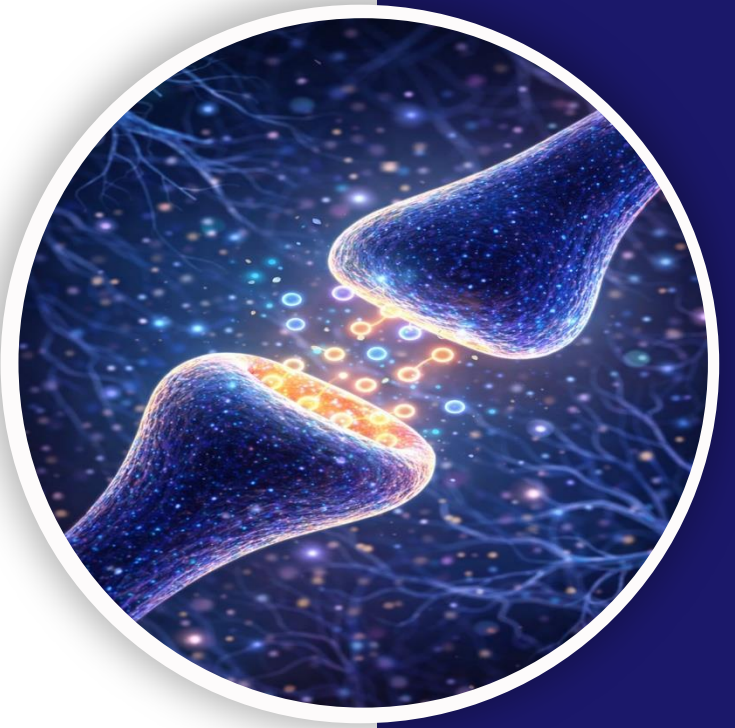
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

GIT Physiology | MID 5

GIT

Secretion pt.3



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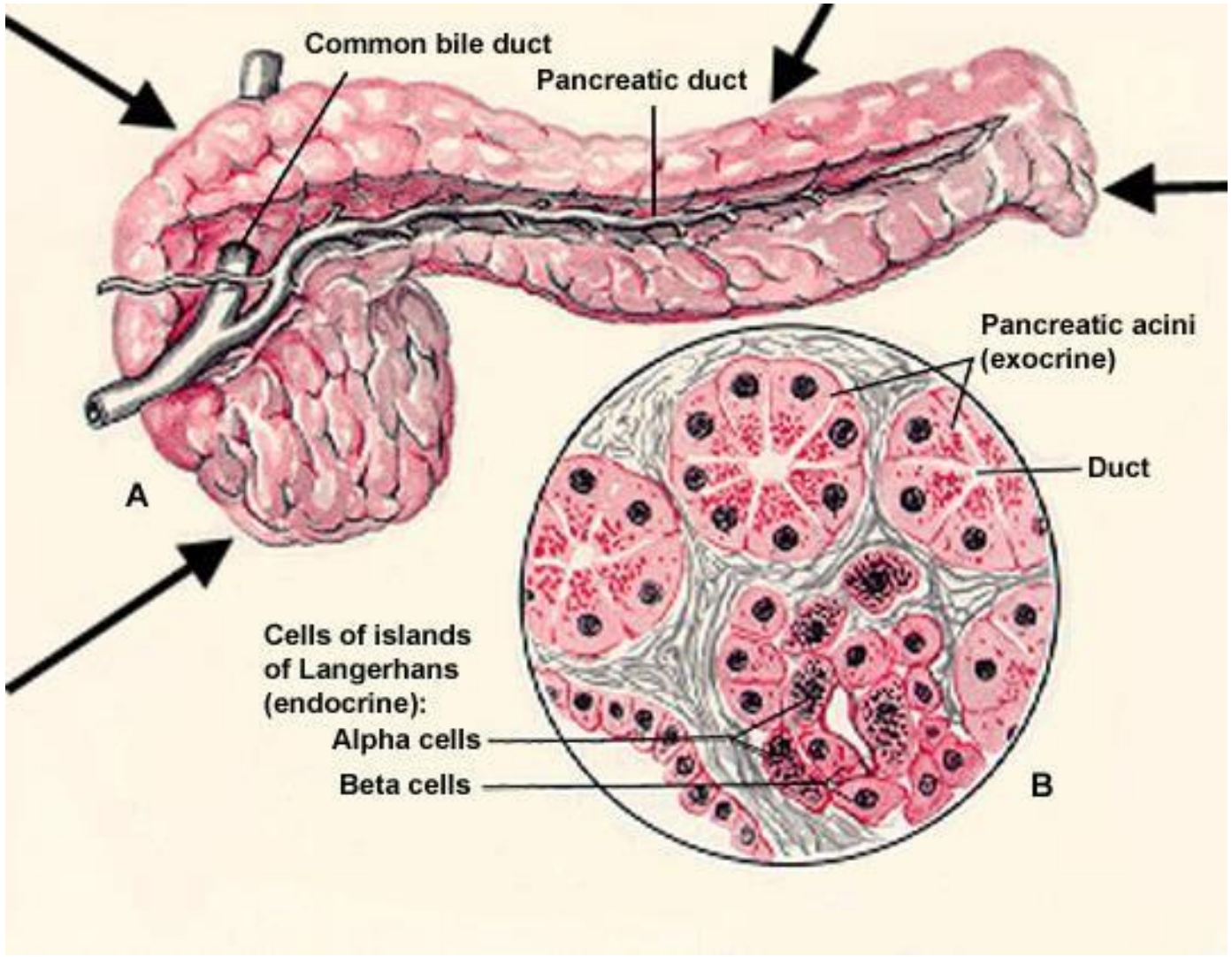
Pancreatic Secretions


Common bile duct
Pancreatic duct
A
Pancreatic acini
(exocrine)
Duct
Cells of islands
of Langerhans
(endocrine):
Alpha cells
Beta cells
B

Exocrine portion

- Enzymes: secreted by acinar cells.
- Water and bicarbonate are secreted by duct cells.

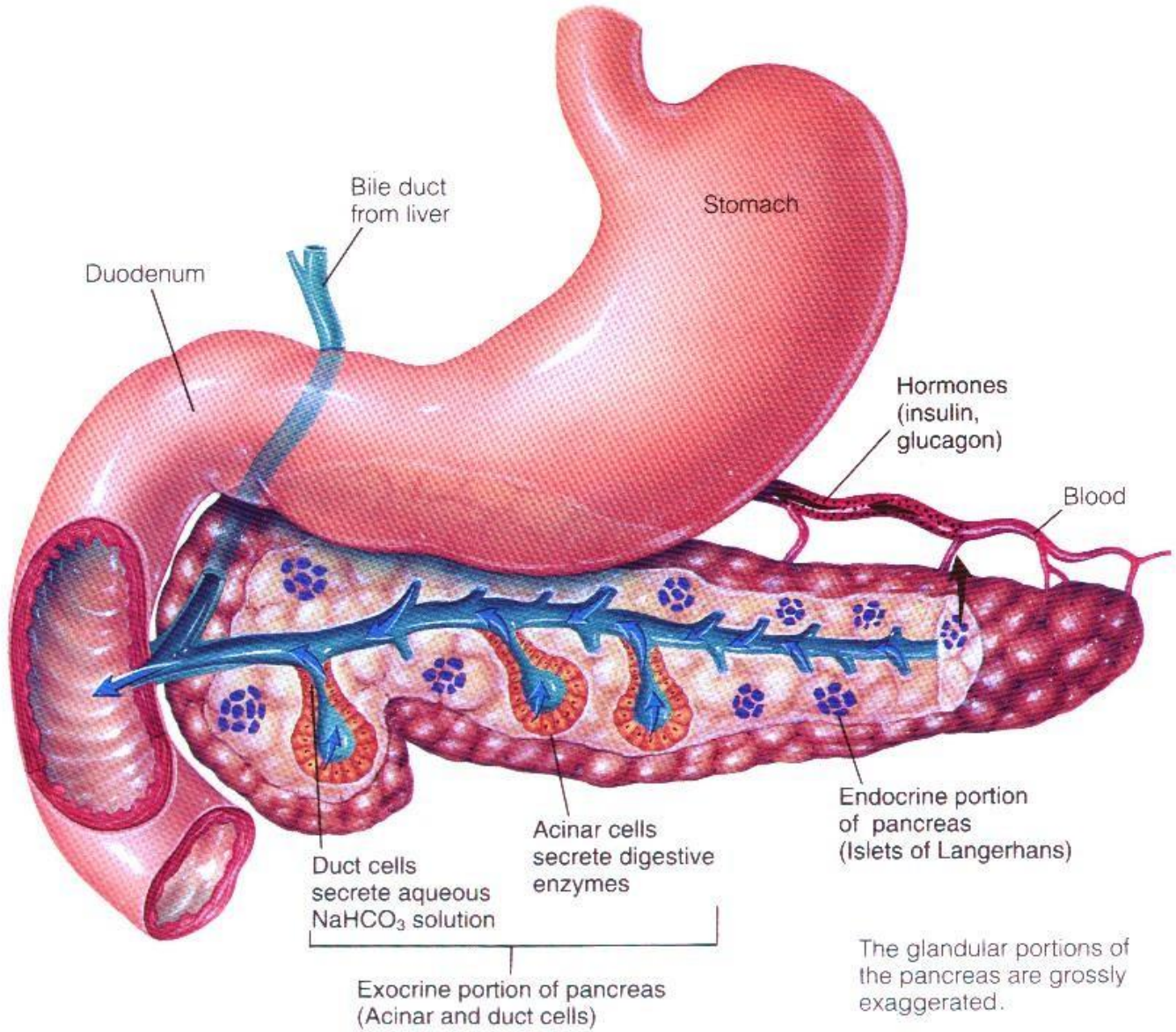
The pancreas consists of two main components: an endocrine part and an exocrine part.

The endocrine portion secretes hormones directly into the bloodstream, allowing them to act on target cells located far from their site of release. In contrast, the exocrine portion produces secretions that are delivered through a duct system into the gastrointestinal tract.

Structurally and functionally, the exocrine pancreas is similar to the salivary glands. It contains two main cell types: acinar cells and ductal cells, which line the ducts.

