

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Physiology of *Gastrointestinal System*
(*GIS*)

By



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***Formation and Enterohepatic
Circulation (L10)***

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- The main digestive function of the liver is the secretion of bile.
- Bile serves two important functions:
 - 1- It plays an important role in fat digestion and absorption by its contents of bile salts.
 - 2- Bile serves as a means for excretion of waste products from the blood. These include especially bilirubin, an end product of hemoglobin destruction.

Bile is secreted in two stages:

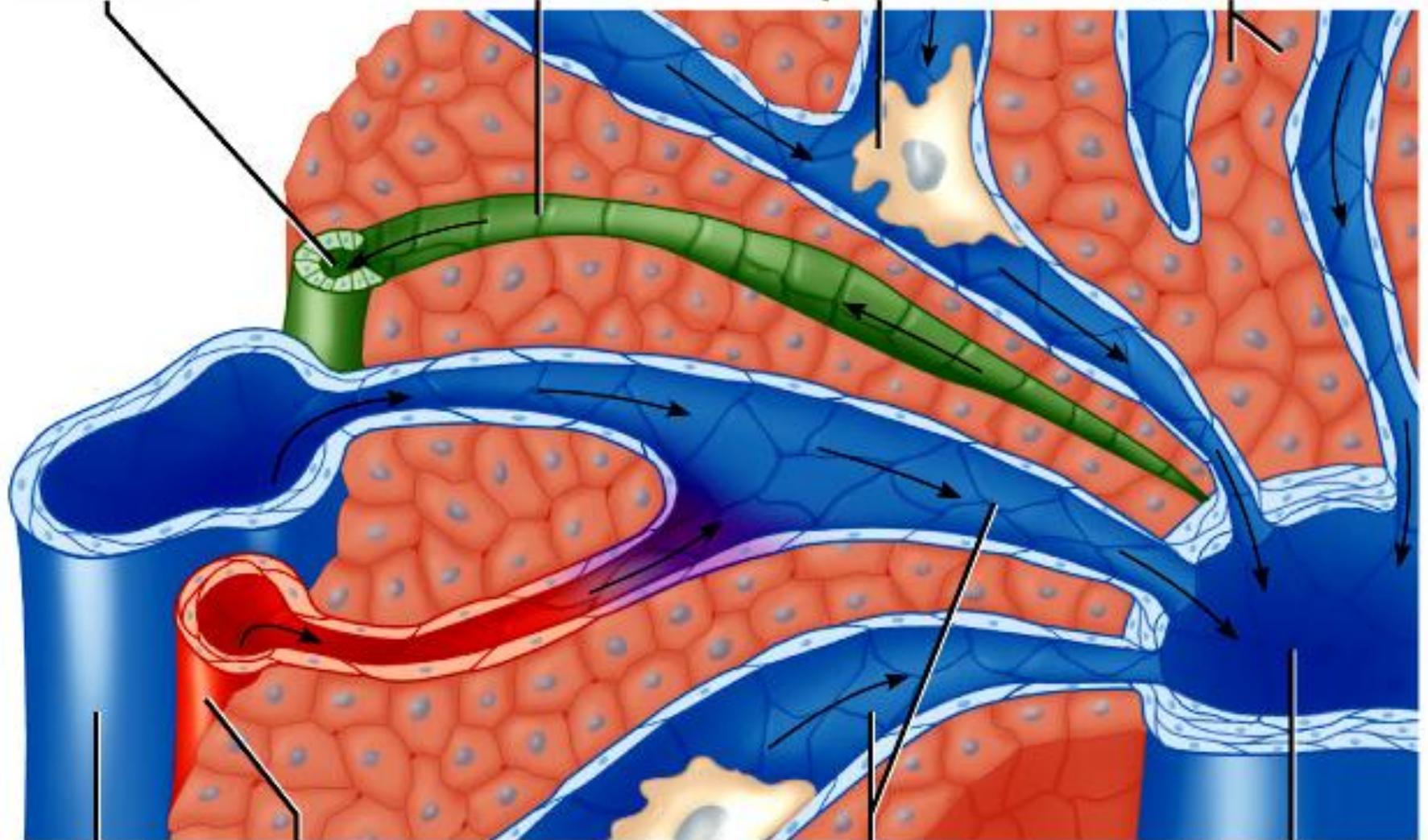
- (1) The initial portion is continually secreted by the hepatocytes. It is secreted into bile canaliculi that originate between the hepatic cells.
- (2) The bile flows in the canaliculi toward the hepatic duct and common bile duct. From these, bile either empties directly into the duodenum or is diverted for minutes up to several hours through the cystic duct into the gallbladder (this is the second portion of liver secretion which is added to the initial bile).

Bile duct

Bile canal

Kupffer cell

Hepatic cells



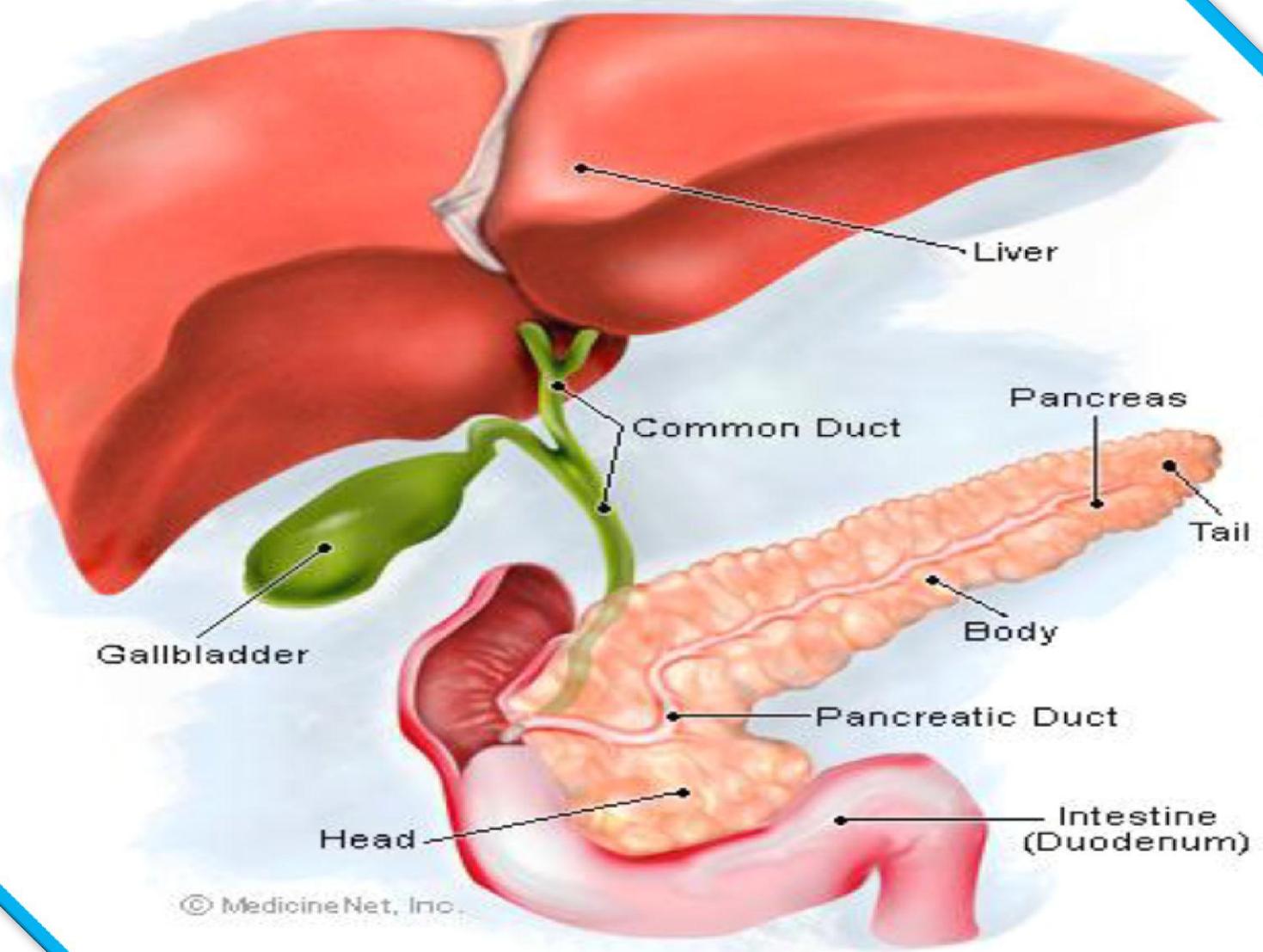
Branch of hepatic portal vein

Branch of hepatic artery

Hepatic sinusoids

Central canal (blood flow out of liver)

Blood flow into liver



Gallbladder

Liver

Common Duct

Pancreas

Tail

Body

Pancreatic Duct

Head

Intestine (Duodenum)

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- Between meals, bile is diverted into gall bladder.
- The gall bladder epithelium extracts salts and H_2O from the stored bile, concentrating bile fivefold up to twentyfold.
- 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 (cholechooduodenal sphincter).

