The alimentary tract provides the body with a continual supply of water, electrolytes, vitamins, and nutrients. To achieve this requires (1) movement of food through the alimentary tract; (2) secretion of digestive juices and digestion of the food; (3) absorption of water, various electrolytes, vitamins, and digestive products; (4) circulation of blood through the gastrointestinal organs to carry away the absorbed substances; and (5) control of all these functions by local, nervous, and hormonal systems.

Figure 62-1 shows the entire alimentary tract. Each part is adapted to its specific functions: some to simple passage of food, such as the esophagus; others to temporary storage of food, such as the stomach; and others to digestion and absorption, such as the small intestine. In this chapter, we discuss the basic principles of function in the entire alimentary tract; in the following chapters, we discuss the specific functions of different segments of the tract.

**General Principles of Gastrointestinal Motility**

**Physiologic Anatomy of the Gastrointestinal Wall**

Figure 62-2 shows a typical cross section of the intestinal wall, including the following layers from outer surface inward: (1) the serosa, (2) a longitudinal smooth muscle layer, (3) a circular smooth muscle layer, (4) the submucosa, and (5) the mucosa. In addition, sparse bundles of smooth muscle fibers, the mucosal muscle, lie in the deeper layers of the mucosa. The motor functions of the gut are performed by the different layers of smooth muscle.

The general characteristics of smooth muscle and its function are discussed in Chapter 8, which should be reviewed as a background for the following sections of this chapter. The specific characteristics of smooth muscle in the gut are the following.

**Gastrointestinal Smooth Muscle Functions as a Syncytium.** The individual smooth muscle fibers in the gastrointestinal tract are 200 to 500 micrometers in length and 2 to 10 micrometers in diameter, and they are arranged in bundles of as many as 1000 parallel fibers. In the longitudinal muscle layer, the bundles extend longitudinally down the intestinal tract; in the circular muscle layer, they extend around the gut.

Within each bundle, the muscle fibers are electrically connected with one another through large numbers of gap junctions that allow low-resistance movement of ions from one muscle cell to the next. Therefore, electrical signals that initiate muscle contractions can travel readily from one fiber to the next within each bundle but more rapidly along the length of the bundle than sideways.
Each bundle of smooth muscle fibers is partly separated from the next by loose connective tissue, but the muscle bundles fuse with one another at many points, so in reality each muscle layer represents a branching latticework of smooth muscle bundles. Therefore, each muscle layer functions as a *syncytium*; that is, when an action potential is elicited anywhere within the muscle mass, it generally travels in all directions in the muscle. The distance that it travels depends on the excitability of the muscle; sometimes it stops after only a few millimeters and at other times it travels many centimeters or even the entire length and breadth of the intestinal tract.

Also, a few connections exist between the longitudinal and circular muscle layers, so excitation of one of these layers often excites the other as well.

**Electrical Activity of Gastrointestinal Smooth Muscle**

The smooth muscle of the gastrointestinal tract is excited by almost continual slow, intrinsic electrical activity along the membranes of the muscle fibers. This activity has two basic types of electrical waves: (1) *slow waves* and (2) *spikes*, both of which are shown in Figure 62-3. In addition, the voltage of the resting membrane potential of the gastrointestinal smooth muscle can be made to change to different levels, and this, too, can have important effects in controlling motor activity of the gastrointestinal tract.

**Slow Waves.** Most gastrointestinal contractions occur rhythmically, and this rhythm is determined mainly by the frequency of so-called “slow waves” of smooth muscle membrane potential. These waves, shown in Figure 62-3, are not action potentials. Instead, they are slow, undulating changes in the resting membrane potential. Their intensity usually varies between 5 and 15 millivolts, and their frequency ranges in different parts of the human gastrointestinal tract from 3 to 12 per minute: about 3 in the body of the stomach, as much as 12 in the duodenum, and about 8 or 9 in the terminal ileum. Therefore, the rhythm of contraction of the body of the stomach is usually about 3 per minute, of the duodenum about 12 per minute, and of the ileum 8 to 9 per minute.

The precise cause of the slow waves is not completely understood, although they appear to be caused by complex interactions among the smooth muscle cells and specialized cells, called the *interstitial cells of Cajal*, that are believed to act as electrical pacemakers for smooth muscle cells. These interstitial cells form a network with each other and are interposed between the smooth muscle layers, with synaptic-like contacts to smooth muscle cells. The interstitial cells of Cajal undergo cyclic changes in membrane potential due to unique ion channels that periodically open and produce inward (pacemaker) currents that may generate slow wave activity.

The slow waves usually do not by themselves cause muscle contraction in most parts of the gastrointestinal tract, except perhaps in the stomach. Instead, they mainly excite the appearance of intermittent spike potentials, and the spike potentials in turn actually excite the muscle contraction.

**Spike Potentials.** The spike potentials are true action potentials. They occur automatically when the resting membrane potential of the gastrointestinal smooth muscle becomes more positive than about −40 millivolts (the normal resting membrane potential in the smooth muscle fibers of the gut is between −50 and −60 millivolts). Note in Figure 62-3 that each time the peaks of the slow waves temporarily become more positive than −40 millivolts, spike potentials appear on these peaks. The higher the slow wave potential rises, the greater the frequency of the spike potentials, usually ranging between 1 and 10 spikes per second. The spike potentials last 10 to 40 times as long in gastrointestinal muscle as the action potentials in large nerve fibers, each gastrointestinal spike lasting as long as 10 to 20 milliseconds.

Another important difference between the action potentials of the gastrointestinal smooth muscle and
those of nerve fibers is the manner in which they are generated. In nerve fibers, the action potentials are caused almost entirely by rapid entry of sodium ions through sodium channels to the interior of the fibers. In gastrointestinal smooth muscle fibers, the channels responsible for the action potentials are somewhat different; they allow especially large numbers of calcium ions to enter along with smaller numbers of sodium ions and therefore are called calcium-sodium channels. These channels are much slower to open and close than are the rapid sodium channels of large nerve fibers. The slowness of opening and closing of the calcium-sodium channels accounts for the long duration of the action potentials. Also, the movement of large amounts of calcium ions to the interior of the muscle fiber during the action potential plays a special role in causing the intestinal muscle fibers to contract, as we discuss shortly.

**Changes in Voltage of the Resting Membrane Potential.** In addition to the slow waves and spike potentials, the baseline voltage level of the smooth muscle resting membrane potential can also change. Under normal conditions, the resting membrane potential averages about −56 millivolts, but multiple factors can change this level. When the potential becomes less negative, which is called depolarization of the membrane, the muscle fibers become more excitable. When the potential becomes more negative, which is called hyperpolarization, the fibers become less excitable.

Factors that depolarize the membrane—that is, make it more excitable—are (1) stretching of the muscle, (2) stimulation by acetylcholine released from the endings of parasympathetic nerves, and (3) stimulation by several specific gastrointestinal hormones.

Important factors that make the membrane potential more negative—that is, hyperpolarize the membrane and make the muscle fibers less excitable—are (1) the effect of norepinephrine or epinephrine on the fiber membrane and (2) stimulation of the sympathetic nerves that secrete mainly norepinephrine at their endings.

**Calcium Ions and Muscle Contraction.** Smooth muscle contraction occurs in response to entry of calcium ions into the muscle fiber. As explained in Chapter 8, calcium ions, acting through a calmodulin control mechanism, activate the myosin filaments in the fiber, causing attractive forces to develop between the myosin filaments and the actin filaments, thereby causing the muscle to contract.

The slow waves do not cause calcium ions to enter the smooth muscle fiber (only sodium ions). Therefore, the slow waves by themselves usually cause no muscle contraction. Instead, it is during the spike potentials, generated at the peaks of the slow waves, that significant quantities of calcium ions do enter the fibers and cause most of the contraction.

**Tonic Contraction of Some Gastrointestinal Smooth Muscle.** Some smooth muscle of the gastrointestinal tract exhibits tonic contraction, as well as, or instead of, rhythmical contractions. Tonic contraction is continuous, not associated with the basic electrical rhythm of the slow waves but often lasting several minutes or even hours. The tonic contraction often increases or decreases in intensity but continues.

Tonic contraction is sometimes caused by continuous repetitive spike potentials—the greater the frequency, the greater the degree of contraction. At other times, tonic contraction is caused by hormones or other factors that bring about continuous partial depolarization of the smooth muscle membrane without causing action potentials. A third cause of tonic contraction is continuous entry of calcium ions into the interior of the cell brought about in ways not associated with changes in membrane potential. The details of these mechanisms are still unclear.

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**Neural Control of Gastrointestinal Function—Enteric Nervous System**

The gastrointestinal tract has a nervous system all its own called the enteric nervous system. It lies entirely in the wall of the gut, beginning in the esophagus and extending all the way to the anus. The number of neurons in this enteric system is about 100 million, almost exactly equal to the number in the entire spinal cord. This highly developed enteric nervous system is especially important in controlling gastrointestinal movements and secretion.

The enteric nervous system is composed mainly of two plexuses, shown in Figure 62-4: (1) an outer plexus lying between the longitudinal and circular muscle layers, called the myenteric plexus or Auerbach’s plexus, and (2) an inner plexus, called the submucosal plexus or Meissner’s plexus, that lies in the submucosa. The nervous connections within and between these two plexuses are also shown in Figure 62-4.

The myenteric plexus controls mainly the gastrointestinal movements, and the submucosal plexus controls mainly gastrointestinal secretion and local blood flow.

Note especially in Figure 62-4 the extrinsic sympathetic and parasympathetic fibers that connect to both the myenteric and submucosal plexuses. Although the enteric nervous system can function independently of these extrinsic nerves, stimulation by the parasympathetic and sympathetic systems can greatly enhance or inhibit gastrointestinal functions, as we discuss later.

Also shown in Figure 62-4 are sensory nerve endings that originate in the gastrointestinal epithelium or gut wall and send afferent fibers to both plexuses of the enteric system, as well as (1) to the prevertebral ganglia of the sympathetic nervous system, (2) to the spinal cord, and (3) in the vagus nerves all the way to the brain stem. These sensory nerves can elicit local reflexes within the gut wall itself and still other reflexes that are relayed to the gut from either the prevertebral ganglia or the basal regions of the brain.
Differences Between the Myenteric and Submucosal Plexuses

The myenteric plexus consists mostly of a linear chain of many interconnecting neurons that extends the entire length of the gastrointestinal tract. A section of this chain is shown in Figure 62-4.

Because the myenteric plexus extends all the way along the intestinal wall and because it lies between the longitudinal and circular layers of intestinal smooth muscle, it is concerned mainly with controlling muscle activity along the length of the gut. When this plexus is stimulated, its principal effects are (1) increased tonic contraction, or “tone,” of the gut wall; (2) increased intensity of the rhythmical contractions; (3) slightly increased rate of the rhythm of contraction; and (4) increased velocity of conduction of excitatory waves along the gut wall, causing more rapid movement of the gut peristaltic waves.

The myenteric plexus should not be considered entirely excitatory because some of its neurons are inhibitory; their fiber endings secrete an inhibitory transmitter, possibly vasoactive intestinal polypeptide or some other inhibitory peptide. The resulting inhibitory signals are especially useful for inhibiting some of the intestinal sphincter muscles that impede movement of food along successive segments of the gastrointestinal tract, such as the pyloric sphincter, which controls emptying of the stomach into the duodenum, and the sphincter of the ileocecal valve, which controls emptying from the small intestine into the cecum.

The submucosal plexus, in contrast to the myenteric plexus, is mainly concerned with controlling function within the inner wall of each minute segment of the intestine. For instance, many sensory signals originate from the gastrointestinal epithelium and are then integrated in the submucosal plexus to help control local intestinal secretion, local absorption, and local contraction of the submucosal muscle that causes various degrees of infolding of the gastrointestinal mucosa.

Types of Neurotransmitters Secreted by Enteric Neurons

In an attempt to understand better the multiple functions of the gastrointestinal enteric nervous system, research workers the world over have identified a dozen or more different neurotransmitter substances that are released by the nerve endings of different types of enteric neurons. Two of them with which we are already familiar are (1) acetylcholine and (2) norepinephrine. Others are (3) adenosine triphosphate, (4) serotonin, (5) dopamine, (6) cholecystokinin, (7) substance P, (8) vasoactive intestinal polypeptide, (9) somatostatin, (10) leu-enkephalin, (11) met-enkephalin, and (12) bombesin. The specific functions of many of these are not known well enough to justify discussion here, other than to point out the following.

Acetylcholine most often excites gastrointestinal activity. Norepinephrine almost always inhibits gastrointestinal activity. This is also true of epinephrine, which reaches the gastrointestinal tract mainly by way of the blood after it is secreted by the adrenal medullae into the circulation. The other aforementioned transmitter substances are a mixture of excitatory and inhibitory agents, some of which we discuss in the following chapter.

Autonomic Control of the Gastrointestinal Tract

Parasympathetic Stimulation Increases Activity of the Enteric Nervous System. The parasympathetic supply to the gut is divided into cranial and sacral divisions, which were discussed in Chapter 60.

Except for a few parasympathetic fibers to the mouth and pharyngeal regions of the alimentary tract, the cranial parasympathetic nerve fibers are almost entirely in the...
vagus nerves. These fibers provide extensive innervation to the esophagus, stomach, and pancreas and somewhat less to the intestines down through the first half of the large intestine.

The sacral parasympathetics originate in the second, third, and fourth sacral segments of the spinal cord and pass through the pelvic nerves to the distal half of the large intestine and all the way to the anus. The sigmoidal, rectal, and anal regions are considerably better supplied with parasympathetic fibers than are the other intestinal areas. These fibers function especially to execute the defecation reflexes, discussed in Chapter 63.

The postganglionic neurons of the gastrointestinal parasympathetic system are located mainly in the myenteric and submucosal plexuses. Stimulation of these parasympathetic nerves causes general increase in activity of the entire enteric nervous system. This in turn enhances activity of most gastrointestinal functions.

**Sympathetic Stimulation Usually Inhibits Gastrointestinal Tract Activity.** The sympathetic fibers to the gastrointestinal tract originate in the spinal cord between segments T5 and L2. Most of the preganglionic fibers that innervate the gut, after leaving the cord, enter the sympathetic chains that lie lateral to the spinal column, and many of these fibers then pass on through the chains to outlying ganglia such as to the celiac ganglion and various mesenteric ganglia. Most of the postganglionic sympathetic neuron bodies are in these ganglia, and postganglionic fibers then spread through postganglionic sympathetic nerves to all parts of the gut. The sympathetics innervate essentially all of the gastrointestinal tract, rather than being more extensive nearest the oral cavity and anus, as is true of the parasympathetics. The sympathetic nerve endings secrete mainly norepinephrine but also small amounts of epinephrine.

In general, stimulation of the sympathetic nervous system inhibits activity of the gastrointestinal tract, causing many effects opposite to those of the parasympathetic system. It exerts its effects in two ways: (1) to a slight extent by direct effect of secreted norepinephrine to inhibit intestinal tract smooth muscle (except the mucosal muscle, which it excites) and (2) to a major extent by an inhibitory effect of norepinephrine on the neurons of the entire enteric nervous system.

Strong stimulation of the sympathetic system can inhibit motor movements of the gut so greatly that this can literally block movement of food through the gastrointestinal tract.

**Afferent Sensory Nerve Fibers from the Gut**

Many afferent sensory nerve fibers innervate the gut. Some of them have their cell bodies in the enteric nervous system itself and some in the dorsal root ganglia of the spinal cord. These sensory nerves can be stimulated by (1) irritation of the gut mucosa, (2) excessive distention of the gut, or (3) presence of specific chemical substances in the gut. Signals transmitted through the fibers can then cause excitation or, under other conditions, inhibition of intestinal movements or intestinal secretion.

In addition, other sensory signals from the gut go all the way to multiple areas of the spinal cord and even the brain stem. For example, 80 percent of the nerve fibers in the vagus nerves are afferent rather than efferent. These afferent fibers transmit sensory signals from the gastrointestinal tract into the brain medulla, which in turn initiates vagal reflex signals that return to the gastrointestinal tract to control many of its functions.

**Gastrointestinal Reflexes**

The anatomical arrangement of the enteric nervous system and its connections with the sympathetic and parasympathetic systems support three types of gastrointestinal reflexes that are essential to gastrointestinal control. They are the following:

1. **Reflexes that are integrated entirely within the gut wall enteric nervous system.** These include reflexes that control much gastrointestinal secretion, peristalsis, mixing contractions, local inhibitory effects, and so forth.

2. **Reflexes from the gut to the prevertebral sympathetic ganglia and then back to the gastrointestinal tract.** These reflexes transmit signals long distances to other areas of the gastrointestinal tract, such as signals from the stomach to cause evacuation of the colon (the gastrocolic reflex), signals from the colon and small intestine to inhibit stomach motility and stomach secretion (the enterogastric reflexes), and reflexes from the colon to inhibit emptying of ileal contents into the colon (the colonoileal reflex).

3. **Reflexes from the gut to the spinal cord or brain stem and then back to the gastrointestinal tract.** These include especially (1) reflexes from the stomach and duodenum to the brain stem and back to the stomach—by way of the vagus nerves—to control gastric motor and secretory activity; (2) pain reflexes that cause general inhibition of the entire gastrointestinal tract; and (3) defecation reflexes that travel from the colon and rectum to the spinal cord and back again to produce the powerful colonic, rectal, and abdominal contractions required for defecation (the defecation reflexes).

**Hormonal Control of Gastrointestinal Motility**

The gastrointestinal hormones are released into the portal circulation and exert physiological actions on target cells with specific receptors for the hormone. The effects of the hormones persist even after all nervous connections between the site of release and the site of action have been severed. Table 62-1 outlines the actions of each gastrointestinal hormone, as well as the stimuli for secretion and sites at which secretion takes place.

In Chapter 64, we discuss the extreme importance of several hormones for controlling gastrointestinal secretion. Most of these same hormones also affect motility in some parts of the gastrointestinal tract. Although the
motility effects are usually less important than the secretory effects of the hormones, some of the more important of them are the following.

Gastrin is secreted by the “G” cells of the antrum of the stomach in response to stimuli associated with ingestion of a meal, such as distention of the stomach, the products of proteins, and gastrin releasing peptide, which is released by the nerves of the gastric mucosa during vagal stimulation. The primary actions of gastrin are (1) stimulation of gastric acid secretion and (2) stimulation of growth of the gastric mucosa.

Cholecystokinin (CCK) is secreted by “I” cells in the mucosa of the duodenum and jejunum mainly in response to digestive products of fat, fatty acids, and monoglycerides in the intestinal contents. This hormone strongly contracts the gallbladder, expelling bile into the small intestine, where the bile in turn plays important roles in emulsifying fatty substances, and allowing them to be digested and absorbed. CCK also inhibits stomach contraction moderately. Therefore, at the same time that this hormone causes emptying of the gallbladder, it also slows the emptying of food from the stomach to give adequate time for digestion of the fats in the upper intestinal tract. CCK also inhibits appetite to prevent overeating during meals by stimulating sensory afferent nerve fibers in the duodenum; these fibers, in turn, send signals by way of the vagus nerve to inhibit feeding centers in the brain as discussed in Chapter 71.

Secretin was the first gastrointestinal hormone discovered and is secreted by the “S” cells in the mucosa of the duodenum in response to acidic gastric juice emptying into the duodenum from the pylorus of the stomach. Secretin has a mild effect on motility of the gastrointestinal tract and acts to promote pancreatic secretion of bicarbonate, which in turn helps to neutralize the acid in the small intestine.

Gastric inhibitory peptide (GIP) is secreted by the mucosa of the upper small intestine, mainly in response to fatty acids and amino acids but to a lesser extent in response to carbohydrate. It has a mild effect in decreasing motor activity of the stomach and therefore slows emptying of gastric contents into the duodenum when the upper small intestine is already overloaded with food products. GIP, at blood levels even lower than those needed to inhibit gastric motility, also stimulates insulin secretion and for this reason is also known as glucose-dependent insulinotropic peptide.

