

Nuturing the Scientific Enterprise

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In the foreword of a soon-to-be published volume, whose chapters were written by 40 leading scientists about their years in the intramural NIH laboratories, Dr. Lewis Thomas has written (1): "We seem to be living through a period (transient, I hope) of public disillusion and discouragement over government and all its works. At all levels, bureaucracy in general is mistrusted, here and abroad. The word is out that government doesn't really work, can't get things right, wastes public money, fumbles along, stalls, gets in the way."

"At such a time, it lifts the heart to look closely at one institution created by the United States government which has been achieving, since its outset, one spectacular, stunning success after another. The National Institutes of Health is not only the largest institution for biomedical science on earth; it is one of this nation's great treasures. As social inventions for human betterment go, this one is a standing proof that, at least once in a while, government possesses the capacity to do something unique, imaginative, useful, and altogether right."

From the perspective of decades, the development of the NIH represents a remarkable accommodation of the public's understandable demands for results from the expenditure of public funds and science's inherent need for independence and elbowroom. The succession of laws that established and molded the NIH were wise, visionary, and enormously beneficial. But as farsighted and wise as the enabling statutes have generally proved to be, the development and maturity of the NIH resulted from sure-handed and enlightened administration of the congressional mandates, accompanied by a tolerant confidence on the part of Congress that its intention would be honored.

It was fortunate that during the period of its explosive growth from 1955 to the late 1960's, the NIH was directed by an unusually able and strong leader—James A. Shannon. Jim Shannon insisted that the congressional mandate to conduct research in cancer, heart disease, and

arthritis, for example, be interpreted broadly. He realized that the scientific base was not sufficient to permit a frontal assault on the diseases themselves. He set about to build the research capability of this country through the intramural program at Bethesda and through a substantial expansion of the mechanisms of grants-in-aid to institutions.

Summary. The National Institutes of Health has given its highest priority to funding investigator-initiated projects and to minimizing year-to-year fluctuations in the number of new and competing awards. Adequate funding for centers, research contracts, intramural research, and training is also necessary for creation of the science base essential to sustaining the powerful momentum of recent progress. The important question for the future is whether the present system is sufficiently flexible and imaginative to keep pace with the contemporary revolution in science.

The Shannon era was a time when year-to-year budget increases for the NIH averaged around 25 percent. What was entirely foreseeable has happened. Although our annual appropriation is now well over \$4 billion—ten times what it was in 1960—the increases for the past decade have barely kept pace with inflation. Our thoughts have turned to preservation; that is, the preservation of the momentum of the burgeoning biomedical research enterprise.

By 1975, the NIH appropriation had just reached \$2 billion, but the positive slope of the growth curve was flattening noticeably. In its report on the 1976 NIH budget, the Senate Appropriations Committee warned that "annual increases should not be routinely expected and it would therefore be prudent to develop a policy for the most effective management of the research grant programs on the basis of relatively constant funding from year to year" (2).

As early as 1974, the NIH had begun accommodating to a relatively constant budget by funding an increasing number of excellent research proposals through shifting funds from among various other program mechanisms. There was a clear need for articulation of policy for guidance through the uncharted funding plateau. In 1978, under the leadership of

Donald Fredrickson and Secretary Joseph Califano, a national conference on health research principles was held in Bethesda. Its purpose was to draw out ideas from the department's health agencies and the research community for a research plan to help guide in the allocation of limited resources. More than 100 nonfederal scientists, many of them representing major segments of the scientific community, participated actively in the conference discussions. All parties to the conference agreed on the essentiality of the federal commitment to ensure a strong "science base" for health. They repeatedly stressed the need for long-term stability in the funding of health research and warned that present research capabilities must be sustained and enhanced to assure future health gains.

These considerations stimulated the

development of the so-called "stabilization strategy" that was conceived to benefit biomedical research. As applied to research project grants, the most important component of the science base, a major goal was to minimize the year-to-year fluctuations in the numbers of new and competing renewal awards and thereby to reduce the likelihood that investigators would forsake research careers because of the appearance of unpredictability of funding opportunities.

Amid the hectic give-and-take of the iterative budget process, the first step toward effecting the stabilization concept was to apply it to research project grants. The goal of funding at least 5000 new and competing renewal research grants, atop a base of moral commitments comprising approximately 11,000 noncompeting continuation grants, became an end in itself—an end to be met, if necessary, by repeated downward negotiations in direct costs from the levels recommended by peer reviewers, by payment of less than full indirect costs, and by reduction in other important program activities.

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The present and continued adherence to the abridged stabilization strategy has become a problem in that it does not reflect a broad view of the needs throughout biomedicine, even though it does much to protect the most important mechanism for the generation of new knowledge—the investigator-initiated research grant. Serious concerns in this regard have been advanced by NIH institute directors, by the NIH director's advisory committee, by national advisory councils, and by other groups representative of the research community or the public at large. However, a superior alternative has yet to be articulated, much less become adopted as broadly and fervently as has the current strategy.

