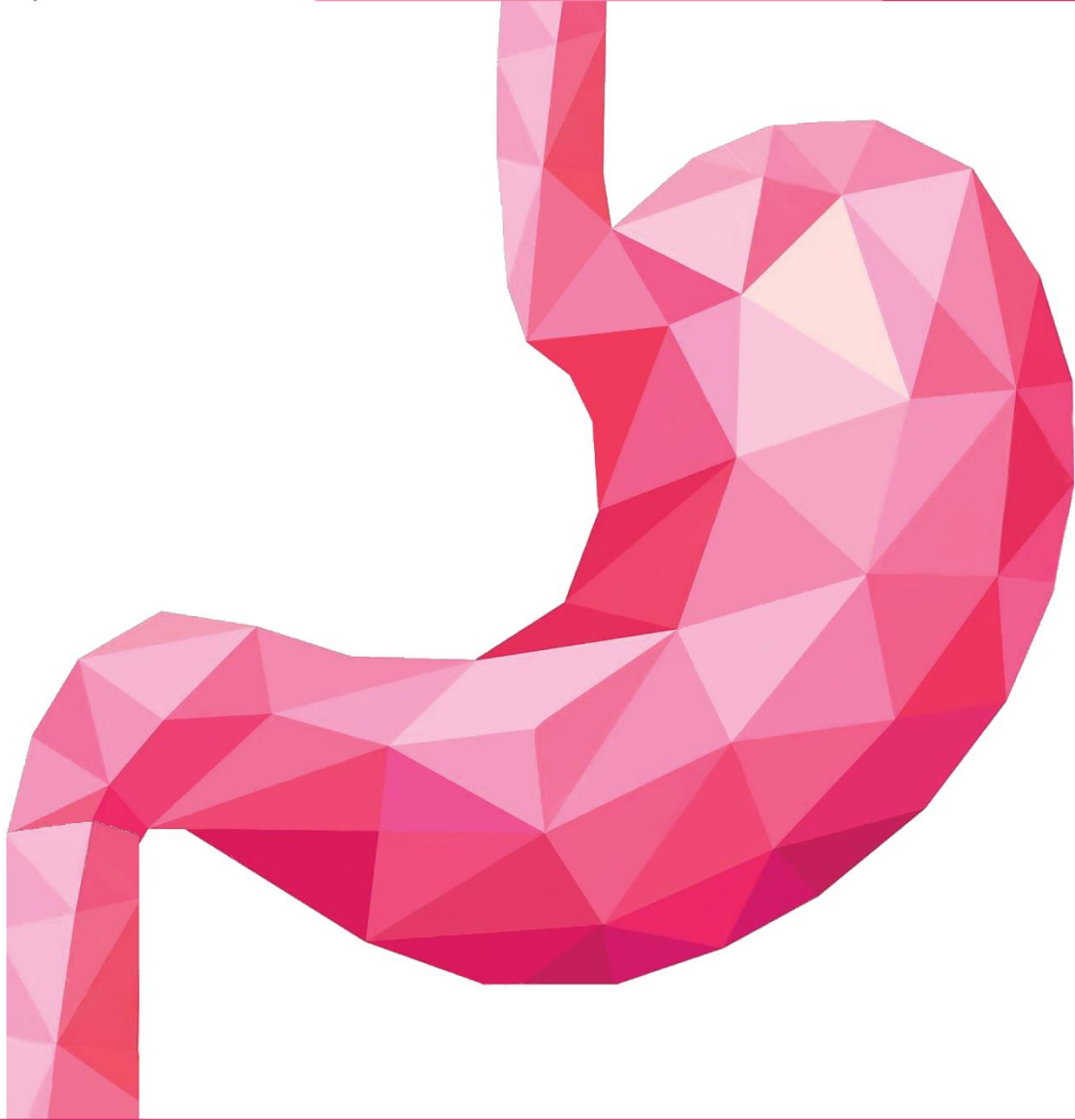




GIS 5

PHYSIOLOGY



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NOTES: -Anything that is underlined and written between [], **wasn't** mentioned by the professor, and was taken from the slides.
 -Anything is written in **red** was taken from the handout.

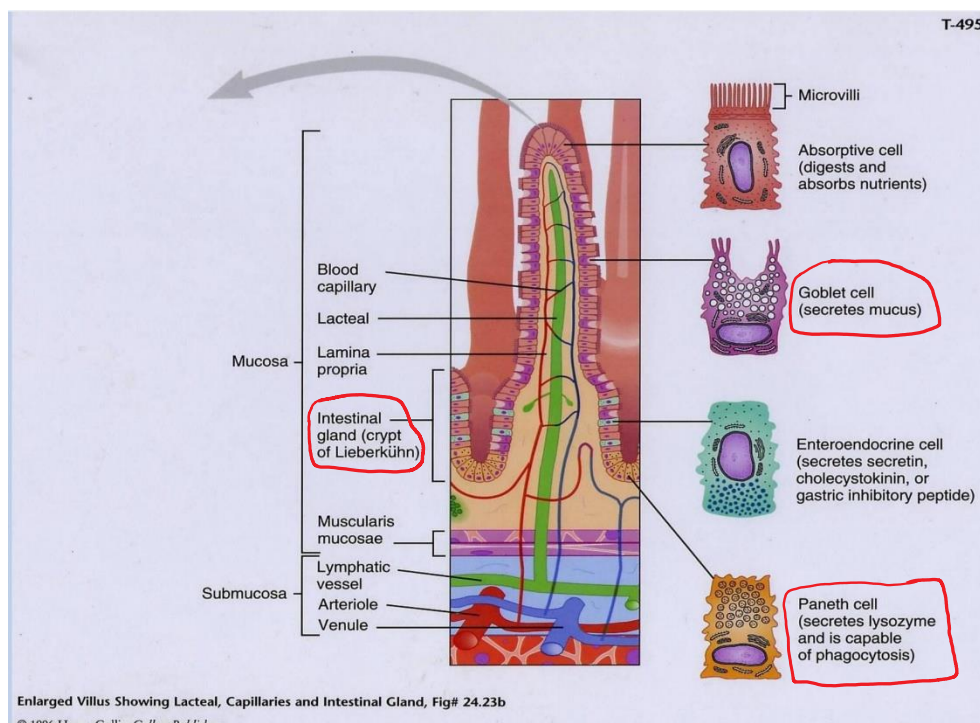
Today we'll start talking about **intestinal secretion**.

We have a lot of secretory structures along the small intestine. As you see in the picture below, these can be found as dispersed cells over the mucosa, or as groups in glands like **crypts of Lieberkühn (intestinal glands)** within the mucosa itself .

Tubular glands in submucosa of duodenum (duodenal glands). These invaginations of epithelium known as crypts of Lieberkuhn which empty into the lumen of duodenum. These glands secrete serous secretion.

**Tubular glands = crypts of Lieberkuhn.
 (secrete serous secretion)**

-Most of the secretions by the small intestine is **serous secretion**, but we can have some cells like **goblet cells, that release mucus**. In addition, we can have paneth cells which release lysozymes.



-Small intestine secrete around 1.5 Liter of serous(mainly) and mucous secretions per day (1500ml/day) .

-So, as we said, we have secretory cells dispersed all over the mucosa (mucosal epithelium) releasing water and electrolytes, and we have goblet cells which release mucus.

Regulation

Secretion of the small intestine is highly regulated, we have neural control, and we have hormonal control .

1-The neural control is achieved by the ANS as well as the ENS.

