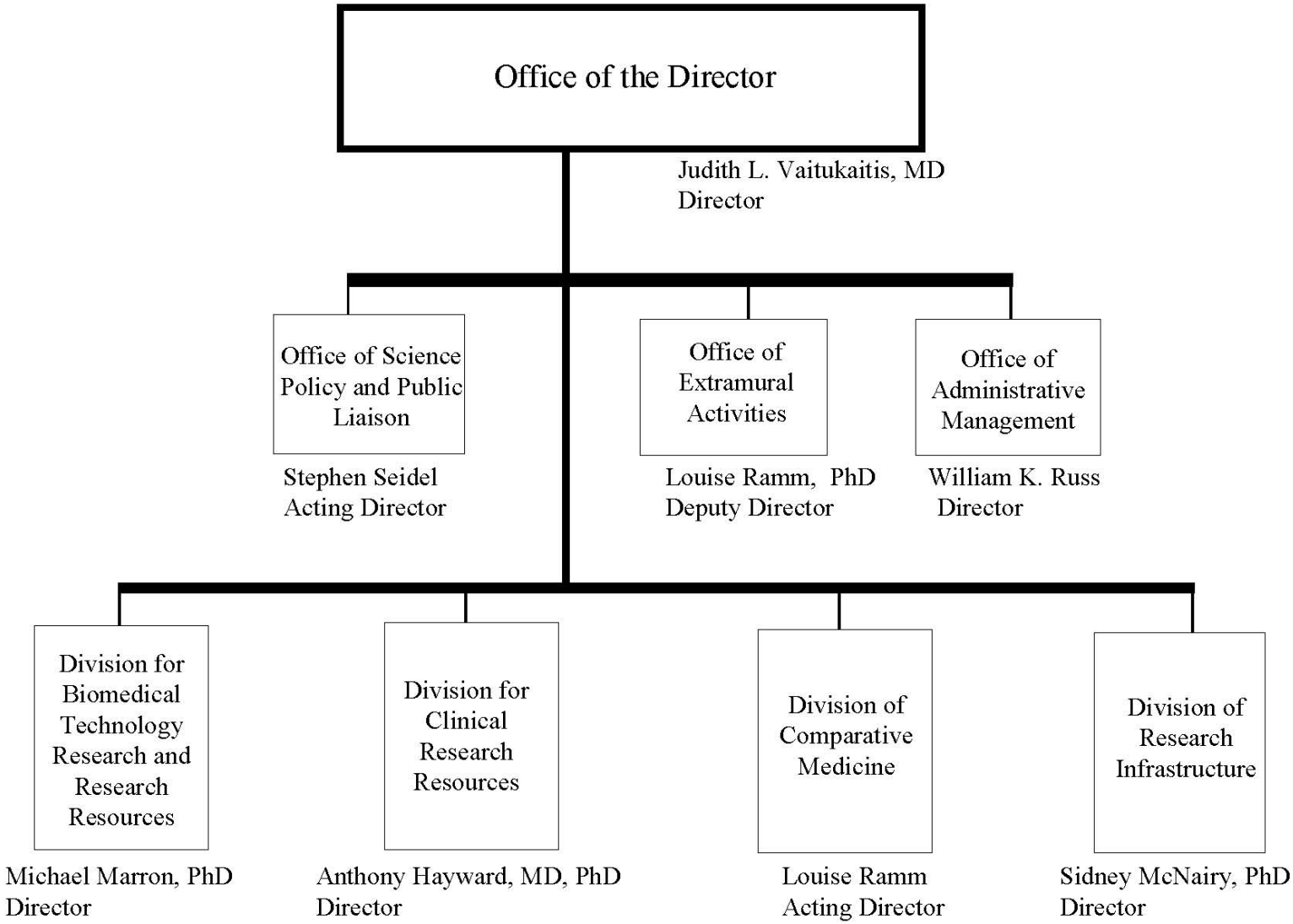
DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

FY 2005 Budget — Page No.

National Center for Research Resources
Organizational Chart



NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

For carrying out section 301 and title IV of the Public Health Service Act with respect to research resources and general research support grants, [$1,186,183,000] *$1,094,141,000:* Provided, That none of these funds shall be used to pay recipients of the general research support grants program any amount for indirect expenses in connection with such grants.

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Omnibus Consolidated Appropriations Act for Fiscal Year 2004]

National Institutes of Health
National Center for Research Resources

Amounts Available for Obligation 1/

Source of Funding	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
Appropriation	$1,146,272,000	$1,186,183,000	$1,094,141,000
Enacted Rescissions	(7,451,000)	(7,125,000)	---
Subtotal, Adjusted Appropriation	1,138,821,000	1,179,058,000	1,094,141,000
Comparative transfer to Buildings and Facilities	(106,000)	(102,000)	(0)
Comparative transfer to Office of the Director for program changes	(157,000)	(0)	(0)
Subtotal, adjusted budget authority	1,138,558,000	1,178,956,000	1,094,141,000
Unobligated Balance, start of year	27,000	0	0
Unobligated Balance, end of year	(27,000)	0	0
Subtotal, adjusted budget authority	1,138,558,000	1,178,956,000	1,094,141,000
Unobligated balance lapsing	(1,000)	---	---
Total obligations	1,138,557,000	1,178,956,000	1,094,141,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2003 - $10,620,000; FY 2004 - $11,450,000; FY 2005 - $12,000,000

Justification

National Center for Research Resources

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

Budget Authority:

FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
116	$1,138,558,000	115	$1,178,956,000	114	$1,094,141,000	-1	-$84,815,000

This document provides justification for the Fiscal Year 2005 activities of the National Center for Research Resources (NCRR), including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2005 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

The National Center for Research Resources (NCRR) is the NIH component that develops and provides biomedical scientists access to the research technologies, nonhuman models, clinical research facilities, and other resources they need to conduct research. Each year, more than 25,000 researchers use NCRR-supported resources for their investigations. Ready access to critical resources gives scientists the freedom to explore novel ideas and make pioneering discoveries that improve human health. In 2003, two such scientists received Nobel Prizes for innovative research and development that relied on NCRR-supported resources. Dr. Roderick MacKinnon of Rockefeller University was co-recipient of the Nobel Prize in Chemistry for his analyses of the structures and functions of ion channels. Dr. MacKinnon's investigations relied heavily on the scientific expertise and advanced instrumentation available at NCRR-supported mass spectrometry and synchrotron radiation facilities. Another NCRR-supported researcher, Dr. Paul Lauterbur of the University of Illinois, Urbana-Champaign, was co-recipient of the Nobel Prize in Physiology or Medicine for his studies that set the stage for the development of magnetic resonance imaging (MRI). From 1990 to 2000, Dr. Lauterbur headed the NCRR-funded Biomedical Magnetic Resonance Research and Technology Center, which further developed applications of MRI for both clinical research and model systems. The contributions of NCRR's programs are more evident than ever before and illustrate NCRR responsiveness to the rapidly evolving needs of investigators.

As research queries become more complex, research teams are required to provide a wider range of expertise. Emerging trends transcend the entire health-research spectrum and require more sophisticated research tools. At the same time, these trends require a complementary expansion in sophisticated networks needed to provide access to federated databases and scalable computing. NCRR has a long history of integrating several disciplines in its biomedical technology research and resources programs that require expertise ranging from fundamental science to advanced physiology. The need for even more interdisciplinary team members is evident by the more complex research themes being examined. It is through flexible, innovative approaches to the support of this complex research that investigators can gain access to tools by traveling to the site or by accessing the technology over the Internet—a virtual research laboratory or resource. Virtual laboratories have been successfully developed and tested for crystallography, mass spectrometry, imaging, computation, and microscopy.

Protein Structure and Function

One rapidly evolving field that depends on both interdisciplinary teams and advanced research networks is proteomics—a comprehensive analysis of protein structure and macromolecular functions within the cell and within membranes. NCRR has long supported resources that enable deciphering protein structure and function, including Dr. MacKinnon's research on the makeup and configuration of ion channels, cited above. Because many proteins function in complexes rather than alone, NCRR now supports an initiative to develop technologies that can delineate the three-dimensional (3-D) structures of macromolecular complexes. This initiative will complement an NIH Roadmap initiative for creating and enhancing technologies that shed light on complex biochemical pathways and molecular interactions, both of which usually involve proteins.

Structures and Mechanisms of Ion Channels

Electrically charged atoms, known as ions, play important roles in bodily processes, such as impulse transmission along nerve cells and muscle contraction. Ions pass into and out of cells through ion channels, which are complex proteins embedded in cell membranes. These proteins form pores that selectively allow the passage of only one type of ion. Collaborating with scientists at NCRR-supported mass spectrometry and X-ray crystallography facilities, Nobel Prize-winning scientist Dr. Roderick MacKinnon and his colleagues at Rockefeller University determined the structure of two types of bacterial ion channels that are similar to ion channels found in mammals. By deciphering the structures, the researchers could determine how the channels permit passage of only one type of ion. Insight into the functioning of ion channels lays the foundation for understanding and developing novel therapies for various neurological, muscular, and kidney diseases that stem from defects in ion channel functions.

Biology's Own Homeland Security Against Chemical Toxicity

Human carboxylesterase 1 (hCE1) is an enzyme that breaks down prescription drugs, illegal drugs, and even chemical warfare agents. Unlike other enzymes, which selectively bind only to certain molecules, hCE1 is nonselective. Using the intense X-rays produced at the NCRR-supported Synchrotron Radiation Structural Biology Resource at Stanford University, researchers analyzed the 3-D structures of hCE1 bound to cocaine and heroin analogs. The images revealed unique structural features, including small pockets deep within the enzyme that

can accommodate and bind to many molecular shapes or many different compounds. Knowing hCE1's structure may lead to the design of versions of the enzyme that might promote cocaine clearance in patients who have overdosed or protect against chemical warfare agents.

