CHAPTER 28

The Physiology of the Liver

Patrick Tso, Ph.D.
James McGill, M.D.

CHAPTER OUTLINE

KEY CONCEPTS

1. The liver sinusoid is lined with sinusoidal cells (endothelial cells), Kupffer cells, and fat storage cells (also called stellate or Ito cells), which perform important metabolic functions and defend the liver.
2. The liver plays an important role in maintaining blood glucose levels and in metabolizing drugs and toxic substances.
3. The liver has a remarkable capacity to regenerate.
4. The liver is extremely important in maintaining an adequate supply of nutrients for metabolism.
5. The liver synthesizes glucose from noncarbohydrate sources, a process called gluconeogenesis.
6. The liver is the first organ to experience and respond to changes in plasma insulin levels.
7. The liver is one of the main organs involved in fatty acid synthesis.
8. The liver aids in the elimination of cholesterol from the body.
9. The liver is a storage area for fat-soluble vitamins and iron.
10. The liver modifies the action of hormones released by other organs.

The liver is the largest internal organ in the body, constituting about 2.5% of an adult's body weight. During rest, it receives 25% of the cardiac output via the hepatic portal vein and hepatic artery. The hepatic portal vein carries the absorbed nutrients from the GI tract to the liver, which takes up, stores, and distributes nutrients and vitamins. The liver plays an important role in maintaining blood glucose levels. It also regulates the circulating blood lipids by the amount of very low density lipoproteins (VLDLs) it secretes. Many of the circulating plasma proteins are synthesized by the liver. In addition, the liver takes up numerous toxic compounds and drugs from the portal circulation. It is well equipped to deal with the metabolism of drugs and toxic substances. The liver also serves as an excretory organ for bile pigments, cholesterol, and drugs. Finally, it performs important endocrine functions.

THE ANATOMY OF THE LIVER

The liver is essential to the normal physiology of many organs and systems of the body. It interacts with the cardiovascular and immune systems, it secretes important substances into the GI tract, and it stores, degrades, and detoxifies many substrates.

The Arrangement of Hepatocytes Along Liver Sinusoids Aids the Rapid Exchange of Molecules

Hepatocytes are highly specialized cells. The bile canaliculus is usually lined by two hepatocytes and is separated from the pericellular space by tight junctions, which are impermeable and, thus, prevent the mixing of contents between the bile canaliculus and the pericellular space (Fig. 28.1). The bile from the bile canaliculus drains into a series of ducts, and it may eventually join the pancreatic duct near where it enters the duodenum. Drainage of bile into the duodenum is partly regulated by a sphincter located at the junction between the bile duct and the duodenum, the sphincter of Oddi (see Chapter 27).

The pericellular space, the space between two hepatocytes, is continuous with the perisinusoidal space (see Fig. 28.1). The **perisinusoidal space**, also known as the **space of Disse**, is separated from the sinusoid by a layer of **sinusoidal endothelial cells**. Hepatocytes possess numerous,

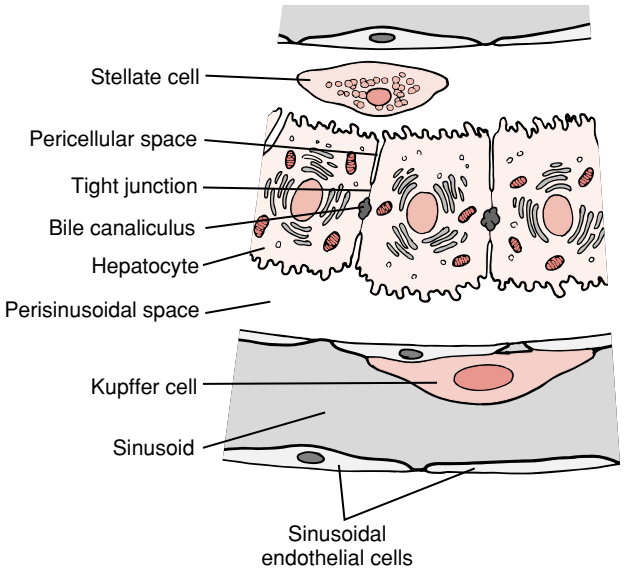

FIGURE 28.1 **The relationship between hepatocytes, the perisinusoidal space, and the sinusoid.**

finger-like projections that extend into the perisinusoidal space, greatly increasing the surface area over which hepatocytes contact the perisinusoidal fluid.

Endothelial cells of the liver, unlike those in other parts of the cardiovascular system, lack a basement membrane. Furthermore, they have sieve-like plates that permit the ready exchange of materials between the perisinusoidal space and the sinusoid. Electron microscopy has demonstrated that even particles as big as chylomicrons (80 to 500 nm in diameter) can penetrate these porous plates. Although the barrier between the perisinusoidal space and the sinusoid is permeable, it does have some sieving properties. For example, the protein concentration of hepatic lymph, assumed to derive from the perisinusoidal space, is lower than that of plasma by about 10%.

Kupffer cells also line the hepatic sinusoids. These are resident macrophages of the **fixed monocyte-macrophage system** that play an extremely important role in removing unwanted material (e.g., bacteria, virus particles, fibrin-fibrinogen complexes, damaged erythrocytes, and immune complexes) from the circulation. Endocytosis is the mechanism by which these materials are removed.

Some perisinusoidal cells contain distinct lipid droplets in the cytoplasm. These fat-storage cells are called **stellate cells** or **Ito cells**. The lipid droplets contain vitamin A. Through complex and typically inflammatory processes, stellate cells become transformed to myofibroblasts, which then become capable of both secreting collagen into the space of Disse and regulating sinusoidal portal pressure by their contraction or relaxation. Stellate cells may be involved in the pathological fibrosis of the liver.

The Liver Receives Venous Blood Through the Portal Vein and Arterial Blood Through the Hepatic Artery

Circulation to the liver is discussed in detail in Chapter 17; here, we will briefly describe some of its unique features. The hepatic portal vein provides about 70 to 80% of the liver's blood supply, and the hepatic artery provides the rest. Hepatic portal blood is poorly oxygenated unlike that from the hepatic artery. The portal vein branches repeatedly, forming smaller venules that eventually empty into the sinusoids. The hepatic artery branches to form arterioles and then capillaries, which also drain into the sinusoids. Liver sinusoids can be considered specialized capillaries. As mentioned earlier, the hepatic sinusoid is extremely porous and allows the rapid exchange of materials between the perisinusoidal space and the sinusoid. The sinusoids empty into the central veins, which subsequently join to form the hepatic vein, which then joins the inferior vena cava.

Hepatic blood flow varies with activity, increasing after eating and decreasing during sleep. Blood flow to the intestines and spleen and, in turn, in the portal vein is predominantly regulated by the splanchnic arterioles. In this way, eating results in increased blood flow to the intestines followed by increased liver blood flow. Portal vein pressure is normally low. Increased resistance to portal blood flow results in **portal hypertension**. Portal hypertension is the most common complication of chronic liver disease and accounts for a large percentage of the morbidity and mortality associated with chronic liver diseases (see Clinical Focus Box 28.1).

The Liver Has an Important Lymphatic System

The hepatic lymphatic system is present in three main areas: adjacent to the central veins, adjacent to the portal veins, and coursing along the hepatic artery. As in other organs, it is through these channels that fluid and proteins are drained. The protein concentration is highest in lymph from the liver.

In the liver, the largest space drained by the lymphatic system is the perisinusoidal space. Disturbances in the balance of filtration and drainage are the primary causes of **ascites**, the accumulation of serous fluid in the peritoneal cavity. Ascites is another common cause of morbidity in patients with chronic liver disease.

