PRESIDENTIAL ADDRESS

Life on the River of Science

Peter Agre

THE YEAR 2010 MARKED THE CENTENNIAL of Mark Twain's death. More than any other American author, Twain exemplified the use of personal anecdotes to illustrate events in our nation's history. With this in mind, I will attempt to share my experiences in science, beginning one half-century ago, with a view for how we as individuals are part of the great river that science has become.

It is my hope to stimulate young scientists and inform the nonscientific public that achieving success in science involves several features. But if my experience is representative, the most important features include basic curiosity, the will to take chances, and the generous attention of family members and teachers. Probably for most individuals who became scientists during this time, guarantees of financial success were not considered, and with no large fortune to lose, it is no surprise that many scientists came from America's large middle class.

Science and Growing Up in the 1950s

While I was a child in the 1950s, "science" was a word familiar to American schoolchildren. Just a decade earlier, the end of World War II, brought about by dropping atomic bombs on Hiroshima and Nagasaki, Japan, made everyone aware that we had entered the nuclear age. Because the polio epidemic had touched tens of thousands of American families, the name of vaccine pioneer Jonas Salk was universally recognized.

The widespread introduction of television into American homes in the 1950s allowed American children to see the special magic of science by watching Don Herbert as "Mr. Wizard" on Saturday mornings. On Sunday evenings, children viewed the Disney show, whose format reflected the four kingdoms of the Disneyland amusement park, one of which, Tomorrowland, focused on science.

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Although it occurred more than 50 years ago, I distinctly recall Wernher von Braun discussing rocketry and space travel. In an unforgettable Disney program, University of California Berkeley Nobel laureate Glenn Seaborg provided a remarkable demonstration of the chemical chain reaction. Holding a spring-loaded mousetrap with a ping-pong ball on it, he sprung the trap and the ball flew. The camera then panned a room with the floor covered with activated mousetraps, each with a ping-pong ball on it. Seaborg tossed in one ping-pong ball, and within seconds the room was a cloud of flying mousetraps and ping-pong balls.

Seal River enters Hudson Bay, 2004

CREDIT: BOB FRENCH

Of course, actual hands-on science trumped even television, and having a father who was head of the chemistry department at St. Olaf College, a small liberal arts school in the rolling farmlands of southern Minnesota, gave me opportunities available to few children. My brothers and I marveled as we added a drop of a colorless solution to a beaker containing another colorless solution that instantly turned brilliant pink. Addition of a drop from a third solution caused the pink color to disappear again. What we first viewed as "magic" became understandable when we learned about alkali, acid, and indicator dyes. Marked by the experience, I recall our third-grade teacher asking us to draw ourselves as adults performing our life's work. I proudly drew a picture of a chemist holding test tubes, since I wanted to be like my father—a chemist.

On a Saturday afternoon in October 1957, Dad came across the meadow to where my brothers and I were playing ball to bring us home for dinner. As we walked, he spoke of the breaking news story on the radio: the launching of Sputnik. We scanned the sky and failed to see the satellite, but it was no less real. More than any other single event, the launching of Sputnik began a remarkable renewal of the already strong American support for science. The motivation was based on the national humiliation of being beaten into space by our adversary, the Soviet Union, but the outcome was very positive.

The outpouring of funds for science and science education affected us directly. Dad wrote a National Science Foundation Fellowship that allowed us to move to Berkeley, California, for a sabbatical year at the University of California. Perhaps resembling the Norwegian equivalent of the Beverly Hillbillies, we packed our old Chevrolet station wagon for the drive across the country. We arrived in Berkeley, a forward-thinking, multicultural community markedly unlike our quiet farming community in southern Minnesota.

A Family's Scientific Hero

Hero figures are important in the development of a child. During our year in California, we became familiar with Dad's new colleagues, including a chemist from Caltech with whom Dad served on the American Chemical Society Education Committee.

