The stomach plays several important roles in human nutrition and has secretory, motor, and humoral functions. These activities are not separate and distinct, but rather represent integrated functions that are required to initiate the normal digestive process.

The stomach has several specific secretory products. In addition to the stomach's best-known product—acid—these products include pepsinogen, mucus, bicarbonate, intrinsic factor, and water. These substances continue the food digestion that was initiated by mastication and the action of salivary enzymes in the mouth. In addition, they help protect the stomach from injury. The stomach also has several important motor functions that regulate the intake of food, its mixing with gastric secretions and reduction in particle size, and the exit of partially digested material into the duodenum. Moreover, the stomach produces two important humoral agents—gastrin and somatostatin—that have both endocrine and paracrine actions. These peptides are primarily important in the regulation of gastric secretion.

Although these functions are important in the maintenance of good health, the stomach is nevertheless not required for survival. Individuals who have had their entire stomach removed (i.e., total gastrectomy) for non-neoplastic reasons can maintain adequate nutrition and achieve excellent longevity.

**FUNCTIONAL ANATOMY OF THE STOMACH**

The basic structure of the stomach wall is similar to that of other regions of the gastrointestinal (GI) tract (see Fig. 40-2); therefore, the wall of the stomach consists of both mucosal and muscle layers. The stomach can be divided, based on its gross anatomy, into three major segments (Fig. 41-1): (1) A specialized portion of the stomach called the cardia is located just distal to the gastroesophageal junction and is devoid of the acid-secreting parietal cells. (2) The body or corpus is the largest portion of the stomach; its most proximal region is called the fundus. (3) The distal portion of the stomach is called the antrum. The surface area of the gastric mucosa is substantially increased by the presence of gastric glands, which consist of a pit, a neck, and a base. These glands contain several cell types, including mucous, parietal, chief, and endocrine cells; endocrine cells are
found only in the antrum. The surface epithelial cells, which have their own distinct structure and function, secrete \( \text{HCO}_3^- \) and mucus.

Marked cellular heterogeneity exists not only within segments (e.g., glands versus surface epithelial cells) but also between segments of the stomach. For instance, as discussed later, the structure and function of the mucosal epithelial cells in the antrum and body are quite distinct. Similarly, although the smooth muscle in the proximal and distal portions of the stomach appear structurally similar, their functions and pharmacologic properties differ substantially.

**With Increasing Rates of Secretion of Gastric Juice, the \( \text{H}^+ \) Concentration Rises and the \( \text{Na}^+ \) Concentration Falls**

The glands of the stomach typically secrete approximately 2 liters/day of a fluid that is approximately isotonic with blood plasma. As a consequence of the heterogeneity of gastric mucosal function, early investigators recognized that gastric secretion consists of two distinct components: parietal- and nonparietal-cell secretion. According to this hypothesis, gastric secretion consists of (1) an \( \text{Na}^+ \)-rich basal secretion that originates from nonparietal cells, and (2) a stimulated component that represents a pure parietal-cell secretion that is rich in \( \text{H}^+ \). This model helps explain the inverse relationship between the luminal concentrations of \( \text{H}^+ \) and \( \text{Na}^+ \) as a function of the rate of gastric secretion (Fig. 41-2). Thus, at high rates of gastric secretion—for example, when gastrin or histamine stimulates parietal cells—intraluminal [\( \text{H}^+ \)] is high whereas intraluminal [\( \text{Na}^+ \)] is relatively low. At low rates of secretion or in clinical situations in which maximal acid secretion is reduced (e.g., pernicious anemia, see box on p. 971), intraluminal [\( \text{H}^+ \)] is low but intraluminal [\( \text{Na}^+ \)] is high.
The Proximal Portion of the Stomach Secretes Acid, Pepsinogens, Intrinsic Factor, Bicarbonate, and Mucus, Whereas the Distal Part Releases Gastrin and Somatostatin

**CORPUS.** The primary secretory products of the proximal part of the stomach—acid (protons), pepsinogens, and intrinsic factor—are made by distinct cells from glands in the corpus of the stomach. The two primary cell types in the gastric glands of the body of the stomach are parietal cells and chief cells.

Parietal cells (or oxyntic cells) secrete both acid and intrinsic factor, a glycoprotein that is required for cobalamin (vitamin B₁₂) absorption in the ileum (p. 970). The parietal cell has a very distinctive morphology (see Fig. 41-1). It is a large triangular cell with a centrally located nucleus, an abundance of mitochondria, intracellular tubulovesicular membranes, and canalicular structures. We discuss H⁺ secretion in the next subchapter and intrinsic factor in Chapter 44.

Chief cells (or peptic cells) secrete pepsinogens, but not acid. These epithelial cells are substantially smaller than parietal cells. A close relationship exists among pH, pepsin secretion, and function. Pepsinogens are endopeptidases (i.e., they hydrolyze “interior” peptide bonds) and initiate protein digestion by hydrolyzing specific peptide linkages. The basal luminal pH of the stomach is 4 to 6; with stimulation, the pH of gastric secretions is usually reduced to less than 2. At pH values that are less than 3, pepsinogens are rapidly activated to pepsins. A low gastric pH also helps prevent bacterial colonization of the small intestine.

In addition to parietal and chief cells, glands from the corpus of the stomach also contain mucus-secreting cells, which are confined to the neck of the gland (see Fig. 41-1), and five or six endocrine cells. Among the latter are enterochromaffin-like (ECL) cells, which release histamine.

**ANTRUM.** The glands in the antrum of the stomach do not contain parietal cells. Therefore, the antrum does not secrete either acid or intrinsic factor. Glands in the antral mucosa contain chief cells and endocrine cells; the endocrine cells include the so-called G cells and D cells, which secrete gastrin and somatostatin, respectively (see Table 40-1). These two peptide hormones function as both endocrine and paracrine regulators of acid secretion. As discussed in more detail later, gastrin stimulates gastric-acid secretion by two mechanisms and is also a major trophic or growth factor for GI epithelial-cell proliferation. As discussed more fully later, somatostatin also has several important regulatory functions, but its primary role in gastric physiology is to inhibit both gastrin release and parietal-cell acid secretion.

In addition to the cells of the gastric glands, the stomach also contains superficial epithelial cells that cover the gastric pits, as well as the surface in between the pits. These cells secrete HCO₃⁻.

The Stomach Accommodates Food, Mixes It with Gastric Secretions, Grinds It, and Empties the Chyme into the Duodenum

In addition to its secretory properties, the stomach also has multiple motor functions. These functions are the result of gastric smooth-muscle activity, which is integrated by both neural and hormonal signals. Gastric motor functions include both propulsive and retrograde movement of food and liquid, as well as a nonpropulsive movement that increases intragastric pressure.

Similar to the heterogeneity of gastric epithelial cells, considerable diversity is seen in both the regulation and contractility of gastric smooth muscle. The stomach has at least two distinct areas of motor activity; the proximal and distal portions of the stomach behave as separate, but coordinated, entities. At least four events can be identified in the overall process of gastric filling and emptying: (1) receiving and providing temporary storage of dietary food

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**GASTRIC pH AND PNEUMONIA**

Many patients hospitalized in the intensive care unit (ICU) receive prophylactic antiulcer treatment (e.g., histamine-2 receptor antagonists, such as cimetidine) that either neutralize existing acid or block its secretion and thereby raise gastric pH. Patients in the ICU who are mechanically ventilated or have coagulopathies are highly susceptible to hemorrhage from gastric stress ulcers, a complication that can contribute significantly to overall morbidity and mortality. These different antiulcer regimens do effectively lessen the risk of developing stress ulcers. However, by raising gastric pH, these agents also lower the barrier to gram-negative bacterial colonization of the stomach. Esophageal reflux and subsequent aspiration of these organisms are common in these very sick patients, many of whom are already immunocompromised or even mechanically compromised by the presence of a ventilator tube. If these bacteria are aspirated into the airway, pneumonia can result. The higher the gastric pH, the greater the risk of pneumonia.
and liquids; (2) mixing of food and water with gastric secretory products, including pepsin and acid; (3) grinding of food so that particle size is reduced to enhance digestion and permit passage through the pylorus; and (4) regulating the exit of retained material from the stomach into the duodenum (i.e., gastric emptying of "chyme") in response to various stimuli.

