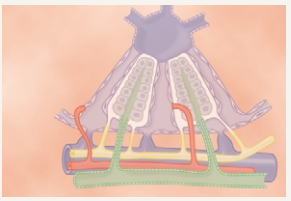
C H A P T E R 7 0

The Liver as an Organ



The liver performs many different functions yet is also a discrete organ, and many of its functions interrelate with one another. This becomes especially evident in abnormalities of the liver, because many of its functions are disturbed simultaneously. The purpose of this chapter is to summarize the liver's different functions, including (1) filtration and storage of blood; (2) metabolism of carbohydrates, proteins, fats, hormones, and foreign chemicals; (3) formation of bile; (4) storage of vitamins and iron; and (5) formation of coagulation factors.

Physiologic Anatomy of the Liver

The liver is the largest organ in the body, contributing about 2 per cent of the total body weight, or about 1.5 kg in the average adult human. The basic functional unit of the liver is the *liver lobule,* which is a cylindrical structure several millimeters in length and 0.8 to 2 millimeters in diameter. The human liver contains 50,000 to 100,000 individual lobules.

The liver lobule, shown in cut-away format in Figure 70–1, is constructed around a *central vein* that empties into the hepatic veins and then into the vena cava. The lobule itself is composed principally of many liver *cellular plates* (two of which are shown in Figure 70–1) that radiate from the central vein like spokes in a wheel. Each hepatic plate is usually two cells thick, and between the adjacent cells lie small *bile canaliculi* that empty into *bile ducts* in the fibrous septa separating the adjacent liver lobules.

In the septa are small *portal venules* that receive their blood mainly from the venous outflow of the gastrointestinal tract by way of the portal vein. From these venules blood flows into flat, branching *hepatic sinusoids* that lie between the hepatic plates and then into the central vein. Thus, the hepatic cells are exposed continuously to portal venous blood.

Hepatic arterioles are also present in the interlobular septa. These arterioles supply arterial blood to the septal tissues between the adjacent lobules, and many of the small arterioles also empty directly into the hepatic sinusoids, most frequently emptying into those located about one third the distance from the interlobular septa, as shown in Figure 70–1.

In addition to the hepatic cells, the venous sinusoids are lined by two other types of cell: (1) typical *endothelial cells* and (2) large *Kupffer cells* (also called reticuloendothelial cells), which are resident macrophages that line the sinusoids and are capable of phagocytizing bacteria and other foreign matter in the hepatic sinus blood.

The endothelial lining of the sinusoids has extremely large pores, some of which are almost 1 micrometer in diameter. Beneath this lining, lying between the endothelial cells and the hepatic cells, are narrow tissue spaces called the *spaces of Disse*, also known as the *perisinusoidal spaces.* The millions of spaces of Disse connect with lymphatic vessels in the interlobular septa. Therefore, excess fluid in these spaces is removed through the lymphatics. Because of the large pores in the endothelium, substances in the plasma move freely into the spaces of Disse. Even large portions of the plasma proteins diffuse freely into these spaces.

Hepatic Vascular and Lymph Systems

The function of the hepatic vascular system is discussed in Chapter 15 in connection with the portal veins and can be summarized as follows.

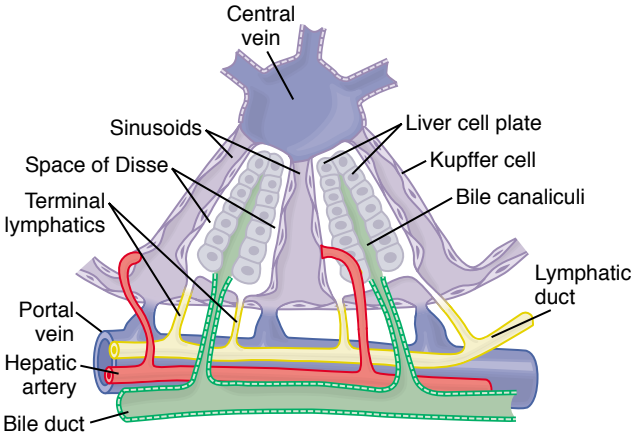


Figure 70–1

Basic structure of a liver lobule, showing the liver cellular plates, the blood vessels, the bile-collecting system, and the lymph flow system composed of the spaces of Disse and the interlobular lymphatics. (Modified from Guyton AC, Taylor AE, Granger HJ: Circulatory Physiology. Vol 2: Dynamics and Control of the Body Fluids. Philadelphia: WB Saunders, 1975.)