Motilin is secreted by the stomach and upper duodenum during fasting, and the only known function of this hormone is to increase gastrointestinal motility. Motilin is released cyclically and stimulates waves of gastrointestinal motility called interdigestive myoelectric complexes that move through the stomach and small intestine every

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Stimuli for Secretion</th>
<th>Site of Secretion</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrin</td>
<td>Protein Distention</td>
<td>G cells of the antrum, duodenum, and jejunum</td>
<td>Stimulates Gastric acid secretion Mucosal growth</td>
</tr>
<tr>
<td></td>
<td>Nerve</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Acid inhibits release)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholecystokinin</td>
<td>Protein Fat Acid</td>
<td>I cells of the duodenum, jejunum, and ileum</td>
<td>Stimulates Pancreatic enzyme secretion Pancreatic bicarbonate secretion Gallbladder contraction Growth of exocrine pancreas Inhibits Gastric emptying</td>
</tr>
<tr>
<td>Secretin</td>
<td>Acid Fat</td>
<td>S cells of the duodenum, jejunum, and ileum</td>
<td>Stimulates Pepsin secretion Pancreatic bicarbonate secretion Biliary bicarbonate secretion Growth of exocrine pancreas Inhibits Gastric acid secretion</td>
</tr>
<tr>
<td>Gastric inhibitory peptide</td>
<td>Protein Fat Carbohydrate</td>
<td>K cells of the duodenum and jejunum</td>
<td>Stimulates Insulin release Inhibits Gastric acid secretion</td>
</tr>
<tr>
<td>Motilin</td>
<td>Fat Acid Nerve</td>
<td>M cells of the duodenum and jejunum</td>
<td>Stimulates Gastric motility Intestinal motility</td>
</tr>
</tbody>
</table>

Table 62-1 Gastrointestinal Hormone Actions, Stimuli for Secretion, and Site of Secretion
90 minutes in a fasted person. Motilin secretion is inhibited after ingestion by mechanisms that are not fully understood.

Functional Types of Movements in the Gastrointestinal Tract

Two types of movements occur in the gastrointestinal tract: (1) propulsive movements, which cause food to move forward along the tract at an appropriate rate to accommodate digestion and absorption, and (2) mixing movements, which keep the intestinal contents thoroughly mixed at all times.

Propulsive Movements—Peristalsis

The basic propulsive movement of the gastrointestinal tract is peristalsis, which is illustrated in Figure 62-5. A contractile ring appears around the gut and then moves forward; this is analogous to putting one’s fingers around a thin distended tube, then constricting the fingers and sliding them forward along the tube. Any material in front of the contractile ring is moved forward.

Peristalsis is an inherent property of many syncytial smooth muscle tubes; stimulation at any point in the gut can cause a contractile ring to appear in the circular muscle, and this ring then spreads along the gut tube. (Peristalsis also occurs in the bile ducts, glandular ducts, ureters, and many other smooth muscle tubes of the body.)

The usual stimulus for intestinal peristalsis is distension of the gut. That is, if a large amount of food collects at any point in the gut, the stretching of the gut wall stimulates the enteric nervous system to contract the gut wall 2 to 3 centimeters behind this point, and a contractile ring appears that initiates a peristaltic movement. Other stimuli that can initiate peristalsis include chemical or physical irritation of the epithelial lining in the gut. Also, strong parasympathetic nervous signals to the gut will elicit strong peristalsis.

Function of the Myenteric Plexus in Peristalsis.

Peristalsis occurs only weakly or not at all in any portion of the gastrointestinal tract that has congenital absence of the myenteric plexus. Also, it is greatly depressed or completely blocked in the entire gut when a person is treated with atropine to paralyze the cholinergic nerve endings of the myenteric plexus. Therefore, effectual peristalsis requires an active myenteric plexus.

Directional Movement of Peristaltic Waves Toward the Anus. Peristalsis, theoretically, can occur in either direction from a stimulated point, but it normally dies out rapidly in the orad (toward the mouth) direction while continuing for a considerable distance toward the anus. The exact cause of this directional transmission of peristalsis has never been ascertained, although it probably results mainly from the fact that the myenteric plexus itself is “polarized” in the anal direction, which can be explained as follows.

Peristaltic Reflex and the “Law of the Gut”. When a segment of the intestinal tract is excited by distention and thereby initiates peristalsis, the contractile ring causing the peristalsis normally begins on the orad side of the distended segment and moves toward the distended segment, pushing the intestinal contents in the anal direction for 5 to 10 centimeters before dying out. At the same time, the gut sometimes relaxes several centimeters downstream toward the anus, which is called “receptive relaxation,” thus allowing the food to be propelled more easily toward the anus than toward the mouth.

This complex pattern does not occur in the absence of the myenteric plexus. Therefore, the complex is called the myenteric reflex or the peristaltic reflex. The peristaltic reflex plus the anal direction of movement of the peristalsis is called the “law of the gut.”

Mixing Movements

Mixing movements differ in different parts of the alimentary tract. In some areas, the peristaltic contractions themselves cause most of the mixing. This is especially true when forward progression of the intestinal contents is blocked by a sphincter so that a peristaltic wave can then only churn the intestinal contents, rather than propelling them forward. At other times, local intermittent constrictive contractions occur every few centimeters in the gut wall. These constrictions usually last only 5 to 30 seconds; then new constrictions occur at other points in the gut, thus “chopping” and “shearing” the contents first here and then there. These peristaltic and constrictive movements are modified in different parts of the gastrointestinal tract for proper propulsion and mixing, as discussed for each portion of the tract in Chapter 63.

Gastrointestinal Blood Flow—“Splanchnic Circulation”

The blood vessels of the gastrointestinal system are part of a more extensive system called the splanchnic circulation, shown in Figure 62-6. It includes the blood flow...
through the gut itself plus blood flows through the spleen, pancreas, and liver. The design of this system is such that all the blood that courses through the gut, spleen, and pancreas then flows immediately into the liver by way of the portal vein. In the liver, the blood passes through millions of minute liver sinusoids and finally leaves the liver by way of hepatic veins that empty into the vena cava of the general circulation. This flow of blood through the liver, before it empties into the vena cava, allows the reticuloendothelial cells that line the liver sinusoids to remove bacteria and other particulate matter that might enter the blood from the gastrointestinal tract, thus preventing direct transport of potentially harmful agents into the remainder of the body.

The nonfat, water-soluble nutrients absorbed from the gut (such as carbohydrates and proteins) are transported in the portal venous blood to the same liver sinusoids. Here, both the reticuloendothelial cells and the principal parenchymal cells of the liver, the hepatic cells, absorb and store temporarily from one half to three quarters of the nutrients. Also, much chemical intermediary processing of these nutrients occurs in the liver cells. We discuss these nutritional functions of the liver in Chapters 67 through 71. Almost all of the fats absorbed from the intestinal tract are not carried in the portal blood but instead are absorbed into the intestinal lymphatics and then conducted to the systemic circulating blood by way of the thoracic duct, bypassing the liver.

Anatomy of the Gastrointestinal Blood Supply

Figure 62-7 shows the general plan of the arterial blood supply to the gut, including the superior mesenteric and inferior mesenteric arteries supplying the walls of the
small and large intestines by way of an arching arterial system. Not shown in the figure is the celiac artery, which provides a similar blood supply to the stomach.

On entering the wall of the gut, the arteries branch and send smaller arteries circling in both directions around the gut, with the tips of these arteries meeting on the side of the gut wall opposite the mesenteric attachment. From the circling arteries, still much smaller arteries penetrate into the intestinal wall and spread (1) along the muscle bundles, (2) into the intestinal villi, and (3) into submucosal vessels beneath the epithelium to serve the secretory and absorptive functions of the gut.

Figure 62-8 shows the special organization of the blood flow through an intestinal villus, including a small arteriole and venule that interconnect with a system of multiple looping capillaries. The walls of the arterioles are highly muscular and are highly active in controlling villus blood flow.

Effect of Gut Activity and Metabolic Factors on Gastrointestinal Blood Flow

Under normal conditions, the blood flow in each area of the gastrointestinal tract, as well as in each layer of the gut wall, is directly related to the level of local activity. For instance, during active absorption of nutrients, blood flow in the villi and adjacent regions of the submucosa is increased as much as eightfold. Likewise, blood flow in the muscle layers of the intestinal wall increases with increased motor activity in the gut. For instance, after a meal, the motor activity, secretory activity, and absorptive activity all increase; likewise, the blood flow increases greatly but then decreases back to the resting level over another 2 to 4 hours.

Possible Causes of the Increased Blood Flow During Gastrointestinal Activity. Although the precise causes of the increased blood flow during increased gastrointestinal activity are still unclear, some facts are known.

First, several vasodilator substances are released from the mucosa of the intestinal tract during the digestive process. Most of these are peptide hormones, including cholecystokinin, vasoactive intestinal peptide, gastrin, and secretin. These same hormones control specific motor and secretory activities of the gut, as discussed in Chapters 63 and 64.

Second, some of the gastrointestinal glands also release into the gut wall two kinins, kallidin and bradykinin, at the same time that they secrete other substances into the lumen. These kinins are powerful vasodilators that are believed to cause much of the increased mucosal vasodilation that occurs along with secretion.

Third, decreased oxygen concentration in the gut wall can increase intestinal blood flow at least 50 to 100 percent; therefore, the increased mucosal and gut wall metabolic rate during gut activity probably lowers the oxygen concentration enough to cause much of the vasodilation. The decrease in oxygen can also lead to as much as a fourfold increase of adenosine, a well-known vasodilator that could be responsible for much of the increased flow.

Thus, the increased blood flow during increased gastrointestinal activity is probably a combination of many of the aforementioned factors plus still others yet undiscovered.

“Countercurrent” Blood Flow in the Villi. Note in Figure 62-8 that the arterial flow into the villus and the venous flow out of the villus are in directions opposite to each other, and that the vessels lie in close apposition to each other. Because of this vascular arrangement, much of the blood oxygen diffuses out of the arterioles directly into the adjacent venules without ever being carried in the blood to the tips of the villi. As much as 80 percent of the oxygen may take this short-circuit route and therefore not be available for local metabolic functions of the villi. The reader will recognize that this type of countercurrent mechanism in the villi is analogous to the countercurrent mechanism in the vasa recta of the kidney medulla, discussed in detail in Chapter 28.

Under normal conditions, this shunting of oxygen from the arterioles to the venules is not harmful to the villi, but in disease conditions in which blood flow to
the gut becomes greatly curtailed, such as in circulatory shock, the oxygen deficit in the tips of the villi can become so great that the villus tip or even the whole villus suffers ischemic death and can disintegrate. Therefore, for this reason and others, in many gastrointestinal diseases the villi become seriously blunted, leading to greatly diminished intestinal absorptive capacity.

**Nervous Control of Gastrointestinal Blood Flow**

Stimulation of the parasympathetic nerves going to the stomach and lower colon increases local blood flow at the same time that it increases glandular secretion. This increased flow probably results secondarily from the increased glandular activity and not as a direct effect of the nervous stimulation.

Sympathetic stimulation, by contrast, has a direct effect on essentially all the gastrointestinal tract to cause intense vasoconstriction of the arterioles with greatly decreased blood flow. After a few minutes of this vasoconstriction, the flow often returns to near normal by means of a mechanism called “autoregulatory escape.” That is, the local metabolic vasodilator mechanisms that are elicited by ischemia override the sympathetic vasoconstriction, returning toward normal the necessary nutrient blood flow to the gastrointestinal glands and muscle.

**Importance of Nervous Depression of Gastrointestinal Blood Flow When Other Parts of the Body Need Extra Blood Flow.** A major value of sympathetic vasoconstriction in the gut is that it allows shutoff of gastrointestinal and other splanchnic blood flow for short periods of time during heavy exercise, when the skeletal muscle and heart need increased flow. Also, in circulatory shock, when all the body’s vital tissues are in danger of cellular death for lack of blood flow—especially the brain and the heart—sympathetic stimulation can decrease splanchnic blood flow to very little for many hours.

Sympathetic stimulation also causes strong vasoconstriction of the large-volume intestinal and mesenteric veins. This decreases the volume of these veins, thereby displacing large amounts of blood into other parts of the circulation. In hemorrhagic shock or other states of low blood volume, this mechanism can provide as much as 200 to 400 milliliters of extra blood to sustain the general circulation.

**Bibliography**


The time that food remains in each part of the alimentary tract is critical for optimal processing and absorption of nutrients. Also, appropriate mixing must be provided. Because the requirements for mixing and propulsion are quite different at each stage of processing, multiple automatic nervous and hormonal mechanisms control the timing of each of these so that they will occur optimally, not too rapidly, not too slowly.

The purpose of this chapter is to discuss these movements, especially the automatic mechanisms of this control.

**Ingestion of Food**

The amount of food that a person ingests is determined principally by intrinsic desire for food called *hunger*. The type of food that a person preferentially seeks is determined by *appetite*. These mechanisms are extremely important for maintaining an adequate nutritional supply for the body and are discussed in Chapter 71 in relation to nutrition of the body. The current discussion of food ingestion is confined to the mechanics of ingestion, especially *mastication* and *swallowing*.

**Mastication (Chewing)**

The teeth are admirably designed for chewing. The anterior teeth (incisors) provide a strong cutting action and the posterior teeth (molars) a grinding action. All the jaw muscles working together can close the teeth with a force as great as 55 pounds on the incisors and 200 pounds on the molars.

Most of the muscles of chewing are innervated by the motor branch of the fifth cranial nerve, and the chewing process is controlled by nuclei in the brain stem. Stimulation of specific reticular areas in the brain stem taste centers will cause rhythmical chewing movements. Also, stimulation of areas in the hypothalamus, amygdala, and even the cerebral cortex near the sensory areas for taste and smell can often cause chewing.

Much of the chewing process is caused by a *chewing reflex*. The presence of a bolus of food in the mouth at first initiates reflex inhibition of the muscles of mastication, which allows the lower jaw to drop. The drop in turn initiates a stretch reflex of the jaw muscles that leads to *rebound* contraction. This automatically raises the jaw to cause closure of the teeth, but it also compresses the bolus again against the linings of the mouth, which inhibits the jaw muscles once again, allowing the jaw to drop and rebound another time; this is repeated again and again.

Chewing is important for digestion of all foods, but especially important for most fruits and raw vegetables because these have indigestible cellulose membranes around their nutrient portions that must be broken before the food can be digested. Also, chewing aids the digestion of food for still another simple reason: Digestive enzymes act only on the surfaces of food particles; therefore, the rate of digestion is absolutely dependent on the total surface area exposed to the digestive secretions. In addition, grinding the food to a very fine particulate consistency prevents excoriation of the gastrointestinal tract and increases the ease with which food is emptied from the stomach into the small intestine, then into all succeeding segments of the gut.

**Swallowing (Deglutition)**

Swallowing is a complicated mechanism, principally because the pharynx subserves respiration and swallowing. The pharynx is converted for only a few seconds at a time into a tract for propulsion of food. It is especially important that respiration not be compromised because of swallowing.

In general, swallowing can be divided into (1) a *voluntary stage*, which initiates the swallowing process; (2) a *pharyngeal stage*, which is involuntary and constitutes passage of food through the pharynx into the esophagus; and (3) an *esophageal stage*, another involuntary phase that transports food from the pharynx to the stomach.

**Voluntary Stage of Swallowing.** When the food is ready for swallowing, it is “voluntarily” squeezed or rolled posteriorly into the pharynx by pressure of the tongue upward and backward against the palate, as shown in
Pharyngeal Stage of Swallowing. As the bolus of food enters the posterior mouth and pharynx, it stimulates epithelial swallowing receptor areas all around the opening of the pharynx, especially on the tonsillar pillars, and impulses from these pass to the brain stem to initiate a series of automatic pharyngeal muscle contractions as follows:

1. The soft palate is pulled upward to close the posterior nares, to prevent reflux of food into the nasal cavities.
2. The palatopharyngeal folds on each side of the pharynx are pulled medially to approximate each other. In this way, these folds form a sagittal slit through which the food must pass into the posterior pharynx. This slit performs a selective action, allowing food that has been masticated sufficiently to pass with ease. Because this stage of swallowing lasts less than 1 second, any large object is usually impeded too much to pass into the esophagus.
3. The vocal cords of the larynx are strongly approximated, and the larynx is pulled upward and anteriorly by the neck muscles. These actions, combined with the presence of ligaments that prevent upward movement of the epiglottis, cause the epiglottis to swing backward over the opening of the larynx. All these effects acting together prevent passage of food into the nose and trachea. Most essential is the tight approximation of the vocal cords, but the epiglottis helps to prevent food from ever getting as far as the vocal cords. Destruction of the vocal cords or of the muscles that approximate them can cause strangulation.

4. The upward movement of the larynx also pulls up and enlarges the opening to the esophagus. At the same time, the upper 3 to 4 centimeters of the esophageal muscular wall, called the upper esophageal sphincter (also called the pharyngoesophageal sphincter), relaxes. Thus, food moves easily and freely from the posterior pharynx into the upper esophagus. Between swallows, this sphincter remains strongly contracted, thereby preventing air from going into the esophagus during respiration. The upward movement of the larynx also lifts the glottis out of the main stream of food flow, so the food mainly passes on each side of the epiglottis rather than over its surface; this adds still another protection against entry of food into the trachea.

5. Once the larynx is raised and the pharyngoesophageal sphincter becomes relaxed, the entire muscular wall of the pharynx contracts, beginning in the superior part of the pharynx, then spreading downward over the middle and inferior pharyngeal areas, which propels the food by peristalsis into the esophagus.

To summarize the mechanics of the pharyngeal stage of swallowing: The trachea is closed, the esophagus is opened, and a fast peristaltic wave initiated by the nervous system of the pharynx forces the bolus of food into the upper esophagus, the entire process occurring in less than 2 seconds.

Nervous Initiation of the Pharyngeal Stage of Swallowing. The most sensitive tactile areas of the posterior mouth and pharynx for initiating the pharyngeal stage of swallowing lie in a ring around the pharyngeal opening, with greatest sensitivity on the tonsillar pillars. Impulses are transmitted from these areas through the sensory portions of the trigeminal and glossopharyngeal nerves into the medulla oblongata, either into or closely associated with the tractus solitarius, which receives essentially all sensory impulses from the mouth.

The successive stages of the swallowing process are then automatically initiated in orderly sequence by neuronal areas of the reticular substance of the medulla and lower portion of the pons. The sequence of the swallowing reflex is the same from one swallow to the next, and the timing of the entire cycle also remains constant from one swallow to the next. The areas in the medulla and lower pons that control swallowing are collectively called the deglutition or swallowing center.

The motor impulses from the swallowing center to the pharynx and upper esophagus that cause swallowing are transmitted successively by the fifth, ninth, tenth, and twelfth cranial nerves and even a few of the superior cervical nerves.

In summary, the pharyngeal stage of swallowing is principally a reflex act. It is almost always initiated by voluntary movement of food into the back of the mouth, which in turn excites involuntary pharyngeal sensory receptors to elicit the swallowing reflex.
Effect of the Pharyngeal Stage of Swallowing on Respiration. The entire pharyngeal stage of swallowing usually occurs in less than 6 seconds, thereby interrupting respiration for only a fraction of a usual respiratory cycle. The swallowing center specifically inhibits the respiratory center of the medulla during this time, halting respiration at any point in its cycle to allow swallowing to proceed. Yet even while a person is talking, swallowing interrupts respiration for such a short time that it is hardly noticeable.

Esophageal Stage of Swallowing. The esophagus functions primarily to conduct food rapidly from the pharynx to the stomach, and its movements are organized specifically for this function.

The esophagus normally exhibits two types of peristaltic movements: primary peristalsis and secondary peristalsis. Primary peristalsis is simply continuation of the peristaltic wave that begins in the pharynx and spreads into the esophagus during the pharyngeal stage of swallowing. This wave passes all the way from the pharynx to the stomach in about 8 to 10 seconds. Food swallowed by a person who is in the upright position is usually transmitted to the lower end of the esophagus even more rapidly than the peristaltic wave itself, in about 5 to 8 seconds, because of the additional effect of gravity pulling the food downward.

If the primary peristaltic wave fails to move into the stomach all the food that has entered the esophagus, secondary peristaltic waves result from distention of the esophagus itself by the retained food; these waves continue until all the food has emptied into the stomach. The secondary peristaltic waves are initiated partly by intrinsic neural circuits in the myenteric nervous system and partly by reflexes that begin in the pharynx and are then transmitted upward through vagal afferent fibers to the medulla and back again to the esophagus through glosopharyngeal and vagal efferent nerve fibers.