The mechanisms by which the stomach receives and empties liquids and solids are significantly different. Emptying of liquids is primarily a function of the smooth muscle of the proximal part of the stomach, whereas emptying of solids is regulated by antral smooth muscle.

ACID SECRETION

The Parietal Cell Has a Specialized Tubulovesicular Structure That Increases Apical Membrane Area When the Cell Is Stimulated to Secret Acid

In the basal state, the rate of acid secretion is low. Tubulovesicular membranes are present in the apical portion of the resting, nonstimulated parietal cell and contain the H-K pump (or H,K-adenosinetriphosphatase [ATPase]) that is responsible for acid secretion. Upon stimulation, cytoskeletal rearrangement causes the tubulovesicular membranes that contain the H-K pump to fuse into the canalicular membrane (Fig. 41–3). The result is a substantial increase (50- to 100-fold) in the surface area of the apical membrane of the parietal cell, as well as the appearance of microvilli. This fusion is accompanied by insertion of the H-K pumps, as well as K+ and Cl- channels, into the canalicular membrane. The large number of mitochondria in the parietal cell is consistent with the high rate of glucose oxidation and O2 consumption that is needed to support acid secretion.

An H-K Pump Is Responsible for Gastric Acid Secretion by Parietal Cells

The parietal cell H-K pump is a member of the gene family of P-type ATPases (p. 63) that includes the ubiquitous Na-K pump (Na,K-ATPase), which is present at the basolateral membrane of virtually all mammalian epithelial cells and at the plasma membrane of nonpolarized cells. Similar to other members of this ATPase family, the parietal cell H-K pump requires both an α subunit and a β subunit for full activity. The catalytic function of the H-K pump resides in the α subunit; however, the β subunit is required for targeting to the apical membrane. The two subunits form a heterodimer with close interaction at the extracellular domain.

The activity of these P-type ATPases, including the gastric H-K pump, is affected by inhibitors that are clinically important in the control of gastric acid secretion. The two types of gastric H-K pump inhibitors are (1) substituted benzimidazoles (e.g., omeprazole), which act by binding covalently to cysteines on the extracytoplasmic surface, and (2) substances that act as competitive inhibitors of the K+ binding site (e.g., the experimental drug Schering 28080). Omeprazole (see the box titled Gastrinoma or Zollinger-Ellison Syndrome) is a potent inhibitor of parietal-cell H-K pump activity and is an extremely effective drug in the control of gastric-acid secretion in both normal subjects and patients with hypersecretory states. In addition, H-K pump inhibitors have been useful in furthering understanding of the function of these pumps. Thus, ouabain, a potent inhibitor of the Na-K pump, does not inhibit the gastric H-K pump, whereas omeprazole does not inhibit the Na-K pump. The colonic H-K pump, whose α subunit has an amino-acid sequence that is similar to that of both the Na-K pump and the parietal-cell H-K pump, is partially inhibited by ouabain but not by omeprazole.

According to the model presented in Figure 41–4, the
key step in gastric-acid secretion is extrusion of H+ into the lumen of the gastric gland in exchange for K+. The K+ taken up into the parietal cells is recycled to the lumen through K+ channels. The final component of the process is passive movement of Cl− into the gland lumen. The apical membrane H-K pump energizes the entire process, the net result of which is the active secretion of HCl. Secretion of acid across the apical membrane by the H-K pump results in a rise in parietal cell pH. The adaptive response to this rise in pH includes passive uptake of CO2 and H2O, which the enzyme carbonic anhydrase (see box on p. 637) converts to HCO3− and H+. The H+ is the substrate of the H-K pump. The HCO3− exits across the basolateral membrane via the Cl−/HCO3− exchanger. This latter process also provides the Cl− required for net HCl movement across the apical/canalicular membrane. The basolateral Na-H exchanger may participate in intracellular pH regulation, especially in the basal state.

Three Secretagogues (Acetylcholine, Gastrin, and Histamine) Directly and Indirectly Induce Acid Secretion by Parietal Cells

The action of secretagogues on gastric-acid secretion occurs via at least two parallel and perhaps redundant mechanisms (Fig. 41-5). In the first, acetylcholine (ACh), gastrin, and histamine bind directly to their respective membrane receptors on the parietal cell and synergistically stimulate and potentiate acid secretion. ACh (see Fig. 15-8) is released from endings of the vagus nerve (cranial nerve X), and as we shall see in the next section, gastrin is released from D cells. Histamine is synthesized from histidine (see Fig. 12-9). The documented presence of ACh, gastrin, and histamine receptors, at least on the canine parietal cell, provides the primary support for this view. In the second mechanism, ACh and gastrin indirectly induce acid secretion as a result of their stimulation of histamine release from enterochromaffin-like (ECL) cells and possibly from mast cells (histaminocytes) in the lamina propria. The central role of histamine and ECL cells is consistent with the observation that histamine-2 receptor antagonists (i.e., H2 blockers), such as cimetidine and ranitidine, not only block the direct action of histamine on parietal cells but also substantially inhibit the acid secretion stimulated by ACh and gastrin. The effectiveness of H2 blockers in controlling acid secretion after stimulation by most agonists is well established in studies of both humans and experimental animals. These drugs are widely prescribed to treat active peptic ulcer disease.

The Three Acid Secretagogues Act Through Either Ca2+/Diacylglycerol or Cyclic Adenosine Monophosphate

Stimulation of acid secretion by ACh, gastrin, and histamine, is mediated by a series of intracellular signal-transduction processes similar to those responsible for the action of other agonists in other cell systems. All three secretagogues bind to specific G-protein-coupled receptors on the parietal-cell membrane (Fig. 41-6).

Acetylcholine binds to an M3 muscarinic receptor (p. 387) on the parietal cell basolateral membrane. This ACh receptor couples to a guanosine triphosphate (GTP)-binding protein (Gαq) and activates phospholipase C (PLC), which converts phosphatidylinositol 4,5-biphosphate (PIP2) to inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG, p. 100). IP3 causes internal stores to release Ca2+, which then probably acts via calmodulin-dependent protein kinase (p. 102). DAG activates protein kinase C (PKC). The M3 receptor also activates a Ca2+ channel.

Gastrin binds to a specific parietal-cell receptor that has been identified as the gastrin-cholecystokinin B (CCK8) receptor. Two related CCK receptors have been identified, CCK4 and CCKb. Their amino-acid sequences are approximately 90% identical, and both are G-protein
CCK receptors have equal affinity for gastrin and CCK. In contrast, the CCKA receptor's affinity for CCK is three orders of magnitude higher than its affinity for gastrin. These observations and the availability of receptor antagonists are beginning to clarify the parallel, but at times opposite, effects of gastrin and CCK in various aspects of GI function. The CCKB receptor couples to Gαi and activates the same PLC pathway as CCK does, which leads to both an increase in [Ca^{2+}]_i and activation of PKC.

The histamine receptor on the parietal cell is an H2 receptor that is coupled to the Gαs GTP-binding protein. Histamine activation of the receptor complex stimulates the enzyme adenyl cyclase, which in turn generates cyclic adenosine monophosphate (cAMP). The resulting activation of protein kinase A leads to the phosphorylation of a number of parietal-cell-specific proteins, including the H-K pump.

