# Pancreatic secretion

The pancreas, which lies parallel to and beneath the stomach, is a large compound gland with most of its internal structure similar to that of the salivary glands.The pancreatic digestive enzymes are secreted by pancreatic acini, and large volumes of sodium bicarbonate solution are secreted by the small ductules and larger ducts leading from the acini.The combined product of enzymes and sodium bicarbonate then flows through a long pancreatic duct that normally joins the hepatic duct immediately before it empties into the duodenum through the papilla of Vater, surrounded by the sphincter of Oddi. The enzymes are secreted by gland cells at the pancreatic end of the duct system, whereas bicarbonate ions are secreted by the epithelial cells lining the ducts.

Pancreatic juice is secreted most abundantly in response to the presence of chyme in the upper portions of the small intestine, and the characteristics of the pancreatic juice are determined to some extent by the types of food in the chyme. (The pancreas also secretes insulin, but this is not secreted by the same pancreatic tissue that secretes intestinal pancreatic juice. Instead, insulin is secreted directly into the blood—not into the intestine—by the islets of Langerhans that occur in islet patches throughout the pancreas.
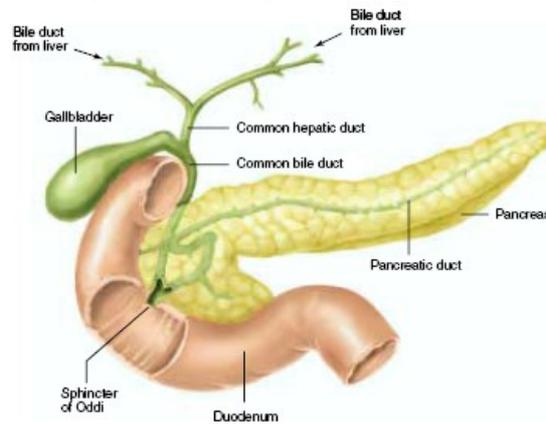


Figure 1

## Pancreatic digestive enzymes

Pancreatic secretion contains enzymes for digesting all of the three major types of food: proteins, carbohydrates, and fats. It also contains large quantities of bicarbonate ions, which play an important role in neutralizing the acidity of the chyme emptied from the stomach into the duodenum. The most important of the pancreatic enzymes for digesting proteins are trypsin, chymotrypsin and carboxypolypeptidase.

The most abundant of these is trypsin. Trypsin and chymotrypsin split whole and partially digested proteins into peptides of various sizes but do not cause release of individual amino acids. However, carboxypolypeptidase does split some peptides into individual amino acids, thus completing digestion of some proteins all the way to the amino acid state.

The pancreatic enzyme for digesting carbohydrates is pancreatic amylase, which hydrolyzes starches, glycogen, and most other carbohydrates (except cellulose) to form mostly disaccharides and a few trisaccharides. The main enzymes for fat digestion are (1) pancreatic lipase, which is capable of hydrolyzing neutral fat into fatty acids and monoglycerides; (2) cholesterol esterase, which causes hydrolysis of cholesterol esters; and (3) phospholipase, which splits fatty acids from phospholipids.

When first synthesized in the pancreatic cells, the proteolytic digestive enzymes are in the inactive forms trypsinogen, chymotrypsinogen and procarboxypolypeptidase, which are all inactive enzymatically. They become activated only after they are secreted into the

intestinal tract. Trypsinogen is activated by an enzyme called enterokinase, which is secreted by the intestinal mucosa when chyme comes in contact with the mucosa. Also, trypsinogen can be autocatalytically activated by trypsin that has already been formed from previously secreted trypsinogen. Chymotrypsinogen is activated by trypsin to form chymotrypsin, and procarboxypolypeptidase is activated in a similar manner.

It is important that the proteolytic enzymes of the pancreatic juice not become activated until after they have been secreted into the intestine because the trypsin and the other enzymes would digest the pancreas itself. Fortunately, the same cells that secrete proteolytic enzymes into the acini of the pancreas secrete simultaneously another substance called trypsin inhibitor. This substance is formed in the cytoplasm of the glandular cells, and it prevents activation of trypsin both inside the secretory cells and in the acini and ducts of the pancreas. And, because it is trypsin that activates the other pancreatic proteolytic enzymes, trypsin inhibitor prevents activation of the others as well. When the pancreas becomes severely damaged or when a duct becomes blocked, large quantities of pancreatic secretion sometimes become pooled in the damaged areas of the pancreas. Under these conditions, the effect of trypsin inhibitor is often overwhelmed, in which case the pancreatic secretions rapidly become activated and can literally digest the entire pancreas within a few hours, giving rise to the condition called acute pancreatitis. This sometimes is lethal because of accompanying circulatory shock; even if not lethal, it usually leads to a subsequent lifetime of pancreatic insufficiency.