This neural control is mediated by **Acetylcholine (Ach) neurons and Vasoactive intestinal polypeptide (VIP) neurons.**

Actually ,VIP acts mainly over the cells, causing inhibition of smooth muscle cells at the walls of the vessel, resulting in vasodilation . This vasodilation results in having more fluids available for the process of secretion .

2-Now the hormonal control is achieved by **secretin**, which increases upon gastric emptying into duodenum.

The stimulus for the release of secretin is to increase proton content in the secretion, so the decrease in pH at the beginning of the small intestine results in more secretion of secretin .

As a result, **secretin increases duodenal secretion.**

Colonic secretions

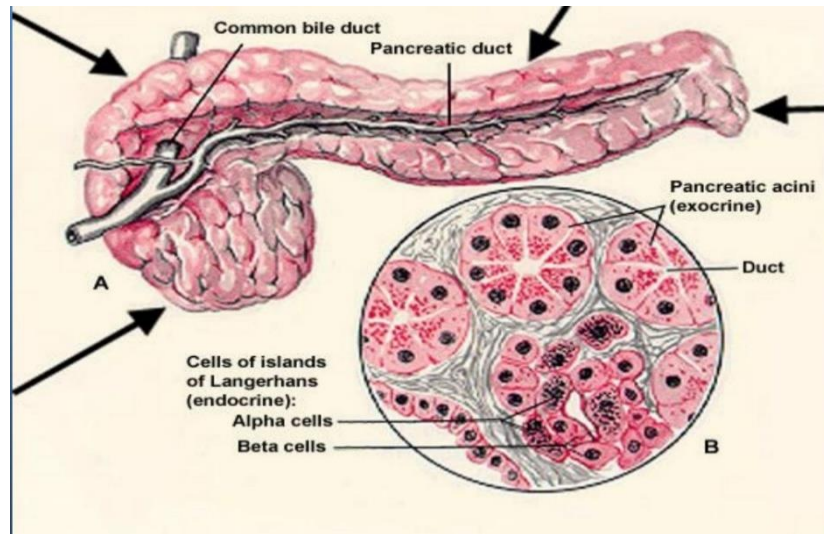
At the level of the colon, most of the secretion is **mucus** but we can have small amounts of serous secretions rich in potassium (K +), and bicarbonate (HCO₃ -) .

Pancreatic Secretions: (1-2 L/day)

pancreas is a secretory organ that releases **serous secretion**, rich in enzymes that are involved in the process of digestion .

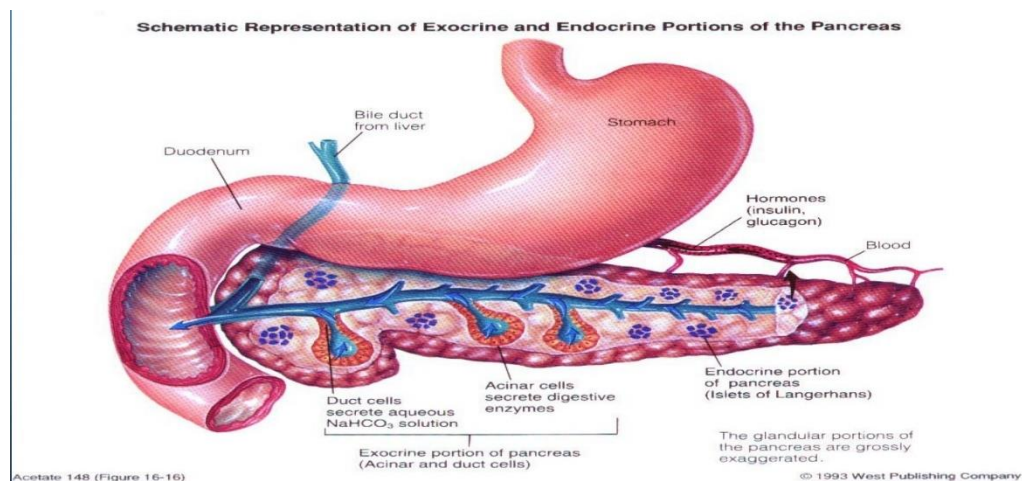
The pancreas is composed of 2 types of secretory structures , we have the **endocrine part (Islets of Langerhans)** of the pancreas , which releases hormones , such as: insulin, glucagon, somatostatin , pancreatic polypeptide ,into the blood.

We also have **exocrine portion** of the pancreas, which releases enzymes, as well as serous secretions rich with bicarbonate. It is involved in the process of digestion of chyme at the level of the small intestine.

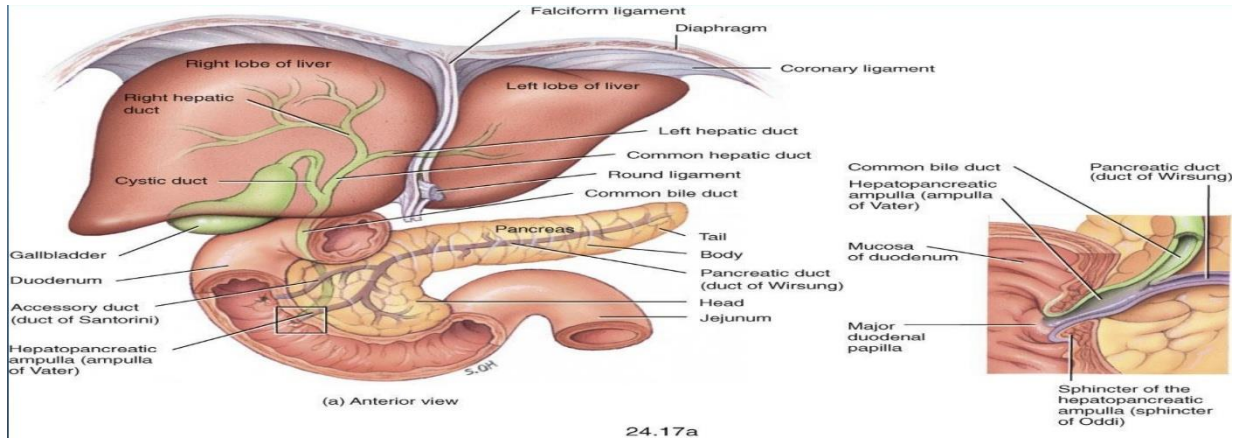


From a functional view, the exocrine part of the pancreas is similar to salivary glands, they have acinar cells which release enzymes. There are duct cells lining the duct, and these cells are specialized in the release of water and bicarbonate (electrolytes).

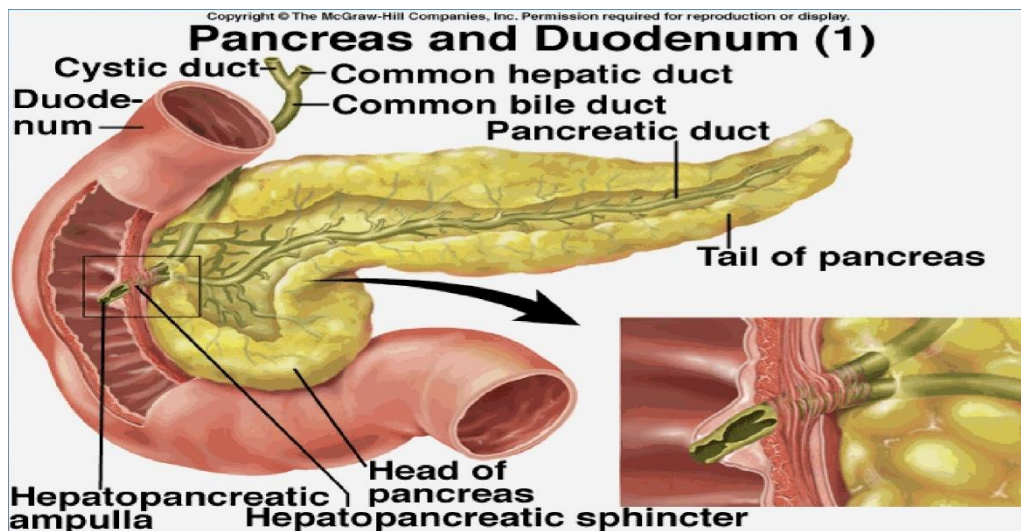
Pancreatic secretions flow toward the duodenum through a duct system. Before reaching duodenum, the pancreatic duct joins a duct coming from the liver (common bile duct), forming the **Hepatopancreatic duct**. Once they have unified, they release their secretions through an anatomical structure at the level of duodenum, called **ampulla of Vater**.



