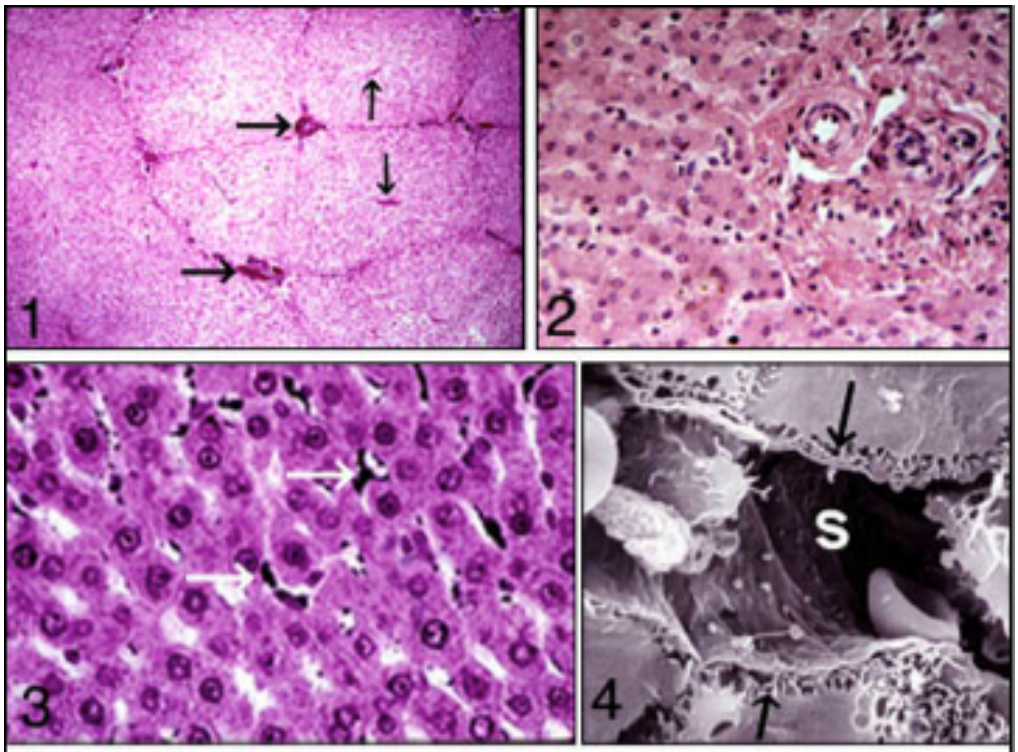
Liver



1. Hepatic lobules. Note the central veins (small arrows) and portal areas (large arrows).
2. A portal area showing the hepatic artery, interlobular bile duct, portal vein, and lymphatic channel. Hepatic cords separated by sinusoids are to the left.
3. Hepatocytes and Kupffer cells (arrows).
4. An SEM of a hepatic sinusoid interior (S) and the surrounding perisinusoidal space (arrows). Courtesy of G. H. Haggis.

The liver is the largest gland in the body weighing about 1.4 kg in an average adult. It acts as both an endocrine and exocrine gland, releasing several substances directly into the bloodstream and secreting bile into a duct system. An important function of the liver is to conjugate lipid soluble molecules (steroids, bilirubin, some drugs) with SO3 or glucuronide, which renders them water soluble for release into the bile and ultimate elimination through the alimentary canal. The liver is uniquely situated with respect to the venous blood flow from the gastrointestinal tract. Blood from the portal vein, which drains the entire gastrointestinal tract and spleen, passes through the substance of the liver before entering the systemic circulation. The smooth muscle in the wall of the portal vein is unique in comparison to other regions of the vasculature in that it is phasic smooth muscle. Phasic smooth muscle has the capacity to generate action potentials and this wave of activity results in rhythmic contractions that aid in moving blood to the liver. The liver therefore receives all of the materials absorbed by the gastrointestinal tract except some lipids, most of which are carried by lymphatics to enter the general circulation. Blood from the spleen, the primary organ in which aged erythrocytes are removed from the blood and broken down, carries the breakdown products of hemoglobin to the liver. Tributaries of the portal vein empty into hepatic sinusoids that drain into hepatic veins. The arrangement in the liver of a set of sinusoids between veins is called the hepatic portal

system. The liver also has an arterial supply from the hepatic artery, and both the venous (portal) and arterial (hepatic) bloods percolate through the liver sinusoids and exit by way of the hepatic vein.

