CHAPTER 32

Hepatic Physiology & Anesthesia

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KEY CONCEPTS

1. The hepatic artery supplies 45% to 50% of the liver's oxygen requirements, and the portal vein supplies the remaining 50% to 55%.
2. All coagulation factors, with the exception of factor VIII and von Willebrand factor, are produced by the liver. Vitamin K is a necessary cofactor in the synthesis of prothrombin (factor II) and factors VII, IX, and X.
3. Many "liver function" tests, such as serum transaminase measurements, reflect hepatocellular integrity more than hepatic function. Liver tests that measure hepatic synthetic function include serum albumin, prothrombin time (PT, or international normalized ratio), cholesterol, and pseudocholinesterase.
4. Albumin values less than 2.5 g/dL are generally indicative of chronic liver disease, acute stress, or severe malnutrition. Increased losses of albumin in the urine (nephrotic syndrome) or the gastrointestinal tract (protein-losing enteropathy) can also produce hypoalbuminemia.
5. The PT, which is normally 11–14 sec, depending on the control value, measures the activity of fibrinogen, prothrombin, and factors V, VII, and X.
6. The neuroendocrine stress response to surgery and trauma is characterized by elevated circulating levels of catecholamines, glucagon, and cortisol. Mobilization of carbohydrate stores and proteins results in hyperglycemia and a negative nitrogen balance (catabolism), respectively.
7. All opioids can potentially cause spasm of the sphincter of Oddi and increase biliary pressure.
8. When the results of liver tests are elevated postoperatively, the usual cause is underlying liver disease or the surgical procedure itself.

FUNCTIONAL ANATOMY

The liver is the heaviest organ in the body, weighing approximately 1500 g in adults. It is separated by the *falciform ligament* into right and left anatomic lobes; the larger right lobe has two additional smaller lobes at its posterior–inferior surface, the caudate and quadrate lobes. In contrast, surgical anatomy divides the liver based on its blood supply. Thus, the right and left surgical lobes are defined by the point of bifurcation of the hepatic artery and portal vein (*porta hepatis*); the falciform ligament therefore divides the left surgical lobe into medial and lateral segments. Surgical anatomy defines a total of eight segments.

The liver is made up of 50,000–100,000 discrete anatomic units called *lobules*. Each lobule is composed of plates of hepatocytes arranged cylindrically around a *centrilobular vein* (Figure 32–1). Four to

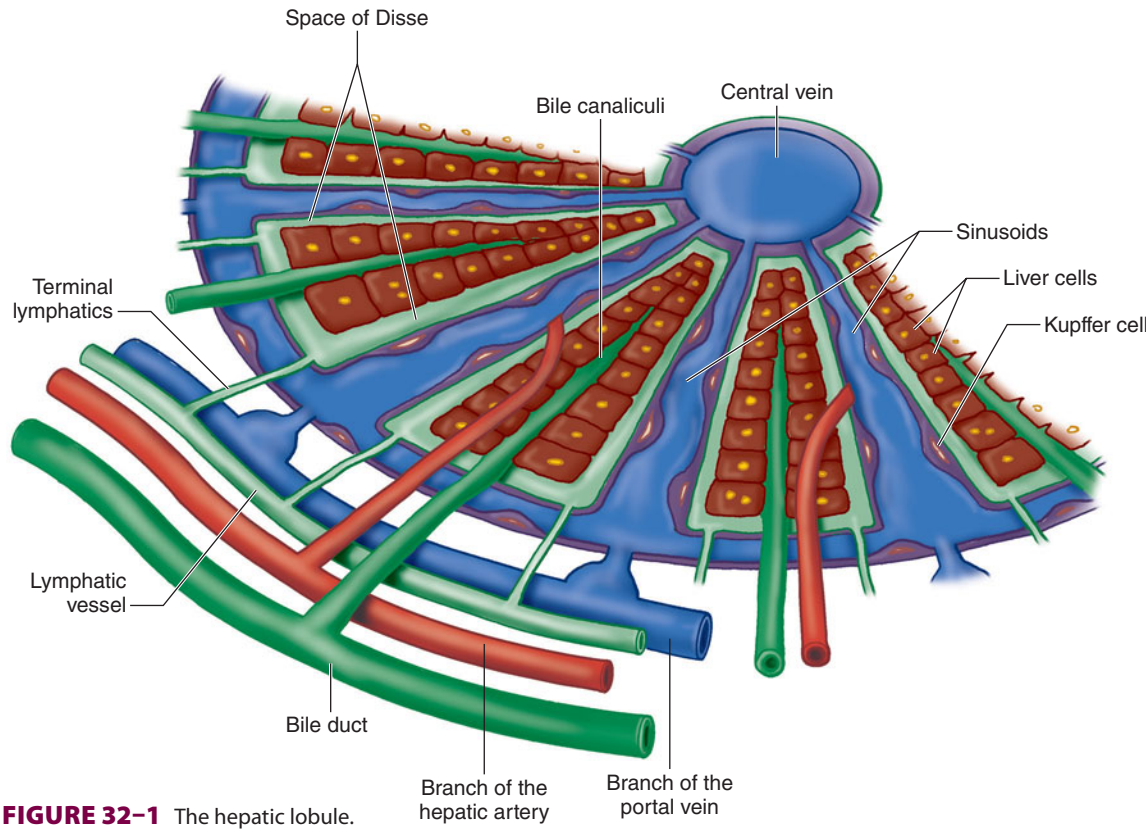

FIGURE 32–1 The hepatic lobule.

five portal tracts, composed of hepatic arterioles, portal venules, bile canaliculi, lymphatics, and nerves, surround each lobule.

In contrast to a lobule, an *acinus*, the functional unit of the liver, is defined by a portal tract in the middle and centrilobular veins at the periphery. Cells closest to the portal tract (zone 1) are well oxygenated; those closest to centrilobular veins (zone 3) receive the least oxygen and are most susceptible to injury.

Blood from hepatic arterioles and portal venules comingle in the sinusoidal channels, which lie between the cellular plates and serve as capillaries. These channels are lined by endothelial cells and by macrophages known as *Kupffer cells*. The Kupffer cells remove bacteria endotoxins, viruses, proteins and particulate matter from the blood. The *space of Disse* lies between the sinusoidal capillaries and the hepatocytes. Venous drainage from the central veins of hepatic lobules coalesces to form the hepatic veins (right, middle, and left), which empty into the inferior vena cava (Figure 32–2). The caudate lobe is usually drained by its own set of veins.

Bile canaliculi originate between hepatocytes within each plate and join to form bile ducts. An extensive system of lymphatic channels also forms within the plates and is in direct communication with the space of Disse.

The liver is supplied by sympathetic nerve fibers (T6–T11), parasympathetic fibers (right and left vagus), and fibers from the right phrenic nerve. Some autonomic fibers synapse first in the celiac plexus, whereas others reach the liver directly via splanchnic nerves and vagal branches before forming the hepatic plexus. The majority of sensory afferent fibers travel with sympathetic fibers.

