Biochemistry For Pharmacy College Students

Metabolism

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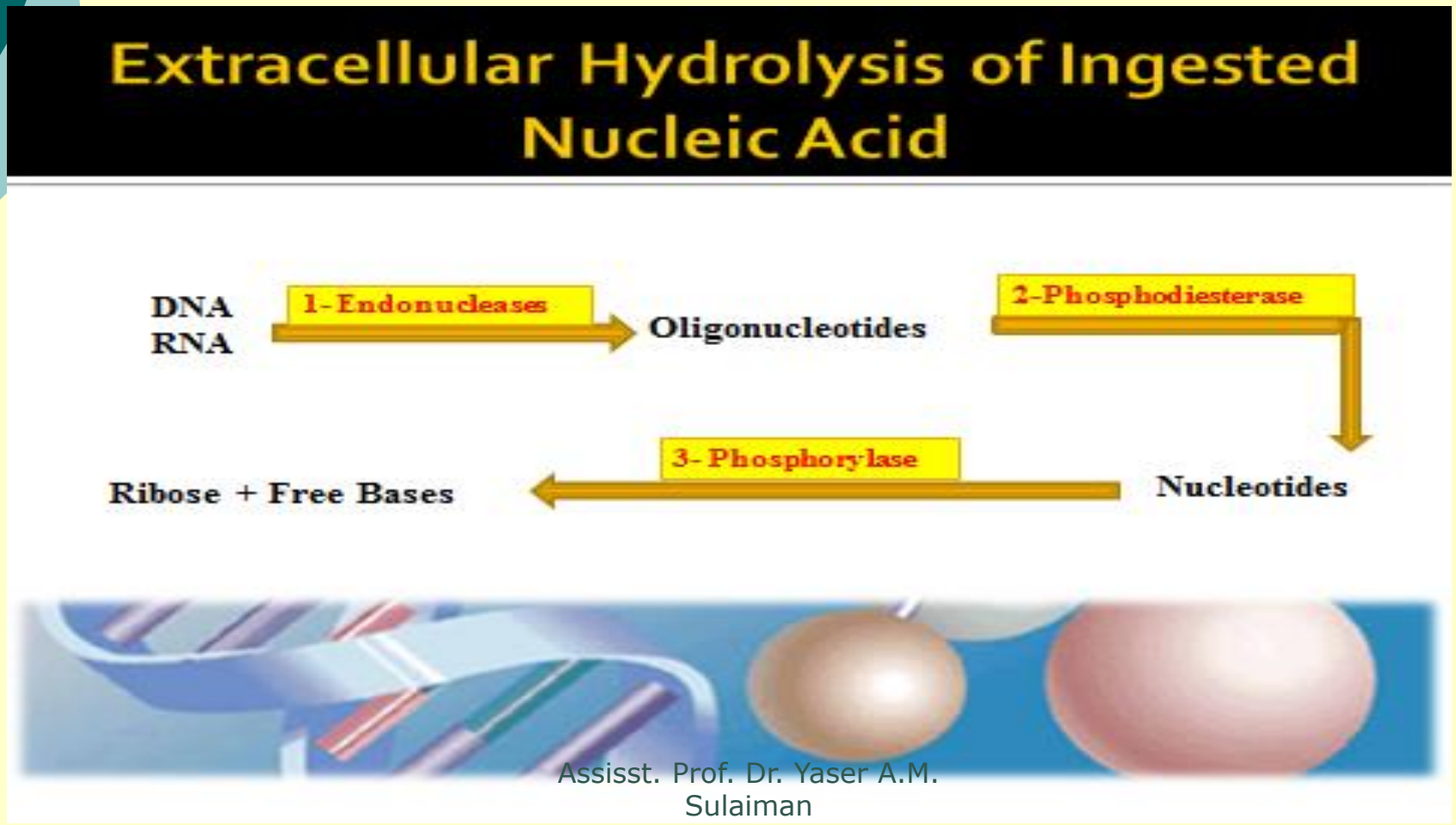
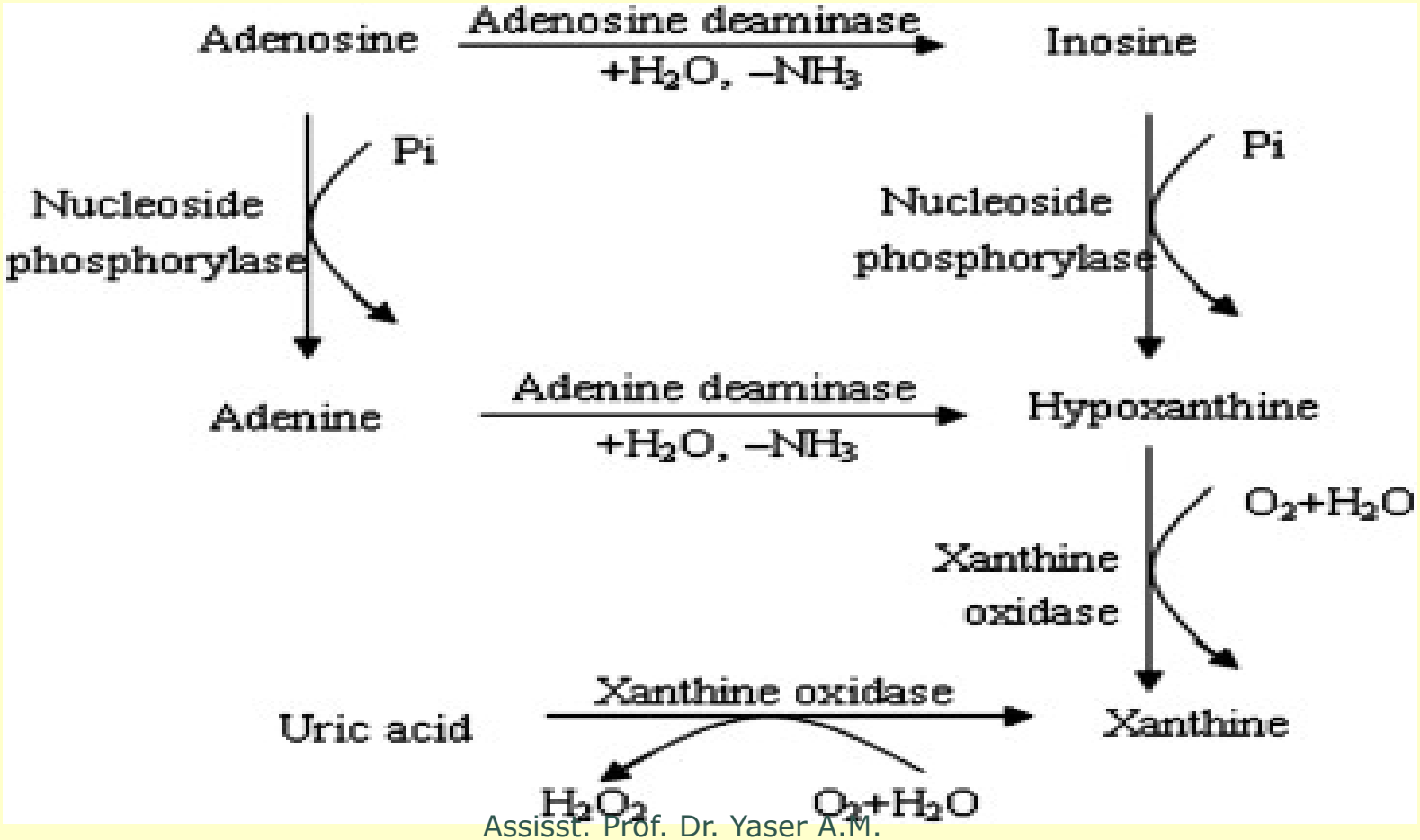
Purine metabolism (Overview)