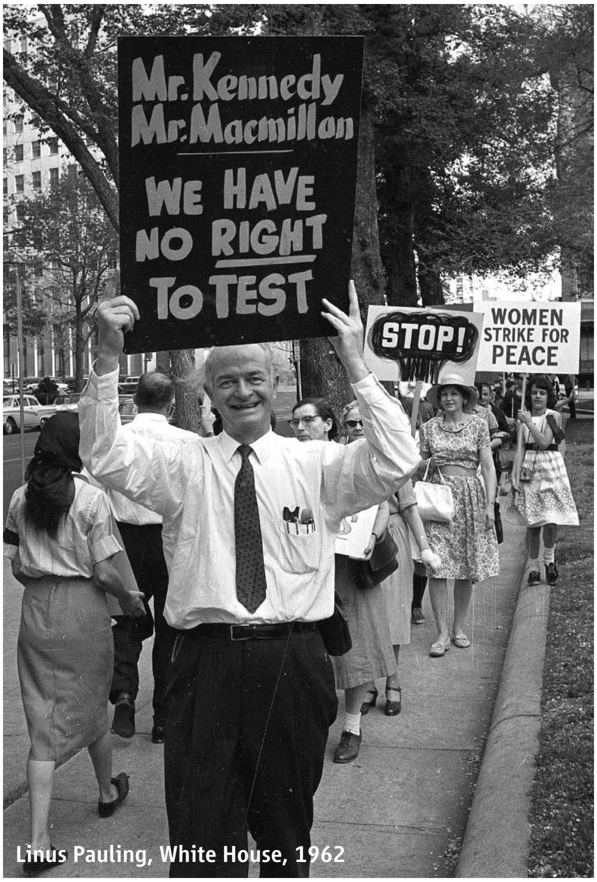
Linus Pauling had an exuberant personality, and we got to know him when he stayed at our house. Eating cornflakes at the breakfast table with the tall, grinning Pauling, wearing a black beret over his curly white hair, was simply unforgettable. Dad always beamed about Pauling, who had received the 1954 Nobel Prize for Chemistry for elucidating the nature of the chemical bond and solving structures of proteins. That he discovered hemoglobin S, the molecular cause of sickle cell anemia, was no less astonishing.

In addition to his brilliant laboratory research, Pauling also had a unique role as a science activist. Well known in the 1950s for his opposition to U.S. nuclear weapons development, Pauling's public visibility caused the U.S. State Department to revoke his passport. Falsely accused of being a communist, Pauling frequently provoked the right wing of American politics during and after the McCarthy era.

Lecturing prodigiously around the world, Pauling often presented technical lectures about chemistry during the day and educational lectures to the public at night. The public lectures focused on the danger of thermonuclear weapons testing, made internationally famous due to publication of his bestseller entitled *No More War* (*1*). A remarkable raconteur, Pauling conveyed nuclear testing information in terms that all could understand, saying that the dangers that radioactive fallout held for the health of innocent people had become an international crisis. Pauling seemingly used every possible opportunity to speak out.

In April 1962, Pauling was one of 49 Nobel laureates invited to a black tie dinner at the White House hosted by President Kennedy—an event Kennedy later recalled as "the most extraordinary collection of talent, of human knowledge, that has ever been gathered together at the White House, with the possible exception of when Thomas Jefferson dined alone." Not about to miss an opportunity to publicly press for an end to nuclear testing, Pauling in shirtsleeves joined a protest on the sidewalks around the White House bearing a sign: "Mr. Kennedy, Mr. Macmillan, WE HAVE NO RIGHT TO TEST."

We viewed this at home on the evening news. Apparently Kennedy was well aware of Pauling's protest and was reported to have smiled when meeting Pauling in the reception line. Known for his wit, Kennedy remarked that he understood that Pauling had been around the White House already (*2*). But he recognized the significance of Pauling's protests, and just 6 weeks before his assassination, the president signed the Limited Test Ban Treaty, preventing nuclear arms testing in the atmosphere, an event that markedly reduced the tension of the nuclear arms race. As Kennedy was being buried in Arlington Cemetery, the Pauling family was preparing for his trip to Oslo to receive his second Nobel: the 1962 Peace Prize.



