METABOLISM OF PORPHYRINS & APPLIED ASPECTS

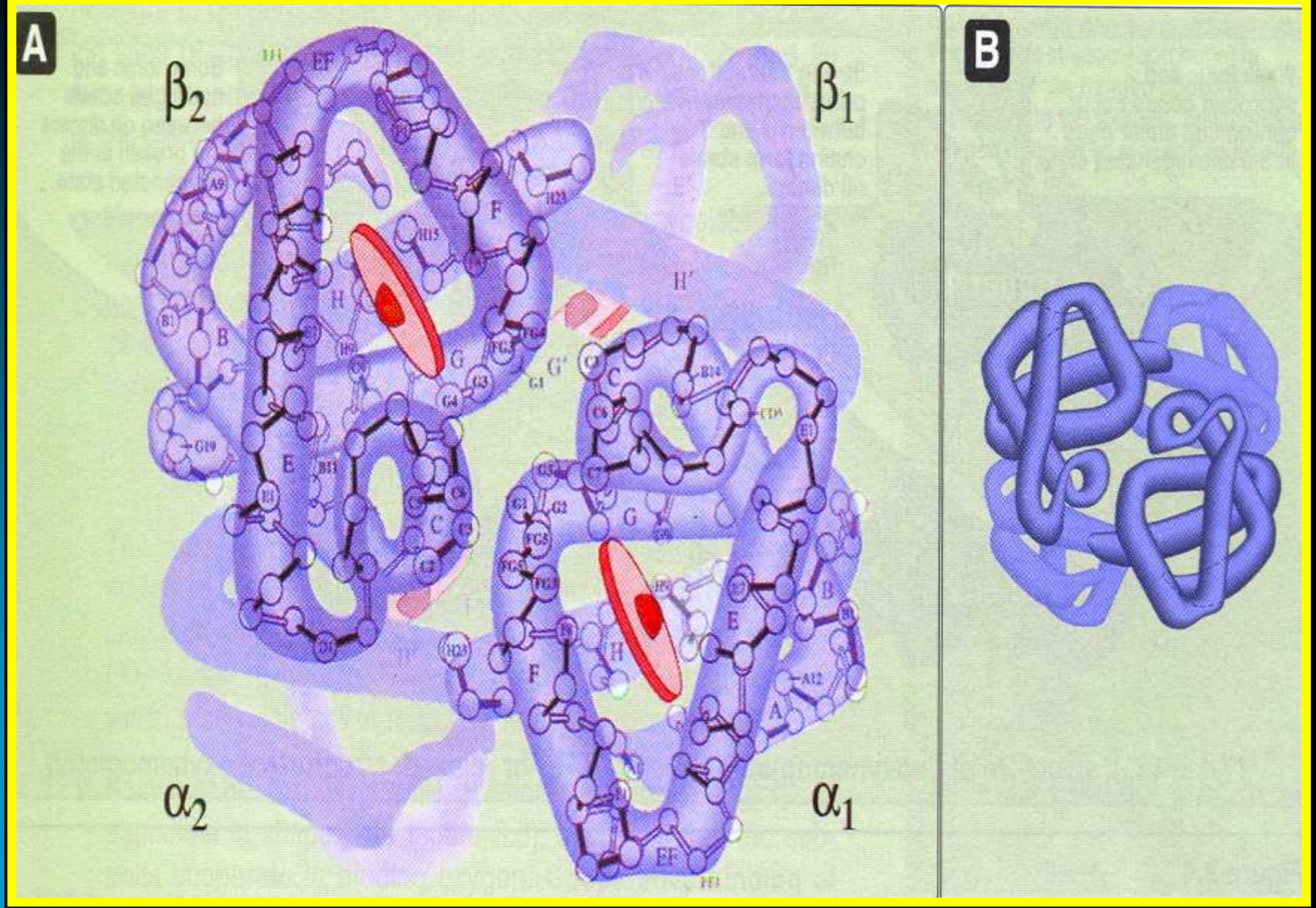
Geeta Bhatia

Lecture Outlines

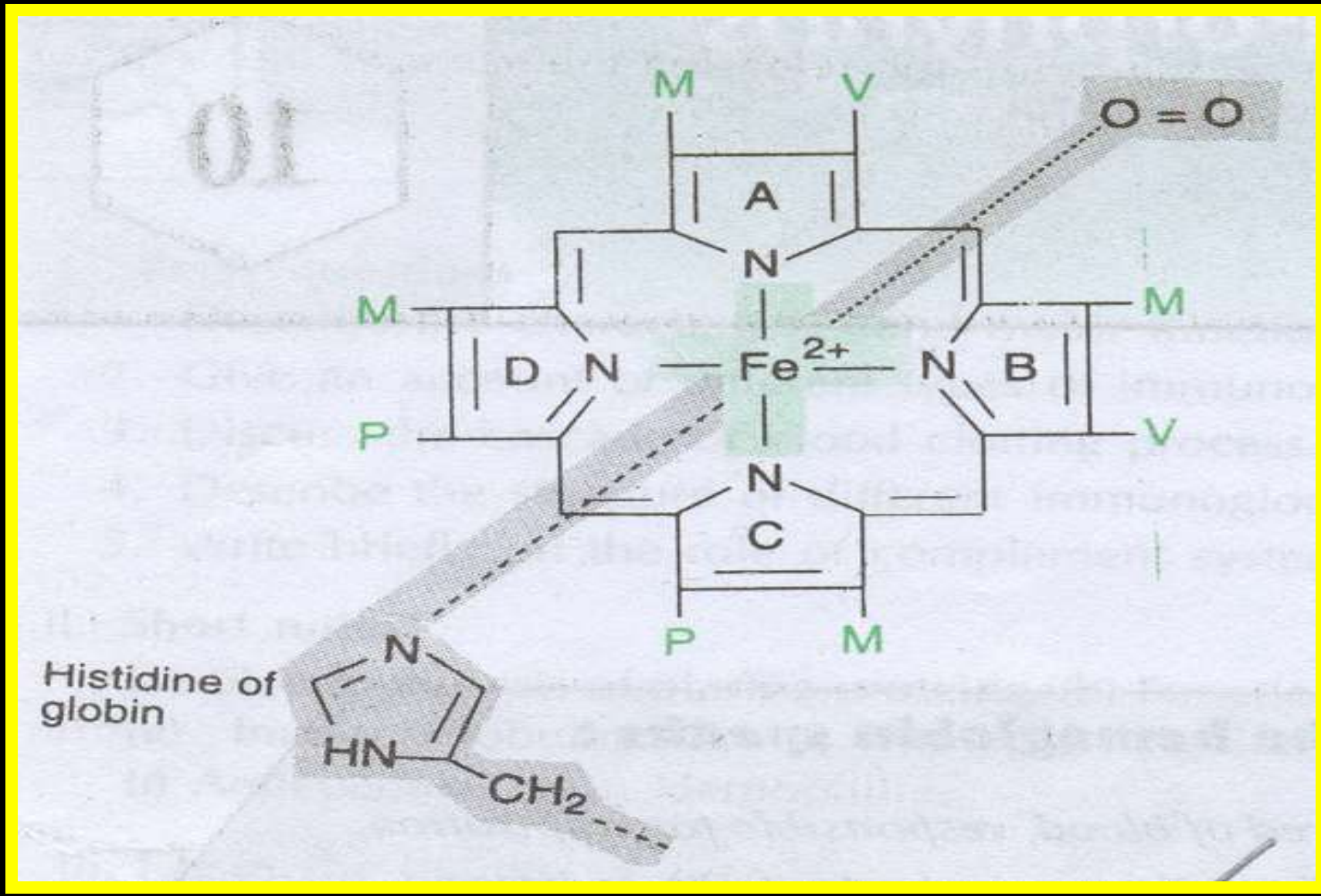
- Introduction.
- Structure of Heme.
  - Porphyrins
- Synthesis of Heme.
  - Regulation of Heme synthesis.
  - Porphyrias.
- Degradation of Heme.
  - Jaundice
    - Hemolytic
    - Hepatocellular
    - Obstructive
    - Neonatal or Physiological
  - Jaundice due to genetic defects

Introduction

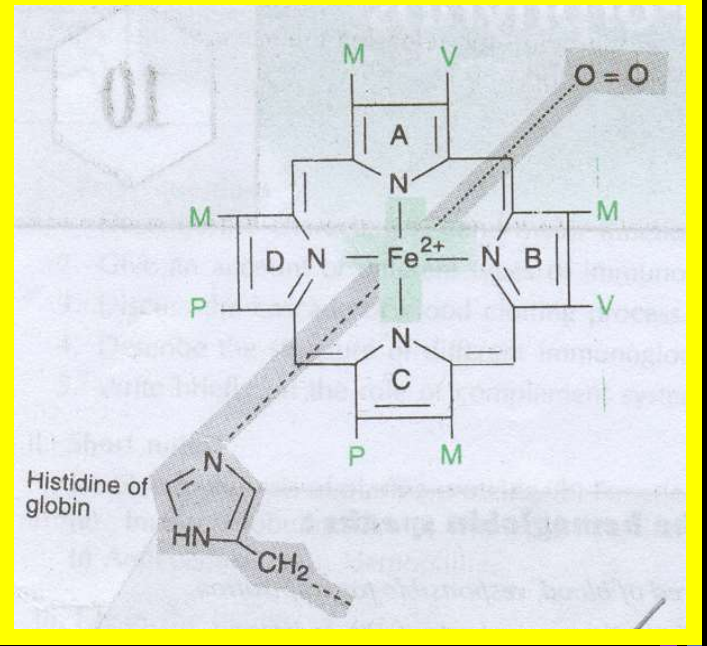
- Heme is the prosthetic group (non protein part) of several proteins and enzymes like;
  - Hemoglobin.
  - Myoglobin.
  - Cytochromes
  - Catalase
  - Peroxidase
- Heme consists of a porphyrin ring coordinated with iron
- Hemoglobin (MW – 64,450) is a tetrameric protein containing:
  - Globin – the protein part.
  - Heme – the non-protein part.


A
β_2
β_1
α_2
α_1
B

Structure of Heme



Structure of Heme



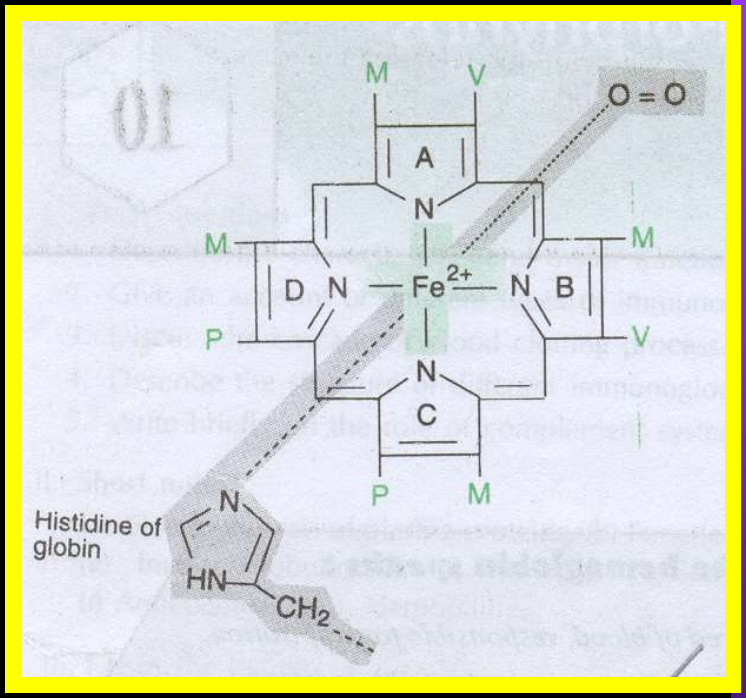
- Heme contains a porphyrin molecule namely protoporphyrin IX, with iron at its center.

- Protoporphyrin IX consists of four pyrrole rings to which four methyl, two propionyl and two vinyl groups are attached as side chains.

- The iron atom is in ferrous (Fe^{2+}) state in the heme of functional hemoglobin. It forms six coordinated bonds.

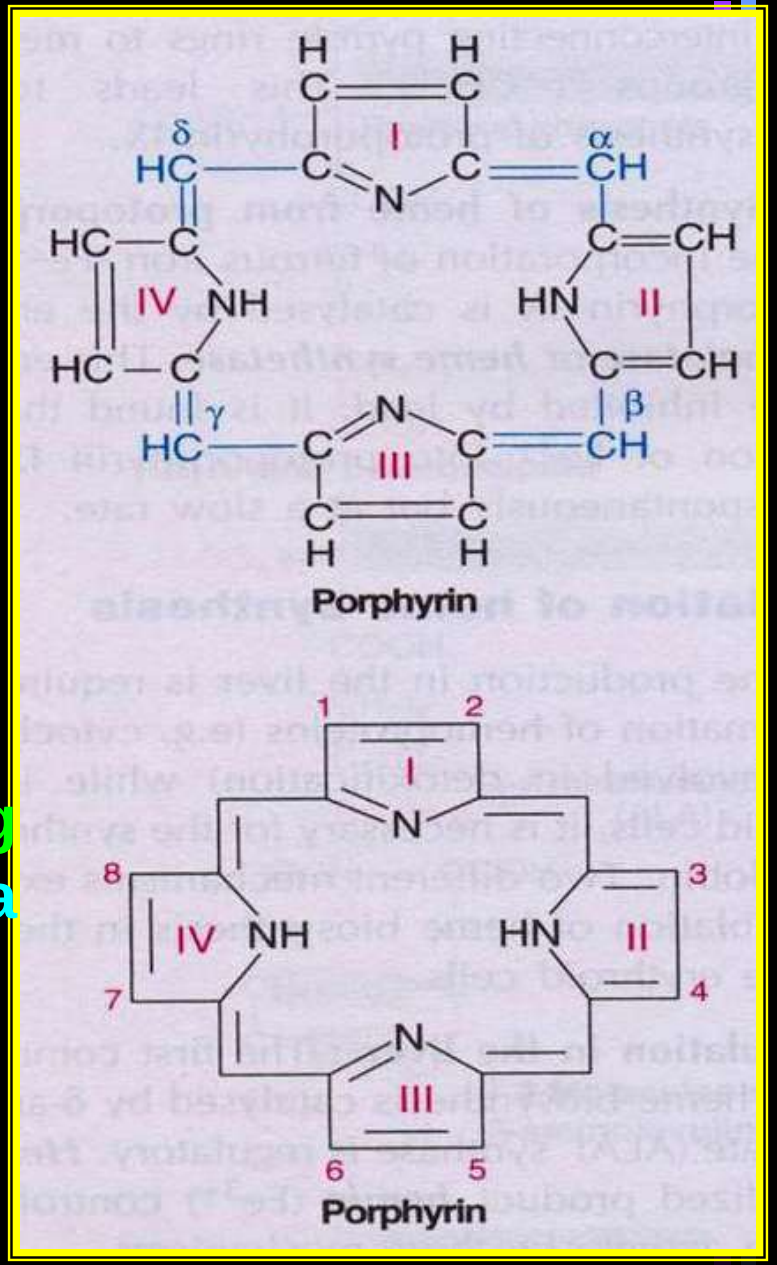
- Iron is held at the centre of the heme by the four nitrogens of porphyrin ring.

- Two bonds are formed on either side of the plannar porphyrin ring.
  - On one side, iron binds with the amino acid histidine of the globin.
  - On the other side, the Fe^{2+} is coordinated to bind to oxygen.

