

Liver

- The largest gland in the body, 3 ½ lbs, right upper quadrant
- Has a unique, dual blood supply; 75% of blood coming in is venous – it's already gone through capillary beds in the stomach, small and large intestine, and the spleen
 - Blood deficient of O₂ but very rich in nutrients from previous capillary beds (lipids, sugars, amino acids, nucleic acids, immunoglobulins)
 - Portal vein is main input
 - Arterial input from hepatic artery – 25% of blood input
- Hylus – different from other organs; portal vein and hepatic artery enter, while bile duct leaves
- Metabolically active
 - Provides needed glucose to body, stores glucose as glycogen
 - Synthesizes albumin (important to blood osmotic pressure)
 - Makes many blood clotting factors
 - Makes nucleic acids, lipoproteins
- Blood exits liver - blood collected in central veins → lead into larger veins → exits via hepatic vein → empty into inferior vena cava (so any interruption in liver blood flow will affect heart, and any defect in heart pumping will affect the liver due to intimate relationship between liver and heart)
- **Portal tract** – where portal vein, hepatic artery and bile duct are all found together; there are many in the liver.
 - Area of tract surrounded by some connective tissue that is easily recognized microscopically
 - Also called portal triad
 - Blood from portal vein and hepatic artery mix in the portal capillaries; capillaries are very wide and discontinuous – so wide they are referred to as **sinusoids**
 - Capillaries empty into a central vein → lead to larger veins exiting the organ
 - Blood and bile flow in opposite directions
- After digestion, intestinal blood coming in via portal vein is overloaded with nutrients
 - Liver constructed to handle large influx through metabolically active hepatocytes in close contact with blood
 - Hepatocytes arranged in plates one cell thick to maximize area of contact between hepatocytes and blood plasma
 - Liver cells bathed by blood plasma on at least 2 or 3 of their 6 sides
 - Incoming blood forced through sinusoid capillary network with reduced vessel walls (discontinuous), no basement membrane and large discontinuities between endothelial cells, strands of collagen called reticular fibers hold loosely arranged endothelial cells together
 - Between liver cell and sinusoid is the pericapillary space (the **Space of Disse**) – here the blood plasma (not interstitial fluid) is sampled by hepatocytes sending pseudopods (cytoplasmic projections) into the space
- **Kupffer cells** – another important type of cell making up wall of sinusoid, spans lumen
 - Large resident macrophages, one of the principal filters of foreign particulate matter and bacteria from the gut
 - After each meal, some gut bacteria escape into blood and enter the liver but are phagocytized by Kupffer cells (blood entering liver nonsterile, blood leaving is sterile)
 - Also removes and disposes old erythrocytes (120 day lifespan)
- Endocrine and exocrine function
 - Endocrine – not an endocrine gland, but directs some of its products directly into the blood
 - Exocrine – makes bile, an exocrine product, which it secretes via ducts to the lumen of duodenum
 - Liver cells continually make bile, which is released into tiny **bile canaliculi** between liver cells → delivered to **bile ducts** → empty into **right and left hepatic ducts** → leave the liver and form **common hepatic duct** → joins **cystic duct** to form **common bile duct** which empties into duodenum at the **ampulla of Vater**
 - Flow of bile is in opposite direction of blood
 - At the ampulla, **Sphincter of Oddi** that is normally closed so bile is backed up and stored in the **gallbladder**.
 - Food stimulates secretion of CCK which causes relaxation of the sphincter and contraction of the gallbladder → bile delivered to small intestine
 - Bile – contains bile salts and bile pigments
 - Bile salts – cholic acids are cholesterol derivatives, their salts (bile salts) are powerful detergents which aid in the emulsification and subsequent absorption of fats in the small intestine
 - Bile pigments – derived mainly from the degradation of hemoglobin and other heme proteins. Destruction of old RBC occurs mainly in macrophages of the spleen and liver Kupffer cells. Hemoglobin is broken down in these cells to globin and heme

