Hematology

Medical Committee
The University of Jorda

- Histology
- Biochemistry
- Pathology
- Pharmacology
- Physiology
- Microbiology

- Handout
- Slide 8
- Sheet

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- lecture number :
- Done BY :

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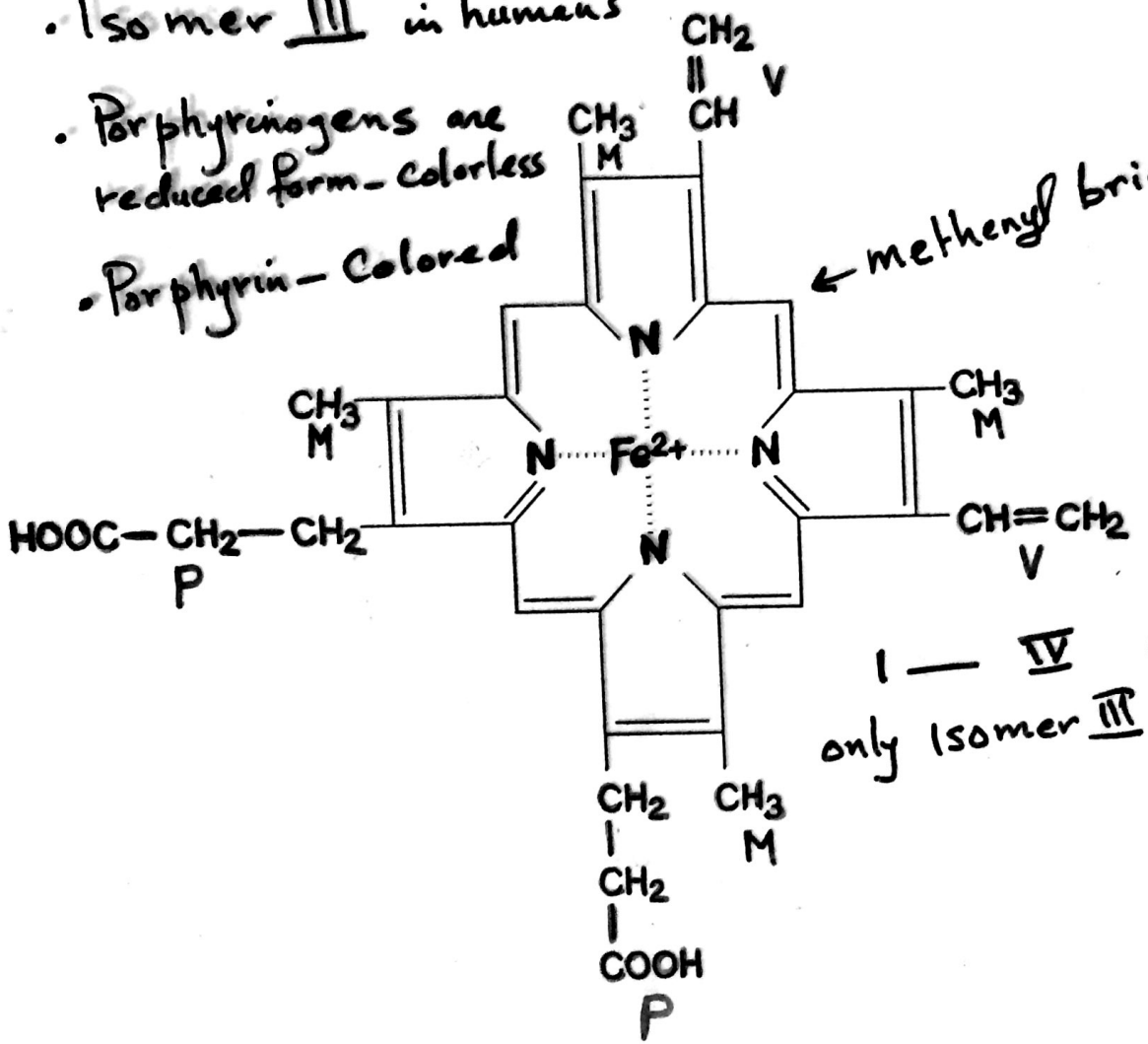
HEME

- The most prevalent metallo porphyrin in human
- Prosthetic group for Hb, Mb, Cyt., Catalase, tryptophan Pyrrolase, NO synthase
- Isomer III in humans
- Porphyrinogens are reduced form - colorless
- Porphyrin - Colored



I — IV isomers

only Isomer III is impt. in human

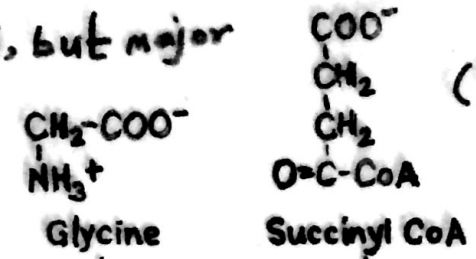
FIGURE 24.6
Structure of heme.

