Hepatobiliary System and Pancreas

The hepatobiliary system comprises of liver, gallbladder and extra hepatic ducts.

The Liver

Liver is the largest gland of the body situated mainly in the right hypochondrium, below the right dome of diaphragm in the abdomen.

The liver may be regarded as a modified exocrine gland that also has other functions. The liver substance is divisible into lobes, each of which consists of numerous lobules (Plate 17.1).

Microscopic Features

Glisson's Capsule

The liver is covered by a capsule (Glisson's capsule) made up of connective tissue. This connective tissue extends into the liver substance through the portal canals where it surrounds the portal triads. The sinusoids are surrounded by reticular fibers.

Hepatic Lobules

In sections through the liver, the substance of the organ appears to be made up of hexagonal areas that constitute the hepatic lobules (Fig. 17.1). In some species (e.g., the pig) the lobules are distinctly demarcated by connective tissue septa, but in the human liver the connective tissue is scanty and the lobules often appear to merge with one another.

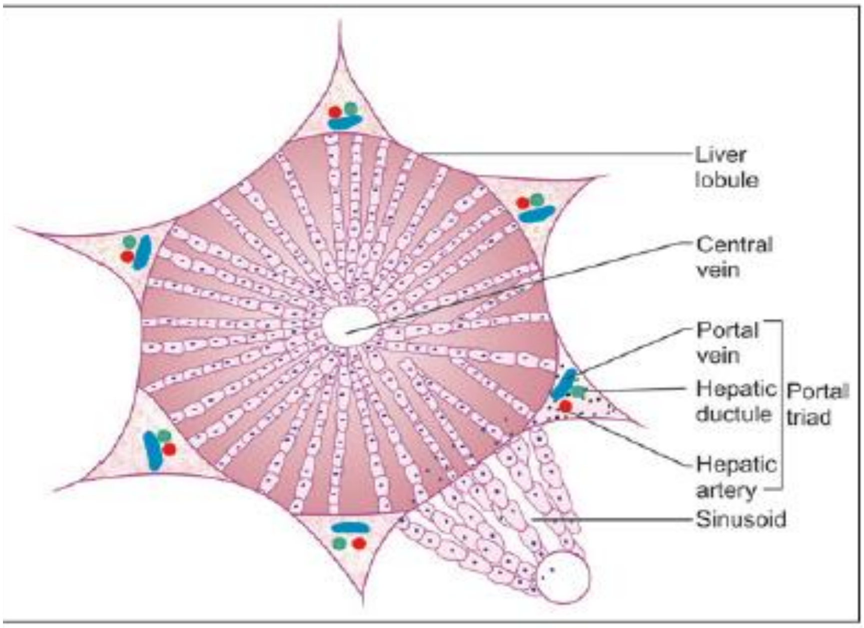


Fig. 17.1: Classic liver lobule (Schematic representation)

In transverse sections, each lobule appears to be made up of cords of liver cells that are separated by sinusoids. However, the cells are really arranged in the form of plates (one cell thick) that branch and anastomose with one another to form a network. Spaces within the network are occupied by sinusoids.

Portal Canal

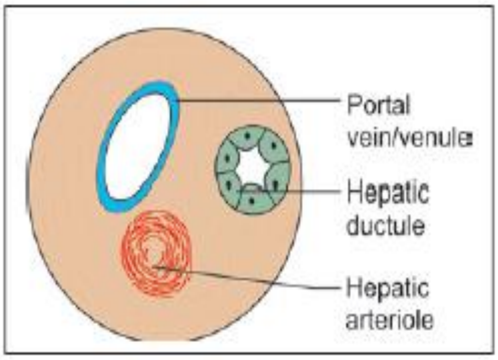


Fig. 17.2: Portal triad
(Schematic representation)

Along the periphery of each lobule there are angular intervals filled by connective tissue. These intervals are called portal canals, the 'canals' forming a connective tissue network permeating the entire liver substance.

Each 'canal' contains:

A branch of the portal vein

A branch of the hepatic artery

An interlobular bile duct

These three structures collectively form a portal triad (Fig. 17.2). Blood from the branch of the portal vein, and from the branch of the hepatic artery, enters the sinusoids at the periphery of the lobule and passes towards its center. Here the sinusoids open into a central vein that occupies the center of the lobule.

The central vein drains into hepatic veins (which leave the liver to end in the inferior vena cava). Blood vessels and hepatic ducts present in portal canals are surrounded by a narrow interval called the **space of Mall**.

Portal Lobules

The vessels in a portal triad usually give branches to parts of three adjoining lobules. The area of liver tissue (comprising parts of three hepatic lobules) supplied by one branch of the portal vein is regarded by many authorities as the true functional unit of liver tissue, and is referred to as a portal lobule (Fig. 17.3).

A still smaller unit, the portal acinus has also been described. It consists of a diamond shaped area of liver tissue supplied by one hepatic arteriole (Fig. 17.4) running along the line of junction of two hepatic lobules. Two central veins lie at the ends of the acinus.

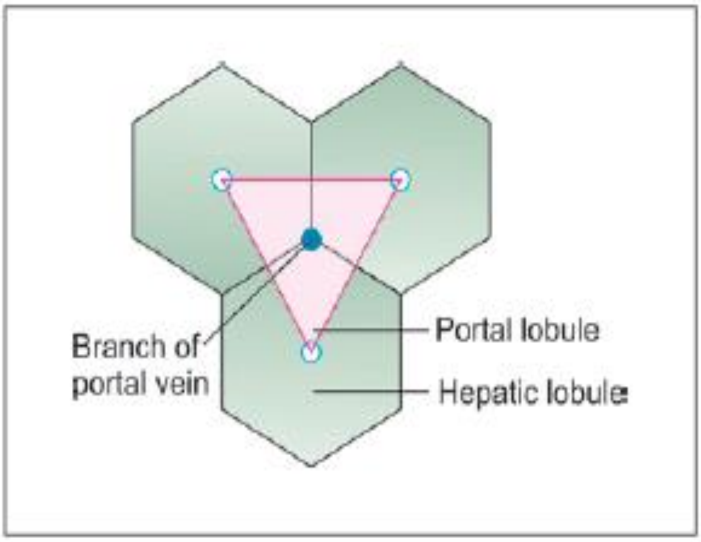


Fig. 17.3: Scheme to show the concept of portal lobules (pink). Hepatic lobules are shaded green. Note that the portal lobule is made up of parts of three hepatic lobules

