

Bacteria, Ulcers, and Ostracism?

H. Pylori and the Making of a Myth

Medicine's purported ostracism of the discovery of H. pylori has achieved a mythological quality. But it isn't true. After appropriate initial scientific skepticism, the hypothesis was accepted right on schedule.

KIMBALL C. ATWOOD IV

In the September/October 2003 SKEPTICAL INQUIRER, I wrote an article critical of the research agenda of the National Center for Complementary and Alternative Medicine (NCCAM) (Atwood 2003). Subsequently, reader Myra Jones argued in a letter to the editor that "we as skeptics should not throw the baby out with the bath water. Just because the NCCAM has funded bad science doesn't mean that . . . some alternative medicine might not have valid claims. Many practices now accepted were once thought crazy by the medical mainstream" (Jones 2004). Part of my reply to her was this: "For example, which practices? Initial skepticism of any new claim is an appropriate part of the scientific approach. . . . Other than that, I challenge Ms. Jones

to name a single example, since the era of scientific medicine began in the second half of the nineteenth century, of a correct claim that faced dogmatic, closed-minded rejection by the 'medical mainstream' for any significant amount of time" (Atwood 2004).

Be careful what you ask for. A few weeks later, the editors received this letter from Dr. Tess Gerritsen:

As a physician, a long-time skeptic, and a member of CSICOP, I'm happy to agree with most of Dr. Atwood's points about

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alternative medicine. However, when he challenged letter writer Myra Jones to come up with a "single example, since the era of scientific medicine began in the second half of the nineteenth century, of a correct claim that faced dogmatic, closed-minded rejection by the 'medical mainstream' for any significant amount of time," I must respond in Ms. Jones's defense.

When I was first starting out in medical practice, back in the early 1980s, the accepted treatment for peptic ulcer disease was a bland diet plus antacids and more antacids. Later, histamine H₂-receptor antagonists were added to the treatment. But that was it, case closed.

Then, in 1984, physicians Warren and Marshall from Australia claimed that peptic ulcer disease was not caused merely by overproduction of gastric acid, but rather by a specific bacterium: *Helicobacter pylori*, to be specific. They recommended antibiotic therapy. Believe me, they were ridiculed by the medical establishment. I recall my colleagues, and even my own physician-husband, scoffing at the idea of peptic ulcers being an infectious disease. For the next thirteen years, most of the "medical mainstream" refused to let go of their calcified notion that the only treatment for ulcers was to combat gastric acid secretion. After all, that was what we all learned in medical school. Therefore, it had to be the truth!

It wasn't until 1997 that the CDC finally put out the word to the nation's doctors: Drs. Warren and Marshall had been correct all along. *Helicobacter pylori* was, indeed, the cause of most cases of peptic ulcer disease. The treatment, at long last accepted by mainstream medicine, is now antibiotics.

This is only one example; I'm sure my physician colleagues can think of others. This is a case where skepticism (my own and that of others) delayed the use of effective ulcer treatment for over a decade. I think Ms. Jones's warning that we "not throw out the baby with the bath water" is indeed a good one. Skepticism is good and healthy, but at its extreme, it can turn into rigid closed-mindedness.

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This is an oft-heard argument. Ms. Jones, in response to my challenge, offered the same example in a private e-mail to SI editor Kendrick Frazier. "CAM" supporters brought it up a couple of years ago at a meeting of the Massachusetts Special Commission on Complementary and Alternative Medical Practitioners, of which I was a member. At least one recent article in a mainstream medical journal has made the same claim, without attribution (Kaptchuk 2003). Medicine's purported ostracism of the discovery of *H. pylori*—to some extent, as we shall see, fostered by one of its discoverers—has achieved a mythical quality.

But it isn't true. I have no reason to doubt that many physicians scoffed when first faced with the notion of a bacterial basis for peptic ulcer disease (PUD). It is not the case, however, that the medical mainstream dogmatically rejected the proposal for an undue period of time. A brief history shows that the hypothesis was accepted right on schedule, but only after "appropriate initial skepticism"—the premise of my challenge—was satisfactorily answered. Some of the other particulars of the mythical version of the story are also incorrect.

