#11 Bile formation and bile salts

objectives :

- Functions of the bile and stages of bile secretion. Characteristics of bile.
- The main constituents of bile.
- Functions of gall bladder.
- Differences between hepatic bile and gall bladder bile. Control of biliary system.
- Primary and secondary bile acids.
- Enterohepatic circulation of bile salts.
- Absorption and uptake of bile acids. Functions of bile acids.

Doctors' notes

Extra

Important

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Resources: 435 Boys' & Girls' slides | Guyton and Hall 12th & 13th edition

Editing file

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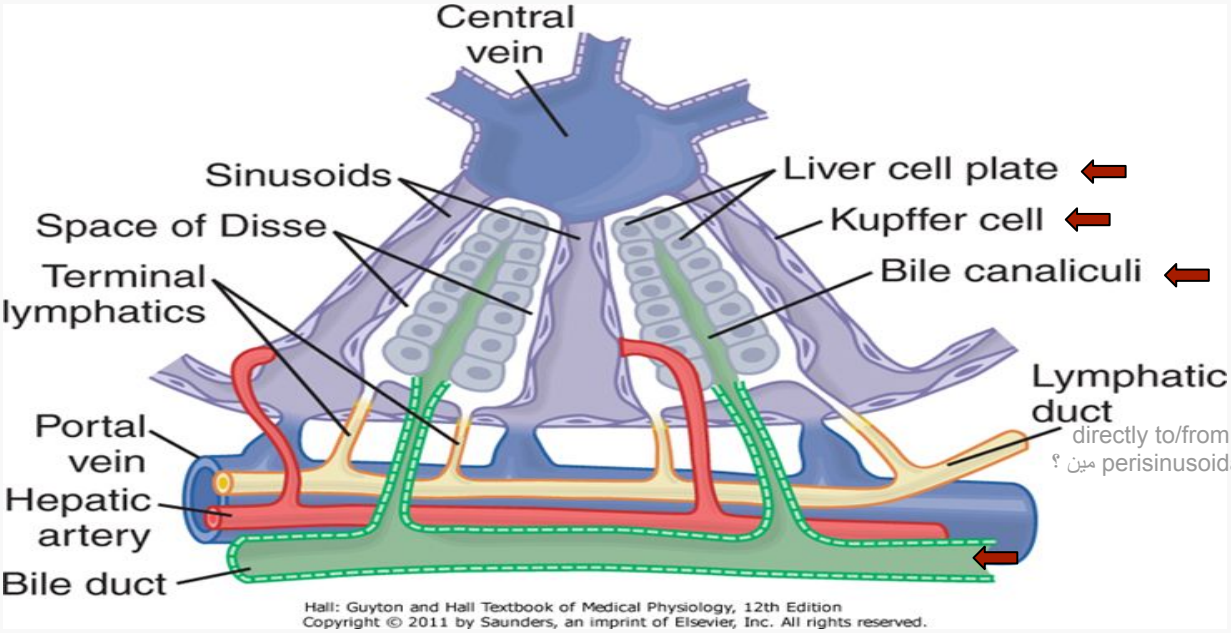
(Study anatomy & histology of the liver before studying this lecture)

The Liver :

- The liver is the largest internal organ/gland in the body, constituting about 2.5% of an adult's body weight. (Anatomy)
- Receives 25% of the cardiac output via the hepatic portal vein and hepatic artery.
- Takes up, stores, and distributes **nutrients and vitamins**.
- Plays an important role in **maintaining blood glucose levels.**
- Regulates the **circulating blood lipids** by the amount of very low–density lipoproteins (VLDL) it secretes.
- Synthesizes many of the circulating **plasma proteins**.
- Takes up numerous toxic compounds and drugs from the portal circulation.
- Serves as an **excretory organ** for bile pigments (i.e. bilirubin which is toxic), cholesterol, and drugs.
- Performs important **endocrine functions.**

Hepatocyte Arrangement Aids in the Rapid Exchange of Molecules :

• **Hepatocytes** are highly specialized cells. (the most important cells)
• **Sinusoidal endothelial cells** separates the perisinusoidal space (Disse space).
• **Endothelial cells** of the liver **lack a basement membrane**. They have **sievelike plates** Tight junction غريل يعني مب that permit the ready exchange of materials between the perisinusoidal space and the sinusoid. Particles as big as chylomicrons (80 to 500 nm wide) can penetrate these porous plates.
• **Kupffer cells** line the hepatic sinusoids and are part of the reticuloendothelial system (monocyte/macrophage)
• **Stellate cells** In inflammatory condition, they become transformed to myofibroblasts, which then become capable of secreting collagen and extracellular matrix into the space of Disse and **regulating sinusoidal portal pressure** by their contraction or relaxation.



The hepatocyte can receive blood by the perisinusoidal space (the white area) or space of disse
In the white area we usually get material and waste products, toxic substances they came from the portal vein, all of them get infiltrated, than they drain into the lymphatic vessels, if this distributed you will end up with portal hypertension, and than accumulation of fluid in peritoneal cavity (ascites). الصورة مهمة تفهمكم أشياء كثيرة لو عرفتوا الترتيب

The Lymphatic System Is Important in Liver Function

The hepatic lymphatic system is present in three main areas		
Adjacent to the central veins	**Adjacent to the portal veins**	**And coursing along the hepatic artery**

- These channels drain fluid and proteins.
- The protein concentration is **highest** in **lymph from** the liver.
- The largest space drained by the lymphatic system is the perisinusoidal space. هذه المعلومة مذكورة بمحاضرة الاناتومي لو ماتتذكرونها راجعوا :)
- Disturbances in the balance of filtration and drainage are **the primary causes of ascites** , the accumulation of serous fluid in the peritoneal cavity.

