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At the Frontier of Vision Research—The National Eye Institute Celebrates 40 Years

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This year marks the 40th anniversary of the National Eye Institute (NEI), during which we celebrate four decades of leadership in basic and clinical science of the eye and vision.

The NEI emerged from the National Institute of Neurological Diseases and Blindness (NINDB) in 1968 as the first government organization solely dedicated to research on human visual diseases and disorders—the establishment owed both to a Congressional interest and from a push by prominent ophthalmologists.¹

Dr. Jules Stein was one of these ophthalmologists. He founded Research to Prevent Blindness, Inc., (RPB) in 1960, and soon after he championed the cause for creating a National Eye Institute. A Gallup poll at the time demonstrated a perceived need for such an organization, revealing that blindness was second only to cancer as the most feared ailment among Americans.

In a separate campaign, Dr. Alfred Edward Maumenee, Jr., chairman of the Ophthalmology Department at Johns Hopkins University, enlisted help from his colleagues to form the Association of University Professors of Ophthalmology in 1966. One of their first acts was to advocate for the creation of a government eye institute.

When the bill to establish an eye institute was introduced in Congress in 1967, Lions Club member Dr. Ralph W. Ryan, former head of the NINDB section on clinical ophthalmology, organized the Lions who sent over 100,000 telegrams and letters to urge bringing the legislation to the floor of the House for a vote.²

President Lyndon B. Johnson signed the law to found the NEI on August 16, 1968. He emphasized his commitment to improving the vision of Americans in his signing statement: “Nearly every family in America has at least one member suffering some form of vision problem or eye disease... These tragedies need not occur... There is much that remains to be learned.”³

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Pioneering randomized controlled trials

Dr. Carl Kupfer became the first director of the NEI in 1970, and within a year he had established an Office of Biometry and Epidemiology, an Office of the Director of Intramural Research, a Laboratory of Vision Research, and a Clinical Branch.

Dr. Kupfer pioneered the use of clinical trials at the National Institutes of Health (NIH), setting the stage for the randomized controlled trials and comparative effectiveness studies that are now critically important to translational research opportunities. His insistence of using the scientific method and analysis of the placebo effect set the standard for current clinical trials. Today, the vision science community continues to uphold the value of well-designed, well-conducted clinical trials as an “indispensable tool of clinical research.”⁴

Results obtained from the first three randomized, masked, controlled clinical trials sponsored by the NEI were extremely valuable for demonstrating the validity of vision loss treatments.⁵ The Diabetic Retinopathy Study,⁶ initiated in 1971, the Diabetic Retinopathy Vitrectomy Study⁷ (1976–83), and the Early Treatment Diabetic Retinopathy Study (1979–85) all clearly demonstrated the success of photocoagulation and of vitrectomy in preventing vision loss in patients who would otherwise go blind.⁸

These research successes launched the NEI into several decades of extensive clinical trials for conditions of glaucoma through the Collaborative Initial Glaucoma Treatment Study (CIGTS),⁹ the Ocular Hypertension Treatment Study (OHTS),¹⁰ and age-related macular degeneration (AMD) including the Age-Related Eye Disease Study (AREDS)¹¹ among others.

The NEI also recognized the value of investigator collaborations by promoting networks to facilitate clinical research. The Pediatric Eye Disease Investigator Group is a consortium of academic and community clinicians who work to understand childhood eye disorders, and the Diabetic Retinopathy Clinical Research Network uses its collaborative power to advance the study of retinopathies. These networks are currently active with NEI support and continue Dr. Kupfer's legacy.

Ground-breaking basic research

The formation of the NEI provided opportunities for basic science of vision to blossom on the NIH campus. In a series of elegant experiments in the mid-1980s, the alphaA-crystallin promoter was identified and characterized, and through mouse models, intramural researchers demonstrated the oncogenic potential of the lens.^{12, 13} In addition to furthering the study of the lens itself, this groundbreaking work in molecular biology had far-reaching consequences for visual science and more broadly for science as a whole.

Basic vision research outside of NIH also flourished due to the strong support of investigator-initiated research, of which the R01 grant mechanism remains the hallmark. In 1986, NEI-supported research established a novel mechanism for ocular cancer in identifying that loss of the function of the Rb tumor suppressor gene can lead to retinoblastoma eye cancer.¹⁴

In 1993 the first structural description of a G-protein coupled receptor, the light sensitive and very stable rhodopsin was reported.¹⁵ This finding increased our understanding of retinal biology and opened new avenues for drug discovery. Several years later, NEI grantee Dr. Peter Agre received the 2003 Nobel Prize in Chemistry for his 1991 discovery of aquaporin, the first known channel that facilitates and regulates water transport across cell membranes, hugely significant for the highly fluid lens.^{16, 17} Scientists have now begun to identify the role of aquaporin in a number of ocular diseases, including Sjogren's syndrome and congenital

cataracts, and other organs and tissues, including the kidney, brain, respiratory tract, and salivary gland.

