IV.
National Institute on Aging

INTRODUCTION

The National Institute on Aging (NIA) conducts and supports biomedical, social, and behavioral research, training, dissemination of health information, and other programs that address the aging process and the diseases, special problems, and needs of the aged. NIA research priorities include Alzheimer's disease; the aging process, frailty, disability, and rehabilitation; health and effective functioning; and long-term care.

NIA awards grants to research institutions through extramural grant programs—the Behavioral and Social Research Program, the Biology of Aging Program, the Geriatrics Program, and the Neuroscience and Neuropsychology of Aging Program. In addition, scientists conduct intramural research through the Epidemiology, Demography, and Biometry Program and the Intramural Research Laboratory Program.

The NIA Office of International Activities coordinates international activities under bilateral, multilateral, and other agreements and works with NIA scientists to develop an overall strategy to advance the NIA mission in international research on aging.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

In fiscal year 1999 (FY 99), the Office of Demography of Aging (ODA), Behavior and Social Research Program, was active in encouraging and supporting production of comparable data by other nations, to continue the momentum fueled by the Denver G8 Summit Meeting in 1997. The last paragraph of the Denver Summit communiqué on population aging has acted as a powerful catalyst and has spurred several international organizations and some national governments to make research on population aging a higher priority in their agendas. It reads as follows:

> We agreed that it is important to learn from one another how our policies and programs can promote active aging and advance structural reforms to preserve and strengthen our pension, health, and long-term care systems. Our governments will work together, within the OECD [Organization for Economic Cooperation and Development] and with other international organizations, to promote active aging through information exchanges and cross-national research. We encourage collaborative biomedical and behavioral research to improve active life expectancy and reduce disability and have directed our officials to identify gaps in our knowledge and explore developing comparable data in our nations to improve our capacity to address the challenges of population aging into the 21st century.

ODA, a major contributor to this communiqué, highlighted current research issues related to population aging, projections, retirement, disability trends, and cross-national research opportunities and stressed the need for appropriate and comparable data. ODA has been asked to participate in preparations for the July 2000 G8 meeting in Okinawa, Japan, where it is likely that issues of aging will again be prominent and will include the implications of aging societies for health and long-term care policy.

In FY 99, as a part of joint efforts with the Institute of Biophysics, University of Linz, Austria, a scientist from the Section of Molecular and Clinical Pharmacology, Laboratory of Clinical Investigation, carried out successful experiments on double-labeled, cyan fluorescent protein at the N terminus and yellow fluorescent protein at the C terminus chimera of the human calcium channel pore-forming alpha 1C subunit prepared at NIA. For the first time, the functional expression of this chimera in tsA201 cells was demonstrated and fluorescence resonance energy transfer was observed as an enhanced fluorescence emission with the yellow fluorescent resonance energy transfers filter, on excitation of the cyan chromophore. This finding allows the research team to extend the study to monitoring of the state-dependent molecular motions of distant parts of the channel protein and resulted in several publications.

The Neuroscience and Neuropsychology of Aging Program supported collaboration between Karolinska Institute, Stockholm, Sweden, and investigators from the University of Colorado Health Sciences Center, Denver. The investigators conducted studies of neural grafts and growth factors, to find methods that may be useful in treating neurodegenerative diseases. The research has identified new neurotrophic factors, the receptors for those factors, and their functional activity in the brain. The findings support the potential use of neurotrophic factors in the treatment of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

County-to-County Activities and Bilateral Agreements

Italy

During FY 99, collaboration between NIA's Epidemiology, Demography, and Biometry (EDB) Program and the Aging Project of the Veneto Region (Progetto Veneto Anziani [PROVA] Study) of Italy continued on an observational investigation designed to depict the causal pathway from disease to disability in a representative group of older Italian men and women. This study focuses on the synergism between cardiovascular and osteoarticular diseases in the study population of 3,000 men and women aged 65 years or older, from the towns of Camposampiero and Rovigo, near Padua. An EDB Program investigator contributed to the development of the study and trained examiners to perform

physical assessments and performance measures of functioning.

Both the National Institute of Neurological Disorders and Stroke and NIA are continuing to work with the National Institute for Research and Care of the Elderly, under the U.S.-Italy Science and Technology Agreement. The Postural Control in the Elderly Study, Ospedale I Fraticini, Florence, includes the development of measures that identify specific components of balance problems and evaluation of how these components contribute to balance problems. A pilot study of reliability of the performance-based tests has been completed. An EDB Program investigator provided consultation on development of the testing instruments and will collaborate on data analysis.

EDB Program investigators continued joint research efforts in the Italian Longitudinal Study on Aging, which is being carried out as part of the Target Project on Aging, of the National Research Council of Italy. The study started in 1991 and has completed two follow-ups of a nationally representative cohort of 5,600 individuals who are 65–84 years old. Investigators are assessing the health status, the transition in physical and cognitive functioning with age, and the biological, socioeconomic, and environmental determinants of healthy aging.

Japan

The EDB Program and Japanese scientists have been involved in a series of studies (the Ni-Hon-Sea Study), to identify whether rates and causes of dementia are the same or different across cultures. Where rates are different, efforts will be made to discover modifiable risk factors. Procedures have been standardized for detection and diagnosis of dementia, which resulted from the cross-cultural, cross-national study of elderly Japanese in Hiroshima and Tokyo (Ni), Japan; Honolulu (Hon), Hawaii; and Seattle (Sea), Washington. Such standardization is essential for making valid and meaningful comparisons of rates and patterns of dementia across sites and will facilitate the study of genetic and environmental risk factors for dementia among migrating ethnic populations.

