Anatomy and Function of the Liver

(NOTE: References listed to the side refer to the entire subsection or diagram below)

I. Anatomy of the Liver

1. Liver is the largest organ in the body weighing 3-4 lbs (ref. 22, p. 490).

Ref. 25, p. 576
Ref. 24, p. 636

2. It is located upper right abdominal cavity, fitting snugly under the dome of the diaphragm and resting on stomach, duodenum (proximal portion of small intestine) (Dorland’s Dictionary) colon and right kidney.

Ref. 22, p. 491

![Figure 1]

3. Prior to discussing anatomy must understand body directions (see Figure 2)

Ref. 23, p. 8
- Superior - uppermost
- Inferior - lowermost
- Anterior - toward front
- Posterior - toward back
6. Ligaments of note for the liver:

Falciiform ligament - attaches the liver to the anterior abdominal wall

Coronary ligament - attaches the liver to the undersurface of the diaphragm.

Lesser Omentum - anchors undersurface of liver to stomach.

7. a) The importance of knowing about the ligaments is to understand the anatomical designation of a liver lobe. The liver is divided into 2 lobes by the falciiform ligament - a right and left lobe (See Figure 5). The right and left lobes of the liver are separated by the falciiform ligament anteriorly and superiorly (ref. 27, p. 505).

Ref. 22, p. 491

Figure 5

b) The left lobe is 1/6 of the liver, with right side takes up the remainder.

Ref. 29, p. 488

Ref. 29, p. 487

c) See Figure 6. The right lobe is further divided into 3 lobes, the caudate lobe, the quadrate lobe, and the right proper lobe. This separation is only apparent on the visceral side. (The quadrate and caudate lobes are really surface projections on the right lobe (ref. 26, p. 430)). Between the caudate and quadrate lobes is the porta hepatis (Porta - Latin for door).
8. Finally - beneath peritoneum there is a covering of fibroelastic tissue called Glisson's capsule, which accompanies blood vessels into the interior of the liver. (Ref. 28, p. 396).

Ref. 30, p. 465

At the porta there is a trunk of connective tissue which extends into interior of the liver. Like a tree it branches substantially furnishing internal support. It also provides pathways by which branches of portal vein, hepatic artery, bile duct, and lymphatic vessel can reach all parts of organ.
II. Liver Physiology

1. Three Basic Functions of Liver (Ref. 1)

a) Vascular
   - One of major blood reservoirs in body. When there is increase in fluid load of blood, the liver can store 200-400 ml. If hemorrhaging, normal blood in liver replaces lost blood. (Ref. 1) During exercise 1-2 pints of blood is sent out into general circulation (ref. 22, p. 492). At rest, 1/4 of blood supply is in liver (ref. 22, p. 492).

b) Metabolic
   - Utilization of nutrients for liver
   - Storage and synthesis of nutrients for body
   - Transformation of various compounds such as drugs, hormones, toxins. Transformed so that compound can be removed by kidneys or bile.

c) Secretory
   - Bile, for aid in digestion of fats
   - Release of stored nutrients to meet body needs
   - Synthesis of components for body

The liver performs many functions: Although it possesses a remarkable activity to regenerate itself in cases of partial removal of tissue, it should be noted that severe injury or disease may lead to a rapid death (ref. 28, p. 398).

2. Look at the big picture.

   There are three fluid systems in liver:
   Blood
   Bile
   Lymph

3. First consider blood flow. (See Figures 7 and 8)

a) Liver receives 1500 ml/min of blood (1/3 cardiac output) (Ref. 2). Blood entering liver comes from two sources:

   (ref. 3,4)

   1’) 2/3 portal vein (veins from digestive organs drain into portal vein)
   2’) 1/3 hepatic artery (from Aorta) This is thus supply of oxygenated blood for liver (Ref. 5)

The fact that 2/3 of blood comes from portal vein is a reflection of the liver's major function being the storage and utilization of nutrients. The organs from which blood
drains into the liver are the stomach, spleen, pancreas, small intestine, and large intestine (Ref. 5). Both the portal vein and the hepatic artery branch repeatedly, making the liver a highly vascular organ.

