PRESIDENTIAL ADDRESS

Grand Challenges and Great Opportunities in Science, Technology, and Public Policy

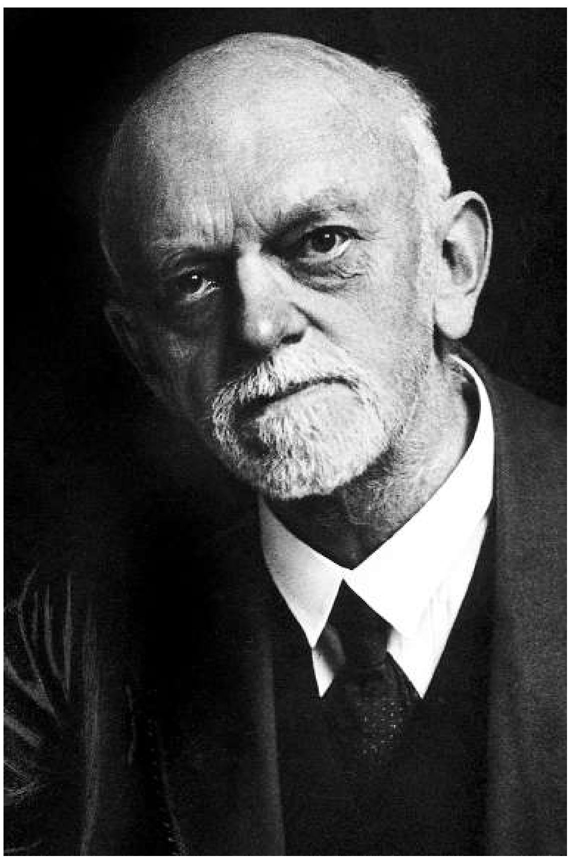
Gilbert S. Omenn

Science is about asking questions and finding credible ways to answer them. Scientists and engineers lay the foundation for practical applications of what is learned, and respond to needs in the broader society, as well as our own curiosity and passion for new knowledge. Economists have attributed more than half of the gains in gross national product and up to 85% of the gains in per capita income over the past several decades to advances in science and technology (*1–3*). Science works best in a culture that welcomes challenges to prevailing ideas and nurtures the potential of all of its people. Scientific ways of thinking and of re-evaluating one's views in light of new evidence help strengthen a democracy.

Many of us are confident that the scientific community could do even more if we are asked to do so and if we organize to accelerate work toward major goals for society. The AAAS theme, "Grand Challenges and Great Opportunities," helped frame the special 125th anniversary issue of *Science* on "What Don't We Know?" (*4*) and an excellent 2006 annual meeting.

The concept and promotion of Grand Challenges can help energize not only the scientific and engineering community, but also students, journalists, the public, and their elected representatives, to develop a sense of the possibilities, an appreciation of the risks, and an urgent commitment to accelerate progress. They can show the added value of further major investments in research and development and education at a time of intense competition for federal funds. They can help the United States sustain its competitive edge in a global economy, while helping other countries to make big gains at the same time.

Curiosity about the worlds around us is an innate feature of humans and a driving force for science. To a variable extent, we are all curious about both the world of nature and the nature of human societies. All species have mechanisms for exploring their environments. Regrettably, as young children progress and ask lots of questions, too many parents and teachers suppress that curiosity by ignoring or criticizing questions they cannot or are unwilling to answer. Instead, we should feed that curiosity and stimulate ourselves in the process.



German mathematician David Hilbert

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To demonstrate the historical roots and disciplinary breadth of the concept, I have selected Grand Challenges in three categories: (i) scientific and engineering fields, with examples from mathematics, physics, environmental sciences, and genomics; (ii) multidisciplinary research and development problems, illustrated with green chemistry for sustainability, energy security, control of global infectious diseases, and international efforts to reduce extreme poverty and hunger; and (iii) science and technology to enhance public understanding and decision-making about risks to health and to economic competitiveness. Finally, I will discuss some schemes for attracting people to Grand Challenges work.

Grand Challenges in Specific Fields

Mathematics. In 1900, a 38-year-old professor from Göttingen, Germany, David Hilbert, dared to define 23 "mathematical puzzles," which kept his contemporary and future colleagues busy for a century (*5*). As he said, "Who of us would not be glad to lift the veil behind which the future lies hidden; to cast a glance at the next advances of our science and at the secrets of its development during future centuries?…A mathematical problem should be difficult in order to entice us, yet not completely inaccessible, lest it mock at our efforts. It should be to us a guide post on the mazy paths to hidden truths, and ultimately a reminder of our pleasure in the successful solution."

The problems ranged from mathematical foundations and prime numbers to geometry, algebraic number theory, and topology. Nearly all have now been solved, or partially solved; each mathematician I consulted has his or her own tally! The solutions have generated additional challenging questions. A century later, the Clay Mathematics Institute of Cambridge, MA, has offered prizes of $1 million each for solutions to seven problems; one is a carryover from the original 23 (the Riemann Hypothesis).

Physics and astronomy. Last year we celebrated the centennial of Einstein's magical year of 1905, which saw his three stunning publications on photons, Brownian motion,

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and special relativity (*6*). Only 11 years earlier, in 1894, a prominent physicist, Albert Michelson, had declared that physics was a mature field and that "[t]he future of physics lies in the 6th decimal place"—an extreme form of filling in the details! Two years later, Roentgen described ionizing radiation. Then came Einstein, Rutherford, Bohr, and the century of physics. Lists of Grand Challenges have become a part of the informal educational process in physics and related fields. As the late David Schramm noted (*7*), "The study of the very large (cosmology) and the very small (elementary particles) is coming together." In 2003, the National Research Council Board on Physics and Astronomy published a strategy for the intersection of physics and astronomy: *Connecting Quarks with the Cosmos: Eleven Science Questions for the New Century* (*7*). These questions sought to understand the creation of matter and energy at the initiation of the universe, the dark matter that pervades the cosmos, the dark energy that appears to be causing the expansion of the universe to accelerate, additional dimensions beyond four of space-time, strong-field gravitational physics, very-high-energy cosmic rays, neutrino mass, and extreme physics of black holes and magnetized neutron stars. Progress has been facilitated in the past two decades by the Hubble Space Telescope, an example of the crucial role of new technology in advancing scientific concepts and experiments.

