



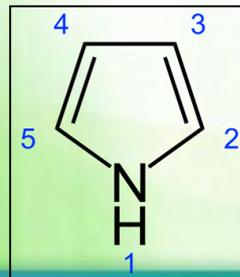
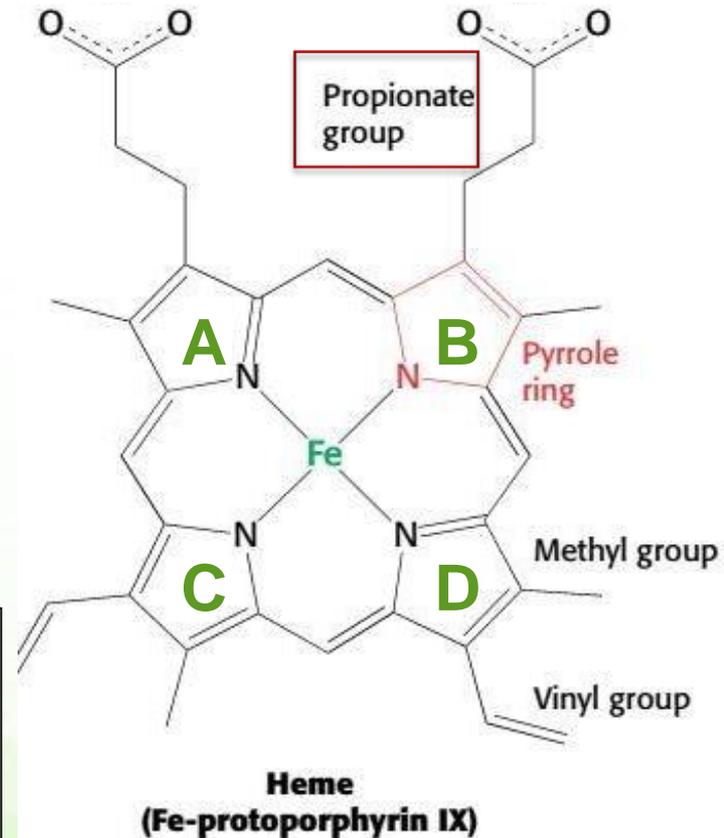
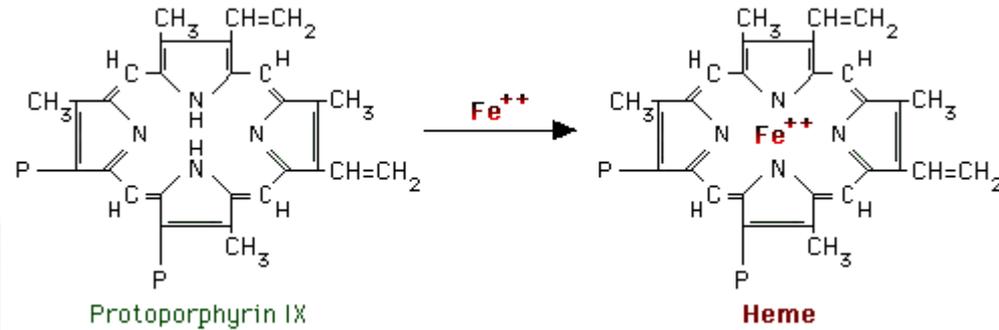
Metabolism of heme

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Heme structure



- It is a complex of protoporphyrin IX + Iron (Fe^{2+})
- The porphyrin is planar and consists of four rings (designated A-D) called pyrrole rings.
- Each pyrrole can bind two substituents.
- Two rings have a propionate group each.
- *Note: the molecule is hydrophobic.*
- Fe has six coordinates of binding.





