

Appropriations Subcommittee Statement on the Fiscal Year 1998 Budget

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March 18, 1997

Mr. Chairman and Members of the Committee, good afternoon. I am pleased to present to you the programs of the National Institute of General Medical Sciences (NIGMS).

Today, I would like to highlight several recent discoveries that have emerged from NIGMS-supported basic research. They are all interesting and important in themselves, and many of them have clear implications for the understanding of disease, but I particularly want to use them to illustrate that important discoveries do not occur in a vacuum, but build on a large body of previous work. By presenting the highlights of the past year's activities, we occasionally give the impression that these discoveries appear full-blown with no previous history. Nothing could be further from the truth. In fact, the vast majority of advances are based on years of painstaking research by many investigators. Isaac Newton said that the reason he could see so far was because he stood on the shoulders of giants. All of the exciting new discoveries I am going to describe similarly have been built on the efforts of a community of scientists. It is one of the goals of the NIGMS to ensure the continuing productivity of this community.

Basic Research Discoveries

One of the benefits of NIGMS' long-term support of basic research areas is that major discoveries can emerge in unexpected places. For example, important findings are now being made in the field of protein degradation. The breakdown of materials in the cell was for many years considered to be an essential process but, until recently, it was not viewed as very interesting or even very complicated. After all, waste removal has never had much appeal. But it turns out that both in our external environment and in our internal environment, in the cell, the process of removing unwanted or obstructive material is complex, highly regulated, and of central importance in our lives. There are indications that the failure of cells and tissues to properly dispose of molecular waste may be a factor in some diseases, including possibly ALS (Lou Gehrig's disease).

A key discovery in how the cell disposes of waste came from the identification 20 years ago of a molecule that was called ubiquitin. Its ubiquitous presence in many different cells and organisms generated the name and suggested that it must play an important role in the functioning of the cell, but that role was a mystery. Over a period of many years, NIGMS investigators were key participants in deciphering the function of ubiquitin in protein degradation and the mechanism by which it operated. It was shown that ubiquitin tags doomed molecules, signaling to the cell that their time is up. The ubiquitin destruction

mechanism particularly comes into play when the cell is stressed, such as by heat or lack of oxygen. When this happens, proteins fall into disarray, unfold from their native state, and become potentially toxic unless they are removed.

Recently, the ubiquitin story has taken an interesting turn. We now know that, in addition to waste disposal, the selective and irreversible destruction of proteins by their coupling to ubiquitin also provides a means of regulating cellular processes. For example, perhaps the most significant new advance in understanding how cell division is controlled comes from the discovery this year by an NIGMS-supported investigator of a large cellular particle involved in the regulation of the cell cycle of growth and division. The particle is a complex structure whose function is to target specific cell cycle proteins for degradation, using ubiquitin as the tag to identify which proteins need to be degraded. This discovery was made using frog eggs, but comparable systems appear to exist in other organisms as well, including mammals. Understanding how this activity fits into the complex process of cell division is likely to provide further insights into the regulation of the cell cycle in normal and aberrant cells. It also demonstrates that the protein degradation system is used in the cell not only to eliminate proteins that are damaged or no longer needed, but in cell regulation as well. As one NIGMS investigator stated in a recent publication, "Protein degradation represents a chapter of cellular regulation that is just beginning to be written."

Another major accomplishment this year was the determination of the detailed atomic structure of a compound known as a chaperonin. This is the latest development in a fascinating story which is tied to one of the central problems in biology: the way protein molecules fold into their active form. It has long been known that the complex, three-dimensional folded structure of a protein can be achieved by the protein alone without any other help. However, a number of years ago a completely unexpected discovery demonstrated that compounds, called chaperonins, help proteins fold. (They were named "chaperonins" by analogy to the "chaperones" who once accompanied and protected young ladies.) Apparently, at least some proteins need a helping hand, or helping molecule, to achieve their mature folded form. As with ubiquitin, the amount of chaperonins in the cell is increased when the cell is stressed.

The utility of chaperonins in the cell's economy and the way they function have been vigorously addressed by several NIGMS-supported researchers, one of whom has determined the structure of a chaperonin in great detail. The newly determined structure shows two large rings of protein forming a doughnut-shaped cavity in which an unfolded protein sits and where it is shielded as it folds. This structure will help in understanding the mechanism of proper folding in the cell and may give clues to dealing with a number of diseases. Failures in correct folding have been implicated in retinitis pigmentosa, Tay-

Sachs disease, and cystic fibrosis. Understanding the rules that predict correct folding, as well as the process by which it occurs, may help clarify the basis of these and other diseases, and perhaps even help correct them.

The problem of protein folding is a very difficult one to solve, and a variety of approaches to understanding this process have been supported by NIGMS for many years, even when progress appeared painfully slow. In recent years the pace has picked up dramatically and major advances have been made, in part due to a continuing investment in this field over a long period of time.

