

13 Science and Technology Policies Concerning the Life Sciences

Gilbert S. Omenn

Introduction

The life sciences are front and center in the public consciousness. And the public has high expectations of benefit. Public attitudes and public advocacy have played significant roles in the congressional and presidential commitments to invest in the life sciences and specifically in the bipartisan commitment to double the budget of the National Institutes of Health (NIH) over a five-year period.

The past several years have been a spectacular time for the life sciences and especially for genetics and genomics. The cover stories of *Nature*¹ and of *Science*² in February 2001 brought us the nearly completed sequences of the human genome as well as many interpretive articles about the findings. The mutually reinforcing work of the public sector and the private sector surely accelerated the pace of this work. The result is that we have reached what has been called “the end of the beginning” in this new era of genomics and its applications. According to Francis Collins, on leave from the University of Michigan during the past 10 years to direct the National Human Genome Research Institute, “Mapping the human genetic terrain may rank with the great expeditions of Lewis and Clark, Edmund Hillary, and the Apollo Program.”³

The big surprise of the human genome sequence, that there are many fewer genes than previously expected, properly attracted a lot

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of attention. This finding immediately put the focus on the products coded for by the genes, namely proteins, and the emerging field of proteomics.⁴

These developments have demonstrated the importance of enabling technologies that make it feasible to ask compelling scientific questions and to identify a plethora of new molecular targets for drug development. The decision to include in the Human Genome Project many other species along with humans (a hot issue in the late 1980s) has been amply rewarded with many insights from comparative genomic analysis. And the requirements for computational advances have attracted engineers, mathematicians, cyberneticists, and other essential new colleagues to this clearly multidisciplinary effort to understand living things.

These accomplishments coincide with a remarkable step-up in the funding for the National Institutes of Health, the major health research agency of the federal government. We survived a period of depressing projections about the likelihood of minimal annual increases in the NIH budget, possibly less than consumer inflation, as a result of the huge federal budget deficits in the early and mid-1990s. A concerted, broad appeal generated the bipartisan commitment to double the NIH budget over a five-year period. That commitment required compounding increases of 15 percent per year. The current fiscal year, FY 2002, is year four of that period. The upcoming appropriation for FY 2003 is widely expected to complete this doubling from \$13 billion to \$27 billion per year for NIH.

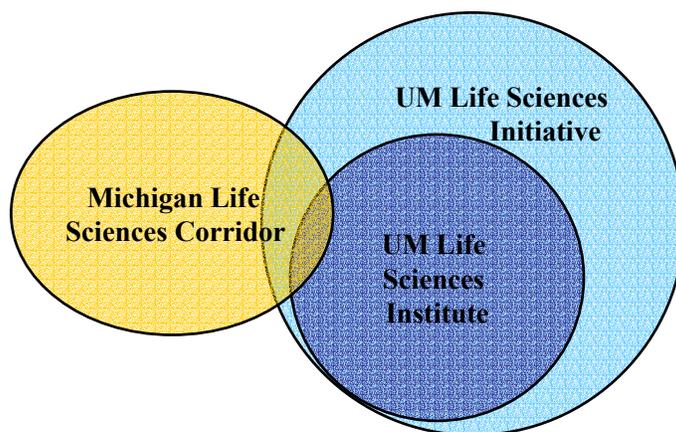
In the last two years, this message supporting research funding has been expanded. We have heard from the Mary Woodard Lasker Charitable Trust's Funding First, Research!America, and a coalition of focused advocacy groups. The new message is that across-the-board funding of science and technology is essential to gain the full benefit of the new biology. Congress acted on this message last year, leading to much-enhanced appropriations for the National Science Foundation (NSF) and the Centers for Disease Control and Prevention (CDC) compared with previous years.

Investments at the State Level

The federal investment and the high expectations of payoff in medical, public health, agricultural, and environmental applications have stimulated much-increased investment in the life sciences at the state level, in the private sector, and at individual universities.

Figure 1 shows the multi-pronged initiative in Michigan, beginning with the construction and endowment of a Life Sciences Institute complex at the University of Michigan.