At the wall of duodenum, there is a sphincter which guards the opening of the Hepatopancreatic duct into duodenum the **sphincter of Oddi**. This sphincter has high functional importance in preventing the reflex of duodenal content back towards the duct system, which is found at the level of pancreas .



In the picture below, we are seeing the structures of the opening of the duct system into the duodenum. There is the **ampulla of Vater** as an anatomical structure. The opening of this duct system is guarded by the sphincter at that level, which is called **Oddi sphincter**.

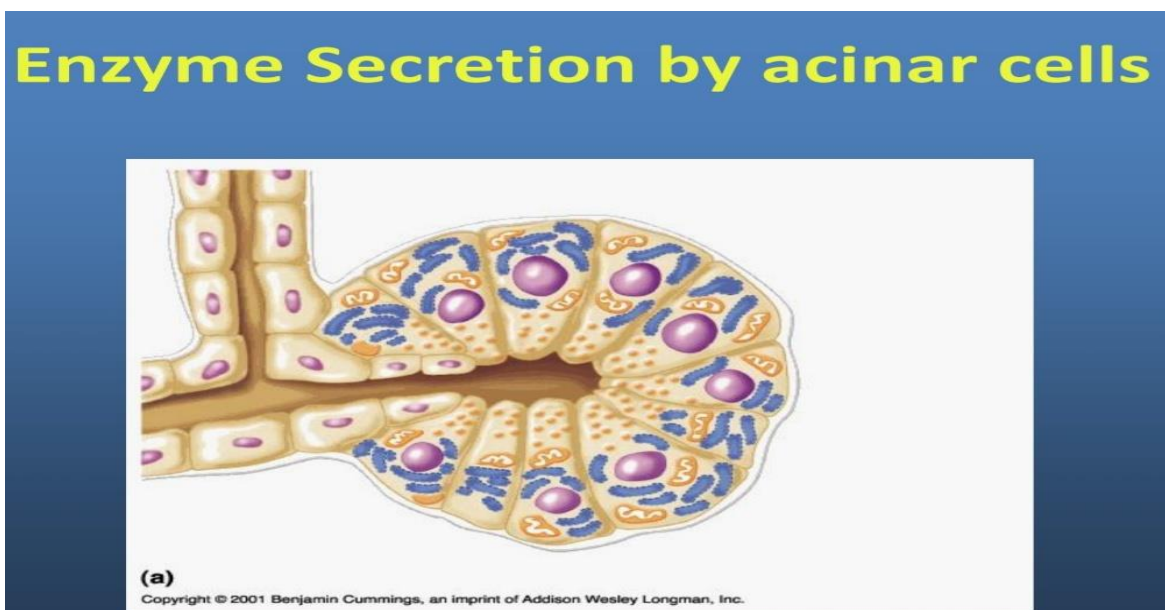


To summarize the functional structures of the pancreas :

- 1- **Endocrine** cells, which are involved in the release of hormones .
- 2- **Exocrine** part of the pancreas, composed of 2 types of cells, the acinar cells as well as the duct cells. The acinar cells secrete enzymes , while the duct cells secrete water and bicarbonate . These are secreted into the duodenum via pancreatic duct and common bile duct, which empty at ampulla of Vater through sphincter of Oddi.

The net pancreatic secretion is high in enzymes and is isotonic and alkaline.

The acinar cells of the pancreas are filled with vesicles (zymogen granules) as you see below, and they are involved in the secretion of enzymes.



Proteolytic enzymes

proteolytic enzymes are released by acinar cells of the pancreas.

We have 3 proteolytic enzymes released:

- 1- **Trypsinogen** [As long as this enzyme is in pancreas, it remains inactive by trypsin inhibitor.]
- 2- **Chymotrypsinogen**
- 3- **Procarboxypeptidase**

These enzymes are released as inactive enzymes, and the process of activation takes place at the level of duodenum . At that level- the mucosa of the duodenum-, we have an enzyme called **enterokinase**, which can phosphorylate **Trypsinogen** , to become **Trypsin** (the active form of the enzyme). Once trypsin is active, it can activate the other enzymes. It can activate **Chymotrypsinogen** to become chymotrypsin, and activate **Procarboxypeptidase** to become Carboxypeptidase. **Trypsin** and **chemotrypsin** act as **endopeptidases**, while **Carboxypeptidases** act as **exopeptidases**.

The **endopeptidase** enzyme can cut the long peptide to smaller peptides by acting in the middle at specific sites .

Exopeptidases act at the end of the long chain of peptide, by hydrolyzing the bond at the carboxylic end between the last aminoacid and the previous aminoacid.

pancreatic amylases

In addition to proteolytic enzymes, the acinar cells release **pancreatic amylase**. This enzyme is released as active enzyme, and is involved in digestion of starch .

Starch is a ramified polysaccharide, and by its digestion, we can get disaccharides.

Lipolytic enzymes

In addition, we have enzymes involved in the digestion of lipids (lipolytic enzymes), which are also released by acinar cells .

We have **lipases**, **phospholipases**, **cholesterol ester hydroxylases**.

There are other structures which help lipases in the process of digestion, called **co-lipases**.

-The activity of **lipases** is at the digestion of triglycerides, producing more precise fatty acids.

[Lipases split triglycerides into monoglyceride + free fatty acids.]

[Their activity requires an oil/water interface, bile salts (secreted by liver) and other co-lipase secreted by the pancreas.]

