Physiology Team

LECTURE 11

Physiology of Bile Salts & Pathogenesis of Gallstones

GASTOINTSTINAL TRACT

Thanks For Cooperation:
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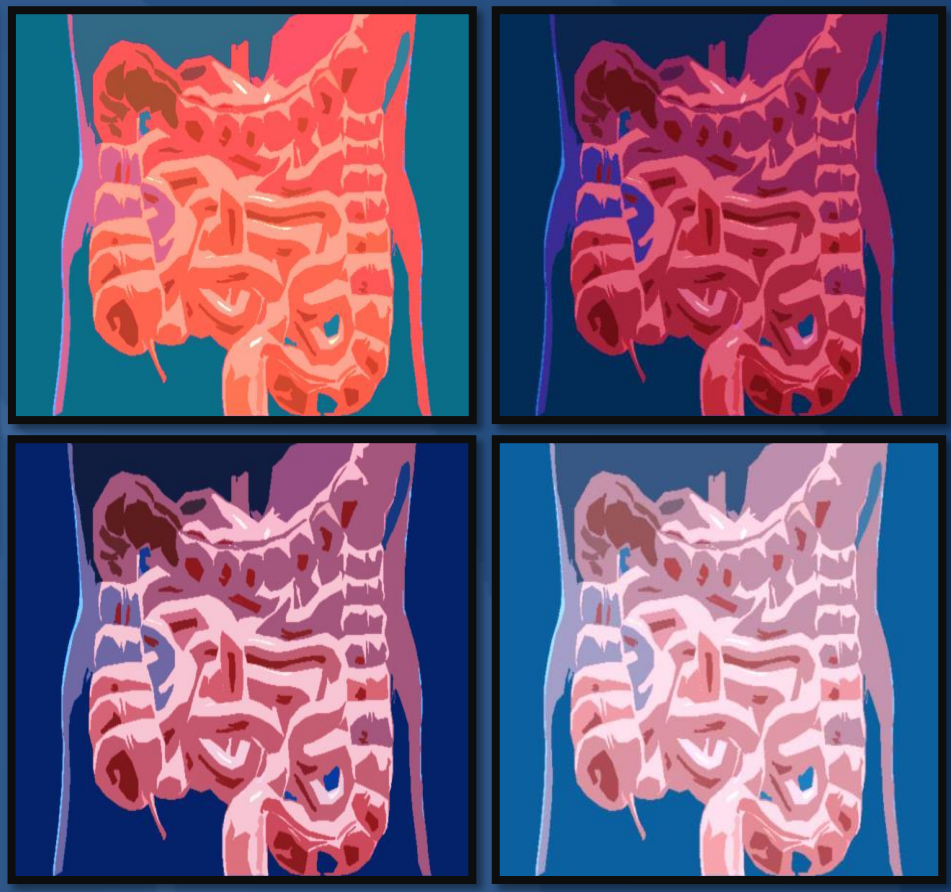

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OBJECTIVES

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At the end of this lecture, student should be able to describe:

- 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

MIND MAP

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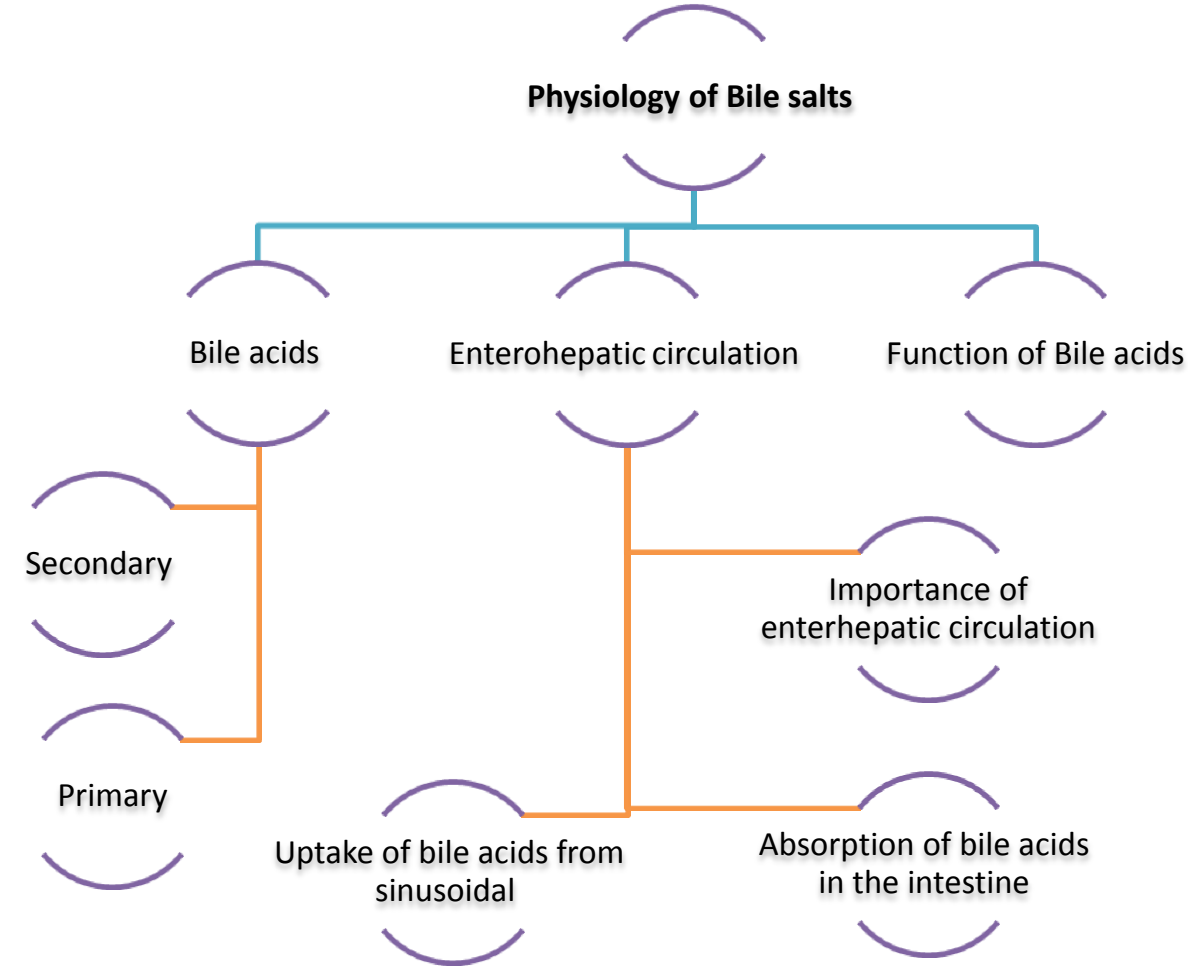

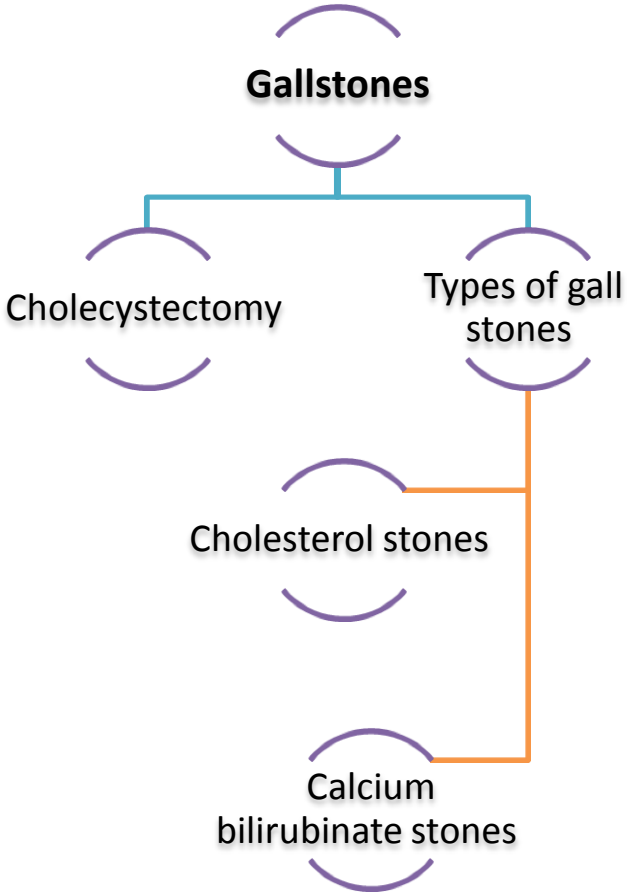

Bile acids & Salts

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First of all, there is a little difference between Biochemistry lecture and physiology lecture. In physiology they said bile acids and salts as they are the same. So Dr. Hayam said in physiology they only care about the function and don't differentiate between bile salts or bile acids, so we can treat them as the same thing and the only reason she puts ''bile salts(acids)'' together is so that in the exam if she asks something about bile salts no one can object and say that in the slides it was the opposite (bile acids).

