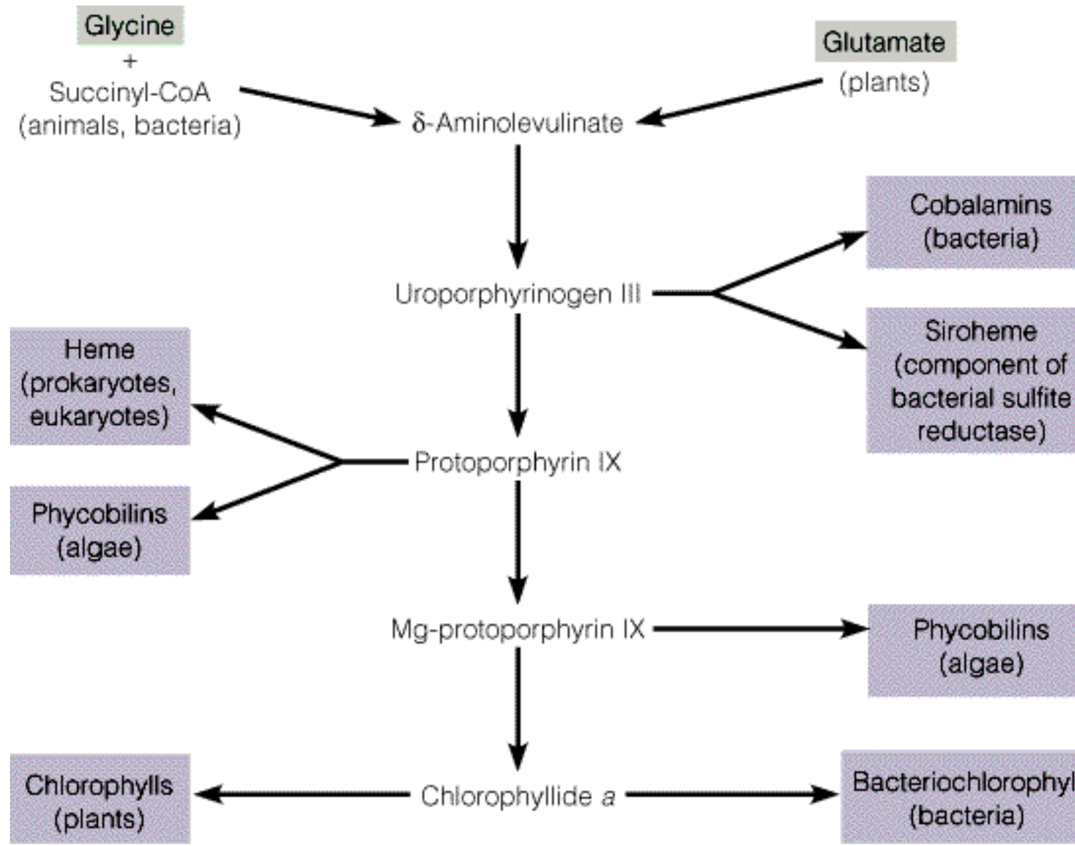
PORPHYRIN AND HEME METABOLSIM

PORPHYRIN

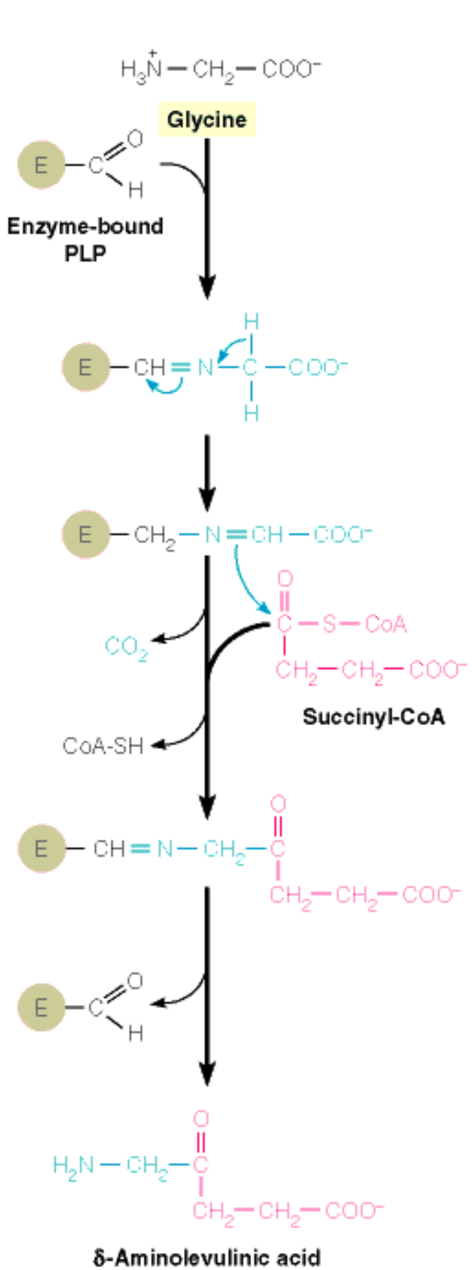
- A major metabolic fate of glycine is the biosynthesis of tetrapyrroles, compounds which contain four linked pyrrole rings. Four classes of these compounds include:

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).

