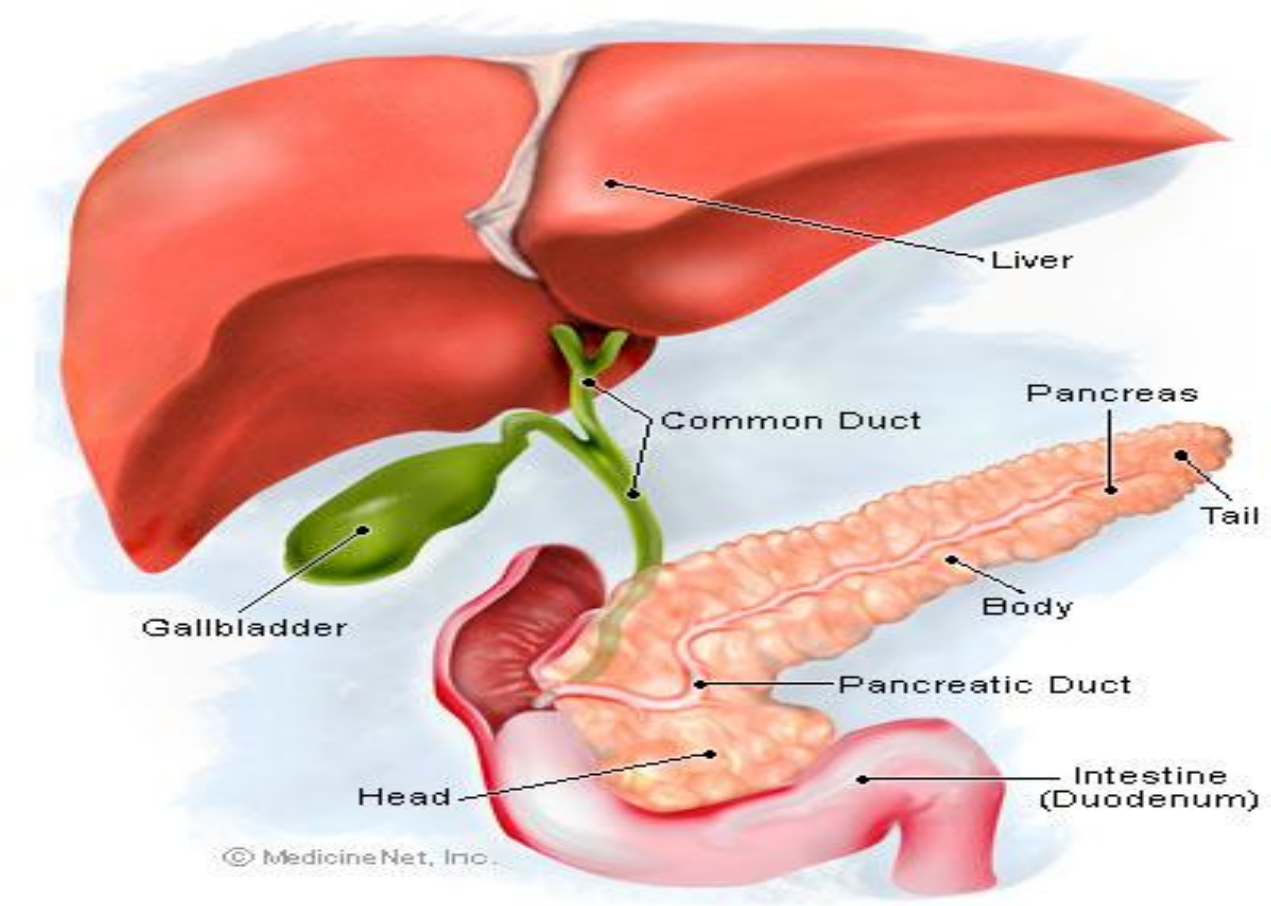
GIT Block

(8,9,10 & 11)th Lecture

Bilirubin Metabolism



PHYSIOLOGY TEAM – 430

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As we have seen in the physiology of pancreas, the pancreatic j**uice is emptied in the duodenal** lumen for digestive and absorptive functions.

This lecture is about the *other* secretory product that's emptied in the duodenal lumen: Bile, and about the pigment which gives bile its yellow colour: Bilirubin.