Structural Organization

A delicate connective tissue capsule that is continuous with the peritoneum invests the liver. The capsule contains numerous elastic fibers and is covered by a mesothelium except for a small bare area where the liver abuts the diaphragm. The liver is composed of epithelial cells, the hepatocytes, arranged in branching and anastomosing plates separated by blood sinusoids. Both form a radial pattern about a central vein that is the smallest tributary of the hepatic vein. The spokelike arrangement of hepatic plates about a central vein constitutes the basis of the classic hepatic lobule, which appears somewhat hexagonal in cross section, with a central vein at the center and portal areas at the corners. The liver consists of about 1 million such units.

A portal area contains a branch of the portal vein, a branch of the hepatic artery, a bile duct, and a lymphatic channel. All are enclosed in a common investment of connective tissue. Blood passes from small branches of the hepatic artery and portal vein into the sinusoids that lie between plates of hepatocytes. Blood flows slowly through the sinusoids toward the center of the lobule and exits through the central vein. Branches of the hepatic artery carry oxygenated blood and provide about 20% of the blood flow within hepatic sinusoids. In contrast, branches of the portal vein carry nutrient rich blood from the gastrointestinal tract and contribute the remaining 80% of the sinusoidal blood flow. Hepatocytes nearest the branches of the portal vein and hepatic artery - that is, at the periphery of the lobule – receive blood with the highest nutrient and oxygen content. Both diminish as blood flows toward the central vein. Due to this arrangement, three zones can be recognized in a hepatic lobule according to the metabolic activity: a zone of permanent function (zone 1) at the periphery, a zone of intermittent activity (zone 2) near the center of the lobule, and a zone of permanent repose (zone 3) near the central vein. Observing the central vein and noting the portal areas at the corners of the lobule can estimate the boundaries of the hepatic lobule.

Also related to the blood supply is a smaller unit of liver structure called the liver acinus or functional unit. The liver acinus is defined as the hepatic tissue supplied by a terminal branch of the hepatic artery and portal vein and drained by a terminal branch of the bile duct. A diamond-shaped area represents it with central veins at two of the opposite comers. Branches of the blood vessels and a branch of the bile duct lie between the two portions of adjacent hepatic lobules that they supply.

An additional lobule is related to the exocrine secretion (of bile) in the liver. This unit is the portal lobule and has a portal canal at its center. It consists of the hepatic tissue that is drained by the bile duct of the portal area. A portal lobule is triangular in shape and contains parts of three adjacent hepatic lobules. A central vein is located at each corner of this unit. The bile produced by hepatocytes flows in a direction opposite that of blood toward the periphery of the classic hepatic lobule.

A single layer of small, dark hepatocytes limits the liver parenchyma beneath the capsule and is called the subcapsular limiting plate. A similar wall of hepatic cells surrounds the portal areas and forms the periportal limiting plate, which is pierced by tributaries of the hepatic artery, portal vein, lymphatic vessels, and bile ductules. The limiting plates of hepatocytes prevent blood from escaping the classic hepatic lobules.

Hepatic Sinusoids

Hepatic sinusoids are larger and more irregular in shape than ordinary capillaries. The sinusoidal lining consists of a simple layer of squamous epithelium supported by very little connective tissue. Three types of cells are associated with the sinusoidal lining: endothelial cells, stellate cells (Kupffer cells or hepatic macrophages), and fat-storing cells (lipocytes).

Endothelial cells constitute the major cellular element of the sinusoidal lining and form a discontinuous endothelium. There is no basal lamina, and the cells are separated by gaps 0.2 to 0.5 μm wide. The endothelial cells also show numerous intracellular fenestrations or pores. The sinusoidal lining is separated from the liver cells by a narrow perisinusoidal space (of Disse).

Blood plasma flows freely through the endothelium and into the space, but the sinusoidal lining does hold back erythrocytes. Although occasional bundles of reticular fibers and fine collagenous fibers are present in the perisinusoidal space, there is no ground substance, and the flow of blood plasma is unhindered. Because the plasma has direct access to the perisinusoidal space, the liver cells are constantly bathed on one surface by fluid that is rich in the nutrients absorbed by the intestinal tract.

Thus, the perisinusoidal space has considerable significance in the exchange of materials between the liver and plasma. The plasmalemma of the hepatocytes that face the perisinusoidal space bear numerous well-developed microvilli that project into the space and greatly increase the surface area and facilitate absorption. Not all the formed tissue fluid is absorbed by the hepatocytes or passes back into the sinusoidal lumen and as a result the liver produces a considerable amount of lymph. The liver produces about half of the lymph found within the thoracic duct. Like bile flow, lymph flows within the perisinusoidal space from the center of the hepatic lobule toward the periphery. Lymphatic vessels within the portal areas course parallel to the branches of the portal vein and ultimately empty into the thoracic duct.