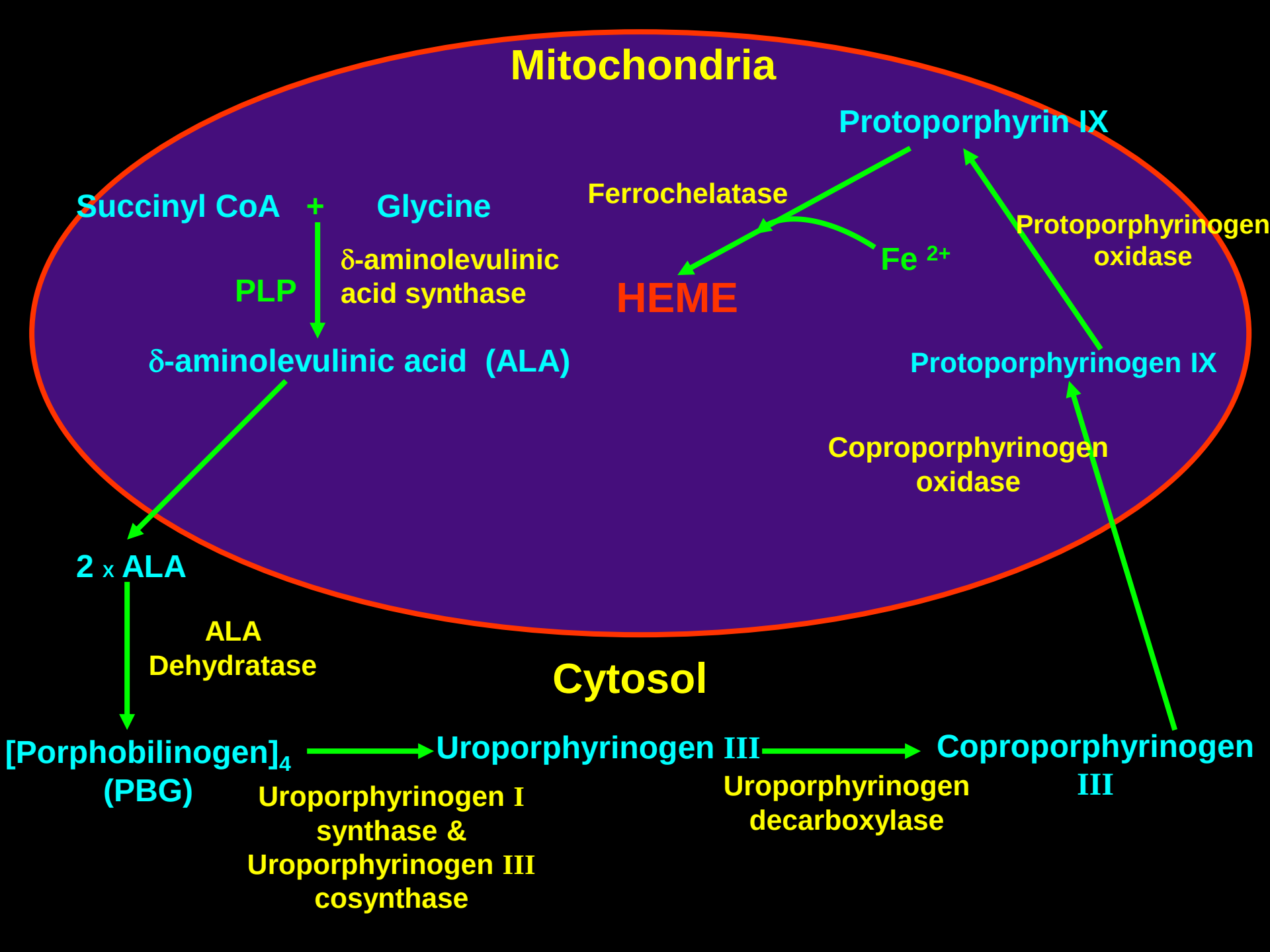


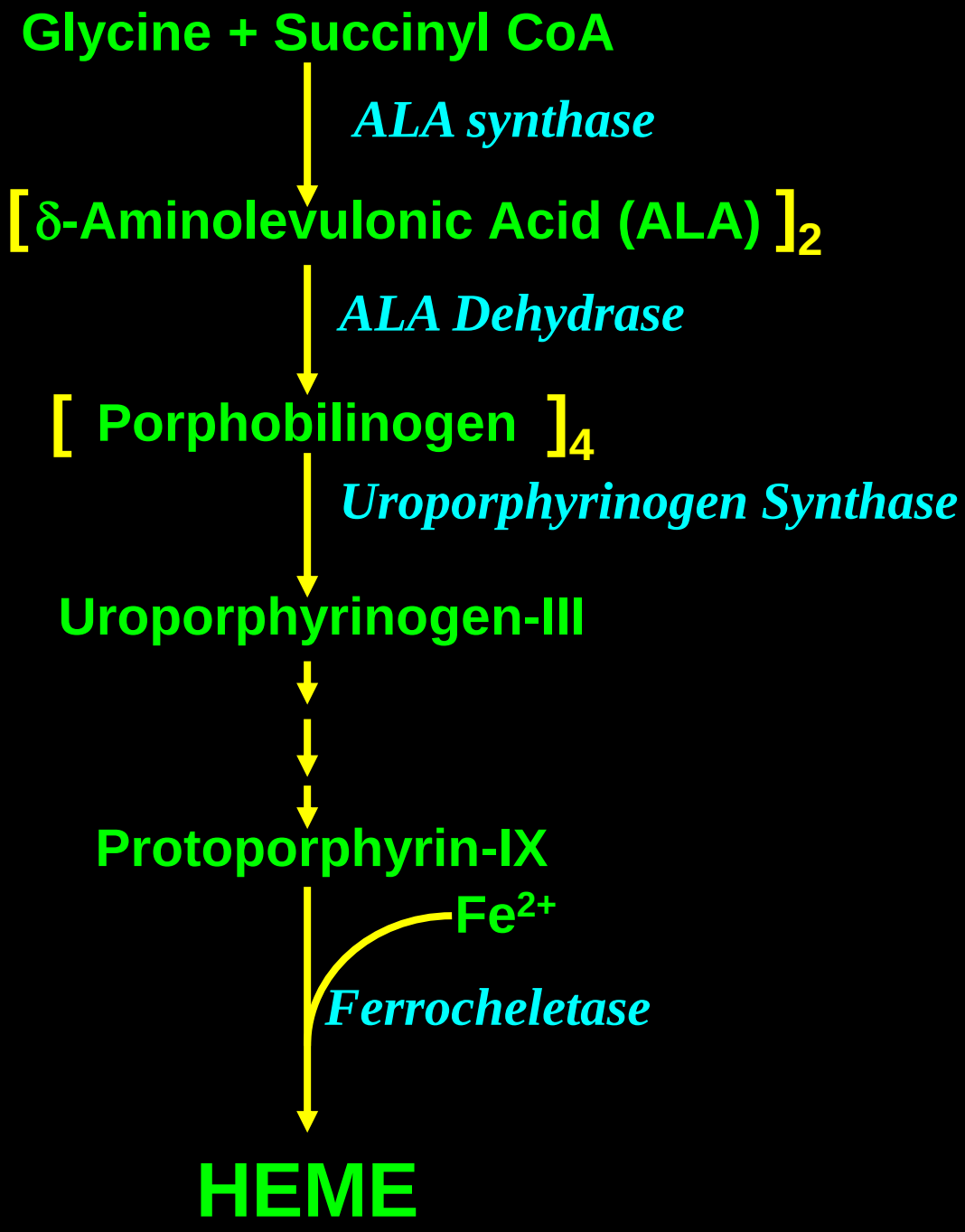
PORPHYRINS

- Porphyrins are cyclic compounds composed of 4 pyrrole rings held together by methenyl (=CH-) bridges.
- Metal ions can bind with nitrogen atoms of pyrrole rings to form complexes.
- Heme is an iron-containing porphyrin while chlorophyll is a magnesium-containing porphyrin.
- Heme and chlorophyll are metalloporphyrins.



BIOSYNTHESIS OF HEME


Mitochondria
Protoporphyrin IX
Succinyl CoA + Glycine
Ferrochelatase
Protoporphyrinogen oxidase
PLP
δ-aminolevulinic acid synthase
Fe 2+
HEME
δ-aminolevulinic acid (ALA)
Protoporphyrinogen IX
Coproporphyrinogen oxidase
2 x ALA
ALA Dehydratase
Cytosol
[Porphobilinogen]4 (PBG)
Uroporphyrinogen III
Coproporphyrinogen III
Uroporphyrinogen I synthase & Uroporphyrinogen III cosynthase
Uroporphyrinogen decarboxylase


Glycine + Succinyl CoA
ALA synthase
[δ-Aminolevulonic Acid (ALA)]2
ALA Dehydrase
[Porphobilinogen]4
Uroporphyrinogen Synthase
Uroporphyrinogen-III
Protoporphyrin-IX
Fe2+
Ferrocheletase
HEME

BIOSYNTHESIS OF HEME

- 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).

- In the liver, the rate of heme synthesis is highly variable, whereas in erythroid cells it is relatively constant, and is matched to the rate of globin synthesis.

- The initial reaction and the last three steps in the formation of porphyrins occur in mitochondria, whereas the intermediate steps of the biosynthetic pathway occur in the cytosol.

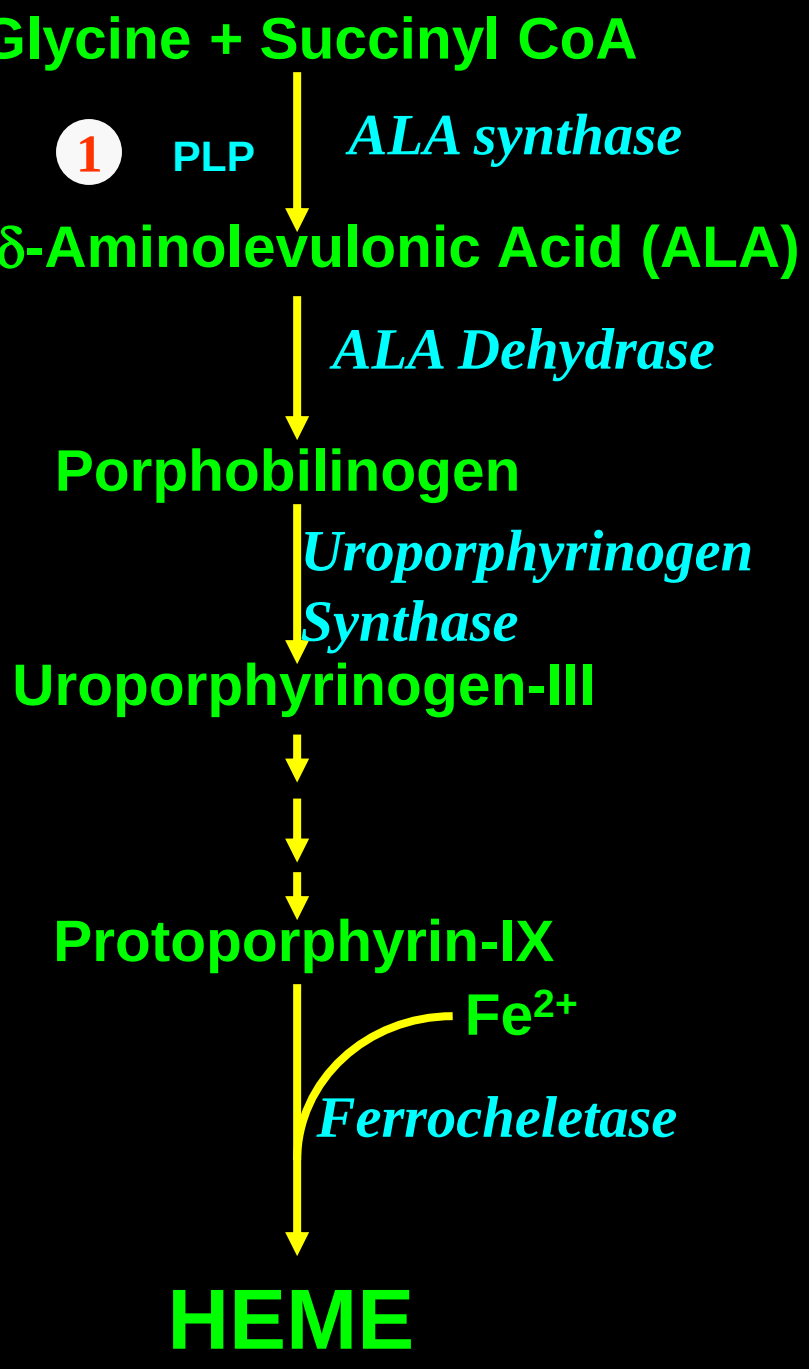
- Mature red blood cells lack mitochondria and are unable to synthesize heme.

1. **Formation of δ-aminolevulinic Acid:** Glycine combines with succinyl CoA to form δ-aminolevulinic Acid (ALA)

Catalyzed by a pyridoxal phosphate (PLP) dependent *δ-aminolevulinate synthase (ALA synthase)* occcuring in the mitochondria.

It is a rate-controlling step in porphyrin synthesis.

Heme decreases the activity of hepatic *ALA synthase* by causing decreased synthesis of the enzyme.

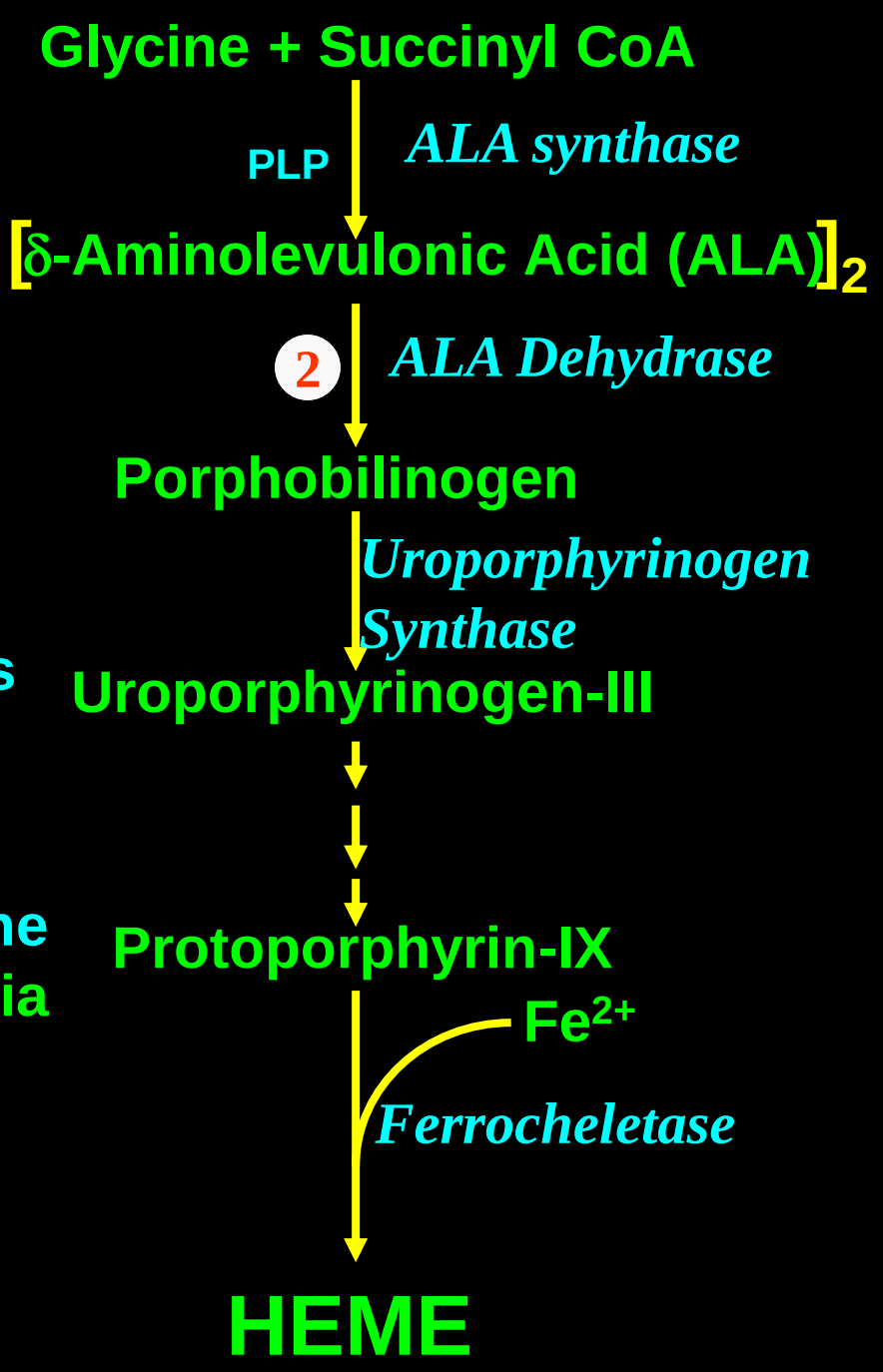


2. Formation of porphobilinogen:

Condensation of two molecules of ALA to form porphobilinogen by *δ-aminolevulinic acid dehydrase.*

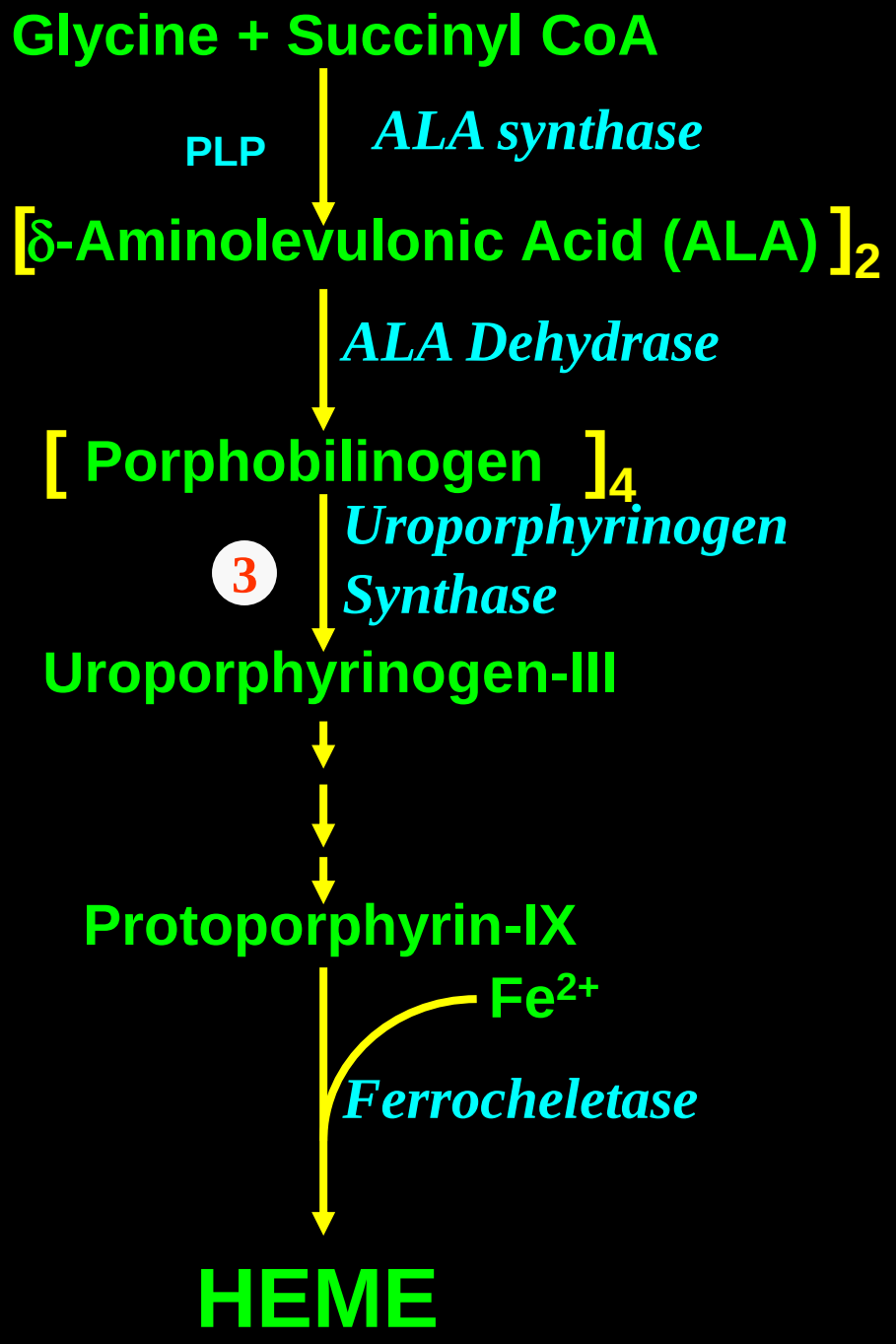
It is inhibited by heavy metal ions like lead.

