XV.
National Eye Institute

INTRODUCTION

The mission of the National Eye Institute (NEI) is to reduce blindness, visual impairment, and eye disease worldwide through basic and applied research and training. Although excellent ophthalmic procedures and systems for delivery of eye care are generally accessible in the developed world, adequate health care is not readily available in all parts of the developing world. This widening gap in visual health between developed and developing nations threatens to have ominous consequences. If present trends continue, the number of blind people—estimated at 24 million worldwide—will more than quadruple during the next 40 years. As many as 90% of these blind people will live in developing countries.

Large-scale disability caused by blindness is not only a costly obstacle to economic development; it is also a catastrophic loss of human potential in the areas of the world most desperately in need of a healthy workforce. In addition, more than 80% of all cases of blindness can be considered avoidable. Therefore, NEI undertakes international activities to facilitate the development and application of effective prevention and treatment programs.

HIGHLIGHTS OF RECENT SCIENTIFIC ADVANCES RESULTING FROM INTERNATIONAL ACTIVITIES

Scientists in NEI's Ophthalmic Clinical Genetics Section, Clinical Branch, have continued their collaboration with scientists in hospitals, clinics, and medical schools outside the United States, in successful efforts to map genes for some inherited diseases. In joint efforts with scientists at the L. V. Prasad Eye Institute, Hyderabad, India, the Sankara Nethralaya Hospital, Madras, India, and the Akdeniz University, Antalya, Turkey, NEI investigators continue to make important headway in efforts to map autosomal-dominant and autosomal-recessive genes for cataract.

Researchers from this Section are also working with researchers from the L. V. Prasad Eye Institute on productive mapping studies of autosomal-recessive genes for retinitis pigmentosa and gelatinous corneal dystrophy. In addition, studies of Bietti crystallin dystrophy and gelatinous corneal dystrophy are being carried out jointly with Juntendo University, Tokyo, Japan, and National Taiwan University Hospital, Taipei.

These successful collaborations, which have grown over the past several years, have also involved the training of scientists from foreign institutions in modern techniques for study of molecular genetics. Many of these scientists have been trained in the laboratories of NEI's Ophthalmic Clinical Genetics Section.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

Barbados

The Barbados Eye Study is a series of epidemiologic investigations conducted among the adult population of Barbados between the ages of 40 and 84 years. These studies measure the frequency of open-angle glaucoma and assess the occurrence of cataract, age-related macular degeneration, and diabetic retinopathy, as well as the factors responsible for these conditions.

These studies began in 1988 with examination of 4,631 individuals for visual acuity, visual field, intraocular pressure, blood pressure, and the presence or absence of diabetes. Four years later in 1992, 3,400 of the 4,631 individuals were reexamined to determine whether existing eye disease had progressed and whether new eye disease was present. The Barbados Incidence Study of Eye Disease II will continue to follow up the surviving cohort for comparison with baseline data. Over a 9-year period, the study will obtain data on incidence, progression, and risk factors for open-angle glaucoma, cataract, and visual impairment.

Brazil

NEI has cooperated with the National Institute of Allergy and Infectious Diseases, National Institutes of Health, and with Escola Paulista de Medicina, Clinica Erexim, and Laboratory Fleury, São Paulo, to develop a research program on the basic mechanisms, immunology, and epidemiology of toxoplasmosis in southern Brazil. The prevalence of ocular toxoplasmosis in this population was more than 30 times higher than previous estimates for the same condition elsewhere in Brazil. In this population, ocular toxoplasmosis appears to be a sequela of postnatal rather than congenital infection. Studies performed in 1993 on blood from newborns in southern Brazil showed a low percentage of newborns with immunoglobulin M positivity, further suggesting that the disease in southern Brazil is acquired. A second survey was conducted in another part of the country. The survey shows an extremely high prevalence of toxoplasmosis, indicating that this disease is not isolated in a particular region of Brazil. Such information will be very useful in the effort to develop a comprehensive treatment program.