Although the enzymes of the pancreatic juice are secreted entirely by the acini of the pancreatic glands, the other two important components of pancreatic juice, bicarbonate ions and water, are secreted mainly by the epithelial cells of the ductules and ducts that lead from the acini.When the pancreas is stimulated to secrete copious quantities of pancreatic juice, the bicarbonate ion concentration can rise to as high as 145 mEq/L, a value about five times that of bicarbonate ions in the plasma. This provides a large quantity of alkali in the pancreatic juice that serves to neutralize the hydrochloric acid emptied into the duodenum from the stomach. The basic steps in the cellular mechanism for secreting sodium bicarbonate solution into the pancreatic ductules and ducts are shown in Figure 2.  They are the following:
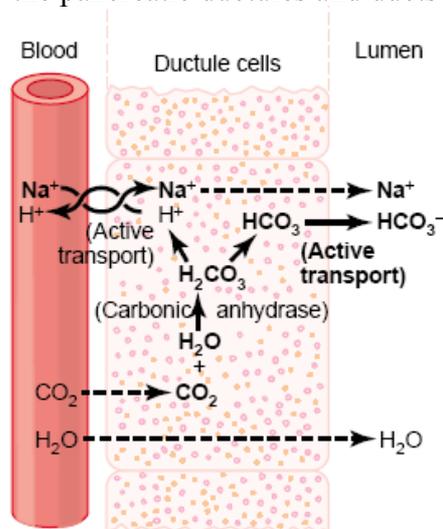


1. Carbon dioxide diffuses to the interior of the cell from the blood and, under the influence of carbonic anhydrase, combines with water to form carbonic acid ($H_2CO_3$). The carbonic acid in turn dissociates into bicarbonate ions and hydrogen ions ($HCO_3^-$ and $H^+$). Then the bicarbonate ions are actively transported in association with sodium ions ($Na^+$) through the luminal border of the cell into the lumen of the duct.

2. The hydrogen ions formed by dissociation of carbonic acid inside the cell are exchanged for sodium ions through the blood border of the cell by a secondary active transport process.

Figure 2 Secretion of sodium bicarbonate solution by the pancreatic ductules and ducts

This supplies the sodium ions ($Na^+$) that are transported through the luminal border into the pancreatic duct lumen to provide electrical neutrality for the secreted bicarbonate ions.

3. The overall movement of sodium and bicarbonate ions from the blood into the duct lumen

creates an osmotic pressure gradient that causes osmosis of water also into the pancreatic duct, thus forming an almost completely isosmotic bicarbonate solution.

**Regulation of pancreatic secretion**

Three basic stimuli are important in causing pancreatic secretion:

1. Acetylcholine, which is released from the parasympathetic vagus nerve endings and from other cholinergic nerves in the enteric nervous system

2. Cholecystokinin, which is secreted by the duodenal and upper jejunal mucosa when food enters the small intestine

3. Secretin, which is also secreted by the duodenal and jejunal mucosa when highly acid food enters the small intestine

The first two of these stimuli, acetylcholine and cholecystokinin, stimulate the acinar cells of the pancreas, causing production of large quantities of pancreatic digestive enzymes but relatively small quantities of water and electrolytes to go with the enzymes. Without the water, most of the enzymes remain temporarily stored in the acini and ducts until more fluid secretion comes along to wash them into the duodenum. Secretin, in contrast to the first two basic stimuli, stimulates secretion of large quantities of water solution of sodium bicarbonate by the pancreatic ductal epithelium.When all the different stimuli of pancreatic secretion occur at once, the total secretion is far greater than the sum of the secretions caused by each one separately. Therefore, the various stimuli are said to "multiply," or "potentiate," one another. Thus, pancreatic secretion normally results from the combined effects of the multiple basic stimuli, not from one alone.

**Phases of pancreatic secretion**

Pancreatic secretion occurs in three phases, the same as for gastric secretion: the cephalic phase, the gastric phase, and the intestinal phase.
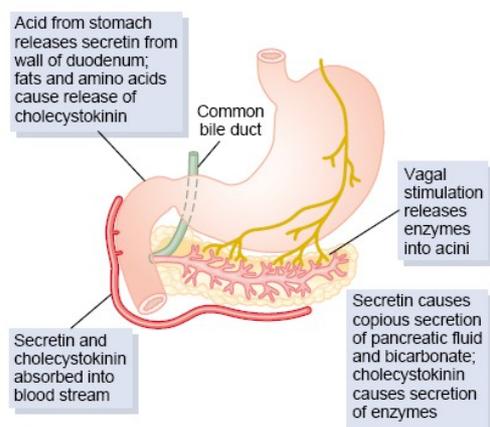
**Cephalic and Gastric Phases.** During the cephalic phase of pancreatic secretion, the same nervous signals from the brain that cause secretion in the stomach also cause acetylcholine release by the vagal nerve endings in the pancreas. This causes moderate amounts of enzymes to be secreted into the pancreatic acini, accounting for about 20 per cent of the total secretion of pancreatic enzymes after a meal. But little of the secretion flows immediately through the pancreatic ducts into the intestine because only small amounts of water and electrolytes are secreted along with the enzymes. During the gastric phase, the nervous stimulation of enzyme secretion continues, accounting for another 5 to 10 per cent of pancreatic enzymes secreted after a meal. But, again, only small amounts reach the duodenum because of continued lack of significant fluid secretion.

