Case 41

Peptic Ulcer Disease: Zollinger-Ellison Syndrome

Abe Rosenfeld, who is 47 years old, owns a house painting business with his brothers. The brothers pride themselves on maintaining high standards and satisfying their customers. For several months, Abe had a number of symptoms, including indigestion, loss of appetite, abdominal pain, and diarrhea. One day, he remarked to his brothers that his diarrhea looked “oily.” The abdominal pain was relieved temporarily by eating and by taking over-the-counter antacids. Finally, he saw his physician, who referred him to a gastroenterologist. Abe underwent fiber-optic endoscopy, which showed an ulcer in the duodenal bulb. To determine the cause of the ulcer, additional tests were performed, including a serum gastrin level, analysis of gastric contents, a pentagastrin stimulation test, and a secretin stimulation test (Table 5-1).

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<thead>
<tr>
<th>TABLE 5-1</th>
<th>Abe’s Laboratory Values and Results of Laboratory Tests</th>
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<tbody>
<tr>
<td>Serum gastrin level</td>
<td>800 pg/mL (normal, 0–130 pg/mL)</td>
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<tr>
<td>Basal gastric H⁺ secretion</td>
<td>100 mEq/hr (normal, 10 mEq/hr)</td>
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<tr>
<td>Pentagastrin stimulation test</td>
<td>No increase in H⁺ secretion</td>
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<tr>
<td>Secretin stimulation test</td>
<td>Serum gastrin increased to 1100 pg/mL</td>
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A computed tomography scan showed a 3-cm mass on the head of the pancreas. The mass was thought to be a gastrinoma (gastrin-secreting tumor). While awaiting surgery to remove the mass, Abe was treated with a drug called omeprazole. Abe underwent laparoscopic surgery, during which the tumor was localized and removed. Abe’s ulcer subsequently healed, and his symptoms disappeared.

QUESTIONS

1. Abe had peptic ulcer disease, which is caused by digestion of the gastrointestinal mucosa by H⁺ and pepsin. What is the mechanism of H⁺ secretion by gastric parietal cells? What are the major factors that regulate H⁺ secretion?

2. The gastroenterologist diagnosed Abe with Zollinger-Ellison syndrome, or gastrinoma (a gastrin-secreting tumor). Abe had two important laboratory findings that were consistent with this diagnosis: (1) an elevated serum gastrin level and (2) an elevated basal level of gastric H⁺ secretion. How does Zollinger-Ellison syndrome increase gastric H⁺ secretion?

3. Why did Abe have a duodenal ulcer?

4. In Abe, pentagastrin, a gastrin analogue, did not stimulate gastric H⁺ secretion. How is this finding consistent with the diagnosis of Zollinger-Ellison syndrome? How does a healthy person respond to the pentagastrin stimulation test?

5. In the secretin stimulation test, Abe’s serum gastrin level increased from his basal level of 800 pg/mL (already very elevated) to 1100 pg/mL. In healthy persons, the secretin stimulation test causes no change, or a decrease, in the serum gastrin level. Propose a mechanism to explain Abe’s response to secretin.
6. Why did Abe have diarrhea?

7. The oily appearance of Abe's stools was caused by fat in the stool (steatorrhea). Why did Abe have steatorrhea?

8. Abe felt better when he ate. Why?

9. What is the mechanism of action of omeprazole? Why was Abe treated with this drug while he awaited surgery?
1. Causative factors in **peptic ulcer disease** include (but are not limited to) increased H⁺ secretion by gastric parietal cells, *Helicobacter pylori* infection, use of nonsteroidal anti-inflammatory drugs (e.g., aspirin), and smoking. The common factor in each etiology is digestion of the gastrointestinal mucosa by H⁺; hence, the dictum, "no acid, no ulcer." As is typical, Abe's ulcer was located in the duodenal bulb. Excess H⁺, delivered from the stomach to the upper duodenum, exceeded the neutralizing capacity of pancreatic and intestinal secretions and digested a portion of his duodenal mucosa.

