SEVENTEENTH

National Heart, Lung, and Blood Institute

Report of the Director

Report of the National Heart, Lung, and Blood Advisory Council

National Institutes of Health
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Seventeenth Report of the Director

The National Heart, Lung, and Blood Institute (NHLBI) supports a comprehensive program of research related to diseases of the heart, blood vessels, lungs, and blood as well as the use and management of blood resources. Since its beginning, the Institute has been strongly committed to improving diagnosis, treatment, and prevention of disease through programs that encompass basic and clinical research, clinical trials and other population-based studies, demonstration and education programs, and research training and career development activities. This approach has led to significant improvements in the public health as reflected by sharply decreased mortality rates for disorders such as coronary heart disease, stroke, and neonatal respiratory distress syndrome.

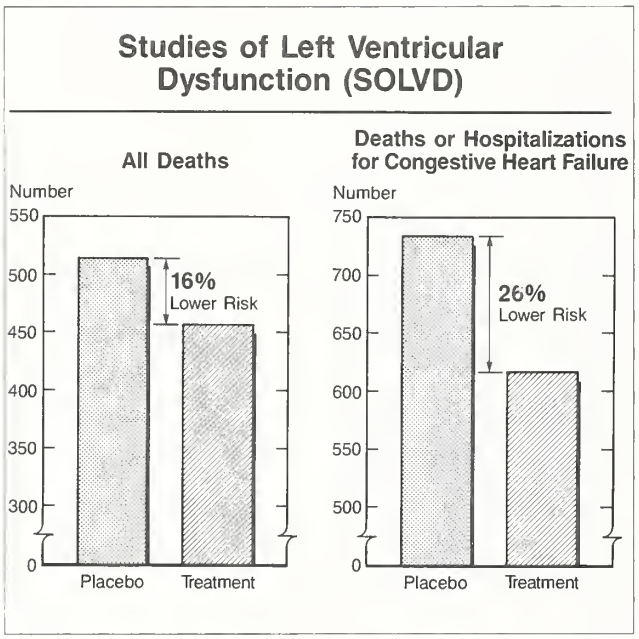
The past two years have brought forth a number of noteworthy scientific achievements that have immediate applicability to the American public. Described under "Progress Highlights," these achievements represent important advances in many of the cross-cutting areas of research identified in the National Institutes of Health (NIH) strategic plan: Behavior and Health; Childhood Health and Mortality; Disease Control and Prevention; Chronic and Recurrent Illness, Rehabilitation, and Aging; the Health of Women; and Health of Minorities and Underserved Populations.

The section on "Areas of Scientific Opportunity" highlights emerging areas of science in which progress is accelerating rapidly as a result of new approaches and disciplines. Many of these advances reflect the application of critical science and technologies underscored in the NIH strategic plan, including molecular medicine, biotechnology, and structural biology.

Progress Highlights

Studies of Left Ventricular Dysfunction (SOLVD)

This large-scale clinical trial evaluated treatment of chronic heart failure, a condition that affects between two and three million Americans and constitutes the leading cause of hospitalization among persons over 65 years of age. This trial demonstrated that use of an angiotensin-converting-enzyme (ACE) inhibitor, enalapril, in patients with overt congestive heart failure reduced overall deaths by 16 percent and deaths or hospitalizations for heart failure by 26 percent. A second trial, in patients with damaged hearts but no heart failure symptoms, found that use of enalapril delayed development of heart failure. Implementation of the findings from this study is expected to save both lives and medical care costs.



National Asthma Education Program (NAEP)

Rapid progress is being made in the control of asthma, a chronic disease that affects about 10 million Americans, a disproportionate number of whom are minorities. Since the start of the NAEP in 1989, the annual number of asthma deaths—which had been rising alarmingly—declined during each of the two successive years. The first major report of the NAEP, *Guidelines for Diagnosis and Management of Asthma*, is being disseminated to thousands of health care professionals throughout the country. In collaboration with the U.S. Department of Education, a guide has been developed to educate school personnel about the role they should play in asthma management. Research is currently under way to develop educational programs geared specifically to Blacks and Hispanics to reduce the excess burden of asthma in those segments of the population.

