XVII.
National Heart, Lung, and Blood Institute

INTRODUCTION

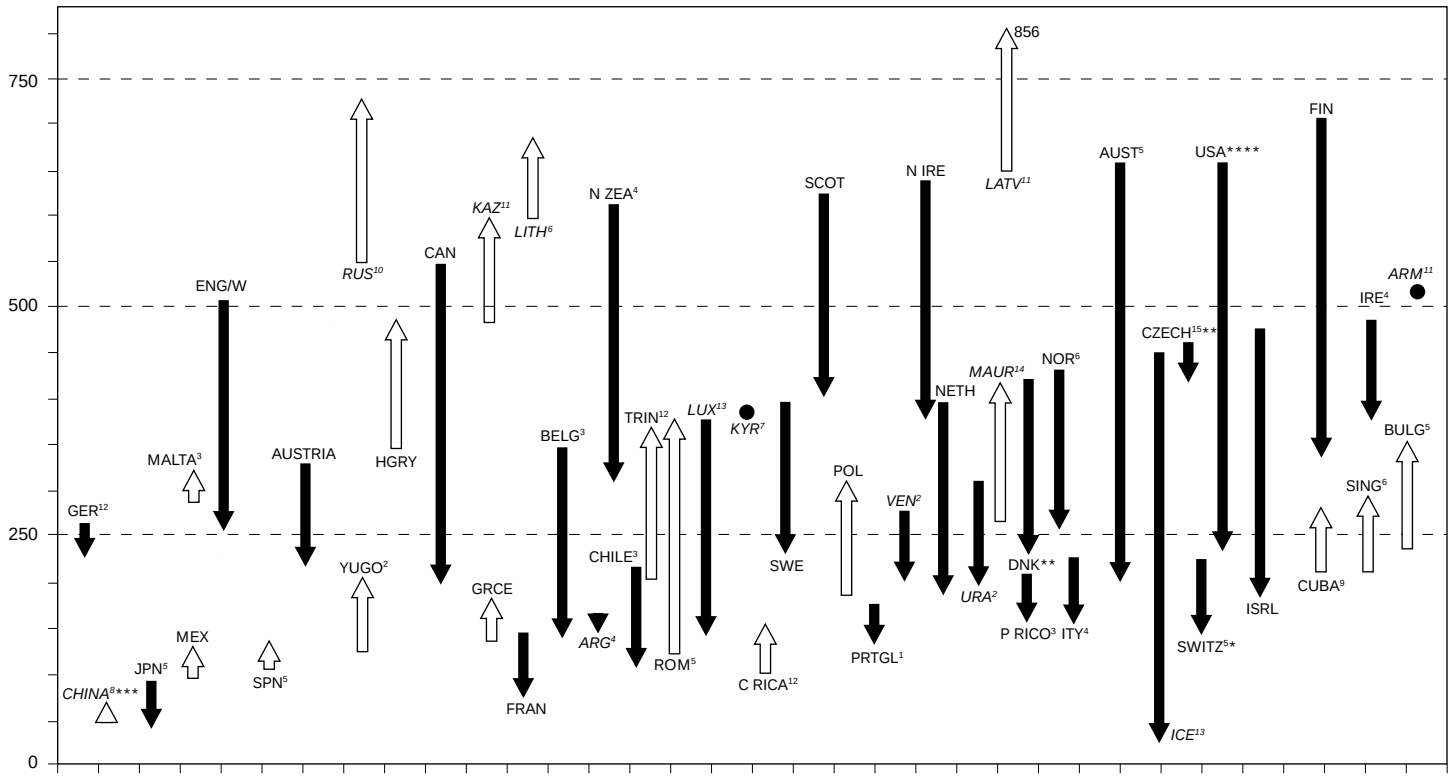
New medical technologies and telecommunications are transforming approaches to the diagnosis, treatment, and prevention of cardiopulmonary disease. Scientific discoveries at the molecular and cellular levels are being made at an incredible pace. Almost every day there are new breakthroughs in our understanding of treatment and intervention strategies, and the interest in developing international collaborations to meet future health challenges has never been greater. World peace has made regional and global initiatives more feasible, and improved funding for research in many countries has generated new opportunities for international partnerships in areas of mutual interest and benefit.

The World Health Organization (WHO) is making renewed efforts to bring attention to the economic consequences of cardiopulmonary disease, especially for countries with increasing populations of older adults. Many developed and developing nations are experiencing the "epidemiologic transition"—from focusing on infectious diseases and their consequences to dealing with the projected number one cause of disability and death, cardiovascular disease (CVD) (Murray CJL, Lopez AD. The Global Burden of Disease. Cambridge, MA: Harvard University Press, 1996).

The international collaborative activities of the National Heart, Lung, and Blood Institute (NHLBI) during fiscal year 2000 (FY 00) generated significant research results. Articles resulting from NHLBI's bilateral collaborative programs are referenced in the section on "Country-to-Country Activities

FIGURE XVII-1.

Death Rates for Coronary Heart Disease, by Country, for Men Ages 35–74 Years, 1970 and 1997 or Closest Year



Rates per 100,000 population. Age adjusted to European Standard Population.
Rates are based on *International Classification of Diseases, 8th revision (ICD-8),* for years before 1979 and on *ICD-9* for years after 1979.
*Rates for all years for Switzerland (SWITZ) are based on *ICD-8.*
**Rates for years beginning in 1994 for Czech Republic (CZECH) and Denmark (DNK) are based on *ICD-10.*
***Rate is for rural areas of China. Rates for urban areas were 71.2 and 99.6 per 100,000 population.
****Rates for the United States (USA) are based on *Public Use Mortality Data Tapes,* National Center for Health Statistics, Centers for Disease Control and Prevention, 1997.
Source: World Health Statistics Annual. WHO (selected issues).

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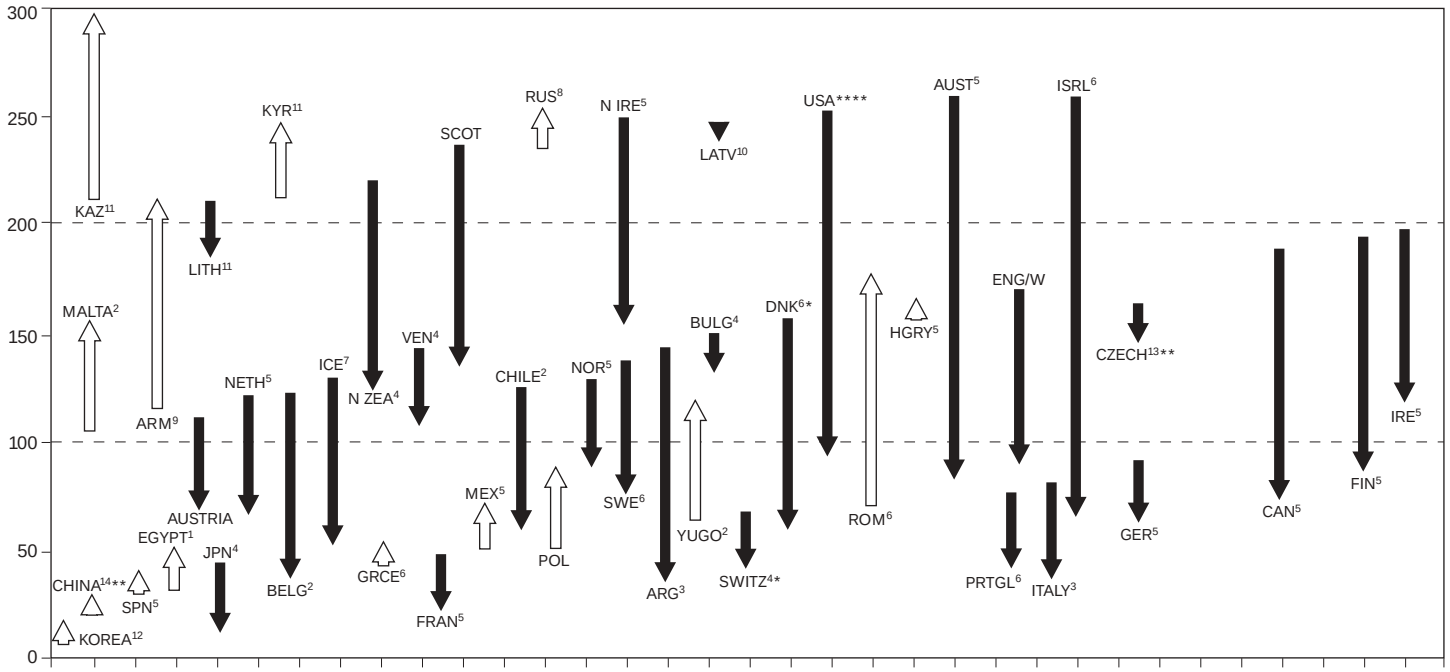
FIGURE XVII-2.

Death Rates for Coronary Heart Disease, by Country, for Women Ages 35–74 Years, 1970 and 1997 or Closest Year



Rates per 100,000 population. Age adjusted to European Standard Population.
Rates are based on *International Classification of Diseases, 8th revision (ICD-8),* for years before 1979 and on *ICD-9* for years after 1979.
*Rates for all years for Switzerland (SWITZ) are based on *ICD-8.*
**Rates for years beginning in 1994 for Czech Republic (CZECH) and Denmark (DNK) are based on *ICD-10.*
***Rate is for rural areas of China. Rates for urban areas were 61.4 and 69.0 per 100,000 population.
****Rates for the United States (USA) are based on *Public Use Mortality Data Tapes,* National Center for Health Statistics, Centers for Disease Control and Prevention, 1997.
Source: World Health Statistics Annual. WHO (selected issues).

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and Bilateral Agreements." This progress provides a strong framework for pursuing the core mission of NHLBI to improve the health of Americans by supporting and conducting research to prevent, detect, diagnose, and treat cardiovascular, lung, and blood diseases and sleep disorders and to ensure a safe blood supply. Among the mechanisms developed to support this mission are partnerships with U.S. universities and research institutes, other Federal agencies, international organizations, and private sector scientific, professional, and public organizations. Using mechanisms designed to obtain high-quality scientific outcomes, the Institute performs the following functions:

- plans, conducts, fosters, and supports basic research, clinical trials, observational studies, and demonstration and education projects;
- plans and directs research in the development, trial, and evaluation of disease interventions and medical devices;
- conducts research on the clinical use of blood and the management of blood resources;
- supports research training and career development of new and established researchers; and
- conducts educational activities, including the development and dissemination of materials for health professionals and the public, with a special emphasis on prevention.

