

XVII.

National Heart, Lung, and Blood Institute

INTRODUCTION

Diseases of the heart, lungs, blood vessels, and blood comprise three of four leading causes of death in the United States. Together they accounted for 51% of all deaths in the United States in 1997. Their associated economic costs are estimated to represent 25% of the total costs due to illness, injury, and death in 1999. Great progress has been made in reducing the burden of these diseases, but it is clear that much remains to be done.

The legislative mission of the National

Heart, Lung, and Blood Institute (NHLBI) is to improve health in the United States 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.

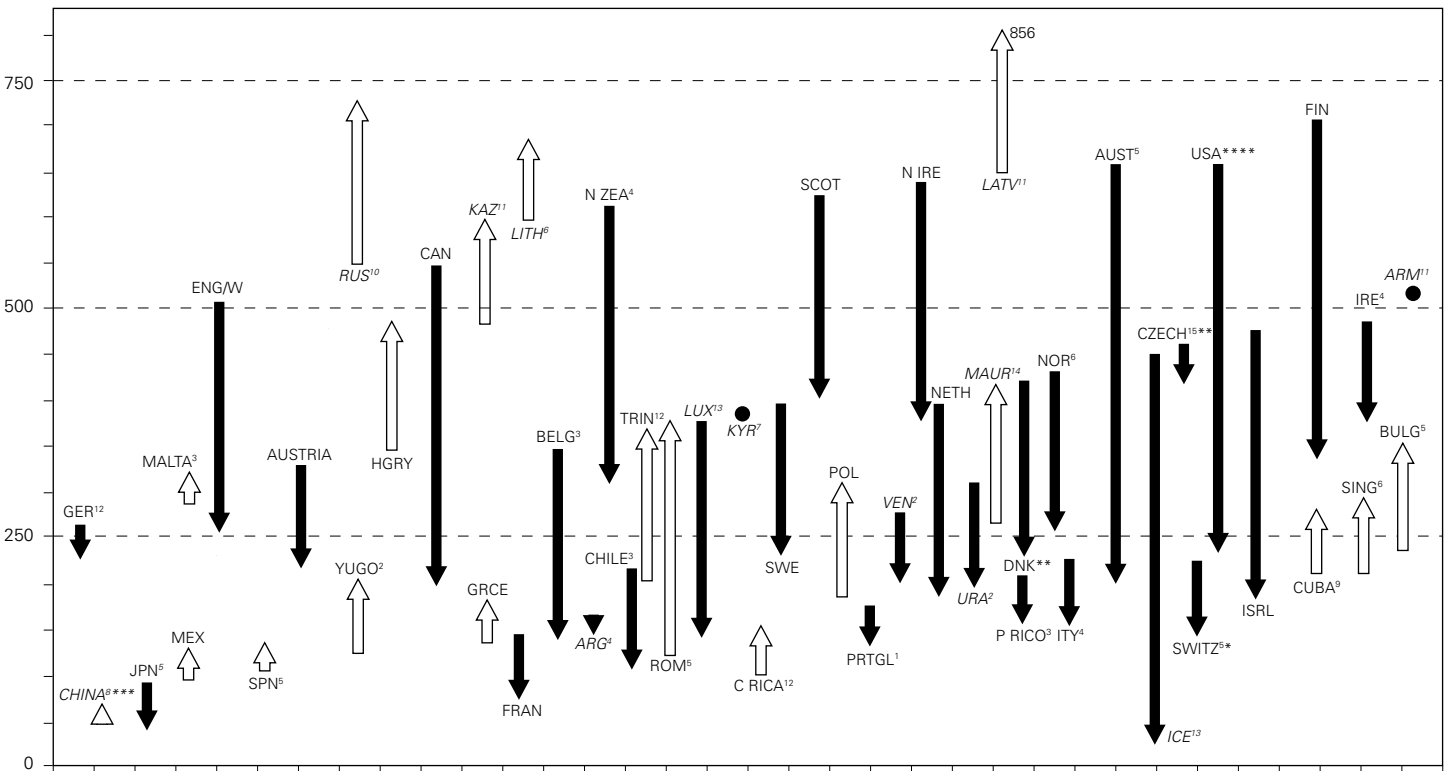
To fulfill its mission, the Institute has formed partnerships with U.S. universities and research institutes, other Federal agencies, international organizations, and private-sector scientific, professional, and public organizations.

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

FIGURE XVII-1.

Death Rates for Coronary Heart Disease by Country for Men Ages 35-74 Years, 1970 and 1995

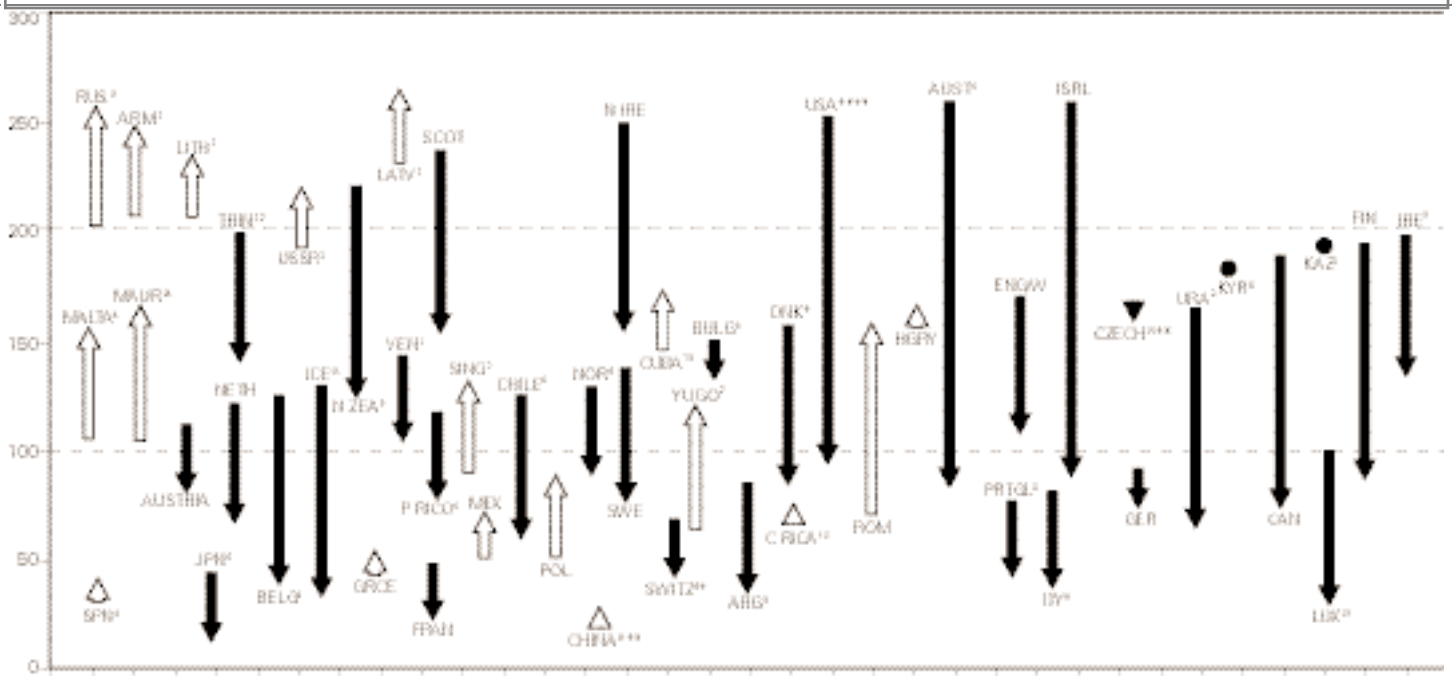


Rate per 100,000 population. Age adjusted to European Standard Population.
 Rates are based on *International Classification of Diseases*, 8th Revision (ICD-8) for years before 1979 and 9th Revision (ICD-9) for years after 1979.
¹Rates for all years for Switzerland (SWITZ) are based on ICD-8.
²Rates for years beginning in 1994 for Czech Republic (CZECH) and Denmark (DNK) are based on ICD-10.
³Rate is for rural areas of China. Rates for urban areas are 71.2 and 99.6 per 100,000 population.
⁴Rates for the United States (USA) are based on *Public Use Mortality Data Tapes*, National Center for Health Statistics, Centers for Disease Control and Prevention, 1995.
 Source: *World Health Statistics Annual*. WHO (selected issues).

¹ 1970 and 1971 ⁹ 1971 and 1990
² 1970 and 1990 ¹⁰ 1991 and 1995
³ 1970 and 1992 ¹¹ 1990 and 1995
⁴ 1970 and 1993 ¹² 1971 and 1991
⁵ 1970 and 1994 ¹³ 1971 and 1992
⁶ 1990 and 1994 ¹⁴ 1971 and 1993
⁷ 1990 ¹⁵ 1993 and 1995
⁸ 1990 and 1994

FIGURE XVII-2. ¶

Death Rates for Coronary Heart Disease by Country for Women Ages 35-74 Years, 1970 and 1995



Rate 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 9th Revision (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. ¶ Rates for rural areas of China. Rates for urban areas are 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, 1995. ¶ Source: World Health Statistics Annual.

development of new and established investigators; and

- conducts educational activities, including the development and dissemination of materials for health professionals and the public, with a special emphasis on disease prevention.

During fiscal year 1998 (FY 98), NHLBI invited a group of accomplished scientists to meet with Institute staff and representatives from three of the major professional societies associated with NHLBI's mission (the American Heart Association, the American Thoracic Society, and the American Society of Hematology); the theme was From Genes to Health and Health to Genes. The participants were asked to focus on broad research themes that transcend the traditional organ-specific domains within the Institute and to specify enabling approaches that would be needed to address these areas effectively. The scientists identified four areas of opportunity and a number of enabling approaches. The four areas are (1) tissue genesis and organogenesis, (2) immunobiology, (3) gene-

environment and gene-gene interactions, and (4) functional genomics. The products of this process have been complemented by the efforts of the Institute's newly formed Board of Extramural Advisors and input from the National Heart, Lung, and Blood Advisory Council. In follow-up of these activities and inputs, the Institute developed a new NHLBI Strategic Plan during FY 99, presenting important scientific opportunities for FY 01-FY 05 within the Institute's mandate. The plan is flexible and dynamic, so that the Institute will be able to respond to evolving national needs, congressional mandates, and advances in scientific knowledge. The plan has been posted on NHLBI's interactive Web site (www.nhlbi.nih.gov). It is anticipated that the new plan will have significant impact on the Institute's future international collaborations with other countries and international organizations.

