The National Institutes of Health in Its Centennial Year

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The laboratory of which the National Institutes of Health (NIH) is a lineal descendant was founded in 1887. During discussions of our plans for a year-long centennial observance with members of our House and Senate appropriations subcommittees, congressional members urged us to set two specific objectives: making NIH better known to the American people, and presenting the attractions of the many roles in health-related research to young people who have not yet formulated career plans. When I was invited to prepare an article for *Science* dealing with my personal experiences as director of NIH since April 1982, it seemed an opportunity to address the same objectives for the scientific community, for in my view there is much misinformation and far too much pessimism throughout the country about the state of biomedical research and its support.

In government the budget is the message.—I. F. Stone (*1*).

THE MOST SATISFYING ASPECT OF MY FIRST 5 YEARS AS director of the National Institutes of Health (NIH) has been the sustained growth of NIH funding, amounting to 70% in dollars as appropriated (Fig. 1) and 28% in real terms. This growth has erased the 14% loss of purchasing power experienced by NIH from fiscal year (FY) 1979 through FY 1982 (Fig. 2). In each of the last 3 years the NIH appropriation has set a new record in constant dollar terms. Of the FY 1987 appropriation of $6.18 billion, 89% is expended in grants and contracts to extramural institutions and in related administrative costs. The overall growth rate of the NIH appropriation since the late 1960s has been 2% per year, even factoring in the three brief intervals when the appropriation lost purchasing power for periods of 2, 1, and 3 years as shown in Fig. 2. In only one of these years, 1970, did the actual appropriation decline from that of the previous year (Fig. 1). In all other years when purchasing power was lost, the explanation was inflation running ahead of the appropriation.

I have dwelt on the recent history of the NIH appropriation in order to gainsay the statements I hear on many university campuses, in many addresses of presidents of professional societies, and from leaders of voluntary health agencies that the NIH appropriation has been slashed, that the federal support of biomedical research is capricious, and that the future is uncertain. My experience convinces me that the opposite is true. Biomedical research has strong champions in the Executive Branch, both houses of Congress, and both parties. The appropriations subcommittees in both houses are painstaking, farsighted, and supportive. They have been unfailingly cordial to government and nongovernment witnesses alike in building a careful legislative record for the ultimate appropriations bill to be advocated in committee and on the floor.

The politics of the budgetary process is one of the first civics lessons to be learned by a new director. The process starts 2 years in advance of the target year while we are allocating and adjusting the appropriation of the current fiscal year and presenting and defending the budget of the next fiscal year. At the beginning of each new budget cycle NIH issues general instructions to each bureau, institute, and division (BID), based on guidance received from the Office of Management and Budget (OMB), the Department of Health and Human Services (DHHS), and the Public Health Service (PHS). We currently prepare 18 separate BID budget proposals, each one of which eventually becomes a separate law, and which collectively are referred to as the NIH budget, although in truth there is no such thing. The budgets prepared by the individual BIDs are integrated in the Office of the Director, NIH, adjusted to conform with policy decisions and guidance, and submitted to the PHS. There the NIH request is integrated with those of other agencies, and a tentative decision is made on the magnitude of each agency's budget. There are appeals of proposed cuts, resulting in some allowances and some denials, and then the PHS budget is submitted to DHHS where the process is repeated. Finally, it is submitted to OMB where the procedure is repeated once more. In late November or early December each year the OMB "passback" is received. Then another round of appeals with final allowances and denials takes place. With the President's decision all internal negotiations on behalf of the budget are over.

Every year before the appropriations hearings, each agency head and institute director is reminded of his or her responsibility to defend the President's budget before the Congress. Each year we receive some variant of the message perhaps best stated by President Harry S. Truman in 1946 (*2*):

> I have noticed that on several occasions certain department and agency officials have shown a tendency to seek from Congress larger appropriations than were contemplated in official budget estimates. . . . While agency witnesses before congressional committees must feel free to supply facts in answer to questions of committee members, I cannot condone the practice of seizing upon any opportunity which presents itself to indicate an opinion, either directly or indirectly, that my estimates are insufficient. . . . I shall expect [agency heads] and their subordinates to support only the President's estimates in hearings and discussions with members of Congress.

