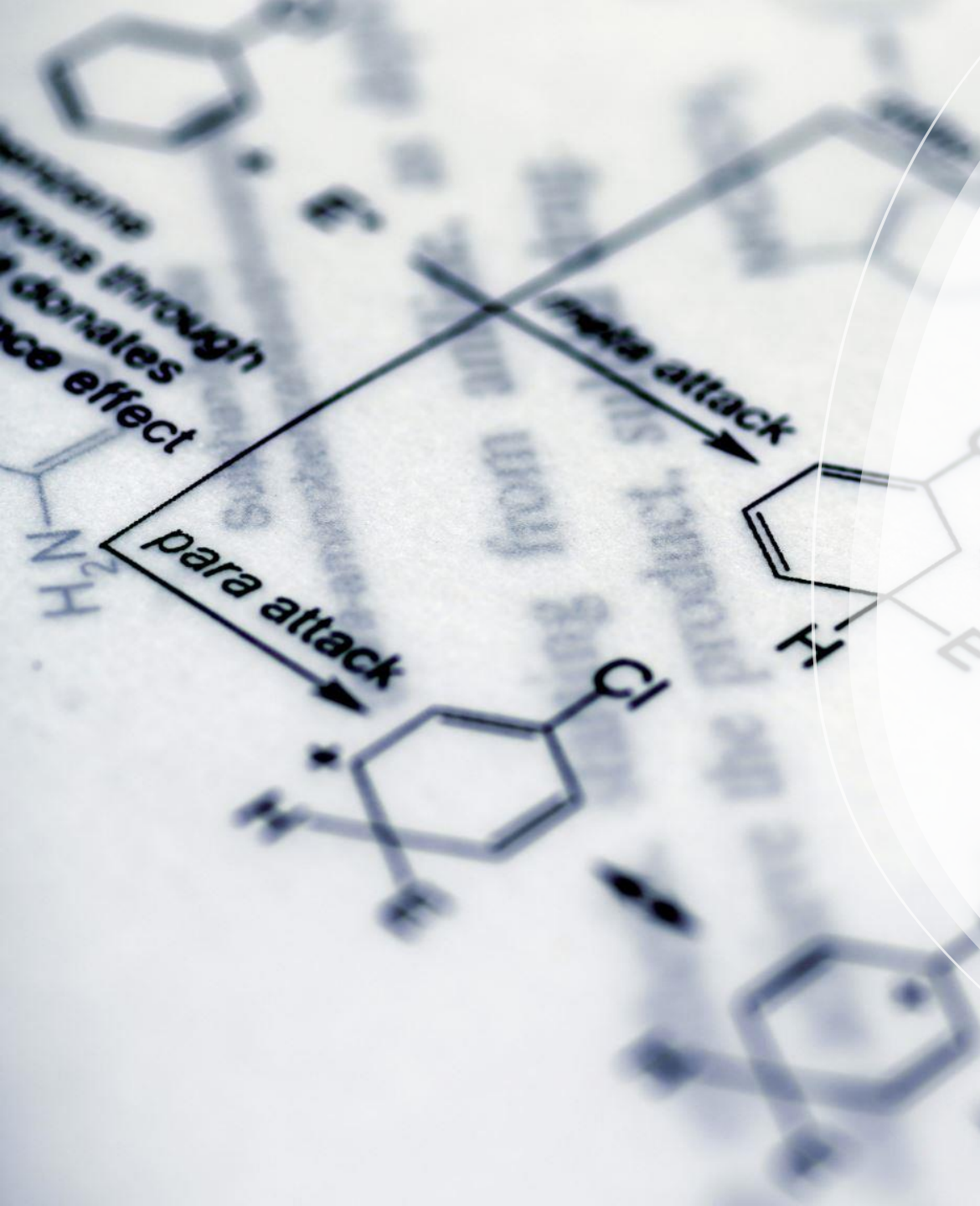


Conversion of Amino Acids to Specialized Products

Prof. Nafez Abu Tarboush

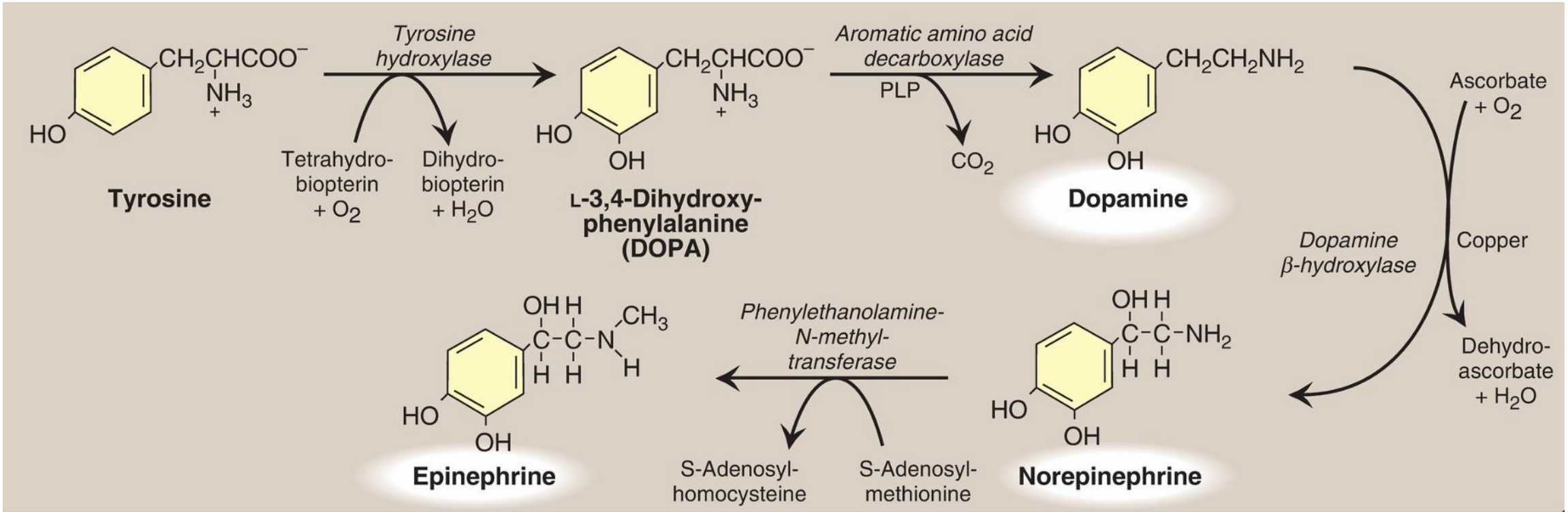
Part I:
Neurotransmitters from Amino Acids: Overview

- Catecholamines (tyrosine)
- Thyroid hormones (tyrosine)
- Serotonin (tryptophan)
- Histamine (histidine)
- GABA (glutamate)
- Glutathione
- Creatine

- These pathways are critical in the brain, periphery, and are targets for many pharmacological agents

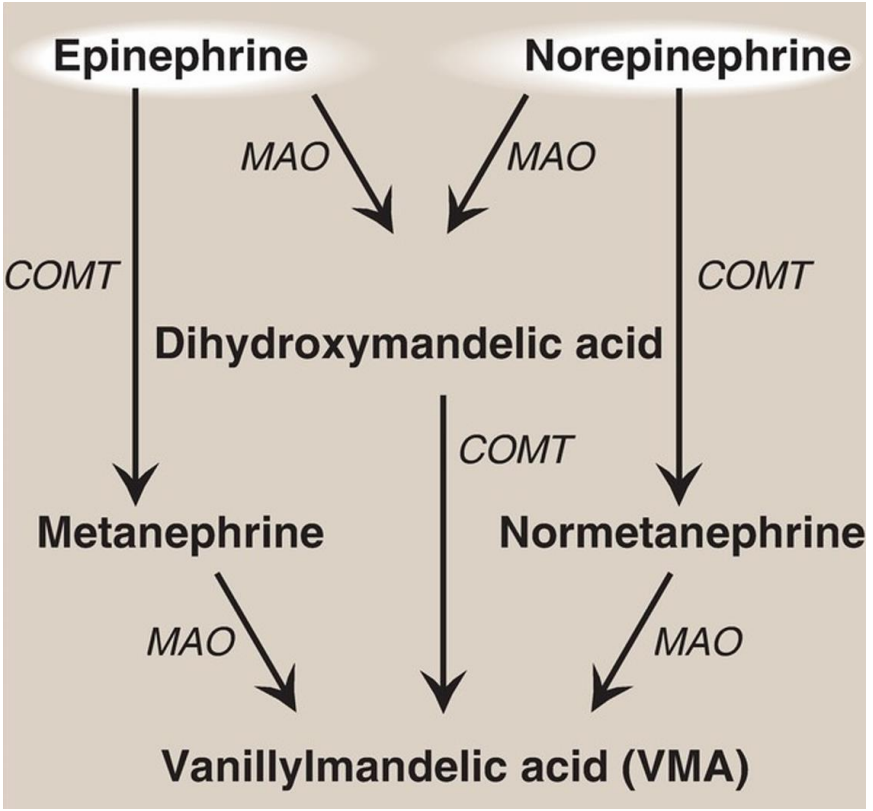
Catecholamine Synthesis

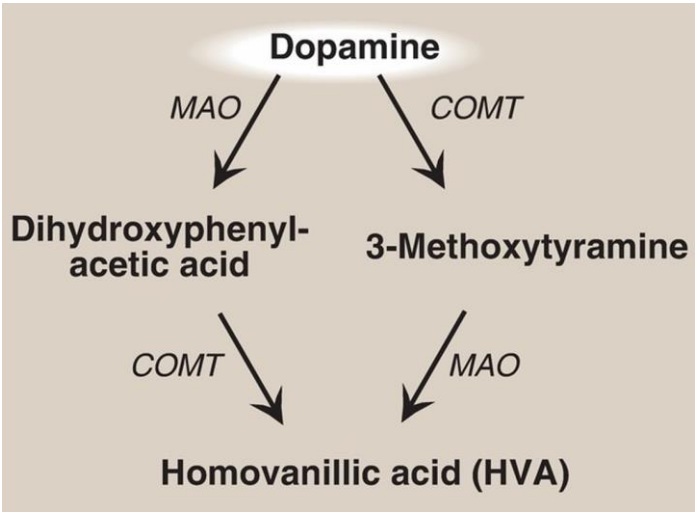
- Synthesis/Clinical Correlation:
- Steps and Coenzymes!
- Parkinson disease: neurodegenerative, idiopathic loss of dopamine-producing cells in the brain, L-DOPA



Catecholamine Degradation

- Degradation/Clinical Correlation:
  - MAO and COMT to VMA
  - Pheochromocytoma (adrenal medulla, excess catecholamines, episodic hypertension)
  - Diagnosis: urinary VMA or plasma metanephrines

