Physiology of *Gastrointestinal System* (L7)

Physiology of Bile Salts & Enterohepatic Circulation

Dr. Hayam Gad
A. Professor of Physiology
College of medicine, KSU

Learning Objectives

01 Functions of the bile and stages of its secretion.

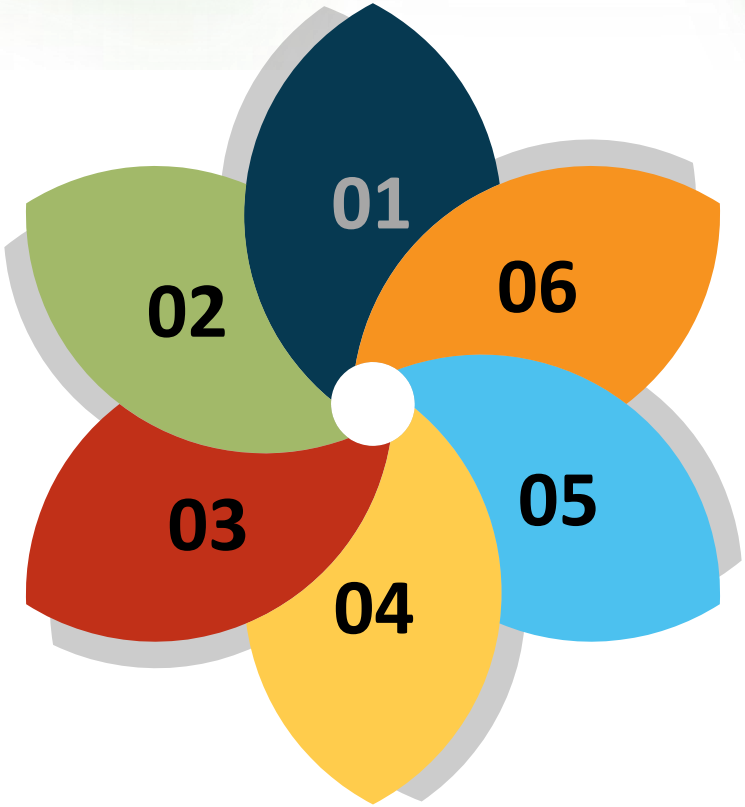
02 Characteristics & main constituents of bile.

03 Functions of gall bladder.

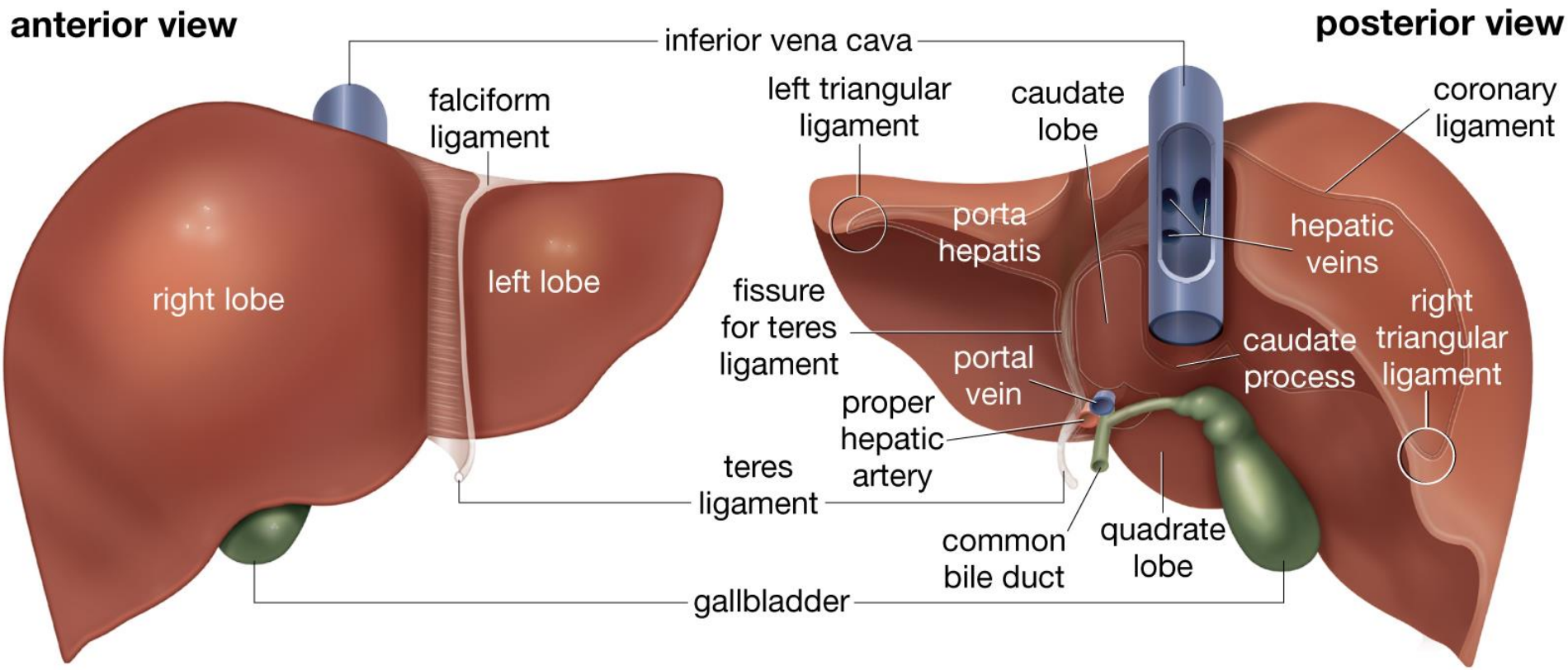
04 Control of biliary system.

05 Enterohepatic circulation of bile salts.

06 Absorption, uptake & functions of bile acids.

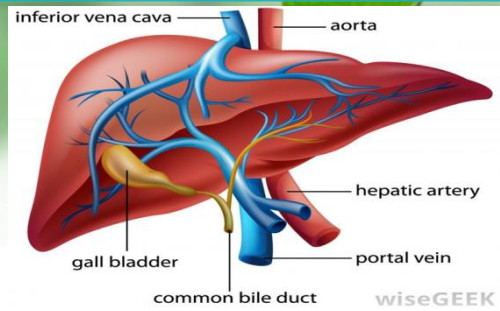


Liver Anatomy



The Liver

-Is the largest internal organ (≈ 2.5% of an adult's body weight).
-Receives 25% of the cardiac output via the portal vein and hepatic artery (dual blood supply).



- Takes up, stores, and distributes nutrients and vitamins.
- Plays an important role in maintaining blood glucose levels.
- Synthesizes many of the circulating plasma proteins.

-Regulates the circulating blood lipids by the amount of very low–density lipoproteins (LDL) it secretes.
-Performs important endocrine functions(as IGF-1, Angiotensinogen, Thrombopoietin).

-Continuously secretes bile, which after storage in gall bladder is discharged into duodenum.
-Takes up numerous toxic compounds & drugs from portal circulation.
-Serves as an excretory organ for bile pigments, cholesterol & drugs.

The Main Digestive Function of The Liver

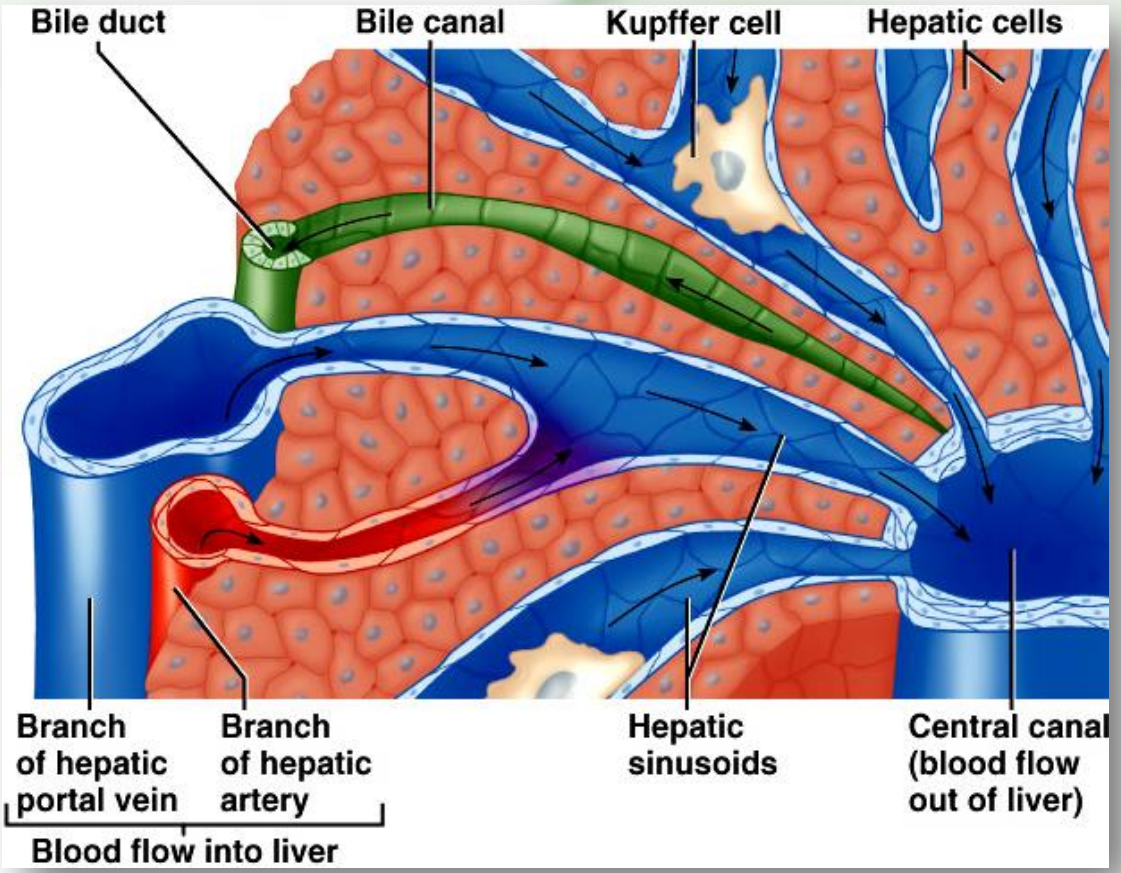
The main digestive function of the liver is the secretion of bile

Bile plays an important role in fat digestion and absorption by its contents of bile salts