Strategy to Improve Important Immunosuppressive Drug

Cyclosporin A is a powerful immunosuppressant used for preventing organ transplant rejection and for treating immunological diseases. Since its discovery, medicinal chemists have failed to substantially improve on cyclosporin A activity by chemically modifying parts of the molecule. Using the intense X-rays produced at the NCRR-supported macromolecular diffraction facility at the Cornell High Energy Synchrotron Source to determine the structure, researchers identified cyclosporin A regions that might be modified to enhance the drug's activity and exert a greater therapeutic effect.

Novel Approaches for Developing Anthrax Therapies

Because of concerns about the possible use of anthrax bacteria (*Bacillus anthracis*) in terrorist attacks, researchers are investigating the basic biology of this infectious agent. Anthrax bacteria release a toxin that selectively kills immune cells called macrophages. Investigators at the University of Oklahoma and their colleagues have identified a cellular enzyme called glycogen synthase kinase-3 beta that is essential to resisting the effects of this toxin. Macrophages known to be resistant to the toxin's effects exhibited no detectable changes in the levels of this enzyme, but when treated with an enzyme inhibitor, the cells succumbed to the anthrax toxin. The results could aid design of molecules that enhance or maintain the enzyme's activities in macrophages and could potentially serve as anthrax therapies. Another possible approach for treating anthrax might focus on the cellular proteins that transport bacterial toxins to a cell's interior. Researchers at the Boston University School of Medicine have identified the proteins that transport the toxin produced by *Corynebacterium diphtheriae,* the bacterium that causes diphtheria. The diphtheria toxin has a structure similar to that of several bacterial toxins, including the anthrax toxin, which suggests that other toxins may be transported by these cellular proteins as well. Techniques for countering the transport proteins ultimately may lead to improved therapies or vaccines for bacterial diseases, including anthrax.

Tamoxifen Activation by Metabolic Enzymes

Tamoxifen is an important therapy for breast cancer and may prevent the disease in healthy women who are at risk. However, in some women, tamoxifen also may increase the risk for cancer in the inner layer of cells within the uterus, or endometrium. Researchers have proposed that endometrial cancer occurs because of the attachment of a tamoxifen metabolite to DNA. Using an extremely sensitive form of a mass spectrometric assay developed at an NCRR-supported research resource, scientists identified the enzyme responsible for converting tamoxifen into the DNA-binding metabolite. This finding may result in a new therapeutic approach to reduce the risk of endometrial cancer associated with tamoxifen therapy.

Rare Diseases

According to the Rare Diseases Act of 2002, a rare disease is a condition that affects fewer than 200,000 people in the United States. The National Organization for Rare Disorders has identified more than 6,000 rare diseases collectively affecting approximately 25 million

Americans. NCRR-funded General Clinical Research Centers have long provided a stable, state-of-the-art environment for the characterization of rare diseases. Such approaches have led to the development of enzyme therapies, including an FDA-approved therapy for Fabry's disease, described in the Story of Discovery below. Clinical research networks that provide investigators support in specialized settings are designed to identify and study affected patients with specific rare diseases that may lead to more effective therapies. Scientists can now combine data from multiple clinical sites and greatly strengthen the power of their studies and complete them in a fraction of the time required in the past. This approach will enhance translation of research findings to the patient.

Story of Discovery: Fabry's Disease—The Path to Treatment

The public may take comfort in knowing that a devastating disease is rare, but patients with the disorder, their family members, and physicians feel quite the opposite. Rare conditions often are more difficult to diagnose, treat, and cure. Such is the case with Fabry's disease, which affects about 1 in 40,000 males worldwide, according to *Harrison's Principles of Internal Medicine,* 15th edition.

The genetic defect of Fabry's disease is transmitted on the X chromosome, and therefore seen in its full-blown form predominantly in males. Fabry's disease is a metabolic disorder in which a defective gene fails to produce the enzyme alpha-galactosidase A. That enzyme deficiency interferes with the breakdown of fatty compounds called glycosphingolipids, particularly globotriaosylceramide (GL-3), which progressively build up in cells and tissues even before birth. Eventually, the buildup of these compounds clogs the small blood vessels of the kidneys, heart, and brain, causing these organs to malfunction. Patients with Fabry's disease rarely survive beyond their early 50s.

Fortunately, the outlook for such patients is likely to improve, now that a recombinant enzyme has become the first FDA-approved treatment for Fabry's disease. This promising new treatment, which involves regular infusions of the enzyme alpha-galactosidase A, clears GL-3 from kidneys, heart, and skin, and reverses the disease's worst pathology. In addition to giving affected patients hope for a better future, FDA approval represents the success of translational medicine, with incremental advances in basic science and clinical research ultimately leading to improved diagnosis and treatment of this devastating rare disease.

The condition was first described more than 100 years ago by German dermatologist Johann Fabry. By 1938, scientists had discovered that the deposits of a fatty substance, later identified as GL-3, in blood vessels throughout the body are responsible for the pathology of the disorder. In the 1960s, scientists pinpointed the inherited defect in alpha-galactosidase A that interferes with the breakdown of GL-3.

In 1970, a study conducted at the University of Minnesota General Clinical Research Center (GCRC) provided the first tantalizing clues that enzyme replacement may hold promise for treating Fabry's disease, although the technological limitations of the day made the therapy impractical. Dr. Robert Desnick and his colleagues showed that GL-3 levels in patients dropped sharply, although temporarily, following an infusion of donated blood plasma that contained a normal concentration of alpha-galactosidase A.

Throughout the 1970s and into the 1980s, scientists continued several approaches to purify and characterize tissue and plasma forms of the enzyme alpha-galactosidase A. In 1986, the field advanced significantly when Dr. Desnick and his colleagues at the Mount Sinai School of Medicine isolated the gene that makes the enzyme. By the early 1990s, a suite of sophisticated new technologies began to emerge in conjunction with genome-sequencing efforts. Dr. Desnick's group developed a technique for generating relatively large quantities of a high-uptake glycoform of human alpha-galactosidase A by inserting the gene for the enzyme into cultured hamster ovary cells. This was soon followed by their development of the first animal model for Fabry's disease. This mouse model lacks the gene for alpha-galactosidase A and—like human patients with Fabry's disease—accumulates GL-3 in plasma and other key organs.

Phase I/II clinical trials conducted at the Mount Sinai GCRC suggested that the enzyme replacement therapy was safe and promising. Ultimately, a multi-center randomized, placebo-controlled Phase III trial was conducted to test the effects of recombinant alpha-galactosidase A in 58 Fabry's disease patients. More than two-thirds of the treatment group—but none of the patients receiving placebo—achieved complete or nearly complete clearance of GL-3 deposits in their kidneys. Similar, or even better, results were observed in skin and heart tissues. Perhaps the most telling result was that, at the end of the study, all patients who had been receiving enzyme replacement infusions elected to continue the therapy, and the entire placebo group asked to receive the therapy as well.

In conjunction with the NIH Office of Rare Diseases and other groups, NCRR is now launching a new Center initiative—the Rare Diseases Clinical Research Network—to address the challenges inherent in diagnosing and treating rare diseases. The Network will enable collaborations among scientists from multiple disciplines and institutions, who will share research resources and patient populations in their investigation of at least 15 rare diseases. In addition to training clinical investigators, participating clinical centers will be working to identify the biomarkers and clinical manifestations of the diseases. NCRR-supported GCRCs will provide valuable resources to the new centers, as they work to develop novel approaches to the diagnosis, prevention, and treatment of rare diseases. Through these and other innovative efforts, NIH will continue to help move basic science out of the laboratory and into the clinic.

Genetic Medicine

Gene Transfer Success

Gene transfer has more commonly been used to correct disorders affecting single bodily functions, such as vision or blood clotting. Now, scientists at the University of Pennsylvania have developed the first gene transfer that treats a disorder that affects multiple body functions. The condition, known as Sly Syndrome, is caused by a gene that produces a defective version of the enzyme beta-glucuronidase, resulting in a life-threatening buildup of carbohydrates in organs throughout the body. To prevent the disease in dogs with the mutant gene, the researchers injected newborn pups with a genetically engineered virus carrying the normal gene, which inserted itself into growing liver cells. The cells then secreted the normal enzyme which reduced carbohydrate buildup in key organs and tissues.

Mutant Mouse Model Helps Explain Heart Failure

Researchers have identified a gene abnormality in humans that leads to a rare condition that causes early heart failure and death. To study how the mutation interferes with heart function, scientists at the NCRR-supported Sarcoplasmic Reticulum Mutant Mouse Resource created transgenic mice carrying the mutation. Studies showed that the mutation disrupted the normal flow of calcium ions within heart muscle cells and interfered with heart muscle relaxation. The researchers speculate that abnormal calcium flow within heart muscle cells may be the primary trigger of heart failure in various types of cardiovascular pathologies. Therapies that restore normal calcium handling may be able to treat these pathologies and prevent heart failure.

