29

The Gastric Phase of the Integrated Response to a Meal

LEARNING OBJECTIVES

Upon completion of this chapter, you should be able to answer the following questions:

1. What are the major functions of the stomach?
2. What are the gross functional regions of the stomach?
3. What is the role of the gastric epithelium in digestion and absorption?
4. What is the role of the proton pump in parietal cell function?
5. What are some examples of how gastric acid secretion is regulated during the postprandial period?
6. What are the differences between gastric mucosal protection and defense?
7. What is the functional anatomy of GI smooth muscle?
8. What is the significance of gap junctions, interstitial cells of Cajal, and pacemaker cells in the functioning of GI smooth muscle?
9. How is the basic electrical rhythm (slow wave) generated, how is it regulated by chemical messengers (hormones, paracrine, neurotransmitters), and what causes contractions associated with the slow wave to occur?
10. What physiological events in gastric motility occur in the gastric phase?

In this chapter, gastrointestinal (GI) tract physiology when food is in the stomach (i.e., the gastric phase of digestion) will be discussed. This includes gastric function and its regulation, in addition to changes in function that occur in more distal regions of the GI tract. The main functions of the stomach are to act as a temporary reservoir for the meal and to initiate protein digestion through secretion of acid and the enzyme precursor pepsinogen. Other functions are listed in Box 29.1.

Food entering the stomach from the esophagus causes mechanical stimulation of the gastric wall via distention and stretching of smooth muscle. Food, predominantly oligopeptides and amino acids, also provides chemical stimulation when present in the gastric lumen. Regulation of gastric function during the gastric phase is dependent on endocrine, paracrine, and neural pathways. These pathways are activated by mechanical and chemical stimuli, which result in intrinsic and extrinsic neural reflex pathways that are important for regulation of gastric function. Afferent neurons that pass from the GI tract to the central nervous system via the vagus nerve (and to a lesser extent to the spinal cord) respond to these mechanical and chemical stimuli and activate parasympathetic outflow.

The endocrine pathways include the release of **gastrin,** which stimulates gastric acid secretion, and the release of **somatostatin,** which inhibits gastric secretion. Important paracrine pathways include **histamine** release, which stimulates gastric acid secretion. The responses elicited by activation of these pathways include both secretory and motor responses; *secretory responses* include secretion of acid, pepsinogen, mucus, intrinsic factor, gastrin, lipase, and HCO_3^-. Overall, these secretions initiate protein digestion and protect the gastric mucosa. *Motor responses* (changes in activity of smooth muscle) include inhibition of motility of the proximal part of the stomach (receptive relaxation) and stimulation of motility of the distal part of the stomach, which causes antral peristalsis. These changes in motility play important roles in storage and mixing of the meal with secretions and are also involved in regulating the flow of contents out of the stomach.

Functional Anatomy of the Stomach

The stomach is divided into three regions: the **cardia,** the **corpus** (also referred to as the *fundus* or *body*), and the **antrum** (Fig. 29.1). However, when discussing the physiology of the stomach, it is helpful to think of it as subdivided into *two functional regions:* the **proximal** and **distal** parts of the stomach. The proximal portion of the stomach (*proximal* because it is the most cranial) and the distal portion of the stomach (furthest away from the mouth) have quite different functions in the postprandial response to a meal, which will be discussed later.

The lining of the stomach is covered with a columnar epithelium folded into **gastric pits;** each pit is the opening of a duct into which one or more gastric glands empty (Fig. 29.2). The gastric pits account for a significant fraction of the total surface area of the gastric mucosa. The gastric mucosa is divided into three distinct regions based on the structure of the glands. The small cardiac glandular region, located just below the lower esophageal sphincter (LES),

• BOX 29.1 Functions of the Stomach

Storage—acts as temporary reservoir for the meal
Secretion of H^+ to kill microorganisms and convert pepsinogen to its active form
Secretion of intrinsic factor to absorb vitamin B_{12} (cobalamin)
Secretion of mucus and HCO_3^- to protect the gastric mucosa
Secretion of water for lubrication and to provide aqueous suspension of nutrients
Motor activity for mixing secretions (H^+ and pepsin) with ingested food
Coordinated motor activity to regulate the emptying of contents into the duodenum

primarily contains mucus-secreting gland cells. The remainder of the gastric mucosa is divided into the **oxyntic** or **parietal** (acid-secreting) **gland region,** located above the gastric notch (equivalent to the proximal part of the stomach), and the pyloric gland region, located below the notch (equivalent to the distal part of the stomach).

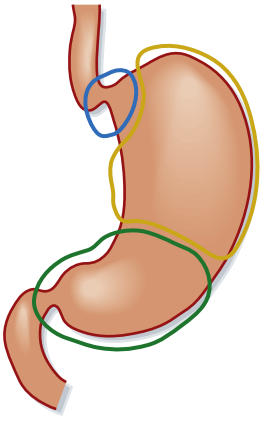
The structure of a gastric gland from the oxyntic glandular region is illustrated in Fig. 29.2. Surface epithelial cells extend slightly into the duct opening. The opening of the gland is called the **isthmus** and is lined with surface mucous cells and a few parietal cells. Mucous neck cells are located in the narrow **neck** of the gland. Parietal or oxyntic cells, which secrete HCl and intrinsic factor (involved in absorption of vitamin B_{12}), and **chief** or **peptic cells,** which secrete pepsinogens, are located deeper in the gland. Oxyntic glands also contain **enterochromaffin-like** (ECL) cells that secrete histamine, and D cells that secrete somatostatin. Parietal cells are particularly numerous in glands in the fundus, whereas mucus-secreting cells are more numerous in glands of the pyloric (antral) glandular region. In addition, the pyloric glands contain G cells that secrete the hormone gastrin. The parietal glands are also divided into regions: the neck (mucous neck cells and parietal cells) and the base (peptic/chief and parietal cells). Endocrine cells are scattered throughout the glands.

Gastric Secretion

Gastric secretion is a mixture of secretions from the surface epithelial cells and cells in the gastric glands. One of the most important components is H^+, which is secreted against a very large concentration gradient. Thus H^+ secretion by the parietal mucosa is an energy-intensive process. The cytoplasm of the parietal cell is densely packed with mitochondria, which have been estimated to fill 30% to 40% of the cell's volume. One major function of H^+ is conversion of inactive pepsinogen (the major enzyme product of the stomach) to pepsins, which initiate protein digestion in the stomach. Additionally, H^+ ions are important for preventing invasion and colonization of the gut by bacteria and other pathogens that may be ingested with food. The stomach also secretes significant amounts of HCO_3^- and mucus, which are important for protection of the gastric mucosa against the acidic and peptic luminal environment. The gastric epithelium also secretes intrinsic factor, which is necessary for absorption of vitamin B_{12} **(cobalamin).**

