Recent milestones in the understanding of gastric acid secretion and treatment of acid-peptic disorders include the (1) discovery of histamine $H_2$-receptors and development of histamine $H_2$-receptor antagonists, (2) identification of $H^+K^+\text{-ATPase}$ as the parietal cell proton pump and development of proton pump inhibitors, and (3) identification of Helicobacter pylori as the major cause of duodenal ulcer and development of effective eradication regimens. This review emphasizes the importance and relevance of gastric acid secretion and its regulation in health and disease. We review the physiology and pathophysiology of acid secretion as well as evidence regarding its inhibition in the management of acid-related clinical conditions.

Is the study of gastric acid now only of historical interest? Many have forgotten the central role acid played in shaping gastroenterology as a specialty. It was in the acid era that our specialty was defined and flourished. Acid was meticulously measured in an attempt to better understand and treat peptic ulcer disease, the major clinical challenge at that time. Fiberoptic endoscopy was developed to better define upper gastrointestinal acid-related mucosal damage. Acid neutralization consumed clinicians. Antacids were dispensed, not by the bottle, but by the case. Neutralizing capacity, taste, sodium content, and adverse effect profile (diarrhea or constipation) of the various antacids were hot issues debated at national meetings because, to adequately control acid, antacids were dosed 1 and 3 hours after meals and at bedtime.\textsuperscript{1} Anticholinergic medications, despite their associated adverse effects, were prescribed before meals and at bedtime to prolong gastric emptying of antacids and to control nocturnal ulcer symptoms.\textsuperscript{2} Gastric freezing and radiation were modalities employed to reduce acid in patients with “medically refractory” symptoms when surgery was not a consideration.\textsuperscript{3} Peptic ulcer surgery was planned based on gastric acid output measurement: high acid secretion generally indicated a more extensive resection. Too much postoperative acid (incomplete vagotomy) meant ulcer recurrence, whereas too little acid (large resection) had nutritional consequences.\textsuperscript{4,5} Milk alkali syndrome, gastric outlet obstruction, and dumping syndrome, complications largely unknown to today’s gastroenterology fellows, were common occurrences.\textsuperscript{6} All this characterized the “BC” (before cimetidine) era of gastroenterology.

Sir James Black’s Nobel Prize winning discovery of $H_2$-receptor antagonists (H2RAs) in 1972 shed new light on acid secretion and changed the practice of gastroenterology forever.\textsuperscript{7} For the first time, acid could be inhibited and ulcers predictably healed. Studies showed that the duration and degree of acid inhibition (percentage of the day $pH >3$) determined ulcer healing, and once daily dosing of H2RAs at bedtime was the most efficient healing regimen.\textsuperscript{8,9} In addition, continuous bedtime administration of the medication could prevent ulcer recurrence, the first step in controlling this chronic condition.

More recently, the identification of hydrogen-potassium-stimulated adenosine triphosphatase ($H^+K^+\text{-ATPase}$) as the proton pump of the parietal cell and Helicobacter pylori (HP) infection as the main cause of gastric and duodenal ulcer (also Nobel Prize winning) heralded a new revolution in our understanding and treatment of acid-peptic disorders.\textsuperscript{10–14} Dosed before mealtime, proton pump inhibitors (PPIs) are the most effective acid inhibitors currently available and are the most widely prescribed class of gastrointestinal medications. Not only can peptic ulcers be healed more rapidly with PPIs, but refractory ulcers have all but disappeared. Eradication of HP with antibiotics, offered, for the first time, a permanent cure for most ulcers.
As the prevalence of HP infection has declined, because of improved sanitation and efforts to eradicate the organism, the prevalence of nonsteroidal anti-inflammatory drug (NSAID)-induced ulcers and HP-negative/NSAID-negative ulcers has risen and is taking on greater clinical importance. Schwarz’s dictum “no acid, no ulcer” remains valid, even today.\(^{15}\) Acid control remains the mainstay for the treatment and prevention of ulcers caused by NSAIDs, gastrinoma (Zollinger–Ellison syndrome [ZES]), and stress as well as HP-negative/NSAID-negative idiopathic ulcers.\(^ {16,17}\)

The era of effective management of ulcers has ushered in a new acid-related challenge, gastroesophageal reflux disease (GERD). Until recently, the clinical importance of reflux had been largely underappreciated because peptic ulcers were so prominent. As with ulcers, the duration and degree of acid inhibition were shown to correlate with healing of erosive esophagitis and control of reflux symptoms.\(^ {18}\) However, a greater degree and duration of 24-hour acid inhibition were required to effectively manage GERD than H2RAs could provide. Although H2RAs could improve the condition, they could not predictably heal esophagitis (especially severe grades) or eliminate symptoms. It was this clinical niche for which the PPIs were ideally suited. PPIs can predictably heal esophagitis, no matter how severe, and prevent recurrence.\(^ {19,20}\) Although currently available PPIs can eliminate most reflux symptoms, better therapies are needed to eliminate nighttime reflux symptoms in patients with endoscopic-negative reflux disease, and alleged extragastric manifestations of GERD such as cough and asthma.\(^ {21–23}\)

The purpose of this review is to reemphasize the importance and relevance of gastric acid secretion and its regulation. We will review the physiology and pathophysiology of acid secretion as well as evidence regarding its inhibition in the management of acid-related clinical conditions. As we reexamine and update this area, we hope to rekindle the excitement surrounding acid that was at the roots of gastroenterology and provide information relevant to the future care of patients with acid-peptic disorders.

**Functional Anatomy of the Stomach**

**Mucosal Anatomy**

The stomach consists of 3 topographic (fundus, corpus, and antrum) and 2 functional (oxyntic and pyloric gland) areas. The oxyntic gland area, the hallmark of which is the oxyntic (\(\text{oxys}\), Greek for acid) or parietal cell, comprises 80% of the organ (fundus and corpus). The pyloric gland area, the hallmark of which is the gastrin or G cell, comprises 20% of the organ (antrum). It is estimated that the human stomach contains $1 \times 10^9$ parietal and $9 \times 10^6$ gastrin cells.\(^ {24}\) There is debate as to whether the cardia, a transition zone of 0–9 mm between the squamous mucosa of the esophagus and the oxyntic mucosa of the stomach, exists as a normal anatomic structure or develops as a result of abnormal reflux. Autopsy and endoscopic studies suggest that cardiac mucosa is absent in over 50% of the general population.\(^ {25}\)

The oxyntic gland area is organized in vertical tubular units that consist of an apical pit region, an isthmus, and the actual gland region that forms the lower part of the unit (Figure 1). The gland consists of a neck and a base. The progenitor cell of the gastric unit, located in the isthmus, gives rise to all gastric epithelial cells. The mu-

