



14

PHYSIOLOGY OF BILE  
SALTS &  
PATHOGENESIS OF  
GALL STONES



GIT

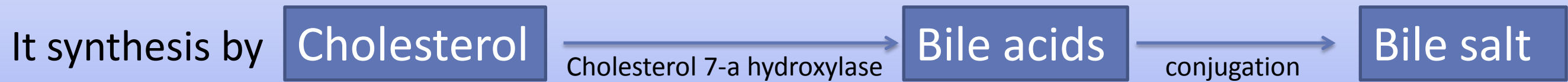
# Learning Objectives

- Primary and secondary bile acids
- Enterohepatic circulation of bile salts
- Absorption of bile acids in the intestinal 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

**Bile:** is a watery mixture of organic and inorganic compounds synthesized by liver.

Mainly consist of = **bile acid** + **bile salt** ( **conjugated bile acid** )



How **bile salt** gets conjugated?

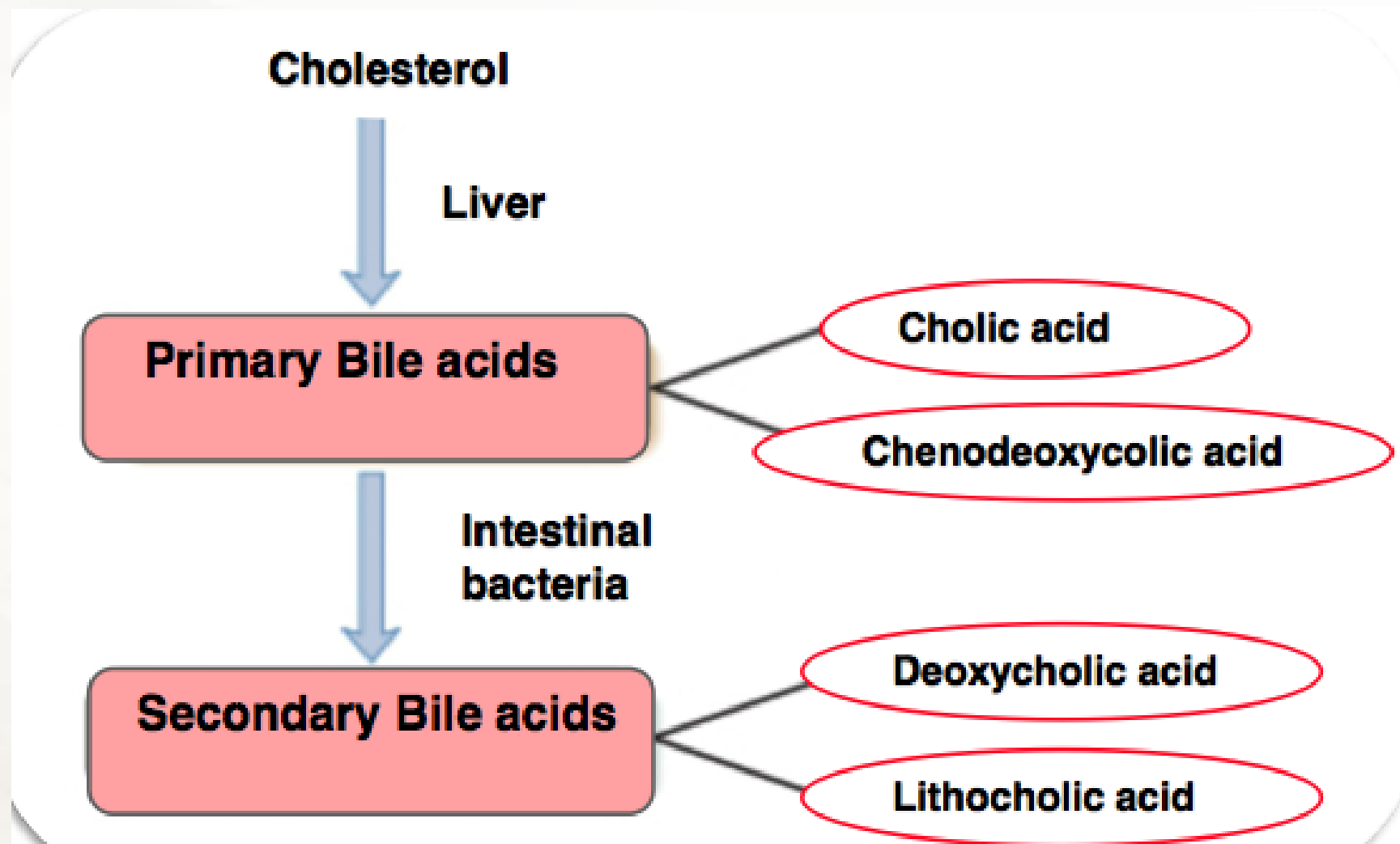
By adding glycin or taurine ( to bile acid ) to form glyco and taurocholic bile.

