

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

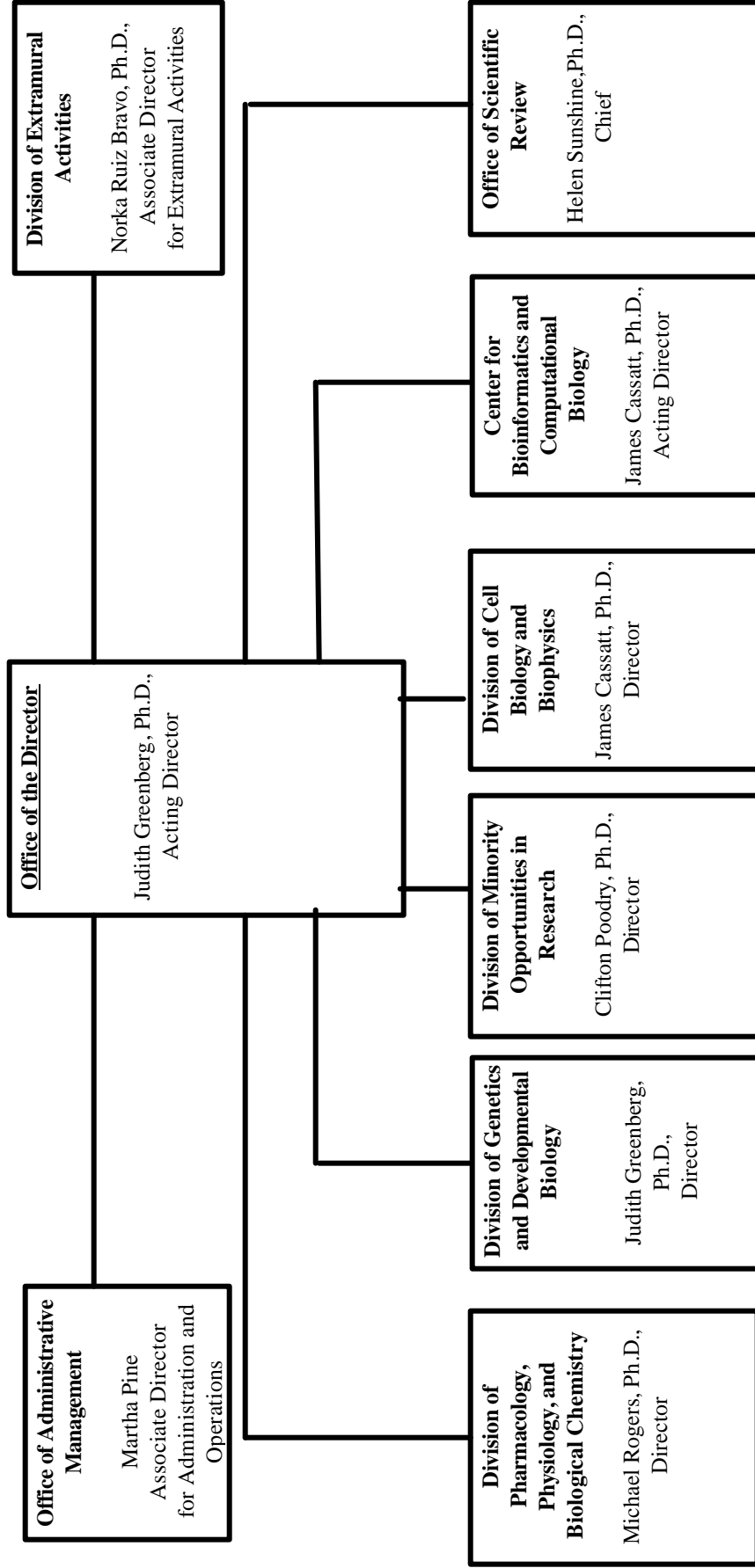
National Institute of General Medical Sciences

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NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of General Medical Sciences

For carrying out section 301 and title IV of the Public Health Service Act with respect to general medical sciences, *\$1,923,133,000*.

**National Institutes of Health
National Institute of General Medical Sciences**

Amounts Available for Obligation 1/

Source of Funding	FY 2003 Amended		
	FY 2002 Actual	President's Budget	FY 2004 Estimate
Appropriation	\$1,725,263,000	\$1,874,243,000	\$1,923,133,000
Enacted Rescissions	(464,000)	(0)	---
Subtotal, Adjusted Appropriation	1,724,799,000	1,874,243,000	1,923,133,000
Real transfer to:			
Other HHS Agencies through Secretary's one-percent transfer authority	(1,863,000)	(0)	(0)
Comparative transfer from:			
Fogarty International Center for International Services Branch	0	0	0
Comparative transfer to:			
Office of the Director for program changes	(180,000)	(195,000)	(0)
National Institute of Biomedical Imaging and Bioengineering	(25,000,000)	(25,000,000)	(0)
Subtotal, adjusted budget authority	1,697,756,000	1,849,048,000	1,923,133,000
Unobligated Balance, start of year	0	0	0
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	1,697,756,000	1,849,048,000	1,923,133,000
Unobligated balance lapsing	(46,000)	---	---
Total obligations	1,697,710,000	1,849,048,000	1,923,133,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2002 - \$231,000 FY 2003 - \$250,000 FY 2004 - \$250,000

**Justification
National Institute of General Medical Sciences**

Authorizing Legislation: Section 301 and Title IV of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority:

FY 2002 Actual		FY 2003 Amended President's Budget		FY 2004 Estimate		Increase or Decrease	
<u>FTEs</u>	<u>BA</u>	<u>FTEs</u>	<u>BA</u>	<u>FTEs</u>	<u>BA</u>	<u>FTEs</u>	<u>BA</u>
165	\$1,697,756,000	166	\$1,849,048,000	163	\$1,923,133,000	(3)	\$74,085,000

This document provides justification for the Fiscal Year 2004 research activities of the National Institute of General Medical Sciences (NIGMS), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2004 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

During its 40 years of existence, NIGMS has become known as the "basic research institute," the "cell institute," the "training institute," and the "Nobel Prize institute." All of these labels are apt. NIGMS supports basic biomedical research that provides the foundation for advances in understanding health and disease. Many of these studies illuminate how cells work, which could lead to the ability to predict and control cellular activity. The Institute has a major commitment to training future scientists, with an emphasis on multidisciplinary studies. And its grantees are often recognized with the highest honor in science, the Nobel Prize.

Two NIGMS grantees received Nobel Prizes in 2002. The prize in physiology or medicine went to Dr. H. Robert Horvitz of the Massachusetts Institute of Technology for his discovery of key genes controlling programmed cell death. This process is essential for embryonic development, and improperly controlled cell death plays a role in illnesses such as AIDS, Parkinson's disease, stroke, and cancer. Dr. Horvitz did his work using an important model system for genetic research, the roundworm *C. elegans*. One of his most significant achievements was showing that humans and *C. elegans* have similar cell death genes. In addition to funding Dr. Horvitz's research for the past 25 years, NIGMS has a long history of supporting the use of *C. elegans* and other non-mammalian model systems for biological research.

The Nobel Prize in chemistry went to Dr. John B. Fenn of Virginia Commonwealth University for his refinement of a technique called mass spectrometry, making it possible to analyze large molecules in biological samples. Dr. Fenn's technique is now widely used for blood and urine testing as well as in basic research studies. By permitting the quick, simultaneous analysis of hundreds of proteins, the technique also helped launch the rapidly growing field of proteomics. This prize underscores the value of NIGMS funding for new tools and techniques that advance health research, which has included extensive support of the development and refinement of mass spectrometry.

Increasingly, NIGMS is becoming known by another label: a "cutting-edge institute" that develops creative new programs to meet changes in science and in the needs of the scientific community. In recent years, the Institute has established such innovative activities as "glue" grants to promote large-scale, collaborative research to answer major biological questions, including how cells move and communicate. NIGMS also led the creation of a network of scientists to study how genes influence the body's response to medicines. This knowledge may lead to "personalized medicines" in the not-too-distant future.

Another important NIGMS investment is its Protein Structure Initiative, a program to determine the structures of thousands of proteins in a fast, automated way. Proteins are the workhorses of the cell, and their shapes tell us a great deal about ways to control their functions. The Institute is also at the forefront of a major shift in science from studying the characteristics and functions of individual biological molecules to investigating how these molecules interact. Central to this effort is modeling and predicting the behavior of complex biological systems by drawing on the expertise and tools of quantitative scientists--including mathematicians, physicists, computer scientists, and engineers--as well as those of biologists.

Among the Institute's newest activities is a program to increase understanding of the basic biology of human embryonic stem cells, which show promise as a valuable model system for biomedical research. Another program combines approaches from evolutionary science and computational biology to understand and predict the development and spread of infectious diseases, including possible bioterrorism agents. Several NIGMS grantees contributed their expertise to fighting the anthrax attacks of the fall of 2001 by modeling the spread of anthrax-tainted letters and the impact of antibiotic use, shedding light on how the anthrax toxin works, and identifying ways to interfere with its activity. Two of these studies are described in the following sections.

