

2016 Association of American Physicians George M. Kober Medal

Introduction of Peter Agre

Paul B. Rothman

Distinguished colleagues, thank you all for being here tonight. It is my great pleasure and honor to introduce the winner of the 2016 George M. Kober Medal, my colleague and friend, Dr. Peter Agre (Figure 1).

The Kober Medal, awarded annually by the Association of American Physicians (AAP), is one of the most prestigious honors in our profession. The list of past winners includes many titans of academic medicine: Francis Collins, Tony Fauci, Victor McKusick, Joseph Goldstein, Michael Brown, Robert Lefkowitz, Helen Taussig, and many others.

The Kober Medal recognizes individuals who have set themselves apart through the pursuit of scientific knowledge and the advancement of medicine through experimentation and discovery.

As a consummate physician-scientist and biomedical innovator, Peter Agre is truly deserving of this great honor.

As many of you know, Dr. Agre is a molecular biologist, physician, and Nobel laureate. He is a professor of molecular microbiology and immunology in the Johns Hopkins University School of Medicine, a Bloomberg Distinguished Professor, and director of the Johns Hopkins Malaria Research Institute.

We are fortunate that he has chosen to spend most of his professional life at Hopkins, save for a couple of years spent at a certain university down south. After serving as vice chancellor for science and technology at Duke University Medical Center from 2005 to 2007, he returned home to Baltimore.

I'll start by sharing a little biographical info about Peter, and then I'll elaborate on the scientific achievements that rocketed

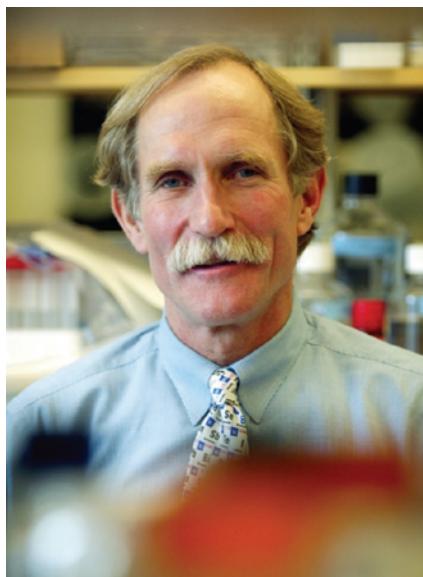


Figure 1. Dr. Peter Agre.

him to notoriety in our field and which have earned him this award today.

Dr. Agre grew up in a Norwegian community in western Minnesota called Northfield. His mother was a farm girl from South Dakota of Swedish and Norwegian descent. She was an avid reader who read to Peter and his siblings every night. Jim and Mark, two of Peter's three brothers, also pursued careers in medicine — they are both psychiatrists — and Peter credits his father, Courtland Agre (Figure 2), who was a professor of chemistry and chairman of the chemistry department at St. Olaf College, for sparking the boys' interest in science.

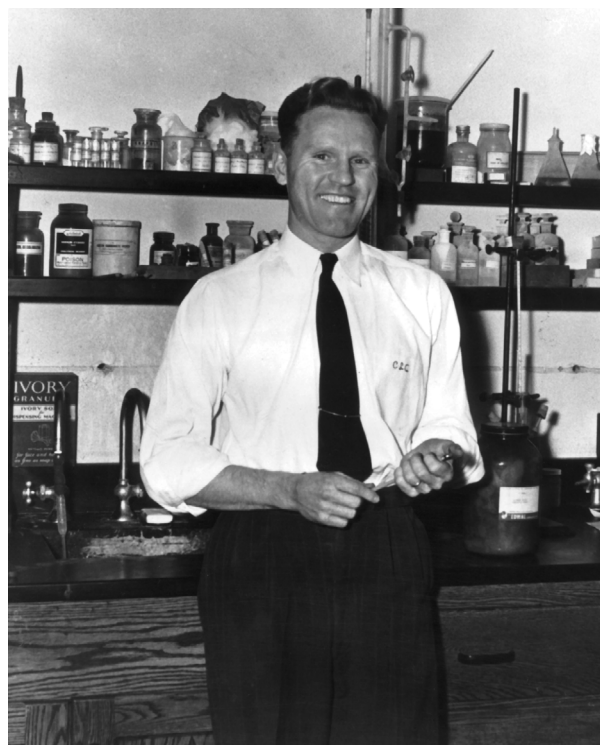


Figure 2. Courtland Agre in his lab at St. Olaf, 1950.

