Iron, porphyrin and hemoglobin metabolism, automated immuno assays

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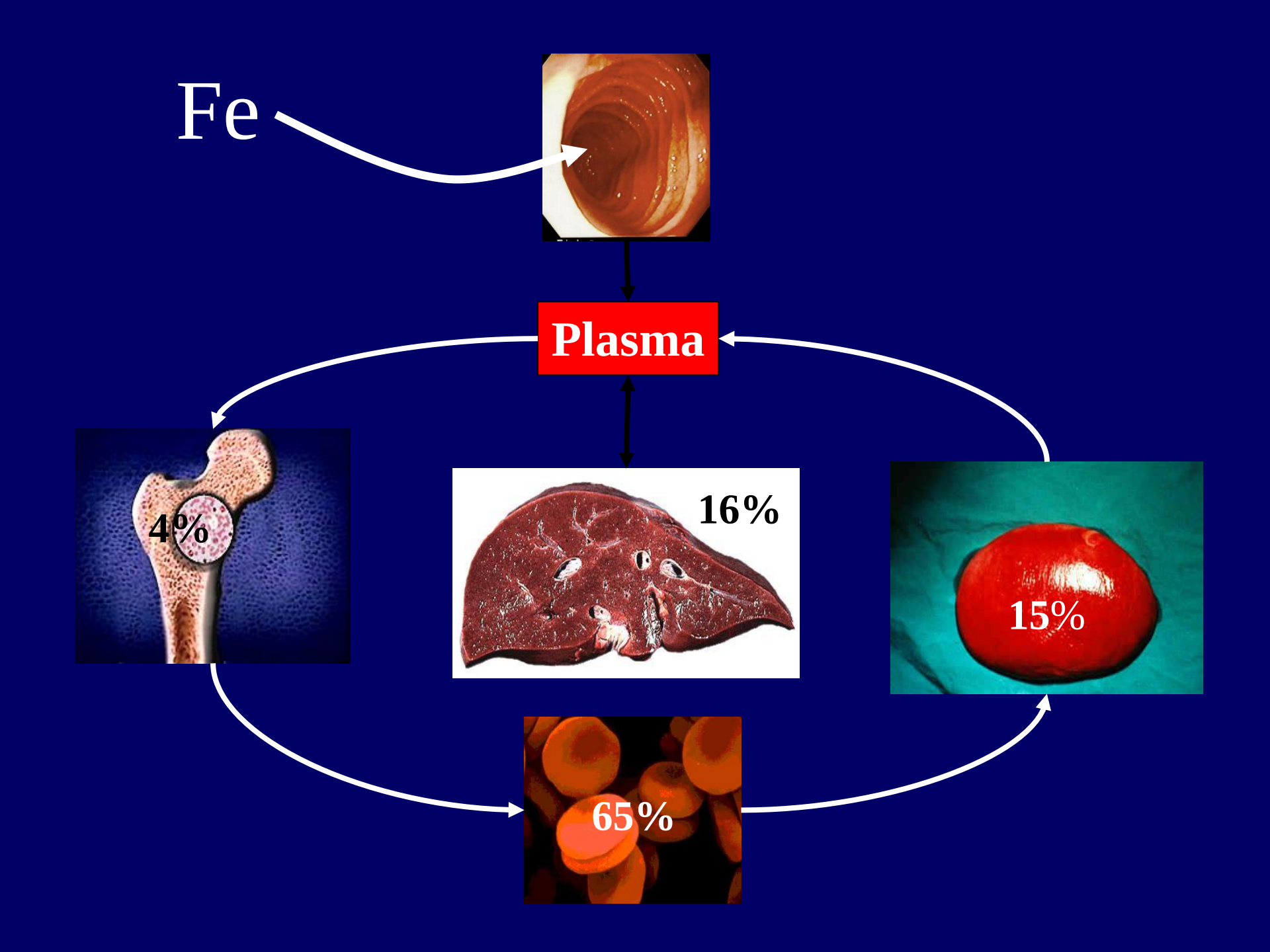
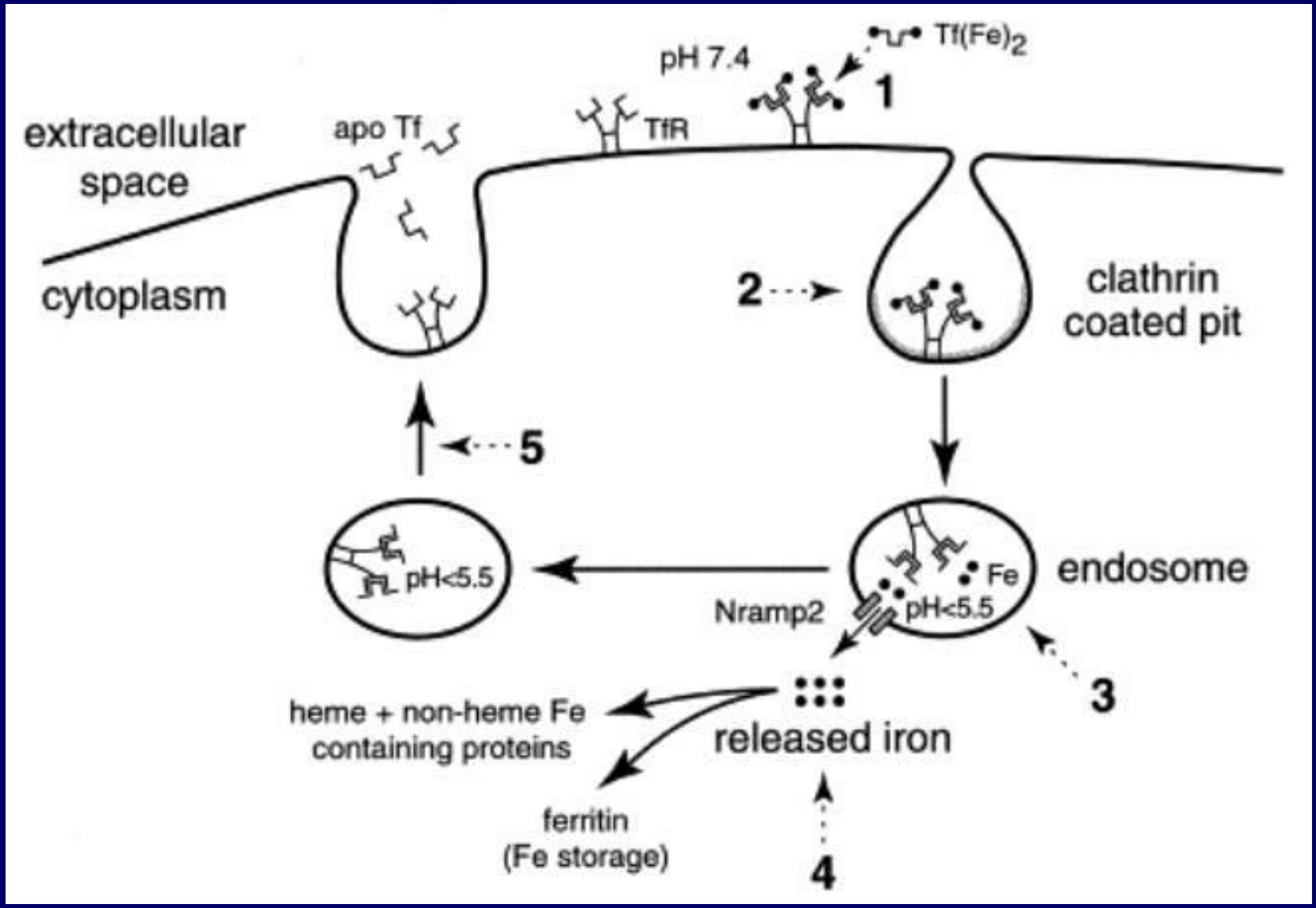
Iron metabolism of the body

