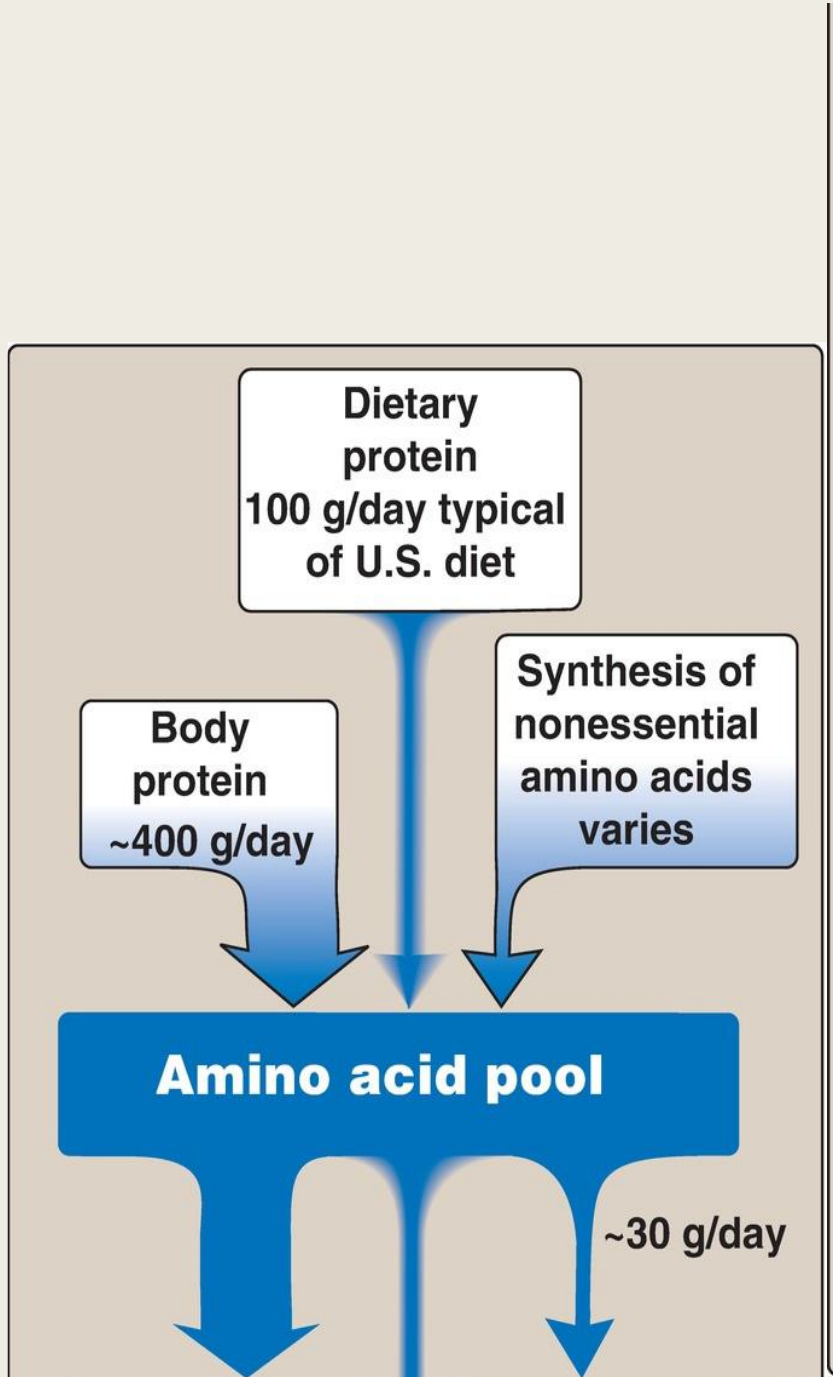
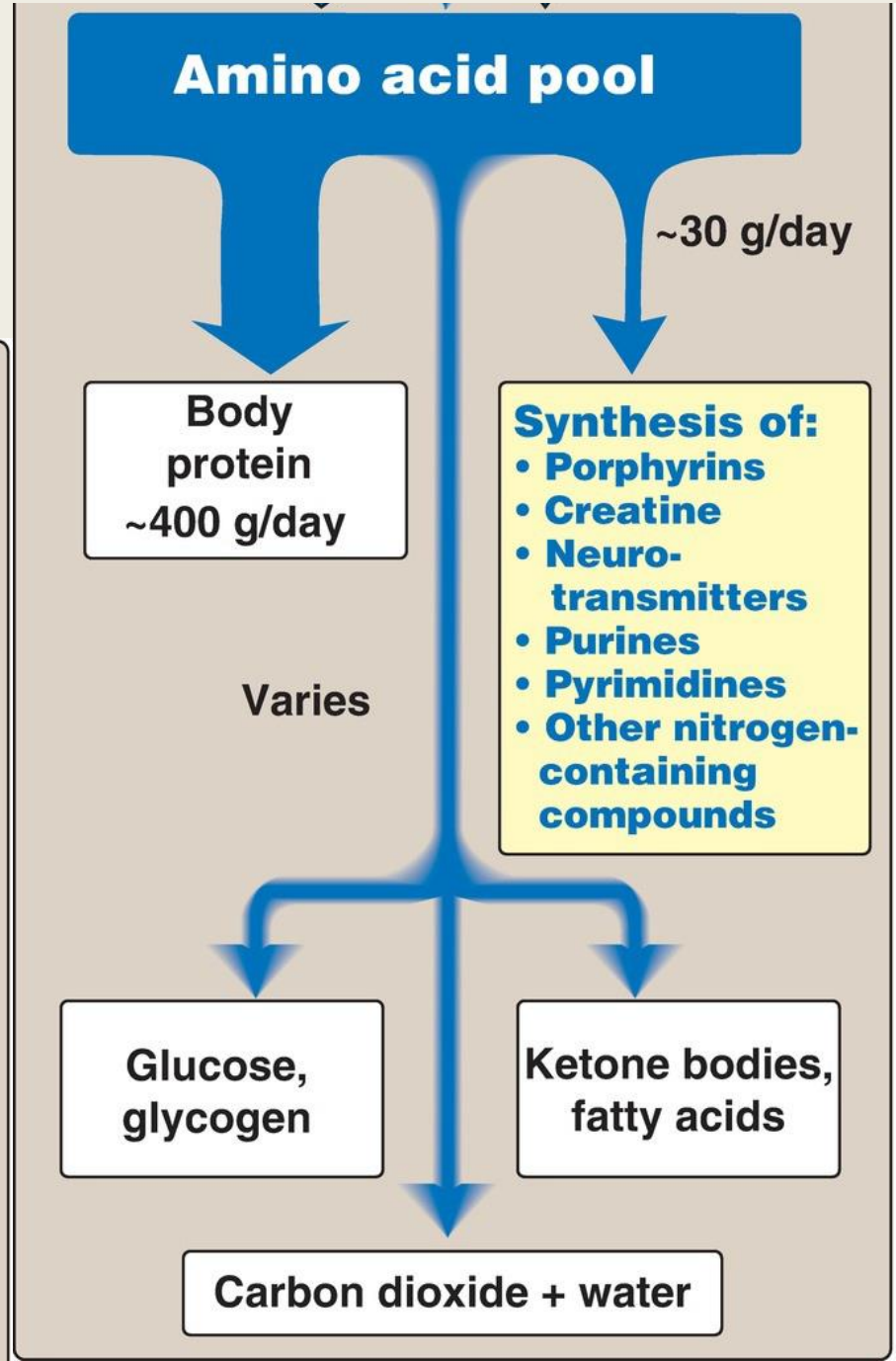
AMINO ACIDS

Conversion to Specialized Products

OVERVIEW

- Porphyrins, neurotransmitters, hormones, purines, and pyrimidines, and nitric oxide





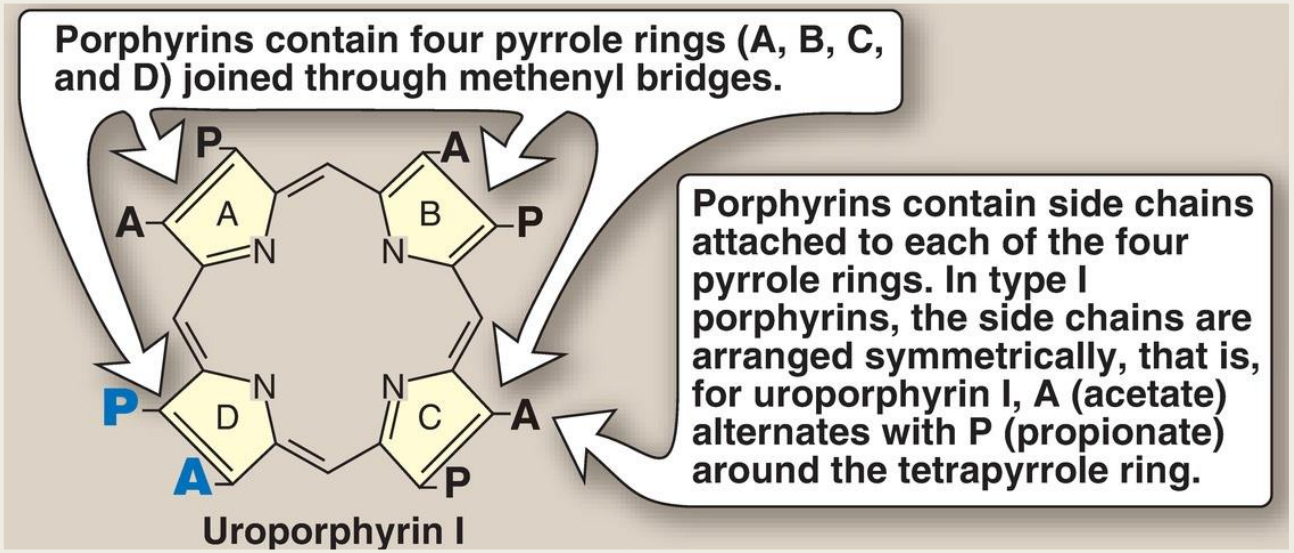
PORPHYRIN METABOLISM

PORPHYRIN METABOLISM

- Cyclic; bind metal ions (usually Fe^{2+} or ferric Fe^{3+})
- The most prevalent is heme:
  - *Fe^{2+} coordinated to tetrapyrrole ring of protoporphyrin IX;*
  - *Prosthetic group for hemoglobin (Hb), myoglobin, cytochromes, the cytochrome P450 (CYP) monooxygenase system, catalase, nitric oxide synthase, and peroxidase*
- Hemeproteins are rapidly synthesized and degraded
  - *6–7 g of Hb is synthesized / day to replace heme lost*
- Synthesis and degradation of the associated porphyrins and recycling of the iron are coordinated with the turnover of hemeproteins

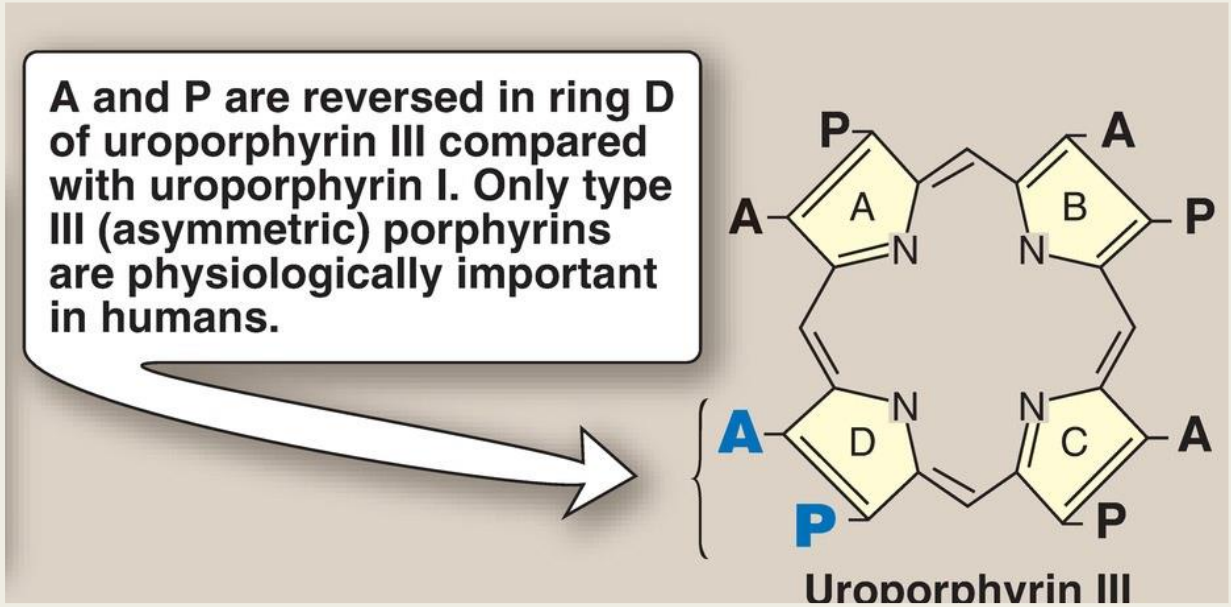
A. Structure

- Cyclic; planar; linking four pyrrole rings through methenyl bridges
- 1. Side chains:
  - *Uroporphyrin: acetate (−CH2−COO−) and propionate (−CH2−CH2−COO−)*
  - *Coproporphyrin: methyl (−CH3) and propionate*
  - *Protoporphyrin IX (heme b): vinyl (−CH=CH2), methyl, and propionate*



