

Appropriations Subcommittee Statement on the Fiscal Year 2002 Budget

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May 16, 2001 and May 23, 2001

Mr. Chairman and Members of the Committee, good morning. I am pleased to present the President's budget request for the National Institute of General Medical Sciences (NIGMS) for FY 2002, a sum of \$1.720 billion, which reflects an increase of \$180 million over the comparable Fiscal Year 2001 appropriation.

The NIH budget request includes the performance information required by the Government Performance and Results Act (GPRA) of 1993. Prominent in the performance data is NIH's second performance report, which compares our FY 2000 results to the goals in our FY 2000 performance plan. As performance trends on research outcomes emerge, the GPRA data will help NIH to identify strategies and objectives to continuously improve its programs.

The NIGMS mission is to support basic biomedical research in disciplines ranging from genetics, chemistry, and cell biology to trauma and burn research. These studies, often carried out in organisms such as yeast, fruit flies, and bacteria, yield a fundamental understanding of the biological processes that underlie all of the functions of life. Insights into the basic behavior of living systems provide the underpinning for subsequent discoveries regarding the way these processes go awry and lead to disease.

It is becoming increasingly clear that research started with the goal of understanding unknown or poorly understood processes can immediately lead to insights about the mechanisms underlying diseases. One example is a research effort focused on a rather esoteric protein that is involved in the way cells process the instructions from DNA. As part of this study, the NIGMS-supported investigators closely examined the makeup of the protein. From its somewhat unique structure, they inferred that the protein could trigger diseases that result from the body's reaction to its own materials, a process known as autoimmunity. Interestingly, this discovery was entirely incidental to the original investigations. When the scientists tested this hypothesis, they found a strong correlation between high levels of immune response to this protein and the occurrence of a disease called systemic lupus erythematosus. This suggests that the occurrence of lupus is a consequence of some aberrant event that results in the accumulation of this protein or in the body's response, or both. We anticipate that this discovery will provide a major tool to allow accurate diagnosis of lupus as well as a clue to possible cures.

Another example of the rapid conversion of a basic understanding of biology to an understanding of disease processes is found in studies being done on copper. Although

copper is most often associated with pennies or the pipes used in plumbing, the metal is also an essential component of biological systems. However, when free in cells and organisms, even a small amount of copper can be very toxic. How does the body process copper in a way that does not cause irreversible damage? NIGMS grantees discovered proteins that "chaperone" copper and protect it from interacting with other cellular components until it reaches its proper destination. These proteins are called "metallochaperones." Some are specific for transporting copper, and some are specific for transporting other essential metals. There are several known hereditary diseases that are the result of defective copper metabolism, and these diseases frequently cause neurodegenerative disorders. It is important to understand just what is going wrong in individuals with these problems. Recent detailed studies on the mechanism of copper transport have shown how the chaperones that carry copper are implicated in the events leading to these diseases.

Finally, a major thrust in modern medicine is the attempt to understand individual responses to drugs based on a person's genetic make-up. For example, certain drugs used to treat cancer can have widely variable effects in patients, and many of these treatments have serious toxicities. On occasion, patients are literally poisoned because their bodies cannot get rid of, or "clear," a drug. For example, patients given the same dose of a commonly used chemotherapy drug, docetaxel, can have wide variations in the amount of time it takes to clear the medication. A solution to this problem may come from many years of basic studies on the behavior of a drug-metabolizing protein nicknamed "CYP3A4." This protein chews up many different drugs, including docetaxel. An NIGMS grantee has developed a simple breath test to measure the activity of CYP3A4, and a small clinical study has shown that patients who exhibit low activity of the protein suffer the greatest docetaxel toxicity. Since blood tests have previously failed to predict docetaxel toxicity, the breath test may offer a promising tool to help physicians administer this drug more safely.

Recent Research Initiatives

NIGMS has recently begun a number of major research initiatives, and I would like to describe our progress in three of them. The first is in the area of pharmacogenetics, an example of which is the docetaxel toxicity research I just described. The goal of this research initiative is to identify the genetic basis of individual variations in drug response, and ultimately to develop tools that will allow individual differences to be determined before drugs are prescribed. We have funded 9 research groups for a total of \$12.8 million in the first year. NIGMS leads the research initiative, and five other NIH components are cofunding projects. The other NIH components are the National Heart, Lung, and Blood Institute; the National Cancer Institute; the National Human Genome Research Institute;

the National Library of Medicine; and the National Institute of Environmental Health Sciences. The centerpiece of the program is the development of a database that will link gene variations to their cellular and molecular consequences, and ultimately to their physiological outcomes. Because many of these studies will initially be on defined populations we have established a Populations Advisory Group to provide advice on how to best proceed with such research. We established a second advisory group to provide a liaison to the pharmaceutical industry. Although this industry is doing a great deal of work in pharmacogenetics, much of it is proprietary. However, there are opportunities for mutually beneficial interactions, and this advisory group has been established to identify those areas.