Worms Shed Light on Cell Biology of Aging

Researchers at Rutgers University and their colleagues analyzed cellular structures in tissues of a simple nematode (round worm) model, *Caenorhabditis elegans*, during aging. By studying hundreds of worms at various points in adulthood, the researchers discovered that the animal's muscle cells began to deteriorate in mid-life in a manner resembling the process that occurs in humans. However, the worm's nervous system remained surprisingly intact. Although the worms were genetically identical, their muscles deteriorated at different rates, indicating that nongenetic random factors play a role in aging. The scientists also examined muscle structure in

worms carrying a "longevity gene," a mutation that caused them to live 60-100 percent longer than wild-type worms. The muscles of the mutant worms remained intact for longer periods during aging, suggesting that the longevity gene may work by prolonging the integrity of muscle cells. The researchers conclude that both genetic and random factors play a role in nematode aging and that *C. elegans* may provide a model for understanding the aging process in humans.

Clustering of Co-expressed Genes in the Genome

Although every cell in the body contains the same set of genes, cells in different tissues produce only the proteins encoded by a subset of their genes. Scientists have long sought to understand how the cells in various tissues know which genes to express. In the worm *C. elegans,* researchers at Stanford University found that genes clustered together on the genome tend to be expressed together. Other studies have shown similar results in human tissues. Understanding the organization of genes within genomes could help researchers determine why certain genes are differentially expressed in specific tissues and perhaps shed light on the mechanisms of genetic diseases.

Innovative Therapeutics

Another emerging trend in biomedical science is the study of stem cells, the precursor cells in the body that hold the potential to replace missing or damaged cells in various tissues, enabling treatment of diseases including Parkinson's and diabetes. Researchers at the NCRR-supported Wisconsin National Primate Research Center were the first to culture embryonic stem cells from nonhuman primates, as described in the Story of Discovery below. NCRR continues to support research for optimizing culture conditions for growing and manipulating animal stem cells. To provide investigators with stem cells from a variety of animal species, NCRR plans to enhance the availability of nonhuman primate stem cells for research.

Story of Discovery: Exploring the Promise of Animal Stem Cells

Stem cells have captured the imagination of scientists and the publiC With their dual capability to replicate themselves and generate daughter cells that can mature into other cell types, stem cells hold the potential to replace missing or damaged cells to treat a wide variety of human disorders, including Parkinson's disease, heart failure, and some insulin-dependent forms of diabetes mellitus type 1. However, before these potential uses are attained, additional basic research must be done to define the microenvironments and factors required to generate specific functional cell types.

One of the most promising lines of research has focused on animal embryonic stem (ES) cells, formed soon after an egg is fertilized and starts dividing. In the developing embryo, ES cells transform, or differentiate, into the many specialized cells that make up an organism.

Research on ES cells was initially hampered by difficulties in maintaining the undifferentiated cells in culture. A major breakthrough came in 1981, when scientists succeeded in culturing mouse ES cells. Subsequent research throughout the 1980s and early 1990s, much of which was NIH-funded, showed that mouse ES cells could differentiate into heart cells, neural cells, and other cells in the body.

Unfortunately, the intricate, multistep technique developed for culturing mouse cells proved unworkable when applied to other mammalian species. Researchers quickly learned that embryos must be removed from the animal at just the right time, and embryonic cells must be cultured under specific conditions to allow them to replicate but not differentiate.

Not until 1995 did scientists achieve the right combination of techniques and conditions for producing ES cell cultures from another mammalian species. Working at the NIH/NCRR-funded Wisconsin National Primate Research Center (NPRC), Dr. James Thomson and his colleagues found that they could grow ES cells from rhesus macaque embryos on a blanket of mouse connective tissue cells, called fibroblasts. These "feeder cells," which secreted substances that supported the growth of the ES cells and prevented them from differentiating, proved to be the critical factor in producing rhesus ES cell cultures. A year later, the Wisconsin researchers succeeded in producing ES cell lines from another nonhuman primate species, the common marmoset.

Importantly, cultured rhesus ES cells appeared to be capable of differentiating into the various cell types of the body. When treated with certain chemicals in culture or injected into immunodeficient mice to avoid problems with immune rejection, the ES cells differentiated into cells characteristically found in bone, muscle, nervous system, and other tissues.

Using knowledge gained from their studies with nonhuman primate cells, Dr. Thomson and his colleagues took a significant step forward in 1998, when they isolated and propagated human ES cells. As in their nonhuman primate studies, the researchers derived their cell lines from cells formed only days after the egg was fertilized and started dividing. Shortly after the Wisconsin group announced their accomplishment, Dr. John Gearhart and his colleagues at Johns Hopkins University reported that they had also derived human ES cell lines, although these researchers used as their source primordial germ cells—precursors of human sperm and eggs. Both lines of research were conducted independent of NIH support and together set the stage for exploring the use of human ES cells for replacement therapies. Subsequently, other research groups developed their own human ES cell lines.

Now that ES cell lines from multiple species are available, scientists are working with animal models to determine whether stem cell transplants might be used to treat human diseases. One area of intensive research involves transplanting stem cell derivatives into the brain or spinal cord to treat neurological disorders or injuries. In one study, scientists at Harvard University injected mouse ES cells into the brains of rats with a condition similar to Parkinson's disease. In this disease, some of the neurons that produce the messenger chemical dopamine have degenerated, causing abnormal movements. The scientists found that the transplanted ES cells differentiated into the dopamine-producing neurons, thereby allowing the rats to perform normally in a motor test.

Using animal models of diabetes, in which the insulin-producing cells in the pancreas have been destroyed, researchers also are exploring the possibility that transplanted stem cells might differentiate into insulin-producing cells and correct diabetes. Spanish researchers have transplanted insulin-producing cells derived from mouse ES cells into the spleens of diabetic mice, where they secreted enough insulin to normalize blood glucose levels. To facilitate research on animal stem cells, NIH has established the National Stem Cell Resource, which maintains and distributes embryonic and postnatally derived stem cells from a variety of nonhuman species.

Besides ES cells, scientists also are studying the efficacy of other stem cell types for replacing damaged tissues. One that looks particularly promising is derived from the connective tissue within the umbilical cord. These so-called umbilical cord mesenchymal (UCM) stem cells, which ordinarily form connective tissue, can be coaxed to form nerve cells when treated with certain chemicals. In one recent study, scientists at Kansas State University transplanted pig UCM cells into the brains of rats and found that about 10 percent of the UCM cells transformed into neurons within six weeks. Although the UCM cells were derived from a different species, they did not provoke an immune response in the rat. In contrast, ES cell transplants, even from the same species, have been shown to induce immune responses in recipients, necessitating the use of harsh immunosuppressive drugs.

Scientists also are experimenting with so-called adult stem cells derived from bone marrow and fat tissue. As the name suggests, adult stem cells are formed later in development and remain undifferentiated long after birth. While ES cells are capable of generating any cell type, adult stem cells generally differentiate into only a few cell types. For example, hematopoietic stem cells from the bone marrow differentiate into the various types of blood cells, and mesenchymal stem cells, also from the bone marrow, differentiate into bone, cartilage, muscle, and related tissues. Recent evidence suggests that adult stem cells may be more adaptable than previously thought. For example, transplants of mesenchymal stem cells in rodents have differentiated into liver and brain cells. Also, hematopoietic stem cells injected intravenously into mice have been shown to migrate into the brain and differentiate into neurons.

The apparent versatility of stem cells makes them possible candidates to replace many current drug and medical interventions in the future. For example, instead of treating Parkinson's patients with the drug L-DOPA, which eventually loses its effectiveness, patients might one day receive transplants of dopamine-producing cells that have been differentiated from embryonic stem cells in the laboratory. Instead of treating diabetes with insulin injections, patients might receive stem cell transplants that generate needed insulin-producing cells. Stem cell transplants also might be used to treat diseases for which effective treatments currently do not exist, such as Alzheimer's disease.

Many scientists view the culturing of stem cells as an unprecedented scientific breakthrough. With their potential for generating almost every cell type in the human body, stem cells may eventually revolutionize the practice of medicine and improve the quality and length of life.

Stem Cell Biology

Adult Stem Cells Produce Blood Cells in Primate Models

All blood cells originate from hematopoietic stem cells (HSCs), located in bone marrow. To better understand how these adult stem cells function in the body, investigators from the Washington National Primate Research Center and elsewhere examined the fate of genetically marked HSCs administered to nonhuman primates. The researchers showed that HSC descendent cells produced different blood cell types for at least two years. This system provides a model that can be probed to study the microenvironments required for normal blood cell development and the effects of chemicals, drugs, and other interventions on that process.

Science Advances

Preventing Ongoing Brain Damage After a Ruptured Aneurysm

When aneurysms (weakened regions of an artery wall) rupture, approximately one-third of cases result in severe oxygen restriction to the brain, and possibly death. Scientists at the University of Vermont found that small-diameter arteries are more constricted than normal during a vasospasm that follows a ruptured aneurysm; it was previously believed that only large-diameter arteries had this response. The findings suggest that small arteries may be important targets for drug therapies.

Mapping Brain Deterioration in Alzheimer's Disease

Autopsies of Alzheimer's disease (AD) patients have revealed that protein tangles—believed to be the source of the damage—start out in one region of the brain and then spread to other regions over time. Using magnetic resonance imaging, researchers at the University of California, Los Angeles, tracked brain changes in advanced AD and normal elderly patients. The images of AD patients showed atrophy occurring first in areas associated with memory and then spreading to regions involved in sensory perception. Development of atrophy closely mirrored both the decline in cognitive function and the spread of protein tangles seen in autopsy studies. A better understanding of the degeneration sequence could contribute to early diagnosis, perhaps even before symptom onset, and lead to improved therapies for AD.

