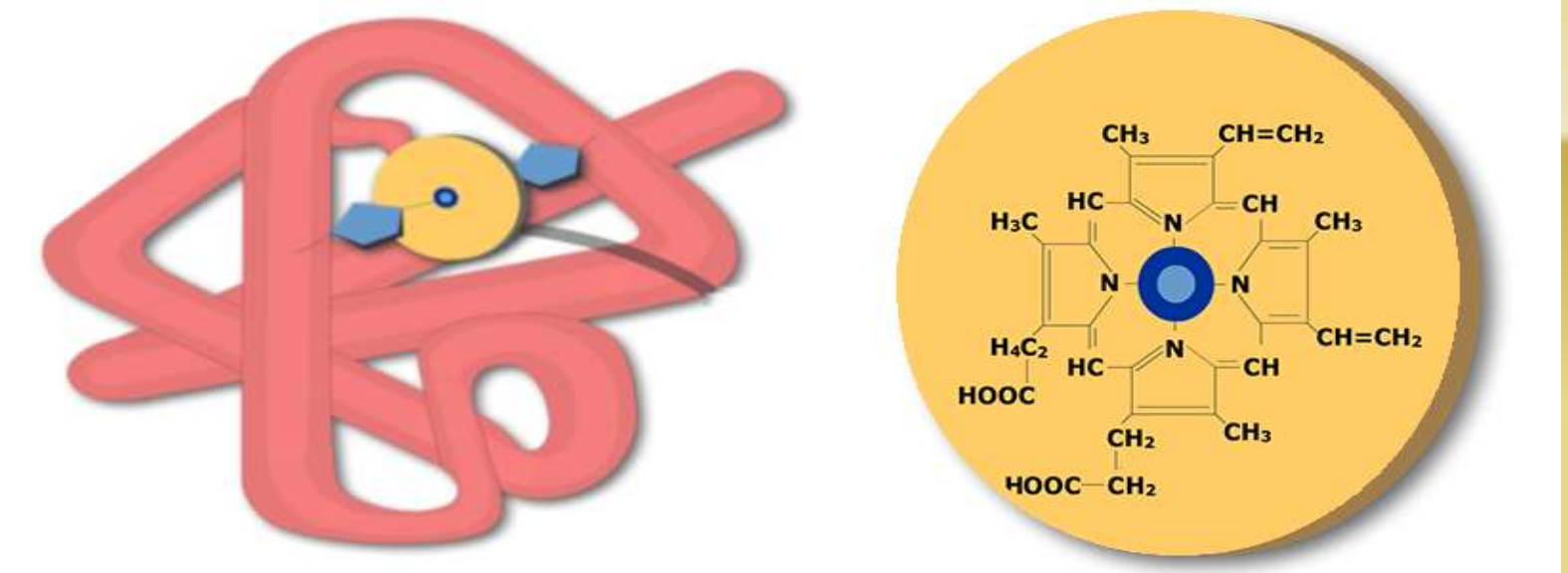
Types of Hb

TABLE 10.1 Normal major types of hemoglobins

Type	*Composition and symbol*	*Percentage of total hemoglobin*
HbA_1	$\alpha_2\beta_2$	90%
HbA_2	$\alpha_2\delta_2$	< 5%
HbF	$\alpha_2\gamma_2$	< 2%
HbA_{1c}	$\alpha_2\beta_2$-glucose	< 5%

Myoglobin

- Myoglobin (Mb) is monomeric oxygen binding hemoprotein found in **heart and skeletal muscle.**
- It has **a single polypeptide (153 amino** acids) chain with heme moiety.
- Myoglobin functions as **a reservoir for oxygen**.
- **It further serves as oxygen carrier that** promotes the transport of oxygen to the rapidly respiring muscle cells.