Before proceeding, I would like to reiterate another point made in the context of the challenge: all biomedical proposals, "CAM" or otherwise, can only be judged according to what is known about nature. The warning that by refusing to commit scarce resources to the investigation of implausible claims, we risk "throwing the baby out with the bath water," implies that we have little basis for deciding which claims merit further investigation. But that isn't true, either.

Background

Medical researchers Robin Warren and Barry Marshall first reported the curious finding of "unidentified curved bacilli on gastric epithelium in active chronic gastritis" (not ulcer) in two letters to the British journal *Lancet*, published on June 4, 1983. They noted that similar bacteria had been described intermittently, possibly as early as the nineteenth century and certainly since 1938, but that these had never been cultured and their significance was unknown. They explained that the bacteria cannot be seen with usual staining methods and surmised that this is why they had typically been overlooked. They reported that the bacteria are found beneath gastric mucus, thus possibly explaining how they might be protected from gastric acid. They noted that similar bacteria had been described in other mammals and were thought to be "commensals"—harmless inhabitants of the gastric mucosa (stomach epithelium). Nevertheless, because Dr. Warren had found the bacteria in biopsy specimens of inflamed gastric mucosa but not in normal ones, Dr. Marshall cautiously suggested, "If these bacteria are truly associated with gastritis . . . they may have a part to play in other poorly understood, gastritis associated diseases (i.e., peptic ulcer and gastric cancer)" (Warren and Marshall 1983).

One year later, in the June 16, 1984, *Lancet*, Marshall and Warren published their first full paper on the topic. They further characterized the bacterium, reported its first successful culture, and established that it was a new species of unclear relation to any previously characterized. At that time, they and others were still referring to it as a form of campylobacter—variously called *C. pyloridis* or *C. pylori*—because of morphologic similarities with other campylobacter species, but Marshall and Warren recognized that there were important differences. These differences eventually led to it being renamed *Helicobacter pylori*.

The authors reaffirmed the association of the bacterium with gastritis, but they now also reported it in association with both gastric and duodenal ulcers. Nevertheless, they remained cautious: "Although cause and effect cannot be proved in a study of this kind, we believe that pyloric campylobacter is etiologically related to chronic antral gastritis and, probably, to peptic ulceration also" (Marshall and Warren 1984). They did not recommend antibiotic treatment but reported that bismuth—an established treatment for PUD when coupled with acid suppression, that seemed to be associated with reduced relapse rates compared to acid suppression alone—was bactericidal to the new "pyloric campylobacter." A bacterial cause of PUD, they suggested, could thus explain the finding of a reduced incidence of relapse in patients treated with bismuth. All of this was plausible but, of course, still new and unproved.

The Initial Response of Investigative Medicine

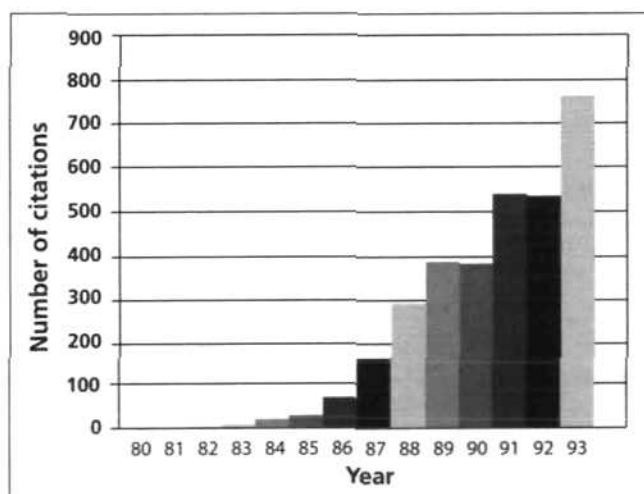
For Marshall and Warren's proposal to gain scientific and clinical momentum, several requirements had to be met: others had to confirm both the bacteriologic and clinical findings; stronger evidence than mere "bystander" status for an etiologic (causative) role of the bacteria in PUD had to be offered and replicated; diagnostic methods less cumbersome and expensive than endoscopy, biopsy, and culture—the methods used by Warren and Marshall—had to be developed; and antibacterial

treatment had to be shown to be more useful—i.e., as safe as but more effective than—standard treatments. The last requirement was not trivial, as I will discuss. All these steps would take time.