The congressional appropriations committees do not hesitate to request additional information from us, for example, the cost of 1000 or 2000 additional new and competing renewal awards or the list of clinical trials that could not be initiated within the President's allowance. We are permitted to answer factual questions of this type. Witnesses for the professional societies and various coalitions and delegations speaking in support of biomedical research provide estimates for the committees of the amounts that could be expended

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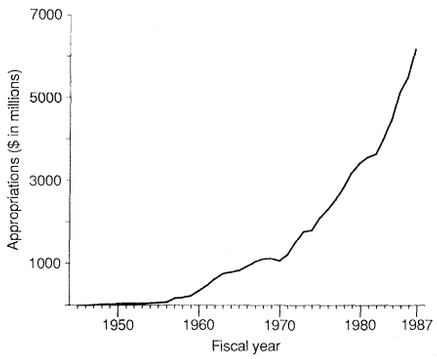

Fig. 1. Total NIH appropriations for FY 1945 to 1987. The transition quarter (TQ) and the programs that have been transferred out to other agencies have been excluded. (TQ refers to the months of July, August, and September in 1976 when the beginning date of the FY changed from July to October.) [Source: NIH Management Data Bank]

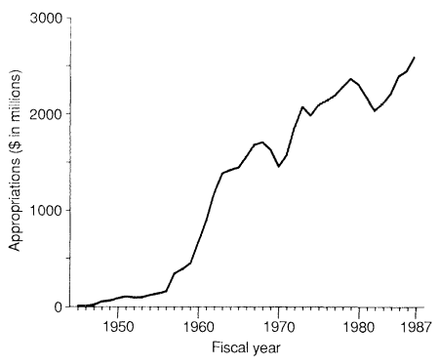

Fig. 2. Total NIH appropriations in constant 1975 dollars for FY 1945 to 1987. The constant dollar conversion is based on the Biomedical Research and Development Price Index (BRDPI). TQ and programs transferred out have been excluded. [Source: NIH Management Data Bank]

on promising high-quality research and training in the various institutes. Eventually an appropriations bill is enacted that allows NIH to support the best quality projects recommended by peer reviewers.

The Administration strategy with respect to the NIH budget seems to have been established in the early 1960s. From that time onward the President's request for NIH has always been increased by the Congress. This has been true regardless of which party is in the White House and which party is in control of the Congress. It is Washington folklore that the permissive role played by the Administration in this budgetary theater achieves a final result that conforms to Administration strategy.

Growth of the Research Enterprise

During the past 5 years we have placed explicit primary emphasis on the investigator-initiated research project grant. This policy has resulted in further growth of the total number of research project grants, primarily R01s, and program project grants (P01s). In 1970 NIH funded 10,000 such awards; in 1982 the number was 15,970; by 1986 we had reached 19,300 awards in these categories. But the total scope of NIH projects is even greater than these figures indicate. When all types of projects are considered, NIH funded more than 28,000 projects involving approximately 50,000 scientists in more than 1,600 institutions in the United States in 1986.

The number of new and competing renewal research project awards made in the past 5 years has crept steadily upward from 5,027 in FY 1982 to 6,354 anticipated in FY 1987. The stabilization policy enunciated in 1979 proposed a protection of all funding mechanisms against wide budgetary fluctuations. The full scope of the policy could not be implemented during its first few years, owing to the loss of purchasing power of the NIH appropriation mentioned above. To do so would have required that NIH depart from its historical position of regarding future year commitments as moral obligations to be met, or very nearly met, before new awards were made. With the growth of the NIH appropriations since 1982 the goals of the stabilization policy have been more nearly achieved. The numeric of 5,000 new and competing renewal awards (more recently 6,000) and 10,000 traineeships and fellowships is about all that has survived of the original broader stabilization policy, which has been criticized as setting de facto ceilings rather than floors. Nevertheless, it is my belief that these policy excerpts have given the appropriations subcommittees targets for budgetary titration in years when smaller numbers of new and competing renewal awards or training positions had been proposed.

The increase in numbers of research project grants has been a result of slow, steady budget growth and of a reduced emphasis on contracts and, to some extent, on centers. There has also been a decline in the fraction of the budget devoted to training, and this last shift reflects primarily the elimination of nonresearch training after the revision of the Public Health Service Act in 1974. The shift of funds among support mechanisms during the past 15 years is shown in Fig. 3.

