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Gastrointestinal Physiology: Part II.

GASTROINTESTINAL SECRETION:

Secretions along digestive system appear as a response to the presence of food in GI tract. The composition of secretions (enzymes and other constituents) varies according to the type of food, and serves to:

- Digest food.
- Lubricate and protect the mucosa.

The composition of secretion includes:

- Organic materials that secretory cells synthesize are stored in vesicles, and then secreted upon stimulation.
- Water and electrolytes are taken from blood vessels, and then secreted by secretory cells.

Many types of secretory glands are found along the GI tract, these include:

- Single-cell secretory glands (goblet cells).
- Pits that represent invaginations of the epithelium in the submucosa in small intestine are known as "Crypts of Lieberkühn" and in the stomach "Tubular glands".
- Complex glands: like mucus glands at lower part of esophagus.
- Organs: like Salivary glands, Pancreas and Liver. Located outside the tubular structure of the GI.

Regulation of glandular secretion:

The role of ENS:

The presence of food in certain segments usually stimulates glandular secretions. This appears as a response to mechanical or chemical stimulation, which induces activation of secretory reflexes that are responsible for the increased secretions by gland.

The role of Autonomic nervous system:

- Parasympathetic stimuli increase the rate of glandular secretions.
- Sympathetic stimuli can cause moderate increase in glandular secretion by increasing vesicular transport (increases secretion of organic materials).

On the other hand it can reduce secretion of water and electrolytes by its effect on vessels (reduces blood flow).

Parasympathetic nerves (rest & digest) →
👉 Increase secretion (make glands release more).
Sympathetic nerves (fight or flight) →
👉 Do two things:
Slightly increase organic secretions (like enzymes).
But can reduce watery/electrolyte secretions by narrowing blood vessels.

Hormonal regulation:

- Some hormones are secreted by the presence of food in digestive organs which affect the glands where they stimulate secretions.

SALIVARY GLANDS SECRETION:

General consideration:

Secretion: is a net movement of water, electrolytes and proteins (starch splitting enzyme (amylase) and glycolproteins) into the lumen of salivary duct.

The role of acinar cells: (1)

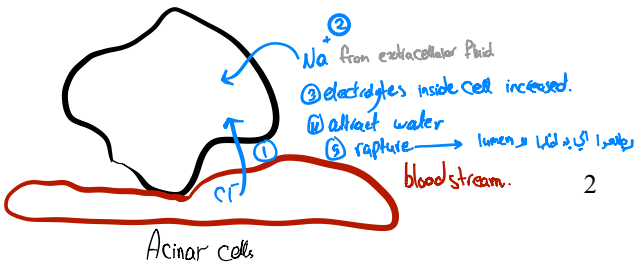
- Secretion of water and electrolytes:

Origin of water and electrolytes is extracellular fluid. The acinar cells are surrounded by capillary plexus which plays an important role in glandular secretion.

Proposed steps of secretion:

1. Active transport of Cl- at the basal portion of the membrane causes more negative membrane potential.
2. Increased negativity of membrane potential attracts the positive ion (Na+).
3. Increase osmotic pressure inside the cell causes water to move inside, which in turn increase hydrostatic pressure inside acinar cells.

Cl⁻ is pumped in → makes the cell more negative.
Na⁺ is drawn in to balance charge.
Water follows Na⁺ and Cl⁻ → increasing pressure.
Pressure pushes out fluid → secretion into ducts.



4. This increase results in minute ruptures at the apical membrane of secretory cells which cause flushing of water, electrolytes and organic materials out of the cell into the lumen.

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- Synthesis and secretion of protein components:

Protein secretion: Proteins (ptyalin, lingual lipase and mucin) are synthesized at ER (endoplasmic reticulum) of acinar cells, then transported by a mean of vesicular transport toward the apical (luminal part) membrane where they are secreted by exocytosis.

The secretory cells are rich in ER and mitochondria. Mitochondria provide sufficient energy supply for transport of nutrients that enter in the constitution of synthesized materials and for the process of synthesis.

The acinar cells secrete primary secretion that contains ptyalin and mucin in a solution of electrolytes. The water and electrolyte concentration in primary secretion is not far from that in extracellular fluid.

role in modifying the primary secretion (produced by the acinar cells) as it passes through the ducts, ultimately determining the final composition of saliva.