Environmental sciences. The search for knowledge about the impact of human societies on our environment has gained in importance as rapid population growth and economic development intensify the stresses human beings place on the biosphere and ecosystems. Advances in biology, computer sciences, and techniques for sensing biological, physical, and chemical phenomena on, below, and above the Earth's surface could help us develop a more sustainable relationship with the Earth and its natural resources.

The National Science Foundation (NSF) commissioned a National Research Council report that selected eight Grand Challenges (Table 1) from 200 nominations (*8*). These were defined as "major scientific thrusts that are compelling for both intellectual and practical reasons, offer potential for major breakthroughs on the basis of recent advances in science and technology, and are feasible with current capabilities, given a serious infusion of resources." The criteria comprised probability of significant payoff, large scope, relevance to environmental issues, feasibility, timeliness, and requirement for multidisciplinary collaboration.

There is a lot of practical value in learning how natural systems work; how human activities and other influences perturb these systems; what causes these perturbations; how changes in one system affect other systems; and how knowledge may guide well-informed choices about means of transforming or restoring ecologic systems.

Genetics and genomics. The life sciences were fairly sleepy for a long time, with even dramatic observations about heredity and biochemistry making only a minor impression between 1860 and 1944. Then McCarty, MacLeod, and Avery's critical experiment showed that DNA, not proteins, carried the molecular message of inheritance. Within a decade, x-ray crystallography of DNA molecules by Rosalind Franklin and Maurice Wilkins and deductions about the role of hydrogen-bonding of antiparallel strands of DNA led James Watson and Francis Crick to propose in 1953 the double-helical structure for DNA and its functional implications. Once the triplet code was cracked, the pace accelerated remarkably, leading eventually to the Human Genome Project.

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When the Human Genome Project was proposed in 1986, it was ridiculed as impossible, absurd, mind-numbingly dull, even dangerous, according to those who feared that the 15-year, \$3 billion estimated price tag would require sacrificing funds for individual research projects to the lure of "big science" (*9*). The U.S. Department of Energy charged ahead with enthusiastic support from its advisory committee and the Congress. The project was then denounced as a scheme for unemployed bombmakers! By 1988, however, a National Academy of Sciences (NAS) panel endorsed a stepped approach, mapping genes on the chromosomes, vastly improving sequencing technologies, and sequencing the smaller genomes of other organisms. These intermediate goals permitted multiple important successes, rather than a single target of finishing the human sequence. National Institutes of Health (NIH) Director James Wyngaarden enlisted Watson to head a special Office for Genome Research, and NIH quickly took the lead. In response to a congressional query about potential risks of genetic knowledge, Watson committed to allocate 3 to 5% of the funding for research and conferences on ethical, legal, and social implications of the Human Genome Project (ELSI).

Competition between Craig Venter's shotgun sequencing approach at the company Celera Genomics and the international public consortium (by then led by Francis Collins) at NIH with many international colleagues heightened public and political interest and accelerated the pace, overcoming major technical hurdles. By now, the sequencing effort, completed 2 years ahead of schedule, has transformed biomedical research. Additional large collaborative projects have analyzed single nucleotide polymorphisms (SNPs) and linked genes in haplotypes (the HapMap) for variation within populations and discovery of biomarkers of disease. Surprises include the relatively low number of genes in humans; the high frequency of splicing of genes or messenger RNAs; the generation of many more proteins than the number of original coding genes; the regulatory role of small interfering RNA molecules; and the significance of repeated triplet sequences in disrupting protein function and causing degenerative neurological diseases.

Proteomics, systems biology, and drug development. Grand Challenges abound in the new era of biology. One of the largest is the effort to detect and measure all of the proteins in cells and in the blood. Proteins are the major effector molecules of the cell—enzymes, receptors, antibodies, and structural proteins. Proteins undergo modifications that change their functions, a huge range of concentrations, and rapid changes in response to physiological processes, diseases, and pharmacological and nutritional stimuli. Proteomics is the study of all the proteins, in analogy to genomics, the study of all the genes. Characterization of a proteome, for example, the plasma proteome (*10*), is more daunting than sequencing a genome, even though proteomics gets a head start from the gene sequence databases. One valuable outcome of such efforts will be the validation of proteins for clinical use as biomarkers of diseases.

1 Grand Challenges

- Biogeochemical cycles (nutrient elements C, O, H, N, S, P and regulators K, Ca, Mb, Fe, Zn) and their perturbations
- Biological diversity and ecosystem functioning
- Climate variability—local and regional
- Hydrologic forecasting—floods, droughts, contamination
- Environmental changes as selection agents on pathogen virulence and host susceptibility to infections
- Markets, treaties, and rules to govern resource extraction and waste disposal
- Land use and land cover dynamics
- Reinventing the use of materials/nearly complete recycling

The complementary Grand Challenge of systems biology (*11*) models the interconnected changes in the whole cell. Genes, messenger RNAs, proteins, protein complexes, and metabolites, plus the mechanisms that up-regulate or down-regulate in-dividual genes or proteins and the corresponding metabolic or signaling pathways in cell networks during development, ag-ing, disease, and recovery from disease, all must be represented. Computational tools for these efforts and for text and data mining are still in developmental stages. Modeling the pathways and networks inside cells and between cells is an exciting, open-ended domain. As part of the NIH Roadmap (see below), seven National Centers for Biomedical Computing have been funded through participation of nearly all of the NIH institutes. Results to be expected from such centers include such findings as a new class of fusion genes (TMPRSS2/ETS) that seem to be critical to development of prostate cancers (*12*).