The musculature of the pharyngeal wall and upper third of the esophagus is striated muscle. Therefore, the peristaltic waves in these regions are controlled by skeletal nerve impulses from the glosopharyngeal and vagus nerves. In the lower two thirds of the esophagus, the musculature is smooth muscle, but this portion of the esophagus is also strongly controlled by the vagus nerves acting through connections with the esophageal myenteric nervous system. When the vagus nerves to the esophagus are cut, the myenteric nerve plexus of the esophagus becomes excitable enough after several days to cause strong secondary peristaltic waves even without support from the vagal reflexes. Therefore, even after paralysis of the brain stem swallowing reflex, food fed by tube or in some other way into the esophagus still passes readily into the stomach.

Receptive Relaxation of the Stomach. When the esophageal peristaltic wave approaches toward the stomach, a wave of relaxation, transmitted through myenteric inhibitory neurons, precedes the peristalsis. Furthermore, the entire stomach and, to a lesser extent, even the duodenum become relaxed as this wave reaches the lower end of the esophagus and thus are prepared ahead of time to receive the food propelled into the esophagus during the swallowing act.

Function of the Lower Esophageal Sphincter (Gastroesophageal Sphincter). At the lower end of the esophagus, extending upward about 3 centimeters above its juncture with the stomach, the esophageal circular muscle functions as a broad lower esophageal sphincter, also called the gastroesophageal sphincter. This sphincter normally remains tonically constricted with an intraluminal pressure at this point in the esophagus of about 30 mm Hg, in contrast to the midportion of the esophagus, which normally remains relaxed. When a peristaltic swallowing wave passes down the esophagus, there is “receptive relaxation” of the lower esophageal sphincter ahead of the peristaltic wave, which allows easy propulsion of the swallowed food into the stomach. Rarely, the sphincter does not relax satisfactorily, resulting in a condition called achalasia. This is discussed in Chapter 66.

The stomach secretions are highly acidic and contain many proteolytic enzymes. The esophageal mucosa, except in the lower one eighth of the esophagus, is not capable of resisting for long the digestive action of gastric secretions. Fortunately, the tonic constriction of the lower esophageal sphincter helps to prevent significant reflux of stomach contents into the esophagus except under abnormal conditions.

Additional Prevention of Esophageal Reflux by Valvelike Closure of the Distal End of the Esophagus. Another factor that helps to prevent reflux is a valvelike mechanism of a short portion of the esophagus that extends slightly into the stomach. Increased intra-abdominal pressure caves the esophagus inward at this point. Thus, this valvelike closure of the lower esophagus helps to prevent high intra-abdominal pressure from forcing stomach contents backward into the esophagus. Otherwise, every time we walked, coughed, or breathed hard, we might expel stomach acid into the esophagus.

Motor Functions of the Stomach

The motor functions of the stomach are threefold: (1) storage of large quantities of food until the food can be processed in the stomach, duodenum, and lower intestinal tract; (2) mixing of this food with gastric secretions until it forms a semifluid mixture called chyme; and (3) slow emptying of the chyme from the stomach into the small intestine at a rate suitable for proper digestion and absorption by the small intestine.
Besides the peristaltic constrictor waves, which was discussed in Chapter 62, consisting of electrical "slow waves" that occur spontaneously in the stomach wall. As the constrictor waves progress from the body of the stomach into the antrum, they become more intense, some becoming extremely intense and providing powerful peristaltic action potential–driven constrictor rings that force the antral contents under higher and higher pressure toward the pylorus.

These constrictor rings also play an important role in mixing the stomach contents in the following way: Each time a peristaltic wave passes down the antral wall toward the pylorus, it digs deeply into the food contents in the antrum. Yet the opening of the pylorus is still small enough that only a few milliliters or less of antral contents are expelled into the duodenum with each peristaltic wave. Also, as each peristaltic wave approaches the pylorus, the pyloric muscle itself often contracts, which further impedes emptying through the pylorus. Therefore, most of the antral contents are squeezed upstream through the peristaltic ring toward the body of the stomach, not through the pylorus. Thus, the moving peristaltic constrictive ring, combined with this upstream squeezing action, called "retropulsion," is an exceedingly important mixing mechanism in the stomach.

**Chyme.** After food in the stomach has become thoroughly mixed with the stomach secretions, the resulting mixture that passes down the gut is called chyme. The degree of fluidity of the chyme leaving the stomach depends on the relative amounts of food, water, and stomach secretions and on the degree of digestion that has occurred. The appearance of chyme is that of a murky semifluid or paste.

**Hunger Contractions.** Besides the peristaltic contractions that occur when food is present in the stomach, another type of intense contractions, called hunger contractions, often occurs when the stomach has been empty for several hours or more. They are rhythmical peristaltic contractions in the body of the stomach. When the successive contractions become extremely strong, they often fuse to cause a continuing tetanic contraction that sometimes lasts for 2 to 3 minutes.

Hunger contractions are most intense in young, healthy people who have high degrees of gastrointestinal tonus; they are also greatly increased by the person’s having lower than normal levels of blood sugar. When hunger contractions occur in the stomach, the person sometimes experiences mild pain in the pit of the stomach, called hunger pangs. Hunger pangs usually do not begin until 12 to 24 hours after the last ingestion of food; in starvation, they reach their greatest intensity in 3 to 4 days and gradually weaken in succeeding days.

**Stomach Emptying**

Stomach emptying is promoted by intense peristaltic contractions in the stomach antrum. At the same time, emptying is opposed by varying degrees of resistance to passage of chyme at the pylorus.

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**Figure 63-2** Physiologic anatomy of the stomach.
**Intense Antral Peristaltic Contractions During Stomach Emptying—“Pyloric Pump.”** Most of the time, the rhythmical stomach contractions are weak and function mainly to cause mixing of food and gastric secretions. However, for about 20 percent of the time while food is in the stomach, the contractions become intense, beginning in midstomach and spreading through the caudad stomach; these contractions are strong peristaltic, very tight ringlike constrictions that can cause stomach emptying. As the stomach becomes progressively more and more empty, these constrictions begin farther and farther up the body of the stomach, gradually pinching off the food in the body of the stomach and adding this food to the chyme in the antrum. These intense peristaltic contractions often create 50 to 70 centimeters of water pressure, which is about six times as powerful as the usual mixing type of peristaltic waves.

When pyloric tone is normal, each strong peristaltic wave forces up to several milliliters of chyme into the duodenum. Thus, the peristaltic waves, in addition to causing mixing in the stomach, also provide a pumping action called the “pyloric pump.”

**Role of the Pylorus in Controlling Stomach Emptying.** The distal opening of the stomach is the pylorus. Here the thickness of the circular wall muscle becomes 50 to 100 percent greater than in the earlier portions of the stomach antrum, and it remains slightly tonically contracted almost all the time. Therefore, the pyloric circular muscle is called the pyloric sphincter.

Despite normal tonic contraction of the pyloric sphincter, the pylorus usually is open enough for water and other fluids to empty from the stomach into the duodenum with ease. Conversely, the constriction usually prevents passage of food particles until they have become mixed in the chyme to almost fluid consistency. The degree of constriction of the pylorus is increased or decreased under the influence of nervous and humoral reflex signals from both the stomach and the duodenum, as discussed shortly.

**Regulation of Stomach Emptying**

The rate at which the stomach empties is regulated by signals from both the stomach and the duodenum. However, the duodenum provides by far the more potent of the signals, controlling the emptying of chyme into the duodenum at a rate no greater than the rate at which the chyme can be digested and absorbed in the small intestine.

**Gastric Factors That Promote Emptying**

**Effect of Gastric Food Volume on Rate of Emptying.** Increased food volume in the stomach promotes increased emptying from the stomach. But this increased emptying does not occur for the reasons that one would expect. It is not increased storage pressure of the food in the stomach that causes the increased emptying because, in the usual normal range of volume, the increase in volume does not increase the pressure much. However, stretching of the stomach wall does elicit local myenteric reflexes in the wall that greatly accentuate activity of the pyloric pump and at the same time inhibit the pylorus.

**Effect of the Hormone Gastrin on Stomach Emptying.** In Chapter 64, we discuss how stomach wall stretch and the presence of certain types of foods in the stomach—particularly digestive products of meat—elicit release of the hormone gastrin from the antral mucosa. This has potent effects to cause secretion of highly acidic gastric juice by the stomach glands. Gastrin also has mild to moderate stimulatory effects on motor functions in the body of the stomach. Most important, it seems to enhance the activity of the pyloric pump. Thus, gastrin likely promotes stomach emptying.

**Powerful Duodenal Factors That Inhibit Stomach Emptying**

**Inhibitory Effect of Enterogastric Nervous Reflexes from the Duodenum.** When food enters the duodenum, multiple nervous reflexes are initiated from the duodenal wall. They pass back to the stomach to slow or even stop stomach emptying if the volume of chyme in the duodenum becomes too much. These reflexes are mediated by three routes: (1) directly from the duodenum to the stomach through the enteric nervous system in the gut wall, (2) through extrinsic nerves that go to the prevertebral sympathetic ganglia and then back through inhibitory sympathetic nerve fibers to the stomach, and (3) probably to a slight extent through the vagus nerves all the way to the brain stem, where they inhibit the normal excitatory signals transmitted to the stomach through the vagi. All these parallel reflexes have two effects on stomach emptying: First, they strongly inhibit the “pyloric pump” propulsive contractions, and second, they increase the tone of the pyloric sphincter.

The types of factors that are continually monitored in the duodenum and that can initiate enterogastric inhibitory reflexes include the following:

1. The degree of distention of the duodenum
2. The presence of any degree of irritation of the duodenal mucosa
3. The degree of acidity of the duodenal chyme
4. The degree of osmolality of the chyme
5. The presence of certain breakdown products in the chyme, especially breakdown products of proteins and, perhaps to a lesser extent, of fats

The enterogastric inhibitory reflexes are especially sensitive to the presence of irritants and acids in the duodenal chyme, and they often become strongly activated within as little as 30 seconds. For instance, whenever the pH of the chyme in the duodenum falls below about 3.5 to 4, the reflexes frequently block further release of acidic stomach...
contents into the duodenum until the duodenal chyme can be neutralized by pancreatic and other secretions.

Breakdown products of protein digestion also elicit inhibitory enterogastric reflexes; by slowing the rate of stomach emptying, sufficient time is ensured for adequate protein digestion in the duodenum and small intestine.

Finally, either hypotonic or hypertonic fluids (especially hypertonic) elicit the inhibitory reflexes. Thus, too rapid flow of nonisotonic fluids into the small intestine is prevented, thereby also preventing rapid changes in electrolyte concentrations in the whole-body extracellular fluid during absorption of the intestinal contents.

**Hormonal Feedback from the Duodenum Inhibits Gastric Emptying—Role of Fats and the Hormone Cholecystokinin.** Not only do nervous reflexes from the duodenum to the stomach inhibit stomach emptying, but hormones released from the upper intestine do so as well. The stimulus for releasing these inhibitory hormones is mainly fats entering the duodenum, although other types of foods can increase the hormones to a lesser degree.

On entering the duodenum, the fats extract several different hormones from the duodenal and jejunal epithelium, either by binding with “receptors” on the epithelial cells or in some other way. In turn, the hormones are carried by way of the blood to the stomach, where they inhibit the pyloric pump and at the same time increase the strength of contraction of the pyloric sphincter. These effects are important because fats are much slower to be digested than most other foods.

Precisely which hormones cause the hormonal feedback inhibition of the stomach is not fully clear. The most potent appears to be cholecystokinin (CCK), which is released from the mucosa of the jejunum in response to fatty substances in the chyme. This hormone acts as an inhibitor to block increased stomach motility caused by gastrin.

Other possible inhibitors of stomach emptying are the hormones secretin and gastric inhibitory peptide (GIP), also called glucose-dependent insulinotropic peptide. Secretin is released mainly from the duodenal mucosa in response to gastric acid passed from the stomach through the pylorus. GIP has a general but weak effect of decreasing gastrointestinal motility.

GIP is released from the upper small intestine in response mainly to fat in the chyme, but to a lesser extent to carbohydrates as well. Although GIP inhibits gastric motility under some conditions, its main effect at physiologic concentrations is probably mainly to stimulate secretion of insulin by the pancreas.

These hormones are discussed at greater length elsewhere in this text, especially in Chapter 64 in relation to control of gallbladder emptying and control of rate of pancreatic secretion.

In summary, hormones, especially CCK, can inhibit gastric emptying when excess quantities of chyme, especially acidic or fatty chyme, enter the duodenum from the stomach.

**Summary of the Control of Stomach Emptying**

Emptying of the stomach is controlled only to a moderate degree by stomach factors such as the degree of filling in the stomach and the excitatory effect of gastrin on stomach peristalsis. Probably the more important control of stomach emptying resides in inhibitory feedback signals from the duodenum, including both enterogastric inhibitory nervous feedback reflexes and hormonal feedback by CCK. These feedback inhibitory mechanisms work together to slow the rate of emptying when (1) too much chyme is already in the small intestine or (2) the chyme is excessively acidic, contains too much unprocessed protein or fat, is hypotonic or hypertonic, or is irritating. In this way, the rate of stomach emptying is limited to that amount of chyme that the small intestine can process.

**Movements of the Small Intestine**

The movements of the small intestine, like those elsewhere in the gastrointestinal tract, can be divided into mixing contractions and propulsive contractions. To a great extent, this separation is artificial because essentially all movements of the small intestine cause at least some degree of both mixing and propulsion. The usual classification of these processes is the following.

**Mixing Contractions (Segmentation Contractions)**

When a portion of the small intestine becomes distended with chyme, stretching of the intestinal wall elicits localized concentric contractions spaced at intervals along the intestine and lasting a fraction of a minute. The contractions cause “segmentation” of the small intestine, as shown in Figure 63-3. That is, they divide the intestine into spaced segments that have the appearance of a chain of sausages. As one set of segmentation contractions relaxes, a new set often begins, but the contractions this time occur mainly at new points between the previous contractions. Therefore, the segmentation contractions “chop” the chyme two to three times per minute, in this way promoting progressive mixing of the food with secretions of the small intestine.

[Figure 63-3 Segmentation movements of the small intestine.]
The maximum frequency of the segmentation contractions in the small intestine is determined by the frequency of electrical slow waves in the intestinal wall, which is the basic electrical rhythm described in Chapter 62. Because this frequency normally is not over 12 per minute in the duodenum and proximal jejunum, the maximum frequency of the segmentation contractions in these areas is also about 12 per minute, but this occurs only under extreme conditions of stimulation. In the terminal ileum, the maximum frequency is usually eight to nine contractions per minute.

The segmentation contractions become exceedingly weak when the excitatory activity of the enteric nervous system is blocked by the drug atropine. Therefore, even though it is the slow waves in the smooth muscle itself that cause the segmentation contractions, these contractions are not effective without background excitation mainly from the myenteric nerve plexus.

**Propulsive Movements**

**Peristalsis in the Small Intestine.** Chyme is propelled through the small intestine by peristaltic waves. These can occur in any part of the small intestine, and they move toward the anus at a velocity of 0.5 to 2.0 cm/sec, faster in the proximal intestine and slower in the terminal intestine. They are normally weak and usually die out after traveling only 3 to 5 centimeters, rarely farther than 10 centimeters, so forward movement of the chyme is very slow, so slow that net movement along the small intestine normally averages only 1 cm/min. This means that 3 to 5 hours are required for passage of chyme from the pylorus to the ileocecal valve.

**Control of Peristalsis by Nervous and Hormonal Signals.** Peristaltic activity of the small intestine is greatly increased after a meal. This is caused partly by the beginning entry of chyme into the duodenum causing stretch of the duodenal wall. Also, peristaltic activity is increased by the so-called gastroenteric reflex that is initiated by distention of the stomach and conducted principally through the myenteric plexus from the stomach down along the wall of the small intestine.

In addition to the nervous signals that may affect small intestinal peristalsis, several hormonal factors also affect peristalsis. They include gastrin, CCK, insulin, motilin, and serotonin, all of which enhance intestinal motility and are secreted during various phases of food processing. Conversely, secretin and glucagon inhibit small intestinal motility. The physiologic importance of each of these hormonal factors for controlling motility is still questionable.

The function of the peristaltic waves in the small intestine is not only to cause progression of chyme toward the ileocecal valve but also to spread out the chyme along the intestinal mucosa. As the chyme enters the intestines from the stomach and elicits peristalsis, this immediately spreads the chyme along the intestine; and this process intensifies as additional chyme enters the duodenum. On reaching the ileocecal valve, the chyme is sometimes blocked for several hours until the person eats another meal; at that time, a gastroileal reflex intensifies peristalsis in the ileum and forces the remaining chyme through the ileocecal valve into the cecum of the large intestine.

**Propulsive Effect of the Segmentation Movements.** The segmentation movements, although lasting for only a few seconds at a time, often also travel 1 centimeter or so in the anal direction and during that time help propel the food down the intestine. The difference between the segmentation and the peristaltic movements is not as great as might be implied by their separation into these two classifications.

**Peristaltic Rush.** Although peristalsis in the small intestine is normally weak, intense irritation of the intestinal mucosa, as occurs in some severe cases of infectious diarrhea, can cause both powerful and rapid peristalsis, called the peristaltic rush. This is initiated partly by nervous reflexes that involve the autonomic nervous system and brain stem and partly by intrinsic enhancement of the myenteric plexus reflexes within the gut wall itself. The powerful peristaltic contractions travel long distances in the small intestine within minutes, sweeping the contents of the intestine into the colon and thereby relieving the small intestine of irritative chyme and excessive distention.

**Movements Caused by the Muscularis Mucosae and Muscle Fibers of the Villi.** The muscularis mucosae can cause short folds to appear in the intestinal mucosa. In addition, individual fibers from this muscle extend into the intestinal villi and cause them to contract intermittently. The mucosal folds increase the surface area exposed to the chyme, thereby increasing absorption. Also, contractions of the villi—shortening, elongating, and shortening again—“milk” the villi so that lymph flows freely from the central lacteals of the villi into the lymphatic system. These mucosal and villous contractions are initiated mainly by local nervous reflexes in the submucosal nerve plexus that occur in response to chyme in the small intestine.

**Function of the Ileocecal Valve**

A principal function of the ileocecal valve is to prevent backflow of fecal contents from the colon into the small intestine. As shown in Figure 63-4, the ileocecal valve itself protrudes into the lumen of the cecum and therefore is forcefully closed when excess pressure builds up in the cecum and tries to push cecal contents backward against the valve lips. The valve usually can resist reverse pressure of at least 50 to 60 centimeters of water.

In addition, the wall of the ileum for several centimeters immediately upstream from the ileocecal valve has a thickened circular muscle called the ileocecal sphincter. This sphincter normally remains mildly constricted and slows emptying of ileal contents into the cecum. However, immediately after a meal, a gastroileal reflex (described
earlier) intensifies peristalsis in the ileum, and emptying of ileal contents into the cecum proceeds.

Resistance to emptying at the ileocecal valve prolongs the stay of chyme in the ileum and thereby facilitates absorption. Normally, only 1500 to 2000 milliliters of chyme empty into the cecum each day.

Feedback Control of the Ileocecal Sphincter. The degree of contraction of the ileocecal sphincter and the intensity of peristalsis in the terminal ileum are controlled significantly by reflexes from the cecum. When the cecum is distended, contraction of the ileocecal sphincter becomes intensified and ileal peristalsis is inhibited, both of which greatly delay emptying of additional chyme into the cecum from the ileum. Also, any irritant in the cecum delays emptying. For instance, when a person has an inflamed appendix, the irritation of this vestigial remnant of the cecum can cause such intense spasm of the ileocecal sphincter and partial paralysis of the ileum that these effects together block emptying of the ileum into the cecum. The reflexes from the cecum to the ileocecal sphincter are mediated both by way of the myenteric plexus in the gut wall itself and of the extrinsic autonomic nerves, especially by way of the prevertebral sympathetic ganglia.

Movements of the Colon

The principal functions of the colon are (1) absorption of water and electrolytes from the chyme to form solid feces and (2) storage of fecal matter until it can be expelled. The proximal half of the colon, shown in Figure 63-5, is concerned principally with absorption, and the distal half with storage. Because intense colon wall movements are not required for these functions, the movements of the colon are normally sluggish. Yet in a sluggish manner, the movements still have characteristics similar to those of the small intestine and can be divided once again into mixing movements and propulsive movements.

