

# The Stomach 8.2

## Learning Objectives

- Identify the parts of the stomach including fundus, body, antrum, and pyloric sphincter
- Distinguish between receptive relaxation and adaptive relaxation
- Identify the location of the pacemaker zone and describe its function
- Describe interstitial cells of Cajal and their function
- Distinguish among propulsion, grinding, and retropulsion
- Define chyme
- List the gastric factors that regulate gastric emptying
- List the duodenal factors that inhibit gastric emptying
- Define the MMC and describe its function
- List the stomach secretions and their cells of origin
- Describe the function of intrinsic factor
- List the three phases of acid secretion
- Describe the role of GRP, SST, and histamine in acid secretion
- List the major factors that regulate acid secretion
- List the apical transport mechanisms for acid secretion by parietal cells

## THE STOMACH STORES FOOD AND RELEASES IT GRADUALLY TO THE SMALL INTESTINE

The purpose of the gastrointestinal (GI) system is to break down food into its component parts and absorb the released nutrients into the blood for use by the rest of the body. Digesting the food into its parts requires enzymatic reactions that take time. The trick is to keep the food in the GI tract long enough to break it down and absorb it, but not so long that we carry around useless extra weight. The stomach stores food and releases it to the intestines at a rate that the intestines can properly process it. It also secretes materials, begins digestion, and absorbs some materials.

## THE STOMACH HAS DISTINCT REGIONS

The stomach is a bulge in the alimentary tract between the **lower esophageal sphincter**, between the stomach and the esophagus, and the **pyloric sphincter** between the stomach and the **duodenum**, the first segment of

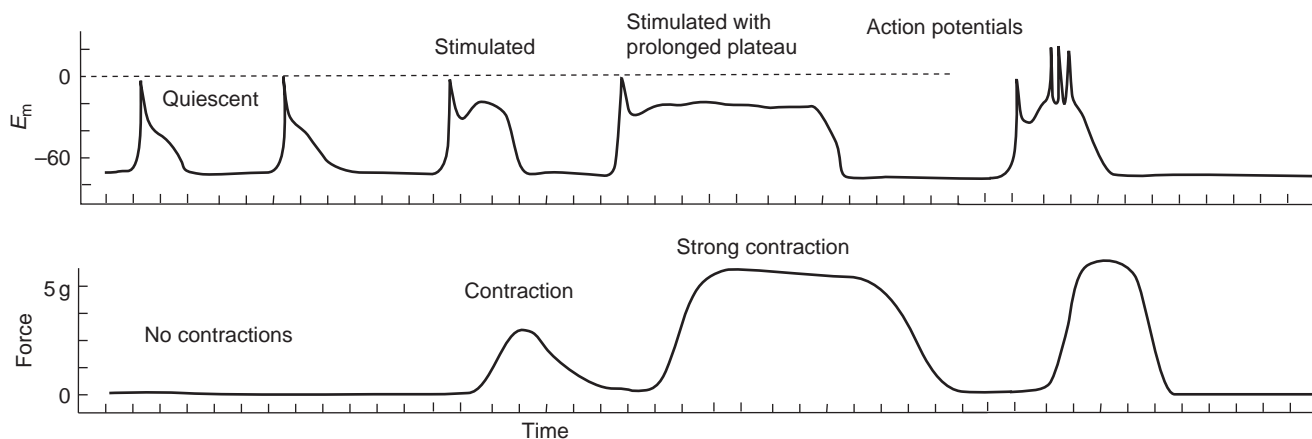
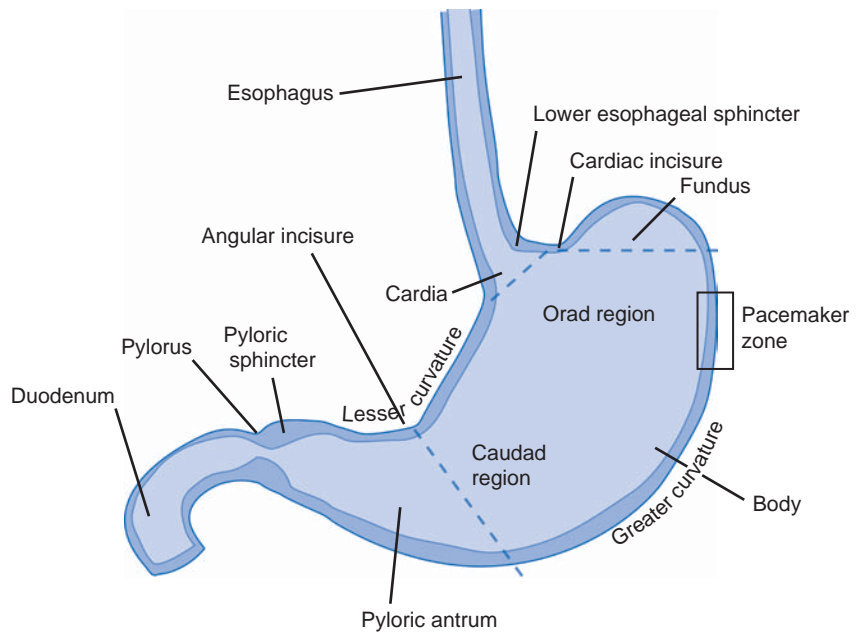
the small intestine. The stomach has several named parts that have no clear anatomical demarcations (see [Figure 8.2.1](#)). The stomach can be divided into two regions based on their different patterns of motility. The term “**orad**” means “toward the mouth,” and the term “**caudad**” means, literally, “toward the tail.” The orad part of the stomach has thinner muscle layers and serves to receive food from the esophagus. The caudad part has thicker walls that generate more force to mix and grind stomach contents and to propel the material into the duodenum.

Most parts of the GI tract have two layers of muscle that contribute to the movement of luminal contents. The stomach has three muscle layers that move food: an outer longitudinal layer, a middle circular layer, and an inner oblique layer that is unique to the stomach. The longitudinal layer is thickest over the curvatures of the stomach and does not cover the anterior and posterior surfaces. The oblique muscle consists of two bands that radiate from the lower esophageal sphincter to fuse with the circular layer in the caudad stomach. The thickness of the longitudinal and circular layers increases from the orad to the caudad stomach.

## GASTRIC MOTILITY IS FUNDAMENTALLY INTRINSIC, BUT IT IS MODULATED BY NERVES AND HORMONES

Intrinsic myogenic contraction forms the basis of gastric motility, and this fundamental motility occurs in the absence of any other influences. The resting membrane potential of stomach smooth muscle cells exhibits a gradient from about  $-48$  mV in cells in the orad stomach to about  $-71$  mV in cells from the antrum. The threshold for contractile activity in all of these cells is about  $-50$  mV. Gastric peristalsis occurs primarily in the distal stomach and is associated with **gastric slow waves**, rhythmic depolarizations of the resting membrane potential, consisting of a rapid depolarization followed by a plateau phase (see [Figure 8.2.2](#)). Although all sites of the caudad stomach generate these membrane potential oscillations, cells along the greater curvature of the stomach show the highest frequency of slow waves,  $3-5 \text{ min}^{-1}$ , and these entrain the rest of the stomach to their high frequency. The gastric slow waves are paced by **interstitial cells of Cajal (ICC)**, stellate

**FIGURE 8.2.1** Structure of the stomach. The esophagus empties into the stomach at the cardia where there is a functional sphincter, the lower esophageal sphincter, also sometimes called the cardiac sphincter. The left margin of the esophagus makes a sharp angle with the stomach called the cardiac incisure. The **fundus** is the part of the stomach superior to this incisure. The **body** and the **antrum** make up the remainder of the stomach. The **pyloric sphincter** regulates the movement of material between the stomach and the duodenum. The stomach can also be divided into an **orad** and a **caudad** region on the basis of its motility.