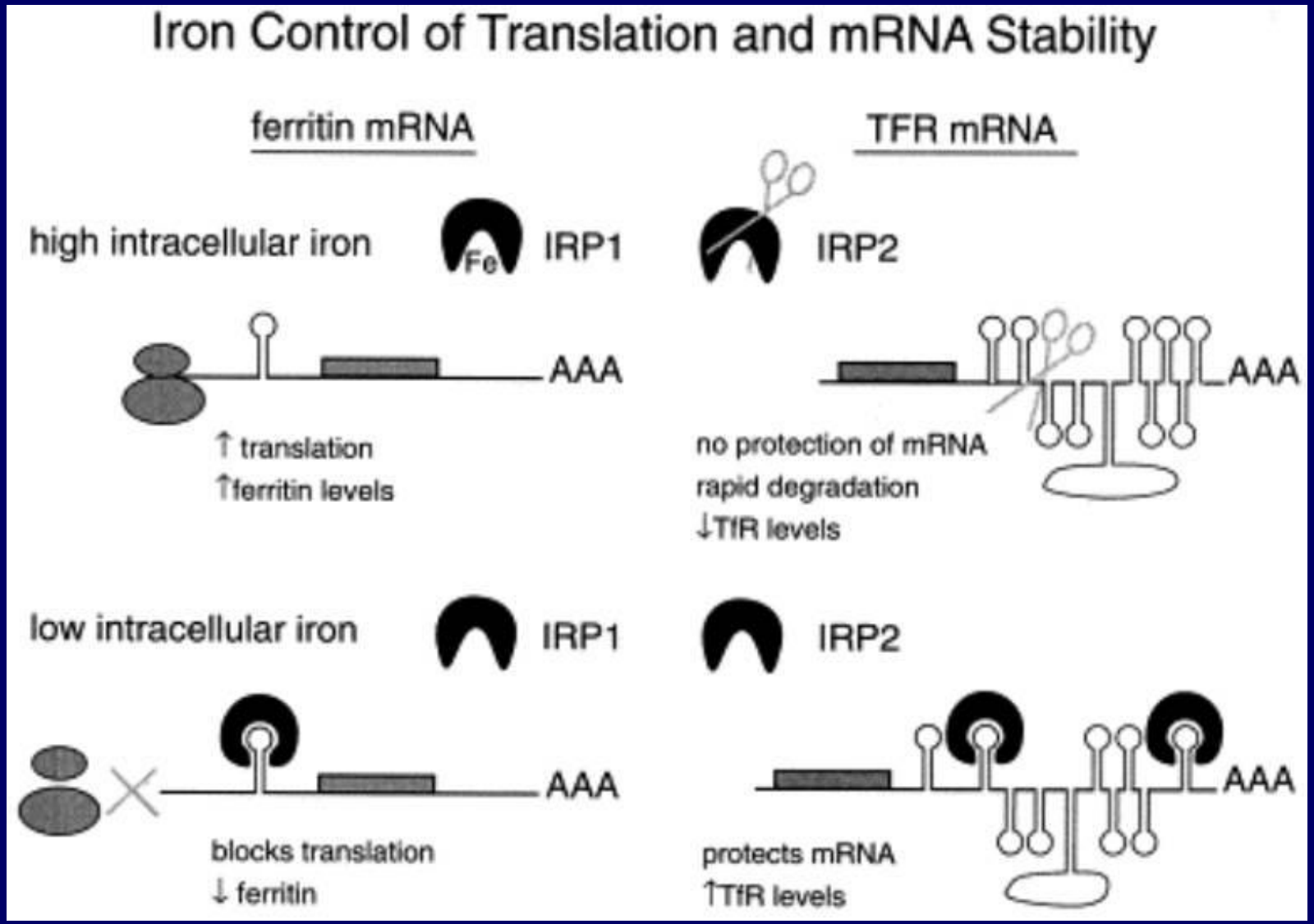
- 4g total Fe, >99% intracellular
- Protein bound!
- 65% RBC hemoglobin
- 34% heme protein or iron binding protein (oxidative phosphorylation, stores, enzyme cofactor)
- Micro-organisms (normal flora)
- Daily intake 20mg, daily need 1-2mg
- Can not be excreted!


