METABOLISM OF PORPHYRINS

TEJASVI NAVADHITAMASTU

"Let our (the teacher and the taught) learning be radiant"

Let our efforts at learning be luminous and filled with joy, and endowed with the force of purpose

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E –content

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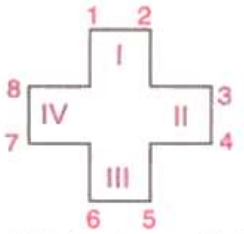
PORPHYRINS

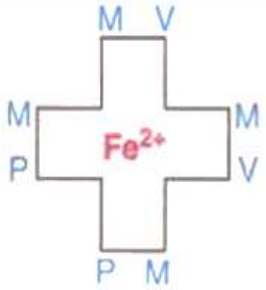
Porphyrins are cyclic compounds composed of 4 pyrrole rings held together by methenyl (=CH−) bridges (***Fig.10.18***). Metal ions can bind with nitrogen atoms of pyrrole rings to form complexes. Heme is an iron-containing porphyrin (***See Fig.10.2***) while chlorophyll is a magnesium-containing porphyrin. Thus heme and chlorophyll are the classical examples of metalloporphyrins.

Presentation and nomenclature of porphyrins

The structure of porphyrins ($C_{20}H_{14}N_4$) has four ***pyrrole rings*** namely I, II, III and IV.



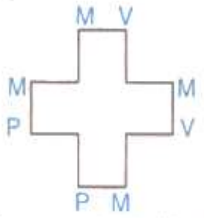
Fischer's model



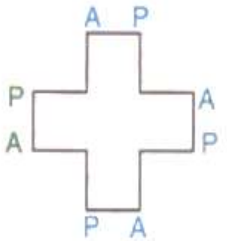
Heme

Hans Fischer, the father of porphyrin chemistry, proposed a shorthand model for presentation of porphyrin structures. Accordingly, each pyrrole ring is represented as a bracket. Thus porphyrin has 4 closed brackets with the 8 substituent positions numbered as shown in ***Fig.10.18***.

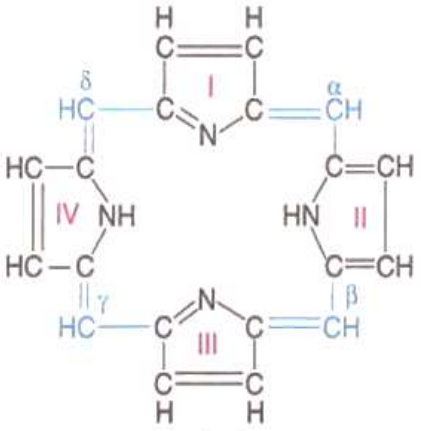
Type I porphyrins : When the substituent groups on the 8 positions are symmetrically arranged they are known as type I porphyrins, e.g. uroporphyrin I.



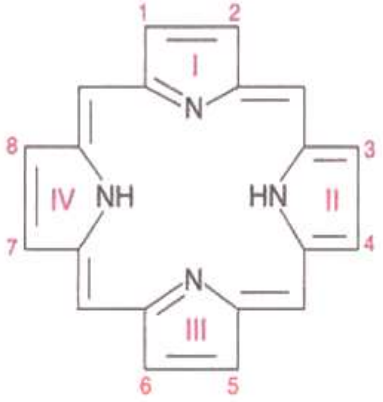
Protoporphyrin IX (III)



Uroporphyrin I



Porphyrin



Porphyrin

Fig. 10.19 : *Fischer's shorthand models of physiologically important porphyrins [A–Acetate ($-CH_2COO^-$); P–Propionyl ($-CH_2CH_2COO^-$); M–Methyl ($-CH_3$); V–Vinyl ($-CH=CH_2$)].*

Biosynthesis

1. Formation of 8-aminolevulinat
2. Synthesis of porphobilinogen
3. Formation of porphyrin ring
4. Conversion of uroporphyrinogen lll to protoporphyrin lX
5. Synthesis of heme from protoporphyrin lX

1. **Formation of δ-aminolevulinate : *Glycine,*** a non-essential amino acid and ***succinyl CoA,*** an intermediate in the citric acid cycle, are the starting materials for porphyrin synthesis. Glycine combines with succinyl CoA to form δ-aminolevulinate (ALA). This reaction catalysed by a pyridoxal phosphate dependent ***δ-amino-levulinate synthase*** occurs in the mitochondria. It is a rate-controlling step in porphyrin synthesis.

2. **Synthesis of porphobilinogen :** Two molecules of δ-aminolevulinate condense to form porphobilinogen (PBG) in the cytosol. This reaction is catalysed by a Zn-containing enzyme ***ALA dehydratase***. It is sensitive to inhibition by heavy metals such as lead.

3. **Formation of porphyrin ring :** Porphyrin synthesis occurs by condensation of four molecules of porphobilinogen. The four pyrrole rings in porphyrin are interconnected by methylene ($-CH_2$) bridges derived from α-carbon of glycine.

The interaction of two enzymes—namely uroporphyrinogen I synthase and uroporphyrinogen III cosynthase—results in condensation of porphobilinogen followed by ring closure and isomerization to produce uroporphyrinogen III.

