GIS

HISTOLOGY

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This sheet is about the histology of large intestine, Appendix, liver, gallbladder and pancreas.

Large intestine

As we all know, the large intestine consists of the cecum, appendix, ascending colon, transverse colon, descending colon, rectum, and anal canal. its main functions are absorption of water, formation of the fecal mass, and production of mucus.

So, we expect the intestinal glands to be long and have a great abundance of goblet and absorptive cells and a small number of enteroendocrine cells.

>> while the main function of the small intestine is absorption of nutritive materials and secretion

-- Remember that the absorption of water is passive, following active transport of sodium out of the basal surfaces of the epithelial cells.

Same as esophagus, stomach and small intestine, intestinal wall is composed of the following layers (from the inner surface outward):

1- Mucosa (mucosal membrane)

which is composed of 3 layers:

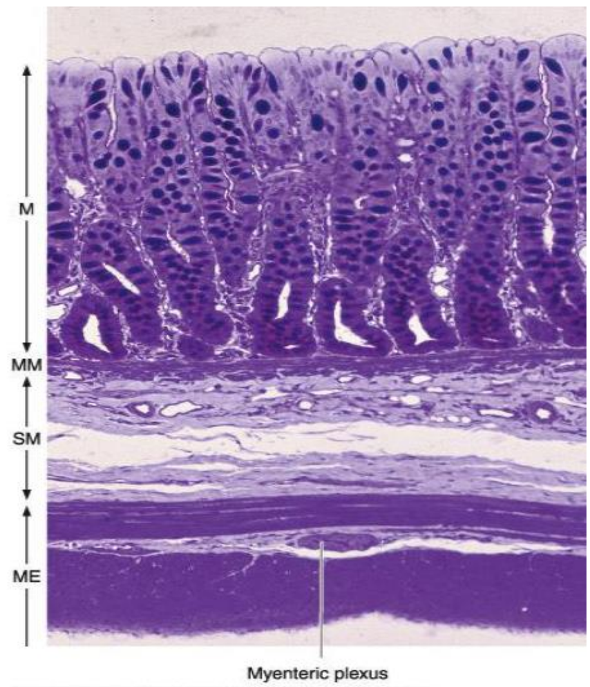
- **Lining epithelium:**

the lining epithelium is simple columnar with 'numerous' goblet cells.

=> the absorptive cells are columnar and have short, irregular microvilli.

=> there are no villi in the large intestine.

=> goblet cells are present in the surface and in the glands of Lieberkühn.



All layers of large intestine

- **Lamina propria:**

which is loose connective tissue containing small glands. it is rich in lymphoid cells and nodules that frequently extend into the submucosa. this makes sense because of the abundant bacterial population of the large intestine.

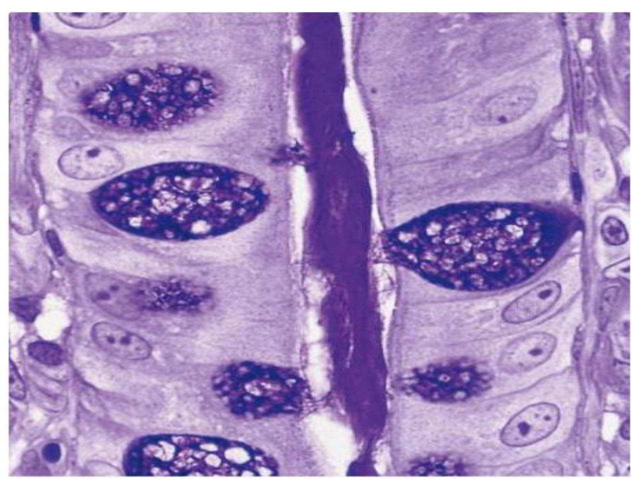
- **Musclaris mucosa:**

a thin layer of smooth muscle

notes:

=> the mucosal membrane of the large intestine has no folds except in its distal [rectal] portion.

=> the mucus is highly hydrated gel that not only lubricate the intestinal surface but also covers bacteria and particulate matter.



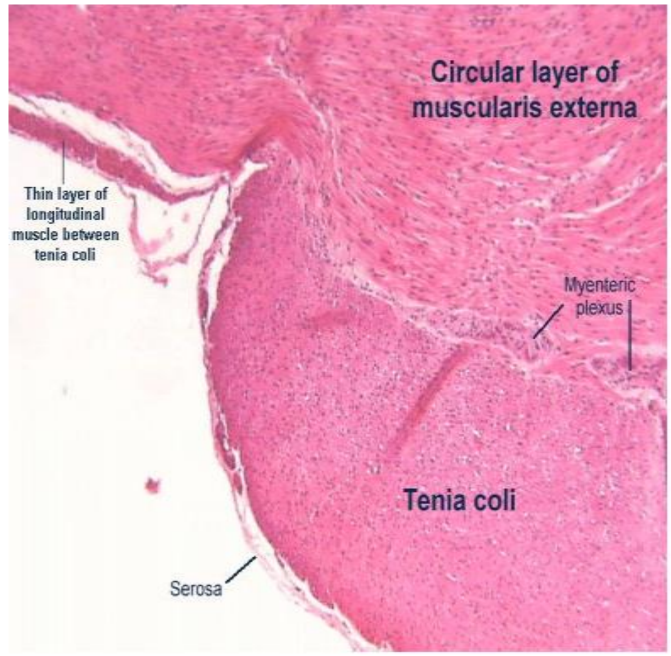
Notice the mucus and the cells producing it

1- **Submucosa:**

contains denser connective tissue with larger blood and lymph vessels.
<u>There is no glands in the submucosa of large intestine.</u>

>> Remember that only duodenum in the small intestine contains Brunner's glands in its submucosa.

2- **Muscularis externa** is composed of smooth muscle cells organized as two sub layers inner circular and outer longitudinal as well as myenteric (Auerbach's) nerve plexus between them. This layer differs from that of the small intestine, because outer longitudinal layer of muscularis of the colon is subdivided into three thickened bands of smooth muscle called **teniae coli**.



>>remember that: tinea coli present throughout the large intestine
except in the appendix and the rectum, the tinea coli of the cecum only reaches to the base of the appendix.