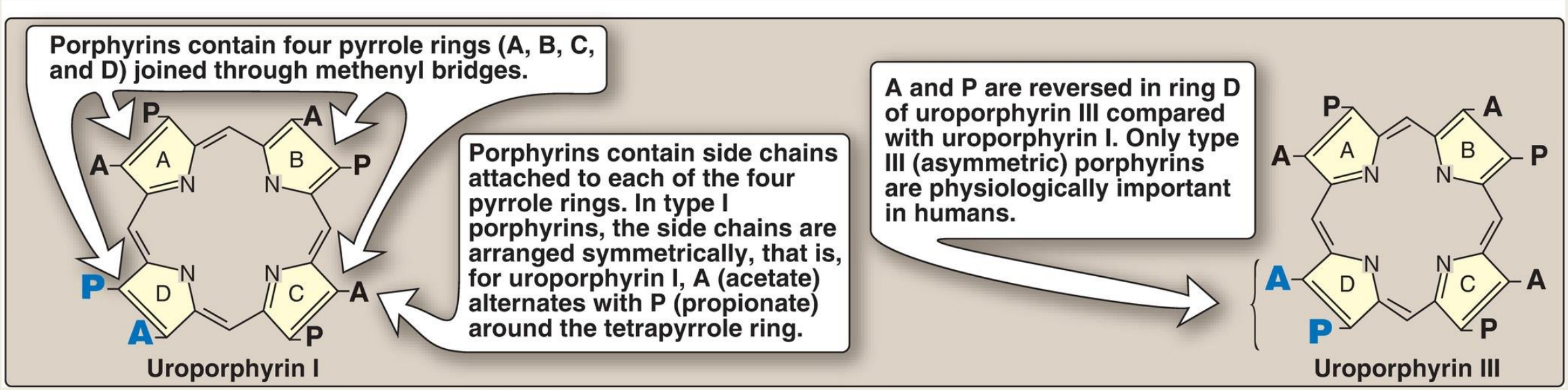
A. Structure

- 2. Side chain distribution:
  - *Different ways*
  - *Only type III porphyrins, (asymmetric substitution on ring D), are physiologically important in humans*
  - *Protoporphyrin IX is a member of the type III series*



A. Structure

- 3. Porphyrinogens:
  - *Porphyrin precursors*
  - *Exist in a chemically reduced, colorless form*
  - *Serve as intermediates between (PBG) and the oxidized, colored protoporphyrins in heme biosynthesis*

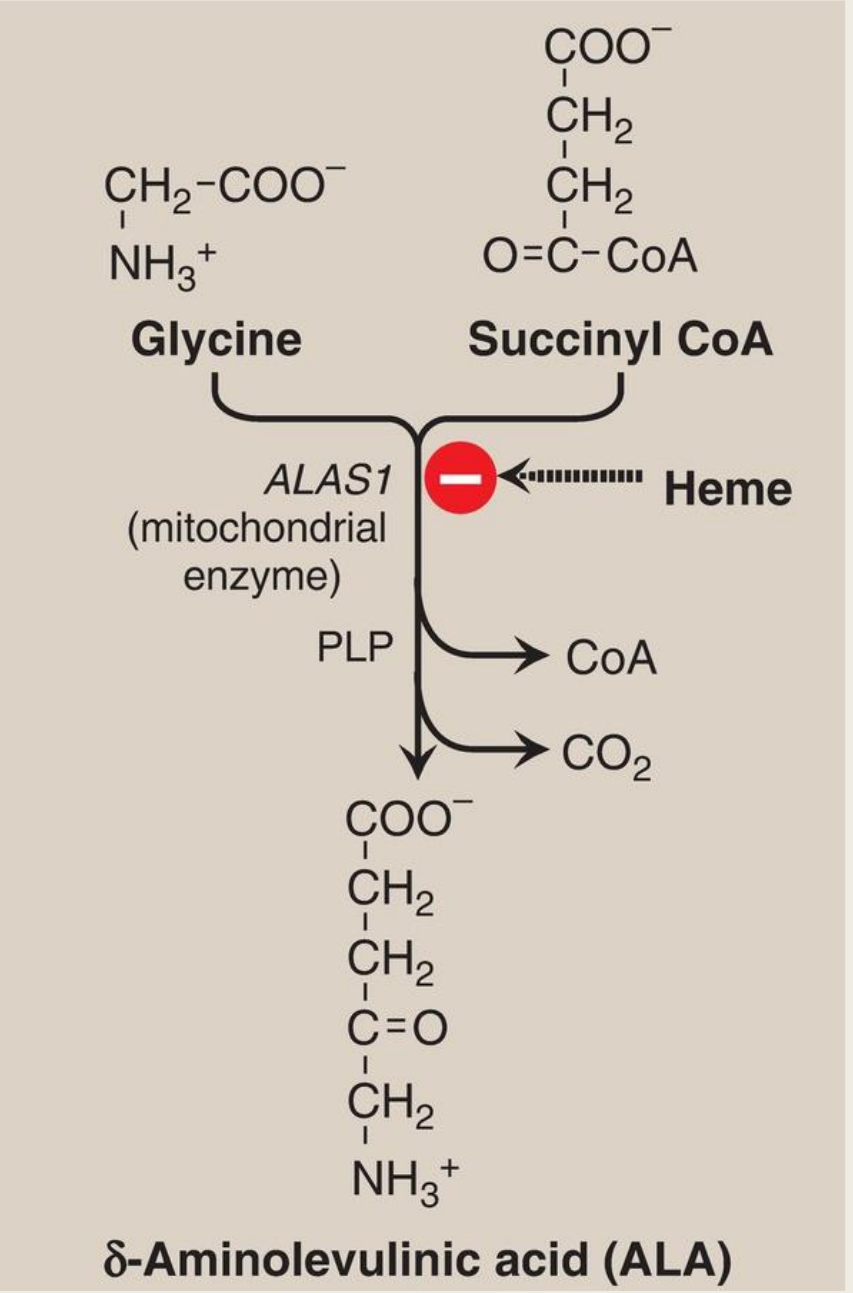


B. Heme biosynthesis

- Liver
  - *Heme proteins (CYP)*
  - *Highly variable*
- Erythrocyte-producing cells of the bone marrow
  - *Hb*
  - *Relatively constant (rate of globin synthesis)*
  - *>85% of all heme synthesis*
- *Mitochondria: initial reaction and last three steps – other steps (cytosol)*

B. Heme biosynthesis

- 1. δ-Aminolevulinic acid formation (ALA):
  - *Glycine and succinyl coenzyme A*
  - *Condensation*
  - *ALA synthase [ALAS], PLP*
  - *Committed and rate-limiting step*
  - *ALAS1 vs. ALAS2*
  - *Loss-of-function mutations in ALAS2 result in Xlinked sideroblastic anemia and iron overload*

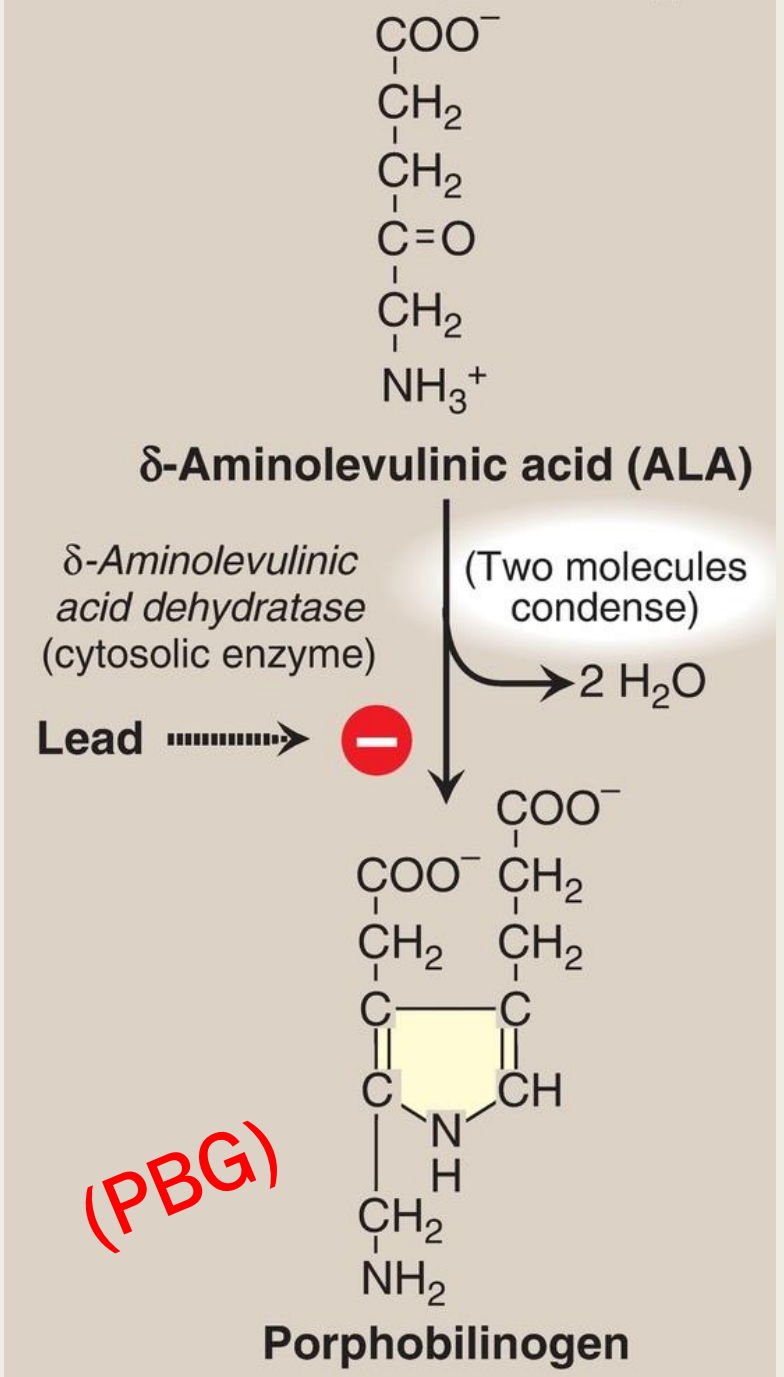


B. Heme biosynthesis – Effects on *ALAS*

- a. Oxidized Heme (hemin) effects (transcription and metabolic):
  - *Decreases the amount (activity) of ALAS1 – repression*
  - *mRNA*
  - *Import into mitochondria*
    - *ALAS2* is controlled by the availability of intracellular iron
- *b. Drug effects:*
  - *Metabolized by the microsomal CYP monooxygenase system (hemeprotein oxidase) (compensatory)*
  - *Significant increase in hepatic ALAS1 activity*