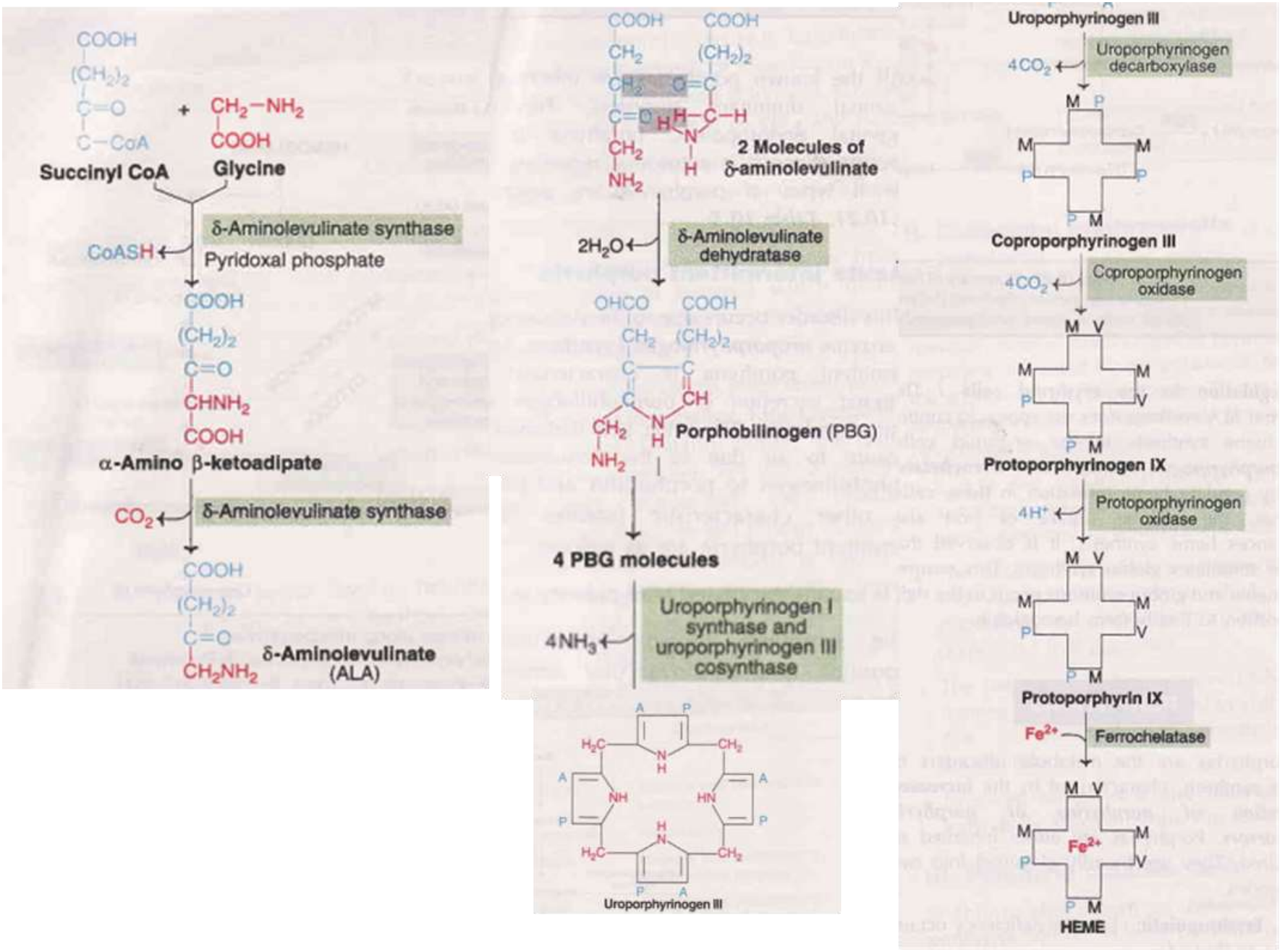
4. **Conversion of uroporphyrinogen III to protoporphyrin IX :** This is catalysed by a series of reactions

(a) Uroporphyrinogen decarboxylase decarboxylates all the four acetate (A) side chains to form methyl groups (M), to produce coproporphyrinogen.

(b) Coproporphyrinogen oxidase converts (oxidative decarboxylation) two of the propionate side chains (P) to vinyl groups (V) and results in the formation of protoporphyrinogen.

(c) Protoporphyrinogen oxidase oxidizes methylene groups ($-CH_2-$) interconnecting pyrrole rings to methenyl groups ($=CH-$). This leads to the synthesis of protoporphyrin IX.

5. **Synthesis of heme from protoporphyrin IX :** The incorporation of ferrous iron (Fe^{2+}) into protoporphyrin IX is catalysed by the enzyme ***ferrochelatase*** or ***heme synthetase.*** This enzyme can be inhibited by lead. It is found that the induction of Fe^{2+} into protoporphyrin IX can occur spontaneously but at a slow rate.