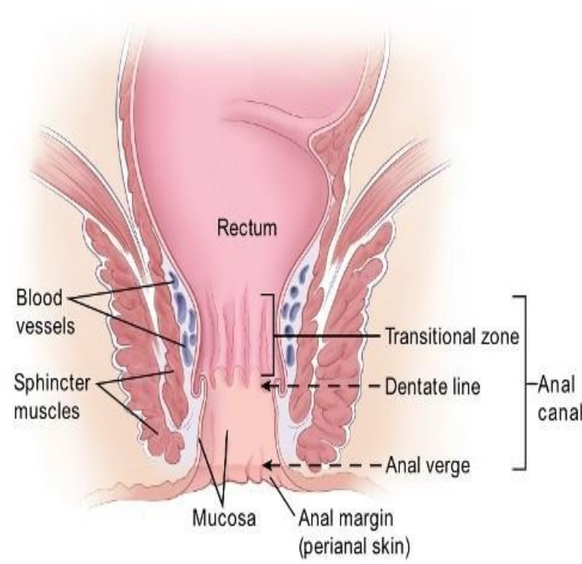
3- **Serosa / Adventitia**:

>> Intraperitoneal organs are covered in serosa (i.e. transverse colon). while retroperitoneal organs are covered in adventitia (i.e. ascending and descending colon) except the anterior wall of these organs because the peritoneum covers their anterior wall.
in the intraperitoneal portions of the colon, the serous layer is characterized by small, pendulous protuberances composed of adipose tissue—the **appendices epiploicae**

>> appendices epiploicae (tags of fat) are small pouches of the peritoneum or extensions from serosa filled with fat and situated along the colon. This aggregation of fat is important for energy.

We said that the mucosal membrane of large intestine has no fold except its distal [rectal] portion and that's because:

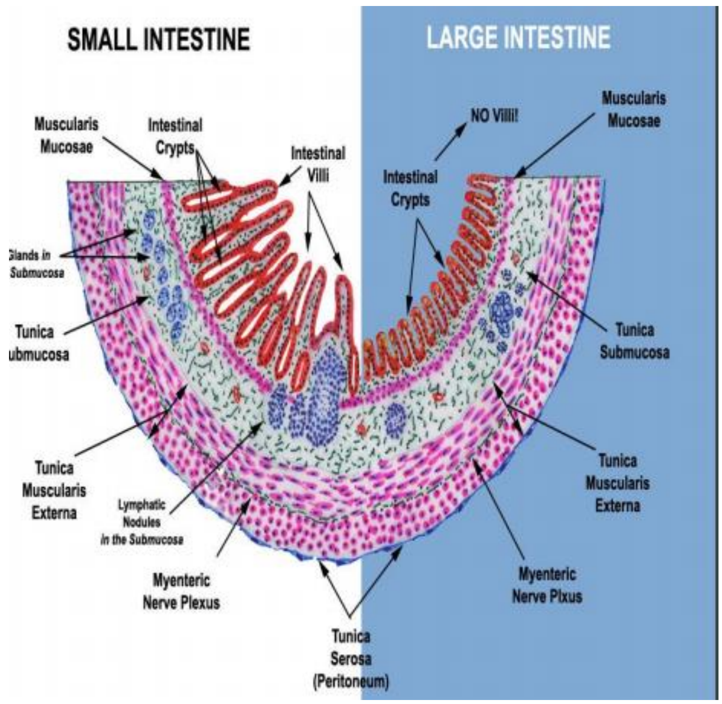
- In the anal region, the mucous membrane forms a series of longitudinal folds, **the rectal columns of Morgagni**



- **These columns connect to the anal orifice to form the anal valves and sinuses**.
- About 2 cm above the anal opening, the intestinal mucosa is replaced by stratified squamous epithelium
- In this region, the lamina propria contains a plexus of large veins that, when excessively dilated and varicose, produces haemorrhoids.
- The muscularis layer gives rise to the anal sphincter
- The adventitia layer connects the anal canal to the surrounding structures

>> extra note: Haemorrhoids are piles in the anal canal. these haemorrhoids go out from the anal canal and might cause bleeding.

Now let's look at the differences between small intestine and large intestine



- In the large intestine the mucosal membrane with **no folds** except in rectum because the mucosa of rectum in the anal canal forms several longitudinal folds called the rectal [anal] columns.
- The mucosa of large intestine appears smooth comparable to mucosa of small intestine with distinct projections.
- Mucosa is thicker in large intestine and contains crypts
- No villi present in large intestine, while small intestine has finger like projections to increase surface area for absorption. Instead, large intestine has a very short projections called microvilli.
- **Intestinal glands of large intestine (also called crypts of Lieberkühn):**
  - **-Enteroendocrine cells:** numerous in small intestine, few in large intestine.
  - **-Paneth cells:** located in the basal portion of small intestinal glands, they are absent in large intestine.
  - **-Goblet cells:** present in the lining of epithelium in mucosa and glands, more numerous in large intestine than in small intestine because one of the functions of large intestines is formation of feces, so we have these glands numerous here to further lubricate the feces.

  These are simple tubular glands. (Epithelial lined tubules open on the apical surface).
- Muscularis mucosae is well developed in the large intestine (two or three bands of smooth muscle are obviously seen), while it is undefined in small intestine

Additional differences:

	Large intestine	**Small intestine**
The crypts of Lieberkühn	All are simple tubular. It has enteroendocrine cells, stem cells and mucous cell (MOST)	Simple or branched tubular. It has Paneth cells (in the base), enteroendocrine cells, stem cells and mucous cell.
The sub-mucosa	filled with lymphatics in the form of lymphatic nodules called the solitary lymphatic nodules (single in the sub-mucosa).	the ileum had the highest concentration of lymphatics in the Payer's patches
The muscularis mucosa	well defined(developed)	ill-defined
Digestion	No role in digestion, just absorption of water	complicated

Extra note [not in slides]:
After the anal valves and the end of the rectal [anal] columns, the epithelium changes (the anal canal begins) and there is an important landmark around this region that divides the anal canal:
Separated by pectinate line into:
Anal canal (upper 2CM endothelium): simple columnar with goblet cells epithelium. (innervated by **ANS**, for stretching only)
Anal canal (lower 2CM ectodermal) stratified squamous non-keratinized epithelium. (innervated by **S4**, sensitive for pain, temperature and touch)
To summarize:
*Anal orifice: stratified squamous keratinized (skin) with hair follicles and sebaceous glands.
*Rectum: simple columnar epithelium with goblet cells

Appendix

- ✓ As we know, the appendix is present in the GI tract, but it has no known role in digestion. It is filled with lymphatic nodules and, therefore, it is a lymphatic organ. The lumen of the appendix is very narrow and that's why in appendicitis, inflammation and edema, the lumen becomes closed which increases the chance of the rupture of the appendix and causes peritonitis which is a serious condition (that's why the treatment is appendectomy).
- ✓ **The lining epithelium of appendix is simple columnar epithelium with few goblet cells** (the appendix does not form feces, therefore, it doesn't need numerous goblet cells). **In the lamina propria there are crypts of Lieberkühn that are also few.**