During these years of the 1980s and 90s, NEI-supported investigators also took advantage of new molecular biology techniques to clone a number of eye disease genes and to develop animal models to understand their roles in cataract, retinopathy, and myopia. Based on these efforts, the vision community has access to more than 500 genes that cause visual loss in a Mendelian inheritance fashion. These genes represent more than 20 percent of all human disease genes currently cloned.

Community-driven progress

More recently, the landscape of science has evolved to feature large, collaborative projects and community tools. Such strategies were particularly emphasized at the NIH under the leadership of Dr. Elias Zerhouni, from 2002 through 2008. We are now in an exciting era in which progress in neuroscience, genetics, and translational medicine affords vision science new opportunities.

The NEI is a core member of the NIH Blueprint for Neuroscience Research, a large-scale trans-NIH program comprised of 14 Institutes that have joined to facilitate collaboration in the areas of neural circuitry, brain and neural plasticity and novel probes to monitor this, and drug-delivery methods for central nervous system diseases.

A major accomplishment of “big science” at the NIH came with establishing the National Center for Human Genome Research in 1989 and the 2003 completion of the Human Genome Project. By 2005, the vision community used these genetic tools with stunning success to identify CFH, a protein involved in the inflammatory cascade, as the first risk factor gene identified for developing AMD.^{18, 19} All of NIH took notice of this feat.

NEI has been building community-wide genetics resources that incorporate diagnostic genotyping information for clinicians and patients, with a research repository of DNA information coupled with anonymized phenotypic information. The National Ophthalmic Disease Genotyping and Phenotyping Network (eyeGENE), launched in 2006, is one of several research resources being developed at NIH for personalized medicine, through which treatments may be designed based on the genetics of an individual's disease. This resource is accumulating samples at a pace of 1000 per year.

In 2007, the NEI was also the first of the NIH Institutes to disseminate information through the NIH National Database of Genotype and Phenotype (dbGaP), which archives and distributes data from studies that explore the relationships between genotype and phenotype. Through this database, the NEI created a repository of 600 DNA samples from the Age-Related Eye Disease Study, which is available to the scientific community.

The next generation of vision research

We can fully expect that vision research will continue to develop as a complex, dynamic, and vibrant multidisciplinary field. New science is moving vigorously toward fundamental understandings of disease processes.

NEI investigators will continue basic, clinical, and applied research projects that address the health needs of people with low vision or who are blind. These endeavors build on our base of visual neuroscience to characterize and enhance residual vision, and to create devices and assistive technologies that individuals can use to carry out everyday tasks.

Building on progress made in understanding neural plasticity, novel prosthetic visual devices are now being tested to transmit images to the brain of visually impaired people. By using an external camera, captured images are communicated through electrodes attached to the retina or tongue, providing a novel input to the brain and thereby substitute for aspects of vision.

We can also expect that vision researchers will incorporate new discoveries from areas of nanobiotechnology for basic discovery and clinical utility. The NEI is the lead administrative institute for the NIH Roadmap Nanomedicine Initiative, which seeks to uncover new cellular mechanisms and biological tools at the nanoscale. This information should result in new therapeutic technologies, devices, and structures for medical diagnosis and treatment.

The future of vision biology will continue to be anchored by our fundamental understanding of the pathophysiology of diseases, with basic scientists and clinicians mutually benefitting from fruitful collaborations. A stellar example is the recent completion of three independent, phase-I clinical trials for Leber congenital amaurosis (LCA). One year after gene therapy, the patients' visual improvements persist, with no untoward side effects observed.²⁰ These findings offer hope that other blinding diseases can be treated with gene therapy and other novel approaches.

As the NEI moves into the fifth decade of leading vision research, the Institute recognizes the critical importance of maintaining a robust research community. NEI will continue to support all areas of vision research while also fostering new disciplines, including proteomics and systems and computational biology. The entire scientific community will thrive on the remarkable opportunities before us, to elucidate the biology of the eye, and to restore the vision of people in need. The American people will continue to benefit from their decision 40 years ago to establish the National Eye Institute.

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