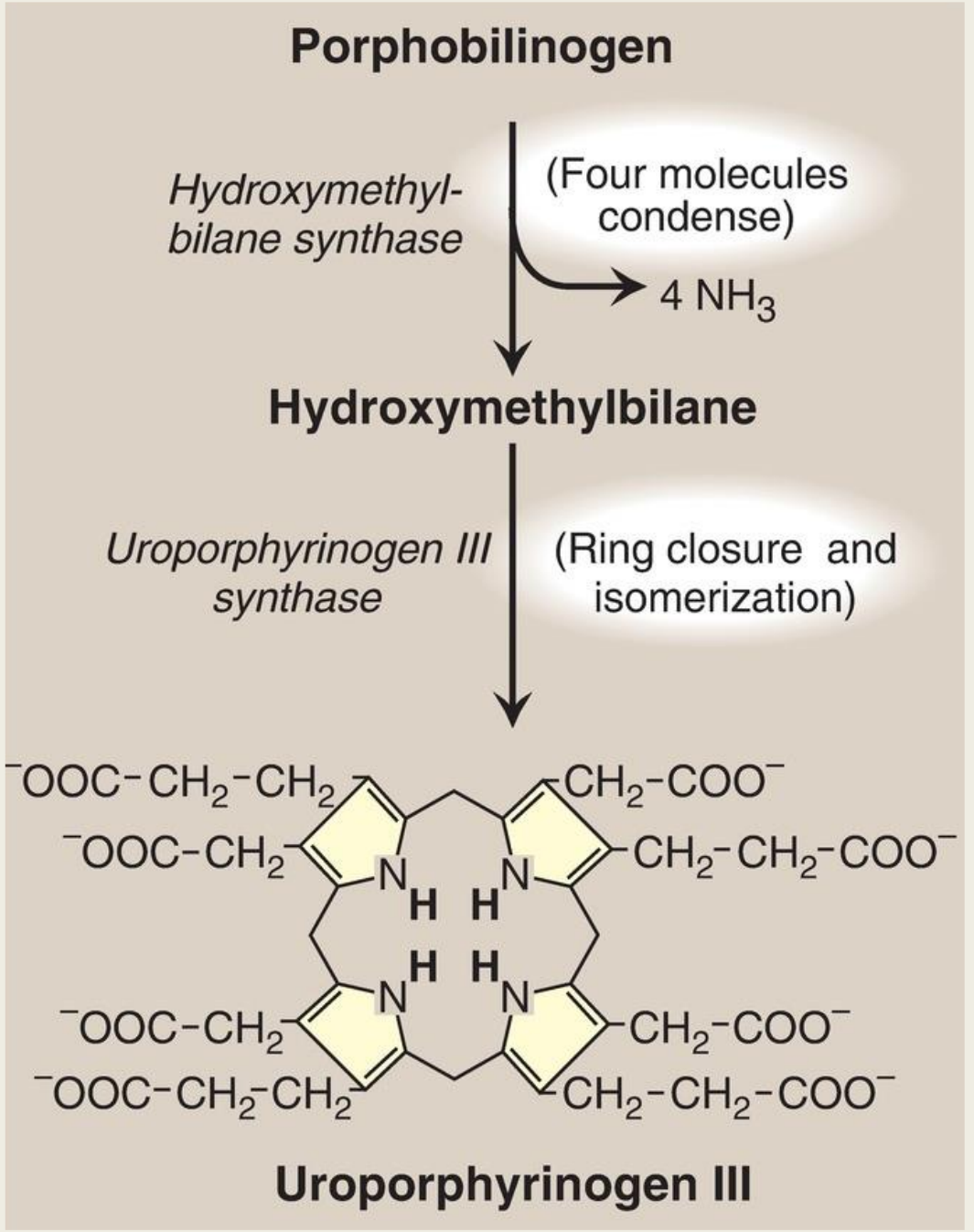
B. Heme biosynthesis

- 2. Porphobilinogen formation (PBG):
  - *2 ALA condensation*
  - *ALA dehydratase (PBG synthase) (Zn)*
  - *Elevation in ALA and anemia seen in lead poisoning*



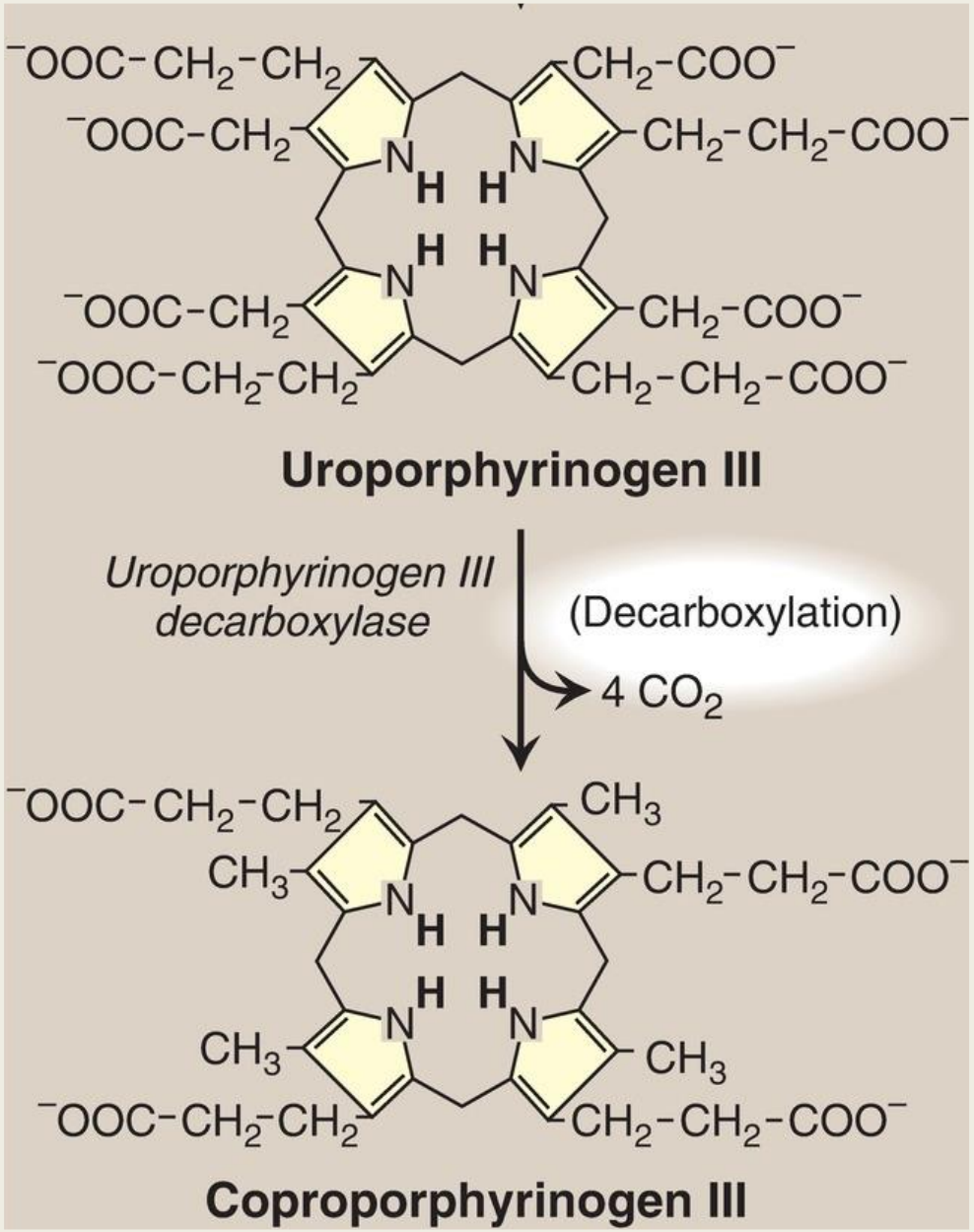
B. Heme biosynthesis

- 3. Uroporphyrinogen formation:
  - *Condensation of four PBG (hydroxymethylbilane)*
  - *Cyclized and isomerized by uroporphyrinogen III synthase*



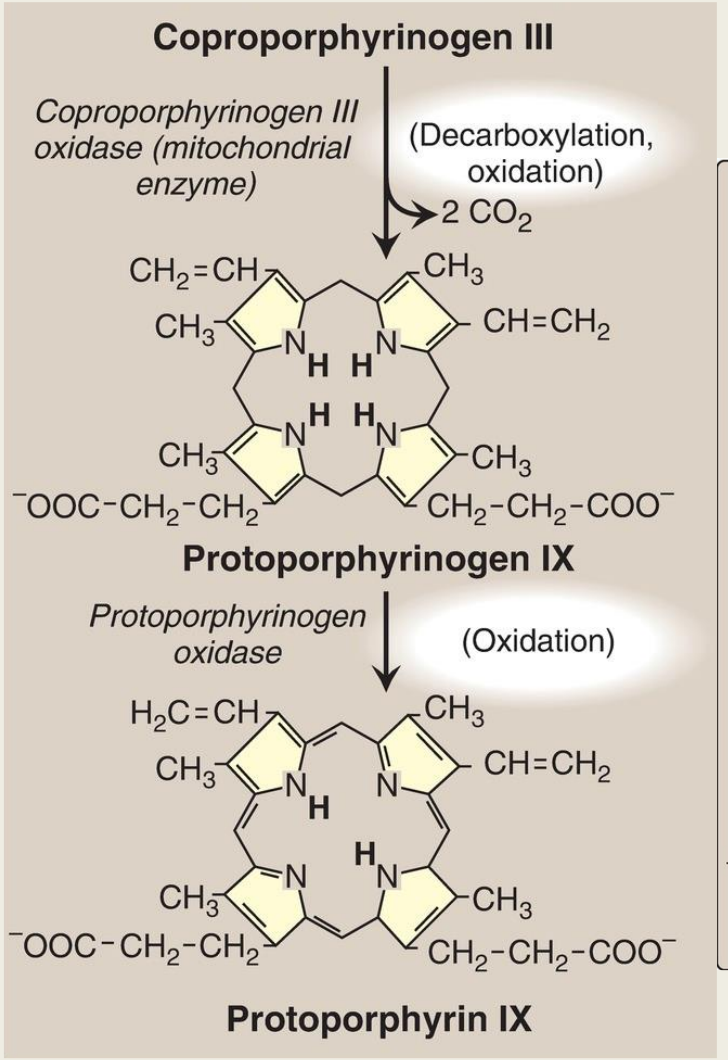
B. Heme biosynthesis

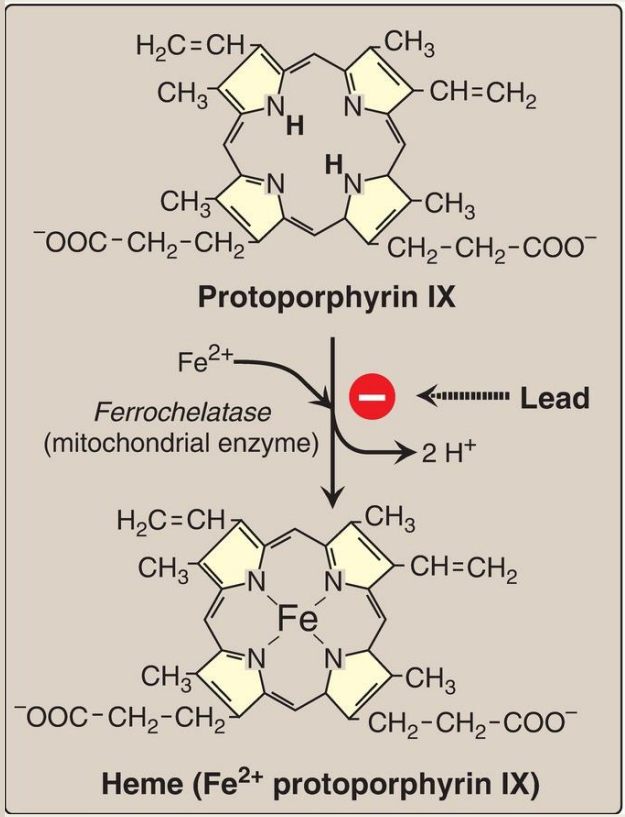
- *4. Decarboxylation of acetate groups*
  - *Uroporphyrinogen III decarboxylase (UROD), generating coproporphyrinogen III*
  - *The reactions occur in the cytosol*



B. Heme biosynthesis

- 5. Heme formation:
  - *Mitochondria*
  - *Coproporphyrinogen III oxidase*
  - *Decarboxylation (2 propionates) to vinyl groups → protoporphyrinogen IX*
  - *Oxidized to protoporphyrin IX*
- 6. Fe^{2+} added to produce heme
  - *Spontaneously*
  - *Rate enhanced by ferrochelatase (Lead)*



