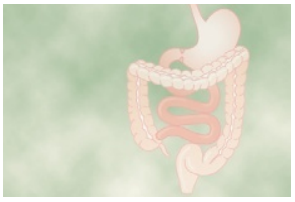
CHAPTER 66

Physiology of Gastrointestinal Disorders



Effective therapy for most gastrointestinal disorders depends on a basic knowledge of gastrointestinal physiology. The purpose of this chapter is to discuss a few representative types of gastrointestinal malfunction that have special physiologic bases or consequences.

Disorders of Swallowing and of the Esophagus

Paralysis of the Swallowing Mechanism. Damage to the fifth, ninth, or tenth cerebral nerve can cause paralysis of significant portions of the swallowing mechanism. Also, a few diseases, such as *poliomyelitis* or *encephalitis,* can prevent normal swallowing by damaging the swallowing center in the brain stem. Finally, paralysis of the swallowing muscles, as occurs in *muscle dystrophy* or in failure of neuromuscular transmission in *myasthenia gravis* or *botulism,* can also prevent normal swallowing.

When the swallowing mechanism is partially or totally paralyzed, the abnormalities that can occur include (1) complete abrogation of the swallowing act so that swallowing cannot occur, (2) failure of the glottis to close so that food passes into the lungs instead of the esophagus, and (3) failure of the soft palate and uvula to close the posterior nares so that food refluxes into the nose during swallowing.

One of the most serious instances of paralysis of the swallowing mechanism occurs when patients are under deep anesthesia. Often, while on the operating table, they vomit large quantities of materials from the stomach into the pharynx; then, instead of swallowing the materials again, they simply suck them into the trachea because the anesthetic has blocked the reflex mechanism of swallowing. As a result, such patients occasionally choke to death on their own vomitus.

Achalasia and Megaesophagus. *Achalasia* is a condition in which the lower esophageal sphincter fails to relax during swallowing. As a result, food swallowed into the esophagus then fails to pass from the esophagus into the stomach. Pathological studies have shown damage in the neural network of the myenteric plexus in the lower two thirds of the esophagus. As a result, the musculature of the lower esophagus remains spastically contracted and the myenteric plexus has lost its ability to transmit a signal to cause "receptive relaxation" of the gastroesophageal sphincter as food approaches this sphincter during swallowing.

When achalasia becomes severe, the esophagus often cannot empty the swallowed food into the stomach for many hours, instead of the few seconds that is the normal time. Over months and years, the esophagus becomes tremendously enlarged until it often can hold as much as 1 liter of food, which often becomes putridly infected during the long periods of esophageal stasis. The infection may also cause ulceration of the esophageal mucosa, sometimes leading to severe substernal pain or even rupture and death. Considerable benefit can be achieved by stretching the lower end of the esophagus by means of a balloon inflated on the end of a swallowed esophageal tube. Antispasmotic drugs (drugs that relax smooth muscle) can also be helpful.

Disorders of the Stomach

Gastritis—Inflammation of the Gastric Mucosa. Mild to moderate chronic gastritis is exceedingly common in the population as a whole, especially in the middle to later years of adult life.

The inflammation of gastritis may be only superficial and therefore not very harmful, or it can penetrate deeply into the gastric mucosa, in many long-standing cases causing almost complete atrophy of the gastric mucosa. In a few cases, gastritis can be acute and severe, with ulcerative excoriation of the stomach mucosa by the stomach's own peptic secretions.

Research suggests that much gastritis is caused by chronic bacterial infection of the gastric mucosa. This often can be treated successfully by an intensive regimen of antibacterial therapy.

In addition, certain ingested irritant substances can be especially damaging to the protective gastric mucosal barrier—that is, to the mucous glands and to the tight epithelial junctions between the gastric lining cells—often leading to severe acute or chronic gastritis. Two of the most common of these substances are excesses of *alcohol* or *aspirin.*

Gastric Barrier and Its Penetration in Gastritis. Absorption of food from the stomach directly into the blood is normally slight. This low level of absorption is mainly due to two specific features of the gastric mucosa: (1) It is lined with highly

resistant mucous cells that secrete viscid and adherent mucus and (2) it has tight junctions between the adjacent epithelial cells. These two together plus other impediments to gastric absorption are called the "gastric barrier."

The gastric barrier normally is resistant enough to diffusion so that even the highly concentrated hydrogen ions of the gastric juice, averaging about 100,000 times the concentration of hydrogen ions in plasma, seldom diffuse even to the slightest extent through the lining mucus as far as the epithelial membrane itself. In gastritis, the permeability of the barrier is greatly increased. The hydrogen ions do then diffuse into the stomach epithelium, creating additional havoc and leading to a vicious circle of progressive stomach mucosal damage and atrophy. It also makes the mucosa susceptible to digestion by the peptic digestive enzymes, thus frequently resulting in a *gastric ulcer.*

Chronic Gastritis Can Lead to Gastric Atrophy and Loss of Stomach Secretions. In many people who have chronic gastritis, the mucosa gradually becomes more and more atrophic until little or no gastric gland digestive secretion remains. It is also believed that some people develop autoimmunity against the gastric mucosa, which also leads eventually to gastric atrophy. Loss of the stomach secretions in gastric atrophy leads to *achlorhydria* and, occasionally, to *pernicious anemia.*

Achlorhydria (and Hypochlorhydria). *Achlorhydria* means simply that the stomach fails to secrete hydrochloric acid; it is diagnosed when the pH of the gastric secretions fails to decrease below 6.5 after maximal stimulation. *Hypochlorhydria* means diminished acid secretion. When acid is not secreted, pepsin also usually is not secreted; even when it is, the lack of acid prevents it from functioning because pepsin requires an acid medium for activity.

Gastric Atrophy May Cause Pernicious Anemia. Pernicious anemia is a common accompaniment of gastric atrophy and achlorhydria. Normal gastric secretions contain a glycoprotein called *intrinsic factor,* secreted by the same parietal cells that secrete hydrochloric acid. Intrinsic factor must be present for adequate absorption of vitamin B_{12} from the ileum. That is, intrinsic factor combines with vitamin B_{12} in the stomach and protects it from being digested and destroyed as it passes into the small intestine. Then, when the intrinsic factor–vitamin B_{12} complex reaches the terminal ileum, the intrinsic factor binds with receptors on the ileal epithelial surface. This in turn makes it possible for the vitamin B_{12} to be absorbed.

In the absence of intrinsic factor, only about 1/50 of the vitamin B_{12} is absorbed. And, without intrinsic factor, an adequate amount of vitamin B_{12} is not made available from the foods to cause young, newly forming red blood cells to mature in the bone marrow. The result is *pernicious anemia.* This is discussed in more detail in Chapter 32.

Peptic Ulcer

A peptic ulcer is an excoriated area of stomach or intestinal mucosa caused principally by the digestive action of gastric juice or upper small intestinal secretions. Figure 66-1 shows the points in the gastrointestinal tract at which peptic ulcers most frequently occur, demonstrating that the most frequent site is within a few centimeters of the pylorus. In addition, peptic ulcers frequently occur along the lesser curvature of the antral end of the stomach or, more rarely, in the lower end of the esophagus where stomach juices frequently reflux.

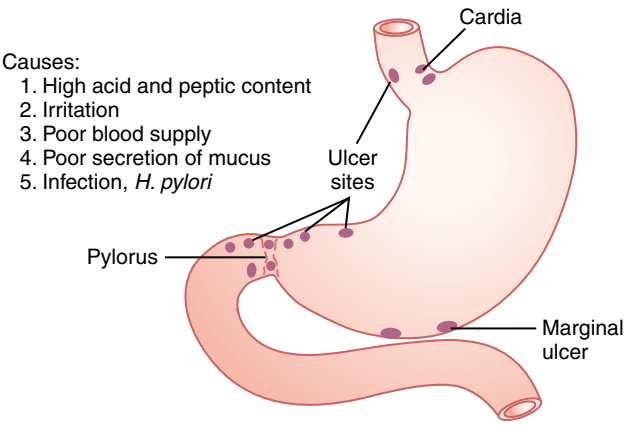


Figure 66-1 Peptic ulcer. *H. pylori, Helicobacter pylori.*

A type of peptic ulcer called a *marginal ulcer* also often occurs wherever a surgical opening such as a gastrojejunostomy has been made between the stomach and the jejunum of the small intestine.

Basic Cause of Peptic Ulceration. The usual cause of peptic ulceration is an *imbalance* between the rate of secretion of gastric juice and the degree of protection afforded by (1) the gastroduodenal mucosal barrier and (2) the neutralization of the gastric acid by duodenal juices. It will be recalled that all areas normally exposed to gastric juice are well supplied with mucous glands, beginning with compound mucous glands in the lower esophagus plus the mucous cell coating of the stomach mucosa, the mucous neck cells of the gastric glands, the deep pyloric glands that secrete mainly mucus, and, finally, the glands of Brunner's of the upper duodenum, which secrete a highly alkaline mucus.

In addition to the mucus protection of the mucosa, the duodenum is protected by the *alkalinity of the small intestinal secretions.* Especially important is *pancreatic secretion,* which contains large quantities of sodium bicarbonate that neutralize the hydrochloric acid of the gastric juice, thus also inactivating pepsin and preventing digestion of the mucosa. In addition, large amounts of bicarbonate ions are provided in (1) the secretions of the large Brunner's glands in the first few centimeters of the duodenal wall and (2) in bile coming from the liver.

Finally, two feedback control mechanisms normally ensure that this neutralization of gastric juices is complete, as follows:

1. When excess acid enters the duodenum, it inhibits gastric secretion and peristalsis in the stomach, both by nervous reflexes and by hormonal feedback from the duodenum, thereby decreasing the rate of gastric emptying.
2. The presence of acid in the small intestine liberates *secretin* from the intestinal mucosa, which then passes by way of the blood to the pancreas to promote rapid secretion of pancreatic juice. This juice also contains a high concentration of sodium bicarbonate, thus making still more sodium bicarbonate available for neutralization of the acid.

Therefore, a peptic ulcer can be caused in either of two ways: (1) excess secretion of acid and pepsin by the gastric mucosa or (2) diminished ability of the gastroduodenal mucosal barrier to protect against the digestive properties of the stomach acid–pepsin secretion.

Specific Causes of Peptic Ulcer in the Human Being

Bacterial Infection by *Helicobacter pylori* Breaks Down the Gastroduodenal Mucosal Barrier and Stimulates Gastric Acid Secretion. At least 75 percent of peptic ulcer patients have been found to have chronic infection of the terminal portions of the gastric mucosa and initial portions of the duodenal mucosa, most often caused by the bacterium *Helicobacter pylori.* Once this infection begins, it can last a lifetime unless it is eradicated by antibacterial therapy. Furthermore, the bacterium is capable of penetrating the mucosal barrier both by virtue of its physical capability to burrow through the barrier and by releasing ammonium that liquefies the barrier and stimulates the secretion of hydrochloric acid. As a result, the strong acidic digestive juices of the stomach secretions can then penetrate into the underlying epithelium and literally digest the gastrointestinal wall, thus leading to peptic ulceration.

Other Causes of Ulceration. In many people who have peptic ulcers in the initial portion of the duodenum, the rate of gastric acid secretion is greater than normal, sometimes as much as twice normal. Although part of this increased secretion may be stimulated by bacterial infection, studies in both animals and human beings have shown that excess secretion of gastric juices for any reason (for instance, even in psychic disturbances) may cause peptic ulceration.

Other factors that predispose to ulcers include (1) *smoking,* presumably because of increased nervous stimulation of the stomach secretory glands; (2) *alcohol,* because it tends to break down the mucosal barrier; and (3) *aspirin* and other nonsteroidal anti-inflammatory drugs that also have a strong propensity for breaking down this barrier.

Treatment of Peptic Ulcers. Since discovery of the bacterial infectious basis for much peptic ulceration, therapy has changed immensely. Initial reports are that almost all patients with peptic ulceration can be treated effectively by two measures: (1) use of *antibiotics* along with other agents to kill infectious bacteria and (2) administration of an acid-suppressant drug, especially *ranitidine,* an antihistaminic that blocks the stimulatory effect of histamine on gastric gland histamine$_2$ receptors, thus reducing gastric acid secretion by 70 to 80 percent.

In the past, before these approaches to peptic ulcer therapy were developed, it was often necessary to remove as much as four fifths of the stomach, thus reducing stomach acid–peptic juices enough to cure most patients. Another therapy was to cut the two vagus nerves that supply parasympathetic stimulation to the gastric glands. This blocked almost all secretion of acid and pepsin and often cured the ulcer or ulcers within 1 week after the operation. However, much of the basal stomach secretion returned after a few months and in many patients the ulcer also returned.

The newer physiologic approaches to therapy may prove to be miraculous. Even so, in a few instances, the patient's condition is so severe, including massive bleeding from the ulcer, that heroic operative procedures often must still be used.

Disorders of the Small Intestine

Abnormal Digestion of Food in the Small Intestine—Pancreatic Failure

A serious cause of abnormal digestion is failure of the pancreas to secrete pancreatic juice into the small intestine. Lack of pancreatic secretion frequently occurs (1) in *pancreatitis* (which is discussed later), (2) when the *pancreatic duct is blocked* by a gallstone at the papilla of Vater, or (3) after the *head of the pancreas has been removed* because of malignancy.

Loss of pancreatic juice means loss of trypsin, chymotrypsin, carboxypolypeptidase, pancreatic amylase, pancreatic lipase, and still a few other digestive enzymes. Without these enzymes, up to 60 percent of the fat entering the small intestine may be unabsorbed, as well as one third to one half of the proteins and carbohydrates. As a result, large portions of the ingested food cannot be used for nutrition and copious, fatty feces are excreted.

Pancreatitis—Inflammation of the Pancreas. Pancreatitis can occur in the form of either *acute pancreatitis* or *chronic pancreatitis.*

The most common cause of pancreatitis is *drinking excess alcohol,* and the second most common cause is *blockage of the papilla of Vater* by a gallstone; the two together account for more than 90 percent of all cases. When a gallstone blocks the papilla of Vater, this blocks the main secretory duct from the pancreas and the common bile duct. The pancreatic enzymes are then dammed up in the ducts and acini of the pancreas. Eventually, so much trypsinogen accumulates that it *overcomes the trypsin inhibitor* in the secretions and a small quantity of trypsinogen becomes activated to form trypsin. Once this happens, the trypsin activates still more trypsinogen, as well as chymotrypsinogen and carboxypolypeptidase, resulting in a vicious circle until most of the proteolytic enzymes in the pancreatic ducts and acini become activated. These enzymes rapidly digest large portions of the pancreas, sometimes completely and permanently destroying the ability of the pancreas to secrete digestive enzymes.

Malabsorption by the Small Intestinal Mucosa—Sprue

Occasionally, nutrients are not adequately absorbed from the small intestine even though the food has become well digested. Several diseases can cause decreased absorption by the mucosa; they are often classified together under the general term *"sprue."* Malabsorption also can occur when large portions of the small intestine have been removed.

Nontropical Sprue. One type of sprue, called variously *idiopathic sprue, celiac disease* (in children), or *gluten enteropathy,* results from the toxic effects of *gluten* present in certain types of grains, especially wheat and rye. Only some people are susceptible to this effect, but in those who are susceptible, gluten has a direct destructive effect on intestinal enterocytes. In milder forms of the disease, only the microvilli of the absorbing enterocytes on the villi are destroyed, thus decreasing the absorptive surface area as much as twofold. In the more severe forms, the villi themselves become blunted or disappear altogether, thus still further reducing the absorptive area of the gut. Removal of wheat and rye flour from the diet frequently results in cure within weeks, especially in children with this disease.

Tropical Sprue. A different type of sprue called *tropical sprue* frequently occurs in the tropics and can often be treated with antibacterial agents. Even though no specific bacterium has been implicated as the cause, it is believed that this variety of sprue is usually caused by inflammation of the intestinal mucosa resulting from unidentified infectious agents.

Malabsorption in Sprue. In the early stages of sprue, intestinal absorption of fat is more impaired than absorption of other digestive products. The fat that appears in the stools is almost entirely in the form of salts of fatty acids rather than undigested fat, demonstrating that the problem is one of absorption, not of digestion. In fact, the condition is frequently called *steatorrhea,* which means simply excess fats in the stools.

In severe cases of sprue, in addition to malabsorption of fats there is also impaired absorption of proteins, carbohydrates, calcium, vitamin K, folic acid, and vitamin B_{12}. As a result, the person suffers (1) severe nutritional deficiency, often developing wasting of the body; (2) osteomalacia (demineralization of the bones because of lack of calcium); (3) inadequate blood coagulation caused by lack of vitamin K; and (4) macrocytic anemia of the pernicious anemia type, owing to diminished vitamin B_{12} and folic acid absorption.

Disorders of the Large Intestine

Constipation

Constipation means *slow movement of feces through the large intestine;* it is often associated with large quantities of dry, hard feces in the descending colon that accumulate because of overabsorption of fluid. Any pathology of the intestines that obstructs movement of intestinal contents, such as tumors, adhesions that constrict the intestines, or ulcers, can cause constipation. A frequent functional cause of constipation is irregular bowel habits that have developed through a lifetime of inhibition of the normal defecation reflexes.

Infants are seldom constipated, but part of their training in the early years of life requires that they learn to control defecation; this control is effected by inhibiting the natural defecation reflexes. Clinical experience shows that if one does not allow defecation to occur when the defecation reflexes are excited or if one overuses laxatives to take the place of natural bowel function, the reflexes themselves become progressively less strong over months or years, and the colon becomes *atonic.* For this reason, if a person establishes regular bowel habits early in life, defecating when the gastrocolic and duodenocolic reflexes cause mass movements in the large intestine, the development of constipation in later life is much less likely.

Constipation can also result from spasm of a small segment of the sigmoid colon. It should be recalled that motility normally is weak in the large intestine, so even a slight degree of spasm is often capable of causing serious constipation. After the constipation has continued for several days and excess feces have accumulated above a spastic sigmoid colon, excessive colonic secretions often then lead to a day or so of diarrhea. After this, the cycle begins again, with repeated bouts of alternating constipation and diarrhea.

Megacolon (Hirschsprung's Disease). Occasionally, constipation is so severe that bowel movements occur only once every several days or sometimes only once a week. This allows tremendous quantities of fecal matter to accumulate in the colon, causing the colon sometimes to distend to a diameter of 3 to 4 inches. The condition is called *megacolon,* or *Hirschsprung's disease.*

A frequent cause of megacolon is lack of or deficiency *of ganglion cells in the myenteric plexus in a segment of the sigmoid colon.* As a consequence, neither defecation reflexes nor strong peristaltic motility can occur in this area of the large intestine. The sigmoid itself becomes small and almost spastic while feces accumulate proximal to this area, causing megacolon in the ascending, transverse, and descending colons.

Diarrhea

Diarrhea results from rapid movement of fecal matter through the large intestine. Several causes of diarrhea with important physiologic sequelae are the following.

Enteritis—Inflammation of the Intestinal Tract. Enteritis means inflammation usually caused either by a virus or by bacteria in the intestinal tract. In usual *infectious diarrhea,* the infection is most extensive in the large intestine and the distal end of the ileum. Everywhere the infection is present, the mucosa becomes irritated and its rate of secretion becomes greatly enhanced. In addition, motility of the intestinal wall usually increases manifold. As a result, large quantities of fluid are made available for washing the infectious agent toward the anus, and at the same time strong propulsive movements propel this fluid forward. This is an important mechanism for ridding the intestinal tract of a debilitating infection.

Of special interest is diarrhea caused by *cholera* (and less often by other bacteria such as some pathogenic colon bacilli). As explained in Chapter 65, cholera toxin directly stimulates excessive secretion of electrolytes and fluid from the crypts of Lieberkühn in the distal ileum and colon. The amount can be 10 to 12 liters per day, although the colon can usually reabsorb a maximum of only 6 to 8 liters per day. Therefore, loss of fluid and electrolytes can be so debilitating within several days that death can ensue.

The most important physiologic basis of therapy in cholera is to replace the fluid and electrolytes as rapidly as they are lost, mainly by giving the patient intravenous solutions. With proper therapy, along with the use of antibiotics, almost no cholera patients die but without therapy up to 50 percent do.

Psychogenic Diarrhea. Everyone is familiar with the diarrhea that accompanies periods of nervous tension, such as during examination time or when a soldier is about to go into battle. This type of diarrhea, called *psychogenic* emotional diarrhea, is caused by excessive stimulation of the parasympathetic nervous system, which greatly excites both (1) motility and (2) excess secretion of mucus in the distal colon. These two effects added together can cause marked diarrhea.

Ulcerative Colitis. Ulcerative colitis is a disease in which extensive areas of the walls of the large intestine become inflamed and ulcerated. The motility of the ulcerated colon is often so great that *mass movements* occur much of the day rather than for the usual 10 to 30 minutes. Also, the colon's secretions are greatly enhanced. As a result, the patient has repeated diarrheal bowel movements.

The cause of ulcerative colitis is unknown. Some clinicians believe that it results from an allergic or immune destructive effect, but it also could result from chronic bacterial

infection not yet understood. Whatever the cause, there is a strong hereditary tendency for susceptibility to ulcerative colitis. Once the condition has progressed far, the ulcers seldom will heal until an ileostomy is performed to allow the small intestinal contents to drain to the exterior rather than to pass through the colon. Even then the ulcers sometimes fail to heal, and the only solution might be surgical removal of the entire colon.

Paralysis of Defecation in Spinal Cord Injuries

From Chapter 63 it will be recalled that defecation is normally initiated by accumulating feces in the rectum, which causes a spinal cord–mediated *defecation reflex* passing from the rectum to the *conus medullaris* of the spinal cord and then back to the descending colon, sigmoid, rectum, and anus.

