بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Metabolism | Final 24

HEME DEGRADATION & BILIRUBIN METABOLISM

Written & Reviewed by : NST

السلام عليكم و رحمة الله و بركاته دفعة نبض العزيزة,

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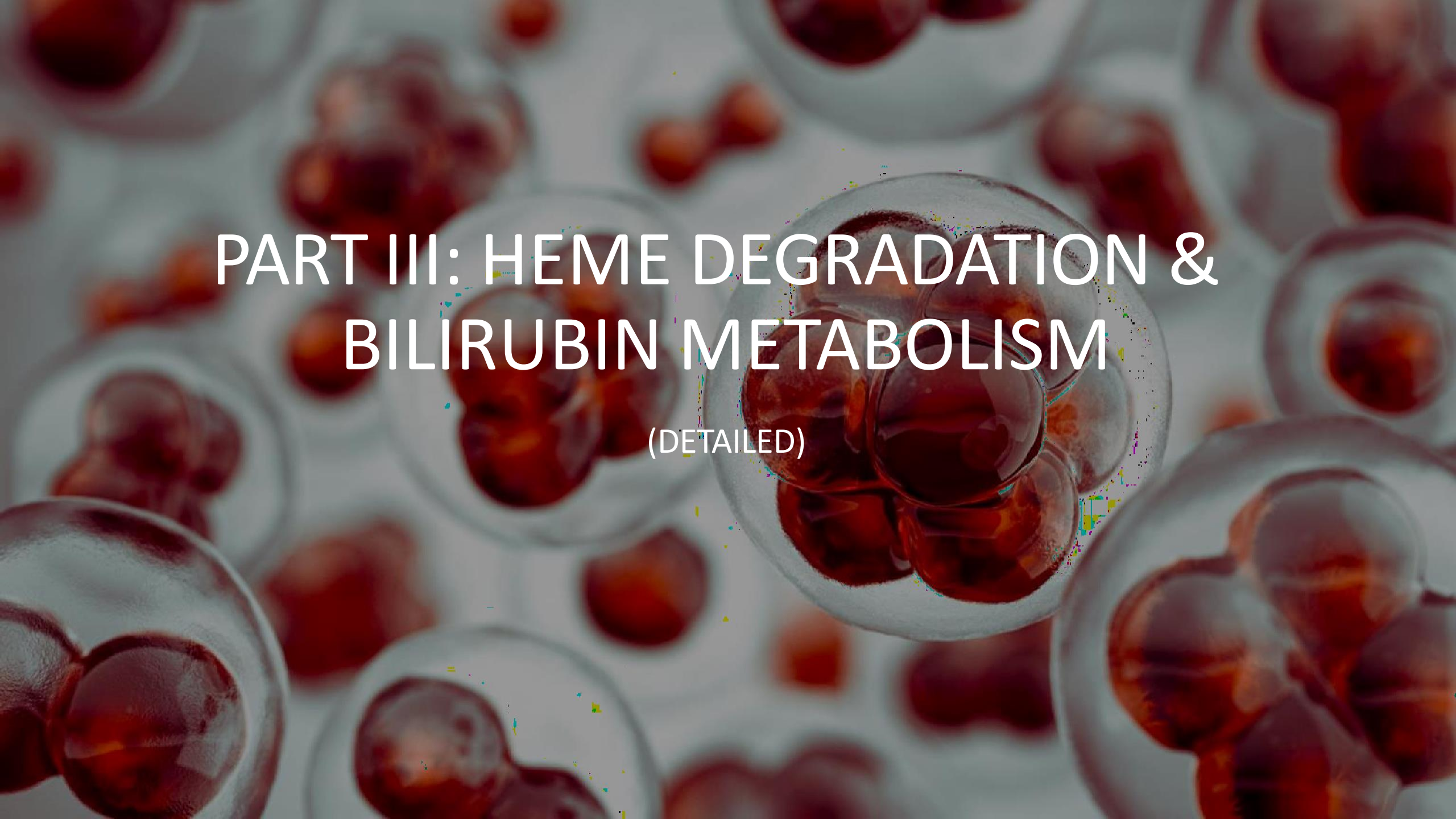


PART III: HEME DEGRADATION & BILIRUBIN METABOLISM

(DETAILED)

This lecture includes **two parts**:
- **Part 1**: concerned with **heme degradation and bilirubin metabolism**
- **Part 2**: concerned with **jaundice**, which is related to heme degradation

General Concept

As we know, the **final degradation of heme occurs inside the liver** (the final metabolism).
However, the **initial degradation processes occur outside the liver**.
Therefore, we should know:
- How heme is degraded
- How the **intermediates of heme metabolism** are transported from other tissues to the liver

Sites of Heme Degradation

The process of heme degradation occurs in **three main sites**:
- **Spleen**
- **Bone marrow**
- **Liver**

But the **final metabolism** of heme occurs **inside the liver**.

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

Why Do We Degrade Heme?

We start by asking an important question:

Why do we have to convert heme into other intermediates? Why do we need to degrade heme?

Heme is a **chemical (macrocyclic) structure** that contains **iron**, which is an essential metal for the body.

Since iron is essential and **cannot be synthesized by the body**, it must be obtained from the diet.

So the question is: **why can't we reuse heme as it is after hemoglobin breakdown?**

Why do we need to break it down and then resynthesize heme again, as discussed in the previous lecture?

The Problem with Free Heme

Heme is present in the body in **very high concentrations**, because:

•Red blood cells are continuously broken down (approximately every **3–4 months**)

•Hemoglobin is degraded

•This results in the production of **large amounts of heme**

The main problem with heme is the **presence of the metal (iron)**.

Free heme is **toxic** because it can:

•Attack **lipids**

•Damage **proteins**

•Cause **DNA damage**

Why Degradation Is Necessary

Because of this toxicity, heme **cannot remain in its free form**.

Therefore, we must:

•**Break down heme**

•**Remove and transfer the metal** to other proteins

- In the case of iron, it is transferred to **ferritin** for storage

•Convert the remaining structure into a **less toxic compound**

The Least Toxic Form of Heme

The least toxic form of heme is **bilirubin**.

So the key goal of heme degradation is:

•To safely handle iron

•And to convert heme into **bilirubin**, which is much less toxic

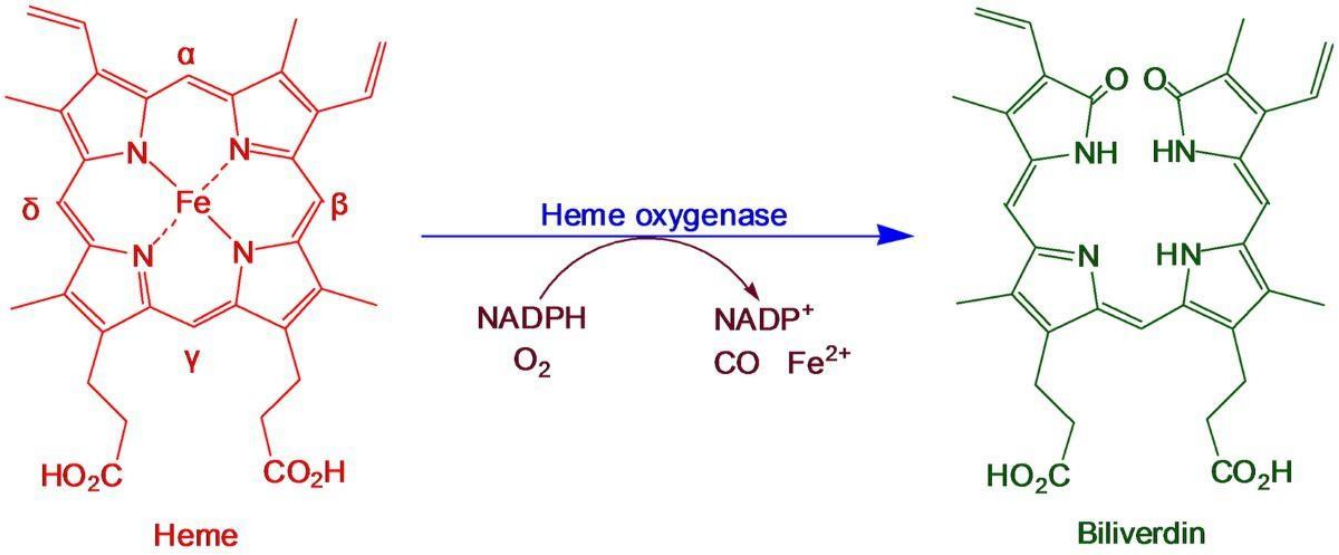
Transition to the Pathway

Now the important question becomes:

How do we convert heme into bilirubin?