Succinyl CoA
Glycine
δ-Aminolevulinate synthase
CoASH
Pyridoxal phosphate
α-Amino β-ketoadipate
CO2
δ-Aminolevulinate synthase
δ-Aminolevulinate (ALA)
2 Molecules of δ-aminolevulinate
2H2O
δ-Aminolevulinate dehydratase
Porphobilinogen (PBG)
4 PBG molecules
4NH3
Uroporphyrinogen I synthase and uroporphyrinogen III cosynthase
Uroporphyrinogen III
Uroporphyrinogen III
4CO2
Uroporphyrinogen decarboxylase
Coproporphyrinogen III
4CO2
Coproporphyrinogen oxidase
Protoporphyrinogen IX
4H+
Protoporphyrinogen oxidase
Protoporphyrin IX
Fe2+
Ferrochelatase
Fe2+
HEME

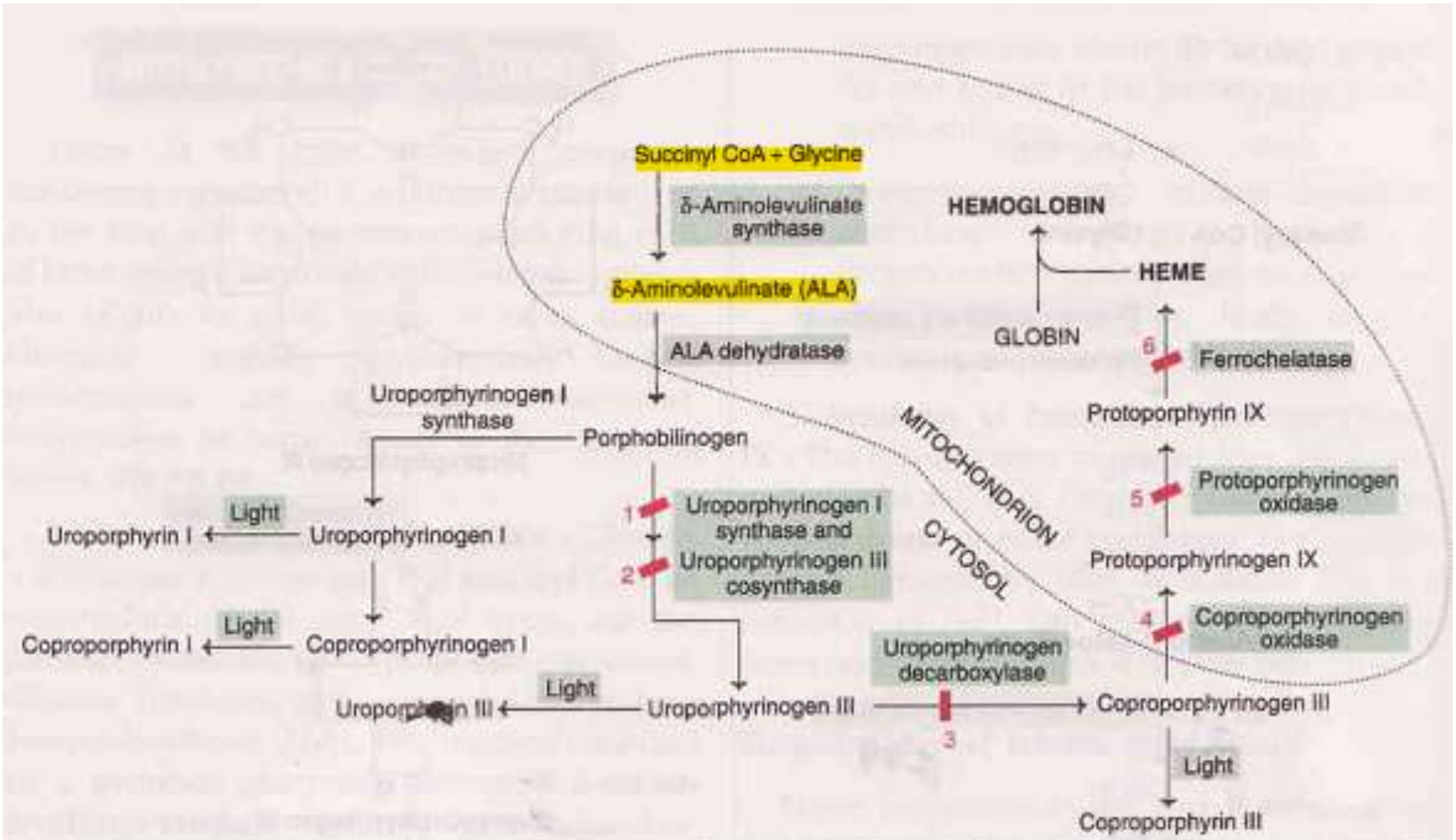


***Fig. 10.21** : Summary of heme synthesis along with porphyrias (1–Acute intermittent porphyria; 2–Congenital erythropoietic porphyria; 3–Porphyria cutanea tarda; 4–Hereditary coproporphyria; 5–Variegate porphyria; 6–Protoporphyria).*

PORPHYRIAS

Porphyrias are the metabolic disorders of heme synthesis, characterized by the ***increased excretion of porphyrins or porphyrin precursors.*** Porphyrias are either inherited or acquired. They are broadly classified into two categories

1. **Erythropoietic :** Enzyme deficiency occurs in the erythrocytes.