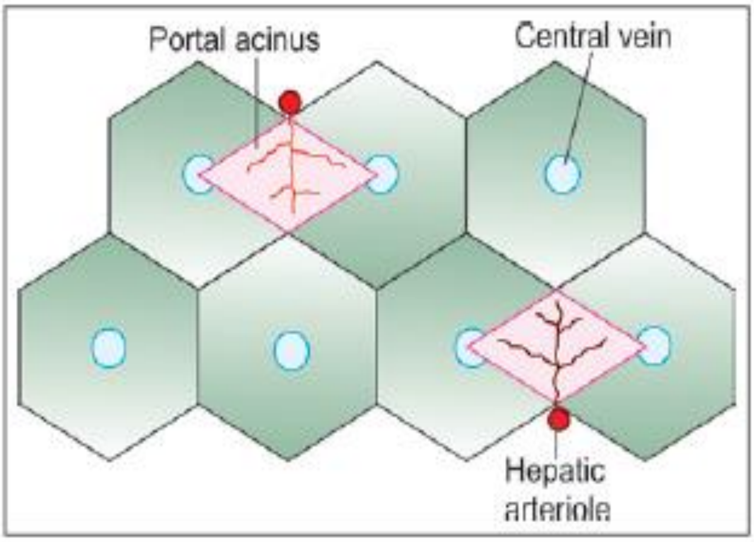
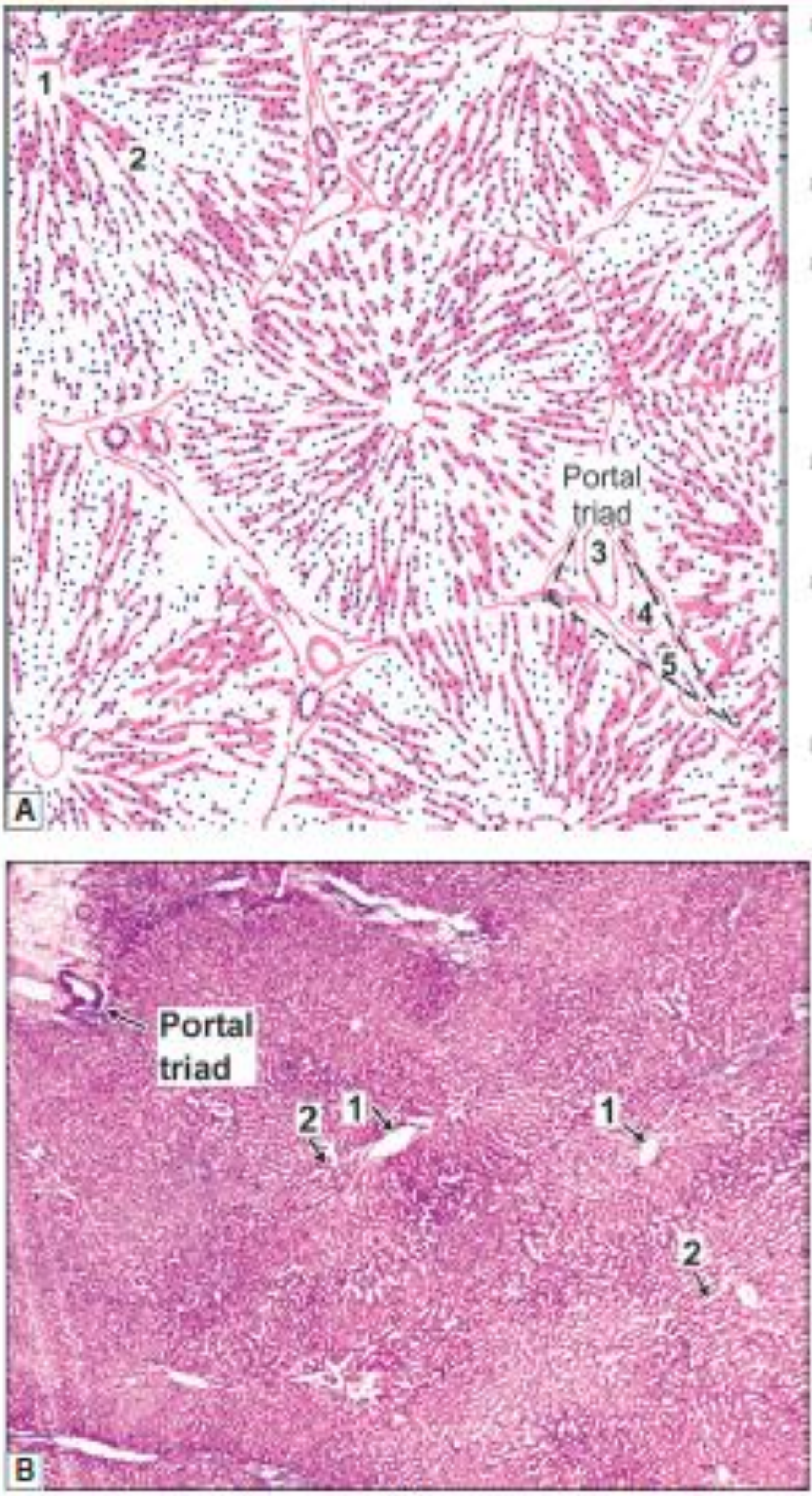


Fig. 17.4: Scheme to show the concept of portal acini (pink)

Plate 17.1: Liver (Panoramic View)



Liver (panoramic view). A. As seen in drawing; B. Photomicrograph

Courtesy: Atlas of Histopathology. Ist Edition. Ivan Damjanov. Jaypee Brothers. 2012. p142

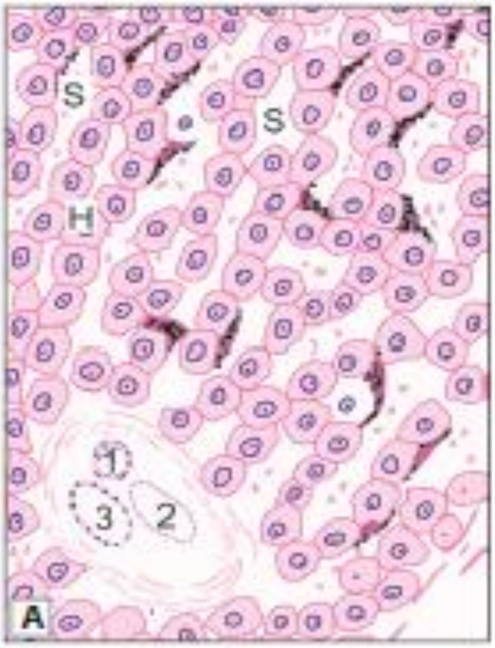
- The panoramic view of liver shows many hexagonal areas called hepatic lobules. The lobules are partially separated by connective tissue
- Each lobule has a small round space in the centre. This is the central vein
- A number of broad irregular cords of cells seem to pass from this vein to the periphery of the lobule. These cords are made up of polygonal liver cells—hepatocytes
- Along the periphery of the lobules there are angular intervals filled by connective tissue
- Each such area contains a branch of the portal vein, a branch of the hepatic artery, and an interlobular bile duct
- These three constitute a portal triad. The identification of hepatic lobules and of portal triads is enough to recognise liver tissue.