Biosynthesis of Heme:

- in all mammalian tissues, but major in liver + bone marrow ↑↑
- 8 mol. of each substrate → heme

e.g. 6-7 gr of Hb synthesized daily

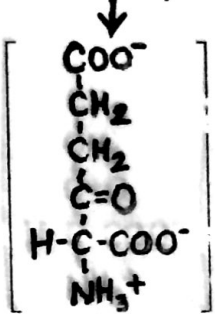
PLP



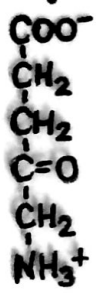
[ALAS] δ-Aminolevulinate synthase (mitochondria) ⊖ ← Hemin

→ CoA

Decreases level of ALAS1 by:
1- ↓ mRNA transcription
2- ↑ mRNA degradation
3- ↓ import of the enz. into mitochondria



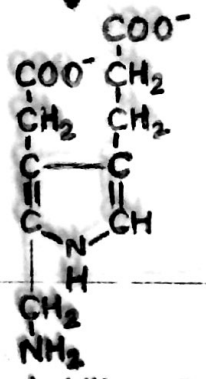
→ CO_2



δ-Aminolevulinic acid (ALA)

δ-Aminolevulinic acid dehydrase (cytosol) Zn (Two molecules condensed) → $2H_2O$

Lead ⊖



Porphobilinogen (PBG)

- In Erythrocyte - heme synthesis is under the control of erythropoietin
  also availability of iron
- Induction of ALAS1 by:-
  - Drugs metabolism require Cyt. P450 [CYP mono-oxygenases]
    - steroid hormones ↑ metabolites
    - ethanol ↑
    - barbiturates ↑
- 85% of all heme synthesis occurs in erythroid tissue

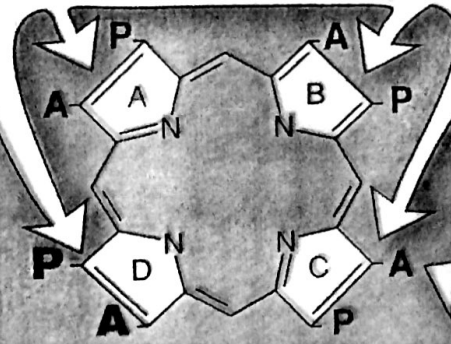
mutation in ALAS-2 (erythroid specific) → X-linked sideroblastic anemia

ALAD

- δ-ALA dehydratase or Porphobilinogen synthase
- in Cytosol
- 280 kD 8-subunits
- sulfhydral enzyme inhibited by heavy metals e.g. lead which replaces Zn^{2+} → ↑ALA and Anemia in lead poisning

(ALAD)

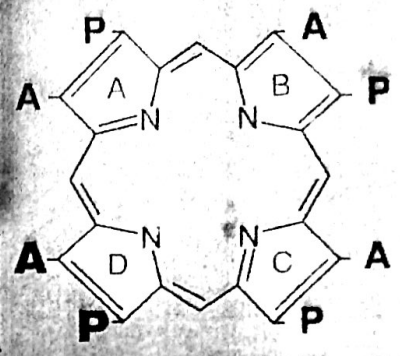
Porphyrins contain four pyrrole rings (A, B, C, and D) joined through methenyl bridges.