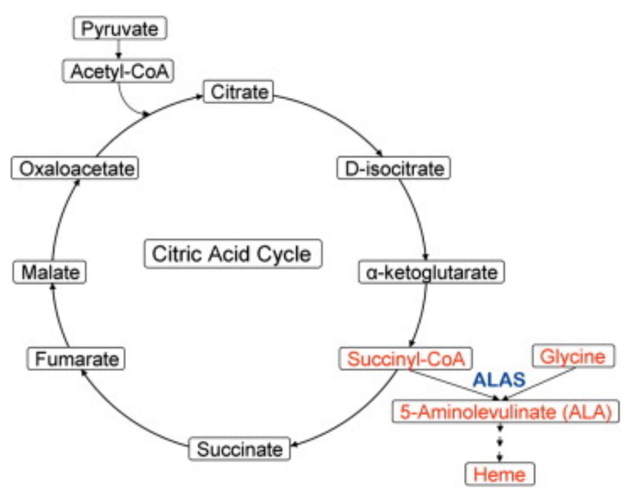


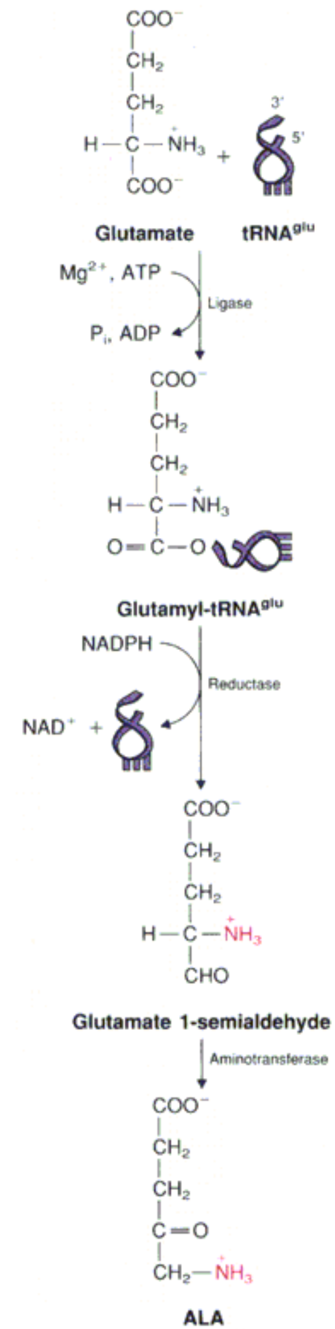
δ-Aminolevulinic acid (ALA)



- 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 synthestase).

- 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.

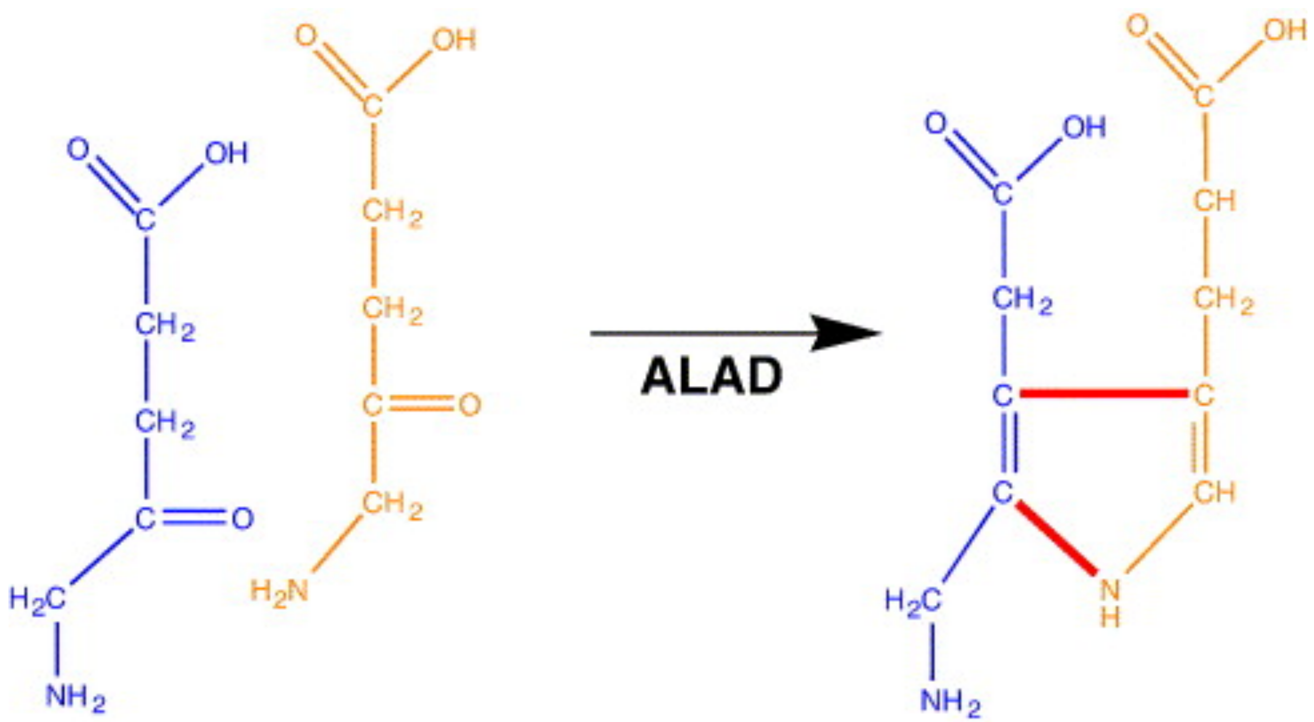




HEME BIOSYNTHESIS

1. All of the nitrogen in heme is derived from glycine and all of the carbons are derived from succinate and glycine. Thus, the process by which heme is synthesized 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).

2. The next step is the synthesis of a substituted pyrrole compound, porphobilinogen from ALA.



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.