Activities With International and Multinational Organizations

In FY 99, the Neuroepidemology Office, EDB Program, collaborated on the study of Cardiovascular Determinants of Dementia (CASCADE), which is funded by the European Union and numerous site-specific grants and is coordinated by the Department of Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam, the Netherlands. The study is based on 1,800 magnetic resonance imaging (MRI) scans, completed in 10 communities throughout Europe, which were assessed qualitatively for white matter lesions and regional brain atrophy. The Neuroepidemology Office is analyzing the relationship of blood pressure, smoking, lipid levels, and depression to these brain changes. The CASCADE study also included a detailed battery of tests for cognitive function that measured memory, as well as executive and motor function. Using these results, the Neuroepidemology Office investigated the consequences of these brain changes in more detail than is usually available in large epidemiologic studies.

Through the Office of International and Refugee Health, of the U.S. Department of Health and Human Services (DHHS), ODA supports interagency agreements with the World Health Organization (WHO) and with the Pan American Health Organization (PAHO). Three WHO projects deal with issues of global health. The first project supports WHO research and WHO's report on "The Global Burden of Disease." This project has led to advances in methods for study of the burden of illness, its distal and proximal causes, and estimates for the future. The researchers have also compiled estimates of the burden of illness and its composition worldwide. The hope is that, by focusing on the distal and proximal causes of morbidity and mortality, it will be possible to make more accurate estimates of morbidity and mortality in the future, both for the United States and for other countries of the world. The second project, an analyses of the cost-effectiveness of health interventions, is closely related to the first project. This work will help to pinpoint which health issues are most important in various countries and regions of the world; to estimate the cost of selected interventions; and to project the consequences of these interventions for health and mortality. The third project addresses differences among countries in the organization of health systems, economic outcomes, and use of medical care for the aged. The goal of this project is to compare the economic incentives in medical care systems and relate these incentives to the allocation of resources and other outcomes across population groups.

Also at WHO, ODA supported the development of "minimum" data sets for research in countries of the African region, in FY 99. Investigators are collating available information from Ghana, Nigeria, South Africa, Tanzania, and Zimbabwe; they will create a systematic and coordinated approach to collecting needed data that could be applied in other countries. In addition to compiling minimal data, this project is stimulating interest in research and policy development in aging and population health in this region. Plans are under way for a meeting of scientists from each country, a coordinator from WHO, and advisors with expertise on data collection and measurement issues relevant to circumstances in specific countries.

Through the DHHS Office of International and Refugee Health, ODA supported PAHO in efforts to document the status of research on aging, in Latin America and the Caribbean, to promote a better understanding of collaborative cross-cultural research opportunities and resources available to researchers in the United States and in Latin America and the Caribbean. As part of this activity, PAHO has planned a regional meeting of the most active and promising researchers in this part of the world.

In addition, ODA supported the development of a global research agenda for population aging, through a contract with the National Academy of Sciences. The main focus of this effort is on populations in industrial nations, but the research agenda will also include developing countries. The Panel on a Research Agenda and New Data for an Aging World met three times in FY 99, including one meeting in London, England, which facilitated an exchange of ideas with European colleagues and representatives from international organizations.

Through the U.S. Bureau of the Census, ODA supported the Population Activities Unit of the United Nations Economic Commission for Europe, in Geneva, Switzerland; OECD; and the United Nations Population Division. Under an interagency agreement with the Population Activities Unit, ODA supported the assembly of cross-nationally

comparable microdata based on (a) the 1990 censuses of population and housing in selected European countries and (b) the documentation of the major ongoing research projects on aging that are being conducted in Europe. (Until very recently, the United States was virtually the only country making census microdata available to the public.) A cross-national workshop on the status of older populations in Europe is planned for December 1999, to promote wider use of the microdata resources that have been compiled so far.

Under the interagency agreement with OECD, ODA supported the compilation of international microdata on treating a spectrum of prevalent conditions in the older population with high aggregate medical expenditure. This project aims to make comparisons across countries in the provisions of health care policies, the approaches to treatment, and health outcomes. As part of the project, the Meeting on Study of Cross-National Differences in the Treatment of Ageing-Related Diseases was held in Paris, France, on May 20–21, 1999. This conference brought together health care and health policy experts from 21 countries.

Through the interagency agreement with the United Nations Population Division, ODA supported plans to make population estimates and projections for 5-year age groups up to age 100 years. Before this project was started, most information was compiled in age categories only up to age 80 years, with a final open-ended category of older than 80 years. This project provided the initiative to compile data resources for 5-year age groups up to age 100 years.

Extramural Programs

Behavioral and Social Research Program

The Behavioral and Social Research Program supports research and research training in behavioral and social sciences in relation to aging processes and the place of older people in society. The Program's international activities emphasize demographic research studies of health and productive functioning in the middle and later years of life and the delivery of services in the various cultures. The focus of these studies includes the work, health, and family responsibilities of men and women approaching retirement, as well as the cognitive functioning of older persons.

In FY 99, the Adult Psychological Development Branch continued to support the Victoria Longitudinal Study conducted by the University of Victoria, British Columbia. This study, which began in 1986, examines changes in cognitive functioning in late life. It is designed to evaluate the direction and magnitude of normal aging-related changes, individual differences in changes, and a wide range of correlates of differential changes (e.g., in systems of memory). The cooperative projects in behavior genetics at Pennsylvania State University, University Park, with the Institute of Gerontology, Jönköping, and Karolinska Institute, Stockholm, also continued to receive support.