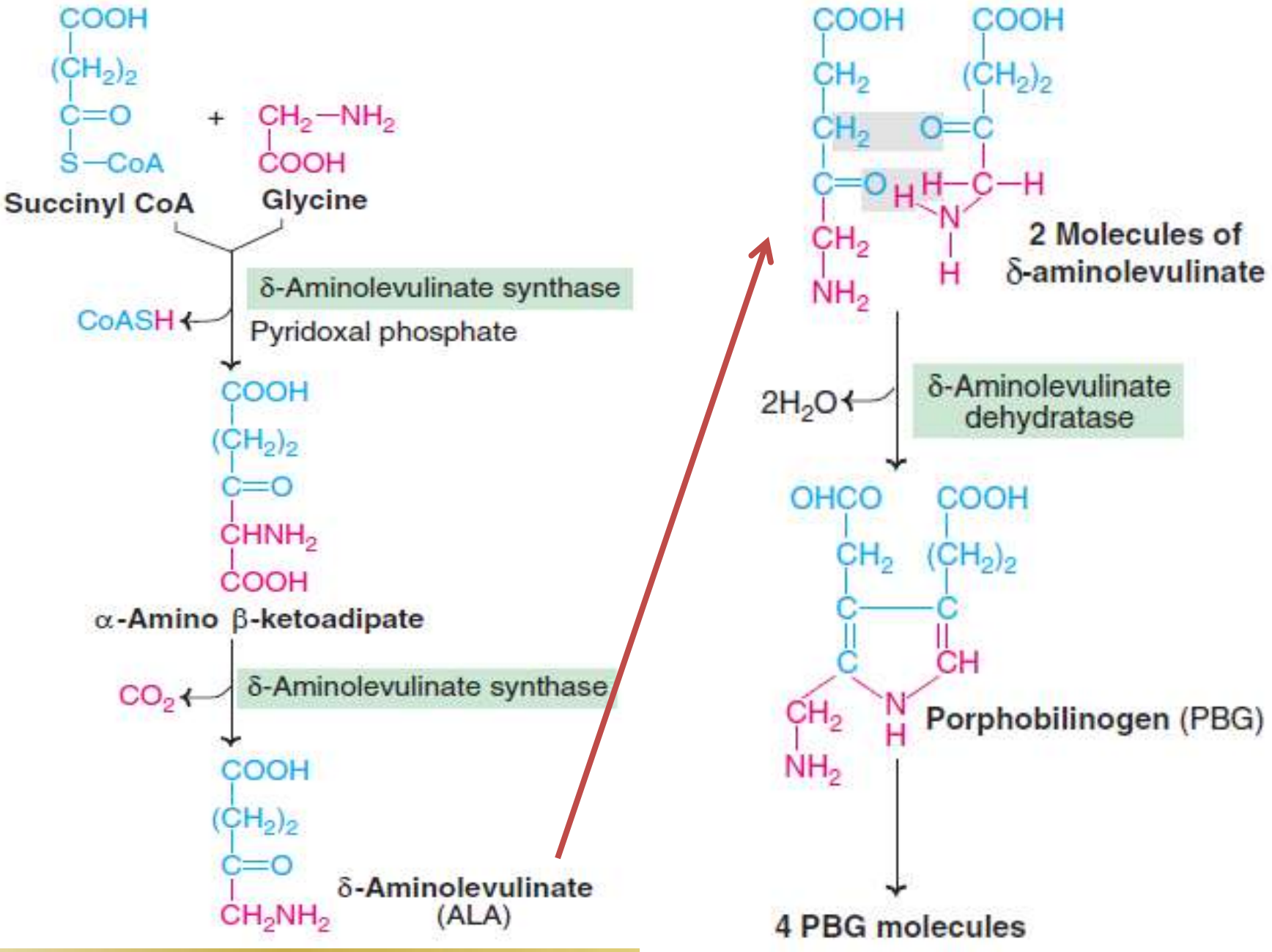


Biosynthesis of Hb

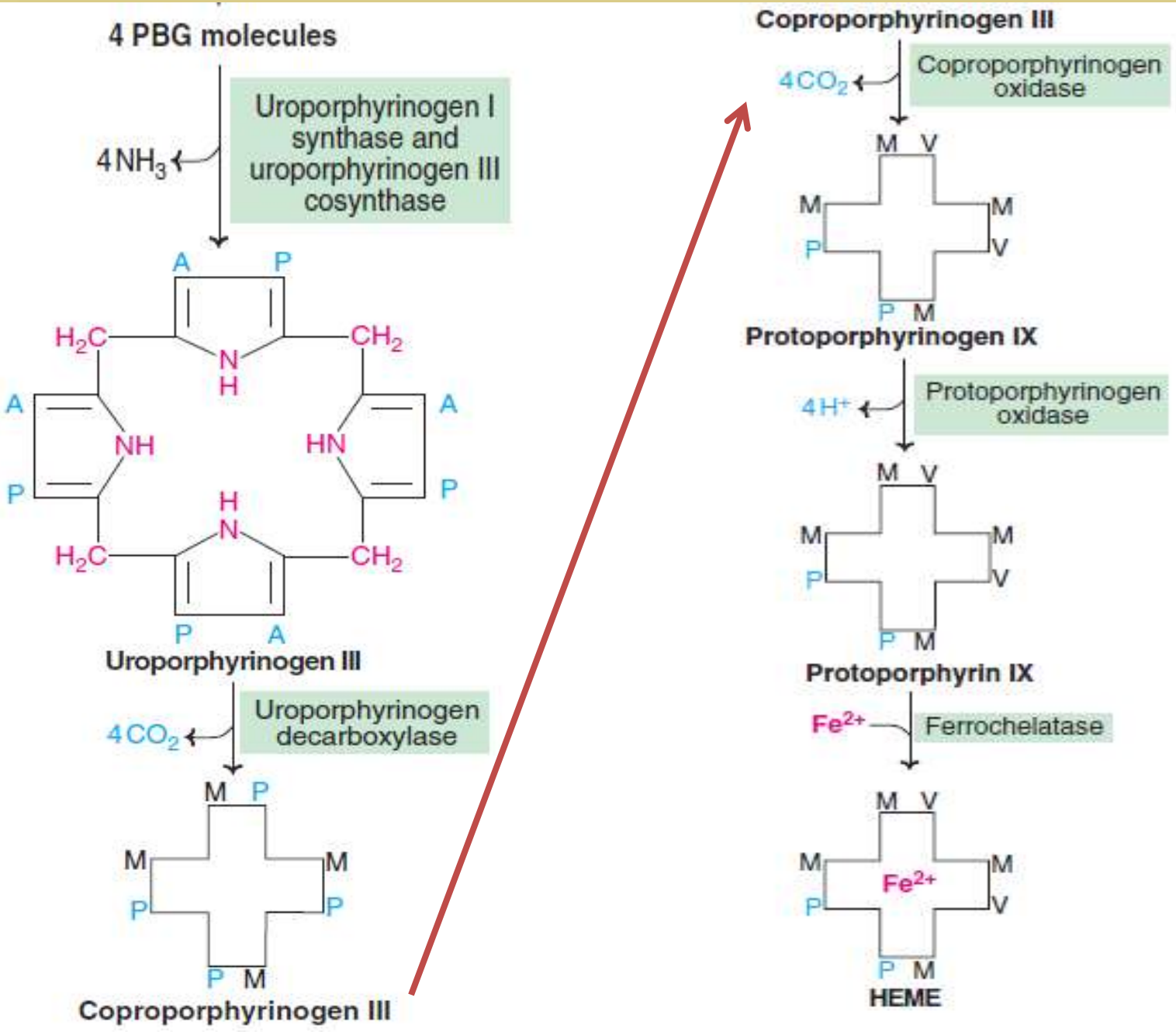
- Heme is the most important porphyrin containing compound.
- It is primarily synthesized in the **liver and the erythrocyte-producing cells** of **bone marrow (erythroid cells).**
- **Heme synthesis** also occurs to some extent in other tissues.
- Biosynthesis of heme occurs in the following stages:

1. **Formation of δ-aminolevulinate.**
2. **Synthesis of porphobilinogen.**
3. **Formation of porphyrin ring.**
4. **Conversion of uroporphyrinogen III to protoporphyrin IX.**
5. **Synthesis of heme from protoporphyrin IX.**

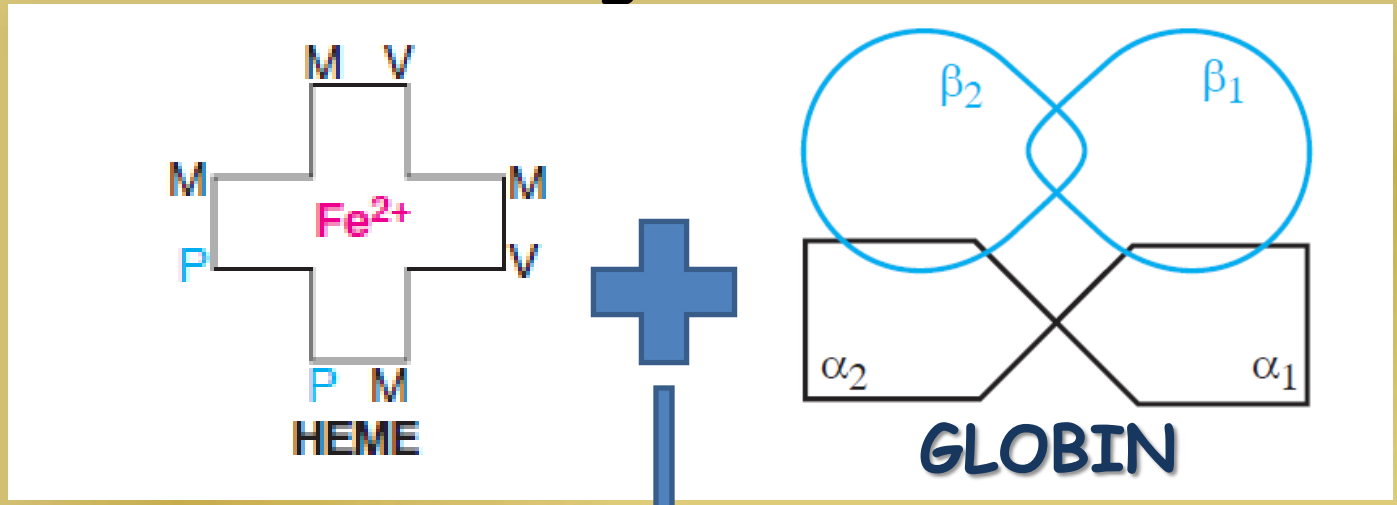
Synthesis of Hb



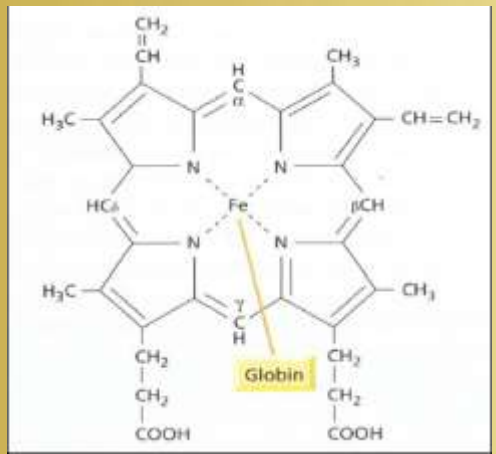
Synthesis of Hb

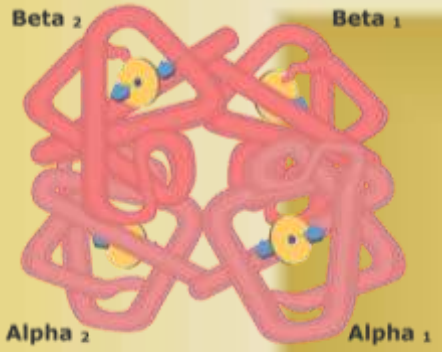


Formation of hemoglobin from heme



HEMOGLOBIN





Regulation of heme synthesis

- Heme production in the liver is required for the formation of hemoproteins (e.g. cytochrome P_{450} involved in detoxification) while in the erythroid cells, it is necessary for the synthesis of hemoglobin.
- Two different mechanisms exist for the regulation of heme biosynthesis in the liver and the erythroid cells.

Regulation of heme synthesis

1. Regulation in the liver :

- **The first committed** step in heme biosynthesis, catalysed by δ-aminolevulinate (ALA) synthase, is regulatory.
- **Heme** or its oxidized product **hemin (Fe3+) controls this** enzyme activity by three mechanisms
  - Feedback inhibition
  - Repression of ALA synthatase
  - Inhibition of transport of ALA synthase from cytosol to mitochondria (the site of action).

Regulation of heme synthesis

2. **Effect of drugs on ALA synthase activity :** **The** activity of ALA synthase is markedly **increased by the administration of a large number of drugs** e.g. **phenobarbital, insecticides, carcinogens etc.**
3. **Regulation in the erythroid cells:**
   - **Uroporphyrinogen synthase and ferrochelatse** mostly regulate heme formation in these cells.

FACTORS CONTROLLING HAEMOGLOBIN FORMATION.

- **Role Of Proteins – First class proteins provide** amino acids.
- **Most imp – food of animal origin, liver, spleen,** kidney & heart
- **Intermediate value – muscles**
- **Least – cereals, dairy products, veg & fruits.**
- **Uptake of iron**

Functions of Haemoglobin

- Transport oxygen to tissues
- Transport Co2 to lungs
- Maintains acid base balance (As a Buffer)