Figure 1
Multi-pronged Life Science Initiatives in Michigan

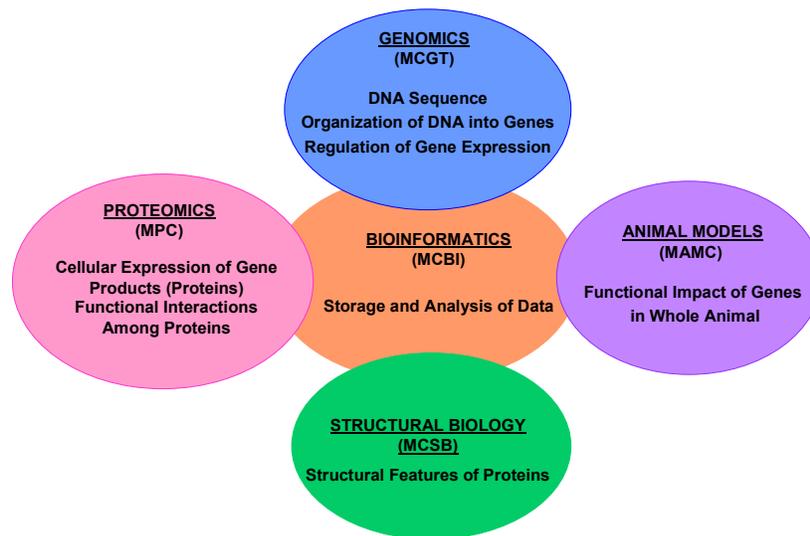


The entire university has been engaged through the Life Sciences Values and Society Program as well as new research buildings in the medical school and in the college of engineering for biomedical engineering. (We even have a Life Sciences Orchestra!) In addition, the state has created the Life Sciences Corridor, embracing Wayne State

University in Detroit, the University of Michigan in Ann Arbor, Michigan State University in East Lansing, and the Van Andel Research Institute in Grand Rapids, together with Pfizer in Ann Arbor, Pharmacia in Kalamazoo, Dow Chemical in Midland, and a growing array of small companies throughout the region. Funding for this Corridor is \$50 million per year. It comes from a 15 percent slice of the Tobacco Settlement Fund. This appropriation is planned for 20 years. We hope to develop the state as one of the nation's premier life sciences research and commercial centers, thereby diversifying the state economy.

In addition to project grants to academics, companies, and especially university/industry collaborations, the Corridor has invested substantially in these early years in five core technology consortia located at lead institutions with a hub-and-spokes structure. Figure 2 shows these areas. The institutions' mission is to serve all comers in the Corridor in these five areas.

Figure 2
Five Core Technologies



What is happening in Michigan and at the University of Michigan illustrates what is happening at leading institutions and aspiring institutions throughout the country. Michael McGeary and Philip M. Smith have reported case studies for California, New Jersey, North Carolina, and Ohio.⁵

Competition among research universities is just as fierce as that among pharmaceutical and biotechnology companies. The University of California (UC), San Francisco is building a huge new campus at Mission Bay; Yale University, Princeton University, the University of Pennsylvania, the University of California, Los Angeles, and many other universities are building major new research buildings. The University of Cincinnati and Indiana University have received large gifts from pharmaceutical companies, and Stanford University from an Internet pioneer. The University of California, Berkeley, the California Institute of Technology, Harvard University, and others have announced bold interdisciplinary investments. And in Seattle a new not-for-profit Institute for Systems Biology has been established.

The research investments are matched by student interest, as numbers of majors in biology and related fields have catapulted upward at universities and colleges. Competition for top faculty and promising students is intense, and the job market in industry and academe is flourishing.

Five Questions

1. How Will the Newly Salient Challenges of Bioterrorism and Globalism Alter the Life Sciences Research and Development (R&D) Agenda?

We now live with an increased sense of vulnerability in every part of our research community and our society. The bioterrorism scare around the multiple infections and five deaths from expertly prepared spores of anthrax has mobilized quite a lot of productive interdisciplinary discussion. The state of our vaccine supplies, the efficacy and safety of older vaccines, and the level of documentation for handling and storing biological, chemical, and radioactive hazards are all suspect. We also have a greater sense of urgency. Part of this urgency is

directed at mobilizing R&D for practical applications in relevant domains. One of these domains is vaccine development, which has been a stepchild of life sciences research for a long time. The liability issues have never been adequately settled, though Congress made a good try more than a decade ago. The budgets for FY 2003 and supplemental requests for FY 2002 show substantial investments at NIH, the Department of Defense, and other agencies around vaccine development for protecting civilian and military populations.

