DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung and Blood Institute

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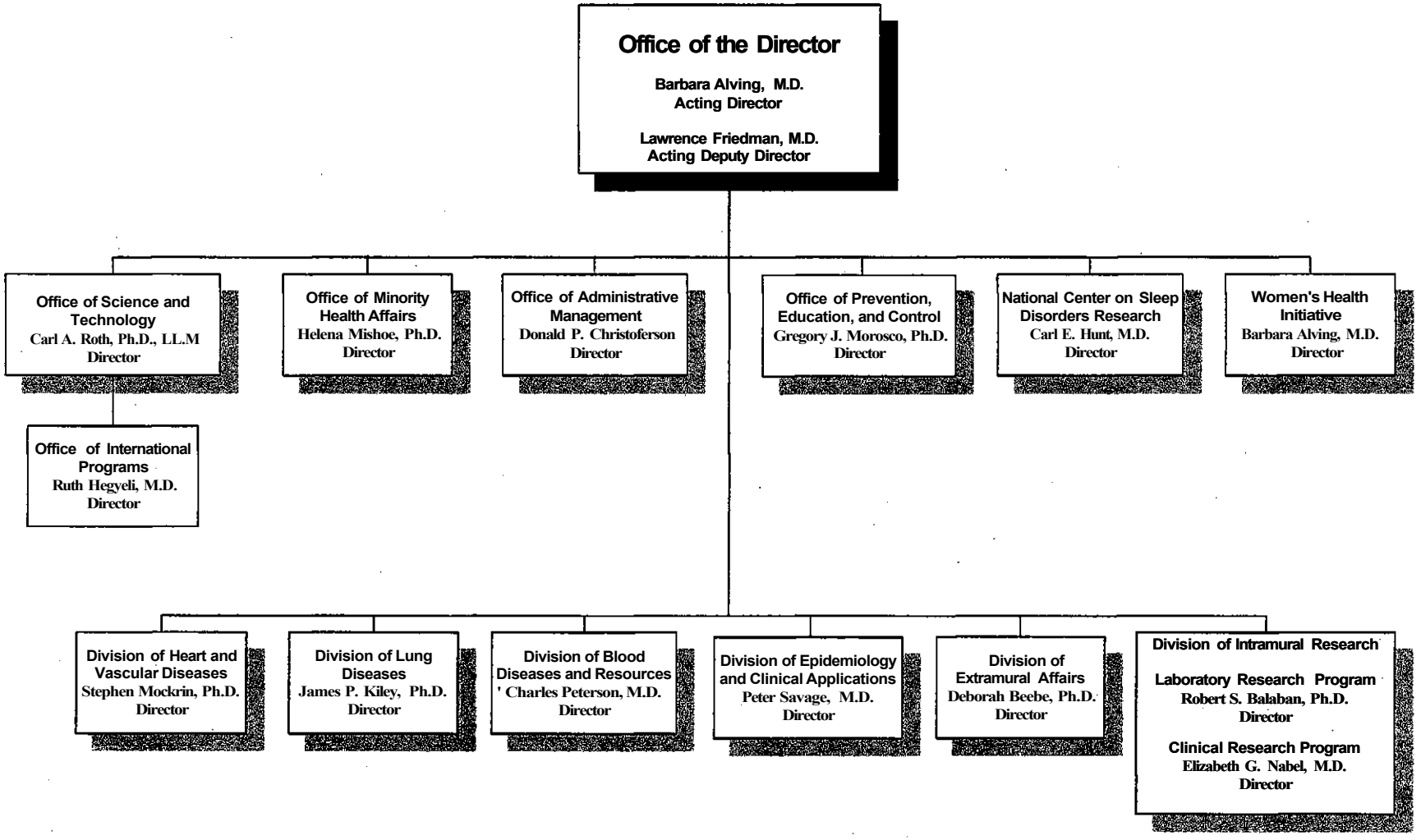

NHLBI-2

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

For carrying out section 301 and title IV of the Public Health Service Act with respect to cardiovascular, lung, and blood diseases and blood products, [$2,965,453,000] *$2,951,270,000.*

[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 Heart, Lung, and Blood Institute

Amounts Available for Obligation 1/

Source of Funding	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Appropriation	$2,897,145,000	$2,965,453,000	$2,951,270,000
Enacted Rescissions	(18,454,000)	(24,252,000)	0
Subtotal, Adjusted Appropriation	2,878,691,000	2,941,201,000	2,951,270,000
Real transfer under NIH Director's one-percent transfer authority to other ICs	4,024,000	0	0
Comparative transfer to NIBIB for Radiology Program	(108,000)	0	0
Comparative transfer to Buildings and Facilities	(477,000)	0	0
Comparative transfer to/from other NIH ICs for NIH Roadmap	(4,024,000)	0	0
Subtotal, adjusted budget authority	2,878,106,000	2,941,201,000	2,951,270,000
Unobligated Balance, start of year	0	0	0
Unobligated Balance, end of year	0	0	0
Subtotal, adjusted budget authority	2,878,106,000	2,941,201,000	2,951,270,000
Unobligated balance lapsing	(114,000)	0	0
Total obligations	2,877,992,000	2,941,201,000	2,951,270,000

1/ Excludes the following amounts for reimbursable activities carried out by this account:
FY 2004 - $7,719,000 FY 2005 - $20,000,000 FY 2006 - $20,000,000
Excludes $1,000,000 in FY 2005 and $1,000,000 in FY 2006 for royalties.

Justification

National Heart, Lung, and Blood Institute

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
799	$2,878,106,000	799	$2,941,201,000	799	$2,951,270,000	0	$10,069,000

This document provides justification for the Fiscal Year 2006 activities of the National Heart, Lung, and Blood Institute (NHLBI), including HTV/AIDS activities. A more detailed description of NTH-wide Fiscal Year 2006 HTV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

INTRODUCTION

The NHLBI provides leadership for a national program in diseases of the heart, blood vessels, lungs, and blood; sleep disorders; and blood resources. It plans and conducts—through work in its own laboratories and through grant- and contract-supported activities in extramural scientific institutions—an integrated and coordinated program of basic research, clinical investigations and trials, observational studies, and demonstration and education projects related to the causes, prevention, diagnosis, and treatment of the diseases under its purview and to the clinical use of blood and all aspects of the management of blood resources. For more than 30 years, the NHLBI Office of Prevention, Education, and Control has supported educational programs for physicians, patients, and the general public to improve awareness, diagnosis, treatment, and prevention of diseases and conditions under the Institute's purview. Since FY 1993, the Institute has been the home of the National Center on Sleep Disorders Research and, since FY 1998, it has had responsibility for the NTH Women's Health Initiative. The NHLBI supports research training and career development of new and established investigators in fundamental sciences and clinical disciplines to enable them to conduct research relative to its mission. In addition, it conducts educational activities, including development and dissemination of materials for health professionals, patients, and the general public, with a strong emphasis on prevention.

The following material summarizes the latest scientific progress and promising future opportunities.

SCIENCE ADVANCES

Cardiovascular Diseases

Obesity-Associated Hypertension

For years scientists have known that obese individuals are prone to develop hypertension (high blood pressure), which increases risk for heart disease and stroke, especially among people with excess abdominal fat. The development of drugs that prevent obesity-associated hypertension has been hindered by a lack of understanding of its biological basis. Recently, NHLBI-funded basic science investigators showed that a protein produced by abdominal fat cells contributes to obesity-related hypertension. When rats gained weight as a result of a high-fat diet, their abdominal fat cells increased production of the protein angiotensinogen. Angiotensinogen is a precursor of angiotensin **n,** which causes blood vessels to constrict and blood pressure to rise. In the study, a weight-gain-associated increase in angiotensinogen production was found only in the abdomen, and not in other tissues. If a similar process is found to contribute to obesity-related hypertension in humans, angiotensinogen production by abdominal fat cells could prove to be a promising new target for therapies to prevent obesity-related hypertension.

Inflammation and Hypertension

Improved understanding of the mechanisms underlying hypertension (high blood pressure)—a major risk factor for heart disease and stroke—is providing new direction for developing therapeutic and preventive strategies. Two recent studies, each of which followed a large number of women for about 8 years, have uncovered evidence of a link between inflammation and hypertension. Both focused on C-reactive protein (CRP), a substance in the blood that indicates the presence and intensity of inflammation and is already known to be associated with cardiovascular disease risk. One study found that elevated levels of CRP were associated with an increased risk of developing hypertension. The second showed that the simultaneous presence of elevated levels of CRP and hypertension increased cardiovascular risk even further, suggesting that they somehow work together.

New Blood Test for Patients at High Risk for Heart Attack

Researchers have recently made progress in their search for improved tests to identify individuals who are on the verge of suffering a heart attack. Millions of patients with chest pain visit emergency departments each year—some are having a heart attack, while others are experiencing angina pain or a much less severe condition such as heartburn, peptic ulcer, or muscle strain. Although traditional emergency room tests are fairly reliable indicators of a heart attack, a major challenge is to identify patients who, despite normal results on initial emergency room tests, are likely to suffer a heart attack in the near future. An NHLBI-supported study found that a single, initial measurement of the blood enzyme myeloperoxidase independently predicted risk of imminent heart attack, as well as risk of major cardiac events (including heart

attack, need for revascularization, and death) in the ensuing 30-day and 6-month periods. The myeloperoxidase level identified patients at risk even in the absence of evidence of heart cell damage. Although further studies are needed, these results suggest that adding a test for myeloperoxidase to traditional emergency room laboratory tests could help doctors identify ' patients at risk of impending heart attack, thereby enabling them to receive appropriate lifesaving treatment more quickly.

Story of Discovery - Good Cholesterol and the Search for the Next Big Breakthrough in Atherosclerosis Therapy

Nearly 30 years ago, scientists became intrigued by a man from rural Italy who had extremely low levels of high-density lipoprotein (HDL) cholesterol, the so-called "good cholesterol." Considerable research, including the Framingham Heart Study, had shown that low levels of HDL increase risk for atherosclerosis and heart disease, while high levels confer protection. Nevertheless, the man exhibited no signs of atherosclerosis or heart disease. Scientists soon discovered that he and several fellow villagers carried a genetic mutation that caused them to produce an altered form of the protein known as apolipoprotein A-1, a major component of HDL. In the early 1990s, an NHLBI-supported researcher demonstrated that administration of this mutant protein—dubbed apo A-1 Milano—to research animals not only prevented atherosclerosis but also shrank atherosclerotic plaques that had already formed.

Meanwhile scientists in Japan began studying a family with strikingly *elevated* levels of HDL and increased longevity. Once again, the unusual HDL levels were shown to be the result of a genetic mutation. In this case, however, the mutation affected production of cholesteryl ester transfer protein (CETP), which promotes the exchange of fats between HDL and other lipoproteins. Subsequent work in animal models suggested that reducing CETP activity might increase HDL levels.

The research on apo A-1 Milano and CETP captivated scientists on the trail of innovative therapies for atherosclerosis. The first major breakthrough in treatment had come in the mid-1980s with the introduction of statins, drugs that lower levels of low-density lipoprotein (LDL),.the "bad cholesterol." Despite widespread use of these highly effective drugs, atherosclerotic coronary artery disease remains the leading cause of mortality in the United States, accounting for 500,000 deaths each year.

Building on the promising findings in animal models, scientists began work on HDL-focused strategies to combat atherosclerosis. Soon, investigators had developed two new drugs, ETC-216, which contains apo A-1 Milano, and torcetrapib, which inhibits CETP.

In 2003, researchers conducted a small clinical trial of ETC-216 among patients with acute coronary syndromes who did not have the apo A-1 Milano mutation. Five weeks of treatment was shown to reduce the volume of atherosclerotic plaques by 4.2 percent, compared with placebo. This was an exciting breakthrough: currently available drugs can prevent atherosclerosis and halt its progression, but ECT-216 is the first to significantly reduce the size of established atherosclerotic plaques. If these results are confirmed in larger trials, treatment with ETC-216 may provide an alternative to more invasive procedures (e.g., angioplasty, bypass surgery) currently used to treat advanced atherosclerosis.

In 2004, scientists conducted a clinical trial, sponsored in part by the NTH, of torcetrapib. The drug alone increased HDL levels by 46 percent and, in combination with a statin, by 61 percent. The next step will be to determine whether torcetrapib also prevents or reverses atherosclerosis. If so, the treatment could help millions of Americans at risk for and suffering from atherosclerosis.

New Approach to Cardiac Pacing

A new cardiac pacemaking technique that uses adult stem cells holds promise for patients with heart rhythm abnormalities. Such patients are routinely treated with implanted electronic pacemaker devices to help their hearts beat regularly and at appropriate rates. Although usually effective, electronic pacemakers have several drawbacks, including the placement of a permanent catheter into the heart and the need for periodic battery replacement. Recent studies suggest that certain adult stem cells—human mesenchymal stem cells (hMSCs)—can be engineered to express pacemaker genes and thereby serve as "natural" pacemakers. When so modified, the hMSCs functioned as biological cardiac pacemakers, affecting the heartbeat of rat heart muscle cells cultured in the laboratory and causing rhythmic activity when injected into the hearts of living dogs. Although much more research is needed, the findings suggest a new technique for treating patients with heart rhythm abnormalities.

New Diagnostic Tool for Cardiovascular Disease

Investigators have produced evidence that a new imaging technique offers superior visualization of artery-clogging atherosclerotic plaques, enabling distinction between stable plaques and dangerous rupture-prone plaques. This highly innovative research built on the knowledge that different proteins are found on the surface of artery walls depending on the stage of plaque development. Scientists developed microbubbles that each carried an antibody to one of these proteins. When the microbubbles were injected into the arteries of pigs with atherosclerotic plaques, the antibodies led the microbubbles to target specific proteins and stick to an area of the artery wall where plaques had developed. Because the microbubbles had been constructed to reflect sound, this technique resulted in better resolution of ultrasound images of the plaques. Although application of these findings awaits studies in humans, they offer hope of an improved ability to diagnose and stage plaque development, and thereby provide appropriate treatment.

Treatment of Cardiac Arrhythmias

A promising new technology for treating cardiac arrhythmias is being tested in animals. Some arrhythmias occur when electrical impulses become disrupted by the presence of abnormal cells in the heart. The arrhythmias can be treated using a procedure called catheter ablation in which doctors insert a slender tube through a blood vessel into the heart and apply high-frequency electrical energy to destroy the abnormal cells. Currently, the most common method for visualizing the catheter and guiding it to the correct location in the heart uses fluoroscopy, a procedure that exposes patients and doctors to ionizing radiation. Recently, researchers designed and tested an alternative catheter-guidance system in a pig model. They generated images of the heart with three-dimensional magnetic resonance imaging, a technique that uses a large magnet, radio frequencies, and a computer. Then they superimposed an image of the catheter onto the heart image and, using a specially designed electromagnetic system, guided the catheter to the correct position to perform the ablation. With this method, they were able to perform accurate

and precise ablation procedures. If the system proves adaptable for use in humans, it could expand the types of arrhytirmias treatable by ablation and eliminate exposure of patients and physicians to X-rays during ablation therapy.

Story of Discovery - The Legacy of Hormone Replacement Therapy

They called it hormone replacement therapy (HRT), and in theory it made perfect sense. When women enter menopause, their estrogen production diminishes sharply, so replacing what their bodies no longer made, some reasoned, would help them retain their youth and health, warding off heart disease and other chronic problems that appear with age. In the 1960s, doctors began to prescribe estrogen widely for postmenopausal women.

The first concern about HRT appeared in 1975 when the results of two studies indicated that estrogen given by itself elevated a woman's risk of uterine cancer. At that time, Premarin® was the fifth most commonly prescribed drug in the United States. Subsequent research indicated that the problem of elevated cancer risk could be overcome, however, by giving progestin along with estrogen, a combination sold under the proprietary name of Prempro®, to women who still had their uterus—those who had undergone hysterectomies could still take the estrogen alone since they were no longer at risk for uterine cancer.

With the risk of uterine cancer eliminated, sales of estrogen and progestin soared. The combined formulation grew in popularity, increasing steadily throughout the 1980s and into 2000, when 46 million prescriptions were written, making it the second most commonly prescribed medication in the United States. Throughout that time, dozens of observational studies validated the popularity of estrogen and progestin therapy among women and physicians. Those studies indicated that the combination HRT lowered the risk of cardiovascular disease, osteoporosis, and Alzheimer's disease, and could even slow the skin aging process.