One might expect that if scientific medicine had dogmatically rejected Warren and Marshall's hypothesis, there would be scant references to their reports for the several years after the initial publications. The opposite is the case: the biomedical world was abuzz with *Campylobacter pylori* from the start, as is demonstrated in the figure. It shows the number of papers listed on PubMed, the online database of the National Library of Medicine, as a function of the calendar year throughout the 1980s and early 1990s. The rate of increase after 1983 is nearly exponential. Anyone who doubts the infatuation that medicine had with *C. pylori* at the time can surf to PubMed and, using the same search criteria that I used to generate the data for the figure, peruse thousands of abstracts.

Within a couple of years of the original report, numerous groups searched for, and most found, the same organism. Bacteriologists were giddy over the discovery of a new species. By 1987—virtually overnight, on the timescale of medical science—reports from all over the world, including Africa, the Soviet Union, China, Peru, and elsewhere, had confirmed the finding of this bacterium in association with gastritis and, to a lesser extent, ulcers. Simpler and less invasive diagnostic methods were devised (Graham et al. 1987; Evans et al. 1989). The possibility of pyloric campylobacter being the cause of gastritis or ulcers was exciting and vigorously discussed, even as it was acknowledged by all, including Marshall and Warren, to require more evidence. Here is a typical opinion, in this instance from the Netherlands: "There is an explosion of interest in the role of *Campylobacter pylori* as a cause of active chronic gastritis. . . . To what extent this intriguing microorganism is causally related to peptic ulcer disease remains to be elucidated, but all the evidence which is available so far supports a pathogenetically important role" (Tytgat and Rauws 1987).

The New England Journal of Medicine, the most widely read medical journal in the world, offered this editorial: "Further unfolding of the details [of the possible etiologic role of



Search performed at PubMed (www.ncbi.nlm.nih.gov/PubMed) using the search terms *campylobacter pylori* or *campylobacter pyloridis* or *campylobacter pyloric* or *campylobacter-like* or *helicobacter pylori* or *curved bacilli gastric*. The 1982 and one of the 1983 citations had to do with animal studies.

Year	Number of citations
1980	0
1981	0
1982	1
1983	2
1984	16
1985	25
1986	58
1987	155
1988	283
1989	383
1990	379
1991	539
1992	538
1993	762

C. pylori in peptic ulcer disease] will be enhanced by the development of an animal model, by epidemiologic studies, and by identification of the source and the virulence properties of specific serotypes of *C. pylori*. The prospects are exciting, intriguing, and promising" (Hornick 1987).

The Quest for Proof of Cause

Establishing that a microbe is the cause of a specific disease is not a simple task. The mere presence of microorganisms, even if reliably found in association with diseased tissue, does not prove that the organism causes the disease. Myriad species of bacteria and fungi are always present in the human large intes-

Unlike anthrax, TB, pneumococcal pneumonia, bubonic plague, malaria, cholera, and other dreaded microbial diseases investigated near the end of the nineteenth century, presumptive *H. pylori* gastritis or even peptic-ulcer disease is not particularly dangerous.

tine, for example, but most never cause diseases. Thus, there must be specific evidence of cause and effect.

The accepted standard for establishing such a causal relation was offered by Robert Koch in 1882, during the flowering of the Germ Theory of disease. As described in his classic lecture "Die Aetiologie der Tuberkulose," Koch established the bacterial cause of tuberculosis by the following steps:

1. He harvested, from post-mortem specimens of human lung and brain tissues taken from patients who had died of tuberculosis, a characteristic bacterium with identical microscopic features in every case.
2. He grew these bacteria by placing specimens of diseased tissue onto appropriate solid-culture media. Solid-culture media, one of Koch's most important innovations, allowed him to discern discrete colonies of bacteria, for the first time providing a method of isolating pure cultures. By serially reintroducing bacteria from these colonies onto new media, he achieved pure cultures of bacteria identical to those originally found but without any possibility of contamination from the original sample. The bacterial progeny manifested the same microscopic features as those he had originally found.
3. When he introduced these offspring into guinea pigs, the result was the characteristic disease of tuberculosis (the guinea-pig variety).
4. He then recovered the identical organism from the diseased guinea-pig tissues (Koch 1882).

