Physiology

Sheet Slide

number 6

Done by Basheq Jehad

Correction Abdullah Alzibdeh

Doctor Mohammad Khatatbeh

In the previous lectures, we were discussing the topic of GI secretions.

Flashback:

From the last lecture, we should all know:

1) Types of secretory cells, like oxyntic (parietal) cells.
2) Composition of gastric juice at low rate and high rate of secretion.
3) Function of gastric secretions (HCl, pepsinogen, gastrin, mucus, and the intrinsic factor).
4) Controls of secretion: neural, hormonal (endocrine), and paracrine.

#REM: Although ANS can act directly, it has a lot of indirect effects to activate enteric neurons, hormonal and paracrine controls of stomach.

5) Receptors of gastrin are CCK receptors- **B**.

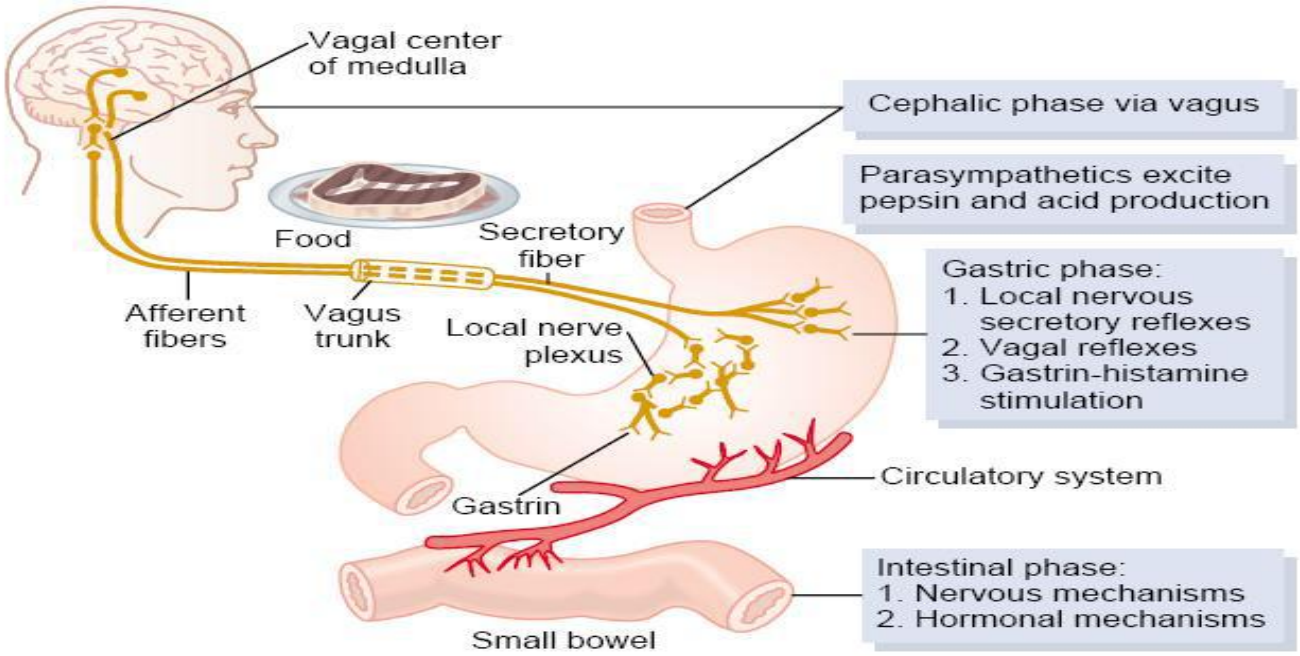
We will see that CCK-**A** receptors are found at the level of the pancreas.

6) Paracrine control is achieved by histamine acting through H2 receptors. By blocking these receptors we inhibit the action over gastric mucosa and oxyntic cells, accordingly we are reducing HCl secretions.

7) Irritation at the level of stomach may generate ulcers resulting from high histamine release which itself may result from activation of <u>enterochromaffin-like cells</u> leading to hyperacidity.
   Somatostatin is also involved with its inhibitory effect over these cells.
   HCl itself is also involved as a negative feedback mechanism to reduce acid secretions.

