THE GASTROINTESTINAL PHYSIOLOGY

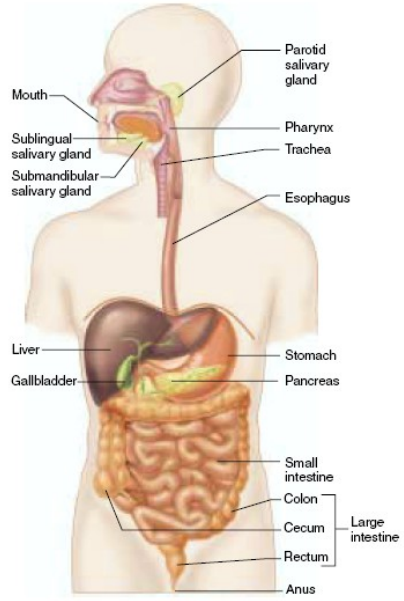


Figure 1 Anatomy of the gastrointestinal system

The gastrointestinal (GI) system includes the gastrointestinal tract (mouth, pharynx, esophagus, stomach, small intestine, and large intestine) plus the accessory organs (salivary glands, liver, gallbladder, and pancreas). The adult gastrointestinal tract is a tube approximately 15 ft long, running through the body from mouth to anus. The overall function of the gastrointestinal system is to process ingested foods into molecular forms that are then transferred, along with salts and water to the body's internal environment.

Most food enters the gastrointestinal tract as large particles containing macromolecules, such as proteins and polysaccharides, which are unable to cross the intestinal epithelium. Before ingested food can be absorbed, therefore, it must be dissolved and broken down into small molecules.

This dissolving and breaking-down process—digestion—is accomplished by the action of hydrochloric acid in the stomach, bile from the liver, and a variety of digestive enzymes that are released by the system's exocrine glands.

Each of these substances is released into the lumen of the GI tract by the process of secretion. The molecules produced by digestion then move from the lumen of the gastrointestinal tract across a layer of epithelial cells and enter the blood or lymph. This process is called absorption. While digestion, secretion, and absorption are taking place, contractions of smooth muscles in the gastrointestinal tract wall serve two functions; they mix the luminal contents with the various secretions, and they move the contents through the tract from mouth to anus. These contractions are referred to as the motility of the gastrointestinal tract. The functions of the gastrointestinal system can be described in terms of these four processes, digestion, secretion, absorption, and motility and the mechanisms controlling them.

With a few important exceptions (to be described later), therefore, the gastrointestinal system does not regulate the amount of nutrients absorbed or their concentrations in the internal environment. Small amounts of certain metabolic end products are excreted via the gastrointestinal tract, primarily by way of the bile, but the elimination of most of the body's waste products is achieved by the lungs and kidneys. The material feces leaving the system at the end of the gastrointestinal tract consists almost entirely of bacteria and ingested material that was neither digested nor absorbed.

The gastrointestinal tract begins with the mouth and digestion starts there with chewing, which breaks up large pieces of food into smaller particles that can be swallowed. Saliva, secreted by three pairs of salivary glands, drains into the mouth through a series of short ducts. Saliva, which contains mucus, moistens and lubricates the food particles before swallowing. It also contains the enzyme amylase, which partially digests polysaccharides. A third function of saliva is to dissolve some of the food molecules. Only in the dissolved state can these molecules react with chemoreceptors in the mouth, giving rise to the sensation of taste. The next segments of the tract, the pharynx and esophagus, contribute nothing to digestion but provide the pathway by which ingested materials reach the stomach. The

muscles in the walls of these segments control swallowing. The stomach is a saclike organ, located between the esophagus and the small intestine. Its functions are to store, dissolve, and partially digest the macromolecules in food and to regulate the rate at which the stomach's contents empty into the small intestine. The glands lining the stomach wall secrete a strong acid, hydrochloric acid, and several protein-digesting enzymes collectively known as pepsin (actually a precursor of pepsin known as pepsinogen is secreted and converted to pepsin in the lumen of the stomach). The primary function of hydrochloric acid is to dissolve the particulate matter in food. The acid environment in the gastric (adjective for "stomach") lumen alters the ionization of polar molecules, especially proteins, disrupting the extracellular network of connectivetissue proteins that form the structural framework of the tissues in food. The proteins and polysaccharides released by hydrochloric acid's dissolving action are partially digested in the stomach by pepsin and amylase, the latter contributed by the salivary glands. A major food component that is not dissolved by acid is fat. Hydrochloric acid also kills most of the bacteria that enter along with food.

The digestive actions of the stomach reduce food particles to a solution known as chyme, which contains molecular fragments of proteins and polysaccharides, droplets of fat, and salt, water, and various other small molecules ingested in the food. Virtually none of these molecules, except water, can cross the epithelium of the gastric wall, and thus little absorption of organic nutrients occurs in the stomach. Digestion's final stages and most absorption occur in the next section of the tract, the small intestine, a tube about 1.5 inches in diameter and 9 ft in length that leads from the stomach to the large intestine. Here molecules of intact or partially digested carbohydrates, fats, and proteins are broken down by hydrolytic enzymes into monosaccharides, fatty acids, and amino acids. Some of these enzymes are on the luminal surface of the intestinal lining cells, while others are secreted by the pancreas and enter the intestinal lumen. The products of digestion are absorbed across the epithelial cells and enter the blood and/or lymph. Vitamins, minerals, and water, which do not require enzymatic digestion, are also absorbed in the small intestine. The small intestine is divided into three segments: an initial short segment, the duodenum, is followed by the jejunum and then by the longest segment, the ileum. Normally, most of the chyme entering from the stomach is digested and absorbed in the first quarter of the small intestine, in the duodenum and jejunum.