Mixing Movements—“Haustrations.” In the same manner that segmentation movements occur in the small intestine, large circular constrictions occur in the large intestine. At each of these constrictions, about 2.5 centimeters of the circular muscle contract, sometimes constricting the lumen of the colon almost to occlusion. At the same time, the longitudinal muscle of the colon, which is aggregated into three longitudinal strips called the teniae coli, contracts. These combined contractions of the circular and longitudinal strips of muscle cause the unstimulated portion of the large intestine to bulge outward into baglike sacs called haustrations.

Each haustrum usually reaches peak intensity in about 30 seconds and then disappears during the next 60 seconds. They also at times move slowly toward the anus during contraction, especially in the cecum and ascending colon, and thereby provide a minor amount of forward propulsion of the colonic contents. After another few minutes, new haustral contractions occur in other areas nearby. Therefore, the fecal material in the large intestine is slowly dug into and rolled over in much the same manner that one spades the earth. In this way, all the fecal material is gradually exposed to the mucosal surface of the large intestine, and fluid and dissolved substances are progressively absorbed until only 80 to 200 milliliters of feces are expelled each day.

Propulsive Movements—“Mass Movements.” Much of the propulsion in the cecum and ascending colon results from the slow but persistent haustral contractions, requiring as many as 8 to 15 hours to move the chyme from the ileocecal valve through the colon, while the chyme itself becomes fecal in quality, a semisolid slush instead of semifluid.
From the cecum to the sigmoid, mass movements can, for many minutes at a time, take over the propulsive role. These movements often occur only one to three times each day, in many people especially for about 15 minutes during the first hour after eating breakfast.

A mass movement is a modified type of peristalsis characterized by the following sequence of events: First, a constrictive ring occurs in response to a distended or irritated point in the colon, usually within the transverse colon. Then, rapidly, the 20 or more centimeters of colon distal to the constrictive ring lose their haustrations and instead contract as a unit, propelling the fecal material in this segment en masse further down the colon. The contraction develops progressively more force for about 30 seconds, and relaxation occurs during the next 2 to 3 minutes. Then, another mass movement occurs, this time perhaps farther along the colon.

A series of mass movements usually persists for 10 to 30 minutes. Then they cease but return perhaps a half day later. When they have forced a mass of feces into the rectum, the desire for defecation is felt.

Initiation of Mass Movements by Gastrocolic and Duodenocolic Reflexes. Appearance of mass movements after meals is facilitated by gastrocolic and duodenocolic reflexes. These reflexes result from distention of the stomach and duodenum. They occur either not at all or hardly at all when the extrinsic autonomic nerves to the colon have been removed; therefore, the reflexes almost certainly are transmitted by way of the autonomic nervous system.

Irritation in the colon can also initiate intense mass movements. For instance, a person who has an ulcerated condition of the colon mucosa (ulcerative colitis) frequently has mass movements that persist almost all the time.

Defecation

Most of the time, the rectum is empty of feces. This results partly from the fact that a weak functional sphincter exists about 20 centimeters from the anus at the junction between the sigmoid colon and the rectum. There is also a sharp angulation here that contributes additional resistance to filling of the rectum.

When a mass movement forces feces into the rectum, the desire for defecation occurs immediately, including reflex contraction of the rectum and relaxation of the anal sphincters.

Continual dribble of fecal matter through the anus is prevented by tonic constriction of (1) an internal anal sphincter, a several-centimeters-long thickening of the circular smooth muscle that lies immediately inside the anus, and (2) an external anal sphincter, composed of striated voluntary muscle that both surrounds the internal sphincter and extends distal to it. The external sphincter is controlled by nerve fibers in the pudendal nerve, which is part of the somatic nervous system and therefore is under voluntary, conscious, or at least subconscious control; subconsciously, the external sphincter is usually kept continuously constricted unless conscious signals inhibit the constriction.

Defecation Reflexes. Ordinarily, defecation is initiated by defecation reflexes. One of these reflexes is an intrinsic reflex mediated by the local enteric nervous system in the rectal wall. This can be described as follows: When feces enter the rectum, distention of the rectal wall initiates afferent signals that spread through the myenteric plexus to initiate peristaltic waves in the descending colon, sigmoid, and rectum, forcing feces toward the anus. As the peristaltic wave approaches the anus, the internal anal sphincter is relaxed by inhibitory signals from the myenteric plexus; if the external anal sphincter is also consciously, voluntarily relaxed at the same time, defecation occurs.

The intrinsic myenteric defecation reflex functioning by itself normally is relatively weak. To be effective in causing defecation, it usually must be fortified by another type of defecation reflex, a parasympathetic defecation reflex that involves the sacral segments of the spinal cord, shown in Figure 63-6. When the nerve endings in the rectum are stimulated, signals are transmitted first into the spinal cord and then reflexly back to the descending colon, sigmoid, rectum, and anus by way of parasympathetic nerve fibers in the pelvic nerves. These parasympathetic signals greatly intensify the peristaltic waves and relax the internal anal sphincter, thus converting the intrinsic myenteric defecation reflex from a weak effort into a powerful process of defecation that is sometimes effective in emptying the large bowel all the way from the splenic flexure of the colon to the anus.

Defecation signals entering the spinal cord initiate other effects, such as taking a deep breath, closure of the glottis, and contraction of the abdominal wall muscles to force the fecal contents of the colon downward and at the same time cause the pelvic floor to relax downward and pull outward on the anal ring to evacuate the feces.

![Figure 63-6 Afferent and efferent pathways of the parasympathetic mechanism for enhancing the defecation reflex.](image-url)
When it becomes convenient for the person to defecate, the defecation reflexes can purposely be activated by taking a deep breath to move the diaphragm downward and then contracting the abdominal muscles to increase the pressure in the abdomen, thus forcing fecal contents into the rectum to cause new reflexes. Reflexes initiated in this way are almost never as effective as those that arise naturally, for which reason people who too often inhibit their natural reflexes are likely to become severely constipated.

In newborn babies and in some people with transected spinal cords, the defecation reflexes cause automatic emptying of the lower bowel at inconvenient times during the day because of lack of conscious control exercised through voluntary contraction or relaxation of the external anal sphincter.

**Other Autonomic Reflexes That Affect Bowel Activity**

Aside from the duodenocolic, gastrocolic, gastroileal, enterogastric, and defecation reflexes that have been discussed in this chapter, several other important nervous reflexes also can affect the overall degree of bowel activity. They are the peritoneointestinal reflex, renointestinal reflex, and vesicointestinal reflex.

The **peritoneointestinal reflex** results from irritation of the peritoneum; it strongly inhibits the excitatory enteric nerves and thereby can cause intestinal paralysis, especially in patients with peritonitis. The **renointestinal** and **vesicointestinal reflexes** inhibit intestinal activity as a result of kidney or bladder irritation, respectively.

**Bibliography**


Throughout the gastrointestinal tract, secretory glands subserve two primary functions: First, digestive enzymes are secreted in most areas of the alimentary tract, from the mouth to the distal end of the ileum. Second, mucous glands, from the mouth to the anus, provide mucus for lubrication and protection of all parts of the alimentary tract.

Most digestive secretions are formed only in response to the presence of food in the alimentary tract, and the quantity secreted in each segment of the tract is usually the precise amount needed for proper digestion. Furthermore, in some portions of the gastrointestinal tract, even the types of enzymes and other constituents of the secretions are varied in accordance with the types of food present. The purpose of this chapter is to describe the different alimentary secretions, their functions, and regulation of their production.

### General Principles of Alimentary Tract Secretion

#### Anatomical Types of Glands

Several types of glands provide the different types of alimentary tract secretions. First, on the surface of the epithelium in most parts of the gastrointestinal tract are billions of single-cell mucous glands called simply mucous cells or sometimes goblet cells because they look like goblets. They function mainly in response to local irritation of the epithelium: They extrude mucus directly onto the epithelial surface to act as a lubricant that also protects the surfaces from excoriation and digestion.

Second, many surface areas of the gastrointestinal tract are lined by pits that represent invaginations of the epithelium into the submucosa. In the small intestine, these pits, called crypts of Lieberkühn, are deep and contain specialized secretory cells. One of these cells is shown in Figure 64-1.

Third, in the stomach and upper duodenum are large numbers of deep tubular glands. A typical tubular gland can be seen in Figure 64-4, which shows an acid- and pepsinogen-secreting gland of the stomach (oxyntic gland).

Fourth, also associated with the alimentary tract are several complex glands—the salivary glands, pancreas, and liver—that provide secretions for digestion or emulsification of food. The liver has a highly specialized structure that is discussed in Chapter 70. The salivary glands and the pancreas are compound acinous glands of the type shown in Figure 64-2. These glands lie outside the walls of the alimentary tract and, in this, differ from all other alimentary glands. They contain millions of acini lined with secreting glandular cells; these acini feed into a system of ducts that finally empty into the alimentary tract itself.

#### Basic Mechanisms of Stimulation of the Alimentary Tract Glands

**Contact of Food with the Epithelium Stimulates Secretion—Function of Enteric Nervous Stimuli.** The mechanical presence of food in a particular segment of the gastrointestinal tract usually causes the glands of that region and adjacent regions to secrete moderate to large quantities of juices. Part of this local effect, especially the secretion of mucus by mucous cells, results from direct contact stimulation of the surface glandular cells by the food.

In addition, local epithelial stimulation also activates the enteric nervous system of the gut wall. The types of stimuli that do this are (1) tactile stimulation, (2) chemical irritation, and (3) distention of the gut wall. The resulting nervous reflexes stimulate both the mucous cells on the gut epithelial surface and the deep glands in the gut wall to increase their secretion.

**Autonomic Stimulation of Secretion**

**Parasympathetic Stimulation Increases Alimentary Tract Glandular Secretion Rate.** Stimulation of the parasympathetic nerves to the alimentary tract almost invariably increases the rates of alimentary glandular secretion. This is especially true of the glands in the upper portion of the tract (innervated by the glossopharyngeal and vagus parasympathetic nerves) such as the salivary glands, esophageal glands, gastric glands, pancreas, and Brunner’s glands in the duodenum. It is also true of some glands in the distal portion of the large intestine, innervated by pelvic parasympathetic nerves. Secretion in the remainder of the small intestine and in the first two thirds of the large intestine occurs mainly...
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Primary secretion:
1. Ptyalin
2. Mucus
3. Extracellular fluid

Saliva

Na\(^+\) active absorption
Cl\(^-\) passive absorption
K\(^+\) active secretion
HCO\(_3\)\(^-\) secretion

Figure 64-2  Formation and secretion of saliva by a submandibular salivary gland.

in response to local neural and hormonal stimuli in each segment of the gut.

Sympathetic Stimulation Has a Dual Effect on Alimentary Tract Glandular Secretion Rate. Stimulation of the sympathetic nerves going to the gastrointestinal tract causes a slight to moderate increase in secretion by some of the local glands. But sympathetic stimulation also results in constriction of the blood vessels that supply the glands. Therefore, sympathetic stimulation can have a dual effect: (1) sympathetic stimulation alone usually slightly increases secretion and (2) if parasympathetic or hormonal stimulation is already causing copious secretion by the glands, superimposed sympathetic stimulation usually reduces the secretion, sometimes significantly so, mainly because of vasoconstrictive reduction of the blood supply.

Regulation of Glandular Secretion by Hormones. In the stomach and intestine, several different gastrointestinal hormones help regulate the volume and character of the secretions. These hormones are liberated from the gastrointestinal mucosa in response to the presence of food in the lumen of the gut. The hormones are then absorbed into the blood and carried to the glands, where they stimulate secretion. This type of stimulation is particularly valuable to increase the output of gastric juice and pancreatic juice when food enters the stomach or duodenum.

Chemically, the gastrointestinal hormones are polypeptides or polypeptide derivatives.

Basic Mechanism of Secretion by Glandular Cells

Secretion of Organic Substances. Although all the basic mechanisms by which glandular cells function are not known, experimental evidence points to the following principles of secretion, as shown in Figure 64-1.

1. The nutrient material needed for formation of the secretion must first diffuse or be actively transported by the blood in the capillaries into the base of the glandular cell.

2. Many mitochondria located inside the glandular cell near its base use oxidative energy to form adenosine triphosphate (ATP).

3. Energy from the ATP, along with appropriate substrates provided by the nutrients, is then used to synthesize the organic secretory substances; this synthesis occurs almost entirely in the endoplasmic reticulum and Golgi complex of the glandular cell. Ribosomes adherent to the reticulum are specifically responsible for formation of the proteins that are secreted.

4. The secretory materials are transported through the tubules of the endoplasmic reticulum, passing in about 20 minutes all the way to the vesicles of the Golgi complex.

5. In the Golgi complex, the materials are modified, added to, concentrated, and discharged into the cytoplasm in the form of secretory vesicles, which are stored in the apical ends of the secretory cells.

6. These vesicles remain stored until nervous or hormonal control signals cause the cells to extrude the vesicular contents through the cells’ surface. This probably occurs in the following way: The control signal first increases the cell membrane permeability to calcium ions, and calcium enters the cell. The calcium in turn causes many of the vesicles to fuse with the apical cell membrane. Then the apical cell membrane breaks open, thus emptying the vesicles to the exterior; this process is called exocytosis.

Water and Electrolyte Secretion. A second necessity for glandular secretion is secretion of sufficient water and electrolytes to go along with the organic substances. Secretion by the salivary glands, discussed in more detail later, provides an example of how nervous stimulation causes water and salts to pass through the glandular
cells in great profusion, washing the organic substances through the secretory border of the cells at the same time. Hormones acting on the cell membrane of some glandular cells are believed also to cause secretory effects similar to those caused by nervous stimulation.

**Lubricating and Protective Properties of Mucus, and Importance of Mucus in the Gastrointestinal Tract**

Mucus is a thick secretion composed mainly of water, electrolytes, and a mixture of several glycoproteins, which themselves are composed of large polysaccharides bound with much smaller quantities of protein. Mucus is slightly different in different parts of the gastrointestinal tract, but everywhere it has several important characteristics that make it both an excellent lubricant and a protectant for the wall of the gut. *First*, mucus has adherent qualities that make it adhere tightly to the food or other particles and to spread as a thin film over the surfaces. *Second*, it has sufficient body that it coats the wall of the gut and prevents actual contact of most food particles with the mucosa. *Third*, mucus has a low resistance for slippage, so the particles can slide along the epithelium with great ease. *Fourth*, mucus causes fecal particles to adhere to one another to form the feces that are expelled during a bowel movement. *Fifth*, mucus is strongly resistant to digestion by the gastrointestinal enzymes. And *sixth*, the glycoproteins of mucus have amphoteric properties, which means that they are capable of buffering small amounts of either acids or alkalis; also, mucus often contains moderate quantities of bicarbonate ions, which specifically neutralize acids.

In summary, mucus has the ability to allow easy slippage of food along the gastrointestinal tract and to prevent excoriatory or chemical damage to the epithelium. A person becomes acutely aware of the lubricating qualities of mucus when the salivary glands fail to secrete saliva, because then it is difficult to swallow solid food even when it is eaten along with large amounts of water.

### Table 64-1 Daily Secretion of Intestinal Juices

<table>
<thead>
<tr>
<th>Type of Secretion</th>
<th>Daily Volume (ml)</th>
<th>pH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva</td>
<td>1000</td>
<td>6.0-7.0</td>
</tr>
<tr>
<td>Gastric secretion</td>
<td>1500</td>
<td>1.0-3.5</td>
</tr>
<tr>
<td>Pancreatic secretion</td>
<td>1000</td>
<td>8.0-8.3</td>
</tr>
<tr>
<td>Bile</td>
<td>1000</td>
<td>7.8</td>
</tr>
<tr>
<td>Small intestine secretion</td>
<td>1800</td>
<td>7.5-8.0</td>
</tr>
<tr>
<td>Brunner’s gland secretion</td>
<td>200</td>
<td>8.0-8.9</td>
</tr>
<tr>
<td>Large intestinal secretion</td>
<td>200</td>
<td>7.5-8.0</td>
</tr>
<tr>
<td>Total</td>
<td>6700</td>
<td></td>
</tr>
</tbody>
</table>

### Secretion of Ions in Saliva

Saliva contains especially large quantities of potassium and bicarbonate ions. Conversely, the concentrations of both sodium and chloride ions are several times less in saliva than in plasma. One can understand these special concentrations of ions in the saliva from the following description of the mechanism for secretion of saliva.

Figure 64-2 shows secretion by the submandibular gland, a typical compound gland that contains acini and salivary ducts. Salivary secretion is a two-stage operation: The first stage involves the acini, and the second, the salivary ducts. The acini secrete a primary secretion that contains ptyalin and/or mucin in a solution of ions in concentrations not greatly different from those of typical extracellular fluid. As the primary secretion flows through the ducts, two major active transport processes take place that markedly modify the ionic composition of the fluid in the saliva.

First, sodium ions are actively reabsorbed from all the salivary ducts and potassium ions are actively secreted in exchange for the sodium. Therefore, the sodium ion concentration of the saliva becomes greatly reduced, whereas the potassium ion concentration becomes increased. However, there is excess sodium reabsorption over potassium secretion, and this creates electrical negativity of about −70 millivolts in the salivary ducts; this in turn causes chloride ions to be reabsorbed passively. Therefore, the chloride ion concentration in the salivary fluid falls to a very low level, matching the ductal decrease in sodium ion concentration.

Second, bicarbonate ions are secreted by the ductal epithelium into the lumen of the duct. This is at least partly caused by passive exchange of bicarbonate for chloride ions, but it may also result partly from an active secretory process.

The net result of these transport processes is that under resting conditions, the concentrations of sodium and chloride ions in the saliva are only about 15 mEq/L each, about one-seventh to one-tenth their concentrations in plasma. Conversely, the concentration of potassium ions is about 30 mEq/L, seven times as great as in plasma, and the concentration of bicarbonate ions is 50 to 70 mEq/L, about two to three times that of plasma.

**Secretion of Saliva**

**Saliva Contains a Serous Secretion and a Mucus Secretion.** The principal glands of salivation are the parotid, submandibular, and sublingual glands; in addition, there are many tiny buccal glands. Daily secretion of saliva normally ranges between 800 and 1500 milliliters, as shown by the average value of 1000 milliliters in Table 64-1.

Saliva contains two major types of protein secretion: (1) a serous secretion that contains ptyalin (an α-amylase), which is an enzyme for digesting starches, and (2) mucus secretion that contains mucin for lubricating and for surface protective purposes.

The parotid glands secrete almost entirely the serous type of secretion, whereas the submandibular and sublingual glands secrete both serous secretion and mucus. The buccal glands secrete only mucus. Saliva has a pH between 6.0 and 7.0, a favorable range for the digestive action of ptyalin.
Parasympathetic nervous regulation of salivary secretion under basal awake conditions. About 0.5 milliliter of saliva, almost entirely of the mucous type, is secreted each minute; but during sleep, little secretion occurs. This secretion plays an exceedingly important role for maintaining healthy oral tissues. The mouth is loaded with pathogenic bacteria that can easily destroy tissues and cause dental caries. Saliva helps prevent the deteriorative processes in several ways.

First, the flow of saliva itself helps wash away pathogenic bacteria, as well as food particles that provide their metabolic support.

Second, saliva contains several factors that destroy bacteria. One of these is thiocyanate ions and several proteolytic enzymes—most important, lysozyme—that (a) attack the bacteria, (b) aid the thiocyanate ions in entering the bacteria where these ions in turn become bactericidal, and (c) digest food particles, thus helping further to remove the bacterial metabolic support.

Third, saliva often contains significant amounts of protein antibodies that can destroy oral bacteria, including some that cause dental caries. In the absence of salivation, oral tissues often become ulcerated and otherwise infected, and caries of the teeth can become rampant.

Function of Saliva for Oral Hygiene. Under basal awake conditions, about 0.5 milliliter of saliva, almost entirely of the mucous type, is secreted each minute; but during sleep, little secretion occurs. This secretion plays an exceedingly important role for maintaining healthy oral tissues. The mouth is loaded with pathogenic bacteria that can easily destroy tissues and cause dental caries. Saliva helps prevent the deteriorative processes in several ways.

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Nervous Regulation of Salivary Secretion

Figure 64-3 shows the parasympathetic nervous pathways for regulating salivation, demonstrating that the salivary glands are controlled mainly by parasympathetic nervous signals all the way from the superior and inferior salivatory nuclei in the brain stem.

The salivatory nuclei are located approximately at the juncture of the medulla and pons and are excited by both taste and tactile stimuli from the tongue and other areas of the mouth and pharynx. Many taste stimuli, especially the sour taste (caused by acids), elicit copious secretion of saliva—often 8 to 20 times the basal rate of secretion. Also, certain tactile stimuli, such as the presence of smooth objects in the mouth (e.g., a pebble), cause marked salivation, whereas rough objects cause less salivation and occasionally even inhibit salivation.