Marked international differences in death rates from cardiovascular and pulmonary diseases, as seen in Figures XVII-1 through XVII-6, continue to raise important scientific questions about the reasons for these differences. The magnitude of these differences demonstrates the value of pursuing bilateral, multilateral, and regional approaches to achieve a better understanding of risk factors associated with cardiopulmonary health and disease. Through international collaboration, the prospect for developing joint programs to prevent and control coronary heart disease, stroke, and chronic obstructive pulmonary disease is strengthened. The NHLBI Strategic Plan on Health Disparities provides yet another basis on which to build increased understanding of international health disparities.

The Institute's international partnerships were expanded and strengthened in FY 00. Regional and global initiatives supported by NHLBI are summarized in the section on "Highlights of Recent Scientific Advances Resulting From International Activities." The Director, NHLBI, was elected president of the World Hypertension League for a 5-year term, a leadership role that will expand the influence of NHLBI's programs in many countries. Such arrangements, together with the Institute's broad research spectrum—including basic research, applied research and development, clinical investigation, population-based studies, and education, training, and development—ensure the prospect of further progress, building on past successes.

NHLBI's international programs during FY 00 were based on national research priority areas included in the National Heart,

TABLE XVII-1.

National Heart, Lung, and Blood Institute: International Activities, Fiscal Year 1999

	Arteriosclerosis	Hypertension	Cerebrovascular Disease	Coronary Heart Disease	Arrhythmias	Heart Failure and Shock	Cardiomyopathies and Infections of the Heart	Pulmonary Cell Biology	Chronic Obstructive Pulmonary Diseases	Pediatric Pulmonary Diseases	Occupational and Immunologic Lung Diseases	Respiratory Failure	Pulmonary Vascular Diseases	Bleeding and Clotting Disorders	Disorders of Red Blood Cells	Blood Resources	AIDS
Australia	•			•													
Canada	•			•	•				•	•		•					
China	•	•	•	•					•		•						
Germany	•	•	•	•					•		•						
India			•														
Italy	•	•		•				•	•	•							
Japan	•	•	•	•					•								
Korea				•													
Pakistan		•		•													
Poland	•	•	•	•	•		•		•								
Russia	•	•	•	•	•	•		•	•	•		•	•	•		•	
South Africa		•															
Uganda																	•
Vietnam															•		
Taiwan									•								

Blood Vessel, Lung, and Blood Program Plan developed by the Institute in collaboration with committees of extramural advisors. Table XVII-1 shows how the international programs intersect with these national research programs.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

The increased globalization of international scientific collaborative activities is reflected in three highlights for FY 00: (1) regional initiatives in hypertension; (2) prevention and control of pulmonary disease; and (3) international collaboration on women's health.

Regional initiatives in hypertension focus on increasing the awareness of hypertension in areas of the world where current and accurate baseline data on the prevalence, treatment, and control of hypertension are not readily available. The Pan American Hypertension Initiative and the Middle East Hypertension Initiative are both designed to bring together leading experts and Ministry of Health officials to develop mechanisms for collaborative exchanges of hypertension information and to develop joint protocols for pilot studies.

Efforts in prevention and control of pulmonary disease highlight World Asthma Day and the Global Initiative on Chronic Obstructive Pulmonary Disease. World Asthma Day was held to increase awareness of asthma as a global health care problem and to promote the implementation of effective management programs. The Global Initiative on Chronic Obstructive Pulmonary Disease is a collaborative venture to develop and implement global strategies for decreasing morbidity and mortality from chronic obstructive pulmonary disease (COPD).

International collaboration on women's health focuses on health promotion and disease control activities developed in partnership with other Institutes of the National Institutes of Health (NIH), the NIH Office of Research on Women's Health, and the Giovanni Lorenzini Foundation, Milan, Italy, and Houston, Texas. These activities address a broad spectrum of health problems associated with menopause in the United States and in other countries. These health problems include CVD, cancer, osteoporosis, and Alzheimer's disease.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

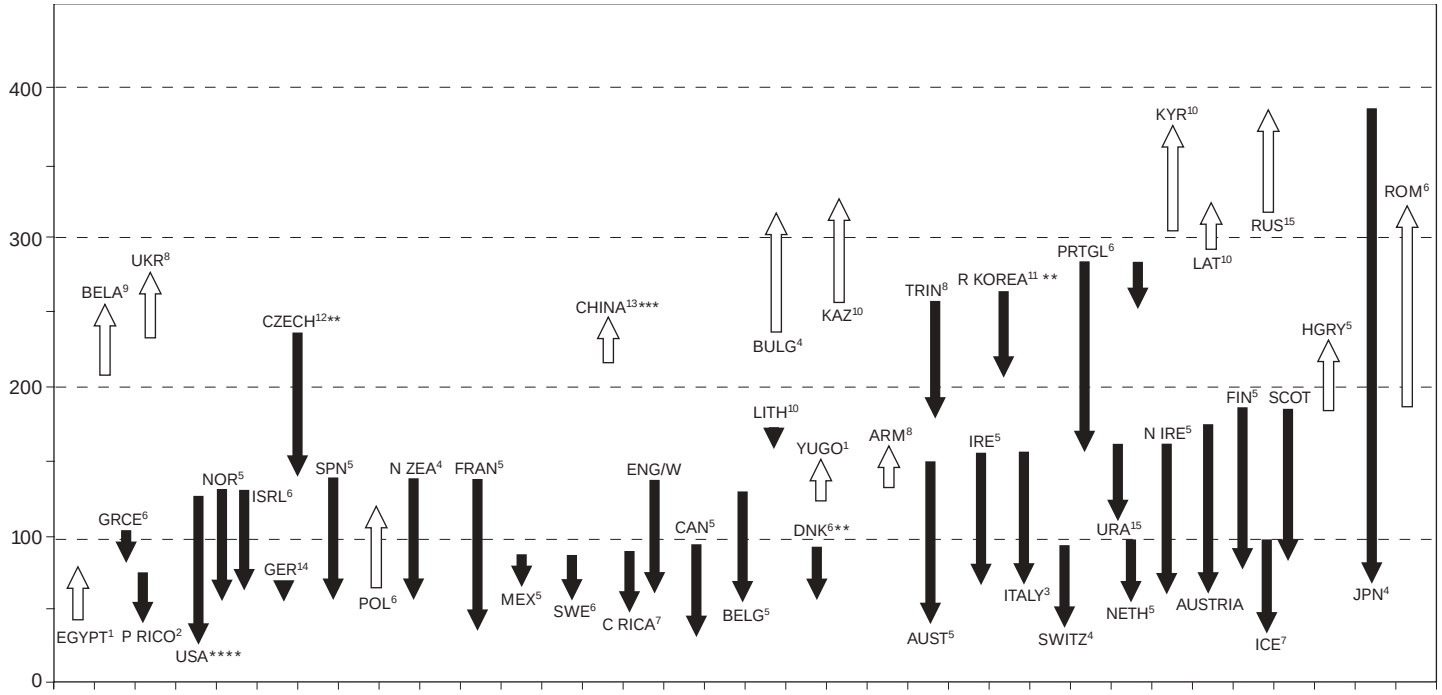
The NHLBI international programs and activities are carried out within the mandates of the National Heart, Blood Vessel, Lung, and Blood Program. The direct costs for NHLBI international activities for FY 00 are summarized in Table XVII-2.

Australia

Institute-supported researchers are participating in scientist exchanges and symposia with Australia, under the auspices of an agreement between NHLBI and the Baker Medical Research Institute (BMRI), Victoria,

FIGURE XVII-3.

Death Rates for Stroke, by Country, for Men Ages 35–74 Years, 1970 and 1997 or Closest Year



Rates per 100,000 population. Age adjusted to European Standard Population.
Rates are based on *International Classification of Diseases, 8th revision (ICD-8),* for years before 1979 and on *ICD-9* for years after 1979.
*Rates for all years for Switzerland (SWITZ) are based on *ICD-8.*
**Rates for years beginning in 1994 for Czech Republic (CZECH), Republic of Korea (R KOREA), and Denmark (DNK) are based on *ICD-10.*
***Rate is for rural areas of China. Rates for urban areas were 246 and 251 per 100,000 population.
****Rates for the United States (USA) are based on Public Use Mortality Data Tapes, National Center for Health Statistics, Centers for Disease Control and Prevention, 1997.
Source: World Health Statistics Annual. WHO (selected issues).

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signed in 1997. The program was initiated in September 1997 with a visit by a senior research officer from the Lipoprotein and Atherosclerosis Laboratory, BMRI, who collaborated with a professor of cardiovascular physiology at the Cardiovascular Research Institute, University of California, San Francisco, in studies of platelet interactions with blood vessel walls. The Australian scientist's expertise on intracellular cholesterol trafficking and the role of apolipoprotein A-1 in cholesterol homeostasis complemented the U.S. researcher's studies of atherosclerosis. In July 1998, NHLBI supported a reciprocal visit to Australia by the U.S. researcher. Joint research has continued with a special emphasis on binding reactions between the P selectin receptor on the endothelial surface and the glycoprotein 1b-X-V complex on the platelet surface.

A joint U.S.-Australia symposium on Cardiac and Vascular Remodeling was held in Atlanta, Georgia, in November 1999. The presentations focused on new knowledge and expertise in remodeling, including platelet interactions with vascular endothelium and platelet glycoproteins, adrenergic and cholinergic influences in cardiac and vascular signaling, the role of the extracellular matrix in atherosclerosis and vascular disease, endothelial function in lipoprotein metabolism, neurohumoral control and vascular function, and molecular aspects of adrenergic signaling in the heart and vasculature.

As a result of this symposium, new joint research projects were planned for FY 00. In September 2000, a senior researcher and head of the Morphology and Electron Microscopy Laboratory, BMRI, worked with the chairman of the Department of Vascular Biology, Scripps Research Institute, La Jolla, California, on plasminogen activator inhibitor (PAI-1) elevation in the plasma, which produces a severe hypofibrinolytic state and is a risk factor for CVD. Much remains to be learned about the regulation of fibrinolytic systems in the vascular wall during remodeling. The researchers are continuing their collaboration by using three mouse models—hypertension, compensatory renal vascular hypertrophy, and carotid artery ligation.