Hepatic Blood Flow

Normal hepatic blood flow is 25% to 30% of the cardiac output and is provided by the hepatic artery and portal vein. The hepatic artery supplies about 45% to 50% of the liver's oxygen requirements,

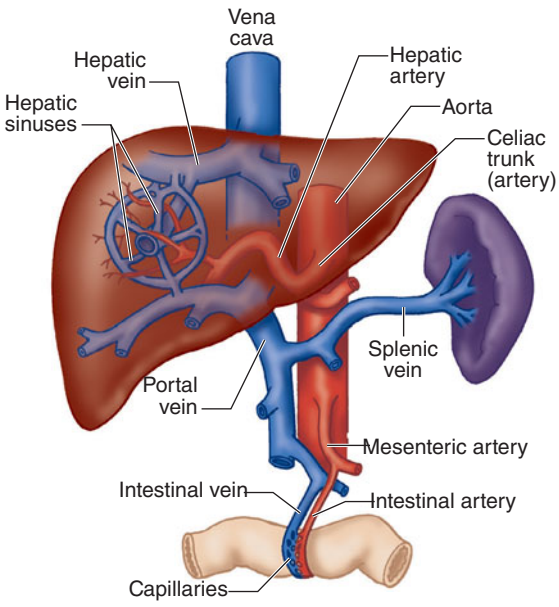

FIGURE 32–2 Hepatic blood flow. (Modified and reproduced, with permission, from Guyton AC: *Textbook of Medical Physiology*, 7th ed. W.B. Saunders, 1986.)

and the portal vein supplies the remaining 50% to 55% (Figure 32–2). Hepatic arterial flow seems to be dependent on metabolic demand (autoregulation), whereas flow through the portal vein is dependent on blood flow to the gastrointestinal tract and the spleen. A reciprocal, though somewhat limited, mechanism exists, such that a decrease in either hepatic arterial or portal venous flow results in a compensatory increase in the other.

The hepatic artery has α_1-adrenergic vasoconstriction receptors as well as β_2-adrenergic, dopaminergic (D_1), and cholinergic vasodilator receptors. The portal vein has only α_1-adrenergic and dopaminergic (D_1) receptors. Sympathetic activation results in vasoconstriction of the hepatic artery and mesenteric vessels, decreasing hepatic blood flow. β-Adrenergic stimulation vasodilates the hepatic artery; β-blockers reduce blood flow, and, therefore, decrease portal pressure.

Reservoir Function

Portal vein pressure is normally only about 7–10 mm Hg, but the low resistance of the hepatic sinusoids allows relatively large blood flows through the portal vein. Small changes in hepatic venous tone and hepatic venous pressure thus can result in large changes in hepatic blood volume, allowing the liver to act as a blood reservoir (Figure 32–3). A decrease in hepatic venous pressure, as occurs during hemorrhage, shifts blood from hepatic veins and sinusoids into the central venous circulation and augments

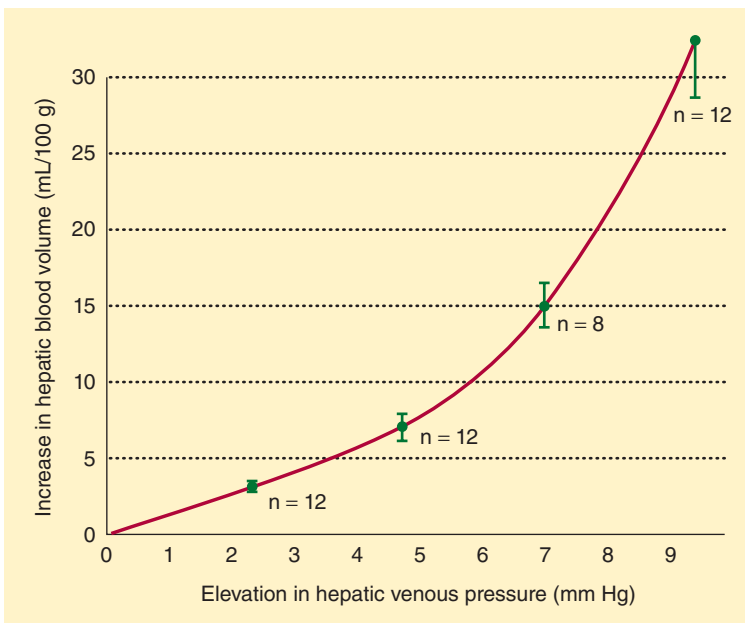

FIGURE 32–3 Hepatic venous compliance and the role of the liver as a blood reservoir. (Modified and reproduced, with permission, from Lautt WW, Greeway CV: Am J Physiol 1976;231:292.)