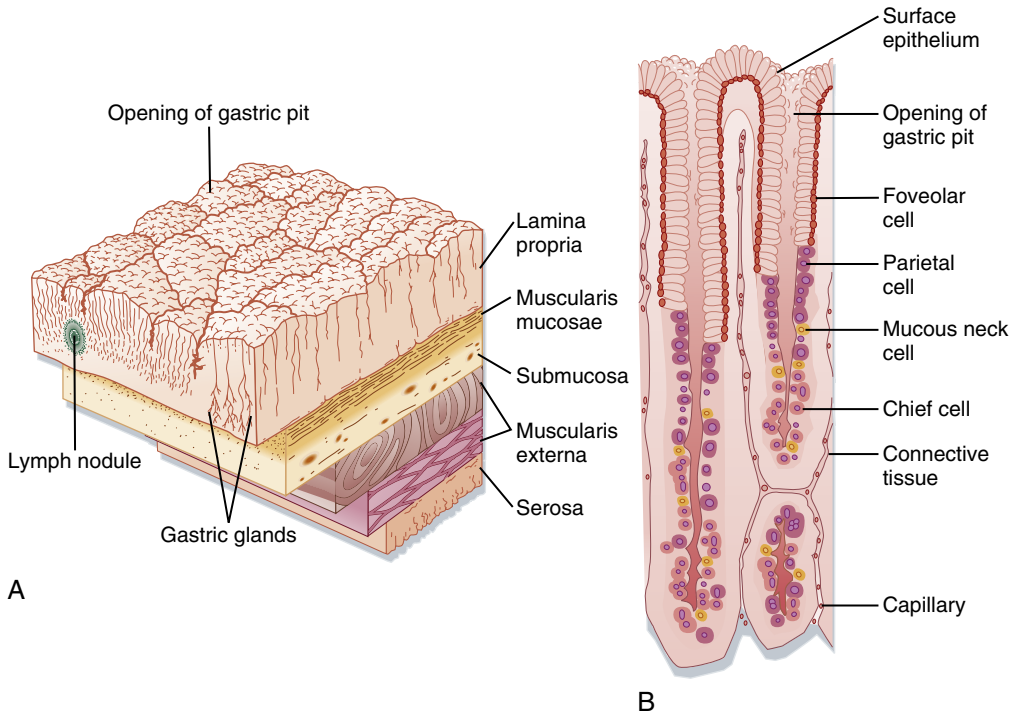
Composition of Gastric Secretions

Gastric secretion consists of inorganic and organic constituents together with water. Among the important components of gastric juice are HCl, salts, pepsins, intrinsic factor, mucus, and HCO_3^-. Secretion of all these components increases after a meal.



Region	Luminal secretion	Motility
LES* and cardia	Mucus HCO_3^-	Prevention of reflux Entry of food Regulation of belching
*LES is part of the esophagus		
Fundus and body	H^+ Intrinsic factor Mucus HCO_3^- Pepsinogens Lipase	Reservoir Tonic force during emptying
Antrum and pylorus	Mucus HCO_3^-	Mixing Grinding Sieving Regulation of emptying

• Fig. 29.1 The three functional regions of the stomach. The regions have different luminal secretions and patterns of smooth muscle activity indicative of their unique functions in response to food. *LES*, Lower esophageal sphincter.



• **Fig. 29.2** Representation of the structure of the gastric mucosa showing a section through the wall of the stomach **(A)** and detail of the structure of gastric glands and cell types in the mucosa **(B)**.

Inorganic Constituents of Gastric Secretion

The ionic composition of gastric secretions depends on the rate of secretion. The higher the secretory rate, the higher the concentration of H^+ ions. At lower secretory rates, $[H^+]$ decreases and $[Na^+]$ increases. $[K^+]$ is always higher in gastric juice than in plasma. Consequently, prolonged vomiting may lead to hypokalemia. At all rates of secretion, Cl^- is the major anion of gastric juice. Gastric HCl converts pepsinogens to active pepsins and provides the acid pH at which pepsins are active.

The rate of gastric H^+ secretion varies considerably among individuals. In humans, basal (unstimulated) rates of gastric H^+ production typically range from about 1 to 5 mEq/hr. During maximal stimulation, HCl production rises to 6 to 40 mEq/hr. The basal rate is greater at night and lowest in the early morning. The total number of parietal cells in the stomach of normal individuals varies greatly, and this variation is partly responsible for the wide range in basal and stimulated rates of HCl secretion.

Organic Constituents of Gastric Secretions

The predominant organic constituent of gastric secretions is **pepsinogen,** the inactive proenzyme of pepsin. Pepsins, often collectively called "pepsin," are a group of proteases secreted by the chief cells of the gastric glands. Pepsinogens are contained in membrane-bound zymogen granules in the chief cells. Zymogen granules release their contents by exocytosis when chief cells are stimulated to secrete (Table 29.1). Pepsinogens are converted to active pepsins by the cleavage of acid-labile linkages. Pepsins also act proteolytically on pepsinogens to form more pepsin. Pepsins are most proteolytically active at pH 3 and below. Pepsins may digest as much as 20% of the protein in a typical meal but are not required for digestion, because their function can be replaced by that of pancreatic proteases. When the pH of the duodenal lumen is neutralized, pepsins are inactivated by the neutral pH.

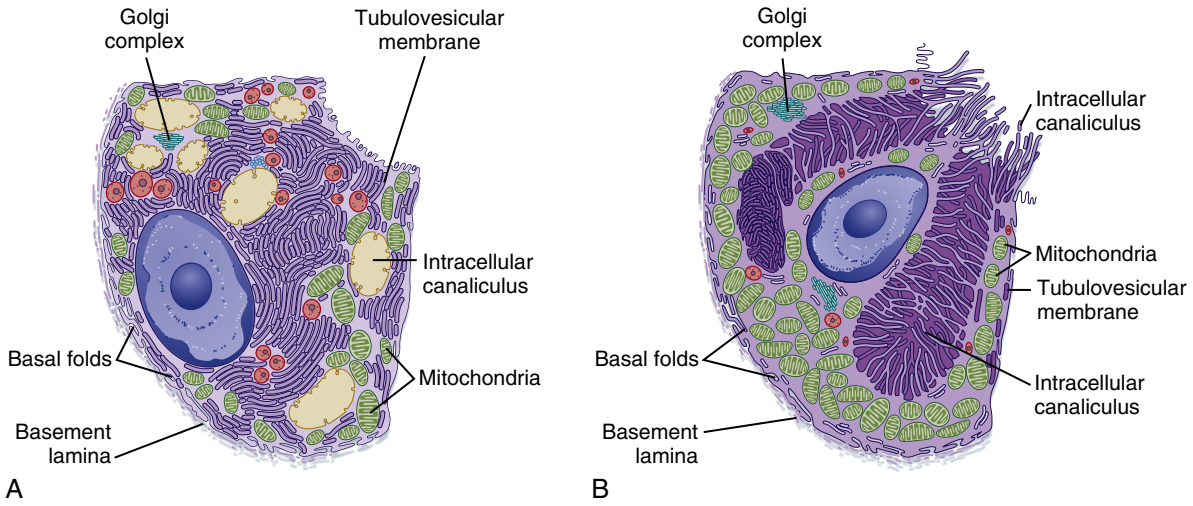
TABLE 29.1 Stimulation of Chief Cells in the Integrated Response to a Meal

Stimulant	Source
Acetylcholine (ACh)	Enteric neurons
Gastrin	G cells in the gastric antrum
Histamine	ECL cells in the gastric corpus
Cholecystokinin (CCK)	I cells in the duodenum
Secretin	S cells in the duodenum

Intrinsic factor, a glycoprotein secreted by parietal cells of the stomach, is required for normal absorption of vitamin B_{12}. Intrinsic factor is released in response to the same stimuli that elicit secretion of HCl by parietal cells.