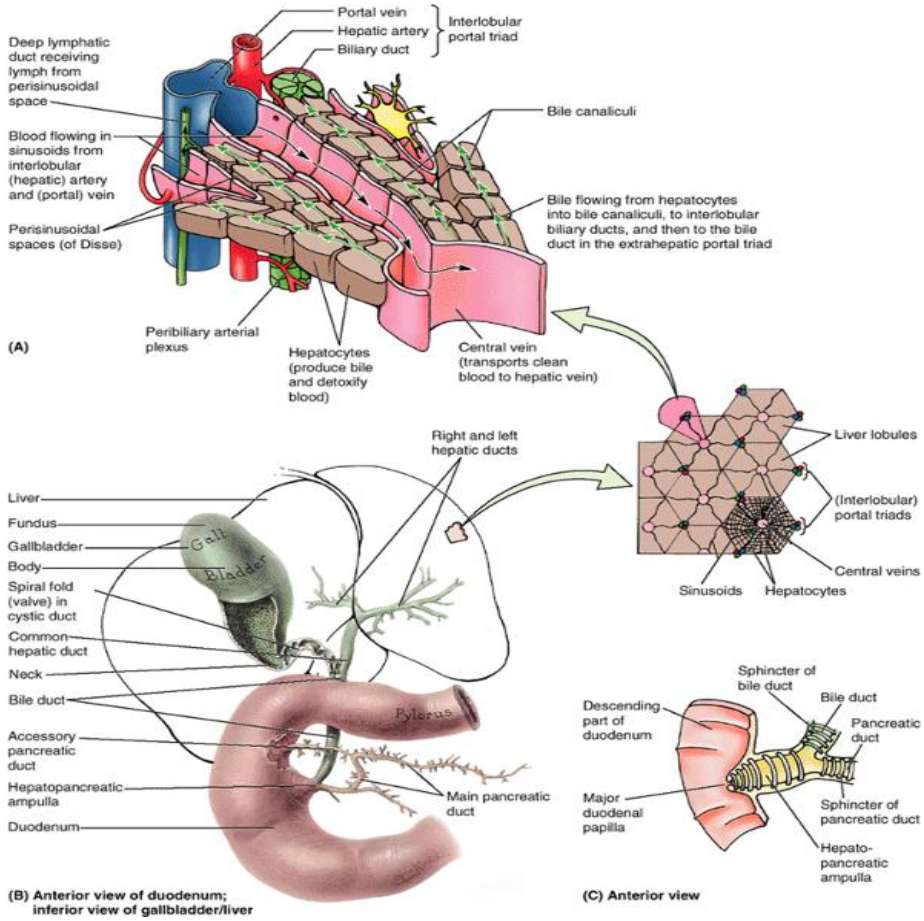
Firstly, let's talk about the liver, the liver is the largest metabolic organ in the body and has a wide variety of functions, our concern in this lecture is its importance in the *digestive system*: secretion of BILE SALTS. (600-1000 ml/day)

What is bile?

Bile is a yellow-green fluid that is made and released by the liver, stored in the gallbladder and passes through the common bile duct into the duodenum where it helps digest fat.

Principal components of bile: cholesterol, salts/acids, phospholipids (lecithin), ions, water and the pigment bilirubin.

Pathway of bile:



- Initially: hepatocytes secrete bile -> Drain into bile canaliculi
  -> Drain to biliary duct (part of the interlobular portal triad)

  -> Drain to **common bile duct** (extrahepatic portal triad)

- **From the common bile duct, bile is either**:

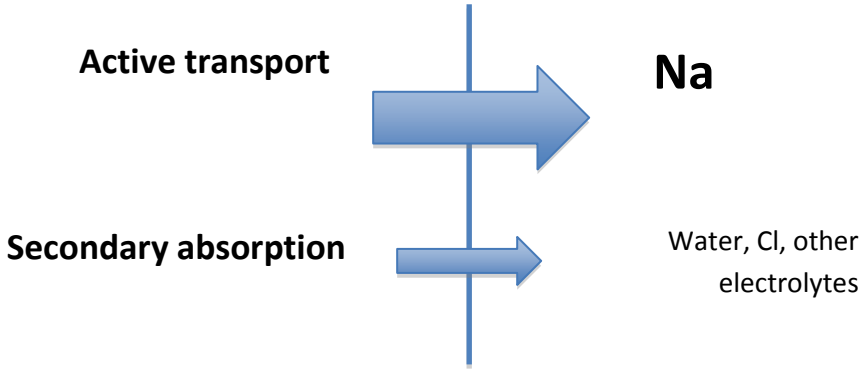
- Emptied directly into duodenum during digestion of meals (*1st portion*) or,
- Flows through cystic duct to gall bladder where it is **stored** until needed in the duodenum (*2nd portion*)

In the gall bladder:

Up to **60 ml** of bile can be stored.

To strengthen the bile's effect in emulsifying fat, the gallbladder concentrates the bile every 12 hours of bile secretion (450 ml approximately) up to 5 folds and could go up to 20 folds in some conditions.

Concentration of bile:



(Gallbladder mucosa, IN -> OUT)

Emptying of the gallbladder means:

Contraction of its wall + relaxation of sphincter of Oddi

What controls emptying of gallbladder?

