بسم الله الرحمن الرحيم

اللهم صل على محمد وآل محمد

السلام عليكم ورحمة الله وبركاته

Gastrointestinal Physiology (Lecture 11)

Physiology of Bile Salts & Pathogenesis of Gall stones

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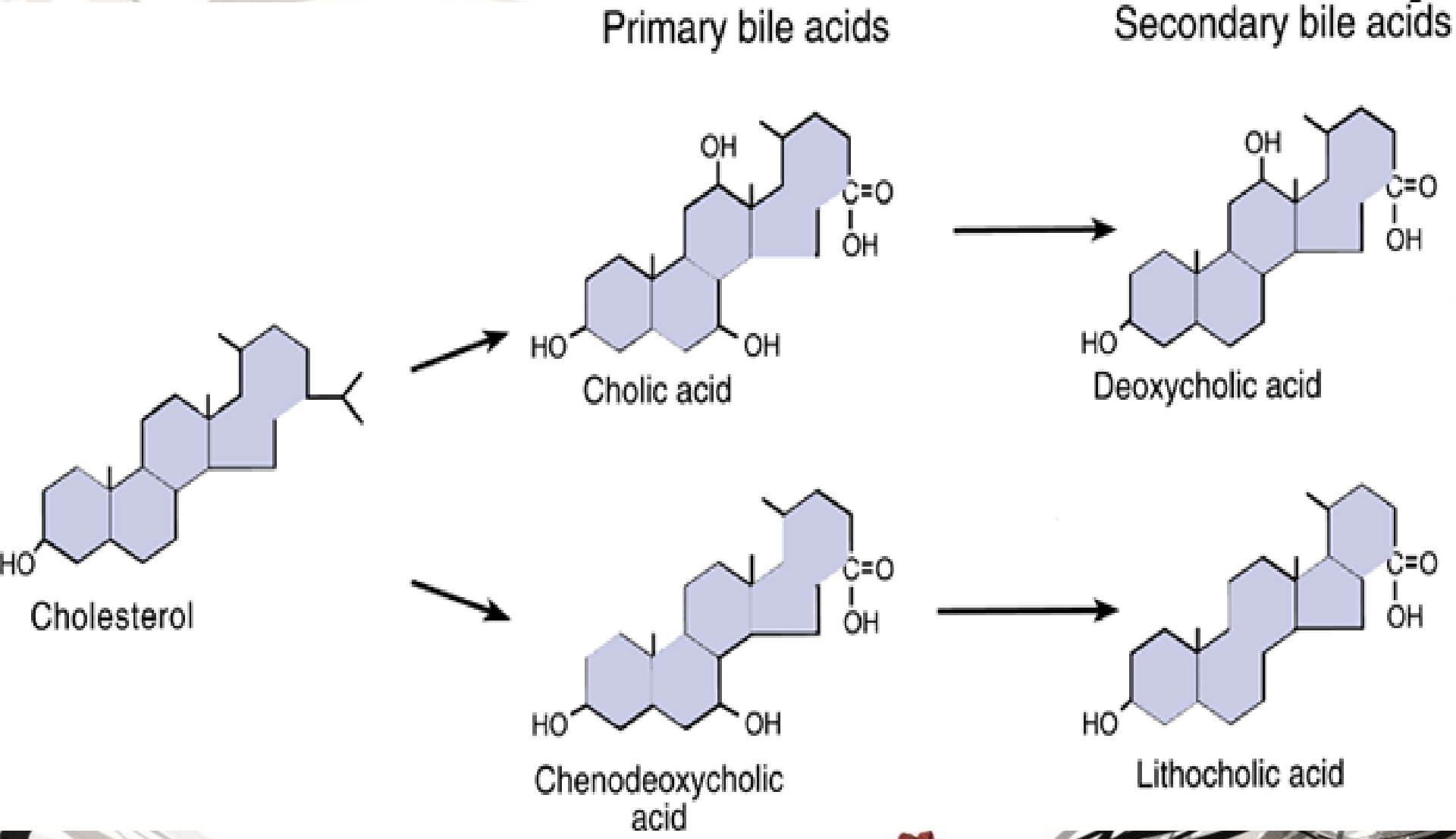
Learning Objectives

- Primary and secondary bile acids
- Enterohepatic circulation of bile salts
- Absorption of bile acids in the intestine lumen
- Uptake of bile acids from sinusoidal blood
- Functions of bile acids
- Cholesterol secretion in bile
- Types of gallstones
- Gallstone risk factors
- Gallstone pathogenesis
- Effects of cholecystectomy

Bile acids & salts

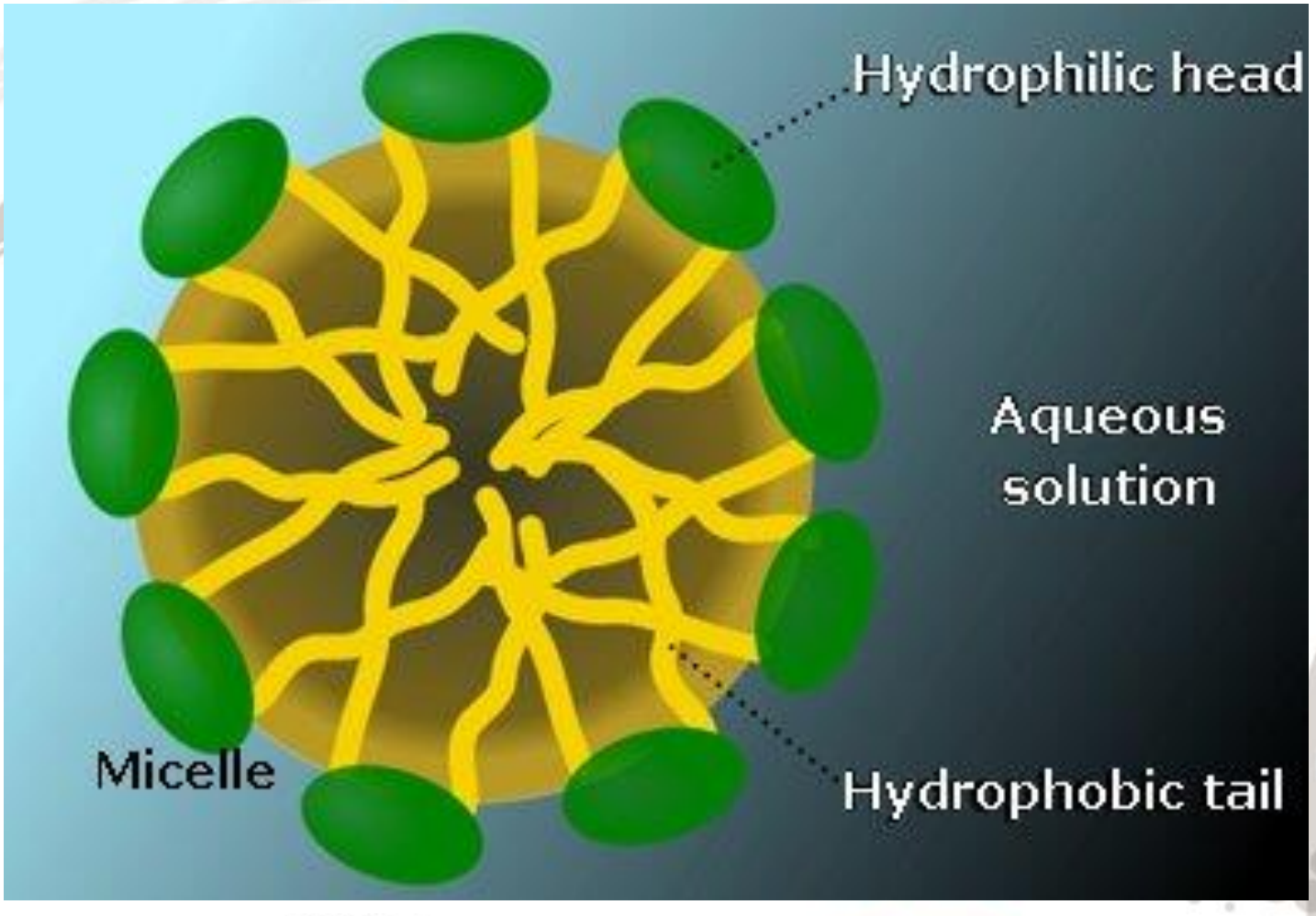
- Bile acids are steroid acids, synthesized in the liver from cholesterol by the enzyme cholesterol 7α-hydroxylase.
- Bile acids include:
  - Primary: cholic, chenodeoxycholic acids.
  - Secondary: deoxycholic, lithocholic acids.
- The principle primary bile acids conjugate with glycin or taurine to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