NHLBI continues to play a leadership role in international health policy and in global efforts to transfer and apply new knowledge to prevent and control heart, lung, and

blood diseases. During FY 99, the Institute strengthened and expanded its international contacts and partnerships across national boundaries, as well as its associations with the World Health Organization (WHO), as a WHO Collaborating Center in Research and Training in Cardiovascular Diseases. The international programs continued to undergo major changes in direction and emphasis to take advantage of new opportunities created by the rapid progress in science and the changing international political and economic situation.

Cardiopulmonary disease is a rapidly growing pandemic, especially in developing countries. Marked international differences in death rates and trends of cardiovascular and pulmonary diseases in men and women, as seen in Figures XVII-1 through XVII-6, raise important scientific questions and provide challenges for international collaborations to explore the reasons for these differences and to prevent and control these diseases. Two joint publications by WHO, Harvard School of Public Health, Boston,

TABLE XVII-1.¶

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

	Arteriosclerosis	Hypertension	Cardiovascular Diseases	Chronic Heart Diseases	Asthmaphysiology	Heart Failure and Shock	Circulatory System and Blood Vessels	Respiratory System and Lung Diseases	Immunology of the Heart	Immunology of the Lung	Chemistry of the Heart and Lung	Basic Research in Lung Diseases	Cardiopulmonary Immunology	Respiratory Failure	Immunology of the Heart and Lung	Stroke and Cerebral Circulation	Diagnosis of Heart Blood Vessels	Blood Hemostasis	Other
Australia→	→	→	→	•¶															
Canada→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
China→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Egypt→	→	•¶																	
Germany→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
India→	→	→	•¶																
Italy→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Japan→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Korea→	→	→	→	•¶															
Pakistan→	→	→	→	•¶															
Poland→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Russia→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
South Africa→	→	•¶																	
Uganda→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Vietnam→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
Taiwan→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→

Massachusetts, and the World Bank have reviewed the major causes of death in the world. "The Global Burden of Disease" and "Global Health Statistics" combine data on deaths and disabilities to create a future medical road map for use by health professionals and policy makers. The authors of these two books predict major changes in global patterns of disease. By 2020, it is anticipated that noncommunicable diseases such as heart disease will become the number one global disease burden, as deaths and disabilities from malnutrition and infection continue to decline. Already, WHO estimates that cardiovascular disease (CVD) alone is responsible for more than 12 million deaths each year and hundreds of billions of dollars in economic losses.¶

At the same time, new solutions are being developed through advances in scientific knowledge and public health action to promote health and control disease. Rapidly advancing information-based technologies are helping physicians and scientists to explore

new ways to share information and data, resulting in global changes in the practice of medicine and science. Instant communications and consultations are being developed through technologies such as electronic mail (e-mail), interactive Web sites, telecommuting, and teleconferencing. Computers, satellite connections, the World Wide Web, and multimedia approaches are facilitating international collaboration in the cardiopulmonary area. These technological advances are significantly improving communications and reducing the time required for analysis and evaluation of data for use by scientists and policy makers.¶

NHLBI's current international collaboration covers the entire research spectrum, including basic research, applied research and development, clinical investigation, population-based studies, demonstration and education, and training and development. The Institute's international programs during FY 1999 built on national research in priority areas included in the National Heart, 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 national research programs.¶

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HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES¶

Three highlights of FY 99 NHLBI international activities reflect the increasing globalization of international activities: (1) development of the Pan American Hypertension Initiative (PAHI), (2) the Global Initiative for Asthma (GINA), and (3) initiation of discussions of a Middle East Hypertension Initiative (MEHI).¶

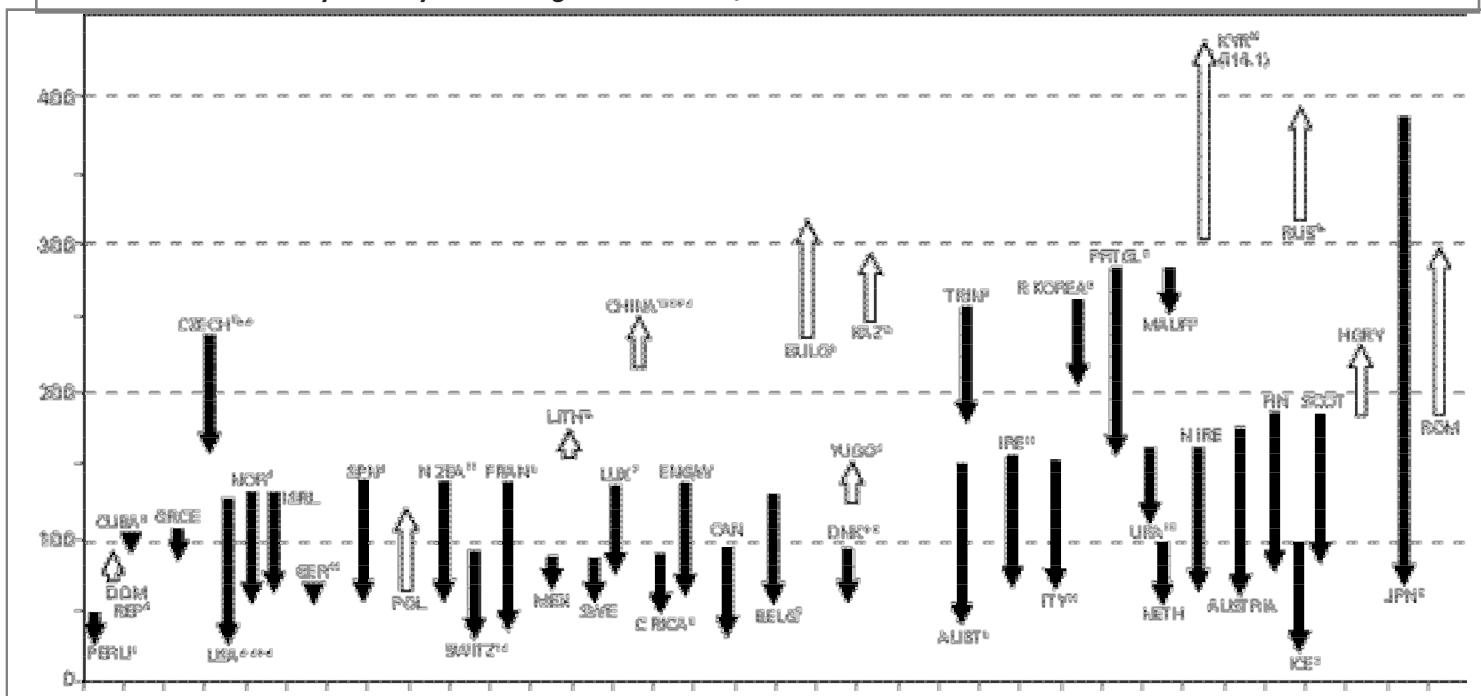
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Pan American Hypertension Initiative¶

Hypertension is the most prevalent CVD in the Americas, affecting approximately one in four adults (about 140 million people). In

FIGURE XVII-3. ¶

Death-Rates for Stroke by Country for Men Ages 35-74 Years, 1970 and 1995



Rate 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 9th Revision (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 are 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, 1995. ¶
 Source: *World Health Statistics Annual*, WHO, (selected issues).

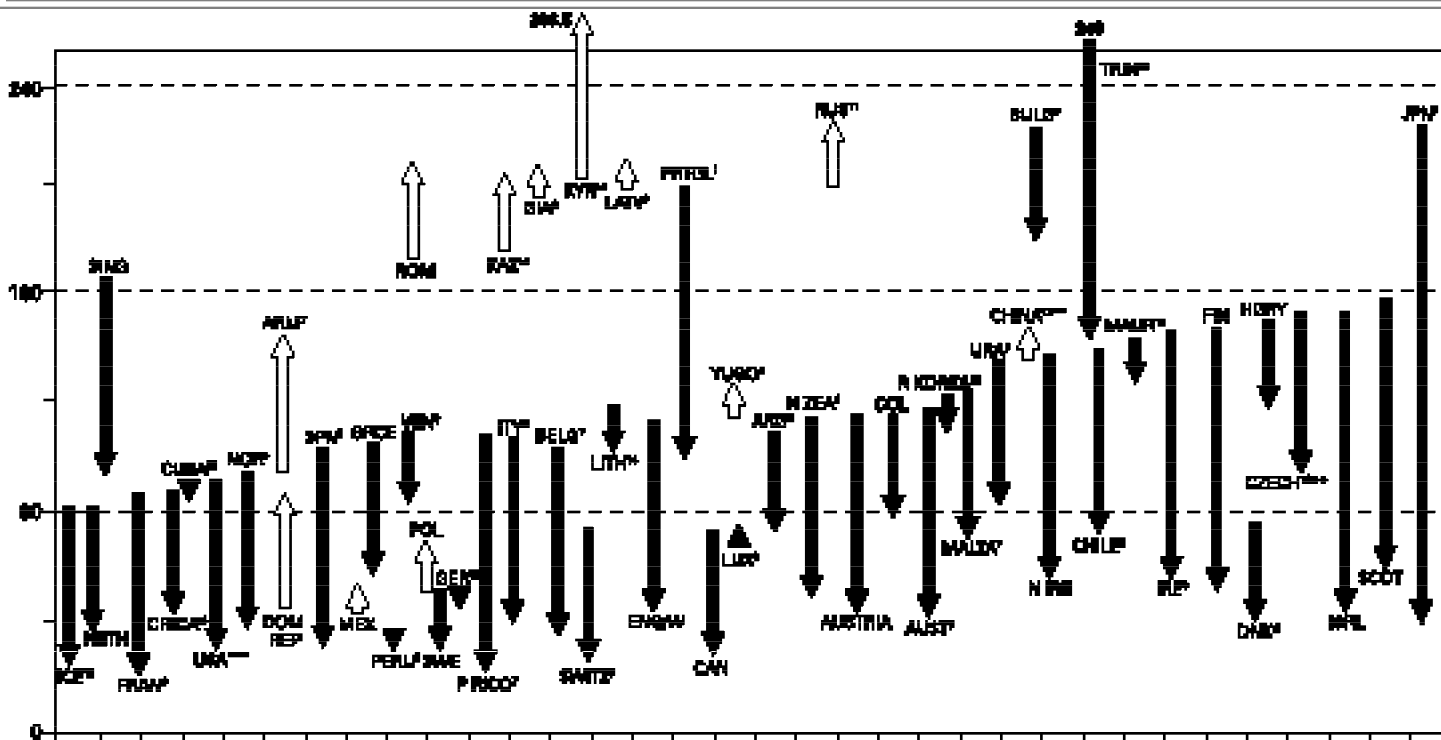
the Americas, as in most nations, hypertension control rates are very poor. Throughout most of the world, fewer than one-fourth of hypertensive patients are adequately controlled. As a result, many people suffer from heart attacks and strokes and die prematurely. To address this challenge in the Americas, the Pan American Health Organization (PAHO) and NHLBI have jointly proposed PAHI. The purpose of PAHI is to advance knowledge and to facilitate action toward the prevention and control of high blood pressure in the Americas. ¶
 PAHI was issued as a call to action at the conclusion of the conference on Global Shifts in Disease Burden: the Cardiovascular Disease Pandemic. This conference, held in May 1998 at PAHO Headquarters in Washington, D.C., was cosponsored by PAHO, WHO, NHLBI, and the Fogarty International Center (FIC). In follow-up of the conference, NHLBI hosted a planning meeting on Translating Science Into Action, at the National Institutes of Health (NIH), in Bethesda, Maryland, in March 1999. The

