LIVER ANATOMY AND PHYSIOLOGY

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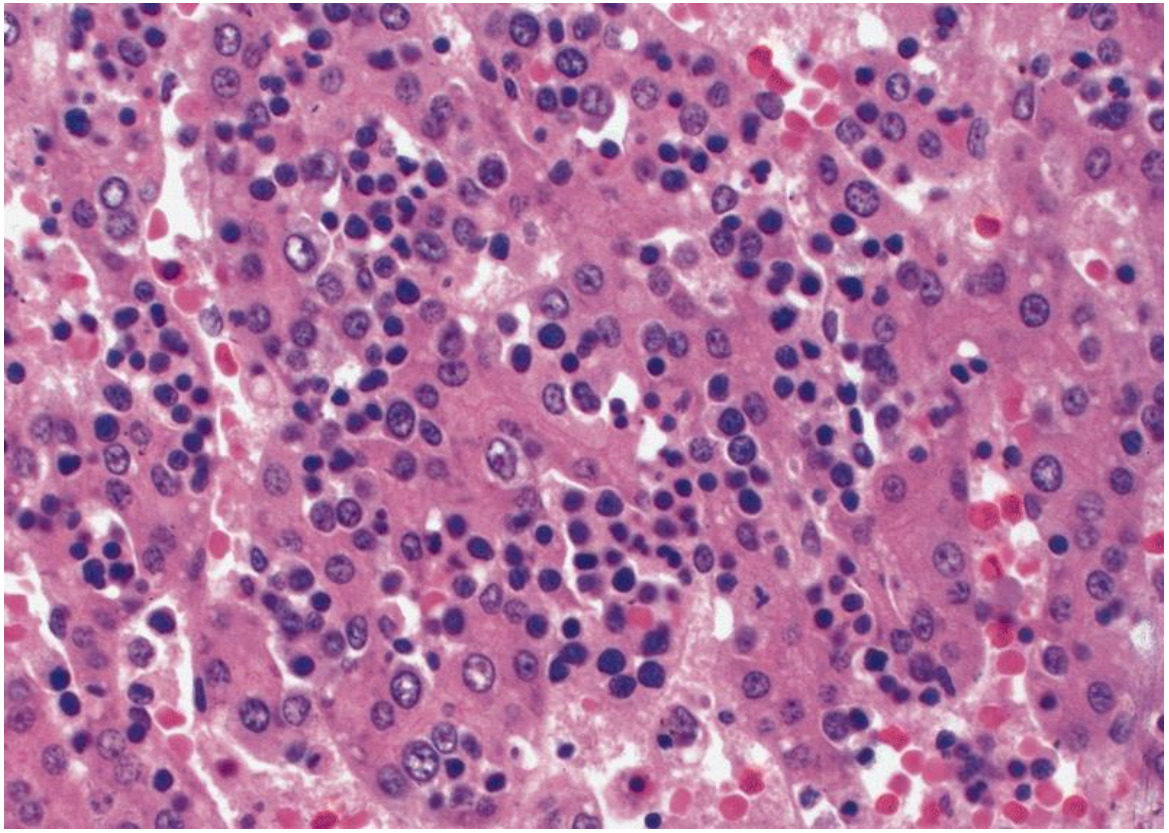
Embryology

- The development of the liver begins with the appearance of the hepatic diverticulum, which buds from the ventral foregut at the end of the third week of gestation. The diverticulum grows into the primitive septum transversum; the liver forms from the endodermal cells of the diverticulum and the mesenchyme that is already present.
- The embryonic and fetal liver is a vascular and hematopoietic organ composed of a complex venous-sinusoidal plexus, cords of hepatocytes, abundant hematopoietic precursors, and macrophages (Kupffer cells), which are also of hematopoietic origin. Most of its blood supply is from the umbilical vein.

Fetal liver



There are cords of hepatocytes and sinusoids that contain many hematopoietic precursors and macrophages.

Fig. 1-1

Ishak KG, Goodman ZD, Stocker JT., “Tumors of the liver and intrahepatic bile ducts. Atlas of Tumor Pathology, Third Series, Fascicle 31. Armed Forces Institute of Pathology, Washington, D.C. 2001.

Embryology

- Wastes (excreted in the bile in the adult) are cleared by the placenta. Nutrient absorption is via the placenta. The fetal liver synthesizes plasma proteins and bile acids while also storing Iron and Copper as well as glycogen. Consequently, a large part of the blood delivered by the umbilical vein bypasses the fetal liver and enters the systemic circulation through the ductus venosus.
- The lining of the large extrahepatic and major intrahepatic bile ducts is derived from the endoderm of the original hepatic diverticulum. The small ducts that drain the hepatic acini, however, are derived from the embryonic ductal plate.