Fe
Plasma
4%
16%
15%
65%

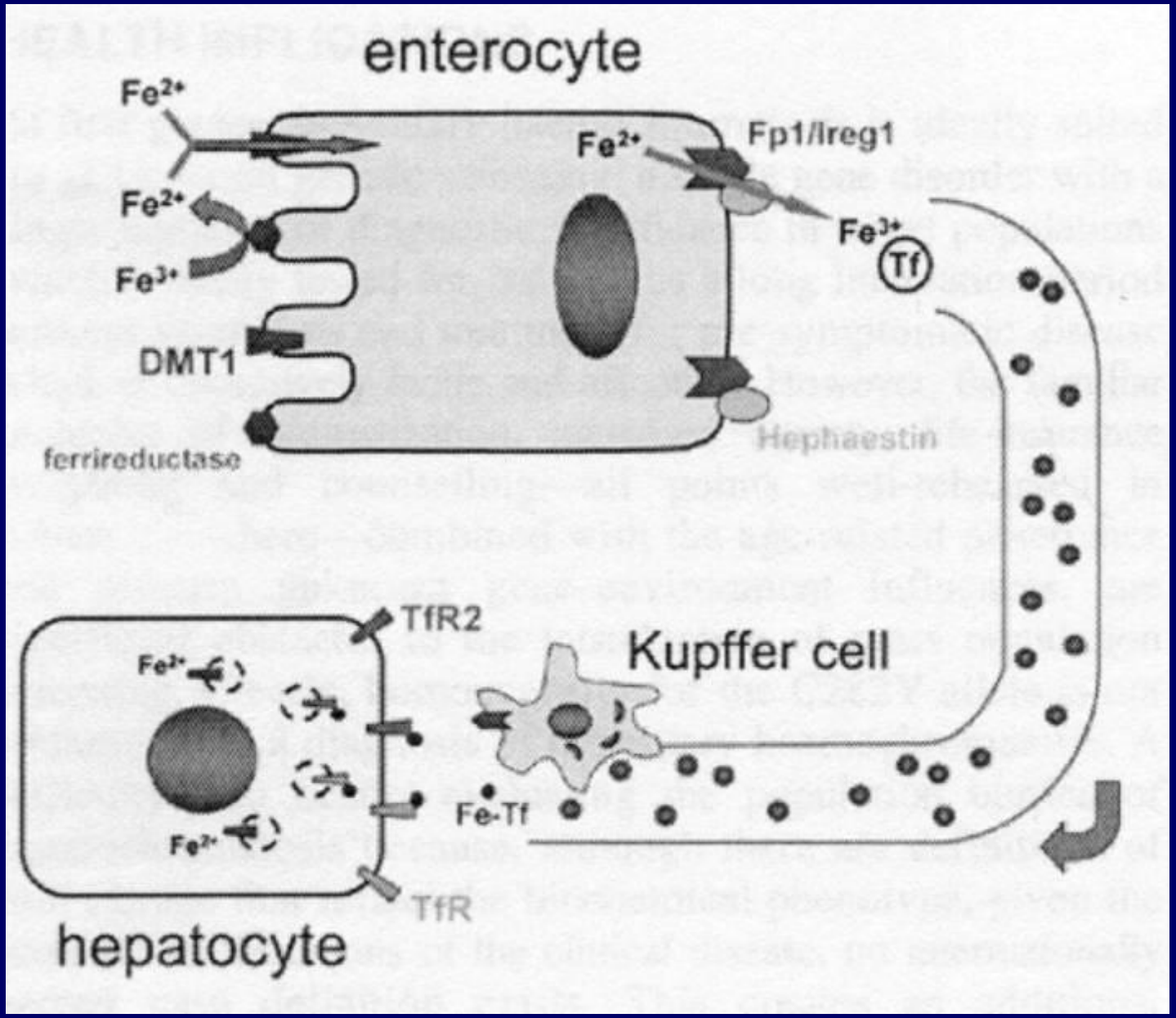
Iron absorption



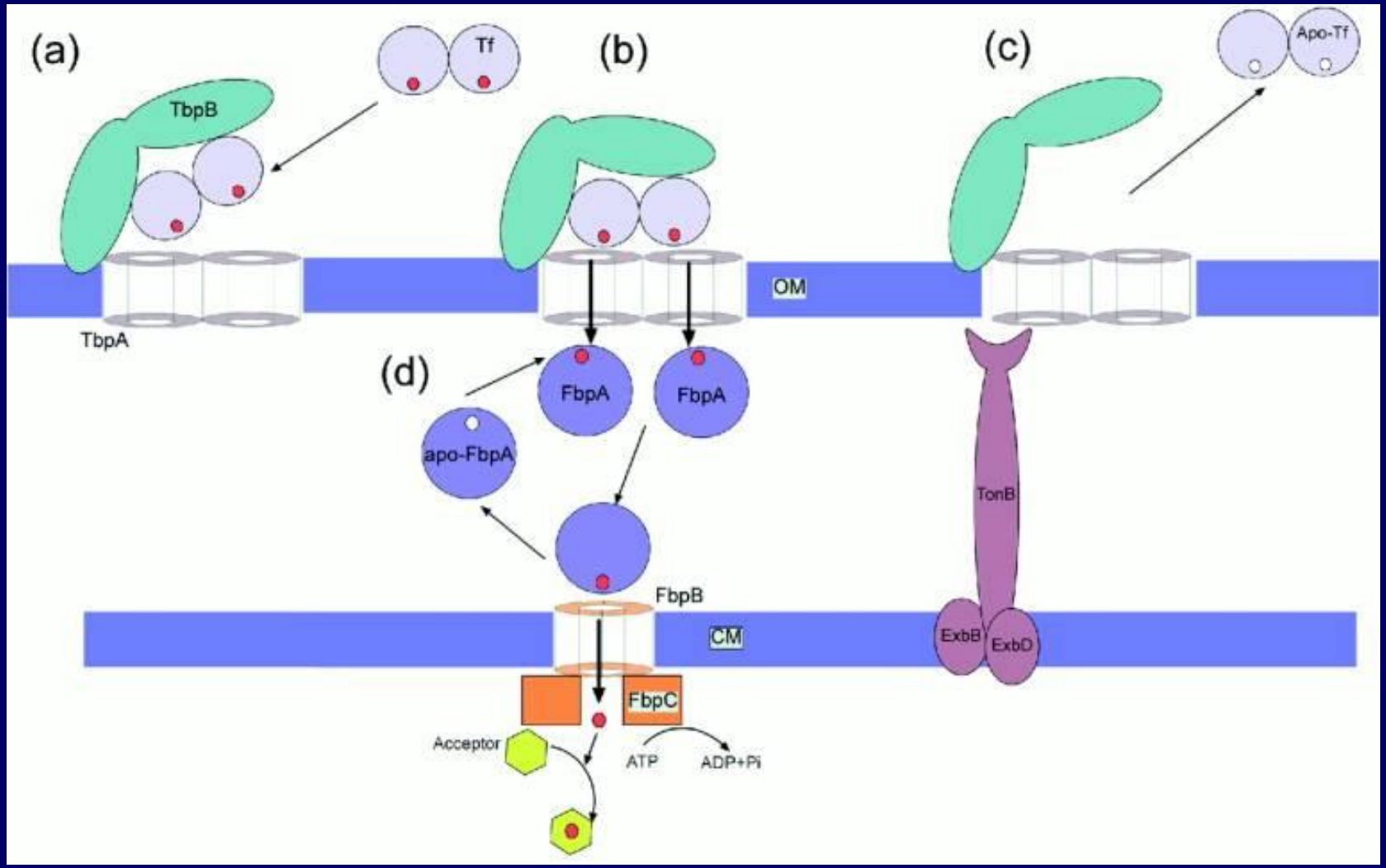
Regulation of iron absorption



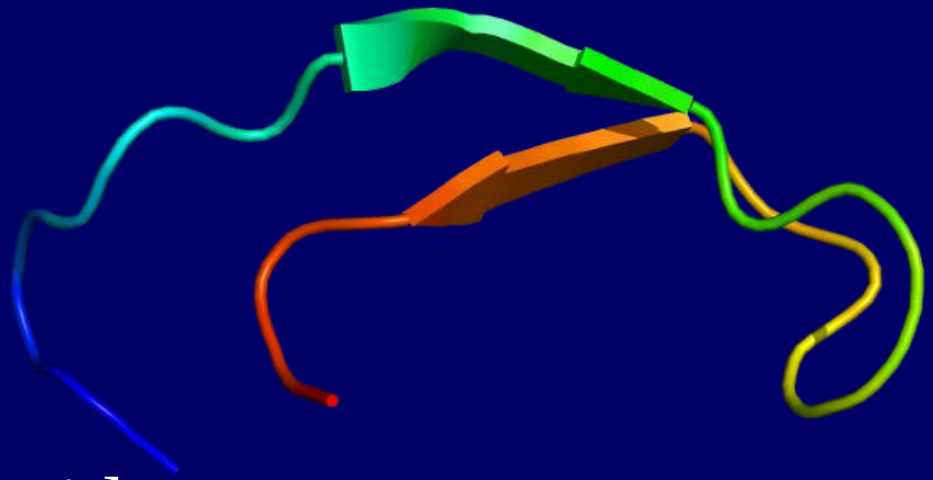
Iron transport



Iron uptake of Gram-negative bacteria

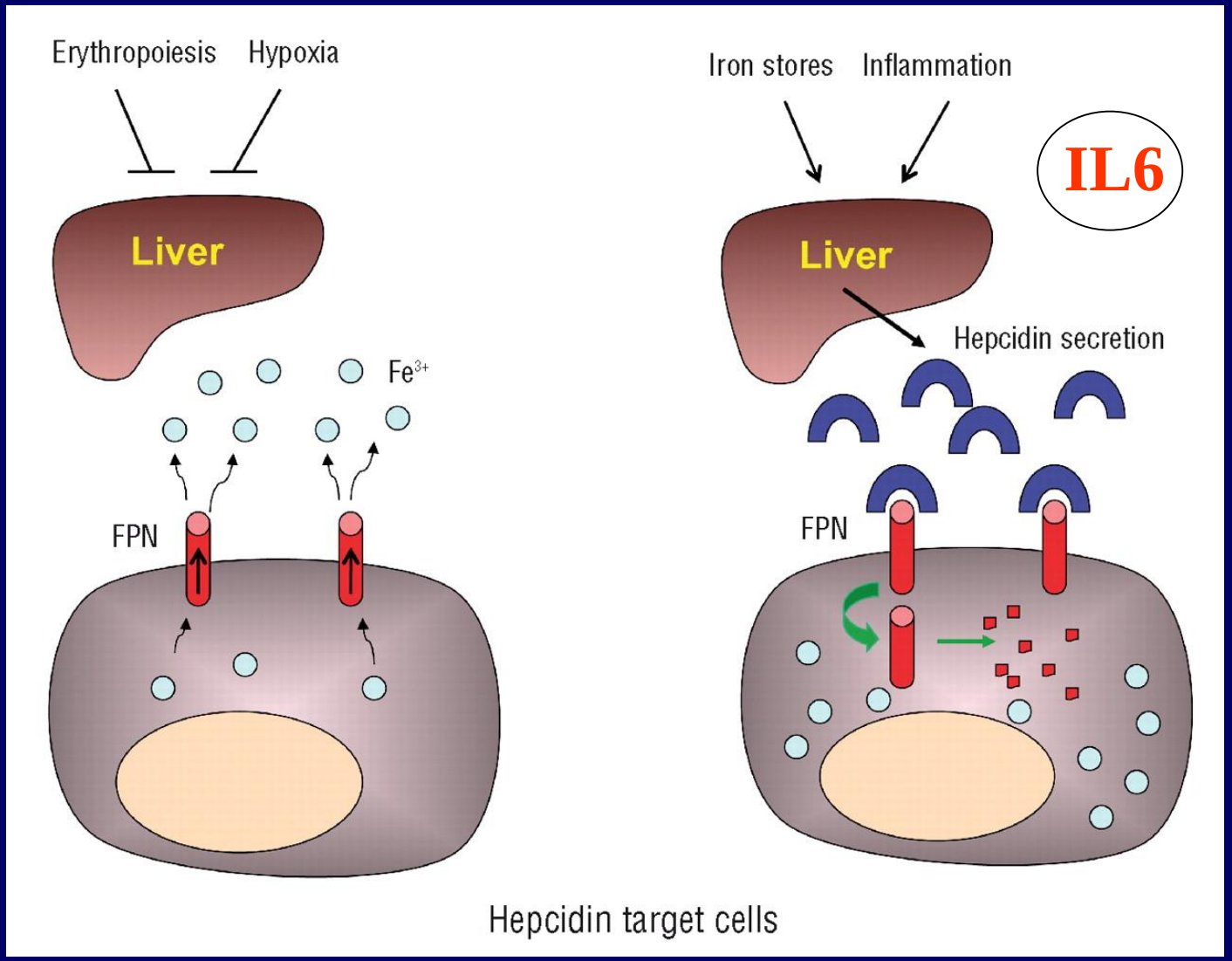


Hepcidin antimicrobial peptide



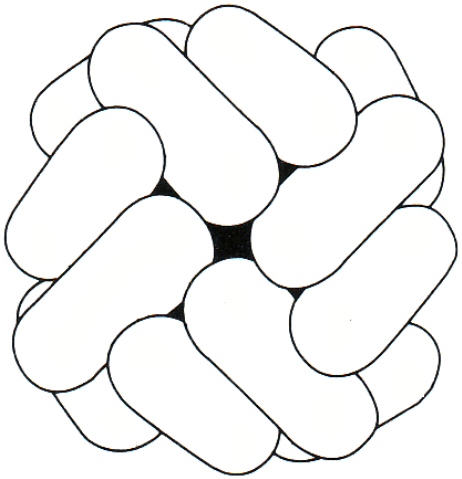
- 25 amino acids
- Produced by liver
- Inhibits Fe absorption by binding to gut enterocytes' ferroportin
- Increases in Fe overload and in inflammation

The hepcidin – ferroportin game



Ferritin ultrastructure

Ferritin

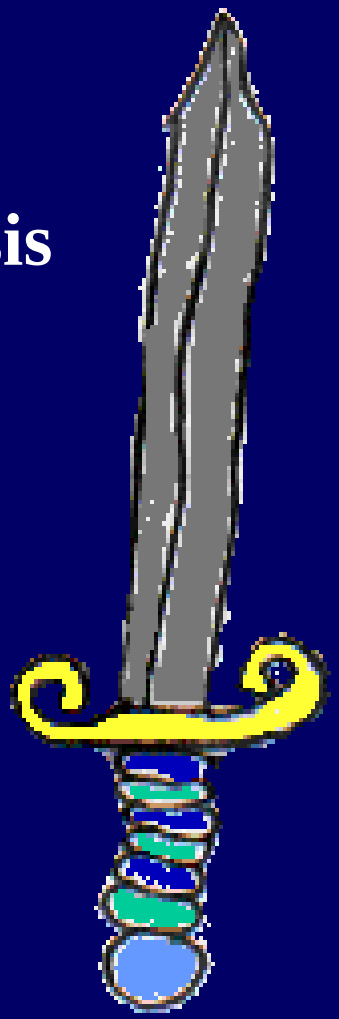


- **Hollow-spheres**
- **24 Peptide subunits**
- **3- and 4-fold channels**
- **Iron stored as $[FeO(OH)]_8[FeO(H_2PO_4)]$ (‘a particle of rust’)**
- **Iron goes in and out as Fe(II) - stored as insoluble Fe(III)**

