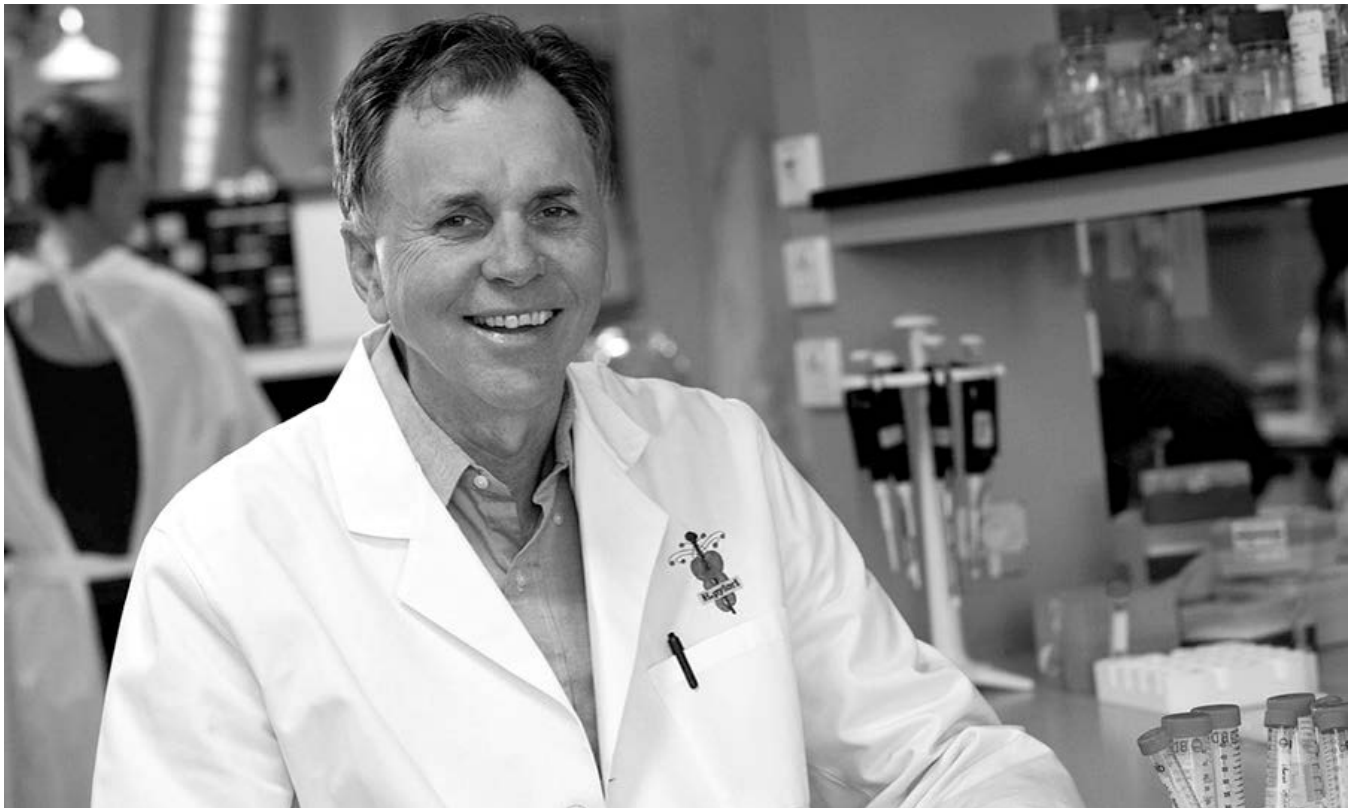
Interview with Dr. Barry J. Marshall, Nobel Laureate

Interviewers: Imindu Liyanage, Kathleen Simms



Dr. Barry J. Marshall
Image Source: University of Western Australia
(https://www.uwa.edu.au/profile/barry-marshall)

Dr. Barry J. Marshall was awarded the 2005 Nobel Prize in Physiology/Medicine for the discovery of Helicobacter pylori as well as its role in peptic ulcers. His work overturned the canonical wisdom that bacteria cannot survive in the stomach as well as establishing a definitive, microbiological treatment for ulcers – estimated to have saved over a million lives.

