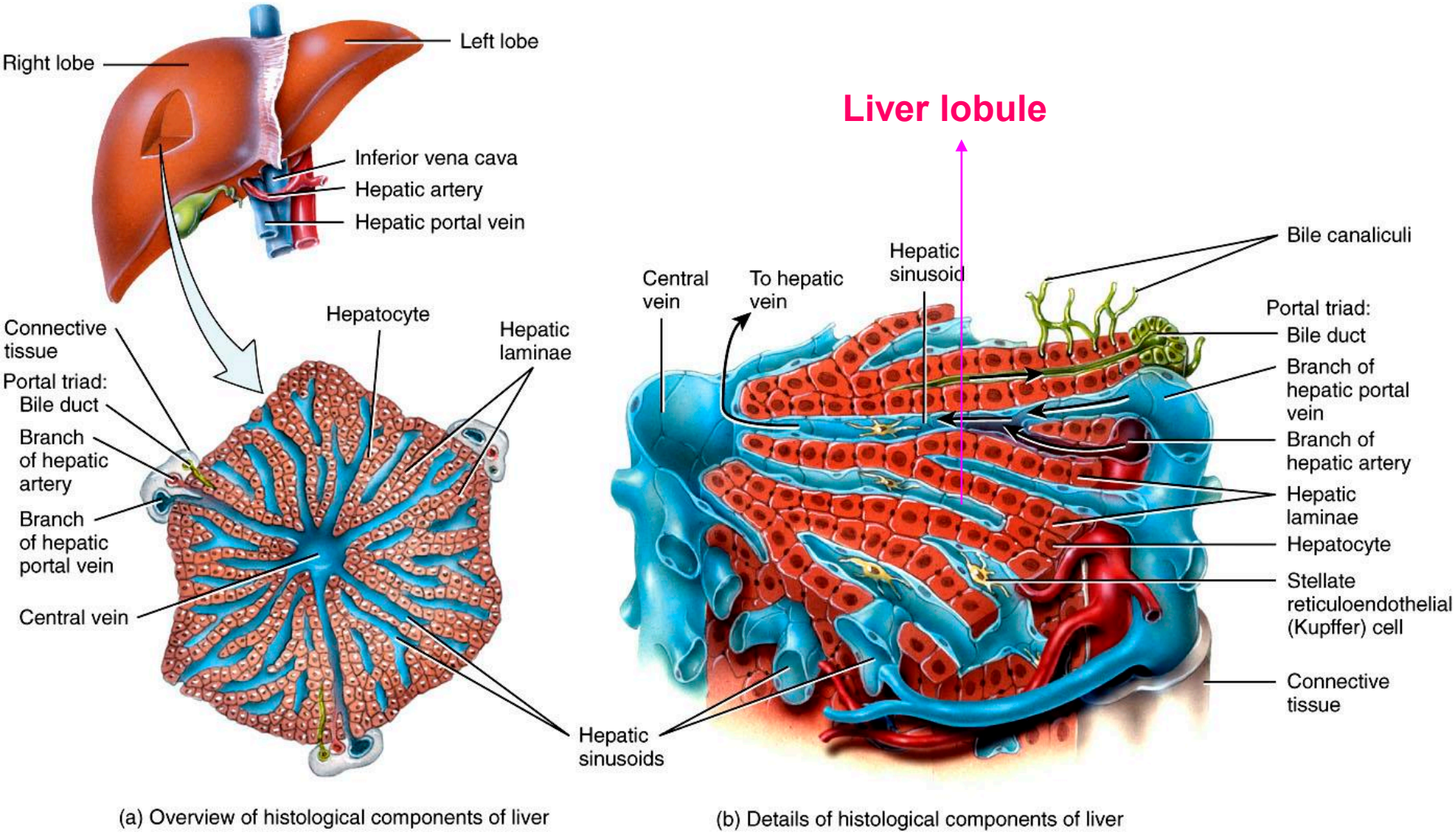
6-Secretion of Bile by the Liver Functions of the Biliary Tree

- liver is the largest gland in the body (1.5 Kg), essential for life.
- The functional unit is the *liver lobule* (hepatocytes around a central vein separated by blood sinusoids).
- The sinusoids are wide fenestrated, contain large Kupffer cells.
- Hepatic vascular system:
  - 1.5 L/minute (27% of CO) , 1L from portal vein, 500ml from hepatic artery.
  - Rich lymphatic drainage.