**FIGURE 8.2.2** Electrical and mechanical activities of stomach smooth muscle cells. Rhythmic depolarization of the smooth muscle cell membrane potential, called slow waves, originates from most cells in the distal stomach. Cells in the pacemaker zone have a higher frequency and establish the **basic electrical rhythm** of the stomach. The cyclic depolarizations consist of a rapid upstroke and a plateau phase. During the interdigestive period, the plateau is usually below threshold for contraction. Stimulation by parasympathetic nerves raises and prolongs the plateau so that contraction occurs because activator  $\text{Ca}^{2+}$  enters the cells during the plateau. Action potentials can be produced which cause even stronger contractions.

cells that lay along the greater curvature, receive inputs from the autonomic nerves or the enteric plexuses, and relay this to muscle cells. These interstitial cells of Cajal are accordingly called **pacemaker cells**, and they set the **basic electrical rhythm** for the stomach.

## EXTRINSIC AND INTRINSIC NERVES CONTROL GASTRIC MOTILITY

Afferent extrinsic nerves, mainly traveling over the vagus and splanchnic nerves, convey sensory information to the central nervous system (CNS), and efferent signals control the smooth muscle. The intrinsic innervation consists of the myenteric plexus, sandwiched between the outer longitudinal and inner circular layers of smooth muscle, and a submucosal plexus.

The myenteric plexus is most prominent of these two systems of intrinsic innervation. Parasympathetic extrinsic innervation originates from the **vagus** and sympathetic from the **celiac ganglion**. The vagus nerve primarily innervates cells in the myenteric plexus. Preganglionic parasympathetic fibers release acetylcholine to activate nicotinic receptors in the enteric ganglia, which excites gastric motility. Postganglionic sympathetic fibers release norepinephrine which inhibits excitatory neurotransmission within the enteric ganglia. Some vagal efferents activate inhibitory myenteric neurons that release vasoactive intestinal peptide (VIP) or nitric oxide (NO). These neurons are important in **receptive relaxation**, discussed below. The net effect of vagotomy is an increased gastric tone, suggesting that normal vagal activity provides a net inhibition of gastric tone.

## A NUMBER OF HORMONES INFLUENCE GASTRIC MOTILITY

Gastrin, ghrelin, and motilin all stimulate gastric motility and decrease the time of emptying of the stomach. These are all hormones that originate from gastrointestinal sources in response to gastrointestinal signals, and details of their origin, secretion, and action will be addressed later. All are protein hormones. Gastrin and ghrelin originate mainly from the stomach, and motilin is believed to initiate the fasting pattern of motility. Cholecystokinin, glucagon, glucagon-like peptide 1 (GLP-1), peptide YY, and somatostatin all decrease stomach motility and delay gastric emptying. These protein hormones originate from the small intestine.

## THE ORAD STOMACH RELAXES TO ACCOMMODATE LARGE MEALS

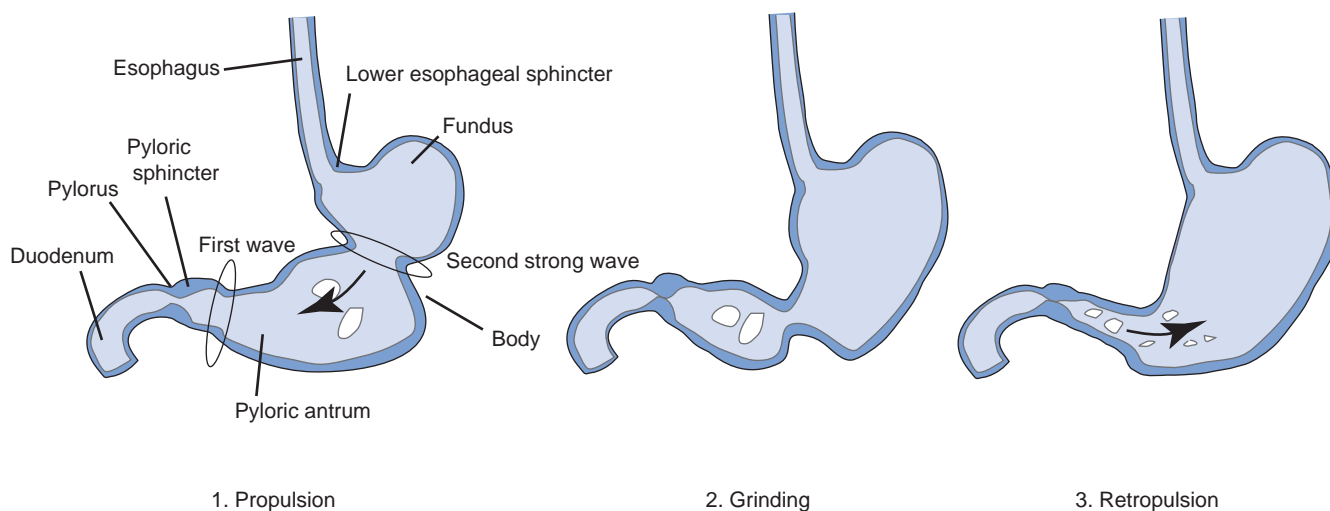
One of the main functions of the stomach is to act as a reservoir of ingested food that can be released to the intestines gradually so as to spread absorption of nutrients over a longer period of time. To do this, the stomach must stretch to accommodate meals. The stomach can hold about 1.5 L of material. Because the fundus maintains a constant tension, or **tone**, the stomach muscles must relax in order for the stomach to expand to receive more food. This gastric accommodation has two parts: **receptive relaxation** and **adaptive relaxation**. Receptive relaxation is the reduction in gastric tone as part of the swallowing program. Receptive relaxation occurs with a dry swallow or with mechanical stimulation of the pharynx or esophagus, and does not require movement of the bolus of food into the stomach. The vagus nerve mediates receptive relaxation by releasing vasoactive intestinal polypeptide (VIP) or nitric oxide (NO). On the other hand, adaptive relaxation begins with activation of stretch receptors upon distension of the stomach. The afferents travel along the vagus nerve

and initiate a reflex in which efferent signals return over the vagus nerve to relax the stomach. Because both afferent and efferent pathways travel over the vagus nerve, this is called a **vagovagal reflex**.

## AFTER A MEAL, GASTRIC CONTRACTIONS RESULT IN PROPULSION, GRINDING, OR RETROPULSION OF STOMACH CONTENTS

The slow waves paced by ICC propagate along the smooth muscle layers through electrical connections between smooth muscle cells. The slow waves travel faster circumferentially than longitudinally, so that the resulting contraction travels as a ring around the stomach from the body towards the antrum. In the interdigestive period, the slow waves are smaller and the plateau phase is below threshold. After a meal (the **postprandial period**), stimulation by the parasympathetic nervous system increases the amplitude and duration of the plateau phase and induces action potentials. These electrical events cause more intense contractions. Sympathetic stimulation reduces the amplitude and duration of the plateau phase, thereby decreasing the frequency of action potentials and the strength of contractions.

**Cinefluoroscopic studies** (X-ray movies) of gastric motility reveal a small ring of contraction that begins in the body of the stomach and propagates toward the antrum. This minor ring of contraction reaches the pylorus and causes it to contract to retain stomach contents. A few seconds after the minor contractile ring begins, a second contractile ring follows it. This more forceful ring propels food toward the pylorus and grinds it against itself. The increased pressure within the antrum causes the stomach contents to squirt back into the body (see [Figure 8.2.3](#)). This **retropulsion** mixes the



**FIGURE 8.2.3** Contractions of the stomach that propel the stomach contents toward the antrum, grind it, and cause retropulsion back into the body of the stomach. These contractions break up the food into a fine dispersion called chyme. The first weak wave causes the pyloric sphincter to close. The second, stronger wave propels food into the antrum where it is ground and then dispersed back into the body of the stomach through the narrow orifice produced by the encircling surfaces of the stomach walls.

stomach contents and helps reduce particle size. This motility of the stomach produces **chyme**, a finely dispersed mixture of food and stomach secretions.