Chile, China, and Nepal

Using a common protocol and examination methods, NEI has been working with three institutions in conducting a population-based survey of childhood refractive error and vision impairment. Surveys were carried out in La Florida (a suburb of Santiago), Chile, in collaboration with Pontifica Universidad Catolica de Chile; in Shunyi County (outside Beijing), China, in collaboration with the Peking Union Medical College Hospital; and in eastern Nepal, in collaboration with Foundation Eye Care Himalaya. Findings have demonstrated wide variations

among these countries, in the prevalence of refractive error in school-age children. This work, which was funded in collaboration with the World Health Organization (WHO), will be reported as four articles in a single issue of a leading ophthalmology journal.

Czech Republic

Researchers from NEI's Laboratory of Molecular and Developmental Biology are collaborating with a researcher at the Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, on cloning the crystallin cDNAs (complementary DNAs) and Pax transcription factors of the scallop. In both scallops and mammals, including humans, the lens crystallin is an aldehyde dehydrogenase. Thus, development of the scallop eye is especially relevant to development of the mammalian eye and the human cornea.

Germany

Scientists from the Laboratory of Molecular and Developmental Biology are working with an investigator at the Institute of Mammalian Genetics, GSF National Research Center for Environment and Health, Neuherberg, to explore the molecular basis for genetic cataracts in two strains of mice (Cat2nop and Cat2t). The Cat2nop mouse carries a mutation in the gene for gamma b crystallin, and the Cat2t mouse carries a mutation in the gene for gamma e crystallin. Both mutations result in a truncated gamma crystallin protein that produces a nuclear cataract. A graduate student from the Institute of Mammalian Genetics, working in the NEI Laboratory, has found that the Cat2nop cataract may be caused by apoptotic events, whereas the Cat2t cataract is due to early arrested growth of primary fiber cells, with secondary apoptotic events.

Other scientists from this NEI Laboratory are collaborating with investigators at the GSF National Research Center for Environment and Health to characterize, at the molecular level, a genetic cataract generated by gamma irradiation. They have found that the mutation is localized to a gene that encodes for the major intrinsic protein of the ocular lens fiber membrane. Identification and characterization of a loss-of-function mutation in the MIP gene, which results in autosomal-dominant cataract in Hfi mice, will serve as a model to enhance understanding of this disease in humans.

In addition, researchers from the Laboratory of Molecular and Developmental Biology are working with an investigator at the University Erlangen-Nürnberg, Erlangen, to complete experiments (a) on the effects of transforming growth factor β on differentiation of the cornea and (b) on the production of transgenic mice in which a second transgene is activated when the mice are given tetracycline. This research will lead to the ability to turn on a foreign gene in transgenic mice.

Scientists at the Laboratory of Mechanisms of Ocular Diseases, NEI, are also working with investigators at the University Erlangen-Nürnberg, to study a protein that is implicated in some forms of primary open-angle glaucoma.

India

The NEI Director and the Associate Director for Applications of Vision Research have continued to participate as consultants to the World Bank in developing and evaluating, with the government of India, the Indian National Blindness Control Project. They have provided technical and analytic assistance in two surveys of the prevalence of blindness and outcomes of cataract surgery. Collaborations are continuing with the Dr. Rajendra Prasad Centre for Ophthalmic Sciences, New Delhi, and the Aravind Eye Hospital, Madurai, to analyze data and report findings of surveys.

The Director and Associate Director have continued to work during fiscal year 1999 (FY 99) with physician-scientists at the Dr. Rajendra Prasad Centre for Ophthalmic Sciences, to develop and evaluate a questionnaire on vision function and quality of life that would be suitable for administration across subpopulations within India. The research follows a protocol that is used in the United States for development of NEI's Visual Functioning Questionnaire, including the use of patient focus groups to collect information on the variety and extent of day-to-day, vision-related problems faced by the visually impaired. Researchers at the London School of Hygiene and Tropical Medicine, England, who are studying quality of life are also participating in this endeavor in applied research.

