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 less developed parts of the 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 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

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, Malmö, Sweden, collaborating with investigators at the State University of New York, Stony Brook, enrolled 255 patients with newly diagnosed disease in the study. Participants were randomly assigned either to receive treatment to lower pressure in the eye or to be observed and receive no treatment or delayed treatment. Recruitment of patients 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.

SUMMARY OF INTERNATIONAL PROGRAMS AND ACTIVITIES

Country-to-Country Activities and Bilateral Agreements

Australia

The Laboratory of Retinal Cell and Molecular Biology, NEI, is collaborating with the Lions Eye Institute, University of Western Australia, Perth, to rescue the mutant phenotype of the RPE65 knockout mouse, a model for certain forms of early-onset retinal dystrophy in humans. This mouse is deficient in the protein RPE65, which is required for the conversion of all-*trans*-retinol to 11-*cis*-retinol, the form of vitamin A necessary for vision. Gene transfer constructs based on adeno-associated virus are being used. This project lays the groundwork for possible gene therapy of human subjects who have retinal dystrophy due to mutations in the RPE65 gene.

Barbados

The Barbados Incidence Study of Eye Disease II (BISED II) is the third in a series of epidemiologic investigations to obtain long-term data on major causes of vision loss in a black population. The Barbados Eye Study, conducted in 1988–1992, measured the prevalence and risk factors for open-angle glaucoma, cataract, age-related macular degeneration, and diabetic retinopathy among a random sample of citizens born in Barbados, who were 40–84 years of age. The study results indicated that open-angle glaucoma and cataract were jointly responsible for more than one-half of the bilateral blindness and most of the visual impairment in Barbados. The Barbados Eye Study was followed by the Barbados Incidence Study of Eye Disease I, which was conducted from 1992 to 1997, to determine 4-year incidence and progression of the major eye diseases. BISED II will collect 9-year incidence and progression data on eye diseases in this population.

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.

Canada

Researchers from the Laboratory of Retinal Cell and Molecular Biology, NEI, are working with an investigator at the Laboratory of Gene Transfer, Center for Research, Université Laval Robert-Giffard, Beauport, Quebec, in the preparation of gene vectors for pigment epithelium–derived factor (PEDF). They are studying the effects of sustained delivery of PEDF in retinas of animal models for retinitis pigmentosa. This research may lead to the development of a therapeutic agent for retinitis pigmentosa. PEDF has been found to delay the death of photoreceptors in a mouse model of inherited retinal degeneration.

China

NEI is providing technical oversight for a 2-year follow-up of children previously enrolled in a population-based survey of childhood refractive error and vision impairment. This epidemiologic research, which was funded in collaboration with the World Health Organization (WHO), is being conducted by Peking Union Medical College Hospital, Beijing.

Czech Republic

Researchers from NEI's Laboratory of Molecular and Developmental Biology (LMDB) are collaborating with an investigator 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.

France

The NEI's Laboratory of Retinal Cell and Molecular Biology has established a collaboration with the Center for Therapeutic Research in Ophthalmology, Université René Descartes, Paris, to develop a sustained delivery system for PEDF. This work may lead to the use of PEDF as a therapeutic agent for retinal degeneration.

Germany

Scientists from LMDB are working with an investigator at the Institute of Mammalian Genetics, National Research Center for Environment and Health, Forschungszentrum für Unwelt und Gesundheit (GSF), 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 LMDB, 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 Laboratory are collaborating with investigators at the GSF National Research Center for Environment and Health to characterize, at the molecular level, a cataract generated by gamma irradiation. They found a mutation that is localized to a gene encoding for the major intrinsic protein of the ocular lens fiber membrane. Identification and characterization of a loss-of-function mutation in the gene for major intrinsic protein, which results in autosomal-dominant cataract in Hfi mice, will serve as a model for use in studies to enhance understanding of this disease in humans.

In addition, scientists from LMDB 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 is expected to 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. In addition, scientists from NEI's Laboratory of Ocular Therapeutics are collaborating with investigators at the University of Marburg to develop aldose reductase inhibitors for the treatment of diabetic eye disease.

India

The Associate Director for Applications of Vision Research has continued to participate as a consultant to the World Bank in developing and evaluating, with the government of India, the Indian National Blindness Control Project. He provided technical and analytic assistance for three district-wide 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 Aravind Eye Hospital, Madurai, to report survey findings in peer-reviewed literature.