Characteristics of bile

- ❧ Bile is a viscous golden yellow or greenish fluid with bitter taste.
- ❧ It is isotonic with plasma and slightly alkaline. NaHCO_3 in bile is responsible for its alkaline reaction and participates with pancreatic and duodenal secretion in neutralization of acid chyme delivered from stomach.
- ❧ The liver produces about 5 L /day, but only 700-1200 ml/day are poured into the duodenum.

What are the components of bile?

The main constituents of bile are:

- ❑ Bile acids (bile salts) (65% of dry weight of bile):
- ❑ Bilirubin and related bile pigments (0.3%).
- ❑ Phospholipids (90% lecithin) (20%).
- ❑ Proteins (5%).
- ❑ Cholesterol (4%), the major route for cholesterol excretion. Cholesterol solubility depends on the relative concentration of cholesterol, bile salts, and phospholipids.

All of these constituents are secreted by hepatocytes into bile canaliculi, along with an isotonic fluid that resembles plasma in its electrolyte conc.

- Electrolytes mainly HCO_3^- , these in addition to H_2O are secreted by epithelial cells that line bile ducts, and contribute to the volume of bile leaving the liver.
 - HCO_3^- aids in neutralization of acid chyme which

Composition of bile

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graph TD; A[Composition of bile] -->|From ducts| B[Aqueous alkaline Solution (NaHCO3)]; A -->|From hepatocytes| C[Organic constituents]; C --> D["Bile salts<br/>Cholesterol<br/>Lecithin<br/>bilirubin"]
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From ducts

Aqueous alkaline
Solution
(NaHCO_3)

From hepatocytes

Organic constituents

Bile salts
Cholesterol
Lecithin
bilirubin

Functions of gall bladder

- I. Gall bladder not only stores bile but it concentrates and acidifies it.

The total secretion of bile each day is about 700-1200 ml per day. The maximum volume of the gall bladder is only 30-60 ml. as much as 12 hours bile secretion can be stored & concentrated in the gall bladder. Bile is normally conc. about 5 folds (up to 12-20 folds).

Concentration & Acidification of bile in the gall bladder occur by:

Active absorption of Na^+ , Cl^- , and HCO_3^- by the lining epithelium.

Associated passive water movement out of the lumen.

This result in drop of pH of gall bladder bile due to decreased NaHCO_3 concentration.

- II. Gall bladder epithelium secretes mucus which has protective function.
- III. Buffer of biliary pressure by storing of bile, so it prevents increase in biliary pressure & enables the liver to secret bile, because hepatic cells can not secret against high pressure.

	Hepatic bile	Gall bladder bile
Water	% 98	% 89
Total solids	2-4 %	11 %
Bile salts	26	145
Bilirubin	0.7	5
Cholesterol	2.6	16
Phospholipids	0.5	4
Na ⁺	145	130
HCO ₃ ⁻	28	10
Ca ⁺⁺	5	23
Cl ⁻	100	25
K ⁺	5	12
pH	8.3	7.5

Control of biliary system

There are 2 aspects for control

1. Secretion of bile by liver cells (choleresis).
2. Control of the discharge of bile into intestine.

- ❑ The human liver secretes bile at a pressure of about 25 cm H₂O. Between the meals, the choledochoduodenal sphincter is normally closed offering a resistance of about 30 cm H₂O.
- ❑ Bile secreted by liver is thus diverted to the gall bladder during the interdigestive periods.
- ❑ Pressure in the lumen of the gall bladder varies between 0-16 cm H₂O.

1. Control of choleresis

Substances that stimulate hepatic secretion of bile (choleresis) are cholaretics.

- ❖ The deriving force for bile secretion is active transport of bile acids into canaliculi with passive H_2O flow along osmotic gradient.
- ❖ In the biliary ducts HCO_3^- is secreted independently of bile acid secretion & is followed passively by water.

Total bile flow is thus due to 2 components:

Bile acid dependent component

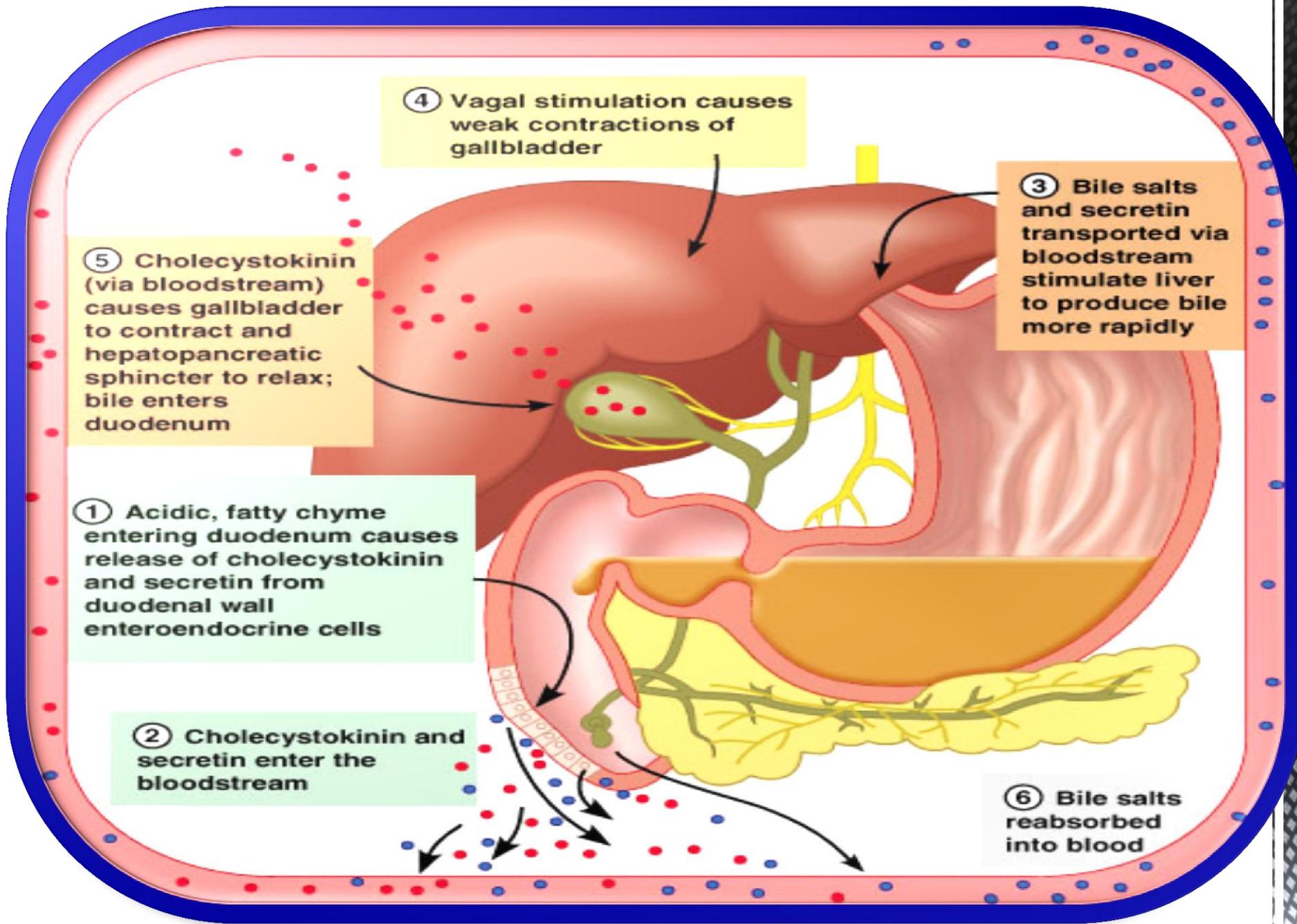
Bile acid independent component

Bile acid dependent component

- The bile acid dependent component depends mainly on the integrity of the enterohepatic circulation.
- At least 90% of the rate of secretion of bile acids is determined by the rate of clearance of reabsorbed bile acids from the portal vein.
- The remaining 10% is due to synthesis of new bile acids by hepatocytes.
- Interruption of the enterohepatic circulation results in markedly reduced choleresis.