But some medical investigators had reservations. The problem, they argued, was that the studies were not randomized, controlled trials and were based on simply comparing those women who chose to take HRT with those who declined it. This could be said to introduce a bias, since women who chose HRT tended to be healthier, less overweight, less likely to smoke, and far more likely to have a regular source of medical care than their counterparts who did not take HRT. Skeptics also pointed out that even the studies that seemed to be more rigorous in their scientific design were still only measuring markers of cardiovascular disease risk, such as high cholesterol levels, rather than the disease itself.

When the leading manufacturer of HRT requested, in 1990, that the U.S. Food and Drug Administration (FDA) approve estrogen and progestin as a therapy for cardiovascular disease the FDA responded with a requirement for a randomized, controlled trial to prove the claim. In response to the FDA, the drug company funded the Heart and Estrogen/Progestin Replacement Study, called HERS.

In 1998, the first results of HERS showed that HRT actually increased slightly a woman's risk of heart attack during her first few years of therapy, and showed no benefit after that. Further follow-up, known as HERS-IJ and published in 2002, showed that no benefits were apparent even with longer duration of follow-up.

The NTH Women's Health Initiative (WHI) began in 1991 to study, among other issues, the relationships between HRT and chronic diseases of aging, diet and cancer, and calcium/vitamin C supplementation and osteoporosis. The HRT portion of the WHI was a randomized, controlled clinical trial that tested either Premarin® or Prempro® against placebo in thousands of postmenopausal women.

In 2002, based on the recommendation of the WHI Data and Safety Monitoring Board, the NTH stopped the estrogen-plus-progestin portion of the study because of a noticeable increase in risks of invasive breast cancer, coronary heart disease, stroke, and pulmonary embolism. Modest beneficial effects were observed, including slight decreases in colorectal cancer and hip fractures, but the benefits were outweighed by the risks for adverse events.

Although the estrogen-plus-progestin component of the WHI was stopped, another portion of the study, the estrogen-alone therapy for postmenopausal women who had undergone hysterectomies, continued. In 2004 the NIH also stopped that trial based on data that estrogen alone caused an increased risk of stroke and deep vein thrombosis and did nothing to forestall heart disease.

The new findings were received by women and their physicians with understandable concern and uncertainty; however the NIH, the FDA, and the DHHS Office of Women's Health moved quickly to provide a clear explanation of the results and consistent recommendations. Women are now advised to consult closely with their physicians as to whether some form of HRT may be appropriate, keeping in mind the question of whether short-term benefits outweigh the long-term risks. Estrogens and progestins should not be used to prevent heart disease, heart attacks, or strokes. If used for hot flashes and other menopausal symptoms, they should be taken at the lowest doses (formulations of which recently received FDA approval) for the shortest duration to reach treatment goals.

Large studies such as the WHI are sometimes criticized for their high costs - about $60 million per year for the WHI alone. But when one considers the more than 40 years that women were receiving a potentially dangerous therapy based on marginal evidence from a large number of small, inexpensive studies that were never designed to answer the most important questions, larger, randomized, controlled clinical trials are well justified.

Atrial Fibrillation in Families

Findings from a multi-generational study of cardiovascular disease risk factors have shed light on the possible heritability of atrial fibrillation (AF), a condition that affects more than two million American adults.[1] The disorder occurs when electrical signals in the heart are fired in very fast, uncontrolled waves, causing the upper chambers (atria) to beat rapidly and irregularly. Severe complications such as stroke and congestive heart failure may ensue. Known risk factors for AF include abnormal heart structure, uncontrolled high blood pressure, and diabetes but, until now, no genetic predisposition was apparent in the general population. Recent findings from the Framingham Offspring Study of AF, which involved over 2,200 participants whose parents were members of the original Framingham Heart Study cohort, showed that having a parent with AF strongly increased an individual's risk of developing the disorder. The overall risk of AF was nearly doubled for people who had at least one parent with AF, compared with those whose parents did not have the condition, and was tripled when one or both parents developed AF before 75 years of age. The study is the first to find a familial connection for AF in a community sample. Its findings open up a new avenue of research on AF and will encourage scientists to search for contributing genetic factors. An understanding of contributing genetic factors could ultimately improve AF treatment and prevention.

Public Access Defibrillation

Although individuals who experience cardiac arrest in a non-hospital setting rarely survive, prompt defibrillation (treatment with a device that shocks the heart into a normal rhythm)

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[1] Fox, CS, Parise H, D'Agostino Sr RB, Lloyd-Jones D M, et al., Parental Atrial Fibrillation as a Risk Factor for Atrial Fibrillation in Offspring. JAMA 291:2851-2855, 2004.

performed by trained medical personnel can improve outcomes. The Public Access Defibrillation (PAD) trial examined whether additional lives could be saved when victims of cardiac arrest were helped by community volunteers who knew how to use an automated external defibrillator (AED) as well as to perform cardiopulmonary resuscitation. The trial, funded by the NHLBI in collaboration with the American Heart Association, trained approximately 20,000 volunteer rescuers at 24 sites in the United States and Canada. Over an average of 21.5 months, survival of sudden-cardiac-arrest victims was markedly better in communities with volunteers able to use the AED. These findings suggest that training laypersons in AED usage may be a worthwhile public health measure. An important next step is to test the safety and effectiveness of the devices in private settings where the majority of out-of-hospital sudden cardiac arrests occur. The NHLBI is currently funding a multi-center study to determine whether providing AEDs to families of people who have a history of heart attack will improve survival rates of those who experience cardiac arrest in their homes.

Preventing Rejection of Heart Transplants

Scientists have developed a new transplantation technique that prevents organ rejection by exploiting the immune system's mechanism for distinguishing "self from "nonself' tissues. Rejection occurs when the immune system recognizes a transplanted organ as "nonself and attacks it as if it were an invading virus or bacteria. Normally, "self tissues are safe because developing immune cells undergo a winnowing-out process in early life: in the thymus gland, cells that are capable of attacking "self tissues are identified and destroyed. Researchers reasoned that if they transplanted a lobe of thymus from an organ donor along with the donor's heart, it would eliminate any immune cells that could attack the donated organ. When this approach was tried in pigs, the organ recipients that also received a lobe of thymus lived longer and experienced less organ rejection than pigs that received only a heart. In humans, the thymus becomes inactive by adulthood, but the procedure could potentially be applicable for children. Currently, children who receive heart transplants are given high doses of immunosuppressive drugs to prevent organ rejection. Unfortunately, the drugs weaken the immune system, putting patients at risk for life-threatening infections. The new transplant method could prevent organ rejection, reduce the need for immunosuppressive drugs, and greatly improve the quality of life of children who receive transplants.

Youthful Origins of Heart Disease

Two recent research reports indicate the importance of addressing cardiovascular disease (CVD) risk in youth, when subtle abnormalities begin to develop.

To learn more about the predictive value of childhood CVD risk factors, researchers examined nearly 500 individuals from the Bogalusa Heart Study, which began following a semi-rural Louisiana cohort of white and African American boys and girls in 1972. Results from an ultrasound examination of the carotid artery performed in 1996 were analyzed in the context of measurements of traditional CVD risk factors taken in childhood. The study found that carotid artery thickening—an indicator of early atherosclerotic changes in the vessel wall—in

asymptomatic healthy young adults was associated with the previous presence of C V D risk factors during their childhood. Specifically, low-density lipoprotein (LDL) cholesterol levels and body mass index in childhood were predictive of increased carotid artery thickness in adulthood. Although additional research is needed to determine if early intervention will lead to reduced subclinical atherosclerosis in young adults, these results suggest that childhood risk factors could be used to assess future risk of heart disease and to guide interventions to reduce that risk.

A second study explored the role of cardiovascular fitness in the development of C V D risk factors in young adults. It focused on participants in the NHLBI-supported Coronary Artery Risk Development in Young Adults (CARDIA) study, who were 18 to 30 years of age when enrolled during the mid-1980s. Researchers compared levels of cardiorespiratory fitness at enrollment, as measured by a treadmill examination, with development of C V D risk factors 15 years later. They found that poor fitness in young adulthood significantly increased the risk of developing hypertension, diabetes, and metabolic syndrome (a constellation of risk factors that includes high blood pressure, high insulin levels, excess body weight, and abnormal cholesterol levels). On the positive side, however, improved fitness over time was associated with a reduced risk. These findings underscore the need to emphasize cardiorespiratory fitness in young adults and develop public health policies that encourage physical activity at all ages.

"Melting" Fat

An innovative approach for treating obesity—starving fat tissue by destroying the blood vessels that feed it—has been identified in the laboratory. Researchers discovered a compound that "homes" to a protein called prohibitin, which is found in the blood vessels surrounding white fat tissue (the tissue that stores fat and contributes to obesity). They modified the compound to cause cell death when it reached its target—the prohibitin—within the blood vessels. When the compound was injected into obese mice, their white fat mass decreased rapidly. They lost about 30 percent of their body weight in 4 weeks without any detectable adverse physiological consequences. Because prohibitin is also found in blood vessels of human white fat, these findings suggest the possibility of developing a new pharmacologic approach to achieve weight loss among obese patients.

Advances in Understanding Preeclampsia

Progress is being made in understanding the etiology of preeclampsia, a pathological increase in blood pressure that affects some women during the late stages of pregnancy. Preeclampsia can retard fetal growth and, in extreme cases, cause the death of both mother and fetus. For years, efforts to prevent and treat the condition have been hindered by a lack of understanding of its causes. Recent research suggests that two proteins, calcitonin-receptor-like receptor (CRLR) and receptor-activity-modulating protein 1 (RAMPi), contribute to the development of preeclampsia. Both proteins are normally produced in the blood vessels of the placenta, where they cause dilation and thereby allow blood flow to the fetus. Investigators showed that levels of CRLR and RAMPi are significantly lower in the placentas of women with preeclampsia than in woman

without the condition, suggesting that a deficiency contributes to preeclampsia. Now that scientists have identified a role for C R L R and R A M P i in preeclampsia, they can explore their potential use in the development of new methods for early diagnosis, prevention, and treatment.

Lung Diseases

Response to Medication in Children with Asthma

Progress is being made in determining ways to individualize therapy for children with asthma. Although a number of options are available for managing mild to moderate asthma, treatment that works for one child often does not work for another. Numerous studies have demonstrated the effectiveness of inhaled corticosteroids (ICS) compared with other therapies, but many physicians and patients prefer not to use them because of concern about side effects, particularly at higher doses, and some studies have documented considerable variability in response to ICS. Other work has indicated that only a small portion of children respond to a drug called montelukast, but those who do respond have excellent results. Prescribing, therefore, has been a trial-and-error process because clinicians could not predict how a given child would respond. NHLBI-supported investigators recently found that children with high levels of one set of biomarkers had a greater likelihood of responding to ICS, while children with high levels of other biomarkers were more likely to respond favorably to montelukast. Use of biomarkers in clinical practice to determine suitability of particular medications may provide physicians with better criteria to individualize therapy for prompt, effective asthma control.

New Clues to Asthma Pathogenesis

The search for new therapies for asthma is building on a modern understanding that chronic asthma is, above all, an inflammatory disease. Research over the last decade demonstrated that the immune system plays an important role in the development and progression of asthma, and efforts are being made to unravel the chain of events that are involved in immune regulation relevant to asthma. Recently, investigators focused attention on a protein called chitin, which is found in molds and insects and can trigger the allergic response in asthma. They found that when mice are exposed to chitin, their lung epithelial cells respond by producing the enzyme acidic mammalian chitinase (AMCase), which breaks down chitin. The AMCase then induces release of an immune system protein, which leads to inflammation and the resultant airway constriction that is characteristic of asthma. Moreover, the investigators observed that when AMCase is blocked, the inflammation and constriction are also blocked. These results offer additional insight into the pathophysiology of asthma and suggest potential targets for new asthma therapies.

Basic Research in Cystic Fibrosis

Study of a mouse model is providing new clues to the pathology of cystic fibrosis (CF), the second most common life-shortening, childhood-onset inherited disease in the United States.[2] CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Lung surfaces become excessively dry and clogged with mucus, leading to inflammation and chronic, life-threatening bacterial infections. CFTR has been shown to act as a chloride ion channel and a regulator of sodium ion channels in the epithelium, or internal lining, of the lung; however, the link between ion transport and CF pathogenesis is not well understood. To determine whether increased sodium transport alone could lead to CF-like lung disease, investigators recently developed a mouse model that overproduces sodium channels. They found that both sodium and water absorption were increased in the lungs, leading to depletion of airway surface liquid—the thin film of water normally found on the epithelial surfaces in healthy lungs. Depletion of the surface liquid caused mucus dehydration, mucus adhesion to airway surfaces, and reduced rates of mucus clearance from the airways. As a result, the mice developed severe, spontaneous CF-like lung disease, with mucus obstruction, airway inflammation, and poor bacterial clearance. These findings establish lack of water in the CF airways as a fundamental defect leading to CF lung disease and possibly other chronic airway diseases, such as bronchitis. They also provide compelling evidence that airway hydration plays a critical role in lung defense and suggest that rehydrating airway surfaces could be an effective form of therapy for CF.

Pulmonary Arterial Hypertension

Scientists have uncovered new clues about susceptibility to pulmonary arterial hypertension (PAH), an often-fatal condition characterized by marked elevation of blood pressure in the pulmonary artery and subsequent development of heart failure. In some cases (secondary PAH) a cause can be identified; in others (idiopathic PAH) no cause has yet been identified. Current understanding is that PAH is the product of a genetic predisposition in combination with one or more secondary trigger factors, such as viral infection or drug exposure. Unfortunately, lack of access to the site of the disease—the lung blood vessels—has limited the ability to study PAH in humans. NHLBI-supported investigators recently broadened their search and began examining blood cells from PAH patients and normal volunteers. Using microarray analysis, the researchers identified a set of 106 genes that distinguish, with high certainty, between patients with PAH and people free of the disease. Furthermore, the study has generated a list of genes that are differentially expressed between patients with secondary and idiopathic forms of PAH. The findings suggest that microarray-expression profiling of blood cells could have significant implications for diagnosis and screening for PAH.

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[2] Grosse SD, Boyle CA, Botkin JR, et al. Newborn Screening for Cystic fibrosis: Evaluation of Benefits and Risks and Recommendations for State Newborn Screening Programs. MMWR RecommRep. 53(RR-13): 1-36,2004.

Exercise and Nighttime Breathing Problems

Over the past decade, much evidence has accumulated regarding the burden of sleep disorders in the United States. Research indicates that untreated sleep disorders contribute to the risk of hypertension, obesity, diabetes, heart disease, infectious diseases, and depression. Moreover, sleep loss has been shown to decrease motivation and impair judgment to an extent comparable to alcohol intoxication. Sleep-disordered breathing (SDB)—a condition in which breathing becomes excessively slow or shallow during sleep or stops altogether for short intervals—can lead to excessive daytime sleepiness and hormonal abnormalities that may disincline people to be physically active. However, the degree to which exercise habits influence SDB has been unclear. Investigators in the Wisconsin Sleep Cohort Study recently examined over 1,000 adults whose reported weekly hours of planned exercise ranged from zero to more than seven. They found that the amount of weekly exercise was inversely correlated with the frequency of SDB events, and this relationship existed independent of body weight, gender, age, or other relevant factors. The results suggest that treatments designed to improve sleep quality could benefit from inclusion of an exercise component.

Blood Diseases and Resources

Diagnosis of Thrombotic Thrombocytopenic Purpura

Researchers have developed a quick and accurate approach to distinguishing thrombotic thrombocytopenic purpura (TTP) from other blood disorders. TTP is a rare but serious blood disorder that develops when ADAMTS-13, an enzyme that circulates in the bloodstream, is not sufficiently active to break down the ultra-large complexes of von Willebrand factor molecules that are secreted by blood vessel walls. When ADAMTS-13 activity is reduced or absent, the concentration of ultra-large complexes increases, which causes circulating platelets to aggregate and clog small blood vessels. This restricts blood flow and rapidly leads to serious health problems that can be prevented only if patients receive transfusions of blood plasma shortly after symptoms begin. Researchers recently developed a method for measuring ADAMTS-13 activity that may serve as the basis for a laboratory diagnostic test for TTP. First they made a new protein, utilizing recombinant DNA technology, that is cleaved by the ADAMTS-13 enzyme. They then developed an assay system using the new protein and plasma from patients as the source of ADAMTS-13 enzyme and showed that they could identify patients with TTP based on lack of ADAMTS-13 activity. The entire test took less than 5 hours and relied on straightforward laboratory techniques—improvements over the multi-day, technically challenging processes currently used. The next steps in translating this approach to clinical practice are to demonstrate that the recombinant protein can be produced on a large scale and to conduct additional studies of the specificity and sensitivity of the assay.