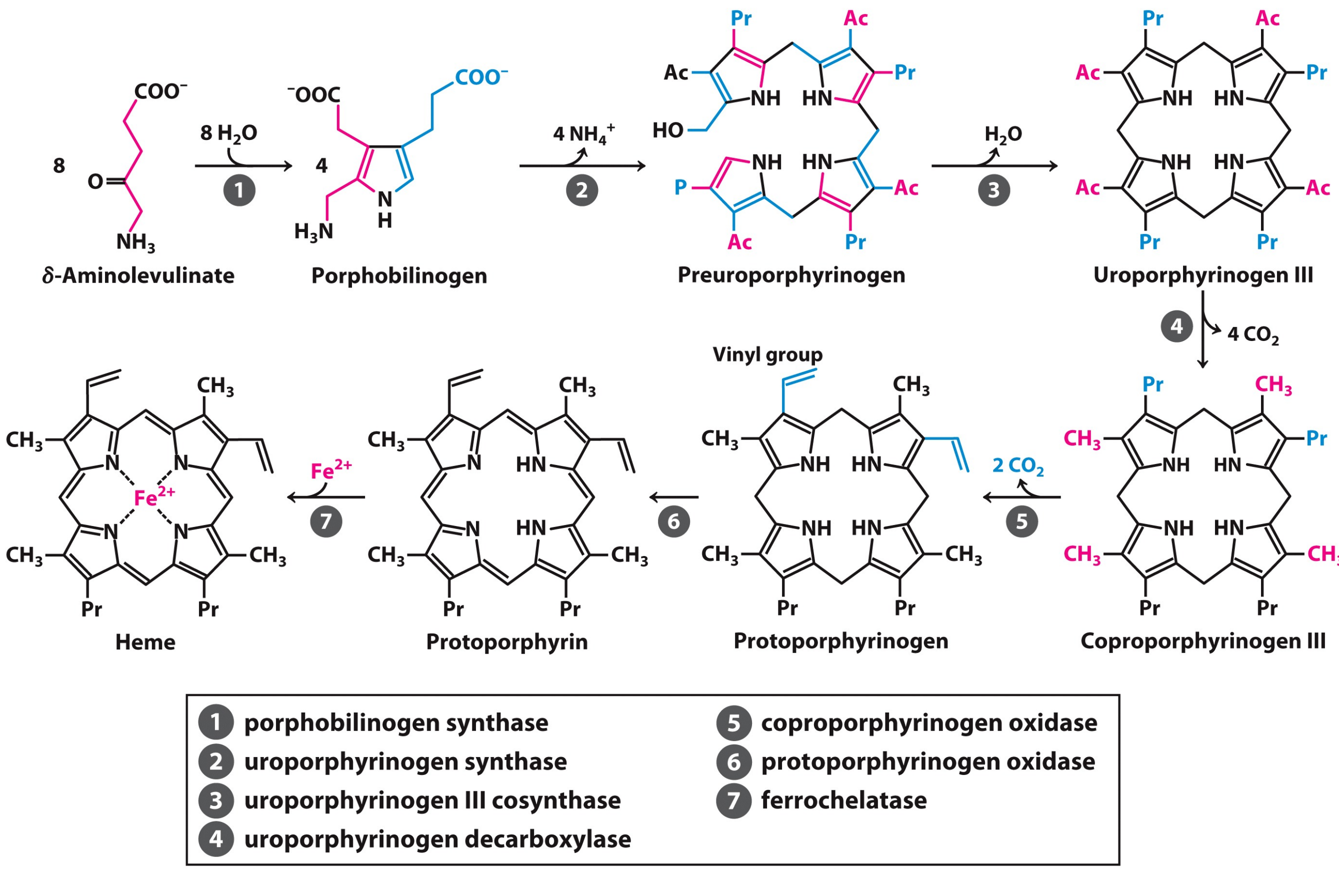
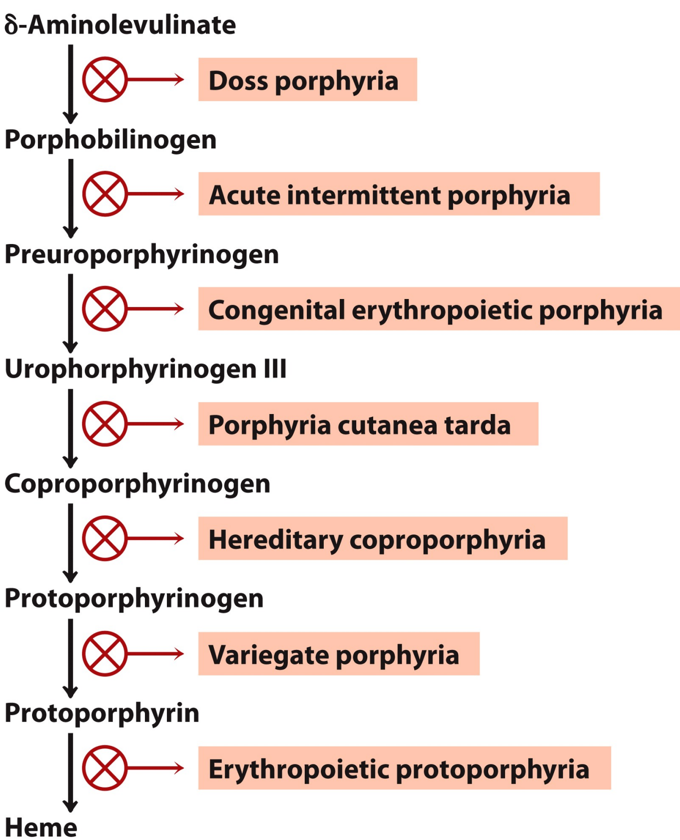