When the spinal cord is injured somewhere between the conus medullaris and the brain, the voluntary portion of the defecation act is blocked while the basic cord reflex for defecation is still intact. Nevertheless, loss of the voluntary aid to defecation—that is, loss of the increased abdominal pressure and relaxation of the voluntary anal sphincter—often makes defecation a difficult process in the person with this type of upper cord injury. But because the cord defecation reflex can still occur, a small enema to excite action of this cord reflex, usually given in the morning shortly after a meal, can often cause adequate defecation. In this way, people with spinal cord injuries that do not destroy the conus medullaris of the spinal cord can usually control their bowel movements each day.

General Disorders of the Gastrointestinal Tract

Vomiting

Vomiting is the means by which the upper gastrointestinal tract rids itself of its contents when almost any part of the upper tract becomes excessively irritated, overdistended, or even overexcitable. Excessive distention or irritation of the duodenum provides an especially strong stimulus for vomiting.

The sensory signals that initiate vomiting originate mainly from the pharynx, esophagus, stomach, and upper portions of the small intestines. And the nerve impulses are transmitted, as shown in Figure 66-2, by both vagal and sympathetic afferent nerve fibers to multiple distributed nuclei in the brain stem that all together are called the "vomiting center." From here, *motor impulses* that cause the actual vomiting are transmitted from the vomiting center by way of the fifth, seventh, ninth, tenth, and twelfth cranial nerves to the upper gastrointestinal tract, through vagal and sympathetic nerves to the lower tract, and through spinal nerves to the diaphragm and abdominal muscles.

Antiperistalsis, the Prelude to Vomiting. In the early stages of excessive gastrointestinal irritation or overdistention, *antiperistalsis* begins to occur often many minutes before vomiting appears. Antiperistalsis means peristalsis *up* the digestive tract rather than downward. This may begin as far down in the intestinal tract as the ileum, and the antiperistaltic wave travels backward up the intestine at a rate of 2 to 3 cm/sec; this process can actually push a large share of the lower small intestine contents all the way back to the duodenum and stomach within 3 to 5 minutes. Then, as these upper portions of the gastrointestinal tract, especially the duodenum, become overly distended, this distention becomes the exciting factor that initiates the actual vomiting act.

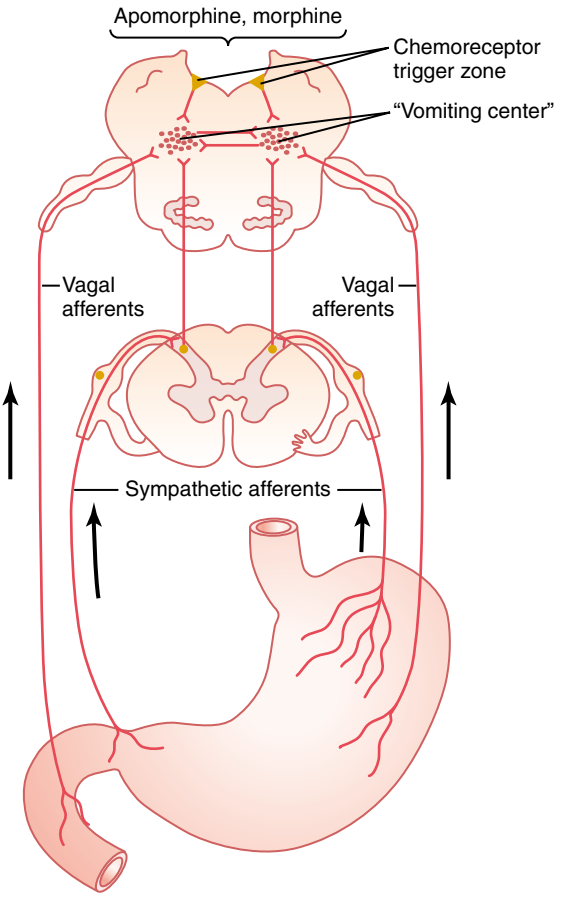


Figure 66-2 Neutral connections of the "vomiting center." This so-called vomiting center includes multiple sensory, motor, and control nuclei mainly in the medullary and pontile reticular formation but also extending into the spinal cord.

At the onset of vomiting, strong intrinsic contractions occur in both the duodenum and the stomach, along with partial relaxation of the esophageal-stomach sphincter, thus allowing vomitus to begin moving from the stomach into the esophagus. From here, a specific vomiting act involving the abdominal muscles takes over and expels the vomitus to the exterior, as explained in the next paragraph.

Vomiting Act. Once the vomiting center has been sufficiently stimulated and the vomiting act instituted, the first effects are (1) a deep breath, (2) raising of the hyoid bone and larynx to pull the upper esophageal sphincter open, (3) closing of the glottis to prevent vomitus flow into the lungs, and (4) lifting of the soft palate to close the posterior nares. Next comes a strong downward contraction of the diaphragm along with simultaneous contraction of all the abdominal wall muscles. This squeezes the stomach between the diaphragm and the abdominal muscles, building the intragastric pressure to a high level. Finally, the lower esophageal sphincter relaxes completely, allowing expulsion of the gastric contents upward through the esophagus.

Thus, the vomiting act results from a squeezing action of the muscles of the abdomen associated with simultaneous contraction of the stomach wall and opening of the esophageal sphincters so that the gastric contents can be expelled.

"Chemoreceptor Trigger Zone" in the Brain Medulla for Initiation of Vomiting by Drugs or by Motion Sickness. Aside from the vomiting initiated by irritative stimuli in the gastrointestinal tract, vomiting can also be caused by nervous signals arising in areas of the brain. This is particularly true for a small area located bilaterally on the floor of the fourth ventricle called the *chemoreceptor trigger zone for vomiting.* Electrical stimulation of this area can initiate vomiting; but, more important, administration of certain drugs, including apomorphine, morphine, and some digitalis derivatives, can directly stimulate this chemoreceptor trigger zone and initiate vomiting. Destruction of this area blocks this type of vomiting but does not block vomiting resulting from irritative stimuli in the gastrointestinal tract itself.

Also, it is well known that rapidly changing direction or rhythm of motion of the body can cause certain people to vomit. The mechanism for this is the following: The motion stimulates receptors in the vestibular labyrinth of the inner ear, and from here impulses are transmitted mainly by way of the brain stem *vestibular nuclei into the cerebellum,* then to the *chemoreceptor trigger zone,* and finally to the *vomiting center* to cause vomiting.

Nausea

Everyone has experienced the sensation of nausea and knows that it is often a prodrome of vomiting. Nausea is the conscious recognition of subconscious excitation in an area of the medulla closely associated with or part of the vomiting center, and it can be caused by (1) irritative impulses coming from the gastrointestinal tract, (2) impulses that originate in the lower brain associated with motion sickness, or (3) impulses from the cerebral cortex to initiate vomiting. Vomiting occasionally occurs without the prodromal sensation of nausea, indicating that only certain portions of the vomiting center are associated with the sensation of nausea.

Gastrointestinal Obstruction

The gastrointestinal tract can become obstructed at almost any point along its course, as shown in Figure 66-3. Some common causes of obstruction are (1) *cancer,* (2) *fibrotic constriction resulting from ulceration or from peritoneal adhesions,* (3) *spasm of a segment of the gut,* and (4) *paralysis of a segment of the gut.*

The abnormal consequences of obstruction depend on the point in the gastrointestinal tract that becomes obstructed. If the obstruction occurs at the pylorus, which results often from fibrotic constriction after peptic ulceration, persistent vomiting of stomach contents occurs. This depresses bodily nutrition; it also causes excessive loss of hydrogen ions from the stomach and can result in various degrees of *whole-body metabolic alkalosis.*

If the obstruction is beyond the stomach, antiperistaltic reflux from the small intestine causes intestinal juices to flow backward into the stomach, and these juices are vomited along with the stomach secretions. In this instance, the person loses large amounts of water and electrolytes. He or she becomes severely dehydrated, but the loss of acid from the stomach and base from the small intestine may be approximately equal, so little change in acid-base balance occurs.

If the obstruction is near the distal end of the large intestine, feces can accumulate in the colon for a week or more.

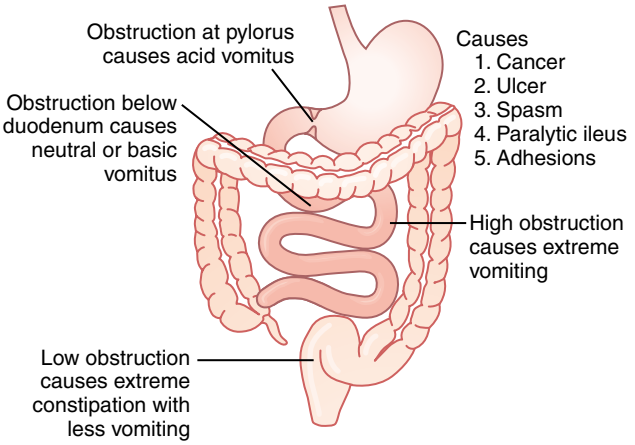


Figure 66-3 Obstruction in different parts of the gastrointestinal tract.

The patient develops an intense feeling of constipation, but at first vomiting is not severe. After the large intestine has become completely filled and it finally becomes impossible for additional chyme to move from the small intestine into the large intestine, severe vomiting does then occur. Prolonged obstruction of the large intestine can finally cause rupture of the intestine itself or dehydration and circulatory shock resulting from the severe vomiting.

Gases in the Gastrointestinal Tract; "Flatus"

Gases, called *flatus,* can enter the gastrointestinal tract from three sources: (1) swallowed air, (2) gases formed in the gut as a result of bacterial action, or (3) gases that diffuse from the blood into the gastrointestinal tract. Most gases in the stomach are mixtures of nitrogen and oxygen derived from swallowed air. In the typical person these gases are expelled by belching. Only small amounts of gas normally occur in the small intestine, and much of this gas is air that passes from the stomach into the intestinal tract.

In the large intestine, most of the gases are derived from bacterial action, including especially *carbon dioxide, methane,* and *hydrogen.* When methane and hydrogen become suitably mixed with oxygen, an actual explosive mixture is sometimes formed. Use of the electric cautery during sigmoidoscopy has been known to cause a mild explosion.

Certain foods are known to cause greater expulsion of flatus through the anus than others—beans, cabbage, onion, cauliflower, corn, and certain irritant foods such as vinegar. Some of these foods serve as a suitable medium for gas-forming bacteria, especially unabsorbed fermentable types of carbohydrates. For instance, beans contain an indigestible carbohydrate that passes into the colon and becomes a superior food for colonic bacteria. But in other instances, excess expulsion of gas results from irritation of the large intestine, which promotes rapid peristaltic expulsion of gases through the anus before they can be absorbed.

The amount of gases entering or forming in the large intestine each day averages 7 to 10 liters, whereas the average amount expelled through the anus is usually only about 0.6 liter. The remainder is normally absorbed into the blood through the intestinal mucosa and expelled through the lungs.

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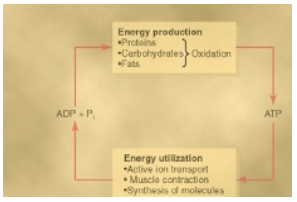
Metabolism of Carbohydrates, and Formation of Adenosine Triphosphate



The next few chapters deal with metabolism in the body—the chemical processes that make it possible for the cells to continue living. It is not the purpose of this textbook to present the chemical details of all the various cellular reactions, because this lies in the discipline of biochemistry. Instead, these chapters are devoted to (1) a review of the principal chemical processes of the cell and (2) an analysis of their physiologic implications, especially the manner in which they fit into the overall body homeostasis.

Release of Energy from Foods, and the Concept of "Free Energy"

Most of the chemical reactions in the cells are aimed at making the energy in foods available to the various physiologic systems of the cell. For instance, energy is required for muscle activity, secretion by the glands, maintenance of membrane potentials by the nerve and muscle fibers, synthesis of substances in the cells, absorption of foods from the gastrointestinal tract, and many other functions.

Coupled Reactions. All the energy foods—carbohydrates, fats, and proteins—can be oxidized in the cells, and during this process, large amounts of energy are released. These same foods can also be burned with pure oxygen outside the body in an actual fire, also releasing large amounts of energy; in this case, however, the energy is released suddenly, all in the form of heat. The energy needed by the physiologic processes of the cells is not heat but energy to cause mechanical movement in the case of muscle function, to concentrate solutes in the case of glandular secretion, and to effect other cell functions. To provide this energy, the chemical reactions must be "coupled" with the systems responsible for these physiologic functions. This coupling is accomplished by special cellular enzyme and energy transfer systems, some of which are explained in this and subsequent chapters.

"Free Energy." The amount of energy liberated by complete oxidation of a food is called the *free energy of oxidation of the food*, and this is generally represented by the symbol ΔG. Free energy is usually expressed in terms of calories per mole of substance. For instance, the amount of free energy liberated by complete oxidation of 1 mole (180 grams) of glucose is 686,000 calories.

Adenosine Triphosphate Is the "Energy Currency" of the Body

Adenosine triphosphate (ATP) is an essential link between energy-utilizing and energy-producing functions of the body (Figure 67-1). For this reason, ATP has been called the energy currency of the body, and it can be gained and spent repeatedly.

Energy derived from the oxidation of carbohydrates, proteins, and fats is used to convert adenosine diphosphate (ADP) to ATP, which is then consumed by the various reactions of the body that are necessary for (1) active transport of molecules across cell membranes; (2) contraction of muscles and performance of mechanical work; (3) various synthetic reactions that create hormones, cell membranes, and many other essential molecules of the body; (4) conduction of nerve impulses; (5) cell division and growth; and (6) many other physiologic functions that are necessary to maintain and propagate life.

ATP is a labile chemical compound that is present in all cells. ATP is a combination of adenine, ribose, and three phosphate radicals as shown in Figure 67-2. The last two phosphate radicals are connected with the remainder of the molecule by high-energy bonds, which are indicated by the symbol ~.

The amount of free energy in each of these high-energy bonds per mole of ATP is about 7300 calories under standard conditions and about 12,000 calories under the usual

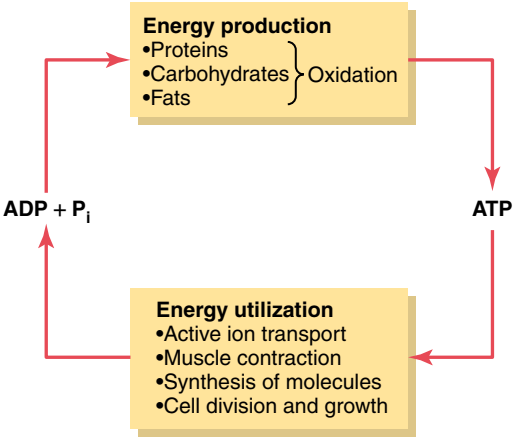


Figure 67-1 Adenosine triphosphate (ATP) as the central link between energy-producing and energy-utilizing systems of the body. ADP, adenosine diphosphate; P_i, inorganic phosphate.

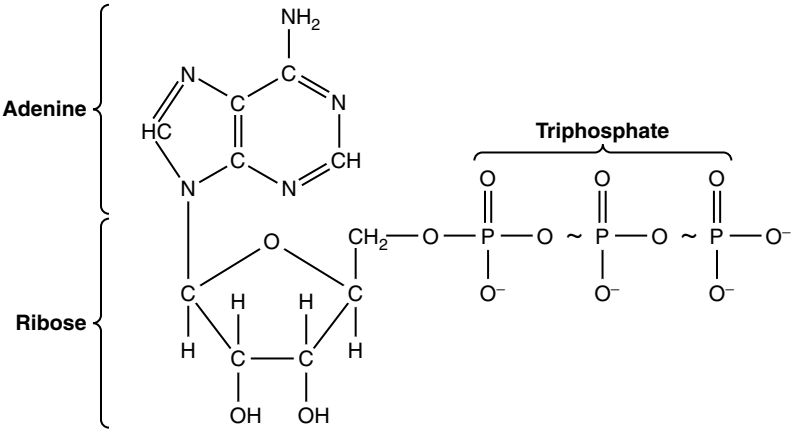


Figure 67-2 Chemical structure of adenosine triphosphate (ATP).

conditions of temperature and concentrations of the reactants in the body. Therefore, in the body, removal of each of the last two phosphate radicals liberates about 12,000 calories of energy. After loss of one phosphate radical from ATP, the compound becomes ADP, and after loss of the second phosphate radical, it becomes *adenosine monophosphate* (AMP). The interconversions among ATP, ADP, and AMP are the following:

$$\text{ATP} \underset{+12{,}000\ \text{cal}}{\overset{-12{,}000\ \text{cal}}{\rightleftharpoons}} \text{ADP} + \text{PO}_3 \underset{+12{,}000\ \text{cal}}{\overset{-12{,}000\ \text{cal}}{\rightleftharpoons}} \text{AMP} + 2\text{PO}_3$$

ATP is present everywhere in the cytoplasm and nucleoplasm of all cells, and essentially all the physiologic mechanisms that require energy for operation obtain it directly from ATP (or another similar high-energy compound, guanosine triphosphate [GTP]). In turn, the food in the cells is gradually oxidized, and the released energy is used to form new ATP, thus always maintaining a supply of this substance. All these energy transfers take place by means of coupled reactions.

The principal purpose of this chapter is to explain how the energy from carbohydrates can be used to form ATP in the cells. Normally, 90 percent or more of all the carbohydrates utilized by the body are used for this purpose.

Central Role of Glucose in Carbohydrate Metabolism

As explained in Chapter 65, the final products of carbohydrate digestion in the alimentary tract are almost entirely glucose, fructose, and galactose—with glucose representing, on average, about 80 percent of these. After absorption from the intestinal tract, much of the fructose and almost all the galactose are rapidly converted into glucose in the liver. Therefore, little fructose and galactose are present in the circulating blood. *Glucose thus becomes the final common pathway for the transport of almost all carbohydrates to the tissue cells.*

In liver cells, appropriate enzymes are available to promote interconversions among the monosaccharides—glucose, fructose, and galactose—as shown in Figure 67-3. Furthermore, the dynamics of the reactions are such that when the liver releases the monosaccharides back into the blood, the final product is almost entirely glucose. The reason for this is that the liver cells contain large amounts of *glucose phosphatase.* Therefore, glucose-6-phosphate can be degraded to glucose

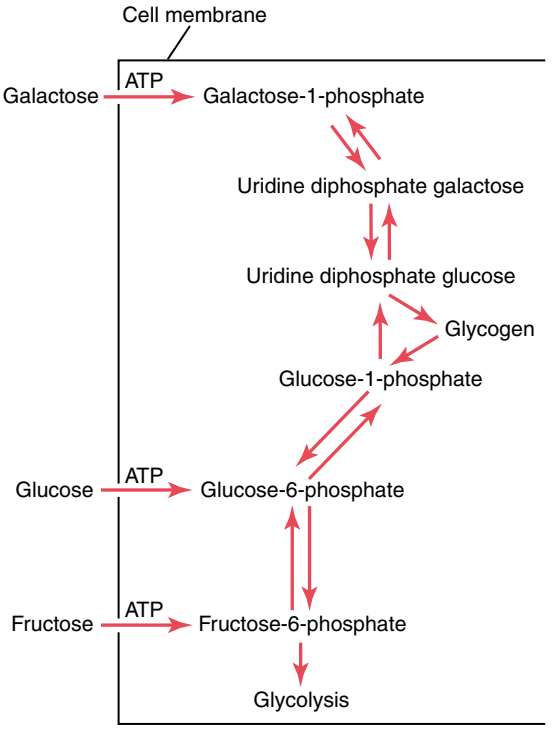


Figure 67-3 Interconversions of the three major monosaccharides—glucose, fructose, and galactose—in liver cells.

and phosphate, and the glucose can then be transported through the liver cell membrane back into the blood.

Once again, it should be emphasized that usually more than 95 percent of all the monosaccharides that circulate in the blood are the final conversion product, glucose.

Transport of Glucose Through the Cell Membrane

Before glucose can be used by the body's tissue cells, it must be transported through the tissue cell membrane into the cellular cytoplasm. However, glucose *cannot easily diffuse through the pores* of the cell membrane because the maximum molecular weight of particles that can diffuse readily is about 100, and glucose has a molecular weight of 180. Yet glucose does pass to the interior of the cells with a reasonable degree of freedom by the mechanism of *facilitated diffusion*. The principles of this type of transport are discussed in Chapter 4. Basically, they are the following. Penetrating through the lipid matrix

of the cell membrane are large numbers of protein *carrier* molecules that can bind with glucose. In this bound form, the glucose can be transported by the carrier from one side of the membrane to the other side and then released. Therefore, if the concentration of glucose is greater on one side of the membrane than on the other side, more glucose will be transported from the high-concentration area to the low-concentration area than in the opposite direction.

The transport of glucose through the membranes of most tissue cells is quite different from that which occurs through the gastrointestinal membrane or through the epithelium of the renal tubules. In both cases, the glucose is transported by the mechanism of *active sodium-glucose co-transport*, in which active transport of sodium provides energy for absorbing glucose *against a concentration difference*. This sodium-glucose co-transport mechanism functions only in certain special epithelial cells that are specifically adapted for active absorption of glucose. At other cell membranes, glucose is transported only from higher concentration toward lower concentration by *facilitated diffusion*, made possible by the special binding properties of membrane *glucose carrier protein*. The details of *facilitated diffusion* for cell membrane transport are presented in Chapter 4.

