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## ANNALS OF MEDICINE

### MARSHALL'S HUNCH

*The unprecedented and very unorthodox findings of an unknown doctor point toward cures for stomach diseases that afflict millions.*

BY TERENCE MONMANEY

So few people believed Dr. Barry J. Marshall when he said that peptic ulcers were an infectious disease caused by bacteria that hid out in the stomach that he decided to make his point in the most vivid way possible. One July day in 1984, he awoke early, skipped breakfast, drove to the hospital—he was then a thirty-two-year-old resident in internal medicine at the Fremantle Hospital, in Perth, Western Australia—went to his lab, donned his white coat, and fixed himself a drink containing about a billion of the suspect bacteria. “Ulcer bugs,” he called them.

As Marshall stood by a high lab bench thoughtfully swirling his turbid bacteria cocktail, a guy who worked in the lab said to him, “You’re crazy.”

Marshall said, “Here goes,” and downed it. He cringed.

“Tastes like swamp water,” he observed.

In a way, Marshall’s self-inoculation experiment appeared to be a gamble that he couldn’t happily win. If he stayed well, he would have proved himself wrong; if his hunch was right, he would become sick, perhaps hideously so. Flouting the established procedure, he hadn’t consulted the hospital’s ethics board, because he figured that it would disallow the experiment as too dangerous. Nor had he told his wife about it: he didn’t want to worry her. He was taking this step, he wrote later, out of “desperation.”

The peptic ulcer, a sometimes deadly and always ghastly crater where the small intestine joins the stomach, hardly seemed to be the glamorous unsolved problem that a young physician would eagerly stake his career on, never mind

his health. True, peptic ulcers were quite common, afflicting nearly one out of ten adults. But drugs such as Zantac and Tagamet greatly eased the disorder by stanching the stomach acid that aggravates the wound. So many people took those ulcer medicines, and for such extended periods, that they were the world’s biggest-selling prescription drugs, with annual sales in the billions of

dollars. And that profit bonanza was supposed to keep growing, as the baby boomers headed into their years of high anxiety. But before Marshall started his self-experiment, he’d established that antibiotics were capable of killing the bug in a test tube, and if he was right about its role in ulcers, antibiotics might be able to cure people of the affliction outright. In a decade or two, he thought, there might be no more ulcers to treat. So his little project actually had astronomical potential. The moment he swallowed the bugs, this unknown physician on the edge of the outback threatened to deprive some of the largest corporations in the world of billions of dollars.

At the same time, Marshall’s theory challenged widely held and seemingly unassailable notions about the cause of ulcers. No physical ailment has ever been more closely tied to psychological turbulence. “The critical factor in the development of ulcers is the frustration associated with the wish to receive love,” one social scientist reported in 1983. She went on, “When this wish is rejected, it is converted into a wish to be fed,” which ultimately leads, she said, “to an ulcer.” In “The Search for the Real Self,” a 1988



*When Dr. Marshall unveiled his theory about ulcers, he might as well have claimed to know the secret of cold fusion.*



book on "the personality disorders of our age," Dr. James F. Masterson states that the peptic ulcer is a "psychosomatic disorder" that typically afflicts people who are "hungering for emotional supplies that were lost in childhood or that were never sufficient to nourish the real self." In the lay manual "Understand Your Ulcer," a highly regarded gastroenterologist declared, "It is a disease of tense, nervous persons who live a strenuous and worrisome life." The book's jacket copy struck a world-weary chord, and described the ulcer as "a disease of civilization, closely linked with the tense tempo of modern life and the hurry of everyday existence."

The idea of American life itself as an ulcer-causing agent runs through the medical literature. The influential 1968 edition of "Stress and Disease" states, "There may even be, at some given time in history or in a particular cultural group, a prevailing type of reaction involving illness, as for example, peptic ulceration." The author, a famed psychiatrist named Harold G. Wolff, suggests that ulcers arise primarily because contemporary society, with its "competitive striving," triggers in some people a reaction (excessive secretion of gastric juice) that is a throwback to "the jungle period of Man's evolutionary development," when "the appropriate thing to do with an opponent or adversary was to kill and eat him." According to this scenario—which seems to draw equally on Darwin, Marx, and Edgar Rice Burroughs—capitalist society poses all the savage threats of primitive life and yet provides none of the satisfactions. Primed for a bloody clash that never comes, we devour our insides instead.

To Marshall, though, the peptic ulcer was not a darkly self-inflicted wound or a symptom of one's failure to cope with stress or a curse of modernity; seldom does microbiology contribute to philosophy, but if there should be such a thing as an ulcer bug an awful lot of gloomy talk about modern life must therefore be nonsense. Marshall first presented his theory outside Australia in 1983, at a gathering of infectious-disease specialists in Brussels. The audience was full of heavyweights, and before them stood this young nobody, tall, thin, loose-limbed. He had moppish brown hair, a smirky smile, that broad Aussie humor. Except for dark rings around his eyes, everything about him was boyish. He smoked a cigarette now and then—a medical heretic to

the core. Marshall had been coached to play down his ideas, to discuss his findings with the proper scientific restraint, but he could not hold back. "I was euphoric," he recalls. His happy-go-luckiness, combined with his inexperience (still a physician-in-training! not even in infectious diseases!), did not that day inspire total confidence in his authority.