## STOMACH AND DUODENAL CONTENTS REGULATE STOMACH EMPTYING

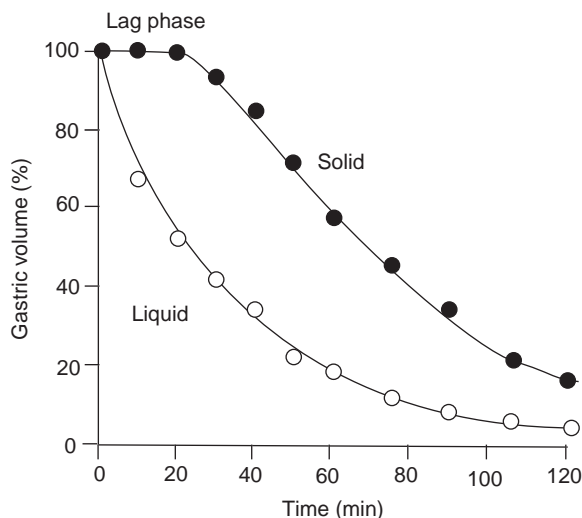
After a meal, the load of food and gastric secretions must be transferred into the small intestine where it can be further digested and absorbed. However, homeostasis of the nutrient content of blood is best served when there is a continuous supply of nutrients. This is achieved by slowing the passage of food so that nutrients are absorbed over a period of hours. Typically the stomach takes about 3 hours to empty. Usually the stomach contains a mixture of liquids, digestible solids, fats, and indigestible solids. The particle size, the amount, and the proportion of each of these constituents influence the rate of gastric emptying. [Figure 8.2.4](#) shows that inert liquids such as water or isotonic saline empty quickest. The rate of gastric emptying of these liquids obeys first-order kinetics:

$$[8.2.1] \quad \frac{dV}{dt} = -kV$$

where  $V$  is the volume in the stomach and  $dV/dt$  is its rate of removal from the stomach to the duodenum. First-order kinetics describe processes that are proportional to the first power of the starting material. The negative sign in the equation indicates that the volume in the stomach decreases with time. The rate is generally described in terms of its half-life or the time required for one-half of the material to disappear. Integration of [Eqn \[8.2.1\]](#) gives

$$[8.2.2] \quad V(t) = V_0 e^{-kt}$$

where  $V_0$  is the starting volume at  $t = 0$ . The half-time of exponential decay occurs when the volume is reduced to one-half of its starting value:  $V(t_{1/2}) = \frac{1}{2}V_0$ . Inserting



**FIGURE 8.2.4** Gastric emptying of liquid versus solid materials. Solid foods exhibit a lag phase while particle size is being reduced. Liquids begin emptying immediately and show first-order kinetics.

this into [Eqn \[8.2.2\]](#), we find that the half-life is related to  $k$ , the rate constant, by

$$[8.2.3] \quad t_{1/2} = \frac{\ln 2}{k} = \frac{0.693}{k}$$

The half-life for gastric emptying of water is about 8–18 minutes.

Gastric emptying of digestible solids is quite different from emptying of liquids: it shows a lag phase of up to an hour in which particle size is continuously reduced. During that time there is little gastric emptying. Following the lag, stomach contents empty with zero-order kinetics, being independent of the volume remaining in the stomach (see [Figure 8.2.4](#)). Consumption of homogenized food in which particle size is less than 0.25 mm abolishes the lag time, suggesting that it is entirely due to inhibition of gastric emptying by large particles that are sensed by mechanoreceptors in the stomach itself. During the processing of a meal, particles that pass into the duodenum are usually less than 0.5 mm.

A variety of stimuli in the duodenum produces reflex inhibition of gastric emptying. These include the following:

- distension of the duodenum;
- irritation of the duodenum;
- acid pH in the duodenum;
- increased osmolarity of the duodenal contents;
- amino acids in the duodenum;
- fat digestion products (e.g., fatty acids, monoglycerides, and diglycerides) in the duodenum.

These factors slow gastric emptying to the rate at which the intestine can process the incoming load of nutrients. The inhibition of gastric emptying by the intestine is called the **enterogastric inhibitory reflex**. This reflex seems to present a constant rate of caloric load to the intestine: fatty substances possess the highest caloric density and inhibit gastric emptying the most.

## NERVES AND GI HORMONES ALTER STOMACH EMPTYING

The vagus nerve is essential to normal gastric emptying because vagotomy causes rapid delivery of liquids regardless of content, probably related to the failure of the stomach to accommodate incoming material. The slowing of gastric emptying by particle size is a function of the stomach alone.

Fat digestion products in the duodenum cause the secretion of **cholecystokinin**, or **CCK**, from the duodenum. CCK is a polypeptide hormone secreted from endocrine I cells scattered throughout the proximal two-thirds of the small intestine. In the blood, CCK has a variety of forms that differ in their number of amino acids. CCK-83 has 83 amino acids, CCK-58 has 58, and so on for CCK-39, CCK-33, and CCK-8. The smaller CCKs are formed by proteolytic cleavage of the larger ones. All of these are active because they all share the same N-terminal sequence of Asp–Tyr–Met–Gly–Trp–Met–Asp–Phe. CCK activates a vagovagal reflex that releases VIP and NO onto the stomach muscle cells, which inhibit the muscle

and thereby slow gastric emptying. Slowing of gastric emptying by CCK makes physiological sense. It takes time to digest and absorb fats. Fat in the duodenum causes CCK release which slows gastric emptying, thereby providing time for the duodenum to process the fats that are delivered to it.

**Glucagon, glucagon-like peptide-1 (GLP-1), peptide YY, and somatostatin** also delay gastric emptying. Enteroendocrine cells in the small intestine secrete GLP-1 and peptide YY in response to luminal nutrients. GLP-1 is the C-amidated 7-36 amino acid peptide derived from proteolysis of proglucagon. GLP-1 is an incretin, meaning that it increases the secretion of insulin by the  $\beta$  cells of the islets of Langerhans in the pancreas, but it also markedly decreases gastric emptying. This has the effect of delaying increases in plasma glucose that typically follows a meal. It is believed that GLP-1 decreases stomach emptying by activating vagal afferents.

Enteroendocrine cells, D-cells, in the stomach secrete **somatostatin** that mainly inhibits gastric, biliary, and pancreatic secretions. It has two forms: SST-14 and SST-28 for the number of amino acids in the polypeptide. Some cells in the CNS also use somatostatin as a neurotransmitter. It decreases gastric emptying, which reduces the acid input into the duodenum. SST also has a variety of other effects, including inhibition of the release of a number of protein hormones.

**Gastrin, ghrelin, and motilin** all increase the rate of gastric emptying. All three are gastrointestinal protein hormones. Gastrin is secreted by G-cells in the pyloric glands in the antrum of the stomach and in the duodenum. It circulates in two forms: Gastrin-17 and Gastrin-34, referring to the number of amino acids in the peptides. The circulating half-life of Gastrin-17 is just 7 minutes, whereas gastrin-34 has a half-life of 30 minutes. Both forms are equally potent in stimulating acid secretion by the parietal cells. Gastrin has structural similarities to CCK and, in fact, exerts its effects through the CCK-2 receptor.