These steps became known as "Koch's postulates" and

resulted, over the next twenty years, in the elucidation of most bacterial and parasitic diseases that had afflicted humankind during historical memory. It would have been more certain for investigators to reintroduce the pure cultures into humans instead of nonhuman animals, because one could not know that all infectious diseases in humans have susceptible hosts in the animal world; and as subsequently has become clear, they don't. For obvious reasons, this has not usually been done.

Part of the problem for *C. pylori* was that for several years after Marshall and Warren had first cultured it, there was no good animal model. Thus efforts to satisfy Koch's postulates were hampered. Fortunately, much had changed since Koch's time, such that a presumption of a microbial cause of a disease could now be based on additional evidence: specific immune responses to the organism, an elucidation of microbial pathogenesis at the tissue and molecular levels, response to specific treatment, and more. An important difference between the *H. pylori* story and what Koch faced is that there were now effective treatments for bacterial diseases, unavailable in Koch's time. Thus a "proof in the pudding" was possible. That eventually became the clincher for *H. pylori*.

Another difference is that unlike anthrax, TB, pneumococcal pneumonia, bubonic plague, malaria, cholera, and other dreaded microbial diseases investigated by Koch and others near the end of the nineteenth century, presumptive *H. pylori* gastritis or even peptic-ulcer disease is not particularly dangerous. It was also eminently treatable in the 1980s even without antibiotics and prior to any knowledge of *H. pylori*—a point that belies any argument that a delay in accepting the bacterial hypothesis caused widespread, unnecessary suffering.

The relatively indolent nature of presumptive *H. pylori* disease led some investigators to attempt to demonstrate cause by the most direct of means. In the 1985 article "Attempt to fulfill Koch's postulates for pyloric *Campylobacter*," Marshall and colleagues reported that a normal volunteer had swallowed a pure culture of the organism. The result was "... a mild illness ... which lasted fourteen days. Histologically proven gastritis was present on the tenth day after the ingestion of bacteria, but this had largely resolved by the fourteenth day. The syndrome of acute pyloric campylobacter gastritis is described" (Marshall et al. 1985).

This constituted highly suggestive evidence that the organism caused gastritis. But it was far from conclusive, because it involved a single subject and was reported by the very author most wedded to the hypothesis. Thus, replication by others would have been required. Perhaps more important was that the subject, who was none other than Marshall himself, failed to develop an ulcer. Note also that the disease resolved without treatment.

As unlikely as it may seem, such a human demonstration was twice repeated with similar results. As late as 1995,

Marshall himself reviewed these studies and conceded that Koch's postulates, still the "gold standard" for demonstrating a microbial cause of a disease, had not been fulfilled for *H. pylori* and peptic-ulcer disease (Marshall 1995).

Persuasive Evidence for Etiology and Treatment

What ultimately convinced the medical world was not this sort of experiment but one that took advantage of the existence of effective antibacterial agents. To introduce the history of this effort, it is necessary to consider the setting in which it was done. As mentioned, there were already highly effective treatments for PUD by the early 1980s. The rate of complete healing of endoscopy-proven duodenal ulcers, after several weeks of treatment with potent inhibitors of acid production, is about 95 percent (Straus 1996). Symptomatic relief occurs within a couple of weeks (McFarland et al. 1990). Such treatment, moreover, is remarkably safe and free of side effects. The same cannot be said for metronidazole, the first widely used antibiotic for *H. pylori*. This and other proposed antibiotic treatments for *H. pylori* have unquestioned side effects, some of which mimic the symptoms of the very disease for which they are prescribed. These can pose significant disincentives for patients who would like to feel better. The selection of strains of *H. pylori* that are resistant to antibiotics, moreover, was reported in the very first large trial of their use. Does any of this sound promising for such a treatment?