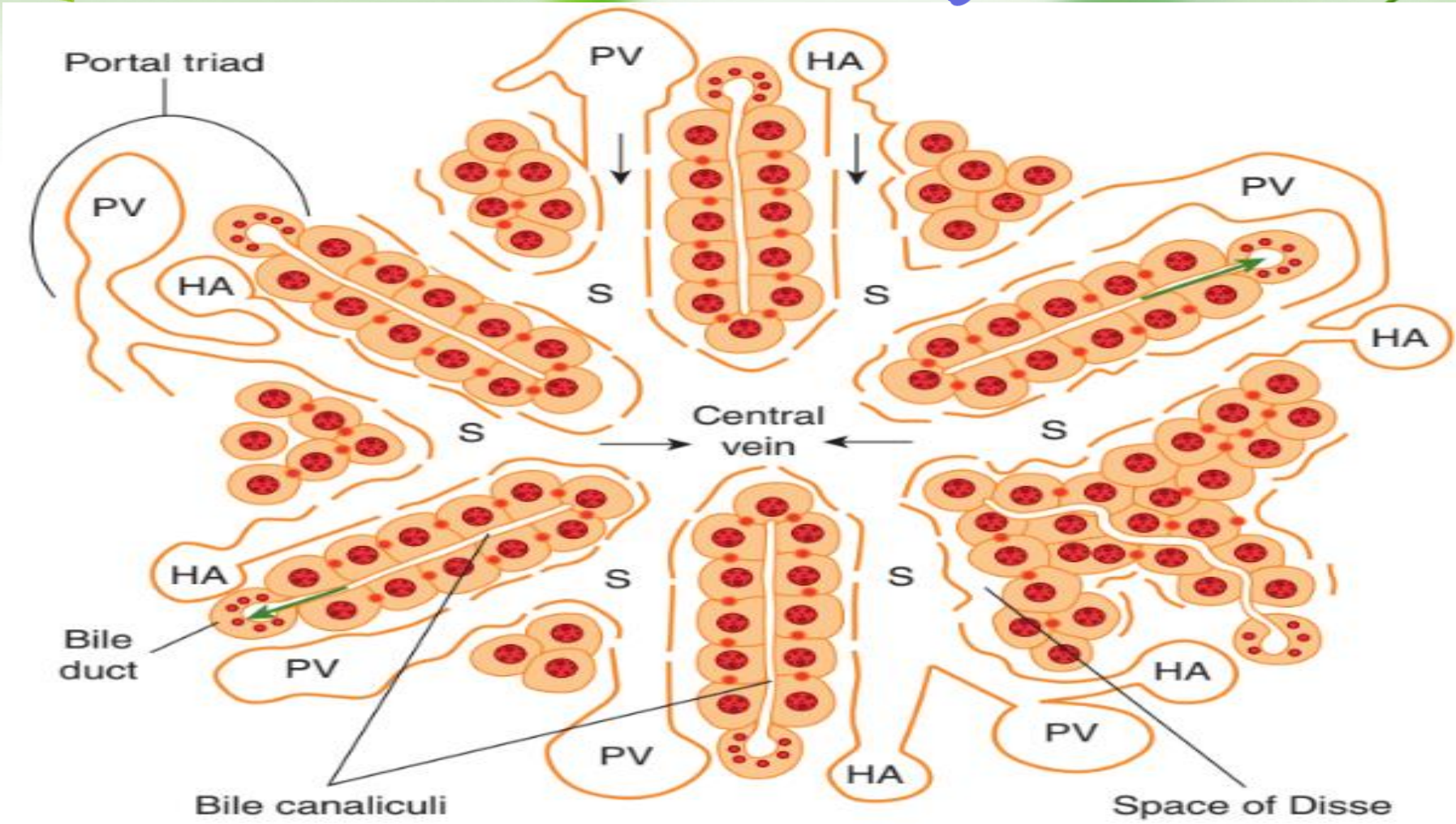
Bile serves as a means for excretion of waste products (especially bilirubin) from the blood

Bile is secreted in two stages:

- The initial portion is continually secreted by the hepatocytes.
- It is secreted into bile canaliculi that originate between the hepatic cells.
- Hepatic Bile: Isotonic secretion, with high Na^+, Cl^- and HCO_3^- and low K^+ and Ca^{2+}.
- The bile flows in the canaliculi toward the hepatic duct and common bile duct.