Sickle Cell Disease Therapy

While investigating the safety and efficacy of decitabine, a compound that might prevent painful sickle cell crises in some patients, researchers improved the manner of administration. Whereas

participants in previous studies had to visit a clinic five times a week to receive intravenous injections, the latest results indicate that less frequent subcutaneous injections of decitabine may be sufficient to increase fetal hemoglobin levels in some sickle cell disease patients. Increased fetal hemoglobin levels are associated with diminished sickle cell symptoms and complications, and studies of larger numbers of patients who will be followed for longer periods are being planned to help clinical researchers understand the benefits and possible shortcomings of decitabine therapy. Meanwhile, researchers are developing decitabine formulations that could be self-injected or even taken orally so that, if approved by the FDA, the drug would be even easier for patients to take.

A study of children who received hydroxyurea therapy for up to 8 years has provided welcome evidence that the drug should be considered for all pediatric patients who have sickle cell disease. Although hydroxyurea therapy is an approved treatment for adults with sickle cell disease, its long-term risks and benefits in youngsters have been uncertain. The study of more than 100 children indicated that long-term hydroxyurea therapy is helpful and that its benefits are sustainable. In contrast, for many adults the therapy becomes less effective over time. Researchers, cognizant of concerns that hydroxyurea could stunt a child's growth, observed that growth rates of patients in the study actually exceeded those of children with sickle cell disease who did not receive hydroxyurea and resembled those of healthy children. Furthermore, concerns that hydroxyurea might mutate DNA or cause liver or kidney damage were not validated.

Hemophilia

Researchers are harnessing gene therapy to develop a new approach to treat people who have hemophilia. Although most patients who have hemophilia A or B can be treated by infusions of clotting factors VTII or DC, respectively, some develop antibodies that inactivate the replacement factors. Since 1999, patients have been treated with commercially available recombinant activated factor VII (FVTIa), which compensates for deficiencies in or antibodies against factor **Vm** or factor IX by operating through a separate pathway in the clotting cascade. Recombinant FVTIa is quickly metabolized, however, and multiple, high-dose infusions usually are required to stop a bleeding episode. Now, researchers are investigating an alternative way to administer FVTIa—delivery of the factor VTI gene to cells via gene therapy. To date, they have developed a gene-delivery approach that generates adequate amounts of FVIIa to stop bleeding in a mouse model of hemophilia B without causing excessive clotting. The next steps, which researchers will continue to pursue in mice, are to determine the long-term effects of continuous FVIIa production and the level of FVIIa needed to prevent spontaneous bleeding episodes.

Progress Against Staphylococcal Infection

Researchers have identified a promising new approach to combat the serious consequences of infection with Staphylococcal bacteria. Staph infections—including common food poisoning and the rarer toxic shock syndrome—are significant causes of illness in communities and hospitals. Moreover, Staphylococcal enterotoxin B (SEB), the toxic product of Staph infections,

has been designated by the CDC as a Category B bioterrorism agent because of its potential to be disseminated widely via food, water, or air. When SEB interacts with cell surfaces, it triggers an acute immune reaction that, in turn, can lead to massive tissue damage and organ failure. Several years ago, basic scientists identified a compound, called a nuclear import inhibitor, that could enter cells and block the SEB-initiated cascade of events that is responsible for the overwhelming reaction. Investigators recently reported that injection of the compound protected mice against SEB-induced damage. The beneficial effect occurred even when the compound was administered after exposure to the toxin, indicating that it could potentially be used in the field or clinic to counteract SEB exposure or Staph infection. Although further studies are needed to determine how the compound is metabolized and its toxicity and efficacy, work is well under way and researchers are already contemplating how the approach might be adapted for use against other biological warfare agents.

New Method for Increasing Hematopoietic Stem Cells

Hematopoietic stem cell transplantation has proven beneficial to many pediatric patients, but its applicability to adult patients has been limited because donors cannot provide a sufficient "dose" of cells. Thus, researchers are working to develop ways to make hematopoietic stem cells multiply. In initial studies, a research team harnessed retroviral gene-transfer technology to stimulate production of homeobox transcription factor HOXB4 (a protein that regulates gene expression) in stem cells and discovered that the protein caused the cells to multiply. As a second step, they engineered a recombinant form of the HOXB4 protein and demonstrated that it could enter stem cells and cause them to multiply when added directly to the media in which the cells were growing. The new approach is more desirable than the initial retroviral gene-transfer method because it eliminates concerns associated with gene therapy. Additional studies are needed to determine if the results, which were obtained from studies of mice, are applicable to stem cells from human umbilical cord blood, bone marrow, or peripheral blood and to establish conditions (e.g., the amount of transcription factor that should be added, whether other proteins should be included in the media) to which human cells respond. Once clinically useful expansion methods are developed, increased numbers of adults will be able to benefit from hematopoietic stem cell transplantation.

NIH ROADMAP

Because the NHLBI focuses on diseases and conditions related to the heart, blood vessels, lungs, blood, and sleep, clinical research is an essential component of its portfolio. Therefore, the Institute has been an enthusiastic participant in the contract solicitation titled ***Re-Engineering the Clinical Research Enterprise: Feasibility of Integrating and Expanding Clinical Research Networks,*** which was issued on December 2, 2003, as part of the NTH Roadmap for Accelerating Medical Discovery to Improve Health. The NHLBI supports clinical research networks to facilitate testing of new products and techniques that may be useful in disease treatment and prevention. Networks currently in place address pediatric and adult asthma, acute respiratory distress syndrome, thalassemia (Cooley's anemia), pediatric heart disease, blood and marrow transplantation, transfusion medicine and hemostasis, chronic obstructive pulmonary disease

(COPD), resuscitation outcomes, and pulmonary fibrosis. Moreover, in fiscal year 2006 clinical research networks in sickle cell disease and heart failure will be initiated. Each network is composed of several clinical centers and a data coordinating center, all of which participate in multiple clinical protocols and work closely with the other institutions in the same network. However, no structure or methodology has been established to promote or facilitate communication *among* the networks. The new contracts awarded under the Roadmap solicitation will support activities to demonstrate how networks can collaborate to conduct clinical trials and other multicenter clinical research studies. Once clinical researchers understand how networks can overcome challenges such as those presented by differences in study management, investigator interests, disease definitions, reporting procedures, data and specimen sharing policies, and informatics tools, they can address more extensive research questions and will be able to conduct clinical research more efficiently than they can in the current system. By applying lessons learned from this roadmap initiative, the NHLBI will be better able to accelerate the pace of heart, lung, blood, and sleep research and to reduce barriers that prevent research advances from reaching the patients who they could benefit.

NEW INITIATIVES

Heart Failure Clinical Research Network

A research network will be established to conduct clinical studies of new approaches to improve outcomes for patients with heart failure. It will provide an infrastructure to enable rapid translation of promising research findings into clinical applications. Despite many advances in treatment, the incidence and prevalence of heart failure are increasing and the long-term prognosis for patients remains poor. Innovative strategies to repair or restore myocardial function are emerging and improved mechanical systems are evolving, but all will require systematic clinical evaluation. The network will have the capability of implementing multiple concurrent clinical studies that may demonstrate the promise of new therapies and furnish the necessary background for larger phase D3 clinical trials.

Innovative Targets and Therapy Development for Ischemic Stroke

A collaborative effort between the NHLBI and the National Institute of Neurological Disorders and Stroke is being established to identify new molecular targets, explore promising agents, and develop innovative therapeutics for cerebral ischemia (impairment of blood flow to the brain). Ischemic stroke, which usually occurs as a result of blockage in an artery, is a leading cause of death and long-term disability in the United States. Prompt restoration of blood flow to the brain can limit stroke damage, but the current approach carries a risk of side effects and is useful only during the first few hours after a stroke occurs. New therapeutics are urgently needed that reduce bleeding risk, minimize neurological damage, and function effectively over longer time periods.

Technologies for Engineering Small Blood Vessels

A new interagency program involving seven NTH components, the Food and Drug Administration, the National Institute of Standards and Technology, and the National Science Foundation will address development of functional small blood vessel substitutes. Its goal is to create living replacement vessels that are able to propagate and repair themselves. Such vessels are urgently needed because the supply of adequate native vessels to use as grafts does not meet demand, existing technologies for large-vessel conduits cannot be reproduced for small-diameter vessels, and small-diameter prosthetic grafts fail at unacceptable rates. The new initiative will focus especially on engineered blood vessel substitutes that have potential applicability to clinical issues in coronary artery disease, peripheral vascular disease, congenital heart disease, and arterio-venous shunting for hemodialysis.

Risk of Cardiovascular and Lung Diseases in Hispanic Populations

The NHLBI, in conjunction with other NTH components, will support a multicenter epidemiologic study to improve knowledge of the burden of cardiovascular and lung diseases among various U.S. Hispanic groups, determine the role of acculturation in the prevalence and development of the diseases, and identify factors that confer susceptibility or risk. If U.S. Hispanics follow the pattern of other immigrant groups, their risk of chronic disease associated with American lifestyle and culture is likely to increase. Indeed, growing rates of obesity and diabetes are already becoming apparent. Observational data are needed to identify modifiable risk factors and uncover ways to ameliorate them. The new study will recruit, examine, and follow four community-based adult cohorts of Cuban, Puerto Rican, Mexican American, and Central American heritage. Closely integrated with the research component of the study will be a community and professional education component, as has been used in the Jackson Heart Study, to take research results back to the communities and attract and train Hispanic researchers in epidemiology and population-based research.

Infectious Agents in the Origins of Chronic Lung Disease

A new program will investigate the role of bacterial, fungal, and viral infectious agents in the origin of chronic lung diseases in humans. Studies suggest that the chronic inflammation, tissue remodeling, and progressive loss of function observed in a number of lung diseases may be the result of incompletely resolved lung infections. Moreover, evidence exists that infectious agents may serve as co-factors or triggers of inflammation or abnormal cell growth and proliferation in genetically susceptible individuals. Chronic lung diseases represent an enormous public health burden in terms of both disability and cost. Identification of a contributing infectious agent in such health conditions could revolutionize approaches to prevention and therapy and improve the long-term prognosis for affected persons.

Critical Issues in Post-Phlebitic Syndrome

The Institute is planning to solicit grant applications for research that may provide a better basis for management of post-phlebitic syndrome, a common aftermath of deep-venous thrombosis (DVT, formation of a blood clot in a leg vein). DVT damages the venous valves, which in turn results in venous reflux and increased fluid pressure in the lower limbs. Post-phlebitic syndrome often ensues, with pain, edema, heaviness and swelling of the leg and, in severe cases, chronic skin ulcerations and discoloration. With an aging population, DVT is likely to become a more serious medical problem and new approaches to treat and prevent post-phlebitic syndrome are needed. Research supported through this initiative is expected to yield a better understanding of how the venous wall responds to a clot, the nature of valve malfunction, and the role of inflammation in the disease process.

Sildenafil for Pulmonary Hypertension (PH) in Adult Patients with Sickle Cell Disease

Although life expectancy for sickle cell disease patients has increased dramatically, PH is a major cause of disability and death. Contracts will be awarded to evaluate a course of treatment with sildenafil (Viagra®) in sickle cell disease patients who have PH. The drug enhances the effect of nitric oxide, a compound that relaxes blood vessel walls. A randomized, double-blind, placebo-controlled phase U clinical trial will test the safety of sildenafil and its efficacy in improving exercise capacity, symptoms, and measures of circulatory function. Because PH is common and severe in persons with sickle cell disease, a positive outcome of this trial would be an important step toward improved patient care.

Sickle Cell Disease Clinical Research Network

The NHLBI will establish a clinical research network to address critical issues in the care of patients with sickle cell disease. The network will provide an avenue for conducting multiple phase m clinical trials to determine the efficacy and effectiveness of new therapies to treat and prevent complications of sickle cell disease and, where appropriate, thalassemia. Despite extensive knowledge regarding the molecular pathology of genetic hemoglobin abnormalities, only a few treatments are available to relieve suffering and reduce premature death. The network will test potential treatments that are emerging from basic studies and phase I and JJ clinical trials. Moreover, it will generate new data that can be used to characterize patients and their clinical course, apply new strategies for improved diagnostic and therapeutic approaches, and examine outcomes of particular concern to patients.

OTHER AREAS OF INTEREST

Partnerships Extend Reach of Heart Disease Awareness Campaign

The Heart Truth campaign, with its Red Dress icon and slogan "Heart Disease Doesn't Care What You Wear—It's the #1 Killer of Women," is raising awareness among women of their risk of heart disease and motivating them to take steps to reduce it. Groundbreaking partnerships

with the fashion industry and corporate America have greatly expanded coverage of the campaign. The Red Dress symbol and information about heart disease are appearing in homes across America through everyday products such as cereal boxes and fashion magazines. Although these avenues are somewhat unconventional health education vehicles, they are enabling the campaign to reach millions of women. *The Heart Truth* Road Show also delivered information directly to women in their communities. The traveling exhibit, which featured red dresses from America's leading fashion designers, provided health screenings to more than 3,900 women and information to more than 87,000 individuals during its five-city tour. The campaign team also addressed the interests of state and local government agencies, health professional organizations, and community groups by offering them opportunities to implement activities in their communities and participate in national events. One such event is National Wear Red Day, which encouraged individuals to wear red to show their support for raising awareness that far more American women die of heart disease than of any other cause. Building on its strong partnership base, the campaign continues to expand its outreach activities to ensure that women know *The Heart Truth* and take their heart health seriously.

New Education Program Planned for Chronic Obstructive Pulmonary Disease

In September 2004, the NHLBI convened a 2-day meeting to develop a national education strategy for chronic obstructive pulmonary disease (COPD), a progressive disease of the airways that greatly impairs the ability to breathe. COPD is a major contributor to suffering, disability, and health care costs, and premature death in the United States. Despite its prevalence, the general public and persons at greatest risk of developing COPD—typically, cigarette smokers—are largely unaware of it. Moreover, many health-care providers overlook opportunities to address COPD. For example, spirometry, a simple diagnostic lung test, is underused, especially among primary care physicians. Treatments that relieve symptoms and improve quality of life, such as short-acting bronchodilators and pulmonary rehabilitation, are available but not widely prescribed. The new COPD educational campaign will be directed at helping at-risk individuals identify symptoms, motivating them to seek diagnostic testing, and encouraging those who have COPD to take an active role in managing the disease. It also will emphasize to health professionals that COPD can be easily recognized and diagnosed, and should be treated aggressively.

Research in Pediatric Heart Disease

Reducing the burden of heart disease in children is a major goal of the Institute that is being addressed by three complementary initiatives. Four Specialized Centers of Clinically Oriented Research in Pediatric Heart Disease were recently awarded to explore the basis of congenital and acquired heart disease in children and accelerate movement of scientific discoveries from the bench to the bedside. A Clinical Research Network in Pediatric Heart Disease, modeled on NHLBI networks focused on other topical areas, has been established to provide the clinical research infrastructure needed to study children's heart disease. Given the diversity of congenital heart disease, even large pediatric cardiovascular centers are often unable to recruit enough patients to study many cardiovascular malformations. This multicenter collaborative

effort will enable recruitment of sufficient numbers of cases for evaluation of new clinical interventions. The third area of special emphasis is pediatric circulatory support. Five contracts have been awarded to facilitate design of innovative circulatory assist devices and other bioengineered systems for infants and children who experience cardiopulmonary failure and circulatory collapse. The objective is to develop support approaches that overcome the size and hemodynamic limitations of currently available pediatric assist devices.

Cardiovascular Disease (CVD) Risk Reduction in American Indians and Alaska Natives

The NHLBI is initiating a new program to address the substantial and growing burden of CVD in American Indians and Alaska natives. Grant applications are being solicited to develop and test culturally appropriate interventions to promote the adoption of lifestyles and behaviors that are known to reduce biological cardiovascular disease risk factors, such as high blood pressure and cholesterol levels, obesity, glucose intolerance, and diabetes. The intent is to develop interventions that are sustainable and capable of being disseminated to other Native communities after completion of the research project. Following announcement of the solicitation, NHLBI staff traveled across the country, conducting seven technical assistance workshops to help Native communities and their research partners prepare responsive grant applications. The Institute plans to fund about four research projects for 5 years each, beginning in July 2005.