participants included representatives from Argentina, Barbados, Brazil, Canada, Chile, Cuba, Mexico, the United States, and Uruguay, and international and regional scientific organizations. The goals of this meeting were to set priorities for actions to reduce the burden of hypertension in the Americas and to identify areas of mutual interest and cooperation among institutions and organizations represented at the meeting. ¶
 The planning meeting culminated in the development of a joint PAHI statement that outlines proposed activities for the future. ¶
 To date, six international organizations have endorsed this statement, in addition to PAHO, NHLBI, and delegates to the March 1999 meeting. The international organizations include the World Hypertension League, 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 Inter-American Society of Cardiology, the Inter-American Heart Foundation, and the Latin

American Society of Nephrology and Hypertension. These partners have indicated their willingness to collaborate in this important international initiative to improve the health of the people of the Americas. ¶
 ¶
Global Initiative for Asthma ¶
 NHLBI, WHO, and experts from a number of countries also collaborate on a joint initiative to address asthma as a serious global health problem. Asthma is estimated to affect more than 150 million people worldwide, and there is evidence that prevalence is on the increase in children in most countries. GINA was established by WHO, NHLBI, and the European Respiratory Society to decrease morbidity and mortality by the development and implementation of an optimal strategy for the management and prevention of asthma. ¶
 Asthma is a chronic condition characterized by a narrowing of the bronchial tubes, swelling of the bronchial tube lining, and mucous secretion that can block the airway, making breathing difficult. The prevalence

FIGURE XVII-4. ¶

Death Rates for Stroke by Country for Women Ages 35-74 Years, 1970 and 1995



Rate 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 9th Revision (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 are 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, 1995. ¶
 Source: *World Health Statistics Annual*, WHO, (selected issues).

1. 1970 and 1971 ¶
 2. 1970 and 1983 ¶
 3. 1970 and 1989 ¶
 4. 1970 and 1990 ¶
 5. 1971 and 1982 ¶
 6. 1971 and 1990 ¶
 7. 1970 and 1992 ¶
 8. 1970 and 1993 ¶
 9. 1970 and 1994 ¶
 10. 1971 and 1994 ¶
 11. 1990 and 1995 ¶
 12. 1985 and 1995 ¶
 13. 1990 and 1995 ¶
 14. 1981 and 1995 ¶
 15. 1971 and 1992 ¶
 16. 1971 and 1995 ¶

of asthma can be as high as 30% among certain populations, and internationally, cases have more than tripled in the last 10 years. In the United States, between 1990 and 1994, the number of people reported to have asthma increased from 10.4 to 14.6 million, including approximately 5.0 million children. ¶
 In December 1998, NHLBI, the American Academy of Allergy, Asthma, and Immunology, the American College of Chest Physicians, and the American Thoracic Society launched a global plan to cut childhood asthma deaths by 50% by 2005. Other international supporting organizations include the European Academy of Allergology and Clinical Immunology and the International Union Against Tuberculosis and Lung Disease. This global effort was announced on the eve of the first World Asthma Day, on December 11, 1998. The theme was Help Our Children Breathe. In announcing the global plan, the chairman of GINA called

on parents, physicians, public authorities, and national organizations to work together. ¶
Middle East Hypertension Initiative ¶
 NHLBI has collaborated with individual countries in the Middle East for a number of years to address the increasing prevalence of CVD. Toward the end of FY 99, the Institute invited hypertension experts from the Middle East to join with U.S. experts for an exploratory meeting to be held in Amman, Jordan, in December 1999, to address the problem of hypertension. Representatives from Egypt, Israel, Jordan, Lebanon, the Palestine Authority, and the United Arab Emirates accepted the Institute's invitation. ¶
 In previous NHLBI collaboration with Egypt, research funded by the Institute, the Egyptian Ministry of Health, and the U.S. Agency for International Development demonstrated that hypertension is a serious problem in the Egyptian population. Other countries in the Middle East have also re-

ported high rates of hypertension. Hypertension is a major risk factor for coronary heart disease, stroke, premature death, and renal failure, making the prevention and control of hypertension an important health priority for the region. ¶
 The purpose of the December 1999 meeting in Jordan is to explore the interest in developing a joint Middle East Hypertension Initiative and plans for future collaboration to reduce the risk of CVD. Discussions will be held on a common protocol to estimate the prevalence of hypertension in Middle Eastern nations. It is anticipated that the ability to compare prevalence rates among countries will stimulate sharing of hypertension prevention, intervention, and evaluation strategies and will become the basis for developing national education campaigns designed to improve cardiovascular health in nations of the Middle East. ¶

TABLE XVII-2.¶

National Heart, Lung, and Blood Institute: International Programs, Direct Costs, Fiscal Year 1999¶

➤	Number➤	Countries➤	Funds paid.¶ (in dollars)¶
Fellowships➤	2➤	United Kingdom➤	31,720 ¶
Grants➤	10➤	Canada➤	2,168,568 ¶
	4➤	United Kingdom➤	530,673 ¶
Contract➤	1➤	Canada➤	347,306 ¶
Cooperative Agreement➤	1➤	Canada➤	91,372 ¶
Total Awards➤	18➤	➤	3,169,639 ¶
Centers for Disease Control and Prevention.¶			
Interagency Agreement➤	1➤	China➤	21,000 ¶
		Pakistan➤	¶
		Poland¶	
University of North Carolina Contract➤	1➤	China➤	366,080 ¶
		Pakistan¶	
		Poland¶	
Bilateral Agreements➤	17➤	➤	315,000 ^b ¶

^a Collaborating countries pay for the costs in their own country. ¶

^b Activities paid for by the National Heart, Lung, and Blood Institute.

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 99 are summarized in Table XVII-2.¶

Argentina¶

An Argentinean exchange scientist worked at NHLBI in the area of asthma prevention, education, and control during April–September 1999. This initial exchange was designed to focus on the Institute’s health education and communication programs, which translate research results to impact on public health. Among the results of the joint effort, the scientist prepared a set of objectives to guide the revision of the report on Acute Exacerbations of Asthma: Care in a Hospital-Based Emergency Department. She also participated in projects related to the National Asthma Education and Prevention Program that may be adapted to Argentinean public health activities. ¶

Australia¶

NHLBI collaborates with Australia under the

auspices of an agreement between NHLBI and the Baker Medical Research Institute (BMRI), Victoria. This cooperation began with a number of visits to NHLBI by health administrators from the Australian Commonwealth, Department of Human Services and Health. The coordinator and an epidemiologist from the South Australia Health Commission, Adelaide, visited NHLBI in 1989 and 1991, respectively, to share knowledge in cardiopulmonary disease prevention and care. These visitors expressed interest in NHLBI’s successful approaches to disease prevention that might be applicable to populations in Australia. ¶

In June 1997, the Director, BMRI, visited NHLBI to discuss a mutually beneficial bilateral program of scientist exchanges. As a result, an agreement was made between NHLBI and BMRI. The program was initiated in September 1997 with a 4-month visit by a senior research officer from the Lipoprotein and Atherosclerosis Laboratory, BMRI, who worked with a professor of cardiovascular physiology at the Cardiovascular Research Institute, University of California, San Francisco, on platelet interactions with the vessel wall. The Australian scientist’s expertise on intracellular cholesterol trafficking and the role of apolipoprotein A-1 in cholesterol homeostasis complemented the

