The liver occupies the center of a diverse spectrum of vital physiologic functions and plays an essential role in maintaining perioperative homeostasis. Patients with advanced liver disease are at high risk of excessive morbidity and mortality following surgery due to failure of one or more of these essential functions. For example, the normal liver moderates the hypotensive response to acute blood loss and hypovolemia through its reservoir function, and helps minimize blood loss through synthesis of coagulation factors and degradation of fibrinolytic substances. Failure of these functions contributes to intraoperative and postoperative hypoperfusion, tissue ischemia, and activation of the systemic inflammatory response, setting the stage for the postoperative development of multisystem organ failure. The liver is the primary regulatory site for metabolism. After oral intake, all nutrients are brought to the liver for processing, followed by controlled distribution to extrahepatic tissues. The liver also helps sustain energy supplies during fasting, is the site of synthesis of almost all the body's proteins, plays a central role in the individual's defense against infection, and modulates inflammatory processes. Predictable termination of the

The hepatic buffer response, in which the hepatic artery blood flow changes reciprocally with changing portal venous flow, is the mechanism by which total oxygen delivery to the liver is maintained. This response is limited in its ability to compensate during conditions of hypoperfusion, inflammation, or shock.

Hepatitis associated with volatile anesthetics is rare overall and is most commonly associated with halothane. The disorder appears to be immune mediated and is best avoided by eliminating halothane from clinical use.

Because of the liver's central role in the inflammatory response, the metabolic demands greatly increase whenever acute-phase proteins are being produced. These demands occur when hepatic oxygen delivery is likely to be compromised, placing the liver in a highly vulnerable situation.

The risk of developing perioperative hepatic dysfunction varies with the preexisting hepatic reserve status; presence of comorbid conditions; and the type, duration, and location of surgery. Commonly employed general and regional anesthetic techniques impart minimal additional stress to the liver.

Currently, there is no commonly available hepatic replacement therapy for acute liver failure. The most effective support for the liver, maintaining adequate perfusion and oxygenation, as well as avoiding secondary toxic insults, must occur before it fails.
pharmacologic effects of many anesthetic agents depends on the liver for metabolic biotransformation into inactive products that can be eliminated.

The liver is a remarkably resilient organ, with unparalleled regenerative capacity and substantial physiologic reserves. Normal function may be present in humans when as much as 80% of the organ has been resected. Insidious hepatic diseases such as chronic hepatitis C can progress silently and destroy the majority of the liver before symptoms develop. Identifying patients with marked limitation of hepatic reserve, but without overt hepatic failure is important, but often difficult. A careful preoperative history and physical examination will help identify patients in whom laboratory evaluation of liver function is appropriate. These patients are often at increased risk for perioperative morbidity and mortality, including development of overt liver dysfunction postoperatively, particularly after major procedures.

As therapy for chronic hepatic diseases improves and the number of patients with chronic hepatitis C continues to rapidly increase, it can be expected that the number of patients with moderate-to-severe liver disease presenting for surgery will rise. These patients may be at extremely high risk for perioperative complications, and it is essential that the anesthesiologist understands the interactions between liver disease, surgical procedures, and anesthetic interventions so an appropriate therapeutic plan can be developed and implemented to optimize patient outcome.

HEPATIC ANATOMY

The liver is the largest gland in the human body with a median weight of 1.8 kg in men and 1.4 kg in women. The liver is covered by peritoneum (Glisson's capsule), except for the gallbladder bed, the inferior vena cava (IVC), the bare area, and the porta hepatis. At the porta hepatis, the connective tissue of the capsule is continuous with the fibrous sheath, which invests the portal vessels and ducts. The capsular peritoneum reflects onto the diaphragm and continues as the parietal peritoneum. The reflections form various ligaments (coronary, triangular, and falciform), which firmly attach the liver to the anterior abdominal wall and diaphragm.

Lobes Versus Segments of the Liver

The customary division of the liver into the right, left, caudate, and quadrate lobes is derived from the topographic anatomy, with the falciform ligament separating the right and left lobes (Fig. 39-1). This anatomic description does not correspond to the branches of the liver's vascular supply and therefore is of limited clinical and physiologic significance. The liver can be divided on a different plane into right and left hemilivers, which have their own blood supplies and duct drainage. The liver can be further divided into a total of eight functionally independent segments, each with its own vascular inflow and outflow, and biliary drainage (Fig. 39-2). The segmental division of the liver was devised by Couinaud, based on the divisions of the portal vein, and more recently modified by Strasberg, based on the more consistent divisions of the hepatic artery and biliary ducts. This anatomic arrangement facilitates limited segmental resection of the liver with relatively bloodless surgical dissection along the planes between segments, and thereby prevents major disruption of hepatobiliary function. With current imaging techniques, radiologists can construct precise, three-dimensional models of a patient's liver, defining the segmental location of lesions and their relation to the vasculature. Such information can help the surgeon decide on the most appropriate operative approach, while enhancing the resectability of a variety of lesions and improving outcome for patients undergoing operations for neoplasm or trauma.
Vascular Supply of the Liver

The liver receives about 25% of the cardiac output, and therefore, has an average blood flow between 100 and 130 mL/minute per 100 g. There are two major sources of blood to the liver: the hepatic artery and the portal vein. The common hepatic artery arises from the celiac trunk and sends off the cystic artery before entering the liver (Fig. 39-1).

**FIGURE 39-1.** Schematic representation depicting the lobar classification of the liver and the extrahepatic portal venous circulation.

3). The portal vein is formed by the confluence of the splenic and superior mesenteric veins, and receives blood from the entire digestive tract, spleen, pancreas, and gallbladder. The hepatic artery delivers about 25% of the total hepatic blood flow but nearly 50% of the hepatic oxygen delivery. The portal vein provides the remaining 75% of total hepatic blood flow and 50% of hepatic oxygen delivery. Because portal venous blood has already perfused the preportal organs (stomach, intestines, spleen, and pancreas) (see Fig. 39-3), it is partially deoxygenated and enriched with nutrients and other substances absorbed from the gastrointestinal tract.

The portal vein has numerous tributaries, which are usually of little importance (see Fig. 39-1). When patients develop portal hypertension, however, these normally rudimentary connections form large portosystemic shunts, permitting portal venous blood to return to the systemic circulation without traversing the liver. These shunts produce many of the pathologic findings and severe complications of portal hypertension (e.g., esophageal varices).

Intrahepatic Circulation

The portal vein and hepatic artery enter the liver at the porta hepatis, where the larger bile ducts join and accompany them. Both vessels bifurcate into left and right branches, which arborize in parallel while diminishing in caliber as they penetrate the hepatic parenchyma to end as terminal hepatic arterioles and portal venules (Fig. 39-4). Most terminal vessels drain directly into the hepatic sinusoids, delivering substrates to, and removing products from, adjacent parenchymal cells. Before this, some arteriolar blood flows through the peribiliary capillary plexus, which plays a major role in bile secretion and absorption (see Fig. 39-4). Hepatic arterial pressure is similar to aortic pressure, while the mean portal vein pressure is approximately 6 to 10 mm Hg. These two afferent vascular systems merge in the sinusoids where the pressure is normally 2 to 4 mm Hg above that of the IVC. The hepatic sinusoids connect the terminal portal vessels with the hepatic venules. The continuity of the sinusoidal wall is interrupted by fenestrations, which facilitate transfer of solutes to the space of Disse for uptake by hepatocytes. Flow through the

Blood drains from the hepatic sinusoids into the central vein and then flows through sublobular veins that join to form one of the three major hepatic veins (right, middle, and left) (Fig. 39-5). A short extrahepatic segment joins each major hepatic vein to the IVC. The caudate lobe drains directly into the IVC through small posterior caudate veins. If thrombosis of the major hepatic veins occurs (Budd-Chiari syndrome), the caudate veins become the key to drainage of hepatic blood into the IVC.
Hepatic Microanatomy: Classic Liver Lobule Versus Acinar Lobule

The functional units of the liver have defied delineation. The organization of the hepatic parenchyma has been conceptualized in two contrasting models: Kierman’s classic lobule and Rappaport’s acinus. Each model can successfully explain some of the pathologic and physiologic processes in the liver, but neither explains them all.

The classic liver lobule is hexagonal on cross section, with six vertically aligned portal canals at the corners and a hepatic venule (central vein) in its center (see Fig. 39-5). Each canal contains connective tissue, lymphatics, nerves, and a portal triad (terminal branches of portal vein, hepatic artery, and bile duct). A lobule consists of an array of anastomosing cords of hepatocytes, separated by vascular channels (lacunae) that radiate from the six portal areas and converge on the hepatic venule at the center of the hexagon. The lacunae contain the capillaries (sinusoids), which are lined by endothelium and scattered Kupffer cells, which protrude into the sinusoidal lumen.

A lacunar labyrinth penetrates the entire lobule, except for the first row of hepatocytes in contact with the portal tract (the limiting plate), where a near continuous wall of hepatocytes separates the interior of the lobule from the portal canal.

Human livers do not have well-defined interlobular connective tissue, making it difficult to visualize the classic lobule. The quest to identify the boundaries of the classic lobule led to the discovery of circumferential terminal hepatic arterioles, portal venules, and bile ductules. Reasoning that these encircling vessels supply segments of contiguous classic lobules that lie between two terminal hepatic venules, Rappaport developed the acinus lobule (acinus) concept. The simple liver acinus is a small parenchymal mass, irregular in size and shape, and arranged around a central axis consisting of a terminal hepatic arteriole, portal venule, bile ductule, lymph vessels, and nerves (Fig. 39-6). Blood enters the center of the acinus and flows centrifugally to the hepatic venules. In contrast to the direction of blood flow, bile flows in the opposite direction from perivenular hepatocytes to the portal tract bile ducts.

FIGURE 39-5. Schematic view of liver lobule: The central vein (CV) lies in the center of the figure surrounded by anastomosing cords of block-like hepatocytes. About the periphery of this schema are six portal areas (PAs) consisting of branches of the portal vein, the hepatic artery, and the bile duct. (Reprinted with permission from Jones AL: Anatomy of the normal liver. In Zakim D, Boyer T [eds]: Hepatology: A Textbook of Liver Disease, 3rd ed, p 3. Philadelphia, WB Saunders, 1996.)
The simple liver acinus lies between two (or more) terminal hepatic venules. The terminal hepatic venule is therefore at the center of a classic liver lobule, but at the periphery of several simple liver acini. The dividing line between adjacent acini would be the watershed of biliary drainage (i.e., distinct acini empty their biliary secretions into distinct axial bile ducts). The conceptual advantage of the acinus concept is that the blood supply and biliary drainage of a portion of parenchyma reside in the same portal tract, whereas multiple portal vein branches and arteries supply each classic lobule.

The physiologic functions of the liver are performed at the liver cell plate, where interaction between the blood and hepatocytes occurs. The liver cell plates are formed by cords of hepatocytes extending as one-cell-thick plates, 12 to 25 hepatocytes in length, between two vascular structures, the portal tract and the terminal hepatic venule. The liver cell plate receives unidirectional perfusion from the portal tract to the hepatic venule via the hepatic sinusoids. This structural organization allows an orderly interaction between blood and hepatocytes. There is a zonal relationship between the cells that constitute the lobule or acinus and their blood supply (see Fig. 39-6). Periportal hepatocytes located close to the terminal vascular branches of the portal vein and hepatic artery are the first to be supplied with oxygen and nutrients (zone 1). The perivenular (centrilobular) area, which is most distant from these terminal vascular branches, has the least resistance to metabolic and anoxic damage (zone 3). The intermediate area is termed zone 2. The oxygen content and nutritive value of the blood progressively decreases as blood flows from zone 1 to zone 3.

**FIGURE 39-6.** Blood supply of the simple liver acinus. The oxygen tension and the nutrient level of the blood in sinusoids decrease from zone 1 through zone 3. Note that the lower left side of the figure also depicts zones 1, 2, and 3 in a portion of an adjacent acinar unit. BD, bile duct; HA, hepatic artery; PV, portal vein; CV, central vein. (Reprinted with permission from Jones AL: Anatomy of the normal liver. In Zakim D, Boyer T [eds]: Hepatology: A Textbook of Liver Disease, 3rd ed, p 3. Philadelphia, WB Saunders, 1996.)
The sequential perfusion of hepatocytes in the liver cell plate allows a progressive qualitative and quantitative modification of the composition of sinusoidal blood as it traverses the liver. There are ultrastructural differences between hepatocytes located in zones 1 and 3, and these hepatocytes attain different functional capabilities. Hepatocytes in zone 1 contain numerous large mitochondria and have the highest concentrations of Krebs cycle enzymes. These cells are adapted for high oxidative activities such as gluconeogenesis, beta-oxidation of fatty acids, amino acid catabolism, ureagenesis, cholesterol synthesis, and bile acid secretion. Zone 3 hepatocytes are relatively anaerobic. Smooth endoplasmic reticulum is more abundant in these cells. Zone 3 is a primary site for glycolysis and lipogenesis. It is also the site for general detoxification and biotransformation of drugs, chemicals, and toxins. The anaerobic milieu of zone 3, however, is also its Achilles heel because these cells are exquisitely susceptible to injury from systemic hypoperfusion and hypoxemia. Sharply defined zone 3 necrosis is also characteristic of injury resulting from accumulation of toxic products of biotransformation as seen in toxicity from acetaminophen and halothane.

**Innervation of the Liver**

The liver is predominantly innervated by two plexuses that enter at the hilum and supply both sympathetic and parasympathetic nerve fibers. The anterior plexus surrounds the hepatic artery and is composed of postganglionic sympathetic fibers from the celiac ganglia and parasympathetic fibers from the anterior vagus nerve. The posterior plexus surrounds the portal vein and bile duct, and is formed from branches of the right celiac ganglia and posterior vagus. Sympathetic nerve fibers predominate and form a rich perivascular plexus around large hilar blood vessels, and follow these vessels to each lobule to reach the sinusoids and hepatocytes. Stimulation of the sympathetic fibers alters hemodynamics and metabolism of the liver. Hepatic vascular resistance increases and blood volume decreases, whereas glycogenolysis and gluconeogenesis increase, producing an increase in the blood glucose concentration. Parasympathetic stimulation increases glucose uptake and glycogen synthesis.

**Hepatic Lymphatic System**

The site of hepatic lymph formation is uncertain, but the most accepted hypothesis is that lymph is formed by filtration of plasma through the sinusoids into the perisinusoidal space of Disse. This lymph travels through the perportal space of Mall (between the limiting plate and portal connective tissue), permeates the connective tissue, and drains into the lymphatic vessels of the portal canal. About 80% of hepatic lymph then travels through a rich plexus of lymphatic channels that surround the hepatic arteries, portal vein, and bile ducts until converging to form 12 to 15 lymph vessels that exit the porta hepatis and ultimately drain into the thoracic duct. The remaining 20% of hepatic lymph either leaves the liver through lymphatic vessels that accompany the hepatic veins to the IVC, or drain via lymphatic trunks within the coronary, triangular, and falciform ligaments that pierce the diaphragm and anastomose with esophageal and retrosternal lymph nodes. Portal hypertension and increased hepatic venous pressure can markedly increase hepatic lymph flow and lead to transudation through the hepatic capsule into the peritoneal cavity, producing ascites.

**REGULATION OF HEPATIC BLOOD FLOW**

Blood flow and oxygen supply to the liver are regulated to fulfill two separate demands. The first is to supply the liver itself with necessary energy substrates and oxygen for its own maintenance needs. The second is from the rest of the body, for which the liver provides vital services. Although the liver as a whole receives 25% of the cardiac output, regional blood flow within the organ is such that certain areas are highly prone to ischemia. The hepatic circulation is regulated by both intrinsic (regional microvascular) and extrinsic (neural and hormonal) mechanisms.

**Intrinsic Circulatory Regulation**

The liver lacks the ability to directly regulate portal venous flow; therefore, regional microvascular regulatory mechanisms must operate almost exclusively by modulating hepatic arteriolar tone. The primary mechanism by which this occurs is called the hepatic arterial buffer response, whereby hepatic arterial flow varies reciprocally with changes in portal venous flow. This response is limited, however, to a 50% reduction of portal venous flow and a corresponding twofold increase in hepatic artery flow. Fortunately, because the hepatic artery carries higher oxygen content, this is an effective mechanism for protecting the liver from ischemic insults.

The hepatic buffer response appears to be mediated via adenosine. Presumably, this potent arteriolar dilator is synthesized at a constant rate and continuously secreted in the vicinity of the terminal hepatic arterioles and portal venules. As flow through the portal vein decreases, less of the perivascular adenosine is “washed out,” leading to its accumulation around hepatic arterioles. The result is increased arteriolar dilatation and an increase in hepatic arterial flow. Conversely, an increase in portal vein flow decreases the periarteriolar adenosine, leading to a
corresponding decrease in hepatic artery flow.

The hepatic arterial system undergoes flow autoregulation when the liver is very active metabolically (postprandial), but not during the fasted state. The metabolic state modifies the composition of portal venous and systemic blood, thereby influencing hepatic blood flow. Decreases in pH and O₂ content, or increases in PCO₂ of the portal blood promote increases of hepatic arterial flow. Postprandial hypersomolarity can increase both hepatic arterial and portal venous blood flow, but this effect would not be relevant in fasted patients. Thus, hepatic flow autoregulation is not likely to be an important mechanism during most anesthetics, given that they are performed in fasted patients.

Extrinsic Circulatory Regulation

Extrinsic factors regulate blood flow through the portal vein indirectly by modulating the tone of arterioles in the preportal splanchnic organs. Portal venous pressure (normally 7 to 10 mm Hg), therefore, reflects both splanchnic arteriolar tone and intrahepatic resistance to flow. Portal venules (presinusoidal sphincters) affect the distribution of blood flow to the sinusoids; however, the hepatic venules (postsinusoidal sphincters) control venous resistance in the liver. Extrinsic mechanisms modulate this postsinusoidal tone, with the sympathetic nervous system as the primary physiologic regulator. Stimulation of α₁-adrenergic receptors increases vascular tone, leading to constriction and a reduction in both blood flow and blood volume in the sinusoids.

Hepatic arteriolar tone is the main determinant of resistance in the hepatic arterial tree. Blood flow through the liver decreases with stimulation of certain arteriolar receptors (α₁-adrenergic and type 1 dopaminergic) and increases with activation of others (β₂-adrenergic).

Humoral Regulators

Myriad humoral substances alter liver blood flow, including gastrin, glucagon, secretin, bile salts, angiotensin II, vasopressin, and catecholamines. In addition, during inflammatory or septic states, cytokines, interleukins, and other inflammatory mediators have been implicated in the alteration of normal splanchnic and hepatic blood flow. Of the systemic hormones, epinephrine is most likely to attain concentrations producing vasoactive effects. Both α-adrenergic and β-adrenergic receptors exist in the hepatic arterial bed, whereas the portal vasculature has only α receptors. An injection of epinephrine directly into the hepatic artery causes vasoconstriction (α₁-adrenergic effect), followed by vasodilation (β₂-adrenergic effect). When injected into the portal vein, epinephrine produces only vasoconstriction. During activation of the sympathetic nervous system, the hepatic circulatory effects of epinephrine and norepinephrine far exceed those of dopamine, which probably has little if any importance as a physiologic modulator of the hepatic circulation. Glucagon induces a graded, long-lasting dilation of hepatic arterioles; it also antagonizes arterial constrictor responses to a wide range of physiologic stimuli, including stress-induced sympathoadrenal outflow. Angiotensin II markedly constricts both hepatic arterial and portal beds, and significantly reduces mesenteric outflow; the result is a substantial decrease in total hepatic blood flow. Vasopressin also intensely constricts splanchnic vessels, markedly reducing flow into the portal vein. This action accounts for the efficacy of high-dose vasopressin (0.2 to 0.4 U/minute intravenously) to alleviate portal hypertension and decrease bleeding from esophageal varices. The splanchnic and hepatic effects of low-dose (0.02 to 0.04 U/minute intravenously) vasopressin for endogenous vasopressin deficiency replacement therapy in sepsis remain controversial. Animal studies document splanchnic vasoconstriction and increases in lactate; however, human studies, although supporting positive renal effects, have documented inconsistent benefits on splanchnic perfusion and hepatic function.7,8

MAJOR PHYSIOLOGIC FUNCTIONS OF THE LIVER

Blood Reservoir

The liver is a vital reservoir of blood in humans. It contains nearly 25 to 30 mL of blood per 100 g of tissue, which represents 10 to 15% of the total blood volume. The autonomic innervation of the liver, coupled with neurohumoral input from the systemic circulation, allows for rapid, precise control of the reservoir volume. Intense sympathetic nervous system stimulation (e.g., pain, hypoxia, hypercarbia) abruptly decreases hepatic blood flow and blood volume; 80% of the hepatic blood volume (approximately 400 to 500 mL) can be expelled within a matter of seconds.

Anesthetics that suppress sympathetic nervous system outflow impair this reservoir function and predispose the patient to circulatory decompensation when significant decreases of intravascular volume occur without immediate
replacement. Severe liver disease exacerbates the hypotensive effects of hypovolemia by impairing vasoconstrictor responses to catecholamines. A total failure of vasoconstriction not only incapacitates the splanchnic reservoir, but also prevents the redirection of blood flow from skeletal muscle beds and splanchnic tissues to the heart and brain.

**Regulator of Blood Coagulation**

The liver helps maintain normal blood clotting in numerous ways. It is responsible for the synthesis of factors involved in coagulation, anticoagulation, and fibrinolysis. All procoagulation factors derive from the liver, with the exception of the endothelial product, Von Willebrand factor (VWF). Although factor VIII clotting factor is produced mostly by hepatocytes, it is also produced in endothelial cells, and adequate functional levels of this factor are often present in patients with liver disease. Precursor proteins for vitamin K-dependent coagulation are synthesized in the liver. Vitamin K catalyzes the activation of these factors (II, VII, IX, and X). Vitamin K absorption depends on bile secretion into the gastrointestinal tract and transformation to active vitamin K by the action of gut bacteria. Vitamin K deficiency results in the production of nonfunctional factors II, VII, IX, and X. The liver also modulates platelet production through the synthesis of thrombopoietin.

The liver synthesizes anticoagulant factors such as antithrombin III, proteins C and S, and fibrinolytic factors. The liver is also responsible for clearance of activated coagulation factors, fibrinolysins, and tissue plasminogen activators. Appropriate clearance of these activated factors is essential for prevention or control of fibrinolytic states.

**Endocrine Organ**

The liver has important endocrine functions. It synthesizes and secretes essential hormones, including insulin-like growth factor-1 (IGF-1), angiotensinogen, and thrombopoietin. IGF-1, formerly called somatomedin, mediates the peripheral actions of hormones produced by other endocrine glands. Angiotensinogen is a precursor of angiotensin II, playing a major role in the regulation of fluid and electrolyte balance. Thrombopoietin stimulates bone marrow precursor cells to differentiate into platelet-generating megakaryocytes.

The liver is also a principal site of hormone biotransformation and catabolism. Thyroxine (T4) is actively taken up by the liver, where it is converted to triiodothyronine (T3). In addition, the liver synthesizes thyroid-binding globulin. Thus, the liver can influence the distribution of thyroid hormones between intracellular and extracellular compartments. Corticosteroids, aldosterone, estrogen, androgens, insulin, and antidiuretic hormone are all inactivated by the liver. The interaction of altered hormone levels and diminished hepatic synthesis of hormone-binding globulins with altered metabolism and receptor regulation leads to significant endocrine abnormalities in patients with liver disease.