This inhibition is responsible for the elevation in ALA and the anemia seen in lead poisoning.



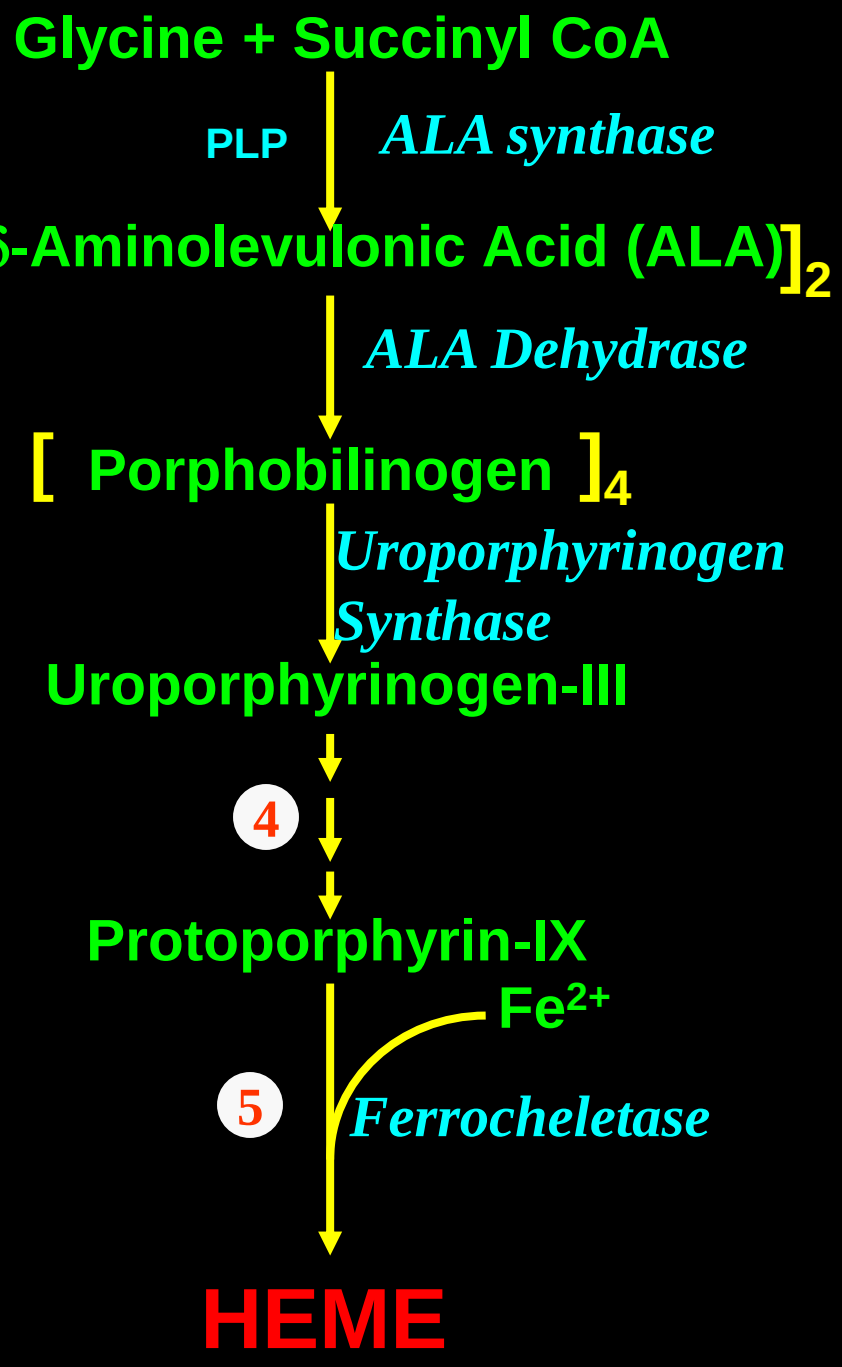
3. Formation of porphyrin ring: Porphyrin synthesis occurs by condensation of four molecules of porphobilinogen. The four pyrrole rings in porphyrin are interconnected by methenyl bridges derived from carbon of glycine.

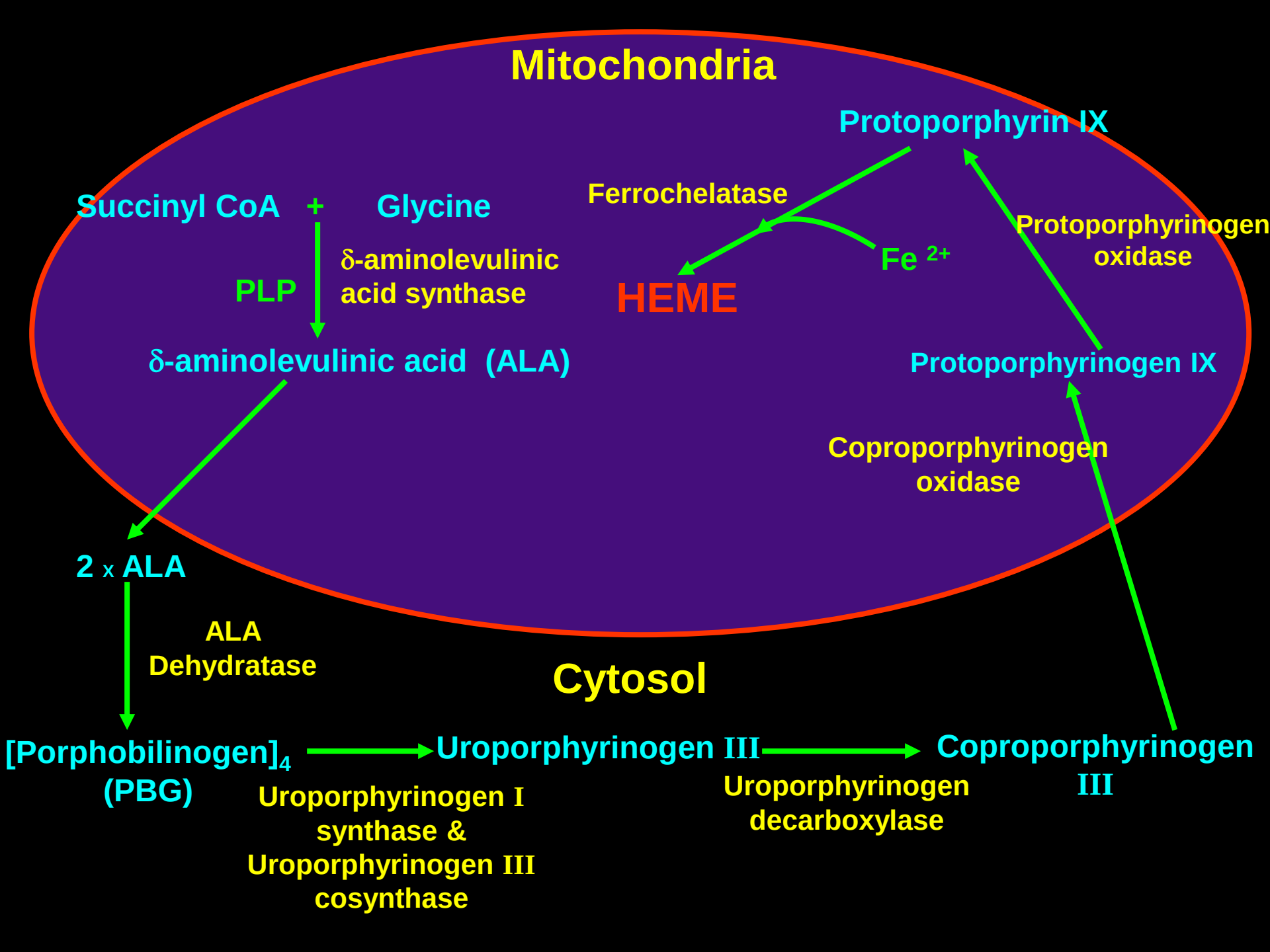
Uroporphyrinogen Synthase causes the condensation of four molecules of porphobilinogen followed by ring closure to produce uroporphyrinogen III.



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

5. Synthesis of heme from protoporphyrin IX: The incorporation of ferrous iron (Fe^{2+}) into protoporphyrin IX is catalysed by the enzyme *ferrochelatase.* This enzyme is inhibited by lead.

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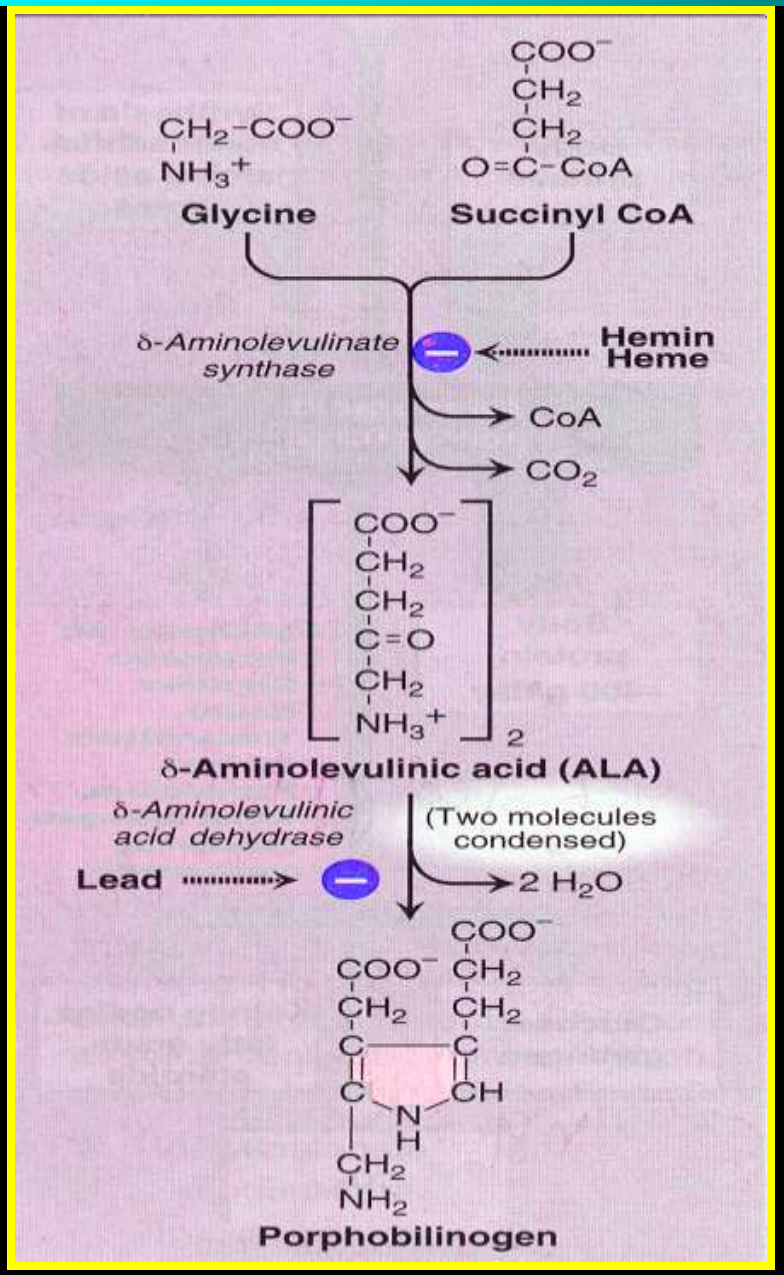
Uroporphyrinogen decarboxylase

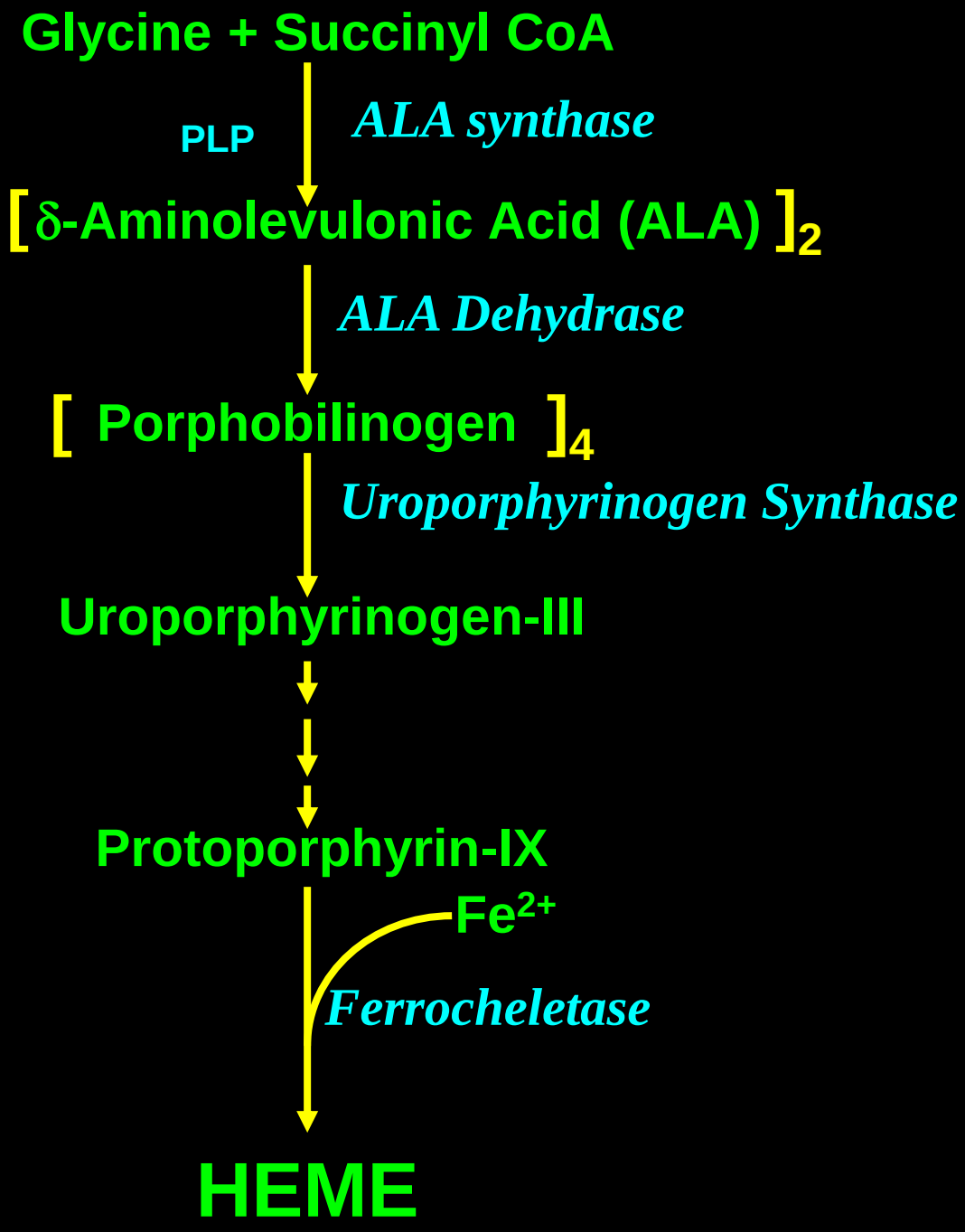
Regulation of Heme Synthesis

Regulation of Heme Synthesis

- ALA synthase is regulated by repression (feed back inhibition) mechanism. Heme inhibits the synthesis of ALA synthase.
- ALA synthase is inhibited by hematin formed by the oxidation of excess heme.
- Drugs like phenobarbital induce heme synthesis by activating ALA synthase.
- The steps catalysed by ferrochelatase and ALA Dehydrase are inhibited by lead.
- Isoniazid (Antituberculous drug) by decreasing the availability of pyridoxal phosphate inhibit heme synthesis.