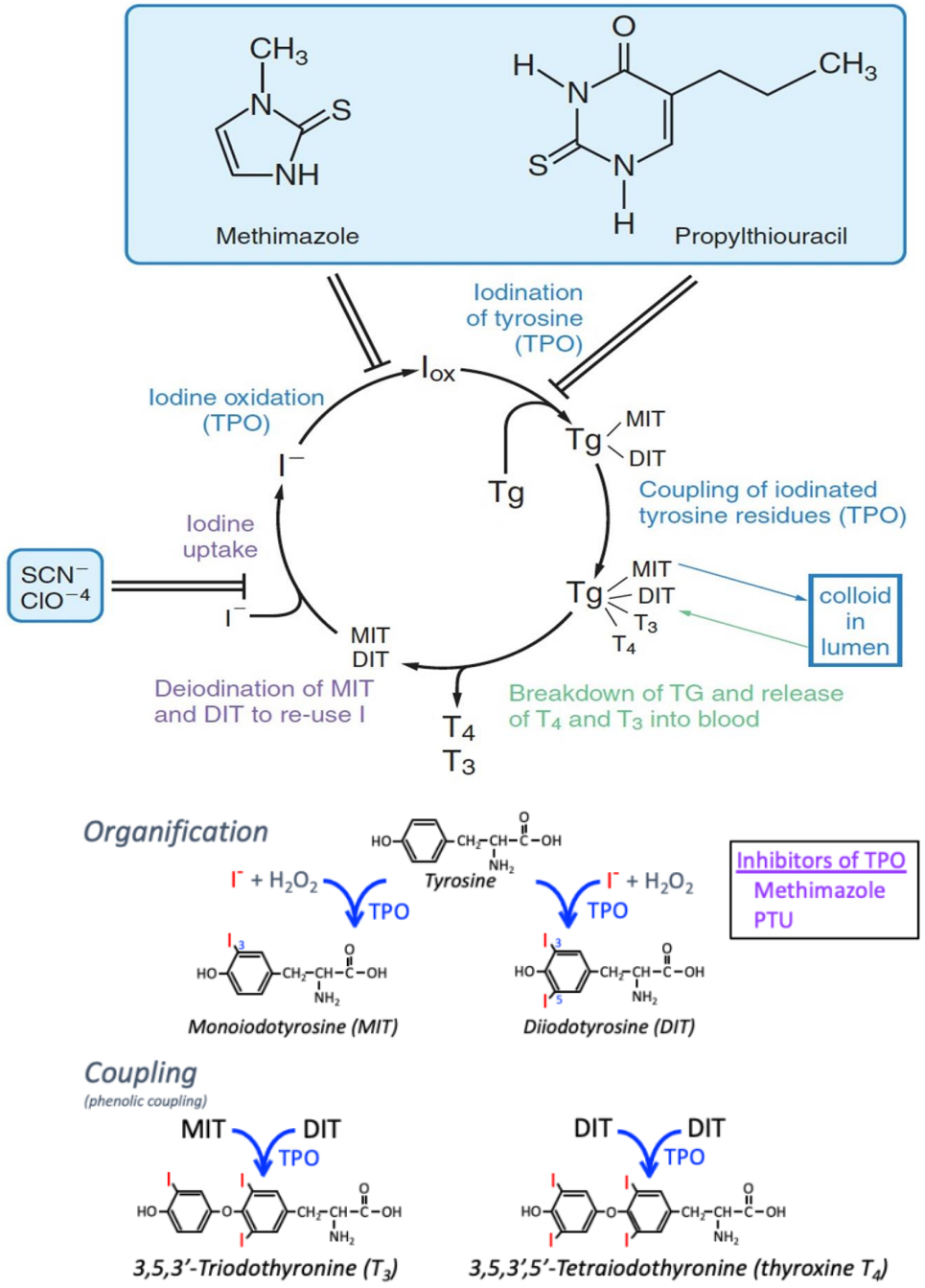




Thyroid Hormones: Synthesis from Tyrosine

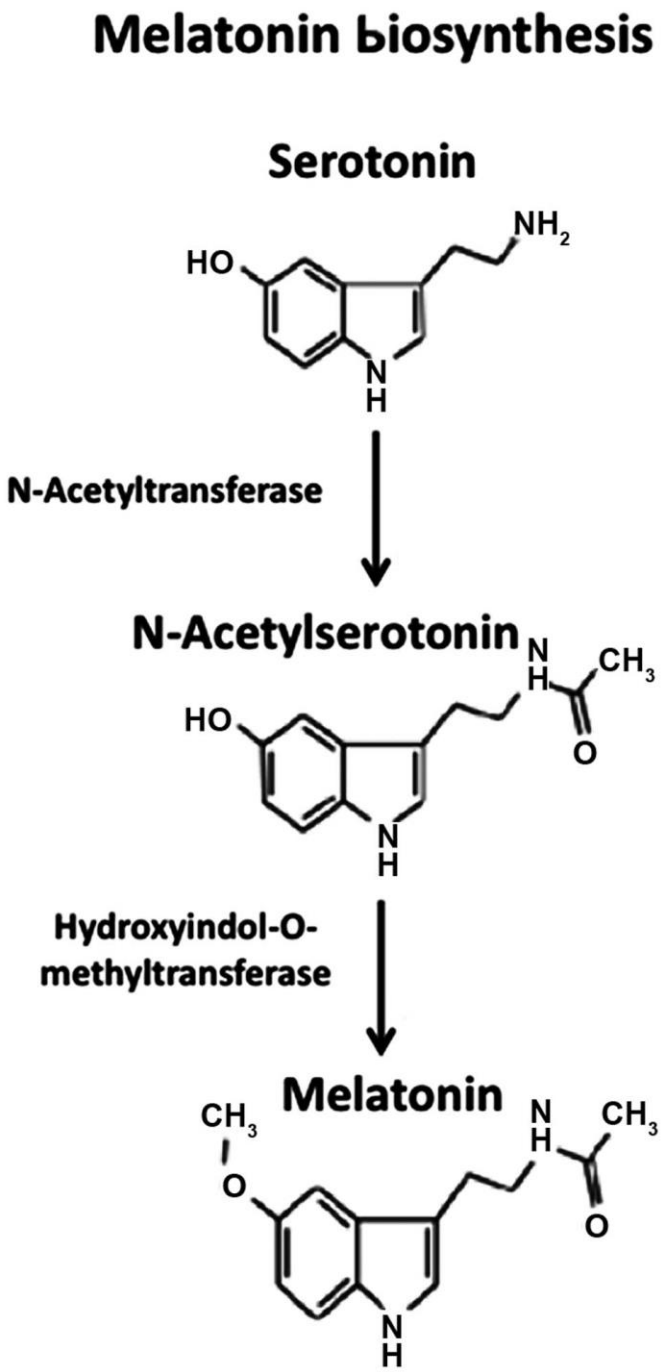
- Thyroid Peroxidase catalyzes:
  - 1) Iodine oxidation
  - 2) Iodination of tyrosine to form MIT/DIT
  - 3) Coupling of MIT/DIT to form T3 and T4

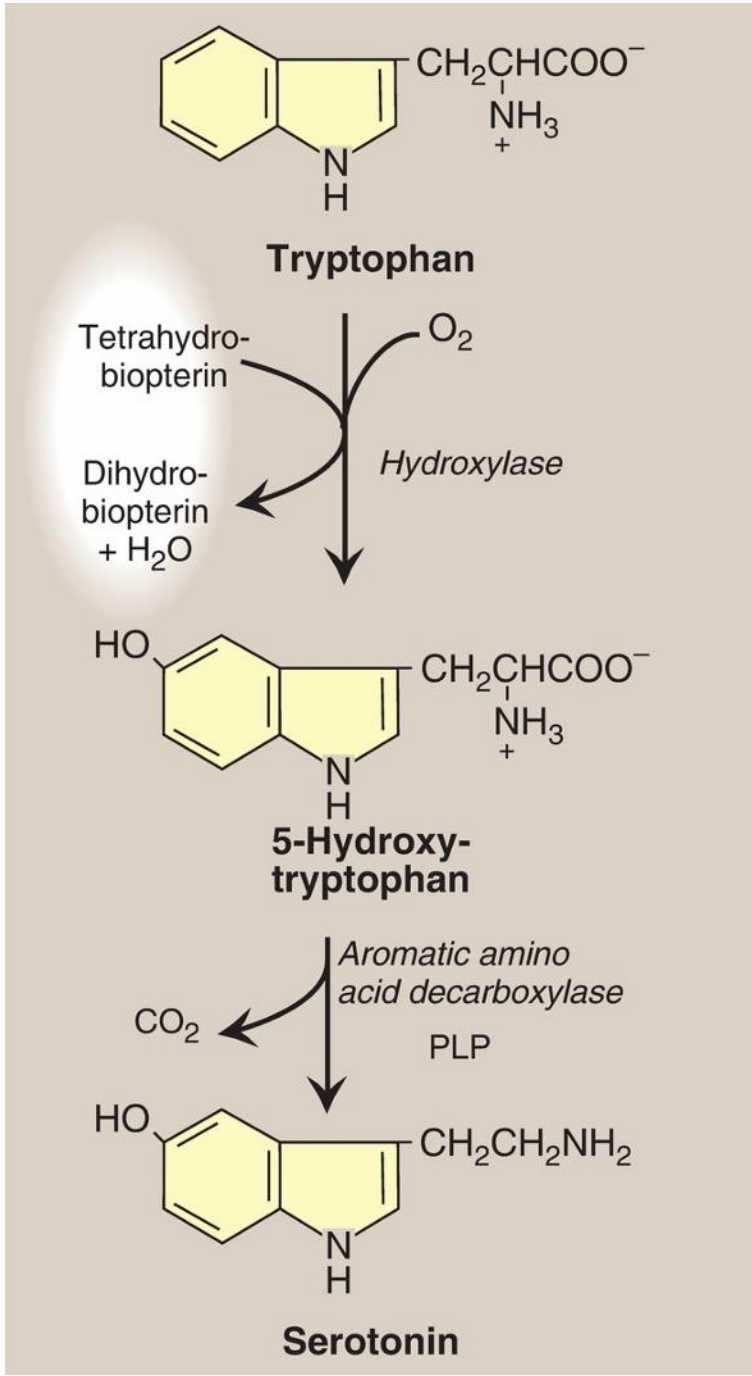
- TSH is the major stimulator
- Synthesis requires iodine



Serotonin

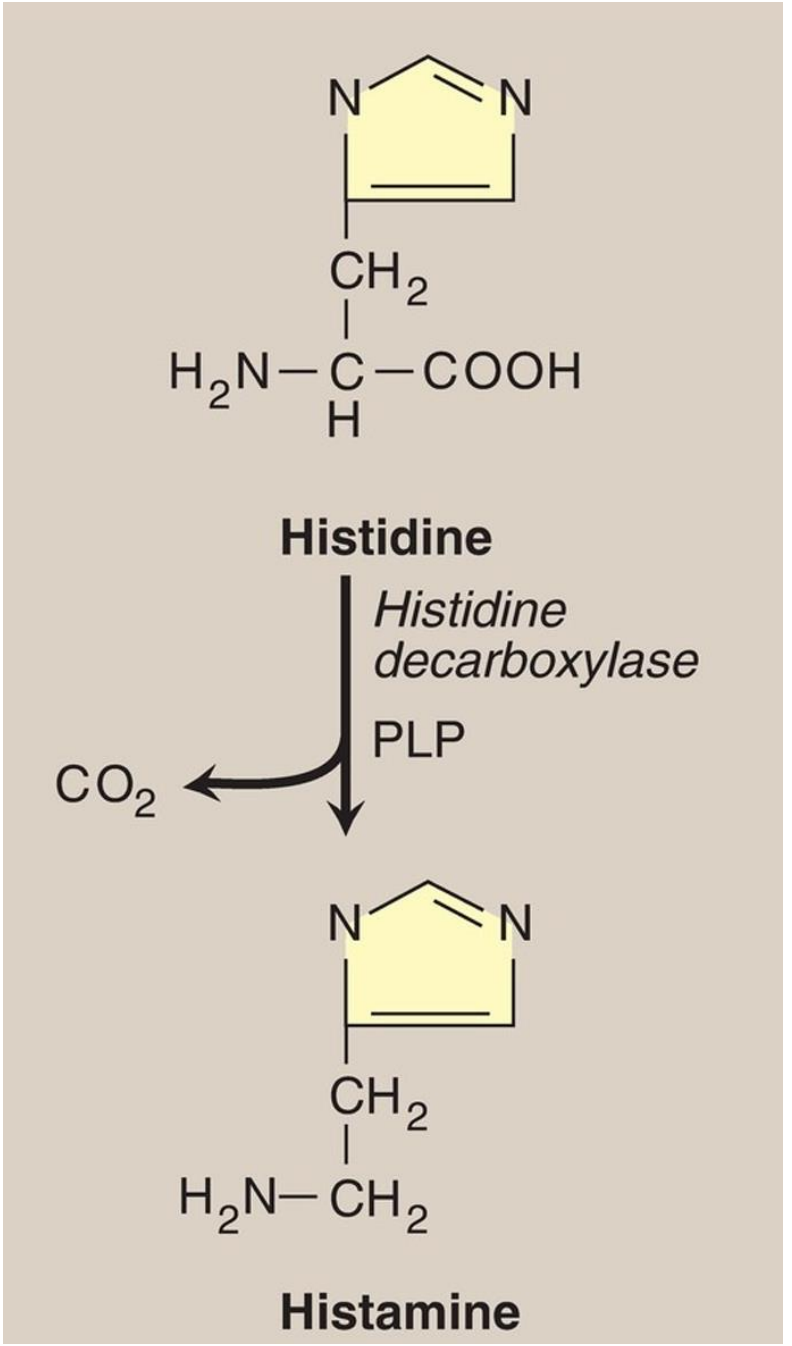
- Serotonin (5-HT): Regulates mood, sleep, appetite
- Precursor to melatonin in the pineal gland





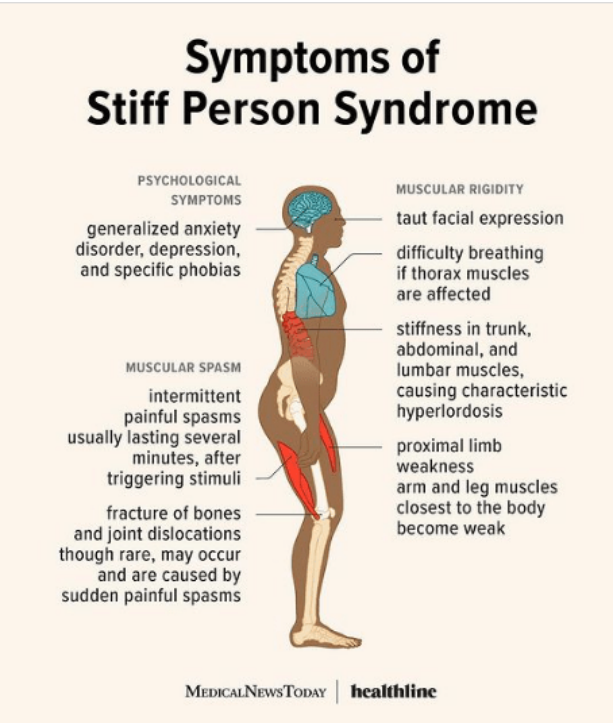
Histamine

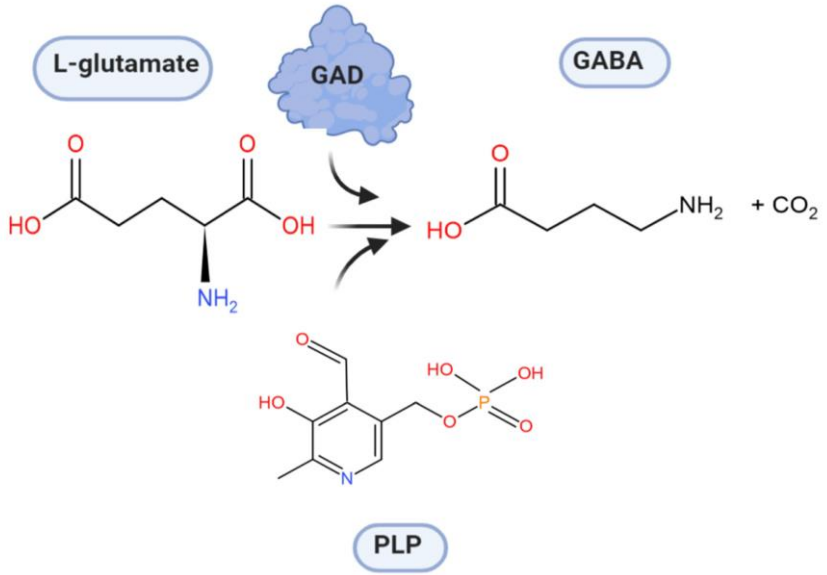
- Histamine:
- Histidine Decarboxylase (PLP-dependent)
- Mediates
  - allergic responses
  - gastric acid secretion (via H2 receptors)
  - wakefulness