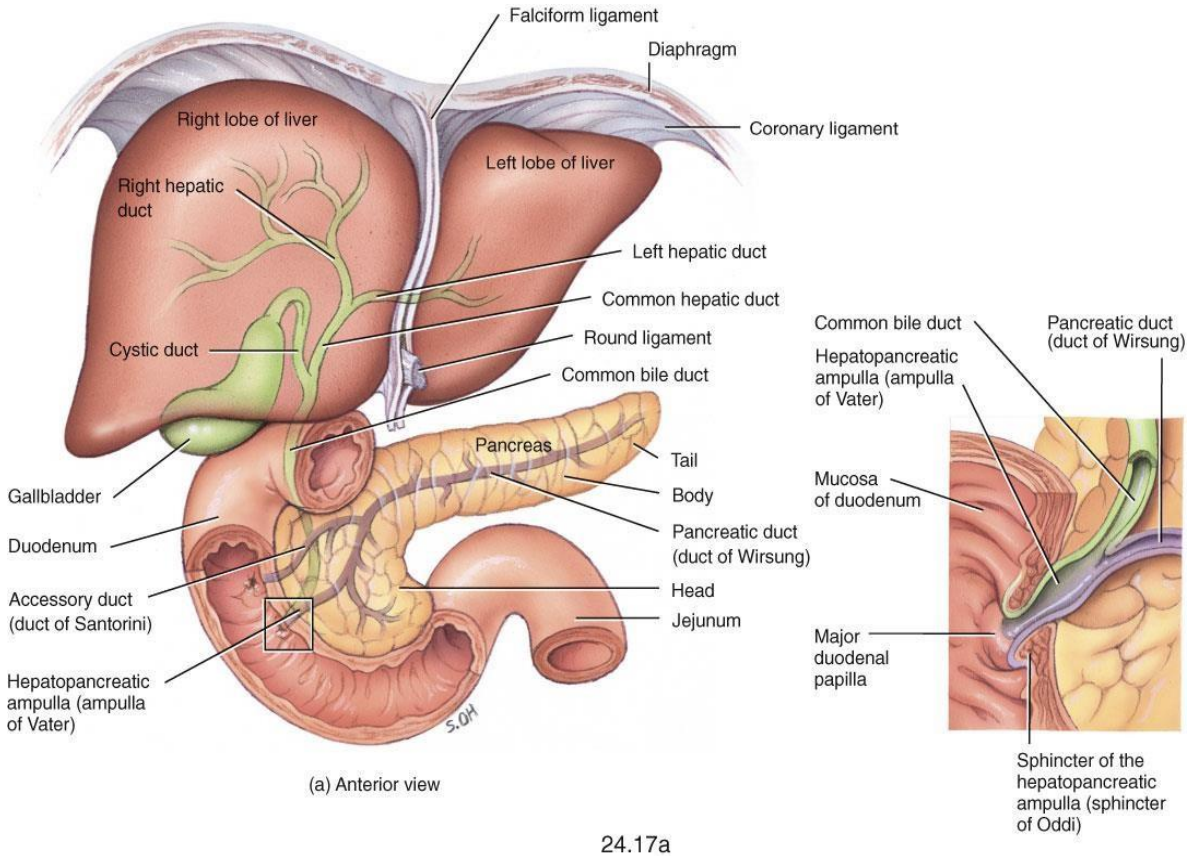
Acinar cells are specialized for the secretion of enzymes (unlike salivary glands, where acinar cells mainly secrete water and electrolytes). Ductal cells, on the other hand, are responsible for secreting water and electrolytes.

Schematic Representation of Exocrine and Endocrine Portions of the Pancreas



Acetate 148 (Figure 16-16)

Fig. 24.17a



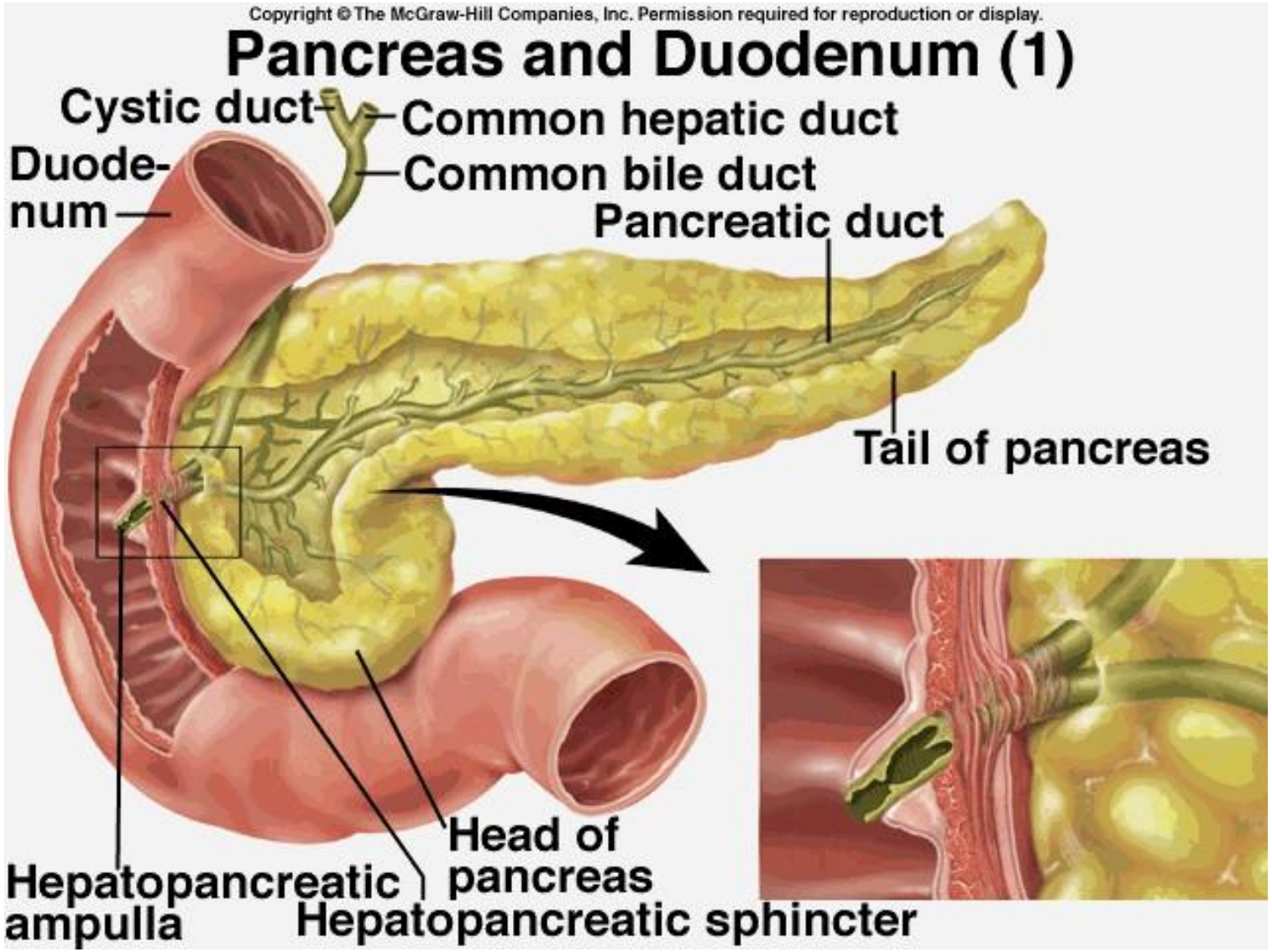
24.17a

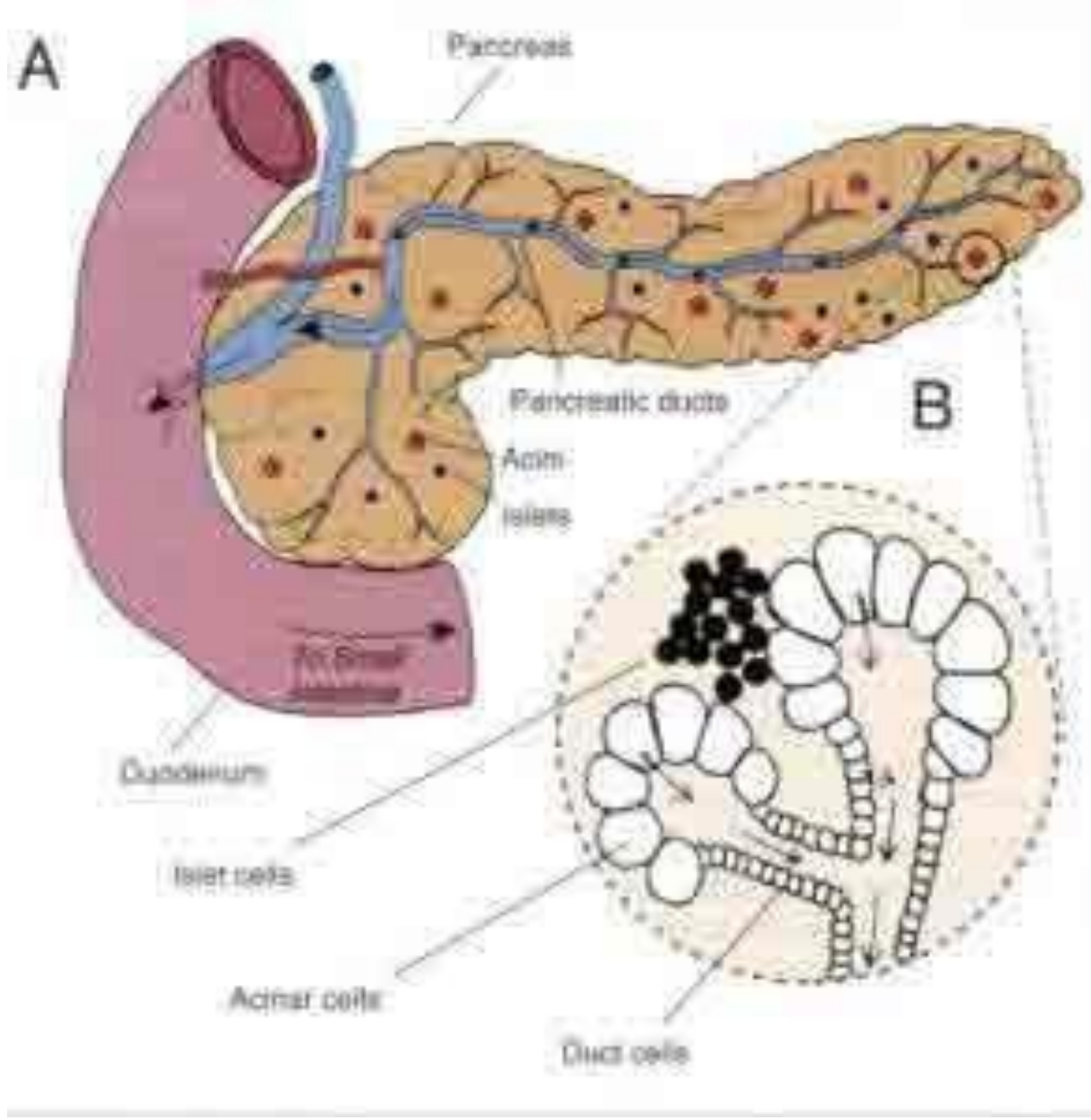
At this site, there is an anatomical structure known as the ampulla of Vater. Surrounding this opening is a sphincter called the sphincter of Oddi, whose function is to prevent the reflux of duodenal contents back into the duct system.

What the Dr. said "The hepatic duct joins with another duct originating from the liver to form the hepatopancreatic duct, which opens into the duodenum."