Guyton corner : Physiologic Anatomy of Biliary Secretion
Bile is secreted in two stages by the liver: (1) The initial portion is secreted by the principal functional cells of the liver, the *hepatocytes;* this initial secretion contains large amounts of bile acids, cholesterol, and other organic constituents. It is secreted into minute *bile canaliculi* that originate between the hepatic cells. (2) Next, the bile flows in the canaliculi toward the interlobular septa, where the canaliculi empty into *terminal bile ducts* and then into progressively larger ducts, finally reaching the *hepatic duct* and *common bile duct.* From these the bile either empties directly into the duodenum or is diverted for minutes up to several hours through the *cystic duct* into the *gallbladder.* In its course through the bile ducts, a second portion of liver secretion is added to the initial bile. This additional secretion is a watery solution of sodium and bicarbonate ions secreted by secretory epithelial cells that line the ductules and ducts. This second secretion sometimes increases the total quantity of bile by as much as an additional 100 percent. The second secretion is stimulated especially by *secretin,* which causes release of additional quantities of bicarbonate ions to supplement the bicarbonate ions in pancreatic secretion (for neutralizing acid that empties into the duodenum from the stomach).

Functions of bile:

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

Bile serves two important functions

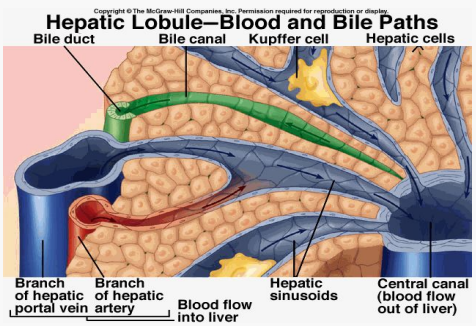
It plays an important role in fat digestion and absorption by its contents of bile salts.

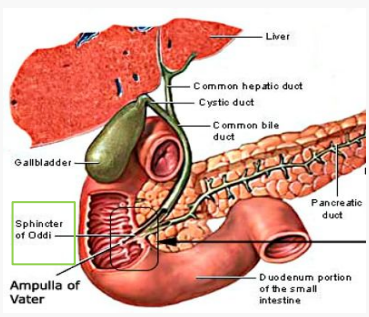
Bile serves as means for excretion of waste products from the blood. These include especially **bilirubin**.

Bile secretion:

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.
- The bile flows in the canaliculi toward the **hepatic duct** and **common bile duct.**
- From common bile duct, bile either empties directly into the **"duodenum"**, or is diverted through the cystic duct into the **"gall bladder"**. (Actively)
- This is the **second** portion of liver secretion which is added to the initial bile
- **Between** meals, bile is diverted into **gall bladder.**
- 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**).





Guyton corner : Bile serves two important functions. first,bile plays an important role in fat digestion and absorption, not because of any enzymes in the bile that cause fat digestion, but because bile acids in the bile perform two functions: (1) they help emulsify the large fat particles of the food into many minute particles, the surface of which can then be attacked by lipase enzymes secreted in pancreatic juice, and (2) they aid in absorption of the digested fat end products through the intestinal mucosal membrane. Second, bile serves as a means for excretion of several important waste products from the blood. These waste products include in particular bilirubin, an end product of hemoglobin destruction, and excesses of cholesterol. Page 827

Characteristic of bile: (Bile doesn't digest it increases the surface area)

- Bile is a **viscous** golden yellow or greenish fluid with **bitter** taste.
- It is **Isotonic** with plasma and slightly alkaline. (Note that all GI secretions are isotonic except for the saliva which is hypotonic)
- **$NaHCO_3$** (Sodium bicarbonate) 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**.

الأرقام بشكل عام غير مهمة

The main constituents of bile are:

Components of bile (Bile is composed of solutes and H2O, the solutes are either organic like mucus, enzymes & bile salts or inorganic and those are electrolytes such as NaHco3)	
From ducts	**From hepatocytes**
• Electrolytes mainly HCO_3^- these in addition to H_2O are secreted by **bile ducts epithelial cells**, and contribute to the volume of hepatic bile. • **HCO_3^-** aids in neutralization of acid chyme. • **Aqueous alkaline solution (NaHCO3)**	• Organic constituents • Bile acids (bile salts) (**65%**) of dry weight of bile. • Phospholipids as Lecithin (**20%**) • Proteins (**5%**) • Cholesterol (**4%**), the major route for cholesterol excretion • Bilirubin and related bile pigments (**0.3%**) All of these constituents are secreted by **hepatocytes** into bile canaliculi, along with an isotonic fluid that resembles plasma in its electrolytes concentration.

Functions of gallbladder:

1- Gallbladder not only stores bile but it concentrates bile.