Marshall told the group that it was his close colleague Dr. J. Robin Warren, a pathologist at the Royal Perth Hospital, who had discovered the bacteria, in 1979, while poring over biopsies of stomach tissue taken from patients with a variety of digestive complaints. And Marshall talked about how he had then pursued Warren's weird observations and how over several months he had found the bacteria in the stomach of almost every patient he saw with stomach inflammation, most patients with chronic severe indigestion, and almost every patient with peptic ulcer (provided that the patient wasn't also regularly consuming large doses of aspirin, which can cause peptic ulcers). The way it looked to Marshall, people infected by the bug first developed stomach inflammation, and then some fraction of those went on to develop chronic indigestion or peptic ulcer. (Later, he even began to think that the bug might cause stomach cancer.) And, as far as he could tell, the bug itself wasn't some new pathogen that had sprung out of the rain forest and into the belly of humanity; he thought that his older patients had probably been infected for decades.

When Marshall finished speaking, an audience member stood up and gently inquired, "Dr. Marshall, what causes peptic ulcers in people who don't have the bacteria?"

"If you don't have the bacteria, you don't have a peptic ulcer," Marshall said. He might as well have said he knew the secret of cold fusion. The scientists chuckled and murmured and shook their heads, a little embarrassed for a junior colleague whose debut was such a disaster. Dr. Martin Blaser, the director of the Division of Infectious Diseases at the Vanderbilt University School of Medicine, was in the audience. Marshall's talk struck him then as "the most preposterous thing I'd ever heard," he says. "I thought, This guy is a madman."

Because of Marshall's remarks in Brussels, and later in print, he quickly gained a dubious notoriety. It was one

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thing to declare that bacteria caused peptic ulcers—nothing like that had ever been proposed before. But bacteria *living* in the stomach? For months or years? Where's this guy from, again—Perth? Can you even get *The New England Journal of Medicine* there? The human stomach is an antiseptic bath designed precisely for killing microbes, like those in food. Gastric juice, a mixture of digestive enzymes and hydrochloric acid, is highly caustic. It can dissolve iron nails. About the only living tissue that could survive prolonged exposure to stomach acid, the thinking went, was the stomach. Considering the masses of bacteria, fungi, yeast, mold, and viruses that plunged almost constantly into the stomach, it was free of live microbes to such a remarkable degree that experts said it was sterile.

But far from simply dismissing Marshall's ideas, dozens of scientists more or less independently paid him the highest tribute their profession could bestow: they set out to prove him wrong. Dr. David Y. Graham, a distinguished gastroenterology researcher at the Veterans Affairs Medical Center in Houston, recalls of his first impression of Marshall's work, "Here's some crazy guy saying crazy things. It seemed that he was going to set the field back years. But the virtue of his idea was that it was testable—it wouldn't be hard to find out if it was true."

As Marshall's critics hastened to point out, maybe the bacteria he had seen in his patients' stomachs were just some contaminant that had stuck to the biopsy specimens. Or maybe the bacteria did live in the stomach but weren't pathogenic—mere colonizers that caused no damage, like a lot of oral bacteria and skin bacteria. Or maybe the stomach bacteria he had found were opportunists—moved in *after* the ulcer had weakened local defenses.

Marshall had hoped to answer those objections by transmitting the infection to experimental animals and following its course. He and his assistants had

managed to culture the bacteria, and in his first animal test he injected the bacteria into the abdomens of two rats. Nothing happened. Next, he fed the bacteria to baby pigs. Again, nothing. Perhaps not surprisingly, given the stuff that rats and pigs eat and the muck they wallow in, the animals easily resisted the stomach bug. "I felt as though I'd failed miserably," Marshall recalls of his negative results, adding, "I was going nowhere fast." It was then that he decided that his next experimental animal would be Barry Marshall.

A few hours after he swallowed the bacteria, his stomach started growling, and it growled the rest of the day. Aside from that, he was fine for a week. On the eighth day, he awoke at dawn, felt nauseated, and vomited. "If I'd had any brains, I would have caught some of it and analyzed it," he says of the vomitus. "But I was half asleep at the time. I did notice it tasted funny—no acid—and I remember thinking that that was strange." That afternoon, he measured his body temperature: normal. Over the next week, he had several headaches but ran no fever. Hunger stalked him. His mother, who was a nurse, mentioned to him that his breath

smelled foul. Later, a few co-workers told him the same thing. He grew tired, irritable, hoarse. He looked pale and drawn.

In the middle of the experiment's second week, Marshall underwent endoscopy and biopsy: a tube with both a tiny video camera and pincers at the lower end was snaked down his gullet; the camera sent pictures to a TV monitor, and the pincers clipped a bit of stomach tissue for analysis. This was a second session: the first session, conducted a few weeks before, had revealed him to be in the pink of health. But now the physician who performed the biopsy noted that Marshall's stomach lining was inflamed, slimy, as punky as an old mushroom. Microscopic analysis of the biopsied material revealed a festering infection—swarms of bacilli seeming to hover around inflamed stomach cells. A third biopsy, performed four days later, revealed no infection: gone. Marshall's immune system had evidently managed to fight off the invasion, and he felt fine.

