CHAPTER 28

Transport & Metabolic Functions of the Liver

First Part

OBJECTIVES

After studying this chapter, you should be able to:

- Describe the major functions of the liver with respect to metabolism, detoxification, and excretion of hydrophobic substances.
- Understand the functional anatomy of the liver and the relative arrangements of hepatocytes, cholangiocytes, endothelial cells, and Kupffer cells.
- Define the characteristics of the hepatic circulation and its role in subserving the liver's functions.
- Identify the plasma proteins that are synthesized by the liver.
- Describe the formation of bile, its constituents, and its role in the excretion of cholesterol and bilirubin.
- Outline the mechanisms by which the liver contributes to whole body ammonia homeostasis and the consequences of the failure of these mechanisms, particularly for brain function.
- Identify the mechanisms that permit normal functioning of the gallbladder and the basis of gallstone disease.

Chapter 28 transport and metabolic function of the liver	• function of liver • biliary system

Liver:

- Largest and essential for life gland
- **Function**:
  1. **Filtering** the blood coming **from GIT** and the blood in the **rest** of the **body**
  2. Conducts **biochemical** and **metabolic functions** (ridding the body of injurious endogenous substances & excreting drug metabolite)
  3. First **port** for absorbed **nutrients**
  4. Supplies most of **plasma proteins**
  5. Synthesizes **bile**

- **Bile** and excreted **metabolites** are **conducted out** of the liver and blood through **biliary system**

INTRODUCTION

The liver is the largest gland in the body. It is essential for life because it conducts a vast array of biochemical and metabolic functions, including ridding the body of substances that would otherwise be injurious if allowed to accumulate, and excreting drug metabolites. It is also the first port of call for most nutrients absorbed across the gut wall, supplies most of the plasma proteins, and synthesizes the bile that optimizes the absorption of fats as well as serving as an excretory fluid. The liver and associated biliary system have therefore evolved an array of structural and physiologic features that underpin this broad range of critical functions.

Functional anatomy:

Liver lobules

- Liver is made from **lobules**
- Each lobule contains hepatic cells arranges in **hexagons**
- Each hexagon contains central vein
- At each corner there are portal trades (a **branches** of **hepatic portal vein**, a **branch of hepatic artery** and a **branch of bile duct**)

Blood percolation

- Blood coming from **GIT** and other viscera reaches the liver via **portal** vein
- Blood coming from the **rest of the body** reaches the liver via **hepatic** artery
- Portal blood and hepatic blood **percolates** in **sinusoids** between plates of hepatic cells
- The percolated blood drained into the **central vein** and then to **hepatic veins** and then to **inferior vena cava**

Extraction processes

- When pass through hepatic plates, the blood **modified chemically**

Bile

- **Bile** (bilirubin, cholesterol, bile slats and waste materials) is formed on the **other side at each plate**
- The bile passes to the intestine via the **hepatic duct**

Blood transit time

- From the portal venules to the central vein **~ 8.4 seconds**

Kupffer cells

- They are **macrophages** that are **anchored** to the **endothelium** of **sinusoid** and **project** into the **lumen**

THE LIVER

FUNCTIONAL ANATOMY

An important function of the liver is to serve as a filter between the blood coming from the gastrointestinal tract and the blood in the rest of the body. Blood from the intestines and other viscera reach the liver via the portal vein. This blood percolates in sinusoids between plates of hepatic cells and eventually drains into the hepatic veins, which enter the inferior vena cava. During its passage through the hepatic plates, it is extensively modified chemically. Bile is formed on the other side at each plate. The bile passes to the intestine via the hepatic duct (Figure 28–1).

Hepatic artery blood also enters the sinusoids. The central veins coalesce to form the hepatic veins, which drain into the inferior vena cava. The average transit time for blood across the liver lobule from the portal venule to the central hepatic vein is about 8.4 s.

Numerous macrophages (**Kupffer cells**) are anchored to the endothelium of the sinusoids and project into the lumen.

