DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

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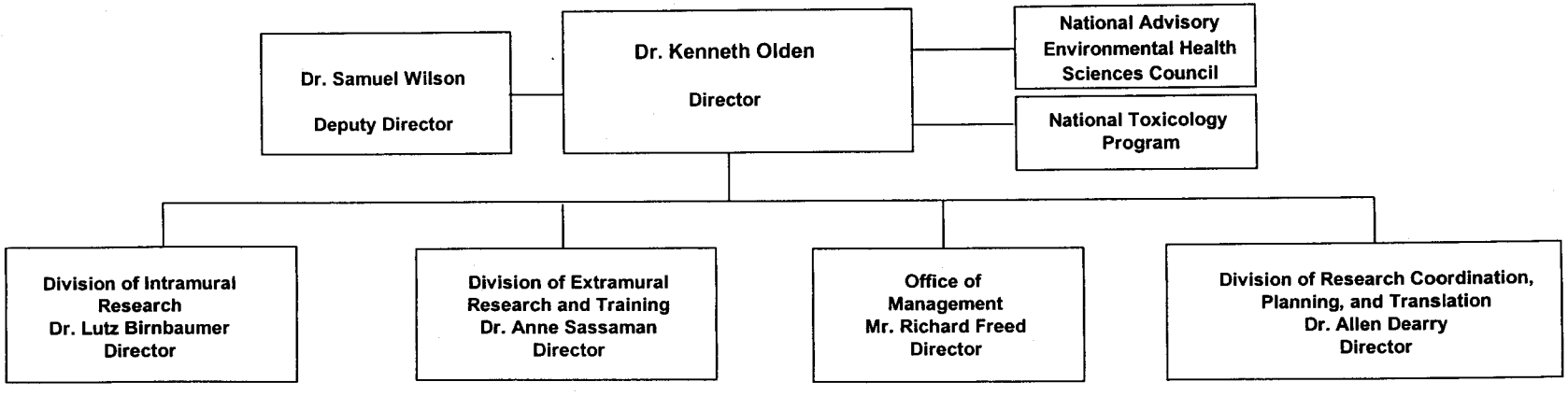
Organization Structure



NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

For carrying out sections 301 and 311 and title IV of the Public Health Service Act with respect to environmental health sciences, [$650,027,000] *$647,608,000.*

[Departments of Labor, Health and Human Services and Related Agencies Appropriations Act, as enacted by the Consolidated Appropriations Act for Fiscal Year 2005].

National Institutes of Health

National Institute of Environmental Health Sciences

Amounts Available for Obligation 1/

Source of Funding	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Appropriation	$636,974,000	$650,027,000	$647,608,000
Enacted Rescissions	(4,582,000)	(5,522,000)	---
Subtotal, Adjusted Appropriation	632,392,000	644,505,000	647,608,000
Real transfer under NIH Director's one-percent transfer authority to other ICs	(2,082,000)	---	---
Comparative transfer to NIBIB for Radiology Program	(102,000)	---	---
Comparative transfer to Buildings and Facilities	(1,227,000)	---	---
Comparative transfer to/from other NIH ICs for NIH Roadmap	2,082,000	---	---
Subtotal, adjusted budget authority	631,063,000	644,505,000	647,608,000
Unobligated Balance, start of year	0	0	0
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	631,063,000	644,505,000	647,608,000
Unobligated balance lapsing	(56,000)	---	---
Total obligations	631,007,000	644,505,000	647,608,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2004 - $ 16,620,666 FY 2005 - $17,000,000 FY 2006 - $17,000,000
Excludes $76,184 in FY 2005 and $169,333 in FY 2006 for royalties.

Justification

National Institute of Environmental Health Sciences

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

Budget Authority:

FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
649	$631,063,000	661	$644,505,000	661	$647,608,000	0	$3,103,000

This document provides justification for the Fiscal Year (FY) 2006 activities of the National Institute of Environmental Health Sciences (NIEHS), including HIV/AIDS activities. A more detailed description of the justification of NIH-wide FY 2006 AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

INTRODUCTION

Presently, the Nation needs better information to promulgate evidence-based environmental health regulatory policies and to prevent or cure most chronic diseases. This paucity of information has an enormous impact on the world's economy, both in terms of costs associated with health care and with regulatory compliancy. In large measure, this situation exists because we still do not understand what role the environment plays in human health and disease. The application of knowledge and technologies developed during the pursuit of the Human Genome Project offers great promise for elucidating mechanisms of gene-environment interactions involved in the development of complex diseases.

For years, the environment was considered to have a minor role in the etiology of human illness; this was, in part, because only radiation, synthetic chemicals and industrial by-products were included in the definition of the environment. But now that the definition of the environment has been expanded to include diet and nutrition, behavior and other social and cultural factors, the thinking is shifting in favor of gene-environment interactions. In fact, studies are now being reported that blow away the myth that "bad genes" are responsible for the majority of human morbidity and mortality. For example, recent studies show that no more than one-third of the cancer burden can be attributed to the action of genes alone (Verkasala, et al., 1999, *Int. J. Cancer* 83:743-749; Lichlenstein, et al., 2000, *NEJM* 343:78-85), only 15% of Parkinson's disease (Tanner et al., 1999, *JAMA*, 281:341-346), and about a third of autoimmune diseases can (Powell, et al., 1999, *Env. Health Pers.* 107 (Suppl. 5), 667-672). A more recent study reported that 90% of individuals with severe heart disease have at least one or more of four classic risk

factors captured in the current definition of the environment (Khat et al., 2003, *JAMA* 290:899-904). Because of these and other findings, it is now generally accepted that more informative, cost-effective, high-throughput methods for assessing and predicting risk resulting from environmental exposures will need to be developed. Otherwise, we will not be able to prevent or cure most chronic diseases, and the costs associated with health care and environmental regulatory compliancy will continue to escalate.

Starting in 1997 and continuing through 2004, NIEHS developed several new research initiatives to respond to this urgent need. Such programs include: the Environmental Genome Project (Kaiser, 1997, *Science* 278:569-570; Brown and Hartwell, 1998, *Nat. Genet.* 18:91-93), the National Center for Toxicogenomics (Kaiser, 2003, *Science* 300:563), and the Mouse Sequencing Project (*Nature* 432: 5, 2004). While the results from these three initiatives will provide generic information relevant to most chronic diseases, other research programs have been developed to address specific diseases such as breast cancer, Parkinson's Disease, and autism.

Story of Discovery: Why Do People Differ In How They Respond To Drugs?

Physicians prescribe the same drug to different people with the same medical condition, but the success of a particular drug treatment for a disease differs dramatically in different individuals. Improvements are seen in many individuals, with perhaps some small side effects. However, in some individuals, uncomfortable and even life-threatening side effects occur. For other individuals, the therapeutic benefits are minimal or nonexistent. Doctors have struggled for years to balance the benefit of pharmaceuticals against the possibility of adverse effects in their patients and the unexplained non-response of some individuals to treatment with what should have been the appropriate drug. This challenge has been difficult because they have no way of predicting who will respond favorably to drug treatment or who will be exquisitely susceptible to undesirable side effects. Unfortunately, adverse drug reactions are a major source of death in the U.S. New information is emerging that may, in the future, give physicians a greater ability to predict drug effects and to tailor drug use to the individual patient, depending on his/her inherited ability to handle the drug. A major source of this information comes from years of investment in environmental health research.

Environmental compounds, such as pesticides and pharmaceuticals, use the same metabolic machinery that processes the substances in our diet. Specialized proteins (enzymes) break down, or metabolize, these compounds so that they can be eliminated from the body. The primary metabolic proteins are found in the liver and are known as cytochrome P-450s (CYP). This large class has numerous subgroups, or subfamilies, which have been extensively studied for the past four decades by environmental scientists. This rich body of information has matched specific P-450s with the individual environmental agents or pharmaceutical drugs they metabolize. More recently, with improved genetic tools, scientists have begun to delve into how the activity of a specific P-450 on a specific compound can vary among individuals. We now know that the genes coding for P-450s can have subtle genetic variations that translate into slight differences in otherwise identical proteins. These differences can make a P-450 that is more efficient, or less efficient, in breaking down its target compound or even cause a particular P-450 to be completely absent in certain individuals. In turn, these alterations in efficiency in P-450 activity are the basis for how some people respond well, and some poorly, to the same drug. Correlating P-450 variations with changes in ability to metabolize particular drugs will enable us to correctly identify which individuals are best suited to a particular drug therapy and to identify which patients need an alternative drug.

One CYP subfamily currently being studied by NIEHS supported scientists is the CYP2C subfamily. It is responsible for the metabolism of 20-30% of clinically used drugs and a number of pesticides and herbicides. NIEHS researchers discovered some of these CYP2C enzymes and later showed that all members of this subfamily are genetically variable. The distribution of these variations is different among ethnic groups, causing some to handle certain drugs poorly and thus be more susceptible to toxic and even life-threatening effects of drugs at doses that would be therapeutic in the general population. These scientists developed genetic tests for

clinical use in people. In these tests, genetic variations in one enzyme, CYP2C9, were shown to affect the metabolism of important drugs including anti-diabetes drugs such as tolbutamide, drugs for epilepsy such as phenytoin, the anticoagulant warfarin used to prevent clotting, diuretics and hypertensive drugs, and numerous non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and celebrex.

CYP2C19 is another clinically important enzyme discovered at NIEHS that metabolizes a wide variety of human drugs such as an important class of anti-ulcer drugs, proton pump inhibitors (the most commonly used is omeprazole or Prilosec). People can be divided into extensive metabolizers (EMs) or poor metabolizers (PMs) of drugs metabolized by CYP2C19. About 2 to 5% of Caucasian are poor metabolizers, as are 5% of African Americans, 13-23% of Asians, and 38-100% of some populations of Polynesia and Micronesia. This enzyme has been shown to have 9 to 12 inherited defective variants, all of which were discovered by NIEHS scientists. Recent studies show the genetic makeup of the individual markedly affects the cure rate for peptic and duodenal ulcers in patients treated with omeprazole and an antibiotic (and genotype could affect cure rates of numerous other proton pump inhibitors metabolized by CYP2C19) because of the marked differences in metabolism of this drug in different individuals.

A third enzyme, CYP2C8, metabolizes the anti-breast cancer drug, paclitaxel. Genetic variations in this enzyme have been shown to affect the metabolism of paclitaxel. As the role of subtle genetic variation in this drug metabolizing enzyme becomes better defined, simple blood tests could be devised to assay these variants. Physicians could then use this information to better select individuals who would benefit from this drug, thus helping reduce toxic side effects of chemotherapy while optimizing its cure rate for breast cancer.