While it is true that NIH has supported at least 5000 new and competing renewal research project grants each year since 1980—and in 1983 the total was over 5300—it would be incorrect to contend that maintenance of this number *per se* has produced stability for the biomedical research enterprise overall. The fact that we have found it necessary to fund research project grants at levels well below those recommended by peer reviewers is a chronic source of concern to all involved. Moreover, repeated and unpredictable reductions in the fraction of total NIH dollars available for all other funding mechanisms, including training and research career awards, research centers, and contracts, has led to less than desirable levels of effort in complementary areas.

One component of the long-range stabilization effort—5000 new and competing grants—is easy to describe and, as things have turned out, is achievable. It is not surprising that this partial expression of a broader objective has become its surrogate and the focus of attention from all concerned. Numerous proposals have been made recently to “stretch” the research dollar by limiting or reducing the amounts paid on individual grants in order to free funds to support additional awards. These proposals have been considered by the NIH and have been found to be lacking in many respects, not the least of which is the implication that research awards represent a full employment program for scientists. The proposal brings to mind a statement in testimony by Philip Handler: “In science the best is vastly more important than the next best,” or John Gardner’s query—“Can we be equal and excellent, too?”

However, in fiscal year 1982, the NIH instituted a formal policy of awarding grants at amounts less than those recom-

mended by the peer review groups as a way of maximizing the number of grants that could be supported within a given budget level. Although, as demonstrated by the 1982 and 1983 experience, this policy has provided short-term relief from budget stringencies, it holds little promise of contributing to long-term solutions. Just as there are limits to the amounts of resources that can be shifted from other program mechanisms to support the funding of research project grants, so are there limits to the reductions that can be made in funds awarded to support of an individual research project grant without defeating the purposes for which those funds were awarded.

Despite the untoward side effects of the recent partial implementation of a stabilization policy, the NIH has no desire to abandon the concept—and we recognize the positive effect of even an incomplete application of this long-range plan during a time of fiscal stringency. It is our conviction that the important needs addressed by the original stabilization strategy remain and that the essential components of the strategy continue to be vital as means for addressing those needs.

Stated in the simplest possible terms, we need to assure adequate levels of support for the entire research enterprise if we are to preserve the momentum of discovery. We believe that the optimal level for progress is to be able to award 45 to 50 percent of approved applications for research support. In the context of the federal budget, the sums needed are not large. Last December I expressed to the director's advisory committee my belief that to achieve such a goal, we would need an additional \$300 million to \$400 million per year for 3 years, with steady funding for new awards thereafter. It is encouraging that the increase for 1984 approaches that projection.

The Association of American Medical Colleges (AAMC) and the Coalition for Health Funding have been untiring in their efforts to improve public awareness of the value and promise of biomedical research as well as its funding needs. That better public understanding was translated again this year into action by the Congress as it made its decisions on the NIH budget. But a projection based on a 50 percent award rate, essentially full funding of grants, and maintenance of balance among the essential mechanisms for research support would require much larger sums, perhaps a doubling of the NIH budget by 1990 even if a modest rate of inflation is assumed.

In speaking of the essential mecha-

nisms for research support, I would include at the minimum adequate funding for centers, for contracts, for intramural research and for training, as well as for research grants. For obvious reasons, we consider first-time grantees a highly important category of investigators who must be adequately supported by NIH awards. In 1982, about 8 percent of our awardees were “first-timers”—this, by the way, is the lowest that ratio has been in a decade. In FY 83, when we funded 39 percent of study section approved awards, this figure rose some but precise figures are not yet available.

At the other end of the grantee spectrum is the outstanding established investigator for whom a mechanism is needed for providing longer term, more flexible support. Another matter requiring attention is the need to replace or purchase the increasingly sophisticated instruments required for today's research. It is estimated that \$20 million a year for 5 years is needed for the acquisition of large-scale shared instrumentation resources with additional funds for the purchase through research grants of smaller instruments. The NIH has recently joined an ongoing study by the National Science Foundation for the purpose of securing a valid current assessment of national need.

Finally, extramural laboratories and facilities are slowly deteriorating. With the exception of funds supplied by the cancer program and more recently by the National Eye Institute, NIH stopped supporting facilities after 1969, and currently lacks legal authority to do so. As a consequence, many of the facilities benefiting from the major NIH construction effort—the health research facilities program—are more than 20 years old, or rapidly approaching that mark. Rather than calling for any new major expansion, the realistic aim of any new federal construction program should probably be less ambitious. It should, however, include new construction to replace outmoded facilities, to relieve overcrowding, and to accommodate changing research requirements, including facilities for dealing with toxic wastes, for laboratory animals, and for major renovation and repair of inferior facilities. There is a dearth of good information on construction needs, and a current study similar to that being conducted on instrumentation deficits is seriously needed.

