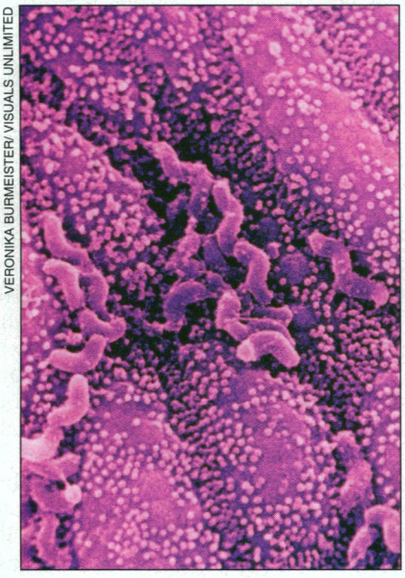
Ulcers as an Infectious Disease

A growing body of evidence suggests that most ulcers may result from bacterial infection—but the news isn't getting to the clinic or to the drug companies that make antacid drugs

Everybody knows the phrase: "Stop it—you're giving me an ulcer." What they probably don't know is that it could be literally true—you can "give someone else an ulcer." Because, it turns out, ulcers are caused by bacterial infection. At least that's what two studies published in the *Annals of Internal Medicine* and the *New England Journal of Medicine* within the past year find. Those studies, say many researchers, nail down the hypothesis, first advanced in the early 1980s, that most peptic ulcers are due to a specific bacterium, which could also be responsible for many cases of gastritis and gastric cancer.

The finding that a bacterium may underlie ulcers flies in the face of conventional wisdom. For half a century, medical dogma has held that stress, diet, smoking, drinking, and other factors cause the vast majority of ulcers by triggering excess acid secretion in the stomach. As a result, a central thrust of ulcer research was developing drugs to suppress stomach-acid secretion. This effort has been tremendously successful: Today, antacids such as cimetidine (Tagamet) and ranitidine (Zantac) are used to treat up to 90% of all ulcers, putting them among the top selling drugs in the United States and accounting for $4.4 billion in sales last year.



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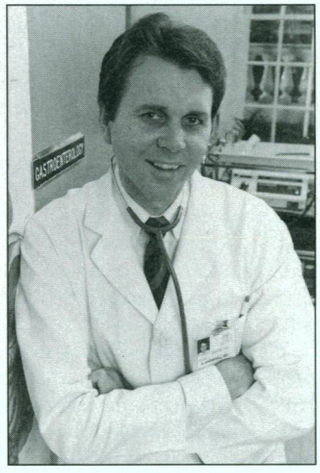

UVA

Marshalling the evidence. Barry Marshall and specimens of *Helicobacter pylori*, the bacterium he believes is responsible for most peptic ulcers.

Yet these drugs aren't very effective. The relapse rate for ulcers with the conventional treatment is about 50% over 6 months and as high as 95% over 2 years. "If we had the same results with cancer or an ear infection, we would consider the treatment unsuccessful," argues Martin Blaser, professor of microbiology and director of the division of infectious diseases at Vanderbilt University in Nashville.

In contrast, recent studies show that treating the bacteria associated with ulcers can reduce the recurrence rate to less than 20%. Nevertheless, though many researchers and clinicians at major research hospitals prescribe antibiotics for ulcers, the clinical community as a whole and the pharmaceutical companies haven't leaped on the bacterial bandwagon. A survey of major drug companies reveals only one working on an antibiotic for ulcer treatment. In fact, the story of the bacterial hypothesis for ulcers seems to be a case study in how medical practitioners and pharmaceutical companies can apparently be slowed by research that overturns received wisdom—to the potential detriment of millions of patients.

From the beginning, the notion that a bacterium causes ulcers faced an uphill struggle. Because of its acidity, mucus lining, and other factors, the stomach has been thought by bacteriologists to be an environment where bacteria are unlikely to grow. The first report of a spiral-shaped bacterium inhabiting the stomach appeared as early as 1892, but attempts to culture a bacterium from stomach tissues failed, and this claim and subsequent ones were dismissed as contaminations of biopsy tissue.