The more we learn about the cellular complexity of tumors (*13*) and the complex interactions of receptor-mediated intracellular signaling pathways, the more we may need to redirect drug development research. Instead of seeking a "magic bullet" that targets a single receptor, pathway, or phenomenon, we may need to simultaneously attack two or more pathways, both for initial benefit and to prevent emergence of resistant cells. This situation may be analogous to multi-antibiotic regimens for microorganisms that are prone to develop resistance to therapy and may force a rethinking of clinical trials for U.S. Food and Drug Administration approvals.

Another challenge for drug development is the heterogeneity of patients and the heterogeneity among what appear to be similar tumors under the microscope. If a drug works well in only 10 to 20% of patients with lung cancers, for example, a pharmacogenomic test that identifies those patients and excludes the others would be better for the patient and those paying for the treatment. The challenge is to learn whether the same mechanism might account for some percentage of cancers of the colon, breast, pancreas, and prostate, so that the total number of cases that could be specifically and effectively treated becomes large, even though drug use is restricted to those able to respond.

Genomic and proteomic analyses are being applied also to the differentiation of embryonic stem cells into nerve, blood, and muscle cells. Understanding how stem cells develop is one of the most basic challenges in biology. Powerful new molecular methods will accelerate this work and, hopefully, its clinical applications.

Grand Challenges in Multidisciplinary R&D

Chemical R&D for sustainability and energy security. The National Research Council Committee on Grand Challenges for Sustainability in the Chemical Industry in 2005 defined sustainability as "a path forward that allows humanity to meet current environmental and human health, economic, and societal needs without compromising the progress and success of future generations" (*14*). Their eight priorities are listed in Table 2.

This agenda is part of the Grand Challenge to mitigate the expected large-scale, adverse consequences of well-documented greenhouse gas accumulation and global climate change. The seventh item offers formidable thermodynamic challenges to combine basic and applied research to "decarbonize" our energy usage and change the environmental balance of carbon dioxide (CO_2) through uses of CO_2.

As advocated in a 1991 NAS report chaired by former Washington Governor Dan Evans, many of the climate-change mitigation actions should be pursued aggressively to decrease our dependence on oil and gas, even if climate change were not a problem. More than 30 years ago, I had the privilege of serving as a key staff person, while a White House Fellow assigned to the Atomic Energy Commission, for the report "Our Nation's Energy Future" (*15*). That report was a clarion call for technological advances in five domains. The first priority, reflecting the early payoff from all energy sources, was much higher efficiency in burning fuels, by using gas turbines and other innovative combined technologies; this is the technological counterpart to reduced use of energy and fuels. Next came more extensive recovery of oil and gas from established fields; clean coal technologies; safe operation of nuclear fission reactors and acceptable disposal of nuclear wastes; and finally, the longer-term technologies for solar, wind, geothermal, and nuclear-fusion energy sources. Regrettably, this agenda has remained fresh for three decades. It is past time to dedicate sustained effort. The urgency for energy security is greater than ever, as reflected in the world map of sources of most imported oil.

Given the rapid growth in energy demand by China, India, and other developing countries and continued growth in well-developed economies, we will need a broad array of energy sources with improved technologies for every aspect of their life cycle. As a generation of nuclear reactors is coming to the end of their expected lifetimes, our country must decide how to keep nuclear energy in our mix. As noted by my successor as AAAS President, John P. Holdren, we need a balanced portfolio of energy sources (*16*). Currently, about 20% of our electricity is generated from nuclear reactors. Nuclear energy and its radioactive wastes must be managed safely and at a competitive price.

A peculiar challenge for the United States is limited access to natural gas. As demand has increased as a result of residential and industrial heating switching to gas without increases in the numbers of pipelines or terminal facilities needed to supply this country, prices have increased, with special vulnerability from the concentration of facilities offshore near New Orleans. The chemical industry, which depends on natural gas as a feedstock for major classes of chemicals, for decades was our leading generator of profitable exports, and later second only to airplanes. Now that industry has been hit with both high energy prices and high feedstock prices; companies are siting new facilities anywhere but in the United States. As noted in the *Wall Street Journal* (*17*), using precious natural gas for its lowest-value application (space heating) reflects disjointed energy policy at the national level both in the private sector and in government. Perhaps such a policy reflects inadequate input from chemists, chemical engineers, and economists.

Global infectious diseases. The Gates Foundation Grand Challenges in Global Health Initiative was launched in 2003 to harness the power of science and technology to dramatically improve health in the world's poorest countries (*18*). Its roots lie in the Great Neglected Diseases of Mankind Program of The Rockefeller Foundation from 30 years earlier. The initiative seeks scientific breakthroughs for preventing, treating, and curing diseases that annually kill millions of people, especially children, in developing countries.

The Gates Foundation looked for "a specific scientific or technological innovation that would remove a critical barrier to solving an important health problem in the developing world with a high likelihood of global impact and feasibility." Based on 1500 suggestions from more than 1000 scientists from around the world, 14 Grand Challenges were identified (Table 3). Awards for 43 projects, involving collaborators in 33 countries, were made in 2005 from a fund with nearly $500 million from the Gates Foundation, in collaboration with the Foundation for the National Institutes of Health, the Wellcome Trust, and the Canadian Institutes of Health Research. The Challenge has generated tremendous interest and high ex-pectations.

