NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

A Fiery Feeling:
An Exploration of Stomach Acid Production

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Preparation

Prior to completing this case study, complete the following in order (the information sequentially builds):

1. *Read:* Hsu, M., A.O. Safadi, & F. Lui. (2023). Physiology, stomach. In:StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. <https://www.ncbi.nlm.nih.gov/books/NBK535425/>
2. *Watch:* PhysioPathoPharmaco. (2017). Parietal cell acid production. [Video]. YouTube. Running time: 5:11 min. <https://youtu.be/6Nzr89rxaNo>
3. *Read:* Cleveland Clinic. (2023). Acid reflux and GERD. [Webpage]. <https://my.clevelandclinic.org/health/diseases/17019-acid-reflux-gerd>

Part I – Jerry's Symptoms

Jerry, a 45-year-old male, 6′1″ (184.5 centimeters), 270 pounds (122.47 kilograms), and BMI of 35.6, was recently diagnosed with type 2 diabetes. By recommendation of his primary care physician, Dr. Alley, Jerry also recently quit smoking. At his routine checkup, Jerry reported that he was experiencing a fiery, burning sensation in his chest. He also expressed that it was worse at night, and he had to sleep in an upright position. Jerry also told Dr. Alley that he was having increased symptoms of his asthma, such as shortness of breath and coughing. Furthermore, Jerry described the feeling of having something like a pill or a piece of food in the throat, which made swallowing difficult for him.

Dr. Alley performed an upper GI endoscopy and found that Jerry had esophagitis (inflammation of the esophagus). The physician also observed an increase in Jerry's saliva production, a symptom commonly associated with stomach acid regurgitation.

Questions

1. What symptoms is Jerry experiencing? Please distinguish between subjective and objective symptoms. (A subjective symptom would only be perceptible to the patient, whereas an objective symptom could be observed or measured by another individual.)
   a. Subjective symptoms:

   b. Objective symptoms:

2. Based on Jerry's symptoms, create two hypotheses of what could be causing his discomfort.

Pat II – Jerry's Diagnosis

When Dr. Alley came back into the room, Jerry asked, "Well Doc, what's wrong with me?"

Dr. Alley explained that during swallowing, a circular band of muscle around the bottom of the esophagus (the lower esophageal sphincter) relaxes to allow food and liquid to flow into the stomach. Then the sphincter closes again. If the sphincter does not close as it should or it weakens, stomach acid can flow from the stomach into the esophagus, which is referred to as acid reflux. This constant backwash of acid irritates the lining of the esophagus, often causing it to become inflamed. This causes the sensation of heartburn.

After a careful examination of Jerry's symptoms and questioning about the frequency of his heartburn, Dr. Alley diagnosed Jerry with gastroesophageal reflux disease (GERD, Figure 1). Jerry asked, "GERD? What's that?"

Dr. Alley explained that GERD refers to chronic acid reflux. "When symptoms of heartburn persist, occurring at least twice a week over an extended period, the condition is considered chronic. GERD or gastroesophageal reflux disease is the medical term for chronic reflux. I recommend treating GERD to prevent damage to your esophagus."

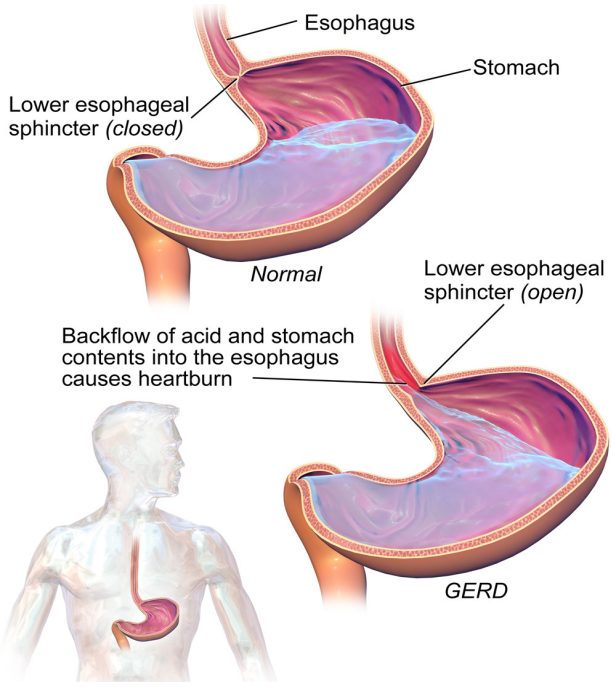

Figure 1. Gastroesophageal Reflux Disease (GERD). *Credit:* BruceBlaus, Wikimedia Commons, CC BY-SA 4.0.