Key

1. Central vein
2. Radiating cords of hepatocytes
3. Branch of portal vein
4. Branch of hepatic artery
5. Interlobular duct

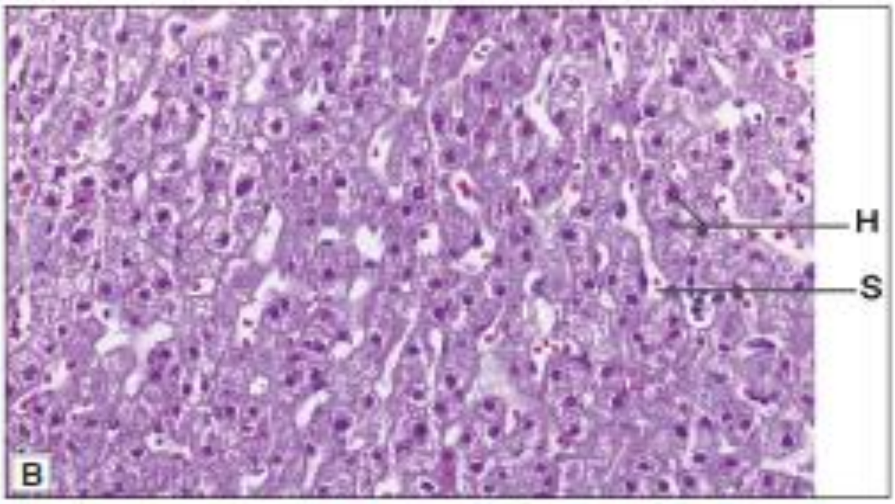
(3–5: Portal Triad)

Plate 17.2: Liver (High Magnification)



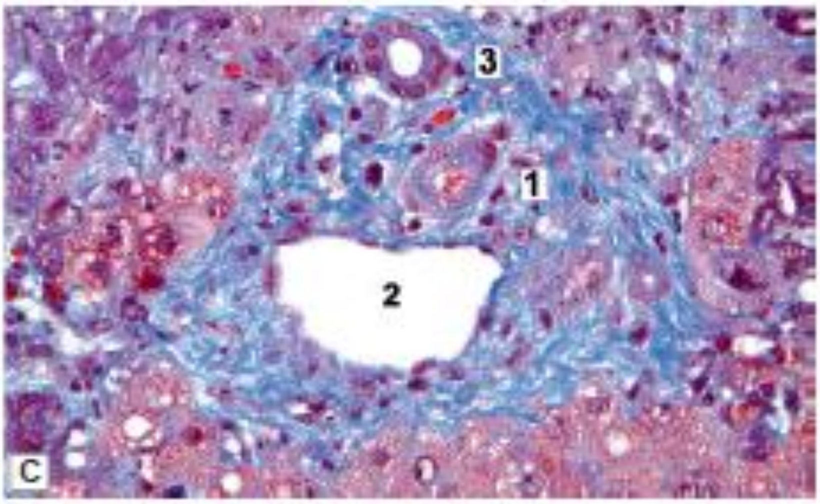
On high magnification:

- The lobule is made up of polygonal liver cells arranged in the form of radiating cords
- The central round nucleus of hepatocyte is surrounded by abundant pink cytoplasm
- The cords are separated from each other by spaces called sinusoids
- The sinusoids are lined by endothelial cells and Kupffer cells (macrophage cells)
- Plate 17.2C shows magnified view of portal tract
- Each portal tract contains a hepatic arteriole, portal venule and one or two interlobular bile ducts. Normally these structures are surrounded by fibroconnective tissue and a few lymphocytes.



Key

1. Hepatic arteriole
2. Portal venule
3. Interlobular bile duct
S. Hepatic Sinusoids
H. Radiating cords of Hepatocytes



Liver (high magnification). A. As seen in drawing; B&C. Photomicrograph
Courtesy: Atlas of Histopathology. Ist Edition. Ivan Damjanov. Jaypee Brothers. 2012. p142

Duct System

Bile secreted by liver cells is poured into bile canaliculi. These canaliculi have no walls of their own. They are merely spaces present between plasma membranes of adjacent liver cells. The canaliculi form hexagonal networks around the liver cells.

At the periphery of a lobule the canaliculi become continuous with delicate intralobular ductules, which in turn become continuous with larger interlobular ductules of portal triads. The interlobular ductules are lined by cuboidal epithelium. Some smooth muscle is present in the walls of larger ducts.

Hepatocytes

Liver is made up, predominantly, of liver cells or hepatocytes. Each hepatocyte is a large cell with a round nucleus, with prominent nucleoli (Plate 17.2).

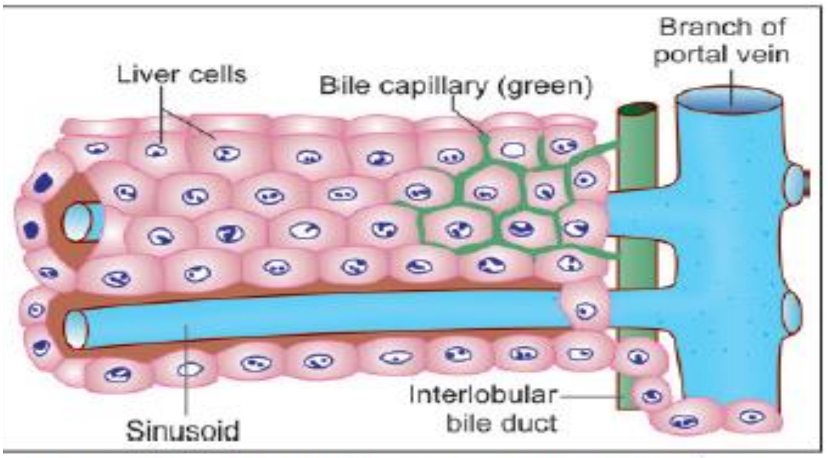


Fig. 17.5: Relationship of bile capillaries to liver cells (Schematic representation)

The cytoplasm of liver cells contains numerous mitochondria, abundant rough and smooth endoplasmic reticulum, a well developed Golgi complex, lysosomes, and vacuoles containing various enzymes. Numerous free ribosomes are present.

These features are to be correlated with the high metabolic activity of liver cells. Stored glycogen, lipids, and iron (as crystals of ferritin and hemosiderin) are usually present. Glycogen is often present in relation to smooth endoplasmic reticulum. Many hepatocytes show two nuclei; or a single polyploid nucleus.

Liver cells are arranged in the form of anastomosing plates, one cell thick; and that the plates form a network in the spaces of which sinusoids lie (Fig. 17.5). In this way each liver cell has a sinusoid on two sides.

The sinusoids are lined by an endothelium in which there are numerous pores (fenestrae). A basement membrane is not seen. Interspersed amongst the endothelial cells there are hepatic macrophages (Kupffer cells). The surface of a hepatocyte can show three kinds of specialisation (Fig. 17.6):

1. **Sinusoidal surface**: The cell surfaces adjoining sinusoids bear's microvilli that project into the space of Disse. The cell surface here also shows many coated pits that are concerned with exocytosis. Both these features are to be associated with active transfer of materials from sinusoids to hepatocytes, and **vice versa**. About 70% of the surface of hepatocytes is of this type.