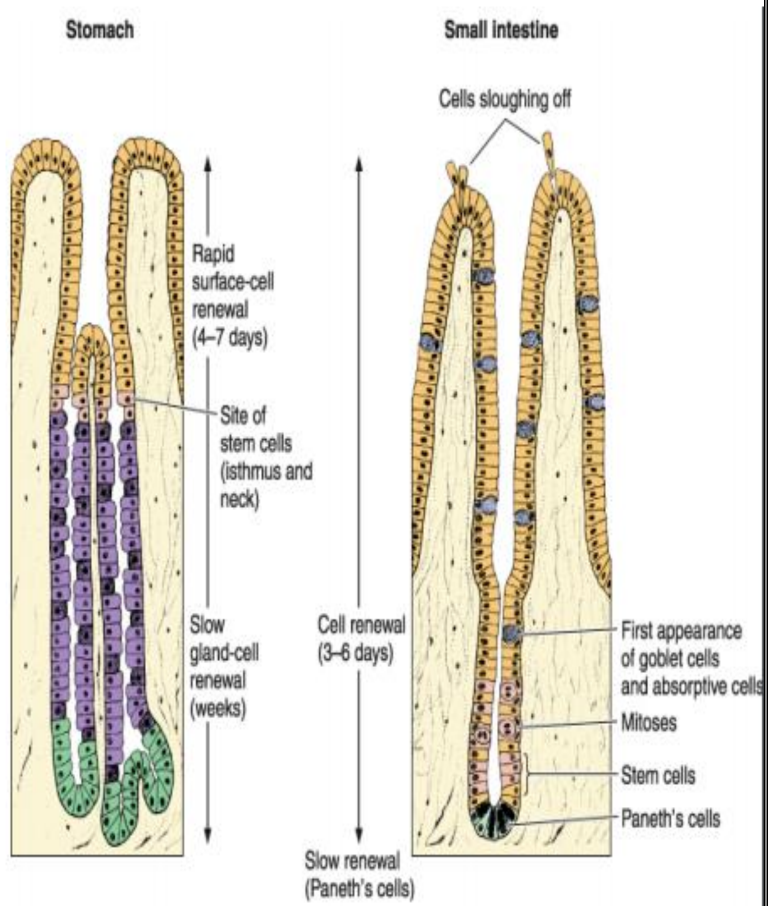
- ➢ The appendix is an evagination of the cecum characterized by a relatively small, narrow, and irregular lumen, caused by the presence of abundant lymphoid follicles in its wall, that form a circular layer in the mucosa and may infiltrate the submucosa.
- ➢ Although its general structure is similar to that of the large intestine (same epithelium), it contains fewer and shorter intestinal glands and has no teniae coli.
- ➢ The muscularis externa of the appendix is usual with an inner circular layer and an outer longitudinal layer. The appendix is covered entirely by serosa (mesoappendix), which is a

two-layered peritoneum that has fats, lymph nodes and appendicular artery (the appendicular artery is a branch of the posterior cecal artery which is a branch of the ileocecal artery which is a branch of the superior mesenteric artery) and vein.. the appendix is part of the midgut.

- **Clinical case:** The appendix is a lymphatic organ and it is important in the immunity of children, but if there was a necessity for appendectomy, we perform it and other lymphatic organs take over the appendix's role in immunity.
  in many abdominal surgeries (other than appendectomy) the appendix is removed even when the appendix is normal especially if the doctor expects appendicitis to occur in the future and the patient is informed after the surgery.
- There are no Paneth cells in the appendix.

Cell Renewal in the Gastrointestinal Tract

- The epithelial cells of the entire gastrointestinal tract are constantly being cast off and replaced with new ones formed through mitosis of stem cells.
- **These stem cells are in** the basal layer of the esophageal epithelium, the neck of gastric glands, the lower half of the intestinal glands and the bottom third of the crypts of the large intestine.
- From this proliferative zone in each region, cells move to the maturation area, where they undergo structural and enzymatic maturation, providing the functional cell population of each region.
- In the small intestine the cells die by apoptosis in the tip of the villi or are sloughed off by mechanical action during function.



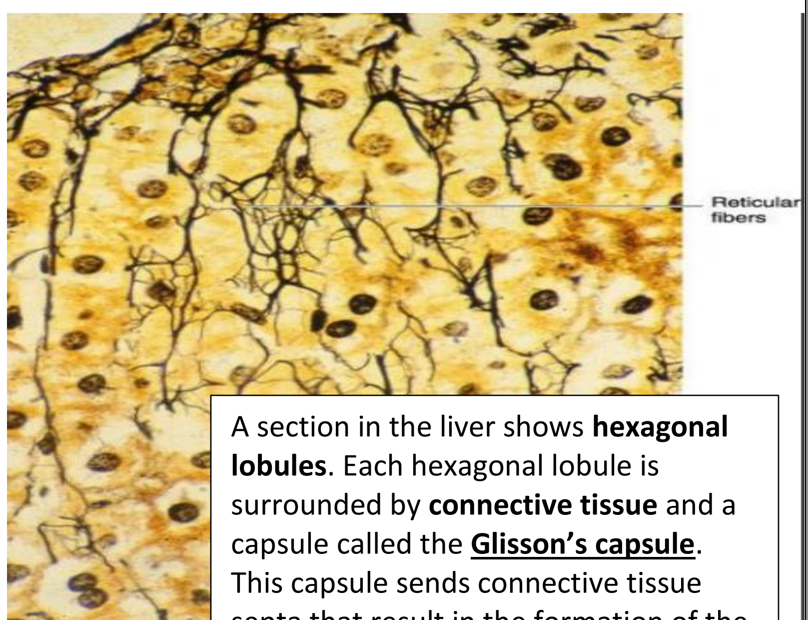
The cells in the intestines have a certain lifespan especially those that are at the surface as they are constantly getting sloughed and, therefore, the stem cells, which are present at the base of the epithelium in the small intestine and in the middle of the stomach, are of great importance. 3-6 days are needed for the stem cells to replace sloughing cells in the small intestine while 4-7 days are needed in the stomach.

The Liver

- The liver is the second-largest organ of the body (the largest is the skin) and the largest gland, weighing about 1.5 kg.
- The liver is the organ in which nutrients absorbed in the digestive tract are processed and stored for use by other parts of the body => It is thus an interface between the digestive system and the blood.
- Most of its blood **(70-80%)** comes from **the portal vein**, arising from the stomach, intestines, and spleen; the smaller percentage **(20-30%)** is supplied by **the hepatic artery.**
- **All the materials** absorbed via the intestines **reach the liver through the portal vein**, **except the complex lipids** (chylomicrons), which are **transported mainly by lymph vessels.**
- The position of the liver in the circulatory system is optimal for gathering, transforming, and accumulating metabolites and for neutralizing and eliminating **toxic substances**.
- Elimination occurs in the bile, an exocrine secretion of the liver that is important for lipid digestion.
- The liver also has the very important function of **producing plasma proteins**, such as albumin, other carrier proteins, **coagulation factors, and growth factors**.
- To summarize: The liver is a major player in the metabolism of carbohydrates, fats and proteins. It also functions in the formation of enzymes and hormones. The liver is important in blood coagulation and in detoxification. The liver stores glycogen.