Story of Discovery: Evolving Microbes

Deadly viruses like HIV or Ebola and menacing bacteria such as those that cause strep throat infections are true chameleons of nature. These and other disease-causing microorganisms adapt to a seemingly unlimited array of conditions by making rapid genetic changes. This microbial evolution outpaces the evolution of the human species by millions of years and creates a moving target for drug designers. By analyzing the evolution of infectious organisms, researchers now have a leg up on how to outwit potentially dangerous microbes. This understanding has helped explain why some microorganisms cause disease and some do not, and it is helping scientists develop

life-saving treatments and vaccines. The predictive power of this relatively new brand of research may also aid in preventing disease outbreaks.

Over the past decade, an explosion of knowledge about the genetics of viruses, bacteria, and fungi has launched a new field that marries evolutionary biology and the study of infectious disease. Sophisticated mathematical and computer-based approaches are helping researchers weave the two areas together. NIGMS has supported discoveries in this field that have clear relevance to public health. Some of these findings are highlighted below. They reflect advances in knowledge about the genetic gymnastics of several different microbes, including *Streptococcus pyogenes* (*S. pyogenes*, one form of strep bacteria), influenza (the flu), and *Helicobacter pylori* (*H. pylori*, the bacterium that is the leading cause of digestive tract ulcers), as well as about the serious problem of antibiotic drug resistance.

Strep

S. pyogenes is a master of infection, causing a spectrum of illnesses from strep throat and tonsillitis to scarlet fever, toxic shock syndrome, sepsis, and necrotizing fasciitis (“flesh-eating disease”). Humans are the only known host for this group of bacteria. Scientists believe that *S. pyogenes* can cause so many different health problems because its set of genetic instructions varies widely among strains. Subtle genetic changes in these strains permit the bacterium to thrive in a variety of body locales, such as the throat or skin. Using mathematical approaches coupled to genetic studies, Dr. Debra E. Bessen of the Yale University School of Medicine has pinpointed several genes that permit this microorganism to live well in either the skin or the throat, but not in both. These genes may be attractive targets for the development of new drugs.

Flu

The best way to fight infectious diseases is to prevent them, and a key element of prevention is the ability to predict disease outbreaks accurately. Mathematicians have joined forces with evolutionary biologists and infectious disease specialists to develop powerful ways to track the evolution of viruses such as influenza A, the constantly changing strain usually blamed for major flu epidemics. A multidisciplinary team of scientists that included Dr. Simon A. Levin of Princeton University recently analyzed a computer database containing DNA sequences representing 560 samples of different flu viruses from the last 16 years. The team discovered patterns of genetic changes that may allow better prediction of which strains of flu will emerge in the coming season. If accurate, such predictions will lead to more effective flu vaccines, preventing illness and saving many lives each year.

***H. pylori* and Anthrax**

A recent study by a biologist-mathematician team uncovered important scientific knowledge about *H. pylori*. Dr. Martin J. Blaser of the New York University School of Medicine and Dr. Glenn F. Webb of Vanderbilt University used mathematical modeling to track different genetic variants of *H. pylori* over time. After creating their model, the researchers checked its accuracy by testing it in animal experiments. The results indicate that *H. pylori*, which often lives nearly indefinitely in its host, undergoes constant evolutionary change through indiscriminate mating between different genetic strains, all within the infected host. Dr. Blaser’s research also had another unexpected benefit: Modeling the infectious behavior of *H. pylori* provided important clues to how the deadly bacterium *Bacillus anthracis*, which causes anthrax, could be spread through the U.S. postal system. Using similar techniques to the *H. pylori* research, Drs. Blaser and Webb mathematically simulated the outbreak of mail-borne anthrax in the fall of 2001 and concluded that all the known cases of infection could be traced back to contamination through the mail from only six original envelopes. The scientists also concluded from this mathematical model that the rapid and widespread use of antibiotics probably averted many additional, potentially deadly infections from this outbreak.

Antibiotic Resistance

The ability of bacteria to evolve rapidly enables them to escape the effects of antibiotics designed to kill them. Antibiotic resistance is an increasing problem throughout the world. Recently, scientists using computer simulation have been able to predict genetic changes that allow bacteria to resist antibiotics. Dr. Barry G. Hall of the University of Rochester simulated microbial evolution in the laboratory by choosing certain bacterial genes and determining through experiment which of the genes are most susceptible to changes that cause resistance to commonly used antibiotics. Remarkably, Dr. Hall and his coworkers found that their modeling techniques match the bacterial evolution that occurs in nature. The researchers' novel approach is likely to have practical value in enabling pharmaceutical companies to create drugs for which bacteria have no evolutionary escape route. Such an approach could also allow drug developers to anticipate how long an antibiotic will be useful: a few months, a year, or a decade. The ability to perform such analyses during the development phase will help to prevent the failure of antibiotic medicines in real-life use.

Science Advances

Some of the major research advances made recently with NIGMS support are described below. Although only the lead scientists are named, coworkers contributed significantly to these achievements.

Understanding Life Processes at the Molecular Level

A Protein to Tie Up Loose Ends

Our genetic material is under constant assault, bombarded by a variety of sources that break the long strands of DNA in our chromosomes. The culprits? Cosmic radiation and highly reactive molecules, called free radicals, found in sources ranging from smog to nitrite food preservatives. Breaks in DNA can cripple cells' ability to make the proteins they need to survive and--if passed on to subsequent generations of cells--can lead to a host of diseases, including cancer. Cells have repair mechanisms that rejoin broken DNA strands, but sometimes the genetic coding for these repair mechanisms is defective. When this happens, cells cannot manufacture the repair proteins they need.

A very serious immune system disorder, severe combined immunodeficiency disease, affects people who inherit a particular type of genetic defect in their cellular repair mechanisms. This disease was featured in the 1976 television movie, *The Boy in the Plastic Bubble*. Researchers located the gene responsible for about 15 percent of severe combined immunodeficiency cases and named it *Artemis*, after the Greek goddess for the protection of children. But the protein product of the *Artemis* gene was unknown.

Dr. Michael Lieber of the University of Southern California's Keck School of Medicine has now identified the Artemis protein and described how it works. He discovered that it is an enzyme essential for repairing breaks in DNA by trimming away the frayed tails left at randomly broken DNA ends. Other proteins then rejoin the DNA segments. This housekeeping activity is crucial for survival in all cells, and those lacking the Artemis protein quickly accumulate fragmented chromosomes as more and more of the DNA strands within the chromosomes break. Dr. Lieber also discovered that Artemis has an additional function within specialized immune system cells

called lymphocytes. These cells use Artemis to shuffle the DNA that makes up immunity genes in order to generate the wide range of antibodies and other molecules needed to combat many different bacteria, viruses, fungi, and other threats. Without the Artemis protein, these immune system molecules fail to develop, leaving the body vulnerable to any number of diseases and infections.

A drug that temporarily inhibits the activity of Artemis could boost the effectiveness of radiation therapy for cancer by blocking the ability of cancer cells to repair themselves after radiation damage. With this goal in mind, Dr. Lieber plans to screen for drugs that inhibit the Artemis protein. Beyond this potential application of Dr. Lieber's research, the new knowledge he has provided about Artemis adds to our general understanding of DNA repair mechanisms, a process vital to the survival of our cells.

Bacteria Study Sheds Light on Cell Communication

Scientists have known for years that bacterial cells use molecules on their surfaces called receptors to help them sense and respond to their environment. Somehow, bacteria are able to sense vanishingly small amounts of an environmental signal--like a nutrient--and then amplify the signal significantly to prompt a quick reaction, such as moving toward food or away from danger. Until recently, scientists were mystified as to how this signal amplification takes place.

Dr. Laura L. Kiessling of the University of Wisconsin, Madison, has uncovered a system that bacterial cells use to sense, analyze, and deliver signals to the cell interior. She chemically manufactured multi-pronged molecules that would attach not to one, but to an entire group of cell-surface receptors called chemoreceptors. These synthetic molecules allowed Dr. Kiessling to control and study cell responses such as bacterial cell motion. She found that bacterial chemoreceptors that sense food and other chemicals in a cell's environment team up in groups to amplify a signal and orchestrate an appropriate response. Chemoreceptors do this, she discovered, by snuggling together on the cell surface into a lattice-type structure that acts sort of like a molecular "nose."

The work may allow researchers to create chemically treated surfaces that repel dangerous microbes on contact. Better knowledge of cell communication among bacteria could also help scientists learn how to dismantle complex "neighborhoods" of communicating bacteria called biofilms, which can coat the surfaces of catheters and other medical devices. Biofilms play a role in a variety of illnesses, including cystic fibrosis and Legionnaire's disease, and infections caused by these bacterial complexes are notoriously resistant to antibiotics. Researchers suspect that human immune cell receptors work in teams, similar to the behavior of *E. coli* bacteria demonstrated in this study. Further investigations might be able to confirm these suspicions and advance progress in understanding the human immune system.

Cells That Live and Let Die

In the developing nervous system, cells play their own version of television's popular *Survivor* series with a bit of a twist. Rather than being voted off by their teammates, some cells in the

developing nervous system will automatically die unless adjacent cells select them to live. Determining how this process works is important, because brain cells that fall short of their normal life spans are associated with such devastating diseases as Parkinson's and Alzheimer's. More than half a million Americans have Parkinson's disease,¹ while Alzheimer's disease affects an estimated 4 million Americans.² On the other hand, many cancerous tumors result in part from cells' escaping the mechanisms that determine when they should die.