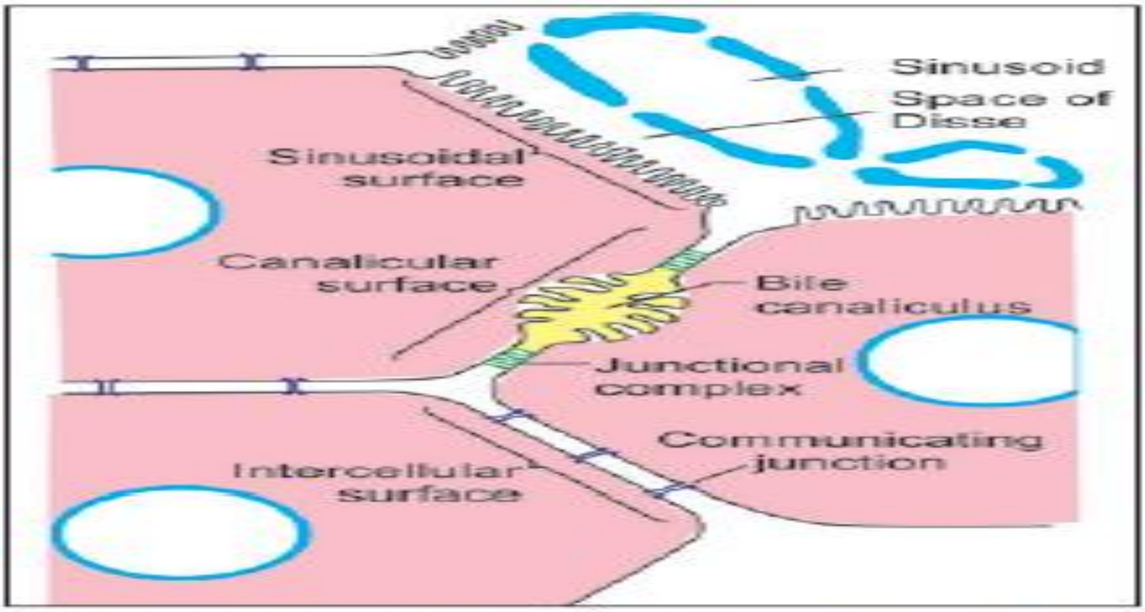


Fig. 17.6: Three functional specialisations of cell surface of a hepatocyte (Schematic representation)

2. **Canalicular surface**: Such areas of cell membrane bear longitudinal depressions that are apposed to similar depressions on neighboring hepatocytes, to form the wall of a bile canaliculus. Irregular microvilli project into the canaliculus. On either side of the canaliculus, the cell membranes of adjoining cells are united by junctional complexes. About 15% of the hepatocyte surface is canalicular.

3. **Intercellular surface**: These are areas of cell surface where adjacent hepatocytes are united to each other just as in typical cells. Communicating junctions allow exchanges between the cells. About 15% of the hepatocyte surface is intercellular.

Space of Disse

The surface of the liver cell is separated from the endothelial lining of the sinusoid by a narrow perisinusoidal space (of Disse) (Fig. 17.7). Microvilli, present on the liver cells, extend into this space. As a result of these factors hepatocytes are brought into a very intimate relationship with the circulating blood. Some fat cells may also be seen in the space of Disse.

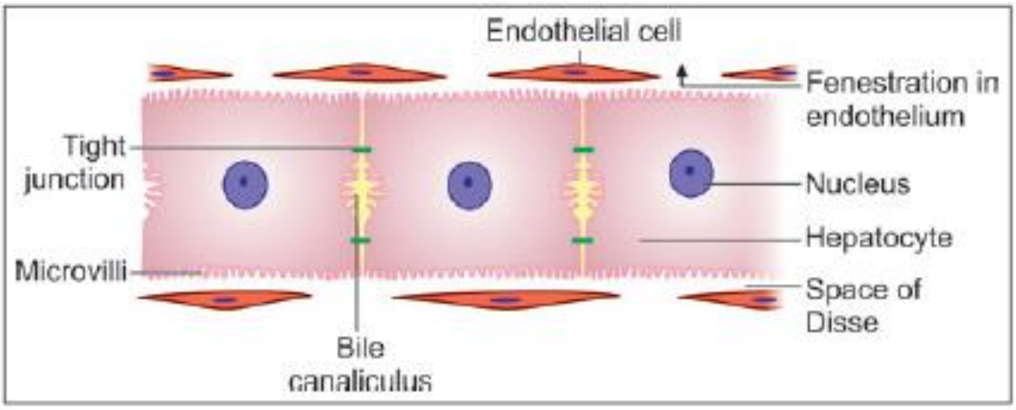


Fig. 17.7: Space of Disse and bile canaliculus (Schematic representation)

Bile

The exocrine secretion of the liver cells is called bile. Bile is poured out from liver cells into very delicate bile canaliculi that are present in intimate relationship to the cells. From the canaliculi bile drains into progressively larger ducts that end in the bile duct. This duct conveys bile into the duodenum where bile plays a role in digestion of fat.

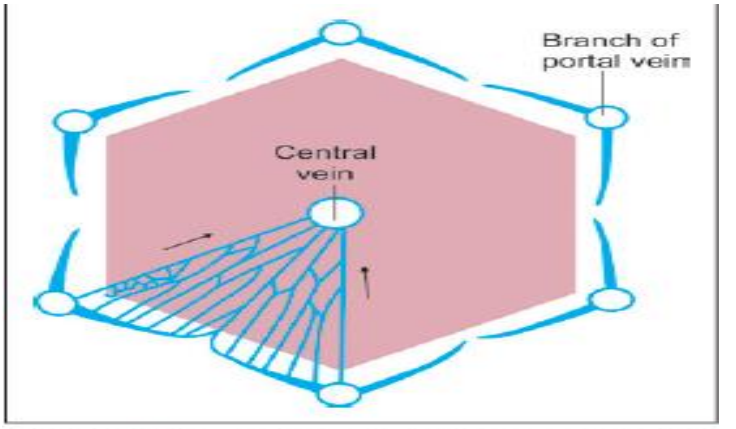


Fig. 17.8: Scheme to show the presence of several branches of the portal vein around a hepatic lobule. The manner in that they open into sinusoids is shown. The intervals between the sinusoids are occupied by liver cells (Schematic representation)

Blood Supply of Liver

In addition to deoxygenated blood reaching the liver through the portal vein (Fig. 17.8), the organ also receives oxygenated blood through the **Hepatic artery** and its branches. The blood entering the liver from both these sources passes through the hepatic sinusoids and is collected by tributaries of hepatic veins. One such tributary runs through the center of each lobule of the liver where it is called the **Central vein** (Fig. 17.8).

Branches of the hepatic artery, the portal vein, and the hepatic ducts, travel together through the liver.

Functions of Liver

The liver performs numerous functions. Some of these are as follows:

1. 1. The liver acts as an exocrine gland for the secretion of bile. However, the architecture of the liver has greater resemblance to that of an endocrine gland, the cells being in intimate relationship to blood in sinusoids. This is to be correlated with the fact that liver cells take up numerous substances from the blood, and also pour many substances back into it.
2. The liver plays a prominent role in metabolism of carbohydrates, proteins and fats. Metabolic functions include synthesis of plasma proteins fibrinogen and prothrombin, and the regulation of blood glucose and lipids.
3. The liver acts as a store for various substances including glucose (as glycogen), lipids, vitamins and iron. When necessary, the liver can convert lipids and amino acids into glucose (gluconeogenesis).
4. The liver plays a protective role by detoxifying substances (including drugs and alcohol). Removal of bile pigments from blood (and their excretion through bile) is part of this process. Amino acids are deaminated to produce urea, which enters the bloodstream to be excreted through the kidneys.
5. The macrophage cells (of Kupffer) lining the sinusoids of the liver have a role similar to that of other cells of the mononuclear phagocyte system. They are of particular importance as they are the first cells of this system that come in contact with materials absorbed through the gut. They also remove damaged erythrocytes from blood.
6. During fetal life the liver is a center for hemopoiesis.

Clinical Correlation

Inflammation in the liver is called hepatitis. It is frequently caused by viruses (viral hepatitis), and by a protozoan parasite **Entamoeba histolytica** (amoebic hepatitis). An abscess may form in the liver as a sequel of amoebic hepatitis.

Cirrhosis of the liver is a disease in which many hepatocytes are destroyed, the areas being filled by fibrous tissue. This gradually leads to collapse of the normal architecture of the liver.