- Hormonal control: CCK, Secretin, Estrogen

- Neural control: via **vagus** nerve, parasympathetic stimulation (and in opposition, sympathetic will *decrease* emptying)

(The concentration of bile in hepatic portal blood controls its own synthesis and this is called feedback control)

Function of bile salts:

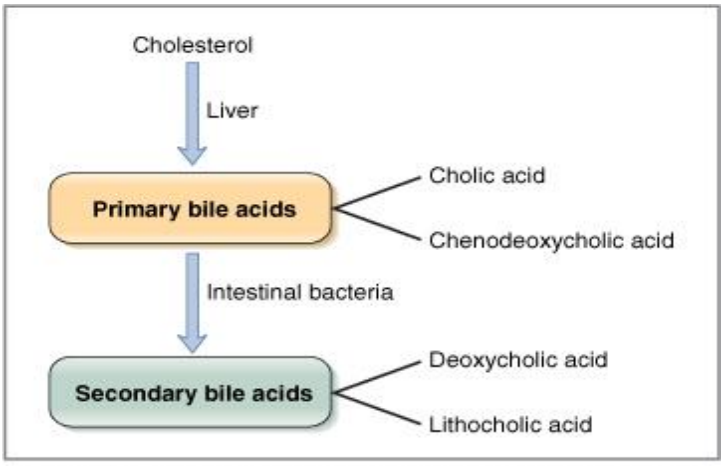
1/ Helps in break down of FAT; *digestion* & its *absorption* from small intestines.

2/ Aids in excretion of waste products from blood such as cholesterol, alkaline phosphate and most importantly here: BILIRUBIN

What is the precursor substance of bile acids?

Cholesterol,

This is what happens: *important figure*



Additional points:

*1ry bile acids have hydroxyl groups + a carboxyl group

** 1ry bile acids conjugate to taurine or glycine

*** Intestinal bacteria dehydroxylate 1ry bile acids to 2ry

At neutral pH bile acids are ionized and are called bile SALTS.

Bile salts	**Bile acids**
More polar	Less polar
Difficulty penetrating cell membrane	Easier
Poor absorption by small Intestines	Better absorption

Enterohepatic circulation

It is the recycling mechanism of BILE SALTS between liver and small intestines.

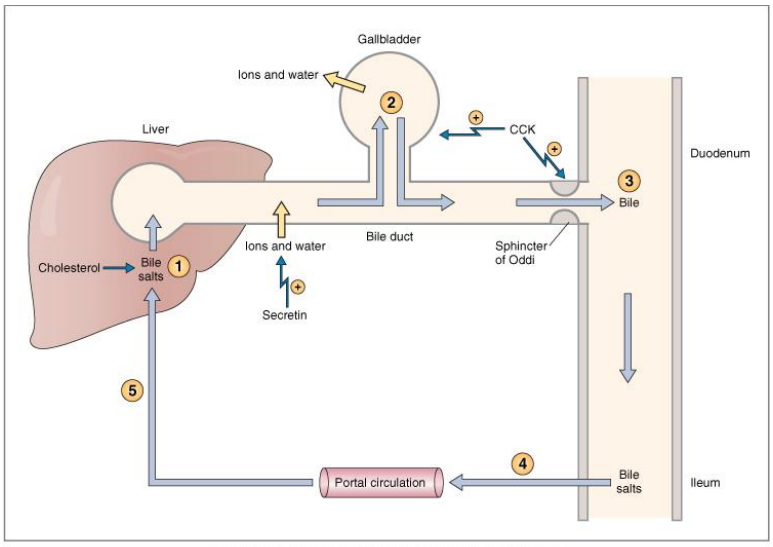
What happens?

In small intestines 94%* of the bile salts are reabsorbed** into blood (*diffusion through mucosa in early portion and active transport in distal ileum*) -> enter portal blood -> pass back to liver -> absorbed almost entirely by hepatocytes*** and are resecreted into bile.

*(The rest are secreted in feces and are replaced by new amounts formed in liver cells)

** FIGURE 1

*** FIGURE 2



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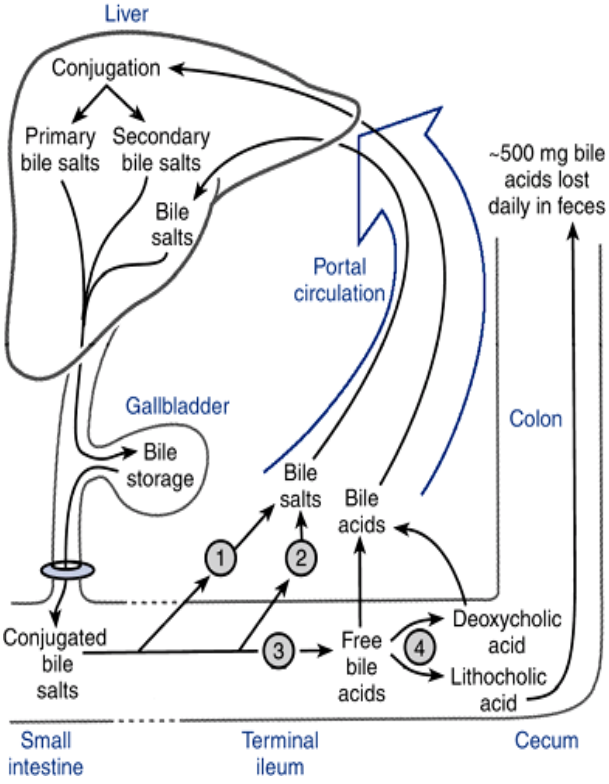
Here, secretin activates the walls of the gallbladder to release more water and ions, meaning a *less* concentrated bile. While in the gallbladder water and ions *get out;* more concentrated bile.