Ghrelin is a 28 amino acid peptide secreted by the oxyntic glands of the stomach. It is made as preproghrelin, which is then cleaved to form ghrelin and **obestatin**. Ghrelin is highly unusual in that it is octanoylated at serine 3 by the enzyme **GOAT (ghrelin O-acyl transferase)**. Ghrelin has a multitude of effects: it stimulates growth hormone release, increases appetite and feeding behavior, increases gastric emptying and gastric and intestinal motility.

M-cells in the duodenum and jejunum secrete motilin, a 22 amino acid peptide that has structural similarities to ghrelin. Motilin is temporally associated with phase III of the interdigestive pattern of motility, the migratory myoelectric complex, and is believed to initiate the MMC in humans.

## THE MIGRATING MOTILITY COMPLEX CLEARS THE STOMACH AND INTESTINE DURING FASTING

The **migrating motility complex (MMC)**, sometimes also called the **migrating motor complex** or **migrating myoelectric complex**, and abbreviated as **MMC**,

describes the pattern of stomach motility during the interdigestive period. This interdigestive motility is quite different from the motility after eating a meal. The MMC consists of three phases that empty the stomach of undigested material. The frequency of MMC varies with the time of day, being slowest in sleep ( $0.25 \text{ h}^{-1}$ ) and more active during the day ( $0.64 \text{ h}^{-1}$ ). After eating, the fed pattern of motility that we have already discussed replaces the MMC. The MMC is not a property of the stomach alone. It describes the interdigestive motility pattern of the whole GI tract. This pattern is said to perform a “housekeeping” function for the GI tract because it cleans it of all materials.

The MMC consists of three phases that together last about 90 minutes. In phase I, the stomach is quiescent for about 50 minutes, some 40–60% of the cycle length. Phase II, lasting another 25–30 minutes, is characterized by increasingly strong but irregular contractions. Phase III lasts only 5–10 minutes, but it includes intense contractions that completely occlude the stomach lumen, sweeping before it all undigested particles that still remain in the stomach.

**Motilin** is a polypeptide 22 amino acids long that is released in pulses every 90 minutes or so during fasting by special M-cells in the duodenum. Spikes of motilin concentration in the blood temporally correlate with the MMC. Myenteric neurons in the stomach possess receptors for motilin, and **atropine** (an antagonist of acetylcholine’s action on muscarinic receptors) blocks motilin’s effects. This suggests that motilin may activate the stomach myenteric plexus which then induces the MMC through cholinergic pathways.

### Clinical Applications: Gastroparesis

Gastroparesis literally means “stomach paralysis.” It refers to a condition of abnormal stomach motility, generally the lack of the normal postprandial motility pattern and delayed gastric emptying. Complete stomach paralysis is fatal in that it is equivalent to a gastrointestinal blockage. Generally gastroparesis results in failure to produce finely divided chyme or failure to propel the food into the small intestine properly.

The cause of gastroparesis often cannot be identified, and is called **idiopathic**, meaning having no identified cause. Common causes are diabetes, infections, hypothyroidism, scleroderma, autoimmune diseases, psychological disorders, radiation treatment in the area, and surgery to the area. Surgery or other damage to the vagus nerve interferes with stomach emptying, and the effect can occur either immediately or years after the surgery. Intestinal blockage can mimic the symptoms of gastroparesis.

Symptoms of gastroparesis included bloating, eructation (burping or belching) early satiety, heartburn, and epigastric pain. Symptoms can depend on the type of food consumed: solid foods, foods high in fat, and carbonated drinks can all trigger symptoms. Nausea and vomiting are also common. Vomiting can occur hours after eating the last meal. Diagnosis can be accomplished by endoscopy (visual

(Continued)

### Clinical Applications: Gastroparesis (Continued)

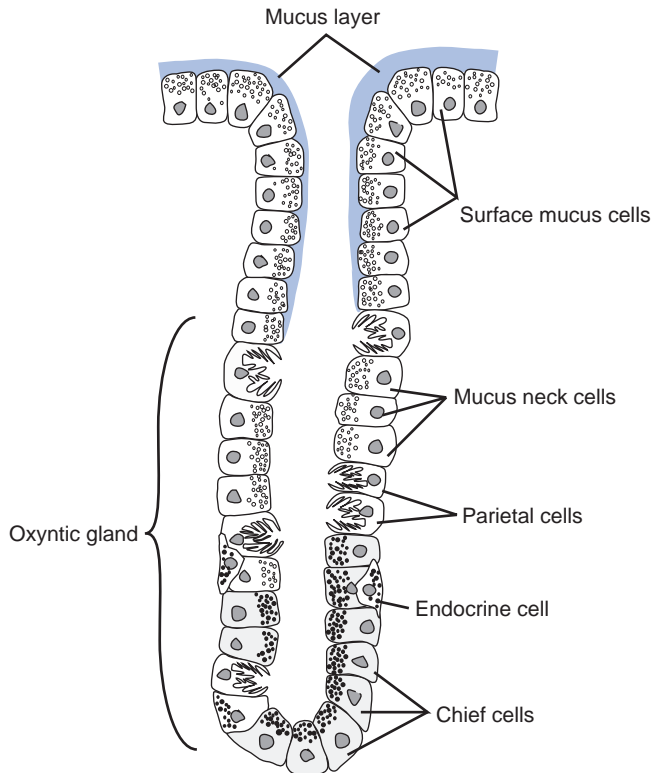
inspection of the stomach and intestine via an inserted tube), gastric manometry, scintigraphic analysis of gastric emptying and gastric accommodation (using  $Tc^{99m}$ ), x-rays and undigestible wireless capsule monitoring using the Smartpill that records pH, temperature and pressure along the GI tract.

There is no cure for gastroparesis. The main approach is to alter the diet to reduce the necessity of the stomach to grind the food. Fatty foods and fibrous foods take longer to empty and should be avoided. Fibrous foods can be cooked longer to soften them. Poorly digested food can collect into a mass called a **bezoar** that can form a blockage, causing nausea and pain. Breaking up bezoars may require endoscopic tools. Even with significant impairment of gastric emptying, thick and thin liquids such as puddings and smoothies can be tolerated well. Severe gastroparesis may require insertion of a feeding tube past the stomach into the jejunum.

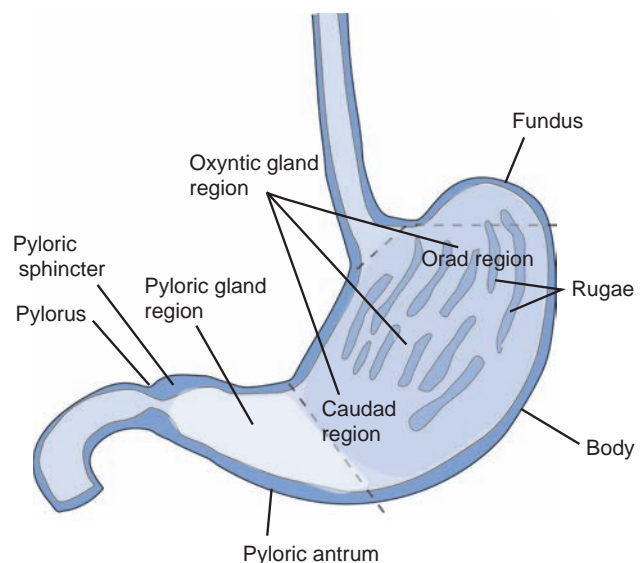
Additional treatments include attempts to normalize motility either medically or electrically. Erythromycin, for example, stimulates motilin receptors and can increase gastric emptying, but often patients develop a tolerance to the drug. Emerging treatment options include gastric pacing or gastric electrical stimulation (GES). Gastric pacing uses a set of pacing wires attached to the stomach and an external power source that delivers high energy excitation at a frequency of about 3 per minute. GES uses an implantable device to deliver low energy stimulation at a frequency of about 12 per minute. Newer designs envision series of electrodes that could provide sequential stimulation of the muscle so as to produce propulsive contractions. These GES devices remain experimental.