Third, we have a renewed interest in infectious disease agents, infectious disease epidemiology, and surveillance of potentially exposed populations. This interest has a special benefit because it requires us to reach across public health, agriculture, ecology, and other fields in ways that we often do not when we focus on silo-style funding or responsibilities of individual state and federal agencies. We need comprehensive public health and agricultural crop and livestock plans for the prevention, detection, mitigation, and surveillance of bioterrorist actions. We need these plans not only for the publicly proclaimed priority agents (starting with smallpox and anthrax), but also for less well-known microbes that attack crops, ecosystems, or animals.

The vulnerability and urgency are likely to fuel productive synergies and joint activity. The R&D community must accept broader connections and reach out to the intelligence world, emergency preparedness and first response forces, law enforcement, and corporate sectors encompassing pharmaceuticals, telecommunications, and information technology, for starters.

Most important, perhaps, we must be increasingly aware of the complex world in which we live. It is a world of diverse cultures and religions, with an increasing gap between the haves and have-nots. We see the growing influence of disenfranchised populations in less developed countries, and the intensifying support of their advocates. These forces threaten the growing world economy. In addition, we hear well-articulated demands that modern medicines and vaccines be made affordable to people with no health care delivery system. (One might note that we could start with our own Medicare program.)

Bioterrorism-related investments are appearing in the federal budget. Of the \$3.7-billion increase proposed for FY 2003 for NIH, \$1.4 billion is for increases in bioterrorism-related R&D and construction at the National Institute of Allergy and Infectious Diseases (NIAID).

In the past two years (including the FY 2002 supplement) the bioterrorism budget has increased from \$50 million to \$1.7 billion. Not everything goes up, of course. For example, funds for extramural research construction (outside the NIH campus in Bethesda, Maryland) would be reduced in the President's budget, as the construction component is focused on intramural NIH and bioterrorism-related facilities. (I think Congress will restore the extramural construction funds.)

At the CDC, there is a modest sleight of hand: R&D would be reduced by nine percent, though some programs are increased. The net is a reduction of \$53 million, reflecting primarily a shift of current bioterrorism R&D activities to the NIH NIAID budget, helping to complete the commitment to doubling the NIH budget.

More broadly, Department of Health and Human Services (DHHS) budgets that are important for the health care research I mention below have been tagged pretty hard. R&D at the Centers for Medicare and Medicaid Services plummets from \$117 million to \$28 million in FY 2003. The Agency for Healthcare Research and Quality, responsible for high-priority work on patient safety and related health care quality issues, must depend entirely on a portion of the evaluation funds of other DHHS agencies, with the total falling from \$300 million to \$251 million (-16 percent).

At the scientific level, our response to the threat of bioterrorism brings the potential of tremendous applications of genomics and proteomics. Many of our most common and some of our most virulent and lethal agents have special survival mechanisms and special virulence mechanisms that distinguish the pathogenic strains of the bacterium from the less pathogenic or nonpathogenic strains that survive only in special parasitic relationships with their host organisms.^{6,7}

This microbiology research is pointing to new targets for treatments and vaccines. For example, *Mycobacterium tuberculosis* has a special glyoxylate pathway that favors its survival in the human lung. The leprosy organism, *Mycobacterium leprae*, and other obligate para-

sites have smaller genomes seemingly adapted to existence dependent on the host for various functions. The pathogenic *Escherichia coli* O157:H7 has 1,387 genes not found in the nonpathogenic *E. coli* K12 commonly living in our intestines. *Vibrio*, *Helicobacter*, and *Yersinia* strains have been shown to have “pathogenicity islands” in the genome sequence. These islands specify proteins that are adhesins, invasins, toxins, and secretory systems—all key proteins for causing damage during infections. Finally, malaria-causing *Plasmodium falciparum* and certain fungi have metal-dependent RNA triphosphatases with no counterpart in humans (or other higher organisms), making these enzymes good targets for new drugs.

In addition to terrorism with biological agents, we are worried about chemical warfare and hazardous chemicals in general. An active area of new work called “toxicogenomics” seeks molecular signatures for the exposures to and effects from carcinogenic, mutagenic, teratogenic, and other toxic chemicals. NIH’s National Institute of Environmental Health Sciences has developed a chip with over 2,000 genes of high relevance to specific pathways important in such toxicities.

2. How Else Do We Need to Broaden the Life Sciences/Health R&D Agenda?

Amidst the extremely productive world of NIH and the larger health sciences and life sciences community in this country, we still have underinvested areas that are very important to the social compact with the American people for payoff from their large investment in basic and applied research. Taxpayers, patients, and health care professionals expect us to generate effective and safe clinical and public health advances from all the spectacular basic biomedical work.