Observing Living Nerve Cells

To observe a tissue under the microscope, a scientist ordinarily must apply a fixative and a stain, both of which kill the tissue. Consequently, the scientist cannot be certain that the image viewed through the microscope accurately reflects the living tissue. Now researchers at Cornell

University and Massachusetts General Hospital have developed a new microscopic technique that allows scientists to view living nerve cells, or neurons, in brain slices. The technique involves applying laser pulses to brain tissue and then capturing the resulting light emitted by the tissue. The scientists found that the subcellular structures responsible for emitting the light were microtubules, which are protein tubes that help to transport chemicals within the cell and also provide a structural scaffolding for neurons and other cells. The imaging technique is sufficiently gentle to allow observation of cells dividing and growing and should be valuable for studying neuronal growth and repair, as well as changes that occur during neurodegenerative diseases.

Using Optical Techniques to Detect Oral Cancer

Oral cancers are a significant and growing public health problem worldwide. With support from NCRR, researchers at the Massachusetts Institute of Technology have developed optical tools to detect oral cancers that are difficult to distinguish via existing methods. Their approach, called trimodal spectroscopy (TMS), involves examining three different optical properties of oral tissue, which together provide information about tissue biochemistry and microscopic structure. Using TMS with patients who had varying degrees of malignancy in their oral cavities, the researchers were able to differentiate cancerous tissue from healthy, noncancerous tissue 96 percent of the time. The results suggest that TMS is a highly sensitive technique that may be used to enhance detection of oral tumors before they become visible to the naked eye.

Treating Diabetes with Islet Cell Transplants and Gene Transfer

Patients with type 1 diabetes who receive a single transplant of insulin-producing pancreatic islet cells can be freed of the need for insulin injections, particularly when a large number of cells are transplanted and patients adhere to a novel immunosuppressive regimen. Using an islet cell transplant regimen known as the Edmonton protocol, researchers at the University of Pennsylvania successfully treated seven patients who frequently experienced dangerous episodes of low blood sugar. All seven achieved independence from insulin injections, although the graft later failed in one recipient. This report confirms the efficacy of the Edmonton protocol. A separate study with mice indicates that diabetes might eventually be treated with a gene transfer technique that blocks the immune system from destroying islet cells. Scientists isolated the adenovirus genes that protect the virus from immune destruction and inserted the genes into nonobese (NOD) diabetic mice, which spontaneously develop a condition similar to human type 1 diabetes. The genetically modified NOD mice expressed the protective adenovirus genes in their islet cells and did not develop diabetes, apparently because the inserted genes protected the cells from immune destruction. The researchers are investigating the possibility of genetically engineering islet cells prior to transplanting them into diabetic patients so that the cells can evade immune system attacks. Ultimately, these genetically engineered transplants might prevent or reverse type 1 diabetes.

Drug Treatment to Enhance Weight Loss in Obese Adolescents

Adolescent obesity is a mounting health problem. To determine whether the weight-loss drug Sibutramine and behavioral therapy might produce more weight loss in adolescents than behavioral therapy alone, researchers at the University of Pennsylvania and their colleagues conducted a clinical trial involving 82 obese adolescents ages 13 to 17. The trial showed that adding Sibutramine to behavioral therapy led to significantly more weight loss than behavioral

therapy alone. However, a significant number of patients experienced elevated heart rate and blood pressure, underscoring the need for careful monitoring. The authors recommend that weight loss drugs be administered to adolescents and children only on an experimental basis until more safety and efficacy studies can be performed.

NIH Roadmap

NCRR programs complement several NIH Roadmap Initiatives. NCRR's scientific mission includes development and support of technologies and research resources to facilitate research of NIH-supported investigators. NCRR is partnering with other NIH components in the following Roadmap initiatives: National Technology Centers for Networks and Pathways; Standards for Proteomics and Metabolomics; Assessment of Critical Reagents for Proteomics; Interdisciplinary Research Centers; National Centers for Biomedical Computing; Integration of Clinical Research Networks. From a technical perspective, NCRR currently provides substantial support for technology development and resources in the highly interdisciplinary area of structural proteomics. Also, the interdisciplinary nature of NCRR's existing clinical research resources provides an obvious national network that can be leveraged to achieve the Roadmap goals. These initiatives will make substantial use of existing NCRR resources and centers.

Future Research Directions

Enhance Genotyping and Phenotyping Studies

To discover the effects that genes have when they are expressed, scientists must decipher an individual's genetic makeup and how it affects physical, biochemical, or other changes. Determining an individual's genotype refers to identifying the alleles, or forms of the genes of interest, that are possessed by the individual. Phenotype refers to the physical, biochemical, physiological, or behavioral characteristics that are associated with expression of specific alleles. The resource, to be funded by NCRR, will support a data-coordinating center to track both human and animal genotypic and phenotypic data and other endpoints.

Enhance the Utility of Alternative Nonhuman Primate Species

Investigators have preferred using rhesus macaques, particularly those of Indian origin, primarily because much is known about the biology of this species. However, a shortage of Indian-origin rhesus macaques for use in biomedical research now exists. There is a critical need for rhesus at the National Primate Research Centers (NPRCs) where investigators continue their efforts to develop an effective AIDS vaccine. Other Old World nonhuman primate species—such as rhesus of Chinese origin, macaques other than rhesus, baboons, and vervets—may be suitable substitutes if more were known about their immune responses, genomes, and other biological factors. To analyze these factors and thereby increase their utility, NCRR will fund an initiative to develop and test new and existing reagents in these species.

Cross-Reference Mutant Mouse Model Informatics Systems

The NCRR-sponsored Mutant Mouse Regional Resource Centers (MMRRC) program functions as a one-stop shop for researchers to donate and acquire mutant mouse models. The program

currently includes four repository distribution centers, electronically linked through an Informatics Coordinating Center. Expanding and cross-referencing this database with similar mouse model informatics systems, such as those at The Jackson Laboratory and the International Mouse Resource, are urgently needed to increase the utility of this database. NCRR plans to fund activities to identify key approaches or methods to develop unifying programs for global databases. There is a rapidly expanding cohort of genetically modified rodents with phenotypic and genotypic data that must be captured for the research community not only to facilitate their research but to assure that unplanned research duplication is avoided.

Expand the Biomedical Informatics Research Network

In FY 2002, NCRR joined with the National Science Foundation, Internet2, and several universities to establish the Biomedical Informatics Research Network (BIRN), a high-performance computer network that links biomedical laboratories around the country. BIRN allows researchers to pool subjects and data; it also gives researchers access to federated databases, bioinformatics tools, and computational resources. In FY 2004, NCRR plans to expand the number and scope of awards under BIRN to build a national infrastructure of computer networks. In addition, several development and analysis centers will be established to collect, monitor, and analyze data generated from clinical studies being conducted throughout the country.

Continued Funding Research Instrumentation

In FY 2002, NCRR established a High-End Instrumentation Program to allow biomedical researchers to purchase instrumentation costing more than $750,000. NCRR will continue to support this program in FY 2005.

Establish a Center for Structural Biology of Macromolecular Complexes

NCRR research centers have led the development of innovative technologies for the identification of proteins and the characterization of protein interactions. As understanding of protein interactions grows, it has become clear that many macromolecules function in complexes rather than alone. These complexes can be strong or weak, last for brief periods or remaining stable for long periods. It is now vital to build technologies that can delineate the 3-D structures of macromolecular complexes. This effort will require a convergence of three complementary technologies for which NCRR currently provides substantial support for technology development and infrastructure: proteomics, electron microscopy, and X-ray crystallography. This Center initiative in structural proteomics will complement ongoing efforts in interaction proteomics.

Increase High-Capacity Broad-Bandwidth Connectivity at Underserved Institutions

Underserved institutions, such as doctoral degree granting minority institutions or institutions in states that historically have not competed well for NIH funding, need access to broad-bandwidth connectivity to foster collaborations with investigators at more established research centers. NCRR will increase the research capacity of institutions by providing high-capacity Internet connectivity. This effort will provide access to sophisticated computational tools and facilitate the acquisition of clinical data relating to diseases that occur disproportionately among ethnic minority and geographically remote populations.

Expand the Research Subject Advocate Program

Regulations, policies, and guidelines of Federal, state and local governments are intended to protect human subjects participating in clinical research projects but, unfortunately, place heavy demands on the time of already-busy clinician researchers. To address this concern, NCRR plans to extend and strengthen the Research Subject Advocate (RSA) program, currently limited to General Clinical Research Centers. NCRR will consider extending RSA coverage to the host institution or medical center that provides a value-added approach. The RSA program will encourage more workshops and other complementary activities for clinical investigators at the host institution as well as for investigators from other nearby institutions. NCRR will encourage collaborations among geographically clustered institutions to assure that investigators are aware of their ethical and medical care responsibilities, intended to enhance the safety of study subjects.

Expand the Rare Diseases Clinical Research Network

To address the challenges inherent in diagnosing and treating rare diseases, NCRR and the NIH Office of Rare Diseases established the Rare Diseases Clinical Research Network. Additional support was provided from several other NIH components. The network consists of a Data and Technology Coordinating Center (DTCC) and seven Rare Diseases Clinical Research Centers (RDCRCs). The consortium of NIH components will provide support for new ancillary sites. This configuration will expand the network over a greater geographic area with more investigators and patients with rare diseases and will accelerate recruitment of research subjects across the RDCRCs.

