

Training workshop on screening, diagnosis and treatment of hepatitis B and C

Session 2

Structure and functions of the liver

Learning objectives

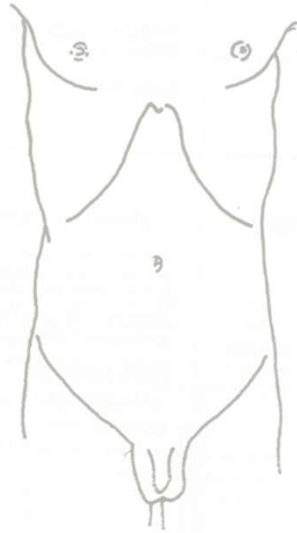
At the end of this session, participants shall be able to understand the following concept

- Gross anatomy of the liver and its blood supply
- Microanatomy of the liver and its vasculature
- Liver fibrosis and its grading
- Functions of liver

I welcome all the participants to this first session of the entire training programme.

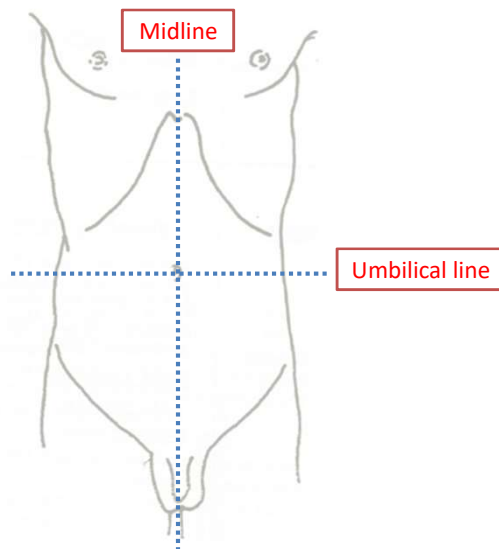
In this session, we will learn about the basics of the liver in terms of its anatomy, microscopic structure, and a few very important physiological functions that are most relevant in the context of viral hepatitis. We will also learn about acute and chronic liver injuries, and development of liver fibrosis in response to longstanding ongoing chronic injury such as chronic viral hepatitis. By the end of the session, we will be able to understand the pathological effect of liver injury and liver fibrosis on the human body.

Quadrants of abdomen



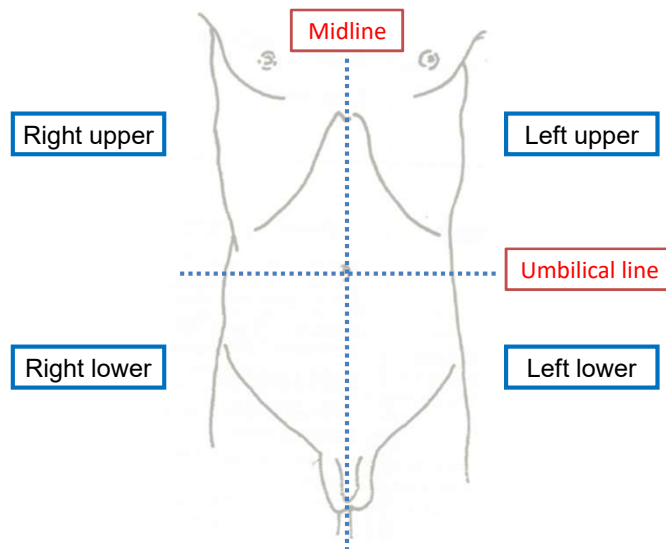
We all know that the abdomen extends vertically from the xiphisternum (above) to pelvic bone (below).

Quadrants of abdomen



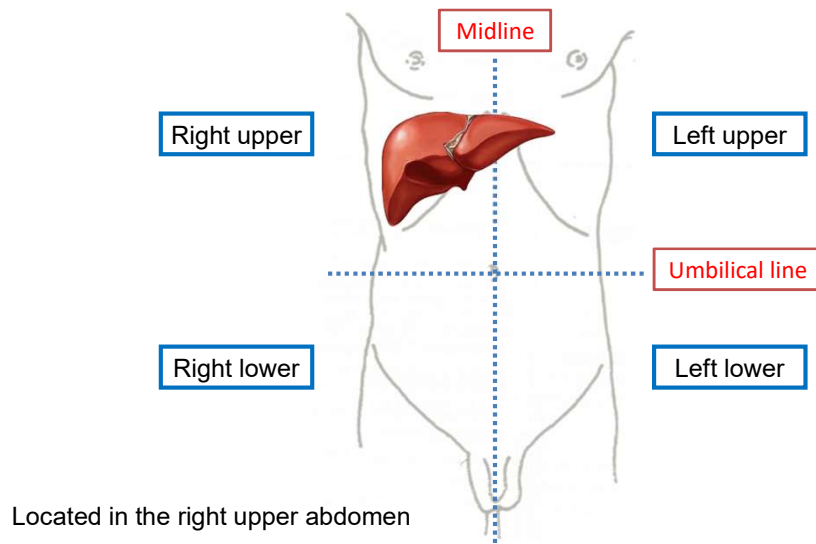
The entire abdomen is divided into four quadrants by a vertical line (from the xiphisternum to the pubic symphysis) and a horizontal line (drawn across the umbilicus).

Quadrants of abdomen



The four quadrants of the abdomen are: right upper, right lower, left upper and left lower.