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**Figure 1.** Functional mucosal anatomy. Somatostatin-containing D cells contain cytoplasmic processes that terminate in the vicinity of acid-secreting parietal and histamine-secreting enterochromaffin-like cells in the oxyntic gland area (fundus and corpus) and gastrin-secreting G cells in the pyloric gland area (antrum). The functional correlate of this anatomic coupling is a tonic paracrine restraint exerted by somatostatin on acid secretion that is exerted directly on the parietal cell as well as indirectly by inhibiting histamine and gastrin secretion.
cus-producing pit cells migrate upward from the progenitor cell toward the gastric lumen. Acid-secreting parietal cells migrate downward to the middle and lower regions of the gland. As parietal cells descend to the deeper regions, they become less active acid producers.26 The turnover time for parietal cells is 54 days in mouse and 164 days in rat.24 In rat and human, zymogenic (chief) cells predominate at the base of the glands and secrete pepsinogen and leptin22; the latter is also present in parietal cells.28 Neuroendocrine cells containing a host of potential hormonal and paracrine signaling agents are contained within the gland, only some of which have been assigned physiologic functions: (1) enterochromaffin (EC) cells contain atrial natriuretic peptide (ANP), serotonin, and adrenomedullin29,30; (2) enterochromaffin-like (ECL) cells contain histamine31,32; (3) D cells contain somatostatin and amylin33,34; and (4) A-like or Gr cells contain ghrelin and obestatin.35,36 Neuroendocrine cells comprise 2% of epithelial cells in rat and 1% in human.32 ECL cells constitute 66% of the neuroendocrine cell population in rat and 30% in human. Somatostatin-containing D cells possess cytoplasmic processes that terminate in the vicinity of parietal and ECL cells. The functional correlate of this anatomic coupling in rat, dog, and human oxyntic mucosa is a tonic paracrine restraint exerted by somatostatin on acid secretion directly as well as indirectly by inhibiting histamine secretion37–39 (Figure 1).

Somatostatin-containing D cells are also present in the pyloric gland area; in this region, they exert a tonic paracrine restraint on gastrin secretion from G cells30,41 (Figure 1). The pyloric gland also contains EC cells (ANP and serotonin), A-like or Gr cells (ghrelin and obestatin), and endocrine cells containing orexin.30,42,43

**Neural Anatomy**

The stomach is innervated by a neural network, the enteric nervous system (ENS), that contains intrinsic neurons and processes of extrinsic efferent and afferent neurons. The ENS, the third division of the autonomic nervous system (the other 2 being the sympathetic and parasympathetic), is often referred to as the “little brain” because it contains as many neurons as the spinal cord, \( \sim 10^8 \), and can function autonomous of central input.44 In rat and guinea pig, most of the intrinsic neural innervation of the stomach originates in the myenteric plexus, located between the circular and longitudinal muscle layers; the submucosal plexus, adjacent to the mucosal layer, contains only a small number of neurons. Humans, in contrast, have a clearly defined submucosal plexus. It should be noted that the vagus nerve contains 80%–90% afferent fibers and only 10%–20% efferent fibers. The efferent fibers are preganglionic and do not directly innervate parietal or neuroendocrine cells but rather synapse with postganglionic neurons of the ENS (Figure 2). The postganglionic neurons contain a variety of transmitters including acetylcholine (ACh), gastrin-releasing peptide (GRP), vasoactive intestinal polypeptide (VIP), pituitary adenylate-cyclase-activating polypeptide (PACAP), nitric oxide, and substance P.45 In rat and human stomach, nerve fibers containing calcitonin gene-related peptide (CGRP) are of extrinsic origin, ie, the cell bodies are located outside the stomach wall.46 Postganglionic neurons of the ENS regulate acid secretion directly as the case for Ach, and/or indirectly by modulating the secretion of gastrin from G cells, somatostatin from D cells, histamine from enterochromaffin-like (ECL) cells, and atrial natriuretic peptide from enterochromaffin (EC) cells.

**Gastric Acid Secretion: Neural, Hormonal, Paracrine, and Intracellular Regulation**

Parietal cells secrete hydrochloric acid at a concentration of approximately 160 mmol/L or pH 0.8. Acid is thought to gain access to the lumen via channels in the mucus layer created by the relatively high intraglandular hydrostatic pressures generated during secretion, approximately 17 mm Hg.47 Most studies indicate that the rate of acid secretion by the human stomach changes little with
The principal stimulants of acid secretion are (1) histamine (paracrine), gastrin (hormonal), and acetylcholine (ACH; neurocrine). Histamine, released from enterochromaffin-like (ECL) cells, binds to H2 receptors that activate adenylate cyclase (AC) and generate cAMP. Gastrin, released from G cells, binds to CCK2 receptors that activate phospholipase C to induce release of cytosolic calcium (Ca++) . Gastrin stimulates the parietal cell directly and, more importantly, indirectly by releasing histamine from ECL cells. ACh, released from intramural neurons, bind to M3 receptors that are coupled to an increase in intracellular calcium. The intracellular cAMP- and calcium-dependent signaling systems activate downstream protein kinases ultimately leading to fusion and activation of H+K+-ATPase, the proton pump.

Histamine
Histamine, produced in ECL cells by decarboxylation of L-histidine by histidine decarboxylase (HDC), stimulates the parietal cell directly by binding to H2 receptors coupled to activation of adenylate cyclase and generation of adenosine 3’,5’-cyclic monophosphate (cAMP). Histamine also stimulates acid secretion indirectly by binding to H3 receptors coupled to inhibition of somatostatin and thus stimulation of histamine and acid secretion (Figure 4). Gastrin, PACAP, VIP, and ghrelin stimulate, whereas somatostatin, CGRP, prostatlandins, peptide YY (PYY), and galanin inhibit histamine secretion. ACh has no direct effect on histamine secretion.

Gastrin
Gastrin, the main stimulant of acid secretion during meal ingestion, is produced in G cells of the gastric antrum and, in much lower and variable amounts, in the proximal small intestine, colon, and pancreas. Gastrin is synthesized as a large precursor molecule of 101 amino acids, which is processed to yield the glycine-extended peptides G34gly and G17gly , which, in turn, are amidated to yield G34amide and G17amide. In human antrum, the concentration of amidated gastrin is approximately 5-fold greater than that of glycine-extended gastrin, whereas in the circulation there are approximately equal concentrations of amidated and glycine-extended gastrins. The half-life of G17 in the plasma of pigs is approximately 3.5 minutes; it is metabolized primarily by the kidney and, in addition, the intestine and liver. In patients with renal insufficiency, fasting blood levels of G17, G34, and Gly-gastrin are elevated. It should be noted that the commercially available test substance pentagastrin (Peptavlon) is not a naturally occurring peptide but rather is a manufactured analogue that contains the biologically active C-terminus sequence Trp-Met-Asp-Phe-NH2.

Gastrin and cholecystokinin (CCK) possess an identical carboxyl-terminal pentapeptide sequence (-Gly-Trp-Met-Asp-Phe-NH2). Two main classes of gastrin/CCK receptors have been characterized: CCK1 (formerly CCK-A) and CCK2 (formerly CCKB or CCKB/gastrin). CCK1 receptors are specific for CCK, whereas CCK2 receptors recognize both CCK and gastrin with high affinity. CCK2 receptors have been identified on human parietal and ECL cells where they are coupled to activation of phospholipase C and release of intracellular calcium. There is debate as to whether activation of the parietal cell CCK2 receptor leads to acid secretion. It seems that intracellular concentrations of cAMP must first be above a threshold before gastrin can directly stimulate the parietal cell. It is thought that the primary action on the parietal cell as well as indirectly by modulating the secretion of neuroendocrine cells.

