

Heme Synthesis and Breakdown

? HEME SYNTHESIS AND BREAKDOWN

Includes:

- ? Structure of heme
- ? Biosynthesis (all steps, sites, enzymes, cofactors)
- ? Regulation
- ? Porphyrrias (all types, features, lab findings)

Everything will be pointwise, exam-focused, with tables in your preferred list format.

? STRUCTURE OF HEME

- Heme = **protoporphyrin IX + ferrous iron (Fe^{2+})**.
- Porphyrin ring = **tetrapyrrole** (four pyrrole rings linked by methenyl bridges).
- Central Fe^{2+} binds:
 - O_2 (in Hb, Mb)
 - Electrons (in cytochromes)
- Side chains on protoporphyrin IX:
 - **4 methyl ($-\text{CH}_3$)**
 - **2 vinyl ($-\text{CH}=\text{CH}_2$)**
 - **2 propionate ($-\text{CH}_2-\text{CH}_2-\text{COO}^-$)**

Function: Essential component of hemoglobin, myoglobin, cytochromes, catalase, peroxidases.

? BIOSYNTHESIS OF HEME

? Overall

- Occurs in **all nucleated cells**, most active in:
 - **Bone marrow (85%)** ? hemoglobin
 - **Liver (15%)** ? cytochromes
 - Pathway takes place partly in **mitochondria** and partly in **cytosol**.
-

? Stepwise Synthesis (With Sites & Enzymes)

? Step 1 – Rate-limiting step

- **Glycine + Succinyl-CoA** ? ?-ALA
 - Enzyme: **ALA synthase**
 - Cofactor: **Pyridoxal phosphate (Vitamin B6)**
 - Site: **Mitochondria**
-

? Step 2

- **ALA** ? **Porphobilinogen (PBG)**

- Enzyme: **ALA dehydratase (PBG synthase)**
 - Inhibited by **lead (Pb)**
 - Site: **Cytosol**
-

? Step 3

- **4 PBG ? Hydroxymethylbilane**
 - Enzyme: **PBG deaminase**
 - Site: **Cytosol**
-

? Step 4

- **Hydroxymethylbilane ? Uroporphyrinogen III**
 - Enzyme: **Uroporphyrinogen III synthase**
 - Site: **Cytosol**
-

? Step 5

- **Uroporphyrinogen III ? Coproporphyrinogen III**
 - Enzyme: **Uroporphyrinogen decarboxylase**
 - Site: **Cytosol**
-

? Step 6

- **Coproporphyrinogen III ? Protoporphyrinogen IX**
 - Enzyme: **Coproporphyrinogen oxidase**
 - Site: **Mitochondria**
-

? Step 7

- **Protoporphyrinogen IX ? Protoporphyrin IX**
 - Enzyme: **Protoporphyrinogen oxidase**
 - Site: **Mitochondria**
-

? Step 8 — Final Step

- **Protoporphyrin IX + Fe²⁺ ? Heme**
 - Enzyme: **Ferrochelatase**
 - Inhibited by **lead (Pb)**
 - Site: **Mitochondria**
-

? Regulation of Heme Synthesis

? 1. Rate-limiting step: ALA synthase

In liver:

- **Inhibited by heme / hemin (end-product inhibition)**

- **Upregulated by drugs** that induce cytochrome P450 (barbiturates, griseofulvin, phenytoin).

In bone marrow:

- Regulated primarily by **iron availability**.

? 2. Lead (Pb) poisoning inhibits:

- **ALA dehydratase**
- **Ferrochelatase**
 ? ? ALA, ? Protoporphyrin
 ? Anemia + neurologic symptoms

? BREAKDOWN OF HEME

Occurs mostly in **reticuloendothelial (RE) cells** of spleen, liver, bone marrow.

? Stepwise Breakdown

? 1. Heme ? Biliverdin

- Enzyme: **Heme oxygenase**
 - Releases **Fe³⁺** and **CO**
 - Requires **O₂** + **NADPH**
-

? 2. Biliverdin ? Bilirubin

- Enzyme: **Biliverdin reductase**
-

? 3. Bilirubin Transport

- Unconjugated bilirubin is **insoluble** ? binds to **albumin**.
-

? 4. Conjugation in Liver

- Bilirubin + UDP-glucuronic acid
 - Enzyme: **UDP-glucuronyltransferase**
 - Forms **bilirubin diglucuronide** (water soluble)
-

? 5. Excretion into Bile

? 6. Intestinal Fate

- Bilirubin ? **Urobilinogen**
 - Urobilin (in urine) ? yellow
 - Stercobilin (in stool) ? brown
-

? PORPHYRIAS

Porphyrias = inherited/acquired disorders of **heme synthesis** due to enzyme defects.

They cause accumulation of **specific intermediates** ? neurovisceral or photosensitive symptoms.