Concomitant with the policy emphases mentioned above, there has been growth in the fraction of the total NIH budget devoted to basic research. In the early 1970s, this figure was no more than 45%; by 1980 it had reached 52%, and in 1986 it was 63%.

The average total cost of research project grants (competing and noncompeting awards) expressed in constant dollars has been remarkably consistent over the past 15 years (Fig. 4). Although the average total cost reached $151,847 in 1986, the constant dollar equivalent is essentially the same as in 1972. However, during this time the indirect cost component for all grant awards increased from 21 to 31.4% of the total award. Accordingly, in constant dollar terms the average direct cost of research project grants declined 13% in the past 15 years.

It is NIH policy to pay the full costs of research and training grants whenever possible. During years in which a minimum number of new and competing renewal awards is specified by law and appropriated funds for the research project grant mechanism do not cover full costs, downward negotiation is obligatory.

Peer Review and Competition

Until the mid-1970s, 70 to 75% of submitted applications were recommended for funding by study sections and national advisory councils. In a typical year NIH was able to fund about one-half of these, for an award rate of 50%. The payline (the priority score that includes 90% of awards) was frequently in the range of 225 or occasionally even 250. Most BID directors felt relatively comfortable with these statistics. During the past 5 years approximately 90% of submitted applications have been recommended for possible funding. The award rate has been 35 to 40%, and the payline for NIH as a whole, about 170 or 180. These statistical shifts have been interpreted by many as consequences of severe budgetary cuts, but as pointed out above, that conclusion is too facile. At least three other factors appear to come into play. These are increased numbers of applications, increased quality of applications, and changes in study section behavior.

In 1970 NIH received 7,570 new and competing renewal applications for R01 and P01 awards. By 1980 this number had reached 13,591, and in 1986 it was 15,858. In 1970 5% of these were amended applications, or "resubmissions"; in 1980 this figure was 15% and in 1986 it was 28% of the total. In addition, as competition has increased, more scientists are submitting multiple applications in the hope that at least one will be funded. This component has increased from 10% of applicants in 1970 to 17% in 1986. The increase in approval rates undoubtedly reflects, in part,

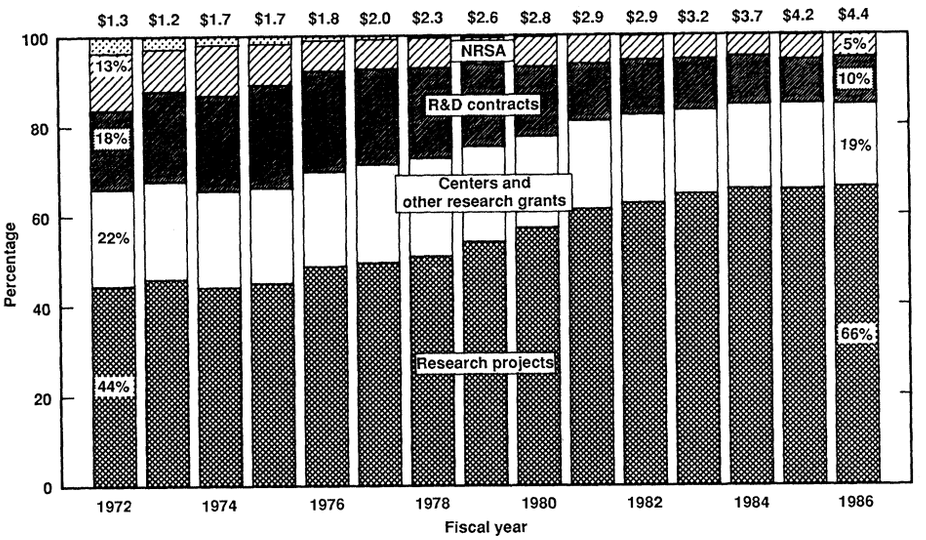

Fig. 3. Allocation of NIH extramural awards by activity for FY 1972 to 1986, showing the percentages of amount awarded; dollars are in billions. The top dotted area represents Construction and Medical Library Grants; 3% is the amount awarded for this category in 1972. The National Research Service Awards (NRSA) section includes pre-NRSA training. TQ is excluded. [Source: NIH, DRG, Statistics and Analysis Branch]

the increased quality of applications. But it may also reflect, in part, changes in study section behavior. Many more applications for which study section members express high enthusiasm are given high priority ratings now than 10 years ago. Therefore paylines are not comparable. In addition, a 38% award rate when 90% of the applications are recommended for approval (34% success rate) is not much different from a 50% award rate when 70% of the applications are approved (35% success rate).