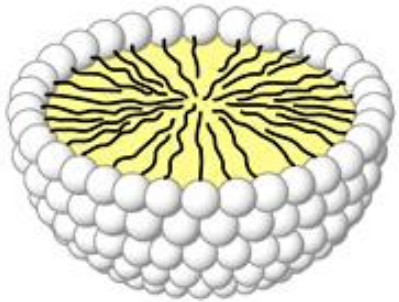
Primary and secondary bile acids



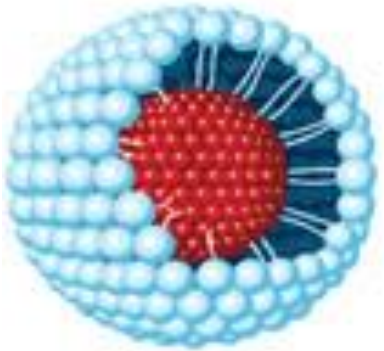
- At a neutral pH, conjugated bile acids are mostly ionized, more water soluble and are present almost entirely as salts of various cations (mostly Na^+) e.g., sodium glycocholate and are called bile salts.
- Bile salts are much more polar than bile acids and have greater difficulty penetrating cell 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.

- 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.

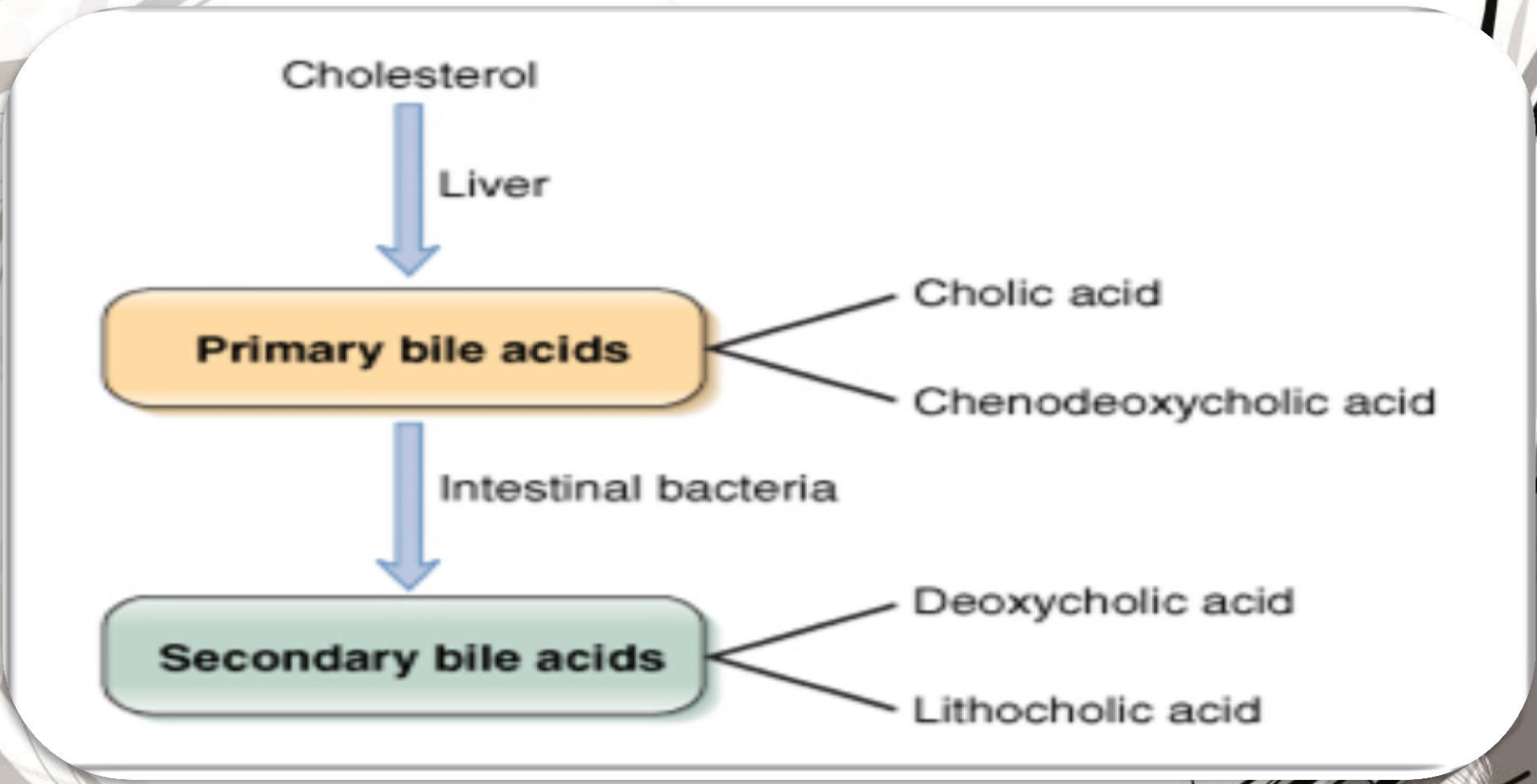

Hydrophilic head
Aqueous solution
Micelle
Hydrophobic tail



Micelle