Insulin Increases Facilitated Diffusion of Glucose

The rate of glucose transport, as well as transport of some other monosaccharides, is greatly increased by insulin. When large amounts of insulin are secreted by the pancreas, the rate of glucose transport into most cells increases to 10 or more times the rate of transport when no insulin is secreted. Conversely, the amounts of glucose that can diffuse to the insides of most cells of the body in the absence of insulin, with the exception of liver and brain cells, are far too little to supply the amount of glucose normally required for energy metabolism.

In effect, the rate of carbohydrate utilization by most cells is controlled by the rate of insulin secretion from the pancreas. The functions of insulin and its control of carbohydrate metabolism are discussed in detail in Chapter 78.

Phosphorylation of Glucose

Immediately on entry into the cells, glucose combines with a phosphate radical in accordance with the following reaction:

$$\text{Glucose} \xrightarrow[+\text{ATP}]{\text{glucokinase or hexokinase}} \text{Glucose-6-phosphate}$$

This phosphorylation is promoted mainly by the enzyme *glucokinase* in the liver and by *hexokinase* in most other cells. The phosphorylation of glucose is almost completely irreversible except in the liver cells, the renal tubular epithelial cells, and the intestinal epithelial cells; in these cells, another enzyme, *glucose phosphatase*, is also available, and when this is activated, it can reverse the reaction. In most tissues of the body, phosphorylation serves to *capture* the glucose in the cell. That is, because of its almost instantaneous binding with phosphate, the glucose will not diffuse back out, except from those special cells, especially liver cells, that have phosphatase.

Glycogen Is Stored in Liver and Muscle

After absorption into a cell, glucose can be used immediately for release of energy to the cell, or it can be stored in the form of *glycogen*, which is a large polymer of glucose.

All cells of the body are capable of storing at least some glycogen, but certain cells can store large amounts, especially *liver cells*, which can store up to 5 to 8 percent of their weight as glycogen, and *muscle cells*, which can store up to 1 to 3 percent glycogen. The glycogen molecules can be polymerized to almost any molecular weight, with the average molecular weight being 5 million or greater; most of the glycogen precipitates in the form of solid granules.

This conversion of the monosaccharides into a high-molecular-weight precipitated compound (glycogen) makes it possible to store large quantities of carbohydrates without significantly altering the osmotic pressure of the intracellular fluids. High concentrations of low-molecular-weight soluble monosaccharides would play havoc with the osmotic relations between intracellular and extracellular fluids.

Glycogenesis—Formation of Glycogen

The chemical reactions for glycogenesis are shown in Figure 67-4. From this figure, it can be seen that *glucose-6-phosphate* can become *glucose-1-phosphate*; this is converted to *uridine diphosphate glucose*, which is finally converted into glycogen. Several specific enzymes are required to cause these conversions, and any monosaccharide that can be converted into glucose can enter into the reactions. Certain smaller compounds, including *lactic acid, glycerol, pyruvic acid*, and some *deaminated amino acids*, can also be converted into glucose or closely allied compounds and then converted into glycogen.

Glycogenolysis—Breakdown of Stored Glycogen

Glycogenolysis means the breakdown of the cell's stored glycogen to re-form glucose in the cells. The glucose can then be used to provide energy. Glycogenolysis does not occur by reversal of the same chemical reactions that form glycogen; instead, each succeeding glucose molecule on each branch of the glycogen polymer is split away by *phosphorylation*, catalyzed by the enzyme *phosphorylase*.

Under resting conditions, the phosphorylase is in an inactive form, so that glycogen will remain stored. When it is necessary to re-form glucose from glycogen, the phosphorylase must first be activated. This can be accomplished in several ways, including the following two.

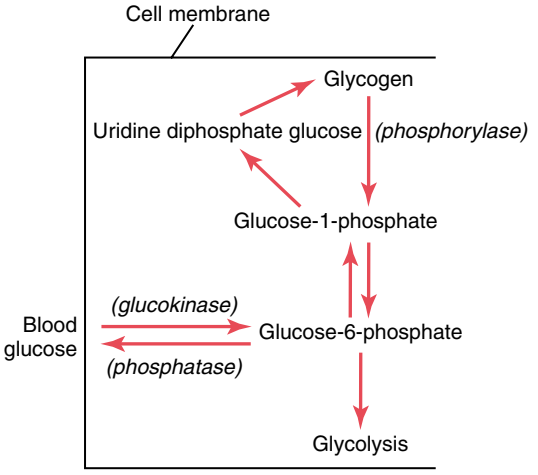


Figure 67-4 Chemical reactions of glycogenesis and glycogenolysis, showing also interconversions between blood glucose and liver glycogen. (The phosphatase required for the release of glucose from the cell is present in liver cells but not in most other cells.)

Activation of Phosphorylase by Epinephrine or by Glucagon. Two hormones, *epinephrine* and *glucagon*, can activate phosphorylase and thereby cause rapid glycogenolysis. The initial effect of each of these hormones is to promote the formation of *cyclic AMP* in the cells, which then initiates a cascade of chemical reactions that activates the phosphorylase. This is discussed in detail in Chapter 78.

Epinephrine is released by the adrenal medullae when the sympathetic nervous system is stimulated. Therefore, one of the functions of the sympathetic nervous system is to increase the availability of glucose for rapid energy metabolism. This function of epinephrine occurs markedly in both liver cells and muscle, thereby contributing, along with other effects of sympathetic stimulation, to preparing the body for action, as discussed fully in Chapter 60.

Glucagon is a hormone secreted by the *alpha cells* of the pancreas when the blood glucose concentration falls too low. It stimulates formation of cyclic AMP mainly in the liver cells, and this in turn promotes conversion of liver glycogen into glucose and its release into the blood, thereby elevating the blood glucose concentration. The function of glucagon in blood glucose regulation is discussed more fully in Chapter 78.

Release of Energy from Glucose by the Glycolytic Pathway

Because complete oxidation of 1 gram-mole of glucose releases 686,000 calories of energy and only 12,000 calories of energy are required to form 1 gram-mole of ATP, energy would be wasted if glucose were decomposed all at once into water and carbon dioxide while forming only a single ATP molecule. Fortunately, cells of the body contain special protein enzymes that cause the glucose molecule to split a little at a time in many successive steps, so that its energy is released in small packets to form one molecule of ATP at a time, forming a total of 38 moles of ATP for each mole of glucose metabolized by the cells.

The next sections describe the basic principles of the processes by which the glucose molecule is progressively dissected and its energy released to form ATP.

Glycolysis—Splitting Glucose to Form Pyruvic Acid

By far the most important means of releasing energy from the glucose molecule is initiated by *glycolysis*. The end products of glycolysis are then oxidized to provide energy. Glycolysis means splitting of the glucose molecule to form *two molecules of pyruvic acid*.

Glycolysis occurs by 10 successive chemical reactions, shown in Figure 67-5. Each step is catalyzed by at least one specific protein enzyme. Note that glucose is first converted into fructose-1,6-diphosphate and then split into two three-carbon-atom molecules, glyceraldehyde-3-phosphate, each of which is then converted through five additional steps into pyruvic acid.

Formation of ATP During Glycolysis. Despite the many chemical reactions in the glycolytic series, only a small portion of the free energy in the glucose molecule is released at most steps. However, between the 1,3-diphosphoglyceric acid and the 3-phosphoglyceric acid stages, and again between the phosphoenolpyruvic acid and the pyruvic acid stages, the packets of energy released are greater than 12,000 calories per mole, the amount required to form ATP, and

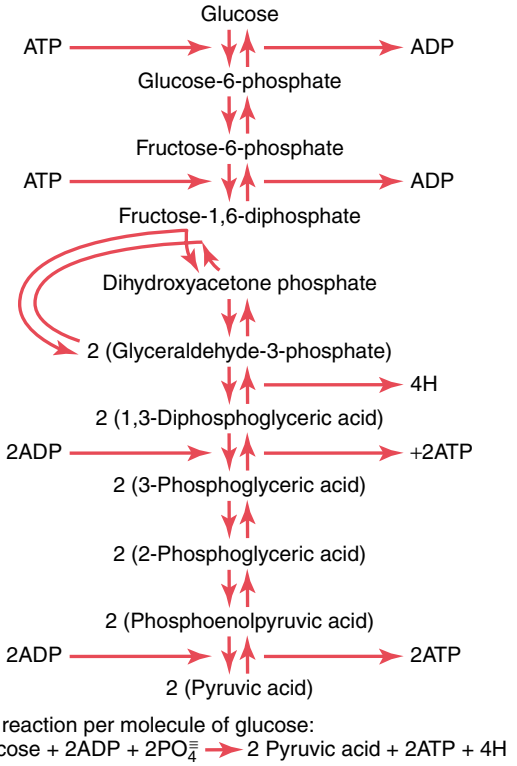


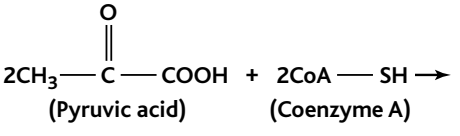
Figure 67-5 Sequence of chemical reactions responsible for glycolysis.

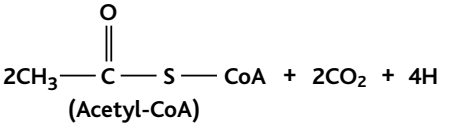
the reactions are coupled in such a way that ATP is formed. Thus, a total of 4 moles of ATP are formed for each mole of fructose-1,6-diphosphate that is split into pyruvic acid.

Yet, 2 moles of ATP are required to phosphorylate the original glucose to form fructose-1,6-diphosphate before glycolysis could begin. Therefore, *the net gain in ATP molecules by the entire glycolytic process is only 2 moles for each mole of glucose utilized*. This amounts to 24,000 calories of energy that becomes transferred to ATP, but during glycolysis, a total of 56,000 calories of energy were lost from the original glucose, giving an overall *efficiency* for ATP formation of only 43 percent. The remaining 57 percent of the energy is lost in the form of heat.

Conversion of Pyruvic Acid to Acetyl Coenzyme A

The next stage in the degradation of glucose is a two-step conversion of the two pyruvic acid molecules from Figure 67-5 into two molecules of *acetyl coenzyme A* (acetyl-CoA), in accordance with the following reaction:





Two carbon dioxide molecules and four hydrogen atoms are released from this reaction, while the remaining

portions of the two pyruvic acid molecules combine with coenzyme A, a derivative of the vitamin pantothenic acid, to form two molecules of acetyl-CoA. In this conversion, no ATP is formed, but up to six molecules of ATP are formed when the four released hydrogen atoms are later oxidized, as discussed later.

Citric Acid Cycle (Krebs Cycle)

The next stage in the degradation of the glucose molecule is called the *citric acid cycle* (also called the *tricarboxylic acid cycle* or the *Krebs cycle* in honor of Hans Krebs for his discovery of the citric acid cycle). This is a sequence of chemical reactions in which the acetyl portion of acetyl-CoA is degraded to carbon dioxide and hydrogen atoms. These reactions all occur in the *matrix of the mitochondrion*. The released hydrogen atoms add to the number of these atoms that will subsequently be oxidized (as discussed later), releasing tremendous amounts of energy to form ATP.

Figure 67-6 shows the different stages of the chemical reactions in the citric acid cycle. The substances to the left are added during the chemical reactions, and the products of the chemical reactions are shown to the right. Note at the top of the column that the cycle begins with *oxaloacetic acid*, and at the bottom of the chain of reactions, *oxaloacetic acid* is formed again. Thus, the cycle can continue over and over.

In the initial stage of the citric acid cycle, *acetyl-CoA* combines with *oxaloacetic acid* to form *citric acid*. The coenzyme A portion of the acetyl-CoA is released and can be used again and again for the formation of still more quantities of acetyl-CoA from pyruvic acid. The acetyl portion, however, becomes an integral part of the citric acid molecule. During the successive stages of the citric acid cycle, several molecules of water are added, as shown on the left in the figure, and *carbon dioxide* and *hydrogen atoms* are released at other stages in the cycle, as shown on the right in the figure.

The net results of the entire citric acid cycle are given in the explanation at the bottom of Figure 67-6, demonstrating that for each molecule of glucose originally metabolized, two acetyl-CoA molecules enter into the citric acid cycle, along with six molecules of water. These are then degraded into 4 carbon dioxide molecules, 16 hydrogen atoms, and 2 molecules of coenzyme A. Two molecules of ATP are formed, as follows.

Formation of ATP in the Citric Acid Cycle. The citric acid cycle itself does not cause a great amount of energy to be released; in only one of the chemical reactions—during the change from α-ketoglutaric acid to succinic acid—is a molecule of ATP formed. Thus, for each molecule of glucose metabolized, two acetyl-CoA molecules pass through the citric acid cycle, each forming a molecule of ATP, or a total of two molecules of ATP formed.

Function of Dehydrogenases and Nicotinamide Adenine Dinucleotide in Causing Release of Hydrogen Atoms in the Citric Acid Cycle. As already noted at several points in this discussion, hydrogen atoms are released during different chemical reactions of the citric acid cycle—4 hydrogen atoms during glycolysis, 4 during formation of acetyl-CoA from pyruvic acid and 16 in the citric acid cycle; *this makes a total of 24 hydrogen atoms released for each original molecule of glucose*. However, the hydrogen atoms are not simply turned loose in the intracellular fluid. Instead, they are released in packets of two, and in each instance, the release is catalyzed by a specific protein enzyme called a *dehydrogenase*. Twenty of the 24 hydrogen atoms immediately combine with nicotinamide adenine dinucleotide (NAD^+), a derivative of the vitamin niacin, in accordance with the following reaction:

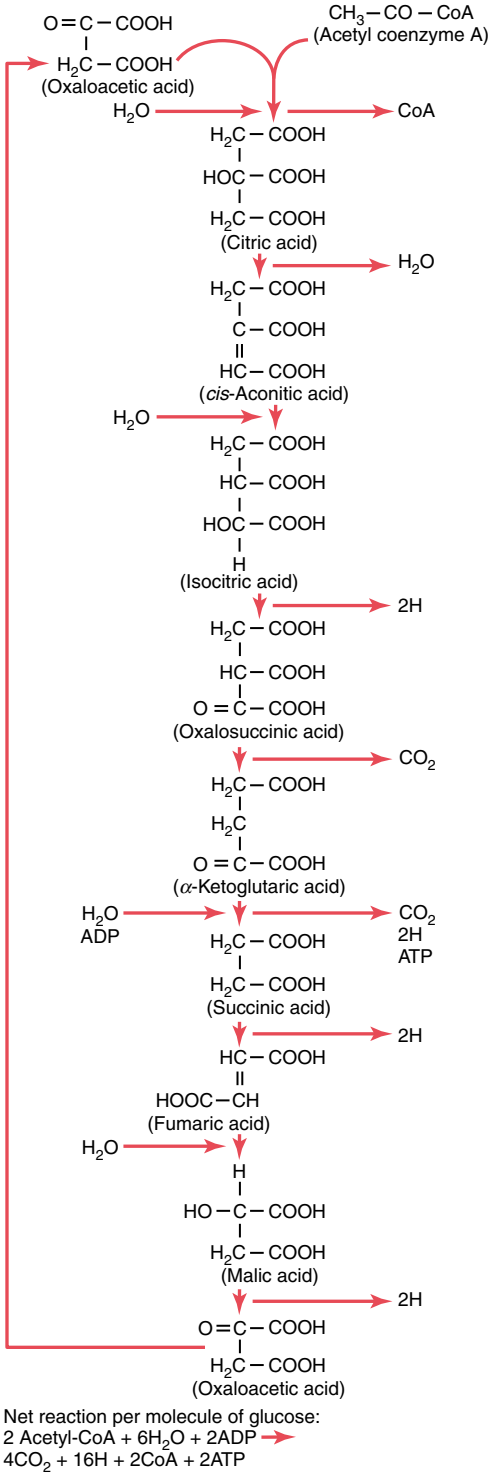
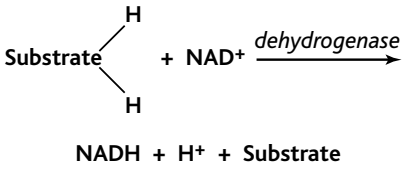


Figure 67-6 Chemical reactions of the citric acid cycle, showing the release of carbon dioxide and a number of hydrogen atoms during the cycle.



This reaction will not occur without intermediation of the specific dehydrogenase or without the availability of NAD^+ to act as a hydrogen carrier. Both the free hydrogen ion and the hydrogen bound with NAD^+ subsequently enter into multiple oxidative chemical reactions that form tremendous quantities of ATP, as discussed later.

The remaining four hydrogen atoms released during the breakdown of glucose—the four released during the citric acid cycle between the succinic and fumaric acid stages—combine with a specific dehydrogenase but are not subsequently released to NAD^+. Instead, they pass directly from the dehydrogenase into the oxidative process.

Function of Decarboxylases in Causing Release of Carbon Dioxide. Referring again to the chemical reactions of the citric acid cycle, as well as to those for the formation of acetyl-CoA from pyruvic acid, we find that there are three stages in which carbon dioxide is released. To cause the release of carbon dioxide, other specific protein enzymes, called *decarboxylases*, split the carbon dioxide away from the substrate. The carbon dioxide is then dissolved in the body fluids and transported to the lungs, where it is expired from the body (see Chapter 40).

Formation of Large Quantities of ATP by Oxidation of Hydrogen—the Process of Oxidative Phosphorylation

Despite all the complexities of (1) glycolysis, (2) the citric acid cycle, (3) dehydrogenation, and (4) decarboxylation, pitifully small amounts of ATP are formed during all these processes—only two ATP molecules in the glycolysis scheme and another two in the citric acid cycle for each molecule of glucose metabolized. Instead, almost 90 percent of the total ATP created through glucose metabolism is formed during subsequent oxidation of the hydrogen atoms that were released at early stages of glucose degradation. Indeed, the principal function of all these earlier stages is to make the hydrogen of the glucose molecule available in forms that can be oxidized.

Oxidation of hydrogen is accomplished, as illustrated in Figure 67-7, by a series of enzymatically catalyzed reactions *in the mitochondria*. These reactions (1) split each hydrogen atom into a hydrogen ion and an electron and (2) use the electrons eventually to combine dissolved oxygen of the fluids with water molecules to form hydroxyl ions. Then the hydrogen and hydroxyl ions combine with each other to form water. During this sequence of oxidative reactions, tremendous quantities of energy are released to form ATP. Formation of ATP in this manner is called *oxidative phosphorylation*. This occurs entirely in the mitochondria by a highly specialized process called the *chemiosmotic mechanism*.

Chemiosmotic Mechanism of the Mitochondria to Form ATP

Ionization of Hydrogen, the Electron Transport Chain, and Formation of Water. The first step in oxidative phosphorylation in the mitochondria is to ionize the hydrogen atoms that have been removed from the food substrates. As described earlier, these hydrogen atoms are removed in pairs: one immediately becomes a hydrogen ion, H^+; the other combines with NAD^+ to form NADH. The upper portion of Figure 67-7 shows the subsequent fate of the NADH and H^+. The initial effect is to release the other hydrogen atom from the NADH to form another hydrogen ion, H^+; this process also reconstitutes NAD^+ that will be reused again and again.

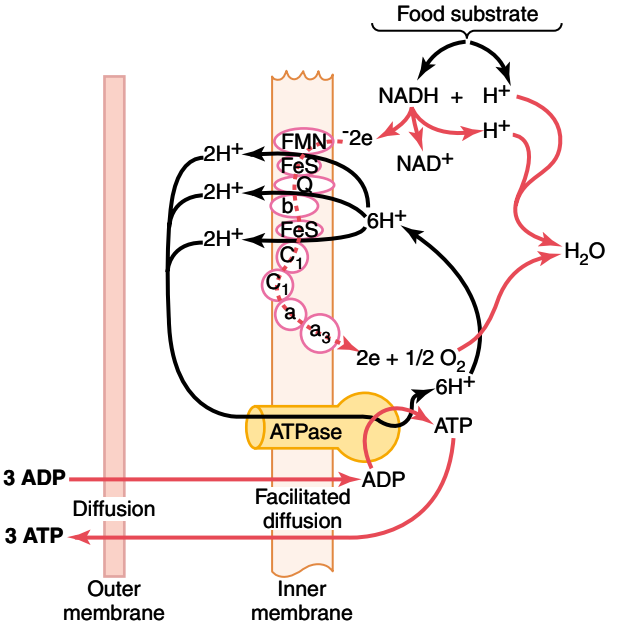


Figure 67-7 Mitochondrial chemiosmotic mechanism of oxidative phosphorylation for forming large quantities of ATP. This figure shows the relationship of the oxidative and phosphorylation steps at the outer and inner membranes of the mitochondrion.

The electrons that are removed from the hydrogen atoms to cause the hydrogen ionization immediately enter an *electron transport chain of electron acceptors* that are an integral part of the inner membrane (the shelf membrane) of the mitochondrion. The electron acceptors can be reversibly reduced or oxidized by accepting or giving up electrons. The important members of this electron transport chain include *flavoprotein*, several *iron sulfide proteins, ubiquinone*, and *cytochromes B, C*1, *C, A*, and *A*3. Each electron is shuttled from one of these acceptors to the next until it finally reaches cytochrome A3, which is called *cytochrome oxidase* because it is capable of giving up two electrons and thus reducing elemental oxygen to form ionic oxygen, which then combines with hydrogen ions to form water.

Thus, Figure 67-7 shows the transport of electrons through the electron chain and then their ultimate use by cytochrome oxidase to cause the formation of water molecules. During the transport of these electrons through the electron transport chain, energy is released that is used to cause the synthesis of ATP, as follows.

