The Liver:
Anatomy, Physiology,
Disease and Treatment

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**Introduction**

The liver is among the most complex and important organs in the human body. Its primary function is to control the flow and safety of substances absorbed from the digestive system before distribution of these substances to the systemic circulatory system. A total loss of liver function leads to death within minutes\(^1\), demonstrating the liver’s importance. This paper will discuss the gross and microscopic anatomy of the liver, and then review its major functions, diseases, and treatments.

**General Description of the Liver**

The liver is the largest gland in the human body, weighing approximately 3 pounds and occupying a large region mostly on the right side of the body, below the diaphragm and behind ribs 5 through 10. A picture can be found in Appendix B. The liver has many functions, primarily including:

- Acting as a gatekeeper between the digestive system and the circulatory system
- Processing toxic substances before they enter general circulation
- Storing and converting nutrients for future use
- Synthesizing most plasma proteins
- Secreting bile into small intestine to break down fats

The details of these functions and others will be covered in later sections.

**Gross Anatomy**

The liver is divided into 4 lobes: right, left, caudate, and quadrate. The right and left lobes are the largest, while the caudate and quadrate are smaller and located posteriorly. Two ligaments are visible anteriorly. Superiorly, the falciform ligament separates the right and left lobes. Inferior to the

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\(^1\) See Heuman, pg. 161.
falciform ligament is the round ligament, which protrudes from the liver slightly. Also visible anteriorly on the most inferior portion of the right lobe is the gallbladder.

Posteriorly, many more interesting structures are visible. The caudate lobe is located superiorly, approximately between the right and left lobes. Adjacent to the caudate lobe is the sulcus for the inferior vena cava. Just inferior to the caudate lobe is the porta hepatis, where the hepatic artery and hepatic portal vein enter the liver. The portal vein carries nutrient laden blood from the digestive system. Inferior to the porta hepatis is the bile duct which leads back to the gallbladder. Finally, the hepatic vein, where post-processed blood leaves the liver, is found inferior and adjacent to the sulcus for the inferior vena cava.

The liver is held on place by a system of mesenteries posteriorly, and is also attached to the diaphragm via the falciform ligament. Additionally, most of the liver is covered by visceral peritoneum.

**Microscopic Anatomy**

The basic functional unit of the liver is the liver lobule. (See diagram in Appendix B). A single lobule is about the size of a sesame seed and is roughly hexagonal in shape. The primary structures in a lobule include:

- Plates of hepatocytes form the bulk of the lobule
- Portal triads at each corner of hexagon
- Central vein
- Liver sinusoids that run from the central vein to the portal triads
- Hepatic macrophages (Kupffer cells)
- Bile canaliculi (“little canals”) – formed between walls of adjacent hepatocytes
- Space of Disse – a small space between the sinusoids and the hepatocytes
The portal triads consist of three vessels: a hepatic portal arteriole, a hepatic portal venule, and a bile duct. The blood from the arteriole and the venule both flow in the same direction – through the sinusoids toward the central vein, which eventually leads to the hepatic vein and the inferior vena cava. Secreted bile flows in the opposite direction – through the bile canaliculi away from the central vein, toward the portal triad, and exiting via the bile duct. As blood flows through the sinusoids and the space of Disse toward the central vein, nutrients are processed and stored by the hepatocytes, and worn out blood cells and bacteria are engulfed by the Kupffer cells.

**Cell Types**

The liver has 5 cell types: hepatocytes, Kupffer cells, sinusoidal endothelial cells, bile duct epithelial cells, and Ito cells.

Hepatocytes represent 60% of the liver’s cells, and about 80% of the liver’s total cell mass\(^2\). Most of the liver’s synthetic and metabolic capabilities stem from the work of hepatocytes. Hepatocytes are arranged in plates only a single cell thick. Blood flowing toward the hepatic vein within the space of Disse passes both exposed surface areas of the hepatocyte plates, and toxins and nutrients within the blood are extracted by the hepatocytes.