b) Blood leaves the liver by hepatic vein which drains vena cava

Ref. 5, p. 10

Figure 7
Figure 8
4.  
   a) Results from animal studies show that:
      - Right extremity receives blood from superior mesenteric vein
      - Left lobe receive from left gastric, inferior mesenteric and splenic veins
   
   b) It is not known for certain if such segmentation of blood flow exists in humans. However, the observations given below support this contention:
      1) Shortness of portal vein may lead to blood staying on side of portal vein that it enters into.
      2) Localization of tumor metastases
      3) Predominance of massive necrosis in acute fatal viral hepatitis in left lobe of liver, (does not receive nutrient rich protective blood from small intestine).

5. Bile Flow

(See Figure 9). This is big picture for the bile flow system. Bile formed in the liver, flows into either the left or right hepatic duct, which unite to form the common hepatic duct, which goes into the common bile duct after uniting with the cystic duct. Bile eventually flows into the small intestine where bile functions as an emulsifier of fats to aid in digestion. The gallbladder acts as a storage chamber for bile (ref. 3, ref. 5, ref. 20).

6. Lymphatics

One half of lymph formed in body under resting conditions arises in the liver.
7. Look at liver from a more microscopic level. In Figure 10 we see the relationship between the vessel systems and the functional unit of the liver cell, the liver lobule.

a) The liver lobule (dimensions: 2mm high 1 mm in diameter (ref. 29, p. 488)) consists of:

1') central vein
2') hepatocytes radiating out from central vein
3') microvessels carrying blood and bile (sinusoids and canaliculi, respectively).

b) The portal triad is at the periphery of the lobule and consists of a branch of the hepatic artery, a branch of the portal vein and an interlobular bile duct.

Ref. 20, p. 394
8. Look at blood flow at microscopic level. Figures 11 and 12 highlight the blood flow going into and out of the sinusoids.

   a) Venous Flow

      Branch of portal vein - to sinusoids - to central vein - to sublobular vein - which eventually coalesce to form the hepatic vein

   b) Arterial Flow

      Notice there are two arterioles (Figure 12), an intralobular and a periportal. Most arterial flow is through the periportal arteriole (ref. 5).

      Ref. 29, pg. 488

Ref. 1 p. 835

![Diagram of liver structure]

Figure 11
c) Sinusoids differ from true capillaries in that they are wider and tend to have leaky walls, due to irregularly spaced cells lining the walls. Openings are too small for passage of red blood cells, the plasma, however, can come into direct contact with hepatocytes. (Ref. 28, p. 396).

d) Millions of sinusoidal spaces in the liver constitute a vast spongework, which can hold large quantities of blood at any given time, thus the liver is considered an important reservoir, which can influence circulating blood volume.

e) Blood entering sinusoids is both oxygenated (hepatic artery) and venous (portal vein).

9. Bile Flow

Bile is secreted by hepatocytes into the bile canaliculi, which eventually empty into interlobular bile ducts, which eventually empty into the hepatic duct (either left or right) which unite to form the common hepatic duct, which unites with the cystic duct to become the common bile duct (Ref. 6) (See Figure 13).
Ref. 5, p. 11

See Figures 9 and 13. Bile, which is produced by hepatic cells, enters canaliculi which drains into bile ductules, which in turn drain into larger ducts. Ultimately all bile is collected into one large duct from each lobe (one for right and one from left) uniting to form the common hepatic duct. The hepatic duct descends for a distance of about 1.5 inches at which point it is joined at an acute angle by the cystic duct, to form the common bile duct. The common bile duct descends behind the head of pancreas, where it joins the pancreatic duct - forming a single dilated tube known as the ampulla of Vater.
The ampulla opens into the duodenum at the duodenal papilla. Muscle tissue associated with the ampulla forms a weak sphincter (of Oddi) but the bile duct (at a point just above merging with the pancreatic duct) has a strong sphincter muscle (of Boyden). When the sphincter muscle of Boyden is closed, bile is prevented from entering intestine, and is thus stored in the gallbladder.

