



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

السلام عليكم ورحمة الله وبركاته

# GASTROINTESTINAL PHYSIOLOGY

(LECTURE 8)

BILIRUBIN METABOLISM



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# LEARNING OBJECTIVES

- \* Fate of red blood cells
- \* Metabolism of bilirubin
- \* Conjugation of bilirubin with glucuronic acid inside hepatocytes
- \* Fate of conjugated bilirubin
- \* Fate of urobilinogen
- \* Differentiation between conjugated & unconjugated bilirubin
- \* Other substances conjugated by glucuronyl transferase.
- \* Other substances excreted in the bile

- Bilirubin is the greenish yellow pigment excreted in bile.
- It is a major end product of hemoglobin degradation.
- It is highly soluble in all cell membranes & is also very toxic.
- Therefore, its excretion in the bile is one of the very important functions of the liver.

# FATE OF RED BLOOD CELLS

- Life span of RBCs in blood stream is 60-120 days.
- Senescent RBCs become too fragile to exist longer in the circulatory system, their cell membranes rupture and they are phagocytosed and/or lysed.
- Normally, lysis occurs extravascularly in the reticulo-endothelial system subsequent to RBC phagocytosis.
- Lysis can also occur intravascularly (in blood stream).
- The hemoglobin is first split into globin & heme.
- The AA formed from breakdown of globin are stored in the body.

# METABOLISM OF BILIRUBIN

- The heme ring is opened to give:
  - \* **Free iron** that is transported in the blood by transferrin and stored in the body as a reservoir for erythropoiesis.
  - \* **Bile pigments:** The 1<sup>st</sup> pigment is biliverdin but it is rapidly reduced by biliverdin reductase to free bilirubin which is gradually released into the plasma.



Red Blood Cells

Hemolysis in splee  
liver, bone marrow

Hemoglobin

Heme

$Fe^{2+}$

Recycled to  
bone marrow

Biliverdin

NADPH

NADP

Bilirubin

Liver

Conjugated bilirubin  
(bilirubin glucuronide)

Carbon  
monoxide (CO)