However, translating basic advances into clinical applications remains difficult. Eliciting support from health care insurers and managed care organizations for the costs of clinical studies and clinical trials has been grim work. We desperately need research-based evidence in medicine and public health of what works and what does not, and what is safe when used as directed and what’s not. Our

knowledge base underlying health care spending of more than a trillion dollars per year is generally inadequate, too short-term, or not generalizable to all the diverse populations of our country, let alone the world. And prevention still gets short shrift, compared with diagnosis and treatment.

We need to address this issue in four areas of research: clinical, multidisciplinary, prevention, and health services.

Clinical Research

For at least 25 years NIH Directors have lamented the decline in the numbers of physician-scientists and in the proportion of research based on studies of patients and populations, as contrasted with studies of animals or isolated molecules. Quite a few initiatives have been mounted, including special training grants (K30, K12), career development awards (K23/24), and research grant mechanisms.

In many ways, studies with human volunteer participants or patients are much more complicated than basic laboratory studies. This is due in part to the many physiological and pathological variables and in part to an increasingly stringent process of protection for the participants under institutional review boards (IRBs). The IRB process of review and approval of proposed studies and of well-documented informed consent from participants is essential, yet challenging for individual researchers and costly for the institutions. For example, at the University of Michigan, we have expanded in recent years from one to four large IRBs. External funding for the additional staff and infrastructure is quite inadequate. Privacy requirements mandated by the Health Insurance Portability and Accountability Act of 1996 put additional burdens on clinical research.

Gene therapy trials were going very slowly even before the near-moratorium following the death in 1999 of 18-year-old Jesse Gelsinger at the University of Pennsylvania. But now we have high expectations that embryonic stem cell research in animals and humans has the potential to yield effective treatments for such important medical problems as spinal cord injury, diabetes mellitus, and Parkinson's disease. But religious and political objections to using human embryonic cells have greatly complicated both publicly and privately funded projects.

Despite the rapidly rising bill for pharmaceuticals and the seeming avalanche of new drugs from pharmaceutical and biotechnology companies, the yield of new drug candidates and new approved drugs seems pretty low at some of the great pharmaceutical companies. David F. Horrobin of Laxdale Ltd, among others, has described gloomy projections and limited benefit so far from genomics in drug development.⁸ While the hottest new cancer drugs (Herceptin for certain breast cancers and Gleevec for an uncommon form of leukemia) are described as overnight “hits” from the new biology, these agents were actually developed several years ago and were considered failures in trials for much more common conditions.⁹

The overriding challenge for clinical research is to go from reductionistic work on the roles of specific genes to work on the functions of those genes and their products in the whole body of an animal and then of patients. Integrative studies assessing all functions, favorable and adverse, are essential.

The euphoria about individualized or personalized medical care, based on pharmacogenomics, will run into practical problems. These problems are due to marked variation not just in individual genetic background but also, and very importantly, in diet, metabolism, personal behaviors (such as smoking, alcohol use, physical activity, and sexual activity), environmental chemical and microbial exposures, medical conditions, and the use of pharmaceuticals and nutraceuticals. Such variation will make many proposed genetic tests insufficiently specific and sensitive to be useful, unless the information about genetic variation can be coupled with information about these other, nongenetic variables.

Multidisciplinary Research

True multidisciplinary/interdisciplinary project teams and large scale are essential for certain kinds of research goals. The Human Genome Project is a notable example. The development of sequencing and synthesizing technologies and machines, automation with robots, and large-scale computation made all the difference in the timetable and even the feasibility on any timetable.

Now the Howard Hughes Medical Institute, which has been the purest of investors in individual researchers, has broadened its agenda by purchasing a farm in Leesburg, Virginia, where they will build facilities for large-scale high-end automated analyses, macromolecular structure/function studies, and the application of advanced computational capabilities. They are not alone. The National Laboratories of the Department of Energy—Pacific Northwest, Lawrence Livermore, Lawrence Berkeley, Argonne, Brookhaven, Oak Ridge, and Los Alamos—are bringing together physical scientists, mathematicians, and engineers with life scientists to address problems in life sciences. Similarly, at universities, cross-college collaborations are in vogue. Most notably, the Governor and the vast University of California system have announced four science and technology clusters, including the California Institute for Bioengineering, Biotechnology, and Quantitative Biomedical Research at UC San Francisco, UC Berkeley, and UC Santa Cruz.