Figure 5–3 shows the mechanism of H⁺ secretion by gastric parietal cells. The apical membrane of the cell, which faces the lumen of the stomach, contains an H⁺-K⁺ ATPase. The basolateral membrane, which faces the blood, contains the Na⁺-K⁺ ATPase and a Cl⁻-HCO₃⁻ exchanger. Inside the parietal cell, CO₂ and H₂O combine to form H₂CO₃, which dissociates into H⁺ and HCO₃⁻. The H⁺ is secreted into the lumen of the stomach by the H⁺-K⁺ ATPase, acidifying the stomach contents to help with digestion of dietary proteins; an acidic gastric pH is required to convert inactive pepsinogen to its active form, pepsin (a proteolytic enzyme). The HCO₃⁻ is exchanged for Cl⁻ across the basolateral membrane and thus is absorbed into gastric venous blood. Eventually, this HCO₃⁻ is secreted into the lumen of the small intestine (through pancreatic secretions), where it neutralizes the acidic chyme delivered from the stomach.

The major factors that stimulate H⁺ secretion by the parietal cells are the parasympathetic nervous system (vagus nerve), gastrin, and histamine (Figure 5–4). (1) Postganglionic parasympathetic nerve fibers (vagus nerve) stimulate H⁺ secretion both directly and indirectly. The parietal cells are directly innervated by postganglionic neurons that release acetylcholine, which activates a muscarinic (M₃) receptor and stimulates H⁺ secretion. The G (gastrin-secreting) cells also have parasympathetic innervation. These postganglionic neurons release bombesin or gastrin-releasing peptide, thus indirectly stimulating H⁺ secretion by increasing gastrin secretion. (2) G cells in the gastric antrum release gastrin, which enters the circulation and stimulates H⁺ secretion by the parietal cells through the cholecystokinin-B (CCK₄) receptor. (3) Finally, histamine is released from enterochromaffin-like cells located near the parietal cells. Histamine diffuses to the parietal cells and activates H₂ receptors, stimulating H⁺ secretion.
In addition to these stimulatory factors, somatostatin, which is released from D cells of the gastrointestinal tract, inhibits H+ secretion in three ways. (1) Somatostatin directly inhibits H+ secretion by parietal cells via a Gi protein. (2) Somatostatin inhibits the release of gastrin from G cells, thus diminishing the stimulatory effect of gastrin. (3) Finally, somatostatin inhibits the release of histamine from enterochromaffin-like cells, thus diminishing the stimulatory effect of histamine. Prostaglandins also inhibit H+ secretion via a Gs protein.

2. In Zollinger-Ellison syndrome, or gastrinoma (a tumor often located in the pancreas), large amounts of gastrin are secreted into the circulation. Gastrin travels to its target tissue, the gastric parietal cells, where it stimulates H+ secretion and causes hypertrophy of the gastric mucosa. Abe had very high circulating levels of gastrin; consequently, he had very high basal levels of gastric H+ secretion.

Physiologic gastrin secretion by the antral G cells can be compared with nonphysiologic gastrin secretion by a gastrinoma. The physiologic secretion of gastrin and, consequently, the physiologic secretion of H+ are regulated by negative feedback. In other words, when the contents of the stomach are sufficiently acidified, the low gastric pH directly inhibits further gastrin secretion. With gastrinoma, the situation is different. The secretion of gastrin by gastrinoma is not feedback-regulated; therefore, even when the stomach contents are very acidic, gastrin secretion continues unabated.

3. Abe’s duodenal ulcer developed because the H+ load delivered from the stomach to the small intestine was greater than could be buffered. Normally, the duodenal mucosa is protected from the acidic stomach contents by neutralizing (high HCO3−) secretions from the pancreas, liver, and intestine. In Abe’s case, unrelenting gastrin secretion led to unrelenting H+ secretion (in excess of what could be buffered). As a result, the acidic contents of the duodenum digested a portion of the duodenal mucosa.
4. In the pentagastrin stimulation test, a gastrin analogue is infused while gastric H+ secretion is monitored. (Gastric contents are sampled through a nasogastric tube.) In healthy persons, the gastrin analogue acts just like endogenous gastrin: it stimulates H+ secretion by gastric parietal cells (usually to a level about threefold higher than basal secretory rates). In Abe, the gastrin analogue did nothing—Abe had such high circulating levels of gastrin from the tumor that H+ secretion was already maximally stimulated. The small additional amount of gastrin that was administered as pentagastrin in the test could not further stimulate H+ secretion.

5. You may have had difficulty with this question. It was included to introduce you to an important diagnostic test for Zollinger-Ellison syndrome. For reasons that are not understood, secretin directly stimulates gastrin secretion by gastrinoma cells, but not by antral G cells. Therefore, when a person with Zollinger-Ellison syndrome is challenged with the secretin stimulation test, the serum gastrin level increases further. When a healthy person is challenged with secretin, the serum gastrin level is decreased or is unchanged.