Many people take two or more drugs, and administration of one drug can affect how fast the person metabolizes a second or third drug. We can also become tolerant to a drug after repeated dosage due to increased metabolism of the drug. NIEHS researchers have identified mechanisms that affect this process and some classes of drugs and herbal remedies which may make a second drug less efficacious when the patient takes more than one drug. Armed with this type of information, physicians could much better manage multi-drug therapies in their clients.

NIEHS scientists are continuing to improve their understanding of individual gene-drug interactions. They are also working toward bringing this information to a practical application. They are developing genetic tests for these polymorphisms that could be used in clinical trials. The ultimate goal is that genetic tests will be available in the future, in clinical settings to personalize drug treatment, to avoid unexpected and life-threatening toxicity due to genetic differences, and to provide the appropriate drug that will produce the best therapeutic benefit for each particular patient. Once a patient's genotype for a panel of P-450s is determined and available in his clinical record, his physician will be able to predict which drugs will be most effective in this patient, and which drugs would be likely to produce dangerous side effects and should thus be avoided.

SCIENCE ADVANCES

Protein Identified that Halts Progression of Alzheimer's Disease

Background: Alzheimer's disease progresses when a toxic protein, known as "beta-amyloid," attacks the brain's nerve cells involved in learning and memory. The beta-amyloid creates sticky plaques and tangles that gradually disable nerve cells, producing memory loss.

Advance: Scientists studied mice genetically engineered with defective genes taken from human patients with early-onset Alzheimer's disease. As expected, the defective genes produced mice with higher-than-normal levels of the toxic beta-amyloid protein. Surprisingly, these mice did not exhibit symptoms of Alzheimer's disease. Looking more closely, the researchers discovered that levels of a specific protein, transthyretin, had increased dramatically in the brains of these mice. When given antibodies that prevented transthyretin from reacting with beta-amyloid, the

mice showed the expected brain cell death. Thus, it appeared that transthyretin was able to protect brain cells from toxic effects of beta-amyloid. To further verify this finding, test tube studies were done in cultured brain cells from the human cortex. These studies showed that pretreating these cells with transthyretin protein minimized brain cell death following exposure to toxic beta-amyloid.

Implications: Researchers have identified a protein in the brain that halts the progression of Alzheimer's disease in human brain tissue. The protein, known as transthyretin, protects brain cells from gradual deterioration by blocking another toxic protein that contributes to the disease process. This discovery provides a new avenue of exploration, where drugs could be developed that boost the brain's levels of transthyretin or methods could be developed for depositing it directly in the brain. It holds the promise of early pretreatment of people at high risk for Alzheimer's disease so they can prevent its development, as well as a possible means to treat people in early stages of the disease so that it doesn't progress and they preserve a higher level of cognitive function.

New Tool to Study Gene Function

Background: RNA silencing is a recently discovered phenomenon that allows genes to be turned off through use of double-stranded RNA. This discovery is being used in laboratories around the world to study gene function and therapeutic applications are being investigated to treat diseases such as cancer, AIDS, hepatitis, Parkinsons disease, and macular degeneration. The short, double-stranded RNA species that direct this process of gene shut down are called small interfering RNAs or siRNAs. Plants have an RNA silencing system that acts as an 'immune system' to protect against molecular parasites including RNA viruses. As a result, many plant viruses have adapted mechanisms to suppress gene silencing. One of these viruses (p19) has been shown to suppress RNA silencing by binding to siRNAs.

Advance: Investigators determined the three-dimensional atomic structure of a specific viral protein and its siRNA. By using biochemical and plant assays, they showed that the p19 protein binds very tightly to siRNAs and selects for the siRNAs based on the length of the double-stranded RNA and apparently not the sequence of the RNA.

Implications: By producing p19 protein, the virus can prevent the destruction of its RNA genome and protein-coding messenger RNAs by suppressing the plant's protective RNA silencing system. Furthermore, because p19 is not specific for viral siRNAs, it can be used as a tool to understand the mechanism of RNA silencing in other organisms, such as humans. A clear grasp of the process by which RNA silencing occurs will be important for its application in research and therapeutic efforts.

Dietary Boron Might Help in Treatment or Prevention of Prostate Cancer

Background: Prostate-specific antigen (PSA) is a well-established marker of prostate cancer. The involvement of PSA in several early events leading to the development of malignant prostate tumors has made it a target for prevention and intervention. There are data that suggest an enzymatic regulatory role for dietary boron, which is an inhibitor of serine protease proteins such

as PSA. This study asked the question "Could dietary supplementation with boron (as boric acid) inhibit PSA and reduce the development and proliferation of prostate carcinomas in mice?"

Advance: Investigators implanted human prostate cancer cells into mice and monitored development of resulting tumors both with, and without, boron supplementation. Supplementation was shown to be beneficial in two ways: (1) the size of tumors was decreased in mice exposed to the low and high dose of boron by 38% and 25%, respectively and (2) serum PSA levels decreased by 88.6% and 86.4%, respectively, as compared to the control group. In addition the boron-supplemented group appeared to have less active cell growth than did the non-supplemented group, indicating that these might be less aggressive tumors. Also, expression of a growth factor indicative of cancer risk was markedly reduced in the tumors of the boron-dosed group compared to controls.

Implication: Low-level boron supplementation reduced tumor size as well as improving several tumor characteristics. This promising model is being evaluated in further studies.

Supplementing with Antioxidants can Help Asthmatic Children

Background: Asthma is a severe respiratory disease whose incidence appears to be increasing. There is some evidence that dietary supplements such as antioxidants can modify the severity of asthma, or even lower our risk of developing it.

Asthma arises from inflammation and constriction of the lung's airways. It is known that the environmental pollutant, ozone, can cause airway inflammation by placing an oxidative burden on lung tissue. Thus, antioxidants might provide a way to reduce ozone-induced asthma. An NIEHS scientist working with investigators at the Mexican National Institute of Public Health studied a group of asthmatic children in Mexico City, an area of high ozone exposure, and found that supplementation with antioxidant vitamins C and E did, in fact, counteract the decreased lung function arising from ozone. There was, however, substantial variability in the effect seen among different children. Thinking that genetic differences might account for some of this variability, the scientists decided to examine the study group by their genetic ability to produce glutathione S-transferase (GSTM1), one of the enzymes that play a major role in protecting cells against oxidative damage.

Advance: GSTM1-deficient children given antioxidant vitamins C and E showed the greatest protection against ozone-induced decreases in lung function. GSTM1-deficient children who were given a placebo (i.e., a tablet with no antioxidants) showed no such protection. Those children who had a fully functioning GSTM1 (i.e., GSTM1 positive) did not exhibit ozone-induced decreases in lung function, regardless of antioxidant status. These results help establish the critical role of GSTM1 in protecting the lungs against oxidative stress, as well as identifying a genetic subtype of children (those lacking GSTM1) that would benefit from antioxidant supplementation.

Implication: Asthmatic children with a GSTM1 genetic deficiency appear to be more susceptible to the deleterious effects of ozone and derive greater benefit from antioxidant supplementation.

NIH ROADMAP

The ability to investigate and understand issues in environmental health requires collaboration between many scientific disciplines: epidemiology, toxicology, molecular biology, clinical sciences, and many others. This circumstance underscores the interest of NIEHS in the first round of Roadmap awards, especially the Interdisciplinary Research Planning Centers, which include a number of exciting projects that will greatly enhance NIEHS's work. One award, at Duke University, will fund investigators to use geographic/spatial methodologies to address combined genetic, social, and environmental factors on child health and development; particular endpoints of interest are autism, ADHD, asthma and obesity. Another project, at the University of North Carolina, is an effort to redefine computational genomics, including a significant emphasis on gene-environment interactions in alcoholism, atherosclerosis and breast cancer. The investigators on this project have strong ties to other significant NIEHS-funded efforts at the same institution: the Toxicogenomics Research Center and the Center for Environmental Health and Susceptibility. The latter Center is also affiliated with another interdisciplinary Roadmap grant focusing on "An interdisciplinary Strategy for Obesity."

An exciting supplemental Roadmap award will enable researchers at Johns Hopkins University to develop and apply statistical methods to incorporate social and behavioral variables into epidemiologic studies of environmental pollutants and health. The intent is to establish an integrated statistical approach for social and environmental epidemiology to characterize risk of a targeted environmental agent while taking other environmental variables into account. This research will provide evidence on health and environmental exposures and will contribute to the statistical methodology in the field of environmental epidemiology and to the foundation of policy decisions, as well as assist researchers in answering challenging questions posed by policy makers.

INITIATIVES

Harnessing Genomic Tools for Environmental Medicine

Environmental Genome Project (EGP): Individuals vary, often significantly, in their response to environmental agents. This variability provides a high "background noise" when scientists examine human populations to identify environmental links to disease. This variability often masks important environmental contributors to disease risk and is a major impediment in environmental medicine. Fortunately the Human Genome Project created tools that can help identify the genetic variations in environmental response genes that can lead to such wide differences in disease susceptibility. NIEHS developed the EGP in 1997 (Kaiser, 1997, *Science*, 278:569-570; Brown and Hartwell, 1998, *Nat. Genet.*, 18:91-93) to catalogue these genetic variants (polymorphisms) and to identify the ones that play a role in human susceptibility to environmental agents. This information is being used in epidemiological studies to better pinpoint environmental contributors to disease. Some recent accomplishments include:

- 325 environmental response genes have been resequenced and entered into a public database. Of the greater than 43,000 single nucleotide polymorphisms (SNPs) identified

in these genes, more than 2,185 were within the coding region. Only about 30% of the identified SNPs had been previously known. Thus, 70% of these discoveries represent new opportunities for identifying important genetic susceptibilities to adverse environmental effects.

- SNPs variants of the paraoxonase gene (*PON1*) were examined. This gene is associated with risk to cardiovascular disease, as well as regulating response to neurotoxic agents such as organophosphate pesticides and chemical warfare agents. Certain variants were identified that altered the effectiveness of PON1 in ways that could increase risk to cardiovascular disease and neurotoxic agents, as well as possibly influencing susceptibility to Gulf War Syndrome.
- Leukemia risk as it relates to SNPs variants identified in the Environmental Genome Project was examined. In one gene that prevents oxidative damage from quinones, individual SNPs were found that increased susceptibility to developing leukemia. Thus, in the 5-20% of the population carrying this variant, exposures to benzene, radiation, and chemotherapeutic agents would confer a greater risk of developing leukemia than in people not having this polymorphism.
- Several functional SNPs that affect enzymes involved in folate metabolism were identified by the Environmental Genome Project. These variants were found to reduce leukemia risk 2-fold to 3-fold in individuals with one copy and 3-fold to 10-fold in individuals with two copies of these variants.