Many people have the misconception that science is a dry, emotionless enterprise, because it's grounded in empirical observation and rational conclusions. But when Peter was young, the senior Dr. Agre would bring Peter and his brothers into his lab on the weekends to try out simple experiments, and he instilled in Peter the sense that science isn't a dreary discipline at all but a true *adventure*. Any of you who know Peter will attest that this spirit of wonder and enthusiasm about the pursuit of knowledge still comes through any time you get him talking about his work.

Peter knew by the third grade that he wanted a career in a lab. However, just because he got the chemistry bug at a young age doesn't mean he necessarily showed an early *aptitude* for chemistry. Quite the opposite actually. He'll be the first to tell you he was a rather subpar chemistry student in high school. He earned a "D" in chemistry his senior year at Theodore Roosevelt High School,

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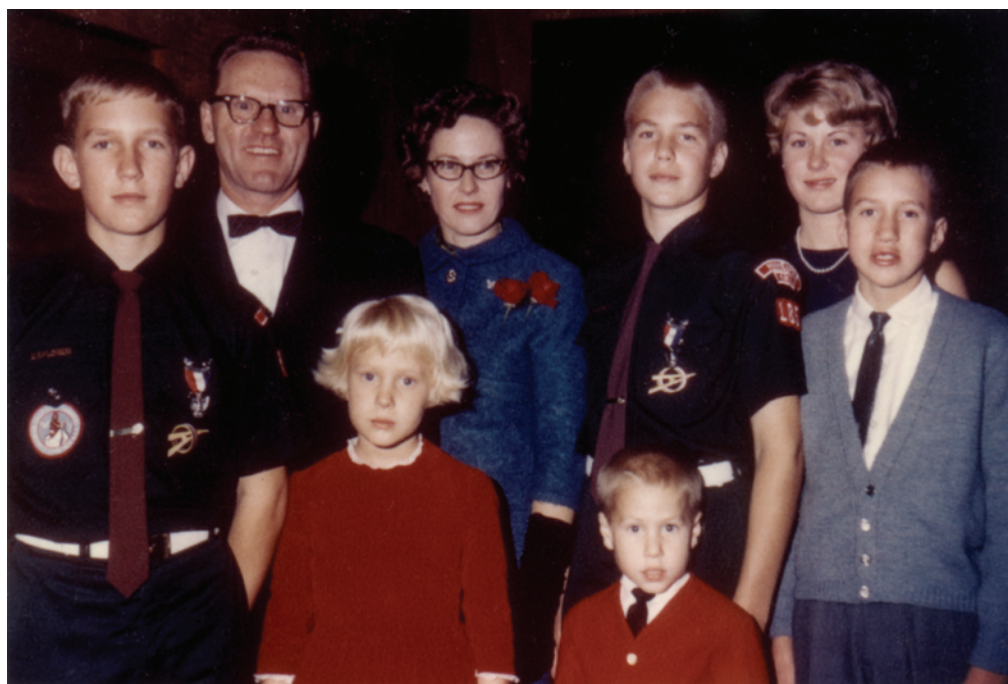


Figure 3. The Agre family in 1965.
Peter is on the left.

despite having a live-in tutor in his chemistry-professor father.

Here's another story he's fond of telling. After one ninth-grade-chemistry classroom experiment, he dumped a bucket of reactive chemicals straight in the sink, and when the potassium oxidized upon hitting the water and ignited the hexane in the solution, it set off a huge explosion that burned his eyebrows off and required a fresh paint job for the classroom!

Peter tells these stories, and others like them, to illustrate his early ineptitude in science.

A little footnote here.... in my opinion, these self-deprecating stories don't just make for humorous anecdotes or serve to show that he has remained humble (which he certainly has). I believe he uses these stories for a specific purpose: to send a message to young people who worry they aren't suited for careers in science or medicine because they can't sit still in class or they didn't go to an elite East Coast college — to send a message that there is no single path to success in our field. Because for Peter, the path to a career in academia started out rocky.