Salivation can also be stimulated or inhibited by nervous signals arriving in the salivatory nuclei from higher centers of the central nervous system. For instance, when a person smells or eats favorite foods, salivation is greater than when disliked food is smelled or eaten. The appetite area of the brain, which partially regulates these effects, is located in proximity to the parasympathetic centers of the anterior hypothalamus, and it functions to a great extent in response to signals from the taste and smell areas of the cerebral cortex or amygdala.

Salivation also occurs in response to reflexes originating in the stomach and upper small intestines—particularly when irritating foods are swallowed or when a person is nauseated because of some gastrointestinal abnormality. The saliva, when swallowed, helps to remove the irritating factor in the gastrointestinal tract by diluting or neutralizing the irritant substances.

Sympathetic stimulation can also increase salivation a slight amount, much less so than does parasympathetic stimulation. The sympathetic nerves originate from the superior cervical ganglia and travel along the surfaces of the blood vessels to the salivary glands.

A secondary factor that also affects salivary secretion is the blood supply to the glands because secretion always requires adequate nutrients from the blood. The parasympathetic nerve signals that induce copious salivation also moderately dilate the blood vessels. In addition, salivation itself directly dilates the blood vessels, thus providing increased salivatory gland nutrition as needed by the secreting cells. Part of this additional vasodilator effect is caused by kallikrein secreted by the activated salivary cells, which in turn acts as an enzyme to split one of the blood proteins, an alpha2-globulin, to form bradykinin, a strong vasodilator.

Esophageal Secretion

The esophageal secretions are entirely mucous and mainly provide lubrication for swallowing. The main body of the esophagus is lined with many simple mucous glands. At the gastric end and to a lesser extent in the initial portion of the esophagus, there are also many compound mucous glands. The mucus secreted by the compound glands in the upper esophagus prevents mucosal excoriation by newly entering...
food, whereas the compound glands located near the esophagogastric junction protect the esophageal wall from digestion by acidic gastric juices that often reflex from the stomach back into the lower esophagus. Despite this protection, a peptic ulcer at times can still occur at the gastric end of the esophagus.

**Gastric Secretion**

**Characteristics of the Gastric Secretions**

In addition to mucus-secreting cells that line the entire surface of the stomach, the stomach mucosa has two important types of tubular glands: *oxyntic glands* (also called *gastric glands*) and *pyloric glands*. The oxyntic (acid-forming) glands secrete *hydrochloric acid*, *pepsinogen*, *intrinsic factor*, and *mucus*. The pyloric glands secrete mainly *mucus* for protection of the pyloric mucosa from the stomach acid. They also secrete the hormone *gastrin*.

The oxyntic glands are located on the inside surfaces of the body and fundus of the stomach, constituting the proximal 80 percent of the stomach. The pyloric glands are located in the antral portion of the stomach, the distal 20 percent of the stomach.

**Secretions from the Oxyntic (Gastric) Glands**

A typical stomach oxyntic gland is shown in Figure 64-4. It is composed of three types of cells: (1) *mucous neck cells*, which secrete mainly *mucus*; (2) *peptic (or chief)* cells, which secrete large quantities of *pepsinogen*; and (3) *parietal (or oxyntic)* cells, which secrete *hydrochloric acid* and *intrinsic factor*. Secretion of hydrochloric acid by the parietal cells involves special mechanisms, as follows.

**Basic Mechanism of Hydrochloric Acid Secretion.** When stimulated, the parietal cells secrete an acid solution that contains about 160 mmol/L of hydrochloric acid, which is nearly isotonic with the body fluids. The pH of this acid is about 0.8, demonstrating its extreme acidity. At this pH, the hydrogen ion concentration is about 3 million times that of the arterial blood. To concentrate the hydrogen ions this tremendous amount requires more than 1500 calories of energy per liter of gastric juice. At the same time that hydrogen ions are secreted, bicarbonate ions diffuse into the blood so that gastric venous blood has a higher pH than arterial blood when the stomach is secreting acid.

Figure 64-5 shows schematically the functional structure of a parietal cell (also called *oxyntic cell*), demonstrating that it contains large branching intracellular *canaliculi*. The hydrochloric acid is formed at the villus-like projections inside these canaliculi and is then conducted through the canaliculi to the secretory end of the cell.

The main driving force for hydrochloric acid secretion by the parietal cells is a *hydrogen-potassium pump* (*H⁺-K⁺ ATPase*). The chemical mechanism of hydrochloric acid formation is shown in Figure 64-6 and consists of the following steps:

1. Water inside the parietal cell becomes dissociated into H⁺ and OH⁻ in the cell cytoplasm. The H⁺ is then actively secreted into the canaliculus in exchange for K⁺, an active exchange process that is catalyzed by H⁺-K⁺ ATPase. Potassium ions transported into the cell by the Na⁺-K⁺ ATPase pump on the basolateral (extracellular) side of the membrane tend to leak into the lumen but are recycled back into the cell by the H⁺-K⁺ ATPase. The basolateral Na⁺-K⁺ ATPase creates low intracellular Na⁺, which contributes to Na⁺ reabsorption from the lumen of the canaliculus. Thus, most of the K⁺ and Na⁺ in the canaliculus is reabsorbed into the cell cytoplasm, and hydrogen ions take their place in the canaliculus.

2. The pumping of H⁺ out of the cell by the H⁺-K⁺ ATPase permits OH⁻ to accumulate and form HCO₃⁻ from CO₂, either formed during metabolism in the cell or entering
the cell from the blood. This reaction is catalyzed by carbonic anhydrase. The HCO$_3^-$ is then transported across the basolateral membrane into the extracellular fluid in exchange for chloride ions, which enter the cell and are secreted through chloride channels into the canaliculus, giving a strong solution of hydrochloric acid in the canaliculus. The hydrochloric acid is then secreted outward through the open end of the canaliculus into the lumen of the gland.

3. Water passes into the canaliculus by osmosis because of extra ions secreted into the canaliculus. Thus, the final secretion from the canaliculus contains water, hydrochloric acid at a concentration of about 150 to 160 mEq/L, potassium chloride at a concentration of 15 mEq/L, and a small amount of sodium chloride. To produce a concentration of hydrogen ions as great as that found in gastric juice requires minimal back leak into the mucosa of the secreted acid. A major part of the stomach’s ability to prevent back leak of acid can be attributed to the gastric barrier due to the formation of alkaline mucus and to tight junctions between epithelia cells as described later. If this barrier is damaged by toxic substances, such as occurs with excessive use of aspirin or alcohol, the secreted acid does leak down an electrochemical gradient into the mucosa, causing stomach mucosal damage.

Basic Factors That Stimulate Gastric Secretion Are Acetylcholine, Gastrin, and Histamine. Acetylcholine released by parasympathetic stimulation excites secretion of pepsinogen by peptic cells, hydrochloric acid by parietal cells, and mucus by mucous cells. In comparison, both gastrin and histamine strongly stimulate secretion of acid by parietal cells but have little effect on the other cells.

Secretion and Activation of Pepsinogen. Several slightly different types of pepsinogen are secreted by the peptic and mucous cells of the gastric glands. Even so, all the pepsinogens perform the same functions. When pepsinogen is first secreted, it has no digestive activity. However, as soon as it comes in contact with hydrochloric acid, it is activated to form active pepsin. In this process, the pepsinogen molecule, having a molecular weight of about 42,500, is split to form a pepsin molecule, having a molecular weight of about 35,000.

Pepsin functions as an active proteolytic enzyme in a highly acid medium (optimum pH 1.8 to 3.5), but above a pH of about 5 it has almost no proteolytic activity and becomes completely inactivated in a short time. Hydrochloric acid is as necessary as pepsin for protein digestion in the stomach, as discussed in Chapter 65.

Secretion of Intrinsic Factor by Parietal Cells. The substance intrinsic factor, essential for absorption of vitamin B$_{12}$ in the ileum, is secreted by the parietal cells along with the secretion of hydrochloric acid. When the acid-producing parietal cells of the stomach are destroyed, which frequently occurs in chronic gastritis, the person develops not only achlorhydria (lack of stomach acid secretion) but often also pernicious anemia because of failure of maturation of the red blood cells in the absence of vitamin B$_{12}$ stimulation of the bone marrow. This is discussed in detail in Chapter 32.

Pyloric Glands—Secretion of Mucus and Gastrin
The pyloric glands are structurally similar to the oxyntic glands but contain few peptic cells and almost no parietal cells. Instead, they contain mostly mucous cells that are identical with the mucous neck cells of the oxyntic glands. These cells secrete a small amount of pepsinogen, as discussed earlier, and an especially large amount of thin mucus that helps to lubricate food movement, as well as to protect the stomach wall from digestion by the gastric enzymes. The pyloric glands also secrete the hormone gastrin, which plays a key role in controlling gastric secretion, as we discuss shortly.
Surface Mucous Cells

The entire surface of the stomach mucosa between glands has a continuous layer of a special type of mucous cells called simply "surface mucous cells." They secrete large quantities of viscid mucus that coats the stomach mucosa with a gel layer of mucus often more than 1 millimeter thick, thus providing a major shell of protection for the stomach wall, as well as contributing to lubrication of food transport.

Another characteristic of this mucus is that it is alkaline. Therefore, the normal underlying stomach wall is not directly exposed to the highly acidic, proteolytic stomach secretion. Even the slightest contact with food or any irritation of the mucosa directly stimulates the surface mucous cells to secrete additional quantities of this thick, alkaline, viscid mucus.

Stimulation of Gastric Acid Secretion

Parietal Cells of the Oxyntic Glands Are the Only Cells That Secrete Hydrochloric Acid. The parietal cells, located deep in the oxyntic glands of the main body of the stomach, are the only cells that secrete hydrochloric acid. As noted earlier in the chapter, the acidity of the fluid secreted by these cells can be great, with pH as low as 0.8. However, secretion of this acid is under continuous control by both endocrine and nervous signals. Furthermore, the parietal cells operate in close association with another type of cell called enterochromaffin-like cells (ECL cells), the primary function of which is to secrete histamine.

The ECL cells lie in the deep recesses of the oxyntic glands and therefore release histamine in direct contact with the parietal cells of the glands. The rate of formation and secretion of hydrochloric acid by the parietal cells is directly related to the amount of histamine secreted by the ECL cells. In turn, the ECL cells are stimulated to secrete histamine by the hormonal substance gastrin, which is formed almost entirely in the antral portion of the stomach mucosa in response to proteins in the foods being digested. The ECL cells may also be stimulated by hormonal substances secreted by the enteric nervous system of the stomach wall. Let us discuss first the gastrin mechanism for control of the ECL cells and their subsequent control of parietal cell secretion of hydrochloric acid.

Stimulation of Acid Secretion by Gastrin. Gastrin is itself a hormone secreted by gastrin cells, also called G cells. These cells are located in the pyloric glands in the distal end of the stomach. Gastrin is a large polypeptide secreted in two forms: a large form called G-34, which contains 34 amino acids, and a smaller form, G-17, which contains 17 amino acids. Although both of these are important, the smaller is more abundant.

When meats or other protein-containing foods reach the antral end of the stomach, some of the proteins from these foods have a special stimulatory effect on the gastrin cells in the pyloric glands to cause release of gastrin into the blood to be transported to the ECL cells of the stomach. The vigorous mixing of the gastric juices transports the gastrin rapidly to the ECL cells in the body of the stomach, causing release of histamine directly into the deep oxyntic glands. The histamine then acts quickly to stimulate gastric hydrochloric acid secretion.

Regulation of Pepsinogen Secretion

Regulation of pepsinogen secretion by the peptic cells in the oxyntic glands occurs in response to two main types of signals: (1) stimulation of the peptic cells by acetylcholine released from the vagus nerves or from the gastric enteric nervous plexus, and (2) stimulation of peptic cell secretion in response to acid in the stomach. The acid probably does not stimulate the peptic cells directly but instead elicits additional enteric nervous reflexes that support the original nervous signals to the peptic cells. Therefore, the rate of secretion of pepsinogen, the precursor of the enzyme pepsin that causes protein digestion, is strongly influenced by the amount of acid in the stomach. In people who have lost the ability to secrete normal amounts of acid, secretion of pepsinogen is also decreased, even though the peptic cells may otherwise appear to be normal.

Phases of Gastric Secretion

Gastric secretion is said to occur in three "phases" (as shown in Figure 64-7): a cephalic phase, a gastric phase, and an intestinal phase.

Cephalic Phase. The cephalic phase of gastric secretion occurs even before food enters the stomach, especially while it is being eaten. It results from the sight, smell, thought, or taste of food, and the greater the appetite, the more intense is the stimulation. Neurogenic signals that cause the cephalic phase of gastric secretion originate in the cerebral cortex and in the appetite centers of the amygdala and hypothalamus. They are transmitted through the dorsal motor nuclei of the vagi and thence through the vagus nerves to the stomach. This phase of secretion normally accounts for about 30 percent of the gastric secretion associated with eating a meal.

Gastric Phase. Once food enters the stomach, it excites (1) long vagovagal reflexes from the stomach to the brain and back to the stomach, (2) local enteric reflexes, and (3) the gastrin mechanism, all of which in turn cause secretion of gastric juice during several hours while food remains in the stomach. The gastric phase of secretion accounts for about 60 percent of the total gastric secretion associated with eating a meal and therefore accounts for most of the total daily gastric secretion of about 1500 milliliters.

Intestinal Phase. The presence of food in the upper portion of the small intestine, particularly in the duodenum, will continue to cause stomach secretion of small amounts of gastric juice, probably partly because of small amounts of gastrin released by the duodenal mucosa. This accounts for about 10 percent of the acid response to a meal.
Inhibition of Gastric Secretion by Other Post-Stomach Intestinal Factors

Although intestinal chyme slightly stimulates gastric secretion during the early intestinal phase of stomach secretion, it paradoxically inhibits gastric secretion at other times. This inhibition results from at least two influences.

1. The presence of food in the small intestine initiates a reverse enterogastric reflex, transmitted through the myenteric nervous system and extrinsic sympathetic and vagus nerves, that inhibits stomach secretion. This reflex can be initiated by distending the small bowel, by the presence of acid in the upper intestine, by the presence of protein breakdown products, or by irritation of the mucosa. This is part of the complex mechanism discussed in Chapter 63 for slowing stomach emptying when the intestines are already filled.

2. The presence of acid, fat, protein breakdown products, hyperosmotic or hypo-osmotic fluids, or any irritating factor in the upper small intestine causes release of several intestinal hormones. One of these is secretin, which is especially important for control of pancreatic secretion. However, secretin opposes stomach secretion. Three other hormones—gastric inhibitory peptide (glucose-dependent insulinotropic peptide), vasoactive intestinal polypeptide, and somatostatin—also have slight to moderate effects in inhibiting gastric secretion.

The functional purpose of intestinal factors that inhibit gastric secretion is presumably to slow passage of chyme from the stomach when the small intestine is already filled or already overactive. In fact, the enterogastric inhibitory reflexes plus inhibitory hormones usually also reduce stomach motility at the same time that they reduce gastric secretion, as was discussed in Chapter 63.

Gastric Secretion During the Interdigestive Period. The stomach secretes a few milliliters of gastric juice each hour during the “interdigestive period,” when little or no digestion is occurring anywhere in the gut. The secretion that does occur is usually almost entirely of the nonoxyntic type, composed mainly of mucus but little pepsin and almost no acid.

Unfortunately, emotional stimuli frequently increase interdigestive gastric secretion (highly peptic and acidic) to 50 milliliters or more per hour, in much the same way that the cephalic phase of gastric secretion excites secretion at the onset of a meal. This increase of secretion in response to emotional stimuli is believed to be one of the causative factors in development of peptic ulcers, as discussed in Chapter 66.

Chemical Composition of Gastrin and Other Gastrointestinal Hormones

Gastrin, cholecystokinin (CCK), and secretin are all large polypeptides with approximate molecular weights, respectively, of 2000, 4200, and 3400. The terminal five amino acids in the gastrin and CCK molecular chains are the same. The functional activity of gastrin resides in the terminal four amino acids, and the activity for CCK resides in the terminal eight amino acids. All the amino acids in the secretin molecule are essential.

A synthetic gastrin, composed of the terminal four amino acids of natural gastrin plus the amino acid alanine, has all the same physiologic properties as the natural gastrin. This synthetic product is called pentagastrin.
before it empties into the duodenum through the papilla of Vater, surrounded by the sphincter of Oddi.

Pancreatic juice is secreted most abundantly in response to the presence of chyme in the upper portions of the small intestine, and the characteristics of the pancreatic juice are determined to some extent by the types of food in the chyme. (The pancreas also secretes insulin, but this is not secreted by the same pancreatic tissue that secretes intestinal pancreatic juice. Instead, insulin is secreted directly into the blood—not into the intestine—by the islets of Langerhans that occur in islet patches throughout the pancreas. These are discussed in detail in Chapter 78.)

Pancreatic Digestive Enzymes

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

The most important of the pancreatic enzymes for digesting proteins are trypsin, chymotrypsin, and carboxy-peptidase. By far the most abundant of these is trypsin.

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

The pancreatic enzyme for digesting carbohydrates is pancreatic amylase, which hydrolyzes starches, glycogen, and most other carbohydrates (except cellulose) to form mostly disaccharides and a few trisaccharides.

The main enzymes for fat digestion are (1) pancreatic lipase, which is capable of hydrolyzing neutral fat into fatty acids and monoglycerides; (2) cholesterol esterase, which causes hydrolysis of cholesterol esters; and (3) phospholipase, which splits fatty acids from phospholipids.

When first synthesized in the pancreatic cells, the proteolytic digestive enzymes are in the inactive forms trypsinogen, chymotrypsinogen, and procarboxypolypeptidase, which are all inactive enzymatically. They become activated only after they are secreted into the intestinal tract. Trypsinogen is activated by an enzyme called enterokinase, which is secreted by the intestinal mucosa when chyme comes in contact with the mucosa. Also, trypsinogen can be autocatalytically activated by trypsin that has already been formed from previously secreted trypsino- gen. Chymotrypsinogen is activated by trypsin to form chymotrypsin, and procarboxy-polypeptidase is activated in a similar manner.

Secretion of Trypsin Inhibitor Prevents Digestion of the Pancreas Itself. It is important that the proteolytic enzymes of the pancreatic juice not become activated until after they have been secreted into the intestine because the trypsin and the other enzymes would digest the pancreas itself. Fortunately, the same cells that secrete proteolytic enzymes into the acini of the pancreas secrete simultaneously another substance called trypsin inhibitor. This substance is formed in the cytoplasm of the glandular cells, and it prevents activation of trypsin both inside the secretory cells and in the acini and ducts of the pancreas. And, because it is trypsin that activates the other pancreatic proteolytic enzymes, trypsin inhibitor prevents activation of the others as well.

When the pancreas becomes severely damaged or when a duct becomes blocked, large quantities of pancreatic secretion sometimes become pooled in the damaged areas of the pancreas. Under these conditions, the effect of trypsin inhibitor is often overwhelmed, in which case the pancreatic secretions rapidly become activated and can literally digest the entire pancreas within a few hours, giving rise to the condition called acute pancreatitis. This is sometimes lethal because of accompanying circulatory shock; even if not lethal, it usually leads to a subsequent lifetime of pancreatic insufficiency.

Secretion of Bicarbonate Ions

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

The basic steps in the cellular mechanism for secreting sodium bicarbonate solution into the pancreatic ductules and ducts are shown in Figure 64-8. They are the following:

1. Carbon dioxide diffuses to the interior of the cell from the blood and, under the influence of carbonic anhydrase, combines with water to form carbonic acid (H₂CO₃). The carbonic acid in turn dissociates into bicarbonate ions and hydrogen ions (HCO₃⁻ and H⁺). Then the bicarbonate ions are actively transported in association with sodium ions (Na⁺) through the luminal border of the cell into the lumen of the duct.

2. The hydrogen ions formed by dissociation of carbonic acid inside the cell are exchanged for sodium ions through the blood border of the cell by a secondary active transport process. This supplies the sodium ions (Na⁺) that are transported through the luminal border into the pancreatic duct lumen to provide electrical neutrality for the secreted bicarbonate ions.
3. The overall movement of sodium and bicarbonate ions from the blood into the duct lumen creates an osmotic pressure gradient that causes osmosis of water also into the pancreatic duct, thus forming an almost completely isosmotic bicarbonate solution.