By the end of 2005, the current 525 candidate genes will be resequenced. NIEHS is currently taking nominations for genes to resequence in FY 2006 and beyond. It is expected that some of these genes will be ones implicated in diseases for which NIEHS has major programmatic interest. Such diseases include asthma, Parkinson's Disease, and other neurodegenerative diseases.

Additionally, as new SNPs models are put in a repository, the extramural community will be encouraged to use these models to explore gene-environment interactions and the functional significance of these genetic variants on human disease.

Comparative Mouse Genomics Centers Consortium: The EGP created the Comparative Mouse Genomics Centers Consortium (CMGCC) to develop transgenic and knockout mouse models based on human DNA sequence variants in environmentally responsive genes. These mouse models are tools to improve understanding of the biological significance of human DNA polymorphisms. At present, the CMGCC has developed 17 single nucleotide polymorphism (SNP) mouse strains available for use by the extramural scientific community. These models exhibit a variety of disease endpoints, including: Werner's Syndrome (aging disorder); diabetes; mammary cancer; gastrointestinal and bladder cancer; prostate cancer; and skin cancer. The Centers have also developed 22 "tools" mouse strains that can help assess important genetic events such as: frame shift indicators; LOH (loss of heterozygosity) indicators; transition indicators; deletion; prostate cancer; and conditional targeting. The available SNP and tools mouse strains may be obtained by directly contacting CMGCC Directors (http://www.niehs.nih.gov/cmgcc/centers.htm). The strains will also be available from the NCRR Mutant Mouse Regional Resource Centers (MMRC) and the NCI Mouse Models of Human Cancers Consortium (MMHCC) Mouse Repository in the near future (mid 2005).

CMGCC investigators are currently constructing an additional 20 SNP mouse strains and 3 tools strains.

Genomic Effort to Improve Relevance of Toxicological Testing in Mice: Environmental scientists often use mice to study how environmental agents might be expected to affect people. Although mouse studies can, in a general sense, indicate the potential of an exposure to cause cancer and other diseases, there is no way to precisely extrapolate these study results to the risk in humans. An important step will be when the individual response genes in both mice and humans are identified and when individual differences (polymorphisms) in these genes are identified both among the different mouse strains and among people. The Environmental Genome Project is identifying the human part of this equation. The mouse component is now being addressed by the NIEHS. A contract has been awarded that will sequence the DNA of 15 mouse strains to pinpoint their genetic differences. DNA sequencing of the entire genome for each strain is expected to be completed by the end of 2006. This information will provide a basis for studies of why they differ in their susceptibility to certain diseases and toxic reactions to environmental agents. Susceptibility differences among various lines can be used to identify genes associated with complex diseases. The ultimate benefit will be to improve our ability to use these mice to study the molecular basis of human diseases such as obesity, cancer, hypertension, diabetes, psychiatric disorders, and aging.

Disease Focused Environmental Medicine

Sister Study of Breast Cancer: A unique study exploring gene-environment interactions in breast cancer development has begun nationwide recruitment. It will look at how genes, activities of daily life, and environmental exposures affect breast cancer risk. In order to get the information quickly, this study recruits 50,000 symptom-free women who have a sister that had breast cancer. These women are at increased risk of breast cancer, share many genes with their affected sibling, and would have experienced many of the same exposures. For these reasons, it is expected that a sufficient number of women will develop breast cancer within 10 years and their genes and exposures can be compared with those women in the study who did not develop the cancer. A broad range of exposures will be examined, including personal care and household products, workplace exposures, and dietary factors. A number of advocacy groups are working with the NIEHS on this project, including the American Cancer Society, Sisters Network, Inc., the Susan G. Komen Breast Cancer Foundation, and the Y-ME Breast Cancer Organization.

Parkinson's Disease: A major impediment in Parkinson's Disease (PD) research has been the lack of rapid communication between epidemiologists, laboratory researchers, and clinicians which prevents the type of multidisciplinary approach this field needs. To encourage advances in this important area of study, NIEHS developed a multidisciplinary Collaborative Centers Program for Parkinson's Disease Environmental Research (CCPDER) in 2002. This multi-institutional approach is designed to accelerate the identification of genetic and environmental factors leading to PD. Collectively, the three centers have expertise in basic neurosciences, human genetics, clinical research, and epidemiology, as well as long-standing interactions with patient groups. A number of important accomplishments through CCPDER and other supported scientists have emerged this past year.

- *Molecular Epidemiology of PD:* Efforts to discover new PD susceptibility genes are underway. Based on preliminary data, this work has led to two U.S. and international patent applications and collaborations with pharmaceutical companies to develop disease modifying therapies directed to specific molecular targets. Once new susceptibility genes are discovered and validated, they will be used to define pathogenesis pathways and provide new targets for disease modifying therapies.
- *PD Registry:* There is no uniform tracking system for PD, a major hurdle in finding clues for environmental triggers of this disease. CCPDER researchers thought that California would be an ideal place to start a comprehensive registry on PD prevalence and distribution. Among California's assets were (1) its agricultural base (and, thus, exposure to agricultural chemicals that might play a role in PD), (2) demographic diversity, (3) population size, (4) experience with registries, and (5) experience in tracking other diseases. The NIEHS and the Michael J. Fox Foundation are cofunding the development of this registry with the State of California. This registry will help to identify the role of environmental factors in the development of PD.
- *PD Mouse Model:* Rodents have traditionally served the research community's need for inexpensive animals that can duplicate life-long exposure scenarios in a relatively brief period of time. For the purpose of studying gene-environment interactions, the mouse is a particularly attractive model. A number of mouse models are being created that have specific alterations in the genes suspected of playing a role in PD development. CCPDER scientists have constructed a mouse model using the herbicide, rotenone, that appears to reproduce a number of the hallmarks of human PD. Such models can be used to determine critical gene-environment trigger for PD development.
- *PD Monkey Model:* Although mice will be an inexpensive and easy model to use, primates remain the animals most relevant for simulating human responses. For some years the research community has been able to duplicate in monkeys the rigidity and loss of muscle control found in human PD by administering the synthetic chemical, MPTP. This model is limited, though, because it does not develop the characteristic brain lesions seen in human PD, called Lewy bodies. CCPDER scientists, in pilot tests, have found that chronic administration of rotenone to monkeys leads to structures in the brain that look like Lewy bodies. If this finding is validated in a larger sample, it will provide a more relevant model for testing therapeutic interventions, as well as gene-environment connections for PD.

Autism: Autism is a devastating behavioral disorder that appears in childhood and lasts a lifetime. Its prevalence might be increasing, although changing diagnostic standards and greater awareness make it difficult to interpret time trends. Genetic factors are suspected of playing a role in autism because it often runs in families. Genetic factors alone, though, are unlikely to provide a full account of autism etiologies. Past studies have shown that "in utero" exposure to an environmental agent, thalidomide, dramatically increases autism risk. As with most disease, autism most likely arises from underlying genetic susceptibilities interacting with specific environmental triggers at particular times of life (in this case, early periods of pre or postnatal development) that confer enhanced vulnerability. A number of people have suspected that the mercury-containing compound thimerosal, used to preserve childhood vaccines, could be an environmental trigger for autism development, based on the established neurotoxicity of higher doses of mercury. Extensive epidemiological studies, however, have failed to provide any

association between vaccines and autism and make clear that the very large increase in autism prevalence over the past ten years cannot be attributed to vaccination.

It is possible, however, that only a subset of children are susceptible to mercury effects, perhaps when coupled with an immunological challenge. Because the genetic susceptibilities of autism and most other neurodevelopmental disorders are not yet known, current epidemiological studies are unable to identify small susceptible cohorts that might be particularly vulnerable to the effects of thimerosal. Preliminary animal studies have provided an intriguing clue that NIEHS is now pursuing. In these studies, different mouse strains were exposed to thimerosal at ages and doses that corresponded to the standard protocol for childhood vaccinations. Only the immunologically deficient strain of mouse exhibited a response. In these mice, behavioral effects were seen and morphological changes were observed in the brain. This study did not have sufficient power to be definitive, but it did provide clues that are worth exploring. Fortunately the NIEHS already had two Children's Environmental Health and Disease Prevention Research Centers devoted to autism. It has provided a supplement to one of these to do more extensive testing of thimerosal in autoimmune-prone (SJL) mice. This Center has expertise in evaluating critical social behaviors, as well as the ability to conduct state-of-the-art stereology to measure brain effects such as volume changes and changes in cell number. This more extensive look at thimerosal-immune co-contributors to brain damage will provide better insight into gene-environment parameters of this disorder than previous studies have.

NIEHS has also undertaken a number of studies to help regulators determine if the extensive body of literature on the mercury form, methyl mercury, can be extrapolated to predict effects on the mercury form used in thimerosal, ethyl mercury. Prior to these studies there was a paucity of data on ethyl mercury distribution and toxicity in the body. Regulators were assuming the two compounds, both of which are organic, might act in a similar way, but had no data from which to work. NIEHS co-sponsored studies in infant monkeys given a vaccination schedule similar to that in humans. Blood levels and tissue distribution of mercury is being compared among monkeys given thimerosal (ethyl mercury) by intramuscular injection and those given oral methyl mercury. Similar experiments were conducted in the more common laboratory animal, the mouse. Both studies have been completed and the results indicate that ethylmercury from thimerosal (intramuscular injection) is excreted much more rapidly from blood and brain than methyl mercury (oral dosing).

NIEHS, through its Centers, is supporting other research relevant to autism. It is recruiting a cohort of 700 autistic children, in addition to control subjects, in California. This study will be examining possible environmental triggers for this disease, with results available after 2006. Animal models are also being developed that will enable researchers to assess social behavior in developing and mature animals. Such models could then be used to examine the effects of various toxicants, including thimerosal, on the development and performance of these behaviors. Another study is examining molecular and cellular mechanisms that might underlie some of the idiosyncratic responses within autistic children to chemicals they might have been exposed to during early stages of brain development. This project will use a variety of cellular and animal models to address immunotoxic and neurotoxic actions of environmental agents of interest.

