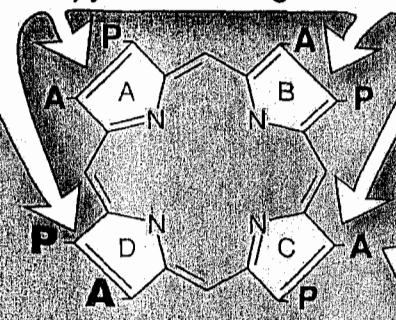
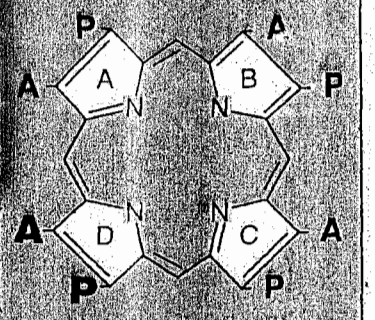
Porphyrins contain four pyrrole rings (A, B, C, and D) joined through methenyl bridges.



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) around 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

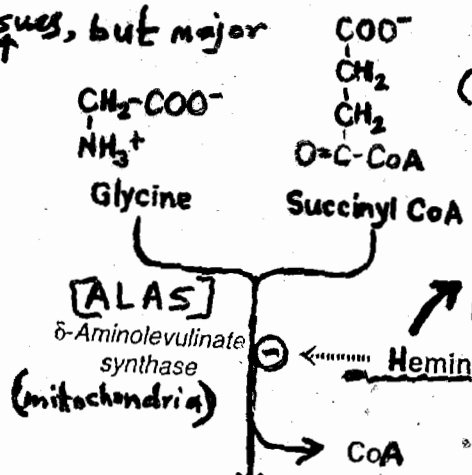
Biosynthesis of Heme:

- in all mammalian tissues, but major in liver & bone marrow ↑↑

- 8 mol. of each substrate → heme

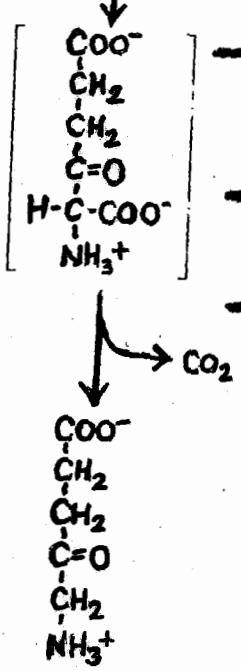
e.g. 6-7 gr of Hb synthesized daily

PLP



↗ Decreases level of ALAS by:
1- ↓ mRNA transcrip
2- ↑ mRNA degrad
3- ↓ import of the enz. into mitochond

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



- In Erythrocyte - heme synthesis is under the control of erythropoietin ALAS-2 also availability of iron

- Induction of ALAS1 by:-

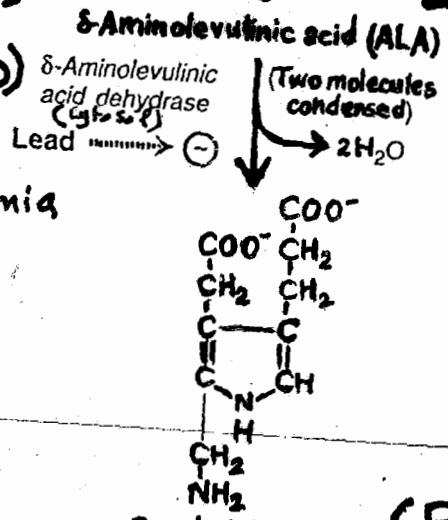
- Drugs metabolism require Cyt. P450 [CYP mono-oxygenases]
  - steroid hormones metabolites ↑
  - ethanol ↑
  - barbiturates ↑