To answer this, we will go through the **metabolic pathway of heme degradation**, starting from heme, moving through intermediates, and ending with bilirubin.

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 1: Formation of Biliverdin (Heme Degradation)

Degradation of heme occurs in **three main sites**:
the **spleen, liver, and bone marrow**, and it takes place inside **macrophages**.
This step is catalyzed by the enzyme **heme oxygenase**, which is a **NADPH-dependent enzyme**.
Heme oxygenase introduces **molecular oxygen (O_2)** into the heme structure.
Heme is a **cyclic (macrocyclic) structure**.
When oxygen is introduced into this cyclic structure, it causes **opening of the ring**, converting heme from a **closed cyclic molecule into a linear molecule**.

Products of the Reaction

The action of heme oxygenase produces:

- **Biliverdin**
  - The **first intermediate** in heme metabolism
  - A **green-colored pigment**
- **Iron (Fe^{2+})**
  - Released from the heme molecule
  - Immediately stored by binding to **ferritin**, which serves as the **iron storage protein**
- **Carbon monoxide (CO)**
  - Released as a by-product
  - Transported in the blood and eliminated through the lungs
  - The **rate of CO production** can be used as an **indirect indicator of heme breakdown**

Color Concept (Important for the Lecture)

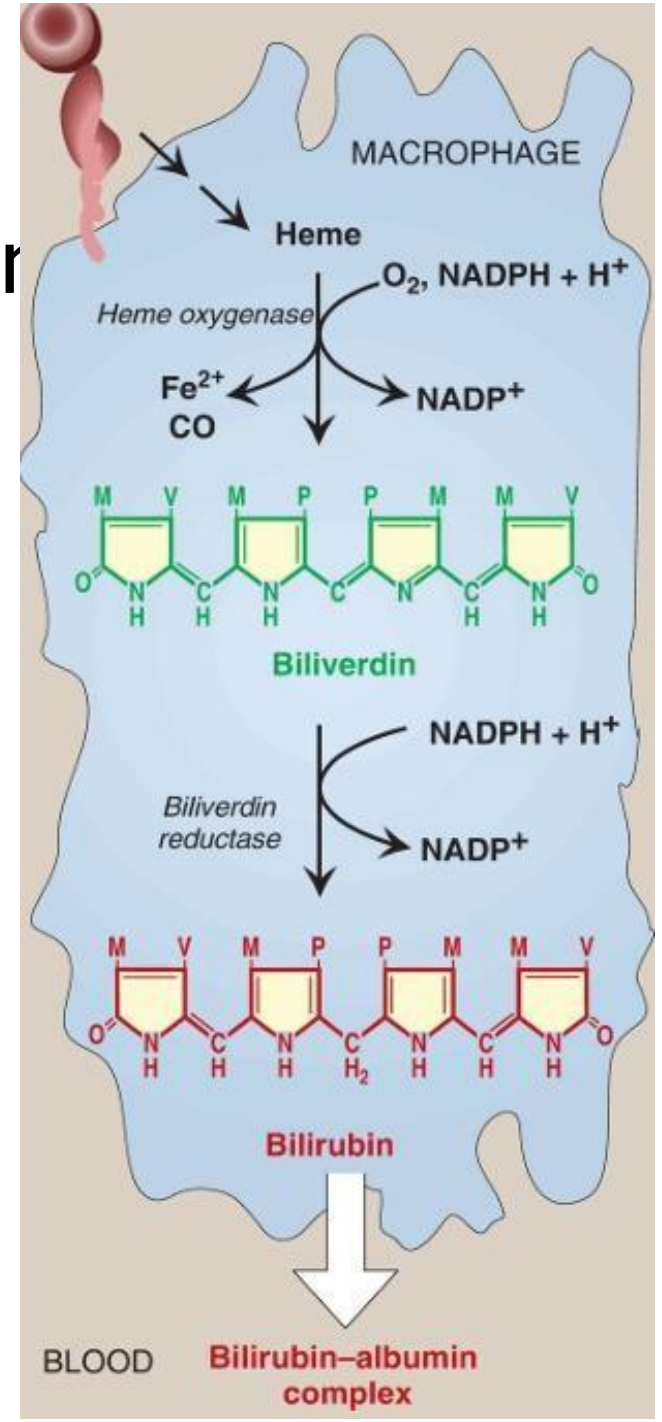
- **Heme** → red color
- **Globin protein** → colorless
- **Hemoglobin** → red because of heme
- **Red blood cells** → red because of heme
- **Blood** → red because of heme
- **Biliverdin** → green color

Key Summary

Heme oxygenase converts **heme (red, cyclic)** into **biliverdin (green, linear)**, while releasing **iron** and **carbon monoxide**.
This step represents the **initial and essential step** in heme degradation.

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



Step 2: Formation of Unconjugated Bilirubin

After the formation of **biliverdin**, the next step in heme degradation is its conversion into **bilirubin**.

Enzyme

- **Biliverdin reductase**
- A **cytosolic enzyme**
- Has **high activity**
- **NADPH-dependent**

Mechanism

Biliverdin contains a **double bond between carbon atoms**.

Biliverdin reductase reduces this double bond, converting it into a single bond.

This reduction reaction uses **NADPH** as a source of electrons.

As a result, **biliverdin is converted into bilirubin**.

Product

- **Unconjugated bilirubin (UCB)**

Properties of Unconjugated Bilirubin

- **Lipid-soluble (hydrophobic)**
- **Poorly soluble in water**
- **Not attached to any other molecule**, therefore called *unconjugated*
- Also known in the medical field as:
  - **Indirect-reacting bilirubin**

Site of Reaction

•These reactions occur in the **cytosol of macrophages**

•Macrophages are found in:

- Bone marrow
- Spleen
- Liver

Transport in Blood

Because unconjugated bilirubin is **fat-soluble**, it cannot circulate freely in plasma. Therefore, it is transported in the blood **tightly bound to albumin**.

•Transport pathway:

- From spleen and bone marrow
- Through the bloodstream
- To the liver

At the liver:

•Bilirubin dissociates from albumin

•Crosses the hepatocyte membrane

•Enters liver cells for further metabolism

Clinical Importance

•Unconjugated bilirubin is **toxic to the CNS**

•It can cross the blood–brain barrier, especially in newborns

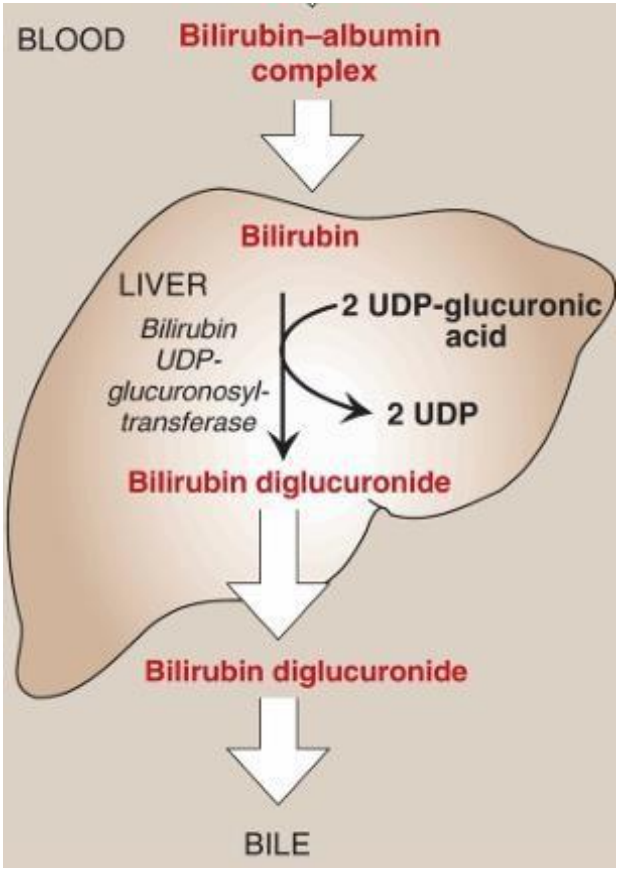
•High levels may cause **kernicterus**

Key Summary

Biliverdin reductase converts **biliverdin** into **unconjugated bilirubin**, a **yellow, lipid-soluble, indirect-reacting molecule** that is transported in blood bound to **albumin** and delivered to the liver for conjugation.

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



Intracellular Handling and Conjugation of Bilirubin in Hepatocytes

Once unconjugated bilirubin reaches the liver and enters hepatocytes, an important question arises:

Is there anything that prevents bilirubin from effluxing out of liver cells as a free molecule?

The answer is **no**. Unconjugated bilirubin can freely diffuse out of hepatocytes.