Hemoglobin

Carboxyhemoglobin

$O_2$

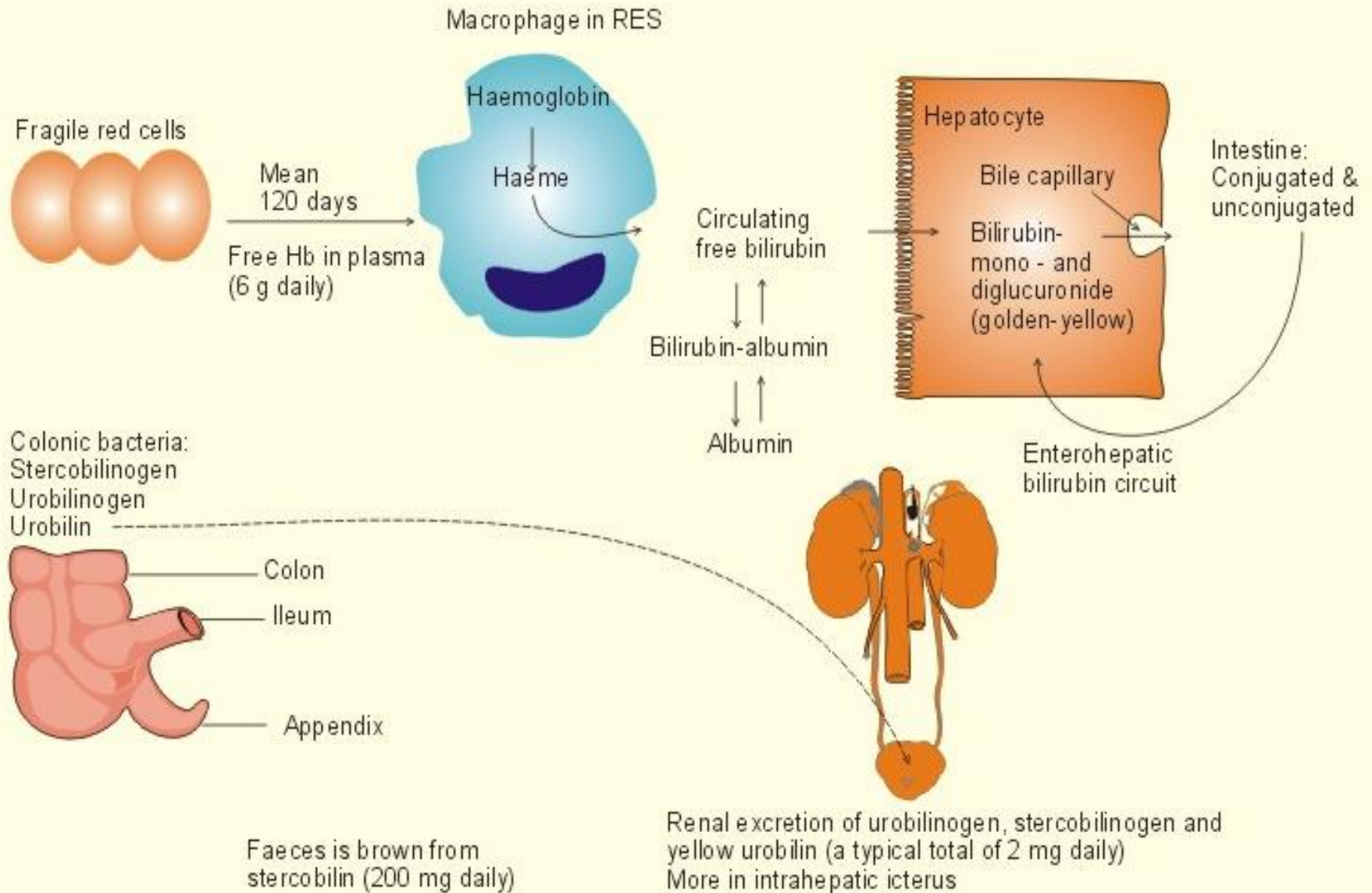
Oxyhemoglobin

Carbon monoxide eliminated  
in exhaled breath

Bilirubin eliminated in bile  
excreted in feces

# Bilirubin Metabolism

Free bilirubin is fat-soluble and toxic  
Conjugated bilirubin is water-soluble and non-toxic