Secretion of Bicarbonate (HCO_3^-)
Duct cells also secrete HCO_3^- into saliva.
This can happen by swapping Cl^- for HCO_3^-

The role of duct cells:

During the flow of saliva through the ducts, two major transport processes are taking place to finalize the ionic composition of saliva:

- Na+ reabsorption and K+ secretion: by the activity of Na+ / K+ pump.

  This will result in a negative trans-cellular potential which induces reabsorption of Cl- ions.

  cells ← Saliva

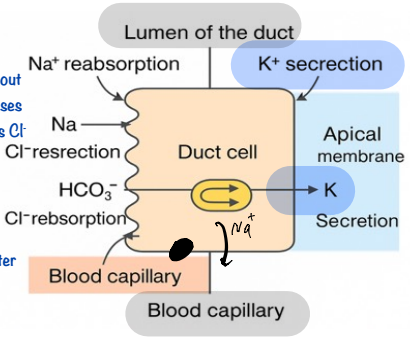
- HCO3- secretion into the duct, partly by exchange of HCO3- for Cl- and may result also by an active transport of HCO3-.

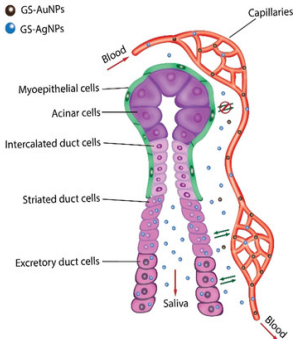
Note: The NET result is a change in the ionic composition of saliva by decreasing Na+ and Cl- concentration to the 1/10 of their plasma concentration and increasing K+ concentration by 7 folds and HCO3- concentration by 2-3 folds.

The final saliva is a hypotonic solution because there is a higher absorption rate of Na+ and Cl- than secretion of K+ and HCO3- by tubular cells.

Duct cells have a Na^+/K^+ pump on their basolateral side (facing the blood). This pump actively transports Na^+ out of the cell into the blood and K^+ from the blood into the cell. The accumulation of Na^+ outside and K^+ inside causes more Na^+ to leave than K^+ enters, making the inside of the cell relatively negative. This negative charge attracts Cl^- ions from the blood into the cell, even though the cell is already negative — because the electrical gradient is stronger than the repelling force. Once inside, Cl^- can be secreted into the saliva.

At the same time, K^+ that entered the cell is secreted into the saliva, and Na^+ is reabsorbed from saliva into the blood. Because more Na^+ and Cl^- are reabsorbed than K^+ and HCO_3^- are secreted, and duct cells have low water permeability, water does not follow the ions, making the final saliva hypotonic (low in solute concentration).





The amount of secretion by saliva is about 1500ml/day. The rate of secretion is less than 0.025 (during sleep) to about 0.5ml/min (during the basal conditions). The spontaneous secretion of saliva is maintained by a constant low level of parasympathetic stimulation.

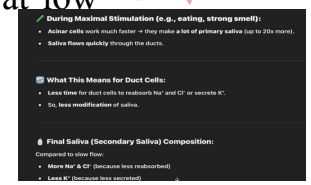
- The amount of saliva secreted by salivary glands is not the same in all glands. And the type of saliva is different also. The parotid glands secrete about 25% of secretion and the type of secretion is *serous*. Submandibular (submaxillary) glands secrete about 70% of the saliva and the type is *mixed*. Sublingual glands secrete about 5% of saliva and the type is *mucus*.

2 types of secretion :-

- The pH of saliva during resting secretion is around 7.0 and approaches 8.0 during active secretion.

يرتفع pH الـ HCO3 لما يزيد إفراز ← خلالها

During maximal stimulation, the formation of primary saliva increased as much as 20 folds by increasing the secretory activity of acinar cells. As a result the flow rate of saliva through the ducts is increased, which may result in relative reduction of the reabsorptive and secretory activity of the duct cells. This will change the composition of secondary (final) saliva (more Na+ and Cl-, and less K+ are found in secondary saliva during high stimulation than their concentration at low rate of flow).



Stimulation of salivation can be induced by:

- Unconditioned salivary reflex: Natural/Automatic

Occurs by stimulation of chemo-receptors and pressure-receptors in oral cavity to the presence of food.

For ex. dental procedures induce activation of pressure receptors. These transmit signals through afferent fibers to salivary centers in the medulla, which transmit stimulatory signals through efferent fibers via extrinsic autonomic nerve fibers to increase salivation.

- Conditioned salivary reflex:

Stimulation of salivation by thinking about, seeing, smelling, or hearing about pleasant food. This is known as (Mouth watering) in anticipation of something delicious to eat.