Children's Health: Exposures that occur very early in life can have greater adverse effect than the same exposures incurred later in life. This unique life stage vulnerability has been a particular focus of NIEHS research. Centers for Children's Environmental Health and Disease Prevention Research were developed in 1998. These Centers recently conducted the first study in humans of the developmental impact of insecticides, as well as providing evidence of a positive health effect from a federal ban of two insecticides. This study measured the impact on fetal growth of two insecticides – chlorpyrifos and diazinon – whose use in households was banned by the federal government starting in 2000. In this study, researchers measured the levels of the two insecticides in blood drawn from the umbilical cords after delivery, both before and after the ban, and correlated those levels with the babies' birth weight and length. They found that prior to January 2001, newborns with combined insecticide exposures in the highest 26th percentile weighed almost half a pound less and were shorter than infants with no detectable pesticide levels. However, when they looked as the relationship between insecticide exposures and fetal growth after January 2001, the exposure levels had reduced substantially and the impact on weight and length was no longer apparent. The differences in fetal growth observed were comparable to differences between babies whose mothers smoke during pregnancy compared to those whose mothers do not. Because low birth weight is the leading cause of infant mortality in the U.S., this study demonstrates the potential power of reducing adverse environmental exposures as a way of improving human health.

The Centers are only one part of NIEHS research in children's health. There is also an extensive intramural and extramural portfolio examining the environment's impact on this vulnerable stage of life. Among the recent findings are:

- New data suggest that pollutants from vehicle emissions and fossil fuels hinder lung development in children and limit breathing capacity for a lifetime. 1,756 school children in Southern California were studied from 4th grade through 12th grade and their "forced expiratory volume" (the volume of air that can be exhaled after taking a deep breath) was assessed regularly, as were the levels of air pollutants where they lived. Over the eight-year period, the children living in polluted communities were five times more likely to have clinically low lung function (less than 80% of expected breathing capacity) compared to children living in communities with cleaner air. This finding is significant because lungs grow to full capacity during the teenage years, stop growing around age 18, then lung capacity gradually declines at the rate of 1% per year.
- A program that targets allergens and tobacco smoke in the home was found to successfully reduce asthma symptoms in inner-city children.
- A large-scale cleft palate study found specific polymorphisms of a gene regulating folate metabolism that appeared to increase risk of cleft palate for children when their mothers took folate supplements during pregnancy.
- A new study suggested that eating more vegetables, fruit and protein before pregnancy lowered risk of having a child develop leukemia, the most common childhood cancer in this country.
-

Obesity: A major contributor to rising health costs is the growing problem of obesity. Currently 65% of the U.S. population is considered overweight or obese (National Center for Health Statistics. Health, United States, 2004). Excess weight is associated with an increased risk of

Type 2 diabetes, heart disease, and several types of cancer. A group at Emory University analyzed health costs from 1987 – 2001 and found that medical bills for obese people constituted 27% of the growth in overall health care spending (Thorpe, et al. Health Affairs. Oct 20, 2004, W4:480-486). Indeed, treating obese patients was 37% more expensive than medical care for normal-weight patients. Environment plays a key role in promoting weight problems. The NIEHS has an Obesity and the Built Environment initiative that examines environmental components of obesity. It involves a five-year evaluation of communities across the U.S. that, through the Robert Wood Johnson Foundation's Active Living by Design Program, are developing new community design and communications strategies to improve physical activity. These improvements involve collaborations among city planning, transportation, crime prevention, traffic safety, land use, and other public entities. The NIEHS will examine the program's impact on physical activity, obesity, and other health indicators and compare these results against communities that have not improved their surroundings to encourage physical activity (Washington Post, Nov 8, 2004). The Institute is also encouraging research to evaluate the role of "in utero", neonatal, and prepubertal exposures to environmental estrogens and other compounds in the onset and development of obesity, as well as examining gene-environment interactions that favor weight gain.

TOXICOLOGY

Nanotechnology: Environmental medicine as practiced by NIEHS is as much about the exposures of the future as it is about exposures of the past. Initiatives to understand the potential adverse effects of technologies using newly generated nanoparticles illustrate this proactive approach. Nanoparticles (i.e., particles on the order of $1/1000^{th}$ of the width of a hair) are an exciting area of research in biomedicine and other industries. Smaller than human cells, nanoscale devices have the potential to deliver therapeutic and imaging agents to specific cells and tissues in ways not presently possible. However, when bulk material is converted to ultrafine nanoparticles, its physical, chemical, and biological properties can be altered in ways that might negatively affect health. So, while many laboratories are focused on exploiting the rich potential of these agents, there is little activity to assess their toxicological properties. NIEHS, under the auspices of the National Toxicology Program (NTP) is addressing this troublesome knowledge gap. It has initiated a program to evaluate the toxicological properties of major nanoscale materials classes and will investigate fundamental questions such as: How are nanoscale materials absorbed, distributed in the body, and taken up by cells? Are there novel toxicological interactions? What are the appropriate detection and quantification methods for nanoscale particles?

Currently studies are looking at absorption of nanoparticles through skin. If they are found to be absorbed, then phototoxicity studies will be initiated in FY 2005 and FY 2006 to examine nanoparticles found in common sunscreens. General questions concerning absorption and fate once in the body of oral and inhaled nanoparticles are also being addressed. Findings from these initial studies will help focus further targeted toxicologic charactizations of effects on the immune and respiratory systems in FY 2006.

Metabolomics (study of small molecules): Newly gained knowledge and recent technological innovations have advanced the ability to observe effects of environmental exposures in human

beings at the molecular level. These advances emerged in part from the mapping of the human genome and are enabling toxicology and biomedical science to achieve personalized assessments of environmental exposures and health risk. In this new sphere of metabolomics, key small molecules (metabolites) in the biochemical processes of the body are easily obtained from human subjects in urine, blood, saliva, or tissue samples and can be profiled to establish their normal molecular patterns in the healthy functioning individual, and to detect changes that denote modification and dysfunction of these molecules produced by exposure to environmental agents. These observations have the advantage of being made directly in the human population and in real-time continuity in living subjects, using samples obtained with minimally invasive procedures. As such technology produces data consistently and predictably from laboratory to laboratory – as such data is harmonized, as scientists say – these techniques may provide a rapid and cost-effective means of determining risk of environmental exposures and in developing means for intervention in, and prevention of, hazardous exposures.

Researchers refer to metabolomics as complementary to proteomics (study of proteins) and transcriptomics (study of RNA, or the transcribed products of genes) – which profile proteins and gene transcripts respectively in biological systems. Collectively, the three disciplines – metabolomics, proteomics and transcriptomics—provide the comprehensive view of exposure and health that is needed to decipher complex exposure-and-disease relationships and the interplay between genes and the environment in disease occurrence. NIEHS takes a leadership role in this revolution in biomedical science and public health and is a central player in the formation of a new international Metabolomics Society, with the mission of promoting development in this field through collaboration between academic, government and private sector researchers, and enhancing publication of research advances. NIEHS has disseminated a Request for Applications for research in metabolomics as a tool to advance environmental health and will make its first awards funding university investigators in early 2005.

OTHER AREAS OF INTEREST

Trans-agency Collaborations

Environmental Monitoring Project with USGS:

The NIEHS and the U.S. Geological Survey (USGS) are developing an innovative approach to environmental monitoring that is more cost efficient and of greater local and national use than current methods. Mercury exposure was studied in the first pilot test of this technique using geo-spatial data and bioinformatics techniques overlaid with fish tissue sampling data of mercury exposure.

Mercury in consumable fish is a health hazard because the brain of an unborn child can sustain permanent damage if a pregnant woman eats mercury-contaminated fish. For this reason, mercury concentrations are regularly measured in fish samples taken from streams, ponds, and rivers across the country. This information, spanning several decades, is kept in databases maintained by the USGS, the EPA, and state agencies. The samples are of fish of varying sizes, a fact that interferes with using this data to accurately predict what levels would exist in larger,

predatory fish, which are the ones most eaten by humans. In the pilot projects, NIEHS and USGS developed statistical tools that could account for differences in mercury concentrations due to different species, sizes, and sample types. This "normalizing" of the data provided the key that was needed to meaningfully extrapolate a wide variety of data into mercury levels as they would appear in relevant types of fish that are consumed. This information can now be used in developing fish consumption advisories. Furthermore, this normalized data allows scientists to use the USGS database to assess trends in fish-mercury concentrations in the Nation's waterways. It also dramatically lowers sampling costs because this model provides a way to use data from a single sample to estimate mercury concentrations in many different types of fish. This database and the maps it generates are publicly available through a website and can be used by environmental health scientists and health agencies across the country. One significant outcome is that the EPA, after reviewing the NIEHS/USGS model, has found it a powerful tool and expects to use it to help EPA achieve its goals of reducing mercury exposures nationwide, as well as to develop cost-benefit analysis of regulatory actions designed to reduce mercury emissions in air (which ultimately deposit in water).

Oceans and Human Health with NSF:

The NIEHS and the National Science Foundation (NSF) created four joint Centers for Oceans and Human Health last year. These centers combine the strengths of NIEHS and NSF in biological and physical sciences to enhance federal research on how oceans affect human health. The centers will bring together experts in biomedical and oceanographic sciences for the first time to study the effects of harmful algal blooms, marine pathogens, and the oceans' vast potential for drug discovery. The combined expertise of the participants will accelerate the pace of scientific discovery, ranging from the development of new sensors for early warning systems to enhanced progress in finding novel compounds with pharmaceutical potential.

The NIH Neuroscience Blueprint:

Overview -- The Blueprint is a framework to enhance cooperation among fourteen NIH Institutes and Centers that support research on the nervous system. Over the past decade, driven by the science, the NIH neuroscience Institutes and Centers have increasingly joined forces through initiatives and working groups focused on specific disorders. The Blueprint builds on this foundation, making collaboration a day-to-day part of how the NIH does business in neuroscience. By pooling resources and expertise, the Blueprint can take advantage of economies of scale, confront challenges too large for any single Institute, and develop research tools and infrastructure that will serve the entire neuroscience community.

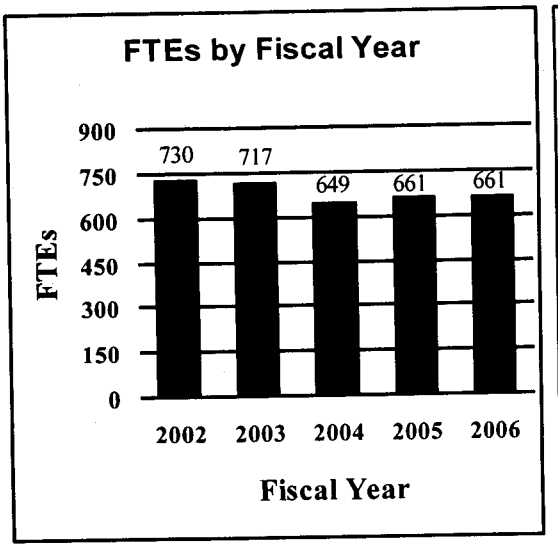
FY2005 -- For fiscal year 2005, the Blueprint participants are developing an initial set of initiatives focused on tools, resources, and training that can have a quick and substantial impact because each builds on existing programs. These initiatives, with the participation of all Blueprint Institutes, include an inventory of neuroscience tools funded by the NIH and other government agencies, enhancement of training in the neurobiology of disease for basic neuroscientists, and expansion of ongoing gene expression database efforts.