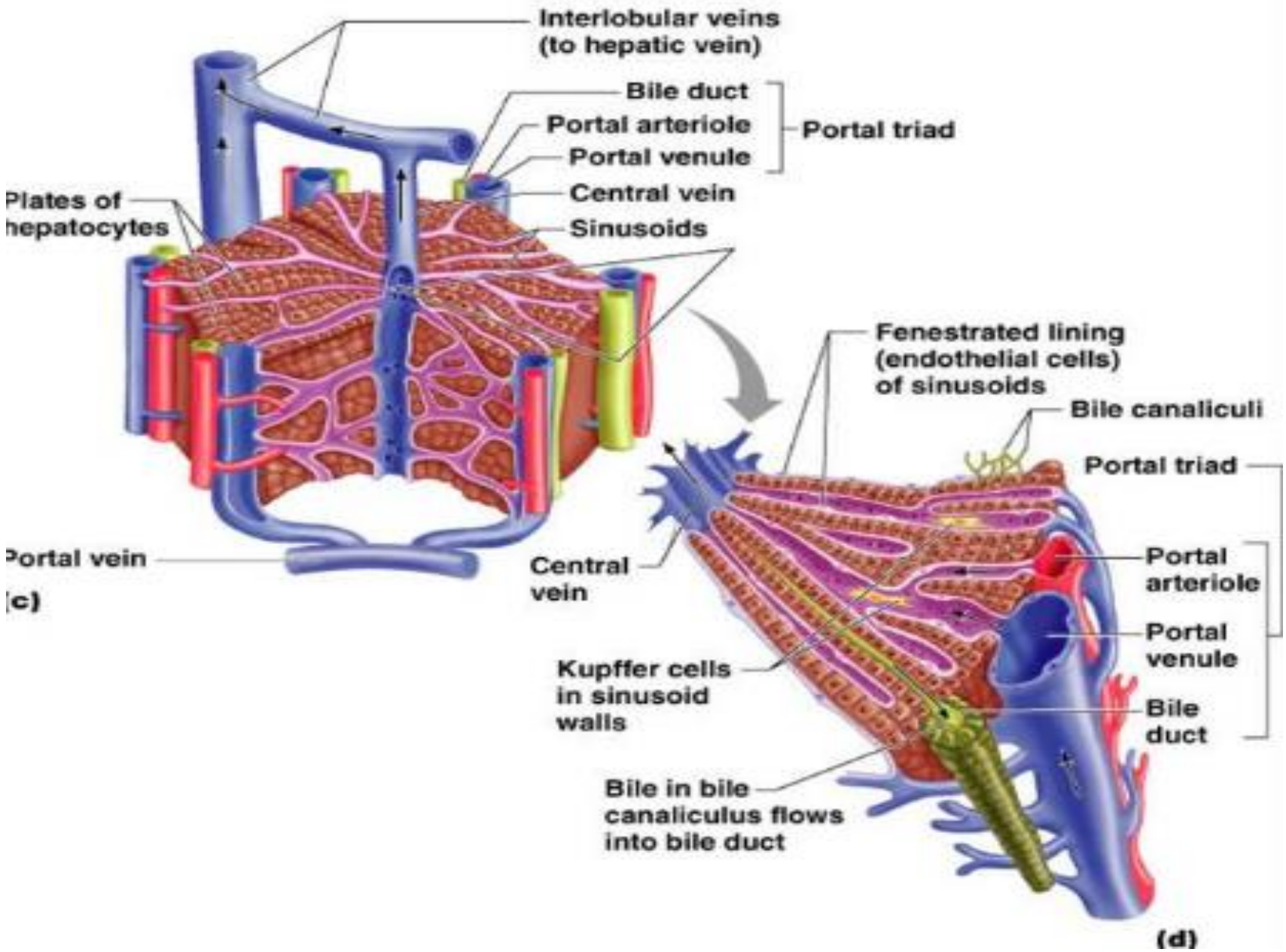
Histology of the Liver

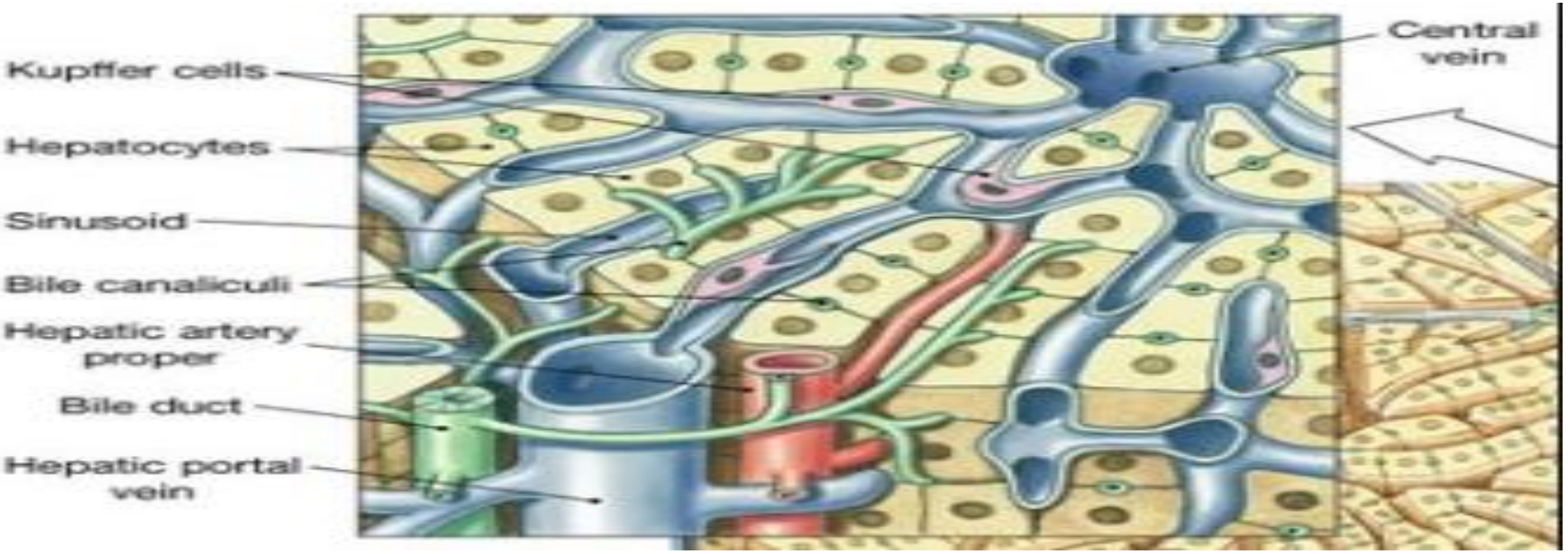


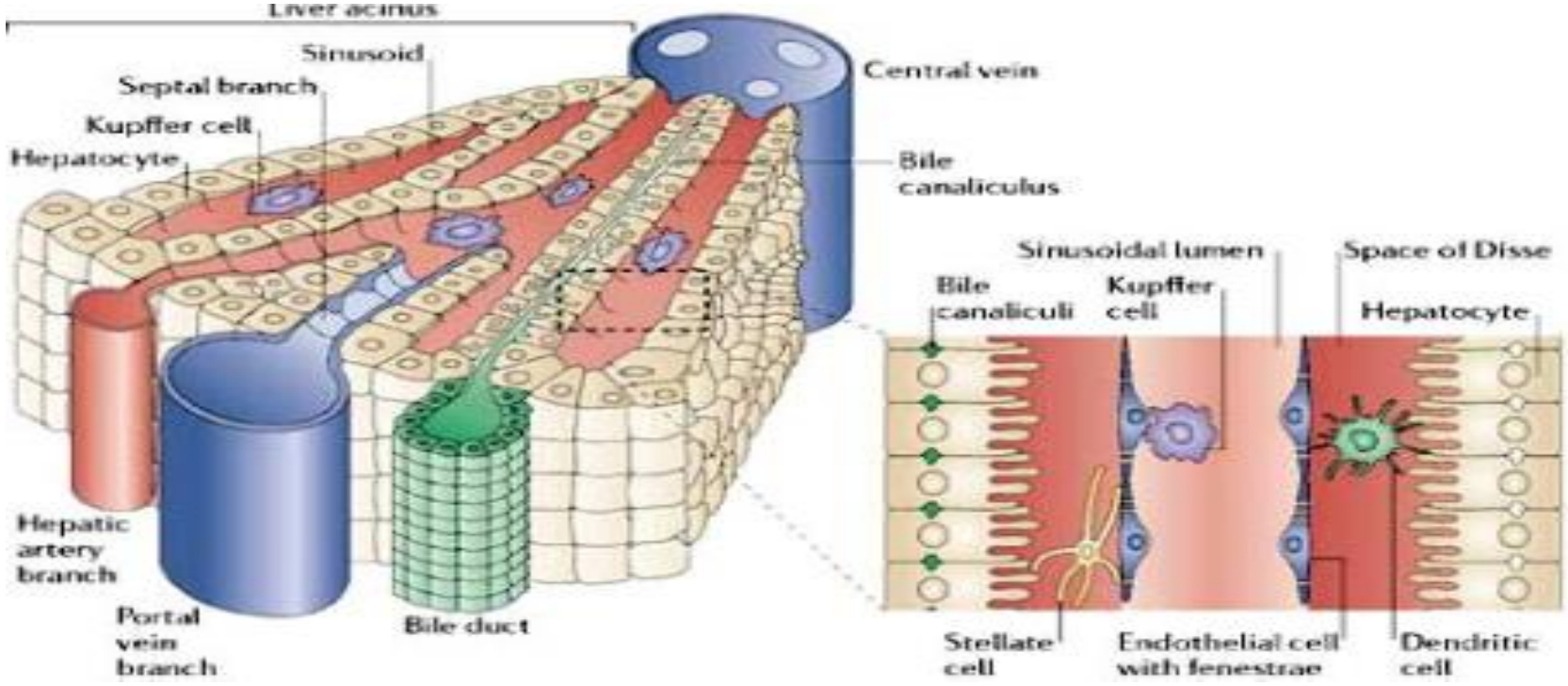
(a) Overview of histological components of liver

(b) Details of histological components of liver

Figure 24.15ab Tortora - PAP 12/e

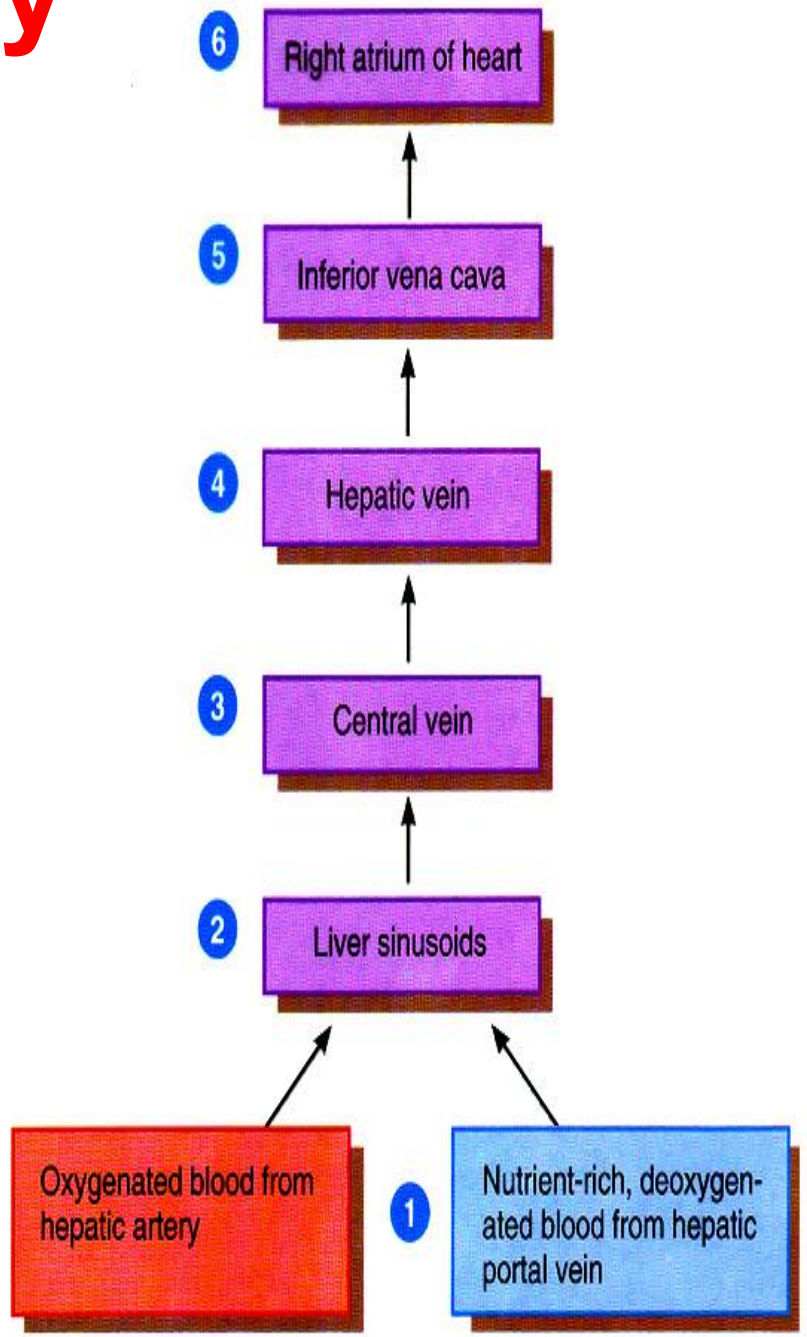

Interlobular veins
(to hepatic vein)
Bile duct
Portal arteriole
Portal venule
Portal triad
Central vein
Sinusoids
Plates of
hepatocytes
Portal vein
(c)
Fenestrated lining
(endothelial cells)
of sinusoids
Bile canaliculi
Portal triad
Portal
arteriole
Portal
venule
Bile
duct
Central
vein
Kupffer cells
in sinusoid
walls
Bile in bile
canaliculus flows
into bile duct
(d)