Figure 22-26
Lehninger Principles of Biochemistry, Sixth Edition

HEME BIOSYNTHESIS

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



Box 22-2
Lehninger Principles of Biochemistry, Sixth Edition

George III in his coronation robes

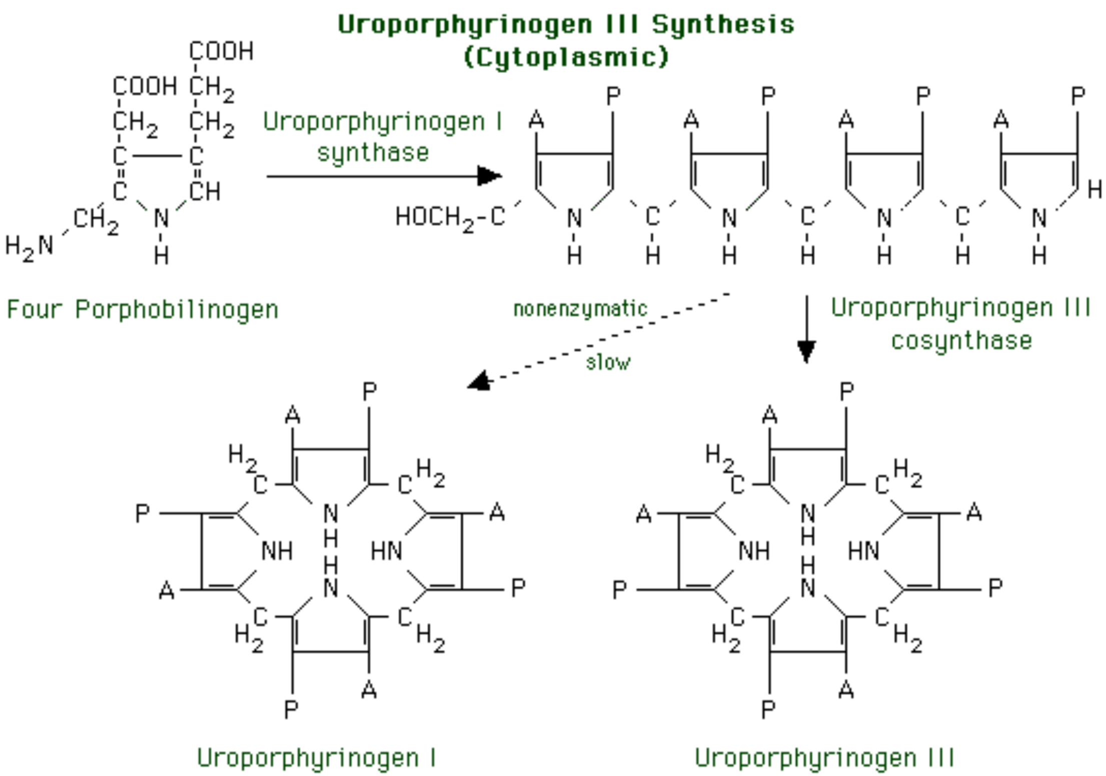
Maria I of Portugal in a c. 1790s

Mary Stuart c.1578.