? MAJOR PORPHYRIAS (Exam Pattern)

? 1. Acute Intermittent Porphyria (AIP)

- Enzyme deficient: **PBG deaminase**
- Accumulation: **ALA, PBG**
- Features:
 - Severe abdominal pain
 - Neuropsychiatric symptoms
 - **NO photosensitivity**
 - Red wine-colored urine

? 2. Porphyria Cutanea Tarda (PCT)

- Enzyme deficient: **Uroporphyrinogen decarboxylase**
- Features:
 - **Photosensitivity**
 - Blisters on sun-exposed skin
 - Red-brown urine

- Most common porphyria.
-

? 3. Congenital Erythropoietic Porphyria

- Enzyme deficient: **Uroporphyrinogen III synthase**
 - Severe photosensitivity
 - Red teeth (erythrodontia)
-

? 4. Hereditary Coproporphyria

- Enzyme deficient: **Coproporphyrinogen oxidase**
 - Mixed: abdominal pain + photosensitivity
-

? 5. Variegate Porphyria

- Enzyme deficient: **Protoporphyrinogen oxidase**
 - Neurovisceral + photosensitivity
-

? Short Summary Table (List Format)

Porphyria – Enzyme Defect ? Symptoms

- **AIP** – PBG deaminase ? abdominal pain, neuropathy, NO photosensitivity

- **PCT** – Uroporphyrinogen decarboxylase ? blistering photosensitivity
- **CEP** – Uroporphyrinogen III synthase ? severe photosensitivity, red teeth
- **HCP** – Coproporphyrinogen oxidase ? pain + photosensitivity
- **VP** – Protoporphyrinogen oxidase ? mixed symptoms

? Lead Toxicity in Heme Synthesis (Rapid Recall)

Lead inhibits:

- **ALA dehydratase**
- **Ferrochelatase**
 - ? ? ALA
 - ? ? Protoporphyrin
 - ? Microcytic anemia

? STRUCTURE OF HEME

- Heme is a **porphyrin ring** with **iron (Fe^{2+})** at the center.
- The ring is called **protoporphyrin IX**.
- It consists of **four pyrrole rings (A, B, C, D)** linked via **methene bridges**.
- Side chains on pyrrole rings include **methyl, vinyl, and propionate groups**.

- The **central Fe²⁺** binds with:
 - 4 nitrogens of the ring
 - 1 binding site for **globin**
 - 1 site for **O², CO, NO** or other ligands (“sixth position”).
- Fe must be in **ferrous form (Fe²⁺)** to bind oxygen (Fe³⁺ cannot bind O²).
- Heme is found in hemoglobin, myoglobin, cytochromes, catalase, and peroxidases.

? BIOSYNTHESIS OF HEME

Occurs in **all tissues**, mainly:

- **85% in bone marrow** (RBC formation)
- **15% in liver** (cytochrome production)

? Location of Steps

- **Mitochondria ? Cytosol ? Mitochondria**

? Step-by-Step Pathway (with key enzymes & regulation)

? 1. Condensation of Glycine + Succinyl CoA ? ?-ALA

- Enzyme: **ALA synthase (ALAS)**
- Cofactor: **Pyridoxal phosphate (Vitamin B₆)**

- Rate-limiting step
 - Occurs in mitochondria
 - Inhibited by **heme (negative feedback)**
 - Induced by many drugs in liver that increase cytochrome P450 demand ? ALAS upregulation
-

? 2. Two molecules of ?-ALA ? Porphobilinogen (PBG)

- Enzyme: **ALA dehydratase (ALA-D)**
 - Location: Cytosol
 - **Lead inhibits ALA dehydratase**, causing ALA accumulation.
-

? 3. Four PBG molecules ? Hydroxymethylbilane (HMB)

- Enzyme: **PBG deaminase (HMB synthase)**
 - Deficiency ? **Acute Intermittent Porphyria**
-

? 4. HMB ? Uroporphyrinogen III

- Enzyme: **Uroporphyrinogen III synthase**
 - If enzyme deficient ? non-physiological type I porphyrins form (photosensitive).
-

? 5. Uroporphyrinogen III ? Coproporphyrinogen III

- Enzyme: **Uroporphyrinogen decarboxylase**
 - Defect ? **Porphyria Cutanea Tarda (PCT)**
 - Most common porphyria
 - Photosensitivity
-

? 6. Coproporphyrinogen III ? Protoporphyrinogen IX

- Enzyme: **Coproporphyrinogen oxidase**
 - Occurs in mitochondria (re-entry).
-

? 7. Protoporphyrinogen IX ? Protoporphyrin IX

- Enzyme: **Protoporphyrinogen oxidase**
-

? 8. Protoporphyrin IX + Fe²⁺ ? Heme

- Enzyme: **Ferrochelatase**
 - Inhibited by **lead**, causing accumulation of **protoporphyrin IX**
 - Final step in mitochondria
-

? Regulation of Heme Synthesis

- **Key regulatory enzyme:** ALA synthase

- Inhibited by **heme/hemin**
- Liver ALAS induced by drugs: barbiturates, alcohol, antiepileptics
- RBC heme synthesis depends on erythropoietin & iron availability

? Lead (Pb) Poisoning – Where Does It Act?

- Inhibits:
 - **ALA dehydratase**
 - **Ferrochelatase**
- Effects:
 - ? ALA
 - ? Protoporphyrin
 - ? Heme synthesis
 - Microcytic hypochromic anemia

? PORPHYRIAS

Porphyrias = **defects in heme biosynthetic enzymes** ? accumulation of intermediates.