Blood Flows Through the Liver from the Portal Vein and Hepatic Artery

The Liver Has High Blood Flow and Low Vascular Resistance. About 1050 milliliters of blood flows from the portal vein into the liver sinusoids each minute, and an additional 300 milliliters flows into the sinusoids from the hepatic artery, the total averaging about 1350 ml/min. This amounts to 27 per cent of the resting cardiac output.

The pressure in the portal vein leading into the liver averages about 9 mm Hg, and the pressure in the hepatic vein leading from the liver into the vena cava normally averages almost exactly 0 mm Hg. This small pressure difference, only 9 mm Hg, shows that the resistance to blood flow through the hepatic sinusoids is normally very low, especially when one considers that about 1350 milliliters of blood flows by this route each minute.

Cirrhosis of the Liver Greatly Increases Resistance to Blood Flow. When liver parenchymal cells are destroyed, they are replaced with fibrous tissue that eventually contracts around the blood vessels, thereby greatly impeding the flow of portal blood through the liver. This disease process is known as *cirrhosis of the liver.* It results most commonly from alcoholism, but it can also follow ingestion of poisons such as carbon tetrachloride, viral diseases such as infectious hepatitis, obstruction of the bile ducts, and infectious processes in the bile ducts.

The portal system is also occasionally blocked by a large clot that develops in the portal vein or its major branches. When the portal system is suddenly blocked, the return of blood from the intestines and spleen through the liver portal blood flow system to the systemic circulation is tremendously impeded, resulting in *portal hypertension* and increasing the capillary pressure in the intestinal wall to 15 to 20 mm Hg above normal. The patient often dies within a few hours because of excessive loss of fluid from the capillaries into the lumens and walls of the intestines.

The Liver Functions as a Blood Reservoir

Because the liver is an expandable organ, large quantities of blood can be stored in its blood vessels. Its normal blood volume, including both that in the hepatic veins and that in the hepatic sinuses, is about 450 milliliters, or almost 10 per cent of the body's total blood volume. When high pressure in the right atrium causes backpressure in the liver, the liver expands, and 0.5 to 1 liter of extra blood is occasionally stored in the hepatic veins and sinuses. This occurs especially in cardiac failure with peripheral congestion, which is discussed in Chapter 22. Thus, in effect, the liver is a large, expandable, venous organ capable of acting as a valuable blood reservoir in times of excess blood volume and capable of supplying extra blood in times of diminished blood volume.

The Liver Has Very High Lymph Flow

Because the pores in the hepatic sinusoids are very permeable and allow ready passage of both fluid and proteins into the spaces of Disse, the lymph draining from the liver usually has a protein concentration of about 6 g/dl, which is only slightly less than the protein concentration of plasma. Also, the extreme permeability of the liver sinusoid epithelium allows large quantities of lymph to form. Therefore, about half of all the lymph formed in the body under resting conditions arises in the liver.

High Hepatic Vascular Pressures Can Cause Fluid Transudation into the Abdominal Cavity from the Liver and Portal Capillaries—Ascites. When the pressure in the hepatic veins rises only 3 to 7 mm Hg above normal, excessive amounts of fluid begin to transude into the lymph and leak through the outer surface of the liver capsule directly into the abdominal cavity. This fluid is almost pure plasma, containing 80 to 90 per cent as much protein as normal plasma. At vena caval pressures of 10 to 15 mm Hg, hepatic lymph flow increases to as much as 20 times normal, and the "sweating" from the surface of the liver can be so great that it causes large amounts of free fluid in the abdominal cavity, which is called *ascites.* Blockage of portal flow through the liver also causes high capillary pressures in the entire portal vascular system of the gastrointestinal tract, resulting in edema of the gut wall and transudation of fluid through the serosa of the gut into the abdominal cavity. This, too, can cause ascites.