Therefore, inside liver cells, unconjugated bilirubin binds to specific intracellular proteins known as **ligandin**, which **prevents its efflux out of the cell** and **directs the bilirubin molecule toward the endoplasmic reticulum (ER)**, where its modification will occur.

Bilirubin Conjugation: Role of Carbohydrates

As will be seen in bilirubin metabolism, this process depends on a **very important enzyme that couples carbohydrates to bilirubin**.

Adding carbohydrates to bilirubin confers an essential property:

👉 **Increased solubility**

Unconjugated bilirubin is lipophilic and poorly water soluble.

By adding carbohydrate moieties, the molecule becomes **water soluble**, which is the key goal of this step.

Glucuronic Acid and Energy Requirement

The carbohydrate added to bilirubin is **glucuronic acid**, which is:

- An **oxidized form of glucose**
- A **modified glucose molecule**

During conjugation:

- **Two molecules of glucuronic acid** are added to bilirubin
- These glucuronic acid molecules are supplied in an activated form, **coupled to UDP (uridine diphosphate)**

UDP serves an essential role by:

- Providing the **energy required for the conjugation reaction**
- Breaking off from glucose to allow transfer of glucuronic acid to bilirubin

As a result, the addition of these two glucuronic acid molecules makes bilirubin **highly water soluble**, which is the central purpose of conjugation.

Key Enzyme: UDP-Glucuronosyltransferase (UGT)

The enzyme responsible for this reaction is **UDP-glucuronosyltransferase (UGT)**.

UGT transfers glucuronic acid from UDP-glucuronic acid to bilirubin.

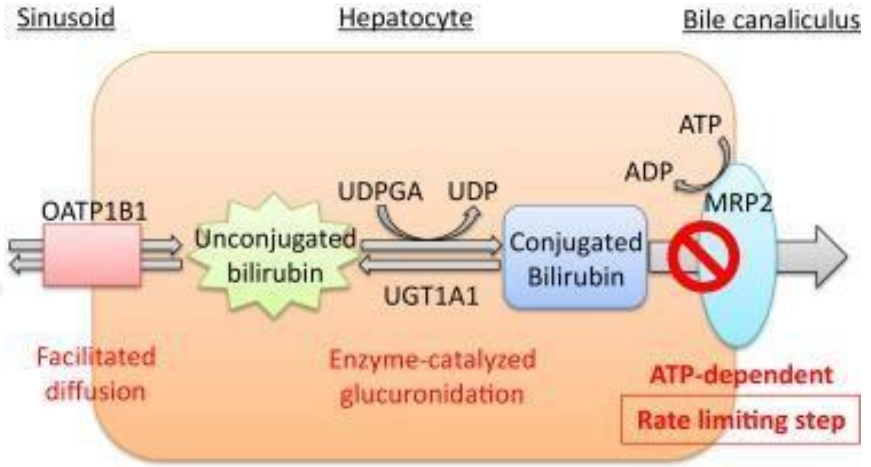
This enzyme is **extremely important**, as it is the **defective enzyme in several disorders of heme and bilirubin metabolism**, which will be discussed later.

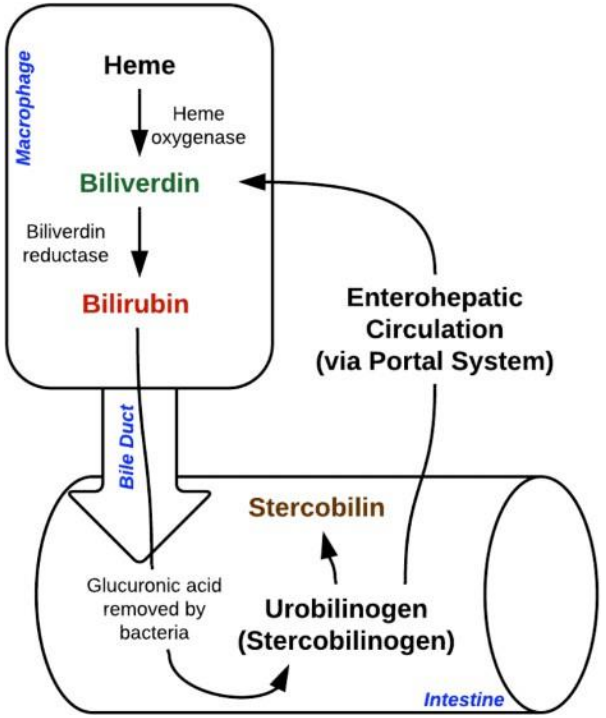
Product of Conjugation
The product of this reaction is:
•**Conjugated bilirubin**
•Also known as **direct-reacting bilirubin**
This conjugation process:
•Occurs **inside hepatocytes**
•Results in release of **UDP** as a by-product

Excretion of Conjugated Bilirubin
Once conjugated bilirubin is formed inside liver cells, the next step is its **excretion**.
Because the main product of the liver is **bile**, conjugated bilirubin must be:
•Ejected from hepatocytes
•Secreted into the **bile canaliculi**
From there, bile flows through:
•Bile ducts
•May be stored in the **gallbladder**
•Passes into the **common bile duct**
•Joins the **pancreatic duct**
•Finally reaches the **duodenum and intestines**
This step completes the hepatic phase of bilirubin metabolism.

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





Active Secretion of Conjugated Bilirubin and Intestinal Fate

Conjugated bilirubin is actively transported out of hepatocytes into the bile through specific membrane transporters known as **MRP2**.

MRP stands for **Multidrug Resistance Protein**, which is a family of **membrane efflux proteins** responsible for transporting toxic or unwanted substances out of liver cells.

These transporters are highly active and function to protect hepatocytes by exporting compounds that the cell does not need or considers toxic. Accordingly, **conjugated bilirubin is actively secreted against its concentration gradient from hepatocytes into the bile canaliculi**.

In addition to conjugated bilirubin, MRP transporters are also involved in the secretion of other metabolites, including certain **epinephrine (adrenaline) metabolites**, which will be discussed later.

Once secreted into bile, conjugated bilirubin travels through the bile ducts, may be stored in the gallbladder, and is eventually delivered to the **intestines**.

Intestinal Metabolism of Bilirubin

Inside the intestines, **intestinal bacteria act on conjugated bilirubin**, first converting it back into **unconjugated bilirubin**, and then further reducing it to **urobilinogen**.

Urobilinogen is a **colorless intermediate** in heme metabolism. This represents the final stage of color transformation in the pathway:

- Heme (red)
- Biliverdin (green)
- Bilirubin (yellow)
- Urobilinogen (colorless)