Jerry paused a moment before saying, "I don't get it. How is my own body fluid hurting my esophagus?"

Dr. Alley replied, "Good question. Stomach acid is very acidic, more acidic than lemon juice. The stomach and esophagus are designed differently. The stomach's lining is designed in such a way to handle the corrosiveness of the stomach acid, but the esophagus is not. Unfortunately, when the stomach acid enters the esophagus, it can burn. When the stomach acid repeatedly enters the esophagus, the body adapts to protect itself. The adaptation is called Barret's esophagus. We want to prevent Barret's esophagus, because those cellular changes increase the risk of cancer."

Jerry still looked a little confused. In order to help him better understand stomach acid production, Dr. Alley showed him a diagram (see Figure 2, next page).

Questions

1. Review your knowledge of stomach acid production by reading the caption for Figure 2 and filling in the empty boxes in the stomach parietal cell. Potential answers include: Cl^-, H^+, HCO_3^-, H^+/K^+ ATPase, H_20, K^+. Answer choices may be used more than once.
2. The parietal cell releases two elements, generally referred to as stomach acid, into the lumen of the stomach. What two ions make up stomach acid?
3. How does H^+ get transported into the stomach lumen?
4. Individuals can experience a transient alkaline tide after eating a meal. What is an alkaline tide? Why would it occur after eating?