Biosynthesis of heme

Sites of synthesis

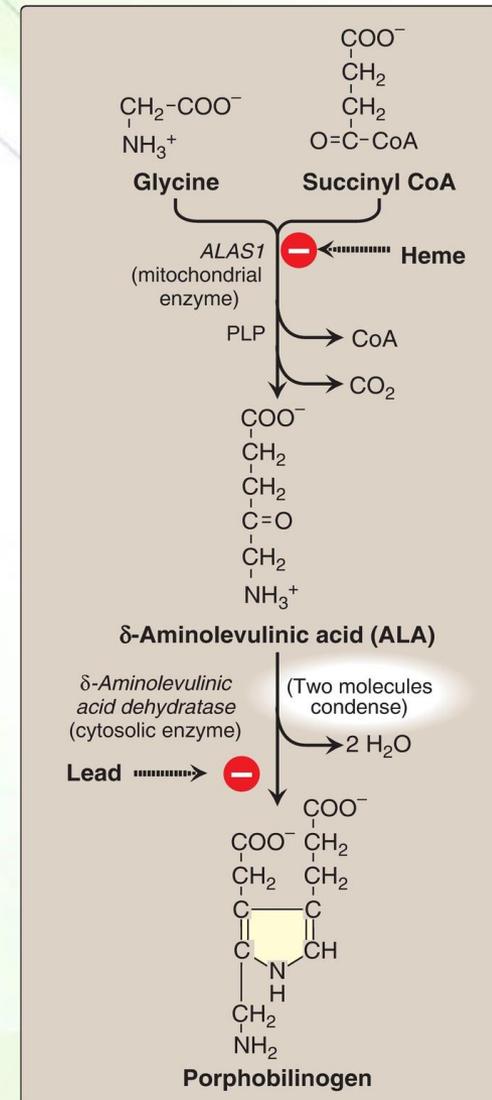


- The major sites of heme biosynthesis are
 - Liver, which synthesizes a number of heme proteins (particularly the CYP proteins),
 - The rate of heme synthesis is highly variable
 - Erythrocyte-producing cells (Hb synthesis)
 - Relatively constant production and matches the rate of globin synthesis, but synthesis is regulated at multiple points.
- Synthesis occurs in
mitochondria → cytosol → mitochondria

Synthesis of heme

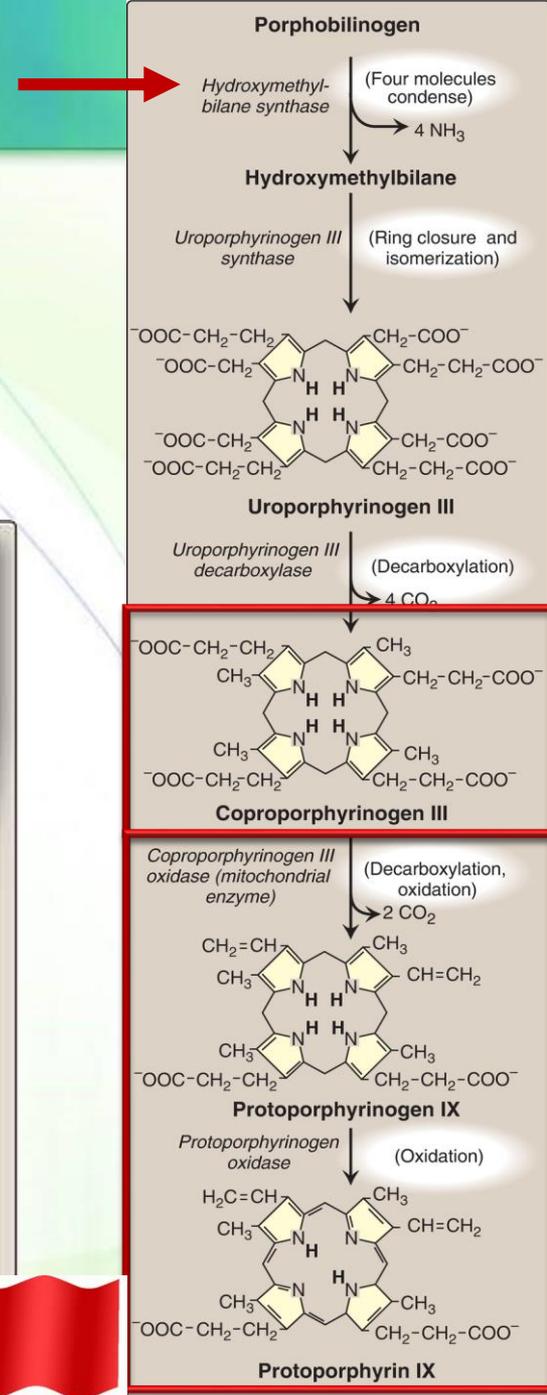
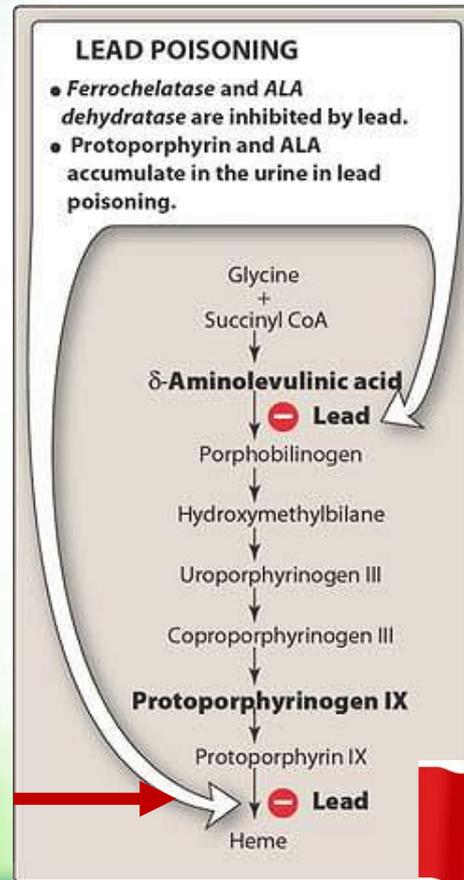


