SPECIAL REPORT

SHATTUCK LECTURE — BIOMEDICAL RESEARCH ENTERS THE STEADY STATE

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TWO and a half years ago, when I was still a private citizen working at the University of California, San Francisco, my colleagues, Mike Bishop and Marc Kirschner, and I offered advice to our new President in *Science* magazine.[1] The first of our 11 recommendations was to increase funding for the National Institutes of Health (NIH) by 15 percent per year, in order to double the NIH budget in five years and restore the success rate for grant applications to at least 30 percent. A year later, just after I had been called to Washington to work for that President as director of the NIH, I had to admit, in a speech to the American Society of Cell Biology, that "our proposal to double the budget by fiscal year 1998 is simply not realistic."[2] By then, I was already reconciled to a more modest goal: "to stay ahead of inflation [for] the next few years." Now, little more than a year later, we are faced with a new Congress intent on a balanced national budget at all costs. As a result, I have been trying to stave off cuts in the NIH budget — some nearly as large as the increases we proposed not so long ago — that would reduce our buying power by about one third early in the next century.

How can we explain such reversals of mood and fortune? From a historical perspective, they reflect three stages in the development of biomedical research: a past that was expansive and successful, a present torn by the demands of adjusting to an end to growth, and an uncertain future that provokes anxiety and sometimes despair. The rapid changes also embody three concurrent but divergent themes in our enterprise: the exhilarating, sustained effects of a wave of scientific achievement made possible by nearly 50 years of continually increasing investment; the sobering effects of a more recent need to adapt to budget deficits, the national debt, and public suspicion of government; and the alarming effects of budget-balancing efforts that would send biomedical research (and many other endeavors that benefit from federal support) into a rapid decline.

THE HISTORICAL CONTEXT

To think constructively about these divergent forces, we must try to put the current problem in a historical context. The golden era of the NIH lasted over 40 years, beginning just after World War II and ending with the downfall of the Soviet empire. At the end of World War II, scientists were regarded as heroes who had provided many of the factors that contributed to victory: chloroquine and synthetic quinine to combat malaria, penicillin for infected wounds, and, of course, the atomic bomb. The passage of the GI Bill ensured that colleges and universities would prosper, that much larger numbers of people would study beyond high school, and that education would be valued. The economy was thriving, the country was optimistic, and the federal government was viewed as the right place for leadership.

No wonder, then, that the NIH was encouraged to expand from a small group of laboratory buildings in Bethesda, Maryland, dedicated by President Franklin Roosevelt just before the war, into a much larger organization that mushroomed on the NIH campus and funded research throughout the country, at universities, medical centers, and private research institutions. Prodded by public enthusiasm for biomedical science, as enunciated by a few famous spokespersons (congressional leaders, such as John Fogarty, Lister Hill, Warren Magnuson, and William Natcher; the philanthropist Mary Lasker; NIH Director James Shannon; and others), the Congress responded with new funds and new health institutes (Table 1).

The end of the Cold War in 1989 found the country in a mood very different from that of 1945. The outcome of this war was seen more as a defeat of the ill-designed economic and political system of our opponents than as a triumph of our own values. Scientists, even those whose research had been handsomely supported by expenditures for defense, were not considered major contributors to our success with the Soviets; after all, nuclear deterrence was based largely on scientific discoveries from an earlier era. Expensive missile-building technology was viewed this time as the source of other woes — most obviously, a national debt that had grown to an unimaginable size in the 1980s. Far from being an economic stimulus that might benefit

Table 1. Congressional Appropriations for the NIH from 1950 to 1995.

FISCAL YEAR	TOTAL APPROPRIATION ($MILLION)	NO. OF NIH COMPONENTS
1950	43	6
1955	67	9
1960	332	9
1965	773	12
1970	1,061	19
1975	2,093	19
1980	3,429	20
1985	5,149	20
1990	7,576	23
1995	11,306	26

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peaceful enterprises, the end of the Cold War was accompanied by an increasingly desperate economic situation. At the same time, other research institutions were showing signs of stress and loss of direction: colleges and universities, some overbuilt and undersubscribed, were having trouble balancing their books, and some large national laboratories were without the clear mission or the review processes needed to maintain a standard of excellence. These factors contributed to the wave of sentiment against the federal government that was dramatically expressed in the recent congressional elections.