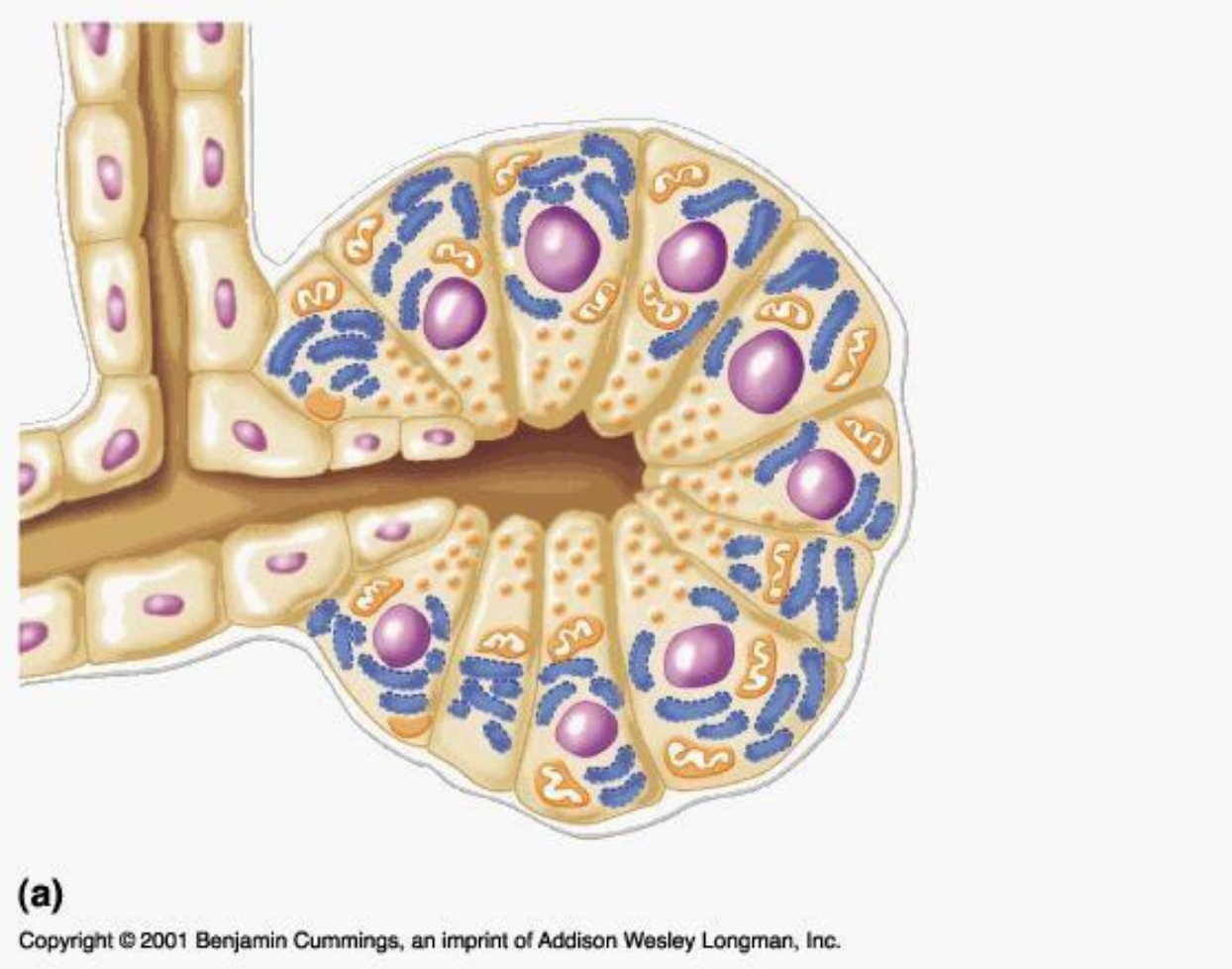
The correct scientifically and regarding to the handout :
The right and left hepatic ducts unite to form the common hepatic duct. The common hepatic duct then joins the cystic duct to form the common bile duct. Finally, the common bile duct joins the pancreatic duct to form the hepatopancreatic ampulla (Ampulla of Vater), which opens into the duodenum. This is the correct anatomical pathway; however, the version mentioned by the doctor is likely a mistake or an oversimplification, although we may still be required to write it as given in the exam.

Pancreas and Duodenum (1)




A
Pancreas
Pancreatic ducts
Acini
Islets
B
Duodenum
Islet cells
Acinar cells
Duct cells

Enzyme Secretion by acinar cells



These are acinar cells, which represent exocrine cells (endocrine cells will be studied later in the endocrine system). Acinar cells are filled with vesicles, indicating that they secrete proteins (enzymes). In contrast, ductal cells lack these vesicles and are therefore specialized for the secretion of water and electrolytes.

Protelytic enzymes:

- **Trypsin (ogen):** activated by **enterokinase** from the duodenum acts as (endopeptidase. As long as this enzyme is in pancreas remains inactive by trypsin inhibitor.

- **Chemotrypsin(ogen):** activated by trypsin and acts as endopeptodase.

- **(Pro) carboxypeptidase:** activated by trypsin and acts as exopeptidase.

Protelytic enzymes:

Acinar cells secrete proteolytic enzymes, which are responsible for protein digestion.

When the suffix “-ogen” is added to an enzyme name, it indicates that the enzyme is in its inactive form. Similarly, the prefix “pro-” before an enzyme name also denotes an inactive form, as in procarboxypeptidase.

Initially, these enzymes are secreted in inactive forms. They are then activated after their secretion reaches the duodenum. In the intestinal mucosa, enterokinase is present, and its function is to convert trypsinogen into trypsin (phosphorylation).

Trypsin can activate other enzymes by cleaving their long amino acid chains at specific sites, resulting in the formation of active chymotrypsin and carboxypeptidase.

Protelytic enzymes:

Trypsin and chymotrypsin act as endopeptidases, meaning they cut peptide bonds within the middle of the chain. In contrast, carboxypeptidase (as indicated by “carboxy,” referring to the C-terminus) is an exopeptidase, meaning it removes one amino acid at a time from the carboxyl end of the chain.

If these enzymes are secreted in their active forms (inside the pancreas) ,the pancreas will be destroyed. This can occur in alcohol intoxication, where the sphincter of Oddi becomes weakened, allowing reflux of duodenal contents back into the pancreatic duct system. These contents include proteolytic enzymes in their active forms, leading to acute pancreatitis, a very dangerous condition in which patients may die within 6 hours if no surgical intervention is performed.

Enzyme for Digestion of Carbohydrates

Pancreatic amylase:

secreted as active enzyme to convert

Starch (polysaccharide) → disaccharides.

Long chain of glucose -> maltose

Note:
Pancreatic amylase can be secreted in its active form (not harmful like protelytic enzymes as we mentioned above).

Lipolytic enzymes

- **Lipase** that split

Triglycerides → monglyceride + free fatty acids.

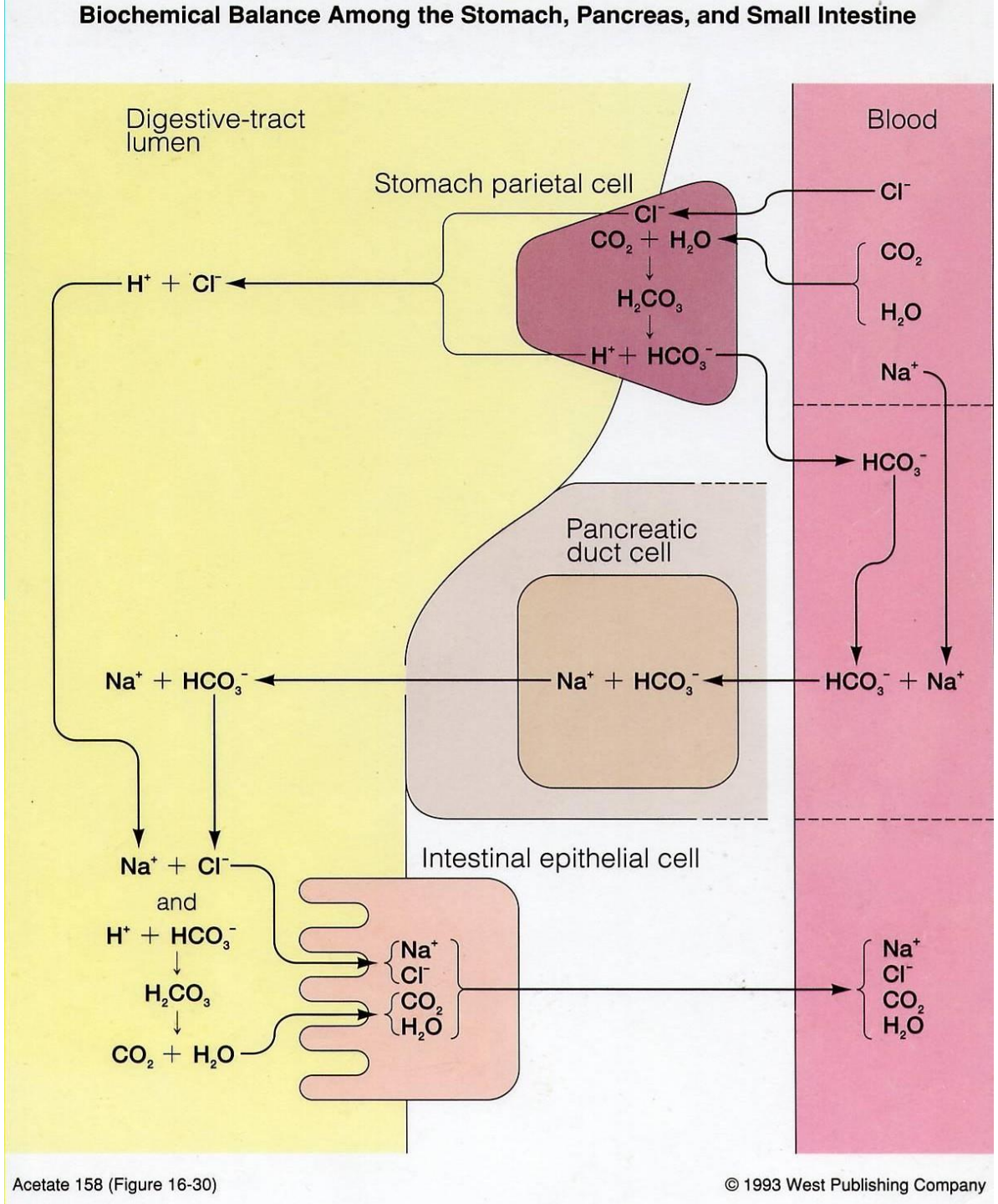
Their activity requires an oil/water interface, bile salts (secreted by liver) and other co-lipase secreted by the pancreas.

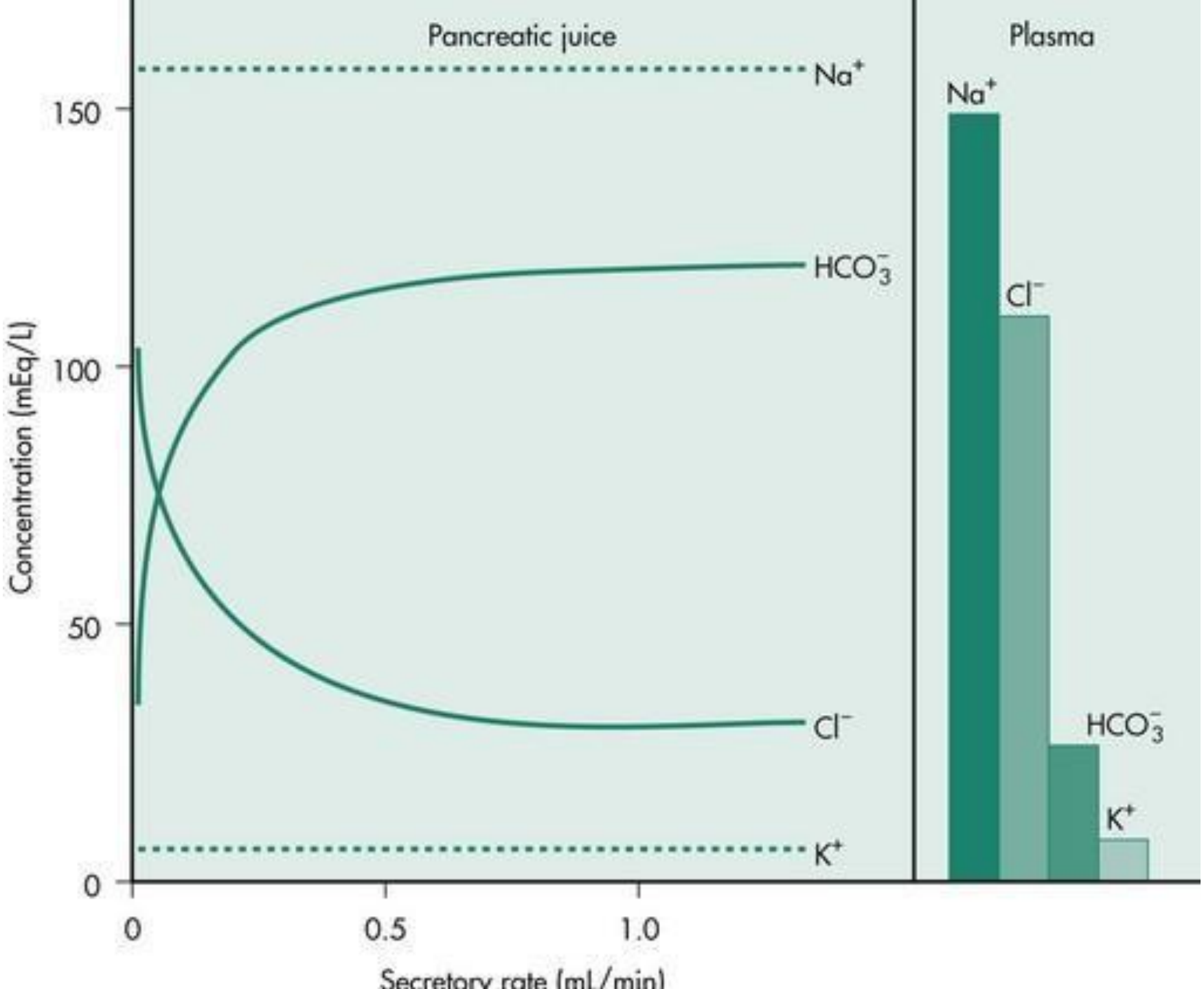
- **Phospholipase.**
- **Cholesterol ester hydroxylase.**

In addition to phospholipase & cholesterol ester hydroxylase we have colipase.