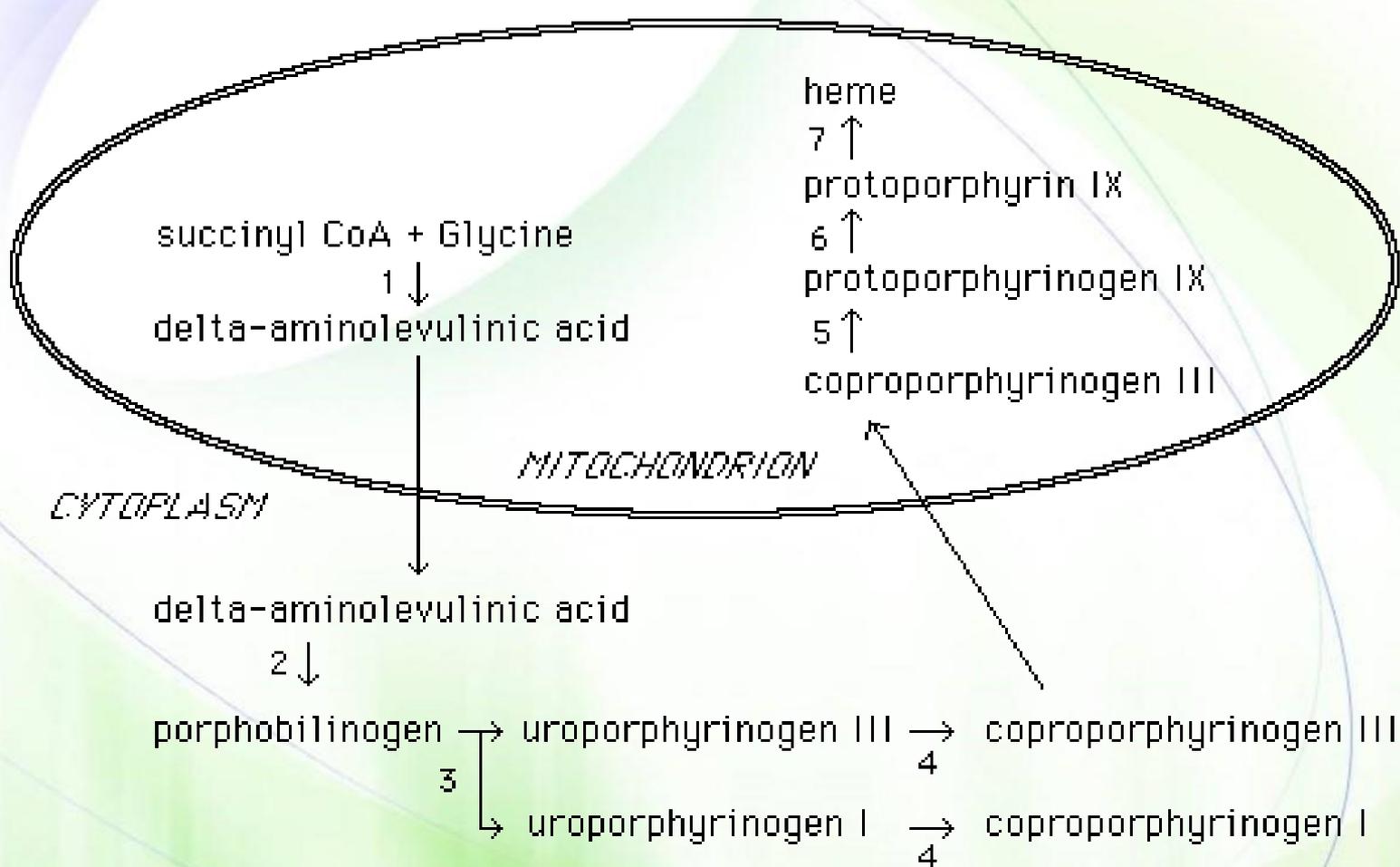
- The first reaction is catalyzed by ALAS1 (liver) or ALAS2 (erythrocytes).
- It is the rate limiting and committed step.
- It requires vitamin B6 (pyridoxal phosphate).
- ALAS1 is regulated by hemin.
 - Degradation of mRNA
 - Inhibition of mitochondrial transport
 - **Drugs induce ALAS1.**
- ALAS2 is regulated by level of iron.
- ALA moves out of mitochondria to cytosol.
- Porphobilinogen is formed by 2X ALA.