8) Controls during:
   a. Cephalic phase : increase gastric activity
   b. Gastric phase : increase gastric activity
   c. Intestinal phase : lots of <u>neural reflexes</u> which are Inhibitory as well as some hormones (e.g.: CCK, secretin, GIP) that inhibit gastric activity

   But some literatures mention that at the beginning of intestinal phase we can have some excitatory effects over stomach, this happens because the upper part of duodenum has G-cells (which secret Gastrin), so by more release of gastrin we have more gastric activity.



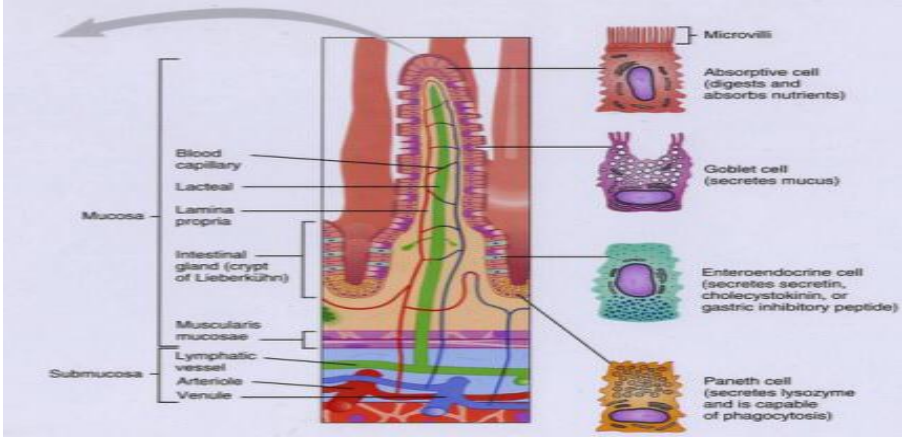
Intestinal Secretions:

Most of the secretion is at the level of small intestine **serous**.

Types of secretory cells:

1) Most cells release water and electrolytes
2) Some cells release mucus
3) Endocrine cells release hormones (involved in regulation of other secretory activities such as: CCK, secretin and so on...)

We can also find **tubular glands** known as **crypts of Lieberkühn** which empty into the lumen of duodenum, these glands secret serous secretions.



Regulation of intestinal secretion:

1) Local neural mechanisms: enteric nervous system control over secretion is mediated by Ach and VIP.
   VIP (vasoactive intestinal peptide) causes vasodilation when secreted; therefore it supplies more fluids for synthesis and secretion processes.
2) Hormonal control is **only** via **secretin** that increases duodenal secretion during intestinal phase. This is an important factor to neutralize the acid delivered into the duodenum from the stomach.

Colonic Secretions:

1) It is mostly **mucus** secretion
2) Small amount of serous secretions which is (mainly alkaline) rich in K^+ and HCO_3^-

K^+ absorption

K^+ actually moves across mucosa according to the electrochemical potential. So, absorption is favored in small intestine, but here in **colon** the potential favors **secretion of K^+** because most of Na^+ is removed.

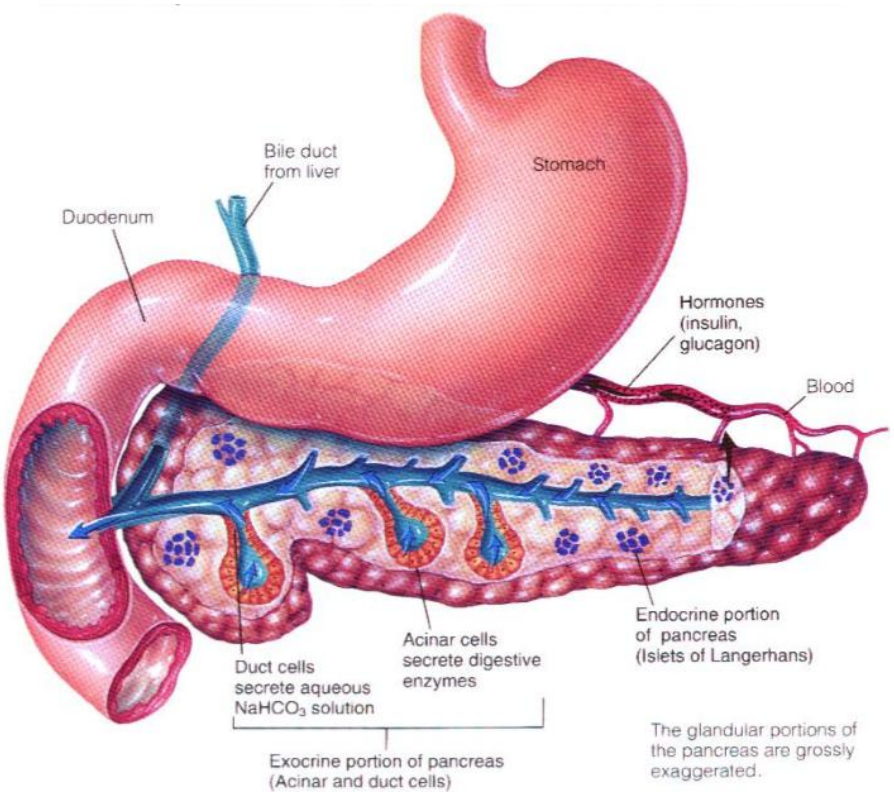
Pancreatic Secretions:

The pancreas has two parts:

1) Endocrine part: you'll take it in the endocrine system
2) Exocrine part: we'll focus on this part for now; cells that form the parenchyma of exocrine pancreatic glands are called acinar cells. When the product of acinar cells is secreted, the secretion flows toward the duodenum via ducts, these ducts are lined by another type of cells called duct cells.
   As you see, pancreatic exocrine glands are **structurally** similar to salivary glands (having acinar cells and duct cells), but the functions of these cells differ between each gland**.**

In salivary glands, acinar cells release water and electrolytes while duct cells only modify (change the composition of) secretions of acinar cells.

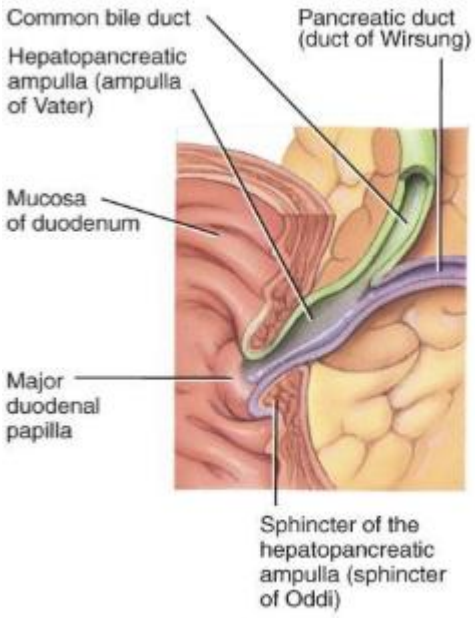
But in pancreatic exocrine glands, acinar cells release proteins and duct cells release water and electrolytes. So, if you are viewing these acinar cells you'll find that they are having a lot of vesicles, which means that these cells are synthesizing proteins and releasing them via vesicular transport, while duct cells don't have that much vesicles.



Exocrine pancreatic secretions flow toward the duodenum through pancreatic duct. But before reaching the duodenum, pancreatic duct unites with common bile duct that is coming from the liver, this union forms **hepatopancreatic ampulla** (also called ampulla of Vater; or hepatopancreatic duct), which enters the duodenum at the major duodenal papilla.

Hepatopancreatic ampulla is an important anatomical landmark; the opening of it into the duodenum is guided by a sphincter which is called **Oddi sphincter** (it is a physiologic sphincter).

The importance of Oddi sphincter is keeping the opening of hepatopancreatic ampulla closed to prevent any reflux from duodenum back toward the ducts.



A sphincter is higher representation of the circular layer of muscles.

Types of enzymes released from acinar cells of pancreas:

1) **Proteolytic enzymes:**
   A) Trypsinogen
   B) Chymotrypsinogen
   C) Procarboxypeptidase
   D) Note that these enzymes are released in an inactive form (proenzymes), and then they get activated in the duodenum, so there is no activation of these enzymes before Oddi sphincter.
   In the duodenum, the first proenzyme that is activated is Trypsinogen; it becomes Trypsin by the aid of Enterokinase enzyme which is found at the mucosa of the duodenum.
   (As the name implies, Enterokinase transforms Trypsinogen into Trypsin by phosphorylation)
   Once trypsin is active it can activate the other enzymes by cleaving some parts of them.
   Trypsin and Chymotrypsin are **endopeptidases**; they break a peptide bond somewhere in the middle of a polypeptide chain.
   While Carboxypeptidase is an **exopeptidase**; which means it removes one amino acid from the carboxylic end.
   Remember: Pepsin (in the stomach) is also an endopeptidase.