First National Sleep Conference

Sleep—or more precisely, lack of sleep—is a topic of great interest to scientists, physicians, and the general public. However, application of research findings on sleep and sleep disorders to clinical situations is only just beginning. To bridge the gap between knowledge and effective health care, the National Center on Sleep Disorders Research, a component of the NHLBI, sponsored the first national sleep conference in March 2004. "Frontiers of Knowledge in Sleep and Sleep Disorders—Opportunities for Improving Health and Quality of Life" addressed the latest evidence regarding healthy and disordered sleep, and explored ways to improve public health and safety. Conference cosponsors were the American Academy of Sleep Medicine, the American Insomnia Association, the American Sleep Apnea Association, the Narcolepsy Network, the National Sleep Foundation, the NTH Office of Rare Diseases, the Restless Legs Syndrome Foundation, and the Sleep Research Society. More than 400 health care providers, public health and education experts, patient advocates, and sleep medicine specialists participated. Their recommendations will be used to formulate a national action plan for implementing clinical practice changes and to enhance the public's knowledge, attitudes, and behaviors related to sleep.

New Test for West Nile Virus Protects Blood Supply

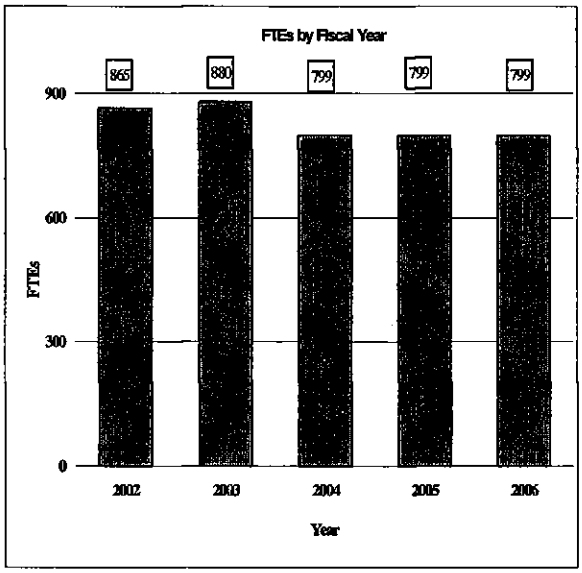
Since 1989, the NHLBI Retrovirus Epidemiology Donor Study (REDS) has been monitoring the incidence of retroviruses and identifying potential new infectious agents among volunteer blood donors. It compiles data on the characteristics and test results of blood donors to identify donors at risk for infection and maintains a serum repository of donor samples for further study. When

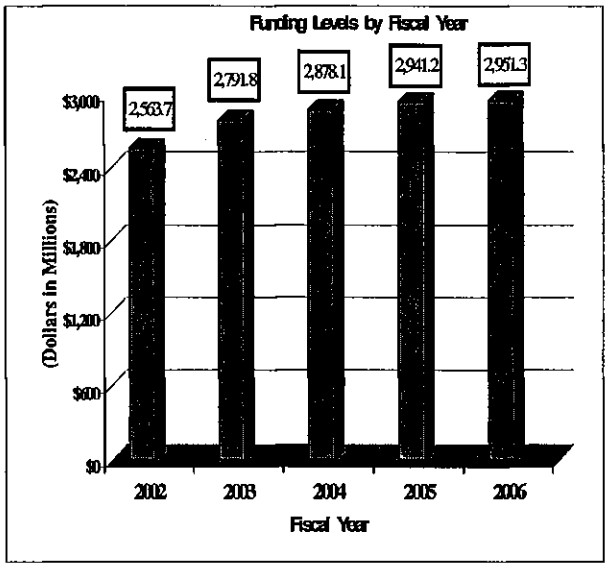
health officials realized that West Nile virus (WNV) could be spread via blood products, REDS investigators and contract-supported Gen-Probe Corporation immediately launched an intensive effort to develop a method to protect the blood supply. The strategy was to modify existing nucleic-acid-amplification testing (NAT) technology, already used to detect HTV and hepatitis C virus in blood, to detect WNV. Within a short nine months, a test had been developed, had received approval from the Food and Drug Administration and was being used to screen blood donated at collection centers throughout the United States. The Centers for Disease Control and Prevention estimates that over 800 blood donors with WNV infection were identified in the first year of NAT screening and their donations discarded. Before the test was developed, WNV posed a serious threat to the blood supply because the virus could spread if a transfusion recipient were given blood from an asymptomatic but infected donor. The rapid implementation of a new test in response to an emerging threat demonstrates the value and flexibility of the infrastructure developed by the NHLBI to ensure the safety of the blood supply.

Budget Policy

The Fiscal Year 2006 budget request for the NHLBI is $2,951,270,000 an increase of $10,069,000 and .3 percent over the FY 2005 Appropriation. Also included in the FY 2006 request, is NHLBI's 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 NTH Overview.

A five year history of FTEs and Funding Levels for NHLBI are shown in the graphs below.



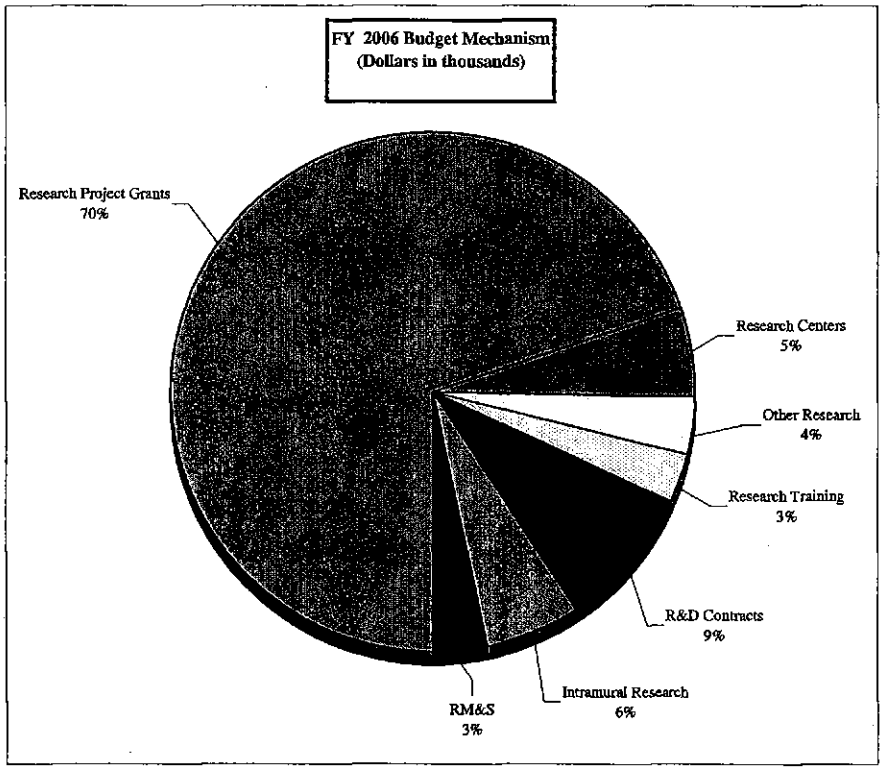


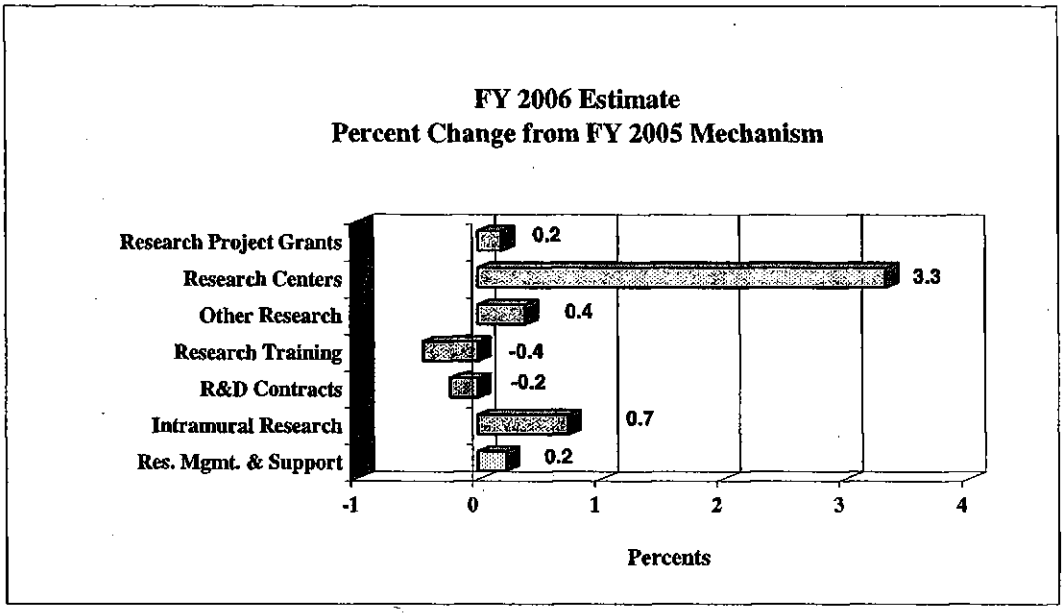
NIH's highest priority is the funding of medical research through research project grants (RPGs). Support for RPGs allows NTH to sustain the scientific momentum of investigator-initiated research while pursuing new research opportunities. The average cost of competing RPGs will be held at the FY2005 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. NTH 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 31. NHLBI will support 1,997 pre- and postdoctoral trainees in full-time training positions.

The Fiscal Year 2006 request includes funding for 59 research centers, 660 other research grants, including 577 clinical career awards, and 192 R & D contracts. When adjusted for Roadmap activities, Intramural Research and Research Management and Support receive increases of 0.5, the same as the NIH total increase.

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




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
0.2
3.3
0.4
-0.4
-0.2
0.7
0.2
-1
0
1
2
3
4
Percents

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute

Budget Mechanism - Total

MECHANISM	FY 2004 Actual		FY 2005 Appropriation		FY 2006 Estimate	
Research Grants:	No.	Amount	No.	Amount	No.	Amount
Research Projects:						
Noncompeting	3,165	$1,444,838,000	3,125	$1,523,222,000	3,130	$1,546,018,000
Administrative supplements	(117)	10,094,000	(85)	5,879,000	(83)	5,460,000
Competing:						
Renewal	662	290,465,000	608	273,146,965	585	262,688,355
New	362	186,834,000	334	175,498,050	321	168,778,350
Supplements	15	1,343,000	14	1,349,985	13	1,298,295
Subtotal, competing	1,039	478,642,000	956	449,995,000	919	432,765,000
Subtotal, RPGs	4,204	1,933,574,000	4,081	1,979,096,000	4,049	1,984,243,000
SBIR/STTR	275	71,530,000	273	74,164,000	270	73,000,000
Subtotal, RPGs	4,479	2,005,104,000	4,354	2,053,260,000	4,319	2,057,243,000
Research Centers:						
Specialized/comprehensive	71	141,594,000	67	153,056,000	55	157,350,000
Clinical research	0	0	0	0	0	0
Biotechnology	2	1,201,000	2	1,865,000	4	2,884,000
Comparative medicine	0	425,000	0	422,000	0	300,000
Research Centers in Minority Institutions	0	0	0	0	0	0
Subtotal, Centers	73	143,220,000	69	155,343,000	59	160,534,000
Other Research:						
Research careers	566	68,330,000	571	68,789,000	577	69,059,000
Cancer education	0	0	0	0	0	0
Cooperative clinical research	26	20,659,000	32	25,498,000	32	25,498,000
Biomedical research support	0	54,000	0	0	0	79,000
Minority biomedical research support	0	2,806,000	0	2,846,000	0	2,846,000
Other	66	16,748,000	50	13,117,000	51	13,200,000
Subtotal, Other Research	658	108,597,000	653	110,250,000	660	110,682,000
Total Research Grants	5,210	2,256,921,000	5,076	2,318,853,000	5,038	2,328,459,000
Research Training:	FTTPs		FTTPs		FTTPs	
Individual awards	189	8,821,000	184	8,846,000	177	8,846,000
Institutional awards	1,846	79,172,000	1,844	79,312,000	1,820	78,916,000
Total, Training	2,035	87,993,000	2,028	88,158,000	1,997	87,762,000
Research & development contracts	198	273,530,000	195	268,938,000	192	268,332,000
(SBIR/STTR)	(2)	(532,000)	(2)	(200,000)	(2)	(200,000)
	FTEs		FTEs		FTEs	
Intramural research	426	165,555,000	430	168,274,000	430	169,517,000
Research management and support	373	94,107,000	369	96,978,000	369	97,200,000
Cancer prevention & control	0	0	0	0	0	0
Construction		0		0		0
Buildings and Facilities		0		0		0
Total, NHLBI	799	2,878,106,000	799	2,941,201,000	799	2,951,270,000
(RoadMap Support)		(9,887,000)		(18,594,000)		(26,371,000)
(Clinical Trials)		(244,982,000)		(249,882,000)		(251,131,000)

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute

Budget Authority by Activity
(dollars in thousands)

ACTIVITY	FY 2004 Actual FTEs	FY 2004 Actual Amount	FY 2005 Appropriation FTEs	FY 2005 Appropriation Amount	FY 2006 Estimate FTEs	FY 2006 Estimate Amount	Change FTEs	Change Amount
Extramural Research:								
Heart and Vascular diseases program		$1,534,400		$1,567,806		$1,626,066		$58,260
Lung Diseases program		544,067		560,062		558,288		(1,774)
Blood diseases and resources program		429,218		459,563		432,271		(27,292)
Centers for sleep disorders research		51,921		53,391		53,474		83
Women's Health Initiative		58,838		35,127		14,454		(20,673)
Subtotal, Extramural research		2,618,444		2,675,949		2,684,553		8,604
Intramural research	426	165,555	430	168,274	430	169,517	0	1,243
Res. management & support	373	94,107	369	96,978	369	97,200	0	222
Total	799	2,878,106	799	2,941,201	799	2,951,270	0	10,069

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute

Summary of Changes

FY 2005 Estimate				$2,941,201,000
FY 2006 Estimated Budget Authority				2,951,270,000
Net change				10,069,000
	FY 2005 Appropriaton		Change from Base	
CHANGES	FTEs	Budget Authority	FTEs	Budget Authority
A. Built-in:				
1. Intramural research:				
a. Within grade increase		52,875,000		$830,000
b. Annualization of January 2005 pay increase		52,875,000		495,000
c. January 2006 pay increase		52,875,000		923,000
d. One less day of pay		52,875,000		(203,000)
e. Payment for centrally furnished services		27,606,000		138,000
f. Increased cost of laboratory supplies, materials, and other expenses		87,793,000		1,664,000
Subtotal				3,847,000
2. Research Management and Support:				
a. Within grade increase		42,649,000		652,000
b. Annualization of January 2005 pay increase		42,649,000		399,000
c. January 2006 pay increase		42,649,000		744,000
d. One less day of pay		42,649,000		(163,000)
e. Payment for centrally furnished services		15,108,000		76,000
f. Increased cost of laboratory supplies, materials, and other expenses		39,221,000		691,000
Subtotal				2,399,000
Subtotal, Built-in				6,246,000

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute

Summary of Changes-continued

CHANGES	2005 Current Estimate Base		Change from Base	
	No.	Amount	No.	Amount
B. Program:				
1. Research project grants:				
a. Noncompeting	3,125	$1,529,101,000	5	$22,377,000
b. Competing	956	449,995,000	(37)	(17,230,000)
c. SBIR/STTR	273	74,164,000	(3)	(1,164,000)
Total	4,354	2,053,260,000	(35)	3,983,000
2. Research centers	69	155,343,000	(10)	5,191,000
3. Other research	653	110,250,000	7	432,000
4. Research framing	2,028	88,158,000	(31)	(396,000)
5. Research and development contracts	195	268,938,000	192	(606,000)
Subtotal, extramural				8,604,000
	FTEs		FTEs	
6. Intramural research	430	168,274,000	0	(2,604,000)
7. Research management and support	369	96,978,000	0	(2,177,000)
8. Cancer control and prevention	0	0	0	0
9. Construction		0		0
10. Building and Facilities		0		0
Subtotal, program		2,941,201,000		3,823,000
Total changes	799		0	10,069,000

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute

Budget Authority by Object

	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Total compensable workyears:			
Full-time employment	799	799	799
Full-time equivalent of overtime & holiday hours	2	2	0
Average ES salary	$149,243	$152,676	$3,433
Average GM/GS grade	11.7	11.7	0.0
Average GM/GS salary	$79,531	$81,360	$1,829
Average salary, grade established by act of July 1,1944 (42 U.S.C. 207)	$90,736	$92,823	$2,087
Average salary of ungraded positions	$97,667	$99,914	$2,247