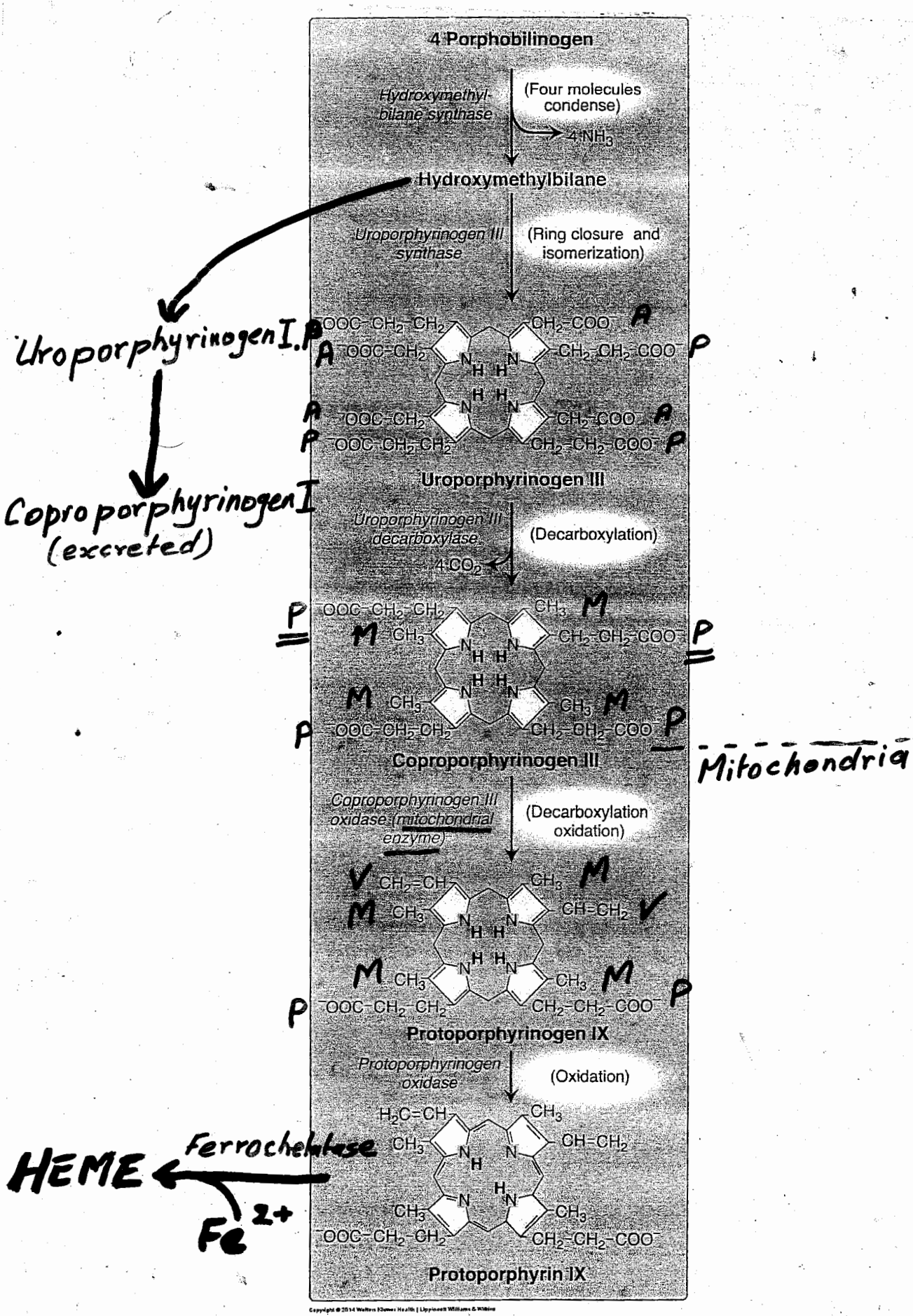
- 85% of all heme synthesis occurs in erythroid tissue.

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+} (ALAD)

