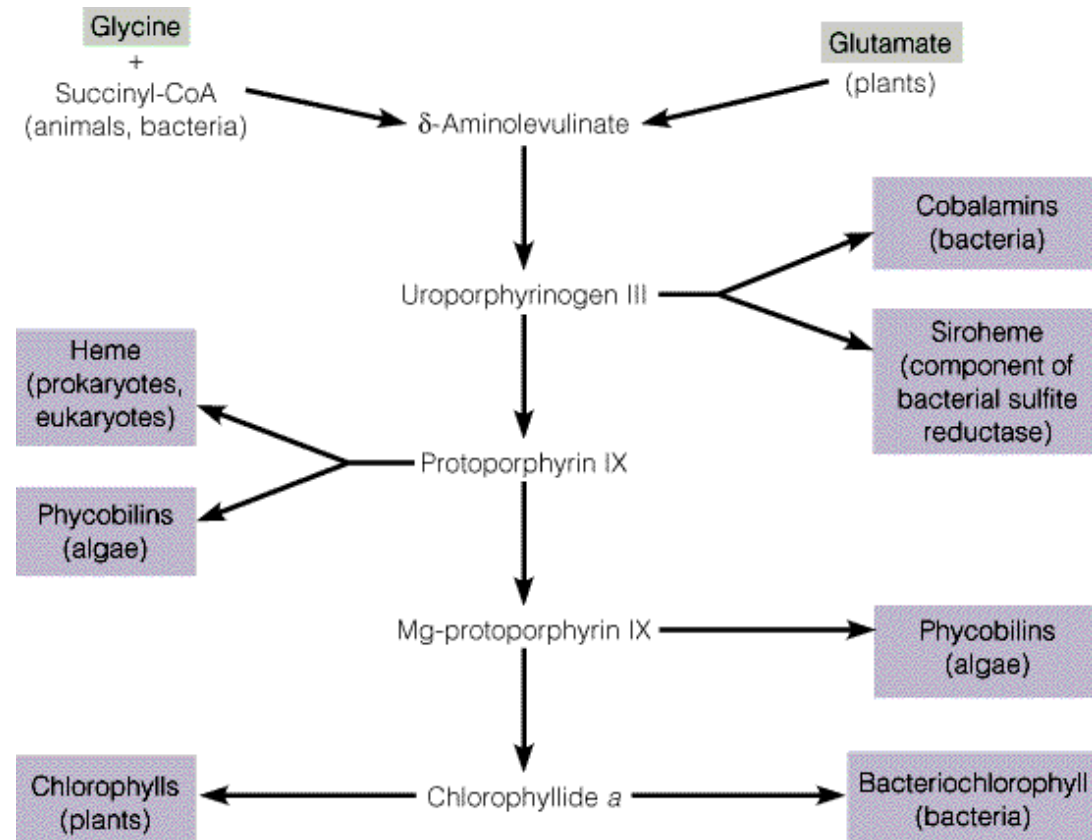


6. PORPHYRIN AND HEME METABOLISM

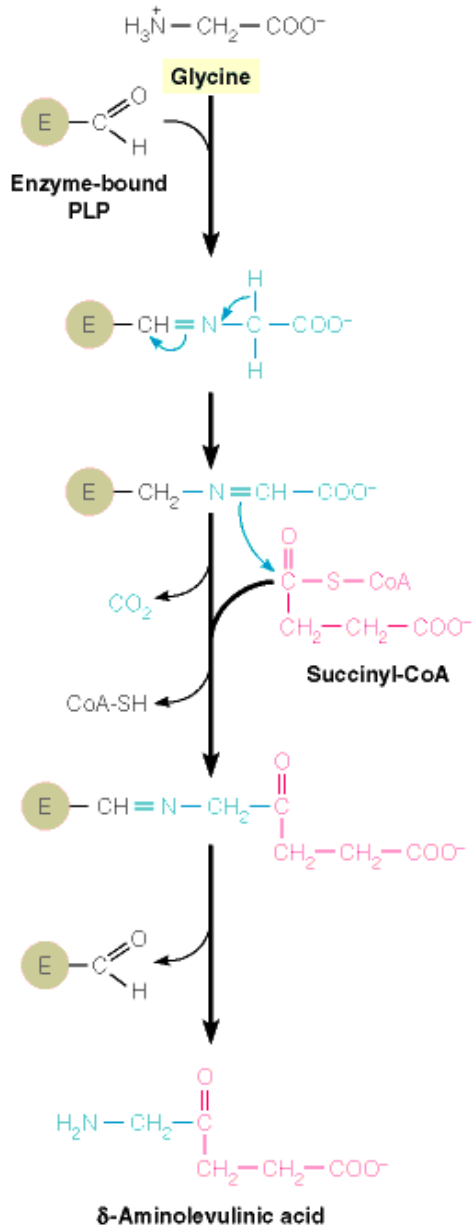
(reviews on Moodle)

