Gastric physiology

Avram M. Cooperman, M.D.
Department of General Surgery

The progressive and recent spectacular advances in gastric physiology have been welcomed by gastroenterologists and surgeons. Most important has been the benefit to patients with epigastric pain, secretory or motility disturbances of the stomach, or a variety of unpleasant sequelae that have followed alteration of normal function. In this review gastric secretion, motility, gastric emptying, and the practical applications of each are discussed.

Because digestion but little absorption takes place in the stomach, the gastric epithelium is suitably arranged to facilitate this. Deep crypts with multiple mucosal glands provide luminal access for the many components of gastric secretion.

There are three anatomical glandular areas of the stomach: cardiac, oxyntic, and pyloric. The cardiac glands occupy a small portion of the upper stomach below the esophagus. The secretions are mucoid and there is a turnover of cells within 48 hours after injury. The pyloric or antral glandular area occupies 10% to 20% of the stomach where mucus, gastrin, and pepsinogens are produced.[1] The oxyntic glands occupy 80% to 90% of the glandular mucosa. At least six types of cells have been identified in this

area and secretions include mucus, pepsinogens, hydrochloric acid, intrinsic factor, histamine, and serotonin. Most research has been directed toward the parietal cell and chief cell, the source of acid and pepsin.

Methods of study

Classic methods of studying gastric physiology have been indirect; an intact animal model was used to derive data. A reliable method has been to position a tube in the stomach under fluoroscopy and aspirate gastric contents. The obvious limitations to this method are incomplete sampling (some of the material may be lost to the duodenum), the nonphysiologic alterations caused by the presence of a tube, and contamination by biliary and pancreatic secretions.

Gastric pouches and fistulas

Perhaps the stimulus for using gastric pouches and fistulas was Beaumont's[2] study of Alexis St. Martin published in 1833. Although gastric fistulas were prepared more than 130 years ago, they do not allow accurate collections during solid meals. Gastric pouches which allowed gastric secretions to be collected from an isolated part of the stomach then became popular. There are two types of pouches, Pavlov[3] (vagally innervated) and Heidenhain[4] (vagally denervated). Much of our present knowledge has been derived from animal pouch studies. There are at least four reasons why pouches do not give an accurate index of gastric secretory rates: (1) Resection of oxyntic glands from the main stomach may cause increased secretory response to meals from a Heidenhain pouch. This may be due to a decrease in suppression of gastrin release by resecting some of the parietal cell mass. (2) There is a question of vagal innervation in some Pavlov pouches. Even though the pouches may show an acid response to insulin hypoglycemia, this does not insure that full vagal innervation to a pouch is intact. (3) When a meal is the stimulus for pouch secretion, the response of the pouch may differ from the main stomach where food and the chemical effects are different. (4) The response and stimuli in animals' pouches may not be the same in man and caution must be exercised in interpreting these studies.

Studies on gastric pouches have yielded voluminous quantities of secretions and an almost equal number of reports. Despite the fact that the acid is produced in the parietal cell, there is no universal agreement on how hydrochloric acid is made or secreted into the gastric lumen. At least five theories have gained support during the past century.[5] The biochemical and electrical events resulting in acid secretion are complex and require 1532 calories per liter of gastric juice.[6] The caloric source is via oxidative metabolism of mucosal cells and anaerobic glycolysis.

Acetylcholine, histamine, or pentagastrin may be the circulating "first messengers." They attach to a receptor on the parietal cell and stimulate adenylcyclase in the cell membrane. Adenylcyclase converts adenosine triphosphate (ATP) to adenosine 3′,5′-cyclic monophosphate (cyclic AMP) and pyrophosphate. Acid secretion then follows.