Then, in April 1982, serendipity struck. Barry J. Marshall, a resident in internal medicine at the Royal Perth Hospital in Western Australia, and pathologist J. Robin Warren were trying to culture a spiral-shaped bacterium Warren had seen in tissue biopsies from more than 100 ulcer patients. Repeated attempts to culture the bacterium had failed, but then the hospital was besieged by an outbreak of antibiotic-resistant *Staphylococcus aureus*. The microbiology lab was swamped, and Marshall's petri dishes remained in an incubator for 5 days, 3 longer than standard—and long enough for bacterial colonies to become visible.

Marshall and Warren named the new bacterium *Campylobacter pyloridis*. (The name was later changed to *Helicobacter pylori* when it was shown by other researchers that the organism did not belong to *Campylobacter*—or any known genus.) In 1983 Marshall and Warren proposed that the new bacterium causes peptic ulcer disease. "I was certain at the time that it would immediately gain universal acceptance and that within 2 years peptic ulcer therapy would be essentially an antimicrobial regimen," says Marshall, now an associate professor of medicine and gastroenterology at the University of Virginia Medical School.

But Marshall's expectations did not come to pass. It wasn't that researchers weren't interested. *H. pylori* possesses a number of unusual traits, and these prompted a flurry of work by microbiologists. Perhaps the most interesting of these, says Blaser, is that the bacterium possesses an unusual form of an enzyme called a urease. This novel urease, present in all *Helicobacters* isolated so far, is 10 to 100 times more active than other bacterial ureases. The enzyme splits urea into carbon dioxide and ammonia, an action that reduces acidity, making it possible for *H. pylori* to live in the highly acid environment of the stomach.

But even if *Helicobacter pylori* can make itself at home in the human stomach, is it the cause of ulcers? The evidence that it is is piling up in the most eminent journals. Last May, David Graham and colleagues at the Baylor College of Medicine, the Veterans Affairs Medical Center, and the Children's Nutritional Research Center, all in Houston, published in the *Annals of Internal Medicine* the results of a randomized clinical trial showing that only 12% of patients with duodenal ulcers and 13% of those with gastric ulcers had a relapse if treated for 2 weeks with a combination of ranitidine, the antibiotics tetracycline and metronidazole, and bismuth subsalicylate (the active ingredient in Pepto-Bismol). In contrast, the recurrence rate for patients receiving only ranitidine

was 95% for duodenal ulcers and 74% for gastric ulcers.

In February of this year, Enno Hentschel and colleagues at the Hanusch Hospital and the University of Vienna School of Medicine provided supporting evidence, reporting in the *New England Journal of Medicine* that duodenal ulcers recurred in only 8% of patients treated with antibiotics—compared with 86% in patients receiving a placebo.

For many researchers this means that the case for a bacterial cause of most ulcers has been made unequivocally. "I don't think there's any question that *H. pylori* infection plays a critical role in all but a small percentage of cases of peptic ulcer disease," said Richard Galbraith, an ulcer specialist at Rockefeller University Medical Center. Gastroenterologists at some major medical centers also find the data compelling enough to prescribe antibiotics for ulcer patients. At the Mayo Clinic, for example, antibiotic therapy has become standard treatment. "Our view here is that if you get rid of the bacterium, you get rid of the ulcer once and for all," says Nicholas J. Talley, associate professor of medicine.

And the benefits of prescribing that kind of therapy might not be merely medical. According to findings presented at a European workshop on *H. pylori*, which will be published as a consensus report in an upcoming issue of *Lancet*, eradicating *H. pylori* has the potential to cut the cost of gastrointestinal medicine by 80% over the next 5 to 10 years.

But the clinical practitioners of gastroenterology aren't rushing to reap these potential benefits. Some gastroenterologists, while accepting the idea that bacteria are associated with the recurrence of ulcers, don't think they're the cause. Says Denis McCarthy, chief of gastroenterology at the University of New Mexico School of Medicine: "I don't think the evidence supports that *Helicobacter* is involved in the initial development of an ulcer. *H. pylori* is certainly part of the jigsaw puzzle, but there is probably some other insult that sets the stage for *Helicobacter* infection." Only 90 miles north of the Mayo Clinic, in Minneapolis, nobody at the University of Minnesota Hospital and Clinic prescribes antibiotics for ulcers. "The case isn't strong enough yet," according to a hospital spokesperson.

