

Asthma

Early studies showed that asthma was caused by both genetic and environmental factors. The National Institutes of Health (NIH) used the doubling of the budget to identify additional environmental and genetic factors that cause asthma and to develop prevention and intervention programs for asthma and other lung diseases.

- **Identified important triggers of childhood asthma risk.** Discovered that cockroach allergens worsen asthma symptoms more than other common allergens. The importance of the timing of exposures to other allergens, e.g. cat allergens, was discovered.
- **Identified simple child-specific interventions.** The study provided specific allergen-reducing interventions tailored to each child's known allergens and included using nonporous covers on mattresses and pillows, air purifiers and vacuums with HEPA (high efficiency particulate air) filters, and professional pest control. Using these specific interventions resulted in 19 % fewer unscheduled clinic visits and a 13 % reduction in use of asthma medication.
- **Allergen assessment.** Completed a nationwide assessment of allergen levels in selected U.S. homes to help in devising national intervention strategies.
- **Identified dietary components of lung disease risk.** Supplementation with antioxidant vitamins C and E counteracted the decreased lung function in asthmatic children arising from ozone exposure.

Cancer

Many cancer deaths could be avoided if the disease is found early and if tests could be done to predict whether cancer would return in patients that have undergone treatment. The doubling of the budget allowed the NIH to develop these tests.

- **Early Detection Research Network (EDRN):** EDRN scientists successfully discovered a number of biomarkers that allow for the earlier detection of breast, prostate, colon, lung, and other cancers.
- **Predicting breast cancer recurrence.** Researchers developed a molecular test to determine the risk of cancer recurrence for women previously treated for early stage, estrogen-dependent breast cancer.

Chronic Diseases

The National Institutes of Health (NIH) used the doubling of the budget to launch a number of important clinical studies to develop treatments for debilitating chronic diseases that seriously reduce the quality of life for a wide segment of the American people.

- **Large Scale Clinical Trials.** Significant trials were conducted on combination therapies for osteoporosis; surgical and non-surgical treatments for back pain; and statin treatment of cardiovascular disease in children with lupus.
- **Biomarkers and Epidemiology Studies.** Examples include a large, multi-center study of the epidemiology of osteoporosis in men; a large public-private partnership to develop a research resource for the study of osteoporosis in men; a large public-private partnership to develop a research resource for the study of osteoarthritis; and studies of the genetics of complex diseases including a number of skin diseases, rheumatoid arthritis, and lupus.
- **Muscular Dystrophy.** Initiatives include the addition of two Senator Paul D. Wellstone Muscular Dystrophy Cooperative Research Centers; and new initiatives to encourage translational research in all forms of muscular dystrophy, and to stimulate career development opportunities for muscle disease researchers.

Congenital Heart Defects

The NIH budget doubling allowed funding for the Pediatric Heart Network which combines study results from adequate numbers of children and adults with congenital heart defects in order to determine if treatments are effective.

- **Improved treatment for Kawasaki Disease.** A clinical trial showed that steroids did not improve outcomes or shorten hospitalizations of patients with Kawasaki Disease, which led to a change in clinical practice that decreased the incidence of side effects from the use of steroids in these patients.
- **Improving surgery for congenital heart defects.** A clinical trial is under way to determine the best surgical approach for patients with hypoplastic left heart syndrome, a severe defect that has the highest mortality risk of all the congenital heart diseases.

Diabetes

An estimated 41 million Americans have pre-diabetes before progressing to full diabetes and its dangerous complications. The NIH conducted the Diabetes Prevention Program (DPP) — a major clinical trial involving over 3,000 subjects to determine if progression to diabetes could be delayed or prevented.

- **Prevention of progression to type 2 diabetes.** An intensive lifestyle intervention reduced progression to type 2 diabetes by 58 percent, and the drug metformin reduced development of diabetes by 31 percent. The benefits were demonstrated for both white and minority populations.
- **Public health campaign launched.** Based on the DPP findings, in 2002, HHS Secretary Tommy G. Thompson launched the first national diabetes prevention campaign in an effort to stem the explosion of diabetes.
- **Enabled continuing studies.** Rates of heart attack, stroke and other diabetes complications are under study to determine the value of the DPP interventions in reducing these highly prevalent diabetes-related diseases.