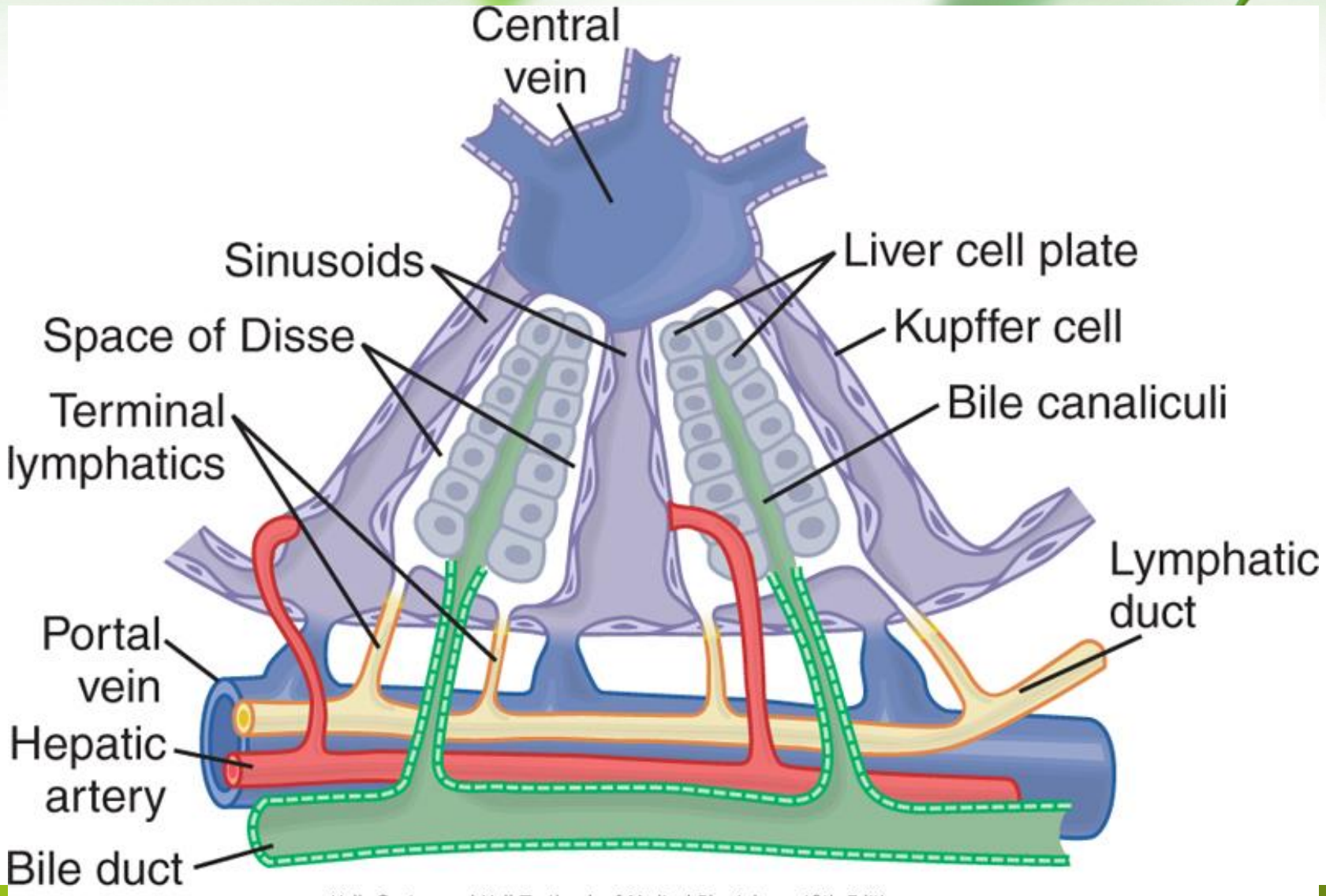


Liver Anatomy

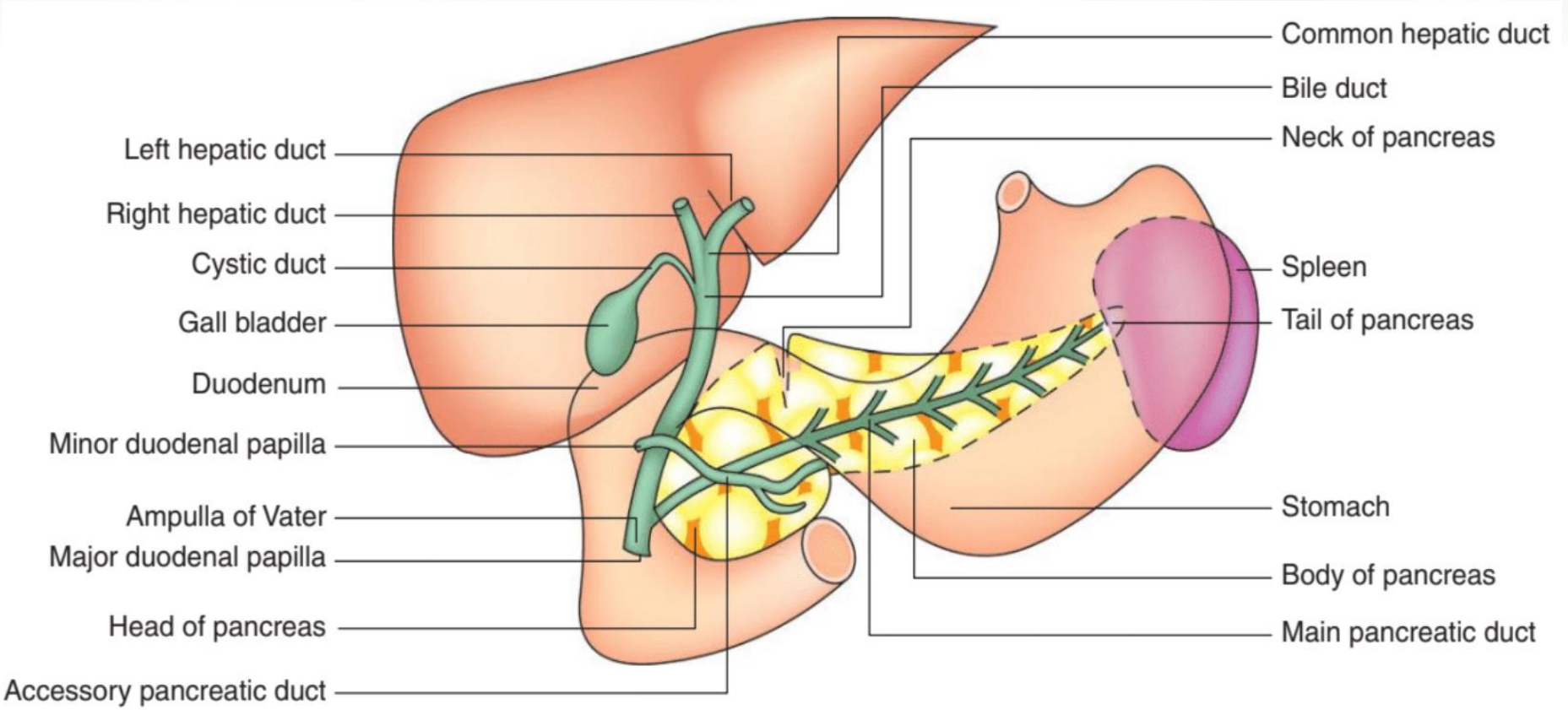


PV: Portal Vein, HA: Hepatic artery, S: Sinusoids

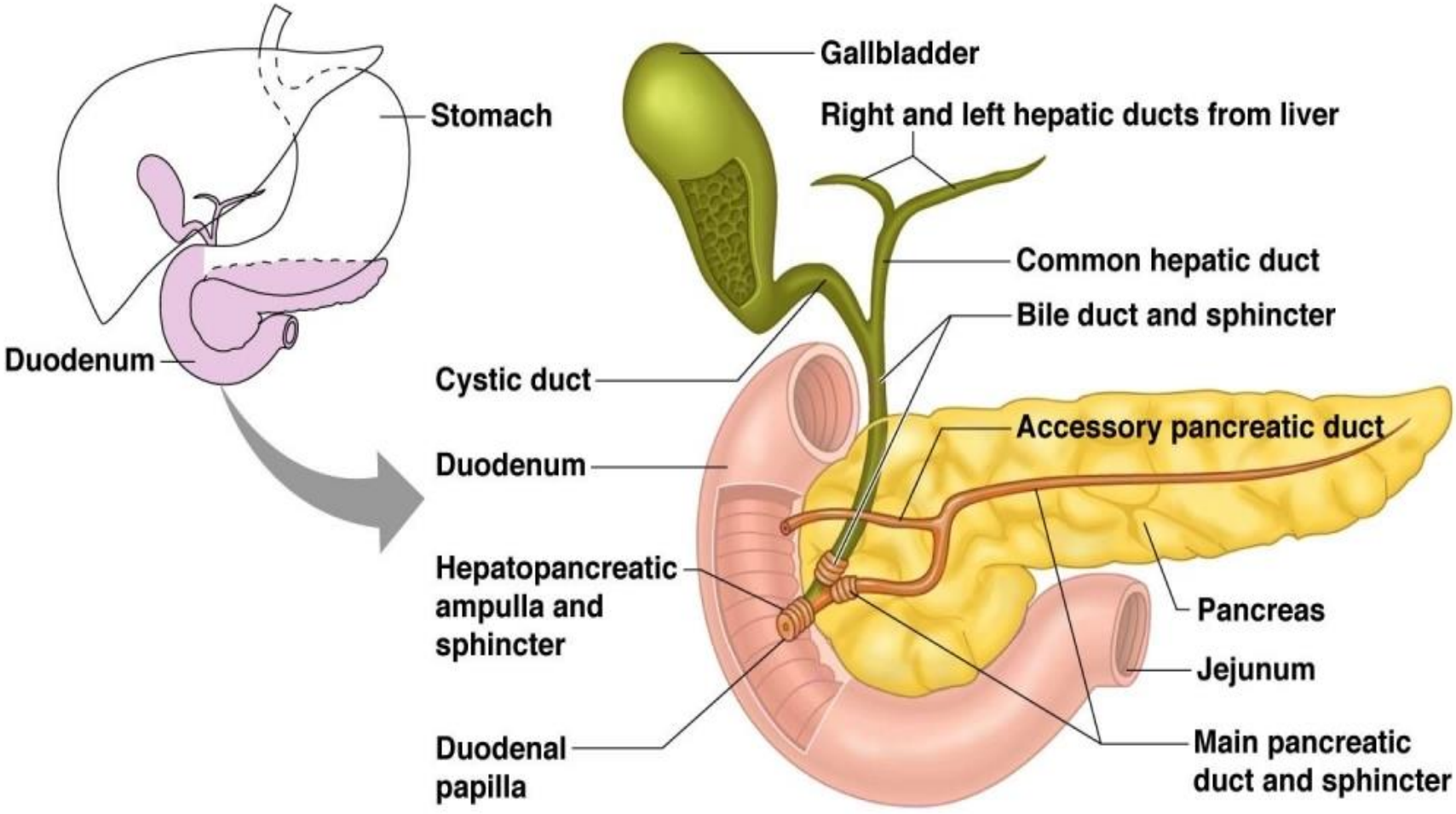
Bile Canaliculi & Ducts



Biliary Tree Anatomy

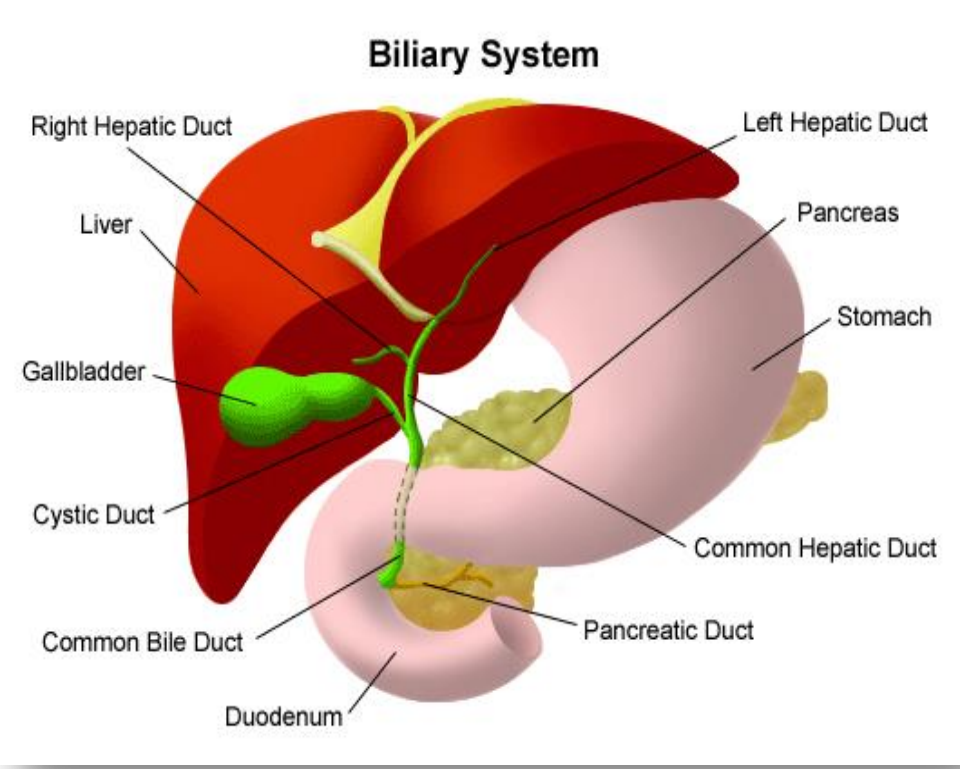


Biliary Tree Anatomy



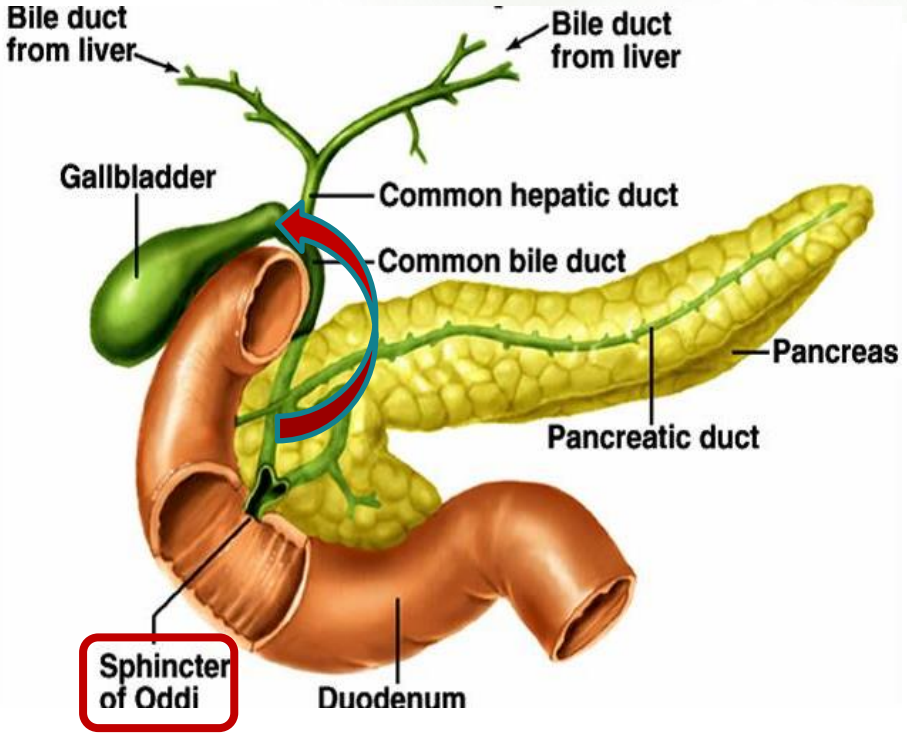
Bile is secreted in two stages: (Cont.)

- From the common bile duct, bile either empties directly into the duodenum or is diverted through the cystic duct into the gallbladder
- Gallbladder bile is the second portion which is added to the initial bile secretion.
- Gallbladder bile: high bile acid anion and Ca^{2+} ; but low Na^{+} , Cl^{-} , HCO_3^{-} and H_2O.



Where the Common Bile Duct Opens

- The common bile duct open into the duodenum in company with the pancreatic duct at the ampulla of vater.
- This opening is guarded by the sphincter of Oddi (choledochoduodenal sphincter).

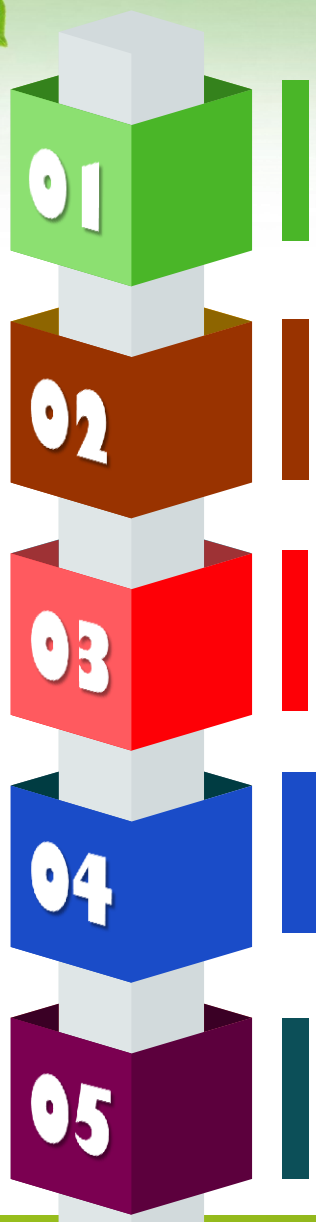


Characteristics of Bile

Bile is	a viscous golden yellow or greenish fluid
pH	It is isotonic with plasma and slightly alkaline (due to $NaHCO_3$). It participates in neutralization of acid chyme delivered from stomach.
Volume	The liver produces about 5 L /day, but only 600-1000 ml/day are poured into the duodenum.

What are the components of bile?

From hepatocytes



Bile acids (bile salts)

(65% of dry weight of bile)

Phospholipids

(As lecithin, 20%)

Proteins (5%)

Cholesterol

(4%), bile is the major route for cholesterol excretion

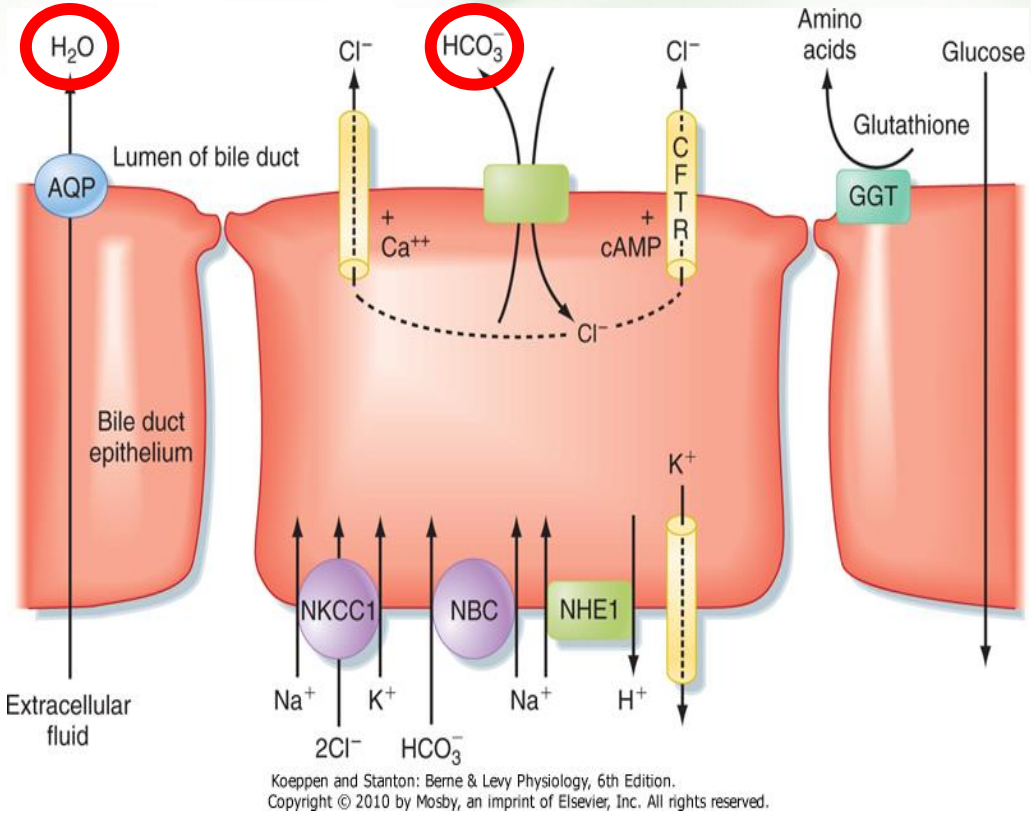
Bile pigments

(as bilirubin, 0.3%)

What are the components of bile? Cont.