- The total secretion of bile each day is about 700-1200 ml per day.
- The **maximum** volume of the gallbladder is only 30-60 ml.
- As much as 12 hours bile secretion can be stored & concentrated in the gallbladder 5-20 folds. (This explains how the gallbladder is capable of storing around 5L daily when it only accommodates 30-60 mL at a time)

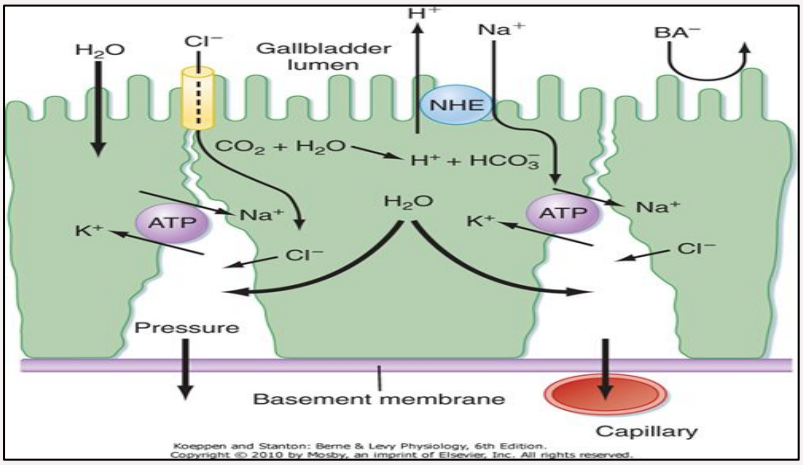
❖ **Concentration of bile in the gallbladder occur by:**

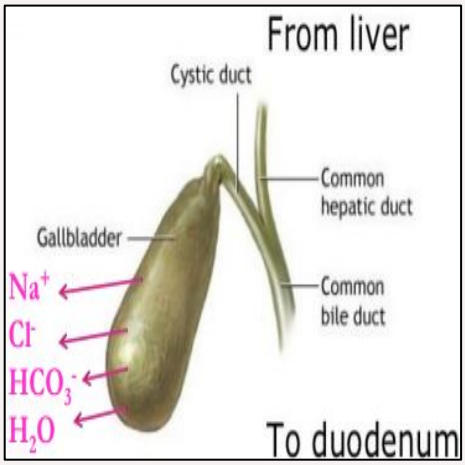
A. Active absorption of Na^+, Cl^-, and $HCO3^-$ by the lining epithelium.

B. Associated passive water movement **out** of the lumen.

This result in **drop** of **pH** of gallbladder bile due to **decrease $NaHCO_3$** concentration.

Note that when there's a need for bile (i.e. you had McDonald's for lunch) bile is secreted from BOTH the gallbladder and the liver simultaneously





2- Gallbladder epithelium secretes mucus which has protective function.

3- Buffer of biliary pressure by storing of bile, so it prevents increase in biliary pressure & enables the liver to secrete bile, because **hepatic cells cannot secrete against high pressure.**

Guyton corner : Storing and Concentrating Bile in the Gallbladder.
Bile is secreted continually by the liver cells, but most of it is normally stored in the gallbladder until needed in the duodenum. The maximum volume that the gallbladder can hold is only 30 to 60 milliliters. Nevertheless, as much as 12 hours of bile secretion (usually about 450 milliliters) can be stored in the gallbladder because water, sodium, chloride, and most other small electrolytes are continually absorbed through the gallbladder mucosa, concentrating the remaining bile constituents that contain the bile salts, cholesterol, lecithin, and bilirubin.Most of this gallbladder absorption is caused by active transport of sodium through the gallbladder epithelium, and this is followed by secondary absorption of chloride ions, water, and most other diffusible constituents. 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 bile & Gallbladder Bile

	Hepatic bile	Gallbladder 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** The acidity of gallbladder bile is essential to solubilize Ca and thus, to avoid gallstones

You just need to know that all the solutes are concentrated in the gallbladder (higher concentrations) except for those absorbed (H2O, Na, HCO3, Cl)

Control of biliary system:

- The human **liver** secretes bile at **pressure** of about 25 cm H_2O.
- Between the meals, the **choledochoduodenal sphincter** is closed offering a resistance of about 30 cm H_2O.
- **Bile** secreted by **liver** is thus diverted to the **gallbladder** during the **interdigestive periods**.
- **Pressure** in the lumen of the **gallbladder** varies between 0-16 cm H_2O.
- **Bile secretion** is **primarily** regulated by a **feedback mechanism**, with **secondary** hormonal and neural controls
- The major determinant of bile acid synthesis is its **concentration** in **hepatic portal blood** (feedback control)

There are 2 aspects of control:

1- Secretion of bile by liver cells (choleresis):

Substances that stimulate hepatic secretion of bile (choleresis) are choleretics. Note that the most potent choleretic is bile salts (on hepatocytes) and then it's secretin (on duct cells or the bile acid independent component)

- 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

2-Control of the discharge of bile into the intestine

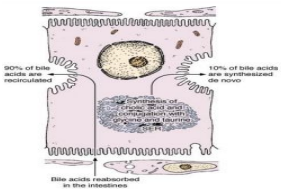
- Discharge of bile into the duodenum occurs by contraction of gallbladder wall and relaxation of Oddi sphincter.
- The highest rate of gallbladder emptying occurs during the intestinal phase.
- Gall bladder evacuants are called cholagogues.
- Discharge of bile into the duodenum is regulated by **nervous**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

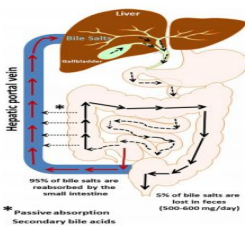
More details are coming up next! (next page)

The most potent cholagogue is CCK

Bile acid dependent component

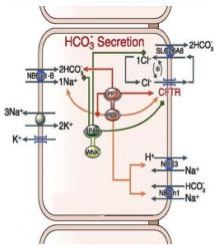
- **90%** of the rate of secretion of bile acids is determined by the rate of clearance of reabsorbed **bile acids** from the portal vein via enterohepatic circulation.
- The remaining **10%** is due to synthesis of new bile acids by hepatocytes.
- Interruption of the enterohepatic circulation results in markedly reduced choleresis.