2. **Hepatic :** Enzyme defect lies in the liver.

Porphyrias are classified in two ways, by symptoms and by pathophysiology. Symptomatically,

Acute porphyrias primarily cause brain and nerve involvement, often with severe abdominal pain, vomiting, neuropathy, and mental disturbances.

Cutaneous porphyrias cause skin problems, often after exposure to sunlight, because porphyrins react with light.[1]

Physiologically, porphyrias are classified as hepatic or erythropoietic based on the sites of accumulation of heme precursors, either in the liver or in the bone marrow and red blood cells.[1]

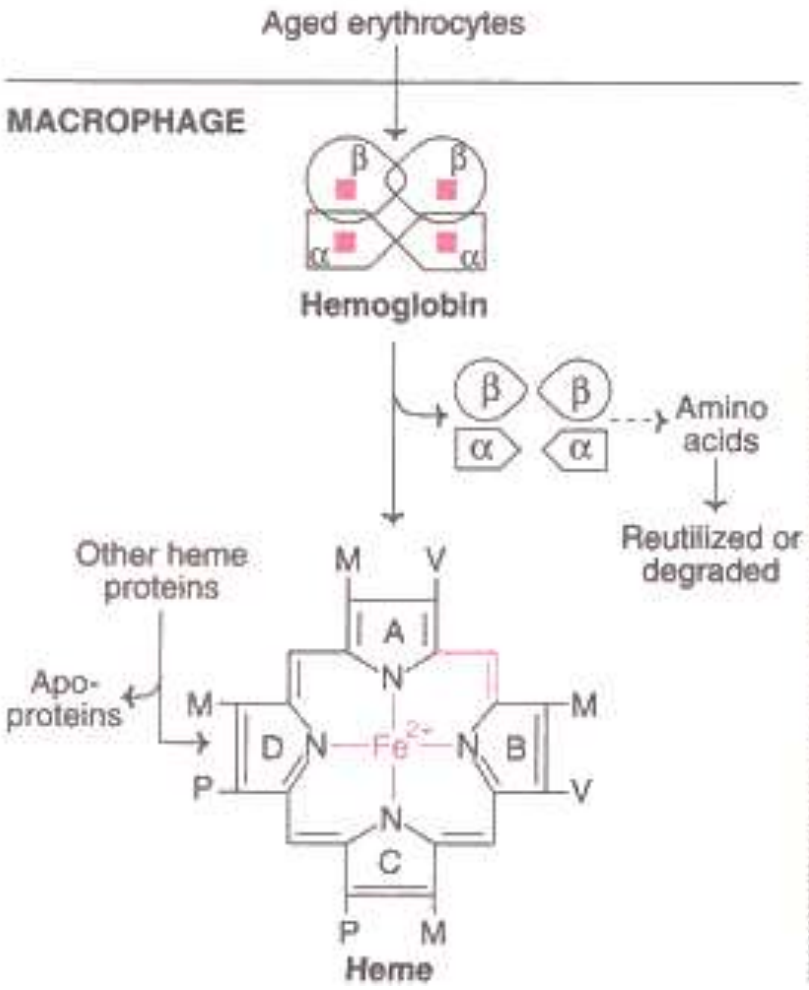
Type of porphyria	*Enzyme defect*	*Characteristics*
Hepatic		
Acute intermittent porphyria	Uroporphyrinogen I synthase	Abdominal pain, neuropsychiatric symptoms
Porphyria cutanea tarda	Uroporphyrinogen decarboxylase	Photosensitivity
Hereditary coproporphyria	Corpoporphyrinogen oxidase	Abdominal pain, photosensitivity, neuropsychiatric symptoms
Variegate porphyria	Protoporphyrinogen oxidase	Abdominal pain, photosensitivity, neuropsychiatric symptoms
Erythropoietic		
Congenital erythropoietic porphyria	Uroporphyrinogen III cosynthase	Photosensitivity, increased hemolysis
Protoporphyria	Ferrochelatase	Photosensitivity

Degradation of Heme to Bile Pigment or Bile Pigment Synthesis

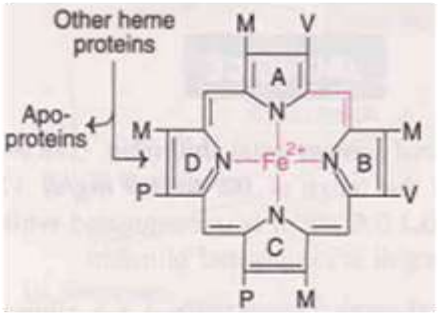
Erythrocytes have a life span of 120 days. At the end of this period, they are removed from the circulation. Erythrocytes are taken up and degraded by the macrophages of the reticuloendothelial (RE) system in the spleen and liver. The hemoglobin is cleaved to the protein part globin and non-protein heme.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

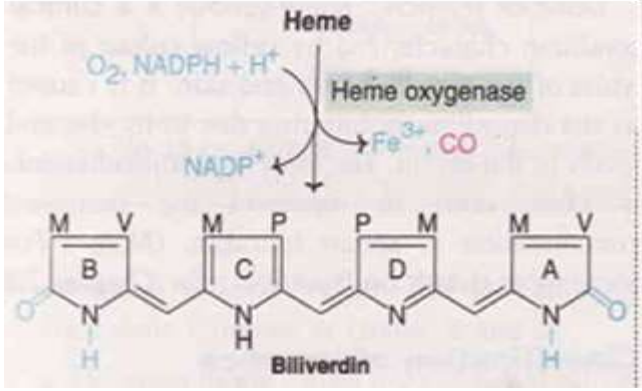
Fate of globin : The globin may be reutilized as such for the formation of hemoglobin or degraded to the individual amino acids. The latter undergo their own metabolism, including participation in fresh globin synthesis.