The Extracellular Hydrolysis of Ingested Nucleic Acid:



Purine metabolism (Overview)



Uric Acid, Hyperuricemia, and Gout

- Uric acid (urate) is the end product of purine degradation in humans
- Hyperuricemia is a serum urate concentration in excess of urate solubility (≥6.8 mg/dL)
  - Results from overproduction and/or underexcretion of uric acid
  - Is a common serum abnormality but does not result in gout without crystal deposition
- Gout is the disease state resulting from deposition of monosodium urate crystals in tissues

Porphyrins & Bile Pigments (Overview)

BIOMEDICAL IMPORTANCE

These two are closely related, because heme is synthesized from porphyrins and iron, and the products of degradation of heme are the bile pigments and iron.

In addition to the heme in hemoglobin and myoglobin, molecules with the porphyrin ring structure include cytochromes, and in plants, the chlorophylls.

Heme is synthesized in most cells. Reticulocytes make ~ 4 x 10^{12} hemes per second.

In all cases, the precursors are glycine and succinyl CoA.

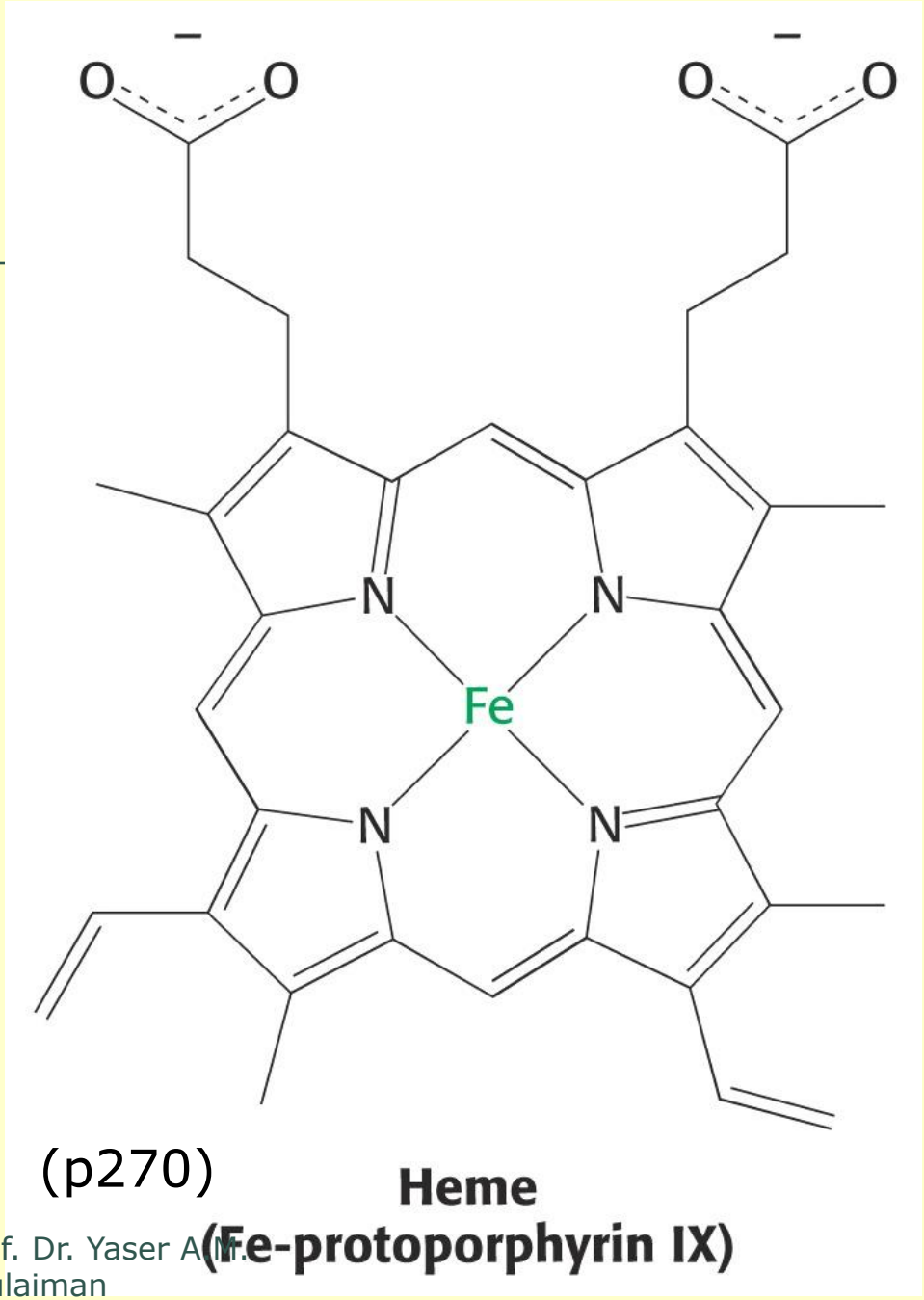
Table 32–1. Examples of some important human and animal hemoproteins.[1]

Protein	Function
Hemoglobin	Transport of oxygen in blood
Myoglobin	Storage of oxygen in muscle
Cytochrome *c*	Involvement in electron transport chain
Cytochrome P450	Hydroxylation of xenobiotics
Catalase	Degradation of hydrogen peroxide
Tryptophan pyrrolase	Oxidation of trypotophan

6.94 x 9.15 in

Heme Structure

- The core protoporphyrin ring structure is constant.
- The sidechains vary in other porphyrins.
- The protein structure determines the properties of the prosthetic group.