![Figure 3. Model illustrating parietal cell receptors and transduction pathways.](image-url)
of gastrin on the parietal cell may be to sensitize it to other secretagogues through cross talk/synergistic interaction between the signaling pathways. Activation of the CCK2 receptor on the ECL cell with release of histamine is presently thought to be the main pathway by which gastrin stimulates acid secretion (Figures 3 and 4).67,68

Gastrin regulates the secretion and synthesis of histamine in a biphasic manner. The first phase involves release of stored histamine. The second phase relates to the replenishment of histamine stores and involves an increase in HDC activity followed by an increase in HDC gene transcription.72 H2 receptor, HDC, and CCK2 receptor knockout mice manifest decreased acid secretion, especially in response to gastrin.73–75

ACh, GRP, secretin, β2/β3-adrenergic agonists, calcium, aromatic amino acids, and alcoholic beverages produced by fermentation stimulate, whereas somatostatin, galanin, and adenosine inhibit gastrin secretion. In addition, at least 2 negative feedback pathways, mediated via release of somatostatin, regulate gastrin secretion. The first is activated by luminal acidity and, in rats, involves sensory CGRP neurons (Figure 4). Low intragastric pH (high intragastric acidity) activates CGRP neurons that, via an axon reflex, stimulate somatostatin and thus inhibit gastrin secretion.76–78 Conversely, when intragastric pH rises (low intragastric acidity), for example, by anti-secretory medications such as PPIs or gastric atrophy, somatostatin secretion is inhibited, and patients develop hypergastrinemia. There is some evidence, in mouse, that bacterial overgrowth induced by hypochlorhydria may also contribute to hypergastrinemia.79 The second negative feedback pathway involves a paracrine pathway whereby gastrin directly stimulates somatostatin and thus attenuates its own secretion (Figure 4).80

Gastrin is also a trophic hormone. CCK2 receptors have been localized to the progenitor zone in oxyntic glands, and chronic hypergastrinemia induces proliferation of ECL and parietal cells directly as well as indirectly via the autocrine or paracrine action of growth factors such as heparin-binding epidermal growth factor, amphiregulin, transforming growth factor-α, metalloproteinases, and regenerating islet-derived 1.81,82 Rats rendered hypergastrinemic with a PPI demonstrate a 5-fold increase in the number of ECL cells and a 1.5-fold increase in the number of parietal cells.83 Gastrin acts directly on ECL cells to induce hyperplasia, dysplasia, and eventually neoplasia (carcinoids).84 In contrast to rodents, humans rarely develop carcinoid tumors in response to hypergastrinemia.

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**Figure 4.** Model illustrating the neural, paracrine, and hormonal regulation of gastric acid secretion. Efferent vagal fibers synapse with intramural gastric cholinergic (ACh) and peptidergic (gastrin-releasing peptide [GRP], vasoactive intestinal peptide [VIP], and pituitary adenylate-cyclase activating peptide [PACAP]) neurons. In the fundus (oxyntic mucosa), ACh neurons stimulate acid secretion directly via M3 receptors on the parietal cell and indirectly by inhibiting somatostatin (SST) secretion, thus eliminating its restraint on parietal cells and histamine-containing enterochromaffin-like (ECL) cells. In the antrum (pyloric mucosa), ACh neurons stimulate gastrin secretion directly and indirectly by inhibiting SST secretion, the latter by a direct effect on the D cell and an indirect effect mediated by inhibition of atrial natriuretic peptide (ANP) secretion from enterochromaffin (EC) cells. GRP neurons, activated by intraluminal protein, also stimulate gastrin secretion. VIP neurons, activated by low-grade distension, stimulate SST and thus inhibit gastrin secretion. PACAP neurons stimulate SST, via release of ANP, and thus also inhibit gastrin secretion. Dual paracrine pathways link SST-containing D cells to parietal cells and to ECL cells in the fundus. Histamine released from ECL cells acts via H2 receptors to inhibit SST secretion. This serves to accentuate the decrease in SST secretion induced by cholinergic stimuli and thus augments acid secretion. In the antrum, dual paracrine pathways link SST-containing D cells to gastrin cells and to EC cells. Release of acid into the lumen of the stomach restores SST secretion in both the fundus and antrum; the latter is mediated via release of calcitonin gene-related peptide (CGRP) from extrinsic sensory neurons. Acute infection with HP also activates CGRP neurons to stimulate SST and thus inhibit gastrin secretion. In duodenal ulcer patients chronically infected with HP, the organism or cytokines released from the inflammatory infiltrate inhibit SST and thus stimulate gastric (and acid) secretion.
unless other factors are present such as chronic atrophic gastritis or gastrinoma associated with multiple endocrine neoplasia type 1 (MEN-1). In the latter, carcinoids occur in 13% to 43%. Because ECL cells contain somatostatin subtype 2 receptors, somatostatin scintigraphy with \[^{111}\text{In}-\text{DTPA}\]octreotide is the preferred imaging method to detect carcinoid tumors with an overall sensitivity of 80% to 100%.86,87

**ACh**

Muscarinic receptors on parietal cells are of the M3 subtype. Like CCK2 receptors, M3 receptors are coupled to activation of phospholipase C with generation of inositol trisphosphate and release of intracellular calcium (Figure 3). Alcoholic beverages produced by fermentation stimulate gastric acid secretion, and the effect may be mediated via activation of M3 receptors. ACh also stimulates acid secretion indirectly by activating M2 and M4 receptors on D cells coupled to inhibition of somatostatin secretion, thus removing the tonic restraint exerted by this peptide on gastrin, ECL, and parietal cells (Figure 4).

**Somatostatin**

The main inhibitor of acid secretion is somatostatin. Somatostatin is synthesized from a 92-amino acid preprosomatostatin precursor molecule that is processed to yield somatostatin-14 and somatostatin-28. Somatostatin-14 is predominantly found in stomach, pancreatic islets, and enteric neurons, whereas somatostatin-28 is the major form in the small intestine.