Classified into:

? 1. Hepatic Porphyrias

(Usually neurovisceral symptoms)

? 2. Erythropoietic Porphyrias

(Usually photosensitivity)

? Major Porphyrias — Enzyme, Accumulated Product, Key Features

? 1. Acute Intermittent Porphyria (AIP)

- Defect: **PBG deaminase**
- Accumulation: ALA, PBG
- Features:
 - Acute abdominal pain
 - Neuropsychiatric symptoms
 - Red-wine urine darkening on standing
 - **No photosensitivity**
- Triggered by drugs, starvation, alcohol
- Treatment: hemin (inhibits ALAS)

? 2. Porphyria Cutanea Tarda (PCT) – MOST COMMON

- Defect: **Uroporphyrinogen decarboxylase (UROD)**
- Accumulation: Uroporphyrin
- Features:

- Photosensitivity
 - Blistering skin lesions
 - Hyperpigmentation
 - Elevated liver enzymes
 - Associated with alcohol, estrogens, HCV infection
-

? 3. Congenital Erythropoietic Porphyrria (CEP / Günther Disease)

- Defect: **Uroporphyrinogen III synthase**
 - Accumulation: Type I porphyrins
 - Features:
 - Severe photosensitivity
 - Red urine
 - Hemolytic anemia
 - Erythrodontia (red-brown teeth that fluoresce)
-

? 4. Hereditary Coproporphyrria (HCP)

- Defect: **Coproporphyrinogen oxidase**
- Features:

- Neurovisceral attacks
 - Variable photosensitivity
-

? 5. Variegate Porphyria

- Defect: **Protoporphyrinogen oxidase**
 - Features:
 - Neurovisceral symptoms
 - Photosensitivity
 - Skin blistering
 - “Mixed” presentation
-

? 6. Erythropoietic Protoporphyria (EPP)

- Defect: **Ferrochelatase**
 - Accumulation: Protoporphyrin IX
 - Features:
 - Photosensitivity
 - Burning sensation in sunlight
 - Mild liver dysfunction possible
-

? Key Differentiation (Ultra-Short Clues)

- **AIP:** Abdominal pain + neuro symptoms; no photosensitivity
- **PCT:** Photosensitivity + blistering; most common
- **CEP:** Childhood onset, severe photosensitivity, red teeth
- **EPP:** Mild photosensitivity, protoporphyrin buildup
- **Variegate/HCP:** Neuro + skin symptoms both present

? CATABOLISM OF HEME

? 1. Site

- Mainly in **reticuloendothelial system (RES)**
 - Spleen
 - Liver
 - Bone marrow
- Occurs when RBCs reach end of lifespan (~120 days) or during hemolysis.

? 2. Step-by-Step Breakdown

? Step 1: Heme → Biliverdin

- Enzyme: **Heme oxygenase**
- Requires: O_2 + NADPH

- Iron (Fe^{2+} ? Fe^{3+}) released and reused
 - Carbon monoxide (CO) also produced
-

? Step 2: Biliverdin ? Bilirubin

- Enzyme: **Biliverdin reductase**
 - Produces **unconjugated bilirubin (indirect)**
 - Water-insoluble ? transported bound to albumin
-

? UNCONJUGATED BILIRUBIN TRANSPORT

- Unconjugated (“indirect”) bilirubin is **lipid-soluble**
 - Strongly bound to **albumin** in blood
 - Cannot be excreted in urine
 - Enters hepatocytes by facilitated transport
-

? CONJUGATION IN LIVER

? Bilirubin + UDP-glucuronic acid ? Bilirubin diglucuronide

- Enzyme: **UDP-glucuronyl transferase (UGT1A1)**
 - Water-soluble form = **conjugated bilirubin (direct)**
 - Secreted into bile canaliculi ? bile ? intestine
-

? INTESTINAL METABOLISM

? 1. Conjugated bilirubin ? Urobilinogen

- By **gut bacteria**

? 2. Urobilinogen fate

- Some absorbed ? liver (enterohepatic circulation)
- Some filtered by kidneys ? **urobilin (yellow)**
- Most converted in colon ? **stercobilin (brown)**

This gives stool its **brown color** and urine its **yellow color**.

? PLASMA BILIRUBIN

? Types of bilirubin measured

1. **Direct bilirubin**

- Water-soluble
- Conjugated
- Can appear in urine

2. **Indirect bilirubin**

- Water-insoluble
- Unconjugated

- Albumin-bound
- Cannot appear in urine

Total bilirubin = Direct + Indirect

? SHUNT BILIRUBIN (IMPORTANT PG TOPIC)

“Shunt bilirubin” refers to **bilirubin formed from heme precursors *other than hemoglobin* before the RBC matures.**

? Where it comes from

- Destruction of **ineffective erythroid precursors** in bone marrow
- Called **intramedullary hemolysis**

? Seen in

- Thalassemia major
- Megaloblastic anemia
- Sideroblastic anemia
- Myelodysplastic syndromes

? Effect

- Elevated **unconjugated bilirubin**
- Normal or mildly reduced hemoglobin

- Reticulocyte count may not rise proportionately

This concept explains jaundice in severe ineffective erythropoiesis without peripheral hemolysis.