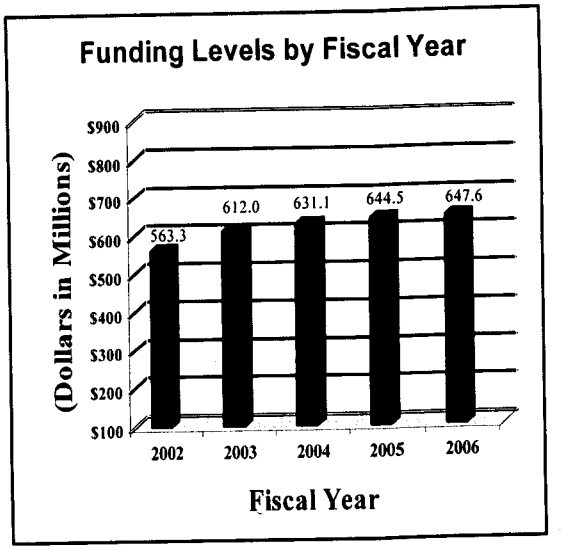
FY2006 -- Advances in the neurosciences and the emergence of powerful new technologies offer many opportunities for Blueprint activities that will enhance the effectiveness and efficiency of neuroscience research. Blueprint initiatives for fiscal year 2006 will include systematic development of genetically engineered mouse strains of critical importance to research on nervous system and its diseases and training in critical cross cutting areas such as neuroimaging and computational biology.

Budget Policy

The Fiscal Year 2006 budget request for the NIEHS is $647,608,000, an increase of $3,103,000 and 0.5 percent over the FY 2005 Appropriation. Also included in the FY 2006 request, is NIEHS' support for the trans-NIH Roadmap initiatives, estimated at 0.89% of the FY 2006 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 NIEHS are shown in the graphs on the following page. Note that the Fiscal Year 2003 and prior FTE figures are not comparable to the figures in the succeeding years due to NIH's consolidations.





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 pursuing new research opportunities. The average cost of competing RPGs will be held at the FY2005 level. There will be no inflationary increases for direct, recurring costs in Noncompeting continuation RPGs.

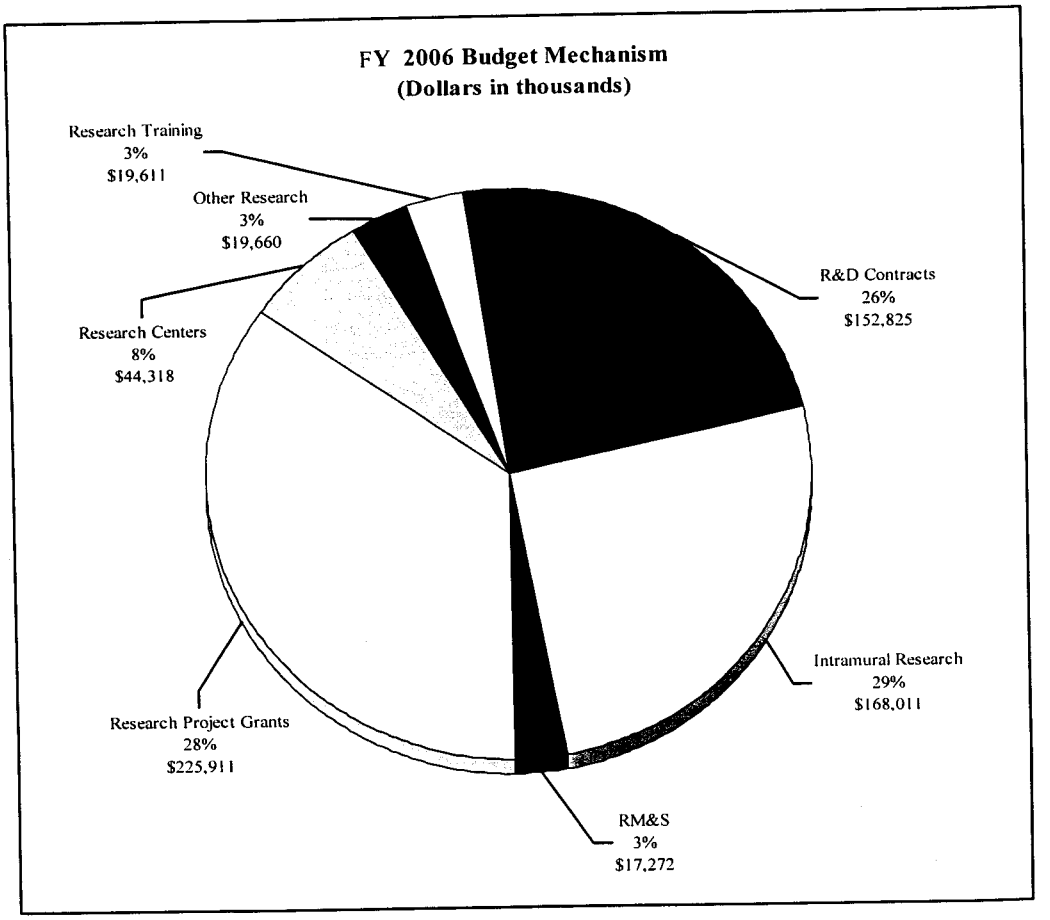
Advancement in medical research is dependent on attracting the best and the brightest to pursue careers in biomedical research. In the Fiscal Year 2006 request, stipend levels for post-doctoral recipients supported through the Ruth L. Kirschstein National Research Service Awards will increase by 4.0% for those with 1-2 years of experience, with all other stipends remaining at the FY2005 levels. NIH will also provide an increase of $500 per post-doctoral fellow, for increased

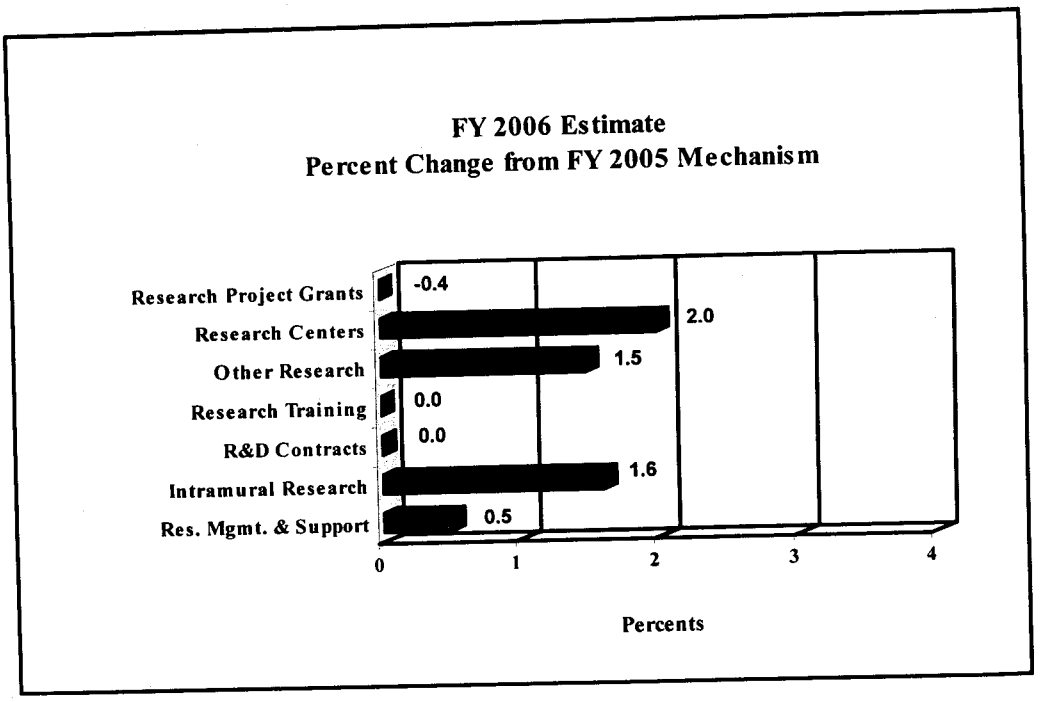
health insurance costs. This increase in stipends and health benefits is financed within the FY2006 request by reducing the number of Full-Time Training Positions by –16. NIEHS will support 509 pre- and postdoctoral trainees in full-time training positions.

The Fiscal Year 2006 request includes funding for 38 research centers, 118 other research grants, including 52 clinical career awards, and 106 R&D contracts. Intramural Research receives an increase of 1.6 percent and includes funds for supporting a laboratory for the newly appointed NIEHS director. Research Management and Support receives an increase of 0.5 percent.

NIEHS is participating in the NIH Neuroscience Blueprint. The FY 2006 request includes $.2 million for a variety of Neuroscience Blueprint initiatives, including neuroscience cores, training initiatives, and the Neuromouse project.

The mechanism distribution by dollars and percent change are displayed below and on the following page.




FY 2006 Estimate
Percent Change from FY 2005 Mechanism
Research Project Grants
Research Centers
Other Research
Research Training
R&D Contracts
Intramural Research
Res. Mgmt. & Support
-0.4
2.0
1.5
0.0
0.0
1.6
0.5
0
1
2
3
4
Percents

NATIONAL INSTITUTES OF HEALTH
National Institute of Environmental Health Sciences