Kupffer cells
Hepatocytes
Sinusoid
Bile canaliculi
Hepatic artery proper
Bile duct
Hepatic portal vein
Central vein


Liver acinus
Sinusoid
Septal branch
Kupffer cell
Hepatocyte
Central vein
Bile canaliculus
Hepatic artery branch
Portal vein branch
Bile duct
Sinusoidal lumen
Space of Disse
Bile canaliculi
Kupffer cell
Hepatocyte
Stellate cell
Endothelial cell with fenestrae
Dendritic cell

Liver: Blood Supply

- Two sources
  - *Hepatic artery* - oxygenated blood from aorta.
  - *Hepatic portal vein* - deoxygenated blood:
    - Absorbed nutrients and toxins from the stomach and intestines.
    - Hormones from the pancreas.
    - Breakdown products of RBCs from the spleen.
- Blood mixes in the sinusoids
- Hepatocytes (liver cells) modify and exchange molecules with the blood.



Liver functions

1. ***Vascular Function:***
   - ***Blood storage:*** **10% of total blood volume 450ml.**
   - ***Blood filtration:*** **99% of bacteria that enter the portal blood from the intestine, small blood clots by are phagocytosed by Kupffer cells that line hepatic sinusoids.**
   - ***Removal of old red blood cells*** **by Kupffer cells.**
2. ***Secretory function (Bile formation):***

Synthesis & secretion of bile salts & bile pigments.

3. Metabolic functions:

1. **Carbohydrate metabolism: gluconeogenesis, glycogenolysis ,.**
2. **Protein metabolism: Deamination of amino acids → ketoacids.**

Conversion of ammonia to urea.
Formation of uric acid.

Synthesis of non essential amino acids.

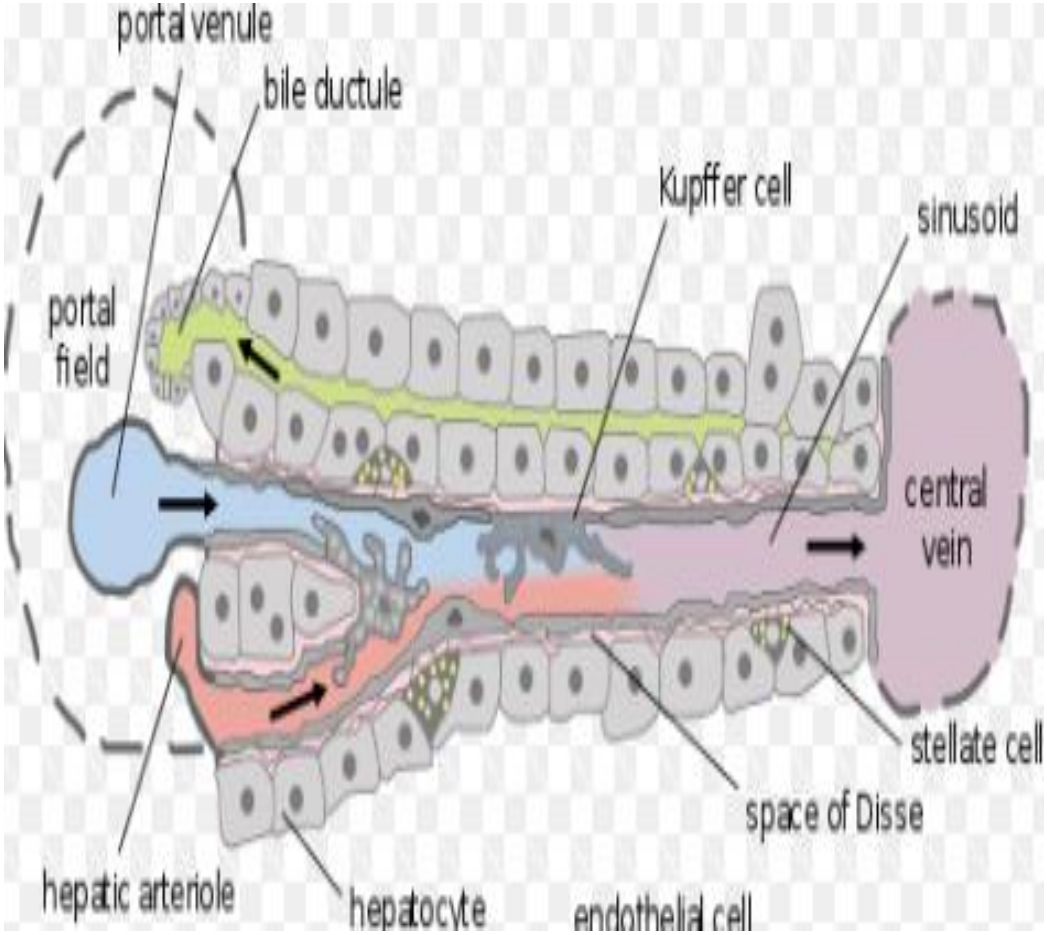
3. **Fat metabolism:**
    1. **Oxidation of fatty acids to supply energy.**
    2. **Synthesis of cholesterol, lipoproteins & phospholipids.**
    3. **Lipogenesis.**
4. **Synthesis of 25 hydroxy-cholecalciferol, plasma proteins (except y globulin), clotting factors.**

4. Storage function:

Glycogen, Vitamin A (ten months), D (3-4 months), B12 (12 months), Iron as ferritin.

5. Excretory function ;bile pigments, cholesterol.

6. **Detoxification of drugs & hormones** (thyroxin, steroid).
7. **Immunity:Kupffer cells.**



Bile

- Bile is an important digestive juice that is secreted by the liver and stored into the gall bladder.
- *Initial secretion* The liver forms and secretes 600-1200 ml of bile/ day by the *liver hepatocytes* into the biliary canaliculi rich in bile acids, cholesterol, lecithin to reach the hepatic duct.
- *Second secretion* by *hepatic ducts* rich in Na&Hco3 then the bile empties into the duodenum or through the cystic duct into the gall bladder.

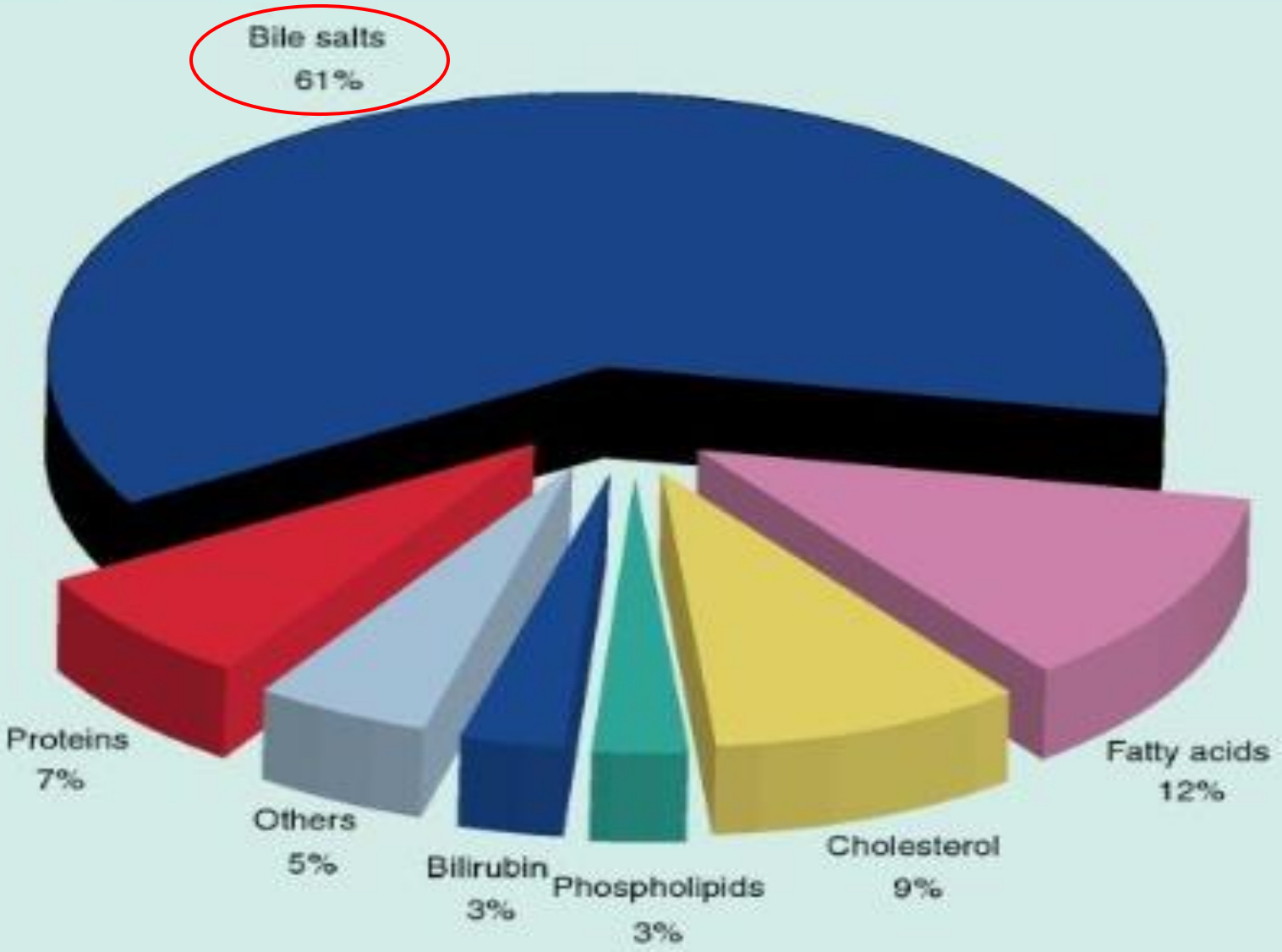
Composition:

Volume: 600-1200 ml/day.

pH: 7.8- 8.6.

	Liver Bile	Gallbladder Bile
Water	97.5 g/dl	92 g/dl
Bile salts	1.1 g/dl	6 g/dl
Bilirubin	0.04 g/dl	0.3 g/dl
Cholesterol	0.1 g/dl	0.3 to 0.9 g/dl
Fatty acids	0.12 g/dl	0.3 to 1.2 g/dl
Lecithin	0.04 g/dl	0.3 g/dl
Na^+	145.04 mEq/L	130 mEq/L
K^+	5 mEq/L	12 mEq/L
Ca^{++}	5 mEq/L	23 mEq/L
Cl^-	100 mEq/L	25 mEq/L
HCO_3^-	28 mEq/L	10 mEq/L

Medscape



Source: Nrurol © Expert Rev Proteomics © 2009 Expert Reviews Ltd

Constituents:

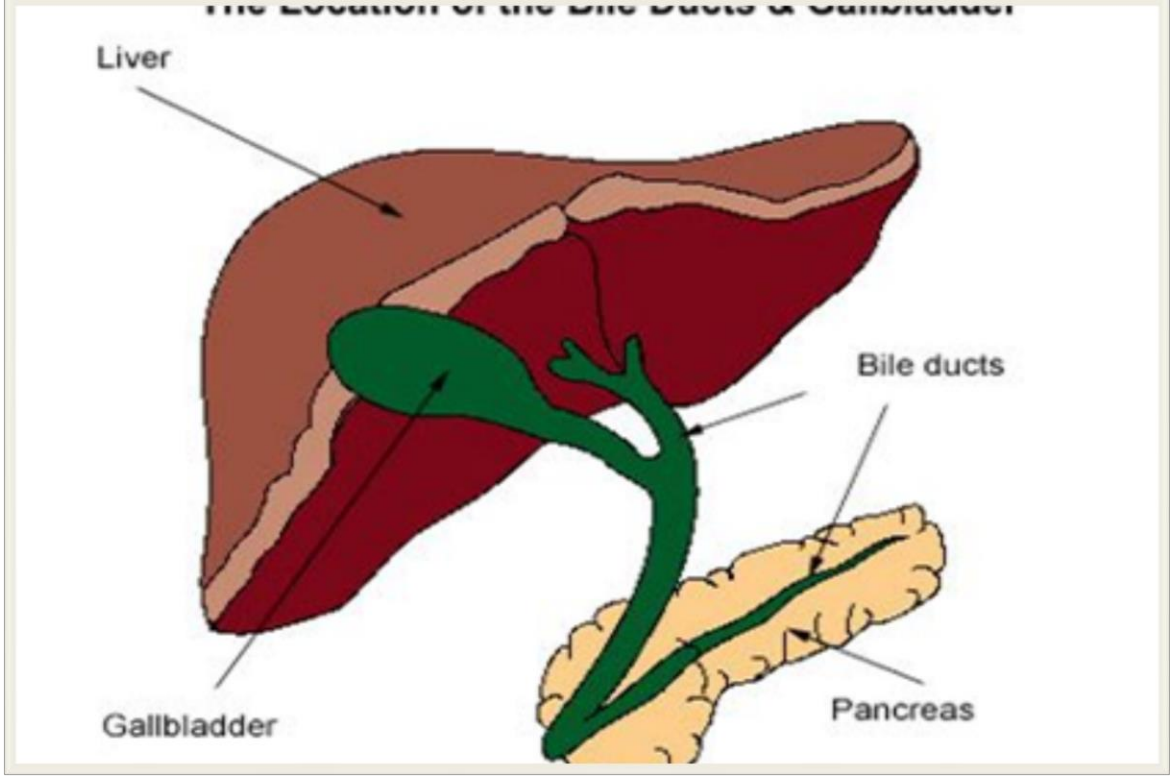
1-Aqueous constituents **(alkaline fluid, 97.5%);**

- **Secreted by *Duct cells.***
- **H_2O, Inorganic salts 0.5% (Na^+, K^+, Ca^{2+}, Cl^-, HCO_3^-).**

2-Organic constituents **(2.5%):**

- **Secreted by *Hepatocytes.***
- **(Bile salts, bile pigments, fatty acids, cholesterol, lecithin).**

3-Alkaline phosphatase enzyme.



Liver continuously synthesize &secretes bile.
Between meals, sphincter of Oddi is closed so secreted bile is moved into the gall bladder to be stored and concentrated.
During meal, bile is secreted from the gall bladder & liver .

Functions of bile

- ***Neutralization of HCl :*** **Share in HCl neutralization in the duodenum due to its high bicarbonate content. Its mucus content protect duodenal mucosa.**

- ***Digestive function:*** **Bile contains bile acids & salts , which are critical for digestion and absorption of fats and fat-soluble vitamins in the small intestine.**

- ***Excretory function:*** **Many waste products *(bilirubin & cholesterol) ,* are eliminated from the body by secretion into bile and elimination in feces.**

Free cholesterol is not soluble in aqueous solutions, but in bile, it is made soluble by *bile acids and lipids like lecithin.*

- **Bile salts are important for cholesterol homeostasis,**
- *Hepatic synthesis of bile acids accounts for the majority of cholesterol breakdown in the body. In humans, roughly **1-2g of cholesterol** are converted to bile acids and eliminated in bile every day*.

Bile salts

- **Bile acids (600 mg daily)are synthesized in the hepatocytes from cholesterol.**
- **Cholesterol is converted into the (primary), bile acids *cholic and chenodeoxycholic acids* which are then conjugated to an amino acid (glycine or taurine) to yield the conjugated form that is actively secreted into canaliculi.**
- **Bile acids contain both hydrophobic (lipid soluble) and polar (hydrophilic) faces. 2ry bile acids deoxycholic , lithocholic acids are formed by *bacterial action in colon.***
- **Tertiary(ursodeoxycholic,sulpholithocholic.**

Functions of bile salts:

1. They help fat digestion by decreasing surface tension of fat globules → *fat emulsification* (*detergent function*) to small droplets.
2. They are essential for absorption of
   - Fatty acids
   - Monoglycerides
   - Cholesterol.
   - Other lipids from the intestinal tract. & fat soluble vitamins (A,D,E, K).

(forming *Micelles* which are water soluble complexes).If absent, 40-50% of fats will lost in feces.

3. They are *cholertics* .i.e. stimulate bile flow.
4. *Laxative action* by stimulating intestinal peristalsis.
5. They are essential for keeping cholesterol dissolved in bile.

