

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

Burden of Chronic Diseases

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April 20, 2007

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Mr. Chairman and Members of the Committee:

I am pleased to present the Fiscal Year (FY) 2008 President's Budget request for the National Heart, Lung, and Blood Institute (NHLBI). The FY 2008 budget includes \$2,925,413,000. The NHLBI provides leadership for an outstanding, visionary, and highly productive research program in heart, lung, and blood diseases. I will briefly describe the Institute's strategic planning process, and then highlight advances in three important research areas.

THE NHLBI STRATEGIC PLAN

With the extensive involvement of the scientific, professional, and patient-advocacy communities, the NHLBI has just completed development of a comprehensive Strategic Plan to guide its efforts in the near future. The Plan identifies a number of basic research areas of focus with the intent of delineating normal and pathological biological mechanisms and exploiting the emerging understanding of these mechanisms to identify biomarkers of disease. Such biomarkers—broadly defined as measurable indicators of genotype, biological or pathological processes, or responses to therapeutic intervention—will facilitate identification of disease subtypes and point the way toward new molecular targets for prevention, diagnosis, and treatment.

The Plan's clinical and translational research goals emphasize transmission of knowledge between basic and clinical research so that findings in one arena rapidly inform and stimulate research in the other. More precise methods of risk-stratification and diagnosis are expected to arise from application of new approaches (e.g., noninvasive imaging, biomarkers) from basic science laboratories. A critical challenge will be to develop personalized preventive and therapeutic regimens based on one's genetic makeup in combination with developmental and environmental exposures. Insights are already emerging, but robust and efficient means of validating both individualized and population-based treatments will be needed to establish an evidence base to guide medical practice.

The Institute is cognizant of the need to improve understanding of the processes involved in translating research into practice and to use that understanding to enable improvements in public health and stimulate further scientific discovery. Particular emphasis will be placed on conducting research in primary prevention and identifying interventions that work in the practice communities that will ultimately constitute the targets for translation and education. As well, the NHLBI will continue to investigate and evaluate new approaches to communicate research advances to the public, and will stress the importance of public involvement in the research process. These are

ambitious tasks, but we are eager to take them on and optimistic about their ultimate success.

Over the past year, the NHLBI has made significant progress on a number of research fronts, but we highlight major advances in three areas.

MARFAN SYNDROME

Marfan syndrome is a genetic disorder of connective tissue—the framework that binds and supports the body. Although the syndrome has many manifestations, the most serious is a weakening (aneurysm) of the aorta that sets the stage for life-threatening ruptures. New research offers hope that losartan, a drug commonly prescribed to treat hypertension, might be effective in preventing this frequent and devastating complication.

After the discovery that Marfan syndrome is associated with a mutation in the gene encoding a protein called fibrillin-1, researchers tried for many years, without success, to develop treatment strategies that involved repair or replacement of fibrillin-1. Recently, a major breakthrough occurred with the discovery that one of the functions of fibrillin-1 is to bind to another protein, TGF-beta, and regulate its effects. After careful analyses revealed aberrant TGF-beta activity in patients with Marfan syndrome, researchers began to concentrate on treating Marfan syndrome by normalizing the activity of TGF-beta. Losartan, which is known to affect TGF-beta activity, was tested in a mouse model of Marfan syndrome. The results, published only last April, showed that the drug was remarkably effective in blocking the development of aortic aneurysms, as well as lung defects associated with the syndrome.

Based on this promising finding, the NHLBI Pediatric Heart Network is now undertaking a clinical trial of losartan in patients with Marfan syndrome. About 600 patients aged 6 months to 25 years will be enrolled and followed for 3 years. This development illustrates the outstanding value of basic science discoveries in identifying new directions for clinical applications. Moreover, the ability to organize and initiate a clinical trial within months of such a discovery is testimony to the effectiveness of the NHLBI Network in providing the infrastructure and expertise to capitalize on new findings as they emerge.