The second major research initiative is in the area of structural genomics. The goal is to determine the three-dimensional structures of all proteins in nature, through a combination of direct experiments and theoretical analysis. Proteins are the worker molecules in every living thing. By determining the structures of proteins, we are better able to understand how each protein functions normally and how faulty protein structures can cause disease. Scientists can use the structures of disease-related proteins to help develop new medicines and diagnostic techniques.

The project was begun in September 2000 through funding nearly \$30 million worth of awards to seven consortia that total 41 participating institutions. These are pilot programs to determine the most effective approaches that will result in rapid production of detailed protein structures. It is important to note that the NIGMS research initiative is part of a world-wide activity in structural genomics that also includes several industrial participants. Together with the Wellcome Trust in the United Kingdom, NIGMS organized an international structural genomics meeting that was held in England in April 2000. A second international meeting was held in the Washington, DC area in April 2001.

The third Institute research initiative provides support to "glue together" groups of investigators working on significant problems that could not be solved if the scientists worked independently. Like the other two research initiatives, it involves the formation of a network of researchers who collaborate and share their results to speed progress toward a major goal. All of these projects reflect changes in how biomedical research is done today. There is an increased emphasis on large-scale and collaborative approaches to important scientific questions. These include studies of complex systems that involve the interaction of many components, such as all of the activities that go on within a single cell and the ways that cells and organs "talk" to each other.

Studying complex systems requires the contributions of more than just biological scientists. It requires the expertise and approaches of physicists, mathematicians,

computer scientists and engineers, all of whom are in a unique position to organize and analyze the vast amounts of data generated by studies of complex systems. To address this need, NIGMS has started programs to encourage these scientists to join their expertise and interests with those of biomedical researchers.

Research Training

NIGMS remains committed to preparing "a cadre of versatile scientists and engineers for research and teaching careers," investing in "an educational system that creates a reservoir of flexible talent for the work force," and ensuring "opportunities for the participation of all groups in science and engineering." These goals, which are quoted from a 1998 Office of Technology Assessment report on the objectives of federal training programs, mirror the Institute's interests. We accomplish these goals through a variety of mechanisms, two of which I will mention. The first is our predoctoral training programs, which have been widely recognized as a means of identifying, stimulating, and rewarding quality research training. They encourage interdisciplinary training, which is a central requirement of all of our training programs. Two recent reports, one by the National Academy of Sciences and one an internal NIH study tracking the career progression of former trainees, have noted the value of these programs in generating a highly qualified group of investigators.

In order to encourage "opportunities for the participation of all groups in science and engineering," we require that our training programs make active efforts to recruit and retain underrepresented minorities. Additionally, our Minority Access to Research Careers (MARC) Program has a strong focus on research training, primarily at the undergraduate level. In Fiscal Year 2000, we supported 644 students at 62 institutions through this program. Although this is a program of very long standing, since 1975, we have several other programs focusing on the training of underrepresented minorities in science, a number of which have been initiated in the past few years. These programs are coupled to intensive outreach efforts that are designed to improve the capabilities of institutions to participate in federal programs and to identify new approaches to bring underrepresented minorities into biomedical research.

Health Disparities

NIGMS has several special activities in the area of health disparities. One is a new collaboration with the Indian Health Service to enhance the capacity and skills of tribal organizations and Native American researchers to conduct high-quality biomedical and behavioral health research and to apply successfully for competitive research grants.

By its very nature, our pharmacogenetics research initiative will likely reveal new information linking differences in response to medicines with genes that are more common

in certain population groups. Such knowledge could contribute to a reduction in health disparities by improving doctors' ability to identify and treat individuals who have these genes. Beyond these general benefits, we are planning to offer research grant supplements for studies that are specifically related to health disparities in response to medicines.

Finally, a proposed NIGMS health disparities initiative would focus on differences between various population groups in the physiological response to traumatic injury. New information about such differences could improve doctors' ability to anticipate how trauma patients are likely to fare, especially which patients are at higher risk of developing a potentially fatal complication called systemic inflammatory response syndrome.

Conclusion

In conclusion, NIGMS sustains and develops programs that provide the research and research personnel required to ensure the continued progress of biomedical research. Our many accomplishments attest to our success in this endeavor, and our recent research initiatives should help us make even more significant contributions to the biomedical research enterprise in the years ahead.

Thank you, Mr. Chairman. I would be pleased to answer any questions that you may have.