More reactions

- 4X PBG form uroporphobilinogen III
- Coproporphyrinogen III moves back into mitochondria.
- The last reaction is spontaneous, but can be catalyzed by ferrochelatase.
- In erythrocytes, synthesis is regulated at ferrochelatase and porphobilinogen deaminase (→).





Porphyrias



- Porphyrias are inherited or acquired disorders caused by a deficiency of enzymes in the heme biosynthetic pathway resulting in elevations in the serum and urine content of intermediates in heme synthesis.
- Porphyria = purple.
- These disorders are classified as either erythroid or hepatic (acute or chronic).
- Abdominal and neuropsychiatric signs or not *versus* photosensitive or not photosensitive (tetrapyrrole or not)



LEAD POISONING

- *Ferrochelatase* and *ALA dehydratase (ALAD)*¹ are particularly sensitive to inhibition by lead.
- Protoporphyrin and ALA accumulate in urine.
- *ALAD* deficiency porphyria is a very rare AR acute hepatic porphyria.

ERYTHROPOIETIC PROTOPORPHYRIA (EPP)

- This chronic AD and AR disease is caused by a deficiency in *ferrochelatase*.
- Protoporphyrin accumulates in erythrocytes, bone marrow, and plasma.
- Patients are photosensitive.



ACUTE INTERMITTENT PORPHYRIA (AIP)

- This acute AD disease is caused by a deficiency in *hydroxymethylbilane synthase*².
- Porphobilinogen and ALA accumulate in the urine.
- Urine darkens on exposure to light and air.
- Patients are not photosensitive.



Succinyl coenzyme A + Glycine

↓
δ-Aminolevulinic acid

↓
δ-Aminolevulinic acid (ALA)

↓
Porphobilinogen

↓
Hydroxymethylbilane

↓
Uroporphyrinogen I

↓
Coproporphyrinogen I

Heme

↑
Protoporphyrin IX

↑
Protoporphyrinogen IX

↑
Coproporphyrinogen III

↑
Coproporphyrinogen III → Spontaneous → Coproporphyrin III

↑
Uroporphyrinogen III → Spontaneous → Uroporphyrin III

↑
Coproporphyrinogen I → Spontaneous → Coproporphyrin I

VARIEGATE PORPHYRIA (VP)

- This acute AD disease is caused by a deficiency in *protoporphyrinogen oxidase*.
- Protoporphyrinogen IX and other intermediates prior to the block accumulate in the urine.
- Patients are photosensitive.