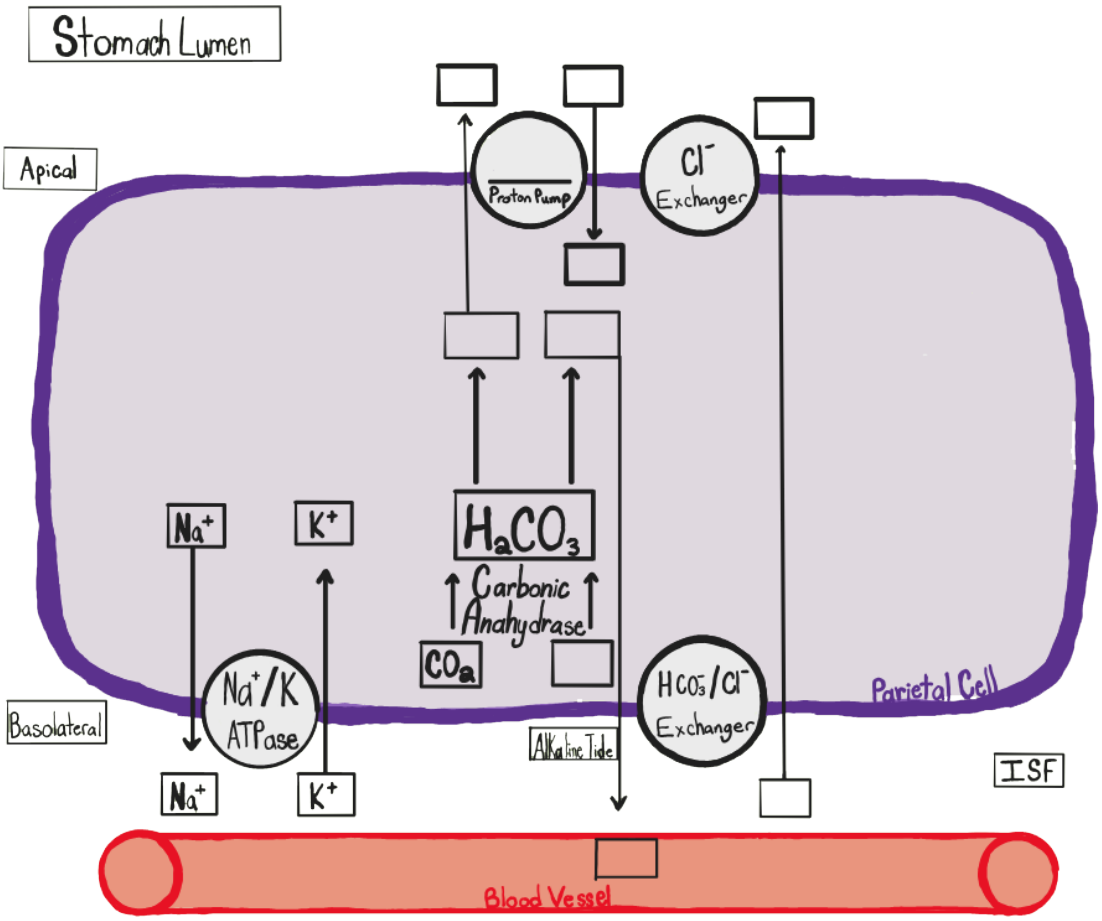

Figure 2. Stomach Acid Production by Parietal Cell. On the basolateral side of the parietal cell, the Na^+/K^+ ATPase pump moves sodium out of the cell and potassium into the cell. Within the parietal cell, in the presence of carbonic anhydrase, CO_2 and H_2O combine to form carbonic acid (H_2CO_3). H_2CO_3 spontaneously splits into bicarbonate (HCO_3^-) and a hydrogen ion (H^+, also known as a proton). On the basolateral surface, bicarbonate (HCO_3^-) is exchanged with a chloride ion (Cl^-), creating an alkaline tide in the blood. Chloride (Cl^-) then moves via facilitated diffusion into the lumen of the stomach. The apical H^+/K^+ pump (the gastric hydrogen potassium pump) actively transports H^+ into the stomach lumen and K^+ into the parietal cell.

Part III – Lifestyle Modifications and Medications

Once Jerry had a better understanding of the diagram his physician had shown him, he asked, "Doc, what can I do about all this?"

Dr. Alley replied, "Both lifestyle modifications and medication can be used to reduce your symptoms and give your esophagus time to heal."

"What type of lifestyle modifications are you referring to?" Jerry asked.

Question

1. List various lifestyle changes that could help Jerry in managing his gastroesophageal reflux disease (GERD).

Dr. Alley explained, "Lifestyle modifications are aimed at reducing substances that irritate your esophagus, stimulate reflex, and reduce your stomach acid production. I'm pleased that you've already taken the difficult step of quitting smoking. You are to be commended! Let's begin with dietary habits. Citrus fruits, carbonated beverages, spicy foods, fatty foods, coffee, and alcohol can further irritate your esophagus and increase the risk of acid reflux. Avoiding these foods and beverage may reduce your symptoms."

"I sure do like my morning cup of coffee, but I'd be willing to try reducing some of these foods. I'm ready to find relief."

"That's fair," replied the physician. "In addition to dietary changes, exercise and weight loss may reduce your symptoms. If you would like, I can schedule a consultation with our nutritionist. They can help you to develop a dietary plan aimed at treating gastroesophageal reflux disease (GERD) and help you to develop a weight loss strategy. Is that something you're interested in?"

Dr. Alley continued to answer Jerry's questions about the effectiveness of lifestyle modifications. Noting Jerry seemed a bit overwhelmed, she handed Jerry an infographic pamphlet. "Here, this pamphlet summarizes many of the things we've discussed. You can take it with you." Jerry started reading and immediately related to some of the common symptoms: heartburn, chest pain, regurgitation, dyspepsia, and esophagitis. His attention quickly turned to the part that said GERD affects about 20% of adults and 10% of children in the United States, with an increase of prevalence in those who are over age 40. That gave Jerry some comfort that he was not alone, but although he was tired of the symptoms he was experiencing, he also felt overwhelmed by the lifestyle changes he would have to make. He looked up from the pamphlet and said, "But Doc, what if I don't want to change these things? Do I have other options?"

"Well," replied Dr. Alley, "there are a variety of medications designed to reduce the production of stomach acid." She pulled out a chart and proceeded to show the different cells of the gastric pit, providing a brief overview of their function.