Regulation of Pancreatic Secretion

Basic Stimuli That Cause Pancreatic Secretion

Three basic stimuli are important in causing pancreatic secretion:

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

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

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

The first two of these stimuli, acetylcholine and cholecystokinin, stimulate the acinar cells of the pancreas, causing production of large quantities of pancreatic digestive enzymes but relatively small quantities of water and electrolytes to go with the enzymes. Without the water, most of the enzymes remain temporarily stored in the acini and ducts until more fluid secretion comes along to wash them into the duodenum. Secretin, in contrast to the first two basic stimuli, stimulates secretion of large quantities of water solution of sodium bicarbonate by the pancreatic ductal epithelium.

**Multiplicative Effects of Different Stimuli.** When all the different stimuli of pancreatic secretion occur at once, the total secretion is far greater than the sum of the secretions caused by each one separately. Therefore, the various stimuli are said to “multiply,” or “potentiate,” one another. Thus, pancreatic secretion normally results from the combined effects of the multiple basic stimuli, not from one alone.

**Phases of Pancreatic Secretion**

Pancreatic secretion occurs in three phases, the same as for gastric secretion: the *cephalic phase*, the *gastric phase*, and the *intestinal phase*. Their characteristics are as follows.

**Cephalic and Gastric Phases.** During the cephalic phase of pancreatic secretion, the same nervous signals from the brain that cause secretion in the stomach also cause acetylcholine release by the vagal nerve endings in the pancreas. This causes moderate amounts of enzymes to be secreted into the pancreatic acini, accounting for about 20 percent of the total secretion of pancreatic enzymes after a meal. But little of the secretion flows immediately through the pancreatic ducts into the intestine because only small amounts of water and electrolytes are secreted along with the enzymes.

During the gastric phase, the nervous stimulation of enzyme secretion continues, accounting for another 5 to 10 percent of pancreatic enzymes secreted after a meal. But, again, only small amounts reach the duodenum because of continued lack of significant fluid secretion.

**Intestinal Phase.** After chyme leaves the stomach and enters the small intestine, pancreatic secretion becomes copious, mainly in response to the hormone **secretin**.

**Secretin Stimulates Copious Secretion of Bicarbonate Ions, Which Neutralizes Acidic Stomach Chyme.** Secretin is a polypeptide, containing 27 amino acids (molecular weight about 3400), present in an inactive form, prosecretin, in so-called S cells in the mucosa of the duodenum and jejunum. When acid chyme with pH less than 4.5 to 5.0 enters the duodenum from the stomach, it causes duodenal mucosal release and activation of secretin, which is then absorbed into the blood. The one truly potent constituent of chyme that causes this secretin release is the hydrochloric acid from the stomach.

Secretin in turn causes the pancreas to secrete large quantities of fluid containing a high concentration of bicarbonate ion (up to 145 mEq/L) but a low concentration of chloride ion. The secretin mechanism is especially important for two reasons: First, secretin begins to be released from the mucosa of the small intestine when the pH of the duodenal contents falls below 4.5 to 5.0, and its release increases greatly as the pH falls to 3.0. This immediately causes copious secretion of pancreatic juice containing abundant amounts of sodium bicarbonate. The net result is then the following reaction in the duodenum:

$$\text{HCl} + \text{NaHCO}_3 \rightarrow \text{NaCl} + \text{H}_2\text{CO}_3$$

Then the carbonic acid immediately dissociates into carbon dioxide and water. The carbon dioxide is absorbed into the blood and expired through the lungs, thus leaving a neutral solution of sodium chloride in the duodenum.
In this way, the acid contents emptied into the duodenum from the stomach become neutralized, so further peptic digestive activity by the gastric juices in the duodenum is immediately blocked. Because the mucosa of the small intestine cannot withstand the digestive action of acid gastric juice, this is an essential protective mechanism to prevent development of duodenal ulcers, as is discussed in further detail in Chapter 66.

Bicarbonate ion secretion by the pancreas provides an appropriate pH for action of the pancreatic digestive enzymes, which function optimally in a slightly alkaline or neutral medium, at a pH of 7.0 to 8.0. Fortunately, the pH of the sodium bicarbonate secretion averages 8.0.

Cholecystokinin—Its Contribution to Control of Digestive Enzyme Secretion by the Pancreas. The presence of food in the upper small intestine also causes a second hormone, CCK, a polypeptide containing 33 amino acids, to be released from yet another group of cells, the I cells, in the mucosa of the duodenum and upper jejunum. This release of CCK results especially from the presence of proteases and peptones (products of partial protein digestion) and long-chain fatty acids in the chyme coming from the stomach.

CCK, like secretin, passes by way of the blood to the pancreas but instead of causing sodium bicarbonate secretion causes mainly secretion of still much more pancreatic digestive enzymes by the acinar cells. This effect is similar to that caused by vagal stimulation but even more pronounced, accounting for 70 to 80 percent of the total secretion of the pancreatic digestive enzymes after a meal.

The differences between the pancreatic stimulatory effects of secretin and CCK are shown in Figure 64-9, which demonstrates (1) intense sodium bicarbonate secretion in response to acid in the duodenum, stimulated by secretin; (2) a dual effect in response to soap (a fat); and (3) intense digestive enzyme secretion (when peptones enter the duodenum) stimulated by CCK.

Figure 64-10 summarizes the more important factors in the regulation of pancreatic secretion. The total amount secreted each day is about 1 liter.

Secretion of Bile by the Liver; Functions of the Biliary Tree

One of the many functions of the liver is to secrete bile, normally between 600 and 1000 ml/day. Bile serves two important functions.

First, bile plays an important role in fat digestion and absorption, not because of any enzymes in the bile that cause fat digestion, but because bile acids in the bile do two things: (1) They help to emulsify the large fat particles of the food into many minute particles, the surface of which can then be attacked by lipase enzymes secreted in pancreatic juice, and (2) they aid in absorption of the digested fat end products through the intestinal mucosal membrane.

Second, bile serves as a means for excretion of several important waste products from the blood. These include especially bilirubin, an end product of hemoglobin destruction, and excesses of cholesterol.

Physiologic Anatomy of Biliary Secretion

Bile is secreted in two stages by the liver: (1) The initial portion is secreted by the principal functional cells of the liver, the hepatocytes; this initial secretion contains large amounts of bile acids, cholesterol, and other organic constituents. It is secreted into minute bile canaliculi that originate between the hepatic cells.

(2) Next, the bile flows in the canaliculi toward the interlobular septa, where the canaliculi empty into terminal bile ducts and then into progressively larger ducts, finally reaching the hepatic duct and common bile duct.
From these the bile either empties directly into the duodenum or is diverted for minutes up to several hours through the cystic duct into the gallbladder, shown in Figure 64-11.

In its course through the bile ducts, a second portion of liver secretion is added to the initial bile. This additional secretion is a watery solution of sodium and bicarbonate ions secreted by secretory epithelial cells that line the ductules and ducts. This second secretion sometimes increases the total quantity of bile by as much as an additional 100 percent. The second secretion is stimulated especially by secretin, which causes release of additional quantities of bicarbonate ions to supplement the bicarbonate ions in pancreatic secretion (for neutralizing acid that empties into the duodenum from the stomach).

**Storing and Concentrating Bile in the Gallbladder.** Bile is secreted continually by the liver cells, but most of it is normally stored in the gallbladder until needed in the duodenum. The maximum volume that the gallbladder can hold is only 30 to 60 milliliters. Nevertheless, as much as 12 hours of bile secretion (usually about 450 milliliters) can be stored in the gallbladder because water, sodium, chloride, and most other small electrolytes are continually absorbed through the gallbladder mucosa, concentrating the remaining bile constituents that contain the bile salts, cholesterol, lecithin, and bilirubin.

Most of this gallbladder absorption is caused by active transport of sodium through the gallbladder epithelium, and this is followed by secondary absorption of chloride ions, water, and most other diffusible constituents. Bile is normally concentrated in this way about 5-fold, but it can be concentrated up to a maximum of 20-fold.

**Composition of Bile.** Table 64-2 gives the composition of bile when it is first secreted by the liver and then after it has been concentrated in the gallbladder. This table shows that by far the most abundant substances secreted in the bile are bile salts, which account for about one half of the total solutes also in the bile. Also secreted or excreted in large concentrations are bilirubin, cholesterol, lecithin, and the usual electrolytes of plasma.

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<tr>
<td>Water</td>
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<td>Bilirubin</td>
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In the concentrating process in the gallbladder, water and large portions of the electrolytes (except calcium ions) are reabsorbed by the gallbladder mucosa; essentially all other constituents, especially the bile salts and the lipid substances cholesterol and lecithin, are not reabsorbed and, therefore, become highly concentrated in the gallbladder bile.

Emptying of the Gallbladder—Stimulatory Role of Cholecystokinin. When food begins to be digested in the upper gastrointestinal tract, the gallbladder begins to empty, especially when fatty foods reach the duodenum about 30 minutes after a meal. The mechanism of gallbladder emptying is rhythmical contractions of the wall of the gallbladder, but effective emptying also requires simultaneous relaxation of the sphincter of Oddi, which guards the exit of the common bile duct into the duodenum.

By far the most potent stimulus for causing the gallbladder contractions is the hormone CCK. This is the same CCK discussed earlier that causes increased secretion of digestive enzymes by the acinar cells of the pancreas. The stimulus for CCK entry into the blood from the duodenal mucosa is mainly the presence of fatty foods in the duodenum.

The gallbladder is also stimulated less strongly by acetylcholine-secreting nerve fibers from both the vagi and the intestinal enteric nervous system. They are the same nerves that promote motility and secretion in other parts of the upper gastrointestinal tract.

In summary, the gallbladder empties its store of concentrated bile into the duodenum mainly in response to the CCK stimulus that itself is initiated mainly by fatty foods. When fat is not in the food, the gallbladder empties poorly, but when significant quantities of fat are present, the gallbladder normally empties completely in about 1 hour.

Function of Bile Salts in Fat Digestion and Absorption

The liver cells synthesize about 6 grams of bile salts daily. The precursor of the bile salts is cholesterol, which is either present in the diet or synthesized in the liver cells during the course of fat metabolism. The cholesterol is first converted to cholic acid or chenodeoxycholic acid in about equal quantities. These acids in turn combine principally with glycine and to a lesser extent with taurine to form glyco- and tauro-conjugated bile acids. The salts of these acids, mainly sodium salts, are then secreted in the bile.

The bile salts have two important actions in the intestinal tract:

1. First, they have a detergent action on the fat particles in the food. This decreases the surface tension of the particles and allows agitation in the intestinal tract to break the fat globules into minute sizes. This is called the emulsifying or detergent function of bile salts.

2. Second, and even more important than the emulsifying function, bile salts help in the absorption of (1) fatty acids, (2) monoglycerides, (3) cholesterol, and (4) other lipids from the intestinal tract. They do this by forming small physical complexes with these lipids; the complexes are called micelles, and they are semisoluble in the chyme because of the electrical charges of the bile salts. The intestinal lipids are “ferried” in this form to the intestinal mucosa, where they are then absorbed into the blood, as will be described in detail in Chapter 65. Without the presence of bile salts in the intestinal tract, up to 40 percent of the ingested fats are lost into the feces and the person often develops a metabolic deficit because of this nutrient loss.

Enterohepatic Circulation of Bile Salts. About 94 percent of the bile salts are reabsorbed into the blood from the small intestine, about one half of this by diffusion through the mucosa in the early portions of the small intestine and the remainder by an active transport process through the intestinal mucosa in the distal ileum. They then enter the portal blood and pass back to the liver. On reaching the liver, on first passage through the venous sinusoids these salts are absorbed almost entirely back into the hepatic cells and then resecreted into the bile.

In this way, about 94 percent of all the bile salts are recirculated into the bile, so on the average these salts make the entire circuit some 17 times before being carried out in the feces. The small quantities of bile salts lost into the feces are replaced by new amounts formed continually by the liver cells. This recirculation of the bile salts is called the enterohepatic circulation of bile salts.

The quantity of bile secreted by the liver each day is highly dependent on the availability of bile salts—the greater the quantity of bile salts in the enterohepatic circulation (usually a total of only about 2.5 grams), the greater the rate of bile secretion. Indeed, ingestion of supplemental bile salts can increase bile secretion by several hundred milliliters per day.

If a bile fistula empties the bile salts to the exterior for several days to several weeks so that they cannot be reabsorbed from the ileum, the liver increases its production of bile salts 6- to 10-fold, which increases the rate of bile secretion most of the way back to normal. This demonstrates that the daily rate of liver bile salt secretion is actively controlled by the availability (or lack of availability) of bile salts in the enterohepatic circulation.

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

Bile salts are formed in the hepatic cells from cholesterol in the blood plasma. In the process of secreting the bile salts, about 1 to 2 grams of cholesterol are removed from the blood plasma and secreted into the bile each day.

Cholesterol is almost completely insoluble in pure water, but the bile salts and lecithin in bile combine physically with the cholesterol to form ultramicroscopic micelles in the form of a colloidal solution, as explained in more detail in Chapter 65. When the bile becomes concentrated in the gallbladder, the bile salts and lecithin become concentrated along with the cholesterol, which keeps the cholesterol in solution. Under abnormal conditions, the cholesterol may precipitate in the gallbladder, resulting in the formation of cholesterol gallstones, as shown in Figure 64-12. The amount of cholesterol in the bile is determined partly by the quantity of fat that the person eats, because liver cells synthesize cholesterol as one of the products of fat metabolism in the body. For this reason, people on a high-fat diet over a period of years are prone to the development of gallstones.

Under abnormal conditions, the cholesterol may precipitate in the gallbladder, resulting in the formation of cholesterol gallstones, as shown in Figure 64-12. The amount of cholesterol in the bile is determined partly by the quantity of fat that the person eats, because liver cells synthesize cholesterol as one of the products of fat metabolism in the body. For this reason, people on a high-fat diet over a period of years are prone to the development of gallstones.

Inflammation of the gallbladder epithelium, often resulting from low-grade chronic infection, may also change the absorptive characteristics of the gallbladder mucosa, sometimes allowing excessive absorption of water and bile salts but leaving behind the cholesterol in the gallbladder in progressively greater concentrations. Then the cholesterol begins to precipitate, first forming many small crystals of cholesterol on the surface of the inflamed mucosa, but then progressing to large gallstones.

Secretions of the Small Intestine

Secretion of Mucus by Brunner’s Glands in the Duodenum

An extensive array of compound mucous glands, called Brunner’s glands, is located in the wall of the first few centimeters of the duodenum, mainly between the pylorus of the stomach and the papilla of Vater, where pancreatic secretion and bile empty into the duodenum. These glands secrete large amounts of alkaline mucus in response to (1) tactile or irritating stimuli on the duodenal mucosa; (2) vagal stimulation, which causes increased Brunner’s glands secretion concurrently with increase in stomach secretion; and (3) gastrointestinal hormones, especially secretin.

The function of the mucus secreted by Brunner’s glands is to protect the duodenal wall from digestion by the highly acidic gastric juice emptying from the stomach. In addition, the mucus contains a large excess of bicarbonate ions, which add to the bicarbonate ions from pancreatic secretion and liver bile in neutralizing the hydrochloric acid entering the duodenum from the stomach.

Brunner’s glands are inhibited by sympathetic stimulation; therefore, such stimulation in very excitable persons is likely to leave the duodenal bulb unprotected and is perhaps one of the factors that cause this area of the gastrointestinal tract to be the site of peptic ulcers in about 50 percent of ulcer patients.

Secretion of Intestinal Digestive Juices by the Crypts of Lieberkühn

Located over the entire surface of the small intestine are small pits called crypts of Lieberkühn, one of which is illustrated in Figure 64-13. These crypts lie between the intestinal villi. The surfaces of both the crypts and the villi are covered by an epithelium composed of two types of cells: (1) a moderate number of goblet cells, which secrete mucus that lubricates and protects the intestinal surfaces, and (2) a large number of enterocytes, which, in the crypts, secrete large quantities of water and electrolytes and, over the surfaces of adjacent villi, reabsorb the water and electrolytes along with end products of digestion.

The intestinal secretions are formed by the enterocytes of the crypts at a rate of about 1800 ml/day. These secretions are almost pure extracellular fluid and have a slightly alkaline pH in the range of 7.5 to 8.0. The secretions are
also rapidly reabsorbed by the villi. This flow of fluid from the crypts into the villi supplies a watery vehicle for absorption of substances from chyme when it comes in contact with the villi. Thus, the primary function of the small intestine is to absorb nutrients and their digestive products into the blood.

**Mechanism of Secretion of the Watery Fluid.** The exact mechanism that controls the marked secretion of watery fluid by the crypts of Lieberkühn is still unclear, but it is believed to involve at least two active secretory processes: (1) active secretion of chloride ions into the crypts and (2) active secretion of bicarbonate ions. The secretion of both ions causes electrical drag of positively charged sodium ions through the membrane and into the secreted fluid as well. Finally, all these ions together cause osmotic movement of water.

**Digestive Enzymes in the Small Intestinal Secretion.** When secretions of the small intestine are collected without cellular debris, they have almost no enzymes. The enterocytes of the mucosa, especially those that cover the villi, contain digestive enzymes that digest specific food substances while they are being absorbed through the epithelium. These enzymes are the following: (1) several peptidases for splitting small peptides into amino acids; (2) four enzymes—sucrase, maltase, isomaltase, and lactase—for splitting disaccharides into monosaccharides; and (3) small amounts of intestinal lipase for splitting neutral fats into glycerol and fatty acids.

The epithelial cells deep in the crypts of Lieberkühn continually undergo mitosis, and new cells migrate along the basement membrane upward out of the crypts toward the tips of the villi, thus continually replacing the villus epithelium and also forming new digestive enzymes. As the villus cells age, they are finally shed into the intestinal secretions. The life cycle of an intestinal epithelial cell is about 5 days. This rapid growth of new cells also allows rapid repair of excoriations that occur in the mucosa.

**Regulation of Small Intestine Secretion—Local Stimuli**

By far the most important means for regulating small intestine secretion are local enteric nervous reflexes, especially reflexes initiated by tactile or irritative stimuli from the chyme in the intestines.

**Secretion of Mucus by the Large Intestine**

**Mucus Secretion.** The mucosa of the large intestine, like that of the small intestine, has many crypts of Lieberkühn; however, unlike the small intestine, there are no villi. The epithelial cells secrete almost no digestive enzymes. Instead, they contain mucous cells that secrete only mucus. This mucus contains moderate amounts of bicarbonate ions secreted by a few non-mucus-secreting epithelial cells. The rate of secretion of mucus is regulated principally by direct, tactile stimulation of the epithelial cells lining the large intestine and by local nervous reflexes to the mucous cells in the crypts of Lieberkühn.

Stimulation of the pelvic nerves from the spinal cord, which carry parasympathetic innervation to the distal one half to two thirds of the large intestine, also can cause marked increase in mucus secretion. This occurs along with increase in peristaltic motility of the colon, which was discussed in Chapter 63.

During extreme parasympathetic stimulation, often caused by emotional disturbances, so much mucus can occasionally be secreted into the large intestine that the person has a bowel movement of ropy mucus as often as every 30 minutes; this mucus often contains little or no fecal material.

Mucus in the large intestine protects the intestinal wall against excoriation, but in addition, it provides an adherent medium for holding fecal matter together. Furthermore, it protects the intestinal wall from the great amount of bacterial activity that takes place inside the feces, and, finally, the mucus plus the alkalinity of the secretion (pH of 8.0 caused by large amounts of sodium bicarbonate) provides a barrier to keep acids formed in the feces from attacking the intestinal wall.

**Diarrhea Caused by Excess Secretion of Water and Electrolytes in Response to Irritation.** Whenever a segment of the large intestine becomes intensely irritated, as occurs when bacterial infection becomes rampant during enteritis, the mucus secretes extra large quantities of water and electrolytes in addition to the normal viscid alkaline mucus. This acts to dilute the irritating factors and to cause rapid movement of the feces toward the anus. The result is diarrhea, with loss of large quantities of water and electrolytes. But the diarrhea also washes away irritant factors, which promotes earlier recovery from the disease than might otherwise occur.

