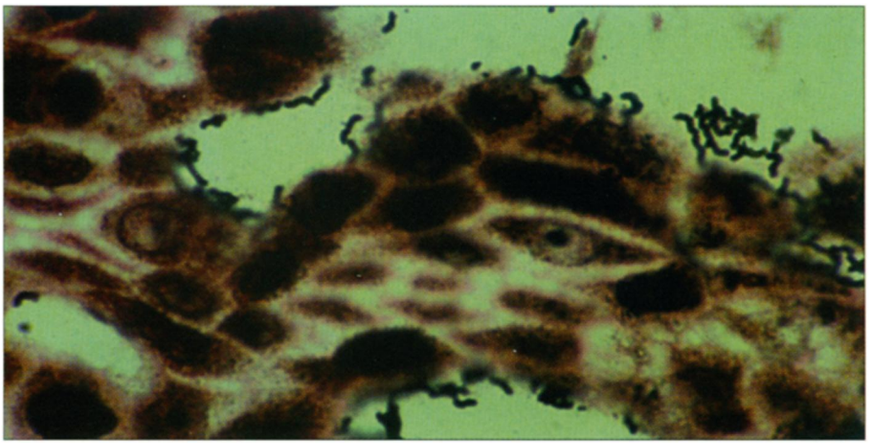
Is Your Stomach Bugging You?

The rise and fall of the bacterium H. pylori

By DAMARIS CHRISTENSEN


Marshall

This picture, taken 8 days after researcher Barry Marshall drank a culture of H. pylori *in 1982, helped prove that the bacterium causes stomach inflammation and potentially ulcers. It shows* H. pylori *(black) on inflamed tissue from Marshall's stomach.*

The chapter of medicine that describes the bacterium *Helicobacter pylori* is a tale of a few individuals taking a stand against the medical wisdom of their day. The once-improbable suggestion that a bacterial infection can cause ulcers is now dogma. Yet a maverick is now arguing that *H. pylori* may have some benefits as well, and so he warns that a wholesale campaign to eradicate the bacterium is premature.

Proving that this bacterium is responsible for ulcers was no small task. Until the 1980s, most physicians believed that high acid concentration in the stomach, stress, and spicy foods were the agents behind ulcers. Nevertheless, Barry J. Marshall and Robin Warren, physicians in Perth, Australia, became convinced that bacteria underlie the problem. They isolated what they believed to be the culprit in 1982. Over the next decade, Marshall and a few colleagues convinced gastroenterologists around the world that *H. pylori* is the leading cause of stomach ulcers.

At least a third to half of people worldwide are infected with *H. pylori*, although most infected people have no symptoms. The frequency of infection varies from country to country. In most developing nations, from 70 to 90 percent of adults harbor the microbe, probably from early childhood. In developed countries, fewer than 10 percent of children become infected, but generally, about 50 percent of 60-year-olds carry the bacterium.

For a small fraction of those who are infected, the consequences can be deadly. The microbe has been linked to stomach, or gastric, cancer, a leading killer worldwide. In their lives, 1 to 3 percent of people infected with *H. pylori* will develop stomach cancer—a risk up to six times that faced by uninfected people.

The bacterium also seems to trigger a much less common malignancy, mucosa-associated lymphoid-tissue lymphoma. This is a cancer of white blood cells found near the stomach lining. In 1994, the World Health Organization classified the bacterium as a carcinogen.

In the United States each year, some 7 million people suffer *H. pylori*–related disease, including ulcers, and thousands die, primarily from gastric cancer. Antibiotics can cure ulcers, and even some cases of the lymphoma.

In 1995, the Digestive Health Initiative, organized by the American Gastroenterological Association and other organizations, launched a campaign to convince consumers and physicians that people having ulcer symptoms should be tested for *H. pylori*. Since then, according to the initiative, the proportion of physicians ready to treat *H. pylori* has risen dramatically.

Just as gastroenterologists are beginning to smell success in their quest to eliminate the ulcer-causing microbe, however, an investigator who has studied *H. pylori* for many years is trying to convince researchers and physicians that the elimination of the microbe may not be such a good idea. Martin Blaser of Vanderbilt University in Nashville says that the bacterium's presumed long acquaintance with mankind may offer benefits.

His preliminary evidence suggests that people who aren't infected with *H. pylori* are more likely to develop reflux—a painful disease in which acid from the stomach backs through a leaky valve and inflames the esophagus. The bacterium may also reduce the risk of the cancer of the esophagus, he says.