Establish a Clinical Informatics Resource

To help clinical investigators collect, analyze, and report their data, NCRR plans to establish a clinical informatics resource. This resource will facilitate data sharing with other research groups, such as the Rare Diseases Clinical Research Network. A major goal of this NCRR initiative will be to provide investigators access not only to expertise for study design, data management and analysis but to bioinformatics tools and scaleable computing. Investigators will be encouraged to use standard vocabularies for data entry and to consider depositing datasets, derived from their studies, to a repository to be mined by additional investigators.

Establish a Research Centers in Minority Institutions Clinical Research Network

A high priority of the Research Centers in Minority Institutions (RCMI) program is to expand the clinical research capacity of those RCMI institutions with affiliated medical schools by further developing their information technologies infrastructure. To support high-quality clinical trials that address ethnic health disparities, NCRR will establish an RCMI Clinical Research Network (RCRN) that will include the requisite technical support and access to Internet2 for collaborative research studies and multisite clinical trials. In addition to the sites constituted for clinical research, the remaining RCMI institutions currently without Internet2 connections, will be added to the RCMInet. This is important for basic scientists' access to databases and technologies for genomics, proteomics, imaging, and health outcomes research.

Increase the Capacity to Perform Health Disparities Research

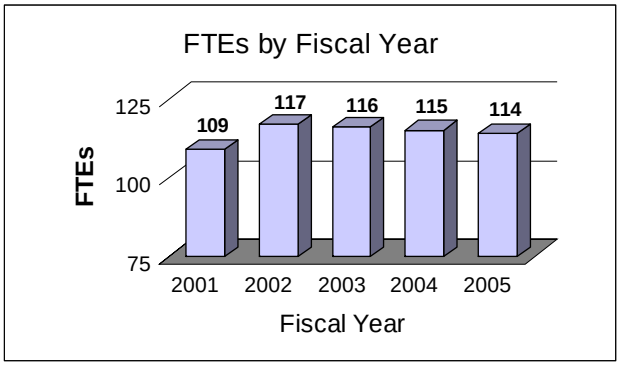
NCRR supports three initiatives intended to discern the causes or factors that contribute to health disparities among racial and ethnic minority populations. The initiatives include: 1)

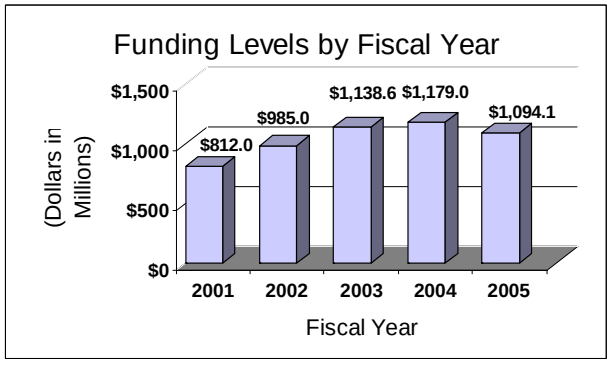
Comprehensive Centers on Health Disparities at minority-serving medical schools affiliated with the RCMI program; 2) a Stroke Prevention and Intervention Research Program that focuses on minorities; and 3) a Clinical Research Education and Career Development award to provide training in clinical research for doctoral and postdoctoral candidates in minority institutions. NCRR will continue support for this important research area.

Budget Policy

The Fiscal Year 2005 budget request for the NCRR is $1,094,141,000, a decrease of $84,814,000 and 7.2 percent over the FY 2004 Final Conference Level. Also included in the FY 2005 request, is NCRR's support for the trans-NIH Roadmap initiatives, estimated at 0.63% of the FY 2005 budget request. This Roadmap funding is distributed through the mechanisms of support, consistent with the anticipated funding for the Roadmap initiatives. A full description of this trans-NIH program may be found in the NIH Overview.

A five year history of FTEs and Funding Levels for NCRR are shown in the graphs below. Note that the Fiscal Year 2001 FTE figure is not comparable to the figures in the succeeding years due to NIH's consolidation of its Human Resources function in FY 2003.





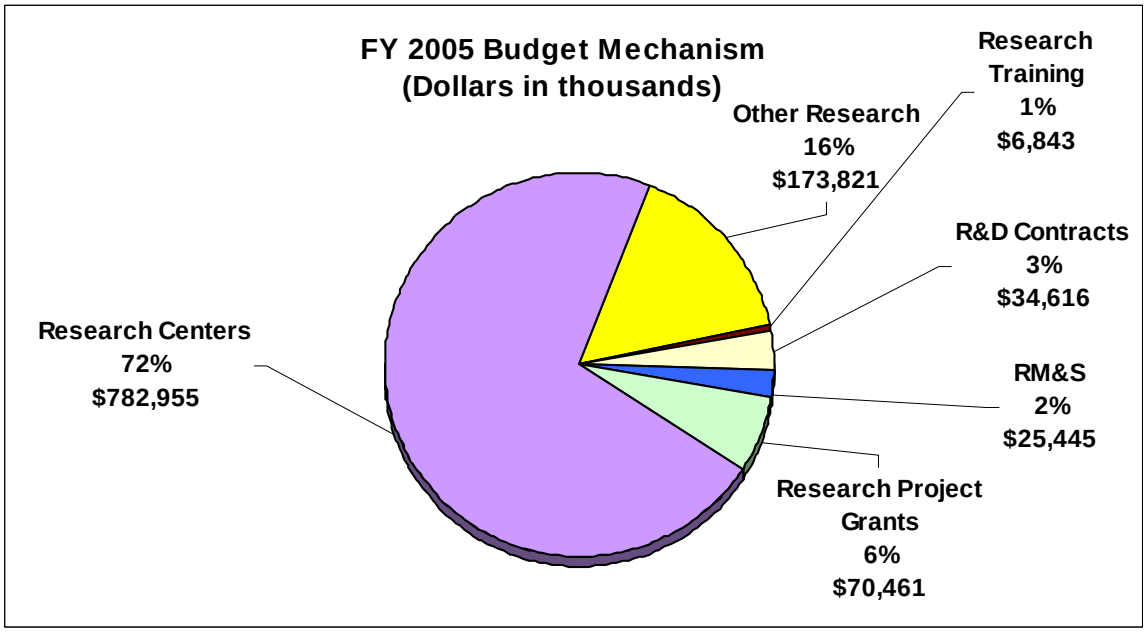
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The FY 2005 NIH request provides for an aggregate 1.3 percent increase in average cost for Research Project Grants, consistent with the Gross Domestic Product deflator. The NCRR is providing an average cost increase of 1.9 percent for direct recurring costs in noncompeting continuation awards. Competing RPGs are based on an average cost increase of 1 percent.

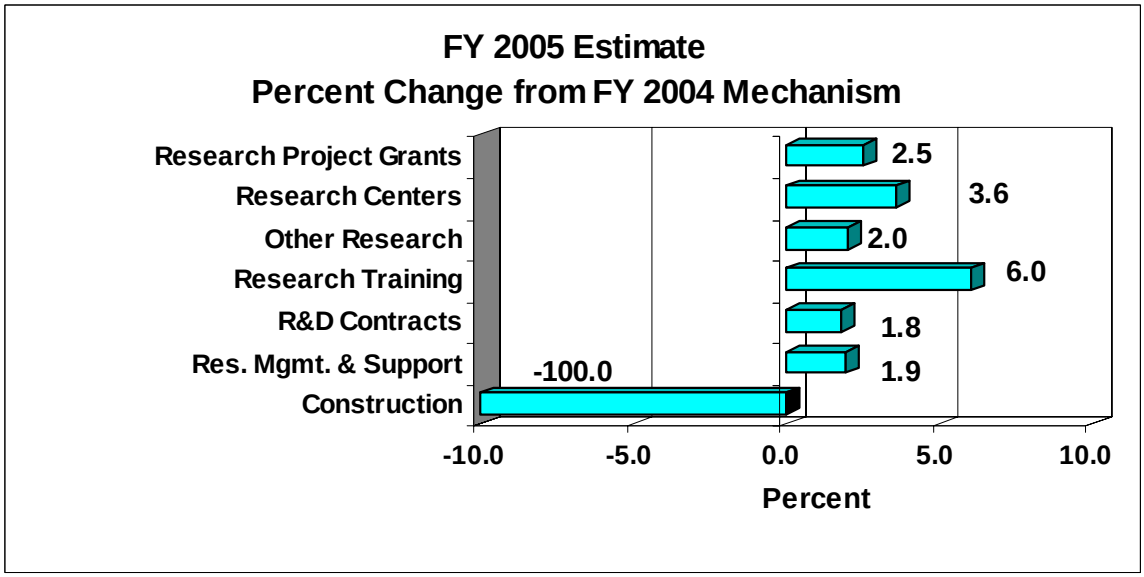
Advancement in medical research is dependent on maintaining the supply of new investigators with new ideas. In the Fiscal Year 2005 request, NCRR will support 151 pre- and postdoctoral trainees in full-time training positions. Stipend levels for pre-doctoral and post-doctoral recipients supported through the Ruth L. Kirschstein National Research Service Awards will remain at FY 2004 levels.

The Fiscal Year 2005 request includes funding for 323 research centers—including over $222 million for 96 centers funded under the Institutional Development Awards (IdeA) program—680

other research grants, including 138 clinical career awards, and 56 R&D contracts. The extramural construction program is not included in the FY 2005 request. Research Management and Support receives increases to support increased pay and estimated inflationary increases in FY 2005.