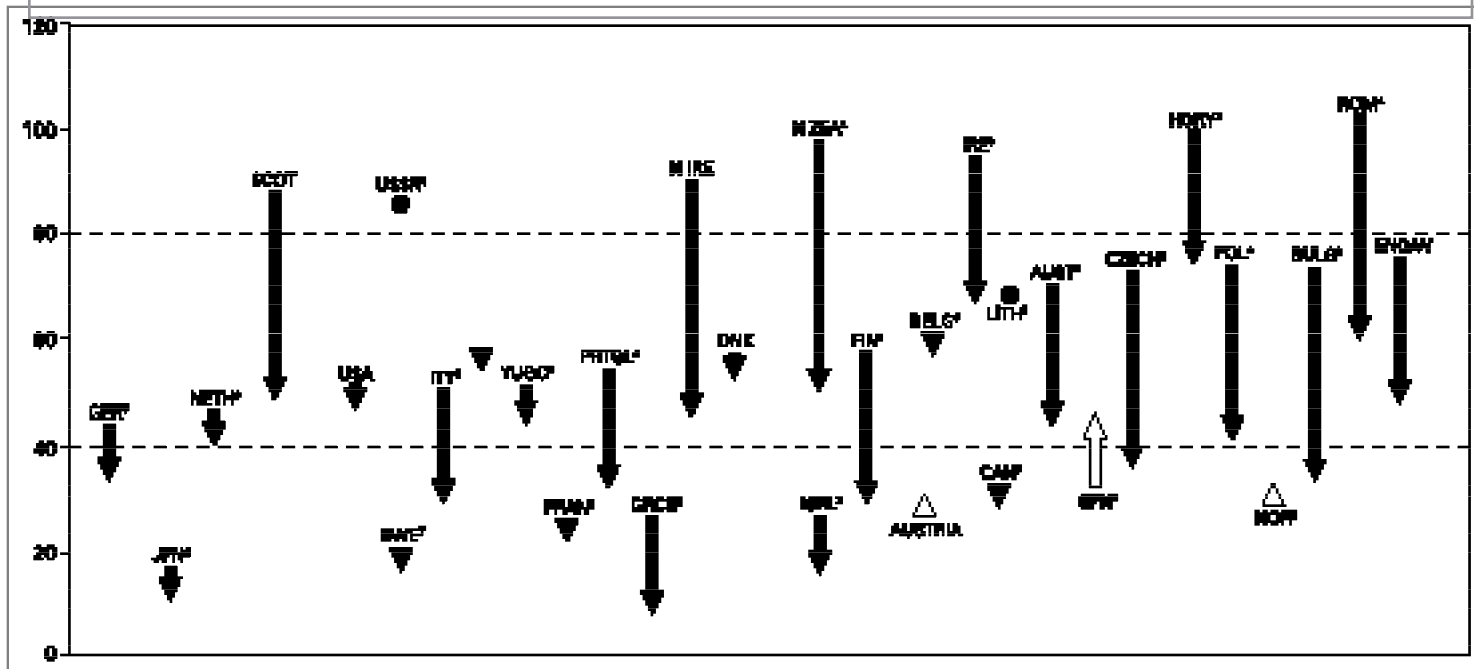
U.S. researcher’s studies of atherosclerosis. This joint research generated new inquiries and methods, providing the basis for further collaboration. In July 1998, NHLBI supported a reciprocal visit to Australia by this U.S. researcher. Studies continued with a special emphasis on binding reactions between the P selectin receptor on the endothelial surface and the glycoprotein 1b-X-V complex on the platelet surface. ¶

The U.S. and Australian investigators continue to collaborate on topics of mutual interest and benefit. In December 1998, the Head of the Cellular Biochemistry Laboratory, BMRI, worked with a professor at the Department of Pharmacology, University of California, Los Angeles, to define pathways involved in cardiac hypertrophy. The main goal of these studies is to examine the role of Gq proteins in hypertrophic responses in adult and neonatal rat cardiomyocytes and the involvement of phospholipase C activation. The U.S. investigator has extensive expertise in studies of hypertrophic signaling and has produced a number of transgenic mouse models applicable to these studies. The Australian scientist has expertise and equipment for complementary studies of inositolide metabolism in cardiomyocytes. (Inositolide is a phospholipid containing a vitamin B complex necessary for growth in the mouse model.) ¶

Also, in May 1999, a senior scientist from the Alfred Baker Medical Unit, Division of Cardiovascular Medicine, BMRI, collaborated with the Head, Division of Metabolism, Endocrinology, and Nutrition, University of Washington, Seattle, on studies of proteoglycan biochemistry and cell biology and the effect of hyperglycemia on the binding of proteoglycans to lipoproteins. They studied the impact of new drug therapies, such as thiazolidinediones, on the synthesis of proteoglycans by vascular smooth muscle cells and on the development of atherosclerosis. Within the vessel wall, highly sulfated and negatively charged glycosaminoglycan chains on proteoglycans produced by endothelial and vascular smooth muscle cells attract and bind positively charged lipoproteins on circulating low-density lipoproteins. The lipoproteins are attracted and retained in the subendothelial space as an early step in the formation of “fatty streaks,” the precursor of atherosclerosis. The researchers also characterized the effects of hyperglycemia

FIGURE XVII-5. ¶

Death Rates for COPD and Allied Conditions by Country for Men Ages 35-74 Years, 1980 and 1997

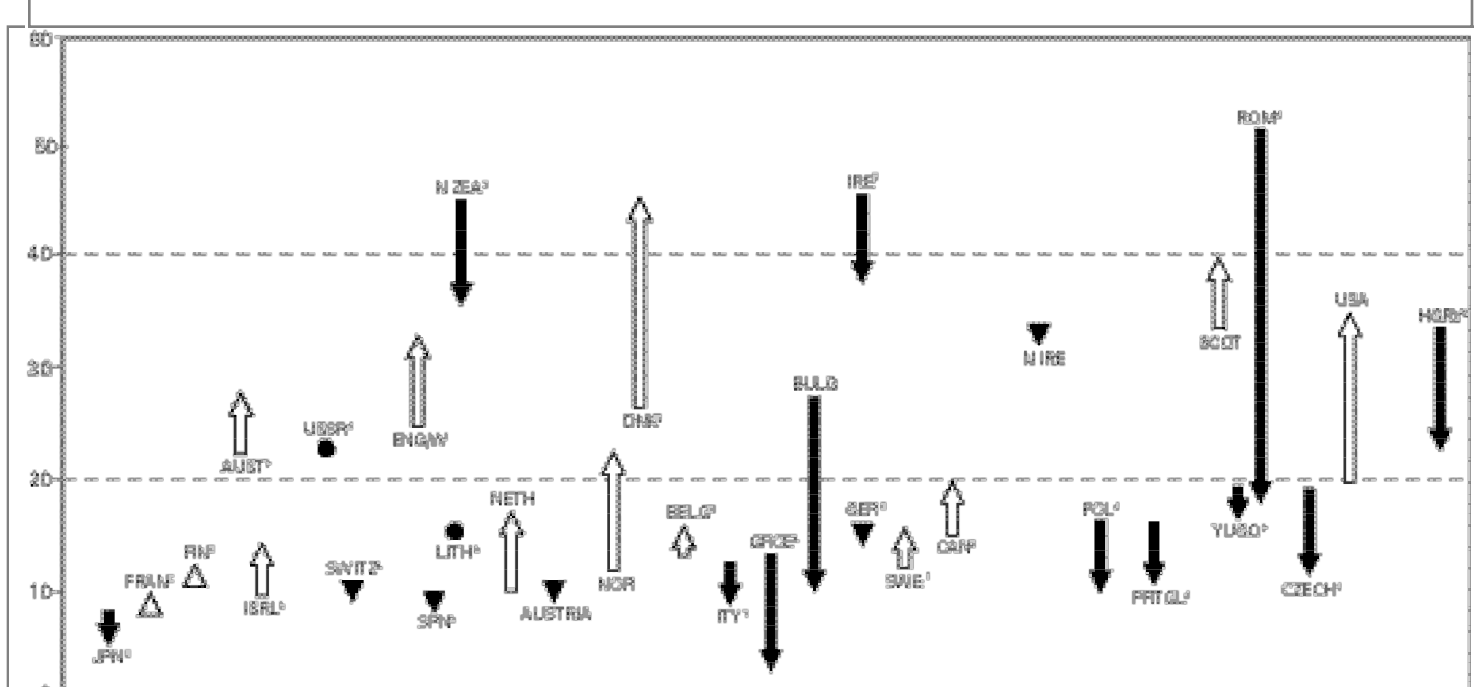


Rate per 100,000 population. Age-adjusted to European Standard Population. ¶
 International Classification of Diseases, 9th Revision (ICD-9), codes 490-496. ¶
 Source: WHO, unpublished data.

- 1. 1980 and 1993
- 2. 1980 and 1994
- 3. 1980 and 1995
- 4. 1980 and 1996
- 5. 1990 and 1997
- 6. 1990
- 7. 1987 and 1996
- 8. 1980 and 1992
- 9. 1996

FIGURE XVII-6. ¶

Death Rates for COPD and Allied Conditions by Country for Women Ages 35-74 Years, 1980 and 1997



Rate per 100,000 population. Age-adjusted to European Standard Population. ¶
 International Classification of Diseases, 9th Revision (ICD-9), codes 490-496. ¶
 Source: WHO, unpublished data.