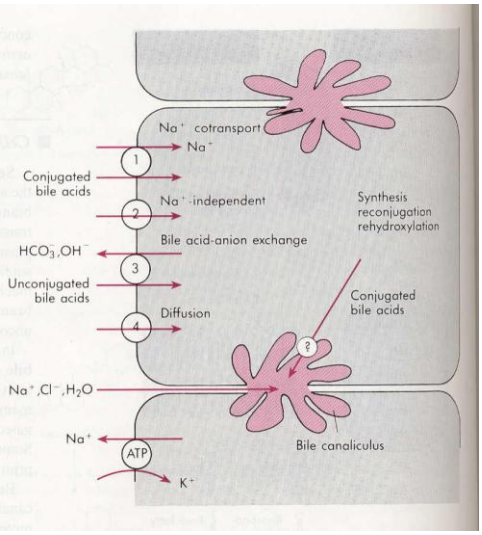
Pathways of reabsorption



figure#1

1- Passive diffusion
2- Active carrier mediated diffusion
3- Deconjugation of salts to acid
4- Transforming primary to 2ry

When they reach the liver that's what happens:



figure#2

Reabsorption back in the hepatocytes:

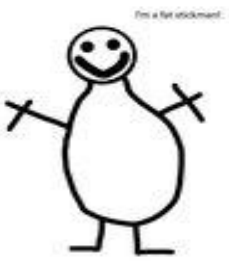
1) Active carried mediated process
2) Facilitated diffusion
3) Exchange (bile & HCO3) or (bile & OH)
4) Passive diffusion

Total bile acid pool: Is the total amount of bile acids in the body, (*ALL: 1ry, 2ry, conjugated, unconjugated*) at any time.

In a healthy adult this ranges between **4-6 g.**

So, the small amount of bile acid pool is good enough for supplying body's needs for lipid absorption by undergoing the *enterohepatic circulation* "cycling" several times per meal,