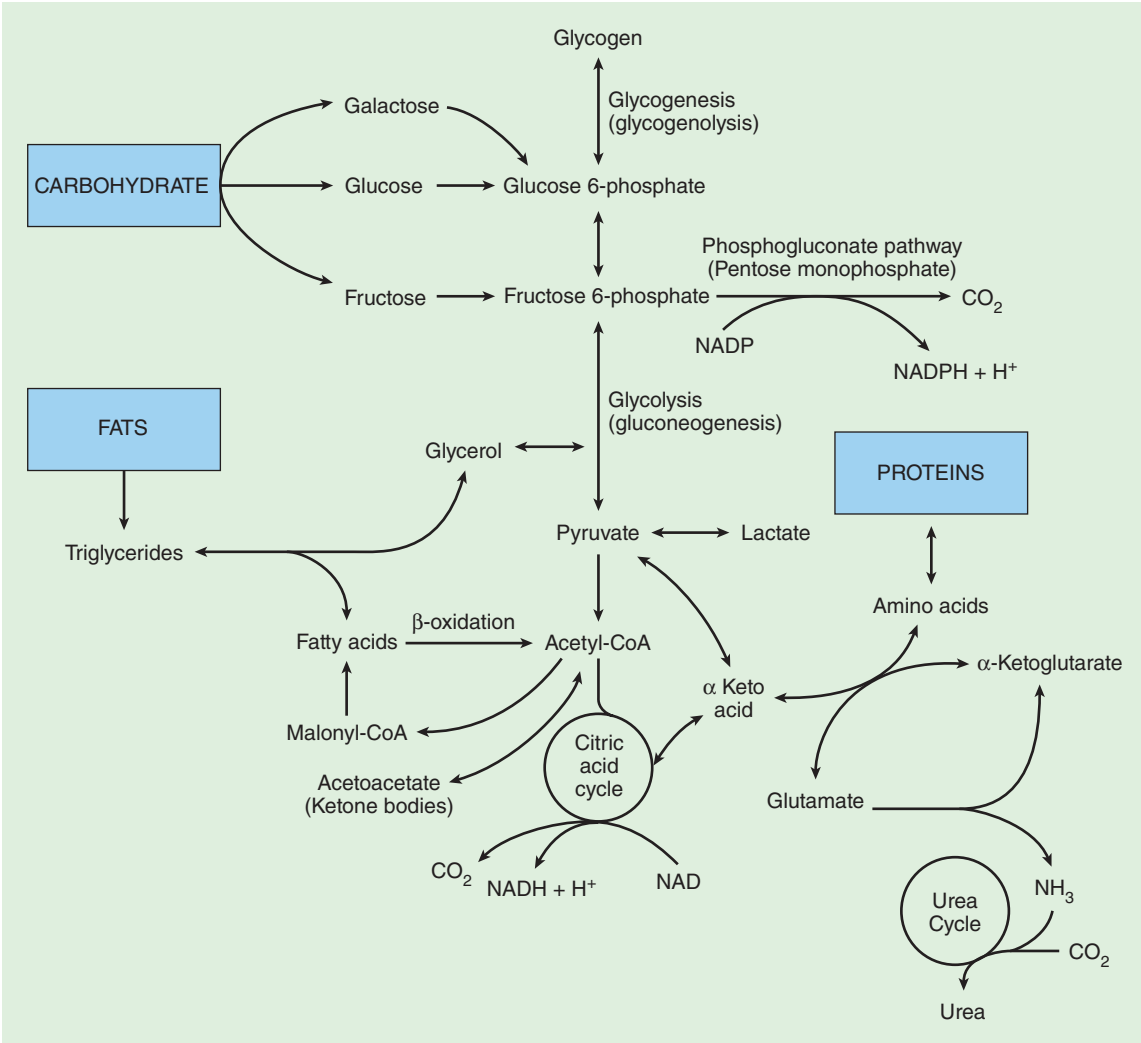

FIGURE 32–4 Important metabolic pathways in hepatocytes. Although small amounts of adenosine triphosphate (ATP) are derived directly from some intermediary reactions, the overwhelming majority of ATP produced is the result of oxidative phosphorylation of the reduced forms of nicotinamide adenine dinucleotide (NADH) and nicotinamide adenine dinucleotide phosphate (NADPH).

circulating blood volume. Blood loss can be reduced during liver surgery by lowering the central venous pressure, thereby reducing hepatic venous pressure and hepatic blood volume. In patients with congestive heart failure, the increase in central venous pressure is transmitted to the hepatic veins and causes congestion of the liver that can adversely affect liver function.

Metabolic Function

The abundance of enzymatic pathways in the liver allows it to play a key role in the metabolism of carbohydrates, fats, proteins, and other substances (see Figure 32–4 and Table 32–1). The final products of carbohydrate digestion are glucose, fructose, and galactose. With the exception of the large amount of fructose that is converted by the liver to lactate,

TABLE 32–1 Metabolic functions of the liver.

Creation and secretion of bile
Nutrient metabolism
Amino acids
Monosaccharides (sugars)
Lipids (fatty acids, cholesterol, phospholipids, lipoproteins)
Vitamins
Phase I and II biotransformation
Toxins
Drugs
Hormones (steroids)
Synthesis
Albumin, α_1-antitrypsin, proteases
Clotting factors
Acute phase proteins
Plasma cholinesterase
Immune function
Kupffer cells

hepatic conversion of fructose and galactose into glucose makes glucose metabolism the final common pathway for most carbohydrates.

All cells utilize glucose to produce energy in the form of adenosine triphosphate (ATP), either aerobically via the citric acid cycle or anaerobically via glycolysis. The liver and adipose tissue can also utilize the phosphogluconate pathway, which provides energy and fatty acid synthesis. Most of the glucose absorbed following a meal is normally stored as glycogen, which only the liver and muscle are able to store in significant amounts. When glycogen storage capacity is exceeded, excess glucose is converted into fat. Insulin enhances glycogen synthesis, and epinephrine and glucagon enhance glycogenolysis. Because glucose consumption averages 150 g/day, and hepatic glycogen stores are normally only about 70 g/day, glycogen stores are depleted after 24 hr of fasting. After this period of fasting, *gluconeogenesis*, the *de novo* synthesis of glucose, is necessary to provide an uninterrupted supply of glucose for other organs.

The liver and kidney are unique in their capacity to form glucose from lactate, pyruvate, amino acids (mainly alanine), and glycerol (derived from fat metabolism). Hepatic gluconeogenesis is vital in the maintenance of a normal blood glucose concentration. Glucocorticoids, catecholamines, glucagon, and thyroid hormone greatly enhance gluconeogenesis, whereas insulin inhibits it.

When carbohydrate stores are saturated, the liver converts the excess ingested carbohydrates and proteins into fat. The fatty acids thus formed can be used immediately for fuel or stored in adipose tissue or the liver for later consumption. Nearly all cells utilize fatty acids derived from ingested fats or synthesized from intermediary metabolites of carbohydrates and protein as an energy source—only red blood cells and the renal medulla are limited to glucose utilization. Neurons normally utilize only glucose, but, after a few days of starvation, they can switch to ketone bodies, the breakdown products of fatty acids that have been synthesized by the liver as an energy source.

To oxidize fatty acids, they are converted into acetylcoenzyme A (acetyl-CoA), which is then oxidized via the citric acid cycle to produce ATP. The liver is capable of high rates of fatty acid oxidation and can form acetoacetic acid (one of the ketone bodies) from excess acetyl-CoA. The acetoacetate released by hepatocytes serves as an alternative energy source for other cell types by reconversion into acetyl-CoA. Insulin inhibits hepatic ketone body production. Acetyl-CoA is also used by the liver for the production of cholesterol and phospholipids, which is necessary in the synthesis of cellular membranes throughout the body.

The liver performs a critical role in protein metabolism. Without this function, death usually occurs within several days. The steps involved in protein metabolism include: (1) deamination of amino acids, (2) formation of urea (to eliminate the ammonia produced from deamination), (3) interconversions between nonessential amino acids, and (4) formation of plasma proteins. Deamination is necessary for the conversion of excess amino acids into carbohydrates and fats. The enzymatic processes, most commonly transamination, convert amino acids into their respective keto acids and produce ammonia as a byproduct.

Ammonia formed from deamination (as well as that produced by colonic bacteria and absorbed through the gut) is highly toxic to tissues. Through

a series of enzymatic steps, the liver combines two molecules of ammonia with CO_2 to form urea. The urea thus formed readily diffuses out of the liver and can then be excreted by the kidneys.

Nearly all plasma proteins, with the notable exception of immunoglobulins, are formed by the liver. These include albumin, α_1-antitrypsin and other proteases/elastases, and the coagulation factors. Albumin is responsible for maintaining a normal plasma oncotic pressure and is the principal binding and transport protein for fatty acids and a large number of hormones and drugs. Consequently, changes in albumin concentration can affect the concentration of the pharmacologically active, unbound fraction of many drugs.

2 All coagulation factors, with the exception of factor VIII and von Willebrand factor, are produced by the liver (see Table 32–2, Figure 32–5, and Chapter 51). Vascular endothelial cells synthesize factor VIII, levels of which are therefore usually maintained in chronic liver disease. Vitamin K is a necessary cofactor in the synthesis of prothrombin (factor II) and factors VII, IX, and X. The liver also produces plasma cholinesterase (pseudocholinesterase), an enzyme that hydrolyzes esters, including some local anesthetics and some muscle relaxants. Other important proteins formed by the liver include protease inhibitors (antithrombin III, α_2-antiplasmin, and α_1-antitrypsin), transport proteins (transferrin, haptoglobin, and ceruloplasmin), complement, α_1-acid glycoprotein, C-reactive protein, and serum amyloid A.

TABLE 32–2 Coagulation factors.