Bile acid independent component

- ❧ This fraction of bile secretion is due to secretion of HCO_3^- followed by water by the biliary duct cells. It depends on active sodium transport.
- ❧ Bile acid independent fraction of bile secretion is stimulated by:
 1. Hormones as secretin, glucagon, CCK and gastrin. They all stimulate HCO_3^- & passive water transfer by the biliary duct cells.
 2. Vagal stimulation also stimulates bile flow. The effect is mediated mainly indirectly, through stimulation of gastric acid secretion, which leads to release of secretin & CCK.



④ Vagal stimulation causes weak contractions of gallbladder

③ Bile salts and secretin transported via bloodstream stimulate liver to produce bile more rapidly

⑤ Cholecystikinin (via bloodstream) causes gallbladder to contract and hepatopancreatic sphincter to relax; bile enters duodenum

① Acidic, fatty chyme entering duodenum causes release of cholecystikinin and secretin from duodenal wall enteroendocrine cells

② Cholecystikinin and secretin enter the bloodstream

⑥ Bile salts reabsorbed into blood

N.B:

➤ Increase portal blood flow during digestion increases bile secretion.

➤ But when the liver is markedly congested bile secretion stops due to increase intrahepatic vascular pressure.

2. Control of the discharge of bile into the intestine

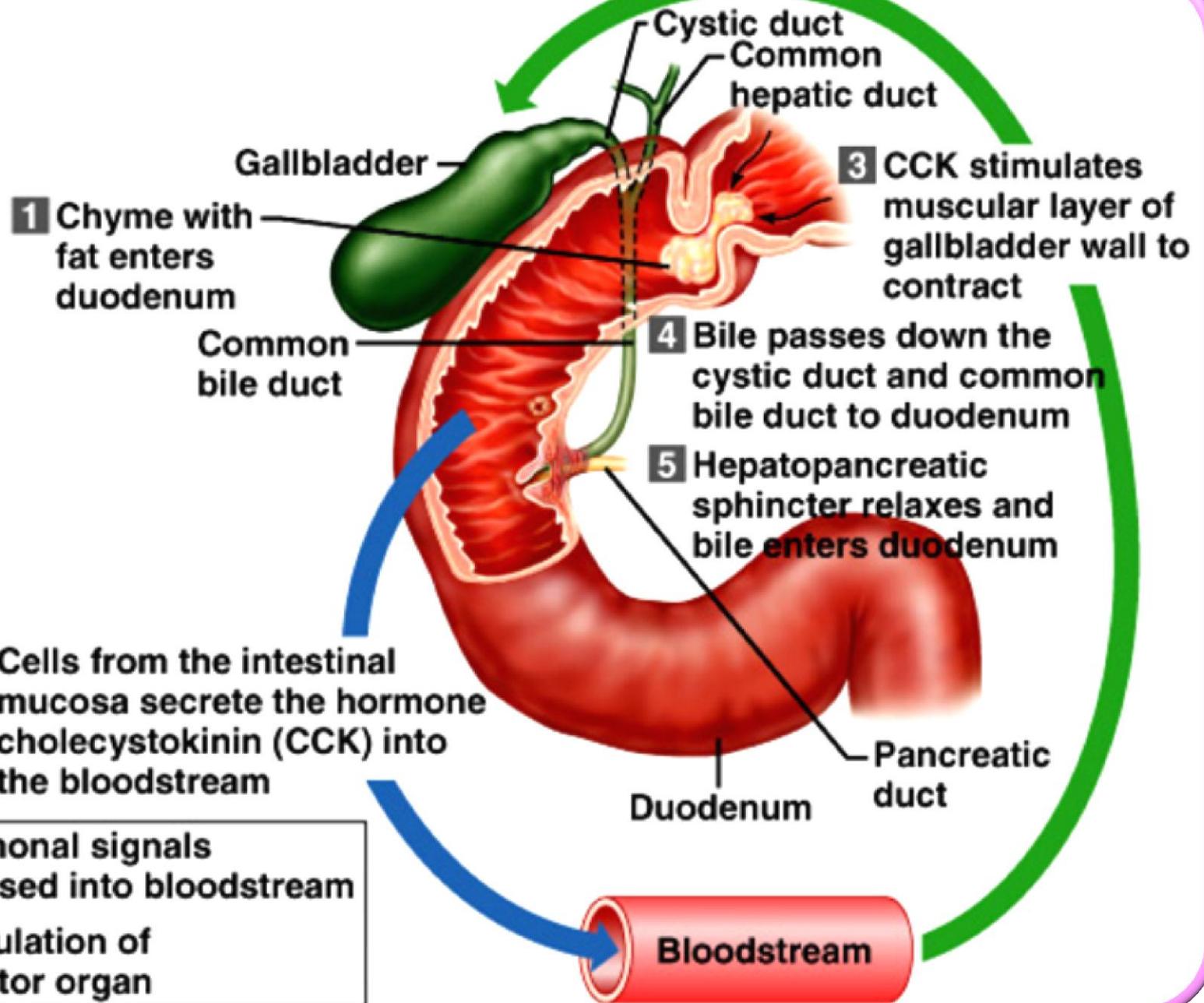
- ❖ Discharge of bile into the duodenum occurs by contraction of gall bladder wall and relaxation of Oddi sphincter. The highest rate of gall bladder emptying occurs during the intestinal phase. Gall bladder evacuants are called cholagogues.
- ❖ Discharge of bile into the duodenum is regulated by nervous & hormonal mechanisms.

A) *The nervous component*

- 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 PNS plays a role in mediating bile secretion.
- Stimulation of the sympathetic nervous system results in relaxation of the gallbladder and reduced bile secretion.

B) The hormonal component is mediated by CCK. The presence of digestive products of fat & proteins releases CCK from the upper intestine into the blood. CCK contracts gall bladder and relaxes sphincter of Oddi, thus discharging bile into the duodenum. Both vagal excitation & secretin augment the action of CCK on the gall bladder.

C) MgSO_4 contract the gall bladder and discharge bile into the intestine as it releases



***Physiology of Bile Salts and
Pathogenesis of Gall stones (11)***

By



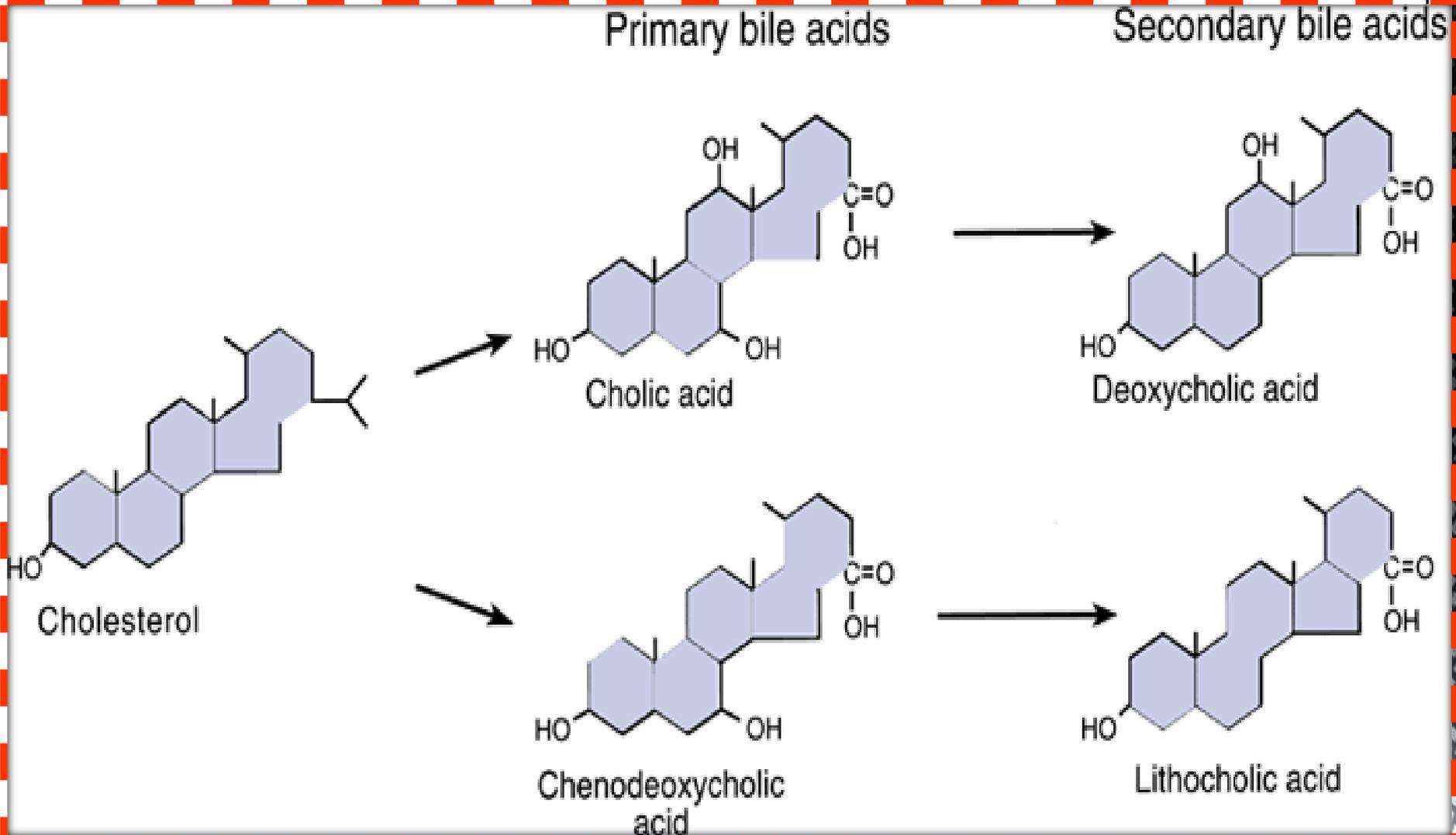
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Bile acids & salts