Use the following questions and Figure 3 (next page) to review the cells of the gastric pit and the regulation of stomach acid production.

Questions

2. Match the cell type with its function.

Cell Type	*Function*
___ Chief cell	a. gastrin production
___ D cell	b. pepsinogen production
___ Enterochromaffin-like cells	c. secrete histamine
___ G cells	d. produce mucus and bicarbonate
___ Mucous cells	e. produce somatostatin
___ Parietal cells	f. produce stomach acid

3. Review the regulation of stomach acid production by completing Figure 3.
   - For the parietal cell, complete the boxes to demonstrate stomach acid production and show membrane transporters on the apical and basolateral sides.
   - To demonstrate how the production of stomach acid is regulated, write the name of signaling molecule released from each of the provided cells. If the signaling molecule stimulates stomach acid production write "+" beside the provided arrow, if the molecule inhibits stomach acid production write a "-" beside the line.

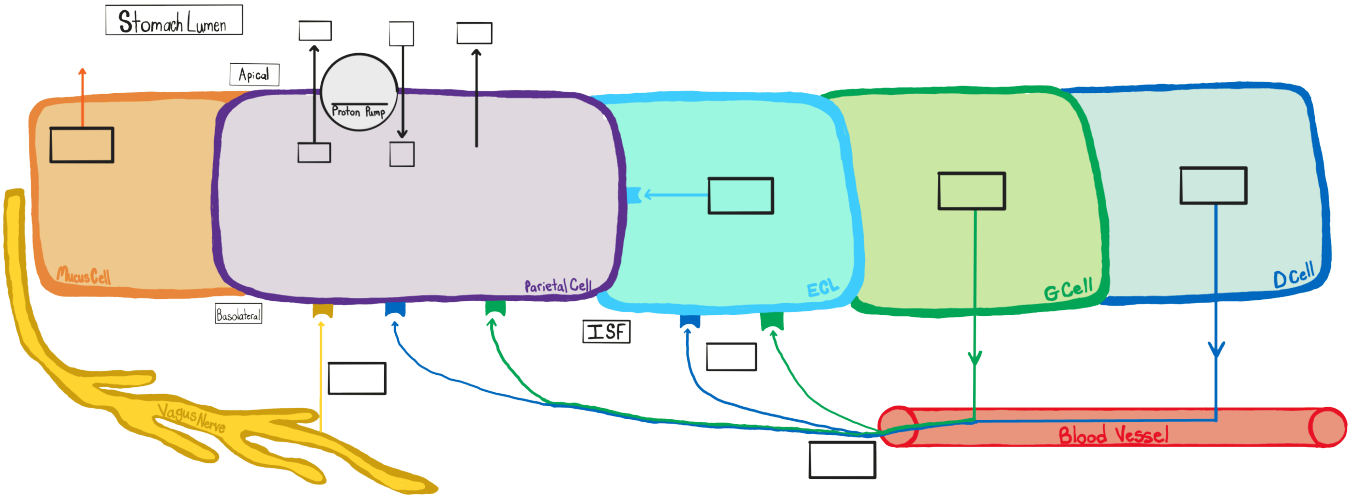

Figure 3. Cells of the Gastric Pit and Regulation of Stomach Acid Production.

4. Complete Table 1 (next page) to summarize how each of the signaling molecules impacts stomach acid production. For the source column, indicate which structure or cell(s) produce the signaling molecule. For the target cell column, indicate which cell(s) contain receptors for the signaling molecule. For the effects column, indicate the cellular changes that occur as a result of the signaling molecule binding to its receptor.

Table 1. Impacts of signaling molecules on stomach acid production.

Signaling Molecule	*Source*	*Target Cell(s)*	*Effects*
Acetylcholine			
Gastrin			
Histamine			
Somatostatin			

5. Which hormones or neurotransmitters bind to receptors on the parietal cell, causing an increase of stomach acid production?

6. Which hormones or neurotransmitters stimulate ECL cells, increasing histamine production, and therefore, indirectly increasing stomach acid production?