Genes, Environment and Disease

Early experiments demonstrated that the combination of genes and the environment caused certain diseases. The NIH used the doubling of the budget to fund the Environmental Genome Project (EGP), in order to find additional diseases caused by the combination of genetic and environmental factors.

- **Identified people with increased risk of cardiovascular disease and pesticide toxicity.** Genetic variants of the paraoxonase gene were identified that may increase risk of cardiovascular disease and neurotoxic agents, and possibly influence susceptibility to Gulf War Syndrome.
- **Identified people with increased risk of leukemia from common exposures.** Identified a gene variant in 5-20% of the population that confers a greater risk of developing leukemia following exposures to benzene, radiation and chemotherapeutic agents.
- **Identified a potential biomarker of autism.** The finding provides a possible molecular event in autism development that is open to intervention strategies and suggests a biomarker for early identification of children at risk for autism.

Health Information

Information technology allows us to collect information and make decisions more quickly and easily. The NIH used the doubling of the budget to create many new information resources for the public, assemble the human genome, and apply new technologies to the health of the American people.

- **Information for the public.** NLM, for the first time, created information resources specifically for patients

families and the public — MedlinePlus, ClinicalTrials.gov, NIHSeniorHealth.gov, attract 7 million users monthly.

- **Assembling the human genome.** NLM kept pace with the 15-fold increase in DNA sequence data, created a suite of accompanying databases and tools for access, and created increasingly refined assemblies of the 3-billion base pair human genome.
- **Implementing telemedicine.** NLM evaluated the impact of advanced networking technologies on health care, research, and public health including community-wide access to electronic health records, and a breast imaging archive and network infrastructure.

Infant Deaths

Several significant problems were causing death and disease in newborn infants. The doubling of the budget allowed NIH to develop new treatments that significantly reduced infant deaths in the U.S. and around the world.

- **Mother to child HIV transmission.** Pediatric clinical trials led to treatments that reduced the transmission rate from 25% to nearly 1% in the United States. By adjusting timing and dosage, it was possible to reduce the transmission levels from 18% to 6.5% in Thailand. In Uganda, a new drug (Nevirapine) reduced the transmission rate from 20% to 12%, despite the fact that mothers were still breastfeeding.
- **Reducing preterm birth.** Progesterone 17P reduced preterm delivery, in subjects at risk, by 30% in both African American and white women.
- **Obstetric-Fetal Pharmacology Research Units.** The program supports new research on the safety and effectiveness of medications used during pregnancy.

Influenza

An important part of flu prevention is predicting where new flu outbreaks will occur and developing ways to prevent them from spreading. Therefore, the NIH developed computer models to predict the spread of infectious diseases. The Model of Infectious Disease Agent Study (MIDAS) is a large group of scientists that develop such models, with specific attention to models for influenza virus.

- **Possible containment of an influenza outbreak.** MIDAS researchers developed models for an influenza outbreak in Southeast Asia that determine optimal intervention strategies to contain the outbreak at its source.
- **Pandemic preparedness for the United States.** MIDAS researchers developed models for the United States that are now actively used as a base to predict the potential impact of a wide range of intervention strategies in the event of a flu pandemic.

International Health

The NIH used the doubling of the budget to expand our capacity to address critical health crises throughout the world while further stabilizing our Nation's health.

- **Began new AIDS and TB training program.** The program strengthens the capacity of low and middle income countries to conduct clinical, operational and health services research. The program developed local expertise to address research questions that arise during the course of the President's Emergency Plan for AIDS Relief (PEPFAR) funding.
- **International Bioethics Curriculum and Career Development Program.** The program provides advanced training for developing country professionals in research ethics so they can provide expertise for ethical review, clinical trials consultation, ethics education and research on ethical issues in their countries
- **Began the International Tobacco and Health Research and Capacity Building Program.** The program has become the major international tobacco research program that is focused on trans-disciplinary research and capacity building projects that address the burden of tobacco consumption in low- and/or middle-income nations.

Mental Disorders

A number of candidate treatments capable of relieving suffering from some of the Nation's most disabling mental disorders were shown to have potential as treatments in small studies with few patients. The doubling of the budget allowed NIH to conduct large clinical trials to determine whether these treatments represented significant therapies for these disorders.