Liver Secretion Of Cholesterol And Gallstone Formation

- **Bile acids are formed in the hepatic cells from cholesterol in the blood plasma.**
- **BS are conjugated in liver by amino acids glycine and taurine to glycocholic and taurocholic acids.**
- **Both form salts by binding to Na, K in alkaline bile**
- **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.**

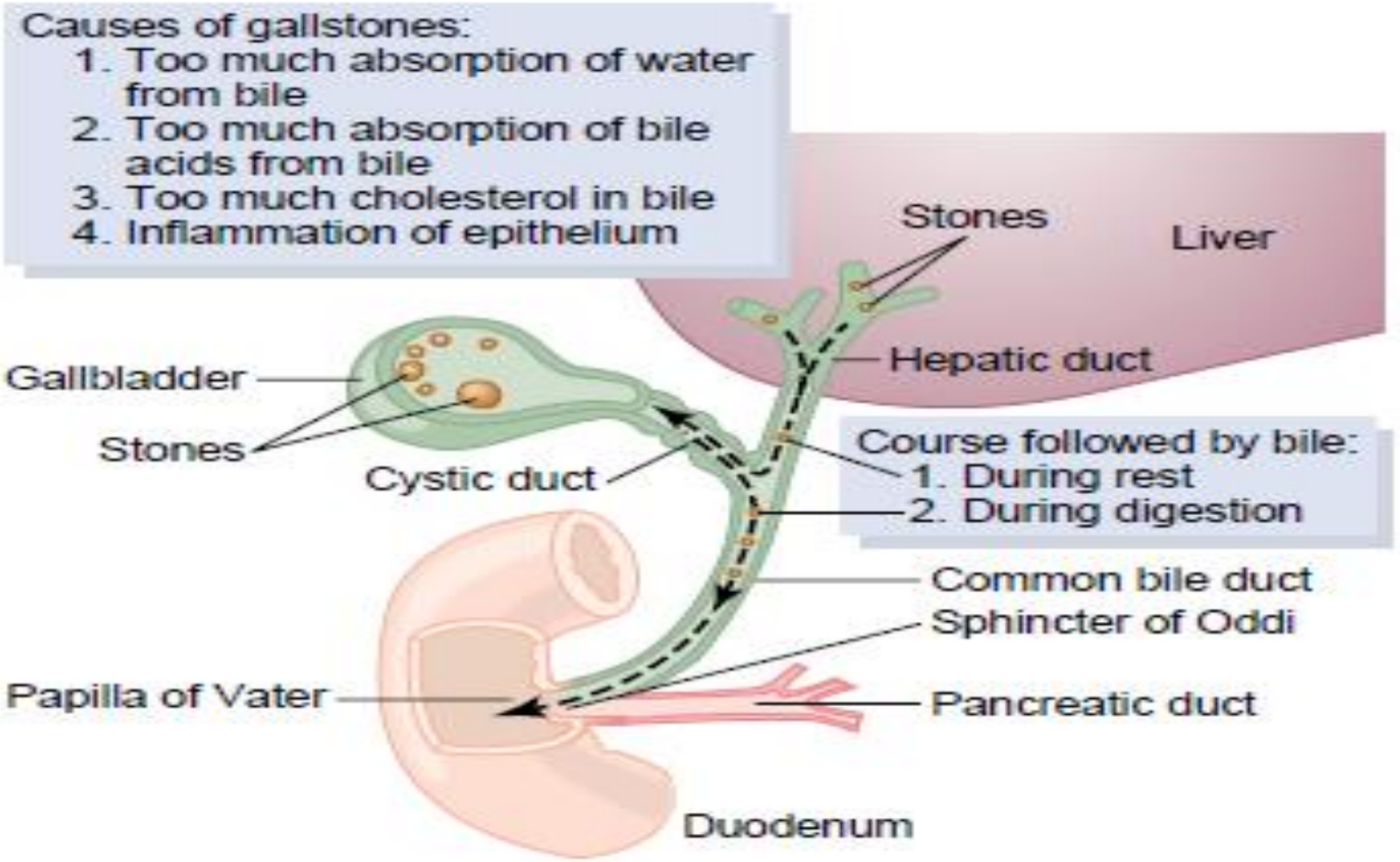
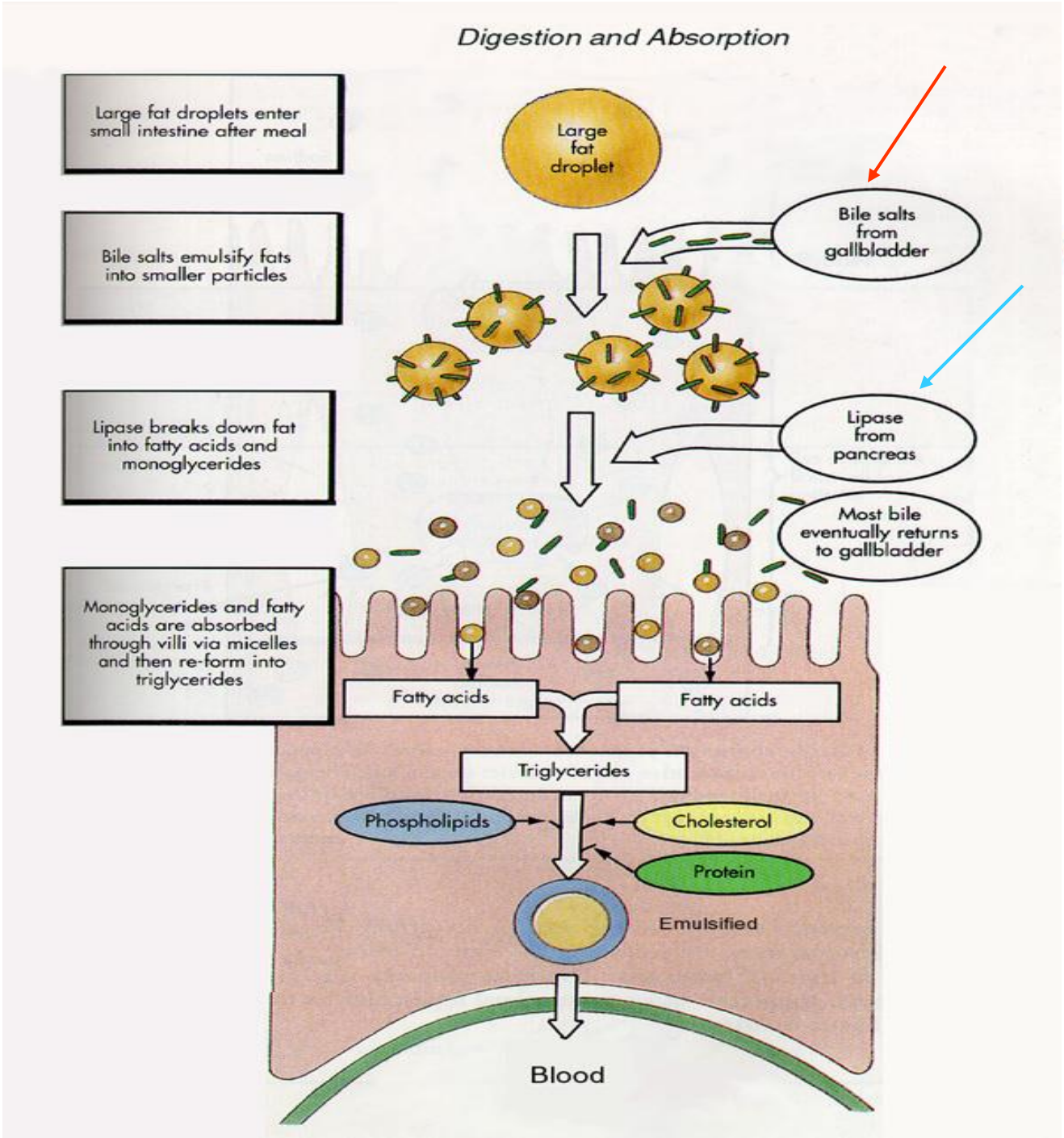
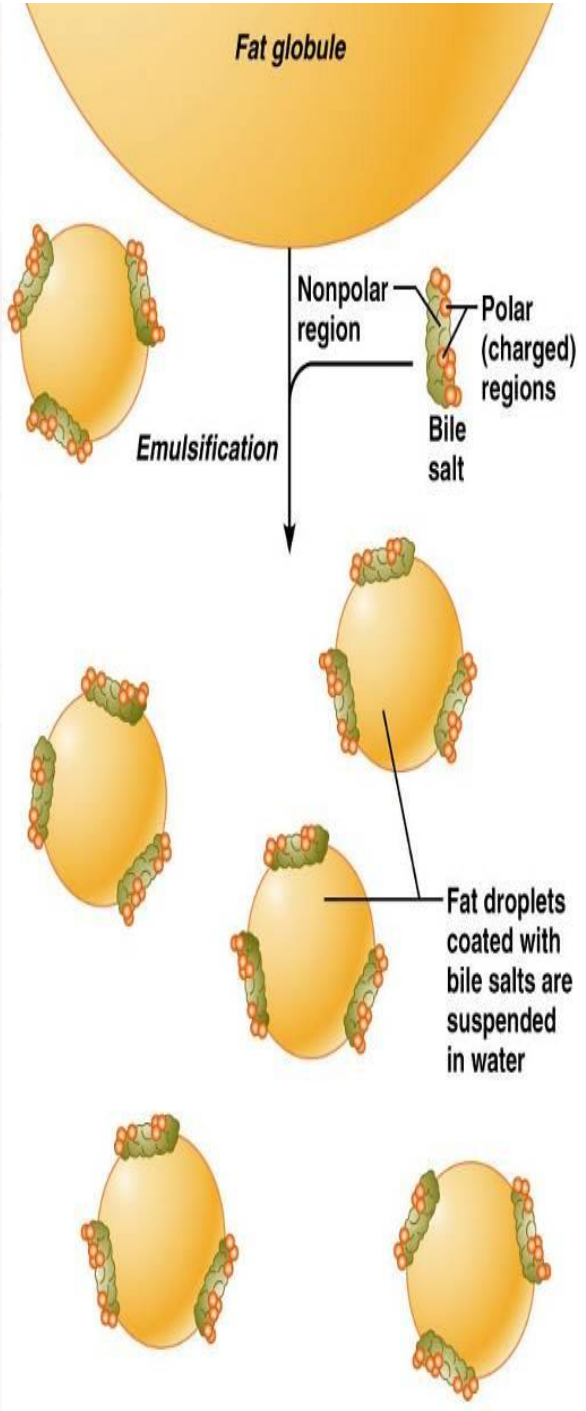
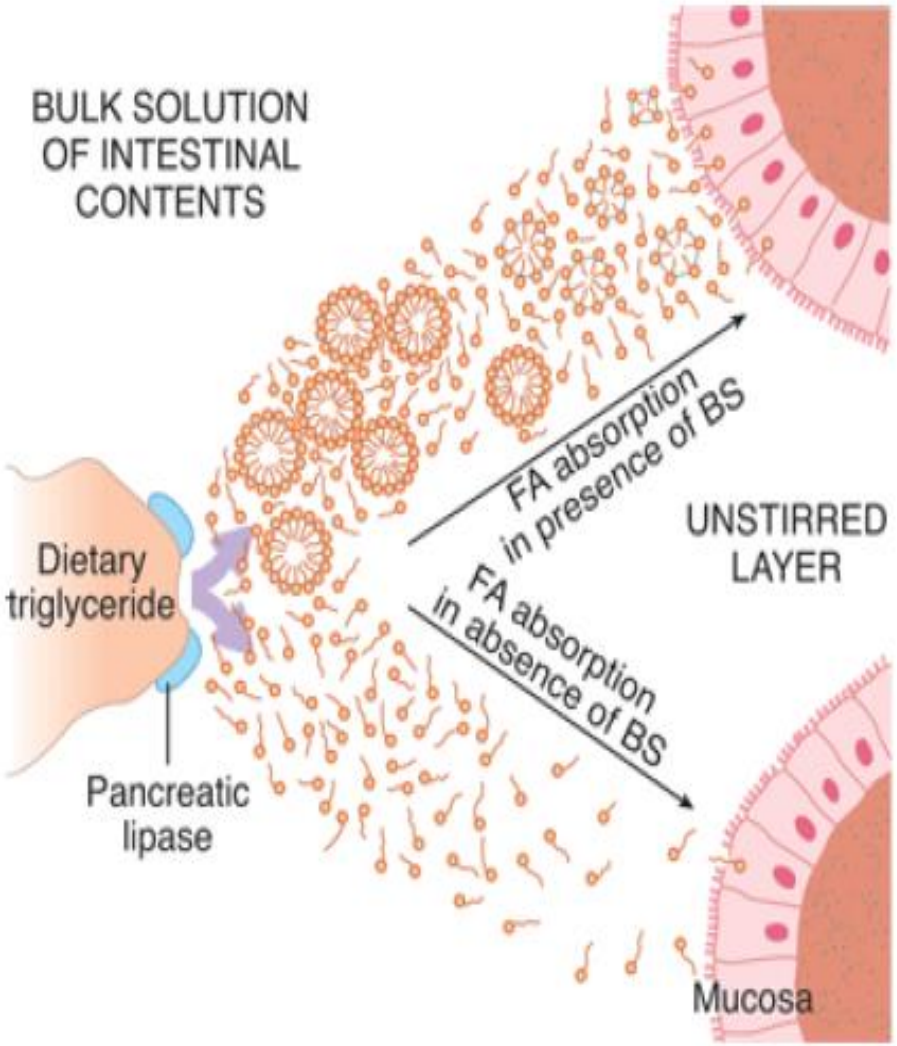