Pumping of Hydrogen Ions into the Outer Chamber of the Mitochondrion, Caused by the Electron Transport Chain. As the electrons pass through the electron transport chain, large amounts of energy are released. This energy is used to pump hydrogen ions from the inner matrix of the mitochondrion (to the right in Figure 67-7) into the outer chamber between the inner and outer mitochondrial membranes (to the left). This creates a high concentration of positively

charged hydrogen ions in this chamber; it also creates a strong negative electrical potential in the inner matrix.

Formation of ATP. The next step in oxidative phosphorylation is to convert ADP into ATP. This occurs in conjunction with a large protein molecule that protrudes all the way through the inner mitochondrial membrane and projects with a knoblike head into the inner mitochondrial matrix. This molecule is an ATPase, the physical nature of which is shown in Figure 67-7. It is called *ATP synthetase*.

The high concentration of positively charged hydrogen ions in the outer chamber and the large electrical potential difference across the inner membrane cause the hydrogen ions to flow into the inner mitochondrial matrix *through the substance of the ATPase molecule*. In doing so, energy derived from this hydrogen ion flow is used by ATPase to convert ADP into ATP by combining ADP with a free ionic phosphate radical (Pi), thus adding another high-energy phosphate bond to the molecule.

The final step in the process is transfer of ATP from the inside of the mitochondrion back to the cell cytoplasm. This occurs by facilitated diffusion outward through the inner membrane and then by simple diffusion through the permeable outer mitochondrial membrane. In turn, ADP is continually transferred in the other direction for continual conversion into ATP. *For each two electrons that pass through the entire electron transport chain (representing the ionization of two hydrogen atoms), up to three ATP molecules are synthesized.*

Summary of ATP Formation During the Breakdown of Glucose

We can now determine the total number of ATP molecules that, under optimal conditions, can be formed by the energy from one molecule of glucose.

1. During glycolysis, four molecules of ATP are formed and two are expended to cause the initial phosphorylation of glucose to get the process going. This gives a net gain of *two molecules of ATP*.
2. During each revolution of the citric acid cycle, one molecule of ATP is formed. However, because each glucose molecule splits into two pyruvic acid molecules, there are two revolutions of the cycle for each molecule of glucose metabolized, giving a net production of *two more molecules of ATP*.
3. During the entire schema of glucose breakdown, a total of 24 hydrogen atoms are released during glycolysis and during the citric acid cycle. Twenty of these atoms are oxidized in conjunction with the chemiosmotic mechanism shown in Figure 67-7, with the release of three ATP molecules per two atoms of hydrogen metabolized. This gives an additional *30 ATP molecules*.
4. The remaining four hydrogen atoms are released by their dehydrogenase into the chemiosmotic oxidative schema in the mitochondrion beyond the first stage of Figure 67-7. Two ATP molecules are usually released for every two hydrogen atoms oxidized, thus giving a total of *four more ATP molecules*.

Now, adding all the ATP molecules formed, we find a maximum of *38 ATP molecules* formed for each molecule of glucose degraded to carbon dioxide and water. Thus, 456,000 calories of energy can be stored in the form of ATP, whereas 686,000 calories are released during the complete oxidation of each gram-molecule of glucose. This represents an overall maximum *efficiency* of energy transfer of 66 percent. The remaining 34 percent of the energy becomes heat and, therefore, cannot be used by the cells to perform specific functions.

Control of Energy Release from Stored Glycogen When the Body Needs Additional Energy: Effect of ATP and ADP Cell Concentrations in Controlling the Rate of Glycolysis

Continual release of energy from glucose when the cells do not need energy would be an extremely wasteful process. Instead, glycolysis and the subsequent oxidation of hydrogen atoms are continually controlled in accordance with the cells' need for ATP. This control is accomplished by multiple feedback control mechanisms within the chemical schemata. Among the more important of these are the effects of cell concentrations of both ADP and ATP in controlling the rates of chemical reactions in the energy metabolism sequence.

One important way in which ATP helps control energy metabolism is to inhibit the enzyme *phosphofructokinase*. Because this enzyme promotes the formation of fructose-1,6-diphosphate, one of the initial steps in the glycolytic series of reactions, the net effect of excess cellular ATP is to slow or even stop glycolysis, which in turn stops most carbohydrate metabolism. Conversely, ADP (and AMP as well) causes the opposite change in this enzyme, greatly increasing its activity. Whenever ATP is used by the tissues for energizing a major fraction of almost all intracellular chemical reactions, this reduces the ATP inhibition of the enzyme phosphofructokinase and at the same time increases its activity as a result of the excess ADP formed. Thus, the glycolytic process is set in motion, and the total cellular store of ATP is replenished.

Another control linkage is the *citrate ion* formed in the citric acid cycle. An excess of this ion also *strongly inhibits phosphofructokinase*, thus preventing the glycolytic process from getting ahead of the citric acid cycle's ability to use the pyruvic acid formed during glycolysis.

A third way by which the ATP-ADP-AMP system controls carbohydrate metabolism, as well as controlling energy release from fats and proteins, is the following: Referring to the various chemical reactions for energy release, we see that if all the ADP in the cell has already been converted into ATP, additional ATP simply cannot be formed. As a result, the entire sequence involved in the use of foodstuffs—glucose, fats, and proteins—to form ATP is stopped. Then, when ATP is used by the cell to energize the different physiologic functions in the cell, the newly formed ADP and AMP turn on the energy processes again, and ADP and AMP are almost instantly returned to the ATP state. In this way, essentially a full store of ATP is automatically maintained, except during extreme cellular activity, such as very strenuous exercise.

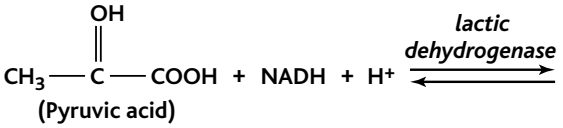
Anaerobic Release of Energy—"Anaerobic Glycolysis"

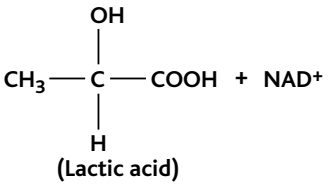
Occasionally, oxygen becomes either unavailable or insufficient, so oxidative phosphorylation cannot take place. Yet even under these conditions, a small amount of energy can still be released to the cells by the glycolysis stage of carbohydrate degradation, because the chemical reactions for the breakdown of glucose to pyruvic acid do not require oxygen.

This process is extremely wasteful of glucose because only 24,000 calories of energy are used to form ATP for each molecule of glucose metabolized, which represents

only a little over 3 percent of the total energy in the glucose molecule. Nevertheless, this release of glycolytic energy to the cells, which is called *anaerobic energy*, can be a lifesaving measure for up to a few minutes when oxygen becomes unavailable.

Formation of Lactic Acid During Anaerobic Glycolysis Allows Release of Extra Anaerobic Energy. The *law of mass action* states that as the end products of a chemical reaction build up in a reacting medium, the rate of the reaction decreases, approaching zero. The two end products of the glycolytic reactions (see Figure 67-5) are (1) pyruvic acid and (2) hydrogen atoms combined with NAD^+ to form NADH and H^+. The buildup of either or both of these would stop the glycolytic process and prevent further formation of ATP. When their quantities begin to be excessive, these two end products react with each other to form lactic acid, in accordance with the following equation:





Thus, under anaerobic conditions, the major portion of the pyruvic acid is converted into lactic acid, which diffuses readily out of the cells into the extracellular fluids and even into the intracellular fluids of other less active cells. Therefore, lactic acid represents a type of "sinkhole" into which the glycolytic end products can disappear, thus allowing glycolysis to proceed far longer than would otherwise be possible. Indeed, glycolysis could proceed for only a few seconds without this conversion. Instead, it can proceed for several minutes, supplying the body with considerable extra quantities of ATP, even in the absence of respiratory oxygen.

Reconversion of Lactic Acid to Pyruvic Acid When Oxygen Becomes Available Again. When a person begins to breathe oxygen again after a period of anaerobic metabolism, the lactic acid is rapidly reconverted to pyruvic acid and NADH plus H^+. Large portions of these are immediately oxidized to form large quantities of ATP. This excess ATP then causes as much as three fourths of the remaining excess pyruvic acid to be converted back into glucose.

Thus, the large amount of lactic acid that forms during anaerobic glycolysis is not lost from the body because, when oxygen is available again, the lactic acid can be either reconverted to glucose or used directly for energy. By far the greatest portion of this reconversion occurs in the liver, but a small amount can also occur in other tissues.

Use of Lactic Acid by the Heart for Energy. Heart muscle is especially capable of converting lactic acid to pyruvic acid and then using the pyruvic acid for energy. This occurs to a great extent during heavy exercise, when large amounts of lactic acid are released into the blood from the skeletal muscles and consumed as an extra energy source by the heart.

Release of Energy from Glucose by the Pentose Phosphate Pathway

In almost all the body's muscles, essentially all the carbohydrates utilized for energy are degraded to pyruvic acid by glycolysis and then oxidized. However, this glycolytic scheme is not the only means by which glucose can be degraded and used to provide energy. A second important mechanism for the breakdown and oxidation of glucose is called the *pentose phosphate pathway* (or *phosphogluconate pathway*), which is responsible for as much as 30 percent of the glucose breakdown *in the liver and even more than this in fat cells*.

This pathway is especially important because it can provide energy independently of all the enzymes of the citric acid cycle and therefore is an alternative pathway for energy metabolism when certain enzymatic abnormalities occur in cells. It has a special capacity for providing energy to multiple cellular synthetic processes.

Release of Carbon Dioxide and Hydrogen by the Pentose Phosphate Pathway. Figure 67-8 shows most of the basic chemical reactions in the pentose phosphate pathway. It demonstrates that glucose, during several stages of conversion, can release one molecule of carbon dioxide and four atoms of hydrogen, with the resultant formation of a five-carbon sugar, D-ribulose. This substance can change progressively into several other five-, four-, seven-, and three-carbon sugars. Finally, various combinations of these sugars can resynthesize glucose. However, *only five molecules of glucose are resynthesized for every six molecules of glucose that initially enter into the reactions*. That is, the pentose phosphate pathway is a cyclical process in which one molecule of glucose is metabolized for each revolution of the cycle. Thus, by repeating the cycle again and again, all the glucose can

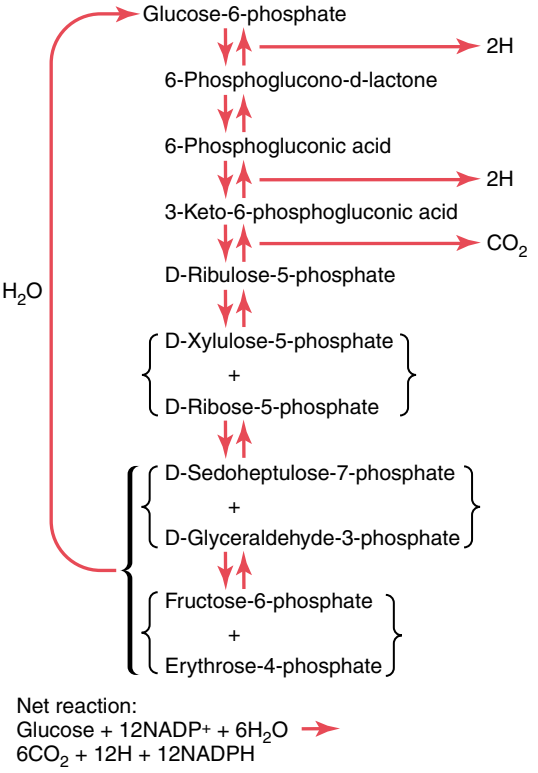


Figure 67-8 Pentose phosphate pathway for glucose metabolism.

eventually be converted into carbon dioxide and hydrogen, and the hydrogen can enter the oxidative phosphorylation pathway to form ATP; more often, however, it is used for the synthesis of fat or other substances, as follows.

Use of Hydrogen to Synthesize Fat; the Function of Nicotinamide Adenine Dinucleotide Phosphate. The hydrogen released during the pentose phosphate cycle does not combine with NAD^+ as in the glycolytic pathway but combines with nicotinamide adenine dinucleotide phosphate ($NADP^+$), which is almost identical to NAD^+ except for an extra phosphate radical, P. This difference is extremely significant because only hydrogen bound with $NADP^+$ in the form of NADPH can be used for the synthesis of fats from carbohydrates (as discussed in Chapter 68) and for the synthesis of some other substances.

When the glycolytic pathway for using glucose becomes slowed because of cellular inactivity, the pentose phosphate pathway remains operative (mainly in the liver) to break down any excess glucose that continues to be transported into the cells, and NADPH becomes abundant to help convert acetyl-CoA, also derived from glucose, into long fatty acid chains. This is another way in which energy in the glucose molecule is used other than for the formation of ATP—in this instance, *for the formation and storage of fat in the body*.

Glucose Conversion to Glycogen or Fat

When glucose is not immediately required for energy, the extra glucose that continually enters the cells is either stored as glycogen or converted into fat. Glucose is preferentially stored as glycogen until the cells have stored as much glycogen as they can—an amount sufficient to supply the energy needs of the body for only 12 to 24 hours.

When the glycogen-storing cells (primarily liver and muscle cells) approach saturation with glycogen, the additional glucose is converted into fat in liver and fat cells and is stored as fat in the fat cells. Other steps in the chemistry of this conversion are discussed in Chapter 68.

Formation of Carbohydrates from Proteins and Fats—"Gluconeogenesis"

When the body's stores of carbohydrates decrease below normal, moderate quantities of glucose can be formed from *amino acids* and the *glycerol* portion of fat. This process is called *gluconeogenesis*.

Gluconeogenesis is especially important in preventing an excessive reduction in the blood glucose concentration during fasting. Glucose is the primary substrate for energy in tissues such as the brain and the red blood cells, and adequate amounts of glucose must be present in the blood for several hours between meals. The liver plays a key role in maintaining blood glucose levels during fasting by converting its stored glycogen to glucose (glycogenolysis) and by synthesizing glucose, mainly from lactate and amino acids (gluconeogenesis). Approximately 25 percent of the liver's glucose production during fasting is from gluconeogenesis, helping to provide a steady supply of glucose to the brain. During prolonged fasting, the kidneys also synthesize considerable amounts of glucose from amino acids and other precursors.

About 60 percent of the amino acids in the body proteins can be converted easily into carbohydrates; the remaining 40 percent have chemical configurations that make this difficult or impossible. Each amino acid is converted into glucose by a slightly different chemical process. For instance, alanine can be converted directly into pyruvic acid simply by deamination; the pyruvic acid is then converted into glucose or stored glycogen. Several of the more complicated amino acids can be converted into different sugars that contain three-, four-, five-, or seven-carbon atoms; they can then enter the phosphogluconate pathway and eventually form glucose. Thus, by means of deamination plus several simple interconversions, many of the amino acids can become glucose. Similar interconversions can change glycerol into glucose or glycogen.

Regulation of Gluconeogenesis. Diminished carbohydrates in the cells and decreased blood sugar are the basic stimuli that increase the rate of gluconeogenesis. Diminished carbohydrates can directly reverse many of the glycolytic and phosphogluconate reactions, thus allowing the conversion of deaminated amino acids and glycerol into carbohydrates. In addition, the hormone *cortisol* is especially important in this regulation, as follows.

Effect of Corticotropin and Glucocorticoids on Gluconeogenesis. When normal quantities of carbohydrates are not available to the cells, the adenohypophysis, for reasons not completely understood, begins to secrete increased quantities of the hormone *corticotropin*. This stimulates the adrenal cortex to produce large quantities of *glucocorticoid hormones*, especially *cortisol*. In turn, cortisol mobilizes proteins from essentially all cells of the body, making these available in the form of amino acids in the body fluids. A high proportion of these immediately become deaminated in the liver and provide ideal substrates for conversion into glucose. Thus, one of the most important means by which gluconeogenesis is promoted is through the release of glucocorticoids from the adrenal cortex.

Blood Glucose

The normal blood glucose concentration in a person who has not eaten a meal within the past 3 to 4 hours is about 90 mg/dl. After a meal containing large amounts of carbohydrates, this level seldom rises above 140 mg/dl unless the person has diabetes mellitus, which is discussed in Chapter 78.

The regulation of blood glucose concentration is intimately related to the pancreatic hormones insulin and glucagon; this subject is discussed in detail in Chapter 78 in relation to the functions of these hormones.

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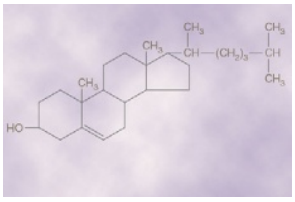
CHAPTER 68

Lipid Metabolism

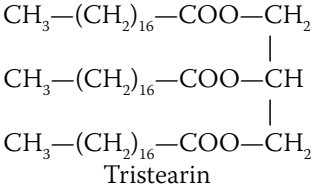


Several chemical compounds in food and in the body are classified as *lipids*. They include (1) *neutral fat*, also known as *triglycerides;* (2) *phospholipids;* (3) *cholesterol;* and (4) a few others of less importance. Chemically, the basic lipid moiety of the triglycerides and the phospholipids is *fatty acids*, which are long-chain hydrocarbon organic acids. A typical fatty acid, palmitic acid, is the following: $CH_3(CH_2)_{14}COOH$.

Although cholesterol does not contain fatty acid, its sterol nucleus is synthesized from portions of fatty acid molecules, thus giving it many of the physical and chemical properties of other lipid substances.

The triglycerides are used in the body mainly to provide energy for the different metabolic processes, a function they share almost equally with the carbohydrates. However, some lipids, especially cholesterol, the phospholipids, and small amounts of triglycerides, are used to form the membranes of all cells of the body and to perform other cellular functions.

Basic Chemical Structure of Triglycerides (Neutral Fat). Because most of this chapter deals with the utilization of triglycerides for energy, the following typical structure of the triglyceride molecule should be understood.



Tristearin

Note that three long-chain fatty acid molecules are bound with one molecule of glycerol. The three fatty acids most commonly present in the triglycerides of the human body are (1) *stearic acid* (shown in the tristearin example), which has an 18-carbon chain and is fully saturated with hydrogen atoms; (2) *oleic acid*, which also has an 18-carbon chain but has one double bond in the middle of the chain; and (3) *palmitic acid*, which has 16 carbon atoms and is fully saturated.

Transport of Lipids in the Body Fluids

Transport of Triglycerides and Other Lipids from the Gastrointestinal Tract by Lymph—the Chylomicrons

As explained in Chapter 65, almost all the fats in the diet, with the principal exception of a few short-chain fatty acids, are absorbed from the intestines into the intestinal lymph. During digestion, most triglycerides are split into monoglycerides and fatty acids. Then, while passing through the intestinal epithelial cells, the monoglycerides and fatty acids are resynthesized into new molecules of triglycerides that enter the lymph as minute, dispersed droplets called *chylomicrons* (Figure 68-1), whose diameters are between 0.08 and 0.6 micron. A small amount of *apoprotein B* is adsorbed to the outer surfaces of the chylomicrons. This leaves the remainder of the protein molecules projecting into the surrounding water and thereby increases the suspension stability of the chylomicrons in the lymph fluid and prevents their adherence to the lymphatic vessel walls.

Most of the cholesterol and phospholipids absorbed from the gastrointestinal tract enter the chylomicrons. Thus, although the chylomicrons are composed principally of triglycerides, they also contain about 9 percent phospholipids, 3 percent cholesterol, and 1 percent apoprotein B. The chylomicrons are then transported upward through the thoracic duct and emptied into the circulating venous blood at the juncture of the jugular and subclavian veins.

Removal of the Chylomicrons from the Blood

About 1 hour after a meal that contains large quantities of fat, the chylomicron concentration in the plasma may rise to 1 to 2 percent of the total plasma, and because of the large size of the chylomicrons, the plasma appears turbid and sometimes yellow. However, the chylomicrons have a half-life of less than 1 hour, so the plasma becomes clear again within a few hours. The fat of the chylomicrons is removed mainly in the following way.