Table 1 Daily secretion of intestinal juice

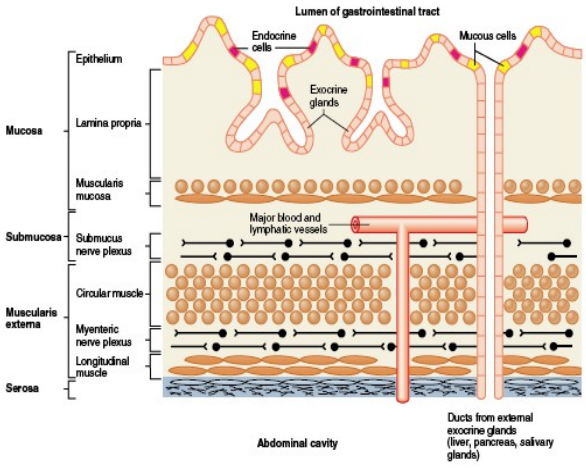
	Daily volume (ml)	**pH**
Saliva	1000	6-7
Gastric secretion	1500	1-3.5
Pancreatic secretion	1000	8-8.3
Bile	1000	7.8
Small intestine secretion	1800	7.5-8
Brunner's gland secretion	200	8-8.9
Large intestinal secretion	200	7.5-8
Total	6700	

Two major glands—the pancreas and liver—secrete substances that flow via ducts into the duodenum. The pancreas**,** an elongated gland located behind the stomach, has both endocrine and exocrine functions, but only the latter are directly involved in gastrointestinal function and are described in this chapter. The exocrine portion of the pancreas secretes digestive enzymes and a fluid rich in bicarbonate ions. The high acidity of the chyme coming from the stomach would inactivate the pancreatic enzymes in the small intestine if the acid were not neutralized by the bicarbonate ions in the pancreatic fluid. The liver**,** a large gland located in the upper right portion of the abdomen, has a variety of functions, which are described in various chapters. Bile contains bicarbonate ions, cholesterol, phospholipids, bile

pigments, a number of organic wastes and—most important—a group of substances collectively termed bile salts**.** The bicarbonate ions, like those from the pancreas, help neutralize acid from the stomach, while the bile salts, as we shall see, solubilize dietary fat. These fats would otherwise be insoluble in water, and their solubilization increases the rates at which they are digested and absorbed. Bile is secreted by the liver into small ducts that join to form a single duct called the common hepatic duct. Between meals, secreted bile is stored in the gallbladder, a small sac underneath the liver that branches from the common hepatic duct. The gallbladder concentrates the organic molecules in bile by absorbing salts and water. During a meal, the smooth muscles in the gallbladder wall contract, causing a concentrated bile solution to be injected into the duodenum via the common bile duct, an extension of the common hepatic duct. The gallbladder can be surgically removed without impairing bile secretion by the liver or its flow into the intestinal tract.

In the small intestine, monosaccharides and amino acids are absorbed by specific transporter-mediated processes in the plasma membranes of the intestinal epithelial cells, whereas fatty acids enter these cells by diffusion. Most mineral ions are actively absorbed by transporters, and water diffuses passively down osmotic gradients. The motility of the small intestine, brought about by the smooth muscles in its walls, mixes the luminal contents with the various secretions, brings the contents into contact with the epithelial surface where absorption takes place, and slowly advances the luminal material toward the large intestine. Since most substances are absorbed in the small intestine, only a small volume of water, salts, and undigested material is passed on to the large intestine. The large intestine temporarily stores the undigested material (some of which is metabolized by bacteria) and concentrates it by absorbing salts and water. Contractions of the rectum, the final segment of the large intestine, and relaxation of associated sphincter muscles expel the feces—defecation.

The average adult consumes about 800 g of food and 1200 ml of water per day, but this is only a fraction of the material entering the lumen of the gastrointestinal tract. An additional 7000 ml of fluid from salivary glands, gastric glands, pancreas, liver, and intestinal glands is secreted into the tract each day. Of the 8 L of fluid entering the tract, 99 percent is absorbed; only about 100 ml is normally lost in the feces.



This small amount of fluid loss represents only 4 percent of the total fluids lost by the body each day (most fluid loss is via the kidneys and respiratory system). Almost all the salts in the secreted fluids are also reabsorbed into the blood. Moreover, the secreted digestive enzymes are themselves digested, and the resulting amino acids are absorbed into the blood.

Figure 2 Hystological structure of the gastrointestinal wall

Structure of the GI tract wall

From the midesophagus to the anus, the wall of the gastrointestinal tract has the general structure illustrated in Figure 2. Most of the tube's luminal surface is highly convoluted, a feature that greatly increases the surface area available for absorption. From the stomach on, this surface is covered by a single layer of epithelial cells linked together along

the edges of their luminal surfaces by tight junctions. Included in this epithelial layer are exocrine cells that secrete mucus into the lumen of the tract and endocrine cells that release hormones into the blood. Invaginations of the epithelium into the underlying tissue form exocrine glands that secrete acid, enzymes, water, and ions, as well as mucus. Just below the epithelium is a layer of connective tissue, the lamina propria, through which pass small blood vessels, nerve fibers, and lymphatic ducts. The lamina propria is separated from underlying tissues by a thin layer of smooth muscle, the muscularis mucosa. The combination of these three layers—the epithelium, lamina propria, and muscularis mucosa—is called the mucosa. Beneath the mucosa is a second connective tissue layer, the submucosa, containing a network of nerve cells, termed the submucous plexus, and blood and lymphatic vessels whose branches penetrate into both the overlying mucosa and the underlying layers of smooth muscle called the muscularis externa. Contractions of these muscles provide the forces for moving and mixing the gastrointestinal contents. The muscularis externa has two layers:

(1) a relatively thick inner layer of circular muscle, whose fibers are oriented in a circular pattern around the tube such that contraction produces a narrowing of the lumen, and

(2) a thinner outer layer of longitudinal muscle, whose contraction shortens the tube. Between these two muscle layers is a second network of nerve cells known as the myenteric plexus. Finally, surrounding the outer surface of the tube is a thin layer of connective tissue called the serosa. Thin sheets of connective tissue connect the serosa to the abdominal wall, supporting the gastrointestinal tract in the abdominal cavity.