Bile acids:

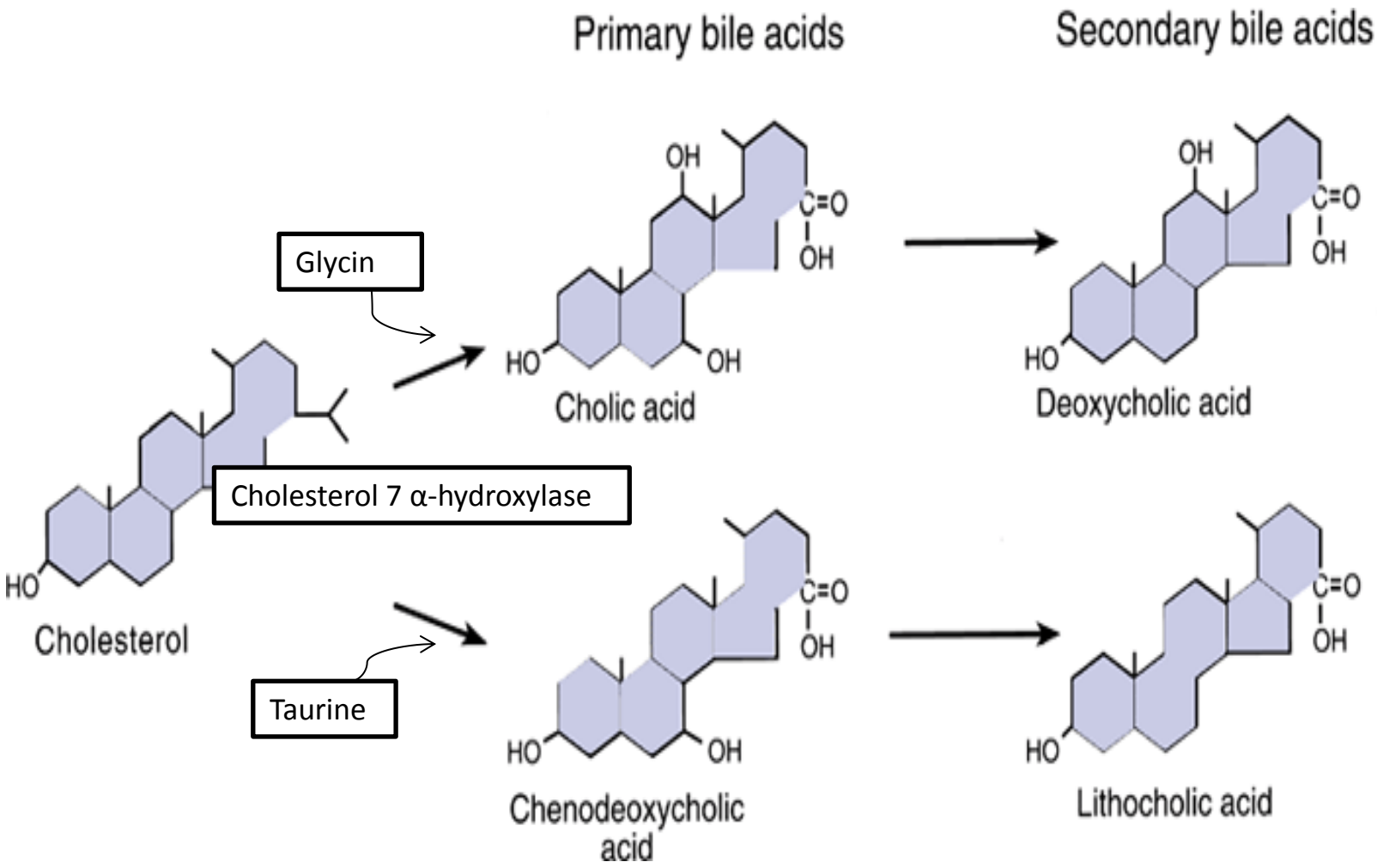
- Bile acids are steroid acids, synthesized in the liver from cholesterol by the enzyme cholesterol 7α-hydroxylase.

Bile acids include:

- **Primary:** cholic, chenodeoxycholic acids. (formed in the liver)
- **Secondary:** deoxycholic, lithocholic acids. (formed in the intestine by bacterial action)

- The principle primary bile acids conjugate with glycin or taurine to form glyco and taurocholic bile acids.

Bile acids & Salts



Primary and secondary bile acids

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- 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.

The bile salts are sodium and potassium salts of bile acids conjugated to glycine or taurine

- 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.