Glycine
Succinyl CoA
δ-Aminolevulinate synthase
Hemin
Heme
CoA
CO_2
2
δ-Aminolevulinic acid (ALA)
δ-Aminolevulinic acid dehydrase
Lead
(Two molecules condensed)
2 H_2O
Porphobilinogen

PORPHYRIAS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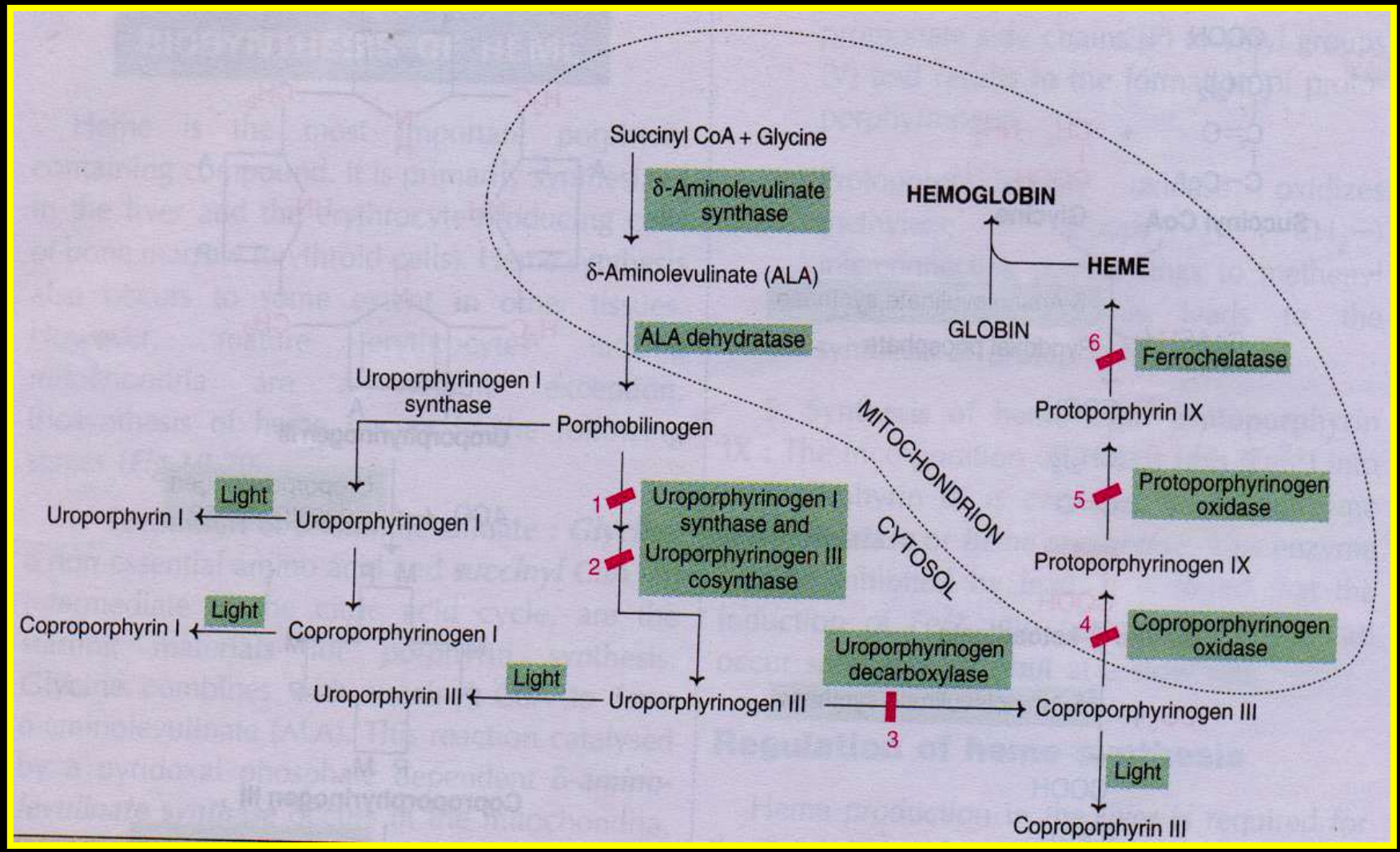
Fe2+
Ferrocheletase
HEME


Succinyl CoA + Glycine
δ-Aminolevulinate synthase
δ-Aminolevulinate (ALA)
ALA dehydratase
Porphobilinogen
Uroporphyrinogen I synthase
Uroporphyrinogen I
Light
Uroporphyrin I
Coproporphyrinogen I
Light
Coproporphyrin I
1
2
Uroporphyrinogen I synthase and Uroporphyrinogen III cosynthase
Uroporphyrinogen III
Light
Uroporphyrin III
Uroporphyrinogen decarboxylase
3
Coproporphyrinogen III
Light
Coproporphyrin III
4
Coproporphyrinogen oxidase
Protoporphyrinogen IX
5
Protoporphyrinogen oxidase
Protoporphyrin IX
6
Ferrochelatase
HEME
HEMOGLOBIN
GLOBIN
MITOCHONDRION
CYTOSOL

PORPHYRIAS

- Porphyrias are a group of inherited or acquired disorders of certain enzymes in the heme biosynthetic pathway.

- Based on the site of the overproduction and accumulation of the porphyrins (or their precursors), Inherited porphyrias are broadly classified as:

  - Hepatic (acute) porphyrias
  - Cutaneous (Erythropoietic) porphyrias,

- They manifest with either neurological complications or with skin problems (or occasionally both).

Porphyrias result in the accumulation and increased excretion of porphyrin precursors (ALA and Porphobilinogen) or porphyrins .

Hepatic (Acute) Porphyria

- The acute, or hepatic, porphyrias primarily affect the nervous system, resulting in abdominal pain (most common presentation), vomiting, acute neuropathy, seziures and mental disturbances.

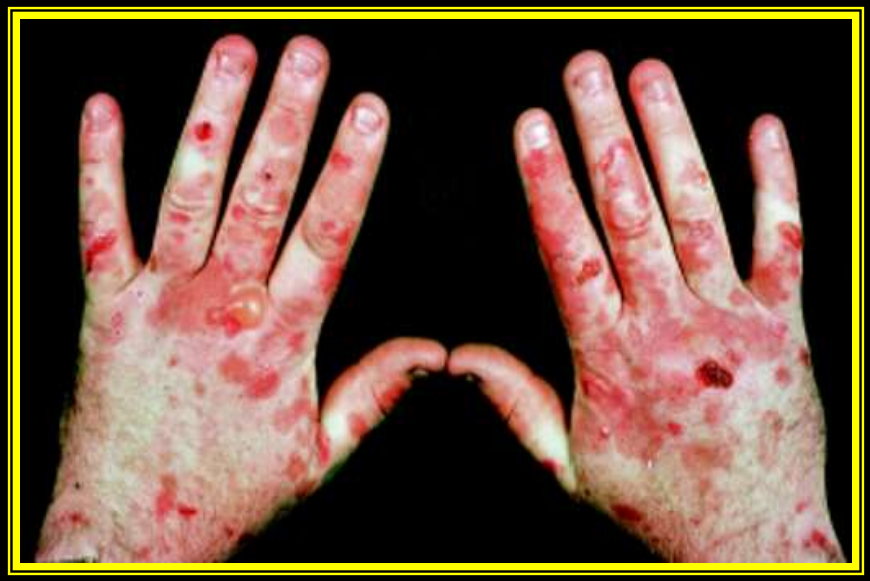
- Cardiac arrythmias and tachycardia (fast heart rate) may develop as the autonomic nervous system is affected.

- The Abdominal Pain can be severe and can, in some cases, be both acute and chronic in nature

Accumulation of the precursors (porphobilinogen and ALA) correlates with the acute attack of the hepatic porphyrias.

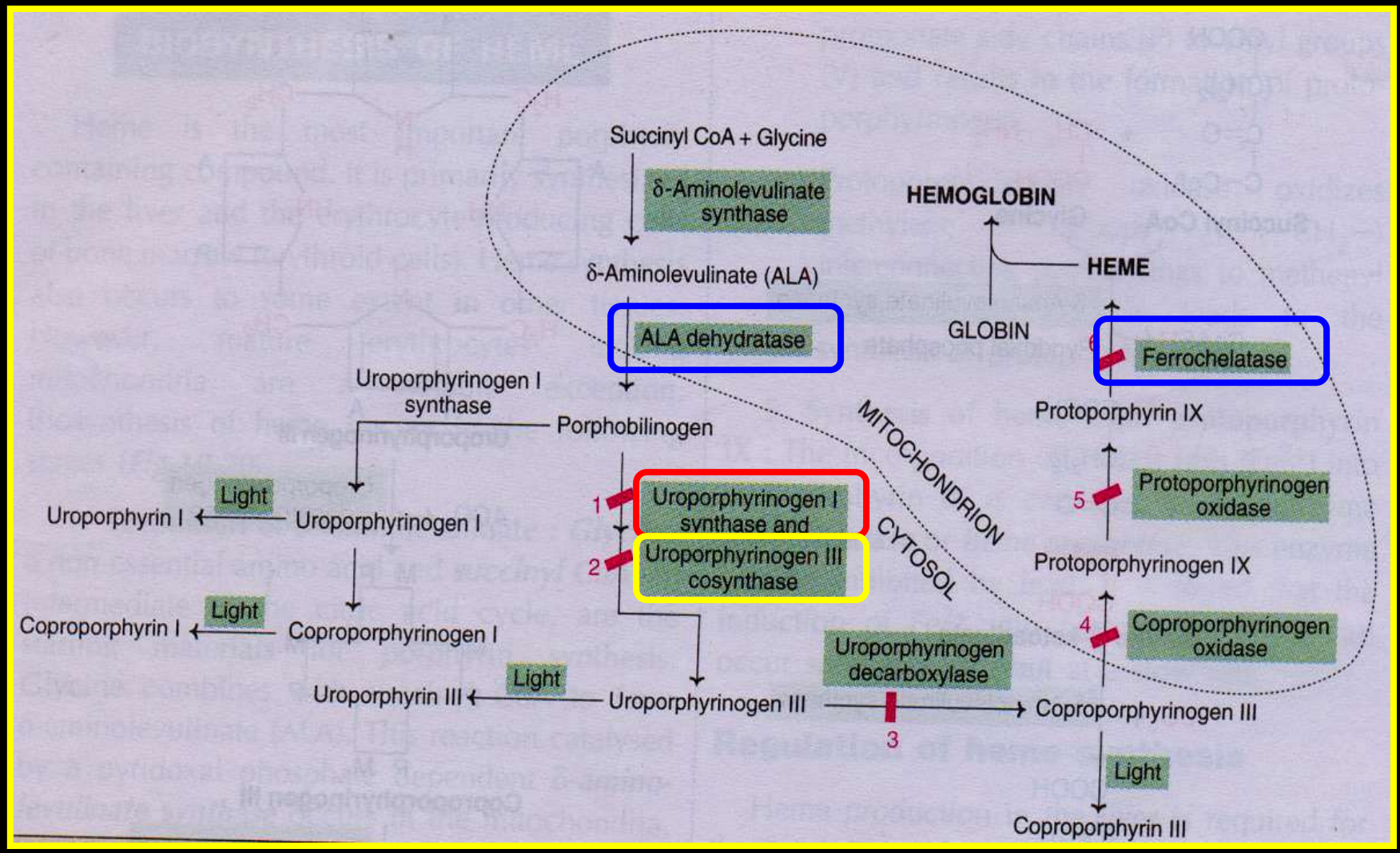
Cutaneous (Erythropoetic) Porphyria

- The cutaneous, or erythropoetic, porphyrias primarily affect the skin, causing photosensitivity (Photodermatits), blisters, necrosis of the skin and gums, itching, and swelling.



Accumulation of porphyrins (photoactive) correlates with skin disease

PORPHYRIAS


Succinyl CoA + Glycine
δ-Aminolevulinate synthase
δ-Aminolevulinate (ALA)
ALA dehydratase
Porphobilinogen
Uroporphyrinogen I synthase
Uroporphyrinogen I
Light
Uroporphyrin I
Coproporphyrinogen I
Light
Coproporphyrin I
1
Uroporphyrinogen I synthase and
2
Uroporphyrinogen III cosynthase
Uroporphyrinogen III
Light
Uroporphyrin III
MITOCHONDRION
CYTOSOL
Uroporphyrinogen decarboxylase
3
Coproporphyrinogen III
Light
Coproporphyrin III
4
Coproporphyrinogen oxidase
Protoporphyrinogen IX
5
Protoporphyrinogen oxidase
Protoporphyrin IX
6
Ferrochelatase
HEME
HEMOGLOBIN
GLOBIN

Acute intermittent porphyria

Deficiency of the enzyme *uroporphyrinogen I synthase.*
Acute intermittent porphyria is characterized by increased excretion of porphyrin precursors like porphobilinogen and δ-aminolevulinate (ALA).

- **Abdominal pain, vomiting, cardiovascular abnormalities, neuropsychiatric disturbances.**

- **The urine gets darkened on exposure to air.**

- **It is usually expressed after puberty.**

- The symptoms are more severe after administration of drugs (e.g. Phenobarbital). This is due to the increased activity of ALA synthase causing accumulation of porphobilinogen and ALA.

- These patients are NOT photosensitive.

- Acute intermittent porphyria is treated by administration of hemin which inhibits the enzyme ALA synthase and the accumulation of ALA and porphobilinogen.

Congenital Erythropoietic Porphyria

This disorder is due to a defect in the enzyme uroporphyrinogen III cosynthase.

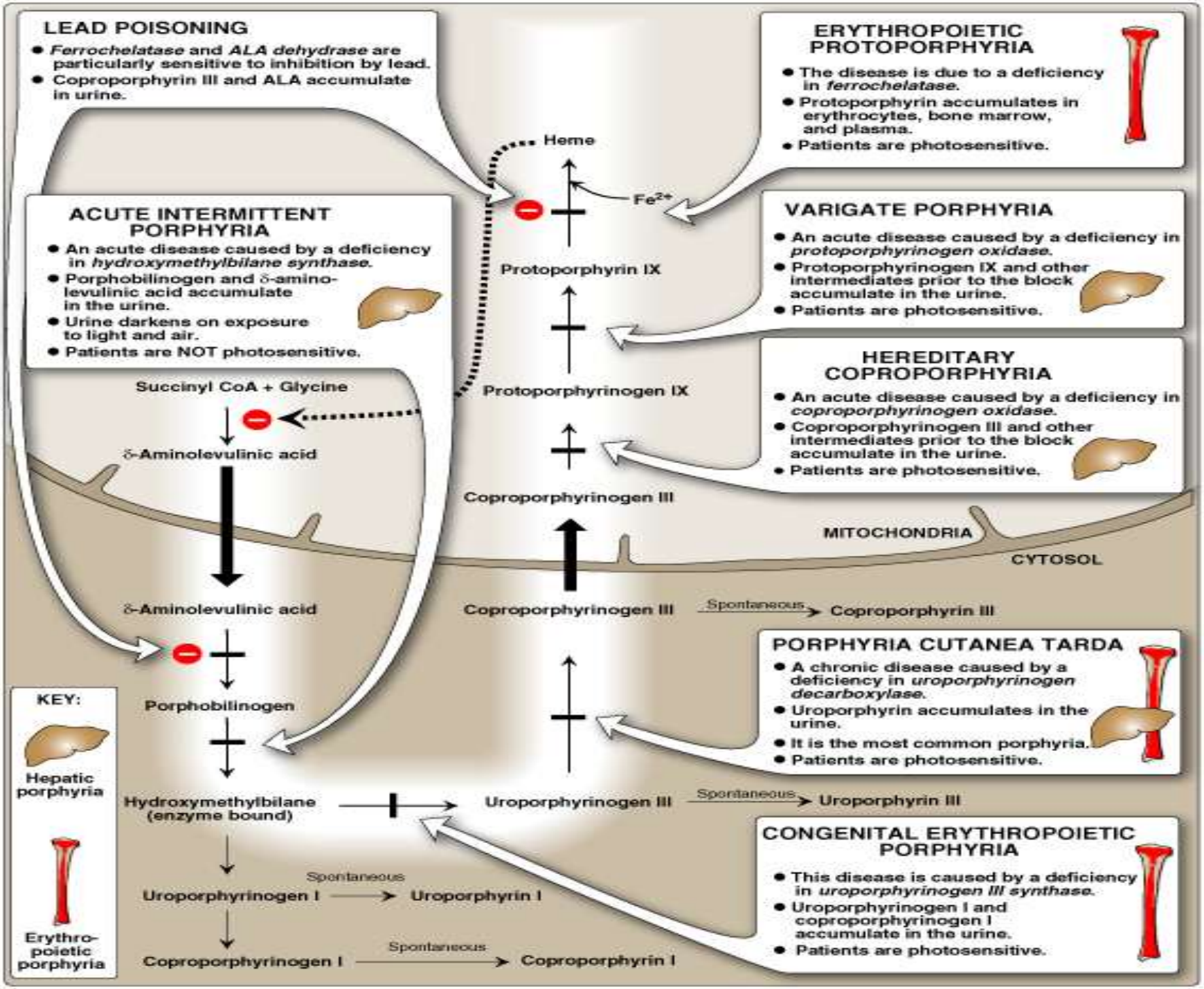
- Congenital disorder mostly confined to erythropoietic tissues.
- The individuals excrete uroporphyrinogen I and coproporphyrinogen I which oxidize respectively to uroporphyrin I and coproporphyrin I (red pigments). Urine dark red in colour.
- The patients are photosensitive (itching and burning of skin when exposed to visible light) due to the abnormal prophyrins that accumulate.
- Red blood cells have a shortened life-span, and anemia often results.

Acquired (toxic) porphyrias

Porphyria can result from lead poisoning. The toxic effect of lead is due to inhibition of ferrochelatase and ALA dehydrase.

There is decreased levels of heme with consequent increased activity of ALA Synthase.

- Headache, nausea and memory loss.
- Abdominal pain, diarrhoea.
- Lead lines in gums.
- Neuropathy (Claw hand, wrist drop).
- Increased urinary ALA.
- Anemia.