The Demography and Population Epidemiology (DPE) Branch funded or cofunded several international efforts in data collection and analytic research. Data collection and archiving studies supported by these grants include the following:

- a study on population aging in Asia (Philippines, Singapore, Thailand, and Taiwan);
- surveys in Bangladesh, Indonesia, and Thailand;
- research to develop standardized measures within the database of the Luxembourg Income Study, Belgium;
- the Whitehall II Study of London-based civil servants in England;
- development and archiving of the German equivalent of the Michigan Panel Study of Income Dynamics;
- a small-grant project investigating the health conditions of the elderly in major urban areas in seven countries in Latin America and the Caribbean;
- a large, nationally representative study of Mexicans aged 50 years old or older and their spouses or partners that is designed to be comparable to the U.S. Health and Retirement Study and the National Health and Nutrition Examination Survey; and
- a biodemography project in Taiwan to examine the association between biological markers and survival.

By analyzing data from the Longitudinal Study of Aging Danish Twins and data on octogenarians, nonagenarians, and centenarians in China, DPE-supported investigators are conducting cutting-edge demographic research on the genetic and nongenetic determinants of longevity and physical and cognitive functioning and on why age-specific mortality decelerates with age.

The DPE Branch funded a new project to analyze differences across countries in changes in medical technology and the potentially important dynamic implications of these differences for changes in medical expenditures and health outcomes. The DPE Branch continued to support a study of how pension and tax policies affect participation in the labor force across a number of industrial countries. A new small-grant project examined Uruguay's decline in mortality from 1882 to 1950.

Through R13 conference grants, the DPE Branch continued to support the Réseau Espérance de Vie en Santé (REVES) meetings on active life expectancy.

DPE Branch grant projects that were completed in FY 99 include surveys of the oldest-old in Australia and Israel, a follow-up of the Malaysian Family Life Survey, and small-grant analytic studies of the elderly in China, Costa Rica, and Vietnam.

ODA continued to support the publication of wall charts on "Global Aging Into the 21st Century" and "Aging in the Americas Into the XXIst Century"; a comparative international chartbook, "Older Workers, Retirement, and Pensions"; an international brief, "Old Age Security Reform in China"; and a revision (in process) of an international population report, "An Aging World II," prepared by the Center for International Research, Bureau of the Census.

Biology of Aging Program

The Biology of Aging Program (BAP) supports studies on the biomarkers of aging, cell biology, endocrinology, pathobiology, physiology, genetics, immunology, molecular biology, and nutrition and metabolism. The Program also supports facilities that provide investigators with aging animals and cell cultures for use in research.

In FY 99, research at Prince Henry's Institute for Medical Research, Victoria, Australia, continued to explore the physiological function of local estrogen biosynthesis in bone and adipose tissue. Understanding those processes is essential to elucidating the role of estrogen in health changes in the elderly. BAP continued to support research on fibroblasts, growth control, aging, and programmed cell death (apoptosis), by an investigator at Lady Davis Institute for Medical

Research, Sir Mortimer B. Davis Jewish General Hospital, Montreal, Quebec. This highly productive research will allow the investigator to ultimately test whether cancer could be the result of a reduced ability of precancerous cells to undergo apoptosis.

Research at the University of Toronto, Ontario, was designed to probe the direct role of the telomerase enzyme and telomerase-associated proteins in cellular replicative senescence in two mammalian species (mouse and human). The investigator has created TEP1-knockout transgenic mice that provide a valuable model to determine whether age-related telomere shortening occurs in vivo and in vitro in the absence of the TEP1 protein. This genetic approach will yield important new information about the function of mammalian telomerase and telomeres, as well as highly valuable molecular reagents for investigating the role of telomerase and telomerase-associated proteins in the biology of aging.

A scientist at McGill University, Montreal, used a unique set of immunoreagents to examine age-related changes in the extracellular matrix of human articular cartilage, by looking for alterations in degradation of type II collagen. Fibrils containing type II collagen provide the tensile properties of cartilage and its molecular integrity. An understanding of how molecular damage to collagen occurs could lead to new therapeutic means of preventing changes that lead to loss of joint function. Comparison of cartilage isolated from diseased and healthy, age-matched knee (a common site for osteoarthritis) and age-matched ankle (a rare site for osteoarthritis) should shed light on whether there is a similarity in changes in aging and osteoarthritis.

Also at McGill University, research continued on aging of the male reproductive system in rats, in FY 99. The work focused on basic cellular and molecular research on aging of the testis, prostate, and epididymis.

The long-term goal of a study at University College, London, England, is to understand growth regulation of the human prostate in middle-aged men. Toward that objective, the investigators worked to isolate and conditionally immortalize epithelial and mesenchymal stem cells derived from human prostate tissue of healthy young men and of older men with benign prostatic hyperplasia.

The Office of Biological Resources and Resource Development provided aged rodents for research on aging, to the following foreign institutions: the University of Sydney and the University of Melbourne, Australia; the University of Alberta, Edmonton; the University of Manitoba, Winnipeg; Memorial University of Newfoundland, St. John's; the University of Toronto and Toronto Hospital; the National Research Council, Ottawa, Ontario; the University of Western Ontario, London; McGill University and the University of Montreal; the National Institute for Longevity Sciences, Obu City, Aichi, the University of Tokyo, and Fukuoka Prefectural University, Japan; and the University of Zürich, Switzerland.

Geriatrics Program

The Geriatrics Program supports research on issues related to the causes, prevention, and treatment of health problems in older people. These issues include physical frailty, osteoporosis, rehabilitation, geriatric pharmacology, geriatric assessment, and training in geriatric care.

In FY 99, the Geriatrics Program collaborated with researchers from the Institute of Health, Rome, Italy, on studying cancer prevalence in the elderly. The Geriatrics Program also worked with the National Cancer Institute at the National Institutes of Health (NIH) and with scientists from Genoa, Italy, and Eindhoven, the Netherlands, in considering (a) ways to assess the impact of an older cancer patient's other health problems on cancer prognosis and treatment and (b) how to expand the knowledge base and technology for assessment of comorbidity.