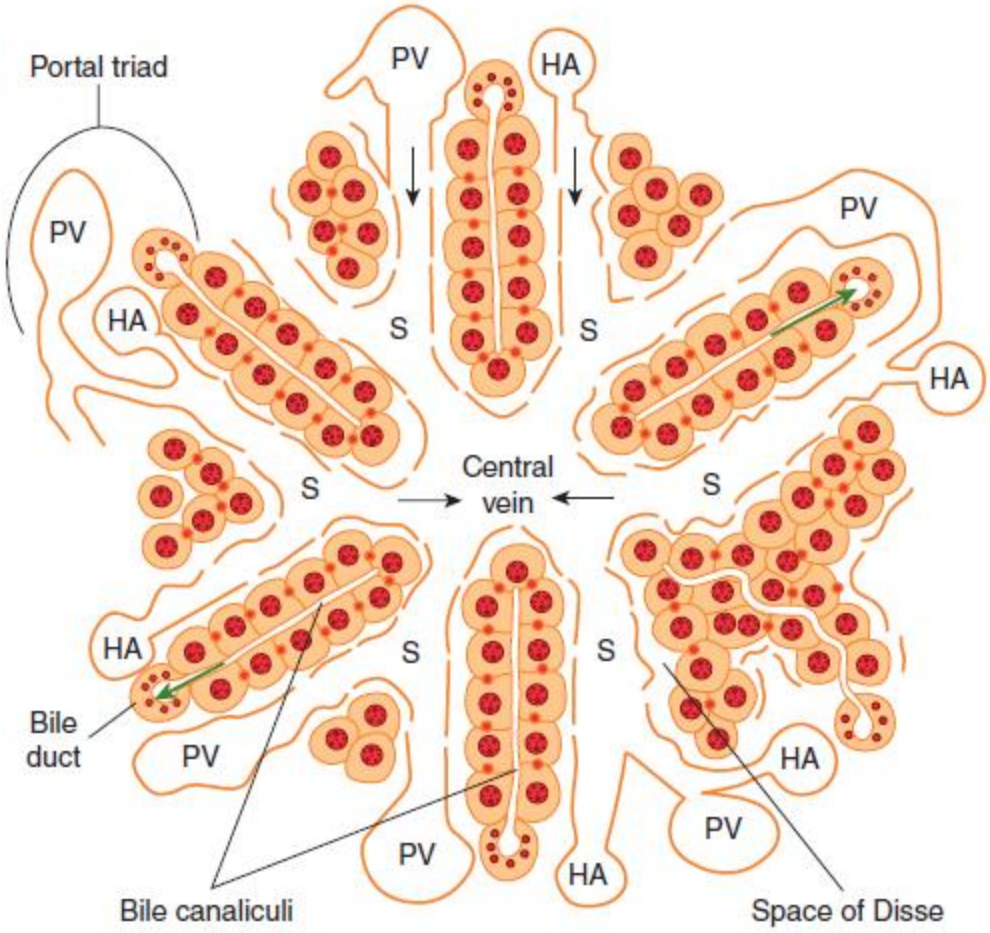


FIGURE 28–1 **Schematic anatomy of the liver.** Hepatocytes are arranged radially in plates surrounding a central vein. Blood is supplied to the liver by branches of the portal vein (PV) and hepatic artery (HA), which empty into sinusoids (S) surrounding the hepatocytes. The direction of blood flow is indicated with black arrows. The endothelial cells that line the sinusoids are fenestrated and thus provide little hindrance to the transfer of substances from the sinusoids to the space of Disse, which abuts the basolateral membrane of the hepatocytes. The apical membranes of adjacent hepatocytes form bile canaliculi, which transfer bile to the bile ducts lined by cholangiocytes. Bile flows in the opposite direction to blood (green arrows). The bile duct, portal vein, and hepatic artery comprise the "portal triad:

Bile and biliary system

Bile

- **Composition:** bilirubin, cholesterol, bile slats and waste materials
- **Formation:** formed on the **other side at each plate**
- **Drainage**: bile passes to the intestine via the **hepatic duct**
- **Flow**:
- Bile canaliculi drain into intralobular bile ducts
- Intralobular bile ducts coalesce vial interlobular bile ducts to form the right and left hepatic ducts
- Right and left bile ducts join outside the liver to form common hepatic duct
- Hepatic ducts from small and large liver lobes unites with cystic duct (gallbladder) to form the common bile duct that enters the duodenum at the duodenal papilla
- The orifice of the papilla surrounded by the **sphincter of Oddi**
- The papilla **units with the main pancreatic** duct just before entering the duodenum
- The sphincter of Oddi is usually closed
- **Control of bile ejection: CCK** relaxes (**open**) the **sphincter** and **contracts** the **gallbladder**

Biliary duct

- **The wall**: **extrahepatic ducts** and **gallbladder** walls contain **fibrous tissue** and **smooth muscles**
- **Lining**: with **columnar epithelium**
- **Glands**: Contains scattered **mucus glandes**
- **Folding**: Gallbladder and cystic duct inner membrane are **extensively folded**. This folding **increases** the **surface area** and increase the **turbulence** flow of bile to **reduces the precipitation of bile** and **reduces** possibility of **gallstone formation**