In stomach, somatostatin cells are closely coupled to their target cells (eg, parietal, ECL, and gastrin cells) either directly via cytoplasmic processes or indirectly via the local circulation. In rat, dog, and human, the functional correlate of this anatomic coupling is a tonic restraint exerted by somatostatin on acid secretion from the parietal cell, histamine secretion from the ECL cell, and gastrin secretion from the G cell. Removing this restraint (ie, disinhibition or elimination of the influence of an inhibitor), by activation of cholinergic neurons, is an important physiologic mechanism for stimulating acid secretion. In the stomach, the actions of somatostatin are thought to be mediated via the somatostatin subtype 2 receptors. Gastrin, GRP, VIP, PACAP, \(\beta_2/\beta_3\)-adrenergic agonists, secretin, ANP, adrenomedullin, amylin, adenosine, and CGRP stimulate, whereas ACh and interferon-\(\gamma\) inhibit somatostatin secretion. As mentioned above, an increase in luminal acidity acts to attenuate acid secretion via a pathway involving release of somatostatin in both antrum and fundus. In mouse, the change in somatostatin secretion is encompassed by luminal acidity in the range of pH 3 to pH 5, which is within the range observed after ingestion of a meal.96

**Miscellaneous Substances**

Most studies report that ghrelin stimulates acid secretion, although one study reported no effect on basal secretion and a decrease in pentagastrin-stimulated acid secretion in awake rats equipped with a gastric fistula.97,98 The stimulatory effect of ghrelin appears to involve the vagus nerve and histamine release because the stimulatory effect is abolished by vagotomy and is associated with an increase in HDC messenger RNA.99,100 ANP, CCK, secretin, glucagon-like peptide, peptide YY, adrenomedullin, amylin, neurotensin, glucose-dependent insulinotropic polypeptide, leptin, and epidermal growth factor stimulate somatostatin and thus inhibit acid secretion.29,30,33,101 CCK may function as a physiologic enterogastrone, ie, an intestinal factor responsible for the inhibition of acid secretion induced by the presence of nutrients in the intestine.102,103 Interleukin-1\(\beta\) and serotonin inhibit acid secretion.104,105

**\(H^+K^+\text{-ATPase}\)**

Parietal cell secretion is increased by activation of intracellular cAMP- and calcium-dependent signaling pathways that activate downstream protein kinases, ultimately leading to fusion and activation of \(H^+K^+\text{-ATPase}\), the proton pump (Figure 3). This enzyme, which consists of 2 subunits, catalyzes the electroneutral exchange of luminal \(K^+\) for cytoplasmic \(H^+\). The \(\alpha\)-subunit carries out the catalytic and transport functions of the enzyme and also contains sequences responsible for apical membrane localization.106 The \(\beta\)-subunit, which is heavily glycosylated, protects the enzyme from degradation and is necessary for trafficking to and from the plasma membrane.107

In the resting unstimulated state, \(H^+K^+\text{-ATPase}\) activity is contained predominantly within cytoplasmic tubulovesicles. Upon stimulation, these vesicles fuse with the apical plasma membrane, resulting in extensive infoldings. Upon cessation of secretion, the \(H^+K^+\text{-ATPase}\) is retrieved from the apical membrane, and the tubulovesicular compartment is reestablished. The precise mechanism regulating trafficking are not known, but data suggest that it involves actin-based microfilaments, small GTPases, docking/fusion proteins, cytoskeletal linkers, and clathrin.108–110

Current PPIs (eg, omeprazole) consist of 2 heterocyclic moieties, a pyridine and a benzimidazole ring, connected by a methylsulfinyl group. They are weak bases (pKa 4–5) that are membrane permeable in the nonprotonated form and relatively impermeable in the protonated form. As a result, they accumulate in acidic spaces with a pH <4. The pKa of a molecule, which is based on a logarithmic scale, refers to the degree of willingness of the compound to accept or donate a proton. When a compound is in an environment with a pH equal to its pKa, half the molecules will be protonated, and half will be nonprotonated. In blood (pH 7.4), PPIs are essentially nonproto-
nated and thus pass readily into and through cells (time to reach peak plasma concentration, ~2 hours; elimination half-life, ~1 hour). However, when they enter the secretory canalculus of the parietal cell (pH <1), >99.9% of the PPI becomes protonated and trapped.111 PPIs then undergo an acid-catalyzed chemical rearrangement, probably to a sulfenamide or sulfenic acid, that permits them to inhibit H+K+-ATPase by forming covalent disulfide bonds with cysteine residues on the luminally exposed α-subunit of the H+K+-ATPase.112 Whereas all PPIs bind to cysteine 813, omeprazole also binds to cysteine 892, lansoprazole to cysteine 321, and pantoprazole to cysteine 822. Because only the inserted H+K+-ATPase is susceptible to blockade by PPIs and an acid environment (pH <4) is necessary for both trapping and activating the PPI, the potency of PPIs is decreased when they are administered during the basal state or when acid secretion is inhibited.113,114 Because most pumps are inserted with breakfast, it is recommended that PPIs be taken a half hour to 1 hour before the first meal. If greater inhibition is needed, an additional dose should be taken before dinner. Seventy percent of primary care physicians and 20% of gastroenterologists prescribe PPIs suboptimally, either at bedtime or unrelated to food intake; this is the most common cause of PPI failure.115

Autoimmune gastritis is an inflammatory disorder of the oxyntic mucosa often associated with antiparietal cell autoantibodies directed against H+K+-ATPase with subsequent loss of parietal cells.116 H+K+-ATPase is a major autoantigen in a subset of patients infected with HP, and these antibodies may play a role in the subsequent development of atrophic gastritis. It is postulated that antibodies are acquired due to molecular mimicry between HP lipopolysaccharide and H+K+-ATPase, both of which contain Lewis epitopes.117 Interestingly, a proportion of patients with duodenal ulcer, approximately 20%, also have antiparietal cell antibodies. These patients have more severe body gastritis, higher gastrin levels, and decreased peak acid outputs compared with patients with duodenal ulcer without antibodies.118

**Apical Channels**

Proton secretion occurs in the parietal cell by exchanging H+ for K+ via the H+K+-ATPase. This is coupled with extrusion of Cl− via an apical chloride channel and K+ via an apical potassium channel. Parietal cell proton secretion is impaired by (1) knockout of KCN2, a gene that encodes single transmembrane domain subunits that regulate the function of voltage-gated potassium channels,119 and (2) inhibition of cystic fibrosis transmembrane conductance regulator, a cAMP-regulated chloride channel present in parietal cells.120 These channels may provide targets for the development of novel antisecretory drugs. For example, AZD0865 [8-[2,6-dimethylbenzyl]amino]-N-(2-hydroxyethyl)-2,3-dimethylimidazo[1,2-α]pyridine-(6-carboxamide), a drug that inhibits H+K+-ATPase by potassium-competitive binding at or near the potassium binding site of the enzyme, may have a more rapid onset and longer duration of effect than PPIs and effectively heals esophagitis.121

**Integrated Response to a Meal: Interplay of Neural, Paracrine, and Hormonal Mechanisms**

Stimuli originating inside and outside the stomach converge on gastric effenter neurons that are the primary regulators of acid secretion. The effector neurons comprise cholinergic neurons and 3 types of noncholinergic neurons: GRP, VIP, and PACAP neurons. The neurons act on target cells directly as well as indirectly by regulating release of gastrin, histamine, somatostatin, and ANP (Figures 2 and 4).