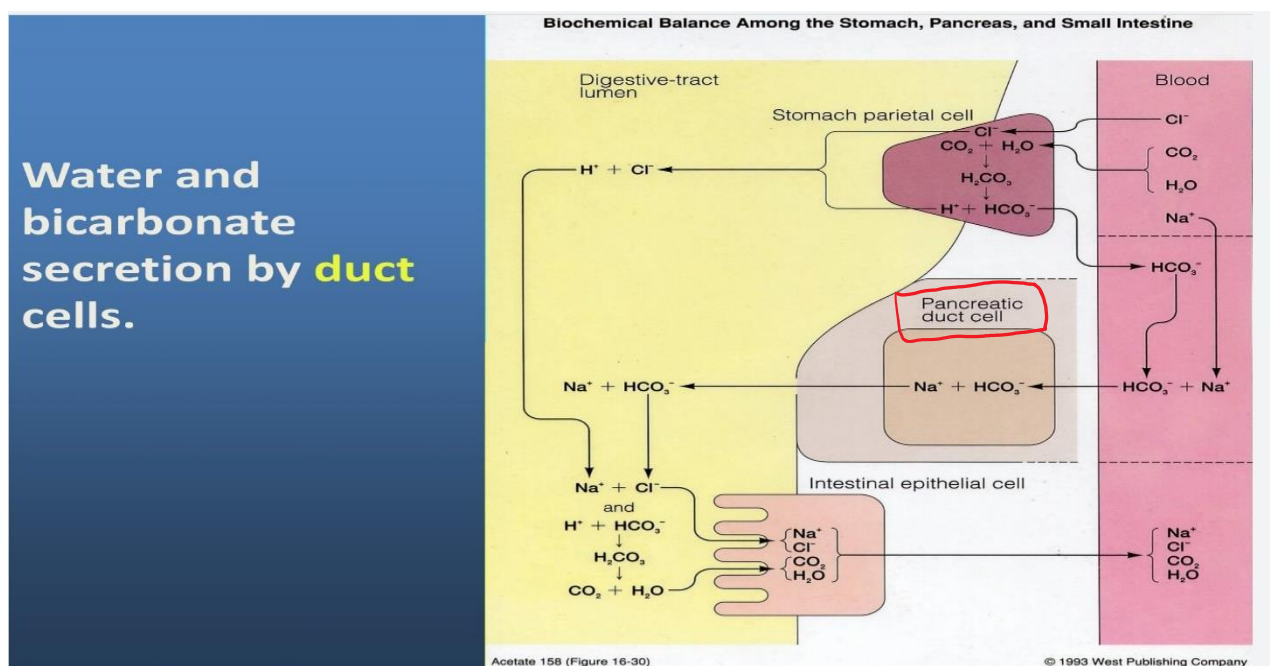
-**Phospholipases** are involved in the digestion of phospholipid.

-**Cholesterol ester hydroxylases** are involved in the modification of cholesterol molecules , for better absorption of these molecules .

Note: Pancreatic insufficiency (characterized by decreased enzyme secretion) is manifested as steatorrhea (yellowish stool due to the presence of undigested fat).

Secretion of water and bicarbonate

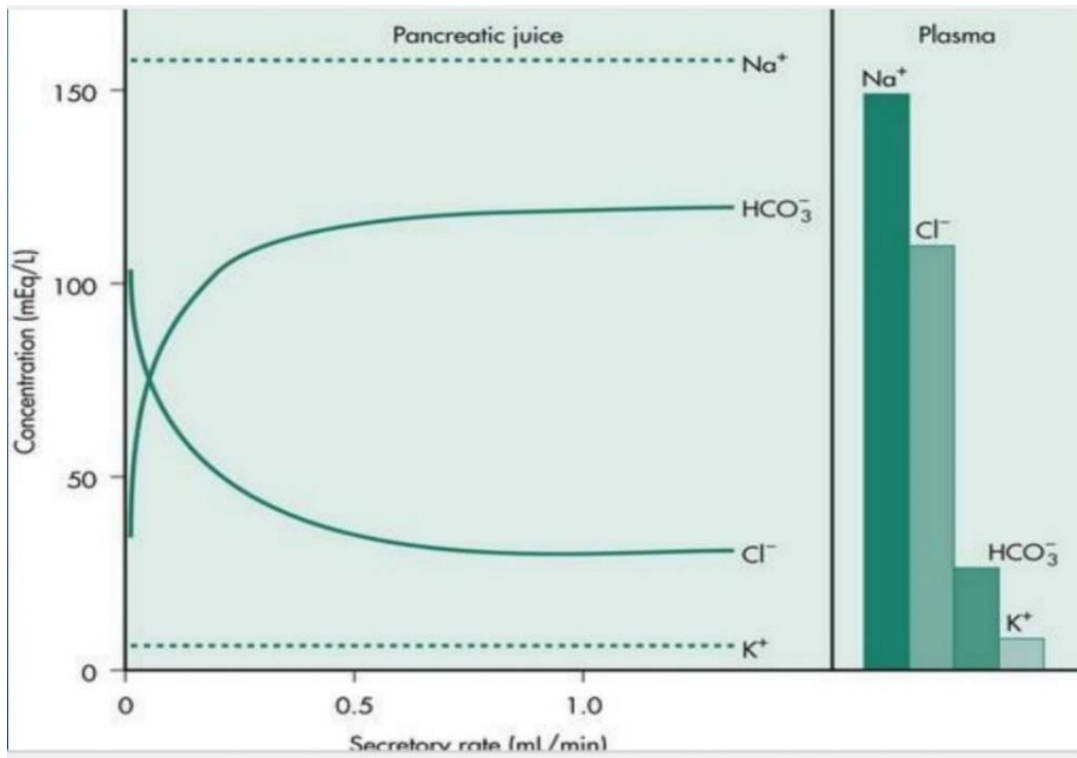
Duct cells of the pancreas release water and electrolytes. The high bicarbonate content in that secretion is important for neutralizing acids after gastric emptying. It also provides alkaline media for the activity of pancreatic digestive enzymes. See below.



The bicarbonate content in the pancreatic juice can vary according to the stimulation process .

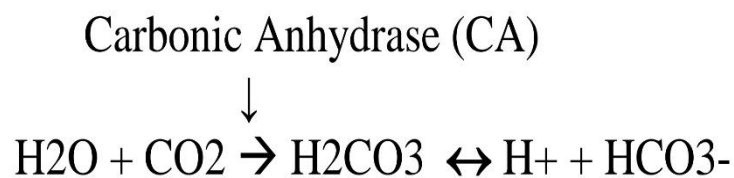
At low rate of stimulation, the **bicarbonate** (HCO_3^-) content is low, while at high rate of stimulation the bicarbonate content is higher .

But, at low rate of stimulation , the **chloride** (Cl^-) content is high, while at the high rate of stimulation the chloride content is low. This indicates that the process of secretion of bicarbonate is a stimulated process , and upon stimulation, more synthesis of bicarbonate and releasing it in pancreatic juice. (See below).



Mechanism of secretion:

An enzyme (CA) is involved in catalyzing the following reaction:



- ✓ **HCO₃⁻ is transported at the luminal border by secondary active transport in exchange with Cl⁻.**
- ✓ **H⁺ is transported by a secondary active transport in exchange with Na⁺ at blood border.**
- ✓ **Na⁺ is transported from the cell by an active transport.**
- ✓ **Water osmosis.**

Regulation

Pancreatic secretion is highly controlled by have both, **neural** and **hormonal** control.

1-The neural control is mainly achieved by ANS, but there are some ENS fibers that reach the pancreas. These fibers also play a role in regulation.

So, the neural control is achieved by the **parasympathetic** nervous system, either **directly** to **increase pancreatic secretion**, or **indirectly** by the activation of some enteric neurons, which release **Ach, VIP, and GRP(Gastrin releasing peptide)**. **These neurotransmitters can act to increase pancreatic secretion.**

The **sympathetic** nervous system can cause **inhibition of pancreatic secretions** by the process of vasoconstriction, reducing fluids available for water and electrolytes secretion.

2- Hormonal control is achieved by **secretin** and **cholecystokinin (CCK)**.

Secretin (major stimulant of water and HCO₃⁻) is released by S-Cells from the duodenal mucosa into the blood. It can act over duct cells, which means it can increase water and electrolyte (HCO₃⁻) secretion. Secretin is secreted into the blood due to acid stimulation.

CCK (Major stimulant of enzyme secretion) is released by duodenal mucosal cells into the blood in response to fat products and proteins in chyme.