Sources of heme : It is estimated that about 80% of the heme that is subjected for degradation comes from the erythrocytes and the rest (20%) comes from immature RBC, myoglobin and cytochromes.



Heme oxygenase : A complex microsomal enzyme namely heme oxygenase utilizes NADPH and O_2 and cleaves the methenyl bridges between the two pyrrole rings (A and B) to form ***biliverdin***. Simultaneously, ferrous iron (Fe^{2+}) is oxidized to ferric form (Fe^{3+}) and released. The products of heme oxygenase reaction are biliverdin (a green pigment), Fe^{3+} and carbon monoxide (CO). Heme promotes the activity of this enzyme.

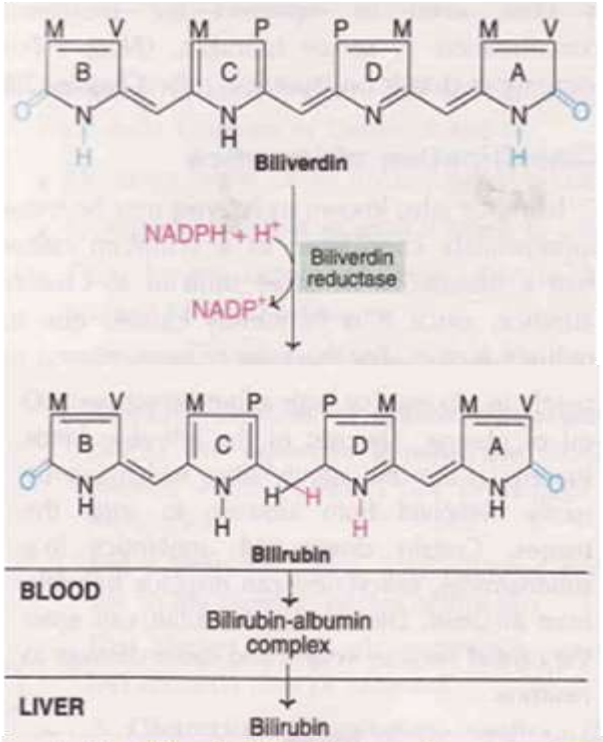




Biliverdin is excreted in birds and amphibia while in mammals it is further degraded.

Biliverdin reductase : Biliverdin's methenyl bridges (between the pyrrole rings C and D) are reduced to methylene group to form ***bilirubin*** (yellow pigment). This reaction is catalysed by an NADPH dependent soluble enzyme, biliverdin reductase (***Fig.10.22***). ***One gram of hemoglobin on degradation finally yields about 35 mg bilirubin.*** Approximately 250-350 mg of

Transport of bilirubin to liver : Bilirubin is lipophilic and therefore insoluble in aqueous solution. Bilirubin is transported in the plasma in a bound (non-covalently) form to albumin. Albumin has two binding sites for bilirubin—a high affinity site and a low affinity site. Approximately 25 mg of bilirubin can bind tightly to albumin (at high affinity sites) per 100 ml of plasma. The rest of the bilirubin binds loosely (at the low affinity sites) which can be easily detached from albumin to enter the tissues. Certain drugs and antibiotics (e.g sulfonamides, salicylates) can displace bilirubin from albumin. Due to this, bilirubin can enter the central nervous system and cause damage to neurons.



As the ***albumin-bilirubin complex*** enters the liver, bilirubin dissociates and is taken up by sinusoidal surface of the hepatocytes by a carrier mediated active transport. The transport system has a very high capacity and therefore is not a limitation for further metabolism of bilirubin. Inside the hepatocytes, bilirubin binds to a specific intracellular protein namely ***ligandin***.

Conjugation of bilirubin

In the liver, bilirubin is conjugated with two molecules of glucuronate supplied by UDP-glucuronate. This reaction, catalysed by ***bilirubin glucuronyltransferase*** (of smooth endoplasmic reticulum) results in the formation of a water soluble bilirubin diglucuronide (***Figs.10.22 and 10.23***). When bilirubin is in excess, bilirubin monoglucuronides also accumulate in the body. The enzyme bilirubin glucuronyltransferase can be induced by a number of drugs (e.g. phenobarbital),