- 1. 1980 and 1993
- 2. 1980 and 1994
- 3. 1980 and 1995
- 4. 1980 and 1996
- 5. 1990 and 1997
- 6. 1990
- 7. 1987 and 1996
- 8. 1980 and 1992
- 9. 1996

and thiazolidinedione on proteoglycan production. The joint research showed that Troglitazone (a form of thiazolidinedione) causes significant inhibition of proteoglycan, making it a potential reducer of fatty streak formation. The joint research continues, and a publication is planned.¶

A joint U.S.-Australia research symposium on Cardiac and Vascular Remodeling is planned for November 1999, in Atlanta, Georgia, in conjunction with the American Heart Association meetings.¶

¶ **Canada**¶

NHLBI supports a number of clinical trials carried out jointly with research groups in Canada. These trials are based on protocols that specify precise interventions and end points and validate new prevention and treatment regimens before introducing them into medical practice. The requirement for large patient populations 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, reduce costs, and most important, make valid comparisons of results in different populations. During FY 99, Canadian scientists participated in the NHLBI studies in cardiovascular and lung diseases described here.¶

¶ **Cardiovascular Diseases**¶

Bypass Angioplasty Revascularization Investigation. This 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 pectoris 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. Recruitment ended in August 1991. 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, cooperate with Johns Hopkins University, Baltimore, Maryland, in a randomized, double-blind, controlled trial that tests

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 primary outcome variables will be the occurrence of graft occlusion at 6 months and the change in severity and extent of atherosclerosis in saphenous vein grafts over 3 years. The study is funded through 2002.¶

¶
Molecular Physiology of Myocardial Troponin-1 Variants. This study by Johns Hopkins University and Queens University, Kingston, Ontario, aims to determine the roles of defects to cardiac-specific proteins in the progression of ischemic injury and cardiomyopathy. The subcontract to Queens University utilizes expert skills of Canadian scientists to probe thin filament regulation of contraction. This grant is funded through 2004.¶

¶ **Lung Diseases**¶

Remodeling of Human Airways in Disease. The objective of this research at the University of British Columbia, Vancouver, is to determine whether the composition of the extracellular matrix in asthma differs from that in chronic obstructive pulmonary disease (COPD) or in healthy subjects. A clinical and tissue registry of more than 1,400 patients, collected over the past 20 years, provides an invaluable resource for studying the mechanisms responsible for remodeling of tissues in patients with asthma or COPD. This grant is funded through August 2003.¶

¶
Molecular Basis of Lung Morphogenesis Injury and Repair. This study by the Children's Hospital, Los Angeles Research Institute, and McMaster University, Hamilton, Ontario, will (1) explore whether excess tumor growth factor β (TGF- β) signaling plays an adverse role in the developing lung and (2) determine the feasibility of novel therapeutic strategies to modulate TGF β signaling. The investigation may lead to prevention and treatment of chronic lung disease in premature infants. It is funded through 2005.¶

¶
Chemokines in Lung Disease of HIV-1 Transgenic Mice. The Clinical Research Institute of Montreal is collaborating in a study to investigate the hypothesis that lymphocytic interstitial pneumonitis is immune me-

diated and driven by the recruitment of immune cells in the lung, through the action of specific chemokines. The overall objectives are (1) to understand the cellular and molecular mechanisms responsible for the lung disease arising in transgenic mice with mutations for CD4 positivity and for human immunodeficiency virus type 1 (HIV-1) and (2) to study the role of chemokines and their receptors in the development of HIV-1 disease. Funding is through June 2004.¶

¶
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 than referral to usual care in slowing the rate of decline of pulmonary function in a population of smokers with mild abnormalities in pulmonary function. This study was merged into the Lung Health Study II, which aims to determine whether patients with COPD 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 is scheduled to end in the fall of 1999.¶

¶
Clinical Centers for Childhood Asthma Management Program. The primary objective of this 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. Follow-up is in progress for this double-blind study, scheduled for completion in 1999.¶

¶
Sleep Research: Regulation of Adenosine in Relation to Sleep. The aim of this Canadian subproject is to investigate the role of adenosine in relation to the brain mechanism that controls sleep. The relationship is being investigated in complementary studies at the University of Pennsylvania, Philadelphia,

and the University of Manitoba, Winnipeg. Funding is through 2002.¶

¶
Specialized Centers of Research Program. In FY 98, McGill University, Montreal, was awarded a grant, under this Program, for a joint project on translational control of fibroblast viability. The goal of this joint research is to develop basic and clinical insights that can serve as the basis for improved therapies for patients with acute lung injury. The special arrangement between the University of Minnesota, Minneapolis, and the Canadian center is essential: (1) to characterizing some of the translation initiation proteins to be used in the joint studies and (2) to maintaining the knockout mice to be used in phase II of the project. The Canadian center will maintain and characterize the knockout mouse colony, prepare and ship mice needed for experiments on a regular basis, and carry out cell-free translation and binding assays on new translation initiation constructs.¶

¶
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 trends and rates 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. Many joint manuscripts are being prepared for publication on the basis of comparative data generated from this exchange program.¶

The 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 been followed 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 been proposed by the U.S. and Chinese scientists participating in these joint studies.¶

The fourth survey was conducted in the fall of 1998. The objectives were to (1) measure the current level of major cardiovascular and cardiopulmonary risk factors among the four Chinese populations being studied in North and South China; (2) compare current levels of major risk factors among these populations; (3) measure changes in major risk factors in comparison to baseline; and (4) explore associations between the change in socioeconomic status and trends of CVD risk factors. The U.S. side 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 will be 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, which will provide crucial data for the joint epidemiologic studies. Plans for the continuation of the collaboration will also be made.¶

¶
Egypt¶
Egypt has one of the highest rates of hypertension in the world, as evidenced by results from a comprehensive project for the prevention and control of hypertension in Egypt that was developed by U.S. and Egyptian scientists in 1991. About one in four adults has elevated blood pressure and is at risk for complications such as heart disease, stroke, kidney failure, and death. The economic impact of hypertension in Egypt can be measured in billions of dollars per year. There is great concern about the future health of the Egyptian population and the need for hypertension prevention and control.¶

The U.S.-Egypt National Hypertension Survey was carried out in 1991-1993, to study the prevalence of hypertension among Egyptians, characterize the influence of environmental and behavioral factors, determine familial and racial influences, and

study the cardiac changes associated with hypertension. The project brought the latest information and technology to bear on the problem.¶

Data were presented at international meetings, and papers were prepared for publication. A Pan-Arab Conference on Hypertension was held in Egypt in 1993 as a direct outgrowth of the U.S.-Egypt collaboration. This meeting was followed by a second joint conference in Lebanon in 1995, and a third Pan-Arab Conference on Hypertension is planned for February 2000, in Abu Dhabi, United Arab Emirates.¶

As a result of the U.S.-Egypt collaboration, a library, information network, and laboratories have been established at the Hypertension Reference Center, Cairo, for physicians and scientists, for consultation and study. The Egyptian team established an Egyptian Hypertension League, and Egypt has joined the World Hypertension League as a member. A self-sustaining research and education program in Egypt was planned. Formal collaboration between the United States and Egypt on phase I of this program was terminated in March 1994 with a final joint meeting in Egypt after completion of the survey. Informal collaboration between U.S. and Egyptian scientists and joint publications of the results continue.¶

Egypt is an invited participant in the planning meeting for the Middle East Hypertension Initiative developed by NHLBI to focus attention on the benefits of collaboration to prevent hypertension and its serious sequelae of heart attack and stroke. The planning meeting will be held in Amman, Jordan, in December 1999.¶

¶
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 pulmonary diseases and involves basic and applied research.¶

Recent collaboration in the cardiovascular area has focused on genetics and animal models. Staff from NHLBI and U.S. and German researchers met in FY 96 to begin to map the rat genome, coordinate their efforts, create cross-referenced reagents, and produce interdigitated maps. In March 1997, scientists from the NIH Rat Genome project

and the European Rat Genome project met for a U.S.-German joint workshop in Toronto. They discussed the progress and status of studies of human subjects, 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 rat 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, the U.S. and German researchers collaborating on this project plan to meet at the Physiological Genomics and Rat Models Meeting, in Cold Spring Harbor, New York, to present major progress in developing data sets and libraries in each country, for joint research. Topics to be discussed include genomics, bioinformatics, expression profiling, comparative mapping, complex trait analysis, model systems, transgenics, and pharmacogenomic risk assessment. ¶

NHLBI collaboration in pulmonary research focuses primarily 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 in current research. Researchers are studying genetic and environmental factors operating in utero and immediately postnatally, because these factors may influence the early onset of asthma. During FY 99, collaboration in research on environmental factors has involved the evaluation of dietary factors influencing the development of asthma in early life. Recent 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 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 ages 4–17 years. Future studies will assess the role of maternal diet, breast milk, and birth weight on the development of the immune system in asthma, which appears early in life. ¶

The most recent U.S.-German workshop in pulmonary research was held in Berlin, in June 1998. The topic was Asthma in Early Childhood. U.S. and German scientists reported on the epidemiology of asthma, genetic markers, cellular mechanisms of airway hyperreactivity, asthma and infection, and primary and secondary prevention of bronchial asthma. The meeting gave investigators from both countries an opportunity to share information, develop new collaborations, and plan new directions for future joint research. ¶

¶ India ¶

NHLBI has collaborated with scientists in India for more than 20 years. Currently, U.S. and Indian researchers collaborate under the terms of the Gandhi-Reagan Science and Technology Initiative begun in 1982. Specific 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 project deals with mutual interest in basic cellular research supported by two research grants: one awarded in FY 98 and another nearing completion. Both grants deal with aspects of the development and differentiation of the nervous system. The scientists are using the latest molecular biology techniques to study growth factors in conditioned C6 glioma media and their implications in viral diseases of the central nervous system. This collaboration has resulted in several 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 manuscripts, one on A Device for Transplantation of Single Cells and another on A Device for Single-Cell Transplantation With Minimal Transfer of Suspension Fluid, deal with 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. ¶

In addition, the joint project has resulted in the generation of a monoclonal antibody (6DS1) 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. The investigators anticipate that this research could lead to the development of a diagnostic tool in the histopathological grading and localization of human brain tumors. ¶

The grant awarded in FY 98 also includes the Chief of the Laboratory of Biochemical Genetics as co-principal investigator and supports joint research on the immortalization of human fetal neurons, the role of trophic factors in their survival, and the study of apoptotic features of selective neuronal death during aging of neurons in culture. The goals of this project are to culture and immortalize human neuronal cell lines and introduce the cells into the rodent central nervous system to assess their differentiation potential. This grant has a duration of 5 years, and it provides international travel costs for continued exchange visits to NHLBI. ¶

In FY 99, the Indian professor worked in the Laboratory of Biochemistry and Genetics, NHLBI, continuing this joint project as a potentially valuable approach to transplantation studies in neurodegenerative diseases. The project is expected to continue toward the genetic manipulation of neurons

in culture to immortalize them and to identify changes in their gene expression during aging.¶

¶ Italy¶

NHLBI has collaborated with Italian scientists under bilateral agreement for more than 20 years. The current joint research effort with Italy is conducted under the auspices of the 5th U.S.-Italy Science and Technology Agreement, signed in Washington, D.C., on November 5, 1997, and 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, are collaborating in cardiovascular and pulmonary research of mutual interest and benefit.¶