The conditioned response is learned and based on previous experience.

Nervous Regulation
Both sympathetic & parasympathetic systems increase salivation, but:
Parasympathetic: Major role → watery saliva.
Sympathetic: Thick, mucus-rich saliva; strong activity may reduce flow by constricting blood vessels to glands.

- Nervous regulation:

Both sympathetic and parasympathetic increase salivation, but by different mechanisms. More increase in the sympathetic activity can reduce salivation by its effects on blood vessel supply.

The functions of saliva:

1. Saliva begins digestion of carbohydrates in the mouth:
   Amylase that breaks polysaccharide into maltose (disaccharide consists of 2 glucose).
2. Facilitate swallowing by:
   - Moistening the food particles.
   - Lubrication by mucus which protects the mucosa during swallowing and allowing easy slippage of solid food, which prevents physical damage to the mucosa.

3. Antibacterial actions:
   - Lysozyme: an enzyme that lyses or destroys certain bacteria.
   - The constant flow of saliva rinsing away materials (food residues, shed epithelial cells, and foreign particles) that may play an important role in oral hygiene and keeping mouth and teeth clean.
   - IgA helping in the destruction of bacteria
4. Solvent for molecules that stimulate taste buds.
5. Facilitate movements of lips and tongue → aids in speech.
6. Bicarbonate neutralizes acids in food and that produced by bacteria → preventing caries.

ESOPHAGEAL SECRETION:

- Mainly **simple mucus glands** and that have secretion with mucoid character, which help in lubrication and protection of esophageal mucosa from excoriation during swallowing process.

- **Compound mucus glands** near the esophago-gasrtic junction with alkaline secretion that protect esophageal wall from the gastric reflux into the esophagus.

GASTRIC SECRETION:

- **Mucus secreting cells**: line all the stomach surface. These cells secret viscid mucus which may have the following functions:

- Lubricating functions that protect against mechanical injury.
- The secreted mucus lines the mucosa prevents proteolytic enzymes to act on the mucosa (protective).
- The secreted mucus has an alkaline pH which neutralize HCl and protect the mucosa from the chemical injury caused by HCl

- **Tubular glands:**

- Oxyntic (gastric glands) : HCl forming glands. Secrete HCl, Intrinsic factor and Mucus.

These glands are composed of 3 types of cells:

- *Mucus neck cells*: secrete mucus and some pepsinogen.
- *Peptic* or *chief cells*: secrete large amount of pepsinogen.
- *Parietal* or *oxyntic cells* secrete HCl and intrinsic factor.

HCl Secretion:

Theory that suggests mechanism of acid secretion by oxyntic (parietal) cells:

duct inside the parietal (oxyntic) cells of the stomach.
It leads from the inside of the cell to the stomach lumen (where the acid goes).

1. Active secretion of Cl- into the canaliculus causes negative potential which induces passive diffusion of K+ and Na+ (mainly K+).
2. The H+ is taken from dissociated water during the reaction catalyzed by carbonic anhydrase. In the presence of CO2 and the activity of carbonic anhydrase, HCO3- and H+ are formed.
   The reaction is:
   $H2O + CO2 \rightarrow H2CO3 \leftrightarrow HCO3^- + H+$
   HCO3- is transported toward interstitial fluid in exchange for Cl-.
3. - Active secretion of H+ by H+/K+ pump into the canaliculus.
   -Active process of Na+ absorption at this level by Na+ pump.

At the basolateral membrane (the side of the parietal cell facing the blood), the Na^+/K^+ ATPase pump is actively working to:
Pump Na^+ out of the cell (into the blood)
Bring K^+ in (into the cell)

The net reactions that result in HCl secretion is:
$H2O + CO2 + NaCl \rightarrow NaHCO3$ (blood) and HCl (lumen)

4. Water is transported into the canaliculus by osmosis.

Ion	Where It Goes	How?
H^+	Into stomach	Via H^+/K^+ pump (active transport, needs ATP)
Cl^-	Into stomach	Follows passively (creates HCl)
Na^+	Into blood	Via Na^+/K^+ pump (not secreted into stomach)
HCO_3^-	Into blood	Exchanged with Cl^- (causes alkaline tide)

when food arrives, strong acid (HCl) is needed to digest it — so secretion shifts from NaCl → HCl.
H^+ in stomach is 3 million times higher than in blood.
Electrical charge shifts from -70mV at rest to -30mV during acid secretion.