**Intestinal Phase.** After chyme leaves the stomach and enters the small intestine, pancreatic secretion becomes copious, mainly in response to the hormone secretin. Secretin is a polypeptide, containing 27 amino acids (molecular weight about 3400), present in an inactive form, prosecretin, in so-called S cells in the mucosa of the duodenum and jejunum. When acid chyme with pH less than 4.5 to 5.0 enters the duodenum from the stomach, it causes duodenal mucosal release and activation of secretin, which is then absorbed into the blood. The one truly potent constituent of chyme that causes this secretin release is the hydrochloric acid from the stomach. Secretin in turn causes the pancreas to secrete large quantities of fluid containing a high concentration of bicarbonate ion (up to 145 mEq/L) but a low concentration of chloride ion. The secretin mechanism is especially important for two reasons: First, secretin begins to be released from the mucosa of the small intestine when the pH of the duodenal contents falls below 4.5 to 5.0, and its release increases greatly as the pH falls to 3.0.This immediately causes copious secretion of pancreatic juice containing abundant amounts of sodium bicarbonate. The net result is then the following reaction in the duodenum:

$$HCl + NaHCO_3 \rightarrow NaCl + H_2CO_3$$
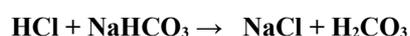
Then the carbonic acid immediately dissociates into carbon dioxide and water. The carbon dioxide is absorbed into the blood and expired through the lungs, thus leaving a neutral solution of sodium chloride in the duodenum. In this way, the acid contents emptied into the duodenum from the stomach become neutralized, so that further peptic digestive activity by the gastric juices in the duodenum is immediately blocked. Because the mucosa of the small intestine cannot withstand the digestive action of acid gastric juice, this is an essential protective mechanism to prevent development of duodenal ulcers. Bicarbonate ion secretion by the pancreas provides an appropriate pH for action of the pancreatic digestive enzymes, which function optimally in a slightly alkaline or neutral medium, at a pH of 7.0 to 8.0. Fortunately, the pH of the sodium bicarbonate secretion averages 8.0.

The presence of food in the upper small intestine also causes a second hormone, cholecystokinin, a polypeptide containing 33 amino acids, to be released from yet another group of cells, the I cells, in the mucosa of the duodenum and upper jejunum. This release of cholecystokinin results especially from the presence of proteoses and peptones (products of partial protein digestion) and long-chain fatty acids in the chyme coming from the stomach. Cholecystokinin, like secretin, passes by way of the blood to the pancreas but instead of causing sodium bicarbonate secretion causes mainly secretion of still much more pancreatic digestive enzymes by the acinar cells. This effect is similar to that caused by vagal stimulation but even more pronounced, accounting for 70 to 80 percent of the total secretion of the pancreatic digestive enzymes after a meal. The differences between the pancreatic stimulatory effects of secretin and cholecystokinin are: (1) intense sodium bicarbonate secretion in response to acid in the duodenum, stimulated by secretin, (2) a dual effect in response to soap (a fat), and (3) intense digestive enzyme secretion (when peptones enter the duodenum) stimulated by cholecystokinin.



Figure 3   Regulation of pancreatic secretion

## Bile secretion

Bile is secreted by liver cells into a number of small ducts, the bile canaliculi, which converge to form the common hepatic duct. Bile contains six major ingredients: (1) bile salts; (2) lecithin (a phospholipid); (3) bicarbonate ions and other salts; (4) cholesterol; (5) bile pigments and small amounts of other metabolic end products, and (6) trace metals. Bile salts and lecithin are synthesized in the liver and help solubilize fat in the small intestine. Bicarbonate ions neutralize acid in the duodenum, and the last three ingredients represent substances extracted from the blood by the liver and excreted via the bile. From the standpoint of gastrointestinal function, the most important components of bile are the bile salts.