It is clear that for a construction program to make any difference in addressing the needs, the monies appropriated would have to be substantial. Past approaches which have limited the total

federal construction contribution to up to some fixed percentage of total costs may be a reasonable condition to impose on any new authority developed. It is encouraging to note that the Congress has recognized that universities and other institutions of higher learning are reaching a point where they will not be able to participate fully in our cooperative research endeavor without assistance.

As important as buildings and adequate instrumentation may be, there is another consideration of even greater moment. This subject is necessarily at the heart of any discussion about preserving the momentum of discovery or of preserving the biomedical research enterprise itself. That subject is research training. In our view, the training and research programs are so closely interwoven as to be practically indivisible. The intense competition for research support has increasingly taken its toll of the amateur or undertrained investigator. The professionalization of research activity has progressively selected against the M.D. scientist who 15 years ago had a much better prospect of success in research applications than the Ph.D. applicant.

Concurrently, there has been a decrease in the number of physicians who are seeking research training. The application of scientific advances to maintain good health and to prevent and treat disease is ultimately the responsibility of the physician. The trained clinical investigator is the critical link between the laboratory and the health care provider. In the face of the explosive growth of basic knowledge in the biomedical sciences which has opened up vast opportunities for clinical research, the shortfall in training of clinical investigators assumes additional significance.

Despite these negative factors and partly to counter them, the NIH has developed several programs in addition to its regular research training grants that are designed to acquaint the physician in training with the excitement and possibilities of biomedical research. At present, the stipends available for support of National Research Service Award trainees are paltry, well below those available in other federal research training programs. Predoctoral stipends should be raised to the \$8100 that is offered by the National Science Foundation. An estimated supplement of some \$34 million would be required to achieve parity under the NRSA program. Our new training programs for exceptional postdoctoral fellows would require more than \$10

million to bring their stipend levels in line with other individuals of equivalent training and experience.

Additional training slots should be made available for the NRSA program to bring it to the level recommended by the National Academy of Sciences. Over a 2-year period, training positions should be increased to about 10,500. Increases are also needed in the career development program at a rate of 200 added awards a year for 3 years. The latter increases, plus the increase in numbers of NRSA trainees, would require an addition of some \$40 million per year over the President's request. Thus, total needs to bring the support to competitive level amount to about \$84 million.

Earlier I spoke of some of the exterior changes that have occurred affecting the long-standing federal-academic partnership. Recently we have seen the beginnings of development of a three-way partnership involving industry as a participant. There have been suggestions that the NIH take some kind of active part in the institution of these new relationships. We have not done so. We believe it preferable that the new forms of joint endeavor continue to evolve as they have been with government playing a facilitative role. Notwithstanding the fact that the areas of collaboration between the universities and industry have broadened significantly and promise to continue in that expansion, I believe it safe to predict that the government will continue as the principal source of funding for basic research.

At the same time, and within the biomedical scientific enterprise itself, there has been a gradual change having profound implications. Nobel Laureate Arthur Kornberg recently called attention to the "confluence of the many discrete and previously unrelated medical subjects into a single unified discipline." He observed that "anatomy, physiology, biochemistry, microbiology, immunology and genetics have now been merged and are expressed in a common language of chemistry" (3).

It is ironic that in the presence of this confluence of the scientific disciplines, there are increasing pressures on the NIH for fragmentation through the creation of new organizational entities each having a relatively narrow focus on a particular set of health problems. Such movements gain much of their strength from, and indeed are an expression of, the public confidence in the power of research. The movements are also an understandable reaction by segments of the biomedical community to the funding

crunch and represent an effort to establish altered research priorities through congressional action.

The NIH and the Department of Health and Human Services have opposed legislation for the creation of new institutes and for the establishment in statute of favored status for specific research programs. Our opposition to these proposals is based not only on their adverse effects on administrative costs and flexibility, but also because the compartmentalization they establish is counter to the direction in which science is moving. At a time when we *can* confidently predict unusually rapid movement in science, but *cannot* predict just where that progress will occur, we need the maximum flexibility for marshaling finite resources for support of science. Organizational structures have a direct influence on funding priorities. Even though such detailed legislative prescriptions may be proposed with the intent of preserving the scientific enterprise, their effect can tend toward another kind of preservation—freezing the enterprise in status quo. That is also a reason we continue to oppose H.R. 2350, the so-called Waxman bill, and to insist that simple reauthorization of expiring authorities and preservation of section 301 of the Public Health Service Act are all that are needed.