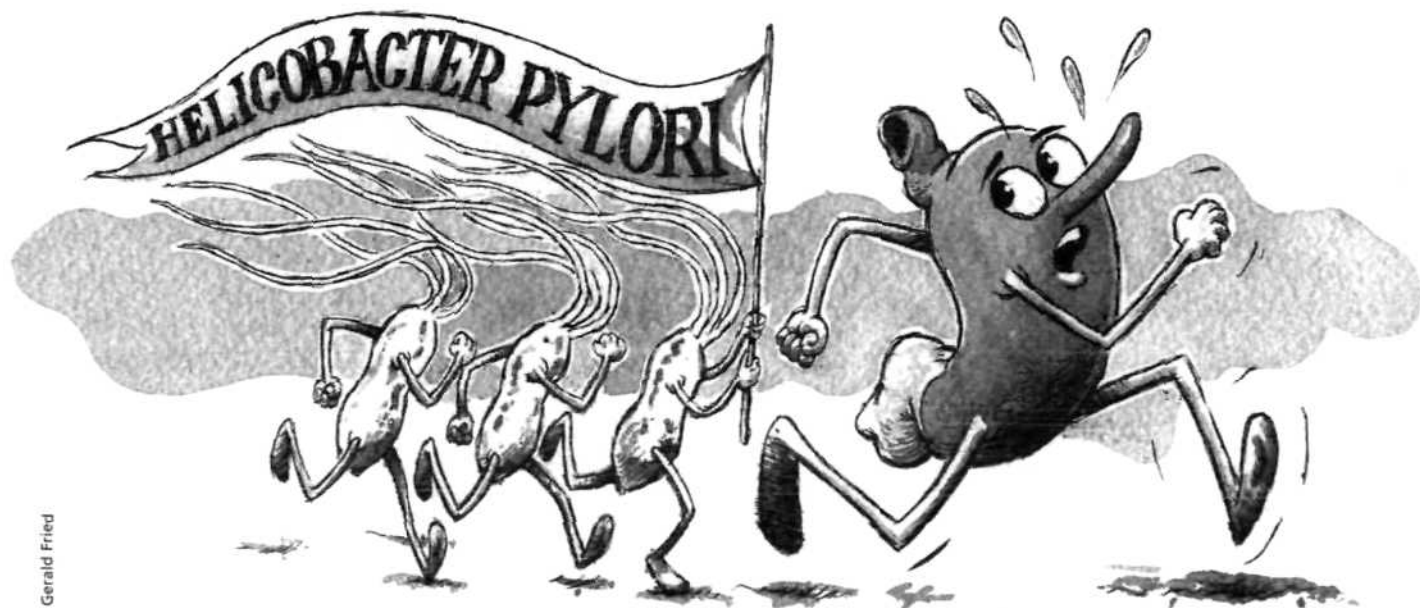
I'm playing the devil's advocate. I am a firm believer in the *H. pylori* hypothesis, and if I had a duodenal ulcer, I would take metronidazole in a heartbeat. This was far from obvious throughout the 1980s, however, not because of dogmatic rejection, but for legitimate scientific and medical reasons. To summarize: Even by the end of the decade, it was not clear either that *H. pylori* caused PUD or, if it did, that specific antibacterial treatment would be preferable to existing treatments.

What finally convinced doubters of both cause and treat-

ment was something that by its very nature took several years to establish. The initial treatment of peptic-ulcer disease was not the problem. The problem was *relapse*. In patients whose ulcers have completely healed after treatment with acid-suppression only, 50–95 percent will recur within two years, although the percentage is much lower if acid suppression is continued indefinitely (Gough et al. 1984). We now know that if temporary acid suppression is coupled with eradication of *H. pylori*, the recurrence rate drops to 5–10 percent.

But consider the time required to complete a trial that could establish this fact. The trial alone requires following about 100 patients for many months (twelve to twenty-four, typically), because ulcer recurrence is the issue. Patient accrual in any clinical trial is not instantaneous but usually occurs over several months or more, and the trial is not complete until the last patient entered has been followed for the planned period. This time is in addition to the usual time required for planning, applying for and receiving grant money, applying for and obtaining human-studies approval, overcoming unforeseen technical obstacles, writing the paper, waiting for a response after submitting it to a journal, revising it based on reviewers' recommendations, revising it again based on copy editors' recommendations, and waiting for ultimate publication. Thus, the least amount of time for such a project to proceed from inception to publication is about four years.