Anatomy

- 60-70% of incoming blood the liver arrives via the portal veins.
- The initial branches of the portal vein, hepatic artery, and bile duct lie outside the liver between the gallbladder fossa and the inferior vena cava. The remaining branches travel within the liver in portal tracts.
- The falciform ligament divides the liver into right and left lobes anatomically. The caudate lobe lies adjacent to the inferior vena cava; the quadrate lobe, adjacent to the gallbladder.

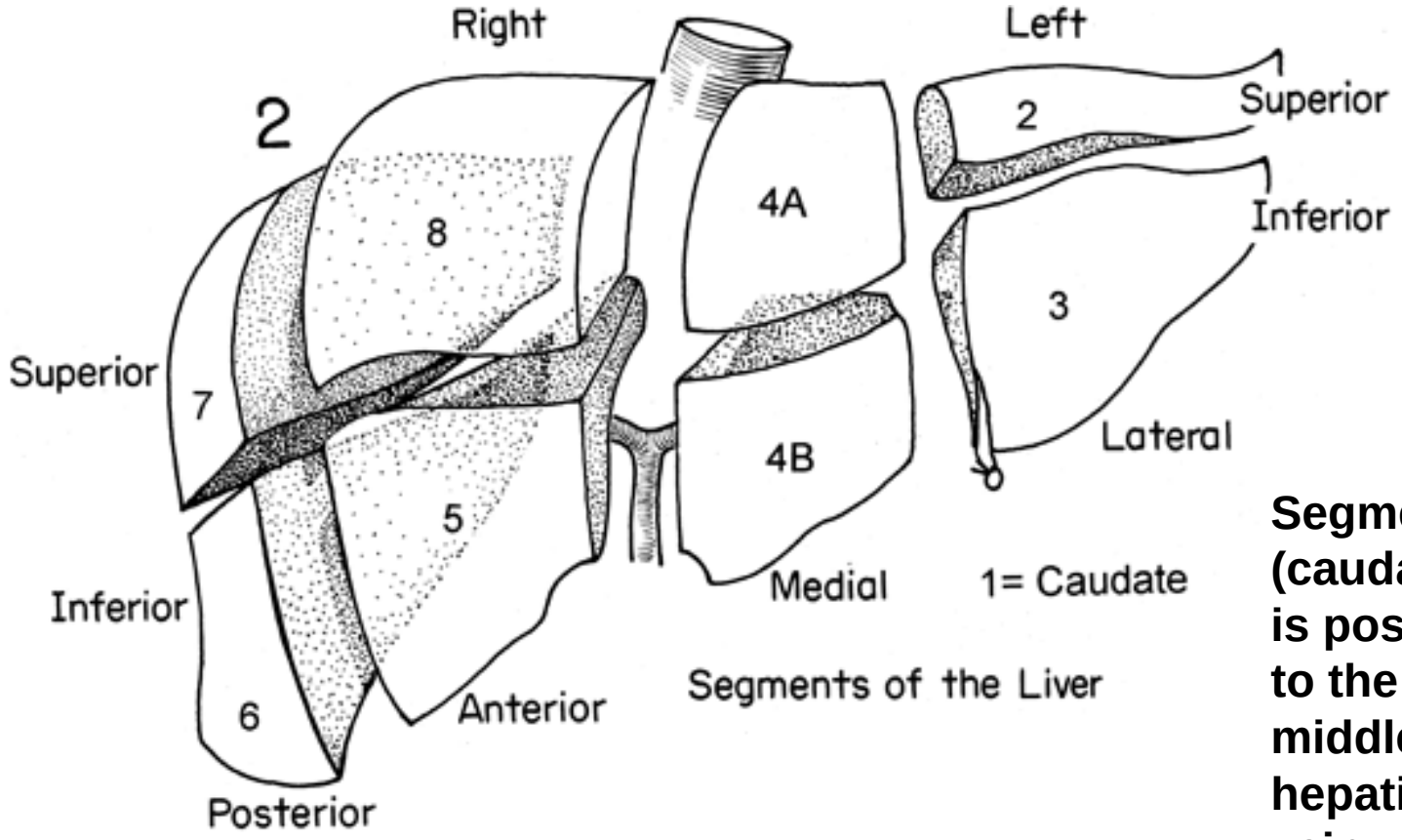
Anatomy

- The portal vein is formed by the union of the superior mesenteric and splenic veins. (The inferior mesenteric vein usually terminates in the splenic vein.)
- The portal vein drains structures supplied by the celiac, superior and inferior mesenteric arteries.
- The portal vein lies posterior to the neck of the pancreas. It lies posterior to the hepatic artery and bile duct.