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





NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Budget Mechanism - Total

MECHANISM	FY 2003 Actual		FY 2004 Final Conference		FY 2005 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	71	$25,689,000	86	$30,320,000	83	$28,638,000
Administrative supplements	(0)	0	(0)	6,000	(1)	155,000
Full funded	0	0	0	0	0	0
Single year	41	11,838,000	39	11,566,000	41	12,281,000
Subtotal, competing	41	11,838,000	39	11,566,000	41	12,281,000
Subtotal, RPGs	112	37,527,000	125	41,892,000	124	41,074,000
SBIR/STTR	82	24,645,000	89	26,845,000	97	29,387,000
Subtotal, RPGs	194	62,172,000	214	68,737,000	221	70,461,000
Research Centers:						
Specialized/comprehensive	87	207,624,000	92	214,298,000	96	222,098,000
Clinical research	106	284,989,000	106	295,411,000	106	303,923,000
Biotechnology	49	81,495,000	50	82,410,000	50	85,056,000
Comparative medicine	53	102,335,000	53	110,221,000	53	116,704,000
Research Centers in Minority Institutions	18	51,770,000	18	53,567,000	18	55,174,000
Subtotal, Centers	313	728,213,000	319	755,907,000	323	782,955,000
Other Research:						
Research careers	168	34,085,000	170	35,093,000	174	35,773,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	164	70,737,000	164	70,760,000	164	70,762,000
Minority biomedical research support	0	0	0	0	0	0
Other	294	63,996,000	341	64,551,000	342	67,286,000
Subtotal, Other Research	626	168,818,000	675	170,404,000	680	173,821,000
Total Research Grants	1,133	959,203,000	1,208	995,048,000	1,224	1,027,237,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	3	119,000	3	121,000	3	121,000
Institutional awards	133	5,500,000	140	6,332,000	148	6,722,000
Total, Training	136	5,619,000	143	6,453,000	151	6,843,000
Research & development contracts	58	31,468,000	56	33,996,000	56	34,616,000
(SBIR/STTR)	(0)	(0)	(0)	(0)	(0)	(0)
	FTEs		FTEs		FTEs	
Intramural research	0	0	0	0	0	0
Research management and support	116	23,048,000	115	24,962,000	114	25,445,000
Cancer prevention & control	0	0	0	0	0	0
Construction		119,220,000		118,497,000		0
Total, NCRR	116	1,138,558,000	115	1,178,956,000	114	1,094,141,000
(RoadMap Support)		(0)		(4,048,000)		(6,900,000)
(Clinical Trials)		(97,803,000)		(101,191,000)		(103,964,000)

NATIONAL INSTITUTES OF HEALTH
National Center for Research Resources

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2003 Actual FTEs	FY 2003 Actual Amount	FY 2004 Final Conference FTEs	FY 2004 Final Conference Amount	FY 2005 Estimate FTEs	FY 2005 Estimate Amount	Change FTEs	Change Amount
Extramural Research:								
Extramural research resources		$1,115,510		$1,153,994		$1,068,696		($85,298)
Subtotal, Extramural research		1,115,510		1,153,994		1,068,696		(85,298)
Research management & support	116	23,048	115	24,962	114	25,445	(1)	483
Total	116	1,138,558	115	1,178,956	114	1,094,141	(1)	(84,815)

NATIONAL INSTITUTES OF HEALTH
National Center for Research Resources

Summary of Changes

FY 2004 Final Conference				$1,178,956,000
FY 2005 Estimated Budget Authority				1,094,141,000
Net change				(84,815,000)
	FY 2004 Budget Base		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$0		$0
b. Annualization of January 2004 pay increase		0		0
c. January 2005 pay increase		0		0
d. One less day of pay		0		0
e. Payment for centrally furnished services		0		0
f. Increased cost of laboratory supplies, materials, and other expenses		0		0
Subtotal				0
2. Research Management and Support:				
a. Within grade increase		11,454,000		199,000
b. Annualization of January 2004 pay increase		11,454,000		12,000
c. January 2005 pay increase		11,454,000		131,000
d. One less day of pay		11,454,000		(45,000)
e. Payment for centrally furnished services		1,836,000		57,000
f. Increased cost of laboratory supplies, materials, and other expenses		11,672,000		232,000
Subtotal				586,000
Subtotal, Built-in				586,000

NATIONAL INSTITUTES OF HEALTH
National Center for Research Resources

Summary of Changes--continued

CHANGES	FY 2004 Budget Base No.	FY 2004 Budget Base Amount	Change from Base No.	Change from Base Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	86	$30,326,000	(3)	($1,533,000)
b. Competing	39	11,566,000	2	715,000
c. SBIR/STTR	89	26,845,000	8	2,542,000
Total	214	68,737,000	7	1,724,000
2. Research centers	319	755,907,000	4	27,048,000
3. Other research	675	170,404,000	5	3,417,000
4. Research training	143	6,453,000	8	390,000
5. Research and development contracts	56	33,996,000	0	620,000
Subtotal, extramural				33,199,000
	FTEs		FTEs	
6. Intramural research	0	0	0	0
7. Research management and support	115	24,962,000	(1)	(103,000)
8. Construction		118,497,000		(118,497,000)
Subtotal, program		1,178,956,000		(85,401,000)
Total changes	115		(1)	(84,815,000)

NATIONAL INSTITUTES OF HEALTH
National Center for Research Resources

Budget Authority by Object

	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	115	114	(1)
Full-time equivalent of overtime & holiday hours	0	0	0
Average ES salary	$145,350	$150,300	$4,950
Average GM/GS grade	11.4	11.4	0.0
Average GM/GS salary	$73,548	$74,651	$1,103
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$99,799	$101,296	$1,497
Average salary of ungraded positions	130,205	132,158	1,953

OBJECT CLASSES		FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease
	Personnel Compensation:			
11.1	Full-Time Permanent	$8,369,000	$8,523,000	$154,000
11.3	Other than Full-Time Permanent	721,000	734,000	13,000
11.5	Other Personnel Compensation	278,000	283,000	5,000
11.7	Military Personnel	96,000	98,000	2,000
11.8	Special Personnel Services Payments	17,000	17,000	0
	Total, Personnel Compensation	9,481,000	9,655,000	174,000
12.1	Civilian Personnel Benefits	2,104,000	2,142,000	38,000
12.2	Military Personnel Benefits	74,000	75,000	1,000
13.0	Benefits for Former Personnel	0	0	0
	Subtotal, Pay Costs	**11,659,000**	**11,872,000**	**213,000**
21.0	Travel & Transportation of Persons	475,000	481,000	6,000
22.0	Transportation of Things	69,000	70,000	1,000
23.1	Rental Payments to GSA	0	0	0
23.2	Rental Payments to Others	11,000	11,000	0
23.3	Communications, Utilities & Miscellaneous Charges	133,000	135,000	2,000
24.0	Printing & Reproduction	242,000	245,000	3,000
25.1	Consulting Services	778,000	788,000	10,000
25.2	Other Services	593,000	601,000	8,000
25.3	Purchase of Goods & Services from Government Accounts	35,066,000	32,580,000	(2,486,000)
25.4	Operation & Maintenance of Facilities	1,549,000	1,569,000	20,000
25.5	Research & Development Contracts	8,454,000	9,238,000	784,000
25.6	Medical Care	0	0	0
25.7	Operation & Maintenance of Equipment	690,000	699,000	9,000
25.8	Subsistence & Support of Persons	0	0	0
25.0	**Subtotal, Other Contractual Services**	**47,130,000**	**45,475,000**	**(1,655,000)**
26.0	Supplies & Materials	146,000	148,000	2,000
31.0	Equipment	1,603,000	1,624,000	21,000
32.0	Land and Structures	0	0	0
33.0	Investments & Loans	0	0	0
41.0	Grants, Subsidies & Contributions	1,117,590,000	1,034,080,000	(83,510,000)
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	**1,167,399,000**	**1,082,269,000**	**(85,130,000)**
	Total Budget Authority by Object	**1,179,058,000**	**1,094,141,000**	**(84,917,000)**

NATIONAL INSTITUTES OF HEALTH
National Center for Research Resources

Salaries and Expenses

OBJECT CLASSES	FY 2004 Final Conference	FY 2005 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$8,244,000	$8,386,000	$142,000
Other Than Full-Time Permanent (11.3)	721,000	734,000	13,000
Other Personnel Compensation (11.5)	278,000	283,000	5,000
Military Personnel (11.7)	96,000	98,000	2,000
Special Personnel Services Payments (11.8)	17,000	17,000	0
Total Personnel Compensation (11.9)	**9,356,000**	**9,518,000**	**162,000**
Civilian Personnel Benefits (12.1)	2,024,000	2,058,000	34,000
Military Personnel Benefits (12.2)	74,000	75,000	1,000
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**11,454,000**	**11,651,000**	**197,000**
Travel (21.0)	475,000	481,000	6,000
Transportation of Things (22.0)	69,000	70,000	1,000
Rental Payments to Others (23.2)	11,000	11,000	0
Communications, Utilities and Miscellaneous Charges (23.3)	133,000	135,000	2,000
Printing and Reproduction (24.0)	242,000	245,000	3,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	778,000	788,000	10,000
Other Services (25.2)	593,000	601,000	8,000
Purchases from Govt. Accounts (25.3)	5,588,000	2,683,000	(2,905,000)
Operation & Maintenance of Facilities (25.4)	1,549,000	1,569,000	20,000
Operation & Maintenance of Equipment (25.7)	690,000	699,000	9,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**9,198,000**	**6,340,000**	**(2,858,000)**
Supplies and Materials (26.0)	146,000	148,000	2,000
Subtotal, Non-Pay Costs	10,274,000	7,430,000	(2,844,000)
Total, Administrative Costs	**21,728,000**	**19,081,000**	**(2,647,000)**