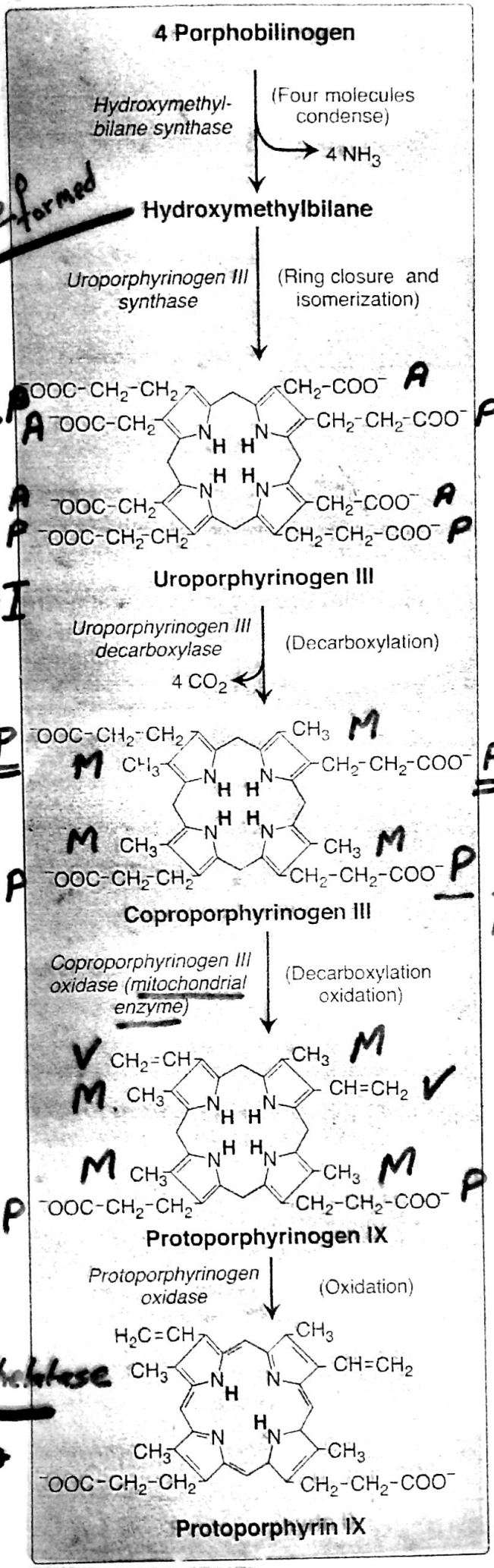
Uroporphyrin I

Porphyrins contain side chains attached to each of the four pyrrole rings. In type I porphyrins, the side chains are arranged symmetrically, that is, for uroporphyrin I, A (acetate) alternates with P (propionate) arcund the tetrapyrrole ring.

A and P are reversed in ring D of uroporphyrin III compared with uroporphyrin I. Only type III (asymmetric) porphyrins are physiologically important in humans.



Uroporphyrin III



also some formed

Uroporphyrinogen I

Coproporphyrinogen I (excreted)

Uro I and Copro I are produced in excess in Erythropoietic Porphyria and excreted in urine