The declines in award and success rates reflect a rate of growth of the applicant pool greater than the rate of growth of appropriations for research project grants. They do not reflect budgetary cuts. As competition for support became more intense, applicants began writing longer applications in response to more and more detailed critiques by study sections. In an effort to improve the efficiency of the awards system and to allow scientists to spend a larger fraction of their time doing research, we have set page limits on applications and have encouraged longer terms of award. In instances in which the award period recommended by a study section is shorter than the time requested and no rationale for shortening has been provided, national advisory councils have recommended restoration of deleted time. For "first-time-ever" recipients of research grants we have introduced the First Independent Research Support and Transition Award (FIRST), a 5-year award of $350,000 direct costs with provisions for carrying over unspent funds from one budget year to the next. This award should allow these new investigators to concentrate on their research for 3 to 4 years unimpeded by the pressure to submit a renewal application 18 months after the start of the project as would occur with a 3-year award. We will need to monitor the FIRST awards to determine whether they indeed encourage greater output and more creativity than were achieved with shorter term awards. We have also introduced the 5-year Method to Extend Research in Time (MERIT) award for mid-career scientists of demonstrated productivity, and we will award a 5-year extension on the basis of a satisfactory progress report rather than a complete competitive renewal application. In addition, the National Institute of Neurological and Communicative Disorders and Stroke has introduced the Senator Jacob Javits Awards in the Neurosciences, and the National Cancer Institute has established the Outstanding Investigator Awards, both of which are made for 7 years to scientists of exceptional merit and productivity. The combined effects of all these efforts have already lengthened the average term of award from 3.1 years in 1982 to 3.7 years in 1986.

The peer review system, whereby grant applications are judged first for scientific merit and technical feasibility and next for program relevance, continues to receive accolades as one of the astute inventions that has ensured quality control of NIH-supported activities and has kept this critical function chiefly in the hands of nonfederal scientists. As a system that involves human judgment it is not flawless, yet it is an innovation of which NIH can be justly proud. From time to time we hear criticisms about the system, that it is an "old boys' network," that it favors the eastern private schools, that it selects against clinical projects, or that it selects against potentially creative projects that may appear riskier than the average. Just a few of these points can be addressed here. For example, of all the Division of Research Grants (DRG) study section members serving in 1986, only 15% had had prior NIH appointments to study sections, compared with 17% of those serving in 1975. Of those members in their first year of appointment in 1986, 17.6% had had prior NIH experience, compared with 19.0% of those first appointed in 1975. With respect to geographical distribution of awards, four of the top ten institutional recipients of NIH funds are on the West Coast. Of concern to me is the number of scientists invited to serve on study sections who decline to do so. There are valid reasons for deferring, such as sabbatical year or the revision of a textbook, but some invitees have refused ever to serve.

Perhaps more than any other subgroup with special interests, the clinical investigators have felt that patient-oriented research fares less well in the application review process than it deserves. They are sometimes critical of the composition of study sections as having inadequate representation by clinical investigators. Reasons for possible underrepresentation are that a considerably higher percentage of M.D. than of Ph.D. invitees declines to serve on study sections, and that a higher percentage of M.D. than of Ph.D. members resigns early.

