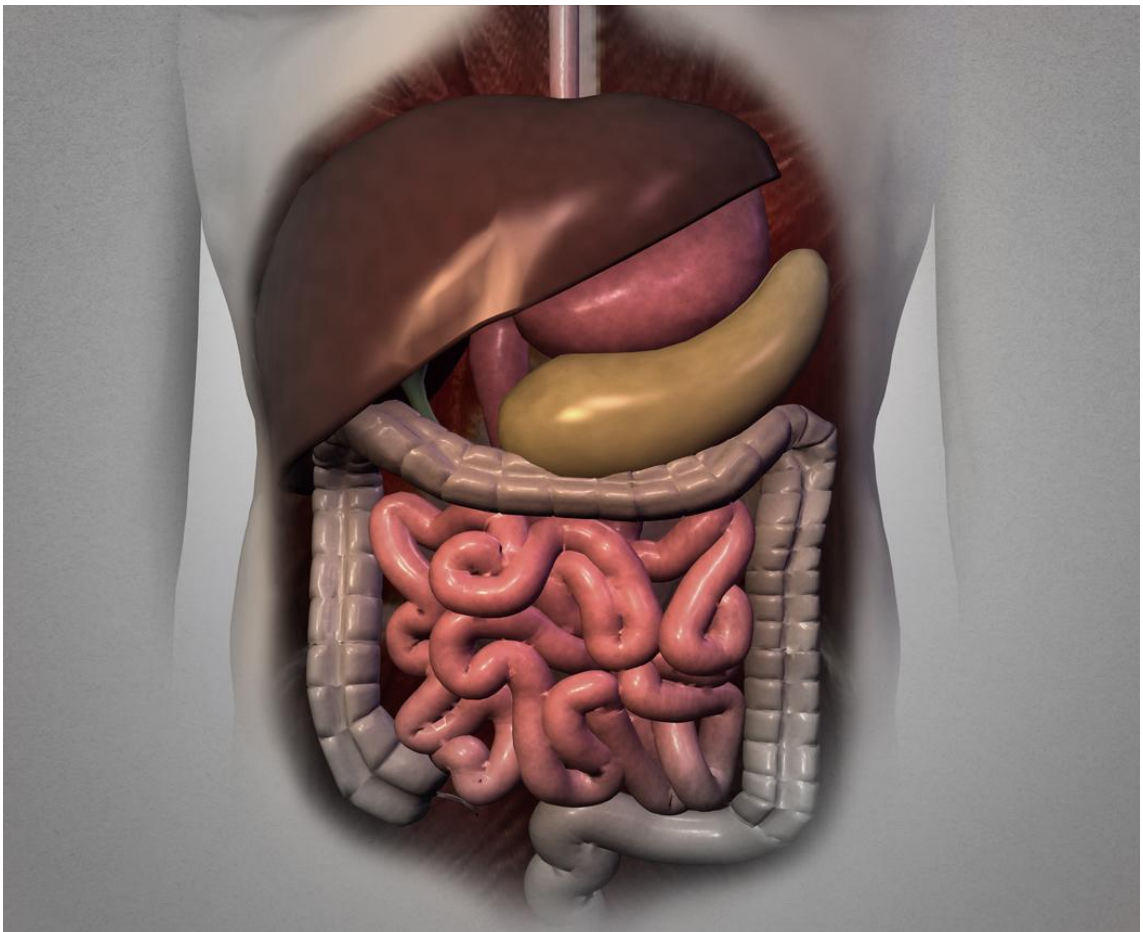

GIT Block

PhysiologyTeam 431

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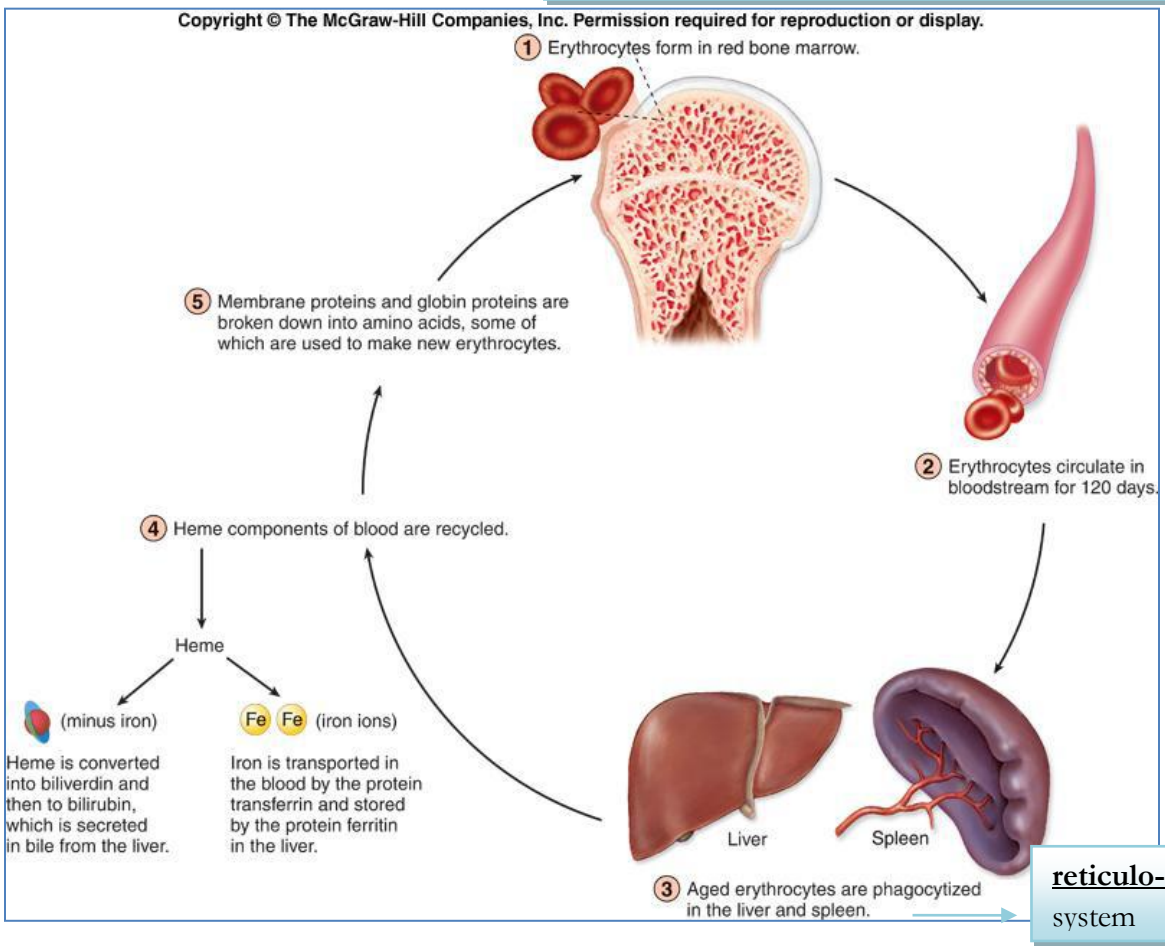
Bilirubin Metabolism

What is bilirubin ?!

- 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 RBCs ..

Important figure illustrating theRBCs fate



reticulo-endothelial system

Fate of RBCs (cont.):

- Life span of RBCs in blood stream is 60-120 days.

- Senescent (old) RBCs become too fragile to exist longer in the circulatory system → their cell membranes rupture → they are phagocytosed and/or lysed