? HYPERBILIRUBINEMIAS (VERY HIGH YIELD)

Classified into:

? 1. Pre-hepatic (Hemolytic) Hyperbilirubinemia

? Key features:

- ? RBC destruction
- ? Unconjugated bilirubin
- No bilirubin in urine
- ? Urobilinogen

? Causes:

- Hemolytic anemia
- Thalassemia
- G6PD deficiency
- Shunt bilirubin (ineffective erythropoiesis)

? 2. Hepatic Hyperbilirubinemia

Due to impaired uptake, conjugation, or excretion.

? A. Impaired uptake

- Drugs (rifampicin)
- Sepsis

? B. Impaired conjugation

- **Gilbert syndrome** (mild ? UGT1A1)
- **Crigler–Najjar type I** (no UGT; severe)
- **Crigler–Najjar type II** (partial deficiency)

? C. Impaired excretion

- **Dubin–Johnson syndrome** (defective canalicular transport)
- **Rotor syndrome** (defective hepatic storage)

? 3. Post-hepatic (Obstructive) Hyperbilirubinemia

? Key features:

- ? Conjugated bilirubin
- Clay-colored stools (? stercobilin)
- Dark urine (? conjugated bilirubin)
- Pruritus (bile salts)

? Causes:

- Gallstones
- Carcinoma of head of pancreas
- Cholangiocarcinoma
- Strictures
- Primary sclerosing cholangitis

? ULTRA-SHORT DIFFERENTIATION

? Unconjugated (Indirect) bilirubin ?

- Hemolysis
- Shunt bilirubin
- Gilbert
- Crigler–Najjar
- Neonatal jaundice

? Conjugated (Direct) bilirubin ?

- Obstruction
- Dubin–Johnson
- Rotor

- Hepatitis/cholestasis

? CONGENITAL HYPERBILIRUBINEMIAS

These are inherited defects in bilirubin **conjugation** or **excretion**.

? 1. Gilbert Syndrome

- Mild ? **UGT1A1** activity
 - Slight ? unconjugated bilirubin (usually <3 mg/dL)
 - Triggered by fasting, stress, infection
 - Completely benign
-

? 2. Crigler–Najjar Syndrome Type I

- Complete absence of **UGT1A1**
 - Very high unconjugated bilirubin (>20 mg/dL)
 - Fatal in infancy due to kernicterus
 - No response to phenobarbital
-

? 3. Crigler–Najjar Syndrome Type II

- Partial deficiency of UGT1A1
 - Moderate unconjugated bilirubin
 - Responds to **phenobarbital** (induces enzyme)
-

? 4. Dubin–Johnson Syndrome

- Defect in **canalicular transport protein (MRP2)**
 - ? conjugated bilirubin
 - Dark, **black pigmented liver**
 - Benign
-

? 5. Rotor Syndrome

- Defect in hepatic **storage/uptake** of conjugated bilirubin
 - ? conjugated bilirubin
 - **Liver is not pigmented** (unlike Dubin–Johnson)
 - Benign
-

? KEY DIFFERENCE (Ultra-Short)

DISORDER	CONJUGATION	EXCRETION	TYPE
Gilbert	?	Normal	Unconjugated
Crigler–Najjar I	Absent	Normal	Unconjugated
Crigler–Najjar II	??	Normal	Unconjugated
Dubin–Johnson	Normal	Defective	Conjugated
Rotor	Normal	Defective uptake/storage	Conjugated

? HEMOLYTIC (PRE-HEPATIC) JAUNDICE

Caused by **increased RBC breakdown** ? overproduction of bilirubin.

? Features:

- ? **Unconjugated bilirubin**
- Normal liver function
- **No bilirubin in urine** (unconjugated is water-insoluble)
- ? **Urobilinogen** (more bilirubin entering gut)
- Dark stools
- Anemia + reticulocytosis

? Causes:

- Hemolytic anemia (autoimmune, hereditary spherocytosis)
- G6PD deficiency
- Sickle cell disease
- Thalassemia
- Malaria
- Shunt bilirubin from ineffective erythropoiesis

? HEPATOCELLULAR (LIVER) JAUNDICE

Due to **damage to hepatocytes** ? impaired uptake, conjugation, and excretion.

? Features:

- ? **Both** unconjugated & conjugated bilirubin
- ? AST/ALT
- **Bilirubin in urine** (conjugated)
- Variable stool color
- ? or ? urobilinogen
- Jaundice + hepatomegaly + systemic symptoms

? Causes:

- Viral hepatitis

- Alcoholic hepatitis
- Drug-induced liver injury
- NAFLD
- Cirrhosis
- Wilson disease, hemochromatosis

? OBSTRUCTIVE (POST-HEPATIC) JAUNDICE

Due to **bile flow blockage**.

? Features:

- ? **Conjugated bilirubin**
- **Very dark urine** (conjugated bilirubin excreted in urine)
- **Clay-colored stool** (? stercobilin)
- Severe itching (bile salts in skin)
- ? ALP & GGT
- ? urobilinogen

? Causes:

- Gallstones
- Carcinoma head of pancreas

- Cholangiocarcinoma
- Primary sclerosing cholangitis
- Biliary atresia
- Strictures

? DIFFERENTIAL DIAGNOSIS OF JAUNDICE (HIGH YIELD)

Here is the **cleanest differentiation**, perfect for exams:

? 1. Hemolytic (Pre-hepatic)

- Bilirubin: **Unconjugated ?**
- Urine bilirubin: **Absent**
- Urine urobilinogen: **?**
- Stool color: Dark
- Enzymes: Normal
- Example: G6PD deficiency

? 2. Hepatocellular

- Bilirubin: Both ?