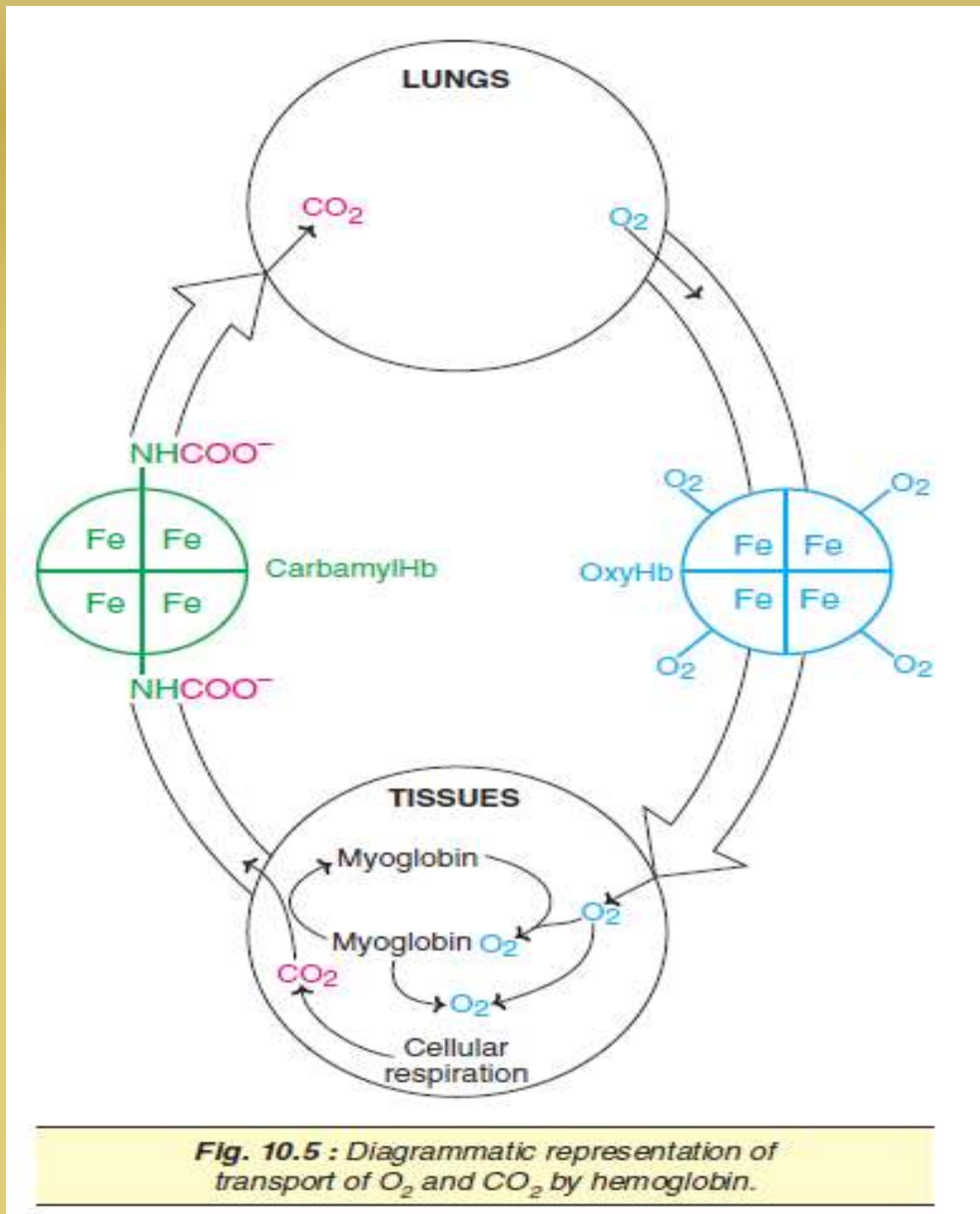
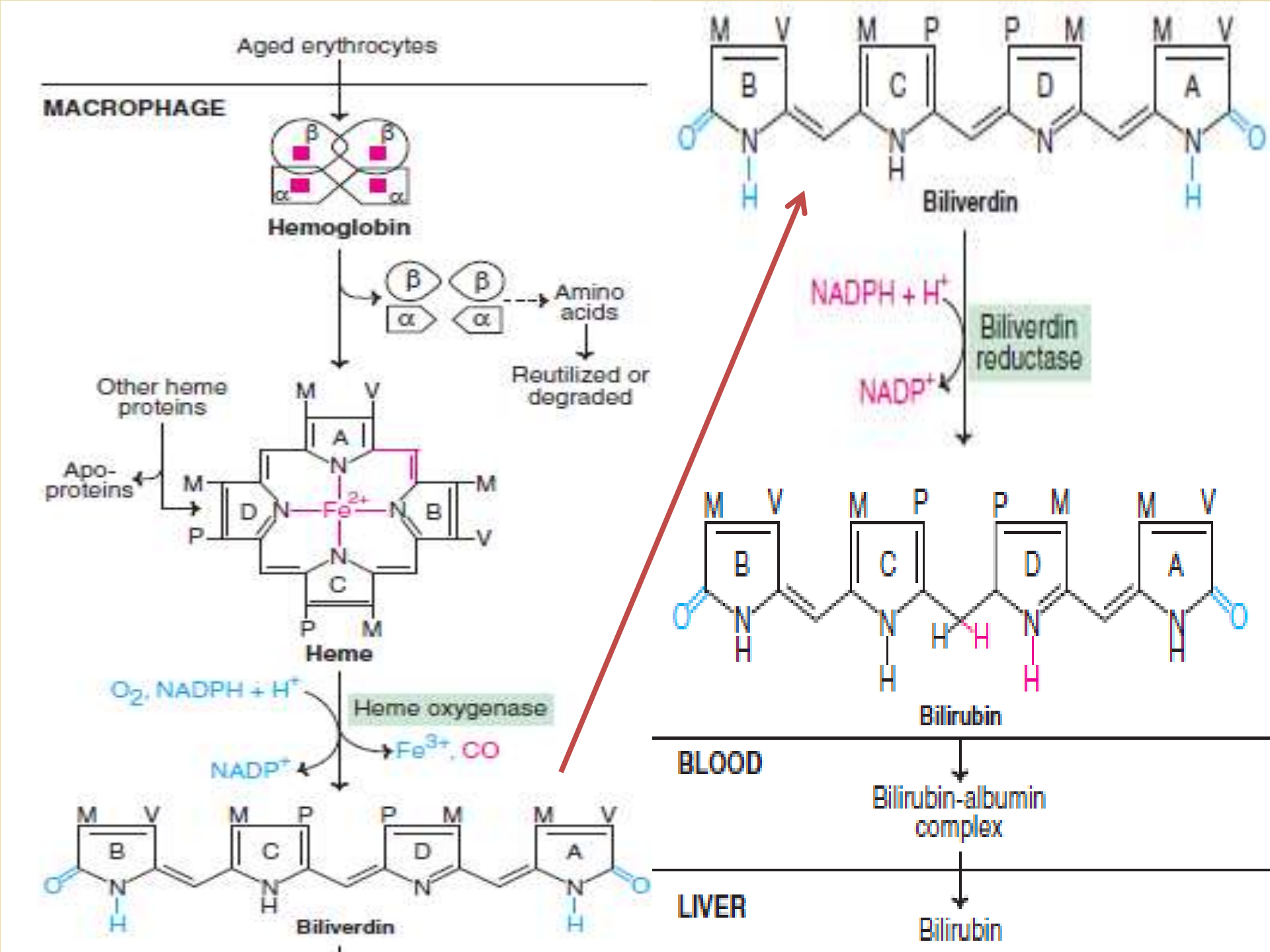


Fig. 10.5 : Diagrammatic representation of transport of O_2 and CO_2 by hemoglobin.