From bile ducts epithelial cells:

- Electrolytes mainly HCO_3^- , in addition to H_2O
- These contribute to the volume of hepatic bile.
- HCO_3^- aids in neutralization of acid chyme.



Composition of Bile

From ducts

Aqueous alkaline Solution ($NaHCO_3$)

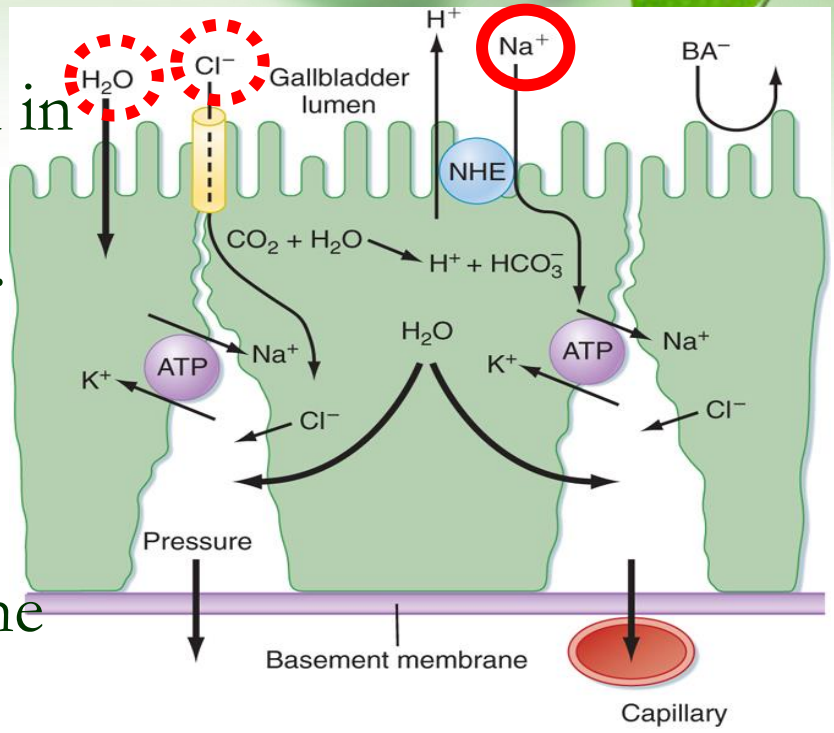
From hepatocytes

Organic constituents

- Bile salts(65%)
- Lecithin (20%).
- Proteins (5%)
- Cholesterol (4%)
- Bilirubin (0.3%)

Storing and Concentrating Bile in the Gallbladder

- Bile is secreted continually by the liver cells and then normally stored in the gallbladder until needed (gallbladder can hold 30 to 60 mL).
- Gallbladder concentrates the bile, during every 12 hours of bile secretion (usually about 450 mL).
- Na^+ is actively transport through the gallbladder mucosa.



- Then, followed by secondary absorption of Cl^-, water, and most other diffusible constituents.
- The tight junctions have low permeability, they resist the passage of Bile Acid anions (BA) out of the lumen.
- Bile is normally concentrated in this way about 5-fold, but it can be concentrated up to a maximum of 20-fold.

Differences Between Hepatic and Gallbladder Bile

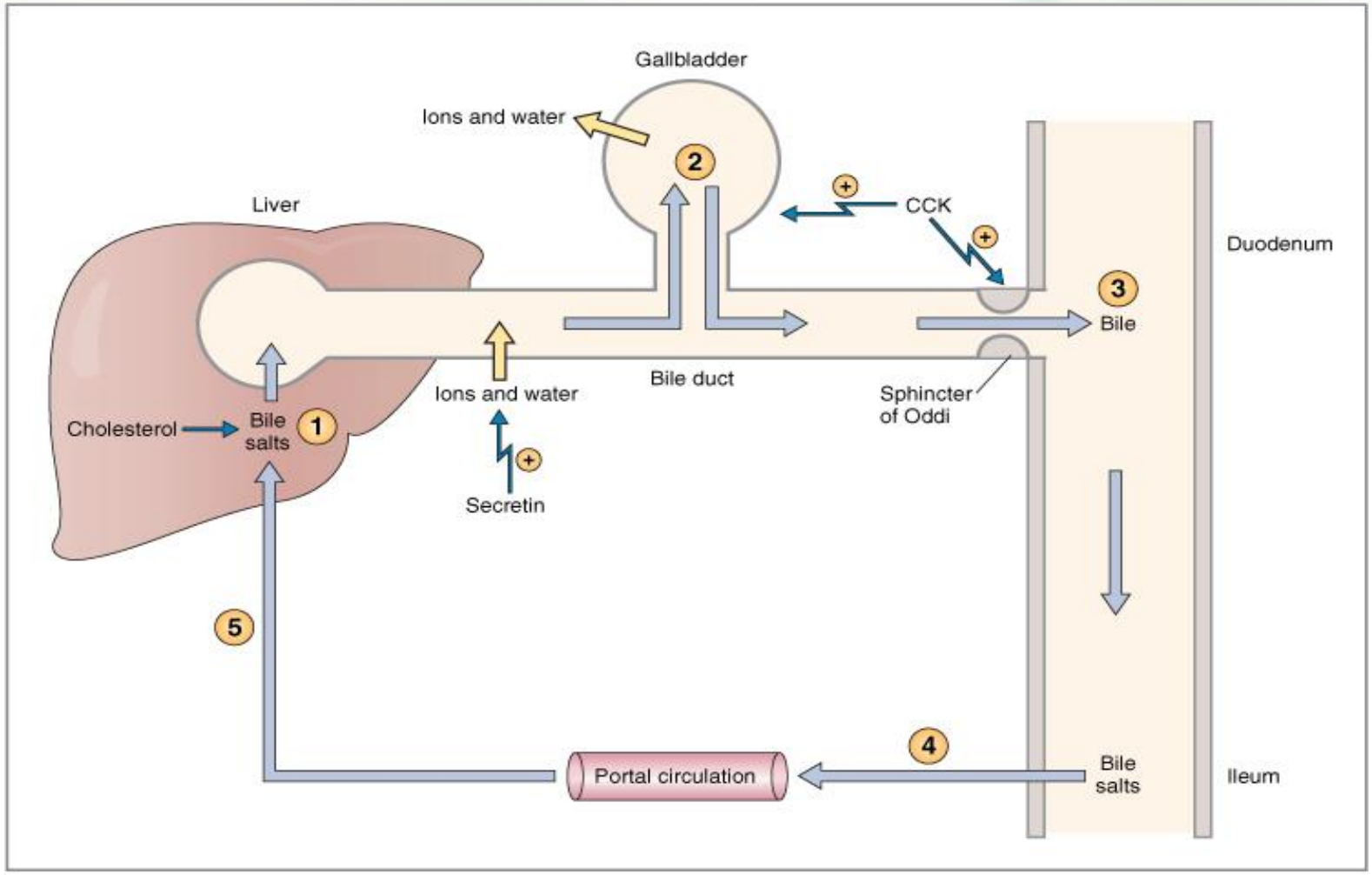
	Hepatic bile	Gall bladder bile
Water (g/dl)	97.5	92
Total solids	2-4 %	11 %
Bile salts (g/dl)	1.1	6
Bilirubin (g/dl)	0.04	0.3
Cholesterol (g/dl)	0.1	0.3-0.9
Fatty acids (g/dl)	0.12	0.3-1.2
Phospholipids	0.5	4
Na^{+}(mEq/L)	145	130
Cl^{-}(mEq/L)	100	25
HCO_3^{-}(mEq/L)	28	10
Ca^{++}(mEq/L)	5	23
K^{+}(mEq/L)	5	12
pH	8.3	7.5

Regulation of Bile Secretion

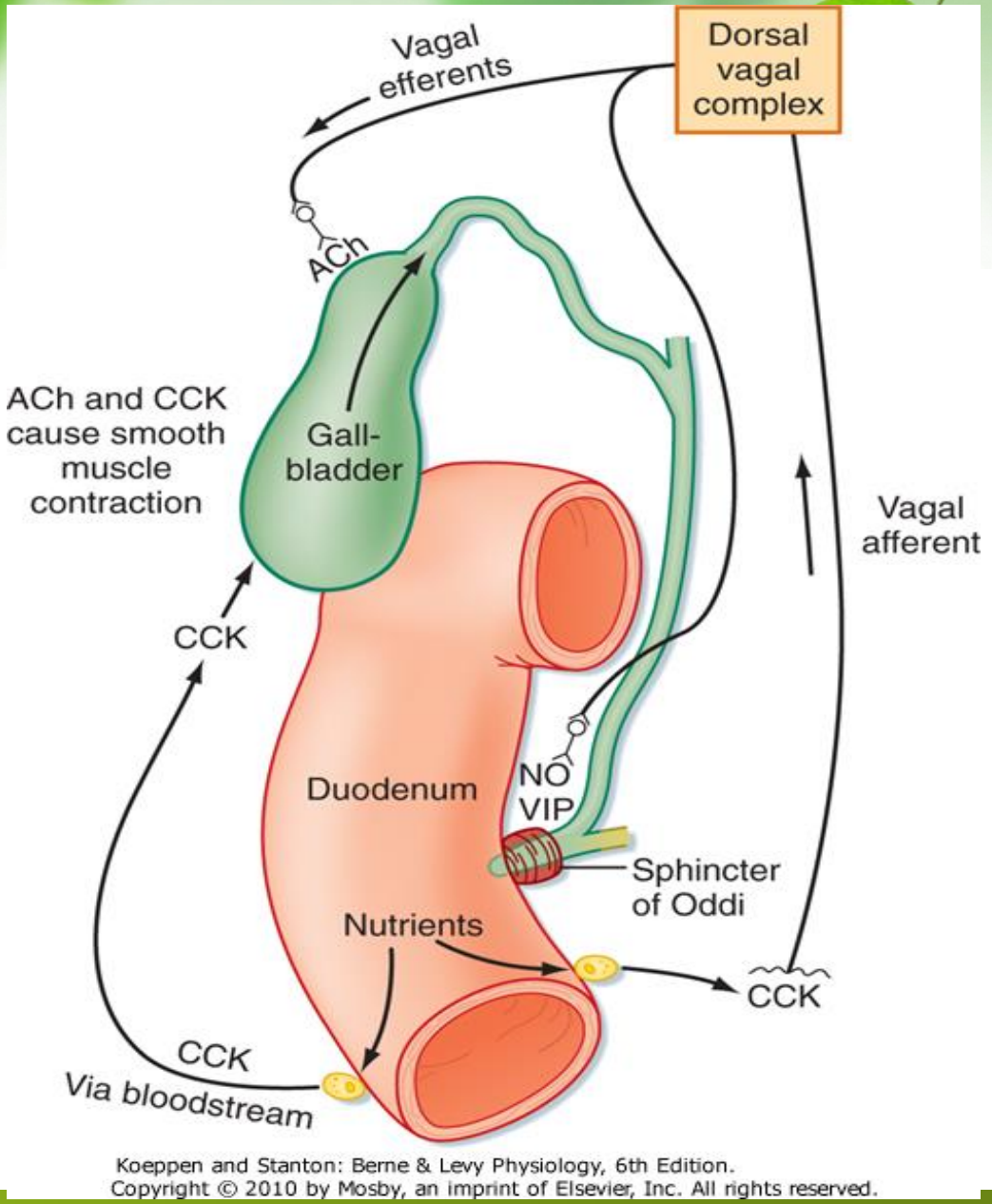
Bile secretion is primarily regulated by a feedback mechanism, with secondary hormonal and neural controls