**Gastrin Is Released by Both Antral and Duodenal G Cells, and Histamine Is Released by Enterochromaffin-Like Cells in the Corpus**

The presence of a gastric hormone that stimulates acid secretion was initially proposed in 1905. Direct evidence of such a factor was obtained in 1938, and in 1964 Gregory and Tracey isolated and purified gastrin and determined its amino-acid sequence. Gastrin has three major effects on GI cells: (1) stimulation of acid secretion by parietal cells (see Fig. 41-5), (2) release of histamine by ECL cells, and (3) regulation of mucosal growth in the corpus of the stomach, as well as in the small and large intestine.

Gastrin exists in several different forms, but the two major forms are G-17, or "little gastrin," a 17-amino acid linear peptide (Fig. 41-7A), and G-34, or "big gastrin," a 34-amino acid peptide (see Fig. 41-7B). A single gene encodes a peptide of 101 amino acids. Several cleavage steps and C-terminal amidation (i.e., addition of a -NH2

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**FIGURE 41-6.** Receptors and signal-transduction pathways in the parietal cell. The parietal cell has separate receptors for three acid secretagogues. Acetylcholine (Ach) and gastrin each bind to specific receptors (M3 and CCKA, respectively) that are coupled to the G protein Goi. The result is activation of phospholipase C (PLC), which ultimately leads to the activation of protein kinase C (PKC) and the release of Ca^{2+}. The histamine binds to an H2 receptor, coupled through Gαs, to adenyl cyclase (AC). The result is production of cAMP and activation of PKA. Two inhibitors of acid secretion also act directly on the parietal cell. Somatostatin and prostaglandins bind to separate receptors that are linked to Goi. These agents thus oppose the actions of histamine: cAMP, cyclic adenosine monophosphate (cAMP), and protein kinase A lead to the phosphorylation of a number of parietal-cell-specific proteins, including the H-K pump.

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**FIGURE 41-7.** Amino acid sequences of the gastrins and CCK. A, A single gene encodes a 101-amino-acid peptide that is processed to both G-17 and G-34. The N-terminal glutamine is modified to create a pyroglutamyl residue. The C-terminal phenylalanine is amidated. These modifications make the hormone resistant to carboxy- and aminopeptidases. B, The final 16 amino acids of G-34 are identical to the final 16 amino acids in G-17. Both G-17 and G-34 may be either not sulfated (Gastrin I) or sulfated (Gastrin II). C. The five final amino acids of CCK are identical to those of G-17 and G-34.
Gastric Function

C terminal) occur during gastrin's post-translational modification, a process that occurs in the endoplasmic reticulum, trans-Golgi apparatus, and both immature and mature secretory granules. The final product of this post-translational modification is either G-17 or G-34. The tyrosine residue may be either sulfated (so-called gastrin II) or nonsulfated (gastrin I); the two forms are equally active and are present in equal amounts. Gastrin and cholecystokinin, a related hormone, have identical C-terminal tetrapeptide sequences (see Fig. 41-7C) that possess all the biologic activities of both gastrin and CCK. Both G-17 and G-34 are present in blood plasma, and their plasma levels primarily reflect their degradation rates. Thus, although G-17 is more active than G-34, the

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**Figure 41-8. Regulation of gastric acid secretion.** In the corpus of the stomach, the vagus nerve not only stimulates the parietal cell directly by releasing Ach, it also stimulates both ECL and D cells. Vagal stimulation of the ECL cells enhances gastric-acid secretion via increased histamine release. Vagal stimulation of the D cells also promotes gastric-acid secretion by inhibiting the release of somatostatin, which would otherwise inhibit—by paracrine mechanisms—the release of histamine from ECL cells and the secretion of acid by parietal cells.

In the antrum of the stomach, the vagus stimulates both G cells and D cells. The vagus stimulates the G cells via CCK (cholecystokinin) releasing Ach, promoting gastrin release. This gastrin promotes gastric-acid secretion by two endocrine mechanisms: directly via the parietal cell and indirectly via the ECL cell, which releases histamine. The vagal stimulation of D cells via Ach inhibits the release of somatostatin, which would otherwise inhibit—by paracrine mechanisms—the release of gastrin from G cells and—by an endocrine mechanism—acid secretion by parietal cells. Luminal H+ directly stimulates the D cells to release somatostatin, which inhibits gastrin release from the G cells, thereby reducing gastric-acid secretion (negative feedback). In addition, products of protein digestion (i.e., peptides and amino acids) directly stimulate the G cells to release gastrin, which stimulates gastric-acid secretion (positive feedback). Ach, acetylcholine; CCK, cholecystokinin B; ECL, enterochromaffin-like; ENS, enteric nervous system.
latter is degraded at a substantially lower rate than G-17. As a consequence, the infusion of equal amounts of G-17 or G-34 produces comparable increases in gastric-acid secretion.

Specialized endocrine cells (G cells) in both the antrum and duodenum make each of the two gastrins. Antral G cells are the primary source of G-17, whereas duodenal G cells are the primary source of G-34. Antral G cells are unusual in that they respond to both luminal and basolateral stimuli (Fig. 41-8). Antral G cells have microvilli on their apical membrane surface and are referred to as an “open-type” endocrine cell. These G cells release gastrin in response to luminal peptides and amino acids, as well as in response to gastrin-releasing peptide (GRP), a 27–amino acid peptide that is released by vagal nerve endings. As discussed later, gastrin release is inhibited by somatostatin, which is released from adjacent D cells.

**Somatostatin, Released by Gastric D Cells, Is the Central Mechanism of Inhibition of Acid Secretion**

Gastric-acid secretion is under close control of not only the stimulatory pathways discussed earlier but also the inhibitory pathways. The major inhibitory pathway involves the release of somatostatin, a polypeptide hormone made by D cells in the antrum and corpus of the stomach. Somatostatin is also made by the δ cells of the pancreatic islets (p. 1084) and by neurons in the hypothalamus (p. 1026). Somatostatin exists in two forms, SS-28 and SS-14, which have identical C termini. SS-28 is the predominant form in the GI tract.

Somatostatin inhibits gastric-acid secretion by both direct and indirect mechanisms (see Fig. 41-8). In the direct pathway, somatostatin coming from two different sources binds to a Gαs-coupled receptor (SST) on the basolateral membrane of the parietal cell and inhibits adenylyl cyclase. The net effect is to antagonize the stimulatory effect of histamine and thus inhibit gastric-acid secretion by parietal cells. The source of this somatostatin can either be paracrine (i.e., D cells present in the corpus of the stomach, near the parietal cells) or endocrine (i.e., D cells in the antrum). However, there is a major difference in what triggers the D cells in the corpus and antrum. Neural and hormonal mechanisms stimulate D cells in the corpus (which cannot sense intraluminal pH), whereas low intraluminal pH stimulates D cells in the antrum.

Somatostatin also acts via two indirect pathways, both of which are paracrine in nature. In the corpus of the stomach, D cells release somatostatin that inhibits the release of histamine from ECL cells (see Fig. 41-8). Because histamine is an acid secretagogue, somatostatin thus reduces gastric-acid secretion. In the antrum of the stomach, D cells release somatostatin that inhibits the release of gastrin from G cells. Because gastrin is another acid secretagogue, somatostatin also reduces gastric-acid secretion by this route. Note that the gastrin released by the G cell feeds back on itself by stimulating D cells to release the inhibitory somatostatin.

The presence of multiple mechanisms by which somatostatin inhibits acid secretion is another example of the redundant regulatory pathways that control acid secretion. An understanding of the regulation of somatostatin release from D cells is slowly evolving, but it appears that gastrin stimulates somatostatin release whereas cholinergic agonists inhibit somatostatin release.