At rest and at low levels of stimulation usually NaCl is secreted and during high rates of stimulation there is HCl secretion.
The potential difference across the cell is about –70mV at rest and drops to about (-30 mV) during stimulation
Concentration of H+ [H+] in canaliculus is about 3 million times that in blood which results in a decreased pH during gastric secretions.
This process needs ATP for H+ pump activity.

Importance of HCl:

- HCl does not usually digest any thing, but it is important in the conversion of the proteolytic enzyme pepsinogen into ***Pepsin*** (active form of enzyme with proteolytic activity).
- Helps in decomposition of connective tissue.
- Helps in defense by killing most microorganisms ingested with food.

Pepsinogen secretion:

Pepsinogen is secreted by peptic (chief) and mucus cells. When secreted, it is inactive. The active form of pepsinogen is ***pepsin***: which is an active proteolytic enzyme with an optimal activity at acidic pH (1.8-3.5).

Importance of Pepsin:

- helps in cleaving longer polypeptides into smaller peptides.

Secretion of the intrinsic factor:

It is secreted by parietal cells (oxyntic cells). This factor is essential for B12 absorption. In the defective production of intrinsic factor such as in gastric mucosal atrophy, pernicious anemia with failure of RBC maturation may occur.

- Pyloric glands:

Contain Mucus cells and G cells that secret Gastrin.
The mucus secreting cells are similar to mucus neck cells of the gastric glands.

Gastrin: secreted by G cells of the pyloric glands into blood. This hormone acts on the body of the stomach to:

- Increases HCl and pepsinogen secretion.

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- It has also trophic effect on gastric mucosa to maintain growth of mucosal cells.

Regulation of Gastric secretions:

Regulation of HCl secretion:

1. Neural:

- Enteric Nervous System: can control by direct stimulation of parietal cells and peptic cells. The effect is mediated by Ach.
- Parasympathetic: vagal activation during cephalic and gastric phases (via long arc reflex) activate:

→ enteric excitatory neurons to release ***Ach***.

→ enteric neurons that innervate enterochromaffin-like cells in the stomach to secrete ***Histamine***.

→ enteric neurons that secrete GRP (gastrin releasing peptide) that acts on G cells to cause secretion of ***Gastrin***.

Neural Control (Nerves):
a. Enteric Nervous System (local nerves in gut):
Releases Acetylcholine (Ach).
Ach stimulates parietal cells directly → HCl secretion.
Also stimulates peptic (chief) cells → pepsinogen release.

b. Parasympathetic Nervous System (via vagus nerve):
Active during cephalic phase (thinking/smelling food) and gastric phase (food in stomach).
Vagus nerve causes:
Release of Ach (stimulates parietal cells).
Stimulation of enterochromaffin-like (ECL) cells → they release Histamine (which also stimulates parietal cells).
Release of GRP (Gastrin Releasing Peptide) → stimulates G cells to release Gastrin (another powerful HCl stimulator).

2. Hormonal control:

- Gastrin: secreted from G cells into the blood and acts on parietal cells to increase HCl secretion.

The release is stimulated by gastric distention, presence of proteins in chyme and vagal stimulation. This hormone acts on a receptor at parietal cells known as CCK-B receptor to increase the intracellular Ca++ and activation of oxyntic cells to secrete HCl. This receptor can also be activated to a lesser extent by CCK (cholecystokinin).

3. Paracrine:

- Histamine: secreted by *enterochromaffin-like cells* in response to vagal stimulation and local inflammation. Diffuses in the extracellular space and activates

parietal cells via H2 receptor by increasing c-AMP as a second messenger.

Net effect = increase HCl secretion.

> ***Note:*** Some antihistaminic drugs that block H2 receptors such as Cimetidine reduces acid secretions.

- Somatostatin (SS): released from paracrine cells in the mucosa and acts on SS receptors of parietal cells to decrease cAMP.

  Net effect → decrease HCl secretion.

Regulation of pepsinogen secretion:

Ach, Gastrin, HCl: HCl acts indirectly by initiating enteric reflexes that causes an increase in pepsinogen secretion by peptic cell.