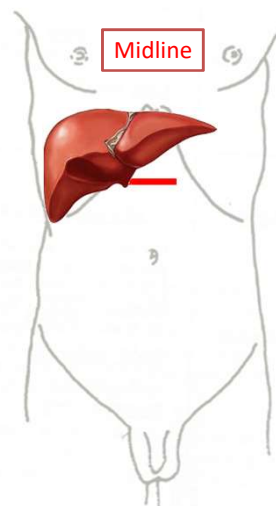
Quadrants of abdomen



The liver is located in the right upper quadrant of the abdomen.

Position of liver

- Located in the right upper abdomen
- Protected by the right rib cage
- Measures: 12–15 cm in vertical direction
- Weight: ~1500 g
- Two lobes
 - Right: Extends till near the right costal margin (the lower edge of the rib cage)
 - Left: Extends midway between xiphisternum and umbilicus



The liver is located deep in the right upper quadrant and is well protected by the right rib cage. Its size, as measured in the right midclavicular line, is about 12–15 cm and its weight is about 1500 g. The weight of the liver is approximately 2.5% of the body weight.

The right lobe of the healthy liver is not usually palpable. The left lobe may be palpable up to midway between the xiphisternum and umbilicus. This means that a palpable left lobe, in isolation, is not of clinical importance. In a patient, the consistency (normal consistency is firm), surface (normal is smooth, non-tender) and margins (normal is regular) of the liver are much more important features than the liver size alone.

Blood supply of liver

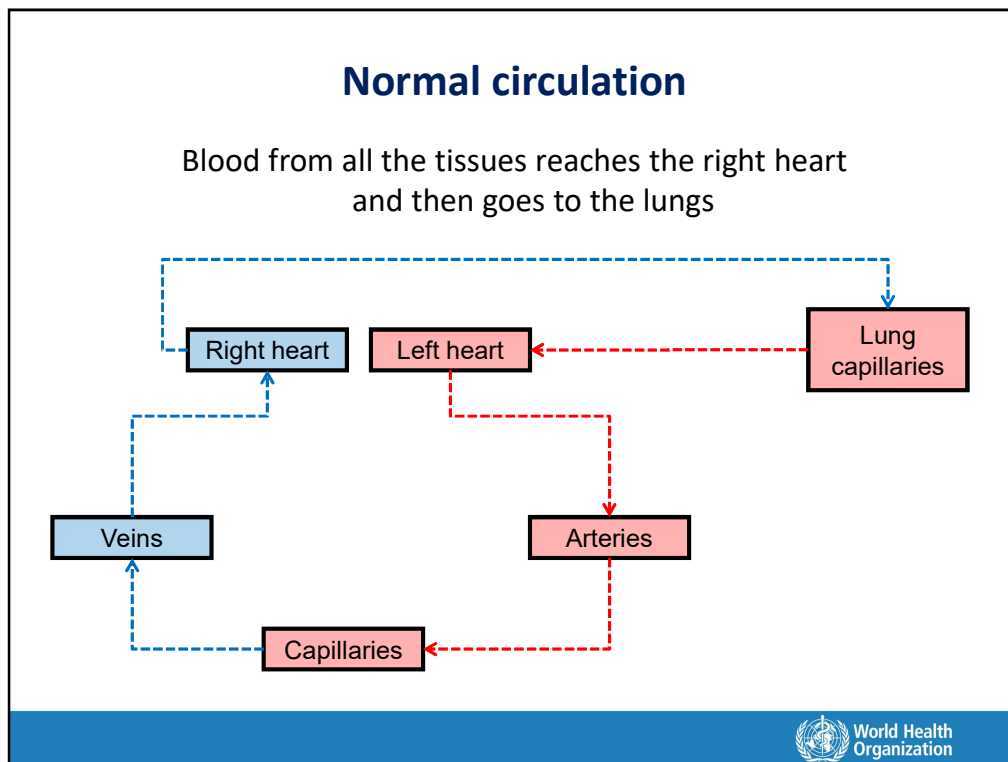
- Blood flow ~ 1500 mL/min
~ 25% of cardiac output (what the heart pumps)
- Dual blood supply
- Nature of blood flow

Hepatic artery	1/3
Venous blood (portal vein) from the intestine	2/3



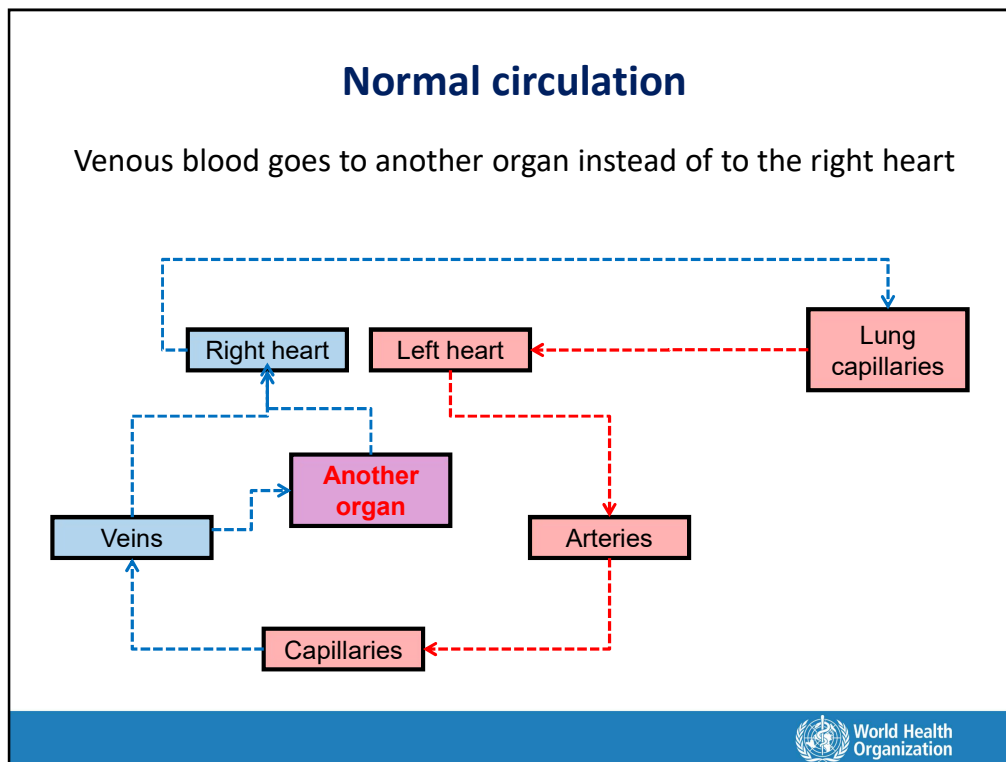
The liver is a very vascular organ. About 1500 mL of blood passes through the liver every minute, which is approximately 25% of the cardiac output (normal cardiac output is 5 L/min). Compared to its weight (which is about 2.5% of the body weight), it receives a massive blood supply.