In the long run, eliminating *H. pylori* may trade one cancer risk for another, Blaser contends. Still, other physicians point out that esophageal cancer is rare, whereas stomach cancer is the 14th-leading cause of cancer death worldwide.

The debate about whether *H. pylori* is good or bad needs immediate attention because the bacterium is a "submerging"—rather than emerging—infection, Blaser says. Beyond the effects of physicians treating *H. pylori* with antibiotics, the microbe is losing ground as community water supplies become cleaner and as overall hygiene improves. *H. pylori* infection is less common among the well-off than the poor, and less common in small families than large ones. These factors in part explain why it's less prevalent in developed countries than in developing countries.

Since 1968, the number of people in the United States infected with *H. pylori* has dropped by 50 percent. Similar trends are apparent in other developed countries.

"As *H. pylori* has been disappearing, peptic-ulcer disease and [lower-stomach] gastric cancers have predictably been decreasing," notes Blaser. "However, maladies such as gastroesophageal reflux disease, Barrett's esophagus [an ulcerlike disease in the esophagus], and cancers of the lower esophagus and gastric cardia [upper stomach] have been dramatically

and progressively increasing."

A few studies have begun to differentiate the effects of *H. pylori* on different segments of the gastrointestinal tract. The work focuses on a virulent strain of *H. pylori* carrying a gene called *cagA*. This strain is more likely than others to cause ulcers and stomach cancer and also to prevent diseases of the upper stomach and esophagus, Blaser contends. The prevalence of *cagA* strains varies from country to country; about 60 percent of *H. pylori* in the United States carries *cagA*.

Last year, a group of researchers working with Blaser showed that people with reflux disease, Barrett's esophagus, and esophageal cancer were less likely to be infected with *cagA* strains than people without these diseases were. The distribution of other strains isn't known.

Not everyone agrees that the link between *H. pylori* and esophageal cancer holds, says Adrian Lee of the University of New South Wales in Sydney. This September, debating Blaser at a meeting on *H. pylori* in Baltimore, Lee suggested that the rise in esophageal cancer and the absence of the bacterium might not be related. Changes in diet, body weight, or environmental exposures, all of which may be associated with both esophageal reflux and the transition to an industrialized lifestyle, might likewise explain the rise, he says.

Others agree with Blaser that there's a trade-off between esophageal cancer and gastric cancer. "An increased risk of esophageal cancer is the price one has to pay for the loss of *H. pylori*," says David Y. Graham of the Baylor College of Medicine in Houston. He suggests, however, that the increased risk of esophageal cancer isn't directly linked to the bacterium but to *H. pylori*'s effect in the stomach.

When there is severe, widespread, and chronic inflammation—such as that often caused by *cagA* strains—the stomach produces less acid. So, infected people are less likely to suffer from severe reflux, which can result from either stomach ulceration or cancer, he says.

While gastroesophageal reflux disease is now a growing problem in some developed countries, Graham notes that excess acid secretion can be easily managed by current medications. Moreover, not all people with high amounts of acid in their stomach also have the leaky valve that allows acid to eat away at the esophagus. "Reflux is a rare disease, and it will remain rare," he says.

Graham notes that epidemiological data suggest that eliminating *H. pylori* is likely to lead to, at worst, 1 esophageal cancer death for every 50 gastric cancer deaths it prevents and may prevent additional deaths due to ulcer complications. Gastric cancer versus esophageal cancer "is a phenomenal problem compared to a trivial problem," he says.

Blaser disagrees. In the United States, the number of esophageal cancers is increasing by 11 percent each year, the fastest increase of any cancer, he notes. He thinks the rise is lagging 20 to 30 years behind declines in *H. pylori* infection.

"I'm alarmed by the trends," he says. "Right now, gastric cancer is the bigger problem, but I'm afraid that the long-term trade-off isn't as favorable as it looks now. I believe we will eventually be looking at an epidemic of esophageal cancer if current trends continue."

Blaser hasn't always been alarmed by the loss of *H. pylori*. "I've spent more than a decade showing that *H. pylori* is bad," he says. "But then I began to think about the biology. If [the bacteria] have been with us for thousands of years, then it follows that the loss of infection seen in the 20th century is the aberration.

"The chances are that the benefits of having *H. pylori* infection at least balanced the costs, or else we would have evolved a better immune response," Blaser says.

It isn't clear when *H. pylori* first infected people or whether it affects other animals. A recent genetic analysis supports an ancient coexistence with humans.