These developments challenge the capabilities of the academic community. Excellent cross-disciplinary training is not easy. Evaluations of faculty for promotions still tend to penalize team efforts, compared with research advances by individual investigators. University and sometimes government laboratory promotion evaluations continue to favor single-author or first-author papers on work that can be conceived, planned, funded, conducted, and analyzed in relatively short time periods. We generally advise young faculty to be sure to make their individual mark and earn their tenure promotion before getting caught up in large team projects. We need to find ways of stimulating and rewarding highly effective team efforts, thereby modeling what we are teaching.

Prevention Research

Promoting better health and preventing diseases and injuries requires a population perspective and research strategy. We have a growing and aging population. It is inevitable that health care will cost a lot more in future decades. One way to moderate that increase and get more value from our research expenditures is to become

more effective in our treatments and especially in preventing or delaying serious illnesses and injuries. In general, we focus on diagnosis and treatment and only minimally on prevention in all aspects of the life sciences and health programs.

Linking information about genetic variation with information about nongenetic variables of behavior, diet, metabolism, environmental exposures, and medical interventions will be essential for credible guidance for disease prevention and health promotion. We must guard against regulations and laws that treat genetic data differently from other medical data, thereby losing the links needed to interpret the significance of genetic variation in both the clinical and the public health setting.

Health Services Research

Recent reports from the Institute of Medicine have documented medical errors causing preventable deaths¹⁰ and the chasm between the present overall quality of care and what we should provide.¹¹ We need to greatly improve the quality of health care. We need research-based evidence of what works and what does not (for patients and for the broader population) and what is safe and what is not. These aims apply not just to individual treatments or technologies, but to patterns of care across settings for people with chronic illnesses and to systems of organization for health care and public health services.

We must aspire to health care characterized by these six attributes: safe, effective, patient-centered, timely, efficient, and equitable. But, as noted above, the President's budget for FY 2003 drastically reduces funding for the federal agencies supporting these kinds of studies.

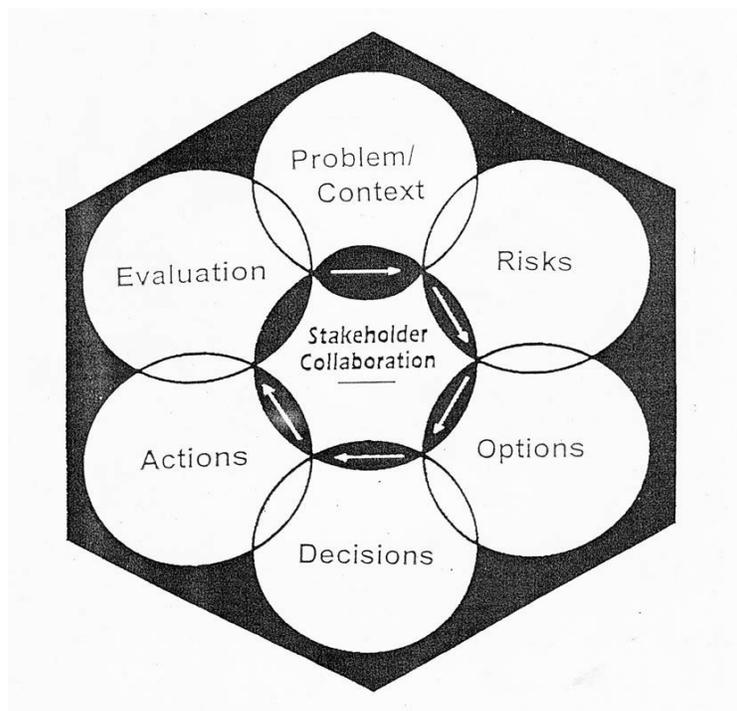
3. How Do We Engage the General Public in Understanding What We Are Doing Scientifically and Medically and in Helping to Direct National Priorities?

Those of us in the research community have much to gain from a more scientifically literate and proactive general public. We want

people to understand what we do and what we seek to accomplish scientifically and medically. We must be willing to listen, too, for communication is a two-way process.

I chaired the Presidential/Congressional Commission on Risk Assessment and Risk Management during 1994–1997. This commission was mandated by the Clean Air Act and given oversight for the full array of federal environmental, health, and safety regulatory agencies. As shown in Figure 3, we put the “stakeholders” in the center of our Framework for Environmental Health Risk Management.

Figure 3
Commission’s Six-Stage Framework for Risk Management



The critical role of stakeholders in setting the context and guiding technical assessments is indicated by the larger ellipse in stage one. The arrow is removed from stage six so as not to encourage “paralysis by analysis.”