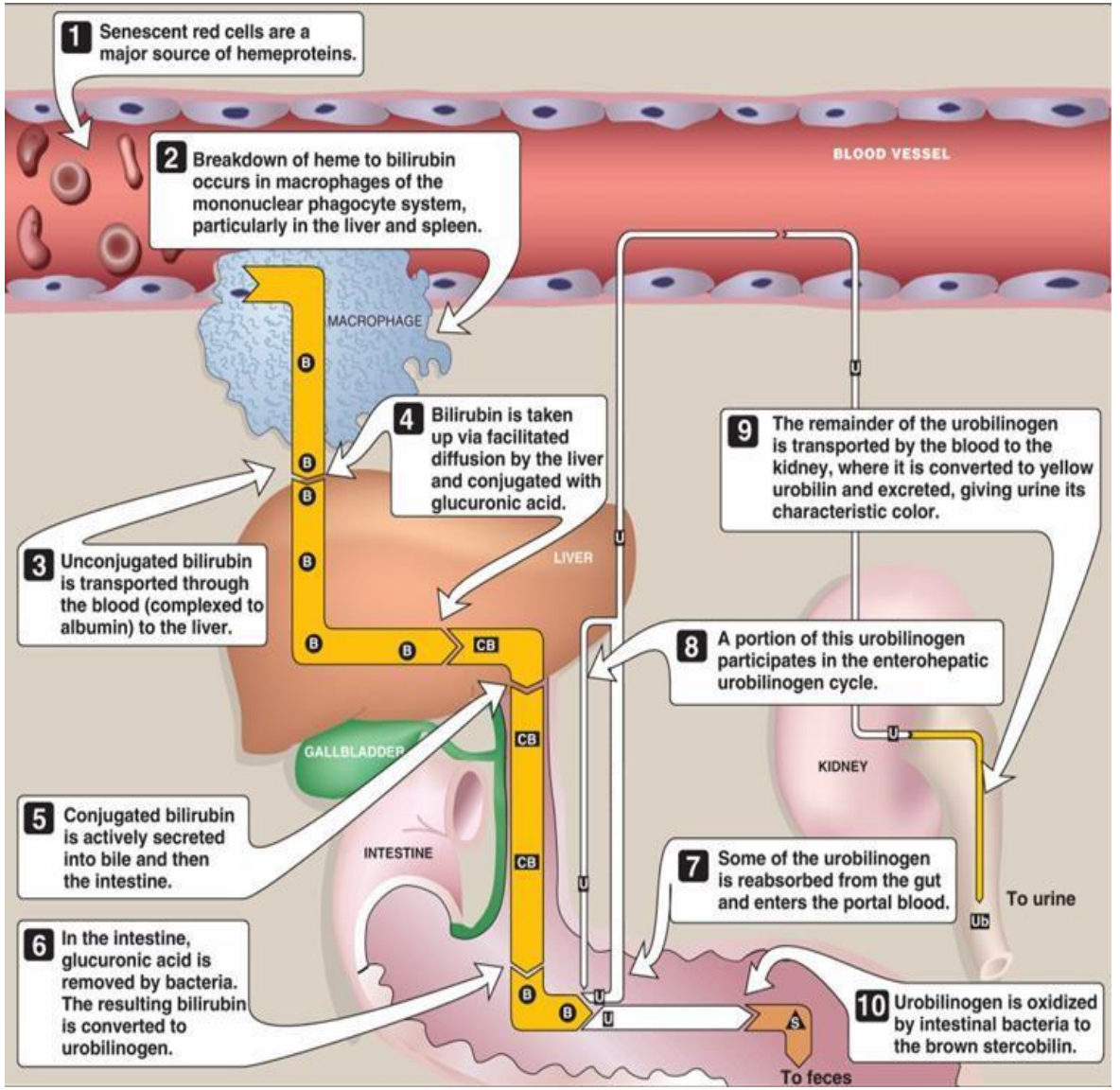
Fate of Urobilinogen

Approximately **80% of urobilinogen** is oxidized by intestinal bacteria into **stercobilin**, a **brown pigment** that gives stool its characteristic color. Thus, the brown color of stool ultimately originates from **heme that was initially present in the blood**.

The remaining **~20% of urobilinogen** is reabsorbed from the intestines into the portal circulation and transported back to the liver. From the liver, it is secreted again into bile and returned to the intestines. This recycling process is known as the **enterohepatic circulation**.

Enterohepatic Circulation & Final Excretion

- ~80% oxidized to stercobilin (brown pigment, responsible for the normal color of stool)
- ~20% reabsorbed into portal blood and re-excreted(via enterohepatic circulation, back to the liver and then to the intestine)
- (~2-5%) escapes, excreted as urobilin (kidneys, where it is oxidized to urobilin, a yellow pigment responsible for the yellow color of urine)



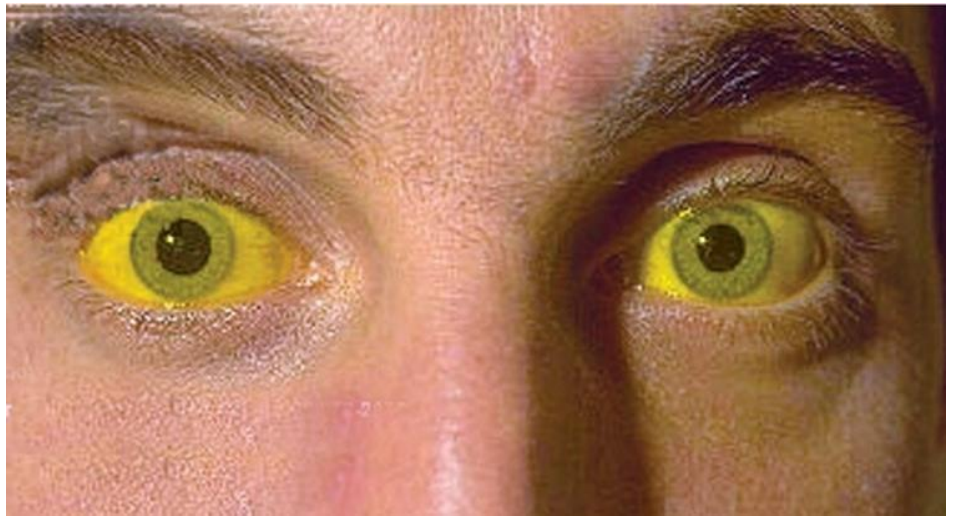
PART IV: JAUNDICE - PATHOPHYSIOLOGY & DIAGNOSIS

(MAJOR EMPHASIS)

Jaundice is defined as a **yellowish discoloration of the skin, sclera, and mucous membranes** resulting from an **elevated level of bilirubin in the blood**.
Jaundice is **not a disease**. Rather, it is a **clinical sign (symptom)** that reflects an underlying disturbance in **bilirubin metabolism**, whether in its production, conjugation, or excretion.
Understanding jaundice requires a clear understanding of the normal pathway of **heme degradation and bilirubin metabolism**, which will be discussed in detail.

Jaundice: Definition and Presentation

- Yellow discoloration of skin, sclera, and mucous membranes (due to high concentration of bilirubin in the blood, which has a yellowish color)
- Elevated serum bilirubin levels (>2-3 mg/dL)
  normally bilirubin levels should not exceed 2–3 mg/dL, equivalent to ~35 µmol/L
- 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



·Bilirubin is lipophilic and can cross cell membranes
(allowing it to accumulate in tissues and, in newborns, cross the blood-brain barrier causing kernicterus and neurological damage)
·Therefore, bilirubin levels must be kept as low as possible
(especially in neonates to prevent bilirubin-induced neurotoxicity

Why Does Bilirubin Level Increase? (Causes of Jaundice)

An elevation in serum bilirubin levels can occur **even when the bilirubin metabolic pathway itself is functioning normally**. The increase depends on **where the defect is located** relative to the liver. Accordingly, jaundice is classified into **three major types**:

- pre-hepatic jaundice.
- hepatic jaundice.
- post-hepatic jaundice.

1) Pre-hepatic (Hemolytic) Jaundice

In this type, **the liver and_attachable bilirubin pathway are not defective**. The pathway (heme → bilirubin) may be working normally, but there is **too much heme** being produced due to **premature RBC breakdown**, overwhelming the system.

Why it happens

There is **overproduction of heme** due to hemolysis (premature RBC destruction), so the body produces **too much bilirubin** before it even reaches the liver.

Examples

- **Hemolytic anemias**
- **Sickle cell anemia**
- **G6PD deficiency**
- **Malaria**
- **Autoimmune hemolysis**

Key defect

-Overproduction of heme → overproduction of bilirubin

-The problem is **not in the liver itself** and **not in the pathway enzymes**; it is in **excess heme load**.

Diagnosis (Laboratory-wise)

1) Total bilirubin

•**Increased**, because hemolysis produces excessive bilirubin.

2) Predominant bilirubin type

•Predominantly **unconjugated bilirubin** (because the excess is produced before hepatic conjugation capacity can keep up).

3) Urine bilirubin

•**Negative**

Because **unconjugated bilirubin is not water soluble (lipophilic)**, it does **not get filtered by the kidneys**.

4) Urine urobilinogen

•**Increased**

Because the liver is not the problem; bilirubin still reaches the intestine, bacteria convert it and urobilinogen rises, and more appears in urine.

5) Stool color

•**Very dark stool**

Because more bilirubin reaches the intestine → more conversion to pigments → darker stool.

6) Haptoglobin (important diagnostic clue)