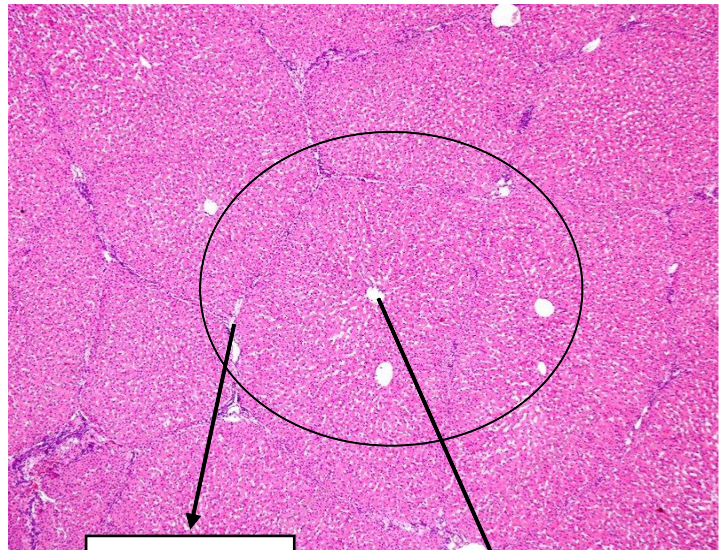
Let's now talk about the histology of the liver:

- Starting from outside, the liver is covered by a thin connective tissue capsule (Glisson's capsule) and this capsule becomes thicker at the hilum, where the portal vein and the hepatic artery enter the organ and where the right and left hepatic ducts and lymphatics exit.
- Also, these vessels and ducts are surrounded by connective tissue all the way to their termination (or origin) in the portal spaces between the liver lobules. [we will talk about spaces and lobules in details]
- At the termination point, a delicate reticular fiber network that supports the hepatocytes and sinusoidal endothelial cells of the liver lobules is formed. [we will talk about hepatocytes and sinusoidal endothelial cells in details]



A section in the liver shows **hexagonal lobules**. Each hexagonal lobule is surrounded by **connective tissue** and a capsule called the **Glisson's capsule**. This capsule sends connective tissue septa that result in the formation of the **lobules.**

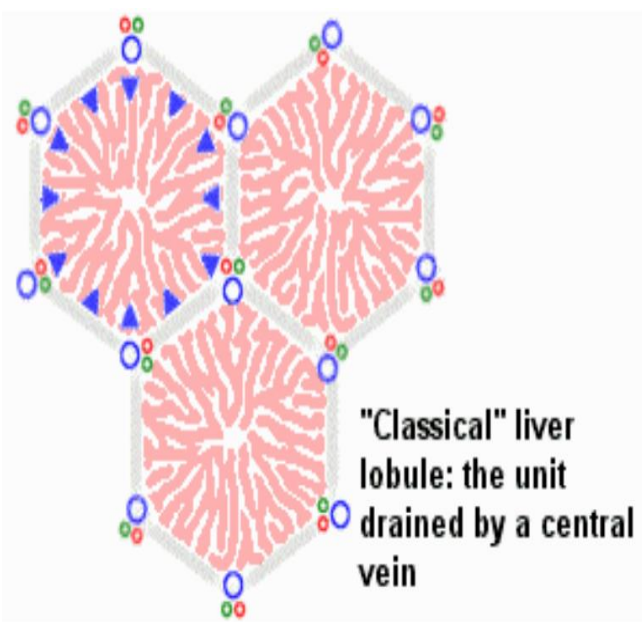
- Inside the liver, the basic structural component is the liver cell, or **hepatocyte.**
  These cells are not arranged haphazardly, they are grouped in interconnected plates and they constitute two-thirds of the mass of the liver.
- In light-microscope sections, structural units called **liver lobules** can be seen [see the picture to the right]
- The liver lobule is formed of a polygonal mass of tissue about 0.7 x 2 mm in size
- with **portal spaces** at the periphery
- and with a vein, called **the central or Centrilobular vein**, in the center



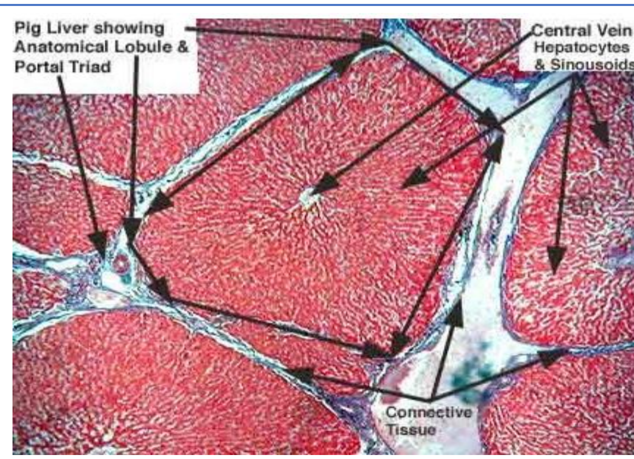
<u>what are the portal spaces?</u>

- regions located in the corners of the lobules, contain connective tissue, bile ducts, lymphatics, nerves, and blood vessels.
- The human liver contains three to six portal spaces <u>per lobule</u>, each with:

1- A venule [branch of **portal vein**]: it contains blood coming from the **superior and inferior mesenteric and splenic veins**, and it's the largest structure.
2- an arteriole (a branch of the hepatic artery): it contains oxygen-rich blood coming from **the celiac trunk of the abdominal aorta**
3- a duct (part of the bile duct system): lined by cuboidal epithelium, carries bile synthesized by the hepatocytes and eventually empties into the hepatic duct
4- lymphatic vessels



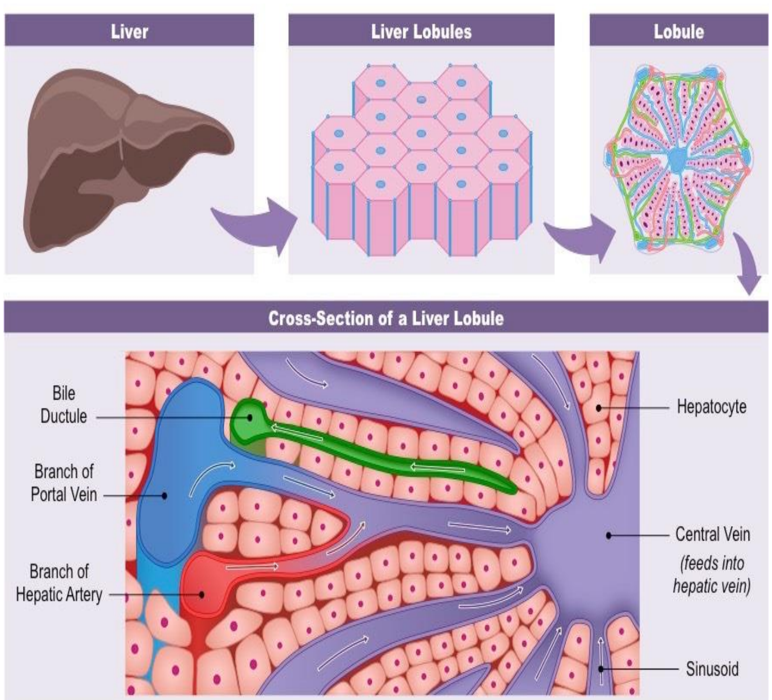
=> note: In certain animals (e.g. pigs), the lobules are separated by a layer of connective tissue
This is not the case in humans, where the lobules are in close contact along most of their length, making it difficult to establish the exact limits between different lobules.