So bile acid + glycin or taurine = bile salt

How **bile acid** gets conjugated?

We have two types of bile acid : **primary** ( in liver ) and **secondary** ( in small intestine ).

The changes occur to primary to become secondary we call it dehydroxylation by bacterial intestine.



## **Why bile acid needs to get conjugated?**

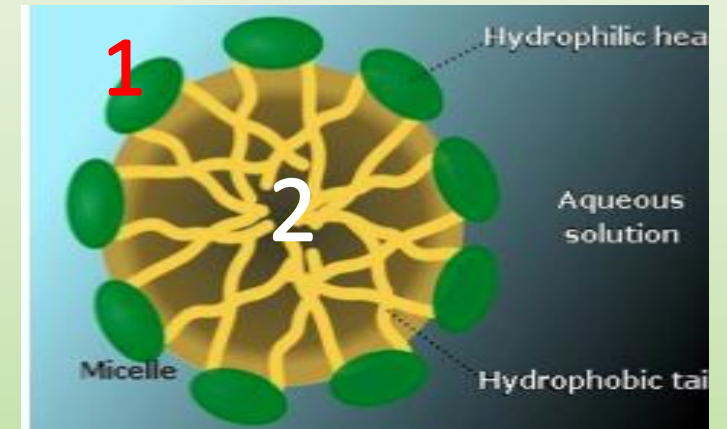
- 1- Because cholesterol is insoluble in pure water. That's why at neutral pH it will conjugate to become more water soluble and have a lot of ions especially cations (  $\text{Na}^+$ ).
- 2- Bile salts are much more polar than bile acids and have greater difficulty penetrating cell membranes .
- 3- 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

- Lipids can not be absorbed alone , they need the help of **micelles** .
- **Micelles** : are bile acids amphipathic that is having both **hydrophilic** outside & **hydrophobic** inside .

Normally bile acid concentration in bile is much greater than critical micelle conc.

**So when bile acid increases its concentration It will join the micelles.**



**What happen if bile acid (primary) is secreted in the duodenum?**

some of bile acids are deconjugated and dehydroxylated in the 7  $\alpha$  position by intestinal bacteria ( as discussed before )

Dehydroxylation results in the production of secondary bile acids as following:

Cholic acid



deoxycholic acid

chenodeoxycholic acid



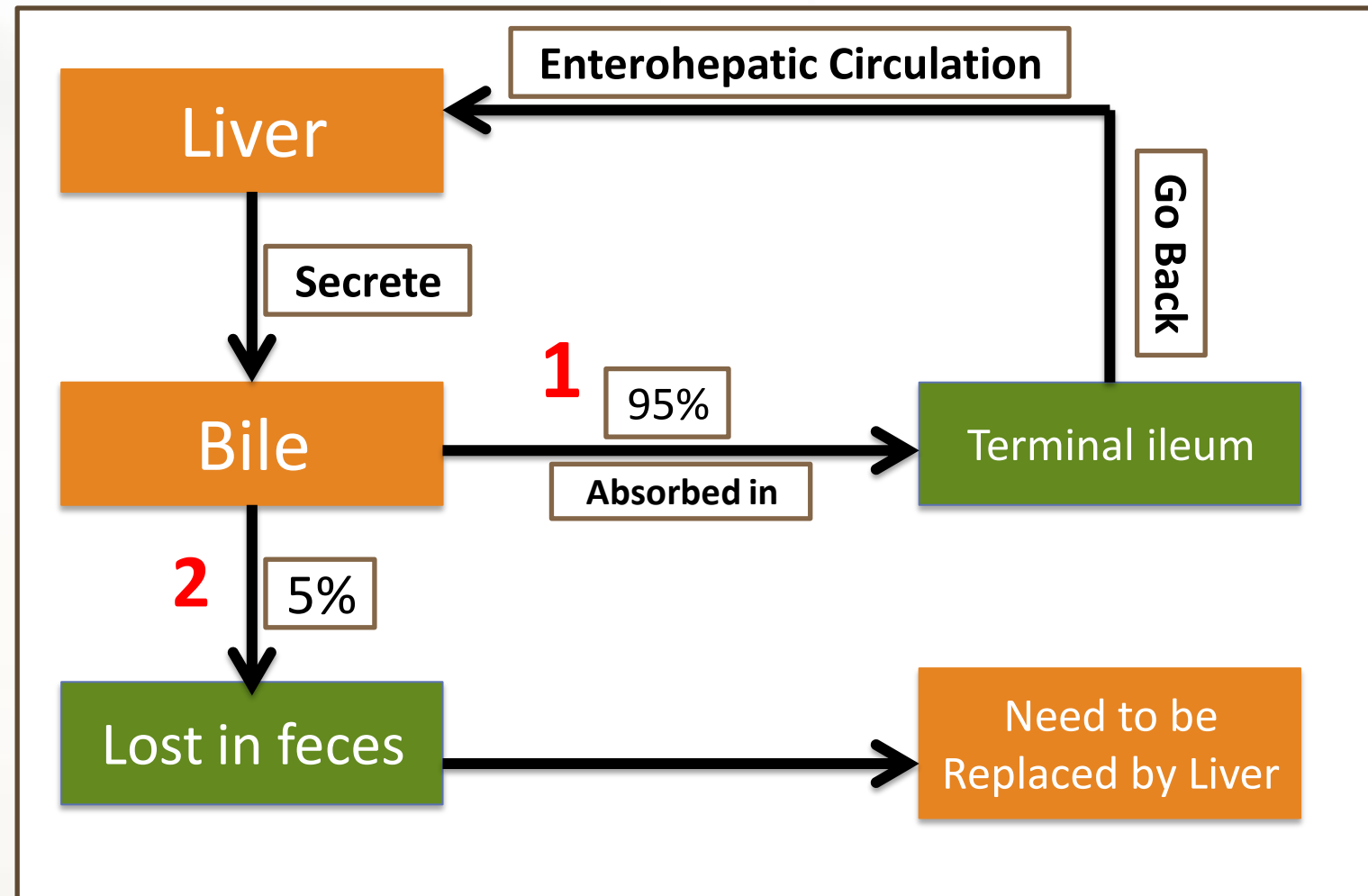
lithocholic acid

# Enterohepatic Circulation of Bile Salts

It is the recycling of bile salts between