LEAD POISONING
Ferrochelatase and ALA dehydrase are particularly sensitive to inhibition by lead.
Coproporphyrin III and ALA accumulate in urine.
ERYTHROPOIETIC PROTOPORPHYRIA
The disease is due to a deficiency in ferrochelatase.
Protoporphyrin accumulates in erythrocytes, bone marrow, and plasma.
Patients are photosensitive.
Heme
Fe2+
ACUTE INTERMITTENT PORPHYRIA
An acute disease caused by a deficiency in hydroxymethylbilane synthase.
Porphobilinogen and δ-amino-levulinic acid accumulate in the urine.
Urine darkens on exposure to light and air.
Patients are NOT photosensitive.
Protoporphyrin IX
VARIGATE PORPHYRIA
An acute disease caused by a deficiency in protoporphyrinogen oxidase.
Protoporphyrinogen IX and other intermediates prior to the block accumulate in the urine.
Patients are photosensitive.
Succinyl CoA + Glycine
Protoporphyrinogen IX
HEREDITARY COPROPORPHYRIA
An acute disease caused by a deficiency in coproporphyrinogen oxidase.
Coproporphyrinogen III and other intermediates prior to the block accumulate in the urine.
Patients are photosensitive.
δ-Aminolevulinic acid
Coproporphyrinogen III
MITOCHONDRIA
CYTOSOL
δ-Aminolevulinic acid
Coproporphyrinogen III
Spontaneous
Coproporphyrin III
PORPHYRIA CUTANEA TARDA
A chronic disease caused by a deficiency in uroporphyrinogen decarboxylase.
Uroporphyrin accumulates in the urine.
It is the most common porphyria.
Patients are photosensitive.
KEY:
Hepatic porphyria
Erythro-poietic porphyria
Porphobilinogen
Hydroxymethylbilane (enzyme bound)
Uroporphyrinogen III
Spontaneous
Uroporphyrin III
CONGENITAL ERYTHROPOIETIC PORPHYRIA
This disease is caused by a deficiency in uroporphyrinogen III synthase.
Uroporphyrinogen I and coproporphyrinogen I accumulate in the urine.
Patients are photosensitive.
Spontaneous
Uroporphyrinogen I
Uroporphyrin I
Spontaneous
Coproporphyrinogen I
Coproporphyrin I

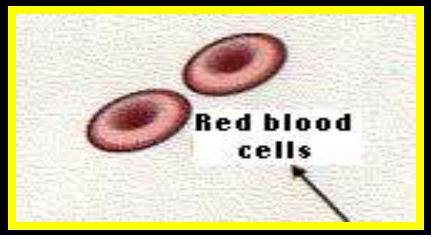
DEGRADATION OF HEME

Degradation of Heme

- After approximately 120 days in the circulation, red blood cells are taken up and degraded by the reticuloendothelial (RE) system, particularly in the liver and spleen.

- About 85% of the heme that is subjected for degradation comes from the erythrocytes and the rest (15%) comes from immature RBC, myoglobin and cytochromes.

(Liver, & Spleen)



Phagocytosis & Lysis

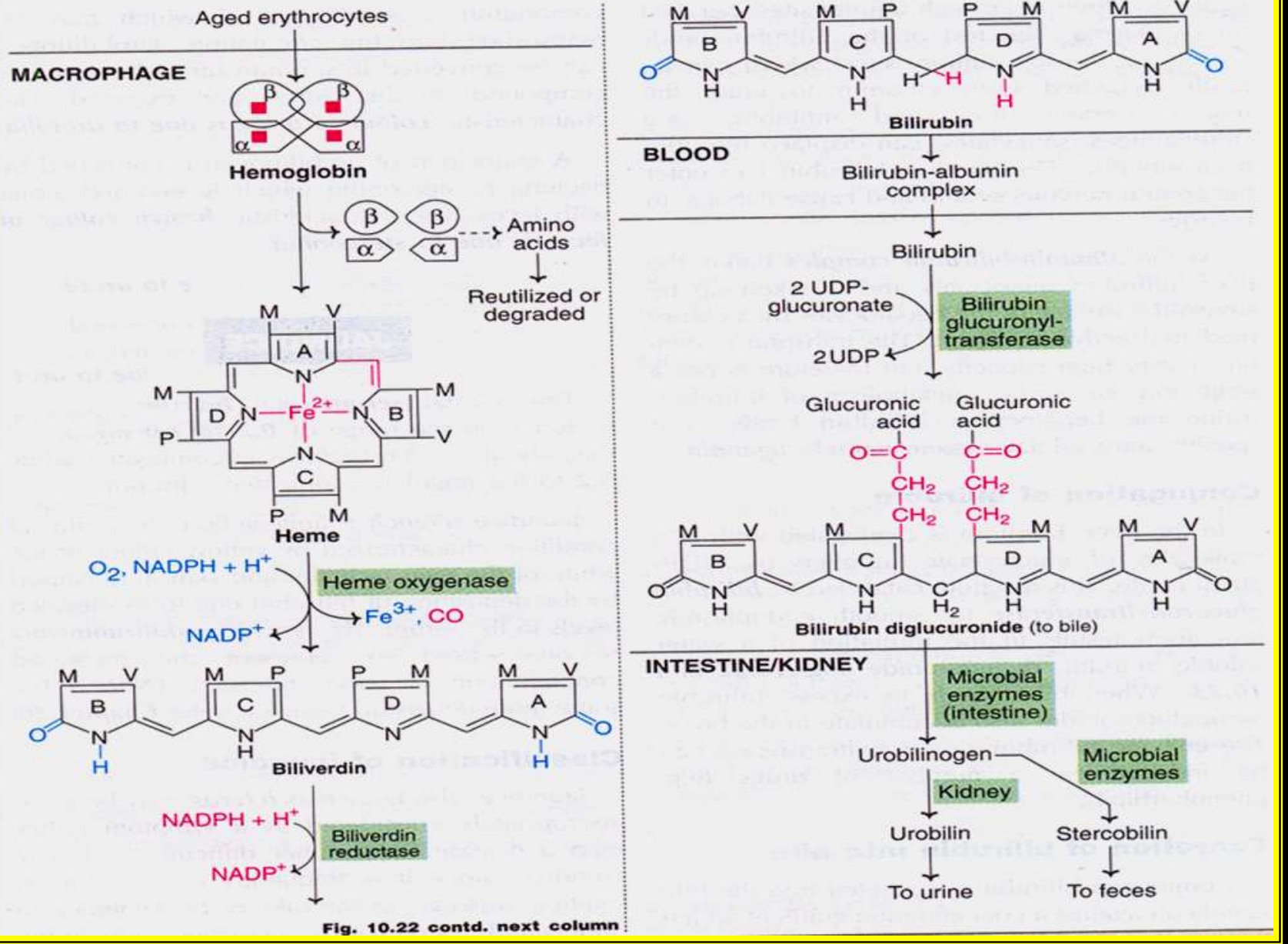
Hemoglobin

Globin → Amino acids → Amino acid pool

Heme → Fe

Heme → Bilirubin → Excreted

- The hemoglobin is cleaved to the protein part globin and non-protein heme.
- About 6g of hemoglobin per day is broken down, and resynthesized in an adult man (70kg).
- **Fate of globin:** Reutilized as such for the formation of hemoglobin or degraded to the individual amino acids which undergo their own metabolism, including participation in fresh globin synthesis.



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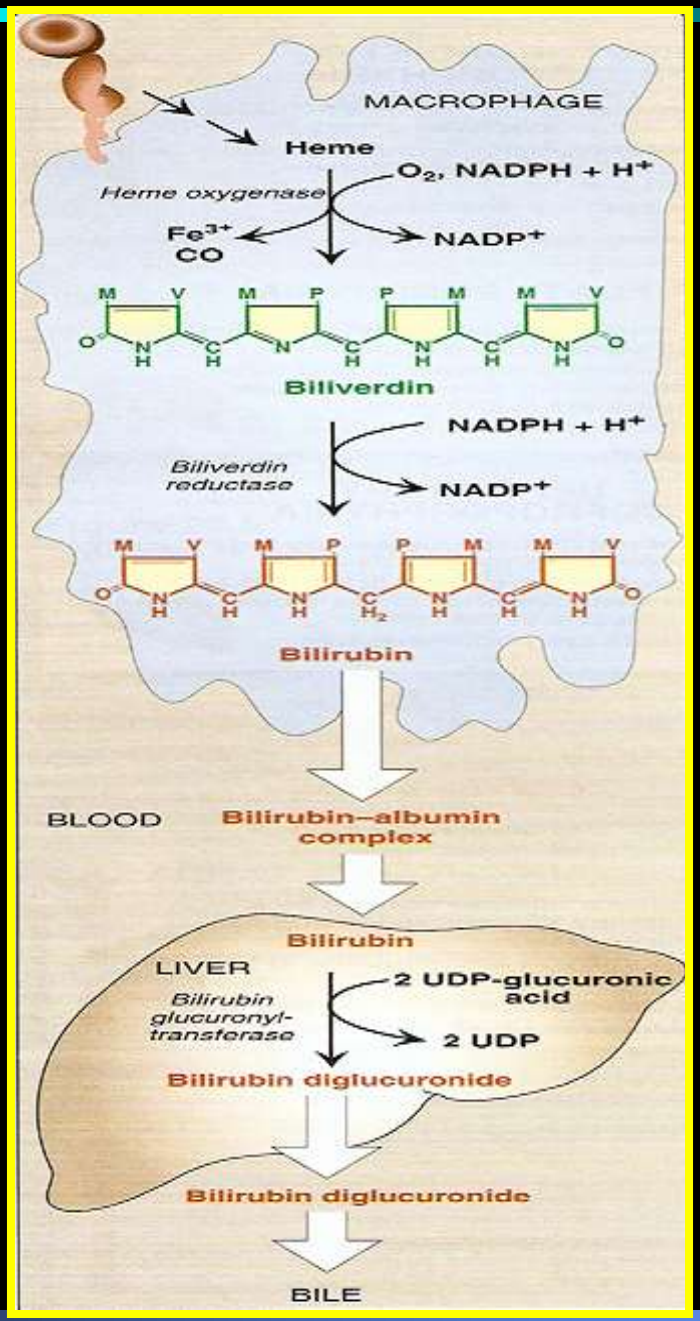
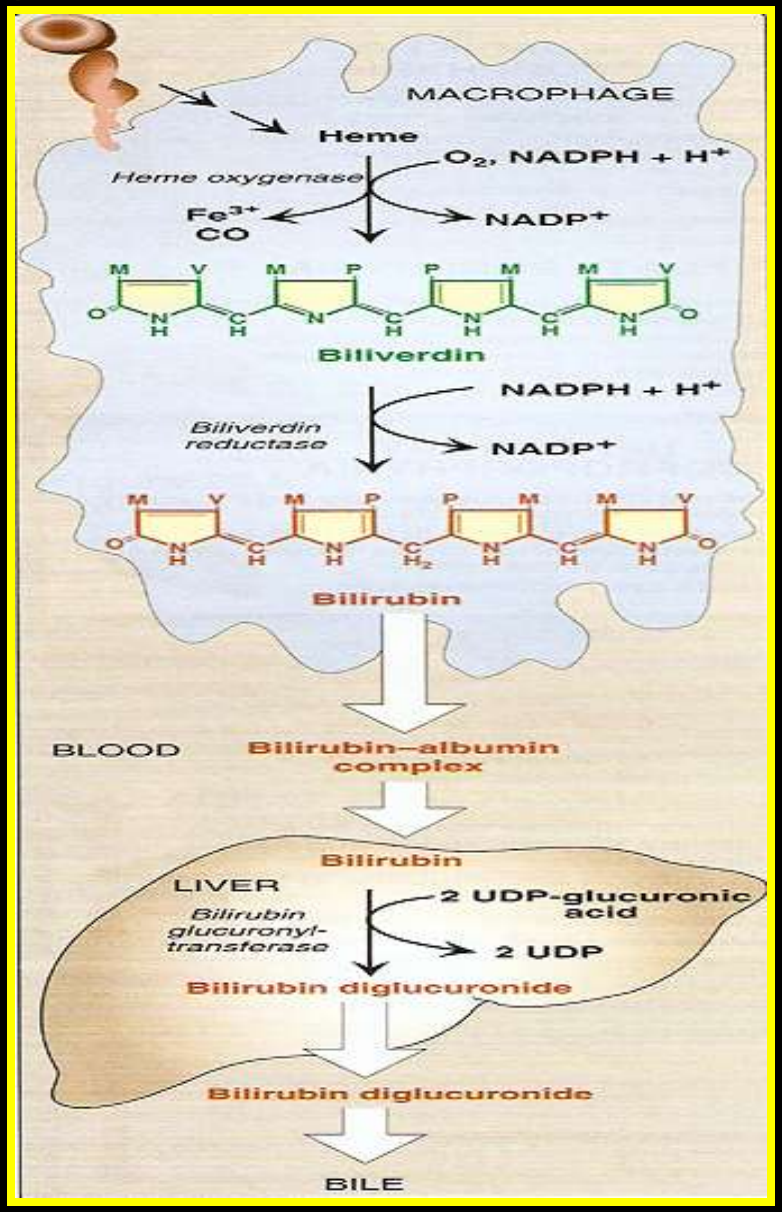

MACROPHAGE
Heme
O_2, NADPH + H^+
Heme oxygenase
Fe^{3+}
CO
$NADP^+$
Biliverdin
NADPH + H^+
Biliverdin reductase
$NADP^+$
Bilirubin
BLOOD
Bilirubin–albumin complex
Bilirubin
LIVER
Bilirubin glucuronyl-transferase
2 UDP-glucuronic acid
2 UDP
Bilirubin diglucuronide
Bilirubin diglucuronide
BILE

Heme Oxygenase

- Utilizes NADPH and O_2 and cleaves the methenyl bridges between the two pyrrole rings (A and B) to form biliverdin.

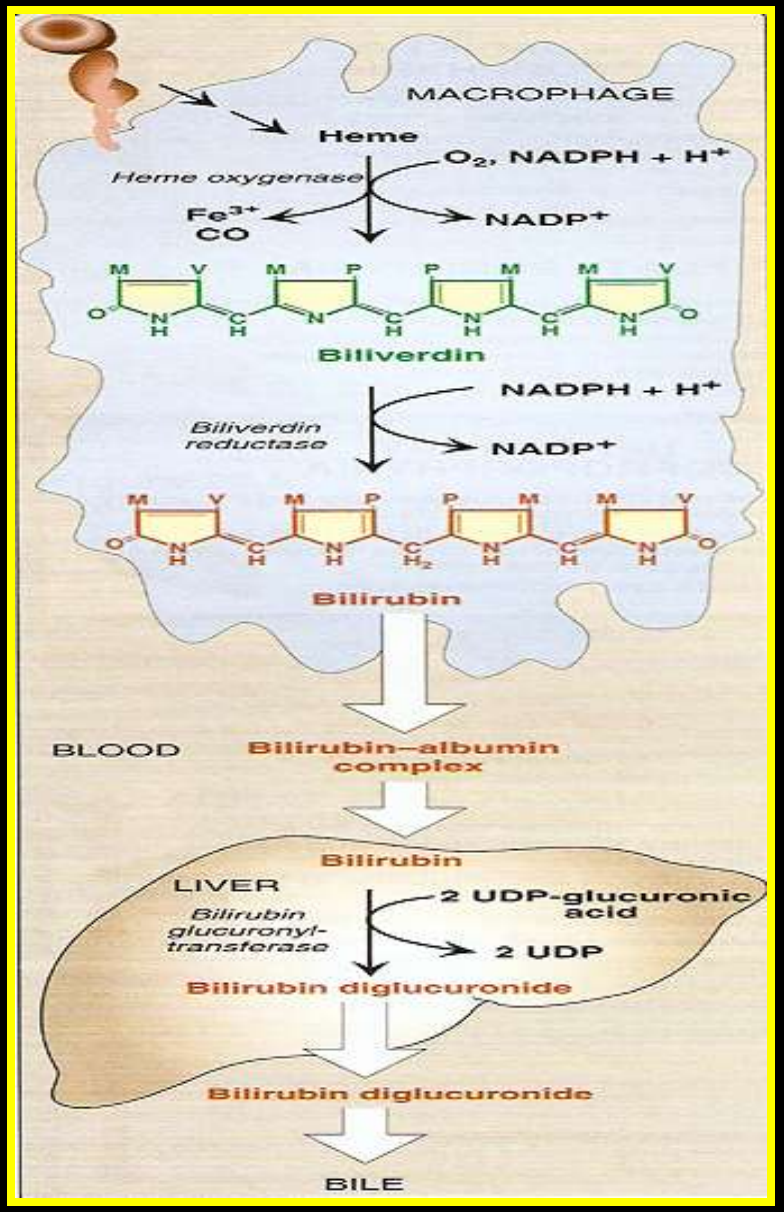
- Simultaneously, ferrous iron (Fe^{2+}) is oxidized to ferric form (Fe^{3+}) and released. The products of heme oxygenase reaction are biliverdin (green pigment), Fe^{3+} and carbon monoxide (CO).

- Biliverdin is excreted in birds while in mammals it is further degraded.