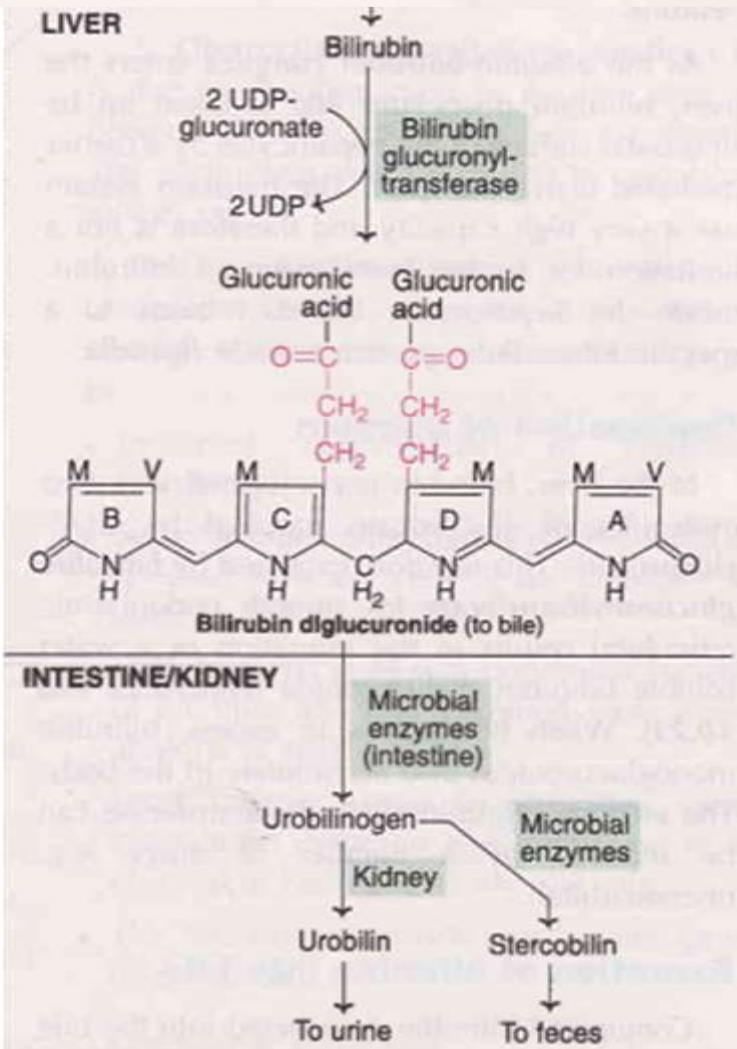
Excretion of bilirubin into bile

Conjugated bilirubin is excreted into the bile canaliculi against a concentration gradient which then enters the bile. The transport of ***bilirubin diglucuronide*** is an active, energy-dependent and rate limiting process. This step is easily susceptible to any impairment in liver function. Normally, there is a good coordination between the bilirubin conjugation and its excretion into bile. Thus almost all the bilirubin (> 98%) that enters bile is in the conjugated form.

Fate of bilirubin

Bilirubin glucuronides are hydrolysed in the intestine by specific bacterial enzymes namely ***β-glucuronidases*** to liberate bilirubin. The latter is then converted to urobilinogen (colourless compound), a small part of which may be reabsorbed into the circulation. Urobilinogen can be converted to urobilin (an yellow colour compound) in the kidney and excreted. The characteristic ***colour of urine is due to urobilin***.

A major part of urobilinogen is converted by bacteria to stercobilin which is excreted along with feces. The characteristic ***brown colour of feces is due to stercobilin.***