- Urine bilirubin: Present
 - Urine urobilinogen: Variable
 - Stool: Normal or pale
 - Enzymes: AST/ALT ?
 - Example: Viral hepatitis
-

? 3. Obstructive (Post-hepatic)

- Bilirubin: **Conjugated ?**
 - Urine bilirubin: Present (very high)
 - Urine urobilinogen: ?
 - Stool: **Clay-colored**
 - Enzymes: ALP/GGT ??
 - Example: Gallstones, pancreatic cancer
-

? ULTRA-SHORT SUMMARY (10 seconds revision)

- **Unconjugated ?**: hemolysis, Gilbert, Crigler–Najjar
- **Conjugated ?**: obstruction, Dubin–Johnson, Rotor

- **Urine dark:** conjugated bilirubin
- **Clay stool:** obstructive jaundice
- **High urobilinogen:** hemolysis
- **Pruritus:** cholestasis

? IMPORTANT POINTS TO REMEMBER (Whole Chapter)

? Structure of Heme

- Heme = **protoporphyrin IX + Fe²⁺** at center.
- Consists of **four pyrrole rings** linked by methene bridges.
- Fe²⁺ must be in **ferrous form** to bind oxygen.
- Found in hemoglobin, myoglobin, cytochromes, catalase, peroxidases.

? Heme Biosynthesis

- Occurs in **mitochondria ? cytosol ? mitochondria**.
- Major sites: **bone marrow (85%), liver (15%)**.
- **ALA synthase** is the **rate-limiting step**.
- Requires **Vitamin B6 (PLP)**.

- Inhibited by **heme (feedback)**; induced by drugs that increase cytochrome P450.

? Lead Poisoning

- Lead inhibits **ALA dehydratase** and **ferrochelatase**.
- Leads to ? ALA, ? protoporphyrin, ? heme synthesis.

? Key Steps to Remember

- Glycine + Succinyl CoA ? ALA (ALAS)
- 2 ALA ? PBG (ALA dehydratase)
- 4 PBG ? Hydroxymethylbilane (PBG deaminase)
- Uroporphyrinogen III ? Coproporphyrinogen
- Coproporphyrinogen ? Protoporphyrin
- Protoporphyrin + Fe^{2+} ? Heme (ferrochelatase)

? Porphyrias (High Yield)

- Due to **enzyme defects in heme pathway** ? accumulation of intermediates.
- **Hepatic porphyrias** ? neurovisceral symptoms.
- **Erythropoietic porphyrias** ? photosensitivity.

? Important Types:

- **Acute Intermittent Porphyria (AIP):**

- ? PBG deaminase
- ? ALA & PBG
- Abdominal pain + neuro symptoms
- No photosensitivity

- **Porphyria Cutanea Tarda (PCT):**

- ? Uroporphyrinogen decarboxylase
- Photosensitivity, blistering
- Most common porphyria

- **Congenital Erythropoietic Porphyria (CEP):**

- ? Uroporphyrinogen III synthase
- Severe photosensitivity, red urine, erythrodontia

- **Erythropoietic Protoporphyria (EPP):**

- ? Ferrochelatase
- Mild photosensitivity

? Catabolism of Heme

- Occurs in **RES** (spleen/liver/bone marrow).
- Heme ? **biliverdin** (heme oxygenase).
- Biliverdin ? **bilirubin** (biliverdin reductase).
- Unconjugated bilirubin ? albumin-bound ? liver.
- Conjugated bilirubin formed by **UGT1A1**.
- Excreted into bile ? intestine ? urobilinogen ?
 - **Urobilin (urine)**
 - **Stercobilin (stool)**

? Shunt Bilirubin

- Bilirubin produced from **ineffective erythropoiesis** (intramedullary destruction).
- Causes isolated **unconjugated hyperbilirubinemia** without hemolysis.

? Plasma Bilirubin

- **Unconjugated (indirect):**
 - Albumin-bound
 - Lipid-soluble
 - Cannot appear in urine

- **Conjugated (direct):**

- Water-soluble
- Appears in urine
- Indicates intrahepatic or obstructive pathology

? Congenital Hyperbilirubinemias

? Unconjugated:

- **Gilbert:** Mild ? UGT
- **Crigler–Najjar I:** Absent UGT (fatal)
- **Crigler–Najjar II:** Marked ? UGT (responds to phenobarbital)

? Conjugated:

- **Dubin–Johnson:** MRP2 defect, black liver
- **Rotor:** Defect in hepatic uptake/storage, normal-colored liver

? Hemolytic (Pre-Hepatic) Jaundice

- ? RBC destruction ? ? unconjugated bilirubin
- No bilirubin in urine
- ? urobilinogen

- Normal liver enzymes
- Seen in hemolysis, thalassemia, G6PD deficiency, shunt bilirubin.