During the digestion of a fatty meal, most of the bile salts entering the intestinal tract via the bile are absorbed by specific sodium-coupled transporters in the ileum (the last segment of the small intestine). The absorbed bile salts are returned via the portal vein to the liver, where they are once again secreted into the bile. This recycling pathway from the intestine to the liver and back to the intestine is known as the enterohepatic circulation (Figure 4). A small amount (5 percent) of the bile salts escape this recycling and is lost in the feces, but the liver synthesizes new bile salts from cholesterol to replace them.
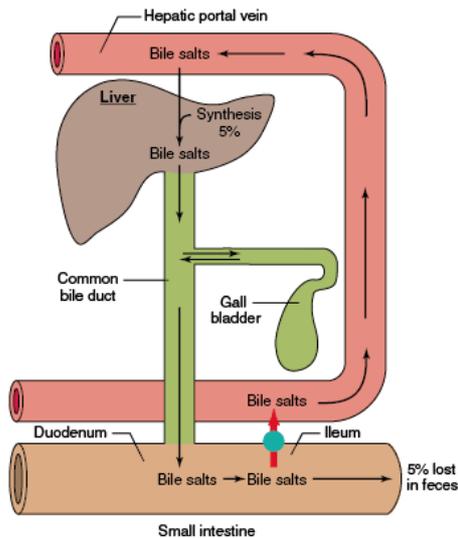
Figure 4

During the digestion of a meal the entire bile salt content of the body may be recycled several times via the enterohepatic circulation.

In addition to synthesizing bile salts from cholesterol, the liver also secretes cholesterol extracted from the blood into the bile. Bile secretion, followed by excretion of cholesterol in the feces, is one of the mechanisms by which cholesterol homeostasis in the blood is maintained . Cholesterol is insoluble in water and its solubility in bile is achieved by its incorporation into micelles (whereas in the blood, cholesterol is incorporated into lipoproteins). Bile pigments are substances formed from the heme portion of hemoglobin when old or damaged erythrocytes are digested in the spleen and liver.

The predominant bile pigment is bilirubin, which is extracted from the blood by liver cells and actively secreted into the bile. It is bilirubin that gives bile its yellow color. After entering the intestinal tract, bilirubin is modified by bacterial enzymes to form the brown pigments that give feces their characteristic color. During their passage through the intestinal tract, some of the bile pigments are absorbed into the blood and are eventually excreted in the urine, giving urine its yellow color.

Like pancreatic secretions, the components of bile are secreted by two different cell types. The bile salts, cholesterol, lecithin, and bile pigments are secreted by hepatocytes, whereas most of the bicarbonate-rich salt solution is secreted by the epithelial cells lining the bile ducts. Secretion of the salt solution by the bile ducts, just like that secreted by the pancreas, is stimulated by secretin in response to the presence of acid in the duodenum. Unlike the pancreas, whose secretions are controlled by intestinal hormones, bile salt secretion is controlled by the concentration of bile salts in the blood—the greater the plasma concentration of bile salts, the greater their secretion into the bile canaliculi. Absorption of bile salts from the intestine during the digestion of a meal leads to their increased plasma concentration and thus to an increased rate of bile salt secretion by the liver.

Although bile secretion is greatest during and just after a meal, some bile is always being secreted by the liver. Surrounding the common bile duct at the point where it enters the duodenum is a ring of smooth muscle known as the sphincter of Oddi. When this sphincter is closed, the dilute bile secreted by the liver is shunted into the gallbladder where the organic components of bile become concentrated as NaCl and water are absorbed into the blood. Shortly after the beginning of a fatty meal, the sphincter of Oddi relaxes and the gallbladder contracts, discharging concentrated bile into the duodenum.
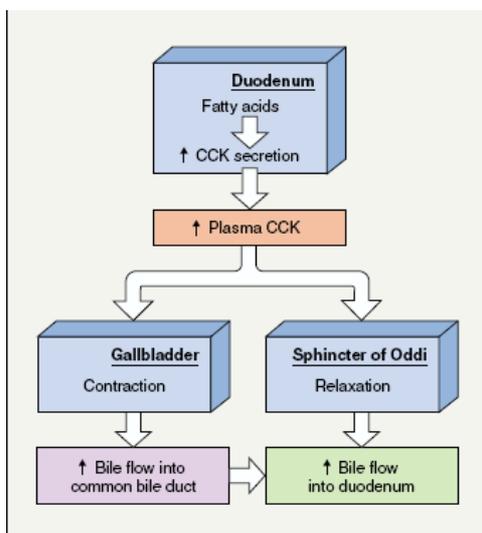


Figure 5

The signal for gallbladder contraction and sphincter relaxation is the intestinal hormone CCK— appropriately so, since as we have seen, a major stimulus for this hormone's release is the presence of fat in the duodenum. ( cholecystokinin received its name: chole, bile; cysto, bladder; kinin, to move).