Solutions could transform health in the world's poorest countries by bringing state-of-the-art solutions to people who need them most. Some projects are focused on adapting existing health tools, like sophisticated laboratory tests, to novel technology platforms practical in settings of developing countries. Others seek to fundamentally redefine our understanding of how to prevent and treat disease, with entirely new vaccines and drugs. Many projects are applying cutting-edge technology that has never before been used to advance global health. For example, the challenge to "improve nutrition" includes work of the Donald Danforth Plant Research Center on cassava, a staple crop with excellent nutritive value, plus value as a biomass fuel source, should there be excess production. Some of these same technologies will be helpful for diseases now at epidemic levels in the United States, including hepatitis C and HIV/AIDS.

The U.N. Millennium Development Goals for 2015. The U.N. Millennium Goals aim to combine science and technology, community organization, empowered women, and donor interest after an unprecedented political commitment at the United Nations in 2000 to overcome the most extreme problems of poverty and hunger in various regions of the world (*19, 20*). The goals are people-centered, time-bound, measurable, and, hopefully, achievable with sustained political support.

The U.N. partnership for development (Table 4) would have an open trading and financial system; tariff and quota-free access for their exports; enhanced debt relief; more generous official development assistance for countries targeting poverty reduction; special efforts for landlocked and small-island developing states; decent, productive work for youth; access to affordable essential drugs; and modern technology, especially Internet and telecom.

At the AAAS R&D Policy Forum in April 2005, Lael Brainerd of The Brookings Institution presented a comprehensive plan for engagement of all categories of science and technology development in this mission. Jeffrey Sachs and many others addressed these goals at the AAAS 2006 Annual Meeting. However, recent progress has been extremely uneven; there is very good improvement in Asia and East Asia, but considerable worsening in sub-Saharan Africa.

Science & Technology to Help Address Societal Risks

Chemical hazards. A well-developed framework has been created since 1970 to identify potential hazards, characterize the risks, and propose actions to reduce risks associated with human or ecosystem exposures to chemicals. In many cases, there is uncertainty from hazard identification studies whether a particular chemical causes harm or not, especially for humans. Even when there is indisputable evidence of adverse health effects at high exposures in rodents, or in highly exposed workers, risk assessors are generally asked to estimate the risks at exposures far below levels at which such effects can be observed. Thus, it is no surprise that experts disagree, but the public and the media often find such admissions unsatisfactory. A decade ago a Presidential/Congressional Commission on Risk Assessment and Risk Management examined the many scientific and policy aspects of regulation of chemicals and proposed a comprehensive framework (see the figure on p. 1703). The special features were the insistence on early, proactive engagement of stakeholders and the guidance to put each problem into a public health context (*21, 22*). "Context" means moving beyond analysis of just one chemical in one environmental medium (air, water, soil, food) for one health effect (cancer, birth defect, etc), as required by individual statutes, to a comprehensive public health analysis. There are many approaches to the complementary challenges of risk communication and risk management, but the critical element is hearing and responding to the questions people want addressed. Affected people often have more pragmatic suggestions for how to reduce risks than do experts or regulators who assume worst-case scenarios. Experts further complicate the message when risks are stated with indefensible precision (like "2.437 × 10^{-4} upper-bound

2 Grand Challenges

Chemistry for Sustainability

- Green chemistry to reduce waste streams, by substitution and catalytic efficiencies
- Life cycle analysis to compare total environmental impact of products and processes
- Toxicology of fate and effects of all chemical inputs and outputs
- An energy mix of fuels from multiple renewable sources
- Chemical feedstocks from renewable sources, especially biomass
- Reduced energy intensity of chemical processing
- Separation, sequestration, and utilization of carbon dioxide
- Science literacy and education about sustainability throughout the public

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lifetime risk"). Accurate communication about probabilities is difficult for most people, including health care professionals who get questions from patients. Lay people regularly challenge risk assessors to examine the chemical soups that we breathe, drink, eat, and touch. It is feasible and useful to test real-world mixtures like diesel exhaust and polluted air (*21, 22*).

Diet and hormones. Diet poses one of the most confusing challenges regarding human health. I led a large cancer-prevention trial with 18,314 men and women at high risk for lung cancers due to cigarette smoking with or without occupational exposure to asbestos. We tested whether daily doses of the vitamins beta-carotene and vitamin A could reduce the incidence of lung cancers. The stunning results were that there was no benefit and, further, there was harm—increases in the rates of lung cancers and rates of overall deaths and cardiovascular deaths (*23, 24*). A complementary study of beta-carotene in 29,000 smokers in Finland showed no benefit and similar harm (*25*). These findings stimulated a new generation of laboratory research on underlying carcinogenic mechanisms.

The Women's Health Initiative was a huge trial with 160,000 women launched in the early 1990s by the NIH to study possible benefits of a reduction of total fats in the diet on heart disease, breast cancer, and colon cancer risks. No such benefits were demonstrated (*26*). Most likely, certain kinds of fats are harmful, while others are fine. The same trial found net harm for most women from the long-term use of hormone-replacement therapy (*27*). The new evidence was frustrating for patients, juicy for journalists, and irritating to doctors, who thought they had been giving well-founded guidance to their patients. The resulting call for individualized decision-making is a logical, but challenging, task in a busy doctor's office.

Microbial hazards: Influenza. At the 2005 AAAS annual meeting, U.S. Centers for Disease Control (CDC) Director Julie Gerberding warned of the risks of a lethal influenza pandemic like the 1918 flu that claimed at least 20 million—probably 50 million—lives when the world's population was one-fourth of the number today. During the past 2 years, H5N1 flu strains have been causing infections and deaths in millions of chickens and other birds. By February 2006 several dozen human deaths from avian flu had been reported, primarily in China, Vietnam, and Thailand. Birds are afflicted in Nigeria, Turkey, and several European and former Soviet Union countries. Living intimately with infected birds is the main route of infection for the relatively few humans affected so far.