What happens if these enzymes were released as active enzymes from the beginning??
They would destroy the pancreas; since they have high digestive activity and are very well concentrated in the small ducts there.

(Remember the role of Oddi sphincter in preventing the reflux of proteolytic enzymes - mainly Trypsin – to the pancreas.)
Some patients have weaknesses in Oddi sphincter, which means there is reflux of duodenal content back to pancreatic duct, this may result in the development of **acute pancreatitis.** These patients may die within 6 hours if there is no proper intervention, so those patients need high emergency intervention to remove that infection or to solve up the problem there.
(This can happen in case of alcohol intoxication; high ingestion of alcohol can cause acute pancreatitis.)

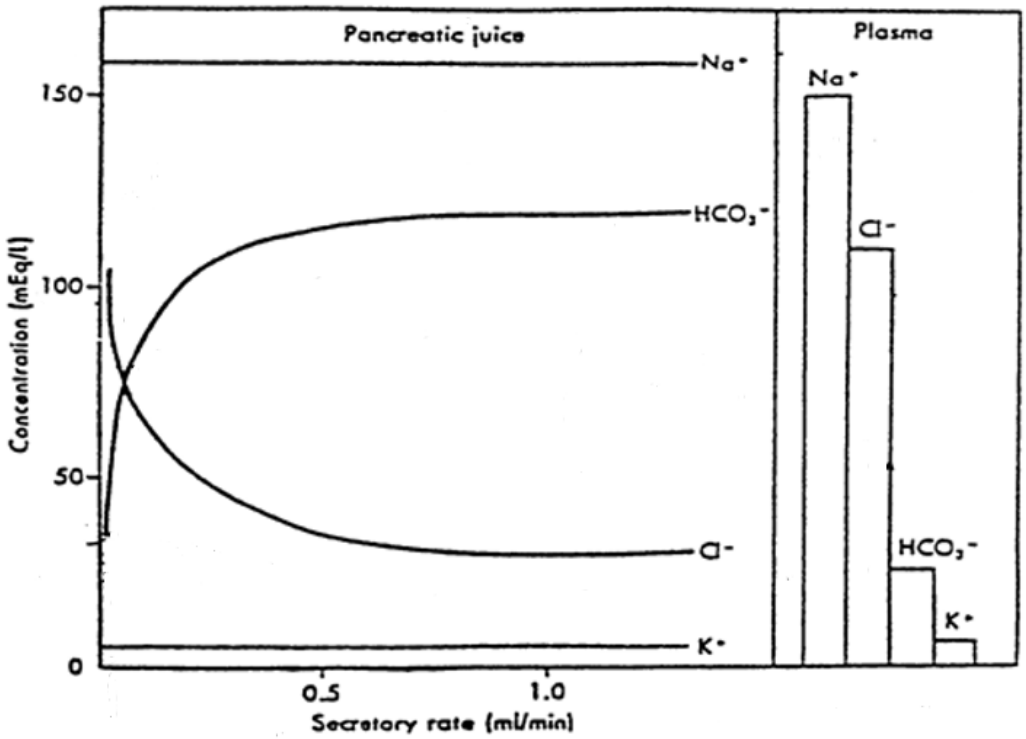
2) **Amylase:** can be released as active enzyme from the beginning and it is involved in digestion of starch

3) **Lipolytic enzymes:**
A) Lipases: these enzymes require co-lipases (also secreted from pancreas) to perform their function in lipid digestion. Lipases also require an oil/water interface and bile salts (secreted by liver).
B) Phospholipases
C) Cholesterol ester hydroxylases

Minutes [10-20]

Water and <u>bicarbonate</u> released from duct cells of pancreas:

Duct cells function in formation of bicarbonate and releasing it to lumen.
In some literature, they say that duct cells take bicarbonate from the interstitial fluid and release it into the lumen, but the fact that bicarbonate secretion is increased by stimulation of duct cells almost prove that duct cells actually **synthesize** bicarbonate by their machinery system and then release it into the lumen.
(This is similar to what happens in oxyntic cells but here bicarbonates are secreted instead of H^+ and H^+ is reabsorbed back)



As shown in the figure above, at low rate of secretion (low stimulation of duct cells) the concentration of bicarbonate in composition of pancreatic juice is low. But when stimulation occurs (at high rate of secretion) the concentration of bicarbonate much increases.