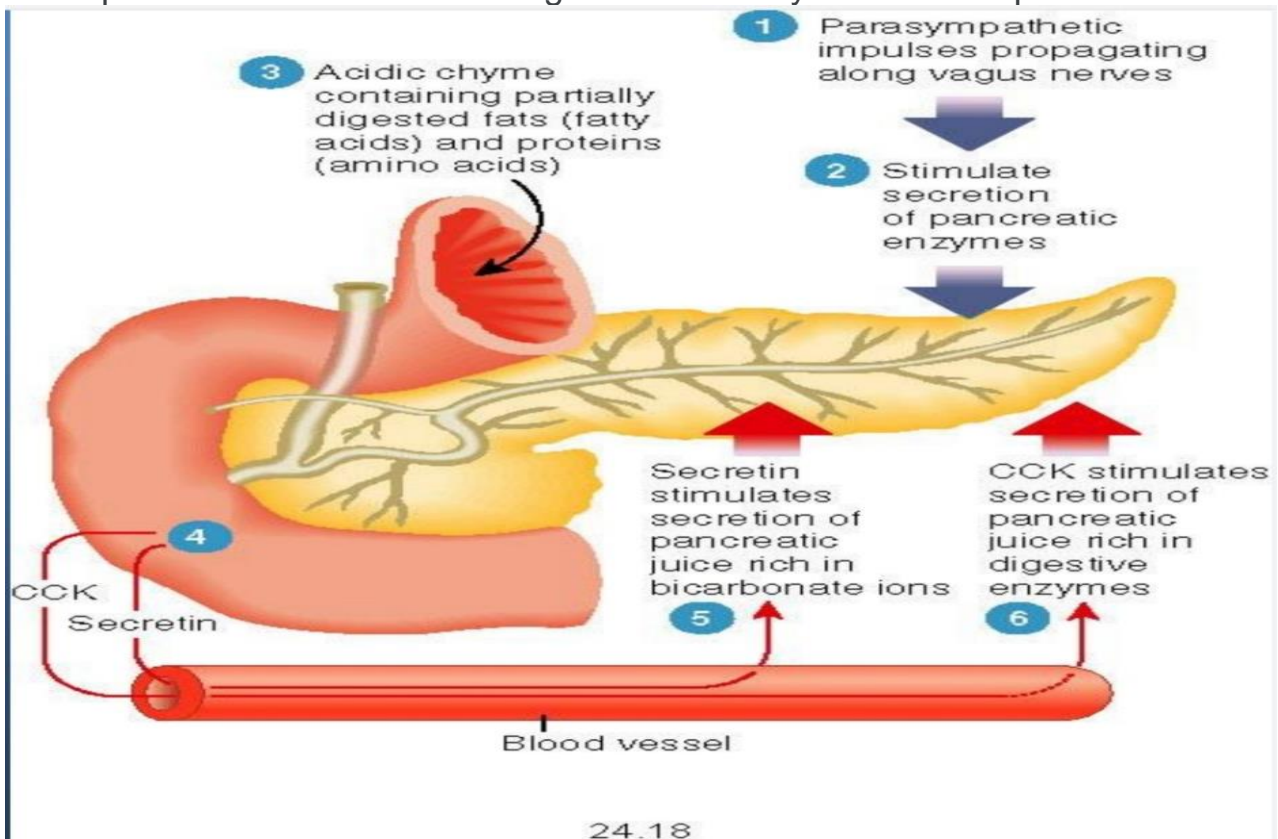
CCK acts on **CCK-A receptor (directly)** which are found at the acinar cells, and increasing their enzymatic secretion.

Also, CCK can stimulate **vago-vagal reflexes (indirect way)**, which in their turn can potentiate the activity of the parasympathetic nervous system over the pancreatic cells to stimulate enzyme secretions.

In addition, **pancreatic polypeptide** is involved in the hormonal control. It acts by **decreasing neural control over the pancreas.**

It can **inhibit Ach release** from the enteric neurons (ENS). It can also **inhibit the parasympathetic** stimulation to the pancreas (inhibits vagal output of the CNS), so their role is decreasing the enzymatic secretion "Inhibitory effect".

The picture below is summarizing both control systems of the pancreas.



We can summarize the control that we are having for pancreatic secretions by 3 phases:

- **During cephalic phase** : an **increase in the pancreatic secretions**, which takes place when seeing, smelling ,tasting , or hearing about food. This process is mediated by parasympathetic control via the vagus nerve.
- **During gastric phase**: an **increase in pancreatic secretions**. This phase can take place by local changes such as the distension of the stomach. This process is also mediated by the vagus nerve.
- **During intestinal phase**: also **increase in pancreatic secretion**. In this phase, presence of aminoacids (aa), fatty acids, protons(H⁺),and distension can activate the process of secretion. This phase is mediated by hormones like : CCK and secretin, also by activating enteropancreatic reflexes ,and also by the release of other hormones.

Liver Secretions

We will start with liver secretion to understand the mechanism by which we obtain bile from liver, and then its secretion from the gallbladder.

Liver has many functions, but we will not go through all these functions.

Instead, we will focus on one of them, which is **secretion of bile**.

Note that the functions below were NOT mentioned by the professor, except the last one.

[Liver functions: 1- Metabolic processing: Process all nutrients after their absorption.

2- Detoxification of body wastes, hormones, drugs, and other foreign bodies.

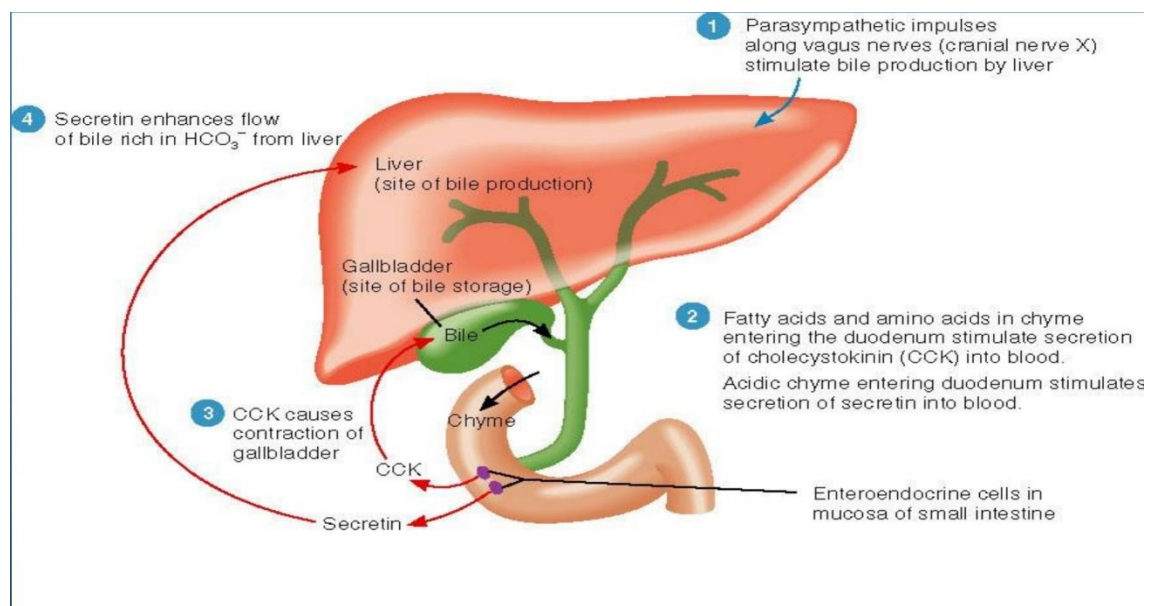
3- Synthesis of plasma proteins, including clotting factors (their synthesis requires vit. K), hormone transporters.