Budget Mechanism - Total

MECHANISM	FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate	
	No.	Amount	No.	Amount	No.	Amount
Research Grants:						
Research Projects:						
Noncompeting	404	$174,752,000	395	$170,965,000	362	$153,969,000
Administrative supplements	(31)	1,770,000	(23)	2,000,000	(25)	2,000,000
Competing:						
Renewal	34	16,055,000	42	13,874,848	57	18,833,240
New	95	25,704,000	86	28,410,444	120	39,648,960
Supplements	1	434,000	2	660,708	2	660,800
Subtotal, competing	130	42,193,000	130	42,946,000	179	59,143,000
Subtotal, RPGs	534	218,715,000	525	215,911,000	541	215,112,000
SBIR/STTR	37	10,809,000	37	10,809,000	37	10,799,000
Subtotal, RPGs	571	229,524,000	562	226,720,000	578	225,911,000
Research Centers:						
Specialized/comprehensive	37	42,137,000	37	43,040,000	37	43,750,000
Clinical research	0	0	0	0	0	0
Biotechnology	0	264,000	0	413,000	1	568,000
Comparative medicine	0	0	0	0	0	0
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	37	42,401,000	37	43,453,000	38	44,318,000
Other Research:						
Research careers	47	5,562,000	46	5,565,000	52	5,818,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	0	0	0	0	0	0
Biomedical research support	0	12,000	0	15,000	0	17,000
Minority biomedical research support	2	1,526,000	4	3,562,000	4	3,562,000
Other	61	10,177,000	60	10,230,000	62	10,263,000
Subtotal, Other Research	110	17,277,000	110	19,372,000	118	19,660,000
Total Research Grants	718	289,202,000	709	289,545,000	734	289,889,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	60	2,348,000	54	2,352,000	52	2,600,000
Institutional awards	458	17,171,000	471	17,259,000	457	17,011,000
Total, Training	518	19,519,000	525	19,611,000	509	19,611,000
Research & development contracts	106	151,001,000	106	152,802,000	106	152,825,000
(SBIR/STTR)	(8)	(1,739,000)	(8)	(1,616,000)	(8)	(1,600,000)
	FTEs		FTEs		FTEs	
Intramural research	570	154,622,000	580	165,361,000	580	168,011,000
Research management and support	79	16,719,000	81	17,186,000	81	17,272,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Buildings and Facilities		0		0		0
Total, NIEHS	649	631,063,000	661	644,505,000	661	647,608,000
(RoadMap Support)		(2,172,000)		(4,075,000)		(5,791,000)
(Clinical Trials)		(2,325,000)		(2,487,000)		(2,590,000)

NATIONAL INSTITUTES OF HEALTH
National Institute of Environmental Health Sciences

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate		Change	
	FTEs	Amount	FTEs	Amount	FTEs	Amount	FTEs	Amount
Extramural Research:								
Biological Response to Environmental Agents		$169,039		$166,092		$164,571		($1,521)
Applied Toxicological Research and Testing		169,063		170,763		170,380		(383)
Biometry and Risk Estimation		59,700		62,039		63,445		1,406
Resource and Manpower Development		61,920		63,064		63,929		865
Subtotal, Extramural research		459,722		461,958		462,325		367
Intramural research	570	154,622	580	165,361	580	168,011	0	2,650
Res. management & support	79	16,719	81	17,186	81	17,272	0	86
Total	649	631,063	661	644,505	661	647,608	0	3,103

NATIONAL INSTITUTES OF HEALTH
National Institute of Environmental Health Sciences

Summary of Changes

FY 2005 Estimate	$644,505,000
FY 2006 Estimated Budget Authority	647,608,000
Net change	3,103,000

CHANGES	FY 2005 Appropriaton FTEs	FY 2005 Appropriaton Budget Authority	Change from Base FTEs	Change from Base Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		$66,723,000		$995,000
b. Annualization of January 2005 pay increase		66,723,000		617,000
c. January 2006 pay increase		66,723,000		1,151,000
d. One less day of pay		66,723,000		(256,000)
e. Payment for centrally furnished services		21,336,000		107,000
f. Increased cost of laboratory supplies, materials, and other expenses		77,302,000		1,330,000
Subtotal				3,944,000
2. Research Management and Support:				
a. Within grade increase		9,099,000		157,000
b. Annualization of January 2005 pay increase		9,099,000		84,000
c. January 2006 pay increase		9,099,000		157,000
d. One less day of pay		9,099,000		(35,000)
e. Payment for centrally furnished services		1,981,000		10,000
f. Increased cost of laboratory supplies, materials, and other expenses		6,106,000		107,000
Subtotal				480,000
Subtotal, Built-in				4,424,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Environmental Health Sciences

Summary of Changes--continued

CHANGES	2005 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	395	$172,965,000	(33)	($16,996,000)
b. Competing	130	42,946,000	49	16,197,000
c. SBIR/STTR	37	10,809,000	0	(10,000)
Total	562	226,720,000	16	(809,000)
2. Research centers	37	43,453,000	1	865,000
3. Other research	110	19,372,000	8	288,000
4. Research training	525	19,611,000	(16)	0
5. Research and development contracts	106	152,802,000	0	23,000
Subtotal, extramural				367,000
	FTEs		FTEs	
6. Intramural research	580	165,361,000	0	(1,294,000)
7. Research management and support	81	17,186,000	0	(394,000)
Subtotal, program		644,505,000		(1,321,000)
Total changes	661		0	3,103,000

NATIONAL INSTITUTES OF HEALTH
National Institute of Environmental Health Sciences

Budget Authority by Object

	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	661	661	0
Full-time equivalent of overtime & holiday hours	2	2	0
Average ES salary	$147,085	$150,900	$3,815
Average GM/GS grade	11.1	11.1	0.0
Average GM/GS salary	$72,500	$74,385	$1,885
Average salary, grade established by act of July 1, 1944 (42 U.S.C. 207)	$89,650	$91,982	$2,332
Average salary of ungraded positions	103,250	105,934	2,684
OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$34,545,000	$35,913,000	$1,368,000
11.3 Other than Full-Time Permanent	16,046,000	16,682,000	636,000
11.5 Other Personnel Compensation	922,000	958,000	36,000
11.7 Military Personnel	955,000	992,000	37,000
11.8 Special Personnel Services Payments	9,419,000	9,681,000	262,000
Total, Personnel Compensation	61,887,000	64,226,000	2,339,000
12.0 Personnel Benefits	13,395,000	13,904,000	509,000
12.1 Military Personnel Benefits	540,000	562,000	22,000
13.0 Benefits for Former Personnel	0	0	0
Subtotal, Pay Costs	**75,822,000**	**78,692,000**	**2,870,000**
21.0 Travel & Transportation of Persons	2,175,000	2,284,000	109,000
22.0 Transportation of Things	390,000	410,000	20,000
23.1 Rental Payments to GSA	1,000	1,000	0
23.2 Rental Payments to Others	2,085,000	2,189,000	104,000
23.3 Communications, Utilities & Miscellaneous Charges	1,097,000	1,151,000	54,000
24.0 Printing & Reproduction	206,000	214,000	8,000
25.1 Consulting Services	1,250,000	1,300,000	50,000
25.2 Other Services	23,112,000	17,397,000	(5,715,000)
25.3 Purchase of Goods & Services from Government Accounts	79,848,000	86,370,000	6,522,000
25.4 Operation & Maintenance of Facilities	8,450,000	6,051,000	(2,399,000)
25.5 Research & Development Contracts	116,087,000	116,030,000	(57,000)
25.6 Medical Care	24,000	24,000	0
25.7 Operation & Maintenance of Equipment	2,095,000	2,180,000	85,000
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	**230,866,000**	**229,352,000**	**(1,514,000)**
26.0 Supplies & Materials	17,991,000	18,710,000	719,000
31.0 Equipment	9,809,000	10,201,000	392,000
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	304,063,000	304,404,000	341,000
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	**568,683,000**	**568,916,000**	**233,000**
Total Budget Authority by Object	**644,505,000**	**647,608,000**	**3,103,000**

NATIONAL INSTITUTES OF HEALTH
National Institute of Environmental Health Sciences

Salaries and Expenses

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$34,545,000	$35,913,000	$1,368,000
Other Than Full-Time Permanent (11.3)	16,046,000	16,682,000	636,000
Other Personnel Compensation (11.5)	922,000	958,000	36,000
Military Personnel (11.7)	955,000	992,000	37,000
Special Personnel Services Payments (11.8)	9,419,000	9,681,000	262,000
Total Personnel Compensation (11.9)	**61,887,000**	**64,226,000**	**2,339,000**
Civilian Personnel Benefits (12.1)	13,395,000	13,904,000	509,000
Military Personnel Benefits (12.2)	540,000	562,000	22,000
Benefits to Former Personnel (13.0)	0	0	0
Subtotal, Pay Costs	**75,822,000**	**78,692,000**	**2,870,000**
Travel (21.0)	2,175,000	2,284,000	109,000
Transportation of Things (22.0)	390,000	410,000	20,000
Rental Payments to Others (23.2)	2,085,000	2,189,000	104,000
Communications, Utilities and Miscellaneous Charges (23.3)	1,097,000	1,151,000	54,000
Printing and Reproduction (24.0)	206,000	214,000	8,000
Other Contractual Services:			
Advisory and Assistance Services (25.1)	262,000	312,000	50,000
Other Services (25.2)	23,112,000	17,397,000	(5,715,000)
Purchases from Govt. Accounts (25.3)	46,534,000	53,056,000	6,522,000
Operation & Maintenance of Facilities (25.4)	8,450,000	6,051,000	(2,399,000)
Operation & Maintenance of Equipment (25.7)	2,095,000	2,180,000	85,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	**80,453,000**	**78,996,000**	**(1,457,000)**
Supplies and Materials (26.0)	17,990,000	18,709,000	719,000
Subtotal, Non-Pay Costs	104,396,000	103,953,000	(443,000)
Total, Administrative Costs	**180,218,000**	**182,645,000**	**2,427,000**

NATIONAL INSTITUTES OF HEALTH

National Institute of Environmental Health Sciences

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

FY 2005 House Appropriations Committee Report Language (H. Rpt. 108-636)

Item

Environmental exposures and lung disease – The Committee is pleased to note NIEHS's support of studies that establish epidemiological links between environmental exposures and the development of lung disease like asthma and COPD. The Committee encourages the Institute to enhance its research into how environmental stimuli interact with the lung to produce lung disease, with emphasis on cellular responses to inhaled pollutants and the subsequent cell signaling steps that lead to disease. (p. 88)

Action taken or to be taken

NIEHS agrees with the Committee that research on the cellular and molecular responses to inhaled environmental pollutants is an important priority. The Institute has long recognized the health consequences of environmental exposures to such pollutants as diesel exhaust particles, ozone, heavy metals, microbial products such as endotoxin and allergens, manufacturing chemicals such as toluene diisocyanante and dioxin, and environmental tobacco smoke. NIEHS continues to support investigator-initiated research and multi-disciplinary, multi-institutional program projects that encompass biochemical research to determine the toxic components of the exposure and pathobiologic research to examine cellular and molecular signaling pathways through which exposures cause oxidative stress, inflammation and injury, or immune system activation. Other NIEHS-supported efforts test the effect of fetal and childhood exposures to ozone and allergens on the structure and function of the developing lung, and the relationship of these changes to the development of childhood and adult lung disease. These studies employ state-of-the-art technologies, including genomics, to assess exposure-initiated changes in gene expression, proteomics to identify changes in the proteins that effect the response, and computer models to link *in vitro* and *in vivo* studies. The NIEHS lung disease portfolio includes asthma, chronic obstructive lung diseases such as fibrosis and emphysema, and granulomatous lung diseases.