Intramural scientists from the Laboratory of Mechanisms of Ocular Diseases have collaborated with colleagues at the Centre for Cellular and Molecular Biology, Hyderabad, to study aging-related modifications to lens crystallins. Cataract typically occurs at an earlier age and is more heavily pigmented in subjects in India than in those in the United States. To elucidate the molecular mechanisms underlying this difference in color, the scientists are comparing the fluorescence spectra for healthy, intact lenses from subjects in India over a wide range of ages with the spectra for eye-bank lenses from age-matched subjects in the United States. The lenses from Indian subjects contain substantially greater amounts of pigmented fluorescent compounds than those from U.S. subjects. These compounds, through their ability to function as photosensitizers, may contribute directly to cataractogenesis.

Another joint effort is the study of the proteins in cataract in Indians. In an attempt to elucidate processes that may contribute to the early onset and high incidence of cataract in India, researchers are comparing the crystallin properties of cataractous lenses from Indians with those of healthy or cataractous lenses from age-matched, eye-bank donors in the United States. The different forms of crystallins that have been identified are being further characterized to determine the mechanisms involved in the expression and formation of these proteins in cataract.

In addition, molecular geneticists at NEI have initiated gene-linkage studies with scientists at Osmania University and the L. V. Prasad Eye Institute, Hyderabad. Participants in these studies are members of selected families with hereditary cataracts. The prevalence of consanguineous marriages in this region of India greatly increases the likelihood of recessive cataract phenotypes. A geneticist from Osmania University, who was trained at NEI in relevant techniques, has returned to Hyderabad to establish a laboratory, so that gene-linkage analysis in individuals with suitable pedigrees can be performed in India. In one family, the cataract trait has been linked to a particular chromosome, and a potential candidate gene has been identified.

An NEI-supported, randomized clinical trial at the Aravind Eye Hospital, Madurai, has been completed. In this study, treatment using intracapsular cataract surgery plus eyeglasses for the resulting aphakia was com-

pared with treatment using extracapsular cataract extraction plus implantation of an intraocular lens. The trial's primary purpose was to compare intraoperative complications, postoperative complications, and visual acuity outcomes by 1 year after the operation. A randomly selected subgroup of the these patients was examined 4 years after surgery, to investigate the incidence of opacification of the posterior capsule. Findings have demonstrated a relatively low incidence among the study population.

Italy

Scientists in the Laboratory of Mechanisms of Ocular Diseases are working with investigators from the University of Modena and the University of Pisa in studying the role of oxidative stress in age-related cataract. The approach has been to use aldose reductase, an enzyme that has an important role in diabetic cataract, as a model enzyme to study the effects of oxidation on structure and function. In addition, the scientists are investigating the mechanisms involved in modifications of crystallin that occur during development of the fiber cells of the lens.

The Collaborative Italian-American Clinical Trial is being conducted to evaluate the effect of multivitamin supplements on the risk of cataract development and progression. To date, 1,020 subjects have been randomly assigned to receive either a multivitamin and mineral supplement or a placebo; subjects will be monitored for 5 years. The study's principal investigators are at the University of Parma and NEI. The study's coordinating centers are the Laboratory for Epidemiology and Biostatistics, Istituto Superiore di Sanità, Rome; the Emmes Corporation, Potomac, Maryland; and the Division of Biometry and Epidemiology, NEI. About 77% of the study cohort has had 2 years of follow-up, and 33% have been monitored for 3 years.

Japan

Investigators in the Laboratory of Molecular and Developmental Biology are cooperating with a scientist at the Riken Institute, who from 1992 through 1995 was a Postdoctoral Fellow in the Laboratory's Regulation of Gene Expression Section. This joint project continues the research on the transcription factor AP2 alpha, which was started at NEI. The work characterized a novel splicing variant in the ocular lens that may have a role in regulating gene transcription in the lens.