7. Which hormones inhibit stomach acid production?

Part IV – A Prilosec Prescription

Dr. Alley prescribed Jerry an H2 blocker. H2 blockers prevent a signaling molecule, histamine, from telling the stomach cells to increase stomach acid production. She explained, "This medication blocks about 70% of 24-hour gastric acid secretion."

Jerry said, "I don't want to add on another medication to take daily. Why can't I just take an antacid?"

Dr. Alley replied, "It seems you're somewhat conflicted on taking an H2 blocker. Antacids work by neutralizing the stomach acid and provide short-term relief. My hope in you trying this medication is that you can experience more sustained relief and we can prevent further health complications. H2 blockers are significantly more effective than antacids. Treatment typically lasts a couple of months, not a lifetime. Would you be willing to try an H2- blocker?"

Jerry nodded. "I'd just like to feel better."

"I understand," said the physician. "I'd like to check back in with you in a few months to see if you're experiencing relief. If the H2 blocker medication doesn't work, and you still have heartburn we can discuss a different class of medication called a proton pump inhibitor. Proton pump inhibitors (PPIs) act differently to decrease stomach acid production but there can be more side effects, which is why we're starting with the H2 blocker."

Questions

1. Complete the following table to compare antacids, H2 blockers, and proton pump inhibitors. If you are unsure how a medication works or its potential side effects, The Medline webpage "Plus, Drug, Herbs, and Supplements" (https://medlineplus.gov/druginformation.html) is an excellent resource.

Table 2. Comparison of antacids, H2 blockers, and proton pump inhibitors.

Treatment	*Drug Name (Brands)*	*Mechanism of Action*	*Potential Side Effects*
Antacids	Calcium carbonate (Tums ® and Rolaids) Aluminum hydroxide and magnesium hydroxide (ant-acid, Mylanta ® Ultimate)		
H2 blockers	Famotidine (Pepcid AC, Zantac 360) Cimetidine (Tagamet)		
Proton Pump Inhibitors	Omeprazole (Prilosec) Esomeprazole (Nexium) Lansoprazole (Prevacid)		

2. The FDA warns that proton pump inhibitors can increase the risk of gastrointestinal infections, specifically *Clostridium difficile* (*C. diff.).* Read the abstract below (Imhann et al., 2016) and provide one potential explanation of why PPIs increase the risk of *C. diff.*

Abstract of "Proton Pump Inhibitors Affect the Gut Microbiome"

Background and aims: Proton pump inhibitors (PPIs) are among the top ten most widely used drugs in the world. PPI use has been associated with an increased risk of enteric infections, most notably *Clostridium difficile*. The gut microbiome plays an important role in enteric infections, by resisting or promoting colonisation by pathogens. In this study, we investigated the influence of PPI use on the gut microbiome.

Methods: The gut microbiome composition of 1815 individuals, spanning three cohorts, was assessed by tag sequencing of the 16S rRNA gene. The difference in microbiota composition in PPI users versus non-users was analysed separately in each cohort, followed by a meta-analysis.

Results: 211 of the participants were using PPIs at the moment of stool sampling. PPI use is associated with a significant decrease in Shannon's diversity and with changes in 20% of the bacterial taxa (false discovery rate <0.05). Multiple oral bacteria were over-represented in the faecal microbiome of PPI-users, including the genus *Rothia* ($p = 9.8\times10^{-38}$). In PPI users we observed a significant increase in bacteria: genera *Enterococcus, Streptococcus, Staphylococcus,* and the potentially pathogenic species *Escherichia coli.*

Conclusions: The differences between PPI users and non-users observed in this study are consistently associated with changes towards a less healthy gut microbiome. These differences are in line with known changes that predispose to *C. difficile* infections and can potentially explain the increased risk of enteric infections in PPI users. On a population level, the effects of PPI are more prominent than the effects of antibiotics or other commonly used drugs.

Back at home, Jerry started taking his H2 blocker prescription regularly, knowing how this would help him to feel normal again very soon. He also made some changes to his diet such as eating fewer fatty foods, drinking less soda, and avoiding spicy foods. Furthermore, Jerry remembered how his physician recommended more exercise to decrease the risk of acid reflux, and so he resumed his favorite activity, golfing.

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