GABA

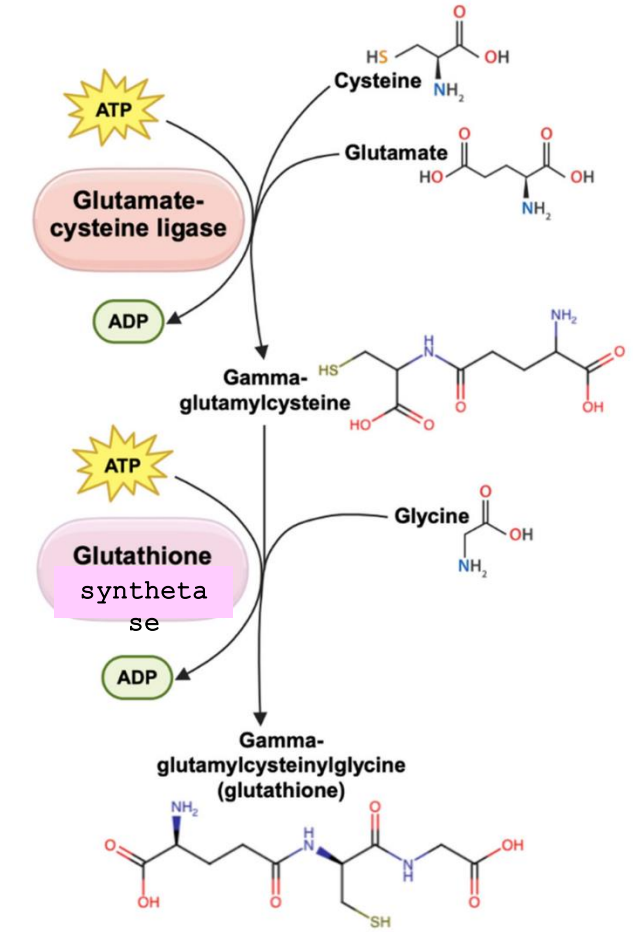
- GABA: The major inhibitory neurotransmitter
- Glutamate Decarboxylase (requires PLP)
- Autoantibodies against this enzyme are seen in Stiff-person syndrome and type 1 diabetes

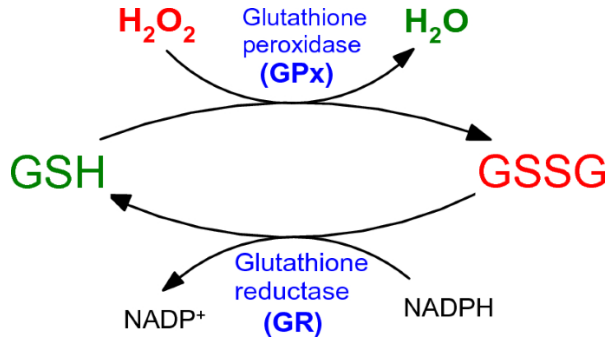




Glutathione: Synthesis and Functions

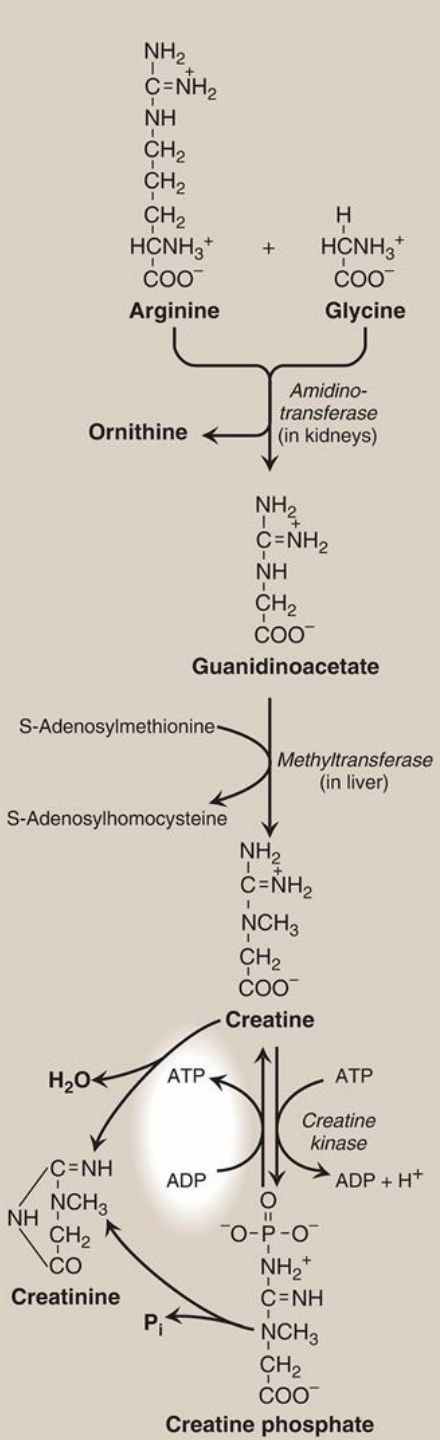
- γ-glutamylcysteinylglycine
- Major intracellular antioxidant
- Synthesis:
  - Glu + Cys (by γ-glutamylcysteine synthetase, rate-limited by cysteine) → + Gly (by glutathione synthetase).
- Glutathione Peroxidase (requires Selenium)
- Regenerated by Glutathione Reductase (requires NADPH)





Creatine and Creatinine Metabolism

- Occurs in the liver
- Gly + Arg → → + SAM (methyl donor) → Creatine
- Transported to muscle/brain and phosphorylated to Phosphocreatine (high-energy reserve)
- Creatinine is the non-enzymatic, irreversible breakdown product of creatine/phosphocreatine
- Its constant production and exclusive renal filtration make serum creatinine a key marker for GFR



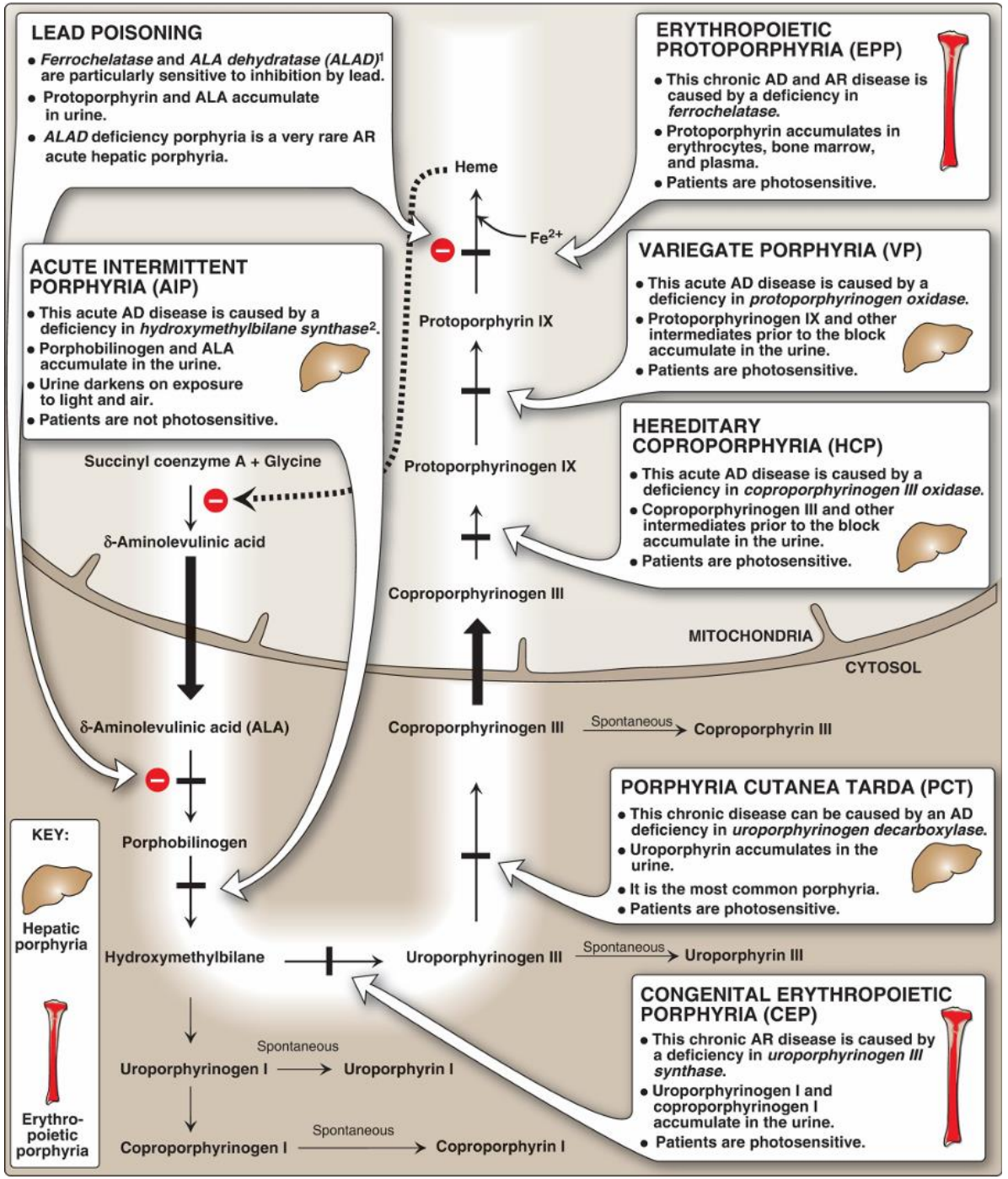
PART II: HEME SYNTHESIS

(DETAILED)

Heme Synthesis: Overview & Location

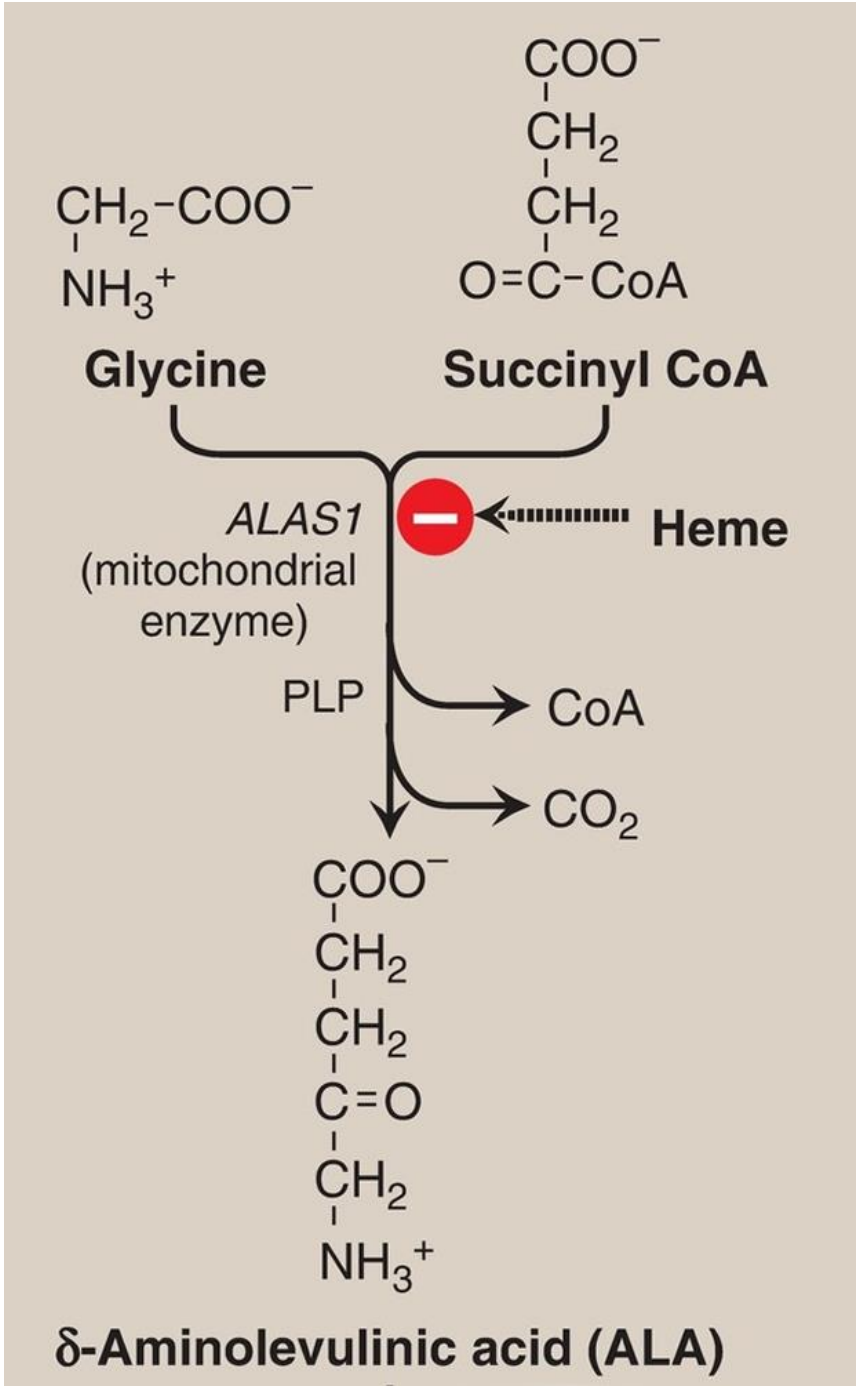
- Heme is a porphyrin ring chelating an iron atom
- It is a prosthetic group for hemoglobin, myoglobin, cytochromes (P450), catalase, and peroxidase
- Erythroid cells synthesize ~85% for hemoglobin; the liver synthesizes the rest for cytochromes
- The pathway is partitioned between the mitochondrion and cytosol
- Precursors: Succinyl-CoA (TCA cycle) and Glycine