**Erythrocyte Breakdown and Bilirubin Excretion**

Bilirubin is an end product of heme degradation. About 300 mg is formed daily, with approximately 75% of bilirubin precursors derived from breakdown of the heme moiety of hemoglobin from senescent erythrocytes by the reticuloendothelial system, and the remainder from breakdown of nonerythrocytic hemoproteins, including cytochrome P450. After reticuloendothelial cells phagocytize senescent erythrocytes and separate the protein portion of hemoglobin from the heme moiety, the heme is oxidized by the microsomal heme oxygenase system to biliverdin. Biliverdin is then rapidly converted to unconjugated bilirubin, which is then released into the bloodstream, where it avidly binds to albumin while being transported to the liver. The albumin-bilirubin complex passes through fenestrations in the sinusoidal-lining cells to enter into the space of Disse where direct contact with the hepatocyte plasma membrane occurs. Binding proteins on the plasma membrane dissociate the unconjugated bilirubin from albumin before uptake into the hepatocyte where the bilirubin binds to cytoplasmic protein and is transported to the endoplasmic reticulum. The bilirubin is then conjugated with carbohydrate moieties, especially glucuronic acid. This reaction is catalyzed by the enzyme uridine diphosphate-glucuronyl transferase; this water-soluble conjugated bilirubin is actively excreted into bile canaliculi, and only a small portion enters the plasma. Conjugated bilirubin passes unchanged through the biliary tree and proximal small intestine. In the terminal ileum and large intestine, bacteria convert most of the conjugated bilirubin to urobilinogen. The intestinal mucosa reabsorbs some urobilinogen, which reaches the liver by mesenteric blood. The liver efficiently extracts the urobilinogen and returns it to the intestine (enterohepatic circulation). Eighty percent of urobilinogens are excreted in the stool. Ten percent is excreted in the urine, and the rest is reabsorbed.

The liver also scavenges free hemoglobin from blood, helping conserve body iron. It synthesizes haptoglobin, which forms complexes with dimers of free intravascular hemoglobin. Receptors on hepatocytes remove these complexes from plasma and thereby prevent the loss of hemoglobin dimers in the urine.
Metabolic Functions of the Liver

Receiving blood from the intestine through the portal vein, the liver is ideally positioned to play a major role in the regulation of carbohydrate, protein, and lipid metabolism. The liver is also the major site for catabolism of various hormones involved in regulating metabolism, including insulin, glucagon, glucocorticoids, thyroxin, and growth hormone.

Carbohydrate Metabolism

The liver plays an important role in maintaining euglycemia. The normal liver receives the dietary carbohydrate intake through the portal circulation. Following a carbohydrate-containing meal, hyperglycemia is prevented by insulin-mediated hepatic extraction of glucose from the portal blood. Excess glucose in the liver is converted to glycogen. The liver can maximally store approximately 75 g of glycogen, which, when broken down, can provide up to 24 hours of available glucose. During fasting, hypoglycemia is initially prevented by glucagon-mediated glycogenolysis: glycogen stores are rapidly mobilized and converted to glucose, which is released into the circulation.

Once glycogen stores are depleted, the continued production of glucose requires muscle catabolism to provide the liver with amino acids. Through the process of gluconeogenesis, certain amino acids (e.g., alanine) undergo oxidative deamination and are converted to glucose. More limited amounts of glucose may be formed by conversion from lactate and glyceraldehyde. In patients with chronic liver disease, hyperglycemia occurs commonly because portosystemic shunting allows direct entry of glucose-rich portal venous blood into the systemic circulation. Hypoglycemia is a late manifestation of advanced liver disease, and when present, a variety of mechanisms may be involved, including impaired glycogen storage, glycogenolysis, and gluconeogenesis. Hypoglycemia may also be seen in patients with large hepatocellular carcinomas secondary to increased glucose uptake by the tumor.

Lipid Metabolism

The liver is the major site of synthesis of fatty acids from excess sugar, protein, and lipid. Fatty acids in the liver are esterified to form triglycerides, cholesterol esters, and phospholipids, and are incorporated into lipoproteins for transport to storage sites in adipocytes. Fatty acids are vital for cellular function because they represent a major energy source for heart and skeletal muscle. Cholesterol is an essential constituent of biological membranes and an important precursor of steroid hormones, vitamins, and bile acids. The body pool of cholesterol in the adult is kept fairly constant by balancing absorption and endogenous synthesis with metabolism and excretion. The liver plays a central role in cholesterol and lipoprotein metabolism. It regulates uptake and excretion of cholesterol and synthesizes the various enzymes and apoproteins needed for cholesterol transport. Biliary secretion of cholesterol and its degradation product, bile acid, represents the major mechanism for elimination of cholesterol from the body.

In the fasted state, fatty acid beta-oxidation to acetyl coenzyme A (acetyl-CoA) in the liver is markedly stimulated by increased glucagon secretion. Acetyl-CoA is further oxidized to carbon dioxide and water or converted to ketone bodies, which are important fuels for extrahepatic organs (e.g., brain, muscle, kidney). Liver dysfunction may result in significant disturbances of cholesterol and lipoprotein metabolism.

Amino Acid Metabolism

The liver is the major site of protein and amino acid metabolism. After ingestion of protein, proteolytic enzymes in the digestive tract efficiently hydrolyze ingested proteins, yielding free amino acids that are absorbed by the gut and transported to the liver via the portal vein. Several distinct sinusoidal membrane transport systems then convey the amino acids into the hepatocyte. When necessary, the liver is able to synthesize the nonessential amino acids and use them to synthesize a large number of biologically essential proteins.

Protein catabolism occurs primarily in the liver. Proteins enter the hepatocyte through endocytosis and are then degraded into their component amino acids in the lysosomes. These may then form substrates for glucose production through gluconeogenesis, enter lipid metabolic pathways, or be further catabolized via transamination and deamination to form keto-acids, ammonia (NH₃), and glutamine. The urea cycle converts ammonia and most other nitrogenous excretory products into urea, which is excreted by the kidney. Patients with significant liver dysfunction may not have the capacity to eliminate nitrogen equivalents adequately through the urea cycle. Consequently, the serum ammonia level rises and hepatic encephalopathy may develop. Because urea is synthesized in the liver, a
normal or low blood urea nitrogen concentration in patients with advanced liver disease provides no assurance that glomerular filtration rate (GFR) is normal.

**Synthesis of Important Proteins**

The liver produces a vast assortment of proteins with important extrahepatic functions. Hepatocytes synthesize albumin; acute-phase proteins; all the coagulation factors and their inhibitors, except for factor VIII; ceruloplasmin; and most of the alpha-globulins and beta-globulins. Albumin accounts for nearly 10% of the protein synthesized by the liver. It constitutes about 60% of total plasma protein and is the primary determinant of the colloid oncotic pressure. Approximately 40% of the total exchangeable albumin pool is located intravascularly, and its serum half-life is about 20 days. This long half-life is one reason why the serum albumin level is not a reliable indicator of the liver's residual synthetic capacity in acute hepatic disease. The serum albumin level is affected by disturbances in synthesis, catabolism, and distribution. The normal liver synthesizes albumin at a rate of approximately 200 g/kg per day. Synthesis may be affected by several factors, including liver disease, dietary availability of amino acids, hormonal balance, plasma oncotic pressure, and heavy alcohol intake. Albumin serves as an important transport vehicle for metabolites (e.g., unconjugated bilirubin, heme, fatty acids), hormones (e.g., thyroxine, cortisol), and metals. Albumin also binds to a variety of pharmacologic agents; therefore, hypoalbuminemia has important consequences for the pharmacokinetics and pharmacodynamics of commonly administered drugs.

**Immunologic Function**

The liver is the largest organ in the reticuloendothelial system. Sinusoidal and perisinusoidal cells of the liver defend the body against microbial invaders and modulate inflammatory and immune responses to foreign materials. Pit cells, sparsely located in the perisinusoidal spaces, possess natural killer and neuroendocrine activities. Kupffer cells may constitute up to 10% of the total hepatic mass. These tissue macrophages police sinusoidal blood flow, filtering out toxins, bacteria, and debris that gain access from the gastrointestinal tract. They are aggressively involved in immune surveillance, participating in phagocytosis, cytolysis, and antigen presentation to T cells, and also may be involved in regulation of T-cell proliferation. Kupffer cells produce a variety of inflammatory mediators and cytokines that initiate and modulate both local and systemic effects of hepatic injury. Impairment of Kupffer cell function may be an important harbinger of sepsis or multiorgan system failure, particularly in the setting of severe gastrointestinal pathology or splanchnic ischemia.

**Pharmacokinetics**

Drug metabolism is primarily a hepatic event. The liver influences the plasma concentration and systemic availability of most orally and parenterally administered drugs. Through its synthesis of drug-binding proteins, the liver affects the partitioning of drugs into the various compartments of the body (apparent volume of distribution, Vd). Plasma proteins, especially albumin and α1-acid glycoprotein, act as sinks to decrease free drug concentrations. Consequently, changes in the concentration of plasma proteins often modify dose-response relationships of drugs.

Hepatic clearance is the sum of all processes by which the liver eliminates a drug from the body. Hepatic biotransformation refers to the metabolism of drugs by hepatocytes with the goal of changing them into inactive water-soluble substances that can be excreted into the bile or urine for elimination from the body. A series of reactions that have been classified as phase 1 and phase 2 participate in these processes. Most drugs contain lipophilic functional groups to facilitate penetration of membrane barriers, thereby expediting gastrointestinal absorption. These same lipophilic groups inhibit excretion, owing to a high degree of protein binding and renal tubular reabsorption. By converting lipophilic substances to metabolites that can be excreted, hepatic enzymes detoxify drugs and terminate their pharmacologic activity. In general, phase 1 reactions (oxidation, reduction, N-dealkylation) modify structural features of drugs to render them more polar than the original compound. Most phase 1 reactions involve the participation of a group of cytochrome P450 isozymes, which are localized in the hepatic microsomes. In phase 2 reactions, catalyzed by transferase enzymes, the water solubility of the product is enhanced beyond that achieved by phase 1 reactions alone. The chemical groups generated by phase 1 reactions serve as receptors for conjugation with polar substances such as sulfate, glucuronic acid, and glutathione. The products of phase 2 reactions are usually less toxic and less biologically active than those of the parent compound. Phase 1 reactions are much more susceptible to inhibition by advanced age or hepatic diseases than are phase 2 reactions.

The ability of the liver to metabolize a drug is referred to as its intrinsic metabolic clearance. Intrinsic clearance, which reflects the fraction of the delivered drug load that is metabolized or extracted during a single pass through the liver, provides the basis for classifying drugs as high-, intermediate-, or low-clearance compounds. High-
clearance drugs (e.g., lidocaine, diphenhydramine, or metoprolol) are so efficiently metabolized that their hepatic clearance approaches the rates at which they traverse the liver (i.e., total hepatic blood flow) (Fig. 39-7). Therefore, hepatic blood flow determines the liver’s ability to eliminate high-clearance drugs. Low-clearance drugs (e.g., diazepam), however, are metabolized at rates that are usually far below their flow rates through the liver; therefore, their hepatic clearances are relatively independent of hepatic blood flow (see Fig. 39-7). Factors that increase the free fraction of drugs (e.g., hypoalbuminemia) are much more consequential for low-extraction than high-extraction drugs. The clearance of low-extraction drugs increases almost linearly as the free fraction increases (Fig. 39-8). Patients with significant liver disease may have marked alterations of pharmacokinetics and pharmacodynamics. Portosystemic shunts allow orally administered drugs to bypass the liver, thereby reducing first-pass clearance. This and the reduction in total hepatic blood flow seen in patients with liver disease prolong the terminal half-life and increases the systemic effects of high-extraction drugs. The dosage of these agents should be reduced by as much as 50%. Hypoalbuminemia causes an increase in the free plasma drug concentration, not only increasing drug effects, but also facilitating elimination of compounds with low hepatic extraction ratios. The volume of distribution of some drugs will be increased in patients with hypoalbuminemia and ascites.

**FIGURE 39-7.** Relationship between hepatic clearance (*ordinate, on left*) and liver blood flow (*abscissa*) as determined by the extraction ratios (ERs) of the drug (*ordinate, on right*). Hepatic clearances of compounds with low extraction ratios are nearly independent of liver blood flow, whereas the clearances of compounds with high extraction ratios vary almost directly with changes in hepatic blood flow. The arrows indicate the normal physiologic range of liver blood flow. (Reprinted with permission from Wilkinson GR, Shand DG: A physiological approach to hepatic drug clearance. Clin Pharmacol Ther 18:377, 1975.)
The complex and poorly quantifiable effects of hepatic dysfunction on drug disposition may render pharmacokinetic, and even pharmacodynamic, predictions precarious. The rational selection of medications for patients with severe liver dysfunction mandates a careful risk–benefit analysis that integrates both pharmacodynamic and pharmacokinetic concerns. At times, cirrhotic patients with coexisting diseases will be better served by use of a hepatically cleared agent (superior efficacy, fewer untoward effects) than by one whose clearance is primarily extrahepatic. In such cases, careful titration of medication is imperative to achieve the desired pharmacologic responses with minimal adverse effects.

**ASSESSMENT OF HEPATIC FUNCTION**

**Laboratory Evaluation of Hepatic Function**

A broad array of biochemical tests is available to assess the multiple functions of the liver and evaluate patients with suspected or established liver disease (Table 39-1). Although collectively called "liver function tests" (LFTs), many (e.g., aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) do not assess a function of the liver but rather are indicative of liver cell injury or dysfunction. LFTs are used to screen for the presence of liver disease, suggest a general category of disease as the etiology, assess prognosis, and monitor the effectiveness of therapy. Many of the routine tests are not specific for liver disease; however, when combined in a battery of tests, the sensitivity and specificity for liver disease is high.

<table>
<thead>
<tr>
<th>TABLE 39-1 Blood Tests and the Differential Diagnosis of hepatic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>BILIRUBIN</td>
</tr>
</tbody>
</table>

FIGURE 39-8. Relationship between hepatic extraction and fraction of unbound drug in blood: increasing free fraction (more unbound drug) usually produces increased extraction. This phenomenon is of greater importance for low-extraction drugs (with almost a direct linear change in extraction ratio with increasing free fraction) than for high-extraction drugs because the latter are almost completely cleared, regardless of extent of binding (nonrestrictive binding). The hepatic clearance (CL) reflects the changes in extraction ratio (E) if blood flow (Q) is constant (CL = Q·E). (Reprinted with permission from Wilkinson GR, Shand DG: A physiological approach to hepatic drug clearance. Clin Pharmacol Ther 18:377, 1975.)
LFTs can be classified into several broad categories. These include tests that reflect (1) hepatocellular damage; (2) obstructed bile flow; (3) hepatic synthetic function; (4) hepatic uptake, conjugation, and excretion; and (5) other aspects of liver function.

### Indices of Hepatocellular Damage

Increased serum activities of AST (formerly, serum glutamic oxalacetic transaminase or SGOT) and ALT (formerly, serum glutamic pyruvic transaminase or SGPT) are detected when there is hepatocellular injury and necrosis. Serum levels of AST and ALT are elevated in almost all types of hepatic disease. ALT is localized primarily to the liver, whereas AST is present in a wide variety of tissues, including liver, heart, skeletal muscle, kidney, and brain. An isolated elevation of the AST level is typically seen in cardiac or muscle disease. Mild elevations of ALT and AST (less than 3-fold) are seen in fatty liver, nonalcoholic steatohepatitis, drug toxicity, and chronic viral hepatitis. Larger increases (3- to 22-fold) are seen in patients with acute hepatitis or exacerbation of chronic hepatitis (alcoholic hepatitis). The highest concentrations are seen in drug-induced or toxin-induced hepatocellular necrosis (including anesthetics), severe viral hepatitis, and ischemic hepatitis complicating circulatory shock.

AST and ALT levels do not correlate with prognosis. A declining level may reflect either recovery from injury or a poor prognosis because of a paucity of surviving hepatocytes. The serum AST/ALT ratio may be helpful.

<table>
<thead>
<tr>
<th>Overload (Hemolysis)</th>
<th>Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aminotransferases</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Alkaline phosphatase</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Bilirubin</strong></td>
<td>Unconjugated</td>
</tr>
<tr>
<td><strong>Serum proteins</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Prothrombin time</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Blood urea nitrogen</strong></td>
<td>Normal</td>
</tr>
<tr>
<td><strong>Sulfobromophthalein/indocyanine green</strong></td>
<td>Normal</td>
</tr>
</tbody>
</table>

diagnostically. A ratio of >2 is characteristically found in alcoholic liver disease, while in viral hepatitis the ratio is typically <1.

Lactate dehydrogenase (LDH) is usually included in liver biochemistry panels. Markedly increased serum levels may be seen in hepatocellular necrosis, shock liver, or hemolysis associated with liver disease. However, LDH has poor diagnostic specificity for liver disease and even measurement of LDH isoenzymes has limited clinical usefulness.

Glutathione S-transferase (GST) is found in multiple organs, but plasma elevation of isoenzyme B is a sensitive indicator of liver damage. GST is rapidly released into the circulation following hepatic injury, and because of its short plasma half-life (90 minutes), monitoring of plasma GST concentrations permits rapid identification of continuing or resolving cellular damage. GST is most abundant in centrolobular (zone 3) hepatocytes, which are most susceptible to injuries from circulatory disturbances and toxic products of drug metabolism. Following such injuries, GST elevations may be disproportionately greater than increases of serum transaminases, which are more highly localized to the periportal (zone 1) hepatocytes.

**Indices of Obstructed Bile Flow**

Alkaline phosphatase (AP) is a family of isoenzymes found in multiple organs, including the liver, bone, kidney, intestines, placenta, and leukocytes. In healthy individuals, most circulating AP originates from the liver or bone. In the liver, AP is concentrated in the microvilli of the bile canaliculi and the sinusoidal surface of hepatocytes. Elevations of serum AP disproportionate to changes of AST and ALT occur with intrahepatic or extrahepatic obstruction to bile flow. It is a highly sensitive test for assessing the integrity of the biliary system. Elevated serum levels of AP may also result from infiltrative liver diseases such as metastatic cancer. Mildly elevated levels of serum AP are nonspecific and may be seen in cirrhosis, hepatitis, or congestive heart failure. The liver is the source of an elevated AP in the majority of cases, but in up to one-third, no evidence of liver disease is found. During pregnancy, AP can nearly double from placental release of the enzyme.

5′-Nucleotidase (5′NT) is an alkaline phosphatase that degrades specific nucleotides. Although it is present in most human tissues, elevated serum levels are believed to be solely of hepatobiliary origin and may reflect the detergent action of bile salts on plasma membranes, which is needed for release of the enzyme into the circulation. 5′NT is markedly increased with intrahepatic or extrahepatic biliary obstruction, with more modest increases seen with other hepatocellular disorders. Serum levels correlate closely with AP levels, and because serum 5′NT is so specific for liver diseases, it is used to determine if an elevated serum AP level is of hepatic origin.

Gamma glutamyl transferase (GGT) is a membrane-bound enzyme widely distributed in a variety of tissues, including the liver. It is found in high concentrations in epithelial cells lining biliary ductules. Serum GGT is the most sensitive laboratory indicator of biliary tract disease. However, because it is ubiquitous, an elevated GGT has limited usefulness due to its poor specificity and has largely been replaced by 5′NT measurements to determine if an elevated AP is of hepatic origin.

Bilirubin is an endogenous organic anion derived primarily from the degradation of hemoglobin released from aging red blood cells. Measurement of serum bilirubin levels is central to the evaluation of hepatobiliary disorders. Serum levels of bilirubin are determined by the van den Bergh reaction, which separates bilirubin into two fractions: a water-soluble direct-reacting form representing conjugated bilirubin and a lipid-soluble indirect-reacting form representing unconjugated bilirubin.

Serum bilirubin levels are measured to confirm the severity of jaundice and to determine the extent of its conjugation. Hyperbilirubinemia has a wide variety of causes (Table 39-2) and is classified as either predominantly unconjugated or predominantly conjugated. Serum concentrations of unconjugated bilirubin between 1 and 4 mg/dL usually indicate a disorder of bilirubin metabolism, such as excessive production (hemolysis), impaired transport into hepatocytes, or defective conjugation by hepatocytes. Even in cases of severe hemolysis, the total serum bilirubin is rarely above 5 mg/dL in the presence of normal liver function. Serum bilirubin levels above 5 mg/dL, or lower levels in association with other LFT abnormalities, usually signify the presence of liver disease. Conjugated hyperbilirubinemia results from impaired intrahepatic excretion of bilirubin or extrahepatic obstruction. With complete biliary tract obstruction, the maximal serum bilirubin level will rarely exceed 35 mg/dL due to renal excretion of conjugated bilirubin. Therefore, total bilirubin levels above 35 mg/dL usually signify severe parenchymal liver disease in association with hemolysis or renal failure.
Indices of Hepatic Synthetic Function

The liver synthesizes and releases a variety of proteins, including albumin and the coagulation factors. Measurement of serum albumin level and assays of coagulation function are the most widely used methods for assessing hepatic synthetic function. Proper interpretation of these tests requires an understanding of the patient's clinical status. Many factors influence the serum albumin level independent of hepatic synthesis. Protein-losing enteropathy, burns, nephrotic syndrome, increased vascular permeability, nutritional deficiency, increased catabolism, and fluid retention can all depress serum albumin levels. A decreasing serum albumin concentration indicates worsening hepatic function in patients with chronic liver disease if none of these other factors is present. Because the half-life in serum is as long as 20 days, the serum albumin level is not a reliable indicator of hepatic protein synthesis in acute liver disease.

In contrast, the prothrombin time (PT) and international normalized ratio (INR) are sensitive indicators of severe hepatic dysfunction (whether patients have acute or chronic liver disease) because of the short half-life of factor VII. However, because most of the coagulation factors are present in quantities that far exceed requirements for normal coagulation, mild-to-moderate hepatic disease may not be detected by measurement of the PT. In acute or chronic hepatocellular disease, the PT may be a useful prognostic indicator. A progressively increasing PT is usually ominous in patients with acute hepatocellular disease, suggesting an increased likelihood of acute hepatic failure. Prolongation of the PT also suggests a poor long-term prognosis in chronic liver disease.

PT depends on normal hepatic synthesis of clotting factors and sufficient uptake of vitamin K. Absorption of vitamin K from the gastrointestinal tract requires adequate biliary secretion of bile salts. In patients with obstructive jaundice, a prolonged PT may be a manifestation of vitamin K deficiency rather than of impaired hepatic synthetic function.

| TABLE 39-2 Causes of Hyperbilirubinemia |

- **UNCONJUGATED (INDIRECT)**
  
  Excessive bilirubin production (hemolysis)
  Immaturity of enzyme systems
  Physiologic jaundice of newborn
  Jaundice of prematurity
  Inherited defects
    - Gilbert's syndrome
    - Crigler-Najjar syndrome
  Drug effects

- **CONJUGATED (DIRECT)**
  
  Hepatocellular disease (hepatitis, cirrhosis, drugs)
  Intrahepatic cholestasis (drugs, pregnancy)
  Benign postoperative jaundice, sepsis
  Congenital conjugated hyperbilirubinemia
    - Dubin-Johnson syndrome
    - Rotor's syndrome
  Obstructive jaundice
  Extrahepatic (calculus, stricture, neoplasm)
  Intrahepatic (sclerosing cholangitis, neoplasm, primary biliary cirrhosis)

function. Prolongation of the PT is not specific for liver disease. It may result from congenital coagulation factor deficiencies, disseminated intravascular coagulopathy, vitamin K deficiency, or the use of drugs that antagonize the prothrombin complex, such as Coumadin.

Indices of Hepatic Blood Flow and Metabolic Capacity
Elimination of the dye indocyanine green (ICG) from the blood provides an estimate of hepatic perfusion and hepatocellular function because it is highly extracted (70 to 95% by the liver following an intravenous injection). Acute changes in hepatic circulation and function can be detected by this test and the ICG method has been a standard technique for comparing effects of various anesthetics on hepatic blood flow.

Hepatic function can also be assessed with substances that are metabolized selectively by the liver. Lidocaine is metabolized by oxidative N-demethylation to monoethylglycinexylidide (MEGX). Its concentration 15 to 30 minutes after intravenous injection of a single dose of lidocaine can be used as a quantitative measure of liver function. The MEGX test may have prognostic value in patients with end-stage liver disease; in one study of well-compensated cirrhotic patients, this test was able to identify patients at increased risk for developing postoperative complications following hepatic resection for carcinoma. Additional metabolic tests for assessing hepatic function include antipyrine clearance from plasma, aminopyrine breath test, caffeine breath test, galactose elimination capacity, and the maximum rate of urea synthesis. These tests have not gained wide acceptance in the United States, and their precise role in clinical practice remains uncertain.