Surfactant Therapy for Neonatal Respiratory Distress Syndrome (RDS)

Recent advances in surfactant replacement therapy have resulted in dramatic decreases in mortality among infants suffering from RDS. RDS is caused by a deficiency of lung surfactant, a substance that lines the alveoli and prevents their collapse. Two drugs were released for treatment of this disorder in 1990: Survanta®, a natural surfactant isolated from cow lung, and Exosurf®, a synthetic preparation. The impact of their use was immediate and dramatic. Provisional figures indicate that death rates from RDS were 34 percent lower in 1990 than in 1989, a decrease attributed to use of this new therapy. Indeed, the overall U.S. infant mortality rate for 1990 was the lowest ever recorded, substantially because of the decrease in RDS deaths.

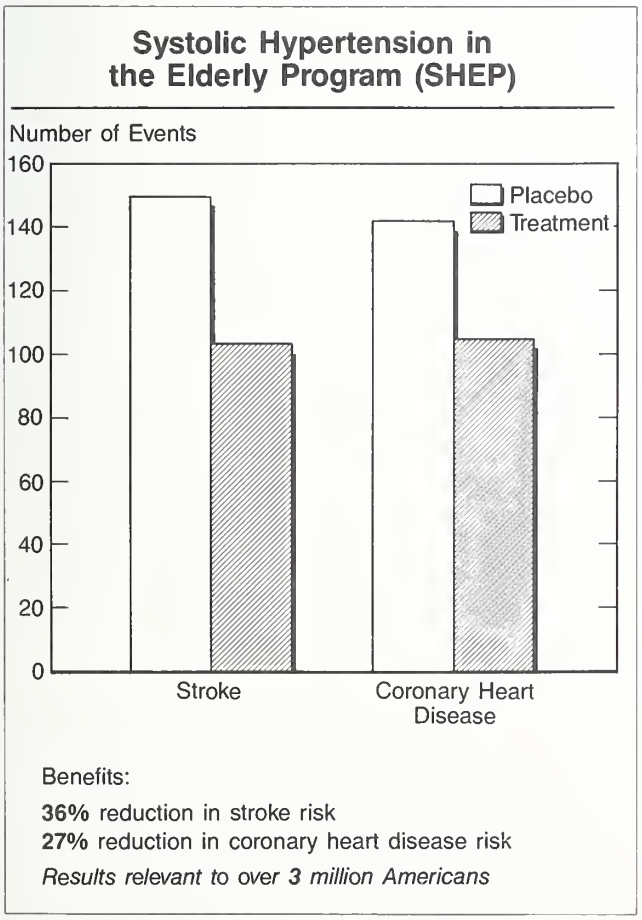
Gender Differences in Smoking Cessation

The Lung Health Study is a multicenter clinical trial of smoking cessation in persons at high risk of developing chronic obstructive pulmonary disease. Because 37 percent of the participants are women, the study provides an excellent opportunity to examine gender differences in smoking cessation patterns. Early results indicate that women experience far more difficulty in quitting smoking and remaining abstinent than do men. Moreover, women who abstained from smoking for two years gained significantly more weight than men. Although men who resumed smoking were able, within one year, to lose most of the weight they had gained, women who relapsed retained most of their weight gain. These findings have important

implications for design of gender-specific approaches to smoking cessation.

Systolic Hypertension in the Elderly Program (SHEP)

This major clinical trial addressed the risks and benefits of treating isolated systolic hypertension (ISH), a common, age-related condition that is associated with an increased risk of stroke, coronary heart disease, heart failure, heart attack, and sudden death. SHEP revealed that treatment with inexpensive, commonly used drugs resulted in average five-year reductions of 36 percent for stroke, 27 percent for coronary heart disease, and 32 percent for all cardiovascular events. These results form the basis for important new medical care recommendations for the three million Americans who have ISH. It is estimated that this simple, safe, effective, and low-cost treatment will result in a reduction of 30 strokes and a total of 55 major cardiovascular events per 1,000 persons treated over five years.