The Liver Can Regenerate

Of the solid organs, the liver is the only one that can regenerate. There appears to be a critical ratio between functioning liver mass and body mass. Deviations in this ratio trigger a modulation of either hepatocyte proliferation or apoptosis, in order to maintain the liver's optimal size. Peptide growth factors—such as transforming growth factor-α (TGF-α), hepatocyte growth factor (HGF), and epidermal growth factor (EGF)—have been the best-studied stimuli of hepatocyte DNA synthesis. After these peptides bind to their receptors on the remaining hepatocytes and work their way through myriad transcription factors, gene transcription is accelerated, resulting in increased cell number and increased liver mass.

Alternatively, a decrease in liver volume is achieved by enhanced hepatocyte apoptosis rates. Apoptosis is a carefully programmed process by which cells kill themselves while maintaining the integrity of their cellular membranes.

CLINICAL FOCUS BOX 28.1

Esophageal Varices, a Common Manifestation of Portal Hypertension

Chronic liver injury can lead to a sequence of changes that terminates with fatal bleeding from esophageal blood vessels. In most forms of chronic liver injury, stellate cells are transformed into collagen-secreting myofibroblasts. These cells deposit collagen into the sinusoids, interfering with the exchange of compounds between the blood and hepatocytes and increasing resistance to portal venous flow. The resistance appears to be further increased when stellate cells contract. The increased resistance results in increased hepatic portal pressure and decreased liver blood flow. This disorder is seen in approximately 80% of patients with **cirrhosis**. In a compensatory effort, new channels are formed or dormant venous tributaries are expanded, resulting in the formation of varicose (unnaturally swollen) veins in the abdomen. Although varicose veins develop in many areas, portal pressure increases are least opposed in the esophagus because of the limited connective tissue support at the base of the esophagus. This structural condition, along with the negative intrathoracic pressure, favors the formation and rupture of **esophageal varices**. Approximately 30% of patients who develop an esophageal variceal hemorrhage die during the episode of bleeding, making it one of the most lethal medical illnesses.

Currently there are no well-recognized treatments to reverse cirrhosis, but numerous strategies are employed to reduce portal hypertension and bleeding. Chief among these is the use of nonselective beta blockers, which enhance splanchnic arteriolar vasoconstriction and thereby reduce portal venous pressure. Bleeding esophageal varices are frequently treated by endoscopic ligation of the varices. Shunts can be placed radiologically or surgically between the portal venous system and the systemic venous to reduce the portal pressure.

In contrast, cell death that results from necroinflammatory processes is characterized by a loss of cell membrane integrity and the activation of inflammatory reactions. Liver cell suicide is mediated by proapoptotic signals, such as tumor necrosis factor (TNF).

THE METABOLISM OF DRUGS AND XENOBIOTICS

Hepatocytes play an extremely important role in the metabolism of drugs and **xenobiotics**—compounds that are foreign to the body, some of which are toxic. Most drugs and xenobiotics are introduced into the body with food. The kidneys ultimately dispose of these substances, but for effective elimination, the drug or its metabolites must be made hydrophilic (polar, water-soluble). This is because reabsorption of a substance by the renal tubules is dependent on its hydrophobicity. The more hydrophobic (nonpolar, lipid-soluble) a substance is, the more likely it will be reabsorbed. Many drugs and metabolites are hydrophobic, and the liver converts them into hydrophilic compounds.

The Liver Converts Hydrophobic Drugs and Xenobiotics to Hydrophilic Compounds

Two reactions (phase I and II), catalyzed by different enzyme systems, are involved in the conversion of xenobiotics and drugs into hydrophilic compounds. In **phase I reactions**, the parent compound is biotransformed into more polar compounds by the introduction of one or more polar groups. The common polar groups are hydroxyl (OH) and carboxyl (COOH). Most phase I reactions involve oxidation of the parent compound. The enzymes involved are mostly located in the smooth ER; some are located in the cytoplasm. For example, alcohol dehydrogenase is located in the cytoplasm of hepatocytes and catalyzes the rapid conversion of alcohol to acetaldehyde. It may also play a role in the dehydrogenation of steroids.

The enzymes involved in phase I reactions of drug biotransformation are present as an enzyme complex composed of the **NADPH-cytochrome P450 reductase** and a series of hemoproteins called **cytochrome P450** (Fig. 28.2). The drug combines with the oxidized cytochrome $P450^{+3}$ to form the cytochrome $P450^{+3}$-drug complex. This complex is then reduced to the cytochrome $P450^{+2}$-drug complex, catalyzed by the enzyme NADPH-cytochrome P450 reductase. The reduced complex combines with molecular oxygen to form an oxygenated intermediate. One atom of the molecular oxygen

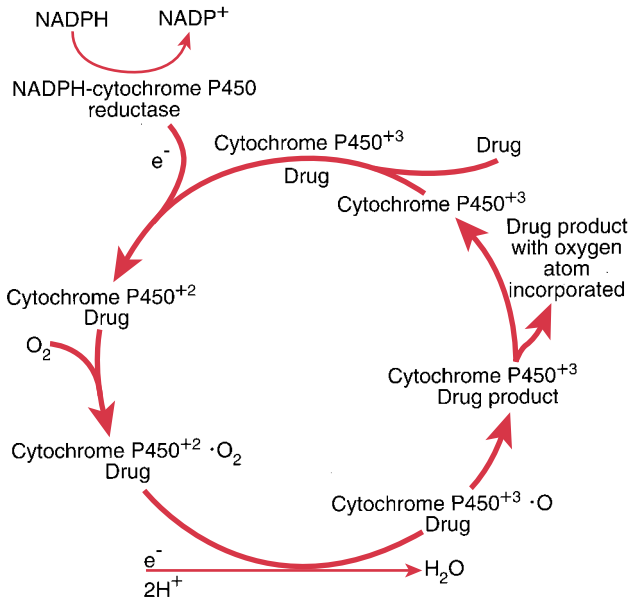

FIGURE 28.2 **Phase I reactions in the metabolism of drugs.**

then combines with two H^+ and two electrons to form water. The other oxygen atom remains bound to the cytochrome $P450^{+3}$-drug complex and is transferred from the cytochrome $P450^{+3}$ to the drug molecule. The drug product with an oxygen atom incorporated is released from the complex. The cytochrome $P450^{+3}$ released can then be recycled for the oxidation of other drug molecules.

In **phase II reactions**, the phase I reaction products undergo conjugation with several compounds to render them more hydrophilic. Glucuronic acid is the substance most commonly used for conjugation, and the enzymes involved are the glucuronyltransferases. Other molecules used in conjugation are glycine, taurine, and sulfates.

Aging, Nutrition, and Genetics Influence Drug Metabolism

The enzyme systems in phase I and II reactions are age-dependent. These systems are poorly developed in human newborns because their ability to metabolize any given drug is lower than that of adults. Older adults also have a lower capacity than young adults to metabolize drugs.

Nutritional factors can also affect the enzymes involved in phase I and II reactions. Insufficient protein in the diet to sustain normal growth results in the production of fewer of the enzymes involved in drug metabolism.

It is well known that drug-metabolizing enzymes can be induced by certain factors, such as polycyclic aromatic hydrocarbons. Persons who smoke inhale polycyclic aromatic hydrocarbons, increasing the metabolism of certain drugs, such as caffeine.