Dr. Hermann Steller of Rockefeller University has identified an important molecular pathway that nervous system cells use to signal neighboring cells to survive. He also identified how the surviving cells stimulate the development of cells that transmit messages within the nervous system. Dr. Steller used fruit fly embryos for his research, but similarities between fruit fly and human cells mean that his findings could provide a model for studying cell death and survival in humans.

This research may one day lead to new treatments for Alzheimer's, Parkinson's, and other degenerative neurological diseases. Such therapies might keep brain cells alive by providing the necessary "survive" signal. With a greater understanding of cell death and survival, scientists also may be able to devise new ways to kill cancer cells. Since one of the traits of cancer is unchecked cell growth, activating the cell death program in cancer cells could halt this disease.

Basic Studies Illuminate Disease Mechanisms

Anthrax Toxin Structure Solved

Three toxic proteins are critical for the deadly effect of the now-familiar anthrax bacterium, *Bacillus anthracis*. One of these toxins, called protective antigen, allows the other anthrax toxins to enter cells. The second, lethal factor, destroys immune system cells that normally defend the body. This process releases inflammatory molecules that can cause sepsis-related shock and death. The third toxin, edema factor, causes potentially lethal swelling and fluid buildup in the body. By itself, edema factor can be deadly. It also makes lethal factor 10 to 100 times more potent.

Scientists already knew the shape and features of the anthrax protective antigen and lethal factor toxins. This year, by solving the structure of edema factor, Dr. Wei-Jen Tang of the University of Chicago completed the detailed, three-dimensional picture of the third and final piece of this deadly triumvirate. Edema factor is harmless until it binds to a molecule called calmodulin. The

¹*Parkinson's Disease--Hope Through Research*, National Institute of Neurological Disorders and Stroke, NIH Publication No. 94-139, September 1994 (updated at http://www.ninds.nih.gov/health_and_medical/pubs/parkinson_disease_htr.htm, July 2001).

²*Alzheimer's Disease Fact Sheet*, Alzheimer's Disease Education and Referral Center, NIH Publication No. 01-3431, September 2001.

new study reveals that edema factor changes its shape dramatically when it binds to calmodulin, creating a pocket in which it carries out the chemical reactions responsible for its toxic effects.

Because it contains a deep, narrow pocket, the activated edema factor appears to be an ideal drug target. By designing a small molecule to clog this pocket, pharmaceutical scientists may be able to develop a drug to combat anthrax infection. Other bacterial diseases that rely on proteins similar to edema factor include whooping cough and a hospital-acquired infection caused by *Pseudomonas aeruginosa*. The structure of edema factor--which grew out of basic research on cell communication--will provide a good starting point for designing new drugs to treat these other diseases as well.

Cells on the Move

Cells move around constantly in the body. This movement is critical for normal processes like the development of embryos and the proper functioning of the immune system. But since errant cell movement is a feature of many diseases, scientists are working to understand the fundamental--but very complicated--biology of the movement of cells. For example, the transformation of a stationary cell into an invasive one is a crucial step in metastasis, the movement of cancer cells throughout the body. While scientists know a lot about how cancer cells travel through the lymphatic system, little is known about how cells dislodge from an original tumor and move elsewhere in the body.

Using fruit flies as a model system to investigate ovary development, Dr. Denise Montell of The Johns Hopkins University School of Medicine figured out how kickstarting a cell-signaling pathway prompts a group of normally stationary cells lining the ovary to travel in the direction of an oocyte (a future egg). Employing clever tools of genetics, she discovered how three molecules work together to trigger a communication relay called the JAK-STAT pathway. Scientists already knew that this signaling pathway plays a role in controlling cell division and cell survival in both flies and humans, and they knew that the relay system is “on” all the time in many cancers. The new work reveals that the JAK-STAT pathway can also convert cells that were “sitting still” into invasive ones that move around.

Understanding how ovarian cells mobilize in fruit flies may help explain how human tumor cells become metastatic. The research is important in revealing a biochemical basis for a poorly understood step in cancer progression. The scientists are now examining ovarian cancer tissue to see if the JAK-STAT pathway can control the movement of human cancer cells.

Stop Cell Death, Help Treat Sepsis?

A body-wide syndrome triggered by sepsis infection is a leading cause of death in hospital intensive care units, striking 750,000 people every year and killing more than 210,000.³ The most severe form of sepsis occurs when bacteria leak into the bloodstream, spilling their poisons and leading to a dangerous condition called septic shock. Blood pressure plunges dangerously low, the heart has difficulty pumping enough blood, and body temperature climbs or falls rapidly. In many cases, multiple organs fail and the patient dies. In recent years, researchers have come to realize that the intestinal tract plays an important role in sepsis. Scientists have found that after a severe infection or injury, cells in the intestinal lining die off in a process called apoptosis.

Researchers now suspect that blocking apoptosis in the intestines of critically ill patients may help prevent death from sepsis. The strategy looks promising in mice, suggesting that it may someday be effective in people. Dr. Craig Coopersmith of Washington University in St. Louis genetically engineered laboratory mice to produce large amounts of a cell death-blocking protein called bcl-2 in their intestines. He then exposed the experimental mice to the bacterium *Pseudomonas aeruginosa*, which can cause sepsis in susceptible people. Remarkably, 40 percent of the mice with bcl-2 escaped infection and survived, compared to only 4 percent of the mice without bcl-2.

This study suggests that minimizing apoptosis in intestinal cells may prevent death in people with sepsis. Effective prevention and treatments are urgently needed, since the death rate from sepsis has climbed more than 90 percent over 20 years,⁴ costing the nation \$16.7 billion per year.³

New Approaches to Therapeutics

Studies of Iron-Pumping Bacteria May Lead to New Antibiotics

The war against drug-resistant bacteria continues to intensify. A few years ago, hospital workers detected strains of *Staphylococcus aureus*--the primary cause of hospital-acquired infections--that are resistant to every known antibiotic medicine. Major killers worldwide such as pneumonia, malaria, tuberculosis, cholera, and gonorrhea are progressively defying all treatment options. And with the ease of international travel, a drug-resistant microbe originating overseas can arrive on U.S. shores within 24 hours. To stem the rising tide of drug-resistant bacteria, scientists are scrambling to design new drugs.

³Angus DC, Linda-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med* 2001;29:1303-10.

⁴Murphy SL. Deaths: final data for 1998. *Natl Vital Stat Rep* 2000;48:1-105.

To become and remain infectious, many disease-causing bacteria literally “pump iron.” That is, they pump the metal from their hosts’ bodies into their cells using proteins in their outer membranes that open and close. These transporter proteins are found in dangerous bacteria such as those that cause cholera, dysentery, blood poisoning, meningitis, and plague.

This year, Dr. Dick van der Helm of the University of Oklahoma, Norman, revealed the structural details of one iron-pumping transporter protein called FecA. According to the new three-dimensional image, FecA looks like a barrel that is open on both ends and plugged in the middle. After iron (and a special carrier protein) enters from the top, this entrance closes behind it, the FecA plug opens, and the iron passes through into the bacterial cell.

A better understanding of how disease-causing bacteria become infectious may lead to new drugs to treat such diseases. Scientists may be able to design novel antibiotics that physically mimic the natural iron carriers. The idea is that the transporter proteins would latch onto the drugs, “think” they contain iron, and actively pump them into bacteria. Once inside, instead of arming the bacteria for infection, the drugs would kill the bacteria. Now that scientists know how the transporter proteins operate, they can try various ways to manipulate them to admit drugs or to keep out iron. More generally, the study improves our understanding of how bacteria obtain essential nutrients.

Cell's Sugary Coating Zaps Cancer

Heparin is an inexpensive medicine that doctors use to “thin” blood and stop it from clotting. The medicine is widely prescribed to treat dozens of health conditions in which blood clotting can be especially dangerous, such as stroke and many heart disorders. Heparin and other complex sugar molecules like it cloak the surfaces of nearly all the cells in our bodies, as well as the surfaces of cancer cells. Recently, scientists have recognized the potential importance of a cell’s sugar “coat” in the development of disease.

Researchers studying the biochemistry of heparin and other natural sugar molecules may have unearthed a potential new use for heparin: treating cancer. To examine the possible role of heparin in cancer, Dr. Ram Sasisekharan of the Massachusetts Institute of Technology injected an enzyme called heparinase into mice with tumors. Heparinase enzymes cut up complex sugars, generating molecules of heparin. These enzymes exist in several forms, each of which cuts complex sugar molecules in different places and generates different “trimmed” forms of heparin. Dr. Sasisekharan found that one particular heparinase treatment slowed the growth of skin, lung, and prostate tumors in the mice. Surprisingly, however, another member of this heparinase enzyme family actually sped tumor growth in mice. Dr. Sasisekharan suspects that the sugary molecules interact with cancer-controlling proteins circulating in the blood and on the surfaces of other cells, and that slightly different forms of heparin can have very different effects on cell growth and cancer.

Further studies are needed to sort out the cancer-slowing and cancer-promoting properties of heparin. If the findings in experimental mice can be repeated in people, the appropriate form of

heparin could potentially be put to use quickly as a cancer treatment, since the medicine has already been demonstrated to be safe for human use and has been approved by the Food and Drug Administration. The results also illuminate a basic mechanism that may contribute to the development of diseases like cancer.