Mitochondria

Ferrochelatase

HEME ← Fe^{2+}

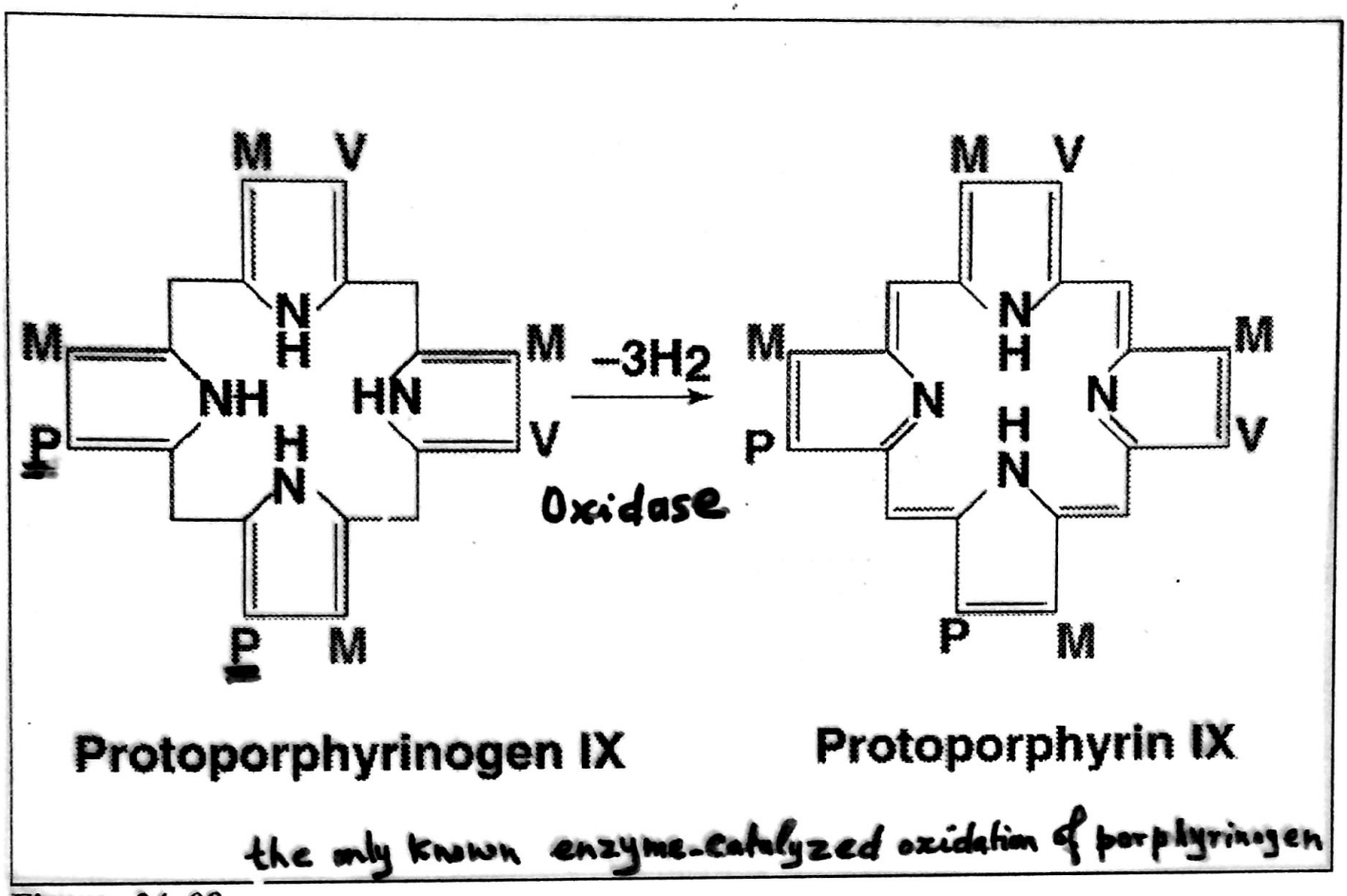
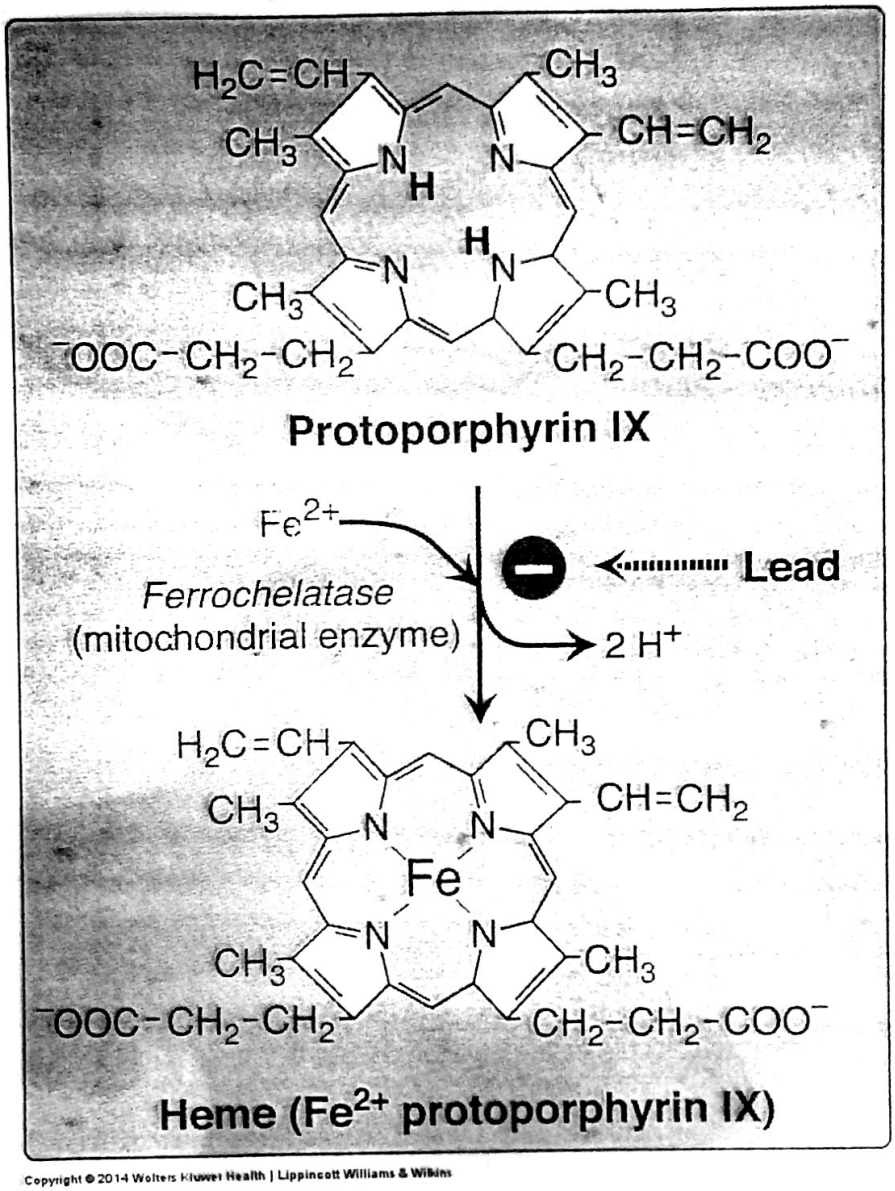