Training and Career Development

During the past 5 years we have supported about 10,500 trainees and fellows per year, a figure within 5% of the number recommended by the Committee on National Needs for Biomedical and Behavioral Research Personnel, which is a National Academy of Sciences committee that was mandated by the Public Health Service Act of 1974. The yield of future NIH grant applicants and awardees from among research fellows with Ph.D. or M.D. degrees or of trainees with Ph.D. degrees has been quite acceptable, but the yield

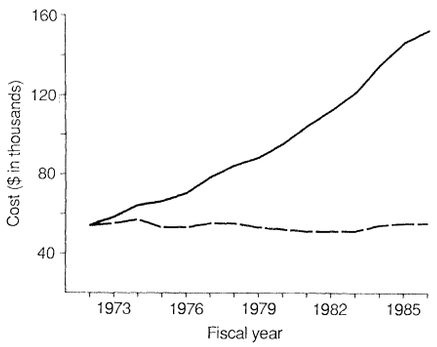

Fig. 4. Average total cost per grant for NIH research project grants for FY 1972 to 1986. Solid line shows total cost for each year; dashed line shows cost converted to constant dollars, using the BRDPI, with 1972 as the base. TQ and programs transferred out have been excluded. [Source: NIH, DRG, Statistics and Analysis Branch]

from among M.D. trainees receiving 9 months or more of PHS support has been low. Only about 20% of M.D.'s who began research training about 1970 ever applied for an NIH research award, and 10% of the total were successful (Figs. 5 and 6). We have urged program directors to select trainees more carefully, and have reminded them that the legislative basis for these awards is research training that implies a research career rather than a subspecialty practice objective. The situation is now improving, and the more recent M.D. trainees have a 30% application rate and 15% of the total have been successful.

The Medical Scientist Training Program (MSTP) has continued to receive a high priority and has been expanded slightly. We currently support 700 students in this combined degree program each year and graduate about 100 each year. Applicants who have M.D.'s and Ph.D.'s, some of whom are MSTP graduates, have the highest success rate of any category of applicants in securing NIH research support.

NIH faces a serious problem in the funding of research training programs. Tuition costs are increasing rapidly in both the predoctoral and Medical Scientist Training programs. Without substantial increases in the appropriations for these activities, we face a dilemma between continuing to pay full tuition costs and maintaining the current number of trainees. In addition, it has proved difficult to secure regular cost of living adjustments in the training category. The last major stipend adjustment was in FY 1985.

NIH continues to support an array of career development programs, the funds for which do not compete with the training programs mentioned above. In 1986 a total of 1335 such awards was funded, of which 244 were new awards. The newest member of the career development series is the Physician (or Dentist) Scientist Award, which provides support for 3 years of basic research experience plus 2 years of transitional activities at a semi-independent research level. The applicant pool has been outstanding. We currently make about 80 new appointments in this category each year.

Intramural NIH Research

Each year the President's budget contains a larger percentage increase for the intramural portion of the research program than for the extramural component. However, the outcome of the complex appropriations process discussed above has been parity of intramural and extramural increases. For example, between 1974 and 1986 the portion of the appropriation for extramural activities grew by 114% and that for intramural programs by 111%. The fraction of the NIH appropriation spent intramurally tends to drop in years of significant growth. In 1987, only 10.5% of the appropriation is being spent intramurally.

The intramural programs and scientists are subject to a rigorous peer review that differs from that accorded grant applications from extramural scientists and is more appropriate to a national laboratory. Each institute has a Board of Scientific Counselors that reviews each intramural program and scientist once every 3 to 4 years. Detailed reports are written that contain recommendations concerning levels of support. Scientific directors make periodic adjustments in allocation of space, funds, and positions based on such reviews. Scientists employed by the Clinical Center because of concomitant service roles are included in this system.

The scientific directors of NIH meet regularly to review proposals for promotion and for conversion to tenure status. Less than 10% of any cohort group of young scientists is eventually offered tenure. Our system is modeled after academic systems, and tenure must be achieved within 7 years. We now have 1,116 intramural scientists with permanent appointments, of whom 428 are physician-scientists.

Special Issues

Two issues that surfaced soon after my appointment as director were full payment of indirect costs and the creation of a separate institute for arthritis research. The President's budget for FY 1982, constructed before my appointment, contained a decision to pay indirect costs at 90% of the audited rate. This proposal had first been made by the National Advisory Eye Council in 1977. The concern was that the rate of indirect costs was growing more rapidly than the NIH budget as a whole, and therefore that indirect costs were consuming an increasing fraction of the research award. The proposal in both the original and subsequent versions was success-