Cellular Mechanisms of Gastric Acid Secretion

Parietal cells have a distinctive ultrastructure (Fig. 29.3). Branching secretory canaliculi course through the cytoplasm



• **Fig. 29.3** Parietal cell ultrastructure. **A,** A resting parietal cell showing the tubulovesicular apparatus in the cytoplasm and the intracellular canaliculus. **B,** An activated parietal cell that is secreting acid. The tubulovesicles have fused with the membranes of the intracellular canaliculus, which is now open to the lumen of the gland and lined with abundant long microvilli.

and are connected by a common outlet to the cell's luminal surface. Microvilli line the surfaces of the **secretory canaliculi.** The cytoplasm of unstimulated parietal cells contains numerous tubules and vesicles called the *tubulovesicular system.* The membranes of tubulovesicles contain the transport proteins responsible for secretion of H^+ and Cl^- into the lumen of the gland. When parietal cells are stimulated to secrete HCl (see Fig. 29.3), **tubulovesicular membranes** fuse with the plasma membrane of the secretory canaliculi. This extensive membrane fusion greatly increases the number of H^+/K^+ antiporters in the plasma membrane of the secretory canaliculi. When parietal cells secrete gastric acid at the maximal rate, H^+ is pumped against a concentration gradient that is about 1 million–fold. Thus the pH is 7 in the parietal cell cytosol and 1 in the lumen of the gastric gland.

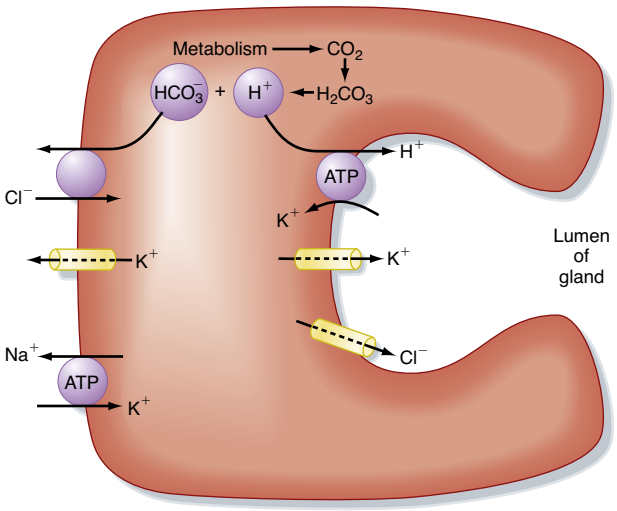
The cellular mechanism of H^+ secretion by the parietal cell is depicted in Fig. 29.4. Cl^- enters the cell across the basolateral membrane in exchange for HCO_3^- generated in the cell by the action of carbonic anhydrase, which produces HCO_3^- and H^+. H^+ is secreted across the luminal membrane by H^+,K^+-ATPase in exchange for K^+. K^+ recycles across the luminal membrane via a K^+ channel. Cl^- enters the lumen via an ion channel (a chloride channel [CLC] family Cl^- channel) located in the luminal membrane. Increased intracellular Ca^{++} and cyclic adenosine monophosphate (cAMP) stimulate luminal membrane conduction of Cl^- and K^+. Increased K^+ conductance hyperpolarizes the luminal membrane potential, which increases the driving force for efflux of Cl^- across the luminal membrane. The K^+ channel in the basolateral membrane also mediates the efflux of K^+ that accumulates in the parietal cell via the activity of H^+,K^+-ATPase. In addition, cAMP and Ca^{++} promote trafficking of Cl^- channels into the luminal membrane, as well as fusion of cytosolic tubulovesicles containing H^+,K^+-ATPase with the membrane of the secretory canaliculi (see Figs. 29.3 and 29.4). Parietal cell secretion of H^+ is also accompanied by transport of HCO_3^- into the bloodstream to maintain intracellular pH.

Secretion of HCO_3^-

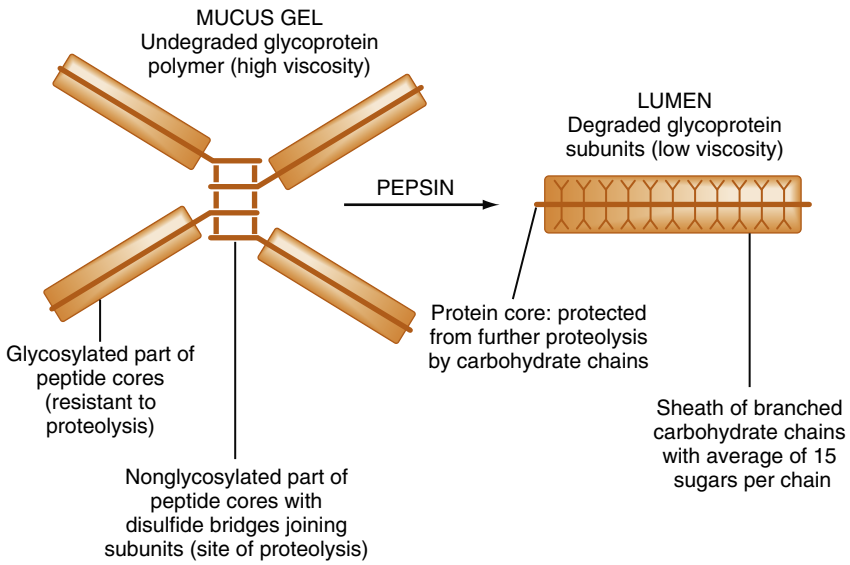
The surface epithelial cells also secrete a watery fluid that contains Na^+ and Cl^- in concentrations similar to those in plasma but with higher K^+ and HCO_3^- concentrations. HCO_3^- is entrapped by the viscous mucus that coats the surface of the stomach; thus, the mucus secreted by the resting mucosa lines the stomach with a sticky alkaline coat. In the postprandial period, rates of secretion of both mucus and HCO_3^- increase.

Secretion of Mucus

Secretions that contain **mucins** are viscous and sticky and are collectively termed *mucus.* Mucins are secreted by mucous



• **Fig. 29.4** Mechanism of H^+ and Cl^- secretion by an activated parietal cell in the gastric mucosa. *ATP*, Adenosine triphosphate.



• **Fig. 29.5** Schematic representation of the structure of gastric mucins before and after hydrolysis by pepsin. Intact mucins are tetramers of four similar monomers of about 500,000 Da. Each monomer is largely covered by carbohydrate side chains that protect it from proteolytic degradation. The central portion of the mucin tetramer, near the disulfide cross-links, is more susceptible to proteolytic digestion. Pepsins cleave bonds near the center of the tetramers to release fragments about the size of monomers.

neck cells located in the necks of gastric glands and by the surface epithelial cells of the stomach. Mucus is stored in large granules in the apical cytoplasm of mucous neck cells and surface epithelial cells and is released by exocytosis.

Gastric mucins are about 80% carbohydrate by weight and consist of four similar monomers of about 500,000 Da each that are linked together by disulfide bonds (Fig. 29.5). These tetrameric mucins form a sticky gel that adheres to the surface of the stomach. This gel is subject to proteolysis by pepsins to release fragments that do not form gels and thus dissolves the protective mucous layer. Maintenance of the protective mucous layer requires continuous synthesis of new tetrameric mucins to replace the mucins cleaved by pepsins.