Miscellaneous Tests
Several other laboratory tests are available for the diagnosis of liver disease but provide no specific information about hepatic function. These include specific serologic tests for hepatitis viruses, autoantibody measurements useful for the diagnosis of primary biliary cirrhosis and the classification of autoimmune hepatitis; specific protein measurements (ceruloplasmin, ferritin, α1-antitrypsin, and α1-fetoprotein) useful for the diagnosis of Wilson’s disease; hemochromatosis; α1-antitrypsin deficiency and hepatocellular carcinoma, respectively; and serum ammonia often followed in patients with, or at risk for, developing hepatic encephalopathy.

Hepatobiliary Imaging
Selection of the most appropriate hepatobiliary imaging technique in a patient depends on the clinical presentation (history, physical examination, and LFT results), an understanding of the uses and limitations of each technique, and whether the test is for diagnosis alone or for therapeutic intervention as well. Plain radiography has a limited role in the evaluation of hepatobiliary disease. Abdominal radiographs can be useful for calcified or gas-containing lesions that may be overlooked or misinterpreted by ultrasonography. These lesions include calcified gallstones, chronic calcific pancreatitis, gas-containing liver abscesses, portal venous gas, and emphysematous cholecystitis.

Ultrasonography is the most commonly used hepatobiliary imaging technique. It has the advantages of low cost, portability, and avoidance of the use of ionizing radiation. Ultrasonography is the primary screening test for hepatic disease, gallstones, and biliary tract disease that may be suspected because of symptoms, abnormal LFT, hepatomegaly, jaundice, or suspicion of a mass lesion. It is the best method for detecting gallstones and confirming the presence of extrahepatic biliary obstruction. It also may be useful for determining the thickness of the gallbladder wall, detecting the presence of ascites, demonstrating portal or hepatic vein thrombosis, evaluating the patency of portosystemic shunts in patients with recurrent variceal bleeding after shunt surgery, and directing thin-needle biopsy of hepatic mass lesions. Its major limitations are its dependence on the operator’s skill and its inability to penetrate bone or air (including bowel gas), which may prevent complete examination of the abdominal organs.

A variety of radioisotopes can be used to study the anatomy and function of the liver and biliary system. Radioisotope scanning of the liver seldom provides a precise diagnosis, and these tests have largely been supplanted by ultrasonography and computed tomography (CT) scanning. However, radioisotope scanning of the biliary tract remains an important investigative tool in patients with suspected acute cholecystitis. Radioisotopes that are cleared rapidly by hepatocytes and excreted into bile permit rapid visualization of the biliary tract. Visualization of the gallbladder rules out obstruction of the cystic duct, while visualization of the biliary tree and common bile duct without the gallbladder confirms obstruction of the cystic duct and presence of cholecystitis.
CT is a complementary examination to ultrasonography and provides information on liver texture, gallbladder disease, bile duct dilatation, and mass lesions of the liver and pancreas. It provides better and more complete anatomic definition than ultrasonography and is less operator dependent. Lesions can be biopsied under CT guidance. The disadvantages of CT scanning are radiation exposure and cost.

The role of magnetic resonance imaging (MRI) for the evaluation of hepatobiliary disease is continually evolving. The algorithm for noninvasive biliary imaging has been markedly altered by the development of magnetic resonance cholangiopancreatography, which has dramatically reduced the need for direct cholangiography for visualization of the bile and pancreatic ducts, and for delineating the most proximal extent of biliary tract obstruction when planning for operative resection or drainage.

Percutaneous transhepatic cholangiography (THC) involves the direct percutaneous injection, through a 22-gauge needle, of contrast into bile ducts in the liver under fluoroscopic guidance. THC may be used to determine the level and cause of biliary obstruction, confirm the presence of cholestasis without obstruction, and evaluate whether a proximal cholangiocarcinoma is surgically resectable. THC can be used for balloon dilation of biliary strictures via a catheter inserted through the tract, for placement of an internal stent to relieve obstruction, or for placement of an external drain.

Endoscopic retrograde cholangiopancreatography (ERCP) uses endoscopy to visualize the ampulla of Vater and guide insertion of a guidewire and catheter through the ampulla to permit selective injection of contrast material into the pancreatic and common bile ducts, which are then imaged radiographically. ERCP has the advantage over THC of not requiring dilation of the biliary tree to achieve a very high procedural success rate. ERCP is the imaging technique of choice in patients with choledocholithiasis because a sphincterotomy and stone extraction can often be performed. Stones can also be removed with this technique in patients with acute cholangitis and severe gallstone pancreatitis. ERCP also permits biopsies, brushings, balloon dilation, and stent insertion to relieve biliary obstruction caused by tumors.

Liver Biopsy
Liver biopsy continues to have a central role in the evaluation of patients with suspected liver disease because it provides the only means of determining the precise nature of hepatic damage (necrosis, inflammation, steatosis, or fibrosis). Liver biopsy plays a key role in the evaluation of otherwise unexplained abnormalities of liver enzymes in patients with or without hepatomegaly. It is used in patients with chronic hepatitis to determine the nature and extent of hepatic injury and degree of inflammation, which for patients with chronic hepatitis C, will be used to determine if antiviral therapy should be initiated. Liver biopsy is also an important tool for determining the etiology of abnormal LFT in the post liver transplant patient (see chapter 53). The presence of coagulopathy (e.g., PT that is 3 seconds greater than control, platelet count <60,000 cells/µL), however, contraindicates percutaneous liver biopsy, although transjugular liver biopsy can be performed safely in these patients.

Hepatic and Hepatobiliary Diseases
Classification of Liver Diseases
For the purposes of the following discussion, liver diseases are divided into two large heterogeneous groups: parenchymal diseases (e.g., viral hepatitis, steatohepatitis, cirrhosis) and cholestatic diseases (e.g., intrahepatic and extrahepatic biliary obstruction). Some diseases are characterized by features of both parenchymal dysfunction and cholestasis.

Prevalence of Hepatobiliary Disease
More than 100 distinct hepatic diseases have been described. Currently, nearly 10% of the American population (25 million) has some form of hepatobiliary disease. Hepatitis B or C afflicts more than 5 million Americans. About 50% of those with hepatitis C may develop cirrhosis, which currently accounts for between 13,000 to 15,000 deaths each year. Alcoholic liver disease remains a problem, becoming severe in 10 to 15% of those who consume large amounts of alcohol over a prolonged period.

Parenchymal Diseases
Viral Hepatitis
Acute hepatitis usually results from a viral infection, although it may also be caused by drugs and toxins. Viral hepatitides are important causes of perioperative hepatic dysfunction. The diagnosis of viral hepatitis depends on the appearance of clinical signs and symptoms, laboratory findings, serologic assays, and, on occasion, liver biopsy. During the incubation period, patients are often asymptomatic and may undergo surgical procedures. When increased ALT and AST and/or jaundice develop postoperatively, it is essential that a comprehensive serologic evaluation be performed to document the viral origin for the liver damage.

Classic acute hepatitis is caused by one of five viruses: hepatitis A (HAV), hepatitis B (HBV), hepatitis C (HCV), hepatitis D (HDV, delta), and hepatitis E (HEV). In the United States, approximately 50% of reported cases of acute viral hepatitis are caused by HBV, 30% by HAV, and 20% by HCV. Chronic hepatitis can occur following HBV, HCV, and HDV infections. All five types of viral hepatitis have similar clinical and laboratory features. Patients may remain asymptomatic, develop influenza-like symptoms, become jaundiced, or develop acute hepatic failure.

HAV infection (infectious hepatitis) is a highly contagious enterovirus transmitted by the intake of fecal-contaminated food. It is not transmitted by blood transfusion. Viremia is present for several days prior to the onset of clinical symptoms. Virus is shed in stool for 14 to 21 days before the onset of jaundice. Patients are usually not infectious after 21 days. There are no chronic carriers, and chronic liver disease does not occur. Fulminant hepatic failure is rare (0.14 to 2%) in the absence of preexisting liver disease. Patients with HBV who acquire a HAV infection typically have an uncomplicated clinical course. In contrast, 41% of patients with chronic hepatitis C who acquire a HAV superinfection progress to fulminant hepatitis with a 35% fatality rate.13

HBV is primarily transmitted through percutaneous inoculation of infected serum or blood products. HBV is present in the serum and body secretions of most patients early in the course of acute hepatitis B. The surface coat of the virus is composed of a polypeptide that acts as the major hepatitis B surface antigen (HBsAg). Development of serum antibodies to HbsAg (anti-HbsAg) confirms immunity. Individuals who have detectable HbsAg for more than 6 months have a chronic HBV infection.

HCV (formerly, non-A, non-B hepatitis), which was discovered in 1989, was the major cause of transfusion-related hepatitis until the 1990s. It is also transmitted by percutaneous inoculation of infected serum or blood products, occupational exposure to blood or blood products, and intravenous drug abuse. Hepatitis C is the most common bloodborne infection in the United States; it accounts for 40% of chronic liver disease. Fortunately, serologic tests for HCV now exist. Because of their use in screening donated blood, HCV has almost been eliminated as a cause of posttransfusion hepatitis. HDV is an RNA strand that coinfects with and requires the helper function of HBV for its replication and expression. HDV may be acquired simultaneously with HBV or may be a superinfection of a patient with prior HBV infection. HBV and HDV coinfection substantially increases the likelihood of fulminant hepatitis and death.

HEV is an enterically transmitted virus that has epidemiologic features resembling HAV. HEV infections occur primarily in Asia, Africa, and Central America.

Other important but infrequent causes of viral hepatitis include cytomegalovirus, Epstein-Barr virus, and herpes simplex. These viruses typically produce benign, anicteric disease and often escape detection preoperatively. However, in rare circumstances, particularly in immunocompromised patients, they can disseminate, causing acute hepatitis, fulminant hepatic failure, and death.14

Acute viral hepatitis occurs after an incubation period that varies with the specific virus involved. The mean incubation period for HAV is 4 weeks, for HBV 12 weeks, and for HCV 7 weeks. Clinical disease is often heralded by the development of constitutional symptoms such as anorexia, nausea, vomiting, and low-grade fever. Dark urine and clay-colored stools usually precede the onset of jaundice. At this point, the liver may be enlarged and tender. Recovery usually takes weeks to months. Many patients with acute viral hepatitis never become clinically jaundiced. AST and ALT levels begin to rise during the prodromal phase and usually reach a peak between 400 to 4,000 IU when the patient is clinically jaundiced. Serologic tests are the mainstay for the diagnosis of viral hepatitis. The diagnosis of hepatitis A is based on the detection of serum immunoglobulin M (IgM) antibody to the HAV capsid or HAV RNA in stool during acute illness; recovery is associated with immunoglobulin G anti-HAV antibody, which confers long-lasting immunity to recurrent HAV infection. The diagnosis of HBV infection is usually made by identifying HbsAg in serum. HbsAg may be present in serum as early as 7 days after HBV infection. Infrequently, levels of HbsAg are too low to be detected during acute HBV infection, and in such cases, the diagnosis can be established by the identification of IgM antibody to the HBV core antigen (IgM anti-Hbc). Hepatitis B antigen (HbeAg) follows the pattern of HbsAg, and recovery is heralded by the disappearance of this antigen, while persistence of HbeAg identifies patients whose blood remains infective. Development of antibody to HbsAg (anti-Hbs) is seen in recovered patients.
The serologic diagnosis of hepatitis C can be made by demonstrating the presence in serum of anti-HCV or the presence of HCV RNA. HBD infection can be identified by demonstrating the presence of anti-HDV antibody.

**Nonviral Hepatitis**

**Toxin and Drug-Induced Hepatitis**

Acute hepatitis may follow the ingestion, inhalation, or parenteral administration of pharmacologic and chemical agents. Drugs and chemicals that are directly toxic to the liver (carbon tetrachloride, acetaminophen, α-amanitin from the toxic mushroom, *Amanita phalloides*) predictably produce dose-dependent liver injury. Each of these direct hepatotoxins produces a pattern of histologic injury that is reasonably characteristic and reproducible. Clinical manifestations of liver injury usually occur within 1 to 2 days of exposure. Acetaminophen not only causes fulminant hepatic failure following ingestion of extremely large doses (suicide attempts), but can also produce chronic liver injury with analgesic doses in susceptible individuals (malnutrition, chronic alcoholism).15

Other drugs (nonsteroidal anti-inflammatory agents, volatile anesthetics, antibiotics, antihypertensives, anticonvulsants) infrequently cause liver injury. These idiosyncratic drug reactions are unpredictable, and the response is not dose dependent. Hepatitis may develop during or shortly after exposure to the drug, but more commonly, clinical signs of liver dysfunction occur 2 to 6 weeks after initiation. Treatment of toxin-induced and drug-induced hepatitis is largely supportive. Failure to discontinue the offending drug promptly may result in progressive hepatitis and death. Hemodialysis may be useful following ingestion of *Amanita phalloides*, whereas *N*-acetylcysteine is used to treat patients with potentially hepatotoxic ingestions of acetaminophen. Liver transplantation may be lifesaving in patients with fulminant hepatitis, resulting from toxin or drug ingestion.

**Toxic Acute Hepatitis and Volatile Anesthetics**

Halothane was introduced in the United States in 1958; concerns linking this agent to acute hepatitis were raised shortly thereafter. To determine the incidence of massive hepatic necrosis after halothane anesthesia, the Committee on Anesthesia of the National Academy of Sciences launched one of the largest epidemiologic studies ever completed: the National Halothane Study.16 From 1959 to 1962, 856,000 anesthetics were retrospectively reviewed. The incidence of fulminant hepatic necrosis terminating in death associated with halothane was found to be 1 per 35,000 anesthetics. The incidence of nonfatal hepatitis, however, may be as low as 1 in 3,000.17 The association prompted a dramatic decrease in the use of halothane, especially in adult patients. Other volatile anesthetic agents have been reported to cause hepatitis, but at a much lower rate (Table 39-3).

<table>
<thead>
<tr>
<th>AGENT</th>
<th>YEAR INTRODUCED IN UNITED STATES</th>
<th>NO. OF CASES OF HEPATITIS</th>
<th>PERCENTAGE OF ANESTHETIC METABOLIZED</th>
<th>FLUOROACETYL METABOLITES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halothane</td>
<td>1958</td>
<td>&gt;500</td>
<td>20-46</td>
<td>Yes</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1972</td>
<td>~50</td>
<td>2.5-8.5</td>
<td>Yes</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1981</td>
<td>6</td>
<td>0.2-2</td>
<td>Yes</td>
</tr>
<tr>
<td>Desflurane</td>
<td>1993</td>
<td>1</td>
<td>0.02</td>
<td>Yes</td>
</tr>
</tbody>
</table>
The classic presentation of volatile anesthetic-associated hepatitis includes fever, anorexia, nausea, chills, myalgias, and rash, followed by the appearance of jaundice 3 to 6 days later. The syndrome characteristically develops after minor uneventful procedures of brief duration (<30 minutes). Overt jaundice indicates severe disease and portends a mortality rate as high as 40%. Other predictors of poor prognosis include a short latency between the anesthetic and the onset of symptoms, certain demographic factors (age >40, obesity), and severe hepatic dysfunction.18

The single most important risk factor for halothane hepatitis is prior exposure to halothane. Previous exposure has also been reported as a factor in isoflurane-associated hepatitis.19 Of the patients who develop jaundice after halothane, 71 to 95% have had at least one prior exposure to this agent.20 Severe reactions occur nearly 10 times more often in patients who have had multiple exposures to halothane than in those having their first halothane anesthetic.21

Demographic factors also provide important information about the risk of developing halothane hepatitis. Obese women appear to be more likely than their nonobese counterparts to contract halothane hepatitis. The disease may also have a genetic basis.22 Some ethnic groups, such as Mexican Americans, seem to be at greater risk, and chromosomal differences have been noted between patients who recovered from halothane hepatitis and halothane-treated patients who never had the disease.23,24 For reasons that are not yet clear, age is also a significant risk factor. Approximately 50% of the cases of halothane-associated fulminant hepatic failure occur in patients older than 50, whereas children are highly resistant to the development of halothane hepatitis.21,25,26 The rare cases documented in children have involved multiple exposures to halothane.27 Notably, neither preexisting liver disease nor concomitant administration of medication has been identified as a risk factor for halothane hepatitis.

Although the incidence of hepatitis appears to correlate with the degree of metabolism of the various agents, the paucity of cases reported with anesthetics other than halothane has cast doubt that any of these anesthetics was actually involved in the hepatic complications (see Table 39-3).

The observation that halothane hepatitis is associated with repeated exposure has led investigators to postulate an immune reaction. Of the halothane taken up during anesthesia, 20 to 46% is metabolized, compared with 2.5 to 8.5% for enflurane, 2 to 5% for sevoflurane, 0.2 to 2% for isoflurane, and 0.02% for desflurane.28,29,30 Each anesthetic, with the exception of sevoflurane, is oxidized via cytochrome P450 2E1 to yield highly reactive intermediates that bind covalently (acylation) to a variety of hepatocellular macromolecules (Fig. 39-9). Halothane anesthesia induces both neoantigens (arising via the reaction of TF-acetyl chloride with hepatic proteins) and autoantigens (lacking TF-acetyl adducts).31,32,33,34,35 Presumably, the TF-acetyl moiety acts as a hapten and enhances the immune recognition of the carrier protein. In susceptible people, these altered hepatic proteins may trigger an immunologic response that causes massive hepatic necrosis.36
Halothane hepatitis is idiosyncratic, affecting only a tiny fraction of those anesthetized with this agent. Neither the incidence nor the severity of the reaction correlates with the dose of halothane administered. The disease has a latency of days, unlike the hepatic injury produced by severe hypoxia or a potent cytotoxin, which typically appears within hours of the insult. Moreover, it is usually accompanied by laboratory findings that are characteristic of an immunologically mediated disorder, such as peripheral eosinophilia, circulating immune complexes, organ nonspecific autoantibodies, and antibodies that bind to antigens isolated from halothane-treated animals (rabbits). Approximately 70% of patients have antibodies that recognize neoantigens (TF-acetyl-modified epitopes), and 90% have antibodies that recognize autoantigens (non-TF-acetyl-modified epitopes). Therefore, preoperative testing for halothane antibodies might identify patients at risk for developing
hepatitis, whereas postoperative testing could help determine if halothane was the likely cause of unexplained postoperative hepatitis. Currently, however, no tests exist that are totally sensitive or specific for detecting the disease. The ELISA test for antibodies has been reported to be approximately 75% sensitive and 88% specific.\textsuperscript{33} Obviously, the easiest way to avoid the risk of halothane-induced hepatitis is to avoid the use of halothane completely, especially in adults. Fortunately, alternative agents are readily available; thus, there has been decreased interest in developing preoperative tests.

Other volatile agents besides halothane also have immunogenic potential. Enflurane metabolism produces acyl adducts (difluromethoxydifluoroacetyl halide) that are similar, but not identical, to those derived from halothane (TF-acetyl halide). Nonetheless, antibodies isolated from patients with halothane hepatitis can bind to hepatic proteins that contain enflurane-induced adducts (neoantigens).\textsuperscript{39}

Isoflurane metabolism also yields highly reactive intermediates (TF-acetyl chloride; acyl ester) that bind covalently to hepatic proteins (see Fig. 39-9). The likelihood that isoflurane causes hepatitis via production of these intermediates appears to be extremely low, however, as just 0.2% of the isoflurane taken up into the body is actually metabolized. Only trace amounts of isoflurane-derived adducts are bound to hepatic proteins following isoflurane anesthesia.

Desflurane, which is similarly biotransformed to trifluoroacyl metabolites, appears even less likely than isoflurane to cause immune injury because only 0.02 to 0.2% of this agent is metabolized (1/1,000th that of halothane). Desflurane metabolites are usually undetectable in plasma, except after prolonged administration. Furthermore, although antibodies from patients with halothane hepatitis clearly react with proteins isolated from halothane-treated or enflurane-treated rats, they do not appear to react with hepatic proteins from desflurane-treated or isoflurane-treated rats.\textsuperscript{36}

Sevoflurane is metabolized more extensively than is isoflurane or desflurane, slightly less than enflurane, and much less than halothane.\textsuperscript{40} The metabolism of sevoflurane (primarily via cytochrome P450 2E1) is rapid (1.5 to 2 times faster than enflurane), and produces detectable plasma concentrations of fluoride and hexafluoroisopropanol (HFIP) within minutes of initiating the anesthetic. The liver conjugates most of the HFIP with glucuronic acid, which is then excreted by the kidney (Fig. 39-10). An important distinction between sevoflurane and the other volatile agents is that sevoflurane produces neither highly reactive metabolites nor fluoroacetylated liver proteins.\textsuperscript{29} There is no evidence that any sevoflurane metabolites cause severe hepatic injury.

At present, the preponderance of evidence supports the immune theory (via TF-acetyl-hapten) of halothane-induced
hepatitis. Nonetheless, it is conceivable that the antigen-antibody responses that accompany anesthesia-induced hepatitis are the result of the hepatic injury, rather than the cause. Most (if not all) patients anesthetized with halothane form the same or similar TF-acetylated liver proteins, but few develop halothane hepatitis. In fact, pediatric anesthesiologists, like halothane hepatitis patients, have been shown to have higher serum autoantibody levels of P450 2E1 than general anesthesiologists and controls, possibly because of their increased occupational exposure to anesthetics. The female pediatric anesthesiologists in this study had higher levels of P450 2E1 autoantibodies than all other anesthesiologists. Despite one female anesthesiologist demonstrating evidence of hepatic injury in the aforementioned study, there are no reports of fulminant halothane hepatitis attributable to occupational exposure. Explanations for these observations, which proponents of the hapten theory must reconcile, include the following: only a few of the TF-acetyl proteins are actually immunogenic, the triggering of an immune response requires a critical threshold of TF-acetylated proteins (antigenic threshold), and only a small fraction of patients are genetically susceptible to these antigens.

Volatile Agents and Hepatic Blood Flow and Oxygen Delivery

Insofar as all halogenated anesthetic agents depress cardiac output and most surgical procedures stimulate a stress response with resultant catecholamine-induced vasoconstriction, it is predictable that hepatic blood flow and oxygen delivery will decrease during general anesthesia with volatile agents. The degree to which hepatic metabolic demands are also depressed with the various agents determines the relative impact on the hepatic supply-demand relationship, and consequently, the potential of each agent for causing hepatic ischemia.

Other perioperative conditions also contribute to hepatic blood flow, oxygen delivery, and metabolic requirements: hemoglobin concentration, oxygen saturation, systemic inflammation, volume status, and temperature. Additional insults such as direct hepatic trauma and hepatotoxic drug exposure, as well as occult preexisting hepatic insufficiency, can obscure the independent effects of the volatile agent.

Both animal and human studies indicate that halothane is more likely than other inhaled anesthetics to produce liver injury, probably because it causes the most cardiovascular and respiratory depression, as well as the greatest reduction in hepatic arterial flow (Fig. 39-11). Consequently, halothane is the most likely of the clinically used vapors to produce, or exacerbate, hepatic hypoxia when blood flow to the liver is critically limited and the adequacy of the oxygen supply-to-demand balance is in question.

Excluding halothane, enflurane decreases hepatic blood flow and splanchnic perfusion more than any other

FIGURE 39-11. Dose-dependent effects of inhaled anesthetics on hepatic arterial flow in chronically instrumented dogs in the absence of a surgical stress. Sevoflurane and isoflurane preserve hepatic arterial flow even at the higher minimum alveolar concentration (MAC) levels. *Differs from sevoflurane and isoflurane at same MAC values (p < .05). †Differs from sevoflurane at same MAC value (p < .05). (Reprinted with permission from Frink EJ Jr: The hepatic effects of sevoflurane. Anesth Analg 8[suppl 6]:546, 1995.)
halogenated vapor in clinical use. It induces dose-dependent decreases in portal venous blood flow and either reduces or leaves unchanged hepatic arterial blood flow. Splanchnic perfusion decreases in parallel with decreased mean arterial pressure and cardiac output. Enflurane also increases splanchnic oxygen extraction, and lowers both hepatic venous and mixed venous oxygen saturation.