Functional anatomy of the liver

- Physiologic right and left lobes, however, are defined by the distribution between the right and left portal veins.
- Functionally, the liver is divided into eight segments, each with independent vascular and biliary pedicles and drainage.
- The caudate lobe is segment I.

Surgical anatomy of the liver



Segment I (caudate) is posterior to the middle hepatic vein.

Zollinger's Atlas of Surgical Operations, 8th Edition Fig. 1-57 2

Anatomical hepatic duct variants

- Confluence of the right and left hepatic ducts usually occurs in up to 75% of patients.
- A triple confluence of the right and left hepatic ducts, with the division of the right anterior and posterior sectoral ducts with a left hepatic duct, occurs in up to 15% of patients.
- In 6%–8%, a right sectoral duct may join the left hepatic duct.
- In 3%, there may be absence of the hepatic duct confluence.
- In 2%, a right posterior sectoral duct may join the neck of the gallbladder.

Anatomical arterial variants

- In up to 25% of cases, the right hepatic artery arises from the superior mesenteric artery.
- In up to 25% of cases, the left hepatic artery is derived completely from the left gastric artery.

Organ structure

- Macroscopically, the liver consists of hexagonal lobules oriented about a terminal hepatic vein with the portal vein at the periphery.
- Microscopically, the hepatic parenchyma is arranged into cribiform, anastamosing sheets iof hepatocytes seen as cords of cells with a radial orientation.
- Bile canaliculi are found between abutting hepatocytes. They drain into the periportal canals of Herring; then, into bile ductules; finally, into terminal bile ducts in the portal tracts.

Normal liver functional lobule

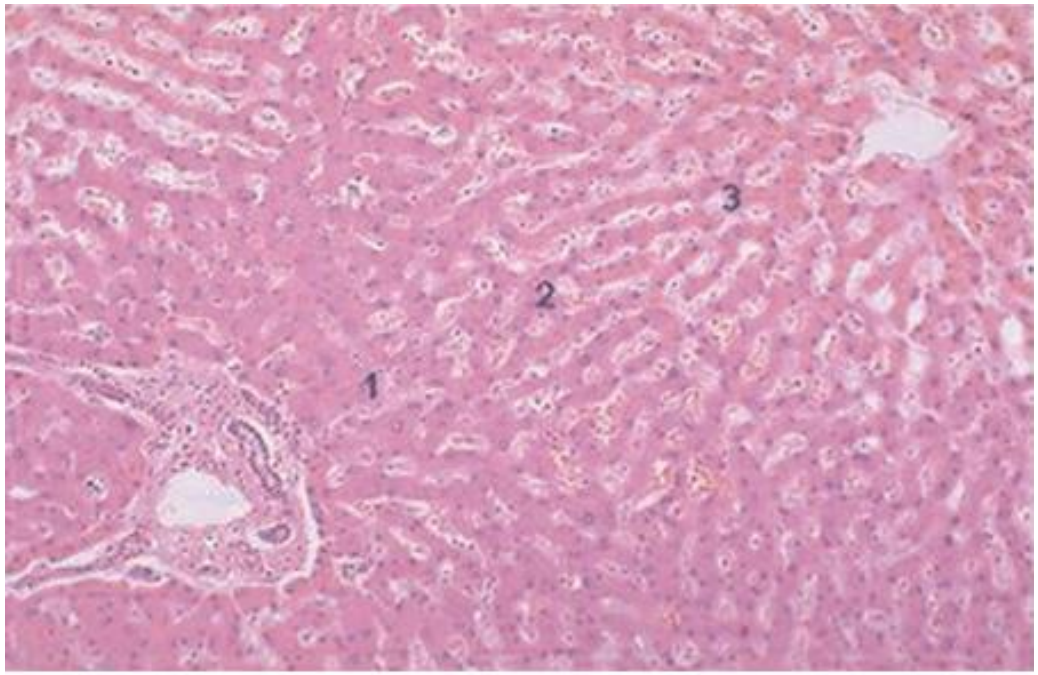


Fig. 15-8 Accessed 04/10/2010

The liver is divided histologically into lobules. The center of the lobule is the central vein. At the periphery of the lobule are the portal triads. Functionally the liver can be divided into three zones, based on oxygen supply. Zone 1 encircles the portal tracts where the oxygenated blood from hepatic arteries enters. Zone 3 is located around central veins, where oxygenation is poor. Zone 2 is located in between