Extending from the luminal surface of the small intestine are fingerlike projections known as villi (Figure 3). The surface of each villus is covered with a layer of epithelial cells whose surface membranes form small projections called microvilli (also known collectively as the brush border). The combination of folded mucosa, villi, and microvilli increases the small intestine's surface area about 600-fold over that of a flat-surfaced tube having the same length and diameter. The human small intestine's total surface area is about 300 m^2, the area of a tennis court. Epithelial surfaces in the gastrointestinal tract are continuously being replaced by new epithelial cells. In the small intestine, new cells arise by cell division from cells at the base of the villi. These cells differentiate as they migrate to the top of the villus, replacing older cells that disintegrate and are discharged into the intestinal lumen. These disintegrating cells release into the lumen their intracellular enzymes, which then contribute to the digestive process. About 17 billion epithelial cells are replaced each day, and the entire epithelium of the small intestine is replaced approximately every 5 days. It is because of this rapid cell turnover that the lining of the intestinal tract is so susceptible to damage by agents, such as radiation and anticancer drugs, that inhibit cell division.

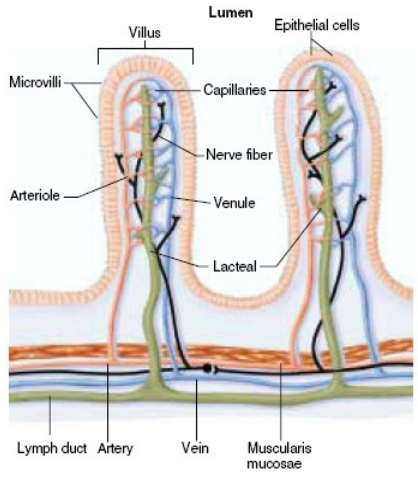


Figure 3 Structure of the villus

The center of each intestinal villus is occupied both by a single blind-ended lymphatic vessel termed a lacteal and by a capillary network Figure 3. Most of the fat absorbed in the small intestine enters the lacteals, while other absorbed nutrients enter the blood capillaries. The venous drainage from the small intestine, as well as from the large intestine, pancreas, and portions of the stomach, does not empty directly into the vena cava but passes first, via the hepatic portal vein**,** to the liver. There it flows through a second capillary network before

leaving the liver to return to the heart. Thus, material absorbed into the intestinal capillaries, in contrast to the lacteals, can be processed by the liver before entering the general circulation.

Regulation of gastrointestinal processes

Unlike control systems that regulate variables in the internal environment, the control mechanisms of the gastrointestinal system regulate conditions in the lumen of the tract.

Gastrointestinal reflexes are initiated by a relatively small number of luminal stimuli: distension of the wall by the volume of the luminal contents; chyme osmolarity (total solute concentration); chyme acidity; and chyme concentrations of specific digestion products (monosaccharides, fatty acids, peptides, and amino acids). These stimuli act on receptors located in the wall of the tract (mechanoreceptors, osmoreceptors, and chemoreceptors) to trigger reflexes that influence the effectors—the muscle layers in the wall of the tract and the exocrine glands that secrete substances into its lumen.

Neural Regulation The gastrointestinal tract has its own local nervous system, known as the enteric nervous system**,** in the form of two nerve networks, the myenteric plexus and the submucous plexus . These neurons either synapse with other neurons in the plexus or end near smooth muscles, glands, and epithelial cells. Many axons leave the myenteric plexus and synapse with neurons in the submucous plexus, and vice versa, so that neural activity in one plexus influences the activity in the other. Moreover, stimulation at one point in the plexus can lead to impulses that are conducted both up and down the tract. Thus, for example, stimuli in the upper part of the small intestine may affect smooth muscle and gland activity in the stomach as well as in the lower part of the intestinal tract. The enteric nervous system contains adrenergic and cholinergic neurons as well as nonadrenergic, noncholinergic neurons that release neurotransmitters, such as nitric oxide, several neuropeptides, and ATP. Many of the effectors mentioned earlier—muscle cells and exocrine glands—are supplied by neurons that are part of the enteric nervous system. This permits that is, independent of the central nervous system (CNS). In addition, nerve fibers from both the sympathetic and parasympathetic branches of the autonomic nervous system enter the intestinal tract and synapse with neurons in both plexuses. Via these pathways, the CNS can influence the motility and secretory activity of the gastrointestinal tract. Thus, two types of neural reflex arcs exist:

(1) short reflexes from receptors through the nerve plexuses to effector cells; and

(2) long reflexes from receptors in the tract to the CNS by way of afferent nerves and back to the nerve plexuses and effector cells by way of autonomic nerve fibers. It should be noted that not all neural reflexes are indicated by signals within the tract. The sight or smell of food and the emotional state of an individual can have significant effects on the gastrointestinal tract, effects that are mediated by the CNS via autonomic neurons.