Desflurane decreases hepatic blood flow in both experimental and clinical settings. Administration of 1 minimum alveolar concentration (MAC) desflurane to patients prior to skin incision reportedly decreases hepatic blood flow by 30% (measured by ICG), similar to the reduction associated with 1 MAC of halothane or isoflurane. Desflurane can markedly reduce oxygen delivery to the liver and small intestine without producing comparable reductions of hepatic oxygen uptake or hepatic and mesenteric metabolism. Therefore, desflurane anesthesia may decrease the oxygen reserve capacity of both the liver and the small intestine.

Isoflurane is much less likely than halothane or enflurane to cause or contribute to hepatic injury. It undergoes minimal biodegradation, and preserves hepatic blood flow and oxygen delivery even during open laparotomy. Sevoflurane anesthesia usually preserves blood flow and oxygen delivery to the liver, even in the presence of positive-pressure ventilation. Patients having elective operations under sevoflurane anesthesia (1 or 2 MAC) experience significant reductions in mean arterial blood pressure, but maintain the hepatic blood flow at preanesthetic levels. Animal data suggest that the hepatic arterial buffer response remains intact. Sevoflurane appears to be the most effective of the inhaled anesthetics for maintaining both blood flow and oxygen delivery to the liver. Thus, it is less likely than either halothane or enflurane to induce liver injury and is no more toxic than desflurane or isoflurane. Its metabolic products are less reactive, and therefore probably less injurious, than those resulting from halothane, enflurane, isoflurane, or even desflurane. Sevoflurane better preserves hepatic blood flow and oxygen delivery than halothane, enflurane, or desflurane; its effects on hepatic perfusion and metabolic function are similar to those of isoflurane.

Other than sevoflurane, desflurane is the least likely of the halogenated vapors to cause severe hepatic injury, based on the immune theory of anesthesia-induced hepatitis. Nonetheless, desflurane produces a greater reduction of hepatic blood flow and oxygen delivery than either isoflurane or sevoflurane. Hence, it may be more likely than the latter agents to cause liver injury in the setting of marginal hepatic oxygenation.

Other Anesthetics and Hepatic Function

Nitrous Oxide
Nitrous oxide produces a mild increase in sympathetic nervous system tone. Consequently, one would expect mild vasoconstriction of the splanchnic vasculature, leading to a decrease in portal blood flow, and mild vasoconstriction of the hepatic arterial system. In addition, N₂O is a known inhibitor of the enzyme methionine synthase, which could potentially produce toxic hepatic effects. Even brief exposures to N₂O at concentrations used clinically are sufficient to produce time-related decreases in methionine synthase activity in the livers of animals and humans, and prolonged exposure will induce a functional vitamin B₁₂ deficiency. Whether the resultant abnormalities in folate and methionine metabolism actually injure the liver is unclear. In a survey of more than 60,000 dentists and chairside assistants, Cohen and coworkers found a higher prevalence of liver disease in professionals who were chronically exposed to nitrous oxide: 1.7-fold higher in dentists, and 1.6-fold higher in their assistants. Other studies suggest that N₂O-containing anesthetics do not cause liver injury in the absence of impaired hepatic oxygenation. In one study, no hepatocellular injury resulted from up to 4 hours of anesthesia with 67% N₂O (in oxygen) and infusions of methohexital. In another, no hepatic dysfunction developed when patients with mild alcoholic hepatitis received N₂O-opioid or N₂O-enflurane anesthetics for peripheral or superficial operations. There is no convincing evidence that nitrous oxide per se causes hepatotoxicity in the absence of a precarious oxygen supply-demand ratio in the liver.

Nonopioid Sedative-Hypnotic Agents
Because it is a sympathomimetic agent, ketamine may produce a moderate increase in serum concentrations of some liver enzymes. Patients anesthetized with ketamine infusion plus oxygen show a dose-dependent increase in biochemical markers of hepatic injury. Despite these findings, it remains unclear whether ketamine causes liver dysfunction by exerting direct hepatotoxic effects, by altering hepatic metabolism, or by increasing serum catecholamines, which would be expected to decrease hepatic blood flow and oxygen delivery.

Other intravenous agents, such as propofol, etomidate, and midazolam, have not been shown to alter hepatic function significantly in patients undergoing minor operative procedures. Although very large doses of thiopental...
Opioids
Opioids have little effect on hepatic function, provided they do not impair hepatic blood flow and oxygen supply. All opioids increase tone of the common bile duct and the sphincter of Oddi, as well as the frequency of phasic contractions, leading to increases in biliary tract pressure and biliary spasm. The effect on the sphincter of Oddi does not favor one opioid over another and is not considered an absolute contraindication to narcotic analgesia, even in cases of pancreatitis.

NONPHARMACOLOGIC CAUSES OF PERIOPERATIVE LIVER DYSFUNCTION

Inflammation and Sepsis
The liver occupies a central position in the inflammatory response, especially when the inflammation is secondary to intra-abdominal sepsis. Because of its location downstream from the splanchnic circulation, bacteria, endotoxin, and proinflammatory cytokines (IL-1, IL-6, and TNF-α) are carried directly to the liver. These interact with sinusoidal Kupffer cells and stimulate hepatocytes to decrease production of certain proteins (mainly albumin), called negative acute-phase reactants, and increase production of others (mainly C-reactive protein and serum amyloid A), called acute-phase reactants. In addition, especially following blunt trauma and burns, complement and coagulation factor production also increase in the liver. Some, such as C-reactive protein and serum amyloid A, up to 30,000-fold, greatly increase the liver's metabolic demands (Fig. 39-12). With inflammation, the resulting changes in systemic vascular resistance; regional blood flow distribution; tissue oxygen extraction; coagulation status; glucose, fat, and protein metabolism; and catecholamine sensitivity can be far reaching and profound. In sepsis, hepatic arterial flow changes in a biphasic manner: an initial transient decrease followed by a marked and sustained increase in flow. The increase in hepatic artery flow occurs independent of changes in portal venous flow, suggesting a dysregulation of the physiologic hepatic arterial buffer response. In sepsis, and inflammation in general, hypovolemia and splanchnic hypoperfusion are common, predictably decreasing oxygen delivery to the liver.

Hypoxia and ischemia

The liver is exquisitely sensitive to hypoxia. In one study, patients with chronic lung disease whose blood oxygen content fell below 9 mL/dL all developed liver injury without developing overt myocardial or cerebral damage. In addition, if moderate hypotension occurs, a hepatitis-like illness (ischemic hepatitis) may follow. Patients develop jaundice, systemic symptoms, and large increases of serum transaminases, which may persist for 3 to 11 days. Liver biopsy shows centrilobular necrosis with little or no inflammatory response. Patients with ischemic hepatitis typically have a history of inadequate systemic perfusion, along with marked increases of serum aminotransferases. The increases are usually of greater magnitude than those associated with viral hepatitis. Prolonged shock or sepsis can cause extreme liver injury; a hepatic lobe or the entire liver may become infarcted, even in the absence of portal venous or hepatic arterial occlusion. The mechanism of ischemic hepatitis is unknown, but it may involve free radical production because hepatocytes contain very high concentrations of xanthine oxidase. Ischemia and reperfusion increase xanthine oxidase activity; this enzyme catalyzes the oxidation of purines to uric acid and the associated reduction of O₂ to superoxide anion, which initiates toxic free radical reactions.

Cardiac Disease

Severe congestive heart failure may be associated with liver dysfunction. The most common cause is ischemic hepatitis from decreased hepatic blood flow secondary to low cardiac output. Cardiac cirrhosis (fibrosis) may result from prolonged recurrent congestive heart failure. Acute liver failure is more likely to occur in patients with preexisting cirrhosis, severe chronic heart failure, or sustained hepatic ischemia, although passive hepatic congestion and fulminant hepatocellular necrosis has been reported from acute, severe elevations of central venous pressures.

Surgical Stress

The surgical stress response includes stimulation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system, and the nonosmotic release of vasopressin; each of these responses may compromise the splanchnic circulation. These effects may persist for many hours or even days after surgery. Laboratory studies indicate that laparotomy, in particular, induces marked mesenteric vasoconstriction and decreases gastrointestinal and hepatic blood flow; acute hypophysectomy and administration of an angiotensin II antagonist can abolish these changes. In addition to the surgical stress response, laparotomy independently decreases blood flow through the intestine and the liver, probably as a result of traction and manipulation of the viscera.

Although reducing the surgical stress response and minimizing tissue injury and inflammation, laparoscopic procedures are not entirely benign with respect to the liver. The increased intra-abdominal pressures induced with insufflation appear to significantly decrease splanchnic perfusion and hepatic blood flow. Procedures performed under cardiopulmonary bypass, with low-flow states and nonpulsatile perfusion, can aggravate preexisting hepatic dysfunction. Administration of catecholamines to improve cardiac performance, either before or after bypass, may decrease hepatic oxygen delivery. Hypothermia during cardiopulmonary bypass probably limits the hepatic injury caused by the abnormal hemodynamics. Hypotension and hemorrhage decrease portal blood flow, but the hepatic arterial buffer response and pressure-flow autoregulation tend to preserve hepatic arterial flow and oxygen delivery. Perfusion at 28°C increases portal flow and slightly decreases hepatic arterial flow. A pump flow rate of 2.4 L/minute per m² maintains total blood flow to the liver better than does a rate of 1.2 L/minute per m². Only at low rates does pulsatile flow appear to be more advantageous than nonpulsatile perfusion in terms of hepatic blood flow.

CHRONIC HEPATITIS

Chronic hepatitis refers to a group of liver disorders of varying etiologies and severity in which hepatic inflammation
and necrosis continue for at least 6 months. Chronic hepatitis was previously classified based on liver biopsy as chronic persistent or chronic active hepatitis. When this early classification was devised, chronic persistent hepatitis was considered to have a good prognosis, whereas chronic active hepatitis was considered a progressive disorder with a poor outcome. However, the prognostic value of these histologic distinctions has been found to be limited; thus, this classification has been supplanted by one based on cause, grade, and stage. Clinical and serologic features allow the establishment of an etiology for chronic hepatitis caused by HBV, HBV plus HDV, HCV, autoimmune hepatitis, drug-associated chronic hepatitis, and a category of cryptogenic chronic hepatitis. Histologic features on liver biopsy are necessary for grading and staging chronic hepatitis. The grade is determined by an assessment of the degree of necrosis and inflammation, and the stage reflects the level of progression of the disease, which is determined by an assessment of the degree of fibrosis.

Patients with chronic HBV infection who are asymptomatic and have normal serum transaminases are called HbsAg carriers. Those with chronic HBV infection who have clinical, laboratory, or pathologic evidence of chronic hepatic disease are diagnosed as chronic hepatitis B. An estimated 0.2 to 0.5% of the American population are chronic carriers of HbsAg. These HBV carriers are at risk for developing cirrhosis and hepatocellular carcinoma. The goal of treatment of chronic hepatitis B is to eradicate HBV infection, and thereby prevent the development of cirrhosis and hepatocellular carcinoma. Current therapy of chronic hepatitis B has limited long-term efficacy and does not yet achieve these goals. However, available therapies can suppress HBV replication and lead to laboratory and histologic improvement. The decision to initiate treatment depends on balancing the patient's age, severity of disease, likelihood of response, and potential adverse effects and complications. Treatment is not recommended for inactive HbsAg carriers. To date, three drugs have been approved for treatment of chronic hepatitis B: injectable interferon α, and two oral agents, lamivudine and adefovir.

Chronic HCV infection follows acute HCV infection in 85% of patients; an estimated 1.8% of the United States population are carriers of HCV. Although the progression of chronic hepatitis C infection to cirrhosis is characteristically slow, end-stage liver disease due to HCV-associated cirrhosis is the most common indication for liver transplantation. At least six distinct genotypes of HCV have been identified by nucleotide sequencing, and differences exist among these genotypes in responsiveness to antiviral therapy. Chronic HCV infection is usually treated with the combination of ribavirin and interferon.

Autoimmune hepatitis is a chronic disease characterized by a wide spectrum of clinical symptoms, seroimmunologic manifestations, and continued hepatocellular necrosis and inflammation, which often progresses to cirrhosis. Extrahepatic features of autoimmunity, seroimmunologic abnormalities, and association with other autoimmune disorders all support an autoimmune pathogenesis. The clinical and laboratory features of autoimmune hepatitis are often similar to those described for chronic hepatitis. Patients with autoimmune hepatitis, however, usually have hypergammaglobulinemia, rheumatoid factor, and other circulating autoantibodies. Immunosuppressive therapy using corticosteroids with or without azathioprine is the mainstay of treatment and leads to symptomatic, clinical, biochemical, and histologic improvement, along with increased survival.

Fatty Liver Disease
Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in the United States. NAFLD is defined as fat accumulation in the liver exceeding 5% by weight. It has been estimated that up to 24% of American adults have NAFLD. It usually becomes manifest in the fifth and sixth decades of life and is more common in women. The two major risk factors for NAFLD are type II diabetes and obesity. In a consecutive autopsy series, 70% of obese patients had fatty liver. Among type II diabetics, it is estimated that 75% have some form of fatty liver.

NAFLD includes a spectrum of hepatic pathology that ranges from fatty liver (steatosis) at its most clinically indolent extreme to the intermediate stage of nonalcoholic steatohepatitis (NASH), characterized by steatosis with lobular inflammation and perisinusoidal fibrosis, to its most severe form, cirrhosis. NAFLD is now believed to be responsible for most cases of what was once classified as cryptogenic cirrhosis, a form that accounts for half of the annual liver-related deaths.

Most patients with NAFLD are asymptomatic, and the presence of an abnormality is often detected by abnormal LFT or hepatomegaly on a routine physician's office visit. The most common LFT abnormality is a 2- to 5-fold elevation of the AST and ALT. The AST/ALT ratio is reported to be <1 in 65 to 90% of patients with NAFLD, which distinguishes it from alcohol-related liver injury.

The pathophysiology of NAFLD is unknown, but present data suggest a multihit hypothesis in which common initial insults promote hepatic steatosis (e.g., obesity, subclinical insulin resistance), and the increased hepatic fat appears to stress the hepatocyte and render it more vulnerable to subsequent insults. This eventually produces some degree of hepatocyte necrosis, which promotes the accumulation of inflammatory cells within
the liver (NASH). In some patients, a fibrotic response predominates, leading to cirrhosis.

The natural history of NAFLD varies according to its histologic type. Patients with steatosis alone usually have a benign clinical course. Significant adverse clinical sequelae, however, occur in patients with NASH and cryptogenic cirrhosis.

There are no proven treatments for NAFLD. Exercise and diet are recommended. Several studies have reported beneficial effects of bariatric surgery when NAFLD is secondary to obesity. When the disease is advanced, the patient is often a poor candidate for liver transplantation due to comorbid conditions such as obesity and the complications of diabetes.

**Alcoholic Liver Disease**

Alcoholic liver disease is defined by the development of three types of liver damage following chronic heavy alcohol consumption: (1) steatosis (fatty liver), (2) alcoholic hepatitis, and (3) cirrhosis. The clinical features and laboratory values frequently do not distinguish among these because compensatory mechanisms can mask extensive liver disease. A liver biopsy is often necessary to arrive at a definitive diagnosis.

Alcoholic steatosis occurs commonly after ingestion of moderate to large amounts of alcohol for even a short period of time. When severe, patients may be symptomatic, with malaise, nausea, anorexia, weakness, abdominal discomfort, and tender hepatomegaly. Mild transaminase and AP elevations may be present. Alcoholic steatosis is usually a benign disorder, and the liver abnormalities will usually resolve with abstinence from alcohol. In contrast, alcoholic hepatitis is a precursor of cirrhosis. Although symptoms may overlap with those of alcoholic steatosis, patients with alcoholic hepatitis may be febrile and jaundiced. There may be up to a 10-fold elevation of the aminotransferases with the AST level characteristically higher than the ALT. Hypoalbuminemia, prolongation of the PT, and marked elevations of the AP may be present. Treatment of alcoholic hepatitis consists of abstinence from alcohol, bed rest, and intake of a normal or high protein diet if hepatic encephalopathy is not present. Corticosteroids are often used to treat patients with severe alcoholic hepatitis, although their use for this indication remains controversial. It should be noted that alcohol abusers have a 2- to 3-fold increase in perioperative morbidity (Fig. 39-13).79

**CIRRHOSIS: A PARADIGM FOR END-STAGE PARENCHYMAL LIVER DISEASE**

This section discusses the pathophysiology of parenchymal liver disease, typified by hepatic cirrhosis, as it relates to anesthesia. Cirrhosis affects more than 3 million Americans and is the twelfth leading cause of death. The most frequent etiologies of cirrhosis in the United States are chronic hepatitis C infection and alcoholism. The most common symptoms are anorexia, weakness, nausea, vomiting, and abdominal pain. Signs include
hepatosplenomegaly, ascites, jaundice, spider nevi, and metabolic encephalopathy. Advanced parenchymal hepatic disease alters the function of nearly every organ and body system.

Cardiovascular Abnormalities

Characteristically, patients with cirrhosis and portal hypertension have a hyperdynamic circulation with a high cardiac output, low peripheral vascular resistance, low to normal arterial blood pressure, normal to increased stroke volume, normal filling pressures, and a mildly elevated heart rate (Table 39-4). The total blood volume is usually increased, but with an altered distribution in which the central “effective” blood volume is decreased, while the splanchnic bed is hypervolemic. Extensive arteriovenous collateralization occurs in many organs and tissues, leading to increased oxygen tension and saturation of the peripheral and mixed venous blood, and a decrease in the arteriovenous oxygen content difference. The mechanism by which these collaterals develop is complex and not completely understood, but may be related to increased plasma levels of glucagon and vasoactive intestinal polypeptide, which can induce peripheral vasodilation, decrease vascular resistance, and increase arteriovenous shunting. Glucagon also reduces the vascular responsiveness to infused catecholamines and other vasopressors in experimental animals. Nitric oxide may also be an important mediator of the hyperdynamic changes that occur in cirrhosis and portal hypertension. Data from normal subjects and patients with cirrhosis reveal a positive correlation between exhaled concentrations of nitric oxide and cardiac index (Fig. 39-14). Some causes of liver disease are also associated with cardiomyopathy (alcoholic liver disease, hemochromatosis); these patients may develop signs and symptoms of congestive heart failure, including decreased peripheral blood flow.

<table>
<thead>
<tr>
<th>TABLE 39-4 Cardiovascular Function in Hepatic Cirrhosis</th>
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<tr>
<td>Decreased vascular resistance (peripheral vasodilation, increased arteriovenous shunting)</td>
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<tr>
<td>Increased cardiac output</td>
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<tr>
<td>Maintained arterial blood pressure, filling pressures, and heart rate (deterioration is late)</td>
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<tr>
<td>Blood volume maintained or increased, but redistributed (splanchnic hypervolemia, central hypovolemia)</td>
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<td>Possible cardiomyopathy</td>
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<tr>
<td>Increased $O_2$ content in mixed venous blood; decreased difference in the $O_2$ contents of arterial and venous blood</td>
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<tr>
<td>Diminished responsiveness to catecholamines</td>
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<tr>
<td>Increased blood flow in splanchnic (extrahepatic), pulmonary, muscular, and cutaneous tissues</td>
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<tr>
<td>Decreased total hepatic blood flow</td>
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<tr>
<td>Maintained hepatic arterial blood flow</td>
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<tr>
<td>Decreased portal venous blood flow</td>
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<tr>
<td>Maintained or decreased renal blood flow</td>
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Hepatic Circulatory Dysfunction

Portal hypertension can complicate the course of many chronic liver diseases but is a hallmark of end-stage cirrhosis. Portal hypertension is a pathologic increase in portal venous pressure, resulting in the formation of portosystemic collaterals, which develop by dilatation and hypertrophy of preexisting vascular channels. It plays an important role in the pathogenesis of ascites and hepatic encephalopathy, leads to the development of esophageal varices, and contributes to the enhanced susceptibility to bacterial infections and altered drug metabolism found in these patients.

In patients with cirrhosis, portal hypertension may result from increased vascular resistance to portal blood flow, which is believed to be the initial factor responsible for an increase in portal pressure. In cirrhotics, this increased resistance occurs mainly in the hepatic sinusoids. Subsequently, increased portal venous inflow occurs as a result of marked splanchnic arteriolar vasodilation. Several humeral vasodilators have been suspected of contributing to splanchnic hyperemia, including glucagon, prostacyclin, endotoxin, and nitric oxide. Eventually, the majority of the blood entering the portal system flows through the collateral circulation, and under these circumstances, the resistance of these vessels markedly influences portal pressure. As portal blood flow to the liver decreases substantially, hepatic arterial flow remains the same or increases. Thus, although the total circulation of the liver decreases, the hepatic oxygen supply is preserved. This decrease in total hepatic blood flow has pharmacokinetic implications that have been previously discussed.

Variceal Hemorrhage

Gastroesophageal variceal hemorrhage is probably the most dreaded complication of portal hypertension. Varices are portosystemic collaterals formed after preexisting vascular channels have been dilated by portal hypertension. They permit the passage of splanchnic venous blood from the high-pressure portal venous system to the low-pressure azygos and hemiazygous veins. Gastroesophageal varices are present in 40 to 60% of cirrhotics, and 25 to 35% of these will bleed. Up to 30% of initial bleeding episodes are fatal, and as many as 70% of survivors of an initial hemorrhage will have a recurrence.

Variceal ruptures typically present as acute severe upper gastrointestinal hemorrhage. Prompt aggressive fluid
resuscitation, blood transfusion, and correction of hemostatic abnormalities are essential, and are usually implemented in an intensive care unit. Endotracheal intubation for airway protection is frequently necessary. Empiric pharmacologic therapy (e.g., with octreotide) is indicated in situations in which variceal bleeding is likely. Subsequent esophagogastroduodenoscopy will define the site of bleeding and permit endoscopic therapy if appropriate.

Treatment of patients with gastroesophageal varices includes prevention of the initial bleeding episode (primary prophylaxis), control of active hemorrhage, and prevention of recurrent bleeding after a first episode (secondary prophylaxis). Empiric pharmacologic treatment (e.g., with octreotide) is indicated in situations in which variceal bleeding is likely. Subsequent esophagogastroduodenoscopy will define the site of bleeding and permit endoscopic therapy if appropriate.

The goal of pharmacologic treatment is to reduce portal and intravariceal pressures. The nonselective beta-blockers, propranolol and nadolol, are effective agents for primary prophylaxis as they produce sustained decreases in portal venous pressure and decrease the risk of bleeding by 40 to 50%. Isosorbide mononitrate added to a beta-blocker may not only produce a further decrease in portal pressure, but also cause increased side effects. Endoscopic band ligation is an acceptable option for primary prophylaxis in patients at high risk for variceal bleeding who cannot tolerate medical therapy.

Patients with acute gastrointestinal bleeding of probable variceal origin are initially treated with intravenous somatostatin or its synthetic analogue octreotide. These drugs stop variceal hemorrhage in up to 80% of patients by reducing portal pressure. The variceal origin of the bleeding is then confirmed endoscopically, and the varices are subsequently treated either by band ligation or sclerotherapy. Current endoscopic therapies are capable of stopping bleeding in approximately 90% of patients.

If variceal bleeding persists or recurs despite endoscopic and pharmacologic therapy, balloon tamponade with a Sengstaken-Blakemore or Minnesota tube may be attempted. These modified nasogastric tubes are infrequently used, but when applied properly, achieve hemostasis in most cases. Because rebleeding frequently occurs after balloon decompression, it should be used as a rescue technique and a bridge to more definitive treatment.