The role of genetics in the regulation of drug metabolism by the liver is less well understood. Briefly, drug metabolism by the liver can be controlled by a single gene or several genes (polygenic control). Careful study of the metabolism of a certain drug by the population can provide important clues as to whether its metabolism is under single gene or polygenic control. Genetic variability combined with the induction or inhibition of P450 enzymes by other drugs or compounds can have a profound effect on what is a safe and effective dose of a medicine.

ENERGY METABOLISM IN THE LIVER

The liver is pivotal in regulating the metabolism of carbohydrates, lipids, and proteins. It also helps to maintain a constant blood glucose concentration by converting other substances, such as amino acids, into glucose.

The Intestine Supplies Nutrients to the Liver

The most of water-soluble nutrients and water-soluble vitamins and minerals absorbed from the small intestine are transported via the portal blood to the liver. The nutrients transported in portal blood include amino acids, monosaccharides, and fatty acids (predominantly short- and medium-chain forms). Short-chain fatty acids are largely derived from the fermentation of dietary fibers by bacteria in the colon. Some dietary fibers, such as pectin, are almost completely digested to form short-chain fatty acids (or volatile fatty acids), whereas cellulose is not well digested by the bacteria. Only a small amount of long-chain fatty acids, bound to albumin, is transported by the portal blood; the most is transported in intestinal lymph as triglyceride-rich lipoproteins (chylomicrons).

The Liver Is Important in Carbohydrate Metabolism

The liver is extremely important in maintaining an adequate supply of nutrients for cell metabolism and regulating blood glucose concentration (Fig. 28.3). After the ingestion of a meal, the blood glucose increases to a concentration of 120 to 150 mg/dL, usually in 1 to 2 hours. Glucose is taken up by hepatocytes by a facilitated carrier-mediated process and is converted to glucose 6-phosphate and then UDP-glucose. UDP-glucose can be used for glycogen synthesis, or **glycogenesis**. It is generally believed that blood glucose is the major precursor of glycogen. However, recent evidence seems to indicate that the lactate in blood (from the peripheral metabolism of glucose) is also a major precursor of glycogen. Amino acids (e.g., alanine) can supply pyruvate to synthesize glycogen.

Glycogen is the main carbohydrate store in the liver, and may amount to as much as 7 to 10% of the weight of a normal, healthy liver. The glycogen molecule resembles a tree with many branches (see Fig. 27.19). Glucose units are linked via α-1,4- (to form a straight chain) or α-1,6 (to form a branched chain) glycosidic bonds. The advantage of such a configuration is that the glycogen chain can be broken down at multiple sites, making the release of glucose much more efficient than would be the case with a straight-chain polymer.

During fasting, glycogen is broken down by **glycogenolysis**. The enzyme **glycogen phosphorylase** catalyzes the cleavage of glycogen into glucose 1-phosphate. Glycogen phosphorylase acts only on the α-1,4-glycosidic bond,

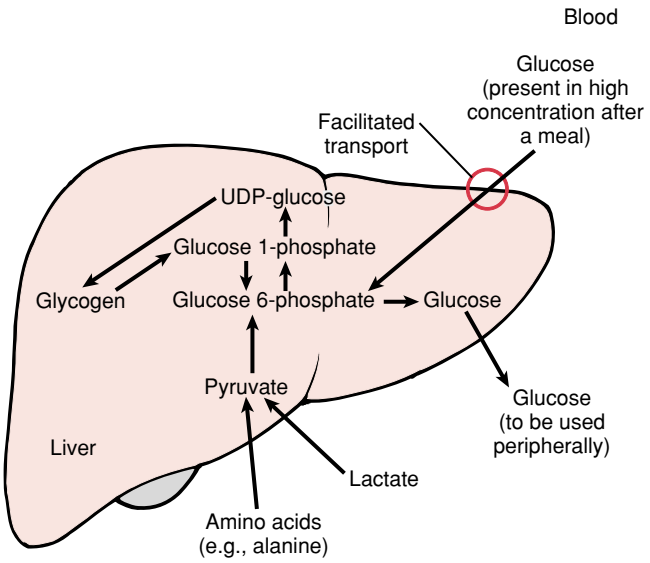

FIGURE 28.3 **The regulation of carbohydrate metabolism in the liver.**

and the enzyme α-1,6-glucosidase is used to break the α-1,6-glycosidic bonds.

Glucose 1-phosphate is converted to glucose 6-phosphate by the enzyme phosphoglucomutase. The enzyme **glucose-6-phosphatase**, which is present in the liver but not in muscle or brain, converts glucose 6-phosphate to glucose. This last reaction enables the liver to release glucose into the circulation. Glucose 6-phosphate is an important intermediate in carbohydrate metabolism because it can be channeled either to provide blood glucose or for glycogen formation.

Both glycogenolysis and glycogenesis are hormonally regulated. The pancreas secretes insulin into the portal blood. Therefore, the liver is the first organ to respond to changes in plasma insulin levels, to which it is extremely sensitive. For instance, a doubling of portal insulin concentration completely shuts down hepatic glucose production. About half the insulin in portal blood is removed in its first pass through the liver. Insulin tends to lower blood glucose by stimulating glycogenesis and suppressing glycogenolysis and gluconeogenesis. Glucagon, in contrast, stimulates glycogenolysis and gluconeogenesis, raising blood sugar levels. Epinephrine stimulates glycogenolysis.

The liver regulates the blood glucose concentrations within a narrow limit, 70 to 100 mg/dL. Although one might expect patients with liver disease to have difficulty regulating blood glucose, this is usually not the case because of the relatively large reserve of hepatic function. However, those with chronic liver disease occasionally have reduced glycogen synthesis and reduced gluconeogenesis. Some patients with advanced liver disease develop portal hypertension, which induces the formation of portosystemic shunting, resulting in elevated arterial blood levels of insulin and glucagon.

The Metabolism of Monosaccharides. Monosaccharides are first phosphorylated by a reaction catalyzed by the enzyme hexokinase. In the liver (but not in the muscle), there is a specific enzyme (glucokinase) for the phosphorylation of glucose to form glucose 6-phosphate. Depending on the energy requirement, the glucose 6-phosphate is channeled to glycogen synthesis or used for energy production by the glycolytic pathway.

Fructose is taken up by the liver and phosphorylated by fructokinase to form fructose 1-phosphate. This molecule is either isomerized to form glucose 6-phosphate or metabolized by the glycolytic pathway. Fructose 1-phosphate is used by the glycolytic pathway more efficiently than glucose 6-phosphate.

Galactose is an important sugar used not only to provide energy but also in the biosynthesis of glycoproteins and glycolipids. When galactose is taken up by the liver, it is phosphorylated to form galactose 1-phosphate, which then reacts with uridine diphosphate-glucose, or **UDP-glucose**, to form UDP-galactose and glucose 1-phosphate. The UDP-galactose can be used for glycoprotein and glycolipid biosynthesis or converted to UDP-glucose, which can then be recycled.

Gluconeogenesis. **Gluconeogenesis** is the production of glucose from noncarbohydrate sources such as fat, amino acids, and lactate. The process is energy-dependent, and the starting substrate is pyruvate. The energy required seems to be derived predominantly from the β-oxidation of fatty acids. Pyruvate can be derived from lactate and the metabolism of glucogenic amino acids—those that can contribute to the formation of glucose. The two major organs involved in the production of glucose from noncarbohydrate sources are the liver and the kidneys. However, because of its size, the liver plays a far more important role than the kidney in the production of sugar from noncarbohydrate sources.