- ✓ 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

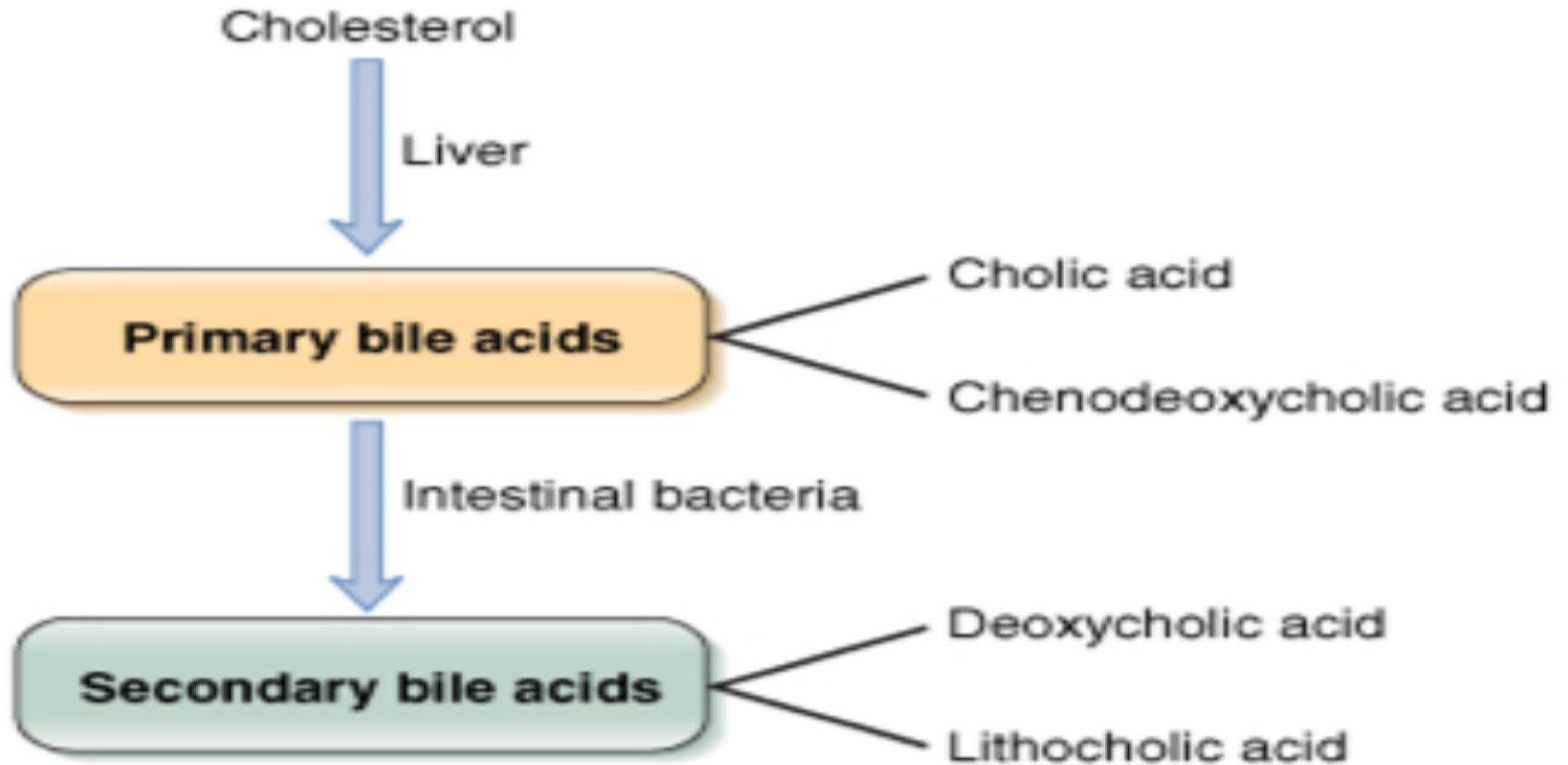


Bile acids & salts (Cont.)

- ✓ 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.

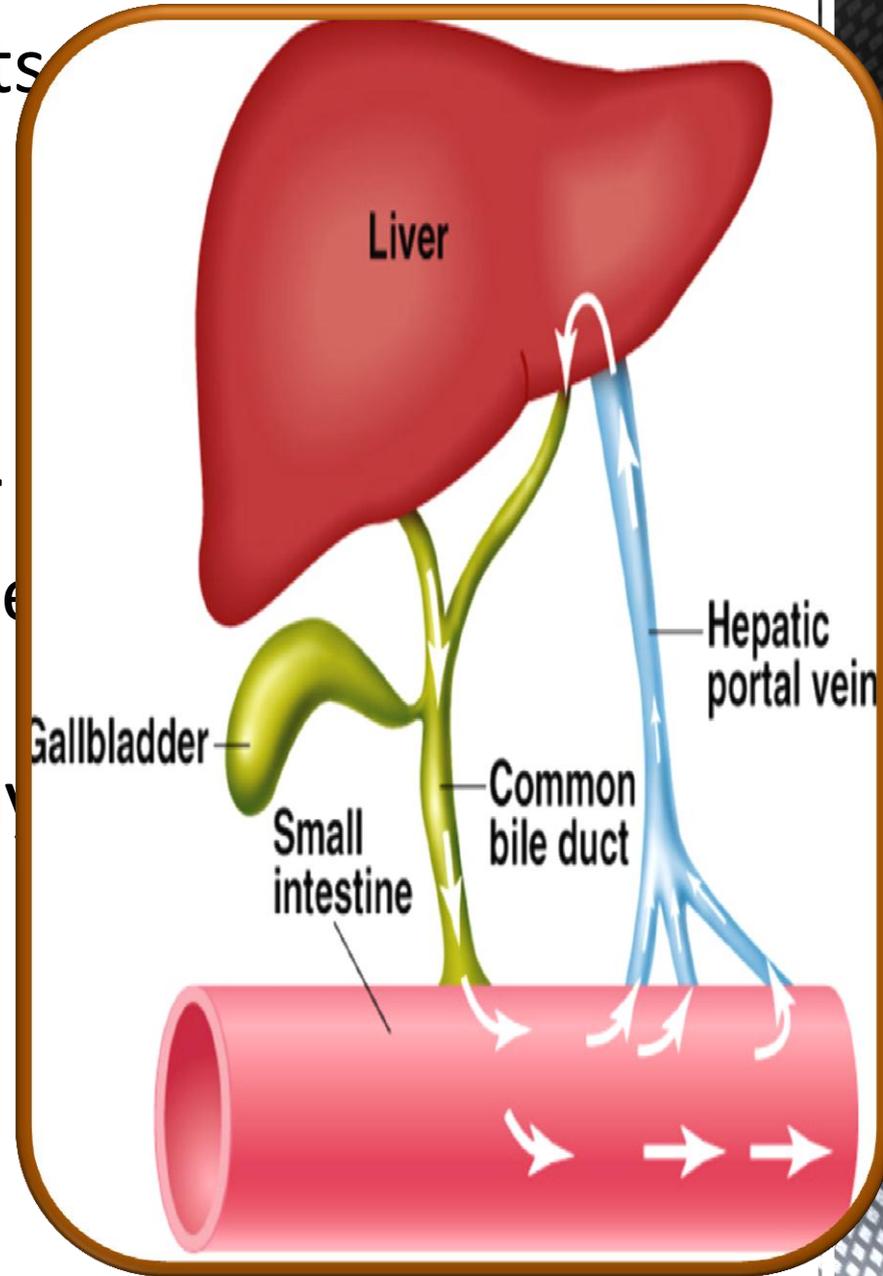
- ✚ Bile acids are amphipathic that is having both hydrophilic & hydrophobic domains and tend to form molecular arrangement called micelles.
- ✚ In bile acid micelle, the hydrophobic side of bile acid faces inside & away from water. The hydrophilic surface faces outward towards the water.
- ✚ Bile acid 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.