Figure 64–12

Formation of gallstones.


Digestion and Absorption
Large fat droplets enter small intestine after meal
Large fat droplet
Bile salts from gallbladder
Bile salts emulsify fats into smaller particles
Lipase breaks down fat into fatty acids and monoglycerides
Lipase from pancreas
Most bile eventually returns to gallbladder
Monoglycerides and fatty acids are absorbed through villi via micelles and then re-form into triglycerides
Fatty acids
Fatty acids
Triglycerides
Phospholipids
Cholesterol
Protein
Emulsified
Blood

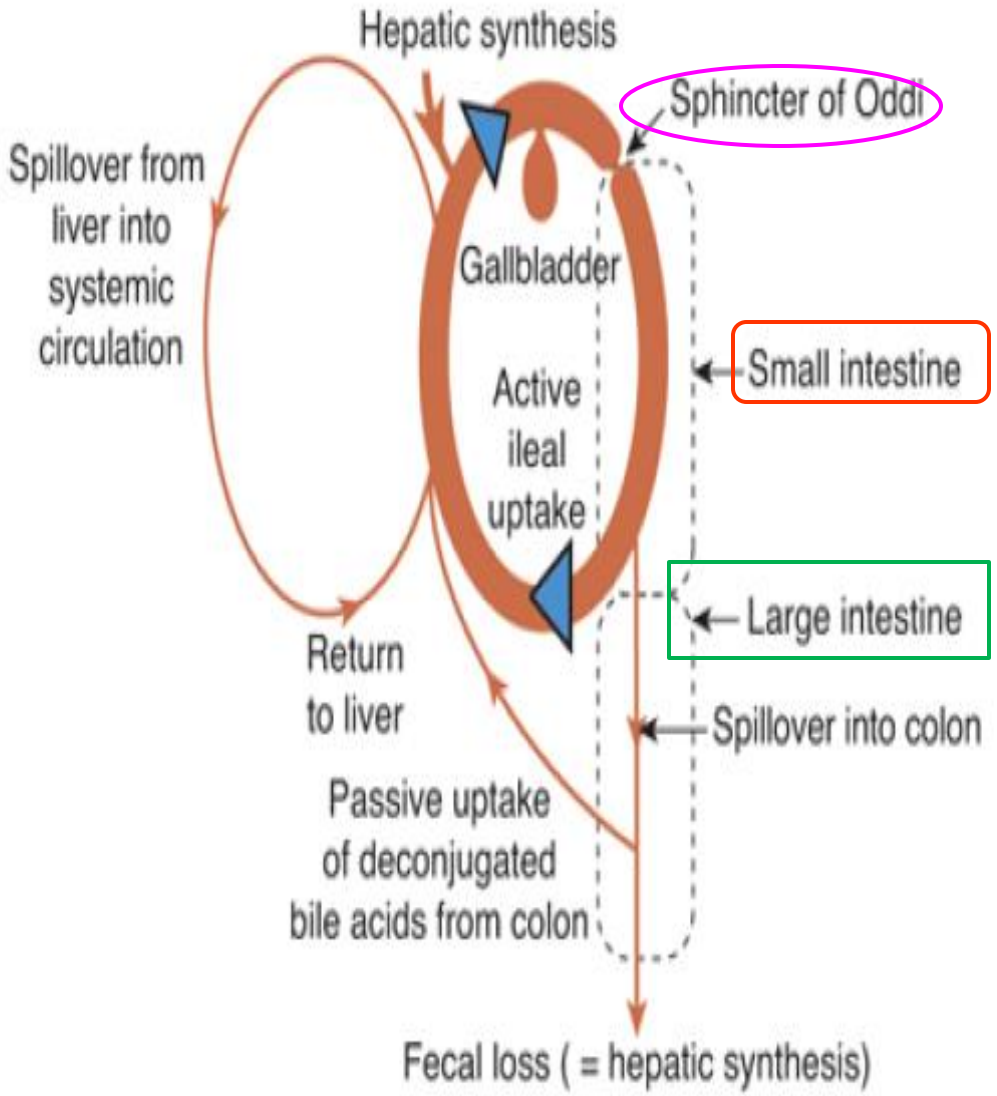

Fat globule
Nonpolar region
Polar (charged) regions
Bile salt
Emulsification
Fat droplets coated with bile salts are suspended in water


BULK SOLUTION
OF INTESTINAL
CONTENTS
FA absorption
in presence of BS
UNSTIRRED
LAYER
Dietary
triglyceride
FA absorption
in absence of BS
Pancreatic
lipase
Mucosa