During the basal state, acid secretion is maintained at an economically low level by the continuous inhibitory restraint exerted by somatostatin on the G cell (gastrin) in the antrum and on the ECL (histamine) and parietal cell (acid) in the fundus/body. During meal ingestion, maximal secretion may be achieved by removing the inhibitory influence of somatostatin while at the same time directly stimulating acid and gastrin secretion. This is accomplished, in large part, by activation of cholinergic neurons (Figure 4). Anticipation of a meal activates central neurons whose input is relayed via the vagus nerve to gastric intramural cholinergic neurons. In the fundus/body, ACh, released from cholinergic neurons, stimulates the parietal cell directly, as well as indirectly, by eliminating the inhibitory paracrine influence of somatostatin on parietal and ECL cells.53,122 The resultant increase in histamine stimulates acid secretion directly via H2 receptors on the parietal cell and indirectly via H3 receptors that mediate suppression of somatostatin secretion (Figure 4).53,123 Thus, histamine, acting via H3 receptors, amplifies the ability of secretagogues to stimulate acid secretion by suppressing somatostatin secretion. The net effect of cholinergic neurons is suppression of all paracrine inhibitory influence (ie, somatostatin) and enhancement of paracrine stimulatory influences (ie, histamine acting via H2 receptors) on parietal cells. There is some evidence that PACAP, a member of the glucagon/VIP superfamily of regulatory peptides, may participate in the regulation of acid secretion, but its precise physiologic role in this region of the stomach is uncertain.30,124,125 PACAP is present in gastric mucosal nerves and is capable of releasing histamine from ECL cells and somatostatin from D cells. The net effect of exogenous PACAP on acid secretion has been reported to be either stimulation or inhibition, depending on the relative contributions of released histamine and somatostatin in each preparation.124,126,127

In antrum, cholinergic neurons stimulate gastrin secretion directly as well as indirectly by suppressing somatostatin secretion (Figure 4).37,38,41,128-139 This is accomplished by a direct inhibitory effect of ACh on somatostatin secretion.
as well as an indirect inhibitory effect mediated by suppression of ANP secretion (Figure 4). In physiologic concentrations, gastrin stimulates parietal cells indirectly by enhancing histamine secretion. In addition, protein activates GRP neurons that stimulate gastrin secretion directly (Figure 4).

As the meal empties the stomach, a number of paracrine and neural pathways are activated to restore the inhibitory influence of somatostatin in the fundus/body and antrum and hence restrain acid secretion (Figure 4). First, a stimulatory paracrine pathway linking gastrin to antral somatostatin cells is activated that acts to restore antral somatostatin secretion after release of gastrin. Second, there is less activation of cholinergic neurons by anticipation of the meal as well as by protein and distention. Third, as distention decreases, VIP neurons are preferentially activated that stimulate somatostatin secretion. Fourth, as the buffering capacity of the meal is lost, antral and fundic/body somatostatin cells are exposed to the full stimulatory effect of luminal acid. Fifth, amylase, released from D cells, stimulates somatostatin secretion. The resultant increase in antral and fundic somatostatin secretion attenuates gastrin and acid secretion and eventually restores the basal interdigestive state. This state is marked by the continuous restraint exerted on G (gastrin), ECL (histamine), and parietal cells (acid) by contiguous somatostatin cells. A decrease in this restraint is sufficient to again initiate acid secretion.

**Perturbations in Acid Secretion Induced by HP**

HP colonizes half the world’s population and is a cause of acute gastritis, chronic gastritis, and gastroduodenal ulceration. Acute infection results in hypochlorhydria, whereas chronic infection results in either hypo- or hyperchlorhydria (Figure 5). Appreciation of the pathways discussed above provides some insight into the mechanisms whereby HP infection may lead to ulceration. Acute infection with HP is associated with hypochlorhydria. The decrease in acid secretion is thought to facilitate survival of the organism and colonization of the stomach. The mechanism whereby HP inhibits acid secretion is multifactorial and includes (1) direct inhibition of the parietal cell (and perhaps ECL cell) by a constituent of the bug (e.g., vacuolating cytotoxin, lipopolysaccharide, or acid-inhibitory factor) and (2) indirect inhibition of parietal cell function as a result of changes in cytokines as well as hormonal, paracrine, and neural regulatory mechanisms. HP itself inhibits human H-K-ATPase α-subunit gene expression. It also elicits secretion of at least 2 cytokines, interleukin 1β and tumor necrosis factor-α, that directly inhibit parietal cell secretion. In preliminary studies, we have shown that HP activates CGRP sensory neurons coupled to stimulation of somatostatin and thus inhibition of gastrin, histamine, and acid secretion.

Chronic infection with HP may be associated with either decreased or increased acid secretion, depending on the severity and distribution of gastritis (Figure 5). Most patients chronically infected with HP manifest a pan gastritis and produce less than normal amounts of acid. Reduced acid secretion, at the onset, is thought to be due to functional inhibition of parietal cells by either products of HP itself or, more likely, products of the inflammatory process, as discussed above for acute infection; this is usually reversible upon eradication of the bug. In such patients, HP may be protective against GERD, Barrett’s esophagus, and esophageal adenocarcinoma as well as augment the antisecretory effect of PPIs. Conversely, rebound acid hypersecretion...
occurs in HP-eradicated patients when PPIs are discontinued, and this may unleash or exacerbate GERD, particularly in patients with large hiatal hernias.\textsuperscript{163,164} Acid hypersecretion lasts at least 8 weeks and is due to hypergastrinemia-induced increases in parietal and ECL cell masses.\textsuperscript{165} With time, atrophy of oxyntic glands with loss of parietal cells may occur, resulting in irreversible achlorhydria.

Approximately 10% to 15% of patients chronically infected with HP have antral predominant inflammation. These patients, who are predisposed to duodenal ulcer, produce increased amounts of acid as a result of reduced antral somatostatin content and elevated basal and stimulated gastrin secretion (Figure 5).\textsuperscript{166–168} The mechanism by which somatostatin secretion is decreased is not known but may involve cytokines induced by the inflammation and/or the production of $\alpha$-methyl histamine, a selective $H_3$-receptor agonist, by HP.\textsuperscript{169,170} One may speculate that the $H_3$-receptor agonist could diffuse across the antral mucosa to interact with $H_3$ receptors on antral somatostatin cells, causing inhibition of somatostatin secretion, and, thus, stimulation of gastrin secretion.\textsuperscript{54} Gastrin, in turn, stimulates histamine secretion from ECL cells leading to enhanced acid secretion. Both interleukin-8 and platelet-activating factor are up-regulated in HP-infected mucosa and are capable of stimulating gastrin release from isolated rabbit and canine G cells.\textsuperscript{171,172}

**Duodenal Ulcer**

Duodenal ulcer patients, as a group, have increased basal and stimulated acid production. Consequently, acid control has always been central to the management. Antacids were the first therapeutic approach used, but, to neutralize luminal acid adequately, they had to be dosed frequently leading to noncompliance and adverse effects.\textsuperscript{173,174} Anticholinergic medications were used to delay gastric emptying and thus prolong the local effect of antacids.\textsuperscript{173} These compounds, however, were nonselective in their antimuscarinic actions and caused gastrointestinal, urinary, central nervous system, and visual adverse effects. Potentially more selective antimuscarinics such as pirenzipine with greater $M_1$ selectivity and less nonspecific adverse effects were used in Europe but were never commercially available in the United States.\textsuperscript{175}