Primary and secondary bile acids

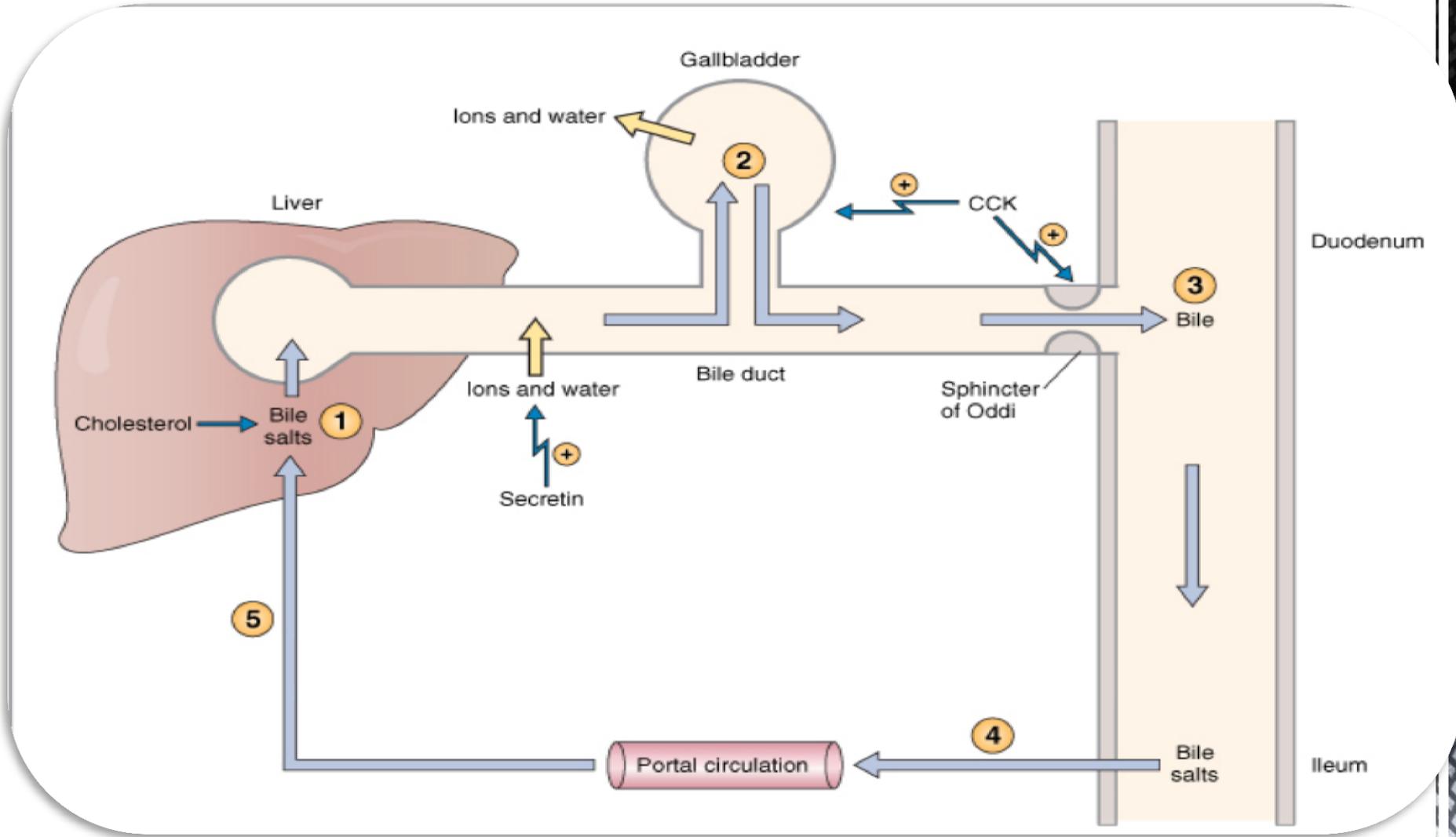


Enterohepatic Circulation of Bile Salts.

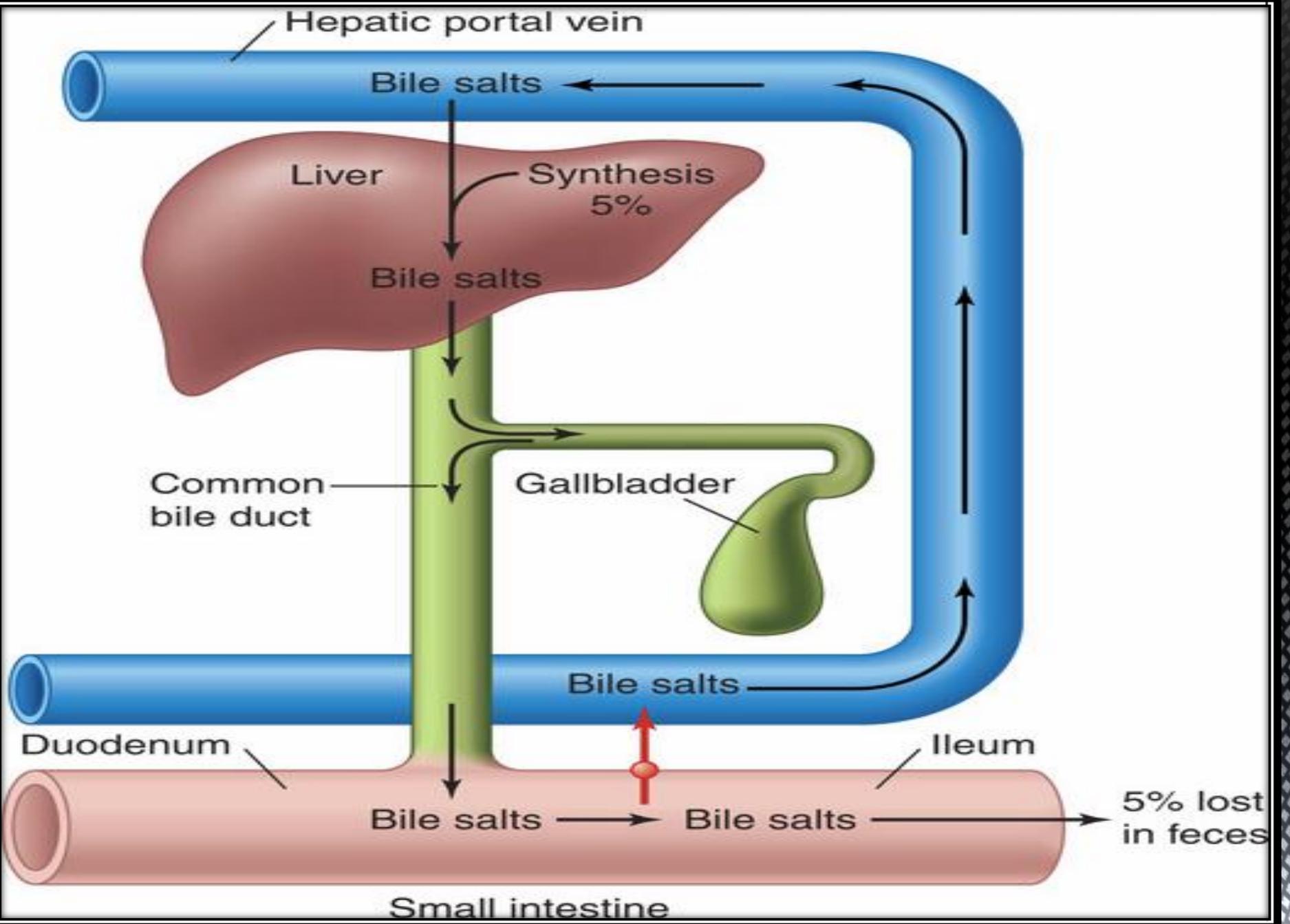
- ❖ It is the recycling of bile salts between the small intestine and the liver.
- ❖ The total amount of bile acids in the body, primary or secondary, conjugated or free at any time is defined as the total bile acid pool. In healthy people, the bile acid pool ranges from 2 to 4 g.