Gluconeogenesis is important in maintaining blood glucose concentrations especially during fasting. The red blood cells and renal medulla are totally dependent on blood glucose for energy, and glucose is the preferred substrate for the brain. Most amino acids can contribute to the carbon atoms of the glucose molecule, and alanine from muscle is the most important. The rate-limiting factor in gluconeogenesis is not the liver enzymes but the availability of substrates. Gluconeogenesis is stimulated by epinephrine and glucagon but greatly suppressed by insulin. Thus, in type 1 diabetics, gluconeogenesis is greatly stimulated, contributing to the hyperglycemia observed in these patients (see Chapter 35).

The Liver Plays an Important Role in the Metabolism of Lipids

The liver plays a pivotal role in lipid metabolism (Fig. 28.4). It takes up free fatty acids and lipoproteins (complexes of lipid and protein) from the plasma. Lipid is circulated in the plasma as lipoproteins because lipid and water are not mis-

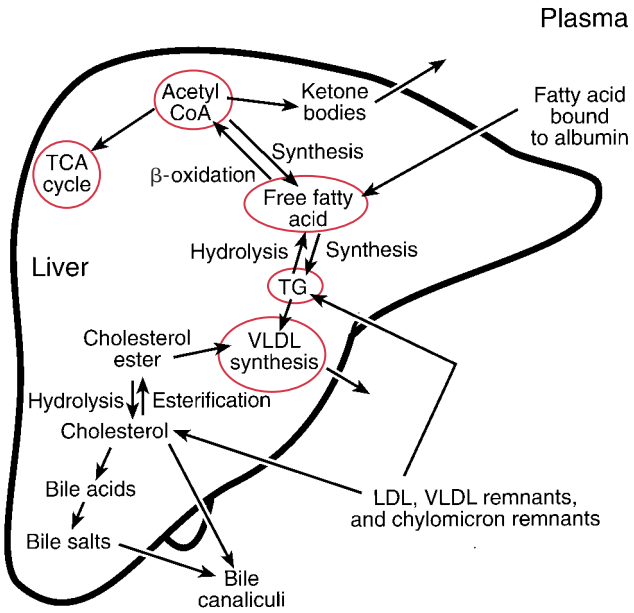

FIGURE 28.4 **The regulation of lipid metabolism in the liver.** LDL, low-density lipoprotein; VLDL, very low density lipoprotein; TG, triglycerides; TCA, tricarboxylic acid.

cible; the lipid droplets coalesce in an aqueous medium. The protein and phospholipid on the surface of the lipoprotein particles stabilize the hydrophobic triglyceride center of the particle.

During fasting, fatty acids are mobilized from adipose tissue and are taken up by the liver. They are used by the hepatocytes to provide energy via β-oxidation, for the generation of ketone bodies, and to synthesize the triglyceride necessary for VLDL formation. After feeding, chylomicrons from the small intestine are metabolized peripherally, and the chylomicron remnants formed are rapidly taken up by the liver. The fatty acids derived from the triglycerides of the chylomicron remnants are used for the formation VLDLs or for energy production via β-oxidation.

Fatty Acid Oxidation and Synthesis. Fatty acids derived from the plasma can be metabolized in the mitochondria of hepatocytes by β-oxidation to provide energy. Fatty acids are broken down to form acetyl-CoA, which can be used in the tricarboxylic acid cycle for ATP production, in the synthesis of fatty acids, and in the formation of ketone bodies. Because fatty acids are synthesized from acetyl-CoA, any substances that contribute to acetyl-CoA, such as carbohydrate and protein sources, enhance fatty acid synthesis.

The liver is one of the main organs involved in fatty acid synthesis. Palmitic acid is synthesized in the hepatocellular cytosol; the other fatty acids synthesized in the body are derived by shortening, elongating, or desaturating the palmitic acid molecule.

Lipoprotein Synthesis. One of the major functions of the liver in lipid metabolism is lipoprotein synthesis. The four major classes of circulating plasma lipoproteins are chylomicrons, very low density lipoproteins (VLDLs), low-density lipoproteins (LDLs), and high-density lipoproteins (HDLs) (Table 28.1). These lipoproteins, which differ in chemical composition, are usually isolated from plasma according to their flotation properties.

Chylomicrons are the lightest of the four lipoprotein classes, with a density of less than 0.95 g/mL. They are made only by the small intestine and are produced in large quantities during fat ingestion. Their major function is to transport the large amount of absorbed fat to the bloodstream.

Very low density lipoproteins (**VLDLs**) are denser and smaller than chylomicrons. The liver synthesizes about 10 times more circulating VLDLs than the small intestine. Like chylomicrons, VLDLs are triglyceride-rich and carry most of the triglyceride from the liver to the other organs. The triglyceride of VLDLs is broken down by **lipoprotein lipase** to yield fatty acids, which can be metabolized to provide energy. The human liver normally has a considerable capacity to produce VLDLs, but in acute or chronic liver disorders, this ability is significantly compromised. Liver VLDLs are associated with an important class of proteins, the **apo B proteins**. The two forms of circulating apo B are B_{48} and B_{100}. The human liver makes only apo B_{100}, which has a molecular weight of about 500,000. Apo B_{100} is important for the hepatic secretion of VLDL. In **abetalipoproteinemia**, apo B synthesis and, therefore, the secretion of VLDLs is blocked. Large lipid droplets can be seen in the cytoplasm of the hepatocytes of abetalipoproteinemic patients.

Although considerable amounts of circulating plasma LDLs and HDLs are produced in the plasma, the liver also produces a small amount of these two cholesterol-rich lipoproteins. LDLs are denser than VLDLs, and HDLs are denser than LDLs. The function of LDLs is to transport cholesterol ester from the liver to the other organs. HDLs are believed to remove cholesterol from the peripheral tissue and transport it to the liver.

The formation and secretion of lipoproteins by the liver is regulated by precursors and hormones, such as estrogen and thyroid hormone. For instance, during fasting, the fatty acids in VLDLs are derived mainly from fatty acids mobilized from adipose tissue. In contrast, during fat feeding, fatty acids in VLDLs produced by the liver are largely derived from chylomicrons.

As noted earlier, the fatty acids taken up by the liver can be used for β-oxidation and ketone body formation. The relative amounts of fatty acid channeled for these various purposes are largely dependent on the individual's nutritional and hormonal status. More fatty acid is channeled to ketogenesis or β-oxidation when the supply of carbohydrate is short (during fasting) or under conditions of high circulating glucagon or low circulating insulin (diabetes mellitus). In contrast, more of the fatty acid is used for synthesis of triglyceride for lipoprotein export when the supply of carbohydrate is abundant (during feeding) or under conditions of low circulating glucagon or high circulating insulin.

Lipoprotein Catabolism. The importance of the liver in lipoprotein metabolism is exemplified by **familial hypercholesterolemia**, a disorder in which the liver fails to produce the LDL receptor. When LDL binds its receptor, it is internalized and catabolized in the hepatocyte. Consequently, the LDL receptor is crucial for the removal of LDL from the plasma. Individuals suffering from familial hypercholesterolemia usually have very high plasma LDLs,

TABLE 28.1 Characteristics of Human Plasma Lipoproteins

Lipoprotein	Source	Density (g/mL)	Size (nm)	Protein	Lipid
Chylomicron	Intestine	< 0.95	80–500	1%	99%
VLDL	Intestine and liver	0.95–1.006	30–80	7–10%	90–93%
LDL	Chylomicron and VLDL	1.019–1.063	18–28	20–22%	78–80%
HDL	Chylomicron and VLDL	1.063–1.21	5–14	35–60%	40–65%

VLDL, very low density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

which predisposes them to early coronary heart disease. Often the only effective treatment is a liver transplant.