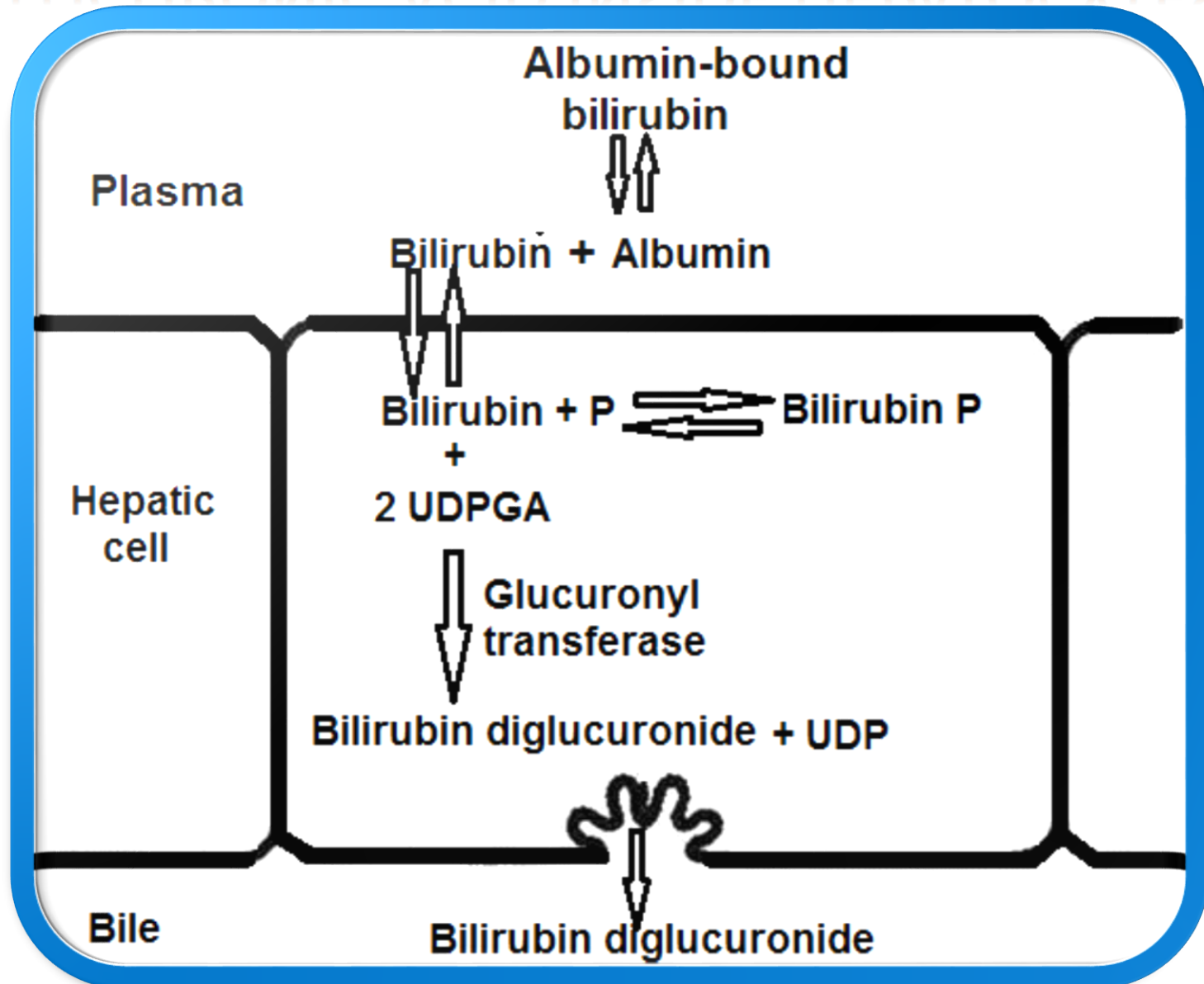




- ✓ The free bilirubin is hydrophobic, immediately combines with plasma proteins (mainly albumin and globulin) forming a water soluble compound (**hemobilirubin**, unconjugated bilirubin) which is rapidly transported to hepatocytes for further metabolism. Even when bound to albumin it's called free bilirubin.
- ✓ Bilirubin is absorbed through the hepatic cell membrane, mediated by a carrier protein (receptor) & combined with Y & Z proteins that trap the bilirubin inside the cells.

- ✓ Thereafter, in the liver cells *hemobilirubin* dissociates into protein and free bilirubin.
- ✓ About 80% of bilirubin conjugates with glucuronic acid catalyzed by the enzyme glucuronyl transferase in the smooth endoplasmic reticulum.
- ✓ Each bilirubin molecule reacts with 2 uridine diphospho-glucuronic acid (UDPGA) molecules to form bilirubin diglucuronide (*cholebilirubin*, conjugated bilirubin) which is more water soluble than the free bilirubin.

# CONJUGATION OF BILIRUBIN WITH GLUCURONIC ACID INSIDE HEPATOCYTES



- ❁ 10% conjugate with sulphate to form bilirubin sulphate.
- ❁ The final 10% conjugate with other substances.
- ❁ These forms of bilirubin are actively secreted by the liver cells by an active transport process into the bile canaliculi.
- ❁ The color of bile is due to bilirubin.
- ❁ In normal adults this results in a daily load of 250-300 mg of bilirubin.
- ❁ Normal plasma concentrations are less than 1 mg/dL.

# FATE OF CONJUGATED BILIRUBIN

- ◆ A small portion of the conjugated bilirubin returns to the plasma either directly into the liver sinusoids or indirectly from the bile ducts or lymphatics.
- ◆ It is bound less tightly to albumin & is excreted in the urine
- ◆ This causes a small portion of the bilirubin in the extracellular fluid always to be of the conjugated type rather than of the free type.

• Small amount of bilirubin glucuronide is deconjugated and absorbed by the small intestine into the portal blood to the liver where it is extracted by the liver cells and conjugate again and excreted in the bile (enterohepatic circulation of bile pigments).

•NB: The intestinal mucosa is relatively impermeable to conjugated bilirubin but permeable to unconjugated bilirubin.