Secretion and enterohepatic circulation of bile salts



- ♠ About 20-30 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, 90 % of bile acids are absorbed and reach the liver through the portal vein.



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

- ❖ 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.
- ❖ Since the amount of bile acids poured into the duodenum each day is 20-30 g, the daily turnover of total bile acid pool through the enterohepatic circulation must be 6-10 times.

Absorption of bile acids in the intestine lumen

❁ Bile acids are absorbed largely in the terminal part of the ileum. They cross the brush border plasma membrane by two routes:

- Active transport process .
- Simple diffusion.

❁ The active transport process is 2^{ry} active transport powered by the Na⁺ gradient across the brush border membrane.

- Conjugated bile acids are the principal substrates for active absorption;
- Unconjugated bile acids have poor affinity for the transporter.

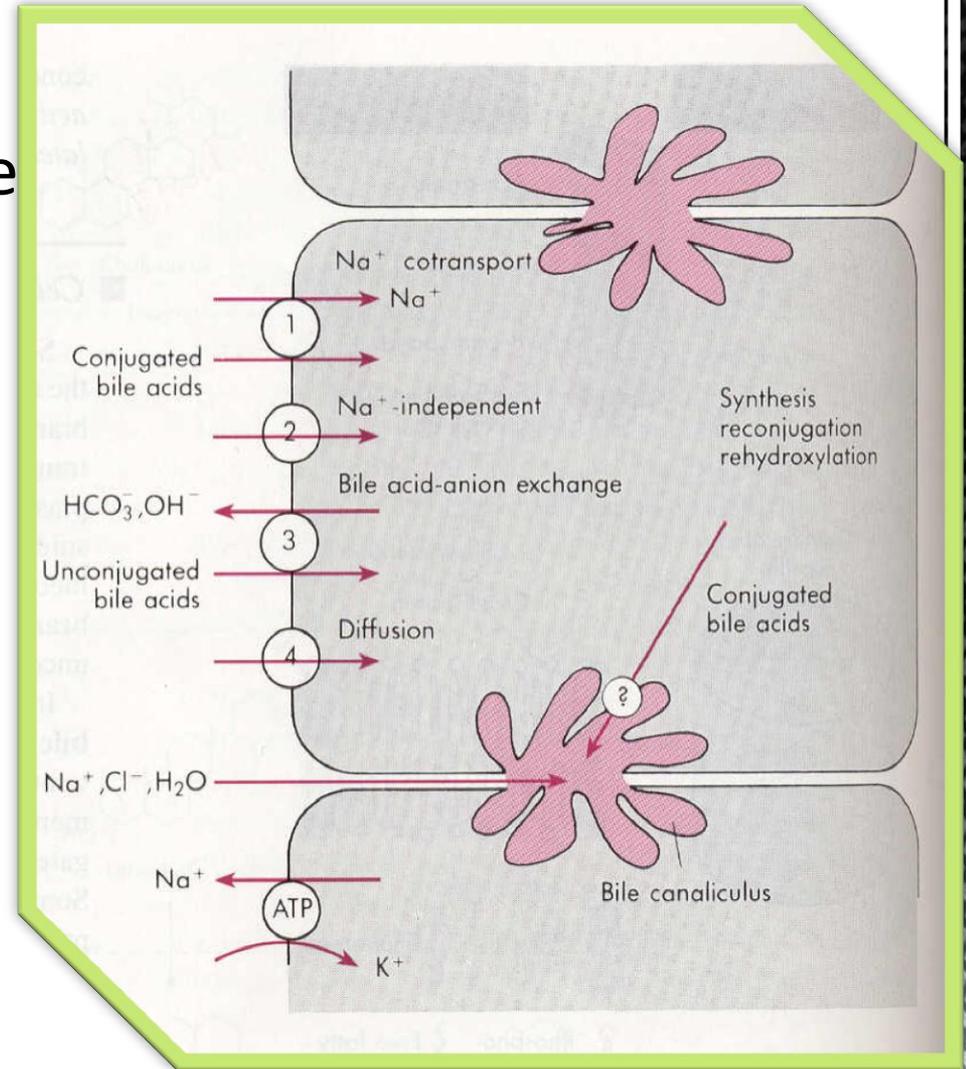
- ❁ However, because unconjugated bile acids are less polar than conjugated bile acids, they are better absorbed by simple diffusion.
- ❁ The fewer hydroxyl groups on a bile acid, the poorer substrate the bile acid is for active absorption & the more nonpolar is the bile acid.
- ❁ For these reasons, dehydroxylation of bile acids by enteric bacteria to form 2^{ry} bile acids enhances absorption of bile acids by diffusion.

- ❁ Bile acids may be bound to proteins, (which remain to be identified), in intestinal epithelial cells.
- ❁ Absorbed bile acids are carried away from the intestine in the portal blood, mostly bound to albumins.

- ❖ 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 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)



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.

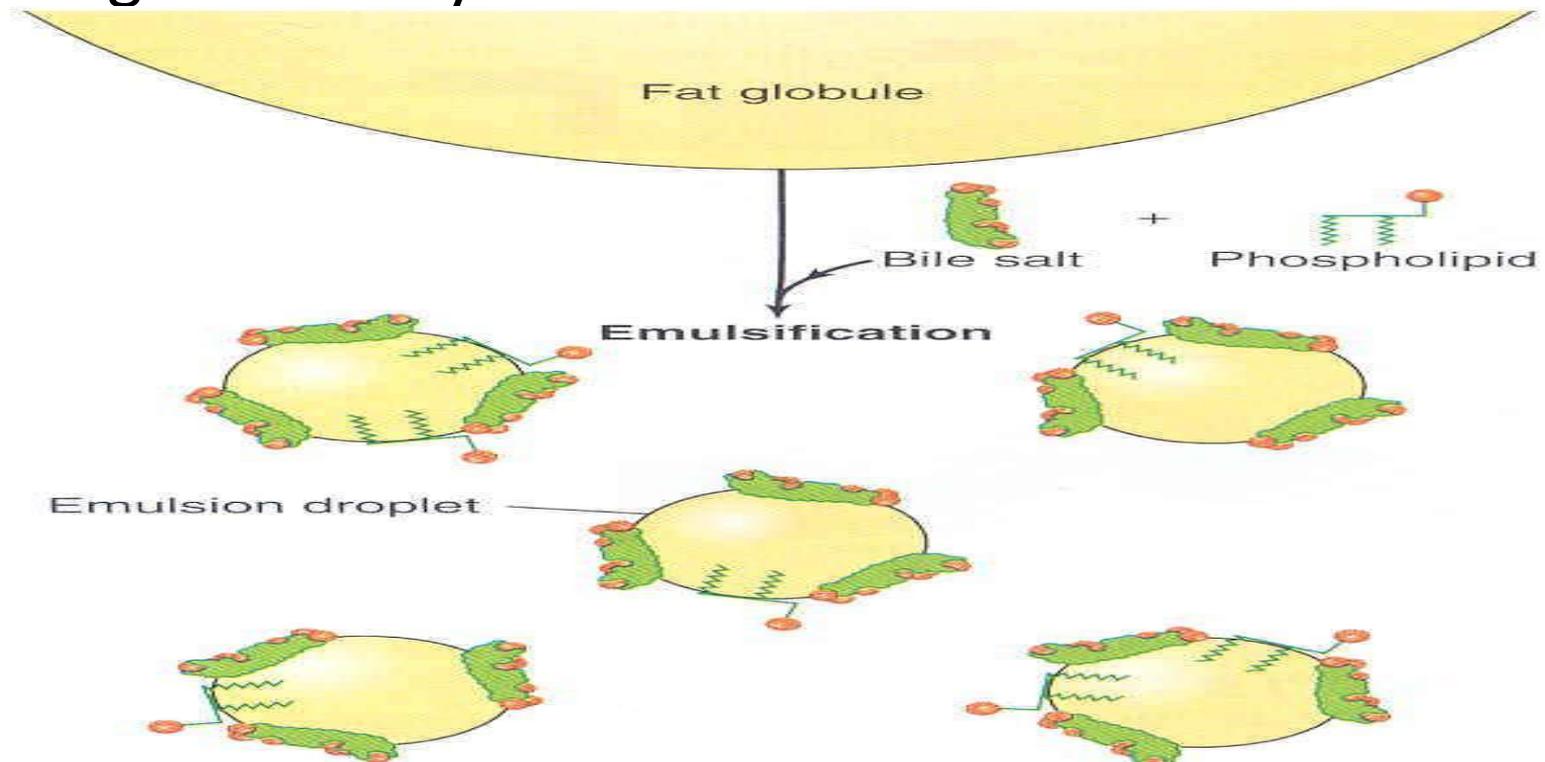
- ❑ In a light eater, the bile acid pool may circulate 3-5 times a day; in a heavy eater, it may circulate 14 to 16 times a day.
- ❑ If enterohepatic circulation is interrupted (e.g. due to obstruction by disease or surgical removal or inflammation of the terminal ileum), bile flow is markedly reduced 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.