Describing the ordeal in the April 15, 1985, issue of *The Medical Journal of Australia*, Marshall and his co-workers pointed out that this bug was no benign colonizer. And yet Marshall was struck

by what an oddly gentle siege he had undergone. He hadn't missed an hour of work. Anyone whose stomach happened to be experiencing an invasion of the bacteria might easily mistake the symptoms for exhaustion or indigestion. Or stress. "We were quite happy just to show that the germ was involved in disease," Marshall says. "It didn't seem necessary for me to go all the way and get an ulcer to make that point. An ulcer—you know, it's quite unpleasant."

IN 1986, Marshall and his family moved to Charlottesville, Virginia, and he is now an associate professor of gastroenterology at the University of Virginia School of Medicine there. His office is in an old brick building that was once a cancer ward. Sprayed across the ceiling



"Remember when life was all Heigh-ho! Come to the fair?"



above his desk are brownish-maroon spots. "Blood," he said. "Probably a punctured aorta."

A decade after the tomatoes flew in Brussels, Marshall continues to talk about the medical dogmas he has been up against—and it seems that he's still fighting a few—but the fact is that he has tenure, and two answering machines can hardly handle all his calls. He possesses an unusual combination of iconoclasm and eminence. He's a towering rebel. Martin Blaser, of Vanderbilt, whose first impression of Marshall was so unfavorable, now has fifteen colleagues in his lab working on the ulcer bug. "He certainly didn't have the bearing or the demeanor of the scientist," Blaser says of Marshall as he appeared in the Brussels gathering. "But, to Barry's credit, he had the vision. In science, you need the vision—and, of course, the precision."

In 1989, after several years of nomenclatural debate, the bacterium that Warren and Marshall discovered was finally named *Helicobacter pylori*, because the rod-shaped bacillus is twisted into a helix and because it generally inhabits the pylorus, the gateway to the duodenum of the small intestine. Few experts now doubt that the bacterium causes a great deal of human misery. Armies of medical scientists have published more than fifteen hundred papers on *Helicobacter*—a torrent of research that has turned up astonishing things. For Marshall, the trumpets of vindication sounded last February, when a definitive clinical trial performed by Austrian scientists finally backed up his prediction. "STUDY CONFIRMS MOST ULCERS ARE CAUSED BY A BACTERIUM, CURABLE BY ANTIBIOTICS," *The Wall Street Journal* announced at the time. Meanwhile, field epidemiologists have been jumping into jeeps and airplanes and running off to test people all over the world for *Helicobacter* infection. They've found it everywhere. To quote a paper in *The Lancet* last fall, "*Helicobacter pylori* is arguably the commonest chronic bacterial infection in man." And, perhaps the most striking development yet, chronic *Helicobacter* infection is now recognized as a major cause of stomach cancer—the world's second most common malignancy.

David Graham, whose first impression of Marshall had been of "some crazy guy," and Mae F. Go, Graham's co-worker in Houston, wrote in the July issue of *Gastroenterology*, "It would have

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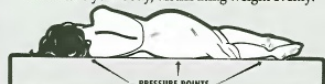
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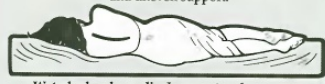
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been unimaginable that such seemingly diverse diseases as gastritis, gastric ulcer, duodenal ulcer, and the intestinal form of gastric carcinoma would all be different manifestations of an infection with a bacterium. The unimaginable has happened." Unprecedented though they may be, the findings have an old-fashioned ring. In this era of the elusive untamable virus, here's a big fat squirming bacterium. And though important work on *Helicobacter* is being done by gene splicers, a lot of crucial stuff can be learned with a microscope. Pasteur could lend a hand. In recent years, historians and sociologists have emphasized that science progresses not by bold leaps of truth—an aggrandizing myth, they say—but by slight adjustments to the accepted framework of ideas. But the discovery of *Helicobacter* is no crummy little paradigm shift. It's a mindblower—tangible, reproducible, unexpected, and, yes, revolutionary. Just the fact that a bug causes peptic ulcers, long considered the cardinal example of a psychosomatic illness, is a spear in the breast of New Age medicine, which invokes the mind-body link as the key to health. What a burden! Happily, *Helicobacter* says it's not our fault.

Julie Parsonnet, a medical epidemiologist at the Stanford University School of Medicine, is a principal author of a key study establishing *Helicobacter's* role in stomach cancer. Originally, she had set out to prove that Marshall was wrong about *Helicobacter*—that it was in fact a harmless stomach colonizer. "It took several years for me to learn that I was wrong," she says. Reflecting on Marshall's role as a prime mover, she says, "All science is going to happen. Somebody was going to find the bacterium sooner or later. But the fact is he did find it. And he wrote it up and he pushed it."