As high school progressed, Peter went from Boy Scout (Figure 3) to self-styled Bolshevik. He prided himself on his counterculture streak — camping throughout Russia and publishing an underground newspaper with his friends. In 1967, he

withdrew from high school. Luckily, he was able to finish all the credits he needed to graduate in night school.

He then enrolled to study chemistry as an undergraduate at Augsburg College, a Lutheran school in Minneapolis. The school took him in spite of his lackluster academic record, partly because his dad had taken a

job there in the chemistry department.

Peter graduated college early in the winter of 1970 and then spent several months traveling alone through Asia (Figure 4), hitchhiking through Japan and Taiwan, riding a motorcycle across Thailand. The trip changed his worldview and inspired a life-long thirst for international travel.



Figure 4. Peter in 1970.



Figure 5. Cuatrecasas lab at Johns Hopkins, 1974.

All eight premed chemistry majors in his class at Augsburg got accepted to medical school, and Peter chose Johns Hopkins, where he enrolled in the fall of 1970. At Hopkins, he worked under Pedro Cuatrecasas in the Department of Pharmacology. There, he was part of the lab that was responsible for the first isolation of the estrogen receptor (Figure 5). He also worked in the infectious diseases group under Brad Sack, determined to purify the *E. coli* toxin.

Even more importantly, while he was a med student at Hopkins, he met his future wife, Mary Macgill (Figure 6), who was working in a neurovirology lab at the time. The two married in 1975, which means they celebrated their 40th wedding anniversary last year. They have four children: three daughters, Sara, Claire, and Carly, and a son, Clarke (Figure 7). And never mind the Kober or the Nobel — these amazing children are Peter's proudest accomplishment.

Peter believed that he needed to train as a physician in order to truly understand

the clinical problems he eventually hoped to address in his lab. So he did his residency in internal medicine at Case Western Reserve University Hospitals of Cleveland (Figure 8).

He then completed a Hematology-Oncology Fellowship at the University of North Carolina at Chapel Hill (UNC), where he met and befriended a hematology professor named John Parker.

Peter's early work investigated the biochemistry of red blood cells. This research

resulted in the discovery of the first known membrane defects in spherocytosis. Hereditary spherocytosis is a disorder where mutations cause red blood cells to be misshapen and thus easily destroyed, leading to hemolytic anemia. Together with Vann Bennett, Peter studied the membranes and discovered they lacked a cytoskeletal protein called spectrin — a study they published in the *New England Journal of Medicine*.

He joined the faculty of the Johns Hop-



Figure 6. Mary Macgill. (A) Peter's wife Mary, with their son Clarke. **(B)** Peter and Mary, who celebrated their 40th wedding anniversary in 2015.



Figure 7. The Agre family.

kins School of Medicine in 1981, taking a pay reduction from his previous staff post at the Wellcome Labs and an adjunct job at UNC for the opportunity to work with some great scientists in Baltimore, including Vann Bennett, his old med school roommate, who was now running his own hematology lab. In fact, we paid him so

little at Hopkins that apparently he had to work at a professional boxing club as a ringside physician to make ends meet!

In Baltimore, Peter set up shop in a tiny lab in the Johns Hopkins Hospital and continued his studies on spherocytosis. His lab also managed to isolate the Rh blood group antigen. “Although the

importance of the blood group antigen Rh was universally recognized,” Peter explained, “I was surprised to learn... that the molecular identity of Rh was completely unknown. The existence of 32-kDa polypeptides in red cells from Rh(D) individuals was reported by two European groups. We initiated a new project on the Rh blood group antigen in the hope that isolation of the polypeptide would allow us to define the components of the Rh antigen. Andy Asimos and I injected a series of rabbits with the partially purified 32-kDa Rh polypeptide. When Andy left for medical school, Barbara Smith, a former blood bank technologist, replaced him and set about purifying the Rh polypeptide with me.”

Within a dozen years at Hopkins, in 1993, Agre rose to the rank of professor of biological chemistry and medicine.