Since the 1st U.S.-Italy Joint Workshop on Measurement and Control of Cardiovascular Risk Factors was held in Rome, in December 1978, between NHLBI and the University of Milan, scientists from both sides have conducted many joint research projects and shared information on a range of topics. Joint symposia have given U.S. and Italian scientists the opportunity to share recent data, develop proposals for new research projects, and discuss new research priorities.¶

The most recent U.S.-Italy joint symposium on CVD was held in Bethesda, Maryland, in November 1998. The topic was Vascular Biology of Atherosclerosis. The following areas were discussed: the pathophysiology of the molecular wall, molecular genetics, immune responses, inflammatory responses, gene therapy, and drug responses. Recommendations for future studies include new technologies, the role of inflammation in CVD, novel approaches to gene therapy, regulation and control of vascular growth, and functional genomics in CVD.¶

The next U.S.-Italy symposium in cardiovascular research is scheduled for December 1999, at the University of Milan. Topics will include genetics and gene therapy, molecular cardiomyopathy, pharmacogenetics of lipid disorders, cholesterol studies in animal models, growth factors, cell proliferation, and collagen synthesis in human atherosclerosis.¶

A U.S.-Italy workshop on pulmonary dis-

ease was held in Ferrara, Italy, in October 1997. It focused on Non-invasive Assessment of Airway Inflammation. Investigators from both sides exchanged information in the following areas: inflammation in chronic obstructive airway disease; the distribution and chronobiology of inflammation; methods and validation of sputum induction and content; circulating markers of airway inflammation; the role of nitric oxide; the differences in airway disease and disease severity; induction of sputum to monitor airway inflammation in clinical trials; and the effects of long-acting bronchodilators on sputum cells and mediators.¶

The next joint meeting in pulmonary research will be held in Palermo, Italy, on October 14-15, 1999. The topic will be Biochemical Markers and Assessment of Lung Diseases: Prognostic, Diagnostic, and Therapeutic Implications. A number of important and timely topics will be discussed. These topics include 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 biomarkers in the early detection of lung cancer.¶

The 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 impaired renal function in patients with cirrhosis; the vasoconstrictors produced in the liver or introduced by portal inflow; and the pathogenesis of hepatic portal hypertension. As a result of this joint effort, the researchers have developed new pharmacological approaches to this clinical problem. They have verified the role of cytochrome P-450-dependent metabolites of arachidonic acid, 20-HETE, and 11,12-EET in the control of portal resistance and response to endothelin-1 and have evaluated their level of inhibition on basal portal pressure and on vasoconstriction by endothelin-1.¶

Another cooperative effort in cardiovascular research relates to cholesterol transport. A scientist from the Institute of Pharmacological Sciences, University of Milan,

worked with the Chairman, Department of Pathology, University of Washington, Seattle, on a project that provided evidence for the role of prenylated proteins in the emergence of cells from the quiescent state to cell-cycle progression. Studies were based on the mitogenic role of platelet-derived growth factor (PDGF) in the Swiss 3T3 cell line. The scientists found that geranylgeranylated protein Rho B plays a role in the control of PDGF-induced cell migration, morphology, and proliferation. The Rho A protein regulates the assembly of focal adhesions and the organization of the actin cytoskeleton. The specific role of Rho B is still unknown. The scientists plan to continue efforts to determine whether Rho B is a key regulator of cytoskeletal integrity, cell morphology, adhesion, and migration in arterial smooth muscle cells and in cardiovascular disorders.¶

Joint pulmonary research continued between professors of pharmacology at the University of Florence and the University of Milan and a professor of medicine and physiology at the Cardiovascular Research Institute, University of California, San Francisco. The focus is the effect of endogenous nitric oxide on bronchoconstriction induced by cold air inhalation in guinea pigs and mediated by kinins and tachykinins. The scientists also studied the role of NK₁ receptors in neutrophil-epithelial interactions. They reported that interleukin 8 (IL-8) injected into the airway lumen of the guinea pig trachea caused neutrophil recruitment. The U.S. researcher had previously shown that neutrophil elastase is the most potent secretagogue of goblet cells involved in peripheral airway obstruction by mucous plugs in critically ill patients with asthma. These studies were followed by a collaborative study in patients with asthma, which showed that nitric oxide also participates in asthmatic bronchomotor responses in human disease. Further collaboration will focus on the role of tachykinins, epithelial cells, and macrophages in the release of IL-8 and on the consequent accumulation of neutrophils in the lungs and airways.¶

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.

She will participate in the 3rd International Symposium on Women's Health and Menopause: Risk Reduction Strategies and Improved Quality of Health, to be held in Venice, in October 1999. In follow-up to the 2nd International Symposium on Women's Health, in Florence, in 1998, NHLBI and the NIH's Women's Health Initiative program hosted a series of joint meetings with the Lorenzini Foundation, in Bethesda, Maryland, in November 1998 and in March 1999. The next meetings are planned for November 1999 and March 2000. At these meetings, a position paper will be developed by 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. This document will be presented during the 4th International Symposium on Women's Health and Menopause, in Washington, D.C., in June 2001. It is anticipated that this presentation will lead to new strategies for the promotion of women's health in the future. ¶

¶ Japan¶

For more than 20 years, NHLBI has coordinated a series of U.S. and Japanese joint projects in research on CVD, providing unique opportunities for comparative studies and new insights into patterns of CVD. This collaboration has shown significant differences in CVD patterns in the United States and Japan, particularly with regard to stroke and coronary heart disease. This observation has led to comparative studies focusing on four areas: (1) dietary studies of the positive or negative effects of calcium, potassium, physical exercise, and alcohol 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 on 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 (NCC), 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 cardiovascular 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 rate 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, whereas that of acute myocardial infarction was 15 and 26 per 100,000 population, respectively. 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, both sides proposed to continue joint studies in the four areas: ¶

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

During FY 98, the principal investigator for the U.S. Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study, which is a cardiovascular data and specimen library at Louisiana State University Medical Center, New Orleans, visited Japan. The purpose was to discuss joint interests with a number of collaborators in Japan, including a cardiovascular pathologist conducting a parallel PDAY study at NCC. He also met

with a researcher at Toho University, Tokyo, regarding publication of immunohistochemical findings on apolipoproteins in the arteries of PDAY subjects. Visits to collaborators at Keio University, Hiroshima, and Kugazama Hospital, Tokyo, focused on studies of peroxidability of lipoproteins and the effects on atherosclerosis. The visit also included scientific discussions at the Department of Medicine, Shimane University, Izumo, regarding participants in the Honolulu Heart Project and the Ten Cities Study in Japan. ¶

A joint study was initiated in November 1998 between the Director of the Minnesota Heart Program, University of Minnesota, Minneapolis, and the Deputy Director, Department of Preventive Cardiology, NCC. 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, data collection methods, and ethical and legal barriers to surveillance projects. In June 1999, the Japanese investigator made a reciprocal visit to the University of Minnesota, bringing with him a data set that was then merged with the U.S. database, for joint analyses. It is anticipated that a significant publication will result from this joint study. ¶

¶ Korea¶

NHLBI cooperates 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 conducted, focusing on the role of oxygen radical-mediated oxidation of proteins and lipids in various biological processes, including aging, atherosclerosis, ischemia-perfusion injury, and inflammation and signal transduction. ¶

In 1992, the Laboratory of Biochemistry initiated a collaboration with the Research Center for Molecular Microbiology (RCMM), Seoul National University. This collaboration was renewed and expanded in 1995 by the Director, NHLBI, and the Director, RCMM. During FY 96, the Director, NHLBI, made a reciprocal visit to RCMM and presented a lecture on Future Directions in Cardiovascular Research. ¶

RCMM cooperation continued during FY 99. Two investigators from the Department of Microbiology, Seoul National University,

collaborated with NHLBI scientists in studies of free radicals and oxidative stress in the signal transduction pathway. They studied the generation of free radicals during the glycation reaction, using electron paramagnetic resonance spectroscopy. Current data from animal pathology studies have shown that advanced glycation end products accumulate in animal tissue, resulting in atherosclerosis, diabetes mellitus, and aging. In addition, the recent findings have shown that glycated proteins can function as catalytic centers for additional free radical generation. These advanced glycation end products are associated particularly with long-lived proteins such as collagen, lens crystalline, and nerve proteins. Joint research findings were published in the *Journal of Biological Chemistry* (January 1996) and will be presented at the 8th Congress of the International Association of Biomedical Gerontology, in Kyongju, Korea, in February 2000.

Other collaborations focused on studies of the activation mechanism of the human manganese superoxide dismutase gene, which is mediated by oxidative stress. The results of this investigation will be published in the *Journal of Biological Chemistry* (December 1999).

Another collaboration, between the Korea Research Institute of Bioscience and Biotechnology and the Laboratory of Cell Signaling, NHLBI, focused on the structural characterization of thioredoxin peroxidase, an antioxidant of hydrogen peroxide (H_2O_2). Although peroxidase is considered to be a toxic byproduct of respiration, increasing evidence suggests that the production of H_2O_2 may be an integral component of membrane receptor signaling. The researchers also studied the second-messenger function of H_2O_2 and the identification of the cellular target molecules on which H_2O_2 acts.

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 is designated a center of excellence by the Korea Science and Engineering Foundation. Under this agreement, Korea and the United States will exchange 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 in August 1999. The focus is on the basic research of

peroxisomal enzymes (enzymes that eliminate H_2O_2), their crystalline structure, the generation of peroxisomal null mice, and the identification of proteins that contain H_2O_2 -sensitive cysteine residues during oxidative stress signaling.

Pakistan
Increasing knowledge and awareness of CVD, its determinants, and effective ways to prevent it are the goals of an agreement between NHLBI and the National Institute of Cardiovascular Diseases, Karachi, which provides the framework for a joint epidemiology study. The community study, initiated in 1993, further aims to expand the Pakistani capacity for assessment and modification of CVD risk factors. One of the questions being explored is whether U.S. CVD prevention programs can be adapted to Pakistani subpopulations to reduce the high rates of morbidity and mortality.