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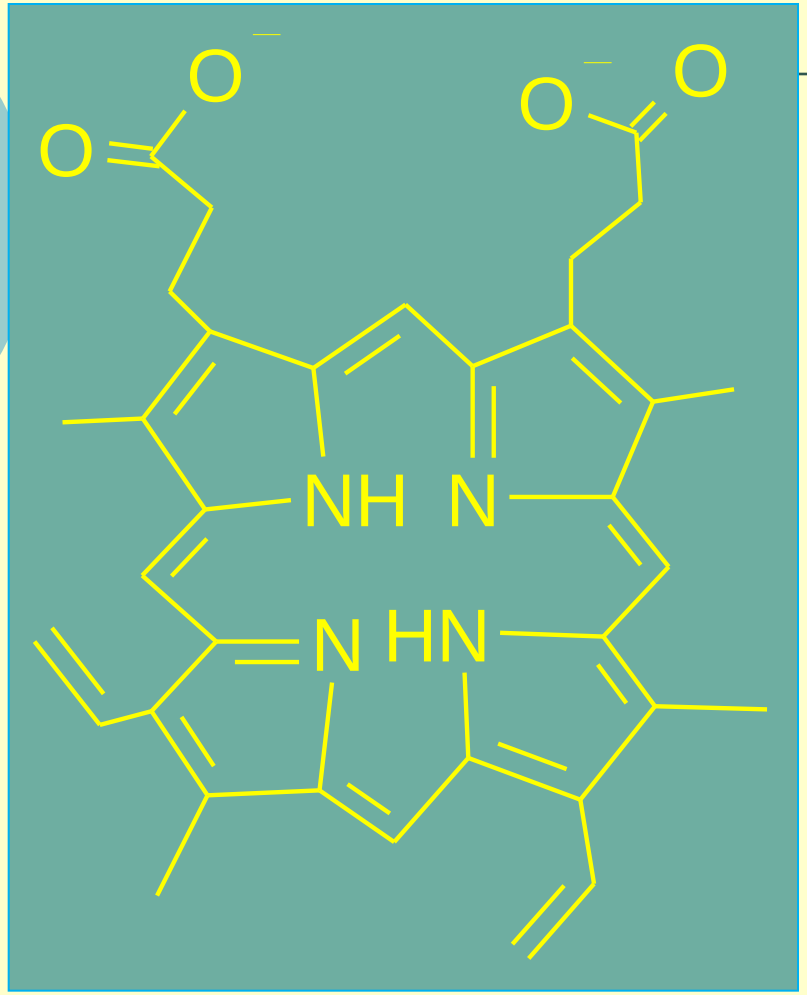
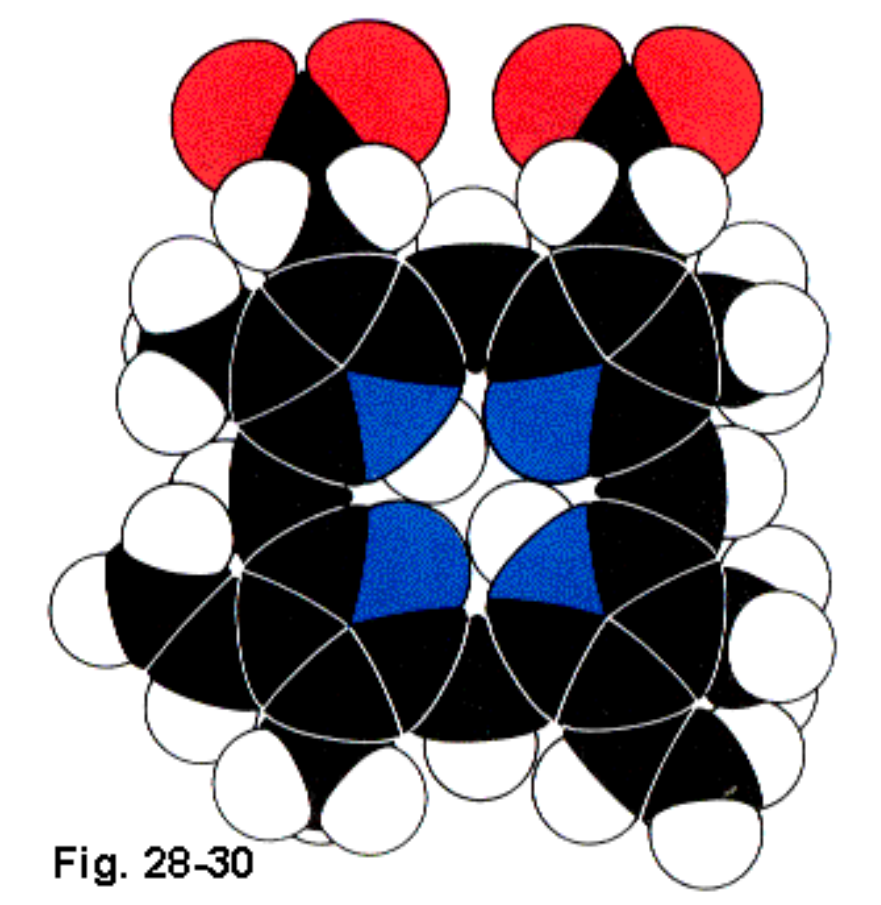
Heme
(Fe-protoporphyrin IX)