PORPHYRIN

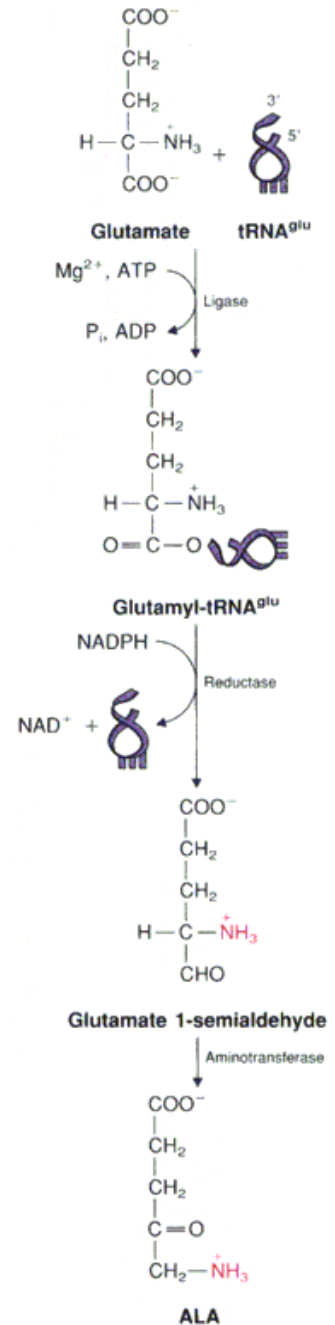
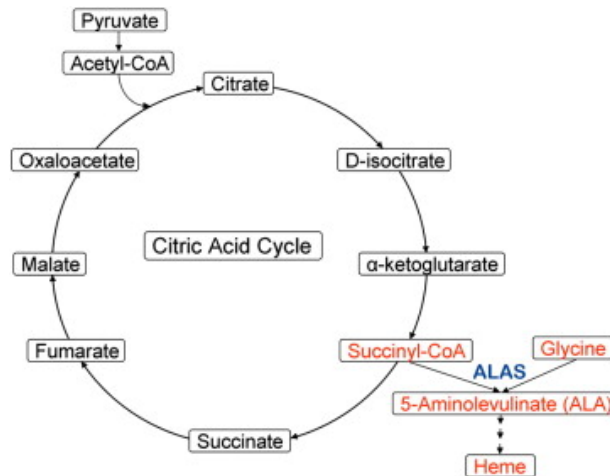
- A major metabolic fate of glycine is the biosynthesis of tetrapyrroles, compounds which contain four linked pyrrole rings. Four classes of these compounds include:
 - 1) Heme (an iron porphyrin);
 - 2) Chlorophylls;
 - 3) Phycobilins (photosynthetic pigments of algae)
 - 4) Cobalamins (Vitamin B12 and derivatives).
- All tetrapyrroles are synthesized from δ -aminolevulinic acid (ALA).



δ -Aminolevulinic acid (ALA)



- In animals, all of the nitrogens of heme are derived from glycine and all of the carbons are derived from succinate and glycine. The pathway is also called the **succinate-glycine pathway**. The first step in the process is catalyzed by a pyridoxal phosphate-containing enzyme, δ -aminolevulinic acid synthetase (ALA synthetase).
- In plants, ALA is made in a process that begins with glutamate, which becomes linked to a tRNA. In plants, synthesis of ALA is regulated by light.



HEME BIOSYNTHESIS

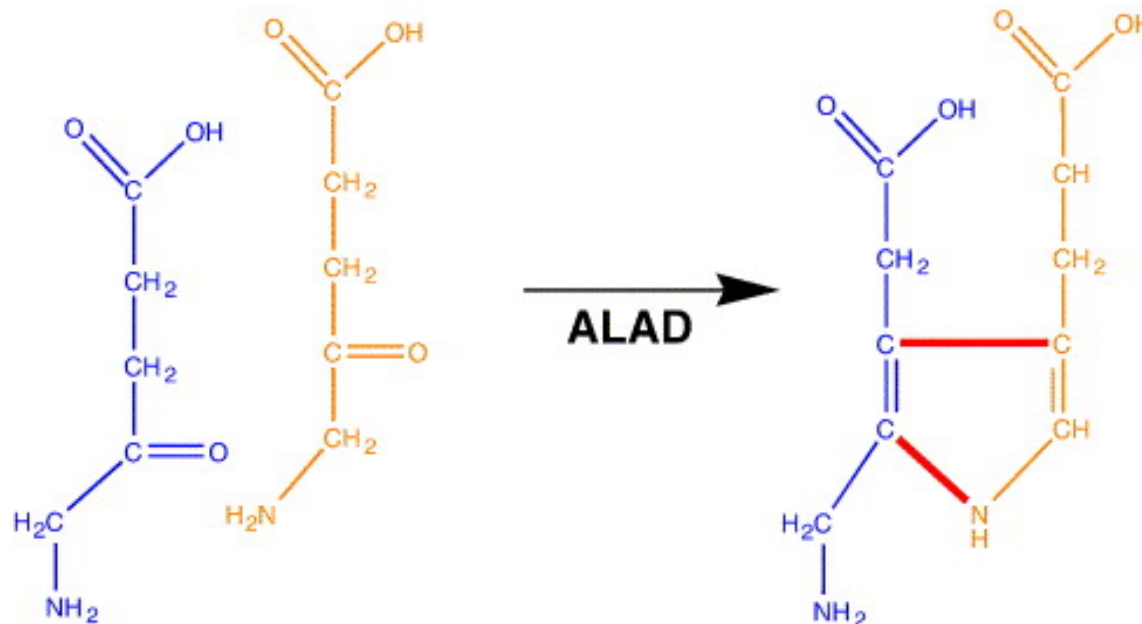
- Heme synthesis occurs in most mammalian cells except mature erythrocytes (no mitochondria)
- 85% of heme synthesis occurs in erythroid precursor cells in bone marrow, the rest in hepatocytes.

1. Heme is synthesized from succinyl-CoA and glycine.

- Pyridoxal phosphate is necessary to activate glycine.
- **Enzyme:** ALA synthase
(rate controlling enzyme in porphyrin synthesis in mammalian liver)
- **location:** mitochondria

