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Excessive Growth of Bacteria May Also Be Major Cause of Stomach Ulcers

Helicobacter pylori has received much attention as *the* cause of stomach ulcers, but new research by scientists at the Howard Hughes Medical Institute (HHMI) at the University of Michigan shows that many other types of bacteria can cause the gastritis and ulcers that can ultimately lead to cancer. The new research suggests that gastritis and ulcers are triggered by bacterial overgrowth, rather than by stomach acidity.

The researchers say their work suggests that long-term treatment of patients with potent acid blockers, called proton pump inhibitors, which produce a more alkaline environment that is unfriendly to acid-tolerant *Helicobacter pylori*, may actually allow the overgrowth of other types of bacteria, including *Lactobacillus*, *Enterobacter*, *Staphylococcus* and *Probionibacterium*. Overgrowth is excessive proliferation of bacteria. Proton pump inhibitors dissipate stomach acid, which serves an important anti-microbial function and protects the body from ingested microorganisms.

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— **Juanita L. Merchant**

The findings were published in articles in the January 2002 issues of *Gastroenterology* and the *American Journal of Physiology* — *Gastrointestinal and Liver Physiology* by HHMI investigator Juanita L. Merchant and colleagues at the University of Michigan.

The researchers were studying the action of the hormone gastrin, which is produced by specific cells in the stomach called G-cells. Gastrin stimulates growth and acid secretion in parietal cells, another set of cells found in the

stomach.

“The textbook understanding of how acid secretion is regulated is that an alkaline pH in the stomach triggers gastrin release,” said Merchant. “Once gastrin has restored an acid pH by stimulating parietal cells, acid production is supposed to shut down by way of a feedback control mechanism in which the suppressing hormone somatostatin is secreted from D-cells that sense the low pH.

“The problem is that when the stomach is infected, gastrin levels rise, and it wasn’t clear why,” she said. “We wanted to understand what was happening during bacterial infection of the stomach that caused this feedback mechanism not to kick in to prevent development of duodenal ulcers by preventing the production of excess acid.”

To determine whether gastrin itself was really central to the damage caused by bacterial infection in the stomach, the researchers studied mice in which the gene for gastrin had been knocked out, leaving the animals with insufficient acid production, which led to stomach inflammation, called gastritis. An important puzzle, said Merchant, was that these knockout mice could not readily be infected with *Helicobacter*.

“Initially we hit a wall, but we realized we actually had a means to an important insight,” said Merchant. “The reason we weren’t able to infect the gastrin-deficient animals with *Helicobacter* was that they were already colonized with large numbers of bacteria. This led us to understand more clearly that pH is regulating the types of organisms that colonize the stomach *Helicobacter* at low pH; mixed flora at high pH.”

When the researchers treated the gastrin-deficient animals with antibiotics, the inflammation decreased, as did the bacterial overgrowth. The scientists also noticed that inflammation triggered an increase in the number of parietal and G-cells.

When the researchers treated normal mice with the proton pump inhibitor omeprazole for two months, they noticed that these mice also developed stomach inflammation that was due to bacterial overgrowth. Treating these animals with antibiotics reduced inflammation and the amount of gastric bacteria. The PPI-treated animals also showed an increase in gastrin production, as well as an increase in the number of G-cells and parietal cells, indicating that their stomachs were attempting to generate acid to battle the bacterial infection. When the omeprazole-treated mice were given antibiotics, gastrin production decreased, as did the number of G-cells and parietal cells in these animals.

“A key finding is that we showed that these abnormal gastrin levels dropped down in omeprazole-treated mice just by giving them antibiotics,” said Merchant. “The question has always been whether this elevation and regulation of gastrin levels was because the secreting cells were regulated by the acid concentration. It turns out that’s not the case, because treating these animals with antibiotics caused their gastrin and parietal cells to return to

baseline levels. The elevation was due to inflammation.”

In the *American Journal of Physiology* article, Merchant and her colleagues demonstrated in mice that gastrin overproduction itself suppresses the ability of the D-cells to secrete somatostatin, which acts to shut down acid production in the stomach.

“The dogma in this field has been that the increase in stomach acid secretion in people infected with *Helicobacter* was because the infection was destroying D-cells,” said Merchant. “We showed that this is not correct. At the same time gastrin is stimulating acid production, it is also inhibiting the D-cell population. Thus, at the same time that the stomach is making efforts to increase acid secretion, it blocks the release of the inhibitor of gastrin and acid secretion.”

Merchant said that her group’s studies showing that omeprazole promotes bacterial overgrowth suggest that physicians should prescribe this class of drugs with caution. Proton pump inhibitors include drugs marketed under the trade names Prilosec® and Prevacid®.

“In treating patients with gastrointestinal disorders, physicians usually aim to increase the pH of the stomach, particularly in patients who are in the intensive care unit, to try to protect their stomach linings from ulceration which physicians initially believed was due only to stomach acid,” said Merchant. “There is also the dogma that most ulcers are due to infections by *Helicobacter* .

“But one important take-home point from our papers is that you don’t want to block acid secretion over the long term just to treat either the bacterial overgrowth or the *Helicobacter* infection, because that’s going to potentially create other problems.” Antibiotics should be used to treat such bacterial overgrowth, which will restore the normal acid-control mechanism, Merchant said.

According to Merchant, many physicians do seem to be limiting prescription of acid-reducing drugs. But proton pump inhibitors may eventually be sold over-the-counter, which could lead to chronic use of the drugs by people who are not being treated by a physician. Merchant emphasized, however, that current over-the-counter acid blockers like Pepcid AC®, Zantac®, and Tagamet®, a class of drugs called H2 receptor antagonists, will not trigger significant bacterial overgrowth because they do not suppress acid as completely as proton pump inhibitors.

“In general, the medical community needs to think more broadly about chronic infections in the stomach, colon, bladder and liver, because inflammation in all of these organs can lead to cancer,” Merchant said. “*Helicobacter* has quite correctly been labeled as a significant carcinogen, but our papers emphasize that other organisms can also cause chronic gastritis that may ultimately lead to cancer.”