The Side Effects of a Misspelling

Many people are surprised to learn that medicines may only work properly in a subset of the people who take them. If a drug doesn't work properly, a person may experience side effects or no therapeutic effect at all. What's more, whether or not people develop side effects--and if they do, which ones they'll have--varies widely. While many factors such as diet and environment can help account for this variability in drug response, a key determinant is genes. A field of research called pharmacogenetics aims to unravel some of the biological reasons why people react so differently to medicines. NIGMS has made a significant investment in this field and has spearheaded the formation of the Pharmacogenetics Research Network. Pharmacogenetics scientists have found many examples where a change in one or a few of the DNA "letters" that spell out genes can cause people to have different responses to medicines.

In a recent case, Dr. Mark J. Ratain of the University of Chicago, who is a Pharmacogenetics Research Network investigator, identified a group of people who develop a bad reaction to a chemotherapy drug called irinotecan, which is used to treat a variety of solid tumors. He discovered that some people have two extra letters in the gene that instructs the body to make a protein that metabolizes irinotecan and other drugs. Because of this tiny genetic difference, these people have less of the protein that breaks down irinotecan and thus have much higher levels of the medicine in their blood than most people given the same dose. When people with the genetic misspelling took irinotecan, their white blood cell counts dropped dramatically, making them more likely to develop a potentially life-threatening infection. The same people also experienced severe diarrhea, which can cause dangerous fluid loss in people who are already very sick.

Future genetic tests that screen for bad reactions to drugs such as irinotecan may help avoid toxic side effects and help determine the appropriate dose of chemotherapy drugs. Studies are under way to identify additional gene misspellings that could help physicians predict how patients will respond to irinotecan and other medicines.

New Initiatives

Modeling the Emergence and Intentional Release of Infectious Diseases

As concern grows over bioterrorism and the emergence of new infectious diseases, NIGMS is designing a program to quantify and address this threat using computational approaches and mathematical modeling. The models will develop scenarios for the spread of microbes, the rate of disease progression in individuals, the effectiveness of different treatment or prevention strategies, and the community response to new infectious diseases. Predictions based on the

models will provide policymakers with critical information that will help them respond quickly to the threat of a new disease or bioterrorism attack.

Stem Cells as Model Systems

In June 2002, NIGMS held a meeting on the basic biology of mammalian stem cells to bring stem cell researchers and basic biologists together to better understand the unique properties of embryonic stem cells (ESC) and to consider how ESC might be used to advance fundamental research. The workshop highlighted many opportunities to use human ESC to study important biological problems and identified activities that are needed to investigate the use of human ESC as a model system.

As a result of that meeting, NIGMS created a program to fund exploratory centers that would include core facilities for the growth and maintenance of human ESC, research on the properties of human ESC that distinguish them from other stem cell populations and more differentiated cells, and pilot projects that test the feasibility of using human ESC as a model system. NIGMS will also provide supplements to existing research grants to encourage and enable investigators who have little or no experience working with human ESC to explore the use of these cells as a new model system or approach to address the aims of the grants. The source of the stem cells is limited to the federally approved cell lines listed on the NIH Human Embryonic Stem Cell Registry.

Complex Biomedical Systems Research

To encourage computational approaches that will deepen understanding of biological processes, NIGMS established Centers of Excellence in Complex Biomedical Systems Research. The first awards--two center grants and three planning grants to lay the groundwork for future centers--were made in July and August 2002. The Institute anticipates that the new centers will foster a multidisciplinary research environment that will develop new computational approaches to particularly difficult biomedical problems, such as development and metabolism. The awards promote innovation and permit a larger scope of activity than would be possible via research grants to individual investigators. NIGMS also expects these centers to lead the way in training the next generation of researchers in computational biology.

Chemical Methodologies and Library Development

When scientists are looking for a new antibiotic or a small molecule to bind to a specific protein, they typically screen hundreds or thousands of chemicals for biological activity. Powerful tools in this endeavor are libraries of diverse chemical structures. But many existing chemical libraries have limited variety because they were assembled using a small number of methods and core chemical scaffolds.

Recognizing the need for new, high-throughput technologies to develop customized, diverse libraries, NIGMS created a program to support Centers of Excellence in Chemical

Methodologies and Library Development. The Institute made the first two center awards in September 2002.

The goal of this program is to engage the best academic chemists in developing a wide range of new methods for library creation. Scientists can then use these methods to generate chemical libraries that are tailored to their specific research needs.

Energizing NMR Research With the World's Biggest Magnets

For many scientists who use nuclear magnetic resonance (NMR) spectroscopy to study the structure and behavior of biological molecules, bigger is better. Larger magnets afford faster, more accurate glimpses of the inner workings of molecules and permit the study of larger molecules, rolling back a major limitation of the technology. NIGMS is supporting the purchase of four NMR spectrometers with 900 MHz magnets, the largest size available. Magnets this powerful have just come on the market, and there are currently only six such instruments in the world. The availability of more 900 MHz magnets to groups of NIGMS-funded investigators is expected to provide a wealth of information about normal cellular processes and the diseases that develop when these processes go awry.

Structural Genomics and Proteomics Technology Branch

A focal point for research that takes a genomic or computational approach to determining protein structures and functions is the new Structural Genomics and Proteomics Technology Branch within the NIGMS Division of Cell Biology and Biophysics. The branch supports the development of high-throughput methods for protein structure determination, bioinformatics as it relates to the analysis of protein structures, and the development of mass spectrometry and other tools for the rapid analysis of biological molecules. It also oversees the research centers and other grants associated with the NIGMS Protein Structure Initiative (PSI) and develops resources to meet the needs of the structural genomics and proteomics communities.

Other Areas of Interest

Research Programs

The four NIGMS glue grants have made significant progress in reaching their scientific milestones and in setting up the infrastructure needed to support these large-scale research endeavors. The grants are focused on cell signaling, cell movement, the role of carbohydrates in cell communication, and inflammation and the host response to injury. One of the greatest challenges the glue grant researchers face is managing and integrating the massive volumes of data they are collecting. To address this challenge, NIGMS offered grant supplements for bioinformatics infrastructure improvement. A number of awardees in the Pharmacogenetics Research Network, another major research program with a large database component, also competed for and received bioinformatics infrastructure supplements. NIGMS is encouraging the discussion and dissemination of standards and best practices in this area.

The nine PSI pilot research centers have made impressive starts at developing tools and approaches for the high-throughput determination of protein structures. NIGMS has held several workshops to address bottlenecks and other technical issues in this field, and it will hold additional workshops in 2003. The Institute also sponsored the development of a Web site for the centers to register the proteins they intend to study. NIGMS is considering additional activities to help the centers develop their full capability. These may include the development of a materials storage bank and a database containing the results of protein production and crystallization experiments.

In early 2003, the PSI Advisory Committee will conduct a progress assessment of the research centers that will include site visits to all nine centers. NIGMS staff members are working with the PSI Advisory Committee to examine the scientific impact and success of the pilot research centers. The results of this examination will be crucial in planning for the organization of the much larger production phase of the PSI, which will begin in FY 2005.

The 12 awards in the Pharmacogenetics Research Network are in their second and third years of funding. The purpose of this network is to bring together investigators studying the role of genetic variation in people's differing responses to a range of medicines. NIGMS led the creation of the network and funds many of the awards; others are funded or co-funded by the National Heart, Lung, and Blood Institute; the National Human Genome Research Institute; the National Cancer Institute; the National Institute of Environmental Health Sciences; and the National Library of Medicine. The goal is to be able to predict how an individual might respond to a drug before it is prescribed and thereby choose the best medication and dose in advance.

Researchers in the pharmacogenetics network are addressing the design, analysis, and clinical application of pharmacogenetic studies, which are large and complex endeavors. At the same time, the scientists have already had several research successes. One of these, the identification of a genetic variation that affects a person's response to the anticancer drug irinotecan, was described in the Science Advances section above. Other studies have shed light on variations in proteins that metabolize two widely used compounds, steroids and the asthma drug albuterol. The latter study revealed that albuterol inhalers could become less effective over time in people who have one variant of the enzyme and who use the inhalers on a daily basis to prevent attacks, rather than on occasion to treat symptoms. Network researchers are also studying responses to drugs involved in treating high blood pressure, high cholesterol, heart disease, depression, and obesity. The scientists are amassing information on drug receptors, drug-metabolizing proteins, and pathways of drug action and elimination, then depositing their data in an electronic library called PharmGKB. As its data collection grows, this library is expected to be a valuable research tool in the future.

Research Training

NIGMS maintains its leading role at NIH in research training by supporting 45 percent of the predoctoral trainees and 28 percent of all of the trainees who receive assistance from NIH. In recognition of the multidisciplinary nature of biomedical research today, the Institute's training

programs stress approaches to biological problems that cut across disciplinary and departmental lines. Such experience prepares trainees to pursue creative research in a wide variety of areas. To address the underrepresentation of minority students in biomedical research training, the Institute requires its institutional training programs to document how they plan to recruit minority students and report on the success of their efforts.

NIGMS trainees frequently contribute to major research advances. Two examples from 2002 are a study that pinpointed the mutations that render the drug Gleevec™ ineffective in some people with leukemia and the discovery of a molecular “switch” that tells the body to store or burn fat.