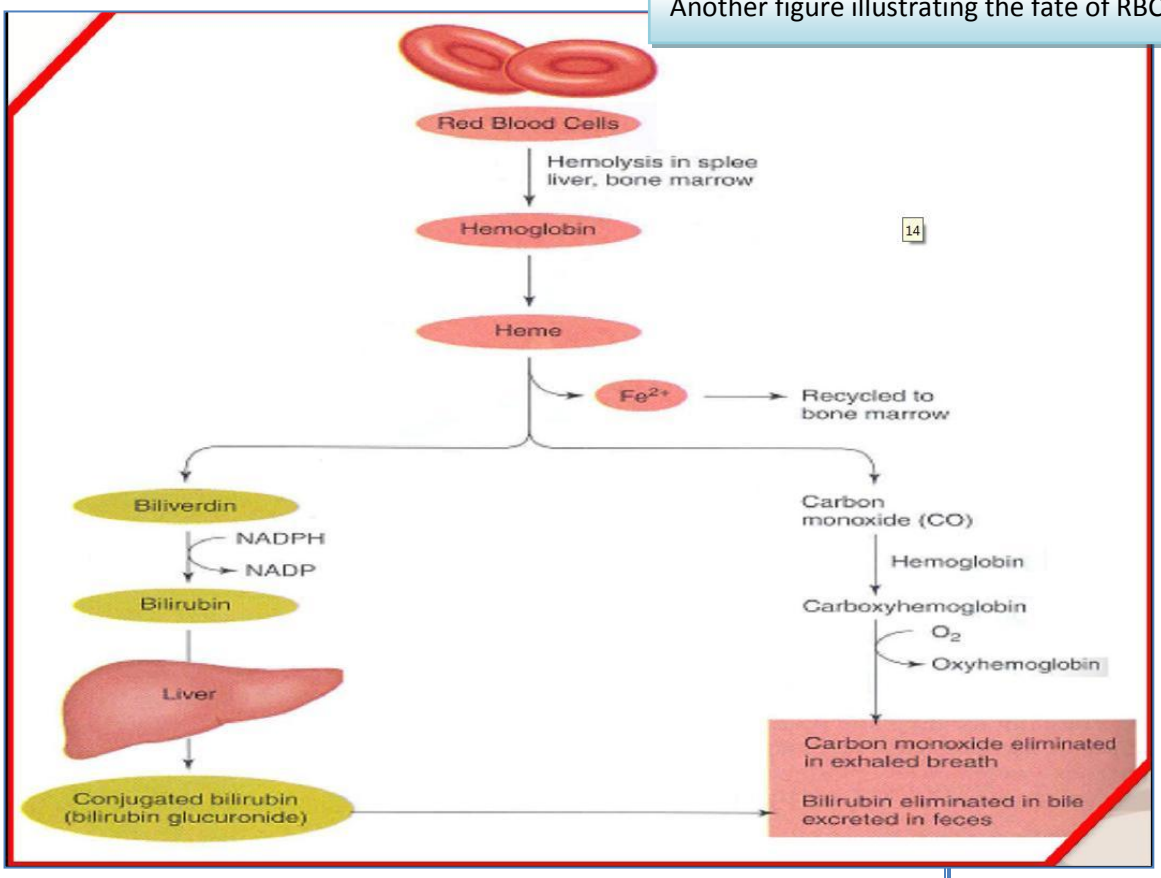
  → Normally, lysis occurs extravascularly in the **reticulo-endothelial** system subsequent to RBC phagocytosis.

  → Lysis can also occur intravascularly (in blood stream).

  →The hemoglobin is then set free and metabolized into globin &heme:

  1. Globin → The AA formed from breakdown of globin are stored in the body and re-localized for protein synthesis.
  2. Heme → free iron +bile pigment called (biliverdin)
     a. free iron → transported in the blood by transferrin and stored in the body as a reservoir for erythropoiesis
     b. pigment called (biliverdin) → biliverdin reduced via reductase enzyme into free **bilirubin**→ releasedinto the circulation.

Another figure illustrating the fate of RBCs



What is the fate of bilirubin ?!

- The free bilirubin is hydrophobic→ immediately combines with plasma proteins (mainly albumin and globulin) → forming a water soluble compound called **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**(most important)conjugates with **glucuronic acid** catalyzed by the enzyme glucuronyltransferase in the smooth endoplasmic reticulum.
  - Each bilirubin molecule reacts with 2 uridinediphospho-glucuronic acid (UDPGA) molecules in the smooth endoplasmic reticulum to form **bilirubin diglucuronide** (cholebilirubin, conjugated bilirubin) which is more water soluble than the free bilirubin.

  - **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 by absorption into the blood from the bile ducts or lymphatics.