The dual nature of iron

Hemoglobin synthesis

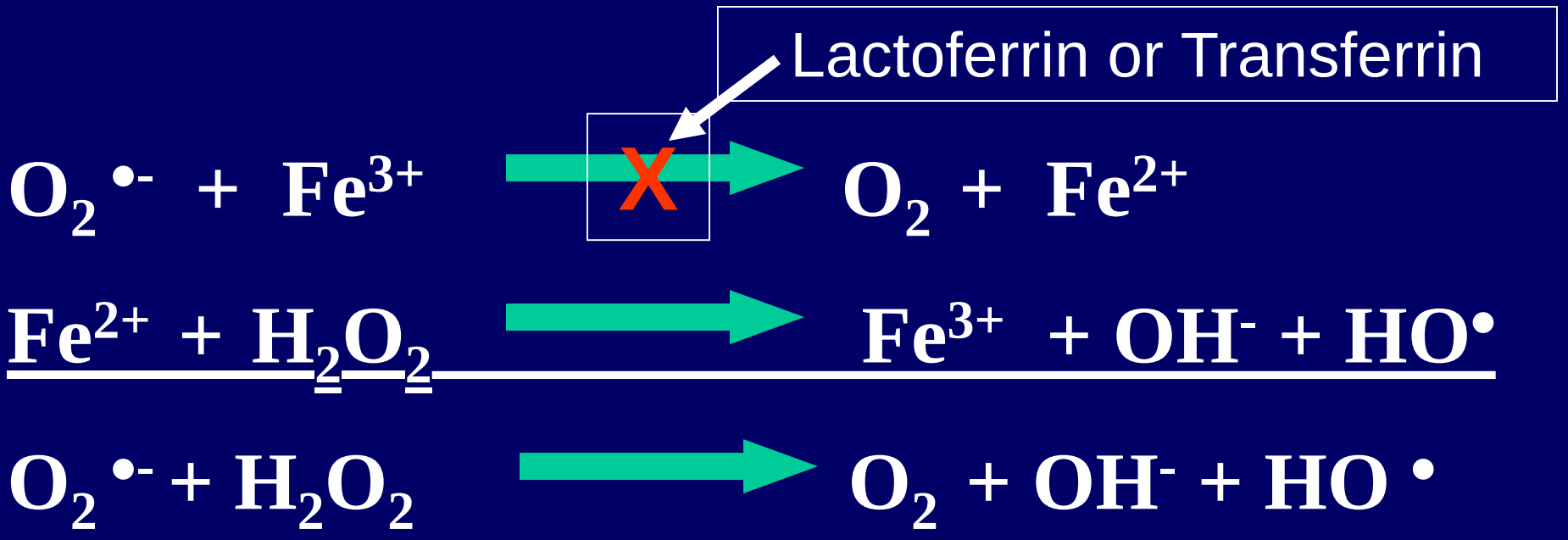
Enzyme cofactor



Oxidative stress

The dual nature of iron
Bound iron is not harmful

The Haber-Weiss reaction



Iron as a pro-oxidant

The Haber-Weiss reaction

$O_2^{\bullet -} + Fe^{3+} \rightarrow O_2 + Fe^{2+}$

$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + HO^{\bullet}$

$O_2^{\bullet -} + H_2O_2 \rightarrow O_2 + OH^- + HO^{\bullet}$

Reaction with lipids: hydroperoxides

$Fe^{2+} + ROOH \rightarrow Fe^{3+} + OH^- + RO^{\bullet}$

Iron metabolism
Measured parameters

Serum iron:	**10-30umol/l**
Transferrin:	**2.0-4.0g/l**
(negative acute phase protein!)	
Transferrin saturation:	**15-30%**
Ferritin:	**17-300ug/l**
Soluble transferrin receptor:	**2-5mg/l**

Hematological parameters

Iron deficiency

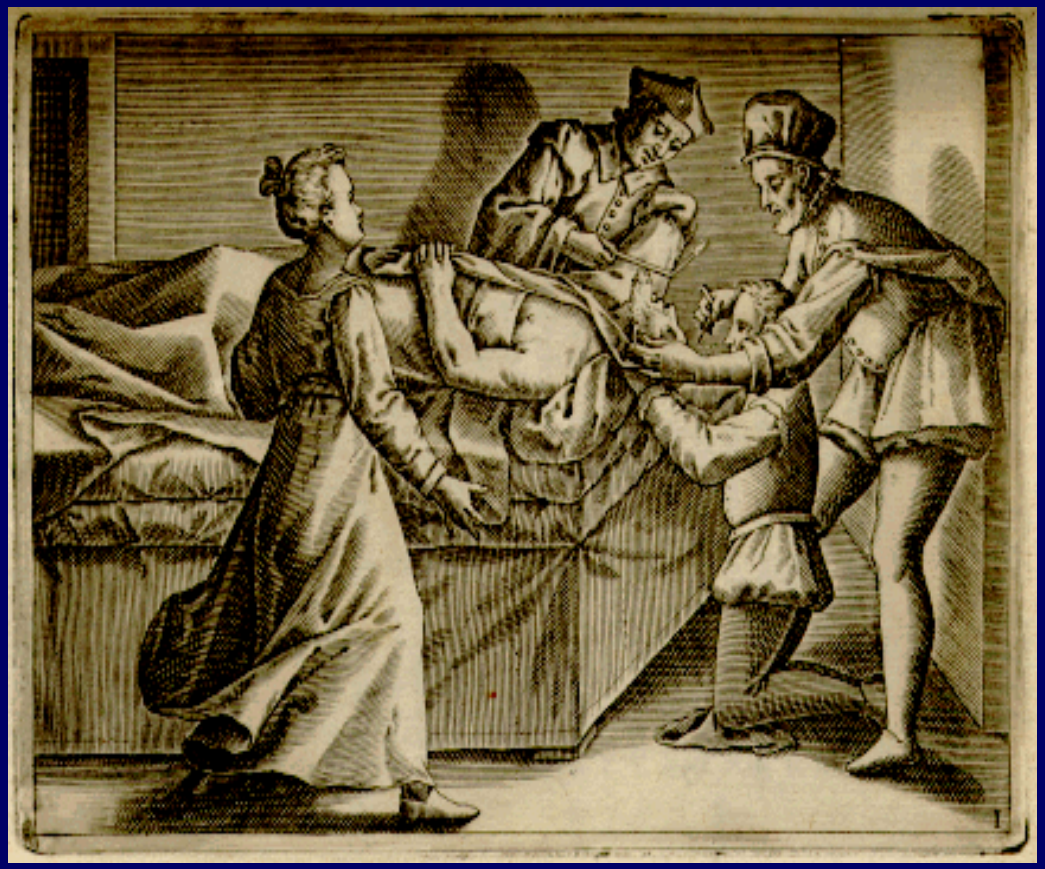
- **Virtual: pregnancy, acute bacterial infection!**

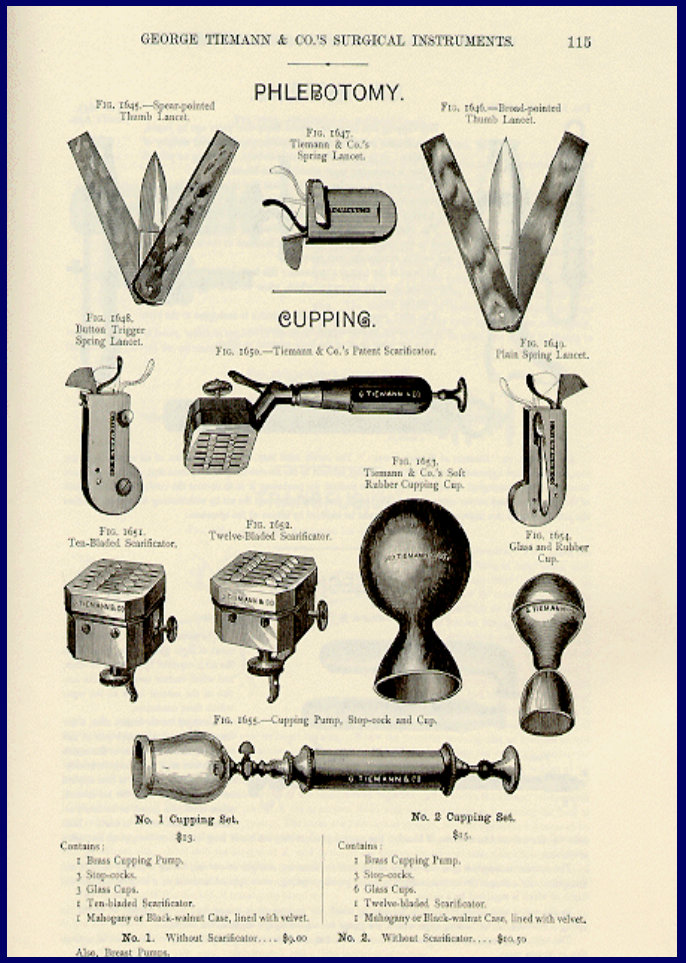
- **Real: microcytosis, anemia**
- **Serum iron, transferrin saturation** ↓
- **Ferritin normal: acute disease**
- **Ferritin ↓ : chronic disease**
- **Soluble transferrin receptor** ↑

Iron excess

- Inherited: hemochromatosis
  transferrin/hemosiderin
- Acquired: repeated transfusions
  excess iron intake
- Serum iron, transferrin saturation
- Ferritin normal: acute disease
- Ferritin : chronic disease
- Soluble transferrin receptor

Treatment of iron excess – in the past and today





GEORGE TIEMANN & CO.'S SURGICAL INSTRUMENTS. 115

PHLEBOTOMY.

Fig. 1645.—Spear-pointed Thumb Lancet.

Fig. 1646.—Broad-pointed Thumb Lancet.

Fig. 1647. Tiemann & Co.'s Spring Lancet.

Fig. 1648. Button Trigger Spring Lancet.

Fig. 1649. Plain Spring Lancet.

CUPPING.

Fig. 1650.—Tiemann & Co.'s Patent Scarificator.

Fig. 1651. Ten-Bladed Scarificator.

Fig. 1652. Twelve-Bladed Scarificator.

Fig. 1653. Tiemann & Co.'s Soft Rubber Cupping Cup.

Fig. 1654. Glass and Rubber Cup.

Fig. 1655.—Cupping Pump, Stop-cock and Cup.