One effect of cirrhosis of the liver is to disrupt the flow of blood through the liver. As a result of increased resistance to blood flow there is increased blood pressure in the portal circulation (**portal hypertension**). In portal hypertension anastomoses between the portal and systemic veins dilate to form varices (e.g., at the lower end of the esophagus). Rupture of these varices can result in fatal bleeding.

When a large number of hepatocytes are destroyed this leads to liver failure. All the above listed functions are interfered with. Hepatic failure may be acute or chronic. Accumulation of waste products in blood (due to lack of detoxification by the liver) ultimately leads to unconsciousness (**hepatic coma**) and death.

Extra Hepatic Biliary Apparatus

The extra hepatic biliary apparatus consists of the gallbladder and the extra hepatic bile ducts.

The Gallbladder

Gallbladder is a muscular sac situated on the visceral surface of the liver in the fossa for gallbladder. The gallbladder stores and concentrates bile. This bile is discharged into the duodenum when required.

The wall of the gallbladder is made up of:

a. A mucous membrane
b. A fibro muscular coat
c. A serous layer that covers part of the organ (Plate 17.3)

Mucous Membrane

The mucous membrane of the gall bladder is lined by a tall columnar epithelium with a striated border. The mucosa is highly folded. In sections, the folds may look like villi.

Fibro muscular Coat

The fibro muscular coat is made up mainly of connective tissue containing the usual elements. Smooth muscle fibers are present and run in various directions.

Serosa

The serous layer has a lining of mesothelium resting on connective tissue. The fundus and lower surface of body of gallbladder is covered by serosa, whereas the upper surface is attached to the fossa for gallbladder by means of connective tissue (adventitia).

Cells of Gallbladder

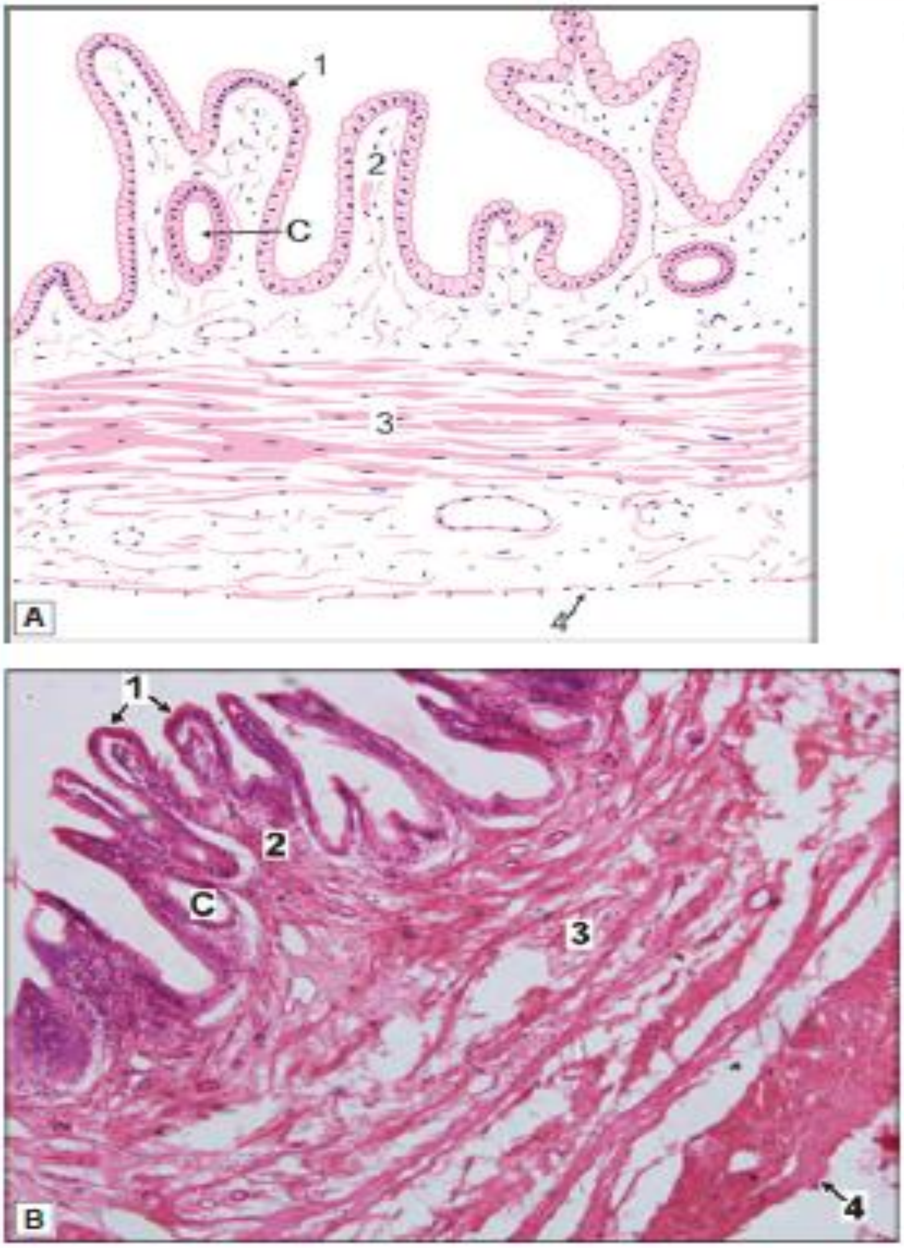
With the EM the lining cells of the gallbladder are seen to have irregular microvilli on their luminal surfaces. Near the lumen the lateral margins of the cells are united by prominent junctional complexes. Numerous blood capillaries are present near the bases of the cells.

These features indicate that bile is concentrated by absorption of water at the luminal surface of the cell. This water is poured out of the cell into basal intercellular spaces from where it passes into blood. Absorption of salt and water from bile into blood is facilitated by presence of Na+ and K+ ATPases in cell membranes of cells lining the gallbladder.

Clinical Correlation

Inflammation of the gallbladder is called cholecystitis. Stones may form in the gallbladder (gallstones). In such cases surgical removal of the gallbladder may be necessary (cholecystectomy).

PLATE 17.3: Gallbladder



Gallbladder. A. As seen in drawing; B. Photomicrograph

- The mucous membrane is lined by tall columnar cells with striated border
- The mucosa is highly folded and some of the folds might look like villi
- Crypts may be found in lamina propria
- Submucosa is absent.
- The muscle coat is poorly developed there being numerous connective tissue fibres amongst the muscle fibres. This is called as fibromuscular coat
- A serous covering lined by flattened mesothelium is seen.