Factor		Approximate Half-Life (h)
I	Fibrinogen	100
II	Prothrombin	80
III	Tissue thromboplastin	—
IV	Calcium	—
V	Proaccelerin	18
VII	Proconvertin	6
VIII	Antihemophilic factor	10
IX	Christmas factor	24
X	Stuart factor	50
XI	Plasma thromboplastin antecedents	25
XII	Hageman factor	60
XIII	Fibrin-stabilizing factor	90

Drug Metabolism

Many exogenous substances, including most drugs, undergo hepatic biotransformation, and the end-products of these reactions are usually either inactivated or converted to more water-soluble substances that can be readily excreted in bile or urine. Hepatic biotransformations are often categorized as one of two types of reactions. *Phase I reactions* modify reactive chemical groups through mixed-function oxidases or the cytochrome P-450 enzyme systems, resulting in oxidation, reduction, deamination, sulfoxidation, dealkylation, or methylation. Barbiturates and benzodiazepines are inactivated by phase I reactions. *Phase II reactions*, which may or may not follow a phase I reaction, involve conjugation of the substance with glucuronide, sulfate, taurine, or glycine. The conjugated compound can then be readily eliminated in urine or bile.

Some enzyme systems, such as those of cytochrome P-450, can be induced by a few drugs, such as ethanol, barbiturates, ketamine, and perhaps benzodiazepines. This can result in increased tolerance to the drugs' effects. Conversely, some agents, such as cimetidine and chloramphenicol, can prolong the effects of other drugs by inhibiting these enzymes. Some drugs, including lidocaine, morphine, verapamil, labetalol, and propranolol, have very high rates of hepatic extraction from the circulation, and their metabolism is therefore highly dependent upon the rate of hepatic blood flow. As a result, a decrease in their metabolic clearance usually reflects decreased hepatic blood flow rather than hepatocellular dysfunction.

The liver plays a major role in hormone, vitamin, and mineral metabolism. It is an important site for the

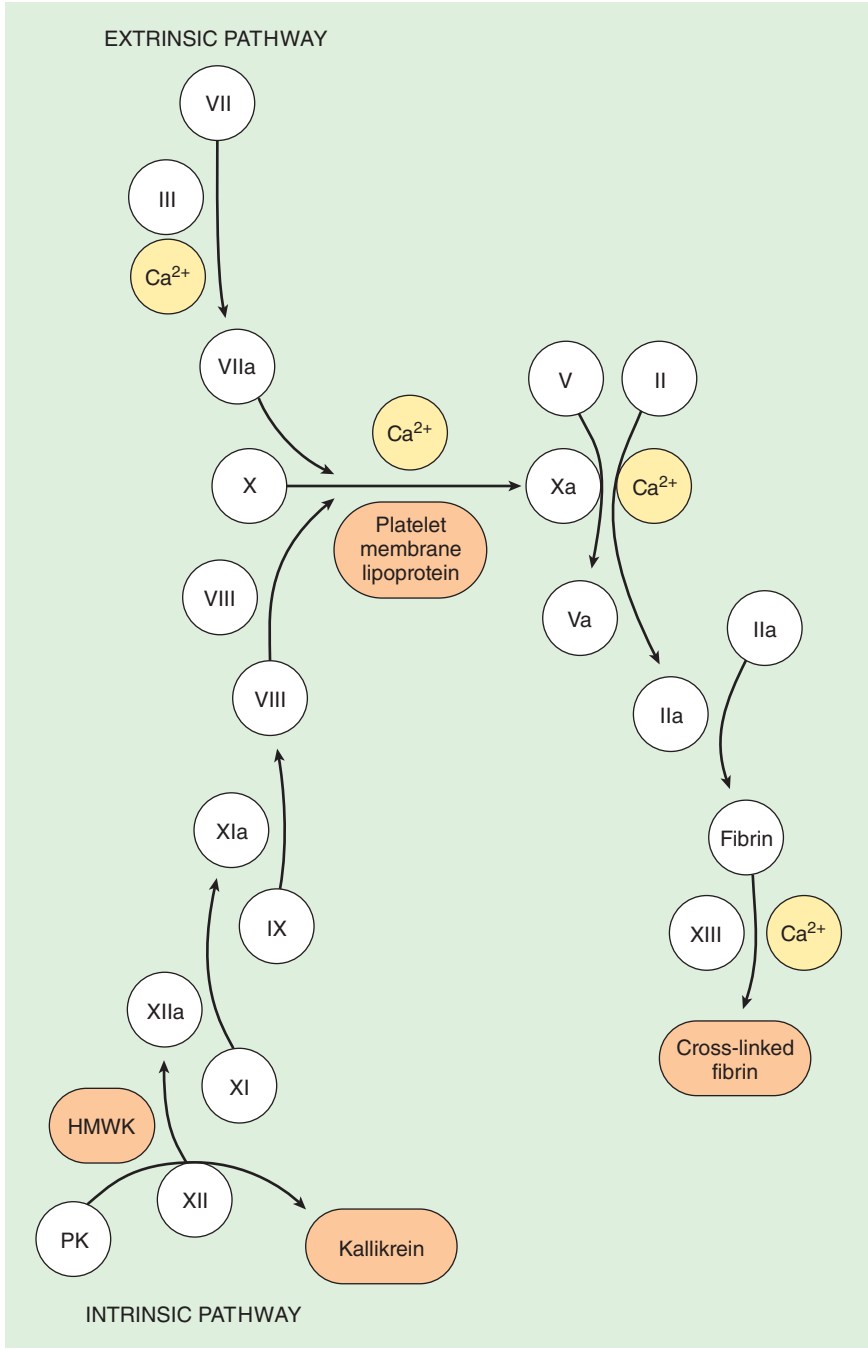

FIGURE 32–5 The intrinsic and extrinsic coagulation pathways.

conversion of thyroxine (T_4) into the more active triiodothyronine (T_3), and degradation of thyroid hormone is principally hepatic. The liver is also the major site of degradation for insulin, steroid hormones (estrogen, aldosterone, and cortisol), glucagon, and antidiuretic hormone. Hepatocytes are the principal storage sites for vitamins A, B_{12}, E, D, and K. Lastly, hepatic production of transferrin and haptoglobin is important because these proteins are involved in iron hemostasis, whereas ceruloplasmin is important in copper regulation.

Bile Formation

Bile (Table 32–3) plays an important role in absorption of fat and excretion of bilirubin, cholesterol, and many drugs. Hepatocytes continuously secrete bile salts, cholesterol, phospholipids, conjugated bilirubin, and other substances into bile canaliculi.

Bile ducts from hepatic lobules join and eventually form the right and left hepatic ducts. These ducts, in turn, combine to form the hepatic duct, which together with the cystic duct from the gallbladder becomes the common bile duct (Figure 32–6). The gallbladder serves as a reservoir for bile. The bile acids formed by hepatocytes from cholesterol are essential for emulsifying the insoluble components of bile and facilitating the intestinal absorption of lipids. Defects in the formation or secretion of bile salts interfere with the absorption of fats and fat-soluble vitamins (A, D, E, and K). Because of normally limited stores of vitamin K, a deficiency can develop in a few days. **Vitamin K deficiency is manifested as a coagulopathy due to impaired formation of prothrombin and of factors VII, IX, and X.**

TABLE 32–3 Composition of bile.

