

Stress Doesn't Cause Ulcers! Or, How To Win a Nobel Prize in One Easy Lesson: Barry Marshall on Being ... Right

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Not that long ago, Barry Marshall was an obscure physician studying the etiology of ulcers at a hospital in Perth, Australia — several thousand literal and figurative miles from the center of the medical universe. His work was unconventional, not to say heretical, and in 1986, he was invited to discuss it at a gastroenterology conference in the United States. His wife came along and, while doing some sightseeing, overheard a conversation among some other gastroenterologists' wives who happened to be sitting in front of her on a bus. "They were talking about this terrible person that they imported from Australia to speak," Marshall told me. "You know: 'How could they put such rubbish in the conference?' "

In 2005, that "terrible person" won the [Nobel Prize in medicine](#). Marshall, along with his colleague and fellow Nobel winner Robin Warren, proved that up to 90 percent of peptic ulcers are caused by a bacterium called *Helicobacter pylori* — not by stress, as medical wisdom had long held. In most of the interviews in this series, I've talked to people about being wrong: about what they've learned from their own mistakes, and about how their work — whether as an astronaut or speculator or lawyer or marriage counselor — affects how they think about error. But in this interview, Marshall and I talk about being right. In particular, we discuss how it feels when everyone thinks you're wrong, what it takes to get the scientific establishment to change its mind, and what it's like to finally be proven right. All that, plus a guest appearance by Adrienne Marshall, Barry's wife, who describes how she felt when Barry decided to test his ulcer theory by drinking a batch of bacteria.

Can you describe the received medical wisdom about ulcers before your research?

Peptic ulcers became more common in the 20th century, at the same time that these theories of Freud and other psychoanalysts became popular. And somehow those meshed, and this tradition emerged that ulcers were caused by stress or turmoil in one's life. I don't know where the data came from, but there was this idea that stress caused high acid levels; maybe there was a small amount of evidence for that, although I haven't been able to find it when I've looked. Anyway, all those things added up to convince people that ulcers were caused by stress. There was no proper data of any kind. It was smoke and mirrors as much as anything else, but terribly convincing for everybody.

Are you saying that there was no basically *no* empirical evidence to support the stress-and-acid hypothesis?

You can always find stress in someone's life if you want to. You ask a few questions and eventually it's, "Yes, I admit, I was worried about something recently." So they tried to find evidence for stress causing ulcers, and whenever they had an experiment which worked, it would just be blown out of all proportion, and everyone would get so much publicity out of it that you would think, "Ah, at last, it's proven." But the data was very bad. And in fact there was plenty of evidence showing that stress didn't make much difference.

What kind of medical advice was dispensed to all these patients with ostensible stress-induced ulcers? "Relax"?

Basically, yes. The medical advice was take antacids and modify your life style. The first drug that came out in the '70s was Tagamet, an acid blocker. By the time Robin Warren and I came along with this idea about bacteria, that was selling \$3 billion of medication per year; it was the world's number one drug. And then that type of medication was the number one drug for about 10 years after that, with global sales of \$8 billion or something. But it didn't work very well. It was quite sad, really; people were so disappointed, because as soon as they stopped taking their drugs, the ulcers came back.

What was it about you that made you more immune to all this received wisdom about ulcers?

I guess all my life I've made my own decisions. My mother was a nurse, and in her era, most diseases weren't understood; people put mustard plasters on knees and rubbed camphor on your chest if you had a cough and did funny things to you if you had tuberculosis — all these things that really made very little difference once proper treatments were brought in. She used to be annoyed with me because I would challenge everything she said and not believe anything unless someone could show me the facts. For some reason, that's just the way I was.

Is that what got you interested in ulcers — the apparent lack of facts?

Something like that. The thing that initially excited me was: "Ah-ha! A falsehood!" Robin and I had been looking into these bacteria, and we found that they can survive in stomach acid. You probably don't think that's particularly weird, because you know that there are bacteria that live in Old Faithful and hot springs and so forth. But it really wasn't well-known in the early '80s that there were bacteria that could survive in all these harsh environments. So it started out as: Let's just prove that these bacteria live in the stomach and try to find out how they do that.