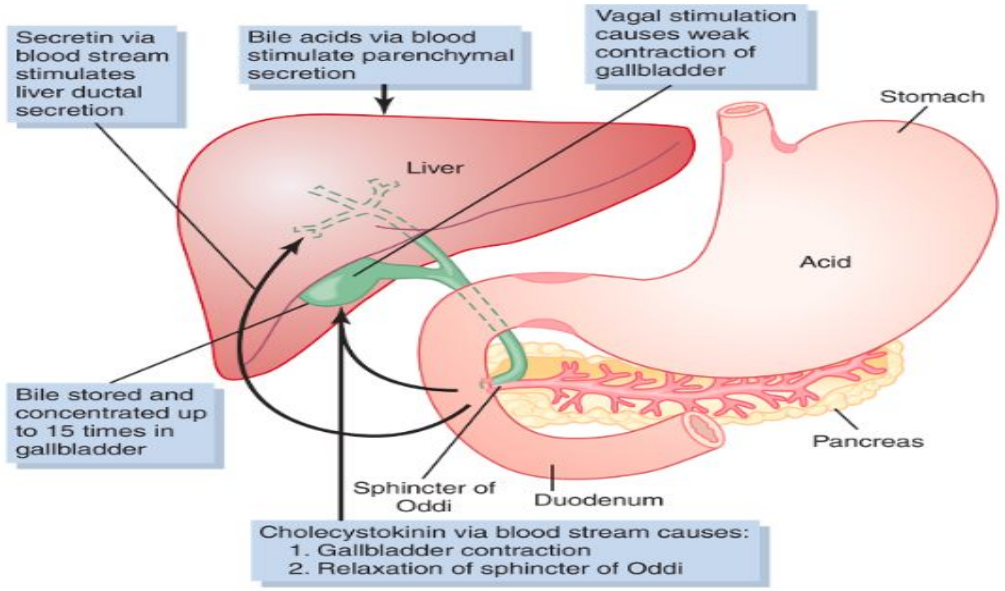
Bile acid independent component

- 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.**
- It is stimulated by :



Biliary duct cells

1-Hormones	2-Vagal stimulation
as **secretin**, **glucagon**, **CCK** and **gastrin**. They all stimulate HCO_3^- & passive water transfer by the biliary duct cells.	also stimulates bile flow. The effect is mediated mainly indirectly, through stimulation of gastric acid secretion, which leads to release of **secretin** & **CCK**



Increase portal blood flow during digestion **increases** bile secretion.But when the liver is markedly **congested** bile secretion stops due to increased intrahepatic vascular pressure.

2-Control of the discharge of bile into the intestine

Discharge of bile into the duodenum is regulated by **nervous** & **hormonal** mechanisms:

The nervous component:

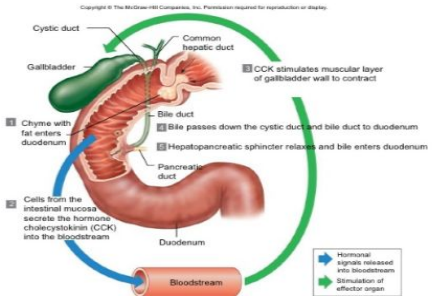
PARASYMPATHETIC (VAGAL)	SYMPATHETIC
• **Contraction** of the gallbladder. • **Relaxation** of the sphincter of Oddi. • **Increased** bile formation. • N.B: bilateral vagotomy results in **reduced** bile secretion after a meal.	• **relaxation** of the gallbladder • **reduced** bile secretion

The hormonal component:

- 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

(same as parasympathetic (vagal)).

- Both **vagal** excitation & **secretin** augment (increase) the action of **CCK** on the **gall bladder.**

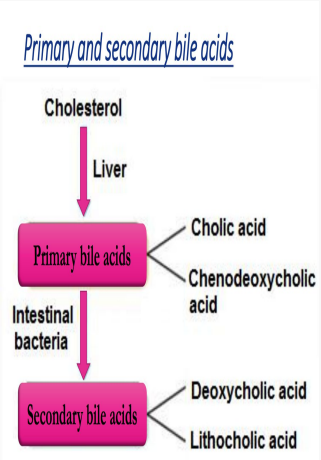


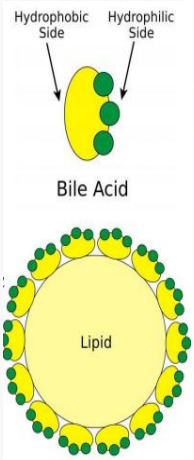
Bile acids and salts :

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

Bile acids include:

- **Primary**: **cholic**, **chenodeoxycholic** acids.
  - The principle primary bile acids **conjugate** with glycine or taurine to form glyco and taurocholic bile acids.
- **Secondary**: **deoxycholic**, **lithocholic** 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.**
- Micelles are **small spherical**, **cylindrical** globules 3 to 6 nm in diameter composed of **20 to 40 molecules** of **bile salt**.