Protoporphyrin IX Structure

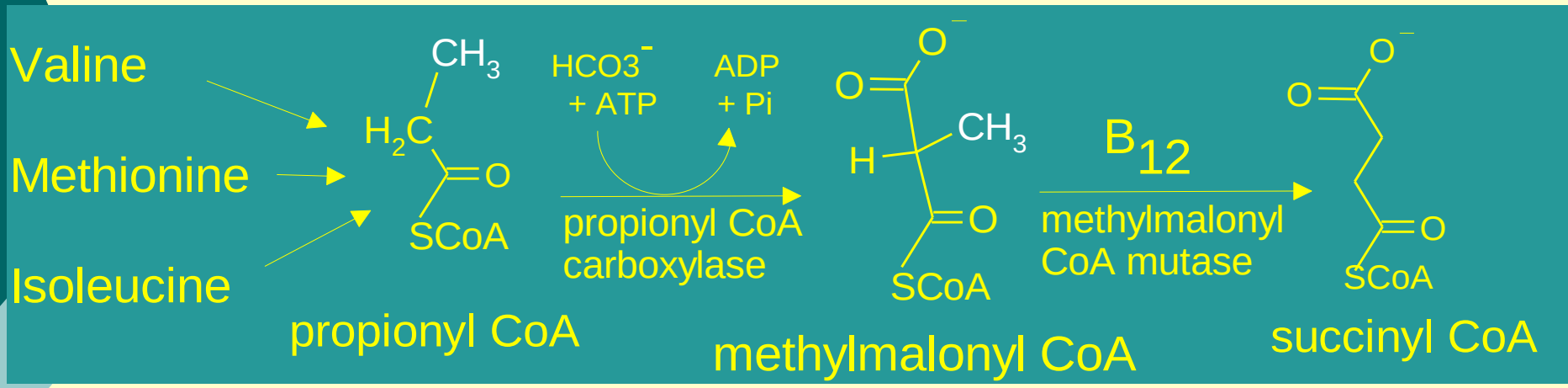




Stryer 4th

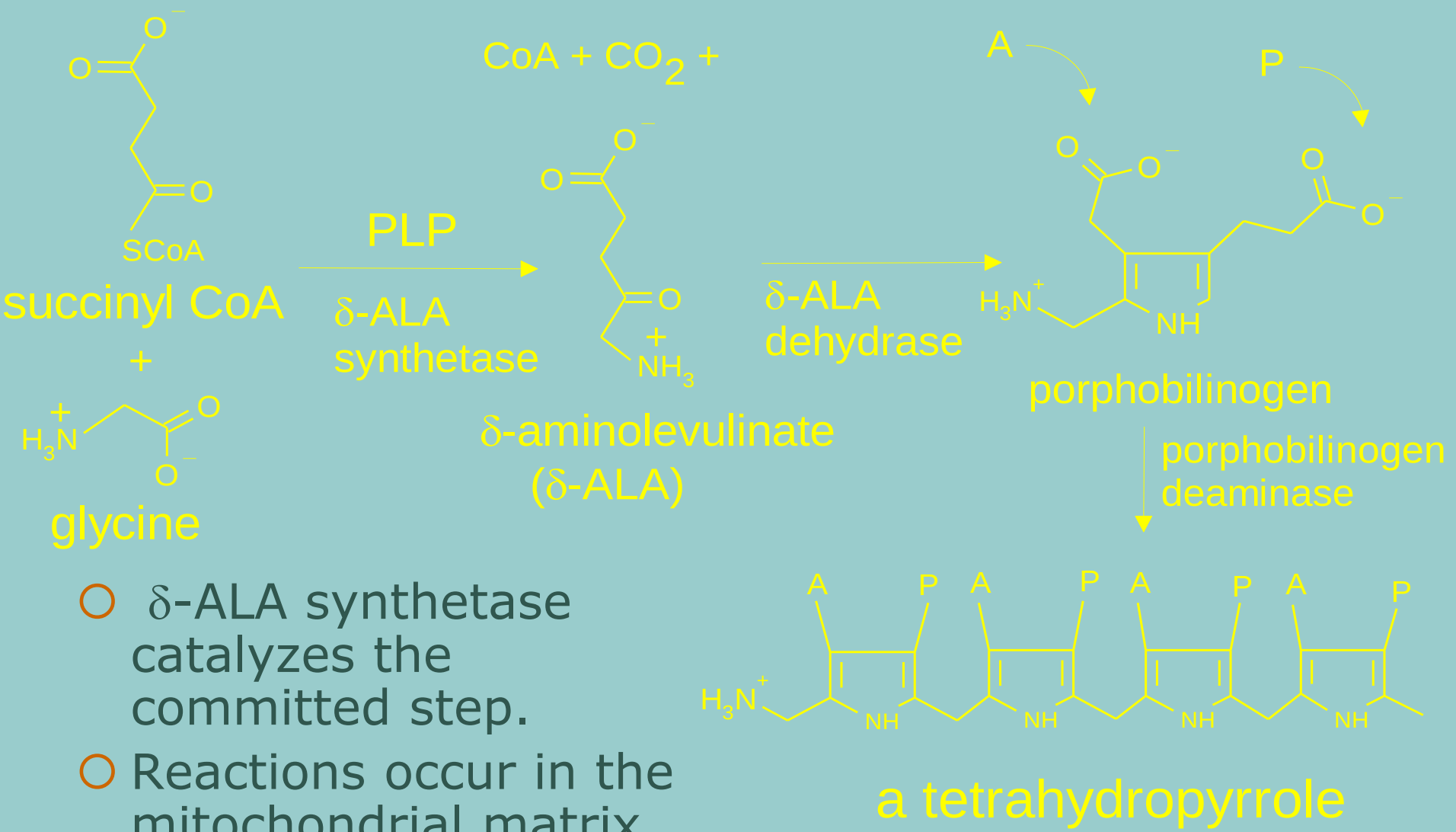
- Fe(II) displaces the two protons in the center.