Around the same time, he aided Tom Pollard (then-director of Cell Biology) in starting a new PhD program in cellular and molecular medicine designed to give lab students a comprehensive understanding of clinical diseases.

In the early 1990s, Agre made the breakthrough that would change his life and define his career. He discovered aquaporins, a family of water channel proteins found throughout nature (Figure 9).



Figure 8. Case Western Reserve University medical residents, 1976. Peter is shown in the green circle.



Figure 9. Peter in 1992, the year in which he discovered aquaporins.

Scientists had spent decades looking for these channels, hoping to finally explain how water is able to move through certain tissues extremely rapidly.

Following in the great tradition of Alexander Fleming and others who have stumbled upon major scientific discoveries almost as if by accident, Agre says his breakthrough can be credited largely to serendipity.

At the time, his lab was researching something unrelated — Rh incompatibility in pregnancy. One day, as he and his

colleagues purified the Rh protein they needed, they noticed a second molecule, a mysterious protein known as 28 kDa, kept appearing in the red blood cells. At first they thought the 28 kDa was a contaminant. But the protein was abundant in the red cell membrane and resembled proteins found in the kidney, the lens of the eye, bacteria, and plant tissues.

“Imagine,” Peter told a magazine writer. “You are driving through Western Maryland and you come upon a town of 200,000 people that’s not on any map.

That’s what it was like.”

Agre was intrigued and set out to uncover what the protein was. On a drive back to Maryland from Disneyland, he stopped into UNC to visit his old friend, Dr. John Parker, the UNC hematologist who had been his attending during his fellowship. Parker was the first person to suggest it was possible that this new protein could be the long-sought water channel.

Working with a postdoc named Greg Preston and Bill Guggino, professor of physiology and pediatrics at Hopkins, Agre designed an experiment to test the hypothesis.

In October 1991, Agre’s lab cloned the DNA encoding the protein they had discovered and injected the corresponding RNA into six frog eggs. Test eggs injected with complementary RNA produced the new protein and became water permeable. In fresh water, they swelled and burst. Control eggs not injected with RNA failed to swell.... Every determination indicated that the new protein is a channel permeated only by water.

When Greg observed this result, he ran into Peter’s office and they erupted with joy! With this discovery, they had put to rest a 100-year-old debate among scientists about how water was able to move so rapidly across cells.

So what made this such a momentous discovery?

Aquaporins, known as “the plumbing system for cells,” play a role in many physiological processes in humans and are impli-



Figure 10. Peter with his lab and his family. (A) The Agre lab on October 8, 2003. (B) Peter with his family at the 2003 Nobel Prize ceremony.



Figure 11. Since 2008, Peter has served as director of the Johns Hopkins Malaria Research Institute at the Bloomberg School of Public Health. In this role, he oversees 20 faculty research groups as well as field activities in Zimbabwe and Zambia. *P. falciparum*, the parasite that causes malaria in humans, also has aquaporins.

cated in multiple clinical disorders, including malaria. From sweating and swelling to urination and crying, water transport is involved, which means so are aquaporins.

If scientists could figure out how to manipulate aquaporins and thus regulate the balance of water in cells, then they could potentially block or inhibit fluid retention in heart disease, cataracts, stroke, or other conditions.

Word spread quickly through the scientific community following the aquaporin discovery, and just over a decade later, in 2003, Dr. Agre was catapulted to worldwide notoriety with his Nobel Prize in Chemistry (Figure 10), which he shared with Roderick MacKinnon of The Rockefeller University.

Having made a name for himself in the field of membrane transport, he formed many fruitful partnerships with Hopkins colleagues and outside labs, primarily in Europe, which were also investigating these issues. And some important achievements arose from these partnerships.

According to Peter, Mark Knepper, at the NIH Laboratory for Kidney and Electrolyte Metabolism, introduced Agre to his junior colleague, Søren Nielsen, at Aarhus University. With Søren in the lead, they defined the sites of expression of AQP1 in kidney, brain, capillaries, and other tissues by high-resolution light microscopy and immunogold electron microscopy.

Using AQP1 protein that Barb Smith purified to homogeneity, collaborators Mark Zeidel at Harvard and Suresh Amubudkar at Hopkins defined the bio-

physical functions of AQP1 reconstituted into synthetic liposomes.