No. 1 Cupping Set.

$13.

Contains:
- 1 Brass Cupping Pump.
- 3 Stop-cocks.
- 3 Glass Cups.
- 1 Ten-bladed Scarificator.
- 1 Mahogany or Black-walnut Case, lined with velvet.

No. 1. Without Scarificator.... $5.00

Also, Breast Pumps.

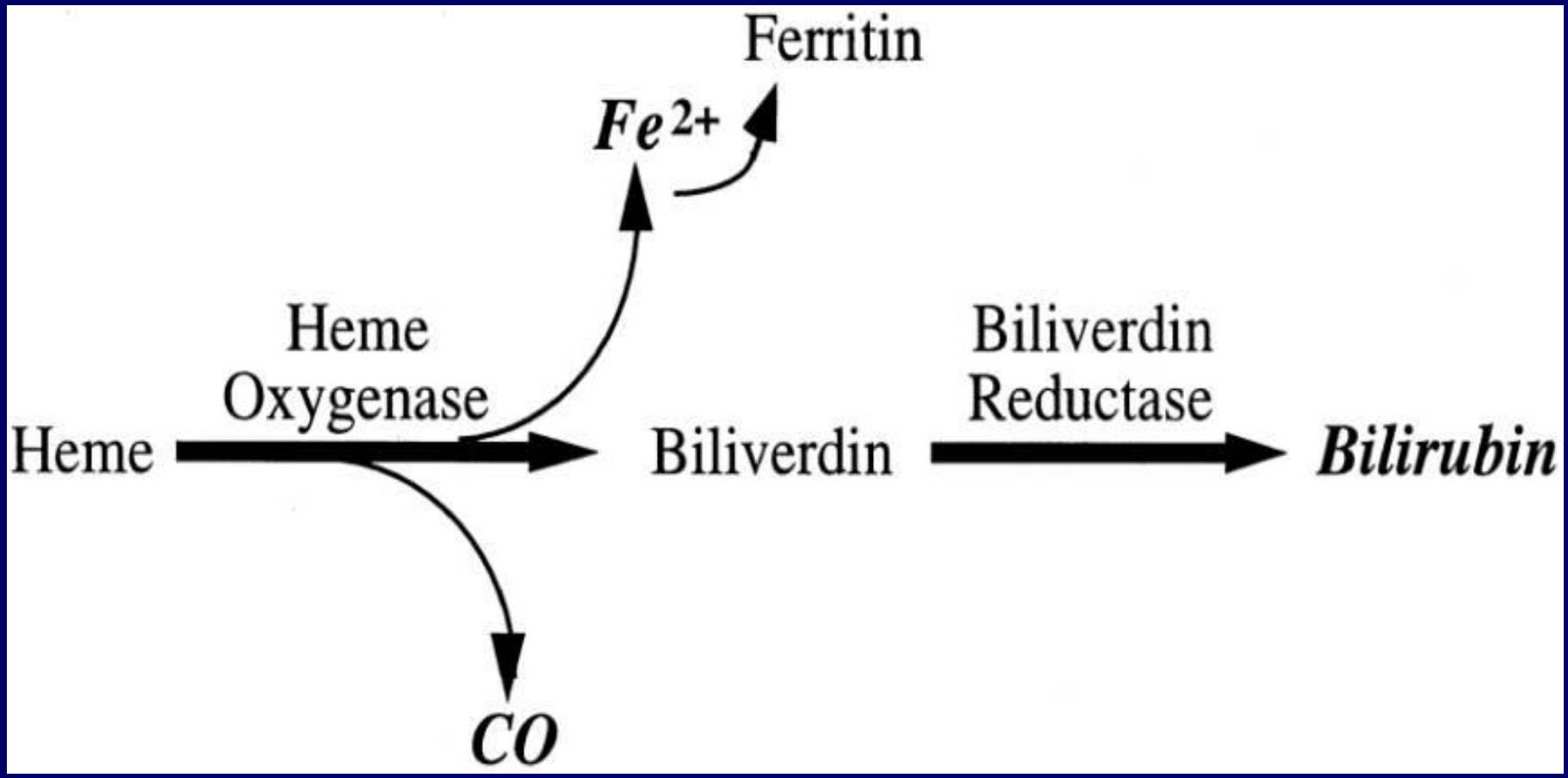
No. 2 Cupping Set.

$15.

Contains:
- 1 Brass Cupping Pump.
- 3 Stop-cocks.
- 6 Glass Cups.
- 1 Twelve-bladed Scarificator.
- 1 Mahogany or Black-walnut Case, lined with velvet.

No. 2. Without Scarificator.... $10.50

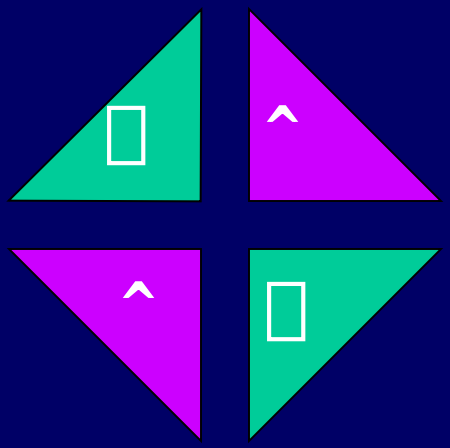
The fate of iron inside the cell

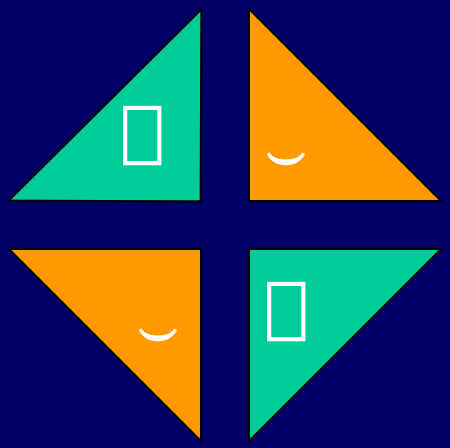


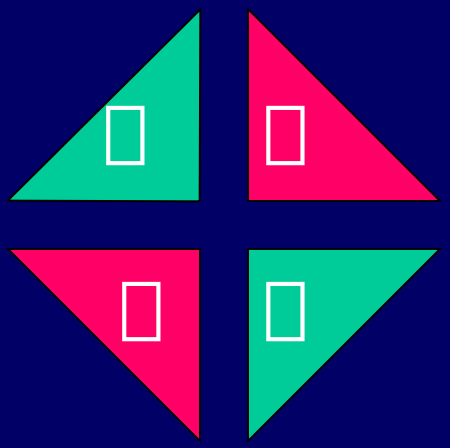
Hemoglobin disorders

- **Mutations of globin protein: hemoglobin variants (e.g. sickle cell anemia)**
- **Inherited globin chain disorders: chain deficiencies (thalassemias)**
- **Change in ligands of heme group: CO-Hgb, Sulf-Hgb, Met-Hgb**