•**Decreased haptoglobin**

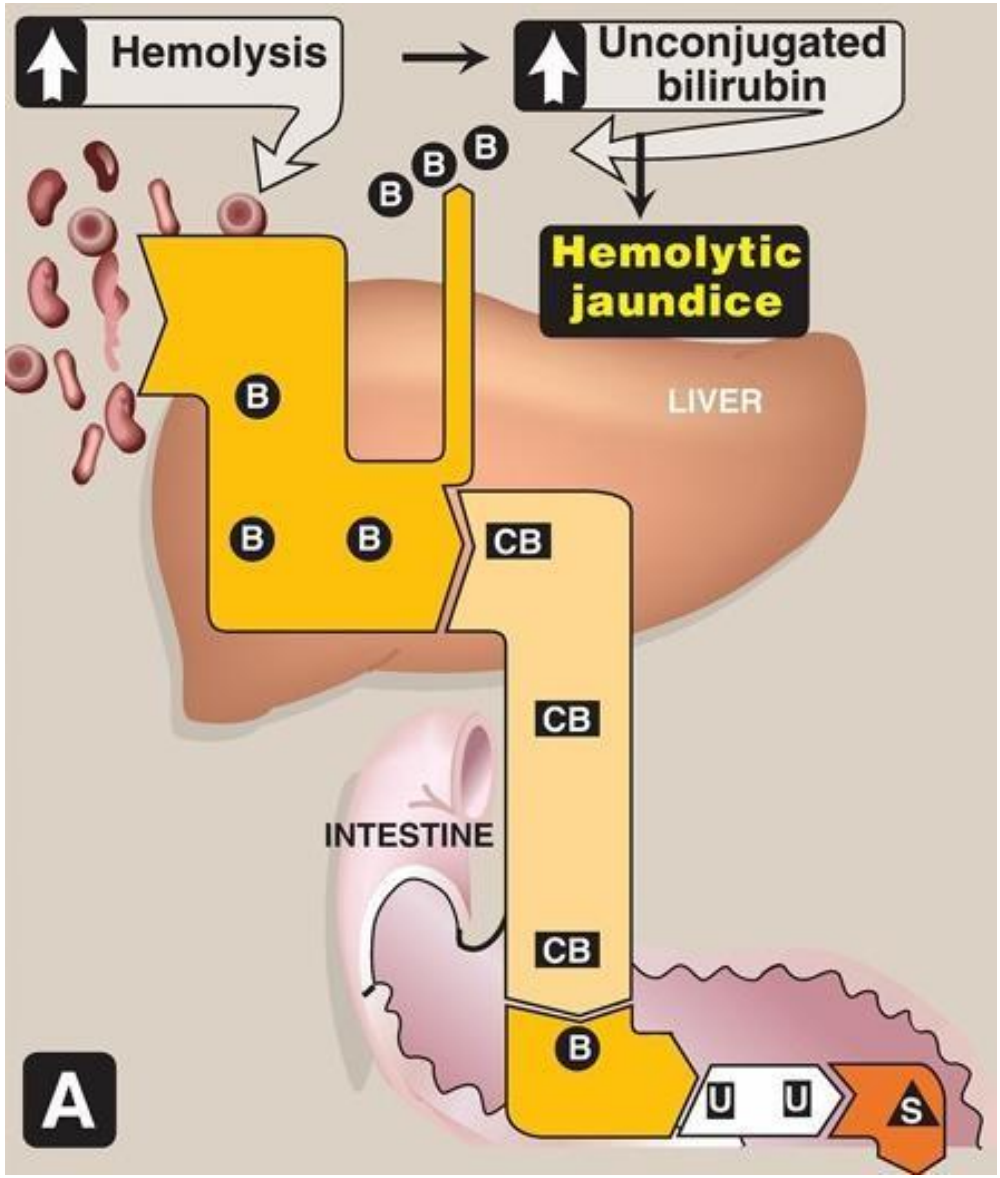
Explanation (as the lecturer said):

Haptoglobin is a plasma protein that **binds free hemoglobin** in the blood. When it binds hemoglobin, the complex is cleared and the **half-life becomes about ~90 minutes**, accelerating hemoglobin handling and helping to recover iron.

So, when there is **too much free hemoglobin due to hemolysis**, haptoglobin gets consumed → **haptoglobin level becomes low**, supporting diagnosis of **pre-hepatic (hemolytic) jaundice**.

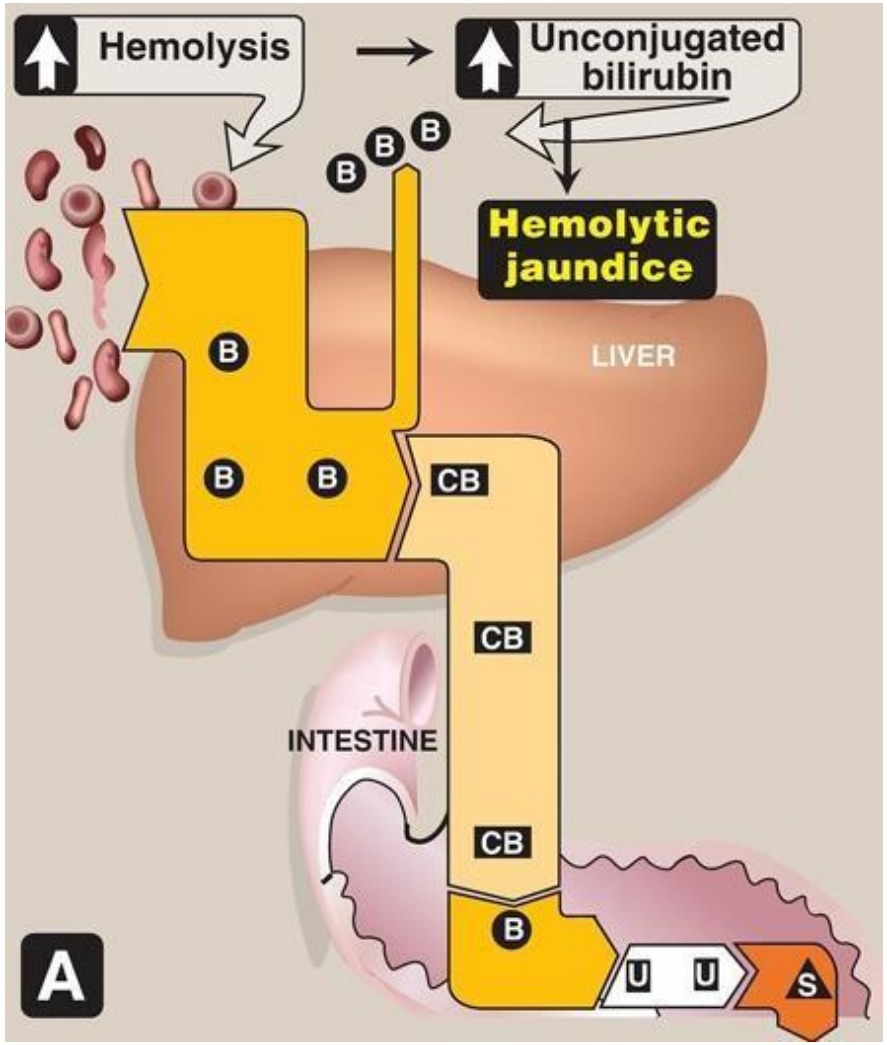
Pre-Hepatic (Hemolytic) Jaundice: Pathogenesis

- 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



2) Hepatic (Hepatocellular) Jaundice

Here, the problem is **inside the liver**: hepatocytes are **not working properly**. Some cells function, others don't—so the liver's ability to process bilirubin is impaired.

Causes mentioned

- **Viral hepatitis (A, B, C)**
- **Fatty liver disease**
- **Alcoholic liver disease**
- **Cirrhosis**
- **Fibrosis**

What happens to bilirubin type

Because liver function is partially impaired:

- You will see **both unconjugated and conjugated bilirubin increased in blood**

("some cells are working and some are not working properly" → mixed pattern).

Diagnosis (Laboratory-wise)

1) Blood bilirubin

- **Both unconjugated + conjugated increased**

2) Urine bilirubin

- **Positive**, because **conjugated bilirubin is present in blood** and it is water soluble.

But it is **not as strongly positive as post-hepatic jaundice**.

3) Urine urobilinogen

- **Usually increased**, **unless** there is a significant problem in bile movement within the liver (intrahepatic cholestasis) that prevents bile from reaching the intestine.

If bile doesn't reach intestine well → urobilinogen formation decreases.

4) Stool color

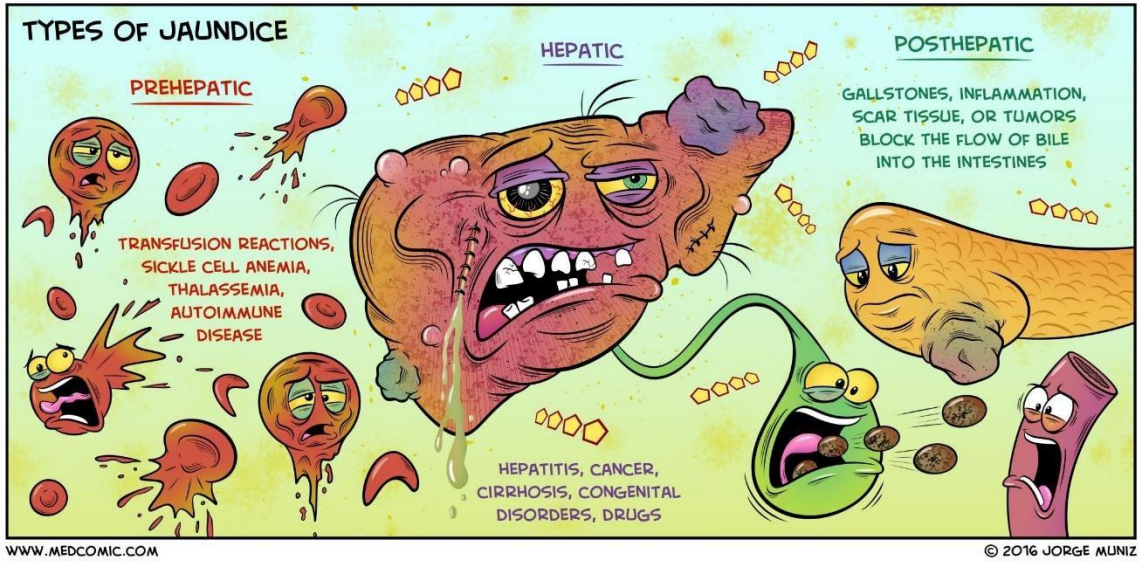
- **Usually not pale**, but **can become pale** if bile flow is significantly reduced and bilirubin is not reaching the intestine (so less urobilinogen → less stercobilin pigment).

