A conversation with Peter Agre

After a 20-year focus on the water channel aquaporin (work for which he shared the 2003 Nobel Prize in Chemistry), Peter Agre has turned his attention to malaria. He currently serves as Director of the Johns Hopkins Malaria Research Institute. The full interview, wherein Agre (Figure 1) displays his witty sense of humor, including vignettes related to running for Senate, dancing to the Buena Vista Social Club, and his desire to be known as the Victor Borge of science can be seen on the *JCI* website at http://www.jci.org/kiosk/cgm.

JCI: Can tell me a little bit about what you were like as a kid?

Agre: I was the oldest son of six children. My mother was a farm girl and never went to college; Dad was a college professor. Dad was all science and math, and mother was much more into the humanities, reading the Bible and the classics. My mother is very religious and was very concerned that we use our talents for the well-being of others less fortunate. We lived in Northfield, Minnesota, just down the hill from St. Olaf College. My friends and I were like the little Norwegian Spanky and Alfalfas, swarming the college, climbing trees, going down the hills in our toboggans. It was a wonderful childhood.

JCI: Did your father's position as a chemistry professor cultivate an early interest in science?

Agre: He definitely was a strong influence, and I always felt totally intimidated by Dad in his ability to do logarithms in his head. He was very gifted in some ways. He was also very obstinate. You might have heard the term stubborn Norwegian, often wrong but never in doubt. Dad was like that.

JCI: Most might not know that you actually finished high school in night school while you were also studying Russian and driving the trucks for the evening shift for a company that was making dummy land mines and military equipment.

Agre: I would write this off as youthful rebellion. When I was 17, I spent a summer traveling through Russia and it was an extremely enlightening experience, and I stopped listening to some of the directions at home with the thought that there are bigger things out there. But working in a factory making war materials and going to night school was not a lot of fun. In the end, I faced the reality that I was not going to lead some glorious Raskolnikoff revolutionary experience.

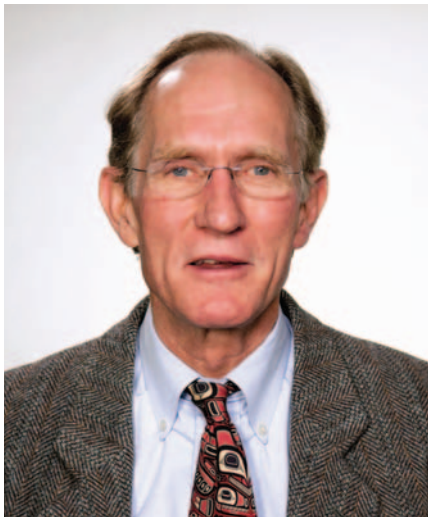

Figure 1. Peter Agre on April 26, 2014.
Image credit: Karen Guth.

I enrolled at Augsburg College, where Dad taught. I got a good background in science, with the idea I would go to medical school. I remember distinctly applying for medical school and kind of being out of my league. The interview was a lot less pleasant than this interview. The Dean for Admissions was a very nice man, but he had some very specific questions. After those, he asked, "Do you have any questions for me?" I didn't come prepared with questions, but I thought for a moment and I recalled that one of the requirements was to take the Minnesota Multiphasic Personality Inventory, which is the gold standard of psychological profiles. I thought for a moment and I said, "What did you learn about me from the MMPI?" He looked into my file, and said, "These results indicate that you lie more than average." He looked down with a little smile on his face and said, "But you lie less than the average medical student." So I don't know what that means. Everything I'm telling you is the truth. Trust me.

JCI: I'll take that under advisement. You took another rather transformative trip around the world before medical school.

Agre: I'd really been interested in Southeast Asia, East Asia, South Asia, the Middle East. I hitchhiked all around Japan for a month and a half, and Taiwan and Hong Kong, and then traveled around Southeast Asia, rented a motorcycle in the hills in Thailand, explored Cambodia.

I made an unexpected bivouac to Vietnam during the Parrot's Beak invasion, in May 1970. I then made my way to India. Eventually I crossed into Afghanistan, Iran, Turkey, Europe, and got back in time to start medical school.

I learned a lot on that trip . . . and my pre-med focus sort of died. It seemed like gutting it out for the next exam was not the highest priority and reinforced my interest in Third World diseases. I joined the wonderful laboratory of Pedro Cuatrecasas, who was investigating the toxin that causes cholera. But I have to say, if you work on diarrheal diseases, don't expect it to enhance your social life. I remember going to a mixer at Goucher College and meeting an attractive young lady who seemed to be interested in me. We were talking, and she asked me, "What kind of medical specialty are you interested in?" I should have said neurosurgery or radiology. But I'm from Minnesota; I told her the truth. I said, "I'm interested in diarrheal diseases," and that was the end of that. I subsequently met my future wife who grew up in a farm and worked in a laboratory at Johns Hopkins and was not squeamish, although she set some limits, saying, "If you are going to work on diarrheal diseases, don't bring your work home at night."

JCI: You mentioned getting your first taste of research, but then you did finish your full clinical training.

Agre: I always had some trepidation about whether I had the intellectual capacity, drive, and organizational skills to survive as a basic scientist. I was truly interested in clinical medicine and did a residency at Case Western Reserve. And I really deeply cared for the patients. I used to stop and see patients on my way home from the hospital on my bicycle in Cleveland. It was not insincere. But I always felt that the diseases and

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the problems the patients had were pretty serious and there were probably better doctors than Peter Agre. So I kept that alive with the idea I would do mostly basic science and support myself with grants. And so, when I joined the faculty at Johns Hopkins, it was at 75% research, 25% clinical. I've kept my MD license alive, getting it renewed every year. My wife's not convinced I'll make it to retirement with grants alone.