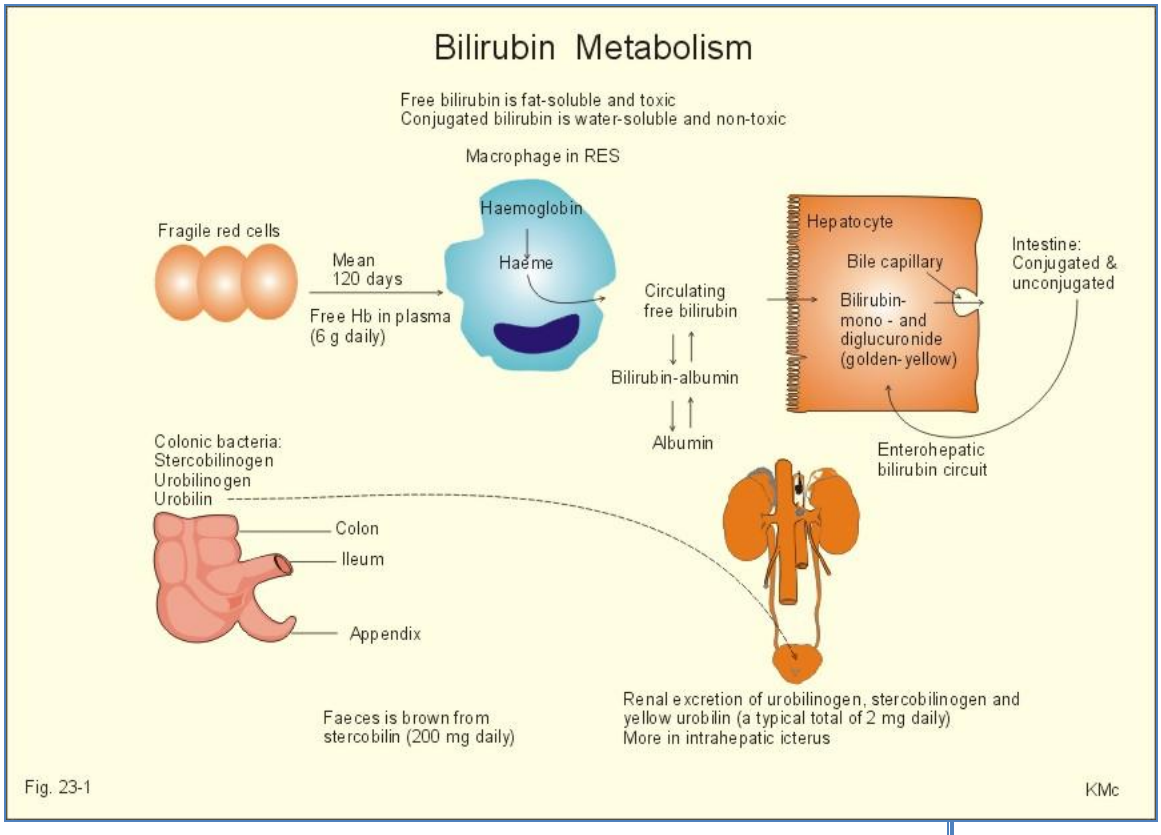
This causes a small portion of the bilirubin in the extracellular fluid always to be of the conjugated type rather than of the free type.

Small amount of bilirubinglucuronide is deconjugated → absorbed by the small intestine → 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 highly permeable to unconjugated bilirubin,WHY ?! (because it's lipid-soluble)

Some of conjugated bilirubin escapes into the blood where it is bound less tightly to albumin& is excreted in the urine(because it's water-soluble).