→ ↑ALA and Anemia in lead poisning





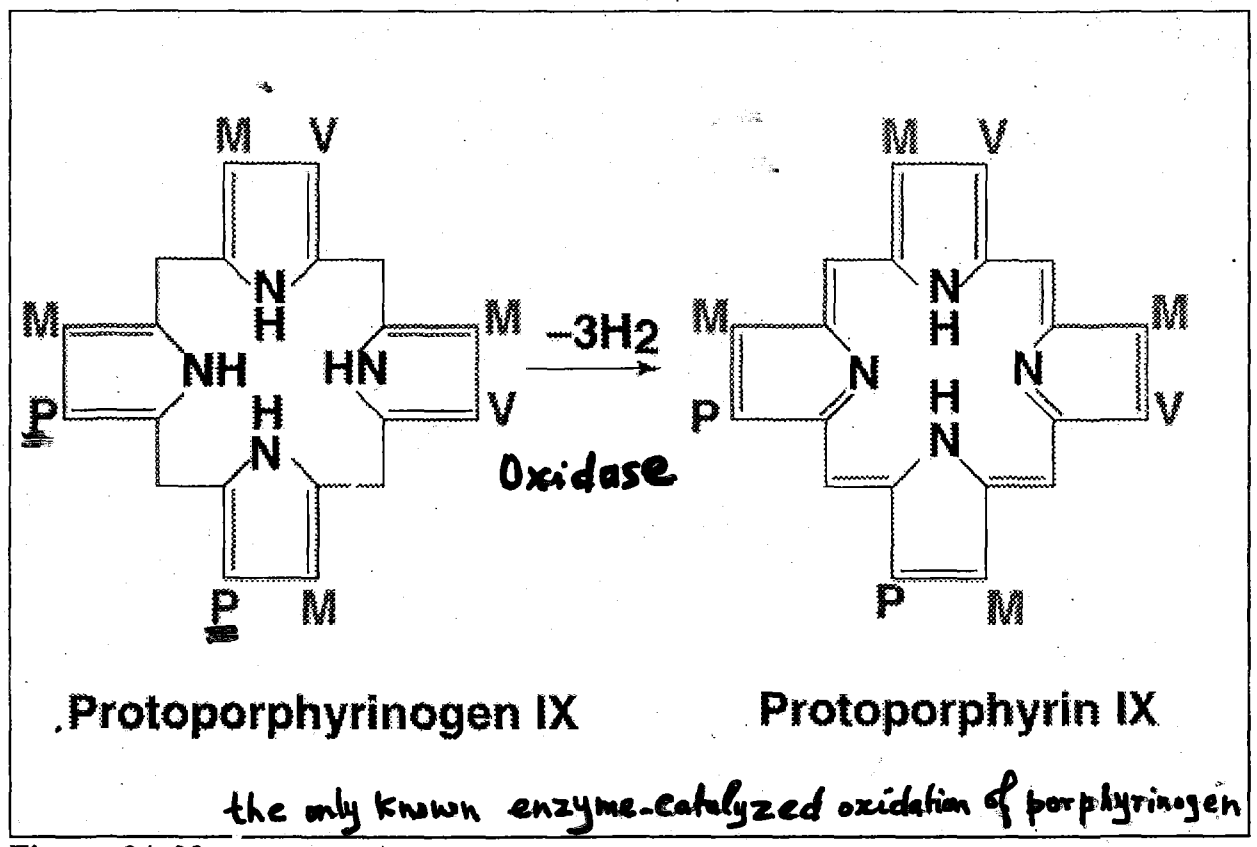