Neuroscience and Neuropsychology of Aging Program

The Neuroscience and Neuropsychology of Aging (NNA) Program supports studies of Alzheimer's disease (AD) and the structure and function of the central nervous system as it ages. The Program funds research and research training in fundamental neuroscience; integrative neurobiology; sleep disorders and biorhythms; dementias of aging; and cognition, sensory, perceptual, and motor processes.

In FY 99, the NNA Program supported collaboration between researchers from the University of Arkansas, Imperial College, London, England, and Glasgow University, Scotland, in studies aimed at elucidating early events in progression of AD. The studies focus on the role of interleukin 1 and other inflammatory molecules in initiating and propagating cell death and injury in AD, epilepsy, Down syndrome, and head injury.

The NNA Program continued to support investigators of the Indo-U.S. Cross-National Dementia Epidemiology Study of the University of Pittsburgh, Pennsylvania, in conjunction with the Centre for Ageing Research, New Delhi, India. The study is examining the distribution of and risk factors for dementing disorders among older people in Ballabgarh, a rural community in Northern India.

Scientists at the University of Washington Medical Center, Seattle, studied the epidemiology of dementia in older Japanese Americans and compared results cross-culturally with those of ongoing studies in Honolulu, Hawaii, and Hiroshima, Japan.

Investigations at Indiana University, Indianapolis, and the University of Ibadan, Nigeria, compared the age-specific prevalence and incidence of dementia disorders, in a sample of African Americans 65 years of age or older living in Indianapolis and a sample of age-matched Nigerians living in Ibadan. This study also compared the neuropathology of aging and of AD in these two groups and includes a prospective case–control study of risk factors for AD.

Researchers from the University of Southern California, Los Angeles, partnered with researchers at Karolinska Institute, Stockholm, and the Institute of Gerontology, Jönköping, to estimate the contribution of genes and environment in the expression of dementia in the Swedish Adoption/Twin Study of Aging.

Collaboration between investigators from the University of Colorado Health Sciences Center, Denver, and Karolinska Institute, Stockholm, provided insights into neuronal survival and maintenance of neural circuits throughout life. The researchers mapped the pattern of gene expression for two related neurotrophic factors (neurturin and neurotrophic factor derived from a glial cell line) and for specific receptor proteins for these factors in the developing and adult nervous system of rodents. Findings suggested multiple independent and overlapping roles for these two neurotrophic factors in the devel-

oping and adult organism. Studies have also implicated an important role for retinoids and related transcription factors in specific neuronal circuits of the adult brain. Continued exploration of the synthesis, localization, and biological effects of these factors and their receptor molecules in the adult and aging nervous system will contribute to understanding of the role of such factors in health and disease and will guide development of treatment strategies based on neurotrophic and other growth factors.

Other joint studies at the University of Colorado Health Sciences Center and Karolinska Institute identified new neurotrophic factors, the receptors for those factors, and their functional activity in the brain. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

International Meetings

October

The Deputy Associate Director, BAP, chaired a session on apoptosis and gave a presentation on Roles for Apoptosis in Aging and Age-Related Diseases at the 6th International Conference of Anticancer Research, in Kallithea, Halkidiki, Greece, in October 1998. The conference was sponsored by the Ministry of Development, General Secretariat for Research and Technology, and the International Institute of Anticancer Research, Kapandriti, Greece, and the International Society for the Study of Comparative Oncology, Silver Spring, Maryland.

Also in October, a scientist from the Laboratory of Clinical Investigation visited the University of Montreal. He presented a lecture on molecular aspects of insulin receptor signaling and discussed plans for collaborating on a project to examine the insulinomimetic effects of vanadium salts. In addition, he visited Merck Frosst Canada, Inc., to present a lecture on the same topic.

In addition, the NIA Associate Director for Extramural Affairs convened the meeting of the Inter-Institute Bioethics Interest Group, in Bethesda, Maryland. For that meeting, the Associate Director organized a series of three sessions on ethical issues in international research. The first session focused on bioethical considerations in planning and conduct of clinical research at foreign sites, particularly in developing nations. A second session compared and contrasted the activities of the Council of Europe Committee on Bioethics with the activities of the European Union and other organizations. The third session addressed ethical issues in research on human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) in developing countries, from the perspective of an NIH research program.

November

The Deputy Associate Director, BAP, was invited by the Danish Centre for Molecular Gerontology to present a report on Cellular Aging and the Molecular Clock and to cochair discussion on "molecular clocks" and changeable processes in the light of molecular, cellular, and animal studies, at the 2nd Annual Meeting on Molecular Clocks and Changeable Processes of Aging, in Middlefart, Denmark, in November 1998. Subsequently, the Deputy Associate Director visited the Danish Center for Molecular Gerontology at Aarhus University, to discuss common research interests with faculty at the center.

Also in November, an EDB Program investigator participated in the IVth Scandinavian Congress on Medicine and Science in Sports, in Lanti, Finland. She gave a presentation on the changes in handgrip strength over 27 years, in Japanese-American men.

December

The Chief, Epidemiology and Demography Office, traveled to Venice, Italy, in December 1998, to collaborate on research on epidemiology of aging by using data from the PROVA Study of Italy. In addition, a visit was made to Florence to consult with investigators on the In Chianti Study.

Also in December, an investigator from the Laboratory of Cardiovascular Science (LCS) visited the Beijing Medical University, China, to present a lecture on calcium sparks.

