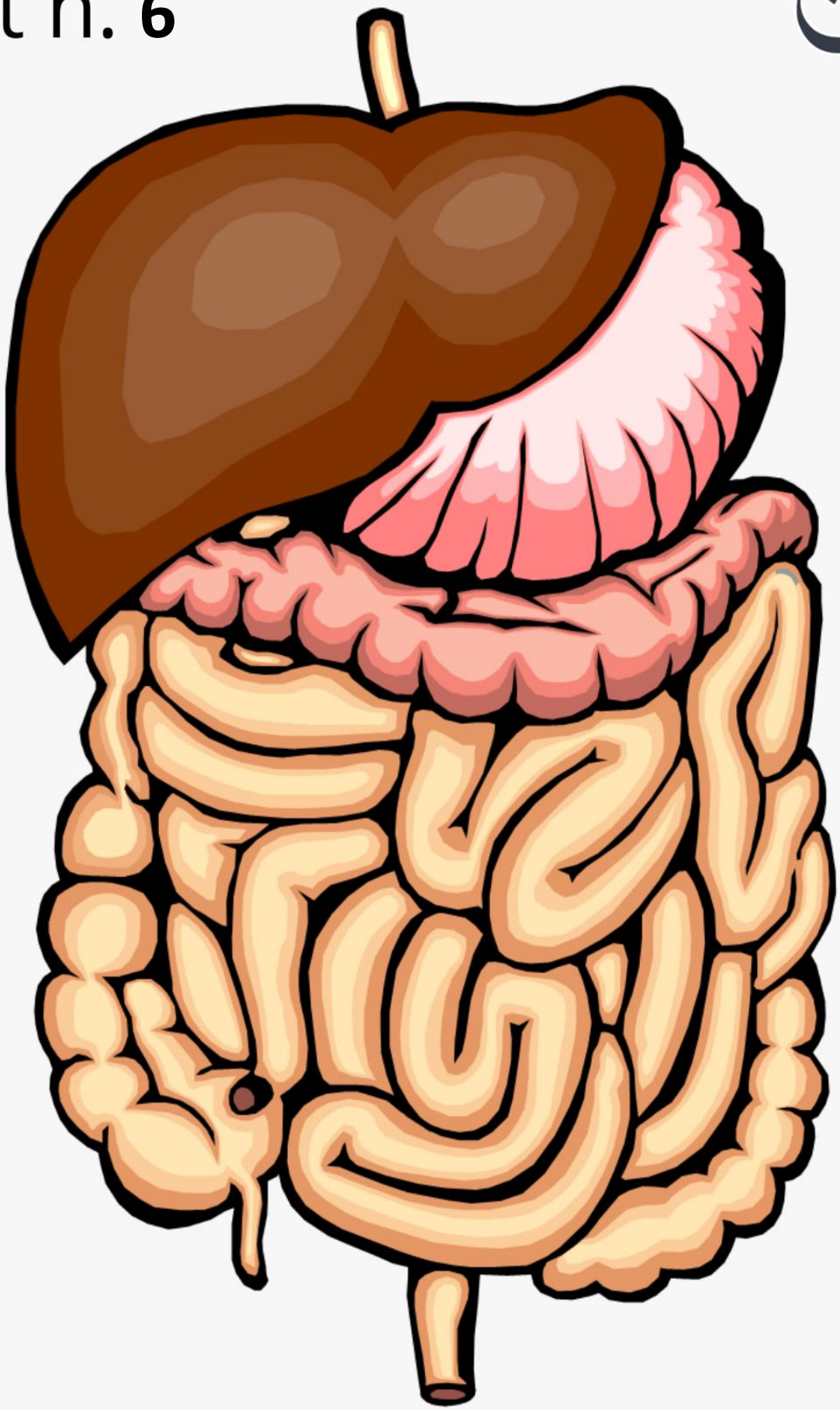
# Physiology

## Sheet n. **6**



Writer: **Hala Mousa** Corrector: **Sara Omar**

Doctor  Slides + handout  additional info  important

# GASTROINTESTINAL SECRETION:

## PANCREATIC SECRETION

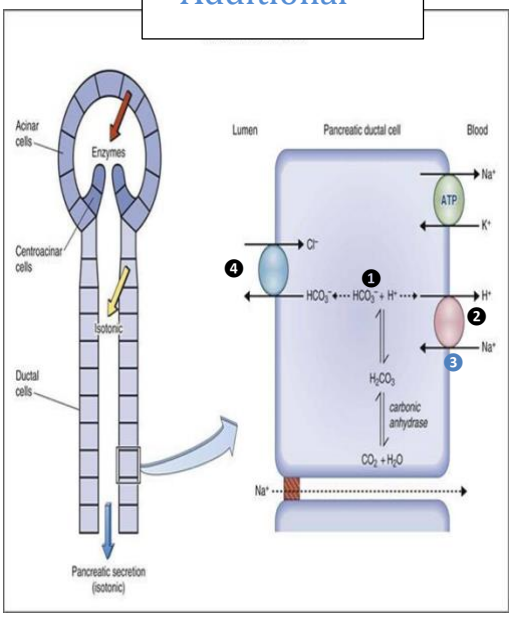
A continuation of the talk about pancreatic enzymes:

Some pancreatic enzymes are released (from acinar cells) as inactive peptides and some are active.

## SECRETION OF WATER AND BICARBONATE:

Ductal cells modify the initial secretion as follows:

Additional

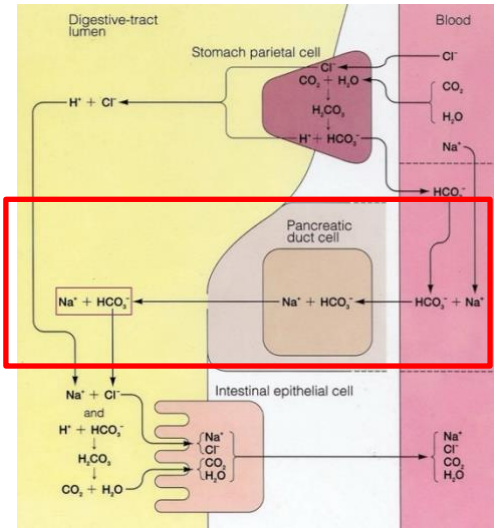



**First of all,(1) carbonic acid is formed via the activity of carbonic anhydrase (2) then H+ is reabsorped toward the blood (interstitial fluid) and HCO3- is secreted toward the lumen. (3) Then, Na+ is actively transported toward the duct cells (opposite to the gastric mechanism in which Cl- was the ion that's actively transported toward the duct) which (4) will attract negatively charged ions from the interstitial fluid (especially Cl-). As a result of the increase in negativity inside duct cells, more bicarbonate will be formed to get secreted (Via Cl-/HCO3- exchange mechanism).**

**Note: the doctor doesn't obligate us to know all of the details as many conflicts exist in literature.**

**Summary:**

**Water and bicarbonate (electrolytes) are secreted by duct cells**




**Mechanism of secretion:**

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