It is important to realize that the majority (about 65%) of the blood supplied to the liver is deoxygenated venous blood (which carries much less oxygen than arterial blood) from the small and large intestine. Only one third of the supply is oxygenated arterial blood and carries a high level of oxygen. This dual blood supply serves three important functions. First, the dual blood supply gives a safety cushion to the liver and keeps it alive even if one supply is terminated because of some pathological state. Second, the venous blood carries several harmful substances, toxins and biological products derived from food and gut bacteria present in the large intestine; the liver acts as a filter that prevents the systemic circulation from exposure to these substances; when this filter function of the liver is impaired, such as in patients with liver failure, these harmful substances reach to the brain and the patient becomes unconscious. Third, venous blood carries a lot of nutrients from the small intestine; these nutrients, if released unchecked into the circulation, will produce metabolic imbalance. The liver acts as a temporary warehouse to store excessive amounts of these nutrients and releases them at the time of need (such as fasting).



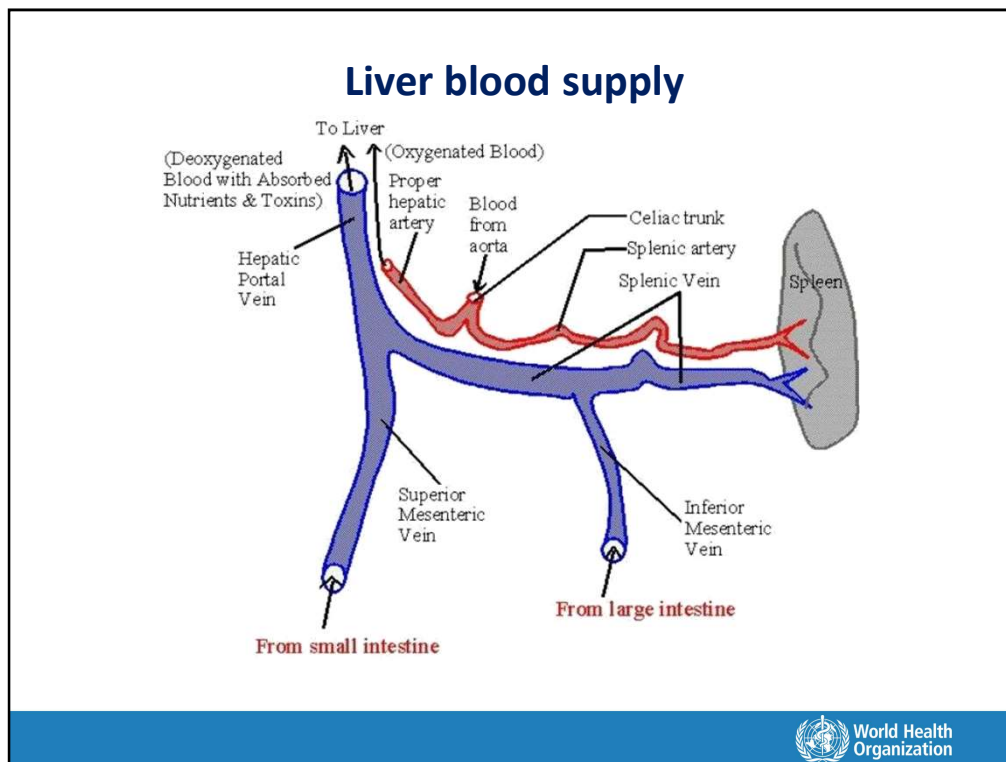
During normal blood circulation, deoxygenated blood is collected from all over the body by the venous system and is pumped by the right side of the heart into the lungs. In the lungs, oxygenation of blood takes place and oxygen-rich blood is returned to the left side of the heart and pumped through the arteries throughout the body.

Capillaries connect arteries to veins. Oxygen and carbon dioxide is exchanged in arteries, and blood collected from the capillaries returns to the lungs through veins.