The liver also plays an important role in the uptake of chylomicrons after their metabolism. After the chylomicrons produced by the small intestine enter the circulation, lipoprotein lipase on the endothelial cells of blood vessels acts on them to liberate fatty acids and glycerol from the triglycerides. As metabolism progresses, the chylomicrons shrink, resulting in the detachment of free cholesterol, phospholipid, and proteins, and the formation of HDL. Chylomicrons are converted to **chylomicron remnants** during metabolism, and chylomicron remnants are rapidly taken up by the liver via chylomicron remnant receptors.

The Production of Ketone Bodies. Most organs, except the liver, can use ketone bodies as fuel. For example, during prolonged fasting, the brain shifts to use ketone bodies for energy, although glucose is the preferred fuel for the brain. The two ketone bodies are acetoacetate and β-hydroxybutyrate. Their formation by the liver is normal and physiologically important. For instance, during fasting a rapid depletion of the glycogen stores in the liver occurs resulting in a shortage of substrates (e.g., oxaloacetate) for the citric acid cycle. There is also a rapid mobilization of fatty acids from adipose tissues to the liver. Under these circumstances, the acetyl-CoA formed from β-oxidation is channeled to ketone bodies.

The liver is efficient in producing ketone bodies. In humans, it can produce half of its equivalent weight of ketone bodies per day. However, it lacks the ability to metabolize the ketone bodies formed because it lacks the necessary enzyme ketoacid-CoA transferase.

The level of ketone bodies circulating in the blood is usually low, but during prolonged starvation and in diabetes mellitus it is highly elevated, a condition known as **ketosis**. In patients with diabetes, large amounts of β-hydroxybutyric acid can make the blood pH acidic, a state called **ketoacidosis**.

Cholesterol Metabolism. The liver plays an important role in cholesterol homeostasis. Liver cholesterol is derived from both *de novo* synthesis and the lipoproteins taken up by the liver. Hepatic cholesterol can be used in the formation of bile acids, biliary cholesterol secretion, the synthesis of VLDLs, and the synthesis of liver membranes. Because the absorption of biliary cholesterol and bile acids by the GI tract is incomplete, this method of eliminating cholesterol from the body is essential and efficient. However, patients with high plasma cholesterol levels might be given additional drugs, such as statins, to lower their plasma cholesterol levels. Statins act by inhibiting enzymes that play an essential role in cholesterol synthesis. VLDLs secreted by the liver provide cholesterol to organs that need it for the synthesis of steroid hormones (e.g., the adrenal glands, ovaries, and testes).

PROTEIN AND AMINO ACID METABOLISM IN THE LIVER

The liver is one of the major organs involved in synthesizing nonessential amino acids from the essential amino acids. The body can synthesize all but nine of the amino acids necessary for protein synthesis.

The Liver Produces Most of the Circulating Plasma Proteins

The liver synthesizes many of the circulating plasma proteins, albumin being the most important (Fig. 28.5). It synthesizes about 3 g of albumin a day. Albumin plays an important role in preserving plasma volume and tissue fluid balance by maintaining the colloid osmotic pressure of plasma. This important function of plasma proteins is illustrated by the fact that both liver disease and long-term starvation result in generalized edema and ascites. Plasma albumin plays a pivotal role in the transport of many substances in blood, such as free fatty acids and certain drugs, including penicillin and salicylate.

The other major plasma proteins synthesized by the liver are components of the complement system, components of the blood clotting cascade (fibrinogen and prothrombin), and proteins involved in iron transport (transferrin, haptoglobin, and hemopexin) (see Chapter 11).

The Liver Produces Urea

Ammonia, derived from protein and nucleic acid catabolism, plays a pivotal role in nitrogen metabolism and is needed in the biosynthesis of nonessential amino acids and nucleic acids. Ammonia metabolism is a major function of the liver. The liver has an ammonia level 10 times higher than the plasma ammonia level. High circulating ammonia levels are highly neurotoxic, and a deficiency in hepatic function can lead to several distinct neurological disorders, including coma in severe cases.

The liver synthesizes most of the urea in the body. The enzymes involved in the urea cycle are regulated by protein intake. In humans, starvation stimulates these enzymes.

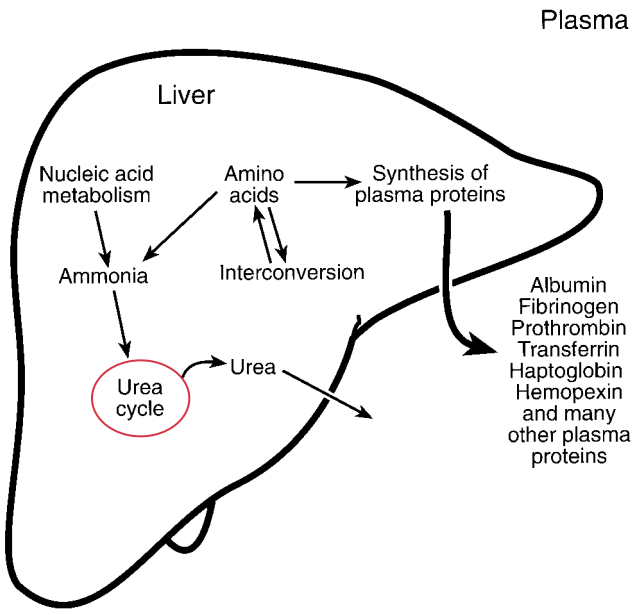

FIGURE 28.5 **The regulation of protein and amino acid metabolism in the liver.**

The Liver Plays an Important Role in the Synthesis and Interconversion of Amino Acids

The **essential amino acids** (see Table 27.7) must be supplied in the diet. The liver can form nonessential amino acids from the essential amino acids. For instance, tyrosine can be synthesized from phenylalanine and cysteine can be synthesized from methionine.

Glutamic acid and glutamine play an important role in the biosynthesis of certain amino acids in the liver. Glutamic acid is derived from the amination of α-ketoglutarate by ammonia. This reaction is important because ammonia is used directly in the formation of the α-amino group and constitutes a mechanism for shunting nitrogen from wasteful urea-forming products. Glutamic acid can be used in the amination of other α-keto acids to form the corresponding amino acids. It can also be converted to glutamine by coupling with ammonia, a reaction catalyzed by glutamine synthetase. After urea, glutamine is the second most important metabolite of ammonia in the liver. It plays an important role in the storage and transport of ammonia in the blood. Through the action of various transaminases, glutamine can be used to aminate various keto acids to their corresponding amino acids. It also acts as an important oxidative substrate, and in the small intestine it is the primary substrate for providing energy.

THE LIVER AS A STORAGE ORGAN

Another important role of the liver is the storage and metabolism of fat-soluble vitamins and iron. Some water-soluble vitamins, particularly vitamin B_{12}, are also stored in the liver. These stored vitamins are released into the circulation when a need for them arises.

The Liver Has a Central Role in Regulating Coagulation

Liver cells are important both in the production and the clearance of coagulation proteins. Most of the known clotting factors and inhibitors are secreted by hepatocytes, some of them exclusively. In addition, several coagulation and anticoagulation proteins require a vitamin K–dependent modification following synthesis, specifically factors II, VII, IX, and X and proteins C and S, to make them effective.

The monocyte-macrophage system of the liver, predominantly Kupffer cells, is an important system for clearing clotting factors and factor-inhibitor complexes. Disturbances in liver perfusion and function result in the ineffective clearance of activated coagulation proteins, so patients with advanced liver failure may be predisposed to developing disseminated intravascular coagulation.