Hormonal Regulation. The hormones that control the gastrointestinal system are secreted mainly by endocrine cells scattered throughout the epithelium of the stomach and small intestine; that is, these cells are not clustered into discrete organs like the thyroid or adrenal glands. One surface of each endocrine cell is exposed to the lumen of the gastrointestinal tract. At this surface, various chemical substances in the chyme stimulate the cell to release its hormones from the opposite side of the cell into the blood. Although some of these hormones can also be detected in the lumen and may therefore act locally as paracrine agents, most of the gastrointestinal hormones reach their target cells via the circulation. Several dozen substances are currently being investigated as possible gastrointestinal hormones, but only four: secretin, cholecystokinin (CCK), gastrin, and glucose-dependent insulinotropic peptide (GIP) have met all the criteria for true hormones. They, as well as several candidate hormones, also exist in the CNS and in gastrointestinal plexus neurons, where they function as neurotransmitters or neuromodulators. In many cases, a single effector cell contains receptors for more than one hormone, as well as receptors for

neurotransmitters and paracrine agents, with the result that a variety of inputs can affect the cell's response. One such event is the phenomenon known as potentiation**,** which is exemplified by the interaction between secretin and CCK. Secretin strongly stimulates pancreatic bicarbonate secretion, whereas CCK is a weak stimulus of bicarbonate secretion. Both hormones together, however, stimulate pancreatic bicarbonate secretion more strongly than would be predicted by the sum of their individual stimulatory effects. This is because CCK potentiates the effect of secretin. One of the consequences of potentiation is that small changes in the plasma concentration of one gastrointestinal hormone can have large effects on the actions of other gastrointestinal hormones.

Phases of gastrointestinal control The neural and hormonal control of the gastrointestinal system is, in large part, divisible into three phases—cephalic, gastric, and intestinal—according to stimulus location. The cephalic phase is initiated when receptors in the head (cephalic*,* head) are stimulated by sight, smell, taste, and chewing. It is also initiated by various emotional states. The efferent pathways for these reflexes include both parasympathetic fibers, mostly in the vagus nerves, and sympathetic fibers. These fibers activate neurons in the gastrointestinal nerve plexuses, which in turn affect secretory and contractile activity. Four types of stimuli in the stomach initiate the reflexes that constitute the gastric phase of regulation: distension, acidity, amino acids, and peptides formed during the digestion of ingested protein. The responses to these stimuli are mediated by short and long neural reflexes and by release of the hormone gastrin. Finally, the intestinal phase is initiated by stimuli in the intestinal tract: distension, acidity, osmolarity, and various digestive products. The intestinal phase is mediated by both short and long neural reflexes and by the gastrointestinal hormones secretin, CCK, and GIP, all of which are secreted by endocrine cells in the small intestine.

Ingestion and processing 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 in themselves are extremely important automatic regulatory systems for maintaining an adequate nutritional supply for the body.

Mastication (Chewing)

The teeth are designed for chewing, the anterior teeth (incisors) providing 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 as well as 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.

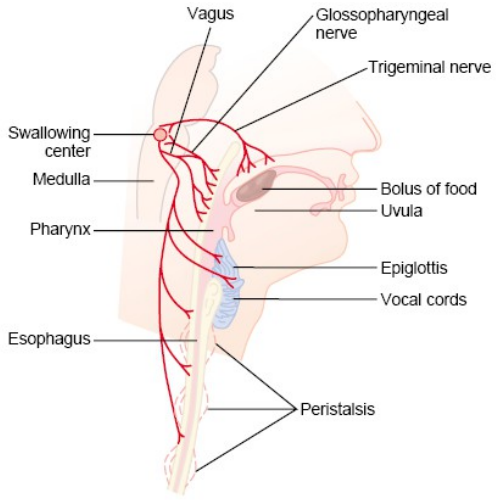


Figure 4 Swallowing mechanism

1.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. From here on, swallowing becomes entirely or almost entirely automatic and ordinarily cannot be stopped.

2.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:

a. The soft palate is pulled upward to close the posterior nares, to prevent reflux of food into the nasal cavities.
b. 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.
c. 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 vocalcords. Destruction of the vocal cords or of the muscles that approximate them can cause strangulation.
d. 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 (pharyngoesophageal sphincter) relaxes, thus allowing food to move 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 that 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.

e. 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.

3.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 glossopharyngeal 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 glossopharyngeal 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.

Regulation 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 5th, 9th, 10th, and 12th 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. 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.

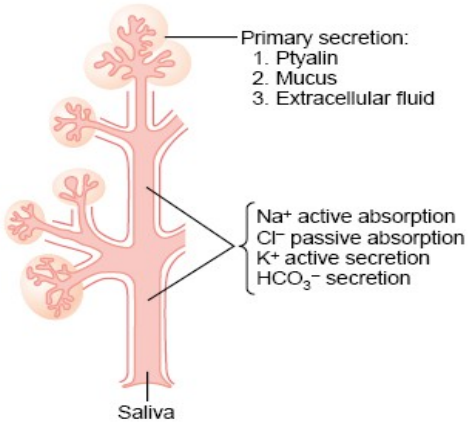
Secretion of salivary glands

The principal glands of salivation are the parotid, submandibular, and sublingual glands; in addition, there are many very small buccal glands. Daily secretion of saliva normally ranges between 800 and 1500 milliliters, as shown by the average value of 1000 milliliters. Saliva contains two major types of protein secretion:

(1) a serous secretion that contains ptyalin (an alfa-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, while 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.



The mechanism for secretion of 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.

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.

Figure 5 Formation and secretion of saliva

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.

During maximal salivation, the salivary ionic concentrations change considerably because the rate of formation of primary secretion by the acini can increase as much as 20-fold. This acinar secretion then flows through the ducts so rapidly that the ductal reconditioning of the secretion is considerably reduced. Therefore, when copious quantities of saliva are being secreted, the sodium chloride concentration rises only to one half or two thirds that of plasma, and the potassium concentration rises to only four times that of plasma.

Under basal awake conditions, about 0.5 milliliter of saliva, almost entirely of the mucous type, is secreted each minute; but during sleep, secretion becomes very little.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 another is 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.