**Secretion of bile by the liver**

One of the many functions of the liver is to secrete bile, normally between 600 and 1000 ml/day.  Table 64–2 gives the composition of bile when it is first secreted by the liver and then after it has been concentrated in the gallbladder. This table shows that by far the most abundant substances secreted in the bile are bile salts, which account for about one half of the total solutes also in the bile. Also secreted or excreted in large concentrations are bilirubin, cholesterol, lecithin, and the usual electrolytes of plasma. In the concentrating process in the gallbladder, water and large portions of the electrolytes (except calcium ions) are reabsorbed by the gallbladder mucosa; essentially all other constituents, especially the bile salts and the lipid substances cholesterol and lecithin, are not reabsorbed and, therefore, become highly concentrated in the gallbladder bile.

**Table 64–2**

**Composition of Bile**

|  | Liver Bile | Gallbladder Bile |
|---|---|---|
| Water | 97.5 g/dl | 92 g/dl |
| Bile salts | 1.1 g/dl | 6 g/dl |
| Bilirubin | 0.04 g/dl | 0.3 g/dl |
| Cholesterol | 0.1 g/dl | 0.3 to 0.9 g/dl |
| Fatty acids | 0.12 g/dl | 0.3 to 1.2 g/dl |
| Lecithin | 0.04 g/dl | 0.3 g/dl |
| $Na^+$ | 145.04 mEq/L | 130 mEq/L |
| $K^+$ | 5 mEq/L | 12 mEq/L |
| $Ca^{++}$ | 5 mEq/L | 23 mEq/L |
| $Cl^-$ | 100 mEq/L | 25 mEq/L |
| $HCO_3^-$ | 28 mEq/L | 10 mEq/L |

Bile serves two important functions: first, bile plays an important role in fat digestion and absorption, not because of any enzymes in the bile that cause fat digestion, but because bile acids in the bile do two things: (1) they help to emulsify the large fat particles of the food into many minute particles, the surface of which can then be attacked by lipase enzymes secreted in pancreatic juice, and (2) they aid in absorption of the digested fat end products through the intestinal mucosal membrane. Second, bile serves as a means for excretion of several important waste products from the blood. These include especially bilirubin, an end product of hemoglobin destruction, and excesses of cholesterol.

Bile is secreted in two stages by the liver: (1) The initial portion is secreted by the principal functional cells of the liver, the hepatocytes; this initial secretion contains large amounts of bile acids, cholesterol, and other organic constituents. It is secreted into minute bile canaliculi that originate between the hepatic cells. (2) Next, the bile flows in the canaliculi toward the interlobular septa, where the canaliculi empty into terminal bile ducts and then into progressively larger ducts, finally reaching the hepatic duct and common bile duct. From these the bile either empties directly into the duodenum or is diverted for minutes up to several hours through the cystic duct into the gallbladder.

In its course through the bile ducts, a second portion of liver secretion is added to the initial bile.This additional secretion is a watery solution of sodium and bicarbonate ions secreted by secretory epithelial cells that line the ductules and ducts. This second secretion sometimes increases the total quantity of bile by as much as an additional 100 per cent. The

second secretion is stimulated especially by secretin, which causes release of additional quantities of bicarbonate ions to supplement the bicarbonate ions in pancreatic secretion (for neutralizing acid that empties into the duodenum from the stomach).
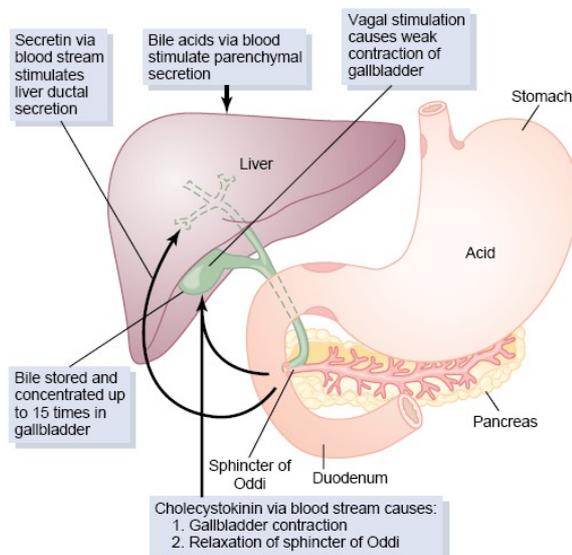


Figure 6 Liver secretion and gallbladder emptying

Bile is secreted continually by the liver cells, but most of it is normally stored in the gallbladder until needed in the duodenum.The maximum volume that the gallbladder can hold is only 30 to 60 milliliters. Nevertheless, as much as 12 hours of bile secretion (usually about 450 milliliters) can be stored in the gallbladder because water, sodium, chloride, and most other small electrolytes are continually absorbed through the gallbladder mucosa, concentrating the remaining bile constituents that contain the bile salts, cholesterol, lecithin, and bilirubin. Most of this gallbladder absorption is caused by active transport of sodium through the gallbladder epithelium, and this is followed by secondary absorption of chloride ions, water, and most other diffusible constituents. Bile is normally concentrated in this way about 5-fold, but it can be concentrated up to a maximum of 20-fold.