The NIEHS has a major research effort to characterize the role of cellular responses and cell signaling steps that lead to lung diseases. Asthma is an immunologic lung disease of enormous public health importance that is exacerbated by exposure to environmental agents (e.g. allergens, endotoxins). NIEHS scientists are studying cyclooxygenase (COX) enzymes in normal lung physiology and in the pathogenesis of inflammatory lung diseases, and developing new animal models to facilitate studies on the biological role of these enzymes in the lung. New studies by

NIEHS scientists, for instance, have shown that the functional roles in the lung of the two COX enzymes, COX-1 and COX-2, vary depending on the stimulus. COX-1 appears to play a more important role in airway inflammation and hyperresponsiveness following allergen challenge; in contrast, COX-2 plays a more critical role in acute inflammation and fibrosis following exposure to certain chemicals. One set of future experiments will focus on generating mice in which human COX-1 is overexpressed, an approach that should provide further insight into the functional role of COX-1 derived molecules in the lung in the response to environmental stimuli, and to determine the mechanisms responsible for altered airway function in these mice. It is expected that the NIEHS research effort in pulmonary disease will continue to be strong in future years. The area of gene-environment interactions in pulmonary disease, and of cellular mechanisms of lung disease and immunity, is a long-term research interest of the new Director of the NIEHS, Dr. David Schwartz, who will assume his position at NIEHS in April 2005.

Item

Juvenile diabetes.– The Committee commends NIEHS efforts on the Environmental Genome Project (EGP), which seeks to understand how individuals differ in their susceptibility to environmental agents and how these susceptibilities change over time. This project may help to identify environmental triggers for diseases such as Type 1 diabetes. The Committee encourages enhanced efforts to interact and coordinate EGP with efforts like NIDDK's Environmental Determinants of Diabetes in the Young (TEDDY) Study, to investigate genetic and gene-environment interactions in the development of prediabetic autoimmunity and Type 1 diabetes. (p. 88)

Action taken or to be taken

The Environmental Genome Project (EGP) has discovered over 14,000 new single polymorphisms in environmentally responsive genes in the DNA repair and cell cycle control genes. We are continuing to look at other pathways that affect one's susceptibility to environmental agents. Genes in the oxidative stress, apoptosis, metabolism, and signal transduction pathways are among those genes in the queue for resequencing this year. Future plans for the EGP include redirecting our single nucleotide polymorphisms (SNP) discovery activities to focus on environmentally related diseases. As there is a greater understanding that environmental and genetic factors likely work together to cause juvenile diabetes, this disease is a worthy candidate to consider in our future plans. NIEHS participated as a co-sponsor of the initiative leading to The Environmental Determinants of Diabetes in the Young (TEDDY) study and remains in contact with NIDDK staff about its progress. We will involve NIDDK staff as we develop the future directions for the EGP.

Item

Mercury – In order to properly research gaps in the area of mercury exposure and brain chemistry, and given recent hearings on mercury exposure and relationships between autism and Alzheimer's disease and mercury exposure, NIEHS is encouraged to pursue studies of how inorganic mercury and organic mercury compounds (including ethyl, methyl, and other forms of mercury from all sources) are processed in the bodies of children and adults. NIEHS is also

encouraged to support studies of the toxic effects of inorganic mercury and organic mercury compounds on the nervous systems of young children, adults, and the elderly and methods of properly removing mercury and mercury-containing compounds from the brains of affected humans. (p. 89)

Action taken or to be taken

NIEHS is actively pursuing studies to characterize the distribution and effects of exposures to all forms of mercury (organic and inorganic) through multiple routes of exposure. In addition to the extensive work which has already been conducted on oral ingestion of methylmercury through dietary sources, NIEHS scientists are conducting evaluation of the tissue distribution of mercuricals (methylmercury, ethylmercury, and thimerosal) following intramuscular injection in mice. To date, the preliminary data suggest that the route of administration significantly influences the tissue distribution and levels of mercury. In comparison to oral methylmercury, minimal levels of mercury were found in blood, kidney, and brain for both methylmercury and ethylmercury intramuscular injections. Experiments were undertaken to replicate and extend findings from these initial studies, with additional measurements taken from the muscle tissue at the injection site. Final analysis of mercury levels in tissue samples from mice has been completed and the results submitted for publication. NIEHS is also collaborating with NIAID to conduct studies in adolescent and infant monkeys to compare the pharmacokinetics and tissue distribution of ethyl mercury (from thimerosal) and methyl mercury. These studies will provide information to address whether or not the guidelines for methyl mercury are also appropriate for ethyl mercury (from thimerosal).

With respect to development of methods for removal of mercury from the body, recent NIEHS-funded studies have identified a novel antidote for methylmercury, namely N-acetylcysteine. These investigators demonstrated that N-acetylcysteine added to drinking water of mice greatly increases the excretion of methylmercury from the body. The researchers are continuing to examine the mechanisms of methylmercury elimination and determine the role of N-acetylcysteine as an antidote.

Item

Toxic exposure and brain development. – Notwithstanding the Institute of Medicine May 2004 report on autism, the Committee believes it is important to develop a more complete understanding of the impact that toxic exposures may have on brain development. There is a convergence of findings from tissue culture studies, animal models, and clinical studies of immune dysfunction in children with autism that suggests a biological link between genetic sensitivity and damage to developing brains from certain toxins. It is important that NIH continue this research to better understand the impact that exposures to mercury (including thimerosal) and other toxins have on brain development. A more complete understanding of the impact of these exposures through research, including animal models, will help to develop more effective interventions. (p. 89)

Action taken or to be taken

The NIEHS agrees with the Committee that more research is needed to understand the effect of neurotoxic exposures on the developing brain. The NIEHS has long recognized that exposures affect fetuses and children differently from adults and that fetuses and children are more vulnerable than adults. Therefore, the NIEHS continues to fund a number of projects examining the effects of lead, mercury, pesticides, industrial chemicals and other neurotoxic exposure on brain development. These projects span the spectrum from very basic mechanistic studies on the developing brain to human-based studies. The NIEHS, in collaboration with EPA, supports a number of Children's Health Research Centers, several of which have research focused on developmental neurotoxicology. Within these Centers, as well as in our regular portfolio, are basic studies that explore how exposures can interfere with cell division, migration, differentiation formation and pruning of synapses, and other processes that are essential for normal brain development. The human-based studies that NIEHS supports have been instrumental in identifying the risk factors to be pursued in animal models.

The NIEHS sponsored a meeting April 28, 2004 on the New Paradigms for Exploring Gene-Environment-Behavior Relationships to examine the influences of early exposure to neurotoxicants on behavior. We hope to encourage research in the development of new animal models for behavioral toxicology that can be used to understand how exposure affects phenotype/genotype issues. The NIEHS is currently evaluating the latest solicitation of applications from the Fetal Basis of Adult Disease Program Announcement which includes neurotoxicology as one of the prime areas of interest. The NIEHS is pursuing, through the expansion of an ongoing study, the confirmation of an observation in the literature suggesting that immune dysfunction plays a role in the effect of thimerosal on the developing brain. The NIEHS will continue to encourage the expansion of research in developmental neurotoxicology by actively championing the field at appropriate scientific meetings.

Item

National Toxicology Program - In order for the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) to carry out its responsibilities under the ICCVAM Authorization Act, the Committee encourages NIEHS to strengthen the resources provided for ICCVAM activities in order to ensure that new and alternative test methods used or recommended for federal regulatory agencies, and those under consideration or planned for use within the National Toxicology Program's toxicity testing project, are validated prior to their use. (p. 89)

Action taken or to be taken

ICCVAM is a permanent interagency committee of the NIEHS under the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), which is charged with the technical review and evaluation of new, revised, and alternative test methods applicable for specific regulatory uses. NICEATM administers the ICCVAM and provides scientific support for ICCVAM and ICCVAM-related activities, including coordination of independent validation studies to evaluate the usefulness and limitations of proposed test methods.

NICEATM has several new goals for FY2005, all of which are supported by the NIEHS: (1) Initiate validation studies on one or more non-animal/non-radioisotopic estrogen receptor binding and transcriptional activation test methods in FYO5 to determine if these test methods can replace current methods that require surgically- manipulated animals; (2) Initiate independent validation studies in FY05 based on expert panel recommendations; (3) Complete independent validation studies on two in vitro cytotoxicity methods in FY05 to determine if the non-animal methods will reduce the number of animals required for acute toxicity studies; and (4) Provide reference chemical data and coordination for a European Centre for the Validation of Alternative Methods (ECVAM) validation study on in vitro methods for estimating dermal irritation potential of chemicals.

In addition, a new Deputy Director for NICEATM will be appointed in either late 2004 or early 2005. This additional person will allow for expansion of NICEATM activities.

Item

Parkinson's Disease – The Committee encourages NIEHS in collaboration with NINDS to gain a greater understanding of the environmental underpinnings of Parkinson's disease. The Committee also encourages NIEHS to intensify its efforts in the Collaborative Centers for Parkinson's Disease Research Program. This initiative facilitates significant collaboration between, clinical medicine, epidemiology, and basic science so that the most promising leads may be investigated more quickly in pursuit of a cure or to reduce the incidence of harmful toxins. (p. 89)

Action taken or to be taken

The NIEHS supports several ongoing research initiatives to address environmental causation in PD and works closely with the NINDS to plan future initiatives in PD. In addition to the three Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER), the NIEHS currently supports many individual investigator-initiated grants in PD. The scope of the NIEHS-funded research in Parkinson's Disease (PD) is considerable and spans studies from molecular epidemiology of environmental risk and protective factors for PD to basic laboratory investigations aimed at developing new animal models, understanding the role of mitochondrial oxidative damage in vulnerable cell populations and defining transport mechanisms for toxicant entry to brain. Understanding the causes of PD will require a synthesis of findings emerging across these disparate disciplines, diseases and experimental settings. NIEHS has taken several steps to encourage such synthesis. A meeting of NIEHS-supported researchers in PD and other neurodegenerative diseases was held in June, 2004 to promote cross-fertilization of ideas among researchers, diseases and disciplines and to identify and prioritize data gaps, future resource needs and research opportunities. The results of this meeting were used to re-fashion an ongoing NIEHS initiative in gene-environment interaction in PD to encourage submission of applications focused on the roles of non-neuronal cells and proteasomal function in environmentally-induced PD.

The NIEHS is also partnering with the NINDS to support a Parkinson's Disease Data Organizing Center (PD-DOC) that will include a repository for environmental exposure and other risk factor data collected from individuals with PD and from unaffected controls. This centralized database

will facilitate data sharing and pooled analysis, providing increased power to detect associations between environmental exposures and genetic and clinical characteristics in persons with PD. To support more meaningful interactions among NIEHS Collaborative Centers for PD Environmental Research, the NIEHS has awarded supplemental funds for the purchase of behavioral testing equipment that will enable greater sharing and comparison of behavioral data collected across the Centers. The NIEHS provided a second supplemental award to these Centers to support a series of meetings that will be used to develop recommendations for standardized PD diagnosis and exposure assessment in epidemiology studies. Common guidelines will facilitate data sharing and interpretation across different Centers and studies. Most recently, the NIEHS provided an opportunity for each Center to apply for competitive supplemental funds to conduct cooperative studies across Centers.