- 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 reconstituted & some 2^{ry} bile acids are rehydroxylated.
- The reprocessed bile acids, together with newly synthesized bile acids, are secreted into bile.

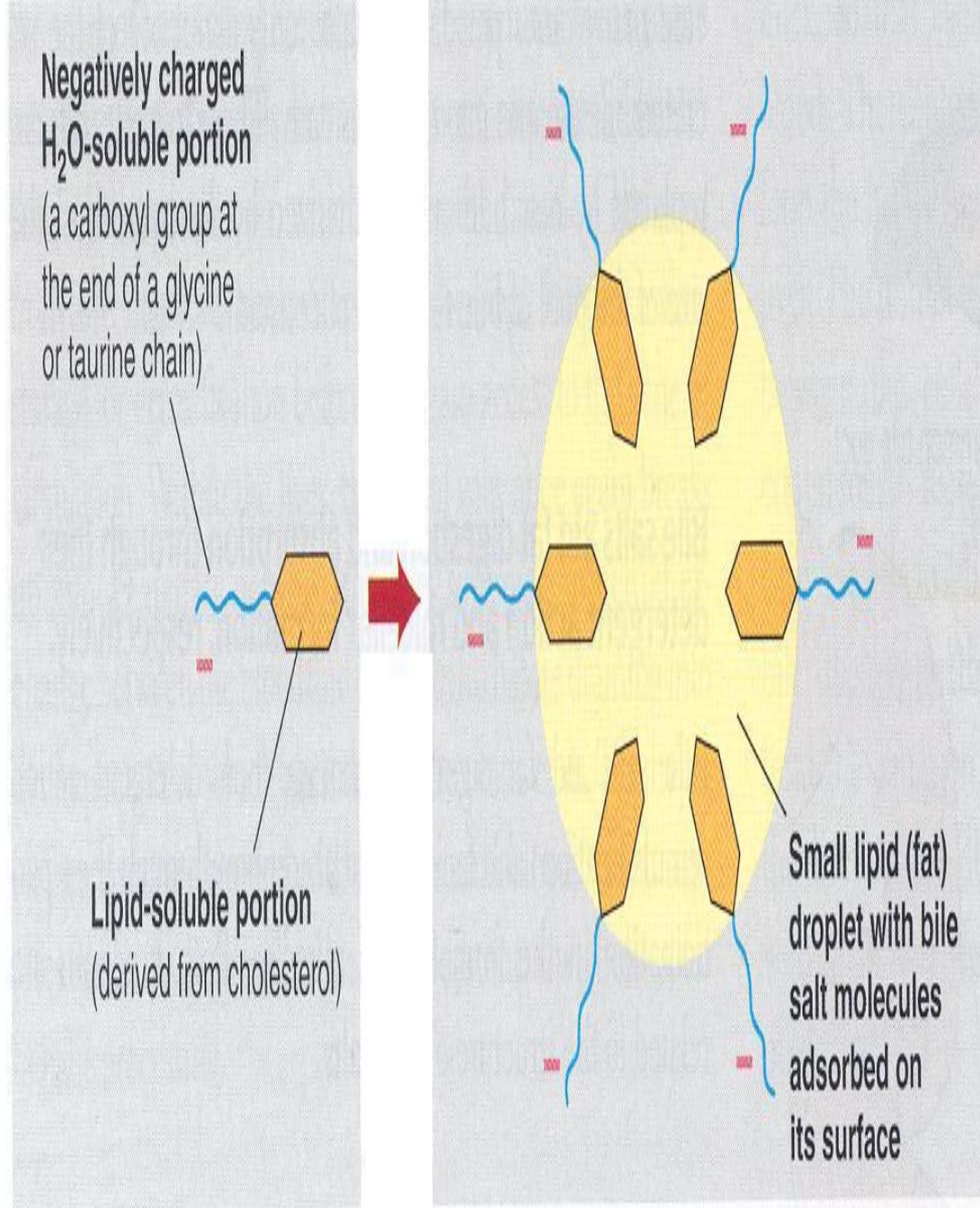
Functions of bile acids

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 the 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.

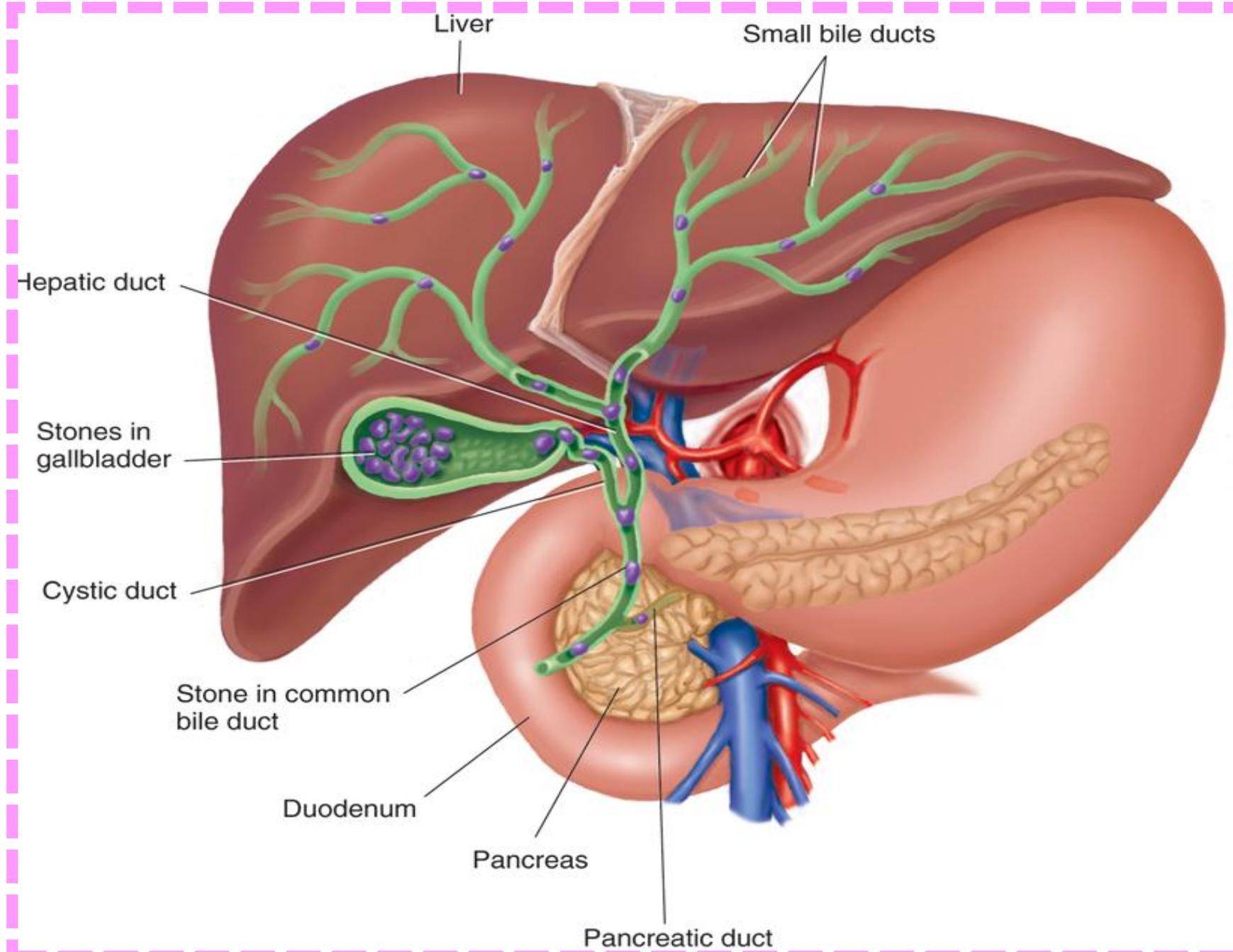
- ❖ The micelles remain stable so long as the concentration of bile acids, phospholipids & cholesterol remain within certain limits.
- ❖ If the relative concentration of any of the constituents alters, e.g. if bile contains more cholesterol than can be solubilized, (bile is supersaturated with cholesterol), 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