Scientists in NEI's Laboratory of Sensorimotor Research are working with a former colleague who is now at the Electrotechnical Laboratory, Tsukuba, on the role of the cortex in the generation of reflex eye movements that are important for stability of the retinal image. Recent findings support the idea that such eye movements are encoded in the activity of a population of cortical cells with a range of properties.

Sweden

Many eye diseases, especially those resulting in retinal degeneration, could be successfully treated if transplantation of the human retina were possible. In animal models, transplanted visual cells do not develop and function normally. However, a new differentiating factor has been discovered and is being investigated by molecular biology techniques at NEI. This factor, a protein that causes neuronal-like differentiation, is being tested in vitro by NEI collaborators in Sweden at the University of Göteborg and the University of Lund, Malmö, to determine whether it will cause retinal cell differentiation. The ultimate purpose of these investigations is to develop cells that could be transplanted into the human eye and function there normally.

The Early Manifest Glaucoma Trial is a multicenter, randomized clinical trial designed to determine whether treatment to reduce intraocular pressure in newly detected open-angle glaucoma affects progression of the disease. The primary purpose of the trial is to compare the effect of immediate treatment designed to lower intraocular pressure with the effect of late treatment or no treatment. Disease progression was measured by increasing loss of visual field, changes in the optic disc, or both. The secondary purposes of the trial are to determine the extent of reduction of intraocular pressure resulting from treatment, to explore factors that may influence the progression of glaucoma, and to describe the natural history of newly detected glaucoma. Investigators at the University of Lund, collaborating with investigators at the State University of New York, Stony Brook, have enrolled 255 patients with newly diagnosed disease. Participants have been randomly assigned either to receive treatment to lower pressure in the eye or to be observed and receive no treatment or delayed treatment. Patient recruitment began in 1993 and was completed in 1997. The investigators are using computerized perimetry and fundus photography for close, long-term follow-up of all patients.

United Kingdom

The United Kingdom Prospective Diabetes Study is a multicenter, randomized clinical trial to determine whether improved control of blood glucose levels or blood pressure in non–insulin-dependent diabetes mellitus (type 2 diabetes) reduces morbidity and mortality. Starting in 1977, 5,102 patients with newly diagnosed type 2 diabetes were treated with diet therapy for 3–4 months. Patients who remained asymptomatic but had high blood glucose levels were then randomly assigned to diet therapy or to treatment with sulfonylurea, insulin, or metformin. In a factorial design, a randomized trial of strict control of blood pressure was carried out in 1,148 patients with type 2 diabetes and hypertension. Patients were assigned to treatment of hypertension with angiotensin-converting enzyme inhibitors or β-blockers or to less tight control of hypertension. All patients' eyes are photographed every 3 years to assess development and progression of diabetic retinopathy. The median duration of follow-up is 12 years.

Scientists at the Laboratory of Molecular and Developmental Biology are working with investigators at Baylor College of Medicine, Houston, Texas, and the Imperial Cancer Research Fund, London, England. These scientists are targeting the expression of the FGF3/int2 gene to the lens. This work will allow researchers to characterize the fibroblast growth factor (FGF) receptors that FGF3 interacts with and the role of secreted FGFs in differentiation in the lens.

Scientists in the Laboratory of Sensorimotor Research, together with a former colleague who is now at the University of St. Andrews, Fife, Scotland, are studying the ability of human subjects to use cognitive information to modify an already programmed saccadic eye movement to a new visual location.

Activities With International and Multinational Organizations

In FY 99, NEI continued to support investi-

gations of blinding eye diseases that have a worldwide impact. These studies are implemented through bilateral agreements between foreign countries and the United States; other types of country-to-country programs such as those supported by the U.S. Agency for International Development; and collaborative activities with WHO, the Pan American Health Organization, and foundations and voluntary organizations such as the Lions Clubs International Foundation.