SICKLE CELL DISEASE

Excellent progress is being made against sickle cell disease, another genetic disorder that affects about 70,000 persons within the United States, mostly of African ancestry. The underlying defect, which deforms red blood cells, wreaks havoc on nearly every organ in the body. Fortunately, NHLBI research has yielded vastly improved treatment for this disease and an increase in life expectancy from the mid-teens to about 50 years of age.

Hydroxyurea, the first specific therapy, was shown in clinical trials to be safe and effective for adult patients and, subsequently, for children between the ages of 5 and 15 years. The treatment reduced anemia, the frequency of painful episodes, and the prevalence of acute chest syndrome—the main hallmarks of the disease—and also reduced mortality. Moreover, hydroxyurea did not adversely affect either normal growth or pubertal development in the children who received it. Two ongoing trials are now exploring other beneficial effects of hydroxyurea. Baby HUG is determining whether administering the drug to infants can prevent early damage to their spleens and kidneys. A second trial, SWITCH, is studying the possibility that children who have suffered a stroke and are now on chronic transfusion and iron chelation therapy can be switched to hydroxyurea treatment to prevent another stroke. It would be of great benefit to these patients to have a treatment that could be taken orally without the side effect of iron overload.

The NHLBI also has an active program exploring cord blood/bone marrow transplantation for sickle cell disease. Heretofore, transplant procedures have been curative but limited to the few patients who have a compatible donor. However, recent cord blood transplant research is showing that success can be achieved with a less-than-perfect tissue match and, consequently, many more patients may be eligible to receive this treatment and avoid the disease's grim consequences.

Overall, it is expected that hydroxyurea therapy, future transplant protocols, and other therapeutic approaches will dramatically improve the lives of many patients with sickle cell disease and reduce the costs of recurrent hospitalizations and long-term care of complications. The NHLBI now has in place a pipeline for drug therapy, a drug screening program, and platforms for clinical trials for this orphan disease that will require multiple therapies for its many sequelae.

COPD

At long last, COPD is moving from obscurity to prominence. Now the 4th most common cause of death in the United States, COPD claims more than 120,000 lives annually—5.1 percent of the death toll. Moreover, for every person who will die of COPD this year, an estimated 200 others will suffer from impaired airway function, more than half of whom are undiagnosed. Once primarily an affliction of cigarette-smoking men, COPD now affects American women nearly equally and occurs surprisingly often among lifelong nonsmokers.

Progress against COPD has been slow and difficult, in part because the illness is complex and often perceived as being self-inflicted. Unlike diseases defined by a particular molecular defect or infectious agent, COPD has no single risk factor, no diagnostic blood test, and no definitive treatment. However, we are now entering a period of rapid discovery and translation into clinically effective interventions for

patients. Investigators are exploring mechanisms of injury and repair to the lungs, pathways involved in the regulation of airway mucous secretion, and genetic and environmental determinants of COPD. Applied studies are developing new methods of lung imaging and testing their ability to provide a better characterization of changes that occur in disease. The NHLBI-supported Lung Tissue Research Consortium is collecting lung tissues for preparation and distribution to researchers for innovative studies. Just this year, we embarked upon the Long-Term Oxygen Treatment Trial to test the efficacy of supplemental oxygen therapy in COPD patients with less-than-severe hypoxemia, and the COPD Clinical Research Network has been in place since 2003 to provide an infrastructure for rapid evaluation of emerging disease-management approaches.

An important and immediate challenge is to narrow the gap between what is commonly being done for COPD patients today and what can, in fact, be done. Many approaches— including drugs, pulmonary rehabilitation, smoking cessation, oxygen therapy, and surgery— are available to improve longevity and quality of life for people with COPD, but they are by no means universally applied. To address this shortfall, the NHLBI has launched a new educational campaign, *Learn More, Breathe Better*. The campaign encourages men and women over age 45 with respiratory symptoms, especially current or former smokers and people who have risks associated with genetics or environmental exposures, to seek spirometric testing and discuss treatment options with their doctors. Physicians are urged to be alert for indicators of COPD among their patients, to offer appropriate diagnostic testing, and to update their strategies for managing the disease. Our hope is that this educational campaign will yield an immediate public health benefit and also set the stage for translation and implementation of new discoveries that are on the horizon.