Colipase is a cofactor that helps pancreatic lipase function properly. It binds to lipase and anchors it to the surface of fat droplets, especially in the presence of bile salts, which would otherwise inhibit lipase activity.

Water and bicarbonate secretion by duct cells.





In the secretion mechanism, sodium is transported actively toward the lumen. Sodium then attracts negatively charged ions from the interstitial fluid, mainly chloride, since it is present in high concentrations.

Ductal cells secrete sodium bicarbonate, making pancreatic juice rich in this substance.

The activity of these cells varies depending on stimulation: when stimulated, secretion increases; when not stimulated, secretion decreases. As a result, the ionic composition of pancreatic juice differs between these states.

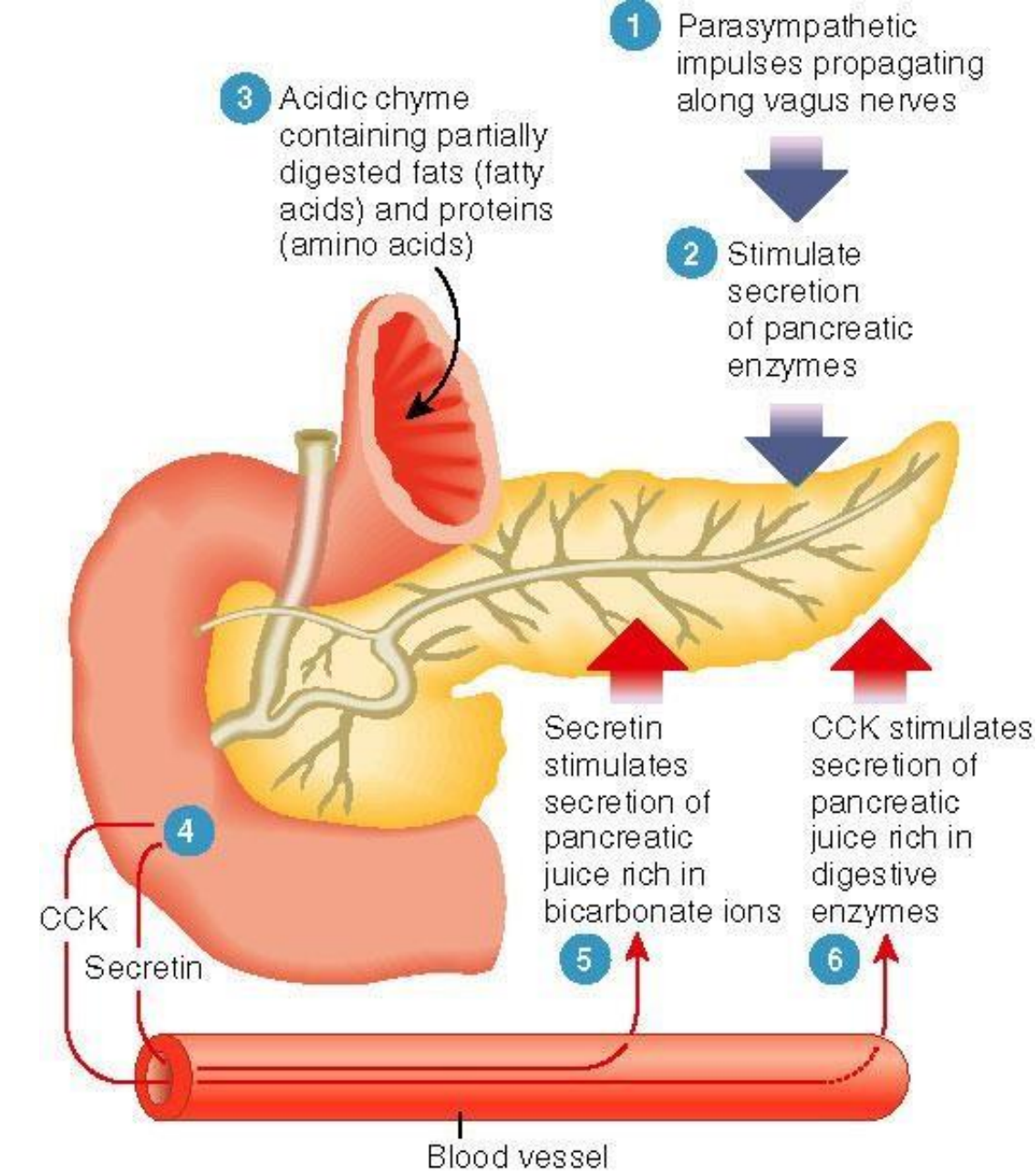
At a low rate of secretion, there is less bicarbonate secretion and higher chloride secretion.

For proper secretion, these cells must be stimulated to synthesize bicarbonate and transport it into the lumen of the duct system.

★ You are not required to know the detailed mechanisms (active vs. passive transport). What you need to know is that at a low secretion rate, there is low sodium bicarbonate and high chloride, and that sodium transport occurs via an active mechanism.

Control of pancreatic secretion:

- Neural
- Hormonal



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Neural Control

- **Parasympathetic:**

  Vagal stimulation → enteric nervous system→ release of Ach, VIP, and GRP (Gastrin releasing peptide).

- **Sympathetic:** indirect inhibition via vasoconstriction

Neural regulation involves both the parasympathetic and sympathetic systems. Increased parasympathetic activity enhances pancreatic secretion, whereas sympathetic activity causes vasoconstriction and decreases secretion.

The enteric nervous system also plays a role. Some of its nerve fibers reach the pancreas, meaning that certain enteric neurons are involved in regulating pancreatic secretion.

Enteric neurons, such as those releasing VIP and acetylcholine (ACh), originate from the enteric nervous system. GRP neurons may also play a role in controlling pancreatic secretion.

In addition, the vagus nerve (CN X) contributes to the regulation of pancreatic secretion during parasympathetic activity.

Hormonal Control

- **Secretin** (duodenal mucosa) → blood → ductal cells → increase water and HCO_3^- secretion.

-CCK (Cholecystokinin):

*→CCK-A receptors (acinar cells) → enzyme secretion.

*→vago-vagal reflex to stimulate enzyme secretions.

CCK (cholecystokinin):
Acinar cells have cholecystokinin A (CCK-A) receptors (which are different from those in the stomach), and their activation strongly stimulates secretion from these cells.

CCK can also enhance neural control by increasing reflex activity that regulates the pancreas. In addition, it causes relaxation of the sphincter of Oddi, facilitating the flow of secretions from both the pancreas and the liver.

Secretin:
Secretin acts on ductal cells, increasing the secretion of water and electrolytes.

A high acid content in the chyme stimulates secretin release. When food passes from the stomach to the duodenum, it is highly acidic, creating a need for bicarbonate to neutralize it. This leads to increased secretion of secretin, which acts on the intestine (where epithelial secretions are alkaline), resulting in increased bicarbonate secretion that helps neutralize the chyme.

Hormonal Control

- **Pancreatic polypeptide:** inhibits the release of enzymes by its inhibitory effect

  *- Inhibits Ach release from enteric nervous system.

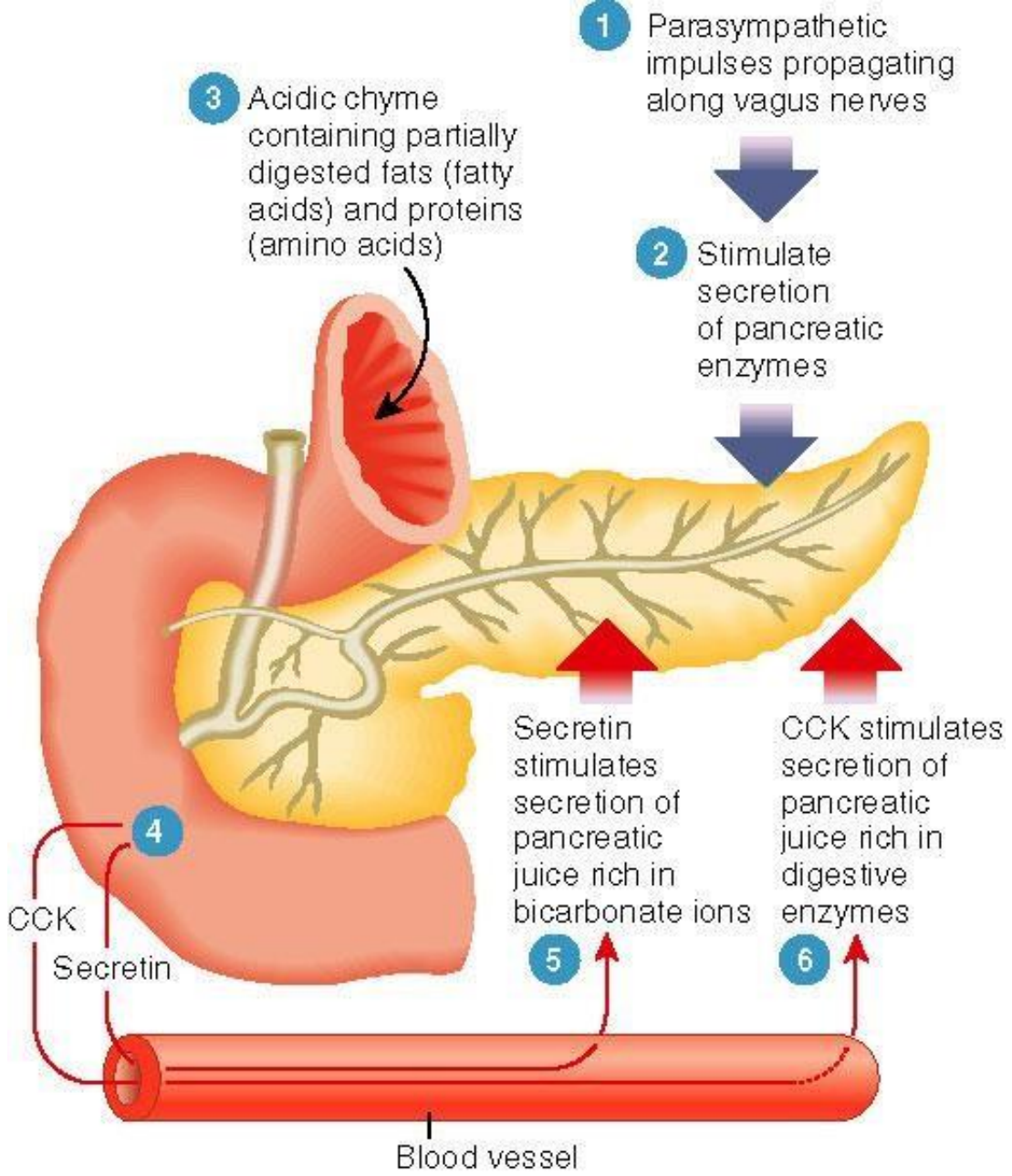
  *- Inhibits vagal output of the CNS.