Regulation of Liver Mass—Regeneration

The liver possesses a remarkable ability to restore itself after significant hepatic tissue loss from either partial hepatectomy or acute liver injury, as long as the injury is uncomplicated by viral infection or inflammation. Partial hepatectomy, in which up to 70 per cent of the liver is removed, causes the remaining lobes to enlarge and restore the liver to its original size. This regeneration is remarkably rapid and requires only 5 to 7 days in rats. During liver regeneration, hepatocytes are estimated to replicate once or twice, and after the original

size and volume of the liver are achieved, the hepatocytes revert to their usual quiescent state.

Control of this rapid regeneration of the liver is still poorly understood, but *hepatocyte growth factor (HGF)* appears to be an important factor causing liver cell division and growth. HGF is produced by mesenchymal cells in the liver and in other tissues, but not by hepatocytes. Blood levels of HGF rise more than 20-fold after partial hepatectomy, but mitogenic responses are usually found only in the liver after these operations, suggesting that HGF may be activated only in the affected organ. Other growth factors, especially epidermal growth factor, and cytokines such as tumor necrosis factor and interleukin-6 may also be involved in stimulating regeneration of liver cells.

After the liver has returned to its original size, the process of hepatic cell division is terminated. Again, the factors involved are not well understood, although *transforming growth factor-β,* a cytokine secreted by hepatic cells, is a potent inhibitor of liver cell proliferation and has been suggested as the main terminator of liver regeneration.

Physiologic experiments indicate that liver growth is closely regulated by some unknown signal related to body size, so that an optimal liver-to-body weight ratio is maintained for optimal metabolic function. In liver diseases associated with fibrosis, inflammation, or viral infections, however, the regenerative process of the liver is severely impaired, and liver function deteriorates.

Hepatic Macrophage System Serves a Blood-Cleansing Function

Blood flowing through the intestinal capillaries picks up many bacteria from the intestines. Indeed, a sample of blood taken from the portal veins before it enters the liver almost always grows colon bacilli when cultured, whereas growth of colon bacilli from blood in the systemic circulation is extremely rare.

Special high-speed motion pictures of the action of Kupffer cells, the large phagocytic macrophages that line the hepatic venous sinuses, have demonstrated that these cells efficiently cleanse blood as it passes through the sinuses; when a bacterium comes into momentary contact with a Kupffer cell, in less than 0.01 second the bacterium passes inward through the wall of the Kupffer cell to become permanently lodged therein until it is digested. Probably less than 1 per cent of the bacteria entering the portal blood from the intestines succeeds in passing through the liver into the systemic circulation.

Metabolic Functions of the Liver

The liver is a large, chemically reactant pool of cells that have a high rate of metabolism, sharing substrates and energy from one metabolic system to another, processing and synthesizing multiple substances that are transported to other areas of the body, and performing myriad other metabolic functions. For these reasons, a major share of the entire discipline of biochemistry is devoted to the metabolic reactions in the liver. But here, let us summarize those metabolic functions that are especially important in understanding the integrated physiology of the body.

Carbohydrate Metabolism

In carbohydrate metabolism, the liver performs the following functions, as summarized from Chapter 67:

1. Storage of large amounts of glycogen
2. Conversion of galactose and fructose to glucose
3. Gluconeogenesis
4. Formation of many chemical compounds from intermediate products of carbohydrate metabolism

The liver is especially important for maintaining a normal blood glucose concentration. Storage of glycogen allows the liver to remove excess glucose from the blood, store it, and then return it to the blood when the blood glucose concentration begins to fall too low. This is called the *glucose buffer function* of the liver. In a person with poor liver function, blood glucose concentration after a meal rich in carbohydrates may rise two to three times as much as in a person with normal liver function.