National Institutes of Health

National Center for Research Resources

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

FY 2004 House Appropriations Committee Report Language (H.Report 108-188)

Item

Clinical trials–….The Committee encourages NCRR to evaluate clinical research partnerships with minority-serving institutions and to expand its support for clinical trials networks for orphan diseases, such as the cystic fibrosis (CF) clinical trials network. This clinical trials system holds promise as a model for other orphan diseases, and the Committee encourages NCRR to consider strategies for the replication of this network for other orphan diseases. (p. 85)

Action taken

The NCRR modified the Guidelines for General Clinical Research Centers (GCRC) to promote the use of GCRC facilities for rare disease research and specifically to stimulate the development of Therapeutic Development Networks similar to the Cystic Fibrosis Network. In FY 2003 a Lysosomal Storage Diseases Network was initiated at the Mt. Sinai GCRC. Further development of clinical trials networking for orphan (rare) diseases is to be expected following the funding of a Data Coordinating Center for Rare Diseases. This cooperative research network was supported with funding from the Office for Rare Diseases and several other collaborating ICs. This partnership will foster collaborative clinical research studies in rare diseases and longitudinal studies of individuals with rare diseases, clinical studies, phase one and two trials, and/or pilot and demonstration projects. The Data Coordinating Center provides a test bed for distributed clinical data management that incorporates novel approaches and technologies for data management, data mining, and data sharing across rare diseases, data types, and platforms. The network described will also lend itself to minority-serving institutions' participation in national studies to examine the factors which impact underrepresented populations.

Item

Animal resources at minority health professions schools– The Committee commends NCRR for its support of recent efforts to upgrade animal research facilities at minority health professions schools including the recent competitive supplement to Research Centers in Minority Institutions (RCMI) for developing and improving institutional animal resources. These upgrades are necessary to assist these institutions in complying with federal regulations and attain accreditation by the appropriate scientific organizations. The Committee encourages NCRR to continue to work in partnership with the National Center on Minority Health and Health Disparities to support this important initiative. (p. 86)

Action taken
In FY 2002, NCRR awarded funds to nine Research Centers in Minority Institutions through competitive supplements for developing and improving institutional animal facilities. NCRR will continue to work closely with these institutions and provide the technical assistance for the design and construction of these projects.

Item
National primate research centers-…. The Committee encourages NCRR to increase the base support for these centers and to conduct a periodic assessment of primate center needs. The first of these assessments should be submitted at the time of the FY 2005 budget request. (p.86)

Action taken
During the last 5 years, investigator demand for nonhuman primate resources for biomedical research has increased significantly. To help meet this increasing demand, the National Primate Research Centers (NPRCs) have promoted the availability of their national resources with the result that the number of NIH grantees alone that utilize these Centers has increased from 466 to 2,293 over the past 5 years.

To determine the extent of the demand, NCRR sponsored a third-party study, "Evaluation of the Regional Primate Research Centers Program" in July 2000 and also sponsored a National Academy of Sciences Workshop on Rhesus Monkey Demands in Biomedical Research in April 2002. The major recommendations of the activities were to enhance the national capacity for conducting nonhuman primate research and encourage broader use of alternative species by the biomedical research community.

Because of the increased demands for nonhuman primates, especially rhesus, the NCRR has significantly increased breeding programs for rhesus macaques. Over the last five years, the number of rhesus macaques at the National Primate Research Centers Program (NPRC) has increased by over 28 percent. The total nonhuman primate census at the 8 Centers has increased from 20,466 to 25,452 animals during this period. These facilities have also dedicated several hundred animals to the creation of Specific Pathogen Free Colonies for AIDS vaccine research. These animals are free of certain viral pathogens which could interfere with this research. The fruits of these breeding strategies are beginning to help meet the increasing demands for rhesus macaques. Furthermore, discussions are underway to increase breeding facilities (through collaborative efforts of the NPRCs) in Nepal, China, and India with the goal of meeting the growing needs for macaques.

The growth of non-human primate research and the corresponding increases in number of animals in research has prompted NCRR to focus on research animal facilities and care. This is particularly true for animals being used in infectious disease studies (biodefense initiatives) that require special housing. In response, NCRR has provided special funding opportunities in FY 2002 and FY 2003 for the NPRCs to expand their biosafety level 3 caging capabilities and to increase their experimental holding capacities.

Because of the increased demand for, and subsequent shortage of, rhesus monkeys in particular, NCRR and the Office of AIDS Research co-sponsored a workshop in April, 2002, at the

National Academy of Sciences to call attention to the limited availability of rhesus and the need for use of not just rhesus, but for other NHP species that are potential animal models for other human biomedical problems. As a consequence, investigators are beginning to utilize other nonhuman primate models for their research. As an example, biodefense investigators are exploring the use of the long-tailed macaque (cynomologus macaque) as an alternative to the rhesus. This species is very similar to the rhesus in many of its physiological parameters and is much more readily available. Thus, the use of other nonhuman primate species may help to alleviate demands for the rhesus macaque.

Item
Research centers at minority institutions (RCMI)-…. The Committee encourages NCRR to strengthen participation from minority institutions and increase resources available in this area. The Committee also encourages NCRR to work with minority institutions with a track record of producing minority scholars in science and technology. (p. 86)

Action taken
NCRR provides co-funding and administrative support for the Clinical Research Education and Career Development (CRECD) Awards in Minority Institutions. The purpose of the CRECD award is to support the development and implementation of curriculum-dependent programs in minority institutions to train selected doctoral and postdoctoral candidates in clinical research, leading to a Master of Science in Clinical Research or Master of Public Health in a clinically relevant area. The CRECD awards will generate well-trained clinical researchers who can lead clinical research projects in a number of health disparity areas. Other NIH Institutes and Centers that co-funded the CRECD Awards include the National Center for Minority Health and Health Disparities; the National Institute of Arthritis and Musculoskeletal and Skin Diseases; the National Institute of Diabetes and Digestive and Kidney Diseases; the National Heart, Lung, and Blood Institute; the National Institute on Aging; the National Eye Institute; and the National Institute on Drug Abuse.

Item
General clinical research centers (GCRC) . The Committee encourages NIH to upgrade GCRC facilities with the sophisticated technologies needed to apply the mapping of the human genome to the study of human disease and response to the threat of bioterrorism and to support local GCRC pilot projects as approved by the NCRR Advisory Council. (p. 86)

Action taken
The Division of Clinical Research intends to fund at least one national resource for genotyping in FY 2004. The genotyping center will analyze samples submitted by GCRC-based investigators as well as clinical investigators at institutions that do not have a GCRC. A steering committee will be responsible for reviewing requests submitted from across the U.S. and set priorities for access. NCRR anticipates that an additional resource may be required by the end of FY 2004 to meet the growing needs of the clinical research community. With having almost completed sequencing the human genome, investigators can begin to systematically explore how genes induce their effects not only in disease states but also the role that genes play in responsiveness to classes of drugs for treatment of hypertension and asthma, for example. The pharmacogenetics and pharmacogenomics of classes of drugs may result in screening studies

that can predict a patient's response. In the final analysis, knowing the genotypes of responders and nonresponders will allow more effective therapy be given to patients on the first attempt

Item
Islet resource centers... The Committee commends NCRR for establishing 10 sites for isolation, purification, and characterization of insulin-producing cells and encourages NCRR to consider expanding this effort. The Committee also encourages NCRR to facilitate this important research by isolating insulin-producing cells for both distribution to researchers and by improving methods to store and transport insulin-producing cells. (p.86)

Action taken
In 2003 NCRR initiated the distribution of insulin producing cells prepared at the specialized sites for this activity. This service is overseen by the Islet Cell Recovery Coordinating Committee and meets the needs of basic researchers without compromising the availability of islets for transplantation. The islets are preferentially used in infusions into appropriate patients; the islet cells that may not be optimal for therapy are referred for basic research studies.

FY 2004 Senate Appropriations Committee Report Language (S.Report 108-89)

Item
Animal Research Facilities-- . The Committee encourages NCRR to continue work in partnership with the National Center on Minority Health and Health Disparities to support this important initiative. (p. 158)

Action taken
Please refer to page NCRR-25 of this document for NCRR's response to this significant item regarding developing and improving institutional animal facilities at Research Centers in Minority Institutions.

Item
Clinical Investigation-- The Committee urges NCRR to continue its efforts to improve the efficiency of clinical investigation by expanding the capabilities of clinical research resources. There are novel ideas and candidate molecules in the academic community that merit expeditious clinical testing. The Committee encourages the NCRR to provide the means to obtain rapid clinical proof of principle that a new molecule or approach is a viable candidate for expanded testing in the clinic. (p. 158)

Action taken
Clinical trials will be expedited by the creation of new electronic clinical research networks. NCRR's development of networks will be part of and will complement the NIH Roadmap initiatives.

Item
Cystic Fibrosis-- .the Committee urges that NCRR provide support for the CF network to facilitate its expansion and also to consider strategies for the replication of this network for other orphan diseases. (p.158)

Action taken
Please refer to page NCRR-25 of this document for NCRR's response to this significant item regarding expansion of clinical research networks.

