Bile Formation and Enterohepatic Circulation

The biliary system

- The hepatic function most important to digestive tract is secretion of bile.
- Hepatic cells continually form bile which is secreted into minute bile canaliculi that lie between hepatic cells.
- Bile canaliculi empty into terminal bile ducts then into larger ducts, finally reaching the hepatic duct & the common bile duct from which bile either empties directly into the duodenum or diverts through the cystic duct into the gall bladder.
- 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 opens 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).

Bile secretion

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.

Composition of Bile

The main constituents of bile are:

- Bile acids (65% of dry weight of bile):
- Primary: cholic, chenodeoxycholic acids.
- Secondary: deoxycholic, lithocholic acids.
- Bile acids account for about half of the total solutes 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 enters the duodenum from the stomach.

Functions of bile

1. Helps fat digestion and absorption by its contents of bile salts.
2. Excretion of waste products as 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 12-18 folds).

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

a. Active absorption of Na^+, Cl^-, and HCO_3^- by the lining epithelium.
b. Associated passive water movement out of the lumen.
c. 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.

Differences between hepatic bile and gall bladder bile

	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 H_2O. Between the meals, the choledochoduodenal sphincter is normally closed offering a resistance of about 30 cm H_2O.

❑ Bile secreted by liver is thus diverted to the gall bladder during the interdigestive peroids.

❑ Pressure in the lumen of the gall bladder varies between 0-16 cm H_2O.

1. *Control of 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*

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.

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 is mediated by vagus nerve & follows psychic influences & food ingestion.
   During this cephalic phase bile is discharged for only a brief period into the duodenum.
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 CCK.

Physiology of Bile Salts and Pathogenesis of Gall stones

Bile salts

- ✓ Bile acids are steroid acids, synthesized in the liver from cholesterol by the enzyme cholesterol 7α-hydroxylase.
- ✓ The principle primary bile acids are cholic acid and chenodeoxycholic acid. These acids conjugate with glycin or taurine to form glyco and taurocholic bile acids.
- ✓ Conjugated bile acids are more water soluble and are present almost entirely as salts of various cations (mostly Na^+) and are called bile salts.
- ✓ 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.

Enterohepatic circulation of bile acids

- ♠ 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 (deoxycholic & lithocholic acids).
- ♠ On reaching the terminal ileum, 90 % of bile acids are absorbed by 2ry active transport i.e. (pumped out by Na^+ - K^+ ATPase in the basolateral border of enterocytes) and reach the liver through the portal vein mostly bound to albumin.

Cellular mechanism of bile secretion

- ❖ Multiple transport mechanisms are located in the hepatocyte plasma membrane for uptake of bile acids from sinusoidal blood.
- ❖ In the hepatcyte cytosole, bile acids are mostly bound to bile acid-binding proteins.
- ❖ These binding proteins prevent the concentrated bile acids from disrupting the membranes of hepatocyte organelles.
- ❖ Almost all deconjugated bile acids are reconjugated with glycine or tuarine, and some secondary bile acids are rehyroxylated to primary bile acids & resecreted in bile along with newly synthesized bile acids.

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.
- ❖ 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.

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.
- ❑ If enterohepatic circulation is interrupted (e.g. due to obstruction by disease or surgical removal of terminal ileum), bile flow is markedly reduced.
- ❑ Deficiency of bile acids leads to defective fat digestion and absorption and steatorrhea.
- ❑ Excess amount of bile acids entering the colon may result in diarrhea.

Absorption of bile acids

❁ 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 conjucated 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.

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

❁ In the hepatocytes, most deconjugated bile acids are reconjugated & some 2^{ry} bile acids are rehydroxylated.

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

Functions of bile acids

1. Digestion of fats:- Bile salts 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 fat can be absorbed. 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.

Radiological tests of biliary function

◙ The function of the gall bladder & biliary ducts may be assessed radiologically (Cholecystography) after oral or I.V administration of a radio-opaque substance which is excreted by the liver into the bile, e.g. tetra-iodophenolphthalein or iopanoic acid.
◙ A non-functioning gall bladder fails to show the opaque material in its cavity.
◙ Gallstones show as filling defects.
◙ The function of the gall bladder may be evaluated further by giving a cholagogue & assessing its contraction. The cholagogue used include ingestion of a fatty meal or administration of $MgSO_4$, CCK or Caerulein.
◙ Caerulein is a peptide with 10 amino acids. It has all the properties of gastrin & CCK. It is used in cholecystography to contract the gall bladder.
◙ Ultrasonography may also be used to detect gallstones & measure the contractility of the gall bladder.