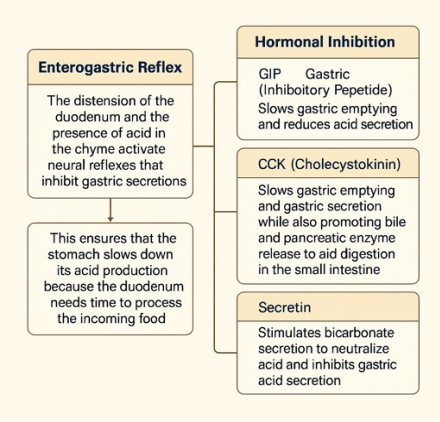
> ***Note***: Excess of acids causes feed back inhibition of gastric secretions by 2 ways:
>
> - Reduction of gastrin release
> - Initiation of inhibitory reflexes.
>
> As a result, this will maintain pH NOT to fall below 3.

3 phases of control of gastric secretions:

- Cephalic phase: by thinking about, smelling, tasting, chewing or swallowing. In this phase vagal stimulation is involved. These acting before food reaching the stomach to stimulate parietal cells and G cells.

- Gastric phase: Acts when food reaches the stomach to cause maximal stimulation of gastric secretions.
  - Distension and the presence of proteins in food stimulates local reflexes and long reflexes which results in increased gastric secretion.
  - Caffeine and alcohol also stimulate acid secretions even no food is present in the stomach.

Stimulating effects are seen right when food enters the duodenum to continue gastric activity briefly.
Inhibitory effects follow soon after, as digestion progresses and the body adjusts to protect the small intestine and regulate gastric acid production.



- Intestinal phase:
  - Excitatory: Distension of the upper portion of the duodenum can slightly stimulate gastric secretions. This effect is probably by the release of gastrin.
  - Inhibitory: the presence of chyme in intestine usually inhibits gastric secretions. The presence of food and acids in duodenum initiates neural reflexes (enterogastric reflex) and causes the release of hormones (GIP, CCK, secretin, enterogastrone). These hormones inhibit acid secretions.

INTESTINAL SECRETION: (1500ml/day)

- Cells of mucosal epithelium secrete mucus, water and electrolytes.
- Tubular glands in submucosa of duodenum (duodenal glands). These invaginations of epithelium known as crypts of Leiberkuhn which empty into the lumen of duodenum. These glands secrete serous secretion.

Regulation:

- Local neural mechanisms that activates secretions is mediated by Ach and VIP (vasoactive intestinal peptide) neurons.
- Secretin: increases duodenal secretion. This is an important factor to neutralize the acid delivered into the duodenum from the stomach.

COLONIC SECRETION:

- Mostly mucus secretion.
- Small amount of serous secretions which is rich in K+ and HCO3-.

PANCREATIC SECRETION: (1-2L/day)

Functional anatomy:

Endocrine portion: Islets of Langherhans secrete *insulin*, *glucagon*, *somatostatin* and *pancreatic polypeptide* release into the blood.

- **Exocrine portion**: *Enzymes*: secreted from acinar cells and *water and bicarbonate* are secreted by duct cells. These are secreted into the duodenum via pancreatic duct and common bile duct. Which empty at ampula of Vater through sphincter of Oddi.
The net pancreatic secretion is high in enzymes and is hypotonic and alkaline.

Secretion of Pancreatic enzymes:

Pancreatic enzymes are synthesized by acinar cells and stored in zymogen granules. The proteolytic enzymes are stored as inactive enzymes and become activated in the duodenum.

1- **Protelytic enzymes:**

- Trypsinogen (trypsin (ogen)): activated by enterokinase from the duodenum (become trypsin). Trypsin acts as an endopeptidase. As long as it is in pancreas, Trypsinogen remains inactive by trypsin inhibitor.
- Chemotrypsin(ogen): activated by trypsin and acts as an endopeptodase.
- (Pro) carboxypeptidase: activated by trypsin and acts as exopeptidase.

2- **Pancreatic amylase**: secreted in an active form to convert polysaccharide in disaccharide.

3- **Lipolytic enzymes:**

- Lipase: esterase that splits triglycerides into monoglyceride and free fatty acids. Their activity requires an oil/water interface, bile salts (secreted by liver) and other co-lipase secreted by the pancreas.
- Phospholipase.
- Cholesterol ester hydroxylase.

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:

Water and bicarbonate are secreted by duct cells. 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.

Mechanism of secretion:

The sodium ions (Na^+) that enter the parietal cell (from the H^+-Na^+ exchanger) are then transported out of the cell to the blood by an active transport mechanism using the Na^+/K^+ ATPase pump. This pump moves sodium out of the cell and potassium (K^+) into the cell, maintaining the proper balance of ions.