- ***The feedback control:*** Concentration of bile acid in hepatic portal blood is the major determinant of its synthesis
- ***Hormonal control:*** Secretin, CCK, and estrogen stimulate bile secretion
- ***Neural control:***
  - Parasympathetic (vagal) stimulation results in contraction of the gallbladder and relaxation of the sphincter of Oddi, as well as increased bile formation.
  - {*Bilateral vagotomy results in reduced bile secretion after a meal, suggesting that the parasympathetic nervous system plays a role in mediating bile secretion*}.
  - By contrast, sympathetic stimulation results in reduced bile secretion and relaxation of the gallbladder.

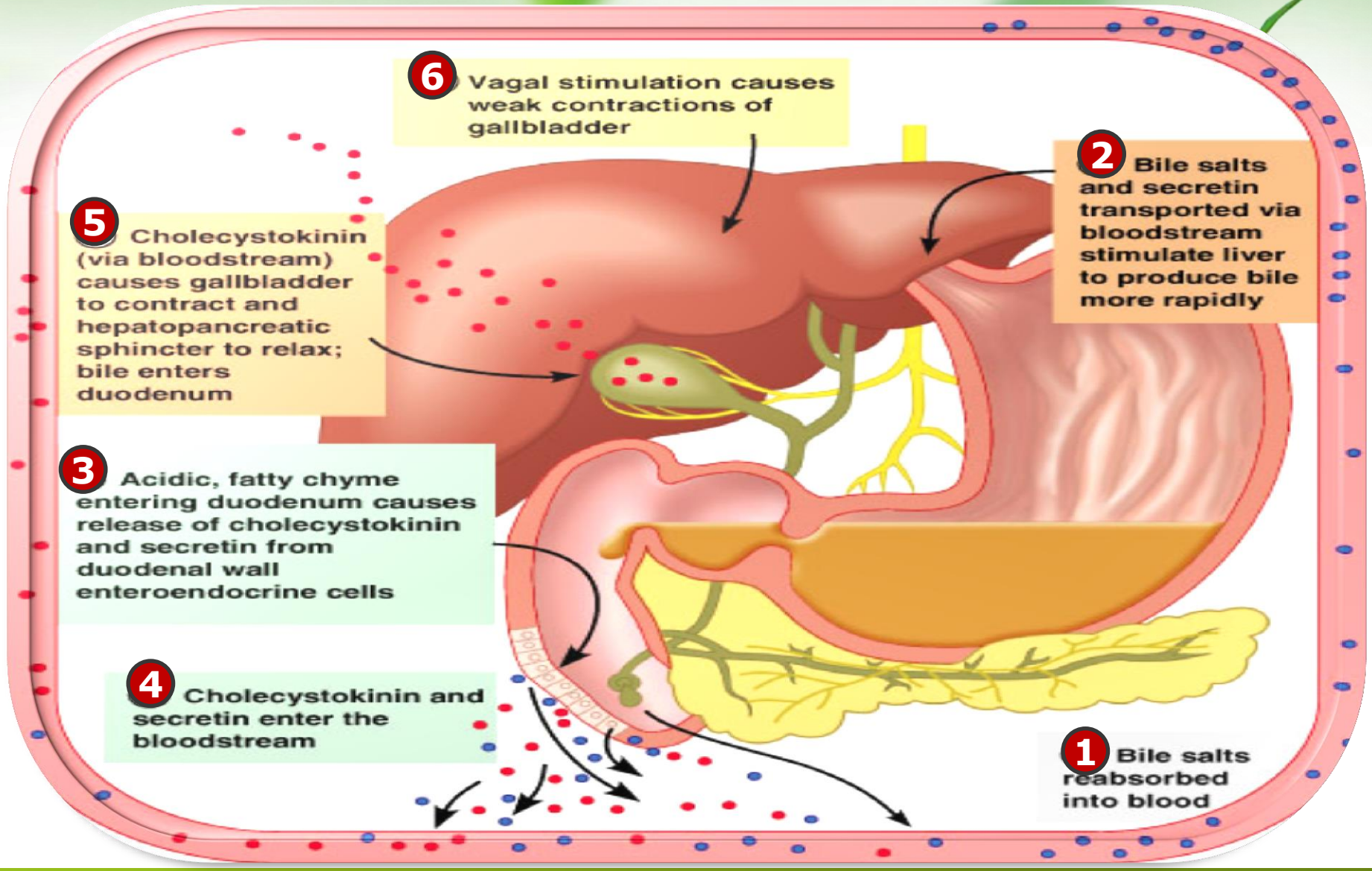
Feedback Control of Bile Secretion through Enterohepatic Circulation of Bile Salts



Neurohumoral Control Of Gallbladder Contraction And Biliary Secretion



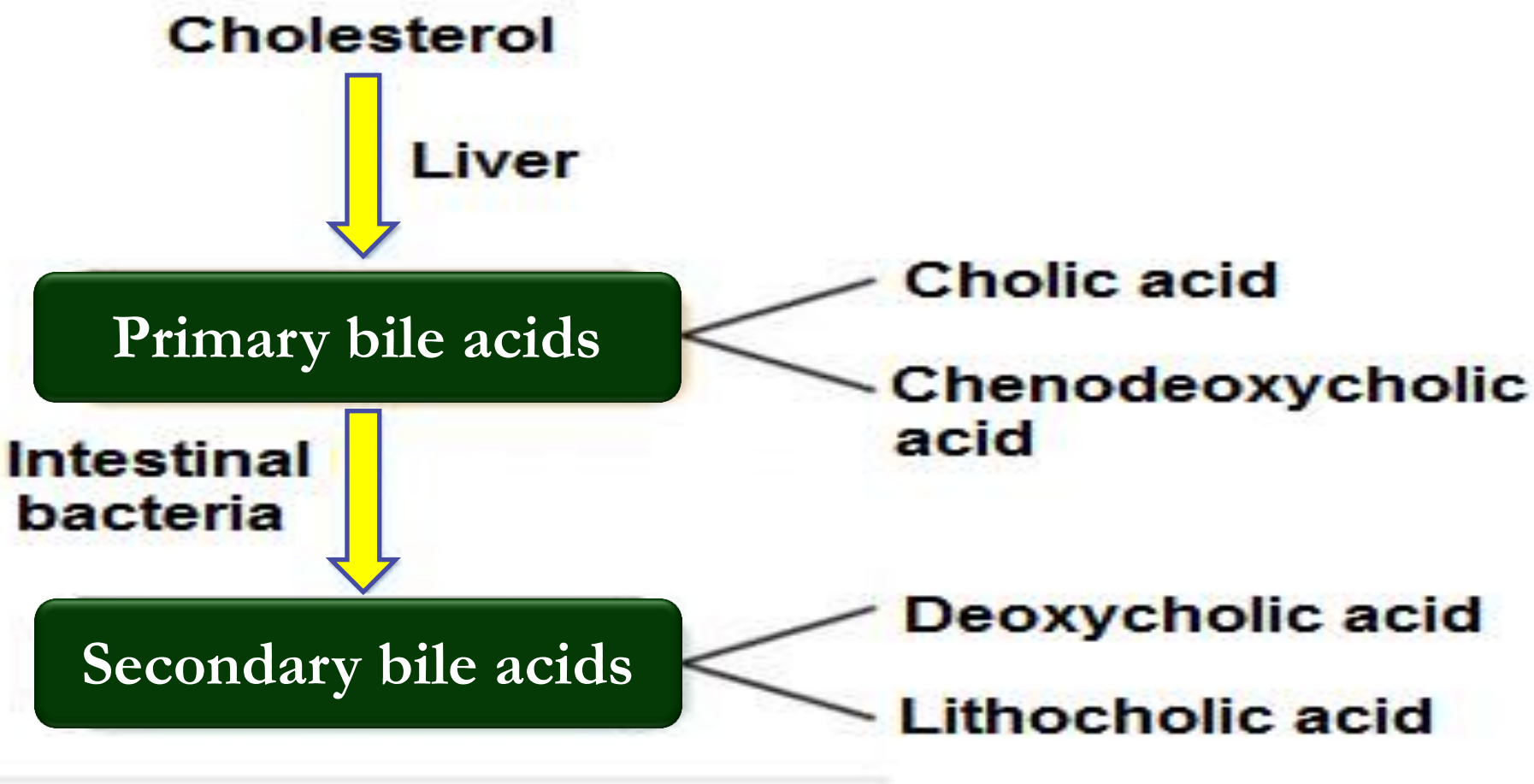
Regulation of Bile Secretion



Bile acids & salts

- **Bile acids are steroid acids, synthesized in the liver from cholesterol by the enzyme *cholesterol 7 α-hydroxylase.* Bile acids include:**
  - Primary: cholic, chenodeoxycholic acids.
  - Secondary: deoxycholic, lithocholic acids.
- **The principle primary bile acids conjugate with glycin or taurine to form glyco and taurocholic bile acids.**

Primary and secondary bile acids

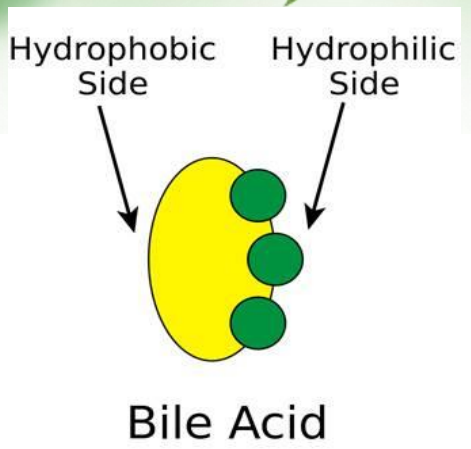


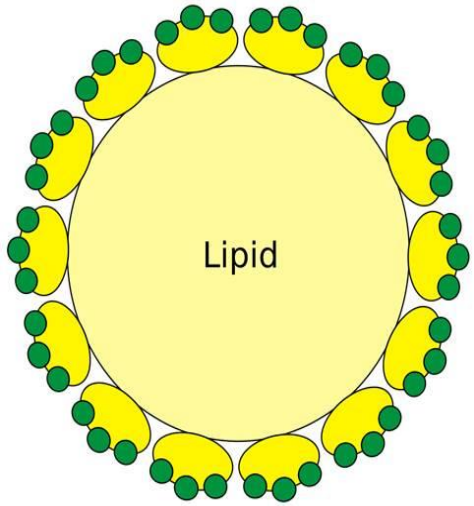
Properties of Bile acids & salts

- At a neutral pH, conjugated bile acids are mostly ionized, more water soluble and are present almost entirely as salts of various cations (mostly Na^+) e.g., sodium glycocholate and are called bile salts.
- Bile salts are much more polar than bile acids and have greater difficulty penetrating cell membranes.
- Consequently, the small intestine absorbs bile salts much more poorly than bile acids.
- This property of bile salts is important because they play an integral role in the intestinal absorption of lipid. Therefore, it is important that the small intestine absorb bile salts only after all of the lipid has been absorbed.