Light eater: 3-5 cycles/day



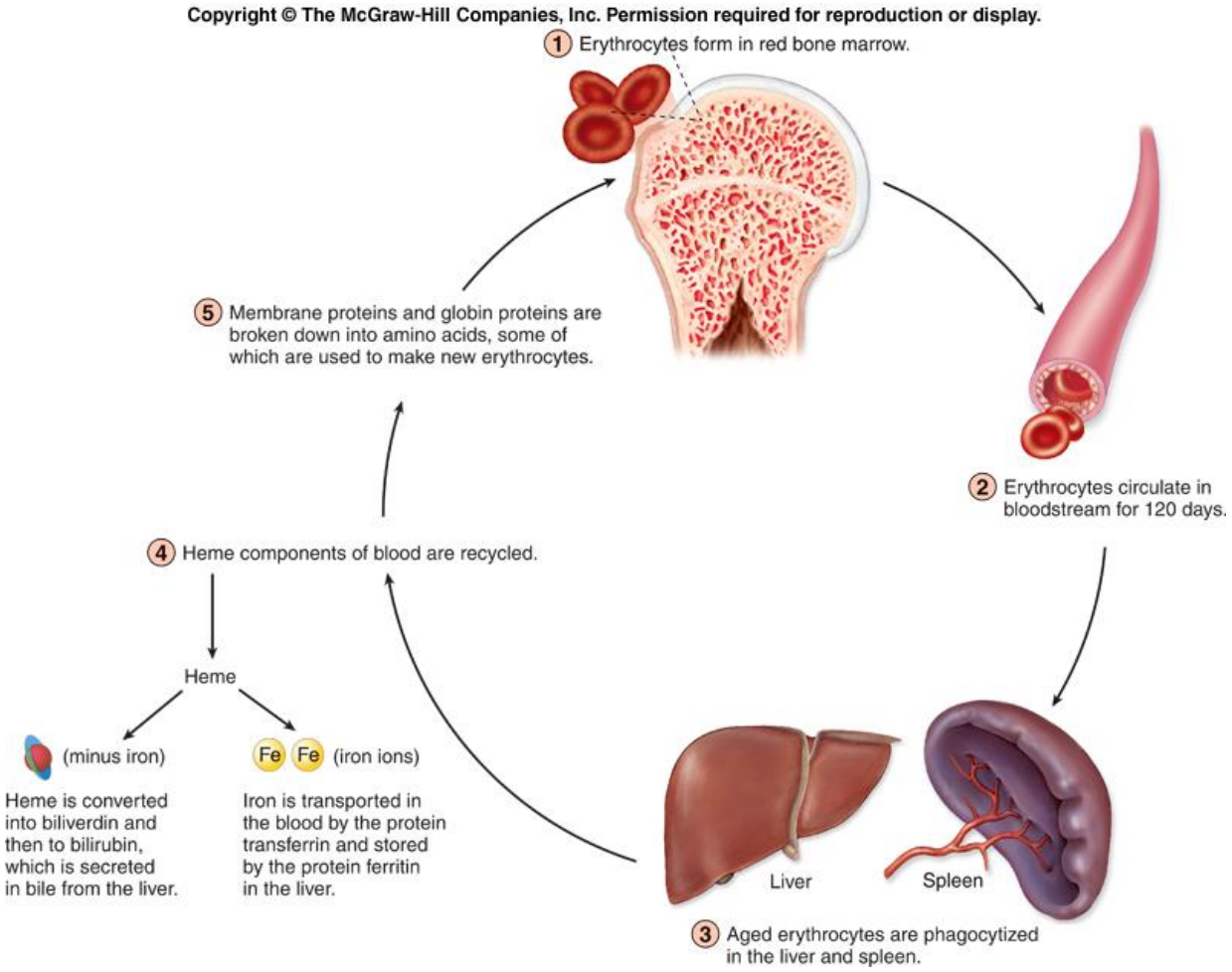
Heavy eater: 14-16 cycles/day

Now, recalling one of the 2 major functions of bile: *excretion* of waste products including: bile acids/salts, cholesterol, ions and water, phospholipids (Lecithini) and bile pigment: **BILIRUBIN**.

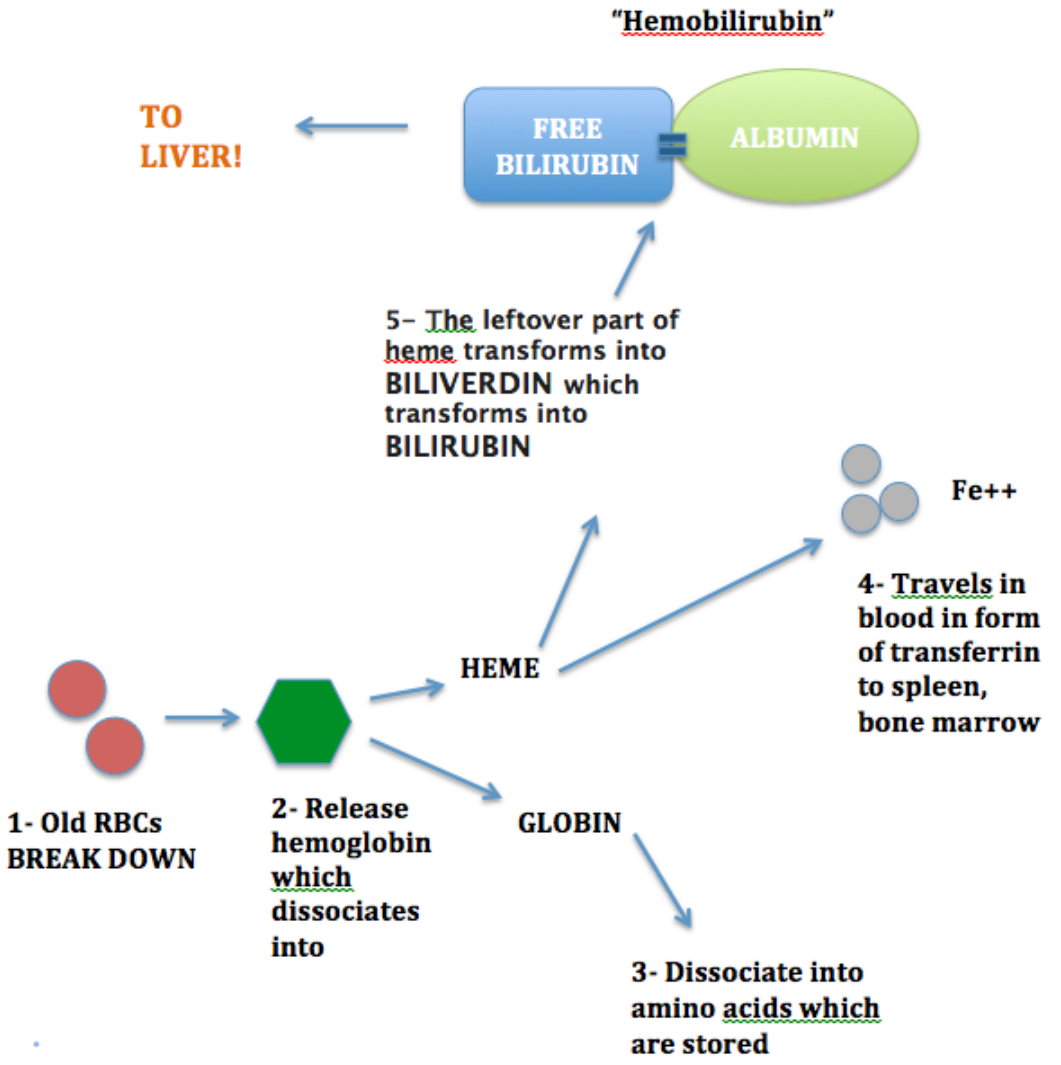
What is bilirubin?