- In bile acid micelle, the **hydrophobic** side of bile acid faces **inside** & away from water. The **hydrophilic** (polar -charged) surface faces **outward** towards the water,
- it allows the entire micelle globule to **dissolve** in the **water** of the digestive fluids and to remain in stable solution.

- The micelles act as a **transport medium** to carry the monoglycerides and free fatty acids to the **brush borders** of the intestinal epithelial cells.

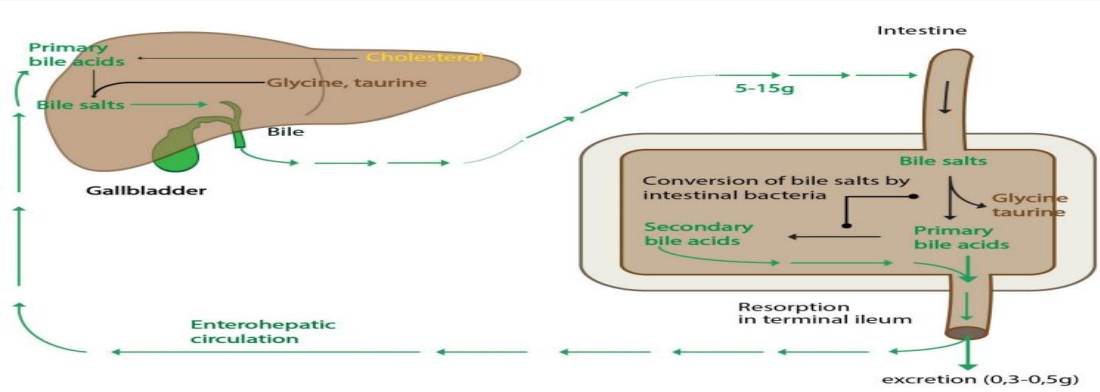
- Bile acid micelles form when the conc. of bile acids **exceed** a certain limit **(critical micelle conc.)**. Above this conc., any additional bile acid will join the micelle.
- Normally **bile acid** conc. in bile is much **GREATER** than **critical micelle** conc.

Enterohepatic circulation of bile salts

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

  (remember we said that :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 **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 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,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 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.

Guyton corner : Enterohepatic Circulation of Bile Salts.
About 94 percent of the bile salts are reabsorbed into the blood from the small intestine, about one half of this by *diffusion* through the mucosa in the early portions of the small intestine and the remainder by an *active transport* process through the intestinal mucosa in the distal ileum. They then enter the portal blood and pass back to the liver. On reaching the liver, on first passage through the venous sinusoids these salts are absorbed almost entirely back into the hepatic cells and then resecreted into the bile.In this way, about 94 percent of all the bile salts are recirculated into the bile, so on the average these salts make the entire circuit some 17 times before being carried out in the feces. The small quantities of bile salts lost into the feces are replaced by new amounts formed continually by the liver cells. This recirculation of the bile salts is called the *enterohepatic circulation of bile salts.*The quantity of bile secreted by the liver each day is highly dependent on the availability of bile salts—the greater the quantity of bile salts in the enterohepatic circulation (usually a total of only about 2.5 grams), the greater the rate of bile secretion. Indeed, ingestion of supplemental bile salts can increase bile secretion by several hundred milliliters per day.f a bile fistula empties the bile salts to the exterior for several days to several weeks so that they cannot be reabsorbed from the ileum, the liver increases its production of bile salts 6- to 10-fold, which increases the rate of bile secretion most of the way back to normal. This demonstrates that the daily rate of liver bile salt secretion is actively controlled by the availability (or lack of availability) of bile salts in the enterohepatic circulation.

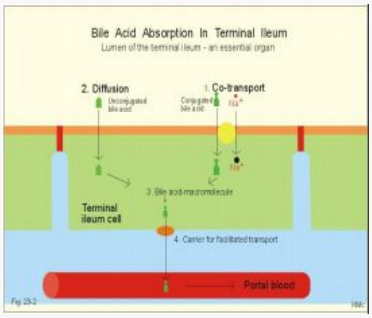
Absorption of bile acids in intestinal lumen :

Bile acids are absorbed largely in the **terminal part of the ileum**.

They cross the brush border plasma membrane by two routes:

1- Active transport process.
It is **2ry active transport** powered by the **Na^+ gradient** across the brush border membrane.

2- Simple diffusion.