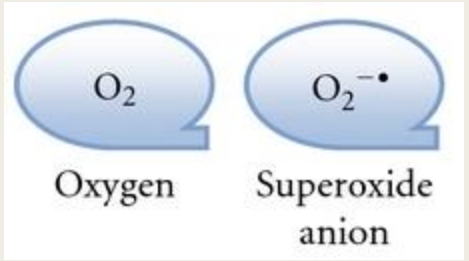


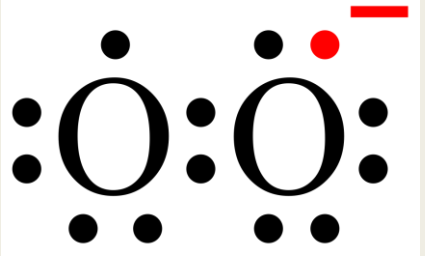
C. Porphyrias (Greek for purple)

- Rare; inherited (AD or AR) (or sometimes acquired)
- Defects in heme synthesis
- Accumulation and increased excretion of porphyrins or porphyrin precursors
- Each porphyria results in the accumulation of a unique pattern of intermediates caused by the deficiency of an enzyme in the heme synthetic pathway
- Classification: Erythropoietic or hepatic (acute or chronic)

C. Porphyrias (Greek for purple)

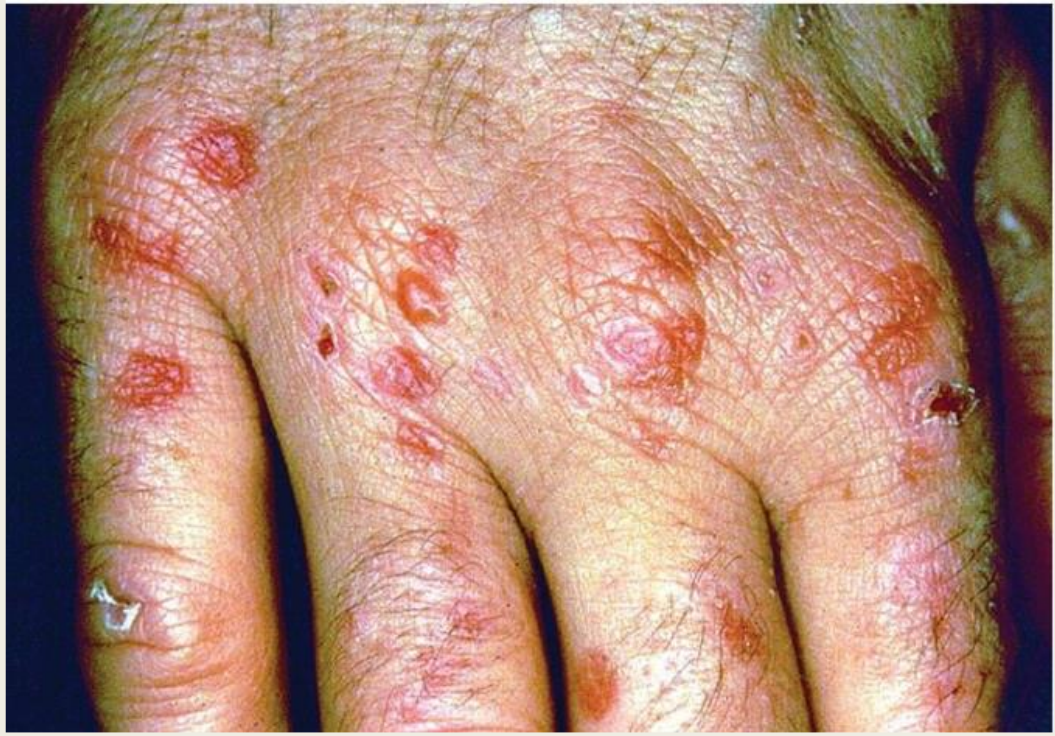
- Clinical manifestations:
  - *Prior to tetrapyrroles*
    - Abdominal and neuropsychiatric signs
  - *Accumulation of tetrapyrroles*
    - Photosensitivity (pruritus)
    - Oxidation of colorless porphyrinogens to colored porphyrins; participate in formation of superoxide radicals from oxygen
    - Oxidatively damage to membranes and release of destructive enzymes from lysosomes

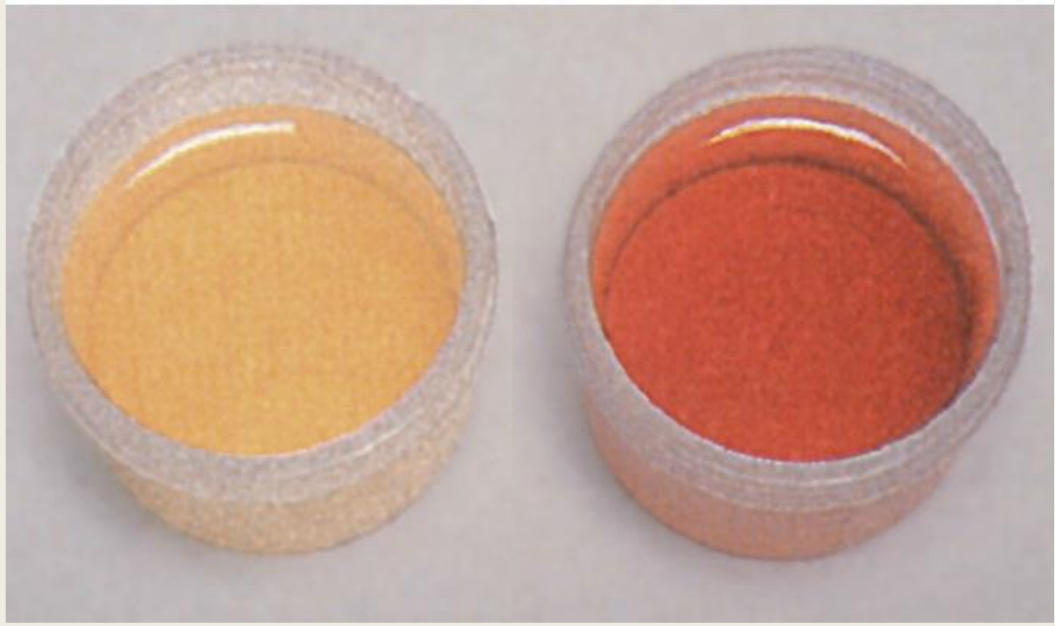




C. Porphyrias

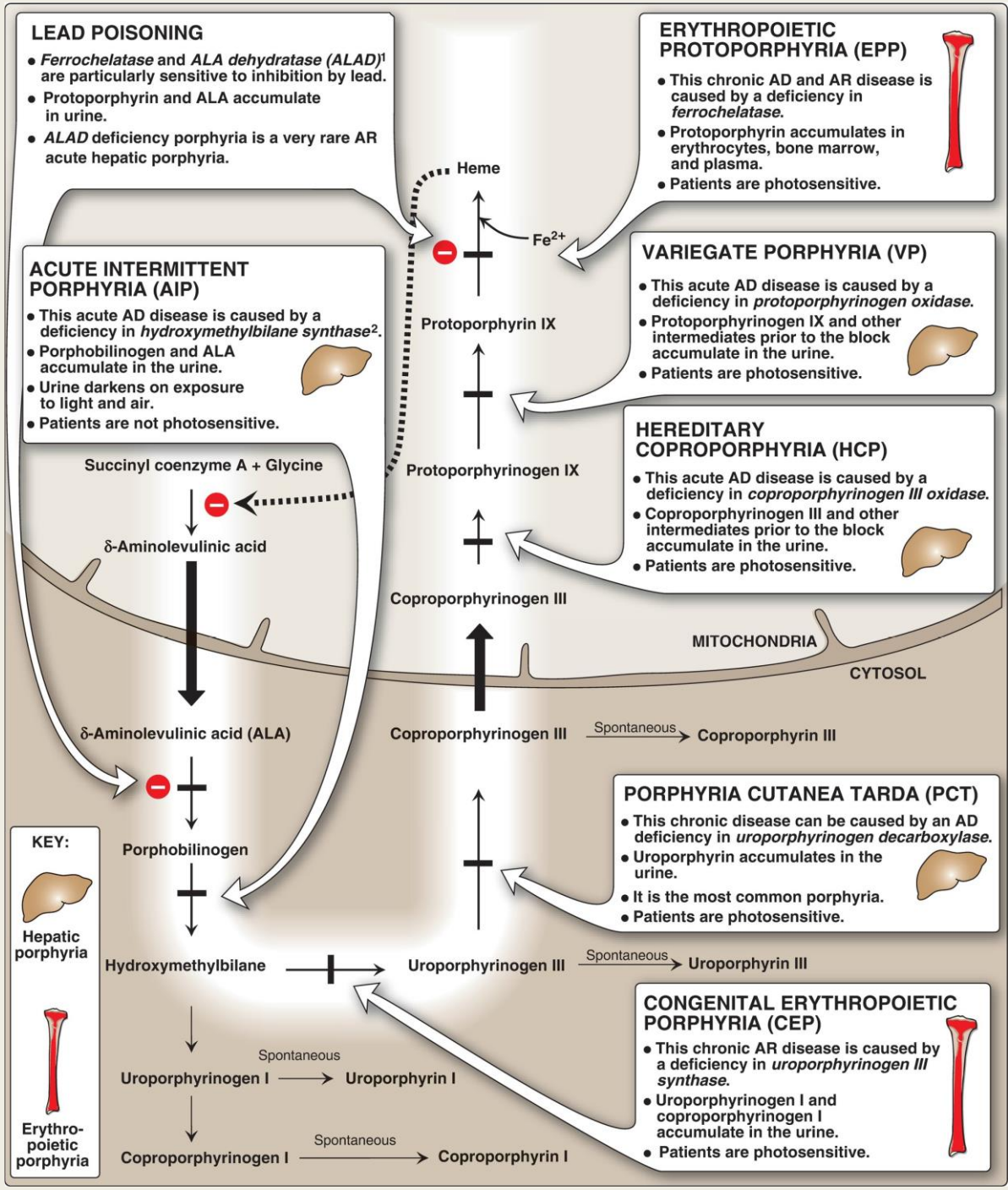
- a. Chronic hepatic porphyria:
  - *Porphyria cutanea tarda (most common)*
  - *Severe deficiency of UROD*
- Mutations to *UROD (*20%, AD)
- Clinical onset: 4th or 5th decade of life
- Cutaneous symptoms; urine (red to brown in natural light and pink to red in fluorescent light)





C. Porphyrias

- b. Acute hepatic porphyrias:
  - *ALA dehydratase–deficiency porphyria; Acute intermittent porphyria; Hereditary coproporphyria; Variegate porphyria*
- Acute attacks of GI, neuropsychiatric, and motor symptoms; photosensitivity
- Symptoms often precipitated by use of drugs (barbiturates and ethanol), why?



Erythropoietic porphyrias

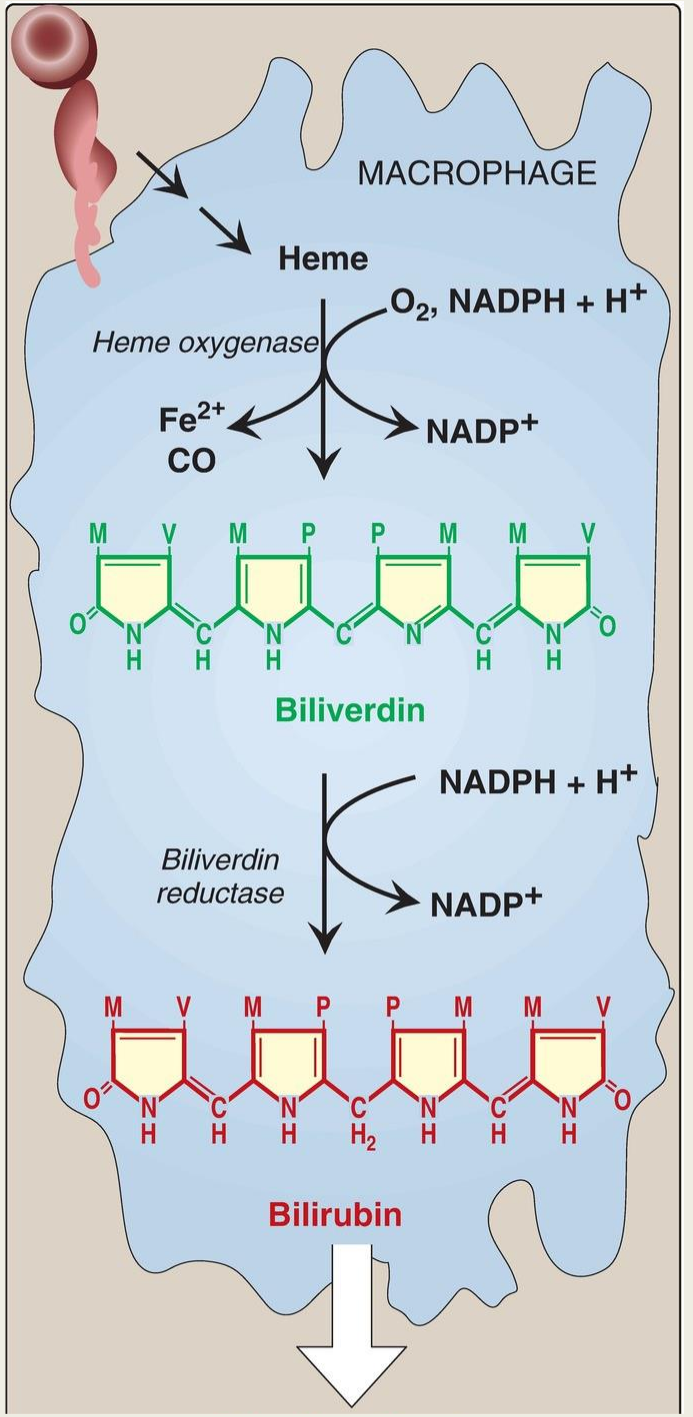
- Chronic erythropoietic porphyrias
  - *Congenital erythropoietic porphyria*
  - *Erythropoietic protoporphyria*
  - *Photosensitivity characterized by skin rashes and blisters that appear in early childhood*