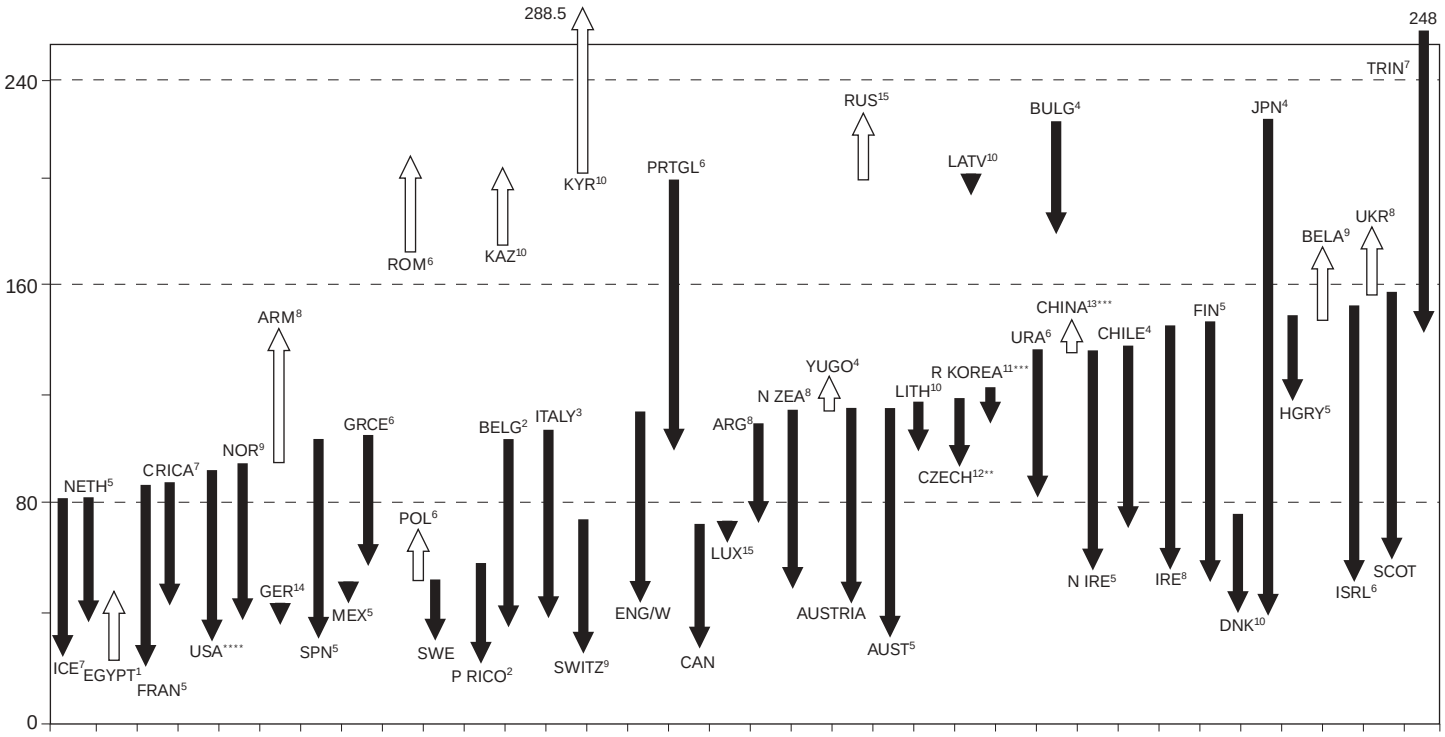
Canada

Research groups in Canada collaborate within the framework of clinical trials supported by NHLBI. Canadian research institutes may also participate on a subcontractual basis in work on grants held by a U.S. scientist.

Clinical trials are based on protocols that specify precise interventions and end points and validate new prevention and treatment regimens before they are introduced into medical practice. The requirement for large populations of patients often makes these studies expensive and difficult to perform. Collaboration with research centers in other countries enables NHLBI to maximize the information obtainable from a finite patient pool, to reduce costs, and, most importantly, to make valid comparisons of results in different populations.

FIGURE XVII-4.

Death Rates for Stroke, by Country, for Women Ages 35–74 Years, 1970 and 1997 or Closest Year



Rates per 100,000 population. Age adjusted to European Standard Population.
Rates are based on *International Classification of Diseases, 8th revision (ICD-8),* for years before 1979 and on *ICD-9* for years after 1979.
*Rates for all years for Switzerland (SWITZ) are based on *ICD-8.*
**Rates for years beginning in 1994 for Czech Republic (CZECH), Republic of Korea (R KOREA), and Denmark (DNK) are based on *ICD-10.*
***Rate is for rural areas of China. Rates for urban areas were 148.3 and 151.3 per 100,000 population.
****Rates for the United States (USA) are based on Public Use Mortality Data Tapes, National Center for Health Statistics, Centers for Disease Control and Prevention, 1997.
Source: World Health Statistics Annual. WHO (selected issues).

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Cardiovascular Diseases

Bypass Angioplasty Revascularization Investigation Trial. The Bypass Angioplasty Revascularization Investigation Trial is assessing the safety and efficacy of percutaneous transluminal coronary angioplasty and coronary artery bypass graft surgery in patients with multivessel disease and severe angina or ischemia who require revascularization and have coronary anatomy suitable for either procedure. Thirteen clinical centers, one of which is Canadian, and three coordinating centers are participating in this trial. The program was initiated in FY 87. Follow-up has been extended until 2003.

Postmenopausal Hormone Replacement Therapy After Coronary Artery Bypass Graft. Montreal Heart Institute, Quebec, and the University of Ottawa Heart Institute, Ontario, collaborate with Johns Hopkins University, Baltimore, Maryland, in a randomized, double-blind, controlled trial testing the hypothesis that postmenopausal hormone replacement therapy in women after coronary artery bypass surgery will reduce the occurrence of graft occlusion and delay the development of graft atherosclerosis. The study is funded through 2002.

Lung Disease

Lung Health Study II. The study of early intervention for COPD in nine U.S. centers and one Canadian center was designed to determine whether special care is more effective in slowing the rate of decline of pulmonary function in a population of smokers with mild pulmonary function abnormalities than referral to usual care. This study was merged into the Lung Health Study II, which aims to determine whether patients with COPD who are assigned to inhaled corticosteroid treatment have a lower rate of decline of pulmonary function and lower incidence of respiratory morbidity than similar patients assigned to placebo treatment. Ancillary studies include the effect of inhaled corticosteroids on adrenal sufficiency, bone mineral density, and osteocalcin levels. The study was completed in FY 00, and the report on the primary end point is scheduled for publication during FY 01.

Clinical Centers for Childhood Asthma Management Program. The primary objective of the Clinical Centers for Childhood Asthma Management Program is to determine, in a population of 5- to 9-year-old children with asthma, whether regular use of either of two classes of anti-inflammatory medications (inhaled corticosteroids or cromolyn sodium), compared with regular bronchodilator medication and with each other, results in greater lung function and less bronchial hyperresponsiveness over a 5-year period. The enrollment is 1,041 subjects, including 123 from Toronto, Ontario. The medical intervention aspect of the study concluded in the fall of 1999, and follow-up is in progress. The study was extended for 4

TABLE XVII-2.

National Heart, Lung, and Blood Institute: International Programs, Direct Costs, Fiscal Year 2000

	Number	Countries	Funds paid (in dollars)
Grants	3	Australia	486,305
	1	Belgium	113,576
	9	Canada	1,883,540
	1	Israel	125,000
	1	Spain	45,555
	2	United Kingdom	366,730
Fellowships	1	Australia	26,916
	1	Canada	36,936
	1	New Zealand	26,916
	1	United Kingdom	33,516
Cooperative Agreements	3	Canada	587,393
Total Awards	24		3,732,383
Centers for Disease Control Contract	1	China	20,000
University of North Carolina Contract	1	China Pakistan Poland Russia	434,839
Bilateral Agreements[a]	14		315,400[b]
International Bioethics Educational and Career Development Award Program			300,000[a]

[a] Collaborating countries pay for costs in their own country.
[b] Funds expended by NHLBI in United States.
[c] Funds paid to John E. Fogarty International Center for Advanced Study in the Health Sciences.

years as an observational trial to monitor the children for long-term effects.

There are many grants that include a Canadian component in both the cardiovascular and pulmonary disease areas. Nine grants were awarded to institutions in Canada for research projects in genetics, sickle cell disease, human immunodeficiency virus (HIV), lung volume reduction, and chemokines in lung disease.

During FY 00, cooperative agreements were used to carry out collaboration between NHLBI and Canadian universities. NHLBI worked with the University of Calgary, Alberta, under a cooperative agreement, in joint studies of pulmonary embolism that are funded to 2005. Under another cooperative agreement, NHLBI collaborated with the Hospital for Sick Children, Toronto, in a study of patients with thalassemia major, to compare the efficacy of the iron-chelating agent deferoxamine, administered by subcutaneous bolus injections or 8-hour subcutaneous infusions (standard therapy). This agreement is funded to 2003.

China

Formal scientific exchanges between NHLBI and China began in 1981 and continue through to the current U.S.-China Agreement in Health, signed in October 1998. Joint protocols were developed for epidemiologic studies in China that could be linked with comparable U.S. studies. The goal was to develop expertise, technology, and personnel for epidemiologic research in China, by using internationally standardized methods to carry out cross-sectional and prospective population studies on cardiovascular and pulmonary diseases and their risk factors. To ensure comparability of data on rates and trends of disease, the studies have involved the Collaborative Studies Coordinating Center, University of North Carolina, Chapel Hill, and the Centers for Disease Control and Prevention, Atlanta, Georgia. Joint articles based on comparative data generated from this exchange program continue to be published.

Initial joint studies in 1983–1985 included more than 10,000 men and women divided into four groups (Beijing and Guangzhou, urban and rural). All four groups have had follow-up for deaths, disease events, and trends in risk factors. Data have been collected over many years to determine the development of hypertension, acute myocardial infarction, and stroke and the occurrence of sudden death in the study participants. The results show that, with new trends in socioeconomic development and new patterns of disease, prevention of cardiovascular and pulmonary diseases is an urgent public health task in China.