Ref. 28, p. 398

b) The gallbladder is musculomembranous sac with an average capacity of 40-50 mL.

1') The gallbladder is located on the undersurface of the liver.

2') Connective tissue and smooth muscle fibers form the framework of the wall of the gallbladder.

3') Except where it is attached to the liver, the external coat of the gallbladder is serous membrane (visceral peritoneum)

4') The function of gallbladder is to store and concentrate bile.

5') There is hormonal regulation of gallbladder contraction. Cholecystokinin and motelin are secreted by duodenal mucosa when fat is present (ref. 31, pp. 1199-1200). Carried in the bloodstream, the hormone cholecystokinin stimulates the smooth muscular wall of the gallbladder to contract and dispatch bile to the duodenum. [Another source says that the hormone secretin also controls bile secretion, causing a 10-20% increase in bile output (ref. 23, p. 469).

Ref. 28, p. 399

c) Bile is formed continuously by hepatic cells at an average rate of 600 to 800 mL per day.

1') Bile is greenish-yellow fluid which contains:
   Water
   Bile Salts
   Bilirubin
   Cholesterol
   Various inorganic salts

2') Bile is alkaline (ref. 31, p. 1195)

3') The function of bile is to aid in the digestion of fats. This is accomplished by bile salts (which are formed from cholesterol) as described below.

   a') Bile salts emulsify fats. Bile salts lower the surface tension of large fat globules so that they can be broken into tiny particles, facilitating more efficient attack of fat-splitting enzymes.

   b') Bile salts help absorption of fatty acids.
Ref. 28, p. 399

d) Bile is concentrated in the gallbladder, which is accomplished by the absorption of water, sodium, chloride and electrolytes by the gallbladder wall. Bile is stored in the gallbladder between meals.

Ref. 31, p. 1199-1200

e) Other facts:

1') Mucosa of the gallbladder wall readily absorbs water and electrolytes.

2') Gallbladders hold about 90 mL of bile. Within 30 min. after eating, the sphincter of Oddi relaxes forcing bile into the duodenum. During cephalic and gastric phases of digestion, gallbladder contraction is mediated by cholinergic branches of the Vagus nerve.
10. See Figure 14.

a) Rappaport visualizes the function unit of the liver as the acinus, with zones around the afferent vessels (ref. 9). The afferent vessels are the terminal hepatic arterioles, terminal portal venules, and the terminal bile ductules (ref. 8). The blood and bile in each zone has a different composition of O₂ and nutrients with there being a gradient of O₂ and nutrients in going from Zone 1 to Zone 3 (ref. 6,7).

Ref. 7,8
b) Location and chemical content of the zones

<table>
<thead>
<tr>
<th>Zone</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zone 1</td>
<td>Closest to portal triad - richest in nutrient and O₂</td>
</tr>
<tr>
<td>Zone 2</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Zone 3</td>
<td>Closest to the central vein - O₂ and nutrients are depleted</td>
</tr>
</tbody>
</table>

Zone 1 - is most metabolically active and most resistant to damage
Zone 3 - most susceptible to injury

![Liver Acinus Diagram](image.png)

Figure 14 (Ref. 7, p. 9)

c) These zones are not fixed - changes with rate of microcirculation. This shifting of zones depends mainly on arteriolar activity (Ref. 8).

d) Heterogeneity of cells between zones. Different characteristics; both in terms of cellular structures and in terms of metabolic processes.

1') Zone 1

a') Oxidative processes via the Krebs acid cycle operates at a high level (Ref. 32, p. 9). Larger and more mitochondria. (ref. 8).
b') Enzymes geared glycogen synthesis are present in high concentrations (Ref. 8).

1") High level of UDP: α-4 glucosyltransferase (UDPGGT) and phosphorylase enzymes makes these hepatocytes the first to deposit and to lyse glycogen. (Ref. 32, p. 9).