HEREDITARY COPROPORPHYRIA (HCP)

- This acute AD disease is caused by a deficiency in *coproporphyrinogen III oxidase*.
- Coproporphyrinogen III and other intermediates prior to the block accumulate in the urine.
- Patients are photosensitive.



MITOCHONDRIA

CYTOSOL

PORPHYRIA CUTANEA TARDA (PCT)

- This chronic disease can be caused by an AD deficiency in *uroporphyrinogen decarboxylase*.
- Uroporphyrin accumulates in the urine.
- It is the most common porphyria.
- Patients are photosensitive.

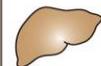


CONGENITAL ERYTHROPOIETIC PORPHYRIA (CEP)

- This chronic AR disease is caused by a deficiency in *uroporphyrinogen III synthase*.
- Uroporphyrinogen I and coproporphyrinogen I accumulate in the urine.
- Patients are photosensitive.



KEY:



Hepatic porphyria

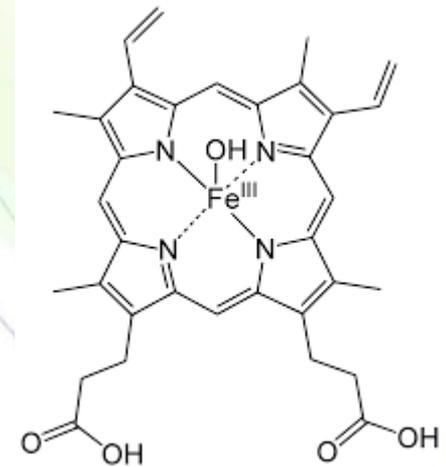


Erythropoietic porphyria

Treatment



- Hemin or hematin strongly inhibits the activity of ALAS.
- Glucose: fasting (hypoglycemia) exacerbates acute porphyria attack due to activation of the transcription factor, PGC-1 α , in the liver induces synthesis of gluconeogenic genes and the ALAS1 gene resulting in accumulation of heme intermediates.





Catabolism of heme

Challenges



- RBCs are the largest storage place of heme.
- Erythrocytes are mainly destroyed by macrophages in the spleen and bone marrow, releasing hemoglobin, which is degraded to heme.
- The protein is metabolized into amino acids
- 6 g/day of hemoglobin are turned over, but
 - First, the porphyrin ring is hydrophobic.
 - Second, iron must be conserved.

Heme degradation

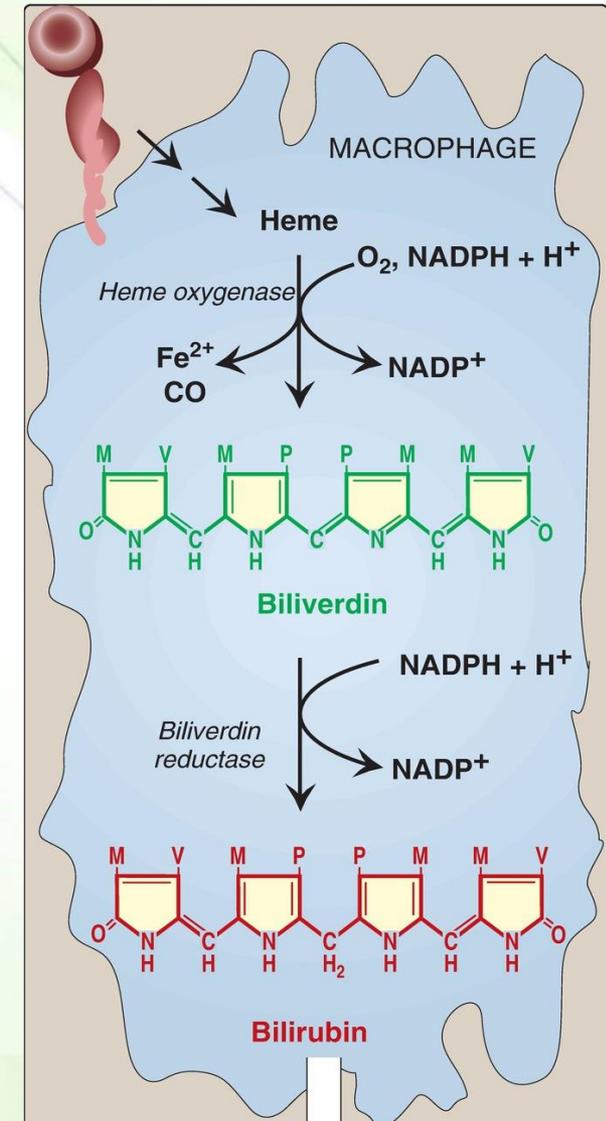


- The roles of heme oxygenase and NADPH
- The production of CO
- The world of colors