**Several Enteric Hormones (“Enterogastrone”) and Prostaglandins Inhibit Gastric-Acid Secretion**

Multiple processes in the duodenum and jejunum participate in the negative-feedback mechanisms that inhibit gastric-acid secretion. Fat, acid, and hyperosmolar solutions in the duodenum are potent inhibitors of gastric-acid secretion. Of these inhibitors, lipids are the most potent, but acid is also quite important. Several candidate hormones have been suggested as the prime mediator of this acid inhibition (Table 41-1). These include CCK (p. 920), secretin (p. 921), vasoactive intestinal peptide (VIP), gastric inhibitory peptide (GIP p. 899), neurotensin, and peptide YY (p. 924). Although each inhibits acid secretion after systemic administration, none has been unequivocally established as the sole physiologic “enterogastrone.”

Evidence suggests that secretin, which is released by duodenal S cells, may have a prime role in inhibiting gastric acid secretion after the entry of fat and acid into the duodenum. Secretin appears to reduce acid secretion by at least three mechanisms: (1) inhibition of antral gastrin release, (2) stimulation of somatostatin release, and (3) direct downregulation of the parietal-cell H⁺ secretory process.

The presence of luminal fatty acids causes enteroendocrine cells in the duodenum and the proximal part of the

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**TABLE 41-1**

<table>
<thead>
<tr>
<th>HORMONE</th>
<th>SOURCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCK (cholecystokinin)</td>
<td>I cells of duodenum and jejunum and neurons in ileum and colon</td>
</tr>
<tr>
<td>Secretin</td>
<td>S cells in small intestine</td>
</tr>
<tr>
<td>VIP (vasoactive intestinal peptide)</td>
<td>ENS neurons</td>
</tr>
<tr>
<td>GIP (gastric inhibitory peptide, or glucose-dependent insulinotropic polypeptide)</td>
<td>K cells in duodenum and jejunum</td>
</tr>
<tr>
<td>Neurotensin</td>
<td>Endocrine cells in ileum</td>
</tr>
<tr>
<td>Peptide YY</td>
<td>Endocrine cells in ileum and colon</td>
</tr>
<tr>
<td>Somatostatin</td>
<td>D cells of stomach and duodenum, δ cells of pancreatic islets</td>
</tr>
</tbody>
</table>

ENS, enteric nervous system.
small intestine to release both GIP and CCK. GIP reduces acid secretion directly by inhibiting parietal-cell acid secretion and indirectly by inhibiting the antral release of gastrin. GIP also has the important function of stimulating insulin release from pancreatic islet cells in response to duodenal glucose and fatty acids and is therefore often referred to as glucose-dependent insulino tropic polypeptide (p. 1073). CCK participates in feedback inhibition of acid secretion by directly reducing parietal-cell acid secretion. Finally, some evidence indicates that a neural reflex elicited in the duodenum in response to acid also inhibits gastric-acid secretion.

Prostaglandin E₂ (PGE₂) inhibits parietal-cell acid secretion, probably by inhibiting histamine’s activation of parietal-cell function at a site that is distal to the histamine receptor. PGE₂ appears to bind to an EP₃ receptor on the basolateral membrane of the parietal cell (see Fig. 41–6) and stimulates GC₈, which in turn inhibits adenylyl cyclase. In addition, prostaglandins also indirectly inhibit gastric-acid secretion by reducing histamine release from ECL cells and gastrin release from antral G cells.

**There Are Four Phases of Acid Secretion: A Basal (or Interdigestive) Phase and Three Phases Associated with Eating**

**Basal State.** Gastric-acid secretion occurs throughout the day and night. Substantial increases in acid secretion occur after meals, whereas the rate of acid secretion between meals is low (i.e., the interdigestive phase). This interdigestive period follows a circadian rhythm; acid secretion is lowest in the morning before awakening and highest in the evening. Acid secretion is a direct function of the number of parietal cells, which is also influenced, at least in part, by body weight. Thus, men have higher rates of basal acid secretion than women do. Considerable variability in basal acid secretion is also seen among normal individuals, and the resting intragastric pH can range from 3 to 7.

In contrast to the low rate of acid secretion during the basal or interdigestive period, acid secretion is enhanced several-fold by eating (Fig. 41–9). It is important to note that regulation of gastric-acid secretion is most often studied in the fasting state, a state in which intragastric pH is relatively low because of the basal H⁺ secretory rate and the absence of food that would otherwise buffer the secreted gastric acid. Experimental administration of a secretagogue in the fasted state thus stimulates parietal cells and further lowers intragastric pH. However, the time course of intragastric pH after a meal can vary considerably despite stimulation of acid secretion. The reason is that intragastric pH depends not only on gastric-acid secretion but also on the buffering power (p. 635) of food and the rate of gastric emptying of both acid and partially digested material into the duodenum.

Regulation of acid secretion during a meal can be best characterized by three separate, but interrelated phases: the cephalic, the gastric, and the intestinal phases. The cephalic and gastric phases are of primary importance. Regulation of acid secretion includes both the stimulatory and inhibitory mechanisms that we discussed earlier (see Fig. 41–8). ACh, gastrin, and histamine all promote acid secretion whereas somatostatin inhibits gastric-acid secretion.

Note that although dividing acid secretion during a meal into three phases has been used for decades, it is somewhat artificial because of considerable overlap in the regulation of acid secretion. For example, the vagus nerve is the central player in the cephalic phase, but it is also important for the vagovagal reflex that is part of the gastric phase. Similarly, gastrin release is a major component of the gastric phase, but vagal stimulation during the...
CEPHALIC PHASE. The smell, sight, taste, thought, and swallowing of food initiate the cephalic phase, which is primarily mediated by the vagus nerve (see Fig. 41-8). Although the cephalic phase has long been studied in experimental animals, especially dogs, recent studies of sham feeding have confirmed and extended the understanding of the mechanism of the cephalic phase of acid secretion in humans. The aforementioned sensory stimuli activate the dorsal motor nucleus of the vagus nerve in the medulla (p. 381), thus activating parasympathetic preganglionic efferent nerves. Insulin-induced hypoglycemia also stimulates the vagus nerve and in so doing promotes acid secretion.

Stimulation of the vagus nerve results in four distinct physiological events—which we have already introduced in Figure 41-8—that together result in enhanced gastric-acid secretion. First, in the body of the stomach, vagal postganglionic muscarinic nerves release acetylcholine, which stimulates parietal-cell \( H^+ \) secretion directly. Second, in the lamina propria of the body of the stomach, the \( ACh \) released from vagal endings triggers histamine release from ECL cells, which stimulates acid secretion. Third, in the antrum, peptidergic postganglionic parasympathetic vagal neurons, as well as other enteric nervous system (ENS) neurons, release GRP, which induces gastrin release from antral G cells. This gastrin stimulates gastric-acid secretion both directly by acting on the parietal cell and indirectly by promoting histamine release from ECL cells. Fourth, in both the antrum and the corpus, the vagus nerve inhibits D cells, thus reducing their release of somatostatin and reducing the background inhibition of gastrin release. Thus, the cephalic phase stimulates acid secretion directly and indirectly by acting on the parietal cell. The cephalic phase accounts for approximately 30% of total acid secretion and occurs before the entry of any food into the stomach.

One of the surgical approaches for the treatment of peptic ulcer disease is cutting the vagus nerves (vagotomy) to inhibit gastric-acid secretion. Rarely performed, largely because of the many effective pharmacologic agents available to treat peptic ulcer disease, the technique has nevertheless proved to be effective in selected cases. Because vagus-nerve stimulation affects several GI functions besides parietal-cell acid secretion, the side effects of vagotomy include a delay in gastric emptying and diarrhea. To minimize these untoward events, there have been successful attempts to perform more "selective" vagotomies, severing only those vagal fibers going to the parietal cell.

CEPHALIC PHASE. The smell, sight, taste, thought, and swallowing of food initiate the cephalic phase, which is primarily mediated by the vagus nerve (see Fig. 41-8). Although the cephalic phase has long been studied in experimental animals, especially dogs, recent studies of sham feeding have confirmed and extended the understanding of the mechanism of the cephalic phase of acid secretion in humans. The aforementioned sensory stimuli activate the dorsal motor nucleus of the vagus nerve in the medulla (p. 381), thus activating parasympathetic preganglionic efferent nerves. Insulin-induced hypoglycemia also stimulates the vagus nerve and in so doing promotes acid secretion.