Benefits of Four Decades of NIH Growth

Perhaps it is not surprising that biomedical scientists were among the last people to understand that we had come to the end of an era. When the social and political themes of the 1990s first emerged, they seemed detached from the prosperous condition of biomedical science. Forty-five years of steadily increasing financial support had produced an enviable record of scientific accomplishment and remarkable improvements in the nation's health (Table 2). This partial list of the changes wrought by investments in biomedical research — by the NIH and its many partners, here and abroad — is stunning. These advances also contributed to the nation's economy, through the growth of the pharmaceutical, biotechnology, and laboratory-supply industries, and encouraged many of our brightest students to train for careers in biomedical research. The support provided to the universities to sustain research efforts and to train new investigators stimulated their growth and improved their quality. By all available measures, the United States assumed world leadership in medical research.

Changes in Federal Support

Still, the first sign that all was not well was apparent as early as 1990. That year, a surprisingly low success rate for NIH grant applications triggered many news stories, congressional concern, a symposium at the National Academy of Sciences about the funding of young scientists,[3] and more political engagement by my colleagues than I had ever seen before. In fact, this initial sign of the crisis now at hand was partly attributable to a technicality: an extension of the average term of NIH grants had increased the proportion of the agency's funds that were already committed to multiyear grants. As a result, even a slight decrease in the rate of growth had a large adverse effect on the success rate for new applications. But over the next few years, even with a return to a more acceptable average term for awards, the success rates did not improve substantially, mainly because budgets did not increase in constant dollars, as they had in earlier times (Table 3).

Table 2. Some of the Major Advances in the Health Sciences in the Past 50 Years.

Vaccines against poliovirus, hepatitis B virus, and many other infectious agents.
Penicillin and many other antibiotic agents.
Recommendations for health-promoting diet and lifestyle, including simple means to lower the incidence of heart disease.
Replacements for many hormonal and vitamin deficiencies.
New methods of contraception.
Tests to protect the blood supply from hepatitis B and C viruses and the human immunodeficiency virus.
New surgical treatments, including organ transplantation and implantation of pacemakers and artificial joints.
Effective therapies for certain leukemias and other cancers.
Drugs effective against mental diseases.
New treatments, such as the use of blood-cell growth factors, developed from recombinant-DNA techniques.
Methods of in vitro fertilization.
Genetic testing for many inherited diseases.

Table 3. Changes in the NIH Budget from 1985 to 1995.

Fiscal Year	Change in Budget (%)*
1985	—
1986	−0.7
1987	+11.6
1988	+2.4
1989	+4.4
1990	+2.1
1991	+3.4
1992	+4.0
1993	−0.2
1994	+1.9
1995	−0.6
Cumulative increase	+31.4

*Calculated on the basis of constant dollars.

The difficulty of obtaining grant support has had complex and sometimes divisive consequences: criticism of the peer-review system and scrutiny of the system for inequities; demoralized and dwindling ranks of clinical researchers, who also suffer from the loss of health care revenues; a generation of disillusioned graduate students and postdoctoral fellows, who say that the future is not what they were promised; and a younger generation of skeptical high-school and college students, who see a scientific career as dauntingly competitive.

Recognizing the Steady State

These symptoms of dis-ease in the biomedical research community have intensified during the five years since the first signs were noted. It is now possible to make a diagnosis: the research enterprise is undergoing a painful transition from an era of growth to an era of steady-state activity. In the steady state, new grants can be funded only when old grants expire, new faculty can be hired only when older faculty retire, and new NIH programs can begin only when other programs have ended.

Perhaps this change should not have been surprising. Growth cannot go on forever, as California Institute of Technology physicist David Goodstein has pointed out.[4] To illustrate his claim that "the era of exponential growth in science is already over," he points to Derek de Solla Price's 1961 calculation that if early rates of scientific growth persisted, the number of journals would reach 1 million by the year 2000 (Fig. 1).[5] But, in fact, the number has plateaued at a mere 40,000 or so. Goodstein goes on to say that although "it is probably still true that 90 percent of all the scientists who ever lived are alive today . . . it cannot go on being true for very much longer. . . . It is a simple mathematical fact that if scientists keep multiplying faster than people, there will soon be more scientists than there are people. That seems very unlikely to happen."[4]

Still, none of us like to acknowledge the end of growth. I continue to ask the administration, at the beginning of each budget cycle, for an appropriation that would restore healthier success rates for grant applications. Our many constituencies go to Congress each year hoping for substantial increases in appropriations for the NIH. And many universities continue to build facilities for biomedical investigators who will be expected to amortize the construction costs with new grants. But during the past year, such efforts have come to seem quixotic at best. Would it not be more sensible to put our energies into optimizing scientific activities in the steady-state environment that is likely to persist for the foreseeable future?