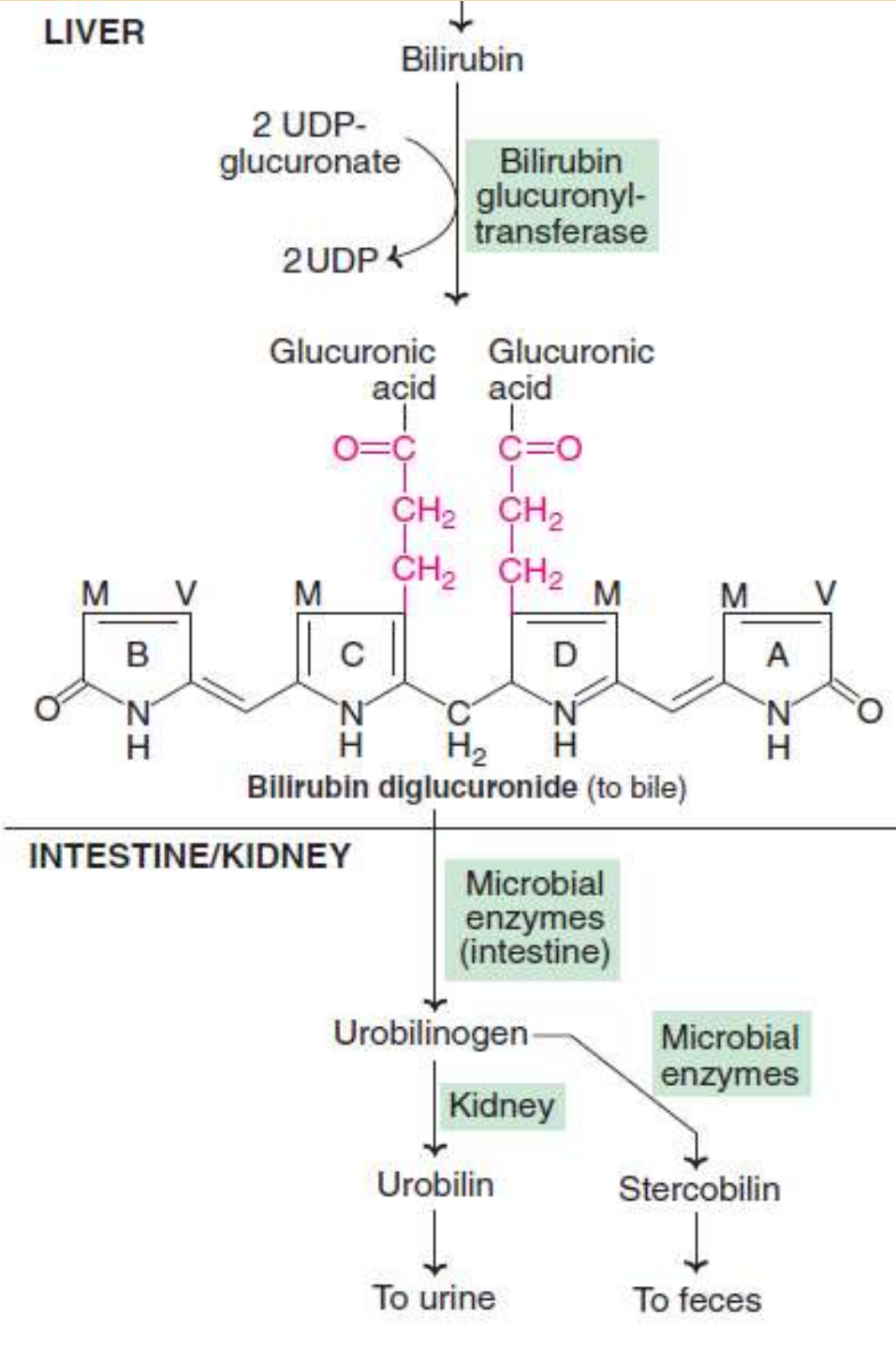
DEGRADATION OF HEME TO BILE PIGMENTS

- Erythrocytes have a **life span of 120 days**. At the end of this period, they are removed from the circulation.
- Erythrocytes are taken up and degraded by the macrophages of the reticuloendothelial (RE) system in the spleen and liver.
- The hemoglobin is cleaved to the protein part globin and non-protein heme.
- About 6 g of hemoglobin per day is broken down, and resynthesized in an adult man (70 kg).


Aged erythrocytes
MACROPHAGE
Hemoglobin
Amino acids
Reutilized or degraded
Other heme proteins
Apo-proteins
Heme
O_2, NADPH + H^+
Heme oxygenase
Fe^{3+}, CO
$NADP^+$
Biliverdin
NADPH + H^+
Biliverdin reductase
$NADP^+$
Biliverdin
Bilirubin
BLOOD
Bilirubin-albumin complex
LIVER
Bilirubin

Transport of bilirubin to liver

- Bilirubin insoluble in aques solution.
- Bind with albumin to form bilirubin-albumin complex.
- Approximately 25 mg of bilirubin can bind tightly to albumin (at high affinity sites) per 100 ml of plasma.