2") Also it is the zone where glucose-6-phosphate dehydrogenase is most active (where gluconeogenesis occurs). (Ref. 32, p. 9).

c') Prime area of protein metabolism and formation of plasma proteins. (Ref. 8)

d') Less lysosomes (Ref. 9)

e') Less smooth endoplasmic reticulum (Ref. 9)

2') **Zone III**

a') Less mitochondria (Ref. 8)

b') Location of glycogen storage and marked glycolytic activity, (Ref. 32, p. 10.)

c') Location of fat and pigment formation (Ref. 8)

d') More lysosomes. (Ref. 9)

e') Lipid laden cells are seen in Zone 3 and in adjacent Zone 2 (ref. 32, p. 10)

f') More smooth endoplasmic reticulum (Ref. 9)

e) Zonal distribution of drug-induced lesions due to where the predominant location of microsomal enzymes involved in metabolism of drug. (Ref. 8)

f) Metabolic differences may be intrinsic to cell or due to location in lobule, with exposure to different levels of oxygen tension, substrate conc. gradients, and other factors. (Ref. 9).

PV = portal vein; ThV = terminal hepatic venule; BD = bile ductule; hep. art = hepatic arteriole; Z1 = periportal area; Z3 = perivenular and periacinar area.
11. See Figure 16. There are two principle cells in the liver, the hepatocyte and the Kupffer cell. The hepatocyte is the parenchymal cell of the liver and the Kupffer cell is the reticuloendothelial cell (macrophage) of the liver.

![Liver cells and sinusoids diagram](image)

**Figure 16**

12. Reticuloendothelial Cells - tissue macrophages

   a) Reticuloendothelial systems are distributed as follows:
      - 60% Liver
      - 5% Spleen
      - 35% Lymph nodes and other tissues

   b) Liver reticuloendothelial cell - Kupffer cell

      1') Functions:
         a') Phagocytic function on foreign and endogenous substances (examples: breakdown of heme to bilirubin, destruction of bacteria)

         b') Storage function: Iron, Vitamin A, lipids

      2') Location: in sinusoid
13. Metabolic Processes (See Figure 17)

a) The liver is the principle organ of metabolism for carbohydrates, proteins and lipids (Ref. 11).

b) The liver has anabolic and catabolic capabilities that all cells have with regard to glucose, amino acids and fatty acids.

Figure 17
14. Carbohydrate Metabolism

a) Liver helps to maintain a normal concentration of glucose in the blood

1') After meals when the blood glucose tends to rise, the liver converts glucose to glycogen and stores the glycogen.

2') When blood glucose falls, the glycogen is converted to glucose, which is released into the blood.

3') Simple sugars such as galactose and fructose are converted to glucose, and are either stored as glycogen or used immediately.

4') If blood glucose level continues to fall, then the liver can form glucose from amino acids and glycerol (process called gluconeogenesis)

15. Lipid Metabolism

a) Metabolism of fats can take place in most cells of the body. Certain activities however occur more rapidly in liver. Fatty acids must first be broken down into small molecules so they can enter the citric acid cycle. It is believed that 60% of the preliminary breakdown of fatty acids in the body occurs in the liver.

b) Other functions:

1') Formation of cholesterol and phospholipids

2') Formation of lipoproteins

3') Synthesis of fat from glucose and amino acids

16. Protein Metabolism

a) Essentially all plasma proteins are synthesized in the liver (except gamma globulins).

b) The liver forms phosphocreatine from amino acids.

c) The liver synthesizes non-essential amino acids.

d) The liver deaminizes amino acids for energy generation or conversion of the amino acid to glucose or fat.
e) The liver removes ammonia from blood, converting it to urea

17. Processes unique for liver or in which liver plays a major role (storage and catabolism)

Ref. 11

a) The liver is unique in that it is the major site of storage for:

1') Iron

a’) Stored in ferritin and hemosiderin (which are ferritin molecules that have lost some of the surface apoferritin, and have the property of being large amorphous aggregates of insoluble material which form granules) in the reticuloendothelial cells (ref. 12).