Gluconeogenesis in the liver is also important in maintaining a normal blood glucose concentration, because gluconeogenesis occurs to a significant extent only when the glucose concentration falls below normal. In such a case, large amounts of amino acids and glycerol from triglycerides are converted into glucose, thereby helping to maintain a relatively normal blood glucose concentration.

Fat Metabolism

Although most cells of the body metabolize fat, certain aspects of fat metabolism occur mainly in the liver. Specific functions of the liver in fat metabolism, as summarized from Chapter 68, are the following:

1. Oxidation of fatty acids to supply energy for other body functions
2. Synthesis of large quantities of cholesterol, phospholipids, and most lipoproteins
3. Synthesis of fat from proteins and carbohydrates

To derive energy from neutral fats, the fat is first split into glycerol and fatty acids; then the fatty acids are split by *beta-oxidation* into two-carbon acetyl radicals that form *acetyl coenzyme A* (acetyl-CoA). This can enter the citric acid cycle and be oxidized to liberate tremendous amounts of energy. Beta-oxidation can take place in all cells of the body, but it occurs especially rapidly in the hepatic cells. The liver itself cannot use all the acetyl-CoA that is formed; instead, it is converted by the condensation of two molecules of acetyl-CoA into *acetoacetic acid,* a highly soluble acid that passes from the hepatic cells into the extracellular fluid and is then transported throughout the body to be absorbed by other tissues. These tissues reconvert the acetoacetic acid into acetyl-CoA and then oxidize it in the usual manner. Thus, the liver is responsible for a major part of the metabolism of fats.

About 80 per cent of the cholesterol synthesized in the liver is converted into bile salts, which are secreted into the bile; the remainder is transported in the lipoproteins and carried by the blood to the tissue cells everywhere in the body. Phospholipids are likewise synthesized in the liver and transported principally in the lipoproteins. Both cholesterol and phospholipids are used by the cells to form membranes, intracellular structures, and multiple chemical substances that are important to cellular function.

Almost all the fat synthesis in the body from carbohydrates and proteins also occurs in the liver. After fat

is synthesized in the liver, it is transported in the lipoproteins to the adipose tissue to be stored.

Protein Metabolism

The body cannot dispense with the liver's contribution to protein metabolism for more than a few days without death ensuing. The most important functions of the liver in protein metabolism, as summarized from Chapter 69, are the following:

1. Deamination of amino acids
2. Formation of urea for removal of ammonia from the body fluids
3. Formation of plasma proteins
4. Interconversions of the various amino acids and synthesis of other compounds from amino acids

Deamination of amino acids is required before they can be used for energy or converted into carbohydrates or fats. A small amount of deamination can occur in the other tissues of the body, especially in the kidneys, but this is much less important than the deamination of amino acids by the liver.

Formation of urea by the liver removes ammonia from the body fluids. Large amounts of ammonia are formed by the deamination process, and additional amounts are continually formed in the gut by bacteria and then absorbed into the blood. Therefore, if the liver does not form urea, the plasma ammonia concentration rises rapidly and results in *hepatic coma* and death. Indeed, even greatly decreased blood flow through the liver—as occurs occasionally when a shunt develops between the portal vein and the vena cava—can cause excessive ammonia in the blood, an extremely toxic condition.

Essentially all the plasma proteins, with the exception of part of the gamma globulins, are formed by the hepatic cells. This accounts for about 90 per cent of all the plasma proteins. The remaining gamma globulins are the antibodies formed mainly by plasma cells in the lymph tissue of the body. The liver can form plasma proteins at a maximum rate of 15 to 50 g/day. Therefore, even if as much as half the plasma proteins are lost from the body, they can be replenished in 1 or 2 weeks.