Primary and secondary bile acids

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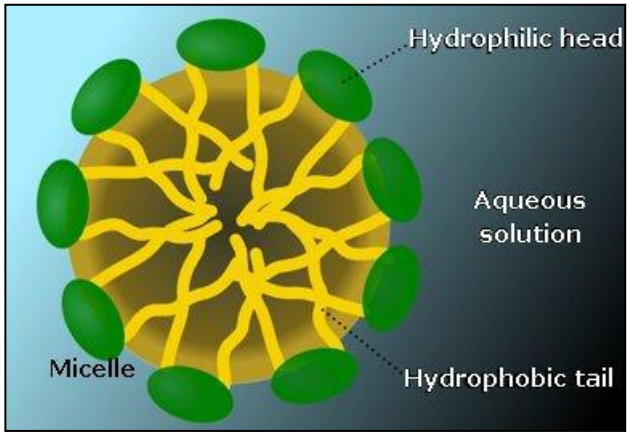
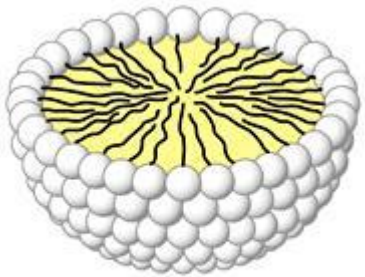
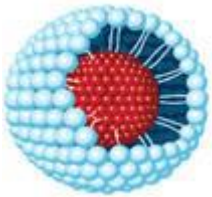
- **Bile acids** are amphipathic that is having both hydrophilic & hydrophobic domains and tend to form molecular arrangement called micelles.
- In **bile acid micelle**, the hydrophobic side of bile acid faces inside & away from water. The hydrophilic surface faces outward towards the water.
- **Bile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





Micelle



Enterohepatic circulation

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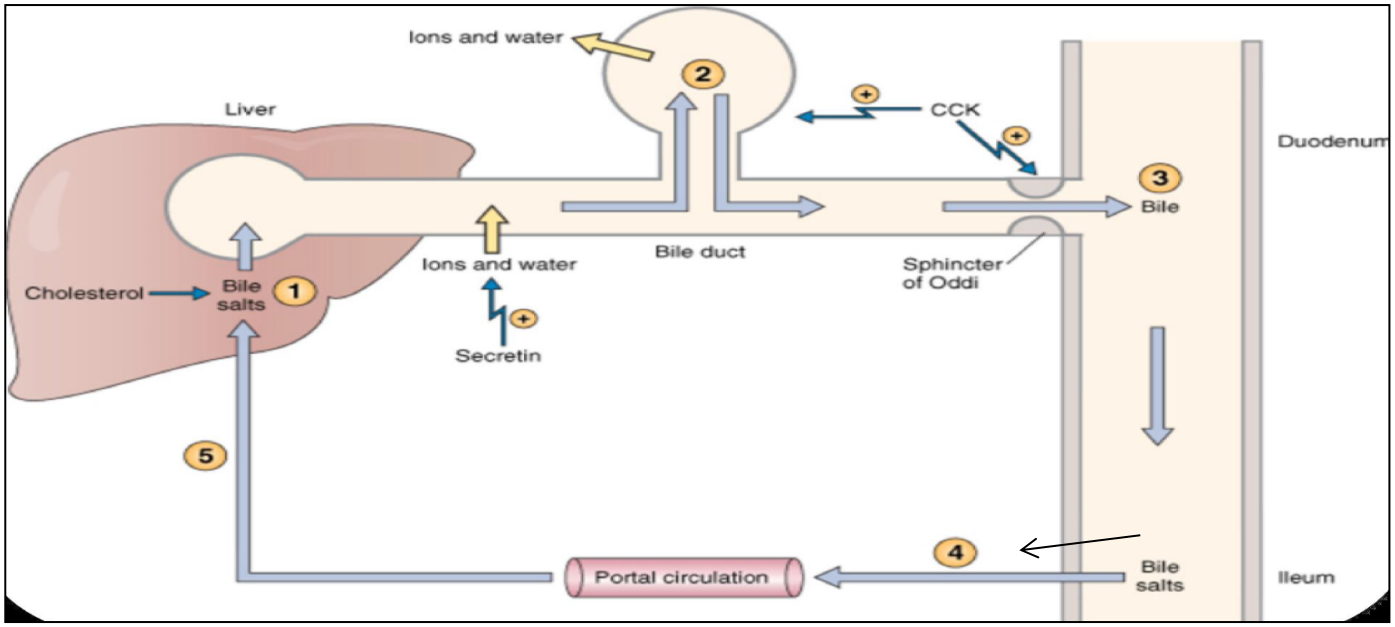
- It is the recycling of bile salts between the small intestine and the liver.

Total bile acid pool:

- The total amount of bile acids in the body, primary or secondary, conjugated or free, at any time.
- In healthy people, the bile acid pool ranges from 2-4 g.

Absorption of bile salts



■ Slides ■ Important ■ Females' Notes ■ Explanation ■ Males' Notes

Primary and secondary bile acids

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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).
And twice per meal.
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.

