The National Institute of General Medical Sciences Probes Cellular and Molecular Bases of Life

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SYNOPSIS

The National Institute of General Medical Sciences has as its mission the support of research and research training in the basic biomedical sciences. Grantees of the Institute have made major discoveries about cell structure and function, the synthesis and transport of body proteins, drug actions in the body, and the body's responses to severe trauma and burns. Advances in the field of genetics—including the development of recombinant DNA technology, in which Institute grantees have been leaders—are beginning to pay off in scientists' ability to understand the growth, differentiation, and development of cells, tissues, and organs; the regulation of gene activity; and the bases of certain genetic diseases. But while much has been learned, the cellular and molecular mechanisms of many illnesses are only beginning to be understood. For this reason, the Institute's support of studies of life processes at their most fundamental levels is expected to continue to produce findings of great importance to the understanding, prevention, and treatment of human disease.

In an "op-ed" piece in The New York Times, Lewis Thomas once observed that science is commonly thought to be a "process of pure reductionism," explaining away mysteries and "concentrating all our attention on measuring things and counting them up." But true science is "not like this at all," he continued. "The scientific method is guesswork, the making up of stories. The difference between this and other imaginative works of the human mind is that science is then obliged to find out whether the guesses are correct, the stories true."

It is just such "guesswork"—the making up and testing of hypotheses about how life processes work at their most basic cellular and molecular levels—that forms the heart of the programs of the National Institute of General Medical Sciences (NIGMS), which is celebrating the 20th anniversary of its establishment in 1983.

NIGMS is the basic research institute of the National Institutes of Health, supporting a broad array of fundamental biomedical studies that lay the essential groundwork for clinical advances in the prevention, diagnosis, and treatment of human disease.

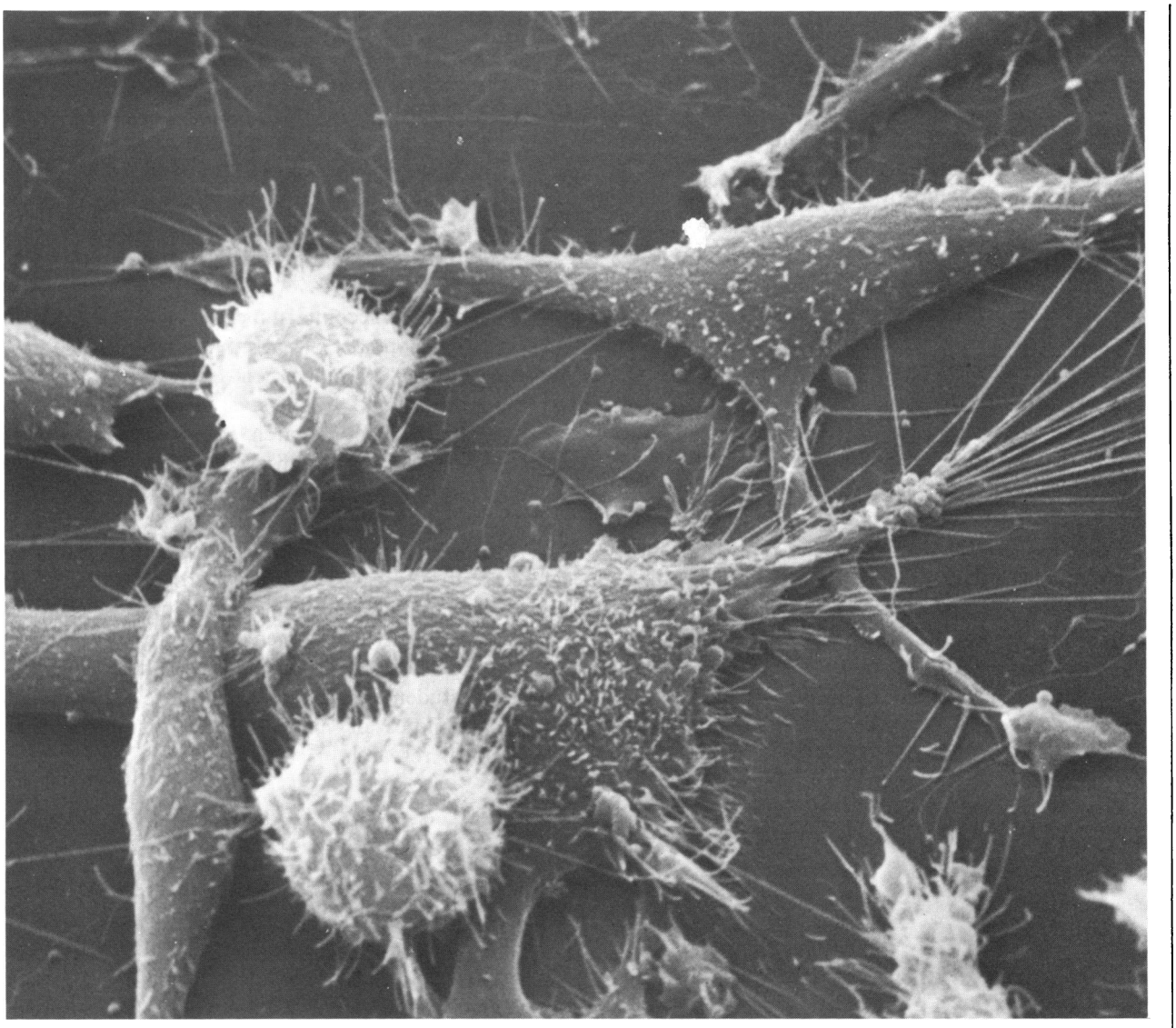
Since—unlike other NIH Institutes—NIGMS has only a tiny intramural research component, the overwhelming majority of these fundamental studies are carried out by scientists at universities, medical schools, and research institutions throughout the country. Although the Institute, on rare occasions, makes use of the contract mechanism to fund special initiatives, most studies are funded through research grants.