Chylomicron Triglycerides Are Hydrolyzed by Lipoprotein Lipase, and Fat Is Stored in Adipose Tissue. Most of the chylomicrons are removed from the circulating blood as they pass through the capillaries of

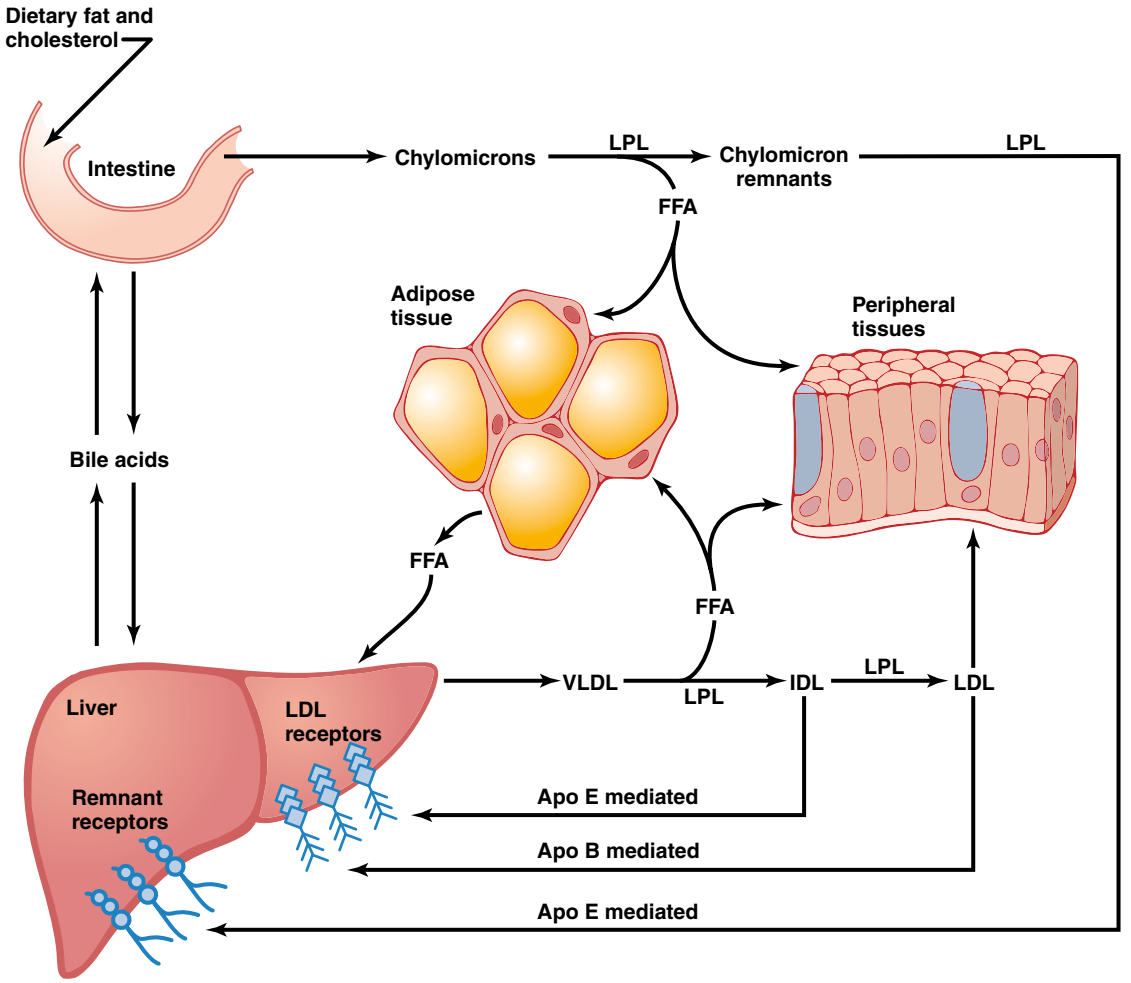


Figure 68-1 Summary of major pathways for metabolism of chylomicrons synthesized in the intestine and very low density lipoprotein (*VLDL*) synthesized in the liver. Apo B, apolipoprotein B; Apo E, apolipoprotein E; FFA, free fatty acids; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase.

various tissues, especially adipose tissue, skeletal muscle, and heart. These tissues synthesize the enzyme *lipoprotein lipase*, which is transported to the surface of capillary endothelial cells, where it hydrolyzes the triglycerides of chylomicrons as they come in contact with the endothelial wall, thus releasing fatty acids and glycerol (see Figure 68-1).

The fatty acids released from the chylomicrons, being highly miscible with the membranes of the cells, diffuse into the fat cells of the adipose tissue and muscle cells. Once inside these cells, the fatty acids can be used for fuel or again synthesized into triglycerides, with new glycerol being supplied by the metabolic processes of the storage cells, as discussed later in the chapter. The lipase also causes hydrolysis of phospholipids; this, too, releases fatty acids to be stored in the cells in the same way.

After the triglycerides are removed from the chylomicrons, the cholesterol-enriched *chylomicron remnants* are rapidly cleared from the plasma. The chylomicron remnants bind to receptors on endothelial cells in the liver sinusoids. *Apolipoprotein-E* on the surface of the chylomicron remnants and secreted by liver cells also plays an important role in initiating clearance of these plasma lipoproteins.

"Free Fatty Acids" Are Transported in the Blood in Combination with Albumin

When fat that has been stored in the adipose tissue is to be used elsewhere in the body to provide energy, it must first be transported from the adipose tissue to the other tissue. It is transported mainly in the form of *free fatty acids*. This is achieved by hydrolysis of the triglycerides back into fatty acids and glycerol.

At least two classes of stimuli play important roles in promoting this hydrolysis. First, when the amount of glucose available to the fat cell is inadequate, one of the glucose breakdown products, *α-glycerophosphate*, is also available in insufficient quantities. Because this substance is required to maintain the glycerol portion of triglycerides, the result is hydrolysis of triglycerides. Second, a *hormone-sensitive cellular lipase* can be activated by several hormones from the endocrine glands, and this also promotes rapid hydrolysis of triglycerides. This is discussed later in the chapter.

On leaving fat cells, fatty acids ionize strongly in the plasma and the ionic portion combines immediately with albumin molecules of the plasma proteins. Fatty acids bound in this manner are called *free fatty acids* or *nonesterified fatty acids*, to distinguish them from other fatty acids in the plasma that exist in the form of (1) esters of glycerol, (2) cholesterol, or (3) other substances.

The concentration of free fatty acids in the plasma under resting conditions is about 15 mg/dl, which is a total of only 0.45 gram of fatty acids in the entire circulatory system. Even this small amount accounts for almost all the transport of fatty acids from one part of the body to another for the following reasons:

1. Despite the minute amount of free fatty acid in the blood, its rate of "turnover" is extremely rapid: *half the plasma fatty acid is replaced by new fatty acid every 2 to 3 minutes*. One can calculate that at this rate, almost all the normal energy requirements of the body can be provided by the oxidation of transported free fatty acids, without using any carbohydrates or proteins for energy.
2. Conditions that increase the rate of utilization of fat for cellular energy also increase the free fatty acid concentration in the blood; in fact, the concentration sometimes increases fivefold to eightfold. Such a large increase occurs especially in cases of *starvation* and in *diabetes mellitus;* in both these conditions, the person derives little or no metabolic energy from carbohydrates.

Under normal conditions, only about 3 molecules of fatty acid combine with each molecule of albumin, but as many as 30 fatty acid molecules can combine with a single albumin molecule when the need for fatty acid transport is extreme. This shows how variable the rate of lipid transport can be under different physiologic conditions.

Lipoproteins—Their Special Function in Transporting Cholesterol and Phospholipids

In the postabsorptive state, after all the chylomicrons have been removed from the blood, more than 95 percent of all the lipids in the plasma are in the form of *lipoprotein*. These are small particles—much smaller than chylomicrons, but qualitatively similar in composition—containing *triglycerides, cholesterol, phospholipids*, and *protein*. The total concentration of lipoproteins in the plasma averages about 700 milligrams per 100 milliliters of plasma—that is, 700 mg/dl. This can be broken down into the following individual lipoprotein constituents:

	mg/dl of Plasma
Cholesterol	180
Phospholipids	160
Triglycerides	160
Protein	200

Types of Lipoproteins. Aside from the chylomicrons, which are themselves very large lipoproteins, there are four major types of lipoproteins, classified by their densities as measured in the ultracentrifuge: (1) *very low density lipoproteins (VLDLs)*, which contain high concentrations of triglycerides and moderate concentrations of both cholesterol and phospholipids; (2) *intermediate-density lipoproteins (IDLs)*, which are very low density lipoproteins from which a share of the triglycerides has been removed, so the concentrations of cholesterol and phospholipids are increased; (3) *low-density lipoproteins (LDLs)*, which are derived from intermediate-density lipoproteins by the removal of almost all the triglycerides, leaving an especially high concentration of cholesterol and a moderately high concentration of phospholipids; and (4) *high-density lipoproteins (HDLs)*, which contain a high concentration of protein (about 50 percent) but much smaller concentrations of cholesterol and phospholipids.

Formation and Function of Lipoproteins. Almost all the lipoproteins are formed in the liver, which is also where most of the plasma cholesterol, phospholipids, and triglycerides are synthesized. In addition, small quantities of HDLs are synthesized in the intestinal epithelium during the absorption of fatty acids from the intestines.

The primary function of the lipoproteins is to transport their lipid components in the blood. The VLDLs transport triglycerides synthesized in the liver mainly to the adipose tissue, whereas the other lipoproteins are especially important in the different stages of phospholipid and cholesterol transport from the liver to the peripheral tissues or from the periphery back to the liver. Later in the chapter, we discuss in more detail special problems of cholesterol transport in relation to the disease *atherosclerosis*, which is associated with the development of fatty lesions on the insides of arterial walls.

Fat Deposits

Adipose Tissue

Large quantities of fat are stored in two major tissues of the body, the *adipose tissue* and the *liver*. The adipose tissue is usually called *fat deposits*, or simply tissue fat.

The major function of adipose tissue is storage of triglycerides until they are needed to provide energy elsewhere in the body. A subsidiary function is to provide heat insulation for the body, as discussed in Chapter 73.

Fat Cells (Adipocytes). The fat cells (adipocytes) of adipose tissue are modified fibroblasts that store almost pure triglycerides in quantities as great as 80 to 95 percent of the entire cell volume. Triglycerides inside the fat cells are generally in a liquid form. When the tissues are exposed to prolonged cold, the fatty acid chains of the cell triglycerides, over a period of weeks, become either shorter or more unsaturated to decrease their melting point, thereby always allowing the fat to remain in a liquid state. This is particularly important because only liquid fat can be hydrolyzed and transported from the cells.

Fat cells can synthesize very small amounts of fatty acids and triglycerides from carbohydrates; this function supplements the synthesis of fat in the liver, as discussed later in the chapter.

Exchange of Fat Between the Adipose Tissue and the Blood—Tissue Lipases. As discussed earlier, large quantities of lipases are present in adipose tissue. Some of these enzymes catalyze the deposition of cell triglycerides from the chylomicrons and lipoproteins. Others, when activated by hormones, cause splitting of the triglycerides of the fat cells to release free fatty acids. Because of the rapid exchange of fatty acids, the triglycerides in fat cells are renewed about once every 2 to 3 weeks, which means that the fat stored in the tissues today is not the same fat that was stored last month, thus emphasizing the dynamic state of storage fat.

Liver Lipids

The principal functions of the liver in lipid metabolism are to (1) degrade fatty acids into small compounds that can be used for energy; (2) synthesize triglycerides, mainly from carbohydrates, but to a lesser extent from proteins as well; and

(3) synthesize other lipids from fatty acids, especially cholesterol and phospholipids.

Large quantities of triglycerides appear in the liver (1) during the early stages of starvation, (2) in diabetes mellitus, and (3) in any other condition in which fat instead of carbohydrates is being used for energy. In these conditions, large quantities of triglycerides are mobilized from the adipose tissue, transported as free fatty acids in the blood, and redeposited as triglycerides in the liver, where the initial stages of much of fat degradation begin. Thus, under normal physiological conditions, the total amount of triglycerides in the liver is determined to a great extent by the overall rate at which lipids are being used for energy.

The liver may also store large amounts of lipids in *lipodystrophy*, a condition characterized by atrophy or genetic deficiency of adipocytes.

The liver cells, in addition to containing triglycerides, contain large quantities of phospholipids and cholesterol, which are continually synthesized by the liver. Also, the liver cells are much more capable than other tissues of desaturating fatty acids, so liver triglycerides normally are much more unsaturated than the triglycerides of adipose tissue. This capability of the liver to desaturate fatty acids is functionally important to all tissues of the body because many structural elements of all cells contain reasonable quantities of unsaturated fats and their principal source is the liver. This desaturation is accomplished by a dehydrogenase in the liver cells.

Use of Triglycerides for Energy: Formation of Adenosine Triphosphate

The dietary intake of fat varies considerably in persons of different cultures, averaging as little as 10 to 15 percent of caloric intake in some Asian populations to as much as 35 to 50 percent of the calories in many Western populations. For many persons the use of fats for energy is therefore as important as the use of carbohydrates is. In addition, many of the carbohydrates ingested with each meal are converted into triglycerides, then stored, and used later in the form of fatty acids released from the triglycerides for energy.

Hydrolysis of Triglycerides. The first stage in using triglycerides for energy is their hydrolysis into fatty acids and glycerol. Then, both the fatty acids and the glycerol are transported in the blood to the active tissues, where they will be oxidized to give energy. Almost all cells—with some exceptions, such as brain tissue and red blood cells—can use fatty acids for energy.

Glycerol, on entering the active tissue, is immediately changed by intracellular enzymes into *glycerol-3-phosphate*, which enters the glycolytic pathway for glucose breakdown and is thus used for energy. Before the fatty acids can be used for energy, they must be processed further in the following way.

Entry of Fatty Acids into Mitochondria. Degradation and oxidation of fatty acids occur only in the mitochondria. Therefore, the first step for the use of fatty acids is their transport into the mitochondria. This is a carrier-mediated process that uses *carnitine* as the carrier substance. Once inside the mitochondria, fatty acids split away from carnitine and are degraded and oxidized.

Degradation of Fatty Acids to Acetyl Coenzyme A by Beta-Oxidation. The fatty acid molecule is degraded in the mitochondria by progressive release of two-carbon segments in the form of *acetyl coenzyme A* (*acetyl-CoA*). This process, which is shown in Figure 68-2, is called the *beta-oxidation* process for degradation of fatty acids.

To understand the essential steps in the beta-oxidation process, note that in equation 1 the first step is combination of the fatty acid molecule with coenzyme A (CoA) to form fatty acyl-CoA. In equations 2, 3, and 4, the *beta carbon* (the second carbon from the right) of the fatty acyl-CoA binds with an oxygen molecule—that is, the beta carbon becomes oxidized.

Then, in equation 5, the right-hand two-carbon portion of the molecule is split off to release acetyl-CoA into the cell fluid. At the same time, another CoA molecule binds at the end of the remaining portion of the fatty acid molecule, and this forms a new fatty acyl-CoA molecule; this time, however, the molecule is two carbon atoms shorter because of the loss of the first acetyl-CoA from its terminal end.

Next, this shorter fatty acyl-CoA enters into equation 2 and progresses through equations 3, 4, and 5 to release still another acetyl-CoA molecule, thus shortening the original fatty acid molecule by another two carbons. In addition to the released acetyl-CoA molecules, four atoms of hydrogen are released from the fatty acid molecule at the same time, entirely separate from the acetyl-CoA.

Oxidation of Acetyl-CoA. The acetyl-CoA molecules formed by beta-oxidation of fatty acids in the mitochondria enter immediately into the *citric acid cycle* (see

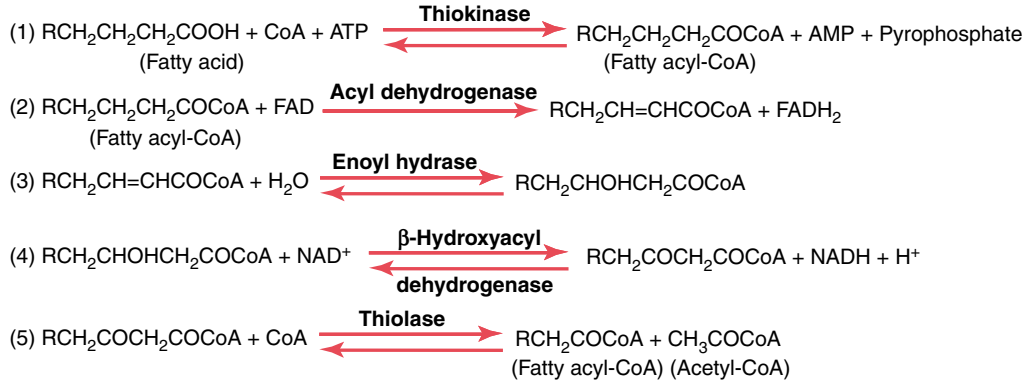


Figure 68-2 Beta-oxidation of fatty acids to yield acetyl coenzyme A.

Chapter 67), combining first with oxaloacetic acid to form citric acid, which then is degraded into carbon dioxide and hydrogen atoms. The hydrogen is subsequently oxidized by the *chemiosmotic oxidative system of the mitochondria*, which was also explained in Chapter 67. The net reaction in the citric acid cycle for each molecule of acetyl-CoA is the following:

$$CH_3COCoA + \text{Oxaloacetic acid} + 3H_2O + ADP \xrightarrow{\text{Citric acid cycle}} 2CO_2 + 8H + HCoA + ATP + \text{Oxaloacetic acid}$$

Thus, after initial degradation of fatty acids to acetyl-CoA, their final breakdown is precisely the same as that of the acetyl-CoA formed from pyruvic acid during the metabolism of glucose. And the extra hydrogen atoms are also oxidized by the same *chemiosmotic oxidative system of the mitochondria* that is used in carbohydrate oxidation, liberating large amounts of adenosine triphosphate (ATP).

Large Amounts of ATP Are Formed by Oxidation of Fatty Acids. In Figure 68-2, note that the four separate hydrogen atoms released each time a molecule of acetyl-CoA is split from the fatty acid chain are released in the forms $FADH_2$, NADH, and H^+. Therefore, for every stearic fatty acid molecule that is split to form 9 acetyl-CoA molecules, 32 extra hydrogen atoms are removed. In addition, for each of the 9 molecules of acetyl-CoA that are subsequently degraded by the citric acid cycle, 8 more hydrogen atoms are removed, making another 72 hydrogens. This makes a total of 104 hydrogen atoms eventually released by the degradation of each stearic acid molecule. Of this group, 34 are removed from the degrading fatty acids by flavoproteins, and 70 are removed by nicotinamide adenine dinucleotide (NAD^+) as NADH and H^+.

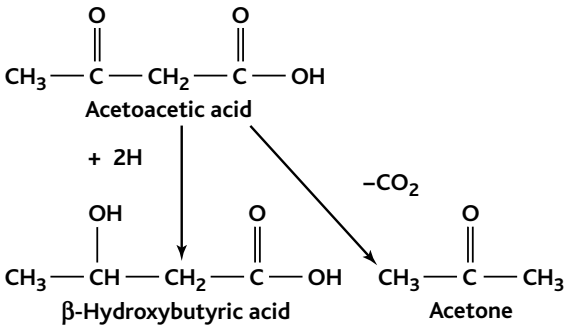
These two groups of hydrogen atoms are oxidized in the mitochondria, as discussed in Chapter 67, but they enter the oxidative system at different points. Therefore, 1 molecule of ATP is synthesized for each of the 34 flavoprotein hydrogens, and 1.5 molecules of ATP are synthesized for each of the 70 NADH and H^+ hydrogens. This makes 34 plus 105, or a total of 139 molecules of ATP formed by the oxidation of hydrogen derived from each molecule of stearic acid. Another nine molecules of ATP are formed in the citric acid cycle itself (separate from the ATP released by the oxidation of hydrogen), one for each of the nine acetyl-CoA molecules metabolized. Thus, a total of 148 molecules of ATP are formed during the complete oxidation of 1 molecule of stearic acid. However, two high-energy bonds are consumed in the initial combination of CoA with the stearic acid molecule, making a *net gain* of 146 molecules of ATP.

Formation of Acetoacetic Acid in the Liver and Its Transport in the Blood

A large share of the initial degradation of fatty acids occurs in the liver, especially when excessive amounts of lipids are being used for energy. However, the liver uses only a small proportion of the fatty acids for its own intrinsic metabolic processes. Instead, when the fatty acid chains have been split into acetyl-CoA, two molecules of acetyl-CoA condense to form one molecule of acetoacetic acid, which is then transported in the blood to the other cells throughout the body, where it is used for energy. The chemical processes are the following:

$$\underset{\text{Acetyl-CoA}}{2CH_3COCoA} + H_2O \underset{\text{other cells}}{\overset{\text{liver cells}}{\rightleftharpoons}} \underset{\text{Acetoacetic acid}}{CH_3COCH_2COOH} + 2HCoA$$

Part of the acetoacetic acid is also converted into *β-hydroxybutyric acid*, and minute quantities are converted into *acetone* in accord with the following reactions:



The acetoacetic acid, β-hydroxybutyric acid, and acetone diffuse freely through the liver cell membranes and are transported by the blood to the peripheral tissues. Here they again diffuse into the cells, where reverse reactions occur and acetyl-CoA molecules are formed. These in turn enter the citric acid cycle and are oxidized for energy, as already explained.

Normally, the acetoacetic acid and β-hydroxybutyric acid that enter the blood are transported so rapidly to the tissues that their combined concentration in the plasma seldom rises above 3 mg/dl. Yet, despite this small *concentration* in the blood, large *quantities* are actually transported, as is also true for free fatty acid transport. The rapid transport of both these substances results from their high solubility in the membranes of the target cells, which allows almost instantaneous diffusion into the cells.

Ketosis in Starvation, Diabetes, and Other Diseases. The concentrations of acetoacetic acid, β-hydroxybutyric acid, and acetone occasionally rise to levels many times normal in the blood and interstitial fluids; this condition is called *ketosis* because acetoacetic acid is a keto acid. The three compounds are called *ketone bodies*. Ketosis occurs especially in starvation, in diabetes mellitus, and sometimes even when a person's diet is composed almost entirely of fat. In all these states, essentially no carbohydrates are metabolized—in starvation and with a high-fat diet because carbohydrates are not available, and in diabetes because insulin is not available to cause glucose transport into the cells.

When carbohydrates are not used for energy, almost all the energy of the body must come from metabolism of fats. We shall see later in the chapter that the unavailability of carbohydrates automatically increases the rate of removal of fatty acids from adipose tissues; in addition, several hormonal factors—such as increased secretion of glucocorticoids by the adrenal cortex, increased secretion of glucagon by the pancreas, and decreased secretion of insulin by the pancreas—further enhance the removal of fatty acids from the fat tissues. As a result, tremendous quantities of fatty acids become available (1) to the peripheral tissue cells to be used for energy and (2) to the liver cells, where much of the fatty acid is converted to ketone bodies.