Although antacids with high neutralizing capacity given 1 and 3 hours after meals and at bedtime could accelerate ulcer healing, pain was not relieved any better by such a regimen than by placebo.\textsuperscript{176} Because ulcer disease could not be cured by antacids, recurrence and complications were common. These issues were addressed with surgery, the goal of which was to reduce acid secretion. The least extensive surgery involved performing a vagotomy to denervate the acid-producing area of the stomach along with a “drainage procedure,” either pyloroplasty or gastroenterostomy. More extensive ulcer surgery involved combining vagotomy with antrectomy, the latter to remove gastrin, the main hormonal stimulant of acid secretion.\textsuperscript{177} The most extensive surgical approach was subtotal gastric resection. Sometimes patients underwent preoperative acid secretory testing, and, if high levels of acid were documented, more extensive resective surgery was done. In fact, the success of surgical “cure” of duodenal ulcer was generally thought to be related to completeness of vagotomy and extent of gastric resection.\textsuperscript{173,178} Unfortunately, surgery proved not to be definitive (1%–10% recurrence rate) and produced its own set of problems including gastric stasis, nutritional deficiencies, altered bowel function, bile reflux gastritis and esophagitis, and gastric remnant cancer.

The development of cimetidine, the first H2RA, ushered in a new era of ulcer management.\textsuperscript{179} Pills, for the first time, could improve ulcer healing at least as well as cumbersome antacids. HRAs blocked both histamine-driven acid secretion and that elicited by gastrin, whose action is mediated primarily by release of histamine from ECL cells.\textsuperscript{180,181} H2RAs were initially dosed 4 times daily, later twice daily, and eventually once daily. The fact that ulcers would heal quickly, even with once daily bedtime administration, drew attention to the importance of nighttime acid in the pathogenesis of duodenal ulcer.\textsuperscript{9} Studies suggested that ulcer healing was related to nocturnal acid control—maintaining intragastric pH $>3$, a pharmacologic endpoint easily and predictably achieved by H2RAs.\textsuperscript{8} In addition to healing duodenal ulcer, it became clear that continuous daily bedtime dosing of H2RAs could prevent ulcer recurrence.\textsuperscript{182} Healing an ulcer with 8 weeks of “full dose” followed by indefinite treatment with “half dose” H2RA dosed at bedtime became the new gold standard for duodenal ulcer management. Elective acid-reducing surgery became less common. However, patient compliance with long-term acid suppressive medication, especially when symptoms no longer prompted dosing, was on occasion suboptimal and resulted in ulcer recurrence and complications, although to a far lesser degree that seen in the “BC” (before cimetidine) era. It was these patients who were referred for acid reducing surgery, mainly highly selective “parietal cell” vagotomy.\textsuperscript{183,184}

Management of acid disorders was revolutionized when PPIs became available.\textsuperscript{185,186} Because PPIs directly inhibit the acid pump, they are capable of reducing basal and stimulated acid secretion independent of stimulus. They are much more effective in controlling intragastric pH than H2RAs and have been shown to be more effective in healing duodenal ulcer and preventing recurrence.\textsuperscript{187}

It is now recognized that most cases of duodenal ulcer are due to infection with HP, and HP is responsible for the perturbations in acid secretion observed in duodenal ulcer patients. Pentagastrin-stimulated peak acid output, an indicator of functional parietal cell mass, is increased
in HP-infected duodenal ulcer patients as is GRP-stimulated peak acid output, an indicator of the stomach’s functional response to endogenous gastrin.\textsuperscript{168,188,189} It is thought that suppression of somatostatin secretion by the infection may be the root cause for these changes (Figures 4 and 5). Eradication of HP restores somatostatin as well as basal and stimulated gastrin and acid secretion, over time, to normal in most individuals, thus providing a permanent cure for duodenal ulcer disease.\textsuperscript{167,168,189–192}

**Gastric Ulcer**

In contrast to duodenal ulcer, gastric ulcer patients, as a group, exhibit normal or decreased basal and stimulated acid production. This suggests that altered gastric mucosal defense may be the primary culprit and may explain the propensity for NSAID-induced ulcer to occur in the stomach. Gastric ulcers have been classified according to their location and concomitant association with duodenal ulcer.\textsuperscript{193} Type I ulcers occur in the gastric body and are generally characterized by low acid secretion, particularly at night. These findings may reflect a greater degree and more generalized mucosal inflammation of the oxyntic mucosa with reduced functional parietal cell mass. Type II ulcers occur in the antrum and are characterized by low, normal, or high acid secretion. Type III ulcers occur within 3 cm of the pylorus, commonly accompany duodenal ulcer, and are characterized by high acid output. Type IV ulcers occur in the gastric cardia and are characterized by low acid secretion.\textsuperscript{194} Thus, it appears that the more distant a gastric ulcer is from the pylorus the more likely acid secretion will be low. This concept formed the basis of gastric ulcer surgery whereby distal ulcers were traditionally managed by resection/drainage and vagotomy, whereas more proximal lesions were treated by resection alone.\textsuperscript{4,195}

Medical therapy for gastric ulcer involves both removing the injurious agent (eg, NSAIDs or HP) and inhibiting acid secretion.\textsuperscript{187,196,197} Healing correlates with duration of acid inhibitory therapy rather than degree of acid suppression during the day or night.\textsuperscript{198} Thus, despite lower acid profiles in the setting of gastric ulcer, H2RAs and PPIs are often prescribed for longer periods of time (8–12 weeks) and at higher doses (generally double dose) than for duodenal ulcer to ensure healing.\textsuperscript{187} Unlike duodenal ulcer, gastric ulcers may be malignant, especially in the setting of HP and achlorhydria. Thus, gastric ulcers should be biopsied and healing documented. Recurrence can be prevented by avoiding NSAIDs, eradicating HP, and/or maintenance antisecretory therapy. As previously discussed, acid secretion may increase after elimination of HP.\textsuperscript{160}

“Stress ulcers” are most commonly located in the proximal stomach, occur in the setting of critical illness and multiple organ failure, and are thought to result from mucosal ischemia and altered mucosal defense.\textsuperscript{199} The latter is central to the pathogenesis of stress ulcer, so it will be discussed more fully in a subsequent review of mucosal defense. Despite the fact that acid secretion is variable, antisecretory medications, by improving the imbalance between aggressive and defensive factors, prevent stress ulcers and the complication of bleeding.\textsuperscript{199–202}

**GERD**

With the decreasing prevalence of ulcer disease, GERD has emerged as the most important acid-related disorder.\textsuperscript{203,204} Because its pathogenesis involves acid in the wrong place, rather than too much acid, treatments have included elevation of the head of the bed, foaming agents, medications to enhance lower esophageal sphincter pressure, and antireflux surgery; unfortunately, all but surgery are often ineffective.\textsuperscript{205} Consequently, medical treatment of GERD has focused on acid inhibition, specifically maintaining pH >4 in the esophagus for as much of the day and especially the night as possible.\textsuperscript{18,206} This goal is best achieved with PPIs because antacids have a short duration of action, and chronic use of H2RAs leads to tachyphylaxis.\textsuperscript{207}

PPIs are superior to H2RAs for treating heartburn and healing erosive esophagitis.\textsuperscript{21,208,209} More severe grades of erosive esophagitis, Los Angeles grades C and D, are more difficult to heal and may require longer treatment duration and higher doses of PPIs.\textsuperscript{21,210} Such a dose response for symptom control is less evident, especially in nonerosive reflux disease.\textsuperscript{211,212} Furthermore, extending duration of therapy or increasing the dose in “non-responders” will not necessarily improve treatment efficacy.