Stimulation of the vagus nerve results in four distinct physiological events—which we have already introduced in Figure 41-8—that together result in enhanced gastric-acid secretion. First, in the body of the stomach, vagal postganglionic muscarinic nerves release acetylcholine, which stimulates parietal-cell \( H^+ \) secretion directly. Second, in the lamina propria of the body of the stomach, the \( ACh \) released from vagal endings triggers histamine release from ECL cells, which stimulates acid secretion. Third, in the antrum, peptidergic postganglionic parasympathetic vagal neurons, as well as other enteric nervous system (ENS) neurons, release GRP, which induces gastrin release from antral G cells. This gastrin stimulates gastric-acid secretion both directly by acting on the parietal cell and indirectly by promoting histamine release from ECL cells. Fourth, in both the antrum and the corpus, the vagus nerve inhibits D cells, thus reducing their release of somatostatin and reducing the background inhibition of gastrin release. Thus, the cephalic phase stimulates acid secretion directly and indirectly by acting on the parietal cell. The cephalic phase accounts for approximately 30% of total acid secretion and occurs before the entry of any food into the stomach.

One of the surgical approaches for the treatment of peptic ulcer disease is cutting the vagus nerves (vagotomy) to inhibit gastric-acid secretion. Rarely performed, largely because of the many effective pharmacologic agents available to treat peptic ulcer disease, the technique has nevertheless proved to be effective in selected cases. Because vagus-nerve stimulation affects several GI functions besides parietal-cell acid secretion, the side effects of vagotomy include a delay in gastric emptying and diarrhea. To minimize these untoward events, there have been successful attempts to perform more "selective" vagotomies, severing only those vagal fibers going to the parietal cell.

GASTRIC PHASE. Entry of food into the stomach initiates the two primary stimuli for the gastric phase of acid secretion (Fig. 41-10A). First, the food distends the gastric mucosa, which activates a vagovagal reflex as well as local ENS reflexes. Second, partially digested proteins stimulate antral G cells.

Distention of the gastric wall—both in the corpus and antrum—secondary to entry of food into the stomach elicits two distinct neurally mediated pathways. The first is activation of a vagovagal reflex (p. 884), in which gastric-wall distention activates a vagal afferent pathway, which in turn stimulates a vagal efferent response in the
dorsal nucleus of the vagus nerve. Stimulation of acid secretion in response to this vagal efferent stimulus occurs via the same four parallel pathways that are operative when the vagus nerve is activated during the cephalic phase (see Fig. 41–8). Second, gastric-wall distention also activates a local ENS pathway that releases ACh, which in turn stimulates parietal-cell acid secretion.

The presence of partially digested proteins (peptones) or amino acids in the antrum directly stimulates G cells to release gastrin (see Fig. 41–8). Intact proteins have no effect. Acid secretion and activation of pepsinogen are linked in a positive-feedback relationship. As discussed later, low pH enhances the conversion of pepsinogen to pepsin. Pepsin digests proteins to peptones, which promote gastrin release. Finally, gastrin promotes acid secretion, which closes the positive-feedback loop. There is little evidence that either carbohydrate or lipid participate in the regulation of gastric-acid secretion. Components of wine, beer, and coffee stimulate acid secretion by this G-cell mechanism.

In addition to the two stimulatory pathways acting during the gastric phase, a third pathway inhibits gastric-acid secretion by a classic negative feedback mechanism, already noted earlier in our discussion of Figure 41–8.

### Gastrinoma or Zollinger-Ellison Syndrome

On rare occasion, patients with one or more ulcers have very high rates of gastric-acid secretion. The increased acid secretion in these patients is most often a result of elevated levels of serum gastrin, released from a pancreatic islet cell adenoma or "gastrinoma" (Table 41–2). This clinical picture is known as the Zollinger-Ellison (ZE) syndrome. Because gastrin released from these islet cell adenomas is not under physiological control, but rather is continuously released, acid secretion is substantially increased under basal conditions. However, the intravenous administration of pentagastrin—a synthetic gastrin consisting of the last four amino acids of gastrin plus β-alanine—provides only a modest increase in gastric-acid secretion. Omeprazole, a potent inhibitor of the parietal-cell H-K pump, is now an effective therapeutic agent to control the marked enhancement of gastric-acid secretion in gastrinoma patients, and thus helps heal their duodenal and gastric ulcers.

In contrast to patients with gastrinoma or ZE syndrome, other duodenal ulcer patients have serum gastrin levels that are near normal. Their basal gastric-acid secretion rates are modestly elevated, but increase markedly in response to pentagastrin. Patients with pernicious anemia (see Box on pernicious anemia on p. 971) lack parietal cells and thus cannot secrete H⁺. In the absence of a low luminal pH, the antral D cell is not stimulated by acid (see Fig. 41–108). Consequently, the release of somatostatin from the D cell is low, and there is minimal tonic inhibition of gastrin release from G cells. It is not surprising, then, that these patients have very high levels of serum gastrin, but virtually no H⁺ secretion (see Table 41–2).

### Table 41–2

<table>
<thead>
<tr>
<th>SERUM GASTRIN (pg/ml)</th>
<th>H⁺ SECRETION (meq/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
</tr>
<tr>
<td>Normal</td>
<td>35</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>50</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>500</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>350</td>
</tr>
</tbody>
</table>

Low intragastric pH stimulates antral D cells to release somatostatin. Because somatostatin inhibits the release of gastrin by G cells, the net effect is a reduction in gastric-acid secretion. The effectiveness of low pH in inhibiting gastrin release is emphasized by the following observation: Although peptones are normally a potent stimulus for gastrin release, they fail to stimulate gastrin release either when the intraluminal pH of the antrum is maintained at 1.0 or when somatostatin is infused.

The gastric phase of acid secretion, which occurs primarily as a result of gastrin release, accounts for 50% to 60% of total gastric acid secretion.

### The Intestinal Phase

The presence of amino acids and partially digested peptides in the proximal portion of the small intestine stimulates acid secretion by three mechanisms (Fig. 41–11). First, these peptones stimulate duodenal G cells to secrete gastrin, just as peptones stimulate antral G cells in the gastric phase. Second, peptones stimulate an unknown endocrine cell to release an additional hormone signal that has been referred to as "entero-oxynin." The chemical nature of this agent has not yet been identified. Third, amino acids absorbed by the proximal part of the small intestine stimulate acid secretion by mechanisms that require further definition.

Of interest, gastric-acid secretion mediated by the intestinal phase is enhanced after a portacaval shunt. Such a shunt—which is used in the treatment of portal hypertension caused by chronic liver disease—diverts the portal blood that drains the small intestine around the liver on its return to the heart. Thus, the signal released from the small intestine during the "intestinal phase" is probably—in normal individuals—removed in part by the liver before reaching its target, the corpus of the stomach. Approximately 5% to 10% of total gastric acid secretion is a result of the intestinal phase.

### Pepsinogen Secretion

**Chief Cells, Triggered by Both cAMP and Ca²⁺ Pathways, Secrete Multiple Pepsinogens That Initiate Protein Digestion**

The chief cells in gastric glands, as well as mucous cells, secrete pepsinogens, a group of proteolytic proenzymes...
Gastric Function

(i.e., zymogens or inactive enzyme precursors) that belong to the general class of aspartic proteinases. They are activated to pepsins by cleavage of an N-terminal peptide. Pepsins are endopeptidases that initiate the hydrolysis of ingested protein in the stomach. Although eight pepsinogens were initially identified on electrophoresis, recent classifications are based on immunologic identity, so pepsinogens are most often classified as group I pepsinogens, group II pepsinogens, and cathepsin E. Group I pepsinogens predominate. They are secreted from chief cells located at the base of glands in the corpus of the stomach. Group II pepsinogens are also secreted from chief cells but, in addition, are secreted from mucous neck cells in the cardiac, corpus, and antral regions.