Thank you for the opportunity to present this snapshot of NHLBI activities. I would be pleased to respond to any questions by Committee members.

Elizabeth G. Nabel, M.D.
Director
National Heart, Lung, and Blood Institute
National Institutes of Health

Elizabeth G. Nabel, M.D., a native of St. Paul, Minnesota, received her M.D. from Cornell University Medical College in 1981. She completed an internship and residency in internal medicine followed by a clinical and research fellowship in cardiovascular medicine at Brigham and Women's Hospital, Harvard University. In 1987, she joined the faculty at the University of Michigan as an Assistant Professor of Medicine and rose through the ranks, becoming Director of the Cardiovascular Research Center in 1992, Professor of Medicine and Physiology in 1994, and Chief of the Division of Cardiology in 1997. A cardiologist with extensive clinical experience, Dr. Nabel has had a distinguished career as a researcher. While at the University of Michigan, she became known for her research on the molecular genetics of cardiovascular diseases.

Dr. Nabel joined the National Heart, Lung, and Blood Institute (NHLBI) in 1999 as the Institute's Scientific Director of Clinical Research. In 2005, Dr. Nabel became Director of the NHLBI where she oversees an extensive national research portfolio of basic and clinical research to prevent, diagnose, and treat heart, lung, and blood diseases. The Institute also conducts educational activities for health professionals, patients, and the general public. The NHLBI budget for fiscal year 2006 is approximately \$2.9 billion.

Dr. Nabel has made many contributions to basic and clinical research on the pathogenesis and treatment of cardiovascular diseases. She has devoted several decades to exploring genes that contribute to vascular disease and strategies for gene transfer to benefit patients with those diseases. She has delineated the mechanisms that regulate the growth of cells and tissues which lead to blood vessel blockages. Her research now focuses on the role of genetic factors in blood vessel diseases, including atherosclerosis and Hutchinson Gilford Progeria Syndrome, a rare, premature aging syndrome.

Dr. Nabel has served as a Visiting Professor at major medical centers throughout the country and delivered major lectureships in Europe and Australia. She has received numerous awards for her scientific accomplishments, including the Willem Einthoven Award from Leiden University in the Netherlands, the Amgen-Scientific Achievement Award from the American Society for Biochemistry and Molecular Biology, and Distinguished Achievement Awards from the Basic Cardiovascular Sciences Council and the Atherosclerosis, Thrombosis, and Vascular Biology Council of the American Heart Association. In 2001, she received an honorary doctorate from the University of Leuven, Belgium and in 2006 from Mt. Sinai School of Medicine, New York.

Dr. Nabel is an elected member of the Institute of Medicine of the National Academy of

Sciences, the American Society of Clinical Investigation, and the Association of American Physicians, as well as a Fellow of the American Heart Association and the American College of Cardiology. She serves on the editorial board of many scientific journals, including being an editorial board member of the *New England Journal of Medicine*, past Board of Reviewing Editors for *Science*, and associate editor for the *Journal of Clinical Investigation*.

A partner on 13 patents, Dr. Nabel is the author of more than 200 scientific publications, and she has mentored more than 45 students and fellows.

Department of Health and Human Services
Office of Budget
Richard J. Turman

Mr. Turman is the Deputy Assistant Secretary for Budget, HHS. He joined federal service as a Presidential Management Intern in 1987 at the Office of Management and Budget, where he worked as a Budget Examiner and later as a Branch Chief. He has worked as a Legislative Assistant in the Senate, as the Director of Federal Relations for an association of research universities, and as the Associate Director for Budget of the National Institutes of Health. He received a Bachelor's Degree from the University of California, Santa Cruz, and a Masters in Public Policy from the University of California, Berkeley