- The Conjugated bile acids are the principal substrates for active absorption.
- Unconjugated bile acids have **poor affinity** for the transporter. They are **less polar** than conjugated bile acids, they are better absorbed by simple 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** WHY? 3 hydroxyl groups 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 :

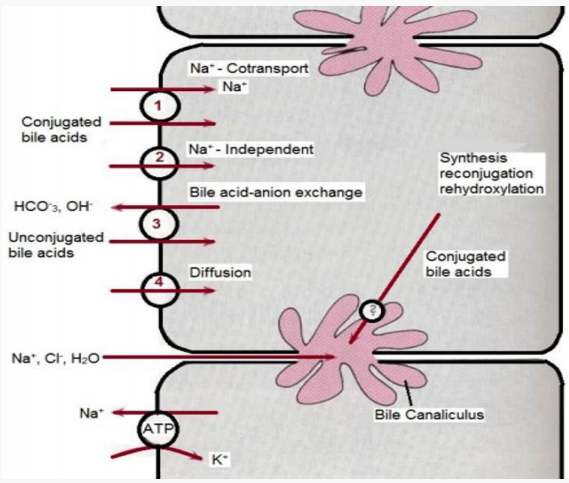
- Multiple transport mechanisms are located in **hepatocyte plasma membrane** for **uptake** of bile **acids** from **sinusoidal blood.**

An active carrier-mediated process
conjugated bile acids-Na^+ cotransport

Facilitated diffusion
Na^+-independent pathway

Bile acid-HCO_3^- or OH^- exchange

Passive diffusion (very little)



Importance of Enterohepatic Circulation of Bile Acids:

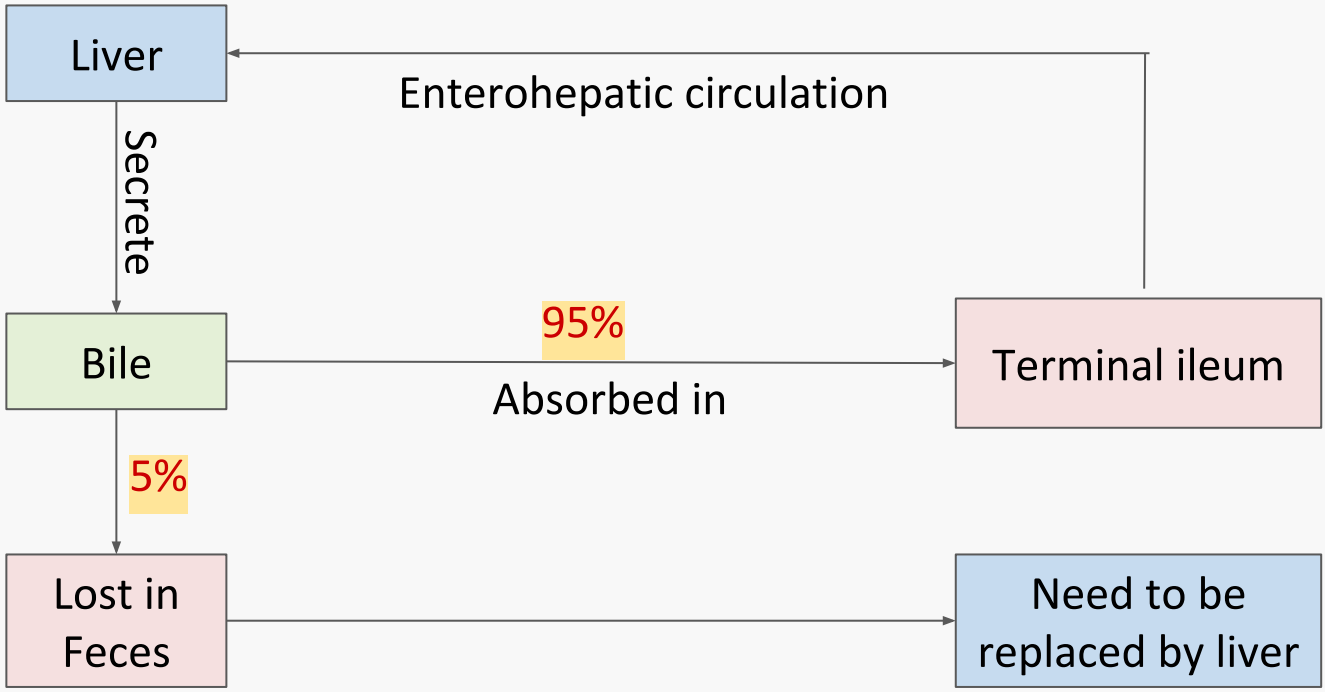
- It is essential for stimulating and maintaining the **secretion of bile** by **hepatocytes**.
- The greater the quantity of bile salts in the enterohepatic circulation, the greater the rate of bile secretion.
- By cycling several times during a meal, a relatively **small bile acid pool** can provide 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 lead to malabsorption e.g., Crohn's disease, Ulcerative Colitis), **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). (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 **reconjugated** & some **2^{ry} bile acids** are rehydroxylated. Primary bile acids are more adsorbed than secondary
- The **reprocessed** bile acids, together with **newly synthesized** bile acids, are secreted into bile.

Cholesterol secretion in the 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 & **phospholipids**.