Linus Pauling, White House, 1962

CREDIT: AP PHOTO

Others have frequently commented on Pauling's exceptional personality. Roughly 9 years ago at a reception in Stockholm, I had the opportunity to meet James Watson. Having reread his classic *The Double Helix* (*3*) on a family wilderness canoe trip the summer before, I complimented Watson on the first sentence—a grabber that draws the reader's attention: "I have never seen Francis Crick in a modest mood." Watson nodded when I explained that Linus Pauling had been a family friend, then grinned broadly and added, "I have also never seen Linus Pauling in a modest mood." To which I thought to myself, "Do heroes really need to be modest?"

Medicine as a Scientific Career

My path to science came not from a pressing ambition to become a prominent researcher but from a desire to pursue a career in medicine. This was in part a cultural emphasis learned early at home. As much as our father emphasized math and science, our mother, a farm girl who never had the opportunity to attend college, was self-taught through a love of reading. And she read to us every night from the children's Bible as well as great books like the Laura Ingalls Wilder series. I remember snuggling with my siblings on the sofa during cold Minnesota evenings as Mother read.

Although I was just a small child, it became obvious to me that two of my five siblings were already manifesting lifelong disabilities: a brother diagnosed with mental retardation and motor skill dysfunction and a sister with a variant of Tourette syndrome and a lack of impulse control. While my parents did not dwell on it excessively, we were nevertheless reminded that all were not equivalently blessed, and we were always encouraged to use our talents for the well-being of those less fortunate.

Also strongly encouraged in our Minnesota Norwegian Lutheran community was a sense of responsibility for those in the developing world. Medical missionaries were widely respected throughout our community. Minnesota Governor Al Quie's sister, a nurse, and her husband, a surgeon, spent their entire careers attending to the health needs of rural Cameroon. Even our congressman, Walter Judd, had spent a decade as a physician serving the poor in rural China.

Having the opportunity to attend Augsburg College in Minneapolis, where Father taught after leaving St. Olaf, I majored in chemistry and received outstanding lectures and laboratory experiences. Several of my Augsburg classmates were from medical missionary families and had grown up in rural Africa, India, and Asia. This group projected sincere altruism without any hint of self-promotion.

Through an introduction to Richard Varco, a 1955 Lasker Award–winning pioneer in heart surgery, I received the opportunity to undertake summer research at the University of Minnesota Heart Hospital. The experience was pivotal in solidifying my interest in medicine. All five of the summer students I worked with have risen to leadership positions in leading institutions of academic medicine. Two of my younger brothers must have reached the same conclusion, since both have gone on to become medical doctors.

Accepted at medical school and having finished my college coursework early in the winter of 1970, I had several months for an elective experience. I chose to use the time backpacking throughout east, southeast, and southern Asia and the Middle East. This allowed me the chance to view exotic places but also the opportunity to visit sites of medical research in Thailand and India that intrigued me greatly. Although "going native" often brings unwanted experiences with traveler's diarrhea and other maladies, I survived the experience excited about the prospect of global health research at Johns Hopkins University, renowned for its international programs.