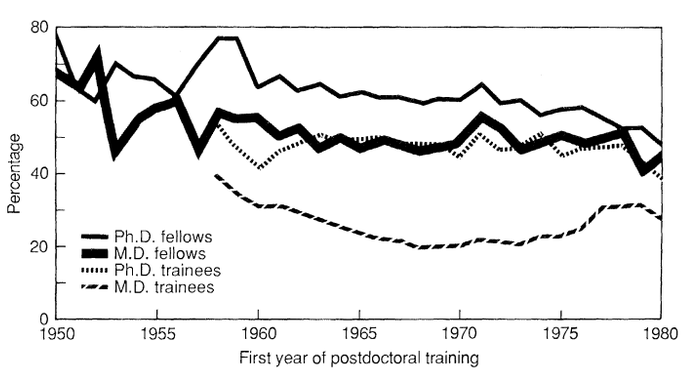

Fig. 5 (**left**). Percentage of NIH-supported postdoctorals becoming NIH grant applicants. [Source: NIH, Office of Program Planning and Evaluation (OPPE)]

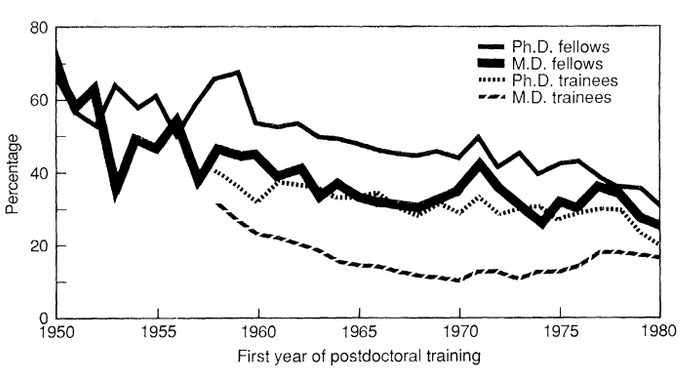

Fig. 6 (**right**). Percentage of NIH-supported postdoctorals becoming NIH grant recipients. [Source: NIH, OPPE]

fully countered by university presidents and their professional associations. In the end, the only modification insisted on by OMB was a cap on faculty salaries and related fringe benefits in the category of indirect costs entitled Departmental Administration, at 3.6% of modified total direct costs. The Health Research Extension Act of 1985, which reauthorized NIH, created a new National Institute of Arthritis and Musculoskeletal and Skin Diseases and the National Institute of Diabetes and Digestive and Kidney Diseases from the former larger National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. In addition, the act established a new National Center for Nursing Research at NIH, thereby transferring essential components of the Health Resources and Services Administration. Both units now have their own appropriations, advisory councils, directors, and core staff.

Dominating the issues confronting NIH in the past 5 years have been the acquired immune deficiency syndrome or AIDS, the use of animals in research, and, to a lesser extent, misconduct in science. More recent issues have included the mission boundaries of NIH with respect to the biotechnology industry and industrial competitiveness, mapping and sequencing the human genome, and the question of "big" versus "little" science in biology.

Since the beginning of the FY 1985 budget, AIDS has become a budgetary item in its own right and it has no longer been necessary to transfer funds from other programs to support AIDS research. The budget for AIDS research at NIH for FY 1987 is $252 million. The President's request for FY 1988 contains $422 million for AIDS research at NIH.

I have been surprised that the degree of coordination of PHS programs related to AIDS is not well known. We have had a PHS Executive Task Force on AIDS since 1984 and have been meeting regularly every other Monday for the past 2 years. In regular attendance are directors of five agencies (*3*) and key members of their staffs, the assistant secretary for health, the deputy assistant secretary for health, and key members of that staff, the Surgeon General of PHS, and members of his staff. There are biweekly reports from eight task forces plus periodic detailed issue reports. Following each meeting, Dr. Anthony S. Fauci, director of the National Institute of Allergy and Infectious Diseases, who chairs the PHS AIDS Subgroups on Therapeutic Intervention and Vaccine R&D, and who also serves as coordinator of NIH-sponsored research on AIDS, convenes the NIH AIDS Executive Committee. Thus, all agencies are kept fully informed of activities in other agencies, and the NIH committee is kept fully informed of events reported earlier that day. In addition, the many collaborations of NIH scientists with industry in drug and vaccine development are coordinated by the NIH interinstitute committees.