There is considerable evidence for and against cyclic AMP as a mediator of gastric acid secretion.[7] Both cyclic AMP and cyclic guanasine monophosphate (GMP) have been found in

high concentrations in the gastric mucosa in frogs, mammals, and man. Basal levels rise with histamine or pentagastrin stimulation. Evidence for the role of cyclic AMP is good in animals but it is less certain in man. There is cyclic AMP in the gastric mucosa, and even though its volume in gastric juice increases after histamine or pentagastrin stimulation the concentration remains unchanged.[8] The hydrogen ion in gastric juice may be derived from the hydrolysis of water within the parietal cell. Intracellular metabolism results in the formation of bicarbonate, and since this forms carbon dioxide and hydroxyl ions ($HCO_3 - O_2 + OH$) many of the latter ions are available to be released. During acid secretion the venous effluent of the cell has increased the levels of bicarbonate (alkaline tide). Chloride ions may move into the parietal cell and gastric lumen against a concentration and electrical gradient. Although electrical potentials are important in establishing an electrical gradient, this is not essential for acid secretion.

The ionic composition of gastric juice changes and varies depending on the stimulus. An increase in hydrogen ion concentration is accompanied by a decrease in sodium ions. Pure parietal cell secretions contain 148 mEq/liter of hydrogen ion, 17 mEq/liter of potassium, and 164 mEq/liter of chloride.

Agonists of gastric acid secretion

A variety of endogenous and exogenous stimuli increase acid output. The three in vivo stimuli include acetylcholine, gastrin, and histamine. Whether a specific receptor for each of these substances is present on the parietal cell is unknown. In 1965 Code[9] suggested that the nonhistamine agonists acted through histamine and its receptors for acid secretion. With the recent discovery of H_2 or histamine receptors in the stomach wall his prophecy may be proved correct, since blocking these receptors decreases acid secretion to all known stimuli including acetylcholine and gastrin.

Basal or unstimulated acid secretion is 1.3 to 4.2 mEq/hr in man, but varies at different time periods in each subject. Maximal stimulated secretion approaches 20 mEq/hr. Antagonists of gastric acid secretion include secretin, cholecystokinin, and pancreozymin (an agonist of acid secretion when given alone, but an antagonist of gastrin stimulated secretion), gastric inhibitory peptide (GIP), glucagon and vasoactive intestinal polypeptide (VIP). The latter may be released by vagal stimulation.[10]

Phases of gastric secretion

Classically, three phases of gastric secretion have been described: cephalic, gastric, and intestinal. Grossman[11] has emphasized that these phases refer to the region where a stimulus for gastric secretion acts and not to a specific mechanism of action.

The cephalic phase refers to stimulation of gastric secretion by agents acting in the head. It is mediated by the vagus nerves and can be abolished by vagotomy. The stimuli include taste, smell, and chewing. The vagal mechanism probably is twofold: direct cholinergic stimulation of the oxyntic glands and the cholinergic release of gastrin. Antral gastrin then stimulates the oxyntic cells. The gastric phase of acid secretion includes long (vagovagal) and short (intra-

mural) reflexes.[11] If a nonacidified antrum is distended, antral gastrin (oxyntic pyloric reflex) is released, resulting in acid secretion.[12,13] A distended, acidified antrum does not increase acid secretion. Food, particularly peptides and amino acids, increases acid secretion.[14] The intestinal phase of acid secretion is caused by neural and humoral mechanisms. In animals several stimuli including food and distention are responsible.[15]

Although increased acid secretion has been shown in patients who have undergone portosystemic shunts or massive small bowel resections, it is unclear what the intestinal stimuli are in normal man. Perhaps in these patients the loss of substances that inhibits gastric acid secretions is more important. At this time whether VIP, enteroxyntin, intestinal gastrin, or other peptides are the humoral agents is speculative.

Parietal cell mass

The average number of parietal cells in human males is 1 billion and 0.8 billion in females. Each parietal cell at peak output produces 20 mEq/hr of acid. The parietal cell population is increased in duodenal ulcer, gastrinoma, and mastocytosis. It is decreased in gastric ulcer, gastric cancer, pernicious anemia, and atrophic gastritis.