The first trial that was both large enough and rigorous enough to be noticed was conceived by Marshall and Warren in 1984 and published in *Lancet* at the very end of 1988 (Marshall et al. 1988). It had followed 100 patients for twelve months. The authors reported that the recurrence rate of duodenal ulcer was much lower in patients whose *H. pylori* were eradicated than in those whose bacteria were not, but there were problems. Such eradication occurred only when the antibiotic tinidazole was combined with bismuth. When tinidazole was given alone, resistant *H. pylori* strains invariably



Gerald Fried

thrived. The authors also reported more unpleasant side effects, including diarrhea, in the groups that took the antibiotic. Thus the results were highly suggestive that eradicating *H. pylori* could prevent ulcer recurrence, but somewhat less suggestive that this could be done effectively in the long run with minimal side effects. Since the authors were the original proponents of the bacterial hypothesis, moreover, any firm conclusions would first require confirmation by others. This was not ostracism; it was appropriate scientific skepticism.

By early 1992, at least three more studies had been published that, in the aggregate, convinced the academic medical world of the causative nature of *H. pylori* in PUD. The trial portion of the last and most influential of these was already underway by September 1988, well before Marshall and Warren's paper was published—further demonstrating the commitment of medical scientists to investigate the hypothesis. This study followed 109 patients for two years, using a triple-antibacterial regimen that was far more effective than that reported by Marshall and Warren. It found, unequivocally, that the recurrence rate of both gastric and duodenal ulcer was far lower in patients whose *H. pylori* had been eradicated. Antibiotic resistance was not apparent because of the triple-drug regimen, and side effects were tolerable (Graham et al. 1992).

This study, according to Lawrence S. Friedman, chair of the American Board of Internal Medicine Subspecialty Board on Gastroenterology, opened the floodgates in the United States. "After that everyone accepted the causative role of *H. pylori*, and everyone, at least among gastroenterologists, treated PUD with antibacterials." According to Dr. Friedman, this was done for duodenal ulcer [DU] even in the absence of specific proof that the patient harbored the organism: "Early on (early 1990s) all patients with duodenal ulcer were assumed to have *H. pylori*; the presence of a DU was justification for treatment of HP, though in practice many physicians still tested for the organism (at endoscopy and to some extent by serology)" (Lawrence Friedman, personal communication).

In case there were still pockets of resistance to the *H. pylori* argument, the National Institutes of Health (NIH) convened a Consensus Conference in February 1994. Marshall was a member of the planning committee. The proceedings were published the following July in the *Journal of the American Medical Association* (NIH Consensus Conference 1994). The report strongly supported the causative role of *H. pylori* in peptic ulcer disease, and unequivocally recommended triple antibacterial treatment for patients with ulcers and *H. pylori*. It also enthusiastically supported further research on the organism and its potential role in cancer of the stomach.

How to Explain the Myth?

That, then, is the history of the *H. pylori* hypothesis and its acceptance by the medical mainstream. Its journey from proposal to acceptance was quite ordinary. The first reports were surprising but intriguing and entirely plausible. The potential implications didn't require a "new paradigm," just a little work. Other investigators quickly jumped on the research bandwagon, and in a matter of a few years, the basic story and

its therapeutic ramifications were established. The profession, as represented by its literature and institutions, readily accepted it. The entire process took about eight years—ten, if one insists on including the NIH coming-out party (I don't), but not the thirteen that has been claimed. This amount of time was entirely appropriate, given the nature of the task.

