Fatty Liver Disease, a Silent Killer of Human Beings

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By

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TABLE OF CONTENTS

Preface vi

Chapter 1 1
Anatomy and physiology of the liver

Chapter 2 45
Liver function tests

Chapter 3 71
Ultrasonography of the liver

Chapter 4 79
Endoscopic ultrasound of the liver

Chapter 5 83
Fibroscan of the liver

Chapter 6 85
Alcohol and the liver

Chapter 7 128
Lipid metabolism and the role of the liver

Chapter 8 151
Etiopathogenesis of nonalcoholic fatty liver disease

Chapter 9 178
Clinical spectrum and diagnosis of nonalcoholic fatty liver disease

Chapter 10 196
Management of nonalcoholic fatty liver disease

PREFACE

A large number of people are now suffering from **type 2 diabetes mellitus**. Due to the development of cooking, more and more high calorific foods are developing consisting of enormous amounts of **saturated fat** and other constituents. As a result a large percentage of people are now suffering from **metabolic syndrome**. The patient becomes obese, may develop diabetes and in some cases **hypertension.** All the factors interact with each other and ultimately lead to **fatty liver disease**. Most people neglect the early stage of fatty liver disease and continue their unrestricted lifestyle. As a result the disease silently progresses to **steatohepatitis**. At this stage the patient may develop symptoms which are the warning signs and will need to go to their doctor for treatment. But asymptomatic individuals with steatohepatitis ultimately develop **fibrosis** which may ultimately develop **cirrhosis**. So, treatment of metabolic syndrome, diabetes, and hypertension will allow the recovery of patients suffering from fatty liver disease. Again, the patients with fatty liver disease may die from cardiovascular disease which also can be taken care of. This book will open all the doors of fatty liver disease – how it develops, what should be the line of investigations and management. The case of **alcohol intake of long duration** is similar.

The target audiences are of different types:

A. Postgraduate students
B. Practitioners
C. Common people

Key words are the following:
Diabetes mellitus, metabolic syndrome, hyperlipidemia, alcohol intake of long duration, fatty liver, steatohepatitis, hepatic fibrosis, diagnosis and management.

Two books: Sole author

A. Clinical Methods and Interpretation
B. Manual of Clinical Medicine

One monograph:

Updates of Dengue Fever

Two monographs are edited:

A. Headache
B. Chronic diarrhea

Articles:

A. 38 original articles in different national and international journals.
B. 2 review articles in national journals.

CHAPTER 1

ANATOMY AND PHYSIOLOGY OF THE LIVER

Morphologically brown-colored and smooth-surfaced, the liver represents 2% of the total body weight in an adult, weighing 1800 grams and 1400 grams respectively in the male and female. Its upper surface is related entirely to the dome of the diaphragm and its visceral surface is related to the following structures **(Fig 1):**

A. Abdominal esophagus
B. Stomach
C. Upper duodenum
D. Hepatic flexure
E. Right colon
F. Right kidney
G. Suprarenal gland.

Externally, the liver has been subdivided into right, and approximately 6 times smaller, left lobes by the falciform ligament; this ligament attaches the liver to the anterior abdominal wall. Its base contains the ligamentum teres or round ligament which contains in its free border, a remnant of the vestigial umbilical vein. In the case of cirrhosis with portal hypertension this vein will be recanalized. This vein runs along the free edge of the falciparum ligament in fetal life and actually joins with the left branch of the portal vein. The falciform ligament, while it passes over the dome of the diaphragm, divides into the following forms:

A. Its right limb joins the upper layer of the coronary ligament.
B. Its left limb will be stretched out as the long and narrow left triangular ligament; it joins the lesser omentum as this arises from the fissure of the ligamentum venosum.

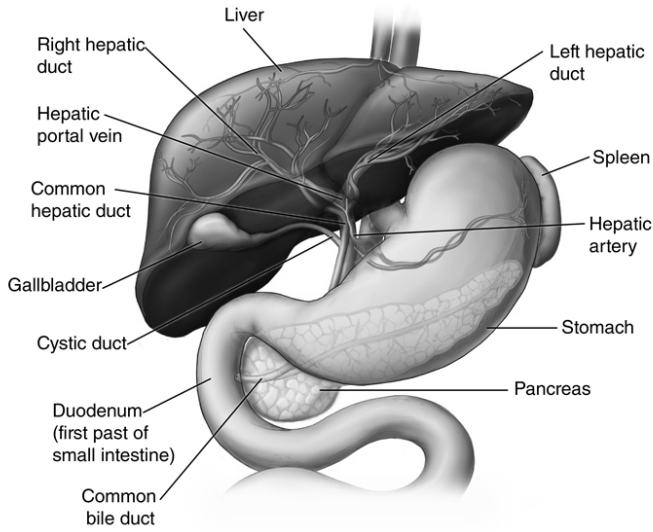

Fig 1: Relation of the liver with other structures

Anatomical subdivision of the liver:

The superior aspect of the liver will be subdivided by the falciparum ligament into two lobes:

A. Large right lobe
B. Smaller left lobe

Posteroinferiorly in the liver an "H" shaped arrangement of fossa as following:

A. Anteriorly and towards the right: There is the presence of the gall bladder fossa.
B. Anteriorly and towards the left: There is a groove for the ligamentum teres.
C. Posteriorly and to the right: There is the presence of a groove for the inferior vena cava.
D. Posteriorly and towards the left: There is a fissure for the ligamentum venosum.