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

$$H_2O + CO_2 \xrightarrow{\text{Carbonic Anhydrase (CA)}} H_2CO_3 \leftrightarrow H^+ + HCO_3^-$$

- HCO_3^- 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.

At high secretion rates, the parietal cells are pumping out more HCl, leading to higher bicarbonate (HCO_3^-) levels in the blood and lower chloride (Cl^-) in the cells.
At low secretion rates, less HCl is being secreted, leading to lower bicarbonate (HCO_3^-) in the blood and higher chloride (Cl^-) in the cells.

Note: The final composition varies with the rate of secretion.
* At high rates: HCO_3^- is high (in blood) and Cl- is low (in cell).
* At low rates : HCO_3^- is low and Cl- is high.

Regulation of pancreatic secretion:

Neural control:

- Parasympathetic: 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).
- Sympathetic: indirect inhibition via vasoconstriction of blood supply to the pancreas.

Hormonal regulation:

- Secretin: major stimulant of water and HCO_3^- secretion. This secreted into the blood by duodenal mucosa to acid stimulation → acts on duct cells to activate HCO_3^- and water secretion in response to the presence of acid in the duodenum.
- CCK (Cholecystokinin): 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 to stimulate enzyme secretions. Other effects of CCK is contraction of the gallbladder and relaxation of sphincter of Oddi by both ways directly and indirectly.

- Pancreatic 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.

3 phases of control of pancreatic secretions:

Cephalic phase: sight, smell, taste or hearing. Reflex is mediated by vagus.

Gastric phase: Distension.
Effect is mediated by vagus.

Intestinal phase: 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.

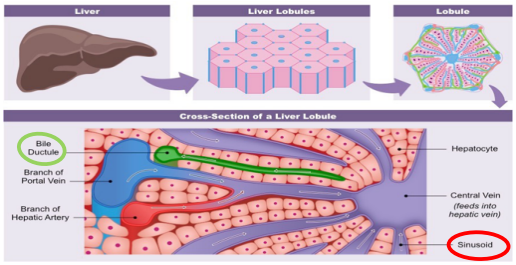
LIVER SECRETIONS:

Largest and the most important metabolic organ. It has importance in the digestive mechanisms by the formation and secretion of **bile salts**.

This organ also performs the following functions:

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**.

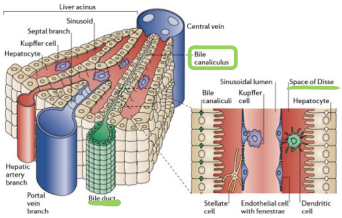
an orange-yellow pigment formed in the liver by the breakdown of hemoglobin and excreted in bile.



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.



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.

Hemoglobin catabolism → Heme + Globin
Heme decomposition → Iron + Biliverdin
Biliverdin conversion → Bilirubin (conjugated with glucuronide, sulfate, or other substances) → Secreted in bile
In the intestine → Bilirubin → Urobilinogen (via bacterial action)
Urobilinogen fate → Reabsorbed → Secreted in urine as urobilin
OR→ Secreted in feces as stercobilin

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.

Note: Jaundice (yellow discoloration of the skin) is caused by the presence of high concentration of bilirubin in the extracellular space.

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).

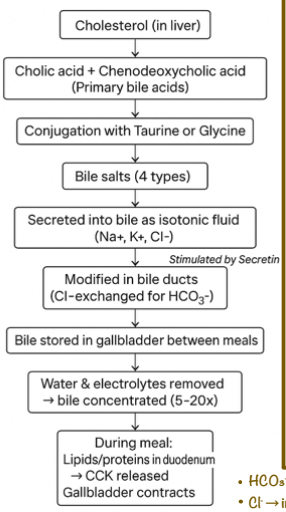
- Bile salts are synthesized by the liver, concentrated in the gallbladder and modified in the lumen.

Synthesis by liver and storage by gallbladder:

- Liver synthesizes two bile acids from cholesterol: *cholic acid* and *chenodeoxycholic acid* (these are primary bile acids). 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*. 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, bile is derived into the gallbladder where it is stored. The epithelium of the gallbladder removes water and electrolytes, 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.



- HCO_3^- → into bile (makes bile alkaline)
- Cl^- → into cholangiocyte (taken out from bile)

The gallbladder contraction is mediated by neural (local and vagal) reflexes as well as hormonal by the activity of CCK which is released by the presence of lipid and protein digestion products in the duodenum.

The bile salts are then reabsorbed actively in the terminal ileum. They are then removed from the blood 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.

بتصنع من أول وجديد

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.