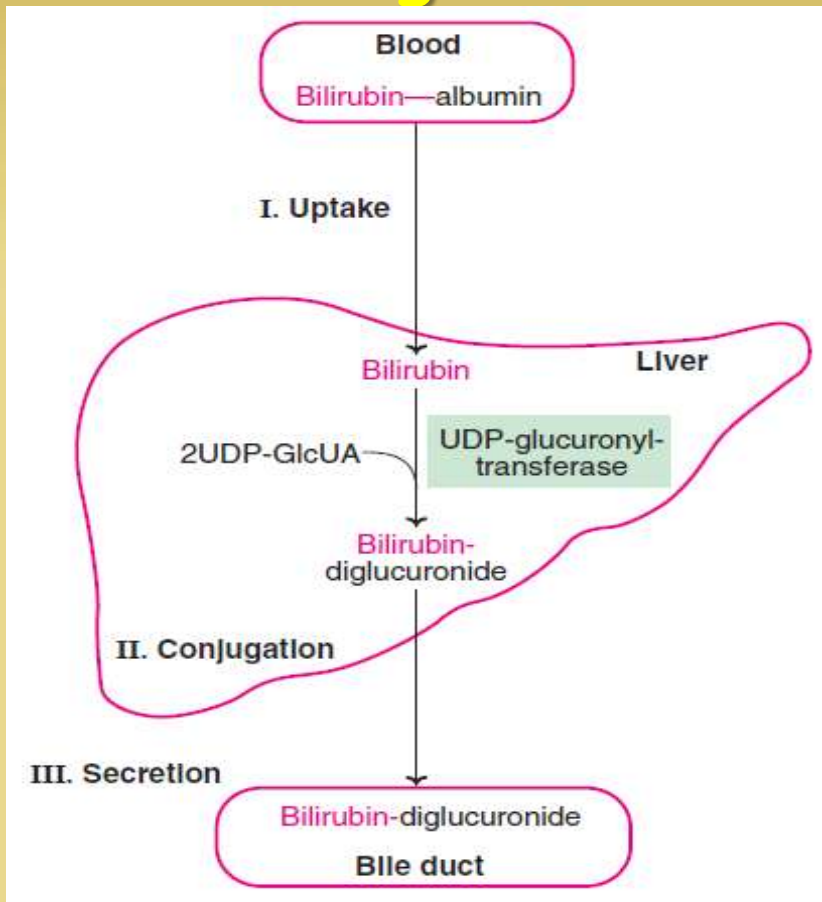
Conjugation of Bilirubin

Bilirubin
+
2 Glucuronate
(by UDPglucuronate)

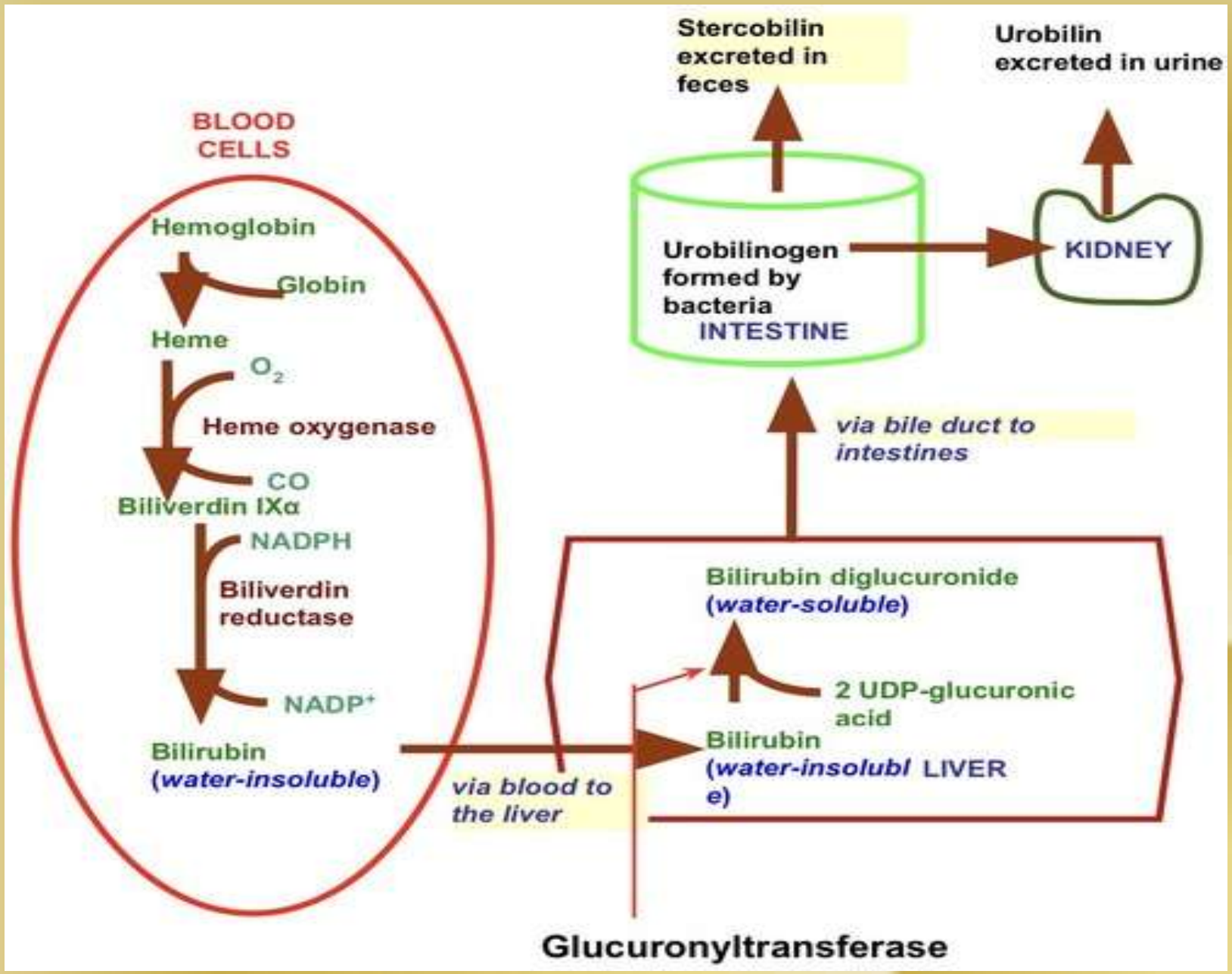
Bilirubin Glucuronyl transferase → **bilirubin diglucuronide**