hemoglobin → biliverdin → bilirubin

bruise → healing

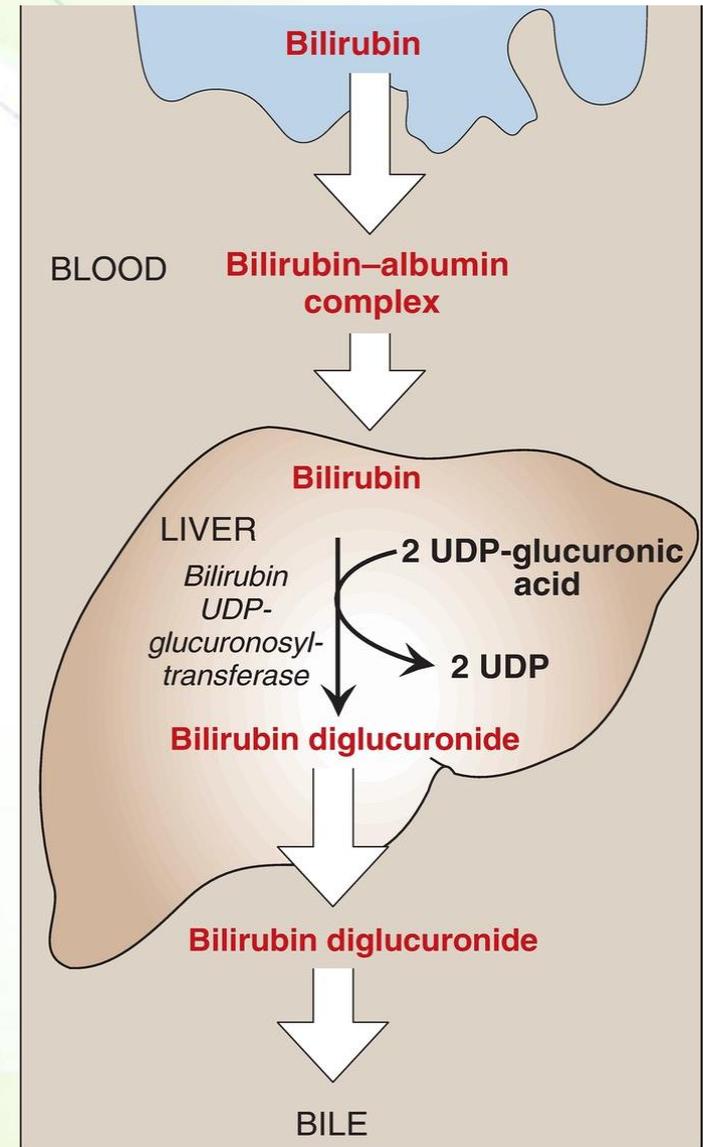
Bruise Age By Color	
Bruise Color	Bruise Age
Red (Swollen, Tender)	0 to 2 Days
Blue, Purple	2 to 5 Days
Green	5 to 7 Days
Yellow	7 to 10 Days
Brown	10 to 14 Days
No further evidence of Bruising	2 to 4 Weeks