Nervous regulation of salivary secretion

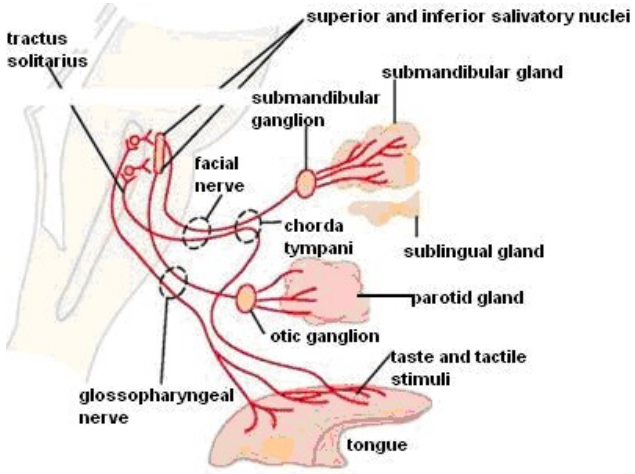


Figure 6 shows the parasympathetic nervous pathways for regulating salivation, demonstrating that the salivary glands are controlled mainly by parasympathetic nervous signals all the way from the superior and inferior salivatory nuclei in the brain stem.

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.

Figure 6 Regulation of salivary secretion

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, 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 vessel walls 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.

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. 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 very abnormal conditions.

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 intraabdominal 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.

Characteristics of the gastric secretions and motility function

The epithelial layer lining the stomach invaginates into the mucosa, forming numerous tubular glands. There are three major exocrine secretions of the stomach—mucus, acid, and pepsinogen—is secreted by a different cell type. In addition, enterochromaffin-like (ECL) cells, which release the paracrine agent histamine, and cells that secrete the peptide messenger somatostatin, are scattered throughout the tubular glands. Stomach mucosa has two important types of tubular glands: oxyntic glands (also called gastric glands) and pyloric glands.

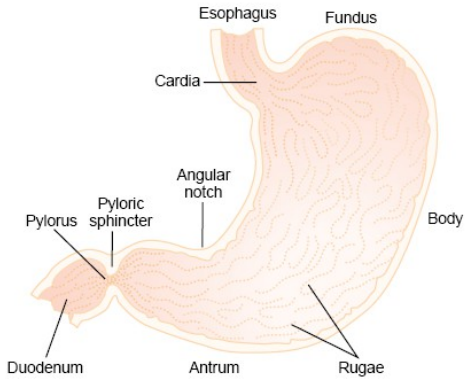
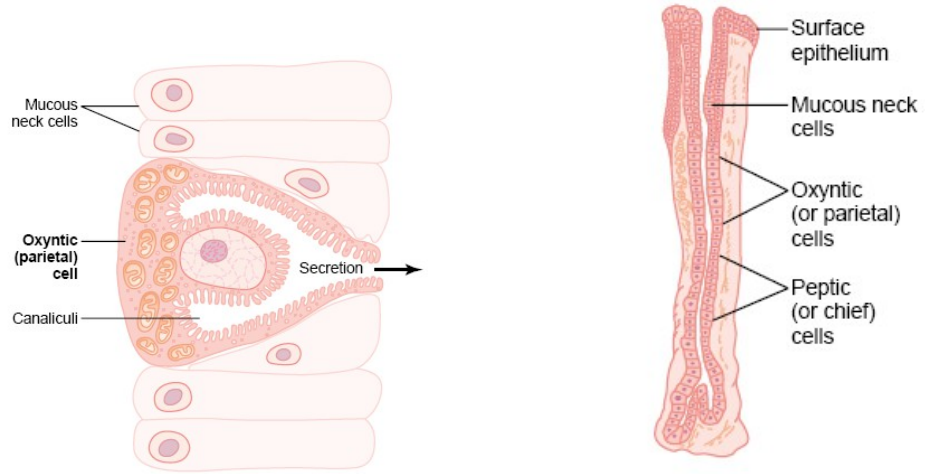


Figure 7 Anatomy of the stomach

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 per cent of the stomach. The pyloric glands are located in the antral portion of the stomach, the distal 20 per cent of the stomach.



A **B**

Figure 8 A) Schematic anatomy of the canaliculi in a parietal cell; **B)** oxyntic gland from the body of the stomach

Basic mechanism of hydrochloric acid secretion

A typical stomach oxyntic gland 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. When stimulated, the parietal cells secrete an acid solution that contains about 160 millimoles of hydrochloric acid per liter, which is almost exactly 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.

Figure 8 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. Different suggestions for the chemical mechanism of hydrochloric acid formation have been offered. One of these, shown in Figure 9 consists of the following steps:

1. Chloride ion is actively transported from the cytoplasm of the parietal cell into the lumen of the canaliculus, and sodium ions are actively transported out of the canaliculus into the

cytoplasm of the parietal cell. These two effects together create a negative potential of -40 to -70 millivolts in the canaliculus, which in turn causes diffusion of positively charged potassium ions and a small number of sodium ions from the cell cytoplasm into the canaliculus. Thus, in effect, mainly potassium chloride and much smaller amounts of sodium chloride enter the canaliculus.

2. Water becomes dissociated into hydrogen ions and hydroxyl ions in the cell cytoplasm. The hydrogen ions are then actively secreted into the canaliculus in exchange for potassium ions: this active exchange process is catalyzed by H+,K+-ATPase. In addition, the sodium ions are actively reabsorbed by a separate sodium pump. Thus, most of the potassium and sodium ions that had diffused into the canaliculus are reabsorbed into the cell cytoplasm, and hydrogen ions take their place in 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. Four chemical messengers regulate the insertion of H,K-ATPases into the plasma membrane and hence acid secretion: gastrin (a GI hormone), acetylcholine (ACh, a neurotransmitter), histamine, and somatostatin (two paracrine agents). Parietal cell membranes contain receptors for all four of these agents. Somatostatin inhibits acid secretion, while the other three stimulate secretion. Histamine is particularly important in stimulating acid secretion in that it markedly potentiates the response to the other two stimuli, gastrin and ACh.

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.