Research Support Programs

Of the Institute's present budget (approximately $335 million in Fiscal Year 1982), some two-thirds goes to the support of basic research in cellular and molecular biology and in genetics. Studies in these fields may yield keys to the forging of clinical weapons against threats to health across the lifespan. inborn genetic defects, cancer, diabetes, arthritis, and many other complex and still little understood disorders.

NIGMS also supports a vigorous program of research in the pharmacological sciences. Multidisciplinary studies in this area seek clearer understanding of the underlying biological mechanisms involved in the action, absorption, and metabolism of drugs in the body. The goal of this research is to pave the way for development of safer, more precisely targeted, and more effective medications.

Finally, through its physiology and biomedical engineering program, NIGMS funds research that applies the physiological, biochemical, physical, and engineering sciences to the solution of important biomedical problems. This program also funds the earliest stages of development of new instruments and techniques that facilitate biomedical research. Proj-



The development of ever more powerful microscopes has made possible an avalanche of discoveries about cells, the fundamental units of life

ects currently being supported in this area range from laboratory studies of cells and tissues to clinical investigations of severe trauma, including burns. Even in these more clinical areas, however, the emphasis lies on uncovering the basic cellular and molecular mechanisms that underlie body responses to injury and the administration of anesthetics.

Special Initiatives

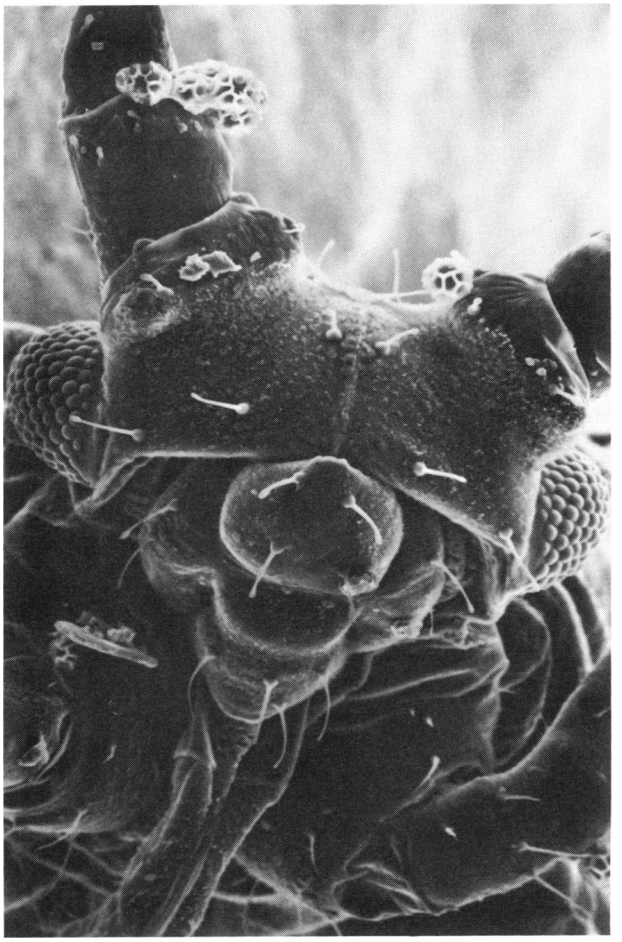
Two special initiatives of the Institute, supported through the contract mechanism, deserve particular mention.