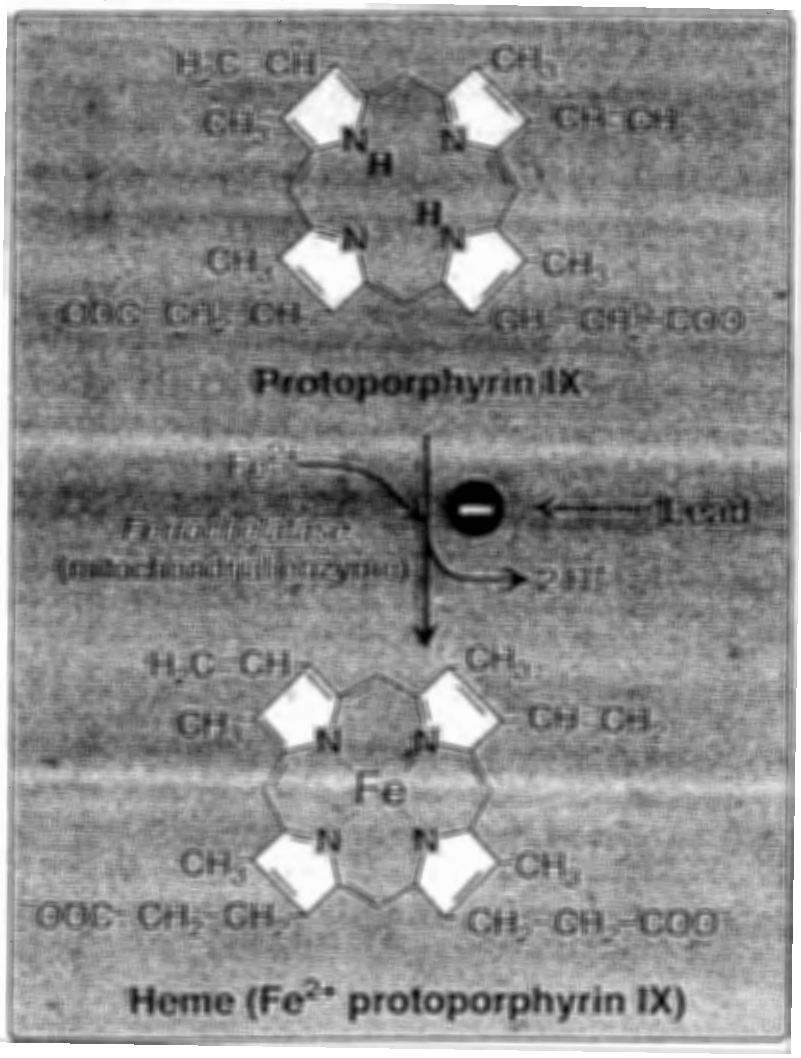