The opposite of that is Cl^-, having high concentration when we are at low rate of secretion and low concentration when we are at high rate of secretion.

What happens is that Na^+ is actively transported toward the lumen and it attracts negatively charged particles, the secretion of high concentrations of bicarbonate (HCO_3^-) reduces the attraction of Cl^- toward the lumen.

Control of pancreatic secretion:

1) Neural control:

A) Enteric neurons reach the pancreas; these neurons control secretion by release of Ach, VIP, and GIP (Gastrin releasing peptide).

B) ANS: - Parasympathetic NS activates ENS

- Sympathetic NS inhibits secretion indirectly through vasoconstriction

2) Hormonal control:

A) CCK acts directly by binding to CCK-**A** receptors on acinar cells so it causes increase in enzyme secretion.

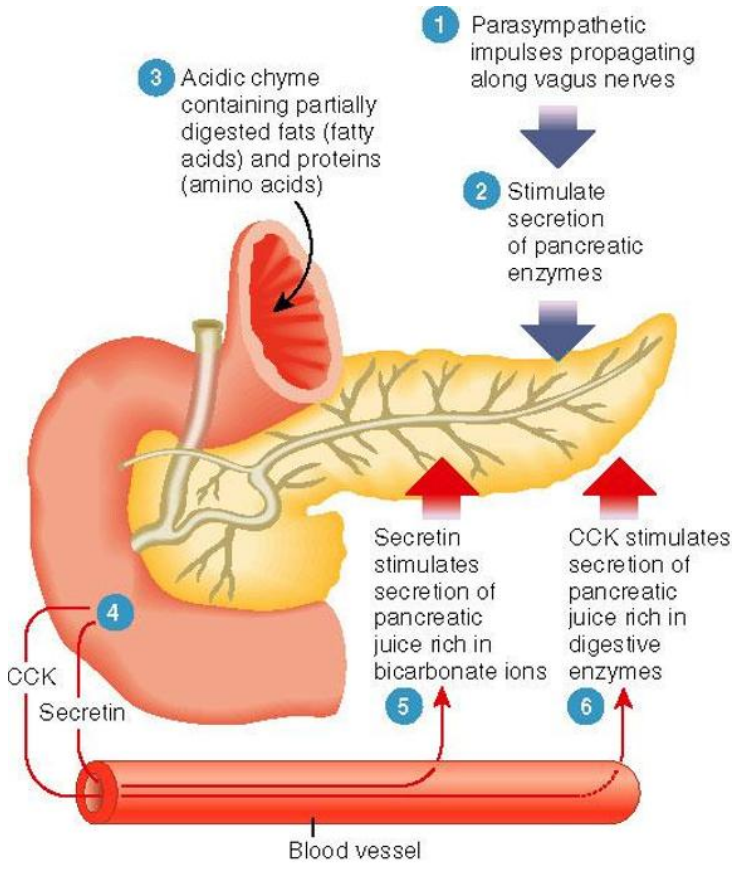
Also, CCK acts indirectly by activating **vagovagal reflex** thereby stimulating the parasympathetic activity which innervates the pancreas.

Vagovagal reflex: Vagal nerve has parasympathetic (efferent) neurons as well as sensory (afferent) neurons. Sensory neurons carry signals to higher centers from the pancreas, and then parasympathetic (efferent) neurons carry other signals from these centers to the pancreas to produce an effect.

B) Secretin release is stimulated by the acidity of the chyme that is emptied in the duodenum. Secretin acts over duct cells increasing secretion of water and electrolytes (bicarbonate) to neutralize the acidity of the chyme.

C) Pancreatic polypeptide has inhibitory on pancreatic secretions (both **exocrine** and endocrine secretions); it acts by inhibiting the release of Ach from enteric nervous system and inhibiting vagal output of the ANS.