Transjugular intrahepatic portal systemic shunt (TIPS) was introduced in the 1990s, and its use has nearly eliminated the need for emergency shunt surgery. TIPS has become the preferred therapy for most bleeding patients who are not controlled by other nonoperative therapies. TIPS effectively decompresses the portal venous circulation with low short-term mortality, but late TIPS failure rates are high.

A surgical portocaval shunt is considered in cases of continued hemorrhage or recurrent bleeding that cannot be controlled by endoscopic and pharmacologic means, and when TIPS is not available or technically feasible. When performed emergently, mortality approaches 40% but is substantially less when the procedure can be performed electively. Liver transplantation is often offered to patients with Childs B and C cirrhosis soon after or even before they bleed from varices. Secondary prophylaxis with nonselective beta-blockers, plus isosorbide mononitrate and band ligation of varices, reduces the incidence of rebleeding.

**Pulmonary Dysfunction**

A variety of disorders may produce hypoxemia in patients with advanced cirrhosis, including intrinsic cardiopulmonary disorders such as congestive heart failure, interstitial lung disease, obstructive airway disease, pleural effusions, and pulmonary vascular disease (Table 39-5). Fluid retention may cause interstitial edema, airway edema, and large volume ascites, all of which may contribute to the development of hypoxemia through ventilation-perfusion mismatch and intrapulmonary shunting from compression of the basal regions of the lung.
In the absence of primary lung disease, the major causes of arterial hypoxemia in patients with advanced cirrhosis may be intrapulmonary vascular dilatations (IPVDs). The clinical triad of chronic liver disease, increased alveolar-arterial oxygen gradient, and evidence of IPVDs is defined as the hepatopulmonary syndrome (HPS). IPVD encompasses two types of vascular abnormalities: (1) vascular dilatation at the precapillary level close to the alveoli, and (2) vascular dilatation resulting in larger arteriovenous communications that may or may not be in proximity to gas exchange units. Supplemental oxygen significantly increases the PaO₂ when precapillary IPVD is contributing to hypoxemia, but has minimal effects when larger arteriovenous communications are the primary etiology of hypoxemia. The pathogenesis of IPVD in HPS is incompletely understood, but enhanced pulmonary production of nitric oxide likely plays a role.

IPVD is most commonly detected using contrast-enhanced echocardiography. In normal patients, injection of microbubbles results in transient echogenicity in the right heart with no contrast in the left heart. Patients with dilated precapillary pulmonary vessels show delayed opacification in the left atrium approximately three to six contractions after visualization of the right ventricle.

As many as 40% of patients with cirrhosis have detectable IPVD, and up to 15% have hypoxemia and functional limitation. Survival of patients with HPS is reduced compared with cirrhotic patients of similar Child-Pugh class without HPS. Severe hypoxemia from HPS increases intraoperative and postoperative risks in liver transplantation. IPVD often resolves completely after liver transplantation.

Hepatic hydrothorax occurs in 4 to 10% of cirrhotic patients. These patients characteristically have pleural effusions in the absence of cardiopulmonary disease, secondary to transfer of ascitic fluid from the peritoneal cavity into the pleural space through diaphragmatic defects. The initial treatment of hepatic hydrothorax consists of sodium restriction, diuretics, and thoracentesis; TIPS may be required in refractory cases. Because most of these patients have end-stage liver disease, liver transplantation becomes the preferred treatment if the previous options fail.

Portopulmonary hypertension refers to the development of pulmonary artery hypertension in patients with portal hypertension. It is usually defined as a mean pulmonary artery pressure >25 mm Hg with a normal pulmonary capillary wedge pressure and an elevated pulmonary vascular resistance (>120 dyne/second per cm²).

Portopulmonary hypertension affects between 4 to 6% of patients referred for liver transplantation. Patients with mean pulmonary artery pressures >35 mm Hg are considered to be high-risk transplant candidates.

**Ascites, Renal Dysfunction, and the Hepatorenal Syndrome**

**Ascites and Edema**

Ascites is the most common of the major complications of cirrhosis. Nearly 50% of cirrhotic patients develop ascites within 10 years of being diagnosed. Because 50% of cirrhotic patients with ascites die within 3 years, the development of ascites is a clear indication for evaluation for liver transplantation.

The pathogenesis of ascites in cirrhosis is complex and not completely understood. Sodium and water retention plays
a key role. Three theories have evolved over time to explain the enhanced sodium and water avidity in patients with cirrhosis. Initially, the “underfilling” theory was proposed. The primary abnormality with this theory is cirrhosis-related hepatic venous block and portal hypertension leading to formation of ascites. This transudation of fluid decreases the effective intravascular volume. The neurohumoral response to “ineffective” plasma volume triggers the kidney to retain sodium and water. Thus, the underfilling hypothesis explains renal sodium retention as a secondary rather than a primary phenomenon (Fig. 39-15).

<table>
<thead>
<tr>
<th>Arterial Underfilling Hypothesis</th>
<th>Overflow Hypothesis</th>
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<tbody>
<tr>
<td>↓ “Effective” Volume</td>
<td>Primary Renal Tubular Retention of Sodium</td>
</tr>
<tr>
<td></td>
<td>↑ Plasma Volume</td>
</tr>
<tr>
<td>↑ Renal Tubular Reabsorption of Sodium</td>
<td>Translocation of Fluid out of Splanchnic Circulation as Ascites</td>
</tr>
<tr>
<td>↑ ECF Volume</td>
<td>Ascites and Edema</td>
</tr>
</tbody>
</table>

FIGURE 39-15. The presumed sequences of events that result in ascites formation according to the arterial underfilling hypothesis and the overflow hypothesis. The proposed primary disorders are shown in the boxes. According to the underfilling hypothesis, cirrhosis induces abnormal Starling forces in the portal venous circulation that cause an unfavorable distribution of the circulating blood volume (decreased effective blood volume). The diminished “effective” volume constitutes an afferent signal to the renal tubules to augment salt and water reabsorption. The attempt to replenish the diminished effective volume results in an expansion of the total blood volume to values far in excess of normal, with resultant ascites and edema formation. The overflow hypothesis holds that the primary disorder is retention of excessive sodium by the kidneys. In the setting of abnormal Starling forces in the portal venous bed, the expanded plasma volume is sequestered preferentially in the peritoneal sac. ECF, extracellular fluid. (Reprinted with permission from Epstein M: Renal functional abnormalities in cirrhosis: Pathophysiology and management. In Zakim D, Boyer TD [eds]: Hepatology: A Textbook of Liver Disease, p 448. Philadelphia, WB Saunders, 1982.)

Subsequent studies determined that total blood volumes were increased in cirrhotic patients with ascites, and this finding led to the proposal of the “overflow” hypothesis to explain the development of ascites in cirrhotics. The primary abnormality with this proposal is sodium and water retention induced by a hepatorenal reflex promoted by portal hypertension. The resulting hypervolemia and increased portal pressure produces “overflow” ascites. Thus, this hypothesis contends that renal sodium retention and plasma volume expansion, rather than plasma volume reduction, are responsible for ascites formation (see Fig. 39-15).

The “peripheral arterial vasodilation hypothesis” was proposed by Schrier and associates in 1988. This theory contends that the primary event leading to sodium and water retention in cirrhosis is splanchnic arterial vasodilation secondary to portal hypertension induced production of vasodilatory mediators such as nitric oxide. At this phase of the disease, ascites has not yet developed, and a hyperdynamic circulation helps maintain systemic perfusion. With disease progression, this compensatory mechanism becomes insufficient to maintain circulatory homeostasis. Enlargement of the intravascular compartment decreases the effective arterial blood volume. Arterial blood pressure decreases, leading to baroreceptor activation, which stimulates three vasoconstrictor systems: the sympathetic nervous system, the renin-angiotensin-aldosterone system, and the nonosmotic release of vasopressin. Renal sodium and water retention increases and contributes to the development of ascites.

The most important initial treatment for patients with ascites resulting from cirrhosis is reduction of sodium intake and diuretic therapy. Fluid intake should be restricted to approximately 1,000 mL per day if the patient also has dilutional hyponatremia. If the patient has significant anasarca, there is no limit to the amount of edema that can

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be safely mobilized. However, once the edema has resolved, 0.5 kg is probably a reasonable daily maximum weight loss, as ascitic fluid is much more slowly mobilized than edema. The diuretics of choice are either spironolactone or amiloride. Furosemide should be used with caution because of the risk of excessive diuresis, which may lead to potentially serious complications including renal failure of prerenal origin, precipitation of hepatorenal syndrome, hyponatremia, hypokalemia, and encephalopathy.

Refractory ascites occurs in 5 to 10% of ascitic patients and is defined as a lack of response to high dose of diuretics (spironolactone, 400 mg/day plus furosemide 160 mg/day). The main clinical features include marked abdominal distension, frequent recurrence of ascites after paracentesis, an increased risk of developing hepatorenal syndrome, and a poor prognosis. Repeated large-volume paracentesis with use of plasma volume expanders is the most widely accepted therapy for refractory ascites. Removal of large amounts of ascitic fluid without the administration of plasma volume expanders is associated with paracentesis-induced circulatory dysfunction (PICD), characterized by reduction of effective arterial blood volume due to shift of intravascular fluid to the peritoneal cavity, with progressive reaccumulation of ascites and marked activation of the renin-angiotensin-aldosterone system.

The hemodynamic status of patients with tense ascites who undergo rapid total paracentesis without fluid resuscitation typically improves for the first 3 hours following the procedure, as a result of release of compression of the IVC and right atrium. Cardiac output increases, whereas pulmonary artery wedge pressure is unchanged and right atrial pressure decreases. Other studies have demonstrated that along with the early increase in cardiac output, there is a decrease in plasma renin and aldosterone levels, a decrease in serum creatinine and BUN, and reduced portal pressures. However, these beneficial effects are transient.

After 3 hours, the hemodynamic status is determined by the development of a relative hypovolemia caused by progressive reaccumulation of ascites. Twenty-four hours after total paracentesis, there is a significant decrease in cardiac output and cardiac filling pressures, accompanied by increased plasma renin and aldosterone concentrations. This effect is prevented by intravenous albumin infusion. Although the use of albumin in this setting remains controversial because of its high cost and the lack of documented improvement in survival, albumin has a greater protective effect on the circulatory system than other expanders. More recent studies suggest that 50% of the plasma expander should be infused immediately after paracentesis, and the other half, 6 hours later. The prevalence of PICD also depends on the amount of ascitic fluid removed because it is an uncommon complication following a low-volume paracentesis. It can be anticipated that similar hemodynamic changes may occur following emergent laparotomy in patients with tense ascites.

Placement of a peritoneal-venous shunt (Le Veen or Denver) was the first treatment specifically designed for patients with refractory ascites. Le Veen introduced the first prosthesis in 1974. It consists of a perforated intra-abdominal tube connected via a one-way valve to a second tube that traverses the subcutaneous tissue to the jugular vein. This creates a continuous passage of ascites into the systemic circulation. Poor long-term patency and excessive complications have led to the near abandonment of this procedure. A TIPS procedure is effective for preventing recurrence of ascites in patients with refractory ascites. TIPS decreases the activity of sodium-retaining mechanisms and improves the renal response to diuretics. This procedure is better than repeated large-volume paracentesis for the long-term control of ascites, but it has several disadvantages, including a high rate of shunt stenosis, which can lead to recurrence of ascites; a high incidence of severe hepatic encephalopathy; a high cost; and lack of availability in some centers. Survival is not improved by TIPS compared with repeated large-volume paracentesis. Thus, TIPS is not considered the first-line treatment for refractory ascites. Liver transplantation may also be a consideration in these patients.

**Spontaneous Bacterial Peritonitis**

Spontaneous bacterial peritonitis (SBP) is characterized by the spontaneous infection of ascitic fluid in the absence of an intra-abdominal source of infection. Its prevalence among patients with ascites ranges between 10 and 30%. SBP is diagnosed when there are ≥250 polymorphonuclear (PMN) cells/mm³ of ascitic fluid. Bacterascites is diagnosed when there are positive ascitic fluid cultures and the neutrophil count is ≤250 cells/mm³. SBP develops secondary to translocation of bacteria from the intestinal lumen to regional lymph nodes with subsequent bacteremia and infection of the ascitic fluid. Aerobic Gram-negative bacteria are most commonly isolated, but Gram-positive isolates are being recovered with increasing frequency. Ascitic fluid should be obtained by paracentesis and should be directly inoculated into blood culture bottles at the bedside rather than be cultured by conventional methods. Prospective clinical trials have demonstrated that cultures will be positive in approximately 80% of instances with the former approach versus 50% with the latter in patients with ≥250 PMN cells/mm³ of ascitic fluid.

Because ascitic fluid PMN count can be assessed much more rapidly than cultures and accurately determines who can benefit from empiric antibiotic coverage, patients with a PMN count <250 cells/mm³ in a clinical setting that is
compatible with ascitic fluid infection should receive empiric antibiotic therapy. Delaying antibiotic therapy until positive ascitic fluid cultures are present likely increases the risk of the patient developing severe sepsis. Patients with ascitic PMN counts <250 cells mm\(^3\) with clinical signs or symptoms of infection should also be treated with empiric antibiotics until ascitic culture results are available. Cefotaxime, a third-generation cephalosporin, appears to be the antibiotic of choice for suspected SBP because it covers 95% of the responsible flora, including the three most common isolates, which are *Escherichia coli*, *Klebsiella pneumonia*, and the pneumococcus.

In a retrospective analysis of 252 episodes of SBP, renal insufficiency developed in 33%.\(^{101}\) The renal dysfunction was transient in 25%, stable in 33%, and progressive in 42%. The overall mortality for an episode of SBP was 24%, but was 54% versus 9% in those with and without the development of renal insufficiency. The development of renal impairment is therefore an important clinical event in the course of SBP. Sepsis-induced decrease in the effective arterial blood volume with subsequent baroreceptor-mediated stimulation of the renin-angiotensin and sympathetic nervous systems, and vasopressin release contribute toward the development renal dysfunction. Direct stimulation of renal vasoconstrictors by endotoxin may also play a role. Sort and associates demonstrated in a randomized, controlled clinical trial of 126 patients with SBP that interventions directed at maintaining effective arterial blood volume (1.5 g/kg albumin within 6 hours of diagnosis of SBP followed by 1 g/kg on day 3) were associated with a significant decrease in development of HRS, and in both the in-hospital and 30-day mortality rates.\(^ {102}\) Data do not exist regarding the efficacy of lower doses of albumin or other plasma volume expanders in preventing HRS.

Long-term antibiotic prophylaxis with a quinolone is recommended following resolution of SBP because there is an estimated 70% probability of recurrence within the first year, and antibiotic prophylaxis has a beneficial effect on patient survival. Short-term quinolone prophylaxis is also recommended for patients with low-protein ascites and gastrointestinal bleeding because bleeding increases bacterial translocation and SBP.

**Pathogenesis of Renal Dysfunction**

The three main renal functional abnormalities in cirrhosis are reduction in sodium excretion, reduction in free water excretion, and a decrease in renal perfusion and glomerular filtration.\(^ {94}\)

The arterial vasodilation characteristic of cirrhosis, with its associated decrease in effective plasma volume, leads to baroreceptor-mediated activation of the sympathetic nervous system. This causes the kidney to release renin, which results in an increased production of angiotensin II and aldosterone. Both aldosterone and increased sympathetic nervous system outflow enhance tubular sodium resorption. In addition, through their vasoconstrictive actions, norepinephrine and angiotensin II cause a redistribution of renal blood flow, which further decreases sodium elimination.

Water homeostasis is disturbed in up to 75% of patients with advanced cirrhosis and ascites (decompensated cirrhosis). In these patients, water retention, increased total body water, and dilutional hyponatremia develop when fluid intake exceeds the impaired renal capacity to excrete free water. Reduced glomerular filtration secondary to impaired perfusion, elevated vasopressin levels caused by nonosmotic hypersecretion and decreased metabolic clearance, and impaired renal production of prostaglandin E2 also contribute to the impairment of free water excretion.

The major consequence of reduced sodium excretion is the development of edema and ascites. When free water clearance becomes significantly reduced, dilutional hyponatremia develops. The main consequence of decreased renal perfusion and GFR is development of the hepatorenal syndrome.

**Hepatorenal Syndrome**

HRS is a functional prerenal failure that occurs in up to 10% of patients with advanced cirrhosis and ascites, and less commonly in patients with acute liver failure. HRS is characterized by intense vasoconstriction of the renal circulation, low glomerular filtration, preserved renal tubular function, and normal renal histology. HRS may be diagnosed after other causes of renal failure are ruled out. The International Ascites Club has suggested five major criteria to confirm the diagnosis of HRS: (1) chronic or acute liver disease with advanced hepatic failure and portal hypertension; (2) a low GFR as assessed by serum creatinine >1.5 mg/dL or creatinine clearance below 40 mL/min; (3) absence of shock, ongoing bacterial infection, fluid losses, or treatment with nephrotoxic drugs; (4) no sustained improvement in renal function after oral diuretic withdrawal and plasma volume expansion; and (5) less than 500 mg/day proteinuria with no ultrasonographic evidence of parenchymal renal disease or urinary obstruction.\(^ {103}\)
HRS has been classified clinically into two types based on its intensity and presentation. Type 1 HRS is characterized by progressive oliguria and a rapid rise in the serum creatinine concentration. Type 1 HRS develops in 5% of cirrhotics hospitalized for acute upper gastrointestinal bleeding, 30% of those admitted for SBP, 10% of patients with ascites treated with total paracentesis, and 25% of patients with severe acute alcoholic hepatitis. SBP commonly precipitates the development of type 1 HRS. The prognosis of type 1 HRS is poor, with a median survival of less than 1 month without therapeutic intervention. Type 2 HRS is usually seen in patients with refractory ascites, and is characterized by a moderate and more stable impairment of renal function.

Pathophysiologically, intense renal vasoconstriction is the final consequence of extreme vasodilation of the splanchnic arterial circulation that reduces the effective arterial blood volume (that sensed by the central arterial circulation). The resulting abnormal distribution of arterial volume is associated with reduced flow to all extrasplanchnic areas, including the kidneys. Splanchnic arterial vasodilation is related to an increased level of both endothelial (prostacyclin and nitric oxide) and nonendothelial vasodilators (e.g., glucagon). Increased activity of both the renin-angiotensin and sympathetic nervous systems mediate the renal vasoconstriction, as well as other intrarenal vasoconstrictor factors such as endothelin, adenosine, and leukotrienes.

Until more recently, the development of type 1 HRS was considered to be an irreversible clinical condition, which in the absence of an emergent liver transplant, was associated with rapid progression to death. Because HRS develops as a consequence of splanchnic arterial vasodilation, drugs that produce splanchnic vasoconstriction have been proposed for treatment of this condition. Several different vasoconstrictors (vasopressin analogs, catecholamines), usually combined with albumin infusion, have been evaluated in small nonrandomized clinical trials. Vasoconstrictor therapy results in an increased arterial blood pressure, near-normalization of the activity of the major endogenous vasoconstrictor systems, and marked increases in renal plasma flow, GFR, and urine volume in approximately two-thirds of patients. These studies have demonstrated that a prolonged improvement in circulatory function, with 1 to 2 weeks of administration of intravenous albumin and vasoconstrictors, is required to reverse HRS, with a lag between the normalization of systemic circulation and the improvement in renal perfusion and GFR. Recurrence of HRS in responding patients after withdrawal of therapy is uncommon.

Octreotide, an inhibitor of the release of gastrointestinal vasodilator peptides such as glucagon and vasoactive intestinal peptide, when combined with midodrine and intravenous albumin, has been shown to have beneficial effects on renal function in a clinical study of five patients with type 1 HRS.

Patients showing an improvement in renal function after vasoconstrictor therapy survive significantly longer than patients who do not respond. Treatment with vasoconstrictors may thus increase the likelihood that patients with HRS will survive long enough to undergo liver transplantation. Transplant survival may be significantly reduced in cirrhotic patients with preoperative renal failure. Reversal of HRS with vasoconstrictor therapy is, therefore, an important tool in patients waiting for a liver transplant.

**Acute Renal Failure and Acute Tubular Necrosis**

Cirrhotic patients are also at risk for developing acute renal failure from acute tubular necrosis (ATN), especially following infection or hypotensive episodes. ATN occurs more frequently after surgical procedures to relieve obstructive jaundice than it does following similar operations on nonjaundiced patients. The impaired vasoconstrictor response to hypovolemia seen in patients with hepatic parenchymal disease and obstructive jaundice limits the normal redistribution of splanchnic blood to the central circulation that occurs with hemorrhage. Therefore, even moderate hemorrhage may produce severe hypotension and cause ATN. In addition, conjugated bilirubin appears to be toxic to renal tubules and may contribute to the development of ATN in jaundiced patients.

The differential diagnosis of acute azotemia in patients with liver disease is outlined in Table 39-6. Of note is the remarkable similarity of the urinary characteristics of prerenal azotemia and HRS. Prompt detection and treatment of hypovolemia may rapidly improve renal function in prerenal azotemia, but this response does not if HRS is present.

| TABLE 39-6 Differential Diagnosis Of Acute Azotemia In Patients With Liver Disease: Important Differential Urinary Findings |
|---------------------------------|---------------------------------|---------------------------------|
| **PRERENAL AZOTEMIA**           | **HEPATORENAL**                 | **ACUTE RENAL**                 |

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Hematologic and Coagulation Disorders

The liver is the site of synthesis of all clotting factors with the exception of von Willebrand factor (vWF), an endothelial product. Anticoagulant (antithrombin III, proteins C and S), and fibrinolytic factors are also products of the liver. Acute or chronic liver disease results in a variable level of impairment of hemostasis from multiple causes: decreased production of coagulation and inhibitor factors, synthesis of dysfunctional clotting factors, quantitative and qualitative platelet defects, vitamin K deficiency, decreased clearance of activated factors, hyperfibrinolysis, and disseminated intravascular coagulation.

Vitamin K is an essential cofactor for the production in the liver of factors II, VII, IX, and X, and also proteins C and S. The precursors of vitamin K-dependent coagulation factors are also synthesized in the liver. Vitamin K is needed for conversion of these factors to active forms by gamma carboxylation of glutamic acid residues in the amino-terminal region of the precursors. The carboxylated residues permit the binding of calcium ions that are essential for their functional activity.

Vitamin K is a fat-soluble vitamin requiring bile salts for absorption from the intestines. Thus, deficiency of the vitamin K-dependent factors results when there is impaired bile salts secretion from either intrahepatic or extrahepatic cholestasis.

Thrombocytopenia occurs in approximately 30 to 64% of patients with advanced chronic liver disease; however, the platelet count is rarely less than 30,000 cells/µL, and spontaneous bleeding is uncommon. The primary cause of thrombocytopenia in cirrhosis is portal hypertension-induced splenomegaly because up to 90% of circulating platelets may be sequestered in the enlarged spleen. Decreased hepatic synthesis and serum levels of the cytokine thrombopoietin are also believed to have a causative role in cirrhotics with thrombocytopenia. Increased destruction of platelets by immune mechanism; coexistent, low-grade, disseminated intravascular coagulation; sepsis; and direct suppression of bone marrow thrombopoiesis by ethanol, folate deficiency, and other drugs may all contribute to the development of thrombocytopenia in patients with chronic liver disease.

Dysfibrinogenemia is the most common qualitative abnormality of clotting factors in patients with liver disease. The abnormal functioning of fibrinogen is caused by an increased degree of sialylation of the molecule. This produces abnormal polymerization of fibrin monomers and leads to a disproportionate prolonged thrombin time, despite mild prolongation of the PT and partial thromboplastin (PTT) and normal amount of fibrinogen.