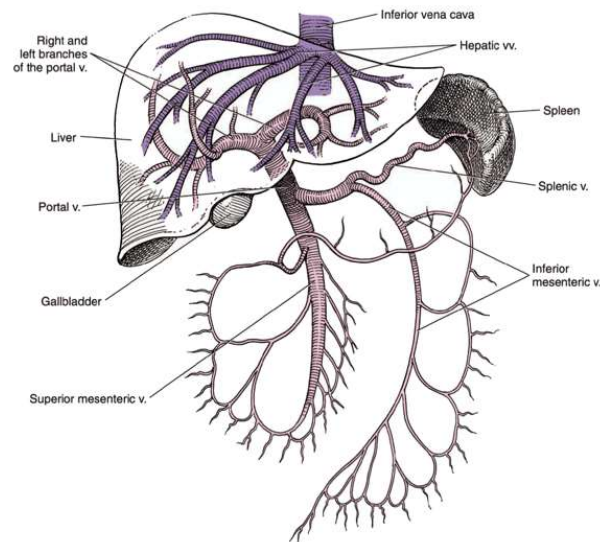
During normal blood circulation, deoxygenated blood is collected from all over the body by the venous system and is pumped by the right side of the heart into the lungs. In the lungs, oxygenation of blood takes place and oxygen-rich blood is returned to the left side of the heart and pumped through the arteries. During normal circulation, the blood collected from the capillaries is returned to the lungs through veins.

In the portal system, the blood returning from the capillaries is not directly returned to the venous system but is again passed through another set of capillaries in another organ or tissue. There are two portal systems in the human body: the pituitary–hypophyseal system in the brain and the second in the liver. The objective of this portal system is to provide the liver with extra circulation time and expose the blood to the extensive network of hepatocyte plates. It helps the liver to perform its metabolic and filtering activities more efficiently.



Almost all the blood coming from the intestine is collected and filtered through the liver.

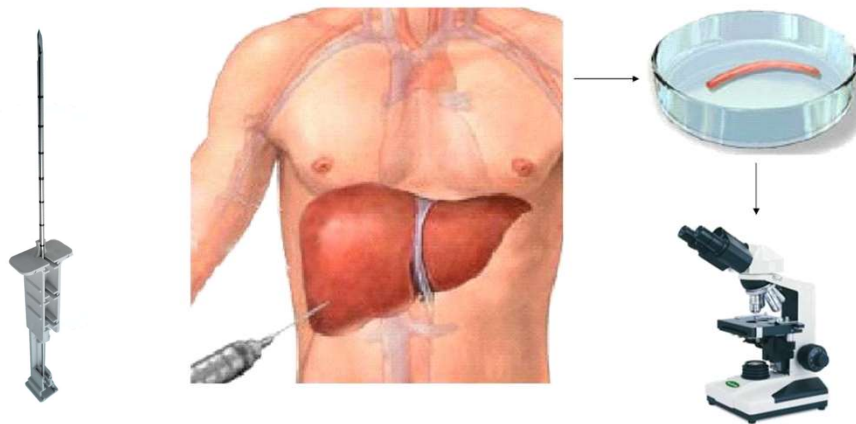
Liver portal system



This picture shows the venous drainage into the portal venous system and the venous drainage of the liver. The portal vein is formed by the superior mesenteric vein (which collect the nutrients and toxin-rich deoxygenated blood from the intestine) and splenic vein (which carries the immune-activated lymphocytes) from the spleen.

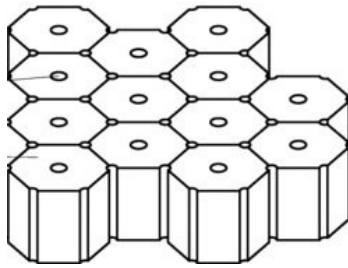
Inside the liver, the portal venous blood is first distributed to the extensive network of sinusoids and is then collected by three hepatic veins: right, middle and left hepatic veins. These hepatic veins drain into the inferior vena cava, which drains into the right side of the heart for oxygenation.

Liver: Microscopic anatomy



Now we will learn the microanatomy of the liver. We have to take out a piece of liver (liver biopsy) with the help of a Tru-Cut biopsy needle and examine it under the microscope. Liver biopsy is a risky procedure and needs hospitalization, skill to perform the biopsy, and a trained pathologist to interpret the findings under the microscope. It carries a finite, though small, risk of death following the procedure. Hence, these days, non-invasive methods are used to study the liver tissue, which we will learn during this course.

Liver: Microscopic anatomy

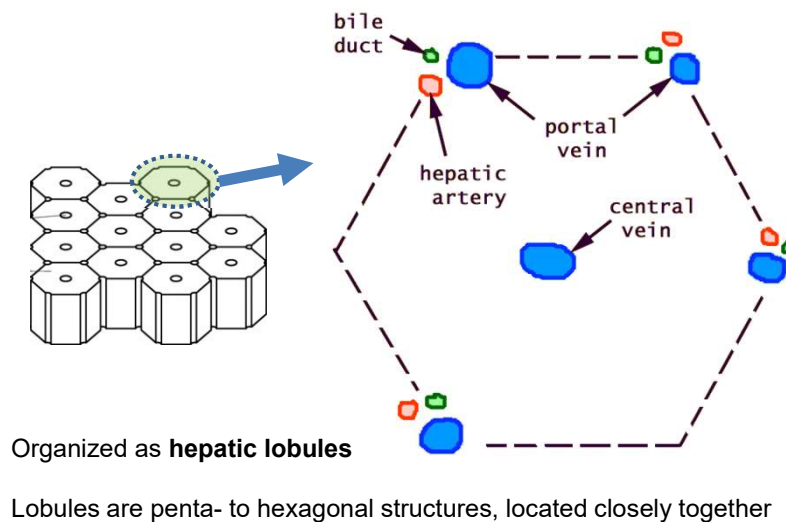


If we see the liver tissue under the microscope, we will find that the hepatocytes (liver parenchymal cells) are organized in **honeycomb**-like structures. These structures are called hepatic lobules. Such lobules are three-dimensional structures and are commonly hexagonal in shape.