The ketone bodies pour out of the liver to be carried to the cells. For several reasons, the cells are limited in the amount of ketone bodies that can be oxidized; the most important reason is the following: One of the products of carbohydrate metabolism is the *oxaloacetate* that is required to bind with acetyl-CoA before it can be processed in the citric acid cycle. Therefore, deficiency of oxaloacetate derived from carbohydrates limits the entry of acetyl-CoA into the citric acid cycle, and when there is a simultaneous outpouring of large quantities of acetoacetic acid and other ketone bodies from the liver, the blood concentrations of acetoacetic acid and β-hydroxybutyric acid sometimes rise to as high as 20 times normal, thus leading to extreme acidosis, as explained in Chapter 30.

The acetone that is formed during ketosis is a volatile substance, some of which is blown off in small quantities in the expired air of the lungs. This gives the breath an acetone smell that is frequently used as a diagnostic criterion of ketosis.

Adaptation to a High-Fat Diet. When changing slowly from a carbohydrate diet to an almost completely fat diet, a person's body adapts to use far more acetoacetic acid than usual, and in this instance, ketosis normally does not occur. For instance, the Inuit (Eskimos), who sometimes live mainly on a fat diet, do not develop ketosis. Undoubtedly, several factors, none of which is clear, enhance the rate of acetoacetic acid metabolism by the cells. After a few weeks, even the brain cells, which normally derive almost all their energy from glucose, can derive 50 to 75 percent of their energy from fats.

Synthesis of Triglycerides from Carbohydrates

Whenever a greater quantity of carbohydrates enters the body than can be used immediately for energy or can be stored in the form of glycogen, the excess is rapidly converted into triglycerides and stored in this form in the adipose tissue.

In human beings, most triglyceride synthesis occurs in the liver, but minute quantities are also synthesized in the adipose tissue itself. The triglycerides formed in the liver are transported mainly in VLDLs to the adipose tissue, where they are stored.

Conversion of Acetyl-CoA into Fatty Acids. The first step in the synthesis of triglycerides is conversion of carbohydrates into acetyl-CoA. As explained in Chapter 67, this occurs during the normal degradation of glucose by the glycolytic system. Because fatty acids are actually large polymers of acetic acid, it is easy to understand how acetyl-CoA can be converted into fatty acids. However, the synthesis of fatty acids from acetyl-CoA is not achieved by simply reversing the oxidative degradation described earlier. Instead, this occurs by the two-step process shown in Figure 68-3, using *malonyl-CoA* and NADPH as the principal intermediates in the polymerization process.

Step 1:

$CH_3COCoA + CO_2 + ATP$ (Acetyl-CoA carboxylase)

$COOH$

CH_2 $+ ADP + PO_4^{-3}$

$O=C-CoA$

Malonyl-CoA

Step 2:

$1\ \text{Acetyl-CoA} + \text{Malonyl-CoA} + 16NADPH + 16H^+ \rightarrow$

$1\ \text{Steric acid} + 8CO_2 + 9CoA + 16NADP^+ + 7H_2O$

Figure 68-3 Synthesis of fatty acids.

Combination of Fatty Acids with α-Glycerophosphate to Form Triglycerides. Once the synthesized fatty acid chains have grown to contain 14 to 18 carbon atoms, they bind with glycerol to form triglycerides. The enzymes that cause this conversion are highly specific for fatty acids with chain lengths of 14 carbon atoms or greater, a factor that controls the physical quality of the triglycerides stored in the body.

As shown in Figure 68-4, the glycerol portion of triglycerides is furnished by α-glycerophosphate, which is another product derived from the glycolytic scheme of glucose degradation. This mechanism is discussed in Chapter 67.

Efficiency of Carbohydrate Conversion into Fat.

During triglyceride synthesis, only about 15 percent of the original energy in the glucose is lost in the form of heat; the remaining 85 percent is transferred to the stored triglycerides.

Importance of Fat Synthesis and Storage. Fat synthesis from carbohydrates is especially important for two reasons:

1. The ability of the different cells of the body to store carbohydrates in the form of glycogen is generally slight; a maximum of only a few hundred grams of glycogen can be stored in the liver, the skeletal muscles, and all other tissues of the body put together. In contrast, many kilograms of fat can be stored in adipose tissue. Therefore, fat synthesis provides a means by which the energy of excess ingested carbohydrates (and proteins) can be stored for later use. Indeed, the average person has almost 150 times as much energy stored in the form of fat as stored in the form of carbohydrate.
2. Each gram of fat contains almost two and a half times the calories of energy contained by each gram of glycogen. Therefore, for a given weight gain, a person can store several times as much energy in the form of fat as in the form

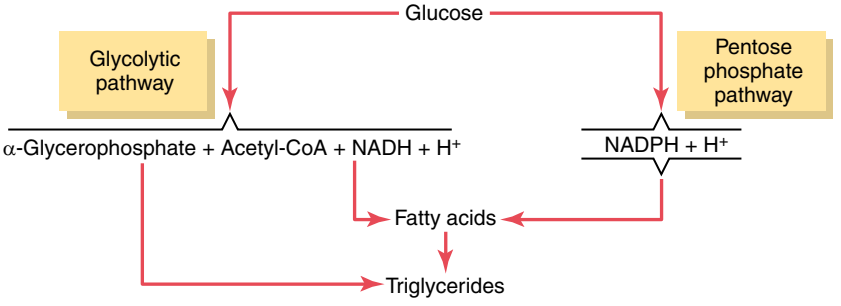


Figure 68-4 Overall schema for synthesis of triglycerides from glucose.

of carbohydrate, which is exceedingly important when an animal must be highly motile to survive.

Failure to Synthesize Fats from Carbohydrates in the Absence of Insulin. When insufficient insulin is available, as occurs in serious diabetes mellitus, fats are poorly synthesized, if at all, for the following reasons: First, when insulin is not available, glucose does not enter the fat and liver cells satisfactorily, so little of the acetyl-CoA and NADPH needed for fat synthesis can be derived from glucose. Second, lack of glucose in the fat cells greatly reduces the availability of α-glycerophosphate, which also makes it difficult for the tissues to form triglycerides.

Synthesis of Triglycerides from Proteins

Many amino acids can be converted into acetyl-CoA, as discussed in Chapter 69. The acetyl-CoA can then be synthesized into triglycerides. Therefore, when people have more proteins in their diets than their tissues can use as proteins, a large share of the excess is stored as fat.

Regulation of Energy Release from Triglycerides

Carbohydrates Are Preferred over Fats for Energy When Excess Carbohydrates Are Available. When excess quantities of carbohydrates are available in the body, carbohydrates are used preferentially over triglycerides for energy. There are several reasons for this "fat-sparing" effect of carbohydrates. One of the most important is the following: The fats in adipose tissue cells are present in two forms: stored triglycerides and small quantities of free fatty acids. They are in constant equilibrium with each other. When excess quantities of α-*glycerophosphate* are present (which occurs when excess carbohydrates are available), the excess α-glycerophosphate binds the free fatty acids in the form of stored triglycerides. As a result, the equilibrium between free fatty acids and triglycerides shifts toward the stored triglycerides; consequently, only minute quantities of fatty acids are available to be used for energy. Because α-glycerophosphate is an important product of glucose metabolism, the availability of large amounts of glucose automatically inhibits the use of fatty acids for energy.

Second, when carbohydrates are available in excess, fatty acids are synthesized more rapidly than they are degraded. This effect is caused partially by the large quantities of acetyl-CoA formed from the carbohydrates and by the low concentration of free fatty acids in the adipose tissue, thus creating conditions appropriate for the conversion of acetyl-CoA into fatty acids.

An even more important effect that promotes the conversion of carbohydrates to fats is the following: The first step, which is the rate-limiting step, in the synthesis of fatty acids is carboxylation of acetyl-CoA to form malonyl-CoA. The rate of this reaction is controlled primarily by the enzyme *acetyl-CoA carboxylase*, the activity of which is accelerated in the presence of intermediates of the citric acid cycle. When excess carbohydrates are being used, these intermediates increase, automatically causing increased synthesis of fatty acids.

Thus, an excess of carbohydrates in the diet not only acts as a fat-sparer but also increases fat stores. In fact, all the excess carbohydrates not used for energy or stored in the small glycogen deposits of the body are converted to fat for storage.

Acceleration of Fat Utilization for Energy in the Absence of Carbohydrates. All the fat-sparing effects of carbohydrates are lost and actually reversed when carbohydrates are not available. The equilibrium shifts in the opposite direction, and fat is mobilized from the adipose cells and used for energy in place of carbohydrates.

Also important are several hormonal changes that take place to promote rapid fatty acid mobilization from adipose tissue. Among the most important of these is a marked decrease in pancreatic secretion of insulin caused by the absence of carbohydrates. This not only reduces the rate of glucose utilization by the tissues but also decreases fat storage, which further shifts the equilibrium in favor of fat metabolism in place of carbohydrates.

Hormonal Regulation of Fat Utilization. At least seven of the hormones secreted by the endocrine glands have significant effects on fat utilization. Some important hormonal effects on fat metabolism—in addition to *insulin lack*, discussed in the previous paragraph—are noted here.

Probably the most dramatic increase that occurs in fat utilization is that observed during heavy exercise. This results almost entirely from release of *epinephrine* and *norepinephrine* by the adrenal medullae during exercise, as a result of sympathetic stimulation. These two hormones directly activate *hormone-sensitive triglyceride lipase*, which is present in abundance in the fat cells, and this causes rapid breakdown of triglycerides and mobilization of fatty acids. Sometimes the free fatty acid concentration in the blood of an exercising person rises as much as eightfold, and the use of these fatty acids by the muscles for energy is correspondingly increased. Other types of stress that activate the sympathetic nervous system can also increase fatty acid mobilization and utilization in a similar manner.

Stress also causes large quantities of *corticotropin* to be released by the anterior pituitary gland, and this causes the adrenal cortex to secrete extra quantities of *glucocorticoids*. Both corticotropin and glucocorticoids activate either the same hormone-sensitive triglyceride lipase as that activated by epinephrine and norepinephrine or a similar lipase. When corticotropin and glucocorticoids are secreted in excessive amounts for long periods, as occurs in the endocrine condition called Cushing's syndrome, fats are frequently mobilized to such a great extent that ketosis results. Corticotropin and glucocorticoids are then said to have a *ketogenic effect*. *Growth hormone* has an effect similar to but weaker than that of corticotropin and glucocorticoids in activating hormone-sensitive lipase. Therefore, growth hormone can also have a mild ketogenic effect.

Finally, *thyroid hormone* causes rapid mobilization of fat, which is believed to result indirectly from an increased overall rate of energy metabolism in all cells of the body under the influence of this hormone. The resulting reduction in acetyl-CoA and other intermediates of both fat and carbohydrate metabolism in the cells is a stimulus to fat mobilization.

The effects of the different hormones on metabolism are discussed further in the chapters dealing with each hormone.

Obesity

Obesity means deposition of excess fat in the body. This subject is discussed in Chapter 71 in relation to dietary balances, but briefly, it is caused by the ingestion of greater amounts of food than can be used by the body for energy. The excess food, whether fats, carbohydrates, or proteins, is then stored

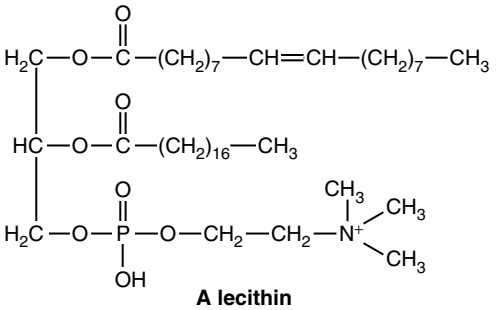
almost entirely as fat in the adipose tissue, to be used later for energy.

Several strains of rodents have been found in which *hereditary obesity* occurs. In at least one of these, the obesity is caused by ineffective mobilization of fat from the adipose tissue by tissue lipase, while synthesis and storage of fat continue normally. Such a one-way process causes progressive enhancement of the fat stores, resulting in severe obesity.

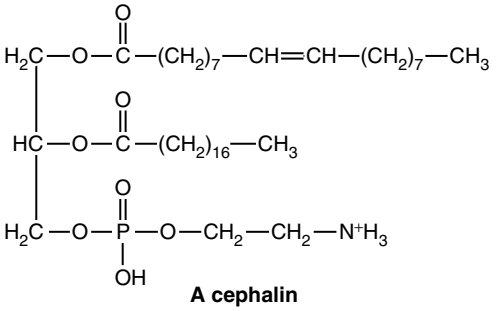
Phospholipids and Cholesterol

Phospholipids

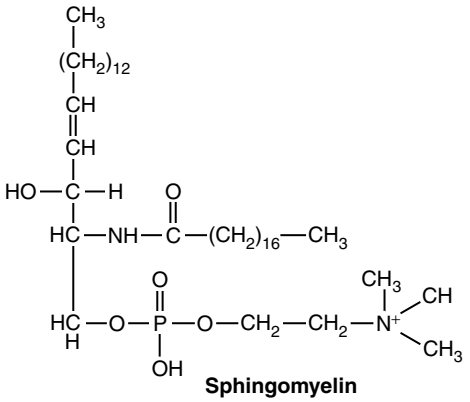
The major types of body phospholipids are *lecithins, cephalins*, and *sphingomyelin;* their typical chemical formulas are shown in Figure 68-5. Phospholipids always contain one or more fatty acid molecules and one phosphoric acid radical, and they usually contain a nitrogenous base. Although the chemical structures of phospholipids are somewhat variant, their physical properties are similar because they are all lipid soluble, transported in lipoproteins, and used throughout the body for various structural purposes, such as in cell membranes and intracellular membranes.



A lecithin



A cephalin



Sphingomyelin

Figure 68-5 Typical phospholipids.

Formation of Phospholipids. Phospholipids are synthesized in essentially all cells of the body, although certain cells have a special ability to form great quantities of them. Probably 90 percent are formed in the liver cells; substantial quantities are also formed by the intestinal epithelial cells during lipid absorption from the gut.

The rate of phospholipid formation is governed to some extent by the usual factors that control the overall rate of fat metabolism because, when triglycerides are deposited in the liver, the rate of phospholipid formation increases. Also, certain specific chemical substances are needed for the formation of some phospholipids. For instance, *choline*, either obtained in the diet or synthesized in the body, is necessary for the formation of lecithin, because choline is the nitrogenous base of the lecithin molecule. Also, *inositol* is necessary for the formation of some cephalins.

Specific Uses of Phospholipids. Several functions of the phospholipids are the following: (1) Phospholipids are an important constituent of lipoproteins in the blood and are essential for the formation and function of most of these; in their absence, serious abnormalities of transport of cholesterol and other lipids can occur. (2) Thromboplastin, which is necessary to initiate the clotting process, is composed mainly of one of the cephalins. (3) Large quantities of sphingomyelin are present in the nervous system; this substance acts as an electrical insulator in the myelin sheath around nerve fibers. (4) Phospholipids are donors of phosphate radicals when these radicals are necessary for different chemical reactions in the tissues. (5) Perhaps the most important of all the functions of phospholipids is participation in the formation of structural elements—mainly membranes—in cells throughout the body, as discussed in the next section of this chapter in connection with a similar function for cholesterol.

Cholesterol

Cholesterol, the formula of which is shown in Figure 68-6, is present in the diets of all people, and it can be absorbed slowly from the gastrointestinal tract into the intestinal lymph. It is highly fat soluble but only slightly soluble in water. It is specifically capable of forming esters with fatty acids. Indeed, about 70 percent of the cholesterol in the lipoproteins of the plasma is in the form of cholesterol esters.

Formation of Cholesterol. Besides the cholesterol absorbed each day from the gastrointestinal tract, which is called *exogenous cholesterol*, an even greater quantity is formed in the cells of the body, called *endogenous cholesterol*. Essentially all the endogenous cholesterol that circulates in the lipoproteins of the plasma is formed by the liver, but all other cells of the body form at least some cholesterol, which is consistent with the fact that many of the membranous structures of all cells are partially composed of this substance.

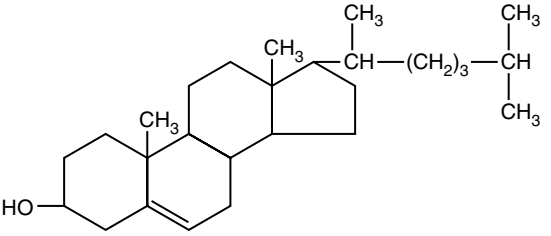


Figure 68-6 Cholesterol.

The basic structure of cholesterol is a sterol nucleus. This is synthesized entirely from multiple molecules of acetyl-CoA. In turn, the sterol nucleus can be modified by means of various side chains to form (1) cholesterol; (2) cholic acid, which is the basis of the bile acids formed in the liver; and (3) many important steroid hormones secreted by the adrenal cortex, the ovaries, and the testes (these hormones are discussed in later chapters).

Factors That Affect Plasma Cholesterol Concentration—Feedback Control of Body Cholesterol. Among the important factors that affect plasma cholesterol concentration are the following:

1. An increase in the *amount of cholesterol ingested each day* increases the plasma concentration slightly. However, when cholesterol is ingested, the rising concentration of cholesterol inhibits the most essential enzyme for endogenous synthesis of cholesterol, 3-hydroxy-3-methylglutaryl CoA reductase, thus providing an intrinsic feedback control system to prevent an excessive increase in plasma cholesterol concentration. As a result, plasma cholesterol concentration *usually* is not changed upward or downward more than ±15 percent by altering the amount of cholesterol in the diet, although the response of individuals differs markedly.
2. A *highly saturated fat* diet increases blood cholesterol concentration 15 to 25 percent, especially when this is associated with excess weight gain and obesity. This results from increased fat deposition in the liver, which then provides increased quantities of acetyl-CoA in the liver cells for the production of cholesterol. Therefore, to decrease the blood cholesterol concentration, it is usually just as important, if not more important, to maintain a diet low in saturated fat as to maintain a diet low in cholesterol.
3. Ingestion of fat containing highly *unsaturated fatty acids* usually depresses the blood cholesterol concentration a slight to moderate amount. The mechanism of this effect is unknown, despite the fact that this observation is the basis of much present-day dietary strategy.
4. *Lack of insulin* or *thyroid hormone* increases the blood cholesterol concentration, whereas excess thyroid hormone decreases the concentration. These effects are probably caused mainly by changes in the degree of activation of specific enzymes responsible for the metabolism of lipid substances.
5. *Genetic disorders* of cholesterol metabolism may greatly increase plasma cholesterol levels. For example, mutations of the *LDL receptor* gene prevent the liver from adequately removing the cholesterol-rich LDLs from the plasma. As discussed later, this causes the liver to produce excessive amounts of cholesterol. Mutations of the gene that encodes *apolipoprotein B*, the part of the LDL that binds to the receptor, also cause excessive cholesterol production by the liver.

Specific Uses of Cholesterol in the Body. By far the most abundant nonmembranous use of cholesterol in the body is to form cholic acid in the liver. As much as 80 percent of cholesterol is converted into cholic acid. As explained in Chapter 70, this is conjugated with other substances to form bile salts, which promote digestion and absorption of fats.

A small quantity of cholesterol is used by (1) the adrenal glands to form *adrenocortical hormones*, (2) the ovaries to form *progesterone* and *estrogen*, and (3) the testes to form *testosterone*. These glands can also synthesize their own sterols and then form hormones from them, as discussed in the chapters on endocrinology.

A large amount of cholesterol is precipitated in the corneum of the skin. This, along with other lipids, makes the skin highly resistant to the absorption of water-soluble substances and to the action of many chemical agents because cholesterol and the other skin lipids are highly inert to acids and to many solvents that might otherwise easily penetrate the body. Also, these lipid substances help prevent water evaporation from the skin; without this protection, the amount of evaporation can be 5 to 10 liters per day (as occurs in burn patients who have lost their skin) instead of the usual 300 to 400 milliliters.

Cellular Structural Functions of Phospholipids and Cholesterol—Especially for Membranes

The previously mentioned uses of phospholipids and cholesterol are of only minor importance in comparison with their function of forming specialized structures, mainly membranes, in all cells of the body. In Chapter 2, it was pointed out that large quantities of phospholipids and cholesterol are present in both the cell membrane and the membranes of the internal organelles of all cells. It is also known that the *ratio* of membrane cholesterol to phospholipids is especially important in determining the fluidity of the cell membranes.

For membranes to be formed, substances that are not soluble in water must be available. In general, the only substances in the body that are not soluble in water (besides the inorganic substances of bone) are the lipids and some proteins. Thus, the physical integrity of cells everywhere in the body is based mainly on phospholipids, cholesterol, and certain insoluble proteins. The polar charges on the phospholipids also reduce the interfacial tension between the cell membranes and the surrounding fluids.

Another fact that indicates the importance of phospholipids and cholesterol for the formation of structural elements of the cells is the slow turnover rates of these substances in most nonhepatic tissues—turnover rates measured in months or years. For instance, their function in brain cells to provide memory processes is related mainly to their indestructible physical properties.

Atherosclerosis

Atherosclerosis is a disease of the large and intermediate-sized arteries in which fatty lesions called *atheromatous plaques* develop on the inside surfaces of the arterial walls. *Arteriosclerosis*, in contrast, is a general term that refers to thickened and stiffened blood vessels of all sizes.

One abnormality that can be measured very early in blood vessels that later become atherosclerotic is *damage to the vascular endothelium*. This, in turn, increases the expression of adhesion molecules on endothelial cells and decreases their ability to release nitric oxide and other substances that help prevent adhesion of macromolecules, platelets, and monocytes to the endothelium. After damage to the vascular endothelium occurs, circulating monocytes and lipids (mostly LDLs) begin to accumulate at the site of injury (Figure 68-7*A*). The monocytes cross the endothelium, enter the *intima* of the vessel wall, and differentiate to become *macrophages*, which then ingest and oxidize the accumulated lipoproteins, giving the macrophages a foamlike appearance.