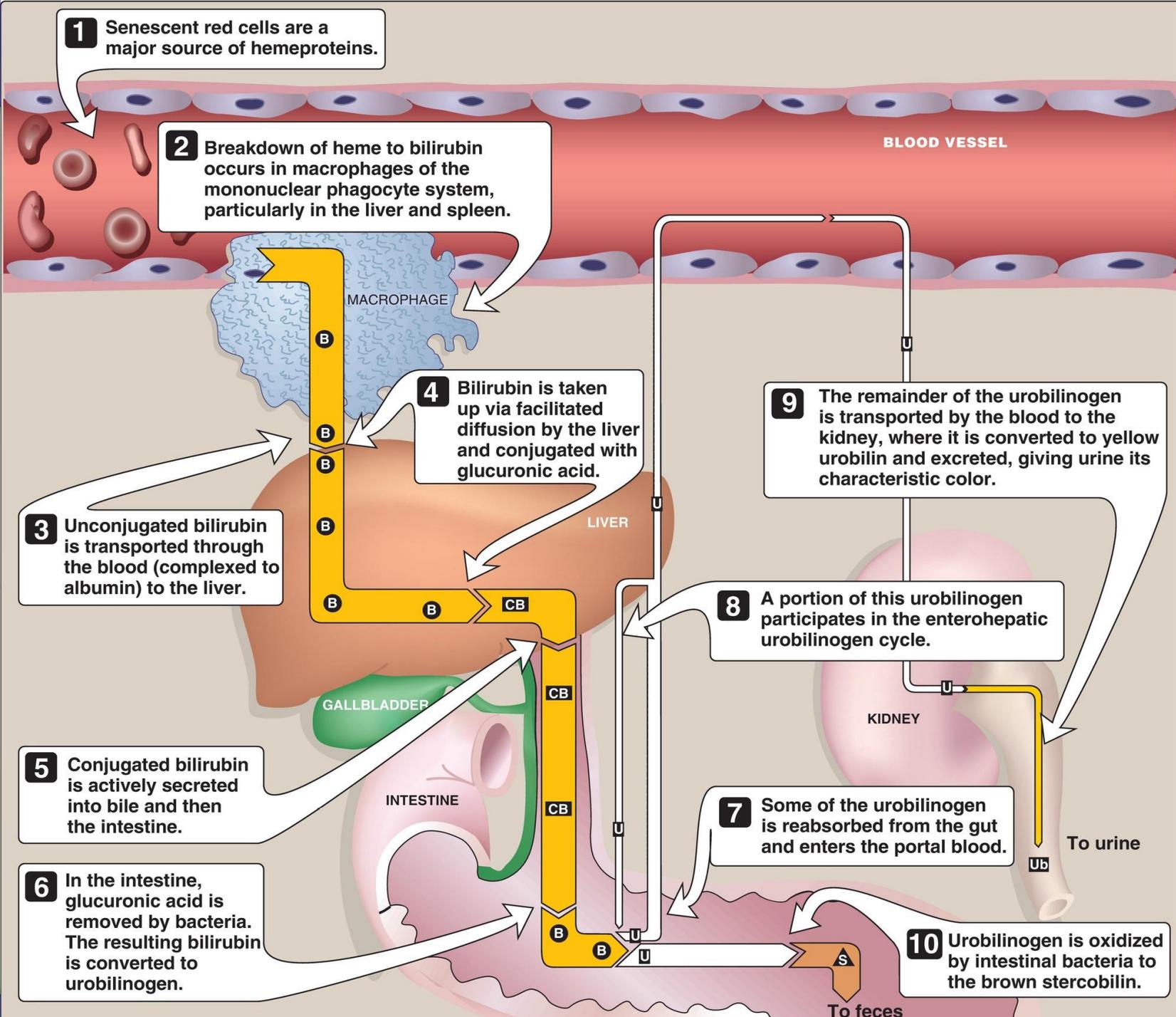


Transport of bilirubin



- The role of albumin
- Salicylates and sulfonamides can displace bilirubin from albumin permitting bilirubin to enter the central nervous system (CNS).
 - This causes the potential for neural damage in infants.
- Formation of bilirubin diglucuronide.
 - Crigler-Najjar I and II and Gilbert syndrome
- Transport into bile
 - Dubin-Johnson syndrome





1 Senescent red cells are a major source of heme proteins.

2 Breakdown of heme to bilirubin occurs in macrophages of the mononuclear phagocyte system, particularly in the liver and spleen.