Using a protocol and examination methods developed for previous collaborative studies in Chile, China, and Nepal, NEI has also been working with L. V. Prasad Eye Institute, Hyderabad, to conduct a population-based survey of childhood refractive error and vision impairment in a rural district of India. Funding for this epidemiologic research was arranged in collaboration with WHO.

With support from the United States-India Fund, through the U.S. Embassy in New Delhi, the NEI Associate Director for Applications of Vision Research continued to work during fiscal year 2000 (FY 00) with physician-scientists at the Dr. Rajendra Prasad Centre for Ophthalmic Sciences, New Delhi, to develop and evaluate a questionnaire on vision function and quality of life that would be suitable for administration across subpopulations in India. The research follows a protocol that was used in the United States for development of NEI's Visual Functioning Questionnaire, including the use of focus groups of patients to collect information on the variety and extent of day-to-day, vision-related problems faced by the visually impaired. Faculty at the London School of Hygiene and Tropical Medicine, England, who are researching quality-of-life assessment, are also participating in this collaborative endeavor in behavioral science 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 mech-

anisms 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 initiated gene-linkage studies with scientists at Osmania University and 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, 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 was linked to a particular chromosome, and a potential candidate gene was identified.

An NEI-supported, randomized clinical trial at Aravind Eye Hospital, Madurai, has been completed. In this study, treatment using intracapsular cataract surgery plus eyeglasses for the resulting aphakia was compared 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 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 scientists from the University of Pisa to study 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. More than 90% of the study cohort have been monitored for 3 years.

Japan

NEI's LMDB is collaborating with a scientist at the Riken Institute, Saitama, to conduct research on the transcription factor AP2 alpha. This work has characterized a novel splicing variant in the ocular lens that may have a role in regulating gene transcription in the lens.

Scientists in the Laboratory of Sensorimotor Research, NEI, 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.

Additionally, NEI scientists from the Laboratory of Ocular Therapeutics are collaborating with colleagues at Fukui University to study the role of galactosemia in producing changes in the eye that are similar to the changes caused by diabetes.

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.

Scientists in NEI's Laboratory of Retinal Cell and Molecular Biology are working with an investigator at the University of Lund to study the effect of PEDF on developing retina. This study will lay the groundwork for the characterization of PEDF as a neurotrophic factor for development of the retina.

Switzerland

In a joint effort with researchers at the University of Zürich, scientists in the Laboratory of Retinal Cell and Molecular Biology are exploring the role of the RPE65 gene in sensitivity to light damage in various strains of mice. It has been determined that RPE65 knockout mice are resistant to levels of light that rapidly cause retinal degeneration in wild-type mice. Because these mice do not produce or regenerate the visual pigment rhodopsin, the scientists concluded that rhodopsin is the light-absorbing component of the photoreceptor cell that mediates light-induced retinal degeneration. This work provides explicit proof for the speculated major role of rhodopsin in this type of retinal damage. The research is continuing with emphasis on other aspects of vitamin A metabolism in RPE65 knockout mice and other mutant mouse strains.

United Kingdom

The United Kingdom Prospective Diabetes Study is a randomized clinical trial to determine whether improved control of blood glucose levels or blood pressure in non–insulin-dependent diabetes mellitus (type 2 diabetes) can reduce morbidity and mortality. Another purpose of the research is to examine the advantages of specific therapies. In this study, improved control of blood glucose levels reduced the risk of major diabetic eye disease and early kidney damage. Improvement in control of high blood pressure in patients with diabetes reduced the risk of death from long-term complications of diabetes by one-third and reduced the risk of stroke and of serious deterioration of vision by more than one-third. Study enrollment ended in 1997, and the cohort of surviving patients will have follow-up for 5 years to assess long-term complications of the disease.

Scientists in NEI's Laboratory of Ocular Therapeutics are collaborating with scientists at Manchester Royal Infirmary, England, to investigate the role of galactosemia in causing retinopathic and neuropathic complications similar to those of diabetes.

LMDB researchers are working with investigators at Baylor College of Medicine, Houston, Texas, and the Imperial Cancer Research Fund, London, England. These researchers 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 00, NEI continued to support international investigations of and interventions for blinding eye diseases. These efforts 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 the World Bank, WHO, the Pan American Health Organization, and foundations and voluntary organizations such as the Lions Clubs International Foundation.