Bone Marrow Transplantation

Nearly 20,000 patients could benefit from a bone marrow transplant each year, but approximately 65 percent cannot find a suitable tissue-type-matched donor among close blood relatives. The National Marrow Donor Program offers a solution to this problem in the form of a registry of persons who have been tissue typed and have agreed to participate as potential donors. The registry more than doubled in size over the past two years and, as of March 1992, included more than 500,000 potential donors, more than 70,000 of whom are members of minority groups. To date, the program has facilitated more than a thousand marrow transplants, with results comparable to those of related-donor transplants. Ongoing research promises to improve the safety and efficacy of marrow transplantation and to extend the range of disorders to which it can be applied successfully.

Treatment of Sickle Cell Disease

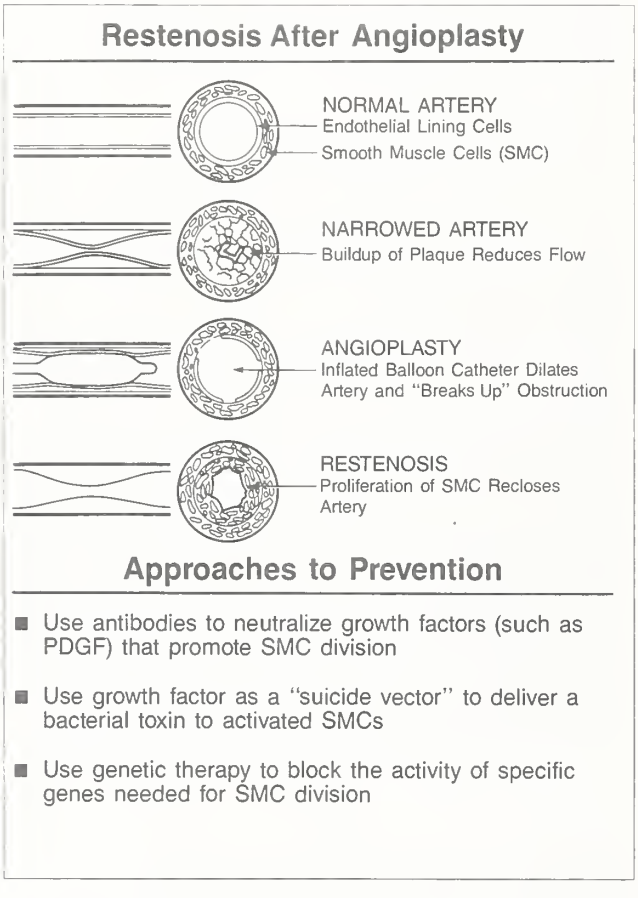
Clinical research has uncovered a promising method to avert the painful crises suffered by patients with sickle cell disease. The approach is based upon reversing the "hemoglobin switch" that naturally occurs at birth. Such a reversal would cause the patient to produce normal fetal hemoglobin instead of defective adult sickle hemoglobin. A small multicenter study found that treatment with hydroxyurea, a common chemotherapeutic agent, increased fetal hemoglobin levels 15 percent or more and decreased the incidence of sickle cell crises. The safety and efficacy of this treatment are now being assessed in a multicenter, randomized, double-blind, placebo-controlled trial. Positive results from this study would have significant implications for reducing the costly recurrent hospitalizations associated with sickle cell crisis.

Areas of Scientific Opportunity

Prevention of Coronary Artery Restenosis

NHLBI-supported researchers have recently developed three innovative approaches to prevent the restenosis (renarrowing) of coronary arteries that frequently occurs after angioplasty. Each seeks to halt the proliferation of smooth muscle cells (SMC) that is the main cause of restenosis. In the first, an

antibody to platelet-derived growth factor (PDGF), a substance that promotes SMC proliferation, was administered to rats that had undergone experimental arterial injury similar to angioplasty. The resultant neutralization of PDGF reduced SMC buildup by 41 percent. A second group of researchers is using recombinant DNA technology to create a protein that includes both a growth factor and a bacterial toxin. This molecule selectively enters activated SMCs and destroys them. In a third approach, investigators are working to halt SMC proliferation by blocking the activity of key genes that are essential for cell division. If proven successful in humans, any one of these strategies could decrease dramatically the cost and risk of repeat angioplasty.