So why the myth? I don't know how it started, but there are a couple of clues. Dr. Gerritsen refers to the Centers for Disease Control and Prevention (CDC) "putting out the word" in 1997. Is it possible that she is remembering the NIH Consensus Conference but got the date wrong? Probably not, because the CDC is not the NIH, and the CDC did publish a report on the topic in 1997. The word that it put out, however, was not "to the nation's doctors that . . . *Helicobacter pylori* was, indeed, the cause of most cases of peptic ulcer disease." On the contrary, it reported that national surveys in 1994 and 1996 had found that 90 percent of primary-care physicians and gastroenterologists in the U.S. already "identified *H. pylori* as the primary cause of PUD." The actual point of the article was to show that "only 27 percent of the *general public* [emphasis added] is aware of the association between *H. pylori* infection and PUD" (CDC 1997). Ironically, 60 percent of the general public still thought that the cause was "stress," a vague, whimsical, and mildly insulting "mind-body" hypothesis that medicine hadn't taken seriously for at least a generation.

To be fair, I will add that the CDC report also mentioned that although most physicians were aware of the *H. pylori* association, many of them (50 percent of primary care docs and 30 percent of gastroenterologists) were still not testing for *H. pylori* in patients with first-time ulcer symptoms. Rather, they were simply treating these patients with acid-suppressors. Ulcer symptoms, however, do not ulcers make. Such symptoms are frequently vague and nonspecific to ulcers *per se* and are similar to the far-more-common symptom complex known as "dyspepsia." Since the NIH consensus panel had specifically recommended not treating *H. pylori* in patients with dyspepsia but no ulcer, even when *H. pylori* was known to be present, it could be argued that these physicians were merely practicing cost-effective medicine: treating first-timers with a safe and inexpensive agent known to both heal ulcers and relieve symptoms promptly in the vast majority of cases while reserving the more invasive and expensive tasks of diagnosing both ulcer and *H. pylori* only for patients whose symptoms recurred after treatment was complete. While this does not refute my thesis, it may explain Dr. Gerritsen's memory of the report.

A bit of digging reveals that Marshall himself has had a hand in nurturing, if not creating, the myth. I tried to contact him to comment for this article, but he has not replied. Most of what I can glean from his Web page makes me think that he and I agree on important issues. For example, he lists Quackwatch, the most useful "CAM" information site on the Web, as one of his favored links (Barry Marshall 2004). (Disclosure: I have several pieces on Quackwatch and collaborate with its creator, Dr. Stephen Barrett, as co-host of the subsidiary NaturoWatch.) Marshall also links to a great debunking of "stress," which I hadn't previously seen (Spencer 2002).

And he has, quite evidently, a good sense of humor.

Nevertheless, there seems to be a bit of the self-promoter about him. I say this good-naturedly and with an affectionate nudge, imagining that someday we may meet and chuckle together. But also linked to his Web site is a 1997 article in *The Sydney Morning Herald* that sets the stage of his humble Western Australian beginnings on a dirt floor in a mining town and then bursts with suggestions of eventual Galileo-like ostracism by the vested interests of the drug industry and the "conservative world of medicine": "Everyone knew that bacteria couldn't survive in the stomach's acid environment. They'd been taught so at medical school" (Sweet 1997).

Huh? Everyone who has taken a microbiology course in the past few decades is aware that there are bacteria adapted to conditions far harsher than inside the stomach, including some that live at near-boiling temperatures and others that use ether—usually a powerful disinfectant—as a food source. Everyone who has studied histology and physiology knows that changes in the body's microenvironment, including acidity, can be dramatic over very small distances (measured in microns). The means by which *H. pylori* withstands the stomach's acid environment have been largely elucidated. The organism has a membrane that is particularly impermeable to acid. The membrane also contains acid-dependent urea channels that begin to admit urea from the stomach juices when the pH is a mere 6 (10,000 times less acidic than the normal stomach pH of 2). The urea is then rapidly transformed to ammonia via the enzyme urease, which the bacterium produces in abundance. Because ammonia is a base, this produces a tiny region of non-acidic space within which the bacterium dwells (Sachs et al. 2003).

Although these mechanisms were not known at the time that *H. pylori* was discovered, the plausibility of such mechanisms existing was never an issue. To argue otherwise is to conjure a "straw man." After all, similar organisms had already been described in the equally acidic stomachs of other mammals. The only questions that investigators in 1983 asked

were: Are the bacteria really there, and if so, what do they do?