Note that: the effect of CCK on vagus nerve and the effect of pancreatic polypeptide on ENS and vagus nerve are two examples of **neuro-hormonal interactions.**



This figure is a summary of pancreatic secretions during the different phases:
Cephalic phase: stimulated by sight, smell, taste or hearing and mediated by the vagus nerve (1, 2)
Gastric phase: stimulated by distention and is also mediated by vagus nerve (1, 2)
Intestinal phase: stimulated by distention and entrance of amino acids, fatty acids, and H^+ into intestinal lumen. It is mediated by CCK, secretin, enteropancreatic reflexes, and other hormones (3, 4, 5, 6)

When will there be no pancreatic secretion?
Pancreatic secretion is inhibited when we finish the whole three phases.

Liver secretions:

The liver has many functions including:

- Metabolic function: Processing all nutrients after their absorption
- Storage organ of glycogen, vitamins, and minerals like iron (ferritin) and copper
- Reticuloendothelial cells (Kupffer cells) are specialized in engulfment and removal of pathogens that can be found in the blood (bacteria and foreign materials).
- Detoxification of body wastes, hormones, drugs, and other foreign bodies
- Synthesis of plasma proteins: including clotting factors (their synthesis requires vitamin K) and hormone transporters
- **Secretion of bile and excretion of cholesterol and bilirubin**

The last function is important in our discussion of digestion and GI secretions. Bile coming from the liver acts as detergent to emulsify lipids and make them soluble, it is important in digestion because it contains **bile salts**. Bile also contains water, electrolytes, cholesterol, phospholipids, and bilirubin (which is one of the wastes intended for excretion).

Minutes [20-30]

Bilirubin: It results from destruction of RBCs.

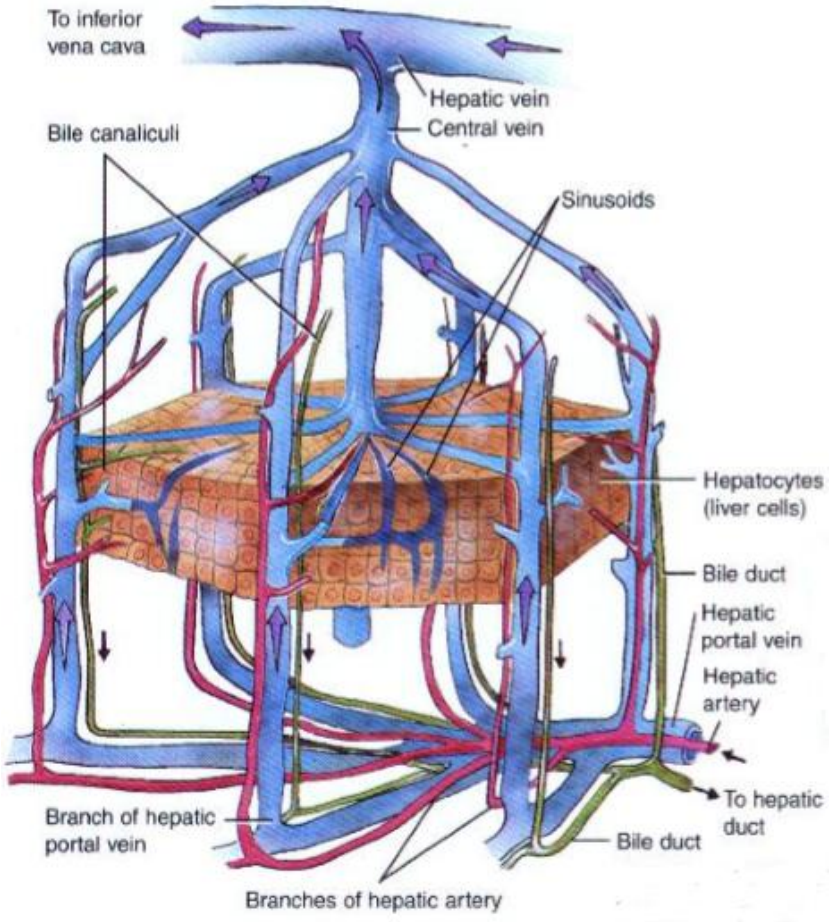
- RBCs contain Hemoglobin
- During catabolism of Hemoglobin, it dissociates into Heme and Globin
- Heme ring is cut and the product is Biliverdin
- Biliverdin goes through transformations to become Bilirubin
- Bilirubin is conjugated with glucuronide, sulfate, and other substances (conjugation is needed to make Bilirubin more soluble in bile; more hydrophilic)
- Then the liver takes Bilirubin from the blood and releases it in the bile.