b’) Percentages stored Iron by location (Ref. 11)
   33.3% Liver
   33.3% Bone Marrow
   33.3% Muscle and Spleen

c’) Distribution of Iron in normal individuals (Ref. 13)

<table>
<thead>
<tr>
<th>Iron Source</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>2500 mg</td>
</tr>
<tr>
<td>Myoglobin</td>
<td>140 mg</td>
</tr>
<tr>
<td>Ferritin and hemosiderin</td>
<td>1000 mg (males)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Transferrin</td>
<td>3 mg</td>
</tr>
<tr>
<td>Enzymes</td>
<td>~ 1 mg</td>
</tr>
</tbody>
</table>

2') Glycogen

a’) Is stored in the liver and the muscle. The glycogen concentration is higher in the liver than in the muscle, but the total mass of muscle makes muscle a bigger storage location for glycogen (Ref. 14). Glycogen is 5 to 8% of the total liver mass while being only 1% of the total muscle mass. (Ref. 11)

b’) Glycogen is present in cytosol in the form of granules, with diameters ranging from 100-400 Å.

3') Retinol - (Vitamin A) - over 90% of Vitamin A is deposited in the liver (Ref. 5) Vitamin A is stored in the reticuloendothelial cells (ref. 16).

4’) The liver also stores large quantities of Vitamin D and B12 (Ref. 28, p. 399). Another source says that the liver stores Vitamin E and K also (ref. 23, p. 469).
2. Unique catabolism processes that occur in the liver

The liver alters exogenous and endogenous substances to make less toxic or less biologically active. This process, which is called biotransformation, diminishes intestinal and renal tubular reabsorption, facilitating excretion (ref. 31, p. 1198). Although this process is mostly protective in nature, sometimes the end-products are toxic.

a) Ketone body formation is a process that occurs exclusively in the liver. Specifically, these ketone bodies are acetacetate and β-hydroxybutyrate. These compounds are formed in the mitochondria of the hepatocyte from the catabolism of free fatty acids. (Ref. 15) The periphery can use ketone bodies (esp. muscle, ref. 5). In conditions of insufficient carbohydrate reserves in the liver (brought about by starvation or diabetes) this process occurs, causing an accumulation of ketone bodies, leading to acidosis and other toxic effects.

b) Ammonia (from amino acid metabolism) is converted to urea (Ref. 5). The liver changes nitrogenous wastes such as ammonia to less toxic urea. (Ref. 23, p. 469).

c) Catabolism of heme to bilirubin.

1') 80% of bilirubin is produced from the breakdown of hemoglobin by the reticuloendothelial cells of the liver and the spleen (ref. 15).

2') The remaining 20% of the bilirubin is produced from newly synthesized heme in bone marrow, and the turnover of myoglobin and heme containing enzymes in hepatic and extrahepatic tissues. (Ref. 15)

d) The catabolism of cholesterol to bile acids occurs in the liver (ref. 16). This process takes place in the cells lining the biliary canaliculi and ductules (ref. 11).

e) Catabolism of steroid hormones

1') Occurs mainly in liver, although not exclusively (ref. 11). Various hormones (gonadal and adrenocortical) are inactivated in the liver and are made more soluble so that they can be excreted in the bile and urine. (Ref. 28, p. 399)

2') Steroids are converted to inactive compounds mainly through reductive processes (reduction of double bonds, reduction of ketone to alcohol functionalities) (ref. 11). Reductive processes are the key to inactivation (except for estradiol) (Ref. 9).

3') Hydroxylases bring about hydroxylation reactions at various positions. This does not play as important a role as reduction reactions in inactivating the steroids (ref. 11).