NEI provides 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 developing countries. The Associate Director for Applications of Vision Research, NEI, continues to serve as a Technical Advisor for the Americas in the SightFirst Program, which has sponsored scores of projects to eradicate cataract in 20 countries in Central and South America.

In FY 00, NEI was also a WHO Collaborating Center for the Prevention of Blindness. The Associate Director for Applications of Vision Research, together with the manager of the WHO Prevention of Blindness Program and Ministry of Health researchers in India, have continued to plan new joint research initiatives in India, specifically for research on childhood blindness and outcomes of cataract surgery.

Extramural Programs

In FY 00, NEI made 10 awards in support of investigator-initiated research projects in five countries. The projects funded by NEI include the following:

- Australia—In a study at the University of Sydney, investigators are exploring the role of growth factors in lens development and cataractogenesis.
- Canada—Clinical research includes the activities of the Ontario Cancer Institute, Toronto, for study recruitment, treatment, and follow-up of patients with ocular melanoma, as part of the Collaborative Ocular Melanoma Study. Basic research at the University of British Columbia, Vancouver, includes examination of basic retinal neuroanatomy and neurochemistry and study of the vitamin A cycle in the retina and the role it may play in retinal diseases. Another research project, at the University of Calgary, Alberta, is focusing on the neural control of ocular growth and refraction, with the aim of identifying mechanisms that cause myopia. Findings in this study suggest that retinal amacrine cells respond differentially to optical defocus.
- Israel—Scientists at Hebrew University, Jerusalem, are performing a genetic study of retinal phototransduction.
- Sweden—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.
- United Kingdom—In addition to the United Kingdom Prospective Diabetes Study, at Oxford University, England, NEI supported research on the role of calcium in the development of cataract and on gene function and gene interaction during the development of the vertebrate eye.

International Meetings

During the past 5 years, NEI has supported a series of epidemiologic field studies in collaboration with WHO. The NEI Associate Director of Applications Research has taken the lead in bringing together research collaborators from developing countries to focus on (1) prevalence of blindness and outcomes of cataract surgery in China (including Hong Kong), India, and Nepal and (2) childhood vision impairment and refractive error in Chile, China, and Nepal. Findings from these research collaborations were reviewed at an international symposium on Eye-Care Research and Delivery, at the National Institutes of Health, in Bethesda, Maryland, on February 14–17, 2000.

This NEI-sponsored symposium included participants from Universidad de La Frontera, Temuco, Chile; Peking Union Medical College Hospital, Beijing, Zhongshan Ophthalmic Center, Guangzhou, and Chinese University of Hong Kong, China; R. P. Center for Ophthalmic Sciences, New Delhi, L. V. Prasad Eye Institute, Hyderabad, and Aravind Eye Hospital, Madurai, India; and Eye Care Himalaya, Kathmandu, Nepal. Representatives from WHO and the World Bank were also present, as were officials from the Ministry of Health in China and the Ministry of Health in India. The symposium concluded with consideration of the implications of these research findings on priorities and strategies for delivery of eye-care services.

Through their active participation in the deliberations of the symposium, research

results were made directly available to WHO, the World Bank, and the Ministries of Health in China and India.

The Associate Director for Applications of Vision Research was invited to present a review on the scope of refractive errors as a cause of visual disability, at a WHO-sponsored Planning Meeting on the Elimination of Avoidable Visual Disability Due to Refractive Errors, in Geneva, Switzerland, on July 3–5, 2000. He noted (a) that because of a lack of uniformity in measurement and other problems, it is difficult to draw conclusions about patterns of the prevalence of refractive error, and (b) that few data are available to assess the magnitude of the problem of untreated refractive errors.

In September 2000, the Group Leader, Collaborative Clinical Research, NEI, attended the International Society for Clinical Biostatistics meeting in Trento, Italy. The society works to stimulate research on the biostatistical principles and methods used in clinical research and promotes improved understanding of the use and interpretation of biostatistics by the general public. The 2000 meeting focused on design and management issues related to clinical trials and workshops on different techniques used by international government agencies and private industry to support and monitor clinical trials.

Intramural Programs and Activities

NEI continued to serve as an international center for research and training on eye disease. In FY 00, 15 Visiting Fellows, 9 Special Volunteers, 5 Postdoctoral Fellows, 5 Intramural Training Associates, 4 Research Fellows, 2 Visiting Scientists, 1 Guest Researcher, and 1 Staff Clinician, 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.