The use of animals in biomedical research is a pervasive and tenacious issue. The animal rights movement is well organized and politically effective. The movement includes a coalition of many groups, ranging from those who acknowledge the need for animals in research but seek higher standards for the care and humane treatment of animals, to those who want to eliminate altogether the use of animals in research. Within recent years there have been numerous break-ins and acts of vandalism involving animal facilities. We advocate high standards and humane treatment of animals in research. The *NIH Guide for the Care and Use of Laboratory Animals* (*4*) has been revised several times. The most recent revision, which went into effect in 1985, requires research-performing institutions to go beyond assurances of compliance with guidelines, to identify problem areas, and to propose a timetable for corrective action. By a secretarial decision we are now performing random site visits, which have frequently disclosed procedural or technical flaws of correctable nature, but have not disclosed gross infractions of guidelines for the humane care and treatment of animals. In the summer and fall of 1986 there was a continuous demonstration by animal rights groups on the NIH campus for more than 4 months, which included a weekly evening candlelight vigil on the front porch of the director's home. Then the demonstrators moved to the Mall area near the Capitol, and they later disbanded for the winter. The animal rights group has now reinstituted the demonstration on the Mall. In this manner they seek political support, in particular to acquire ownership or guardian status of the so-called "Silver Spring monkeys."

In December 1985 the entire meeting of the Advisory Committee to the Director, NIH, was devoted to the question of the mission of NIH. The group discussed whether NIH should explicitly consider ways to promote American industrial competitiveness. The meeting included outside guests representing biotechnology firms as well as speakers from other federal agencies, including the Office of Science and Technology Policy, which had originally raised this question. There was division of opinion on one issue only. Representatives of the smaller biotechnology firms felt there might be a role for NIH in the training of practitioners of "generic applied research," a type of process engineer who might, for example, develop scale-up procedures of general use to the industry. This point was opposed by representatives of the larger biotechnology firms who stated that the opportunity to patent a process was every bit as important as that of patenting a product. The dominant message was articulated by Dr. Theodore Cooper, vice chairman of the Board of The Upjohn Company, who stated "let NIH be NIH." His point was that the greatest service NIH could render on behalf of American industrial competitiveness was to continue to support basic research leading to discoveries that industry could translate into products, in other words to persevere in the kind of research that had given birth to the new biotechnology industry in the first place.

In October 1986 the Advisory Committee to the Director, NIH, addressed the topic of the potential role of NIH in sequencing the human genome. Once again we invited leading experts to discuss the issue. Four main conclusions were reached. First, methods for handling the vast amount of information being generated by existing sequencing activities need to be expanded and supported more adequately. Second, considerable improvement in methods is needed, for example, in the identification of restriction endonucleases that are "rare cutters" and yield large DNA fragments, in cloning of larger DNA fragments, and in methods for automation of sequencing. Third, complete physical and genetic maps of the human genome should be developed as rapidly as possible. And, fourth, sequencing of the human genome is a laudable scientific objective of potentially immense importance, but for the present we should concentrate on sequencing genes of special biological interest. There was some sentiment for sequencing one or more model chromosomes to ascertain what additional information would result. In general the committee felt that an all-out effort to sequence the human genome should await further developments. Finally, two additional important points were emphasized: namely, that projects on the human genome, including sequencing, should proceed within the usual peer review system as the best method for assurance of quality control, and that the incremental costs of the sequencing project should be met by new monies that are not competitive with other research. Perhaps if the present cost of sequencing of approximately $1 per nucleotide can be reduced by methodological developments by a factor of 10, priority issues will be less difficult to decide.

The issue of sequencing and the decision to establish a limited number of structural biology centers for the minute exploration of the AIDS virus and development of antiviral agents have generated a heightened interest in the question of big science in biology. The NIH has taken a few steps in that direction with program project grants and center awards, but the dominant mechanism remains the

investigator-initiated research project grant. By providing generous support and maximum flexibility, the Howard Hughes Medical Institute has assisted in the funding of large units with specific program orientations in more than 20 leading institutions. But the issue of the role of big science in biological research has never been seriously addressed as public policy. The topic is scheduled to receive that attention in an upcoming study to be conducted by the Institute of Medicine of the National Academy of Sciences.