## THE STOMACH SECRETES HCl, PEPSINOGEN, MUCUS, GASTRIC LIPASE, AND INTRINSIC FACTOR

The lining of the stomach at rest is thrown into thick, velvety folds called **rugae**. These contain microscopic invaginations, called **gastric pits**, that each open into four or five gastric glands. Gastric glands come in two varieties. The **oxyntic glands** (see Figure 8.2.5) in the orad stomach make up 75% of the total number of glands. The remaining 25% are **pyloric glands** in the antrum and pylorus (see Figure 8.2.6). Specialized **parietal cells** secrete HCl and **intrinsic factor**. The HCl activates the proteolytic enzyme, **pepsinogen**, to form **pepsin**, and sets the acid environment for peptic proteolysis of dietary protein. The acid environment is also bacteriostatic but not bacteriocidal—the stomach has a thriving microbiota, but the acid prevents its overgrowth. Intrinsic factor is a 45-kDa glycoprotein that binds **vitamin B<sub>12</sub>** (**cobalamin**). Intrinsic factor is necessary for absorption of vitamin B<sub>12</sub> in the terminal ileum by receptor-mediated endocytosis. **Intrinsic factor is the only essential secretion of the stomach**, and human life is not sustainable without it. Persons with total gastrectomies (removal of the stomach) must inject themselves with vitamin B<sub>12</sub>.



**FIGURE 8.2.5** Structure of the oxyntic gland. Gastric pits open into a channel leading into a cluster of oxyntic glands, one of which is shown here. The surface mucus cells secrete mucus to line the stomach and protect it from its acid environment. The mucus contains mucin and  $HCO_3^-$  to neutralize stomach acid. The acid is secreted by parietal cells, whose appearance changes drastically from the quiescent to the stimulated states. These cells also secrete intrinsic factor, which is necessary for the absorption of vitamin B<sub>12</sub> in the terminal ileum. Mucus is also secreted by cells in the neck of the gland. Pepsinogen is a heterogeneous mixture of isozymes that are secreted by the chief cells. Endocrine cells of various types lie interspersed among the secretory cells.



**FIGURE 8.2.6** Location of the pyloric glands and oxyntic glands in the stomach. The oxyntic glands, comprising 75% of the gastric glands, secrete HCl, intrinsic factor, mucus, and pepsinogen. The pyloric glands cover the gastric antrum and pylorus and contain G-cells that secrete **gastrin** into the circulation. The **rugae** are folds in the stomach lining.

Surface epithelial cells, specialized mucus cells of the neck, and mucus cells in the glands also secrete mucin, a high molecular weight glycoprotein. The mucin monomers are cross-linked by disulfide bonds to form a hydrated gel that lines the stomach. It protects the epithelium from the corrosive effects of the acid and from the physical abrasion of stomach contents, and it lubricates stomach contents. The mucus gel traps  $\text{HCO}_3^-$  that neutralizes stomach acid, so there is a gradient in pH from acidic in the lumen to near neutral pH adjacent to the cells that are covered with mucus.

**Chief cells** synthesize **pepsinogen** as a 43-kDa inactive precursor and package it into granules that are stored in the apex of the cells. Stimulation of the cells in response to food in the stomach causes exocytosis of the granule. Contact of pepsinogen with acid converts it to its active form, **pepsin**, with a molecular weight of 35 kDa. Pepsinogen actually consists of seven different isozymes. Although pepsin is a potent protease, it is unnecessary for the complete digestion of dietary protein because pancreatic enzymes can handle the job in the absence of pepsin.

## ACID SECRETION IS REGULATED IN FOUR PHASES: THE BASAL PHASE, CEPHALIC PHASE, GASTRIC PHASE, AND INTESTINAL PHASE

### THE CEPHALIC PHASE IS MEDIATED BY THE VAGUS NERVE THROUGH ACETYLCHOLINE AND GASTRIN

The cephalic phase of gastric secretion is mediated entirely through the vagus nerve. A variety of sensory stimuli including the sight, smell, and taste of food elicits acid secretion in the stomach. It contributes about 30–50% to the total postprandial acid production. The vagus nerve is the sole neural link between the brain's higher functions and gastric secretion. It exerts its effects through two separate pathways: direct stimulation by acetylcholine and indirect through gastrin.

Parietal cells possess M3 cholinergic receptors that turn on acid secretion. Stimulation of the vagus excites postganglionic parasympathetic neurons in the stomach, which then release acetylcholine onto parietal cells to stimulate acid secretion.

Cephalic efferents in the vagus nerve release gastrin-releasing peptide (GRP) onto **G-cells** in the pyloric glands and these release **gastrin**. Atropine, a muscarinic cholinergic antagonist, blocks the direct effects of vagal stimulation on parietal cells, but it does not block the release of gastrin. [Figure 8.2.7](#) illustrates the cephalic phase of gastric acid secretion.

Gastrin is a polypeptide hormone secreted by G-cells in pyloric glands in the antrum of the stomach and in the duodenum. It circulates in two forms: Gastrin-17 and Gastrin-34, referring to the number of amino acids in their sequences. The circulating half-life of Gastrin-17 is just 7 minutes, whereas Gastrin-34 has a half-life of 30 minutes. Both forms are equally potent in stimulating

acid secretion by the parietal cells. Gastrin has structural similarities to CCK and, in fact, exerts its effects through the CCK-2 receptor.

Gastrin released from the G-cells during the cephalic phase stimulates parietal cells directly and indirectly through **histamine** released from enterochromaffin-like cells (ECL cells) in the lamina propria nearby the parietal cells. Thus histamine is a **paracrine** hormone that affects nearby cells rather than traveling through the blood. Mast cells in the stomach also release histamine, but they are not closely apposed to the parietal cells. The histamine diffuses through the extracellular fluid to the parietal cells where it binds to  $\text{H}_2$  receptors. These receptors are blocked by **cimetidine**.