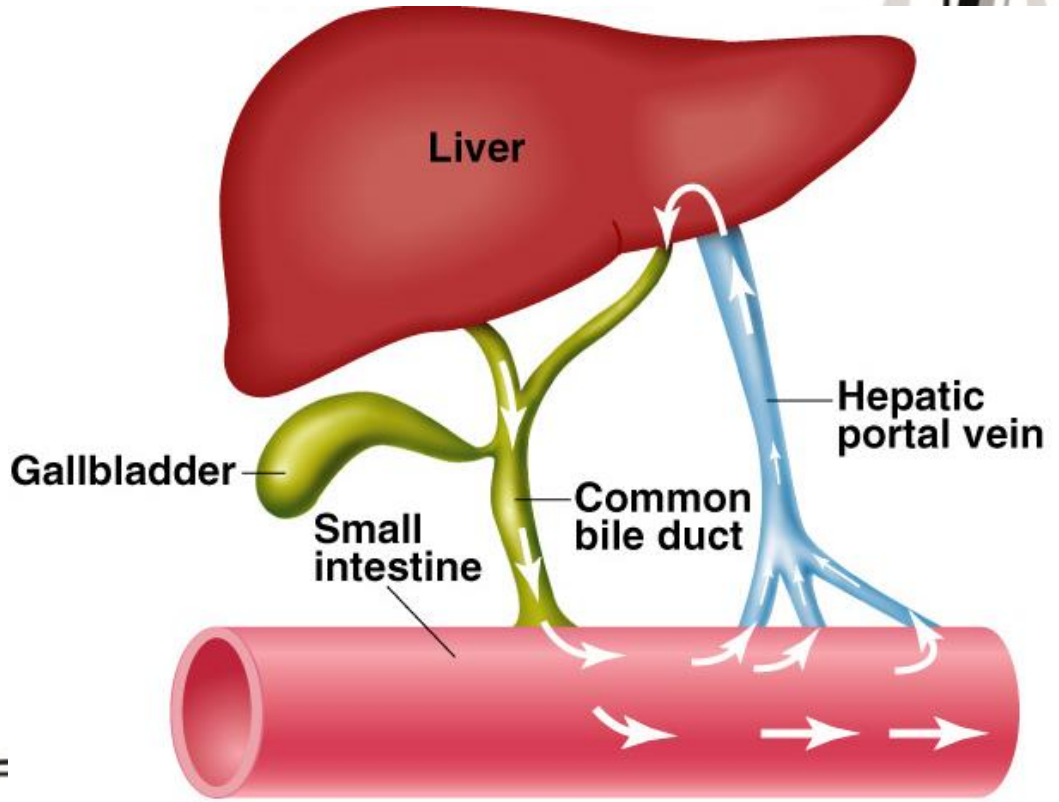


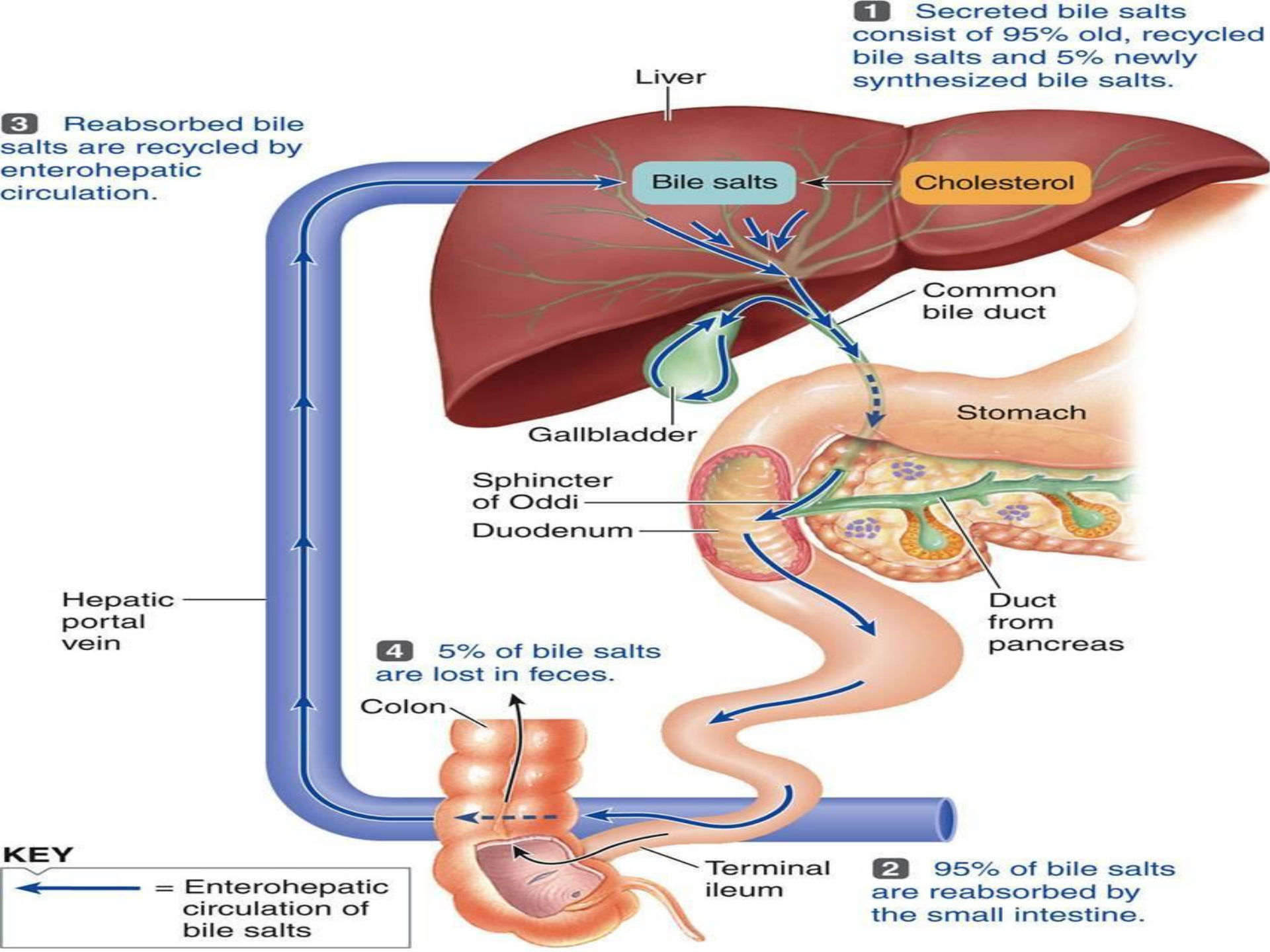
Primary and secondary bile acids

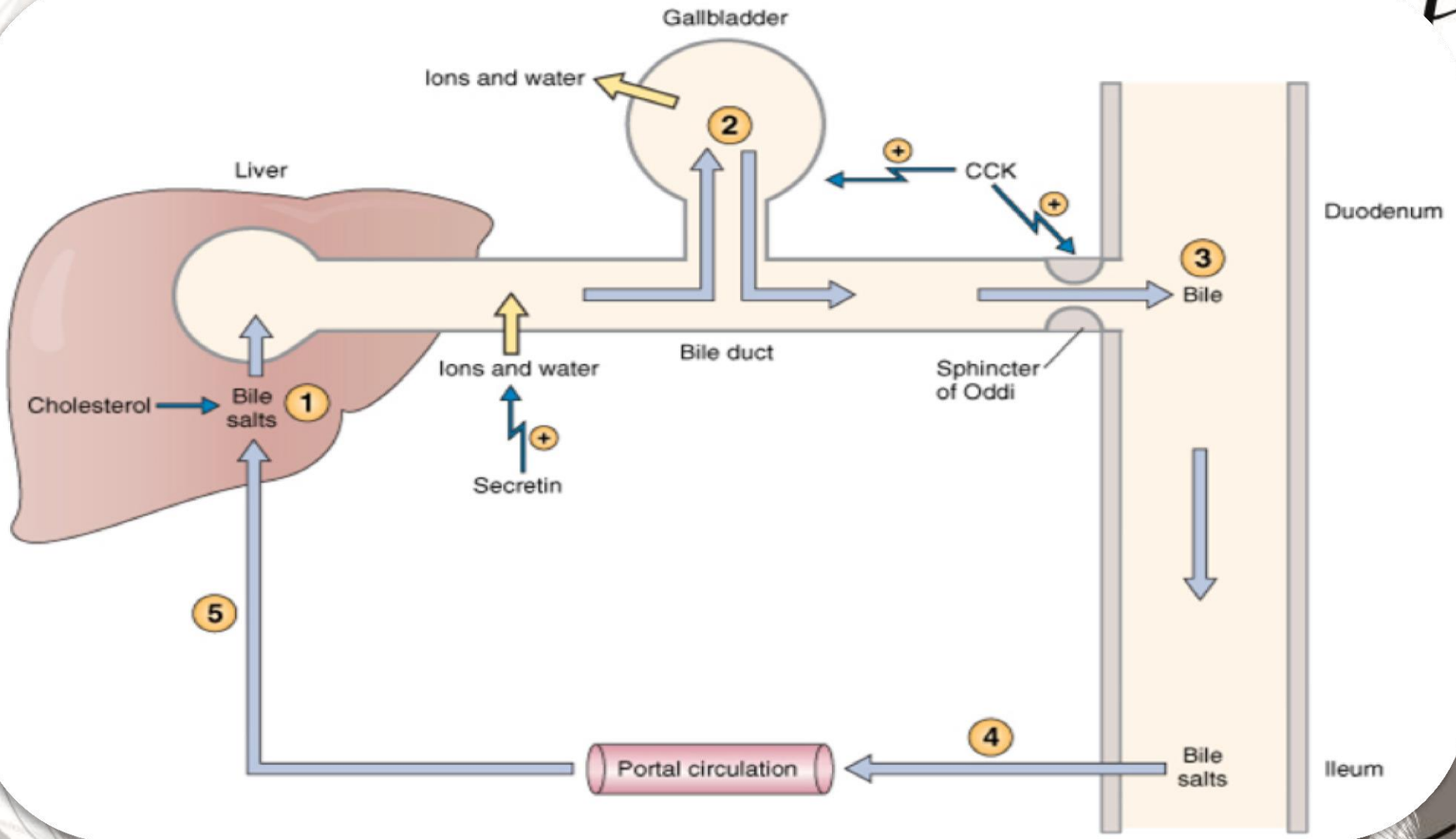


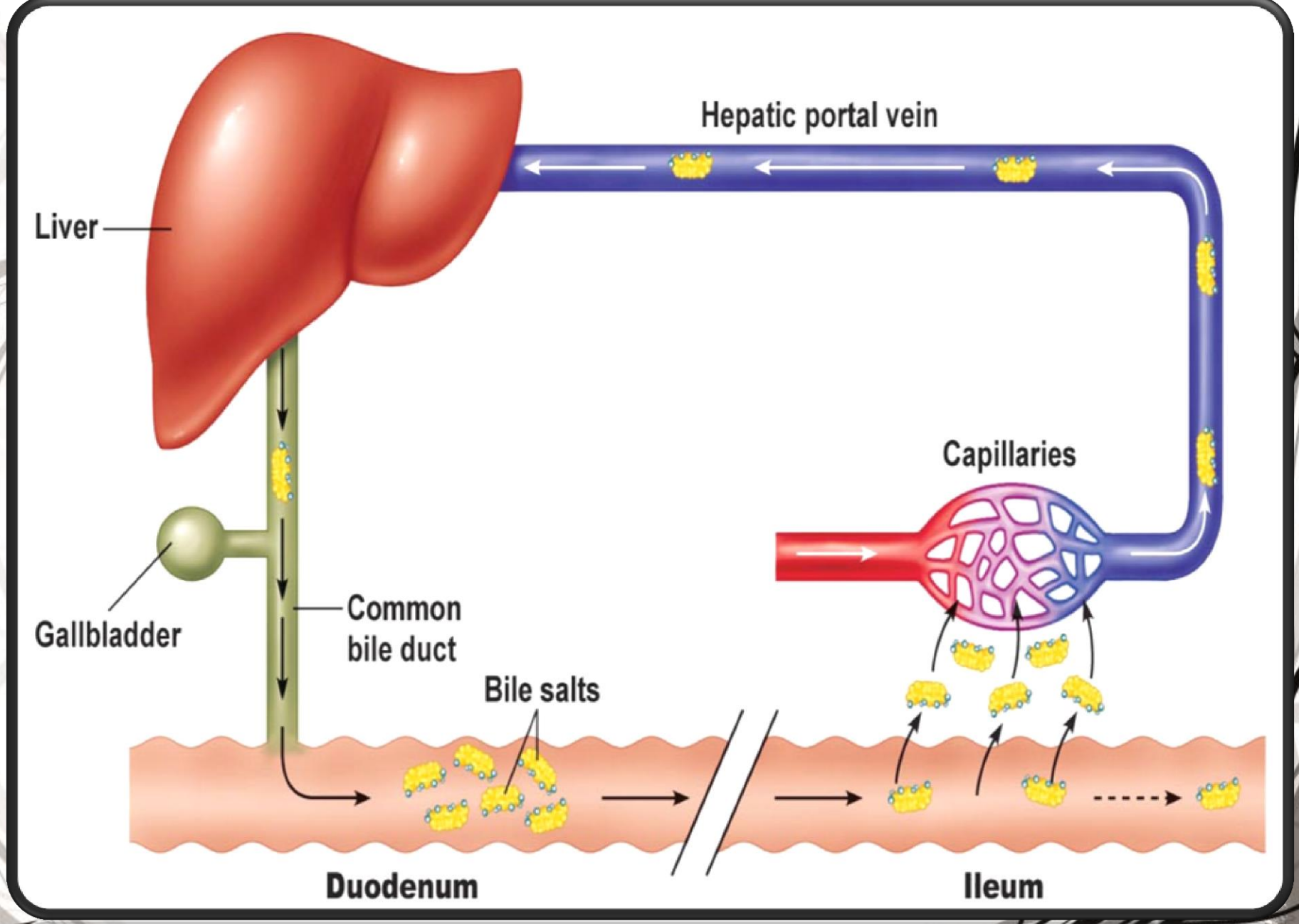
Enterohepatic Circulation of Bile Salts

- 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 2-4 g.

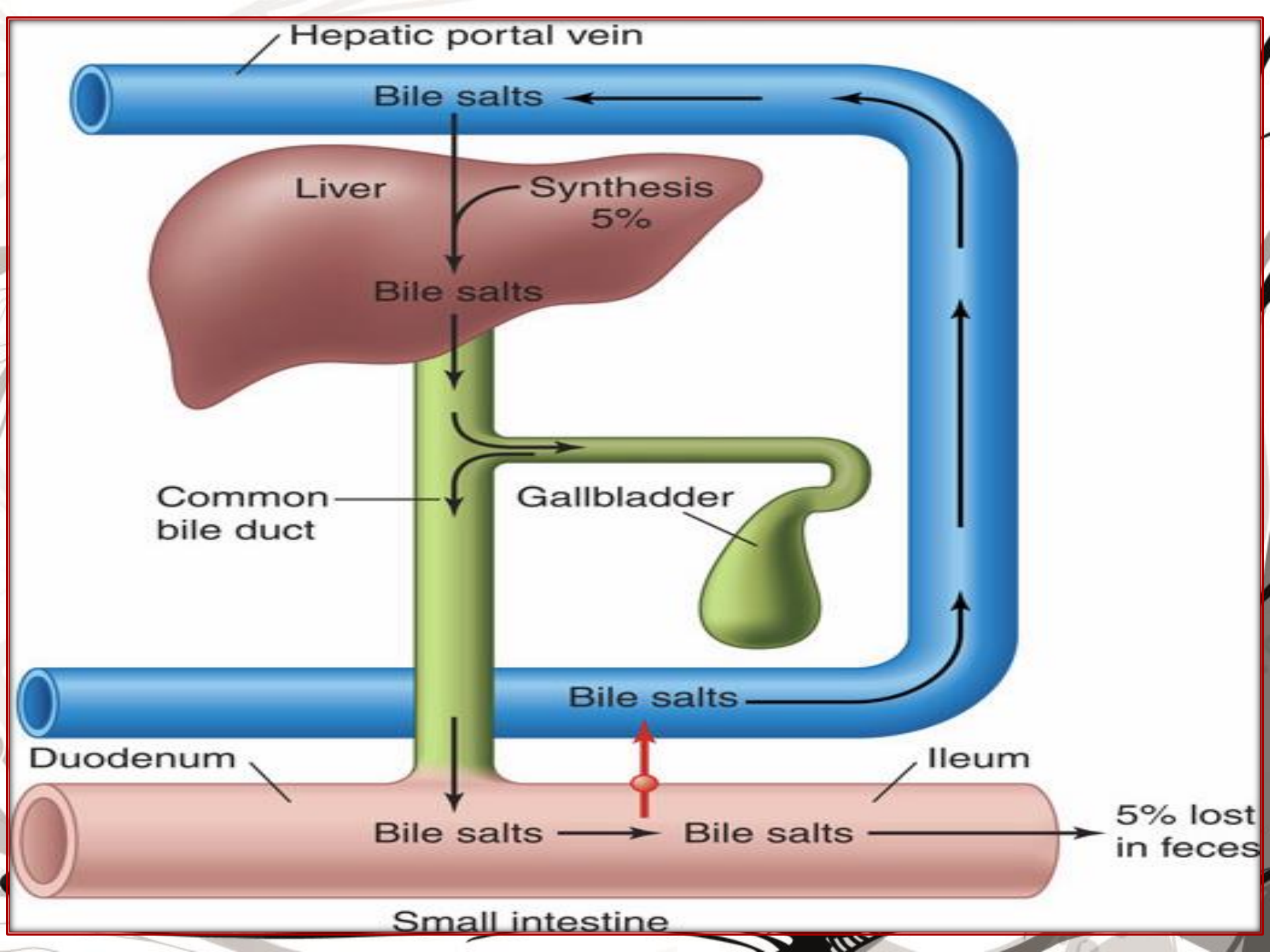



1 Secreted bile salts consist of 95% old, recycled bile salts and 5% newly synthesized bile salts.
Liver
3 Reabsorbed bile salts are recycled by enterohepatic circulation.
Bile salts
Cholesterol
Common bile duct
Gallbladder
Stomach
Sphincter of Oddi
Duodenum
Hepatic portal vein
Duct from pancreas
4 5% of bile salts are lost in feces.
Colon
Terminal ileum
2 95% of bile salts are reabsorbed by the small intestine.
KEY
= Enterohepatic circulation of bile salts


Gallbladder
Ions and water
2
Liver
CCK
Duodenum
3
Bile
Bile duct
Ions and water
Sphincter of Oddi
Cholesterol
Bile salts
1
Secretin
5
4
Portal circulation
Bile salts
Ileum


Hepatic portal vein
Liver
Capillaries
Gallbladder
Common bile duct
Bile salts
Duodenum
Ileum

- About 20-30 g of bile acids are poured into the duodenum /day (the daily turnover of total bile acid pool through the enterohepatic circulation must be 6-10 times).
- 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.