97% water
<1% bile salts
Pigments
Inorganic salts
Lipids Cholesterol Fatty acids
Lecithin
Alkaline phosphatase

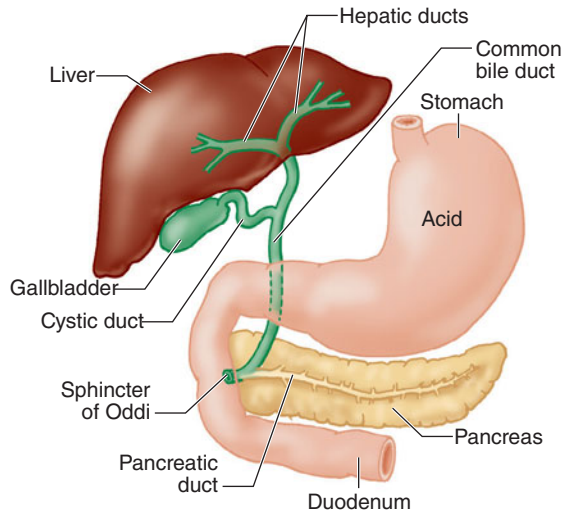

FIGURE 32–6 The biliary system. (Modified and reproduced, with permission, from Guyton AC: *Textbook of Medical Physiology*, 7th ed. W.B. Saunders, 1986.)

Bilirubin is primarily the end-product of hemoglobin metabolism. It is formed from degradation of the heme ring in Kupffer cells. Bilirubin is then released into blood, where it readily binds to albumin. Hepatic uptake of bilirubin from the circulation is passive, but binding to intracellular proteins traps the bilirubin inside hepatocytes. Bilirubin is conjugated by the hepatocytes, primarily with glucuronide, and actively excreted into bile canaliculi.

LIVER TESTS

The most commonly performed liver tests are neither sensitive nor specific. No one test evaluates overall hepatic function, reflecting instead one aspect of hepatic function that must be interpreted in conjunction with other tests and clinical assessment of the patient.

3 Many "liver function" tests, such as serum transaminase measurements, reflect hepatocellular integrity more than hepatic function. Liver tests that measure hepatic synthetic function include

TABLE 32–4 Abnormalities in liver tests.[1, 2, 3]

	Parenchymal (Hepatocellular) Dysfunction	Biliary Obstruction or Cholestasis
AST (SGOT)	↑ to ↑↑↑	↑
ALT (SGPT)	↑ to ↑↑↑	↑
Albumin	0 to ↓↓↓	0
Prothrombin time	0 to ↑↑↑	0 to ↑↑[4]
Bilirubin	0 to ↑↑↑	0 to ↑↑↑
Alkaline phosphatase	↑	↑ to ↑↑↑
5′-Nucleotidase	0 to ↑	↑ to ↑↑↑
γ-Glutamyl transpeptidase	↑ to ↑↑↑	↑↑↑

[1]Adapted from Wilson JD et al. (eds): *Harrison's Principles of Internal Medicine*, 12th ed. McGraw-Hill, 1991.

[2]AST, aspartate aminotransferase; SGOT, serum glutamic-oxaloacetic transaminase; ALT, alanine aminotransferase; SGPT, serum glutamic pyruvic-transferase.

[3]↑, increases; 0, no change; ↓, decreases.

[4]Usually corrects with vitamin K.

serum albumin, prothrombin time (PT, or international normalized ratio [INR]), cholesterol, and pseudocholinesterase. Moreover, because of the liver's large functional reserve, substantial cirrhosis may be present with few or no laboratory abnormalities.

Liver abnormalities can often be divided into either parenchymal disorders or obstructive disorders based on laboratory tests (Table 32–4). Obstructive disorders primarily affect biliary excretion of substances, whereas parenchymal disorders result in generalized hepatocellular dysfunction.

Serum Bilirubin

The normal total bilirubin concentration, composed of conjugated (direct), water-soluble and unconjugated (indirect), lipid-soluble forms, is less than 1.5 mg/dL (<25 mmol/L) and reflects the balance between bilirubin production and excretion. Jaundice is usually clinically obvious when total bilirubin exceeds 3 mg/dL. A predominantly conjugated hyperbilirubinemia (>50%) is associated with increased urinary urobilinogen and may reflect hepatocellular dysfunction, congenital (Dubin–Johnson or Rotor syndrome) or acquired intrahepatic cholestasis, or extrahepatic biliary obstruction. Hyperbilirubinemia that is primarily unconjugated may be seen with hemolysis or with congenital (Gilbert or Crigler–Najjar syndrome) or acquired defects in bilirubin conjugation. Unconjugated bilirubin is neurotoxic, and high levels may produce encephalopathy.

Serum Aminotransferases (Transaminases)

These enzymes are released into the circulation as a result of hepatocellular injury or death. Two aminotransferases are most commonly measured: aspartate aminotransferase (AST), also known as serum glutamic-oxaloacetic transaminase (SGOT), and alanine aminotransferase (ALT), also known as serum glutamic pyruvic-transferase (SGPT).

Serum Alkaline Phosphatase

Alkaline phosphatase is produced by the liver, bone, small bowel, kidneys, and placenta and is excreted into bile. Normal serum alkaline phosphatase activity is generally 25–85 IU/L; children and adolescents have much higher levels, reflecting active growth. Most of the circulating enzyme is normally derived from bone; however, with biliary obstruction, more hepatic alkaline phosphatase is synthesized and released into the circulation.

Serum Albumin

The normal serum albumin concentration is 3.5–5.5 g/dL. Because its half-life is about 2–3 weeks, albumin concentration may initially be normal with acute liver disease. Albumin values less than 2.5 g/dL are generally indicative of chronic liver disease, acute stress, or severe malnutrition. Increased losses of albumin in the urine (nephrotic syndrome) or the gastrointestinal tract (protein-losing enteropathy) can also produce hypoalbuminemia.

Blood Ammonia

Significant elevations of blood ammonia levels usually reflect disruption of hepatic urea synthesis. Normal whole blood ammonia levels are 47–65 mmol/L (80–110 mg/dL). Marked elevations usually reflect severe hepatocellular damage and may cause encephalopathy.

Prothrombin Time

5 The PT, which normally ranges between 11–14 sec, depending on the control value, measures the activity of fibrinogen, prothrombin, and factors V, VII, and X. The relatively short half-life of factor VII (4–6 h) makes the PT useful in evaluating hepatic synthetic function of patients with acute or chronic liver disease. Prolongations of the PT greater than 3–4 sec from the control are considered significant and usually correspond to an INR >1.5. Because only 20% to 30% of normal factor activity is required for normal coagulation, prolongation of the PT usually reflects either severe liver disease or vitamin K deficiency. (See Table 32–5 for a list of coagulation test abnormalities.)