- **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.
- 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 intestinal lumen

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Bile salts in the intestine lumen are absorbed largely in the terminal part of the ileum via **2 pathways:**

1. Passive diffusion
2. An active carrier-mediated process powered by the Na+ gradient across the brush border membrane.

Bile acids are absorbed as

1. **Primary bile acids** after de-conjugation of bile salts to bile acids.
2. **Secondary bile acids** after 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

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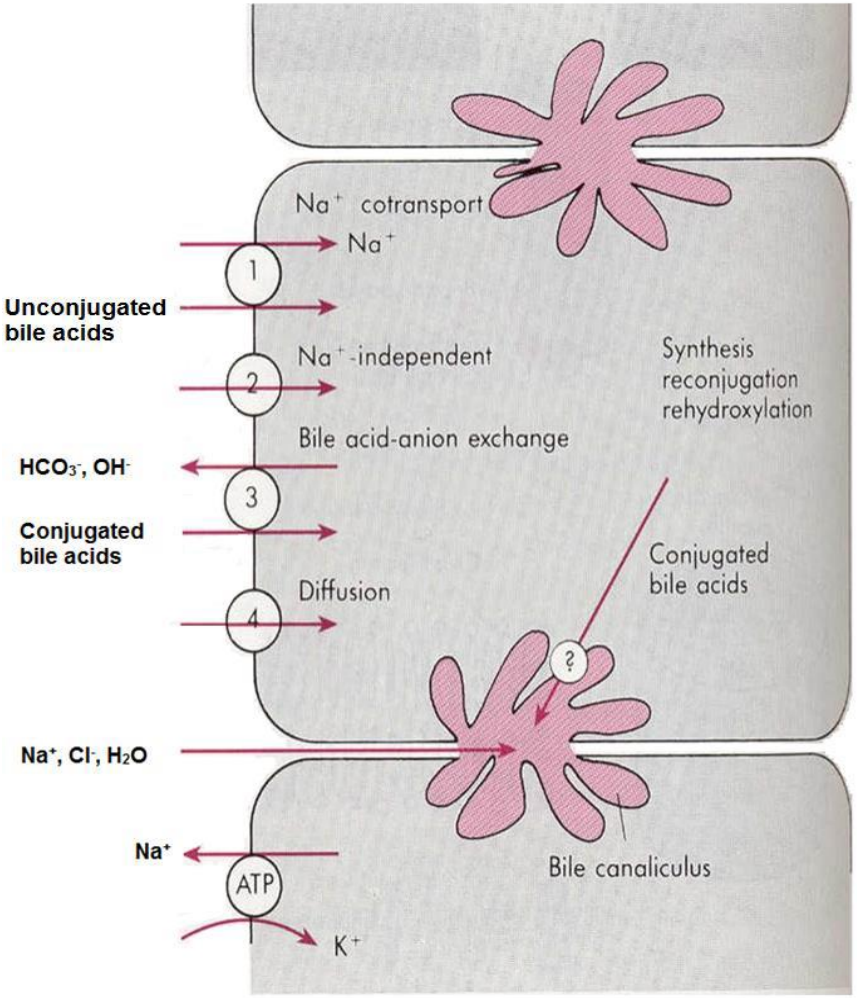
- Multiple transport mechanisms are located in hepatocyte plasma membrane for uptake of bile acids from sinusoidal blood.

- An active carrier-mediated process
- Facilitated diffusion
- Bile acid-HCO3-or OH- exchange
- Passive diffusion (very little)



Importance of enterohepatic circulation of bile acids

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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. If enterohepatic circulation is interrupted , e.g. due to obstruction by disease or surgical removal or inflammation of the terminal ileum (bile salts reabsorption is prevented), bile flow is markedly reduced and large quantities of bile salts are lost in the feces.

Because when the enterohepatic circulation is interrupted, the liver can't increase the rate of bile salts production to a sufficient degree to compensate for the loss, and fat digestion is compromised.

- **N.B:** Excess amount of bile acids entering the colon may result in diarrhea.
- If bile acids is decreased below the normal level >> constipation