Normal liver functional lobule

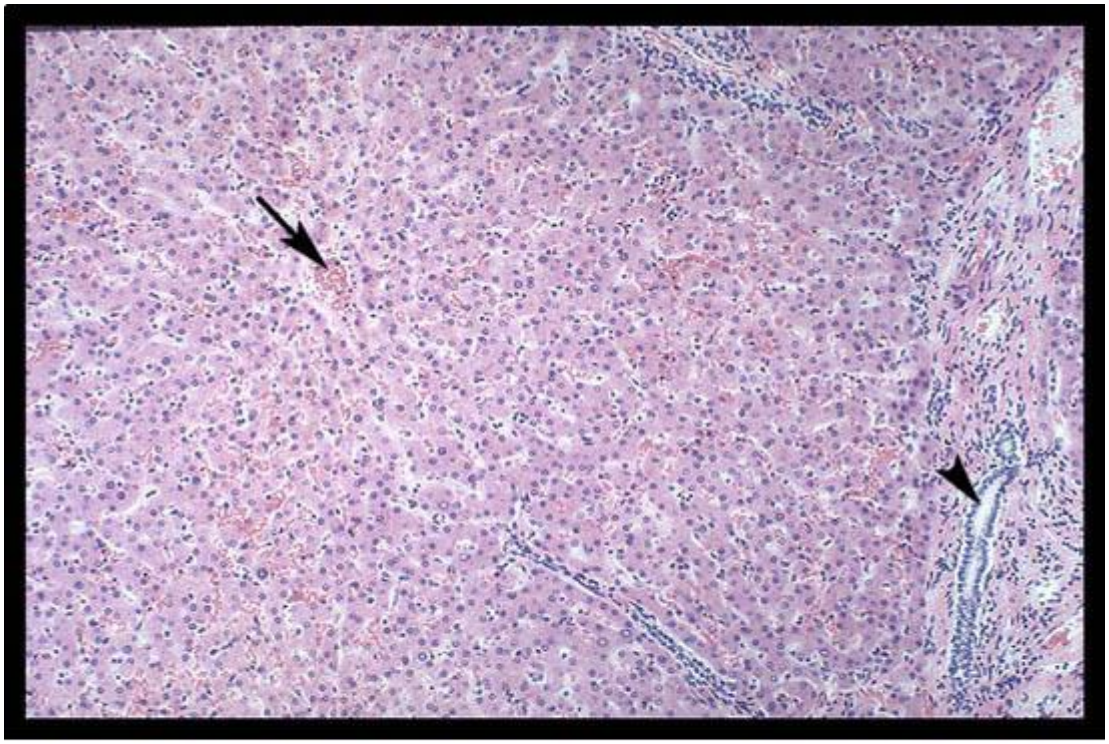


Fig. 15-2 Accessed 03/21/2010.

The central vein (arrow) is positioned in the center of the field, from which radiate plates of hepatocytes toward the portal tracts (arrowhead).