Control requires timely and open cooperation among nations. Remarkable improvements in rapid PCR (polymerase chain reaction)–based testing for H5N1 viruses in birds and humans now permit real-time monitoring and much more effective surveillance, timely culling of poultry, and potential timely use of vaccines and antiviral drugs, where available, if needed. Nevertheless, experts are anxious and determined that we step up our preparations, contingencies, and political will (*28, 29*).

Are we ready? The World Health Organization, the NIH, CDC, and Department of Homeland Security in the United States, and counterpart agencies in other countries, are doing many things right. The grand challenge is to understand what is required for an avian flu strain to mutate sufficiently to be transmitted from birds to humans and from humans to humans, and to be lethal in humans. These questions are being actively investigated. The 1918 virus has been reconstituted, and new vaccine production methods that bypass the months-long, nonstorable preparation of viral antigen in chicken eggs seem promising, but will take years to test fully. Adjuvants are being tested in combination with the viral antigen(s) to try to reduce the dose of vaccine required, thereby covering many more people with the same supply. Legal, ethical, and organizational aspects are being explored, including involvement of the Council on Foreign Relations and the Royal Institution World Assembly. A pandemic in which large numbers of health care personnel would fall ill could become chaotic and catastrophic. Finally, the competition among nations and within nations for access to drugs and vaccine in shortage circumstances could become ugly. In sum, this is a really big hazard, with quite uncertain probabilities and unknown timing.


University of Chicago and Aspen Institute cosmologist David Schramm

Countering terrorism. Immediately after the September 11, 2001, terrorist attacks on America, the NAS undertook an urgent, multifaceted analysis of what science and technology, broadly engaged, could do in *Making Our Nation Safer: The Role of Science and Technology in Countering Terrorism* (*30*). The Academies did not wait for a request or a contract for a long-term study. The leadership recognized that the nation needed the scientific community to step forward and create a blueprint for a comprehensive program that would take advantage of available technologies and ongoing R&D, and also invest in new R&D and technology assessment. One element was the capability to create psychological profiles of potential terrorists. This timely report of multiple working groups was welcomed by the Bush Administration, and helped ensure high-level positions for R&D and for technology in the eventual Department of Homeland Security. Unfortunately, the recommendations have been applied incompletely since the first year.

The risk of bioterrorism became real in October 2001, when anthrax spores were mailed to congressional offices and contaminated several postal facilities. In response, our country has made a large, appropriate investment in the sciences of counterbioterrorism. One of the most sensitive issues about microorganisms with high toxicity for humans or plant crops or agriculturally important animals is whether some kinds of research should be secret and not

CREDIT: M. GILSON/COURTESY OF THE UNIV. OF CHICAGO published in the open scientific literature. Sharing methods, databases, and strains greatly facilitates collaborative research advances, at the same time raising fears.

A dramatic example is the reconstitution of the influenza virus thought to have been responsible for the 1918 pandemic. We need such knowledge and techniques to accelerate development of new influenza vaccines in a race against the spread of the virus across the world. But potent new technologies raise the dual specter of inadvertent release and of deliberate misuse by terrorist states, organizations, or even individuals. For examples, RNA interference (the discovery that won the 2006 Nobel Prize in Physiology or Medicine) that can silence specific genes; synthetic biology to produce novel proteins; nanomaterials; and informatics permit specific modifications of microorganisms and potentially of human targets unimaginable just a few years ago. The National Academies report *Globalization, Biosecurity, and the Future of the Life Sciences* (*31*) documented extensive life-sciences research around the world. It focused on these technologies.

Disaster resilience. Even before Hurricanes Katrina and Rita hit the Gulf Coast, the National Research Council Disasters Roundtable convened its 12th Workshop in 2004 and published in 2005 *Creating a Disaster-Resilient America* (*32*). They defined Grand Challenges as "fundamental problems in S&T whose solution can be advanced by coordinated and sustained investments in research, education, communication, and application of knowledge and technology." Such investments would aim to reduce the loss of life and property from natural, technological, and human-induced disasters. The emphasis is predictive capability and preparedness to minimize effects of disasters. Examples are building codes in earthquake-prone regions in California, which greatly reduced casualties in the San Francisco Bay area in 1989, compared with a similar-magnitude earthquake in Georgia of the former Soviet Union that claimed about 100 times as many lives that same year; the trans-Alaska oil pipeline's successful design that withstood a magnitude 7.9 quake in the Denali Fault in November 2002; and the buildings in Washington State that sustained only very limited damage after the magnitude 6.8 Nisqually earthquake in February 2001.

In general, we have been foolish to permit, and even to financially assist, return of displaced populations to floodplains and earthquake-prone regions. We clearly lack comprehensive planning and the political will to prevent recurrences of these disasters. Maybe we don't marshal the scientific and engineering evidence at timely points in the process. Along the Mississippi River, one might inquire how well the building codes and emergency preparedness plans protect against major consequences from long-awaited earthquakes in this region. The Mid America Earthquake Center at the University of Illinois–Urbana/Champagne has an active program in this area. The underlying principle, of course, is Benjamin Franklin's expression, "An ounce of prevention is worth a pound of cure." How true that might have been in New Orleans!