When our children were born, we made a family decision. Mary would stay home with the kids because the research was all consuming. We lived on my salary, which was pretty modest, and so to supplement this, I worked as a ringside physician at boxing matches. This was not Atlantic City or Las Vegas. These were the smokers; if you've ever seen the beginning of the Rocky movies, that was what it was like — inside the steel workers' hall.

The boxers were hitting each other unbelievably hard, and I was supposed to provide medical care. And in a flash, so fast I didn't see it, one boxer got knocked through the ropes. He's on his back, fixed gaze straight up, he's not breathing, so I hustle over there and I thought he was dead. I called the officials to get an ambulance. At that point, he blinked, took a breath, and I realized he was unconscious, but with his eyes open, and would probably be able to recover. After a few minutes, he sat up. And we walked him back to the locker room and the fans were screaming, "Doc, are you going to let him continue?" I said, "No. This fight is over." "Boo!"

JCI: Around this same time, you started focusing in a little bit more on hematology-based laboratory problems.

Agre: Vann Bennett, who was my roommate in medical school and who I started working with in the lab, is also fearless as a scientist. He would ask the hardest questions; he would purify proteins that never before had been isolated. He would sort out the specific, physical, chemical, binding kinetics. He was working on red cells as the source of the protein ankyrin, asking how does the cell skeleton bind to the cell membrane? He found it does, through ankyrin.

And so I, as a hematologist, thought, "Why don't we look at some of the inherited defects of cell shape, like spherocytosis and elliptocytosis?" And that's how the research started. We had a wealth of patients from the countryside, and because there was some consanguinity due to interfamily marriage, recessive diseases appeared. We discovered the likely basis of spherocytosis: the structural protein named spectrin was deficient. Later, Wendell Rosse, a Duke hematologist, suggested we turn our attention to the Rhesus blood group antigen, well known clinically, but never defined biochemically. So one thing led to another.

JCI: Through your studies of trying to figure out the molecular identity of the Rh factor, you stumbled onto the 28-kilodalton protein that would change the course of your career.

Agre: We isolated the 30-kilodalton Rh protein by brute, biochemical force. It was denatured when we got it, but it had a slight shadow that preceded it, which we had assumed to be a breakdown product of 28 kilodaltons. We raised antibodies, but the antibodies only reacted with the breakdown product. We finally recognized that the 28-kilodalton protein was just a contaminant.

So a wiser, more focused, better-behaved scientist would have dropped it. But it's curiosity that drives science. By sheer luck and conversations with really wonderful scientists, like John Parker at UNC, we put it together as the archetypal water channel, later called aquaporin.

JCI: In 2003, you were recognized with the Nobel Prize in Chemistry for this work. Your father had always talked about how the Nobel was like the Holy Grail.

Agre: Well, I guess I became aware of the Nobel early on as a child because Dad did mention this. He invited Linus Pauling [Nobel in Chemistry, 1954 and Peace, 1962] to stay with us, and we followed it every year. Dad died in '95, so he was not alive when I won. Receiving the Nobel was a really pleasant event. But I try not to take it that seriously.

JCI: I saw a talk you gave about some of the hoopla that surrounded winning the prize. You showed a slide that was the marquee of a liquor store that said, "Congrats, Dr. Agre!" So you faced it with some humor.

Agre: Actually, somebody else (William Zinkham from Hopkins) took that picture. The implication that Wells Liquor Store, a discount liquor store — the implication that I'm their best customer is a blatant exaggeration!

JCI: You mentioned Linus Pauling. He won a second Nobel Prize for his work on ending the nuclear arms race. What are you aiming to do now that you have this platform?

Agre: Well, I've always been interested in the public side of science, human rights and global health. The problem with being interested in those issues in science is, who's going to pay the rent? I served one term as Vice Chancellor at Duke; I was there to bolster the Duke scientific presence. I also ran for the Presidency of the American Association for the Advancement of Science, and I was elected. I got those positions probably because of the credibility you get with the Nobel. The interest was there before, but there's no plan to become Linus Pauling Junior. No one could do that.

JCI: What are you looking to accomplish at the Hopkins Malaria Research Institute?

Agre: The Hopkins Malaria Institute has a broad approach. We're not just drug development or vaccine development or epidemiology; we have people doing multiple activities. This is made possible by a fantastic gift from Michael Bloomberg. Previously, there were only two faculty scientists studying malaria, and now there are 20. With cell-biological and structural biological approaches, vaccine development, drug development, and very interesting mosquito research, we are looking for ways to disarm the most dangerous animals in the world: Anopheles mosquitoes.

JCI: Do you think we'll defeat malaria in our lifetime?

Agre: Maybe you'll see that, but I don't expect to. This has always been the issue of what comes later in science. And sometimes, it's years later. I think we can tighten the thumbscrews on the epidemic, but it has to be achieved everywhere. Cuba was able to eliminate malaria by traditional public health measures, but it's just an island. Sub-Saharan Africa is enormous. The approaches are not likely to be successful in my lifetime, but we've got to try.

JCI: If you had to do it all over again, and you couldn't be a medical doctor or a scientist, what other profession do you think might have intrigued you?

Agre: I think if I had been born in another family, I would have been attracted to international journalism. I'm not sure I would've been successful because I don't know if I'm aggressive in the effective way.

Ushma S. Neill