? Hepatocellular Jaundice

- Hepatocyte damage ? impaired uptake, conjugation, excretion
- ? both conjugated & unconjugated bilirubin
- ? AST/ALT
- Urine bilirubin present
- Variable stool/urobilinogen

? Obstructive (Post-Hepatic) Jaundice

- Blocked bile flow
- ? conjugated bilirubin
- Clay-colored stool
- Dark urine
- Pruritus (bile salts)
- ? ALP & GGT
- ? urobilinogen

? Differential Diagnosis — Quick Rule

FEATURE	HEMOLYTIC	HEPATOCELLULAR	OBSTRUCTIVE
Type of bilirubin	Unconj ?	Both ?	Conj ?
Urine bilirubin	Absent	Present	Present (high)
Urine urobilinogen	?	Variable	?
Stool color	Dark	Normal/light	Pale (clay)
Enzymes	Normal	AST/ALT ?	ALP/GGT ?

? Ultra-Short Revision

- ALA synthase = rate-limiting; inhibited by heme.
- Lead inhibits ALA dehydratase & ferrochelatase.
- AIP = neuro symptoms, no photosensitivity.
- PCT = most common porphyria, blistering.
- Unconjugated ? : hemolysis, Gilbert, Crigler–Najjar.
- Conjugated ? : obstruction, Dubin–Johnson, Rotor.
- Clay stool + dark urine = obstructive jaundice.
- Urobilinogen ? = hemolysis.

? MCQs — Heme Synthesis, Breakdown & Jaundice (Whole Chapter)

1. The central metal ion of heme that binds oxygen is:

- A. Fe^{3+}
- B. Mg^{2+}
- C. Cu^{2+}
- D. **Fe^{2+}**

Answer: D

2. The rate-limiting enzyme in heme biosynthesis is:

- A. Ferrochelatase
- B. ALA dehydratase
- C. PBG deaminase
- D. **ALA synthase**

Answer: D

3. Which vitamin is required as a cofactor for ALA synthase?

- A. Vitamin C
- B. Vitamin K
- C. **Vitamin B6 (PLP)**
- D. Vitamin A

Answer: C

4. Lead inhibits which two enzymes in heme synthesis?

- A. ALA synthase & PBG deaminase
- B. **ALA dehydratase & ferrochelatase**
- C. Uroporphyrinogen decarboxylase & coproporphyrinogen oxidase
- D. Heme oxygenase & biliverdin reductase

Answer: B

5. A patient presents with acute abdominal pain, psychiatric symptoms, and red urine. No photosensitivity. Which porphyria is most likely?

- A. PCT
- B. CEP
- C. Variegate porphyria
- D. **Acute Intermittent Porphyria**

Answer: D

6. Porphyria Cutanea Tarda is caused by a deficiency of:

- A. PBG deaminase
- B. ALA synthase
- C. **Uroporphyrinogen decarboxylase**
- D. Ferrochelatase

Answer: C

7. The porphyria associated with blistering photosensitivity and dark-colored (“tea-colored”) urine is:

- A. AIP
- B. CEP
- C. **PCT**
- D. Crigler–Najjar

Answer: C

8. Which enzyme converts heme to biliverdin?

- A. Biliverdin reductase
- B. UDP-glucuronyl transferase
- C. **Heme oxygenase**
- D. Ferrochelatase

Answer: C

9. Unconjugated bilirubin is transported in the blood mainly bound to:

- A. Hemoglobin
- B. Ceruloplasmin
- C. Transferrin
- D. **Albumin**

Answer: D

10. Conjugation of bilirubin requires:

- A. ATP
- B. Vitamin B6
- C. CoA
- D. **UDP-glucuronic acid**

Answer: D

11. Which bilirubin fraction is water-soluble and appears in urine?

- A. Unconjugated
- B. **Conjugated**
- C. Delta bilirubin
- D. Shunt bilirubin

Answer: B

12. Bilirubin diglucuronide is excreted through the:

- A. Renal tubules
- B. Blood plasma
- C. **Bile canaliculi**
- D. Portal vein

Answer: C

13. The major pigment responsible for the brown color of stool is:

- A. Urobilin
- B. **Stercobilin**
- C. Biliverdin
- D. Porphobilinogen

Answer: B

14. A 6-month-old with severe unconjugated hyperbilirubinemia not responding to phenobarbital likely has:

- A. Gilbert syndrome
- B. PCT
- C. **Crigler–Najjar type I**
- D. Dubin–Johnson syndrome

Answer: C

15. Dubin–Johnson syndrome is characterized by:

- A. Unconjugated hyperbilirubinemia
- B. **Conjugated hyperbilirubinemia + dark pigmented liver**
- C. Enzyme destruction of UGT
- D. Kernicterus

Answer: B

16. Which congenital disorder shows conjugated hyperbilirubinemia without liver pigmentation?

- A. AIP
- B. Gilbert
- C. Dubin–Johnson
- D. **Rotor syndrome**

Answer: D

17. In hemolytic jaundice, you expect:

- A. ? Conjugated bilirubin
- B. ? **Unconjugated bilirubin**
- C. ? ALP
- D. Clay-colored stool

Answer: B

18. Which type of jaundice has increased urobilinogen in urine?

- A. Obstructive
- B. Hepatocellular
- C. **Hemolytic**
- D. Congenital conjugated jaundice

Answer: C

19. A patient presents with severe pruritus, dark urine, and clay-colored stools. Most likely diagnosis?

- A. Hemolysis
- B. Hepatitis
- C. **Obstructive jaundice**
- D. Gilbert syndrome