Note: Gallbladder can be differentiated from small intestine by –

- Absence of villi
- Absence of goblet cells
- Absence of submucosa
- Absence of proper muscularis externa

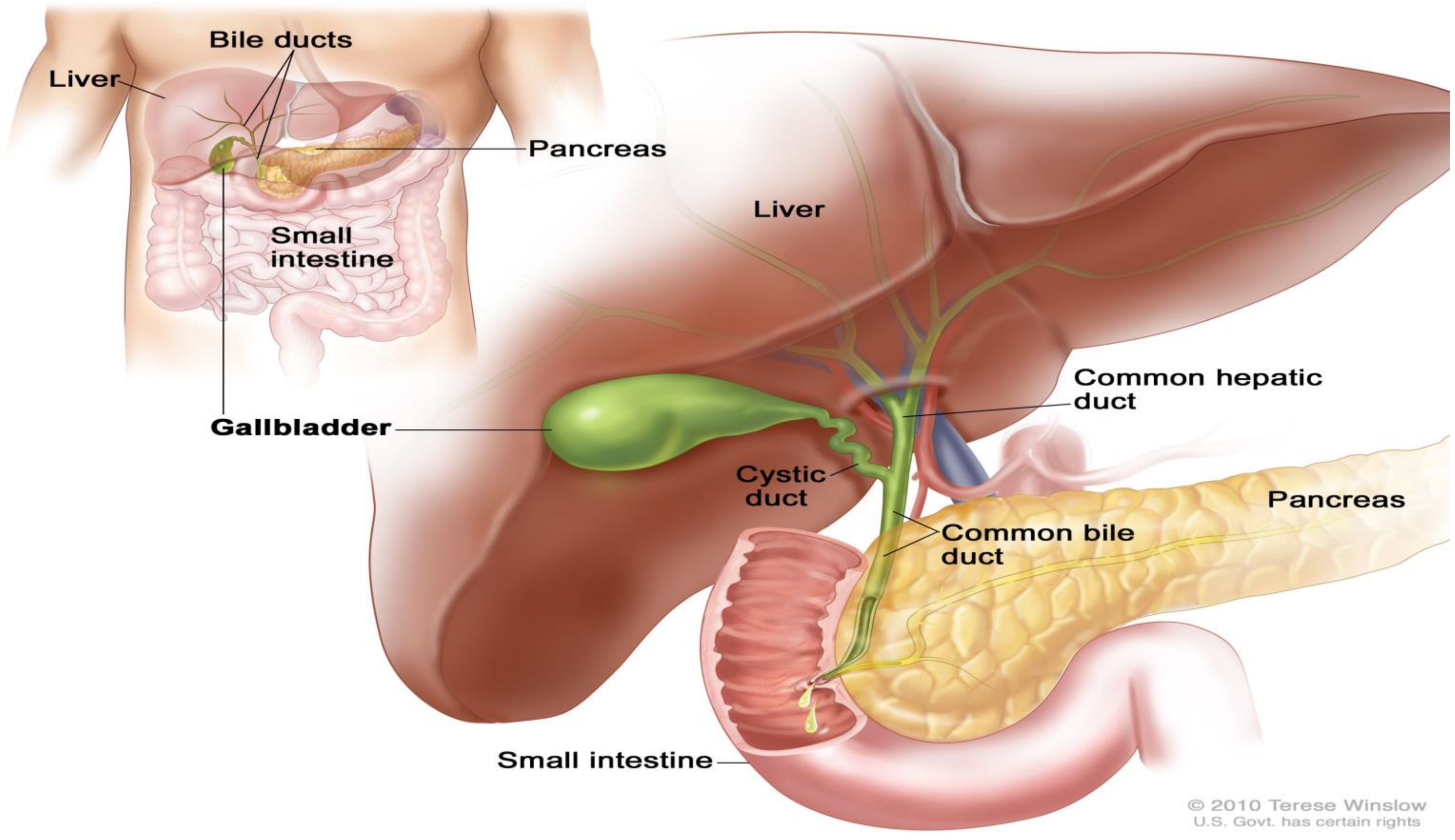
Key

1. Mucous membrane lined by tall columnar cells with striated border
2. Lamina propria
3. Fibromuscular coat
4. Serosa

C. Crypt in lamina propria

The Extra Hepatic Ducts

These are the right, left and common hepatic ducts; the cystic duct; and the bile duct. All of them have a common structure. They have a mucosa surrounded by a wall made up of connective tissue, in which some smooth muscle may be present. The mucosa is lined by a tall columnar epithelium with a striated border.



Hepato-pancreatic Duct

At its lower end the bile duct is joined by the main pancreatic duct, the two usually forming a common hepato-pancreatic duct (or ampulla) that opens into the duodenum at the summit of the major duodenal papilla.

The mucosa of the hepato-pancreatic duct is highly folded. These folds are believed to constitute a valvular mechanism that prevents duodenal contents from entering the bile and pancreatic ducts.

Sphincter of Oddi

Well-developed smooth muscle is present in the region of the lower end of the common hepato-pancreatic duct. This muscle forms the **Sphincter of Oddi**.

From a functional point of view this sphincter consists of three separate parts. The **Sphincter Choledochus** surrounds the lower end of the bile duct. It is always present, and its contraction is responsible for filling of the gallbladder. A less developed **Sphincter Pancreaticus** surrounds the terminal part of the main pancreatic duct (Fig. 17.9).

A third sphincter surrounds the hepato-pancreatic duct (or ampulla) and often forms a ring round the lower ends of both the bile and pancreatic ducts. This is the **Sphincter Ampullae**.