Properties of Bile acids & salts (Cont.)

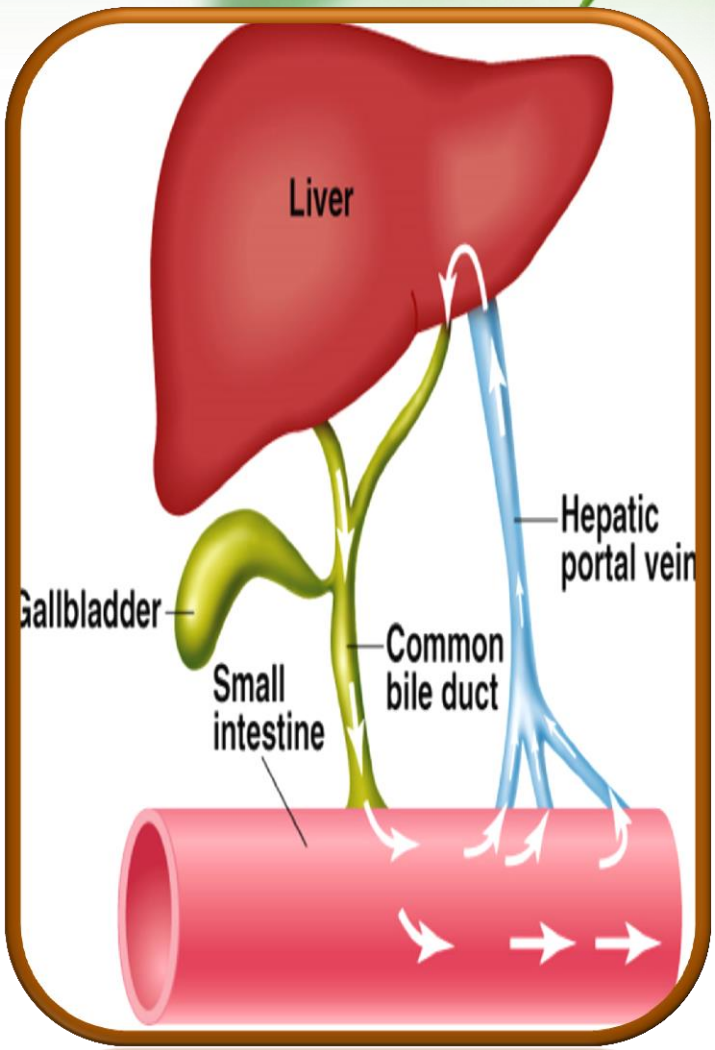
- Bile acids are amphipathic that is having both hydrophilic & hydrophobic domains and tend to form molecular arrangement called micelles.
- In bile acid micelle, the hydrophobic side of bile acid faces inside & away from water. The hydrophilic surface faces outward towards the water.
- Bile acid micelles form when the conc. of bile acids exceed a certain limit ***(critical micelle conc.)***. Above this conc., any additional bile acid will join the micelle.
- Normally bile acid conc. in bile is much greater than critical micelle conc.



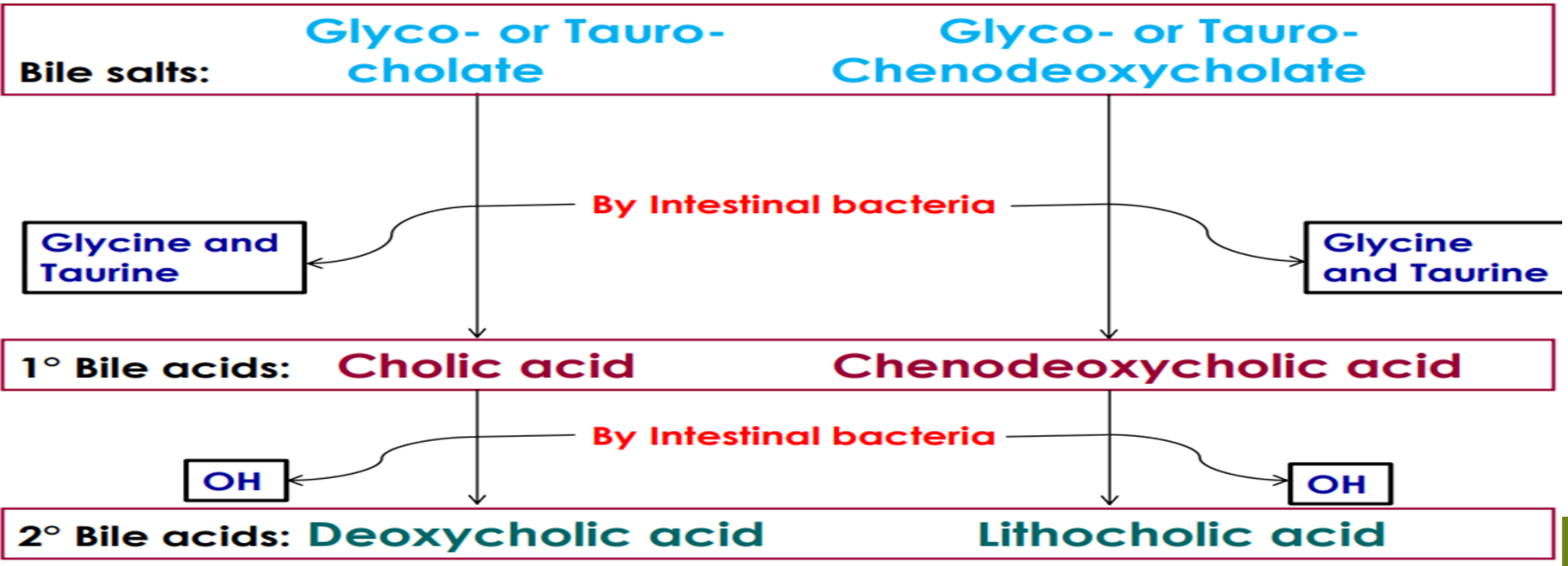


Enterohepatic Circulation of Bile acids.

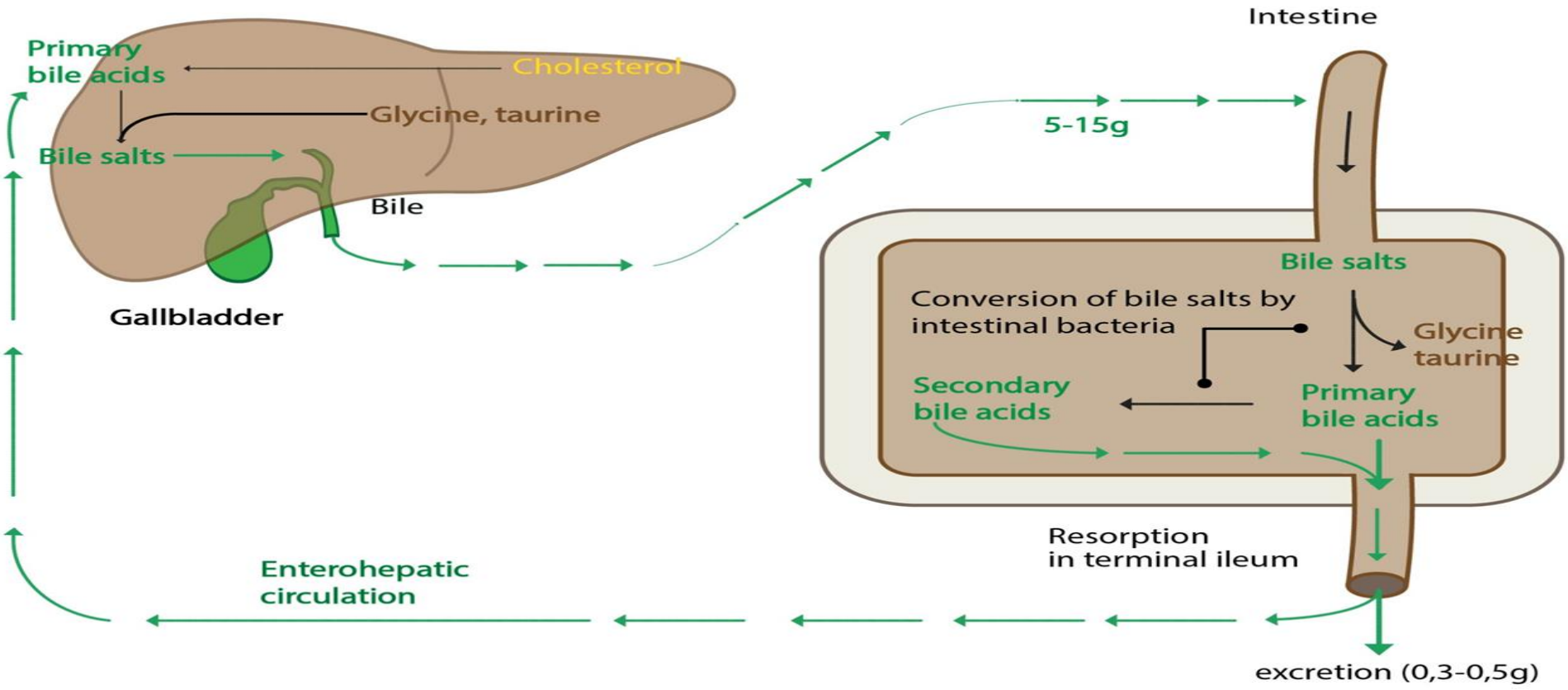
- It is the recycling of bile salts between the small intestine and the liver.
- The total amount of bile acids in the body, primary or secondary, conjugated or free, at any time is defined as the *total bile acid pool*.
- In healthy people, the bile acid pool ranges from 2 to 4 g.



- About 5-15 g of bile acids are poured into the duodenum/day.
- In the intestine, some of bile acids are deconjugated and dehydroxylated in the 7 α position by intestinal bacteria that normally colonize in the digestive tract.
- Dehydroxylation results in the production of secondary bile acids. Cholic acid is converted to deoxycholic acid and chenodeoxycholic acid to lithocholic acid.