Heme Synthesis: Overview & Location



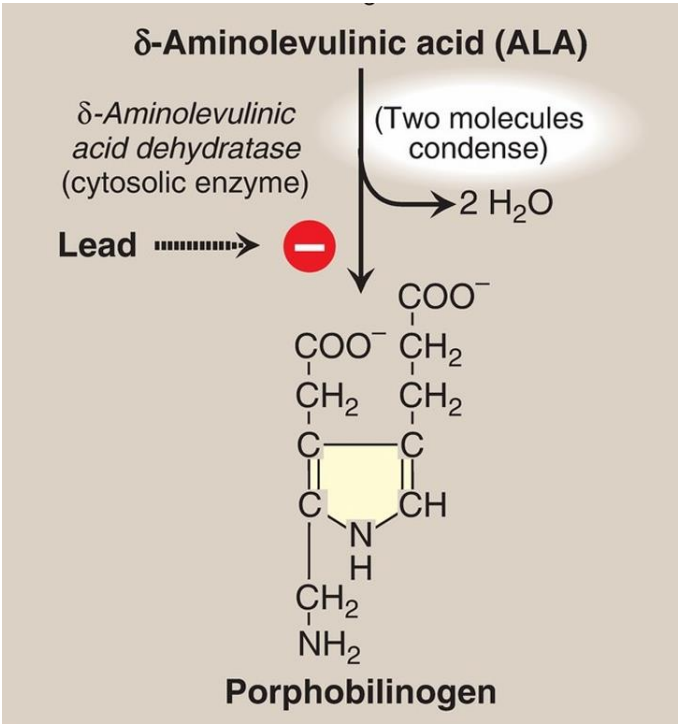
Step 1: Formation of δ-Aminolevulinic Acid (ALA)

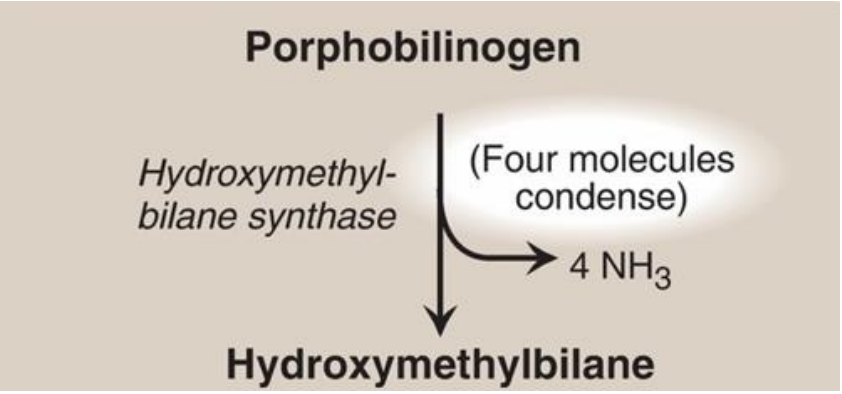
- Mitochondrial
- ALA Synthase (ALAS) (PLP)
- The committed and rate-limiting step in heme synthesis
- There are two isozymes: ALAS1 (liver, regulated) and ALAS2 (erythroid, constitutive)
- Heme inhibits ALAS1



Steps 2 & 3: From ALA to Porphobilinogen (PBG)

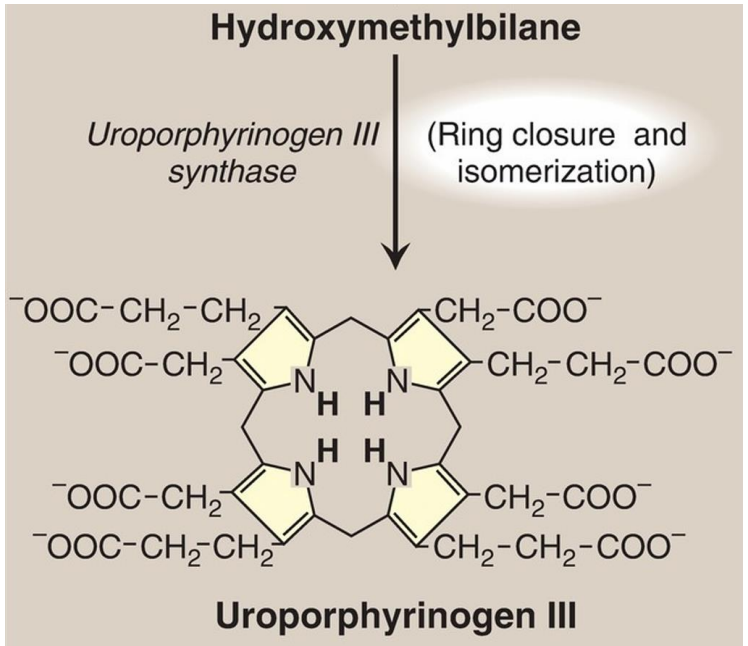
- Step 2 (Cytosol): Porphobilinogen (PBG)
  - ALA Dehydratase (Porphobilinogen Synthase)
  - Toxicity: highly sensitive to lead (↑ALA)
  - Major biochemical lesion in lead poisoning
- Step 3 (Cytosol): 4 PBG → Hydroxymethylbilane via PBG Deaminase (Hydroxymethylbilane synthase)

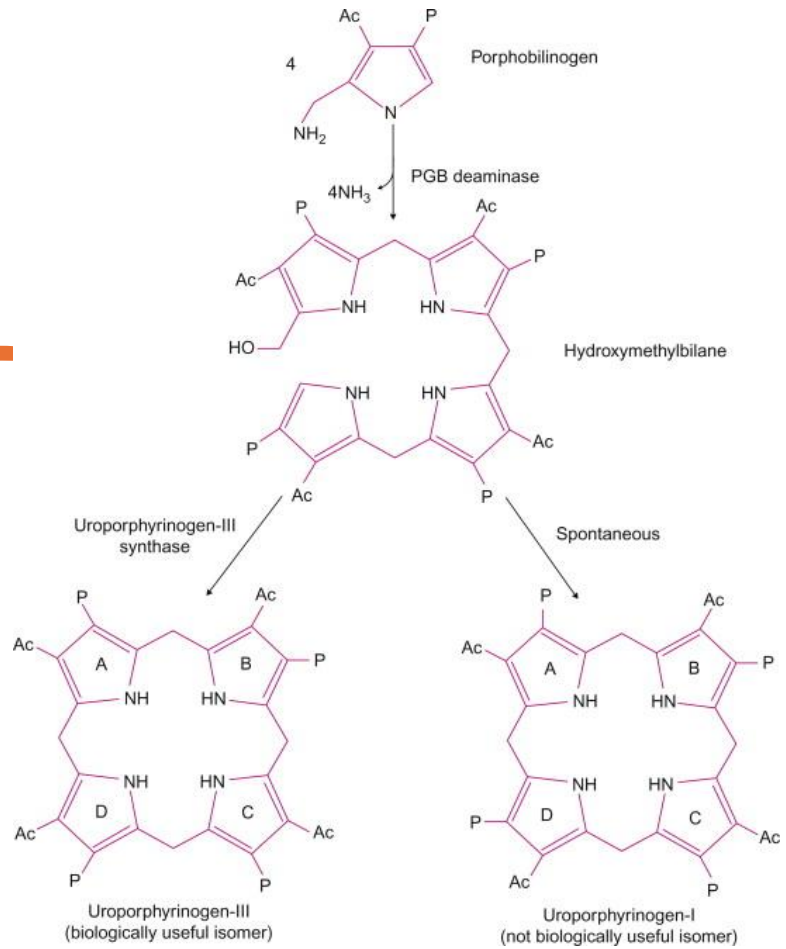




Steps 4 & 5: Formation of Uroporphyrinogen III

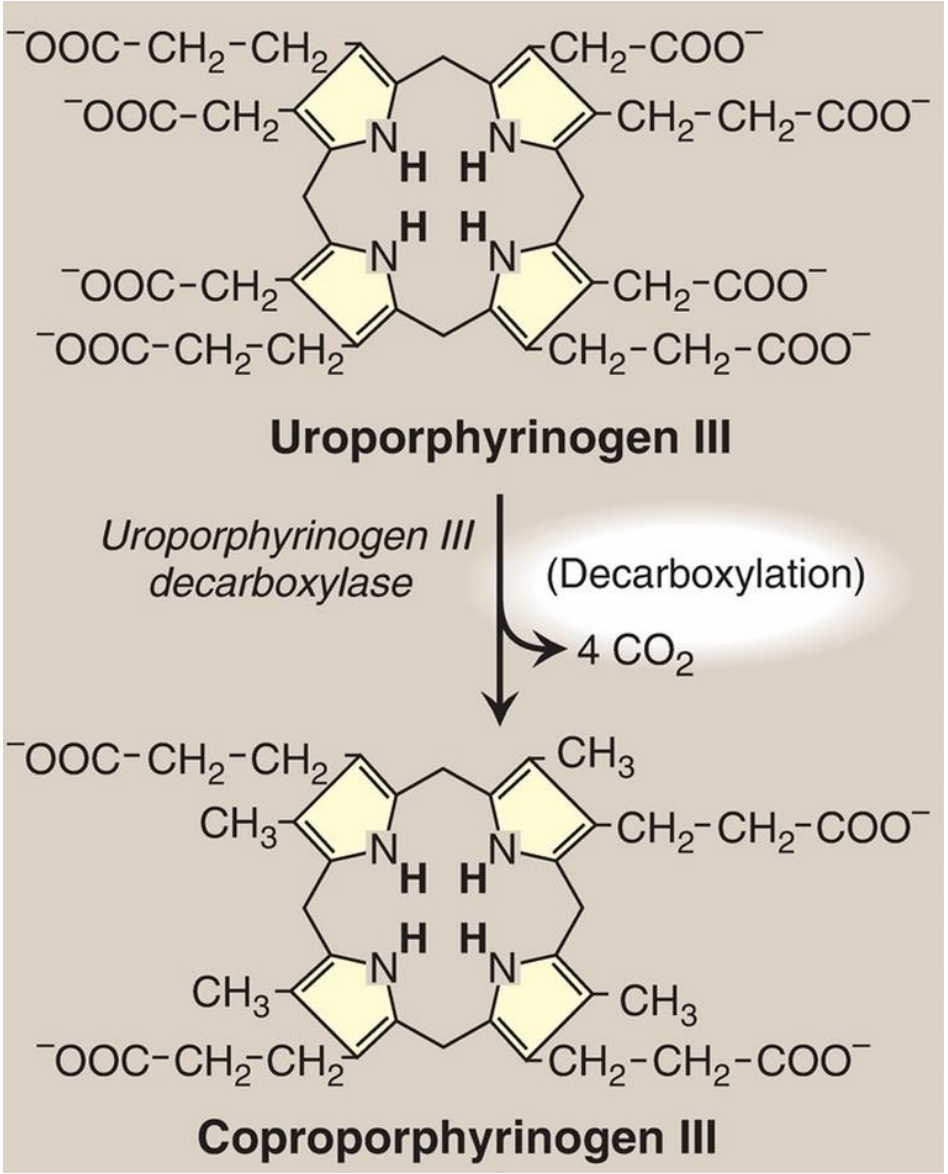
- Step 4 (Cytosol): spontaneous cyclization to Uroporphyrinogen I
- Step 5 (Cytosol): Uroporphyrinogen III Synthase
- A deficiency causes Congenital Erythropoietic Porphyria





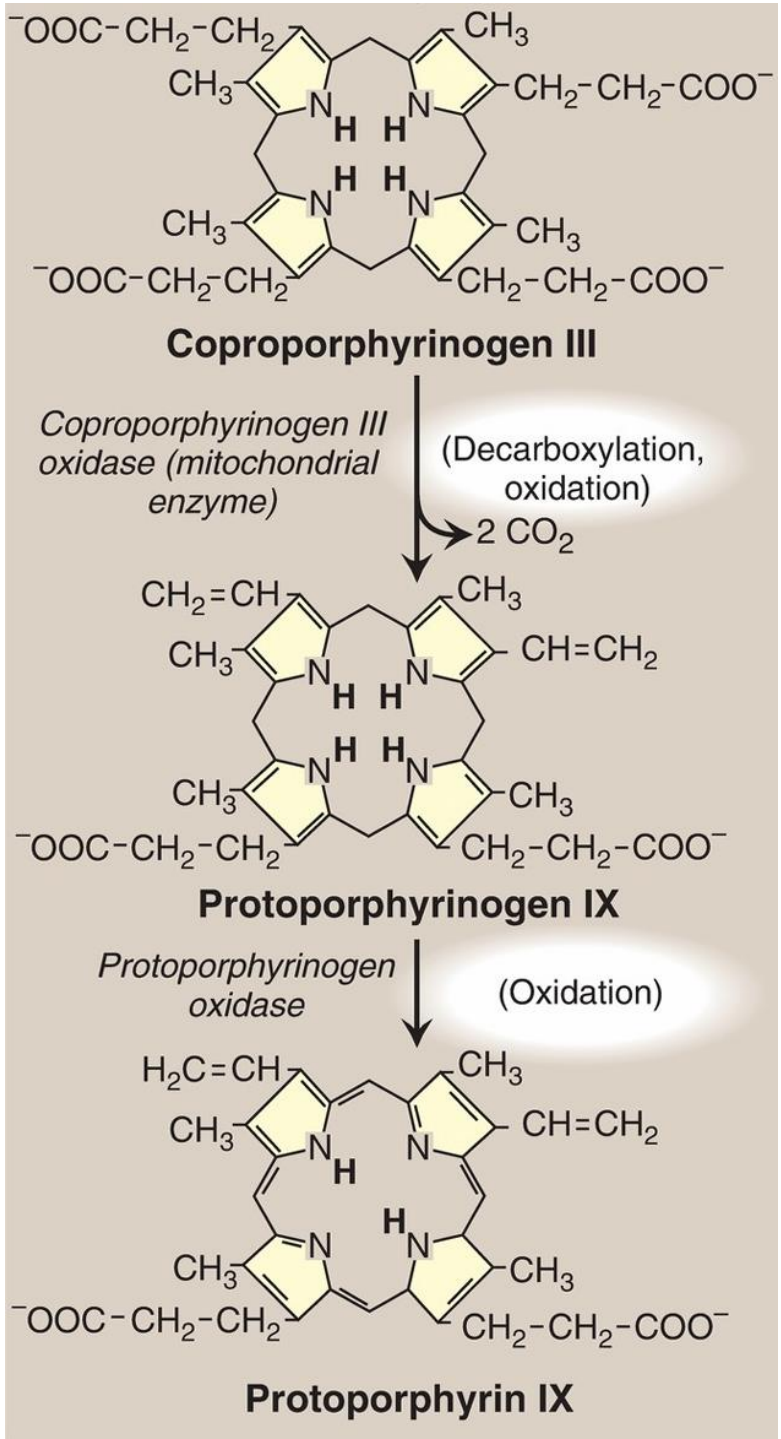
Decarboxylation to Coproporphyrinogen III