Figure: 24_08
Action of protoporphyrinogen IX oxidase, an example of the conversion of a porphyrinogen to a porphyrin



Porphyrias

- Deficiency of any of the enzyme in heme biosynthesis - inherited or acquire

- Results in accumulation and increased excretion of porphyrin or precursors (ALA or

- All inherited as autosomal dominant except erythropoietic porphyria - recessiv

- 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 recess type

Insufficient Cosynthase ⟶ Uroporphyrinogen III ↓
Uroporphyrinogen I ↑M

⟶ ↑ 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
  photo excited porphyrins are quite reactive

Lead Poisning :-

Ferrochelatase & ALA dehydratase are inhibited

⟶ Protoporphyrine & ALA accumelate in Urine

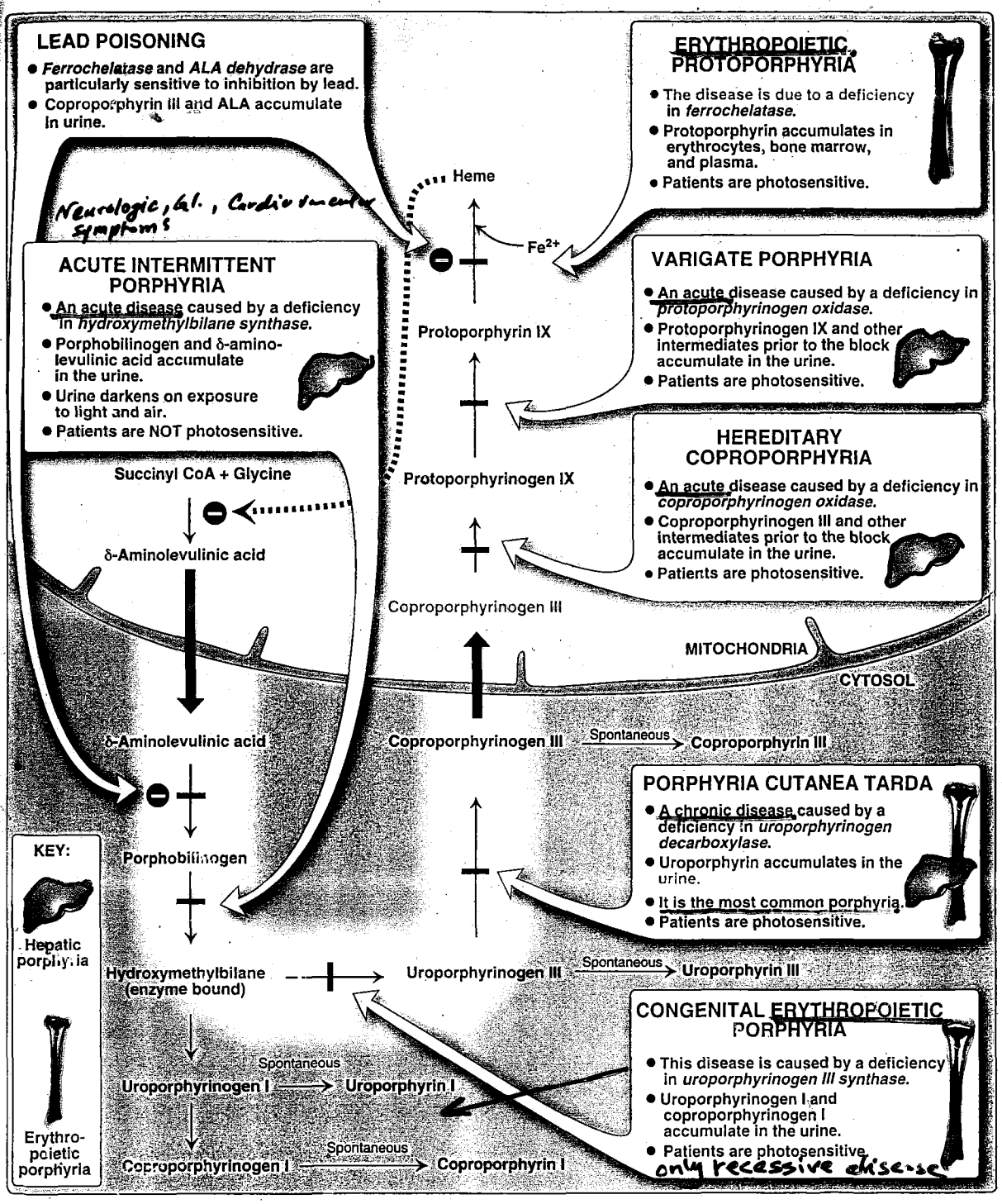


Figure 21.7
Summary of heme synthesis.

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

PORPHYRIAs

Acquired Porphyria

Lead poisning →

Succinyl-CoA + Glycine

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

δ-ALA

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

PBG

(3) Uroporphyrinogen-I synthase

Hydroxymethylbilane

(4) Uroporphyrinogen-III Cosynthase

Uroporphyrinogen-III

(5) Uroporphyrinogen decarboxylase

Coproporphyrinogen III

(6) oxidase

Protoporphyrinogen III

(7) oxidase

Protoporphyrin

(8) Ferrochelatase

HEME

Genetic Porp

Acute Intermit Porphyria (King George III)

Congenital Erythropoietic

- The only autosomal Recessive

Porphyria Cutanea tarda [Hepatic] (Most common genetic Porphyria). Chronic hepatic Porphyr