In August 2002, NIGMS held a meeting to discuss issues related to its pharmacological sciences predoctoral training grant program. These issues include recent declines in the number of applications for such programs and a reduction in the number of scientists who are skilled in “systems and integrative” pharmacological research, which is done in animals, as opposed to in test tubes. Meeting participants, who were all stakeholders in the area of pharmacological sciences training, suggested various ways to address these concerns.

The Institute has several research training programs that focus on areas in which there is a particularly serious need for well-prepared scientists. One of these programs, the Medical Scientist Training Program (MSTP), supports training leading to the combined M.D.-Ph.D. degree and produces investigators who can bridge the critical gap between basic and clinical research. In addition to providing training in the biological, chemical, and physical sciences, the program encourages and supports training in computer science, social and behavioral science, economics, epidemiology, public health, bioengineering, biostatistics, and bioethics. In FY 2002, the MSTP supported 933 trainees.

Another special program, the Pharmacology Research Associate (PRAT) Program, is NIGMS’ only intramural activity. PRAT fellows conduct 2 years of postdoctoral research in NIH intramural laboratories, working in such cutting-edge areas as neurobiology, tumor biology, and cell signaling.

AIDS Program

NIGMS support related to AIDS falls into three areas: program project grants that fund structure-based drug design, AIDS-related research training in molecular biophysics, and research grants to improve understanding of AIDS and its associated opportunistic infections.

NIGMS initiated its AIDS-related program project grants in 1987 to bring together crystallographers, chemists, and biologists to determine the detailed, three-dimensional structures of potential drug targets in HIV. In 2002, a team led by one of the program’s grantees, Dr. Edward Arnold of Rutgers, The State University of New Jersey, was part of an international collaboration involving government, industry, and academic scientists that discovered several new potential anti-AIDS drugs, including compounds that can block all known drug-resistant strains of the virus. Two of these drugs have shown promise in Phase I and Phase II clinical

trials; the third is scheduled for Phase I trials. One of the drugs that has reached Phase II trials is a viable candidate for treating AIDS in the developing world because it is relatively easy and inexpensive to manufacture.

The NIGMS research training program in molecular biophysics, which was established in 1988, prepares scientists to apply the techniques of physics and computer modeling to biological problems, chief among them HIV infection. Graduates of this program are trained to use structural biology in the design of drugs to fight HIV.

Minority Opportunities in Research

NIGMS has a long-standing commitment to increasing the number and capabilities of underrepresented minorities engaged in biomedical research. The focal point for this effort is the Division of Minority Opportunities in Research (MORE). The goal of the MORE Division is to encourage minority students to pursue training for scientific careers and to enhance the science curricula and faculty research capabilities at institutions with substantial minority enrollments. Through MORE's programs, NIGMS takes a leading role at NIH in research and research training activities targeted to underrepresented minorities.

The MORE Division has three components: the Minority Access to Research Careers (MARC) Branch, the Minority Biomedical Research Support (MBRS) Branch, and a section that handles special initiatives. Both MARC and MBRS commemorated their 30th anniversaries in 2002.

Minority Access to Research Careers Branch

MARC supports student and faculty research training and enables institutions with substantial minority enrollments to strengthen their biomedical research training capabilities. As a result, these schools are able to interest students in, and prepare them for, pursuing doctoral study and biomedical research careers.

MARC offers Undergraduate Student Training in Academic Research (U*STAR) institutional grants, predoctoral fellowships, faculty predoctoral and senior fellowships, a visiting scientist program, and grants for ancillary training activities. MARC also manages a program of NIH predoctoral fellowships for minorities.

In FY 2002, MARC supported 640 undergraduate students at 57 institutions, 32 MARC predoctoral fellows, 2 faculty fellows, and 105 NIH predoctoral fellows.

Minority Biomedical Research Support Branch

MBRS awards grants through three programs: Support of Continuous Research Excellence (SCORE), Research Initiative for Scientific Enhancement (RISE), and Initiative for Minority Student Development (IMSD).

The SCORE Program assists biomedical research faculty at minority-serving institutions in developing competitive research programs that increase the number of underrepresented minorities who are professionally engaged in biomedical research. The RISE Program enhances the research environment at minority-serving institutions to increase the interest, skills, and competitiveness of students and faculty in pursuit of biomedical research careers. The IMSD encourages institutions with established research programs to initiate or expand activities to improve the academic and research capabilities of underrepresented minority students and to facilitate their progress toward careers in biomedical research.

In FY 2002, 647 faculty members at 115 institutions worked on 477 MBRS research projects. MBRS also supported 1,261 undergraduate and 719 graduate students, who worked as research assistants on scientific projects at their own institutions or in other settings, including laboratories at research-intensive institutions and in industry.

Special Initiatives

MORE supports several special initiatives that strive to develop new approaches for the recruitment and retention of minority biomedical scientists. One such activity is the Bridges to the Future Program, which is co-sponsored by NIGMS and the NIH National Center on Minority Health and Health Disparities. This program encourages students in associate's or master's degree programs to make the transition to the next level of training (the bachelor's or Ph.D. degree, respectively) toward careers in biomedical research. Since the inception of the Bridges Program in 1992, NIGMS has supported 141 programs, 11 of which received initial funding in FY 2002.

The division also supports two innovative awards to foster the development of new skills. The MORE Faculty Development Award enables eligible faculty members to update or enhance their research skills by spending a summer (or one academic term) every year for 2 to 5 years in full-time research in a research-intensive laboratory outside their home institutions. The Institutional Research and Academic Career Development Award combines a traditional postdoctoral research experience with an opportunity to develop teaching skills through mentored assignments at a minority-serving institution. The goals of the program are to provide a resource to motivate the next generation of scientists at minority-serving institutions and to promote linkages between research-intensive and minority-serving institutions that can lead to further research and teaching collaborations.

NIGMS continues to partner with the Indian Health Service on the Native American Research Centers for Health (NARCH) Program. This program encourages research on diseases and health conditions of importance to American Indians and Alaska Natives. It also prepares Native American biomedical and behavioral scientists and health professionals to compete for NIH funding. A third goal is to increase the capacity of both the research-intensive organizations and the Native American organizations to work together to produce competitive research proposals. Since the NARCH Program began in 2001, NIGMS has funded 11 NARCH grants, 3 of which were new in FY 2002.

Another successful ongoing activity is the MORE Division's support of workshops, mini-courses, and meetings in a number of areas, including grant writing and program evaluation. The division's future plans include supporting mentored research experiences for underrepresented minority medical students, studying what works to promote success in science, and stimulating training and curriculum development in the quantitative sciences.

Success Stories

Reflecting their exceptional achievements in nurturing students who are interested in research careers, two MORE program directors were among ten individual recipients of this year's Presidential Awards for Excellence in Science, Mathematics, and Engineering Mentoring. They are Dr. Therese Markow, a professor of ecology and evolutionary biology at the University of Arizona, and Dr. Bharati Mehrotra, a professor of biology at Tougaloo College.

A former participant in two NIGMS minority programs received the 2002 Alan T. Waterman Award, which is the highest honor given to a young researcher by the National Science Foundation. Dr. Erich Jarvis, an assistant professor in the department of neurobiology at Duke University Medical Center, participated in the MARC and MBRS programs as an undergraduate student at the City University of New York, Hunter College. He was also a MARC predoctoral fellow at The Rockefeller University.

Also in 2002, the National Science Board's Public Service Award went to the Society for Advancement of Chicanos and Native Americans in Science (SACNAS). The award recognized SACNAS' support, guidance, and mentoring of budding young Latino and Native American scientists and engineers. The SACNAS annual conference, which NIGMS co-sponsors, provides opportunities for many undergraduate and graduate students to participate in their first scientific meeting and hear talks by leading scientists.

Many participants in MORE programs go on to productive academic careers and professions in research or research administration. This shows that the educational strategy of involving students in hands-on research experiences is one that works. Among this year's success stories are:

- Dr. Cassandra Smith, a former MBRS program participant at Stillman College, is now a professor of biology and chair of the Division of Natural Sciences, Mathematics, and Computer Science at Voorhees College. She also directs the school's RISE program.
- Dr. Victor Vandell, a former MBRS program participant at Chicago State University, is now a staff scientist and head of the mass spectrometry laboratory at Hercules Incorporated in Wilmington, Delaware.

- Dr. Roslyn Blake Edson, a former MARC trainee at the City University of New York, City College, is now assurance coordinator in the Office for Human Research Protections of the U.S. Department of Health and Human Services.

Innovations in Management and Administration

NIGMS encourages its employees to streamline work processes and reduce paperwork and administrative burdens through innovations in management and administration.

Administrative Best Practices and Efficiencies

NIGMS continues to partner with the National Heart, Lung, and Blood Institute and the National Institute of Neurological Disorders and Stroke to share administrative best practices and collaborate on solving common problems. This interaction has been very productive. In 2002, for example, members of the group conducted a preliminary examination of NIH and grantee institution experiences with modular grants and Just-in-Time information collection procedures. A report on this effort was shared with the Deputy Director for Extramural Research, NIH, so that the broader NIH extramural community can draw on the findings of the preliminary assessment.