Within each lobule, the individual liver cells (hepatocytes) are well organized. We can compare the liver with a large school, liver lobule with a classroom, and each hepatocyte with every single chair inside the classroom. In a well-organized classroom, the chairs are organized in rows and placed at a definite distance, which facilitates easy movement of the students/teachers inside the classroom.

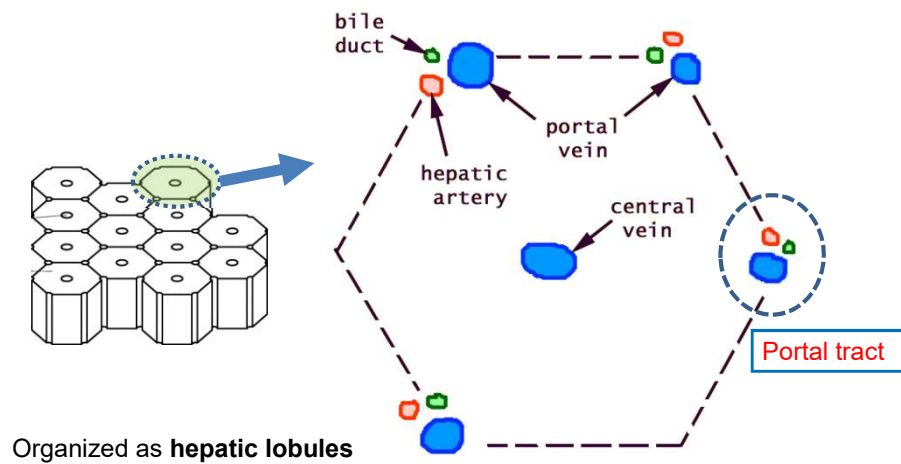
Similarly, inside a liver lobule, hepatocytes are organized in the form of plates (akin to rows in a classroom), which are separated by sinusoids through which blood flows easily without much resistance.

Liver: Microscopic anatomy



Each liver lobule has the following 3 structures in each corner of its hexagon: bile duct (green), portal vein (blue) and hepatic artery (pink). Usually there is one of each of these but sometimes there may be 2–4 bile ducts and sometimes only 2 structures. In the centre of each lobule there is one central vein (blue), which drains into the hepatic veins.

Liver: Microscopic anatomy

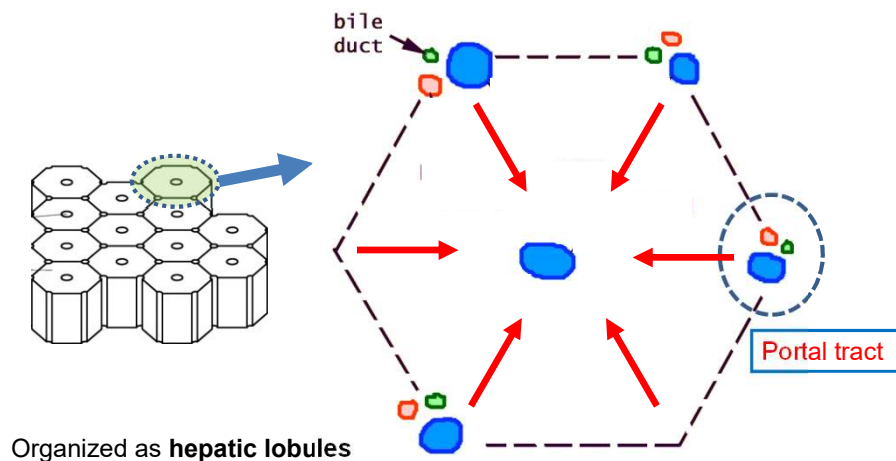


Organized as **hepatic lobules**

Lobules are penta- to hexagonal structures, with **portal tracts** at each corner and central vein in the middle

The three structures, along with the surrounding plate of hepatocytes, at the corner of the hepatic lobule are collectively called a **portal tract**.

Liver: Microscopic anatomy

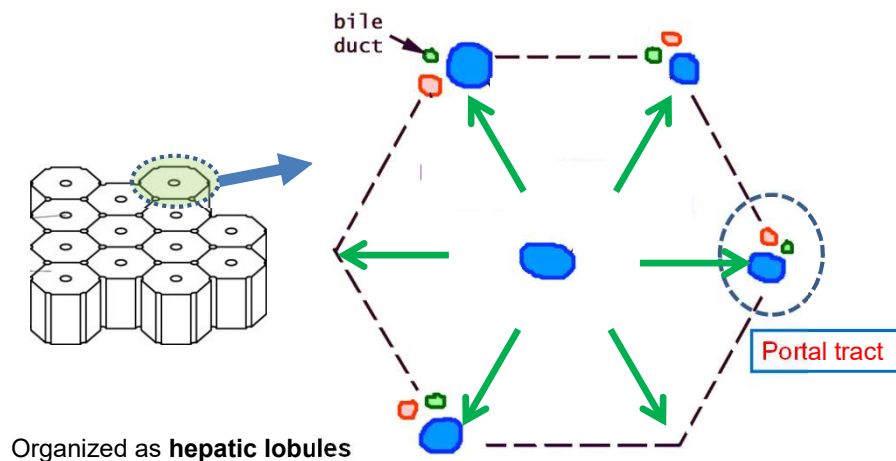


Organized as **hepatic lobules**

Lobules are penta- to hexagonal structures, with **portal tracts** at each corner and central vein in the middle

In each lobule, blood from the branches of the portal vein and hepatic artery enters from the corner and flows in a centripetal direction to drain into the central vein. This flow of blood is slow and under low pressure, which gives adequate time for exchange of material between the blood and surrounding hepatocytes.