Human Gene Therapy

The first human gene therapy experiments were recently carried out by NHLBI intramural researchers in collaboration with scientists from the National Cancer Institute. In one protocol, gene therapy was performed in a child with adenosine deaminase (ADA) deficiency, a condition characterized by severe immune dysfunction. A normal gene for ADA was inserted into the patient's own lymphocytes, which were then grown in tissue culture and returned to her. As a result, this patient's immune function improved sufficiently to enable her to attend kindergarten. A second protocol involved patients with advanced malignant melanoma. A normal human gene for tumor necrosis factor (TNF) was inserted into the patient's tumor-infiltrating lymphocytes (TIL) in the hope that the TIL would home in on tumor cells and release their toxins. The Institute is actively exploring the applicability of gene therapy to other diseases, including hemoglobinopathies such as Cooley's anemia.

Nuclear Magnetic Resonance (NMR)

Noninvasive techniques such as magnetic resonance imaging offer unprecedented prospects for study of intact tissue in the laboratory and identification of its biochemical composition in normal and diseased states. To capitalize fully upon this unique scientific opportunity, NHLBI installed an NMR system with the highest magnetic field strength available for whole body human studies in its Laboratory of Cardiac Energetics. Currently, the instrument is providing images that are fourfold better than standard clinical machines. Initial studies are focused upon glucose utilization in diabetes and cardiac ischemia. The potential benefits of this exciting new program include analysis of cardiac function and anatomy without the use of harmful ionizing radiation; development of new noninvasive diagnostic procedures for detection and characterization of early heart disease; possible elimination of invasive diagnostic techniques such as catheterization and angiography; and development of new strategies for prevention and treatment of heart disease.

Hemophilia

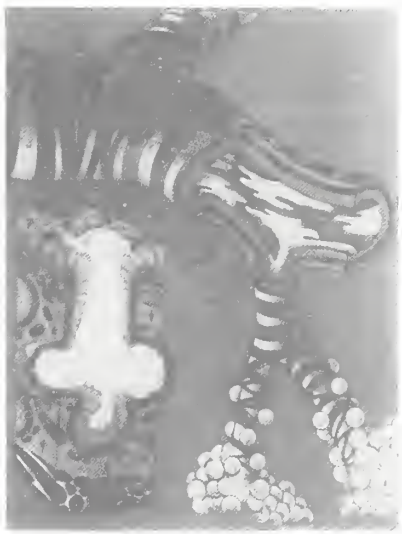
Recent advances in genetic engineering have improved prospects for treatment of hemophilia, a bleeding disorder caused by an inherited deficiency of blood-clotting factors. For the past 20 years, patients have been treated with injections of clotting factors obtained from pooled human plasma,

with the attendant risk of viral transmission. The recent cloning of the factor VIII gene paved the way for production of large quantities of recombinant factor VIII (rFVIII) in cell culture. Now undergoing testing in two clinical trials, rFVIII is expected to provide a safe and effective alternative to current treatment. Even more exciting are the prospects for a cure of hemophilia through recombinant gene therapy. Initial success has been reported in a dog model of hemophilia B, and a number of NHLBI-supported investigators are working to develop techniques for incorporating correct clotting factor genes into the body cells of humans.

Cystic Fibrosis (CF)

Considerable success has been realized in the quest for ways to combat the thick, sticky mucus that clogs the airways of CF patients. Building upon recent understanding that defects in chloride and sodium transport are responsible for this abnormal mucus, NHLBI-supported researchers have identified two naturally occurring substances called nucleotides that appear to correct the chloride defect and a diuretic, amiloride, that resolves the sodium transport problem. Studies in progress will determine whether a combination of these agents can produce a thinner, more normal mucus. Meanwhile, researchers in the NHLBI intramural program successfully used a modified cold virus to implant a normal copy of the human CF gene in the lungs of living animals. Subsequent tests showed that the inserted gene caused the lung cells to manufacture the critical human protein that is missing in CF patients. The same group also reported very promising results of a study of aerosolized recombinant human deoxyribonuclease I (DNase) in CF patients. Short-term therapy with DNase improved lung function significantly in patients with airflow limitation due to purulent airway secretions. These findings hold much potential for reducing the morbidity and mortality associated with CF.