Kupffer cells are macrophages that reside in the sinusoids. These cells help clear out old red blood cells and bacteria. They also break down heme (the iron-containing pigment in hemoglobin) into bilirubin, which then becomes one of the chief pigments of bile. A later by-product of bilirubin gives feces its characteristic brown color.

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\(^2\) See Heuman, et al, pg. 159.
Sinusoidal endothelial cells are fenestrated (Latin for “windows”), meaning they have large pores that allow most proteins to pass freely through the sinusoidal endothelium into the space of Disse, where they can make direct contact with hepatocytes. The pores are also bi-directional, meaning that proteins created by the liver and other substances stored or processed by the liver can also be passed back into the blood.

Bile duct epithelial cells line the interlobular bile ducts within the portal triads. Bile production is discussed later in this paper.

Ito cells are found in the space of Disse. They are important because when the liver is injured, the Ito cells transform into cells that produce collagen, which leads to liver fibrosis. If this occurs on a large scale, it can lead to cirrhosis of the liver. Cirrhosis is a serious disease of the liver that is covered later in this paper.

**Liver Functions**

The liver has 4 essential functions:

1) Synthesis of many proteins that circulate in the blood. These include albumin, coagulation factors, alphal-antitrypsin, very low density lipoprotein, and many others.

2) Stores nutrients for later use. The liver balances the supply of nutrients with demand. For example, the liver stores glucose as glycogen, and converts it back to glucose as needed. If the supply of glycogen is depleted, the liver can also synthesize glucose from amino acids, lactate, and glycerol, although this is less efficient than breaking down glycogen into glucose. Additionally, the liver metabolizes fatty acids, cholesterol, and amino acids. When there is a surplus of glucose in the bloodstream, the liver can convert excess glucose and amino acids into
fatty acids for storage. The liver both synthesizes cholesterol and removes it from circulation. Finally, the liver can synthesize non-essential amino acids when needed by the body.

3) Detoxification and elimination of toxic substances. Toxins are detoxified by the liver’s ability to metabolize lipophillic compounds. These compounds (bound to albumin) enter the liver sinusoids and then the area of Disse. Enzymes in the hepatocytes (cytochrome P-450 enzymes) are involved in the metabolism of the lipophillic compounds, which include toxins and many drugs.

4) Production of bile. Bile acts as a detergent, and breaks fats down into smaller components so they can be digested in the small intestine. Bile also provides a way for the liver to remove wastes, including bilirubin, cholesterol, and toxins. Bile is formed in the biliary canaliculi, which drain into the interlobular bile ducts. These ducts then merge with other ducts, forming larger intermediate ducts, which eventually merge into the right and left hepatic ducts, which themselves merge into the common hepatic duct, which merges with the cystic duct from the gallbladder, finally forming the common bile duct, which empties into the small intestine.

**Interrelationships with Other Organs**

The liver interacts with many other organs. Following the flow of blood, the liver receives its arterial blood supply from the hepatic arteries. The hepatic arteries are distal to the celiac trunk, which is distal to the abdominal aorta. Thus the liver receives its oxygenated blood supply from the heart. Nutrient laden blood from the digestive system and blood leaving the spleen enters the liver though the hepatic portal vein. Processed blood leaving the liver through the hepatic veins drains into the inferior vena cava, completing the connection to the heart.

The liver affects digestion through its formation of bile, which is secreted into the small intestine. The gallbladder is essentially an overflow area for the liver’s bile duct. The liver is full of lymph glands,
which provide fluid drainage and immune system support. The liver synthesizes many blood proteins, showing its relation to that “organ”. The liver also has a supply of nerves, showing its relationship with the nervous system. Finally, liver disease often causes problems in the renal system, demonstrating a relationship with the kidneys.