Liver: Microscopic anatomy

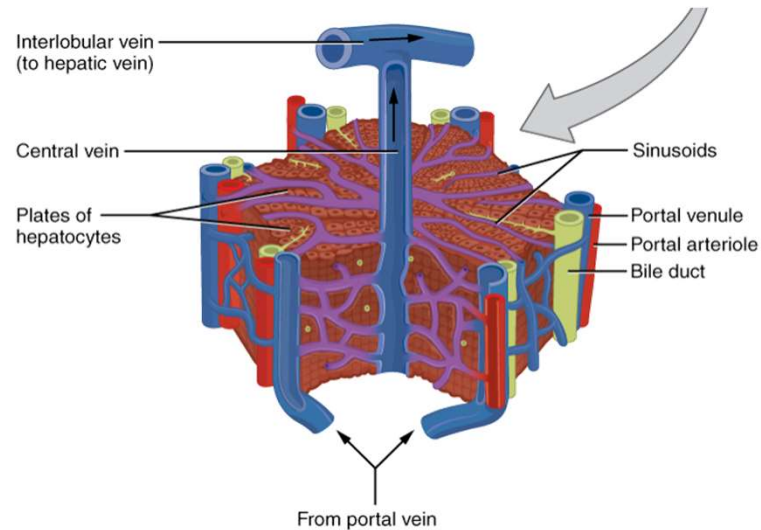


Organized as **hepatic lobules**

Lobules are penta- to hexagonal structures, with **portal tracts** at each corner and central vein in the middle

Bile is produced by hepatocytes. The bile produced by hepatocytes flows in a centrifugal direction (opposite to the flow of blood) to drain into a branch of the bile duct located in the corner of the lobule.

Microscopic anatomy of liver



This is a three-dimensional picture of a hexagonal liver lobule. Each lobule is a three-dimensional structure, which shows the portal tract at each of the corner. Each portal tract has a branch of the portal vein (blue), hepatic artery (red) and bile duct (light green). The entire lobule is packed with hepatocytes organized in the form of plates (brown), which are separated by blood-filled sinusoids (purple).

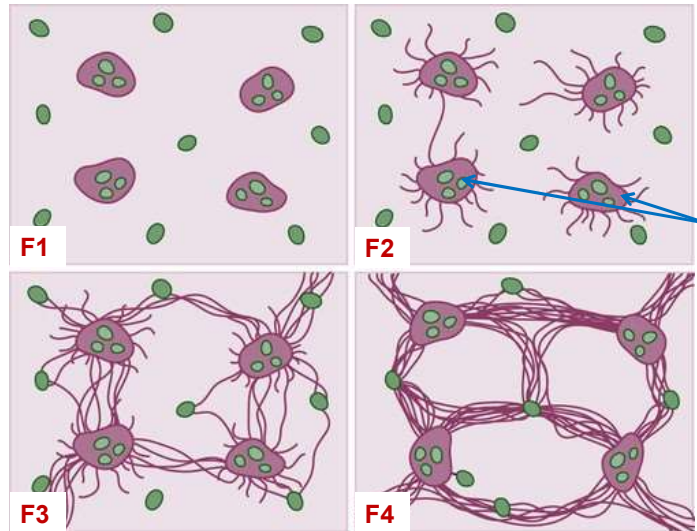
Causes of liver injury

- The liver can be damaged by many insults (**separate talk**)
- Major causes
 - Infections, especially viruses
 - Hepatitis viruses – A to E
 - Non-infectious causes
 - Alcohol
 - Drugs
 - Non-alcoholic fatty liver disease

Till now we have learnt about the normal structure of the liver.

The liver can be injured by any number of agents but the major causes are viral infections (hepatitis viruses such as hepatitis B or C), toxins (alcohol) or drugs (anti-tuberculosis drugs such as INH, rifampicin, pyrazinamide; antiepileptic drugs – phenytoin; paracetamol; oral contraceptive pills, etc.).

Prolonged liver injury leads to scarring (fibrosis)



Fibrosis starts around the portal area and extends gradually into the lobular parenchyma. There are four grades of fibrosis: F1, F2, F3, F4.

Response of the liver to injury

- Acute (short-term) injury
 - Inflammation
 - Swelling and mild enlargement
 - Death of cells and impairment of liver function
- Chronic (long-term) injury
 - Chronic inflammation
 - Fibrosis (scarring)

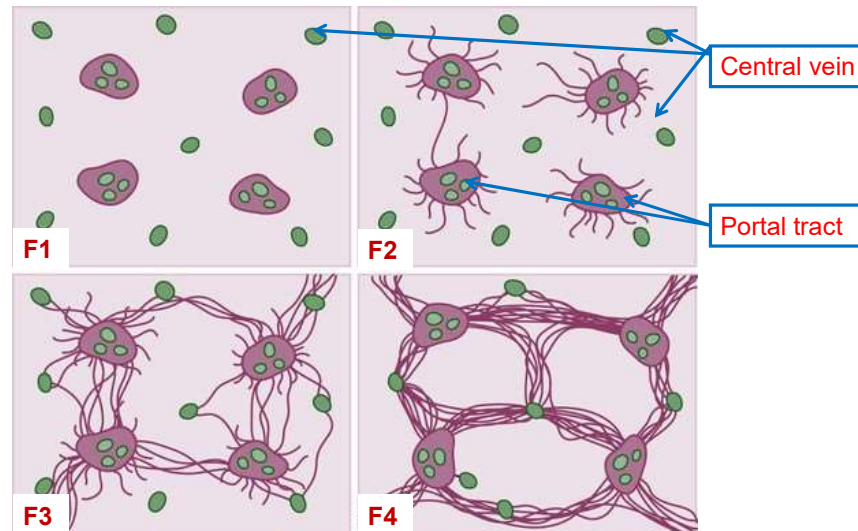
Regardless of the cause, liver injury manifests in form of hepatitis which means inflammation of the liver. There are five components of inflammation. What are these? (The 5 components are: rubor – redness, calor – heat, dolor – pain, tumor – swelling, and loss of function).