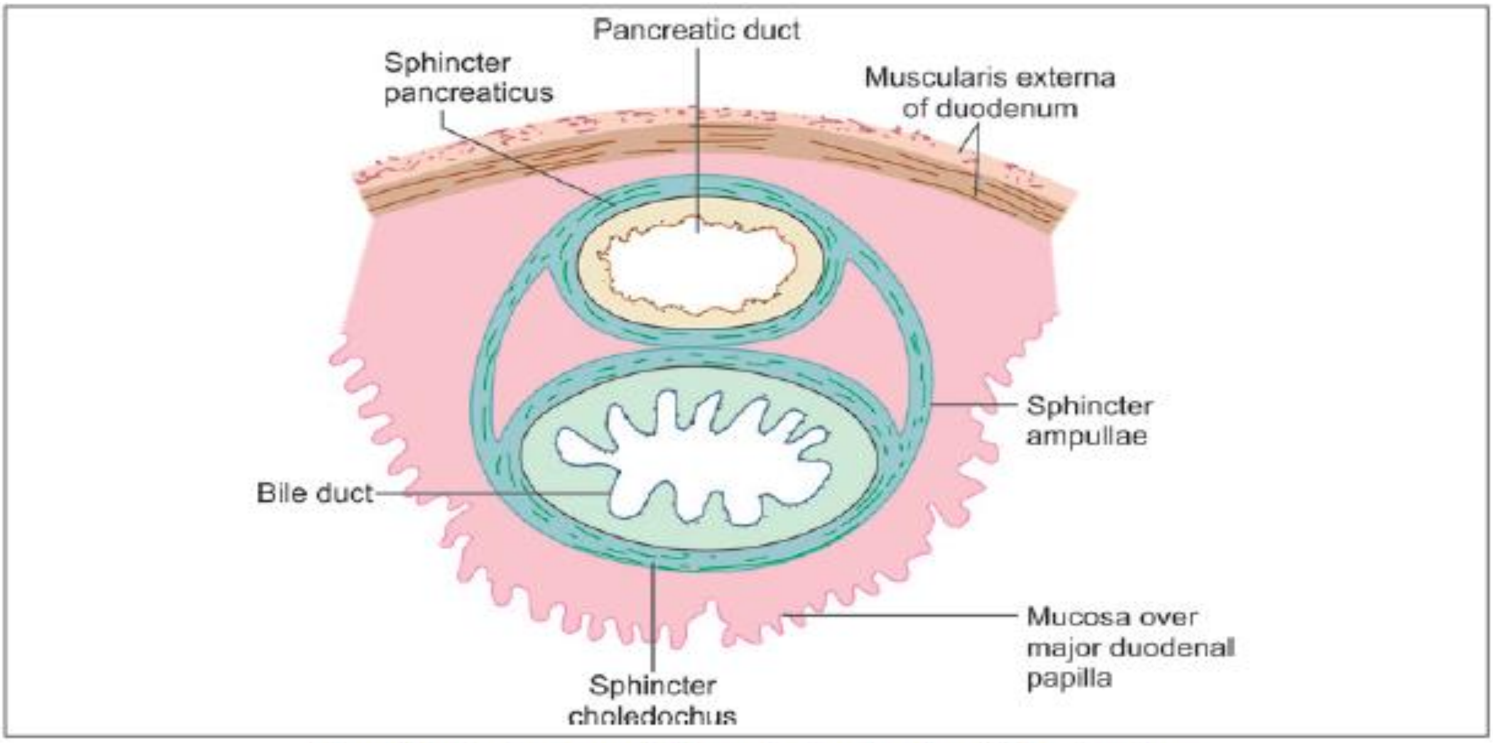


Fig. 17.9: Section through the major duodenal papilla to show the components of the sphincter of Oddi (Schematic representation)

Clinical Correlation

Blockage of the bile duct (by inflammation, by a gallstone, or by carcinoma) leads to accumulation of bile in the biliary duct system, and within the bile capillaries. As pressure in the passages increases bile passes into blood leading to jaundice. The sclera, the skin, and the nails appear to be yellow in colour, and bile salts and pigments are excreted in urine. Jaundice occurring as a result of such obstruction is called **obstructive jaundice**. Jaundice is seen in the absence of obstruction in cases of hepatitis. A gallstone passing through the bile duct can cause severe pain. This pain is **Biliary Colic**.

The Pancreas

The pancreas extends from the concavity of the duodenum, on the right to the spleen and on the left in the posterior abdominal wall. The pancreas is covered by connective tissue that forms a capsule for it. Septa arising from the capsule extend into the gland dividing it into lobules. Each pancreatic islet is surrounded by a network of reticular fibers.

It is a gland that is partly exocrine, and partly endocrine, the main bulk of the gland being constituted by its exocrine part (Plate 17.4).

--The exocrine pancreas secretes enzymes that play a very important role in the digestion of carbohydrates, proteins and fats. After digestion, and absorption through the gut, these products are carried to the liver through the portal vein.

--The endocrine pancreas produces two very important hormones, **insulin** and **glucagon**. These two hormones are also carried through the portal vein to the liver where they have a profound influence on the metabolism of carbohydrates, proteins and fats.

The functions of the exocrine and endocrine parts of the pancreas are thus linked. The linkage between the two parts is also seen in their common embryonic derivation from the endodermal lining of the gut.

The exocrine Pancreas

The exocrine pancreas is in the form of compound tubuloalveolar serous gland.

Note: Its general structure is very similar to that of the parotid gland, but the two are easily distinguished because of the presence in the pancreas of endocrine elements.

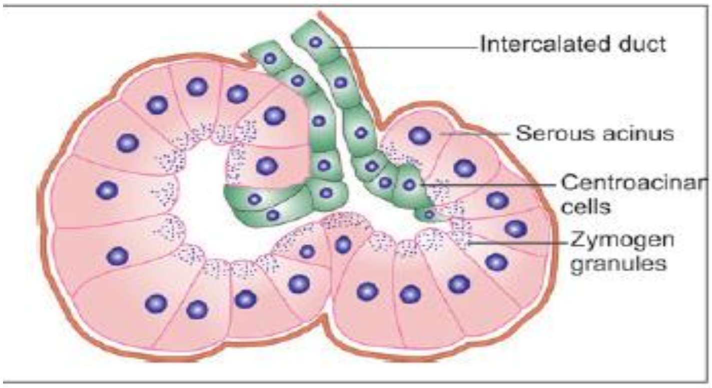


Fig. 17.10: Pancreatic serous acinus

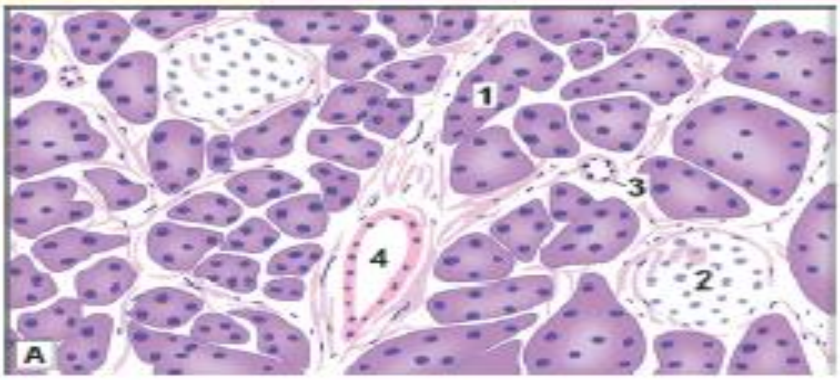
Capsule

A delicate capsule surrounds the pancreas. Septa extend from the capsule into the gland and divide it into lobules.

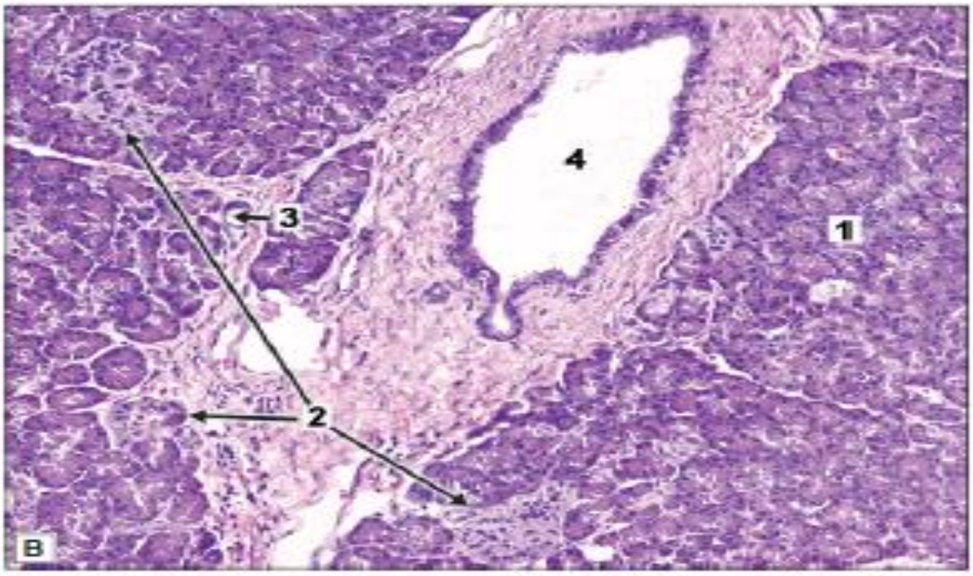
Pancreatic Acini

The secretory elements of the exocrine pancreas are long and tubular (but they are usually described as acini as they appear rounded or oval in sections). Their lumen is small (Fig. 17.10).

Plate 17.4: Pancreas



- This is a gland made up of serous acini
- The cells forming the acini of the pancreas are highly basophilic (bluish staining) The lumen of the acinus is very small.
- Some acini may show pale staining (centroacinar cell) in the centre.
- Amongst the acini some ducts are seen
- The ducts have a distinct lumen, lined by cuboidal epithelium.
- At some places the acini are separated by areas where we see aggregations of cells quite different from those of the acini.