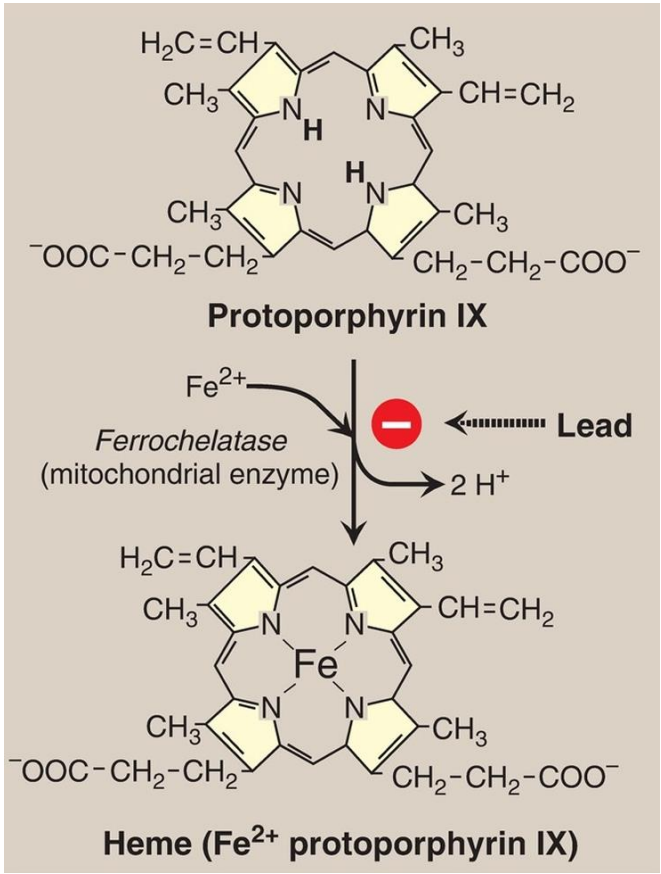
- Step 6 (Cytosol): decarboxylation to methyl groups
- Uroporphyrinogen Decarboxylase
- Product: Coproporphyrinogen III
- Clinical Note: Deficiency causes Porphyria Cutanea Tarda, the most common porphyria, associated with photosensitivity and skin fragility

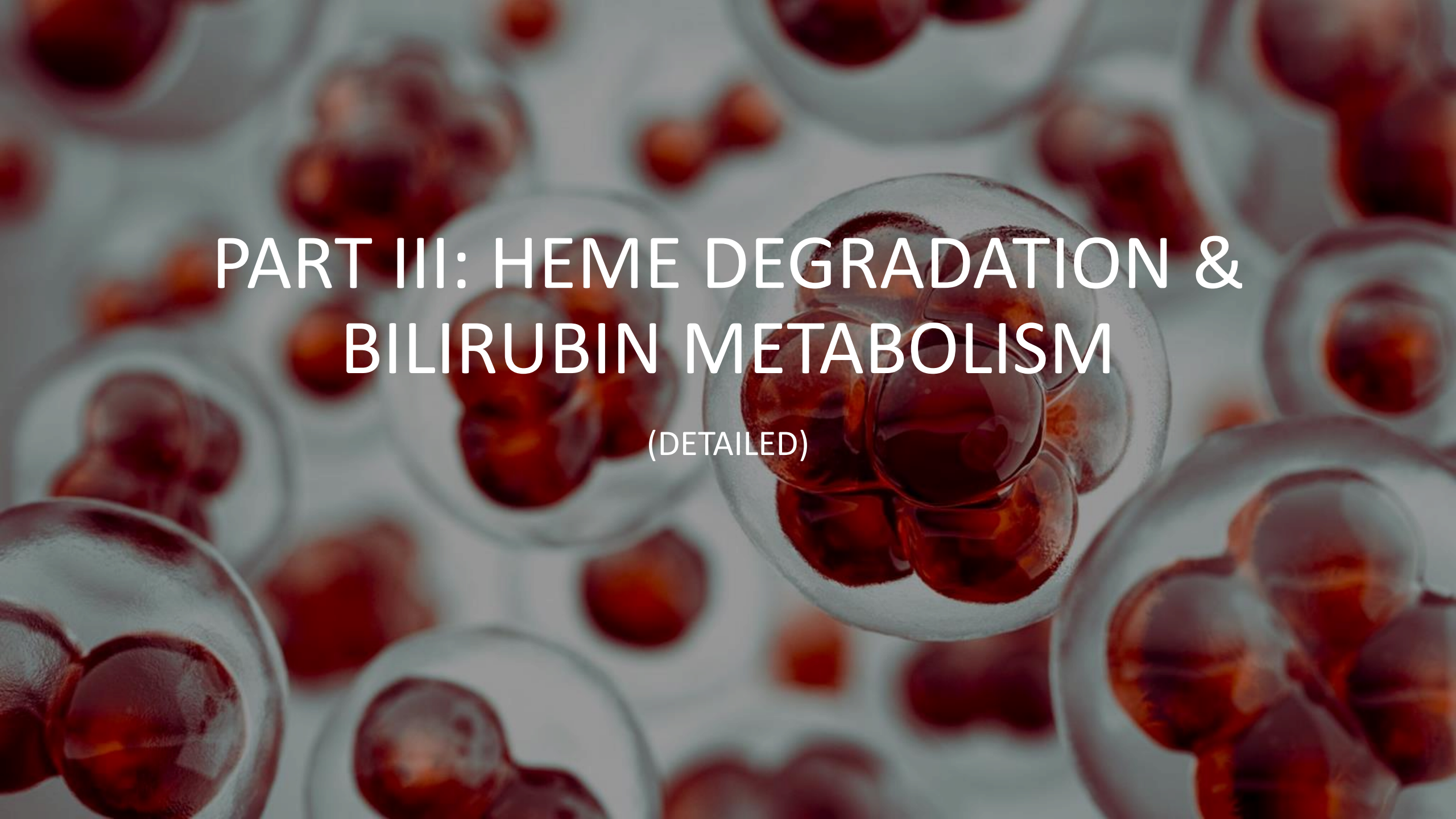


Steps 8 & 9: Mitochondrial Steps to Heme

- Coproporphyrinogen Oxidase & Protoporphyrinogen Oxidase (inhibited by lead)
- Final Step (Mitochondrion): (Ferrochelatase, lead)
- Iron deficiency results in Zinc being inserted instead, forming zinc protoporphyrin







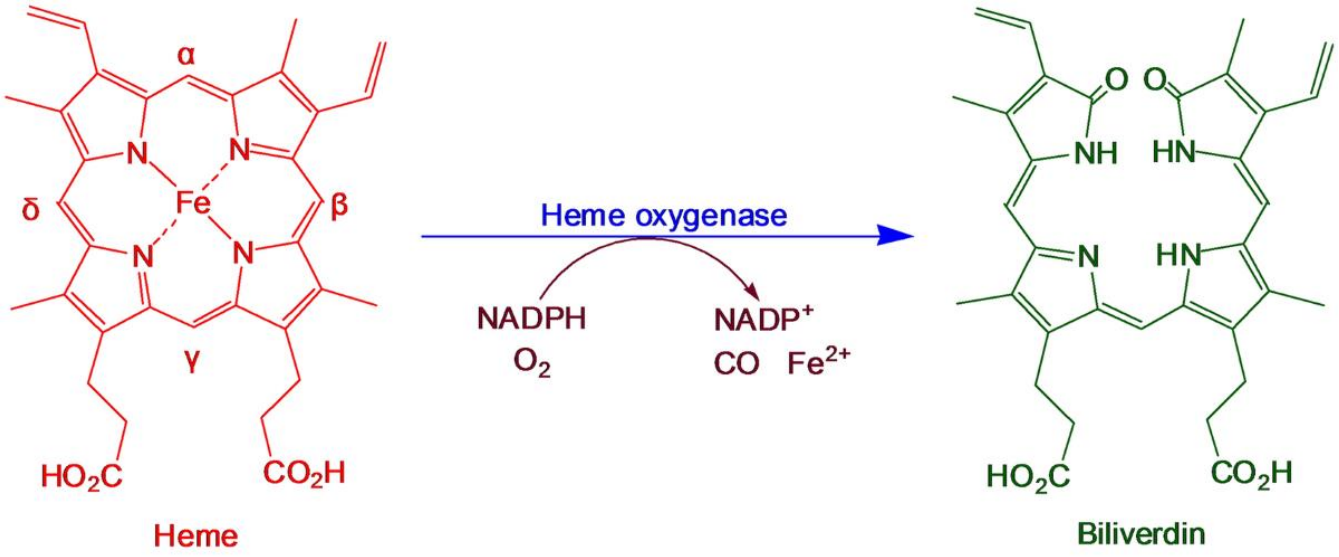
PART III: HEME DEGRADATION & BILIRUBIN METABOLISM

(DETAILED)

Heme Degradation: Overview

- Approximately 250-300 mg of heme is degraded daily, primarily from senescent RBCs destroyed by macrophages in the spleen, liver, and bone marrow
- The released heme is degraded to bilirubin, a process that conserves iron and converts a potential toxin into an excretable waste product

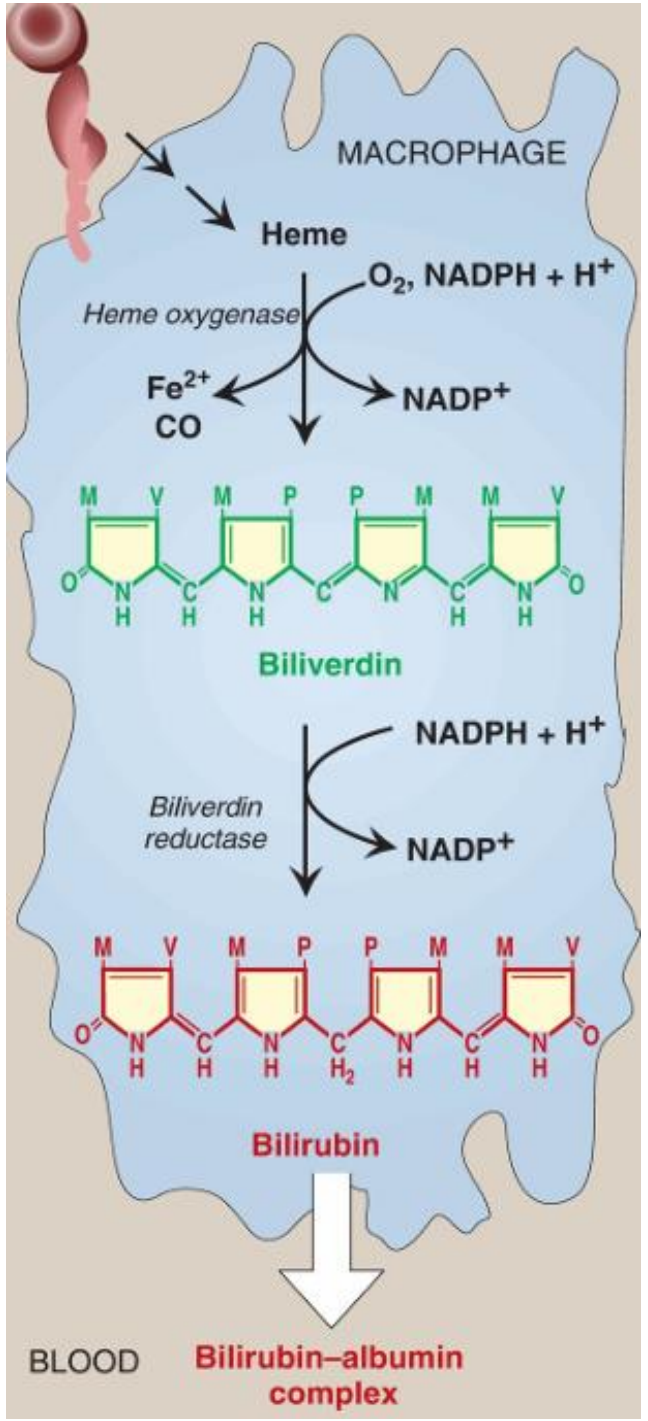
Step 1: Formation of Biliverdin



- Heme Oxygenase
- Products:
  - Biliverdin: A green, water-soluble pigment
  - Carbon Monoxide (CO): lungs; its production rate can be used to estimate heme turnover
  - Iron (Fe^{2+}): Recycled and stored as ferritin

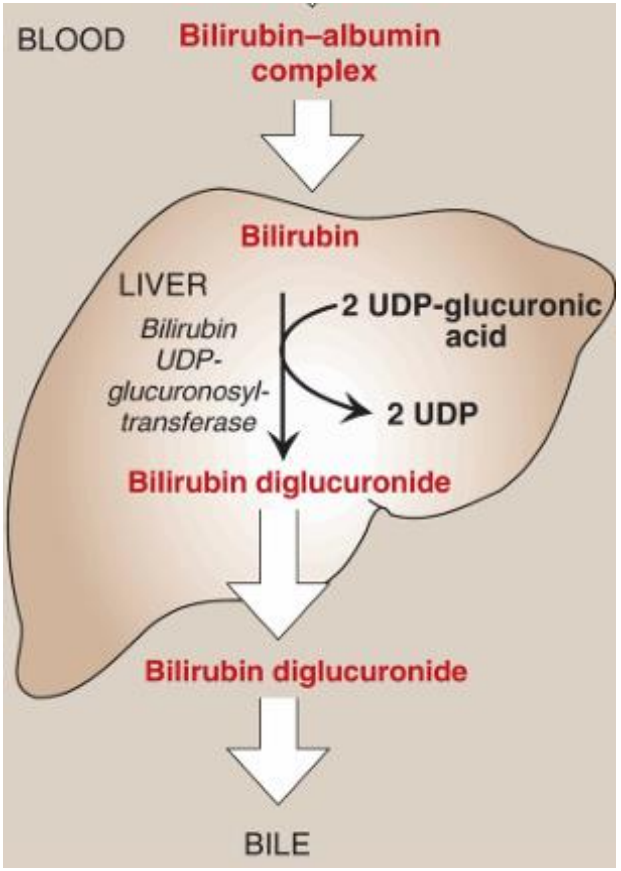
Step 2: Formation of Unconjugated Bilirubin