4- Storage organ of glycogen, iron (ferritin), copper, and vitamins.

5- Removal of bacteria and foreign materials by reticuloendothelial cells (Kupffer cells).]

6- Excretion of cholesterol and bilirubin.

Bile flows to the duodenum through a duct system. Before reaching the duodenum, bile is diverted towards the gallbladder. There, bile undergoes modification, so that it is more concentrated and to have this concentrated and secreted, according to the needs during digestion process. (This picture will be further explained later on).



Bile secretion

Bile is composed of **bile salts which are the important constituents for digestion and absorption of lipids**, water, electrolytes, cholesterol, phospholipids and waste intended for excretion, (bilirubin). [Bile acts as detergent to emulsify lipids and make them soluble.]

The digestion and absorption of lipids present a special problem. The environment in the lumen of intestine is an aqueous environment in which lipids are not soluble. To make lipids soluble, bile is added to the small intestine at the level of duodenum. Bile acts as detergent to emulsify lipids and make them soluble.

Bilirubin is resulting from the **destruction of RBCs and decomposition(catabolism) of the hemoglobin structure.**

[Hemoglobin → Heme + Globin.

Heme ring → iron + biliverdin.

Biliverdin → bilirubin secreted with bile as conjugated bilirubin.]

These **bilirubin** molecules are uptaken by hepatocytes, conjugated to either glucuronides, sulfate, or other substances, and then released with bile as unwanted material.

Functional structures of the liver:

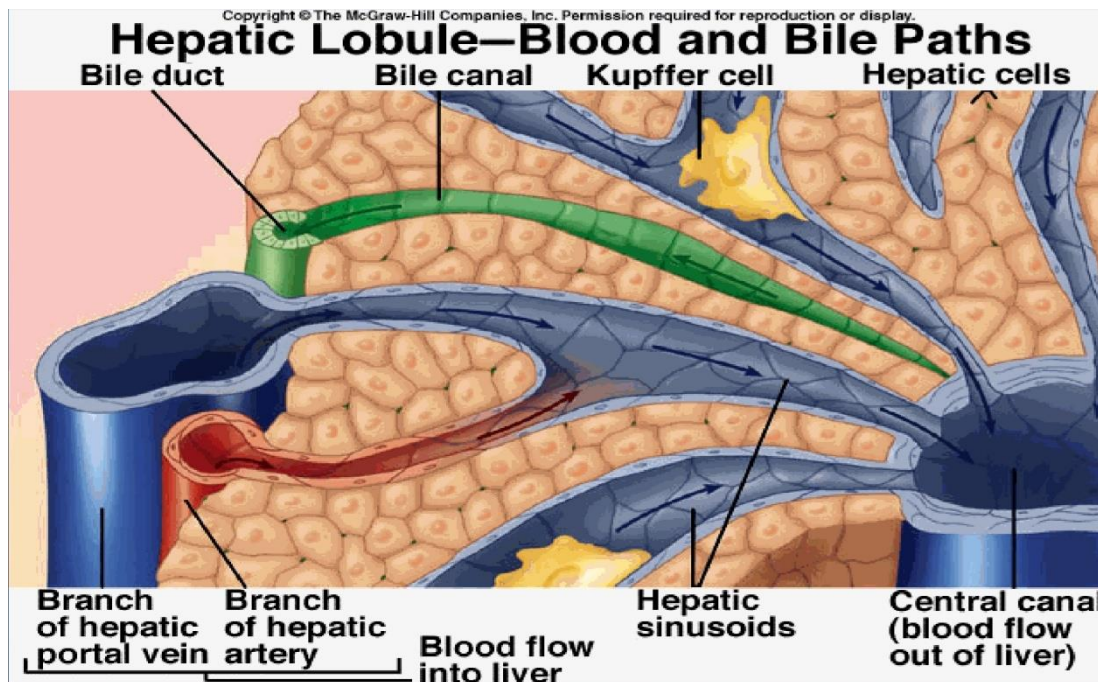
The functional unit is called hepatic lobule. Hepatic cells in this unit have hexagonal arrangement that surround the central vein. At the outer edges of the hexagonal structure of the lobule, there are three vessels:

A branch of the hepatic artery

A branch of the portal vein.

A bile duct.

As you see from the structure of the hepatic lobule below, hepatocytes have 2 sides, one of these sides face the blood vessel, and the other side faces the bile canaliculi. These cells can uptake products from the blood circulation, and release it into bile canaliculi.



Excreted **bilirubin**, which is now part of bile, undergoes bacterial modification in the small intestine, becoming **urobilinogen**. **Urobilinogen** can be reabsorbed and secreted in urine in the form of **urobilin**. It could also be secreted with feces as **stercobilin**.

Jaundice

Increased bilirubin concentration in the extracellular fluid results in a medical condition which is called **Jaundice (the yellow discoloration of the skin)**. This can happen by increasing the destruction of RBCs which results in increased **unconjugated bilirubin** in body fluids.

Other causes of jaundice is by obstruction, at the level of the common bile duct, which results in the back flow of bilirubin toward body fluids. In this case, the levels of **conjugated bilirubin** is increasing in body fluids. Jaundice could also occur due to the destruction of hepatocytes in hepatitis or hepatic diseases.

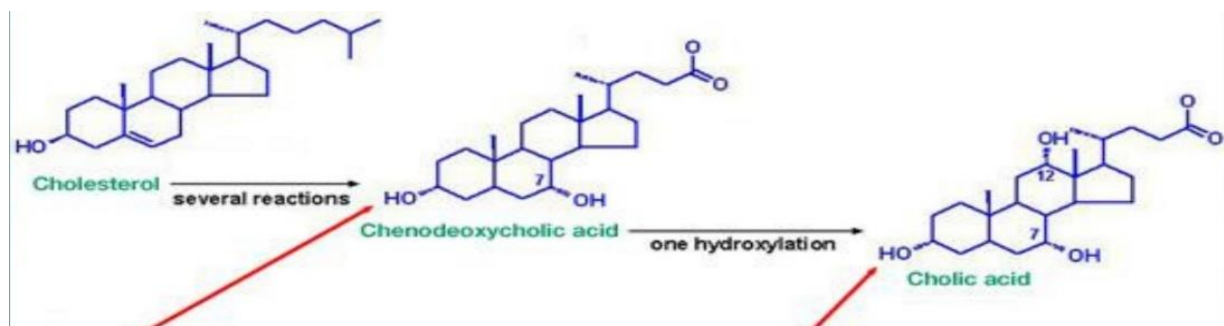
Bile formation

Bile acids are synthesized by hepatocytes. The synthesis of bile acids start from **cholesterol** molecule, forming **cholic acid** and **chenodeoxycholic acid** (these are primary bile acids).

Bile acids are usually secreted as bile salts rather than as bile acids, so cholic acids are conjugated with either **Glycine** or **Taurine** to get **bile salts**.

Thus, bile contains 4 bile acids conjugated to one of these amino acids.