Reflections

Nobelist Christian de Duve has written (*5*), "Although it is always difficult to judge one's own time in historical perspective, one cannot help the feeling that the second half of this century will be remembered for one of the great breakthroughs of human knowledge—perhaps the greatest to date, as it concerns the basic mechanisms of life." In this centennial year, scientist and author Lewis Thomas has said (*6*), "I think the general public is aware of the fact that we are in the early stages of a genuine revolution in biological science. We're beginning to understand at a deep level how living cells and tissues really work. The effects that this revolution is now having and will have in the years ahead on medicine itself are simply incalculable. All of this had its beginnings in the NIH, starting around 40 years ago. All by itself this magnificent institution stands as the most brilliant social invention of the 20th century anywhere."

REFERENCES AND NOTES

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2. H. S. Truman, "Memorandum for the Director of the Bureau of the Budget" (The White House, Washington, DC, 15 November 1946).
3. The five agencies are the Food and Drug Administration; the National Institutes of Health; the Centers for Disease Control; the Alcohol, Drug Abuse, and Mental Health Administration; and the Health Resources and Services Administration.
4. *NIH Guide for the Care and Use of Laboratory Animals* (NIH 86-23, Government Printing Office, Washington, DC, January 1986).
5. C. de Duve, *A Guided Tour of the Living Cell* (Rockefeller Univ. Press/Freeman, New York, 1984), vol. 1, p. 17.
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Research Articles

Multiple Global Regulators Control *HIS4* Transcription in Yeast

KIM T. ARNDT, CORA STYLES, GERALD R. FINK

Gene expression is dependent on the interaction of DNA binding factors with distinct promoter control elements to activate RNA synthesis. The expression of the *HIS4* gene in yeast is under two different control systems. One of these, general amino acid control, involves a DNA binding protein, GCN4, that stimulates transcription in response to amino acid starvation by binding to 5′-TGACTC-3′ sequences in the *HIS4* promoter region. A second system, the basal level control, stimulates *HIS4* transcription in the absence of amino acid starvation. The basal level transcription of the *HIS4* gene is under the control of two genes, *BAS1* and *BAS2*, which are also required for the control of purine biosynthesis. In addition, *BAS2* is required for the utilization of organic phosphates in the growth medium. Genetic mapping and DNA sequence analysis show that *BAS2* is *PHO2*, a gene previously identified as a regulator of phosphate metabolism. Direct biochemical analysis shows that the *BAS2* gene encodes a protein that binds to both the *HIS4* and *PHO5* promoters. The involvement of a single DNA binding protein in the regulation of histidine, adenine, and phosphate metabolism suggests that yeast may use a few key DNA binding proteins to coordinate the regulation of diverse metabolic pathways.

THE SEQUENCE OF ENZYME-CATALYZED REACTIONS RESULTing in the biosynthesis of amino acids is virtually identical in the yeast *Saccharomyces cerevisiae* and bacteria, but the regulation of genes that encode these enzymes is very different. In bacteria, starvation for a single amino acid leads to increased transcription of only those genes in the cognate pathway. For example, enteric bacteria respond to starvation for histidine by increased expression (derepression) of all ten enzymes in the pathway for histidine biosynthesis (*1*) but do not derepress the genes for other amino acid biosynthetic enzymes. In contrast, yeast and many other fungi respond to starvation for a single amino acid by turning on the transcription of many unrelated amino acid biosynthetic pathways (*2*). For example, starvation for histidine leads not only to derepression of the enzymes for histidine biosynthesis but also the biosynthetic enzymes for arginine, isoleucine, leucine, tryptophan, and lysine (*3*). This cross-pathway regulation, known as general amino acid control, has been shown to act at the level of transcription (*4*).

A second difference is that bacteria completely stop transcription of the genes for their amino acid biosynthetic enzymes when the amino acids are present in the growth medium. Under similar conditions of surfeit, addition of amino acids to the growth medium or the presence of large internal pools of the amino acids, yeast cells maintain high levels of amino acid biosynthetic gene expression. We call the high level of transcription in the presence of amino acid excess the basal level control.

In this article, we identify cis- and trans-acting elements that mediate the control of the basal transcription levels of the *HIS4* gene and show that these elements are distinct from those that regulate the general control starvation response. Although we anticipated that the basal level control might be specific to the histidine genes,

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