Fat-Soluble Vitamins Are Stored in the Liver

Vitamin A comprises a family of compounds related to retinol. Vitamin A is important in vision, growth, the maintenance of epithelia, and reproduction. The liver plays a pivotal role in the uptake, storage, and maintenance of circulating plasma vitamin A levels by mobilizing its vitamin A store (Fig. 28.6). Retinol (an alcohol) is transported in chylomicrons mainly as an ester of long-chain fatty acids (see Chapter 27). When chylomicrons enter the circulation, the triglyceride is rapidly acted on by lipoprotein lipase; the triglyceride content of the particles is significantly reduced, while the retinyl ester content remains unchanged. Receptors in the liver mediate the rapid uptake of chylomicron remnants, which are degraded, and the retinyl ester is stored.

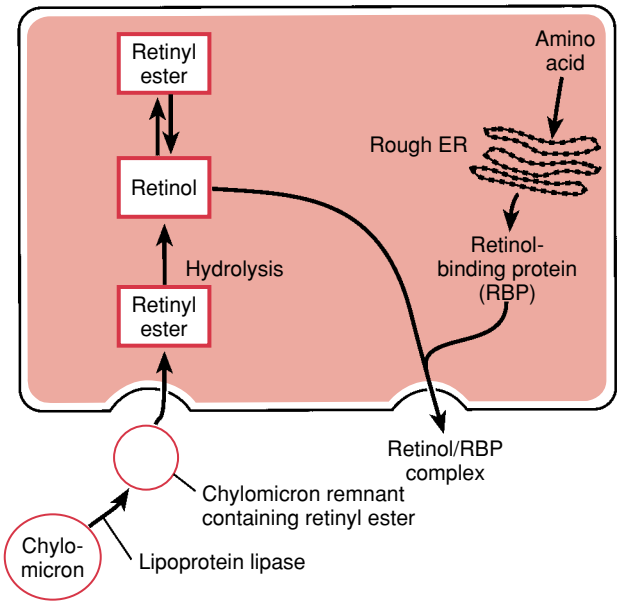

FIGURE 28.6 **The metabolism of vitamin A (retinol) by the hepatocyte.**

When the vitamin A level in blood falls, the liver mobilizes the vitamin A store by hydrolyzing the retinyl ester (see Fig. 28.6). The retinol formed is bound with **retinol-binding protein** (RBP), which is synthesized by the liver before it is secreted into the blood. The amount of RBP secreted into the blood is dependent on vitamin A status. Vitamin A deficiency significantly inhibits the release of RBP, whereas vitamin A loading stimulates its release.

Hypervitaminosis A develops when massive quantities of vitamin A are consumed. Since liver is the storage organ for vitamin A, hepatotoxicity is often associated with hypervitaminosis A. The continued ingestion of excessive amounts of vitamin A eventually leads to portal hypertension and cirrhosis.

Vitamin D is thought to be stored mainly in skeletal muscle and adipose tissue. However, the liver is responsible for the initial activation of vitamin D by converting vitamin D_3 to 25-hydroxy vitamin D_3, and it synthesizes vitamin D-binding protein.

Vitamin K is a fat-soluble vitamin important in the hepatic synthesis of prothrombin. Prothrombin is synthesized as a precursor that is converted to the mature prothrombin, a reaction that requires the presence of vitamin K (Fig. 28.7). Vitamin K deficiency, therefore, leads to impaired blood clotting.

The largest vitamin K store is in skeletal muscle, but the physiological significance of this and other body stores is

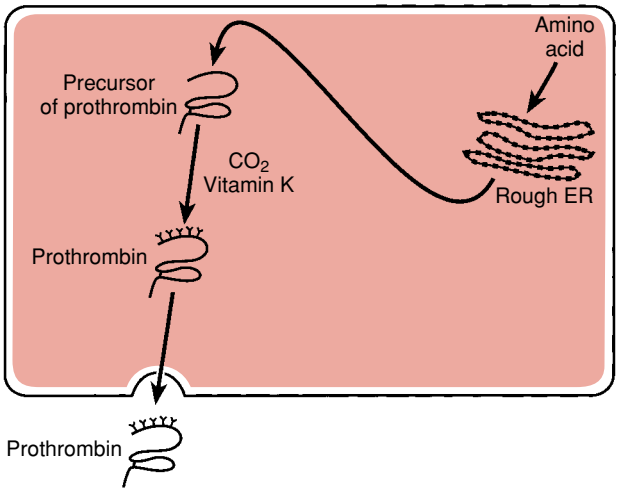

FIGURE 28.7 **The formation and secretion of prothrombin by the hepatocyte.**

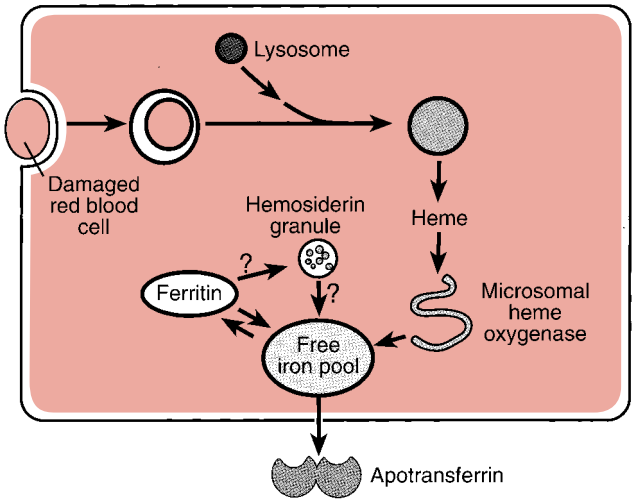

FIGURE 28.8 **The possible pathways following phagocytosis of damaged red blood cells by Kupffer cells.** (Modified from Young SP, Aisen P. The liver and iron. In: Arias I, Jakoby WB, Popper H, et al., eds. The Liver: Biology and Pathobiology. New York: Raven, 1988.)

unknown. The dietary vitamin K requirement is extremely small and is adequately supplied by the average North American diet. Bacteria in the GI tract also provide vitamin K. This appears to be an important source of vitamin K because prolonged administration of wide-spectrum antibiotics sometimes results in hypoprothrombinemia. Because vitamin K absorption is dependent on normal fat absorption, any prolonged malabsorption of lipid can result in its deficiency. The vitamin K store in the liver is relatively limited, and therefore, hypoprothrombinemia can develop within a few weeks. Vitamin K deficiency is not uncommon in the Western world. Parenteral administration of vitamin K usually provides a cure.

The Liver Is Important in the Storage and Homeostasis of Iron

The liver is the major site for the synthesis of several proteins involved in iron transport and metabolism. The protein **transferrin** plays a critical role in the transport and homeostasis of iron in the blood. The circulating plasma transferrin level is inversely proportional to the iron load of the body—the higher the concentration of ferritin in the hepatocyte, the lower the rate of transferrin synthesis. During iron deficiency, liver synthesis of transferrin is significantly stimulated, enhancing the intestinal absorption of iron. **Haptoglobin**, a large glycoprotein with a molecular weight of 100,000, binds free hemoglobin in the blood. The hemoglobin-haptoglobin complex is rapidly removed by the liver, conserving iron in the body. **Hemopexin** is another protein synthesized by the liver that is involved in the transport of free heme in the blood. It forms a complex with free heme, and the complex is removed rapidly by the liver.

The spleen is the organ that removes red blood cells that are slightly altered. Kupffer cells of the liver also have the capacity to remove damaged red blood cells, especially those that are moderately damaged (Fig. 28.8). The red cells taken up by Kupffer cells are rapidly digested by secondary lysosomes to release heme. Microsomal **heme oxygenase** releases iron from the heme, which then enters the free iron pool and is stored as ferritin or released into the bloodstream (bound to apotransferrin). Some of the ferritin iron may be converted to **hemosiderin granules**. It is unclear whether the iron from the hemosiderin granules is exchangeable with the free iron pool.