**Carbonic Anhydrase (CA)**

**↓**

**H20 + CO2 → H2CO3 ↔ H+ + HCO3-**

- **HC03- 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 Nat at blood border.**
- **Na+ is transported from the cell by an active transport.**
- **Water osmosis.**

- **The pancreatic secretion has an alkaline pH to neutralize the acids when emptied into the duodenum from the stomach and provide an optimal pH for enzymatic function.**

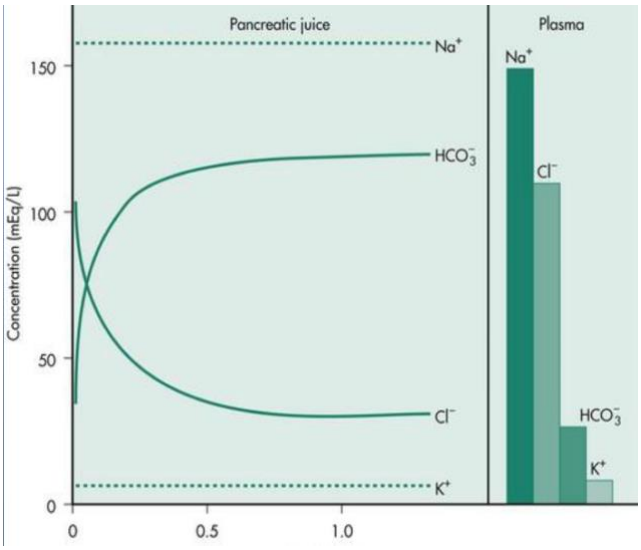
**The composition of pancreatic secretions varies with the flow rate as follows:**

**At low flow rates, Na+ that's actively transported will attract Chloride ions to ductal cells.**

**So, HCO3- is low and Cl- is high.**

**At high flow rates, Na+ will increase the concentration of HCO3- inside cells.**

**So, HCO3- is high and Cl- is low.**




# REGULATION OF PANCREATIC SECRETION:

- **How are these secretions regulated ?**

**Between meals, we don't need these large amounts of secretions to act. However, at the intestinal phase and while it's filled with food, the pancreas gets stimulated to secrete about 2 liters of the pancreatic juice per day. This control is achieved by 2 means, which are:**