Succinyl CoA Biosynthesis



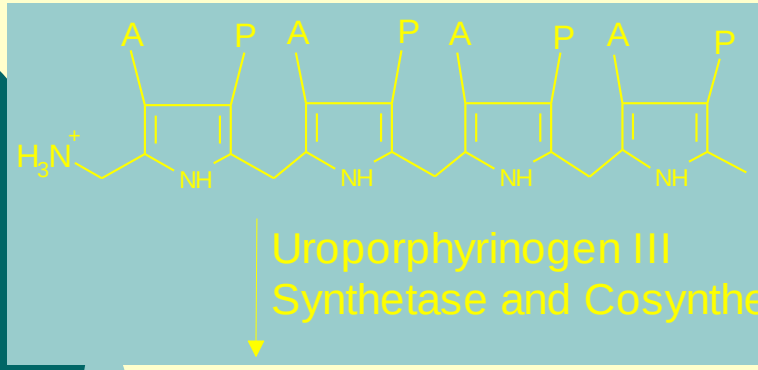
- One heme precursor, succinyl CoA. can be made from propionyl CoA, or from α-ketoglutarate in the Krebs cycle.
- Propionyl CoA can be made from amino acids, or from the oxidation of odd-numbered fatty acids.
- After propionyl CoA is carboxylated, the conversion of methylmalonyl CoA to succinyl CoA requires vitamin B_{12}.

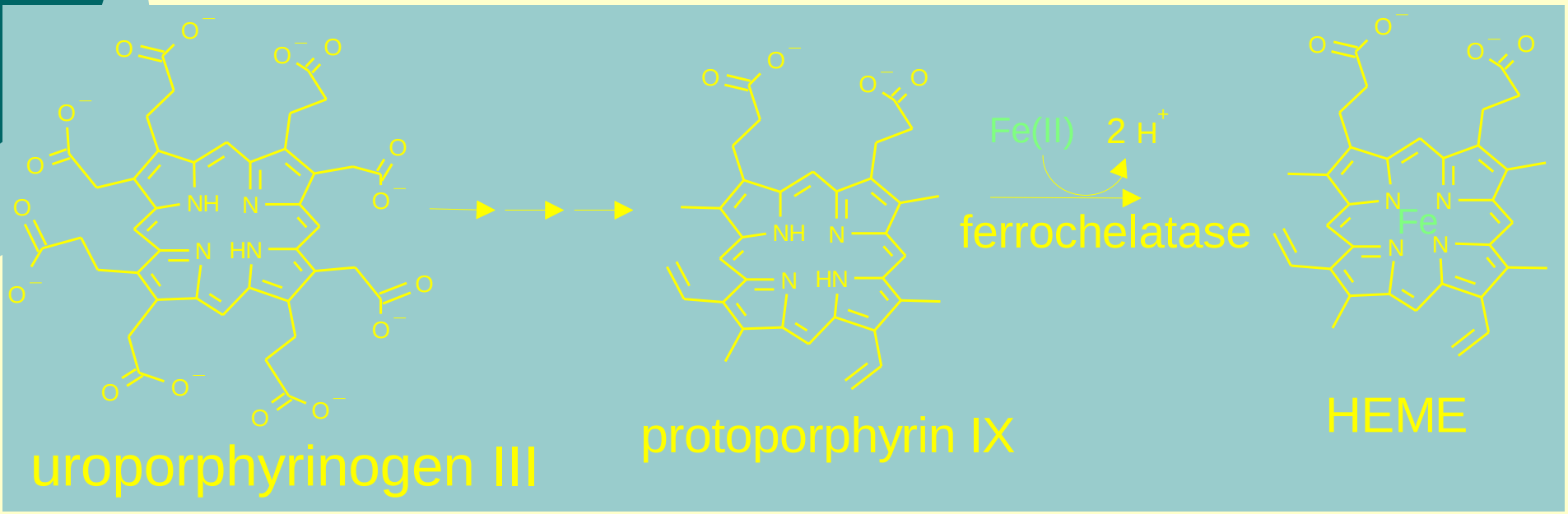
Heme Biosynthesis: Part 1



- δ-ALA synthetase catalyzes the committed step.
- Reactions occur in the mitochondrial matrix.
- 8 succinyl CoA & 8 glycine.