The study participants are divided between intervention families and control families, and their progress is being compared. Data analysis will assess the short-term effectiveness of the intervention. The partnership of both institutes is evident in the design, planning, data standardization, control, and analysis. Exchanges of scientists, joint meetings, and development of joint research publications are also included within the scope of the project. A no-cost extension of the project was approved through May 2000. Two Pakistani scientists, including the coordinator for the joint study, visited the University of North Carolina, Chapel Hill, during FY 99 to discuss issues of data comparability with U.S. counterparts and to work on joint research reports. A second rescreen of the study participants is scheduled for the fall of 1999. It is expected that the results will lead to improved evaluation of changing risk factors over time.

Poland
The NHLBI-Poland collaboration in CVD research was first conducted under the umbrella U.S.-Poland Agreement for Health Cooperation, signed by the U.S. Secretary of State, Henry Kissinger, and the Deputy Prime Minister and Chairman of the Planning Commission of the Polish People's Republic, Mieczyslaw Jajkowski, on October 8, 1974. Specific joint interests in cardiopulmonary research are outlined in Summaries of Dis-

cussions between NHLBI and the Polish National Institute of Cardiology. The most recent document was signed in August 1998, after a U.S.-Poland Joint Workshop in Cardiopulmonary Disease, in Rockville, Maryland, in March 1998.

Marked differences in CVD and risk factor trends in the two countries are of special interest for joint research. For instance, although the magnitude of the disability from ischemic heart disease is high in both countries, death rates in the United States from 1974 to 1994 declined by 43%, while they increased in Poland by approximately 70%. For COPD, mortality rates declined slightly in the United States for men and significantly so in Poland for men and women during 1980-1993. The United States experienced a significant increase in these rates for women during the same period (World Health Statistics Annual, WHO). Also, with the introduction of a free-market system in Poland in 1989, trends in mortality rates attributed to smoking in the adult population, aged 35-69 years, increased about 64% in men and almost 10-fold in women, whereas mortality not attributed to smoking remained stable. The United States has been successful in establishing nationwide public health policies to reduce cigarette smoking, whereas Poland has not yet introduced such policies. These differences in trends have provided 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 POLMONICA 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. In these joint efforts, scientists in Warsaw, Krakow, and the United States have assessed the prevalence of cardiopulmonary diseases and their risk factors in urban and rural populations, as well as differences between trends in the United States and Poland.

In October 1998 and April 1999, researchers from the Collaborative Studies Coordinating Center and the University of Alabama, Birmingham, collaborated with scientists in Warsaw and Krakow to complete comparisons of epidemiologic data.

They prepared a series of joint manuscripts on heart rate variability, community surveillance correlates, hypertension incidence and mortality, smoking and lipids, correlates of weight gain, and low lipids and mortality.¶

Scientist exchanges continued to be a valuable tool to develop new initiatives and facilitate cutting-edge joint research projects. During FY-99, a researcher from the Department of Medicine, Jagellonian University, Krakow, carried out joint research with the Director of the Center for Experimental Therapeutics and Reperfusion Injury, Brigham and Women's Hospital, Boston. The Polish researchers provided samples from their population of patients with aspirin-triggered asthma, and the U.S. researchers measured the presence of 15-epi-lipoxin A₄. The joint research showed that activated cells from patients with asthma had less ability to generate lipoxins than cells from healthy subjects. This finding suggests that an enzyme defect and/or lowering of activity may be risk factors in aspirin-sensitive asthmatics and in other subgroups of asthmatics. An abstract on these results was presented at the 1999 American Thoracic Society, American Lung Association International Conference, in San Diego, California, in April 1999.¶

Also in FY 99, a new collaboration of mutual benefit was initiated between researchers at the Center for Clinical and Experimental Medicine, Warsaw, and Harvard Medical School, Brigham and Women's Hospital, Boston, Massachusetts. This joint work focuses on basic cardiopulmonary research utilizing genetically engineered mice. To facilitate this program, a Polish researcher visited the U.S. hospital to share new technologies important in maintaining and genotyping this animal model in Warsaw. Continued collaborations in this area are planned for FY 00.¶

¶
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, during a meeting between the coordinators of the U.S.-Russian collaboration in cardiopulmonary research—the Director of NHLBI, the Director of the Cardiology Research Center of Russia, and the Director of the National Center for Preventive Medicine,

Moscow—an agreement was reached to restructure the collaboration into two main areas: CVD and pulmonary disease. The priority areas agreed on for CVD include basic research; prevention, education, and control in heart disease; hypertension; continued joint epidemiologic studies; and management of ischemic heart disease. For pulmonary disease, the priority areas are basic research, genetic studies, prevention, asthma, and pulmonary hypertension. Exchanges of scientists in pulmonary and cardiovascular research will be continued.¶

NHLBI, along with four other NIH Institutes, has also been an active participant in the Gore-Chernomyrdin subcommittee meetings in the priority area of health promotion and disease prevention. (The four Institutes are the National Cancer Institute, the National Institute on Drug Abuse, the National Institute on Alcohol Abuse and Alcoholism, and the National Institute of Dental and Craniofacial Research.) Exchanges of information with Russian colleagues have been ongoing, to discuss potential collaborative projects that may build on previously successful research projects and to establish new and alternative mechanisms for funding joint research.¶

During FY-99, a U.S.-Russia Joint Symposium in Basic Research in Cardiovascular and Pulmonary Diseases was held in New Orleans, Louisiana, on March 4–6, 1999. From each side, five scientists in the cardiovascular area and two scientists in the pulmonary area participated. The presentations addressed cellular mechanisms of human atherosclerosis, vascular remodeling, molecular regulation of differentiation in smooth muscle cells, molecular mechanisms of endothelial cell dysfunction, hypoxic signaling pathways in vascular cells, association of *Chlamydia pneumoniae* and atherosclerosis, and vessel wall biology and gene therapy.¶

Scientists from both countries proposed the following topics for future collaboration in the area of basic research on heart and vascular diseases:¶

1. molecular mechanisms of contraction in smooth muscle cells;¶
2. gene regulation and delivery to specific targets in the cardiovascular system;¶
3. cellular differentiation and its regulation in the vasculature and in atherosclerosis;¶
4. cell interaction, inflammation, and in-

fectious agents in atherogenesis; and¶

5. biomechanics and cellular signaling in the cardiovascular system.¶

A Joint U.S.-Russia Symposium on Basic Research in Cardiovascular and Pulmonary Diseases is planned to be held in Russia in FY 01.¶

Future plans for exchanges of scientists in the pulmonary research area were also discussed during the New Orleans symposium. The following topics were proposed for future collaboration:¶

1. gene regulation and delivery to specific targets in the pulmonary system;¶
2. biomechanics and cellular signaling in the pulmonary system;¶
3. pathogenic mechanisms of primary pulmonary hypertension; and¶
4. cell interaction, inflammation, and infectious agents in pulmonary disease.¶

A U.S.-Russia Joint Symposium on Arrhythmia was held in Moscow, on May 24–27, 1999. Seven U.S. scientists participated with their Russian counterparts in discussions of topics including atrial and ventricular arrhythmias, antiarrhythmic drugs, and stratification of risk for sudden cardiac death.¶

The scientists proposed the following topics for future collaboration in the area of arrhythmia:¶

1. risk stratification for sudden cardiac death and its prevention through development of patient populations, databases, and clinical trials—resources that enable detailed clinical studies in high-impact areas of public health;¶
2. basic clinical and epidemiologic studies to prevent lethal arrhythmias in heart failure patients;¶
3. development, evaluation, and clinical testing of pharmacological and nonpharmacological therapies for arrhythmias, including catheter ablation technologies; and¶
4. consideration of exploration of genetic population resources and new molecular variation studies, in basic and clinical approaches to treatment of difficult arrhythmias.¶

A joint U.S.-Russia Symposium on Arrhythmia is planned for the United States in FY 01.¶

Three Russian scientists will visit the United States in November 1999. The scientists will participate in the American Heart Association meeting in Atlanta, Georgia, on

November 7–10, 1999, and also will visit laboratories in the United States that have been agreed on by both countries. This scientific visit will provide an opportunity for U.S. and Russian scientists to develop joint research proposals of mutual interest and benefit. ¶

¶ **South Africa¶**

U.S. and South African scientists have collaborated since 1996 on the growing problem of hypertension in both countries. The 2nd U.S.-South Africa Workshop on Hypertension in Blacks was held at the NIH, in Bethesda, Maryland, in July 1998. Both sides 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. ¶

In follow-up of the workshop, there were exchanges of scientists and information. The deans of Tulane University, New Orleans, Louisiana, and the National School of Public Health, at the Medical University of Southern Africa, Medunsa, exchanged information during FY 99. ¶

A South African scientist visited the United States in March–April 1999 to continue joint research on salt sensitivity in black hypertensives with U.S. researchers in cardiovascular epidemiology and clinical applications at Wayne State University, Detroit, Michigan. This visit was in follow-up of joint plans to study salt sensitivity in black hypertensives by linking ongoing studies in both countries. The scientists also developed a joint protocol to ensure standardized methodologies for fieldwork and laboratory analyses that will be compared. A joint research proposal was prepared and submitted for consideration for funding. ¶

¶ **Uganda¶**

The impact of tuberculosis on human immunodeficiency virus (HIV) disease is the topic of a 5-year grant awarded to a scientist from Case Western Reserve University, Cleveland, Ohio, for research in Uganda. This research will investigate the hypothesis that the interaction of tuberculosis and HIV

during active tuberculosis predisposes the host to progression of HIV through both virologic and immunologic events. The research will also explore the central role played in the process by the interaction of macrophages with T cells. The Ugandan counterpart for this research is the Joint Clinical Research Center, Kampala. The award is expected to begin in 1999 and continue for 5 years. ¶

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Vietnam → → → →
U.S. and Vietnamese officials and scientists have collaborated since 1993 in research on blood diseases, such as aplastic anemia and hepatitis. The cooperation between NHLBI and the Institutes of Blood Transfusion and Hematology, in Hanoi and Ho Chi Minh City, also includes the safety of the blood supply, which is an important concern for patients requiring blood transfusions and their physicians. This joint research has developed as an extension of the 10-year U.S.-Thai cooperation. ¶