Liver inflammation (or hepatitis) could be either acute or chronic.

Acute hepatitis is characterized by sudden and massive death of hepatocytes over a short period of time and is characterized by all the five components of inflammation. Clinically we find liver enlargement (tumor); tenderness on palpation (dolor); jaundice with or without coagulopathy/encephalopathy (loss of function).

In contrast, chronic hepatitis is caused by slow but long-standing injury, which leads to an ongoing process of cell death and healing. Healing during chronic hepatitis is seen as fibrosis.

Prolonged liver injury leads to scarring (fibrosis)



Scarring: particularly affects the central vein and portal tracts (blood vessels)

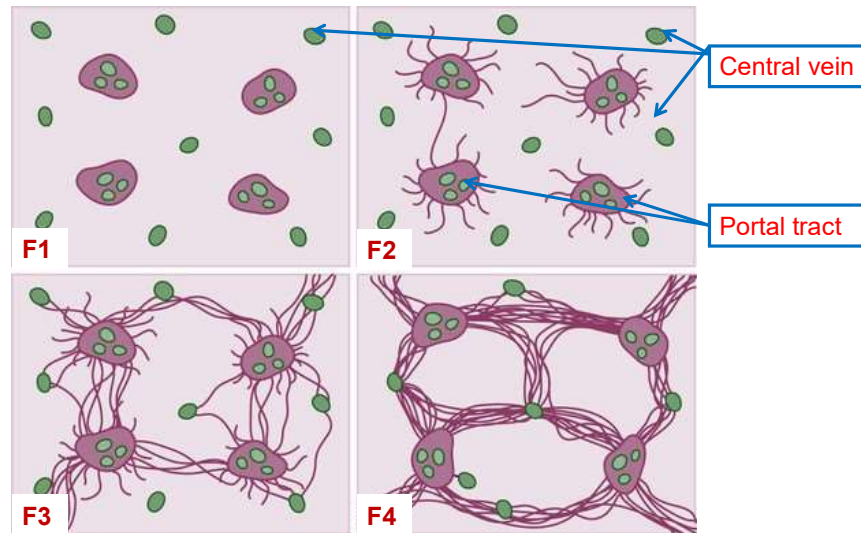
F1 indicates fibrosis in the portal area; the fibrosis has not extended beyond the limiting plate of the portal tract.

F2 indicates portal fibrosis with fibrous septae; thin septae are developing, which have started extending from the portal tract to the liver parenchyma; very few **thin** septae might be seen joining two adjacent portal tracts.

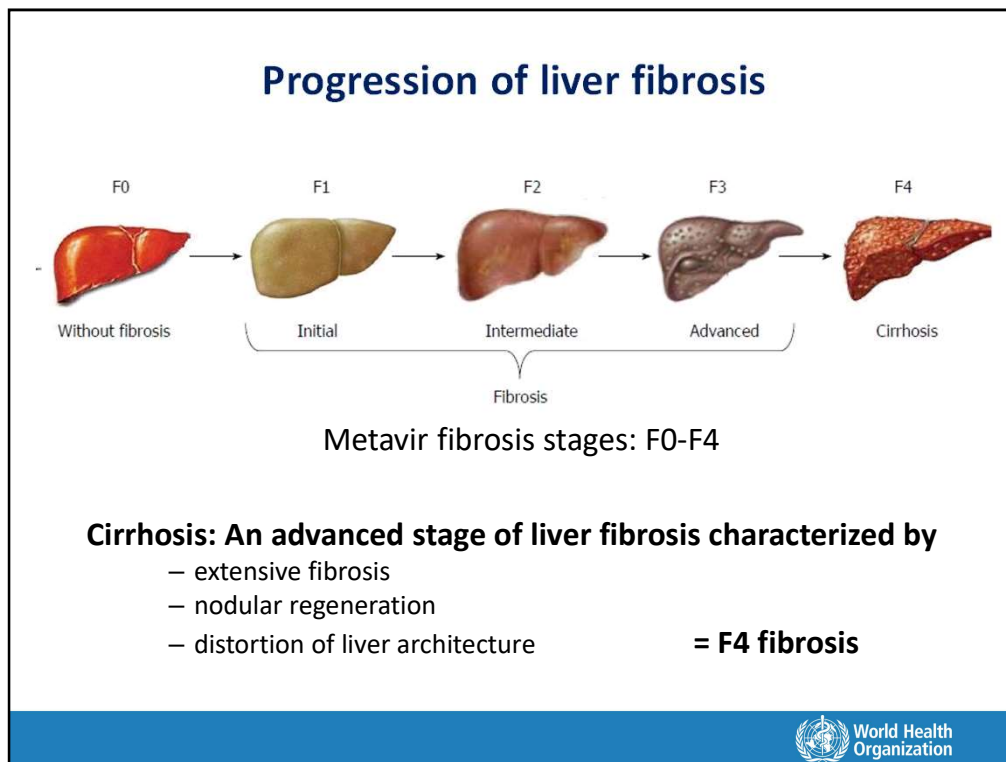
F3 indicates numerous septae without cirrhotic nodules; a number of **thick** fibrous bands can be seen connecting adjacent portal tracts, which convert each liver lobule into a single nodule surrounded by a thick fibrous band; there will be no or very few **thin** bands from the portal tract to the central vein.