Answer: C

20. In obstructive jaundice, urine bilirubin is:

- A. Absent
- B. Normal
- C. **Markedly elevated**
- D. Increased urobilinogen

Answer: C

21. Which liver enzyme is MOST elevated in obstructive jaundice?

- A. AST
- B. ALT
- C. LDH
- D. **ALP**

Answer: D

22. Which condition shows both conjugated and unconjugated bilirubin elevation?

- A. Obstruction
- B. Hemolysis
- C. **Hepatocellular jaundice**
- D. Gilbert syndrome

Answer: C

23. Shunt bilirubin arises from destruction of:

- A. Reticulocytes in spleen
- B. Mature RBCs
- C. **Ineffective erythroid precursors in bone marrow**
- D. Kupffer cells

Answer: C

24. Which porphyria shows severe photosensitivity, hemolysis, and red fluorescent teeth?

- A. PCT
- B. AIP
- C. **CEP (Günther disease)**
- D. EPP

Answer: C

25. A patient develops abdominal pain and red urine after barbiturate use. Which enzyme is deficient?

- A. ALA synthase
- B. **PBG deaminase**
- C. Ferrochelatase
- D. Heme oxygenase

Answer: B

? CLINICAL CASE–BASED QUESTIONS (Whole Chapter)

1. A 20-year-old woman presents with severe abdominal pain, confusion, and psychiatric symptoms. Her urine darkens on standing. She has no photosensitivity. Symptoms started after taking anti-epileptic medication.

Diagnosis: Acute Intermittent Porphyria

Mechanism: ? PBG deaminase ? ? ALA & PBG ? neurotoxicity

Trigger: Drugs inducing ALA synthase (cytochrome P450 inducers)

2. A middle-aged alcoholic man presents with blistering lesions on sun-exposed areas and hyperpigmentation. Urine shows increased uroporphyrins. Liver enzymes mildly elevated.

Diagnosis: Porphyria Cutanea Tarda

Mechanism: ? Uroporphyrinogen decarboxylase ? photosensitivity

3. A child has severe photosensitivity, red urine, hemolytic anemia, and red-brown teeth that fluoresce under UV light.

Diagnosis: Congenital Erythropoietic Porphyria (CEP)

Mechanism: ? Uroporphyrinogen III synthase ? Type I porphyrins accumulate

4. A young adult develops burning pain and swelling of the skin within minutes of sunlight exposure. Mild elevation of protoporphyrin is noted. Liver function is normal.

Diagnosis: Erythropoietic Protoporphyria

Mechanism: ? Ferrochelatase ? ? Protoporphyrin IX ? photosensitivity

5. A worker in a battery factory develops microcytic anemia, abdominal pain, and irritability. Labs show increased ALA, increased free erythrocyte protoporphyrins, and normal ferritin.

Diagnosis: Lead poisoning

Mechanism: Lead inhibits ALA dehydratase & ferrochelatase ? ? heme synthesis

6. A 15-day-old neonate has jaundice with very high unconjugated bilirubin. Kernicterus signs are present. No response to phenobarbital therapy.

Diagnosis: Crigler–Najjar Syndrome Type I

Mechanism: Complete absence of UGT1A1 ? severe unconjugated bilirubin

7. A teenager develops mild jaundice during fasting, illness, or stress. Unconjugated bilirubin is slightly elevated; all liver enzymes normal.

Diagnosis: Gilbert Syndrome

Mechanism: Mild ? UGT1A1 activity

8. A child has moderate unconjugated jaundice that improves significantly with phenobarbital.

Diagnosis: Crigler–Najjar Syndrome Type II

Mechanism: Partial UGT deficiency

9. A young adult presents with persistent conjugated hyperbilirubinemia. The liver is darkly pigmented on biopsy. No pruritus, normal LFTs.

Diagnosis: Dubin–Johnson Syndrome

Mechanism: Defective canalicular excretion pump (MRP2)

10. Another adult presents with conjugated hyperbilirubinemia but biopsy shows a normal-colored liver.

Diagnosis: Rotor Syndrome

Mechanism: Defective uptake/storage of conjugated bilirubin

11. A patient with G6PD deficiency develops jaundice after taking antimalarial drugs. Labs show ? unconjugated bilirubin, anemia, reticulocytosis. No bilirubin in urine.

Diagnosis: Hemolytic jaundice

Mechanism: RBC destruction ? ? heme breakdown ? ? unconjugated bilirubin

12. A patient with viral hepatitis shows jaundice, elevated AST/ALT, bilirubin in urine, and normal stool color.

Diagnosis: Hepatocellular jaundice

Mechanism: Impaired uptake, conjugation, and excretion

13. A patient has severe pruritus, dark urine, clay-colored stools, and very high ALP levels.

Diagnosis: Obstructive jaundice

Mechanism: Blocked bile flow ? ? conjugated bilirubin

14. A 2-year-old child with thalassemia major has jaundice despite no significant hemolysis. Reticulocyte count normal.

Diagnosis: Shunt bilirubin

Mechanism: Ineffective erythropoiesis ? intramedullary destruction ? ? unconjugated bilirubin

15. After thrombolysis for myocardial infarction, a patient develops worsening chest pain and rising troponin again. ROS markers are elevated.