## STRETCH RECEPTORS AND CHEMORECEPTORS IN THE STOMACH REGULATE $\text{H}^+$ SECRETION IN THE GASTRIC PHASE

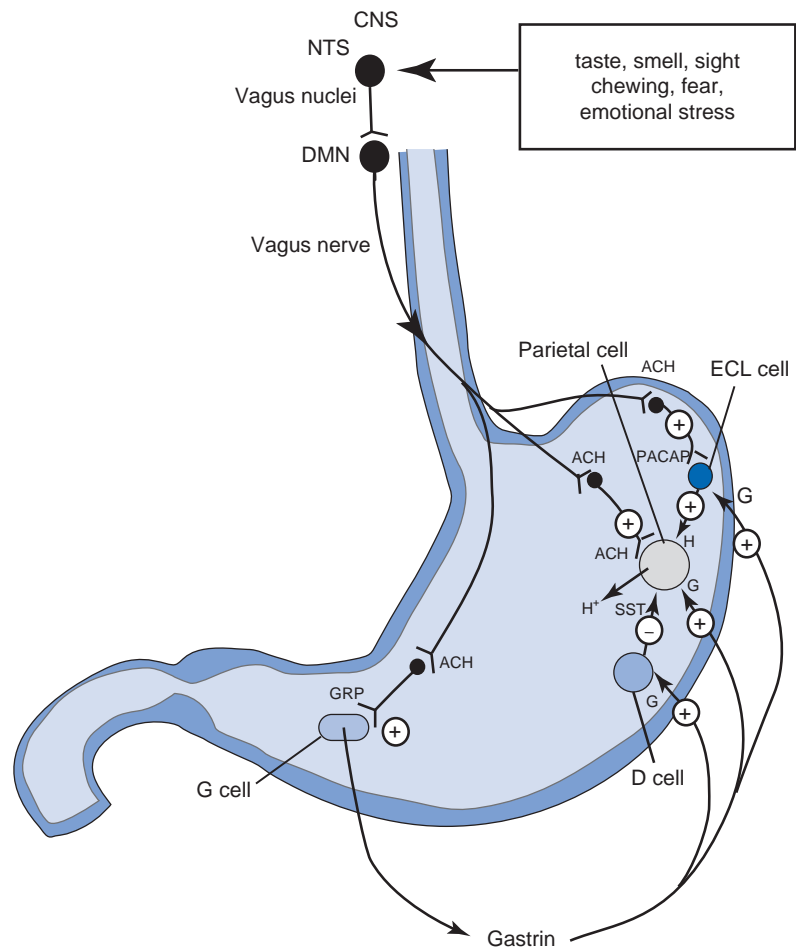
The gastric phase accounts for about 60% of the secretory response to a meal. Stretch receptors in the walls of the stomach increase their firing rate upon distension of the stomach following a meal. Afferent stretch receptor sensory information travels along the vagus nerve to the CNS where efferent vagal connections begin. These complete a **long reflex arc** that increases parietal cell HCl secretion. This effect of stretching the fundus and body of the stomach is nearly abolished by proximal vagotomy. Stretch of the antrum also elicits a long vagovagal reflex that stimulates parietal cell acid secretion. Stretch of the antrum, in addition, releases gastrin that stimulates acid secretion (see [Figure 8.2.8](#)).

Antral pH below 3.0 inhibits gastrin release evoked by antral distension, by nutrients in the stomach, or by cephalic stimulation. This forms a negative feedback loop: gastrin stimulates acid secretion which in turn shuts off gastrin secretion. The effect is mediated by acid stimulation of D-cells, enteroendocrine cells that secrete **somatostatin**, which mainly inhibits gastric, biliary, and pancreatic secretion. It has two forms: SST-14 and SST-28 for the number of amino acids in the polypeptide.

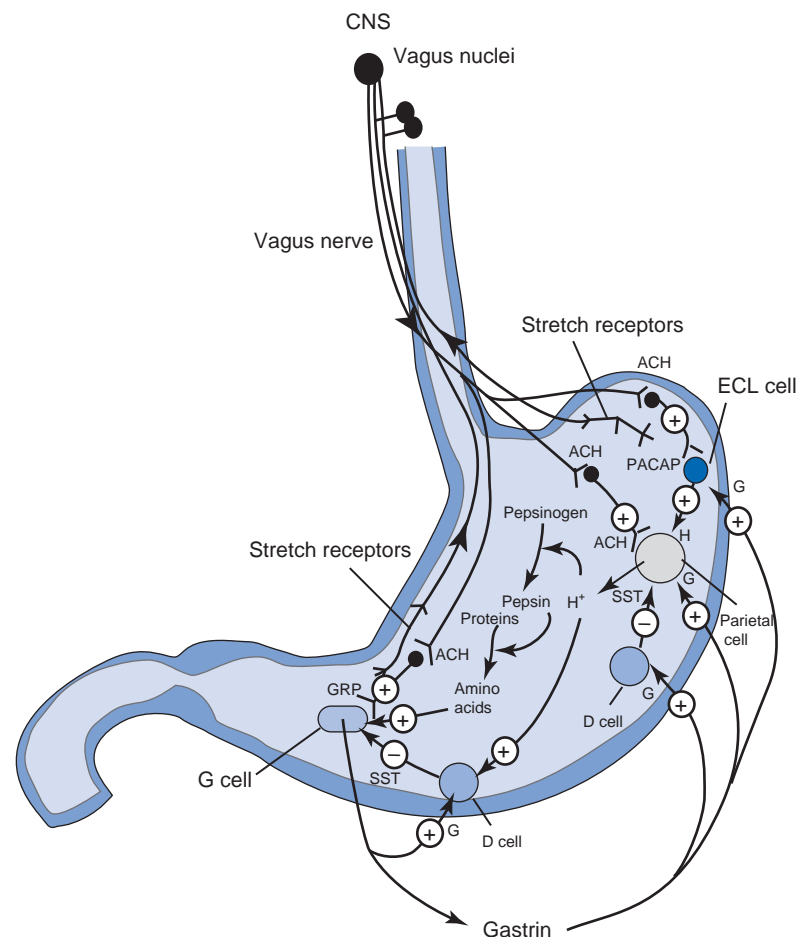
Amino acids produced by the digestion of dietary protein potently stimulate acid secretion by increasing gastrin release. Intact proteins are poor secretagogues, whereas proteolytic digests of these proteins are effective. Phenylalanine and tryptophan have the greatest ability to release gastrin. This effect is blocked by stomach pH below 3.0, but it is not blocked by atropine or vagotomy, suggesting that the amino acids directly affect the G-cells.

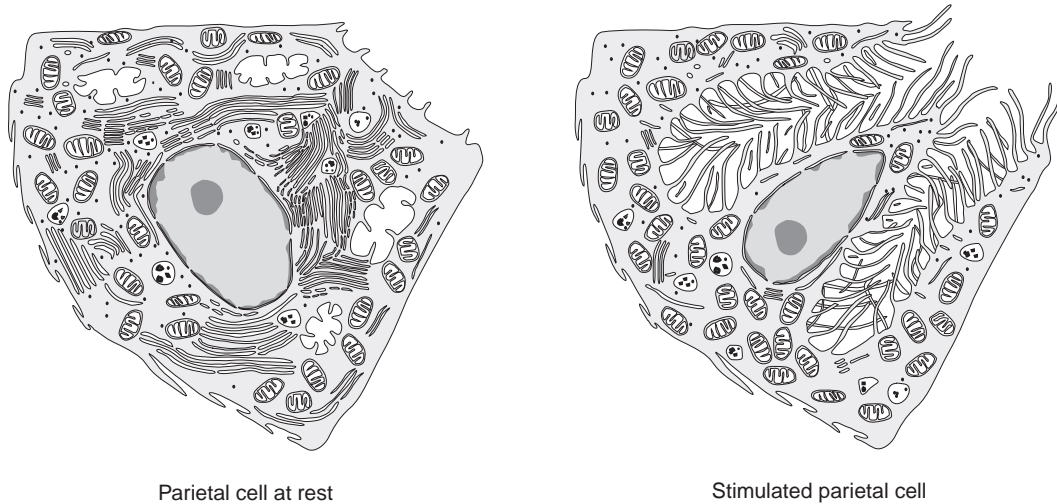
**Caffeine**, **alcohol**, and **calcium** also stimulate gastric acid secretion. Pure ethanol only modestly stimulates acid secretion, whereas red wine and beer potently increase gastrin release and acid secretion. This suggests that amines or amino acids in these drinks are the actual secretagogues and that the effect is mediated by gastrin. Caffeine stimulates acid secretion, but so does decaffeinated coffee. Oral calcium also stimulates gastrin release and acid secretion. The effect is independent of its buffering action and is probably due to direct effects of the  $\text{Ca}^{2+}$  ion.