Nighttime or supine acid reflux has been linked to more severe esophagitis, complicated GERD, and extraesophageal reflux manifestations.\textsuperscript{213} Nocturnal acid secretion is low in volume but highly concentrated and may be difficult to inhibit with once daily PPI treatment.\textsuperscript{214} Nocturnal acid breakthrough, a situation in which intragastric pH (not intraesophageal) falls to and remains <4 for more than 1 hour overnight occurs in 73% of both GERD patients and normal volunteers.\textsuperscript{215} Several strategies have been proposed to manage nighttime acid including administering the once daily PPI before dinner, twice daily dosing of PPI (before breakfast and dinner), adding an H2RA at bedtime to a regimen of once or twice daily PPI, or prescribing an immediate release PPI at bedtime.\textsuperscript{216,217} Although these approaches are successful to varying degrees in controlling nocturnal acid secretion, none have been shown conclusively to improve GERD outcomes in the short- or long-term.

GERD is a chronic condition that requires long-term treatment in most individuals. Maintenance acid suppression seems to be the most effective long-term medical approach. As with acute healing, preventing relapse is best achieved with PPIs, with full dose being better than half dose.\textsuperscript{19} In patients who experience breakthrough GERD symptoms, compliance, appropriate timing of
medications, and lifestyle modifications should be emphasized. Once heartburn is under control, many patients will take their medications on demand rather than daily, as prescribed.\(^\text{218}\) Others take the PPIs inappropriately, ie, between meals or at bedtime.\(^\text{219}\) As discussed previously, PPIs are most effective when taken before meals.\(^\text{114}\)

The role of HP eradication in the management of GERD remains controversial, and there is no compelling reason to test for HP in patients with GERD.\(^\text{220}\) It is unlikely that cure of infection will positively impact symptoms to any great degree, and there is evidence that it might actually worsen symptoms.\(^\text{221}\) Most patients chronically infected with HP manifest a pangastritis and produce less than normal amounts of acid. In these patients, HP infection may actually protect against GERD (also, Barrett’s esophagus and esophageal adenocarcinoma), and eradication may augment acid secretion.\(^\text{161,222,223}\) Not only may HP protect against GERD, but HP may make GERD more responsive to treatment by augmenting the acid-inhibitory effect of PPIs.\(^\text{224}\) Thus, eradication of HP has the potential to both increase acid secretion and decrease the efficacy of PPIs, thereby making GERD more difficult to control.\(^\text{160,223}\)

### Gastric Acid Hypersecretion

There are a number of uncommon conditions in which gastric acid secretion is abnormally high and ulcers develop. In patients with systemic mastocytosis, high histamine levels, as a consequence of increased numbers of mast cells, continuously stimulate parietal cells to secrete acid.\(^\text{225}\) When a portion of gastric antrum is retained in the afferent remnant after antrectomy with Billroth II anastomosis, it is bathed in alkaline secretions leading to decreased somatostatin secretion, hypergastrinemia, increased acid production, and anastomotic ulcers.\(^\text{78,96,226}\) Acid hypersecretion can also result from chronic hypercalcemia of any cause because calcium directly stimulates gastrin secretion from human G cells and acid secretion from parietal cells.\(^\text{227,228}\)

The best characterized acid hypersecretory condition is ZES.\(^\text{17,229}\) ZES is caused by a gastrin-producing tumor (gastrinoma) that results in gastric acid hypersecretion. Gastrin, synthesized by the tumor, is secreted into the bloodstream where it binds to CCK\(_\text{2}\) receptors on acid-producing parietal and histamine-containing ECL cells to induce secretion as well as proliferation. The clinical correlate of the proliferation is rugal hypertrophy with prominent gastric folds. ZES should be suspected in patients with refractory erosive esophagitis, multiple peptic ulcers, ulcers in the distal duodenum or jejunum, complicated ulcers, recurrent ulcers after acid-reducing surgery, ulcers associated with diabetes, and a family history of MEN-1 or any of the endocrinopathies associated with MEN-1.\(^\text{230}\) Approximately 25% of patients with ZES have MEN-1, an autosomal dominant disorder characterized by pancreatic endocrine tumors, pituitary adenomas, and hyperparathyroidism; in the latter, hypercalcemia can further stimulate acid secretion. Diarrhea may be a prominent symptom, occurring in 65% of ZES patients, and is due to the large volume of acid, which inactivates pancreatic lipase and damages the proximal small bowel absorptive mucosa.

Diagnosis of gastrinoma includes serum gastrin radioimmunoassay, secretin stimulation test, and, more recently, somatostatin receptor scintigraphy and endoscopic ultrasound. The basis of the secretin test is that normally, in the antrum, somatostatin cells tonically restrain gastrin secretion from G cells. Secretin stimulates the G cell directly and, at the same time, inhibits the G cell indirectly by stimulating somatostatin secretion; the effect of the latter dominates, and gastrin is not stimulated. Because the gastrinoma does not contain functionally coupled somatostatin cells, the effect of secretin is solely stimulation of gastrin secretion from the tumor.\(^\text{231–233}\) After an overnight fast, 0.4 \(\mu\text{g/kg}\) secretin is given intravenously over 1 minute. Two baseline values are obtained then blood is collected at 1, 2, 5, 10, and 30 minutes. An increase in gastrin of more than 200 pg/mL over the preinjection value indicates ZES; more then 90% of ZES patients exhibit an increase in gastrin at 2 or 5 minutes. Almost all gastrinomas contain somatostatin receptors, and somatostatin receptor scintigraphy using \[^{111}\text{In-DPTA-Dphe1}\]-octreotide is considered the initial localization study of choice, with a 71% sensitivity and 86% specificity for primary tumors and 92% detection for metastatic disease.\(^\text{234,235}\)

Total gastrectomy, initially the treatment of choice to prevent life-threatening complications, has been abandoned in favor of antisecretory therapy and selective surgical resection of the gastrinoma. H2RAs represented the first viable medical therapy to control acid hypersecretion. Unfortunately, increasingly large doses were required, and acid suppression was often inconsistent. Consequently, gastrinoma enucleation or parietal cell vagotomy was often added to suppress acid secretion. The goal of antisecretory therapy is to reduce acid secretion to less than 10 mEq/h (<5 mEq/h if patient underwent prior gastric acid-reducing surgery) as measured 1 hour before the next dose.\(^\text{230}\) Today, PPIs are the antisecretory therapies of choice and are able to control acid secretion and prevent complications in most patients with ZES, although very high doses of medication (eg, omeprazole 120 mg/day) may be necessary, especially in patients with MEN-1.\(^\text{236}\)

### Safety of Acid Suppression

Acid suppression continues to be the major medical strategy to treat acid-peptic disorders. For decades, millions of patients have had their acid neutralized or inhibited effectively and safely first with antacids then with H2RAs and now with PPIs. Because antacids are
rarely used anymore as primary therapy for acid-related disorders, their adverse effects, including diarrhea; constipation; interference with drug absorption; and rare renal, metabolic, and acid base disturbances are only of historical importance.