Figure: 24_08
Action of protoporphyrinogen IX oxidase, an example of the conversion of a porphyrinogen to a porphyrin



Porphyrias

- Deficiency of any of the enzyme in heme biosynthesis - inherited or acquired
- Results in accumulation and increased excretion of porphyrin or precursors (ALA or PBG)
- All inherited as autosomal dominant except erythropoietic porphyria - recessive
- Mutations are very heterogenous
- Porphyria is classified
  - Erythropoietic
  - hepatic
    - Acute
    - chronic
- photosensivity
  - Accumulation of tetrapyrrole → Colored Porphyrins → ROS $\xrightarrow{\text{damage}}$ release of lysosomal enz.
- The most common acquired form — lead poisoning
  - δ-ALA dehydratase & ferrochelatase ↓
  - δ-ALA & Protoporphyrin accumulate
  - Anemia → Hb ↓
  - Energy production ↓ ← Cytochromes ↓
- Defect prior to tetra pyrroles synthesis → Abdominal and neuropsychiatric signs

II.

e.g. **Congenital Erythropoietic Porphyria** } only recessive type

Insufficient Cosynthase → Uroporphyrinogen III ↓
Uroporphyrinogen I ↑↑

→ ↑ uroporphyrine I
↑ coproporphyrine I

Signs & Symptoms :-

- Premature destruction of erythrocyte
- Red urine (large amount of porphyrin I)
- Teeth exhibit strong red fluorescence under U.V. light
- Skin is sensitive to light
  photoexcited porphyrins are quite reactive

Lead Poisning :-

Ferrochelatase & ALA dehydratase are inhibited

→ Protoporphyrine & ALA accumulate in urine

PORPHYRIAS

Acquired Porphyria:-

(1) Lead poisning →

Succinyl-CoA + Glycine

(1) ↓ δ-ALA Synthase [Inhibited by hemin]

δ-ALA

(2) ↓ δ-ALA dehydratase (ALAD) deficiency v. rare

PBG

(3) ↓ hydroxy methyl bilane synthase

Hydroxymethyl bilane

(4) ↓ Uroporphyrinogen-III cosynthase

Uroporphyrinogen-III

(5) ↓ Uroporphyrinogen decarboxylase

Coproporphyrinogen III

(6) ↓ oxidase

Protoporphyrinogen III

(7) ↓ oxidase

Protoporphyrin

(8) ↓ Ferrochelatase

HEME

(2) Lead poisning →

Genetic Porphyria

- Acute Intermittent Porphyria (King George III)
- → Congenital Erythropoietic
  - the only autosomal Recessive
- → Porphyria Cutanea tarda [Hepatic] (Most common genetic Porphyria); chronic hepatic Porphyria
- Hereditary Coproporphyria
- Variegate Porphyria
- Protoporphyria (Erythropoietic)

Clinical Symptoms

- Acute abdominal pain
- Psychiatric disturbances
- Peripheral neuropathy
- photosensivity (in some)
- Hepatic damage (in some)