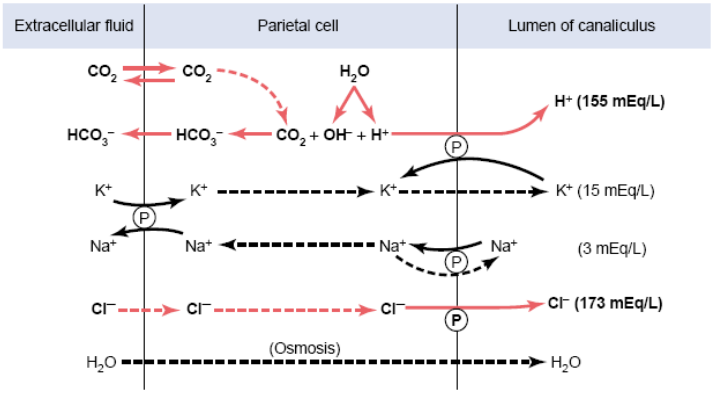


Figure 9 The mechanism for secretion of hydrochloric acid (P pumps, dashed lines free diffusion or osmosis)

4. Finally, carbon dioxide, either formed during metabolism in the cell or entering the cell from the blood, combines under the influence of carbonic anhydrase with the hydroxyl ions (from step 2) to form bicarbonate ions. These then diffuse out of the cell cytoplasm into the extracellular fluid in exchange for chloride ions that enter the cell from the extracellular fluid and are later secreted into the canaliculus.

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 can be stimulated to secrete histamine in several different ways:

(1) Probably the most potent mechanism for stimulating histamine secretion is 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.
(2) In addition, the ECL cells can be stimulated by (a) acetylcholine released from stomach vagal nerve endings and (b) probably also 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.

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 digestive juices 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.

During a meal, the rate of acid secretion increases markedly as stimuli arising from the cephalic, gastric, and intestinal phases alter the release of the four chemical messengers described in the previous paragraph. During the cephalic phase, increased activity of the parasympathetic nerves to the stomach's enteric nervous system results in the release of ACh from the plexus neurons, gastrin from the gastrin-releasing cells, and histamine from ECL cells. Once food has reached the stomach, the gastric phase stimuli—distension by the volume of ingested material and the presence of peptides and amino acids released by digestion of luminal proteins—produce a further increase in acid secretion. These stimuli use some of the same neural pathways used during the cephalic phase, in that nerve endings in the mucosa of the stomach respond to these luminal stimuli and send action potentials to the enteric nervous system, which in turn, can relay signals to the gastrin-releasing cells, histamine-releasing cells, and parietal cells. In addition, peptides and amino acids can act directly on the gastrin-releasing endocrine cells to promote gastrin secretion.

The concentration of acid in the gastric lumen is itself an important determinant of the rate of acid secretion for the following reason. Hydrogen ions (acid) stimulate the release of somatostatin from endocrine cells in the gastric wall. Somatostatin then acts on the parietal cells to inhibit acid secretion; it also inhibits the release of gastrin and histamine. The net result is a negative-feedback control of acid secretion; as the acidity of the gastric lumen increases, it turns off the stimuli that are promoting acid secretion.

Increasing the protein content of a meal increases acid secretion. This occurs for two reasons. First, the more protein ingested, the more peptides are generated in the stomach's lumen, and these peptides, as we have seen, stimulate acid secretion. The second reason is more complicated and reflects the effects of proteins on luminal acidity. Before food enters the stomach, the H^+ concentration in the lumen is high because there are few buffers present to bind any secreted hydrogen ions; therefore, the rate of acid secretion is low because high acidity inhibits acid secretion. The protein in food is an excellent buffer however, and so as protein enters the stomach the H^+ concentration drops as the hydrogen ions bind to the proteins. This decrease in acidity removes the inhibition of acid secretion. The more protein in a meal, the greater the buffering of acid, and the more acid secreted. We now come to the intestinal phase controlling acid secretion, the phase in which stimuli in the early portion of the small intestine influence acid secretion by the stomach. First, high acidity in the duodenum triggers reflexes that inhibit gastric acid secretion. This inhibition is beneficial for the following reason. The digestive activity of enzymes and bile salts in the small intestine is

strongly inhibited by acidic solutions, and this reflex ensures that acid secretion by the stomach will be reduced whenever chyme entering the small intestine from the stomach contains so much acid that it cannot be rapidly neutralized by the bicarbonate-rich fluids simultaneously secreted into the intestine by the liver and pancreas.

Acid, distension, hypertonic solutions, and solutions containing amino acids, and fatty acids in the small intestine reflexly inhibit gastric acid secretion. Thus, the extent to which acid secretion is inhibited during the intestinal phase varies, depending upon the volume and composition of the intestinal contents, but the net result is the same—balancing the secretory activity of the stomach with the digestive and absorptive capacities of the small intestine. The inhibition of gastric acid secretion during the intestinal phase is mediated by short and long neural reflexes and by hormones that inhibit acid secretion by influencing the four signals directly controlling acid secretion: ACh, gastrin, histamine, and somatostatin. **The hormones released by the intestinal tract that reflexly inhibit gastric activity are collectively called enterogastrones and include secretin, CCK, and additional unidentified hormones.**

Table 2 Control of HCl secretion during a meal

Stimuli	Pathways	Result
Cephalic phase Sight Smell Taste Chewing	Parasympathetic nerves to enteric nervous system	↑HCl secretion
Gastric contents (gastric phase) Distension ↑Peptides ↓H^+ concentration	Long and short neural reflexes, and direct stimulation of gastrin secretion	↑HCl secretion
Intestinal contents (intestinal phase) Distension ↑H^+ concentration ↑Osmolarity ↑Nutrient concentrations	Long and short neural reflexes; secretin, CCK, and other unspecified duodenal hormones	↓HCl secretion

Secretion and activation of pepsinogen. Pepsin is secreted by chief cells in the form of an inactive precursor called pepsinogen. The acidity in the stomach's lumen alters the shape of pepsinogen, exposing its active site so that this site can act on other pepsinogen molecules to break off a small chain of amino acids from their ends. 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. Pepsin is active only in the presence of a high H^+ concentration. It becomes inactive, therefore, when it enters the small intestine, where the hydrogen ions are neutralized by the bicarbonate ions secreted into the small intestine. The primary pathway for stimulating pepsinogensecretion is input to the chief cells from the enteric nervous system. During the cephalic, gastric, and intestinal phases, most of the factors that stimulate or inhibit acid secretion exert the same effect on pepsinogen secretion. Thus, pepsinogen secretion parallels acid secretion. Pepsin is not essential for protein digestion since in its absence, as occurs in some pathological conditions, protein can be completely

digested by enzymes in the small intestine. Hydrochloric acid is as necessary as pepsin for protein digestion in the stomach.