The cross bar of the "H" is the porta hepatis. It measures 5 cm in length, and contains the following structures:

A. Anteriorly and to the right: The right and left hepatic ducts fuse into the common hepatic duct.
B. Posteriorly and to the left: The hepatic artery divides into two branches, left and right.
C. Posteriorly: The portal vein divides into left and right branches.
D. Other structures entering the porta hepatis are:
    a. Parasympathetic nerves arising from the hepatic branch of the anterior vagus nerve.
    b. Sympathetic nerves from the celiac axis.

On the inferior surface of the liver there are two lobes separated by the portal vein:

A. The quadrate lobe presents anteriorly between the gall bladder and the round ligament.
B. The caudate lobe with the papillary tubercle and the caudate process presents posteriorly along the inferior vena cava in front of the porta hepatis. This lobe is drained by both the right and left hepatic ducts. The right and left portal veins and the hepatic artery provide the arterial supply and this lobe is drained through small venous branches which directly drain into the inferior vena cava.

According to the Couinaud classification, the liver has been subdivided into eight independent functional segments in a clockwise manner. Each of these segments has its own portal triad consisting of

A. Hepatic arterial branch
B. Portal branch
C. Bile duct
D. Hepatic venous branch for providing outflow.

The following segments of the liver are **(Fig 2):**

A. Segment II: Anterior segment of the left lobe
B. Segment III: Posterior segment of the left lobe
C. Segment IV: Medial segment of the left lobe.

Segments II and III are collectively called the left lateral segment.

Segments II, III and IV are collectively known as the functional left lobe of the liver.

D. Segment V: Anterior segment of the right lobe
E. Segment VII: Anterior segment of the right lobe
F. Segment VI: Posterior segment of the right lobe
G. Segment VII: Posterior segment of the right lobe.
H. Segment I: This represents the caudate lobe of the liver located posteriorly.

Outflow of the liver occurs through the three hepatic veins:

A. The right hepatic vein divides the right lobe into two segments:
    a. Anterior segment
    b. Posterior segment.
B. The middle or central hepatic vein divides the liver into two lobes:
    a. Right lobe
    b. Left lobe.
C. The left hepatic vein divides the left lobe into two segments:
    a. Medial segment
    b. Lateral segment.

These hepatic veins pass through the substances of the liver in the postero superior direction and ultimately drain into the inferior vena cava at the postero superior aspect of the liver. But the middle hepatic vein opens into the left vein prior to termination.

The portal vein divides the liver into two segments:

A. Upper segment
B. Lower segment.

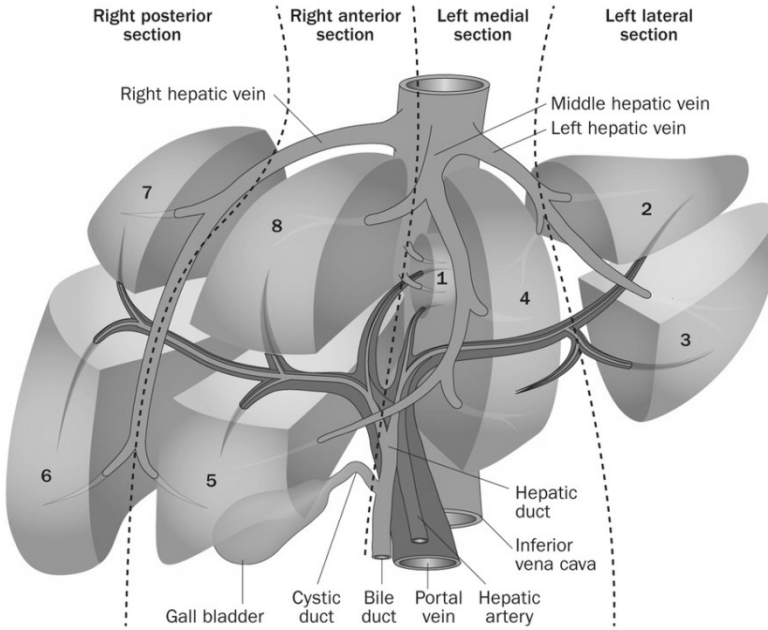

Fig 2: Different segments in the liver

The segmental anatomical description of the liver is of immense importance to the radiologist as well as the surgeon.[1,2] Because a resection of the liver depends upon the accurate localization of the liver anatomy as it reduces mortality and morbidity. Segmentectomies are based on the Couinaud classification.

A. Bisegmentectomy or left lateral segmentectomy means the resection of segments II and III.
B. Left medial segmentectomy is the resection of segment IV.
C. Right anterior segmentectomy means the resection of segments V and VIII.
D. Right posterior segmentectomy means the resection of segments VI and VII.
E. Left hepatectomy means the resection of segments II, III and IV.
F. Right hepatectomy means the resection of segments V, VI, VII and VIII.
G. Extended right hepatectomy means the resection of segments IV, V, VI, VII and VIII.