2. In the **cytosol** 2 mol of ALA condense by **ALA dehydratase** to form 2 mol of H₂O and porphobilinogen (PBG)

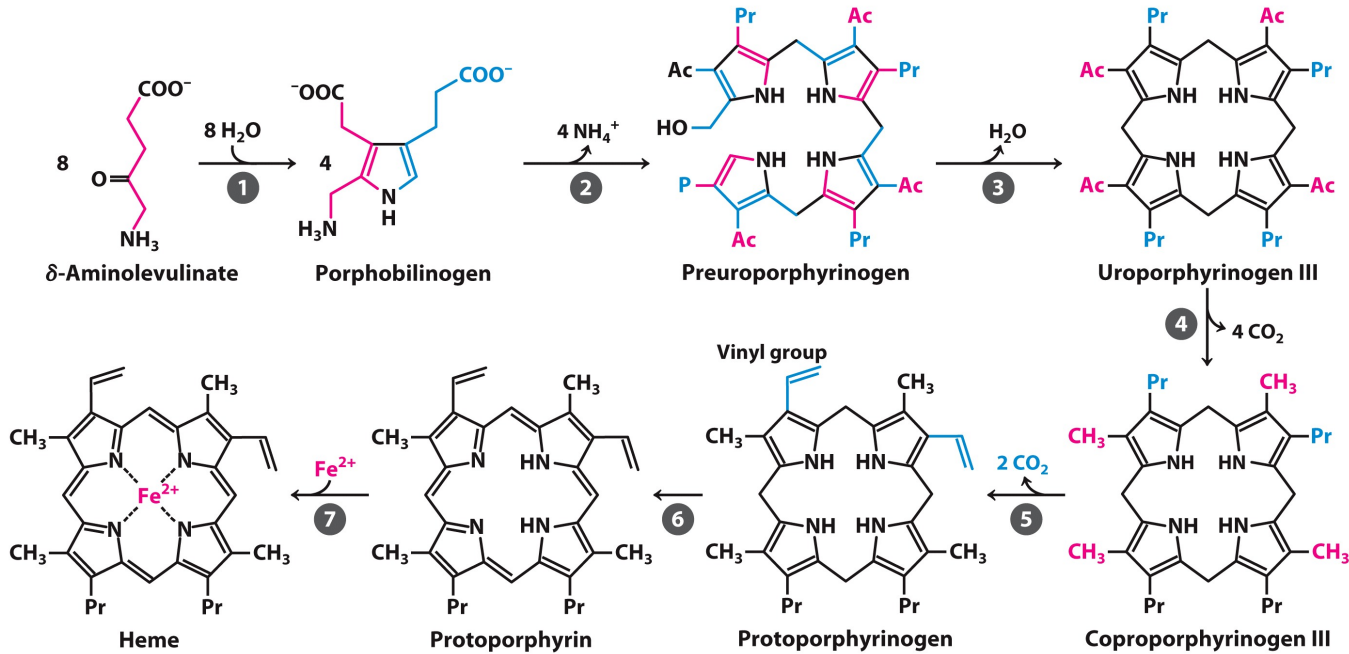
- ALA dehydratase is a zinc containing enzyme, sensitive to inhibition by lead (lead poisoning)



HEME BIOSYNTHESIS

- Heme biosynthetic enzymes have been intensively studied in recent years.
- All of the genes involved have been cloned and the crystal structures of all of the enzymes have been determined. The complex heme biosynthetic pathway can be dissected into four basic processes:

- (1) Formation of the pyrrole.
- (2) Assembly of the tetrapyrrole.
- (3) Modification of the tetrapyrrole side chains.
- (4) Oxidation of protoporphyrinogen IX to protoporphyrin IX and insertion of iron.



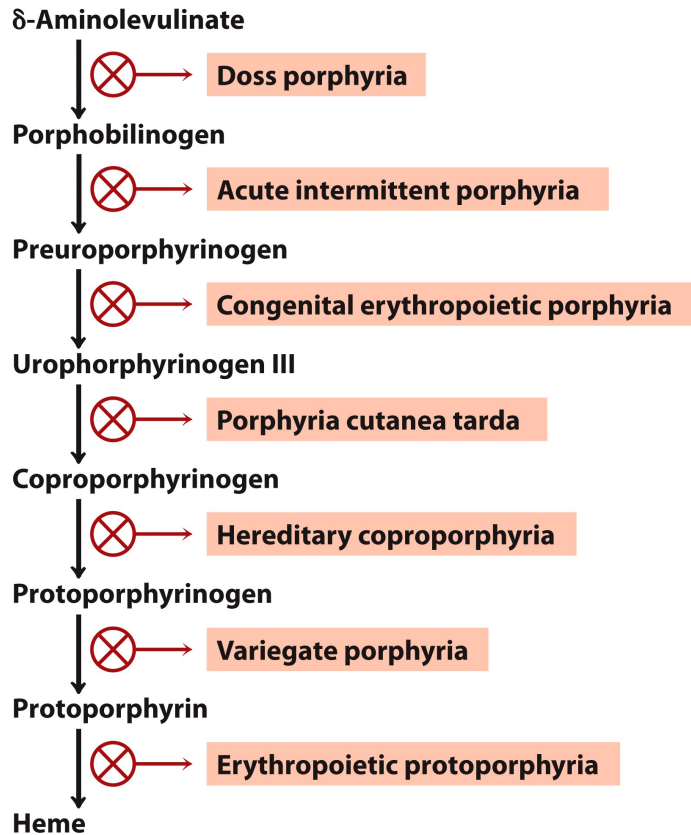
- | | | | |
|---|---------------------------------|---|----------------------------|
| 1 | porphobilinogen synthase | 5 | coproporphyrinogen oxidase |
| 2 | uroporphyrinogen synthase | 6 | protoporphyrinogen oxidase |
| 3 | uroporphyrinogen III cosynthase | 7 | ferrochelatase |
| 4 | uroporphyrinogen decarboxylase | | |

mitochondria

Figure 22-26
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HEME BIOSYNTHESIS

The porphyrias are a group of rare diseases in which chemical substances called porphyrins accumulate with high metabolism.



Box 22-2
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George III in his coronation robes