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
11.1 Full-Time Permanent	$44,500,000	$46,050,000	$1,550,000
11.3 Other than Full-Time Permanent	21,300,000	22,040,000	740,000
11.5 Other Personnel Compensation	2,339,000	2,390,000	51,000
11.7 Military Personnel	1,531,000	1,588,000	57,000
11.8 Special Personnel Services Payments	8,000,000	8,225,000	225,000
Total, Personnel Compensation	77,670,000	80,293,000	2,623,000
12.0 Personnel Benefits	16,400,000	16,995,000	595,000
12.1 Military Personnel Benefits	1,299,000	1,350,000	51,000
13.0 Benefits for Former Personnel	155,000	160,000	5,000
Subtotal, Pay Costs	95,524,000	98,798,000	3,274,000
21.0 Travel & Transportation of Persons	3,400,000	3,425,000	25,000
22.0 Transportation of Things	290,000	292,000	2,000
23.1 Rental Payments to GSA	0	0	0
23.2 Rental Payments to Others	300,000	303,000	3,000
23.3 Communications, Utilities & Miscellaneous Charges	1,416,000	1,420,000	4,000
24.0 Printing & Reproduction	1,206,000	1,206,000	0
25.1 Consulting Services	273,000	274,000	1,000
25.2 Other Services	13,555,000	13,600,000	45,000
25.3 Purchase of Goods & Services from Government Accounts	159,976,000	156,967,000	(3,009,000)
25.4 Operation & Maintenance of Facilities	2,061,000	2,100,000	39,000
25.5 Research & Development Contracts	214,930,000	215,000,000	70,000
25.6 Medical Care	2,678,000	2,685,000	7,000
25.7 Operation & Maintenance of Equipment	5,827,000	5,850,000	23,000
25.8 Subsistence & Support of Persons	0	0	0
25.0 Subtotal, Other Contractual Services	399,300,000	396,476,000	(2,824,000)
26.0 Supplies & Materials	16,785,000	17,125,000	340,000
31.0 Equipment	15,965,000	16,000,000	35,000
32.0 Land and Structures	0	0	0
33.0 Investments & Loans	0	0	0
41.0 Grants, Subsidies & Contributions	2,407,011,000	2,416,221,000	9,210,000
42.0 Insurance Claims & Indemnities	0	0	0
43.0 Interest & Dividends	4,000	4,000	0
44.0 Refunds	0	0	0
Subtotal, Non-Pay Costs	2,845,677,000	2,852,472,000	6,795,000
Total Budget Authority by Object	2,941,201,000	2,951,270,000	10,069,000

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute

Salaries and Expenses

OBJECT CLASSES	FY 2005 Appropriation	FY 2006 Estimate	Increase or Decrease
Personnel Compensation:			
Full-Time Permanent (11.1)	$44,500,000	$46,050,000	$1,550,000
Other Than Full-Time Permanent (11.3)	21,300,000	22,040,000	740,000
Other Personnel Compensation (11.5)	2,339,000	2,390,000	51,000
Military Personnel (11.7)	1,531,000	1,588,000	57,000
Special Personnel Services Payments (11.8)	8,000,000	8,225,000	225,000
Total Personnel Compensation (11.9)	77,670,000	80,293,000	2,623,000
Civilian Personnel Benefits (12.1)	16,400,000	16,995,000	595,000
Military Personnel Benefits (12.2)	1,299,000	1,350,000	
Benefits to Former Personnel (13.0)	155,000	160,000	5,000
Subtotal, Pay Costs	95,524,000	98,798,000	3,274,000
Travel (21.0)	3,400,000	3,425,000	25,000
Transportation of Things (22.0)	290,000	292,000	2,000
Rental Payments to Others (23.2)	300,000	303,000	3,000
Communications, Utilities and Miscellaneous Charges (23.3)	1,416,000	1,420,000	4,000
Printing and Reproduction (24.0)	1,206,000	1,206,000	0
Other Contractual Services:			
Advisory and Assistance Services (25.1)	273,000	274,000	1,000
Other Services (25.2)	13,555,000	13,600,000	45,000
Purchases from Govt. Accounts (25.3)	0	0	0
Operation & Maintenance of Facilities (25.4)	2,061,000	2,100,000	39,000
Operation & Maintenance of Equipment (25.7)	5,827,000	5,850,000	23,000
Subsistence & Support of Persons (25.8)	0	0	0
Subtotal Other Contractual Services	21,716,000	21,824,000	108,000
Supplies and Materials (26.0)	16,742,000	17,081,500	339,500
Subtotal, Non-Pay Costs	45,070,000	45,551,500	481,500
Total, Administrative Costs	140,594,000	144,349,500	3,755,500

NATIONAL INSTITUTES OF HEALTH

National Heart, Lung, and Blood Institute

SIGNIFICANT ITEMS IN HOUSE AND SENATE APPROPRIATIONS COMMITTEE REPORTS

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

Item

Cardiovascular health study - The Committee is aware that the Cardiovascular Health Study, initiated in 1987 to determine risk factors for development and progression of heart disease, stroke and other cardiovascular diseases in nearly 6,000 Americans age 65 and older, is scheduled to end in 2005. The wide variety and complexity of data and samples collected in the Cardiovascular Health Study represent a unique national research resource. The Cornmittee encourages NHLBI to initiate a proposal to stimulate innovative use of Cardiovascular Health Study data and material, provide opportunities for open, efficient use of the information for the entire scientific community, and continue follow-up of study participants, (p. 67)

Action taken or to be taken

The NHLBI has issued a request for contract proposals titled "Enhancing the Use of Longitudinal Data on Cardiovascular Disease arid its Risk Factors in Older Adults: The Cardiovascular Health Study (CHS)." Its purpose is to increase and facilitate use of the extensive longitudinal data and samples collected over 17 years from participants in the CHS by (1) promoting innovative utilization of this resource by new collaborators who will develop independently funded research projects, (2) ensuring open and efficient access to CHS data and specimens by the entire scientific community, (3) continuing follow-up of participants for cardiovascular disease events and maintenance of the sample repository, and (4) providing a transition from the current contract-funded, NHLBI-directed study to a study directed by a steering cornmittee of investigators with independently acquired funding for continued use of the cohort. Analysis and publication of new and extant study data will continue. The new contract is planned for award in fiscal year 2005.

Item

Heart failure management - The Cornmittee is concerned that heart failure is a major cause of hospitalization and readmission. Medicare recipients represent about 65 percent of repeat hospitalizations within one year. Yet, perhaps 50 percent of these hospitalizations are avoidable. -The Cornmittee encourages NHLBI to consider initiating a randomized trial to evaluate management strategies for heart failure patients in terms of their ability to prevent death or hospital readmission. (p. 67)

Action taken or to be taken

Evidence is accumulating that programs designed to improve management of heart care by health-care providers and patients can reduce hospitalizations and possibly save more money

than they cost. The NHLBI has funded some studies of heart failure disease management, including development of technologies for better monitoring of patients. More research is needed, however, to clarify what types of disease management work best in specific patient subgroups and in particular health-care settings, as well as to understand the role of reimbursement and other factors in the voluntary adoption of disease management programs by health-care providers.

The NHLBI is establishing a Heart Failure Clinical Research Network to evaluate new methods to diagnose, manage, and treat heart failure. It will provide support for an infrastructure to develop, coordinate, and conduct multiple collaborative proof-of-concept clinical protocols to improve heart failure outcomes. The NHLBI anticipates funding up to eight regional clinical centers and one data coordinating center. The network is expected to provide an excellent opportunity for rapidly translating basic research results into clinical applications that will be directly applicable to improved patient care.

Item

Cardiovascular risk in American Indians and Alaskan Natives - The Committee is aware that American Indian and Alaska Native communities bear a heavy burden of heart disease, stroke and other cardiovascular diseases and few preventive interventions have been tested. The Committee encourages NHLBI to evaluate approaches to reducing behavioral cardiovascular disease risk factors such as obesity, diet, smoking, sleep restriction, stress, and sedentary lifestyle in the American Indian and Alaskan Native populations, (p. 67)

Action taken or to be taken

The NHLBI request for grant applications (RFA) "Community-Responsive Interventions to Reduce Cardiovascular Risk in American Indians and Alaska Natives" was published April 28, 2004, in the *NIH Guide to Grants and Contracts.* Its purpose is to develop and test culturally appropriate interventions to promote the adoption of healthy lifestyles and improve behaviors related to cardiovascular disease risk, such as weight reduction, regular physical activity, and smoking cessation. These lifestyles and behaviors are known to affect biological cardiovascular disease risk factors, such as high blood pressure and cholesterol levels, obesity, glucose intolerance, and diabetes. The intent of this program is to develop interventions that are sustainable and capable of being disseminated to other Native communities following completion of the research project.

Following issuance of the RFA, NHLBI staff traveled across the country, conducting seven technical assistance workshops to help Native communities and their research partners prepare responsive applications. Applications have already been received in response to this initiative, and their scientific peer review is planned for February/March 2005. The Institute plans to fund about four research projects for five years each beginning in July 2005.

Item

Tissue engineered blood vessel replacement and repair - The Committee is aware that a need exists to develop alternatives to natural blood vessels for the adults who endure heart artery

bypass surgery and for the children born with complex heart defects who need multiple blood vessel grafts. The Cornmittee encourages NHLBI to begin an initiative to complement existing tissue engineered research programs to stimulate efforts to "grow" small-diameter, functional blood vessels, (p. 68)

Action taken or to be taken

The goal of tissue engineering and organ fabrication is to create living replacement organs and tissues that have the advantages of self-propagation and self-repair. Complex three-dimensional structures, such as tissue-engineered blood vessels, present many challenges. Small-vessel substitutes are needed because the supply of adequate native vessels to use as grafts does not meet demand, existing technologies for large-vessel conduits cannot be reproduced for small-diameter grafts, and small-diameter prosthetic grafts fail at clinically unacceptable rates.

To meet these needs, the NHLBI is initiating a program to foster development and application of innovative technologies to the engineering of small blood vessels. This work will focus particular attention on the following:

- Coronary artery disease: development of new alternatives to saphenous vein grafts, and identification of the structural/functional components that mimic native vessel function and methodologies that permit off-the-shelf availability for clinical use.

- Peripheral vascular disease: development of new graft materials that accommodate continued growth and remodeling in the presence of various disease conditions.

- Congenital heart disease: development of systemic artery-to-pulmonary-artery shunts for complex single ventricle anatomy, coronary artery anomalies, and Kawasaki disease-associated coronary aneurysms.

- Arterio-venous shunting: development of methods to improve vascular access in hemodialysis patients with end-stage renal disease.

The NHLBI has committed $15 million to this 5-year, interagency effort in collaboration with the National Institute of Biomedical Imaging and Bioengineering, the National Institute on Aging, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Institute of Child Health and Human Development, the National Eye Institute, the National Institute of Neurological Disorders and Stroke, the Food and Drug Administration, the National Institute of Standards and Technology, and the National Science Foundation.

Item

Cooley's anemia - The Committee remains supportive of the focused research effort that is being undertaken by the Thalassemia Clinical Research Network, which is comprised of the leading research institutions in the field of thalassemia, or Cooley's anemia. In addition, the Committee

suggests that NHLBI should consider including patients with related hemoglobinopathies whenever such inclusion will enhance the scientific validity of the research being conducted, (p. 68)

Action taken or to be taken

The Thalassemia Clinical Research Network continues to update its patient registry to identify potential participants for future clinical trials. Currently, the Network is completing its clinical study on osteoporosis in patients with Cooley's anemia to assess the influence of variables such as treatment regimens, iron overload, endocrine and genetic factors, and immune function on response to treatment. Two other ongoing clinical studies include investigations of (1) the effects of ICL670 or deferoxamine on biomarkers of oxidant stress and mitochondrial function in thalassemia patients and (2) the safety of treatment with peginterferon alfa-2a and ribavirin in thalassemia patients who have hepatitis C. A new clinical study will begin in 2005 to examine the effects of two drugs, LI and deferoxamine, on iron chelation in thalassemia patients who also suffer from heart disease.

The NHLBI is taking steps to foster development of an alliance between two of its existing programs, the Thalassemia Clinical Research Network and the Comprehensive Sickle Cell Centers. In April 2004, members of both Steering Cornmittees met with staff of the NHLBI to discuss their intersecting scientific and clinical interests, and a working group composed of members of the two programs will be held in the summer of 2005 to discuss possible collaborations. The future Sickle Cell Clinical Research Network will involve research groups and community organizations involved in both diseases.

Item

COPD education and prevention program - The Committee encourages NHLBI to implement an education and prevention program for chronic obstructive pulmonary disease (COPD). In developing such an education and prevention program, NHLBI is encouraged to work closely with patient and physician organizations and existing coalitions to coordinate with on-going activities in the community. Early identification of those at-risk for or who have COPD is essential in the effort to stem the growth of the population with COPD. The Committee encourages NHLBI to enhance its efforts in this area, including epidemiological studies of patients who are at-risk for or who have this disease as well as a national education campaign for providers and the public about COPD. (p. 68)

Action taken or to be taken

On September 22-23,2004, the NHLBI convened an Education Strategy Development Workshop on COPD in Alexandria, Virginia. It brought together relevant stakeholders—COPD patients and caregivers, members of advocacy organizations, clinicians, representatives of national health organizations and coalitions, and Federal government representatives—to identify current activities and gaps in COPD education. Participants were asked to make recommendations to the NHLBI for education and awareness activities based on presentations made at the workshop, as well as their own knowledge and experiences. A plan for NHLBI educational activities on COPD, which will begin in fiscal year 2005, is being developed based on the workshop results.

Preliminary recommendations made by workshop participants include developing and implementing a public awareness campaign for COPD patients, persons at risk of developing COPD, and health-care providers.

The NHLBI also is supporting a national assessment of COPD and asthma as a component of the National Health and Nutrition Examination Surveys to be conducted in 2007 and 2008. Two pulmonary function tests will be conducted with an intervening bronchodilator challenge. This information will provide estimates of the magnitude of these diseases in the United States to guide prevention and education programs. In addition, community-based studies of pulmonary function are being conducted in an African American population (Jackson Heart Study), and in African Americans and whites in the Coronary Artery Risk Development in Young Adults (CARDIA) study.

Item

Coronary heart disease and diabetes - . . . .The Committee encourages NHLBI to develop research initiatives to examine coronary artery disease in at-risk patients with diabetes, including studies of high diabetes incidence populations such as African-Americans, Hispanic Americans, and Native Americans. The Committee also encourages NHLBI to support educational programs directed to health professionals, patients, and the public to raise awareness of increased risk for heart disease and stroke for diabetics, (p. 68)

Action taken or to be taken

The NHLBI supports a growing body of research on cardiovascular complications of diabetes, including several clinical trials of treatment strategies. A number of projects focus on pre-diabetic and diabetic cardiovascular complications in minority populations. Two studies in Mexican American families seek to identify genes associated with a predisposition to develop coronary artery disease. A study in African American women will examine linkages between hypertension and diabetes to determine whether specific hormones that are elevated in this population contribute to an accelerated onset of the cardiovascular disease. In addition, the NHLBI continues to support the Stop Atherosclerosis in Native Diabetes Study (SANDS) in Native American diabetic patients, the Strong Heart Study of coronary disease and diabetes in American Indians, and the Genetics of Coronary Artery Disease in Alaska Natives (GOCADAN) study. The NHLBI is also developing three major initiatives to examine coronary artery disease in populations with a high incidence of diabetes, one in Hispanic subgroups and two in African Americans.

At the national level, the NHLBI is collaborating with the National Institute of Diabetes and Digestive and Kidney Diseases and its National Diabetes Education Program on the "Be Smart About Your Heart: Control the ABCs of Diabetes" campaign, which highlights the link between diabetes and cardiovascular disease. The campaign encourages people with diabetes to control not only their blood glucose (sugar), but also their blood pressure and cholesterol. At the community level, the NHLBI is supporting a number of outreach and education efforts to educate health professionals, patients, and local communities about preventing and controlling cardiovascular disease. The NHLBI has developed cardiovascular health training materials to facilitate and support community cardiovascular health activities that help minority populations

identify risk factors, seek appropriate treatment, and adopt healthy lifestyle behaviors. Each training manual discusses diabetes as a disease and also as a risk factor for heart disease. In addition, the NHLBI has funded 12 Enhanced Dissemination and Utilization Centers in high-risk communities. Several of them use lay health workers to educate community and family members about heart disease and the need to prevent and control diabetes.