5) Liver enzymes

- **AST and ALT increased** because liver cells are damaged/breaking down.

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)

3. Post-Hepatic (Obstructive) Jaundice

Post-hepatic jaundice occurs **after the liver**.
In this condition:
•Hepatocytes are **fully functional**
•Bilirubin is **normally conjugated**
•But bile **cannot reach the intestine** due to obstruction
As a result, conjugated bilirubin accumulates in the liver and then **flows back into the systemic circulation**, causing jaundice.

Causes
•**Gallstones** (most common) حصى المرارة
•Obstruction of the **common bile duct**
•**Pancreatic head carcinoma**
- The common bile duct joins the pancreatic duct near the head of the pancreas
- Tumors in this region can compress the bile duct

Key Defect
•Impaired bile flow (**cholestasis**)
•Failure of conjugated bilirubin to reach the intestine
•Regurgitation of conjugated bilirubin into the blood

(Anatomical Emphasis)
•Obstruction of the **biliary tree**, particularly the **common bile duct**.
•Important anatomical relation:
- The **common bile duct** joins with the **pancreatic duct**.
- Both pass near the **head of the pancreas** before entering the intestine.

•Therefore, **carcinoma of the head of the pancreas** can compress the bile duct and **block bile secretion into the intestine**.

Diagnosis (Laboratory-wise)

1) Blood Bilirubin

- **Total bilirubin: markedly increased**
- Predominantly **conjugated bilirubin**
  - Because **all hepatocytes are functioning and conjugating bilirubin normally**
  - Unlike hepatic jaundice, the issue is **not partial cell dysfunction**, but **complete obstruction**

2) Urine Bilirubin

- **Strongly positive**
- More markedly positive than in hepatic jaundice
- Reason:
  - Large amounts of **water-soluble conjugated bilirubin** are present in blood
  - Easily filtered by the kidneys and excreted in urine

3) Urine Urobilinogen

- **Low or absent**
- Reason:
  - Bilirubin does **not reach the intestines**
  - Intestinal bacteria cannot convert bilirubin into urobilinogen

4) Stool Color

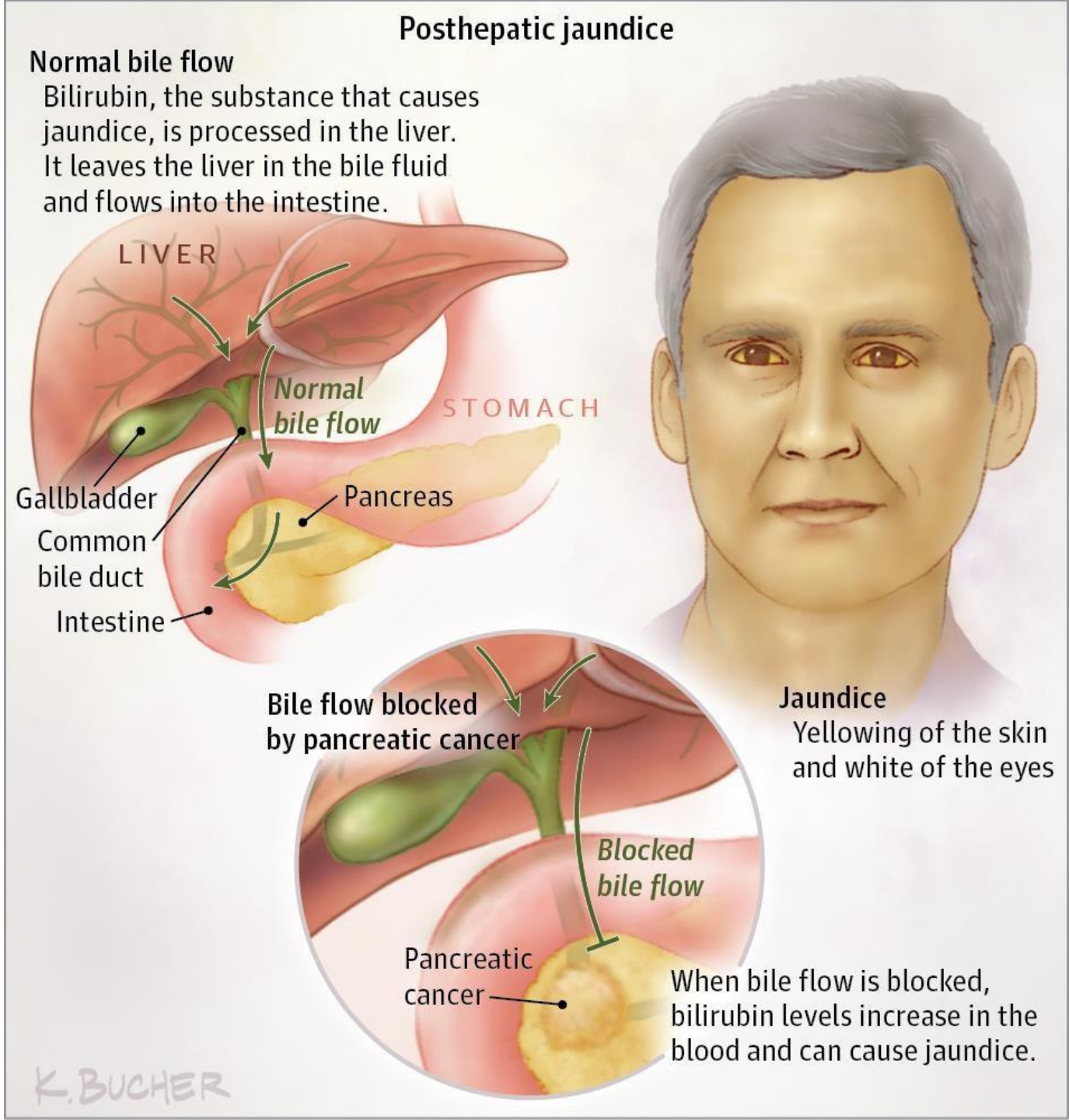
- **Pale / clay-colored stool**
- Due to:
  - Absence of urobilinogen in the intestine
  - No conversion to **stercobilin**, the brown pigment responsible for normal stool color

5) Additional Clinical Feature

- **Pruritus (itching)**
- Caused by accumulation of **bile salts and bile components** in the blood due to cholestasis