Maria I of Portugal in a c. 1790s

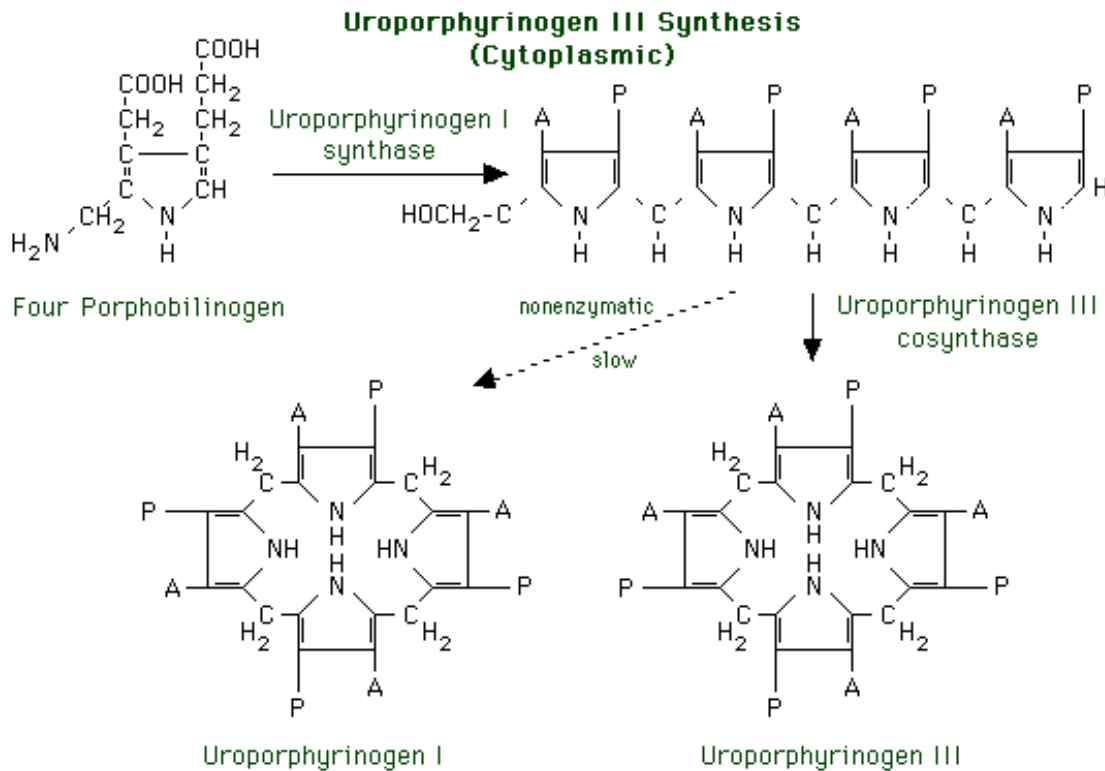


Mary Stuart c. 1578.

HEME BIOSYNTHESIS

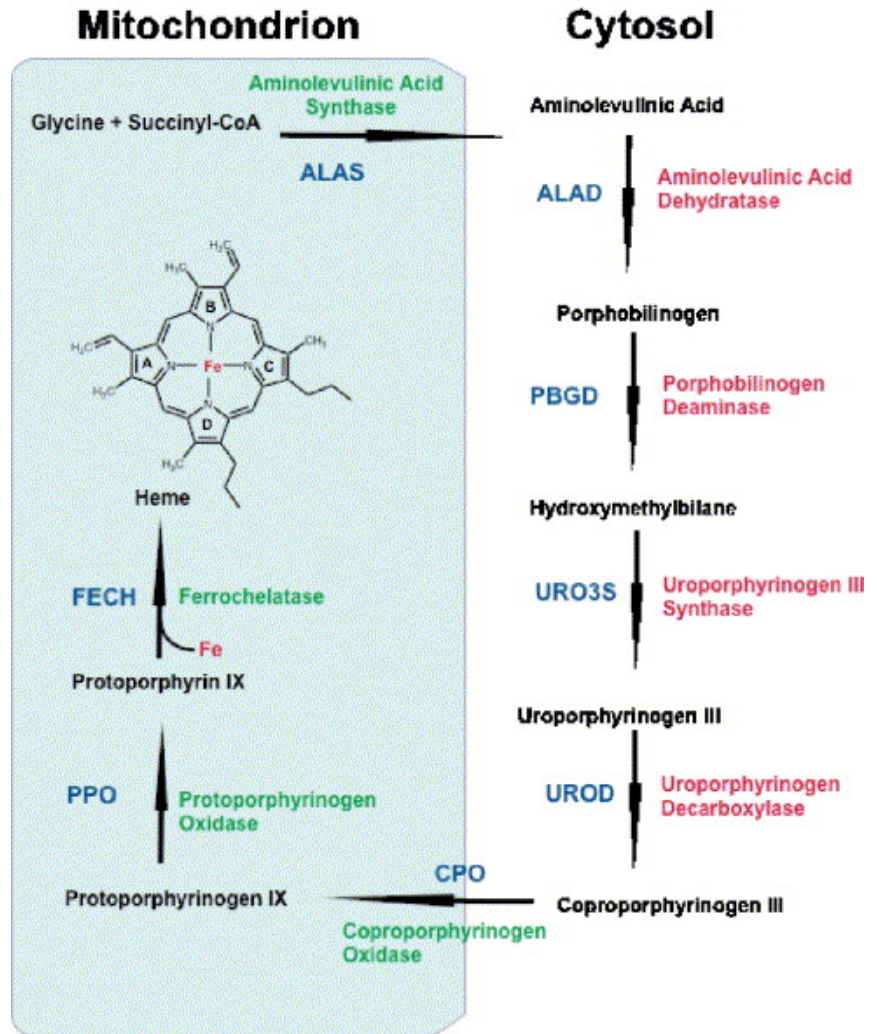
Porphyrins: the vampire diseases

Note that uroporphyrinogen III is an asymmetric compound. It arises from action of uroporphyrinogen I synthase and uroporphyrinogen III cosynthase. If only the first enzyme is active, the symmetric compound, uroporphyrinogen I is produced. In the hereditary condition called congenital erythropoietic porphyria, the uroporphyrinogen III cosynthase is defective and the symmetric type I porphyrins accumulate, causing the urine to turn red, the skin to become photosensitive, and the teeth to become fluorescent. Because insufficient heme is produced, anemia results.