We seek to get interested and affected (or potentially affected) people engaged as early as possible in the process, before the “experts” decide what questions need to be addressed and what questions will be neglected. We held bimonthly hearings throughout the country over two years. Our experience was so compelling that we published a short volume for lay persons that gave examples of real situations in which public engagement had been active (sometimes perceived positively and sometimes not). This volume illustrated how our Framework translated into risk communication at the community level.¹² We found that lay people are often impressive in their ability to evaluate and balance certain risks against other risks, risks against benefits, risks against costs, and benefit against costs. Also, they can often suggest practical, less extreme, and less costly ways of achieving the desired protection.

One example of the power of public engagement involves genetically modified foods. For the past few years, especially in Europe, debates about the safety of genetically modified crops and foods have been vehement and frustrating. The agribusinesses and researchers that developed such crops, in many cases, had compelling ecological and public health objectives, including resistance to pests, drought, temperature shifts, salinity, or other environmental stressors. Another objective was reducing the use of pesticides. Unfortunately, the companies resisted the requests to label their products and the opportunity, if not the responsibility, to educate the public and the critics about the benefits of their technological advances. In addition, they did not demonstrate their respect for the need to assess potential or observed adverse effects.

Currently we have a lively and very public debate in this country about cloning embryonic stem cells for the purpose of developing new treatments for serious diseases (not for reproducing humans). This debate is a test of very strong contending forces with seemingly incommensurate value systems. Our leaders need inputs about how to proceed and about what is acceptable and desirable for the country.

In my opinion, President George W. Bush made a remarkable and powerful speech in the form of a science lesson on August 9, 2001. His description of the potential benefits from embryonic stem cell research and its applications seemed compelling to me. Of course,

he then shifted into a different kind of message about the resistance of certain groups to any use of embryos, even those marked to be discarded. Finally, he presented an unexpected resolution, calling upon the scientific community (at least those supported with public funds in the United States) to spend a few years sorting out what can be accomplished with existing stem cell lines cultured in the laboratory.

Senator Arlen Specter (R-PA), Senator Orrin Hatch (R-UT), other political leaders, and prominent patient advocates called for a much broader research opportunity. The evidence has mounted that the number and variety of stem cell lines are much more limited than the President's original statement indicated. (Meanwhile, a little-noted remark in his speech bears emphasis: He recalled the enthusiasm 10 to 15 years ago about treating Parkinson's disease with fetal cells, not embryonic stem cells. The attempt fizzled.)

The public clearly influences the national priorities for life sciences research. For decades, the "disease-of-the-month" process in Congress led to new institutes at NIH and special increases in funding. In the late 1990s, NIH Director Harold Varmus and Research!America leaders Paul Rogers and Mary Woolley led the campaign to increase support for a broad array of research related to the life sciences, not just at NIH, and not just for particular diseases or institutes. I commend those in Congress and those in advocacy organizations for overcoming narrow special interest advocacy to recognize that advances for any particular disease may well come from unexpected quarters across highly interconnected areas of research.

Public Opinion Data

Research!America conducted a poll in six states (including Michigan) in 1998. The results may be of broad interest.¹³ To the question, "How important is it that the United States maintain its role as a world leader in medical research?" Ninety-four percent nationally and 98 percent in Michigan said that it is very or somewhat important (nationally, 55 percent said very important and 39 percent said somewhat important; in Michigan, 83 percent said very important and 15 percent said somewhat important).

Another question was “Is it important to our state economy (in Michigan)?” Overwhelmingly, 90 percent responded very or somewhat important. The response was 93 percent for the importance of clinical research. Remarkably, at a time when we worry about people’s fears about getting involved in research, 59 percent responded that they would be “willing to personally participate in clinical trials.” The majority said they were motivated by a desire to help others more than to benefit themselves, recognizing that they themselves would not be the direct beneficiaries. Amazingly, 87 percent thought “health services research” is valuable—and that was before the publicity about the challenges the nation faces in patient safety and health care quality.

Economic Analyses

Funding First, an organization created by the Mary Woodard Lasker Charitable Trust, commissioned a report by an independent group of leading economists, who were organized by the president of the University of Chicago. It was titled “Exceptional Returns: The Economic Value of America’s Investment in Medical Research.”¹⁴

Everyone is aware that technologies have transformed medical care. Examples are pharmaceuticals, vaccines, open-heart and laparoscopic surgeries, biotechnology, intensive care units, artificial organs and prostheses, transplants, and clinical information systems. According to this report, improving the health of the American people accounts for half of the gain in living standards in the past 50 years.