Currently Dr. Marshall is a Clinical Professor at the University of Western Australia, where he leads the Marshall Centre for Infectious Diseases Research and Training (founded in his honour). Dr. Marshall further serves as a Consultant Gastroenterologist at the Sir Charles Gairdner Hospital. His present research interests expand on his ground-breaking work and is seeking novel strategies to manage immunity via the microbiome as well as devise early diagnostic methods for bowel syndromes.

UTMJ: Dr. Marshall, you have previously likened the gut microbiome to an extra organ, could you clarify how you see the role of the microbiota, as we understand it today?

BJM: The microbiome is largely controlled by your diet, plus a genetic factor like your blood group and a component you inherit or catch from your mother. After you develop it, it's going to influence how you absorb or metabolize food; it may produce certain hormones and chemicals which maybe there in smaller or larger amounts. So you can see that the gut microbiome could potentially be like another organ, almost like an endocrine organ in some respects. Understanding it and ultimately figuring out how to use it in beneficial ways for patients is going to be a big advance.

UTMJ: Would you say that we should consider it distinct from the other organ systems?

BJM: Yes. I suppose that a proportion of what goes on in your gut is going to be related to maintaining and holding the microbiome in a certain way. I don't want to overhype the microbiome, because I know that you can do without it. For instance, germ-free mice that don't have a microbiome actually live longer than other mice; so, there are good and bad aspects to carrying around a microbiome. In humans, it can change from time to time, depending on diet. It actually changes rather rapidly, so I think there's ways we can use it, and probably, it's beneficial to have it.

UTMJ: There was a time when medical textbooks said that the stomach would kill all bacteria. What led you to the idea that organisms could not only survive but thrive in the stomach and beyond?

BJM: It's hard to say how I developed the idea. I was always interested in microbiology, it's just something that came naturally to me. But I guess the idea started when I met Dr. [Robin] Warren, who's a pathologist. On tissue sections taken from biopsies of the stomach, he could see these curved bacteria. He showed them to me and said, "I've been seeing this for a couple of years, nobody else is interested, everybody says it's contamination; but how could it possibly be if they're all identical and I'm seeing them in a number of patients."

At that point I was immediately interested, because I knew that the medical books said that bacteria don't exist in the stomach – it's too acidic. So, I said, "wow, this could be a good paper." I'd never written a paper before, and wouldn't it be good if my first paper would be helping Dr. Warren with the discovery of this new bacteria. Just any kind of publication would have been fun for me, and so we went off on this quest, if you like. That was about July 1981, and for the next 6 months, we played around with them in different ways. We were trying to figure out how could these bacteria live in the stomach, and could they be cultured, and where did they come from, and what were they?

We didn't start off focusing on ulcers. With the pathology we knew [then], we were looking at whether these bacteria made some inflammation in the stomach and then one thing could lead to another, and inflammation could lead to some disease. That inflammation, which was called gastritis, was a histological phenomenon you could see in biopsies, but there was hardly anybody that believed gastritis was a disease, because we knew that in most countries, a majority of people had gastritis. We thought you get it when you get older, so practically nobody was doing any work on it. So, it was a great project to start off with.

UTMJ: So how did you eventually identify helicobacter?

BJM: At that time, there was some excitement about other enteric bacteria, particularly Campylobacter. It had been one of those bacteria that we could culture for many years, and we were starting to see epidemics of it from time to time from people drinking contaminated milk. […] So, we had a few clues about how to grow these bacteria, but we had to spend a lot of time studying ulcers and stomach bacteria. Really we were like babes in a wood, we didn't realize how difficult it was going to be. Fortunately, if you don't understand something is a difficult task, you may tackle it in a new way.

One thing we struggled with was where and how to sample these bacteria. It was actually Dr. Warren who said to me, "when you take these biopsies Barry, don't take them near ulcers because the anatomy is so screwed up […]. Take your biopsies away from the ulcer, because we're just trying to find where these bacteria live and what they're doing there." Lo and behold, that was the key that unlocked the linkage between helicobacter in the stomach and the ulcers.

Along the way, we studied lots of people, and looked closely at their biopsies and the wall of their stomach with normal histological sections. We could see that really there was no other bacteria in the stomach except ones you swallowed from time to time. These would be just passing through, and be sitting on the top of the stomach, and so that gave us a pretty good concept that led onto how we think about the microbiome now […].