the small intestine and the liver.

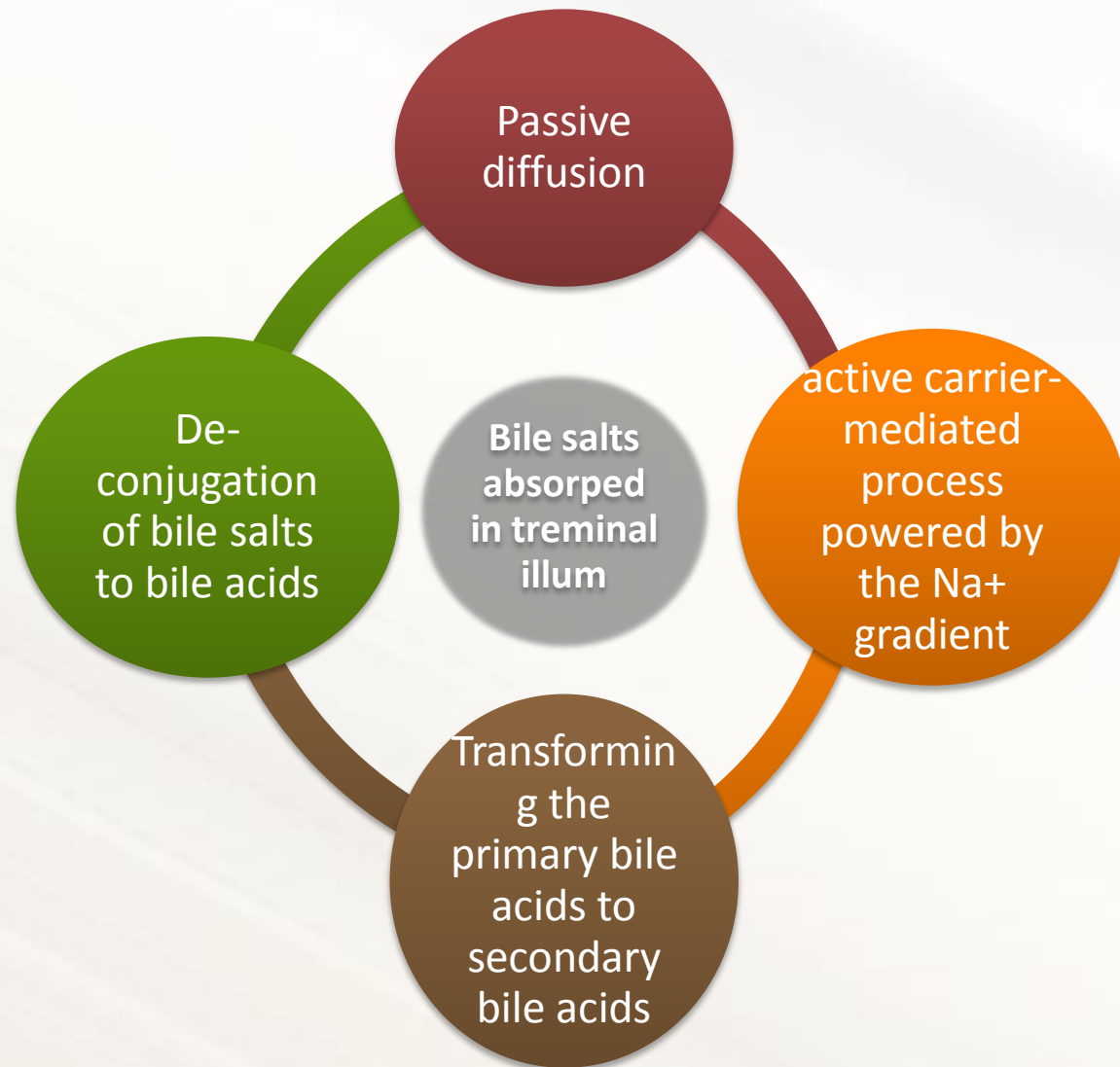
1- On reaching the **terminal ileum**, 90-95 % of **bile salts** are absorbed and reach the liver through the portal vein.