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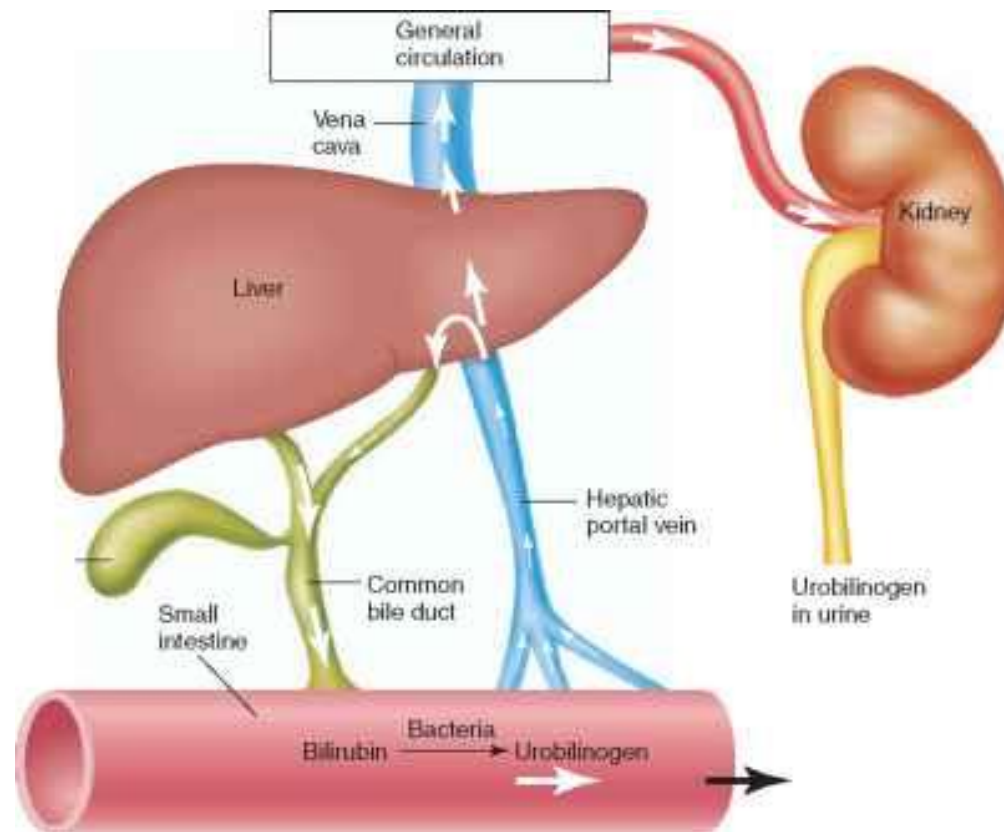
💧 The majority of conjugated bilirubin passes via the bile ducts to the intestine where it is transformed through bacterial action into urobilinogen which is highly soluble.

# FATE OF UROBILINOGEN

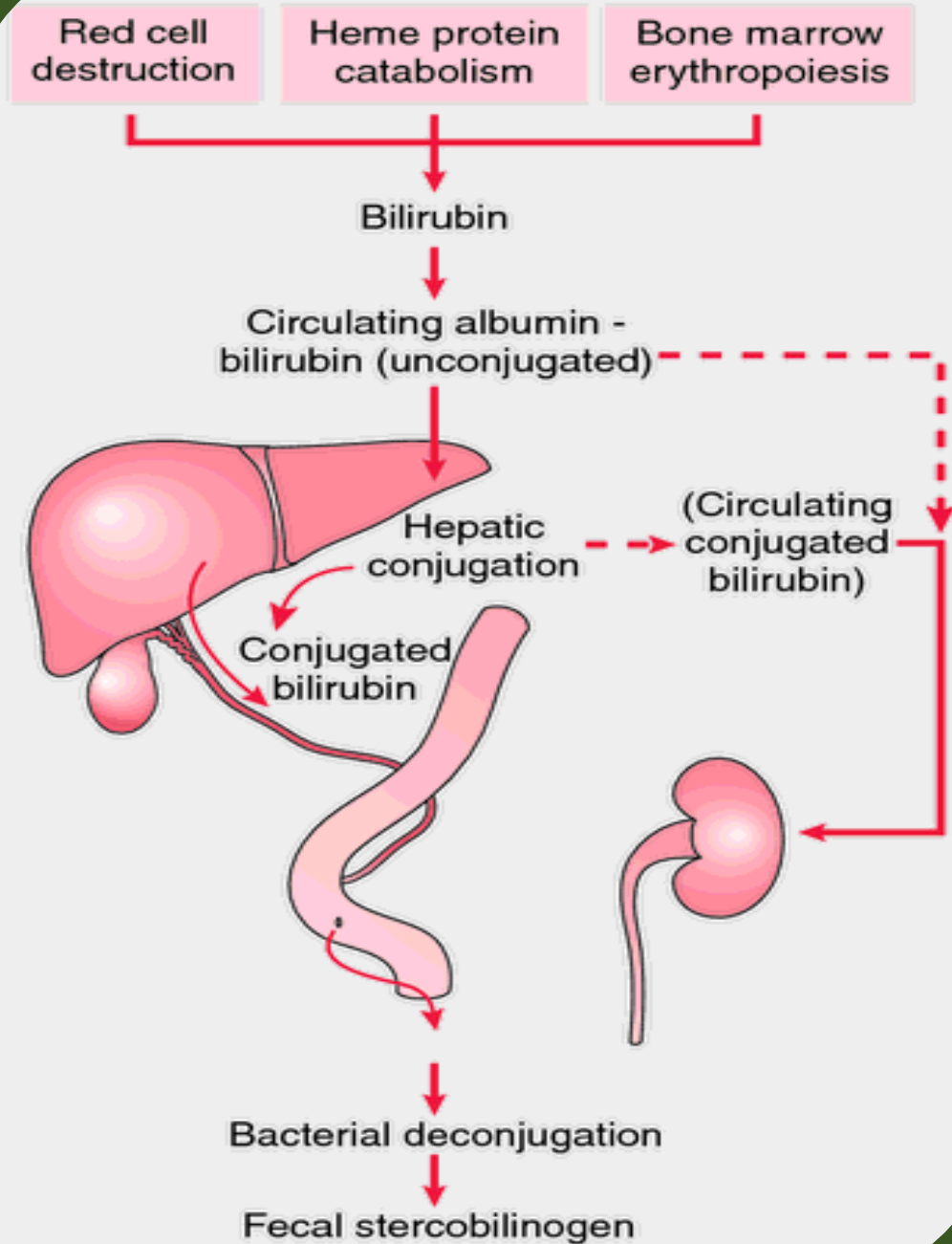
- Most of urobilinogen (70%) in the intestine is converted into stercobilinogen, oxidized and excreted in the feces as stercobilin that causes dark brown color of the feces.
- Some of urobilinogen (20 %) is reabsorbed through the intestinal mucosa into the portal vein and passes to the liver and reexcreted by the hepatic cells in the bile (enterohepatic circulation of urobilinogen).