2. Increased δ-aminolevulinic acid synthase activity

- Common feature of the hepatic porphyrias
- Increase in ALAS1 synthesis (derepression)
- Accumulation of toxic intermediates
- **3. Treatment:**
  - *Acute: medical support (analgesia, anti-emetic)*
  - *Intravenous injection of hemin and glucose (↓ ALAS1 synthesis)*
  - *Protection from sunlight*
  - *Ingestion of β-carotene (radical scavenger)*
  - *Phlebotomy*

D. Heme degradation

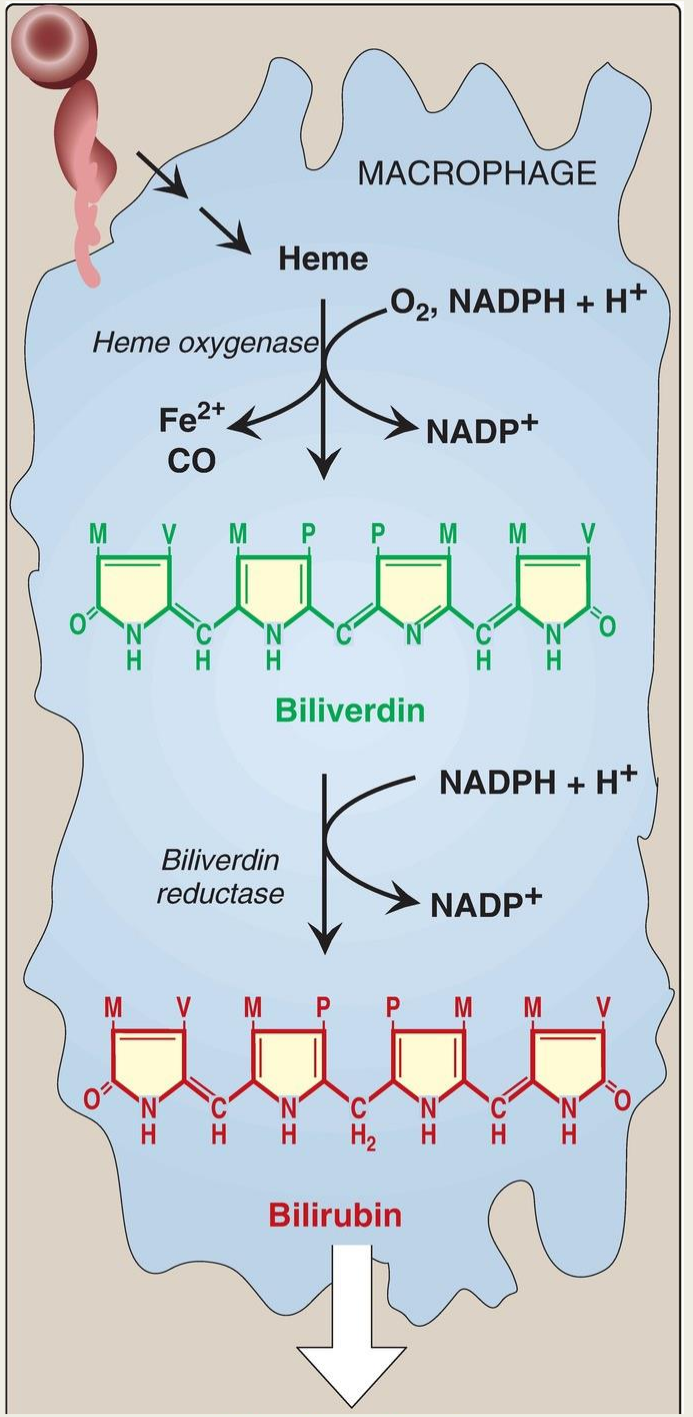
- ~85% of heme destined for degradation (senescent RBCs)
- ~15% from hemeproteins
- 1. Bilirubin formation (mammals):
  - *Microsomal heme oxygenase in macrophages*
  - *NADPH, O_2 → 3 successive oxygenations (ring opening)*
  - *Linear biliverdin (green), CO, and Fe^{2+}*
  - *Reduction: red-orange bilirubin*



D. Heme degradation

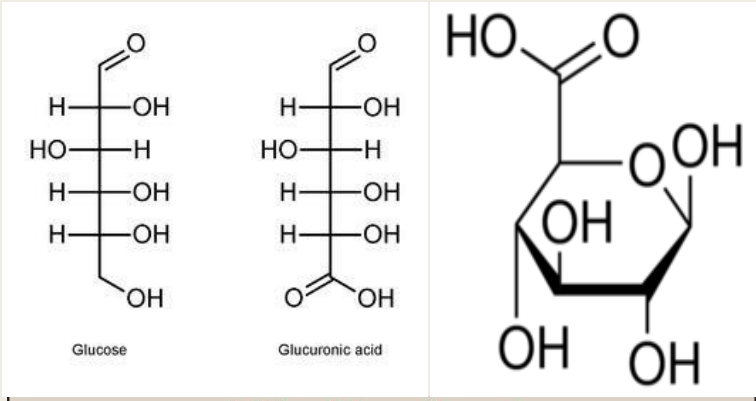
- *Bilirubin and derivatives: collectively termed bile pigments – bruise changing colors*

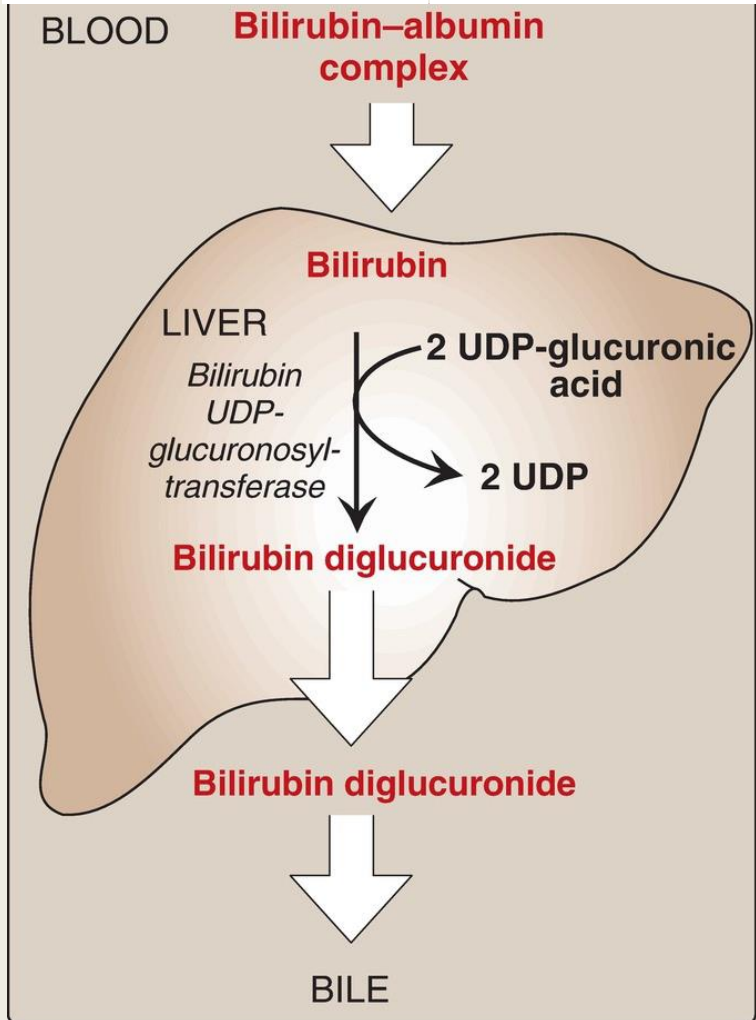
- Bilirubin may function at low levels as an antioxidant (oxidized to biliverdin, then reduced by *biliverdin reductase)*



D. Heme degradation

- 2. Bilirubin uptake by the liver:
  - *Binding noncovalently to albumin (aspirin)*
  - *Facilitated diffusion to hepatocytes (ligandin)*
- 3. Bilirubin diglucuronide formation:
  - *Sequential addition of 2 glucuronic acid (conjugation)*
  - *Microsomal bilirubin UDP-glucuronosyltransferase (bilirubin UGT); (UDP)-glucuronic acid*
  - *Conjugated bilirubin (CB): bilirubin diglucuronide*
  - *Crigler-Najjar I (most severe) and II and Gilbert syndrome: varying degrees of bilirubin UGT deficiency*