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

أستغفر الله العظيم وأتوب إليه

Comparison: The Three Types of Jaundice

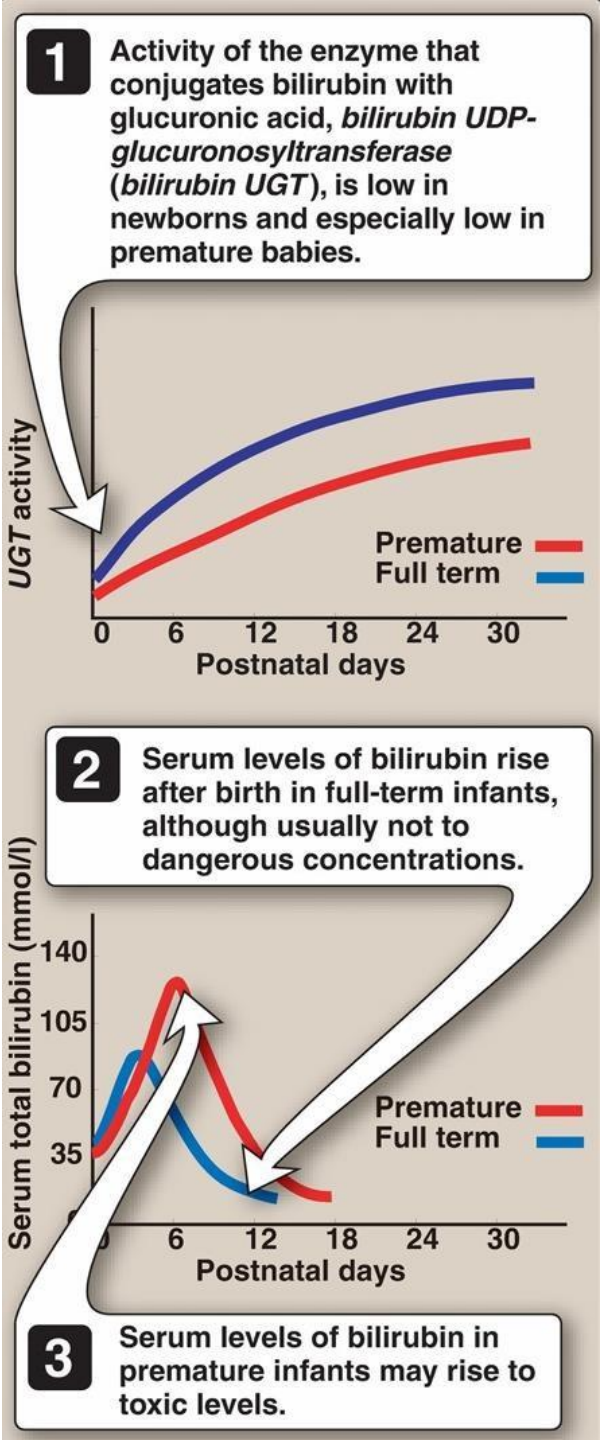
Feature	Pre-Hepatic	Hepatic	Post-Hepatic
Main Defect	Overproduction	Hepatocellular Injury	Obstruction
Bilirubin Type	**Unconjugated ↑↑**	**Mixed ↑**	**Conjugated ↑↑↑**
Urine Bilirubin	Negative	Positive	**Positive**
Urine Urobilinogen	**Increased**	Variable	**Decreased/Absent**
Stool Color	Dark	Variable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

Things that we can depend on in the diagnosis for prehepatic, hepatic & Post hypnotic

When discussing jaundice, one important condition that must be mentioned is **neonatal (physiological) jaundice**, which commonly occurs in newborns during the **first period of life** and usually lasts for **the first couple of weeks**. This condition is more frequent and more severe in **preterm infants** compared to full-term infants.
The explanation of neonatal jaundice can be clearly understood by correlating **bilirubin levels** with the **activity of the conjugating enzyme**, as illustrated in the figure.

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.



1. Activity of Bilirubin UDP-Glucuronosyltransferase (UGT)

The enzyme responsible for bilirubin conjugation is **bilirubin UDP-glucuronosyltransferase (UGT)**, which catalyzes the attachment of glucuronic acid to unconjugated bilirubin, making it water soluble.

At **birth (day 0)**, UGT activity is **low in all newborns**.

During the **first days of life (day 1–2)**, the activity remains **markedly low**.

As hepatocytes mature after birth, they begin **inducing the expression of UGT**, leading to a **gradual increase in enzyme activity with postnatal age**.

•In **full-term infants**, UGT activity rises relatively faster and reaches a **functionally adequate level by about two weeks (≈14 days)**.

•In **preterm infants**, UGT activity is **significantly lower at birth** and increases **much more slowly**, requiring a **longer period** to reach similar levels. In highly premature infants, this maturation may take **more than one month**.

This delayed enzyme maturation is the primary biochemical reason for neonatal jaundice.

2. Serum Bilirubin Levels in Full-Term Infants

Because UGT activity is initially low after birth, **serum bilirubin levels rise during the first few days of life** in full-term infants.

However, as UGT activity increases with time:

•Bilirubin conjugation improves

•Bilirubin excretion becomes more efficient

•Serum bilirubin levels **gradually decline**

In most full-term infants, bilirubin levels **do not reach dangerous concentrations**, making neonatal jaundice in this group **physiological and self-limiting**.

3. Serum Bilirubin Levels in Preterm Infants

In **preterm infants**, the combination of:

•**Markedly reduced UGT activity**

•**Delayed enzyme maturation**

•**High red blood cell turnover**

results in:

•A **higher rise in serum bilirubin**

•A **longer duration of hyperbilirubinemia**

As shown in the figure, **bilirubin levels in premature infants may rise to toxic levels**, unlike in full-term infants.

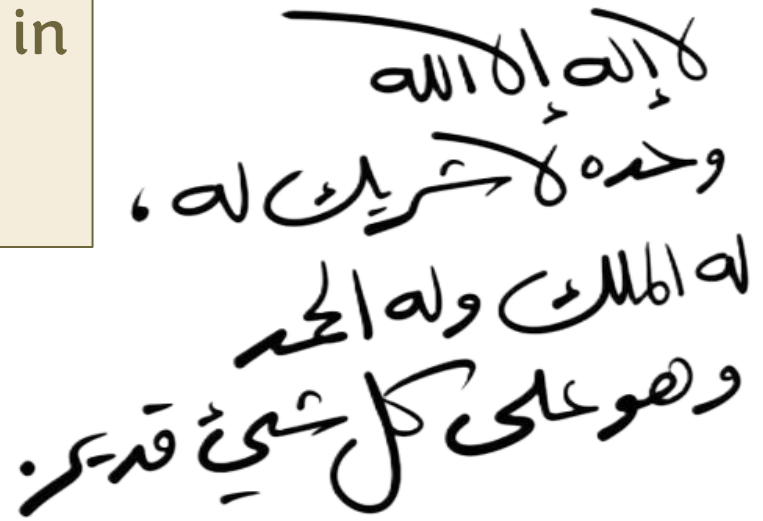
Clinical Significance

Because unconjugated bilirubin is **lipophilic** and the **blood-brain barrier is immature** in newborns, especially in premature infants, excessive bilirubin can cross into the brain and cause **kernicterus**.

Kernicterus is a form of **bilirubin-induced neurotoxicity** that may lead to:

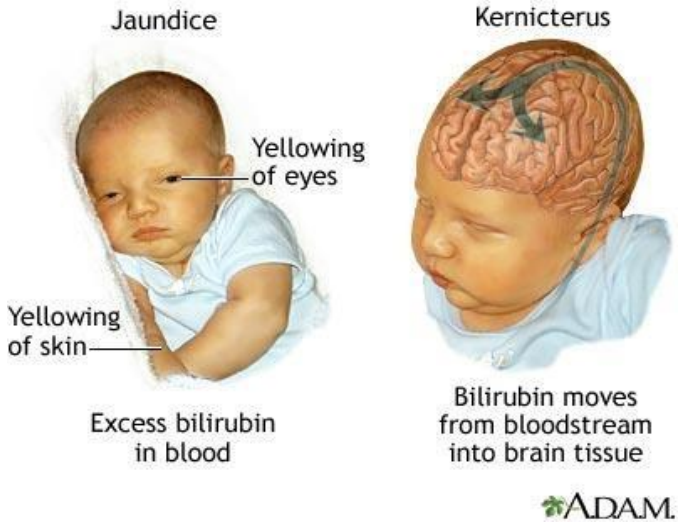
- Permanent neurological damage
- Mental retardation

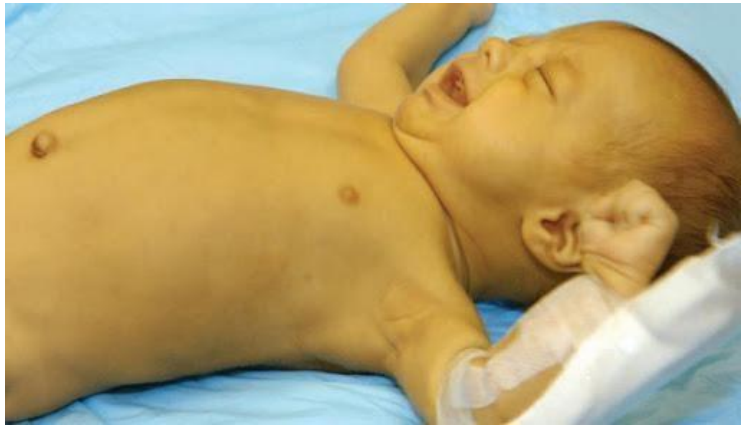
Therefore, neonatal jaundice, although often physiological, must be **closely monitored**, particularly in **preterm and highly premature infants**, to prevent bilirubin from reaching toxic levels.