Hepatic portal vein
Bile salts
Liver
Synthesis
5%
Bile salts
Common
bile duct
Gallbladder
Bile salts
Duodenum
Ileum
Bile salts
Bile salts
5% lost
in feces
Small intestine

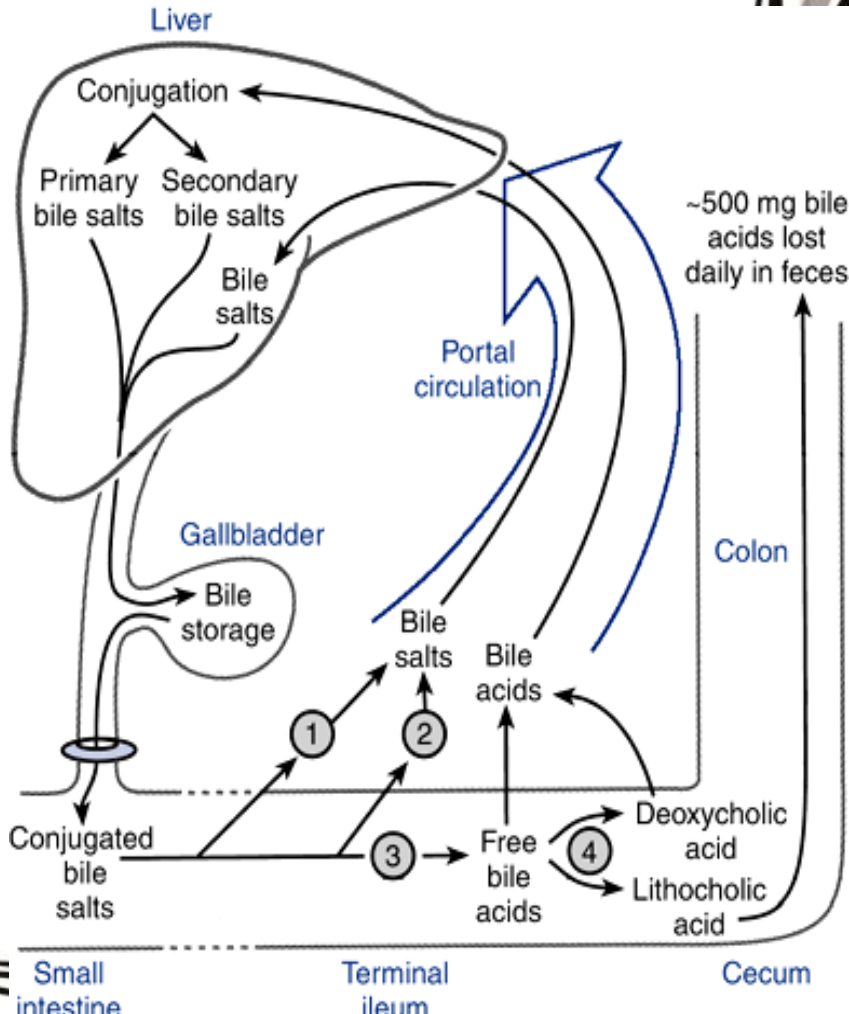
- On reaching the terminal ileum, 90 % of bile acids are absorbed and reach the liver through the portal vein.

- About 0.2-0.6 g of bile acids are lost in feces daily (15-35% of total bile acid pool)). These are replaced by new synthesis in liver so that the total bile acid pool is maintained constant at 2 - 4 g.

Absorption of bile acids in the intestine lumen

Bile salts in the intestine lumen are absorbed largely in the terminal part of the ileum via four pathways:

- Passive diffusion
- An active carrier-mediated process powered by the Na^+ gradient across the brush border membrane.
- De-conjugation of bile salts to bile acids
- Transforming the primary bile acids to secondary bile acids



Absorbed bile acids are carried away from the intestine in the portal blood, mostly bound to albumins.

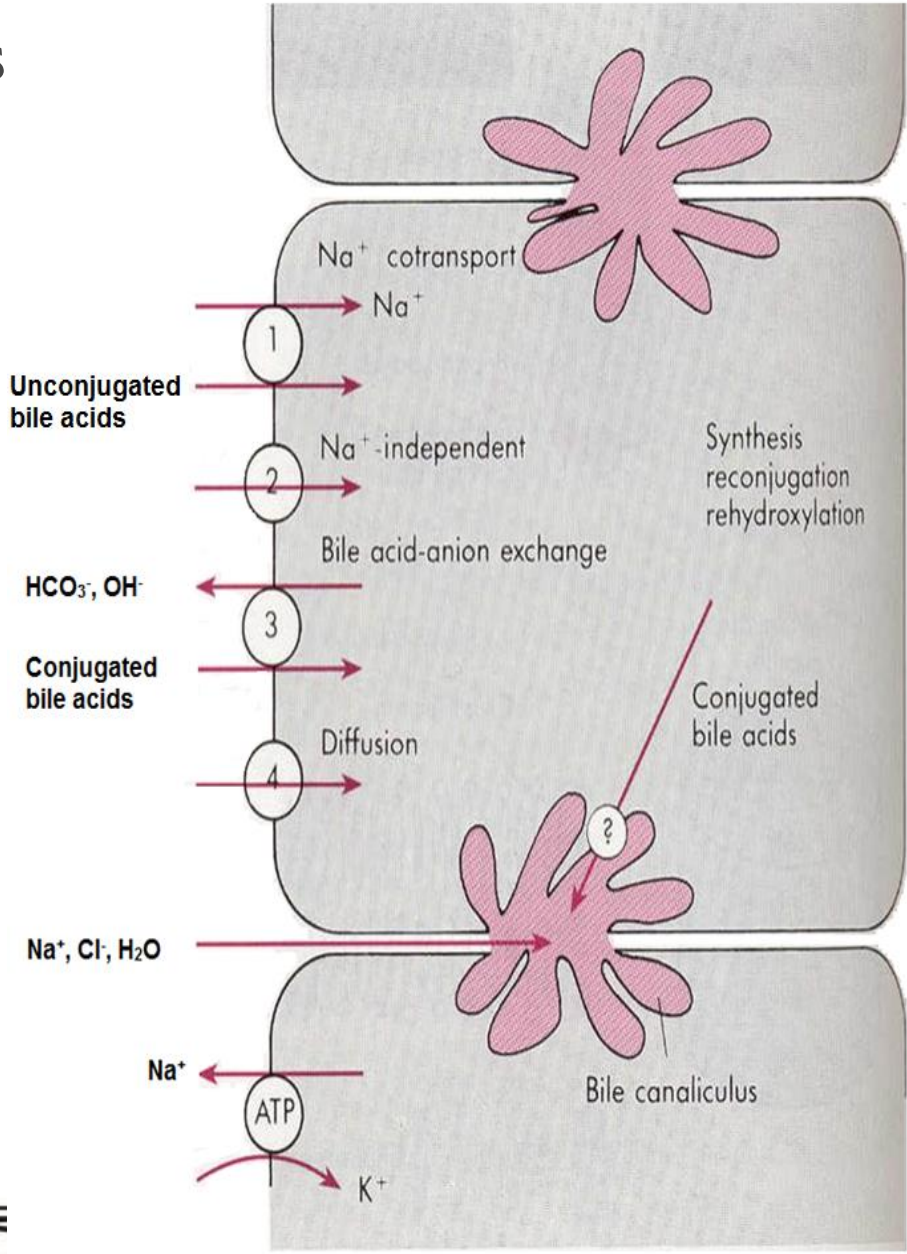
N.B:

- In the small intestine, cholic acid is absorbed faster than chenodeoxycholic acid, and primary bile acids are absorbed better than secondary bile acids.
- Some unconjugated bile acids are absorbed passively in the colon and reach the liver through portal vein.

Uptake of bile acids from sinusoidal blood

Multiple transport mechanisms are located in 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)