Accommodating to the Steady State

In recent months, I have come to recognize that many of the initiatives recently proposed or undertaken at the NIH — and in other domains of the scientific establishment — are designed to cope with the steady state. Some of these initiatives address issues fundamental to the conduct of biomedical science; others attempt to generate money for research by achieving savings through operational efficiencies.

For example, we have been working hard to improve the peer-review process at the NIH. We are experimenting with streamlined methods — such as electronic communications, a triage system for reviewing applications, and postponement of the filing of administrative forms until a grant seems likely to be funded — to save money and effort and to produce more judicious and more understandable decisions. We have debated proposals for distributing our funds more equitably. These plans could give more young investigators a chance to develop independent research programs, prevent abrupt terminations of advanced research careers, and ensure the vitality of the more fragile components of our enterprise, such as patient-oriented research and basic research that lacks an obvious connection to improved health.

Others are also grappling with the emergence of the steady state. The Committee on Science, Engineering, and Public Policy of the National Academy of Sciences recently issued a response to the frequent accusation that the country is training too many new scientists.[6] The committee concluded — wisely, I believe — that we should not reduce the size of our Ph.D. programs but instead help them to produce scientists acquainted with and equipped for many kinds of careers — in education, business, journalism, law, and other fields — not just highly specialized, laboratory-based careers.

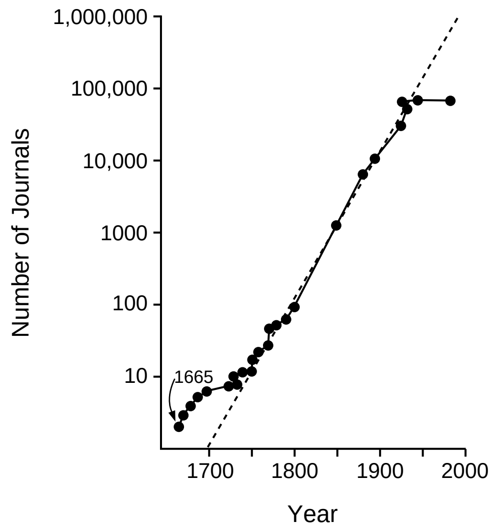

Figure 1. Cumulative Number of Journals Founded from 1665 to the Present.

The broken line shows the trend based on the years 1750 to 1950. Adapted from Goodstein, with the permission of the publisher.[4]

Taken to its logical extreme, planning an optimal steady-state environment for the research supported by the NIH could have profound effects on the way we do business. We could recommend how laboratory groups should be configured in the stable world. (For example, the groups might be smaller, with fewer trainees and more technicians who have advanced degrees, and these smaller groups might be obliged to work together in research consortia to achieve efficiency and technical diversity.) Going further, we could try to determine the right numbers, sizes, and types of grants in our portfolio. At the bottom of all such proposals is the need to achieve a balance between two, sometimes conflicting pressures: the short-term demand for health-promoting results of research and the long-term need to maintain the vitality of the research enterprise.

Raising such issues may be a useful means to focus attention on our problems. But it is prudent to worry about a solution to our predicament that seems like a planned economy. (We should at least have learned that lesson from the failure of communism in the Cold War.)

Any attempt to plan substantial changes in the way science is practiced and supported must inevitably weigh stability against competition. I believe that American science has profited greatly from competition based on expert review and that science in other countries has often been penalized by premature offers of lifelong support. If we are to think concretely about the steady-state world, as I believe we must try to do, it will be important to retain a healthy level of competition. This is one way to ensure that the steady state is dynamic and not static. Still, the competitive mode has its limits, and we may have reached them.

But are we equipped to envision, let alone determine, the correct shape of biomedical science in a steady state? Such planning is not consistent with our national traditions or with the accepted values of our field. When central planning is attempted, it can deteriorate into corporate advertising or uninspired social determinism. Evolution under enlightened guiding principles seems a more desirable outcome. To develop such principles, we require detailed knowledge of how individual investigators, departments, and entire institutions have functioned in the recent past. It is not difficult to use our computerized data bases to determine what the NIH investments have been, but a systematic survey to identify all sources of money across departments or disciplines has not, to my knowledge, been undertaken. Until such information is available, even on a limited scale, it may be premature to say what we want.