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

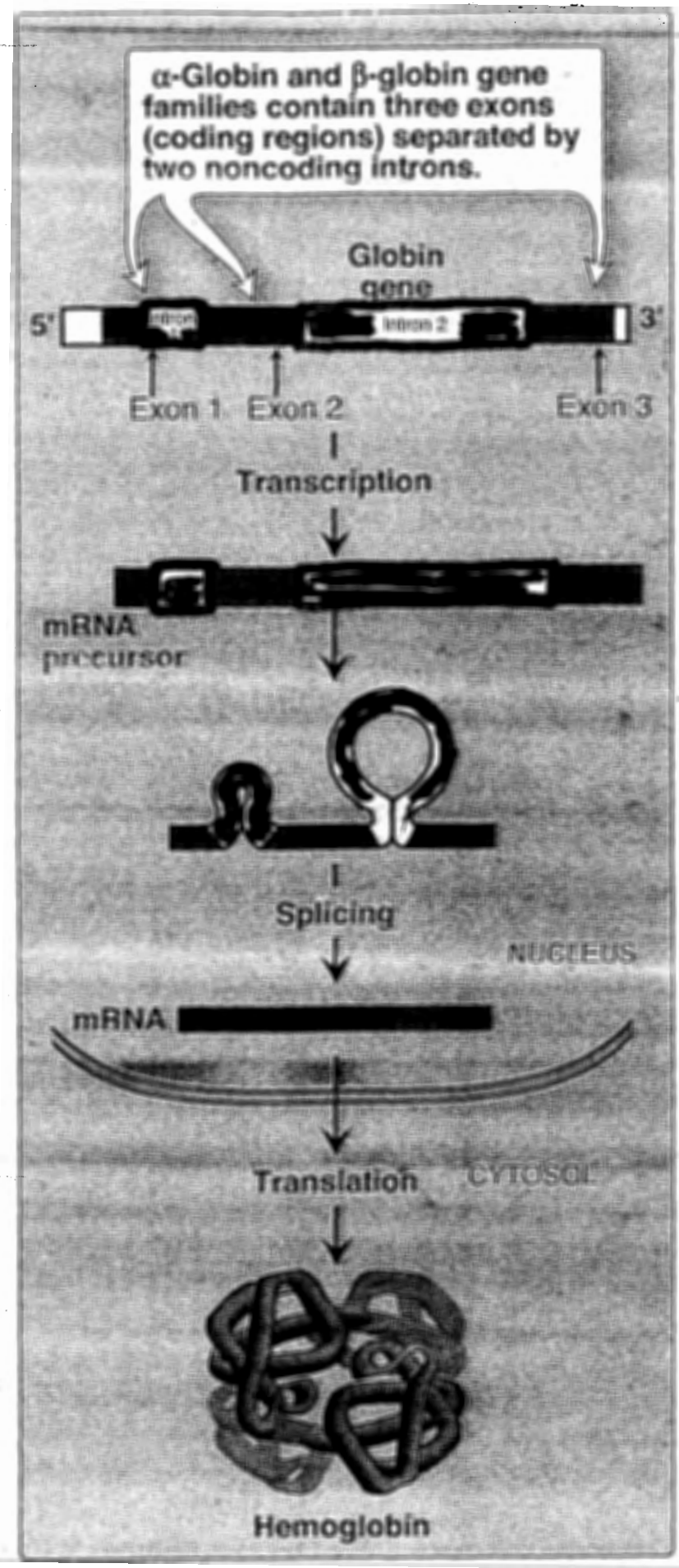
Lead poisning →

Treatment & Management:-

Hemin, antioxidants, Avoid sun light

→ inhibit ALAS → ↓ Heme

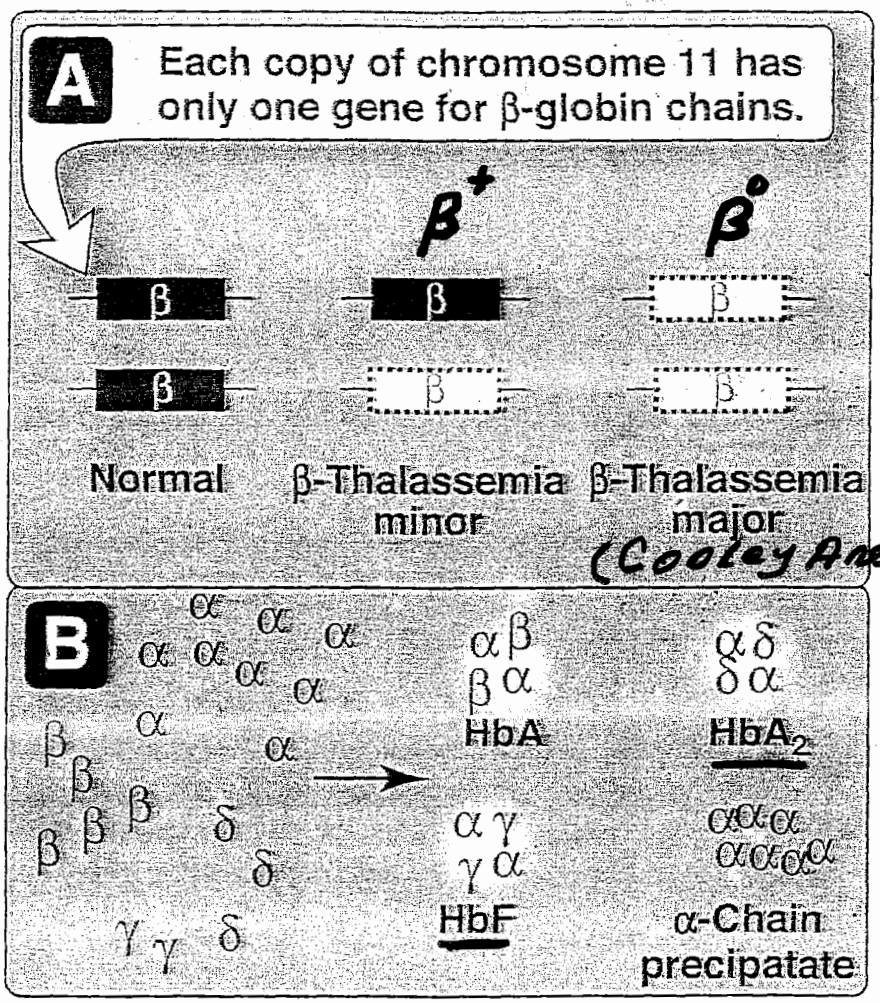
Glo bin
Cha ins
Syn thesis



THALASSEMIA

- Decreased synthesis of α- or β-
  - → Globin chain precipitate
  - → Hemolysis
  - → Hypochromic anemia

β-thalassemia

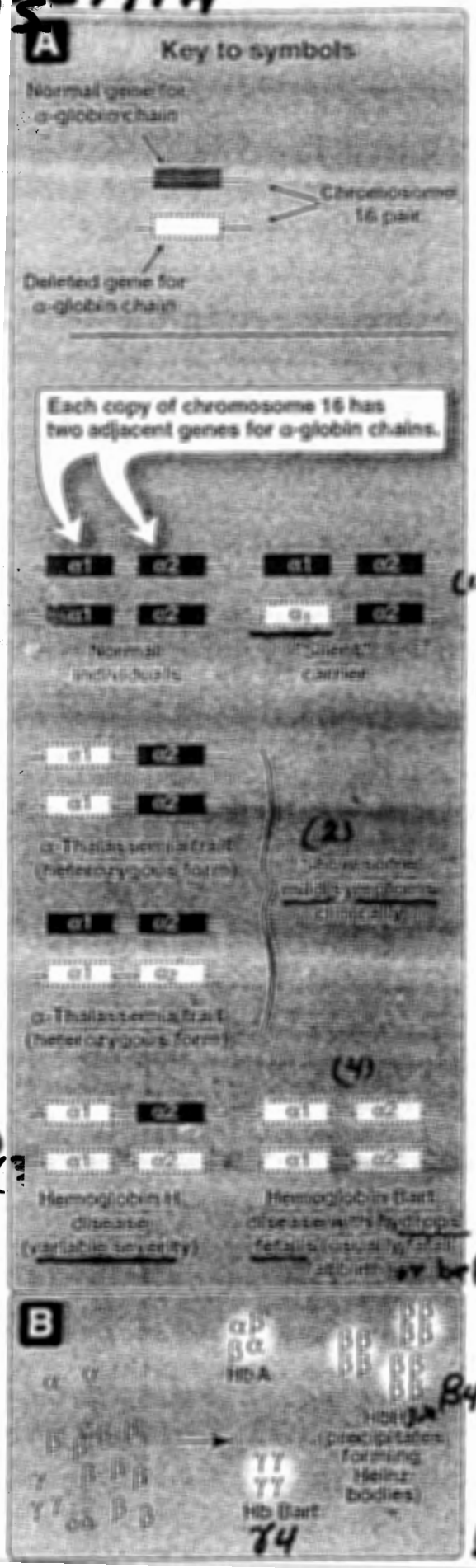


$Hb\,A_2 \uparrow$; $HbF \uparrow$

α chains ⟶ α_4 (Cooley's Hb)
- → α_4 precipitates
- → Heinz bodies
- → Cell membrane damage → Premature death of erythrocyte

Manifestation of β-thalassemia appears only after birth (because of HbF); becomes severly anemic during the 1st or 2nd year of life.

α-THALASSEMIA



} in total loss of α-chain

lore

HbH ↑
HbBart ↑

Soluble Hb but without sigmoid kinetics. Useless O_2 deliverer to tissues.