H. Extended left hepatectomy means the resection of segments II, III, IV, V and VII.

Intrahepatic vascular systems:

Hepatic artery **(Fig 3):**

From the celiac artery the following branches arise:

A. Common hepatic artery
B. Splenic artery
C. Phrenic artery
D. Left gastric artery.

Origin of the second hepatic artery:

A. In 18% of cases – from the left gastric artery
B. In 10% of cases – from the superior mesenteric artery.

From the common hepatic artery, the following branches arise prior to extending to the proper hepatic artery:

A. Gastroduodenal artery
B. Right gastric artery.

In the porta hepatis proper the hepatic artery runs close to the portal veins, occasionally coiling around the vein, and has been divided into two branches:

A. Right hepatic artery from which the cystic branch arises.
B. Left hepatic artery from which the middle hepatic artery occasionally arises.

There is the presence of the sphincter prior to the further division into smaller branches to interlobular arteries and then to intralobular arterioles which supply the hepatic lobules.[3] Then the arterial blood will enter into the sinusoids through the terminal branches.

The following regions are supplied by the hepatic artery:

A. Peribiliary vascular plexus as the greatest arteriolar compartment
B. Portal interstitium
C. Vasa vasorum of the portal vein
D. Vasa vasorum of the hepatic vein

E. Capsule of the liver.

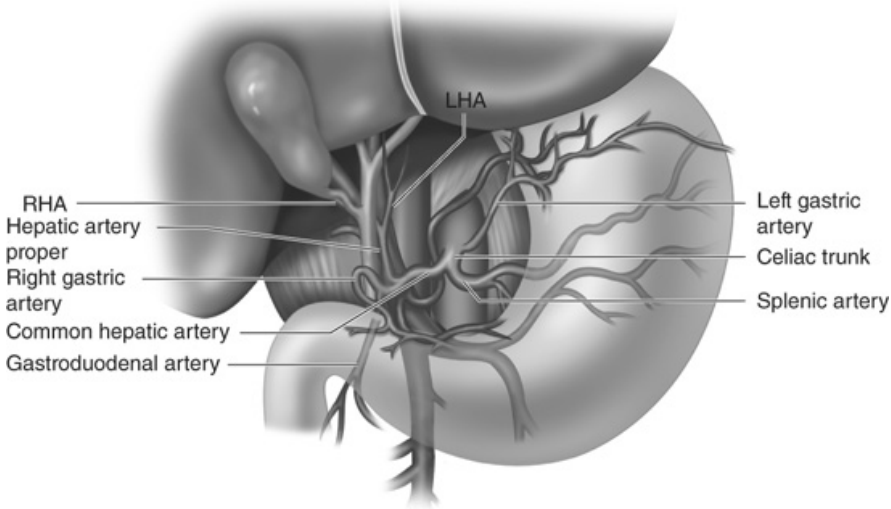

Fig 3: Arterial supply in the liver

Pressure in the hepatic artery: 100 mm of Hg.

Pressure in the hepatic arterioles: 30–40 mm of Hg[4].

Hepatic blood flow (70% is supplied by the portal vein and 20% to 25% is supplied by the hepatic vein):

In the case of women: 1200 ml/minute

In the case of men: 1800 ml/minute.

Total liver volume accounts for 10% to 15% of total blood volume in a normal adult.

Oxygen consumption of the liver is 6 ml/minute/100 gram of wet weight.

There are three zones in the liver lobules.

A. Zone 1: This is the acino-peripheral region where there is the best supply of oxygen and aerobic metabolism.
B. Zone 3: This is the centroacinar region which has the lowest oxygen supply and anaerobic metabolism.

C. Zone 2: This zone is between zones 1 and 3.

A decrease in blood supply occurs in the following conditions:

A. Old age
B. Sleep
C. Fasting condition
D. Standing condition.

The blood flow into the sinusoids is influenced by the following:

A. Neural factors:
    a. Adrenergic receptors
    b. Dopaminergic receptors.
B. Anatomical mechanism.
C. Vasoactive substances:
    a. Carbon monoxide
    b. Endothelin
    c. Adenosine.

Portal vein (Fig 4):

Posterior to the pancreatic isthmus the superior mesenteric vein and the splenic vein join to form the portal vein. The inferior mesenteric vein joins the splenic vein near the origin of the portal vein. Now the portal vein runs through the hepatoduodenal ligament and reaches the porta hepatis where it divides into the right and left branches.

A. The right branch takes two veins:
    a. Cystic vein
    b. Two veins from the caudate lobe.
B. The left branch flows with the paraumbilical vein.

Now the branches extend into the portal tract, here they merge with the interlobular veins which divide into the conductor veins or the venulae interlobulares. These conductor veins again divide into the distributor veins which ultimately continue as the terminal branches. So portal blood passes through the periportal limiting plate via the venous inlets of hepatocytes and ultimately enters into the hepatic sinusoids. Again, the terminal branches of the hepatic artery join with the sinusoids. So, the hepatic sinusoids contain 75% of the portal venous blood and 25% of the hepatic arterial blood. From the sinusoids the mixed blood will enter into the central hepatic vein or the terminal hepatic vein via the venous capillaries.