- Enzyme: Biliverdin Reductase (cytosolic, high activity)
- Product: Unconjugated Bilirubin (UCB)
- Lipid-soluble (hydrophobic)
- Tightly bound to albumin in plasma, and toxic to the CNS (kernicterus)
- Also called "indirect-reacting" bilirubin



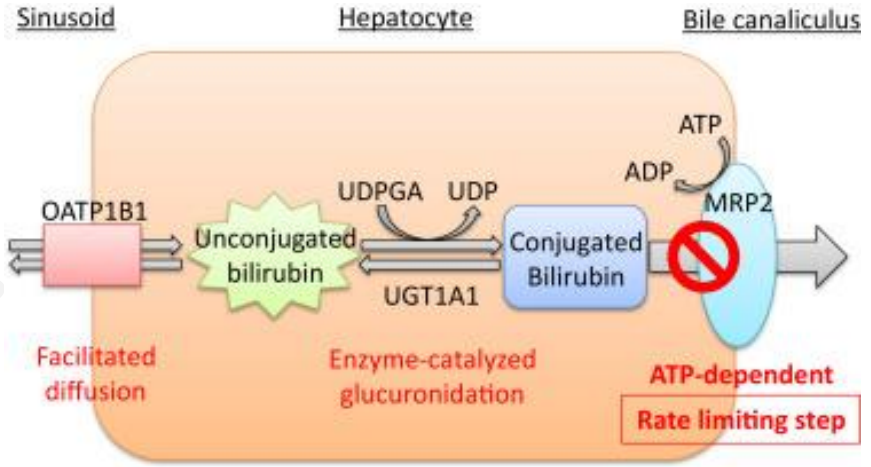
Transport, Uptake, & Conjugation

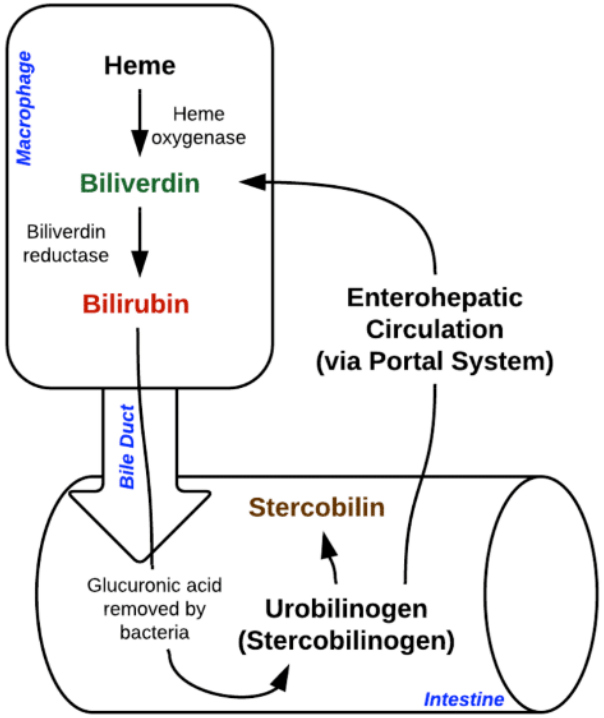
- UCB-albumin →liver (dissociation) → Facilitated diffusion → Intracellular carrier proteins (e.g., ligandin) (preventing efflux)→ endoplasmic reticulum for conjugation
- UCB + 2 UDP-Glucuronic Acid → Bilirubin Diglucuronide
- UDP-Glucuronosyltransferase (UGT) (ER)
- Significance: Conjugation (hydrophilic), non-toxic, and ready for biliary excretion
- Conjugated Bilirubin (CB), or "direct-reacting" bilirubin



Biliary Excretion & Intestinal Fate

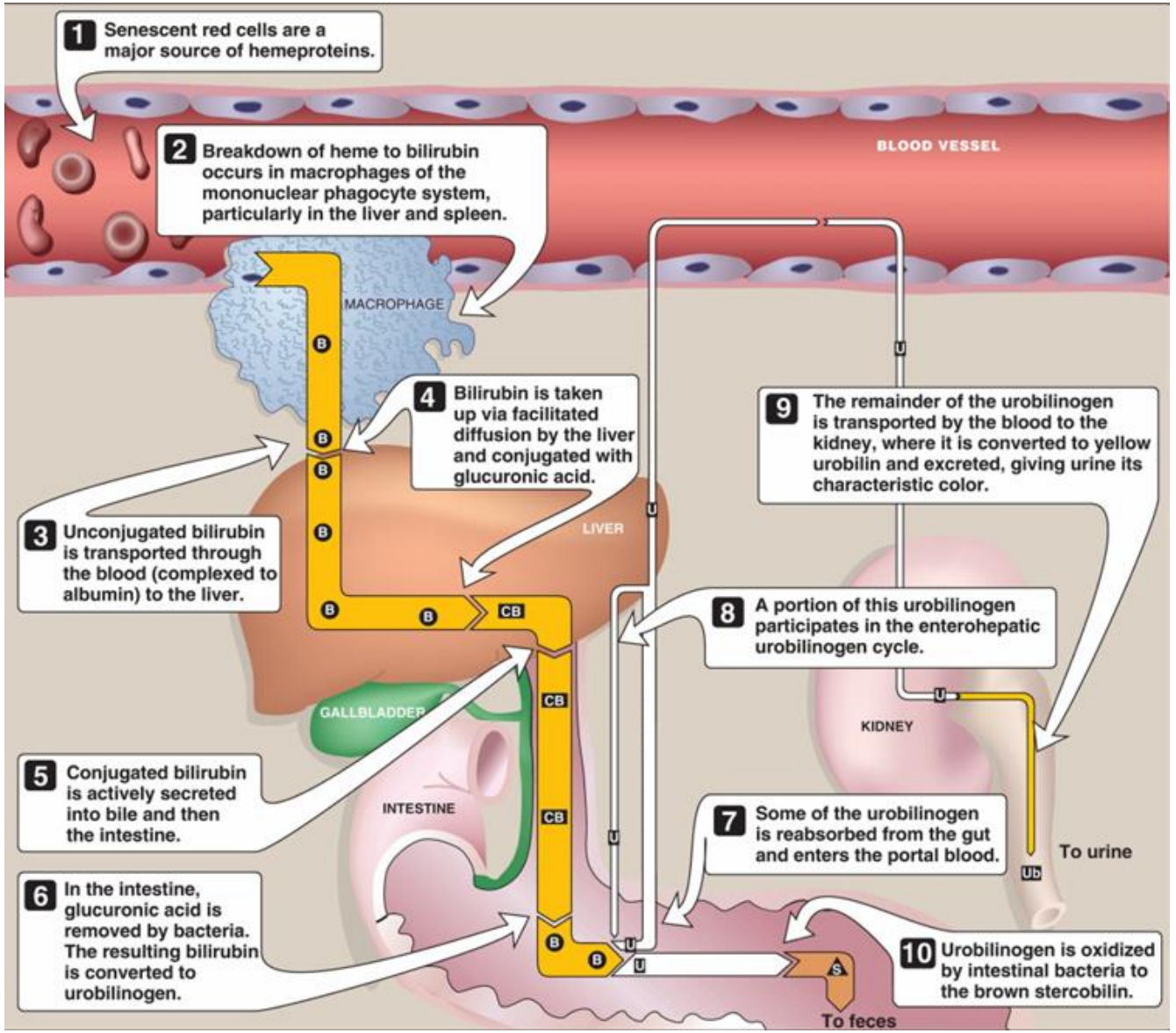
- Actively transported into bile (MRP2)
- Bacterial β-glucuronidases deconjugate it back to UCB
- Also, bacteria reduces it back to a colorless compound called urobilinogen





Enterohepatic Circulation & Final Excretion

- ~80% oxidized to stercobilin (brown pigment)
- ~20% reabsorbed into portal blood and re-excreted (enterohepatic circulation)
- (~2-5%) escapes, excreted as urobilin (kidneys, yellow pigment)

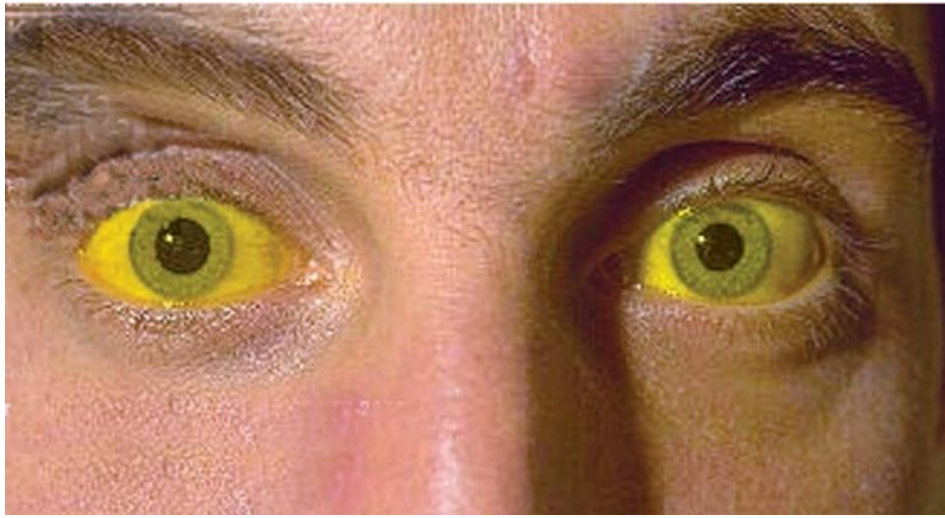


PART IV: JAUNDICE - PATHOPHYSIOLOGY & DIAGNOSIS

(MAJOR EMPHASIS)

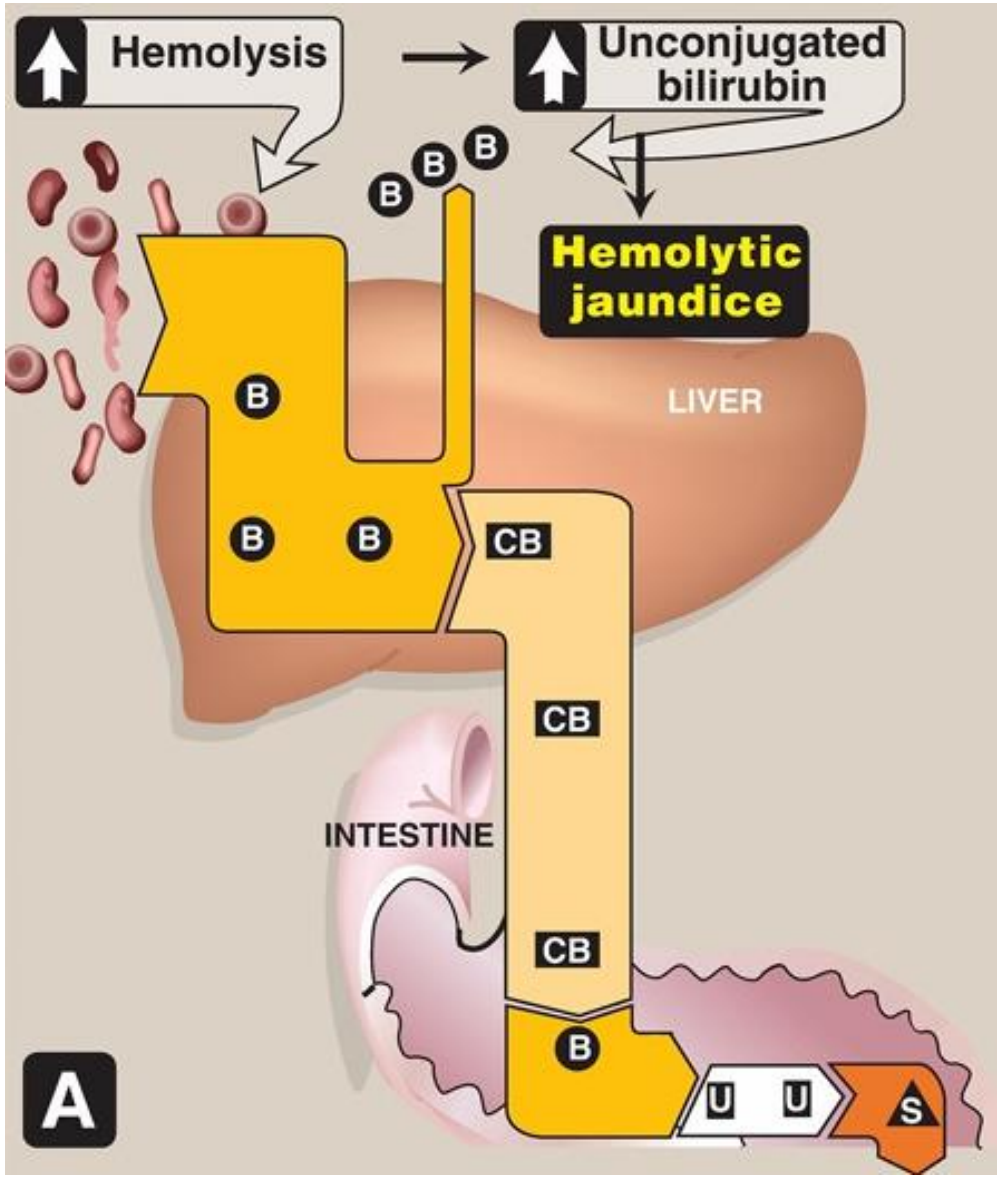
Jaundice: Definition and Presentation

- Yellow discoloration of skin, sclera, and mucous membranes
- Elevated serum bilirubin levels (>2-3 mg/dL)
- Scleral icterus is an early sign due to the high elastin content that binds bilirubin
- It is a symptom, not a disease, indicating a disorder in bilirubin metabolism