Diagnosis: Reperfusion injury

Mechanism: Sudden oxygen ? massive ROS ? further injury, contracture bands

16. A man presents with jaundice and increased urobilinogen in urine; no bilirubin in urine; stool is dark.

Diagnosis: Hemolytic jaundice

Mechanism: High bilirubin load ? more urobilinogen

17. A patient with gallstones has extreme itching, conjugated bilirubin in urine, and pale stools.

Diagnosis: Extrahepatic biliary obstruction

Mechanism: No bilirubin enters intestine ? ? stercobilin

18. A newborn with jaundice responds promptly to phototherapy.

Diagnosis: Neonatal physiological jaundice

Mechanism: Low UGT activity at birth

19. An alcoholic man with ascites has elevated conjugated and unconjugated bilirubin, high AST/ALT, and peripheral stigmata of chronic liver disease.

Diagnosis: Hepatocellular jaundice from alcoholic hepatitis/cirrhosis

Mechanism: Hepatocyte dysfunction

20. A patient's stool is dark brown and urine yellow, but serum bilirubin is mildly raised and unconjugated. Liver enzymes normal.

Diagnosis: Mild hemolysis

Mechanism: Excess RBC destruction with intact liver function

? VIVA VOCE — Heme Synthesis, Breakdown & Jaundice (Whole Chapter)

1. What is the basic structure of heme?

Heme is **protoporphyrin IX with Fe²⁺** at its center.

2. Why must iron be in the ferrous state (Fe²⁺)?

Because only Fe²⁺ can bind oxygen.

3. Where does heme synthesis occur?

Partly in **mitochondria** and partly in **cytosol**.

4. What is the rate-limiting enzyme in heme synthesis?

ALA synthase.

5. Which vitamin is required for ALA synthase?

Vitamin B6 (pyridoxal phosphate).

6. Which step of heme synthesis is inhibited by heme?

ALA synthase (feedback inhibition).

7. Name the two enzymes inhibited by lead.

ALA dehydratase and **ferrochelatase**.

8. Which porphyria presents without photosensitivity?

Acute Intermittent Porphyria (AIP).

9. Why is AIP neurotoxic?

Accumulation of **ALA & PBG** causes neuronal dysfunction.

10. Which porphyria is the most common?

Porphyria Cutanea Tarda (PCT).

11. Which enzyme is deficient in PCT?

Uroporphyrinogen decarboxylase.

12. Which porphyria shows red-brown teeth and severe photosensitivity?

Congenital Erythropoietic Porphyria (CEP).

13. What is the final step of heme formation?

Insertion of Fe^{2+} into protoporphyrin IX by **ferrochelatase**.

14. Where is heme breakdown initiated?

In the **reticuloendothelial system (RES)**—mainly spleen.

15. What enzyme converts heme to biliverdin?

Heme oxygenase.

16. What enzyme converts biliverdin to bilirubin?

Biliverdin reductase.

17. What form of bilirubin is bound to albumin in plasma?

Unconjugated (indirect) bilirubin.

18. Which bilirubin fraction appears in urine?

Conjugated bilirubin.

19. What enzyme conjugates bilirubin in the liver?

UDP-glucuronyl transferase (UGT1A1).

20. What happens to conjugated bilirubin in the intestine?

Converted to **urobilinogen** by gut bacteria.

21. What gives urine its yellow color?

Urobilin.

22. What gives stool its brown color?

Stercobilin.

23. What is shunt bilirubin?

Unconjugated bilirubin formed from **ineffective erythropoiesis** (intramedullary destruction).

24. Which congenital disorder has complete absence of UGT?

Crigler–Najjar Syndrome Type I.

25. Which congenital disorder shows mild unconjugated jaundice during stress?

Gilbert syndrome.

26. Which congenital disorder has conjugated hyperbilirubinemia with a black liver?

Dubin–Johnson syndrome.

27. Which shows conjugated hyperbilirubinemia without liver pigmentation?

Rotor syndrome.

28. What is the main feature of hemolytic jaundice?

Unconjugated hyperbilirubinemia with no bilirubin in urine.

29. What is the hallmark of obstructive jaundice?

Clay-colored stools, dark urine, and pruritus.

30. Which jaundice type shows ? ALP and ? GGT?

Obstructive (post-hepatic) jaundice.

31. Why does hepatocellular jaundice show both conjugated and unconjugated bilirubin elevation?

Because hepatocyte **uptake, conjugation, and excretion** are impaired.

32. Which type of jaundice shows increased urobilinogen in urine?

Hemolytic jaundice.

33. Which type shows decreased urobilinogen?

Obstructive jaundice.

34. What causes clay-colored stools in obstruction?

Lack of bilirubin reaching the intestine ? no stercobilin.

35. What causes dark urine in obstructive jaundice?

Excess **conjugated bilirubin** excreted by kidneys.

36. What does phenobarbital do in Crigler–Najjar Type II?

Induces **UGT1A1**, lowering bilirubin.

37. What is the significance of carbon monoxide in heme breakdown?

It is a byproduct of **heme oxygenase** activity.

38. What does ferrochelatase insert into protoporphyrin IX?

Fe²⁺?

39. Which bilirubin fraction rises first in viral hepatitis?

Conjugated bilirubin (due to impaired excretion).

40. What is the most important lab test to differentiate obstructive from hepatocellular jaundice?

ALP and GGT levels (high in obstruction).