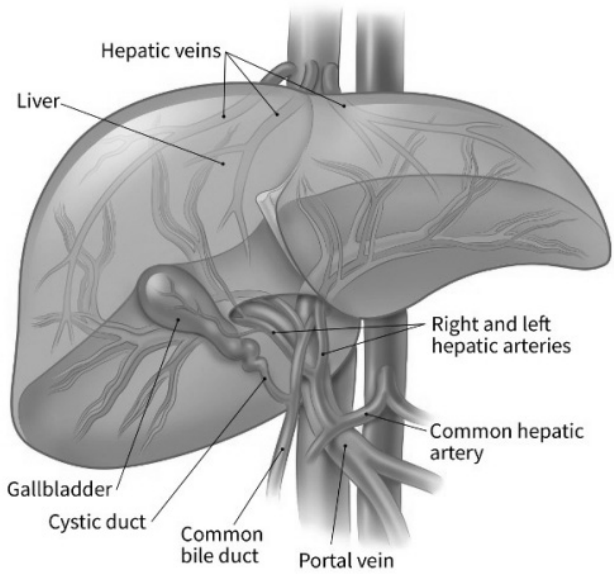

Fig 4: Portal vein in the liver

Hepatic vein (Fig 5):

This vein arises from the central hepatic vein at the center of the hepatic lobule. The central hepatic veins run at acute angles as the sublobular veins. These veins join together to form the collecting veins. These veins in turn fuse to form 5 trunk veins, these are:

A. Right superior hepatic vein
B. Left superior hepatic vein
C. Right hepatic vein
D. Left hepatic vein
E. Intermediate hepatic vein.

These veins then progress intersegmentally, and receive branches from adjacent segments.

The group of superior hepatic veins drains into the inferior vena cava at the posterior surface of the liver below the diaphragm.

The group of inferior hepatic veins varies in respect to the diameter, number and draining sites.

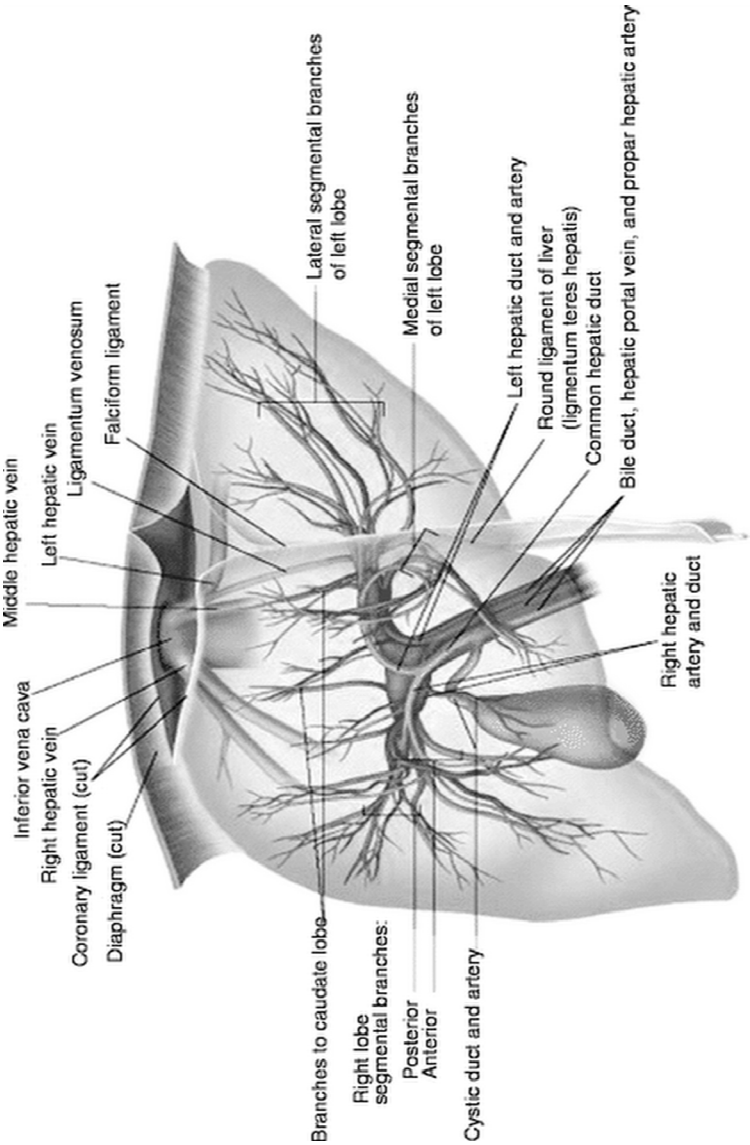

Fig 5: Hepatic vein and its branches

Biliary system:

This system starts as the bile capillaries which are formed as a groove bounded by 2 adjacent liver cells, so they have no wall, but they are surrounded by a special zone of the cell membrane i.e. the pericanalicular ectoplasm. The surface of the bile canaliculi is increased by the presence of microvilli. These canaliculi extend into the ampulla like extension called Haring's canal which is the beginning of the ductules called intermediate ductules. Here the ductules are lined by cuboidal epithelial cells. Due to their extreme proneness to damage they are also described as the "Achilles' heel of the liver". These peri ductules merge with the following:

A. Cholangioles
B. Biliferous ductules
C. Perilobular ductules.

These ductules end in the interlobular bile ducts with a diameter of more than 50 μm which run into the connective tissue wedges of the portal tract which are called Glisson's triangles. These ducts will be interconnected with each other to form larger septal ducts of 100–400 μm in diameter and segmental ducts of 0.4–0.8 mm. Again, these ducts continue to the right and left hepatic ducts which join at the porta hepatis into the common hepatic duct. This common hepatic duct joins with the cystic duct to form the common bile duct or the ductus choledochus.[5,6]

Lymph vessels:

Lymph arises from the following areas:

A. Disse's space – this is the main source of the lymph.
B. Mall's space which lies in between the lining plates and the portal connective tissue.

Lymph capillaries start at the adventitia of the sublobular veins running along the hepatic veins and drain into the para caval lymph nodes. These vessels have valves which direct the flow of the lymph in one direction. These vessels are extensively present in all portal fields mainly the capsule of the liver and the perivascular connective tissue. The lymph from the liver reaches the thoracic duct via the valved lymph trunks which are interconnected.

Sinusoidal cells: These cells comprise 31 million/mg of liver tissue, and constitute 6.3% of liver volume.

Four different types of sinusoidal cells are seen in the liver. These are:

A. **Endothelial cells:** These cells constitute 2.8% of the total liver cell volume. These are flat cells. They have connections with neighboring endothelial cells as well as the microvilli of hepatocytes. They form the continuous lining of the sinusoids which possess many intercellular spaces; here arterial and portal blood combine and their entry as well as their exit are being controlled by sinusoidal sphincters. Sinusoids have a collection of small pores having a diameter of 0.1 μm which is known as a sieve plate. Sinusoids also contain large pores of 0.5 μm in diameter called fenestrae. Functions of these cells:
   a. These pores act as a filter of the components of the blood.
   b. They have scavenging functions.[7]
   c. These sinusoids are responsible for regulating the exchange of fluid and material in between the blood present in the sinusoids and the hepatocytes.
   d. They are responsible for maintaining the balance of lipids, cholesterols and vitamin A.
   e. The following are formed and secreted by endothelial cells:[7,8]
      i. Cytokines like, II, 1, IF, α-TNF
      ii. Matrix, like, collagen, fibronectin
      iii. Growth factors, like, HGF, IGF, FGF
      iv. Vasoactive factors, like, nitric oxide, endothelin.

   These cells can be damaged by the following factors:
   a. Toxins
   b. Alcohol
   c. Hypoxia
   d. Different viruses
   e. Increased pressure in the sinusoids.

These endothelial cells, Disse spaces and vascular hepatocytes are named as a “perisinusoidal functional unit”.

B. **Kupffer cells:** These cells constitute 25% of sinusoidal cells. They are derived from monocytes and are released by stem cells in the bone marrow and are responsible for monocytic phagocytosis. They are called “stellate cells” for their villiform irregular and star-shaped surface. These cells are randomly

distributed in the sinus endothelium. They also connect adjacent cells and sinusoidal spaces with the help of ramifications and pores. Sinusoidal blood will wash the charged Kupffer cells. These cells have the following functions:

a. Phagocytosis – this is a very important function of Kupffer cells.
b. They have the greatest intravascular phagocytosis.
c. Signal substances, like, cytokines, growth factors, erythropoietin, eicosanoids, proteins and enzymes.
d. Toxins, antigen-antibody complexes, and purines are cleared by these cells.

The actions of these cells are reduced by the following factors:

a. Alcohol
b. Drugs, like, mitomycin, α-methyldopa.[9, 10, 11]

C. **Ito cells:** These are called fat storing cells or lipocytes as they contain numerous cytoplasmic fat droplets and abundant vitamin A and lie in the Disse space. Retinol ester is absorbed by hepatocytes and hydrolyzed to retinol and passes either into the blood or is transported into the Ito cells and stored. These cells constitute 1.4% of the total volume of the liver. The greatest number of Ito cells is present in zone 3 of the acinus. The functions of the Ito cells are the following:

a. They regulate the width of the sinus endothelium.
b. They regulate the microvascular tone as well as the regeneration of cells.
c. Their filaments and organelles are responsible for protein synthesis.
d. They have the capability of transforming into myofibroblasts.
e. These cells synthesize the following substances:
   i. Collagen type I, III and IV.
   ii. Fibronectin
   iii. Laminin
f. These can express a protein called Desmin
g. These cells are responsible for fibrogenesis and intralobular fibrosis.[12, 13]

D. **PIT cells:** These were first demonstrated in the rat's sinusoidal cells. But later on, they were demonstrated in the sinusoids and the Disse space. Pseudopodia are present in these cells. The functions of these cells are:

a. They are the natural killer cells and responsible for the destruction of tumor or foreign cells and necrosed cells.

b. Their classification as APUD cells can be justified because of the polarized distribution of their granulae.[9, 14, 15]