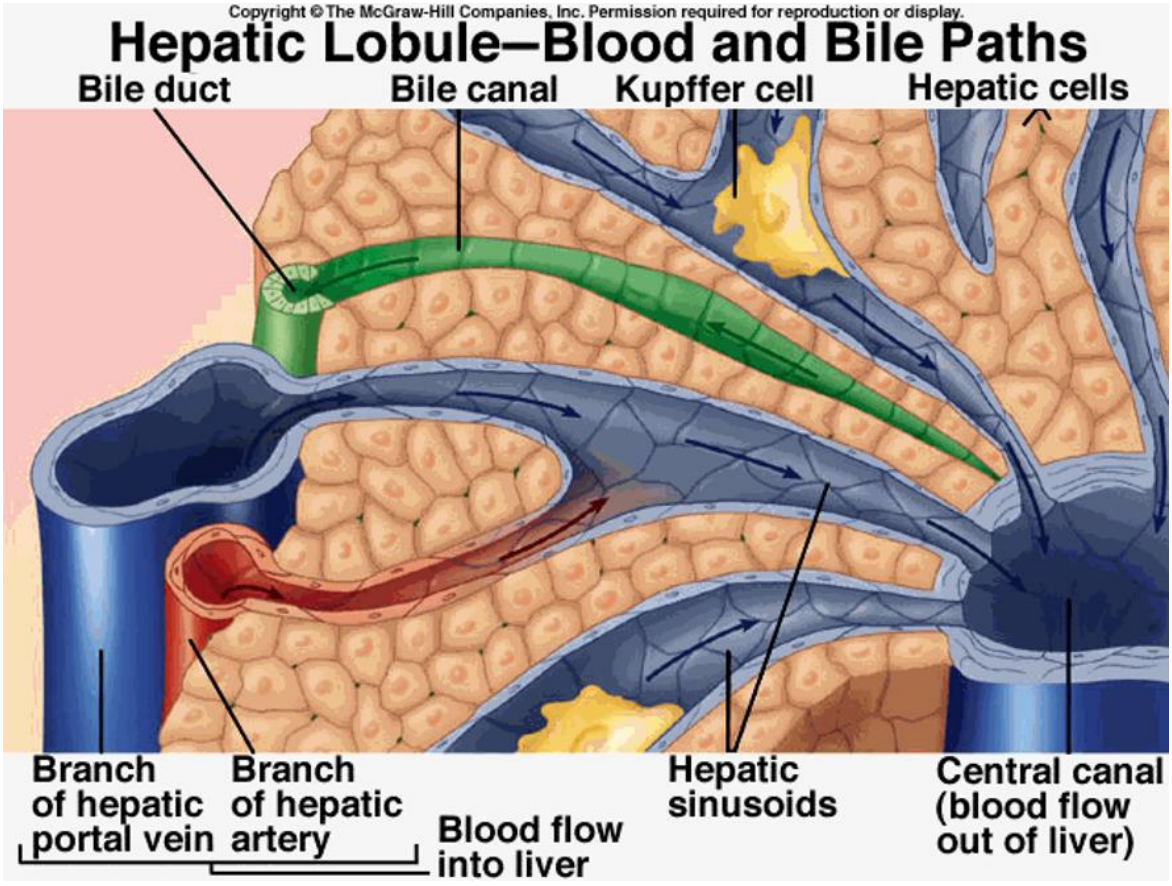
An increase of Bilirubin level (hyperbilirubinemia) in our fluids (blood and interstitial fluids) will result in the developing of **jaundice**, the causes of this condition are divided to:

- **Prehepatic causes**: like hemolytic anemia where there is high rate of destruction of RBCs and consequently high concentration of Bilirubin (The amount of Bilirubin exceeds the normal capacity of the liver)
- **Hepatic causes**: here the liver is unable to take or conjugate Bilirubin leading to its accumulation.
- **Posthepatic causes**: here the liver takes Bilirubin, conjugates it normally, and secret it. But it DOES NOT reach the intestine as a result of blockage (obstruction) of hepatic ducts by a stone, or as a consequence of **cancer of the head of pancreas** (since part of the hepatic duct passes through the head of pancreas).