3 Unconjugated bilirubin is transported through the blood (complexed to albumin) to the liver.

4 Bilirubin is taken up via facilitated diffusion by the liver and conjugated with glucuronic acid.

5 Conjugated bilirubin is actively secreted into bile and then the intestine.

6 In the intestine, glucuronic acid is removed by bacteria. The resulting bilirubin is converted to urobilinogen.

8 A portion of this urobilinogen participates in the enterohepatic urobilinogen cycle.

7 Some of the urobilinogen is reabsorbed from the gut and enters the portal blood.

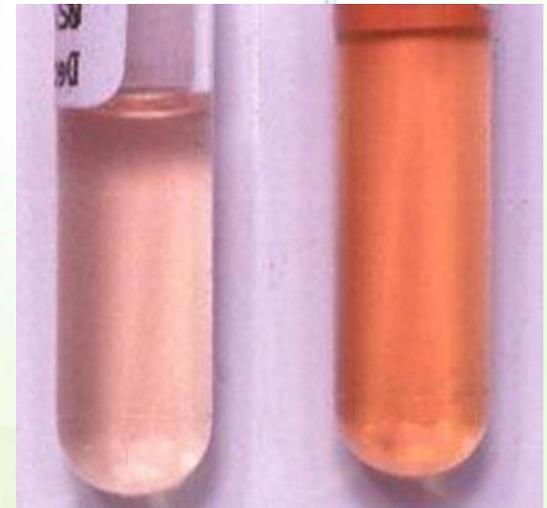
9 The remainder of the urobilinogen is transported by the blood to the kidney, where it is converted to yellow urobilin and excreted, giving urine its characteristic color.

10 Urobilinogen is oxidized by intestinal bacteria to the brown stercobilin.

Measurement of bilirubin



- It is done via a reaction known as Van den Bergh reaction.
- Direct measurement of conjugated bilirubin (in water)
- Total measurement of bilirubin (in ethanol or methanol)
- Indirect unconjugated bilirubin = total bilirubin – direct bilirubin



Lab results of jaundice



**Unconjugated
hyperbilirubinemia**

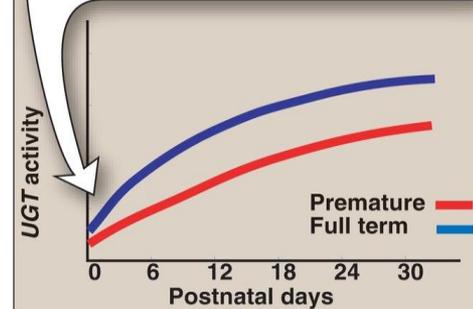
**Conjugated
hyperbilirubinemia**

Sample	Indices	Unconjugated hyperbilirubinemia		Conjugated hyperbilirubinemia	
		Normal	Hemolytic Jaundice	Hepatic Jaundice	Obstructive Jaundice
Serum	Total Bil	< 1mg/dl	> 1mg/dl	> 1mg/dl	> 1mg/dl
	Direct Bil	0 ~ 0.8mg/dl		↑	↑↑
	Indirect Bil	< 1mg/dl	↑↑		
Urine	Color	normal	deeper	deep	deep
	Bilirubin	—	—	+ +	+ +
	Urobilinogen	A little	↑	uncertain	↓
	Urobilin	A little	↑	uncertain	↓ Clayish color
Stool	Color	normal	deeper	lighter or normal	Argilous (complete obstruction)

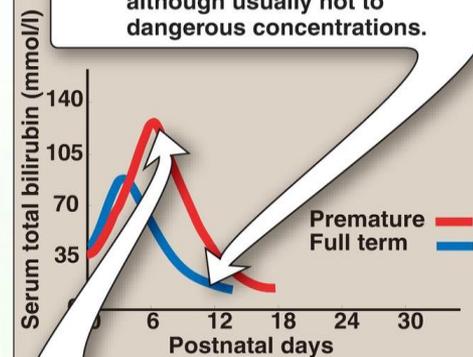
Jaundice in newborns



1 Activity of the enzyme that conjugates bilirubin with glucuronic acid, *bilirubin UDP-glucuronosyltransferase (bilirubin UGT)*, is low in newborns and especially low in premature babies.



2 Serum levels of bilirubin rise after birth in full-term infants, although usually not to dangerous concentrations.



3 Serum levels of bilirubin in premature infants may rise to toxic levels.