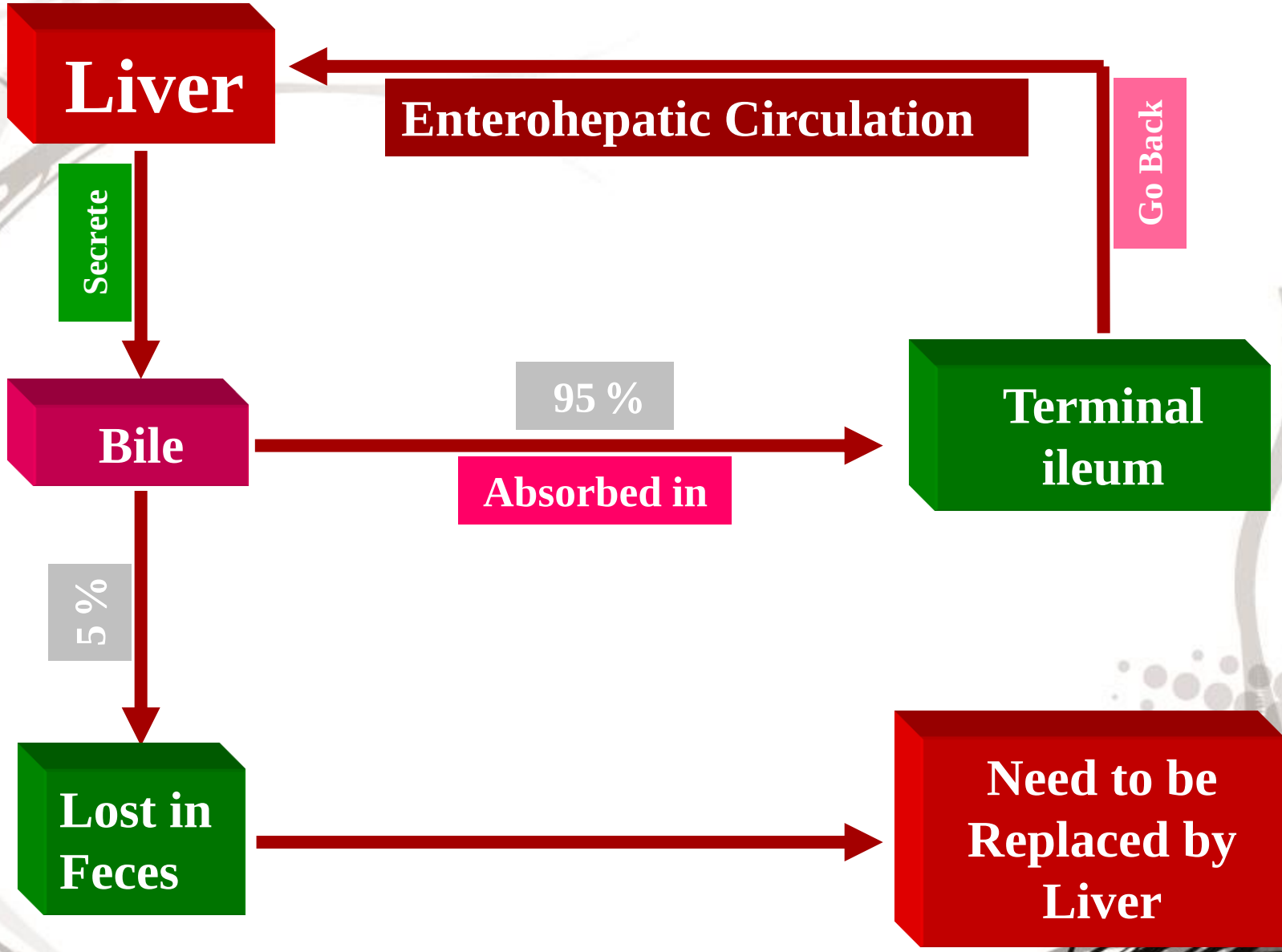
Importance of enterohepatic circulation of bile acids

- It is essential for stimulating and maintaining the secretion of bile by hepatocytes.
- The greater the quantity of bile salts in the enterohepatic circulation, the greater the rate of bile secretion.
- By cycling several times during a meal, a relatively small bile acid pool can provide the body with sufficient amounts of bile salts to promote lipid absorption.

- 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.
- If enterohepatic circulation is interrupted (e.g. due to obstruction by disease or surgical removal or inflammation of the terminal ileum), bile flow is markedly reduced and large quantities of bile salts are lost in the feces.
- Depending on the severity of illness, malabsorption of fat may result (steatorrhea).

N.B:

Excess amount of bile acids entering the colon may result in diarrhea.


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

Enterohepatic Circulation → **Needed for** → **Recycling of Bile Salts**

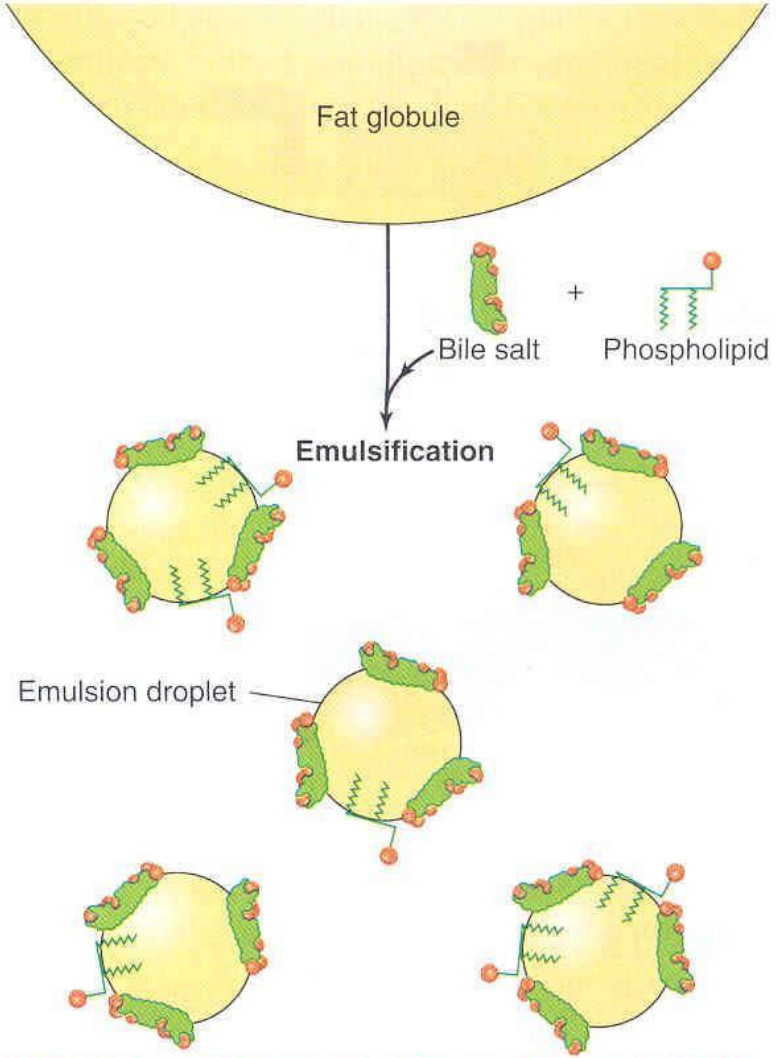
Why Recycling of Bile Salts is needed?

Single meal → **Requires** → **Up to 5 times the available Bile Salts**

- Hepatocytes extract bile acids, essentially clearing the bile acids from the blood in a single pass through the liver.
- In the hepatocytes, most deconjugated bile acids are reconjugated & some 2^{ry} bile acids are rehydroxylated.
- The reprocessed bile acids, together with newly synthesized bile acids, are secreted into bile.