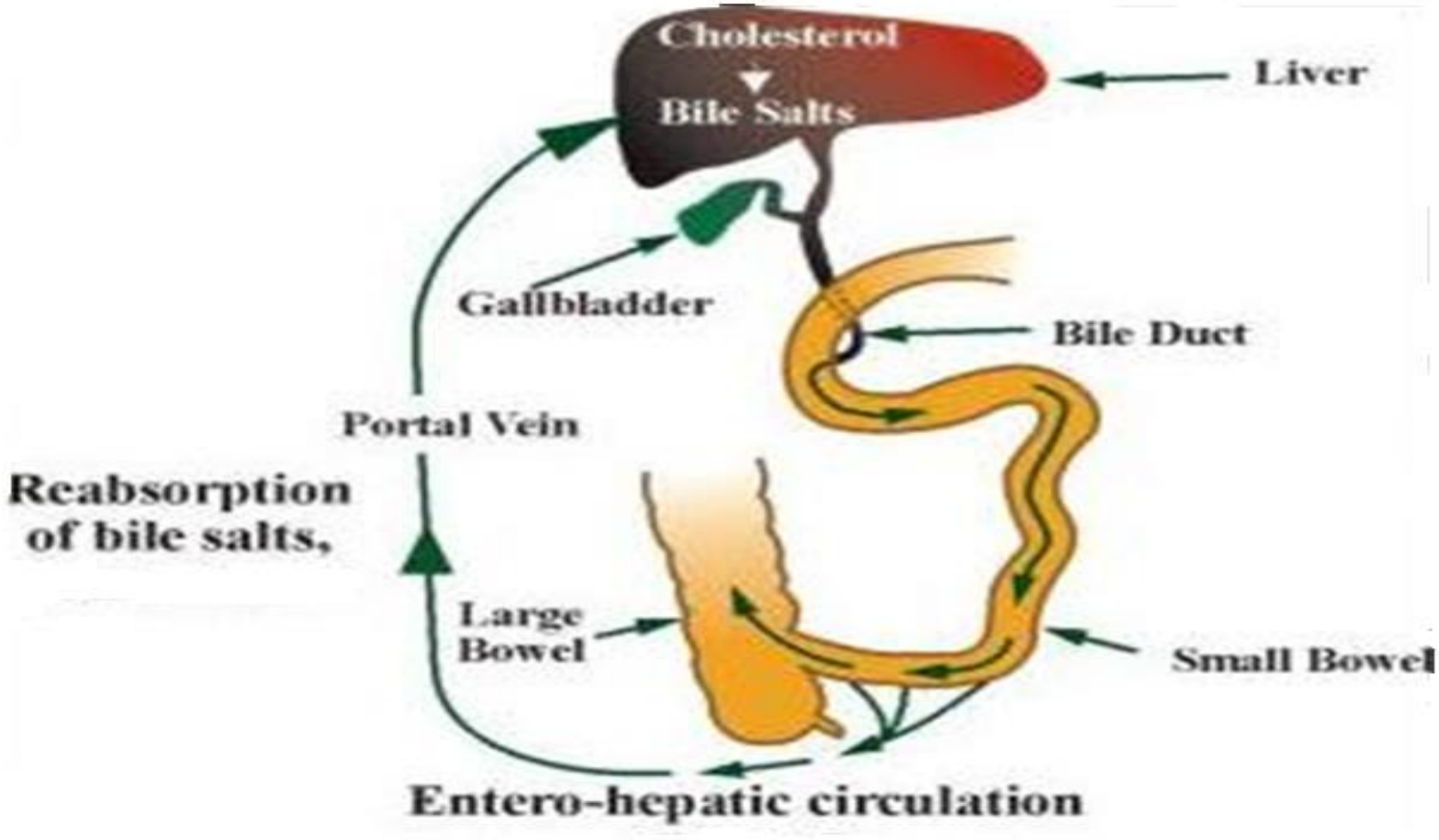
Enterohepatic circulation

- 94% of bile salts are reabsorbed, 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 from the *Terminal ileum* and returned to the liver to be secreted.

- 5-10% enter the colon → salts of deoxy (reabsorbed) and lithocholic acid (insoluble and excreted in the stool). *2nd bile salts.*
- The total bile salt pool in the body is 3.5 gm (recycles 6-8 times), and the amount lost in stools (0.2-0.4 gm/day) is replaced by new synthesis in the liver.


Hepatic synthesis
Sphincter of Oddi
Spillover from liver into systemic circulation
Gallbladder
Small intestine
Active ileal uptake
Large intestine
Return to liver
Spillover into colon
Passive uptake of deconjugated bile acids from colon
Fecal loss (= hepatic synthesis)

- **If the enterohepatic circulation is interrupted → liver cannot compensate and signs of bile salt deficiency appear** ***(steatorrhea, deficiency of fat soluble vitamins , cholesterol stones).***



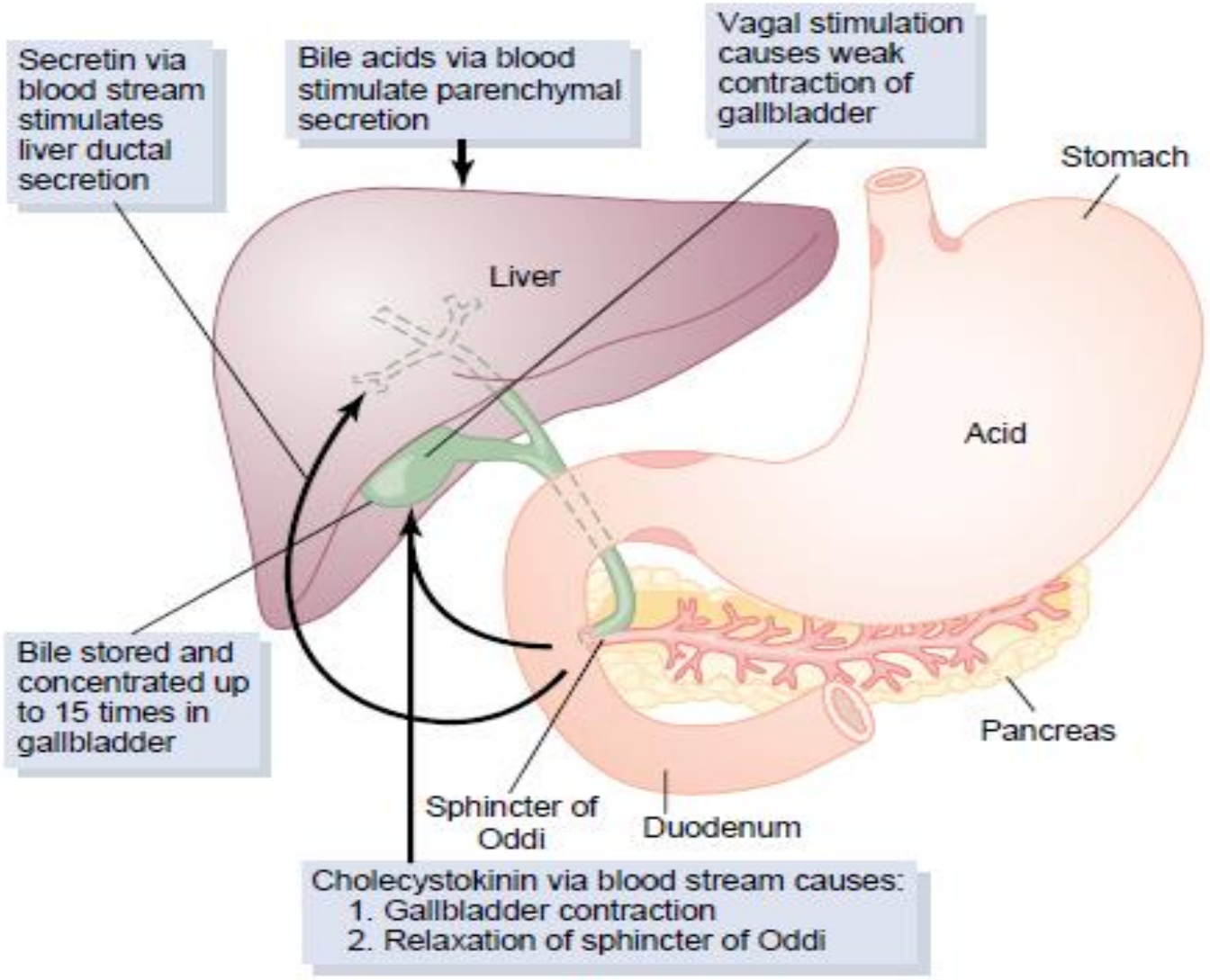
Regulation of bile secretion

Bile secretion by the liver is increased by:-

- ***Chemical mechanism;*** **Bile salts returned to the liver by the enterohepatic circulation stimulate further bile secretion.**
- ***Hormonal mechanism;*** ***Secretin*** **stimulate the aqueous alkaline portion of bile and increase bile flow.**
- ***Neural mechanism;*** **occurs in the cephalic phase of digestion . Mediated via the** ***Vagus nerve*** **& cause increased water & bicarbonate content of bile.**