Pepsinogen secretion in the basal state is approximately 20% of its maximal secretion after stimulation. Although pepsinogen secretion generally parallels the secretion of acid, the ratio of maximal to basal pepsinogen secretion is considerably less than that for acid secretion. Moreover, the cellular mechanism of pepsinogen release is quite distinct from that of H+ secretion by parietal cells. Release of pepsinogen across the apical membrane is the result of a novel process called compound exocytosis, in which secretory granules fuse with both the plasma membrane and other secretory granules. This process permits rapid and sustained secretion of pepsinogen. After stimulation, the initial peak in pepsinogen secretion is followed by a persistent lower rate of secretion. This pattern of secretion has been interpreted as reflecting an initial secretion of preformed pepsinogen, followed by the secretion of newly synthesized pepsinogen. However, recent in vitro studies suggest that a feedback mechanism may account for the subsequent reduced rate of pepsinogen secretion.

Two groups of agonists stimulate chief cells to secrete pepsinogen. One group acts through adenylyl cyclase and cAMP, and the other acts through increases in [Ca2+].

**AGONISTS ACTING VIA cAMP.** Chief cells have receptors for secretin/VIP, β₂-adrenergic receptors, and EP2 receptors for PGE₂. All these receptors activate adenylyl cyclase. At lower concentrations than those required to stimulate pepsinogen secretion, PGE₂ can also inhibit pepsinogen secretion, probably by binding to another receptor subtype.

**AGONISTS ACTING VIA Ca²⁺.** Chief cells also have M₁ muscarinic receptors for acetylcholine, as well as receptors for the gastrin/CCK family of peptides. Unlike gastric acid secretion, which is stimulated via the CCK₂ receptor, pepsinogen secretion is stimulated via the CCK₁ receptor, which has a much higher affinity for CCK than for gastrin. Activation of both the M₁ and CCK₁ receptors causes Ca²⁺ release from intracellular stores via IP₃ and thereby raises [Ca²⁺]. However, uncertainty exists about whether increased Ca²⁺ influx is also required and about whether PKC also has a role.

Of the agonists just listed, the most important for pepsinogen secretion is ACh released in response to vagal stimulation. Not only does ACh stimulate chief cells to release pepsinogen, it also stimulates parietal cells to secrete acid. This gastric acid produces additional pepsinogen secretion via two different mechanisms. First, in the stomach, a fall in pH elicits a local cholinergic reflex that results in further stimulation of chief cells to release pepsinogen. Thus, the ACh that stimulates chief cells can come both from the vagus and from the local reflex. Second, in the duodenum, acid triggers the release of secretin from S cells. By an endocrine effect, this secretin stimulates the chief cells to release more pepsinogen. The exact role or roles of histamine and gastrin in pepsinogen secretion are unclear.

**Low pH Is Required for Both Pepsinogen Activation and Pepsin Activity**

Pepsinogen is inactive and requires activation to a protease, pepsin, to initiate protein digestion. This activation occurs by spontaneous cleavage of a small N-terminal peptide fragment (the activation peptide), but only at a pH that is less than 5.0 (Fig. 41-12). Between pH 5.0 and 3.0, spontaneous activation of pepsinogen is slow, but it is extremely rapid at a pH that is less than 3.0. In addition, pepsinogen is also autoactivated; that is, newly formed pepsin itself cleaves pepsinogen to pepsin.

Once pepsin is formed, its activity is also pH dependent. It has optimal activity at a pH between 1.8 and 3.5; the precise optimal pH depends on the specific pepsin, type and concentration of substrate, and osmolality of the solution. pH values above 3.5 reversibly inactivate pepsin, and pH values above 7.2 irreversibly inactivate the enzyme. These considerations are sometimes useful for establishing optimal antacid treatment regimens in peptic ulcer disease.

Pepsin is an endopeptidase that initiates the process of protein digestion in the stomach. Pepsin action results in the release of small peptides and amino acids (peptones) that, as noted earlier, stimulate the release of gastrin from antral G cells; these peptones also stimulate CCK release from duodenal I cells. As previously mentioned, the peptones generated by pepsin stimulate the very acid secretion required for pepsin activation and action. Thus, the peptones that pepsin releases are important in initiating a coordinated response to a meal. However, most protein entering the duodenum remains as large peptides, and nitrogen balance is not impaired after total gastrectomy.

Digestive products of both carbohydrates and lipid are also found in the stomach, although secretion of their respective digestive enzymes either does not occur or is not a major function of gastric epithelial cells. Carbohydrates and lipid are degraded to other smaller molecules, but their digestive products are not transported to the small intestine, where they are further digested. The digestion of proteins is the major function of the stomach. Pepsin is an endopeptidase that initiates the process of protein digestion in the stomach. Pepsin action results in the release of small peptides and amino acids (peptones) that, as noted earlier, stimulate the release of gastrin from antral G cells; these peptones also stimulate CCK release from duodenal I cells. As previously mentioned, the peptones generated by pepsin stimulate the very acid secretion required for pepsin activation and action. Thus, the peptones that pepsin releases are important in initiating a coordinated response to a meal. However, most protein entering the duodenum remains as large peptides, and nitrogen balance is not impaired after total gastrectomy.

**FIGURE 41-12.** Activation of the pepsinogens to pepsins. At pH values from 5 to 3, pepsinogens spontaneously activate to pepsins by the removal of an N-terminal "activation peptide." This spontaneous activation is even faster at pH values that are below 3. The newly formed pepsins themselves—which are active only at pH values below 3.5—also can catalyze the activation of pepsinogens.
secretion of enzymes that hydrolyze starch or other saccharides. Similarly, although lipid digestion is also initiated in the mouth by lingual lipase, significant lipid digestion occurs in the stomach as a result of both the lingual lipase that is swallowed and gastric lipase, both of which have an acid pH optimum (p. 962).

**PROTECTION OF THE GASTRIC SURFACE EPITHELIUM AND NEUTRALIZATION OF ACID IN THE DUODENUM**

At maximal rates of H+ secretion, the parietal cell can drive the intraluminal pH of the stomach to 1 or less (i.e., [H+] > 100 mM) for long periods. The gastric epithelium must maintain an H+ concentration gradient of over a million-fold because the intracellular pH of gastric epithelial cells is approximately 7.2 (i.e., [H+] = 60 nM) and plasma pH is about 7.4 (i.e., [H+] = 40 nM). Simultaneously, there is a substantial plasma-to-lumen Na+-concentration gradient of approximately 30 because plasma [Na+] is 140 mM whereas intragastric [Na+] can reach values as low as 5 mM, but only at high secretory rates (see Fig. 41-2). How is the stomach able to maintain these gradients? How is it that the epithelial cells are not destroyed by this acidity? Moreover, why do pepsins in the gastric lumen not digest the epithelial cells? The answer to all three questions is the so-called gastric diffusion barrier.

Although the nature of the gastric diffusion barrier had been controversial, it is now recognized that the diffusion barrier is both physiologic and anatomic. Moreover, it is apparent that the diffusion barrier represents at least three components: (1) relative impermeability to acid of the apical membrane and epithelial cell tight junctions in the gastric glands; (2) a mucous-gel layer varying in thickness between 50 and 200 μm overlying the surface epithelial cells; and (3) an HCO₃⁻-containing microclimate adjacent to the surface epithelial cells that maintains a relatively high local pH.