5. Depending on the severity of illness, malabsorption of fat may result (steatorrhea).

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

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

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

Functions of bile acids

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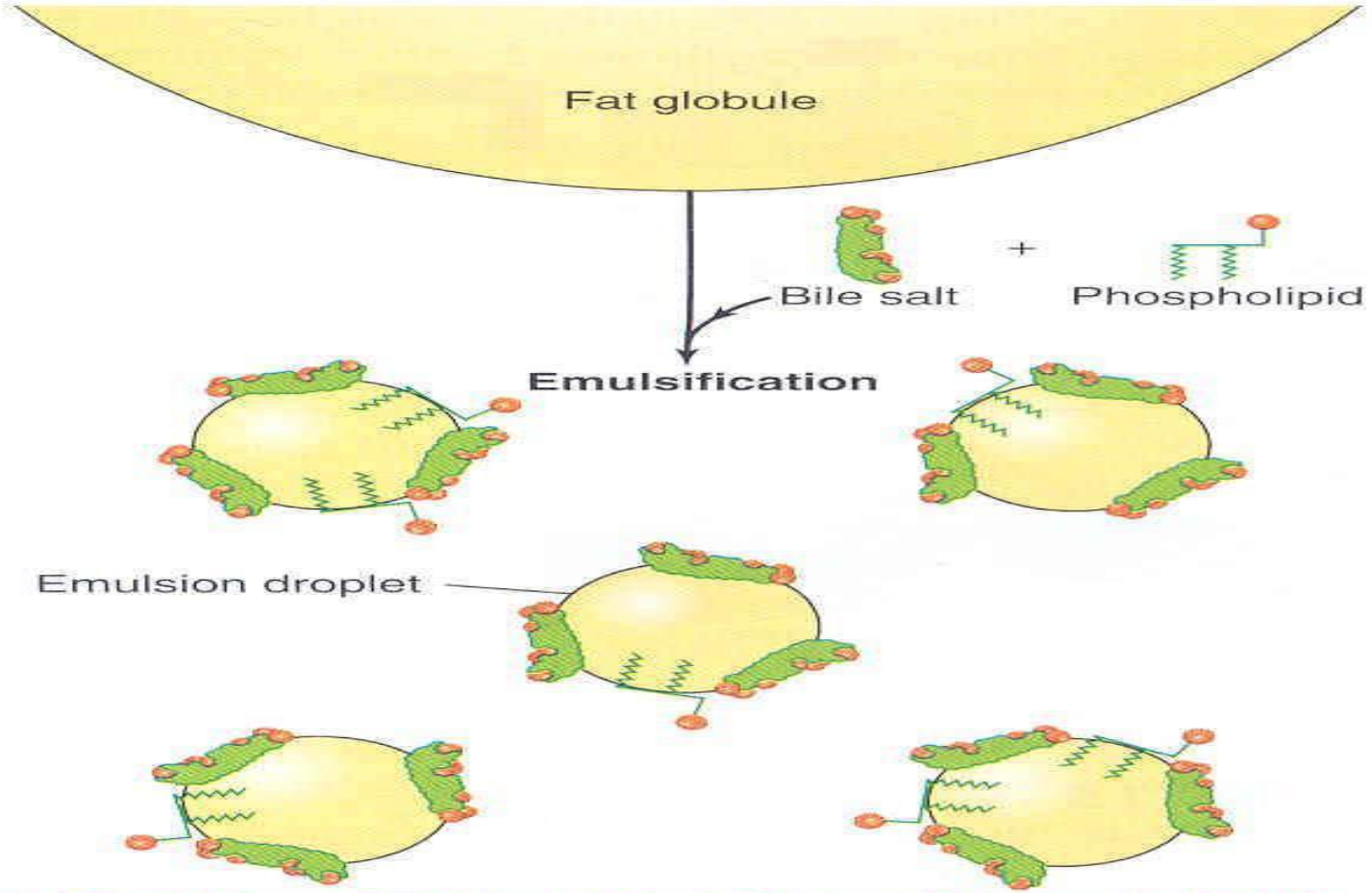
Digestion of fats	Absorption of fats	absorption of fat soluble vitamins
• Bile salts have a detergent action that help fat digestion by decreasing fat surface tension resulting in **emulsification** of fats into small particles. • This increase the surface area upon which the digestive enzymes will act. 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.	• 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).	• bile acids are essential for absorption of fat soluble vitamins • (A, D, E,K).

In liver	–ve feedback effect		Anti putrefactive
• **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.	• 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.	• They have a –ve feedback effect on the synthesis of cholesterol by the intestinal mucosal cells.	• 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, leading to putrefaction

emulsification of fats .



Emulsification of fat by bile salts and phospholipids

Cholesterol secretion in the bile

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- 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 concentratio of cholesterol**, cholesterol gallstones may form in the gall bladder.