A series of joint publications have resulted from the U.S.-China collaboration, including a Data Preview on Electrocardiographic Data, published in English, in September 1999. Two articles were published in the International *Journal of Epidemiology* during FY 00: "Serum uric acid and its correlates in Chinese adult populations, urban and rural, of Beijing" and "Electrocardiographic findings between northern and southern Chinese population samples."

The fourth and final survey for these studies was completed in the spring of 1999. The objectives were to (1) measure major cardiovascular and cardiopulmonary risk factors among the four Chinese populations being studied in North and South China; (2) compare major risk factors among these populations; (3) compare changes in major risk factors with baseline levels; and (4) explore associations between changes in socioeconomic status and trends of CVD risk factors. The United States provided the supplies and spare parts for laboratory equipment needed to conduct the testing of the participants in the Chinese study. A joint working meeting was held in Chapel Hill, North Carolina, on November 3–6, 1999, to review the results from the fourth survey and the progress made on laboratory tests that provide crucial data for the joint epidemiologic studies.

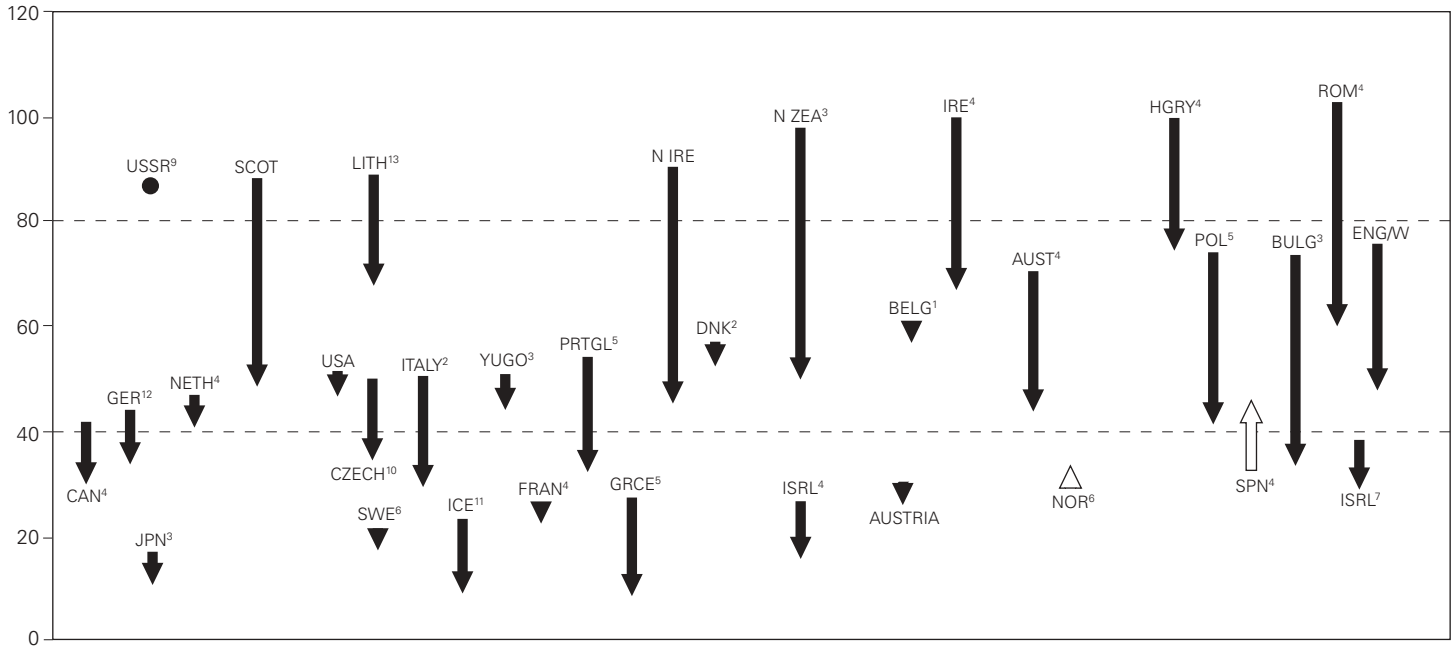
Plans have been made for the 20th Anniversary of the U.S.-China Collaboration in Cardiopulmonary Research, to be celebrated at a joint U.S.-China meeting in Beijing, in June 2001.

Germany

The United States and Germany are cooperating in biomedical research under an agreement signed in 1976 and renewed periodically since then. The cooperation encompasses research on cardiovascular and

FIGURE XVII-5.

Death Rates for COPD and Allied Conditions, by Country, for Men Ages 35–74 Years, 1980 and 1997 or Closest Year



Rates per 100,000 population. Age adjusted to European Standard Population.
Rates are based on *International Classification of Diseases, 9th revision (ICD-9),* codes 490–496.
Source: World Health Statistics Annual. WHO (unpublished data).

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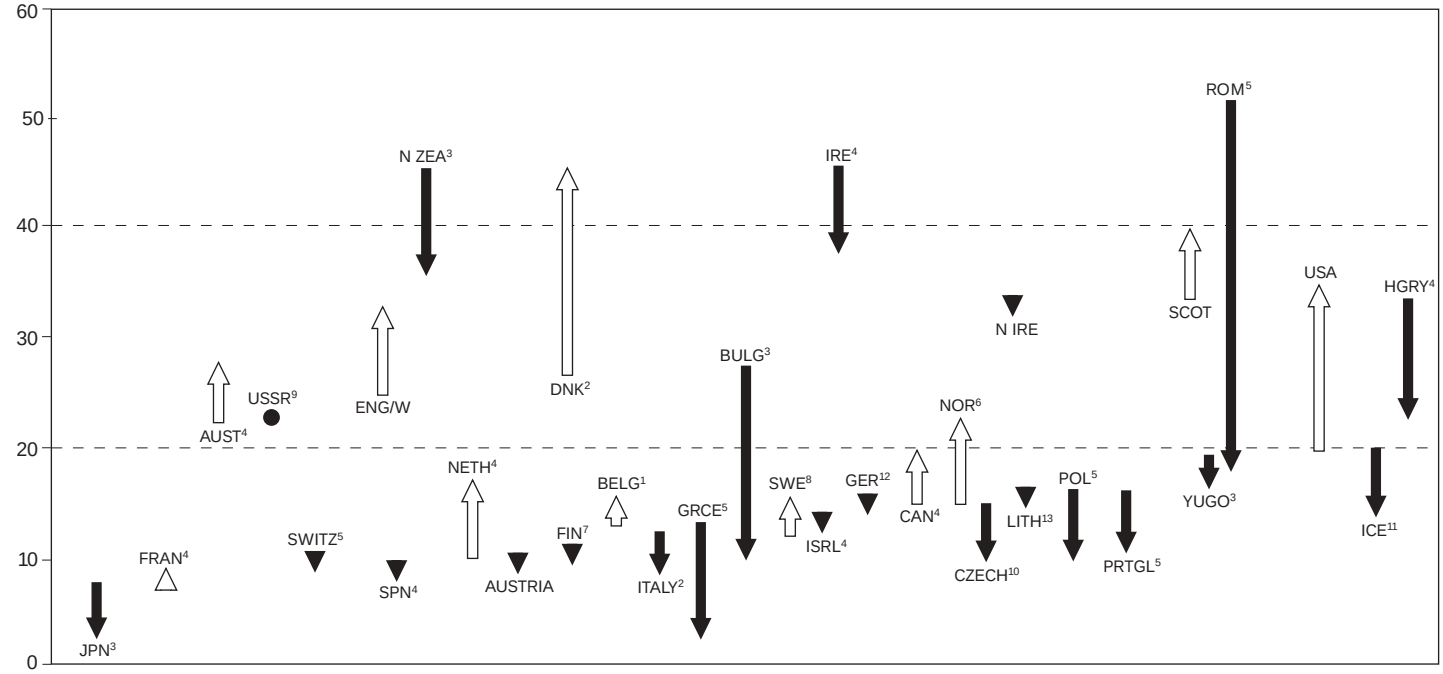
FIGURE XVII-6.

Death Rates for COPD and Allied Conditions, by Country, for Women Ages 35–74 Years, 1980 and 1997 or Closest Year



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Rates are based on *International Classification of Diseases, 9th revision (ICD-9),* codes 490–496.
Source: World Health Statistics Annual. WHO (unpublished data).

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pulmonary diseases and involves basic and applied research.

Since 1996, collaborations in the cardiovascular area have focused on genetics and animal models, including mapping the rat genome, creating cross-referenced reagents, and producing interdigitated maps. At a U.S.-German workshop in Toronto, scientists discussed the progress and status of human studies, the development of rat models, genetic mapping, cDNA (complementary DNA) libraries, bioinformatics, communications and shared technologies, and radiation hybrid panels. The completion of a high-density, integrated genetic linkage and radiation hybrid map is a landmark in the field of genomic science. This map is considered to be a major, central, and essential resource for understanding genetics in the rat *(Rattus norvegicus)*—one of the primary animal models for human medical research. The map was a collaborative effort of several groups, including researchers at the Medical College of Wisconsin, Milwaukee, and the Whitehead Institute at Massachusetts Institute of Technology, Boston.

In December 1999, a meeting on U.S.-German cooperation was held during the Physiological Genomics and Rat Models Meeting, in Cold Spring Harbor, New York. U.S. and German investigators compared their progress in developing data sets and libraries in each country, for joint research. Topics discussed included genomics, bioinformatics, expression profiling, comparative mapping, complex trait analysis, model systems, transgenics, and pharmacogenomic risk assessment.

In May 2000, the Director, NHLBI, participated in a U.S.-German meeting, in Bonn, on collaborations in vascular research by NHLBI and the Association of Clinical Research Centers of German Universities. Mutual interests and priorities were shared in anticipation of future joint collaborations under the auspices of the bilateral exchange program.

The collaborations in the pulmonary area have focused on basic and clinical research on asthma. Prevalence of asthma has been increasing in Western industrial countries over the past 30 years. Because one-half of all asthma cases are diagnosed by age 3 years and 90% are diagnosed by age 6 years, factors associated with the early onset of asthma are of primary interest. U.S. and German researchers are studying genetic and environmental factors operating in utero and immediately postnatally, which may influence the early onset of asthma.