One is the Human Genetic Mutant Cell Repository, established in 1972 at the Institute for Medical Research, Camden, N.J., to stimulate and facilitate research on human genetic disorders. The repository "banks" cell lines from patients with well-characterized genetic disorders and members of their families, from individuals with chromosomal abnormalities, and from normal persons whose cells serve as controls. Cultures from these cell lines, with supporting documentation, are provided to requesting investigators worldwide. Thus these scientists are able to study disorders by using cells with which they might not ordinarily work, or to which they would not have access in their own research settings.

A second special initiative is a recently inaugurated DNA and RNA sequence data bank for whose formation NIGMS served as catalyst. Planning for the data bank was undertaken because the next decade is expected to generate an avalanche of im-

portant information on the nature of genes. The Institute's leaders believe it is vital that this enormous mass of data be carefully collated and effectively disseminated among scientists who are working to understand how genes make human beings and other organisms what they are.

With cosponsorship by NIGMS, the National Institute of Allergy and Infectious Diseases, the National Cancer Institute, the NIH Division of Research Resources, the National Science Foundation, and the Departments of Energy and Defense, the Genetic Sequence Data Bank (GenBank) became a reality on October 1, 1982. The new data bank, under the management of Bolt Beranek and Newman Inc., of Cambridge, Mass., will store all published DNA and RNA sequences of more than 50 base pairs in length. Data distribution is primarily off-line, by means of computer-readable magnetic tapes, but limited on-line access is also available. A hard-cover compendium of data will be published annualiy.



Studies of the genetics of lower forms of life, such as this fruitfly, are teaching NIGMS-supported scientists much about the way genes work in man

Research Training Support

A special concern of NIGMS is ensuring a continuing supply of talented new investigators in the biomedical sciences. Through individual fellowships and institutional training grants, the Institute currently supports two-thirds of the predoctoral trainees funded by the National Institutes of Health and one-third of the total number of NIH-funded research trainees.

A significant accomplishment of the Institute has been its development of a graduate training program leading to the combined MD-PhD degree. For the country's best and brightest students who hope to pursue biomedical research careers, the program provides support for both medical training and the strict discipline and studies required for a doctorate in the basic biomedical sciences.

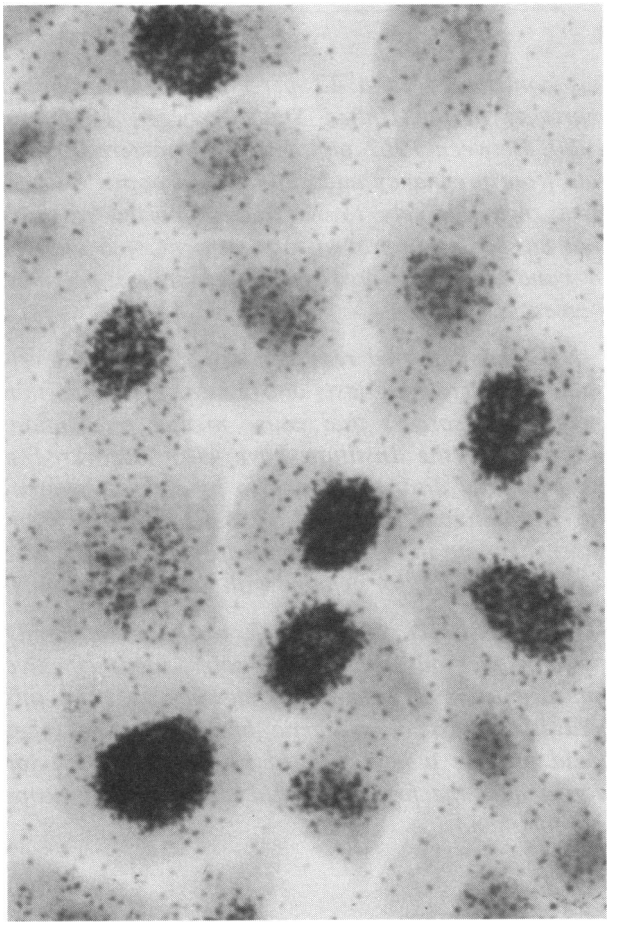
Another NIGMS training initiative, the Minority Access to Research Careers Program, seeks to strengthen research training at institutions with significant minority enrollments, to provide support for highly selected minority undergraduate and predoctoral students, and thus to increase the numbers and capabilities of minority scientists engaged in biomedical research.