## Neural Control:

**Via the ANS ⬇**

- **Parasympathetic (increasing):**

  **Vagal stimulation is excitatory via stimulation of neurons in the enteric nervous system innervating the acinar cells. These causes local release of Ach, VIP, and GRP (Gastrin releasing peptide).**

  **Some nuerons of the ENS reach the pancreas and innervate the pancretic cells, while no enteric neurons can reach the salivary glands hence the control over them is solely autonomic.**

- **Sympathetic (decreasing):**

  **indirect inhibition via vasoconstriction of blood supply to the pancreas.**

## Hormonal regulation:

- **Secretin: It acts on duct cells. That's why it's a major stimulant of water and HCO3- secretion (the same effects that used to emerge in the small intestine). This secreted into the blood by duodenal mucosa to acid stimulation → acts on duct cells to activate HCO3- and water secretion in response to the presence of acid in the duodenum.**

- **CCK (Cholecystokinin): It acts on acinar cells which bear the CCKA receptor (CCKB receptors are in the stomach) the major stimulant of enzyme secretion. Released by duodenal mucosal cells into the blood in response to fat products and proteins in chyme. Acts directly through CCK-A receptors on acinar cells to increase enzymatic secretion.**

  **CCK also acts indirectly through vagovagal reflex in which sensory fibers of the vagus nerve carry sensory information and then a reflex is carried by efferent fibers of the vagus nerve to stimulate enzyme secretions (so it potentiates the parasympathetic control).**
  **Other effects of CCK is contraction of the gallbladder (stimulatory —> $CCK_A$ receptors) and relaxation of sphincter of Oddi (inhibitory —> $CCK_B$ receptors) by both ways directly and indirectly.**

  **So CCK has inhibitory effects over the stomach and sphincter of Oddi through through $CCK_B$ and stimulatory effects over acinar cells and gallbladder through $CCK_A$**

### What is vagovagal reflex?

**The vagovagal reflex** is a feedback loop involving the vagus nerve that regulates digestive functions. Initiated by stimuli like food presence or stomach stretching**, (1) sensory fibers of the vagus nerve transmit signals to the brainstem**, which **(2) processes and generates appropriate responses**. **(3) Motor signals are then sent back to the gastrointestinal tract**, directing actions like enzyme release and muscle contraction or relaxation, maintaining digestion and internal balance.

### How does CCK stimulate vagovagal reflex?

**Cholecystokinin (CCK)**, released in response to fats and proteins in the small intestine, enhances the vagovagal reflex by **modulating sensory signals via the vagus nerve.** This amplifies the reflex's effects on digestive organs, stimulating the gallbladder to release bile, prompting the pancreas to secrete digestive enzymes, and slowing gastric emptying.

**Together, CCK and the vagovagal reflex coordinate digestive processes, optimizing nutrient absorption and metabolism in response to dietary components, particularly fats and proteins.**

- **Pancretic polypeptide : inhibits the release of enzymes by its inhibitory effects:**
  - **On the release of Ach from enteric nervous system.**
  - **On vagal output of the CNS.**

**But in general, the main mean of control to decrease the pancreatic secretions is by neural control ➞inhibition of acetylcholine and vagovagal reflexes.**

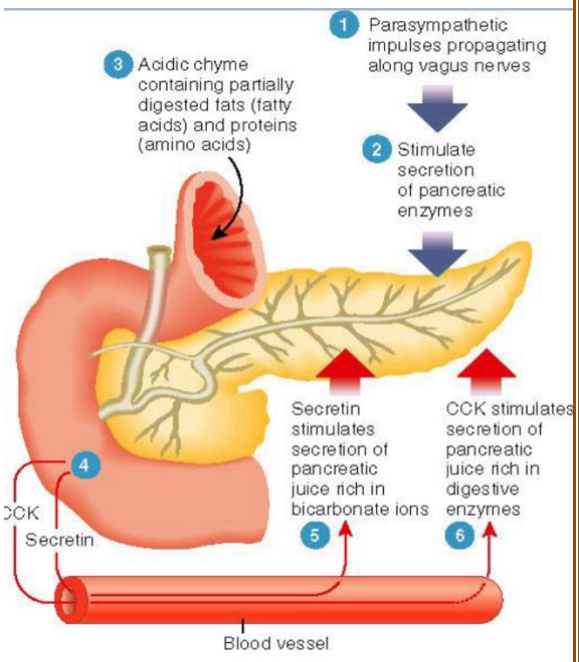
## 3 PHASES OF CONTROL OF PANCREATIC SECRETIONS:

- **Cephalic phase (increase): sight, smell, taste or hearing. Reflex is mediated by vagus.**

- **Gastric phase (increase): Distension. Effect is mediated by vagus.**

- **Intestinal phase (increase): local changes are caused by: Aminoacids (aa), Fatty acid, Distension. The effect of local changes is Mediated by CCK, secretin, enteropancreatic reflexes and other hormones.**

**Inhibition of pancreatic secretions simply occur when there's no food.**




## LIVER SECRETIONS

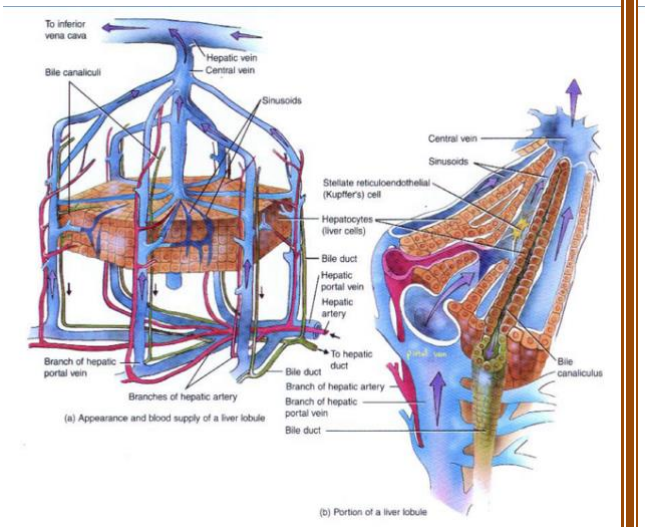
**Largest and the most important metabolic organ. It has importance in the digestive mechanisms by the formation and secretion of bile salts which are important for the digestion and absorption of lipids.**

**This organ also performs the following functions (read only)**

1. **metabolic processes: 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 (our focus!!)**

# 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.**

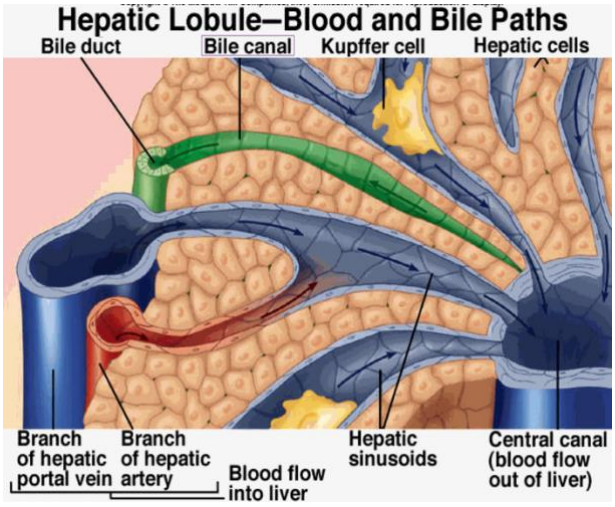



**At the outer edges of the hexagonal structure of the lobule there are three vessels:**

**-A branch of the hepatic artery**

**-A branch of the portal vein (which drains blood of the small intestine to the liver)**

**-A bile duct.**




**Blood from the branch of the hepatic artery and the portal vein from the periphery run into Sinusoid (bigger capillaries), which run between rows of hepatocytes to the central vein (which collects blood). So blood circulates from periphery towards the center. 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 is a duct system that collects bile to get it released into the duodenum , that 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.**