Hyperfibrinolysis is a common finding in patients with advanced liver disease and results from decreased hepatic clearance of plasminogen activator. This complication may be documented by the finding of decreased whole blood

<table>
<thead>
<tr>
<th>SYNDROME</th>
<th>FAILURE (ACUTE TUBULAR NECROSIS)</th>
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<tbody>
<tr>
<td>Urinary sodium concentration</td>
<td>&lt;10 mEq/L</td>
</tr>
<tr>
<td>Urine-to-plasma creatinine ratio</td>
<td>&gt;30:1</td>
</tr>
<tr>
<td>Urinary osmolality</td>
<td>Exceeds plasma osmolality by at least 100 mOsm</td>
</tr>
<tr>
<td>Urinary sediment</td>
<td>Normal</td>
</tr>
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euglobulin clot lysis time, with elevated levels of D-dimer, fibrin, and fibrinogen degradation products.

Diagnosing disseminated intravascular coagulation in cirrhotic patients is difficult. The diagnosis is suggested when there is a known triggering event associated with progressive worsening of coagulation test results and platelet counts, as well as a disproportionate reduction of factor V with a concomitant decreased level of a previously normal factor VIII.

Disorders of coagulation rapidly develop in patients with severe acute liver failure because of the brief half-life of some of the clotting factors. Factors II, V, VII, IX and X are all reduced in acute liver failure. As a consequence, the PT and INR become markedly elevated, serving as prognostic indicators and predictors of the need for transplantation. Reduced concentrations of the vitamin K-dependent factors are due predominantly to a combination of decreased hepatic synthesis and increased consumption of coagulation factors, rather than to vitamin K deficiency.

Thrombocytopenia is also a frequent finding in patients with acute liver failure with platelet counts below 100,000 cells/µL, developing in approximately 66% of patients at some point in their clinical course.

Quantitative and qualitative abnormalities of fibrinogen are also seen, and there is often evidence of excessive thrombin activity, increased fibrinogen turnover, and fibrinolysis, but the relative contributions of disseminated intravascular coagulopathy and impaired hepatic synthesis/clearance to the development of hemostatic abnormalities in acute liver failure remains unclear.

Spontaneous bleeding occurs infrequently in patients with advanced liver disease, and prophylactic treatment is not generally required. Bleeding, however, accounts for 60% of all deaths in cirrhotics having abdominal surgery; therefore, correction of coagulation abnormalities is appropriate prior to major surgical procedures and invasive diagnostic studies. A PT prolonged by >3 seconds or a platelet count of <50,000 cells/µL are considered contraindications to elective surgery.108

Perioperative management includes blood component therapy guided by laboratory studies. Fresh frozen plasma contains all the clotting factors, and administration of 10 to 20 mL/kg will usually correct the PT to nearly normal levels, but the effect lasts for no more than 12 to 24 hours. Vitamin K may improve the PT in patients with cholestatic disease. In these instances, 10 mg subcutaneous vitamin K should be given for 3 consecutive days. Platelets should be infused prophylactically prior to elective surgery when the platelet count is less than 60,000 cells/µL.109

**Endocrine Disorders**

The presence of advanced cirrhosis invariably leads to abnormal regulation and function of multiple endocrine systems. The prevalence and severity of endocrine dysfunction are increased in diseases such as hemochromatosis, in which both the liver and endocrine organs are damaged by a common pathophysiologic process. Cirrhotic patients often have abnormal glucose utilization. The mechanism of this phenomenon is rather complex and includes increased fatty acid concentration in the plasma, which antagonizes the effects of insulin on glucose uptake by skeletal muscles. In addition, plasma levels of growth hormone and glucagon are often increased, and undoubtedly contribute to the glucose intolerance and other derangements of intermediary metabolism that occur in patients with hepatic dysfunction. Patients with cirrhosis are also prone to hypoglycemia. This may reflect glycogen depletion secondary to malnutrition or alcohol-induced glycogenolysis and interference with gluconeogenesis. Severe cirrhosis may also impair hepatic conversion of lactate to glucose.

Abnormal metabolism of sex hormones causes gonadal dysfunction in both men and women. Men undergo feminization, often developing gynecomastia along with a decrease in the size of their testes and prostate gland. The frequency of impotence increases, and sperm counts typically decrease. Women with liver dysfunction commonly exhibit oligomenorrhea or amenorrhea.

**Hepatic Encephalopathy**

Hepatic encephalopathy (HE) is a complex reversible metabolic encephalopathy presenting as a wide spectrum of neuropsychiatric abnormalities in patients with hepatocellular failure and/or increased portal-systemic shunting. The clinical manifestations are highly variable and range from minimal changes in personality or altered sleep patterns without overt signs of HE (minimal HE), to confusion, lethargy, somnolence, and coma. Thirty to 60% of cirrhotics have at least minimal HE. Several well-recognized factors can precipitate HE in patients with cirrhosis who were previously stable (Table 39-7). A large dietary protein load, gastrointestinal hemorrhage, constipation,
hypokalemia, diuretics, and azotemia produce an increased blood ammonia level. Surgery, associated with anesthesia and dehydration, can precipitate an episode of HE because of decreased hepatic perfusion. Sepsis can precipitate HE through increased ammonia production due to protein catabolism, impaired hepatic perfusion, and the effects of cytokines on the central nervous system. Psychoactive drugs can also precipitate HE. The diagnosis has to be made on the basis of clinical findings. Several other conditions that may present in a similar fashion must be excluded, including chronic subdural hematoma, Wernicke's encephalopathy, and electrolyte disturbances.

<table>
<thead>
<tr>
<th>PRECIPITATING FACTOR</th>
<th>POSSIBLE MECHANISMS</th>
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<tbody>
<tr>
<td>Excessive dietary protein</td>
<td>Increased ammonia production</td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
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<tr>
<td>Gastrointestinal bleeding</td>
<td></td>
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<tr>
<td>Infection</td>
<td></td>
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<tr>
<td>Azotemia</td>
<td></td>
</tr>
<tr>
<td>Diarrhea and vomiting</td>
<td>Dehydration with electrolyte and acid-base imbalance, increased ammonia generation, and decreased hepatic perfusion, increasing blood ammonia level</td>
</tr>
<tr>
<td>Diuretic therapy</td>
<td></td>
</tr>
<tr>
<td>Paracentesis</td>
<td></td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Adverse effect on liver and brain function</td>
</tr>
<tr>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Sedatives/hypnotics</td>
<td>Action at the GABA_A/benzodiazepine receptor complex</td>
</tr>
<tr>
<td>Creation of portal-systemic shunt</td>
<td>Reduced hepatic metabolism</td>
</tr>
</tbody>
</table>

It is commonly believed that HE is caused by substances that under normal circumstances are efficiently metabolized by the liver, rather than by insufficient synthesis of substrates essential for normal neurologic function. This notion is consistent with the development of HE in patients following portosystemic bypass who do not have significant intrinsic liver disease. More than 20 different compounds have increased blood concentrations when liver function is impaired. Of these, ammonia has been considered the most important factor in the genesis of HE. Ammonia is produced in the intestine by catabolism of proteins, amino acids, and biogenic amines. Forty percent is derived from intestinal bacterial metabolism of nitrogenous substances, and most of the remainder from digestion of dietary protein. The concentration of ammonia in portal venous blood is high, and a high degree of extraction occurs in the liver where the ammonia is converted to urea and glutamine. This detoxification is impaired in cirrhotics as a result of impaired conversion by the liver and marked portal-systemic shunting. Increased ammonia levels in blood result in increased diffusion of ammonia into the brain. Variation in the transfer of ammonia across the blood-brain barrier may explain the poor relationship between the blood ammonia level and the degree of hepatic encephalopathy. Ammonia has many deleterious effects on brain function. Although this ion seems to play a central role, the clinical features of HE differ from those of pure ammonia intoxication, and therefore, other mechanisms must be involved.

The clinical and neurophysiologic manifestations of HE seem to reflect a global depression of central nervous system function caused by an increase in inhibitory neurotransmission. The observation of an improvement in mental status after the administration of flumazenil, a benzodiazepine receptor antagonist, in some patients with advanced HE who have not taken benzodiazepines supports a role for an increased GABAergic tone. One possible mechanism is an
increased availability of agonist ligands of the GABA receptor complex. These are called natural benzodiazepines and bind to the benzodiazepine site of the GABA receptor. Natural benzodiazepines accumulate in the brains of patients with HE, and it has been suggested that they may induce a decrease in consciousness.

Other putative mechanisms include the effects of a group of potentially neurotoxic compounds of colonic origin (mercaptans, short-chain fatty acids, manganese), impairment of cerebral energy metabolism, gliopathy secondary to astrocyte swelling, and disruption of the blood-brain barrier. Patients with liver failure have an increase in plasma levels of aromatic amino acids and a decrease in branched-chain amino acids. It has been proposed that this imbalance enhances the entry of aromatic amino acids into the brain and that these are channeled into the synthesis of abnormal biogenic amines, which are released along with, or instead of, normal neurotransmitters. These false neurotransmitters (octopamine, phenylethanolamine) are relatively inactive. However, this hypothesis has not been supported by in vivo or postmortem studies. Administration of intravenous branched-chain amino acids does not produce beneficial effects in acute HE.

The main principles of treatment of HE have not been evaluated by randomized clinical trials but rather have been accepted on the basis of clinical observation. Most episodes of HE in patients with cirrhosis are initiated by an identifiable precipitating factor. Because effective methods exist to control most of these, a key component of the treatment of HE is to identify and treat the precipitating cause. Often, the elimination of these factors leads to an improvement without need for any additional therapy. If no precipitating factor can be identified or if rapid improvement does not occur with treatment, therapy should be initiated to reduce the production and absorption of ammonia. Dietary protein intake should be restricted, to an extent dependent on the severity of HE. However, severe restriction of dietary protein is no longer recommended because of the adverse effects of severe malnutrition on liver function and short-term prognosis.

Lactulose (β-galactosidofructose) is a nonabsorbable disaccharide that is not broken down by intestinal enzymes following oral administration, but is metabolized by enteric bacteria in the cecum to lactate and acetate. This produces a reduction of ammonia absorption from the large intestine (because it is converted to ammonium) and net movement of NH₃ from the blood into the bowel. In addition, lactulose enhances the growth of non–urease-producing bacteria, thereby reducing the bacterial production of ammonia, and it also has cathartic activity.

Neomycin is an alternative to lactulose for patients who do not tolerate the disaccharide or have unsatisfactory results. It reduces the intestinal production of ammonia by reducing the population of urease-producing bacteria and may also have nonbacterial effects. Prolonged use should be avoided because of possible toxicity from the small amount of drug that is absorbed. Neomycin is as effective as lactulose.

Zinc deficiency is common in cirrhotics due to increased urinary excretion and malnutrition. Two of the five enzymes responsible for the metabolism of ammonia to urea are zinc dependent; thus, it has been suggested that zinc deficiency contributes to the development of HE. Whether zinc supplementation in this population is beneficial has not been established. Flumazenil, a selective antagonist of the central benzodiazepine receptor, produces a transient improvement in the mental status of some patients with HE, but has no sustained benefits. The dopamine agonists, bromocriptine and levodopa, were introduced to restore the decreased activity of central neurotransmitters caused by false neurotransmitters. Although the false neurotransmitter hypothesis is now questioned, these drugs may help chronic HE patients with extrapyramidal manifestations, which are believed to develop as a result of manganese accumulation in the basal ganglia.

It appears clear that encephalopathic changes are associated with clinically important alterations in pharmacodynamics and pharmacokinetics of various medications. For example, cerebral uptake of benzodiazepines increases substantially, which may reflect an increase in the density or affinity of benzodiazepine receptors or a leaky blood-brain barrier. Drugs administered to patients with advanced hepatic disease require careful titration against effect.

Orthotopic liver transplantation cures HE. Medical management for HE is mainly used for patients who do not yet meet the criteria for liver transplantation, who are waiting for a transplant, or who are not transplant candidates. Without transplantation, overt HE in the patient with chronic liver disease has a poor prognosis, with a survival rate of 42% at 1 year and 23% at 3 years.

**Uncommon Causes of Cirrhosis**

**Wilson's Disease**

Wilson's disease (hepatolenticular degeneration) is a hereditary disease characterized by decreased hepatocellular excretion of copper into the bile and decreased binding of copper to apoceruloplasmin, resulting in hepatic copper...
accumulation, hepatic injury, and decreased ceruloplasmin levels in the blood. Eventually, copper is released into the bloodstream and is deposited in various organs, especially the brain, cornea, and kidneys. Untreated, it is a lethal disease with progressive lenticular degeneration, accompanied by chronic liver disease leading to cirrhosis. Wilson's disease has an autosomal recessive pattern of inheritance. Homozygotes have a defect of the hepatic enzyme required for transmembrane transport of copper into the bile. Wilson's disease occurs worldwide with an average prevalence of approximately 30 affected individuals per million population. It can present clinically as liver disease, as a progressive neurologic disorder, or as a psychiatric illness.

The clinical presentation of liver dysfunction in patients with Wilson's disease can range from asymptomatic, with only biochemical evidence of damage, to fulminant liver failure requiring urgent liver transplantation for survival. Histologically, steatosis and focal hepatocellular necrosis occur early, with progression to fibrosis and cirrhosis, which is present in most untreated patients by the second decade of life. Neurologic dysfunction typically becomes evident later than liver disease. Tremors, gait disturbances, and slurring of speech are common manifestations, simulating Parkinson's disease. Kayser-Fleischer rings are a pathognomonic sign but are present in only 50 to 62% of patients with Wilson's disease at the time of diagnosis. They represent copper deposition in Decemet's membrane of the cornea and usually require a slit-lamp examination for their identification.

A combination of clinical findings and biochemical testing is necessary to establish the diagnosis of Wilson's disease. Recognition of Kayser-Fleischer rings, increased liver copper concentrations on percutaneous biopsy samples, reduced concentration of ceruloplasmin in the blood, and increased urinary copper excretion can point to the correct diagnosis prior to development of neurologic symptoms. A hepatic copper content of ≥250 µg/g dry weight is the best biochemical evidence for Wilson's disease. The combination of a blood ceruloplasmin level <200 mg/L associated with the presence of Kayser-Fleischer rings is also diagnostic.

Lifelong pharmacologic treatment is given to symptomatic patients or to those with active disease. The oral chelating drugs D-penicillamine or trientine bind copper and thereby promote urinary excretion. Liver transplantation corrects the underlying hepatic defect, but is reserved for patients with decompensated liver disease unresponsive to medical therapy and for patients presenting with fulminant hepatic failure.

Hereditary Hemochromatosis

Hemochromatosis is a hereditary disease characterized by excessive iron absorption from the duodenum and subsequent tissue deposition producing organ damage, which is frequently irreversible. Hemochromatosis may be the most common autosomal-recessive genetic disease in Caucasians. It is estimated that 1 in 10 to 20 Caucasians carry the disease gene, and 1 in 400 are homozygotes who are at risk of clinical disease. It is currently impossible to predict whether and to what extent the mutation will be expressed and, in a small percentage of homozygotes, laboratory evidence of altered iron metabolism never develops.

Hemochromatosis occurs when intestinal absorption of dietary iron exceeds bodily needs. The primary site for regulating iron absorption is in duodenal mucosa cells. Duodenal iron absorption is normally minimized when body iron stores are increased. In hemochromatosis, this step is inappropriately controlled, and although iron overload is present, enterocytes continue to transfer unneeded iron into the bloodstream. A gradual and progressive expansion of the plasma iron compartment occurs that produces an increased transferrin-saturation value (the earliest detectable biochemical abnormality in hemochromatosis).

Symptomatic organ involvement usually does not begin until the fourth or fifth decade of life, and reflects injury induced by parenchymal iron deposition. The nonspecific initial symptoms often found in these patients, such as unexplained weakness, lethargy, and arthralgias, makes consideration of hemochromatosis unlikely. Subsequently, liver disease often predominates and may range from transaminitis to end-stage cirrhosis with signs of portal hypertension. Hepatomegaly is the most common physical finding on presentation, found in 80% of patients, followed by increased skin pigmentation in 75%. Once the patient has developed cirrhosis, the chances of developing hepatocellular carcinoma are increased 200-fold.

In addition to hepatic infiltration, iron deposition frequently affects: (1) islet cells of the pancreas producing diabetes mellitus; (2) the pituitary gland, producing hypogonadotrophic hypogonadism, impotence, and hypothyroidism; (3) the myocardium, frequently with dysrhythmias, while up to one-third of untreated patients die of cardiac failure; and (4) the skin, with a characteristic bronze discoloration.

Thanks to increasingly early diagnosis, the classic triad of cirrhosis, diabetes mellitus, and bronze skin is now rare in adult-onset hemochromatosis. The best diagnostic test is the serum transferrin saturation level, which is normally less than 50%. In the absence of significant liver disease, which would lead to decreased hepatic transferrin
synthesis, a transferrin saturation level consistently greater than 62% is associated with a greater than 90% chance of hemochromatosis. Suggestive laboratory results should be followed by a liver biopsy; the presence of substantial stainable iron in parenchymal liver cells is characteristic of hemochromatosis.

Once the diagnosis is confirmed by liver biopsy, the patient should be treated by repeated phlebotomy to remove excess iron from tissues and the blood. If initiated early in the course of the disease, organ damage can be prevented and survival improved. Established organ damage cannot be reversed, but progression can be slowed.

Primary Biliary Cirrhosis
Primary biliary cirrhosis (PBC) accounts for up to 2% of worldwide deaths from cirrhosis. It is a chronic progressive cholestatic liver disease of unknown etiology that most commonly affects middle-age women. Genetic factors play a role in the development of PBC, but it is not inherited in a simple dominant or recessive pattern. PBC is characterized by portal inflammation, destruction of the small intrahepatic bile ducts, and progressive scarring. It commonly presents as unexplained hepatomegaly or an elevated alkaline phosphatase level in an asymptomatic patient. Fatigue and pruritus are often the initial symptoms. Jaundice is a late manifestation of the disease. The antimitochondrial antibody test is positive in 95% of patients and is relatively specific for the disease. There is a strong association between PBC and other autoimmune diseases. The diagnosis should be confirmed by percutaneous liver biopsy, which also provides staging and prognostic data. The median survival of symptomatic patients is approximately 7 years. There is no generally accepted effective medical treatment, although cholestyramine may alleviate pruritus. Liver transplantation is the only treatment that improves survival.

α-1-Antitripsin Deficiency
Patients with homozygous deficiency of serum α-1-antitrypsin (α-1-AT) develop a slowly progressive liver disease that most commonly progresses to asymptomatic cirrhosis, which may be complicated by the development of hepatocellular carcinoma. Adult patients with this disorder often have emphysema. The molecular basis for the disease is related to a single nucleic acid substitution. The diagnosis is suggested by the presence of hepatomegaly, mild LFT abnormalities, and the absence of α-1-AT on serum protein electrophoresis. The diagnosis is confirmed by direct measurement of serum α-1-AT and/or demonstration of characteristic periodic acid-Schiff-positive, diastase-resistant globules adjacent to portal tracts on liver biopsy.

Budd-Chiari Syndrome
Budd-Chiari syndrome is a heterogeneous group of disorders characterized by outflow obstruction of blood, from the liver to the right heart. The pathologic processes responsible for the syndrome can be categorized into three groups: those that affect the hepatic venules, those obstructing the major hepatic veins, and those preventing the flow of blood from the hepatic veins into the right atrium.

Hepatic veno-occlusive disease refers to obstruction of hepatic venous outflow at the level of the central or sublobular veins. Cytotoxic agents used in preparation of patients for bone marrow transplantation are the most common causes of the disease in the United States. Obstruction of the major hepatic veins is most commonly related to an underlying hypercoagulable state, including myeloproliferative disorders or malignancies that involve the hepatic veins either directly or by extension of tumor thrombus. Obstruction of the IVC proximal to the right atrium is commonly the result of either a membranous intracaval web or caval thickening.

Obstruction of venous outflow results in increased hepatic sinusoidal pressure and portal hypertension. Hepatic venous stasis and congestion causes hypoxic damage to adjacent hepatic parenchymal cells and cells lining the sinusoids. Hepatocyte necrosis develops in centrilobular regions followed by fibrosis, nodular regeneration, and ultimately, cirrhosis.

The clinical presentation is highly variable, and depends on the extent and rapidity of hepatic vein occlusion and on the development of a collateral circulation to decompress the sinusoids. Symptoms include right upper quadrant tenderness secondary to hepatomegaly and abdominal distension due to ascites. Laboratory evaluation usually reveals modest alteration in liver function tests and low serum albumin. Rarely, fulminant liver failure occurs if there is rapid and complete occlusion of the hepatic veins and secondary thrombosis of the portal vein as the result of hepatic outflow obstruction.

A variety of noninvasive tests can be used to support the diagnosis of Budd-Chiari syndrome. Doppler ultrasonography of the liver is the most cost-effective radiographic tool for initial evaluation when the syndrome is suspected. It will reveal absent or diminished hepatic venous blood flow, thrombosis of the IVC, and liver and spleen

P.1100
enlargement. CT and MRI scanning are more expensive alternatives. Once the diagnosis is suggested by its clinical features and noninvasive radiographic evaluation, venography with cannulation of the hepatic veins is usually performed. The diagnosis is confirmed by a “spiderweb.” If appropriate, a number of interventional procedures can then be performed, including thrombolytic therapy and balloon angioplasty.117

Untreated, Budd-Chiari syndrome will result in death within months to years. Therapy includes medical management and relief of hepatic venous outflow obstruction to prevent further hepatic injury or liver transplantation in selected patients, especially those with fulminant liver failure.

Medical therapy is limited primarily to anticoagulation and thrombolysis. The latter is considered in patients with acute onset of the syndrome, especially if angiography reveals fresh thrombus in the hepatic veins and IVC. The thrombolytic agent is infused directly into the thrombosed vein for approximately 24 hours. Percutaneous transluminal angioplasty of localized segments of narrowed hepatic veins or inferior vena caval webs may result in dramatic improvement, although the risk of restenosis is high. This may be prevented with intravascular metal stent placement.

The mainstay of therapy involves surgical intervention. By relieving sinusoidal hypertension, portosystemic shunting may reverse hepatic necrosis and prevent the development of cirrhosis. The most commonly used technique is a side-to-side portocaval shunt. Liver transplantation is usually reserved for those patients with decompensated cirrhosis, fulminant hepatic failure, or failure of a portosystemic shunt.117

HEPATOCELLULAR CARCINOMA

Primary hepatocellular carcinoma (HCC) is one of the most common tumors in the world and the third most frequent cause of death from cancer. It occurs in the United States with an incidence of 2.4 individuals per 100,000 population. HCC usually arises in a cirrhotic liver. Cirrhosis secondary to chronic viral hepatitis accounts for the large majority of HCC worldwide but only 30 to 40% of reported cases in America. Thus, there are many individuals in whom no obvious cause can be identified. Inherited metabolic diseases, including hemochromatosis, α-1-antitrypsin deficiency, and Wilson's disease, are well known to be risk factors for the development of HCC. Another implicated factor is alcohol. Alcoholic cirrhosis may clearly result in HCC, but it is uncertain whether alcohol is directly carcinogenic or whether associated hepatocellular injury and regeneration, iron accumulation, or coexistent hepatitis C infection is responsible.

HCC may escape early clinical detection because it occurs in patients with underlying cirrhosis, and the clinical findings may suggest progression of the underlying disease. The most common presenting complaint is abdominal pain, and the most frequent finding on physical examination is an abdominal mass. Serum alpha fetoprotein (AFP) values are greater than 500 µg/L in about 70 to 80% of patients with HCC. Unfortunately, AFP has a low specificity and levels may be elevated in pregnancy, germ cell tumors, and acute or chronic hepatitis. Hepatic ultrasound has greater sensitivity and specificity than AFP levels when used for HCC screening. Three imaging procedures are in common use for diagnosing HCC, ultrasonography, helical CT, and MRI. The sensitivity and specificity of radiologic studies for detection of HCC is unknown.

Chemoembolization is widely used for treatment of HCC. No studies have shown a long-term survival advantage in treated versus untreated patients. Surgical resection offers a chance for cure; however, few patients have a resectable tumor at the time of presentation. Patients with two or fewer lesions, each smaller than 5 cm, which are encapsulated and have no evidence of macroscopic vascular invasion are the best candidates for hepatic resection. Operative mortality in cirrhotics is approximately 10%.118 Liver transplantation may be considered as a therapeutic option for patients who have a single lesion ≤5 cm or three or fewer lesions ≤3 cm. Survival after transplantation in these groups is similar to that of patients transplanted for nonmalignant disease.