H2RAs are generally well tolerated with adverse effects observed in 1.5% of treated patients compared with 1.2% of placebo patients. Rare adverse effects include mental confusion (<0.2%), gynecomastia, interstitial nephritis (0.001%), interference in the absorption of drugs requiring an acid environment such as ketoconazole and itraconazole, and cytochrome P450 interactions. Although cimetidine is capable of inhibiting the catalytic activity of one or more cytochrome P450 enzymes (CYP1A2 and CYP2C19), clinically significant drug interactions are very rare.

PPIs are safe drugs, but concerns have been voiced regarding potential adverse effects related to hypergastrinemia, rebound acid hypersecretion, malabsorption, infection, and drug interactions. Since the introduction of omeprazole, there was concern that PPI-induced hypergastrinemia may have untoward effects. In rats, ECL cells, under stimulation of gastrin, evolve through hyperplasia to dysplasia and eventually to carcinoid tumors. Humans respond to a decrease in luminal acid with a lesser increase in serum gastrin than rats and do not develop gastric carcinoids unless in the settings of severe atrophic gastritis (pernicious anemia) or ZES associated with MEN-1. The possibility exists that hypergastrinemia could exert trophic effects outside of the stomach and influence the growth of premalignant and malignant cells because CCK2 receptors have been identified in a variety of tissues including Barrett’s esophagus, stomach, pancreas, and colon as well as in cancers derived from these and other tissues (esophageal adenocarcinoma, gastric adenocarcinoma, pancreatic adenocarcinoma, neuroendocrine tumors, colon adenocarcinoma, medullary thyroid cancer, small cell lung cancer, leiomyosarcoma, and stromal ovarian cancer). Although there is no convincing evidence that hypergastrinemia per se induces neoplasia, the possibility exists that it might accelerate the growth and invasiveness of cancers harboring its receptor.

In humans, there is a prolonged rebound hypersecretion in HP-negative individuals after discontinuation of a PPI, with increases in both basal and maximal acid output. The phenomenon occurs after as little as a 2-month course of therapy and lasts at least 2 months after the PPI is stopped. The pathophysiology is thought to be due to the trophic effect exerted by gastrin on histamine-containing ECL cells leading to their hyperplasia and hypertrophy. The reason the phenomenon does not occur in HP-positive individuals may be due to the fact that HP as well as cytokines induced by the inflammatory infiltrate inhibit acid secretion and thus mask the rebound.

The clinical relevance of rebound hypersecretion is that patients may become physiologically addicted to PPIs. That is, the increased acid secretion after discontinuation of PPIs may induce or exacerbate acid-peptic disorders such as GERD and dyspepsia causing patients to resume antisecretory therapy. One way to prevent this from happening might be to, instead of abrupt discontinuation, taper the PPI and switch to tapering doses of H2RAs over a period of 2 months.

Chronic hypochlorhydria induced by PPIs could interfere with absorption of nutrients such as vitamin B-12, iron, and calcium. Several reports indicate that chronic use of PPIs may result in low levels of vitamin B-12 probably by impairing acid-induced release of B-12 from food. The recommended daily allowance of B-12 is 2 µg/day, and total body stores are 2.5 mg. Vitamin B-12 deficiency because of PPIs is rare, probably because acid secretion is not completely inhibited and the body has relatively large stores.

Acid is thought to facilitate dietary iron absorption. Exposure to acid frees heme iron from its apoprotein and converts nonheme iron, which is largely in the form of ferric hydroxide, to the absorbable ferrous form. PPIs have been used to decrease iron absorption in patients with hereditary hemochromatosis. Despite the fact that medicinal iron is in the ferrous form, there is a single report of 2 patients in whom iron deficiency did not respond to treatment until PPIs were discontinued.

In a recent population-based study, long-term PPI therapy was implicated as a cause of hip fractures in older women. Although the relative risk of fractures increased with dose and duration of acid suppression, the absolute risk of fractures remained very low. The basis for this is not known but may involve interference with calcium absorption or bone metabolism. This finding requires confirmation before patients receiving benefit from PPIs are advised to stop them.

Gastric acid protects against bacterial overgrowth and enteric infection. Two recent epidemiologic studies have implicated PPIs as a risk factor for the development of community, as well as hospital-acquired Clostridium difficile-associated disease. Because ingested C difficile spores are not susceptible to destruction by acid, these findings may not represent true cause and effect. It is likely that the finding was confounded by the fact that patients receiving PPIs were more likely to be sicker and more susceptible to infection when exposed to antibiotics. A similar argument may be advanced for the association between acid suppressive medications and community-acquired pneumonia. In these studies, confounders such as concomitant pulmonary disease and severe GERD, which might predispose to pneumonia, were not controlled.

All PPIs are metabolized by the cytochrome P450 family of enzymes. There had been some concern that omeprazole and other PPIs, through inhibition of certain
cytochrome P450 enzymes, might increase the half-life of certain medications such as theophylline, phenytoin, diazepam, and warfarin. Because PPIs are in the bloodstream for a relatively short time (plasma half-life, ~1 hour) and are relatively weak inhibitors of cytochrome P450, clinically relevant drug-drug interactions are extremely rare (<0.1 per million packages) and do not constitute a major clinical risk.

**Conclusion**

Gastric acid remains an important pathogenic factor for a variety of common upper gastrointestinal disorders. Over time, the prevalence as well as the management of these disorders has changed. Generations of gastroenterologists and surgeons measured acid output and tailored medical and surgical treatment of peptic ulcer disease based on the results. The management of these disorders has been revolutionized by the introduction of potent antisecretory medications and the understanding of the role of HP in their pathogenesis. As a result, the quantitative measurement of gastric acid secretion, for the most part, has become obsolete. Nevertheless, gastric acid secretion and its inhibition will continue to be important to gastroenterology as a specialty, at least for the foreseeable future. Have we reached the zenith in our understanding of gastric acid physiology and the development of pharmacologic treatments for acid-peptic disorders? We do not think so. These disorders remain prominent, and there is much still to be discovered by future clinical and basic investigators.

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