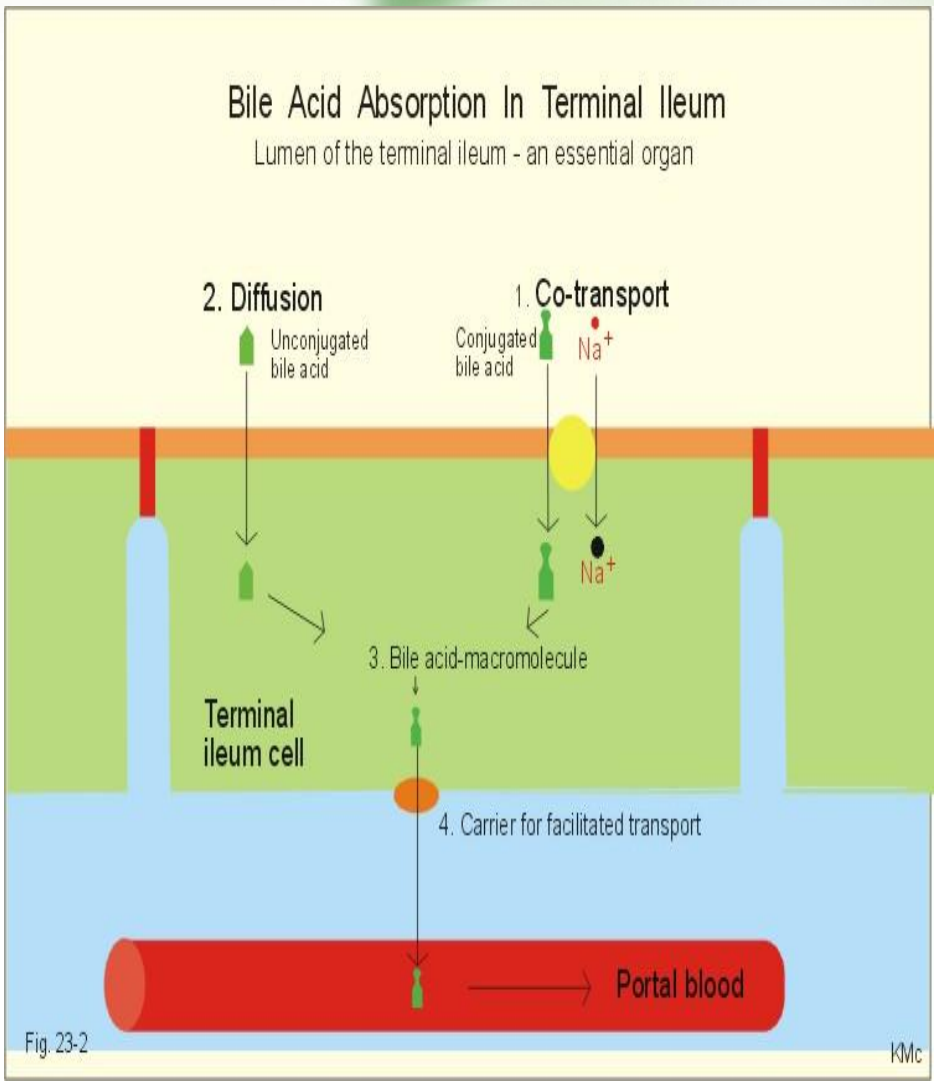


- On reaching the terminal ileum, about 95% of bile acids are absorbed and reach the liver through the portal vein.
- About 0.3-0.5 g of bile acids are lost in feces daily (15-35% of total bile acid pool). These are replaced by new synthesis in liver.



Absorption of bile acids in the small intestinal

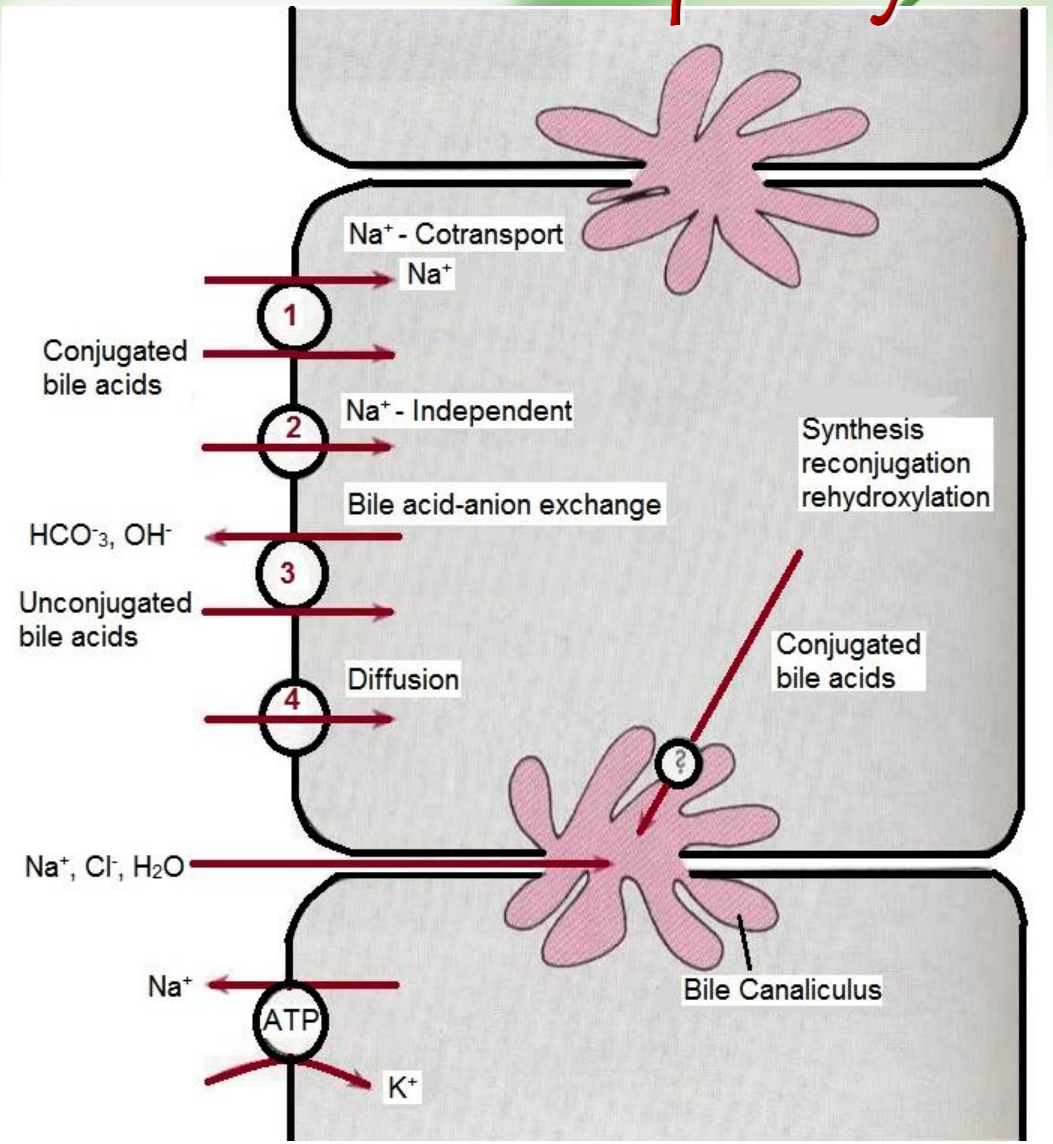
- **Bile acids are absorbed largely in the <u>terminal part of the ileum</u>. They cross the brush border plasma membrane by two routes:**
  - **Conjugated bile acids** are ***<u>2ry active transported</u>*** powered by the Na^+ gradient across the brush border membrane.
  - **Unconjugated bile acids** are better absorbed by ***<u>simple diffusion.</u>*** (They are less polar).



Absorption of bile acids back into hepatocytes

Multiple transport mechanisms are located in the hepatocyte plasma membrane for uptake of bile acids from sinusoidal blood.

- **An active carrier-mediated process.**
- **Facilitated diffusion.**
- **Bile acid-HCO_3^- or OH^- exchange.**
- **Passive diffusion (very little).**



Absorption of bile acids back into hepatocytes...Cont.

1

- Hepatocytes extract bile acids, essentially clearing the bile acids from the blood in a single pass through the liver.

2

- In the hepatocytes, most deconjugated bile acids are reconjugated & some 2ry bile acids are rehydroxylated.

3

- The reprocessed bile acids, together with newly synthesized bile acids, are secreted into bile.

Importance of Enterohepatic Circulation of Bile acids

1. It is essential for stimulating & maintaining the secretion of bile by hepatocytes.

2. The greater the quantity of bile salts in the enterohepatic circulation, the greater the rate of bile secretion.

3. By cycling several times, a relatively small bile acid pool can provide the body with sufficient amounts of bile salts to promote lipid absorption.

Importance of Enterohepatic Circulation of Bile acids...cont.

4

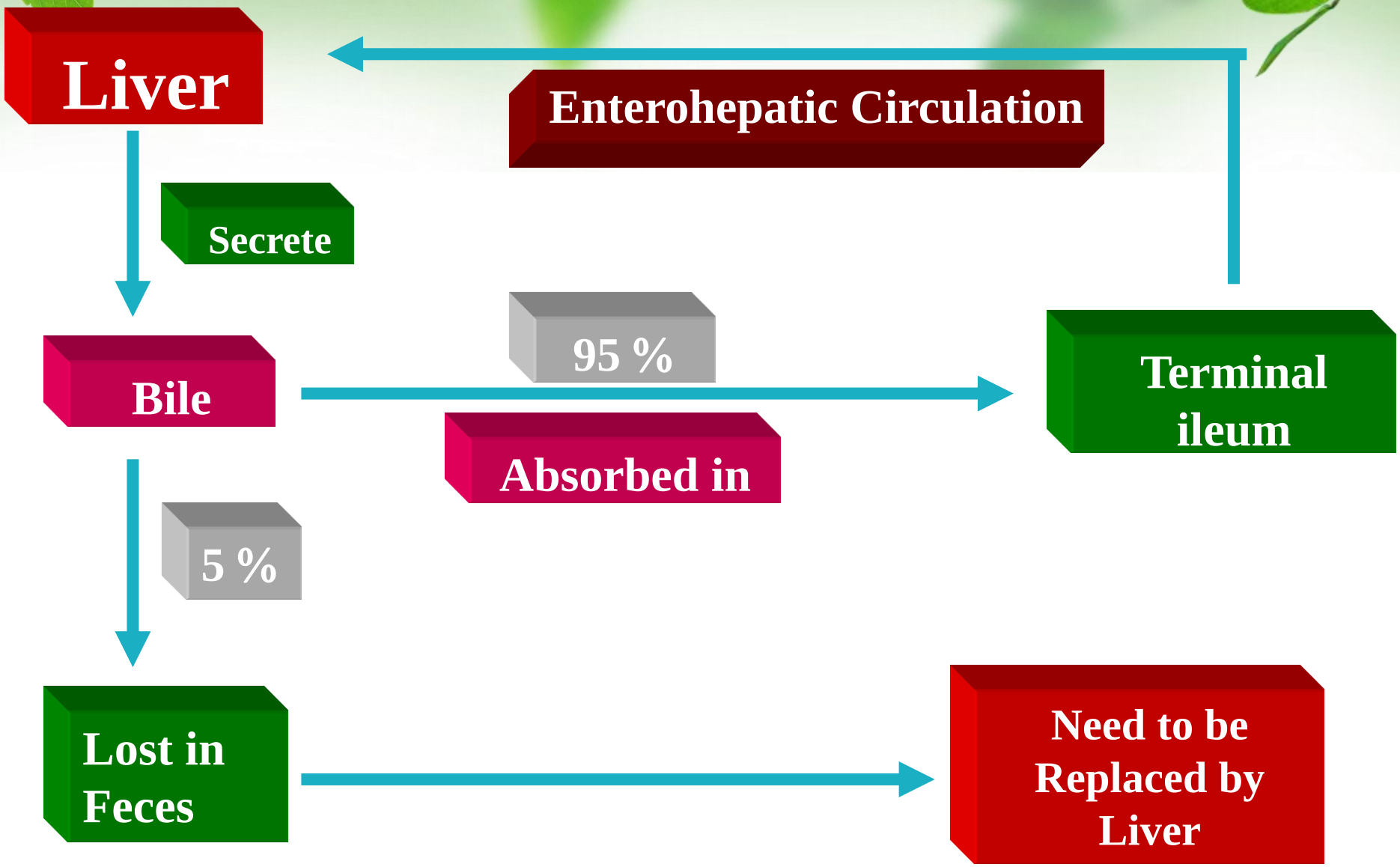
- In a light eater, the bile acid pool may circulate 3-5 times a day; in a heavy eater, it may circulate 14 to 16 times a day.