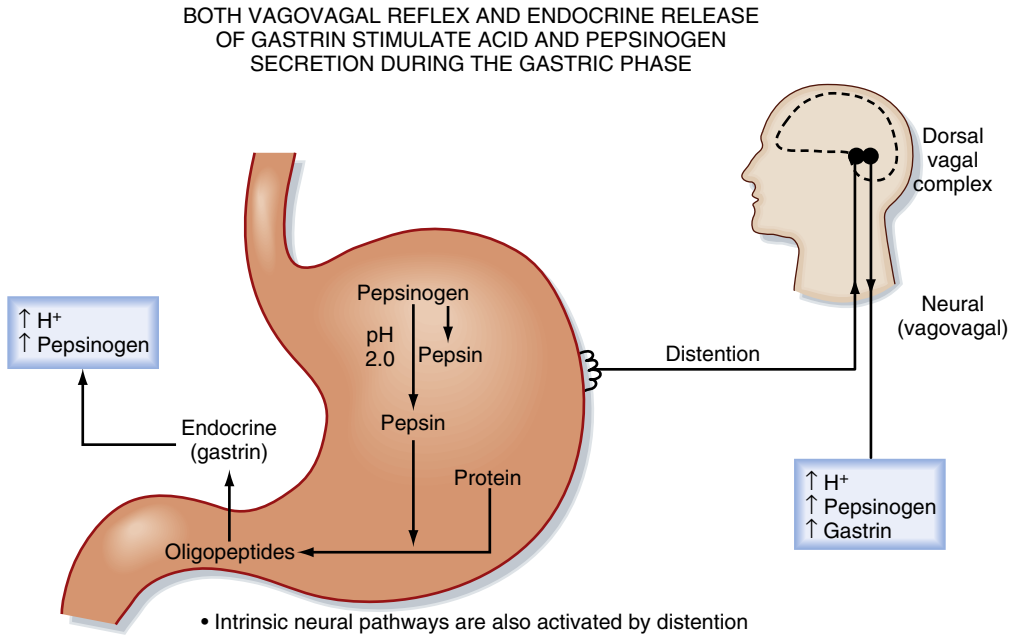
Mucus is secreted at a significant rate in the resting stomach. Secretion of mucus is stimulated by some of the same stimuli that enhance acid and pepsinogen secretion, especially acetylcholine released from parasympathetic nerve endings.

Regulation of Gastric Secretion

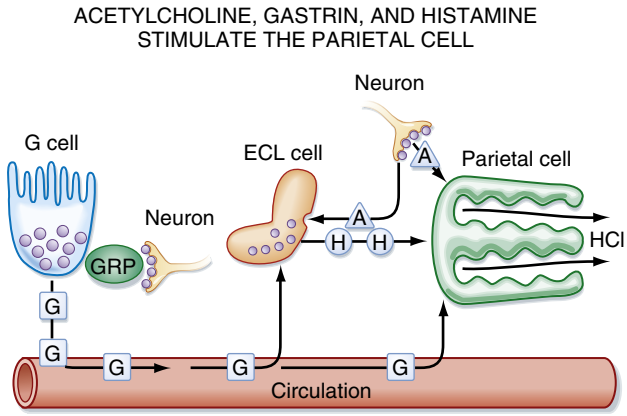
Parasympathetic innervation via the vagus nerve is the strongest stimulant of gastric H^+ secretion. Extrinsic efferent fibers terminate on intrinsic neurons that innervate parietal cells, ECL cells that secrete the paracrine mediator histamine, and endocrine cells that secrete the hormone gastrin. In addition, vagal stimulation results in secretion of pepsinogen, mucus, HCO_3^-, and intrinsic factor. Stimulation of the parasympathetic nervous system also occurs during the cephalic and oral phase of the meal. However, the gastric phase produces the largest stimulation of gastric secretion of the postprandial period (Fig. 29.6).

Stimulation of gastric acid secretion is an excellent example of a "feed-forward" (or cascade) response that uses endocrine, paracrine, and neural pathways. Activation of intrinsic neurons by vagal efferent activity results in release of acetylcholine from nerve terminals, which activates cells in the gastric epithelium. Parietal cells express muscarinic receptors and are activated to secrete H^+ in response to vagal efferent nerve activity. In addition, parasympathetic activation, via gastrin-releasing peptide from intrinsic neurons, releases gastrin from G cells located in the gastric glands in the gastric antrum (see Fig. 29.6). Gastrin enters the bloodstream and, via an endocrine mechanism, further stimulates the parietal cell to secrete H^+. Parietal cells express cholecystokinin type B (CCKB) receptors for gastrin. Histamine is also secreted in response to vagal nerve stimulation, and ECL cells express muscarinic and gastrin receptors. Thus, gastrin and vagal efferent activity induce release of histamine, which potentiates the effects of both gastrin and acetylcholine on the parietal cell. Hence activation of parasympathetic (vagal) outflow to the stomach is very efficient at stimulating the parietal cell to secrete acid (Figs. 29.7 and 29.8).

In the gastric phase, the presence of food in the stomach is detected and activates **vagovagal reflexes** to stimulate secretion. Food in the stomach results in distention and stretch, which are detected by afferent (or sensory) nerve endings in the gastric wall. These are the peripheral terminals of vagal afferent nerves that transmit information to the brainstem and thereby drive activity in vagal efferent fibers, a vagovagal reflex (see Fig. 29.6). In addition, digestion of proteins increases the concentration of oligopeptides and free amino acids in the lumen, which are detected by **chemosensors** in the gastric mucosa. Oligopeptides and amino acids also stimulate vagal afferent activity. The exact nature



• **Fig. 29.6** Neural regulation of gastric acid secretion in the gastric phase of the meal is mediated by the vagus nerve. The stimulation that occurs in the cephalic and oral phases (before food reaches the stomach) results in stimulation of parietal cells to secrete acid and chief cells to secrete pepsinogen. Thus, when food reaches the stomach, protein digestion is initiated by generating protein hydrolysate, which further stimulates secretion of gastrin from the mucosa of the gastric antrum. In addition, gastric distention activates a vagovagal reflex that further stimulates gastric acid and pepsinogen secretion.

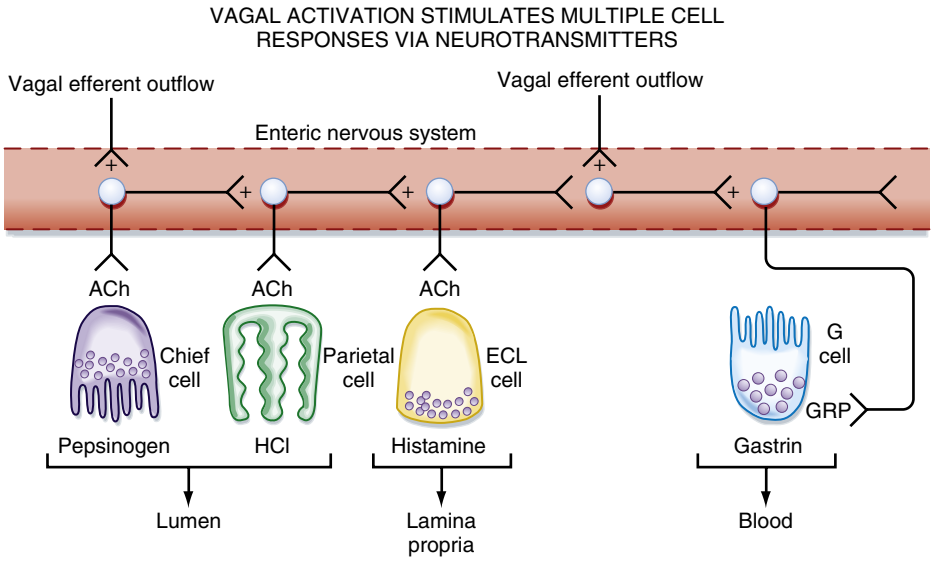


• **Fig. 29.7** The parietal cell is regulated by neural, hormonal, and paracrine pathways. Activation of vagal parasympathetic preganglionic outflow to the stomach acts in three ways to stimulate gastric acid secretion. There is direct neural innervation and activation of the parietal cell via release of acetylcholine (A) from enteric neurons, which acts on the parietal cell via muscarinic receptors. In addition, neural activation of the ECL cell stimulates release of histamine *(H)*, which acts via a paracrine pathway to stimulate the parietal cell. Finally, G cells located in gastric glands in the gastric antrum are activated by release of gastrin-releasing peptide *(GRP)* from enteric neurons, which acts on the G cell to stimulate release of gastrin *(G)*. Gastrin thereafter acts via a humoral pathway to stimulate the parietal cell.

of the chemosensors is not clear but may involve endocrine cells that release their contents to activate nerve endings. This topic will be discussed in more detail in Chapter 30.