When food begins to be digested in the upper gastrointestinal tract, the gallbladder begins to empty, especially when fatty foods reach the duodenum about 30 minutes after a meal. The mechanism of gallbladder emptying is rhythmical contractions of the wall of the gallbladder, but effective emptying also requires simultaneous relaxation of the sphincter of Oddi, which guards the exit of the common bile duct into the duodenum. By far the most potent stimulus for causing the gallbladder contractions is the hormone cholecystokinin. This is the same cholecystokinin discussed earlier that causes increased secretion of digestive enzymes by the acinar cells of the pancreas.The stimulus for cholecystokinin entry into the blood from the duodenal mucosa is mainly the presence of fatty foods in the duodenum. In addition to cholecystokinin, the gallbladder is stimulated less strongly by acetylcholine-secreting nerve fibers from both the vagi and the intestinal enteric nervous system.They are the same nerves that promote motility and secretion in other parts of the upper gastrointestinal tract. In summary, the gallbladder empties its store of concentrated bile into the duodenum mainly in response to the cholecystokinin stimulus that itself is initiated mainly by fatty foods. When fat is not in the food, the gallbladder empties poorly, but when significant quantities of fat are present, the gallbladder normally empties completely in about 1 hour.

**Function of bile salts in fat digestion and absorption**

The liver cells synthesize about 6 grams of bile salts daily. The precursor of the bile salts is cholesterol, which is either present in the diet or synthesized in the liver cells during the

course of fat metabolism. The cholesterol is first converted to cholic acid or chenodeoxycholic acid in about equal quantities. These acids in turn combine principally with glycine and to a lesser extent with taurine to form glyco- and tauroconjugated bile acids. The salts of these acids, mainly sodium salts, are then secreted in the bile. The bile salts have two important actions in the intestinal tract: First, they have a detergent action on the fat particles in the food. This decreases the surface tension of the particles and allows agitation in the intestinal tract to break the fat globules into minute sizes. This is called the emulsifying or detergent function of bile salts. Second, and even more important than the emulsifying function, bile salts help in the absorption of (1) fatty acids, (2) monoglycerides, (3) cholesterol, and (4) other lipids from the intestinal tract. They do this by forming very small physical complexes with these lipids; the complexes are called micelles, and they are semi-soluble in the chyme because of the electrical charges of the bile salts. The intestinal lipids are "ferried" in this form to the intestinal mucosa, where they are then absorbed into the blood. Without the presence of bile salts in the intestinal tract, up to 40 per cent of the ingested fats are lost into the feces and the person often develops a metabolic deficit because of this nutrient loss.

About 94 percent of the bile salts are reabsorbed into the blood from the small intestine, about one half of this by diffusion through the mucosa in the early portions of the small intestine and the remainder by an active transport process through the intestinal mucosa in the distal ileum. They then enter the portal blood and pass back to the liver. On reaching the liver, on first passage through the venous sinusoids these salts are absorbed almost entirely back into the hepatic cells and then are resecreted into the bile. The small quantities of bile salts lost into the feces are replaced by new amounts formed continually by the liver cells. This recirculation of the bile salts is called the enterohepatic circulation of bile salts. The quantity of bile secreted by the liver each day is highly dependent on the availability of bile salts—the greater the quantity of bile salts in the enterohepatic circulation (usually a total of only about 2.5 grams), the greater the rate of bile secretion. Indeed, ingestion of supplemental bile salts can increase bile secretion by several hundred milliliters per day. The daily rate of liver bile salt secretion is actively controlled by the availability (or lack of availability) of bile salts in the enterohepatic circulation.

In addition to the strong stimulating effect of bile acids to cause bile secretion, the hormone secretin that also stimulates pancreatic secretion increases bile secretion, sometimes more than doubling its secretion for several hours after a meal. This increase in secretion is almost entirely of a sodium bicarbonate-rich watery solution by the epithelial cells of the bile ductules and ducts, and not increased secretion by the liver parenchymal cells themselves. The bicarbonate in turn passes into the small intestine and joins the bicarbonate from the pancreas in neutralizing the hydrochloric acid from the stomach. Thus, the secretin feedback mechanism for neutralizing duodenal acid operates not only through its effects on pancreatic secretion but also to a lesser extent through its effect on secretion by the liver ductules and ducts.