**Bibliography**


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The major foods on which the body lives (with the exception of small quantities of substances such as vitamins and minerals) can be classified as carbohydrates, fats, and proteins. They generally cannot be absorbed in their natural forms through the gastrointestinal mucosa and, for this reason, are useless as nutrients without preliminary digestion. Therefore, this chapter discusses the processes by which carbohydrates, fats, and proteins are digested into small enough compounds for absorption and the mechanisms by which the digestive end products, as well as water, electrolytes, and other substances, are absorbed.

### Digestion of the Various Foods by Hydrolysis

**Hydrolysis of Carbohydrates.** Almost all the carbohydrates of the diet are either large polysaccharides or disaccharides, which are combinations of monosaccharides bound to one another by condensation. This means that a hydrogen ion (H\(^+\)) has been removed from one of the monosaccharides, and a hydroxyl ion (−OH) has been removed from the next one. The two monosaccharides then combine with each other at these sites of removal, and the hydrogen and hydroxyl ions combine to form water (H\(_2\)O).

When carbohydrates are digested, the above process is reversed and the carbohydrates are converted into monosaccharides. Specific enzymes in the digestive juices of the gastrointestinal tract return the hydrogen and hydroxyl ions from water to the polysaccharides and thereby separate the monosaccharides from each other. This process, called hydrolysis, is the following (in which R"-R’ is a disaccharide):

\[
R"\cdot R' + H_2O \xrightarrow{\text{digestive enzyme}} R"OH + R'H
\]

**Hydrolysis of Fats.** Almost the entire fat portion of the diet consists of triglycerides (neutral fats), which are combinations of three fatty acid molecules condensed with a single glycerol molecule. During condensation, three molecules of water are removed.

Digestion of the triglycerides consists of the reverse process: the fat-digesting enzymes return three molecules of water to the triglyceride molecule and thereby split the fatty acid molecules away from the glycerol. Here again, the digestive process is one of hydrolysis.

**Hydrolysis of Proteins.** Proteins are formed from multiple amino acids that are bound together by peptide linkages. At each linkage, a hydroxyl ion has been removed from one amino acid and a hydrogen ion has been removed from the succeeding one; thus, the successive amino acids in the protein chain are also bound together by condensation, and digestion occurs by the reverse effect: hydrolysis. That is, the proteolytic enzymes return hydrogen and hydroxyl ions from water molecules to the protein molecules to split them into their constituent amino acids.

Therefore, the chemistry of digestion is simple because, in the case of all three major types of food, the same basic process of hydrolysis is involved. The only difference lies in the types of enzymes required to promote the hydrolysis reactions for each type of food.

All the digestive enzymes are proteins. Their secretion by the different gastrointestinal glands was discussed in Chapter 64.

### Digestion of Carbohydrates

**Carbohydrate Foods of the Diet.** Only three major sources of carbohydrates exist in the normal human diet. They are sucrose, which is the disaccharide known popularly as cane sugar; lactose, which is a disaccharide...
found in milk; and *starches*, which are large polysaccharides present in almost all nonanimal foods, particularly in potatoes and different types of grains. Other carbohydrates ingested to a slight extent are *amylose*, *glycogen*, *alcohol*, *lactic acid*, *pyruvic acid*, *pectins*, *dextrins*, and minor quantities of *carbohydrate derivatives in meats*.

The diet also contains a large amount of cellulose, which is a carbohydrate. However, no enzymes capable of hydrolyzing cellulose are secreted in the human digestive tract. Consequently, cellulose cannot be considered a food for humans.

**Digestion of Carbohydrates in the Mouth and Stomach.** When food is chewed, it is mixed with saliva, which contains the digestive enzyme *ptyalin* (an *α*-amylase) secreted mainly by the parotid glands. This enzyme hydrolyzes starch into the disaccharide *maltose* and other small polymers of glucose that contain three to nine glucose molecules, as shown in Figure 65-1. However, the food remains in the mouth only a short time, so probably not more than 5 percent of all the starches will have become hydrolyzed by the time the food is swallowed.

However, starch digestion sometimes continues in the body and fundus of the stomach for as long as 1 hour before the food becomes mixed with the stomach secretions. Then activity of the salivary amylase is blocked by acid of the gastric secretions because the amylase is essentially nonactive as an enzyme once the pH of the medium falls below about 4.0. Nevertheless, on the average, before food and its accompanying saliva do become completely mixed with the gastric secretions, as much as 30 to 40 percent of the starches will have been hydrolyzed by the time the food is swallowed.

In general, the carbohydrates are almost totally converted into *maltose* and/or other small glucose polymers before passing beyond the duodenum or upper jejunum.

**Digestion of Carbohydrates in the Small Intestine**

**Digestion by Pancreatic Amylase.** Pancreatic secretion, like saliva, contains a large quantity of *α*-amylase that is almost identical in its function with the *α*-amylase of saliva but is several times as powerful. Therefore, within 15 to 30 minutes after the chyme empties from the stomach into the duodenum and mixes with pancreatic juice, virtually all the carbohydrates will have become digested.

In general, the carbohydrates are almost totally converted into *maltose* and/or other small glucose polymers before passing beyond the duodenum or upper jejunum.

**Hydrolysis of Disaccharides and Small Glucose Polymers into Monosaccharides by Intestinal Epithelial Enzymes.** The enteroxyttes lining the villi of the small intestine contain four enzymes (*lactase*, *sucrase*, *maltase*, and *α-dextrinase*), which are capable of splitting the disaccharides lactose, sucrose, and maltose, plus other small glucose polymers, into their constituent monosaccharides. These enzymes are located in the enterocytes covering the intestinal microvilli brush border; so the disaccharides are digested as they come in contact with these enterocytes.

Lactose splits into a molecule of *galactose* and a molecule of *glucose*. Sucrose splits into a molecule of *fructose* and a molecule of *glucose*. Maltose and other small glucose polymers all split into multiple molecules of *glucose*. Thus, the final products of carbohydrate digestion are all monosaccharides. They are all water soluble and are absorbed immediately into the portal blood.

In the ordinary diet, which contains far more starches than all other carbohydrates combined, glucose represents more than 80 percent of the final products of carbohydrate digestion, and galactose and fructose each represent seldom more than 10 percent.

The major steps in carbohydrate digestion are summarized in Figure 65-1.

**Proteins of the Diet.** The dietary proteins are chemically long chains of amino acids bound together by *peptide linkages*. A typical linkage is the following:

\[
\text{R} - \text{CH} - \text{C} - \text{OH} + \text{H} - \text{N} - \text{CH} - \text{COOH} \rightarrow
\]

\[
\text{NH}_2 \quad \text{H} \quad \text{NH}_2 \quad \text{H} \quad \text{R} \quad \text{R}
\]

\[
\text{R} - \text{CH} - \text{C} - \text{N} - \text{CH} - \text{COOH} + \text{H}_2\text{O}
\]

\[
\text{O} \quad \text{O}
\]

The characteristics of each protein are determined by the types of amino acids in the protein molecule and by the sequential arrangements of these amino acids. The physical and chemical characteristics of different proteins important in human tissues are discussed in Chapter 69.
Digestion of Proteins in the Stomach. Pepsin, the important peptic enzyme of the stomach, is most active at a pH of 2.0 to 3.0 and is inactive at a pH above about 5.0. Consequently, for this enzyme to cause digestion of protein, the stomach juices must be acidic. As explained in Chapter 64, the gastric glands secrete a large quantity of hydrochloric acid. This hydrochloric acid is secreted by the parietal (oxyntic) cells in the glands at a pH of about 0.8, but by the time it is mixed with the stomach contents and with secretions from the nonoxyntic glandular cells of the stomach, the pH then averages around 2.0 to 3.0, a highly favorable range of acidity for pepsin activity.

One of the important features of pepsin digestion is its ability to digest the protein collagen, an albuminoid type of protein that is affected little by other digestive enzymes. Collagen is a major constituent of the intercellular connective tissue of meats; therefore, for the digestive enzymes of the digestive tract to penetrate meats and digest the other meat proteins, it is necessary that the collagen fibers be digested. Consequently, in persons who lack pepsin in the stomach juices, the ingested meats are less well penetrated by the other digestive enzymes and, therefore, may be poorly digested.

As shown in Figure 65-2, pepsin only initiates the process of protein digestion, usually providing only 10 to 20 percent of the total protein digestion to convert the protein to proteoses, peptones, and a few polypeptides. This splitting of proteins occurs as a result of hydrolysis at the peptide linkages between amino acids.

Most Protein Digestion Results from Actions of Pancreatic Proteolytic Enzymes. Most protein digestion occurs in the upper small intestine, in the duodenum and jejunum, under the influence of proteolytic enzymes from pancreatic secretion. Immediately on entering the small intestine from the stomach, the partial breakdown products of the protein foods are attacked by major proteolytic pancreatic enzymes: trypsin, chymotrypsin, carboxypolypeptidase, and proelastase, as shown in Figure 65-2.

Both trypsin and chymotrypsin split protein molecules into small polypeptides; carboxypolypeptidase then cleaves individual amino acids from the carboxyl ends of the polypeptides. Proelastase, in turn, is converted into elastase, which then digests elastin fibers that partially hold meats together.

Only a small percentage of the proteins are digested all the way to their constituent amino acids by the pancreatic juices. Most remain as dipeptides and tripeptides.

Digestion of Peptides by Peptidases in the Enterocytes That Line the Small Intestinal Villi. The last digestive stage of the proteins in the intestinal lumen is achieved by the enterocytes that line the villi of the small intestine, mainly in the duodenum and jejunum. These cells have a brush border that consists of hundreds of microvilli projecting from the surface of each cell. In the membrane of each of these microvilli are multiple peptidases that pro- trude through the membranes to the exterior, where they come in contact with the intestinal fluids.

Two types of peptidase enzymes are especially important, aminopolypeptidase and several dipeptidases. They succeed in splitting the remaining larger polypeptides into tripeptides and dipeptides and a few into amino acids. Both the amino acids plus the dipeptides and tripeptides are easily transported through the microvillar membrane to the interior of the enterocyte.

Finally, inside the cytosol of the enterocyte are multiple other peptidases that are specific for the remaining types of linkages between amino acids. Within minutes, virtually all the last dipeptides and tripeptides are digested to the final stage to form single amino acids; these then pass on through to the other side of the enterocyte and thence into the blood.

More than 99 percent of the final protein digestive products that are absorbed are individual amino acids, with only rare absorption of peptides and very, very rare absorption of whole protein molecules. Even these few absorbed molecules of whole protein can sometimes cause serious allergic or immunologic disturbances, as discussed in Chapter 34.

Digestion of Fats

Fats of the Diet. By far the most abundant fats of the diet are the neutral fats, also known as triglycerides, each molecule of which is composed of a glycerol nucleus and three fatty acid side chains, as shown in Figure 65-3.
Neutral fat is a major constituent in food of animal origin but much, much less so in food of plant origin.

In the usual diet are also small quantities of phospholipids, cholesterol, and cholesterol esters. The phospholipids and cholesterol esters contain fatty acid and therefore can be considered fats. Cholesterol, however, is a sterol compound that contains no fatty acid, but it does exhibit some of the physical and chemical characteristics of fats; plus, it is derived from fats and is metabolized similarly to fats. Therefore, cholesterol is considered, from a dietary point of view, a fat.

**Digestion of Fats in the Intestine.** A small amount of triglycerides is digested in the stomach by lingual lipase that is secreted by lingual glands in the mouth and swallowed with the saliva. This amount of digestion is less than 10 percent and generally unimportant. Instead, essentially all fat digestion occurs in the small intestine as follows.

The First Step in Fat Digestion Is Emulsification by Bile Acids and Lecithin. The first step in fat digestion is physically to break the fat globules into small sizes so that the water-soluble digestive enzymes can act on the globule surfaces. This process is called emulsification of the fat, and it begins by agitation in the stomach to mix the fat with the products of stomach digestion.

Then, most of the emulsification occurs in the duodenum under the influence of bile, the secretion from the liver that does not contain any digestive enzymes. However, bile does contain a large quantity of bile salts, as well as the phospholipid lecithin. Both of these, but especially the lecithin, are extremely important for emulsification of the fat. The polar parts (the points where ionization occurs in water) of the bile salts and lecithin molecules are highly soluble in water, whereas most of the remaining portions of their molecules are highly soluble in fat. Therefore, the fat-soluble portions of these liver secretions dissolve in the surface layer of the fat globules, with the polar portions projecting. The polar projections, in turn, are soluble in the surrounding watery fluids, which greatly decreases the interfacial tension of the fat and makes it soluble as well.

When the interfacial tension of a globule of nonmiscible fluid is low, this nonmiscible fluid, on agitation, can be broken up into many tiny particles far more easily than it can when the interfacial tension is great. Consequently, a major function of the bile salts and lecithin, especially the lecithin, in the bile is to make the fat globules readily fragmentable by agitation with the water in the small bowel. This action is the same as that of many detergents that are widely used in household cleaners for removing grease.

Each time the diameters of the fat globules are significantly decreased as a result of agitation in the small intestine, the total surface area of the fat increases manyfold. Because the average diameter of the fat particles in the intestine after emulsification has occurred is less than 1 micrometer, this represents an increase of as much as 1000-fold in total surface areas of the fats caused by the emulsification process.

The lipase enzymes are water-soluble compounds and can attack the fat globules only on their surfaces. Consequently, this detergent function of bile salts and lecithin is very important for digestion of fats.

**Triglycerides Are Digested by Pancreatic Lipase.** By far the most important enzyme for digestion of the triglycerides is pancreatic lipase, present in enormous quantities in pancreatic juice, enough to digest within 1 minute all triglycerides that it can reach. In addition, the enterocytes of the small intestine contain additional lipase, known as enteric lipase, but this is usually not needed.

End Products of Fat Digestion Are Free Fatty Acids. Most of the triglycerides of the diet are split by pancreatic lipase into free fatty acids and 2-monoglycerides, as shown in Figure 65-4.

![Figure 65-4 Digestion of fats.](image)

Bile Salts Form Micelles That Accelerate Fat Digestion. The hydrolysis of triglycerides is a highly reversible process; therefore, accumulation of monoglycerides and free fatty acids in the vicinity of digesting fats quickly blocks further digestion. But the bile salts play the additional important role of removing the monoglycerides and free fatty acids from the vicinity of the digesting fat globules almost as rapidly as these end products of digestion are formed. This occurs in the following way.

Bile salts, when in high enough concentration in water, have the propensity to form micelles, which are small spherically, cylindrical globules 3 to 6 nanometers in diameter composed of 20 to 40 molecules of bile salt. These develop because each bile salt molecule is composed of a sterol nucleus that is highly fat-soluble and a polar group that is highly water-soluble. The sterol nucleus encompasses the fat digestate, forming a small fat globule in the middle of a resulting micelle, with polar groups of bile salts projecting outward to cover the surface of the micelle. Because these polar groups are negatively charged, they allow the entire micelle globule to dissolve in the water of the digestive fluids and to remain in stable solution until the fat is absorbed into the blood.

The bile salt micelles also act as a transport medium to carry the monoglycerides and free fatty acids, both of which would otherwise be relatively insoluble, to the brush borders of the intestinal epithelial cells. There the monoglycerides and free fatty acids are absorbed into the blood, as discussed later, but the bile salts themselves are released back into the chyme to be used again and again for this “ferrying” process.

Digestion of Cholesterol Esters and Phospholipids. Most cholesterol in the diet is in the form of...
cholesterol esters, which are combinations of free cholesterol and one molecule of fatty acid. Phospholipids also contain fatty acid within their molecules. Both the cholesterol esters and the phospholipids are hydrolyzed by two other lipases in the pancreatic secretion that free the fatty acids—the enzyme cholesterol ester hydrolase to hydrolyze the cholesterol ester, and phospholipase A₂ to hydrolyze the phospholipid.

The bile salt micelles play the same role in “ferrying” free cholesterol and phospholipid molecule digestates that they play in “ferrying” monoglycerides and free fatty acids. Indeed, essentially no cholesterol is absorbed without this function of the micelles.

Basic Principles of Gastrointestinal Absorption

It is suggested that the reader review the basic principles of transport of substances through cell membranes discussed in Chapter 4. The following paragraphs present specialized applications of these transport processes during gastrointestinal absorption.

Anatomical Basis of Absorption

The total quantity of fluid that must be absorbed each day by the intestines is equal to the ingested fluid (about 1.5 liters) plus that secreted in the various gastrointestinal secretions (about 7 liters). This comes to a total of 8 to 9 liters. All but about 1.5 liters of this is absorbed in the small intestine, leaving only 1.5 liters to pass through the ileocecal valve into the colon each day.

The stomach is a poor absorptive area of the gastrointestinal tract because it lacks the typical villus type of absorptive membrane, and also because the junctions between the epithelial cells are tight junctions. Only a few highly lipid-soluble substances, such as alcohol and some drugs like aspirin, can be absorbed in small quantities.
but their distribution is less profuse in the distal small intestine. The presence of villi on the mucosal surface enhances the total absorptive area another 10-fold.

Finally, each intestinal epithelial cell on each villus is characterized by a *brush border*, consisting of as many as 1000 *microvilli* 1 micrometer in length and 0.1 micrometer in diameter protruding into the intestinal chyme; these microvilli are shown in the electron micrograph in Figure 65-7. This increases the surface area exposed to the intestinal materials at least another 20-fold.

Thus, the combination of the folds of Kerckring, the villi, and the microvilli increases the total absorptive area of the mucosa perhaps 1000-fold, making a tremendous total area of 250 or more square meters for the entire small intestine—about the surface area of a tennis court.

Figure 65-6A shows in longitudinal section the general organization of the villus, emphasizing (1) the advantageous arrangement of the vascular system for absorption of fluid and dissolved material into the portal blood and (2) the arrangement of the “central lacteal” lymph vessel for absorption into the lymph. Figure 65-6B shows a cross section of the villus, and Figure 65-7 shows many small *pinocytic vesicles*, which are pinched-off portions of infolded enterocyte membrane forming vesicles of absorbed fluids that have been entrapped. Small amounts of substances are absorbed by this physical process of *pinocytosis*.

Extending from the epithelial cell body into each microvillus of the brush border are multiple actin filaments that contract rhythmically to cause continual movement of the microvilli, keeping them constantly exposed to new quantities of intestinal fluid.

## Absorption in the Small Intestine

Absorption from the small intestine each day consists of several hundred grams of carbohydrates, 100 or more grams of fat, 50 to 100 grams of amino acids, 50 to 100 grams of ions, and 7 to 8 liters of water. The absorptive capacity of the normal small intestine is far greater than this: as much as several kilograms of carbohydrates per day, 500 grams of fat per day, 500 to 700 grams of proteins per day, and 20 or more liters of water per day. The *large* intestine can absorb still additional water and ions, although very few nutrients.

### Absorption of Water by Osmosis

#### Isosmotic Absorption

Water is transported through the intestinal membrane entirely by *diffusion*. Furthermore, this diffusion obeys the usual laws of osmosis. Therefore, when the chyme is dilute enough, water is absorbed through the intestinal mucosa into the blood of the villi almost entirely by osmosis.

Conversely, water can also be transported in the opposite direction—from plasma into the chyme. This occurs especially when hyperosmotic solutions are discharged from the stomach into the duodenum. Within minutes, sufficient water usually will be transferred by osmosis to make the chyme isosmotic with the plasma.

### Absorption of Ions

#### Sodium Is Actively Transported Through the Intestinal Membrane

Twenty to 30 grams of sodium are secreted in the intestinal secretions each day. In addition, the average person eats 5 to 8 grams of sodium each day. Therefore, to prevent net loss of sodium into the feces, the intestines must absorb 25 to 35 grams of sodium each day, which is equal to about one seventh of all the sodium present in the body.

Whenever significant amounts of intestinal secretions are lost to the exterior, as in extreme diarrhea, the sodium reserves of the body can sometimes be depleted to lethal levels within hours. Normally, however, less than 0.5 percent of the intestinal sodium is lost in the feces each day because it is rapidly absorbed through the intestinal mucosa. Sodium also plays an important role in helping to absorb sugars and amino acids, as subsequent discussions reveal.

The basic mechanism of sodium absorption from the intestine is shown in Figure 65-8. The principles of this mechanism, discussed in Chapter 4, are also essentially the same as for absorption of sodium from the gallbladder and renal tubules as discussed in Chapter 27.