That led to ulcers via the side door, if you like, because we were trying to find out who had the bacteria — and lo and behold, we noticed that everybody with ulcers had them. So we said, "Hang on a minute, scientists have been trying to find the cause of ulcers for 50 years. Have they checked out the possibility that it could be an infection?" The answer was, "No, because it's impossible for bacteria to live in the stomach. We wouldn't even consider that."

At what point did you start to suspect that your own theory was right?

We pretty well knew that we had discovered the cause of ulcers within two years of starting the work. One reason was that I was starting to treat a few people with antibiotics, and nine out of 11 seemed to be cured. At the time, the cure rate for ulcers with any other treatment would have been one out of 11. So even though that work was anecdotal and not blinded and not publishable, it was very convincing.

I assume another reason you were so certain is that — rather famously — you swallowed a bunch of *Helicobacter* bacteria to prove that it caused stomach problems. Not to be blunt, but: What were you thinking? Was that just a way of bypassing the human studies review board process? Were you so convinced that you were right and just impatient to prove it?

It was a decision point. I had to find out if the bacteria could really affect a healthy person and cause gastritis. I'd been working very hard in the previous 12 months on piglets, but I have to tell you that piglets aren't piglets for very long. They just about grow before your eyes, so after six months I had nearly full-sized pigs in our offices and I was wrestling with them and it was chaos. And you can't infect pigs very easily, it turns out, so that failed rather miserably. And the skeptics were so determinedly skeptical that I felt like: I'm never going to prove to these guys that the bacteria are harmful. By then everybody knew that 40 percent of the population had the bacteria and did not have ulcers, so that was making life difficult for me. So I took some bacteria off a patient and cooked it up.

If nothing had happened, it really would have been a spanner in the works for the whole theory. I thought, "If it doesn't work, I'll quiet down about the whole thing; maybe I'll just run away and do some other career for a while because I'm wrong." But then of course it worked.

What did your colleagues think?

I didn't quite explain to my boss what I was doing. He was passing the endoscope on me and I was lying there gagging away, he says, "Barry, I'm not sure why you asked me to do this test on you, and I don't want you to tell me." It was don't ask, don't tell. I wrote the experiment up in the third person, because it was very disreputable to be doing a self-experiment of one and then writing it up, and the editor of the medical journal of Australia stuck his neck out and published it. Afterward a couple of people figured out that it was really a self-experiment on me, but I didn't own up to it straight away.

You didn't realize it was going to be a great PR stunt?

No, I didn't. I was always very embarrassed talking about it. Then the word leaked out, and it's kind of a funny story, actually. After our *Lancet* paper was published in 1984, Robin and I went out to dinner with our wives, and we were having a few drinks and I let slip that I'd done the experiment. So then he goes home and in the middle of the night, he gets a phone call from a journalist in the United States who'd gotten the time difference wrong. The journalists said, "I'm from [Star](#)," and Robin thought it was like [Time magazine](#) or something, and he gave this very in-depth interview about these bacteria that might cause ulcers. At the end the journalist said, "How can you be so sure these bacteria are really harmful?" and Robin says, "Well, Dr. Marshall drank them, and he got so sick he half killed himself!" That was the alcohol talking.

So they write this article in *Star* that's like "Australian Researcher Experiments on Guinea Pig Lab Assistant!"

I have to ask: How did your wife feel about this little stunt?

[Hollering into the distance] Adrienne, come up here! [To me] I'm not allowed to tell other people what she thinks.

That seems like a good policy.

Adrian [laughing]: I was a bit worried about him. He was very sick, and he didn't talk to me about it ahead of time or I would have probably suggested strongly that he not go ahead with it. But I was more surprised by the reaction of his colleagues when it came out that it was actually a self-experiment. He already had a reputation for being a bit rash and a bit of a hothead, and I fully expected his colleagues to write him off as a complete lunatic. But it was the exact opposite. They all thought it was a wonderful thing to do, which surprised us both, I think. He got a lot of credibility for it, which I wouldn't have expected.

By the time of that self-experiment, Barry, you were reasonably sure that you were right, and you'd been saying so in public for quite some time. Can you describe the general response you received when you first began to publicize your work?