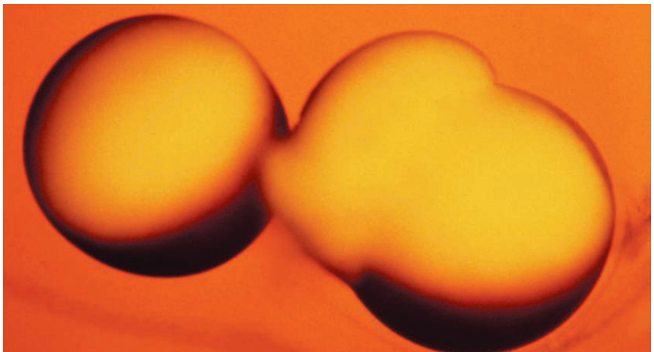
Early Research Experiences

Probably the most important experience for any young scientist is the opportunity to join an exciting laboratory. Although algorithms may exist for matching students with labs, my experience suggested that personal contact may be much more informative. As a first-year medical student at Johns Hopkins, I became close personal friends with Vann Bennett, a fellow medical student who had been a Stanford wrestler and a big-wave surfer in Hawaii. Vann and I shared a love for vigorous physical exercise, such as bicycle camping trips throughout the Appalachians. Vann's fascination with biochemistry was something that I grew to admire, and I envied his special bravado—often skipping class assignments to pursue his independent research in a laboratory.

Intrigued by our medical school lectures in microbiology, I became fascinated by the recent advances in understanding the molecular basis of cholera, a horrible diarrheal disease that was sweeping through Asia, killing tens of thousands of infants and small children. I began working on a related project, the molecular basis of the well-known malady *E. coli* traveler's diarrhea, in the lab of R. Bradley Sack, a young infectious disease researcher at Hopkins. With Brad's support, I made steady progress, studying the toxin by injecting crude mixtures into the lumen of ligated segments of rabbit small intestine that then became swollen with secreted diarrheal fluid. It soon became clear that purification of the toxin would require more sophisticated technical expertise.

It was through Vann that I came to join the lab led by Pedro Cuatrecasas, a brilliant Spanish-born physician scientist who had trained at the National Institutes of Health (NIH) with Christian Anfinsen, who had shared the 1972 Nobel Prize in Chemistry for establishing that the primary sequence of a protein, staphylococcal nuclease, determined the structure and catalytic activity of the enzyme.

Although only in his 30s, Pedro had already achieved great recognition for pioneering the technique of "affinity chromatography" to biological problems (*4*). This novel concept used an insoluble matrix of polymeric beads to which small molecules had been covalently attached, and through which complicated biological mixtures such as cytoplasm or solubilized membranes could be filtered. Using affinity chromatography, success had been achieved in isolating, for the first time, receptors for hormones such as insulin, epidermal growth factor, and estrogen. For this work, Pedro was to subsequently share the 1987 Wolf Foundation Prize in Medicine. Despite the fame he achieved from affinity chromatography, Pedro always encouraged us to seek important biological problems, rather than simply seeking problems to apply our technical repertoire to.



Xenopus oocytes placed in hypo-osmolar solution: control oocyte (left) and oocyte expressing the 28-kD protein (right)

CREDIT: ADAPTED FROM G. M. PRESTON, T. P. CARROLL, W. B. GUGGINO, P. AGRE, *SCIENCE* 256, 385 (1992)

After purification of cholera toxin in 1970 and recognition that ganglioside membrane lipids served as receptor sites, Pedro entered the field to characterize the membrane events of cholera toxin activation of membrane adenylate cyclase. This also made the Cuatrecasas lab well suited for studying the elusive *E. coli* enterotoxin. Using ganglioside affinity gels we had prepared, we succeeded in adsorbing the enterotoxin activity to the affinity columns and were able to elute highly enriched subunits of the enterotoxin from the column, allowing us to raise antibodies and develop an immunoassay to diagnose *E. coli* enterotoxic diarrhea from crude stool samples (*5*).

The prospect of using our new technique to screen individuals in the field in Bangladesh, where diarrheal diseases were rampant, was our long-term objective. As is not uncommon, scaling up a prototype lab test for clinical testing was not simple. Having committed my entire senior year of medical school to the project, it was still not ready for field testing, so I decided to remain an extra year as a postdoctoral fellow in Pedro's lab. This was considered highly questionable by the medical student advisors, as well as most of my medical school classmates, since graduating and becoming resident physicians are equivalent to the Holy Grail for medical students.