Hepatic lobules:

- The whole liver is composed of small hexagonal structures called hepatic lobules
- Small branches of the portal vein pass at the edges of each hexagon (the portal vein collects all the blood from the GI after absorption and passes it to the liver)
- At each center of lobule there is a central vein
- The blood collected from the intestine passes in between hepatocytes from the branch of portal vein to the central vein through **sinusoids** (a sinusoid is a large capillary but has a similar wall), movement from the **periphery to the center** of the lobule
- The other pole of the hepatocyte (that is not facing a sinusoid) is facing another canalicular structure where we have bile flow from the **center to the periphery** of the lobule
- At the periphery bile is collected in small bile ducts, then passed to bigger and bigger bile ducts until the formation of left and right hepatic ducts, these two ducts form the common hepatic duct.


To inferior vena cava
Hepatic vein
Central vein
Bile canaliculi
Sinusoids
Hepatocytes (liver cells)
Bile duct
Hepatic portal vein
Hepatic artery
To hepatic duct
Branch of hepatic portal vein
Bile duct
Branches of hepatic artery


Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.
Hepatic Lobule—Blood and Bile Paths
Bile duct
Bile canal
Kupffer cell
Hepatic cells
Branch of hepatic portal vein
Branch of hepatic artery
Blood flow into liver
Hepatic sinusoids
Central canal (blood flow out of liver)

Before reaching the duodenum, common hepatic duct passes its content of bile into a vesicular organ called gallbladder (or cholecyst).

When the Oddi sphincter is contracted (closed) and the muscular layer of gallbladder is relaxed, the bile pressure in the ducts is higher than in the gallbladder, that's why bile is diverted toward the gallbladder.

Right after meals, the muscular layers of this vesicular organ (gallbladder) contract so the pressure of bile there becomes higher than in hepatic ducts. As a result, bile flows through common bile duct toward the duodenum (but it still cannot pass into the duodenum unless Oddi sphincter is relaxed)
Remember: Before reaching the duodenum, common bile duct unites with pancreatic duct forming **hepatopancreatic duct** (hepatopancreatic ampulla or ampulla of Vater).

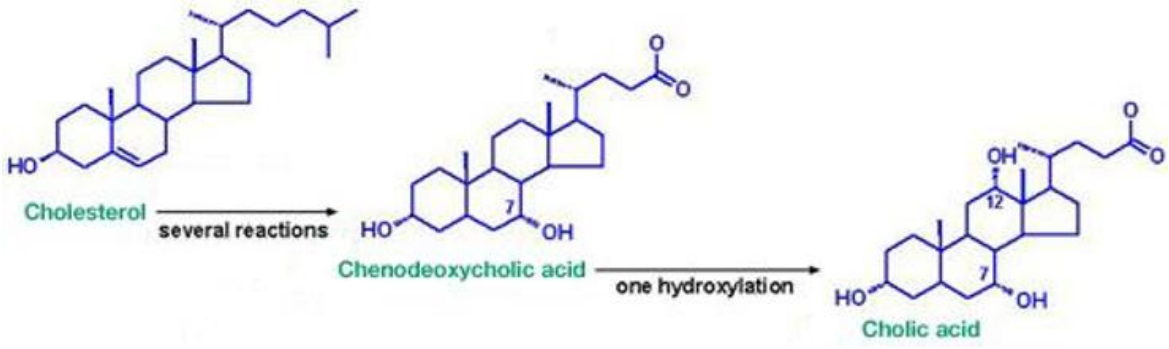
At the gallbladder, water and some electrolytes are reabsorbed from the stored bile by epithelium so the bile becomes more concentrated (its concentration increases up to 20 folds through this modification)

Bile modifications in the gallbladder: *Not to be memorized of course*

	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
Lethicin	0.04 g/dL	0.3 g/dL
Na^{+}	145 mEq/L	130 mEq/L
K^{+}	5 mEq/L	12 mEq/L
Ca^{+2}	5 mEq/L	23 mEq/L
Cl^{-}	100 mEq/L	25 mEq/L
HCO_3^{-}	28 mEq/L	10 mEq/L

g/dL = gram per deciliter
mEq/L = milliequivalent per liter

Bile salts are synthesized from <u>cholesterol</u> molecules



Chenodeoxycholic acid and Cholic acid are conjugated either with Glycine or with Taurine (two amino acids), this conjugations produces 4 bile salts.

Minutes [30 – 40]