In other cases, however, it isn't a matter of skepticism, it's simply that word from the research community isn't filtering through to the clinician. "The majority of physicians are still treating ulcers as they have for the past 20 years," says Blaser. A gastroenterologist in private practice, who insisted on anonymity, described the growing support for treating ulcers with antibiotics as "news to me. Most of us in private practice depend on drug company literature to learn of new therapeutic approaches."

And the drug company literature isn't filled with news of antibiotic treatments partly because drug companies don't appear to be interested in developing them. Calls by *Science* to a variety of major drug companies revealed only two—Astra Pharmaceuticals and Abbott Laboratories—that acknowledged they were working on developing antibiotics for use in treating ulcer disease.

Perhaps even better than new antibiotics would be a vaccine, given early in childhood. "This is the only approach that will ultimately succeed, because the ability of *H. pylori* to mutate and swap DNA segments makes it unlikely that resistance will not develop," says McCarthy. At least two biotechnology firms, Orovax, in Cambridge, and Chiron, in Berkeley, are currently developing an *H. pylori* vaccine.

While it would certainly be exciting to have a vaccine against ulcers, the role of *H. pylori* in human disease may not end with that condition. Epidemiological and biopsy data suggest that *H. pylori* infection may be a crucial first step in the genesis of gastric carcinoma. "What the evidence seems to show is that once a person is infected with *Helicobacter*, they remain infected for life. In most people, nothing develops except perhaps for a mild inflammation of the stomach lining," said Blaser, who has accumulated some of the epidemiological data. "In some patients, *Helicobacter* infection leads to ulcers, and in a third group it produces chronic atrophic gastritis, which is a well-known precursor of gastric carcinoma."

It's not known what factors determine which of these three outcomes is realized. Nor do researchers have the answer to another key question: how the bacterium is transmitted. Epidemiological data showing that infection rate is highest where sanitation levels are lowest suggest that in developing countries oral-fecal transmission may be the most common route of infection. Those data, however, don't explain how transmission occurs in the United States and other developed countries.

Such mysteries will be unraveled some day, and if by then ulcers have gone the way of polio and smallpox, Marshall, nearly everyone agrees, deserves major credit. "Though he can certainly be on the outrageous side"—he once dosed himself with the bacterium to make his case—"he probably deserves a Nobel Prize for this work," says McCarthy. Marshall would no doubt not refuse the Nobel Prize, but he's not convinced his work is done. The main task, he says, is to get news of his conclusion to where doctor meets patient. "We need to do a better job getting this information into the hand of the practitioners outside of the major research institutions if this discovery is ever going to have a major effect on health care in America."

–Joseph Alper

EVOLUTION

Why Some Fishes Are Hotheads

JAMES D. WATT

A warm body. The yellowfin tuna...

Anyone who has taken a swim in a cold lake knows how fast the water drains heat from your body. Fish have it worse; water not only surrounds their bodies but circulates across their gills as they breathe. No wonder most of the 30,000 species of bony fishes don't try to warm themselves: They are cold-blooded, their body temperature fluctuating with that of the water. But the tunas, the swordfish, and several dozen other fishes don't give in to the cold. To animal physiologist Barbara Block, how and why these fishes came to be warm in some parts of their bodies was an irresistible evolutionary puzzle. In this issue of *Science* (see p. 210), Block and her team at the University of Chicago provide what other biologists are hailing as some of the best evidence yet about what drove the evolution of endothermy, or internal warming, in these fishes—and insight, says Block, into how the trait evolved in other animals.

For years, researchers have debated two hypotheses about why animals first became endothermic: as a means of maintaining body warmth so that they could be active in habitats of varying temperature (the "niche expansion" hypothesis) or as a byproduct of the high metabolism needed to sustain an active lifestyle (the "aerobic capacity" hypothesis). Their fish studies, say Block and her students John Finnerty, Alexandre Stewart, and Jessica Kidd, give strong support to niche expansion as a driving force. By using the tools of molecular biology to probe evolutionary history, they found that the three different groups of endothermic fishes evolved the trait independently. And in each case the trait evolved as the fishes' ancestors expanded their ranges into colder waters.

Other evolutionary biologists are embracing that conclusion. "Before, what we had were 'Gee-whiz' observations about warm-blooded fish," says James Spotila, an endo-