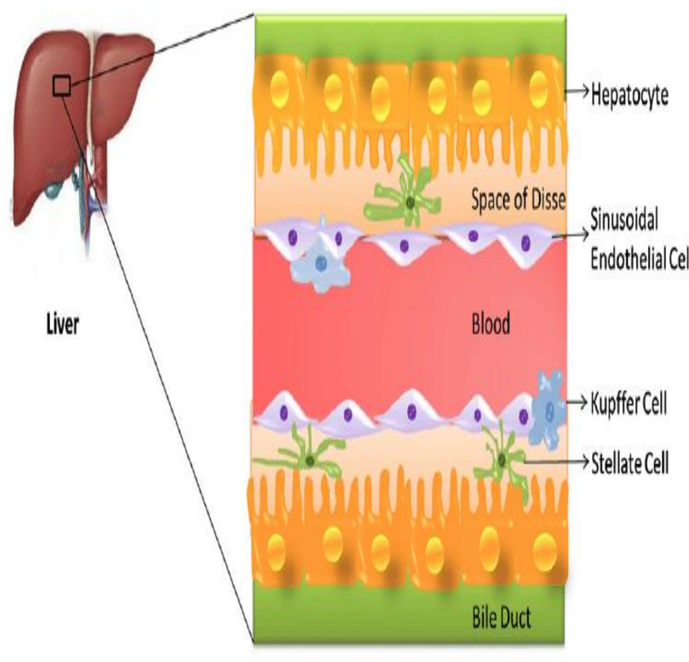


What are liver sinusoids?

- As we said, the hepatocytes in the liver lobule are radially disposed and are arranged like the bricks of a wall. These cellular plates are **directed from the periphery of the lobule to its center** and anastomose freely, forming a labyrinthine and sponge like structure. The space between these plates contains capillaries, **the liver sinusoids.**
- sinusoidal capillaries are irregularly dilated vessels composed solely of a **discontinuous layer of fenestrated endothelial cells.**
- The fenestrae are about 100 nm in diameter, have no diaphragm, and are grouped in clusters
- There are also spaces between the endothelial cells, which, together with the cellular fenestrae and a discontinuous basal lamina (depending on the species), give these vessels great permeability.

=> to explain these sentences furthermore, we mentioned that the portal spaces contain a venule which is a branch of the portal vein and an arteriole which is a branch of the hepatic artery. the content of these two structures should pass throughout the lobules to allow the absorption of nutritive materials from the venule to the hepatocytes and absorption of oxygen important for life from the arteriole to the hepatocytes. Accordingly, the plates of hepatocytes are separated by these spaces called liver sinusoids. [to summarize, liver sinusoids contain the content of the venule and arteriole]. These spaces aren't true spaces, they are capillaries lined by endothelium. What makes this endothelium so special, is that the cells are not adherent to each other, they are discontinuous. Also, the basal lamina is discontinuous giving the capillaries huge permeability. Notice that, after the process of absorption, the remnant blood [contains waste products] goes back to the central veins which will group together forming right and left hepatic veins that drain into the inferior vena cava.





Liver Sinusoidal Functional Unit

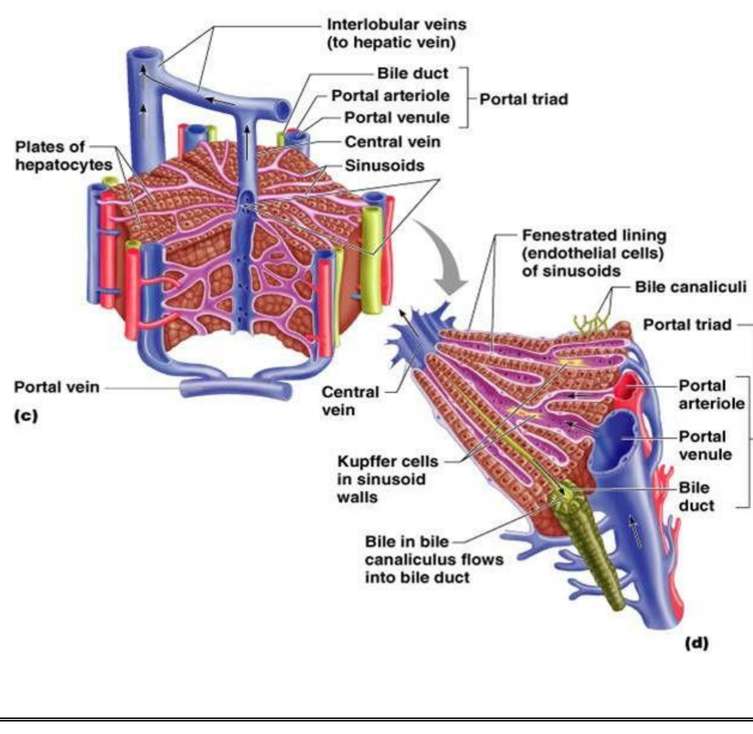
- The fenestrae and discontinuity of the endothelium allow the free flow of plasma but not of cellular elements into the space of Disse.
- Thus, permitting an easy exchange of molecules (including macromolecules) from the sinusoidal lumen to the hepatocytes and vice versa.
- Which allows the release of the large number of macromolecules (e.g. lipoproteins, albumin, fibrinogen) secreted into the blood by hepatocytes and it enables the liver to take up and catabolize many of these large molecules.

=> Refer to the previous picture, there is a subendothelial space known as **the space of Disse** separates the endothelial cells from the hepatocytes.
The basolateral side of the hepatocyte, which lines the space of Disse, contains many **microvilli** and demonstrates endocytic and pinocytic activity.

- The sinusoid is surrounded and supported by a delicate sheath of reticular fibers.
- In addition to the endothelial cells, the sinusoids contain macrophages known as **Kupffer cells.** These cells are found on the luminal surface of the endothelial cells, within the sinusoids. Their main functions are to **metabolize aged erythrocytes, digest haemoglobin, secrete proteins related to immunological processes, and destroy bacteria that eventually enter the portal blood through the large intestine.** Kupffer cells account for 15% of the liver cell population. Most of them are in the periportal region of the liver lobule, where they are very active in phagocytosis.
- In the space of Disse (perisinusoidal space), **fat-storing cells**, also called **stellate or Ito's cells**, contain **vitamin A rich lipid inclusions.** In the healthy liver, these cells have several functions, such as: 1- uptake, storage, and release of retinoids. 2- synthesis and secretion of several extracellular matrix proteins and proteoglycans. 3- secretion of growth factors and cytokines, and the regulation of the sinusoidal lumen diameter in response to different regulators (e.g., prostaglandins, thromboxane A2).