Katrina and the aftermath. As emphasized in the Disaster Resilience report and demonstrated tragically soon afterward in New Orleans, disaster mitigation requires integrated, long-term processes that combine technical with organizational, social, and economic dimensions to deliver the four R's: robustness, redundancy, rapidity, and resourcefulness. The hurricane-associated floods and their aftermath revealed the consequences of neglected engineering upgrades and lack of preparedness and coordination at all levels of government. They also laid bare deep-seated social, economic, and political disparities along racial lines. We repeat history and do not learn its lessons. The Great Flood of 1927 that inundated parts of many states along the Mississippi River might have prepared us to prevent the New Orleans debacle.

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>
> *–David Schramm*

Comprehensive scientific and engineering guidance and strategic national investment should restore the protective wetlands south of New Orleans; unfortunately, these wetlands had been permitted to recede over many years, which reduced the area's capacity to withstand flood surges. Meanwhile, the Mecca for Music and the Arts mega-project proposed by New Orleans native Wynton Marsalis and the Bring Back New Orleans Cultural Committee may help rekindle the spirit of the city and its special place in the cultural heritage of our country.

Risks to the economy. Senators Lamar Alexander and Jeff Bingaman during 2005 tapped the scientific community for urgent recommendations on how to enhance our economic competitiveness. The resulting report from the National Academies, *Rising Above The Gathering Storm* (*1*), recommends that billions of dollars be invested for better teaching of math and science and for sustained growth in federal support of R&D, including an Advanced Research Projects Agency–Energy program. It also calls for easing access of foreign scientists to this country as visitors, students, and permanent residents, and continuation and expansion of the tax credit for R&D by corporations. Together with the Council on Competitiveness, this report galvanized bipartisan proposals in the Congress. The AAAS Board wrote to President Bush urging action. Thus, it was gratifying to hear the president support math and science teaching, increased budgets for physical sciences, and renewal of the expiring R&D tax credit (*33*). The education component would begin to address the "quiet crisis" Shirley Ann Jackson discussed in her 2005 AAAS presidential address (*34*): projected extreme shortages of well-prepared women and men to pursue careers in science and engineering, just as the knowledge-based world economy demands high skills.

Despite the catchy title of Tom Friedman's book, *The World Is Flat*, we are a long way from a level playing field globally or within any country. Nevertheless, the effects of globalization, instant communication, and outsourcing of tasks have created grave uncertainty about the competitiveness of our companies and our workforce for the long term. Freeman Dyson told the University of Michigan graduates in 2004 that—just like France, Spain, and Great Britain—America's time as the dominant country in the world will be limited. My response is that a cooperative future should be our goal, rather than a future dominated by one new economic or military superpower.

Anti-science attacks. Ever since Darwin's original writings, the intersection of various religious beliefs about the origins of the world and of humans with observations of natural selection for reproductive advantage has stimulated speculation, debate, and periods of intense conflict. The literature on this subject is rich and fascinating. For examples, Ursula Goodenough has written of the *Sacred Depths of Nature* and "the epic of evolution" (*35*), and Randolph Nesse and George Williams have addressed *Why We Get Sick* from the viewpoint of evolutionary biology (*36*, *37*).

Some of our problems arise from misunderstandings about specific words. In science, the term "theory" carries connotations of elegance and a strong evidentiary basis. The "theory" of evolution is ranked together with the theory of gravitation. To most laypersons, however, "theory" is closer to "speculation." Thus, we should recognize by now that it is a diversionary battle to insist on explaining the meaning of "theory" when we should be explaining the meaning of evolution and of natural selection. Darwin used the phrase "descent with modification," but the sound-bite of "survival of the fittest" has long conjured up images unrelated to reproductive fitness. Finally, when applied to evolution, the terms "random" and "chance" can irritate those who celebrate the remarkable designs in nature, however they arose. The results of natural selection are not random; it is mutations that may arise in random fashion, although not all mutations are equally likely at the molecular level.

The good news is that we are successfully turning the attacks on the teaching of evolution to our advantage, helping many more people, including scientists, to learn more about evolution and, more broadly, learning more about scientific ways of thinking. In 1984 and 1999, the NAS issued reports on *Science and Creationism* and in 1998 on *Teaching about Evolution and the Nature of Science*. An update will be issued in 2007. Evolution is the most important single concept in biology and is essential to understanding geology and astronomy.

Evolution is an ongoing process, highlighted as the 2005 Breakthrough of the Year by *Science* (*38*) in recognition of new results that show natural selection in action. In our own academic community of Ann Arbor and the adjacent blue-collar city of Ypsilanti, Michigan, this year's combined Community Reads book selection is *The Beak of the Finch* by Jonathan Weiner (*39*). The book has engaged thousands of local people in seminars and courses on the theme of Revolutions in Science: the people, theories, explanations and discoveries that challenged our thinking and changed the world. Weiner describes the work of Rosemary and Peter Grant, modern evolutionists painstakingly studying 13 species of Darwin's finches for 33 years on the island of Daphne Major in the Galápagos. They are doing what Darwin could not do—going back to the Galápagos year after year, seeing there what Darwin did not imagine could be seen at all in brief periods of time.

Darwin marshaled an enormous amount of evidence that evolution has occurred, but he never saw it happen. He was in the Galápagos (for just 5 weeks) only once during his 5-year voyage on the H.M.S. *Beagle*. In *On the Origin of Species*, he described natural selection as "silently and insensibly working, whenever and wherever opportunity offers…We see nothing of these slow changes in progress…we see only that the forms of life are now different from what they formerly were" (*40*). Evolutionists are now observing evolution of species in real time on isolated island laboratories around the globe.