Combating the Negative State

To this point, I have considered the state of biomedical science from the optimistic perspective that we can eventually accommodate to constant rather than expanding support from the government. But during the past few months, those of us who have been reading the recommendations of congressional budget committees have learned that many members of Congress are willing to consider large reductions in NIH funding in the next fiscal year. Moreover, we have heard proposals that funding should be frozen at these lower levels for several additional years, while inflation continues, until the national budget is balanced in the year 2002.

Two plans were initially aired. The House Budget Committee proposed to reduce the NIH budget for fiscal year 1996 to a level 5 percent below that in fiscal year 1995 (or 9 percent below the 4 percent increase that the Clinton administration has proposed for 1996 to maintain the steady state). The Senate Budget Committee intended to reduce the fiscal year 1996 budget to a level 10 percent below the level in 1995 (or 14 percent below the President's request). Events took a more favorable turn when one of the strongest champions of biomedical research, Senator Mark Hatfield of Oregon, proposed an amendment that would restore most of the money that the Senate Budget Committee had proposed to cut below the 1995 level. With the help of thousands of scientists and patient advocates who petitioned their congressional representatives, this amendment was approved by the resounding vote of 85 to 14 on May 24. The final House–Senate budget resolution, however, would still leave the NIH budget 1 percent below the 1995 level in 1996 and 3 percent below the current level until the year 2002, when a balanced budget would be achieved.

To appreciate the cumulative effects of this proposal, the numbers have to be viewed in the context of the annual inflationary rate for biomedical research, which is 4.3 percent (Fig. 2). With this rate of inflation, we would lose nearly a third of our purchasing power by the year 2002 if the joint budget resolution were followed. (In contrast, the plan recently announced by President Clinton for balancing the budget by the year 2005 would hew quite closely to the inflationary projection.)

Of course, the budget resolution is an early phase

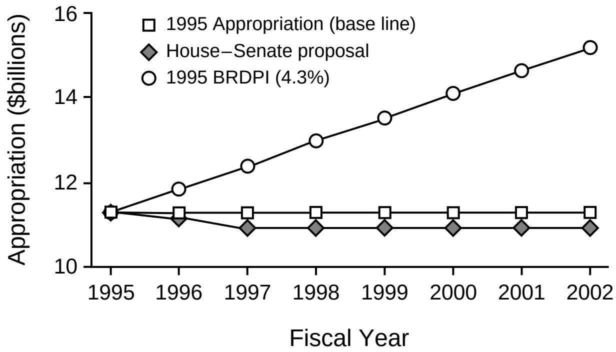

Figure 2. NIH Budget Projections from 1995 to 2002, Based on the Recommendations of the House–Senate Budget Conference, the Biomedical Research and Development Price Index (BRDPI), and Constant Appropriations Equal to the Fiscal Year 1995 Base Line.

of the process required to allocate public money to agencies such as the NIH. The next phase occurs when the Appropriation Subcommittees in the House and the Senate meet to allocate their assigned funds to the many programs under their jurisdiction. Thus far, the NIH has fared well, perhaps even surprisingly well, in this crucial part of the process. Under the strong leadership of Rep. John Porter of Illinois, the House Labor, Health and Human Services, and Education Appropriations Subcommittee designated $11.92 billion for the NIH, a proposal that has been endorsed by the full Appropriations Committee and the entire House of Representatives. This amount represents a 5.7 percent increase (more than $600 million) over the 1995 budget for the NIH, or somewhat more than the President proposed to keep pace with inflation.

Now a parallel appropriations process must take place in the Senate, and any differences between the two legislative bodies must be resolved before the appropriations bill goes to the White House for the President's signature or veto. So there will be many more events that merit close attention before the NIH can know whether it will be operating above or below the steady-state funding level in fiscal year 1996. Furthermore, we will be facing similar budgetary battles for several more years, until a balanced budget is within sight and the national debt has been markedly reduced.

Some Arguments for NIH Funding

For these reasons, I believe it is prudent to marshal the arguments for the NIH — and for other programs that we endorse — to ensure that the best things that the government does for our society survive the frenzy of the budget cutters. Four such arguments have seemed especially effective to me in recent months.