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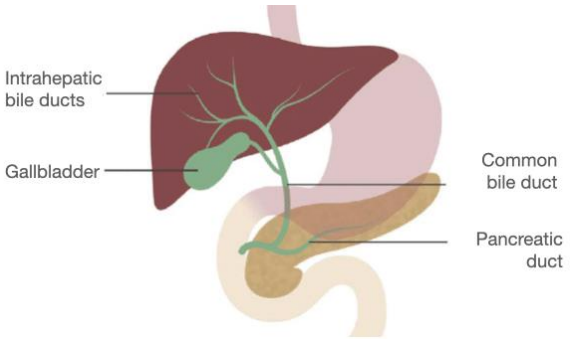
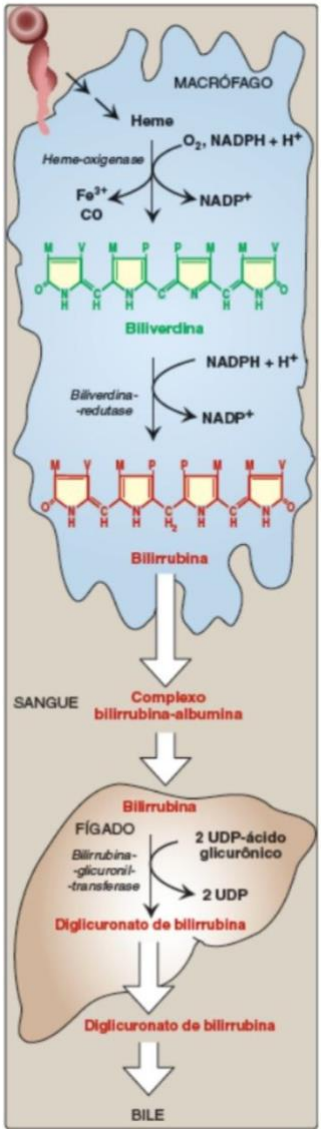



**So bile circulates from the center toward the periphery . Before bile is emptied to the duodenum, the bile duct unifies with the pancreatic duct and the combined duct opens into the duodenum.**

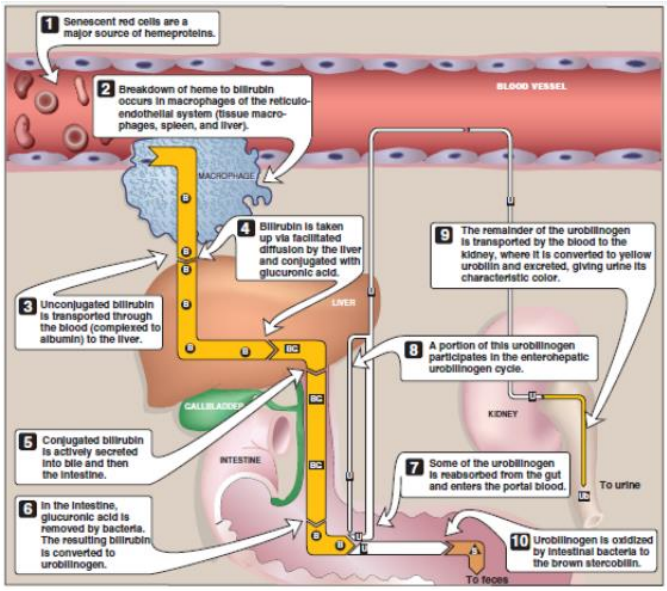
**The space between sinusoid and hepatocytes (space of Disse). In this space lymphatic circulation takes place.**

# EXCRETION OF BILIRUBIN WITH BILE:




- **Bilirubin results from the catabolism of hemoglobin → Heme + Globin**
- **Heme ring decomposed into iron + biliverdin**
- **Biliverdin is transformed into bilirubin and secreted in bile as conjugated with (glucoronide, sulfate, other substances).**
- **In intestine, bilirubin is transformed (by bacterial action) into urobilinogen. This will be reabsorbed and secreted in urine as (urobilin) or secreted with feces as stercobilin.**

Additional figures




- **<u>Note: Jaundice (yellow discoloration of the skin) is caused by the presence of high concentration of bilirubin in the extracellular space.</u> <u>It occurs either due to high destruction of RBCs (*prehepatic jaundice*, high amounts of unconjugated bilirubin) or due to a proplem in the liver (*posthepatic jaundice*, high amounts of conjugated bilirubin ).</u>**

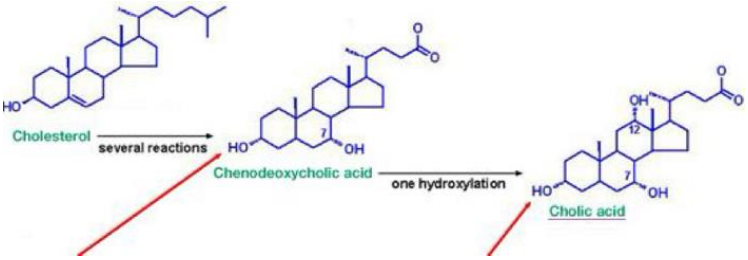
# BILE SYNTHESIS AND SECRETION:

- **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.**

- **Bile is composed of bile salts, water electrolytes, cholesterol, phosphlipids and wastes intended for excretion, (bilirubin).**
- **Bile salts are synthesized by the liver, concentrated in the gallbladder and modified in the lumen.**