Gastric emptying

The proximal portion of the stomach regulates the emptying of liquids. This area increases its capacity by distension of the fundus with little increase in pressure. The small rise in pressure relative to the large volumes of secretion and ingestion enable the stomach to accomodate large volumes (receptive relaxation).[16] This process is also facilitated by vagal inhibitory fibers in the wall of the stomach. Humoral agents may also play a role. Gastrin delays gastric emptying, lowers intragastric pressure, and inhibits proximal gastric contractions.[17] Whether this mechanism is active in man at the concentration of circulating gastrin is unknown. The role of other hormones (e.g., secretin and motilin) which alter motor activity in vitro also remains unknown in man.

The distal stomach regulates the emptying of solids.[16] Its peristaltic waves which synchronously course toward the lesser curvature and pylorus forcefully conduct gastric secretions and food through the pylorus (propulsion). Since only a small volume leaves the stomach before the pylorus closes, most of the bolus is repelled by the closed pyloric sphincter. This propulsion retropulsion sequence further facilitates the "mill action" of the antrum. The frequency of distal gastric contractions is 3/min in man. The force of the peristaltic contractions varies; the more vagal the stimuli that release impulses, the more acetylcholine is released and the stronger the contractions.

The pyloric sphincter is a high pressure zone that influences gastric emptying by regulating the time and rate at which the stomach empties. Since the characteristics of the sphincter have only recently been defined, the influences of neural and humoral factors on this sphincter need further definition. Despite a patulous pylorus, erect position, and a full, distended stomach, gravity plays little to no role in gastric emptying in man.

A variety of foods, chemicals, and hormones influence the rate of gastric emptying. Gastric volume recep-

tors located in the stomach wall discharge when the gastric muscle is stretched, causing an increase in the rate of emptying. Most gut hormones (gastrin, secretin, glucagon, GIP, VIP) delay emptying of the stomach. Motilin stimulates contraction of the fundus. Whether this effect is physiologic or pharmacologic in man is not known. Osmoreceptors located in the duodenum deep to the brush border also delay gastric emptying. Sugars, sorbitol, and sulfate delay emptying. Concentration of gastric acid also has an effect on gastric emptying. The greater the concentration of acid, the greater the delay in gastric emptying. The strength of the acid is less important. The area of duodenum sensitive to acidification is the first 5 cm. Fatty acids, particularly from C_{10} to C_{14}, are effective in altering emptying. Amino acids, particularly tryptophan, also delay gastric emptying. An osmoreceptor in the duodenum is probably the controlling mechanism for regulation.

Protection against autodigestion

Despite high concentrations of hydrochloric acid in the stomach, autodigestion of gastric mucosa does not normally occur. A gastric mucosal barrier has been considered the normal defense mechanism against gastric acid. Hollander[18] originally proposed that the mucosal barrier consisted of two components, mucus and gastric mucosal cells. The protective effect of mucus is in doubt, since it has weak neutralizing and buffering properties and acid easily diffuses through it.

The cellular component damaged by numerous agents (e.g., bile and aspirin) has not been anatomically identified. Whether it is the mucosal cell or intercellular bridges or both is not certain.

In a thorough review, Silen[19] proposed that this barrier is not static but ever changing. It is influenced by gastric secretion, acid base balance, and blood supply to the mucosa. Hydrogen ions may normally diffuse through the mucosa without damage. Measurement of back diffusion (diffusion of acid from lumen through cell) may not necessarily mean that injury to the mucosal barrier has occurred. Submucosal and mucosal blood flow are important because acid from back diffusion may be cleared when blood flow is satisfactory, but result in damage when flow is reduced.