ACTUALLY, Warren and Marshall were not the first to observe *Helicobacter* in the human stomach. Since the turn of the century, other medical workers (as Marshall learned when he delved into the literature) had glimpsed the bug, had even published microscopic pictures of stomach tissue in which these bacteria were in evidence, but they neglected to pursue it or identify it. Then, in the fifties, a supposedly definitive study of human gastrointestinal flora concluded that the stomach was microbe-free, and thus it came to be viewed as a "sterile" or-

gan. No longer did many pathologists even bother to check the stomach for resident bacteria, and, more significant, those who found the microbe doubted their own eyes. They did not see it because they did not believe in it.

Meanwhile, during the seventies, gastroenterologists perfected the endoscope, which allowed them to gaze directly upon living digestive tissue, making it much easier to perform meaningful biopsies and also to diagnose gastritis and peptic ulcer more accurately. And microbiologists developed new techniques for identifying and culturing fastidious bacteria like *Helicobacter*, which requires a trace of oxygen but drowns in air. When Warren was reached in Perth by phone and asked how he managed to discover *Helicobacter*, he said, "It was something that came out of the blue. I happened to be there at the right time, because of the improvements in gastroenterology in the seventies." Warren's voice was soft, and classical music was coming from a radio on his desk. He went on, "Mind you, I never saw any patients. All I got were little bits of stomach tissue in a bottle. Anyone who said there were bacteria in the stomach was thought to be slightly crackers. By the time Barry Marshall turned up, I think my colleagues in the department believed me. But I needed a clinician to help me—to see how my findings were related to symptoms, whether or not getting rid of the bacteria got rid of the symptoms."

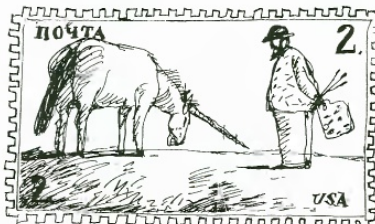
After Marshall had begun to establish links between *Helicobacter* and gastritis, he was able to see certain other nagging mysteries in a new light. One concerned the ulcer medicine DeNol, which had been marketed for years in Europe. DeNol contains the heavy metal bismuth—a low-tech, old-fashioned therapeutic. Bismuth subsalicylate is the active ingredient in Pepto-Bismol. A couple of small studies had shown that DeNol prevented the recurrence of peptic ulcers better than any of the newer high-tech acid-blocking drugs did. And yet no re-

searcher, not even DeNol's manufacturer, knew why. The entry on bismuth preparations in a standard modern pharmacology text says, "The mechanism of its action is unknown."

Marshall had an idea, though, because heavy-metal compounds had been used to fight infectious microbes in the days before the discovery of highly specific antibiotics like penicillin. Pepto-Bismol was originally marketed as a therapy for cholera infantum, a type of bacterial diarrhea that struck babies. From 1984 to 1988, Marshall and his colleagues treated hundreds of ulcer patients with combinations of antibiotics and DeNol. He was running an "underground clinic," he says, giving patients antibiotics even as his supervisor, a gastroenterologist of the old school, was prescribing for them acid-blocking drugs, Valium, peace and quiet, and psychotherapy. In 1988, Marshall and eight co-workers in Perth threw down the gauntlet, announcing in *The Lancet* that their combined bismuth-and-antibiotic therapy healed ulcers far better than one of the most commonly prescribed acid-blockers.

So far, researchers at various medical centers have performed a dozen studies showing that antibiotics, administered alone or with a bismuth-containing agent, can cure ulcers and generally prevent their recurrence by wiping out *Helicobacter* infection. In February of this year, the Austrian researchers reported their dramatic findings, in *The New England Journal of Medicine*. The researchers treated fifty-two ulcer patients with two antibiotics (metronidazole and amoxicillin) and the acid-blocker ranitidine, or Zantac, and another fifty-two patients with placebos and ranitidine. The antibiotics wiped out the infection in forty-six patients, and of those only one had a recurrence of ulcers (most likely because of heavy aspirin intake). Of those who received the acid-blocker but not antibiotics, forty-two had an ulcer relapse. "Our results support the concept of a cause-and-effect relation between *H. pylori* infection and recurrent duodenal ulcer," the Austrians dryly noted. They went on, "We now offer this combination of antibiotics and ranitidine to patients with *H. pylori*-associated chronic duodenal ulcer disease, as an alternative to long-term drug-maintenance therapy or elective surgery."

From now on, it appears, acid-blockers





will be used as an adjunct to antibiotics in ulcer therapy. This promises unsurpassed relief to millions of people—and considerable savings. A standard maintenance regimen of Zantac—the world's No. 1 prescription drug, with an estimated three billion dollars in sales last year—runs about a hundred dollars a month. Over the years, a person with a recurring ulcer might easily spend ten or fifteen thousand dollars keeping it quiet. In contrast, a twelve-day ulcer-curing course of the antibiotics amoxicillin and metronidazole, which are generic drugs, would cost about twenty dollars. All told, Marshall estimates that an ulcer can be cured outright for six hundred and fifty dollars, including the costs of visits to a physician, antibody tests, endoscopy, and drugs.