Mucus Abnormality in Cystic Fibrosis



New Approaches to Treatment

- Give combination of the diuretic amiloride and nucleotides to produce a more "watery" mucus
- Use a "common cold" virus to deliver the normal cystic fibrosis gene to the lung cells
- Use the enzyme DNase to fragment the sticky DNA portion of purulent mucus

Seventeenth Report of the National Heart, Lung, and Blood Advisory Council

The goals of the National Heart, Lung, and Blood Institute (NHLBI) are to prevent, diagnose, treat, and cure heart, blood vessel, lung, and blood diseases and to provide for an adequate and safe blood supply for the Nation. To achieve these goals, the Institute supports a comprehensive and balanced program that incorporates basic and clinical investigations, clinical trials, epidemiologic studies, and demonstration and education projects. These efforts have resulted in extraordinary progress in the quest to improve the public health and have led, in turn, to new and exciting avenues for research. This document focuses on new scientific opportunities, issues related to research cost considerations, and several specific mechanisms of research support.

Scientific Opportunities

This year, the NHLBI has been a major and enthusiastic participant in the development of the first corporate long-range strategic plan of the National Institutes of Health (NIH). This plan was conceived to identify areas of research that promise significant dividends for the Nation's future health, to nurture the intellectual base of biomedical research and the conditions that lead to breakthroughs on the cutting edge of science, and to provide approaches for addressing broad administrative and science policy issues that affect the ability of NIH to carry out its mandate. The plan identifies a number of promising areas of science to be pursued and details specific initiatives within each area. The NHLBI

initiatives developed for this plan comprise the most auspicious opportunities for research on the heart, blood vessels, lungs, and blood—the collective forward thinking of the Institute and its scientific advisors. The maintenance of strong research training and career development programs that encourage young investigators to focus on cardiovascular, lung, and blood diseases is essential to the plan's success.

In the area of biotechnology, for example, the ability to create new animal models of human diseases by disrupting the expression of endogenous genes or by introducing defective human genes into the animal offers a host of exciting possibilities for understanding basic pathogenetic mechanisms of many diseases. The strategic plan includes an NHLBI initiative to develop and use the full range of transgenic animal approaches to understand normal and altered cardiovascular and pulmonary function at the molecular, biochemical, cellular, and physiological levels; to elucidate gene-environment interactions; and to develop and evaluate innovative therapies and diagnostic procedures.

The NHLBI leads the NIH effort in gene therapy and bone marrow transplantation research, a key feature of the strategic plan panel report on molecular medicine. In that promising area, an initiative is proposed to expand research on identification of the genetic basis of human disease, the use of animal models (particularly nonhuman primates) to develop gene therapy for human disease, the use of hematopoietic bone marrow cells as a general target of therapeutic genes, and the mechanisms of transferring genes into other specifically targeted tissues and cells.

Another promising area of science is structural biology, a discipline that has, over the past decade, evolved tools and techniques for understanding the highly organized interactions of molecules in the living cell. Of critical interest to the NHLBI is a new initiative to determine the structure of the active sites of growth factors, cytokines, and their cellular receptors to understand their role in cardiovascular, pulmonary, and blood diseases. This information will eventually enable the molecular design of growth factors useful in the prevention and treatment of cardiovascular and pulmonary diseases and in the treatment of blood cell production abnormalities, immunologic defects, and marrow suppression due to cancer chemotherapy.