The economists looked at the value of medical research in greater detail. They compared what is invested each year from public and private sponsors (now over \$50 billion per year) and what is gained in employment, sales, and the estimated value at various ages of extending life and improving health. For just the 20-year period 1970–1990, their analysis yielded the stunning conclusion that the increases in life expectancy were worth \$57 trillion to American society. For future benefits, they estimated, for example, that reduction of just 20 percent in death rates from cancers would be worth \$10 trillion to Americans, which is double the national debt. They also compiled

estimates of prevalence and calculated estimates of the annual economic cost of selected uncured diseases (i.e. opportunities), including heart disease, cancer, Alzheimer, diabetes, arthritis, depression, stroke, and osteoporosis.

I believe we have a moral imperative to invest in biomedical research. Also, polls demonstrate overwhelming bipartisan public support for investments in research to improve medical care. But, funds must be directed wisely. Of the \$1.3 trillion spent on health care annually in this country, I estimate that at least one-fourth goes to “chasing the symptoms” of patients with common diseases we do not yet know how to effectively treat—or prevent. Examples are the common cancers (except lung cancer, due primarily to smoking), neurodegenerative and psychiatric conditions, arthritis, and gastrointestinal disorders. As clinicians and health care systems administrators we must do what we can to help current patients, but we should not remain ignorant and impotent as we prepare to care for our children and grandchildren.

4. What Can We Expect for Federal Funding of Life Sciences Research in the Period beginning in FY 2004?

The 15.8-percent increase in the President’s Budget Request for FY 2003 for NIH will complete the bipartisan commitment to double the NIH budget from \$13 billion in FY 1998 to \$27 billion in FY 2003. We can count on Congress to make good on that commitment for NIH. As noted in response to question 1 above, the request does include some special, large investments for bioterrorism-related activities (necessary at this juncture in the nation’s history) and some small transfers from other agencies.

But what will be the “bow-wave” into the following years from the continuing obligations of grants that have already been made? What kinds of one-time commitments might be made by NIH in FY 2003 and the rest of FY 2002?

Table 1 summarizes the history of NIH R&D expenditures (a little less than the total agency appropriation) for the past decade and the projections of the budget by the President and the Office of Management and Budget (OMB) for the next five years (FY 2003- FY 2007).¹⁵

Table 1
NIH Funding History

Years	Appropriations	Percent Increases
1992-1998	\$9.6 to 13.1B	2.8, 5.9, 2.7, 6.2, 6.9, 7.3
1998-2003	\$13.1 to \$26.5B	14.4, 14.9, 14.9, 15.1, 16.0
2004-2007	\$27.0 to \$28.9B	2.1, 2.2, 2.3, 2.3

The NIH Tide Lifted NSF

1998-2003	\$2.5 to \$3.5B	6.8, 9.8, 13.3, 6.2, 3.5
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Source: Research & Development FY 2003: AAAS Report XXVII, pp 65-66; OMB data/projections.

Few seem to recall the modest increases for NIH in the early 1990s, when the federal deficit dominated decision making and inflation rates were higher than they are currently. With annual increases between 2.7 and 7.3 percent, the NIH budget grew from \$9.6 billion to \$13.1 billion over six years from 1992 to 1998 (36 percent). During the budget cycles from FY 1998 to FY 2003, the annual increases have been 14 to 16 percent per year, ensuring doubling (“rule of 72”) with compounding of the increases. For the four-year period after FY 2003, however, the official OMB projection is only about two percent per year (a cumulative total of 9.1 percent from FY 2003 to FY 2007).

Lest we think that everyone else suffered as NIH prospered, the bottom of Table 1 shows that the National Science Foundation has grown from \$2.5 billion to \$3.5 billion from FY 1998 to FY 2003, with a high prospect that Congress will be much more generous than the 3.5 percent increase proposed in the President's budget. For perspective, I recall our efforts in the Carter White House to push NSF above the \$1 billion mark in the late 1970s.