Hepatocytes (Fig 6): These cells were first discovered by MH Dutrochet in 1824. These are polygonal cells with six or more faces corresponding to their individual position. The life span of hepatocytes is 150–200 days, and these cells perish as oncocytes – this programmed death of old cells is known as apoptosis. The contoured cell membrane of hepatocytes has been divided into three compartments defined by morphological as well as functional cellular polarization:

A. 37% of the external area of this cell membrane is a sinusoidal surface with numerous microvilli which increase the absorptive and secretory functions of hepatocytes. They lie in the space of Disse. Part of the membrane often protrudes through the fenestrae into the sinusoid and thus comes in contact with the blood.
B. 12% of the outer membrane of the hepatocyte consists of canalicular surface – this is the secretory pole of the cell.
C. 50% of the external membrane constitutes the smooth intercellular fissure and it is connected with the space of Disse but this fissure is completely separated from canaliculi by tight junctions, it is also called the zonula occludens – it only accepts the exchange of water and cations.

The other two zones, intermediate junctions and desmosomes are also known as the zonula adhaerens and the macula adhaerens respectively. Both are sealed by membrane proteins but they contain tube-like connections (gap junctions) which connect two adjacent hepatocytes and facilitate intercellular exchange. But at the time of hepatocellular death these junctions will be closed to prevent the progression of cell death.

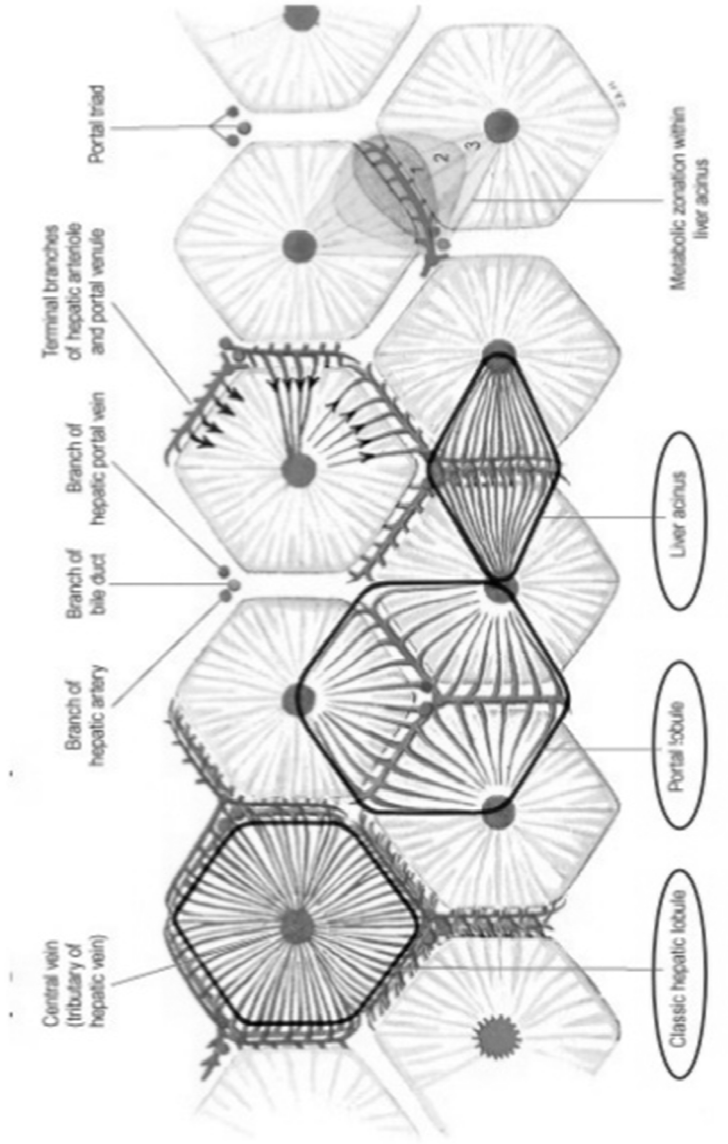

Fig 6: Figure of hepatocytes

Biliary epithelial cells: These cells are organ typical. They line the biliary duct. These contain fewer mitochondria, the endoplasmic reticulum, and an absence of cytochrome P 450 but they are rich in cytoskeleton and Golgi apparatus as well as vesicles. These cells are responsible for biligenesis.[16]

Nervous system: Nerves of the liver consists of:

A. Fiber from sympathetic ganglia T_7 to T_{10}.
B. Vagus nerve
C. Right phrenic nerve.

They produce two plexuses. These are:

A. At the porta hepatis around the hepatic artery
B. Around the portal vein and biliary tract.

Hepatic lobules:

There are three types of hepatic lobules. These are:

A. **Central vein lobule:** This looks like a type of hexagonal architecture with a portal tract at the corners. It consists of 15–25 liver cells radially arranged and placed in between limiting lamellae and the central vein. These arrangements of the liver cells are due to the suction effect of the right ventricle. In between the liver cell plates there are hollow spaces where the space of Disse and sinusoids are located. Each lobule is limited by surrounding periportal fields. This limiting plate is made of basophilic and glycogen free liver cells which have a chromatin rich nucleus and the plate is penetrated by capillaries. As it is unicellular it lies perpendicular to the remaining liver plates. In the periportal side it is limited by the space of Mall, so it is enriched only by periportal sinusoidal blood on the lobular side. This limiting plate constitutes a dividing wall in between the parenchyma and the mesenchyma. This lobular architecture shifts the periportal field with branches of the hepatic artery and the portal vein towards the periphery and the central vein in the center, as a result there will be a centripetal blood flow.
B. Portal vein lobule: In this type of lobule, the periportal field and the central veins constitute the center and the limiting points respectively. The main characteristic of this lobule is the glandular character of the liver. Here the direction of flow is

centrifugal i.e. from the center towards the periphery, whereas the direction of biliary flow is from the periphery towards the center i.e. centripetal.