PREGNANCY-RELATED DISORDERS

Well-known disorders of pregnancy that can cause fulminant hepatic failure during the third trimester or in the immediate postpartum period include acute fatty liver of pregnancy (AFLP) and the HELLP syndrome (Hemolysis, Elevated Liver enzymes, Low Platelets). In addition, parturients are unusually susceptible to morbidity and mortality from hepatitis E infection and herpes simplex hepatitis.

Acute Fatty Liver of Pregnancy

AFLP occurs in the late stages of pregnancy. Although severe cases are rare (frequency of 1/6,659 deliveries in a 1999 report), it is now recognized to exist in a broad clinical spectrum ranging from mild to severe hepatic disease. The pathogenesis is unclear, but an association between inherited defects in beta-oxidation of fatty acids and AFLP
is now well established. Some affected patients have an inherited long-chain 3-hydroxyacyl-CoA dehydrogenase
deficiency, which causes a defect in intramitochondrial beta-oxidation of fatty acids. Other patients with AFLP have
a defect in beta-oxidation caused by deficiency of carnitine palmitoyltransferase I.

Affected women usually present in the third trimester with symptoms related to hepatic failure. Initial symptoms
are variable, and include nausea, vomiting, abdominal pain, and encephalopathy. Modest elevations of serum
transaminases (<750 U/L) are usual. Jaundice is common as is laboratory evidence of renal dysfunction and
leukocytosis. Prolongation of the prothrombin time and other laboratory findings of disseminated intravascular
coagulation are often present and help distinguish AFLP from HELLP syndrome. Severely affected patients have
complications typical of any form of fulminant hepatic failure, including hepatic coma and renal failure. Some
patients are asymptomatic, with the diagnosis made during evaluation of abnormal liver function tests. Imaging
techniques have not been consistently useful for confirming the diagnosis of AFLP. Although a liver biopsy can be
diagnostic, it is often contraindicated because of coagulopathy. Therefore, the diagnosis of AFLP is clinical. When a
biopsy is available, the characteristic histologic finding is microvesicular fatty infiltration most prominent in the
central zone, with sparing of the periportal hepatocytes.

When AFLP is diagnosed, delivery of the fetus is expedited, usually by induction of labor or, occasionally, cesarean
section, because AFLP improves in response to termination of pregnancy. After delivery, maximal supportive care
is required as the liver recovers. Most affected women recover completely, although severe cases may require
prolonged intensive care. On rare occasions, liver transplantation has been necessary. Recurrence of AFLP with
future pregnancy is uncommon.

Preeclampsia and HELLP Syndrome

HELLP syndrome was defined by Weinstein in 1982. It is now recognized to be a common and potentially ominous
complication of preeclampsia, affecting 10% of women with this disorder, and 20% of women with severe
preeclampsia. The presence of HELLP syndrome is associated with an increased risk of maternal (1%) and perinatal
(up to 20.4%) death. The diagnosis of HELLP syndrome is made clinically by the presence of signs of preeclampsia
and laboratory evidence of hemolysis (elevated serum LDH level, schistocytes and burr cells on peripheral smear),
elevated serum transaminases due to ischemic hepatocellular necrosis (up to several thousand IU), and
thrombocytopenia (<100,000 cells/µL). Hyperbilirubinemia occurs in approximately 40% of cases of HELLP, and may
be caused by hemolysis and liver dysfunction. The presence of full-blown coagulopathy is rare and should raise
concern for the presence of hepatic failure caused by AFLP. It should be noted that there is considerable
disagreement in the medical literature about the diagnostic criteria for the HELLP syndrome.

Liver biopsy is rarely warranted, but when performed, the specimens usually demonstrate periportal hemorrhage
and fibrin deposition with periportal hepatic necrosis. Both macrovesicular and microvesicular fat are present, but
steatosis is usually modest and is unlike the pericentral microvesicular fat seen in AFLP. The liver involvement in
HELLP syndrome is most frequently misdiagnosed as viral hepatitis, although thrombocytopenia is an uncommon
finding in the latter disease. AFLP also should be considered, but is usually associated with more severe liver failure
and not necessarily with thrombocytopenia. All affected patients should be considered to have severe preeclampsia.
Once the diagnosis is made, management is primarily supportive. There is a consensus of opinion that prompt
delivery is indicated if the syndrome develops beyond 34 weeks’ gestation or earlier if life-threatening morbidity
develops in the mother. When HELLP syndrome develops prior to 34 weeks’ gestation, management is controversial
with the choice of either providing supportive care with close monitoring of mother and fetus until the fetus is
mature, or administration of corticosteroids to accelerate fetal lung maturity followed by delivery after 24 hours.

In most affected patients, all abnormalities associated with preeclampsia and HELLP syndrome resolve after
delivery, leaving no hepatic sequelae. Rarely, the condition worsens progressively after delivery with further
diminution of the platelet count and development of sepsis with multisystem organ failure.

Hepatic Rupture, Hematoma, and Infarct

These conditions occur in preeclampsia and may be the extreme end of the spectrum of HELLP syndrome. Patients
with spontaneous rupture of the liver present close to term with abdominal pain and distension, as well as
cardiovascular collapse. The rupture results from extravasation of blood, presumably from one or several
microscopic areas of periportal hemorrhage with subsequent separation of Glisson's capsule from the liver surface
and eventual capsule rupture. The diagnosis depends on a high index of suspicion and identification of
hemoperitoneum on abdominal ultrasonography, CT scan, or MRI. If the rupture goes undiagnosed, death results for
both mother and fetus. Aggressive management is essential, with vigorous hemodynamic support, rapid delivery of
the fetus, and surgical repair of the liver. Some patients may have a contained subcapsular hematoma without frank rupture into the peritoneum. These patients may be managed expectantly with serial hepatic CT scans.

Hepatic infarction typically occurs in the third trimester and presents with right upper quadrant pain, fever, leukocytosis, and marked elevations of serum transaminases. The infarcts can be seen on abdominal CT scan. Management is supportive.

CHOLESTATIC DISEASE

Cardiovascular Dysfunction
The presence of bile salts in circulating blood (choleemia) can impair myocardial contractility. Choleemia also blunts the response to norepinephrine, angiotensin II, and isoproterenol, probably by interfering with their binding to membrane receptors. Less severe hemodynamic perturbations occur in patients with biliary obstruction than in those with cirrhosis. However, the pattern of the pathophysiologic change is remarkably similar: increases in peripheral vasodilatation, cardiac output, and portal venous pressure, and a decrease in portal venous blood flow.

Coagulation Disorders
Cholestatic disease predisposes the patient toward development of coagulopathy primarily related to vitamin K deficiency. During even brief episodes of biliary obstruction, coagulopathy can result from a deficiency of coagulation factors whose activation depends on the presence of vitamin K. Absorption of vitamin K depends on the excretion of bile into the gastrointestinal tract. Long-lasting biliary obstruction can cause liver injury, with subsequent deterioration in the hepatic synthesis of proteins, including coagulation factors. Usually, the coagulation disorders are moderate, and parenteral vitamin K corrects the problem. If this treatment is not fully effective, one should suspect that the disease is not purely cholestatic and that hepatic parenchymal injury exists. If such patients need urgent surgery, the coagulopathy will require immediate treatment with fresh frozen plasma. The failure of parenteral vitamin K to correct a prolonged prothrombin time typically indicates the presence of severe hepatic parenchymal dysfunction and portends a poor prognosis.

PERIOPERATIVE MANAGEMENT
PREOPERATIVE

Hepatic Evaluation and Preparation
As with any preoperative evaluation, the history, physical exam, and laboratory tests are the initial modalities employed. While obtaining the history, inquiry should be made about risk factors and the presence of symptoms attributable to chronic liver disease. The history should include questions about prior episodes of jaundice and their relationship to surgical procedures and the anesthetic techniques used, blood product transfusions, use of alcohol and other recreational drugs, current medications (including herbal preparations), family history of jaundice or liver disease, travel history, and an occupational history (exposure to hepatotoxins). In the review of systems, the patient should be asked about easy bruising, anorexia, weight loss or gain, fatigue, nausea, vomiting, pain with fatty meals, pruritus, abdominal distension, and episodes of gastrointestinal bleeding.

The usage of prescription, over-the-counter medications, and herbal preparations is ubiquitous. Polypharmacy is unfortunately the rule, rather than the exception, especially in elderly and debilitated patients who undergo major operations. Thus, the capacity of pharmacologic agents to injure the liver is an important perioperative concern. Some 500 to 1,000 therapeutic agents have been implicated in causing a broad spectrum of liver diseases. These diseases may be classified in accordance with whether the drug produces primarily direct cell toxicity (necrosis), cholestasis, or steatosis. Most forms of drug-induced liver disease are benign and of little consequence (e.g., estrogen-induced cholestasis), producing only transient alterations of LFT. Severe drug toxicities, which are typically dose related (acetaminophen), or idiosyncratic (halothane), are responsible for 15 to 30% of cases of fulminant hepatic failure and 20 to 50% of cases of chronic nonviral hepatitis. Moreover, when drug reactions produce hepatocellular necrosis, the estimated case fatality approaches 50%.

Drugs known to produce hepatocellular injury and centrilobular necrosis include acetaminophen, isoniazid, and methyl dopa. Other cytotoxic drugs include oxphenisatin, rifampin, papaverine, phenytoin, indomethacin, monoamine oxidase inhibitors, and amitriptyline. The use of dantrolene for treatment of muscle spastic disorders has been associated with the development of hepatic failure in patients receiving the drug for more than 60 days. Cholestatic reactions often result from drugs such as chlorpromazine, phenylbutazone, and androgenic and anabolic
steroids. In at least one case, erythromycin (ethylsuccinate form) has caused hepatic failure that had initially been attributed to halothane administration.

A drug's potential to cause hepatotoxicity is influenced by various pharmacologic (other drugs) or pathophysiologic (hepatitis) factors. For example, the combination of trimethoprim and sulfamethoxazole is nearly five times more frequently associated with hepatotoxicity than sulfamethoxazole alone. By inducing hepatic microsomal drug-metabolizing systems, some drugs can markedly increase the injurious potential of others by altering their metabolism to favor the production of toxic metabolites. For example, phenobarbital increases the hepatotoxicity of various drugs, including chemotherapeutic agents (methotrexate) and antibiotics (tetracycline).123

Ethanol is obviously an important hepatotoxin. Although elective surgery is not contraindicated in patients with alcoholic steatosis, the mortality from acute alcoholic hepatitis, even without surgery, is significant. Animal studies indicate that alcohol ingestion increases the likelihood that centrilobular necrosis will develop after halothane anesthesia, which may relate to the ability of ethanol to increase hepatic hypoxia. Therefore, if alcoholic hepatitis is suspected, further examination of liver function is warranted before performing an elective operation.

The physical examination of the patient with chronic liver disease is particularly valuable because the patient may appear ill before there is laboratory evidence of hepatic dysfunction. The examination should focus on signs such as scleral icterus, jaundice, ascites, splenomegaly, palmar erythema, gynecomastia, asterixis, testicular atrophy, spider angioma, petechiae, and ecchymosis. The liver may be enlarged with a tender soft and smooth edge if the patient has hepatitis, or firm and nodular with cirrhosis or malignancy. Patients with chronic hepatitis often have extrahepatic manifestations, including arthritis, skin rashes, and thyroiditis.

Acute liver failure has a distinct clinical presentation. Typically, nonspecific symptoms such as nausea and malaise are followed by the rapid onset of jaundice and subsequently altered mental status, which may progress to coma with clinical and radiologic evidence of cerebral edema.

If no suspicion of liver dysfunction arises from a thorough history and physical exam, then laboratory tests for liver function do not need to be routinely sent because of the low prevalence of disease. Routine testing may yield false-positive results, engendering patient anxiety and prompting the performance of expensive, unnecessary, and potentially dangerous invasive tests. If, however, hepatic dysfunction is known or suspected, then the degree of dysfunction should be quantified by applying either the Child-Pugh or Model of End-stage Liver Disease (MELD) scoring system. A dilemma arises when a patient without any risk factors or stigmata of liver disease is found to have one or more abnormal LFT abnormalities on a recent blood test (e.g., routine yearly employment health assessment). The prudent action may be to delay surgery and repeat the tests later. This conservative approach helps ensure a patient is not in the early stages of a disease process (e.g., hepatitis) that may abruptly worsen and may minimize the medical-legal risk for the anesthesiologist. Acute hepatitis (viral, alcoholic, ischemic, or drug related) is associated with increased perioperative risk and mortality. For nonemergent procedures, supportive care allowing an improvement in their overall condition will diminish their perioperative risk. Therefore, in the presence of acute hepatic disease, elective surgery should be postponed (Fig. 39-16).
Perioperative Risk Associated with Acute and Chronic Liver Disease

Because of our limited ability to support a failing liver, the perioperative risks associated with acute and chronic liver disease present significant challenges. The increased surgical morbidity and mortality associated with varying degrees of liver insufficiency have been described in detail for over four decades. What remains less clear, however, is whether perioperative outcomes can be improved with proactive interventions.

Regardless of the etiology, an increased magnitude of liver dysfunction is associated with a higher probability of morbidity and mortality. Thus, it is important to quantify and grade preoperative liver dysfunction. Most risk assessment studies about liver disease address expected life span in reference to the prioritization of candidates for liver transplant. In 1999, a new classification system called MELD was designed to predict the outcome of decompressive therapy for portal hypertension. MELD integrates weighted values of three parameters: serum bilirubin, INR, and serum creatinine:

\[
\text{MELD score} = 0.957 \times \log_e (\text{creatinine mg/dL}) + 0.378 \times \log_e (\text{bilirubin mg/dL}) + 1.120 \times \log_e (\text{INR}) + 0.643
\]

The model was developed from prospective data. MELD has since been adopted by the United Network of Organ Sharing in the United States to prioritize patients for liver transplantation.

Child and Turcotte first described their classification system in 1964. They selected five parameters—serum albumin, serum bilirubin, ascites, encephalopathy, and nutritional status—each graded at one of three levels of severity, and combined to generate an assignment to one of three classes (A to C). Mortality was assessed following portosystemic shunt operations. In 1972, Pugh modified the Child-Turcotte system, replacing the subjective assessment of nutritional status with the more objective PT (Table 39-8).

<table>
<thead>
<tr>
<th>PRESENTATION</th>
<th>POINTS</th>
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<tbody>
<tr>
<td>Albumin (g/dL)</td>
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<tr>
<td>&gt;3.5</td>
<td>1</td>
</tr>
<tr>
<td>2.8–3.5</td>
<td>2</td>
</tr>
<tr>
<td>&lt;2.8</td>
<td>3</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td></td>
</tr>
<tr>
<td>Seconds prolonged</td>
<td></td>
</tr>
<tr>
<td>&lt;4</td>
<td>1</td>
</tr>
<tr>
<td>4–6</td>
<td>2</td>
</tr>
<tr>
<td>&gt;6</td>
<td>3</td>
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<tr>
<td>International normalized ratio</td>
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<td>&lt;1.7</td>
<td>1</td>
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<tr>
<td>1.7–2.3</td>
<td>2</td>
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<tr>
<td>&gt;2.3</td>
<td>3</td>
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<tr>
<td>Bilirubin (mg/dL)</td>
<td></td>
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<tr>
<td>&lt;2</td>
<td>1</td>
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<tr>
<td>2–3</td>
<td>2</td>
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<td>&gt;3</td>
<td>3</td>
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<td>Ascites</td>
<td></td>
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<tr>
<td>Absent</td>
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<tr>
<td>Slight-moderate</td>
<td>2</td>
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<tr>
<td>Tense</td>
<td>3</td>
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<tr>
<td>Encephalopathy</td>
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<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Grade I-II</td>
<td>2</td>
</tr>
<tr>
<td>Grade III-IV</td>
<td>3</td>
</tr>
</tbody>
</table>

TABLE 39-8 Modified Child-Pugh Score
It is important to note that surgical mortality from hepatic shunt and transplant procedures is less than that from other major surgery. In 1997, Rice et al. reported a retrospective analysis of 40 consecutive patients over a 5-year period undergoing general anesthesia for surgery, including 28 abdominal procedures, 2 coronary artery bypass grafts, 5 orthopaedic procedures, and 5 miscellaneous procedures. By multiple logistic regression analysis, an INR greater than 1.6 and encephalopathy were associated with a greater than 10- and 35-fold increased mortality risk, respectively. However, Child classification and Pugh score failed to predict 30-day mortality. Also in 1997, Mansour and associates studied mortality of patients with liver disease undergoing abdominal surgery. Their retrospective analysis from a single institution reported operative 30-day mortality on 92 cirrhotic patients during a 12-year period. Types of surgery were divided into four categories: cholecystectomy, hernia repair, gastrointestinal, and miscellaneous procedures. Twenty-six percent of operations were performed as emergencies. Child class A was associated with 10% mortality, class B with 30%, and class C with 82%. Gastrointestinal procedures and emergent operations were associated with the highest mortality. For comparison, the 3-month mortality in patients hospitalized for liver complications but not undergoing surgery was 4% for Child class A, 14% for class B, and 51% for class C.

MELD score has shown comparable prediction of short-term, nonoperative mortality in advanced cirrhosis when compared with the Child classification. Except for liver transplantation and shunt procedures, MELD is not commonly used to predict perioperative morbidity and mortality. The scoring of liver disease is only one component of evaluating perioperative risks. Other considerations are the patient's age; coexisting diseases; and the type, location, and duration of the surgery. Accurate assessment and communication of perioperative risks is an essential condition of informed consent.

Scant data exist to support lengthy preoperative admissions for “optimization,” especially for patients with mild hepatic dysfunction having minor operative procedures. Patients with severe or long-standing hepatic dysfunction, however, may benefit from aggressive inpatient correction of certain abnormalities. Liver-related conditions that may benefit from preoperative correction or optimization include ethanol dependency, coagulopathy, malnutrition, anemia, SBP, and hepatic encephalopathy. Esophageal varices can be treated as previously discussed. Preoperative coagulopathy warrants particular attention. Ideally, coagulation abnormalities should be corrected preoperatively, and this should help minimize intraoperative blood loss and thereby decrease the risk of major complications, including development of postoperative HRS. Significant coagulation abnormalities must be corrected prior to performing a spinal or epidural anesthetic. Increased PT or INR in patients with either cholestasis or obstructive jaundice may respond to a few days of vitamin K therapy, but if unsuccessful or if the urgency of surgery does not allow adequate time for a response, administration of fresh frozen plasma is indicated. Platelet transfusion should be considered for patients with evidence of platelet dysfunction or thrombocytopenia (<100,000 cells/µL).

Minor operations do not cause postoperative liver dysfunction in healthy patients. Even patients with marginal hepatic function usually tolerate peripheral procedures without hepatic complications, including those who receive halothane anesthesia. A randomized study in patients with mild alcoholic hepatitis compared spinal versus general anesthesia (enflurane plus N2O plus opioid) and found no anesthesia-related differences in values of LFTs following peripheral or superficial surgery.
Major operations (especially laparotomy) are often associated with hepatic dysfunction or injury. The magnitude of the abnormality depends more on the type of operation than on a particular anesthetic technique. Nonetheless, hepatic dysfunction subsequent to major surgery is rarely of concern in healthy patients. In contrast, patients with advanced hepatic disease (marginal hepatic function) who undergo major operations, such as laparotomy, have extremely high postoperative morbidity and mortality. These patients are probably unable to tolerate the surgical stress, which contributes to decreased hepatic oxygen supply.

Medications needed to control the myriad complications of severe liver disease should be continued throughout the perioperative period. Preoperative sedatives, when indicated, should be used in lower doses because of the marked derangements in pharmacokinetics and pharmacodynamics associated with advanced liver disease. These patients may have a full stomach, even if they have not taken food or fluid for several hours, because of hiatal hernia, massive ascites, and decreased gastric and intestinal motility. Therefore, premedication may include an H2-receptor blocker, metoclopramide, as well as sodium citrate.

**Anticipated Pharmacokinetic and Pharmacodynamic Alterations**

Drugs administered to patients with advanced hepatic disease require careful titration against effect. It appears clear that encephalopathic changes are associated with clinically important alterations in the pharmacodynamics and pharmacokinetics of various medications. For example, cerebral uptake of benzodiazepines increases substantially, which may reflect an increase in the density or affinity of benzodiazepine receptors or a leaky blood-brain barrier. Data concerning the pharmacokinetics of midazolam in patients with advanced liver disease are conflicting. One study demonstrated a significant decrease in clearance and elimination half-life, whereas another study demonstrated only slightly impaired disposition in cirrhotic patients. The pharmacokinetics of single doses of sufentanil and propofol were found to be similar in cirrhotic patients and those with normal hepatic function, although some differences in elimination time were observed. Such findings imply that administering infusions or multiple doses of certain intravenous drugs can result in prolonged pharmacologic effects because of impaired hepatic elimination in patients with advanced hepatic disease. The differences in the results of these studies are probably a consequence of certain differences in the binding proteins, as well as in the accumulation of endogenous binding inhibitors such as bilirubin. These findings might explain a smaller degree of midazolam protein binding in cirrhotic individuals, with a subsequent increase in the free fraction of the drug and enhancement of the pharmacologic effect in cirrhotic patients.

For thiopental, total plasma clearance and total apparent volume of distribution at the steady state are unchanged in cirrhotic patients. Therefore, the elimination half-life is not prolonged. Thiopental has a low extraction ratio, so its clearance is independent of hepatic blood flow. Nonetheless, decreases in plasma protein binding, which are often unpredictable, may cause excessive pharmacologic responses to standard doses of the various agents used to induce anesthesia.

The plasma clearance of fentanyl is significantly lower in cirrhotic patients than in control subjects. The total apparent volume of distribution does not change, but the elimination half-life increases owing to decreased plasma clearance. With alfentanil, the free fraction also increases, and this agent exerts prolonged and pronounced effects in cirrhotic patients with advanced liver disease.

The data regarding morphine pharmacokinetics in cirrhotic patients are contradictory. For example, Patwardhan and associates reported that the pharmacokinetics of morphine in cirrhotic patients and healthy people are similar. They suggested that the “reported intolerance to the central effects of morphine cannot be explained by impaired drug elimination and increased availability of morphine to cerebral receptors.” Other investigators, however, reported that the clearances of free morphine and its metabolites are decreased and their half-lives prolonged in cirrhotic patients compared with healthy control subjects.

Although hepatic disease often produces substantial pharmacokinetic changes, it can also lead to important pharmacodynamic alterations. Patients with cirrhosis, particularly those with hepatic encephalopathy, are much more sensitive to sedatives (e.g., opioids, benzodiazepines) than are healthy people. For example, at equal plasma concentrations of diazepam, more pronounced encephalographic alterations occur in those with severe hepatic disease than in healthy people. By contrast, pharmacologic responses to some medications decrease in patients with cirrhosis and portal hypertension as a result of the pathophysiologic changes associated with the disease. Increases in plasma concentrations of certain vasodilatory substances antagonize responses to catecholamines and other vasoconstrictors. Patients, as well as animals with portal hypertension, have elevations of plasma glucagon, which substantially reduces the responses of a variety of blood vessels to catecholamines. Thus, while patients with advanced liver disease often require reduced doses of central nervous system depressants, they
require increased doses of catecholamine or addition of a nonadrenergic vasoconstrictor (vasopressin) when such therapy is needed to support blood pressure.