But for me, remaining associated with the colorful members of Pedro's team was much more exciting. The group included several that had bypassed lucrative careers in clinical medicine to follow their passions for science. Looking back years later, I think it was clearly the people in Pedro's lab that made science irresistibly appealing to me: Vann; Gianfredo Puca, a debonair Neopolitan film actor who revolutionized the understanding of femininity by purifying the estrogen receptor; Ignacio Sandoval, a Spanish leftist whose love of biology was only exceeded by his hatred of the Franco regime; Naji Sahyoun, a loyal Palestinian; and Marvin Siegel, the son of an orthodox rabbi, became lifelong best friends after working closely together in the lab. And even more importantly, I had met my future wife, Mary, who worked in a neurovirology laboratory at Johns Hopkins, and our lives took on a special tone resembling *La Bohème* with a science orientation.

Pathway to a Discovery

The reason one lab makes a discovery where others have failed has been an issue long debated in science. It may well be that each lab is unique in its own way, but this seems overly simplistic, and it may be that a few generalizations are reasonable. So I will summarize, with a little editorializing, how our lab came to discover the protein now known as aquaporin-1 (AQP1), the first defined molecular water channel—using our story to communicate seven "pearls" for younger scientists.

1. **Be lucky by keeping your eyes wide open.** After joining the faculty at Johns Hopkins in 1984, my small laboratory was working on human erythrocyte membranes. We set out to isolate the core 32-kD membrane protein of the Rhesus blood group antigens. In addition to the 32-kD Rh, a 28-kD membrane protein copurified. We subsequently realized that the smaller polypeptide was a contaminant and was unrelated to Rh.
2. **Consult the wisdom of your colleagues.** The nature of the 28-kD protein was intriguing. Unlike most proteins, the 28-kD polypeptide stained poorly with Coomassie blue, so had not been noticed previously. When it was purified to homogeneity, we realized that the 28-kD membrane protein was extremely abundant and seemed to be a homotetrameric protein, suggesting that it might be a membrane channel. N-terminal protein sequencing provided sufficient information for cDNA cloning that showed that the new protein was related to a series of functionally undefined proteins from diverse organisms, including plants. I spoke with numerous colleagues about the possible role for the 28-kD protein, until one had an insightful idea.
3. **Respect but don't overcompartmentalize work and family life.** Despite the need to share responsibilities for the raising of children and contributing to domestic duties, it is important to remain flexible. The conversation that helped elucidate the function of the new 28-kD protein occurred at the end of one of our family camping trips. While returning from the Everglades, we stopped in Chapel Hill, North Carolina, so that Mary could visit friends, the children would have a chance to play with their former playmates, and I could drop in on some of my scientific friends. This was to become just one of many examples where our family life catalyzed a scientific advance.
4. **Great ideas come when you least expect them.** What began as a casual visit with my former professor John Parker, a hematologist and membrane physiologist at the University of North Carolina School of Medicine, became a major event. I shared with Parker what I knew about the 28-kD protein. John quickly recognized that the protein might be something long sought by physiologists: the membrane channel for water. Workers in multiple labs worldwide had generated indirect evidence supporting the existence of water channels, but none had isolated the putative channel and established its molecular identity.
5. **Team up with those bearing needed expertise.** Parker also suggested that I contact Bill Guggino when I returned to Hopkins. Guggino, a membrane-channel physiologist, used techniques in his lab for the expression and study of membrane ion channels. This allowed our postdoctoral fellow Gregory Preston to perform a simple assay demonstrating that frog eggs expressing the new protein became osmotically active and exploded when placed in distilled water (*6*). This began a long series of collaborations with an expanding group of aquaporin scientists around the world, including renal physiologists at NIH, structural biologists in Basel and Kyoto, microscopists in Aarhus, neuroscientists in Oslo, eye researchers in London and Tokyo, and others. Together, many scientists provided new insight into the fundamental processes involved in renal concentration, vision, skin integrity, brain edema, thermal stress, arsenic clearance, and obesity, as well as the adaptation of plants to drought (*7*).
6. **Don't take yourself too seriously.** In the beginning, it was difficult not to take every advance in the aquaporin field personally and view newcomers and competitors with great suspicion. It soon became obvious that we were simply a small section of a new field of science. When the Nobel call eventually came from the Royal Swedish Academy of Science, it was my 78-year-old mother who put it in proper context, "That's very nice, but don't let it go to his head." Her intent was to communicate that awards are nice, but doing something useful for others is really important.
7. **Science is about new adventures.** The idea of working in global health had been my original career ambition. With the recognition of aquaporins in the parasite causing malaria, we cautiously entered the field. In many ways, this marked a new direction for our lab, but one that we were eager to follow. And with a new direction came a new opportunity: directorship of the Johns Hopkins Malaria Research Institute (JHMRI) at the Bloomberg School of Public Health (*8*). The new role has been a challenge, but it has been a delight to be part of a program with as much global importance as malaria research. The JHMRI lab programs in Baltimore and fieldwork in rural Zambia are both stimulating and rewarding. And the ease with which malaria crosses borders, killing hundreds of thousands of African children, is a clear reminder of the international aspects of science.