C. Liver acinus: On the basis of the microcirculatory hepatic unit, the hepatic acinus can be assessed. The center of the acinar structure is formed by:
   a. The portal vascular bundle
   b. Terminal branches of the hepatic artery
   c. The fan-shaped diverging portal vein after its penetration into the lobule.

The above vessels are responsible for the circular blood supply of the related hepatic parenchyma. The shape of this area is rhomboid with its outer angles formed by two central veins of the adjacent lobule and the diagonal corresponds to the central and portal vessels. Central veins present at the periphery of the acinus which drains the venous blood – it is known as the terminal hepatic venule or the terminal hepatic vein. This acinus also acts as a secretory unit for bile transport. Here, blood flow occurs centrifugally and bile flow occurs centripetally. Three or more acini form the complex acinus. According to recent findings, zones 1 to 3 do not surround the terminal afferent vessels like an onion but are arranged in a circular form.

The blood supply in different zones of the acinus varies according to the distance of the liver cells from the periportal areas as well as the terminal vessels respectively.

A. Zone 1: This has the highest supply of oxygen and substrates. It is present adjacent to the limiting lamellae.
B. Zone 2: This is the intermediate zone having less blood supply. Since it has no functional boundaries, this zone has two imaginary halves which can be added to zone 1 and zone 3.[17]
C. Zone 3: This is present nearer to the center so obviously has a very low blood supply. It has least resistance to damage by different insults. Again, it has least regenerative capacity.

Again, zones around the periportal area, three concentric circles A, B and C, are formed and have a similar decrease in blood supply.

Stroma of the liver: The extracellular matrix is a dynamic component of the complex macromolecules produced by Ito cells. It has both mechanical as well as physiological functions. The matrix components include:

A. Collagen: This has a half-life of 30 days. It is degraded by the matrix-metalloproteinase which is also formed by Ito cells. The degradation product hydroxyproline will be either excreted through urine or oxidized into carbon-di-oxide and water. The types of collagens are:
    a. Large fibrils: Collagen I, III. Type I is present around the portal tract in bundles. Type IV is present around the portal bile duct and the blood vessels.
    b. Net structure: Collagen IV.
    c. Small fibrils: Collagen V, VI.
B. Glycoproteins
C. Elastin
D. Glycosaminoglycans
E. Proteoglycans

Four types of stromal tissue are present. These are:

A. Capsule of the liver: This consists of endothelial cells, collagen and elastic fibers. This capsule and the falciform ligaments are supplied by the phrenicoabdominal branch of the phrenic nerve. In the case of liver biopsy there may be referred pain towards the shoulder. The inner surface of the capsule is attached to the liver parenchyma in the area of the interlobar connective tissue. The following structures are present in the liver capsule:
    a. Blood vessels: These vessels anastomose with branches of the portal veins.
    b. Lymph vessels
    c. Rudimentary bile ducts.
B. Perivascular connective tissue: This starts from the porta hepatis as tree-like branching surrounding interlobular vessels, the central hepatic vein along with its tributaries. This structure prevents the suctioned induced collapse of the venous vessels which is developed as a result of respiration dependent negative pressure in the pleural cavity.
C. Lattice fiber network: This lies on the hepatic cell plates providing mechanical support for the sinusoids and as the directrix of hepatocyte regeneration. Through this layer

microvilli of hepatic cells extend into the Disse space which is 15–20% of the liver volume. The exchange of different substances occurs between the liver cells and the blood through this space. The width of this space varies with the resorptive as well as the secretory capacity of the hepatocytes.

D. Portal tract: In the portal tract the following structures are enclosed in the perivascular connective tissue:
   a. Portal vein
   b. Hepatic arterioles
   c. Bile ducts
   d. Lymph vessels
   e. Nerve fibers.

Continuous-lining hepatocytes immediately bordering the portal tract are known as the limiting plate.

Functions of the liver:

The integrity of the morphological and functional areas of the liver cells is vital for the health of human beings. About 500 different biochemical processes occur in a single liver cell. About 12 metabolic processes occur in the liver cell either continuously or according to specific requirements. These metabolic processes are responsible for synthesis, degradation, activation or deactivation of different substances. Intermediate products or the end products generated during the metabolic pathways may be used for other pathways. Again, there are links in different metabolic pathways. The following metabolic functions occur in liver cells:

A. ***Bilirubin metabolism:*** This organic anion is produced from the aging erythrocytes in the following organs:
   a. Spleen
   b. Bone marrow
   c. Liver – hepatocytes and Kupffer cells
   d. Kidneys
   e. Bone marrow.