The makers of the leading acid-blocking drugs were not initially among Marshall's biggest fans. Marshall says he tried right from the start to interest pharmaceutical firms in his findings. "I wrote a letter to all the major drug companies," he recalls. "I said, 'Look, I've got some major new advances related to ulcers, and I'd like to tell you about them and ask for some support.' They wrote back—practically a form letter—'Dear Dr. Marshall, we're very pleased to know you've got major new findings, but research funding is very tight this year, blah, blah, blah, congratulations, blah, blah, keep up the good work.' And that was about all I got." What a difference a decade makes. Now, pharmaceutical giants as well as university labs and small firms are scrambling to cash in on *Helicobacter*. Everything from new diagnostic tests to new antibiotics are in the works. Recently, Marshall says, he has helped to conduct clinical trials of new drugs, funded by Glaxo (maker of Zantac) and other major drug companies.

Graham, whose research team has done important studies on antibiotic treatment of ulcers, recently told me, "Over time, within perhaps even my lifetime, we should be able to eliminate ulcer disease from the human race."

It takes a kind of cunning for *Helicobacter pylori* to fill its niche, for the adult human stomach is one of nature's most hostile habitats. Each day, the stomach normally produces about half a gallon of gastric juice, whose strong hydrochloric acid and digestive enzymes readily tear meat and microbes apart. Gastric juice is like a binary chemical

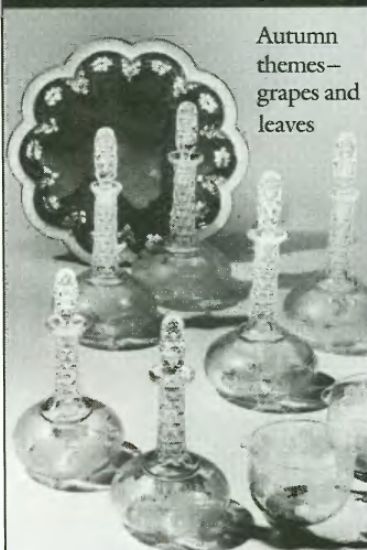
weapon—so destructive that it's constituted only on the way to the target. As cells in the stomach lining secrete the raw ingredients of gastric juice into the mucus that coats the stomach lining, the ingredients mix into an even more caustic brew, which then oozes into the cavity. There the gastric juice breaks pabulum down chemically while muscles in the stomach wall act to crush it. The viscoelastic mucus, as thick as axle grease, keeps the stomach from digesting itself.

Once *Helicobacter* reaches the stomach, it probably does not linger out in the open cavity—a tossing sea of toxic chemicals. It heads for cover. The bacterium's helical shape seems to have been designed for speedy travel in a dense medium. *Helicobacter* is living torque; a microscopic Roto-Rooter, it corkscrews through the mucus. Then, instead of penetrating the cells of the stomach lining, it settles in the mucus just beyond the lining. More often than not, it settles in the pylorus. No one knows why. Under the microscope, a *Helicobacter* infection looks like a satellite image of an armada gathered off a ragged shore. At one end of the bacterium is a cluster of long, wispy, curving flagella, which may serve as anchors. It's a graceful menace.

*Helicobacter* possesses a vital defense against stomach acid, and this adaptation, too, is a marvel of evolutionary design. Its coat is studded with enzymes that convert urea—a waste product, virtually unlimited supplies of which can be found in the stomach—directly into carbon dioxide and also into ammonia, a strong alkali. Thus *Helicobacter* ensconces itself in an acid-neutralizing mist. In like fashion, it generates another anticid—bicarbonate, as in Alka-Seltzer.

A *Helicobacter* infection that establishes itself succeeds largely because the immune system can't reach it. In response to a *Helicobacter* invasion, immune-system cells in the bone marrow produce white blood cells, killer cells, and other microbe destroyers, and those float through the bloodstream to the very edge of the stomach lining—and go no farther, because the lining holds them back. The *Helicobacter*, hovering in the mucus, are out of range. And yet the immune system sends reinforcements. Killer cells pile up, gorging the stomach lining; permanently alerted, seldom engaged, the killers become trigger-happy. Some die, fall apart, and spill their microbe-fighting com-

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pounds into the host tissue. Friendly fire begets friendly fire. Metabolic hell breaks loose. The lining is now inflamed: acute gastritis. Micronutrients are pumped from the bloodstream to the front lines, to feed the killers, but loads of them seep out of the stomach lining and into the mucus. Offshore, the *Helicobacter* feast; having drawn the immune system into battle, the bacteria now loot the provisions. "I propose that inflammation is good for *Helicobacter*," Blaser says. "That's what it wants."

Chronic gastritis, a standoff between the bacteria and the host's immune system, may persist for years—decades, according to some estimates. As it happens, whatever serious damage is done to stomach or intestinal tissue is apparently done not by the bacteria themselves but by the inflammatory response they provoke. That the host plays such a large role in his own pathology may help explain why *Helicobacter* infection affects different people differently. (Also, scientists recently discovered that there are at least two strains of *Helicobacter pylori*, and that one of them is far more likely to cause a peptic ulcer than any other.) Inevitably, though, for *Helicobacter* to be really successful it has to meet a parasite's final challenge: to start another colony before the host dies.