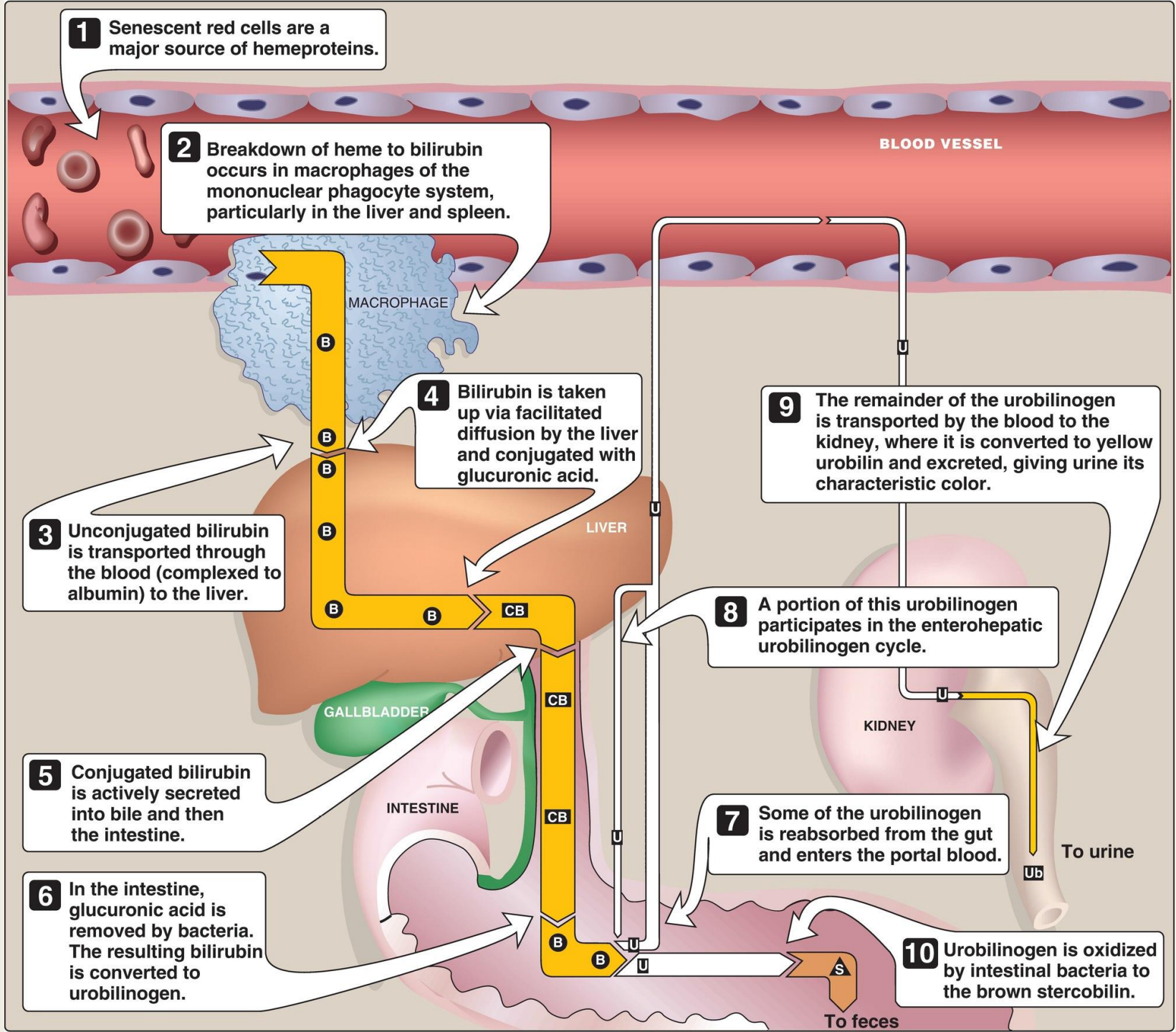




Bilirubin secretion into bile and Urobilin formation

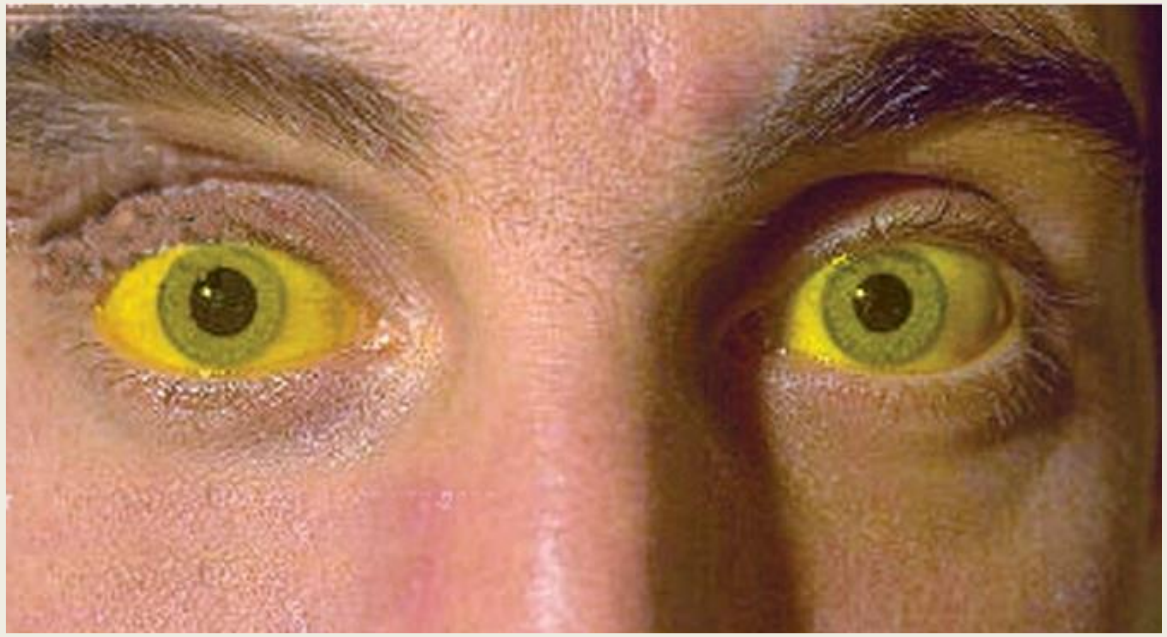
- Bilirubin secretion:
  - *Active transport; rate-limiting step (liver disease)*
  - *Dubin-Johnson syndrome: A rare deficiency in the transport protein*
  - *Unconjugated bilirubin (UCB) not secreted*
- Urobilin formation (intestines):
  - *CB is hydrolyzed and reduced by bacteria: urobilinogen (colorless)*
  - *Bacterial oxidation to stercobilin (feces)*
  - *Reabsorption: portal blood → resecreted (enterohepatic urobilinogen cycle)*
  - *The remainder: to the kidney → urobilin (urine)*

Bilirubin Metabolism



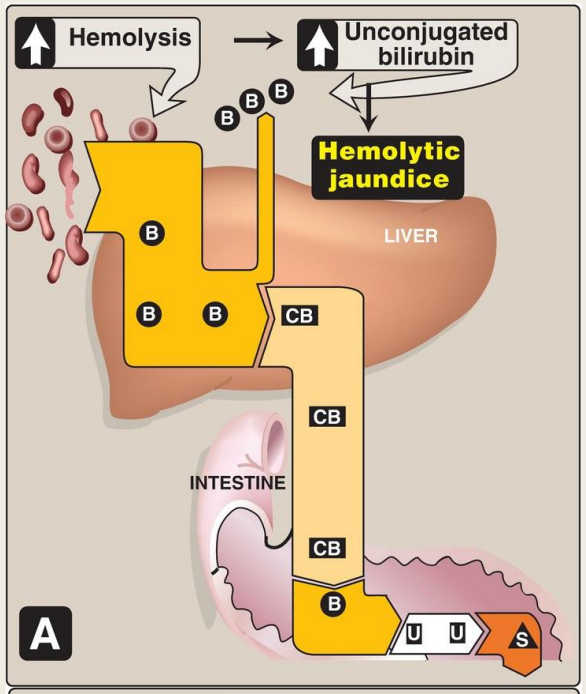
Jaundice

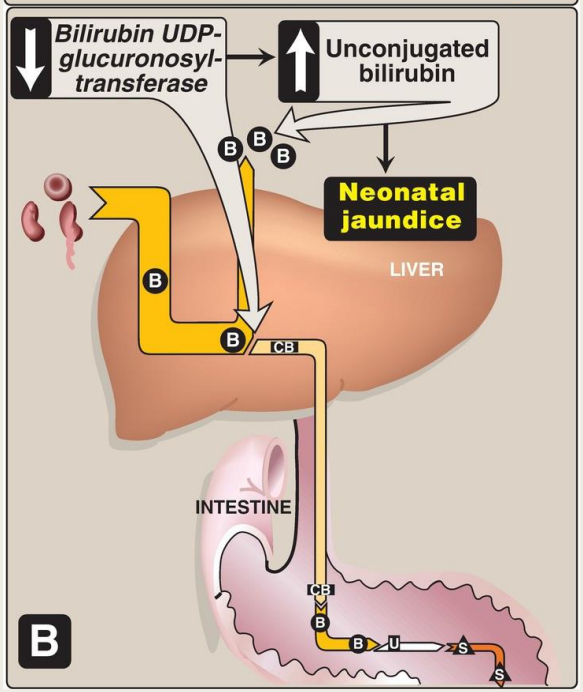
- Yellow color of skin, nail beds, and sclerae
- Bilirubin deposition secondary to hyperbilirubinemia
- Not a disease
- Blood bilirubin levels are normally ≤1 mg/dl
- Jaundice is seen at 2–3 mg/dl



Types

- a. Hemolytic (prehepatic):
  - *Normal production (300 mg/day)*
  - *Liver capacity: >3,000 mg of bilirubin/day (conjugate and excrete); why?*
- However, in extensive hemolysis fail!
  - *Sickle cell anemia; pyruvate kinase deficiency; glucose 6-phosphate dehydrogenase deficiency*
  - *Unconjugated hyperbilirubinemia (jaundice)*
- Urinary urobilinogen is increased, why?





b. Hepatocellular (hepatic)

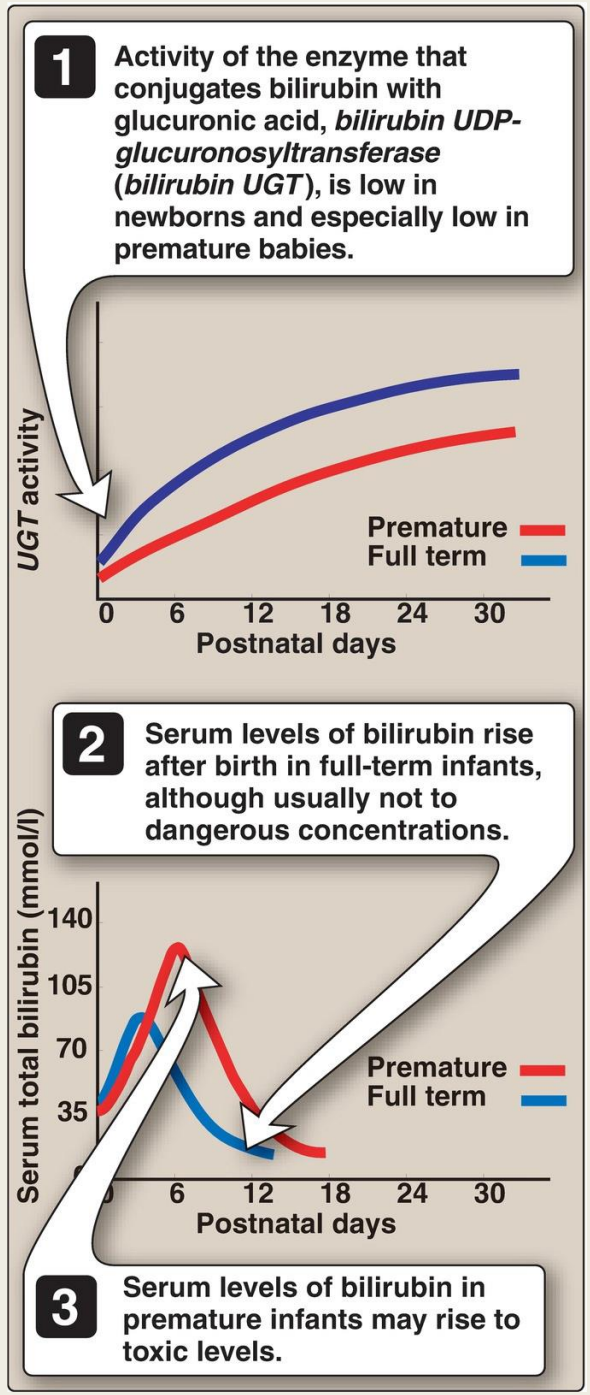
- Damage to liver cells (decreased conjugation)
- Urobilinogen is increased in the urine, why? decreased enterohepatic circulation
- Urine darkens, whereas stools may be a pale (clay)
- High *ALT* and *AST*
- Intrahepatic cholestasis (CB not efficiently secreted), so what?
  - *Regurgitation*
  - *Conjugated hyperbilirubinemia*

c. Obstructive (posthepatic)

- Obstruction of the common bile duct (extrahepatic cholestasis)
- Stools are pale (clay)
- Conjugated hyperbilirubinemia, why?
- Urinary bilirubin: CB is eventually excreted in urine (which darkens over time)
- Urinary urobilinogen is absent, why?