Pancreatic polypeptide inhibits excitatory neurons, thereby reducing parasympathetic (vagal) stimulation.
Thus, it represents a neurohormonal interaction. This effect is not mediated only by CCK; pancreatic polypeptide also contributes by inhibiting pancreatic secretion.

Control of pancreatic secretion:

- **Cephalic phase**
- **Gastric phase**
- **Intestinal phase**

Regulation of secretion can be summarized according to the phases of digestion.
During the **cephalic phase**, parasympathetic activity is increased, which stimulates pancreatic secretion.
During the **gastric phase**, continued parasympathetic activity also promotes secretion.
During the **intestinal phase**, secretion is further stimulated by hormonal release, particularly **Cholecystokinin** and **Secretin**, in addition to neural reflexes. These mechanisms enhance and potentiate secretion.



24.18

3 phases of control of pancreatic secretions

Cephalic phase: sight, smell, taste or hearing. Mediated by vagus.

Gastric phase: Distension. Mediated by vagus.

Intestinal phase: Aminoacids (aa), Fatty acids, H+, Distension.

Mediated by CCK, secretin, enteropancreatic reflexes, other hormones.

We will have inhibition when we have no more phases

Liver Secretions

Although the liver has numerous functions, discussing them comprehensively would require covering a large part of biochemistry. Therefore, the focus here is not on all hepatic functions, but specifically on one function only: bile secretion.

Liver functions

- Metabolic processing: Process all nutrients after their absorption.

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

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

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

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

- Excretion of cholesterol and bilirubin.

Bile secretion

- Bile acts as detergent to emulsify lipids (lipid digestion) and make them soluble.

Bile is composed of **bile salts**, water & - electrolytes, cholesterol, phospholipids and wastes intended for excretion, (bilirubin).

Bile salts should not be confused with bilirubin:
bile salts participate in the digestion of lipids, whereas bilirubin is a waste product that the body excretes
Remember:
Bilirubin is generated during the breakdown of red blood cells, specifically from hemoglobin.

Liver functions

- Metabolic processing: Process all nutrients after their absorption.

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

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

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

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

- **Excretion of cholesterol and bilirubin.**

Excretion of bilirubin in the bile

- Bilirubin results from the catabolism of hemoglobin → Heme + Globin
- Heme ring → iron + biliverdin
- Biliverdin → bilirubin secreted with bile as conjugated (glucoronide, sulfate, other substances).

the degradation of the heme component ultimately leads to the formation of bilirubin. The concentration of bilirubin in body fluids is clinically important, because an increase in its level results in jaundice.

The doctor won't ask about them in detail

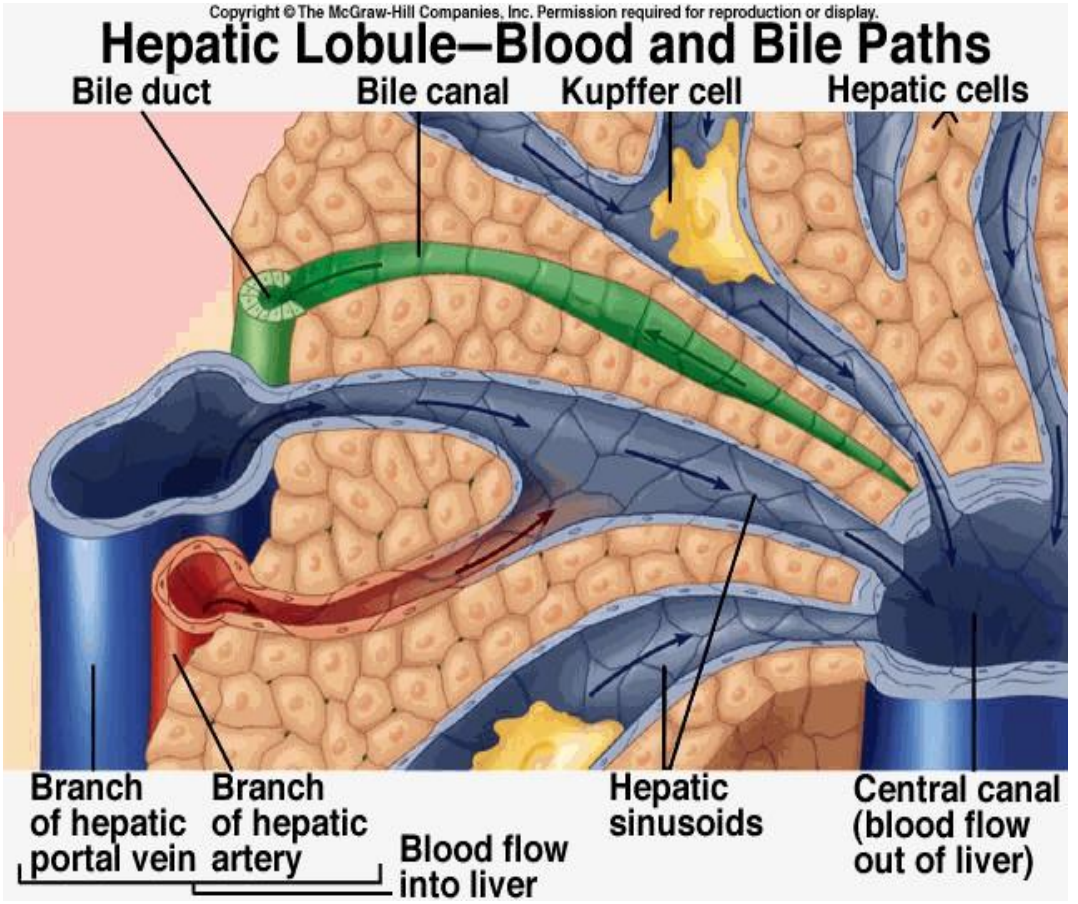
Remember from biochem:
Bilirubin is a pigment produced during the breakdown of red blood cells. Hemoglobin is separated into heme and globin, and degradation of the heme component ultimately forms bilirubin.

Bilirubin must undergo conjugation in the liver, mainly with glucuronic acid, to become more water-soluble. This increased solubility facilitates its excretion from the body through bile.
Elevated bilirubin levels in body fluids produce the clinical condition known as jaundice.

Bilirubin may increase in several conditions, particularly hemolytic diseases, where excessive destruction of red blood cells increases bilirubin production, and biliary obstruction, where blockage of the bile ducts prevents normal excretion of bilirubin, causing it to reflux back into the circulation.

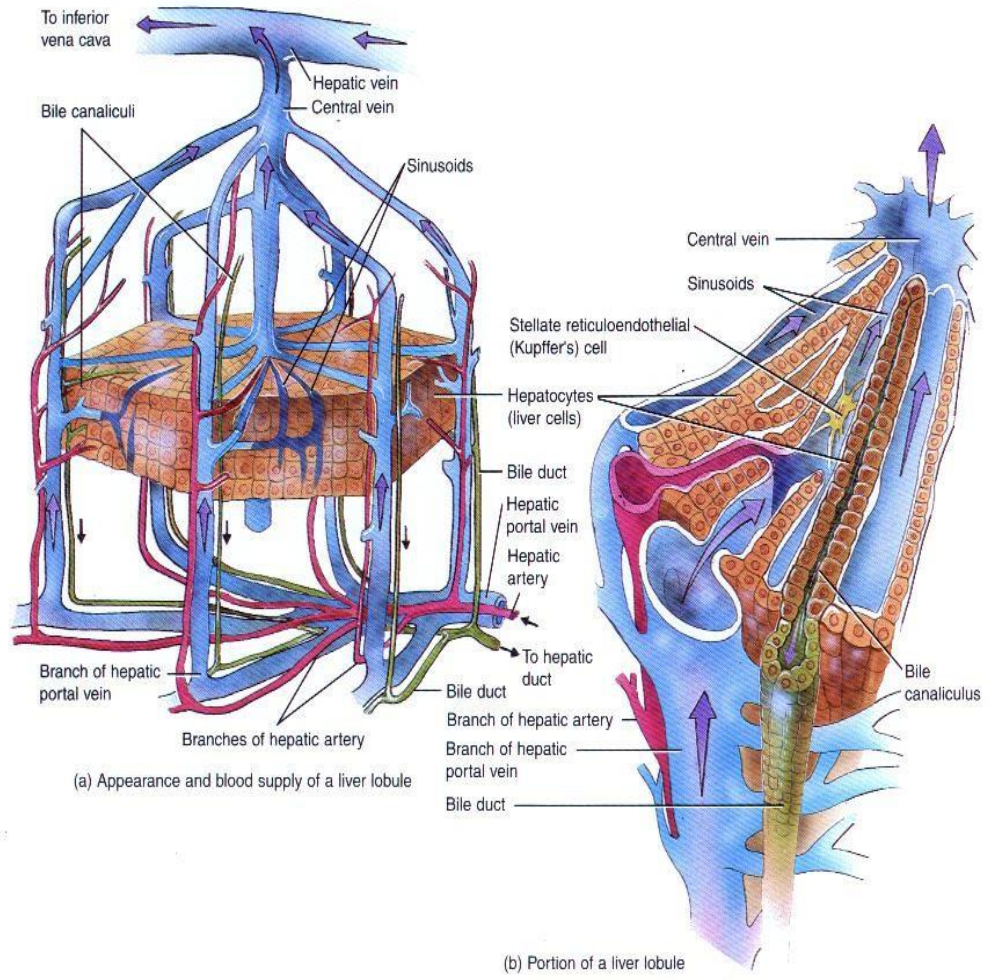
The cause of jaundice can often be differentiated by determining whether bilirubin is conjugated or unconjugated. Predominantly unconjugated bilirubin is commonly associated with hemolysis, whereas predominantly conjugated bilirubin suggests biliary obstruction.
Clinically, jaundice is often classified into three categories: prehepatic, hepatic, and posthepatic. Prehepatic jaundice is usually related to excess hemolysis, hepatic jaundice results from liver dysfunction, and posthepatic jaundice is caused by obstruction of bile flow(conjugated bilirubin). Bilirubin may also be referred to as indirect (unconjugated) or direct (conjugated) bilirubin.

The functional structural unit of the liver is the **hepatic lobule**. It is classically described as a **hexagonal unit** composed of hepatocytes arranged in plates around a central vein.
At the periphery of the lobule are the **portal triads**, which contain branches of the portal vein, hepatic artery, and bile duct. The portal vein brings nutrient-rich blood collected from the gastrointestinal tract to the liver, where it divides into smaller branches.
Blood from the peripheral branches of the portal vein and hepatic artery flows through **sinusoids** toward the **central vein** located in the middle of the lobule. Sinusoids are specialized wide capillary channels **(discontinuous capillaries lined by fenestrated endothelial cells that allow efficient exchange between blood and hepatocytes)**.



Hepatocytes are positioned between the sinusoids and have two functional surfaces. One surface faces the blood within the sinusoids, allowing uptake and release of substances. The opposite surface faces the bile canaliculi, which are small channels that collect bile secreted by hepatocytes.
Blood flows from the periphery of the lobule toward the central vein, whereas bile flows in the opposite direction—from the center toward the periphery—where it enters progressively larger bile ducts.

branches of the portal vein are located at the periphery of the hepatic lobule, while the central vein lies at its center.
Bile produced by hepatocytes is collected through progressively larger bile ducts, which merge to form the right and left hepatic ducts. These unite to form the common hepatic duct. The biliary system then joins the pancreatic duct, and their secretions enter the duodenum.
Before reaching the intestine, bile is temporarily stored and concentrated in the **Gallbladder**. The wall of the gallbladder contains smooth muscle. When the gallbladder relaxes, intraluminal pressure decreases, allowing bile to flow into it from the biliary ducts.
After a meal, the gallbladder contracts, expelling stored bile into the duct system and then into the duodenum.
Therefore, the release of bile into the intestine is primarily regulated by controlling gallbladder activity, specifically its relaxation and contraction.