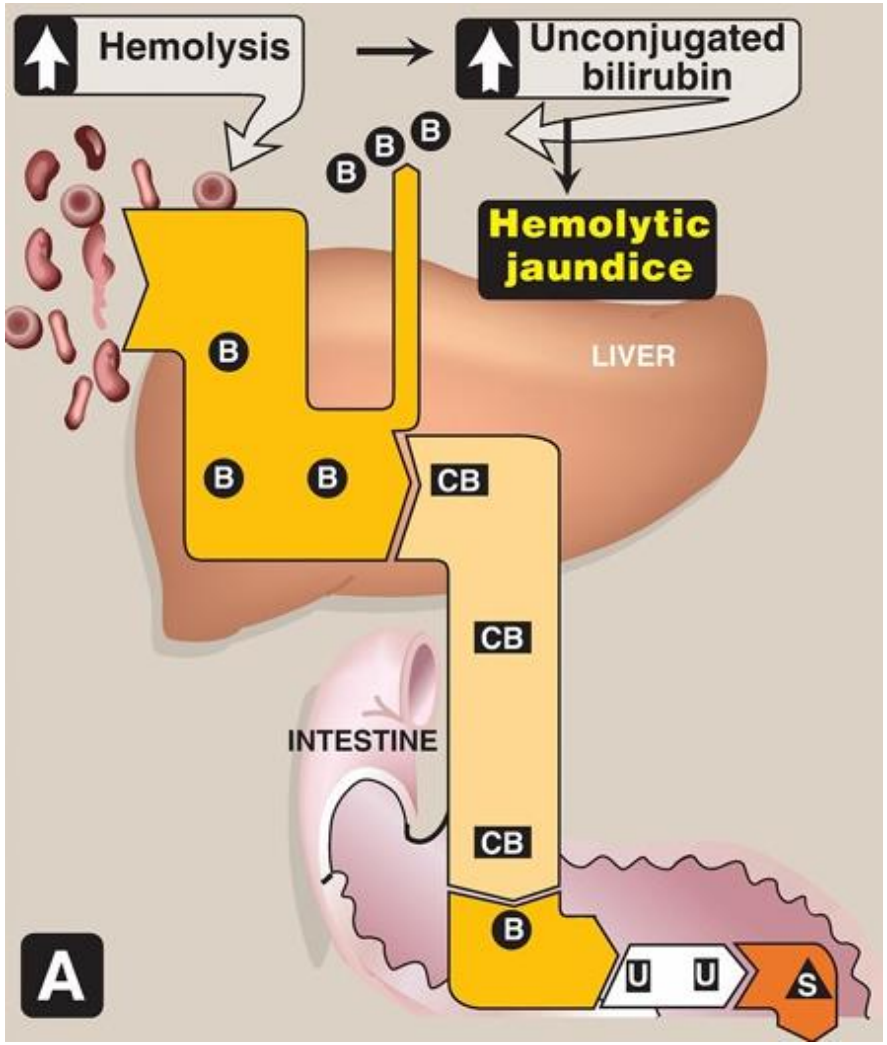
Pre-Hepatic (Hemolytic) Jaundice: Pathogenesis

- Cause: Excessive destruction of red blood cells (hemolysis)
- Overwhelms the liver's conjugation capacity
- Examples: Sickle cell anemia, G6PD deficiency, autoimmune hemolysis, malaria
- Key Defect: Overproduction of bilirubin from heme



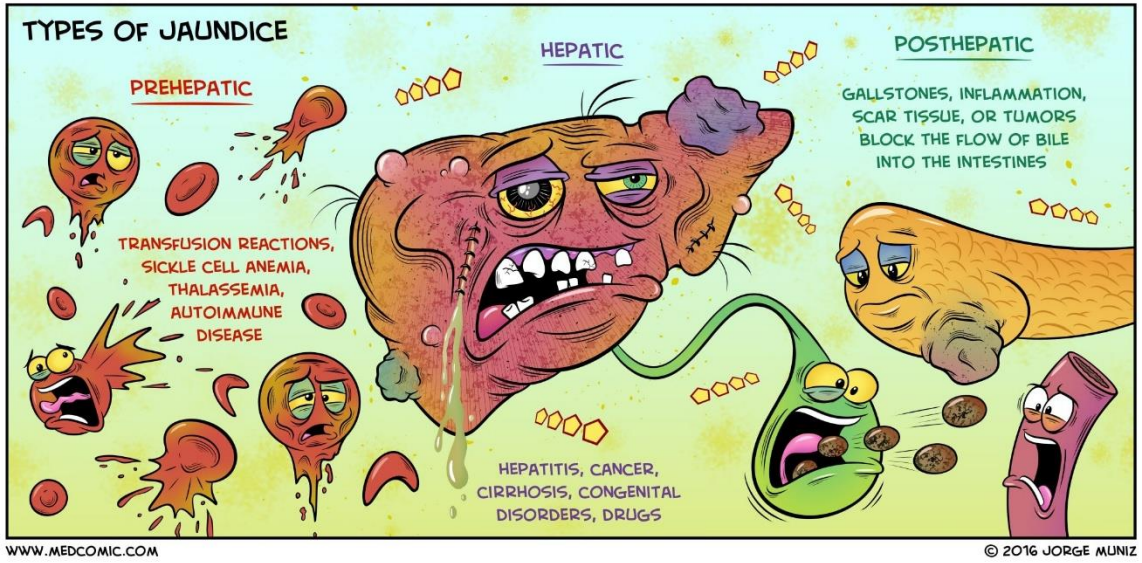
Pre-Hepatic Jaundice: Laboratory Findings

- Total Bilirubin: Increased (mostly unconjugated)
- Urine Bilirubin: NEGATIVE??
- Urine Urobilinogen: Markedly INCREASED??
- Stool Color: Very dark brown (high stercobilin)
- Other: low haptoglobin



Hepatic (Hepatocellular) Jaundice: Pathogenesis

- Cause: Liver cell damage impairs all phases of bilirubin metabolism: uptake, conjugation, and excretion
- Examples: Viral hepatitis (Hep A, B, C), alcoholic liver disease, cirrhosis, drug-induced liver injury (e.g., acetaminophen overdose)
- Key Defect: Dysfunction of hepatocytes



Hepatic Jaundice: Laboratory Findings

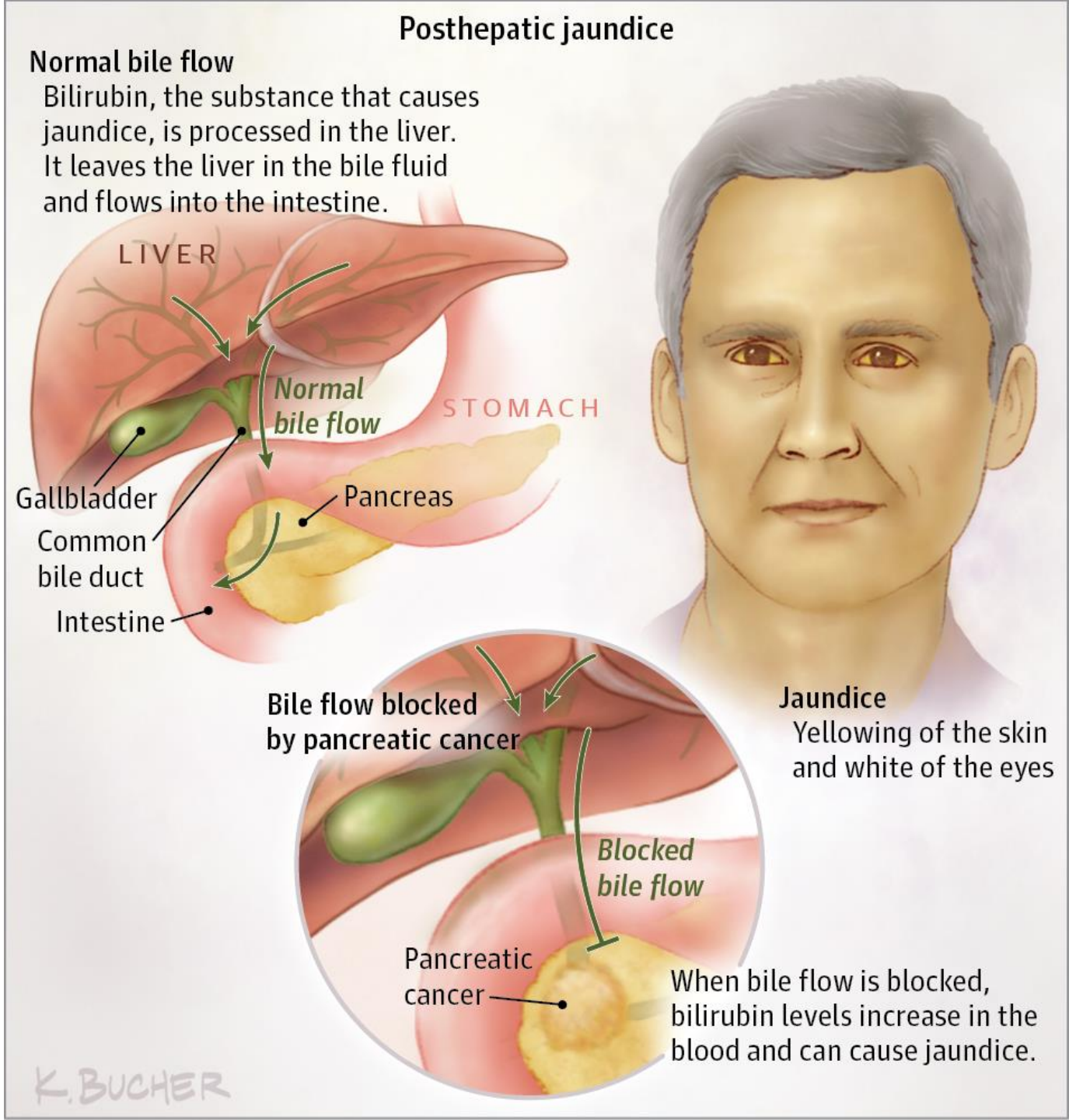
- Total Bilirubin: Increased (both unconjugated and conjugated)??
- Urine Bilirubin: POSITIVE??
- Urine Urobilinogen: often increased (if intrahepatic cholestasis predominates, it may be decreased).

- Stool Color: May be pale if cholestasis is significant

- Other: Elevated liver enzymes (AST, ALT)

Post-Hepatic (Obstructive) Jaundice: Pathogenesis

- Cause: Physical obstruction
- Examples: Gallstones, pancreatic head carcinoma, bile duct stricture
- Key Defect: Mechanical blockage of bile flow



Post-Hepatic Jaundice: Laboratory Findings

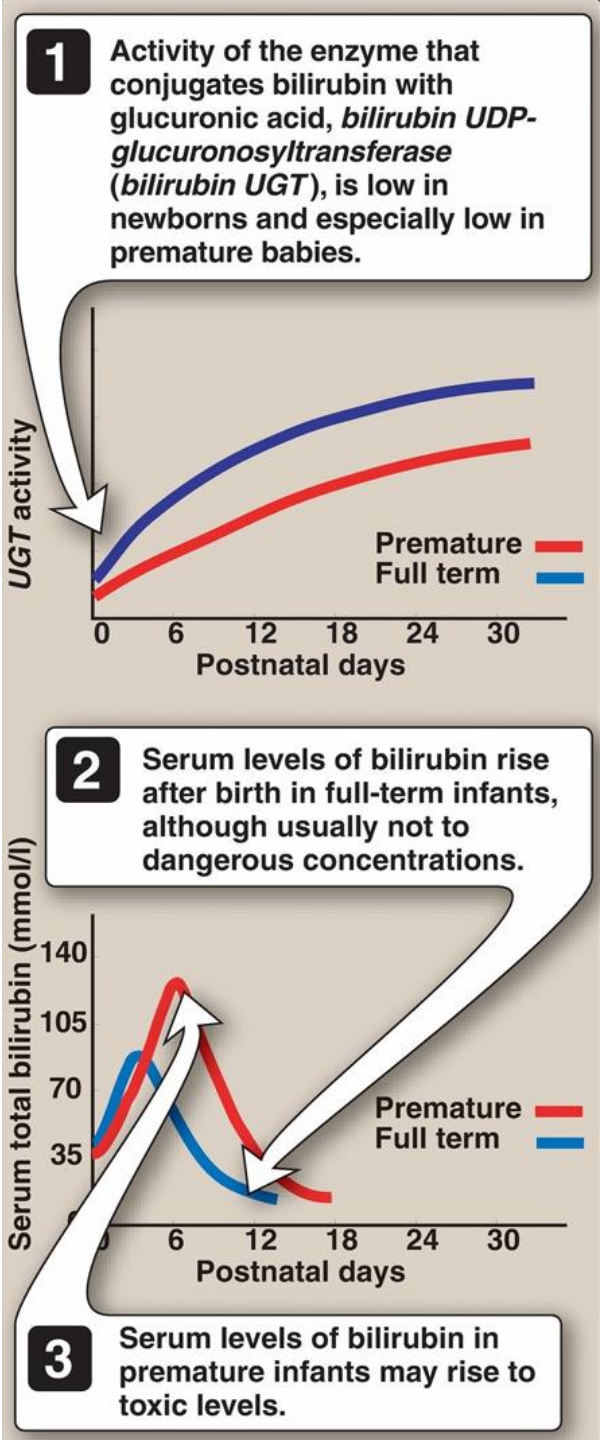
- Total Bilirubin: Markedly increased (mostly conjugated)??
- Urine Bilirubin: Strongly POSITIVE??
- Urine Urobilinogen: NEGATIVE or LOW
- Stool Color: Pale, clay-colored
- Other: Pruritus due to bile salt retention