Also present in the sinusoidal lining are actively phagocytic cells, variously called hepatic macrophages or Kupffer cells. These form part of the sinusoidal lining and are irregularly shaped cells that expose the greater part of their cytoplasm to the blood in the sinusoid and extend processes between the endothelial cells.

Unlike the neighboring endothelial cells, the cytoplasm of the hepatic phagocytes contains vacuoles, lysosomes, Golgi bodies, and short profiles of granular endoplasmic reticulum. Phagocytized material also may be present. These cells are part of the mononuclear system of macrophages and arise from monocytes of the bone marrow.

The third type of cell is located on the side of the sinusoidal lining that faces the perisinusoidal space. This cell accumulates lipid and is most numerous in the peripheral and intermediate zones of the hepatic lobule. They have been called lipocytes, fat-storing, stellate, or interstitial cells, and function to store vitamin A.

Hepatocytes

The parenchyma of the liver consists of large polyhedral hepatocytes arranged in plates that radiate from the region of the central vein. The surfaces of an individual hepatocyte either contact an adjacent liver cell or border on a perisinusoidal space. This latter surface bears numerous well-developed microvilli. The plates of hepatocytes are supported by a delicate stroma that consists primarily of reticular fibers. The nuclei of hepatocytes are large and round and usually occupy the center of the cell. A single nucleus usually is present, but as many as 25% of hepatocytes are binucleate. There also is considerable variation in the size of nuclei

from cell to cell, reflecting the polyploid nature of hepatocytes. The cytoplasm of hepatocytes is rich in organelles-large arrays of granular endoplasmic reticulum, a moderate amount of smooth endoplasmic reticulum, mitochondria, Golgi complexes, peroxisomes, and lysosomes. Inclusions such as glycogen and lipid also are common. Glycogen often appears as dense rosettes (alpha particles) made up of smaller beta particles. The alpha particles measure 20 to 30 nm in diameter. The cytoplasm is variable in appearance and changes with the nutritive state of the organ. Tiny channels, the bile canaliculi, course through the parenchyma between hepatocytes to end in the bile ducts of the portal areas. Bile canaliculi represent an expansion of the intercellular space, and their walls are formed by the adjacent plasmalemma of two neighboring hepatocytes. Short microvilli extend from the cell membrane into the lumen. At the margins of the canaliculus, occluding junctions similar to the zonula occludens of other epithelia joins the plasma membranes. They form an occluding seal to prevent bile from escaping into the intercellular spaces between hepatocytes. Golgi complexes of hepatocytes often lie adjacent to the canaliculi. The bile canaliculi show intermittent contractions.

Hepatocyte Function

Hepatocytes are extraordinarily metabolically active cells that perform a wide variety of functions. Hepatocytes are involved in the conversion of ammonium to urea, can perform gluconeogenesis (conversion of lipids and amino acids into glucose), synthesize cholesterol, as well as take up immunoglobulin A (IgA) and release it as a secretory from of IgA into the bile and ultimately into the lumen of the small intestine. Hepatocytes play a major role in the metabolism and storage of carbohydrates, fats, and proteins. A primary function of hepatocytes is to store carbohydrate in the form of glycogen. Hepatic glycogen functions to maintain normal blood glucose levels (70-100 mg/100 ml). During a high-carbohydrate meal as the blood glucose concentration begins to rise a rapid pulse of insulin secretion occurs that results in an increase in the insulin glucagon ratio. The rise in insulin concentration suppresses hepatic glucose production and increases its uptake up take by insulin-dependent tissues. It is thought that a glucokinase, translocated from the nucleus to the cytosol during high glucose concentration catalyzes the phosphorylation of glucose and promotes glucose entry into hepatocytes. Insulin regulates glucokinase activity by both transcription and translocation in the hepatocytes. The storage form of glucose (glycogen) consists of glucose molecules linked by α 1, 4 glycosidic bonds. Glycogen synthase catalyzes the synthesis of glycogen. Glycogen breakdown occurs during fasting and exercise that results in a decrease in the insulin glucagon ratio, and secretion of epinephrine. The latter binds to α- and β-adrenergic receptors on the hepatocytes. Liver glycogen is degraded by a hepatic glycogen phosphorylase to glucose-6-phosphate, which in turn is catalyzed to free glucose by the enzyme, glucose-6-phosphatase, localized within the cisternae of the endoplasmic reticulum. Glucose-6-phosphate is transported into the lumen of endoplasmic reticulum by a specific glucose-6-phosphate transporter protein where it is hydrolyzed to glucose and phosphate by glucose-6-phosphatase. Glucose is transported out of the endoplasmic reticulum and across the plasmalemma of the hepatocyte by glucose transport proteins. Hepatocytes also play a vital role in maintaining blood lipid levels; by the uptake of fatty acids and the esterification of fatty acids to triglycerides, which occurs within the smooth endoplasmic reticulum. The triglycerides are then complexed to proteins within the Golgi complexes of hepatocytes to form a variety of lipoproteins. Hepatocytes synthesize high-density lipoproteins (HDL) molecules, which facilitate the flow of excess cholesterol and triacylglycerides in the plasma back to the liver for metabolism. Hepatocytes also produce very-low-density lipoproteins (VLDL) that are rich in