Marshall, who was interviewed for the *Morning Herald* article, offers no clarification when the reporter writes, "Marshall took at least a decade longer than he expected to persuade colleagues that ulcer patients with *H. pylori* should be treated with antibiotics" (Sweet 1997). That may be, but it wasn't because of ostracism. Marshall had previously written, in a technical monograph, "In my naïveté I expected *H. pylori* to be immediately accepted as the cause of duodenal ulcer," [but] "the presence of *H. pylori* in many apparently healthy persons has made its pathogenic role harder to understand and has delayed wide acceptance of the new bacterium as an important pathogen" (Marshall 1991).

Another link from Marshall's Web site is to a radio interview in which he and others discuss the history of *H. pylori*, particularly with regard to its several near-discoveries prior to Warren's finding in 1979 (four years before the letters in the *Lancet*). In that interview is this telling exchange among three people: Sharon Carleton (the moderator), Irvin Modlin (a gastroenterologist from Yale), and Marshall.

Sharon Carleton: One component you don't mention is finance, money. How much influence do you think the drug companies have had in the past in trying to keep the truth at bay, or was it really primarily the medical establishment itself?

Irvin Modlin: I think those two components are almost inseparable; there's little doubt in my mind that in a world where ulcers had been declared to be acid-related, corporations that were involved in the manufacture of acid-suppressive agents didn't want to even conceive that there would be any other possibility for the pathogenesis of peptic ulceration. And of course, many of the people who were in a position to evaluate any other possibilities were heavily indebted to corporate support for their own research work and were, I think, not necessarily overtly but in a sort of covert or subtle way influenced to almost look the other way.

Sharon Carleton: In his own chapter in the book, Barry Marshall asks rhetorically, was there a conspiracy to keep the



Gerald Fried

H. pylori story under wraps? His answer—yes. But this was fired more by inertia and bad advice than by the drug companies' malice.

Barry Marshall: Well, you have to take pity on them because one particular company who's now in the *H. pylori* business with everybody else was Glaxo, and after the helicobacter meeting that we had in Chicago one year, their stock dropped from \$20 down to \$18 which represented about a billion dollars off the value of their company (ABC Science 2003).

What's missing from this pharmaceutical conspiracy theory is evidence that drug companies were successful in suppressing *H. pylori* research, even if this was their intent. The effectiveness of the "covert or subtle" means suggested by Dr. Modlin is simply not supported by the historical record, a fact that Dr. Marshall appears to have acknowledged. But it seems that even as Marshall equivocates when his champions trumpet conspiracy theories, he coyly encourages them. And yet, to paraphrase Galileo, medical science *does* move. It is my hope that Marshall the Quackwatch fan will read this article and recognize that his nurturing of the myth has given unintended succor to quackery.

Thus, the basis for the challenge remains untainted. The legend of *H. pylori* and peptic ulcer disease was a good try, because it is so widely believed, but it fails to stand up to scrutiny. In this case, as in modern medicine in general, progress resulted from the vigorous investigation of a plausible hypothesis—even if there was early skepticism and even if certain "vested interests" may have preferred otherwise. That said, I respectfully urge any remaining doubters to conduct their own research prior to submitting further nominees for exceptions to this rule.

Epilogue

An interesting article appeared in *New Scientist* a couple of years ago. It turns out that *H. pylori* lives in "around half the world's population" and "in parts of the developing world as many as 90 percent of the population carries the bug," but "only a fraction of these people ever get sick" (Hamilton 2001). Thus it may be a commensal after all. Of more concern is that it may protect against esophageal cancer, a disease that is recently on the rise even as rates of *H. pylori* carriage are falling. The question of whether it is wise to eradicate *H. pylori* thus remains open. Such is the nature of science: to march on. To Marshall's credit, I found the article linked from his own *H. pylori* laboratory Web site (*Helicobacter pylori* Research Laboratory 2004).

Acknowledgement

I am indebted to Ed Leadbetter, Professor of Molecular and Cell Biology at the University of Connecticut. As a student in his microbiology course at Amherst College in 1973, I learned to expect the marvelous adaptive mechanisms to be found among the prokaryotes.

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