Regulation of pepsinogen secretion by the peptic cells in the oxyntic glands is much less complex than regulation of acid secretion; it occurs in response to two 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.

Secretion of Intrinsic Factor. The substance intrinsic factor, essential for absorption of vitamin B12 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 B12 stimulation of the bone marrow.

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. 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 a very 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.

Phases of Gastric Secretion

Gastric secretion is said to occur in three “phases” : 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 20 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 70 per cent 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.

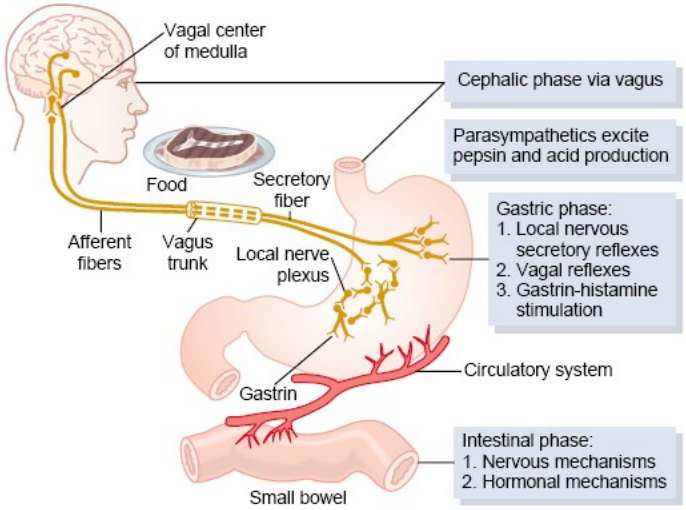


Figure 10 Phases of gastric secretion and their regulation

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 as well as through 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.
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, vasoactive intestinal polypeptide, and somatostatin—also have slight to moderate effects in inhibiting gastric secretion.
The functional purpose of inhibitory gastric secretion by intestinal factors 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.

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 usually is 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 very 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.

Motor functions of the stomac

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.

Figure 11 shows the basic anatomy of the stomach. Anatomically, the stomach is usually divided into two major parts: (1) the body and (2) the antrum. Physiologically, it is more appropriately divided into (1) the "oral" portion, comprising about the first two thirds of the body, and (2) the "caudad" portion, comprising the remainder of the body plus the antrum.

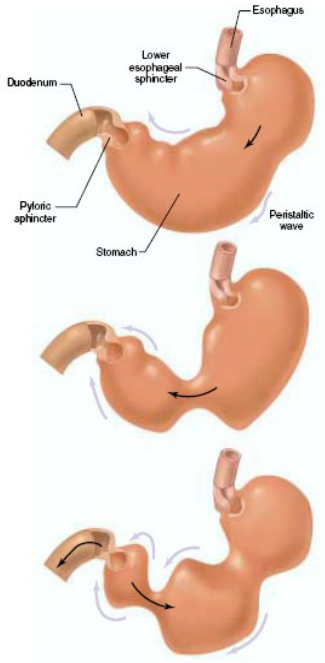


Figure 11 Movements of the peristaltic waves in the stomach

1. **Storage function of the stomach**

As food enters the stomach, it forms concentric circles of the food in the orad portion of the stomach, the newest food lying closest to the esophageal opening and the oldest food lying nearest the outer wall of the stomach. Normally, when food stretches the stomach, a "vagovagal reflex" from the stomach to the brain stem and then back to the stomach reduces the tone in the muscular wall of the body of the stomach so that the wall bulges progressively outward, accommodating greater and greater quantities of food up to a limit in the completely relaxed stomach of 0.8 to 1.5 liters. The pressure in the stomach remains low until this limit is approached.

2. **Mixing and propulsion of food in the stomach**

The digestive juices of the stomach are secreted by gastric glands, which are present in almost the entire wall of the body of the stomach except along a narrow strip on the lesser curvature of the stomach.

These secretions come immediately into contact with that portion of the stored food lying against the mucosal surface of the stomach. As long as food is in the stomach, weak peristaltic constrictor waves, called mixing waves, begin in the mid- to upper portions of the stomach wall and move toward the antrum about once every 15 to 20 seconds. These waves are initiated by the gut wall basic electrical rhythm, 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.

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.

3.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. 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 per cent of the time while food is in the stomach, the contractions become intense, beginning in midstomach and spreading through the caudad stomach no longer as weak mixing contractions but as 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."

The distal opening of the stomach is the pylorus. Here the thickness of the circular wall muscle becomes 50 to 100 per cent 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.

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.

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. Stomach wall stretch and the presence of certain types of foods in the stomach—particularly digestive products of meat—elicit release of a hormone called 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.

When food enters the duodenum, multiple nervous reflexes are initiated from the duodenal wall that 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 wholebody extracellular fluid during absorption of the intestinal contents. 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). 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 does inhibit gastric motility under some conditions, its effect at physiologic concentrations is probably mainly to stimulate secretion of insulin by the pancreas. 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.