Gallstones

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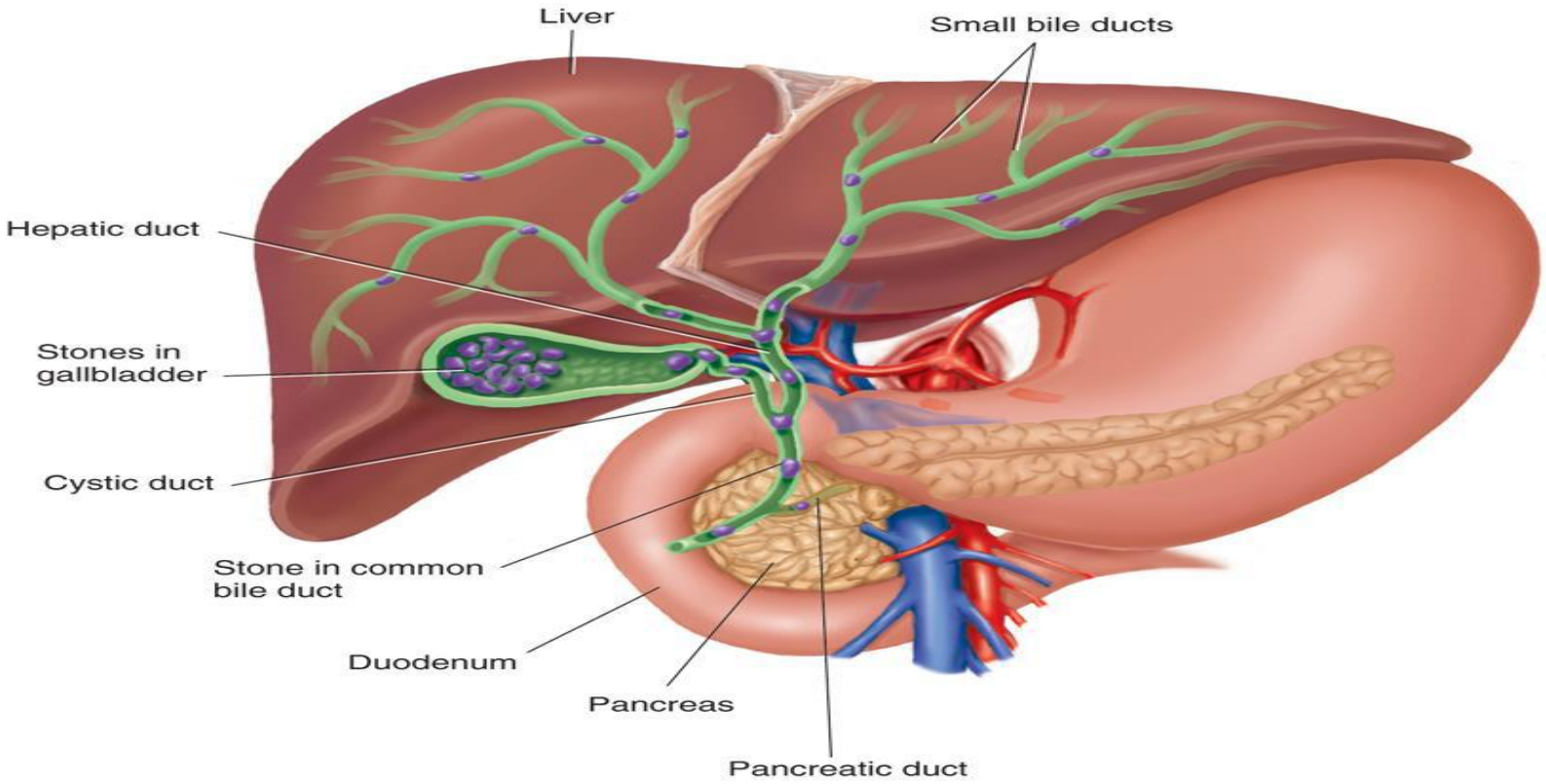
Gall stones may be formed in the gall bladder or bile ducts. When a substance that is not normally present appears in the bile or when the relative composition of the bile changes so that the normal constituent precipitates



Comment types of gallstones:

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Cholesterol stones	Calcium bilirubinate stones
under abnormal conditions the cholesterol may precipitate resulting in formation of cholesterol gallstones.	The main constituent is calcium salt of unconjugated bilirubin.
1. Too much absorption of water from the bile. 2. Too much absorption of bile salts & lecithin from bile. • (cholesterol is normally present in bile in micelles made up of lecithin and bile salts, so increase absorption of lecithin and bile salts will lead to absence of micelles and deposition of cholesterol in the bile) 1. Too much secretion of cholesterol in bile. 2. 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.	In liver diseases, bile may contain elevated levels of unconjugated bilirubin with increased incidence of forming bile pigment stones. (Calcium bilirubinate stones form if the conjugated bilirubin in the bile is deconjugated by the action of β – Glucuronidase found in certain bacteria. The free bilirubin combines with calcium and calcium bilirubinate is highly insoluble in bile)

Gallstones risk factors

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1. "Female, Fat, Forty, Fertile"
2. Oral contraceptives
3. DM
4. Rapid weight loss (gastric bypass pts)
5. Fatty diet
6. Obesity
7. Prolonged fasting
8. Ileal resection
9. Hemolytic states
10. Cirrhosis
11. Vagotomy
12. Hyperlipidemia

dieting may cause a shift in the balance of bile salts and cholesterol in the gallbladder. The cholesterol level is increased and the amount of bile salts is decreased.

13. Bile duct stasis (biliary stricture, congenital cysts, pancreatitis, sclerosing cholangitis)

Gallstones pathogenesis

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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**: common in Asians (due to their eating habit), contain Ca++ palmitate, found in bile ducts, following biliary dysmotility and bacterial infection. Bile (not the gall bladder) is essential for digestion.

Effects of Cholecystectomy

- 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.

- Bile acids are formed in the liver from cholesterol. During the conversion, hydroxyl groups and a carboxyl group are added to the steroid nucleus.