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

Definitions

❖ Cholelithiasis = gallstones
❖ Acute calculous cholecystitis = occlusion of the cystic duct by gallstone leading to gallbladder inflammation
❖ Chronic calculous cholecystitis = recurrent episodes of cystic duct obstruction leading to scarring and a nonfunctional gallbladder
❖ Chronic acalculous cholecystitis = symptoms of biliary colic, no gallstones, and an abnormal gallbladder ejection fraction
❖ Acute cholangitis = bacterial infection of the biliary ducts
❖ Choledocholithiasis = CBD stones
❖ Mirizzi syndrome = when gallstones lodged in either the cystic duct or the Hartmann pouch of the gallbladder, externally compressed the common hepatic duct (CHD), causing symptoms of obstructive jaundice

Types of gallstones

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

1. Cholesterol stones:

Under abnormal conditions the cholesterol may precipitate resulting in formation of cholesterol gallstones which often block the bile duct & cause loss of hepatic secretion to the gut.
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.
  - This 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.

- As a result cholesterol begins to precipitate forming stones.

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.

Gallstone Complications

- Acute cholecystitis: 10-20% of pts with symptomatic gallstones
  - GB gangrene
  - GB perforation into adjacent viscus .
  - Cholecystoenteric fistula & the stone can cause small bowl obstruction (gallstone ileus)
  - GB empyema (Pus-filled GB due to bacterial proliferation in obstructed GB. Usu. more toxic, high fever.)
  - Emphysematous cholecystitis (More commonly in men and diabetics. Severe RUQ pain, generalized sepsis. Imaging shows air in GB wall or lumen)
- Choledochohlithiasis: 8-15% of pts with symptomatic gallstones
  - Cirrhosis
  - Cholangitis
  - Pancreatitis

Symptomatic cholelithiasis

- Biliary colic
- Provocation/Timing: meals (50%), nighttime
- Quality: constant
- Radiation: RUQ to the R scapula (Boas' sign)
- Severity: "severe"
- PE: (+) Murphy's sign
- The pain occurs due to a stone obstructing the cystic duct, causing wall tension; pain resolves when stone passes
- Pain usually lasts 1-5 hrs, rarely > 24hrs
- Exam, WBC, and LFT normal in this case
- Treatment: Laparoscopic cholecystectomy

Acute calculous cholecystitis

- Persistent cystic duct obstruction leads to GB distension, wall inflammation & edema
- Pain usu. persists >24hrs & associated with nausea, vomiting and fever
- Palpable/tender or even *visible* RUQ mass
- Treatment: Cholecystectomy usually within 48hrs

Acute acalculous cholecystitis

- In 5-10% of cases of acute cholecystitis.
- More likely to progress to gangrene, empyema, perforation due to ischemia.
- Caused by gallbladder stasis from lack of enteral stimulation by cholecystokinin.
- **Tx**: Emergent cholecystectomy usually open.
- If pt is too sick, percutaneous cholecystostomy tube and interval cholecystectomy later on.

Chronic calculous cholecystitis

♦ Recurrent inflammatory process due to recurrent cystic duct obstruction, 90% of the time due to gallstones
♦ Overtime, leads to scarring/wall thickening
♦ Treatment: laparoscopic cholecystectomy

Choledocholithiasis

- Can present similarly to cholelithiasis, except with the addition of jaundice
- DDx: cholelithiasis, hepatitis, sclerosing cholangitis
- **Tx**: Endoscopic retrograde cholangiopancreatography (ERCP)
- Stone extraction and sphincterotomy
- Interval cholecystectomy after recovery from ERCP

Cholangitis

❖ Infection of the bile ducts due to CBD obstruction 2ndary to stones, strictures
❖ Charcot's triad seen in 70% of pts
❖ May lead to life-threatening sepsis and septic shock
❖ Emergent decompression via ERCP or perc transhepatic cholangiogram (PTC)
❖ Used to require emergency laparotomy

Gallstone pancreatitis

♣ 35% of acute pancreatitis 2ndary to stones
♣ Pathophysiology
♣ Reflux of bile into pancreatic duct and/or obstruction of ampulla by stone
♣ ALT > 150 (3-fold elevation)
♣ Once pancreatitis resolving, ERCP with stone extraction/sphincterotomy
♣ Cholecystectomy before hospital discharge

Effects of Cholecystectomy:

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