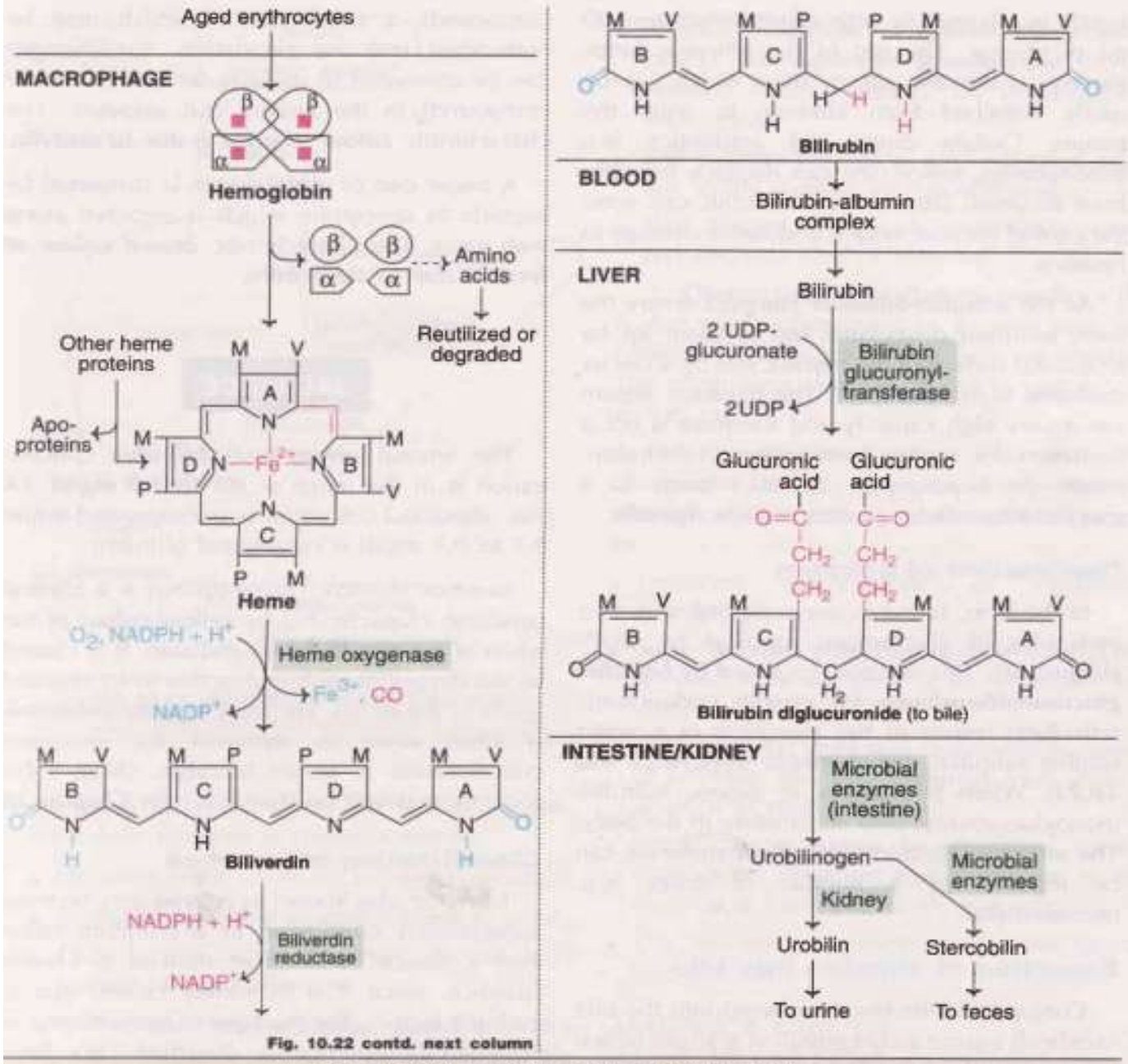
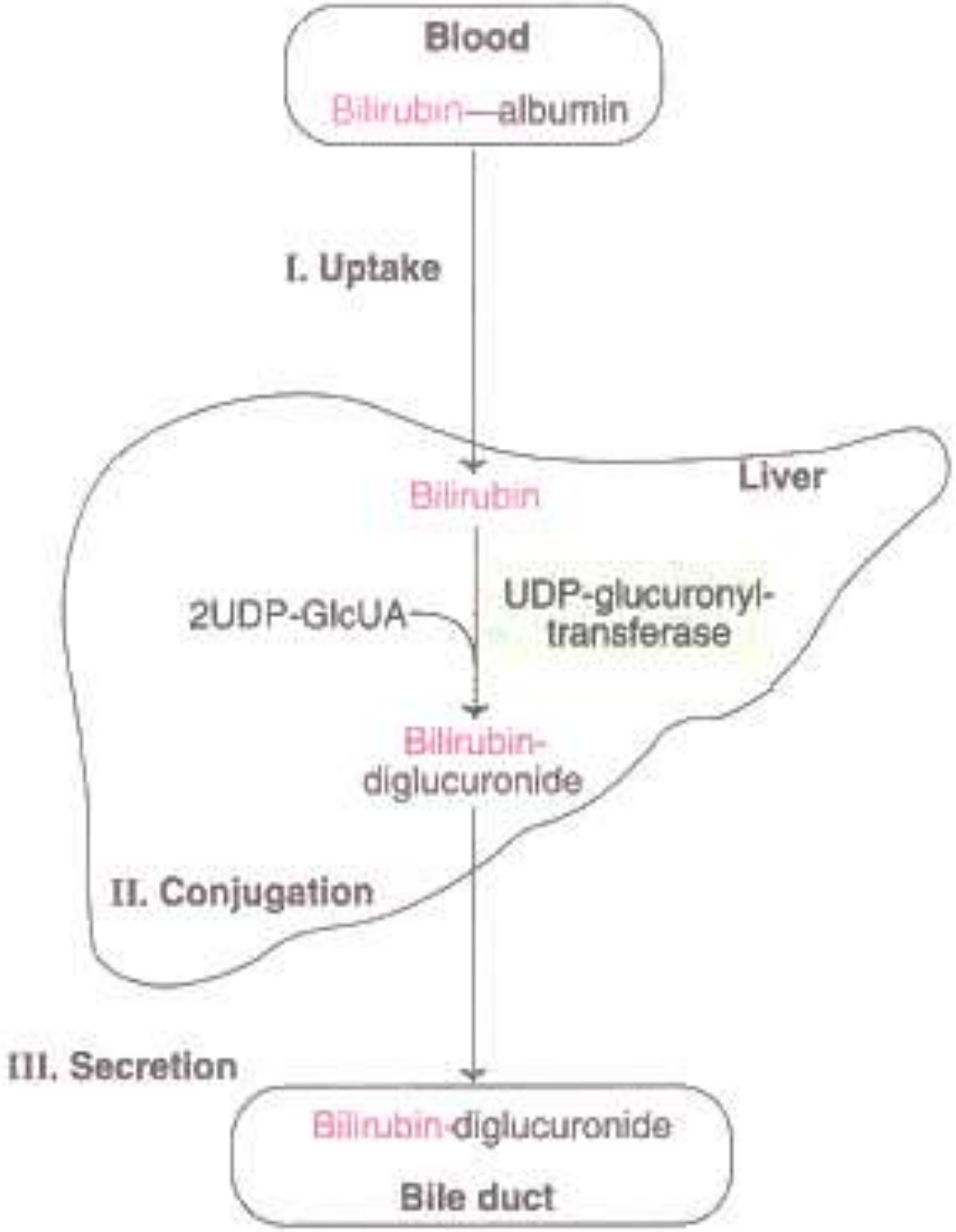
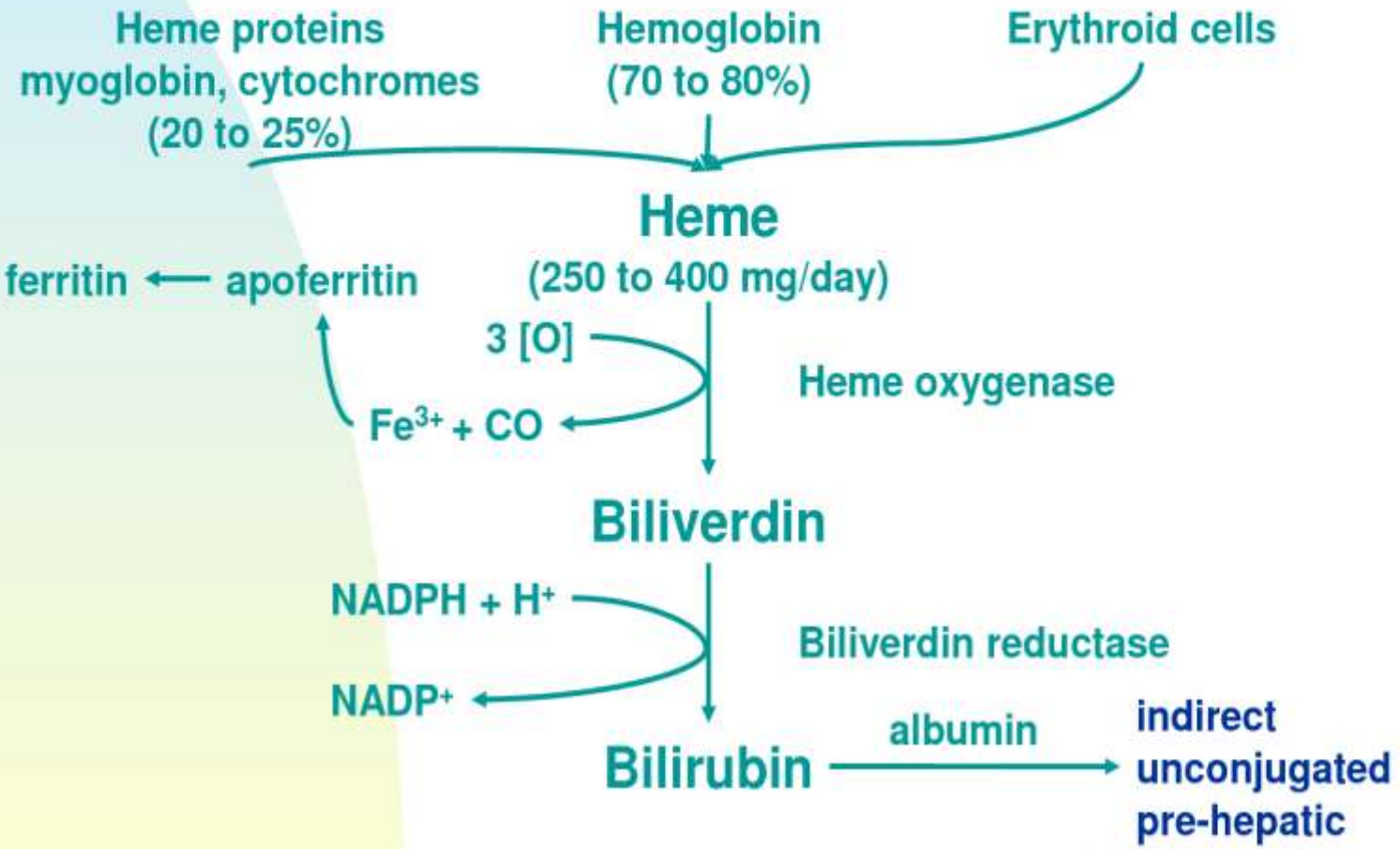


Fig. 10.22 contd. next column

***Fig. 10.22** : Degradation of heme to bile pigments*
***(Note** : Colours used in structures represent change in the specific reaction only).*


Blood
Bilirubin—albumin
I. Uptake
Liver
Bilirubin
2UDP-GlcUA
UDP-glucuronyl-transferase
Bilirubin-diglucuronide
II. Conjugation
III. Secretion
Bilirubin-diglucuronide
Bile duct

Bilirubin Production



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3. David L. Nelson; Michael M. Cox “Lehninger Principles of Biochemistry” Seventh Edition, Macmillan 2017, ISBN:9781464187957

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