**INTRAOPERATIVE**

**Monitoring and Vascular Access**

In addition to using the routine array of monitors required by the American Society of Anesthesiologists (ASA), the need for invasive monitoring and degree of vascular access will be dictated by the severity of the liver disease and type of surgery. For severely ill patients or major operative procedures, cannulation of an artery is important for direct and continuous blood pressure monitoring, as well as for periodic determinations of blood gases, electrolytes, hematocrit, and other laboratory data as needed during surgery. Because patients with advanced liver disease may present with multiple complex hemodynamic abnormalities, a central venous catheter, or even a pulmonary artery catheter may be of utility for confirming diagnoses of hypovolemia, abdominal compartment syndrome, distributive shock, or congestive heart failure, as well as for following responses to therapeutic intervention and for monitoring trends as the case progresses. In addition, because coagulopathies can accompany even mild hepatic insufficiency, the surgical bleeding encountered may be far in excess of that anticipated based on normal circumstances. Large-bore vascular access is encouraged for all but the most minor of procedures. Intraoperative monitoring of coagulation status presents formidable challenges; baseline values may be abnormal despite lack of bleeding. Intraoperative PT, PTT, and platelet count usually take too long for results to be of much utility during a large blood-loss operation. Assessing the activated clotting time and thromboelastography may be helpful, although clinical assessment remains the standard for intraoperative diagnosis of coagulopathy.151

**Selection of Anesthetic Technique**

For most cases, the presence of liver disease will not alter the choice of anesthetic technique based on other common considerations. Regional anesthesia is generally the preferred technique in patients without coagulation abnormalities who are undergoing peripheral surgery. However, it would be difficult to justify using regional anesthesia or analgesia for patients with overt coagulopathies or for those having major or lengthy operations. Local anesthesia with sedation is usually the least invasive for relatively minor procedures, such as sclerotherapy. Adequate sedation is essential to minimize sympathetic stimulation and resultant decreases in hepatic blood flow and oxygen delivery. A short-acting benzodiazepine, such as midazolam combined with remifentanil, or a low dose of fentanyl, will usually provide sedation, anxiolysis, and analgesia. As mentioned, patients with advanced hepatic disease have extensive pharmacodynamic and pharmacokinetic abnormalities, so each medication should be titrated carefully to achieve the desired effect.

**Induction of General Anesthesia**

Rapid-sequence induction (or awake intubation of the trachea) is indicated in patients perceived to be at risk for aspiration pneumonitis (full stomach). All widely used intravenous induction agents have been administered to patients with advanced hepatic disease. For patients who do not require rapid-sequence induction, careful titration of the anesthetic will minimize hemodynamic lability while achieving the desired anesthetic effect. Succinylcholine is a reasonable choice to facilitate endotracheal intubation, after screening for the usual contraindications (e.g., prolonged immobility or critical illness, hyperkalemia). Although severe liver dysfunction can markedly decrease cholinesterase activity and may prolong the effect of succinylcholine somewhat, this rarely causes a clinical problem. When using nondepolarizing neuromuscular blocking agents to induce anesthesia, consider that the initial dose to achieve total relaxation may be higher than in healthy patients. This increased dose requirement results primarily from pharmacokinetic alterations and pertains to relaxants such as rocuronium, atracurium, and pancuronium, but not to vecuronium.

**Maintenance of Anesthesia**

Intraoperative liver injury can develop from oxygen deprivation, the stress response, drug toxicity, blood transfusion, and infection. An impairment of hepatic oxygen supply can occur at any step in the process of delivering oxygen to the liver. Hypoxic hypoxia may result from inadequate \( FIO_2 \), right-to-left-shunting, or

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mismatch. Anemic hypoxia may develop when the oxygen-carrying capacity of the blood (hematocrit) is inadequate. Circulatory hypoxia may result from systemic (hypovolemia, arterial hypotension, reduction in cardiac output) or
regional (decrease in hepatic blood flow and oxygen supply) hemodynamic disorders. Delivery of blood and oxygen to the liver may decrease owing to systemic circulatory disturbances, surgical manipulation of the liver or adjacent structures, or from endogenous vasoconstrictors (e.g., renin-angiotensin, catecholamines, antidiuretic hormone). Anesthetics, exogenous vasoconstrictors, and other medications that impair electron transport or cellular metabolism could also induce histotoxic hypoxia.

In addition to ensuring adequate blood flow and oxygen supply, one must always consider the oxygen supply-demand relations in the liver. Experimental data indicate that severe surgical stress during fentanyl (moderate dose) anesthesia can produce a somewhat higher hepatic oxygen supply and uptake than an identical stress during isoflurane anesthesia; this results in similar values of hepatic oxygen supply-uptake ratio with the two anesthetics. Taking this into consideration, the guiding principle is to maintain adequate pulmonary and cardiovascular function, including cardiac output, blood volume, and perfusion pressures. One should strive to prevent arterial hypotension by adequate blood and volume replacement, and by avoidance of relative overdoses of anesthetics or other blood pressure-lowering drugs. Vasodilation, a reduced perfusion pressure, and a decrease in blood velocity will inevitably increase oxygen extraction in all tissues, including those in the preportal area. A decrease in blood velocity and increased oxygen extraction will cause a decrease in venous oxygen content—in this case, decreased oxygen content in the portal venous blood. A reduction in portal blood oxygen content or flow usually leads to a compensatory increase in hepatic arterial flow. Thus, hepatic injury after moderate systemic arterial hypotension is a relatively rare event. However, in the presence of severe liver dysfunction, the ability of autoregulatory mechanisms to increase hepatic arterial blood flow may be diminished or abolished. Therefore, with severe hepatic disease, the hepatic arterial blood flow may not increase appropriately when portal blood flow or oxygen content decreases. This might lead to hepatic oxygen deprivation. Thus, the lesson is clear: take all precautions to avoid arterial hypotension and low cardiac output states.

A particular challenge exists when the operative procedure is on the splanchnic tissues or on the liver itself. In these cases, one objective is to minimize potential for hemorrhage by decreasing the portal blood pressures. Judicious limitation of fluids during the operative resection to maintain a low CVP (<5 mm Hg) has been associated with significantly decreased blood loss, while maintaining renal function in a retrospective analysis of hepatic resection cases.

When performing general anesthesia, it seems prudent to avoid halothane, and possibly enflurane, because they cause the most prominent decreases in hepatic blood and oxygen supply, and are associated with the highest incidences of postoperative hepatic dysfunction. Isoflurane and probably sevoflurane appear to be the anesthetics of choice for inhalational anesthesia. Nitrous oxide does not appear to be associated with major hepatic complications in patients with advanced liver disease, despite its abilities to produce sympathomimetic effects and to limit the maximum oxygen content of arterial blood.

Consideration for the clinical use of halothane should take into account the following issues and concerns:

1. In children, halothane hepatitis is extremely uncommon, even after repeated exposures to halothane.
2. In adults, the disease rarely occurs after a single exposure to halothane; repeated anesthetics, however, especially in obese, middle-age women, over a brief period (<6 weeks) seem to substantially increase the risk of the disease.
3. No totally reliable tests exist for detecting halothane hepatitis or susceptibility to the disease.
4. Halothane can markedly decrease hepatic blood flow and oxygen supply, and often causes mild, transient liver injury.
5. Halothane anesthetics have potential legal liability implications, which may plague anesthesiologists whenever unexplained hepatic dysfunction develops in the postoperative period.

Why use halothane? The main advantages of halothane over other agents appear to be its low cost and its utility as an inhalational induction agent. However, when potential legal costs are factored into the equation, the cost-benefit analysis might actually favor the elimination of halothane from anesthesia practice. Sevoflurane has emerged as the alternative inhalation induction agent of choice.

Opioids are reasonable to include in the anesthetics of patients with hepatic disease. Despite certain pharmacokinetic concerns (decreased clearance and prolonged half-life), fentanyl is probably the opioid of choice. Interestingly, fentanyl neither decreases the hepatic oxygen or blood supply nor prevents an increase in hepatic oxygen requirements when used in moderate doses. Therefore, the oxygen supply-demand relation in the liver is no
better with a fentanyl-based anesthetic than during anesthesia with isoflurane.\textsuperscript{152} It seems that anesthetic management using inhaled agents (especially isoflurane or sevoflurane) alone or in combination with nitrous oxide, and small doses of fentanyl would be the method of choice, provided that adequate hemodynamic parameters are maintained. Many other agents also have favorable risk–benefit profiles for patients with advanced hepatic disease.

Because substantial alterations in pharmacokinetics occur in patients with advanced hepatic disease, dose requirements for a variety of medications can be unpredictable. For example, the hepatic clearance of lidocaine may be increased by more than 300\% and benzodiazepines by more than 100\%. Drugs that bind to proteins usually have a decreased volume of distribution, so a lower initial dose would be required. The volume of distribution of other agents, such as muscle relaxants, may increase substantially for various reasons, including an increase in γ-globulin concentration or the presence of edema. These factors appear to account for the so-called “resistance” to such agents and explain why the initial dose requirements of these medications are increased in cirrhotic patients. However, subsequent dose requirements may be decreased, and drug effects prolonged, owing to decreases in hepatic blood flow and impaired hepatic clearance, and possible concurrent renal dysfunction. Advanced hepatic disease does not appear to significantly affect the pharmacokinetics of vecuronium, although some dose-dependent pharmacokinetic alterations may occur. These alterations may be the result of a limited hepatic uptake capacity, which is usually exceeded at doses greater than 0.15 mg/kg. At lower doses, hepatic dysfunction does not affect the pharmacokinetics or duration of action of vecuronium.\textsuperscript{154}

Severe hepatic dysfunction per se does not contraindicate the use of any specific muscle relaxant. Atracurium (and cis-atracurium) have a theoretical advantage because their elimination occurs mainly by Hofmann decomposition, making their clearance relatively independent of renal or hepatic function. Despite elimination and clearance profiles, which match those in healthy patients, the volumes of distribution of these agents are larger in cirrhosis and, accordingly, the distribution half-life is shorter in patients with hepatorenal dysfunction compared with normal individuals. The only situation that appears to prolong the elimination half-life of atracurium is marked metabolic acidosis, which may decrease the rate of Hofmann decomposition.\textsuperscript{155}

The pharmacokinetics of many muscle relaxants in conditions of cholestasis and obstructive jaundice may be altered: prolonged duration of action has been demonstrated.\textsuperscript{156} However, especially when postoperative ventilation is planned, any nondepolarizing agent can be used successfully. Titration of any relaxant must be made according to transcutaneous nerve stimulation monitoring. Although pharmacokinetic studies in patients with hepatic cirrhosis provide interesting data that are helpful in understanding the pathogenic aspects of chronic liver disease, the results do not necessarily have significant value for predicting the safety of a drug. The degree of hepatic dysfunction affects the degree of pharmacokinetic disorder, and both are dynamic processes that may vary during the course of a procedure; therefore, the best way to avoid complications when administering medications is to titrate to effect.

**Fluids and Blood Products**

Standard indications for intravascular resuscitation and transfusion of blood products apply to the patient with hepatic insufficiency. No prospective data exist, demonstrating superiority of either a crystalloid-based or colloid-based resuscitation strategy. Because of this lack of conclusive data, the choice of fluid continues to engender spirited opinion and debate. Clearly, colloids represent a higher cost, and some may contribute to coagulopathy, especially at higher doses; however, despite these limitations and lack of documented benefit, they remain the resuscitation fluid of choice for some practitioners.\textsuperscript{157} Normovolemic hemodilution has been described as a blood conservation technique for hepatic resections with some success, but is not routinely used for nonhepatic cases in patients with liver insufficiency.\textsuperscript{158}

Monitoring of central filling pressures may assist in administering proper fluid therapy and maintaining renal perfusion. The contents of infused solutions should be initially selected and then adjusted based on periodic determinations of serum electrolyte concentrations.

**Vasopressors**

Patients with hepatic disease, either parenchymal or cholestatic, have peripheral vasodilatation, systemic shunting, and a reduced sensitivity to vasopressor drugs. The exact reason for the decreased pressor sensitivity is unclear. However, data from in vitro and in vivo experiments indicate that bile acids contribute to the vasodilatation and hypotension that often occur in patients with biliary obstruction.\textsuperscript{120} Conceivably, a decreased responsiveness to vasoactive substances (including catecholamines) is responsible for the interesting and clinically important observation that patients with biliary obstruction are often intolerant of even small blood losses. A moderate loss (10\%) of blood volume in animals with experimentally induced biliary obstruction causes severe (~50\%) arterial
hypotension. Intact animals respond to such blood loss with an approximately 15% decrease in blood volumes in both the pulmonary and splanchnic vascular beds. Animals with biliary obstruction have only a 7% decrease of their pulmonary blood volume and no change in splanchnic blood volume. If we can extrapolate these results to humans, patients with biliary obstruction would have an impaired hemodynamic response to blood loss. An impairment of the ability to translocate blood from pulmonary and splanchnic blood reservoirs to the systemic circulation would render patients highly susceptible to arterial hypotension from bleeding. Furthermore, the results would indicate the urgency of expeditiously replacing perioperative volume losses in this patient population. The anesthesiologist should be aware that biliary decompression can be accompanied by severe cardiovascular collapse.

POSTOPERATIVE

Liver Dysfunction and Management

Postoperative liver dysfunction is common but rarely severe (Table 39-9). Although it is usually asymptomatic, it may progress to overt liver failure on rare occasions. Mild, transient increases in serum concentrations of hepatic enzymes are often detectable within hours of surgery, but do not usually persist for more than 2 days. Such subclinical hepatocellular injury occurs in as many as 20% of patients who receive enflurane anesthesia, and in nearly 50% of those receiving halothane. Jaundice rarely occurs in healthy patients following minor operations, but appears in up to 20% of patients after major surgical procedures. Jaundice is typically the earliest sign of serious hepatic or hepatobiliary dysfunction, and therefore, requires prompt medical attention. Marked increases of serum aminotransferase activities are an ominous finding, reflecting extensive hepatocellular necrosis.

TABLE 39-9 Causes of Postoperative Liver Dysfunction

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<thead>
<tr>
<th>Hepatocellular</th>
<th>Drugs</th>
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<tr>
<td></td>
<td>Anesthetics</td>
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<tr>
<td></td>
<td>Ischemia</td>
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<tr>
<td></td>
<td>Shock, hypotension, iatrogenic injury</td>
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<td></td>
<td>Viral hepatitis</td>
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| Cholestasis | Benign postoperative cholestasis |
|            | Sepsis |
|            | Bile duct injury |
|            | Drugs |
|            | Antibiotics, antiemetics |
|            | Choledocholithiasis or pancreatitis |
|            | Cholecystitis |
|            | Gilbert syndrome |

Some cases of severe postoperative liver dysfunction are apparent hours after surgery (e.g., with hypoxic injury), whereas other cases are delayed in onset for days to weeks (e.g., with anesthesia-induced hepatitis). With severe postoperative liver dysfunction, residual liver function may fall below a critical threshold, leading to the development of hepatic encephalopathy. If encephalopathy occurs within 2 weeks of the onset of jaundice or within 8 weeks of the initial manifestation of hepatic disease, the disorder is defined as fulminant hepatic failure. Fulminant hepatic failure has a variety of causes. The mortality rate from fulminant hepatic failure correlates with the severity of encephalopathy. The shorter the interval between the appearance of jaundice and presentation of encephalopathy, the worse the prognosis.

Successful treatment of patients with fulminant hepatic failure requires the clinician to make prompt and accurate predictions about the outcome of the disease. Proper recognition of reversible disease obviates unnecessary orthotopic liver transplantation (OLT). Irreversible cases of fulminant hepatic failure require immediate identification. Otherwise, the severe complications of fulminant hepatic failure that develop may render patients unacceptable candidates for OLT. Several bioartificial liver (BAL) devices are in various stages of development to...
provide “liver replacement therapy.” Most use porcine or human hepatocytes as a bridge to transplantation or regeneration. Other artificial liver devices are based on albumin dialysis and are undoubtedly effective in removing protein-bound toxins, and uncontrolled evidence shows some survival benefit. Although initial animal studies demonstrated survival benefit of BAL devices, to date, no prospective randomized trial has shown improved survival using these devices.

Hemolysis and Transfusion

Reabsorption of large surgical or traumatic hematomas and transfusions of red blood cells are major causes of postoperative jaundice in the absence of overt hepatocellular dysfunction. At least 10% of transfused erythrocytes hemolyze within the initial 24 hours following a blood transfusion (the bilirubin load is about 250 mg per unit transfused). A normal liver readily clears the bilirubin that results from mild hemolysis. With severe hemolysis, the excessive bilirubin leads to unconjugated hyperbilirubinemia, which persists until the liver conjugates and excretes the excess bilirubin. Excessive bilirubin loads can also result from severe hemolytic disorders, including hemoglobinopathies (e.g., sickle cell disease) or derangements of erythrocyte metabolism (e.g., glucose-6-phosphate dehydrogenase [G6PD] deficiency). These problems may be seen in the perioperative period as a result of hypovolemia, hypoxia, hypothermia or stress, exacerbations of sickle cell disease, or G6PD deficiency. Other causes of significant hemolysis include transfusion reactions and prosthetic cardiac valves.

CAUSES OF POSTOPERATIVE LIVER DYSFUNCTION UNRELATED TO PERIOPERATIVE FACTORS

Asymptomatic and Preexisting Hepatic Injury

Although postoperative liver dysfunction can clearly result from anesthetic or surgical interventions, it is often unrelated to perioperative factors. For example, it can arise from preexisting liver disease that has escaped preoperative detection. According to a study by Schemel, the prevalence of acute, asymptomatic liver disease in a healthy-appearing surgical population may approach 0.25%. During a 1-year period, Schemel and coworkers performed multiple laboratory screening tests in 7,620 patients (ASA Physical Status I) scheduled for elective surgical procedures. Eleven of these patients (approximately 1 per 700) were found to have abnormal increases of AST, ALT, and LDH, and the proposed surgeries were cancelled. All 11 proved to have overt hepatic disorders (infectious mononucleosis, viral hepatitis, cirrhosis, or alcoholic hepatitis), and three later became clinically jaundiced (overall incidence of jaundice of 1:2,540). If any of these three patients actually received a halogenated anesthetic, with the subsequent development of overt hepatic disease between the 6th and 14th postoperative days, their diseases may well have been diagnosed erroneously as anesthesia-induced hepatitis. None of the 7,609 patients who underwent anesthesia and surgery exhibited laboratory evidence of preexisting hepatic disease, and none developed unexplained postsurgical jaundice. Another clinical study has documented a prevalence of unsuspected preoperative hepatic dysfunction similar to that reported by Schemel. Thus, it appears that approximately 1 of every 2,500 healthy patients who undergo surgery and anesthesia may have clinically significant postoperative liver dysfunction that is totally unrelated to surgery or anesthesia, and that a preexisting disease is more likely than an anesthetic agent to cause severe postoperative liver dysfunction.

Congenital Disorders

Gilbert's syndrome (familial unconjugated hyperbilirubinemia) is the most common cause of jaundice in the United States. It is a benign metabolic disorder characterized by a decrease in the activity of the hepatic enzyme bilirubin glucuronyltransferase, which is required for hepatocyte uptake of unconjugated bilirubin. Affected individuals may have modest increases in their unconjugated bilirubin level preoperatively, but become jaundiced postoperatively secondary to exacerbation of the condition by commonly occurring postoperative factors such as stress, fasting, fever, and infection. The diagnosis is suggested by the combination of clinical (jaundice without dark urine) and laboratory (unconjugated hyperbilirubinemia) abnormalities.

Crigler-Najjar syndrome (congenital nonhemolytic jaundice) is a much less common congenital disorder that exhibits either an absence (type 1) or marked decrease (type 2) of bilirubin glucuronyltransferase producing unconjugated hyperbilirubinemia. Surgical and anesthesia-related problems are apparently minimal in patients with either Gilbert's or Crigler-Najjar syndrome.

Conjugated bilirubin is excreted into the bile by a rate-limited, energy-requiring mechanism. Dubin-Johnson and Rotor's syndromes are congenital disorders that exhibit a defect in the biliary excretory mechanism, resulting in an
increased conjugated bilirubin level. Surgery can exacerbate these abnormalities.

CONCLUSION: PREVENTION AND TREATMENT OF POSTOPERATIVE LIVER DYSFUNCTION

Identifying patients at high risk for developing liver dysfunction or for having an exacerbation of preexisting liver disease is of utmost importance for minimizing the morbidity and mortality in such patients. Thus, a careful preoperative evaluation is required to detect preexisting liver disease and to identify important risk factors for anesthesia-induced hepatic injury. Perioperative physicians who are armed with an understanding of the interactions among liver disease, surgical procedures, the physiologic stress response, and anesthetic interventions can formulate and orchestrate therapeutic plans to optimize patient outcome.

When liver abnormalities are recognized preoperatively, it is prudent to defer elective procedures until the course of the disease can be determined. For operations that cannot be deferred, clinically significant pathophysiologic changes associated with the liver disease (e.g., coagulopathy, fluid and electrolyte abnormalities) should be corrected as soon as practical.

Which anesthetic technique best preserves the function of the liver? The choice of anesthesia is usually an insignificant issue for peripheral or minor surgery (operations that do not affect splanchnic blood flow), even in patients with severe liver disease. Regional anesthetic techniques, when appropriate (e.g., absence of coagulopathy), are often preferred because they minimize the cardiovascular and pulmonary perturbations associated with anesthesia. In addition, at least for certain types of procedures such as laparoscopic cholecystectomy, the addition of epidural anesthesia to a general anesthetic technique may decrease the circulating levels of endogenous catecholamines by mitigating the surgical stress response. This effect seems to persist into the postoperative period, when epidural pain management is maintained. The selection of pharmacologic anesthetic agents may also have important implications, especially in patients undergoing major operations. A rational approach to general anesthesia would include the use of agents that preserve cardiac output and do not adversely affect the oxygen supply-demand relationships of the liver (e.g., isoflurane, sevoflurane, fentanyl, remifentanil). Throughout the perioperative period, medications must be carefully titrated to achieve the desired pharmacologic effects while minimizing untoward effects; this can be challenging because pharmacokinetics and pharmacodynamics of many drugs are often unpredictable in patients with hepatobiliary dysfunction.

A primary goal during the maintenance of anesthesia is to ensure the adequacy of splanchnic, hepatic, and renal perfusion, especially in patients with severe liver disease who undergo major abdominal operations. Although well tolerated in the absence of liver disease, hepatic hypoperfusion in patients recovering from infectious hepatitis or chronic alcoholics can have devastating consequences. These patients may be highly susceptible to hepatic ischemia because of critically compromised liver blood flow, impaired pressure-flow autoregulation, and a dysfunctional hepatic arterial buffer response. In such cases, invasive monitoring of the circulation may be indicated so acute hypoperfusion can be rapidly detected and expeditiously treated.

Although anesthesia-induced hepatitis rarely occurs, we must remain aware of the association between this disorder and the use of halogenated vapors. As halothane usage for inhalation inductions and general anesthesia maintenance is increasingly supplanted by sevoflurane, the incidence of this complication decreases with each passing year. In the final analysis, completely avoiding the use of halothane is perhaps the single most effective way to decrease the incidence of anesthesia-induced hepatitis.

When postoperative hepatic injury occurs, the mainstay of therapy is supportive. A thorough search is required to identify any reversible cause of the injury. The hepatotoxic potentials of all medications merit consideration. Discontinue any medication that is suspect. Investigate all potential sources of sepsis because the presence of sepsis mandates rapid, aggressive therapy. Consider extrahepatic biliary obstruction in the differential diagnosis because this may require prompt surgical intervention. In some cases, identifying the pathogen or documenting the type of hepatic injury requires a percutaneous liver biopsy. Judicious use of biochemical tests and imaging studies, which can help delineate hepatocellular from cholestatic dysfunction, usually shortens the list of diagnostic possibilities and provides useful prognostic information.

Unfortunately, fulminant hepatic failure is often survived only with orthotopic liver transplantation. Given that organ donors are far fewer than those in need, many must endure our currently inadequate means of supporting this essential organ when it fails. Caring for patients whose liver is failing can be a frustrating endeavor. Perhaps the future holds promise for a supportive intervention as dialysis has provided for renal failure. In the mean time, our efforts at mitigating the tragedy of liver failure will continue to be best directed at prevention.
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