During FY 99 and FY 00, collaborative interest focused on evaluating dietary factors that may influence the development of asthma in early life. Analyses by researchers at the Channing Laboratory, Brigham and Women's Hospital, Boston, Massachusetts, and the Munich Children's Hospital suggest that obesity and dietary fats, particularly margarine, may be related to asthma and atopy. Changes in diet during pregnancy, especially in the consumption of vitamins and polyunsaturated (N-3 and N-6) and saturated fatty acids, are exposures that may explain the increase in allergy and asthma. The researchers have also identified strong associations between body mass index and asthma and atopy, on the basis of data developed in the U.S. National Health and Nutrition Examination Survey on 3,000 children aged 4–17 years.

India

NHLBI has collaborated with scientists in India for more than 20 years. Currently, U.S. and Indian researchers are conducting joint research under the terms of the Gandhi-Reagan Science and Technology Initiative begun in 1982. Joint projects are reviewed for support by the Indo-U.S. Science and Technology Subcommission. In addition, in-country support is provided by NHLBI.

An NHLBI Nobel Laureate and Chief of the Laboratory of Biochemistry and Genetics and an emeritus scientist in the Department of Biochemistry, All India Institutes of Medical Sciences, New Delhi, continue their joint research. The scientists are using the latest molecular biology techniques in joint studies of the development and differentiation of the nervous system.

This collaboration has resulted in new discoveries, leading to a series of publications, including a report on "An IL-6 (interleukin 6)–mediated growth loop in the human glioblastoma multiforme cell line U87-MG" and a report on "Monoclonal antibodies against human glioblastoma multiforme (U87-MG)." Two other articles, one on "A device for transplantation of single cells" and another on "A device for single-cell transplantation with minimal transfer of suspension fluid," report on a new technology for transplanting single identified cells into specific regions of the brain with a high degree of precision. The Indian investigator is using this device to microinject cells into neonatal and adult brains and to evaluate the state of transplanted cells by species-specific monoclonal antibodies.

The joint project has resulted in the generation of a monoclonal antibody ($6DS_1$) against a human glioblastoma multiforme cell line that recognizes the 38-kilodalton, cell-surface antigen on glial tumors. The scientists have also purified the antigen protein from the glioblastoma multiforme cell line U87-MG and have used it to produce hybridomas secreting monoclonal antibodies that may recognize specific epitopes on this protein. It is anticipated that this joint research could lead to the development of a diagnostic tool for histopathological grading and localization of human brain tumors.

Another study focuses on immortalization of human fetal neurons, the role of trophic factors in their survival, and the study of apoptopic features of selective neuronal death during aging of neurons in culture. The goals are to culture and immortalize human neuronal cell lines and introduce these cells into the rodent central nervous system to assess their differentiation potential. The project is expected to continue toward the genetic manipulation of neurons in culture, immortalizing them, and identifying changes in their gene expression during aging. In addition, during the most recent exchange visit to NHLBI, the investigators initiated joint studies on neurogenesis and neural cell lineage, using *Drosophila* as a model system.

Italy

NHLBI and Italian scientists have collaborated in research under bilateral agreements for more than 20 years. The current joint research effort with Italy is conducted under the auspices of (1) the 5th U.S.-Italy Science and Technology Agreement, signed in Washington, D.C., on November 5, 1997, and (2) a joint statement on international cooperation, entitled A New Partnership for a New Century, signed on May 6, 1998, by President Bill Clinton and Prime Minister Romano Prodi. Under these agreements, NHLBI and the Institute of Pharmacology, University of Milan, collaborate on specific

cardiovascular and pulmonary research projects of mutual interest and benefit.

The most recent U.S.-Italy symposium in cardiovascular research was held at the University of Milan, in December 1999. Topics included genetics and gene therapy; gene transfer studies in hyperlipidemic animals, including intracellular signaling of smooth muscle cells after vascular injury; pharmacogenetics; genetic epidemiology; phenotype expression of genetic cardiomyopathies; the genetics of cardiac morphology and function, including the sustained correction of CVD by using adeno-associated virus vectors; and mitochondrial DNA defects associated with cardiomyopathies. A summary of this meeting, signed by representatives of the United States and Italy, in March 2000, included an agreement to continue the bilateral cooperation in CVD research.

A U.S.-Italy workshop on Biochemical Markers and Assessment of Lung Diseases: Prognostic, Diagnostic, and Therapeutic Implications was held in Palermo, on October 14–15, 1999. Topics included markers of chronic infection and inflammation and remodeling in asthma; the analysis and significance of cells and chemicals in sputum, in asthma and in COPD; genetic susceptibility to lung cancer; assessment of sleep-disordered breathing and its sequelae; and the potential clinical role of biological markers (biomarkers) in the early detection of lung cancer.

These joint symposia have generated collaborative research projects in a number of areas. For instance, U.S. and Italian scientists are cooperating on research in vasoconstriction in the liver. This project is a collaboration between New York Medical College, Valhalla, and the Institute for Clinical and Experimental Medicine, Padua. The scientists are studying impairment of renal function in patients with cirrhosis, vasoconstrictors produced in the liver or introduced by portal inflow, and pathogenesis of hepatic portal hypertension. As a result of this joint effort, the researchers have developed new pharmacological approaches to this clinical problem.

A researcher from the Department of Pulmonary Pathophysiology, Italian National Research Council, collaborated with a scientist at the University of Wisconsin, Madison, during the summer of 2000. The aim of the project was to assess whether hypoxia (too little O_2 in the blood) and hypercapnia (too much CO_2 in the blood) affect arterial baroreflex function in healthy subjects. Previous data by the Madison research group showed that asphyxia increases muscle–nerve sympathetic activity in healthy, awake subjects. In patients with sleep-disordered breathing, the increase in muscle–nerve sympathetic activity persists for some time after return to normoxic conditions. This finding suggests a potentially important mechanism for the pathogenesis of hypertension.

NHLBI's cooperation with Italy has expanded to place new emphasis on research in women's health. The Associate Director for International Programs, NHLBI, served on the international planning committees of the 1st, 2nd, and 3rd International Symposia on Women's Health in Menopause, which were held under the auspices of the Italian national Campaign on Women's Health and Menopause. The third symposium, on Risk Reduction Strategies and Improved Quality of Health, was held in Venice, Italy, in October 1999. Also, in follow-up to the second symposium, the Women's Health Initiative program of NHLBI and the NIH hosted a series of meetings with representatives of the Giovanni Lorenzini Foundation, in Bethesda, Maryland. These meetings, involving an international working group of about 20 prominent scientists, researchers, and clinicians from a variety of medical and biomedical disciplines relevant to this field of research, focused on the development and publication of an international position paper on state-of-the-art knowledge of a broad spectrum of health problems associated with menopause. This document will be presented during the 4th International Symposium on Women's Health and Menopause, in May 2001, in Washington, D.C. It is anticipated that this presentation will lead to new strategies for the promotion of women's health in the future.

Japan

NHLBI has collaborated with Japan for more than 20 years in a series of joint projects in CVD research, providing unique opportunities for comparative studies and new insights into differing patterns of disease in the two countries. Significant differences in patterns for stroke and coronary heart disease have been found. These observations led to comparative studies focusing on four areas: (1) dietary studies of the positive or negative effects of calcium and potassium intake, physical exercise, and alcohol use on hypertension; (2) studies of the progression of hypertension in children, as a predictor of high blood pressure in adults; (3) pathology studies of intracerebral arteriosclerosis; and (4) community-based intervention for dietary and other risk factors.

NHLBI's current cooperation with Japanese scientists is based on a U.S.-Japan Agreement on Cooperation in Research and Development in Science and Technology, signed in June 1988 and renewed in June 1993. Periodic Summaries of Discussion outlining specific collaborative activities in basic research, epidemiology, and community studies have been signed by the Director, NHLBI, and the president of the National Cardiovascular Center, Osaka. The most recent document was signed in April 1998 at the conclusion of a joint U.S.-Japan symposium in Nara. At that meeting, scientists reported the results of ongoing joint research, as well as new findings in genetic epidemiology.

The delegates to the U.S.-Japan symposium reported further increases in CVD risk factors in Japanese populations and marked differences in CVD patterns in the United States and Japan, as diets became more westernized. The prevalence of hypercholesterolemia has increased in Japan over the past 10 years. The incidence of stroke in Japan continues to be higher than that of acute myocardial infarction. The age-adjusted annual incidence of first stroke in 1997 was 99 in men and 58 in women per 100,000 population, and the incidence of acute myocardial infarction was 15 in men and 26 in women per 100,000 population. U.S. delegates reported on population trends in the prevalence and incidence of CVD in the United States; effective strategies for risk reduction of atherosclerosis; genetic epidemiology of CVD risk factors; and the use of whole-genome screens to find new genes for atherosclerosis susceptibility. Participants also discussed the economic and epidemiologic impact of hypertension and its treatment, as well as advances in health economics.

At the conclusion of the 1998 symposium, representatives of the United States and

Japan proposed to continue joint studies in four areas:

1. prevention of hypertension through diet and other nonpharmacological approaches;
2. high blood pressure and other cardiovascular risk factors among children and young adults;
3. comparative pathology studies of atherosclerotic and hypertension lesions; and
4. programs for community intervention and prevention of CVD.

A joint study continues between the director of the Minnesota Heart Program, University of Minnesota, Minneapolis, and the deputy director, Department of Preventive Cardiology, NCC, Osaka. The U.S. researcher gained new insights on stroke surveillance in Japan and shared methods used in the Minnesota Twin Cities Study. The scientists compared case ascertainment, stroke classification, and data collection, as well as ethical and legal barriers to surveillance projects. In June 1999, the Japanese investigator made a reciprocal exchange visit to the University of Minnesota, bringing with him a data set that was merged with the U.S. database for joint analyses. It is anticipated that a significant publication will result from this joint study.

Plans have been made for the U.S.-Japan Symposium on Genetic Epidemiology, to be held in Honolulu, Hawaii, in January 2001. Researchers from Japan and the United States will discuss current knowledge in gene discovery methods, including microarrays; identification of single nucleotide polymorphism markers in the DNA of diseased patients; evolving genetic epidemiology studies; genetic susceptibility to essential hypertension; hyperuricemia; thrombosis; and gene–environment interactions. Proposals for future joint research projects are expected as a result of this meeting.