Point-of-Care Viscoelastic Coagulation Monitoring

This technology provides a "real time" assessment of the coagulation status and utilizes thromboelastography (TEG®), rotation thromboelastometry (ROTEM®), or Sonoclot® analysis to assess global coagulation via the viscoelastic properties of whole blood (Figure 32–7). A clear picture is provided of the global effect of imbalances between the procoagulant and anticoagulant systems and the profibrinolytic and antifibrinolytic systems and the resultant clot tensile strength, allowing precise management of hemostatic therapy. The rate of clot formation, the strength of the clot, and the impact of any lysis can be observed. The presence of disseminated intravascular coagulation can be evaluated, as can the effect of heparin or heparinoid activity. In addition, platelet function can be assessed, including the effects of platelet inhibition.

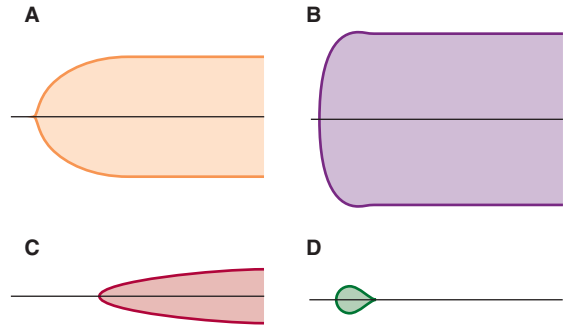

FIGURE 32–7 Examples of typical thromboelastograph tracings. **A**: Normal. **B**: Hypercoagulation. **C**: Hypocoagulation (eg, thrombocytopenia). **D**: Fibrinolysis. (Reproduced, with permission, from Johansson PI, Stissing T, Bochsen L, et al: Thrombelastography and thromboelastometry in assessing coagulopathy in trauma. Scand J Trauma Resusc Emerg Med 2009;17:45.)

TABLE 32–5 Coagulation test abnormalities.[1]

	PT	PTT	TT	Fibrinogen
Advanced liver disease	↑	↑	N or ↑	N or ↓
DIC	↑	↑	↑	↓
Vitamin K deficiency	↑↑	↑	N	N
Warfarin therapy	↑↑	↑	N	N
Heparin therapy	↑	↑↑	↑	N
Hemophilia				
Factor VIII deficiency	N	↑	N	N
Factor IX deficiency	N	↑	N	N
Factor VII deficiency	↑	N	N	N
Factor XIII deficiency	N	N	N	N

[1]PT, prothrombin time; PTT, partial thromboplastin time; TT, thrombin time; N, normal; DIC, disseminated intravascular coagulation.

EFFECT OF ANESTHESIA ON HEPATIC FUNCTION

Hepatic blood flow usually decreases during regional and general anesthesia, and multiple factors are responsible, including both direct and indirect effects of anesthetic agents, the type of ventilation employed, and the type of surgery being performed.

Decreases in cardiac output reduce hepatic blood flow via reflex sympathetic activation, which vasoconstricts both the arterial and the venous splanchnic vasculature.

The hemodynamic effects of ventilation can also have a significant impact on hepatic blood flow. Controlled positive-pressure ventilation with high mean airway pressures reduces venous return to the heart and decreases cardiac output; both mechanisms can compromise hepatic blood flow. The former increases hepatic venous pressure, whereas the latter can reduce blood pressure and increase

sympathetic tone. Positive end-expiratory pressure (PEEP) further accentuates these effects.

Surgical procedures near the liver can reduce hepatic blood flow up to 60%. Although the mechanisms are not clear, they most likely involve sympathetic activation, local reflexes, and direct compression of vessels in the portal and hepatic circulations.

β-Adrenergic blockers, α_1-adrenergic agonists, H_2-receptor blockers, and vasopressin reduce hepatic blood flow. Low-dose dopamine infusions may increase liver blood flow.

Metabolic Functions

The effects of the various anesthetic agents on intermediary hepatic metabolism involving carbohydrate, fat, and protein are poorly defined. An endocrine stress response secondary to fasting and surgical trauma is generally observed. The neuroendocrine stress response to surgery and trauma is characterized by elevated circulating levels of catecholamines, glucagon, and cortisol and results in the mobilization of carbohydrate stores and protein, causing hyperglycemia and negative nitrogen balance (catabolism). The neuroendocrine stress response may be at least partially blunted by regional anesthesia, deep general anesthesia and/or pharmacological blockade of the sympathetic system, with regional anesthesia having the most salutary effect on catabolism. All opioids can potentially cause spasm of the sphincter of Oddi and increase biliary pressure. Naloxone and glucagon may relieve opioid-induced spasm.

Procedures in close proximity to the liver frequently result in modest elevations in lactate dehydrogenase and transaminase concentrations regardless of the anesthetic agent or technique employed. When the results of liver function tests are elevated postoperatively, the usual cause is underlying liver disease or the surgical procedure itself. Persistent abnormalities in liver tests may be indicative of viral hepatitis (usually transfusion related), sepsis, idiosyncratic drug reactions, or surgical complications. **Postoperative jaundice can result from a variety of factors (Table 32–6), but the most common cause is overproduction of bilirubin because of resorption of a large hematoma or red cell breakdown following transfusion.** Nonetheless, all other causes should be considered. Correct diagnosis requires a careful review of preoperative liver function and of intraoperative and postoperative events, such as transfusions, sustained hypotension or hypoxemia, and drug exposure. Currently utilized volatile anesthetic agents have minimal, if any, direct adverse effect upon hepatocytes.

TABLE 32–6 Causes of postoperative jaundice.

Prehepatic (increased bilirubin production)
Resorption of hematomas
Hemolytic anemia transfusion
Senescent red cell breakdown
Hemolytic reactions
Hepatic (hepatocellular dysfunction)
Preexisting liver disease
Ischemic or hypoxemic injury
Drug-induced
Gilbert's syndrome
Intrahepatic cholestasis
Halothane
Posthepatic (biliary obstruction)
Postoperative cholecystitis
Postoperative pancreatitis
Retained common bile duct stone
Bile duct injury
Miscellaneous

CASE DISCUSSION

Coagulopathy in a Patient with Liver Disease (also see Chapter 51)

A 52-year-old man with a long history of alcohol abuse presents for a splenorenal shunt after three major episodes of upper gastrointestinal hemorrhage from esophageal varices. Coagulation studies reveal a PT of 17 sec (control: 12 sec), INR of 1.7, and a partial PT of 43 sec (control: 29 sec). The platelet count is 75,000/μL.

What factors can contribute to excessive bleeding during and following surgery?

Hemostasis following trauma or surgery is dependent on three major processes: (1) vascular spasm, (2) formation of a platelet plug (primary

hemostasis), and (3) coagulation of blood (secondary hemostasis) in addition to adequate surgical control of bleeding sites. The first two are nearly immediate (seconds), whereas the third is delayed (minutes). A defect in any of these processes can lead to a bleeding diathesis and increased blood loss.

Outline the mechanisms involved in primary hemostasis.

Injury to smaller blood vessels normally causes localized spasm as a result of the release of humoral factors from platelets and local myogenic reflexes. Sympathetic-mediated vasoconstriction is also operative in medium-sized vessels. Exposure of circulating platelets to the damaged endothelial surface causes them to undergo a series of changes that results in the formation of a platelet plug. If the break in a vessel is small, the plug itself can often completely stop bleeding. If the break is large, however, coagulation of blood is also necessary to stop the bleeding.