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

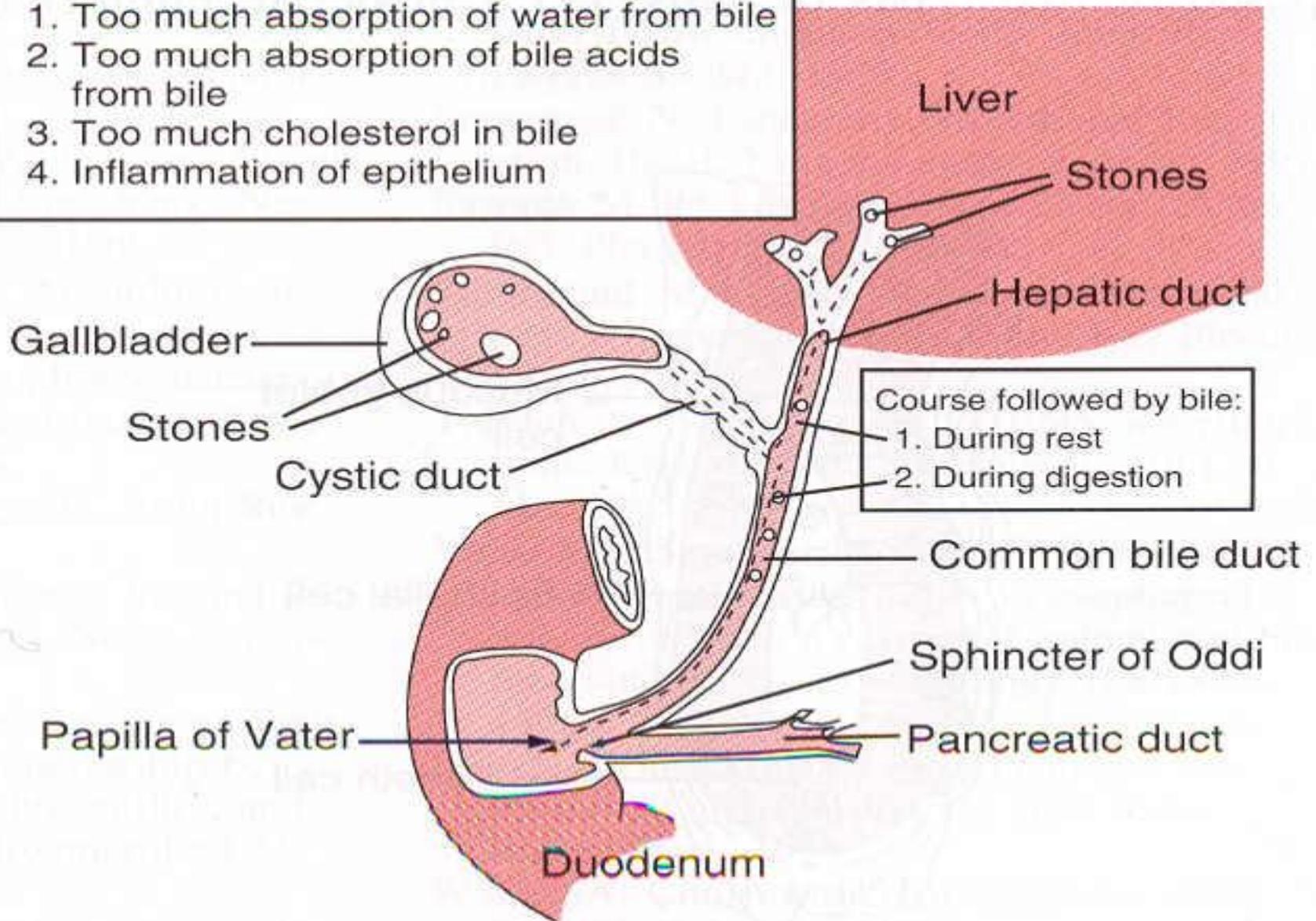
The causes may be:

- Too much absorption of water from the bile.
- Too much absorption of bile salts & lecithin from the 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:

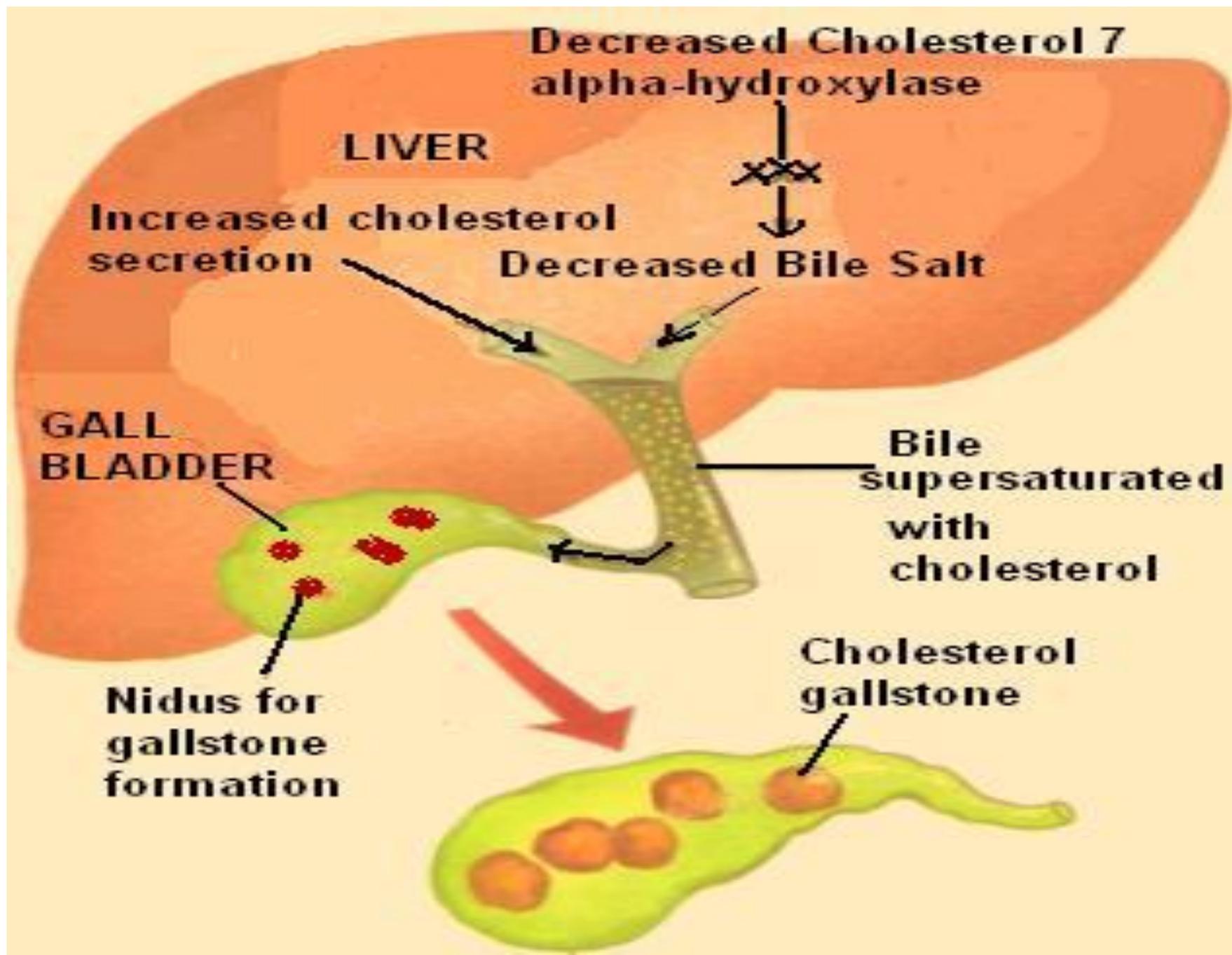
- ❖ The main constituent is calcium salt of unconjugated bilirubin.
- ❖ In liver diseases, bile may contain elevated levels of unconjugated bilirubin.
- ❖ Individuals with liver disease have an increased incidence of forming bile pigment stones.

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.



Effects of Cholecystectomy:

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

سبحانك اللهم وبحمدك أشهد أن لا إله إلا أنت،
استغفرك وأتوب إليك