When you start off with a new idea like this, all your scientific pals set out to prove you wrong. That's the scientific process. In my case, people were especially interested in showing that I was wrong, because at the time I was not at the pinnacle of gastroenterology, or even in the mainstream. I didn't know all of its secret teachings, if you like. I would just charge in with this stuff about bacteria, and nobody wanted to be told that they had spent their life doing research on something that somebody in western Australia figured out in 12 months. You can imagine that would be a bit difficult to stomach.

That makes it sound like the driving force was ego and insider/outsider status as much as it was the scientific process.

Well, and money. I think there was a strategy in the pharmaceutical industry to keep the new bacteria theory of ulcers under wraps. At the time we made the discovery, a new antacid was coming out every year or two that was stronger or better in some way, and as each drug was rolled out, the pharmaceutical companies funded scientists to do clinical studies on people with ulcers.

If these had been truly scientific people who were genuinely interested in discovery, as soon as they heard about the new bacteria [theory], they would've said to the investigator, "We're testing 300 patients with ulcers; can you just take an extra biopsy and check for bacteria? We want to know what's going on here." But they didn't do that, because the only purpose of these trials was to get a new indication and extended registration for the FDA. If you look at it from a business point of view, it could only do your market harm and lower your share price to find out that you could actually cure people with antibiotics. And that was their point of view.

Let me play devil's advocate for a moment. It's easy to characterize your story as the triumph of an evidence-driven outsider over a bunch of insiders and their vested interests, but isn't what happened actually a pretty good example of how science is supposed to work? As you said a moment ago, the scientific process involves trying to prove other people wrong, and in that sense, the fact that you were subjected to a lot of intense questioning and skepticism and so forth seems appropriate.

Right, sure, that's part of it. In retrospect, I was partly to blame, because I would get data that was rather preliminary and try to publish it because it was exciting and novel and original, even though we didn't yet have any kind of double-blind studies.

But also, we felt it was important to act. Maybe it would have been different if we'd been talking about [a cure for] a skin rash or something; maybe you can afford to wait five years until that's proved. But people died from ulcers all over the place and were having their stomachs or half their stomachs removed; there were permanent, mutilating operations and deaths going on around us. And yet to test our idea, you just needed to take some antibiotics. So we weren't very ashamed about trying to get our message out, even though it was rather preliminary.

Thomas Kuhn distinguishes between what he calls normal and extraordinary science, the latter being the type that brings about a complete change — the famed "paradigm shift" — in a field. Which one do you think describes your work? One can arrive at new ideas and theories and solutions without ushering in a whole new paradigm, after all.

It was definitely a paradigm shift, because it got this stress thing debunked. And the implications of that are much bigger: What else is supposedly caused by stress that we can debunk? A lot of these things that are supposedly caused by stress, you try to track down the reason for that link, and there isn't one, except the fact that we don't have any better cause. Everything that's supposedly caused by stress, I tell people there's a Nobel Prize there if you find out the real cause.

So that's one thing that happened. The second thing is that by 1980, everyone was feeling pretty confident that infectious diseases were going to be wiped out and there wasn't going to be any more problem with them. [H1N1](#) is enough to wake us up to the fact that we don't know everything about infectious disease, but it really happened with *Helicobacter* first. People had been seriously studying ulcers for 50 years, billions of dollars were spent, and then — what do you know, it's a bacteria. So you have to ask, what other infectious diseases are we missing? I reckon a lot of these mysterious chronic diseases are related to some infectious agent that's been a trigger. It might have happened when you were a child and now it [the infectious agent] is long gone, but it sets you up for a problem later in life. We'll see if I'm right.

Speaking of which, did you find it frustrating that so many people felt you were wrong?

It didn't really faze me too much that everybody thought I was wrong, but it annoyed me that I was having trouble getting research grants and so forth. And at times I'd get internally angry, especially when I was junior and people in senior roles and positions of power could block my

plans and go ahead and order for someone to have surgery or continue on with some treatment which was useless.

But it must have been annoying for them, too, because you couldn't tell me anything. I just knew so much. After a couple of years, Robin Warren and I knew more about every aspect of ulcers than practically everyone in the world, because we read nothing else for two years.

When and how did you start to convince people?