Formation of the platelet plug can be broken down into three stages: (1) adhesion, (2) release of platelet granules, and (3) aggregation. Following injury, circulating platelets adhere to subendothelial collagen via specific glycoprotein (GP) receptors on their membrane. This interaction is stabilized by a circulating GP called *von Willebrand factor* (vWF), which forms additional bridges between subendothelial collagen and platelets via GPIb. Collagen (as well as epinephrine and thrombin) activates platelet membrane-bound phospholipases A and C, which, in turn, results in the formation of thromboxane A_2 (TXA_2) and platelet degranulation. TXA_2 is a potent vasoconstrictor that also promotes platelet aggregation. Platelet granules contain a large number of substances, including adenosine diphosphate (ADP), factor V, vWF, fibrinogen, and fibronectin. These factors attract and activate additional platelets. ADP alters platelet membrane GPIIb/IIIa, which facilitates the binding of fibrinogen to activated platelets.

Describe the mechanisms involved in normal coagulation.

Coagulation, often referred to as secondary hemostasis, involves formation of a fibrin clot, which usually binds and strengthens a platelet plug. Fibrin can be formed via one of two pathways (*extrinsic* or *intrinsic*; Figure 32–5) that involve calcium and activation of soluble coagulation precursor proteins in blood (Table 32–2). Regardless of which pathway is activated, the coagulation cascade ends in the conversion of *fibrinogen* to *fibrin*. The extrinsic pathway of the coagulation cascade is triggered by the release of a tissue lipoprotein, *thromboplastin*, from the membranes of injured cells and is likely the more important pathway in humans. The intrinsic pathway can be triggered by the interaction between subendothelial collagen with circulating Hageman factor (XII), high-molecular-weight kininogen, and prekallikrein. The latter two substances are also involved in the formation of bradykinin.

Thrombin plays a central role in coagulation because it not only activates platelets, but also accelerates conversion of factors V, VIII, and XIII to their active forms. Conversion of prothrombin to thrombin is markedly accelerated by activated platelets. Thrombin then converts fibrinogen to soluble fibrin monomers that polymerize on the platelet plug. The cross-linking of fibrin polymers by factor XIII is necessary to form a strong, insoluble fibrin clot. Finally, retraction of the clot, which requires platelets, expresses fluid from the clot and helps pull the walls of the damaged blood vessel together.

What prevents coagulation of blood in normal tissues?

The coagulation process is limited to injured areas by localization of platelets to the injured area and by maintenance of normal blood flow in uninjured areas. Normal endothelium produces *prostacyclin* (prostaglandin I_2, PGI_2), which is a potent vasodilator that also inhibits platelet activation and helps to confine the primary hemostatic process to the injured area. Normal blood flow is important in clearing activated coagulation factors, which are taken up by the monocyte–macrophage scavenger system. Multiple inhibitors of coagulation are normally present in plasma, including antithrombin III, protein

C, protein S, and tissue factor pathway inhibitor. Antithrombin III complexes with and inactivates circulating coagulation factors (with the notable exception of factor VII), and protein C specifically inactivates factors V and VIII. *Heparin exerts its anticoagulant activity by augmenting the activity of antithrombin III*. Protein S enhances the activity of protein C, and deficiencies of protein C and protein S lead to hypercoagulability. Tissue factor pathway inhibitor antagonizes the action of activated factor VII.

What is the role of the fibrinolytic system in normal hemostasis?

The fibrinolytic system is normally activated simultaneously with the coagulation cascade and functions to maintain the fluidity of blood during coagulation. It is also responsible for clot lysis once tissue repair begins. When a clot is formed, a large amount of the protein *plasminogen* is incorporated. Plasminogen is then activated by tissue plasminogen activator (tPA), which is usually released by endothelial cells in response to thrombin, and by Hageman factor (XII). The resulting formation of *plasmin* degrades fibrin and fibrinogen, as well as other coagulation factors. Urokinase (found in urine) and streptokinase (a product of bacteria) are also potent activators of plasminogen to plasmin. The action of tPA is localized because (1) it is absorbed into the fibrin clot, (2) it activates plasminogen more effectively on the clot, (3) free plasmin is rapidly neutralized by a circulating α_2-antiplasmin, and (4) circulating tPA is cleared by the liver. Plasmin degrades fibrin and fibrinogen into small fragments. These fibrin degradation products possess anticoagulant activity because they compete with fibrinogen for thrombin; they are normally cleared by the monocyte–macrophage system. The drugs ε-aminocaproic acid (EACA) and tranexamic acid inhibit the conversion of plasminogen to plasmin. Endothelium also normally secretes a plasminogen activator inhibitor (PAI-1) that antagonizes tPA.

What hemostatic defects are likely to be present in this patient?

Multifactorial coagulopathy often develops in patients with advanced liver disease. Three major causes are usually responsible: (1) vitamin K deficiency due to dietary deficiency or to impaired absorption or storage, (2) impaired hepatic synthesis of coagulation factors, and (3) splenic sequestration of platelets resulting from hypersplenism. To complicate matters further, patients with cirrhosis typically have multiple potential bleeding sites (esophageal varices, gastritis, peptic ulcers, and hemorrhoids) and frequently require multiple blood transfusions. With severe liver disease, patients may also have decreased synthesis of coagulation inhibitors and may fail to clear activated coagulation factors and fibrin split products because of impaired Kupffer cell function; the resultant coagulation defect resembles, and becomes indistinguishable from, disseminated intravascular coagulation (DIC).

What is DIC?

In DIC, the coagulation cascade is activated by the release of endogenous tissue thromboplastin or thromboplastin-like substances, or by direct activation of factor XII by endotoxin or foreign surfaces. Widespread deposition of fibrin in the microcirculation results in consumption of coagulation factors, secondary fibrinolysis, thrombocytopenia, and a microangiopathic hemolytic anemia. Diffuse bleeding, and, in some cases, thromboembolic phenomena, usually follows. Treatment is generally aimed at the underlying cause. Supportive measures include transfusion of coagulation factors and platelets. Heparin therapy is controversial, but may benefit patients with thromboembolic phenomena.

What is primary fibrinolysis?

This bleeding disorder is due to uncontrolled fibrinolysis. Patients may have a deficiency of α_2-antiplasmin or impaired clearance of tPA. The latter may be common in patients with severe liver disease and during the anhepatic phase of liver transplantation. The disorder may occasionally be encountered in patients with carcinoma of the prostate. Diagnosis is often difficult, but is suggested by a bleeding diathesis with a low fibrinogen level but relatively normal coagulation tests and platelet count (below). Treatment includes

fresh frozen plasma or cryoprecipitate and possibly either EACA or tranexamic acid.

How are coagulation tests helpful in evaluating inadequate hemostasis?