HEME BIOSYNTHESIS

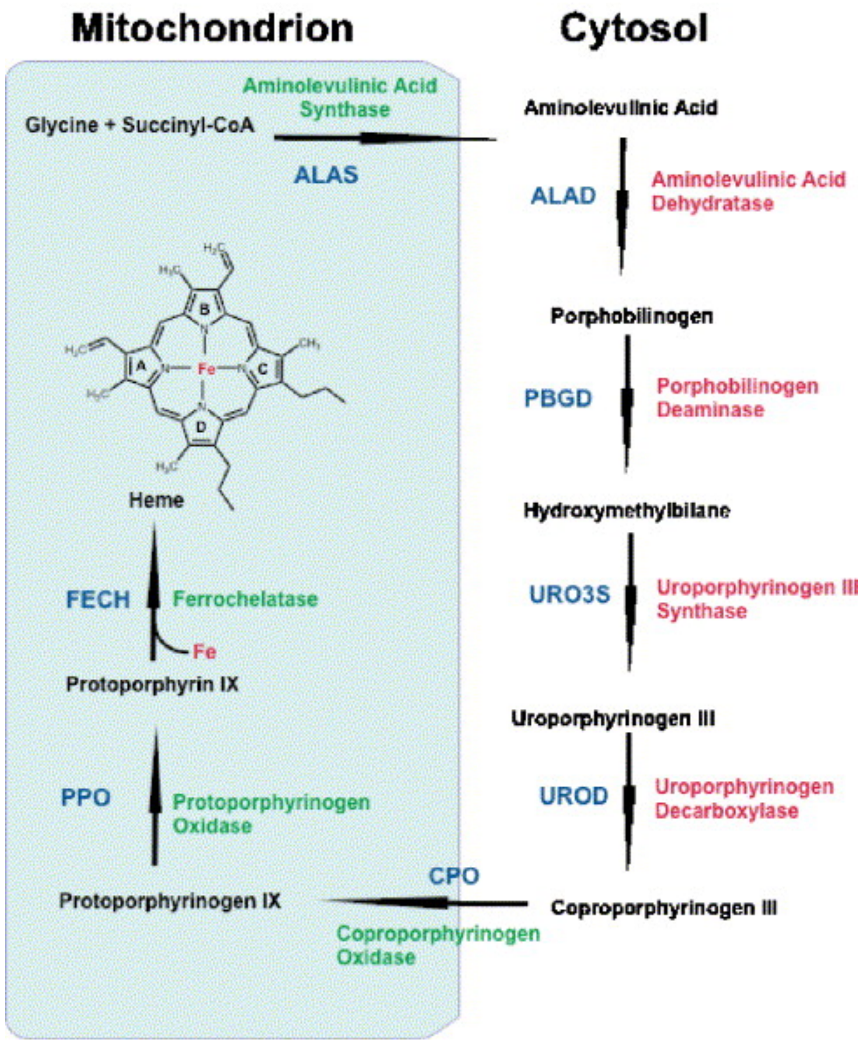
Porphirias: the vampire diseases

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

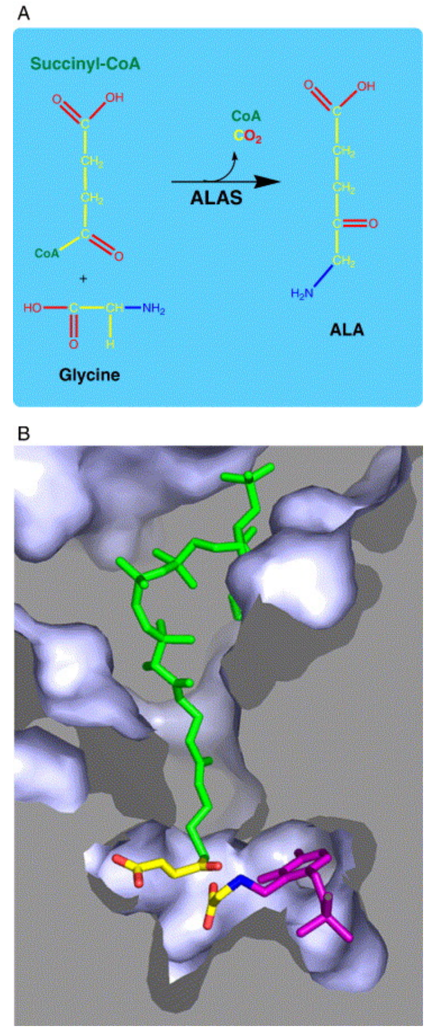
- Most iron in mammalian systems is routed to mitochondria to serve as a substrate for ferrochelatase.
- Ferrochelatase inserts iron into protoporphyrin IX to form heme which is incorporated into hemoglobin and cytochromes, the dominant hemoproteins in mammals.
- Tissue-specific regulatory features characterize 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.

Biochimica et Biophysica Acta (BBA) - Molecular Cell Research, Volume 1763, Issue 7, 2006, 723–736

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, CO_2 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.

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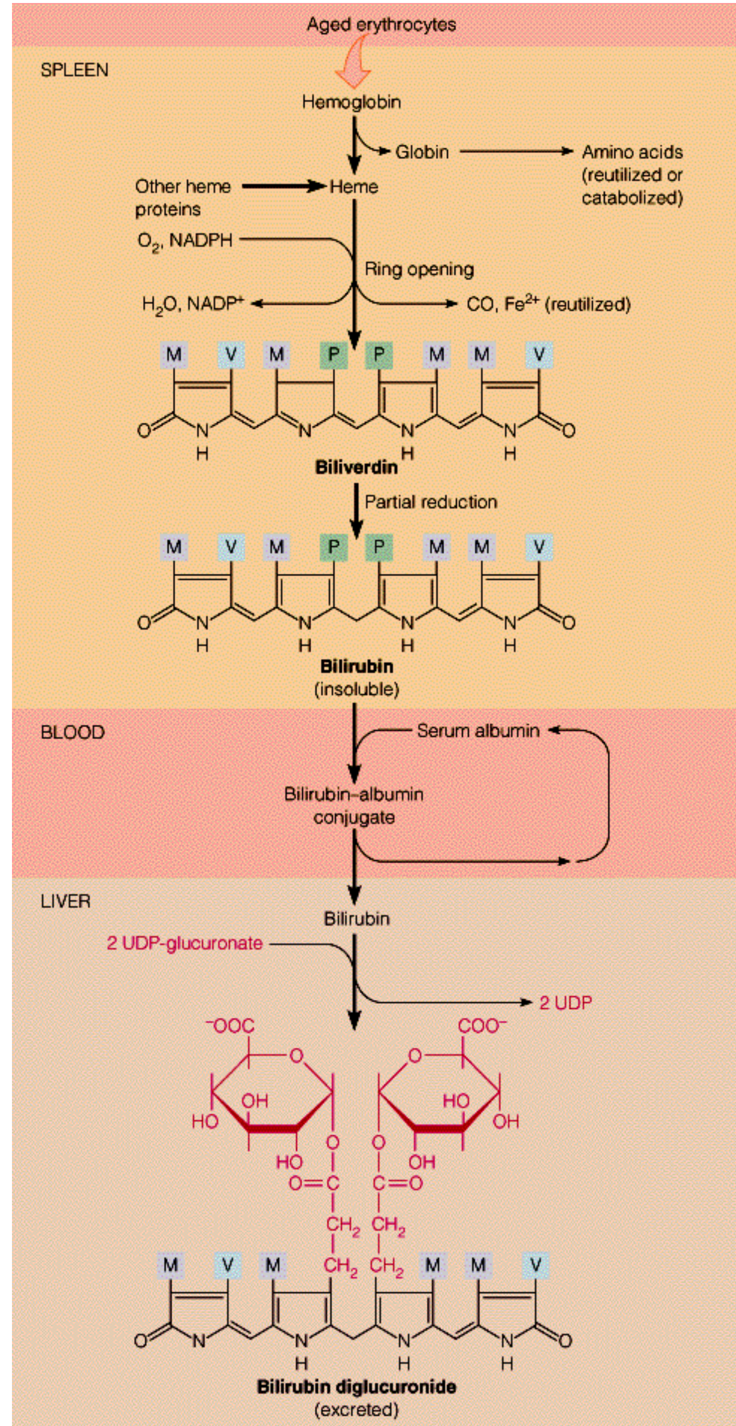
HEME DEGRADATION

- 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 gluruonic acid is essential for passage through the body. Accumulation of bilirubin in the blood leads to icterus.