The means by which *Helicobacter* usually travels from person to person remain something of a mystery. There are sound ideas about how the infection spreads, but very little hard data nailing down the routes. The bacterium's exotic requirements for food and shelter, in addition to its susceptibility to oxygen, imply that it does not survive long outside the human body. After numerous pathological studies, it has still not been shown to infect the blood or any tissues besides the gastrointestinal tract; and so researchers believe that blood does not carry or transmit the bacterium. Nor is there any evidence that the bacterium is sexually transmitted or acquired.

At the moment, the best clinical and epidemiological evidence is that human beings acquire *Helicobacter* orally. A study published last November showed, for the first time, that *Helicobacter* can be found in fecal matter. As a result of that finding, many researchers believe that a large number, if not a majority, of *Helicobacter* infections are acquired by the ingestion of waste-tainted water or food, or by oral

contact with waste-tainted skin. But that is probably not the only transmission route. The mouth, besides serving as the entrance for the bacteria, appears to be an exit as well. Microbiologists have found live bacteria in the dental plaque of some persons with *Helicobacter* stomach infections; presumably, the bacteria do not colonize the mouth but only pass through. A common symptom of active gastritis and peptic ulcer is belching, and it is likely that such an eruption (not to mention vomiting) blasts *Helicobacter* into the mouth. Given that, one can conceive of scenarios. For instance, a man with an ulcer retires for the night, but his sleep is troubled by gastroesophageal reflux—heartburn. The backwash carries *Helicobacter*. Upon awakening, he kisses his wife good morning. She washes the *Helicobacter* down with coffee. The exchange of microbes gives new meaning to the old notion that people can give each other ulcers.

WITHIN a few years after Marshall first proclaimed that *Helicobacter* caused human disease, and in spite of what a 1991 scholarly review called the "nearly universal initial skepticism" that greeted his idea, researchers had developed new screening tests for the infection. One commonly used test looks for serum antibodies. (Even though the immune system may not engage the bacteria directly, it can generate antibodies from bacterial corpses and sloughed-off parts.) Seizing on the antibody test, medical researchers rather quickly charted the broad scope of *Helicobacter* infection.

In rural Gambia, British researchers found that ninety per cent of the children they tested had been infected by the age of five. In the Ivory Coast, researchers found the infection in most of the three-to-six-year-olds they tested. In some parts of Africa, researchers have observed, the infection "is almost universal among adults." In Bangkok, a *Helicobacter*-antibody survey of poor children in a local orphanage found that seventy-four per cent of them had become infected by age four. In China and Vietnam, in Papua New Guinea, in Colombia and Peru, in Algeria, in Burkina Faso, in every Third World country tested so far, researchers have documented startlingly high rates of infection. And more often than not the infection appears to have been acquired in childhood.

Because researchers don't know exactly how *Helicobacter* is transmitted, they're at a loss to explain why the Third World populations tested seem all but saturated with the infection. Generally, though, high rates of gastrointestinal infections are associated with a low standard of living, partly because of poor or nonexistent sanitation. But a lack of plumbing may not be the entire answer. In Burkina Faso, for instance, some women premasticate food for their babies, and it is conceivable, as medical researchers working there have pointed out, that mothers are thus passing the bacteria to their children.

In the developed world, *Helicobacter* infection is somewhat less common, on the whole, and it is rare among the very young. An antibody survey in France found that less than one per cent of those under the age of six had the infection. In England, a broad survey found the infection in only ten per cent of those under twenty, but in fifty per cent of those over fifty. A similar pattern seems to hold in the United States. Graham, after analyzing numerous studies conducted in the United States, has derived a rough *Helicobacter* equation: age group equals scope of infection. Accordingly, about twenty per cent of people in their twenties are infected, thirty per cent of people in their thirties, and so on. The correlation between age and infection puzzles researchers. One possible explanation is that people in the industrialized nations simply tend to pick up the infection later in life than people elsewhere. But many researchers favor another model—that a greater percentage of older people are infected because *Helicobacter* got transmitted much more frequently in the past. This model assumes that changes in the standard of living—less crowding, smaller families, more effective sanitation—have gradually curbed the spread of *Helicobacter*. Also, the extensive use of antibiotics for other infectious diseases, especially in children, may have incidentally reduced *Helicobacter* infections.

Waning or not, the infection is common, even in the industrialized world. For a bacterium that was discovered only a decade ago, and the mere idea of which had been scorned as preposterous, to be globally endemic is amazing. In a 1991 monograph, Marshall says, "In my naiveté, I expected *H. pylori* to be immediately accepted as the cause of duodenal