Tools for Medicine and Industry

The step-by-step progress of science also yields tools that are of enormous importance both to industry and in the basic research laboratory. The evolution of the biotechnology industry is the premier example, where the tools of the trade are the basic research discoveries of the past 40 years that can be used to manipulate molecules and cells as well as to design new drugs. For example, the function of another category of proteins involved in molecular waste disposal in all living systems, the proteases, has been under study for decades, much of it by NIGMS-supported investigators. The development of the viral protease inhibitors to combat AIDS could not have happened without this detailed understanding. In addition, specific research leading to a new protease inhibitor that may offer advantages over existing drugs in this class was begun with support from the NIGMS program on the structural biology of AIDS-related molecules.

Another tool for discovery is transgenic, or knockout, mice--mice which have had genes introduced or removed. Two NIGMS investigators have been largely responsible for the development of this approach, and its applications have been numerous in drug discovery, in the development of therapies, and in detection strategies. Furthermore, transgenic technology has also been applied to new products in agriculture, including the production of pest-resistant crops. The highlighted basic research discoveries on the chart are those in which NIGMS investigators played a major role. As you can see, many of the fundamental advances that contributed to the development of transgenic organisms emerged from NIGMS-supported research. Most recently, NIGMS support has contributed to the development of mice that can be useful in understanding cystic fibrosis and high blood pressure. In general, however, as applications of transgenic mice move from fundamental studies to applications in the understanding of specific diseases, support by other NIH institutes predominates.

Interim Funding for Investigators

All of these discoveries built upon and were supported by many outstanding investigators whose individual contributions make up the body of science. It sometimes appears that progress moves seamlessly, without a hitch, because discoveries appear with such frequency. However, investigators sometimes stall in their efforts. In order to insure that temporary difficulties do not permanently cripple an otherwise productive laboratory, and to maintain momentum in the field, we have instituted a bridge funding mechanism for investigators whose applications fall just beyond our funding range. Our analysis demonstrated that in recent years close to 65 percent of investigators in the range to be supported resubmit and receive funding within one year. Consequently, we are providing a reduced level of support to individuals in this range in order to prevent a hiatus in funding from derailing their activities. This is intended to benefit the investigators by allowing them time to maintain their progress; to benefit the government by insuring that an investment in individuals and research is not lost; and to benefit science generally by maintaining the scope and breadth of effort that ultimately yield the discoveries that transform our world.

Training Programs

For progress in basic research to be maintained in the future, it is essential that we as a nation continue to produce well-trained new investigators. A recent assessment of NIGMS programs showed that, in general, the most exciting new areas are the ones that are the most highly populated by new investigators. This has elements of both cause and effect, since new investigators are drawn to these fields and their vigor and fresh ideas help to propel these exciting areas of research. The high quality of the basic biomedical research generated by these scientists is a testimony not only to their intelligence and drive, but also to the high quality of their training. Much of this is attributable to the institutional predoctoral training programs of NIGMS, which have a strong multidisciplinary focus and are widely viewed as the "gold standard" for training in basic research in the biomedical sciences. In order to insure that they remain of high quality, we conduct periodic reviews of our training programs. Currently, NIH is carrying out a large-scale review of predoctoral training programs, and NIGMS is reviewing the career progression of graduates of its Medical Scientist Training Program.

Minorities in Research

Science--and the Nation--will benefit if the new investigators we produce reflect the diversity of our population. To that end, NIGMS supports a set of programs designed to increase the number of scientists who are members of minority groups that have traditionally been underrepresented in biomedical research. These programs take a variety of approaches, including the support of research projects and research training at institutions with significant minority enrollments.

While much attention has been paid to such minority programs in recent years, it is instructive to view them through the lens of history. As you know, much of the pattern for federal support of research was set by Presidential science advisor Vannevar Bush in a 1945 report entitled *Science: The Endless Frontier*. In that document, he quotes from an advisory committee, which said, "We think we probably would not, even if we were all-wise and all-knowing, write you a plan whereby you would be assured of scientific leadership at one stroke....We think it is much the best plan, in this constitutional Republic, that opportunity be held out to all kinds and conditions of men whereby they can better themselves. This is the American way, this is the way the United States has become what it is. We think it is very important that circumstances be such that there be no ceilings, other than ability itself, to intellectual ambition." This sentiment is applicable to all of our programs, but in particular it reflects the purpose of the Minority Opportunities in Research (MORE) program, which is to insure that underrepresented minorities have an opportunity to achieve the scientific leadership of which Bush wrote.

Mr. Chairman, the Fiscal Year 1998 budget for the NIGMS is \$992,032,000. I would be pleased to answer any questions that you may have.