HEME BIOSYNTHESIS REGULATION

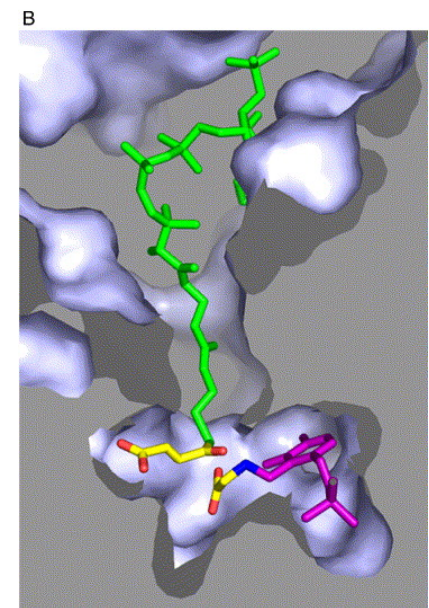
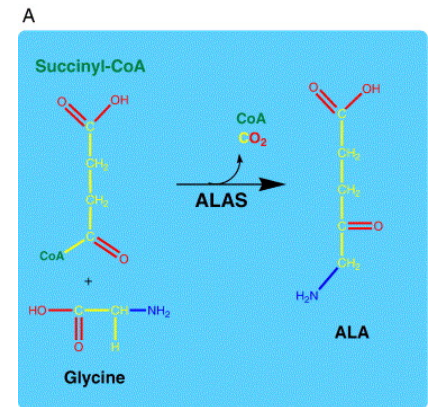
- Most iron in mammalian systems is routed to mitochondria to serve as a substrate for ferrochelatase.
- Ferrochelatase inserts iron into protoporphyrin IX to form heme which is incorporated into hemoglobin and cytochromes, the dominant hemoproteins in mammals.
- Tissue-specific regulatory features characterize the heme biosynthetic pathway.
- In erythroid cells, regulation is mediated by erythroid-specific transcription factors and the availability of iron as Fe/S clusters.
- In non-erythroid cells the pathway is regulated by heme-mediated feedback inhibition.



The heme biosynthetic pathway. Mitochondrial enzymes are depicted in green and cytosolic enzymes in red. Abbreviations used in the text are capitalized.

HEME BIOSYNTHESIS REGULATION

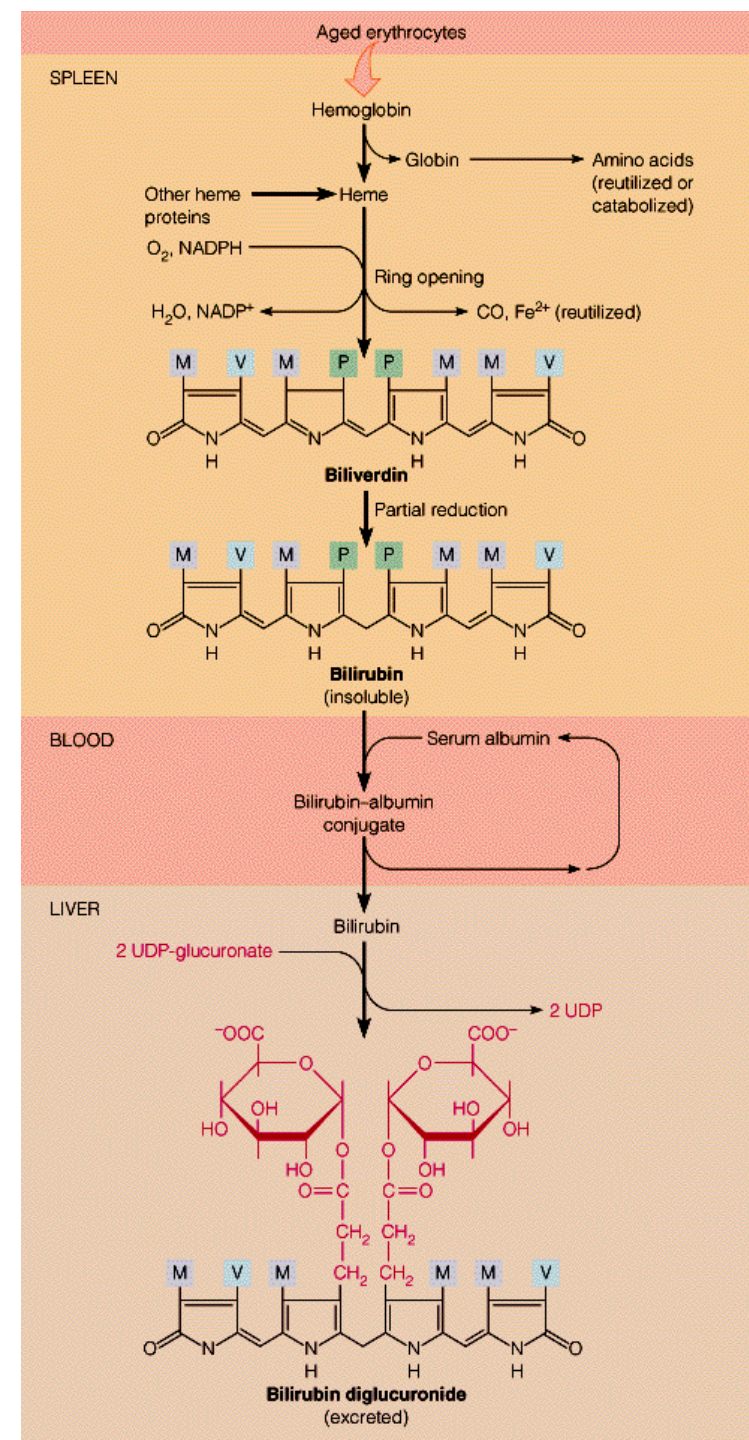
- The major regulatory step in heme synthesis is the ALA synthetase reaction. Through **feedback inhibition**, heme regulates the enzyme.
- Heme also inhibits the **translation** of ALA synthetase.
- At even higher levels, heme blocks **transport** of ALA synthetase to the mitochondrion - its site of action.
- The reaction is catalyzed by two different ALA synthases, one expressed ubiquitously (ALAS1) and the other expressed only erythroid precursors (ALAS2).
- Regulation of these two forms of ALAS is mediated by different mechanisms but both forms require pyridoxal 5-phosphate (PLP) as a cofactor.