It is particularly interesting that plasma protein depletion causes rapid mitosis of the hepatic cells and growth of the liver to a larger size; these effects are coupled with rapid output of plasma proteins until the plasma concentration returns to normal. With chronic liver disease (e.g., cirrhosis), plasma proteins, such as albumin, may fall to very low levels, causing generalized edema and ascites, as explained in Chapter 29.

Among the most important functions of the liver is its ability to synthesize certain amino acids and to synthesize other important chemical compounds from amino acids. For instance, the so-called nonessential amino acids can all be synthesized in the liver. To do this, a keto acid having the same chemical composition (except at the keto oxygen) as that of the amino acid to be formed is synthesized. Then an amino radical is transferred through several stages of *transamination* from an available amino acid to the keto acid to take the place of the keto oxygen.

Other Metabolic Functions of the Liver

The Liver Is a Storage Site for Vitamins. The liver has a particular propensity for storing vitamins and has long been known as an excellent source of certain vitamins in the treatment of patients. The vitamin stored in greatest quantity in the liver is vitamin A, but large quantities of vitamin D and vitamin B_{12} are normally stored as well. Sufficient quantities of vitamin A can be stored to prevent vitamin A deficiency for as long as 10 months. Sufficient vitamin D can be stored to prevent deficiency for 3 to 4 months, and enough vitamin B_{12} can be stored to last for at least 1 year and maybe several years.

The Liver Stores Iron as Ferritin. Except for the iron in the hemoglobin of the blood, by far the greatest proportion of iron in the body is stored in the liver in the form of *ferritin.* The hepatic cells contain large amounts of a protein called *apoferritin,* which is capable of combining reversibly with iron. Therefore, when iron is available in the body fluids in extra quantities, it combines with apoferritin to form ferritin and is stored in this form in the hepatic cells until needed elsewhere. When the iron in the circulating body fluids reaches a low level, the ferritin releases the iron. Thus, the apoferritin-ferritin system of the liver acts as a *blood iron buffer,* as well as an iron storage medium. Other functions of the liver in relation to iron metabolism and red blood cell formation are considered in Chapter 32.

The Liver Forms a Large Proportion of the Blood Substances Used in Coagulation. Substances formed in the liver that are used in the coagulation process include *fibrinogen, prothrombin, accelerator globulin, Factor VII,* and several other important factors. Vitamin K is required by the metabolic processes of the liver for the formation of several of these substances, especially prothrombin and Factors VII, IX, and X. In the absence of vitamin K, the concentrations of all these decrease markedly, and this almost prevents blood coagulation.

The Liver Removes or Excretes Drugs, Hormones, and Other Substances. The active chemical medium of the liver is well known for its ability to detoxify or excrete into the bile many drugs, including sulfonamides, penicillin, ampicillin, and erythromycin.

In a similar manner, several of the hormones secreted by the endocrine glands are either chemically altered or excreted by the liver, including thyroxine and essentially all the steroid hormones, such as estrogen, cortisol, and aldosterone. Liver damage can lead to excess accumulation of one or more of these hormones in the body fluids and therefore cause overactivity of the hormonal systems.

Finally, one of the major routes for excreting calcium from the body is secretion by the liver into the bile, which then passes into the gut and is lost in the feces.

Measurement of Bilirubin in the Bile as a Clinical Diagnostic Tool

The formation of bile by the liver and the function of the bile salts in the digestive and absorptive processes of the intestinal tract are discussed in Chapters 64 and 65. In addition, many substances are excreted in the bile and then eliminated in the feces. One of these is the greenish yellow pigment *bilirubin.* This is a major end product of hemoglobin degradation, as pointed out in Chapter 32. However, it also provides *an exceedingly valuable tool for diagnosing both hemolytic blood*