Part of it had to do with David Graham, who was chief of medicine at Baylor, in Texas, and a thought leader in gastroenterology. Graham started off as a real skeptic but quickly turned around. To his credit, Graham never said that I was wrong. He said, "I don't know, and I'm going to find out." And a couple of years later, he said, "I've checked it out and it looks pretty good, it looks like it could be true."

And then in 1993 or '94, the [NIH](#) had a consensus conference, and [Tachi Yamada](#) summed it up. Yamada is currently the head of [the Global Health Program of] the Gates Foundation; he's a very, very smart guy, and he said, "Looks like it's proven: Bacteria cause ulcers, and everybody needs to start treating ulcers with antibiotics." It was just like night and day after that. The whole thing just went ballistic.

How did it feel to finally be acknowledged as right in such a public and universal way?

It was very satisfying to prove [my critics] wrong. People used to say to me afterward, "Barry, do you feel vindicated?" And I'd say, "I felt vindicated 10 years ago, because I knew what the result was going to be." There's a saying, "Science is not a democracy." It doesn't matter how many millions of people there are on the other side. There's one right, and it's perfectly possible for all the rest to be wrong. And ultimately all those guys were proved wrong, and they either retired or they came over the side of *Helicobacter*.

I love that it took retirement. It's like that quip by the physicist Max Planck, who said that science proceeds by funerals.

It wasn't quite death, but close. David Graham said, "The great thing about Marshall's theory is that if he's wrong, it's going to be so easy to disprove." The point he was making was that if it's a good hypothesis, you can test it. And ours was very testable; you just had to give people antibiotics and see if they got better. And they did. So everybody who was trying to prove us wrong, if they were good scientists, they just changed sides.

If they weren't good scientists, they kind of clammed up and kept doing what they were doing. If they were running a stress-based business — and there were certainly people, particularly in New York, who did psychoanalysis for ulcer patients and ran stress institutes and things like that — a lot of these guys, it had been their whole life. I do feel sorry for them, but I'm glad it wasn't me, that's all I can say. I'd probably be having a lot of trouble with my ego if I'd found out that all my life's work was for naught.

These days, do you find that everyone believes your theory?

Well, not patients, necessarily. Even now I see people who've got ulcers, and they think they're caused by stress. And I say, "Where have you been for the last 20 years? Have you been under a rock?" It just amazes me that there are still doctors out there that don't know this.

Who's to blame for that? Are health care providers and public health workers failing to spread the word, or is the idea just so entrenched in the culture that it's difficult to eradicate?

It's like a religion or something. It's like there's a certain part of your life when you learn things, and then you just stop. I'll say to patients, "Don't you know that ulcers are caused by bacteria? You need some antibiotics." And they'll say to me, "No, no, no. My doctor told me that in my case, it's definitely stress."

Let me turn the tables for a moment. What have you yourself been most wrong about?

It was very difficult to convince me that *Helicobacter* doesn't always make people unwell. Because I was interested in ulcers, I was seeing people who were very sick from it, but my colleagues would say, "You know, Barry, 40 percent of the Australian population have *Helicobacter*, and most of those people don't really have any symptoms." And I'd say, "Well, you didn't really ask them the right questions, you've got to ask them this and that." I spent several years trying to separate out people with *Helicobacter* from people who don't have it on the basis of things like, do they feel nauseated, are they burping, do they have bad breath or headaches — all those kind of vague systems.

I've had to pull back on this. Now I say, "Probably 75 percent of people with *Helicobacter* have nothing wrong with them." They go through life with minimal syndromes. It's like having dandruff in your stomach. If you had that, you wouldn't ever know about it. Your stomach would look a bit weird if you looked inside, but you wouldn't feel anything at all.

That being said, I'm still trying to hold my ground on this. There's a history of ulcers in my mom's family, and although she swears she has no stomach symptoms at all, I said, "I better just treat you the same way as everybody else." So I gave her antibiotics. Three weeks later she said to me, "You know, since I took those antibiotics, I've just been feeling great. I have more energy, I feel more positive." I've heard that from a lot of people over the years. So I think there may be a subtle syndrome where you're not at your top performance if you have *Helicobacter* in your stomach. If you've had something mild all your life, then you don't really know what normal is until you take the problem away.