January

An investigator from LCS won a Chinese National Nature Science Foundation Award for Outstanding Young Investigator Overseas, in January 1999.

March

An investigator from the Laboratory of Clinical Investigation visited the University of Toronto in March 1999 and presented a lecture on the regulation of gene expression by nutrients in rodent adipocytes. He also discussed possible collaboration with scientists from the Cell Biology Program at the Hospital for Sick Children, Toronto.

In addition, scientists from the Laboratory of Genetics attended the Human Genome Organization 1999 International Meeting in Brisbane, Australia, and presented a lecture on developmental genomics and aging.

April

The Chief, Neuroepidemiology Office, gave a presentation on risk factors for stroke in female migraineurs and nonmigraineurs, at the 51st Annual Meeting of the American Academy of Neurology, in Toronto, in April 1999. She used data from the Genetic Epidemiology of Migraine study in the presentation. The Chief also attended discussions on the Ni-Hon-Sea Study in Honolulu, Hawaii. The purpose of this study is to determine whether rates and causes of dementia are the same across cultures.

Also in April, a medical sociologist from Italy's National Cancer Institute, Milan, and three biostatisticians from the Institute of Health, Rome, participated with staff from the Geriatrics Program in a work session on cancer prevalence in the elderly, in Bethesda, Maryland.

In addition, scientists from the Laboratory of Genetics participated in the Dutch Human Genetics Society's 50th Anniversary Symposium, in Amsterdam, the Netherlands, and presented a lecture on genetics of aging.

May

The Chief, Geriatric Epidemiology Office, was invited to speak at a workshop on the Veneto Elderly Care, in Verona, Italy, in May 1999. This epidemiologic study is aimed at assessing the outcome of hospital care, at 6 months and 1 year after hospitalization for the elderly with hip fracture, heart failure, or stroke. The Chief also made a presentation in Brescia on inflammation and aging and held collaborative discussions with investigators in the In Chianti Study in Florence.

Also in May, the Chief, Neuroepidemiology Office, at the invitation of the Netherlands Institute for Health Studies, presented a lecture in Rotterdam, on the design, im-

plementation, and analysis of multicenter studies.

In addition, scientists from the Laboratory of Cellular and Molecular Biology (LCMB) spoke at the AMPERE VII NMR School, Zakopane, and visited the Institute of Physics, Warsaw, Poland.

June

The Director, Office of Nutrition, was invited by the Canadian Institute of Food Science and Technology, Apple Hill, Ontario, to give a lecture on The Cutting Edge of Aging Research in Nutrition, at their 41st Annual Conference, in Kelowna, British Columbia, in June 1999.

Also in June, the Chief, Neuroepidemiology Office, attended the 3rd International Meeting on Cardiovascular Risk Factors for Dementia, in Rome, Italy. The Chief gave a presentation on the geographic distribution of dementia across Europe, to this meeting of investigators in the CASCADE study.

The Director, Clinical Endocrinology and Osteoporosis Research, Geriatrics Program, was invited to participate in the Nobel Assembly Frontiers in Medicine Symposium, Longitudinal Research on the Menopause—Methodological Challenges, at Karolinska Institute, Stockholm, in June. The title of her presentation was The Study of Women's Health Across the Nation (SWAN): Rationale and Design of a Ten-Year Multiethnic, Multidisciplinary Study of Menopause.

In addition, the Chief, Epidemiology and Demography Office, was an invited speaker at the third advanced postgraduate course on Frailty in Old Age, of the European Academy for Medicine of Aging, in Sion, Switzerland. The Chief gave a lecture entitled Evaluation of Functional Status in Different Aging Populations: Outcomes Instruments Review.

Scientists from LCMB attended the 61st Annual Meeting of the College on Drug Dependence and gave a presentation on Structure–Activity Relationships at the Monoamine Transporters and Sigma Receptors for a Novel Series of Rimcazole Analogs, in Acapulco, Mexico, in June.

July

The Behavioral and Social Research Program and its Demography of Aging Centers, in conjunction with the Rockefeller Foundation, sponsored a meeting on Causes and Consequences of Early Retirement: What Policymakers Know and What They Need to Know, at the Bellagio Study and Conference Center, in Italy, in July 1999. The objectives of the meeting were (1) to assess current knowledge about early retirement and the health and economic circumstances of older persons in the United States and Europe; (2) to establish an agenda for continued research and development of data resources on aging and participation in the labor force around the world, after dissemination of the G7 Denver Communiqué on Aging; and (3) to put forward a more coherent scientific foundation for informing policies related to aging. The meeting brought together a group of prominent scholars (including NIA grantees) with expertise in research on aging, from the United States and several European countries, as well as selected government officials with responsibility for policies related to aging. One consensus of the conference was that the incentive effects of policy need to be addressed more explicitly in redesigning public policy to accommodate the aging of the population around the world. The meeting set the stage for increased cross-national collaboration on research and database development in aging. This collaboration has already led to discussions of and planning for a European Health and Retirement Survey.

Also in July, a workshop on Comorbidity Assessment of Older Cancer Patients was convened at the NIH, Bethesda, Maryland. The meeting, initiated by the NIA Geriatric Program, was cosponsored with the National Cancer Institute. Participants included scientists from Genoa, Italy, and Eindhoven, the Netherlands. Objectives of the meeting addressed (a) methods to assess the impact that other health problems in older patients with cancer have on prognosis and therapy for cancer and (b) ways to expand the knowledge base and technology for comorbidity assessment.

A scientist from LCS was invited to participate in an International Interdisciplinary Symposium on Respiration, in Tokyo, Japan, in July. A book based on this symposium is scheduled to be published soon.