Pepsinogens are the precursors and inactive form of pepsin, a protein with a molecular weight of 42,500. Pepsin is relatively resistant to acid denaturation and is stable at a pH less than 12.0. Pepsin has active proteolytic properties at a gastric pH of 1 to 5.5. At a pH of 3.5 to 5.5 pepsin changes the physical properties of protein molecules, decreasing viscosity and clotting but not releasing breakdown products.[20]

Pepsinogen is synthesized in the polysome in the RNA system on the endoplasmic reticulum, is transferred across the membrane into the tubular system, and then to the Golgi body where it is encapsulated to form granules. When stimulated the granules are discharged and released.

Seven pepsinogen molecules have been classified into two major groups: group I pepsinogens (1–5) and group II pepsinogens (6–7). Group I pepsinogens are found only in the mucous neck and chief cells in oxyntic gland mucosa. Group II pepsinogens are found in the pyloric

gland mucosa, antrum, and in Brunner's glands.[21]

Assessing gastric emptying

There are many ways to measure emptying in laboratory and clinical situations. We recently reviewed the available methods and summarized the roentgenographic and isotopic techniques.[22] Certainly the easiest method is the use of barium roentgenography. It is difficult to determine when the stomach is 25%, 50%, or 75% full using a barium meal. The isotopic method with technetium 99 may also be used to measure emptying. Although it is easily applicable for liquid meals there has been less certainty about its accuracy for solids. Recently this method has been modified by the use of chicken liver.[23] Chicken wings are injected with the isotope, the animal is killed, and the liver is cooked in a microwave oven. This ensures uniform distribution of the isotope in the liver and a palatable meal for the patient.[21] Other quantitative methods are available that allow separation and calculation of solid and liquid components of a test meal, but these are complex and investigative only.[24] Using these combined data on secretion, motility and emptying, a number of abnormalities have been described in many disease states.

Effects of vagotomy

The effects of vagotomy on the stomach and other abdominal viscera are many and varied depending upon the type of vagotomy (truncal, selective, or parietal cell). All three vagotomies are followed by a 75% to 80% reduction in basal acid output and a 55% to 70% reduction in peak acid output. Pepsinogen secretion is similarly decreased after all three operations. Serum gastrin rises after vagotomy (regardless of the type). This is due to lack of acid inhibition of gastrin. There are distinct differences in motility after each of these vagotomies. Parietal cell vagotomy leaves antral and pyloric innervation intact and denervates only the proximal stomach (the emptying of liquids). Thus a more rapid emptying of liquids occurs, but usually not enough to cause dumping or diarrhea.

Total gastric vagotomy (truncal or selective) denervates both the proximal and distal areas of the stomach causing liquids to empty more quickly and stasis of solids in the distal area. A drainage procedure is required which further alters emptying and removes the barriers for duodenal or jejunal reflux.

Duodenal ulcer

There is considerable overlap in acid secretory studies in patients with duodenal ulcer and in a normal population. In general, ulcer patients secrete more acid in a fasting state and have twice as many oxyntic cells as normal patients; they require less stimulation to double their basal acid output, have increased levels of food stimulated gastrin, and suppress the release of gastrin by antral acidification more poorly than normal patients; ulcer patients have stronger peristaltic contractions and empty food more rapidly. All of these may explain the inability of the duodenum to neutralize acid secretions.

Gastric ulcer

Gastric ulcers typically occur on the lesser curvature of the stomach usually in an area of antral or pyloric

mucosa adjacent to acid secreting fundic mucosa. The peculiar susceptibility of this mucosa to ulceration is not easily explained. Most gastric ulcer patients are hyposecretors of acid, have slower gastric emptying and lower pyloric sphincter pressures. Increased back diffusion of acid produces significantly more back diffusion in patients with gastric or duodenal ulcers or in controls.