Bile acids are classified as:

1. **Primary:** synthesized by the hepatocyte, which include cholic acid and chenodeoxycholic acid. Bile acids are secreted as conjugates of taurine or glycine.
   - When bile enters the GI tract, bacteria present in the lumen act on the primary bile acids and convert them to secondary bile acids by dehydroxylation.
2. **Secondary:** it is the converted form of primary by the bacteria in the lumen include deoxycholic acid and lithocholic acid.

- Conjugated bile acids ionize more readily than the unconjugated bile acids and, thus, usually exist as salts of various cations.
- 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.

Function of Bile Salts in Fat Digestion and Absorption

- They have a detergent action (emulsifying) on the fat particles in the food which decreases the surface tension of the particles.
- They help in the absorption of fatty acids, monoglycerides, cholesterol, and other lipids from the intestinal tract.

- **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.

Enterohepatic Circulation of Bile Salts

Males' Slide

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- The enterohepatic circulation of bile salts is the recycling of bile salts between the small intestine and the liver. In healthy people, the bile acid pool ranges from 2 to 4 g. 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.
- The intestine is normally extremely efficient in absorbing the bile salts by carriers located in the distal ileum. Inflammation of the ileum can lead to their malabsorption and result in the loss of large quantities of bile salts in the feces e.g., inflammatory bowel diseases.

- Bile salts or bile acids in the portal circulation are absorbed via four pathways into hepatocytes:

1. An active carrier-mediated process: conjugated bile acids-Na co-transport.
2. Facilitated diffusion: Na-independent pathway.
3. Bile acid-HCO_3 or Bile acid-OH exchange.
4. Passive diffusion (very little).

SUMMARY

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- Bile acids classified as *primary and secondary*
- **Bile salts** are more water soluble than bile acids so that they have difficultly penetrating cell membrane
- They are important in fat digestion and cholesterol excretion and many other functions.
- About **90%** of bile acids in the intestine are reabsorbed to the liver, and the rest excreted with feces.
- The greater the quantity of bile salts in the enterohepatic circulation, the greater the rate of bile secretion because presence of bile salts in liver stimulate bile secretion.
- Gallstone is due to a substance that is not normally present appears in the bile or when the relative composition of the bile changes so that the normal constituent precipitates
- **These is 2 types of gallstones:** cholesterol gallstones, Calcium bilirubinate stones
- Usually patients undergo cholecystectomy maintain normal health.
- Bile is Made from cholesterol
- Bile salt is important for fat digestion : It emulsify fat to small droplets so pancreatic lipase can work on these droplets (note that pancreatic lipase is water soluble)
- Gall bladder stores and concentrate bile until there is a need for it.

QUESTIONS

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Q1) Which one of the following is primary bile acid:

A- Deoxycholic
B- chenodeoxycholic
C- lithocholic

Q2) Bile salts polarity comparing with bile acids :

A- more polar
B- less polar
C- Same polarity

Q3) Bile acids are:

A- Hydrophobic
B- Hydrophilic
C- Amphipathic

Q4) The total bile acid pool is:

A- 7-9 g
B- 2-4 g
C- 10-20 g

Q5) The absorption of bile salts occurs in :

A- Jejunum
B- Duodenum
C- Terminal ileum

Q6) Which one of the following is true about the conversion of primary bile acids to 2nd bile acids:

A- Cholic acid >> Deoxycholic acid
B- chenodeoxycholic >> Deoxycholic
C- Deoxycholic >> lithocholic

Q7) Which one of the following is cause of gallstones:

A. Inflammation of large intestine
B. Too much cholesterol in bile
C. GERD

B
A
C
B
C
A
B

■ Slides ■ Important ■ Females' Notes ■ Explanation ■ Males' Notes

QUESTIONS

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Q8) Bile acids have – ve feedback on which of the following hormones :

A- gastrin

B- CCK

C- secretin

Q9) Gall stones formed in :

A- Gallbladder

B- Bile duct

C- both a+b

Q10) Which of the following can lead to cholesterol stone formation :

A- To much secretion of water

B- To much secretion of bile salts

C- To much secretion of cholesterol

Q11) Synthesis of Bile acid takes place in :

A. Gallbladder

B. Stomach

C. Liver

D. Duodenum

Q12) Black pigment stones found in …… following …… :

A- Bile duct , bacterial infection

B- Gallbladder , cirrhosis

C- Gallbladder , biliary dysmotility

B
C
C
C
B
C
A

Q13) Cholic acid is converted to deoxycholic acid in:

A. Liver

B. Gall bladder

C. Intestine

Q14) which one of the flowing is NOT a pathway for absorption of bile acid into hepatocyte:

A. Na^+/K^+-ATPase

B. Facilitated diffusion: Na-independent pathway.

C. Bile acid-HCO_3 or Bile acid-OH exchange.

THE END

Physiology Team

If there are any Problems or Suggestions,
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