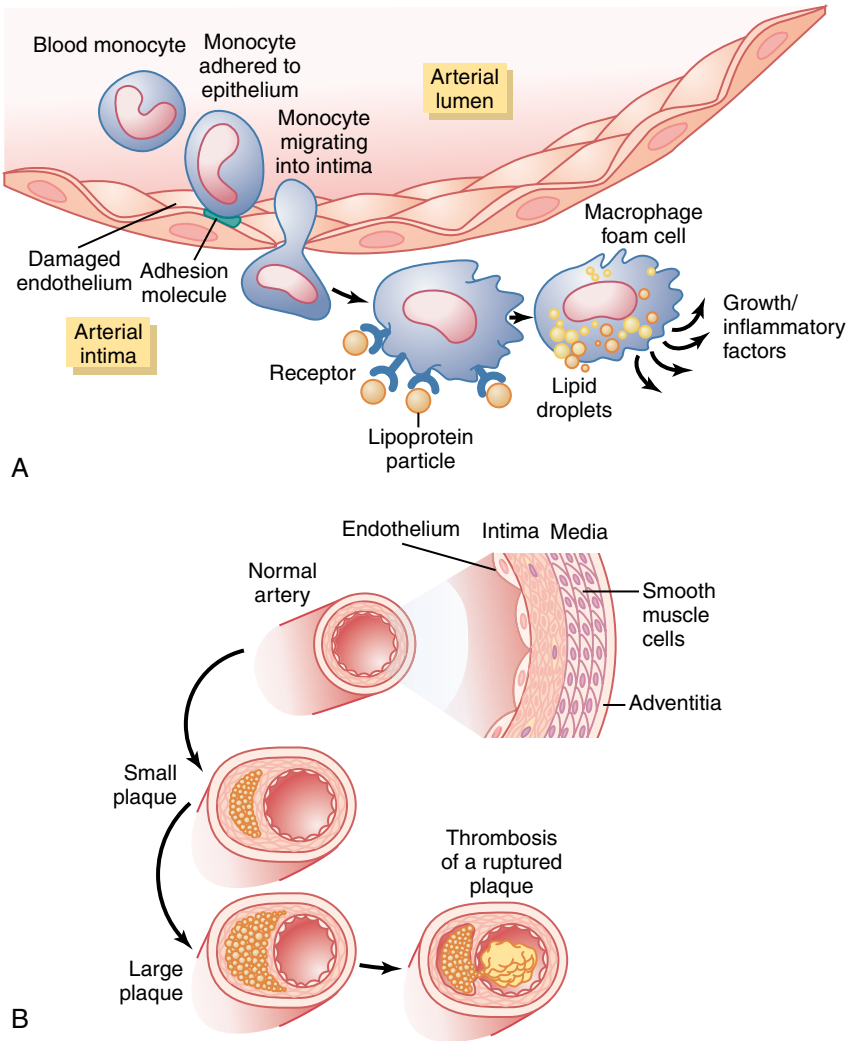


Figure 68-7 Development of atherosclerotic plaque. *A*, Attachment of a monocyte to an adhesion molecule on a damaged endothelial cell of an artery. The monocyte then migrates through the endothelium into the intimal layer of the arterial wall and is transformed into a macrophage. The macrophage then ingests and oxidizes lipoprotein molecules, becoming a macrophage foam cell. The foam cells release substances that cause inflammation and growth of the intimal layer. *B*, Additional accumulation of macrophages and growth of the intima cause the plaque to grow larger and accumulate lipids. Eventually, the plaque could occlude the vessel or rupture, causing the blood in the artery to coagulate and form a thrombus. (Modified from Libby P: Inflammation in atherosclerosis. Nature 420:868, 2002.)

These *macrophage foam cells* then aggregate on the blood vessel and form a visible *fatty streak*.

With time, the fatty streaks grow larger and coalesce, and the surrounding fibrous and smooth muscle tissues proliferate to form larger and larger plaques (see Figure 68-7*B*). Also, the macrophages release substances that cause *inflammation* and further proliferation of smooth muscle and fibrous tissue on the inside surfaces of the arterial wall. The lipid deposits plus the cellular proliferation can become so large that the plaque bulges into the lumen of the artery and greatly reduces blood flow, sometimes completely occluding the vessel. Even without occlusion, the fibroblasts of the plaque eventually deposit extensive amounts of dense connective tissue; *sclerosis* (fibrosis) becomes so great that the arteries become stiff and unyielding. Still later, calcium salts often precipitate with the cholesterol and other lipids of the plaques, leading to bony-hard calcifications that can make the arteries rigid tubes. Both of these later stages of the disease are called "hardening of the arteries."

Atherosclerotic arteries lose most of their distensibility, and because of the degenerative areas in their walls, they are easily ruptured. Also, where the plaques protrude into the flowing blood, their rough surfaces can cause blood clots to develop, with resultant thrombus or embolus formation (see Chapter 36), leading to a sudden blockage of all blood flow in the artery.

Almost half of all deaths in the United States and Europe are due to vascular disease. About two thirds of these deaths are caused by thrombosis of one or more coronary arteries. The remaining one third are caused by thrombosis or hemorrhage of vessels in other organs of the body, especially the brain (causing strokes), but also the kidneys, liver, gastrointestinal tract, limbs, and so forth.

Basic Causes of Atherosclerosis—the Roles of Cholesterol and Lipoproteins

Increased Low-Density Lipoproteins. An important factor in causing atherosclerosis is a high blood plasma concentration of cholesterol in the form of low-density lipoproteins. The plasma concentration of these high-cholesterol LDLs is increased by several factors, including eating highly saturated fat in the daily diet, obesity, and physical inactivity. To a lesser extent, eating excess cholesterol may also raise plasma levels of LDLs.

An interesting example occurs in rabbits, which normally have low plasma cholesterol concentrations because of their vegetarian diet. Simply feeding these animals large quantities of cholesterol as part of their daily diet leads to serious atherosclerotic plaques throughout their arterial systems.

Familial Hypercholesterolemia. This is a disease in which the person inherits defective genes for the formation of LDL receptors on the membrane surfaces of the body's cells. In the

absence of these receptors, the liver cannot absorb either intermediate-density or low-density lipoprotein. Without this absorption, the cholesterol machinery of the liver cells goes on a rampage, producing new cholesterol; it is no longer responsive to the feedback inhibition of too much plasma cholesterol. As a result, the number of VLDLs released by the liver into the plasma increases immensely.

Patients with full-blown familial hypercholesterolemia may have blood cholesterol concentrations of 600 to 1000 mg/dl, levels that are four to six times normal. Many of these people die before age 20 because of myocardial infarction or other sequelae of atherosclerotic blockage of blood vessels throughout the body.

Heterozygous familial hypercholesterolemia is relatively common and occurs in about one in 500 people. The more severe form of this disorder caused by homozygous mutations is much rarer, occurring in only about one of every million births on average.

Role of High-Density Lipoproteins in Preventing Atherosclerosis. Much less is known about the function of HDLs compared with that of LDLs. It is believed that HDLs can actually absorb cholesterol crystals that are beginning to be deposited in arterial walls. Whether this mechanism is true or not, HDLs do help protect against the development of atherosclerosis. Consequently, when a person has a high *ratio* of high-density to low-density lipoproteins, the likelihood of developing atherosclerosis is greatly reduced.

Other Major Risk Factors for Atherosclerosis

In some people with perfectly normal levels of cholesterol and lipoproteins, atherosclerosis still develops. Some of the factors that are known to predispose to atherosclerosis are (1) *physical inactivity* and *obesity*, (2) *diabetes mellitus*, (3) *hypertension*, (4) *hyperlipidemia*, and (5) *cigarette smoking*.

Hypertension, for example, increases the risk for atherosclerotic coronary artery disease by at least twofold. Likewise, a person with diabetes mellitus has, on average, more than a twofold increased risk of developing coronary artery disease. When hypertension and diabetes mellitus occur together, the risk for coronary artery disease is increased by more than eightfold. And when hypertension, diabetes mellitus, and hyperlipidemia are all present, the risk for atherosclerotic coronary artery disease is increased almost 20-fold, suggesting that these factors interact in a synergistic manner to increase the risk of developing atherosclerosis. In many overweight and obese patients, these three risk factors do occur together, greatly increasing their risk for atherosclerosis, which in turn may lead to heart attack, stroke, and kidney disease.

In early and middle adulthood, men are more likely to develop atherosclerosis than are women of comparable age, suggesting that male sex hormones might be atherogenic or, conversely, that female sex hormones might be protective.

Some of these factors cause atherosclerosis by increasing the concentration of LDLs in the plasma. Others, such as hypertension, lead to atherosclerosis by causing damage to the vascular endothelium and other changes in the vascular tissues that predispose to cholesterol deposition.

To add to the complexity of atherosclerosis, experimental studies suggest that *excess blood levels of iron* can lead to atherosclerosis, perhaps by forming free radicals in the blood that damage the vessel walls. About one quarter of all people have a special type of LDL called lipoprotein(a), containing an additional protein, *apolipoprotein(a)*, that almost doubles the incidence of atherosclerosis. The precise mechanisms of these atherogenic effects have yet to be discovered.

Prevention of Atherosclerosis

The most important measures to protect against the development of atherosclerosis and its progression to serious vascular disease are (1) maintaining a healthy weight, being physically active, and eating a diet that contains mainly unsaturated fat with a low cholesterol content; (2) preventing hypertension by maintaining a healthy diet and being physically active, or effectively controlling blood pressure with antihypertensive drugs if hypertension does develop; (3) effectively controlling blood glucose with insulin treatment or other drugs if diabetes develops; and (4) avoiding cigarette smoking.

Several types of drugs that lower plasma lipids and cholesterol have proved to be valuable in preventing atherosclerosis. Most of the cholesterol formed in the liver is converted into bile acids and secreted in this form into the duodenum; then, more than 90 percent of these same bile acids is reabsorbed in the terminal ileum and used over and over again in the bile. Therefore, any agent that combines with the bile acids in the gastrointestinal tract and prevents their reabsorption into the circulation can decrease the total bile acid pool in the circulating blood. This causes far more of the liver cholesterol to be converted into new bile acids. Thus, simply eating *oat bran*, which binds bile acids and is a constituent of many breakfast cereals, increases the proportion of liver cholesterol that forms new bile acids rather than forming new LDLs and atherogenic plaques. *Resin agents* can also be used to bind bile acids in the gut and increase their fecal excretion, thereby reducing cholesterol synthesis by the liver.

Another group of drugs called *statins* competitively inhibits *hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase*, a rate-limiting enzyme in the synthesis of cholesterol. This inhibition decreases cholesterol synthesis and increases LDL receptors in the liver, usually causing a 25 to 50 percent reduction in plasma levels of LDLs. The statins may also have other beneficial effects that help prevent atherosclerosis, such as attenuating vascular inflammation. These drugs are now widely used to treat patients who have increased plasma cholesterol levels.

In general, studies show that for each 1 mg/dl decrease in LDL cholesterol in the plasma, there is about a 2 percent decrease in mortality from atherosclerotic heart disease. Therefore, appropriate preventive measures are valuable in decreasing heart attacks.

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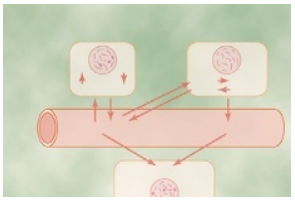
Protein Metabolism



About three quarters of the body solids are proteins. These include structural proteins, enzymes, nucleoproteins, proteins that transport oxygen, proteins of the muscle that cause muscle contraction, and many other types that perform specific intracellular and extracellular functions throughout the body.

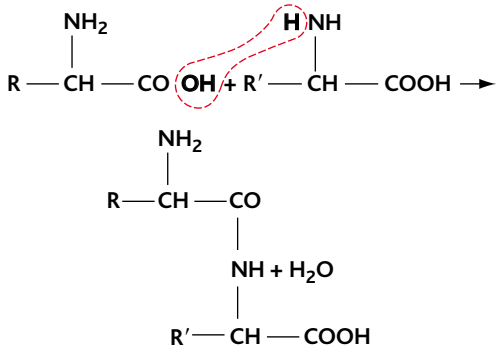
The basic chemical properties that explain proteins' diverse functions are so extensive that they constitute a major portion of the entire discipline of biochemistry. For this reason, the current discussion is confined to a few specific aspects of protein metabolism that are important as background for other discussions in this text.

Basic Properties

Amino Acids

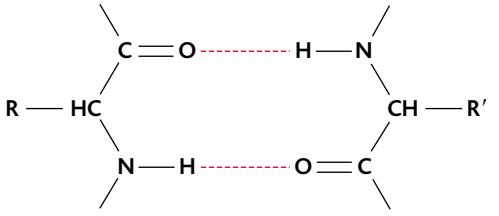
The principal constituents of proteins are amino acids, 20 of which are present in the body proteins in significant quantities. Figure 69-1 shows the chemical formulas of these 20 amino acids, demonstrating that they all have two features in common: each amino acid has an acidic group (—COOH) and a nitrogen atom attached to the molecule, usually represented by the amino group (—NH_2).

Peptide Linkages and Peptide Chains. The amino acids of proteins are aggregated into long chains by means of *peptide linkages*. The chemical nature of this linkage is demonstrated by the following reaction:



Note in this reaction that the nitrogen of the amino radical of one amino acid bonds with the carbon of the carboxyl radical of the other amino acid. A hydrogen ion is released from the amino radical, and a hydroxyl ion is released from the carboxyl radical; these two combine to form a molecule of water. After the peptide linkage has been formed, an amino radical and a carboxyl radical are still at opposite ends of the new, longer molecule. Each of these radicals is capable of combining with additional amino acids to form a *peptide chain*. Some complicated protein molecules have many thousand amino acids combined by peptide linkages, and even the smallest protein molecule usually has more than 20 amino acids combined by peptide linkages. The average is about 400 amino acids.

Other Linkages in Protein Molecules. Some protein molecules are composed of several peptide chains rather than a single chain, and these chains are bound to one another by other linkages, often by *hydrogen bonding* between the CO and NH radicals of the peptides, as follows:



Many peptide chains are coiled or folded, and the successive coils or folds are held in a tight spiral or in other shapes by similar hydrogen bonding and other forces.

Transport and Storage of Amino Acids

Blood Amino Acids

The normal concentration of amino acids in the blood is between 35 and 65 mg/dl. This is an average of about 2 mg/dl for each of the 20 amino acids, although some are present in far greater amounts than others. Because the amino acids are relatively strong acids, they exist in the blood principally in the ionized state, resulting from the removal of one hydrogen atom from the NH_2 radical. They actually account for 2 to 3 milliequivalents of the negative ions in the blood. The precise distribution of the different amino acids in the blood depends to some extent on the types of proteins eaten, but the concentrations of at least some individual amino acids are regulated by selective synthesis in the different cells.

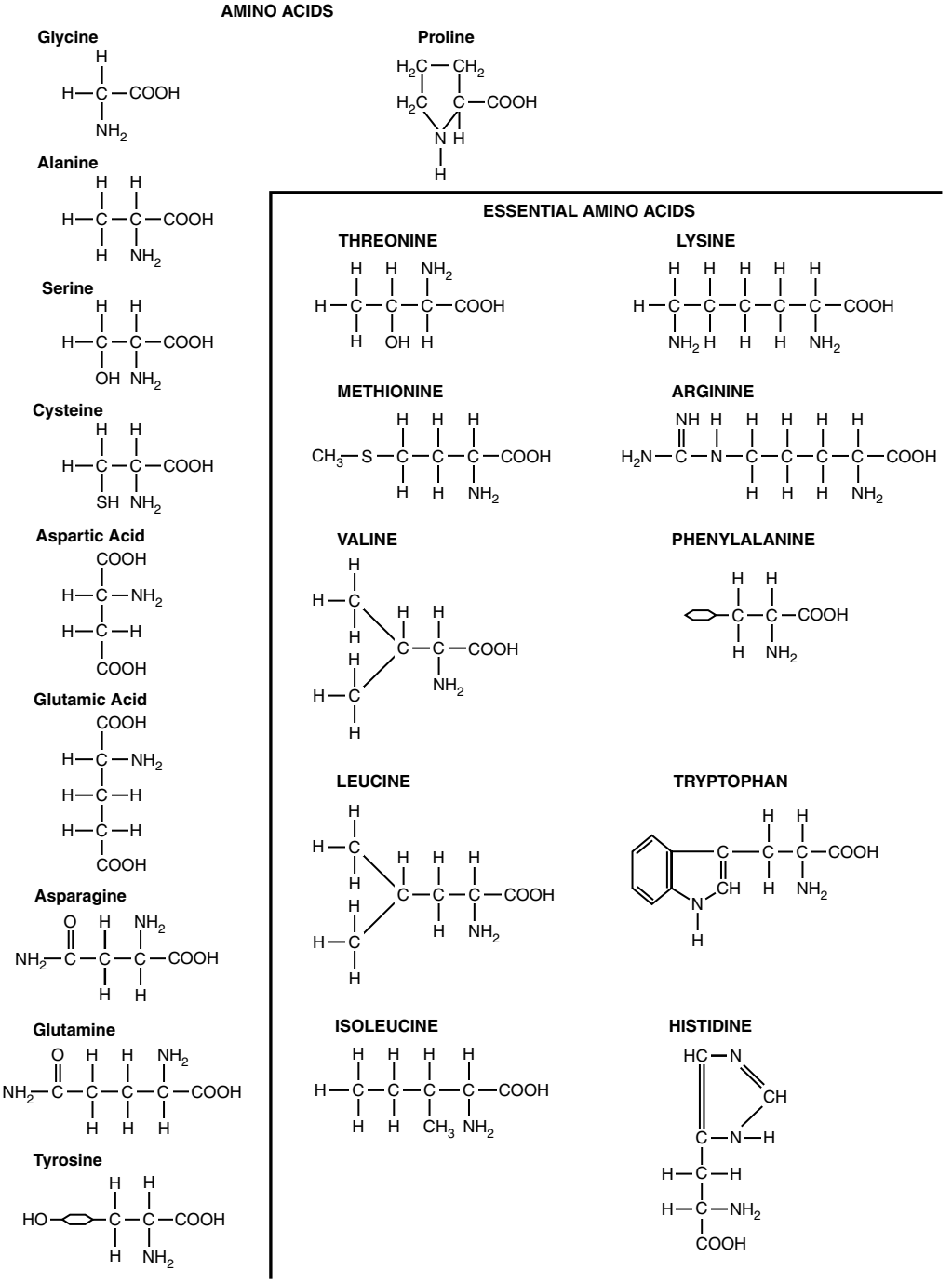


Figure 69-1 Amino acids. The 10 *essential* amino acids cannot be synthesized in sufficient quantities in the body; these essential amino acids must be obtained, already formed, from food.

Fate of Amino Acids Absorbed from the Gastrointestinal Tract. The products of protein digestion and absorption in the gastrointestinal tract are almost entirely amino acids; only rarely are polypeptides or whole protein molecules absorbed from the digestive tract into the blood. Soon after a meal, the amino acid concentration in a person's blood rises, but the increase is usually only a few milligrams per deciliter, for two reasons: First, protein digestion and absorption are usually extended over 2 to 3 hours, which allows only small quantities of amino acids to be absorbed at a time. Second, after entering the blood, the excess amino acids are absorbed within 5 to 10 minutes by cells throughout the body, especially by the liver. Therefore, almost never do large concentrations of amino acids accumulate in the blood and tissue fluids. Nevertheless, the turnover rate of the amino acids is so rapid that many grams of proteins can be carried from one part of the body to another in the form of amino acids each hour.

Active Transport of Amino Acids into the Cells. The molecules of all the amino acids are much too large to diffuse readily through the pores of the cell membranes. Therefore, significant quantities of amino acids can move either inward or outward through the membranes only by facilitated transport or active transport using carrier mechanisms. The nature of some of the carrier mechanisms is still poorly understood, but a few are discussed in Chapter 4.

Renal Threshold for Amino Acids. In the kidneys, the different amino acids can be *actively reabsorbed* through the proximal tubular epithelium, which removes them from the glomerular filtrate and returns them to the blood if they should filter into the renal tubules through the glomerular membranes. However, as is true of other active transport mechanisms in the renal tubules, there is an upper limit to the rate at which each type of amino acid can be transported. For this reason, when the concentration of a particular type of amino acid becomes too high in the plasma and glomerular filtrate, the excess that cannot be actively reabsorbed is lost into the urine.

Storage of Amino Acids as Proteins in the Cells

Almost immediately after entry into tissue cells, amino acids combine with one another by peptide linkages, under the direction of the cell's messenger RNA and ribosomal system, to form cellular proteins. Therefore, the concentration of free amino acids inside the cells usually remains low. Thus, storage of large quantities of free amino acids does not occur in the cells; instead, they are stored mainly in the form of actual proteins. But many of these intracellular proteins can be rapidly decomposed again into amino acids under the influence of intracellular lysosomal digestive enzymes; these amino acids can then be transported back out of the cell into the blood. Special exceptions to this reversal process are the proteins in the chromosomes of the nucleus and the structural proteins such as collagen and muscle contractile proteins; these proteins do not participate significantly in this reverse digestion and transport back out of the cells.

Some tissues of the body participate in the storage of amino acids to a greater extent than others. For instance, the liver, which is a large organ and has special systems for processing amino acids, can store large quantities of rapidly exchangeable proteins; this is also true to a lesser extent of the kidneys and the intestinal mucosa.