The strategic plan for disease control and prevention includes a special emphasis on diet and fitness to promote good health, with particular reference to racial and cultural differences. Within this context, an NHLBI initiative will evaluate the effects of a wide range of dietary components and physical activity regimens on blood lipids and blood pressure, with an eye to developing a scientific basis for new recommendations to prevent cardiovascular diseases. This is an area of research that has enormous public health potential and will flower with enhanced scientific attention. A second prevention initiative focuses upon the role of exposure to oxidants in the development and clinical consequences of atherosclerosis. This research would include animal studies to assess oxidant and free-radical effects on the heart and the arteries and on longevity; small studies in humans of production of, protection from, and effects of oxidized, low-density lipoprotein; and a full-scale clinical trial of antioxidant and antithrombotic therapy in the prevention of cardiovascular diseases. Other studies, such as identification of risk factors and optimal management strategies for asthma, are important aspects of prevention research.

The initiatives described above represent only a sampling of the many exciting and timely scientific opportunities that exist today. Building upon a solid foundation of basic and clinical research, the Institute has achieved a balanced and comprehensive program that continues to gather momentum as new ideas, discoveries, and disciplines come into play. Maintaining that momentum, within the fiscal and administrative constraints that currently prevail, is a major challenge to the Institute. During the past year, the NHLBI and its Advisory Council addressed a range of issues that relate to sustaining its continued vitality and growth. The remainder of this report will elaborate upon these topics.

Cost Considerations

An issue of particular concern is the funding of new and competing renewal research project grants. Over the past several years, the NHLBI has wrestled with the increasingly difficult problem of selecting—from among numerous highly meritorious investigator-initiated grant applications—those that would allow the Institute to meet congressional mandates for numbers of competing awards without going over budget. In the past, the strategy was to pay grants according to scientific merit (that is, in order of their percentiled priority scores) but to limit costs through "downward negotiation" of the actual amount awarded.

Recent events made it clear that other approaches were needed. Specifically, the Congress directed the NIH to consider the total cost of research project grant applications and to avoid any downward negotiations in arriving at funding decisions. These additional constraints stimulated exploration of a number of methods for introducing the concept of cost- effectiveness into the assessment of grant applications. Specifically, the NHLBI developed a "value function" model that can be used to rank grants according to a mathematical score that reflects both scientific merit and cost, with scientific merit receiving the lion's share of weight. Application of this function makes it possible to highlight a "gray area" of grants near the margin that merit closer examination in terms of cost-effectiveness. When faced with grants having similar percentile ranks but widely varying resource requirements, for example, the Institute may opt to fund a handful of modestly priced grants rather than a single costly grant. On the other hand, the Institute may elect to support an expensive grant if it is in an area of high program priority.

This approach was discussed in detail at the September 1991 meeting of the Advisory Council. The Council expressed its support through passage of the following motions:

- That cost be made a factor in funding considerations; that is, adopt the concept of the value function model.
- That the scientific judgment of staff be inserted into the funding decision given their overview of all applicants, the variability of judgments between the study sections, and their knowledge of where the science is, and hence, the need for support. It is also recommended that the Director report on this issue to the Council as appropriate.
- That NIH, by all means possible and appropriate, educate the Congress, the Administration, the health professions, and the public as to NIH's efforts to improve the management and the use of fiscal resources it is responsible for and that a special effort be made to present the achievements of the biomedical enterprise and its contribution to the economic well-being of the Nation.

The value function approach was subsequently used for the first time to assist NHLBI funding decisions following the October 1991 Council meeting. Had the Institute made awards according to straight percentile ordering, only 139 applications that had percentile scores of 18.9 or less could have been funded within the available dollars. Using the value function, the Institute was able to identify a number of grant applications for special programmatic and cost review. After much thought and discussion, the decision was made to skip over three relatively costly applications near the margin. As a result, a total of 161 applications could be funded, all of which had percentiles of 21.8 or less. Thus, the net impact of the value function analysis was an increase of 18 awards over what would have been funded had NHLBI continued to rely solely upon percentiles.