# SYNTHESIS BY LIVER AND STORAGE BY GALLBLADDER:

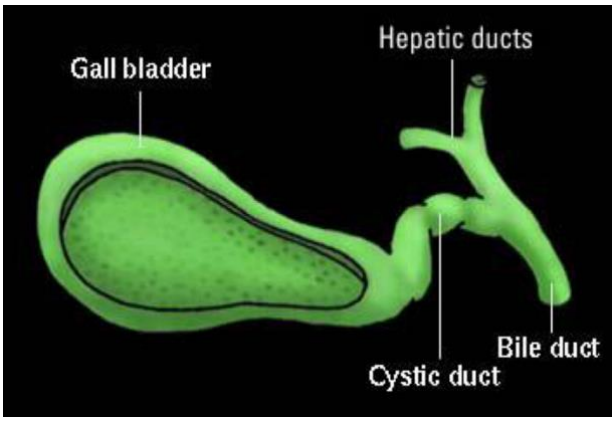
- Liver synthesizes two bile acids from cholesterol: cholic acid and chenodeoxycholic acid (these are primary bile acids). At the level of the liver, Bile acids are usually




secreted as bile salts rather than as bile acids.

- Transformation appears by conjugation of bile acids with either taurine or glycine (amino acids).One part of bile salts is composed of fat (which is lipo-soluble) and the other part (which is conjugated) is hydro-soluble. The conjugation process serves for making it more hydro-soluble and the final molecule is amphipathic.

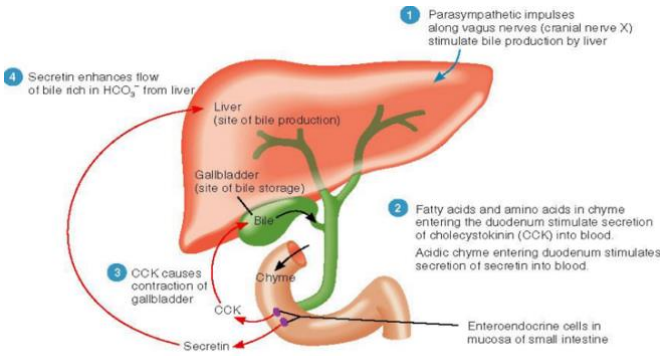
- Thus, bile contains 4 bile acids conjugated to one of these amino acids.
- The primary bile secretion is isotonic and contains also Na+,K+, and Cl-.
- The secretion enters the duct system where the cells lining the duct modify it by exchanging HCO3- for Cl-.
- The secretion of HCO3- is increased by the activity of the hormone secretin.




- Between meals (the gallbladder is relaxed and sphincter of oddi is closed) ,bile is derived into the gallbladder (a vesicular organ) where it is stored.

- How is it redirected toward the gallbladder? Between meals, the pressure inside the gallbladder decreases as it relaxes and the duct has a higher pressure so bile will flow from the high pressure towards the low therefore reaching the gallbladder.

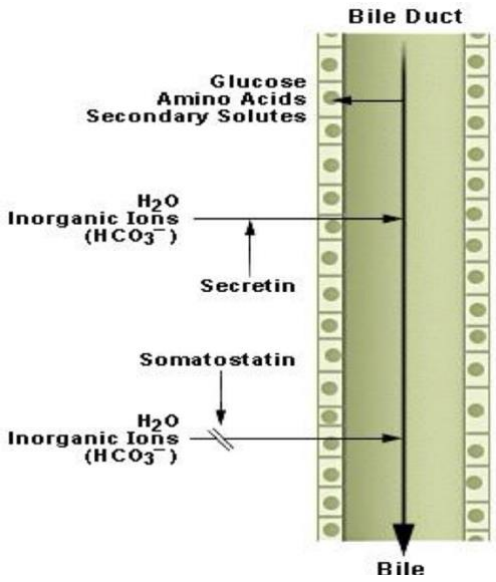
- The epithelium of the gallbladder removes water and electrolytes (modifications, it becomes more concentrated), which results in 5-20 fold concentration of bile.




- During meal the gallbladder is contracted and the sphincter of Oddi is relaxed, as a result bile flows into the intestine.

Some proplems may arise within the gallbladder, like hypomotility which leads to the formation of stones. Also, deformations in its shape can lead to malfunctions in which bile is stored for a longer time within its parenchyma and more absorption of water and electrolytes will also lead to the formation of stones.