- Small amount of urobilinogen escapes to the general circulation and excreted by the kidneys in the urine where it is oxidized to urobilin when the urine is exposed to air.



# NORMAL BILIRUBIN METABOLISM



# DIFFERENTIATION BETWEEN CONJUGATED & UNCONJUGATED BILIRUBIN

- By Van den Bergh reaction:



- ① **If the bilirubin is of the conjugated type:**

An immediate reaction occurs with Van den Bergh reagent (which gives a colorimetric change), and the reaction is called **a direct Van den Bergh reaction.**

Conjugated bilirubin + Diazo reagent  Purple color

## ② If the bilirubin is of the unconjugated (free) type:

Adding ethanol to the plasma precipitates the protein and frees bilirubin from its protein complex so that it can combine with Van den Bergh reagent. This causes the colorimetric changes to be much stronger, and the additional result is called the **indirect Van den Bergh reaction**.

- Unconjugated bilirubin + Ethanol  Free bilirubin
- Free bilirubin + Diazo reagent  Purple color.

- **Biphasic Van den Bergh reaction:**

- ❖ It occurs when blood contains both conjugated and unconjugated bilirubin.
- ❖ In this case purple color appears without adding alcohol and is intensified after adding it.

N.B: Transport of bilirubin in plasma occurs in two forms:

## Unconjugated bilirubin

## Conjugated bilirubin

Indirect reacting bilirubin-hemobilirubin

Direct reacting bilirubin-cholebilirubin

The chief form of bilirubin in the blood

Present in low conc. in the blood.

Bound to albumin.

Bound to glucuronic acid

Not filtered through renal glomeruli

Filtered through renal glomeruli

Not present in urine.

Excreted in urine

Water insoluble

Water soluble

Toxic substance

Non-toxic substance

# OTHER SUBSTANCES CONJUGATED BY GLUCURONYL TRANSFERASE

- The glucuronyl transferase system in the smooth endoplasmic reticulum catalyzes the formation of the glucuronides of a variety of substances in addition to bilirubin.
- The list includes steroids & various drugs.
- These other compounds can compete with bilirubin for the enzyme system when they are present in appreciable amounts.

- In addition several barbiturates, antihistamines, anticonvulsants and other compounds can cause marked proliferation of the smooth endoplasmic reticulum in the hepatic cells, with a concurrent increase in hepatic glucuronyl transferase activity.
- Phenobarbital has been used successfully for the treatment of a congenital disease in which there is a relative deficiency of glucuronyl transferase (type 2 UDP-glucuronyl transferase deficiency).



# OTHER SUBSTANCES EXCRETED IN THE BILE

- ✧ Cholesterol & alkaline phosphatase are excreted in the bile.
  - In patients with jaundice due to intra or extra hepatic obstruction of the bile duct, the blood levels of these 2 substances usually rise.
  - A much smaller rise is generally seen when the jaundice is due to non obstructive hepatocellular disease.
- ✧ Adrenocortical, other steroid hormones & a number of drugs are excreted in the bile and subsequently reabsorbed (enterohepatic circulation)

Thank You

The image features the words "Thank You" in a highly decorative, cursive script. The letters are filled with a deep red color and have a thick, gold-colored outline. The text is embellished with clusters of vibrant red roses and green foliage. Two white doves are depicted in flight, one positioned above the letter 'h' and the other above the letter 'o' in "You". The entire graphic is set against a plain white background.