(A) Synthesis of 5-aminolevulinic acid (ALA). Decarboxylation of glycine followed by condensation with Succinyl-CoA is catalyzed by aminolevulinic acid synthase (ALAS). Pyridoxal Phosphate is required as a co-factor. The products are ALA, CO₂ and CoA. (B) The crystal structure of the active site of *R. capsulatus* ALAS. Pyridoxal Phosphate (PLP) (fuchsia), first forms a covalent linkage with lysine (lys 391 in human ALAS). Incoming glycine induces a transient trans-aldimine (Schiff base) with PLP binding glycine rather than lysine. Succinyl-CoA (green) is condensed with the α carbon of glycine with the displacement of CoA (green) and the carboxyl group of glycine (yellow and red). ALA is released and PLP rebinds to the lysine of ALAS.

HEME DEGRADATION

- Heme degradation - Erythrocytes have a lifetime of about 120 days. Aged erythrocytes are destroyed upon passage through the spleen or liver. The basic pathway of heme breakdown is the following:
- Heme → Biliverdin → Bilirubin → (passage through blood to liver as bilirubin-albumin complex) → Bilirubin Diglucuronide → excretion.
- Bilirubin is insoluble in aqueous solutions, so complexing with albumin and gluconic acid is essential for passage through the body. Accumulation of bilirubin in the blood leads to icterus.



HEME DEGRADATION

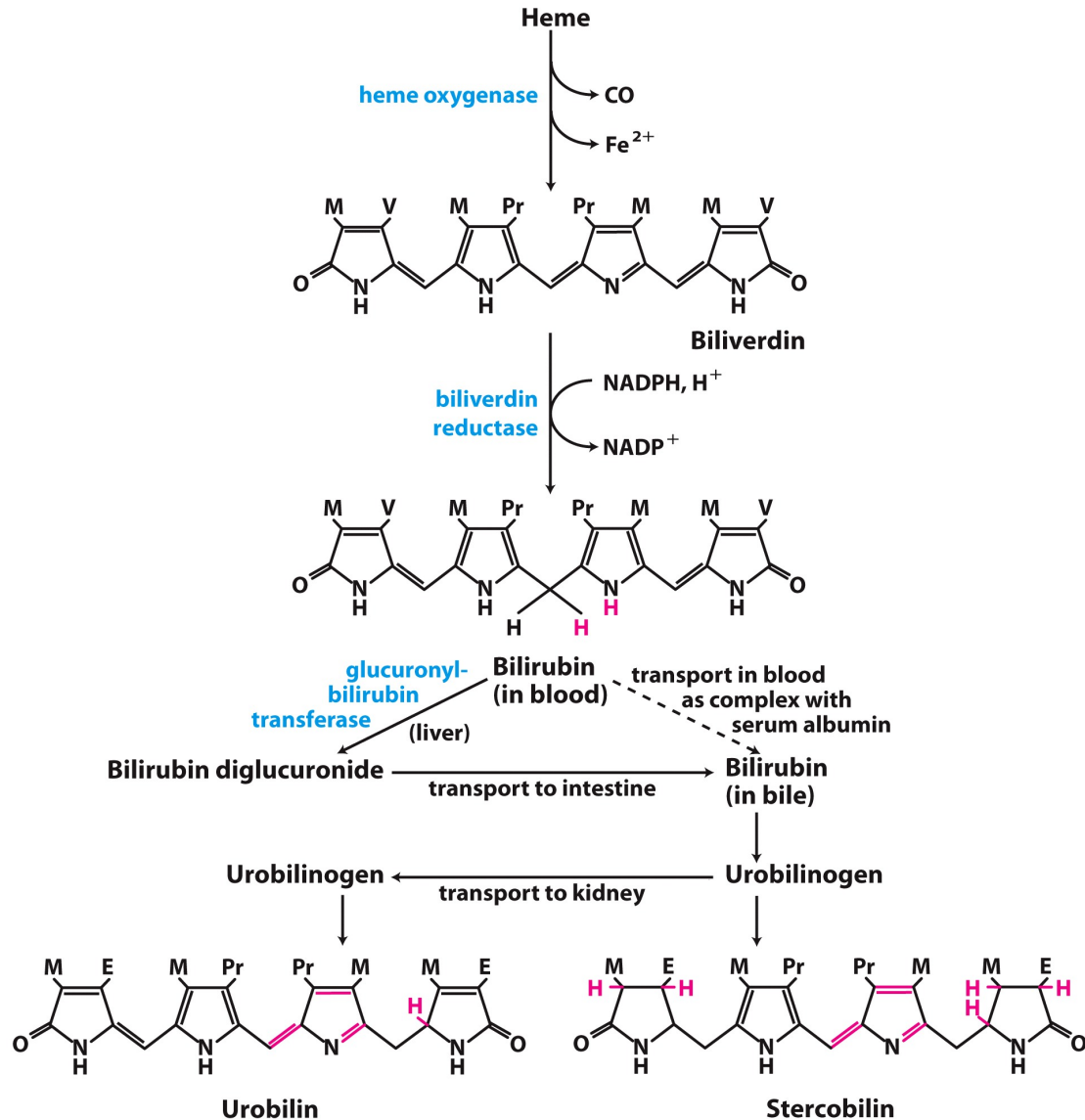
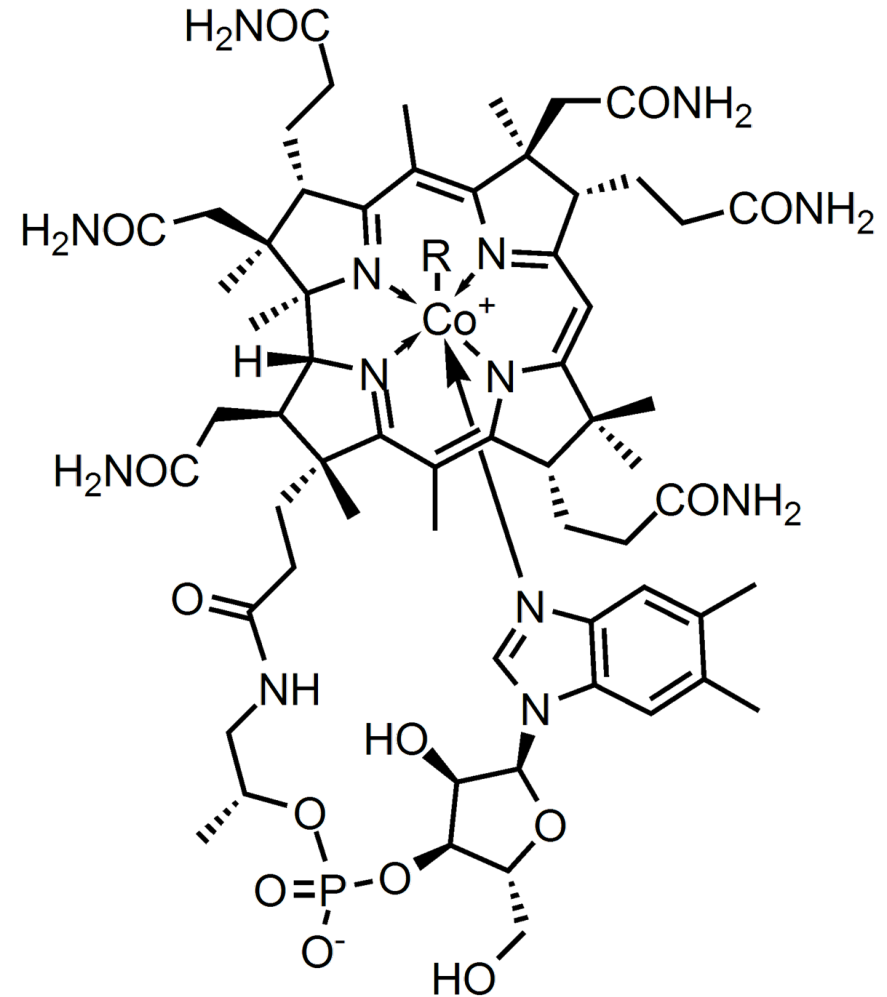