The diagnosis of coagulation abnormalities can be facilitated by measurement of the activated partial thromboplastin time (aPTT), PT, thrombin time (TT), fibrin degradation products (see below), and fibrinogen level (Table 32–5). The aPTT measures the intrinsic pathway (factors I, II, V, VIII, IX, X, XI, and XII). The whole blood clotting time and activated clotting time (ACT) also measure the intrinsic pathway. In contrast, the PT measures the extrinsic pathway (factors I, II, V, and VII). The TT specifically measures conversion of fibrinogen to fibrin (factors I and II). The normal plasma fibrinogen level is 200–400 mg/dL (5.9–11.7 μmol/L). Because heparin therapy primarily affects the intrinsic pathway, in low doses it usually prolongs the aPTT only. In high doses, heparin also prolongs the PT. In contrast, warfarin primarily affects vitamin K-dependent factors (II, VII, IX, and X), so the PT is prolonged at usual doses, and the aPTT is prolonged only at high doses. In vivo plasmin activity can be evaluated by measuring circulating levels of peptides cleaved from fibrin and fibrinogen by plasmin, namely *fibrin degradation products* (FDPs) and d-dimers. Patients with primary fibrinolysis usually have elevated FDPs, but normal d-dimer levels.

What tests are most helpful in evaluating inadequate primary hemostasis?

The most commonly performed tests include a platelet count and a bleeding time, but also include thromboelastography (TEG®), rotation thromboelastometry (ROTEM®), and Sonoclot® analysis (see Figure 32–7 and Chapter 51). Patients with normally-functioning platelets and platelet counts above 100,000/μL have normal primary hemostasis. The normal platelet count is 150,000–450,000/μL, and the bleeding time is generally not affected by the platelet count when the latter is greater than 100,000/μL. When the platelet count is 50,000/μL, excessive bleeding generally occurs only with severe trauma or extensive surgery. In contrast, patients with platelet counts under 20,000/μL develop significant bleeding following even minor trauma. Thrombocytopenia usually results from one of three mechanisms: (1) decreased platelet production, (2) splenic sequestration of platelets, or (3) increased platelet destruction. The third mechanism may fall under one of two categories of destruction: immune or nonimmune. Nonimmune destruction includes vasculitis or DIC.

A prolonged bleeding time with a normal platelet count implies a qualitative platelet defect. Although the bleeding time is somewhat dependent on the technique employed, values longer than 10 min are generally considered abnormal. Significant intraoperative and postoperative bleeding may be expected when the bleeding time exceeds 15 min. Specialized testing is required to diagnose specific platelet functional defects.

What are the most common causes of qualitative platelet defects?

The most common platelet defect is due to inhibition of TXA_2 production by aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs). In contrast to aspirin, which irreversibly acetylates and inactivates cyclooxygenase for the life of the platelet (up to 8 days), enzyme inhibition by other NSAIDs is reversible and generally lasts only 24 hr. Increasingly patients are treated with a variety of anti platelet agents such as clopidogrel which impair platelet function. Assays of platelet function are available to determine the degree to which platelet function is inhibited.

What is von Willebrand's disease?

The most common inherited bleeding disorder (1:800–1000 patients) is *von Willebrand's disease*. Patients with this disorder produce a defective vWF or low levels of a normal vWF (normal: 5–10 mg/L). Most patients are heterozygous and have relatively mild hemostatic defects that become apparent clinically only when they are subjected to major surgery or trauma or following ingestion of NSAIDs. In addition to helping link platelets, vWF serves

as a carrier for coagulation factor VIII. As a result, these patients typically have a prolonged bleeding time, decreased plasma vWF concentration, and decreased factor VIII activity. Acquired forms of von Willebrand's disease may be encountered in patients with some immune disorders and those with tumors that absorb vWF onto their surface. At least three forms of the disease are recognized, ranging in severity from mild to severe.

Treatment with desmopressin (DDAVP) can raise vWF levels in some patients with mild von Willebrand's disease (as well as normal individuals). The drug is usually administered at a dose of 0.3 mcg/kg 30 min before surgery. Patients who do not respond to DDAVP should receive cryoprecipitate or factor VIII concentrates, both of which are rich in vWF; prophylactic infusions are generally recommended before and after surgery twice a day for 2–4 days to guarantee surgical hemostasis.

What other hereditary hemostatic defects may be encountered in anesthetic practice?

The most common inherited defect in secondary hemostasis is *factor VIII deficiency* (**hemophilia A**). This X-linked abnormality is estimated to affect 1:10,000 males. Disease severity is generally inversely related to factor VIII activity. Most symptomatic patients experience hemarthrosis, bleeding into deep tissues, and hematuria. Symptomatic patients generally have less than 5% of normal factor VIII activity. Classically, patients present with a prolonged aPTT, but a normal PT and bleeding time. The diagnosis is confirmed by measuring factor VIII activity in blood. Affected patients generally do not experience increased bleeding during surgery when factor VIII levels are more than 30%, but most clinicians recommend increasing factor VIII levels to more than 50% prior to surgery. Normal (fresh frozen) plasma, by definition, is considered to have 1 U of factor VIII activity per milliliter. In contrast, cryoprecipitate has 5–10 U/mL, whereas factor VIII concentrates have approximately 40 U/mL. Each unit of factor VIII transfused is estimated to raise factor VIII levels 2% per kilogram of body weight. Twice-a-day transfusions are generally recommended following surgery because of the relatively short half-life of factor VIII (8–12 h). Administration of DDAVP can raise factor VIII levels 2- to 3-fold in some patients. EACA or tranexamic acid may also be used as adjuncts.

Hemophilia B (also known as Christmas disease) is the result of an X-linked hereditary deficiency of factor IX. The disease is very similar to hemophilia A, but much less common (1:100,000 males). Measurement of factor IX levels establishes the diagnosis. Perioperative administration of fresh frozen plasma is generally recommended to maintain factor IX activity at more than 30% of normal. Recombinant or monoclonal purified factor IX is available.

Factor XIII deficiency is extremely rare, but notable in that the aPTT, PT, TT, and bleeding times are normal. The diagnosis requires measurement of factor XIII levels. Because only 1% of normal factor XIII activity is generally required, patients are treated by a single transfusion of fresh frozen plasma.

Do normal laboratory values exclude a hemostatic defect?

A bleeding diathesis may exist even in the absence of gross abnormalities on routine laboratory tests. Some hemostatic defects are often not detected by routine testing, but require additional specialized tests. A history of excessive bleeding after dental extractions, childbirth, minor surgery, minor trauma, or even during menstruation suggests a hemostatic defect. Conversely, there may be no excess bleeding despite abnormal laboratory testing. A family history of a bleeding diathesis may suggest an inherited coagulation defect, but such history is often absent because the increased bleeding is often minor and goes unnoticed.

Hemostatic defects can often be differentiated by their clinical presentation. Bleeding in patients with primary hemostatic defects usually immediately follows minor trauma, is confined to superficial sites (skin or mucosal surfaces), and often can be controlled by local compression. Small pinpoint hemorrhages from capillaries in the dermis

(petechiae) are typically present on examination. Bleeding into subcutaneous tissues (ecchymosis) from small arterioles or venules is also common in patients with platelet disorders. In contrast, bleeding that results from secondary hemostatic defects is usually delayed following injury, is typically deep (subcutaneous tissues, joints, body cavities, or muscles), and is often difficult to stop even with compression. Hemorrhages may be palpable as hematomas or may go unnoticed when located deeper (retroperitoneal). Coagulation may be impaired by systemic hypothermic or subnormal temperature of the site of bleeding, even when coagulation test (PT, aPTT, bleeding time) results are normal and there is no history of hemostatic defects.