**Liver Diseases and Treatments**

One way to classify liver disorders is by their duration. A chronic disorder lasts for more than 6 months; a subacute disorder lasts for 3 to 6 months; while an acute disorder occurs over a period less then 3 months. A very severe disorder that leads to liver failure within 6 weeks is termed fulminant. Some of the common disorders of the liver include cirrhosis, viral hepatitis, alcoholic liver disease, hemochromatosis, and liver cancer.

1) **Cirrhosis** is a widespread and progressive chronic liver condition in which hepatocyte activity is depressed due to excessive amounts of fibrous scar tissue inhibiting blood flow. This blood flow obstruction can cause portal hypertension, which leads to additional complications, including shunting of veins around the liver. Other complications of portal hypertension include swollen veins in the esophagus (varices) and accumulation of fluid in the abdomen (ascites). Other potential complications of cirrhosis include bleeding problems, kidney disorders, osteoporosis, and liver cancer. Any chronic liver disease can eventually lead to cirrhosis, which is believed to be irreversible. The only treatment options are to treat the condition that caused the cirrhosis, and liver transplantation.

2) The term hepatitis refers to inflammation of the liver. Hepatitis can have several causes, the most common being viruses or alcoholism. Viral hepatitis comes in several forms, the most
common being hepatitis B (40%), hepatitis A (32%), and hepatitis C\(^3\). HVB and HVC are spread by the blood, and can become chronic conditions, which can lead to cirrhosis. A vaccine has been developed for HVB, which has helped control its spread. HVC often becomes chronic, and thus can be life-threatening. Viral hepatitis has several treatment options, which frequently have undesirable side effects. Interferon is used for treating HBV and HCV. Interferons are so named because they interfere with viral replication. The body makes interferon naturally, but supplementing this with synthetically made interferon can sometimes be beneficial against viral hepatitis. However, the selection criteria for who should use interferons are quite stringent, attesting to the downsides of this therapy. Additionally, interferon is available by injection only, and is quite expensive. Newer forms of antiviral therapy exist, but interferon is still the most common.

3) Alcoholic Liver Disease comes in 3 major varieties: alcoholic fatty liver, alcoholic hepatitis, and alcoholic cirrhosis. All 3 can occur alone or even together in the same patient. The primary form of treatment is abstinence from drinking alcohol.

a. Fatty liver is the most common, and the least harmful. It can occur within days of moderate to heavy drinking. Fat accumulates in the cytoplasm of liver cells, causing the liver to swell, sometimes to large proportions. Fatty liver often has no symptoms, and can disappear as quickly as it appears.

b. Alcoholic hepatitis is inflammation of the liver, and can exist as either acute or chronic conditions. Symptoms can very greatly, from asymptomatic to severe fever, nausea, and abdominal pain. Acute hepatitis can often cause death, and the chronic form often leads to cirrhosis. On the bright side, alcoholic hepatitis is also potentially reversible, if recovery occurs and the patient abstains from drinking.

\(^3\) See Marieb, pg. 921.
c. Alcoholic cirrhosis, like all forms of cirrhosis, is often life-threatening. The disease is characterized by regenerative nodules of hepatic tissue completely surrounded by fibrous scar tissue. The scar tissue grows faster than liver cells can regenerate, and the growing network of scar tissue inhibits blood flow as described earlier. Once cirrhosis develops, the risk of liver cancer elevates substantially, even if the patient abstains from drinking for several years.