In January 1999, a Vietnamese scientist worked with staff of the Hematology Branch, including the Bone Marrow Transplantation Unit, NHLBI, for 3 months of joint research on bone marrow transplantation, developing protocols for bone marrow transplantation in Vietnam and comparing rates of graft-versus-host disease in Vietnamese and U.S. populations. He also interacted productively with staff in NIH research laboratories focused on the management of malignant blood diseases. ¶

The Head, Hematology Branch, NHLBI, as well as the Head, Department of Transfusion Medicine, and a representative of the American Red Cross visited Vietnam to present another in a series of seminars to Vietnamese scientists and health care professionals in Hanoi and Ho Chi Minh City. The seminars addressed blood transfusion safety and the organization of blood transfusion services. Plans were made to continue joint research on seronegative hepatitis in patients in Hanoi. Proposals were developed for the next series of lectures, as well as exchanges of scientists for FY 00 in transfusion medicine. The scientists met with investigators at the National Institute of Hematology and Blood Transfusion, Hanoi, and the Bach Mai Hospital, Hanoi University Medical School. The Vietnamese scientist in Ho Chi Minh City has been re-elected as president of the

Vietnamese national hematology society. ¶
Collaborative interests were further strengthened during the visit, when the Director, National Institute of Hematology and Blood Transfusion, agreed to cooperate on collection of valuable serum and stool specimens from patients with seronegative acute hepatitis, which is reported to be particularly common in Vietnam. U.S. scientists will use these specimens for molecular studies seeking to discover a new virus responsible for this type of acute hepatitis, fulminant hepatitis of childhood, and post-hepatitis aplastic anemia. Specimens of liver and bone marrow from such cases have not proved useful in experiments, probably because they are too damaged due to the late stage of disease. Scientists in both countries are looking forward to continued collaboration. ¶

¶ **Activities With International and Multinational Organizations¶**

Combating heart, lung, and blood diseases globally was the focus of the NHLBI activities with international agencies and multinational organizations during FY 99. NHLBI staff serve as consultants to PAHO, WHO, and other international organizations that contribute to worldwide plans for the prevention and control of CVD and pulmonary and blood diseases in both developed and developing countries. New collaborations with PAHO in CVD research were initiated in FY 99, in recognition of the jointly celebrated 50th year anniversaries of NHLBI and WHO. ¶

Since 1980, the Institute has served as a WHO Collaborating Center for Cardiovascular Research and Training for the Americas and, in this role, provides information and data for use throughout the world. The center provides advisory services to WHO, 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 and control of CVD and advances in basic research. ¶

The NHLBI Director and senior staff participate in WHO advisory committee meetings and contribute to WHO reports in a number of areas. The Director also serves as special advisor to the World Hypertension League board. The Coordinator of the Institute's National High Blood Pressure Ed-

education Program is the North American editor of the World Hypertension League Newsletter. ¶

The Director, NHLBI, has been elected president of the World Hypertension League beginning in August 2000. ¶

During FY 99, NHLBI actively participated in meetings and symposia with international and multinational organizations. In September 1999, the Director, Division of Lung Diseases, represented the executive committee of GINA at a meeting in Harare, Zimbabwe. Scientists from eight countries (Botswana, Cameroon, Ghana, Malawi, South Africa, Sudan, Zambia, and Zimbabwe) met to discuss medical problems associated with asthma. The meeting was sponsored by the Pan African Workshop on Allergy and Asthma Immunology and GINA. The participants agreed on the importance of discussions between African respiratory physicians, allergists, and health education specialists to begin to collect information on the growing problem of asthma in Africa and on challenges related to a shortage of funds for medications, manpower development, and research. GINA meetings were also conducted in Brussels, Belgium, in January, and in Salzburg, Austria, in March 1999. World Asthma Day 2000 will take place on May 3, 2000, when educational and communications activities will be held in more than 35 countries throughout the world. ¶

NHLBI is collaborating with PAHO on PAHI in North, Central, and South America and the Caribbean. Hypertension is the most prevalent CVD in the Americas, affecting approximately one in four adults (about 140 million people). After the May 1998 PAHO-NHLBI-FIC conference on Global Shifts in Disease Burden: the Cardiovascular Disease Pandemic, NHLBI hosted an NHLBI-PAHO planning meeting on Translating Science into Action, at the NIH, in Bethesda, in March 1999. Participants included representatives from Argentina, Barbados, Brazil, Canada, Chile, Cuba, Mexico, Uruguay, the United States, and international and regional scientific organizations. The planning meeting culminated in a joint PAHI statement in English and in Spanish, outlining proposed activities for the future. In addition to PAHO, NHLBI, and delegates to the March 1999 meeting, six international organizations have endorsed the PAHI state-

ment. A joint article by the Directors of PAHO and NHLBI has been prepared for publication in the World Hypertension League Newsletter. ¶

¶ **Extramural Programs ¶**

NHLBI supports a broad range of research projects through international grants, contracts, cooperative agreements, and fellowships with foreign institutions. These international activities provide valuable opportunities to draw on worldwide resources and expertise. ¶

¶ **Grants ¶**

NHLBI supported 14 projects involving foreign investigators during FY 99; 11 grants were awarded to institutions in Canada. The studies covered a broad spectrum of research topics, including the following: activated mutants as probes of granulocyte-macrophage colony-stimulating factor receptor function; genetic risk factors for hyperhomocysteinemia; cardiac lesions in HIV-1 transgenic mice; pathological assessment of lung volume reduction; and remodeling of human airways in disease. Four grants were awarded to institutions in the United Kingdom. These dealt with a community-based study on occupational asthma; antithrombin activation and proteinase inhibition; social and occupational influences on health and illness; and the ontogeny of fetal sensitization to allergens and asthma. ¶

¶ **Cooperative Agreements ¶**

In FY 99, NHLBI initiated collaboration with the University of British Columbia, Vancouver, and with 10 other International Lung Health Study centers in the United States, in a follow-up study of smoking intervention, to determine the benefits of the program over a 12- to 15-year period. Canadian researchers also studied the role of gender, airways reactivity, weight gain, and comorbidities in determining the rate of decline in pulmonary function. ¶

¶ **Fellowships ¶**

A fellowship and award extension were given to a researcher at the University of Cambridge, England, for studies of antithrombin activation and inhibition of proteinase. ¶

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Contracts ¶

A contract was 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, or 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. The Childhood Asthma Management Program study has enrolled 1,041 children; 41% are girls and 31% are in minority groups. The clinical center is now in the transition phase in which daily medication is stopped, to determine whether the effects of 4 1/2 years of anti-inflammatory therapy are dependent on continuous administration of medication or whether the therapy has affected the course of disease. Publication of major outcomes of the study is expected in the spring of 2000. ¶

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International Meetings ¶

During FY 99, the NHLBI staff contributed to a number of international planning meetings. The Director, NHLBI, participated in a meeting of the World Hypertension League, in Buenos Aires, Argentina; the meeting 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, in Geneva, Switzerland. ¶

An NHLBI representative participated in the G8 Cardio meeting in Rome, Italy, in October 1998. This meeting involved the G8 countries: Canada, France, Germany, Italy, Japan, Russia, the United Kingdom, and the United States. The goal of Cardio is concerted action to support a feasibility study and the development of a test model for a global cardiovascular database project. ¶

Institute staff made presentations at the December 1998 WHO conference on Today and Tomorrow of Health Promotion, in Warsaw, Poland, and the International Workshop on Social Marketing Planning Systems and Models of Health Behavior, in Mérida, Mexico, in April 1999. In March

<p>1999, NHLBI hosted a planning meeting on Translating Science Into Action, at the NIH in Bethesda, in collaboration with PAHO.¶</p> <p>Other international meetings in the cardiovascular area in which NHLBI staff participated were the following:¶</p> <ul style="list-style-type: none"> ■ Diabetes and Cardiovascular Disease Conference, in Winnipeg, Manitoba;¶ ■ 14th Annual International Interdisciplinary Conference on Hypertension in Blacks, in Toronto;¶ ■ International Society for Magnetic Resonance in Medicine Workshop on Flow and Motion in Cardiovascular Magnetic Resonance Imaging, in London, England;¶ ■ Delphic Conference on the Development of a Revised Definition of Myocardial Infarction for the 21st Century, in Nice, France;¶ ■ 2nd International Congress on Coronary Artery Disease, in Munich, Germany;¶ ■ meeting for the Prevention and Control 	<p>of Cardiovascular Diseases in the Americas, in Mexico City, Mexico;¶</p> <ul style="list-style-type: none"> ■ Annual Meeting of the International Society for Hematotherapy and Graft Engineering, in Oslo, Norway; and¶ ■ 70th European Atherosclerosis Society Congress, in Geneva, Switzerland.¶ <p>Also during FY 99, the Director for the National Center on Sleep Disorders Research participated in the 6th International Symposium on Sleep and Respiration, in Banff, Alberta, to present a talk on sleep disorders from a national health perspective. His presentation focused on NHLBI's activities to raise awareness of sleep disorders among primary care physicians in the United States.¶</p> <p>In the area of basic research, the Chief, Laboratory of Biochemistry, participated in the XIIIth International Biophysics Congress, in New Delhi, India, and an NHLBI scientist presented a lecture on Functional Imaging of the Heart, at the International</p>	<p>Symposium in Ultrafast Magnetic Resonance Imaging in Medicine, in Kyoto, Japan.¶</p> <p>¶</p> <p>Intramural Programs and Activities¶</p> <p>Scientists from many countries have been given the opportunity to conduct research under the NIH Visiting Program. In FY 99, 44 Visiting Associates, 104 Visiting Fellows, 40 Special Volunteers, and 44 Visiting Scientists participated in joint research in the NHLBI Division of Intramural Research. Countries represented included the following: Argentina, Australia, Austria, Canada, Chile, China, Denmark, Finland, France, Germany, Iceland, India, Iran, Israel, Italy, Japan, Korea, Mexico, Morocco, the Netherlands, Nigeria, Peru, the Philippines, Poland, Portugal, Romania, Russia, South Africa, Spain, Sweden, Switzerland, Turkey, Ukraine, United Kingdom, Vietnam, and Taiwan.</p>
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