From 1 gram of hemoglobin 36.2 mg of bilirubin is produced.

The daily output of bilirubin is 250–350 mg.

Hemoglobin has been broken down to heam + globin

↓←Heam oxygenase

This enzyme complex contains inducible cytochrome 450 which increases bilirubin production if the hemoglobin level is elevated.

↓←Biliverdin Ixα

Bilirubin reductase

↓

Bilirubin Ixα

(Apolar, water soluble lipophilic toxic substance)

A small portion of bilirubin will come from the degradation of other metalloprophyrins

↓

Bilirubin binds with albumin to produce bilirubin + albumin complexes

[If the serum bilirubin concentration is >4 mg/dl, the binding capacity of the albumin will be exceeded. In the case of acidosis, the binding capacity of the albumin will be decreased or the binding capacity of the albumin will be oversaturated; hepatocytes are prone to be damaged by an unbound fraction of bilirubin diffused into the cells. But albumin bilirubin complexes act as an anti-oxidant to intercept free radicles or oxygen radicles.[18]

10%–20% of shunt bilirubin is formed from the breakdown of the erythrocyte precursors in the bone marrow in the first 3 days of life and a smaller proportion is produced in the liver.]

↓

Albumin bilirubin complexes will be transported to the sinusoidal membrane of the hepatocyte

↓

There is dissociation of this complex. Albumin will bind to the sinusoidal surface of the cell membrane

↓

Bilirubin uptake is mediated through non-specific membrane glycoprotein against the concentration gradient into the hepatocyte

↓

Binding of bilirubin with the Y protein (ligandin) is affected in the cytosol of the hepatocyte thus preventing movement from the cytosol into the cellular organelles and back diffusion into the bloodstream

↓

When the bilirubin concentration is increased and the Y protein is saturated, the excess bilirubin will bind to the Z protein (transport reserve protein, acid binding protein) in large amounts in spite of the low affinity of this protein to bilirubin

↓

Bilirubin will be conjugated in the sarcoplasmic endoplasmic reticulum with glucouronic acid through the action of UDP-glucuronyl transferase mediated by microsomal enzymes to form bilirubin monoglucuronide (20%–40%) and subsequently diglucuronidation takes place in the riboplasmic endoplasmic reticulum. This bilirubin diglucuronide is water soluble, conjugated, and eliminated in bile and urine.

↓

A small amount of bilirubin is covalently bound to protein and reaches the serum as δ-bilirubin having a half-life of 14 days

↓

This conjugated bilirubin is actively excreted into the biliary canaliculi by means of nonspecific transport proteins independent of bile acids. Many substances sometimes compete for these nonspecific protein carrier systems

↓

Bilirubin is transported with cholesterol, bile acids and phospholipids as mixed micelles

↓

Bilirubin diglucuronide is excreted into the intestine along with the bile. No absorption takes place from the gall bladder and the intestine

↓

Bilirubin glucoronide will be broken down to glucouronic acid moieties and bilirubin by enteric bacteria

↓

Released bilirubin is converted into stereoisomeric urobilinogen by bacterial reductase

↓

This urobilinogen will be oxidized into urobilin and stercobilin. These products along with their degradation products make the color of the stool brown

↓

1% of urobilinogen is reabsorbed and transported back to the liver through the portal vein and resecreted into the bile. This is known as the enterohepatic circulation

↓

1.0–3.5 mg/day of urobilinogen is excreted in urine and 40–280 mg/day of stercobilinogen is excreted in stool.

Porphyrin metabolism:

This is the prosthetic groups of hemoproteins, like, hemoglobin, myoglobin, cytochromes, etc. The parent compound of porphyrin is tetranuclear pyrolic dye, porphin. 80%–85% of heam synthesis usually takes place in bone marrow and 15% takes place in the liver. Two-thirds of the heam synthesized in the liver is required for cytochrome P450 formation. Daily, approx. 300 mg of heam are produced of which 1% is excreted in urine and stool.

In the mitochondria of liver cells, the beginning and completion of heam occur through a series of cytosolic reactions.

Succinyl CoA + glycine
δ-aminolevulinic acid synthatase — **Liver**
δ-aminolevulinic acid ↓
Porphobilinogen synthetase
Porphobilinogen
↓ Deaminase — **Cytosol**
Pre-uroporphyrinogen
↓ Uroporphyrinogen III synthatase
Uroporphyrinogen III
↓ Uroporphyrinogen decarboxylase Coproporphyrinogen III
Oxidase
↓Protoporphyrinogen — **Liver**
Oxidase
↓Protoporphyrin
↓Ferrochelatase
Heam

Δ-aminolevulinic acid is subject to negative feedback control by the heam produced, so that the heam can control its synthesis. Porphyrin as the irreversible oxidation product is excreted through urine. In pathological conditions they are stored in the cells but an intermediary product, like protoporphyrin IX is excreted in the urine and other products, like, coproporphyrin III and uroporphyrin I are excreted in stool. The following drugs are responsible for inducing δ-aminolevulinic acid:

A. Barbiturates
B. Estrogen
C. Androgen
D. Fasting