Ueli Aebi, a former Hopkins colleague, introduced Agre to Andreas Engel at the University of Basel in Switzerland. Andreas and his grad student Tom Walz prepared membrane crystals containing Agre's highly purified AQP1 protein and determined the structure by negative staining electron microscopy, atomic force microscopy, and electron crystallography.

Hopkins colleague and Executive Vice Dean Landon King furthered Agre's work on the regulation and function of aquaporin water channel proteins, focusing on the role of water channels in lung function.

And so on.

In 2005, Peter moved to Duke University where he served as vice chancellor for science and technology. In that role, he helped shape Duke's biomedical research enterprise.



Figure 12. Peter at the Pyongyang University of Science and Technology.



Figure 13. Peter with fellow Eagle Scouts, 50 years later.

Since returning to Hopkins on January 1, 2008, he has served as director of the Johns Hopkins Malaria Research Institute at the Bloomberg School of Public Health, where he succeeded Dr. Diane Griffin. It turns out that *P. falciparum*, the parasite that causes malaria in humans, also has aquaporins. In this role as director, Peter oversees 20 faculty research groups as well as field activities in Zimbabwe and Zambia (Figure 11).

Agre's influence extends well beyond the laboratory, as he's deeply involved in numerous global issues. As a member of the National Academy of Sciences and the National Academy of Medicine, he previously chaired their Committee on Human Rights, which advocates for health professionals and scientists anywhere in the world who are unjustly imprisoned.

Knowing Peter's zeal for global activism, it probably won't surprise you to learn that his hero and role model growing up was Linus Pauling, who was not only a brilliant scientist but also one of this country's leading peace activists. When Peter

was a kid, Pauling even came to stay with his family for a few days while presenting lectures in the area, and that experience left quite a mark. Pauling, Peter has said, was "more engaging than anyone (he and his siblings) had ever met." Pauling and his wife spent years protesting the proliferation of nuclear arms and the hysteria over the perceived threat posed by communists in the Cold War period and was the winner of a Nobel Peace Prize eight years after his Nobel win in chemistry.

From 2009 to 2011, Agre served as president and chair of the board of advisors of the American Association for the Advancement of Science (AAAS). As part of the AAAS Center for Science Diplomacy, Agre has led visits of US scientists to North Korea (Figure 12), Myanmar (Burma), Iran, and Cuba. He once wrote, "The international network of scientists who know other scientists represents unique opportunities to use science to foster friendships worldwide."

Peter, along with others, has noted that in countries that are our policy foes,

where we don't have good diplomatic relations, people tend to have a negative impression of Americans, but they still rate us very highly when it comes to our science and technology. In other words, good science has the potential to bridge cultures, as Peter has demonstrated again and again on his trips abroad.

Dr. Agre holds 17 honorary doctorates from around the world and a Commandership in the Royal Norwegian Order of Merit. He is an Eagle Scout and recipient of the Distinguished Eagle Scout Award (Figure 13).

Oh, and he once appeared on *The Colbert Report* to discuss the relationship between government and science and the decline in scientific knowledge among the American public, which makes him infinitely cooler than me in the eyes of my teenage children.

I am so honored to have this opportunity to talk about Peter's journey into medicine — which brought him from noodling around in the lab at a small college in Minnesota to his current quest to eradicate a deadly disease that afflicts more than 200 million people around the globe.

In spite of his singular achievements, Peter is as humble a person as you're likely to meet. In preparing for today, I watched an interview with him where he was asked how it felt to make the aquaporin discovery. He said that, while a lot of Nobel winners relish the attention they draw from around the world, he sees himself less as a descendent of Albert Einstein than as a Huck Finn-like figure — or as he put it — "a happy-go-lucky individual with a good team of scientists and friends, looking for adventure."

And he certainly found it. Or rather, *it* found *him*.

Address correspondence to: Paul B. Rothman, Johns Hopkins Medicine, 733 N. Broadway, Suite 100, Baltimore, Maryland 21205-2196, USA. Phone: 410.955.3180; E-mail: prothma1@jhmi.edu.