Information Technology Management

NIGMS has engaged in a number of information technology management activities aimed at enhancing administrative efficiency. For example, it is moving aggressively toward achieving Capability Maturity Model Level II, which is the industry standard for a comprehensive software quality process. This entails instituting rigorous information technology planning, establishing documentation standards and ensuring that the standards are met, and adopting a new standard software development protocol based on business needs and project management plans.

The Institute is a leader at NIH in using new, automated tools to gather, analyze, and report financial information from various databases. As part of this effort, NIGMS staff members are playing active roles in developing the NIH Business and Research Support System, a consolidated, NIH-wide resource planning database.

NIH Competitive Service Center Participation

NIGMS' ongoing service center arrangements continue to be successful. A Center for Scientific Review service center reimburses NIGMS grant peer review consultants, and a National Institute of Child Health and Human Development service center handles NIGMS' committee management activities. The Institute is also a user of the NIH Office of Extramural Research's National Research Service Awards Payback service center.

Streamlined Work Processes

NIGMS has arranged to use the National Cancer Institute's Electronic Imaging System on a trial basis in FY 2003. This system is a centralized repository of grant information documents and images. Using such a system should facilitate the Institute's transition to electronic grants administration in the coming years. As one step toward this goal, NIGMS now provides grant applications in electronic formats, rather than on paper, to its peer reviewers and advisory council members. Another activity that will inform future streamlining efforts and electronic workflow is the ongoing development of business maps of critical work processes.

Capitalizing on Scientific Opportunities

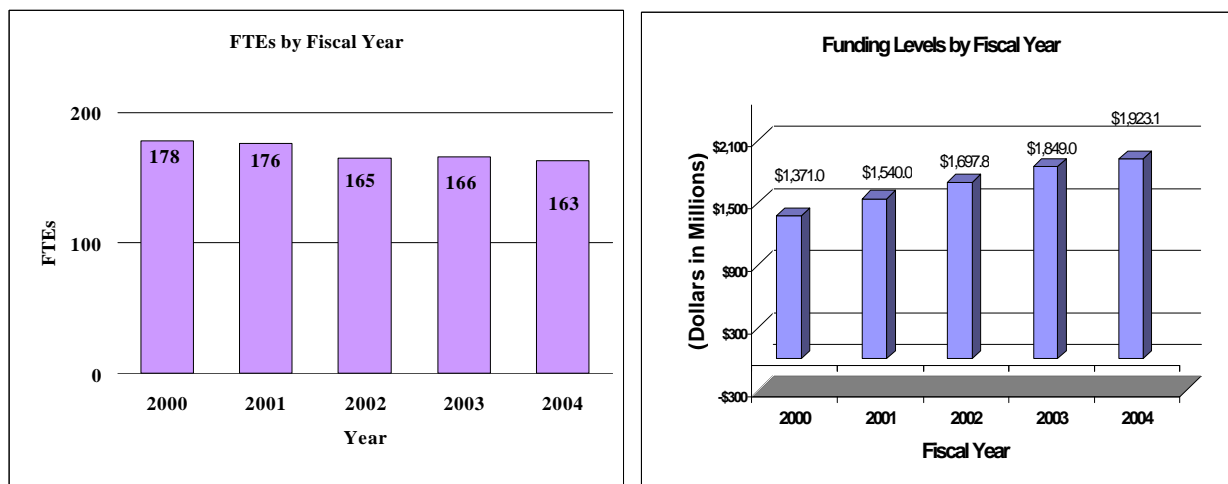
In recent years, NIGMS has created a variety of programs to stimulate research and respond to needs identified by the scientific community. A series of meetings in the spring of 1998 provided valuable input from a wide range of prominent scientists and led to the NIGMS glue grants, the Pharmacogenetics Research Network, and a set of programs focused on understanding complex biomedical systems.

NIGMS held another meeting about scientific opportunities in September 2002. The goal of this meeting was to identify the most significant scientific problems that basic biomedical researchers are likely to be addressing in the year 2010. Participants also discussed needed tools and resources, as well as anticipated experimental approaches. NIGMS will use the advice from these experts to help frame its research and training program planning.

In a related activity, NIGMS staff evaluated the grant portfolios of the Institute's scientific divisions in the summer of 2002. The goal of this activity was to ensure a proper balance in research support and to identify research gaps or other issues in the scientific areas within NIGMS' mission.

Budget Policy

The Fiscal Year 2004 budget request for the NIGMS is \$1,923,133,000 including AIDS, an increase of \$74,085,000 and 4 percent over the FY 2003 amended President's Budget Request. A five year history of FTEs and Funding Levels for NIGMS are shown in the graphs below. Note that Fiscal Years 2001 and 2000 FTEs are not comparable for the NIH Human Resources functional consolidation.

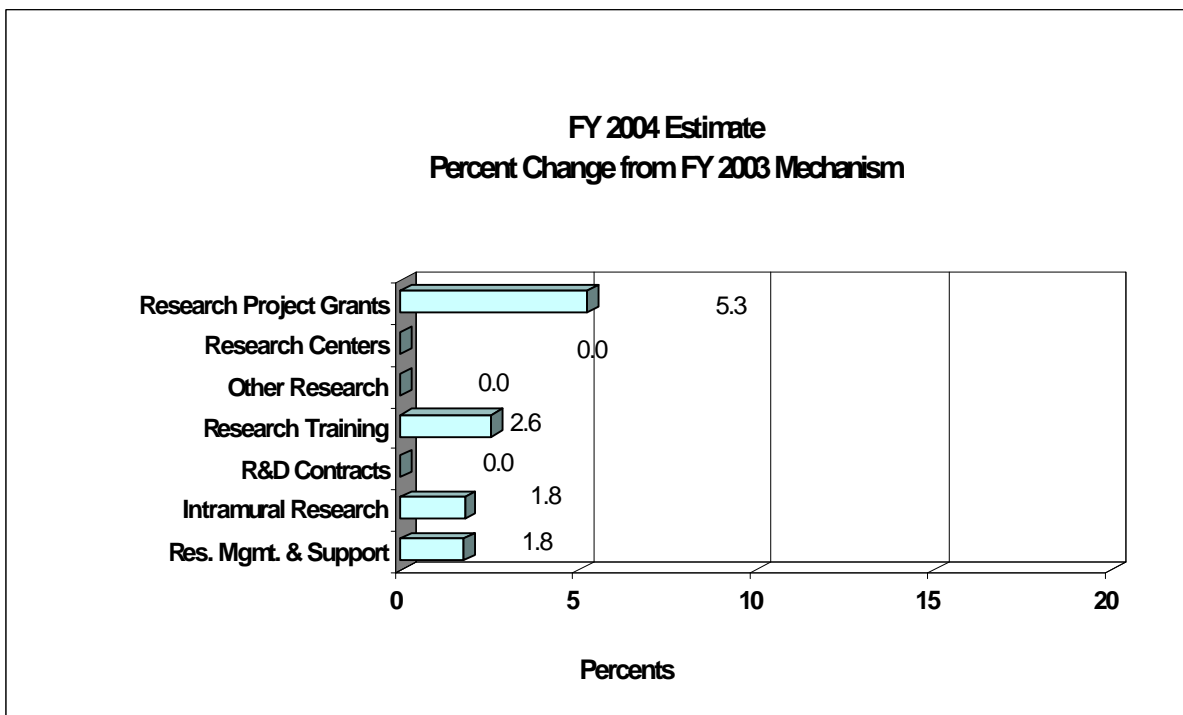
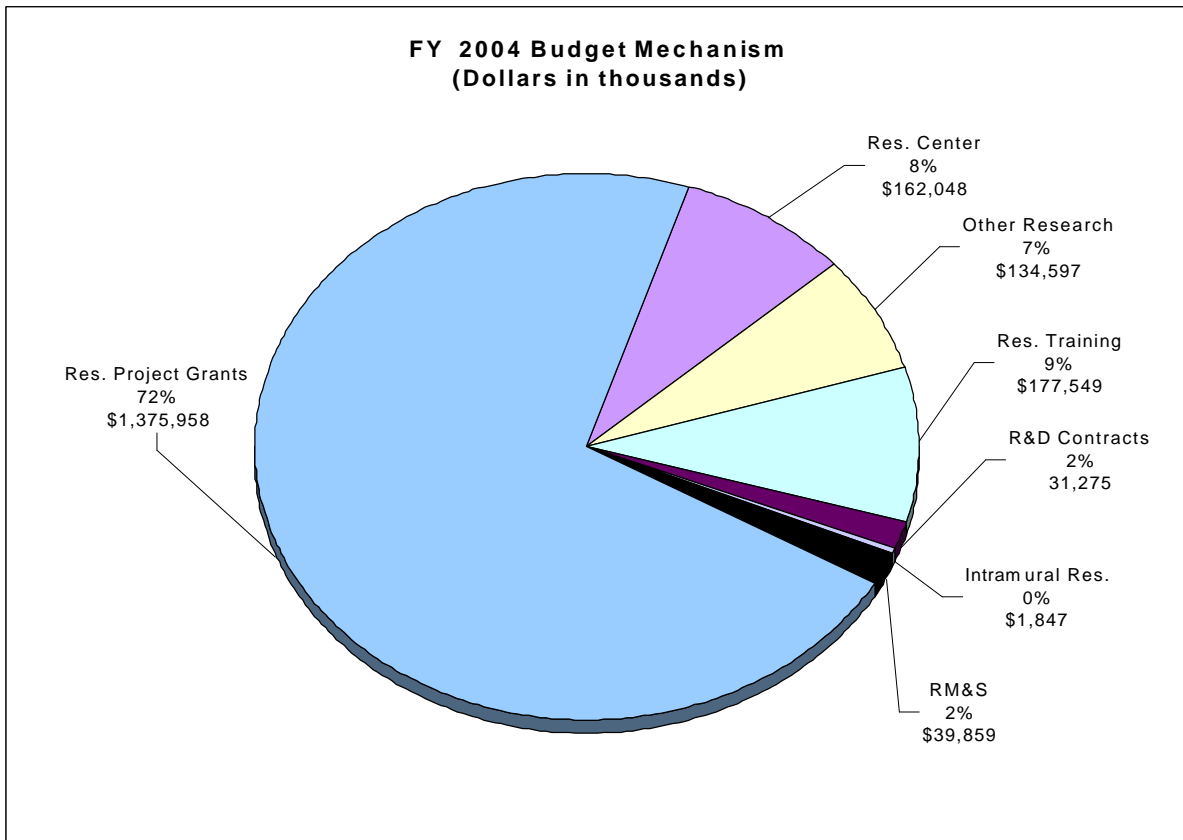


NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. NIGMS will provide an aggregate average cost increase of 3.6 percent for RPGs. In FY 2004, NIGMS will fully fund 68 new RPGs, the majority of which will be Academic Research Enhancement Awards.

Promises for advancement in medical research are dependent on maintaining the supply of new investigators with new ideas. In the Fiscal Year 2004 request, NIGMS will support 4,454 pre- and postdoctoral trainees in full-time training positions, the same number as in FY 2003. Stipend levels for NRSA trainees will increase by 4 percent over Fiscal Year 2003 levels for predoctoral fellows, and from 4-1 percent, based on years of experience, for postdoctoral fellows.

The Fiscal Year 2004 request includes funding for 49 research centers, 277 other research grants, including 43 career awards, and 24 R&D contracts. Intramural Research and Research Management and Support receive increases of 1.8 percent over FY 2003.

The mechanism distribution by dollars and percent change are displayed below:



NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Budget Mechanism - Total

MECHANISM	FY 2002 Actual		FY 2003 Amended President's Budget		FY 2004 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
<u>Research Projects:</u>						
Noncompeting	2,927	\$856,795,000	2,977	\$897,954,000	3,084	\$974,792,000
Administrative supplements	(242)	14,566,000	(242)	15,003,000	(242)	15,003,000
Full funded	0	0	0	0	68	16,874,000
Single year	1,007	307,304,000	1,114	353,490,000	997	324,382,000
Subtotal, competing	1,007	307,304,000	1,114	353,490,000	1,065	341,256,000
Subtotal, RPGs	3,934	1,178,665,000	4,091	1,266,447,000	4,149	1,331,051,000
SBIR/STTR	143	37,551,000	155	40,639,000	172	44,907,000
Subtotal, RPGs	4,077	1,216,216,000	4,246	1,307,086,000	4,321	1,375,958,000
<u>Research Centers:</u>						
Specialized/comprehensive	35	114,773,000	45	149,588,000	49	149,588,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	17,569,000	0	12,460,000	0	12,460,000
Comparative medicine	0	15,000	0	0	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	35	132,357,000	45	162,048,000	49	162,048,000
<u>Other Research:</u>						
Research careers	38	8,887,000	43	9,605,000	43	9,605,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	2,000,000	0	0	0	0
Minority biomedical research support	150	91,787,000	159	100,048,000	159	100,048,000
Other	69	17,977,000	75	24,944,000	75	24,944,000
Subtotal, Other Research	257	120,651,000	277	134,597,000	277	134,597,000
Total Research Grants	4,369	1,469,224,000	4,568	1,603,731,000	4,647	1,672,603,000
<u>Research Training:</u>	<u>FTEs</u>		<u>FTEs</u>		<u>FTEs</u>	
Individual awards	510	19,382,000	510	20,426,000	510	21,051,000
Institutional awards	3,944	147,035,000	3,944	152,648,000	3,944	156,498,000
Total, Training	4,454	166,417,000	4,454	173,074,000	4,454	177,549,000
Research & development contracts (SBIR/STTR)	20 (0)	24,531,000 (0)	24 (0)	31,275,000 (0)	24 (0)	31,275,000 (0)
Intramural research	<u>FTEs</u> 18	<u>FTEs</u> 1,664,000	<u>FTEs</u> 18	<u>FTEs</u> 1,814,000	<u>FTEs</u> 15	<u>FTEs</u> 1,847,000
Research management and support	147	35,920,000	148	39,154,000	148	39,859,000
Cancer prevention & control	0	0	0	0	0	0
Construction	0	0	0	0	0	0
Total, NIGMS	165	1,697,756,000	166	1,849,048,000	163	1,923,133,000
(Clinical Trials)		(0)		(0)		(0)

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2002		FY 2003		FY 2004		Change	
	Actual		Amended President's Budget		Estimate			
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
<u>Extramural Research:</u>								
Biomedical Research		\$1,493,755		\$1,635,006		\$1,703,878		\$68,872
Biomedical Research Training		166,417		173,074		177,549		4,475
Subtotal, Extramural research		1,660,172		1,808,080		1,881,427		73,347
Intramural research	18	1,664	18	1,814	15	1,847	(3)	33
Res. management & support	147	35,920	148	39,154	148	39,859	0	705
Total	165	1,697,756	166	1,849,048	163	1,923,133	(3)	74,085

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Summary of Changes

2003 Amended President's Budget		\$1,849,048,000	
2004 Estimated Budget Authority		1,923,133,000	
Net change		74,085,000	
CHANGES	2003 Amended President's Budget Base		Change from Base
	FTEs	Budget Authority	FTEs Budget Authority
A. Built-in:	18		(3)
1. Intramural research:			
a. Within grade increase		\$1,187,000	\$29,000
b. Annualization of January 2003 pay increase		1,187,000	9,000
c. January 2004 pay increase		1,187,000	18,000
d. One extra day of pay		1,187,000	5,000
e. Payment for centrally furnished services		227,000	5,000
f. Increased cost of laboratory supplies, materials, and other expenses		400,000	6,000
Subtotal			72,000
2. Research Management and Support:	148		
a. Within grade increase		15,130,000	249,000
b. Annualization of January 2003 pay increase		15,130,000	117,000
c. January 2004 pay increase		15,130,000	227,000
d. One extra day of pay		15,130,000	58,000
e. Payment for centrally furnished services		8,272,000	165,000
f. Increased cost of laboratory supplies, materials, and other expenses		15,752,000	271,000
Subtotal			1,087,000
Subtotal, Built-in			1,159,000

**NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences**

Summary of Changes--continued

CHANGES	2003 Amended President's Budget Base			
			Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	2,977	\$912,957,000	107	\$76,838,000
b. Competing	1,114	353,490,000	(49)	(12,234,000)
c. SBIR/STTR	155	40,639,000	17	4,268,000
Total	4,246	1,307,086,000	75	68,872,000
2. Research centers	45	162,048,000	4	0
3. Other research	277	134,597,000	0	0
4. Research training	4,454	173,074,000	0	4,475,000
5. Research and development contracts	24	31,275,000	0	0
Subtotal, extramural				73,347,000
6. Intramural research	<u>FTEs</u> 18	1,814,000	<u>FTEs</u> (3)	(39,000)
7. Research management and support	148	39,154,000	0	(382,000)
8. Cancer control and prevention	0	0	0	0
9. Construction			0	0
Subtotal, program		1,849,048,000		72,926,000
Total changes	166		(3)	74,085,000

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Budget Authority by Object

	FY 2003 Amended Pres. Budget	FY 2004 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	166	163	(3)
Full-time equivalent of overtime & holiday hours	1	1	0
Average ES salary	\$142,428	\$145,276	\$2,848
Average GM/GS grade	10.7	10.7	0.0
Average GM/GS salary	\$66,890	\$68,237	\$1,347
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	\$0	\$0	\$0
Average salary of ungraded positions	94,100	96,247	2,147
OBJECT CLASSES	FY 2003 Amended Pres. Budget	FY 2004 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	\$7,898,000	\$8,064,000	\$166,000
11.3 Other than Full-Time Permanent	4,927,000	5,079,000	152,000
11.5 Other Personnel Compensation	381,000	393,000	12,000
11.7 Military Personnel	0	0	0
11.8 Special Personnel Services Payments	0	0	0
Total, Personnel Compensation	13,206,000	13,536,000	330,000
12.1 Civilian Personnel Benefits	3,111,000	3,207,000	96,000
12.2 Military Personnel Benefits	0	0	0
13.0 Benefits for Former Personnel	0	0	0
Subtotal, Pay Costs	16,317,000	16,743,000	426,000
21.0 Travel & Transportation of Persons	481,000	553,000	72,000
22.0 Transportation of Things	39,000	45,000	6,000
23.1 Rental Payments to GSA	0	0	0
23.2 Rental Payments to Others	17,000	24,000	7,000
23.3 Communications, Utilities & Miscellaneous Charges	152,000	213,000	61,000
24.0 Printing & Reproduction	792,000	1,114,000	322,000
25.1 Consulting Services	125,000	165,000	40,000
25.2 Other Services	3,737,000	2,702,000	(1,035,000)
25.3 Purchase of Goods & Services from Government Accounts	72,047,000	74,411,000	2,364,000
25.4 Operation & Maintenance of Facilities	559,000	786,000	227,000
25.5 Research & Development Contracts	858,000	858,000	0
25.6 Medical Care	0	0	0
25.7 Operation & Maintenance of Equipment	122,000	172,000	50,000
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	77,448,000	79,094,000	1,646,000
26.0 Supplies & Materials	300,000	421,000	121,000
31.0 Equipment	1,830,000	359,000	(1,471,000)
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	1,751,672,000	1,824,567,000	72,895,000
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	0	0	0
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	1,832,731,000	1,906,390,000	73,659,000
Total Budget Authority by Object	1,849,048,000	1,923,133,000	74,085,000