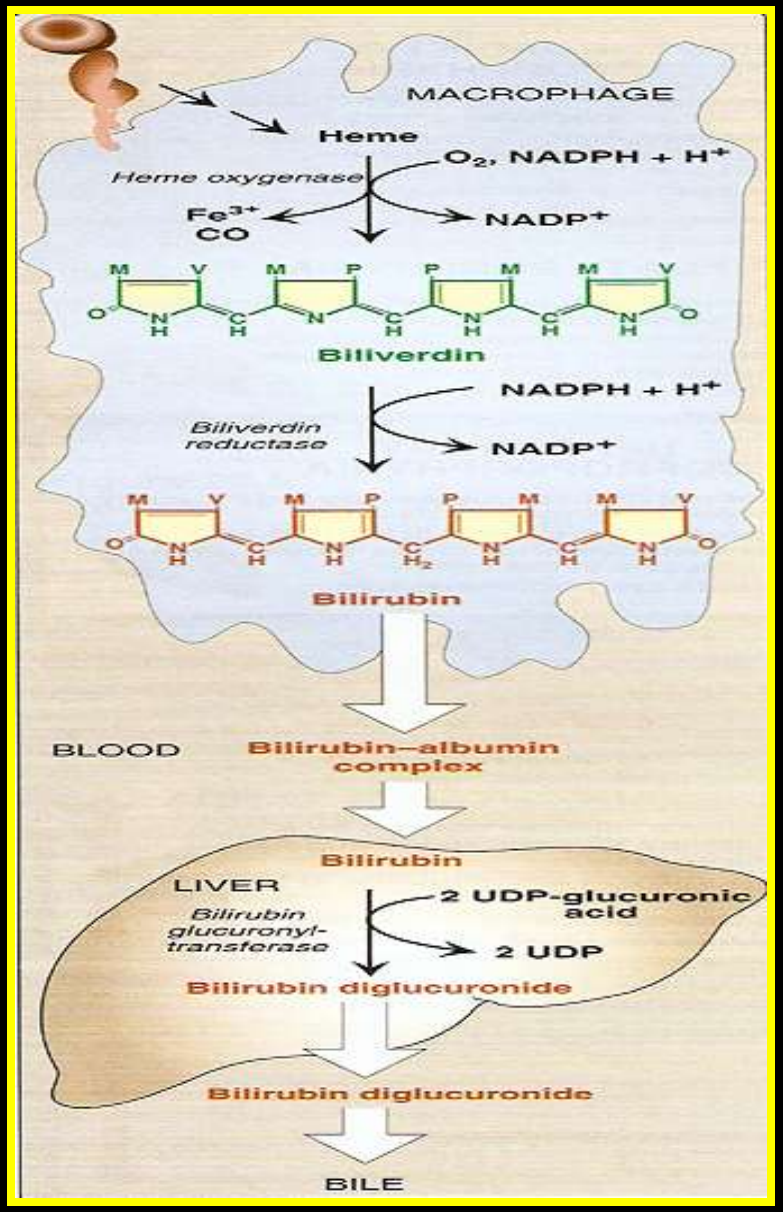
Biliverdin Reductase

- Biliverdin's methenyl bridges (between the pyrrole rings C and D) are reduced to form bilirubin (yellow pigment).
- This reaction is catalysed by an NADPH dependent enzyme *biliverdin reductase.*
- Approximately 250-350mg of bilirubin is daily produced in human adults. The term bile pigments is used to collectively represent bilirubin and its derivatives.



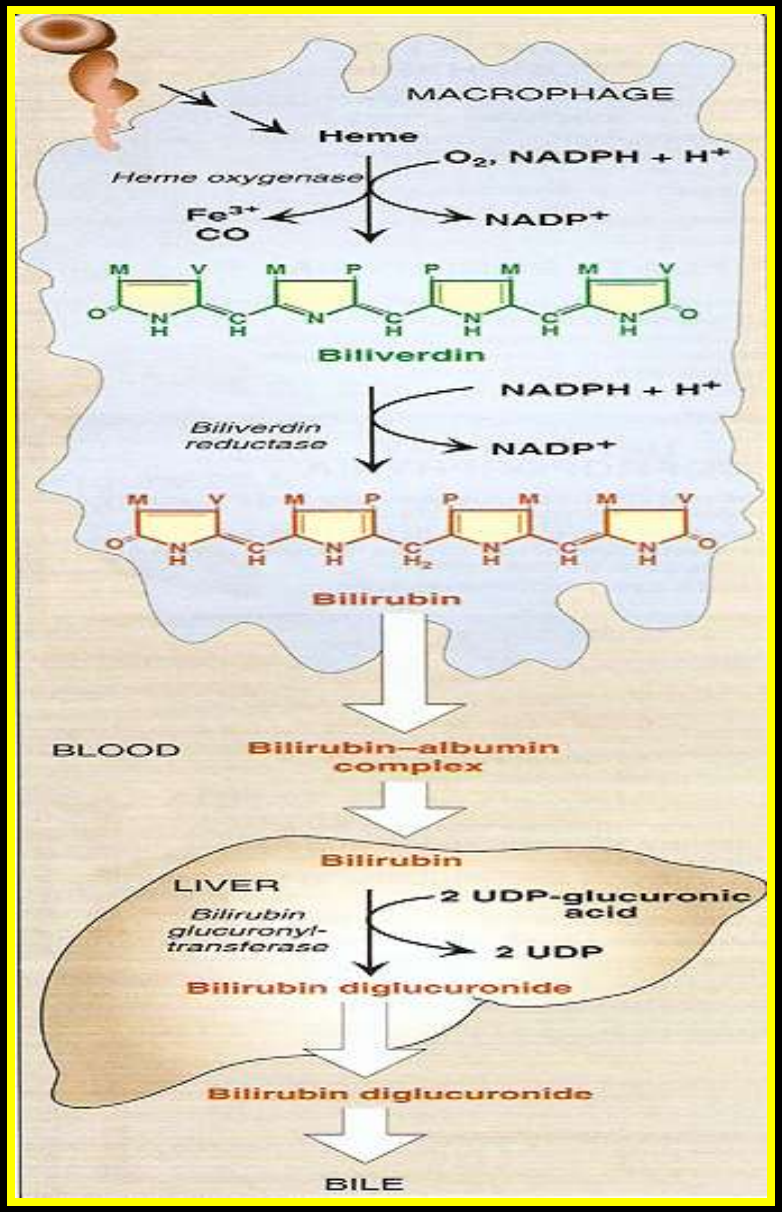
Transport of bilirubin to liver

- Bilirubin is lipophilic and therefore insoluble in aqueous solution.
- Bilirubin is transported in the plasma in a bound form to **albumin.**
- Inside the hepatocytes, bilirubin binds to a specific intracellular protein ***ligandin*.**



Conjugation of bilirubin

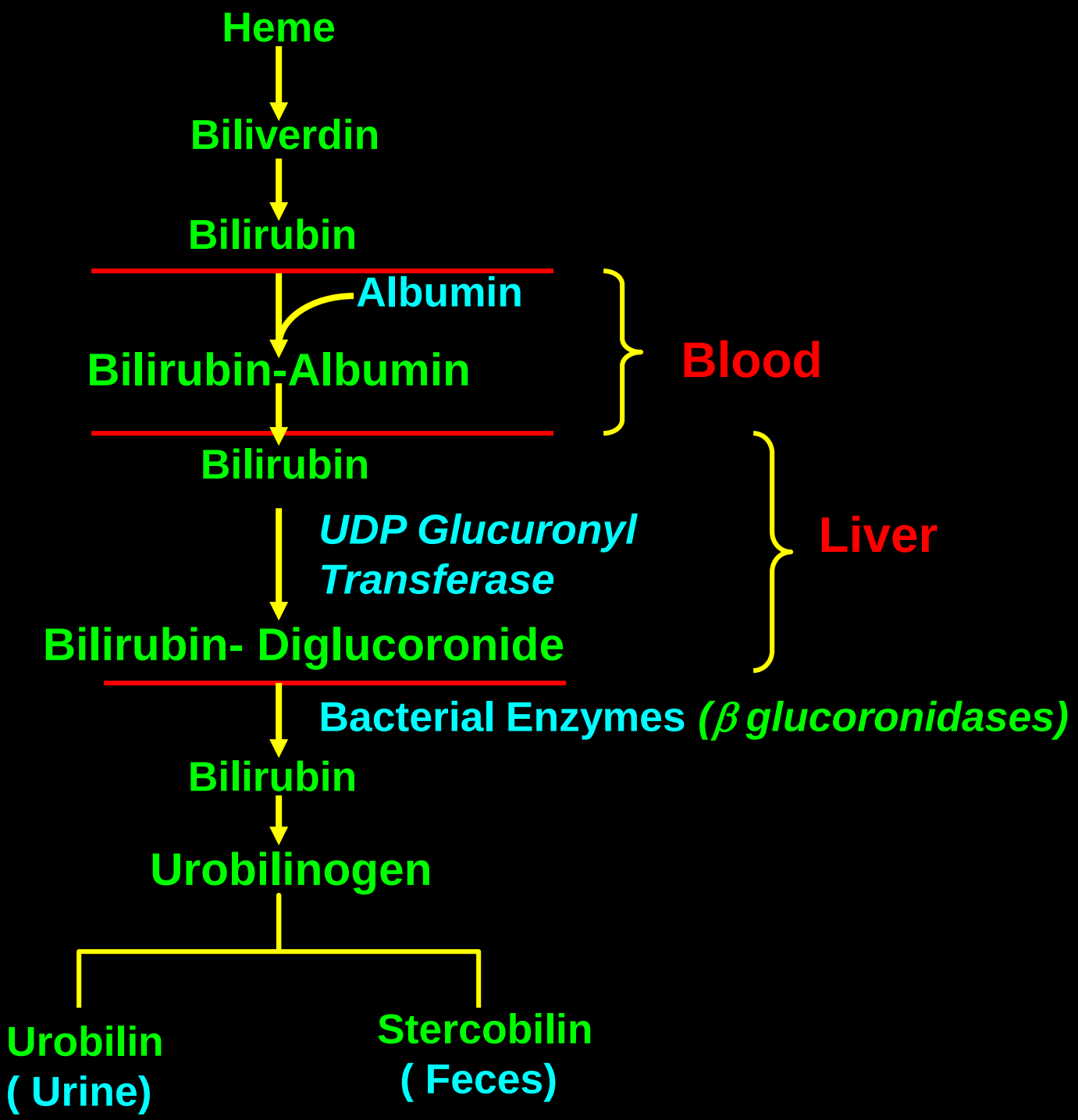
- In the liver, bilirubin is conjugated with two molecules of glucuronate supplied by UDP-glucuronate.
- This reaction, catalysed by *bilirubin glucuronyltransferase* results in the formation of a water soluble bilirubin diglucuronide (conjugated bilirubin).
- The enzyme *bilirubin glucuronyltransferase* 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. All the bilirubin (>98%) that enters bile is in the conjugated form.

- This energy-dependent is susceptible to impairment in liver disease. Unconjugated bilirubin is normally not excreted.


Heme
Biliverdin
Bilirubin
Albumin
Bilirubin-Albumin
Blood
Bilirubin
UDP Glucuronyl Transferase
Liver
Bilirubin- Diglucoronide
Bacterial Enzymes (β glucoronidases)
Bilirubin
Urobilinogen
Urobilin (Urine)
Stercobilin (Feces)

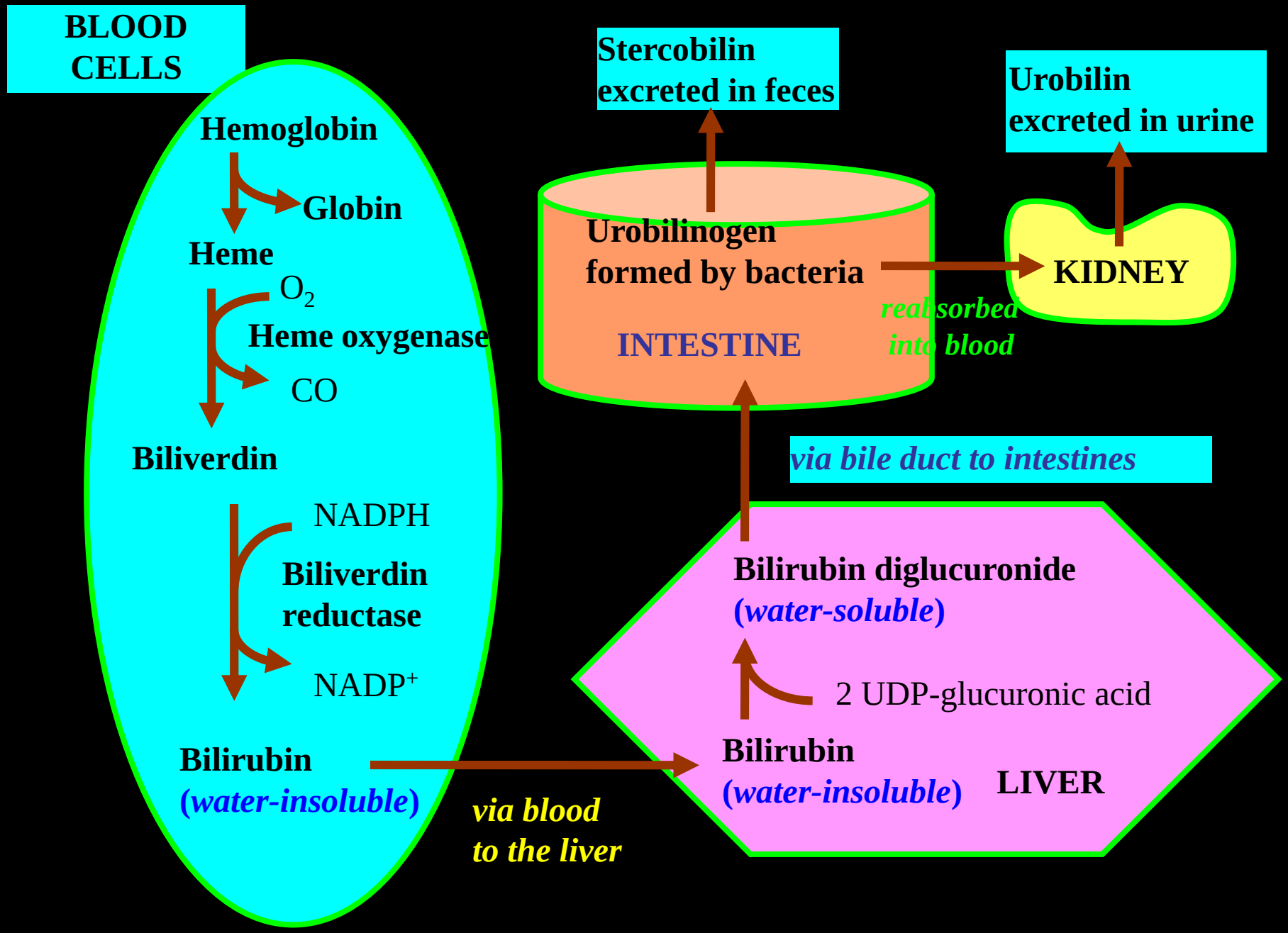
Fate of bilirubin

- Bilirubin glucuronides are hydrolysed in the intestine by bacterial enzymes *(β glucoronidases)* to liberate bilirubin.

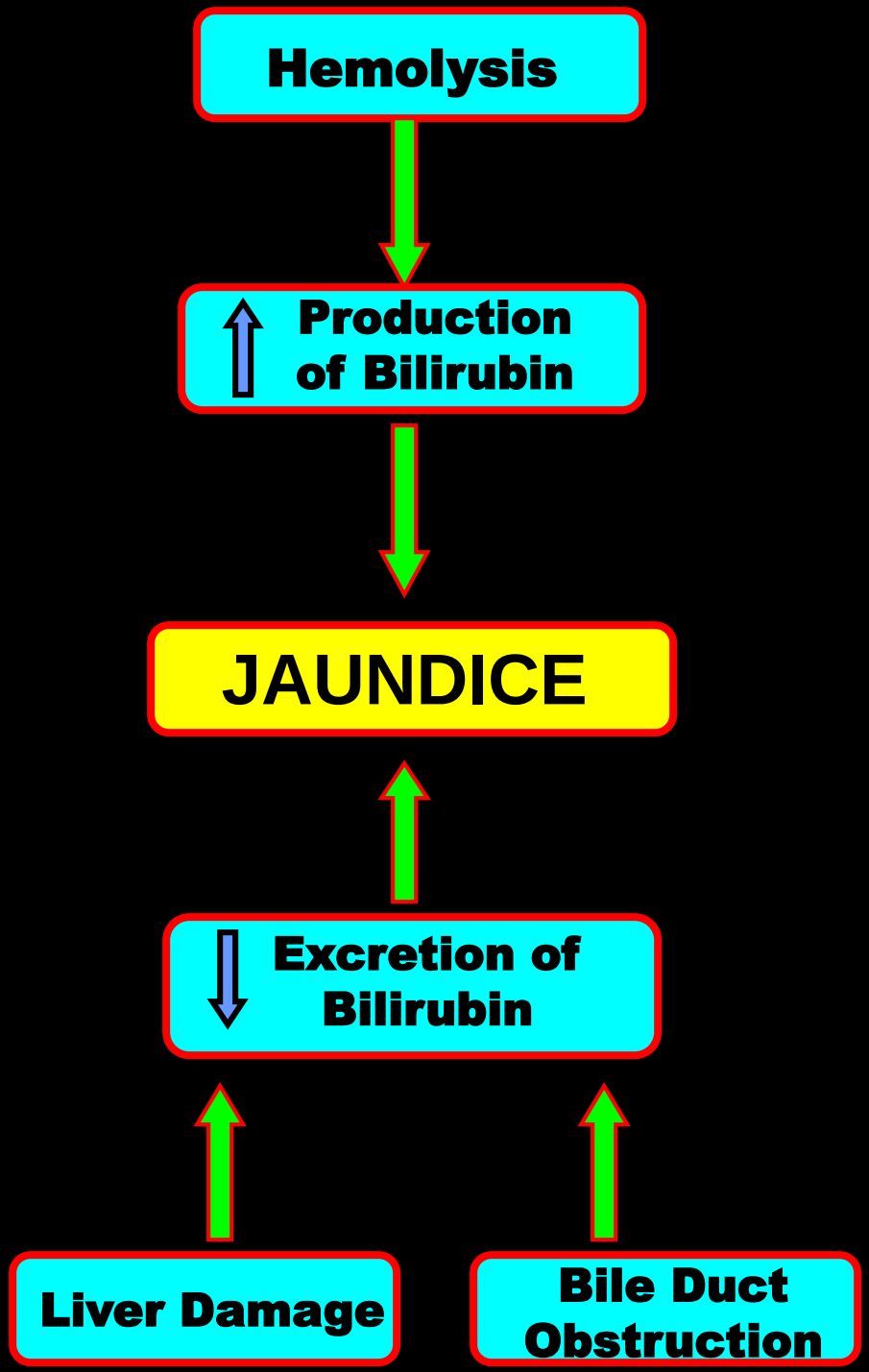
- Bilirubin is then converted to urobilinogen (colourless compound), a small part of which may be reabsorbed into the circulation.