Item

Wound healing - The Committee commends the institute for its research on the acceleration of vascular disease in type 1 diabetes. The Committee also encourages the Institute to be a key player in initiatives to advance wound healing, with particular emphasis on wounds associated with juvenile diabetes, (p. 69)

Action taken or to be taken

Impaired wound healing is a significant complication of diabetes that diminishes quality of life and can lead to prolonged hospitalization and, sometimes, a major amputation. The NHLBI and the National Institute of Diabetes and Digestive and Kidney Diseases held a workshop in 2004 to identify opportunities for new research in this area. In addition, the NHLBI supports a growing portfolio of research on wound healing. One promising avenue focuses on abnormalities in vascular function in the macro- and micro-circulation of wound areas. Another project is evaluating diabetic patients at high risk for foot ulceration. State-of-the-art, non-invasive imaging techniques are being used to assess altered metabolism in muscle tissue, biochemical markers of endothelial activation, and skin oxygenation and microcirculation. Animal models of diabetes are also being used to identify molecules that induce closure of ischemic wounds by restoring a mature microvasculature.

Item

Transmissible spongiform encephalopathies - The Committee encourages NHLBI to enhance its efforts to develop a diagnostic test for TSE that would be suitable for screening the blood supply. Currently, there is no suitable method for identifying TSE-infected blood. In addition, the Committee encourages NHLBI to seek new technologies and procedures for inactivating blood-borne causative agents for human TSEs, further ensuring a safe blood supply. Human TSEs, for which there are no known treatments, include Creutzfeld-Jakob disease and new variant Creutzfeldt-Jakob disease, (p. 69)

Action taken or to be taken

The NHLBI and the NTNDS are jointly supporting an extramural contract program to develop tests to detect transmissible spongiform encephalopathies (TSEs). The first two cases of variant Creutzfeldt-Jakob disease linked to blood transfusion were reported in the United Kingdom during the past year. These observations substantiate findings from previous studies of TSE agents (abnormal prions) in laboratory animals, which have shown that the agents are present in blood, but in such low concentrations that current tests are not sensitive enough to detect them. Hence, investigators in the NHJJBl/NINDS-sponsored program are developing procedures to concentrate TSE agents to levels that can be detected with current assays. The NHLBI also supports a grant to develop a test to detect low levels of abnormal prion proteins using a

technology based on fluorescence of abnormal prions. The major goal of both programs is to develop tests that can detect TSEs in asymptomatic individuals and would be suitable for screening the U.S. blood supply.

The NHLBI also acknowledges the need for procedures to inactivate and/or remove abnormal prion proteins from blood and blood components. The Institute is supporting studies in which investigators are developing methods using gamma-irradiation to inactivate prions in plasma-derived protein products while preserving the products' integrity and functions. Moreover, concentration procedures that are being developed for use in combination with TSE assays are also being evaluated for their capability of removing or separating infectious prions from blood and blood products.

Item

Neurofibromatosis (NF) - Significant advances continue to be made in research on NFs implications with heart disease and in particular its involvement with hypertension and congenital heart disease which together affect over fifty million Americans. Accordingly, the Committee urges NHLBI to enhance its NF research portfolio, (p. 69)

Action taken or to be taken

The NHLBI supports research on neurofibromatosis-related diseases of the heart and blood vessels. In the past year, the Institute encouraged research in the area of neurofibromatosis-related congenital heart disease by providing travel funds for an investigator to attend the annual meeting of the National Neurofibromatosis Foundation International Consortium for the Molecular and Cell Biology of NF1 and NF2 and also to expand his research effort by hiring additional personnel. The NHLBI recently funded a second investigator as part of a Specialized Center of Clinically Oriented Research to address congenital heart disease associated with Noonan syndrome, a genetic disorder that causes abnormal development of multiple parts of the body, which is known to occur in some neurofibromatosis patients and may have a shared biological mechanism. An association between neurofibromatosis and elevated blood pressure, possibly due to the presence of secondary or concomitant diseases such as pheochromocytoma, has been observed in a small number of patients. Pheochromocytoma, a tumor of the adrenal gland, produces hormones that can lead to a severe increase in blood pressure. NHLBI-supported research addresses the regulation of blood pressure by the sympathetic nervous system and vasoactive hormones. These studies may, in turn, help medical researchers understand the mechanisms underlying the elevated blood pressure seen in pheochromocytoma, which could have an impact on the study of cardiovascular disease in patients with neurofibromatosis.

Item

Myelodysplasia and myeloproliferative disorders - The Cornmittee commends NHLBI for its new research initiatives in myelodysplasia (MDS) and myeloproliferative disorders (MPDs), which resulted from a recent conference involving the Institute and NCI. MPDs and MDS are chronic disease of bone marrow cells that can develop into acute leukemia. The Committee encourages NHLBI and NCI to bring together scientific and clinical experts in this field to explore collaborative research and crosscutting mechanisms to further this research agenda, (p. 70)

Action taken or to be taken

The NHLBI acknowledges the need to advance the research agenda for study of MDS and MPDs. As noted by the Committee, recommendations from the state-of-the-science meeting jointly supported by the NHLBI and NCI in March 2003 resulted in two research initiatives, described below; they will be funded in FY 2005. The meeting also stimulated an increase in investigator-initiated research grant applications.

The NHLBI and the NCI are jointly supporting a request for grant applications (RFA) for research to uncover critical genetic, biochemical, and molecular pathways that operate in the emergence and progression of MPDs. Through studies on basic stem cell biology, it is hoped that the mechanisms of stem cell mutagenesis, abnormal proliferation, and deregulated cellular physiology will be uncovered. Use of animal models for hypothesis-testing and pre-clinical therapeutic exploration is encouraged. Profiling biologic and clinical markers of MPDs should improve disease characterization and early diagnosis as well as enhance discovery of therapeutic biologic targets occurring at different stages of disease.

The NHLBI is also supporting an RFA for similar research on the etiology and progression of MDS. The use of gene expression analysis and identification of relevant gene products and cellular molecular profiles may be instrumental in discovering key features of disease pathogenesis. Identifying biologic markers of MDS should improve disease characterization, permit earlier diagnosis, and identify targets that can be exploited for either preventative or therapeutic intervention.

Additionally, the NHLBI and the NCI are co-funding the Bone Marrow Transplant Clinical Research Network, where protocols for both MPD and MDS are under consideration.

Item

Obstructive sleep apnea - The Committee commends the Institute for its work on obstructive sleep apnea. This disorder affects approximately 80 percent of the elderly and if left untreated it significantly increases risk for hypertension, coronary artery disease, heart failure and stroke. The Committee encourages the Institute to include surgical treatments in its work to define useful treatments for this disorder, (p. 70)

Action taken or to be taken

Surgery is one important treatment option for treating obstructive sleep apnea (OSA), especially in children. The NHLBI has launched several programs to enhance research in this area. As a result of one initiative released in 1999 and another released in 2001, the NHLBI now funds 30 grants that address OSA in children, including surgical treatments. This ongoing research is complemented by new recommendations in the 2003 National Sleep Disorders Research Plan. Collectively, these activities are enhancing momentum in the field and establishing the foundation for future clinical trials comparing medical and surgical treatment options for OSA across the age spectrum.

Item

Sleep disorders - The Committee commends the National Center on Sleep Disorders Research for its progress and is pleased that the Center has sponsored the translational conference, Frontiers of Knowledge in Sleep and Sleep Disorders. The Cornmittee encourages the National Center to partner with other Federal agencies, such as the Centers for Disease Control and Prevention, as well as voluntary organizations, to develop a sleep education and public awareness initiative that will provide a forum for dissemination of the outcomes of the sleep translational conferences, (p. 70)

Action taken or to be taken

As a followup to the translational conference, the National Center on Sleep Disorders Research (NCSDR), the NHLBI Office of Prevention, Education, and Control, and the National Sleep Foundation (NSF) are collaborating with Federal agency officials, legislators, and professionals in the sleep field to determine the most appropriate partnership methods to develop broad public awareness and education activities about sleep and sleep disorders.

A conference was held November 12,2004, to develop an action plan to advance public sleep-related health awareness and to implement a cost-effective education initiative to improve sleep literacy and sleep health behaviors. Its specific objectives included a review of NHLBI, CDC, and NSF experiences to date in developing partnerships and implementing public health-related initiatives, and a discussion of lessons learned. The long-term goal of this planning process is to assemble a representative coalition of key stakeholders from the sleep community and from the medical, nursing, public health education, and other communities with appropriate expertise in designing, implementing, and evaluating an effective public health initiative to improve sleep literacy.

Item

Marfan syndrome - The Committee commends NHLBI for its support of research opportunities to study this life threatening, degenerative genetic disorder. Marfan syndrome is characterized by cardiovascular, skeletal and ocular manifestations and its cardiovascular complications result in premature death. Insights gained from research in this area can have implications for the understanding of other connective tissue disorders, other genetically mediated diseases, and the larger population of aging adults with thoracic aneurysms of a variety of causes which can lead to aortic dissection. The Cornmittee urges NHLBI to expand its collaborative efforts with other institutes to support research in this area. (p. 70)

Action taken or to be taken

In 2005, the NHLBI plans to establish and maintain a national registry of patients with Marfan Syndrome and other connective tissue diseases who are receiving treatment for cardiovascular complications. The need for such a registry was identified at a meeting that the NHLBI held with the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and members of the National Marfan Foundation and an NHLBI-convened working group to review the current status of Marfan-related and other genetic thoracic aortic aneurysm diseases. The registry will include information about patients, care providers, hospitals, and clinical interventions; stored

blood and tissue specimens; family pedigrees; and data on extra-cardiac complications. The NHLBI will collaborate with the NIAMS, the National Eye Institute, the National Institute of Dental and Craniofacial Research, and the National Human Genome Research Institute in monitoring the work of the registry to enable development of standardized reporting of patient characteristics, indications for surgical intervention and other treatments, and adverse events. This approach is expected to facilitate clinical evaluation and patient management. The resulting resource should also enhance future research to improve fundamental understanding, treatment, and management of genetic aortic aneurysms and other cardiac and extra-cardiac complications.

Item

Alpha-1 antitrypsin deficiency - The Committee is aware that Alpha-1 antitrypsin deficiency is often misdiagnosed as asthma or Chronic Obstructive Pulmonary Disease (COPD). Individuals with Alpha-1 exhibit symptoms of advanced emphysema between 30 and 50 years of age, even in the absence of tobacco use. Alpha-1 is a major cause of transplantation in adults and a leading cause of liver transplantation in children. The Committee commends NHLBI for its plans to conduct a state-of-the-science conference on Alpha-1 leading towards a five-year research agenda. -NHLBI is also encouraged to collaborate with NTDDK and other institutes to enhance its research portfolio, encourage screening and detection, raise public awareness about Alpha-1 and provide appropriate information to health professionals, (p. 70)

Action taken or to be taken

To promote research that may lead to improvements in health care for patients with alpha-1, the NHLBI is supporting studies of alpha-1 antitrypsin and the enzyme it inhibits, development of a genetic mouse model of alpha-1, human genetic studies of factors that may modify the expression of alpha-1 lung disease, and an early-phase gene therapy study in patients with alpha-1. The NHLBI also supports relevant basic research on protein processing, gene therapy, proteases, and lung inflammation. Alpha-1 is closely related to the more common condition chronic obstructive pulmonary disease (COPD), for which specific genetic risk factors have yet to be identified. Li the past year, the NHLBI convened two workshops to aid in developing a strategic approach for better control of both alpha-1 and COPD. Participants in the first were asked to make recommendations for education and awareness activities, and those in the second were asked to evaluate the state of the science and make recommendations for future research. Representatives of the alpha-1 community were actively involved in both meetings. Based on input from the workshops, the NHLBI is developing strategies for enhancing early detection and proper diagnosis of COPD, for furthering investigations of pathogenetic mechanisms, and for improving methods of testing potential therapeutics. The Institute will continue its cooperation with investigators, clinicians, patient advocates, and other NTH components to improve treatment and ultimately find a cure for alpha-1.

Item

Lung repair -Respiratory failure is often a result of irreversible lung injury. This may occur acutely in conditions such as acute respiratory distress syndrome (ARDS) or chronically with

disorders such as COPD or pulmonary fibrosis. The Cornmittee encourages NHLBI to promote the use of stem cells in animal models to study lung repair and organogenesis as a method to reverse respiratory failure, (p. 71)

Action taken or to be taken

In 2001, the NHLBI provided stimulus for the use of stem cells in studies of organogenesis and repair, with the view that this approach might lead to unique opportunities for reversal of functional organ failure. Several initiatives were designed and issued to encourage the participation of the heart, lung, and blood research communities in this new Cell-Based Therapies Program. Some initial exploratory/developmental research grants were funded under an NHLBI request for innovative concepts and approaches to developing functional tissues and organs for heart, vascular, lung, and blood applications. In 2002, the NHLBI sponsored a workshop, "Cell-Based Therapies for Regenerative and Reparative Medicine: Vision, Scope and Directions," which outlined an approach for developing research plans for heart, lung, blood and sleep disorders. Several scientific areas were recommended as high priority for advancement of cell-based therapies. Studies relevant to lung repair were funded under two subsequent NHLBI initiatives, "Basic Research on Mesenchymal Stem Cell Biology" and "Research on Stem Cell Biology and Cell-Based Therapies for Heart, Lung, Blood and Sleep Disorders."

Stem cells may have the potential for reconstituting locally damaged tissue under conditions that regulate appropriate stem cell activity. A working group on "Stem Cells in Lung Morphogenesis, Repair, Regeneration and Transformation" convened in 2003 to assess the status of ongoing studies. The NHLBI recently solicited applications for "Centers of Excellence in Translational Human Stem Cell Research" to accelerate application of the latest advances in stem cell biology for the development of new diagnostic or therapeutic uses and facilitate preclinical studies employing human stem cells in animal models of disease. Several applications focused on lung disease have been received. Successful applications will be funded in FY 2005. A workshop to identify specific issues involved in the use of bone marrow progenitor cells to promote lung repair is planned for 2005.

Item

Von WillebrandDisease - The Committee encourages NHLBI to establish a universal treatment algorithm (after consultation with established medical associations) for the treatment of Von Willebrand disease. At present there is no accepted treatment algorithm in the United States for this condition. The Committee also recognizes that Von Willebrand disease is an under-recognized and under-diagnosed disease. The Committee believes that there are instances where women who are suffering from idiopathic menorrhagia are needlessly subjected to invasive procedures such as hysterectomies. The Committee encourages NHLBI to launch a pilot program among obstetricians and gynecologists treating patients, especially young women, with idiopathic menorrhagia to provide a blood test for Von Willebrand disease. Such a program would act to confirm if a link exists between menorrhagia and Von Willebrand disease in addition to providing the benefits of early detection and treatment, (p. 71)

Action taken or to be taken

The NHLBI, in consultation with the American Society of Hematology, has formed a working group to examine the current science in the area of von Willebrand Disease and develop science-based clinical recommendations for diagnosis, treatment, and management of this bleeding disorder. The audience for the recommendations is practicing primary care physicians, including general practitioners, family practitioners, internists, gynecologists, and pediatricians. The guidelines are scheduled for completion by late summer 2005, and they will be widely disseminated by the NHLBI, the American Society of Hematology, and other interested groups.

In June 2004, the NHLBI convened a panel of experts to explore research needs in the area of bleeding disorders in women. The group identified a need for increased research to improve diagnosis and treatment of von Willebrand Disease. The NHLBI plans to use the recommendations of this working group to expand research in this important area. During the past year, the NHLBI met with representatives of the CDC, the American Society of Hematology, and the National Hemophilia Foundation to discuss bleeding disorders in women. The Institute will continue to work with these agencies and the American College of Obstetricians and Gynecologists to develop strategies to address these issues.

Item

Heart disease and kidney disease - There is a well-established and significant link between heart disease, hypertension and kidney disease. With 41 million people having decreased kidney function, and in the face of an ever aging population, the need to develop better treatment and prevention strategies to address this linkage will only increase over the coming decade. The Committee encourages NHLBI to collaborate more fully with NTDDK to develop appropriate research initiatives that can be undertaken cooperatively, and encourages NHLBI to sponsor a workshop on hypertension as it relates to heart and kidney disease with input from the renal community to address these issues, (p. 71)

Action taken or to be taken

The NHLBI continues to pursue a number of avenues to enhance understanding of interactions between cardiovascular and kidney disease. Recently, two meetings were organized to develop strategies to address this issue. The "Cardiovascular Disease in Chronic Kidney Disease" workshop (jointly sponsored by the NHLBI and the NEDDK), held in March 2003, recommended strategies to reduce the burden of cardiovascular disease in patients with kidney failure or the early-stage chronic kidney disease and to improve knowledge of relevant risk factors. The NHLBI-sponsored working group, "Cardio-Renal Connections in Heart Failure and Cardiovascular Disease," convened in August 2004, evaluated current knowledge of interactions between the cardiovascular system and the kidney; identified critical gaps in knowledge, understanding, and application of research tools; and made specific recommendations for NHLBI initiatives in cardio-renal interactions and their relationship to cardiovascular disease.