References

1. Hogben CA, Kent TH, Woodward PA, et al: Quantitative histology of the gastric mucosa; man, dog, cat, guinea pig, and frog. Gastroenterology **67:** 1143–1154, 1974.
2. Beaumont W: Experiments and Observations on the Gastric Juice and the Physiology of Digestion. Plattsburgh, New York, Allen, 1833.
3. Pavlov IP: The Work of the Digestive Glands; lectures. Translated by Thompson WH, London, CG Griffen & Co, 1902.
4. Heidenhain R: Ueber die Absonderung der Fundusdrüsen des Magens. Arch ges Physiol **19:** 148–166, 1879.
5. Hunt JN, Wan B: Electrolytes of mammalian gastric juice, *in* Handbook of Physiology. Alimentary Canal. v. 2, section 6. Secretion. Code CF, Heidel W, eds. Washington, DC, American Physiological Society, 1967, pp 781–804.
6. Davenport HW: Physiology of the Digestive Tract, ed 3. Chicago, Year Book Medical Publishers, 1971.
7. Kimberg DV: Cyclic nucleotides and their role in gastrointestinal secretions. Gastroenterology **67:** 1023–1064, 1974.
8. Sachs G, Shah G, Strych A, et al: Properties of ATPase of gastric mucosa. 3. Distribution of HCO_3-stimulated ATPase in gastric mucosa. Biochim Biophys Acta **266:** 625–638, 1972.
9. Code CF: Histamine and gastric secretions; a later look, 1955–1965. Fed Proc **24:** 1311–1321, 1965.
10. Schaffalitzky de Muckadell OB, Fahrenkrug J, Holst JJ: Release of vasoactive intestinal polypeptide (VIP) by electric stimulation of the vagal nerves. Gastroenterology **72:** 373–375, 1977.
11. Grossman MI: Neural and hormonal stimulation of gastric secretion of acid, *in* Handbook of Physiology. Alimentary Canal. v. 2, section 6. Secretion. Code CF, Heidel W, eds. Washington, DC, American Physiological Society, 1967, pp 835–863.
12. Debas HT, Konturek SJ, Walsh JH, et al: Proof of a pyloro-oxyntic reflex for stimulation of acid secretion. Gastroenterology **66:** 526–532, 1974.
13. Debas HT, Walsh JH, Grossman MI: Evidence for oxyntopyloric reflex for release of antral gastrin. Gastroenterology **68** (Pt 1): 687–690, 1975.
14. Konturek SJ, Tasler J, Obtulowicz W, et al: Comparison of amino acids bathing the oxyntic gland area in the stimulation of gastric secretion. Gastroenterology **70:** 66–69, 1976.
15. Sircus W: The intestinal phase of gastric secretion. Q J Exp Physiol **38:** 91–100, 1953.
16. Cannon WB: The Mechanical Factors of Digestion. London, Edward E. Arnold, 1911.
17. Wilbur BG, Kelly KA: Gastrin pentapeptide decreases canine gastric transmural pressure. Gastroenterology **67:** 1139–1142, 1974.
18. Hollander F: The two-component mucous barrier; its activity in protecting the gastroduodenal mucosa against peptic ulceration. Arch Intern Med **93:** 107–120, 1954.
19. Silen W: New concepts of the gastric mucosal barrier. Am J Surg **133:** 8–12, 1977.
20. Fordtran JS: Pepsinogens and pepsins in peptic ulcer, *in* Gastrointestinal Disease: Pathophysiology, Diagnosis, Management. Philadelphia, WB Saunders Co, 1973, pp 189–194.
21. Samloff IM: Pepsinogens, pepsins, and pepsin inhibitors. Gastroenterology **60:** 586–604, 1971.
22. Cooperman AM, Cook SA: Gastric emptying—physiology and measurements. Surg Clin North Am **56:** 1277–1287, 1976.
23. McGregor IL, Martin P, Meyer JH: Gastric emptying of solid food in normal man and after subtotal gastrectomy and truncal vagotomy with pyloroplasty. Gastroenterology **72:** 206–211, 1977.
24. Malagelada JR, Longstreth GF, Summerskill WH, et al: Measurement of gastric functions during digestion of ordinary solid meals in man. Gastroenterology **70:** 203–210, 1976.