**FIGURE 8.2.7** The cephalic phase of gastric acid secretion. Sensory stimuli such as the sight, smell, and taste of food produce efferent activity from the brain (the nucleus tractus solitarius and dorsal motor nucleus of the vagus) to stimulate parietal cells to secrete acid. The mediator in this pathway is acetylcholine (ACh), which exerts its effects on the parietal cells through a muscarinic (M3) cholinergic receptor. In a second pathway, vagal stimulation releases gastrin from G-cells in the antrum, which then stimulates acid secretion. Gastrin stimulation of the parietal cells is both direct and indirect. In the direct pathway, parietal cells respond to gastrin through gastrin receptors on their membranes. In the indirect pathway, gastrin stimulates histamine (H) release from **enterochromaffin-like (ECL) cells**. Vagal stimulation also relieves inhibition of acid secretion by **somatostatin, SST**, secreted by D-cells in the body and antrum. Parietal cells thus have receptors for acetylcholine (ACh), gastrin (G), histamine (H), and somatostatin (SST).

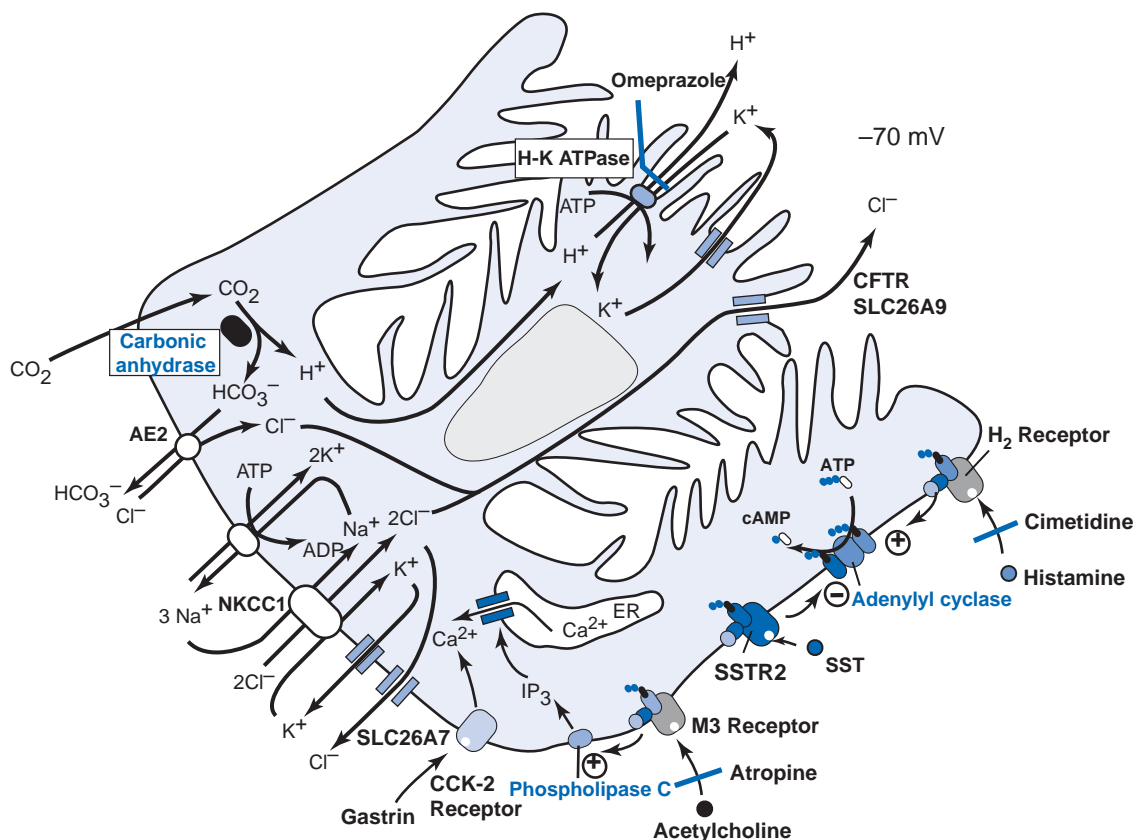


**FIGURE 8.2.8** The gastric phase of acid secretion. Acid secretion by the parietal cell is stimulated by acetylcholine, gastrin (G), and histamine (H). Acetylcholine (ACh) is released by vagal efferents in response to stretch receptors located in the fundus. These exert their effects over a vagovagal reflex. Enterochromaffin-like cells (ECL) release histamine in response to gastrin levels, and gastrin directly stimulates parietal cell acid secretion. Gastrin is secreted by G-cells in the antrum. Gastrin release is stimulated by stretch of the antrum, mediated by a long vagovagal reflex. Amino acids in the stomach lumen also stimulate gastrin release. Gastrin release is feedback inhibited by acid through stimulation of D-cells that secrete somatostatin (SST). Somatostatin release is stimulated by stomach acid and by gastrin, which forms a short negative feedback loop.





**FIGURE 8.2.9** Resting and stimulated parietal cells. The resting cell contains a large number of tubulovesicles that contain the  $\text{H}^+, \text{K}^+$ -ATPase pump protein. When the cell is stimulated, the tubulovesicles fuse with the plasma membrane, forming a plasma membrane with a well-developed system of microvilli from which the cell secretes HCl.



**FIGURE 8.2.10** The mechanism of HCl secretion by parietal cells. M3 receptors bind acetylcholine that is released from vagus efferent nerves. These M3 receptors are coupled to a  $G_q$  protein whose  $\alpha$  subunit activates phospholipase C that releases IP3 from phosphatidylinositol bisphosphate. The IP3 releases  $\text{Ca}^{2+}$  from intracellular stores. This effect of acetylcholine is blocked by **atropine**.  $\text{H}_2$  receptors bind histamine released by ECL (enterochromaffin-like cells) near the parietal cell in response to circulating gastrin. These  $\text{H}_2$  receptors are blocked by **cimetidine**. Histamine binding to  $\text{H}_2$  receptors activates adenyl cyclase and formation of cAMP and activation of protein kinase A, PKA. The signaling mechanism of gastrin is not established, but it appears to involve CCK-2 receptors that increase cytosolic  $\text{Ca}^{2+}$  but by a mechanism distinct from acetylcholine. SST binds to a receptor that activates a  $G_i$  mechanism. Activation of these pathways results in a variety of effects, including fusion of tubulovesicles in the cytosol to the apical membrane, which results in insertion of the  $\text{H}^+, \text{K}^+$ -ATPase,  $\text{K}^+$  channel, and  $\text{Cl}^-$  channel into the apical cell membrane. All three of these proteins are required for HCl secretion. Inhibition of the  $\text{H}^+, \text{K}^+$ -ATPase by proton pump inhibitors, such as **omeprazole**, inhibits acid secretion. The basolateral membrane contains a  $\text{HCO}_3^- - \text{Cl}^-$  exchanger (anion exchanger 2 (AE2) = SLC4A2) that helps supply  $\text{Cl}^-$  for apical secretion. The  $\text{HCO}_3^-$  that is exchanged for  $\text{Cl}^-$  is produced by the hydration of  $\text{CO}_2$  catalyzed by **carbonic anhydrase**. The basolateral membrane also contains the  $\text{Na}^+, \text{K}^+$ -ATPase, which transports three  $\text{Na}^+$  out of the cell and two  $\text{K}^+$  ions into the cell for each ATP that is hydrolyzed. A  $\text{Na}^+ - \text{H}^+$  exchanger is also present on the basolateral membrane. Secretion of acid into the stomach is thus accompanied by secretion of base  $\text{HCO}_3^-$  into the blood. The parietal cell acidifies the stomach contents while it alkalinizes the blood.

### Clinical Applications: Peptic Ulcers

Gastric and duodenal ulcers form when the protective linings of the stomach or duodenum are destroyed by acid and pepsin, causing **peptic ulcers**. These are an erosion of the lining of the stomach that can penetrate to the blood vessels, causing a bleeding ulcer. They can penetrate all the way through the wall, causing a perforated ulcer in which stomach contents leak into the peritoneal cavity.