ALA + PBG ↑

Impair function of
- abdominal nerve
- CNS

ATPase ↓
Conduction Paralysis

PHOTOSENSIVITY

Treatment & Management:-

Heming, antioxidants, Avoid sunlight → to inhibit ALAS → ↓ Heme

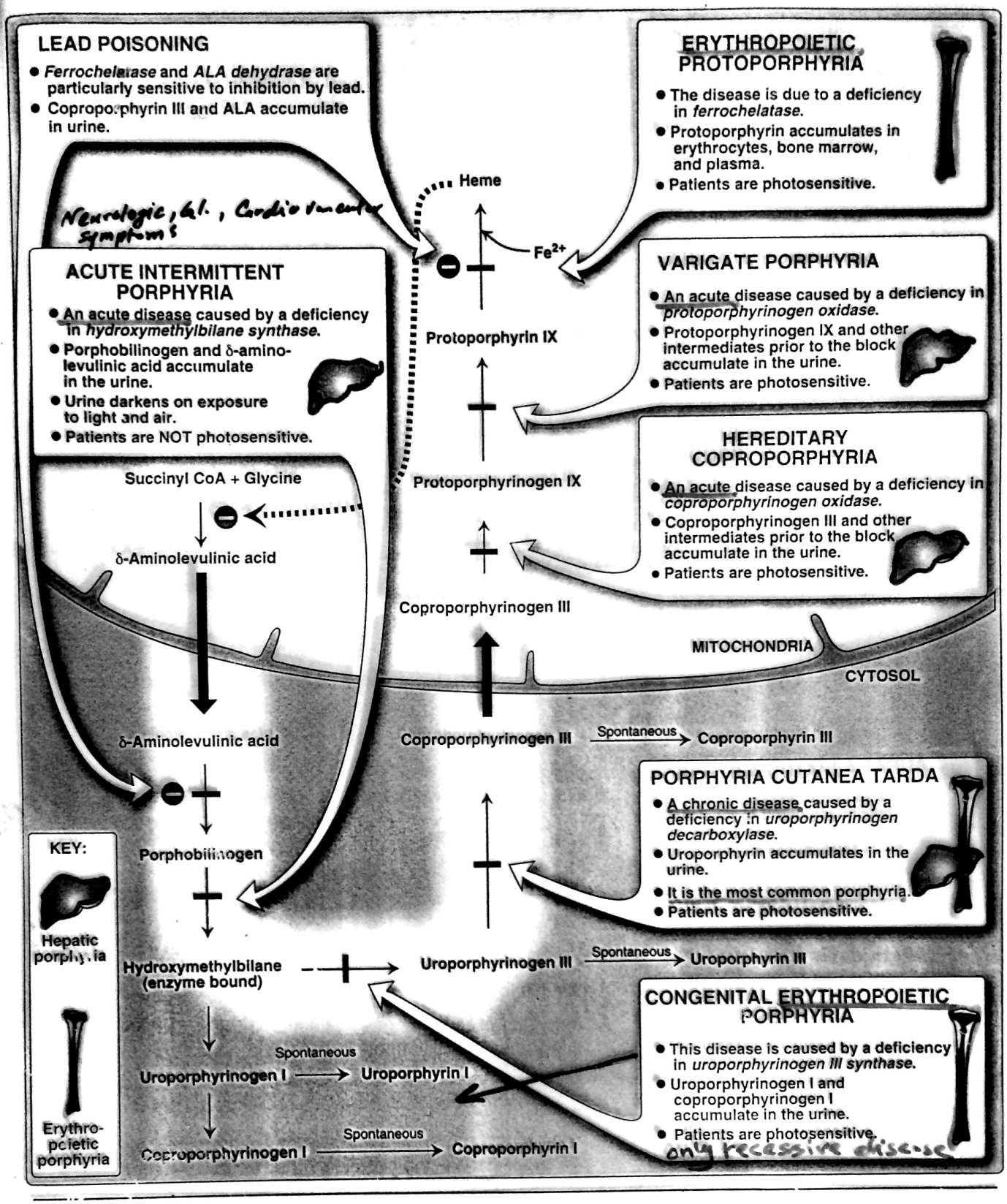


Figure 21.7
Summary of heme synthesis.

- Increased ALA synthase activity – since ↓ Heme conc.
- Treatment
  - Administration of hemin
  - Avoidance of sunlight
  - free-radical scavenger e.g. β-carotene, vit. C, E