Histology of the Liver, Fig# 24.19a-b

bilirubin

Bilirubin (by bacterial action) → urobilinogen → reabsorbed and secreted in urine (urobilin).

Or in feces →stercobilin.

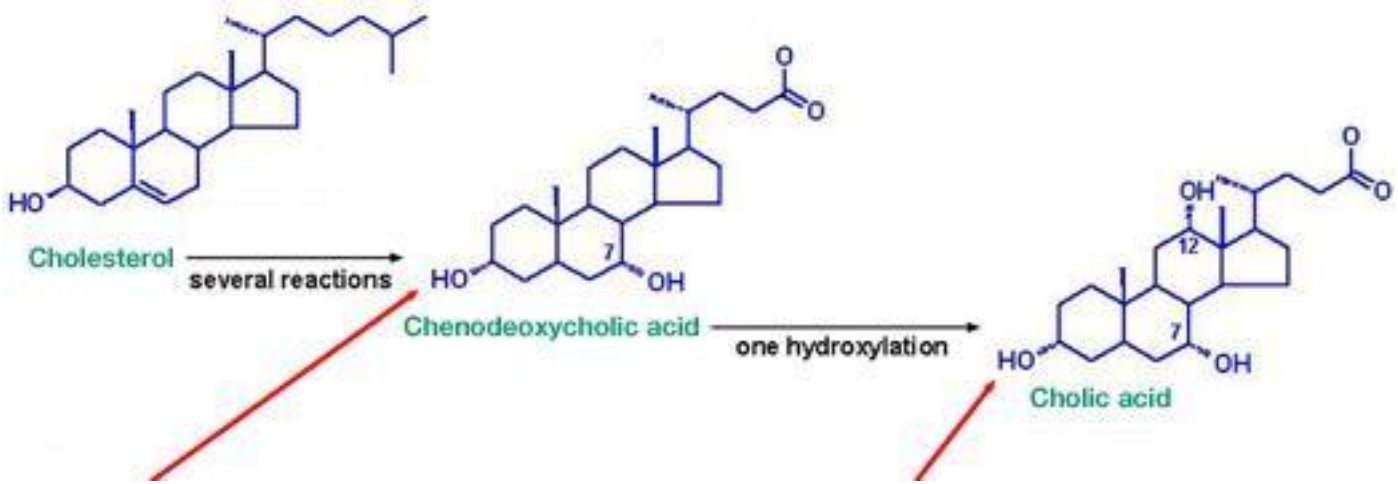
Jaundice is cause by large quantity of bilirubin in the extracellular space.

Bile formation

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

-Synthesized as primary bile acids from cholesterol (*cholic* and *chenodeoxycholic acid*)

Bile salts



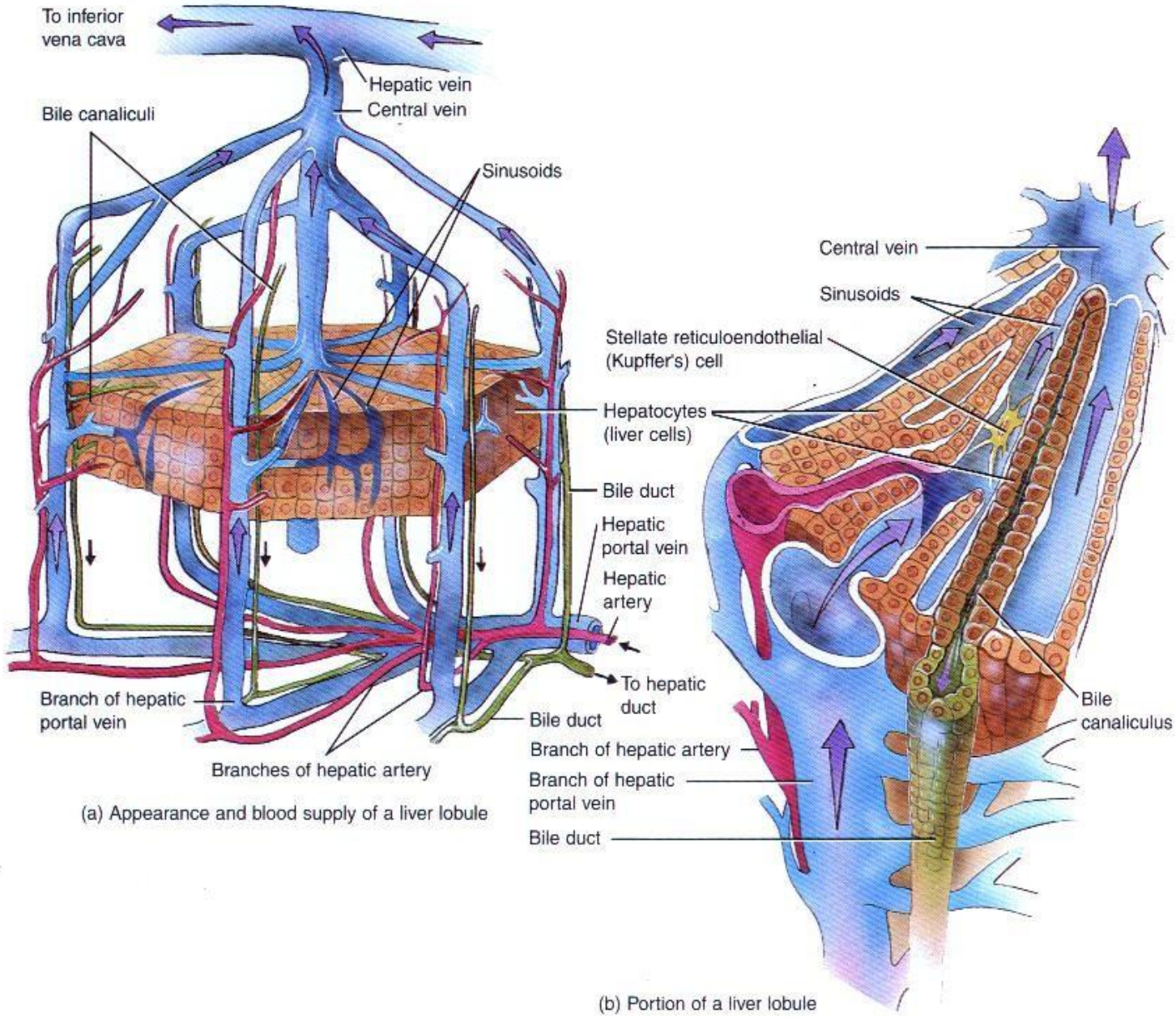
Bile acids → Conjugated to Glycine or Taurine→ Bile salts

Conjugation is important because it increases the water-soluble (hydrophilic) portion of the molecule, making it more **amphipathic**—that is, possessing both hydrophilic and hydrophobic regions.
Cholesterol itself is largely hydrophobic and poorly soluble in water. After conversion to bile acids and conjugation, the resulting bile salts become more effective amphipathic molecules, which enables them to function efficiently in lipid digestion and emulsification.

Bile

- Between meals, bile →gallbladder where it is stored. The epithelium of the gallbladder removes water and electrolytes → 5-20 fold concentration of bile.

Explanation:
In the **Gallbladder**, bile undergoes a concentration process during storage.
The constituents of bile may become concentrated approximately **5 to 20 times** compared with freshly secreted hepatic bile.
Therefore, the composition of bile secreted directly from the liver differs from that of bile stored in the gallbladder.
Concentration occurs mainly through the absorption of **water and electrolytes** by the gallbladder epithelium. As water is removed, the remaining bile components become more concentrated.