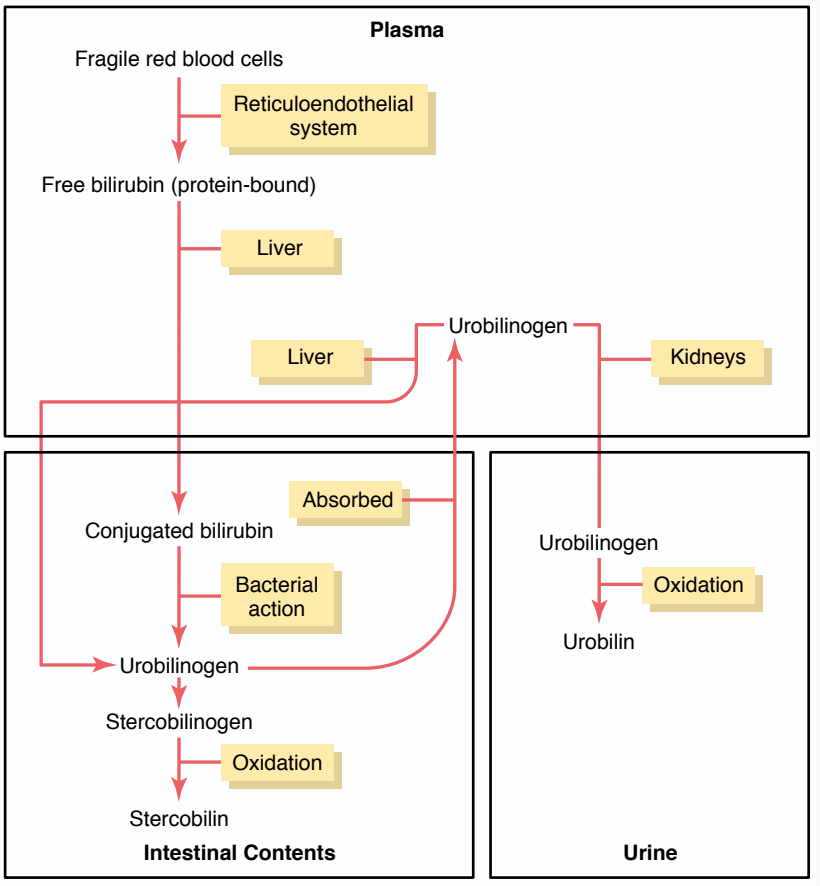


Figure 70–2

Bilirubin formation and excretion.

diseases and various types of liver diseases. Therefore, while referring to Figure 70–2, let us explain this.

Briefly, when the red blood cells have lived out their life span (on average, 120 days) and have become too fragile to exist in the circulatory system, their cell membranes rupture, and the released hemoglobin is phagocytized by tissue macrophages (also called the reticuloendothelial system) throughout the body. The hemoglobin is first split into *globin* and *heme,* and the heme ring is opened to give (1) free iron, which is transported in the blood by transferrin, and (2) a straight chain of four pyrrole nuclei, which is the substrate from which bilirubin will eventually be formed. The first substance formed is *biliverdin,* but this is rapidly reduced to *free bilirubin,* which is gradually released from the macrophages into the plasma. The free bilirubin immediately combines strongly with plasma albumin and is transported in this combination throughout the blood and interstitial fluids. Even when bound with plasma protein, this bilirubin is still called "free bilirubin" to distinguish it from "conjugated bilirubin," which is discussed later.

Within hours, the free bilirubin is absorbed through the hepatic cell membrane. In passing to the inside of the liver cells, it is released from the plasma albumin and soon thereafter conjugated about 80 per cent with glucuronic acid to form *bilirubin glucuronide,* about 10 per cent with sulfate to form *bilirubin sulfate,* and about 10 per cent with a multitude of other substances. In these forms, the bilirubin is excreted from the hepatocytes by an active transport process into the bile canaliculi and then into the intestines.

