

# FY 2006 NIEHS Director's Statement

Department of Health and Human Services National Institutes  
of Health

## FY 2006 Budget Request

**Witness appearing before the Subcommittee on Labor-HHS-Education Appropriations**

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**National Institute of Environmental Health Sciences, 2005**

**William Beldon, Deputy Assistant Secretary, Budget**

Mr. Chairman and Members of the Committee:

I am pleased to present the Fiscal Year (FY) 2006 President's budget request for the National Institute of Environmental Health Sciences (NIEHS). The FY 2006 budget includes \$647,608,000, an increase of \$3,103,000 over the FY 2005 enacted level of \$644,505,000 comparable for transfers proposed in the President's request.

## Introduction

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"Genetics loads the gun, but environment pulls the trigger."

Judith Stern, University of California, Davis

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 compliance. 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 through the pursuit of the Human Genome Project offers great promise for elucidating mechanisms of gene-environment interactions in the development of complex diseases.

For years, the environment was considered to have a minor role in the etiology of human illness. But, in recent years, the thinking has shifted in favor of gene-environment interactions. 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 (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, 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 information relevant to most chronic diseases, other research programs have been developed to address specific diseases such as breast cancer, Parkinson Disease, and autism. Today, I will briefly describe several of these initiatives and their implications for human health and disease.

## Genetic Differences in Susceptibility to Drugs and Environment

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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, often masking important environmental contributors to disease risk. 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 Environmental Genome Project (EGP) to catalogue these genetic variants (polymorphisms) and to identify the ones that play a role in human susceptibility to environmental agents. This information is already being used in epidemiological studies to better pinpoint environmental contributors to disease. Also, several important variants have been discovered that are associated with risk for chronic illnesses such as leukemia, cardiovascular disease, and neuronal dysfunction.

## Animal Models Predisposed to Environmental Risk

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The usefulness of the susceptibility data generated in the EGP is enhanced by the availability of animal models with the exact sequence variations discovered by resequencing of the human environmental response genes. Therefore, NIEHS developed a university-based Mouse Genomics Centers Consortium to create mice with such variations and provide them to the scientific community. To date, approximately 20 well-characterized mouse models have been developed. These models represent a variety of disease endpoints, including: Werner's syndrome (aging disorder), diabetes, mammary cancer, gastrointestinal and bladder cancer, prostate cancer, and skin cancer.

## Effort to Improve Relevance of Animal models

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Environmental health scientists often use mice to predict how environmental agents might affect people. Although mouse studies can 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. Information on the similarities and differences in homologous genes between human and mouse is important to improve accuracy in predicting human risk. While laboratory mice might look alike, the 100 different strains used in medical research differ significantly in their behavior, physiology and susceptibility to drugs and environmental agents (e.g., carcinogens), and scientists are eager to discover the differences in the genetic sequences that underlie these traits, with the goal of finding counterparts in humans. NIEHS initiated a mouse sequencing project to decipher the genomes of the 15 mouse strains used most frequently in research to predict human risk. Such data will improve environmental risk assessment decisions and will help researchers in choosing the most appropriate strain for studying toxicity.

## Sister Study of Breast Cancer

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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. To get the information quickly, this study is recruiting 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 of 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, along with genetic analysis. The principal investigator has the active support of the American Cancer Society, Sisters Network, Inc., the Susan G. Komen Breast Cancer Foundation, and the Y-ME Breast Cancer Organization.

## Parkinson's Disease

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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. 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. Accomplishments to date include: efforts to discover new PD susceptibility genes; development of a registry in California to track the disease; development of mouse models with specific alterations in genes suspected of playing a role in PD, and efforts to develop a primate model of PD that exhibits the most prominent clinical features of the disease.

## Autism

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Autism is a devastating behavioral disorder that most likely arises from underlying genetic susceptibilities interacting with specific environmental exposures during pre- or postnatal development. 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. It is possible, however, that only a subset of children are susceptible to mercury effects, perhaps when coupled with an immunological challenge. Preliminary animal studies have provided an intriguing clue to possible susceptibilities 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 reported and morphological changes were observed in the brain. However, this study did not have sufficient power to be definitive. Fortunately, the NIEHS already had two Children's Environmental Health and Disease Prevention Research Centers devoted to autism. Thus, the Institute provided a

supplement to one of these Centers 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 occur. This more extensive look at thimerosal-immune co-contributors to brain damage may provide better insight into this disorder than previous studies have. In addition, the same Center is recruiting a cohort of 700 autistic children, and appropriate control subjects, to further examine the role of gene-environment interactions in the etiology of autism.

## Obesity and the Built Environment

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Obesity is a major contributor to human disease and rising health care costs. NIEHS is collaborating with the Robert Wood Johnson Foundation to examine how community design influences physical activity. This so-called Active Living Design Program is working with local governments to influence city planning and land use decisions. The program's impact on physical activity, obesity, and other health indicators will be assessed. The Institute is also encouraging research to evaluate the role of "in utero," neonatal, and pre-puberty 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.

## Nanotechnology

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Nanotechnology is an exciting area of research with broad implications for multiple industries, including medicine and communication. For example, 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 adversely 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), has initiated a program to evaluate the toxicological properties of the major classes of nanoscale materials 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?

## NIH Roadmap and Environmental Health Research

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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. Thus, Roadmap initiatives such as the Interdisciplinary Research Planning Centers will greatly enhance NIEHS' work. Examples include: the use of geographic/spatial methodologies to address combined genetic, social, and environmental factors on child health and development, and an effort to redefine computational genomics with emphasis on gene-environment interactions in alcoholism, atherosclerosis and breast cancer. Both projects have strong ties to other significant NIEHS-funded programs at the same institutions.

Thank you for the opportunity to comment on the important work supported by the NIEHS. I will be happy to answer any questions you might have.