Previous joint NHLBI-NIDDK workshops have resulted in a number of NHLBI and NTDDK programs, including research initiatives on hypertension and its deleterious effects on the kidney and the heart. In 2002, the NHLBI started the "Genetic Susceptibility to Target Organ Damage in

High Blood Pressure" program to identify factors that may predispose certain individuals to hypertension-induced heart and kidney damage. During the period 2003-2006^ the NHLBI and the NJDDK are co-sponsoring an initiative that invites small businesses to develop a diagnostic screening test for salt sensitivity, which is a major risk factor for both heart and kidney disease. At present, NHLBI and NTDDK scientific staff are considering establishing a jointly supported clinical research network in hypertension that would include studies on the contribution of kidney disease to heart and vascular disorders. A related initiative, "Quantitative Integrative Physiology of Hypertension," currently in the early stages of development, would address the interaction between major cardiovascular biological pathways and subsequent damage to the heart and kidney.

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

Item

Advanced Imaging Technology for Heart Disease and Stroke - The Committee is aware that heart perfusion PET scans using Rubidium-82 are considered the "gold standard" for determining the extent of muscle damage to the heart following a heart attack. The Corrrmittee encourages the NHLBI to expand its research efforts into the role of biological imaging and PET in delivering more accurate information to determine appropriate treatment for heart disease patients, (p. 103)

Action taken or to be taken

The NHLBI is funding research on many imaging techniques for rapid, accurate diagnosis and treatment of heart disease and stroke, both noninvasive (e.g., positron emission tomography—PET, magnetic resonance imaging—MRI, ultrasound, computer-assisted tomography—CT) and invasive (e.g., optical coherence tomography, near-infrared spectroscopy). A growing body of clinical and experimental evidence suggests that cardiac MRI may prove to be more beneficial than PET, because MRI can detect the delivery of blood to the heart with better spatial resolution than PET and MRI used with contrast agents to determine myocardial viability is nearly as accurate as observations made directly at autopsy. Thus, contrast-enhanced MRI is quickly being adopted as the gold standard for determining the extent of irreversible damage in the heart. Ultra-fast CT methods for imaging coronary vessels and observing calcified regions therein have also been significantly improved, and they may reduce reliance on invasive coronary artery catheterization to evaluate the extent of disease.

Collaborations between academic institutions and industry are particularly fmitful in developing imaging technologies, as evidenced by projects funded by the NHLBI through the Bioengineering Research Partnerships and Bioengineering Research Grant programs. Noninvasive molecular and cellular imaging is an area that is likely to have enormous impact on diagnosis and treatment of heart disease and stroke in the near future. The NHLBI, in collaboration with the Institute for Circulatory Health of Canada, recently funded an initiative to develop improved methods for applying targeted imaging with molecular probes to study specific disease processes. A second aim of this initiative is to improve methods for cell tracking, which will play an essential role in

improving cell-based therapies for repairing damaged heart muscle. Cardiac imaging is also a potential topic for support by a second initiative, the NHLBI Programs of Excellence in Nanotechnology, scheduled to start in April 2005.

Item

American Indians and Alaskan Natives Community -Responsive Interventions to Reduce Cardiovascular Risk - The Committee is aware that American Indian and Alaska Native communities bear a heavy burden of heart disease, stroke and other cardiovascular diseases. But, few preventive interventions have been tested. Tribal leaders have urged that research in their communities focus on finding solutions for the most serious issues these populations face, including heart disease, stroke and other cardiovascular diseases. To address the concerns of the tribal leaders, the Committee strongly urges the NHLBI to start a planned initiative to evaluate approaches to reducing behavioral cardiovascular disease risk factors such as obesity, diet, smoking, sleep restriction, stress, and sedentary lifestyle in the American Indian and Alaskan Native populations. A central part of this research will be the development of interventions that can be incorporated into community patient care programs or delivered through other public health avenues in native communities, (p. 103)

Action taken or to be taken

Please refer to page NHLBI-33 of this document for NHLBI's response to this significant item regarding American Indians and Alaskan Natives Community - Responsive Interventions to Reduce Cardiovascular Risk.

Item

Cardio-thoracic Surgery - The Committee commends the Institute for its efforts to increase research in the role of cardio-thoracic surgery in the treatment and management of heart and lung diseases. Reestablishing the cardio-thoracic intramural program is an important component of this effort. To support this renewed activity, the Committee encourages the Institute to increase the representation of cardiovascular and thoracic surgeons at all levels, including the advisory council, (p. 104)

Action taken or to be taken

The NHLBI convened a working group of cardiac surgeons in May 2004 to assess cardiac surgery research, identify critical gaps in current knowledge, determine areas of opportunity, and generate specific recommendations for future research activities. The major recommendation was to create a Cardiovascular Surgery Clinical Research Network to enable cardiac surgery researchers to collaborate on emerging clinical issues affecting surgical therapies. Such a network would improve the prospects for conducting clinical trials, such as comparisons of surgical therapies with percutaneous catheter interventions and medical therapies for heart disease. The working group also recommended immediate initiation of a multi-center, randomized, clinical trial to compare off-pump coronary artery bypass (OPCAB) with conventional on-pump coronary artery bypass (ONCAB) surgery. They noted that currently only about 25 percent of coronary bypass procedures are performed using off-pump surgery, despite many reports in the medical literature about its benefits. To resolve the apparent uncertainty among heart surgeons about the

appropriate role of the on-pump procedure, the NHLBI is developing an initiative, "Effectiveness of Off-Pump versus Conventional Coronary Artery Bypass Graft Surgery," to investigate whether OPCAB results in lower mortality or fewer complications than ONCAB surgery. In addition, the working group recommended that the NHLBI support investigations that address the translation of basic research findings into clinical trials, particularly in light of difficulties in obtaining support for research that requires large animal models.

The NHLBI has recently engaged a cardio-thoracic surgeon (through the Intergovernmental Personnel Act (TPA) Mobility Program) to provide advice on program development in cardiac surgery research.

Item

Cardiovascular Diseases - The Committee continues to regard research into the causes, cure, prevention and treatment of heart disease, stroke and other cardiovascular diseases as a major concern for our Nation and urges the NIH and the NHLBI to make these diseases a top priority. Cardiovascular diseases remain the leading cause of death in the United States and a major cause of permanent disability. The Committee continues to strongly support increased efforts to study heart disease, stroke and other cardiovascular diseases. The Cornmittee is very concerned that funding over the years for cardiovascular disease research has not kept pace with the scientific opportunities, the number of Americans afflicted with cardiovascular diseases and the economic toll these diseases impose on our Nation. Concerned that cardiovascular disease research still receives disproportionately low funding, the Corrimittee urges the Institute to aggressively expand its research portfolio and dramatically increase its resources dedicated to cardiovascular disease research through all available mechanisms, (p. 104)

Action taken or to be taken

The NHLBI has an expansive portfolio of research in cardiovascular diseases. It includes a number of large clinical trials to improve the prevention and treatment of coronary artery disease, heart failure, arrhythmias, and sudden cardiac death. The following are examples: the BARI-2D trial to evaluate the benefits of immediate versus delayed revascularization and of insulin-sensitizing drugs to control blood sugar in patients with coronary artery disease and type 2 diabetes; the STTCH trial to assess the benefits of coronary artery bypass surgery and surgical reshaping of the heart in heart failure patients who have coronary artery disease; the ESCAPE trial to evaluate the efficacy of pulmonary artery catheterization in patients with severe heart failure following a heart attack; PEACE trial to test whether adding an ACE inhibitor to standard therapy is beneficial to patients with known coronary artery disease and preserved left ventricular function; the ACES study to investigate the ability of the antibiotic azithromycin to prevent coronary events in adult patients with coronary artery disease; the Heart Failure-ACTION trial to assess the effect of aerobic exercise training in patients with heart failure; and the ACCORD trial to evaluate the effects of intensive control of blood glucose, blood pressure, and blood lipids on cardiovascular events in type 2 diabetic patients.

A number of large epidemiologic studies are also under way to document cardiovascular risk in various subgroups of the population, including the following: the Framingham Heart Study, the

NHLBI's longest-running program; the Multi-Ethnic Study of Atherosclerosis, which is looking at sub-clinical cardiovascular disease in adults of white, African-American, Hispanic, and Chinese race/ethnicity; the Strong Heart Study of American Indians; the GOCADAN study of Alaska natives; and the Jackson Heart Study of African Americans in Mississippi. A new program is being initiated to investigate risk of cardiovascular and lung disease in Mexican Americans, Puerto Ricans, Cubans, and Central Americans.

The NHLBI also supports a diverse and growing portfolio of basic and methodologic research activities that will provide a foundation of future clinical advances. Prominent research areas include the following: innovative therapies involving transfer of cells and/or genes; new circulatory assist devices for infants; improved imaging methods to diagnose cardiovascular diseases more reliably, less invasively, and at earlier stages; application of nanotechnology to diagnose and treat cardiovascular diseases; application of protepmics to identify combinations of blood proteins that may serve as markers of cardiovascular disease; use of tissue engineering to produce small-diameter, functional blood vessels; innovative study designs and analytical strategies to perform genome-wide association studies on heart diseases; and exploration of the role of nutrition and diet in the causation and treatment of heart failure.

Item

Cardiovascular Health Study - The Committee is aware that the Cardiovascular Health Study, initiated in 1987 to determine risk factors for development and progression of heart disease, stroke and other cardiovascular diseases in nearly 6,000 Americans age 65 and older, is scheduled to end in 2005. The wide variety and complexity of data and samples collected in the Cardiovascular Health Study represent an unique national research resource. The Committee urges the NHLBI to initiate a planned proposal to stimulate innovative use of Cardiovascular Health Study data and material, provide opportunities for open, efficient use of the information for the entire scientific community, and continue follow-up of study participants, (p. 104)

Action taken or to be taken

Please refer to page NHLBI-32 of this document for NHLBI's response to this significant item regarding Cardiovascular Health Study.

Item

Chronic Obstructive Pulmonary Disease [COPD] Education and Prevention Program - The Committee urges the NHLBI to implement an education and prevention program for Chronic Obstructive Pulmonary Disease [COPD]. To enhance the proper diagnosis and early detection of COPD, NHLBI is urged to launch an effort to reach out to the more than 13.3 million Americans living with COPD and the 24 million individuals yet to be diagnosed. In developing such an education and prevention program, the NHLBI is encouraged to work closely with patient and physician organizations and existing coalitions to coordinate with on-going activities in the community. Early identification of those at-risk for or who have COPD is essential in the effort to stem the growth of this segment of population. The Committee encourages NHLBI to enhance its efforts in this area, through all available mechanisms, as appropriate, including working with national lung organizations, such as the American Thoracic Society and the American Lung

Association to develop epidemiological studies of patients who are at-risk for or who have this disease as well on a national education campaign for providers and the public about COPD. (p. 104)

Action taken or to be taken

Please refer to page NHLBI-35 of this document for NHLBI's response to this significant item regarding Chronic Obstructive Pulmonary Disease [COPD] Education and Prevention Program.

Item

Cystic Fibrosis - The Committee understands that cystic fibrosis researchers are evaluating a number of compounds as possible therapies for CF. This will require the completion of clinical trials enrolling a significant number of participants. The Committee encourages NHLBI, which has a long and successful record in supporting trials on therapies for chronic disease, to expand its involvement in trials to demonstrate the effective use of approved therapies in CF patients and especially trials to examine the use of approved products in pediatric patients with CF. (p. 105)

Action taken or to be taken

The NHLBI is committed to continued support of clinical trials for the management of chronic respiratory diseases, including cystic fibrosis (CF). In FY 2004, the Institute, in partnership with the National Institute of Diabetes and Digestive and Kidney Diseases, the Cystic Fibrosis Foundation, and several companies, initiated a clinical trial for early treatment of Pseudomonas aeruginosa (Pa) in young children with CF. It explores the "window of opportunity" in early Pa acquisition during which aggressive anti-Pa treatment with approved therapies could be effective in eradicating this organism and preventing or slowing the recurrent cycle of infection that leads to irreversible lung destruction and, eventually, death. It will be the largest clinical trial involving children with CF ever conducted in the United States.

Other NHLBI-supported studies are leading to promising treatment strategies. For instance, mounting evidence from safety and dose-escalation (Phase I and Phase U) clinical trials in children and adults suggests that compounds such as phenylbutyrate may someday provide a therapy for CF by increasing CFTR (the protein product of the CF gene) trafficking to the cell surface. Animal studies exploring the efficacy of airway administration of xylitol, a simple sugar commonly used in "sugarless" chewing gum that inhibits bacterial growth, have led to clinical studies in normal volunteers and young patients with CF. Multidisciplinary programs in gene therapy for CF have successfully overcome a number of barriers, leading to the development of an adeno-associated vector that has received approval for use in clinical trials.

Findings from NHLBI-supported basic and clinical research have also contributed to the strong scientific basis for two new CF treatments used in clinical practice: Pulmozyme®, a mucus-thinning drug, and tobramycin, an inhaled antibiotic. NHLBI continues to support a broad program of basic and clinical research in CF focused on discovery of new and improved treatments for this devastating disease.

Item

Heart Failure Management - The Committee is concerned that heart failure is a major cause of hospitalization and readmission. Medicare recipients represent about 65 percent of repeat hospitalizations within 1 year. Yet, perhaps 50 percent of these hospitalizations are avoidable. The Committee urges NHLBI to initiate a planned multi-center, randomized trial to evaluate management strategies for heart failure patients in terms of their ability to prevent death or hospital readmission. Costs, quality of life, physician compliance, and patient adherence to prescribed treatment will also be assessed. This clinical trial will identify and disseminate useful and effective tools for translation of proven heart failure therapies into patient care. (p. 105)

Action taken or to be taken

Please refer to page NHLBI-32 of this document for NHLBI's response to this significant item regarding Heart Failure Management.

Item

Marfan Syndrome - The Committee commends NHLBI for its support of research opportunities to study this life-threatening, degenerative genetic disorder. Marfan syndrome is characterized by cardiovascular, skeletal and ocular manifestations, and its cardiovascular complications result in premature death. Insights gained from research in this area can have implications for the understanding of other connective tissue disorders, other genetically mediated diseases, and the larger population of aging adults with thoracic aneurysms. The Committee urges NHLBI to expand its collaborative efforts with other institutes to support research, awareness of aortic dissection and help reduce the number of premature cardiovascular deaths resulting from undiagnosed genetic conditions, (p. 106)

Action taken or to be taken

Please refer to page NHLBI-40 of this document for NHLBI's response to this significant item regarding Marfan Syndrome.

Item

Minority Health - The Committee notes lung disease disproportionately affects many minority groups. The Committee urges NHLBI to work with other Institutes and Centers to develop an epidemiologic approach to determine the disproportionate impact of airway disease on minority populations, (p. 106)

Action taken or to be taken

The NHLBI supports four Centers for Reducing Asthma Disparities that comprise partnerships between research-intensive and minority-serving institutions and are dedicated to examining why certain racial, ethnic, and socioeconomic groups are more severely affected by asthma than other populations. Each center has several research projects. They address topics such as the role of psychosocial factors in disparities in asthma care over time, differences in symptom perception among racial and ethnic groups and the effects of such differences on care-seeking behavior, improvement of communications between patients and their doctors about asthma, and potential genetic factors that may explain different susceptibility to severe asthma or variations in response

to therapy. Most of the centers include an epidemiologic assessment of risk factors for severe disease, and the results will provide direction for the design of interventions to close the gaps between ethnic groups. To further stimulate research, provide a forum for exchanging study findings, and promote collaboration with other NTH components in addressing this issue, the NHLBI is co-sponsoring a National Conference on Asthma Disparities with Northwestern University in February 2005. Other federal agencies, such as the Agency for Healthcare Research and Quality, will also participate. Several epidemiologic approaches to examining the reasons for sustained disparities and identifying potential targets for intervention will be highlighted at this conference. Additionally, the NHLBI is participating in an NIH-wide program announcement to stimulate community-based research approaches to studying diseases that disproportionately affect minority communities. It is expected to yield grant applications related to many different conditions, including asthma. Frequent meetings among all investigators, regardless of the health condition on which their grant focuses, will promote an exchange of information that may enhance understanding of causes of health disparities and point the way to potential remedies.