Normal adult hemoglobins

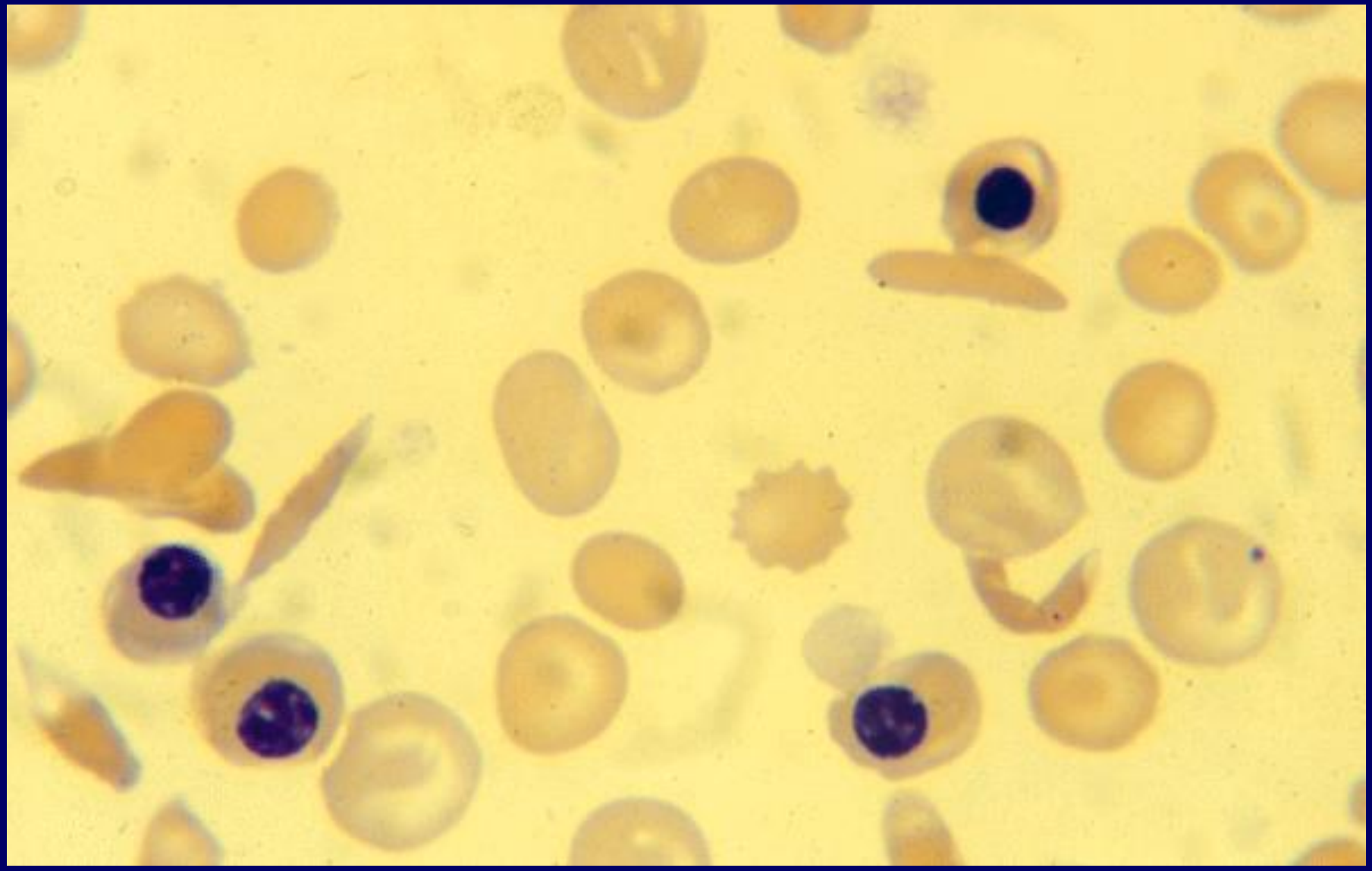




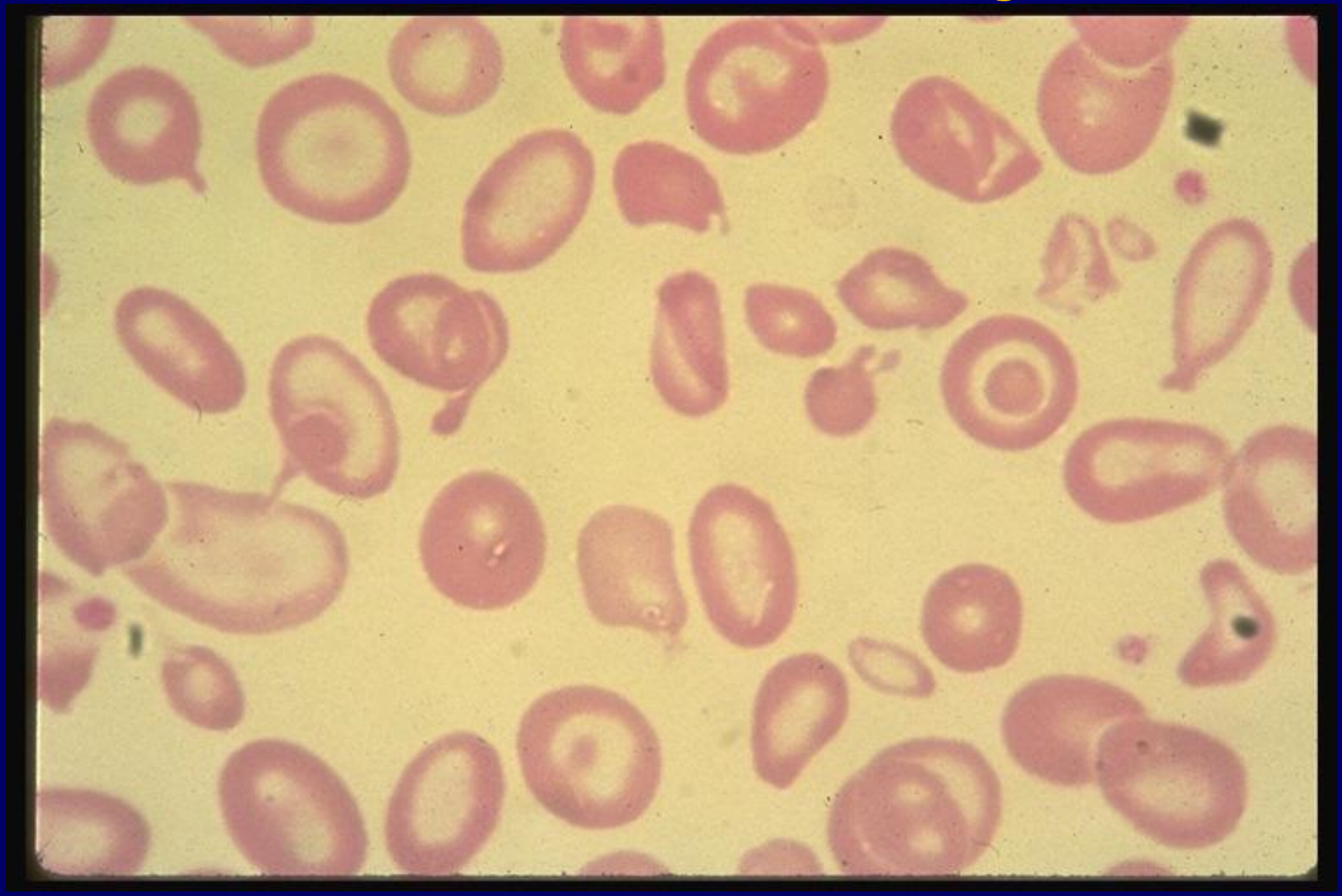


HbA	HbF	HbA_2
98%	~1%	<3.5%

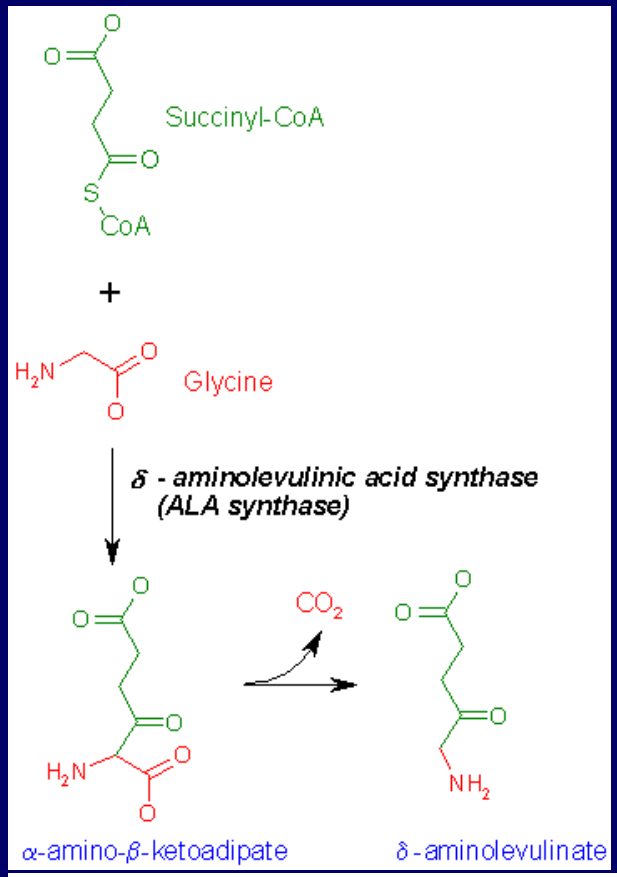
Sickle cell anemia



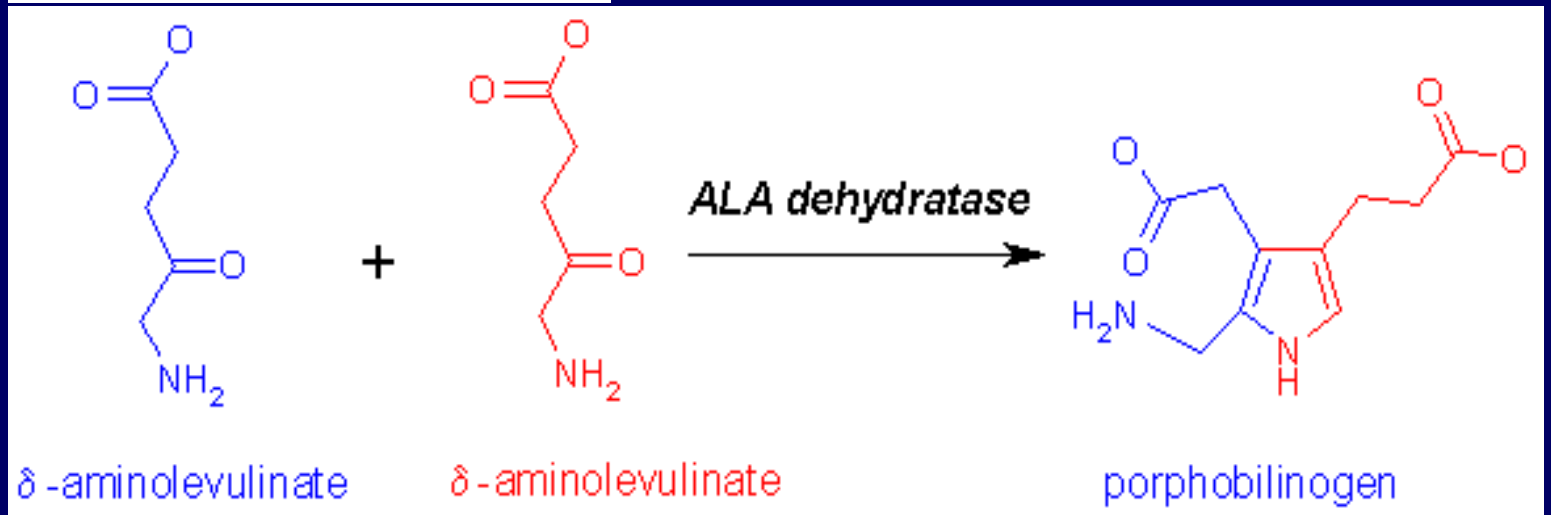
Beta thalassemia major