Formation and Fate of Urobilinogen. Once in the intestine, about half of the "conjugated" bilirubin is converted by bacterial action into the substance *urobilinogen,* which is highly soluble. Some of the urobilinogen is reabsorbed through the intestinal mucosa back into the blood. Most of this is re-excreted by the liver back into the gut, but about 5 per cent is excreted by the kidneys into the urine. After exposure to air in the urine, the urobilinogen becomes oxidized to *urobilin;* alternatively, in the feces, it becomes altered and oxidized to form *stercobilin.* These interrelations of bilirubin and the other bilirubin products are shown in Figure 70–2.

Jaundice—Excess Bilirubin in the Extracellular Fluid

Jaundice refers to a yellowish tint to the body tissues, including a yellowness of the skin as well as the deep tissues. The usual cause of jaundice is large quantities of bilirubin in the extracellular fluids, either free bilirubin or conjugated bilirubin. The normal plasma concentration of bilirubin, which is almost entirely the free form, averages 0.5 mg/dl of plasma. In certain abnormal conditions, this can rise to as high as 40 mg/dl, and much of

it can become the conjugated type. The skin usually begins to appear jaundiced when the concentration rises to about three times normal—that is, above 1.5 mg/dl.

The common causes of jaundice are (1) increased destruction of red blood cells, with rapid release of bilirubin into the blood, and (2) obstruction of the bile ducts or damage to the liver cells so that even the usual amounts of bilirubin cannot be excreted into the gastrointestinal tract. These two types of jaundice are called, respectively, *hemolytic jaundice* and *obstructive jaundice*. They differ from each other in the following ways.

Hemolytic Jaundice Is Caused by Hemolysis of Red Blood Cells. In hemolytic jaundice, the excretory function of the liver is not impaired, but red blood cells are hemolyzed so rapidly that the hepatic cells simply cannot excrete the bilirubin as quickly as it is formed. Therefore, the plasma concentration of free bilirubin rises to above-normal levels. Likewise, the rate of formation of *urobilinogen* in the intestine is greatly increased, and much of this is absorbed into the blood and later excreted in the urine.

Obstructive Jaundice Is Caused by Obstruction of Bile Ducts or Liver Disease. In obstructive jaundice, caused either by obstruction of the bile ducts (which most often occurs when a gallstone or cancer blocks the common bile duct) or by damage to the hepatic cells (which occurs in *hepatitis*), the rate of bilirubin formation is normal, but the bilirubin formed cannot pass from the blood into the intestines. The free bilirubin still enters the liver cells and becomes conjugated in the usual way. This conjugated bilirubin is then returned to the blood, probably by rupture of the congested bile canaliculi and direct emptying of the bile into the lymph leaving the liver. Thus, *most of the bilirubin in the plasma becomes the conjugated type* rather than the free type.

Diagnostic Differences Between Hemolytic and Obstructive Jaundice. Chemical laboratory tests can be used to differentiate between free and conjugated bilirubin in the plasma. In hemolytic jaundice, almost all the bilirubin is in the "free" form; in obstructive jaundice, it is mainly in the "conjugated" form. A test called the *van den Bergh reaction* can be used to differentiate between the two.

When there is total obstruction of bile flow, no bilirubin can reach the intestines to be converted into urobilinogen by bacteria. Therefore, no urobilinogen is reabsorbed into the blood, and none can be excreted by the kidneys into the urine. Consequently, in *total* obstructive jaundice, tests for urobilinogen in the urine are completely negative. Also, the stools become clay colored owing to a lack of stercobilin and other bile pigments.

Another major difference between free and conjugated bilirubin is that the kidneys can excrete small quantities of the highly soluble conjugated bilirubin but not the albumin-bound free bilirubin. Therefore, in severe obstructive jaundice, significant quantities of conjugated bilirubin appear in the urine. This can be demonstrated simply by shaking the urine and observing the foam, which turns an intense yellow. Thus, by understanding the physiology of bilirubin excretion by the liver and by the use of a few simple tests, it is often possible to differentiate among multiple types of hemolytic diseases and liver diseases, as well as to determine the severity of the disease.

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