Excretion of bilirubin into bile:

- Conjugated bilirubin is excreted into the bile canaliculi against a concentration gradient which then enters the bile.



Fate of bilirubin



NORMAL RANGE OF BILIRUBIN

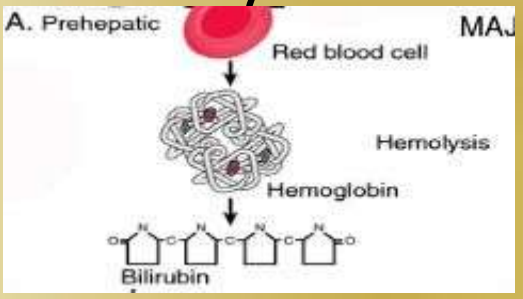
- The normal **serum total bilirubin concentration** is in the range of **0.2 to 1.0 mg/dl.**
- about 0.2-0.6 mg/dl is unconjugated
- while 0.2 to 0.4 mg/dl is conjugated bilirubin.

JAUNDICE

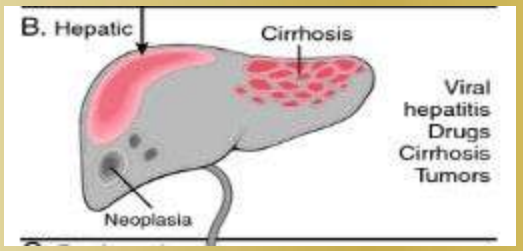
- Jaundice (French : Jaune-yellow) is a clinical condition characterized by yellow colour of the white of the eyes (sclerae) and skin.
- It is caused by the deposition of bilirubin due to its elevated levels in the serum. The term **hyperbilirubinemia** is often used to represent the increased concentration of serum bilirubin.

Classification:

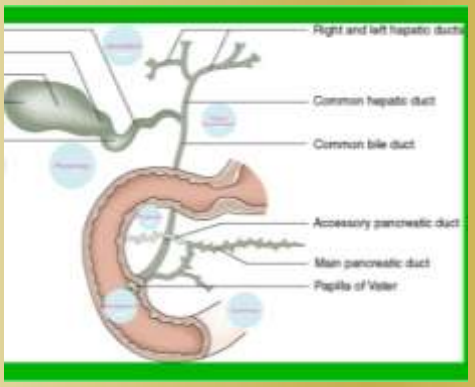
1. Hemolytic



2. Hepatic



3. obstructive.



Hemolytic Jaundice	Hepatic Jaundice	Obstructive Jaundice
Normal SGOT SGPT	**SGOT** ↑↑↑ **SGPT** ↑↑↑	SGOT ↑ SGPT ↑
Normal ALP GGT 5NT	Slightly increased ALP GGT 5NT	**Marked increased ALP** **GGT** **5NT**
Total bilirubin ↑	Total bilirubin ↑↑	Total bilirubin ↑
Indirect bilirubin ↑	**Indirect bilirubin** ↑↑	Indirect bilirubin ↑
Direct bilirubin Normal	**Direct bilirubin** ↑↑	**Direct bilirubin** ↑↑↑
Reticulocyte count ↑	Prothrombin time increased (short term marker of synthetic capability of liver)	
Urinary urobilinogen present	Serum albumin decreases (marker of long term liver damage or chronic conditions)	**Urinary urobilinogen absent**
Absent urine bilirubin	**Bilirubin and bile salt present in urine**	**Bilirubin and bile salt present in urine**
Hb decreases		Itching due to increased bile acids in blood (stimulates mast cells)
RBC count decreases		Pale colored stool
Splenomegaly		Xanthomas due to increased cholesterol

thank you!