Item
Extramural Facilities Construction at Minority Institutions-- The Committee encourages NCRR to give priority consideration to supporting extramural facilities construction projects at historically minority institutions which have developed a comprehensive plan to address the disproportionate impact of cancer in minority communities. (p. 158)

Action taken
Three NCRR construction awards were made in FY 2003 to historically minority institutions. Tuskegee University received a major award for building a National Bioethics Center with funding from NCRR and the National Center on Minority Health and Health Disparities. Other awards were made to Charles R. Drew University of Medicine and Science for a Biomedical Research Unit and Meharry Medical College for the Center for Molecular and Behavior Neuroscience.

The Tuskegee University (TU) National Bioethics Center award will support the Deep South Network for Cancer Control project; the Bioethics Core for the Tuskegee University Cancer Center; pilot studies on bioethical issues in oral cancer research and health care in minority populations; and the TU-University of Alabama, Birmingham Comprehensive Cancer Center Partnership which promotes the development of research by minority scientists.

The Charles R. Drew University of Medicine and Science Biomedical Research Unit will provide state-of-the-art research facilities for complex metabolic disorders (diabetes, hypertension, and obesity), HIV, drug addiction, cardiovascular and related diseases, and cancer research projects. Drew serves the needs of disadvantaged and largely uninsured constituents who are located in South Central Los Angeles. In addition to these two awards, Meharry Medical College's award allowed the institution to expand space and strengthen neuroscience research at the College by constructing new laboratory and research support facilities for the Center for Molecular and Behavioral Neuroscience. The College's research strategic plan focuses on addressing weaknesses in four tiers of research that includes a cancer research initiative.

Item
Graduate Training in Clinical Investigation Awards-- .The Committee believes that the graduate training awards authorized in the Clinical Research Enhancement Act should be implemented in fiscal year 2004 with a budget sufficient to support 200 students. (p. 159)

Action taken
NCRR initiated the Mentored Clinical Research Scholar (K12) awards to institutions in response to the Clinical Research Enhancement Act. Initally, eleven awards were made in FY2002, sufficient to support physician scholars. Additional career development of five more awards were made in 2003, increasing the total pool of candidates to 48. Increases in the number of trainees per site should allow for the support of over 100 trainees through this mechanism.

Item

Islet Resource Centers-- The Committee commends NCRR for establishing 10 sites for isolation, purification, and characterization of insulin-producing cells, and it encourages the Center to expand and extend these efforts by creating additional sites. The Committee also encourages NCRR to facilitate this important research by isolating insulin-producing cells both for distribution to researchers as well as for transplantation, and by improving methods to store and transport insulin-producing cells. (p.160)

Action taken

Please refer to page NCRR-28 of this document for NCRR's response to this significant item regarding islet resource centers.

Item

National Primate Research Centers-- The Committee values the critical role played by the eight National Primate Research Centers [NPRCs] and thanks the National Center for Research Resources (NCRR) for the two recent evaluations it sponsored to assess the needs of the NPRCs and NPRCs Users: An Evaluation of the Regional Primate Research Centers Program and a National Academy of Sciences Workshop on Rhesus Monkey Demands in Biomedical Research. Recognizing that the NPRCs have independently developed a 5 Year Advancement Initiative to effectively implement the recommendations set forth in these two evaluations and to address the upgrades and program expansions needed to meet the demanding research needs of the Nation, the Committee expects NCRR to fully commit to the initiative. This commitment ensures that the NPRCs will continue to fulfill the national need for primate resources and expertise, and contribute to the overall effectiveness of the Federal investment in biomedical research. (p.160)

Action taken

Please refer to page NCRR-26 of this document for NCRR's response to this significant item regarding the National Primate Research Centers.

Item

Plant-Based Medicinal Products- The Committee continues its interest in accelerating the development and commercialization of plant-based medicinal products, and it encourages the NCRR to actively collaborate with plant scientists in developing novel useful products. (p.160)

Action taken

Dr. Stephen Straus, Director of the National Center for Complementary and Alternative Medicine (NCCAM) will address the GCRC Program Directors at the 2004 annual meeting in Chicago, Illinois to promote GCRC research into complementary and plant based medicinal products.

Item

Positron Emission Tomography- The Committee continues to urge NCRR to support research resource centers for the development and refinement of positron emission tomography [PET] as a unique imaging technology to diagnose and stage diseases of the brain, including Alzheimer's disease. (p. 160)

Action taken

As with MRIs and fMRIs, PET scans of the brain have been in use in several General Clinical Research Centers (GCRCs) to study, for example, depression, alcohol dependence, sleep, stroke rehabilitation, compulsive behavior, schizophrenia, post- traumatic stress disorder, trauma, and deafness. GCRC resources for PET scanning were also significantly strengthened with the award of supplementary funding to the Brookhaven National Labs to support isotope generation for those isotopes that have very short half-lives and must be generated on site.

The NCRR-supported National Primate Research Centers and other animal research resources are progressively using more PET scans and hosting more neuroscience research. Several investigators have submitted proposals to NCRR's Shared Instrumentation Grant program to acquire PET scanning equipment for both human and animal studies.

In FY2003, NCRR provided funds to acquire PET scanners at imaging research centers at the University of Iowa (Iowa City) and Vanderbilt University (Nashville). These scanners will support research on new radiotracers, optimization of PET for technical assessment of response to therapy, gene expression, malignant transformation, cerebral plasticity, forebrain development, antipsychotic drug mechanisms of actions, cerebral neurotransmitter interactions and hallucination drugs.

Item

Research Centers at Minority Institutions- …. The Committee encourages NIH to strengthen participation from minority institutions and increase resources available in this area. The Committee also encourages NIH to work with minority institutions with a track record of producing minority scholars in science and technology. (p. 160)

Action taken

Please refer to page NCRR-27 of this document for NCRR's response to this significant item regarding addressing the health research and training needs of minority populations.

NATIONAL INSTITUTES OF HEALTH
National Center for Research Resources

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2004 Amount Authorized	2004 Final Conference	2005 Amount Authorized	2005 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$1,054,006,000	Indefinite	$1,087,298,000
National Center for Research Resources	Section 401	42§285b	Indefinite		Indefinite	
Biomedical and Behavioral Research Facilities	Section 481A Section 481B			118,497,000		$0
National Research Service Awards	Section 487	42§288	a/	6,453,000	b/	6,843,000
Total, Budget Authority				1,178,956,000		1,094,141,000

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 Center for Research Resources

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1996	316,544,000 2/	390,339,000	304,267,000 2/	390,339,000
Rescission				(41,000)
1997	309,344,000 2/	416,523,000	324,844,000 2/	415,095,000 3/
1998	333,868,000 2/	436,961,000	455,805,000	453,883,000
1999	421,721,000 2/4/	513,948,000	554,819,000	554,819,000
Rescission				(373,000)
2000	469,684,000 2/	642,311,000	625,988,000	680,176,000
Rescission				(3,619,000)
2001	602,728,000 2/	832,027,000	775,212,000	817,475,000
Rescission				(52,000)
2002	974,038,000	966,541,000	1,014,044,000	1,012,627,000
Rescission				(89,000)
2003	1,090,217,000	1,090,217,000	1,161,272,000	1,146,272,000
Rescission				(7,451,000)
2004	1,053,926,000	1,053,926,000	1,186,483,000	1,186,183,000
Rescission				(7,125,000)
2005	1,094,141,000			

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 reduction of $50,000.
4/ Reflects a decrease of $1,274,000 for the budget amendment for Bioterrorism.

NATIONAL INSTITUTES OF HEALTH

National Center for Research Resources

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
Office of the Director	8	8	8
Office of Extramural Activities	38	37	36
Office of Administrative Management	17	17	17
Office of Science Policy & Public Liaison	8	8	8
Division for Clinical Research Resources	11	11	11
Division for Biomedical Technology Research and Research Resources	10	10	10
Division of Comparative Medicine	10	10	10
Division of Research Infrastructure	14	14	14
Total	116	115	114
FTEs supported by funds from Cooperative Research and Development Agreements	(0)	(0)	(0)

FISCAL YEAR	Average GM/GS Grade
2001	11.4
2002	11.4
2003	11.4
2004	11.4
2005	11.4

NATIONAL INSTITUTES OF HEALTH
National Center for Research Resources

Detail of Positions

GRADE	FY 2003 Actual	FY 2004 Final Conference	FY 2005 Estimate
ES-6	1	1	1
ES-5			
ES-4	3	3	3
ES-3	1	1	1
ES-2			
ES-1			
Subtotal	5	5	5
Total - ES Salary	$712,500	$726,750	$751,000
GM/GS-15	14	14	14
GM/GS-14	25	25	25
GM/GS-13	12	12	12
GS-12	12	11	11
GS-11	12	12	11
GS-10	1	1	1
GS-9	8	8	8
GS-8	5	5	5
GS-7	9	9	9
GS-6	5	5	5
GS-5	3	3	3
GS-4	1	1	1
GS-3			
GS-2			
GS-1			
Subtotal	107	106	105
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General			
Director Grade	1	1	1
Senior Grade			
Full Grade			
Senior Assistant Grade			
Assistant Grade			
Subtotal	1	1	1
Ungraded	21	21	21
Total permanent positions	110	113	113
Total positions, end of year	134	133	132
Total full-time equivalent (FTE) employment,end of year	116	115	114
Average ES level	ES-4	ES-4	ES-4
Average ES salary	$142,500	$145,350	$150,300
Average GM/GS grade	11.4	11.4	11.4
Average GM/GS salary	$70,651	$73,548	$74,651