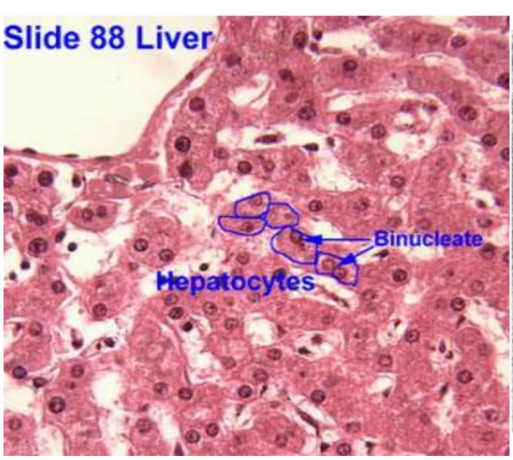
<u>What about the bile ducts?</u>

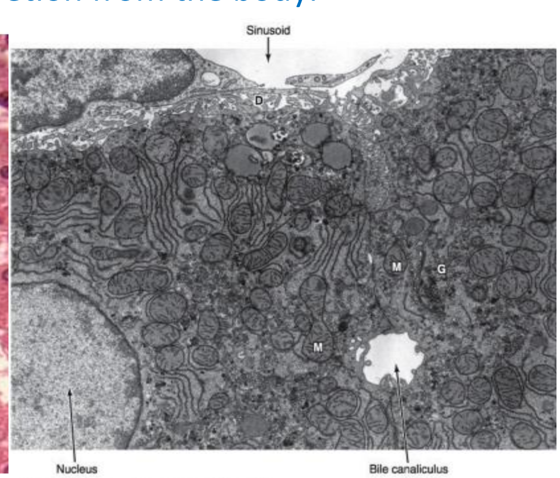
in the other side of the interconnected plates of hepatocytes, another space is formed for collecting the bile produced by hepatocytes, this space is known as bile canaliculus. The bile moves in the opposite direction of blood of the venule and arteriole, entering bile ductules present in the periphery, all bile ductules are going to group together forming right and left hepatic ducts, which unit forming common hepatic duct, that joins cystic duct forming common bile duct.

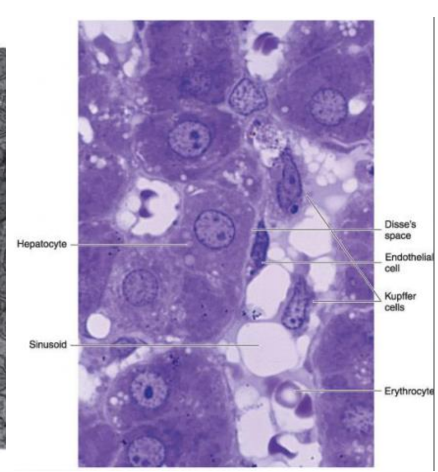


Additional notes about the hepatocytes and bile canaliculus:

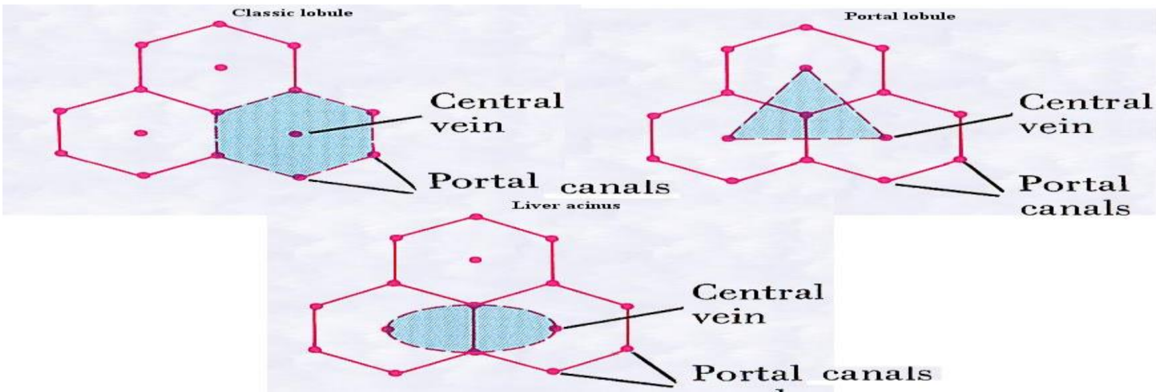
- Hepatocytes are polyhedral, with six or more surfaces, and have a diameter of 20-30 um
- the cytoplasm of the hepatocyte is eosinophilic, mainly because of the large number of mitochondria and some smooth endoplasmic reticulum
- Hepatocytes located at different distances from the portal spaces show differences in structural, histochemical, and biochemical characteristics
- The surface of each hepatocyte is in contact with the wall of the sinusoids, through the space of Disse, and with the surfaces of other hepatocytes
- Wherever two hepatocytes abut, they delimit a tubular space between them known as **the bile canaliculus**
- At the periphery, bile enters **the bile ductules**, or **Hering's canals** composed of cuboidal cells
- The canaliculi, the first portions of the bile duct system, are tubular spaces 12 um in diameter
- They are limited only by the plasma membranes of two hepatocytes and have a small number of microvilli in their interiors
- The cell membranes near these canaliculi are firmly joined by tight junctions
- Gap junctions are frequent between hepatocytes and are sites of intercellular communication
- The bile flow therefore progresses in a direction opposite to that of the blood, ie, from the center of the lobule to its periphery.
- The surface of the hepatocyte that faces the space of Disse contains many microvilli that protrude into that space, but there is always a space between them and the cells of the sinusoidal wall
- The hepatocyte has one or two rounded nuclei with one or two nucleoli, Some of the nuclei are polyploid
- In the hepatocyte, the rough endoplasmic reticulum forms aggregates dispersed in the cytoplasm; these are often called **basophilic bodies.** Several proteins (e.g. blood albumin, fibrinogen) are synthesized on polyribosomes in these structures
- the smooth endoplasmic reticulum is responsible for the processes of oxidation, methylation, and conjugation required for inactivation or detoxification of various substances before their excretion from the body.