Each liver cell is also opposed to several **bile canaliculi** The canaliculi drain into intralobular bile ducts, and these coalesce via interlobular bile ducts to form the right and left hepatic ducts. These ducts join outside the liver to form the common hepatic duct. The cystic duct drains the gallbladder. The hepatic duct unites with the cystic duct to form the common bile duct (Figure 28–1). The common bile duct enters the duodenum at the duodenal papilla. Its orifice is surrounded by the **sphincter of Oddi,** and it usually unites with the main pancreatic duct just before entering the duodenum. The sphincter is usually closed, but when the gastric contents enter the duodenum, cholecystokinin (CCK) is released and the gastrointestinal hormone relaxes the sphincter and makes the gallbladder contract.

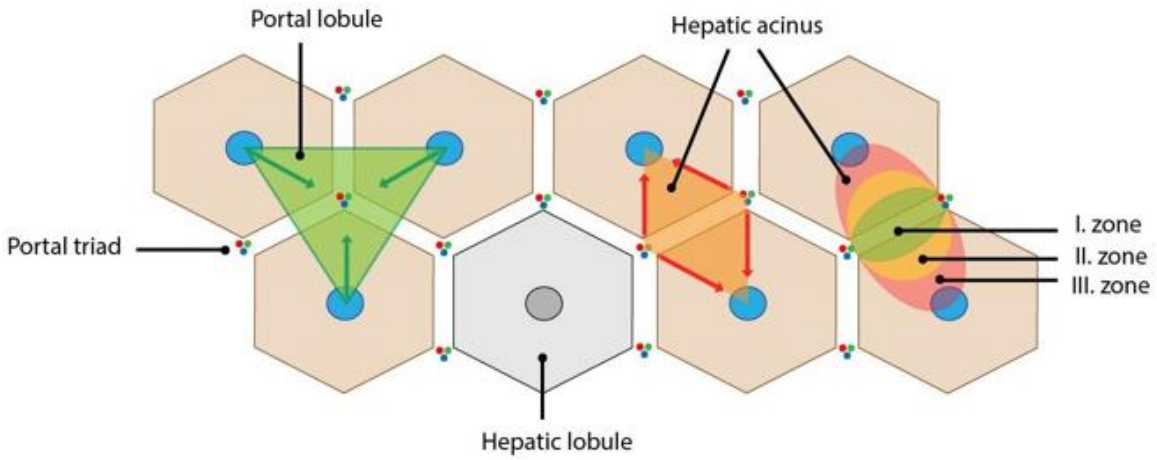
The walls of the extrahepatic biliary ducts and the gallbladder contain fibrous tissue and smooth muscle. They are lined by a layer of columnar cells with scattered mucous glands. In the gallbladder, the surface is extensively folded; this increases its surface area and gives the interior of the gallbladder a honeycombed appearance. The cystic duct is also folded to form the so-called spiral valves. This arrangement is believed to increase the turbulence of bile as it flows out of the gallbladder, thereby reducing the risk that it will precipitate and form gallstones.

Liver acini

- **Area:** Between the central vein of a lobule to that of another
- **Shape**: **been** like-ended to **grapes** or **berries** each on a vascular stem
- **Humber** in human: **100,000 acini/ liver**
- **Zones**: I, II, III.
  1. **Zone I**: In the **center** of the acinus; **close** to the **portal trade**; **well oxygenated**
  2. **Zone II**: In the **middle** of the acinus; **moderately well oxygenated**
  3. **Zone III**: In the **periphery** of the acinus; **close** to **central vein**; **least well oxygenated** (susceptible to **hypoxia** and **noxious injury**)
- When blood flow from zone I to zone III its oxygen is extracted by hepatocytes and is drained into the central vein

HEPATIC CIRCULATION

Large gaps occur between endothelial cells in the walls of hepatic sinusoids, and the sinusoids are highly permeable. The way the intrahepatic branches of the hepatic artery and portal vein converge on the sinusoids and drain into the central lobular veins of the liver is shown in Figure 28–1. The functional unit of the liver is the acinus. Each acinus is at the end of a vascular stalk containing terminal branches of portal veins, hepatic arteries, and bile ducts. Blood flows from the center of this functional unit to the terminal branches of the hepatic veins at the periphery . This is why the central portion of the acinus, sometimes called zone 1, is well oxygenated, the intermediate zone (zone 2) is moderately well oxygenated, and the peripheral zone (zone 3) is least well oxygenated and most susceptible to anoxic injury. The hepatic veins drain into the inferior vena cava. The acini have been likened to grapes or berries, each on a vascular stem. The human liver contains about 100,000 acini.