Histology of the Liver, Fig# 24.19a-b

Hepatic Lobule—Blood and Bile Paths

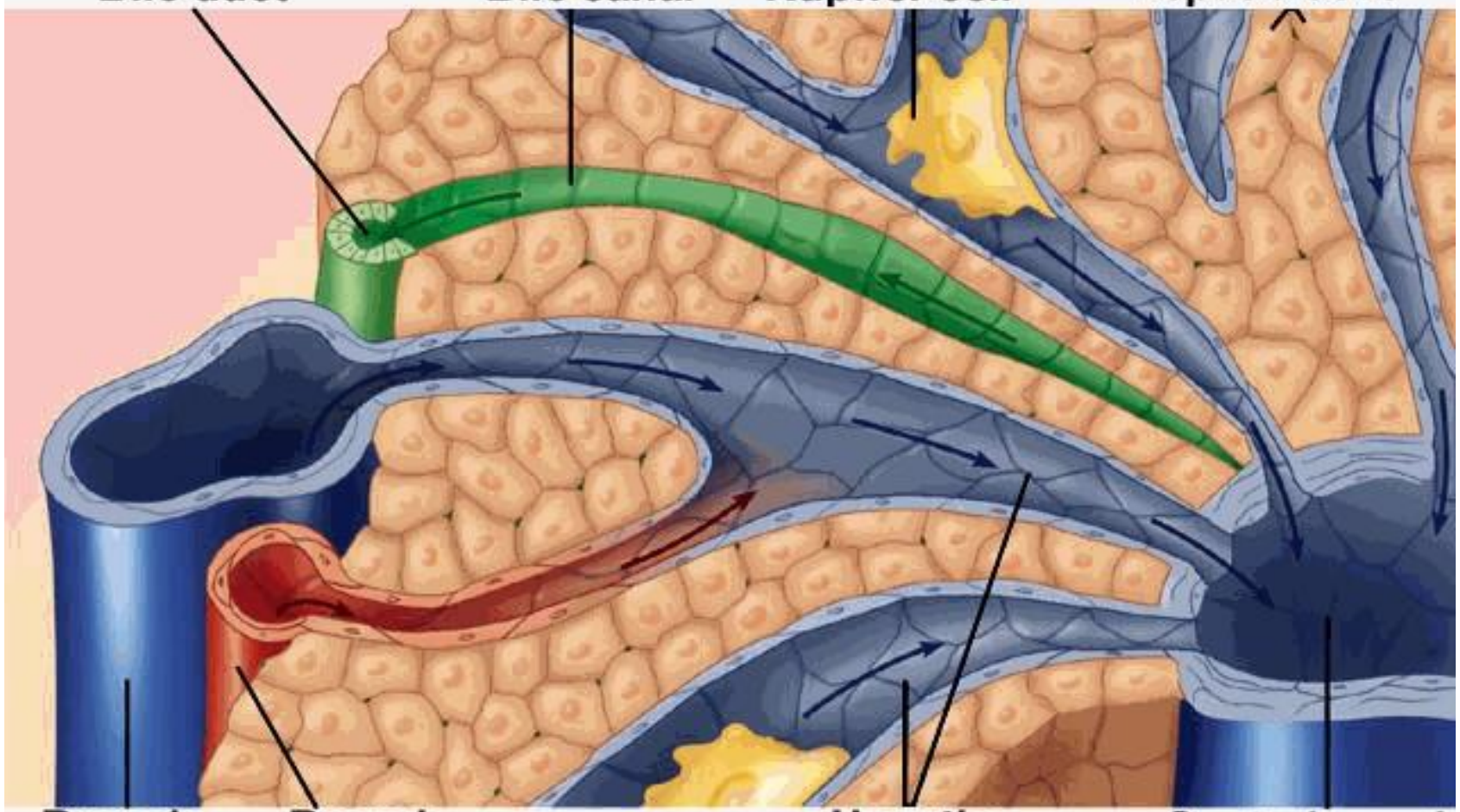
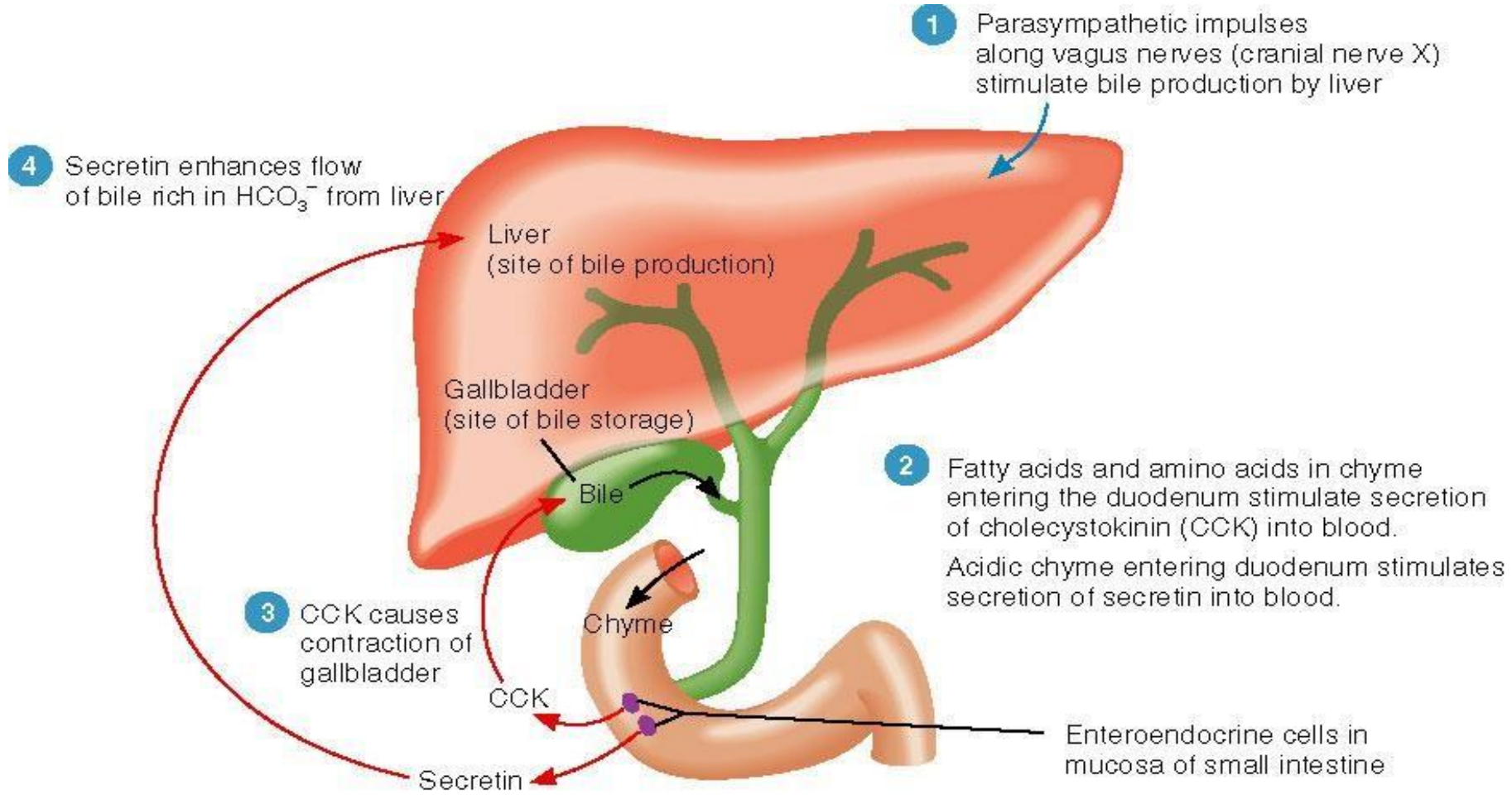
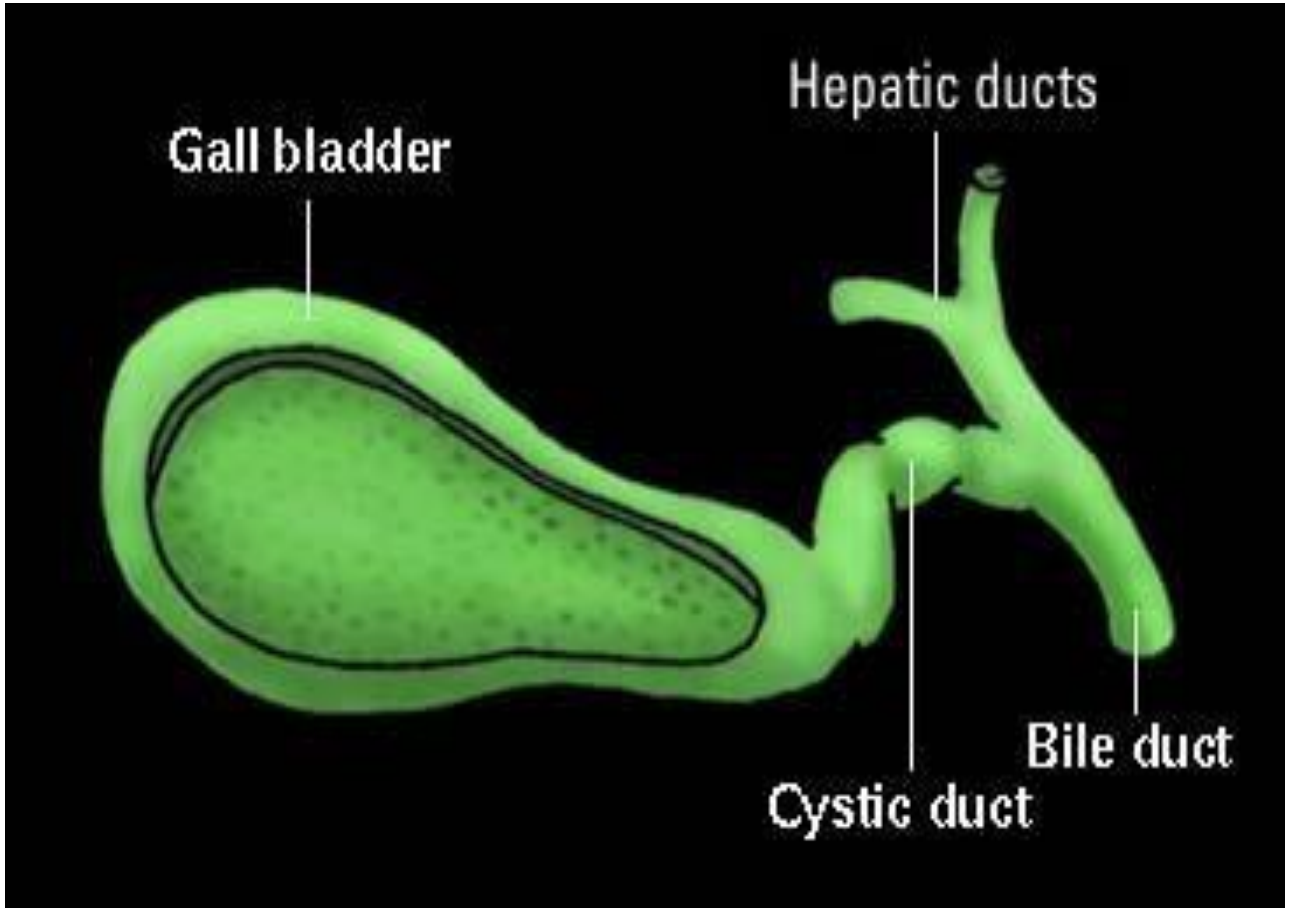


Fig. 24.21



24.21

The **Gallbladder** normally has a characteristic anatomical shape, but it is susceptible to several diseases. One common disorder is the formation of **gallstones**.
A major factor in gallstone formation is **reduced gallbladder motility (hypomotility)**. When gallbladder emptying is impaired, bile remains stored for prolonged periods and is not completely evacuated during contraction. Bile stasis promotes precipitation of its constituents, leading to stone formation.
Structural abnormalities or deformities of the gallbladder may also impair its motility and increase the risk of gallstones.
Inflammation of the gallbladder (**cholecystitis**) is also associated with gallstones. In some cases, stones may lead to inflammation, while in others inflammation may contribute to impaired motility and subsequent stone formation. Thus, the relationship between gallstones and inflammation may be bidirectional.



The composition of bile secreted directly from the liver differs from that of bile released from the **Gallbladder**, because bile becomes concentrated during storage in the gallbladder.
As a result, some bile constituents may increase approximately five fold, whereas others may become concentrated up to twentyfold. Exact numerical values are less important than understanding that gallbladder bile is significantly more concentrated than hepatic bile.

	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
Chlolesterol	0.1 gm/dl	0.3 to 0.9 gm/dl
Fatty Acids	0.12 gm/dl	03 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

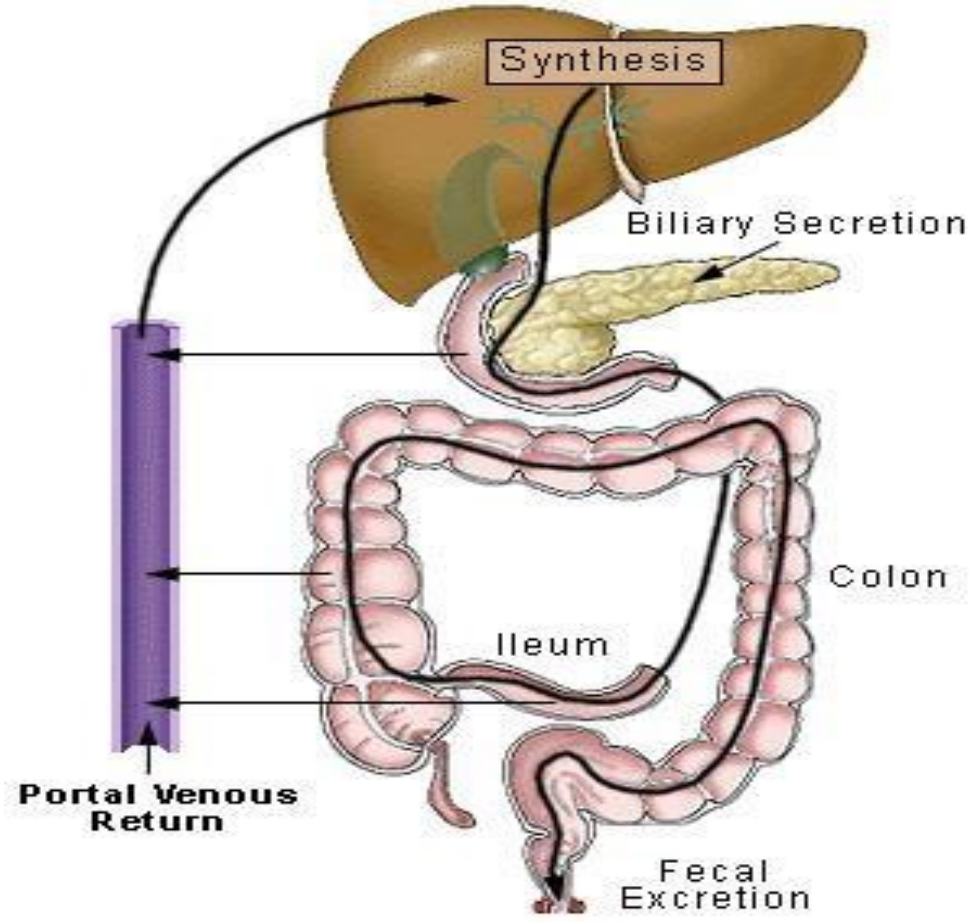
Enterohepatic circulation

After bile salts perform their role in lipid digestion, most are not lost from the body. Instead, they are reabsorbed in the intestine and returned to the liver through the **portal vein**, where hepatocytes take them up and resecrete them into bile. This recycling process is known as the **enterohepatic circulation**.