F4 indicates cirrhosis, nodule formation or findings suggestive of nodule formation; there will be a number of thick bands extending from the portal tract to both adjacent portal tracts as well as the central veins. Hence, the entire liver lobule is converted into a clump of multiple smaller nodules each surrounded by thick fibrous septae.

Prolonged liver injury leads to scarring (fibrosis)



Fibrosis affects the flow of blood through the portal tracts and hepatic lobules



The spectrum of liver disease ranges from minimal fibrosis to cirrhosis.

Without antiviral therapy, chronic hepatitis gradually progresses to cirrhosis in 20–30 years.

The Metavir fibrosis staging system is a scoring system for assessing liver fibrosis based on pathological findings.

F4 Metavir fibrosis stage is also known as cirrhosis.

Effect of lobular disorganization



Distortion of the architecture of the liver lobule leads to hindrance in blood flow, just as the difficulty caused in trying to move about in a classroom with disorganized chairs.

The fibrosis converts the non-turbulent, low-pressure blood flow in the lobule sinusoids into a turbulent high-pressure flow. This stage is known as portal hypertension.

Effect of liver injury

Two effects

- Impairment of liver function
- Impairment of blood circulation through the liver

As a part of the inflammation of liver injury, there are two types of adverse effects: impairment of liver function and impairment of blood circulation through its parenchyma.

Functions of the liver

Several functions, including some of the following

Glucose metabolism

- During the feeding phase Move glucose into glycogen stores
- During fasting Move sugar from stores to the blood

Excretory function

- Bile pigments (bilirubin)
- Bile salts Important for absorption of fats
- Other harmful substances

Synthetic function

- Albumin
- Coagulation factors



There are three major functions of the liver: (i) glucose metabolism, which maintains the blood glucose within an acceptable range; (ii) excretion of waste substances from the body in the bile; and (iii) synthesis of important body proteins such as albumin and coagulation factors.

Role of albumin: maintains the oncotic pressure; the half-life is 21 days, which is important to know in cases of liver dysfunction.

Liver disease: Effect on liver function

Several functions, including some of the following

Glucose metabolism

- During the feeding phase Blood sugar too high (hyperglycaemia)
- During fasting Blood sugar too low (hypoglycaemia)

Excretory function

- Bile pigments (bilirubin) Jaundice
- Bile salts Poor absorption of fats
- Other harmful substances Unconsciousness

Synthetic function

- Albumin Edema, (ascites)
- Coagulation factors Deranged coagulation, bleeding



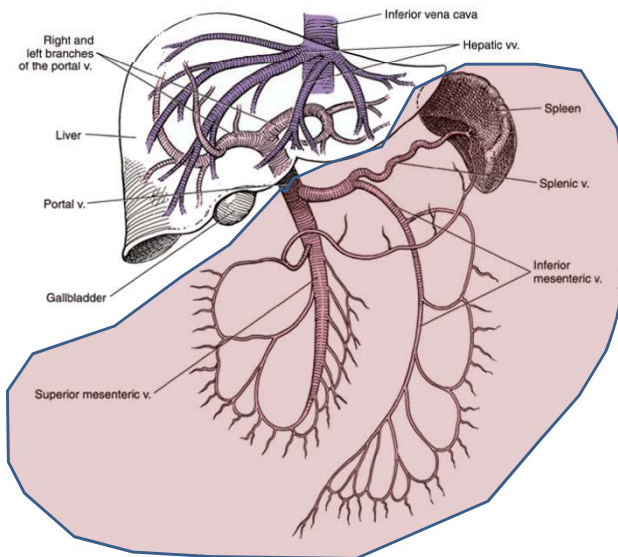
Impaired glucose metabolism results in postprandial hyperglycaemia and post-fasting hypoglycaemia.

Impaired excretion of bilirubin results in jaundice. Impaired clearance of toxic wastes may lead to unconsciousness.

Albumin is the main protein that maintains the oncotic pressure and maintains the body vascular volume. If albumin is not synthesized then fluid will move out from the blood vessels to the third spaces such as the peritoneal cavity and pleural cavities. It results in ascites and pleural effusion.

Impaired synthesis of coagulation factors will lead to bleeding manifestations.

Effect of cirrhosis on liver circulation



Decreased blood flow through the liver leads to high pressure in the portal venous system or **portal hypertension**

Blood vessels proximal to the liver get congested, which is known as portal hypertension.

Liver disease: Effect on blood circulation

- Obstruction of blood flow through the hepatic lobules leads to increased pressure in the portal vein
- Portal hypertension = increased pressure in the portal vein
- Manifestations
 - Development of collateral veins Abnormally enlarged veins (varices)
 - Exudation of fluid into abdomen Ascites
 - Congestion of venous system Splenomegaly >pancytopenia

Portal hypertension results in congestive splenomegaly, ascites, and formation of collaterals at various places. The newly formed collateral vessels manifest as esophageal varices or gastric varices. Hypersplenism results in pancytopenia, in particular, thrombocytopenia.

Summary

- An organ located in the right upper abdomen
- Has dual blood supply, including via the portal vein
- Is metabolically highly active, with many functions
- Continuing liver injury, irrespective of the cause, leads to liver fibrosis of varying degrees (F0 to F4)
- Advanced fibrosis (e.g. F4 or cirrhosis) is associated with
 - Impaired liver function
 - Impaired blood flow through the liver, leading to increased pressure in the portal vein (= portal hypertension)

In summary, the liver is a highly metabolically active organ located in the right upper quadrant of the abdomen. It has a dual blood supply.

Chronic liver injury results in liver fibrosis, which could range from F1 to F4 or cirrhosis.

Fibrosis results in portal hypertension.