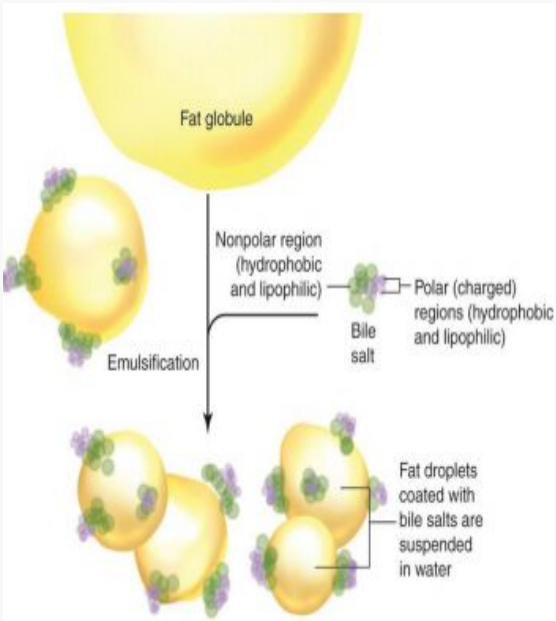
Enterohepatic circulation — Needed for → Recycling of bile salts

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 acids are essential for absorption of fat soluble vitamins **(A, D, E and K)**

4. In the colon bile acids :
1- inhibit reabsorption of water & electrolytes
2- stimulate intestinal motility
3- 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.

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.

SUMMARY

Bile functions

- fat digestion and absorption
- excretion of waste especially bilirubin.

Bile secretion:

Secretion by hepatocytes. → flows to the hepatic duct and common bile → empties directly into the duodenum

OR → diverted through the cystic duct into the gall bladder

❖ Characteristic of bile:

- viscous golden\green
- Bitter
- isotonic
- $NaHCO_3$(alkaline)
- 5 L / day Produced , 700-1200 ml/day poured

❖ Functions of gallbladder:

1. Storage (max vol 30-60 ml)
2. Secretion of mucus
3. Buffering of bile pressure

Components of bile	
From ducts	**From hepatocytes**
• HCO_3^- & H_2O secreted by **epithelial cells**, and contribute to the volume. • HCO_3^- • $NaHCO_3$	• Organic constituents • Bile acids (bile salts) (65%) of dry weight of bile. • Phospholipids, (90%) as Lecithin (20%) • Proteins (5%) • Cholesterol (4%), the major route for cholesterol excretion • Bilirubin and related bile pigments (0.3%)

SUMMARY

There are 2 aspects of control:

1- Secretion of bile by liver cells (choleresis):

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

- 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

2-Control of the discharge of bile into the intestine

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

Bile acid dependent component

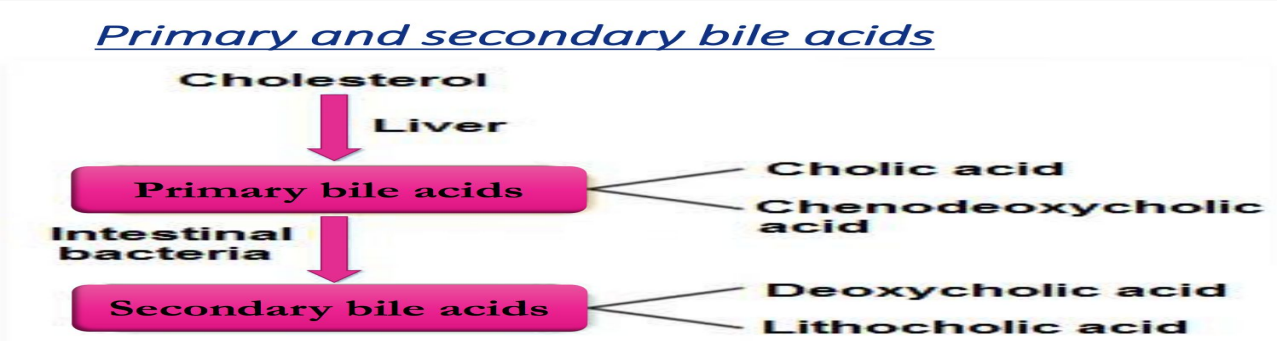
- It depends mainly on the integrity of the enterohepatic circulation.
- At least 90% reabsorbed bile acids from the portal vein.
- 10% synthesis of new bile acids
- Interruption of the enterohepatic circulation results in markedly reduced choleresis.

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.**
- It is stimulated by :

SUMMARY

2-Control of the discharge of bile into the intestine		
nervous mechanisms		**hormonal mechanisms.**
PARASYMPATHETIC (VAGAL)	SYMPATHETIC	
Contraction of the gallbladder. Relaxation of the sphincter of Oddi. Increased bile formation. *bilateral vagotomy results in reduced bile secretion after a meal.	• relaxation of the gallbladder • reduced bile secretion	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 (same as parasympathetic (vagal)). vagal excitation & secretin augment(increase) the action of CCK on the gall bladder.



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.)

❖ Absorption of bile acids in intestinal lumen :

Bile acids are absorbed largely in the **terminal part of the ileum.**

They cross the brush border plasma membrane by two routes:

1- Active transport process. It is 2ry active transport powered by the Na+ gradient across the brush border membrane.

2- Simple diffusion.

SUMMARY

Functions of bile acids :

- **Digestion & Absorption of fats**
- bile acids are essential for absorption of fat soluble vitamins (A, D, E and K)
- In the colon bile acids inhibit reabsorption of water & electrolytes, may cause diarrhea.
- In the liver, bile salts are important for stimulating bile secretion and flow (choleretic action).
- 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
- 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.

Guyton corner

Role of Secretin in Controlling Bile Secretion.