**Vagal Stimulation and Irritation Stimulate Gastric Mucous Cells to Secret Mucin, a Glycoprotein That Is Part of the Mucosal Barrier**

The mucus layer is largely composed of mucin, phospholipids, electrolytes, and water. Mucin is the high-molecular-weight glycoprotein (p. 40) that contributes to the formation of a protective layer over the gastric mucosa. Gastric mucin is a tetramer consisting of four identical peptide chains joined by disulfide bonds. Each of the four peptide chains is linked to long polysaccharides, which are often sulfated and thus mutually repulsive. The ensuing high carbohydrate content is responsible for the viscosity of mucus, which explains, in large part, its protective role in gastric mucosal physiology.

Mucus is secreted by three different mucous cells: surface mucous cells (i.e., on the surface of the stomach), mucous neck cells (i.e., at the point where a gastric pit joins a gastric gland), and glandular mucous cells (i.e., in the gastric glands in the antrum). The type of mucus secreted by these cells differs; mucus that is synthesized and secreted in the glandular cells is a neutral glycoprotein, whereas the mucous cells on the surface and in the gastric pits secrete both neutral and acidic glycoproteins. Mucin forms a mucous-gel layer in combination with phospholipids, electrolytes, and water. This mucous-gel layer provides protection against injury from noxious luminal substances, including acid, pepsins, bile acids, and ethanol. Mucin also lubricates the gastric mucosa to minimize the abrasive effects of intraluminal food.

The mucus barrier is not static. Abrasions can remove pieces of mucus. When mucus comes in contact with a solution with a very low pH, the mucus precipitates and sloughs off. Thus, the mucous cells must constantly secrete mucus. Regulation of mucous secretion by gastric mucosal cells is less well understood than is regulation of the secretion of acid, pepsinogens, and other substances by gastric cells. The two primary stimuli for inducing mucous secretion are vagal stimulation and physical and chemical irritation of the gastric mucosa by ingested food. The current model of mucous secretion suggests that vagal stimulation induces the release of ACh, which leads to increases in [Ca²⁺], and thus stimulates mucus secretion. In contrast to acid and pepsinogen secretion, CAMP does not appear to be a second messenger for mucus secretion.

**Gastric Surface Cells Secrete HCO₃⁻ Stimulated by Acetylcholine, Acids, and Prostaglandins**

Surface epithelial cells both in the corpus and in the antrum of the stomach secrete HCO₃⁻. Despite the relatively low rate of HCO₃⁻ secretion—in comparison to acid secretion—HCO₃⁻ is extremely important as part of the gastric mucosal protective mechanism. The mucus-gel layer provides an unstirred layer under which the secreted HCO₃⁻ remains trapped and maintains a local pH of approximately 7.0 versus an intraluminal pH in the bulk phase of 1 to 3. As illustrated in Figure 41-13A, an electrogenic Na/HCO₃ co transporter (NBC) appears to mediate the uptake of HCO₃⁻ across the basolateral membrane of surface epithelial cells. The mechanism of HCO₃⁻ exit from the cell into the apical mucus layer is unknown but may be mediated by a channel.

Similar to the situation for mucus secretion, relatively limited information is available about the regulation of HCO₃⁻ secretion. The present model suggests that vagal stimulation mediated by ACh leads to an increase in [Ca²⁺], which in turn stimulates HCO₃⁻ secretion. Sham feeding is a potent stimulus for HCO₃⁻ secretion via this pathway. A second powerful stimulus of gastric HCO₃⁻ secretion is intraluminal acid. The mechanism of stimulation by acid appears to be secondary to both activation of neural reflexes and local production of PGE₂. Finally, evidence suggests that a humoral factor may also be involved in the induction of HCO₃⁻ secretion by acid.
Mucus Protects the Gastric Surface Epithelium by Trapping an HCO₃⁻-Rich Fluid Near the Apical Border of These Cells

Mucous cells on the surface of the stomach, as well as in the gastric pits and neck portions of the gastric glands, secrete both HCO₃⁻ and mucus. Why is this barrier so effective? First, the secreted mucus forms a mucous-gel layer that is relatively impermeable to the diffusion of H⁺ from the gastric lumen to the surface cells. Second, beneath this layer of mucus is a microclimate that contains fluid with a high pH and high [HCO₃⁻], the result of HCO₃⁻ secretion by gastric surface epithelial cells (see Fig. 41-13A). Thus, this HCO₃⁻ neutralizes most acid that diffuses through the mucus layer. Mucosal integrity, including that of the mucosal diffusion barrier, is also maintained by PGE₂, which—as we saw in the previous section—stimulates mucosal HCO₃⁻ secretion.

Deep inside the gastric gland, where no obvious mucus layer protects the parietal, chief, and ECL cells, the impermeability of the cells’ apical barrier appears to exclude H⁺ even at pH values as low as 1. The paradox of how HCl secreted by the parietal cells emerges from the gland and into the gastric lumen may be explained by a process known as viscous fingering. Because the liquid emerging from the gastric gland is both extremely acidic and presumably under pressure, it can tunnel through the mucous layer covering the opening of the gastric gland onto the surface of the stomach. However, this stream of acid apparently does not spread laterally, but rather rises to the surface as a “finger” and thus does not neutralize the
HCO₃⁻ in the microenvironment between the surface epithelial cells and the mucus.

The mucous-gel layer and the trapped alkaline HCO₃⁻ solution protect the surface cells not only from H⁺ but also from pepsin. The mucus per se acts as a pepsin-diffusion barrier. The relative alkalinity of the trapped HCO₃⁻ inactivates any pepsin that penetrates into the mucus. Recall that pepsin is reversibly inactivated at pH values that are above approximately 3.5 and irreversibly inactivated by pH values approximately above 7.2. Thus, the mucus/HCO₃⁻ layer plays an important role in preventing “autodigestion” of the gastric mucosa.

**Entry of Acid into the Duodenum Induces the Release of Secretin From S Cells, Thus Triggering the Secretion of HCO₃⁻ by the Pancreas and Duodenum, Which in Turn Neutralizes Gastric Acid**

The overall process of regulating gastric-acid secretion involves not only stimulation and inhibition of acid secretion—which we discussed earlier—but also neutralization of the gastric acid that passes from the stomach into the duodenum. The amount of secreted gastric acid is reflected by a fall in intragastric pH. We have already seen that this fall in pH serves as the signal to antral D cells to release somatostatin and thus inhibit further acid secretion, a classic negative-feedback process. Likewise, low pH in the duodenum serves as a signal for the secretion of alkali to neutralize gastric acid in the duodenum.

**Breakdown of the Gastric Barrier**

Integrity of the gastric-epithelial barrier can be conveniently judged by maintenance of a high lumen-negative transepithelial potential difference (PD) of about -60 mV. Several agents that cause mucosal injury, including mucosal ulceration, can alter the mucosal diffusion barrier. Sialicylates, bile acids, and ethanol all impair the mucosal diffusion barrier and result in H⁺ (acid) backdiffusion, an increase in intraluminal [Na⁺], a fall in PD, and mucosal damage (see Fig. 41–13B). Three decades ago, Davenport proposed an attractive model to explain how H⁺, after having breached the mucosal diffusion barrier, produces injury to the gastric mucosa. Although several details of this original model have been modified during the ensuing years, it is still believed that entry of acid into the mucosa damages mast cells, which release histamine and other mediators of inflammation. The histamine and other agents cause a local vasodilatation that increases blood flow. If the damage is not too severe, this response allows the surface cells to maintain their production of mucus and HCO₃⁻. However, if the injury is more severe, inflammatory cells release a host of agents—including platelet-activating factor (PAF), leukotrienes, endothelins, thromboxanes, and oxidants—that reduce blood flow (ischemia) and result in tissue injury, including capillary damage.

**Prostaglandins** play a central role in maintaining mucosal integrity. For example, prostaglandins prevent or reverse mucosal injury secondary to sialicylates, bile, and ethanol. This protective effect of prostaglandins is the result of several actions, including their ability to inhibit acid secretion, stimulate both HCO₃⁻ and mucus secretion, increase mucosal blood flow, and modify the local inflammatory response induced by acid.