In saying this, however, I am aware that adamant refusal on the part of the scientific and academic community to consider change is shortsighted. Such a posture would ignore the history of the development of the NIH—institute by institute and most of them disease-oriented. It was from such specificity that public interest and vigorous support was drawn.

Last June, we asked the Institute of Medicine of the National Academy of Sciences to make an objective study of the organizational structure of the NIH and, considering scientific developments and economic conditions, to recommend the establishment of standards for determining the need for any substantial change in the organizational structure of the agency. We expect the study to be completed and to have a report from the IOM in November 1984.

In that connection, permit me to lay to rest one bit of false speculation that has circulated in some quarters of the scientific community; namely, that NIH's hidden agenda in sponsoring the IOM study is to do away with categorical institutes. I can categorically say that we did not and do not have such an intention.

In summary, the scientific enterprise

is alive and reasonably healthy—but it could be much more so. To flourish vigorously, to utilize to the full our vast human resources for greater progress in health research, additional sums are needed for many purposes, but equally we need a renewal of the long-range commitment to excellence and accelerated progress, and to preservation of managerial flexibility within the enterprise itself.

The AAMC has consistently and effectively supported this position. In that connection, I urge you to read carefully the analysis and exposition of principles for the support of biomedical research just issued by the AAMC executive

council. This little blue book, titled *Preserving America's Preeminence in Medical Research*, is an exceptionally clear, balanced, and persuasive statement deserving of widespread attention.

Most of you will remember another influential report issued by the AAMC in 1965. It was written by Lowell T. Coggeshall and titled *Planning for Progress Through Medical Education*. In the report was an observation that fits exactly the context of my remarks and, in a sentence, captures the ideas I have endeavored to present. In Dr. Coggeshall's words—as valid now as when they were written—"The important question for the future is whether the present system

is sufficiently flexible and imaginative to keep pace with the contemporary revolution in medical sciences and the changing expectations of the American people" (4).

References and Notes

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3. A. Kornberg, from "Biology and technology," unpublished manuscript, 1982.
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RESEARCH ARTICLE

Major *pol* Gene Progenitors in the Evolution of Oncoviruses

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Oncoviruses, a subfamily of Retroviridae (1), are the causative agents of naturally occurring tumors in diverse vertebrate species. Unlike most viruses, which are spread only as infectious agents, oncoviruses can also be transmitted within the germ line of the host.

of mice and in certain murine tumors (3). Later studies revealed the existence of infectious retroviruses containing extensive homology to the A particle genome as well (4). Type B viruses have been found only in murine species. Such viruses have been established as etiologi-

tionships among different oncovirus genera. One of the most useful approaches has been the demonstration of shared antigenic determinants in their translational products. Interspecies cross-reactivity was initially observed for several early isolates of type C viruses (8). The advent of radioimmunological techniques made it possible to demonstrate the presence of interspecies determinants common to the respective *gag*, *pol*, and *env* gene products of all known mammalian type C viruses (9). Such studies have led to the conclusion that mammalian type C viruses arose from a common progenitor. The detection of immunological relatedness between the major structural proteins of type B and D viruses, as well as between mammalian type C and D viruses, has suggested that evolutionary links may also exist among these three major oncovirus genera (10).

Efforts to analyze the structural and evolutionary relationships between different oncoviruses have been facilitated by the ability to isolate and amplify these viral genomes by molecular cloning techniques. In the present studies, we used molecular hybridization and nucleotide sequence analysis to detect and localize related genes of viruses representing different oncovirus genera. We have now established the existence of major *pol* gene families in the evolution of oncoviruses, as well as other previously undetected evolutionary linkages.

Oncoviruses have been classified on the basis of their morphological properties (2). Even though four different genera have been recognized (Table 1), vi-

Abstract. *The genetic relationships among molecularly cloned prototype viruses representing all of the major oncovirus genera were investigated by molecular hybridization and nucleotide sequence analysis. One of the major progenitors of the pol genes of such viruses gives rise to mammalian type C viruses and another gives rise to type A, B, D, and avian type C oncoviruses. Evidence of unusual patterns of homology among the env genes of mammalian type C and D oncoviruses illustrates that genetic interactions between their progenitors contributed to the evolution of oncoviruses.*

Under such conditions, these viruses are passed from one generation to the next and often in an unexpressed form. The widespread distribution of oncoviruses among vertebrates implies that this intimate association has persisted through a considerable period of evolution.

The oncovirus genera have been classified by morphologic criteria (2). Defective intracisternal type A viral particles were initially observed in early embryos

cally responsible for mammary tumors of the mouse (5). Type C viruses, which are widely distributed among birds and mammals, cause leukemia and other tumors [see (6) for reviews]. The most recently described type D oncoviruses are so far limited to primate species, and their oncogenicity remains to be established (7).

In recent years, efforts have been made to ascertain the evolutionary rela-

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