- Urobilinogen can be converted to urobilin (a 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.


BLOOD CELLS
Hemoglobin
Globin
Heme
O2
Heme oxygenase
CO
Biliverdin
NADPH
Biliverdin reductase
NADP+
Bilirubin (water-insoluble)
via blood to the liver
Bilirubin (water-insoluble)
LIVER
2 UDP-glucuronic acid
Bilirubin diglucuronide (water-soluble)
via bile duct to intestines
INTESTINE
Urobilinogen formed by bacteria
reabsorbed into blood
KIDNEY
Stercobilin excreted in feces
Urobilin excreted in urine

Jaundice


Hemolysis
Production of Bilirubin
JAUNDICE
Excretion of Bilirubin
Liver Damage
Bile Duct Obstruction

JAUNDICE

- The normal serum total bilirubin concentration is in the range of 0.2 to 1.0mg/dl of this, about 0.2-0.8mg/dl is unconjugated (Indirect) while 0.0 to 0.2mg/dl is conjugated (Direct) bilirubin.

- Jaundice (icterus) 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 when the total serum bilirubin concentration level exceeds 1mg/dl

Hyperbilirubinemia

Two forms:

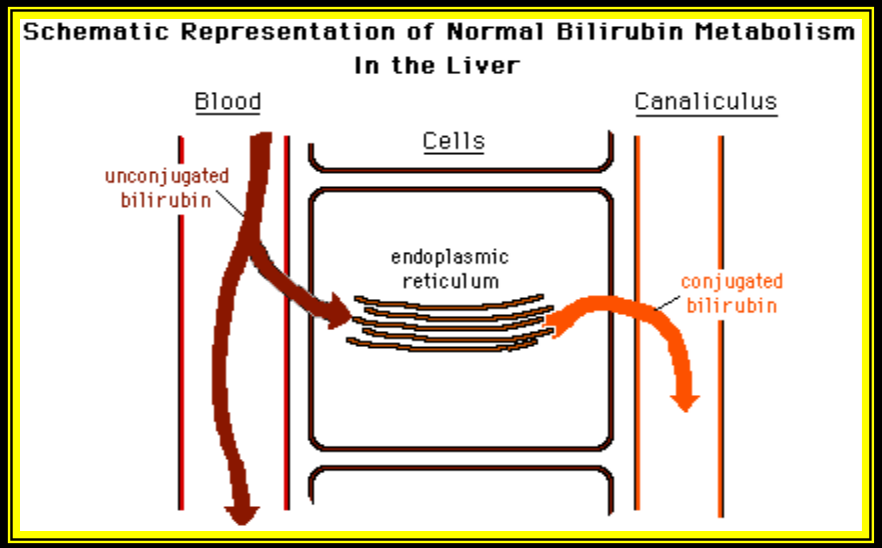
- **Elevation in Direct /Conjugated (Water soluble) bilirubin.**
- **Elevation in Indirect/ Unconjugated (Water insoluble) bilirubin.**

Classification of jaundice

Jaundice is classified into

- **Hemolytic**
- **Hepatocellular**
- **Obstructive**
- **Neonatal or Physiological**

Hemolytic Jaundice



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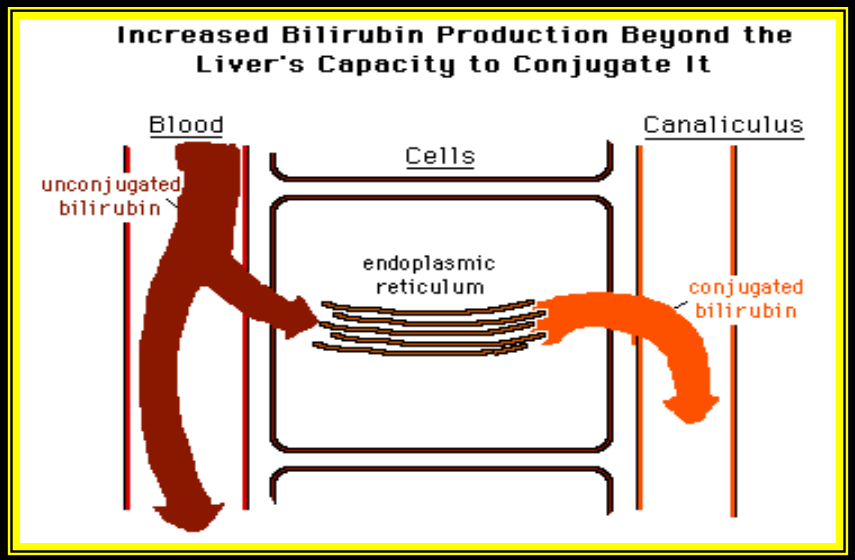
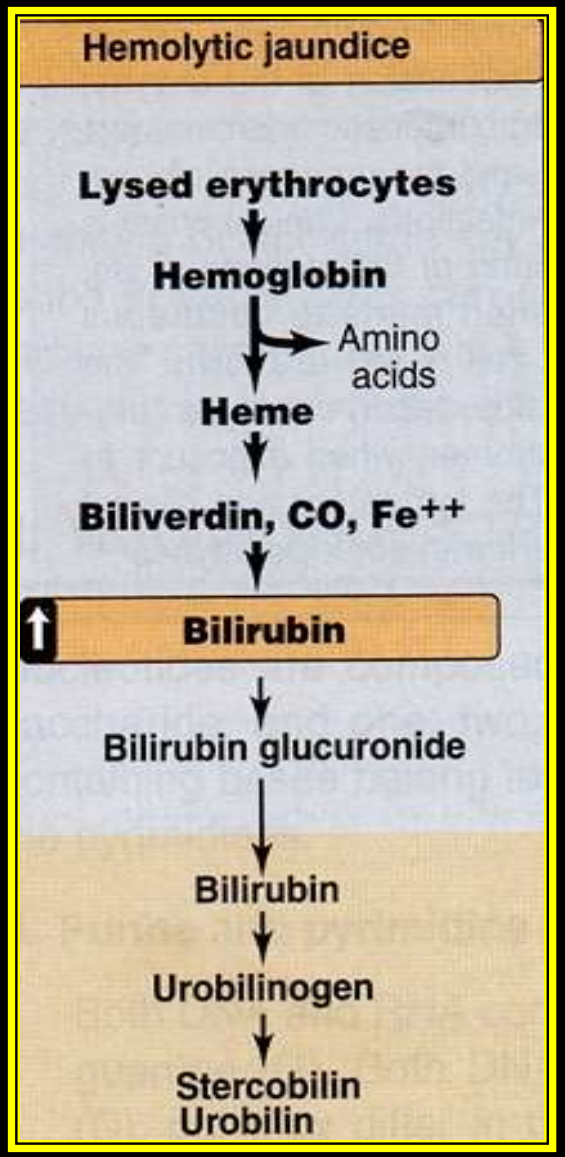


Hemolytic Jaundice



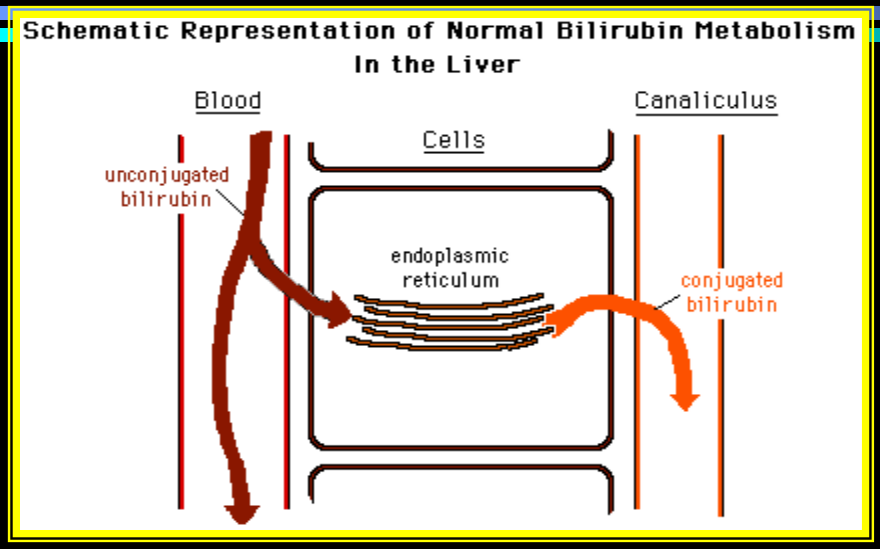
Hemolytic jaundice (Pre hepatic)

This condition is associated with increased hemolysis of erythrocytes (e.g. incompatible blood transfusion, malaria, sickle-cell anemia). This results in the overproduction of bilirubin beyond the ability of the liver to conjugate and excrete.

In hemolytic jaundice, more bilirubin is excreted into the bile leading to the increased formation of urobilinogen and stercobilin and urobilin. Hemolytic jaundice is characterized by

- Elevation in the serum unconjugated bilirubin
- Increased excretion of urobilinogen (urobilin) in urine (Dark Urine).
- Dark brown colour of feces due to high content of stercobilin.

Obstructive Jaundice



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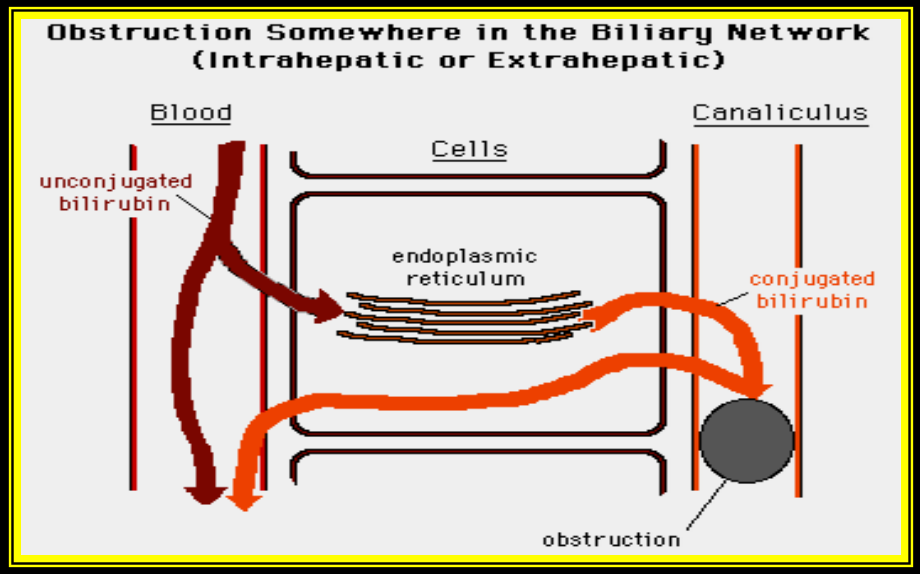
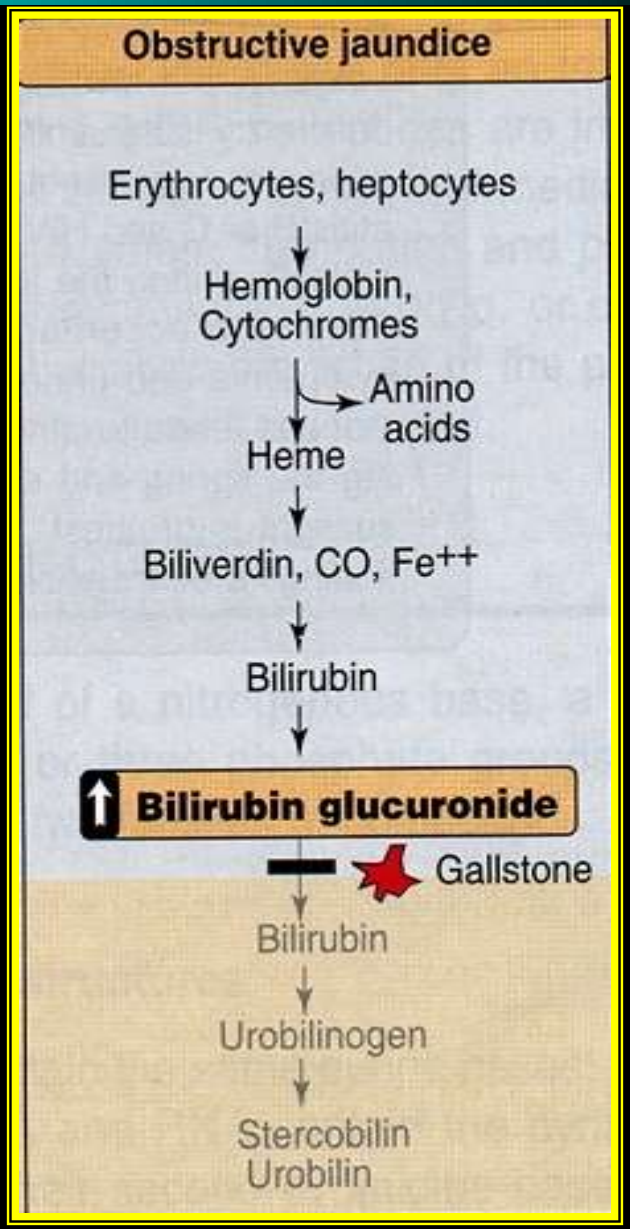


Obstructive Jaundice



Obstructive Jaundice (Post hepatic)

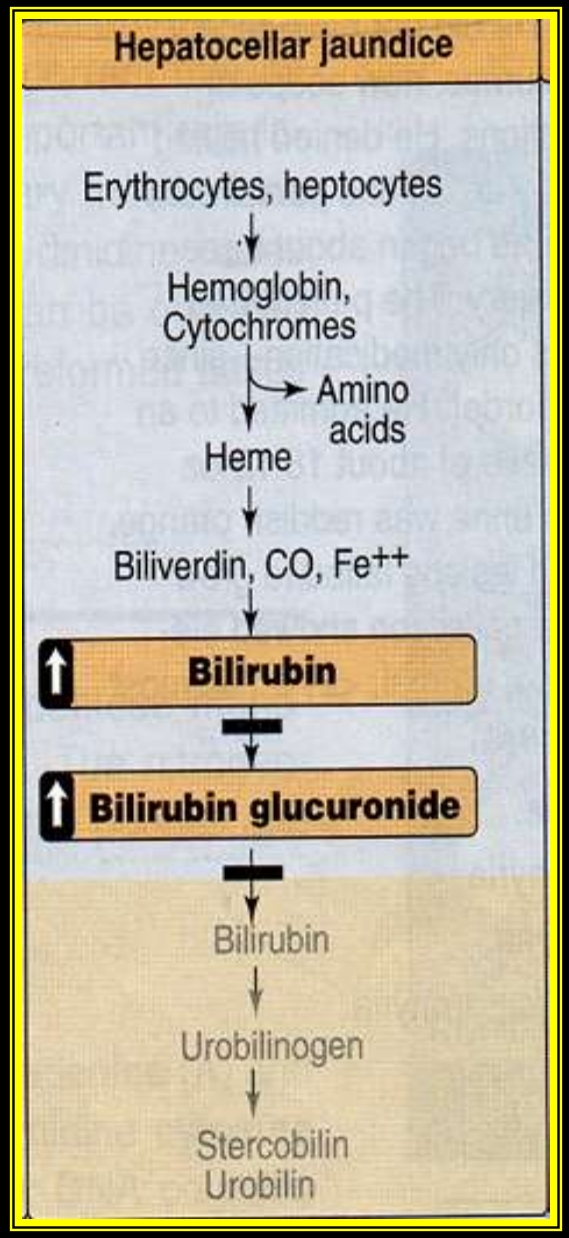
- This is due to an obstruction in the bile duct that prevents the passage of bile into the intestine. The Obstruction may be caused by gall stones.

- Due to the blockage in bile duct, the conjugated bilirubin from the liver enters the circulation.

Obstructive jaundice is characterized by

- **Increased concentration of conjugated bilirubin in serum.**
- **Serum alkaline phosphatase (ALP) is elevated as it is released from the cells of the damaged bile duct.**
- **Dark coloured urine due to elevated excretion of bilirubin and clay (light) coloured feces due to absences of stercobilin.**
- **Feces contain excess fat indicating impairment in fat digestion and absorption in the absence of bile.**
- **The patients experience nausea and gastrointestinal pain.**

Hepatocellular Jaundice


Hepatocellar jaundice
Erythrocytes, heptocytes
Hemoglobin,
Cytochromes
Amino
acids
Heme
Biliverdin, CO, Fe++
Bilirubin
Bilirubin glucuronide
Bilirubin
Urobilinogen
Stercobilin
Urobilin

Hepatocellular jaundice (Hepatic)

- This type of jaundice is caused by dysfunction of the liver due to damage to the parenchymal cells.
- Viral infection (viral hepatitis), poisons and toxins (chloroform, carbon tetrachloride) cirrhosis of liver, cardiac failure.
- Viral hepatitis is the most common.