## CONTROL OF BILE SECRETION:

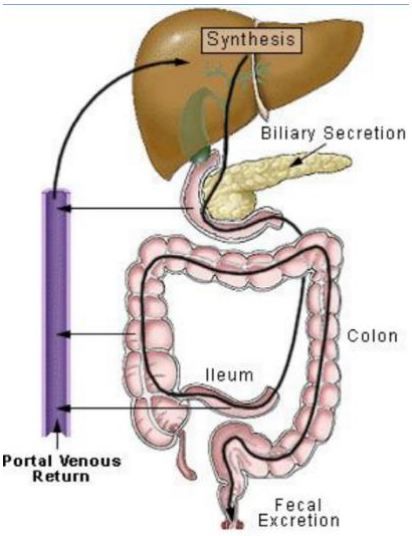



- Thses processes are controlled by the autonomic nervous system. The gallbladder contraction is mediated by neural (local and vagal) reflexes as well as hormonal by the activity of CCK (that's the main function of CCK, hence the name 'cholecyst' which means gallbladder in *Latin*) which is released by the presence of lipid and protein digestion products in the duodenum.

What's the stimulus leading to the secretion of CCK? High Fat content
What's the stimulus leading to the secretion of Secretin? High acid content

- Somatostatin has inhibitory effects over the secretion.

- The bile salts (most of them) are then reabsorbed actively in the terminal ileum (recycling). They are then removed from the blood (in the portsl vein) by the liver and resecreted into the bile. During a normal meal, the entire bile salt pool is recirculated twice. This is known as the *enterohepatic circulation.* About 20% of bile salts are lost daily into feces. This quantity is replaced by de novo synthesis of bile acids by the hepatocytes.




- Once they are in the intestine these bile acids are modified to secondary bile acid by the activity of bacteria that dehydroxylate them which result in the conversion of
  - Cholic acid into deoxycholic acid.
  - Chenodeoxycholic acid into lithocholic acid.

# Digestion and Absorption

- **The specialized organ for the process of absorption is the small intestine, mainly the upper part.**

- **Digestion process occurs by the activity of enzymes that catalyze carbohydrates, lipids and proteins.**

- **Absorption occurs by specialized epithelial cells.**

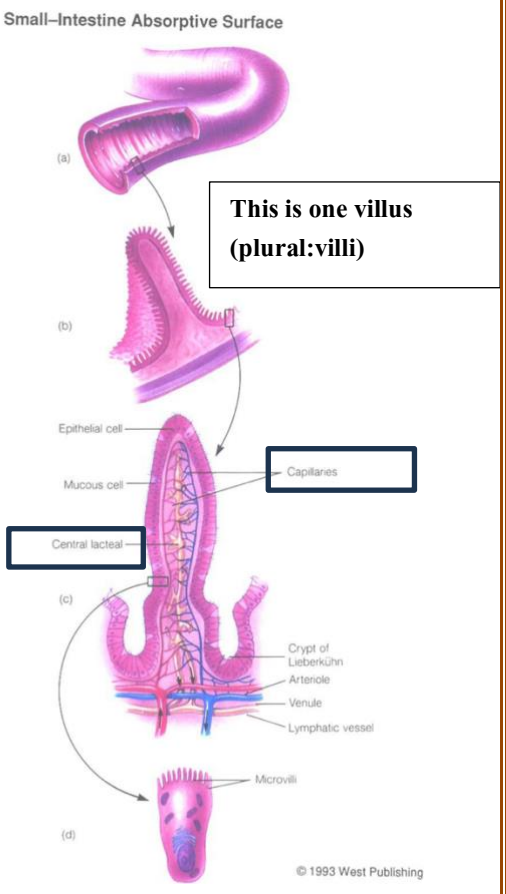
## GENERAL CONSIDERATIONS:

- **No absorption in esophagus, little in the stomach and vast majority of absorption occurs in small intestine. The small intestine has specialized structures to increase the absorptive capacity by increasing the absorptive surface area of the mucosa.**
- **Most nutrients are absorbed before reaching the ileum.**
- **Colon is responsible for final removal of electrolytes and water, but the lower part of the small intestine is responsible for the primary absorption of water and electrolytes.**

## INTESTINAL SPECIALIZATION:

- **What makes the small intestine the principal organ of absorption? What does it look like?**