Korea

NHLBI and Korean scientists are collaborating in basic research. The initial cooperation was established with the Korean Advanced Institute of Science and Technology under the U.S.-Korea Science and Technology Agreement, originally signed in 1976. A series of joint projects has been completed, focusing on the role of oxygen radical–mediated oxidation of proteins and lipids in different biological processes, including aging, atherosclerosis, ischemia–perfusion injury, and inflammation and signal transduction.

Collaboration between the Laboratory of Biochemistry, NHLBI, and the Research Center for Molecular Microbiology, Seoul National University (SNU), was initiated in 1992, expanded in 1995, and continued during FY 00. Two investigators from the Department of Microbiology, SNU, worked with NHLBI scientists at the NIH, in Bethesda, Maryland, in studies of free radicals and oxidative stress in the signal transduction pathway. Subsequently, an NHLBI researcher made a reciprocal visit to SNU. He presented the joint findings at the 8th Congress of the International Association of Biomedical Gerontology, in February 2000, in Kyongju, Korea. These findings were also published in the *Journal of Biological Chemistry*.

This collaboration focuses on free-radical generation mediated by the glycated proteins, which is monitored with electron paramagnetic resonance spectroscopic methods. Current data from animal pathology studies show that advanced glycation end products accumulate in animal tissue, resulting in atherosclerosis, diabetes mellitus, and aging. In addition, findings have shown that glycated proteins can function as catalytic centers for additional free-radical generation. These advanced glycated end products are associated particularly with long-lived proteins such as collagen, lens crystalline, and nerve proteins.

Additional joint studies by the NHLBI Laboratory of Biochemistry and SNU have focused on the transcriptional activation mechanism of the human gene for mitochondrial manganese-containing superoxide dismutase (MnSOD), which is mediated by tetradecanoylphorbol acetate during oxidative stress. Mitochondria are particularly prone to oxidative DNA damage, because they metabolize more than 95% of the oxygen. MnSOD is the primary defensive enzyme against oxidative stress and suppresses tumorigenicity. These results were published in the *Journal of Biological Chemistry* (December 1999).

In April 1999, NHLBI initiated a program of collaboration with the largest women's university in the world, Ewha Women's University, Seoul. This university has been designated a center of excellence by the Korea Science and Engineering Foundation. Under this agreement, Korea and the United States are exchanging scientists for joint research between Ewha's Center for Cell Signaling Research and NHLBI's Laboratory of Cell Signaling. Two Korean research associates initiated this exchange program, which began in August 1999 and is continuing into FY 00. The focus is on the basic research of peroxiredoxins, enzymes that eliminate hydrogen peroxide; their crystalline structure; the generation of peroxiredoxin-null mice; and the identification of proteins that contain hydrogen peroxide–sensitive cysteine residues during oxidative stress signaling.

Pakistan

The U.S.-Pakistan collaboration was designed in 1993 as a joint epidemiologic study to increase knowledge and awareness of CVD, its determinants, and effective ways to prevent it. One of the questions being explored is whether CVD prevention programs in the United States can be adapted to Pakistani subpopulations, to reduce rising rates of CVD morbidity and mortality. The aim of this community study is to expand the Pakistani capacity for CVD risk factor assessment and modification. The two groups of study participants are intervention families and control families, and their progress is being compared. Rescreening was initiated in September 1999 and was continuing as of August 2000. U.S. funding for the study ended in May 2000. Several joint research manuscripts have been prepared for publication. A joint article, "Planning and implementation of a cardiovascular prevention strategy in a lower middle class community in Pakistan—a preliminary report," was published in the *Journal of the College of Physicians and Surgeons,* Pakistan.

Poland

The NHLBI-Poland collaboration in CVD research began under the U.S.-Poland Agreement for Health Cooperation, signed in 1974. Specific cardiopulmonary research areas have been outlined in Summaries of Discussions between NHLBI and the Polish National Institute of Cardiology. The most recent document was signed in August 1998, in follow-up of a U.S.-Poland Joint Workshop in Cardiopulmonary Disease, in Rockville, Maryland, in March 1998.

Marked differences in trends in cardiopulmonary disease and risk factors in the

two countries are of special interest for joint research. For instance, although the magnitude of mortality from coronary heart disease was high in both countries from 1970 to 1997, U.S. death rates for persons aged 35–74 years declined by 66%, whereas the rates for a similar group in Poland increased by 48%.

Mortality for COPD declined slightly in the United States for men and significantly in Poland for men and women, during 1980 to 1997. However, COPD rates increased significantly for U.S. women during the same period (*World Health Statistics Annual,* WHO).

Findings in joint studies reinforced the risk of smoking, as evidenced by the marked increases in mortality due to smoking during the last two decades in Poland. In a population of adults aged 35–69 years, rates increased about 64% in men and almost 10-fold in women. Establishment of nationwide public health education and policies in the United States has been somewhat successful in reducing cigarette smoking. Poland has yet to introduce such policies. These differences in trends provide a focus for joint research into the etiology of cardiopulmonary diseases and their risk factors.

Since 1980, the Collaborative Studies Coordinating Center, Chapel Hill, North Carolina, has carried out joint analyses to compare epidemiologic data from the Pol-MONICA Study with data from the U.S. Lipid Research Clinics Program Prevalence Study (U.S.-Poland Collaborative Study) and the U.S. Atherosclerosis Risk in Communities study. These joint efforts by scientists in Warsaw, Kraków, and the United States have assessed the prevalence of cardiopulmonary diseases and their risk factors in urban and rural populations as well as differences in trends in the United States and Poland.

In May 2000, a working meeting was held in Kraków, where the collaborating scientists worked to complete a series of joint manuscripts on heart rate variability; hypertension incidence and mortality; smoking and lipids; correlates of weight gain; low lipid levels and mortality; comparisons of medical care; and community health surveillance correlates, including smoking trends and differences between stroke mortality trends in Polish populations and in African Americans and whites in the United States.

A final working meeting is planned for March 2001, to be held at the Collaborative Studies Coordinating Center, Chapel Hill. Epidemiologists from both countries will work to complete joint manuscripts on nutrition and lung function; trends in incidence of myocardial infarction; survival at 1 year after myocardial infarction; differences in cardiac autonomic control and hypertension; education and scores for risk of coronary heart disease; and correlates of obesity.

Russia

The NHLBI collaboration with Russia and the former Soviet Union has been ongoing for more than 25 years under a series of agreements. In February 1998, an agreement was reached to restructure the joint research into two main areas: CVD and pulmonary disease. The priority areas agreed on for CVD include basic research; prevention, education and control of heart disease, especially lethal arrhythmias; hypertension; continued joint epidemiologic studies; and management of ischemic heart disease. In pulmonary diseases, the priority areas are basic research, genetic studies, prevention, asthma, and pulmonary hypertension.

Three Russian scientists visited the United States on November 6–24, 1999. They participated in the American Heart Association Meeting, in Atlanta, Georgia, and visited laboratories in the United States. U.S. and Russian scientists developed joint research proposals in the areas of molecular genetic studies in patients with atrial fibrillation; clinical investigations of anti-arrhythmic effects of novel agonists of purinergic receptors in patients with supraventricular tachyarrhythmias; vessel remodeling; airway smooth muscle migration and fibrinolysis; and angiogenesis and cell signaling.

A Russian scientist conducted joint research with U.S. scientists at the University of Pennsylvania, in July–September 2000. The scientists investigated the interaction of urokinase with cell-surface receptors (uPAR/CD87, LRP/a_2-MR, and a novel kringle-binding target) and their role in urokinase-induced chemotaxis. A joint research proposal is being prepared for consideration for funding.

South Africa

Since 1996, the increasing prevalence of hypertension in both the United States and South Africa has led scientists in both countries to pursue collaboration through scientific exchange programs. During May 2000, NHLBI staff met with the South African Coordinator and U.S. scientists involved in the joint research, to review progress since the 1998 2nd U.S.-South Africa Workshop on Hypertension in Blacks and to discuss potential plans for continued exchange activities.

The 1998 workshop was held at the NIH, in Bethesda, Maryland. At that time, representatives of the United States and South Africa agreed to exchange scientists and information over the next 2 years in the following areas identified as high priority:

1. joint studies on salt sensitivity, body mass index, and hypertension;
2. hypertension in pregnancy;
3. community studies of hypertension prevention and intervention; and
4. exchanges between deans of U.S. and South African Schools of Public Health.

A South African scientist visited the United States in March–April 1999 to continue joint research on salt sensitivity in blacks with hypertension, with U.S. researchers in cardiovascular epidemiology and clinical applications, at Wayne State University, Detroit, Michigan. The scientists developed a joint protocol to ensure standardized methods for fieldwork and laboratory analyses that will be compared. A joint research proposal was prepared for consideration for funding. Information was exchanged between the deans of Tulane University, New Orleans, Louisiana, and the National School of Public Health, Medical University of Southern Africa, during FY 99.

The scientists are interested in exchanging information in the area of endocrine imbalances, salt sensitivity, and obesity. Plans for joint research will be developed for consideration by representatives of South Africa and the United States.

Uganda

A scientist from Case Western Reserve University, Cleveland, Ohio, is collaborating with researchers at the Joint Clinical Research Center, Kampala, on a study of the impact of tuberculosis on HIV disease. This joint research is investigating the hypothesis that the interaction of tuberculosis and

HIV during active tuberculosis predisposes the host to progression of HIV through both virological and immunologic events. The scientists are also exploring the central role played in the process by the interaction of macrophages with T cells. This research project began in 1999 and will continue for 5 years.

Vietnam

NHLBI cooperates with the Blood Transfusion and Hematology Center, Ho Chi Minh City, and the National Institute of Hematology and Blood Transfusion, Bachmai University Hospital, Hanoi, on blood disease research, including aplastic anemia and hepatitis. This collaboration, which began as an extension of the 10-year, U.S.-Thai cooperation, has been under way since 1993. Joint training seminars and exchanges of scientists for joint research have taken place annually.

Vietnamese coordinators, including the Director, Blood Transfusion and Hematology Center, and the Director, National Institute of Hematology and Blood Transfusion, visited the NIH in December 1999. They reviewed the status of ongoing research, discussed potential joint research projects, and attended meetings of the American Society for Hematology, in New Orleans, Louisiana.