More than 80% of secreted bile salts are normally recovered and reused. A smaller proportion is lost in the feces, partly because of intestinal modifications, particularly in the colon; however, **the doctor will not ask about these modifications**.

The liver compensates for these losses by synthesizing new bile salts from cholesterol, a process known as **de novo synthesis**.

Drugs that reduce intestinal reabsorption of bile salts can help lower blood cholesterol levels. By preventing bile salt reabsorption, the liver is forced to use more cholesterol to synthesize new bile salts, thereby reducing circulating cholesterol.



Modification in the intestine

- Modified to secondary bile acid:

- Cholic acid → deoxycholic acid. Chenodeoxycholic acid → lithocholic acid

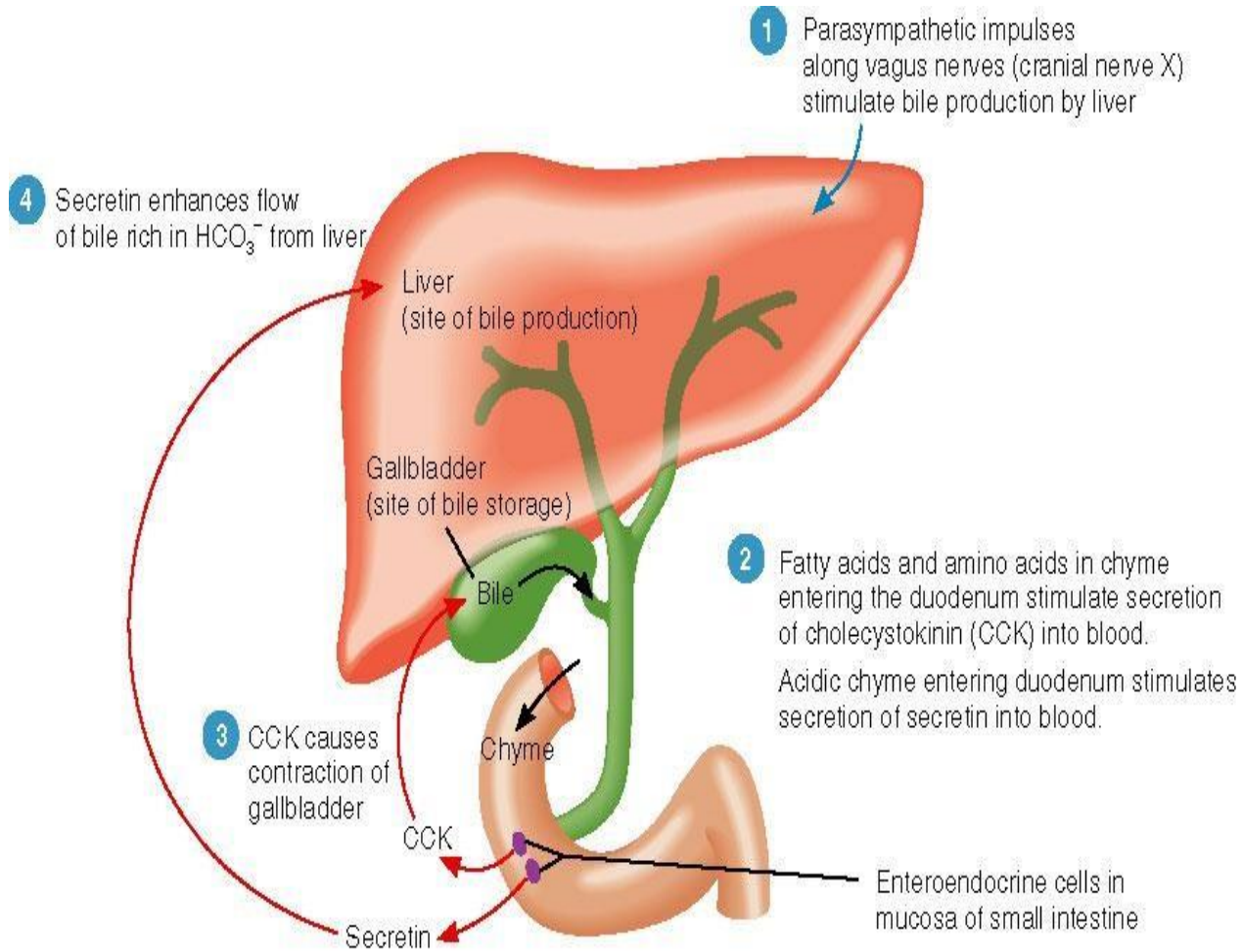
Fig. 24.21

Bile secretion into the intestine is regulated mainly by controlling **gallbladder activity**, particularly its contraction and relaxation. This regulation involves both neural and hormonal mechanisms. The **autonomic nervous system** contributes to gallbladder contraction through reflex pathways, thereby promoting bile release.

The principal hormonal regulator is **Cholecystokinin (CCK)**, whose major action in this context is to stimulate contraction of the gallbladder and promote bile secretion.

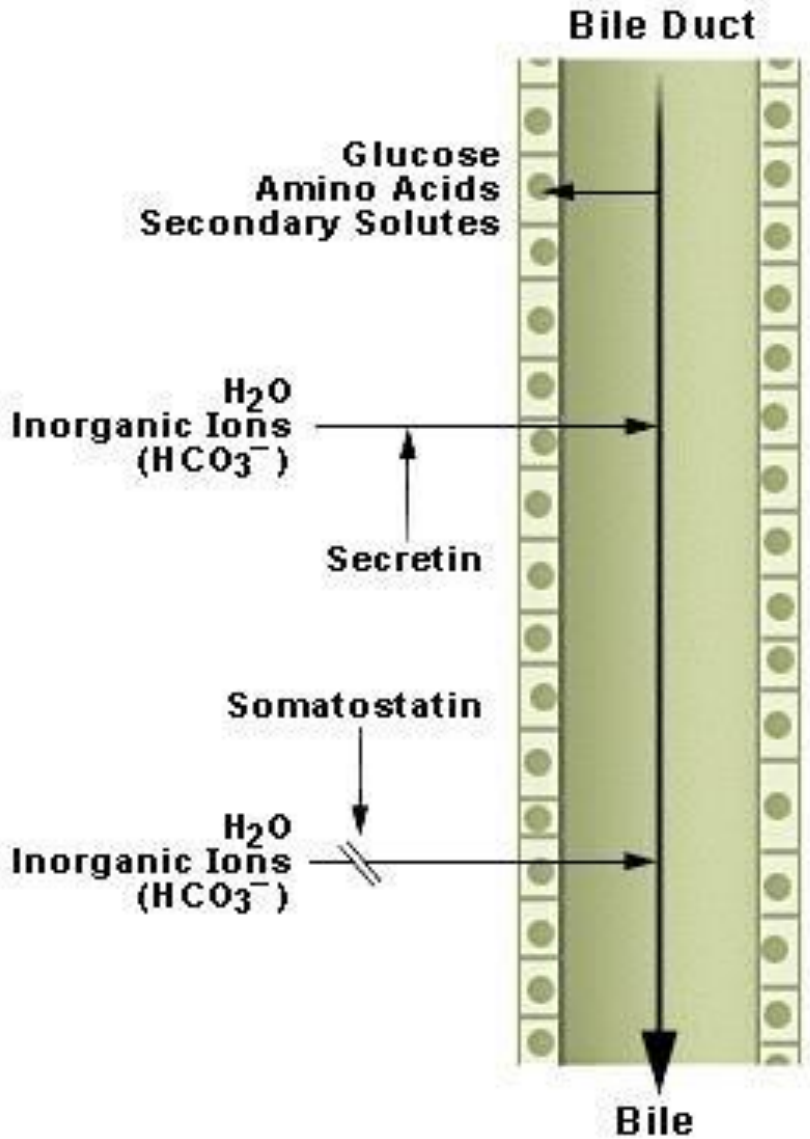
CCK is released when chyme enters the **Duodenum**, especially when the intestinal contents are rich in fats. Fat in the duodenum stimulates intestinal endocrine cells to secrete CCK.

Once released, CCK causes gallbladder contraction, leading to the expulsion of bile into the intestine. Although CCK has several physiological functions, its key role here is the regulation of bile release.



24.21

Biliary secretion is also regulated at the level of the **bile duct cells** (cholangiocytes), which modify bile as it passes through the duct system.
The main hormonal stimulant of these duct cells is **Secretin**. Secretin promotes the secretion of water and electrolytes, particularly bicarbonate-rich fluid, into the bile ducts, thereby increasing bile volume and altering its composition.
Some literature also describes an inhibitory effect of **Somatostatin**, which can suppress the activity of bile duct cells. However, somatostatin is not considered the primary regulator of this process.
Therefore, secretin is the principal hormone involved in stimulating bile duct secretion.



DR.'S HANDOUT

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.

-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.

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

-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:

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.

> ***Note:*** The final composition varies with the rate of secretion.
> *At high rates: HCO_3^- is high and Cl^- is low.
> *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**.

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.

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.

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.

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.

رسالة من الفريق العلمي:

ولعلّني رغم احتياجي أنطَوي
وألوذُ بالصَّلَواتِ والخَلَواتِ

النَّاسُ تهجُرُني لعيبٍ واحدٍ
واللهُ يقبَلُني على عِلّاتي

نسّقتُ ألفَ قصيدةٍ في فَهمِهم
واللهُ يعرِفُني بغيرِ لُغَاتِ

النَّاسُ عن وَجَعِي ستُغمِضُ عَينَها
واللهُ داوى مَوجِعِي بِأَنَاةٍ

في قُربِه كلُّ المَخاوفِ تنجَلِي
في حُبِّه أحبَبتُ حتمًا ذاتي

بليغةٌ هي الأبياتُ هذه، فكم قد سبقَ وأُسيءَ فَهمُك؟ بل كم مرّةً لاقيتَ مِن العِبادِ جفوةً ونُفرةً مُستقاةً مِن إساءةِ ظنٍّ أو فَهمٍ أو ما شابه؟ كم قد أوضحتَ وشرحتَ وفنّدتَ وبرَّرتَ ولم ينلْكَ بعد ذا كُلِّه إلّا الصُّدودُ وصفعُ الأبوابِ وشجُّ الفؤادِ؟ كم مرّةً أُلقِيَ بمناقِبِكَ كُلِّها عَرَضَ الحائطِ لمثلبةٍ واحدةٍ، بل لِهَفوةٍ ما تعمّدتَ إتيانَها حتّى وإن تُبتَ منها وعنها أقلعتَ؟ عُدَّ إن كُنتَ عادًّا، وأحصِ إن كُنتَ مُحصِيًا، هذا إن استعطتَ إلى ذلك سبيلًا؛ فهذي من نقائصِ نُفوسِنا وعيوبِها - لا غَرَوَ علينا تزكيتها وإن كنّا لن نصلَ إلى درجة الكمال فهي لله - الّتي تنزّه عنها ربُّنا جلّ في عُلاه، سُبحانَكَ اللّهُمَّ، أنّى يكونُ لكَ شَريكٌ في كمالِكَ وكَرَمِ عَفوِكَ، الحمدُ لكَ أنْ لم تترُكنا رُعاعًا نرتجي رحمةً ورِضًا مِن لَدُن لئيمِ طِباعٍ أو قاسي قلبٍ،

الحمدُ للهِ أنَّ اللهَ هُوَ اللهُ..

لا تنسَونا مِن صالحِ دُعائِكُم

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V1 → V2			