There is also an important negative feedback mechanism whereby the presence of acid in the distal part of the stomach (antrum) induces a feedback loop to inhibit the parietal cell such that meal-stimulated H^+ secretion does not go unchecked. When the concentration of H^+ in the lumen reaches a certain threshold (<pH 3), somatostatin is released from endocrine cells in the antral mucosa. Somatostatin has a paracrine action on neighboring G cells to decrease the release of gastrin and thereby decrease gastric acid secretion (Fig. 29.9).

The receptors on the parietal cell membrane for acetylcholine, gastrin, and histamine, as well as the intracellular second messengers by which these secretagogues act, are shown in Fig. 29.10. Histamine is the strongest agonist of H^+ secretion, whereas gastrin and acetylcholine are much weaker agonists. However, histamine, acetylcholine, and gastrin potentiate one another's actions on the parietal cell. Antagonists of H_2 histamine receptors (e.g., cimetidine [Tagamet]) block secretagogue-stimulated acid secretion. Thus, much of the response to gastrin results from gastrin-stimulated release of histamine. Gastrin also has important trophic effects; elevation of gastrin levels causes ECL cells to increase in size and number. Binding of histamine to H_2 receptors on parietal cell plasma membranes activates adenylyl cyclase and elevates the cytosolic concentration of cAMP. These events stimulate H^+ secretion by activating basolateral K^+ channels and apical Cl^- channels and by causing more H^+,K^+-ATPase molecules and Cl^- channels to be inserted into the apical plasma membrane (see Fig. 29.4). Acetylcholine binds to M_3 muscarinic receptors and opens Ca^{++} channels in the apical plasma membrane. Acetylcholine also elevates intracellular [Ca^{++}] by promoting release of Ca^{++} from intracellular stores, which enhances H^+ secretion by activating basolateral K^+ channels and causing more H^+,K^+-ATPase molecules and Cl^- channels to be inserted into

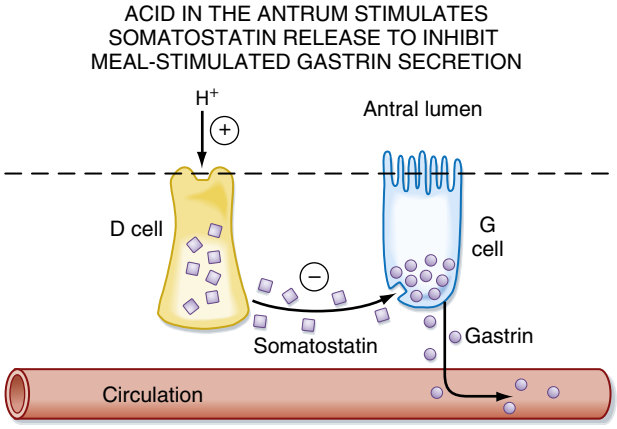


• **Fig. 29.8** Feedback regulation of gastric acid secretion by release of somatostatin and its action on G cells in the gastric antrum. Endocrine cells in the mucosa of the gastric antrum sense the presence of H^+ and secrete somatostatin. This in turn acts on specific receptors on G cells to inhibit release of gastrin and thus bring about inhibition of gastric acid secretion.

the apical plasma membrane. Gastrin enhances acid secretion by binding to CCKB receptors (see Fig. 29.10).

Digestion in the Stomach

Some digestion of nutrients occurs in the stomach. However, this is not required for full digestion of a meal; intestinal digestion is sufficient. Some amylase-mediated digestion of carbohydrates occurs in the stomach. Amylase is sensitive to pH and inactivated at low pH; however, some amylase is active even in the acidic gastric environment of the stomach because of substrate protection, meaning that when carbohydrate occupies the active site of amylase, it protects the enzyme from degradation.



• **Fig. 29.9** Vagal parasympathetic stimulation of gastric secretions via enteric neurons. Vagal preganglionic neurons innervate the myenteric and submucosal plexus. The terminals of the vagal preganglionic neurons innervate many enteric neurons and thus bring about changes in function as described in Fig. 29.7. *ACh*, Acetylcholine; *GRP*, gastrin-releasing peptide.

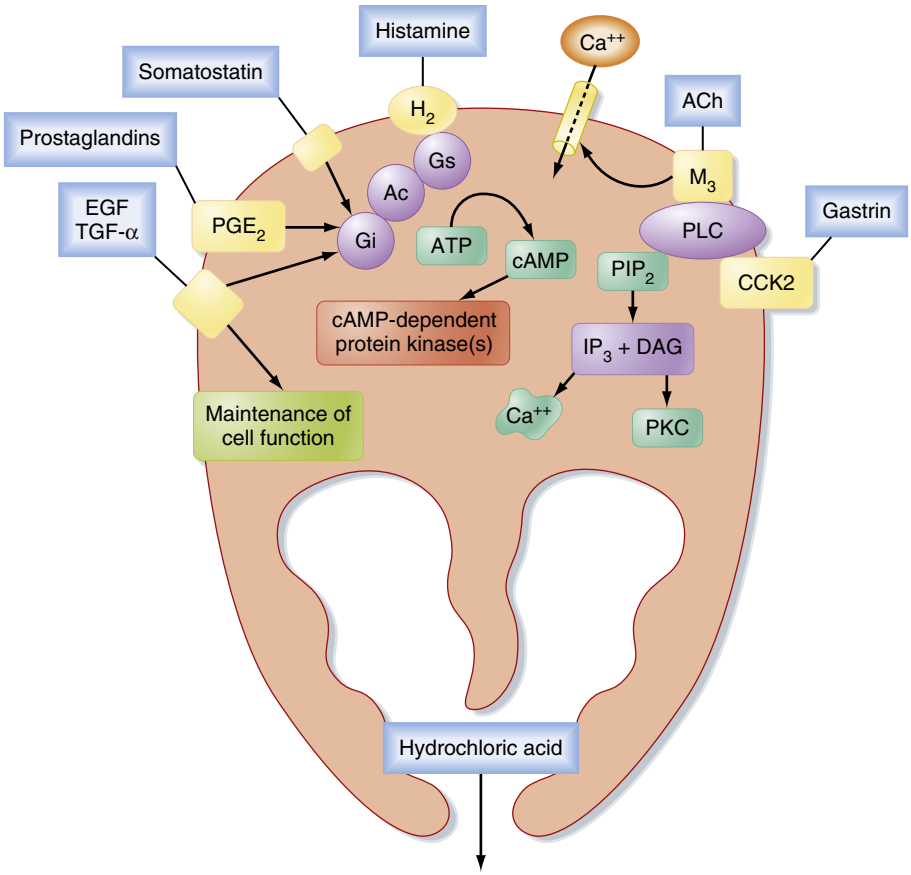
Digestion of lipids also starts in the stomach. The mixing patterns of gastric motility result in formation of an emulsion of lipids and **gastric lipase,** which attaches to the surface of lipid droplets in the emulsion and generates free fatty acids and monoglyceride from dietary triglyceride. However, the extent of hydrolysis of triglyceride is approximately 10%, and gastric hydrolysis is not essential for normal digestion and absorption of dietary lipids. Moreover, as discussed in the next chapter, the products of lipolysis are not available for absorption in the stomach because of its low luminal pH.