In addition, a scientist from the Laboratory of Biological Chemistry (LBC) was invited to give a lecture on The Role of the von Hippel-Lindau (VHL) Tumor-Suppressor Gene in Protein Processing, at Mainz University, in Germany, in July.

September

The EDB Associate Director, as a WHO temporary advisor, attended the International Consultative Meeting on Healthy Aging Development, in Kobe, Japan, in September 1999.

Also in September, the Chief, Epidemiology and Demography Office, was invited to make a presentation on disease ascertainment in epidemiologic studies and the natural history and risk factors for disability, at the 4th Pan American Congress on Gerontology and Geriatrics, in Havana, Cuba.

The Chief, Cancer Section, Geriatrics Program, was the invited keynote speaker at the 2nd International Conference on Treatment of Tumors in the Elderly, at Catholic University of the Sacred Heart, Rome, Italy, in September. The meeting was cosponsored by the Radiation Therapy Oncology Group and the Oncology Geriatric Group. The presentation was entitled The Elderly in the 3rd Millennium: Programs of the National Institute on Aging. The Chief also gave a presentation on Leading Causes of Cancer Deaths in Older Persons. Both reports were published in the *International Journal of Radiological Sciences*, in April/June, 1999.

In addition, the Director, Office of Nutrition, was invited to Showa University, Tokyo, Japan, to attend the 3rd International Conference on Nutrition and Aging, in September, and later to give a presentation on Food, Quality of Life, and Aging.

A workshop on Imaging and Biological Markers for Diagnosis and Progression of Alzheimer's Disease, organized by the NNA Program, was held in Bethesda, Maryland, in September. The meeting, which included a number of scientists and representatives from pharmaceutical companies in England, Germany, and Japan, focused on the potential usefulness of various neuroimaging modalities and biological markers in the initial diagnosis of AD and in assessment of disease progression and response to treatments.

Scientists from the Laboratory of Genetics attended the World Federation of Scientists Annual International Seminar on Planetary Emergencies and the 21st International Fetoscopy Group Meeting, in Italy, in September. They presented lectures on devel-

opmental genomics and aging and on premature ovarian failure, respectively.

An LCMB investigator participated in the EMBO (European Molecular Biology Organ) Workshop on Molecular and Cellular Gerontology, in Olivone, Valle di Blenio, Ticino, Switzerland, in September.

Intramural Programs and Activities

Epidemiology, Demography, and Biometry Program

The EDB Program conducts and supports research in the epidemiology of health and disease and the demographic and social factors that affect the health status of older persons. Program staff develop and analyze data generated by contracts and obtained from other sources, including the Bureau of the Census, the National Center for Health Statistics, and other public agencies.

In FY 99, intramural scientists in the EDB Program worked with investigators from Canada, Finland, Iceland, Italy, the Netherlands, and the United Kingdom and have organized the collaborative activities presented here.

Canada

A postdoctoral researcher from the Center on Aging, University of Manitoba, Winnipeg, completed a 1-month visit in the Neuroepidemiology Office. She examined the relationship of smoking to subclinical and clinical brain disease by using data from the Honolulu-Asia Aging Study.

Finland

After a 2-year fellowship in the Epidemiology and Demography Office, an investigator returned to the University of Jyväskylä as an associate professor of Gerontology and Public Health. As a co-investigator of two of the EDB Program's longitudinal studies—the Women's Health and Aging Study and the Honolulu-Asia Aging Study—she performed several analyses of physical activity, strength, and balance. The investigator has visited the Epidemiology and Demography Office to collaborate on research using data from these studies and has presented findings to her Finnish colleagues and the international scientific community.

Iceland

In an attempt to meet an anticipated need for new resources to study genetic susceptibility and gene–environment interaction in diseases of old age, EDB Program investigators developed a 7-year clinical research project to be performed in collaboration with the Icelandic Heart Association, in Reykjavik. The EDB Program is reviewing a proposal from the Icelandic Heart Association for this project, in response to the sole-source request for proposals. The project would build on the Reykjavik Study—a unique, established, longitudinal cohort study in Iceland, which is under the supervision of the Icelandic Heart Association. All surviving cohort members would be reexamined; in 1996, there were approximately 20,000 survivors aged 63–90 years. Several site visits to Reykjavik were made in support of this collaborative effort.

A medical student from the University of Iceland, Reykjavik, completed a research internship in the spring of FY 99, under the guidance of the epidemiologist in the Epidemiology and Demography Office. She has written an abstract on the impact of insomnia on cognitive functioning in older persons, by using data from all four sites of the Established Populations for Epidemiologic Studies of the Elderly.

Italy

A physician-researcher from the University of Ferrara began a 2-year fellowship with the Epidemiology and Demography Office. He is pursuing work to characterize the association between several age-related chronic conditions and the decline of physical function in older, frail women. In particular, his activity will be focused on endocrinologic, metabolic, and nutritional factors.

A geriatrician from the University of Verona visited the Geriatric Epidemiology Office as an Exchange Scientist. He conducts a study in Verona that is parallel to the EDB Program's Health and Body Composition (HEALTH ABC) Study, and his collaborative work focuses on a comparison of methods for assessment of body fat in older men and women participating in the studies.

Senior investigators in the EDB Program contributed to the theoretical and developmental components of the In Chianti Study, a study of 1,450 subjects that is being conducted in the Tuscany Region. The study goal is to understand multiple risk factors that influence loss of ability to walk in older persons. The Geriatric Department, National Research Institute, is the coordinating center for the study. Collaborating institutions are the local municipalities of Greve in Chianti e Bagno a Ripoli; the Tuscany Region Health Authority; and the Institute of Gerontology, University of Florence. The study has received a grant from the Italian Ministry of Health.