It is a waste product of RBCs breakdown, yellow, toxic and highly soluble in all cell membranes.

Red blood cells life cycle:



Before reaching the liver, in the circulation, bilirubin is called "unconjugated" or hemobilirubin, here's what happens:

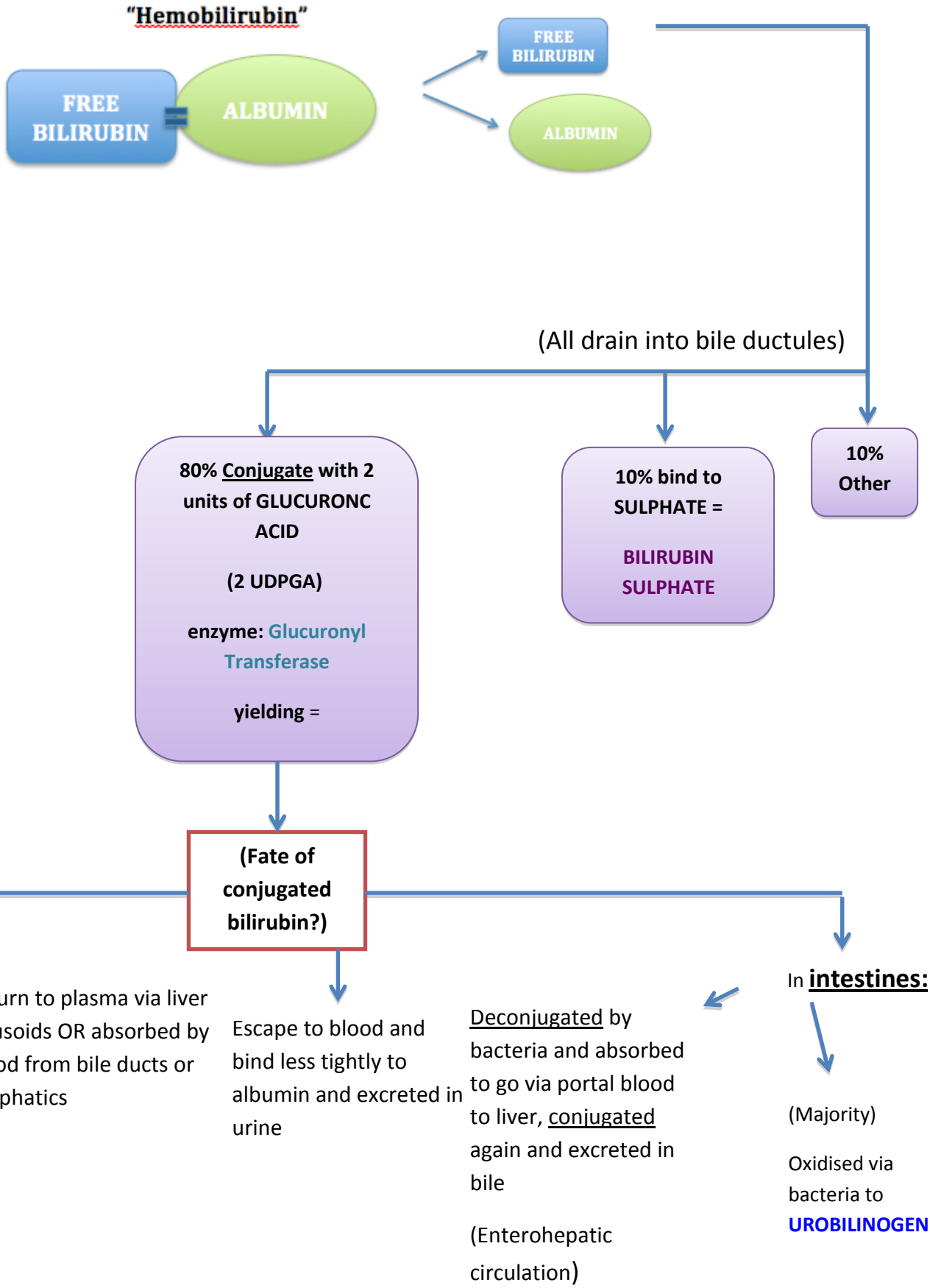


Free bilirubin immediately binds to plasma proteins (albumin or globulin) and travels to the liver.