The motive power for sodium absorption is provided by active transport of sodium from inside the epithelial cells through the basal and lateral walls of these cells into paracellular spaces. This active transport obeys the usual laws of active transport: It requires energy, and the energy process is catalyzed by appropriate adenine triphosphatase (ATP) enzymes in the cell membrane (see Chapter 4). Part of the sodium is absorbed along with chloride ions; in fact, the negatively charged chloride ions are mainly passively “dragged” by the positive electrical charges of the sodium ions.

Active transport of sodium through the basolateral membranes of the cell reduces the sodium concentration inside the cell to a low value (≈50 mEq/L), as shown...
The next step in the translocation of 
$\text{HCO}_3^-$ Often large quantities of bicarbonate -
ion absorption is rapid and occurs mainly by diffusion
(i.e., absorption of sodium ions through the epithelium
creates electronegativity in the chyme and electropositivity
in the paracellular spaces between the epithelial cells).
This effect of aldosterone on the intestinal tract is the same as
that achieved by aldosterone in the renal tubules, which
also serves to conserve sodium chloride and water in the
body when a person becomes dehydrated.

Absorption of Chloride Ions in the Small Intestine. In the upper part of the small intestine, chloride ion absorption is rapid and occurs mainly by diffusion
(i.e., absorption of sodium ions through the epithelium
creates electronegativity in the chyme and electropositivity
in the paracellular spaces between the epithelial cells).
Then chloride ions move along this electrical gradient
to “follow” the sodium ions. Chloride is also absorbed
across the brush border membrane of parts of the ileum
and large intestine by a brush border membrane chloride-
bicarbonate exchanger; chloride exits the cell on the baso-
lateral membrane through chloride channels.

Absorption of Bicarbonate Ions in the Duodenum and Jejunum. Often large quantities of bicarbonate ions must be reabsorbed from the upper small intestine
because large amounts of bicarbonate ions have been
secreted into the duodenum in both pancreatic secretion
and bile. The bicarbonate ion is absorbed in an indirect
way as follows: When sodium ions are absorbed, moderate amounts of hydrogen ions are secreted into the lumen of the gut in exchange for some of the sodium. These hydrogen ions in turn combine with the bicarbonate ions
to form carbonic acid ($\text{H}_2\text{CO}_3$), which then dissociates to
form water and carbon dioxide. The water remains as part
of the chyme in the intestines, but the carbon dioxide is readily absorbed into the blood and subsequently expired
through the lungs. Thus, this is so-called “active absorption
of bicarbonate ions.” It is the same mechanism that
occurs in the tubules of the kidneys.

Secretion of Bicarbonate Ions in the Ileum and Large Intestine—Simultaneous Absorption of Chloride Ions
The epithelial cells on the surfaces of the villi in the ileum, as
well as on all surfaces of the large intestine, have a special capability of secreting bicarbonate ions in exchange for absorption
of chloride ions (see Figure 65-8). This is important because it
provides alkaline bicarbonate ions that neutralize acid products formed by bacteria in the large intestine.

Extreme Secretion of Chloride Ions, Sodium Ions, and Water from the Large Intestine Epithelium in Some Types of Diarrhea. Deep in the spaces between the intestinal epithelial folds are immature epithelial cells that continually

![Figure 65-8 Absorption of sodium, chloride, glucose, and amino acids through the intestinal epithelium. Note also osmotic absorption of water (i.e., water “follows” sodium through the epithelial membrane).](image-url)
divide to form new epithelial cells. These in turn spread outward over the luminal surfaces of the intestines. While still in the deep folds, the epithelial cells secrete sodium chloride and water into the intestinal lumen. This secretion in turn is reabsorbed by the older epithelial cells outside the folds, thus providing flow of water for absorbing intestinal digestates.

The toxins of cholera and of some other types of diarrheal bacteria can stimulate the epithelial fold secretion so greatly that this secretion often becomes much greater than can be reabsorbed, thus sometimes causing loss of 5 to 10 liters of water and sodium chloride as diarrhea each day. Within 1 to 5 days, many severely affected patients die from this loss of fluid alone.

Extreme diarrheal secretion is initiated by entry of a subunit of cholera toxin into the epithelial cells. This stimulates formation of excess cyclic adenosine monophosphate, which opens tremendous numbers of chloride channels, allowing chloride ions to flow rapidly from inside the cell into the intestinal crypts. In turn, this is believed to activate a sodium pump that pumps sodium ions into the crypts to go along with the chloride ions. Finally, this extra sodium chloride causes extreme osmosis of water from the blood, thus providing rapid flow of fluid along with the salt. All this excess fluid washes away most of the bacteria and is of value in combating the disease, but too much of a good thing can be lethal because of serious dehydration of the whole body that might ensue. In most instances, the life of a cholera victim can be saved by administration of tremendous amounts of sodium chloride solution to make up for the loss.

**Active Absorption of Calcium, Iron, Potassium, Magnesium, and Phosphate.** Calcium ions are actively absorbed into the blood, especially from the duodenum, and the amount of calcium ion absorption is exactly controlled to supply the daily need of the body for calcium. One important factor controlling calcium absorption is parathyroid hormone secreted by the parathyroid glands, and another is vitamin D. Parathyroid hormone activates vitamin D, and the activated vitamin D in turn greatly enhances calcium absorption. These effects are discussed in Chapter 79.

Iron ions are also actively absorbed from the small intestine. The principles of iron absorption and regulation of its absorption in proportion to the body’s need for iron, especially for the formation of hemoglobin, are discussed in Chapter 32.

Potassium, magnesium, phosphate, and probably still other ions can also be actively absorbed through the intestinal mucosa. In general, the monovalent ions are absorbed with ease and in great quantities. Conversely, bivalent ions are normally absorbed in only small amounts; for example, maximum absorption of calcium ions is only 1/50 as great as the normal absorption of sodium ions. Fortunately, only small quantities of the bivalent ions are normally required daily by the body.

**Absorption of Nutrients**

**Carbohydrates Are Mainly Absorbed as Monosaccharides**

Essentially all the carbohydrates in the food are absorbed in the form of monosaccharides; only a small fraction is absorbed as disaccharides and almost none as larger carbohydrate compounds. By far the most abundant of the absorbed monosaccharides is glucose, usually accounting for more than 80 percent of carbohydrate calories absorbed. The reason for this is that glucose is the final digestion product of our most abundant carbohydrate food, the starches. The remaining 20 percent of absorbed monosaccharides is composed almost entirely of galactose and fructose, the galactose derived from milk and the fructose as one of the monosaccharides digested from cane sugar.

Virtually all the monosaccharides are absorbed by an active transport process. Let us first discuss the absorption of glucose.

**Glucose Is Transported by a Sodium Co-Transport Mechanism.** In the absence of sodium transport through the intestinal membrane, virtually no glucose can be absorbed. The reason is that glucose absorption occurs in a co-transport mode with active transport of sodium (see Figure 65-8).

There are two stages in the transport of sodium through the intestinal membrane. First is active transport of sodium ions through the basolateral membranes of the intestinal epithelial cells into the blood, thereby depleting sodium inside the epithelial cells. Second, decrease of sodium inside the cells causes sodium from the intestinal lumen to move through the brush border of the epithelial cells to the cell interiors by a process of secondary active transport. That is, a sodium ion combines with a transport protein, but the transport protein will not transport the sodium to the interior of the cell until the protein also combines with some other appropriate substance such as glucose. Intestinal glucose also combines simultaneously with the same transport protein and then both the sodium ion and glucose molecule are transported together to the interior of the cell. Thus, the low concentration of sodium inside the cell literally “drags” sodium to the interior of the cell and along with it the glucose at the same time. Once inside the epithelial cell, other transport proteins and enzymes cause facilitated diffusion of the glucose through the cell’s basolateral membrane into the paracellular space and from there into the blood.

To summarize, it is the initial active transport of sodium through the basolateral membranes of the intestinal epithelial cells that provides the eventual motive force for moving glucose also through the membranes.

**Absorption of Other Monosaccharides.** Galactose is transported by almost exactly the same mechanism as glucose. Conversely, fructose transport does not occur by the sodium co-transport mechanism. Instead, fructose is transported by facilitated diffusion all the way through the intestinal epithelium but not coupled with sodium transport.

Much of the fructose, on entering the cell, becomes phosphorylated, then converted to glucose, and finally transported in the form of glucose the rest of the way into the blood. Because fructose is not co-transported with sodium, its overall rate of transport is only about one half that of glucose or galactose.
Absorption of Proteins as Dipeptides, Tripeptides, or Amino Acids

As explained earlier in the chapter, most proteins, after digestion, are absorbed through the luminal membranes of the intestinal epithelial cells in the form of dipeptides, tripeptides, and a few free amino acids. The energy for most of this transport is supplied by a sodium co-transport mechanism in the same way that sodium co-transport of glucose occurs. That is, most peptide or amino acid molecules bind in the cell’s microvillus membrane with a specific transport protein that requires sodium binding before transport can occur. After binding, the sodium ion then moves down its electrochemical gradient to the interior of the cell and pulls the amino acid or peptide along with it. This is called co-transport (or secondary active transport) of the amino acids and peptides (see Figure 65-8). A few amino acids do not require this sodium co-transport mechanism but instead are transported by special membrane transport proteins in the same way that fructose is transported, by facilitated diffusion.

At least five types of transport proteins for transporting amino acids and peptides have been found in the luminal membranes of intestinal epithelial cells. This multiplicity of transport proteins is required because of the diverse binding properties of different amino acids and peptides.

Absorption of Fats

Earlier in this chapter, it was pointed out that when fats are digested to form monoglycerides and free fatty acids, both of these digestive end products first become dissolved in the central lipid portions of bile micelles. Because the molecular dimensions of these micelles are only 3 to 6 nanometers in diameter, and because of their highly charged exterior, they are soluble in chyme. In this form, the monoglycerides and free fatty acids are carried to the surfaces of the microvilli of the intestinal cell brush border and then penetrate into the recesses among the moving, agitating microvilli. Here, both the monoglycerides and fatty acids diffuse immediately out of the micelles and into the interior of the epithelial cells, which is possible because the lipids are also soluble in the epithelial cell membrane. This leaves the bile micelles still in the chyme, where they function again and again to help absorb still more monoglycerides and fatty acids.

Thus, the micelles perform a “ferrying” function that is highly important for fat absorption. In the presence of an abundance of bile micelles, about 97 percent of the fat is absorbed; in the absence of the bile micelles, only 40 to 50 percent can be absorbed.

After entering the epithelial cell, the fatty acids and monoglycerides are taken up by the cell’s smooth endoplasmic reticulum; here, they are mainly used to form new triglycerides that are subsequently released in the form of chylomicrons through the base of the epithelial cell, to flow upward through the thoracic lymph duct and empty into the circulating blood.

Direct Absorption of Fatty Acids into the Portal Blood. Small quantities of short- and medium-chain fatty acids, such as those from butterfat, are absorbed directly into the portal blood rather than being converted into triglycerides and absorbed by way of the lymphatics. The cause of this difference between short- and long-chain fatty acid absorption is that the short-chain fatty acids are more watersoluble and mostly are not reconverted into triglycerides by the endoplasmic reticulum. This allows direct diffusion of these short-chain fatty acids from the intestinal epithelial cells directly into the capillary blood of the intestinal villi.

Absorption in the Large Intestine: Formation of Feces

About 1500 milliliters of chyme normally pass through the ileocecal valve into the large intestine each day. Most of the water and electrolytes in this chyme are absorbed in the colon, usually leaving less than 100 milliliters of fluid to be excreted in the feces. Also, essentially all the ions are absorbed, leaving only 1 to 5 mEq each of sodium and chloride ions to be lost in the feces.

Most of the absorption in the large intestine occurs in the proximal one half of the colon, giving this portion the name absorbing colon, whereas the distal colon functions principally for feces storage until a propitious time for feces excretion and is therefore called the storage colon.

Absorption and Secretion of Electrolytes and Water. The mucosa of the large intestine, like that of the small intestine, has a high capability for active absorption of sodium, and the electrical potential gradient created by absorption of the sodium causes chloride absorption as well. The tight junctions between the epithelial cells of the large intestinal epithelium are much tighter than those of the small intestine. This prevents significant amounts of back-diffusion of ions through these junctions, thus allowing the large intestinal mucosa to absorb sodium ions far more completely—that is, against a much higher concentration gradient—than can occur in the small intestine. This is especially true when large quantities of aldosterone are available because aldosterone greatly enhances sodium transport capability.

In addition, as occurs in the distal portion of the small intestine, the mucosa of the large intestine secretes bicarbonate ions while it simultaneously absorbs an equal number of chloride ions in an exchange transport process that has already been described. The bicarbonate helps neutralize the acidic end products of bacterial action in the large intestine.

Absorption of sodium and chloride ions creates an osmotic gradient across the large intestinal mucosa, which in turn causes absorption of water.

Maximum Absorption Capacity of the Large Intestine. The large intestine can absorb a maximum of 5 to 8 liters of fluid and electrolytes each day. When the
total quantity entering the large intestine through the ileocecal valve or by way of large intestine secretion exceeds this amount, the excess appears in the feces as diarrhea. As noted earlier in the chapter, toxins from cholera or certain other bacterial infections often cause the crypts in the terminal ileum and in the large intestine to secrete 10 or more liters of fluid each day, leading to severe and sometimes lethal diarrhea.

Bacterial Action in the Colon. Numerous bacteria, especially colon bacilli, are present even normally in the absorbing colon. They are capable of digesting small amounts of cellulose, in this way providing a few calories of extra nutrition for the body. In herbivorous animals, this source of energy is significant, although it is of negligible importance in human beings.

Other substances formed as a result of bacterial activity are vitamin K, vitamin B₁₂, thiamine, riboflavin, and various gases that contribute to flatus in the colon, especially carbon dioxide, hydrogen gas, and methane. The bacteria-formed vitamin K is especially important because the amount of this vitamin in the daily ingested foods is normally insufficient to maintain adequate blood coagulation.

Composition of the Feces. The feces normally are about three-fourths water and one-fourth solid matter that is composed of about 30 percent dead bacteria, 10 to 20 percent fat, 10 to 20 percent inorganic matter, 2 to 3 percent protein, and 30 percent undigested roughage from the food and dried constituents of digestive juices, such as bile pigment and sloughed epithelial cells. The brown color of feces is caused by stercobilin and urobilin, derivatives of bilirubin. The odor is caused principally by products of bacterial action; these products vary from one person to another, depending on each person’s colonic bacterial flora and on the type of food eaten. The actual odoriferous products include indole, skatole, mercaptans, and hydrogen sulfide.

Bibliography
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. Antispasmodic 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 falls 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.

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 mucous 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 mucusal 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, 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.

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, carboxylypolypeptidase, 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 carboxylypolypeptidase, 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.

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.
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 B₁₂. 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 B₁₂ 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 fiber bundles 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.

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.

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 cauterity 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.
Bibliography

Hunt KA, van Heel DA: Recent advances in coeliac disease genetics, Gut 58:473, 2009.
Metabolism and Temperature Regulation

67. Metabolism of Carbohydrates, and Formation of Adenosine Triphosphate
68. Lipid Metabolism
69. Protein Metabolism
70. The Liver as an Organ
71. Dietary Balances; Regulation of Feeding; Obesity and Starvation; Vitamins and Minerals
72. Energetics and Metabolic Rate
73. Body Temperature Regulation, and Fever
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
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:

\[
\begin{align*}
\text{ATP} & \quad \text{ADP} + \text{PO}_3^- + 12,000 \text{ cal} \\
\text{ADP} + \text{PO}_3^- & \quad \text{AMP} + \text{2PO}_3^- + 12,000 \text{ cal}
\end{align*}
\]

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 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:

\[
\text{Glucose} + \text{ATP} \rightarrow \text{Glucose-6-phosphate}.
\]

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.
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 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 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 $\alpha$-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:

$$2 \text{Acetyl-CoA} + 6\text{H}_2\text{O} + 2\text{ADP} \rightarrow 4\text{CO}_2 + 16\text{H} + 2\text{CoA} + 2\text{ATP}$$
As it is expired from the body (see Chapter 40). dissolved in the body fluids and transported to the lungs, enzyme, called , to cause the release of carbon dioxide, other specific pro-

formation of acetyl-CoA from pyruvic acid, we find that 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.

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, C₁, Cₐ, and A₃. 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:

$$\text{CH}_3\text{C}==\text{COOH} + \text{NADH} + \text{H}^+ \xrightarrow{\text{lactic dehydrogenase}} \text{CH}_3\text{C}==\text{COOH} + \text{NAD}^+$$

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 be converted back into glucose.
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 phosphoglucone 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 phosphoglucone 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.

**Bibliography**


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: \( \text{CH}_3(\text{CH}_2)_{14}\text{COOH} \).

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.

\[
\begin{align*}
\text{CH}_3(\text{CH}_2)_{16}\text{COO} & \rightarrow \text{CH}_2^+ \\
\text{CH}_3(\text{CH}_2)_{16}\text{COO} & \rightarrow \text{CH} \\
\text{CH}_3(\text{CH}_2)_{16}\text{COO} & \rightarrow \text{CH}_2
\end{align*}
\]

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.
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, $\alpha$-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:

<table>
<thead>
<tr>
<th>Lipoprotein Constituent</th>
<th>mg/dl of Plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>180</td>
</tr>
<tr>
<td>Phospholipids</td>
<td>160</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>160</td>
</tr>
<tr>
<td>Protein</td>
<td>200</td>
</tr>
</tbody>
</table>

**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
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).
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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:

\[
\text{Citric acid cycle} \quad \begin{align*}
  \text{CH}_3\text{COCoA} + \text{Oxaloacetic acid} + 3\text{H}_2\text{O} + \text{ADP} \\
  \rightarrow 2\text{CO}_2 + 8\text{H} + \text{HCoA} + \text{ATP} + \text{Oxaloacetic acid}
\end{align*}
\]

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 FADH₂, 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:

\[
\text{Acetyl-CoA} \rightarrow \text{Acetoacetic acid} \rightarrow \beta\text{-Hydroxybutyric acid} \rightarrow \text{Acetone}
\]

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:

\[
\begin{align*}
  \text{CH}_3\text{COCoA} + \text{H}_2\text{O} & \rightarrow \text{Acetyl-CoA} \\
  \text{CH}_3\text{COCH}_2\text{COOH} + 2\text{HCoA} & \rightarrow \text{Acetoacetic acid}
\end{align*}
\]

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.

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 of carbohydrate.

**Figure 68-3** Synthesis of fatty acids.

**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 \( \alpha \)-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 \( \alpha \)-glycerophosphate are present (which occurs when excess carbohydrates are available), the excess \( \alpha \)-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 \( \alpha \)-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-sparing 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.

**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 in the form of cholesterol esters.
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 68-7A). 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.
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 68-7B). 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. (Modified from Libby P: Inflammation in atherosclerosis. Nature 420:868, 2002.)

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.

**Bibliography.**


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 (—NH₂).

**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:

\[
R - C H - C O - O H + R' - C H - C O O H \rightarrow R - C H - C O - O H + R' - C H - C O O H
\]

\[
\text{NH₂} \quad \text{H} \quad \text{NH} \quad \text{COOH}
\]

\[
R - C H - C O - O H + R' - C H - C O O H \rightarrow R - C H - C O - O H + R' - C H - C O O H
\]

\[
\text{NH₂} \quad \text{H} \quad \text{NH} \quad \text{COOH}
\]

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:

\[
\begin{align*}
\text{C} & \equiv \text{O} & \text{NH} & \equiv \text{N} & \text{R} & \equiv \text{H} \\
& \text{O} & \text{C} & \equiv \text{H} & \text{N} & \equiv \text{N} \\
\text{R} & \equiv \text{H} & \text{N} & \equiv \text{N} & \text{R} & \equiv \text{H}
\end{align*}
\]

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 NH₂ 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.
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
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 they 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 (B₆). 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:

\[
\text{α-Ketoglutaric acid} + \text{Amino acid} \rightarrow \text{Glutamic acid} + \text{α-Keto acid} + \text{NAD}^+ + \text{H}_2\text{O} \rightarrow \text{NADH} + \text{H}^+ + \text{NH}_3
\]

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 (NH₃). 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](image-url) 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:

$$2\text{NH}_3 + \text{CO}_2 \rightarrow \text{H}_2\text{N} - \text{C} - \text{NH}_2 + \text{H}_2\text{O}$$

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:

- **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:

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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:

1. **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**.

2. **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 sparsers**.

### 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 extracellular 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
...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.

**Bibliography**