An Italian scientist compared the genetic makeup of four strains of the bacterium from people in Europe, China, Japan, and New Zealand. He showed that slight differences in the DNA of the strains were consistent with patterns of human migration that began 100,000 years ago.

"The overlap between genetically distinct human and *H. pylori* populations supports the hypothesis that *Helicobacter* was already established in man's stomach at least 100,000 years ago, before the beginnings of the human migrations, and followed him thereafter," says Rino Rappuoli, who works in the Siena, Italy, laboratory of Chiron, a biotech firm based in Emeryville, Calif. His report appeared in the May 21 SCIENCE.

Nevertheless, Rappuoli isn't convinced by Blaser's arguments. "The idea that *H. pylori* must be doing something good because it has been with man for so long is a nice speculation, [but] the data that have been put forward for this theory are not yet convincing," says Rappuoli.

Blaser suggests that the inflammation *H. pylori* triggers in the stomach is valuable. He notes that when *Escherichia coli*, a normal gut inhabitant, inflames the linings of the intestines, it stimulates a response that helps the human immune system fight other invaders.

Some findings are beginning to support this hypothesis, says Blaser. He says that in a recent study, people infected with *H. pylori* had stronger immune responses to a cholera vaccine than did people who weren't infected.

H. pylori may also prevent other, possibly more harmful bacteria from infecting the stomach, says Hans G. Boman of the Karolinska Institute in Stockholm. In the April 22 NATURE, he reported that *H. pylori* makes a compound that kills other bacteria. With these intriguing findings, Boman says, physicians should wait for more studies on possible benefits of *H. pylori* before aggressively pursuing any program to eradicate the bacterium.

These concerns aren't enough to change Graham's opinion that "the only good *H. pylori* is a dead *H. pylori*." He contends that the comparison of *H. pylori* to *E. coli*, as a possibly beneficial bacterium, doesn't hold. The inflammation caused by *H. pylori* is much more severe and more likely to cause disease than is the reaction triggered by the strains of *E. coli* that normally live in the human gut. The strength of those reactions implies that the immune system is still trying to get rid of *H. pylori* and that the bacterium hasn't had a long history of infecting humans, says Graham.

He suggests that people might not have acquired *H. pylori* until they began to domesticate sheep. Shepherds in modern Italy are about 80 times as likely to be infected with *H. pylori* as are their siblings who aren't shepherds or as is the general population, Graham says. In the July 10 LANCET, he showed that 60 percent of raw milk samples from sheep on Italian farms contain traces of DNA from *H. pylori*. This suggests that the bacterium could have been transmitted to people centuries ago from sheep—perhaps its original host—via milk, he says.

Antibiotic therapy isn't perfect at eliminating the bacterium, possibly because *H. pylori* hides under the thick layer of mucus that protect the stomach lining against gastric juices. Even a combination of antibiotics eliminates only about 80 percent of infections.

Nevertheless, there's little question about the benefit of antibiotic therapy for people suffering from ulcers. Getting rid of *H. pylori* infection also cures about half the patients with mucosa-associated lymphoid-tissue lymphoma. Medical organizations recommend that physicians test anyone with stomach cancer for *H. pylori* infection and treat them with antibiotics if they are infected, although the benefits of such treatment haven't been demonstrated.

It isn't clear whether getting rid of *H. pylori* in people with no symptoms will reduce the risk of their later developing stomach cancer. Once the bacterium has been eliminated, adults rarely become reinfected. Several analyses have suggested that one-time screening for *H. pylori* infection among high-risk groups (such as those with a family history of the disease or a Japanese or Korean heritage) would be worthwhile.

If eliminating *H. pylori* infection reduced a person's chance of developing stomach cancer by just 15 to 25 percent, once-in-a-lifetime screening and treatment might be as effective in preventing stomach cancer as are repeated mammograms for breast cancer or blood tests for prostate cancer, says A. Mark Fendrick of the University of Michigan in Ann Arbor.

Widespread screening, however, raises questions about whom to treat. Although preventive measures would benefit people who otherwise would go on to develop ulcers or cancer, most infected people never develop any symptoms. The drug regimen to kill the bacterium is expensive—perhaps prohibitively so in the countries with the largest numbers of people infected with *H. pylori*. Widespread treatment also might speed development of antibiotic resistance among bacteria.

Most physicians don't yet recommend widespread screening for *H. pylori* among people who have no symptoms of stomach ailments. "Vaccines—the most effective medical practice in controlling infectious diseases—may represent the ultimate solution," says Rappuoli. Several vaccines are now under development.