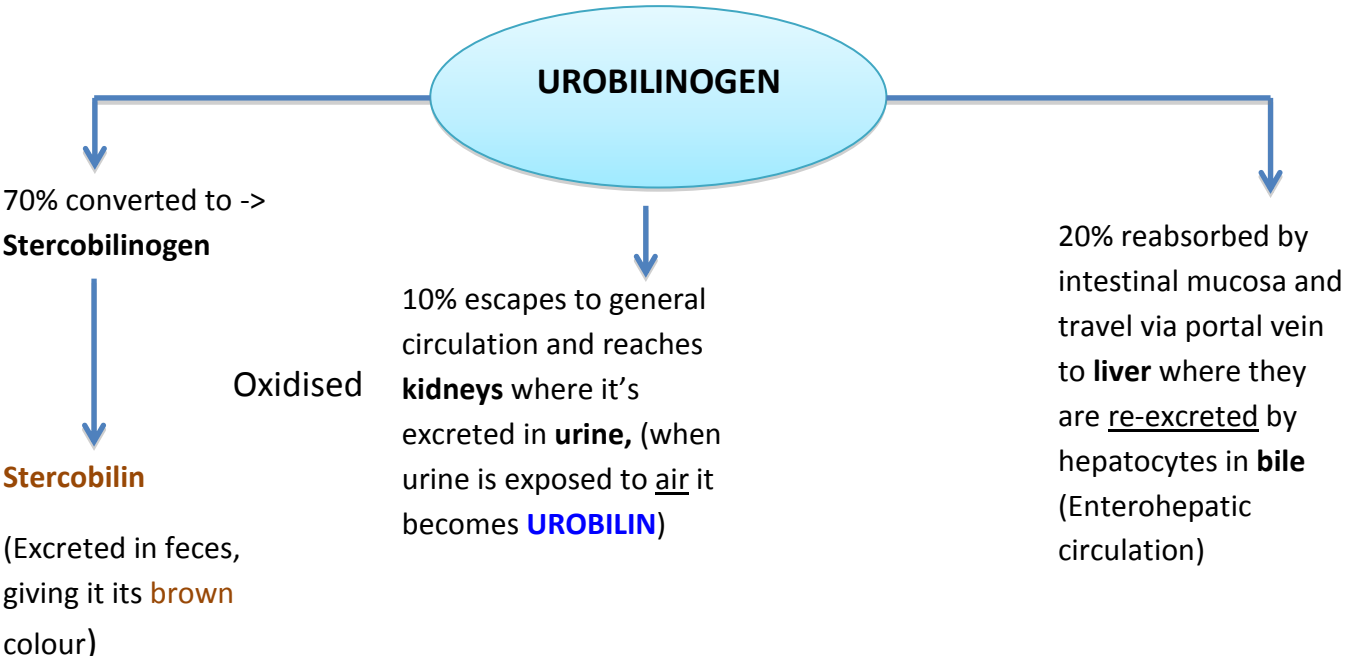
This unconjugated bilirubin is lipid-soluble and must be made water-soluble to be excreted.

Okay, so upon reaching the liver, unconjugated bilirubin "hemobilirubin" is *absorbed* into hepatocytes with the help of receptor proteins, and is *trapped* inside by **Y** and **Z** proteins.

Inside hepatocytes:



Urobilinogen is *colourless* and *highly soluble*, what happens next?



{Instant Feedback}:

- What was the major product that bound to free bilirubin inside hepatocytes?

Glucuronic Acid

- What is the level of its absorption in the intestines?

It is poorly absorbed.

- And what was the enzyme that catalyzed the reaction?

Glucuronyltransferase

Let's talk about glucuronyltransferase,

Present in: Smooth Endoplasmic Reticulum

Function: Catalyzes the formation of glucuronides, e.g.

What other substances my also increase the activity of Glucuronyltransferase?

Steroids, antihistamines, anticonvulsants & barbiturates all cause marked proliferation of SER in demand for the enzyme's activity.

Criggel-Najjar Syndrome

It is a disorder caused by deficiency of glucuronyltransferase, leading to high levels of unconjugated bilirubin.