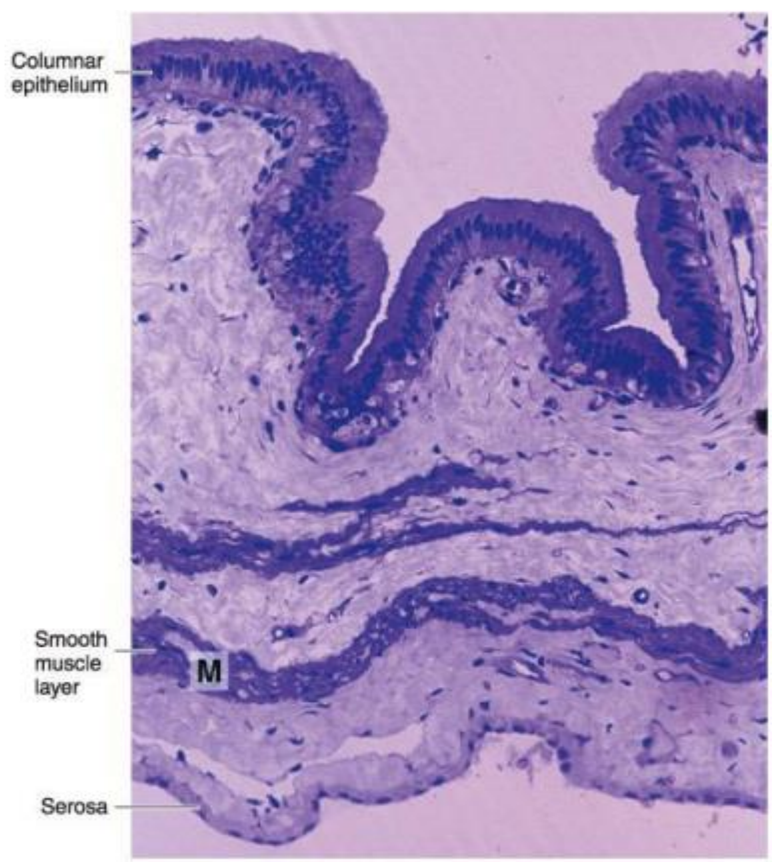


extra note [not in slides]:
There are three types of lobules: **the classical lobule** (the central vein is in the middle and the portal triads at the edges), **the portal lobule** (the portal triad is in the middle and at the edges are three central veins from three classical lobules, this shape emphasizes the bile flow) and the final form is **the acinus lobule** (has a diamond shape, formed at the edges by two central veins and two portal triads from two classical lobules, the axis between the portal triads has a higher amount of oxygen than the axis between the two central veins).



The gall bladder

=> The gallbladder is a hollow, pear-shaped organ attached to the lower surface of the liver, it concentrates bile (about 20 times) and its capacity is 30-50ml.
=> The bile coming from the liver goes to the duodenum, but it finds the sphincter of Oddi closed so it moves back, but towards the gallbladder, and there absorption of water occurs thereby concentrating the bile. [For efficient absorption of water, the mucosa has abundant foldings]
=> The wall of the gallbladder consists of a **mucosa composed of simple columnar epithelium and lamina propria**, **a layer of smooth muscle**, **a perimuscular connective tissue layer**, and a **serous membrane. [No muscularis mucosa or submucosa]**
=> The mucosa has abundant folds that are particularly evident when the gallbladder is empty
=> The epithelial cells are rich in mitochondria. All these cells are capable of secreting small amounts of mucus.
=> The muscularis externa is composed of irregular (oblique) smooth muscles with collagen and elastic fibers in between.



=> **Tubuloacinar mucous glands** near the cystic duct are responsible for the production of most of the mucus present in bile (**no goblet cells**).
=> The main function of the gallbladder is to store bile, concentrate it by absorbing its water, and release it when necessary into the digestive tract
=> Contraction of the smooth muscles of the gallbladder is induced by **cholecystokinin**, a hormone produced by enteroendocrine cells located in the epithelial lining of the small intestine. Release of cholecystokinin is, in turn, stimulated by the presence of dietary fats in the small intestine.
=> **No peristaltic movements.**

The gall-bladder is embedded in the liver, therefore, the exposed surfaces are covered by **serosa**, while the area that is directly attached to the liver is covered by **connective tissue** and receives direct blood supply from the liver and that's why no gangrene occurs in the gall-bladder (gangrene may occur in the appendix, but not in the gall-

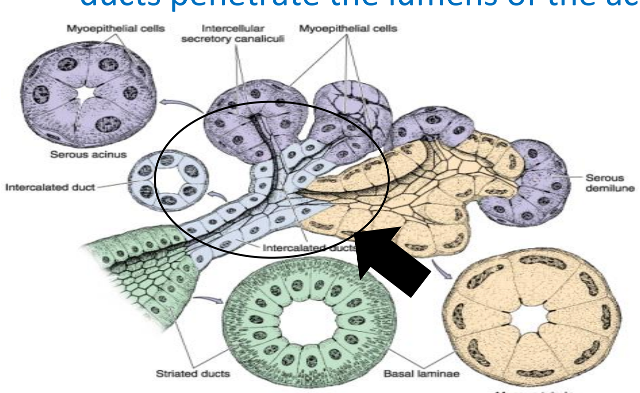
Pancreas

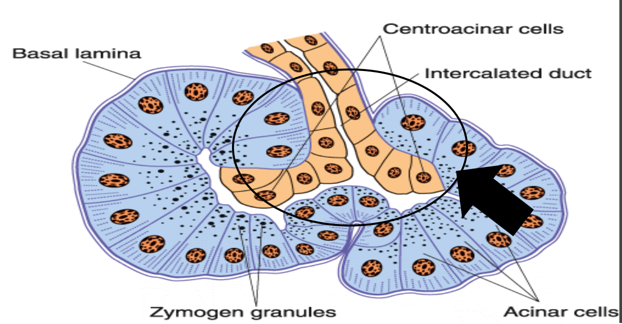
- The pancreas is a mixed exocrine-endocrine gland that produces digestive enzymes and hormones
- **The enzymes** are stored and released by cells of the **exocrine** portion, arranged in **acini**
- **The hormones** are synthesized in clusters of **endocrine** epithelial cells known as **islets of Langerhans**
- **The exocrine portion of the pancreas is a compound acinar gland, similar in structure to the parotid gland**

  so, let's look at the differences between the parotid and pancreas:

  1- In histological sections, a distinction between the two glands can be made based on the absence of striated ducts and the presence of the islets of Langerhans in the pancreas. Remember that the parotid gland contains straited ducts and doesn't contain islets of Langerhans [exocrine only].