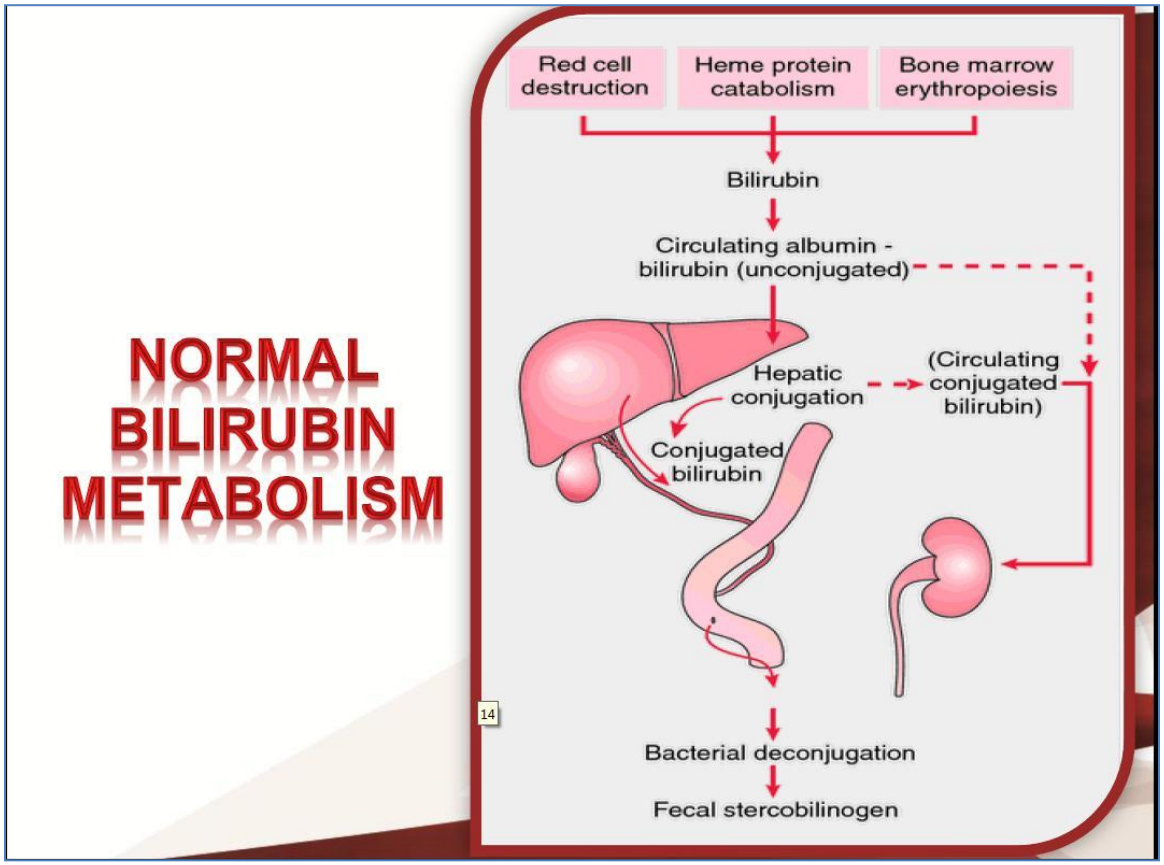
The majority of conjugated bilirubin passes via the bile ducts to the intestine where it is transformed through bacterial action into urobilinogen which is highly soluble



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 and unconjugated

WHY is it important to differentiate between conjugated and unconjugated bilirubin ?!

** To differentiate between different types of jaundice ; pre-hepatic, hepatic or post-hepatic causes ..

WHAT is van den Bergh reaction &**HOW** is it done?!

** It is a chemical reaction used to measure bilirubin levels in blood, and the reaction produces azo-bilirubin. By van den Bergh reaction using Diazo reagent (diazotized sulphanilic acid) we can differentitae between the two as follow:

1. **if bilirubin is of conjugated type:**

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

- Conjugated bilirubin + Diazo reagent →Purple color

2. **if bilirubin is of unconjugated (free) type:**

Adding ethanolto the plasma, WHY?
**because ethanol 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 **INDIRECTvan den Bergh reaction.**

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

3. **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.

Differentiation between conjugated and unconjugated (cont.)

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 glucorunyltransferase

WHY is it important to know them ?!!

** They can compete with bilirubin and their presence may cause jaundice..

- The glucuronyltransferase 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 glucuronyltransferase activity. (can be used as atreatment for inhancing the conjugation for bilirubin)

- **Phenobarbital** has been used successfully for the treatment of a congenital disease in which there is a relative deficiency of glucuronyltransferase (type 2 UDP-glucuronyltransferase deficiency).