A study of inflammation and heart disease in the EDB Program's HEALTH ABC Study was included as one of five projects that are part of the program on Heart Failure, Pathological Aging, and Disability in the Elderly Research. The project is cofunded by the Catholic University, Rome, and the Italian Ministry of Research, as part of the Programs of Relevant National Interest.

The Netherlands

As a part of the Rotterdam Scan Study, the EDB Program is supporting the volumetric analysis of the hippocampus and the amygdala, which will be measured on MRI, in a population-based sample of 568 persons aged 60–90 years. Analyses will focus on the relationship of subclinical measures of atherosclerosis to atrophy. Atrophy of the hippocampal area is thought to be an important marker for incipient and clinical AD, yet very little is known about the risk factors associated with this atrophy. The study is also funded by the Netherlands Scientific Organization and is conducted in collaboration with the Department of Epidemiology and Biostatistics, Erasmus University Medical School, Rotterdam.

In FY 99, the Neuroepidemiology Office began a project based on the prospective Rotterdam Study. The new study includes 7,046 subjects with incident dementia. It is estimated that, over a 5-year follow-up, approximately 400 cases of AD will develop. The project involves analyses of the age at menopause in relation to the risk for cognitive decline and incident AD; circulating levels of estrogen (estradiol and estrone) in relation to the risk for cognitive decline and AD; and the interaction among estrogen markers, apolipoprotein E4, and the risk for AD and cognitive decline. This study is funded by the International Alzheimer's Disease Foundation, the Netherlands, and is conducted in collaboration with the Department of Epidemiology and Biostatistics and the Department of Internal Medicine, Erasmus University Medical School, Rotterdam.

A postdoctoral researcher from the Institute for Research in Extramural Medicine of the Vrije University, Amsterdam, visited the Epidemiology and Demography Office as an Exchange Scientist. She conducted collaborative investigations of the mutual relationships between emotional and physical function and disease status in older populations, by using data from the Women's Health and Aging Study and the Longitudinal Aging Study, Amsterdam.

United Kingdom

A clinical senior research associate from the University of Cambridge, England, spent 11 months in the Epidemiology and Demography Office. The Commonwealth Fund sponsored this visitor on a Harkness Fellowship. His fellowship project focused on health policy on aging and specifically on the use of epidemiologic studies to inform policy in the United Kingdom and the United States. Analysis of issues related to patterns of disability, needs, and use of health care and social care are planned.

The Chief, Geriatric Epidemiology Office, continued work on inflammation, as well as analysis of polymorphisms of a promoter region allele for the gene for interleukin 6. A professor of cardiovascular genetics at the University College of London Medical School, England, who has developed a new method for genotyping, is collaborating on this project.

Intramural Research Laboratory Program

NIA carries out laboratory and clinical research at the Gerontology Research Center, Baltimore, and the NIH, Bethesda, Maryland. Studies at NIA focus on the basic mechanisms of aging and how basic biological changes in health and disease states differ from the normal changes occurring during the aging process. The Intramural Research Program consists of nine research laboratories and the Longitudinal Studies Section, which is also responsible for conducting the Baltimore Longitudinal Study of Aging (BLSA). NIA intramural scientists often collaborate with foreign investigators, and the Intramural Research Program gives many international researchers the opportunity to train and work in NIA's laboratories.

In FY 99, four NIA laboratories (Cardiovascular Science, Genetics, Immunology, and Personality and Cognition) and the EDB Program began joint planning of a research project on genetic factors in age-related conditions. The studies are to be carried out in the "founder population" of Sardinia, Italy—a relatively homogenous population that facilitates analyses. In the first phase, the project would permit a comparison of the variation of physical factors (e.g., arterial stiffness and personality factors) in the Sardinian population with those in the mixed population in BLSA. The goal is to determine whether the means and the variation differ in the two populations. In the second phase, studies would proceed to an analysis of genes involved in complex traits. Investigators would focus on a few genes in the Sardinian population that provide entry points for the analysis of conditions that may involve as many as 20 genes overall.

Laboratory of Biological Chemistry

LBC established collaborations with Canadian and German investigators. Researchers in the T Lymphocyte Signaling Unit worked with researchers at the University of Western Ontario, London, to study particular aspects of the molecular signaling events that regulate activation of T lymphocytes. This joint research effort resulted in publication of a report in the *Journal of Immunology*, in February 1999. The Unit also hosted a researcher from the Transplantation and Immunobiology Group, Robarts Research Institute, London, Ontario, who presented a seminar for scientists at the Gerontology Research Center, Baltimore.

Scientists at Mainz University, Germany, joined an LBC scientist to study the interaction of pVHL tumor-suppressor protein with cellular proteins and to investigate the post-transcriptional regulation of vascular endothelial growth factor by pVHL protein. A graduate student from Mainz University obtained a grant from the German government to conduct these studies in LBC for 1 year. LBC also served as host to a scientist from Düsseldorf, who was awarded a German fellowship to conduct research on the effects of singlet oxygen on gene expression and cell survival.

Laboratory of Cardiovascular Science

An investigator from LCS collaborated with an investigator at Hebrew University, Jerusalem, Israel, to determine the effects of heat acclimation. This study, originally undertaken in Israel to determine the effects of desert climate, led to the unexpected discovery that heat acclimation provides protection against heart damage due to interruption of blood flow (heart attack). The mechanism of this protection is being examined by using methods to study single heart muscle that were developed at LCS.