Gastric Mucosal Protection and Defense

Mucus and HCO_3^- protect the surface of the stomach from the effects of H^+ and pepsins. The protective mucus gel that forms on the luminal surface of the stomach, as well as alkaline secretions entrapped within it, constitutes a **gastric mucosal barrier** that prevents damage to the mucosa by gastric contents (Fig. 29.11). The mucus gel layer, which is about 0.2 mm thick, effectively separates the HCO_3^--rich secretions of the surface epithelial cells from the acidic contents of the gastric lumen. The mucus allows the pH of epithelial cells to be maintained at nearly neutral despite a luminal pH of about 2. Mucus also slows the diffusion of acid and pepsins to the epithelial cell surface. Protection of the gastric epithelium depends on both mucus and HCO_3^- secretion.

Gastrointestinal Motility

To understand GI motility it is necessary to review some properties of smooth muscle function. The motion of the gut wall governs the flow of the luminal contents along its length; the main patterns of motility are mixing **(segmentation)** and propulsion **(peristalsis).** In addition, smooth muscle activity in the stomach and colon serves a storage function.



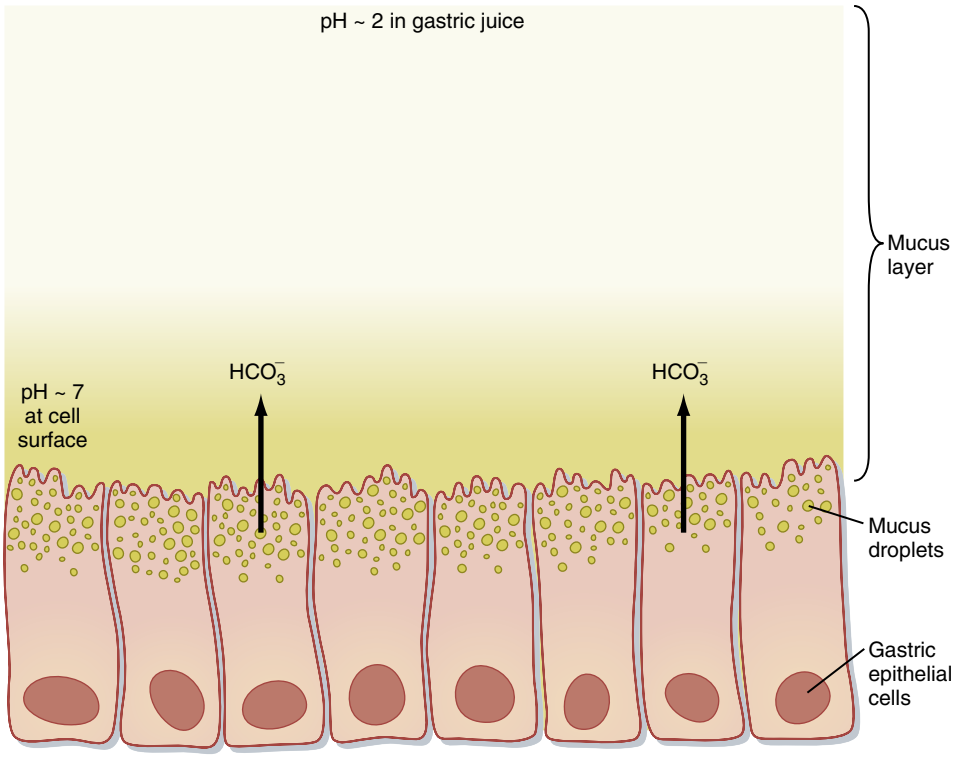
• **Fig. 29.10** Signal transduction mechanisms showing the mechanism of action of agonists (secretagogues) and antagonists that regulate secretion in parietal cells. Acetylcholine (ACh) binds to muscarinic M_3 receptors. Histamine acts via the H_2 receptor. Gastrin binds to the cholecystokinin type B (CCKB) receptor. Activation of M_3 and CCKB receptors results in opening of Ca^{++} channels and release of Ca^{++} from intracellular stores and thus an increase in cytosolic [Ca^{++}]. Activation of H_2 receptors activates adenylyl cyclase to increase intracellular levels of cAMP. *Ac*, Adenylyl cyclase; *ACh*, acetylcholine; *CCK*, cholecystokinin; *DAG*, diacylglycerol; *EGF*, epidermal growth factor; *IP_3*, inositol triphosphate; *PGE_2*, prostaglandin E_2; *PIP_2*, phosphatidylinositol 4,5-diphosphate; *PKC*, protein kinase C; *PLC*, protein lipase C; *TGF-α*, transforming growth factor α.

Functional Anatomy of Gastrointestinal Smooth Muscle

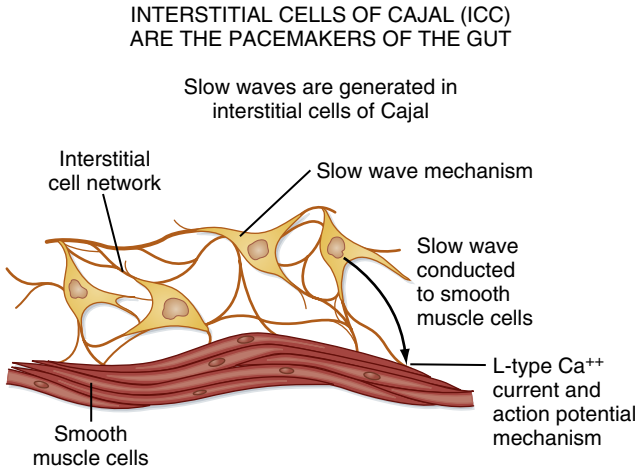
The smooth muscle in the GI tract is similar in structure to other smooth muscle found in the body. Fusiform cells are packed together in bundles surrounded by a connective tissue sheath. Gap junctions functionally couple the smooth muscle cells so that contraction of bundles occurs synchronously. The **interstitial cells of Cajal** (ICCs) are a specialized group of cells in the intestinal wall that are involved in transmission of information from enteric neurons to smooth muscle cells (Fig. 29.12). It is also thought that ICCs are **"pacemaker"** cells that have the capacity to generate the basic electrical rhythm, or *slow-wave activity,* that is a consistent feature of GI smooth muscle (Fig. 29.13).