Portal area

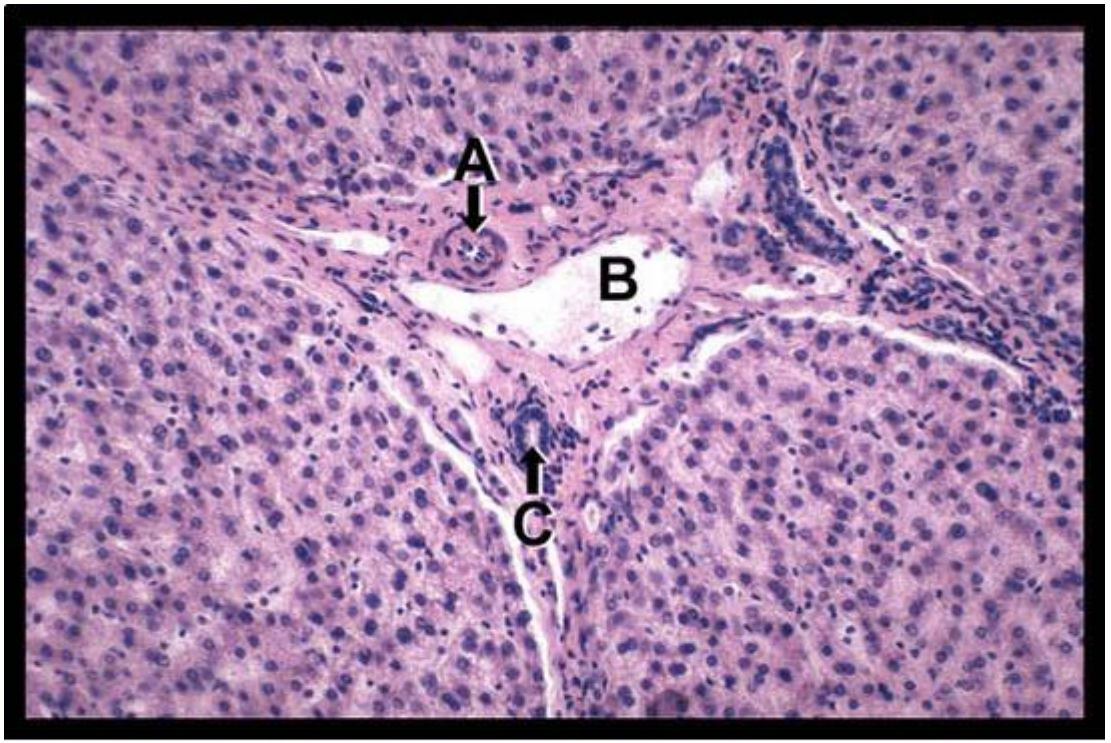


Fig. 15-4 Accessed 03/21/2010

The portal triad consists of three structures: hepatic artery (A), portal vein (B), and bile duct (C). A lymphatic vessel is also considered to be a component of the portal tract, but it is not always present in the section.

Organ structure

- Hepatocytes immediately abutting the portal tract are referred to as the limiting plate.
- Between the cords of hepatocytes are vascular sinusoids that terminate in the terminal hepatic vein.
- Hepatocytes in the vicinity of the terminal hepatic vein are called “centriloular”; hepatocytes in the vicinity of the portal tract are called “periportal.”
- Thrombosis of the hepatic vein, Budd-Chiari syndrome, leads to passive congestion of the liver as in right heart failure. Preservation of the middle hepatic vein is critical in maintaining hepatic function after liver resection.

Organ structure

- Kupffer cells are phagocytic cells attached to the luminal face of endothelial cells in vascular sinusoids. When stressed, they produce TGF-β and PDGF.
- Fat containing perisinusoidal stellate cells are found in the extrasinusoidal space of Disse. They participate in the metabolism and storage of Vitamin A. When inflamed, they transform into type IV collagen producing myofibroblasts. (Types I and III collagen are found in the space of Disse.)
- Iron storage gives the liver its brown color.

Patterns of hepatic injury

- Balloon degeneration refers to cell swelling where the cytoplasm has irregular clumped organelles and large clear spaces.
- Feathery degeneration refers to the foamy appearance of the swollen cell from retention of bilirubin metabolites.
- Steatosis refers to collections of triglyceride droplets in the cytoplasm. The droplet collections may be small (microvesicular) or large (macrovesicular) and do not displace the nucleus.

Patterns of hepatic injury

- Microvesicular steatosis is seen in acute fatty liver of pregnancy as well as in valproic acid toxicity.
- Macrovesicular steatosis is seen in obesity, diabetes mellitus, and those with Hepatitis C infection.
- Both microvesicular and macrovesicular steatosis may be present in alcoholic fatty liver.
- Centrilobular necrosis is characteristic of ischemic injury.
- Periportal necrosis is seen in eclampsia.

Patterns of hepatic injury

- Fibrosis generally indicates irreversible hepatic damage.
- Fibrosis develops about portal tracts or the terminal hepatic vein (hepatitis, biliary disease) or fibrous tissue may be deposited directly within the space of Disse (alcoholic fibrosis, Budd-Chiari).
- Fibrous septate may bridge from portal to portal, portal to central, or central to central zones depending upon the type of injury.
- With continuing fibrosis, the liver is subdivided into nodules of proliferating hepatocytes surrounded by fibrous tissue, “cirrhosis.”