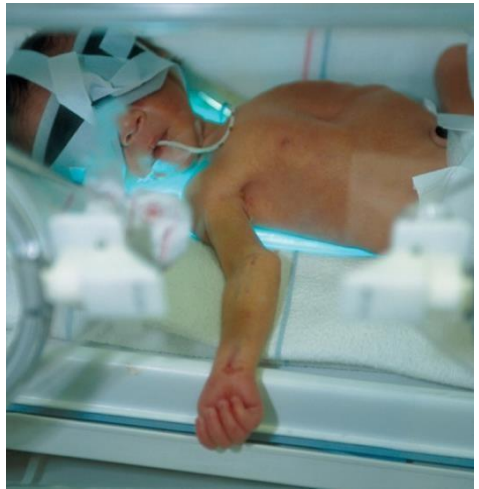


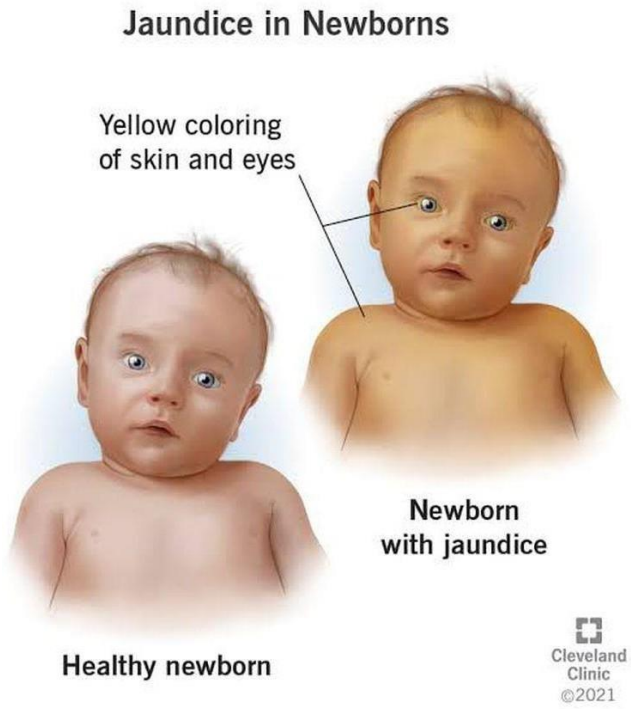
Neonatal Jaundice (Physiologic)

- 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)









In jaundice, the discoloration of the skin becomes evident when bilirubin accumulates in tissues. If bilirubin levels continue to rise, especially in newborns, **unconjugated bilirubin may cross into brain cells**, leading to **kernicterus**, a serious and potentially irreversible condition.
Therefore, treatment is required to **reduce bilirubin levels and prevent neurotoxicity**

Phototherapy (Blue Light Therapy)
The standard treatment for neonatal jaundice is **phototherapy**, which involves exposing the newborn to **blue light**.
Blue light acts on unconjugated bilirubin present in the skin and blood and **converts bilirubin into structural isomers** through a process known as **photoisomerization**.

Mechanism of Action
•Unconjugated bilirubin is **lipophilic and poorly water soluble**
•Blue light converts bilirubin into **more water-soluble isomers**
•These isomers:
- Do **not require conjugation by UGT**
- Can be **excreted directly in bile and urine**

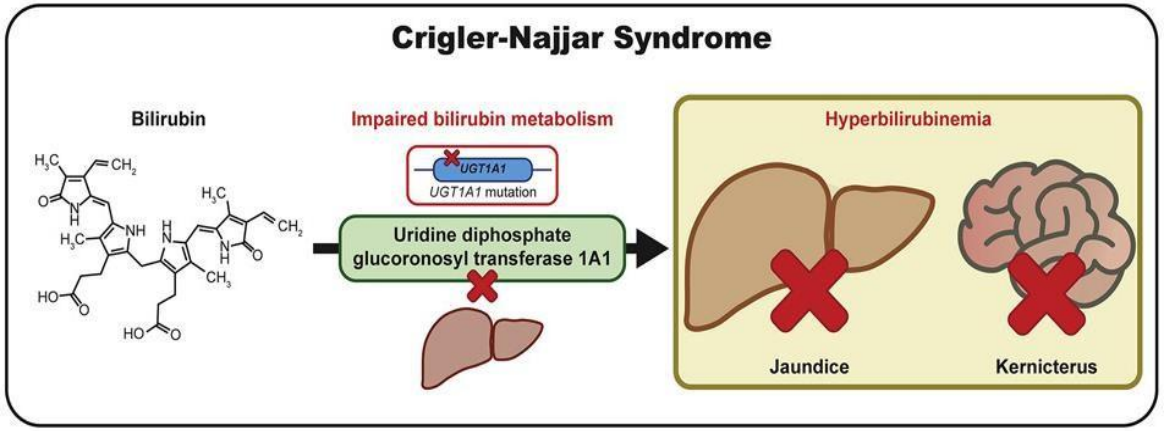
Thus, phototherapy bypasses the immature conjugation system in newborns and allows bilirubin to be eliminated safely.

Clinical Outcome
By converting bilirubin into a more soluble form:
•Serum bilirubin levels decrease
•Risk of bilirubin crossing the blood-brain barrier is reduced
•**Kernicterus is prevented**
Phototherapy is therefore an **effective and safe treatment**, especially important in **preterm infants**, where UGT activity is still very low.

Inherited Disorders of Bilirubin Metabolism

most severe form of UGT deficiency

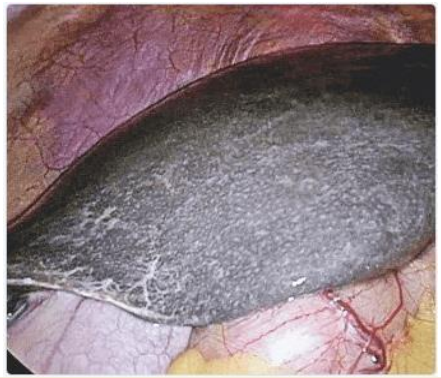
- **Crigler-Najjar Syndrome Type I:**
  - Complete deficiency of UGT (the enzyme is totally absent)
  - Severe unconjugated hyperbilirubinemia, kernicterus(very risky life condition), fatal without liver transplant (patients cannot live without liver transplant and repeated plasma exchange)
- **Crigler-Najjar Syndrome Type II:** partial deficiency of UGT the same enzyme is affected, but not completely, less severe
  - ·Moderate unconjugated hyperbilirubinemia
  - ·Less severe than Type I (**not as dangerous as type I**)
  - ·Usually does not require liver transplantation



Inherited Disorders of Bilirubin Metabolism

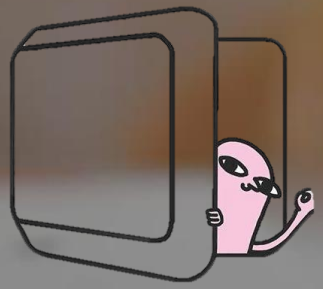
- **Gilbert Syndrome**:
  - Mild (~30%) reduction in UGT activity (the enzyme is still working at about 70% efficiency)
  - Benign(no major problem and no treatment is required)
  - , very common (~5-10% population) (you should be familiar with it; it is common in the population)
  - Mild, unconjugated hyperbilirubinemia during stress, fasting, or illness (especially under stressful conditions such as exams)

- **Dubin-Johnson Syndrome**: Defect in hepatic excretion of conjugated bilirubin (MRP2) (**UGT activity is normal; the problem is in the transporter, not the enzyme**). Causes <u>conjugated hyperbilirubinemia</u>
  - Liver has a characteristic black pigmentation(true black pigmentation of the liver; very characteristic finding)



Black pigmentation results from accumulation of **epinephrine metabolites (this transporter normally ejects epinephrine metabolites; when MRP2 is defective, they accumulate inside hepatocytes and cause the black color)**

Thank you and hope you’ll do great in exam



رسالة من الفريق العلمي:

Additional Resources:

اعتدنا في كل مرة أن نكتب رسائلنا دعمًا وتحفيزًا لغيرنا، لا لأنفسنا، لكن هذه المرة تأتي هذه الكلمات من الفريق العلمي إلى الفريق العلمي نفسه.
نكتبها تقديرًا لجهود بُذلت بصمت، ولعطاء استمر رغم ضغط هذا الفصل الدراسي وثِقله على الجميع، ورغم التعب الذي لم يكن خفيًا على أحد. ومع ذلك، لم يتوقف السعي، ولم تخفت الهمّة.
ونخصّ بالامتنان مسؤولي الفريق العلمي، شاكرين لهم وجودهم، ودعمهم، وحسن إدارتهم في أوقات لم تكن سهلة، فكانوا سندًا وعونًا، وسببًا في استمرار العطاء.
إن وجودكم نعمة، وجهودكم محل تقدير واعتزاز، وأثرها باقٍ لا يزول.

شكرًا يُقال بالقلب قبل اللسان، ويُثبت أن العطاء حين يخلص... لا يضيع.
بارك الله بكم وجزاكم عنا خير الجزاء ورفع قدركم في الدارين ونفع بكم هذه الأمة

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
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V1 → V2			