Item

Myelodysplasia and Myeloproliferative Disorders - The Committee commends NHLBI for its new research initiatives in Myelodysplasia [MDS] and Myeloprohferative Disorders [MPDs), which resulted from a recent conference involving the Institute and NCI. MPDs and MDS are chronic diseases of bone marrow cells that can develop into acute leukemia. The Committee encourages NHLBI and NCI to bring together scientific and clinical experts in this field to explore collaborative research and crosscutting mechanisms to further this research agenda, (p. 106)

Action taken or to be taken

Please refer to page NHLBI-38 of this document for NHLBI's response to this significant item regarding Myelodysplasia and Myeloproliferative Disorders.

Item

National Asthma Education and Prevention Program [NAEPP] - The Cornmittee commends the NAEPP for its leadership in helping to educate physicians, asthma patients, their families, and the general public regarding asthma and its management. The Cornmittee urges NAEPP to enhance the role that its advisory committee plays in helping to coordinate asthma education throughout the United States. The Children's Health Act of 2000 included provisions for NAEPP to develop, in conjunction with other Federal agencies and voluntary and professional health organizations, a Federal plan to respond to asthma. This plan will include the roles and responsibilities of several Federal agencies in combating asthma. The Committee would like to be kept apprised on the progress of NAEPP's planning efforts, and urges NHLBI to move forward as early as possible, (p. 106)

Action taken or to be taken

The NHLBI-coordinated Federal Liaison Group on Asthma (FLGA) of the NAEPP continues to meet on a quarterly basis to share information and explore opportunities for cross-agency collaborations and partnership activities. The FLGA maintains a fact sheet on frequently-asked questions about asthma prevalence that is updated annually with data from the National Center for

Health Statistics. This basic reference allows Federal agencies to present consistent asthma data to the public and speak with a common voice. Through information exchange at the FLGA meetings, Federal agencies have identified the following ways to improve coordination of efforts for implementing community-based asthma programs. The Centers for Disease Control and Prevention (CDC) has collaborated with the National Institute of Allergy and Infectious Diseases to implement an intervention developed by the National Cooperative Inner-City Study aimed at reducing among inner-city children the number of days with symptoms and the number of acute-care and emergency-room visits for asthma. The Centers for Medicare and Medicaid Services has developed a method for generating state Medicaid asthma statistics for children that can be used to assist other Federal agencies in planning asthma programs. The Health Resources and Services Administration's Bureau of Primary Health Care has collaborated with the Environmental Protection Agency to support clinical and administrative leaders from health care centers to participate in asthma quality improvement programs, with a focus on enhancing guidelines-implementation and reducing health disparities. The NHLBI in partnership with the CDC is developing a lessons-learned document based on evaluation of recent school asthma research and community-based interventions. The NHLBI also is collaborating with the Department of Housing and Urban Development to plan asthma education interventions for implementation in public housing communities.

In the coming year the FLGA will continue to look for opportunities to enhance coordination of Federal agency activities in the following five goal areas: asthma data, schools and child care centers, community-based interventions, enhanced guidelines-implementation, and asthma research and prevention.

Item

Obstructive Sleep Apnea - The Committee commends the Institute for its work on obstructive sleep apnea, a disorder that affects approximately 80 percent of the elderly, and which if left untreated significantly increases risk for hypertension, coronary artery disease, heart failure and stroke. The Institute is encouraged to include surgical treatments in its search for useful treatments for this disorder, (p. 107)

Action taken or to be taken

Please refer to page NHLBI-39 of this document for NHLBI's response to this significant item regarding Obstructive Sleep Apnea.

Item

Pediatric Asthma Network - The Committee recognizes that little is known about the optimal treatment for asthma in infants and young children. The Committee urges NHLBI to use the research amassed through the Pediatric Asthma Clinical Research Network to provide clearer choices for childhood asthma therapy, to encourage the development and dissemination of new therapies, and to identify optimum asthma management strategies for children, (p. 107)

Action taken or to be taken

The Childhood Asthma Research and Education Network is dedicated to answering clinical questions of concern to the medical community and families of children with asthma, and providing guidance about appropriate therapies for the varying degrees and types of asthma. For example, the Network just completed a study that identified characteristics of patients who are more likely to respond to inhaled corticosteroids than to other asthma medications. In March 2005 the Network will present the findings of a major clinical trial that is evaluating the potential preventive benefits of treating young children at risk of developing persistent asthma. In May 2005 the outcome of a trial comparing three different asthma treatments will provide guidance to physicians in making the best choice for starting children on daily therapy. Research results will be presented at national meetings, published in major medical journals, disseminated through the NHLBI information office, and included in the National Asthma Education and Prevention Program's Expert Panel update of the asthma clinical practice guidelines. Additional studies are under way to examine optimal treatment for infants who wheeze when they have viral infections, to compare two different treatment strategies for children with more severe asthma, and to determine whether identifying genetic variations can help predict a child's response to common asthma medications and thereby enable physicians to tailor medical regimens to individual patient circumstances.

Item

Pulmonary Hypertension - Pulmonary Hypertension [PH] is a rare, progressive and fatal disease that predominantly affects women, regardless of age or race. PH causes deadly deterioration of the heart and lungs and is a secondary condition in many other serious disorders such as scleroderma and lupus. The Committee continues to view research in this area as a high priority and commends NHLBI's efforts to promote PH related research. For fiscal year 2005, the Cornmittee encourages the Institute to increase funding for basic research, gene therapy and clinical trials of promising pharmaceuticals, and to take appropriate measures to ensure the submission of high quality proposals in this area. (p. 107)

Action taken or to be taken

The NHLBI supports a robust research effort in pulmonary hypertension (PH). In fiscal year 2004, its portfolio included more than 80 projects on PH, some of which originated in response to the NHLBI Program Announcement "Cellular and Molecular Mechanisms of PH," which called for innovative studies using human lung tissues. The Institute, in conjunction with the Pulmonary Hypertension Association, the NTH Office of Rare Diseases, and the Centers for Disease Control and Prevention, recently sponsored an International Scientific Conference on Pulmonary Hypertension.

In fiscal year 2005, the NHLBI will support new grants to investigate the causes of PH associated with sickle cell anemia via a solicitation titled "Pulmonary Complications of Sickle Cell Anemia." -Also in 2005, the Institute will announce two new programs: "Specialized Centers of Clinically Oriented Research (SCCOR) in Pulmonary Vascular Disease," which will promote multidisciplinary basic and clinical research related to PH and other pulmonary vascular diseases, and "Sildenafil for Pulmonary Hypertension in Adult Patients with Sickle Cell Disease," a phase

II clinical trial to determine the safety and efficacy of sildenafil (Viagra®) in such patients." Other activities anticipated for fiscal year 2005 include consideration of an investigator-initiated multicenter clinical trial application on PH treatment, a workshop on "Cellular and Molecular Mechanisms of Right Heart Failure," which will address an important problem affecting many PH patients, and another workshop on "Bone Marrow Progenitor Cells in Lung Repair and Regeneration," which will include discussions of recent research that is exploring the potential of bone marrow progenitor cells to ameliorate PH.

Item

Sleep Disorders - The Committee commends the National Center on Sleep Disorders Research for its progress and is pleased that the Center has sponsored the translational conference Frontiers of Knowledge in Sleep and Sleep Disorders. The Committee urges the Center to partner with other Federal agencies, such as the Centers for Disease Control and Prevention, as well as voluntary health organizations such as the National Sleep Foundation, to develop a sleep education and public awareness initiative that will provide a forum for dissemination of the outcomes of the sleep translational conference, and serve as an ongoing, inclusive mechanism for public and professional awareness on sleep and sleep disorders. Several institutes and public health service agencies have had success with these collaborative models, (p. 107)

Action taken or to be taken

Please refer to page NHLBI-40 of this document for NHLBI's response to this significant item regarding Sleep Disorders.

Item

Thrombosis and Thrombophilia - The Committee is concerned that too little is known about the basic science of thrombosis and thrombophilia, major causes of death and disability in this country. The Committee strongly urges the Institute to expand its support for basic research into their underlying causes in order to improve diagnosis and treatment for these conditions. The Committee also strongly urges the Institute to use all available mechanisms to support this research and urges collaboration with the thrombophilia centers funded by CDC. (p. 108)

Action taken or to be taken

The NHLBI recognizes the importance of additional research in thrombosis and thrombophilia. Accordingly, in September 2004 the Institute implemented an initiative on Inflammation and Thrombosis, which resulted in the award of 12 new grants. The NHLBI is also in the process of implementing another initiative, titled Critical Issues in Post-phlebitic Syndrome, for FY 2006. Post-phlebitic syndrome is a common and chronic complication of deep-vein thrombosis. The results of the studies supported by these two grant solicitations are likely to improve our understanding of thrombosis and accelerate preclinical studies. In addition, the NHLBI plans to bring together a working group of experts in FY 2005 to define the basic research directions needed to improve the diagnosis and treatment of thrombosis and thrombophilia. The CDC will be invited to participate in this meeting. The recommendations of the group will form a basis for future NHLBI action to expand research in this area of science.

Item

Tissue Engineered Blood Vessel Replacement and Repair - The Committee is aware that a need exists to develop alternatives to natural blood vessels for the adults who endure heart artery bypass surgery and for the children born with complex heart defects who need multiple blood vessel grafts. The Corrrmittee encourages the NHLBI to initiate a planned initiative to complement existing tissue engineered research programs to stimulate efforts to "grow" small-diameter, functional blood vessels, (p. 108)

Action taken or to be taken

Please refer to page NHLBI-33 of this document for **NHLBrs** response to this significant item regarding Tissue Engineered Blood Vessel Replacement and Repair.

Item

Tuberculosis and AIDS - The Committee supports the important research on the interaction of tuberculosis and AIDS conducted by the NHLBI AIDS research program and encourages NHLBI to strengthen its research in this important area. (p. 108)

Action taken or to be taken

The NHLBI supports research on tuberculosis (TB), AIDS, and interactions between TB and infection with human immunodeficiency virus (HIV). This work includes animal studies and clinical, behavioral, educational, and basic laboratory projects. The Institute funds several clinical studies to evaluate new treatments. One is examining the lung immune responses of patients who are infected with both HTV and TB and are enrolled in a trial of early antiretroviral therapy plus anti-TB therapy. Another is testing the effects of augmenting the usual treatment for TB with aerosolized interferon-gamma. Both TB patients and TB-HfV-infected patients who have moderately advanced pulmonary TB will be followed to see how the combined treatment affects their recovery and their lung immune responses. A third study is examining the regulation of HTV replication in lung macrophages in the presence of TB.

Other projects that address TB-HIV co-infection include several behavioral research studies: An education program for health department workers is testing a new algorithm for identifying contacts of TB patients at highest risk of being infected with TB and two other projects are assessing interventions to improve compliance with treatment for latent TB infection. All three studies address the high rate of HTV co-infection. The Tuberculosis Curriculum Coordinating Center, an educational program to improve access to educational and training opportunities in TB for medical and health professional schools, addresses dual TB-HIV infections.

In September 2004, the NHLBI held a working group meeting on the genetics of TB to summarize current projects and to identify research needs and future directions. A new Request for Applications on "Mechanisms of HTV-Related Pulmonary Complications" encourages innovative research on the roles of co-infections, immune factors, and genetic predisposition in the pathogenesis of HTV-related pulmonary diseases.

Item

Von Willebrand Disease - The Committee encourages NHLBI to establish a universal treatment algorithm (after consultation with established medical associations such as the American Society of Hematology) for the treatment of Von Willebrand disease. At present there is no accepted treatment algorithm in the United States for this condition. The Committee also recognizes that Von Willebrand disease is an under-recognized and under-diagnosed disease. The Committee believes that there are instances where women who are suffering from idiopathic menorrhagia are needlessly subjected to invasive procedures such as hysterectomies. The Committee encourages NHLBI to launch a pilot program among obstetricians and gynecologists treating patients, especially young women, with idiopathic menorrhagia to provide a blood test for Von Willebrand Disease. Such a program would act to confirm if a link exists between menorrhagia and Von Willebrand Disease in additional to providing the benefits of early detection and treatment, (p. 108)

Action taken or to be taken

Please refer to page NHLBI-42 of this document for NHLBI's response to this significant item regarding Von Willebrand Disease.

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute

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	$2,853,043,000	Indefinite	$2,863,508,000
Institute	Section 41B	42§285b	Indefinite		Indefinite	
National Research Service Awards	Section 487(d)	42§288	*al*	88,158,000	b/	87,762,000
Total, Budget Authority				2,941,201,000		2,951,270,000

a/ Amounts authorized by Section 301 and Tide IV of the Public Health Act.
b/ Reauthorizing legislation will be submitted.

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute

Appropriations History

Fiscal Year	Budget Estimate to Congress	House Allowance	Senate Allowance	Appropriation 1/
1997	$1,320,555,000 2/	$1,438,265,000	$1,344,724,000 2/	$1,432,529,000 4/
1998	1,404,770,000 2/	1,513,004,000	1,534,898,000 3/	1,531,061,000
1999	1,641,524,000 2/5/	1,720,344,000	1,793,697,000	1,793,697,000
Rescission	0	0	0	(1,188,000)
2000	1,759,806,000 2/	1,937,404,000	2,001,185,000	2,040,291,000
Rescission				(10,867,000)
2001	2,069,582,000 2/	2,321,320,000	2,328,102,000	2,299,100,000
Rescission				(875,000)
2002	2,567,429,000	2,547,675,000	2,618,966,000	2,576,125,000
Rescission				(3,063,000)
2003	2,778,728,000	2,791,411,000	2,820,011,000	2,812,011,000
Rescission				(18,278,000)
2004	2,867,995,000	2,867,995,000	2,897,595,000	2,897,145,000
Rescission	0	0	0	(18,454,000)
2005	2,963,953,000	2,963,953,000	2,985,900,000	2,965,453,000
Rescission	0			(24,252,000)
2006	2,951,270,000			

1/ Reflects enacted supplementals, rescissions, and reappropriations.
21 Excludes funds for HTV/AIDS research activities consolidated in the NTH Office of AIDS Research.
3/ Excludes procurement reform, rent, and salary and expense reductions of $1,118,000.
4/ Excludes enacted administrative reduction of $472,000.
5/ Reflects a decrease of $5,161,000 for the budget amendment for bioterrorism.

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute

Detail of Full-Time Equivalent Employment (FTEs)

OFFICE/DIVISION	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Office of the Director	9	9	9
Women's Health Initiative	5	5	5
Office of Special Concerns	2	2	2
Office of Science and Technology	38	38	38
Office of International Program	7	6	6
Office of Prevention, Education, and Control	33	33	33
Office of Administrative Management	70	70	70
Office of Minority Health Affairs	3	4	4
Division of Heart and Vascular Diseases	46	46	46
Division of Epidemiology and Clinical Applications	55	55	55
Division of Lung Diseases	18	17	17
Division of Blood Diseases and Resources	19	19	19
Division of Intramural Research	400	400	400
Division of Extramural Affairs	91	92	92
National Center on Sleep Disorders Research	3	3	3
Total	799	799	799

FISCAL YEAR	Average GM/GS Grade
2002	11.4
2003	11.4
2004	11.7
2005	11.7
2006	11.7

NATIONAL INSTITUTES OF HEALTH
National Heart, Lung, and Blood Institute

Detail of Positions

GRADE	FY 2004 Actual	FY 2005 Appropriation	FY 2006 Estimate
Total - ES Positions	10	10	10
Total - ES Salary	$1,439,184	$1,492,434	$1,526,760
GM/GS-15	85	85	85
GM/GS-14	90	90	90
GM/GS-13	139	139	139
GS-12	95	95	95
GS-11	44	44	44
GS-10	6	6	6
GS-9	38	38	38
GS-8	62	62	62
GS-7	29	29	29
GS-6	8	8	8
GS-5	10	10	10
GS-4	5	5	5
GS-3	3	3	3
GS-2	2	2	2
GS-1	0	0	0
Subtotal	616	616	616
Grades established by Act of July 1, 1944 (42U.S.C. 207):			
Assistant Surgeon General			
Director Grade	14	14	14
Senior Grade	3	3	3
Full Grade			
Senior Assistant Grade			
Assistant Grade			
Subtotal	17	17	17
Ungraded	226	226	226
Total permanent positions	634	634	634
Total positions, end of year	869	869	869
Total full-time equivalent (FTE) employment,end of year	799	799	799
Average ES salary	$143,918	$149,243	$152,676
Average GM/GS grade	11.7	11.7	11.7
Average GM/GS salary	$76,693	$79,531	$81,360