Bile salts are formed in the hepatic cells from cholesterol in the blood plasma. In the process of secreting the bile salts, about 1 to 2 grams of cholesterol are removed from the blood plasma and secreted into the bile each day. Cholesterol is almost completely insoluble in pure water, but the bile salts and lecithin in bile combine physically with the cholesterol to form ultramicroscopic micelles in the form of a colloidal solution. When the bile becomes concentrated in the gallbladder, the bile salts and lecithin become concentrated along with the cholesterol, which keeps the cholesterol in solution. Under abnormal conditions, the cholesterol may precipitate in the gallbladder, resulting in the formation of cholesterol gallstones. The amount of cholesterol in the bile is determined partly by the quantity of fat that the person eats, because liver cells synthesize cholesterol as one of the products of fat

metabolism in the body. For this reason, people on a high-fat diet over a period of years are prone to the development of gallstones. Inflammation of the gallbladder epithelium, often resulting from low-grade chronic infection, may also change the absorptive characteristics of the gallbladder mucosa, sometimes allowing excessive absorption of water and bile salts but leaving behind the cholesterol in the bladder in progressively greater concentrations. Then the cholesterol begins to precipitate, first forming many small crystals of cholesterol on the surface of the inflamed mucosa, but then progressing to large gallstones.
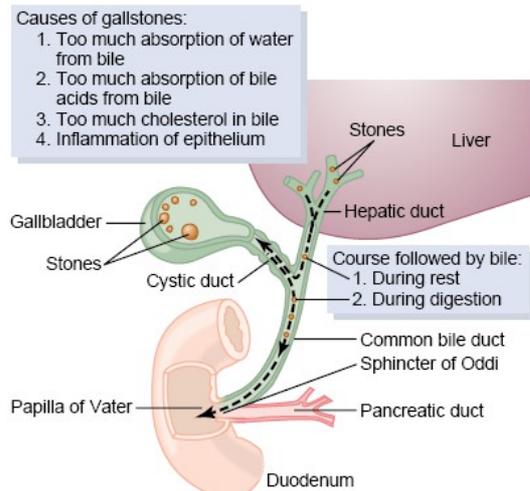


**Figure 64–12**

Formation of gallstones.

## Physiology of the Liver

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 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 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 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.
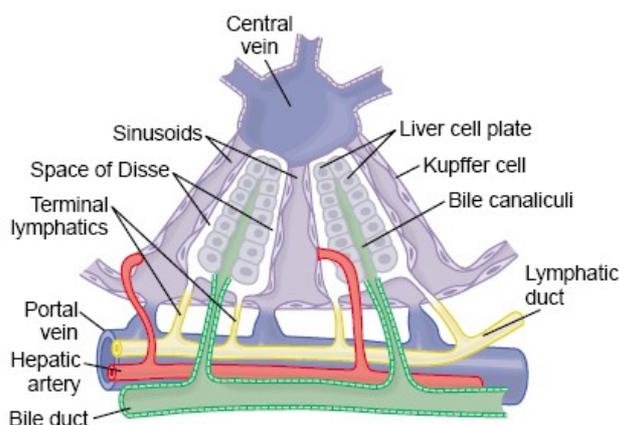
Figure 7 Basic structure of a liver lobule

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. 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.

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. 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.

**1.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 percent 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. 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. 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.

**2.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.

**3.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. In liver diseases associated with fibrosis, inflammation, or viral infections, however, the regenerative process of the liver is severely impaired, and liver function deteriorates.

**4.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.

**5.Metabolic functions of the liver**

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

**a)Carbohydrate metabolism-** the liver performs the following functions:
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.

**b)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, 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 percent 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.

**c)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, 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.

The liver synthesizes many of the circulating plasma proteins exception of part of the gamma globulins, albumin being the most important. It synthesizes about 3 g of albumin a day. Albumin plays an important role in preserving plasma volume and tissue fluid balance by maintaining the colloid osmotic pressure of plasma. Plasma albumin plays a pivotal role in the transport of many substances in blood, such as free fatty acids and certain drugs, including penicillin and salicylate. The other major plasma proteins synthesized by the liver are components of the complement system, components of the blood clotting cascade (fibrinogen and prothrombin), and proteins involved in iron transport (transferrin, haptoglobin, and hemopexin). The 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.

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.

**6.The metabolism of drugs and xenobiotics**

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

on its hydrophobicity. The more hydrophobic (nonpolar, lipid-soluble) a substance is, the more likely it will be reabsorbed. Many drugs and metabolites are hydrophobic, and the liver converts them into hydrophilic compounds. The 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.

### 7.The Liver - 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 B12 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 B12 can be stored to last for at least 1 year and maybe several years.