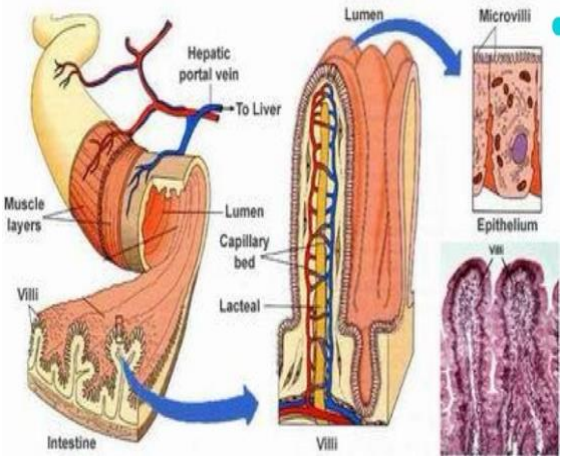
- **Presence of mucosal folds (Folds of Kerkring or Circular Folds) increases the surface area three folds.**
- **Mucosa also has other structures called villi (capillary like structures) which increase surface area 10 more folds.**
- **The lumenal surface of the epithelial cells has microvilli (or brush border), which increase surface area 20 folds.**
  **The net increase in the surface area is about 600 folds. If we take 1 $cm^2$ of the functional unit, it will equal 600 $cm^2$ which is important for the fast removal and absorption of nutrients.**



**Villus:**

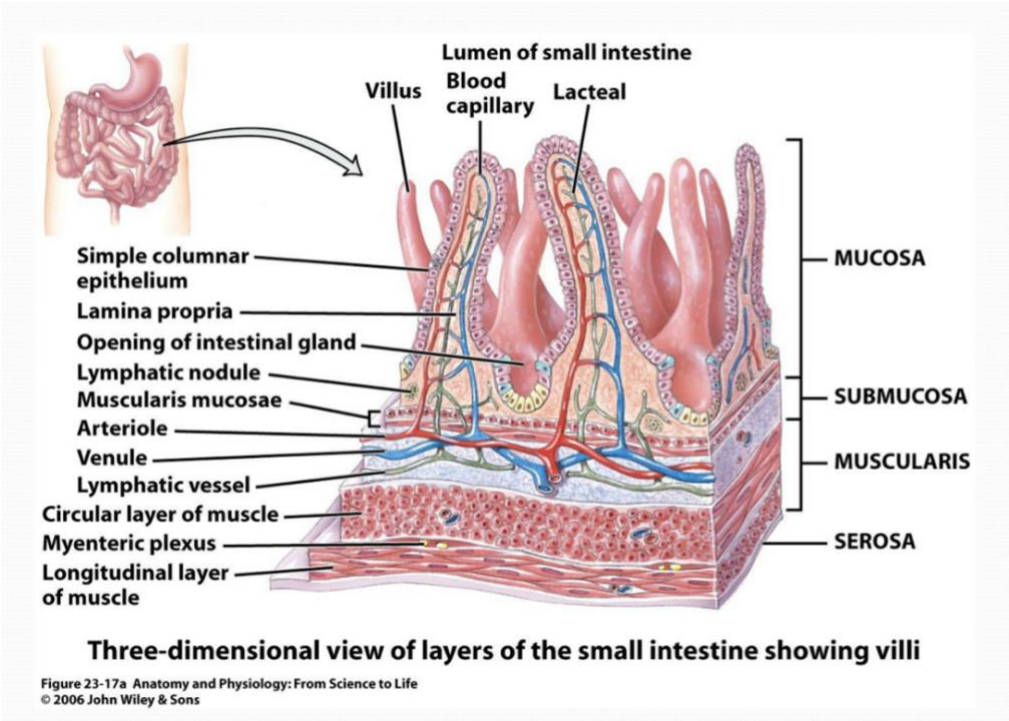
**This specialized structure has:**

- **Highly vascularized: Capillary network which removes the absorbed nutrients very quickly. This process maintains a concentration gradient between lumen and blood in capillaries.**
- **Lymphatic network of lactels removes lipids and maintains gradient for lipid absorption.**




## * OTHER STRUCTURES THAT HELP IN ABSORPTION AND DIGESTION:

- **Enteric innervation (mainly the submucosal plexus): provides mechanism to regulate secretion of secretory cells and blood flow to intestinal mucosa.**
- **Smooth muscle cells of the muscularis mucosa which allow villi to wave in lumen and folds to move, which permit more spreading of chyme over the absorptive area.**
- **Beside the enzymes we've talked about, there are even more enzymes found at the luminal membrane of absorptive cells which are called Brush border enzymes.**
  **At the surface of microvilli, cells are equipped with enzymes which help in the final digestion of carbohydrates and proteins.**




**Three-dimensional view of layers of the small intestine showing villi**

Figure 23-17a Anatomy and Physiology: From Science to Life
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