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Salaries and Expenses

OBJECT CLASSES	FY 2003 Amended Pres. Budget	FY 2004 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	\$7,898,000	\$8,064,000	\$166,000
Other Than Full-Time Permanent (11.3)	4,927,000	5,079,000	152,000
Other Personnel Compensation (11.5)	381,000	393,000	12,000
Military Personnel (11.7)	0	0	0
Special Personnel Services Payments (11.8)	0	0	0
Total Personnel Compensation (11.9)	13,206,000	13,536,000	330,000
Civilian Personnel Benefits (12.1)	3,111,000	3,207,000	96,000
Military Personnel Benefits (12.2)	0	0	0
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	16,317,000	16,743,000	426,000
Travel (21.0)	481,000	553,000	72,000
Transportation of Things (22.0)	39,000	45,000	6,000
Rental Payments to Others (23.2)	17,000	24,000	7,000
Communications, Utilities and Miscellaneous Charges (23.3)	152,000	213,000	61,000
Printing and Reproduction (24.0)	792,000	1,114,000	322,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	100,000	140,000	40,000
Other Services (25.2)	3,737,000	2,702,000	(1,035,000)
Purchases from Govt. Accounts (25.3)	16,518,000	18,430,000	1,912,000
Operation & Maintenance of Facilities (25.4)	559,000	786,000	227,000
Operation & Maintenance of Equipment (25.7)	122,000	172,000	50,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	21,036,000	22,230,000	1,194,000
Supplies and Materials (26.0)	300,000	421,000	121,000
Subtotal, Non-Pay Costs	22,817,000	24,600,000	1,783,000
Total, Administrative Costs	39,134,000	41,343,000	2,209,000

National Institute of General Medical Sciences

SIGNIFICANT ITEMS IN SENATE APPROPRIATION
COMMITTEE REPORT

The following section represents FY 2003 Congressional requirements for reports and significant items derived from Senate Report 107-216. These actions discussed below are contingent on inclusion of similar language and funding in the final FY 2003 appropriation and related reports. Additional items may be transmitted at a later date as a result of the final Conference report.

Item

Behavioral science research and training – As the NIH Institute most concerned with basic research, the NIGMS has provided leadership in basic research on physiological and biological structures and functions that may play roles in numerous health conditions. The Committee encourages the NIGMS to develop collaborations with other Institutes, such as the NCI and NIMH, and the Office of Behavioral and Social Sciences Research to fund basic research to integrate physiological knowledge of predisease pathways with behavioral studies.

Action to be Taken

The NIGMS primarily supports fundamental areas of biomedical science of a structural or functional nature, which provide the foundation for disease-targeted studies by the other components of the NIH. NIGMS supports a limited number of studies in the area of behavioral research using animal models. Such work is relevant to the study of more complex behaviors in higher organisms supported by other institutes at the NIH.

Research training in the behavioral sciences is supported through NIGMS' Medical Scientist Training Program, Systems and Integrative Biology training program, and programs of the Minority Opportunities in Research Division. All of these programs solicit applications for research training support in a broad range of disciplines, explicitly including the behavioral and social sciences.

The NIH Office of Behavioral and Social Sciences Research (OBSSR) has proposed to the Director, NIH that an examination of how NIH might best pursue future research and research training efforts in the basic behavioral and social sciences be conducted. The OBSSR proposal envisioned that a working group of institute representatives will be convened in 2003. NIGMS would participate on that group.

Item

Medical Scientist Training Program (MSTP) – The Committee understands that translating the human genome into cures and therapies is the next great challenge for modern medicine. To meet that challenge, a new generation of scientists must be trained. The MSTP is

a highly competitive program that trains physicians for careers in biomedical research by supporting them as they earn both M.D. and Ph.D. degrees. The Committee strongly urges the NIGMS to provide additional funds to increase the number of promising physicians it trains through this program.

Action to be Taken

NIGMS recognizes the importance of its training programs for providing the most critical element of good research: well-prepared scientists. One such program is the Medical Scientist Training Program (MSTP), which supports training that leads to both a Ph.D. and an M.D. degree. The Institute acknowledges the Committee's recommendation to increase the funding, and therefore, the number of trainees supported by the MSTP program. However, in supporting training for the next generation of scientists, NIGMS must carefully balance its support for MSTP and for its other valuable training programs.

The number of MSTP trainees has grown steadily over the past six years, from 823 trainees in FY 1997 to 933 trainees in FY 2002. NIGMS believes that the program will continue to achieve its goal of training a significant number of promising physicians-scientists for years to come.

NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2003 Amount Authorized	2003 Amended President's Budget	2004 Amount Authorized	2004 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite		Indefinite	
Medical Sciences	Section 41B	42§285b	Indefinite	\$1,675,974,000	Indefinite	\$1,745,584,000
National Research Service Awards	Section 487(d)	42§288	a/	173,074,000	b/	177,549,000
Total, Budget Authority				1,849,048,000		1,923,133,000

a/ Amounts authorized by Section 301 and Title IV of the Public Health Act.

b/ Reauthorizing legislation will be submitted.

**NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences**

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1995 2/	\$882,189,000	\$877,113,000	\$877,113,000	\$876,889,000 3/
1996	907,674,000 2/	946,971,000	897,465,000 2/	946,971,000
Rescission				(75,000)
1997	936,573,000 2/	1,003,772,000	953,214,000 2/	998,387,000 4/
1998	992,032,000 2/	1,047,963,000	1,058,969,000	1,065,947,000
1999	1,111,439,000 2/5	1,150,840,000	1,197,825,000	1,197,825,000
Rescission				(799,000)
2000	1,194,068,000 2/	1,298,551,000	1,352,843,000	1,361,668,000
Rescission				(7,248,000)
2001	1,389,492,000 2/	1,548,313,000	1,554,176,000	1,535,823,000
Rescission				(125,000)
2002	1,720,206,000 2/	1,706,968,000	1,753,465,000	1,725,263,000
Rescission				(124,000)
2003	1,874,243,000			
2004	1,923,133,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.

2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.

3/ Excludes enacted administrative reductions of \$227,000.

4/ Excludes enacted administrative reductions of \$83,000.

5/ Reflects a decrease of \$3,447,000 for the budget amendment for bioterrorism.

**NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences**

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2002 Actual	FY 2003 Amended Pres. Budget	FY 2004 Estimate
Office of the Director	14	15	15
Office of Scientific Review	14	14	14
Office of Administrative Management	31	31	31
Division of Extramural Activities	38	38	38
Genetic and Developmental Biology Division	13	13	13
Pharmacology, Physiology, and Biological Chemistry Division	32	32	29
Cell Biology and Biophysics Division	14	14	14
Bioinformatics and Computational Biology Center	1	1	1
Minority Opportunities in Research Division	8	8	8
Total	165	166	163
FTEs supported by funds from Cooperative Research and Development Agreements			
	(0)	(0)	(0)
FISCAL YEAR	Average GM/GS Grade		
2000	11.2		
2001	10.7		
2002	10.7		
2003	10.7		
2004	10.7		

**NATIONAL INSTITUTES OF HEALTH
National Institute of General Medical Sciences**

Detail of Positions

GRADE	FY 2002 Actual	FY 2003 Amended Pres. Budget	FY 2004 Estimate
ES-6		1	1
ES-5			
ES-4	3	3	3
ES-3	1	1	1
ES-2			
ES-1			
Subtotal	4	5	5
Total - ES Salary	\$552,501	\$712,137	\$726,380
GM/GS-15	11	11	11
GM/GS-14	19	20	20
GM/GS-13	21	21	21
GS-12	11	11	11
GS-11	5	5	5
GS-10	1	1	1
GS-9	8	8	8
GS-8	16	16	16
GS-7	14	14	14
GS-6	4	4	4
GS-5	3	3	3
GS-4	3	3	3
GS-3	1	1	1
GS-2			
GS-1			
Subtotal	117	118	118
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General			
Director Grade			
Senior Grade			
Full Grade			
Senior Assistant Grade			
Assistant Grade			
Subtotal	0	0	0
Ungraded	62	62	59
Total permanent positions	114	113	111
Total positions, end of year	183	182	179
Total full-time equivalent (FTE) employment, end of year	165	166	163
Average ES level	ES-4	ES-4	ES-4
Average ES salary	\$138,125	\$142,428	\$145,276
Average GM/GS grade	10.7	10.7	10.7
Average GM/GS salary	\$64,887	\$66,890	\$68,237