Heme synthesis

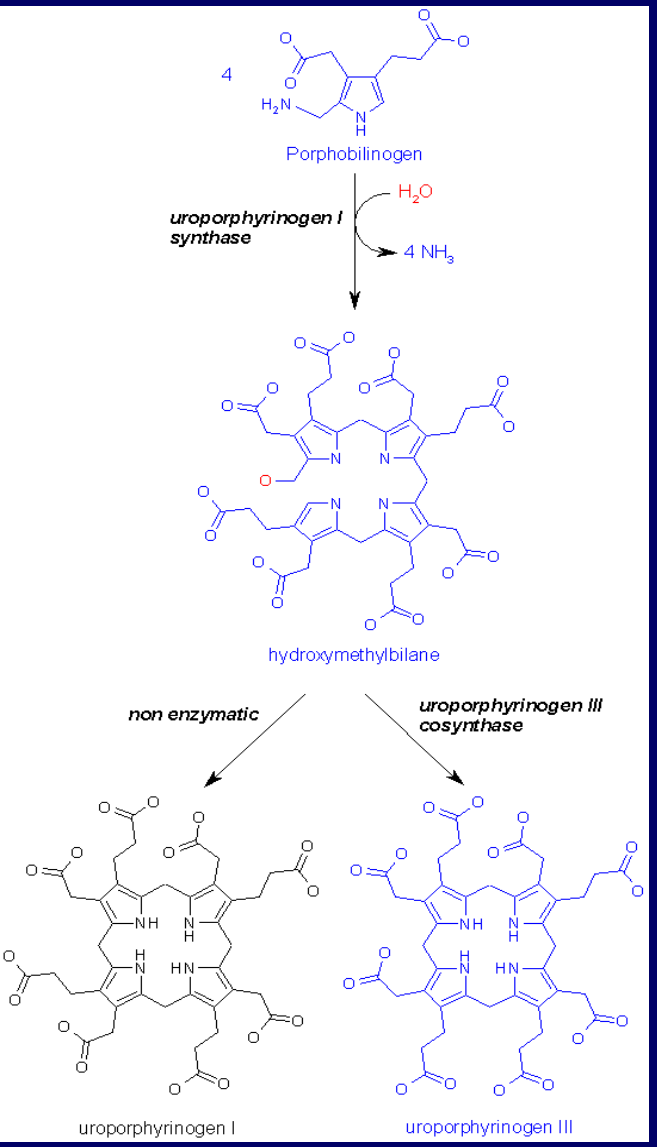


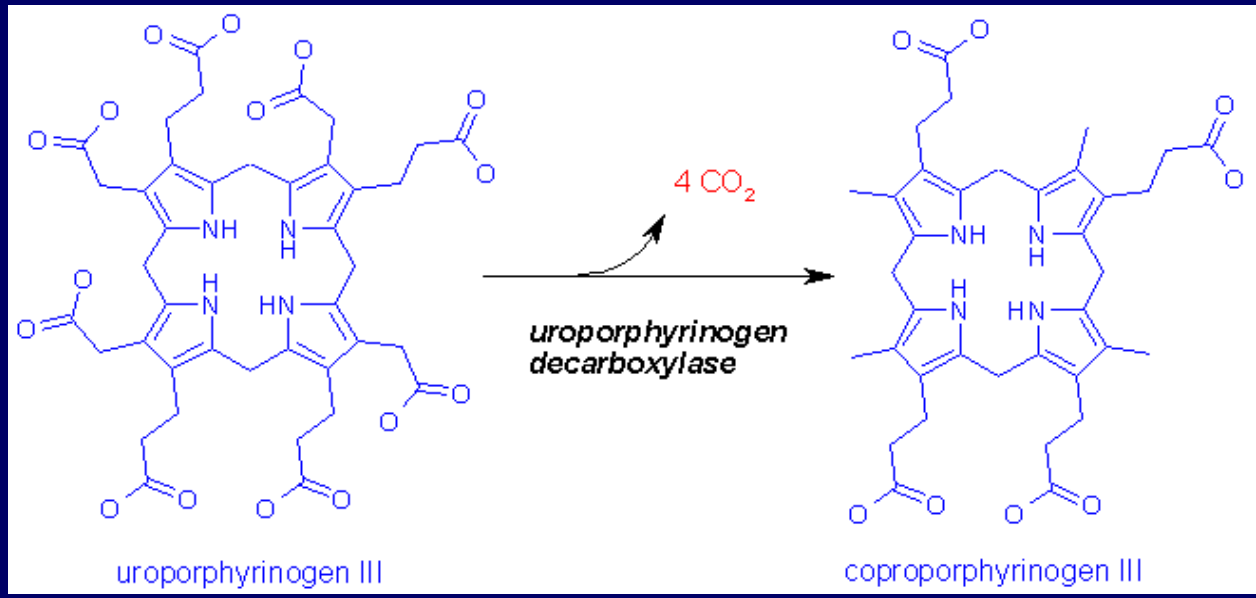
Water soluble molecules: urine



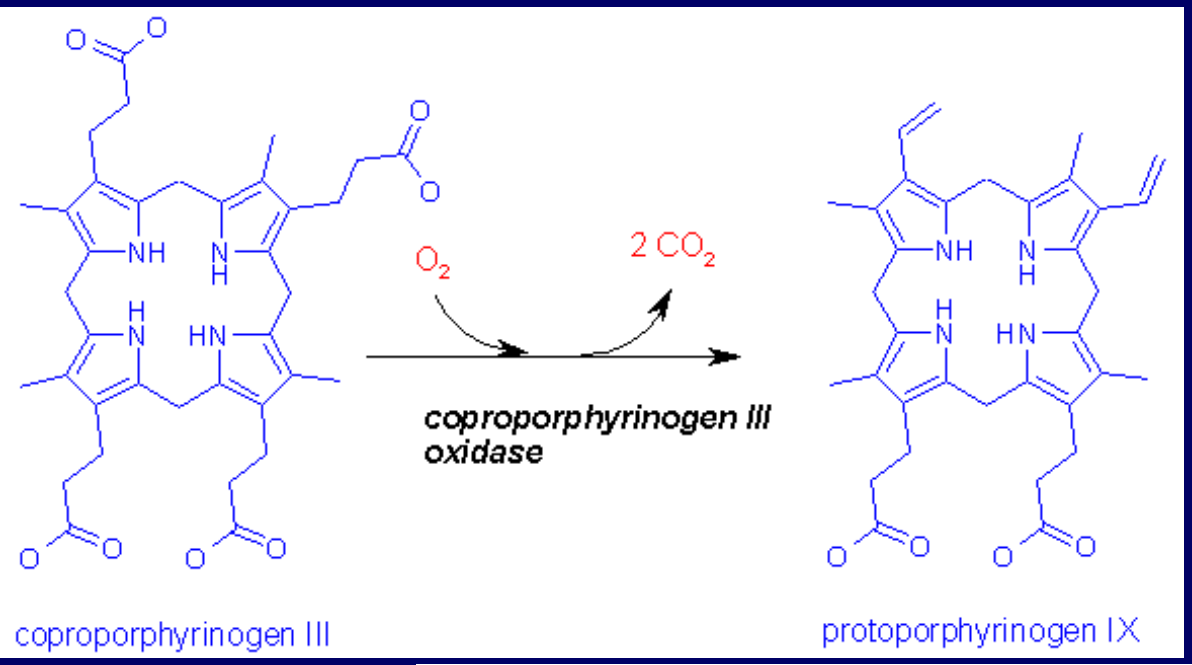
Heme synthesis

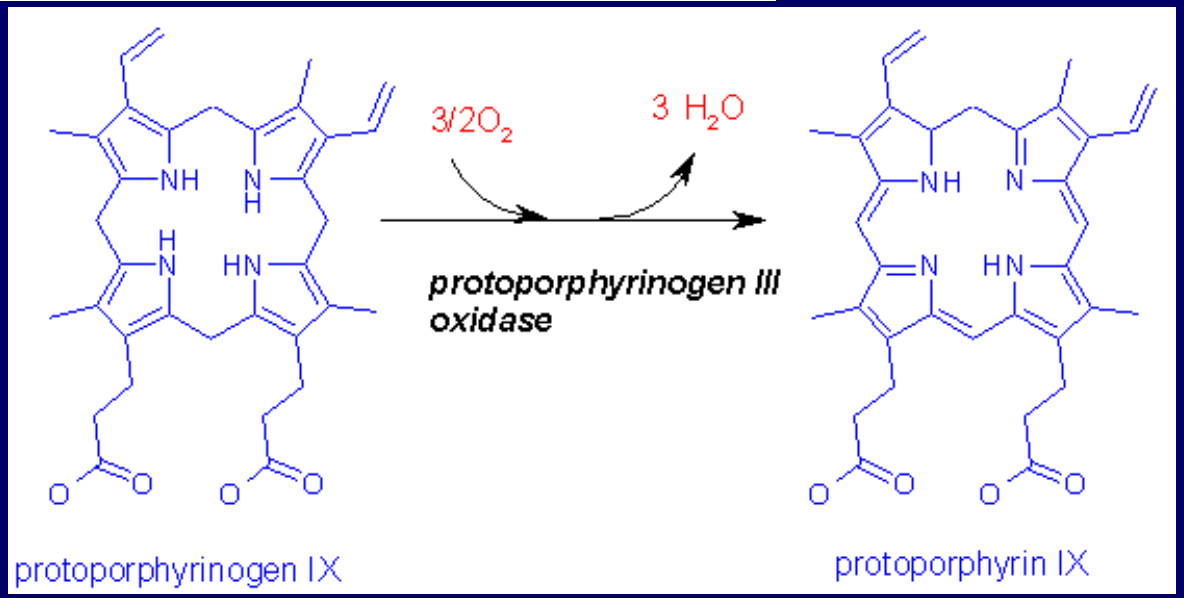
Lipid soluble molecules: tissues (skin)