First, it is inappropriate to curtail a government program simply because it must "share the pain" of budget reduction. The Congress and the administration have an obligation to decide which programs they value most and to nurture them, even in rough times. It is a mistake to assume that every agency can absorb a 5 or 10 percent decrease simply by resetting internal priorities. This is especially true of agencies, such as the

NIH, that are setting priorities every year by choosing among programs and selecting only the most highly qualified applicants to receive support.

Second, budget makers must distinguish between the services and the investments provided by government agencies. At an embassy dinner this spring, an influential Republican senator told me that cutting the NIH budget made him just as uncomfortable as cutting funds for Amtrak or National Public Radio. I am a contented rider on the Metroliner and a devoted listener of Morning Edition, but I know there is an important distinction between reducing the schedules of these services and reducing expenditures by the NIH. When federal funds are invested, not simply spent, even short-term reductions have long-term effects. When we cannot afford to support an excellent grant application, the effect is greater than an inconvenient train schedule. We waste a resource in which the country has already made an appreciable investment, we forfeit knowledge on which others could build, we deprive ourselves and our children of better health, and we send a signal to our gifted youth that biomedical science lacks a future.

Third, we must recognize and advertise the many benefits of NIH-supported research. Laura D'Andrea Tyson, the President's chief economic advisor, has maintained that federally supported research has an average economic return of 150 percent, which is even better than the return on private investment in research. The benefits of biomedical research are especially great. In addition to the economic stimulus provided to the industries that depend on our discoveries, the benefits include reduced expenditures for medical conditions that we have learned to prevent and hard-to-estimate values that the public places on improved health and extended life. The public needs to be repeatedly reminded of the many vaccines against bacterial and viral infections, the drugs that control psychiatric illnesses, the fluoridation of drinking water to prevent dental caries, the preventive strategies that have halved the rates of mortality from coronary artery disease and stroke, and effective treatments of certain cancers. These are just a few of the NIH-sponsored advances whose multiple benefits demand continued emphasis. The possibility of impeding new achievements — gene therapy for inherited diseases, methods to alleviate chronic neurologic diseases, or new treatments for common cancers – should be a powerful disincentive to reduce the NIH budget.

Finally, the public must be reminded that it highly values many things the federal government does with its discretionary money. By all reputable polls, our citizens are enthusiastic supporters of biomedical research and would even consider raising taxes to pay for it. I seriously doubt that the public would have endorsed the cuts that the House and Senate Budget Committees proposed for the NIH; the public simply did not know what was happening.

In his brilliant essay, "I Love Big Government," in the *Washington Post Magazine,*[7] Bob Garfield attempts to counter the proposal to return "power and autonomy to the states," by reminding us of the importance of certain federal functions. Without them, Garfield imagines, [we] might have, say, a Vermont Division of Antitrust, but it would scarcely put the fear of God in a person. Think of taking medicine regulated by the Utah Food and Drug Administration. Imagine pinning your cancer-cure hopes on the South Dakota Institutes of Health. Imagine the U.S. Virgin Islands Centers for Disease Control. The New Hampshire Aviation Administration. The Wyoming Secret Service. The Idaho Aeronautics and Space Administration. The Massachusetts Intelligence Agency. The Arkansas Reserve.

A Modest Proposal for the NIH

In my role as a federal administrator, I have suggested that the biomedical research enterprise has been undergoing a difficult but manageable change. But it is now also threatened with the more perilous prospect of declining fortunes. As a bench scientist, physician, and citizen, I must ask, Why should this be? Why should the NIH — with its popular goals, productive record, economic benefits, central role in sustaining our universities and training new scientists, and prospects for improving health — be valued any less by the federal government than Social Security and other mandatory entitlement programs?

The vicissitudes of the past few years and months have convinced me that the government and the public should find the means to secure a stable fiscal base for the NIH. Under such a plan, the NIH would be guaranteed a budget not less than that of the previous year, with an inflationary increment determined on the basis of the rate of inflation in biomedical research and development. This plan would not create entitlements for individual scientists or scientific programs. Trainees would continue to compete for jobs in the academic, government, and industrial sectors. Investigators would still compete for support in both the extramural and intramural research communities. Institutes and centers would compete for allocations within the fixed NIH budget, and initiatives within each component of NIH would compete for support. Congress and the administration would be able to supplement funding to meet specific threats to health or to increase the total size of the enterprise, if the economy permitted such supplements and they were justified by the science. Within this secure framework, NIH-supported investigators would be encouraged to think sensibly about the state of the enterprise and to develop the principles to guide its evolution. This would be a legacy at least as great as a balanced budget to present to future generations.

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