NEI continues to provide technical advice to the Lions Clubs International Foundation in the development of its $100 million SightFirst initiative, a global sight-conservation program aimed at substantially reducing the prevalence and incidence of preventable and curable vision loss. In addition, the Associate Director for Applications of Vision Research continues to serve as a technical advisor for the Americas and to the SightFirst Program of the Lions Clubs International Foundation. This program has sponsored scores of cataract eradication projects involving about 20 countries in Central and South America.

NEI also continued its activities as a WHO Collaborating Center for the Prevention of Blindness, during FY 99. The NEI Director served on the WHO Special Advisory Panel in the Prevention of Blindness. The Director of NEI and the Associate Director for Applications of Vision Research, NEI, together with the manager of the WHO Prevention of Blindness Program and researchers in India, have continued to plan new collaborative research initiatives in India, specifically for research on childhood blindness and outcomes of cataract surgery.

Extramural Programs

In FY 99, NEI made eight awards in support of investigator-initiated research projects in five countries. The clinical projects funded by NEI include the Early Manifest Glaucoma Trial in Sweden and the United Kingdom Prospective Diabetes Study (see also the section on "Country-to-Country Activities and Bilateral Agreements"), as well as clinic activities in Canada for the multicenter Collaborative Ocular Melanoma Study.

Basic research funded by NEI includes the following projects:

- Australia—exploration of the role of growth factors in lens development and cataractogenesis, to investigate the relationship between specific growth factors and differentiation in the lens and to study the role of growth factors in cataract formation.
- Canada—one project will study factors controlling the number and quality of composition of photoreceptor synapses—the gaps between nerve cells through which neurotransmitters and other chemical messengers pass from one cell to the next in two species of flies: the fruit fly and housefly. This study will greatly advance knowledge of the development of the visual system and provide a basic model of synapse formation. Another project will examine the molecular properties of rod membrane proteins.
- Israel—research on the molecular mechanisms of phototransduction and how defects in this signaling pathway can lead to retinal degeneration.
- United Kingdom—investigation of calcium in the physiology of normal and cataractous lenses to better understand the role that increased calcium levels in cataractous lesions may have on the development of cataract.

Before the award of grants, each of these foreign projects was specifically approved by the National Advisory Eye Council. This review is performed to ensure that these grants present special research opportunities with specific relevance to the mission and objectives of NEI.

International Meetings

In March 1999, the Associate Director for Applications of Vision Research chaired a plenary session on Impact of Mass Surgical Interventions on the Cataract Backlog and presented papers on (1) Vision Impairment and Refractive Errors in Children and (2) Quality of Life Outcomes in Cataract Patients in Nepal and China, at the XVIIth Congress of the Asia-Pacific Academy of Ophthalmology, in Manila, Philippines.

In September 1999, the Associate Director for Applications of Vision Research chaired a session on Cataract Surgery Outcomes and made presentations on (1) Visual Function and Quality of Life Assessment in Cataract Surgery and (2) Methods for Multicountry Survey of Visual Impairment and Rehabilitation Error in Children, at the 6th General Assembly of the International Agency for the Prevention of Blindness, in Beijing, China.

Intramural Programs and Activities

NEI continued to serve as an international center for research and training on eye disease. In FY 99, 21 Special Volunteers, 20 Postdoctoral Fellows, 4 Visiting Fellows, 3 Research Fellows, 2 Visiting Scientists, and 2 Guest Researchers from countries throughout the world conducted research at NEI's intramural facilities in Bethesda, Maryland. Their work included basic laboratory investigations on the molecular structure and development of the visual system, sensory and motor disorders of vision, and the biochemical bases of retinal and corneal diseases and the development of cataract. In addition, Visiting Scientists collaborated with NEI investigators in clinical studies to define, prevent, and treat vision disorders, such as genetic and developmental defects, ocular inflammatory disease, and ocular complications due to systemic conditions such as diabetes.