Other substances excreted in the bile

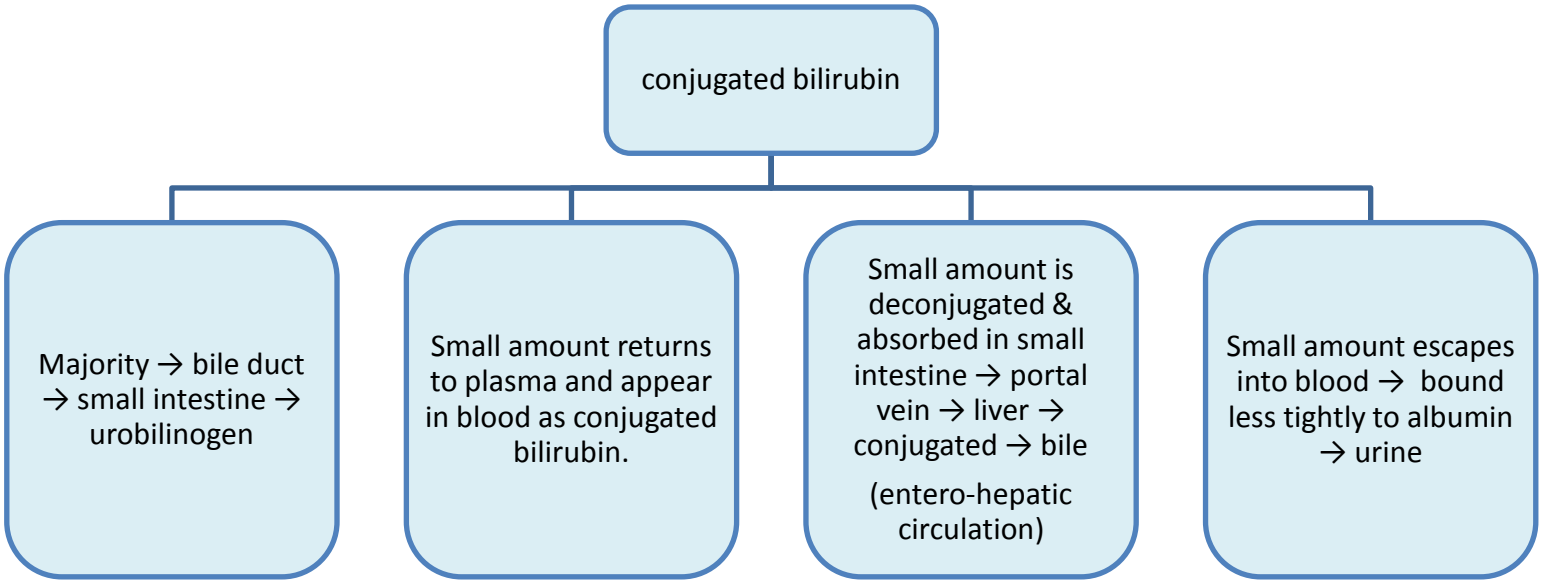
- Cholesterol&alkaline phosphatase are excreted in the bile.
    - In patients with jaundice due to intra or extra hepatic obstruction of the bile duct, the blood levels of these 2 substances usually RISE.
    - A much smaller rise(not as high as if with bile duct obstruction) is generally seen when the jaundice is due to non obstructivehepatocellular disease.

- Adrenocortical, other steroid hormones & a number of drugs are excreted in the bile and subsequently reabsorbed (enterohepatic circulation)