  2- Another characteristic detail is that in the pancreas the initial portions of intercalated ducts penetrate the lumens of the acini **[compare the intercalated ducts of the two glands, parotid to left and pancreas to right]**

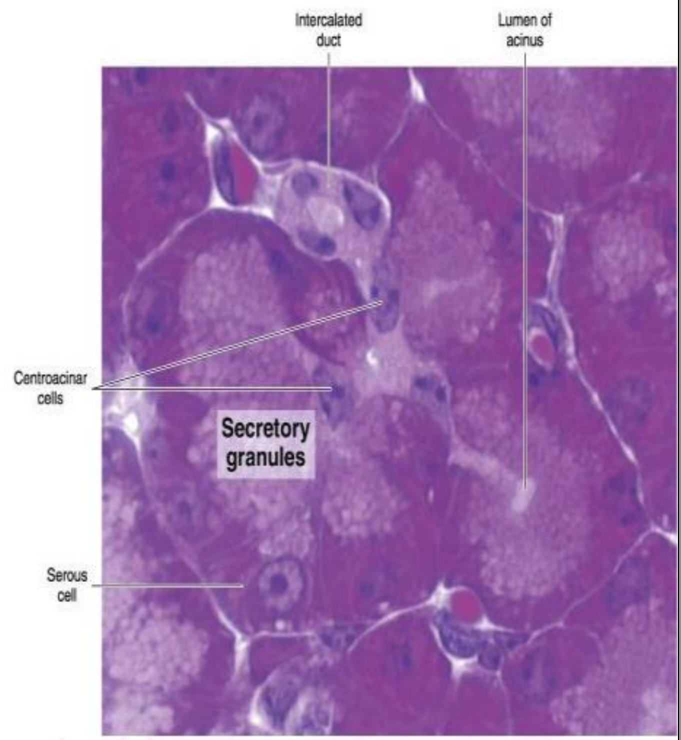




3- Nuclei, surrounded by a pale cytoplasm, belong to **centroacinar cells** that constitute the intraacinar portion of the intercalated duct **[refer to the previous picture to see the centroacinar cells]** These cells are found only in pancreatic acini

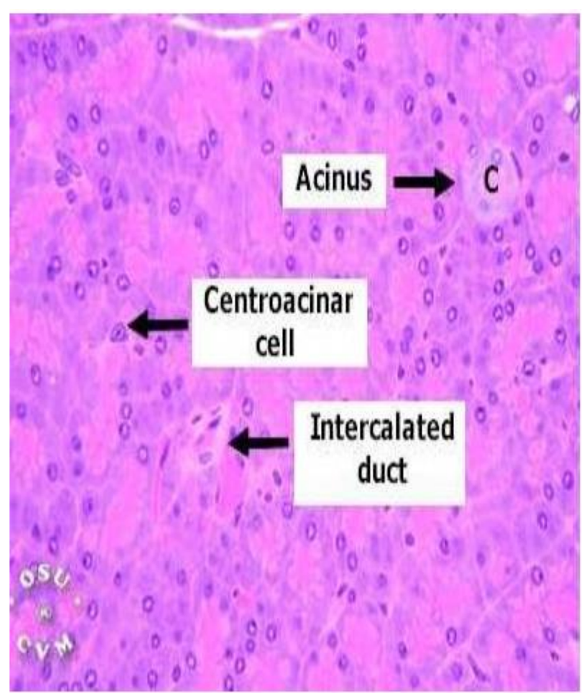
4- Intercalated ducts are tributaries of larger intralobular ducts that, in turn, form larger interlobular ducts lined by columnar epithelium, located within the connective tissue septa. There are no striated ducts in the pancreatic duct system.

- The exocrine pancreatic acinus is composed of several **serous cells** surrounding a lumen.
- These cells are highly polarized, with a spherical nucleus, and are typical protein secreting cells.
- The number of zymogen granules present in each cell varies according to the digestive phase and attains its maximum in animals that have fasted.
- A thin capsule of connective tissue covers the pancreas and sends septa into it, separating **the pancreatic lobules**.
- The acini are surrounded by a basal lamina that is supported by a delicate sheath of reticular fibers.
- The pancreas also has a rich capillary network, essential for the secretory process. [endocrine]



➔ To summarize the characteristics of pancreatic acini are: no striated ducts, centroacinar cells and polarity of the cells. Remember that intercalated ducts are lined by simple cuboidal epithelium (4-5 cells in number).

- **The exocrine pancreas secretes 1500-3000 mL of isosmotic alkaline fluid per day containing water, ions, and several proteases**, examples: trypsinogens 1, 2, and 3, chymotrypsinogen, proelastases 1 and 2, protease E, kallikreinogen, procarboxypeptidases A1, A2, B1, and B2, amylase, lipases (triglyceride lipase, colipase, and carboxyl ester hydrolase), phospholipase A2, and nucleases (deoxyribonuclease and ribonuclease).
- Most of the enzymes are stored as **proenzymes** in the secretory granules of acinar cells, **being activated in the lumen of the small intestine after secretion**
- **Enterokinase**, an intestinal enzyme, cleaves trypsinogen to form trypsin, which then activates the other proteolytic enzymes in a cascade.



- Pancreatic secretion is controlled mainly through two hormones: **secretin** and **cholecystokinin** that are produced by enteroendocrine cells of the intestinal mucosa (duodenum and jejunum).

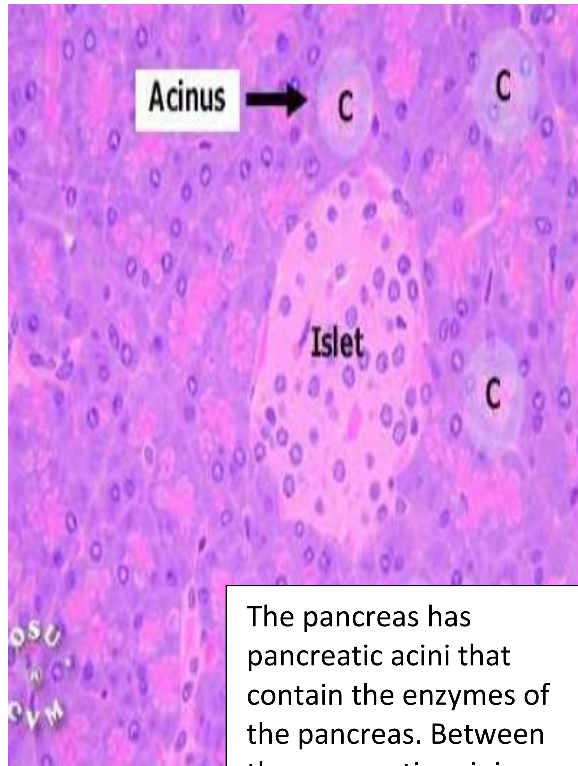
- What about the endocrine portion of the pancreas **[islets of Langerhans]?**

The islets of Langerhans contain **4 types of cells**, but under the light microscope we can only see the **alpha cells (large)** and **the beta cells (small)**:

➔The alpha cells secrete the glucagon hormone which is responsible for increasing the glucose concentration in the blood.

➔ The beta cells (more numerous) secrete insulin which decreases the glucose concentration in the blood (the glucose concentration is maintained, by insulin and glucagon, between 70-110 mg/dL).

➔ clinical case: In diabetes mellitus patients, beta cells release little or no insulin and, therefore, the glucose level in blood would be high (more details will be taken in the endocrine system).



The pancreas has pancreatic acini that contain the enzymes of the pancreas. Between the pancreatic acini we find islets of Langerhans which form the endocrine part of the pancreas.

THE END
GOOD LUCK ^_^

إن الأمور إذا التوت وتعقّدت.. جاء القضاء من الفضاء فحلّها
فاصبر لها فلعلّها ولعلّها.. ولعلّ من خلق السماء يحلُّها