The scientists hypothesize that the same virus that causes hepatitis/aplastic anemia may also be responsible for fulminant hepatitis of childhood and non A–non G (seronegative) acute viral hepatitis. Difficulties in isolating viral genomic sequences from samples of tissue from patients with hepatitis, aplastic anemia, and fulminant hepatitis may result from complications occurring weeks or months after acute infection or may occur because cells in the samples are scanty and there is degradation of DNA and RNA. It is therefore important to obtain samples from patients early in the course of their disease, as in acute viral hepatitis. The scientists plan to perform serological studies of hepatitis G virus and other viruses as samples from Vietnam become available. Exchanges of scientists may be pursued in conjunction with collaborative studies on non A–non G acute viral hepatitis. A formal protocol has been approved by the NHLBI Institutional Review Board. The longer-term objective is to obtain approvals from the Office of Protection From Research Risks for potential clinical trials.

The Chief, Hematology Branch, Intramural Research Division, NHLBI, visited Hanoi and Ho Chi Minh City, in March 2000, with two extramural scientists. They presented lectures on hemostatis and blood coagulation. Discussions focused on research related to seronegative acute hepatitis. Potential exchanges of scientists for research on asthma, a common and serious problem, especially in Vietnamese children, were also discussed.

A Vietnamese scientist from Hanoi worked with the Chief, Hematology Branch, Intramural Research, NHLBI, in November 1999–March 2000 to continue joint studies on bone marrow transplantation, transfusion of blood components, and treatment of patients with hematologic malignancies. Work began on laboratory research for the collection of blood specimens and tissues, with use of approved protocols.

A Vietnamese scientist visited NHLBI in September–December 2000 for joint research focusing on molecular biology and the application of gene amplification to laboratory hematology.

Taiwan

U.S.-Taiwan exchange activities for research on asthma were developed in follow-up of the August 1999 visit to the United States of two Taiwanese scientists representing the National Yang-Ming University, Veterans General Hospital, Taipei, and the National Chen-Kung University Medical Center, Tainan. They explored the potential for joint studies on prevention and treatment of asthma. The jointly developed program for the visit included meetings at the University of Minnesota, Minneapolis, and Harvard University, Boston, Massachusetts. At the conclusion of the visit, a joint planning meeting was held at NHLBI between the Director, Division of Lung Diseases, NHLBI, and the Taiwanese scientists, to develop scientific topics of mutual interest and benefit, as a basis for further exchange activities. As a result of these discussions, plans are being made for a Joint Workshop on Childhood Asthma, to be held in Taipei, on January 12–16, 2001.

NHLBI takes a multifaceted approach to the prevention of asthma through improved understanding of its causes, greater knowledge of pathogenesis, improved techniques for early diagnosis, and more effective management. In June 2000, the National Science Council of Taiwan agreed to fund a 3-year project on U.S.-Taiwan cooperation in research on asthma, making it possible for Taiwanese scientists to participate in joint efforts to prevent and control asthma in children.

Regional and Global Initiatives

Hypertension

Hypertension is among the most prevalent cardiovascular conditions throughout the world, including in the Americas and the Middle East. Because control rates are very poor, many people have heart attacks and strokes and die prematurely. In many countries, accurate baseline data on the prevalence, awareness, treatment, and control of hypertension are not available. Important questions remain to be answered regarding whether the prevalence and determinants of hypertension and its complications in specific regions of the world are similar to those identified in the West and in other developing countries. To address this challenge, NHLBI has partnered in the development of two regional initiatives—the Pan American Hypertension Initiative (PAHI), which targets the countries of the Western Hemisphere, and the Middle East Hypertension Initiative (MEHI), which targets countries of the Middle East.

Pan American Hypertension Initiative

PAHI has been under way since the 1998 conference on Global Shifts in Disease Burden: the Cardiovascular Disease Pandemic, where NHLBI and the Pan American Health Organization (PAHO) agreed (1) to partner in developing a response to the need to improve cardiovascular health in the Americas and (2) to initiate a collaborative program for the prevention and control of hypertension.

Comparison of hypertension prevalence rates among countries in the Americas is difficult, because different measurement standards have been used in various large-scale surveys. Twelve hypertension experts from NHLBI, PAHO, and several South American countries held a Working Group Meeting on Blood Pressure Measurement Standards, in Washington, D.C., on June 12–13, 2000. The purpose was to develop a blood pressure

measurement standard for use in the Americas. The experts discussed a variety of methods used in national hypertension surveys and clinical trials, which have produced prevalence estimates of hypertension. As a result of the discussions, a proposed common protocol for a blood pressure measurement standard and surveillance system has been proposed for adoption in the region. The goal is to encourage nations to report blood pressure prevalence estimates based on similar measurement and recording procedures, to enable comparisons of blood pressure prevalence estimates among the nations of North, Central, and South America and the Caribbean.

At a meeting of the Directing Council at PAHO Headquarters, on September 29, 2000, the ministers of health of countries of North, Central, and South America and the Caribbean unanimously endorsed a joint resolution to give CVD, particularly hypertension, increased attention in future public health programs in the Americas.

The June 2000 meeting was in follow-up of two previous gatherings of experts (May 1998 and March 1999). NHLBI hosted a planning meeting on Translating Science Into Action, in March 1999, to set priorities for actions to reduce the burden of hypertension in the Americas and to identify areas of cooperation among the participating countries, institutions, and organizations. As a result, a joint PAHI statement was developed and endorsed by PAHO, NHLBI, and six international organizations, including the Inter-American Heart Foundation, the Inter-American Society of Cardiology, the Inter-American Society of Hypertension, the Pan American Network of CARMEN Programs (Comprehensive Intervention Programs to Reduce Risk Factors for Non-Communicable Diseases), the Latin American Society of Nephrology and Hypertension, and the World Hypertension League (WHL).

In May 1998, the challenge of CVD in the Americas led NHLBI, PAHO, WHO, and the John E. Fogarty International Center for Advanced Study in the Health Sciences, NIH, to cosponsor the conference on Global Shifts in Disease Burden: the Cardiovascular Disease Pandemic. At the conference, it was noted that advances in public health and medical technology have reduced the number of deaths from infectious disease and acute illnesses in many areas of the world. As a result, people are living longer, and CVDs are on the rise. This epidemiologic transition has already reached the Americas. Hypertension is the most prevalent CVD in the Americas. When researchers apply national prevalence estimates from well-conducted epidemiologic studies to populations in the Americas, it is estimated that approximately one in four adults (about 140 million) have elevated blood pressure warranting treatment or some form of monitoring.

Middle East Hypertension Initiative

Building on previous collaborative experiences with individual Middle Eastern countries, in December 1999, the Institute sponsored an exploratory meeting including U.S. and Middle Eastern experts in hypertension. The meeting was held in Amman, Jordan, and was chaired by the Director, NHLBI. Participants included the Coordinator, National High Blood Pressure Education Program, NHLBI, and representatives from Egypt, Israel, Jordan, Lebanon, the Palestinian Authority, and the United Arab Emirates. Representatives from WHO and the U.S. Department of Health and Human Services, Office of International and Refugee Health, also participated.

The purpose of the Amman meeting was to explore the level of interest in developing joint plans for future collaboration to reduce the risk of CVD in the region. Discussions were held regarding a common protocol to estimate blood pressure prevalence. By comparing prevalence rates among countries in the region, it is anticipated that the sharing of strategies for hypertension prevention, intervention, and evaluation will be stimulated and will become the basis for developing national education programs designed to improve cardiovascular health. The meeting participants agreed to collaborate to achieve these goals.

Prevention and Control of Pulmonary Disease

Pulmonary diseases are among the leading burdens of disease throughout the world and are projected to increase through 2020. NHLBI participated with the Global Initiative on Asthma (GINA) in developing World Asthma Day, in May 2000. The Institute is also a collaborator with WHO in developing the Global Initiative for Obstructive Lung Disease (GOLD).

World Asthma Day

World Asthma Day was held on May 3, 2000, with a web-telecast press conference conducted by the Director, NHLBI, from London, England. The aims were to increase awareness of asthma as a global health care problem; communicate scientific progress being made; and involve public authorities and organizations of patients in implementation of effective management programs.

The theme was Let Every Person Breathe, in recognition of the need for the world's asthma sufferers to have equal access to timely diagnosis, appropriate treatment, and education to help control their condition. Events included press conferences, poster contests, slide shows, exhibitions, launches of web sites, and asthma screenings. Participants from around the world were invited to preregister online, to participate in the web conference.

Global Initiative for Chronic Obstructive Lung Disease

The first workshop of the GOLD initiative was held at the World Congress on Lung Health, in Florence, Italy, in late August 2000. GOLD is a collaborative venture between WHO and NHLBI to improve the management and prevention of COPD and to develop and implement global strategies for decreasing morbidity and mortality from the disease. The specific objectives of GOLD are to

- recommend effective COPD management and prevention strategies for use in all countries;
- increase awareness of the medical community, public health officials, and the general public that COPD is a public health problem;
- decrease morbidity and mortality from COPD through implementation and evaluation of effective programs for diagnosis and management;
- promote study of reasons for the increasing prevalence of COPD, including environmental factors; and
- implement effective programs to prevent COPD.

Women's Health

The Institute has collaborated in a public–private partnership with the Giovanni Lorenzini Foundation, Milan, Italy, and Houston, Texas, in the development and

cosponsorship of three international conferences in Italy since the mid-1990s. These conferences, which focus on Women's Health in Menopause, address not only CVD, but other health problems such as cancer and osteoporosis, as well as use and impact of hormone replacement therapy. Collaborating with the Giovanni Lorenzini Foundation and NHLBI on the next international conference on Women's Health in Menopause: Improved Quality of Life are the National Cancer Institute, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute on Aging, and the NIH Office of Research on Women's Health. The conference will be held in Washington, D.C., in May 2001. In preparation for this international meeting, the Institute is cosponsoring the development and publication of an international position paper, entitled Women's Health and Menopause: a Comprehensive Approach. It is anticipated that this series of conferences and the development of this international document will have a significant influence on the future management of cardiovascular health in women and on other areas of health promotion and disease control.