5

- If enterohepatic circulation is interrupted (e.g. due to obstruction or surgical removal or inflammation of the terminal ileum), bile flow is markedly reduced.

6

- Large quantities of bile salts enter the colon (diarrhea) and lost in the feces. Depending on the severity of illness, malabsorption of fat may result (steatorrhea).


Liver
Enterohepatic Circulation
Secrete
Bile
95 %
Terminal ileum
Absorbed in
5 %
Lost in Feces
Need to be Replaced by Liver

Enterohepatic Circulation

Needed for

Recycling of Bile Salts

Why Recycling of Bile Salts is needed?

Single meal

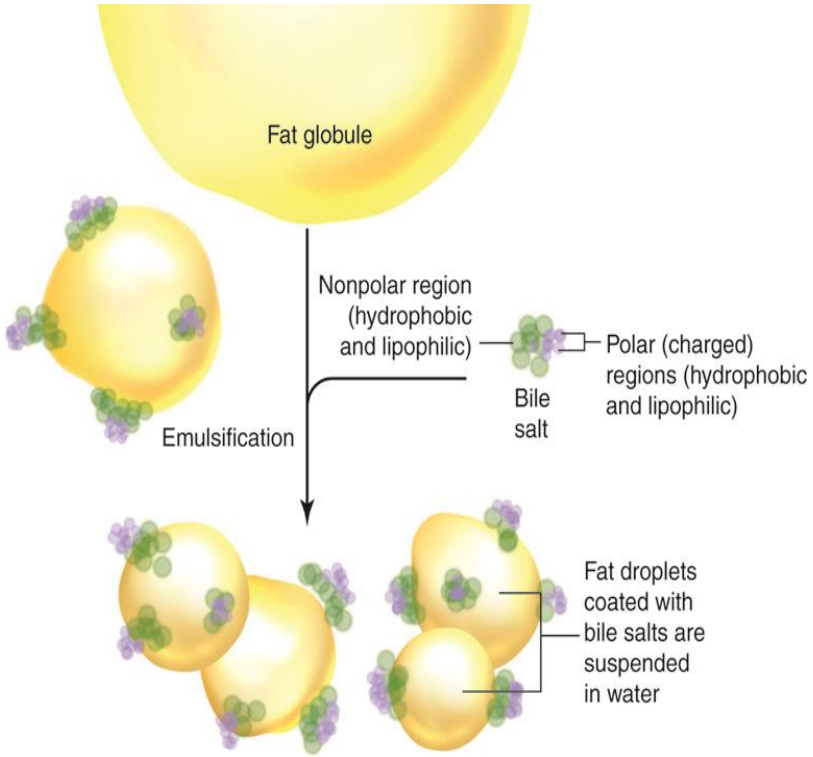
Requires

Up to 5 times the available Bile Salts

Functions of bile acids

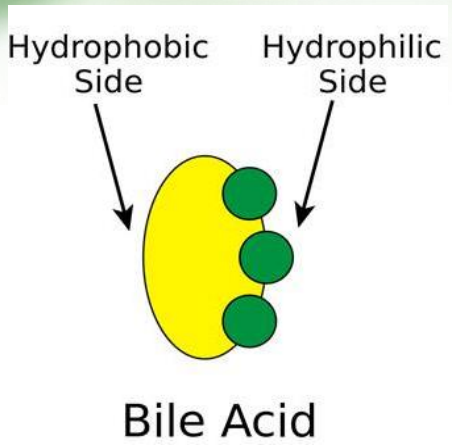
1. Digestion of fats:-

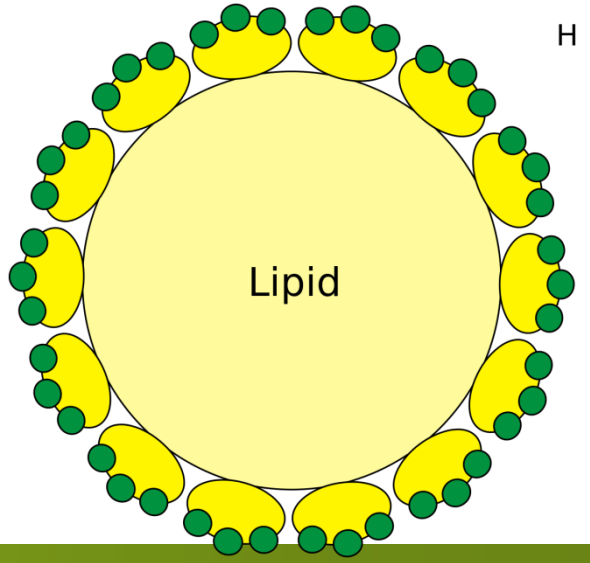
- Bile salts have a detergent action that help fat digestion by decreasing fat surface tension resulting in emulsification of fats into small particles.
- This increase the surface area upon which the digestive enzymes will act.



2. Absorption of fats:-

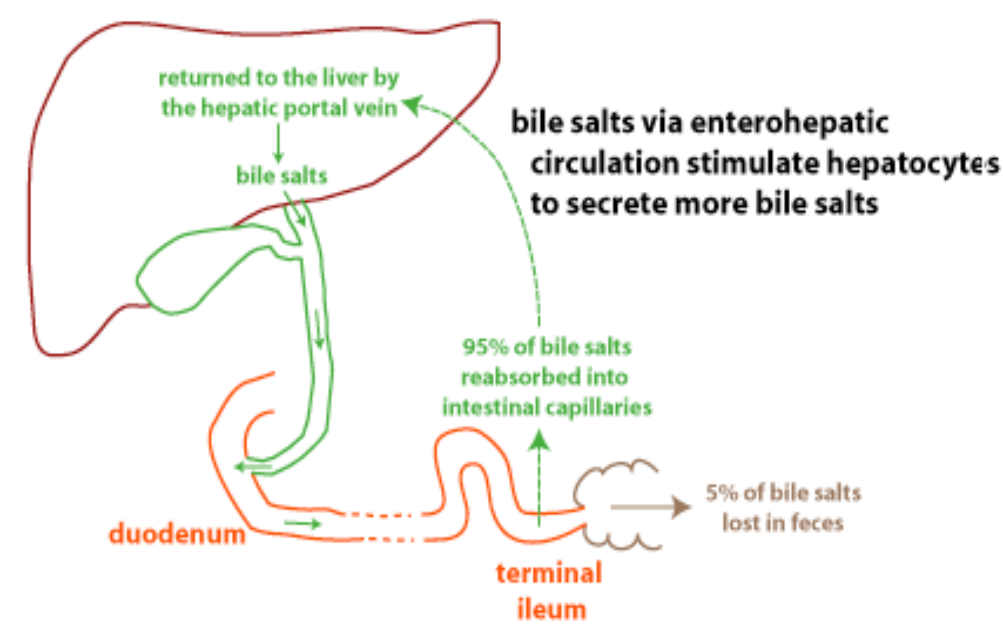
- Bile salts combine with fats to form micelles (water soluble compounds) from which fatty acids, monoglycerides, cholesterol, and other lipids can be absorbed from the intestinal tract.
- Without the presence of bile salts in intestinal tract, up to 40% of lipids are lost into the stools (steatorrhea).





3. Bile salts are essential for absorption of fat soluble vitamins (A, D, E and K).

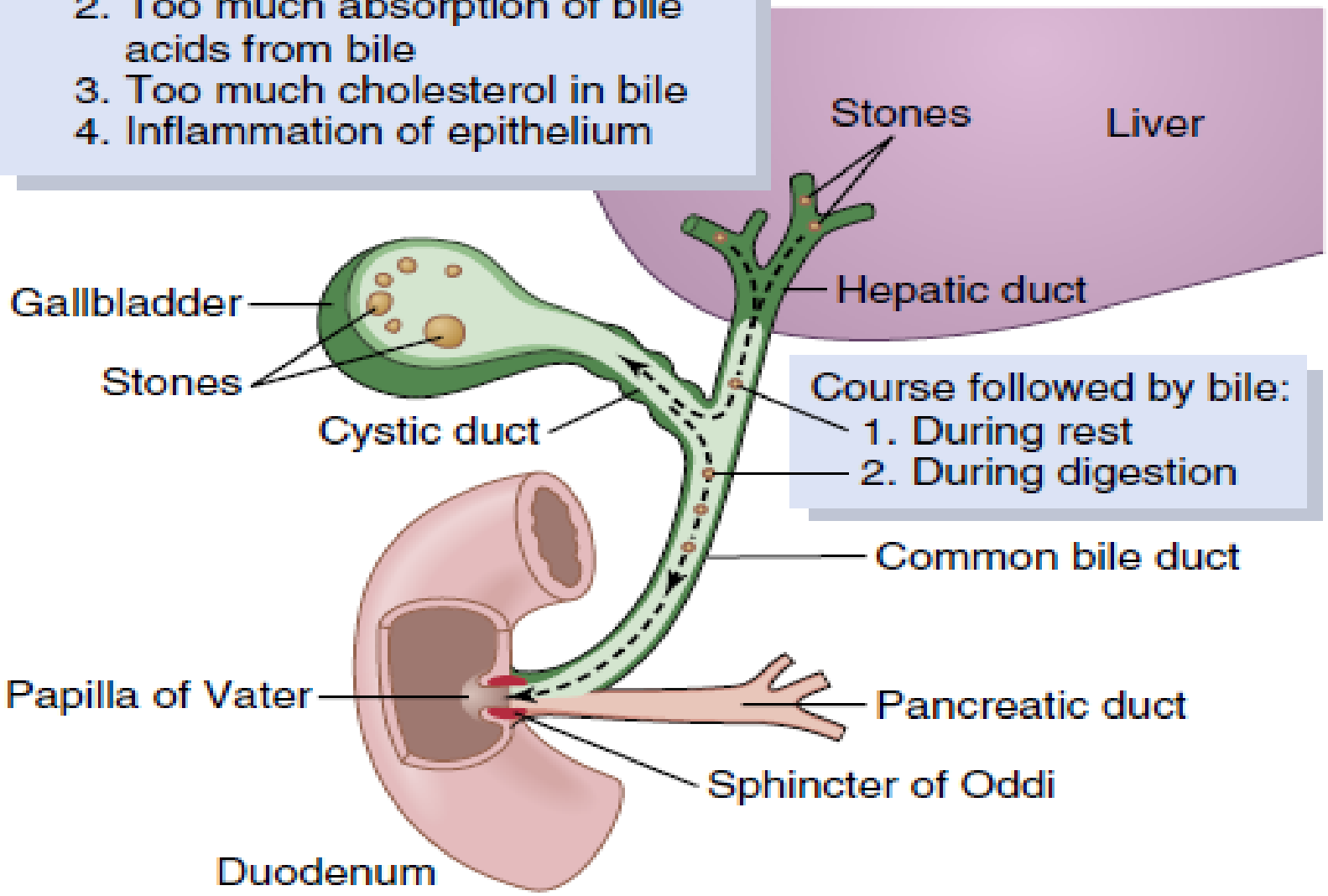
4. In the liver, bile salts are important for stimulating bile secretion and flow (choleretic action).



5. Bile salts also take part in the formation of micelles which render cholesterol soluble in bile.

Causes of gallstones:

1. Too much absorption of water from bile
2. Too much absorption of bile acids from bile
3. Too much cholesterol in bile
4. Inflammation of epithelium

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