Rural Zambia, 2008

CREDIT: PETER AGRE

Science as a Tool for International Diplomacy

Science has always been one of the most international of human endeavors, and this trend is certainly increasing. Every year, thousands of young scientists come to the United States from abroad to undertake scientific education and research. Thus, science provides a unique approach to advancing good will toward America in the international arena.

It is no secret that the U.S. government is viewed negatively in the Muslim world, especially after the military intrusions in Iraq and Afghanistan. The Zogby Poll [(*9*); see table below] reveals a clear bimodal response. The great majority of citizens of five moderate Arab nations held distinctly unfavorable views of the United States in general. In marked contrast, these same individuals held favorable views of U.S. science and technology. This provides an opportunity to use our background as nongovernment scientists to reinforce the positive: that U.S.-generated science and technology may improve the lives of people all around the world.

	U.S. in General		U.S. Science and Technology	
Country	Favorable	Unfavorable	Favorable	Unfavorable
Morocco	11%	88	90	08
Saudi Arabia	04	94	48	51
Jordan	15	78	83	13
Lebanon	20	69	52	46
UAE	14	73	84	12

[From *Impressions of America* (*9*)]

Having the chance as president of AAAS to participate in some outstanding programs, one stood out as particularly appealing: the AAAS Center for Science Diplomacy. The potential to establish contact and engage with scientists in countries considered adversarial to the U.S. government is an opportunity for science to serve as a unique bridge. Founded in 2008, the center is directed by Vaughan Turekian, an atmospheric geochemist and international policy expert, with special advisor Norman Neureiter, a chemist with extensive policy experience. I was greatly pleased to participate as senior scientist in a series of trips abroad (*10*).

Recognizing that some of our visits were to countries where there are serious intergovernmental tensions related to a wide range of issues such as proliferation, human rights, and economic openness, each visit was undertaken with an independent nongovernmental organization and with private funding, in most cases from the Richard Lounsbery Foundation. Efforts were made to inform appropriate U.S. authorities of such visits, but it was to be plain in every case that we served as representatives of the U.S. scientific and research community, not the U.S. government.

University of Havana, 2009

Cuba. Together with members of the New America Foundation, a trip to Havana, Cuba, was made in November 2009. Our trip, the first AAAS visit since 1997, included a visit to the Finlay Center for Vaccines Research and Production, where we observed the Cuban efforts to prevent infectious diseases such as type B meningococcal meningitis. Endemic before the Revolution, malaria has been eliminated from Cuba, despite a heavy malaria presence in Haiti, just to the east. Cuban efforts to provide universal prenatal health care have succeeded in raising the average life span to 78+ years, equivalent to that in the United tates.