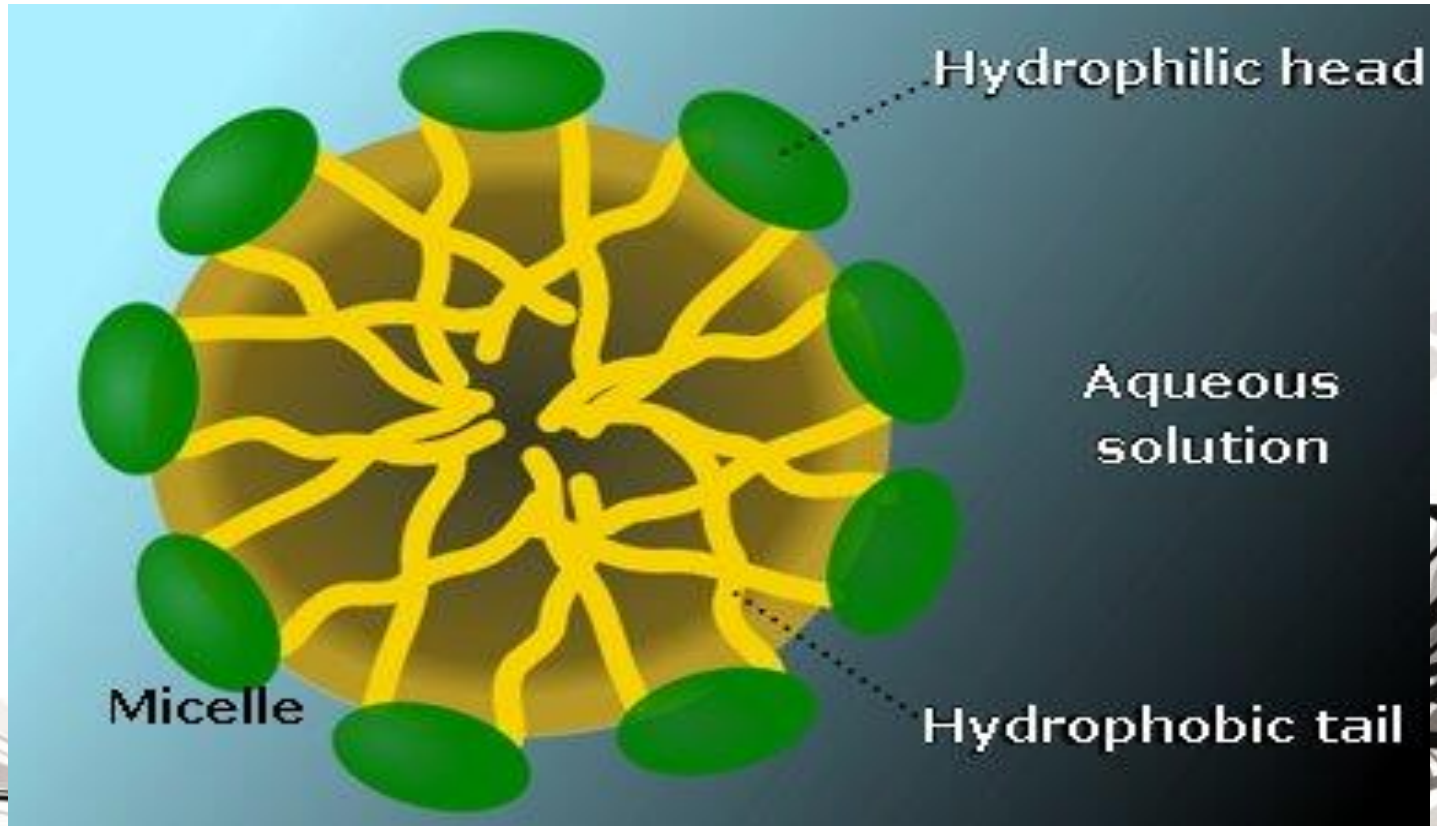
Functions of bile acids

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.



Emulsification of fat by bile salts and phospholipids

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 acids are essential for absorption of fat soluble vitamins (A, D, E and K).
4. In the colon bile acids inhibit reabsorption of water & electrolytes, stimulate intestinal motility, prevent constipation & may cause diarrhea.
5. In the liver, bile salts are important for stimulating bile secretion and flow (choleretic action). They also take part in the formation of micells which render cholesterol soluble in bile.

6. Bile acids have a –ve feedback effect on the release of CCK from its cells in the upper intestine & thus contribute to the regulation of pancreatic secretion & the discharge of bile into intestine.
7. They have a –ve feedback effect on the synthesis of cholesterol by the intestinal mucosal cells.
8. Anti putrifactive: Bile acids have no direct anti septic effect but they prevent putrifaction by absorption of fat. In their absence undigested fats cover the protein particles & hinder their digestion.

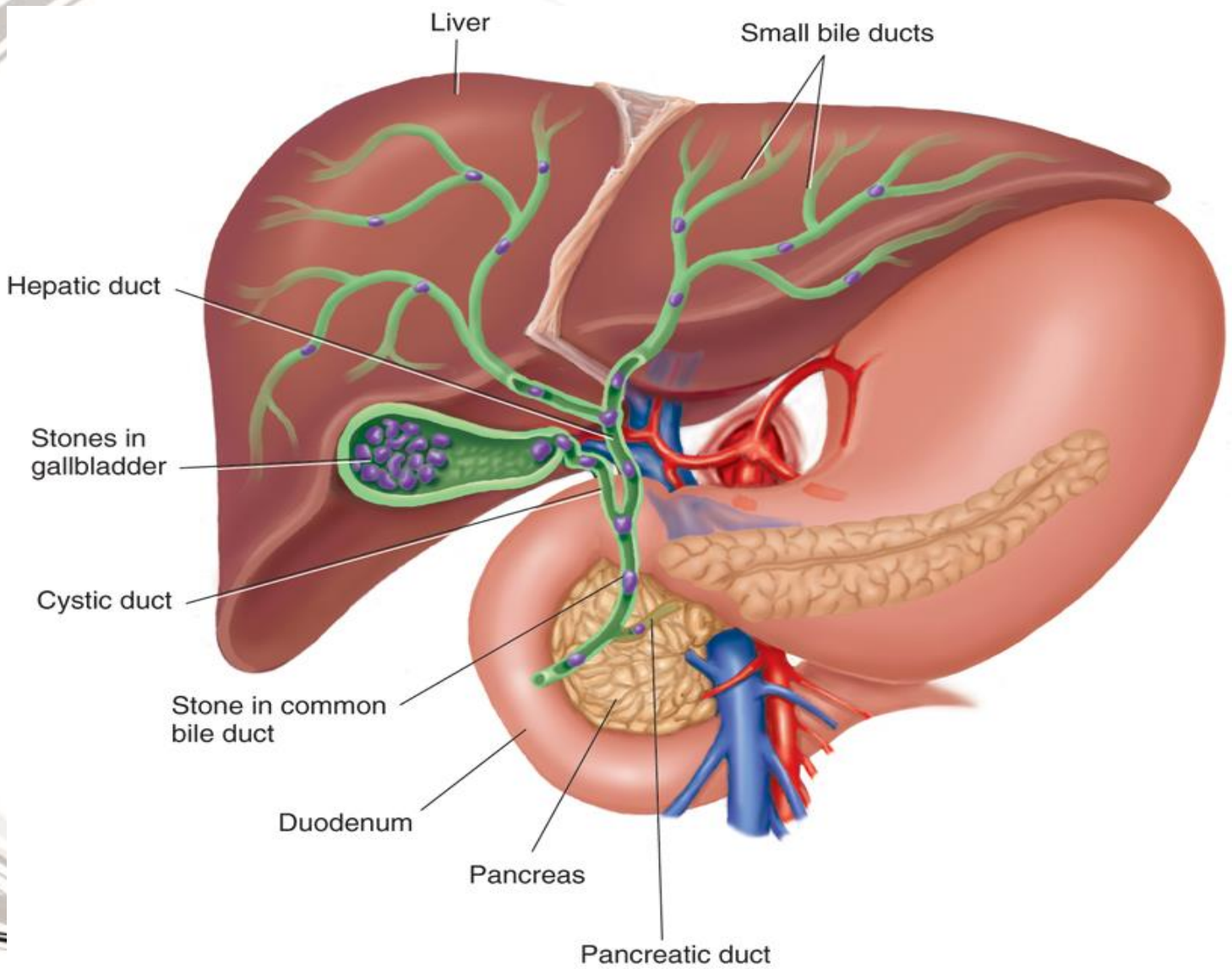
Cholesterol secretion in bile

- About 1-2g of cholesterol appears in bile per day.
- No specific function is known for cholesterol in the bile & it is presumed that it is simply a byproduct of bile salt formation & secretion.
- Cholesterol is water insoluble; it is solubilized by incorporation in micelles along with the bile acids & phospholipid.

- The micelles remain stable so long as the concentration of bile acids, phospholipids & cholesterol remain within certain limits.
- If the relative concentration of any of the constituents alters, e.g. if bile contains more cholesterol than can be solubilized, (bile is supersaturated with cholesterol), cholesterol may be precipitated out of solution.
- In people who produce bile with a high conc. of cholesterol, cholesterol gallstones may form in the gall bladder.

Types of gallstones

Gall stones may be formed in the gall bladder or bile ducts.