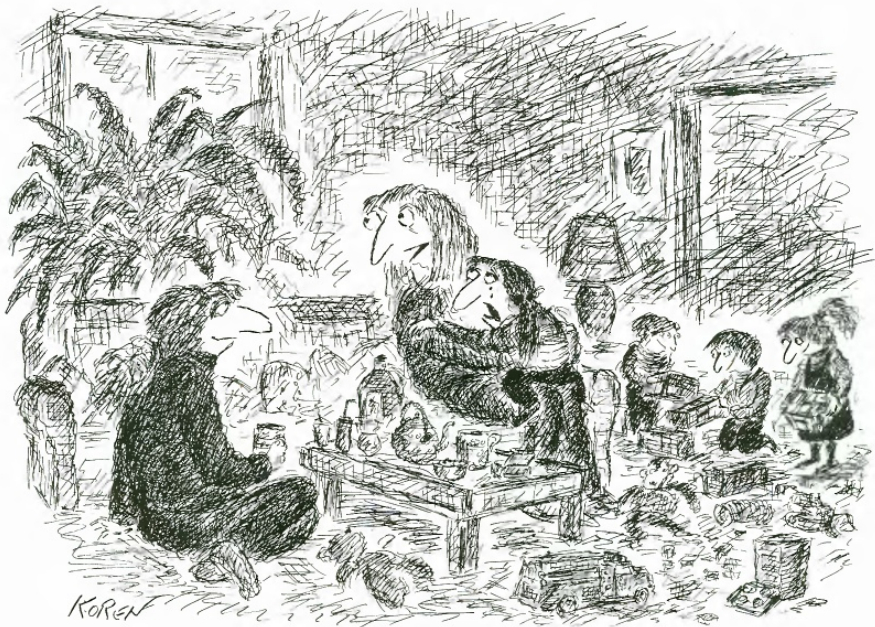
ulcer and gastritis, but I did not expect it to be the world's most common bacterial infection."

A REMARK that Marshall made in his first paper on *Helicobacter* could be compared to the wise-alecky "it has not escaped our notice" in James Watson and Francis Crick's landmark DNA paper of 1953. These as yet unidentified bacteria, Marshall wrote, "may have a part to play in other poorly understood, gastritis associated diseases," including, he said parenthetically, "gastric cancer." As he recalls it, he was basically connecting the dots. "Once I'd become convinced that the germ was involved in gastritis, I just looked up gastritis in a textbook and saw what *it* was associated with," he says. "And one of those things was stomach cancer."

Naturally, the experts thought he was crazy. To be sure, they'd suspected that stomach cancer somehow slowly arose out of chronic gastritis. According to one authoritative evaluation, published in 1986, "the entire process leading from superficial gastritis to gastric carcinoma is thought to take from 16 to 24 years."

No, as the experts saw it, the problem with Marshall's cancer claim was the bacteria. A bacterium had never before been causally connected to such a common human cancer. Besides, the thinking went, stomach cancer was too complex and too important to be brought on by a picayune gut bacterium. Worldwide, stomach cancer was the second-leading malignancy, and it would have been the leader if not for cigarettes, because lung cancer was No. 1. In the Third World, stomach cancer was extremely common—downright epidemic in parts of Asia and Latin America. Oddly, though, stomach cancer had been steadily disappearing from the industrialized world. In the United States, stomach cancer had been the leading fatal cancer before 1940. Since then, it had not merely tapered off but plummeted, to No. 8. By the late seventies, stomach-cancer deaths stood at one-sixth their former peak. The change was a total mystery—"an unplanned triumph," public-health authorities said.

Marshall had checked a number of his



*"She's not very good at defending herself, but she does very well at identifying her feelings."*

stomach-cancer patients in Australia for the bug, and he had nearly always found it. That was encouraging—it didn't disprove his idea—but it didn't prove it, either, because stomach cancer generally strikes older people, and most of them, it turned out later, have *Helicobacter* anyway. In any event, the main contribution he made to the unfolding cancer research was his self-inoculation experiment: by helping to prove that the bug caused gastritis, he forced even the naysayers to take the idea seriously.

By the late eighties, epidemiologists had pieced together the global distribution of *Helicobacter*, and they could see that it nearly matched that of stomach cancer: high rates in Third World nations, low rates in industrialized nations. As for the most dramatic feature of stomach-cancer epidemiology, the steep decline in places like the United States, that trend fitted in very nicely with the idea that industrialization curbed *Helicobacter* transmission.

Still, the population surveys fell short of establishing a cause-and-effect relationship; there was no telling which came first, the tumor or the bug. Finally, in the fall of 1991, two major studies on

*Helicobacter* and stomach cancer added to the equation the crucial missing dimension—that of time. One study drew on several thousand Japanese-American men in Hawaii who had enrolled in a health program in the sixties. The other study (Parsonnet, of Stanford, was a co-author) drew on more than a hundred thousand California residents who had enrolled in a health-maintenance organization in the sixties. The key to both studies was that the enrollees had had blood taken in that decade, and the blood samples had been frozen.

The researchers first tracked down all cases of stomach cancer in both groups and then performed a *Helicobacter*-antibody test on the patients' previously donated blood. The tests showed that nearly all the patients had been previously infected with *Helicobacter*. Obviously, the infection had come before the malignancy. But what was most significant was that the infection was nearly half again as common among the stomach-cancer patients as among enrollees without cancer who were of the same sex and age and had a similar background. Tallying the odds, the researchers found that, over all, *Helicobacter* infection multiplied an



individual's likelihood of developing stomach cancer from three to six times. And for some people the danger was even greater. Among blacks in the California group, the infection increased the stomach-cancer risk nine times; among women, the risk rose to eighteen. By comparison, smoking cigarettes for years is thought to increase one's risk of developing lung cancer twenty times. Clearly, long-term *Helicobacter* infection can act as a potent carcinogen.