Activities With International and Multinational Organizations

NHLBI focuses activities with international and multinational organizations on combating heart, lung, and blood diseases globally, including serving in a consultancy and advisory capacity, as well as initiating regional activities of potential long-term benefit to underserved populations. NHLBI staff serve as consultants to WHO, PAHO, and other international organizations that contribute to worldwide plans for the prevention and control of cardiovascular, pulmonary, and blood diseases in both developed and developing countries. The Director, NHLBI, and senior staff participate in WHO advisory committee meetings and contribute to WHO scientific reports in a number of areas. In addition, NHLBI collaborates with WHO in its Integrated Programs for Community Health in Noncommunicable Diseases, and PAHO/WHO is a partner with NHLBI in PAHI. (See the section on "Regional and Global Initiatives.")

The Institute has served as a WHO Collaborating Center for Cardiovascular Research and Training for the Americas since 1980. In this role, NHLBI provides advisory services, assists in the training of WHO Fellows, and provides advice on the collection and exchange of information and data on activities in the field of CVD research, especially prevention, control, and advances in basic research.

The Director, NHLBI, serves as a special advisor to the WHL Board and was elected president of WHL beginning in August 2000. The Coordinator of NHLBI's National High Blood Pressure Education Program, is the North American editor of the *WHL Newsletter.*

NHLBI supports two important resources used in nutrition research in the United States as well as other countries. The Nutrient Data System of the University of Minnesota, Minneapolis, is an automated dietary interview method that is linked to data on the content of 92 nutrients in 16,000 brand name food items. The Nutrient Data System is in use in several NHLBI international collaborative studies, including cardiopulmonary epidemiologic studies in China and the Intermap international blood pressure study in China, England, Japan, and the United States. NHLBI supports the U.S. Department of Agriculture in efforts to generate analytic data for the U.S. National Food Composition Database. These data from chemical analysis are an international research resource: they represent the world's largest source of primary information on the nutrient content of foods and are used by many countries that lack the resources to establish their own databases.

NHLBI, WHO, and experts from a number of countries also collaborate on GINA, which aims to decrease morbidity and mortality by implementating an optimal strategy for the management and prevention of asthma. The report on the WHO/NHLBI Workshop on Global Strategy for Asthma Management and Prevention, which was published in 1995, provided information on the epidemiology, pathophysiology, management, prevention, risk factors, mechanisms, education, and socioeconomic issues relating to asthma. Three concise companion reference materials have been prepared for patients, physicians, and nurses. These sources offer recommendations for designing and delivering effective asthma management and prevention programs in communities around the world. Building on the GINA model, a similar strategy is under way for the diagnosis and management of COPD globally.

Extramural Programs

NHLBI supports a broad range of research projects at foreign institutions through investigator- initiated grants and fellowships and by contracts and cooperative agreements. These international activities provide valuable opportunities to draw on worldwide resources and expertise.

Grants

During FY 00, NHLBI supported 17 grant projects initiated by foreign investigators. Institutions in Australia received three awards. Research projects focused on activated mutants of receptors for granulocyte–macrophage colony-stimulating factor, interleukin 3 and interleukin 5 as probes to study receptor function, regulation of hematopoiesis by thrombopoietin, and atherosclerosis associated with protease inhibitors in HIV-infected patients. One award was made to the University of Antwerp, Belgium, to study the molecular determinants of potassium channel drug blockers. Nine grants were awarded to institutions in Canada for research projects in genetics, sickle cell disease, HIV, reduction of lung volume, and chemokines in lung disease. Scientists in England received two awards—to the University College of London, to explore social and occupational influences on disease, and to the University of Southampton, to investigate fetal sensitization to allergens and asthma. Technion-Israel Institute of Technology, Technion City, was awarded a grant to investigate interindividual differences in the response to chronic, intermittent hypoxia, by examining (1) production of vascular endothelial growth factor and (2) coronary collateral circulation in human subjects in the environment of a sleep laboratory. A Spanish investigator received an award to carry out a community-based study of occupational asthma.

Fogarty International Research Collaborative Awards

Four NHLBI parent grants were the basis for Fogarty International Research Collaborative Awards for joint international research projects. Work under a grant to the Medical Centre for Postgraduate Education, Warsaw,

Poland, built on the regulation of cardiac substrate metabolism during stress. The modulation of class III anti-arrhythmic drug effects was the topic of the parent grant for a research project with Centro Universitario de Investigaciones Biomedicas, Colima, Mexico. Universidad Catolica de Chile, Santiago, is a collaborator on an NHLBI grant on tumor necrosis factor-α and angiotensin II interactions. Research on B protein for potassium channel modulation is the topic of collaboration with the Second Military Medical University, Shanghai, China.

Cooperative Agreements

In FY 00, NHLBI collaborated with the University of Calgary, Alberta, under a cooperative agreement to study pulmonary embolism. Approximately 600,000 U.S. residents sustain pulmonary embolism each year, and one-third of these episodes are fatal. Pulmonary embolism is underdiagnosed and therefore undertreated. The investigators are studying problems inherent in ventilation–perfusion lung scanning and pulmonary angiography, as well as the accuracy of a relatively new and minimally invasive alternative: spiral computed tomography scanning with intravenous contrast dye. Under a second cooperative agreement, NHLBI collaborated with the Hospital for Sick Children, Toronto, in a study of patients with thalassemia major, to compare the effectiveness of the iron-chelating agent deferoxamine, administered by subcutaneous bolus injections or 8-hour subcutaneous infusions (standard therapy). A third cooperative agreement was awarded to the University of Manitoba to participate in the long-term follow-up of the Lung Health Study.

Fellowships

During FY 00, a fellowship was awarded to an investigator at the Victor Chang Cardiac Research Institute, Sydney, Australia, for gene expression analysis of cardiomyocytes. Also, a fellowship was awarded to a scientist from Montreal General Hospital, Quebec, to study gene mapping of coronary heart disease. A researcher at the University of Cambridge, England, was awarded a fellowship to study antithrombin activation and proteinase inhibition. Another fellowship award was given to a researcher at Canterbury Health, Ltd., School of Medicine, Christ Church, New Zealand, to develop expertise in diagnostic techniques such as mass spectrometry and patient evaluation protocols in a diabetes clinic setting.

Contracts

NHLBI awarded three contracts to institutions in Canada during FY 00. A contract continued with the Hospital for Sick Children, Toronto, to provide a clinical center for the Childhood Asthma Management Program. The main objective of the study is to determine the long-term effects of three modes of therapy (inhaled albuterol alone, albuterol with inhaled budesonide, and albuterol with nedocromil) on pulmonary function over a 5-year period. Other objectives include determining the effects of these therapies on bronchial responsiveness, asthma symptoms, days of limited activity, use of health care resources, long-term side effects, and physical and psychological growth and development.

Also, a contract was awarded to the London Health Science Institute, Ontario, for inclusion in the NIH Iron Overload and Hereditary Hemochromatosis Field Study. This study seeks to determine the prevalence in a primary care population, by race and ethnicity, of (1) iron overload, (confirmed elevation of transferrin saturation) and hereditary hemochromatosis; (2) demonstrable clinical and pathological abnormalities related to iron overload and hereditary hemochromatosis; and (3) genetic variants related to iron overload and hereditary hemochromatosis and iron overload.

A third contract was awarded to McMaster University, Hamilton, Ontario, for a study of prevention of CVD in patients with diabetes mellitus. The objectives are to assess whether the rate of major CVD events can be reduced more by the intensive control of blood sugar and blood lipid levels and blood pressure than by conventional control regimens.

International Meetings

During FY 00, NHLBI staff contributed to a number of international planning meetings. The Director, NHLBI, participated in meetings of the Executive Board of GINA, in Brussels, Belgium; a meeting of the Board of Governors of the U.S.-Israel Binational Science Foundation, in Jerusalem; and an International Planning Meeting at WHO, Geneva, Switzerland.

NHLBI staff made presentations at a number of international meetings, including the following:

- 1st International Conference on Women, Heart Disease, and Stroke, in Victoria, British Columbia;
- French Society of Cardiology meeting, in Paris;
- Medical Statistics: Current Developments in Statistical Methods, in Frankfurt, Germany; and
- Wenner-Gren Foundation's International Symposium on Scientifically Based Biological Assessment of Long-term Stress in Daily Life, in Stockholm, Sweden.

NHLBI staff chaired a session on the Genetic Systems in the Rat, at a meeting in Göteborg, Sweden. In addition, staff cochaired the Joint Symposium on Genetic and Pharmacological Approaches in Vascular Biology, in Milan, Italy.

NHLBI was also represented at many international meetings, including the following:

- American Thoracic Society 2000 International Conference, in Toronto, Ontario;
- International Society of Hematology Congress, in Toronto, Ontario;
- Global Initiative for Asthma Symposium, in Hong Kong, China;
- Global Forum for Health Research, in London, England;
- 3rd International Congress on Coronary Artery Disease, in Lyon, France;
- 12th International Cardiostim Congress 2000, in Nice, France;
- 1st U.S.-European Meeting on the Molecular Basis of Heart Disease, in Paris, France;
- 2nd International Multiple Comparisons Procedures Conference, in Berlin, Germany;
- Symposium on Central Chemosensitivity 2000, in Bochum, Germany;
- NATO (North Atlantic Treaty Organization) Science Program, in Budapest, Hungary;
- International Symposium on Cardiovascular Risk in Special Populations, in Bologna, Italy;
- European Respiratory Society Conference, in Florence, Italy;
- 21st meeting of the International Society for Clinical Biostatistics, in Trento, Italy;
- New Frontiers of Research in Pneumology and the Global Initiative for Asthma/ Global Initiative for Obstructive Lung Dis-

ease executive committee meetings, in Italy and Spain;

- XXII[nd] Congress of the European Society of Cardiology, in Amsterdam, the Netherlands; and
- Global Initiative on COPD, in Spain.

Intramural Programs and Activities

Scientists from many countries have been given the opportunity to conduct research in NHLBI laboratories under visiting scientist programs. In FY 00, 99 Visiting Fellows, 57 Visiting Scientists, 11 Visiting Associates, and 10 Special Volunteers participated in joint research in the Division of Intramural Research, NHLBI. Countries represented included the following: Argentina, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Denmark, Finland, France, Germany, Iceland, India, Israel, Italy, Jamaica, Japan, Korea, Mexico, Morocco, the Netherlands, Peru, the Philippines, Poland, Portugal, Russia, Singapore, Spain, Sweden, Switzerland, Turkey, the United Kingdom, Vietnam, and Taiwan.