2- about 0.2-0.6 g of bile salts are **lost in feces** daily (15- 35% of total bile acid pool)  
\***These are replaced by new synthesis in liver.**



**Total bile acid pool**: is The total amount of bile acids in the body, primary or secondary, conjugated or free, at any time.  
It should be ranges from **2-4 g** (that's why the lost in faces is replaced)

# Absorption of bile salts in intestine



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

## Notes:

- 1- primary bile salts are absorbed better than secondary .
- 2- cholic acid is absorbed faster than chenodeoxycholic acid,
- 3- unconjugated bile acids are absorbed passively in the colon

## Uptake of bile acids from sinusoidal blood

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

1. **An active carrier-mediated process**
2. **Facilitated diffusion**
3. **Bile acid-HCO<sub>3</sub>-or OH-exchange**
4. **Passive diffusion (very little)**

# Importance of enterohepatic circulation of bile acids

1. It is essential for stimulating and 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 during a meal, a relatively small bile acid pool can provide the body with sufficient amounts of bile salts to promote lipid absorption

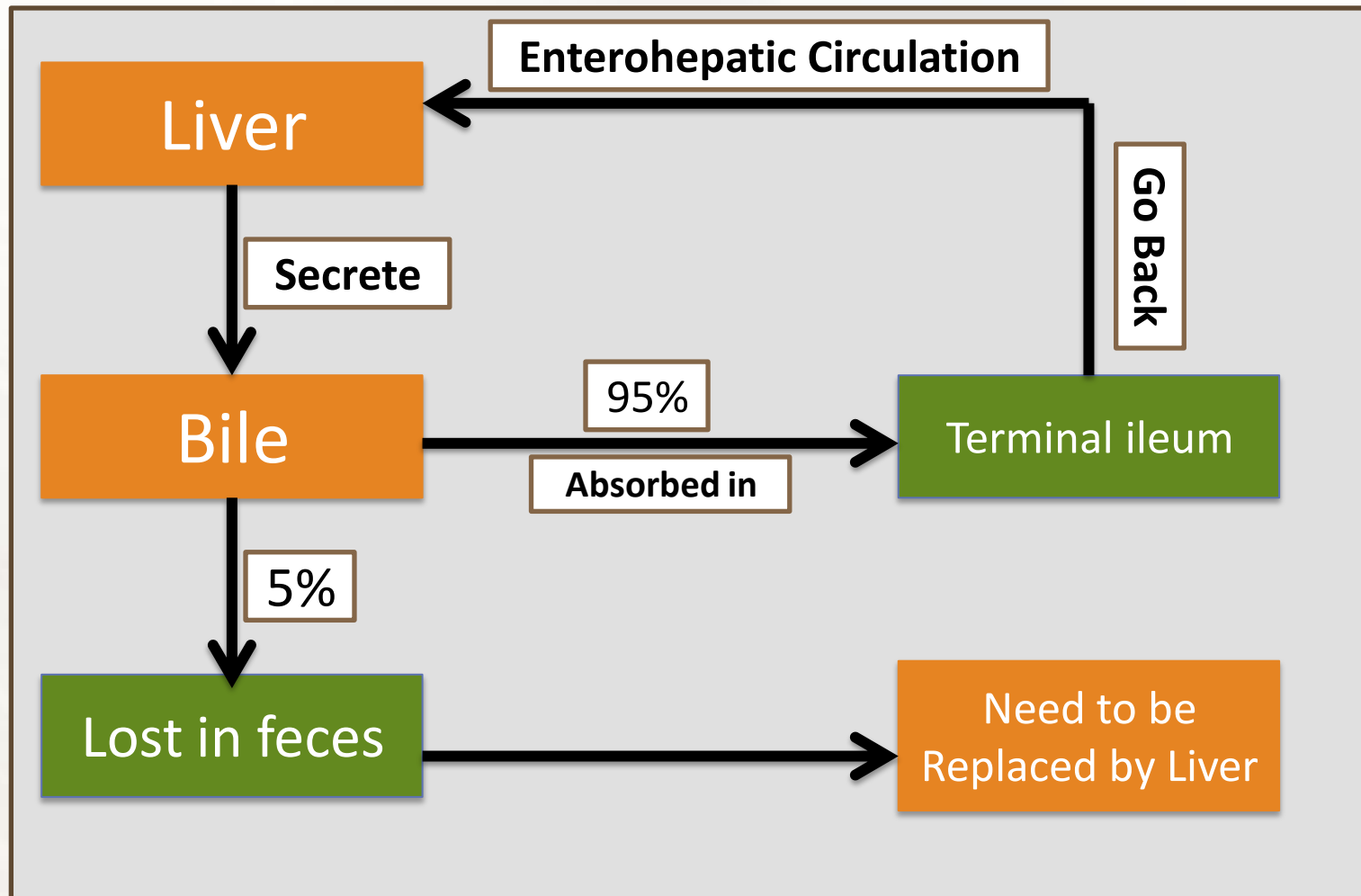
4. In a light eater, the bile acid pool may circulate 3-5 times a day; in a heavy eater, it may circulate 14 to 16 times a day.

5. If enterohepatic circulation is interrupted (e.g. due to obstruction 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.

6. 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





**Enterohepatic Circulation is 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 reconstituted & some 2ry bile acids are rehydroxylated.
- The reprocessed bile acids, together with newly synthesized bile acids, are secreted into bile.

## 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).

# Functions of bile acids

**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 micelles 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.

## Functions of bile acids

7. They have a –ve feedback effect on the **synthesis of cholesterol** by the intestinal mucosal cells.

### 8. Anti putrefactive:

Bile acids have **no direct anti septic effect** but they prevent putrefaction by absorption of fat. In their absence undigested fats cover the protein particles & hinder their digestion.

- ✓ 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 & phospholipids
- ✓ 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.
- ✓ bile with a **high concentration of cholesterol**, cholesterol gallstones may form in the gall bladder.

# TYPES OF GALL STONES

Gall stones may be formed in the gall bladder or bile ducts. **The commonest 2 types are**

1-cholesterol

2-Calcium bilirubinate stones(pigmented)

## 1.Cholesterol stones

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 results from chronic infection → changes the **absorptive characteristics** of gall bladder mucosa → excessive absorption of water & bile salts.

## 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

## Risk factors for gallstones

- 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

# PATHOPHYSIOLOGY OF GALL STONES

Gallstones due to imbalance rendering cholesterol & calcium salts insoluble

Pathogenesis of **cholesterol** gallstone:

- 1) cholesterol supersaturation in bile.
- 2) Crystal nucleation.
- 3) stone growth.

**Black** pigment stones:

contain **Ca<sup>++</sup>** salts, following hemolytic conditions or cirrhosis, found in the gallbladder.

**Brown** pigment stones:

Asians, contain **Ca<sup>++</sup>** palmitate, found in bile ducts, following biliary dysmotility and bacterile infection

## EFFECT OF CHOLYCYSTECTOMY

- ✓ 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.



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**GOOD LUCK**

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