Significantly, the Hawaii and California studies arrived at the same estimate for the amount of stomach cancer caused by the bacteria: sixty per cent. Worldwide, then, *Helicobacter* may be responsible for something like half a million cancer deaths a year. The vast extent of the toll is forcing experts to rethink cancer causality and also to recalculate basic cancer risks—especially those risks attributed to diet. For years, public-health agencies have promoted the idea that a large proportion of human cancer—about a third—was triggered by what we ate or didn't eat. And stomach cancer was considered among the most important of all diet-related cancers. It has been linked to excessive intake of preservatives such as salt, pickling brine, and nitrites (remember the nitrite scare?), and to low intake of fresh fruits and vegetables. Of course, what we eat still may be involved in stomach cancer; not all stomach-cancer victims carry *Helicobacter*, and most people with the bug don't get cancer, so it could well be that some other factor works in concert with the bug. But the starring etiological role once enjoyed by dietary factors has been shrunk to a supporting role, if not a bit part. Suddenly, our diet looks much less carcinogenic. Marshall says, "Americans tend to worry about environmental or dietary chemicals causing cancer, but those do not seem so important now, because of *H. pylori*."

The exact process by which *Helicobacter*-induced gastritis can lead to malignancy rather than peptic ulceration is a matter of speculation. Blaser, who was a co-author of the Hawaii study, believes that the decisive factor may be age at the time of infection. Cancer may be the expression of a *Helicobacter* infection acquired early in life, he says, whereas an ulcer may reflect a somewhat later

acquisition or infection with an especially ulcerogenic *Helicobacter* strain. Roughly, the odds that, say, a twenty-year-old infected with *Helicobacter* will develop a peptic ulcer in his lifetime are fifty-fifty, Marshall says; that he'll develop stomach cancer, one in a hundred. "The key thing about *H. pylori* infection is that it doesn't come and go," Blaser says. "It persists in most people probably for life. It can do its damage acutely or chronically, or maybe both. It's remarkable to have one organism that we're attributing to at least two diseases."

It has not escaped anyone's notice that the working out of *Helicobacter's* role in stomach cancer immediately suggests a means of preventing many cases of the disease. For some time, Marshall has been running a sort of modest cancer-prevention program. It hinges on the evidence that primary relatives of people with gastric cancer have an elevated risk of developing the disease. Until recently, that clustering was usually attributed to



genetic factors; now researchers figure that it reflects familial transmission of *Helicobacter*. Whenever a person with stomach cancer walks into Marshall's Virginia clinic, he insists on testing the person's spouse, children, and siblings for *Helicobacter*. If any of them test positive, he recommends antibiotic therapy for them to eradicate the infection, cure any underlying gastritis, and thus, he hopes, reduce the likelihood that they will develop stomach cancer. Perhaps this triumph will be planned.

THESE days, Marshall is studying another noisome, wickedly common gastrointestinal ailment—non-ulcer dyspepsia, or indigestion. It is not the sexiest problem going, but it afflicts tens of millions of Americans, and it is responsible for a large portion of the billion dollars spent each year on over-the-counter antacids and other digestive aids. Marshall thinks that the root cause of many cases is *Helicobacter pylori* infection.

His colleagues are not surprised to find him making that point, and the skeptics are no less skeptical this time around. Dr. Loren Laine, writing in *Gastroenterology* last year, said, "Multiple studies have failed to document that

symptoms of nonulcer dyspepsia correlate with the presence of *H. pylori* and treatment studies have not convincingly documented that eradication leads to resolution of symptoms."

"I'm having a lot of trouble showing that that disorder is related to *H. pylori*," Marshall says. "But I don't get too upset anymore. I think it's just that the right clinical trials haven't been done yet." What makes dyspepsia so difficult to study is its subjectivity: the symptoms are the varied, fleeting discomforts common to many gut problems. For some reason, chronic recurring dyspepsia is more common among women than among men.

To study the problem, Marshall has struck upon a deeply innovative medical technique: he listens to his patients and takes what they say seriously. Every day, at whatever time they wish, a number of his dyspeptic patients get a phone call from Marshall's computer. His recorded voice asks how they feel, asks about their symptoms that day, what medications they've been taking, any side effects—an automated medical diary. He is treating them with antibiotics, to rid them of *Helicobacter*, and he wants to find out if their symptoms vanish as the bugs do. That, he says, is the only way of linking infection and indigestion. The recording reminds the patients of Dr. Marshall's number, in the event that any of them want to speak with him personally. "Thank you," the recording says. Showing off the computers that keep in touch with his patients, he said, "I'm something of a hacker." He added, "We have another recording, done by a nice American woman, for people who don't speak Australian."

"A lot of the experts up in their ivory towers believe that non-ulcer dyspepsia is a psychiatric or functional disorder," Marshall explained. "What I see often is a forty- or fifty-year-old woman with a twenty-year history of vague digestive symptoms—pain, discomfort, never gets worse, never gets better. Usually, she's been to a lot of doctors—men—and they can't find anything wrong, so they say she's neurotic. Usually, she's had her gallbladder removed—which made no difference, probably only made things worse. And the thing is, by now the women themselves are convinced they're basket cases, because they've been told that so often. I don't think these women are crazy. But it has been very difficult convincing my colleagues of that." ♦