Hepatic pressures

- **Portal venous pressure : 10mmHg**
- **Hepatic venous pressure**: **5mmHg**
- **Hepatic arterial pressure** : **90mmHg**
- **Sinusoidal pressure: lower** than the **portal venous** pressure. This produce a **marked drop of pressure** along the **hepatic arterioles**
- **Relation between hepatic arterial and portal pressures**: **Inverse** (maintained by **adenosine removal** from the region around the arterioles)
- **Adenosine** (**vasodilator**): is **produced by metabolism** at a **constant rate**. When **portal flow is reduced** (between meals), it is **washed away more slowly**, and the local accumulation of adenosine **dilates** the terminal **arterioles**
- **The sinusoids**: **Between meals**, many are **collapsed**; **following meals**, portal flow increases, the sinusoids are **recruited gradually** (so linear increase in portal pressure with portal flow occurs when all sinusoids have been recruited). This is important to prevent fluid loss from the highly permeable liver under normal conditions
- **Fluid accumulation in abdomen**: If **hepatic pressure** are **increase** in diseases (**cirrhosis**), many **liters of fluids accumulate** in the **peritoneal cavity** as **ascites**

Portal venous pressure is normally about 10 mm Hg in humans, and hepatic venous pressure is approximately 5 mm Hg. The mean pressure in the hepatic artery branches that converge on the sinusoids is about 90 mm Hg, but the pressure in the sinusoids is lower than the portal venous pressure, so a marked pressure drop occurs along the hepatic arterioles. This pressure drop is adjusted so that there is an inverse relationship between hepatic arterial and portal venous blood flow. This inverse relationship may be maintained in part by the rate at which adenosine is removed from the region around the arterioles. According to this hypothesis, adenosine is produced by metabolism at a constant rate. When portal flow is reduced, it is washed away more slowly, and the local accumulation of adenosine dilates the terminal arterioles. In the period between meals, moreover, many of the sinusoids are collapsed. Following a meal, on the other hand, when portal flow to the liver from the intestine increases considerably, these "reserve" sinusoids are recruited. This arrangement means that portal pressures do not increase linearly with portal flow until all sinusoids have been recruited. This may be important to prevent fluid loss from the highly permeable liver under normal conditions. Indeed, if hepatic pressures are increased in disease states (such as the hardening of the liver that is seen in cirrhosis), many liters of fluid can accumulate in the peritoneal cavity as ascites.

Hepatic innervation and hepatic blood flow

- **Intrahepatic portal vein radicles and hepatic arteries :** the **smooth** muscles innervated by **noradrenergic vasoconstrictor** nerve fibers
- **Vasodilator nerve fibers**: **NO**

Changed blood flow:

1. **In increased systemic venous pressure (as in heart failure)**: **portal vein** radicles **dilate** passively and liver **blood flow increase and** hepatic venous flow extremely reduced (congestion)
2. **In diffused adrenergic discharge** (reflexly to reduces systemic BP), **intrahepatic portal radicles constrict**, portal pressure rises and **the blood flow through** liver is brisk (high), bypassing most of the organs and most of the blood in the liver enters the systemic circulation
3. **Constriction** of **hepatic arterioles** divers blood from the liver; while, **constriction** of **mesenteric arteries** reduces portal inflow
4. **In sever shock**, hepatic blood flow may be reduced to such as degree that patchy **necrosis** of liver takes place

The intrahepatic portal vein radicles have smooth muscle in their walls that is innervated by noradrenergic vasoconstrictor nerve fibers reaching the liver

The vasoconstrictor innervation of the hepatic artery comes from the hepatic sympathetic plexus. No known vasodilator fibers reach the liver. When systemic venous pressure rises, the portal vein radicles are dilated passively and the amount of blood in the liver increases. In heart failure, this hepatic venous congestion may be extreme. Conversely, when diffuse noradrenergic discharge occurs in response to a drop in systemic blood pressure, the intrahepatic portal radicles constrict, portal pressure rises, and blood flow through the liver is brisk, bypassing most of the organ. Most of the blood in the liver enters the systemic circulation. Constriction of the hepatic arterioles diverts blood from the liver, and constriction of the mesenteric arterioles reduces portal inflow. In severe shock, hepatic blood flow may be reduced to such a degree that patchy necrosis of the liver takes place.