**-for 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 apoferritinferritin system of the liver acts as a blood iron buffer, as well as an iron storage medium.

### 8. Coagulation.
Liver cells are important both in the production and the clearance of coagulation proteins. Most of the known clotting factors and inhibitors are secreted by hepatocytes, some of them exclusively. 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. In addition, several coagulation and anticoagulation proteins require a vitamin K–dependent modification following synthesis, specifically factors II, VII, IX, and X and proteins C and S, to make them effective. The monocyte-macrophage system of the liver, predominantly Kupffer cells, is an important system for clearing clotting factors and factor-inhibitor complexes. Disturbances in liver perfusion and function result in the ineffective clearance of activated coagulation proteins, so patients with advanced liver failure may be predisposed to developing disseminated intravascular coagulation.

### 9.Endocrine functions of the liver
The liver is important in regulating the endocrine functions of hormones. It can amplify the action of some hormones. It is also the major organ for the removal of peptide hormones. As discussed before, the liver converts vitamin D3 to 25-hydroxy vitamin D3, an essential step before conversion to the active hormone 1,25-hydroxy vitamin D3 in the kidneys. The liver is also a major site of conversion of the thyroid hormone thyroxine (T4) to the biologically more potent hormone triiodothyronine (T3). The regulation of the hepatic T4 to T3 conversion occurs at both the uptake step and the conversion step. Due to the liver's relatively large reserve in converting T4 to T3, hypothyroidism is uncommon in patients with liver disease. In

advanced chronic liver disease, however, signs of hypothyroidism may be evident. The liver modifies the function of growth hormone (GH) secreted by the pituitary gland. Some growth hormone actions are mediated by insulin-like growth factors made by the liver. The liver helps to remove and degrade many circulating hormones. Insulin is degraded in many organs, but the liver and kidneys are by far most important. The presence of insulin receptors on the surface of hepatocytes suggests that the binding of insulin to these receptors results in degradation of some insulin molecules. There is also degradation of insulin by proteases of hepatocytes that do not involve the insulin receptor. Glucagon and growth hormone are degraded mainly by the liver and the kidneys. The liver may also degrade various GI hormones (e.g., gastrin), but the kidneys and other organs probably contribute more significantly to inactivating these hormones.

**Measurement of bilirubin in the bile as a clinical diagnostic tool**
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. However, it also provides an exceedingly valuable tool for diagnosing both hemolytic blood diseases and various types of liver diseases. 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". 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 percent with glucuronic acid to form bilirubin glucuronide, about 10 percent with sulfate to form bilirubin sulfate and about 10 percent 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.
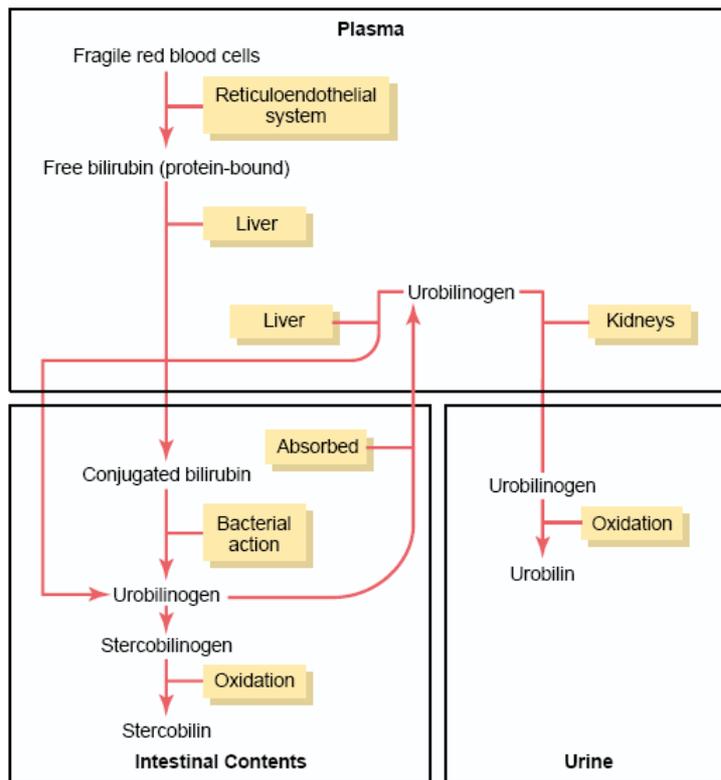
Once in the intestine, about half of the "conjugated" bilirubin is converted by bacterial action into the substance urobilinogen, which is highly soluble. Some of the urobilinogen is reabsorbed through the intestinal mucosa back into the blood. Most of this is re-excreted by the liver back into the gut, 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.

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. 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 abovenormal 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. 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.