An empty stomach has a volume of only about 50 ml, and the diameter of its lumen is only slightly larger than that of the small intestine. When a meal is swallowed, however, the smooth muscles in the fundus and body relax before the arrival of food, allowing the stomach's volume to increase to as much as 1.5 L with little increase in pressure. This is called receptive relaxation and is mediated by the parasympathetic nerves to the stomach's enteric nerve plexuses, with coordination by the swallowing center in the brain. Nitric oxide and serotonin released by enteric neurons mediate this relaxation. As in the esophagus, the stomach produces peristaltic waves in response to the arriving food. Each wave begins in the body of the stomach and produces only a ripple as it proceeds toward the antrum, a contraction too weak to produce much mixing of the luminal contents with acid and pepsin. As the wave approaches the larger mass of wall muscle surrounding the antrum, however, it produces a more powerful contraction which both mixes the luminal contents and closes the pyloric sphincter, a ring of smooth muscle and connective tissue between the antrum and the duodenum. The pyloric sphincter muscles contract upon arrival of a peristaltic wave. As a consequence of sphincter closing, only a small amount of chyme is expelled into the duodenum with each wave, and most of the antral contents are forced backward toward the body of the stomach, thereby contributing to the mixing activity in the antrum.

The rhythm (three per minute) of gastric peristaltic waves is generated by pacemaker cells in the longitudinal smooth muscle layer. These smooth-muscle cells undergo spontaneous depolarization-repolarization cycles (slow waves) known as the basic electrical rhythm of the stomach. These slow waves are conducted through gap junctions along the stomach's longitudinal muscle layer and also induce similar slow waves in the overlying circular muscle layer. In the absence of neural or hormonal input, however, these depolarizations are too small to cause significant contractions. Excitatory neurotransmitters and hormones act upon the smooth muscle to further depolarize the membrane, thereby bringing it closer to threshold. Action potentials may be generated at the peak of the slow wave cycle if threshold is reached and thus cause larger contractions. The number of spikes fired with each wave determines the strength of the muscle contraction. Thus, whereas the frequency of contraction is determined by the intrinsic basic electrical rhythm and remains essentially constant, the force of contraction and therefore the amount of gastric emptying per contraction are determined reflexly by neural and hormonal input to the antral smooth muscle. The initiation of these reflexes depends upon the contents of both the stomach and small intestine. All the factors previously discussed that regulate acid secretion can also alter gastric motility. For example, gastrin, in sufficiently high concentrations, increases the force of antral smooth-muscle contractions.

Distension of the stomach also increases the force of antral contractions through long and short reflexes triggered by mechanoreceptors in the stomach wall. Therefore, the larger a meal, the faster the stomach's initial emptying rate. As the volume of the stomach decreases,

the force of gastric contractions and the rate of emptying also decrease. In contrast, distension of the duodenum or the presence of fat, high acidity, or hypertonic solutions in its lumen all inhibit gastric emptying just as they inhibit acid and pepsin secretion. Fat is the most potent of these chemical stimuli. Autonomic nerve fibers to the stomach can be activated by the CNS independently of the reflexes originating in the stomach and duodenum and can influence gastric motility. Decreased parasympathetic or increased sympathetic activity inhibits motility. Via these pathways, pain and emotions such as sadness, depression, and fear tend to decrease motility, whereas aggression and anger tend to increase it. These relationships are not always predictable, however, and different people show different gastrointestinal responses to apparently similar emotional states. As we have seen, a hypertonic solution in the duodenum is one of the stimuli inhibiting gastric emptying. This reflex prevents the fluid in the duodenum from becoming too hypertonic since it slows the rate of entry of chyme and thereby the delivery of large molecules that can rapidly be broken down into many small molecules by enzymes in the small intestine. A patient who has had his stomach removed because of disease (for example, cancer) must eat a number of small meals. A large meal, in the absence of the controlled emptying by the stomach, would rapidly enter the intestine, producing a hypertonic solution. This hypertonic solution can cause enough water to flow (by osmosis) into the intestine from the blood to lower the blood volume and produce circulatory complications. The large distension of the intestine by the entering fluid can also trigger vomiting in these patients. All these symptoms produced by the rapid entry of large quantities of ingested material into the small intestine are known as the dumping syndrome.

Once the contents of the stomach have emptied over a period of several hours, the peristaltic waves cease and the empty stomach is mostly quiescent. During this time, however, there are brief intervals of peristaltic activity that will be described along with the events controlling intestinal motility.

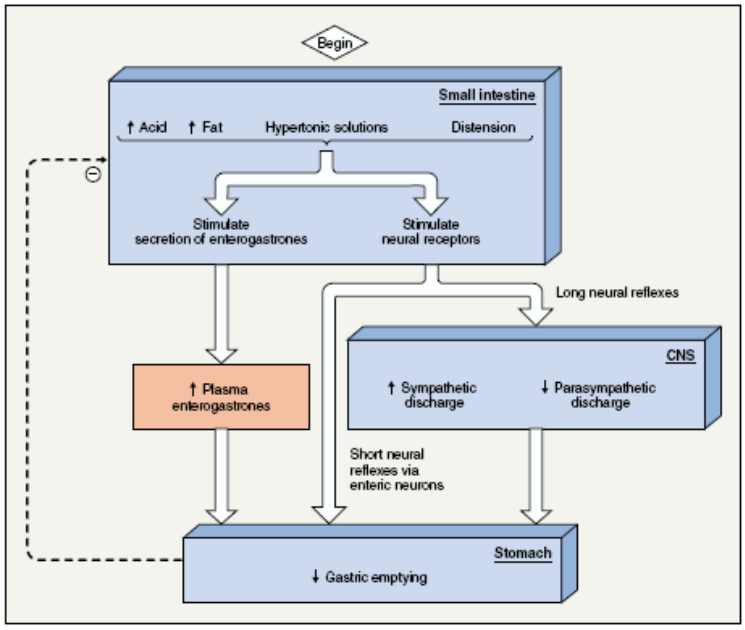


FIGURE 17–24
Intestinal-phase pathways inhibiting gastric emptying.