HEME DEGRADATION

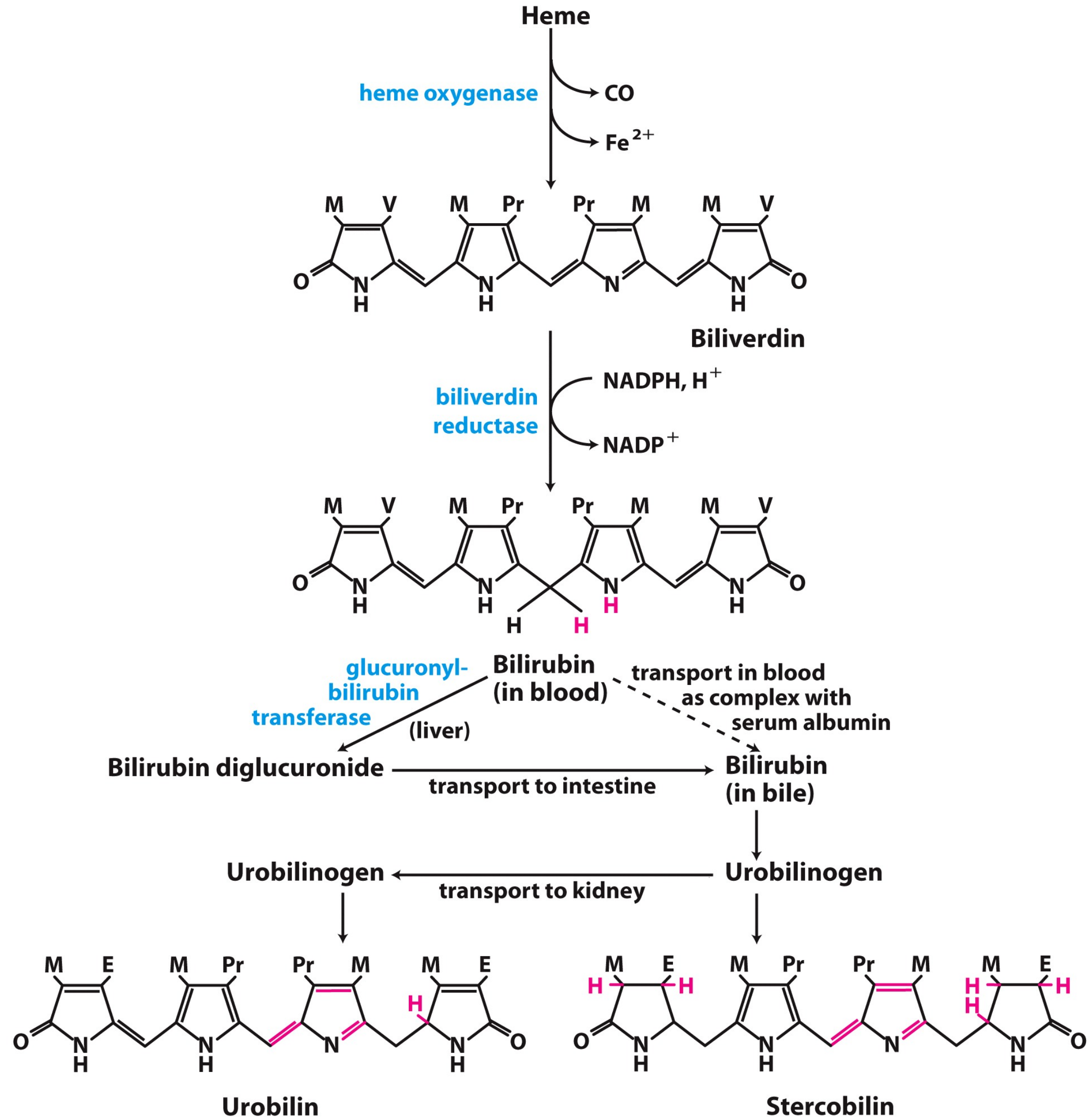
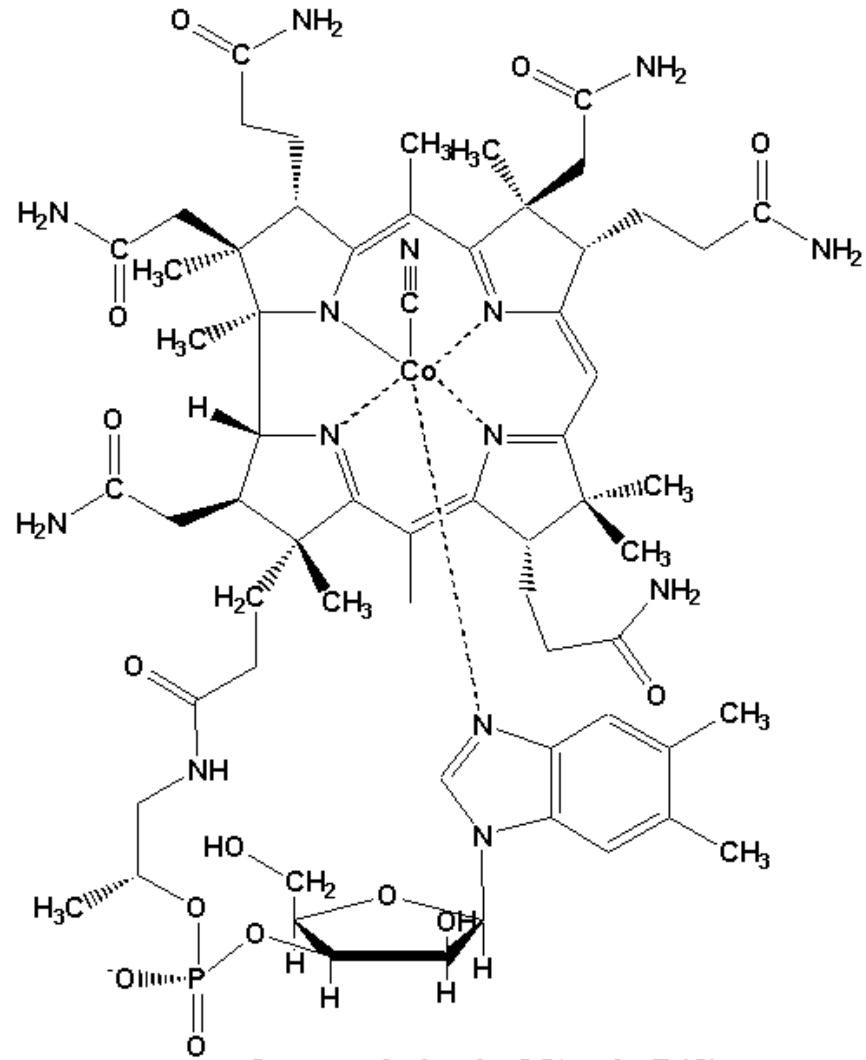