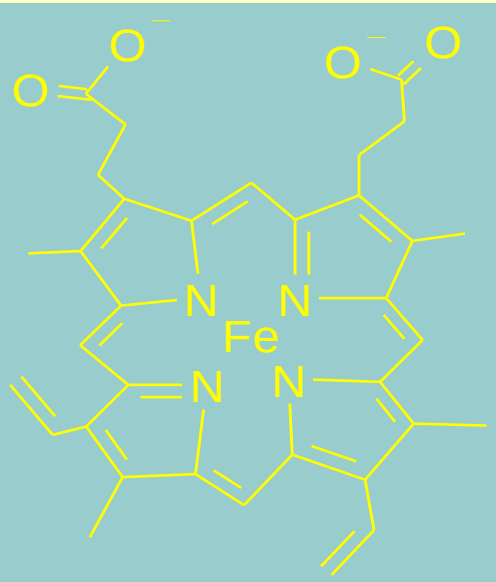
Heme Biosynthesis: Part 2

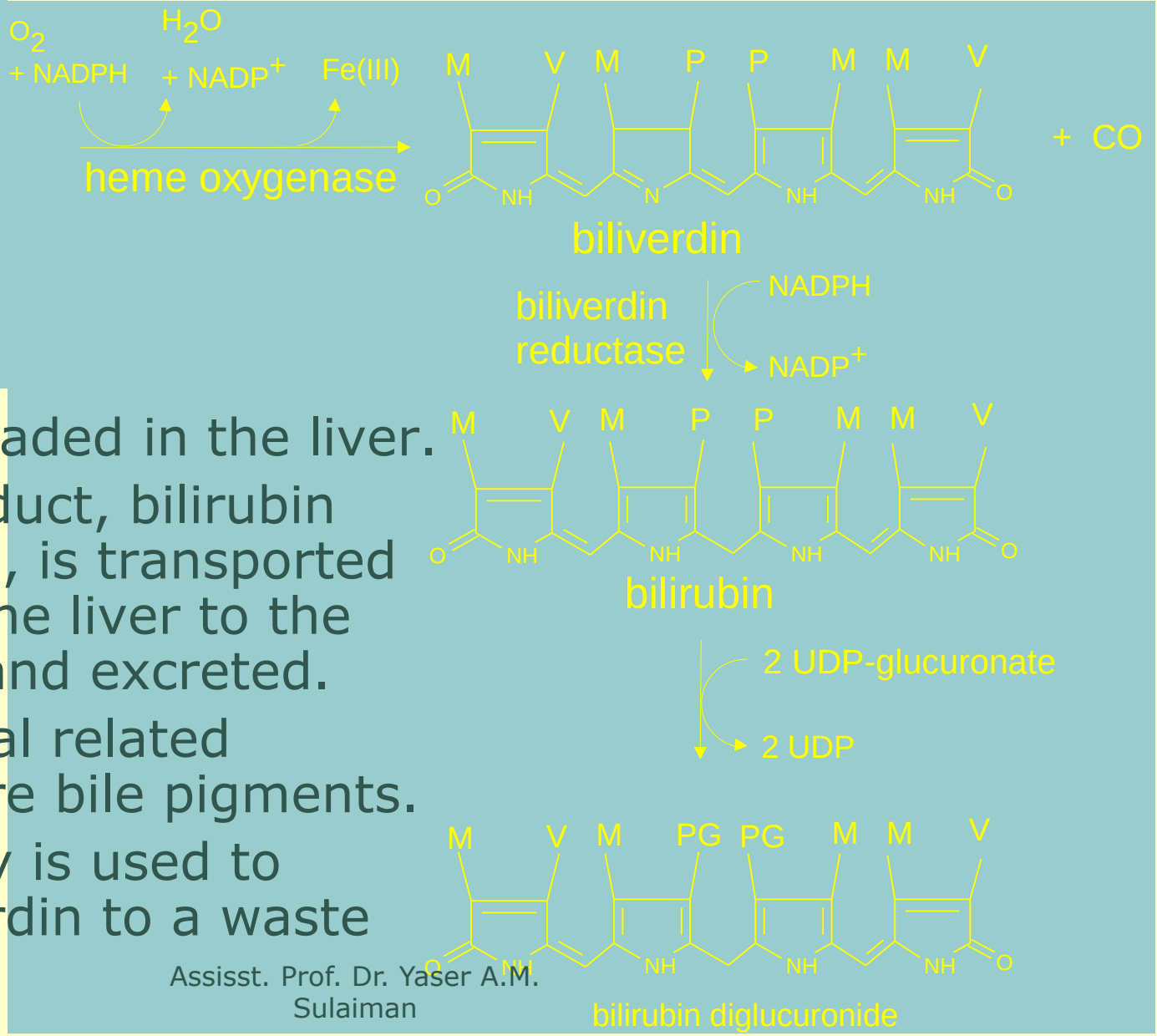




- Notice that one of the pyrrole rings was "rotated" by the uroporphyrinogen cosynthetase making the cyclic uroporphyrinogen III asymmetric
- The multiple arrows are several decarboxylations.

Heme Degradation





- Heme is degraded in the liver.
- The final product, bilirubin diglucuronide, is transported in bile from the liver to the gall bladder and excreted.
- It, and several related structures, are bile pigments.
- Notice energy is used to reduce biliverdin to a waste product.