**HELICOBACTER PYLORI**

During the past decade, our understanding of the etiology of duodenal and gastric ulcers has radically changed. Abundant evidence now indicates that the majority of peptic ulcers are an infectious disease in that most (but not all) ulcers are caused by _H. pylori_, a gram-negative bacillus that colonizes the antral mucosa. Nonsteroidal anti-inflammatory drugs (NSAIDs) are responsible for approximately 20% of ulcers. Although almost all ulcers that are not associated with NSAID use are secondary to _H. pylori_ infestation, many, if not most, individuals with evidence of _H. pylori_ infestation do not have peptic ulcer disease. The factor or factors responsible for _H. pylori_-induced inflammation or ulceration are not known. However, the increase in gastric-acid secretion that is present in most patients with duodenal ulcers may occur because _H. pylori_-induced antral inflammation inhibits the release of somatostatin by antral D cells. Because somatostatin normally inhibits gastrin release by antral G cells, the result would be increased gastrin release and thus increased gastric-acid secretion. Indeed, as noted in Table 41–2, serum gastrin levels are modestly elevated in patients with duodenal ulcers.

Inhibition of acid secretion heals, but does not cure _H. pylori_-induced peptic ulcers. However, antibiotic therapy that eradicates _H. pylori_ cures peptic ulcer disease.
epithelial cells (villus and/or crypt cells) as the cellular source of HCO₃⁻ secretion, but the possibility that duodenal HCO₃⁻ originates, at least in part, from duodenal submucosal Brunner glands has not been excluded. Patients with duodenal ulcer disease tend to have both increased gastric-acid secretion and reduced duodenal HCO₃⁻ secretion. Thus, the increased acid load in the duodenum is only partially neutralized, so the duodenal mucosa has increased exposure to a low-pH solution.

**FILLING AND EMPTYING OF THE STOMACH**

**Gastric Motor Activity Plays a Role in Filling, Churning, and Emptying**

Gastric motor activity has three functions: (1) The receipt of ingested material represents the reservoir function of the stomach and occurs as smooth muscle relaxes. This response occurs primarily in the proximal portion of the stomach. (2) Ingested material is churned and thus altered to a form that rapidly empties from the stomach through the pylorus and facilitates normal jejunal digestion and absorption. Thus, in conjunction with gastric acid and enzymes, the motor function of the stomach helps initiate digestion. (3) The pyloric antrum, pylorus, and proximal part of the duodenum function as a single unit for emptying into the duodenum the modified gastric contents (“chyme”), consisting of both partially digested food material and gastric secretions. Gastric filling and emptying are accomplished by the coordinated activity of smooth muscle in the esophagus, lower esophageal sphincter, and proximal and distal portions of the stomach, as well as the pylorus and duodenum.

The pattern of gastric smooth-muscle activity is distinct during fasting and after eating. The pattern during fasting is referred to as the migrating myoelectric (or motor) complex (MMC), which we already discussed in connection with the small intestine (p. 889). This pattern is terminated by eating, at which point it is replaced by the so-called fed pattern. Just as the proximal and distal regions of the stomach differ in secretory function, they also differ in the motor function responsible for storing, processing, and emptying liquids and solids. The proximal part of the stomach is the primary location for storage of both liquids and solids. The distal portion of the stomach is primarily responsible for churning the solids and generating smaller liquid-like material, which then exits the stomach in a manner that is similar to that of ingested liquids. Thus, the gastric emptying of liquids and solids is closely integrated.

**Filling of the Stomach Is Facilitated by Both Receptive Relaxation and Gastric Accommodation**

Even a dry swallow relaxes both the lower esophageal sphincter and the proximal part of the stomach. Of course, the same happens when we swallow food. These relaxations facilitate the entry of food into the stomach. Relaxation in the fundus is primarily regulated by a vagovagal reflex and has been called receptive relaxation. In a vagovagal reflex, afferent fibers running with the vagus nerve carry information to the central nervous system (CNS), and efferent vagal fibers carry the signal from the CNS to the stomach and cause relaxation via a mechanism that is neither cholinergic nor adrenergic. The result is that intragastric volume increases without an increase in intragastric pressure. If vagal innervation to the stomach is interrupted, gastric pressure rises much more rapidly.

Quite apart from the receptive relaxation of the stomach that anticipates the arrival of food after swallowing and esophageal distention, the stomach can also relax in response to gastric filling per se. Thus, increasing intragastric volume, as a result of either food entering the stomach or gastric secretion, does not produce a proportionate increase in intragastric pressure. Instead, small increases in volume do not cause increases in intragastric pressure until a threshold is reached, after which intragastric pressure rises steeply (Fig. 41-14A). This phenomenon is due to active dilatation of the fundus and has been called gastric accommodation. Vagotomy abolishes a major portion of gastric accommodation, so increases in intragastric volume produce greater increases in intragastric pressure. However, the role of the vagus nerve in gastric...
accommodation is one of modulation. It is generally believed that the enteric nervous system (p. 883) is the primary regulator permitting the storage of substantial amounts of solids and liquids in the proximal part of the stomach without major increases in intragastric pressure.

The Stomach Churns Its Contents Until the Particles Are Small Enough to Be Gradually emptied into the Duodenum

The substance most rapidly emptied by the stomach is isotonic saline or water. Emptying of these liquids occurs without delay and is faster the greater the volume of fluid. Acidic and caloric fluids leave the stomach more slowly, and fatty materials exit even more slowly (see Fig. 41–14B). Solids do not leave the stomach as such, but must first be reduced in size (i.e., mastication). Particles greater than 2 mm in size do not leave the stomach during the immediate postprandial digestive period. The delay in gastric emptying of solids occurs because solids must be reduced in size to less than 2 mm; at that point, they are emptied by mechanisms that are similar to those of liquids.

Movement of solid particles toward the antrum is accomplished by the interaction of propulsive gastric contractions and occlusion of the pylorus, a process termed propulsion (Fig. 41–15A). Gastric contractions are initiated by the gastric pacemaker, which is located on the greater curvature, approximately at the junction of the proximal and middle portions of the stomach. These contractions propel the luminal contents toward the pylorus, which is partially closed by contraction of the pyloric musculature before delivery of the bolus. This increase in pyloric resistance represents the coordinated response of antral, pyloric, and duodenal motor activity. Once a bolus of material is trapped near the antrum, it is churned to help reduce the size of the particles, a process termed grinding (see Fig. 41–15B). Only a small portion of gastric material—that containing particles smaller than 2 mm—is propelled through the pylorus to the duodenum. Thus, most of the gastric contents are returned to the body of the stomach for pulverization and shearing of solid particles, a process known as retropulsion (see Fig. 41–15C). These processes of propulsion, grinding, and retropulsion repeat multiple times until the gastric contents are emptied. Particles larger than 2 mm are initially retained in the stomach but are eventually emptied into the duodenum by MMCs during the interdigestive period that begins approximately 2 hours or more after eating.

Modification of gastric contents is associated with the activation of multiple feedback mechanisms. This feedback usually arises from the duodenum (and beyond) and almost always results in a delay in gastric emptying. Thus, as small squirts of gastric fluid leave the stomach, chemoreceptors and mechanoreceptors—primarily in the proximal but also in the distal portion of the small intestine—sense low pH, a high content of calories, lipid, or some amino acids (i.e., tryptophan), or changes in osmolarity. These signals all decrease the rate of gastric emptying by a combination of neural and hormonal signals, including the vagus nerve, secretin, CCK, and GIP released from duodenal mucosa. Delayed gastric emptying represents: the coordinated function of fundic relaxation; inhibition of antral motor activity; stimulation of isolated, phasic contractions of the pyloric sphincter, and altered intestinal motor activity.

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