IN THE CLINIC

There are times when the gastric mucosal barrier fails. Superficial breakdowns of the GI lining not involving the submucosa are called *erosions.* They generally heal without intervention. In contrast, breakdowns of the GI lining involving the muscularis and deeper layers are called *ulcers.* Gastric and duodenal erosions and ulcers occur as a result of an imbalance between the mechanisms that protect the mucosa and aggressive factors that can break it down. A healthy stomach/duodenum has ample natural protection against the destructive effects of H^+. Factors that magnify the harmful effect of H^+ on the stomach/duodenum or act separately from H^+ include pepsin, bile, the bacterium *Helicobacter pylori,* and the class of drugs known as *nonsteroidal anti-inflammatory drugs* (NSAIDs). Indeed, ulcer disease is becoming more common as the population ages and has more need of NSAIDs for non-GI complaints such as arthritis. Alcohol, tobacco, and caffeine are also risk factors for ulcers. Infectious agents can also cause gastritis (inflammation of the gastric epithelium). *H. pylori* is a spiral bacterium that has now become widely recognized as one factor that can lead to gastritis, ulcer formation, and in humans, gastric carcinoma. *H. pylori* can exist in the stomach because it secretes an enzyme, urease, that converts urea to NH_3, which is used to buffer H^+ by forming NH_4^+. An aggressive regimen of antibiotic treatment, sometimes in combination with an H^+,K^+-ATPase inhibitor, can often eliminate the infection, after which the gastritis and ulcer symptoms improve.



• **Fig. 29.11** The surface of the stomach is protected by the gastric mucosal barrier. Buffering by the HCO_3^--rich secretions and the high viscosity of the layer of mucus allow the pH at the cell surface to remain near 7, whereas the pH in the gastric juice in the lumen is 2.



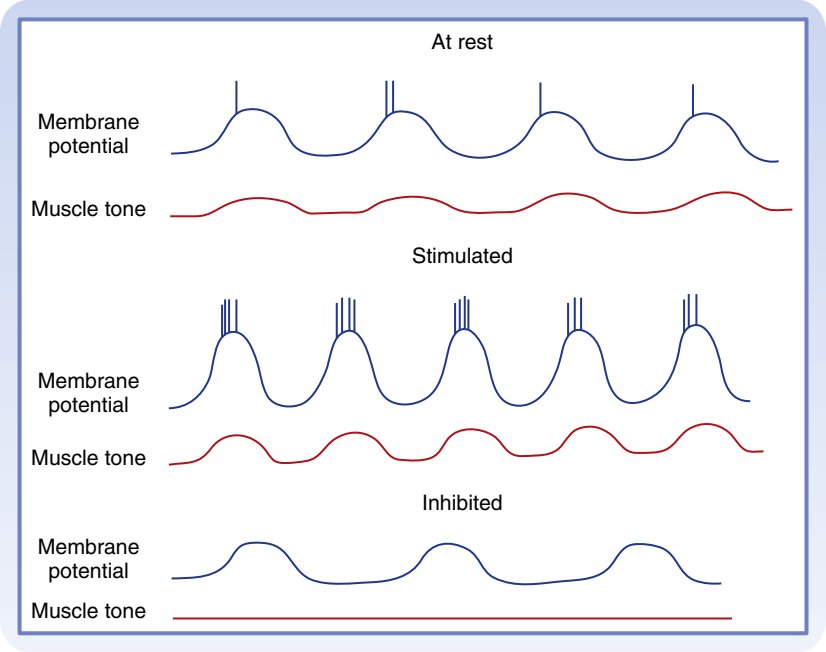
• **Fig. 29.12** Diagrammatic representation of the interstitial cells of Cajal network in the smooth muscle wall of the GI tract.

Electrophysiology of Gastrointestinal Smooth Muscle

The cyclic variation in resting membrane potential of GI smooth muscle is called the *basic electrical rhythm* or *slow wave*. The frequency of slow waves is 3 to 5 per minute in the stomach and about 12 to 20 per minute in the small intestine; it decreases to 6 to 8 per minute in the colon. The frequency of the slow wave is set by a pacemaker region in the different regions of the GI tract (see Fig. 29.13). The amplitude and, to a lesser extent, the frequency of the slow wave can be modulated by the activity of intrinsic and extrinsic nerves, and by hormones and paracrine substances. If the depolarization of the slow wave exceeds the threshold, a train of action potentials may be triggered during the peak of the slow wave. The rising phase of the action potential is caused by flow of ions through channels that conduct both Ca^{++} and Na^+ and are relatively slow to open. The Ca^{++} that enters the cell during the action potential initiates contraction. The extent of depolarization of the cells and the frequency of action potentials are enhanced by some hormones and paracrine agonists and by neurotransmitters from excitatory enteric nerve endings (e.g., acetylcholine and substance P). Inhibitory hormones and neuroeffector substances (e.g., vasoactive intestinal polypeptide and nitric oxide) hyperpolarize the smooth muscle cells and may diminish or abolish action potential spikes.

Slow waves that are not accompanied by action potentials elicit little or no contraction of the smooth muscle cells. Much stronger contractions are evoked by the presence of action potentials. The greater the number of action potentials that occur at the peak of a slow wave, the more intense the contraction of the smooth muscle. Because smooth muscle cells contract rather slowly (about a 10th as fast as skeletal muscle cells), the individual contractions caused by each action potential in a train do not cause distinct twitches; rather they sum temporally to produce an increasing level of tension.

Between the trains of action potentials, the tension developed by GI smooth muscle falls, but not to zero. This nonzero resting, or baseline, tension of smooth muscle is called



• **Fig. 29.13** Amplitude of slow wave determines the strength of muscle contraction. The slow wave will initiate a contraction in smooth muscle when it reaches a threshold amplitude. The amplitude of the slow wave is altered by release of neurotransmitters from enteric neurons.

tone. The tone of GI smooth muscle is altered by neurotransmitters, hormones, paracrine substances, and drugs. Tone is important in the sphincters and also in regions where storage of contents is important, such as the stomach and colon.

AT THE CELLULAR LEVEL

There are two types of **interstitial cells of Cajal** in the GI tract, c-Kit$^+$ and platelet-derived growth factor (PDGFR) alpha$^+$ cells. These cells are of mesenchymal origin and have multiple processes that form gap junctions with the smooth muscle cells. Electrical coupling between ICCs and smooth muscle cells forms a syncytium whereby conductance changes in one cell type affect the excitability of the other type of cells. ICCs are the pacemaker cells of the GI smooth muscle, and this function depends upon the release of Ca^{2+} from intracellular stores. They are localized within the smooth muscle in close association with the myenteric plexus and are closely associated with the varicosities of motor neurons in the smooth muscle layer suggesting ICCs are innervated. Thus, neural signals regulate the excitability of the musculature via ICCs and the syncytium. Studies in mutant mice that fail to develop ICCs confirm the obligatory role of these cells in generating slow waves in GI smooth muscle. There are several motility disorders in humans in which a role for ICCs have been reported; these include diabetic gastropathy, idiopathic gastroparesis, intestinal pseudo-obstruction, and slow transit constipation.

Specialized Patterns of Motility

Peristalsis is a moving ring of contraction that propels material along the GI tract. It involves neurally mediated contraction and relaxation of both muscle layers. Peristalsis occurs in the pharynx, esophagus, gastric antrum, and the small and large intestine.

Segmental contractions produce narrow areas of contracted segments between relaxed segments. These movements allow mixing of the luminal contents with GI tract secretions and increase exposure to the mucosal surfaces where absorption occurs. Segmentation occurs predominantly in the small and large intestine.