4) Hemochromatosis is a condition in which too much iron is contained in the body. It is the most common genetic disease in the United States among people of European origin, but does not have to be inherited. Chronic hemochromatosis can lead to cirrhosis, cancer, impotence, and heart problems. Iron damages the body through its promotion of oxidation, increasing the level of free radicals in the body. Harmful levels of iron can be accumulated in the body simply by eating too much of the wrong foods and supplements. The human body uses approximately 1 to 2 milligrams of iron daily. However, the average diet contains between 10 and 20 milligrams of iron. Furthermore, iron is not expelled from the body easily. In hemochromatosis, the body cannot absorb iron as effectively, and also cannot detect when iron levels are too high. This excess iron is then absorbed into the body’s organs, particularly the liver. Hemochromatosis also can co-exist along with other liver problems, making matters much worse for the patient. Hemochromatosis is treated by lowering the level of iron in the body. The most common method is via phlebotomies. A phlebotomy is purposefully removing blood from the body, typically using a catheter, and discarding the blood. This must be done weekly over a long period of time to eliminate high levels of iron – perhaps years. For example, to deplete 25 grams of blood, it would take two years of weekly phlebotomies. Diet

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4 See Palmer, pg. 243.
5 See Palmer, pg. 245.
6 See Palmer, pg. 249.
is also very important to patients with hemochromatosis. Iron needs to be kept to a minimum, as well as alcohol and medications that may do further damage to the liver.

5) Liver cancer. Liver tumors are not always malignant. One type of benign tumor is Hemangioma, which is a non-malignant tumor filled with blood. Treatment is not necessary for these tumors. Malignant tumors fall into two major categories: Metastatic and primary liver tumors. A metastatic tumor is a malignant growth whose primary growth site is someplace other than the liver. The liver is a frequent target of metastatic cancers, as it is the primary filter of venous blood from several organs, such as the colon. The prognosis for patients with metastatic liver cancer is typically poor; most patients die within 1 year of diagnosis. The most common primary liver malignant cancer is hepatocellular carcinoma (HCC). HCC is one of the most common cancers in the world, although it is currently relatively uncommon in the U.S. This is largely due to the higher incidence of viral hepatitis in Southeast Asia and Africa. Hepatitis C often leads to cirrhosis, and cirrhosis often leads to primary liver cancer. Liver tumors can be detected and identified using a combination of blood tests, imaging studies, and liver biopsies. As with metastatic liver tumors, the prognosis for patients with primary liver cancer is quite poor. Liver cancer is treated most often with surgery, where the tumor is cut out of the liver. Large sections of the liver can be removed and the liver will often be able to regenerate itself to its previous full size. Unfortunately, this does not work for patients with cirrhosis. In that case, a liver transplant is the best option. Liver transplants and some more advanced liver treatments are discussed below. Another treatment option for liver cancer, strangely enough, is direct injection of alcohol into the tumor.

**Advanced Treatment of Liver Disease**

Liver transplantation is often the best option for either liver cancer or cirrhosis. However, there is an extreme shortage in the number of donor organs available, and there are restrictions on who can
receive liver transplants. Due to these problems, alternatives are constantly being sought. Some of the primary areas of research involve gene therapy, xenotransplants, and bioartificial livers.

1) Scientists have found that they can reduce and even reverse the amount of fibrosis that occurs in damaged livers by controlling the level of a gene named HGF (hepatocyte growth factor) in rats\(^7\). If this can be extended to humans, it would obviously have enormous benefits.

2) Xenotransplants are being pursued for replacements of all types of organs. Several companies have developed breeds of transgenic animals that would present less of an immunological barrier than the xenotransplants used in the past. For example, Ximerex, Inc is developing hybrid livers that consist of pig livers partially repopulated with human cells. Baboon livers have already been transplanted into humans, although with poor success thus far.

3) Bioartificial livers are also being developed. Currently, these are most often used to bridge the gap while waiting for a liver transplant. For example, the HepatAssist Liver Support System employs a hollow-fiber membrane bioreactor containing \(7 \times 10^9\) cryopreserved porcine hepatocytes along with associated equipment to provide temporary liver functionality. In one study using the HepatAssist system (which is now in phase III clinical trials), 30 day patient survival rates improved to 90% compared to a normal level of 50-60%\(^8\).

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\(^7\) See Qi Z.
\(^8\) See Lanza, pg. 553
Appendix A – References

Appendix B - Diagrams