It was long believed that Kupffer cells were the only cells involved in iron storage, but recent studies suggest that hepatocytes are the major sites of long-term iron storage. Transferrin binds to receptors on the surface of hepatocytes, and the entire transferrin-receptor complex is internalized and processed (Fig. 28.9). The apotransferrin (not containing iron) is recycled back to the plasma, and the released iron enters a labile iron pool. The iron from transferrin is probably the major source of iron for the hepatocytes, but they also derive iron from haptoglobin-hemoglobin and hemopexin-heme complexes. When hemoglobin is released inside the hepatocytes, it is degraded in the secondary lysosomes, and heme is released. Heme is processed in the smooth ER and free iron released enters the labile iron pool. A significant portion of the free iron in the cytosol probably combines rapidly with apoferritin to form ferritin. Like Kupffer cells, hepatocytes may transfer some of the iron in ferritin to hemosiderin.

Iron is absolutely essential for survival, but iron overload can be extremely toxic, especially to the liver where it can cause **hemochromatosis**, a condition characterized by excessive amounts of hemosiderin in the hepatocytes. The hepatocytes in patients with hemochromatosis are defective and fail to perform many normal functions.

ENDOCRINE FUNCTIONS OF THE LIVER

The liver is important in regulating the endocrine functions of hormones. It can amplify the action of some hormones. It is also the major organ for the removal of peptide hormones.

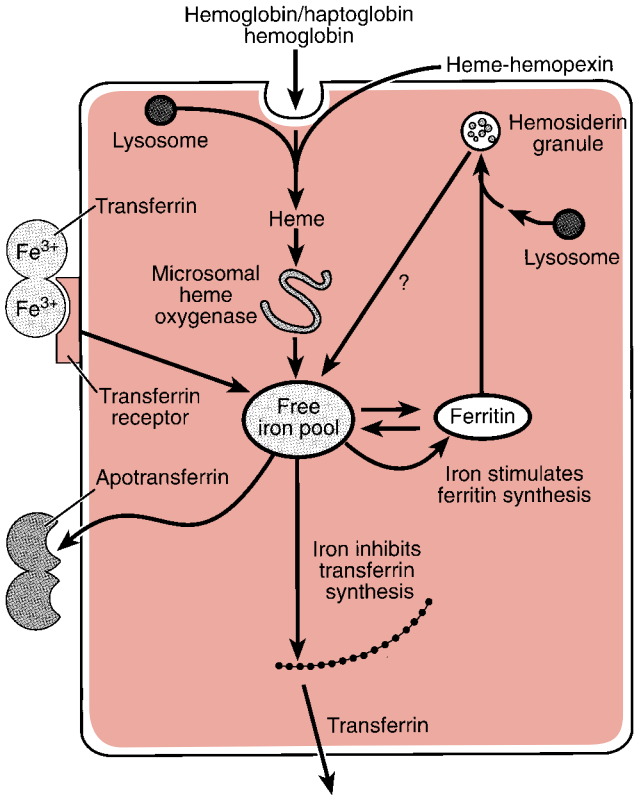

FIGURE 28.9 The possible pathways followed by iron in the hepatocyte. (Modified from Young SP, Aisen P. The liver and iron. In: Arias I, Jakoby WB, Popper H, et al., eds. The Liver: Biology and Pathobiology. New York: Raven, 1988.)

The Liver Can Modify or Amplify Hormone Action

As discussed before, the liver converts vitamin D_3 to 25-hydroxy vitamin D_3, an essential step before conversion to the active hormone 1,25-hydroxy vitamin D_3 in the kidneys. The liver is also a major site of conversion of the thyroid hormone thyroxine (T_4) to the biologically more potent hormone triiodothyronine (T_3). The regulation of the hepatic T_4 to T_3 conversion occurs at both the uptake step and the conversion step. Due to the liver's relatively large reserve in converting T_4 to T_3, hypothyroidism is uncommon in patients with liver disease. In advanced chronic liver disease, however, signs of hypothyroidism may be evident.

The liver modifies the function of growth hormone (GH) secreted by the pituitary gland. Some growth hormone actions are mediated by **insulin-like growth factors** made by the liver (see Chapter 32).

The Liver Removes Circulating Hormones

The liver helps to remove and degrade many circulating hormones. Insulin is degraded in many organs, but the liver and kidneys are by far most important. The presence of insulin receptors on the surface of hepatocytes suggests that the binding of insulin to these receptors results in degradation of some insulin molecules. There is also degradation of insulin by proteases of hepatocytes that do not involve the insulin receptor.

Glucagon and growth hormone are degraded mainly by the liver and the kidneys. The liver may also degrade various GI hormones (e.g., gastrin), but the kidneys and other organs probably contribute more significantly to inactivating these hormones.

REVIEW QUESTIONS

DIRECTIONS: Each of the numbered items or incomplete statements in this section is followed by answers or by completions of statements. Select the ONE lettered answer or completion that is BEST in each case.

1. The first step in alcohol metabolism by the liver is the formation of acetaldehyde from alcohol, a chemical reaction catalyzed by
   (A) Cytochrome P450
   (B) NADPH-cytochrome P450 reductase
   (C) Alcohol oxygenase
   (D) Alcohol dehydrogenase
   (E) Glycogen phosphorylase
2. The arterial blood glucose concentration in normal humans after a meal is in the range of
   (A) 30 to 50 mg/dL
   (B) 50 to 70 mg/dL
   (C) 120 to 150 mg/dL
   (D) 220 to 250 mg/dL
   (E) 300 to 350 mg/dL
3. Both the liver and muscle contain glycogen, yet, unlike liver, muscle is not capable of contributing glucose to the circulation because muscle
   (A) Does not have the enzyme glucose-6-phosphatase
   (B) Glycolytic activity consumes all of the glucose it generates
   (C) Does not have the enzyme glucose-1-phosphatase
   (D) Does not have the enzyme glycogen phosphorylase
   (E) Is not as capable of gluconeogenesis as is the liver
4. The hepatocyte is compartmentalized to carry out specific functions. In which subcellular compartment does fatty acid synthesis occur?
   (A) Cytoplasm
   (B) Mitochondria
   (C) Nucleus
   (D) Endosomes
   (E) Golgi apparatus
5. The small intestine secretes various triglyceride-rich lipoproteins, but the liver secretes only
   (A) Chylomicrons
   (B) VLDLs
   (C) LDLs
   (D) HDLs
   (E) Chylomicron remnants
6. Because free ammonia in the blood is toxic to the body, it is transported in which of the following non-toxic forms?
   (A) Histidine and urea
   (B) Phenylalanine and methionine
   (C) Glutamine and urea
   (D) Lysine and glutamine
   (E) Methionine and urea
7. In patients with a portacaval shunt (connection between the portal vein and vena cava), the circulating glucagon level is extremely high because the
   (A) Pancreas produces more glucagon in these patients
   (B) Kidney is less efficient in removing the circulating glucagon in these patients

(continued)

(C) Liver normally is the major site for the removal of glucagon
(D) Small intestine produces more glucagon in these patients
(E) Blood flow to the small intestine is compromised

8. Which protein is made by the liver and carries iron in the blood?
(A) Hemosiderin
(B) Haptoglobin
(C) Transferrin
(D) Ceruloplasmin
(E) Lactoferrin