In addition to the strong stimulating effect of bile acids to cause bile secretion, the hormone *secretin* that also stimulates pancreatic secretion increases bile secretion, sometimes more than doubling its secretion for several hours after a meal. This increase in secretion is almost entirely secretion of a sodium bicarbonate–rich watery solution by the epithelial cells of the bile ductules and ducts, and not increased secretion by the liver parenchymal cells themselves. The bicarbonate in turn passes into the small intestine and joins the bicarbonate from the pancreas in neutralizing the hydrochloric acid from the stomach. Thus, the secretin feedback mechanism for neutralizing duodenal acid operates not only through its effects on pancreatic secretion but also to a lesser extent through its effect on secretion by the liver ductules and ducts.

Liver Secretion of Cholesterol and Gallstone Formation

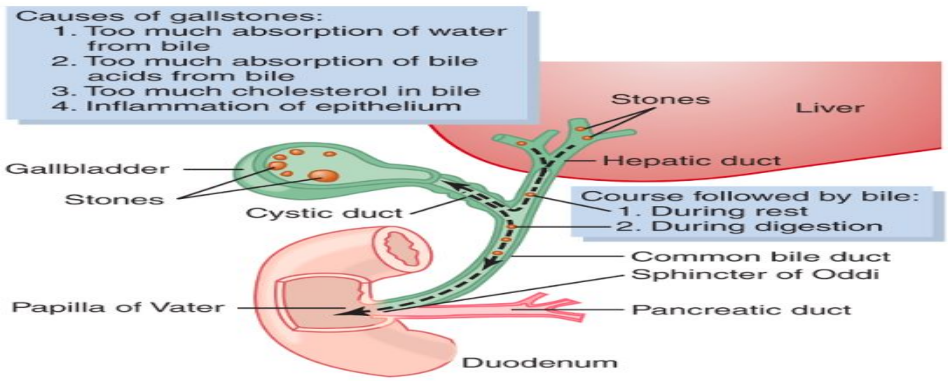
Bile salts are formed in the hepatic cells from cholesterol in the blood plasma. In the process of secreting the bile salts, about 1 to 2 grams of cholesterol are removed from the blood plasma and secreted into the bile each day.

Cholesterol is almost completely insoluble in pure water, but the bile salts and lecithin in bile combine physically with the cholesterol to form ultramicroscopic *micelles* in the form of a colloidal solution. When the bile becomes concentrated in the gallbladder, the bile salts and lecithin become concentrated along with the cholesterol, which keeps the cholesterol in solution.

Formation of gallstones.

Under abnormal conditions, the cholesterol may precipitate in the gallbladder, resulting in the formation of *cholesterol gallstones,*The amount of cholesterol in the bile is determined partly by the quantity of fat that the person eats, because liver cells synthesize cholesterol as one of the products of fat metabolism in the body. For this reason, people on a high-fat diet over a period of years are prone to the development of gallstones.

Inflammation of the gallbladder epithelium, often resulting from low-grade chronic infection, may also change the absorptive characteristics of the gallbladder mucosa, sometimes allowing excessive absorption of water and bile salts but leaving behind the cholesterol in the gallbladder in progressively greater concentrations. Then the cholesterol begins to precipitate, first forming many small crystals of cholesterol on the surface of the inflamed mucosa, but then progressing to large gallstones.



MCQs

1-Concentration of bile in the gall bladder occur mainly by:

A-- Active absorption of Na+
B- portal pressure
C - intestinal absorption
D - passive water movement+Associated Active transport of glucose

2-Which of the following cells can regulate portal pressure :

A- Endothelial cell
B- myofibroblast
C- Kupffer
D- None of them

3-bile acids are mostly ionized and are referred to as bile salts at:

A- Low ph
B- High ph
C- Neutral ph
D- Don't affected by ph

4-perisinusoidal space drain into :

A- Portal vein
B- Hepatic artery
C- Bile canalucli
D- Lymphatic duct

5-The sinusoids empty into:

A- central veins
B- portal vein
C- hepatic vein
D- inferior vena cava

6-which of the following is function of bile :

A- emulsification of lipid
B- excretion of waste products from the blood
C- erythrocyte destruction
D- A&B

7-Which one of the following is primary bile acid:

A- Deoxycholic
B- Chenodeoxycholic
C- lithocholic
D- chenocarboxycholic

8-bile acids are :

A- hydrophilic
B- hydrophobic
C- amphipathic

9-Regulation of Bile Secretion occur primary by:

A- cck& secretin
B- parasympathetic
C- sympathetic
D- bile acid conc in hepatic portal blood

answer key: 1:A , 2:B , 3:C , 4:D , 5:A , 6:D , 7:B , 8:C , 9:D.

مع جزيل الشكر لمصمم قالب العمل : هشام الغفيلي

خولة العمَّاري
نجود الحيدري
نورة الطويل
لولوة الصغير
لجين السواط
رزان السبتي
ربى السليمي
ديما الفارس
خولة العريني
ملاك الشريف
منيرة الحسيني
مروج الحربي
أفنان المالكي
دلال الحزيمي
رناد القحطاني
سارة الخليفة
فرح مندوزا
مي العقيل
نورة الخراز
سارة الخليفة
نورة الخيال
رغد النفيسة
منيرة السلولي
نوف العبدالكريم
سها العنزي
نورة القحطاني

عمر آل سليمان
عبدالعزيز الحماد
عبدالرحمن السياري
محمد أبونيان
عبدالرحمن البركه
إبراهيم النفيسه
محمد البشر
عمر العتيبي
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عبدالله الجعفر
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