4') Metabolites are more polar but are still not very hydrophobic. In this chemical state they will be bound to serum proteins and cannot be filtered by kidneys. They are converted to more polar metabolites - mainly through the formation of glucuronide and sulfate conjugates (ref. 11). Almost all steroid metabolites are excreted by the kidneys as water-soluble glucuronides or sulfates (ref. 9). Thus
the major route of excretion of steroid metabolites is urinary, except for estradiol [which is excreted both in the urine (50-70%) and the bile (30-50%)] (Ref. 11).

f) Detoxification and modification of xenobiotics [foreign materials such as drugs and poisons (ref. 11)] to promote excretion. Drugs are eliminated through the bile and urine (ref. 28, p. 339).

1') The liver is the major site of drug metabolism (ref. 15)

2') Many biochemical reactions take place in detoxification (Ref. 11,15):

- oxidation
- reduction
- hydroxylation
- deamination
- dealkylation
- methylation
- conjugation

3') One of the more important oxidation reactions involves cytochrome P-450. Let's get some background.

a') Microsomes of the liver contain a group of protein molecules (called mixed-function oxidases) that oxidize various chemicals (such as steroids, fatty acids, drugs, pesticides and carcinogens) (Ref. 11). Microsomes are spherical vesicles derived from endoplasmic reticulum after disruption of the cell by centrifugation. (Ref. 17)

b') One of these oxidases is cytochrome P-450 (so termed because of the spectral absorption at 450 nm) (Ref. 11).

c') Hepatic P-450 is recognized as one of the most important systems for oxidation of drugs and xenobiotics. (Ref. 11)

d') There are multiple forms of P-450.

-One source says there are 3 to 6 forms (ref. 19), while another source states that there is variability of the structure of P-450 on the order of immunoglobulins (ref. 11)!

e') Presentation of different substrates for oxidation results in the stimulation of the production of different forms of cytochrome P-450. (Ref. 11)

f') Level of active drug will be determined by functioning capability of liver

1") Enzyme activity may be severely reduced in severe liver disease leading to intensification or prolongation of drug action (ref. 15).
2") The activity of the P-450 system can be induced or inhibited by certain drugs (must be aware of this when drugs are coadministered; there may be a different steady state for the drug when it is coadministered with another drug (ref. 11)):

- Phenobarbital, alcohol - induce P-450 system
- Cimetidine - inhibits P-450 system

g) Catabolism of substances also takes place through the phagocytic functions of the reticuloendothelial cells.

18. Unique anabolic processes in which the liver plays a sole or major role

a) The liver is the major site of triglyceride, phospholipid and cholesterol synthesis (ref. 15); and lipoprotein synthesis (ref. 28, 399)

b) Facts about cholesterol synthesis:

1') 90% of the synthesis of cholesterol occurs in the liver and the gut (ref. 9).

2') 80% of the cholesterol that is synthesized is converted to bile acids, the remainder is packaged into lipoproteins which is carried to the tissues (Ref. 1).

Ref. 9

3') Esterification of the cholesterol with fatty acids. Seventy percent of the cholesterol is esterified in plasma; Very little esterification occurs in the liver. Esterification reactions take place mostly in the blood.

b) Serum Proteins

1') The majority of serum proteins are synthesized in the liver with exception of IgG and hemoglobin (ref. 11). The liver synthesizes albumin and globulins (with the exception of γ-globulin, which is formed in lymph nodes and lymphoid tissues) (Ref. 31, p. 1198).

Ref. 9

2') Proteins are synthesized in rough endoplasmic reticulum of the liver cells and released into the hepatic sinusoids (ref. 9).

3') Proteins are important for the diagnosis of hepatic function. One would expect a decrease synthesis of serum proteins with hepatic dysfunction. This however does not manifest itself unless the hepatic disease is severe or long standing. Also some proteins have increased concentration in the serum with disease, as given below:

a') Important proteins that decrease in concentration with hepatic disease:

<table>
<thead>
<tr>
<th>Protein</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>12-14 days</td>
</tr>
<tr>
<td>Prealbumin</td>
<td>1.9 days</td>
</tr>
</tbody>
</table>

[12-14 days half life (ref. 21)]
(1.9 days half-life makes it an extremely sensitive indicator)