Normally, peptic ulcers are prevented by the combination of the protective layer of mucus, secretion of acid-neutralizing  $\text{HCO}_3^-$  into the mucus, and replacement of epithelial cells by new cells produced from stem cells within the epithelium. Ulcers form when these protective measures fail, either because of overproduction of acid or weakened protective barriers. It was once believed that excess acid production was the primary cause of peptic ulcers. Now it is accepted that a bacterium, *Helicobacter pylori*, weakens the protective barrier and so contributes to the etiology of peptic ulcers. Some of the remaining cases are due to **NSAIDs**: nonsteroidal anti-inflammatory drugs such as aspirin and a host of artificial drugs such as ibuprofen, indomethacin, and naproxen. These drugs inhibit an enzyme called COX-2 or

**cyclooxygenase**. As a side effect, these NSAIDs reduce  $\text{HCO}_3^-$  secretion by the stomach mucosa.

*H. pylori* was first associated with gastritis (an inflammation of the stomach) in 1983 by Warren and Marshall. These bacteria are curved, gram-negative bacteria about  $0.5\ \mu\text{m} \times 3\ \mu\text{m}$ , with four to seven sheathed flagella at one pole of the cell. These bacteria survive in the inhospitable stomach environment because they possess large amounts of **urease**. This enzyme produces  $\text{NH}_4^+$  from urea, and the ammonium neutralizes the acid in the local environment of the bacterium. Warren and Marshall earned the 2005 Nobel Prize in Physiology or Medicine.

About 80% of persons with duodenal ulcers test positive for *H. pylori*, and cure of their infection cures the ulcer. How the bacterium causes ulcers is not established. However, at least some people develop ulcers without *H. pylori*'s help. Initially the scientific community was incredulous at the prospect that peptic ulcers could be an infectious disease. The pendulum has swung to near universal acceptance of the central importance of *H. pylori*, and now the pendulum is swinging again to a more qualified view of its importance.

### NUTRIENTS IN THE INTESTINE AFFECT STOMACH ACID SECRETION

In 1929, Feng and coworkers observed that infusion of fat into the duodenum inhibited gastric acid secretion by releasing an inhibitory hormone from the small intestinal mucosa. They named this hormone enterogastrone. It is likely that enterogastrone is not one hormone but a family of them, all of which feed back onto the stomach to limit its acid secretion. Candidate hormones include CCK, secretin, somatostatin, and neurotensin. Release of these materials and their control of gastric acid secretion constitute the **intestinal phase** of gastric secretion.

### THE SURFACE MEMBRANE $\text{H}^+, \text{K}^+$ -ATPASE, OR PROTON PUMP, ACTIVELY SECRETES HCL

At rest, parietal cells contain a number of small intracellular **canaliculi** (small canals) and a number of **tubulovesicles**. These are intracellular, membrane-bound structures that appear as long tubes within the cytoplasm. These tubulovesicles contain the  $\text{H}^+, \text{K}^+$ -ATPase pump. Stimulation of the parietal cell causes fusion of the tubulovesicles with the apical cell membrane. Upon its translocation to the apical membrane, the  $\text{H}^+, \text{K}^+$ -ATPase pump begins pumping  $\text{H}^+$  ions into the lumen in exchange for  $\text{K}^+$  ions. The changes in parietal cell structure upon stimulation of acid secretion are illustrated in Figure 8.2.9. How parietal cells secrete an acidic solution while maintaining a neutral cytosolic pH is not known. The scheme shown in Figure 8.2.10 is a reasonable hypothesis that incorporates the known ion transport mechanisms in the parietal cells.

### SUMMARY

The main function of the stomach is to store food and to release it to the intestines at a rate whereby the intestines can process it. The stomach mixes the food and grinds it into a finely divided chyme that increases the surface area of the food in preparation for digestion. The stomach also secretes mucin, water, HCl, pepsinogen, and intrinsic factor. Pepsinogen begins protein digestion and intrinsic factor is necessary for the absorption of vitamin  $\text{B}_{12}$  (cobalamin) in the terminal ileum.

The lower esophageal sphincter marks the beginning of the stomach, and the pyloric sphincter marks its caudal end. The stomach consists of the fundus, the body, and the antrum. The stomach expands to accommodate a meal. Receptive relaxation refers to the relaxation of the stomach in response to swallowing, and it is part of the swallowing program. Stretch receptors in the stomach also relax it through a vagovagal reflex. Stomach motility is controlled locally through the myenteric plexus, which is influenced by vagal inputs from the parasympathetic nervous system and by sympathetic inputs from the celiac ganglion. ICCs in the greater curvature have the highest intrinsic frequency of slow waves, which are rhythmic membrane potential depolarizations, and therefore these cells are pacemakers for the stomach. These cells set the frequency of stomach motility. The stomach grinds the food to produce a finely dispersed mixture of food and secretions.

Sensors in the stomach and in the duodenum regulate stomach emptying. Large particles excite mechanosensors in the stomach that delay stomach emptying. Distension, irritation, acid, increased osmolarity, amino acids, and fat digestion products in the duodenum all

inhibit gastric emptying. All of these regulate the rate of stomach emptying to be commensurate with intestinal processing. This is the enterogastric inhibitory reflex. It is caused by the vagus nerve and by a variety of GI hormones including CCK and secretin.

During fasting, motility shifts to the MMC (migrating motility complex, migrating myoelectric complex, migrating motor complex), which lasts about 90 minutes. It includes a phase of strong propulsive contractions that moves all luminal contents forward, clearing the gut. Increase in motilin, a 22 amino acid hormone produced in the duodenum, is temporally associated with the MMC.

Gastric glands in the stomach secrete mucin, acid, intrinsic factor, and pepsinogen. The parietal cells secrete acid and intrinsic factor. Chief cells secrete pepsinogen that is activated to pepsin by stomach acid.

Acid secretion requires an apical proton pump ( $H^+$ ,  $K^+$ -ATPase),  $K^+$  channel, and  $Cl^-$  channel. In the unstimulated state, the proton pump resides in tubulovesicles beneath the apical membrane of the parietal cells. Upon stimulation, the tubulovesicles fuse with the apical membrane and the proton pump begins pumping  $H^+$  ions into the lumen. The parietal cell has receptors for gastrin, acetylcholine, histamine, and somatostatin. Acid secretion has cephalic, gastric, and intestinal phases. The cephalic phase is initiated by sensations associated with food intake: smell, sight, and taste, or even thinking about food. These stimulate acid secretion directly through the vagus nerve and release of acetylcholine, and indirectly through the vagus nerve by increasing gastrin secretion by G-cells in the antrum.

Vagal stimulation also causes histamine release from ECL cells in the vicinity of the parietal cells. Gastrin also activates the ECL cells. Somatostatin, SST, is released by D-cells and inhibits acid secretion. Stretch, acid, and protein digestion products regulate acid secretion in the gastric phase. Stretch of the antrum increases gastrin release through a long vagovagal reflex, and gastrin then stimulates acid secretion. Amino acids stimulate gastrin release. High stomach acidity activates D-cells in the antrum that release SST to inhibit gastrin release to stop acid secretion.

## REVIEW QUESTIONS

1. What is gastric accommodation and how does it differ from receptive relaxation? What causes each?
2. Why do gastric contractions occur in two waves, one stronger than the other?
3. How does gastric motility differ after a meal and during the interdigestive period?
4. What is the enterogastric inhibitory reflex? What is its purpose?
5. What stimulates acid secretion? What inhibits it?
6. The Zollinger–Ellison syndrome often results from a carcinoma of the duodenum or pancreas that produces gastrin. What do you expect happens to the stomach in these cases?
7. What is the only essential secretion of the stomach?
8. What cells secrete HCl? What cells secrete pepsinogen? What cells secrete gastrin?