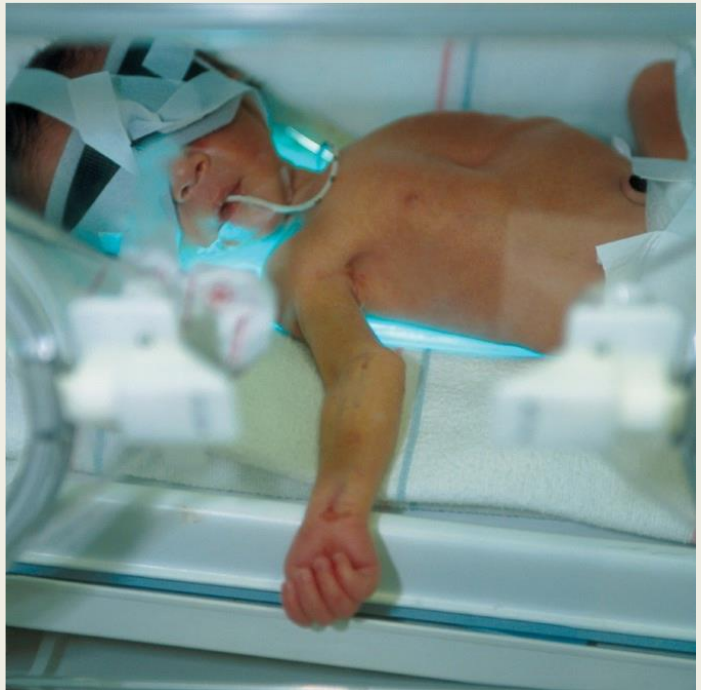
Jaundice in newborns

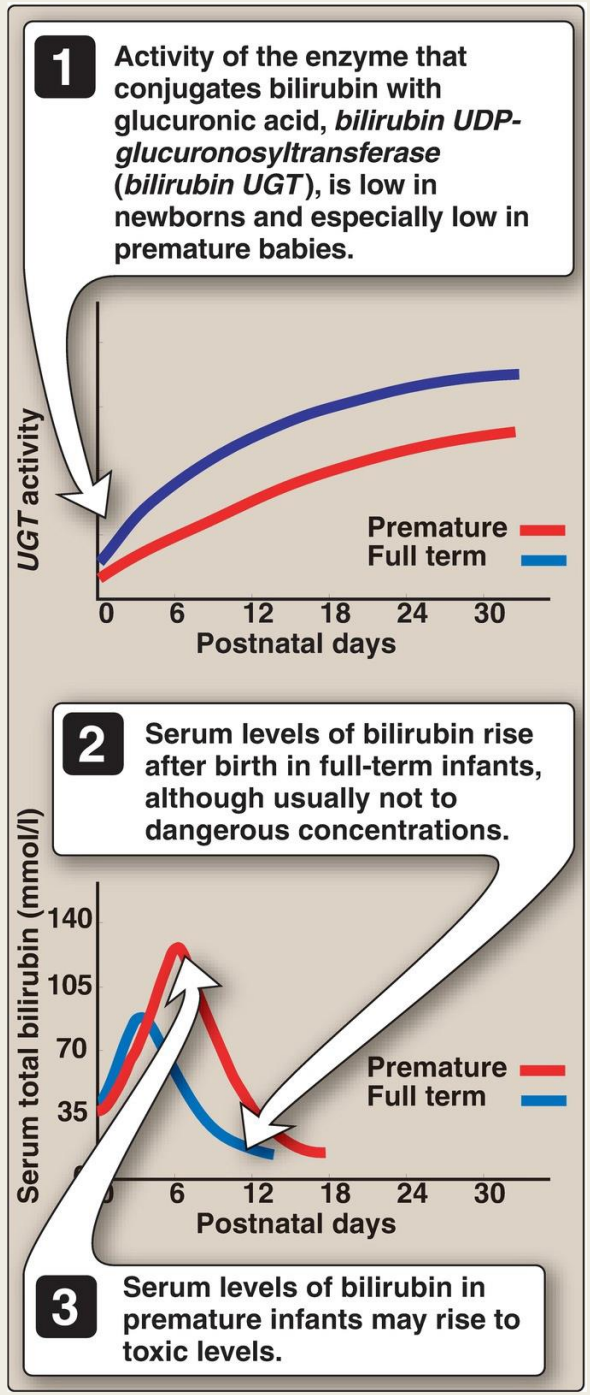
- 60% of full term and 80% of preterm
- First postnatal week
- Transient, physiologic jaundice
- *UGT activity* is low at birth
- Reaches adult levels in about 4 weeks
- Binding capacity of albumin (20–25 mg/dl)



Jaundice in newborns

- Can diffuse into the basal ganglia, causing toxic encephalopathy (kernicterus) and a pathologic jaundice
- Blue fluorescent light!
- Only UCB crosses BBB - and only CB appears in urine (solubility)





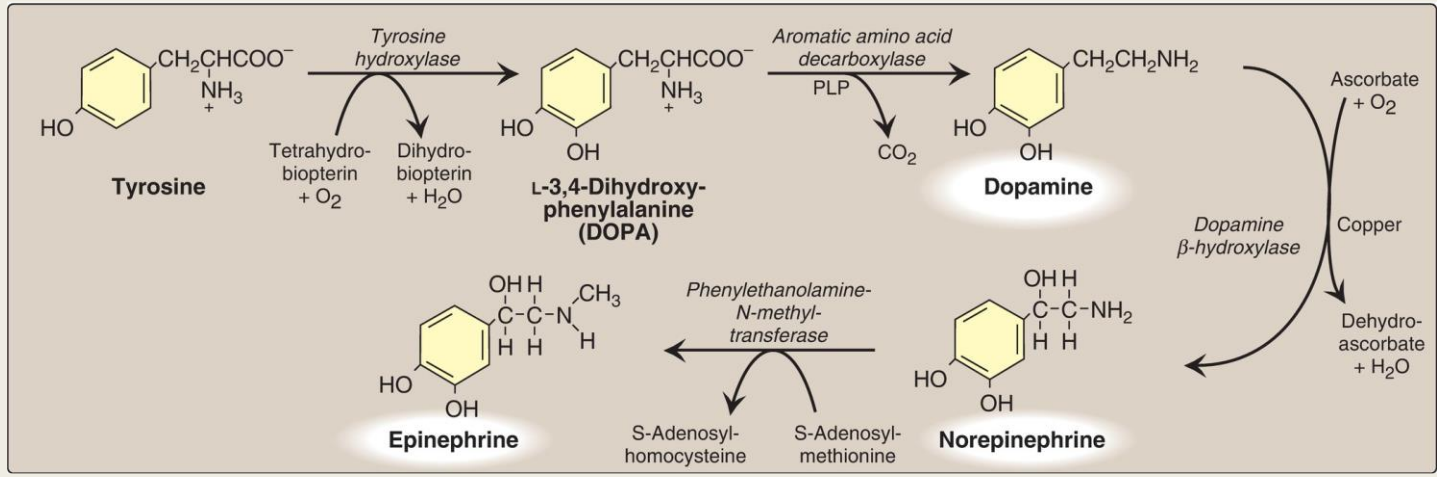
Bilirubin measurement

- Van den Bergh reaction
  - *Diazotized sulfanilic acid reacts with bilirubin to form red azodipyrroles that are measured colorimetrically*
  - *CB reacts rapidly with the reagent (within 1 minute) and is said to be direct reacting*
  - *UCB reacts more slowly. Why?*
  - *In methanol: both CB and UCB react (total bilirubin) value*
- Normal plasma, only ~4% of the total bilirubin is conjugated, where is the rest? (bile)

OTHER NITROGEN-CONTAINING COMPOUNDS

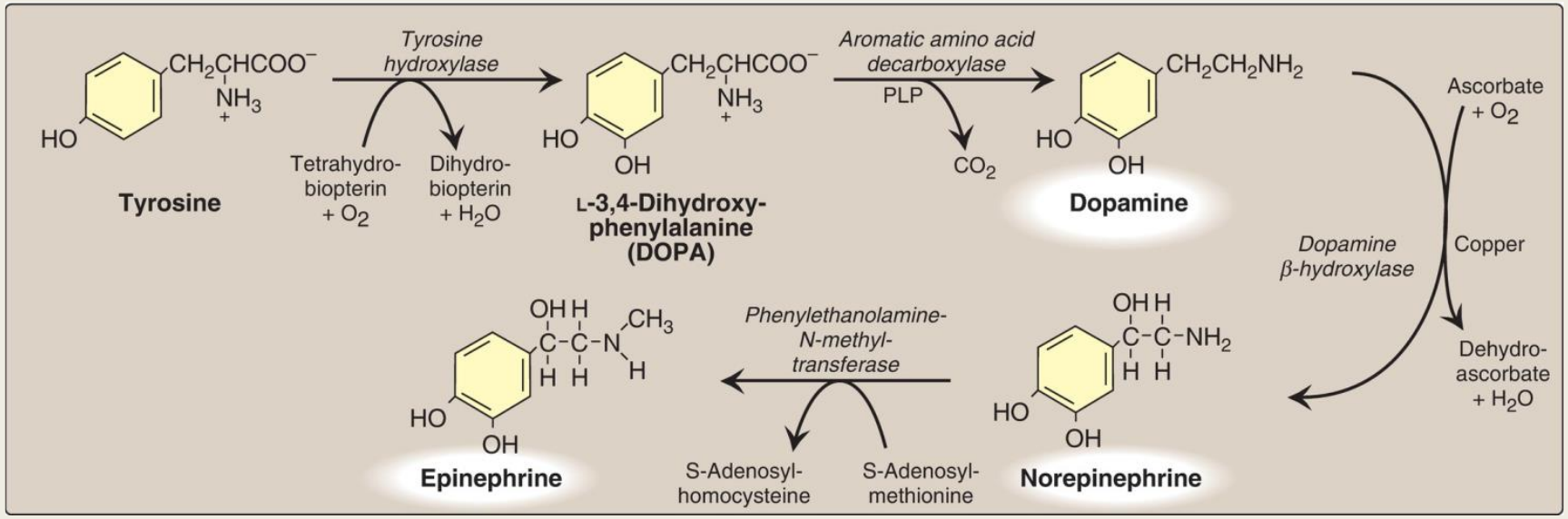
Catecholamines

- Dopamine, norepinephrine (NE), and epinephrine (or, adrenaline)
- biologically active amines (catecholamines)
- Site of synthesis
- 1. Function
  - *Outside the CNS, hormones regulators of carbohydrate and lipid metabolism*
- 2. Synthesis: tyrosine
  - *BH4-requiring enzyme is abundant in the CNS, the sympathetic ganglia, and the adrenal medulla*
  - *Rate limiting step of the pathway*



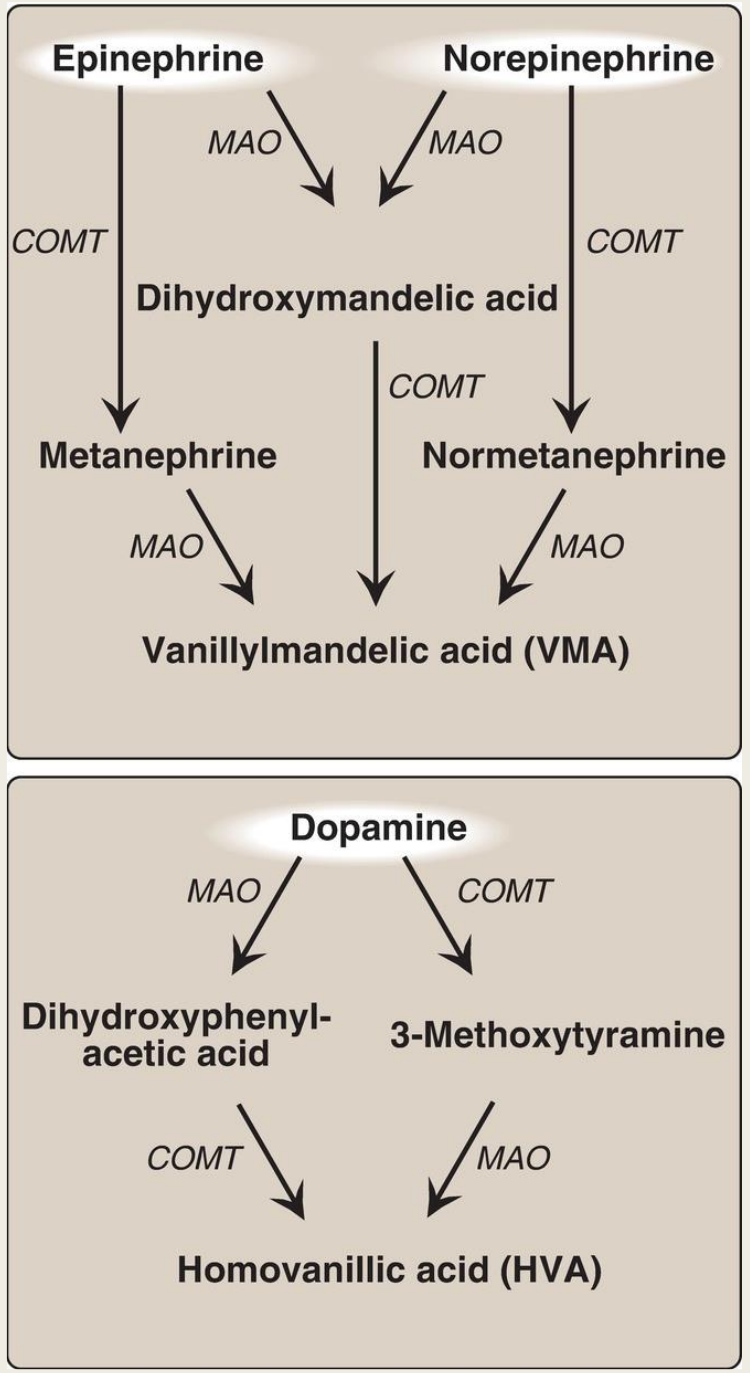
Parkinson disease

- Neurodegenerative movement disorder
- Insufficient dopamine production
- Idiopathic loss of dopamine-producing cells in the brain
- L-DOPA (levodopa) is the most common treatment, why?