Figure 22-27
Lehninger Principles of Biochemistry, Sixth Edition

COBALAMINS: VITAMIN B_{12}

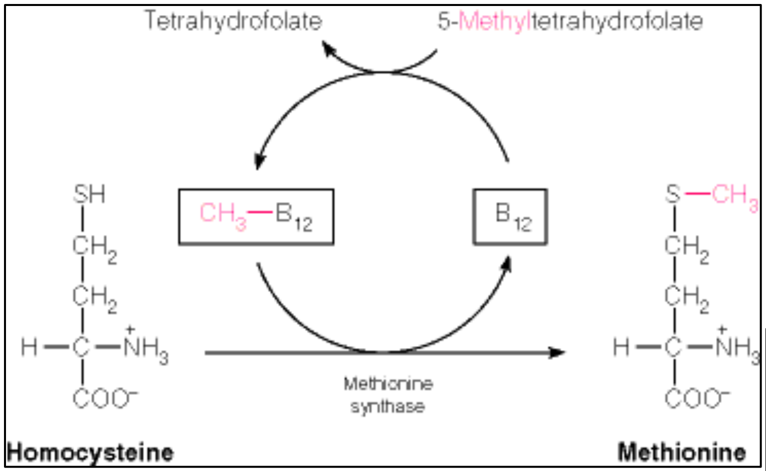
- The metal cobalt in vitamin B_{12} is coordinated with a tetrapyrrole ring system, called a corrin ring, which is simiilar to the porphyrin ring of heme compounds.
- The cyanide attached to the cobalt in the structure is an artifact of the isolation and is replaced by water or a hyrdoxyl group in cells.
- The presence of cobalt and amide nitrogens gives B_{12} compounds the name cobamides or cobalamins.
- About 15 different B_{12}-requiring reactions are known, most of which occur in a few bacterial species that carry out specialized fermentations.

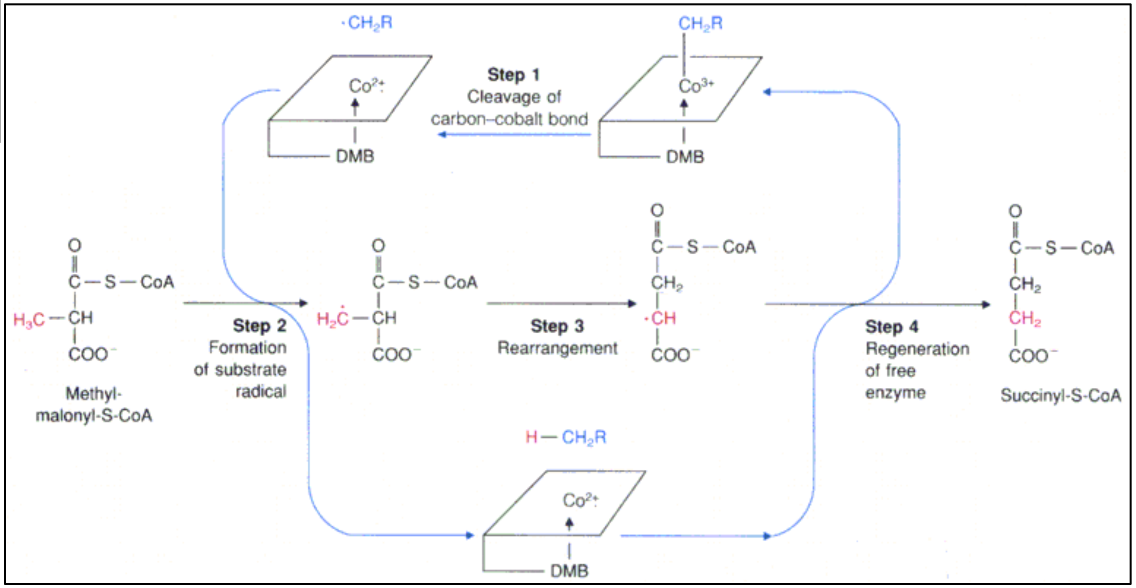


Cyanocobalamin (Vitamin B12)

COBALAMINS: VITAMIN B_{12}

- 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

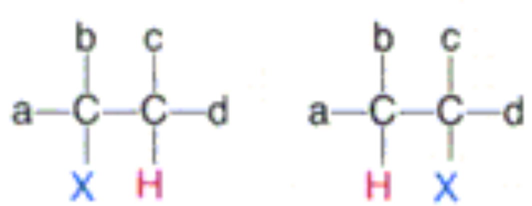
Oxidation of Odd-Numbered Fatty Acids: the intramolecular rearrangement catalyzed by methylmalonyl-CoA mutase.