6. Abe had diarrhea because a large volume of gastric juice was secreted along with H+. When the volume of gastrointestinal secretions exceeds the absorptive capacity of the intestine, diarrhea occurs. (Another feature of the diarrhea in Zollinger-Ellison syndrome is steatorrhea, which is discussed in the next question.)

7. Abe had fat in his stool (steatorrhea) because he did not adequately absorb dietary lipids. To understand how steatorrhea can occur, it is helpful to review the steps involved in normal fat digestion and absorption (Figure 5–5). Dietary lipids are digested by three pancreatic enzymes: pancreatic lipase digests triglycerides; cholesterol ester hydrolase digests cholesterol esters; and phospholipase A2 digests phospholipids. (1) The products of lipid digestion (i.e., monoglycerides, fatty acids, cholesterol, and lysolecithin) are solubilized in micelles in the intestinal lumen. The outer layer of the micelles is composed of bile salts, which have amphipathic properties. "Amphipathic" means that the molecules have both hydrophilic and hydrophobic regions and are, accordingly, soluble in both water and oil. The hydrophilic portion of the bile salts is dissolved in the aqueous solution of the intestinal lumen. The hydrophobic portion of the bile salts is dissolved in the center of the micelle, which contains the products of lipid digestion. In this way, hydrophobic dietary lipids can be solubilized in the "unfriendly" aqueous environment of the intestinal lumen. (2) At the apical membrane of the intestinal cells, the products of lipid digestion are released from the micelles and diffuse into the cell. (3) Inside the intestinal cells, the lipids are re-esterified, packaged in chylomicrons, and (4) transported into lymphatic vessels. Each step in the process of lipid digestion and absorption is essential; if any step is defective, lipid absorption is impaired.
Figure 5–5 Absorption of lipids in small intestine. The numbers correspond to the steps discussed in the text. ApoB, β-lipoprotein; Chol, cholesterol; CholE, cholesterol ester; FFA, free fatty acids; LysoPL, lysolecithin; MG, monoglycerides; PL, phospholipids; TG, triglycerides.

With this lengthy introduction, we can now determine which step in Abe’s lipid digestion and absorption was impaired. Abe had three major defects in lipid digestion and absorption, all related to the acidic pH of his intestinal contents. (1) Pancreatic enzymes are inactivated at acidic pH (the optimal pH for pancreatic lipase is 6). Thus, digestion of dietary lipids to absorbable compounds was impaired. (2) Bile salts are weak acids that exist primarily in their nonionized (HA) form at acidic pH. In this nonionized form, the bile salts are lipid-soluble and are absorbed “too early” in the small intestine (before micelle formation and lipid absorption are complete). Normally, bile acids are absorbed in the terminal portion of the small intestine (the ileum) via the enterohepatic circulation (after they have completed their absorptive work for the dietary lipids). (3) Acid damages the mucosa of the small intestine, thereby reducing the surface area for absorption of lipids. Thus, for all of these reasons, the “oil” that Abe saw in his stool was undigested, unabsorbed triglycerides, cholesterol esters, and phospholipids.

8. Abe felt better when he ate because food is a buffer for H⁺. Some of the excess H⁺ was “mopped up” by the food in his stomach, reducing the load of free H⁺ that was delivered to the small intestine.

9. Omeprazole inhibits the H⁺-K⁺ ATPase in gastric parietal cells. This class of drugs is sometimes called the “proton pump inhibitors.” Recall that H⁺-K⁺ ATPase secretes H⁺ from the parietal cell into the lumen of the stomach. While awaiting surgery to remove the gastrinoma, Abe was treated with this drug, which reduced the amount of H⁺ secreted.
Key topics

Acetylcholine
Bile salts
Cholecystokinin-B receptor
Chylomicrons
Diarrhea
Enterohepatic circulation
Gastrin
Gastrinoma
G cells
H⁺-K⁺ ATPase
*Helicobacter pylori*
Histamine
Micelles
Nonsteroidal anti-inflammatory drugs (NSAIDs)
Omeprazole
Pancreatic lipase
Parietal cells
Peptic ulcer disease
Somatostatin
Steatorrhea
Vagus nerve
Zollinger-Ellison syndrome