Degradation

- Oxidative deamination (*Monoamine oxidase)* (*MAO*)
- O-methylation (*catechol-O-methyltransferase)* (*COMT*); SAM
- Products excreted in urine as vanillylmandelic acid (VMA) and homovanillic acid (HVA)
- Pheochromocytomas: excessive production of catecholamines

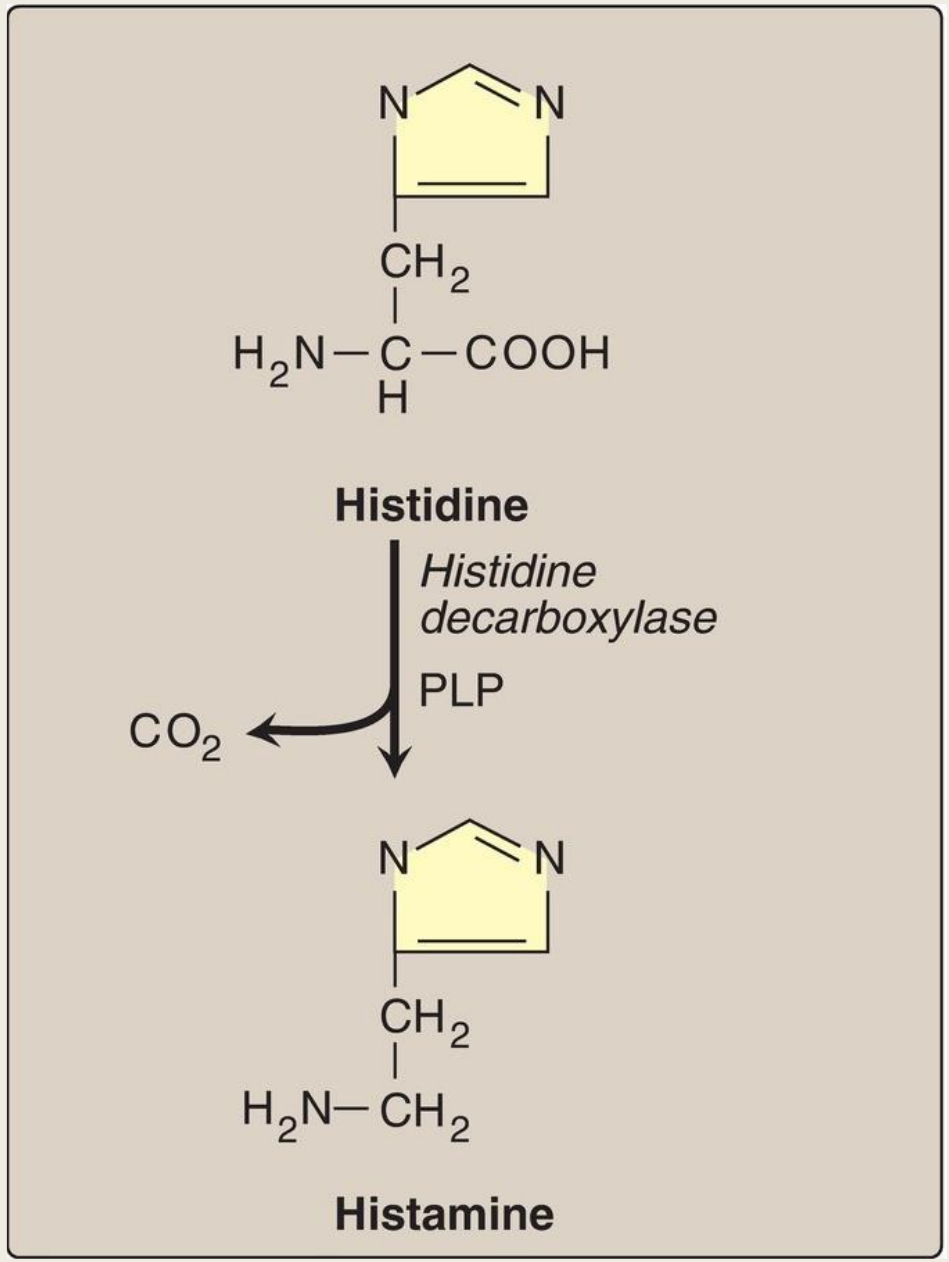


Monoamine oxidase inhibitors

- Irreversibly or reversibly
- Permitting neurotransmitter molecules to escape degradation
- Accumulate within the presynaptic neuron and to leak into the synaptic space (activation of receptors → antidepressant action)

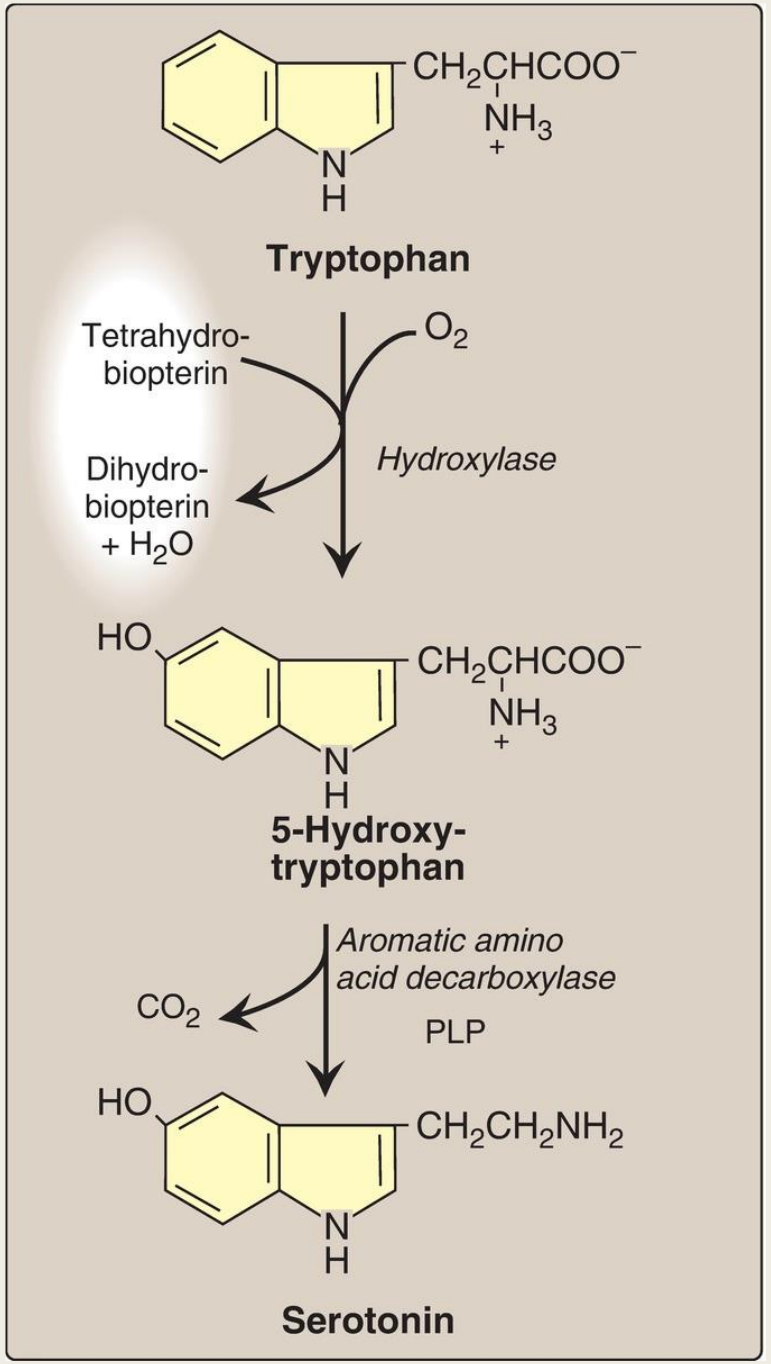
Histamine

- Allergic and inflammatory reactions and gastric acid secretion
- Powerful vasodilator
- Decarboxylation
- PLP
- Histamine has no clinical applications, but agents that interfere with the action of histamine have important therapeutic applications.



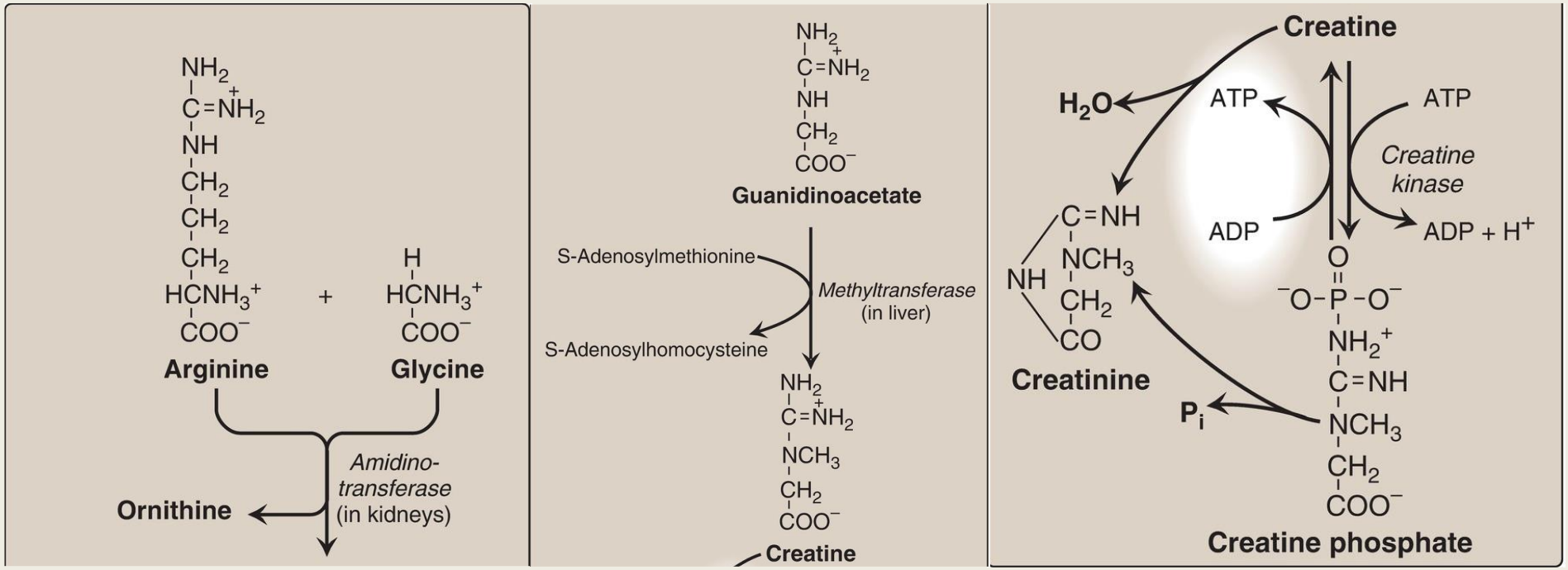
Serotonin

- 5-hydroxytryptamine (5-HT)
- The largest amount (intestinal mucosa), smaller amounts occur in CNS (neurotransmitter)
- Hydroxylated tryptophan (BH4) then Decarboxylated to 5-HT
- Serotonin has multiple physiologic roles
- Selective serotonin reuptake inhibitors (SSRI)
- *MAO*



Creatine

- Creatine phosphate (phosphocreatine)
- A high-energy compound (small but rapid) that can be reversibly transferred to adenosine diphosphate, why?
  - *Intense muscular contraction*
  - *Amount of creatine phosphate is proportional to muscle mass*



Creatine

- 1. Synthesis:
  - *liver and kidneys*
  - *Glycine and guanidino group of arginine, plus a methyl group (SAM)*
  - *Reversibly phosphorylated (creatine kinase; ATP)*
  - *Creatine kinase (MB isozyme)*
- 2. Degradation:
  - *Spontaneously cyclize at a slow but constant rate to form creatinine (urine)*
  - *Proportional to the total creatine phosphate content (estimate muscle mass)*
  - *~1–2 g of creatinine/day*

Melanin

- Tyrosine
- A defect in melanin production results in oculocutaneous albinism
- The most common type being due to defects in copper-containing *tyrosinase*