- **Treatment for adolescent with depression study (TADS).** The results showed that the combination of fluoxetine and cognitive behavioral therapy was more effective than either treatment alone, greatly decreasing significant suicidal thoughts.
- **Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE).** Over 1,400 patients participated in this study of five different medications. The results showed that newer — often more expensive — antipsychotic drugs were not much more effective than conventional medications.
- **Sequence Treatment Alternatives to Relieve Depression (STAR*D).** A treatment approach emphasizing systematic and comprehensive patient monitoring resulted in an improvement in depression remission from 22 to 33%.

- **Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD).** This large multi-pronged study identified the most effective long-term and acute treatments for people with bipolar disorder as well as interventions to prevent relapse.

Neurological Disease

Neurological diseases are a wide array of disorders that afflict millions of Americans. Many of these diseases are genetic. The NIH used additional funding from the doubling to apply new genetic techniques to the diagnosis and treatment of neurological diseases.

- **Genes discovered.** Scientists identified more than 100 genes associated with neurological diseases including ALS (Lou Gehrig's disease), Parkinson's disease, epilepsy, spinal muscular atrophies, and muscular dystrophies.
- **Better diagnostics.** For ataxias, muscular dystrophies, spinal muscular atrophy, and dozens of other diseases, discovering the gene for each disease led to DNA tests that, usually for a few hundred dollars, could give a definitive diagnosis within a week.
- **Therapies developed in animal models.** Promising therapies were developed in gene-based animal models for many untreatable diseases. Therapeutic strategies that are moving into human clinical testing include ALS, Huntington's disease, ataxias, and muscular dystrophy.

Non-invasive Diagnostics

As diagnostic tests are simplified, more people can be tested more rapidly. NIH used the doubling of the budget to develop a unique area known as salivary diagnostics. This noninvasive diagnosis of medical conditions using biomarkers easily obtained in saliva is especially relevant when dealing with children or elderly people.

- **Survey of proteins in saliva.** The first comprehensive catalog of proteins found in the oral fluids of healthy individuals was assembled.
- **Measurement of C-reactive protein in human saliva with a microchip array system.** C-reactive protein is a marker of inflammation in blood; it is elevated in people with periodontal disease and may predict increased risk of heart disease.
- **Detection of elevated levels of four distinct cancer-associated molecules in saliva.** The test identified individuals with oral cancer with a 90% accuracy rate compared to healthy controls.

Protein Structures for Drug Development

Knowing the structure of a protein involved in a disease allows scientists to find drugs that can block the protein and stop the disease. The NIH knew that more drugs could be developed if more structures of proteins were known. The doubling of the budget was used to fund the Protein Structure Initiative (PSI). The PSI focuses on determining the three-dimensional structure of a large number of proteins — a critical first step in the development of new drugs.

- **Determination of over 1300 protein structures.** Within five years (2000-2005) the protein structure output increased 10-fold, with a 4-fold reduction in the cost per structure.
- **Protein modeling.** Each solved protein structure serves as the basis for computer modeling of many additional proteins of the same or related families. The initiative has therefore created a strong multiplier effect.

Stroke

Stroke is a major cause of death and disability in Americans and there are limited effective treatment options. The doubling allowed NIH to launch a number of different types of studies to improve the prevention and treatment of stroke.

- **The Warfarin Aspirin Symptomatic Intracranial Disease clinical trial.** The findings showed that, for many people, aspirin prevents stroke effectively — in fact, as well as warfarin, a drug that requires blood tests at least once per month and carries risk of substantial side effects, including major hemorrhage and heart attack.
- **The CLOTBUST trial.** This trial of 126 patients showed that using ultrasound in combination with t-PA may improve the effectiveness of this drug in breaking up clots and restoring blood flow to the brain. Additional research will standardize the combined therapy and study it in a larger group of patients.
- **The African American Antiplatelet Stroke Prevention Study.** The study showed that aspirin is safer and as effective as ticlopidine for prevention of a second stroke in this population.
- **The International Study of Unruptured Intracranial Aneurysms.** The results now help doctors predict which people with a brain aneurysm will benefit from surgical repair to prevent a stroke, and which will be better off with careful monitoring.