UTMJ: It's not everyday that one overturns a fundamental paradigm. How did you contend with the inevitable controversy and pushback?

BJM: Having seen Helicobacter under the microscope, and having cultured it, there is just no doubt about it. It's proven as far as you're concerned. It's not one of those things that you have any doubt about yourself.

The controversy was if so many people have the bacteria, and all these people turned out perfectly fine and don't have symptoms, how could it be a pathogen. So many times in the past people have found bacteria on the skin, bacteria on the mouth, and obviously in the colon. So to then come along and say, oh by the way, thousands of researchers have been working for fifty or one hundred years on the cause of ulcers, and have not noticed these bacteria, is understandably controversial. I have to say that were I to switch roles, and someone from Australia published a letter in the Lancet about bacteria causing ulcers – I would have probably [had my doubts].

It did take quite a few resources to check out a new discovery. Really the people doing ulcer research and stomach research were interested in acid as the cause of ulcers. They weren't focused on the microbiome or microbiology, and so it wasn't really possible for someone who was not in that area to check it out. The best I could say was I'm neutral, and I'm going to wait to see what happens?

A lot of gastroenterologists were willing to stick their neck out and give it a go. A good friend of mine actually, a top researcher from the United States, Dr. David Graham (he was Professor and Chief of Medicine at Baylor College of Medicine in Texas) said, "the great thing about the bacteria theory of ulcers is that it's going to be so easy to disprove". You can take that in the good scientific way, which is that if it's a good hypothesis, you can test it.

So if I said to you that bacteria caused some [disease], well then that's easy to test: give me some antibiotics, give them to somebody with the disease and they should get better. We were in the throws of doing that kind of research, and within a couple of years, everybody was trying that out […].

UTMJ: Speaking of proving your hypothesis, perhaps one of your most famous experiments was ingesting H. pylori on purpose to prove its virulence. Can you tell us how that experiment came about?

BJM: Well the good scientific way of studying a new bacterium is to develop an animal model, put the bacterium in the animal model and look at what diseases come about. Hopefully you fulfil Koch's Postulates, which means that putting a pure-culture bacterium on an animal model is going to cause to the disease to arise. But if the bacterium is well adapted to humans, like Helicobacter pylori, which has been specific to humans for maybe a million years, going as far back as we can tell, it didn't necessarily have the correct proteins on its surface to attach to the stomach of different animals. I mentioned to you that your blood group determines a little bit about what kind of microbiome you're going to have. So, it can be very challenging to grow a bacterium specific to humans in another organism.

I was getting stuck trying to prove [Helicobacter] is a human pathogen. After a couple of years, there was an argument that […] the ulcers come first and then after a while they effect the ecology in the stomach and the microbiome changes in these ulcers. It was very difficult to get past that. At that stage, we had tried many animals, including pigs, and they all turned out to be immune. The crucial question is does it effect humans, not does it effect animals. So, I needed to get this experiment done.

It was July 1984, we got some cultures from a patient of mine and I scraped a couple of petri dishes with bacteria, and around 2 o'clock in the morning, I drank it, and thought let's see what happens. Of course, I was doing a busy clinical job, so it wasn't a very good experiment. I was also trying to be objective. After a few days, I developed dyspepsia, then after a few more days, nausea, vomiting, bad breadth, and my stomach was gurgling in different ways. Finally, I had the endoscopy and showed the biopsies to my colleagues and sent a few down to Dr. Warren in his pathology department and they all said: you've been infected with bacteria and you have gastritis – which is the main thing which we think leads on to everything else.

So that was it, we fulfilled Koch's postulates for gastritis. I didn't actually develop an ulcer and after two weeks, we got rid of the bacteria. The reason people with ulcers can't remember when the caught the bacteria is that they probably caught it years ago. At that point we pretty much worked out the whole sequence of events, which explained a lot. But again, people didn't have to believe it. It was only one case, I was also slightly embarrassed to admit that I was experimenting on myself, which was not scientific. You can imagine that if every medical discovery was based on a self-experiment on one person, we'd be believing all kinds of crazy things. So one thing led to another, but it did mean that I changed my career and that this was going to be the most important thing I could do at that stage. After a couple more years, we got some funding and started doing some real research.