Figure 22-27

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COBALAMINS: VITAMIN B₁₂

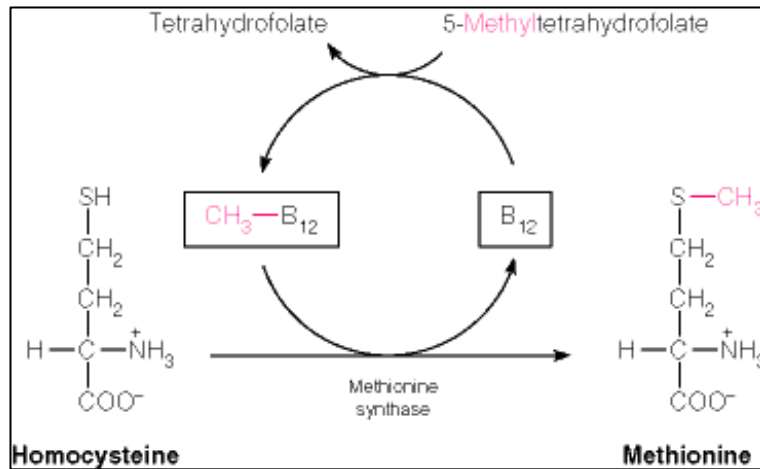
- The metal cobalt in vitamin B₁₂ is coordinated with a tetrapyrrole ring system, called a corrin ring, which is similar to the porphyrin ring of heme compounds.
- The cyanide attached to the cobalt in the structure is an artifact of the isolation and is replaced by water or a hydroxyl group in cells.
- The presence of cobalt and amide nitrogens gives B₁₂ compounds the name cobamides or cobalamins.
- About 15 different B₁₂-requiring reactions are known, most of which occur in a few bacterial species that carry out specialized fermentations.



R = 5'-deoxyadenosyl, Me, OH, CN

COBALAMINS: VITAMIN B₁₂

- Only two reactions occur to a significant extent in mammalian metabolism: the synthesis of methionine from homocysteine (see below) and isomerization of D-methylmalonyl-CoA to succinyl-CoA.