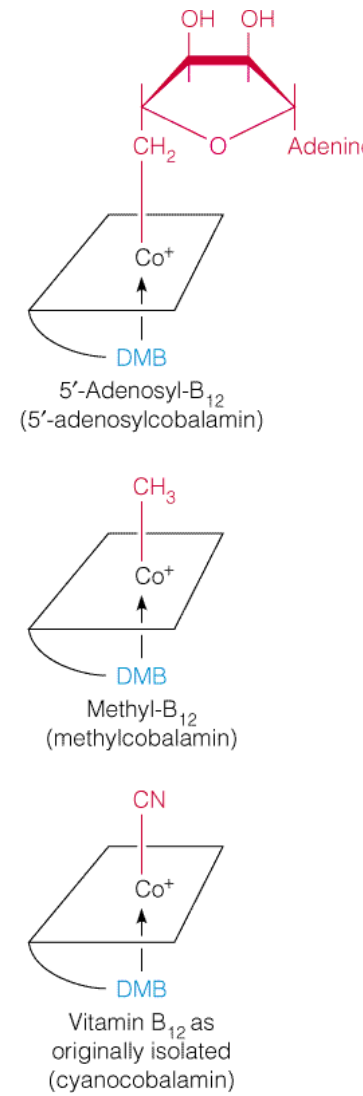
COBALAMINS: VITAMIN B_{12}

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

(1) methyl group transfer or

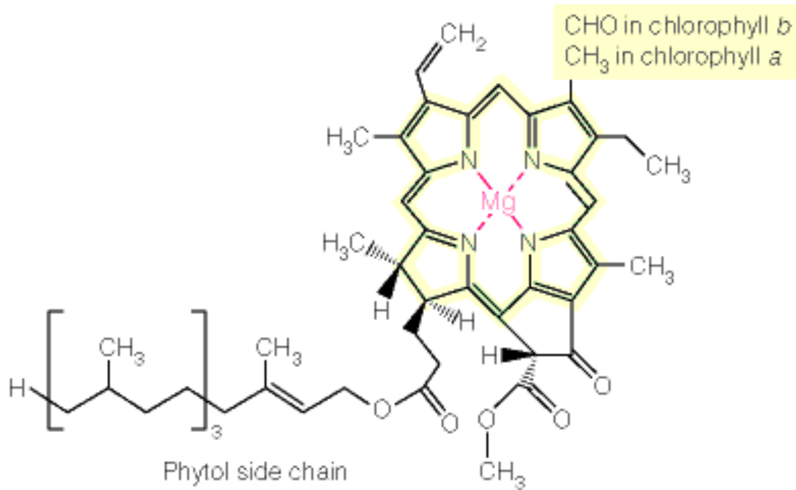
(2) adenosylcobalamin-dependent isomerizations. The isomerizations exchange a carbon-bound hydrogen with another carbon-bound functional group as shown here. The one exception is an intermolecular transfer reaction catalyzed by a ribonucleotide reductase of Lactobacillus.



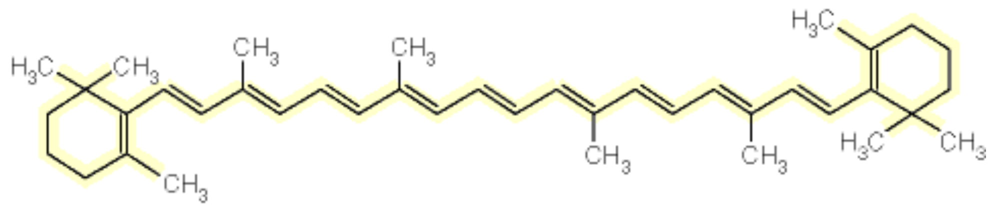


B12 coenzymes have either a methyl group or a 5'-adenosyl moiety linked to cobalt making them the first known organometallics in metabolism

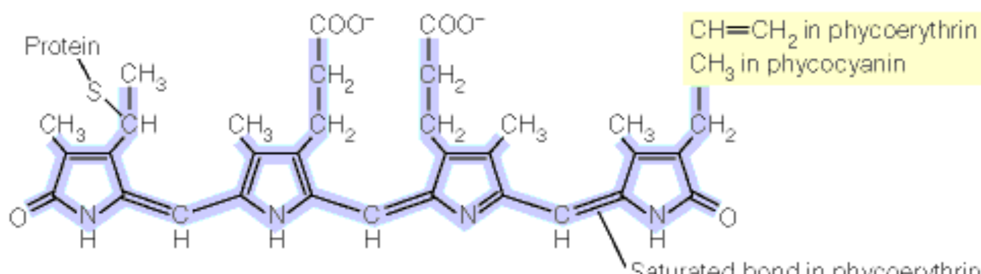
CHLOROPHYLLS



(a) Chlorophylls *a* and *b*



(b) β-Carotene



(c) Phycocyanin