Damage to the liver adversely affects the bilirubin uptake and the secretion of conjugated bilirubin into the bile by liver cells. Hepatic jaundice is characterized by

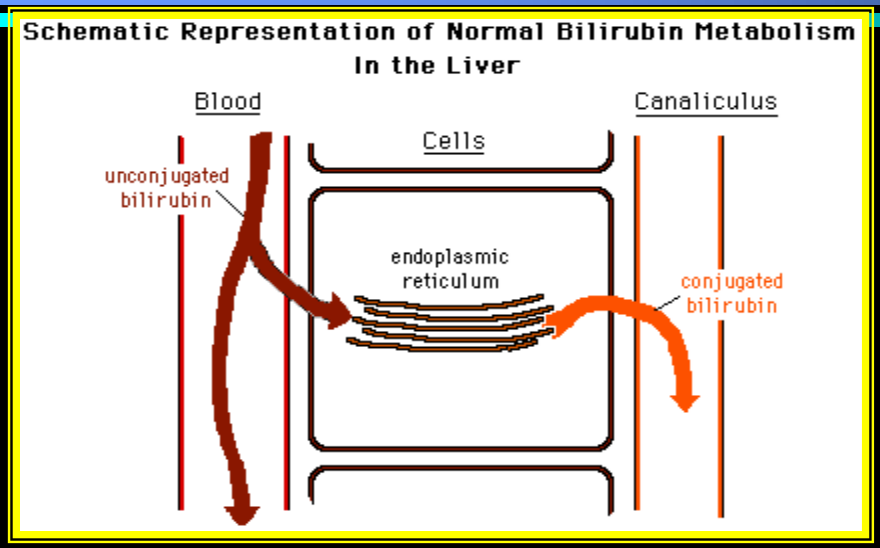
- Increased levels of unconjugated and conjugated bilirubin in the serum.

- Increased activities of alanine transaminase (SGPT) and aspartate transaminase (SGOT) released into circulation due to damage to hapatocytes.

- The urine is dark ,whereas the stools are light clay colored.

- The affected individuals experience nausea and anorexia (loss of appetite).

Neonatal Jaundice



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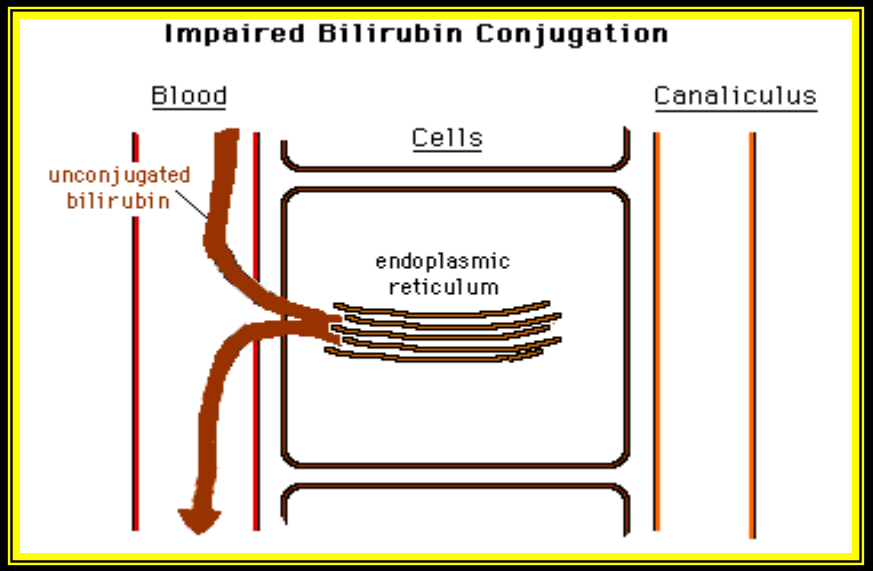
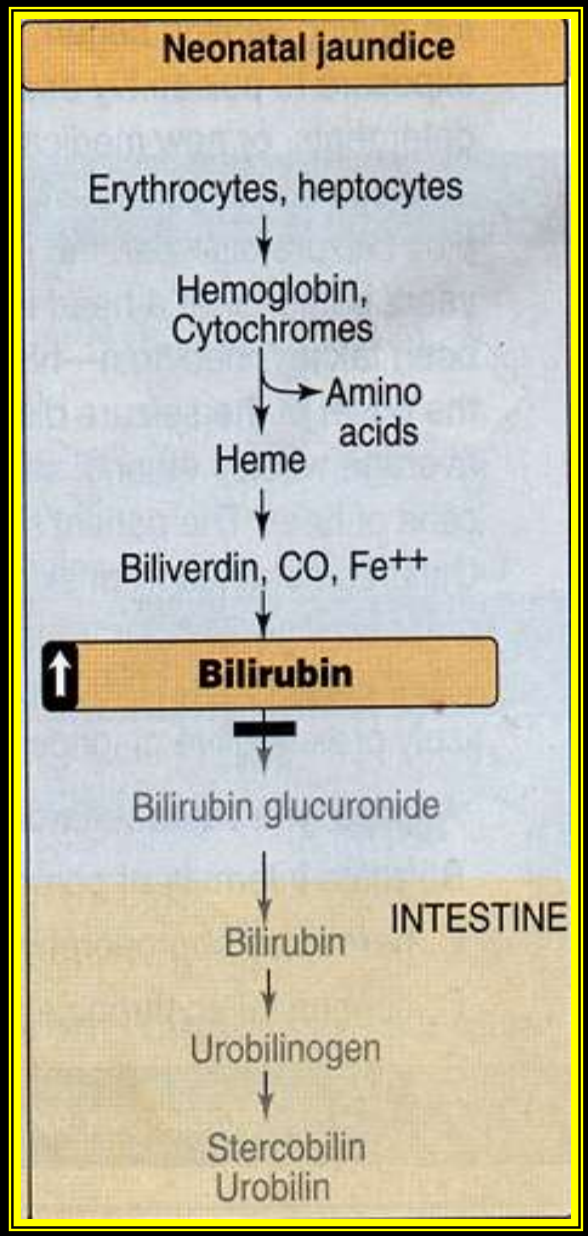


Neonatal Jaundice



Neonatal-physiologic jaundice

- It is caused due to immature hepatic system for the uptake, conjugation and secretion of bilirubin.

- The activity of the enzyme *UDP-glucuronyltransferase* is low in the newborn.

- There is also a limitation in the availability of the substrate UDP-glucuronic acid for conjugation.

- Serum uncojugated bilirubin is highly elevated (may go beyond 25mg/dl), which can cross the bloodbrain barrier.

- This results in hyperbilirubinemic toxic encephalopathy or kernicturus that causes mental retardation.

- The drug phenobarbital is used in the treatment of neonatal jaundice, as it can induce bilirubin metabolizing enzymes in liver.

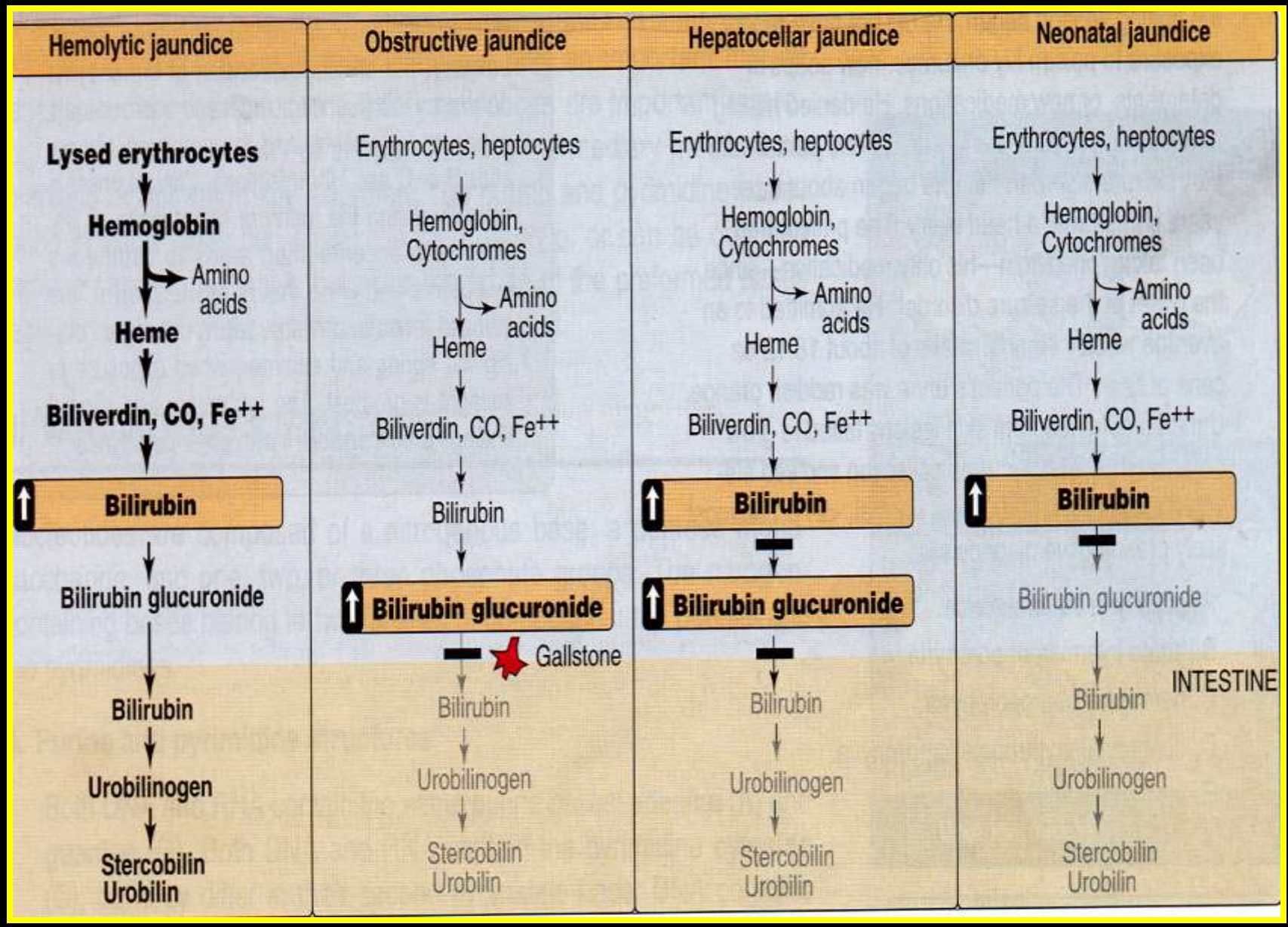
- In some neonates, blood transfusion may be necessary to prevent brain damage.

Phototherapy

- The toxic unconjugated bilirubin gets converted into a non-toxic isomer namely lumirubin.

- Lumirubin can be easily excreted by the kidneys in the unconjugated form (in contrast to unconjugated bilirubin which cannot be excreted).

- Serum bilirubin is monitored every 12-24 hours, and phototherapy is continuously carried out till the serum bilirubin becomes normal (< 1mg/dl).


Hemolytic jaundice
Lysed erythrocytes
Hemoglobin
Amino acids
Heme
Biliverdin, CO, Fe++
Bilirubin
Bilirubin glucuronide
Bilirubin
Urobilinogen
Stercobilin
Urobilin
Obstructive jaundice
Erythrocytes, heptocytes
Hemoglobin, Cytochromes
Amino acids
Heme
Biliverdin, CO, Fe++
Bilirubin
Bilirubin glucuronide
Gallstone
Bilirubin
Urobilinogen
Stercobilin
Urobilin
Hepatocellar jaundice
Erythrocytes, heptocytes
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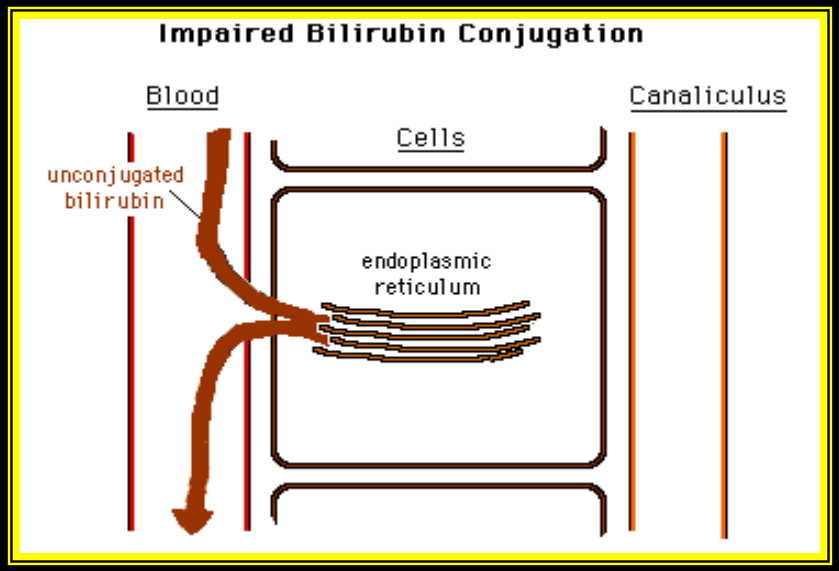
Bilirubin
Urobilinogen
Stercobilin
Urobilin
INTESTINE

JAUNDICE DUE TO GENETIC DEFECTS

Crigler-Najjar syndrome type I

- This is also known as congenital non-hemolytic jaundice. It is a rare disorder and is due to a defect in the hepatic enzyme *UDP-glucuronyltransferase*.

- Children die within first two years of life.



Crigler-Najjar syndrome type II

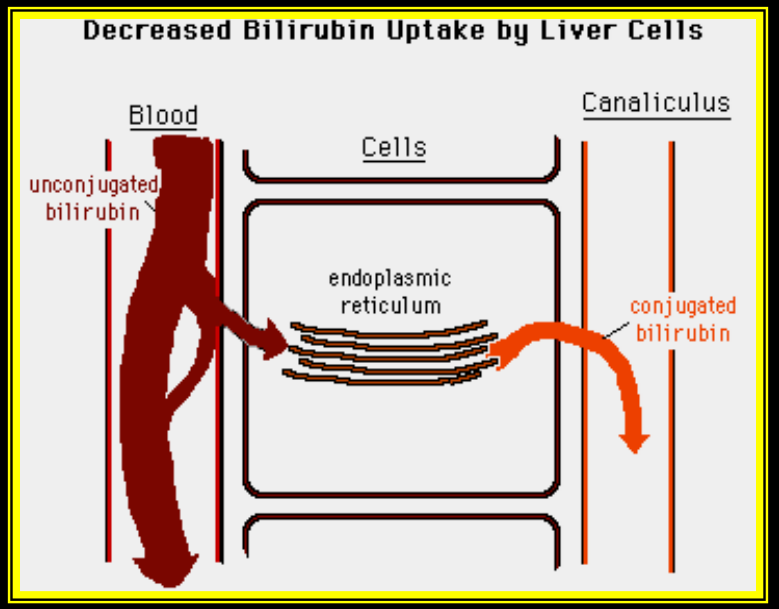
- A rare hereditary disorder and is due to a less severe defect in the bilirubin conjugation.

- Hepatic *UDP-glucuronyltransferase* that catalyses the addition of second glucuronyl group is defective.

- The serum bilirubin concentration is usually less than 20mg/dl and is less dangerous than type I.

Gilbert's disease

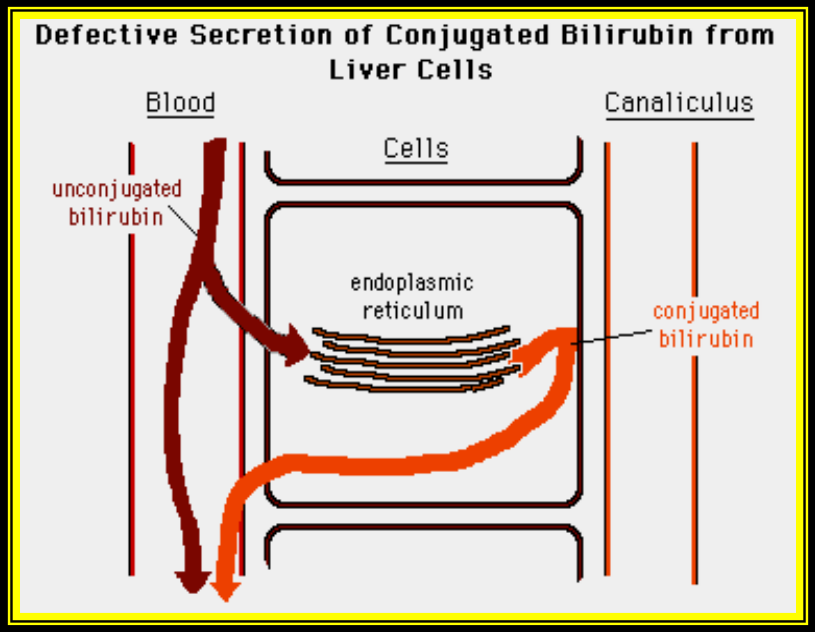
- A defect in the uptake of bilirubin by liver cells.
- Increased Unconjugated bilirubin



Dubin-Johnson syndrome

- Associated with inability of the hepatocytes to secrete conjugated bilirubin after it has been formed.

- Conjugated bilirubin returns to the blood and is elevated.



THANK YOU