Treatment: Phenobarbital

Back to bilirubin,

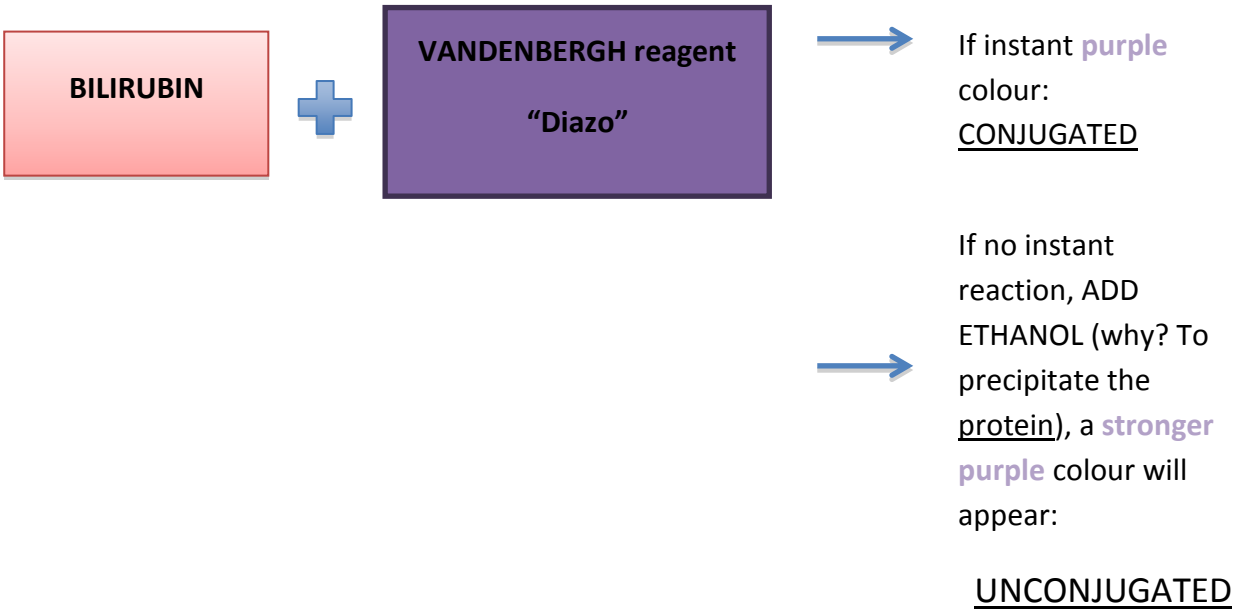
What are the differences between conjugated and unconjugated bilirubin?

Conjugated bilirubin/ Cholebilirubin	**Unconjugated bilirubin/ Hemobilirubin**
Water-soluble	Lipid-soluble
Loosely bound to albumin	Tightly bound to albumin
Non toxic	Toxic
Excreted in urine	Excreted in feces (after conversion to urobilinogen)
Low concentrations in blood	Main form of bilirubin in blood
Direct	Indirect

Conjugated bile acids are usually found as salts of many cations because they are ionized more quickly than unconjugated bile acids.

E.g. Na glycocholate

How to differentiate between conjugated and unconjugated bilirubin?



What is a biphasic reaction?

It is a reaction where vandenbergh reagent is added on a mixture of *both* conjugated and unconjugated bilirubin

What do we see?

At first purple colouration appears and after adding alcohol a *stronger* purple colour is seen.

Values:

Bilirubin load daily/adults = **250-300 mg**

Serum bilirubin concentration = **0.3-1.2 mg/dL**

What happens if the serum bilirubin exceeds normal levels?

If it exceeds **2.0 mg/dL**; hyperbilirubinemia occurs; Jaundice.

{Note: I will briefly talk about jaundice here but please check the next lecture for further elaboration.}

What is jaundice?

It is when bilirubin is formed more rapidly than it can be excreted leading to its accumulation in blood. Clinically, patients' skin, sclerae and mucous membranes appear *yellowish*.

What causes jaundice?

There are 3 different ways:

-**Prehepatic**: Problem occurs *before* the liver (excessive breakdown of RBCs resulting in the liver being presented with more bilirubin than it's capable of excreting)

-**Hepatic**: problem is *in* the liver (e.g. decrease hepatocyte uptake, impaired conjugation, decrease hepatocyte excretion of bile glucuronides)

-**Posthepatic**: problem occurs *after* the liver (e.g. obstruction; gallstones)

What are gallstones?

Gallstones are hard, dust-like deposits that form *inside* the gallbladder. Their sizes vary from very tiny to as large as a golf ball! It is due to increase in bile components.

Here are the causes:

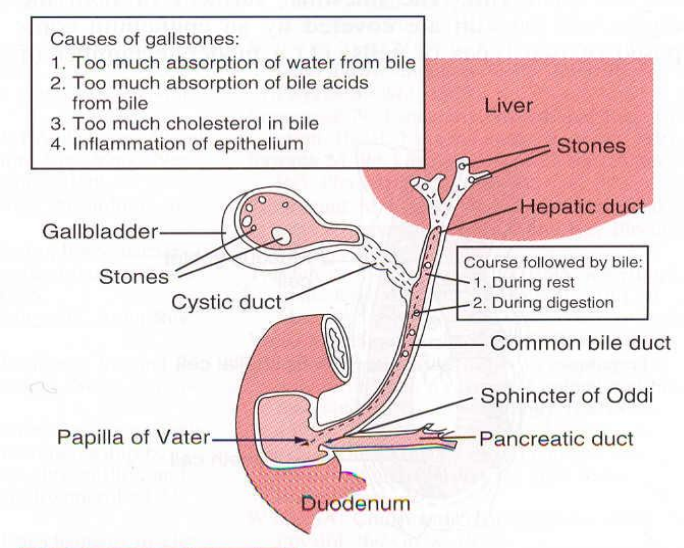


FIGURE 64–12
Formation of gallstones.

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