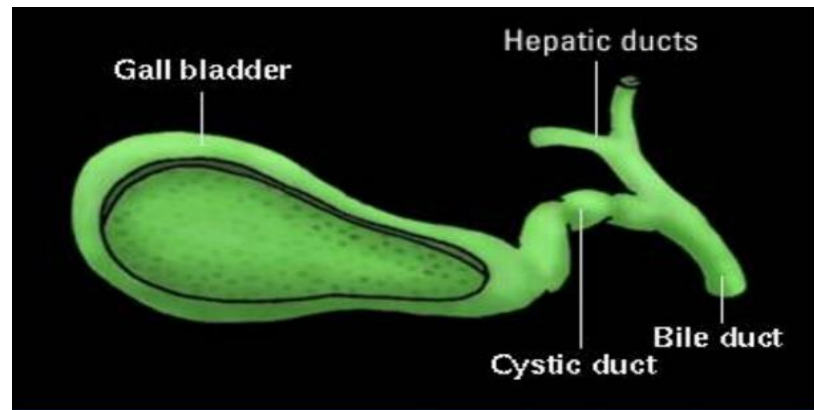
Bile acids are then sent to the gallbladder to be modified and to increase their concentration.



- The primary bile secretion is isotonic and contains also Na^+ , K^+ , and Cl^- .
- The secretion enters the duct system where the cells lining the duct modifies it by exchanging HCO_3^- for Cl^- .
- The secretion of HCO_3^- is increased by the activity of the hormone secretin.

Between meals , bile is stored at the gallbladder, where water and electrolytes are removed. This process increases the concentration of bile constituents up to 20 folds [from 5-20 folds], including bile salts.

This is the structure of gallbladder where we have storage and concentration of bile.



After the contraction of the gallbladder, concentrated bile is released into the bile duct, which opens into the duodenum.

The picture below shows the variations in constituents between **bile released by the liver** and **bile released by the gallbladder**, after the process of concentration (removal of water and electrolytes).

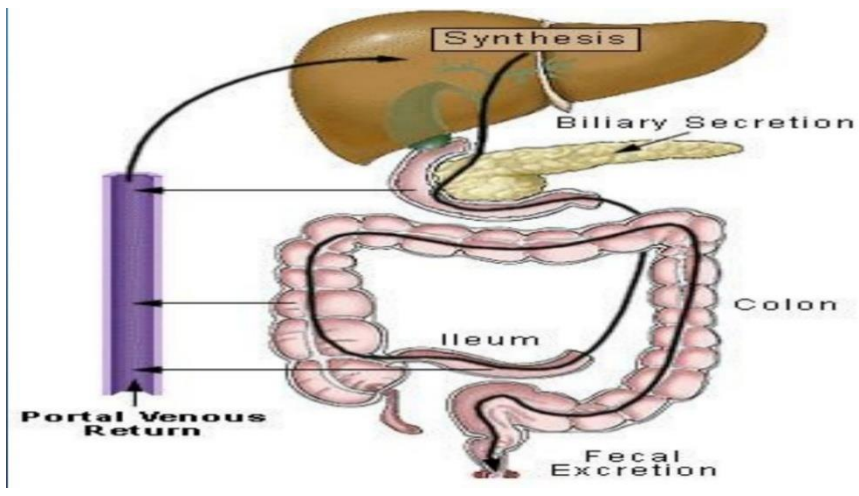
An increase of up to 20 times in some constituents is seen after gallbladder modification occurs.

	LIVER BILE	GALLBLADDER BILE
Water	97.5 gm/dl	92 gm/dl
Bile Salts	1.1 gm/dl	6 gm/dl
Bilirubin	0.04 gm/dl	0.3 gm/dl
Cholesterol	0.1 gm/dl	0.3 to 0.9 gm/dl
Fatty Acids	0.12 gm/dl	0.3 to 1.2 gm/dl
Lecithin	0.04 gm/dl	0.3 gm/dl
Na ⁺	145 mEq/liter	130 mEq/liter
K ⁺	5 mEq/liter	12 mEq/liter
Ca ⁺⁺	5 mEq/liter	23 mEq/liter
Cl ⁻	100 mEq/liter	25 mEq/liter
HCO ₃ ⁻	28 mEq/liter	10 mEq/liter

After performing their function at the level of small intestine, we can have a process of modification of these bile salts, obtaining modified **secondary bile acids**. For example: **cholic acid can be transformed into deoxycholic acid**, and **chenodeoxycholic acid can be modified into lithocholic acid**.

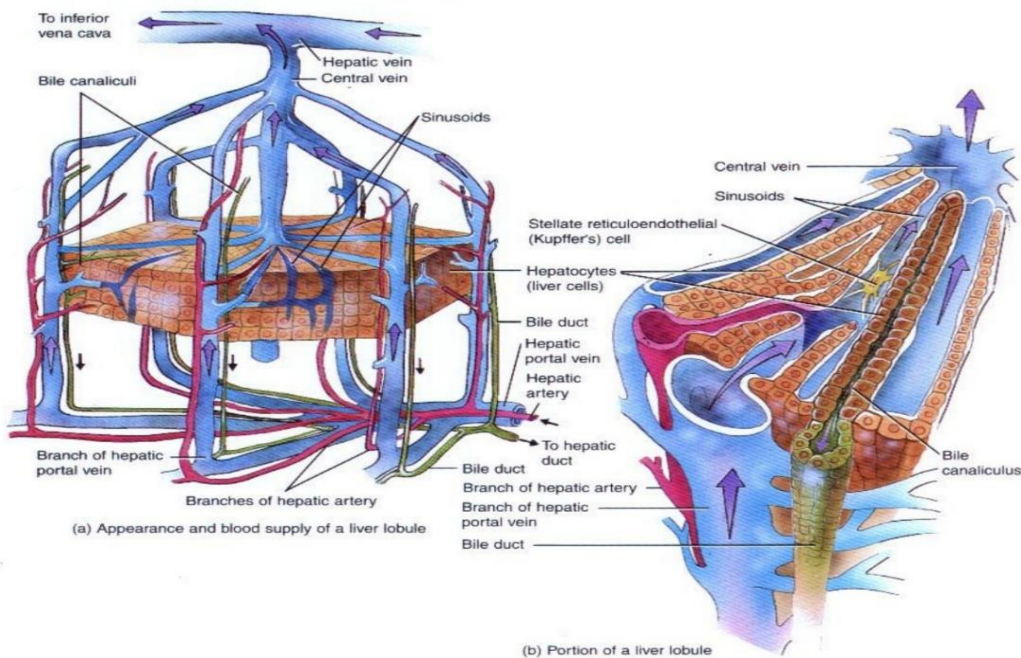
After performing their job at the level of small intestine, and after the modification process, 20% of these bile salts will be lost with feces.

A process of recycling of these bile salts takes place, in which reabsorption of 80% of these salts is performed. They are collected and released into the portal vein. In the liver, these bile salts are re-released into the bile circulation again.



Enterohepatic circulation

Shown below, the structure of hepatic lobule. It is a **hexagonal structure**. At the edges of this hexagonal structure, there are branches of the portal vein which has collected blood from the small intestine. This blood (coming from the small intestines) circulates from these branches to the portal vein, from the periphery toward the central vein at the centre of this hexagonal structure, through **sinusoids**. (Branches of portal → portal → sinusoids → central vein).

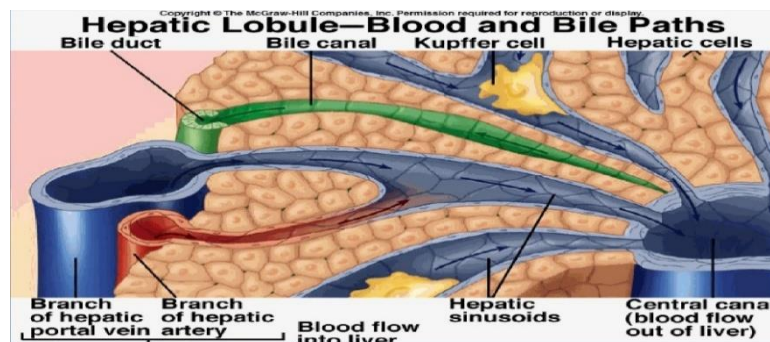


Histology of the Liver, Fig# 24.19a-b
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Hepatocytes can uptake bile salts and resecret them into bile canaliculi. Hepatocytes have the ability to synthesize new bile acids to replace the 20% loss of these bile salts with feces. This process is called **de novo synthesis of bile salt**.