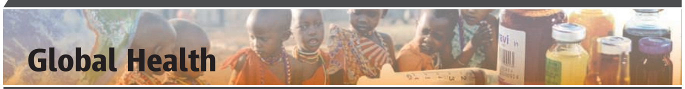
The power of direct observation and the testing of hypotheses drive us to challenge unexpected findings until they cannot be explained away. Such logical thinking is the opposite of learning a catechism. The pressure on teachers to ignore evolution or lump it with a particular religious view of "creation science" or its reincarcation "intelligent design" is harmful. It first neglects the beliefs and views of many other religions and cultures and then usurps the already-limited time to interest children and their families in the math and science essential to their being prepared for good jobs and effective citizenry in the knowledge-based, technological economy of this new century. The AAAS Board has taken a strong stand in denouncing anti-science legislation and mixing of religion and science in the science classroom.

We now have a comprehensive verdict on the matter of the teaching of evolution in the schools from Judge John E. Jones III of the U.S. District Court in Pennsylvania in the case of *Kitzmiller et al. v. Dover School District et al.* (*41*). He made clear that intelligent design is a direct descendant of creation science and should have no standing in a science classroom. I strongly share that view. I would add that many scientists are themselves religious and compartmentalize their professional activities and their religious beliefs. As Daniel Boorstin quoted Goethe in *The Seekers—The Story of Man's Continuing Quest to Understand His World*, "When we do science, we are pantheists; when we do poetry, we are polytheists; when we moralize, we are monotheists." The AAAS has been very active in these matters, including a highly successful Forum with and for high school science teachers, *Evolution on the Front Line*, and the AAAS Dialogue on Science, Ethics, and Religion (DoSER).

Mobilizing for Grand Challenges

All Americans are familiar with the highest-visibility Grand Challenges of recent decades.

3 Grand Challenges



Global Health

Improve childhood vaccines
- Create effective single-dose vaccines useful soon after birth
- Prepare vaccines that do not require refrigeration
- Develop needle-free delivery systems

Create new vaccines
- Devise reliable tests for live-attenuated vaccines in model systems
- Solve how to design antigens for effective protective immunity
- Learn which immunological responses are protective

Control insects that transmit disease agents
- Develop a genetic strategy to deplete or incapacitate a disease-transmitting insect population
- Develop an analogous chemical strategy

Improve nutrition
- Create a full range of optimal, bioavailable nutrients in a single staple plant

Improve drug treatment of infectious diseases
- Discover drugs and delivery systems that minimize emergence of drug-resistant microorganisms

Cure latent and chronic infection
- Create therapies to cure latent infections
- Create immunological methods that can cure latent infection

Measure health status accurately and economically in developing nations
- Develop technologies that permit quantitative assessment of population health
- Develop technologies that allow assessment of individuals for multiple conditions or pathogens at point of care

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They had well-defined, readily understood, time-limited goals and support from the highest levels politically: Franklin Roosevelt's assignment to develop and test a nuclear bomb in the Manhattan Project before the Nazis did so; John F. Kennedy's call in 1961 "to put a man on the moon and bring him safely home by the end of the decade"; and the sequencing of the Human Genome DNA within 15 years.

Less visible Grand Challenges have included directed research under the Defense Advanced Research Project Agency (DARPA), founded after Sputnik in 1958, which has been judged so often successful that proposals periodically emerge to try similar high-risk, high-payoff, highly directed approaches in energy R&D and in biomedical research; the construction of major physics and astronomy facilities to advance particle physics and studies of the universe; and the War on Cancer, which set out in 1971 to enhance survival and prevent new cancers, an elusive target, despite quite remarkable growth in knowledge about cancer biology and some dramatically effective therapies.

All of these initiatives had clear R&D priorities backed up by substantial, sustained investments by the federal government and by universities, companies, and states committed to shared goals.

NIH Roadmap. In the biomedical domain, the NIH and the biomedical research community supported by NIH have met high standards for excellence and progress in generating knowledge and in bringing physical sciences, engineering, and informatics together with the new biology. The aim now is to achieve a more predictive, personalized, and preventive system of health care, especially for complex common diseases. Both a NAS committee (*42*) and the NIH Director, Elias Zerhouni, concluded that NIH as a whole could do more than NIH as a loose federation of 27 institutes and centers, mostly focused on different sets of diseases. Thus, the NIH has launched an institutional experiment, starting with just 0.5% of the $28-billion NIH budget in 2004, called the NIH Roadmap for Medical Research (*43*). The Roadmap recognizes revolutionary changes in the underlying science and technology, risk factors and treatments that in-fluence multiple different common diseases that are investigated by different institutes of the NIH, and barriers to translating results in the laboratory into studies and results in patients. The Roadmap is organized to exploit new pathways to discovery (genomics, proteomics, computational biology), to re-engineer the clinical research enterprise (integrating training, clinical research centers, clinical research, and innovations in clinical care), and to build highly interdisciplinary research teams to achieve scale and complexity in research, while preserving the investigator-initiated foundation of biomedical and behavioral research.

Meanwhile, the not-for-profit Howard Hughes Medical Institute, which directly supports 320 of the world's most outstanding scientists, has adopted a complementary strategy for "big science" to meet the Grand Challenge of exploiting multidisciplinary approaches to disease processes. Their 700-acre Janelia Farms Research Center in Virginia features advanced instrumentation, powerful computational capability, and a very active visiting scientists program. Their models are the famously productive Medical Research Centers of Great Britain and the Bell Labs in their heydays.

Posing challenging questions. To celebrate the 125th anniversary year of *Science*, the editors created a 1 July 2005 special issue with 125 questions about "What Don't We Know?" (*4*). These questions cover a great diversity of challenges in various fields. Like Hilbert's puzzles, these questions should stimulate scientists in numerous fields to step up, take some risks, and reach beyond the horizon.