Primary Causes:

α- thalassemia :-
gene deletion

β- thalassemia :-
- Point mutation in the Promotor
- mutation in the translational initiation codon
- point mutation in the Poly-adenylation signal
- mutations → splicing abnormalities

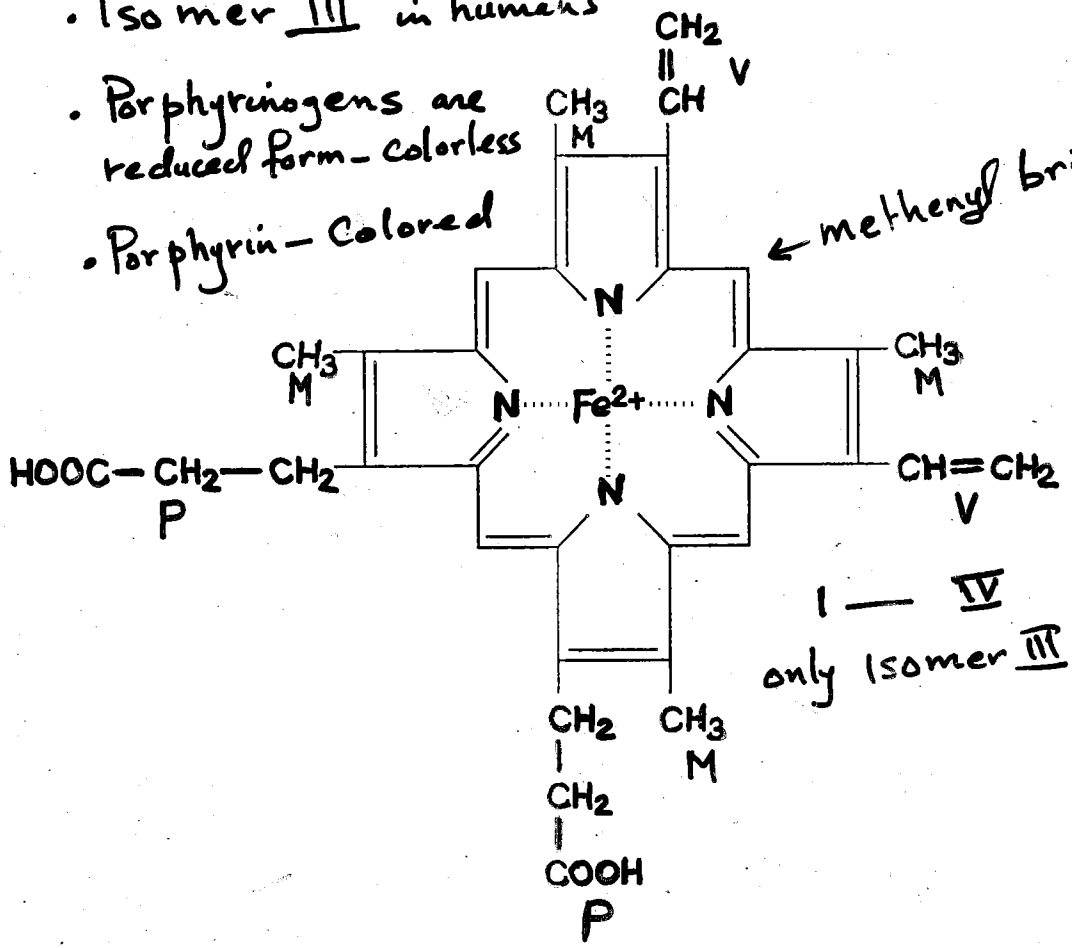
- HbE $\beta^{26 Glu-lys}$
  structural and quantity abnormality
  60% of β-globin is made

- Hereditary persistance of fetal Hb (HPFH)
  → continue to make HbF in adult
  → Benign

HEME

- The most prevalent metallo porphyrin in human
- Prosthetic group for Hb, Mb, Cyt., Catalase, tryptophan Pyrrolase
- Isomer III in humans
- Porphyrinogens are reduced form – colorless
- Porphyrin – Colored

NO synthase



I — IV isomers

only Isomer III is impt. in human

FIGURE 24.6
Structure of heme.