Patterns of hepatic injury

- Direct toxic or ischemic hepatocyte necrosis induces an inflammatory reaction.
- The reaction is generally confined to the portal tracts but (activated T-lymphocytes) may spill over into periportal parenchymal tissue.
- Apoptotic hepatocytes are scavenged by Kupffer cells (and circulating monocytes) within hours. Kupffer cells and lymphocytes release TGF-β, MMP2, and TIMP-1 and -2, promoting fibrogenesis.
- Hepatocellular proliferation is marked by mitoses, thickening of the hepatic cords, and some disorganization of the parenchymal structure. Bile ductule proliferation occurs.

Patterns of hepatic injury

- Fibrosis generally indicates irreversible hepatic damage. Types I and III collagen deposited. Steelate cells proliferate. PDGFR-β induces activation into myofibroblasts. Endothelin-1 promotes vascular constriction by myofibroblasts.
- Fibrosis develops about portal tracts or the terminal hepatic vein (hepatitis, biliary disease) or fibrous tissue may be deposited directly within the space of Disse (alcoholic fibrosis, Budd-Chiari). Usually only type IV collagen is found in the space of Disse.

Patterns of hepatic injury

- Fibrous septate may bridge from portal to portal, portal to central, or central to central zones depending upon the type of injury.
- With continuing fibrosis, the liver is subdivided into nodules of proliferating hepatocytes surrounded by fibrous tissue, “cirrhosis.” Delivery of blood to hepatocytes is compromised.
- Estrogen increases gut permeability to endotoxins. The expression of CD14 (LPS receptor) increases in Kupfer cells. Women more susceptible to injury.

Physiology of the fed state

- Absorption continues 2-4 hours after food intake. Insulin levels elevated.
- Glucose is phosphorylated to glucose-6-phosphate via glucokinase catalysis (irreversible). **Glucokinase is only found in the liver.**
- Phosphorylation of fructose-6-phosphate to fructose-1,6-biphosphate via phosphofructokinase-1 catalysis (irreversible). **Limiting step in glucose metabolism.**
- Insulin stimulates phosphofructokinase-2, driving production of fructose-2,6- biphosphate, stimulating phosphofructokinase-1.

Physiology of the fed state

- Oxidative phosphorylation of fructose-1,6-biphosphate to dihydroxyacetone phosphate Dihydroxyacetone phosphate enters the mitochondrion via the glycerol phosphate shuttle.
- Dihydroxyacetone phosphate conversion occurs to phosphoenolpyruvate which then spontaneously tautomerizes to pyruvate via pyruvate kinase catalysis (irreversible).
- The resulting pyruvate may be converted into lactate (requiring vitamin B_1) or enter the TCA cycle in the mitochondrion. NAD regenerated.

Physiology of the fed state

- OR
- Glucose-6-phosphate either enters the HMP (pentose pathway) shunt where it produces ribose-5-phosphate for nucleotide synthesis, reduces NADP for fatty acid and steroid biosynthesis as well as to maintain reduced glutathione.
- Glucose in excess of energy needs is converted to and stored as glycogen in liver and muscle. (GSK3 is inactivated by phosphorylation and cannot convert glycogen synthase to its inactive form).

Physiology of the fed state

- Amino acids are catabolized and enter the TCA cycle in the mitochondrion or are utilized for protein synthesis.
- Fatty acids enter the mitochondrion and are converted to acetyl-CoA. Liver releases fats as VLDL.
- Adipose tissue removes free fatty acids from the lipoproteins and synthesizes and stores triglycerides.
- Fatty acids in excess of energy needs are stored as cholesterol and triglycerides.

Physiology of the fasting state

- Glucagon levels are elevated.
- Glycogen reserves degraded. Glycogen is catabolized to glucose-6-phosphate. Pyruvate is generated via glycolysis. Excess glucose-6-phosphate is catabolized to glucose and enters the circulation. (Glucose-6-phosphatase is found in the endoplasmic recticulum.)
- Gluconeogenesis begins when glycogen reserves exhausted (12-24 hours). Muscle incapable of gluconeogenesis.

Glycolysis/gluconeogenesis interaction

- Gluconeogenesis occurs primarily in the liver (minor activity in kidney and small intestine). The irreversible steps in the glycolytic pathway that cannot be used in gluconeogenisis in the cell are bypassed by reactions catalysed by non-glycolytic enzymes.
- The glucose generated supplies energy needs of brain, heart, adrenal medulla, erythrocytes. These organs only use glucose.