Comparison: The Three Types of Jaundice

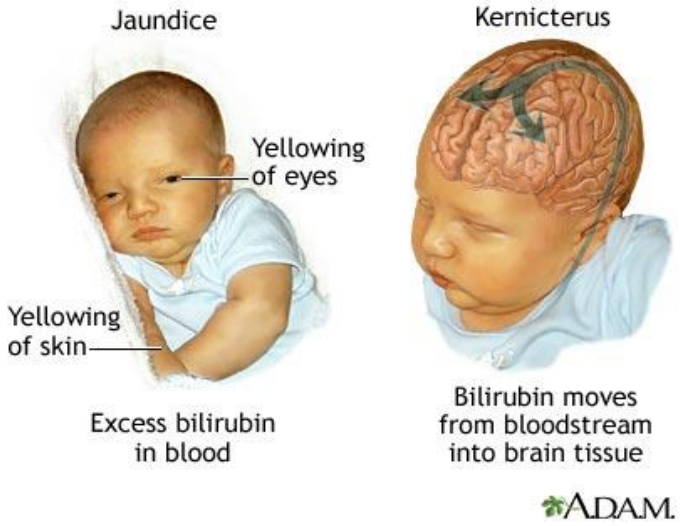
Feature	Pre-Hepatic	Hepatic	Post-Hepatic
Main Defect	Overproduction	Hepatocellular Injury	Obstruction
Bilirubin Type	**Unconjugated ↑↑**	**Mixed ↑**	**Conjugated ↑↑↑**
Urine Bilirubin	Negative	Positive	**Positive**
Urine Urobilinogen	**Increased**	Variable	**Decreased/Absent**
Stool Color	Dark	Variable	**Pale/Clay**
Key Labs	Low haptoglobin	High ALT, AST	High ALP, GGT

Neonatal Jaundice (Physiologic)

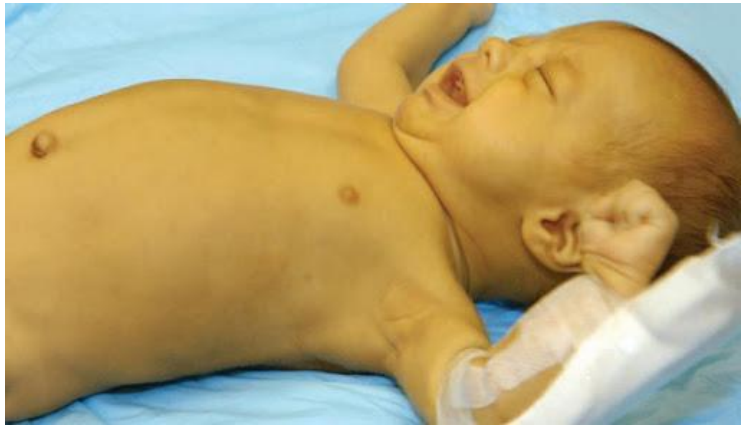
- Common in newborns due to:
  - High RBC turnover
  - Immature hepatic uptake and UGT activity (conjugation)
  - Sterile gut (delayed bacterial colonization) → increased enterohepatic circulation of UCB
- Usually appears on day 2-3, peaks by day 5, resolves by 2 weeks.

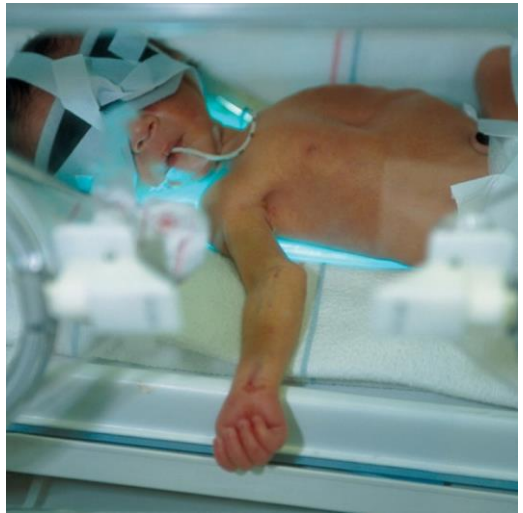


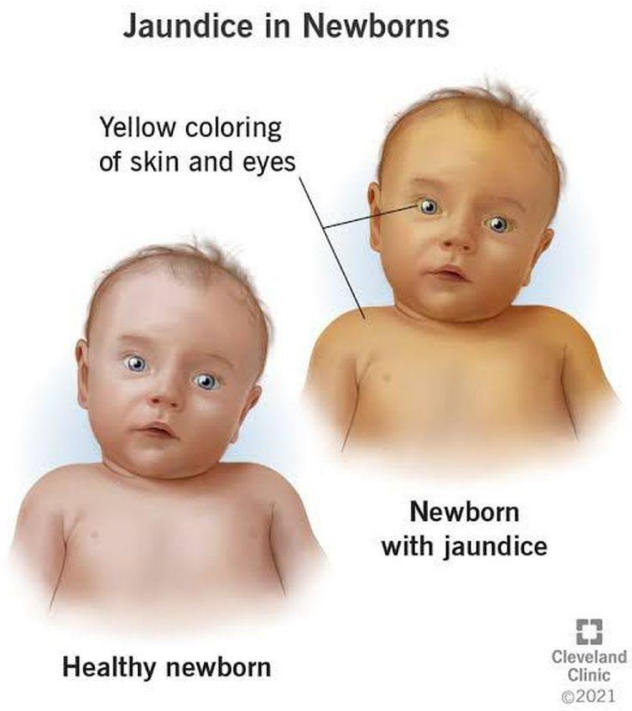
Neonatal Jaundice (Physiologic)



- Risk: If levels rise too high, UCB can cross the immature blood-brain barrier and cause kernicterus (permanent neurological damage)
- Treated with phototherapy (converts UCB to water-soluble isomers)

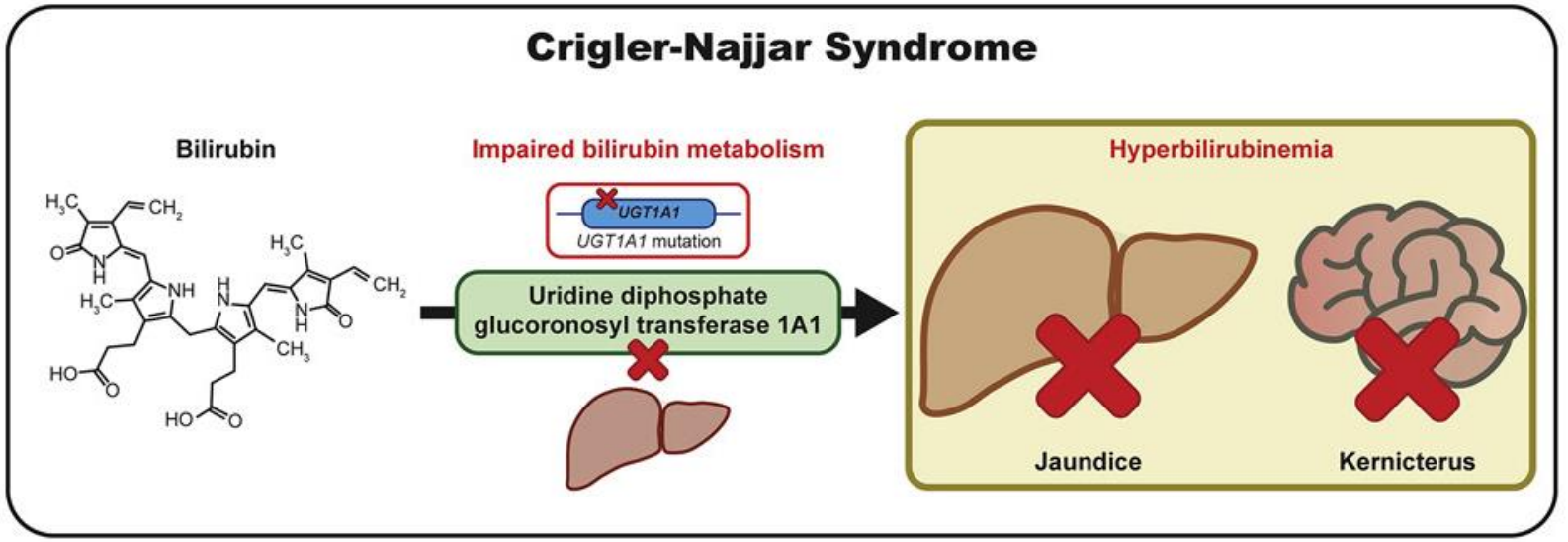






Inherited Disorders of Bilirubin Metabolism

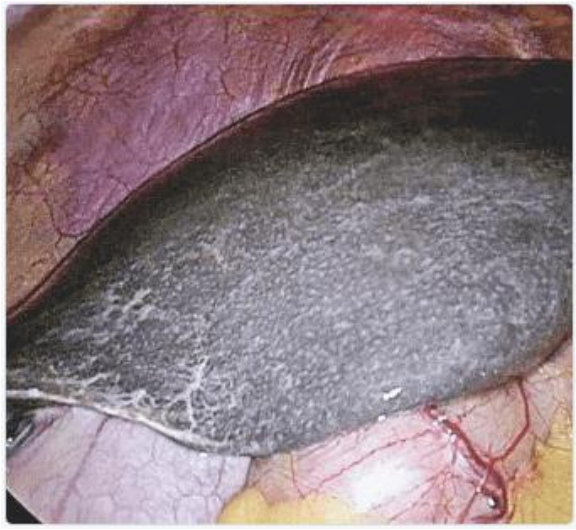
- Crigler-Najjar Syndrome Type I:
  - Complete deficiency of UGT
  - Severe unconjugated hyperbilirubinemia, kernicterus, fatal without liver transplant
- Crigler-Najjar Syndrome Type II: partial deficiency of UGT, less severe

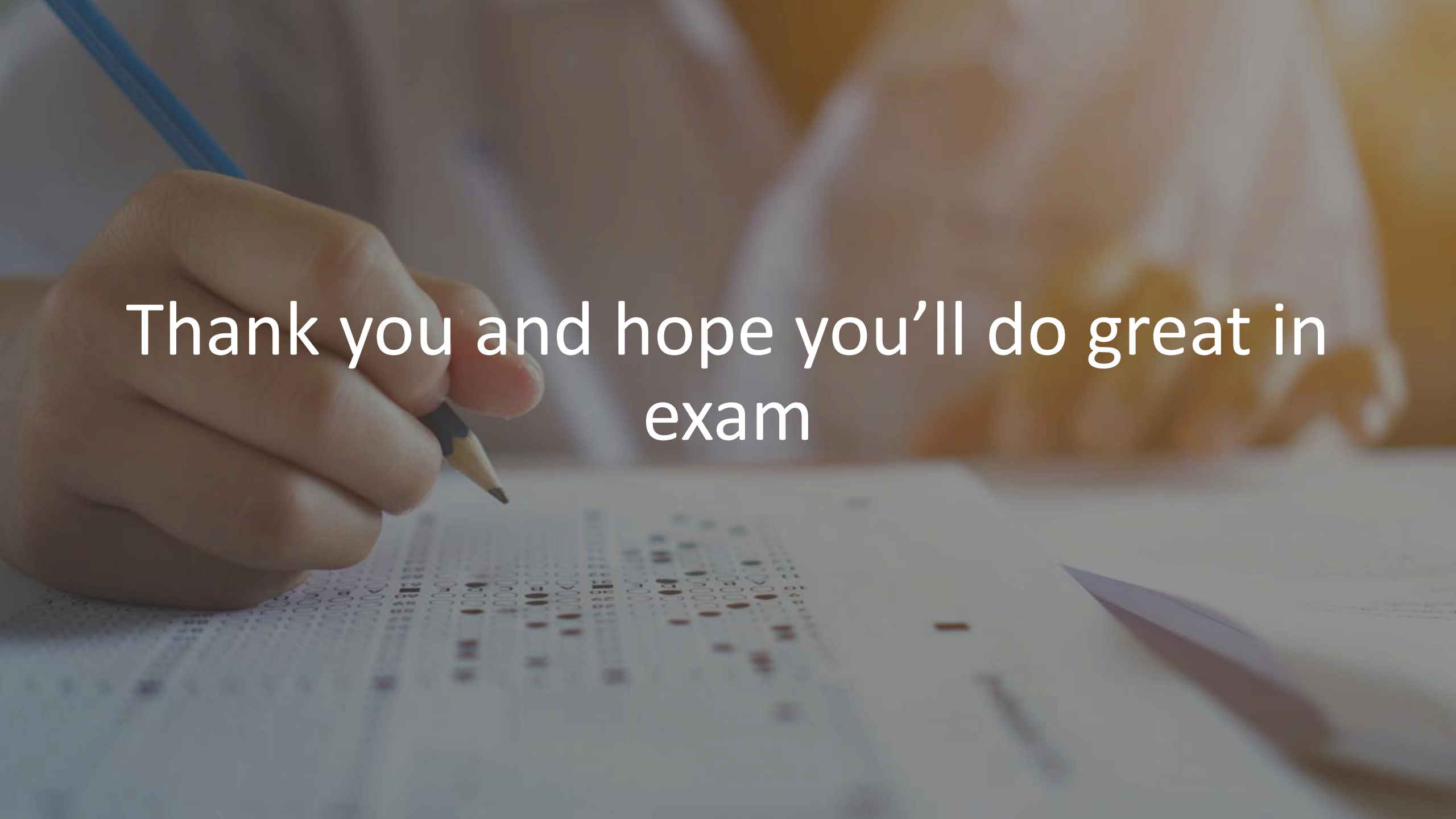


Inherited Disorders of Bilirubin Metabolism

- Gilbert Syndrome:
  - Mild (~30%) reduction in UGT activity
  - Benign, very common (~5-10% population)
  - Mild, unconjugated hyperbilirubinemia during stress, fasting, or illness

- Dubin-Johnson Syndrome: Defect in hepatic excretion of conjugated bilirubin (MRP2). Causes conjugated hyperbilirubinemia.
  - Liver has a characteristic black pigmentation




Thank you and hope you’ll do great in exam