- Hemoglobin – contains two α and two β chains of globin with a heme and Fe in each chain. When broken down in the macrophage, the amino acids from the peptide chains are reused by the body and the Fe is transported and stored mainly in the liver and bone marrow and the heme is converted into a green pigment called **biliverdin** which is reduced to a red pigment called **bilirubin** (modified, it is the major constituent of bile pigment).
 - Bilirubin is first conjugated in the blood to albumin → carried to the liver → enters the hepatocytes → liver cell conjugates bilirubin making it more soluble → released into tiny bile canaliculi between liver cells → bile duct → gallbladder → intestine
 - Bacteria in intestine convert bilirubin into pigmented compounds called urobilinogens which are excreted in urine (yellow color) and some in feces (brown color), 20% reabsorbed in ileum and colon to get retaken up by liver (not a useless waste product, a powerful antioxidant)
 - Excess conjugated or unconjugated bilirubin can cause jaundice
- Gallbladder
 - Structure
 - Simple columnar epithelium, no villi, no goblet cells
 - Short, stubby microvilli (not as abundant as a brush border)
 - Thin lamina propria, with smooth muscularis beneath (only muscular layer, no muscularis mucosa or submucosa, unique)
 - Underneath muscularis, thick serosa with fat, connective tissue and some vessels; lined with simple mesothelium
 - When empty, epithelium thrown up into temporary folds (not villi) that disappear when gallbladder is full
 - Bile concentration
 - Na^+ and Cl^- enter cells apically via a cotransporter
 - Na^+ actively transported out along the lateral borders. Cl^- follows via Cl^- channel
 - Water moves into hypertonic medium between cells, causing swelling of lateral borders
 - Increased hydrostatic pressure forces water and salts into capillaries in the lamina propria
 - The bile remaining in the gall bladder is thus concentrated
- General Liver Functions
 - Metabolic
 - Hepatic glucose output from glycogen stores and also gluconeogenesis
 - Lipid
 - Uptake of plasma free fatty acids with conversion to triglyceride
 - Lipoprotein synthesis
 - Maintenance of nitrogen balance – urea formation from amino acid nitrogen
 - Synthetic Activities
 - Protein, glycogen, creatine, ketone bodies, cholesterol
 - Conjugation, deamination, solubilization, detoxification
 - Storage
 - Metals – iron, copper
 - Fat-soluble vitamins (A, D, K, E)
 - Vitamin A – not stored in hepatocytes, but in **stellate** cells located in the space of Disse. These cells have been implicated in the induction of hepatic fibrosis. Hepatic fibrosis is a wound-healing process that occurs when the liver is injured chronically, such as in chronic alcoholism. Hepatic stellate cells are responsible for the excess production of collagen and other extracellular matrix components. Recent studies suggest that there is an antagonistic relationship between the storage of vitamin A and production of collagen in hepatic stellate cells.
 - Vitamin K – important in blood clotting
 - **Biliary disease** – decrease in bile salts → decreased fat absorption → decreased vitamin K absorption → malfunction in blood clotting (must be corrected before surgery to remove gallbladder)
 - Vitamin B_{12} (cyanocobalamin) – stored in liver, complex porphyrin derivative containing cobalt (only known function for Co in body)
 - Deficiency results in **pernicious anemia**
 - Historically: found that it could be relieved by daily ingestion of raw or lightly cooked liver (presence of intrinsic factor, mucoprotein made by parietal cells, needed for absorption). Francis Minot
 - Parietal cells destroyed by autoimmunity
 - Cured by injection of B_{12} , not ingestion without intrinsic factor
- Hepatocyte – parenchymal cell of the liver

- Many are binucleate, large nucleolus indicating active ribosome production
- **Plasmalemma** – plasma membrane
 - Exocrine domain – faces bile canaliculi, more than one exocrine (apical) surface
 - Sinusoidal surface – completely separate from bile canaliculi (apical surface)
 - Has extensive rough ER for synthesis of plasma proteins
 - Has much smooth ER for glycogen synthesis
 - Detoxification enzymes – peroxisomes, lysosomes,
 - Numerous mitochondria – part of krebs urea cycle operates in liver mitochondria
 - Amino acid nitrogen in mitochondrion → after many reactions forms citrulline → exits mitochondrion into cytosol → through a series of reactions converted to arginine → urea formed by arginase → ornithine remains and reenters mitochondrion → cycle resumed (first description of metabolic cycle)
- Liver lobule – classically a hexagon of tissue with portal tracts in the corner and central vein in the middle
 - Plates of liver cells separated by sinusoids that radiate toward the central vein
 - Portal triads on outskirts, central vein in the middle of a field of hepatocytes
 - Blood flows from triads towards central vein
 - Bile flows away from central vein towards triads
- Sinusoid – loosely arranged endothelial cells held together by thin strands of collagen with no real basement membrane
 - Thin strands of collagen made of reticular fibers
 - Space of Disse – lies between sinusoid wall and plasma membrane of the liver cell
 - Site of nutrient interchange between liver cell and sinusoid
- Kupffer cells – make up walls of sinusoids along with endothelial cells
 - Become enlarged after phagocytosing
- Bile canaliculi – walls consist of the plasma membranes of adjacent liver cells, tight junctions seal them
 - Blood travels in canaliculi, completely separate from the blood in sinusoids
 - Eventually bile canaliculi get simple cuboidal cell walls (then called **canals of herring**) and lead into bile ducts in the portal tract
- Lymph also formed in the liver as fluid leaks out of sinusoids; most returns to the blood, but some seeps between liver cells into lymphatic vessels located in the portal tract
- Ways of viewing liver structural units
 - **Classic liver lobule** – hexagon, with central vein at the center
 - Stresses the endocrine function of the liver, with substances produced by the liver entering the blood (blood flows from the portal space, or the points of the hexagon, to the central vein)
 - **Portal lobule** – triangular unit with portal canal (triad) at center
 - Stresses the exocrine function of the liver with bile flowing from the central vein to the portal space
 - **Liver Acinus** – more recently considered to better represent the blood flow and function of the liver
 - Diamond-shaped unit of liver parenchyma with zones of liver tissue irrigated by the smallest terminal branches of the portal vein hepatic artery
 - Divided into three zones with different exposures
 - Zone 3 - the furthest from source of oxygen and nutrients
 - Cells here first to deteriorate during ischemic injury
 - Zone 1 – first cells exposed to toxic substances in the blood