DMB: 5,6-dimethylbenzimidazole

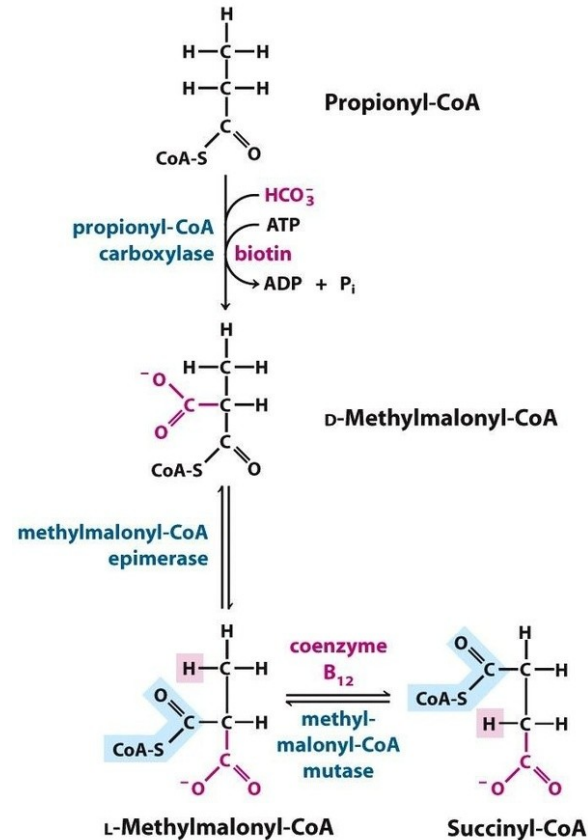


Figure 17-11
Lehninger Principles of Biochemistry, Fifth Edition
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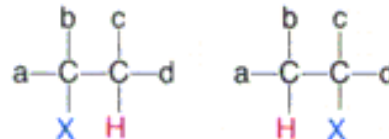
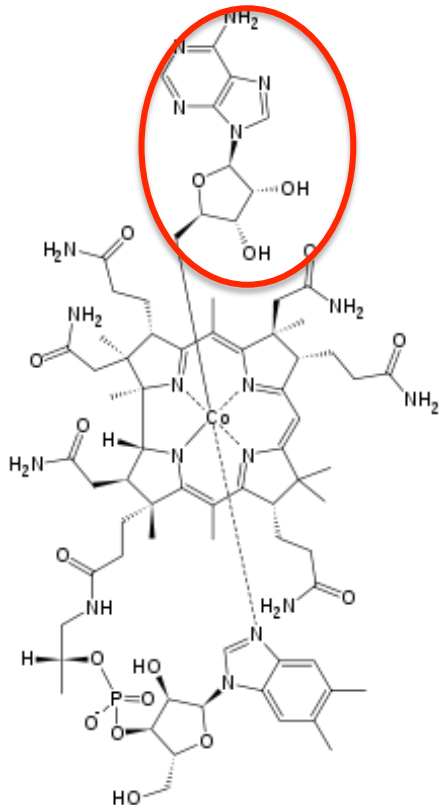
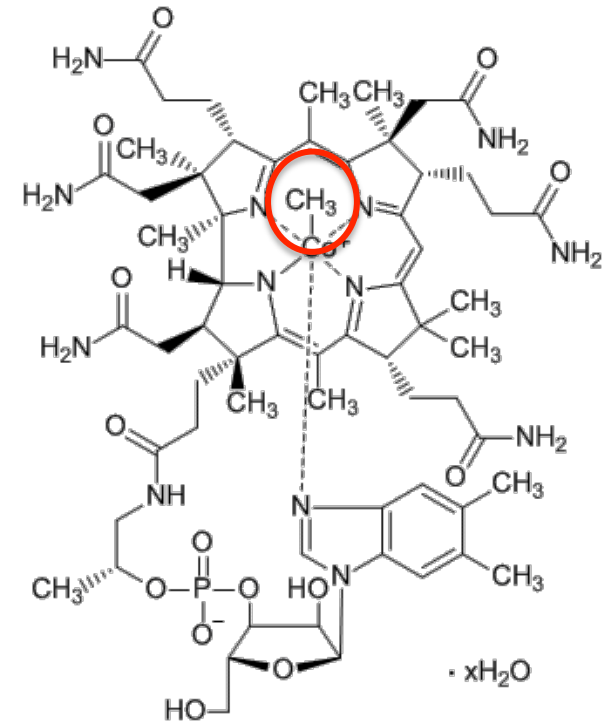
Oxidation of Odd-Numbered Fatty Acids: the intramolecular rearrangement catalyzed by methylmalonyl-CoA mutase.

COBALAMINS: VITAMIN B₁₂

- With one exception, the known B12-requiring reactions involve either

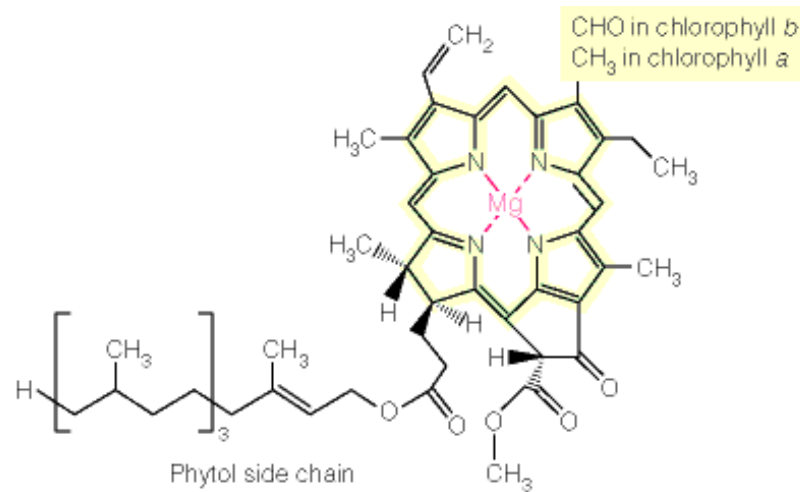
(1) methyl group transfer or

(2) adenosylcobalamin-dependent isomerizations. The isomerizations exchange a carbon-bound hydrogen with another carbon-bound functional group as shown here.

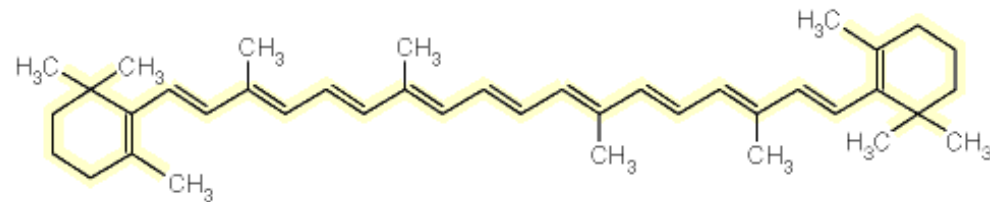


B12 coenzymes have either a methyl group or a 5'-adenosyl moiety linked to cobalt making them the first known organometallics in metabolism

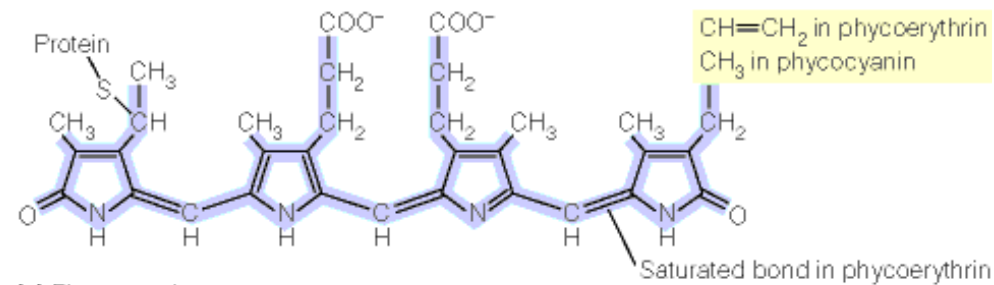
CHLOROPHYLLS



(a) Chlorophylls a and b



(b) β -Carotene



(c) Phycocyanin