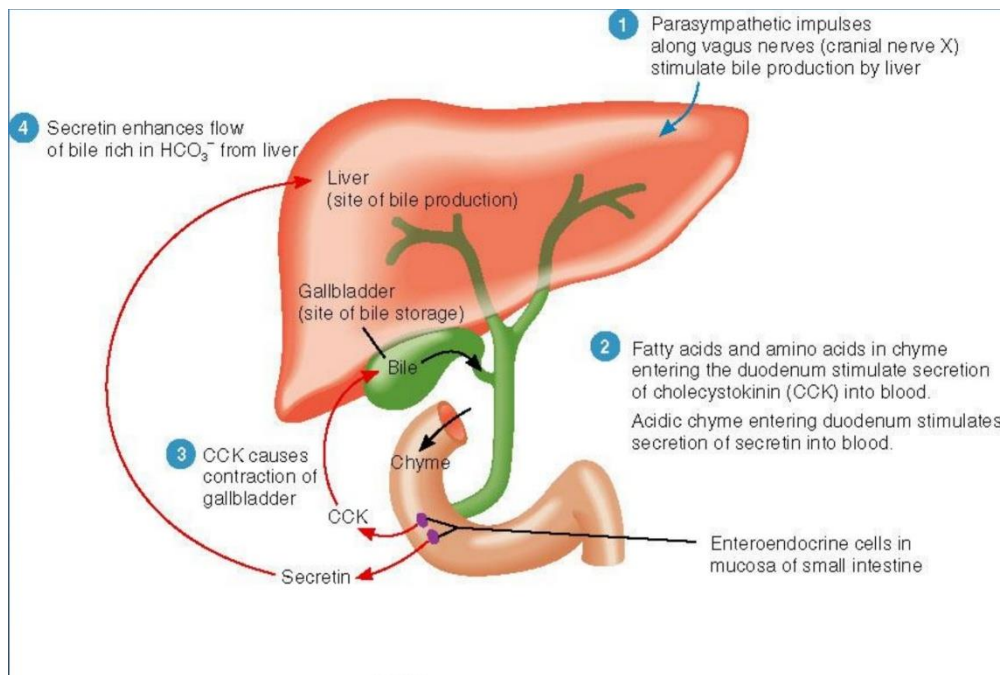
So, we have bile salts circulating between the small intestine and the liver, re-secreted again into bile canaliculi, and reused again more and more. This process of recycling is called **enterohepatic circulation of bile salts**.

This figure, again, shows how the **blood** circulates from the edges of the hepatic lobule, from the branch of the portal vein, towards the central vein through sinusoids. **Bile** is secreted from the centre toward the edges through bile canaliculi, then collected at the edges with the help of small bile ducts.



As shown below, bile is collected by the **left and right hepatic ducts** which unify to form the **common hepatic duct**, the common hepatic duct then joins the **cystic duct** (coming from the gallbladder) to form the **common bile duct**. Before its release, bile is stored in the gallbladder and modified there. At this stage, the sphincter of Oddi is constricted, and doesn't allow the release of bile into the small intestine.

Upon stimulation and the contraction of the smooth muscle cells at the wall of the gallbladder, an increase in pressure inside the gallbladder takes place, which results in the flow of bile back toward common bile duct, and then that bile is flowing toward duodenum. This process is accompanied by **relaxation of Oddi sphincter**, which results in flow of that bile from the common bile duct into the duodenum.



So the gallbladder is the site where we have storage and concentration of bile in between meals.

Once we have a meal, the gallbladder contracts so that the bile is released in the ducts.

The process of secretion from the gallbladder is a stimulated process. At the level of gallbladder, we have the control of bile secretion.

Summary from the handout : Blood from the branch of the hepatic artery and the portal vein from the periphery run into sinusoid, which run between rows of hepatocytes to the central vein. The hepatocytes are arranged in two cell layer thick, so that each hepatocyte has one side faces sinusoidal blood.

The other side of hepatocyte faces bile carrying channel called (bile canaliculus), which carry bile to a bile duct at the periphery of the lobule.

From bile duct, bile flows into the common bile duct, then in duodenum.

The space between sinusoid and hepatocytes (space of Disse). In this space lymphatic circulation takes place.

Regulation

The process of release of concentrated bile is a **controlled process** by the contraction of the gallbladder. The contraction of this vesicular organ is achieved by activation of the **parasympathetic fibers** which are innervating this vesicular organ, in addition, we have **hormonal control** for the activity of this organ, for example we have **CCK** involved, which can also cause contraction of the gallbladder.

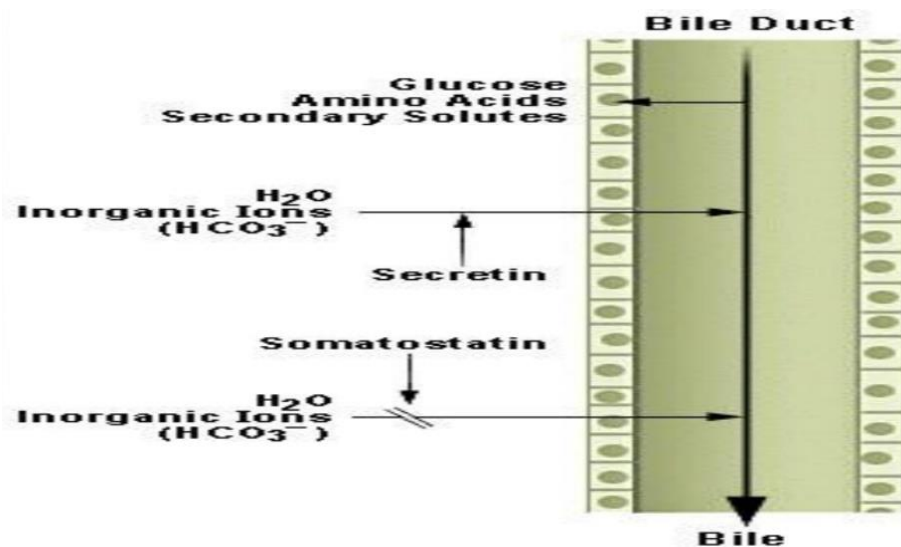
The release of **CCK** is related to **fat** content & **protein** in chyme. **Any increase in fat -or protein- content in chyme stimulates more release of CCK.**

Actually, that's the main activity for CCK hormone, is to cause contraction of the gallbladder.

Also we have another effect for the **CCK**, it can **inhibit smooth muscle cells of Oddi sphincter** and causing **relaxation** of this sphincter, which facilitate the flow of bile from the gallbladder into ducts, then toward duodenum.

The second hormonal control is achieved by **secretin**, which is acting over duct cells, to **increase** water and electrolytes secretion.

As you're seeing below, **secretin** is stimulating the activity of duct cell, **increasing** the water and electrolytes secretion. In the other hand, we have an **inhibitory control** achieved by **Somatostatin**, which also acts over the duct cell, but this time to **decrease** water and electrolyte secretion.



Alright, we're done! Thank you for being patient. ❤️