Glycolysis/gluconeogenesis interaction

- Phosphofructokinase, the rate limiting enzyme in glycolysis, is allosterically inhibited by high levels of ATP, and stimulated by low levels of AMP.
- Fructose-1,6-biphosphatase is the rate limiting enzyme in gluconeogenesis. It is inhibited by low levels of AMP.
- Fructose-2,6-biphosphatase activates posphofructokinase-1, thus inhibiting fructose-1,6-biphosphatase. This occurs even in the face of high levels of ATP.

Physiology of the fed state

- Slow protein breakdown in muscles supplies amino acids to liver. Branched chain amino acids preferentially degraded in muscle. Amino acids are catabolized and enter the TCA cycle in the mitochondrion.
- Lipolysis occurs in adipose tissue in response to glucagon. Fatty acids and glycerol taken up by liver. Fatty acids enter the the mitochondrion and are converted to acetyl-CoA.
- Insulin upregulates GluT4 in muscle and fat. It decreases circulating level of fatty acids by inhibition of hormone sensitive lipoprotein lipase in adipose tissue.

Physiology of the fasting state

- After 2-3 days of fasting, fatty acid levels reach their peak in the blood. Ketogenesis increases.
- Ketone bodies are only produced in the liver. They are a product of acetyl-CoA metabolism.
- Acetyl CoA carboxylase is inhibited by long chain fatty acids. This decreases the formation of malonyl CoA.
- Carnitine to acyl-transferase is stimulated by a decrease in malonyl-CoA. Stimulates β-oxidation and generation of acetyl-CoA.

Physiology of the fasting state

- Acetyl-CoA allosterically activates pyruvate carboxylase, the rate limiting enzyme in the TCA cycle. This leads to production of oxaloacetate. Biotin is required.
- Oxaloacetate must be converted into malate or aspartate in order to cross the mitochondrial membrane. There it leads to generation of phosphoenolpyruvate.
- If oxaloacetate is depleted, acetyl-CoA is not generated via the TCA cycle.
- Pyruvate is dehydrogenated to acetyl-CoA in mitochondria via pyruvate dehydrogenase catalysis (irreversible). Regenerates NAD.

Ketone body synthesis

- Thiolase condenses two acetyl-CoA units to form aceto-acetyl CoA. this enzyme is only present in the liver.
- HMG-CoA synthase condenses acetyl-CoA with aceto-acetyl CoA to form HMG-CoA.
- HMG-CoA lyase converts HMG-CoA to acetoacetate. Acetoacetate is converted to β-hydroxybutyrate and enters the bloodstream.
- The ketone bodies acetoacetate and β-hydroxybutyrate are used by muscle and brain where they are metabolized to acetyl-CoA.
- Death generally ensues at 45 days of fasting.

Starvation

- **Kwashiorkor** is protein malnutrition.
- Negative Nitrogen balance and lack of essential amino acids leads to inability to synthesize necessary proteins.
- Diet is **adequate** in caloric intake
- Decreased serum protein leads to edema (osmotic pressure). Fatty liver as lipids accumulate (unable to be coated with protein for transport).
- Niacin deficient (rash)