9. The level of drug metabolizing enzymes in the liver determines how fast a drug is removed from the circulation. Therefore, it would be expected to find drug metabolizing enzymes
(A) Higher in smokers than in nonsmokers
(B) Similar in smokers and nonsmokers
(C) Lower in smokers than in nonsmokers
(D) Stimulated by malnutrition
(E) Higher in newborns than in adults

10. Phase I reactions of drug metabolism refer to the
(A) Conjugation of drugs with glucuronic acid
(B) Conjugation of drugs with glycine or taurine
(C) Introduction of one or more polar groups to the drug molecule
(D) Introduction of one or more hydrophobic groups to the drug molecule
(E) Conjugation of drugs with sulfate

11. The level of circulating 1,25-dihydroxycholecalciferol is significantly reduced in patients with chronic liver disease because
(A) The liver can no longer efficiently convert 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol
(B) The liver can no longer efficiently convert vitamin D to cholecalciferol
(C) The liver can no longer efficiently convert vitamin D to 25-hydroxycholecalciferol
(D) The liver can no longer efficiently convert cholecalciferol to 1,25-dihydroxycholecalciferol
(E) The intestine has impaired absorption of 1,25-hydroxycholecalciferol

12. The liver removes LDLs in the blood by the LDLs binding to
(A) LDL receptors and then internalizing them
(B) HDL receptors and then internalizing them
(C) The albumin present on LDLs and then internalizing them
(D) The transferrin present on LDL and then internalizing them
(E) The ceruloplasmin on LDLs and then internalizing them

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CASE STUDIES FOR PART VII • • •

Case Study for Chapter 26

Dysphagia

A 51-year-old woman is evaluated for difficulty in swallowing solid foods. She experiences chest pain while attempting to eat and often regurgitates swallowed food. Fluoroscopic examination of a barium swallow reveals a dilated lower esophagus with considerable residual barium remaining after the swallow. A manometric motility study of esophageal motility following a swallow reveals an absence of primary peristalsis in the distal third, without relaxation of contractile tone in the lower esophageal sphincter.

Questions

1. What is the explanation for the woman's dysphagia?
2. What is the most likely explanation for the failure of the lower esophageal sphincter relaxation during the swallow?
3. What are the possible treatments for the woman's condition?

Answers to Case Study Questions for Chapter 26

1. The best explanation for the patient's dysphagia is failure of the lower esophageal sphincter to relax (achalasia).
2. Loss of the ENS in the region of the lower esophageal sphincter and gastric cardia is the histoanatomic hallmark of lower esophageal sphincter achalasia. Failure of the sphincter to relax reflects the loss of inhibitory motor innervation of the sphincteric muscle.
3. There are several possible treatments. The time-tested treatment is pneumatic dilation of the lower esophageal sphincter, by placing a balloon in the lumen of the sphincter. Pharmacological approaches include calcium channel blockers (e.g., nifedipine) to relax the smooth muscle of the sphincter, and local endoscopic injection of botulinum toxin, an inhibitor of ACh release from nerve terminals.

Reference

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Case Study for Chapter 27

Lactose Intolerance

A 9-year-old Chinese American boy regularly complains of abdominal cramps, abdominal distension, and diarrhea after drinking milk. A gastroenterologist administers 50 g of lactose by mouth to the child and measures an increase in the boy's expired hydrogen gas.

Questions

1. How is lactose digested and absorbed in the small intestine?
2. Explain the symptoms that accompany lactose intolerance.
3. Why was the lactose breath test done?
4. How common is lactose intolerance?
5. What can be done about lactose intolerance?

Answers to Case Study Questions for Chapter 27

1. Lactose is hydrolyzed by a brush border enzyme called lactase to glucose and galactose. The monosaccharides are then absorbed by sodium-dependent secondary active transport.

2. If the lactase enzyme is deficient, lactose will not be broken down and will remain in the intestinal lumen. The osmotic activity of the lactose draws water into the intestinal lumen and results in a watery diarrhea. In the colon, bacteria metabolize the lactose to lactic acid, carbon dioxide, and hydrogen gas. The extra fluid and gas in the intestine result in distension and increased motility (cramps).
3. The child might have had an allergy to proteins in milk. The lactose breath test results indicate lactose intolerance.
4. In the most of the world's population, intestinal lactase activity is high during childhood, but falls after ages 5 to 7 to low adult levels. The prevalence of lactose intolerance in adults is about 100% in Asian Americans, 95% in Native Americans, 81% in African Americans, 56% in Mexican Americans, and 24% in white Americans. Lactose intolerance is common (about 50 to 70%) in adult Americans of Mediterranean descent, but is low (0 to only a few %) in those of northern European ancestry.
5. Avoiding foods that contain lactose (milk, dairy products) is recommended for persons who are lactose-intolerant; however, calcium and caloric intake should not be compromised. Milk can be pretreated with an enzyme obtained from bacteria or yeasts that digests lactose, or lactase pills can be taken with meals.

Case Study for Chapter 28

Budd-Chiari Syndrome

A 51-year-old woman complained of 4 days of epigastric abdominal pain. She reported having been healthy all her life. She admitted to having gained approximately 9 kg (20 lb) over the preceding 6 months, which was unusual. Upon examination by her physician, she is found to have a distended abdomen that is tender in the area between her ribs at the top of her abdomen.

An exploratory laparotomy reveals an enlarged liver and no other disease. A liver biopsy is taken and reportedly shows no significant abnormalities. For unstated reasons, the patient is later taken for a venogram and was found to have thrombosis of her hepatic veins, Budd-Chiari syndrome. She is subsequently referred to a tertiary hospital. Initially, the patient is treated with diuretic medication (spironolactone and furosemide to increase renal excretion of sodium and water) and intermittent paracentesis (insertion of a needle into the peritoneal space, evacuating fluid, which relieves the abdominal distension and discomfort). She subsequently undergoes placement of a transjugular intrahepatic portosystemic shunt (TIPS), which serves to lower portal pressure by shunting blood into systemic veins. She is also given warfarin, an anticoagulant.

Questions

1. What is the probable explanation for her abdominal pain, distension, and weight gain over 6 months?
2. What is the rationale for giving an anticoagulant, and how does warfarin work?

Answers to Case Study Questions for Chapter 28

1. A common explanation for abdominal discomfort, distension, and weight gain in women is pregnancy. Her age makes this unlikely but not impossible. Any disorder that results in fluid retention may present with these symptoms. Common causes of marked abdominal fluid retention are nephrotic syndrome (the kidneys fail to adequately remove excess water), congestive heart failure (the heart fails to adequately pump blood to the kidneys, reducing their ability to remove excess water), and liver dysfunction (usually from an excess pressure in the sinusoids resulting in increased fluid loss into the abdomen). The general term to describe excess fluid in the abdominal cavity is ascites. Alternatively, symptoms may be due to intraabdominal malignancies, such as malignant ascites or large tumors. In a woman of this age, ovarian cancer would be considered a likely cause.
2. The anticoagulant warfarin was given to treat the patient's hypercoagulable disorder and to maintain shunt patency. Clotting factors, mostly produced in the liver, have a series of glutamic acid residues that must be carboxylated by a vitamin K–dependent carboxylase in order for them to bind to endothelial cells and activate platelets necessary for clot formation. The reduced form of vitamin K is a necessary cofactor for the carboxylation. During carboxylation of the clotting factor, vitamin K becomes an epoxide. Warfarin is thought to disrupt the vitamin K cycle, thereby preventing the necessary carboxylation of clotting factors. The liver continues to synthesize these factors, but they lack effect and therefore clotting is limited.