Laboratory of Cellular and Molecular Biology

LCMB hosted several foreign investigators for short visits. A scientist from the Mario Negri Institute of Pharmacology, Milan, Italy, consulted on a joint study of cytokine production in the brains of transgenic mice serving as models of AD. An investigator from Fukuoka University, Japan, conducted collaborative research on age-related alterations in nitric oxide production in the brain. A scientist from Petrov Institute, St. Petersburg, Russia, consulted on joint research to examine whether treatment of rats with compounds that suppress appetite or increase insulin sensitivity can retard the rate of aging. A researcher from the University of Basel, Switzerland, consulted on a collaboration in stereological analysis of neurons, synapses, and glia in brains of normal aged mice and those of transgenic mouse models of AD.

Laboratory of Clinical Investigation

As a part of collaborative efforts with the Institute of Biophysics at the University of Linz, Austria, an investigator from the Laboratory of Clinical Investigation carried out successful experiments on double labeling at the N terminus and at the C terminus chimera of the human calcium channel pore-forming alpha 1C subunit prepared at NIA. (See also the section on "Highlights of Recent Scientific Advances Resulting From International Activities.")

An investigator from the Diabetes Section worked with scientists in Canada on a project involving the mechanism of action of vanadium salts in insulin-responsive cellular systems. This productive relationship resulted in a report to be published in *Biochemistry* (November 1999).

The Laboratory of Clinical Investigation hosted several foreign scientists. An investigator from the University of Montreal helped the Diabetes Section to examine the

signaling pathways underlying the anti-apoptotic function of the insulin receptor. Researchers from Korea and Russia collaborated in elucidating the importance of cellular reduction–oxidation potential in insulin responsiveness.

Laboratory of Genetics

Scientists in the Laboratory of Genetics collaborated with scientists in Canada, Finland, Italy, and Japan on studies of age-related conditions of embryonic development in relation to aging. This research included investigation of (1) the function of Werner syndrome protein in a protein complex; (2) genes selectively turned on or off when immortal cells become mortal; (3) genes present at one end of both the X and Y chromosomes; and (4) the genetic basis for premature ovarian failure.

A scientist visiting from Japan has been awarded a fellowship from the Japanese Society for the Promotion of Science to study the gene expression profile associated with limited cell longevity. In other joint research conducted in the Laboratory, an investigator from Chile embarked on the study of a gene involved in hereditary premature ovarian failure and the basis for menopause, and an investigator from Jordan studied mouse gene expression in developing embryos. A researcher from Mexico started investigating two genes regulating organ size and body size in mice and humans that, when disrupted, lead to enlarged internal organs and early onset of pathologic conditions.

The Laboratory hosted scientists from the National Genome Center and the University of Helsinki, Finland, and the National Research Council Institute, Cagliari, the University of Modena, and the International Institute of Genetics and Biophysics, Naples, Italy.

Laboratory of Immunology

Scientists in the Laboratory of Immunology worked with scientists in Germany, Japan, and Scotland. Studies of differential chemokine receptor expression on subsets of human T cells and investigation of the role of chemokines and their receptors in various inflammatory neuritis models benefited from collaboration with scientists at the University of Tübingen, Germany. A researcher in Japan, at the Fukuoka Prefectural University, worked with researchers in the Laboratory, using in vivo microdialysis to examine the effects of chemokines and amyloid beta on nitric oxide production by rodent hippocampal neurons. Investigators at the Lister Research Laboratories, University of Edinburgh, Scotland, contributed to studies of CD40 expression on various human carcinoma cells and the role of anti-CD40 agents on cell growth and viability.

The Laboratory of Immunology hosted a researcher in immunology from Korea, who worked on the differential gene expression and biochemical signaling in cycling and aging murine and human T lymphocytes.

Laboratory of Molecular Genetics

Investigators in the Laboratory of Molecular Genetics collaborated with investigators in Australia, Denmark, England, France, Germany, Italy, the Netherlands, Norway, Slovakia, and Sweden, in studying DNA repair and transcription in human disorders of premature aging and in older individuals. Scientists in the Laboratory worked with scientists at Copenhagen University and Aarhus University, Denmark, through a collaborative organization, The Danish Center for Molecular Gerontology. The projects involve the role of topoisomerases in DNA repair, the functions of the Werner and Cockayne proteins, and the differential expression of specific proteins in old versus young cells. Researchers in the Laboratory also collaborated with researchers in the Netherlands and in Norway on studies of DNA repair in nuclear and mitochondrial DNA from knockout mice lacking various DNA repair genes.

Laboratory of Personality and Cognition

The Laboratory of Personality and Cognition hosted scientists from Canada and France. A neuropsychologist from Canada examined the relationship among age, cortisol concentrations, and hippocampal morphology in BLSA participants. In particular, he investigated whether high cortisol concentrations are associated with reduced hippocampal volume.

A French investigator extended his methodological work on use of partial volume for correction of physiological measures, including studies of cerebral blood flow using positron emission tomography (PET). These methods were applied to brain images from BLSA participants. By combining information from high-resolution MRI with PET images, it is possible to account for signal loss and distortion due to the interaction of the distribution of tracer in the brain with PET detection and image-reconstruction systems.

Research Resources Branch

Investigators from Canada, China, and Scotland performed studies in the Research Resources Branch. A mathematical statistician from Canada worked in the laboratory to develop multilevel or mixed-effects regression models for the classification of preclinical disease states in longitudinal studies of aging. A scientist from Shanghai, China, worked on the creation of a murine conditional knockout of the μ opioid receptor via Cre-lox technology. Creation of this model is a collaborative effort to study the role of this receptor in peripheral analgesia, by scientists at the Laboratory of Cellular and Molecular Biology, National Committee on Scientific Research, Paris, France, and the Clinic of Anesthesiology, Free University of Berlin, Germany. A researcher from Scotland studied cell-specific expression of the gene for dopamine.