A bit more detail about the NIH budget: There is a 57.3 percent increase for NIAID (to \$4.0 billion), mostly for AIDS and bioterrorism; a 12.2 percent increase for the National Cancer Institute (to \$5.5 billion); and eight to nine percent increases for all other institutes. NIH estimates that it will be able to support 35,920 new research grants in FY 2003, of which 9,854 would be new grants and 26,000 would be continuing multiyear grants. NIH has proposed issuing some multiyear awards paid in full at the beginning, thereby avoiding the continuation funding, but making fewer new awards. Congress has generally rejected this approach in the past. For those in smaller states, the NIH Institutional Development Award (IDeA) program, similar to NSF's EPSCoR (Experimental Program to Stimulate Competitive Research), is increased. And the social and behavioral sciences components of the NIH budget are estimated to increase by 10 percent to a total of \$2.6 billion in FY 2003. Much of that amount is embedded in large program projects.

We can expect that the groundwork will be laid this budget season for the expectations of much higher than two percent increases in FY 2004, through the same broad-based public advocacy and patient advocacy that has gained bipartisan support in the recent past. David Korn *et al.* have proposed a set of "principles" that would require six to eight percent increases annually in the post-doubling era, i.e. similar to the average increase over the past four decades.¹⁶

5. How Will Advances in Biomedical Research Impact the Coming Train Wreck between Demands for and Costs of Health Care?

A train wreck is coming. On one side is the growing, aging population, the needs of the uninsured, and the demands of the insured population for health care. On the other side is the willingness to

pay. Patients themselves generally pay only a small portion of the total cost of health care. The rest is paid by the taxpayer, who seems to dissociate this benefit from the tax burden, and the employer, who considers this cost globally uncompetitive. A good test of our capacity to meet basic coverage needs will be the ability of Congress and the President to plug the gaping hole in Medicare—the lack of coverage for outpatient prescriptions.

The biomedical, behavioral, and health services research agenda is importantly related to the health care cost equation. In fact, the social compact that yields generous support for research is based on an expectation of the benefit of improved health for the American people and people elsewhere. To honor that compact we need to do five things.

First, we should recognize the enormous cost of those conditions we cannot treat effectively, let alone prevent, at present. I addressed that matter above. A rough estimate of the cost is \$300 billion per year.

Second, we should put more emphasis, especially with public funds, on scientifically interesting yet low-cost interventions for which there is no proprietary payoff for the pharmaceutical industry. An excellent example is folic acid fortification of the food supply to reduce plasma total homocysteine levels. This would greatly reduce the incidence of one of the most serious categories of birth defects—neural tube closure defects (spina bifida and anencephaly).¹⁷ It is also very likely that folic acid (and vitamin B12) administration through fortification (or through supplementation) to reduce circulating homocysteine will significantly reduce the nation's number one cause of death—cardiovascular diseases (heart attack, stroke, and peripheral vascular disease).¹⁸

We already have compelling evidence that fortification, even at a concentration less than that thought to be necessary for full benefit, has increased folate levels and reduced homocysteine levels in U.S. and Canadian populations. The evidence is so strong that clinical trials in North America designed to test whether homocysteine-lowering will really reduce cardiovascular deaths may be unable to show any further benefit.¹⁹ Another clinical trial has shown that administration of these B vitamins after angioplasty surgery of the

coronary arteries greatly reduces restenosis (obstruction) of the arteries.²⁰ In addition, the cost of such fortification of cereal grains is extremely low, and everyone receives the “treatment.”

Fortification has been deferred in the United Kingdom and Europe, presumably to wait for results from cardiovascular prevention trials.

Third, we should be aware of the very high cost of bringing effective new drugs to the marketplace. We need to refine the regulatory process both to make approvals less costly and to require post-marketing surveillance to recognize adverse effects more readily and intervene more expeditiously when necessary.

Fourth, we must recognize that academic medical centers, facing lower rates of payment for clinical care, will be less able to support the environment for grant-funded research. Increases at NIH are small compared with the squeeze on Medicare and Medicaid payments.

Finally, as noted under Health Services Research above, we must invest in learning what works and what does not, what is safe and what is not. And we must make our health care much more patient-centered, recognizing the importance of chronic care for common conditions and encouraging patients and families to become knowledgeable and contribute actively to the management of their condition.²¹

Conclusion

Lest one think that all of these challenges are unique to our time, here is a wonderful quotation from exactly 100 years ago from Sir William Osler, professor of medicine at Johns Hopkins University and then at the University of Oxford:

To wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the cause of disease, to correlate the vast stores of knowledge, that they may be quickly available for the prevention and care of disease—these are the ambitions of medicine.²²

That statement made in 1902, holds true today. We may wonder how those who follow us will view our own state of knowledge and practice 100 years ago from now.

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