Much broader questions arise from the policy and social ends of the spectrum. Why do we accept combustion methods that waste the majority of the energy generated? Why do we tolerate excessive use of depletable fossil fuels, especially in light of global warming? Why are we paralyzed about nuclear energy over questions of safer operations and management of highly radioactive wastes?

Why do we tolerate the poor performance of our educational system? We know that there are excellent school systems and individual schools, teachers, principals, and students that perform at outstanding levels. The AAAS Project 2061 on Science Literacy for All Americans has provided, in collaborations with science teacher organizations, standard-setting groups, and selected school districts, spectacular materials for schools to utilize. The Congress enacted the No Child Left Behind Act. Yet we seem to be failing to achieve higher performance, let alone excellence, on any significant scale in this diverse country.

What can we do to bring fresh ideas to our persistent failure to emphasize prevention and health promotion and to achieve universal coverage in our health care system (*44*)? Can our research yield credible designs to reduce the burden of employer-based health insurance costs, especially for companies competing globally?

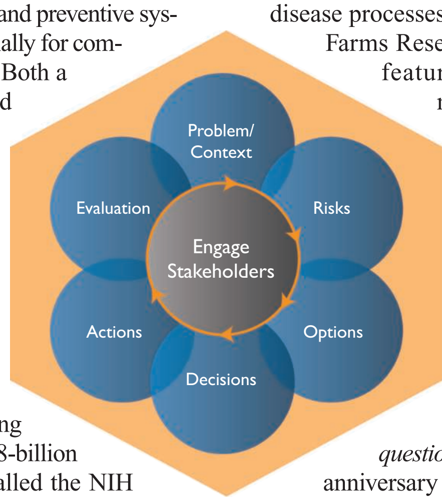
Internationally, we face the consequences of lack of curiosity and ignorance about people of different cultures, different religions, and different world views. How can we change this situation in settings ranging from our K-12 (kindergarten through 12th grade) and higher-education communities to our national intelligence apparatus?

Prizes. In addition to the well-known Nobel Prize, the Lasker Awards, the Wolf

4 Grand Challenges

UN Development Goals for 2015

- Eradicate extreme poverty and hunger
- Achieve universal primary education for boys and girls
- Promote gender equality and empower women
- Reduce child mortality rate before age 5 by two-thirds
- Improve maternal health and reduce mortality ratio by 75%
- Combat HIV/AIDS, malaria, and other diseases
- Ensure sustainability, increasing access to safe drinking water
- Develop a global partnership for development



Commission's Six-Stage Framework for Risk Management. Note the central role of stakeholders in setting the context and guiding the technical assessments. The arrow is removed from stage six so as not to encourage "paralysis by analysis." [Adapted from (*21*)]

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Prize, the General Motors Cancer Prizes, and our own awards at the AAAS annual meeting recognize research excellence. A memorable award was the Waterman Award, for work by a scientist before age 35, to Richard Muller of the Lawrence Berkeley Laboratory in 1978. He had completed three groundbreaking projects in the separate fields of astrophysics, optics, and radio-dating. The award cited the fact that his projects were so far beyond conventional wisdom and contemporary knowledge that his peer-reviewed research grant proposals had been rejected by several agencies, including NSF, which made the award! Muller had been supported on institutional funds at the Lawrence Berkeley National Laboratory by the director, Walter Alvarez, who recognized enormous potential and compelling ideas in a young scientist.

Special prizes can bring public attention to a challenge. A classic example is the enormous prize offered by the British Parliament in 1712 for a practical measure of longitude (*45*). The Ansari Project X offered $10 million to the first team to achieve space flight with private funds; the winner was a group assembled by Paul Allen, who probably responded to the competition more than the money! A DARPA challenge required robots to be designed to traverse difficult terrain; none succeeded in the first year, apparently due to misperceiving creosote plants as boulders, but four did so in the second round. The seven Clay Mathematics Prizes are awaiting solutions. Remarkably, the first recognized to be solved, the Poincaré Conjecture, by Grigori Perelman of St. Petersburg, led to complications from the rules requiring peer-reviewed publication and then rejection of the funds by the reclusive mathematician (*46*). The Methusaleh Foundation has posted a $3 million reward for a dramatic increase in longevity in an experimental animal model. An Eli Lilly Company spinoff, Innocentive Inc., uses the Internet to pose problems for scientists or engineers anywhere on the planet to solve, with specific payoffs from $5000 to $100,000 for those first to submit a documented solution or product that meets the explicit criteria of their client. The Grainger Challenge Prize for Sustainability, administered by the National Academy of Engineering, offers $1 million, $200,000, and $100,000 prizes for the best low-cost household devices to make arsenic-contaminated drinking water safe in developing countries (*47*).

Closing Remarks

In tight budget times, the peer-review process for research funding becomes more cautious than ever, requiring more so-called preliminary data until the project is nearly done before it is proposed. This situation disadvantages young people seeking their first grants and established scientists with fresh ideas. A public process of eliciting and publicizing Grand Challenges in various fields may be an antidote to this overly conservative trend (*48*). We should dare to study hard problems, individually when feasible, and in teams when the challenge demands multidisciplinary effort.

As an organization with many effective, but largely unconnected, programs and activities, I think the AAAS could play a larger role in this process, partly by taking advantage of the activities and outputs of our own programs, committees, sections, and affiliates. The NAS have demonstrated that they can step up on urgent matters, with the Counter-Terrorism report in 2002 and *Rising Above The Gathering Storm* in 2005. In their own fields, the scientific and engineering societies could do the same and join to address broader challenges.

I am certain the public and the media will be interested. And I am hopeful that young people will understand better what we do and what we hope to achieve in science and technology as they consider their own career prospects. Finally, I hope we can entice our political leaders, regionally and nationally, to call upon the scientific community to step up on these and other Grand Challenges.

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