Program Projects

Certain funding mechanisms, by virtue of their inherent high cost, tend to be identified by the value function as possible candidates for special consideration. The program project grant, with an average yearly cost in excess of $1.2 million, is such a mechanism and has thus been the focus of considerable discussion. Beginning with fiscal year 1992, the

NHLBI instituted new procedures for handling program projects that fall within the "gray area" of the value function described above and would not be selected for funding. Such grants are disaggregated into their component research subprojects, each of which has an individual percentiled priority score and a cost that includes a proportionate share of the program project's core costs. These research subprojects, now reborn as regular research grants (R01s), are then reintroduced into the value function model and considered for funding as any other grant. This strategy enables the Institute to preserve the most meritorious aspects of program projects with moderate priority scores, yet meet its goal of paying the congressionally specified number of research project grants within the available budget.

The Advisory Council strongly endorses continued support for this vital mechanism. The program project grant has proved to be a very important mechanism for accomplishing research that the NHLBI is mandated to support. These grants not only enable support of a large number of investigators from a diversity of disciplines but also facilitate maintenance of an appropriate balance between cardiovascular, pulmonary, and hematologic research.

Research Centers

The previous Advisory Council report highlighted research centers as a critical area of progress and opportunity, and the message bears reiteration. Overall, 70 to 80 percent of NHLBI-supported clinical research is conducted in its research centers; for a number of disease areas, centers are the exclusive source for NHLBI support of clinical research. Over the years, the research conducted by Institute-supported centers has contributed directly to improvements in the public health and reductions in health care costs by developing new approaches to diagnosis, treatment, and prevention.

Currently, the Institute supports 64 centers in 15 subject areas. Our last report urged development of centers in four new areas: vascular biology and medicine, sudden cardiac death, heart failure, and bone marrow transplantation. A fifth topic, pediatric cardiovascular disease, is an additional area of scientific opportunity that should be addressed by a new centers program. Pediatric cardiovascular diseases, including congenital heart disease, rheumatic heart disease, Kawasaki disease, and arrhythmias, are a significant source of morbidity and mortality in the United States. The advancing state of knowledge in many basic science areas—biochemistry, molecular biology, genetics, bioengineering—presents new opportunities for understanding normal and abnormal cardiac development. Establishment of multidisciplinary research centers in pediatric cardiovascular disease will facilitate the full and rapid expansion of these opportunities.

Population-Based Studies

The past year marked the successful conclusion of three major NHLBI clinical trials: the Systolic Hypertension in the Elderly Program (SHEP), the Studies of Left Ventricular Dysfunction (SOLVD), and the Cardiac Arrhythmia Suppression Trial (CAST). SHEP found that treatment of isolated systolic hypertension, a common condition in older persons, resulted in average five-year reductions of 36 percent for stroke, 27 percent for coronary heart disease, and 32 percent for all cardiovascular events. SOLVD demonstrated that treating chronic congestive heart failure with an angiotensin-converting-enzyme inhibitor, enalapril, reduced overall deaths by 16 percent and deaths or hospitalization for heart failure by 26 percent. CAST was halted upon determination that use of the drug moricizine resulted in a significant number of excess deaths in heart attack survivors who had mild arrhythmias. The results of these trials have enormous implications, not only for the survival and quality of health of patients with such conditions, but also for the costs associated with their care.

Because many interventions—pharmacologic, surgical, or hygienic—are used without an adequate scientific basis, an urgent need exists for clinical trials to evaluate experimental interventions. Given sufficient funds, NHLBI has developed plans for trials in such diverse areas as evaluation of prevention

and treatment strategies for peripheral arterial disease, comparison of various regimens of beta-2 agonist therapy for asthma, determination of the risks and benefits of T-cell depletion of bone marrow for allogeneic transplantation, and the use of hydroxyurea in sickle cell disease. The Advisory Council expresses its strong support for clinical trials and other population-based studies as research mechanisms of demonstrated utility that can rapidly bring new scientific knowledge into clinical practice.

Conclusion

Considerable progress has been made in the Institute's quest to reduce the toll of heart, blood vessel, lung, and blood diseases and to meet the Nation's need for blood resources. But much more remains to be accomplished. In this age of great progress and promise for biomedical research, the Council supports the Institute in its efforts to capitalize fully upon the myriad scientific opportunities that unfold.

National Heart, Lung, and Blood Advisory Council

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