There are also characteristic pathological patterns of motility. During **spasm,** maximal contractile activity occurs continuously in a dysregulated manner. In **ileus,** contractile activity is markedly decreased or absent; it often results from irritation of the peritoneum, such as occurs in surgery, peritonitis, and pancreatitis.

Gastric Motility

Functional Anatomy of the Stomach

As discussed, the stomach is divided into two functional regions—proximal and distal, with sphincters at either end. The LES and *cardia* (defined as the region of the stomach immediately surrounding the LES) have important functions. Relaxation of the LES and cardia allows entry of food from the esophagus into the stomach and the release of gas, called *belching*. By maintaining tone, reflux of contents from the stomach back into the esophagus is largely prevented.

The proximal part of the stomach (the fundus together with the corpus or body) produces slow changes in tone

TABLE 29.2 The Stomach Alters the Physical and Chemical Characteristics of the Meal

Input	Output
Bolus	Emulsion, suspension (particles < 2 mm)
Triglyceride	Triglyceride plus small amounts of 2-monoglycerides and free fatty acids
Protein	Protein plus small amounts of peptides and amino acids
Starch	Starch plus oligosaccharides
Water, ions	Addition of large amounts of water and ions of low pH

compatible with its reservoir function. It is important for receiving and storing food and for mixing the contents with gastric juice (Table 29.2). Generation of tone in the proximal portion of the stomach is also an important driving force in the regulation of gastric emptying. Low tone and consequently low intragastric pressure are associated with delayed or slow gastric emptying, and an increase in tone in this region is required for gastric emptying to occur.

The distal part of the stomach is important in the mixing of gastric contents and for propulsion through the pylorus and into the duodenum. The muscle layers in the region of the gastric antrum are much thicker than in the more proximal regions of the stomach, and thus the antrum is capable of producing strong phasic contractions. Contractions initiated by the slow wave begin in the midportion of the stomach and move toward the pylorus. The strength of these contractions varies during the postprandial period. In the gastric phase of the meal the pylorus is usually closed, and these antral contractions serve to mix the gastric contents and reduce the size of solid particles (grinding). However, eventually these antral contractions are also important in emptying the stomach of its contents.

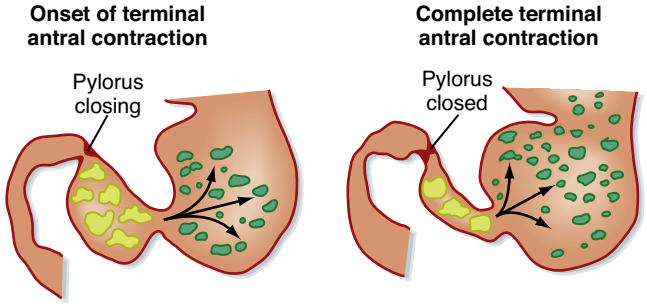
The pyloric sphincter is the **gastroduodenal junction** and is defined as an area of thickened circular muscle. This is a region of high pressure generated by tonic smooth muscle contraction. It is important in regulating gastric emptying.

Control of Gastric Motility in the Gastric Phase

Gastric motility is highly regulated and coordinated to perform the functions of storage and mixing. Regulation of emptying of contents into the small intestine, an important part of gastric motor function, will be considered in detail in the discussion of the duodenal phase of the meal in Chapter 30.

The stimuli regulating gastric motor function that result from the presence of the meal in the stomach are both mechanical and chemical and include distention and the presence of products of protein digestion (amino acids and small peptides). The pathways regulating these processes are predominantly neural and consist of vagovagal reflexes initiated by extrinsic vagal afferent fibers that terminate in the muscle and mucosa. Mucosal afferents respond to chemical stimuli, and mechanosensitive afferents respond to distention and contraction of smooth muscle. This afferent stimulation results in reflex activation of vagal efferent (parasympathetic) outflow and activation of enteric neurons that innervate the smooth muscle. Activation of enteric neurons produces both inhibitory and excitatory effects on gastric smooth muscle; these effects vary depending on the region of the stomach. Thus, distention of the gastric wall results in inhibition of smooth muscle in the proximal portion of the stomach and subsequent reflex accommodation, which allows entry and storage of the meal to occur with minimal increase in intragastric pressure.

In contrast, the predominant motor pattern of the distal part of the stomach in the gastric phase of the meal is activation of smooth muscle to produce and strengthen the antral contractions. The rate of antral contractions is set by the gastric pacemaker; however, the magnitude of the contractions is regulated by release of neurotransmitters from enteric neurons, including substance P and acetylcholine, which increase the level of depolarization of the smooth muscle and therefore produce stronger contractions. In this phase of the meal the pylorus is mostly closed. Thus, antral contractions will tend to move the contents toward the pylorus; however, because the pylorus is closed, the contents will be returned to the more proximal part of the stomach. In this way the gastric contents will be mixed. In addition, antral contractions can occlude the lumen, and thus larger particles will be dispersed (Fig. 29.14).



Force for retropulsion is increased pressure in terminal antrum as the antral contraction approaches the closed pylorus.

• **Fig. 29.14** Coordinated activity in the smooth muscle of the proximal and distal portions of the stomach and the pyloric sphincter results in mixing and grinding in the gastric antrum. The peristaltic wave moves down the gastric body and antrum toward the pylorus. If the pylorus is closed, the contents of the gastric antrum are retropulsed back into the more proximal part of the stomach. This pattern of motility results in grinding and mixing of the food with secretions from the gastric wall and eventually leads to a reduction in particle size and the presence of digestive products that will empty into the duodenum.

IN THE CLINIC

Gastroparesis is a disorder in which gastric emptying is slowed. Symptoms occur during or after eating and include feeling of fullness after a meal, nausea, vomiting, and decreased appetite. Diabetes is the most common cause of gastroparesis and likely involves damage to the neural innervation to the stomach that leads to a failure of strong antral contractions or pyloric relaxation. However, it can also be a postoperative complication after abdominal procedures, including bariatric surgery or in response to drugs that impair muscle contraction, such as opiates. Mild gastroparesis is relatively common in the general population. The precise cellular mechanisms are poorly understood but may inflammatory processes that led to loss of ICCs and neuroinflammation. Treatment of gastroparesis involves nutritional interventions and prokinetic drugs, including metoclopramide that has cholinergic and antidopaminergic actions. A more experimental treatment involves gastric electrical stimulation (GES), which involves the use of a pacemaker to stimulate the nerves and muscles.

Key Concepts

1. The main functions of the stomach are storage and initiation of protein digestion.
2. Regulation of gastric function is driven by extrinsic and intrinsic neural pathways together with key humoral (gastrin) and paracrine (histamine) mediators.
3. The key secretions from the stomach are acid and pepsinogen, which together begin protein digestion.
4. H^+ is secreted across the apical plasma membrane of parietal cells via H^+,K^+-ATPase.
5. The stomach also secretes intrinsic factor, which is involved in absorption of vitamin B_{12}.
6. The gastric epithelium secretes HCO_3^- and mucus to form a gel-like mucosal barrier that protects it against the acidic and peptic luminal contents.
7. The smooth muscle of the gut wall undergoes cyclic changes in membrane potential, termed the *basic electrical rhythm* or the *slow wave.*
8. The interstitial cells of Cajal are pacemakers in the gut wall, and they set the frequency of the slow wave.
9. The proximal part of the stomach undergoes a slow change in tone compatible with its storage function.
10. The distal part of the stomach undergoes phasic contractions that can vary considerably in strength.
11. Gastric emptying is regulated by vagovagal reflexes.