Research Achievements

In his Nobel Prize lecture in Stockholm in December 1980, Dr. Paul Berg—a longtime grantee of the Institute—pointed out that "Just as our present knowledge and practice of medicine relies on a sophisticated knowledge of human anatomy, physiology, and biochemistry, so will dealing with disease in the future demand a detailed understanding of the molecular anatomy, physiology, and biochemistry of the human genome. There is no doubt," he went on to say, "that the development and application of recombinant DNA techniques has put us at the threshold of new forms of medicine."

The development of recombinant DNA technology is a striking illustration of how long years of basic research efforts often pay off in ways that would have been impossible to predict at the outset of those efforts.

Today, of course, recombinant DNA technology has well-known applications in the manufacture of important biological substances such as human growth hormone, insulin, and interferon; in the development of new vaccines; and in the prenatal diagnosis of certain genetic disorders. But, even more important, it is also a powerful research tool



Autoradiography shows darkened mouse cell nuclei, verifying successful gene transplants. Such work may eventually lead to gene therapy for human genetic disorders

whose use not only may shed light on genetic mutations, on the way tissues differentiate in the developing human body, and on the way malignancies arise, but also may eventually make possible the treatment of certain now-incurable genetic diseases.

Recombinant DNA technology was developed by scientists carrying out basic studies in genetics—the majority of them with NIGMS support. Two of these scientists—Stanford University's Dr. Berg and Dr. Walter Gilbert, of Harvard—shared the 1980 Nobel Prize in Chemistry for their achievements with respect to recombinant DNA and DNA sequencing. (More than 20 NIGMS grantees have won Nobel honors since the Institute's establishment.)

But while the development of recombinant DNA technology has gained the lion's share of popular attention, many other advances have also played critical roles in the biological revolution that has shaped the world today. These advances, funded in large part by NIGMS, include elucidation of the fundamentals of nucleic acid structure and function, clarification of the mechanisms by which genetic information is expressed and transmitted, development of knowledge about transposable genetic elements (so-called jumping genes), elucidation of the fine structure of cells and the functions of cell organelles, discoveries about the synthesis and transport of body proteins and the structure and function of cell membranes, and elucidation of the mechanisms of drug metabolism in the body.

The successful development of an artificial skin that surgeons can use to close extensive burn wounds has been a particularly gratifying application of fundamental knowledge, gained from studies in cell biology, to the solution of a serious clinical problem. The product of more than a decade of intensive collaborative effort by NIGMS-funded researchers at Massachusetts Institute of Technology and Harvard University, the manmade skin has been successfully grafted on a number of patients with burn wounds covering 50 percent to 90 percent of their bodies. The patients showed no evidence of inflammation, infection, or rejection of the artificial skin grafts, which were eventually replaced by grafts of the patients' own skin. Moreover, wounds that had initially been closed with artificial skin showed less scarring and contracture than are usually seen with conventional grafting methods.

A new Stage II version of the manmade skin has been successfully tested on animals and will shortly be tried on burn patients. This refined version will be seeded with living cells—taken from an unharmed area of the patient's own skin—that can regrow as epidermis over the burn wound, under the protection of the manmade, biodegradable covering.

The Road Ahead

As NIGMS marks its 20th anniversary, it is surely appropriate to look back with pride at the achievements for which the Institute's supporting role has been critical. But it is equally appropriate to remember that the cellular and molecular bases of many illnesses are only beginning to be understood.

Indeed, it is because so *little* is known that studies of basic cellular and molecular mechanisms frequently turn up findings of great importance to the understanding, prevention, and treatment of human disease. For this reason, NIGMS remains committed to support of the kinds of basic, untargeted research that have led to the advances outlined previously—and that can be expected to build on this base to produce still greater achievements.