triacylglycerides that travel to skeletal muscle and fat cells where the triacylglycerides are hydrolyzed by the enzyme lipoprotein lipase to fatty acids. Low-density lipoprotein (LDL) molecules on the other hand are rich in cholesterol and carry cholesterol to cells throughout the body that have LDL receptors.

Amino acids are deaminated in the liver to produce urea, which is excreted by the kidney. The liver also has functions in protein metabolism; synthesis of fibrinogen, prothrombin, and albumin; and storage of several vitamins (primarily A, D, B2, B3, B4 and B12).

Enzymes within hepatic peroxisomes have the ability to metabolize alcohol. Enzymes associated with the smooth endoplasmic reticulum, on the other hand, are involved in the deactivation of some hormones, lipid soluble drugs, and toxins, which is another important function of hepatocytes. Detoxified materials are excreted by hepatocytes into the bile and conducted by the biliary duct system to the intestinal tract for elimination.

Bile is a complex exocrine alkaline secretion of the liver and contains ions, water, bicarbonate, bile acids (taurocholic and glycocholic), bile pigment (bilirubin glucuronide), phospholipids, cholesterol, lecithin, and neutral fats. Hepatocytes produce between 500 and 900 ml of bile daily. Bile acids/salts act as emulsifying agents and are important in the breakdown of fat to micelles in the intestinal lumen during digestion. Most bile acids (about 80%) are reabsorbed in the ileum to be secreted once again into the bile. This reuse of bile acids is referred to as the enterohepatic circulatory system.

Bilirubin is produced in the spleen and liver as a result of the breakdown of the heme component of hemoglobin in damaged or old erythrocytes by macrophages at these locations. The bilirubin taken up by hepatocytes is then conjugated with glucuronic acid to form bilirubin glucuronide, which is excreted into the bile. Bacterial action on this molecule after its entry into the intestinal tract converts it to urobilinogen. Of the urobilinogen formed, some is lost in the feces, some is absorbed and returned to the liver, and some is excreted by the kidneys.

Bile Ducts

Bile canaliculi unite with bile ducts in the portal canals via small, interconnecting channels called bile ductules. They are small and have thin walls, and their small lumina are surrounded by a low cuboidal epithelium that rests on a distinct basal lamina. The terminal ductules pass through the periportal limiting plate and empty into interlobular bile ducts of the portal areas. The lumina of the bile ducts increase in diameter as they course toward the exterior, and the lining epithelium increases in height. Interlobular ducts unite to form the extrahepatic ducts, in which the surrounding layers of connective tissue become thicker and the lining epithelium becomes tall columnar. Two large extrahepatic ducts, the left and right hepatic ducts, exit the lobes of the liver and unite to form the major excretory duct of the liver, the common hepatic duct. It is joined by the cystic duct from the gallbladder to form the common bile duct (ductus choledochus), which empties into the duodenum. The major extrahepatic ducts are lined by a tall columnar, mucus-secreting epithelium. The remainder of the wall consists of a thick layer of connective tissue that is rich in elastic fibers and often contains numerous lymphocytes and occasional migrating granulocytes. Bundles of smooth muscle cells, running in longitudinal and oblique directions, are present in the common bile duct and form an incomplete layer that spirals about the lumen. Near the wall of the duodenum, the smooth muscle forms a complete investment and thickens to form a small sphincter, the sphincter choledochus. Distal to this region, the common bile duct and the major pancreatic duct merge as they pass through the intestinal wall and empty through a common structure, the hepatopancreatic ampulla. As the ducts pierce the duodenal wall, a common sphincter of smooth muscle surrounds them.

Bile is produced continuously by the liver and ultimately leaves the organ through the extrahepatic duct system. Hepatocytes produce between 500-900 ml of bile daily. Resistance at the sphincters forces bile to enter the cystic duct and pass into the gallbladder, where it is stored. Bile formation occurs primarily at two anatomic sites: bile canaliculi and bile ductules. Secretin increases secretion of ductular bile, which is rich in bicarbonate. Glucagon increases canalicular bile secretion.