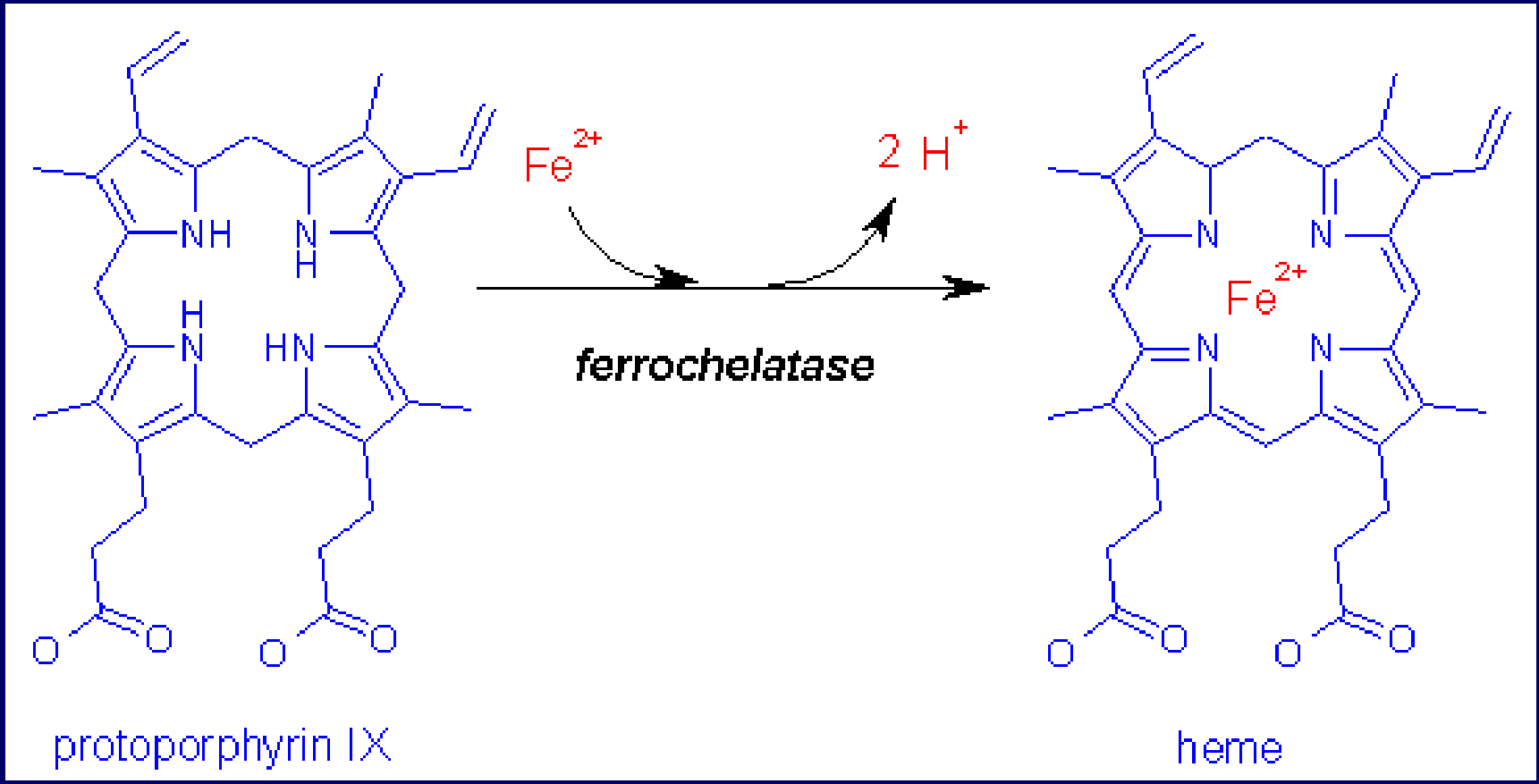


Heme synthesis





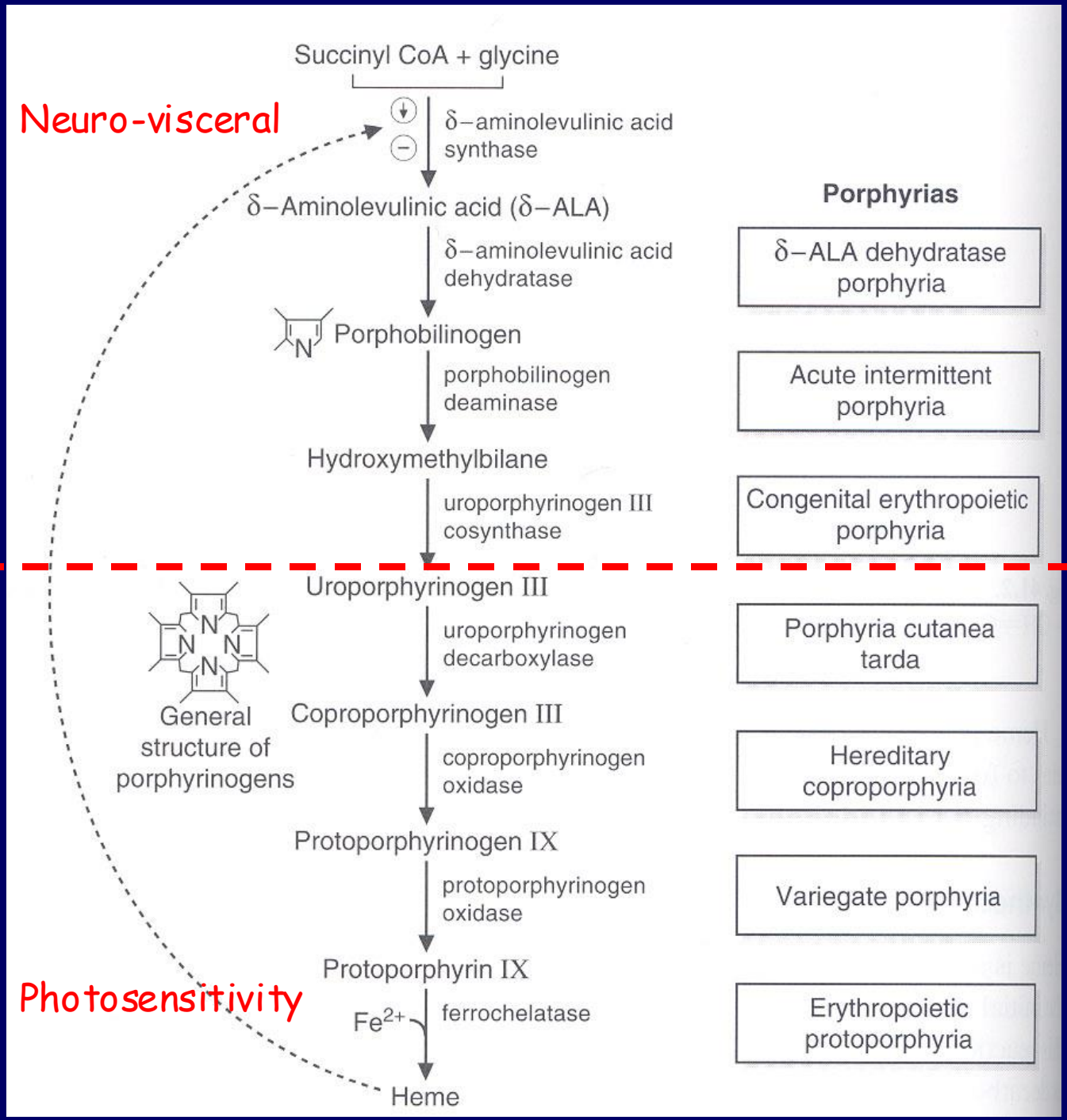
Heme synthesis



Porphyrias

- **Congenital:** **enzyme block**
  precursors – neuro-visceral symptoms
  hydrophobic precursors – light sensitivity
- **A precipitating factor is always needed!**

- **Acquired:** **heavy metal poisoning (lead)**
  enzyme block


Succinyl CoA + glycine
Neuro-visceral
δ–aminolevulinic acid synthase
δ–Aminolevulinic acid (δ–ALA)
δ–aminolevulinic acid dehydratase
Porphobilinogen
porphobilinogen deaminase
Hydroxymethylbilane
uroporphyrinogen III cosynthase
Uroporphyrinogen III
uroporphyrinogen decarboxylase
Coproporphyrinogen III
coproporphyrinogen oxidase
Protoporphyrinogen IX
protoporphyrinogen oxidase
Protoporphyrin IX
Fe2+
ferrochelatase
Heme
Photosensitivity
General structure of porphyrinogens
Porphyrias
δ–ALA dehydratase porphyria
Acute intermittent porphyria
Congenital erythropoietic porphyria
Erythropoeitic
Porphyria cutanea tarda
Hereditary coproporphyria
Variegate porphyria
Erythropoietic protoporphyria
Erythropoeitic