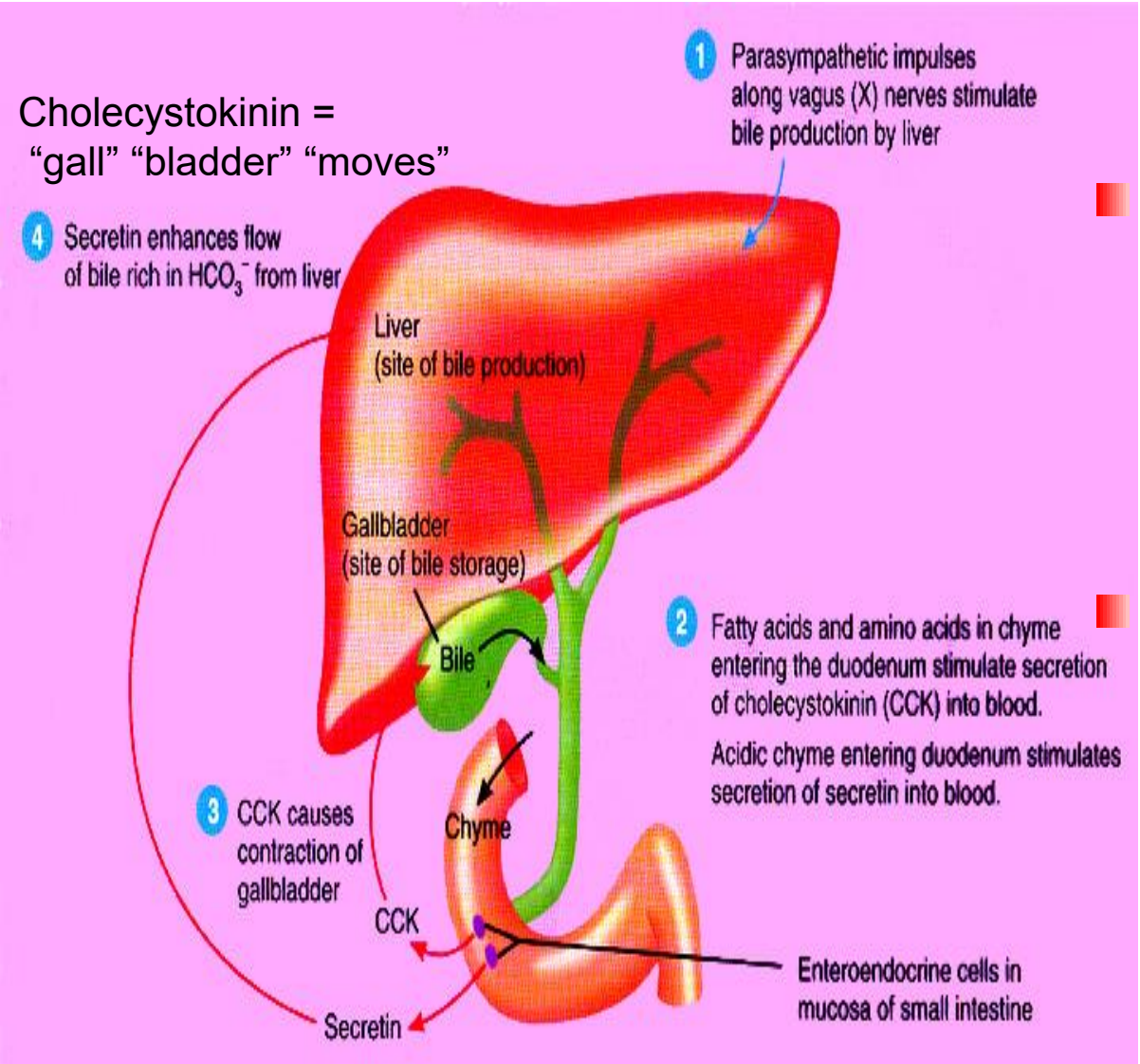
Choleretics ***are substances that increase bile formation by the liver and bile flow .e.g. bile salts &*** **secretin.**

Cholagogue ***are substances that increase move bile from the gall bladder and increase bile flow .e.g.*** **CCK**


Secretin via blood stream stimulates liver ductal secretion
Bile acids via blood stimulate parenchymal secretion
Vagal stimulation causes weak contraction of gallbladder
Stomach
Liver
Acid
Bile stored and concentrated up to 15 times in gallbladder
Pancreas
Sphincter of Oddi
Duodenum
Cholecystokinin via blood stream causes:
1. Gallbladder contraction
2. Relaxation of sphincter of Oddi

nptying.

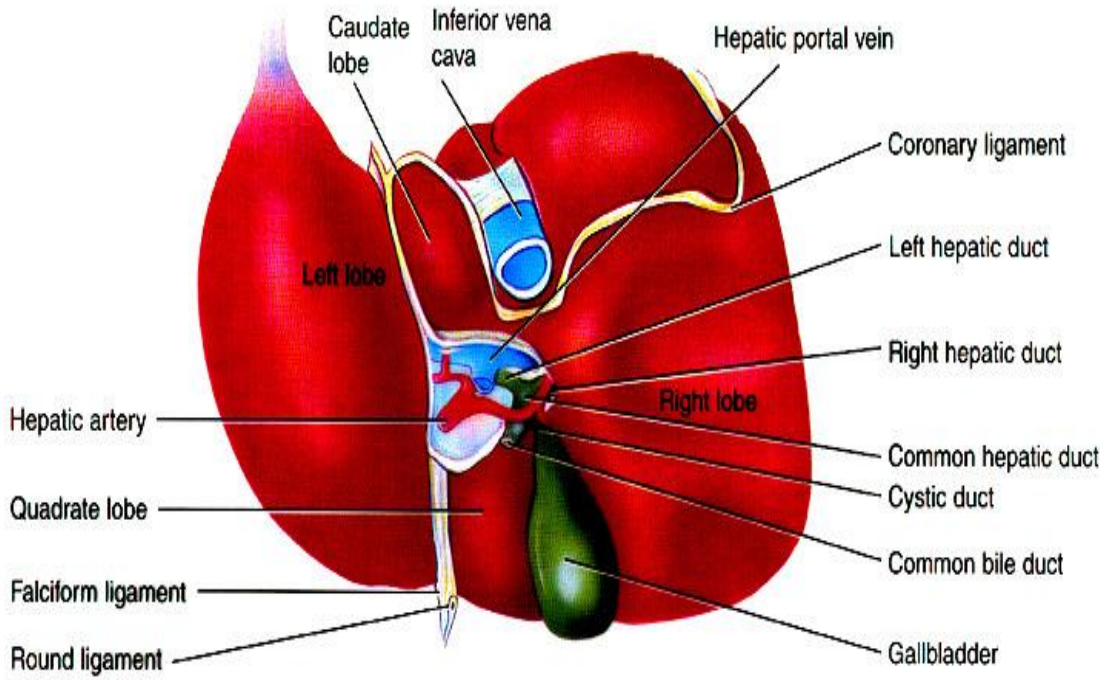
Liver:
Bile Synthesis



- **Regulation of bile production/secretion**
  - ***Nervous control*** **from parasympathetic via Vagus nerve**
  - ***Auto regulation*** **by sensing the presence of fatty acids and amino acids in the acidic chyme**
  - ***Hormonal control*** **by the secretion of the Enteroendocrine, CCK and secretin, from the duodenum**

Gall Bladder

- Pear-shaped sac, 7-10 cm long
- Physiology
  - Stores and concentrates bile between meals
  - CCK stimulates bile release for fatty meals
  - when the small intestine is empty, the hepatopancreatic sphincter closes, forcing bile into the gallbladder for storage



Pathology: gallstones

Functions Gall Bladder

***1-Storage of bile*: between meals, the sphincter of oddi is tonically contracted, so bile flow retrograde upwards through the cystic duct to be stored in the gall bladder.**

***2-Concentration of bile :* by active reabsorption of Na+, followed by passive reabsorption of water and most electrolytes, except calcium (bile salts increase 5-10 times, water content decreases to 89%).**

3-Acidification of bile: due to bicarbonate reabsorption during concentration, pH= 7-7.4 (prevents Ca^{2+} ppt and formation of gall stones).

4-Secretion of mucus: (white bile) from mucous glands in the mucosa: it ***Protects*** the gall bladder wall against highly concentrated bile salts, gives the bile a semi fluid consistency, and acts as a lubricant in the small intestine.

5-Evacuation: by contraction of wall and relaxation of sphincter.