By this point, nobody still believed me. But I started to get a couple of early publications and some interest from the Lancet in the UK, and then from some colleagues in the United States, like George Buck in Huston, and a lot of good Campylobacter bacteriologists in Canada. I went to a meeting on Campylobacter in Ottawa, and really everyone was very excited by then.

I could tell you that after our first publication, Dr. Warren and I took our wives out to a nice restaurant, and Dr. Warren's wife said, "you know, if you're right about this, you could win the Nobel Prize, it's pretty important". Then Robin [Dr. Warren] said, "Barry when do you think we'll win it", and I said, "next year". Of course, it was 23 years before we got to that stage, so it was quite the journey.

UTMJ: Where do you see your research and the field of the microbiota progressing in the coming years?

BJM: Talking about the microbiota, I think we were correct that the gastric content (the stomach) doesn't really have very much of a microbiota. One of the things that acid does is sterilize your food. You can imagine that for stone age man, anything with protein would have been edible – things like dead animals and out of season fruit. Also, humans were pretty unhygienic in those days, so it was useful to sterilize your food in the stomach. It can then come in intimate contact with the intestine, and be absorbed, then finally […] it goes into the colon where the grassy bits and cellulose and various other things like carbohydrates get broken down further and you can extract more nutrition out of then. So it's adds quite a bit of extra value to have a microbiome, depending on what you were eating.

I'm interested in [the microbiome] and we're doing research on it here. It's quite a difficult thing to study because realistically you're measuring something in feces, and healthy people don't go around collecting fecal samples. So you have to be well organized to do stud-

ies on the microbiome. But when you see somebody who took antibiotics, and their bowel habits changed afterwards, obviously you've done something to them. Maybe, one out of ten or one out of twenty people who get antibiotics are at risk of a syndrome like that. So understanding what you've done and perhaps what's missing from the microbiome is very important.

The future is not going to be fiddling around handling feces, and taking fecal transplants. It's going to be something like we have 250 different cultures of microbiome bacteria here in our refrigerator, and according to this analysis, you're missing this enzyme that metabolises this sugar, and you're missing this one that produces methane from this product. So, you can go one further step and look into the metabolome, because that's what these bacteria do. You may benefit from the products that some bacteria make, or maybe there's something that bacterium A produces, that helps to nourish and maintain bacteria B, C, and D – which are useful for producing something else. So doing this in a scientific way, the future is very rosy. I think replacing exactly what you need, in a nice way – like how we take probiotics in yogurt, [is] where we're going to be with this in a few years time.

At the moment […], people are making a lot of observations about different things. For example, does [the microbiome] really effect your mood, or your feeling of well being. It may affect your psyche in different ways. Who knows what else? There's a little bit of tantalizing data in mouse models, etcetera and we're having a lot of people making observations surrounding early reports and translating into animal models in different ways. So when we understand the data, and have the production lines to analyze people with this, I think it's going to turn into a therapy that people will benefit from.

It's a great thing. Maybe 10% of what you read in the new journals, like such and such observed in such and such disease, in small numbers – that kind of thing; probably 10% of that will pay off and turn into something that will be useful for everybody. […] But that's a great thing.

UTMJ: Is there anything else you would like to add?

BJM: People need to be critical of the literature because there's a lot of smoke and not much fire there at the moment. If you sift through the literature, anybody can get some fecal samples and run it through a machine and they're not necessarily experienced in microbiology and gastroenterology. It's got to be the other way now, because it's now very easy to do microbiology experiments without thinking too much about what this means in real world patients. Just follow the scientific process, be sceptical, try and prove everyone else wrong – which is a bit annoying for them at times. If you can prove them wrong, this could be the next big thing.

UTMJ: Duly noted Dr. Marshall. On behalf of the University of Toronto Medical Journal, we are immensely grateful for your time. It's certainly not every day we converse with a Nobel Laurate, or the founder of a major scientific discipline. We do sincerely appreciate your time.

BJM: Thanks very much, and certainly anything to do with microbiology and the gut, Canada [has] a terrific track record for that kind of research. I'm looking forward to a lot of success.