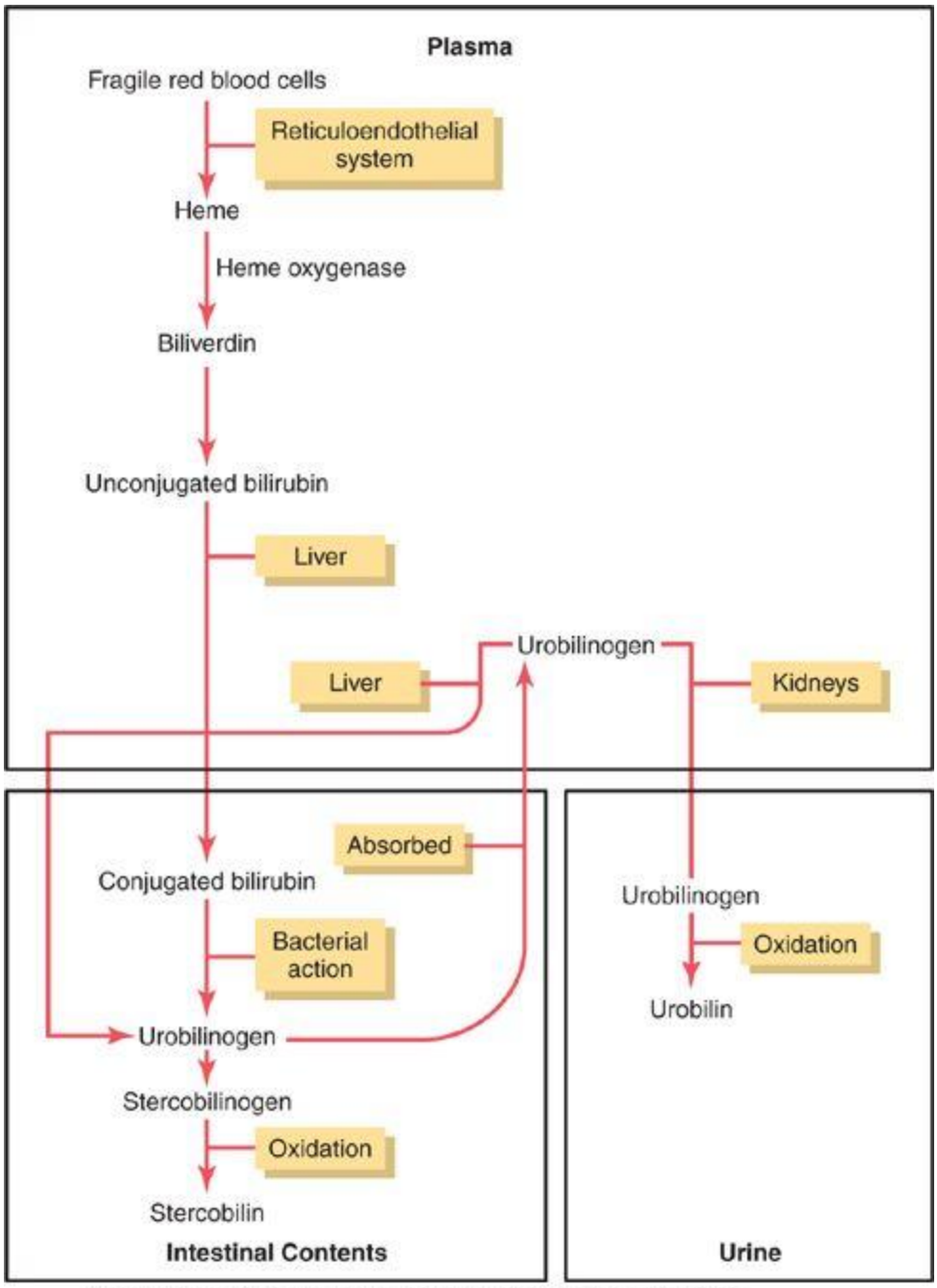
Summary

1- Bilirubin is the greenish yellow pigment of bile, formed from lysis of the "heme" part of hemoglobin –by reticuloendothelial system- to iron &biliverdin, then from biliverdin to bilirubin by biliverdinreductase.

2- released into the blood & combines tightly with albumin or globulin → unconjugated bilirubin → hepatocytes → absorbed by carrier protein (receptor) → dissociated to free bilirubin & protein → free bilirubin conjugates with glucuronic acid with help of glucuronyltransferase→ bilirubin glucuronide (conjugated bilirubin).



3- urobilinogen
- 70%→stercobilinogen→stercobilin→feces
- 20% reabsorbed → portal vein → liver →reexcreted to bile
- Small amount escapes to general circulation → urine→urobilin



Hall: Guyton and Hall Textbook of Medical Physiology, 12th Edition

Review Questions

1. **What isn't a fate of bilirubin**?

A. Transferring into urobilinogen

B. Excreted in urine via general circulation

C. Dissociating into amino acids that deposit on the intestinal wall

D. Returning to plasma

2. **The heme molecule**:

A. Breaks into iron and globin

B. Breaks into iron then travels to spleen

C. Breaks into iron molecules then transforms into biliverdin

D. Breaks into iron which travel to pancreas

3. **After secretion of bile, it is drained into**:

A. Common bile duct

B. Hepatic duct

C. Portal vein

D. Bile canaliculi

4. **Upon emptying the gallbladder:**

A. The walls contract and sphincter of the oddi relaxes

B. The walls relax and sphincter of the oddi contracts

C. Sympathetic stimulation increases

D. Will remain closed until it is completely filled with bile

5. One of the functions of bile is:

A. Protein absorption

B. Fat emulsification

C. Preserving cholesterol

D. Carbohydrate digestion

6. What is true about bile acids?

A. 2ry bile acids conjugate with glycine

B. Deoxyxholic is a 1ry acid

C. 1ry acids undergo dehydroxylation by bacteria

D. 2ry bile acids have a hydroxyl group

7. What isn't true about enterohepatic circulation?

A. Majority of bile salts are recycled

B. Urobilinogen undergoes recycling

C. Stercobilinogen undergoes recycling

D. There are multiple means of reabsorption

8. **What is a correct Vanderbergh reaction with both conjugated and unconjugated biles?**

A. Purple colouration followed by colourless solution

B. Purple colouration and no change upon adding alcohol

C. No colour change unless alcohol is added

D. Purple colour followed by dark purple upon alcohol addition

9. **One of the causes of jaundice is**:

A. Hypotension

B. Increase fatty food intake

C. Liver cirrhosis

D. Inflammatory bowel disease

Answers

1- C

2- C

3- D

4- A

5- B

6- C

7- C

8- D

9- C