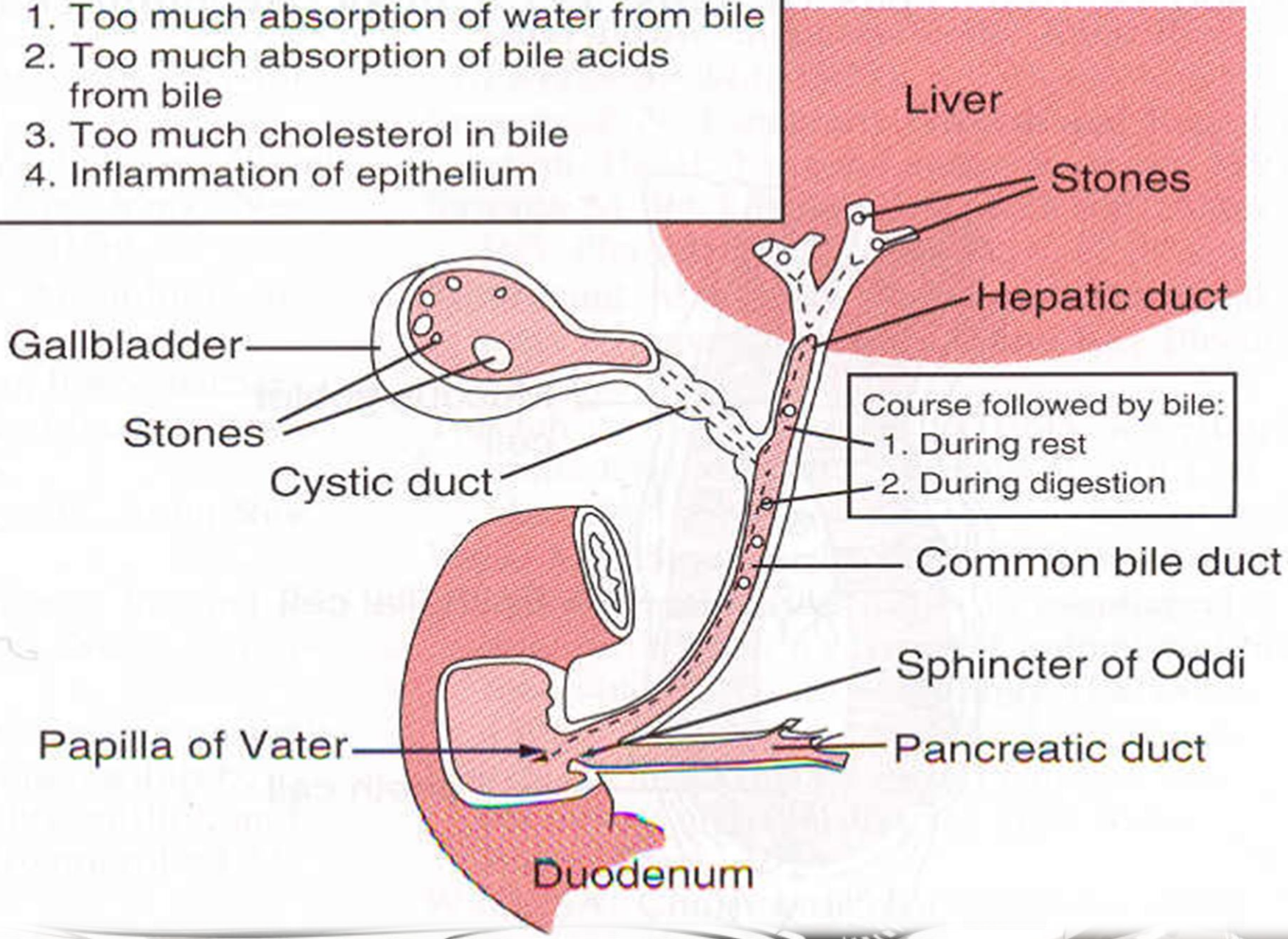
The commonest 2 types are:

1.Cholesterol stones: under abnormal conditions the cholesterol may precipitate resulting in formation of cholesterol gallstones. The causes may be:

- Too much absorption of water from the bile.
- Too much absorption of bile salts & lecithin from bile.
- Too much secretion of cholesterol in bile.
- Inflammation of the epithelium of the gall bladder that often results from chronic infection which changes the absorptive characteristics of gall bladder mucosa allowing excessive absorption of water & bile salts that are necessary to keep cholesterol in solution.

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



2.Calcium bilirubinate stones:

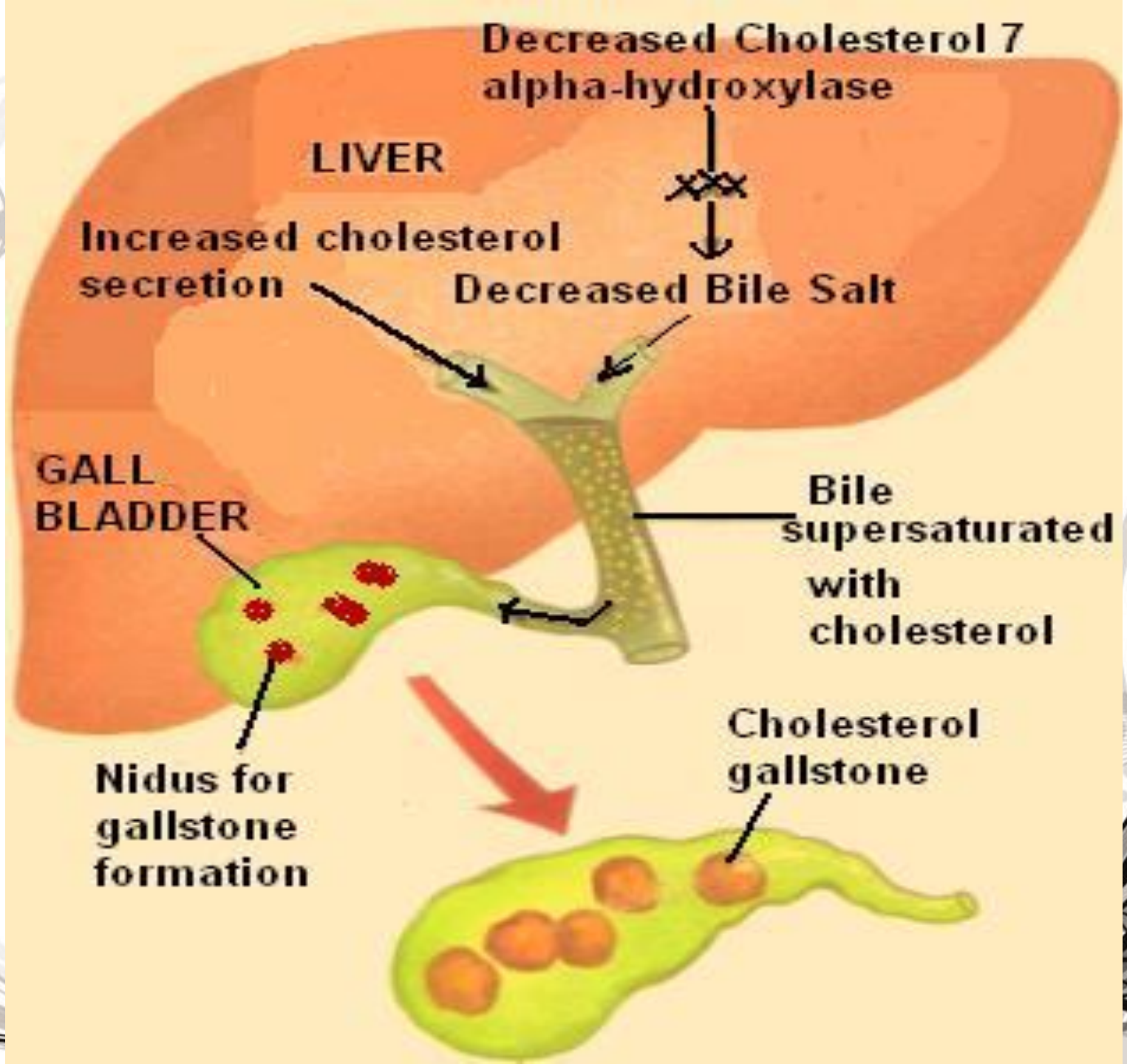
- The main constituent is calcium salt of unconjugated bilirubin.
- In liver diseases, bile may contain elevated levels of unconjugated bilirubin with increased incidence of forming bile pigment stones.

GALLSTONE RISK FACTORS

- "Female, Fat, Forty, Fertile"
- Oral contraceptives
- Obesity
- Rapid weight loss (gastric bypass pts)
- Fatty diet
- DM
- Prolonged fasting
- Ileal resection
- Hemolytic states
- Cirrhosis
- Bile duct stasis (biliary stricture, congenital cysts, pancreatitis, sclerosing cholangitis)
- Vagotomy
- Hyperlipidemia

GALLSTONE PATHOGENESIS

- Gallstones due to imbalance rendering cholesterol & calcium salts insoluble.
- Pathogenesis of cholesterol gallstones involves: (1) cholesterol supersaturation in bile, (2) crystal nucleation, (3) stone growth.
- Black pigment stones: contain Ca^{++} salts, following hemolytic conditions or cirrhosis, found in the gallbladder.
- Brown pigment stones: Asians, contain Ca^{++} palmitate, found in bile ducts, following biliary dysmotility and bacterial infection.


Decreased Cholesterol 7
alpha-hydroxylase
LIVER
Increased cholesterol
secretion
Decreased Bile Salt
GALL
BLADDER
Bile
supersaturated
with
cholesterol
Nidus for
gallstone
formation
Cholesterol
gallstone

Effects of Cholecystectomy:

- Bile (not the gall bladder) is essential for digestion.
- After removal of the gall bladder bile empties slowly but continouslly to the intestine allowing digestion of fats sufficient to maintain good health & nutrition.
- Only high fat meals need to be avoided.

Thank You