If doctors screen for the microbe and treat those who are infected or if a vaccine is developed and widely used, *H. pylori*'s disappearance is likely to accelerate, warns Blaser. Unlike many physicians, he recommends against testing for and treating *H. pylori* infection in people with stomach pain but no proven ulcer.

"*H. pylori* can be good or bad, depending on context. It's entirely possible that physicians in the future will be administering selected *H. pylori* strains to colonize selected patients to reduce risks for particular diseases," he says.

"I completely disagree," Lee counters. "Just at the time that we've finally started to convince people that this bug causes gastric cancer, this doubt is stopping us from going on and aggressively eradicating this disease."

Debate over whether it's worth eradicating a microbe that causes few symptoms in most people isn't new, Graham says. "A hundred years, ago doctors debated whether to treat asymptomatic syphilis and decided it should be done," he says. Today, asymptomatic cases are still treated aggressively.

Once better therapies or vaccines to fight *H. pylori* are developed, says Graham, "we should get rid of every case." □

Biomedicine

From San Francisco, at the 39th annual Interscience Conference on Antimicrobial Agents and Chemotherapy

Vaccines without a sticking point

Getting vaccinated generally means enduring an unpleasant needle jab. Preliminary studies in mice, however, suggest that injectable liquid vaccines can be processed, dried to a powder, and painlessly pushed into the skin with a puff of helium gas from a pneumatic gun.

The skin is an ideal target for vaccines, says Dexiang Chen of PowderJect Vaccines of Madison, Wis. It contains a powerful network of immune cells acting as the body's primary defender against infection (SN: 9/11/99, p. 164).

Powders made from flu, tetanus, hepatitis B, and other vaccines induced immune responses in mice as well as injected vaccines do, Chen reports. Because immune cells lie close to the skin's surface, the powdered vaccine can contain just a tenth the amount of material required in standard formulations and still work—at least in mice, he says.

"This technique is preliminary but promising," says Philippe H. Lagrange of the St. Louis Hospital in Paris. Most liquid vaccines require refrigeration, but the powdered vaccines will probably be stable at room temperature, making them especially useful in developing countries, he adds.

So far, Chen and his colleagues have not worked with any vaccines that contain live, weakened viruses. Drying these formulations will be more complicated, but possible, Chen says. —*D.C.*

New drug gets a grip on HIV

Currently available anti-HIV drugs either block the virus from copying itself into a person's genes or prevent the virus from spreading through the body. Because HIV mutates rapidly, these drugs become less effective at keeping the infection from developing into AIDS. A small protein called T-20, a novel drug that prevents HIV from binding to its target cells, may offer some hope to patients whose current drugs are failing.

People with high concentrations of HIV in their blood despite having taken combinations of AIDS medicines participated in a trial led by J. Lalezari of Quest Clinical Research in San Francisco. Each of the 55 patients switched to a new mix of drugs that included injections of T-20. After 4 months, virus concentrations fell significantly in 33 of the volunteers. In 20, the virus became too rare to be measured.

These results are comparable to those seen with several experimental therapies undertaken after standard AIDS drugs have failed, says Michael S. Saag of the University of Alabama at Birmingham. Last year, researchers there reported that intravenous infusions of T-20 alone controlled HIV in a smaller group of patients (SN: 11/7/98, p. 292).

Although HIV will probably develop resistance to T-20 eventually, it should take some time because "we are looking at something with a totally different method of action than current drugs," says Saag. T-20 has few side effects, and patients seem willing to inject the drug twice a day, he reports. —*D.C.*

Curbing the common cold?

A new drug helps fight viruses responsible for the common cold. These pathogens, known as rhinoviruses, need to subtly alter the shape of their outer shell in order to infect cells. The drug, called pleconaril, blocks that shift.

People taking pleconaril did not suffer sore throats and stuffy noses as long as people getting a placebo did, says Frederick G. Hayden of the University of Virginia School of Medicine in Charlottesville. He found that 347 adults with moderate or severe colds suffered for 10.5 days when given pleconaril. The 168 people given a placebo endured their sniffles for 14 days.

"This is one of the first studies showing that an agent might reduce not only the severity but the length of viral infections," said William A. Craig of the University of Wisconsin-Madison.

Other studies presented at the conference confirm that pleconaril also benefits patients suffering from more serious diseases—viral meningitis and bloodborne infections caused by enteroviruses, which are close relatives of rhinoviruses. —*D.C.*