Release of Amino Acids from the Cells as a Means of Regulating Plasma Amino Acid Concentration. Whenever plasma amino acid concentrations fall below normal levels, the required amino acids are transported out of the cells to replenish their supply in the plasma. In this way, the plasma concentration of each type of amino acid is maintained at a reasonably constant value. Later, it is noted that some of the hormones secreted by the endocrine glands are able to alter the balance between tissue proteins and circulating amino acids. For instance, growth hormone and insulin increase the formation of tissue proteins, whereas adrenocortical glucocorticoid hormones increase the concentration of plasma amino acids.

Reversible Equilibrium Between the Proteins in Different Parts of the Body. Because cellular proteins in the liver (and, to a much less extent, in other tissues) can be synthesized rapidly from plasma amino acids, and because many of these proteins can be degraded and returned to the plasma almost as rapidly, there is constant interchange and equilibrium between the plasma amino acids and labile proteins in virtually all cells of the body. For instance, if any particular tissue requires proteins, it can synthesize new proteins from the amino acids of the blood; in turn, the blood amino acids are replenished by degradation of proteins from other cells of the body, especially from the liver cells. These effects are particularly noticeable in relation to protein synthesis in cancer cells. Cancer cells are often prolific users of amino acids; therefore, the proteins of the other cells can become markedly depleted.

Upper Limit for the Storage of Proteins. Each particular type of cell has an upper limit with regard to the amount of proteins it can store. After all the cells have reached their limits, the excess amino acids still in the circulation are degraded into other products and used for energy, as discussed subsequently, or they are converted to fat or glycogen and stored in these forms.

Functional Roles of the Plasma Proteins

The major types of protein present in the plasma are *albumin, globulin*, and *fibrinogen*.

A major function of *albumin* is to provide *colloid osmotic pressure* in the plasma, which prevents plasma loss from the capillaries, as discussed in Chapter 16.

The *globulins* perform a number of *enzymatic functions* in the plasma, but equally important, they are principally responsible for the body's both natural and acquired *immunity* against invading organisms, discussed in Chapter 34.

Fibrinogen polymerizes into long fibrin threads during blood coagulation, thereby *forming blood clots* that help repair leaks in the circulatory system, discussed in Chapter 36.

Formation of the Plasma Proteins. Essentially all the albumin and fibrinogen of the plasma proteins, as well as 50 to 80 percent of the globulins, are formed in the liver. The remaining globulins are formed almost entirely in the lymphoid tissues. They are mainly the gamma globulins that constitute the antibodies used in the immune system.

The rate of plasma protein formation by the liver can be extremely high, as much as 30 g/day. Certain disease conditions cause rapid loss of plasma proteins; severe burns that denude large surface areas of the skin can cause the loss of several liters of plasma through the denuded areas each day. The rapid production of plasma proteins by the liver is valuable in preventing death in such states. Occasionally, a person with severe renal disease loses as much as 20 grams of plasma protein in the urine each day for months, and it is continually replaced mainly by liver production of the required proteins.

In *cirrhosis of the liver*, large amounts of fibrous tissue develop among the liver parenchymal cells, causing a reduction in their ability to synthesize plasma proteins. As discussed in Chapter 25, this leads to decreased plasma colloid osmotic pressure, which causes generalized edema.

Plasma Proteins as a Source of Amino Acids for the Tissues. When the tissues become depleted of proteins, the plasma proteins can act as a source of rapid replacement. Indeed, whole plasma proteins can be imbibed in toto by tissue macrophages through the process of pinocytosis; once in these cells, they are split into amino acids that are transported back into the blood and used throughout the body to build cellular proteins wherever needed. In this way, the plasma proteins function as a labile protein storage medium and represent a readily available source of amino acids whenever a particular tissue requires them.

Reversible Equilibrium Between the Plasma Proteins and the Tissue Proteins. There is a constant state of equilibrium, as shown in Figure 69-2, among the plasma proteins, the amino acids of the plasma, and the tissue proteins. It has been estimated from radioactive tracer studies that normally about

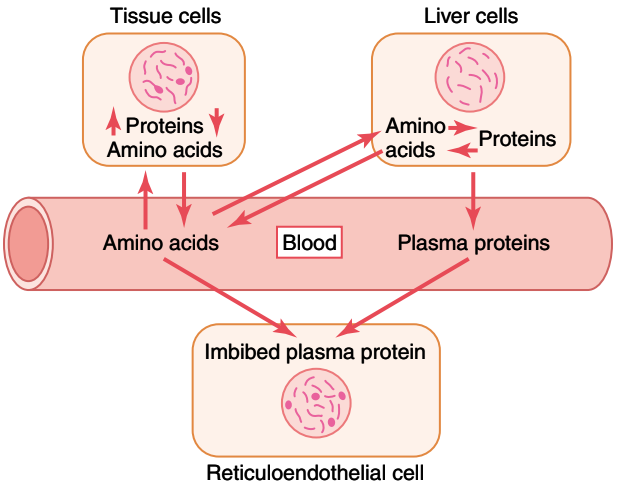


Figure 69-2 Reversible equilibrium among the tissue proteins, plasma proteins, and plasma amino acids.

400 grams of body protein are synthesized and degraded each day as part of the continual state of flux of amino acids. This demonstrates the general principle of reversible exchange of amino acids among the different proteins of the body. Even during starvation or severe debilitating diseases, the ratio of total tissue proteins to total plasma proteins in the body remains relatively constant at about 33:1.

Because of this reversible equilibrium between plasma proteins and the other proteins of the body, one of the most effective therapies for severe, acute whole-body protein deficiency is intravenous transfusion of plasma protein. Within a few days, or sometimes within hours, the amino acids of the administered protein are distributed throughout the cells of the body to form new proteins as needed.

Essential and Nonessential Amino Acids

Ten of the amino acids normally present in animal proteins can be synthesized in the cells, whereas the other 10 either cannot be synthesized or are synthesized in quantities too small to supply the body's needs. This second group of amino acids that cannot be synthesized is called the *essential amino acids*. Use of the word "essential" does not mean that the other 10 "nonessential" amino acids are not required for the formation of proteins, but only that the others are *not essential in the diet* because they can be synthesized in the body.

Synthesis of the nonessential amino acids depends mainly on the formation of appropriate α-keto acids, which are the precursors of the respective amino acids. For instance, *pyruvic acid*, which is formed in large quantities during the glycolytic breakdown of glucose, is the keto acid precursor of the amino acid *alanine*. Then, by the process of *transamination*, an amino radical is transferred to the α-keto acid, and the keto oxygen is transferred to the donor of the amino radical. This reaction is shown in Figure 69-3. Note in this figure that the amino radical is transferred to the pyruvic acid from another chemical that is closely allied to the amino acids—*glutamine*. Glutamine is present in the tissues in large quantities, and one of its principal functions is to serve as an amino radical storehouse. In addition, amino radicals can be transferred from *asparagine, glutamic acid*, and *aspartic acid*.

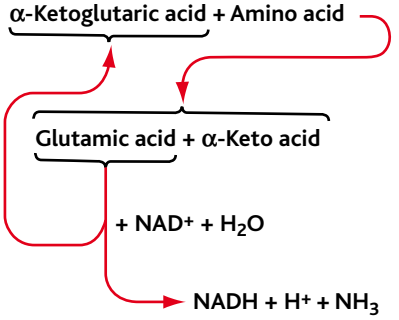
Transamination is promoted by several enzymes, among which are the *aminotransferases*, which are derivatives of pyridoxine, one of the B vitamins (B_6). Without this vitamin, the amino acids are synthesized only poorly and protein formation cannot proceed normally.

Use of Proteins for Energy

Once the cells are filled to their limits with stored protein, any additional amino acids in the body fluids are degraded and used for energy or are stored mainly as fat or secondarily as glycogen. This degradation occurs almost entirely in the liver, and it begins with *deamination*, which is explained in the following section.

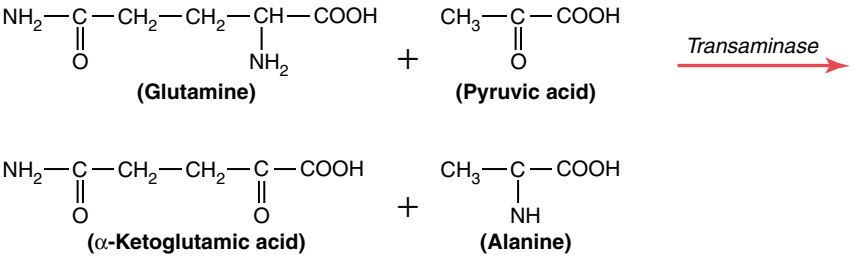
Deamination. Deamination means removal of the amino groups from the amino acids. This occurs mainly by *transamination*, which means transfer of the amino group to some acceptor substance, which is the reverse of the transamination explained earlier in relation to the synthesis of amino acids.

The greatest amount of deamination occurs by the following transamination schema:



Note from this schema that the amino group from the amino acid is transferred to α-ketoglutaric acid, which then becomes glutamic acid. The glutamic acid can then transfer the amino group to still other substances or release it in the form of ammonia (NH_3). In the process of losing the amino group, the glutamic acid once again becomes α-ketoglutaric acid, so the cycle can be repeated again and again. To initiate this process, the excess amino acids in the cells, especially in the liver, induce the activation of large quantities of *aminotransferases*, the enzymes responsible for initiating most deamination.

Figure 69-3 Synthesis of alanine from pyruvic acid by transamination.

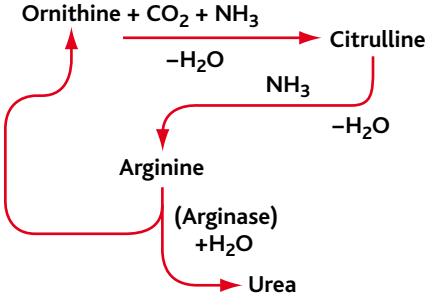


Urea Formation by the Liver. The ammonia released during deamination of amino acids is removed from the blood almost entirely by conversion into urea; two molecules of ammonia and one molecule of carbon dioxide combine in accordance with the following net reaction:

$$2\,NH_3 + CO_2 \rightarrow H_2N{-}\underset{\underset{O}{\|}}{C}{-}NH_2 + H_2O$$

Essentially all urea formed in the human body is synthesized in the liver. In the absence of the liver or in serious liver disease, ammonia accumulates in the blood. This is extremely toxic, especially to the brain, often leading to a state called *hepatic coma*.

The stages in the formation of urea are essentially the following:



After its formation, the urea diffuses from the liver cells into the body fluids and is excreted by the kidneys.

Oxidation of Deaminated Amino Acids. Once amino acids have been deaminated, the resulting keto acids can, in most instances, be oxidized to release energy for metabolic purposes. This usually involves two successive processes: (1) The keto acid is changed into an appropriate chemical substance that can enter the citric acid cycle, and (2) this substance is degraded by the cycle and used for energy in the same manner that acetyl coenzyme A (acetyl-CoA) derived from carbohydrate and lipid metabolism is used, as explained in Chapters 67 and 68. In general, the amount of adenosine triphosphate (ATP) formed for each gram of protein that is oxidized is slightly less than that formed for each gram of glucose oxidized.

Gluconeogenesis and Ketogenesis. Certain deaminated amino acids are similar to the substrates normally used by the cells, mainly the liver cells, to synthesize glucose or fatty acids. For instance, deaminated alanine is pyruvic acid. This can be converted into either glucose or glycogen. Alternatively, it can be converted into acetyl-CoA, which can then be polymerized into fatty acids. Also, two molecules of acetyl-CoA can condense to form acetoacetic acid, which is one of the ketone bodies, as explained in Chapter 68.

The conversion of amino acids into glucose or glycogen is called *gluconeogenesis*, and the conversion of amino acids into keto acids or fatty acids is called *ketogenesis*. Of the 20 deaminated amino acids, 18 have chemical structures that allow them to be converted into glucose, and 19 of them can be converted into fatty acids.

Obligatory Degradation of Proteins

When a person eats no proteins, a certain proportion of body proteins is degraded into amino acids and then deaminated and oxidized. This involves 20 to 30 grams of protein each day, which is called the *obligatory loss* of proteins. Therefore, to prevent net loss of protein from the body, one must ingest a minimum of 20 to 30 grams of protein each day; to be on the safe side, a minimum of 60 to 75 grams is usually recommended.

The ratios of the different amino acids in the dietary protein must be about the same as the ratios in the body tissues if the entire dietary protein is to be fully usable to form new proteins in the tissues. If one particular type of essential amino acid is low in concentration, the others become unusable because cells synthesize either whole proteins or none at all, as explained in Chapter 3 in relation to protein synthesis. The unusable amino acids are deaminated and oxidized. A protein that has a ratio of amino acids different from that of the average body protein is called a *partial protein* or *incomplete protein*, and such a protein is less valuable for nutrition than is a *complete protein*.

Effect of Starvation on Protein Degradation. Except for the 20 to 30 grams of obligatory protein degradation each day, the body uses almost entirely carbohydrates or fats for energy, as long as they are available. However, after several weeks of starvation, when the quantities of stored carbohydrates and fats begin to run out, the amino acids of the blood are rapidly deaminated and oxidized for energy. From this point on, the proteins of the tissues degrade rapidly—as much as 125 grams daily—and, as a result, cellular functions deteriorate precipitously. Because carbohydrate and fat utilization for energy normally occurs in preference to protein utilization, carbohydrates and fats are called *protein sparers*.

Hormonal Regulation of Protein Metabolism

Growth Hormone Increases the Synthesis of Cellular Proteins. Growth hormone causes the tissue proteins to increase. The precise mechanism by which this occurs is not known, but it is believed to result mainly from increased transport of amino acids through the cell membranes, acceleration of the DNA and RNA transcription and translation processes for protein synthesis, and decreased oxidation of tissue proteins.

Insulin Is Necessary for Protein Synthesis. Total lack of insulin reduces protein synthesis to almost zero. Insulin accelerates the transport of some amino acids into cells, which could be the stimulus to protein synthesis. Also, insulin reduces protein degradation and increases the availability of glucose to the cells, so the need for amino acids for energy is correspondingly reduced.

Glucocorticoids Increase Breakdown of Most Tissue Proteins. The glucocorticoids secreted by the adrenal cortex *decrease* the quantity of protein in *most* tissues while increasing the amino acid concentration in the plasma, as well as increasing *both liver proteins and plasma proteins*. It is believed that the glucocorticoids act by increasing the rate of breakdown of extrahepatic proteins, thereby making increased quantities of amino acids available in the body fluids. This allows the liver to synthesize increased quantities of hepatic cellular proteins and plasma proteins.

Testosterone Increases Protein Deposition in Tissues. Testosterone, the male sex hormone, causes increased deposition of protein in tissues throughout the body, especially the contractile proteins of the muscles (30 to 50 percent increase). The mechanism of this effect is unknown, but it is definitely different from the effect of growth hormone, in the following way: Growth hormone causes tissues to continue

growing almost indefinitely, whereas testosterone causes the muscles and, to a much lesser extent, some other protein tissues to enlarge for only several months. Once the muscles and other protein tissues have reached a maximum, despite continued administration of testosterone, further protein deposition ceases.

Estrogen. Estrogen, the principal female sex hormone, also causes some deposition of protein, but its effect is relatively insignificant in comparison with that of testosterone.

Thyroxine. Thyroxine increases the rate of metabolism of all cells and, as a result, indirectly affects protein metabolism. If insufficient carbohydrates and fats are available for energy, thyroxine causes rapid degradation of proteins and uses them for energy. Conversely, if adequate quantities of carbohydrates and fats are available and excess amino acids are also available in the extracellular fluid, thyroxine can actually increase the rate of protein synthesis. In growing animals or human beings, deficiency of thyroxine causes growth to be greatly inhibited because of lack of protein synthesis. In essence, it is believed that thyroxine has little specific effect on protein metabolism but does have an important general effect by increasing the rates of both normal anabolic and normal catabolic protein reactions.

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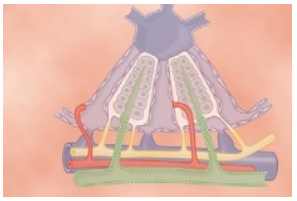
CHAPTER 70

The Liver as an Organ



Although the liver is a discrete organ, it performs many different functions that interrelate with one another. This becomes especially evident in abnormalities of the liver because many of its functions are disturbed simultaneously. This chapter summarizes 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 percent of the total body weight, or about 1.5 kilograms (3.3 pounds) 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 cell types: (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.

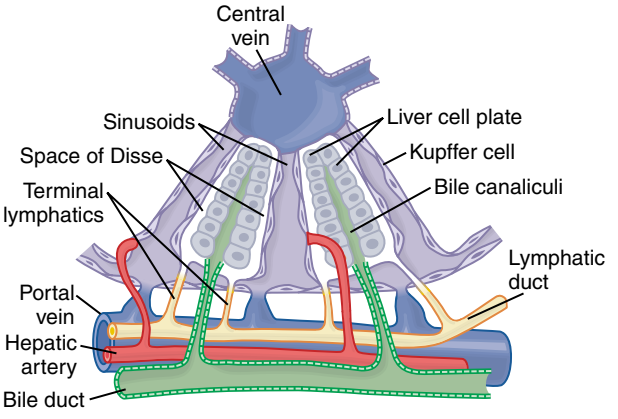


Figure 70-1 Basic structure of a liver lobule, showing the liver cellular plates, the blood vessels, the bile-collecting system, and the lymph flow system composed of the spaces of Disse and the interlobular lymphatics. (Modified from Guyton AC, Taylor AE, Granger HJ: Circulatory Physiology. Vol 2: Dynamics 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 percent 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 chronic alcoholism or from excess fat accumulation in the liver and subsequent liver inflammation, a condition called *nonalcoholic steatohepatitis, or NASH*. A less severe form of fat accumulation and inflammation of the liver, *nonalcoholic fatty liver disease* (NAFLD), is the most common cause of liver disease in many industrialized countries, including the United States, and is usually associated with obesity and type II diabetes.

Cirrhosis 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 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. 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 high 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 percent 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 percent 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 important in 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 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 percent 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 in 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. Then 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 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.

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 percent 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 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 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*, also called *unconjugated bilirubin*, which is gradually released from the macrophages into the plasma. This form of bilirubin immediately combines strongly with plasma albumin and is transported in this combination throughout the blood and interstitial fluids.

Within hours, the unconjugated 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.

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

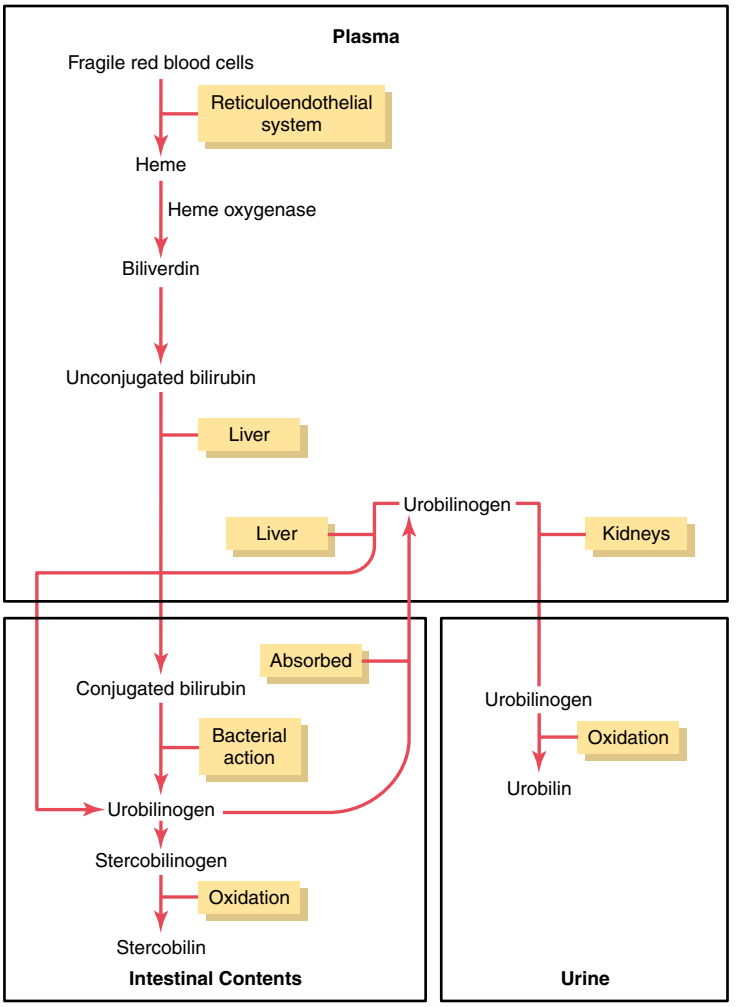


Figure 70-2 Bilirubin formation and excretion.

this is re-excreted by the liver back into the gut, but about 5 percent 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 and deep tissues. The usual cause of jaundice is large quantities of bilirubin in the extracellular fluids, either unconjugated or conjugated bilirubin. The normal plasma concentration of bilirubin, which is almost entirely the unconjugated 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 unconjugated 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 unconjugated type.

Diagnostic Differences Between Hemolytic and Obstructive Jaundice. Chemical laboratory tests can be used to differentiate between unconjugated and conjugated bilirubin in the plasma. In hemolytic jaundice, almost all the bilirubin

is in the "unconjugated" 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 unconjugated and conjugated bilirubin is that the kidneys can excrete small quantities of the highly soluble conjugated bilirubin but not the albumin-bound unconjugated 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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