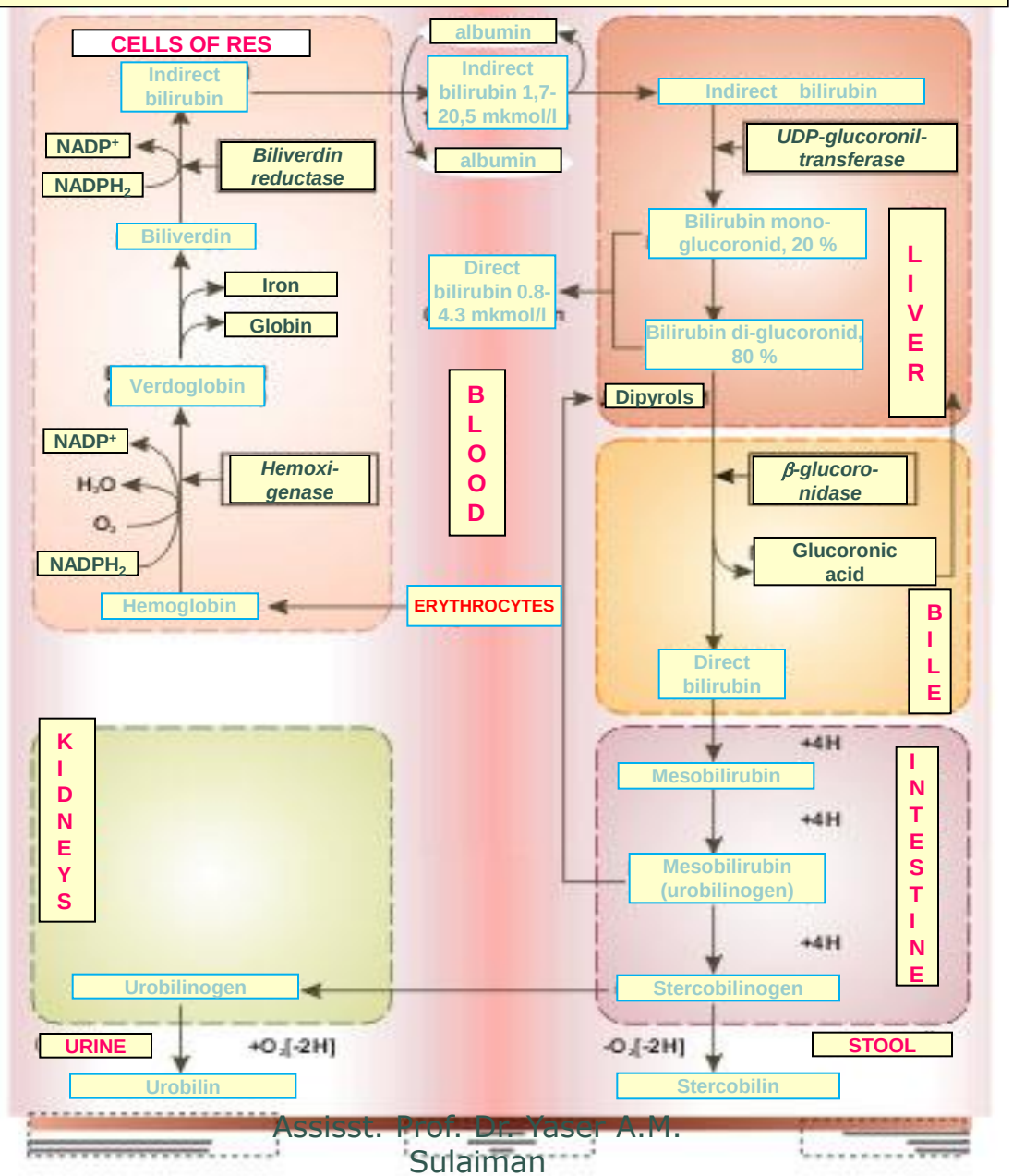
Hb Heme Life Cycle

- Synthesized in red blood cell precursors.
- Spends about 120 days in the bloodstream.
- Identified as "old" by the spleen, which disrupts the rbc membrane, freeing the Hb.
- Transported to the liver as a haptoglobin-hemoglobin complex.
- Degraded in the liver to amino acids, Fe(III) and bilirubin diglucuronide.
- The iron is transported to other cells, bound to transferrin, for reuse.
- Bilirubin diglucuronide excreted by gall bladder.

Bile

- About 500 ml per day of bile is made by the liver, which excretes it and transfers it to the gall bladder.
- The gall bladder concentrates bile and excretes it into the intestinal lumen.
- The three main dissolved constituents are glycocholate (~80%), phospholipids (~15%) and cholesterol (~5%).
- Glycocholate, a fat-solubilizing detergent, is reabsorbed by the intestinal epithelium.
- The other constituents, such bile pigments, are minor.

NORMAL METABOLISM OF BILE PIGMENTS



ABNORMAL METABOLISM OF BILE PIGMENTS

- The porphyrias are a group of diseases caused by abnormalities in the pathway of biosynthesis of the various porphyrins.
- The most more prevalent clinical condition is jaundice, due to elevation of bilirubin in the plasma. This elevation is due to overproduction of bilirubin or to failure of its excretion and is seen in numerous diseases ranging from hemolytic anemias to viral hepatitis and to cancer of the pancreas.