- These aggregations form the pancreatic islets: pale staining cells arranged as groups, surrounded by blood vessels.
- In the photomicrograph, an interlobular duct lined by cuboidal epithelium is surrounded by lobules of acinar cells which have small basal nuclei and granular eosinophilic or slightly basophilic cytoplasm. Islets of Langerhans appear as groups of small cells with lightly stained cytoplasm.

Key

1. Serous acini inside lobules
2. Islet of Langerhans
3. Intralobular duct
4. Interlobular duct

Pancreas. A. As seen in drawing; B. Photomicrograph

Secretory Cells

The cells lining the alveoli appear triangular in section, and have spherical nuclei located basally. In sections stained with haematoxylin and eosin the cytoplasm is highly basophilic (blue) particularly in the basal part. With suitable fixation and staining numerous secretory (or zymogen) granules can be demonstrated in the cytoplasm, specially in the apical part of the cell. These granules are eosinophilia. They decrease considerably after the cell has poured out its secretion.

With the EM the cells lining the alveoli show features that are typical of secretory cells. Their basal cytoplasm is packed with rough endoplasmic reticulum. A well-developed Golgi complex is present in the supra-nuclear part of the cell. Numerous secretory granules (membrane bound, and filled with enzymes) occupy the greater part of the cytoplasm (except the most basal part).

Centro-acinar Cells

In addition to secretory cells, the alveoli of the exocrine pancreas contain **Centro-acinar cells** that are so called because they appear to be located near the center of the acinus. These cells really belong to the intercalated ducts that are invaginated into the secretory elements. Some cell bodies of autonomic neurons, and undifferentiated cells are also present in relation to the secretory elements.

The secretory cells produce two types of secretion:

-- One of these is watery and rich in bicarbonate. Bicarbonate is probably added to pancreatic secretion by cells lining the ducts. It helps to neutralise the acid contents entering the duodenum from the stomach. Production of this secretion is stimulated mainly by the hormone **secretin** liberated by the duodenal mucosa.

--The other secretion is thicker and contains numerous enzymes (including trypsinogen, chymotrypsinogen, amylase, lipases, etc.). The production of this secretion is stimulated mainly by the hormone cholecystokinin (pancreozymin) liberated by endocrine cells in the duodenal mucosa.

Secretion by cells of the exocrine pancreas, and the composition of the secretion, is influenced by several other amines produced either in the gastrointestinal mucosa or in pancreatic islets. (These include gastrin, vasoactive intestinal polypeptide, and pancreatic polypeptide). Secretion is also influenced by autonomic nerves, mainly parasympathetic.

The enzymes are synthesised in the rough endoplasmic reticulum. From here they pass to the Golgi complex where they are surrounded by membranes, and are released into the cytoplasm as secretory granules. The granules move to the luminal surface of the cell where the secretions are poured out by exocytosis. Within the cell the enzymes are in an inactive form. They become active only after mixing with duodenal contents. Activation is influenced by enzymes present in the epithelium lining the duodenum.

Duct System

Secretions produced in the acini are poured into **Intercalated ducts** (also called **intralobular ducts**). These ducts are invaginated deeply into the secretory elements (Fig. 17.10). As a result of this invagination, the interacalated ducts are not conspicuous in sections.

From the intercalated ducts the secretions pass into larger, **interlobular ducts**. They finally pass into the duodenum through the **Main Pancreatic Duct** and the **Accessory Pancreatic Duct.** The cells lining the pancreatic ducts control the bicarbonate and water content of pancreatic secretion. These actions are under hormonal and neural control. The walls of the larger ducts are formed mainly of fibrous tissue. They are lined by a columnar epithelium.

The terminal part of the main pancreatic duct is surrounded by a sphincter. A similar sphincter may also be present around the terminal part of the accessory pancreatic duct

The Endocrine Pancreas

The endocrine pancreas is in the form of numerous rounded collections of cells that are embedded within the exocrine part. These collections of cells are called the pancreatic islets, or the islets of Langerhans. The human pancreas has about one million islets. They are most numerous in the tail of the pancreas.

Each islet is separated from the surrounding alveoli by a thin layer of reticular tissue. The islets are very richly supplied with blood through a dense capillary plexus. The intervals between the capillaries are occupied by cells arranged in groups or as cords. In ordinary preparations stained with haematoxylin and eosin, all the cells appear similar, but with the use of special procedures three main types of cells can be distinguished.

Alpha Cells (a-Cells)

In islets of the human pancreas the **alpha cells** (or **A-cells**) tend to be arranged towards the periphery (or cortex) of the islets. They form about 20% of the islet cells. They contain smaller granules that stain brightly with acid fuchsin. They do not stain with aldehyde fuchsin. The alpha cells secrete the hormone **Glucagon**.

Beta Cells (b-Cells)

The **beta cells** (or **B-cells**) tend to lie near the center (or medulla) of the islet. About 70% of the cells of islet are of this type. The beta cells contain granules (larger than alpha cells) that can be stained with aldehyde fuchsin. When seen with electron microscopy, the granules of beta cells are fewer, larger, and of less electron density than those of alpha cells. The beta cells secrete the hormone **Insulin**.

Delta Cells (D-Cells)

Delta cells (or **D-cells**), like alpha cells, are also peripherally placed. The delta cells (also called type III cells) stain black with silver salts (i.e., they are argyrophilic).

When seen with electron microscopy, the granules of delta cells appear to be round or ovoid with low electron density. The delta cells probably produce the hormones gastrin and somatostatin. Somatostatin inhibits the secretion of glucagon by alpha cells, and (to a lesser extent) that of insulin by beta cells.

PP cells

Apart from the three main types of cells described above some other types are also present in the islets of Langerhans. These are the PP cells containing pancreatic polypeptide (and located mainly in the head and neck of the pancreas), probably containing vasoactive intestinal polypeptide (or a similar amine). A few cells secreting serotonin, motilin and substance polypeptide are also present.

Blood Supply

The gland is richly supplied with blood vessels that run through the connective tissue. The capillary network is most dense in the islets. Here the endothelial lining is fenestrated providing intimate contact of islet cells and circulating blood.

Lymphatics are also present in the pancreas.

Nerve Supply

The connective tissue of the pancreas also serves as a pathway for nerve fibers, both myelinated and unmyelinated. Groups of neurons are also present. Pancreatic islets are richly innervated by autonomic nerves. Noradrenaline and acetylcholine released at nerve endings influence secretion by islet cells.

Clinical Correlation

Acute pancreatitis: Acute pancreatitis is an acute inflammation of the pancreas presenting clinically with ‘acute abdomen’. The condition occurs in adults between the age of 40 and 70 years and is more common in females than in males. The onset of acute pancreatitis is sudden, occurring after a bout of alcohol or a heavy meal. Characteristically, there is elevation of **serum amylase** level within the first 24 hours and elevated serum lipase level after 3–4 days.

Chronic pancreatitis: Chronic pancreatitis or **chronic relapsing pancreatitis** is the progressive destruction of the pancreas due to repeated mild and subclinical attacks of acute pancreatitis. Most patients present with recurrent attacks of severe abdominal pain at intervals of months to years. Weight loss and jaundice are often associated.