The University of Havana generates a large number of science graduates, but laboratory opportunities are limited. Certainly the investment of funds in laboratories to train young scientists could be mutually beneficial to Cuba and the United States. Potential scientific collaborations could be rapidly undertaken once the five-decade political standoff between our governments is resolved.

Democratic People's Republic of Korea (DPRK; North Korea). The AAAS Center for Science Diplomacy worked for more than a year with the U.S. Civilian Research Development Foundation to gain an invitation to visit Pyongyang in December 2009. Located only ~500 miles east of Beijing, Pyongyang exists in a world apart from the hustle and thickly polluted air of the vibrant Chinese capital. Having only a modest power grid, Pyongyang has crystal-clear air and is impeccably neat but frigid due to a lack of interior heating.

It was obvious from our visit that young North Koreans have great prowess with computer systems—also made clear from ongoing collaboration between Kim Chaek University in Pyongyang and Syracuse University in New York. DPRK agricultural and health sciences were far less advanced and represent areas where the United States could be helpful to the DPRK.

After we had spent 1 week under the watchful eyes and gracious hospitality of the State Academy of Science, our hosts exhibited a warmhearted response when presented with the necktie I had worn during my Nobel lecture in Stockholm.


Bridge across Zambezi, Livingstone, Zambia, 2008

CREDITS: PETER AGRE

Pyongyang University of Science and Technology, 2009

CREDIT: PETER AGRE

Emblazoned on the shield of the Johns Hopkins Department of Medicine is the word *Aequanimitas*. The term means "imperturbability." The tie, bearing this word, was given with our wish that it be worn by the first DPRK scientist who wins a Nobel. Although the political distance between our governments has not decreased in the months after our trip, it should be kept in mind that well-intentioned scientists reside in the DPRK. When the U.S. and DPRK governments finally establish an accord, it is expected that the pursuit of peaceful areas of science may be a bridging mechanism.

Myanmar (Burma). Another country of current difficulty due to its longstanding military junta is Myanmar, a nation of 59 million people with rich natural resources. Together with the U.S. Collection Humanitarian Corps, a visit was organized in April 2010. Of several ministries visited, the Ministry of Health may have been most important, because of the heavy infestation of malaria throughout the countryside that is problematic to neighboring countries. Since our visit, national elections have been held, and the national leader and 1991 Nobel Peace Prize Laureate Aung Sang Suu Kyi has been released from confinement in her home. Although internationally recognized democracy has not yet returned to Burma, it is possible that continued scientific dialogue may contribute to the transparent and ongoing interactions with the international community that serve as a precondition for any sustainable and effective system of governance .

India. The world's largest democracy, India and the United States have had longstanding science engagement. It was a privilege to attend the 10th anniversary of the Indo-U.S. Science and Technology Forum in December 2010. This included visits to the National Institute of Malaria Research, other laboratories, and university campuses, and a public lecture on science. Despite India's many social and economic problems, an air of optimism is readily apparent in India, and science seems a large part of it.

Given our longstanding mutual support, Indian scientists shared observations that reveal their views of Americans. After my lecture to outstanding high-school science students at the University of Delhi, I was presented with a painting of the beautiful multiarmed Hindu goddess Saraswati, who is widely worshiped throughout India as the bearer of enlightenment. Our international friends can tell us things we in the United States need to hear.

Final Reflection

Science is the medium of our life's work. Whether we are frustrated or joyful, we always know that each new day in the lab brings an opportunity to make profound advancements in the understanding of nature that may improve the well-being of others.

One of the talented young people from China in our lab always took the optimistic approach, summarized by the Mandarin character for "crisis." It is actually two characters: wei, meaning "time of danger," and ji, meaning "time of opportunity."

For me, the crisis of living in today's world includes dangers such as increasing microbial drug resistance, the obesity epidemic, environmental damage, the need for sustainable energy supplies, and hostile relations between countries. It seems clear to me that solutions to each will come through the great opportunities provided by science. And with that in mind, I am optimistic about the future.

危机

Wei Ji – Mandarin for "crisis"

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