Kwashiokor

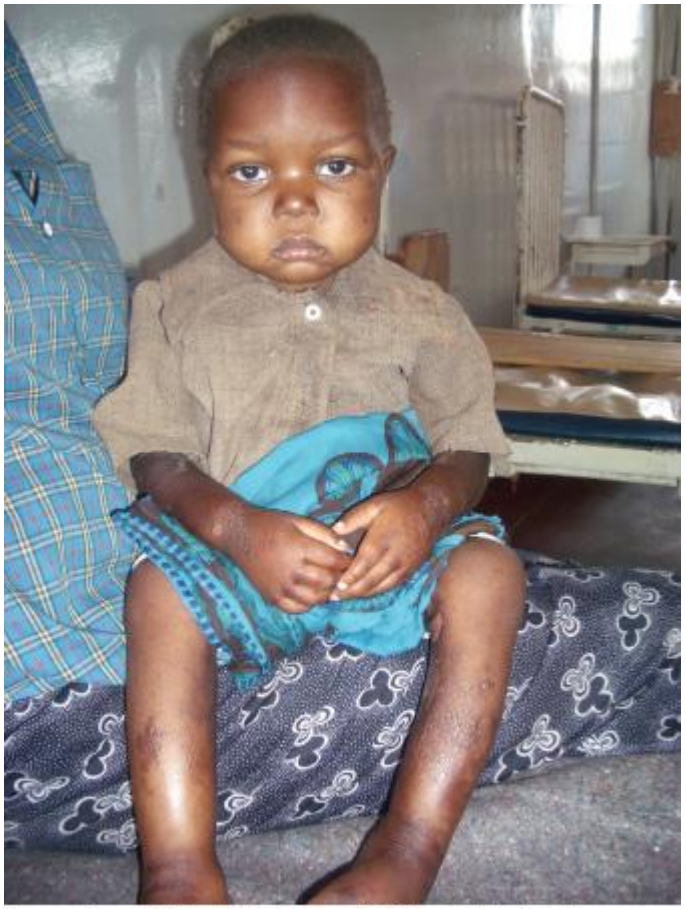


Fig. 21.48, Accessed 03/21/2010

- **A Zambian child with typical light hair, moon facies, peripheral edema, and dry skin of kwashiorkor.**

(Photo contributor: Meg Jack, MD.)

Starvation

- **Marasmus** is calorie malnutrition.
- Diet is **inadequate** in caloric intake.

Source: Knoop KJ, Stack LB, Storrow AB, Thurman RJ: *The Atlas of Emergency Medicine, 3rd Edition:* http://www.accessmedicine.com

- **An African infant with severe marasmus due to poor feeding following maternal death. The infant is severely underweight with loose skin and little subcutaneous fat.**

(Photo contributor: Meg Jack, MD.) Fig. 21.49 Accessed 03/21/2010

Clinical consequences of liver disease

- Hepatic failure results when 80-90% of hepatic function has been lost. Rapidly fatal without liver transplant.
- Massive hepatic necrosis characteristic of acetaminophen toxicity (38% of all cases). Drugs and toxins account for 14%; Hepatitis A, 4%. Hepatitis B, 8%.
- Hepatic dysfunction without necrosis is seen in Reye's syndrome (interferes with carnitine metabolism), acute fatty liver of pregancy, as well as tetracycline and valproate toxicity (ribosome).

Clinical consequences of liver disease

- Overt jaundice is invariably present. It is first visible in the sclerae when total bilirubin >2.0g/dl.
- Color change noted in the face when bilirubin levels at 5mg/dl; in mid-abdomen, at 15mg/dl; in soles, at 20mg/dl.
- Rise in serum bilirubin, urine bilirubin, and urine urobilinogen precede clinical jaundice. This may reflect primary liver injury or hemolysis.
- Elevated urine bilirubin with normal or depressed levels of urine urobilinogen are compatible with common duct obstruction.

Clinical consequences of liver disease

- Fetor hepaticus is a musty body odor appreciated when splanchnic blood is shunted from the portal to the systemic circulation. It is related to the formation of mercaptans by intestinal bacteria acting on ingested sulfur-containing amino acids.
- Impaired estrogen metabolism may lead to gynecomastia and hypogonadism in men.
- Palmar erythema, and spider angiomata of the skin are local vasodilatory changes resulting from impaired estrogen metabolism.

Clinical consequences of liver disease

- Hypoalbuminemia may lead to peripheral edema.
- Vitamin K dependent procoagulant synthesis is impaired. A prolonged prothrombin time is a poor prognostic factor.
- Most Nitrogen waste from muscle is sent to the liver as alanine.
- Most tissues sequester ammonia by synthesizing glutamine (glutamate synthase removes ammonia) and sending it primarily to the liver to be converted into urea.

Clinical consequences of liver disease

- Some urea can be excreted into the intestine.
- Bacteria in the intestine metabolize urea to ammonia.
- Ammonia absorbed through the intestine goes into the portal circulation. Ammonia is generally converted to urea by the liver. However, as protein synthesis is diminished, little urea is produced. Excess accumulation of ammonia results.
- The kidneys generally don’t send nitrogen to the liver but simply excrete ammonia directly into the urine.

Clinical consequences of liver disease

- Converting glutamate to glutamine in the brain depletes TCA cycle intermediates. This reduces NADH, and, subsequently, ATP production. Further, GABA production diminishes. This may impair neurotransmission
- Excess glutamine also increases mitochondrial permeability. Brain edema may be seen.
- In severe liver disease, asterexis (wrist-flap) is commonly found.

Clinical consequences of liver disease

- Decreased renal perfusion secondary to systemic vasodilatation, renal afferent arteriole vasoconstriction due to activation of the renal sympathetic nervous system as well as production of vasoactive mediators decrease GFR.
- The ability to concentrate urine is retained, however. There is no proteinuria. Urine Sodium levels are low, unlike those seen in acute tubular necrosis.