FY 2005 Senate Appropriations Committee Report Language (S. Rpt. 108-345)

Item

Breastfeeding and Toxins – Recent reports on the presence of flame retardants and other environmental toxins in human breastmilk have given rise to concerns about the safety of breastfeeding. Recognizing that these reports may offer mixed messages about this public health concern, the Committee reaffirms the goal of Healthy People 2010 of "Increasing the proportion of mothers who breastfeed their babies." The Committee also strongly urges the National Institute of Children's Health and Human Development, the National Institute of Nursing Research, the National Institute of Environmental Health Sciences, the Centers for Disease Control and Prevention, Department of Health and Human Services' Office of Women's Health to hold a consensus meeting with health professionals, to include nursing and breastfeeding and lactation professionals. The consensus meeting should focus on environmental toxins and breastfeeding and appropriate public risk communication. (p. 134)

Action taken or to be taken

NIEHS supports the current HHS recommendations on breastfeeding as outlined in the HHS Blueprint for Action on Breastfeeding (http://www.4woman.gov/Breastfeeding/blueprntbk2.pdf). A recent analysis by NIEHS scientists showed that breastfed babies had less risk of dying in the postneonatal period than children who had never been breastfed, and that breastfeeding has the potential to prevent hundreds of postneonatal deaths each year in the U.S. Periodically, however, we are reminded that industrial chemicals and pesticides appear in virtually all human milk, and have done so since DDT was first reported in human milk in 1951. For the last two decades, NIEHS has done and supported epidemiologic studies of the consequences of pollutants in breast milk. Those studies have found that polychlorinated biphenyls passed from mother to fetus while the child is in the womb result in subtle, detrimental effects on the mental and motor development of the child, but that exposure through breast milk does not appear to do further harm. Although this information is available in the scientific literature, in professional publications like those of the American Association for Pediatrics, in the HHS breastfeeding document, and periodically is the subject of reports in the lay press, the material is not much covered in clinical training and can be difficult for a new mother to find on her own or from her medical provider. NIEHS staff have had discussions with scientific staff at the HHS Office on Women's Health (OWH), who chair the interagency Committee on Women and the Environment. NIEHS will explore with OWH the best ways to bring interagency focus through this Committee to the issue of public communication and outreach on breastfeeding.

Item

Environmental Health and Nursing – According to the final report of the Nursing and Environmental Health Roundtable, held in the fall of 2002, there is a significant need to build a cadre of registered nurse researchers specializing in environmental health. During the last decade, increased emphasis has been placed on the impact of environment on human health and the need for nurses to engage in research to advance knowledge in this field. Several nurse researchers received funding for environmental health projects focused on prevention of lead

exposures, environmental factors and asthma, pesticide exposures among workers and their families, environmental awareness, and occupational health. Despite these efforts, significant needs still exist. Environmental health nurse researchers bring knowledge in nursing research methods as well as more traditional areas of environmental health research, such as human disease manifestation, risk assessment, and risk management. Many of the priority areas of environmental health nursing research rely on methods of exposure assessment, risk assessment, and risk communication. This Committee urges the National Institute of Environmental Health Sciences to create specific nurse research fellowships with the goal of increasing the number of registered nurse researchers specializing in the area of environmental health. (p. 134)

Action taken or to be taken

The National Institute of Environmental Health Sciences (NIEHS) is currently working with representatives from the National Institute for Nursing Research, the Centers for Disease Control and Prevention (National Center for Environmental Health and Agency for Toxic Substances and Disease Registry), Health Resources and Services Administration, and the U.S. Environmental Protection Agency to address many of the recommendations outlined in the 2002 Roundtable Report and the IOM Report, "Nursing, Health and Environment." One of the primary objectives of this group is to encourage research training and career development opportunities for nurse researchers and practitioners in the field of environmental health. In coordination with these agencies, NIEHS is examining how to establish a research fellowship that best meets the needs for nurses interested in pursuing research in environmental health. NIEHS is also in contact with the American Public Health Association's newly established Environmental Health Task Force (a joint group between the Environment Section and Public Health Nursing Section) regarding issues of nurse training, research and translation to practice.

Item

Pacific Center for Environmental Health – The Committee encourages NIEHS to establish a Pacific Center for Environmental Health to further study the short-term and long-term health effects of volcanic emissions as well as other environmental issues. Such environmental concerns should include food and waterborne illness, fish contamination by pesticides and heavy metals, and pesticide residue in food and water. (p. 135)

Action taken or to be taken

In February 2004, NIEHS held a town meeting in Honolulu, Hawaii to hear the concerns of citizens and scientists on the environmental health problems on the islands of Hawaii. Approximately 100 members of the public were present to discuss environmental health concerns of the region. Presentations were given by University of Hawaii researchers on the respiratory health effects of volcanic emissions, interdisciplinary research on oceans and human health, and the effects of heptachlor contamination and the health effects in children and on the role of the environment in autism. In the discussion period we heard concerns from citizens on the effects of water contamination in waterways in Oahu on fish health and possible human health outcomes from eating contaminated fish and other environmental and land use issues. Members of two NIEHS Children's Environmental Health Centers discussed the concerns of

parents of children with autism for several hours. In addition, it was announced that NIEHS and the National Science Foundation (NSF) made an award to the University of Hawaii for a Center for Oceans and Human Health, which will be one of four such Centers funded in the U.S. In follow-up, NIEHS staff spoke with Dr. Bruce Anderson, past health director and currently on the faculty at the School of Medicine, about the eligibility criteria for the development of an NIEHS Environmental Health Sciences Center in Hawaii and offered advice and assistance to the University if they decide to pursue such funding.

Item

Parkinson's Disease – The Committee urges NIEHS in collaboration with NINDS to gain a greater understanding of the environmental underpinnings of Parkinson's disease. The Committee also strongly urges NIEHS to intensify its efforts in the Collaborative Centers for Parkinson's Disease Research Program – as this initiative facilitates significant collaboration among genetics, clinical medicine, epidemiology, and basic science so that the most promising leads may be investigated more quickly in pursuit of a cure or to reduce the incidence of harmful toxins. (p. 135)

Action taken or to be taken

Please refer to page NIEHS - 32 of this document for the NIEHS response to this significant item regarding Parkinson's Disease.

NATIONAL INSTITUTES OF HEALTH
National Institute of Environmental Health Sciences

Authorizing Legislation

	PHS Act/ Other Citation	U.S. Code Citation	2005 Amount Authorized	FY 2005 Appropriation	2006 Amount Authorized	2006 Budget Estimate
Research and Investigation	Section 301	42§241	Indefinite	$624,894,000	Indefinite	$627,997,000
Health Sciences	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	a/	19,611,000	b/	19,611,000
Total, Budget Authority				644,505,000		647,608,000

a/ Amounts authorized by Sections 301and 311 and Title IV of the Public Health Act.

b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH
National Institute of Environmental Health Sciences

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1997	$289,114,000 2/	$308,258,000	$294,745,000 2/	$308,487,000
1998	313,583,000 2/	328,583,000	331,969,000	330,108,000
1999	349,021,000 2/3/	356,047,000	375,743,000	375,743,000
Rescission				(249,000)
2000	390,718,000 2/	421,109,000	436,113,000	444,817,000
Rescission				(2,368,000)
2001	460,971,000 2/	506,730,000	508,263,000	502,549,000
Rescission				(495,000)
2002	561,750,000	557,435,000	585,946,000	566,639,000
Rescission				(1,942,000)
2003	609,705,000	609,705,000 4/	617,258,000	618,258,000
Rescission				(4,019,000)
2004	630,774,000	630,774,000	637,074,000	636,974,000
Rescission				(4,582,000)
2005	650,027,000	650,027,000	655,100,000	650,027,000
Rescission				(5,522,000)
2006	647,608,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
2/ Excludes funds for HIV/AIDS research activities consolidated in the NIH Office of AIDS Research.
3/ Reflects an increase of $931,000 for the budget amendment for bioterrorism.
4/ Reflects the President's Budget Request.

NATIONAL INSTITUTES OF HEALTH
National Institute of Environmental Health Sciences

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Office of the Director	19	19	19
Division of Research Coordination, Planning, and Translation	34	34	34
Division of Intramural Research	470	478	478
Division of Extramural Research and Training	61	63	63
Office of Management	65	67	67
Total	649	661	661
FTEs supported by funds from Cooperative Research and Development Agreements	(0)	(0)	(0)

FISCAL YEAR	Average GM/GS Grade
2002	10.4
2003	10.4
2004	11.1
2005	11.1
2006	11.1

NATIONAL INSTITUTES OF HEALTH
National Institute of

Detail of Positions

GRADE	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Total - ES Positions	1	1	1
Total - ES Salary	$143,489	$147,085	$150,900
GM/GS-15	38	39	39
GM/GS-14	60	60	60
GM/GS-13	70	70	70
GS-12	61	66	66
GS-11	112	113	112
GS-10	4	3	3
GS-9	59	63	62
GS-8	22	23	22
GS-7	45	45	45
GS-6	2	3	3
GS-5	4	4	4
GS-4	9	9	9
GS-3	1	1	1
GS-2	2	2	2
GS-1	0	0	0
Subtotal	489	501	498
Grades established by Act of July 1, 1944 (42 U.S.C. 207):			
Assistant Surgeon General			
Director Grade	9	9	9
Senior Grade	1	1	1
Full Grade			
Senior Assistant Grade			
Assistant Grade			
Subtotal	10	10	10
Ungraded	150	155	158
Total permanent positions	479	513	513
Total positions, end of year	650	667	667
Total full-time equivalent (FTE) employment,end of year	649	661	661
Average ES salary	$143,489	$147,085	$150,900
Average GM/GS grade	11.1	11.1	11.1
Average GM/GS salary	$70,700	$72,500	$74,385

NATIONAL INSTITUTES OF HEALTH
National Institute of Environmental Health Sciences

New Positions Requested

	FY 2006		
	Grade	Number	Annual Salary
Clinical Investigator	Title 42	2	$170,000
Staff Scientist	Title 42	3	85,000
Investigator	Title 42	1	85,000
Research Fellow	Title 42	1	80,000
Biologist	GS-13	1	80,000
Health Policy Administrator	GS-14	1	96,000
Total Requested		9	