

National Plan for Eye and Vision Research



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Eye Institute

Cover:
Confocal micrograph of normal human retina labeled by immunofluorescence, courtesy of
Drs. Ann H. Milam, Anand Swaroop, and the *Journal of Biological Chemistry*

INTRODUCTION

Over the past 30 years, the National Eye Institute (NEI) has engaged in a strategic planning process that culminated in the publication of a series of national plans for vision research. This process actively involved the National Advisory Eye Council (NAEC), members of the vision research community, outside public groups, and professional and advocacy groups in assessing progress, identifying needs and opportunities, and developing strategies for research conducted and supported by the NEI. While these national plans were not designed to be a detailed blueprint for research, they were useful in identifying the most pressing needs and opportunities in vision research. The highest priority for the funding of research has been and continues to be supporting the highest quality of research that will help achieve the goals and objectives that emerge from the strategic planning process.



The NEI strategic planning process responded to advances in scientific knowledge and technology, as well as to the external requirements and resources that determined the level of funding available to support vision research. The development of this current Strategic Plan was no exception. In an era of unique and exciting scientific opportunity, an innovative new process was devised to keep the Plan as current as possible, so that the research priorities can be articulated to the scientific community, to the public, within the Executive Branch of the Federal Government, and to the Congress in response to requests for this information. This process allows the opportunity to more rapidly identify and bring emerging areas of science to bear on vision problems.

This new strategic planning process consists of two phases or components. The first phase of the process is similar to that used for the development of preceding strategic plans. Panels of experts representing each of the NEI's programmatic research areas were asked to assess progress made since the implementation of the previous plan, determine the most critical or promising areas of research need or opportunity, and develop goals and objectives that address these areas. Information from these panels was the basis for this current Strategic Plan and is included in the sections that follow and on the NEI website at <http://www.nei.nih.gov/strategicplanning>. In addition, the National Eye Health Education Program (NEHEP) Partnership meets every 2 years to review and evaluate progress, identify new critical areas for applied research, and make recommendations regarding the NEHEP. The results of this ongoing planning process are also included in this Strategic Plan and on the website and will continue to assist the NEHEP Planning Committee in updating and refining NEHEP goals and objectives.

The second phase of the strategic planning process is an ongoing effort to conduct workshops, conferences, and symposia in critical or emerging areas of science to explore how they might be applied to diseases of the eye and disorders of vision. Reports from such forums are being posted on the NEI website at <http://www.nei.nih.gov/strategicplanning> and will assist the program planning panels in periodic evaluation and updating of the needs and opportunities in vision research and the refinement of the NEI's goals and objectives.

VISION STATEMENT AND MISSION

Our eyes and the parts of our brain that allow us to understand the visual information we receive from our eyes make up a unique and awe-inspiring sense known as sight. Our eyesight provides intimate detail of our daily life in the world around us. It allows us to recognize the faces of those who are important to us and perform complex tasks for work or pleasure that would otherwise be impossible.

Out of its concern for the eyesight of the American people, the Congress created the NEI in 1968. In recognition of its special responsibility to address the visual health needs of the Nation, the NEI and the NAEC offer this vision and commitment for the future:

The National Eye Institute will continue to protect and improve the visual health of the Nation through the support and performance of the highest quality laboratory and clinical research aimed at increasing our understanding of the eye and visual system in health and disease and developing the most appropriate and effective means of prevention, treatment, and rehabilitation, and through the timely dissemination of research findings and information that will promote visual health.



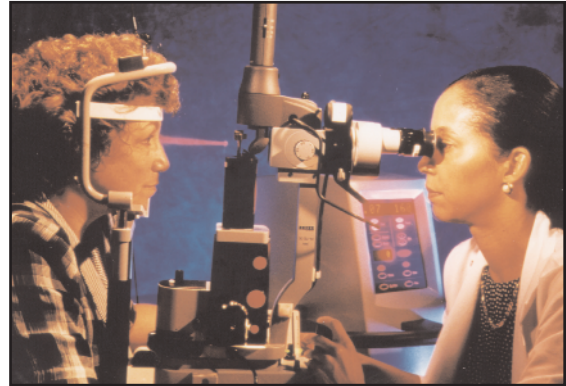
This vision statement is the logical extension of the NEI mission to “conduct and support research, training, health information dissemination, and other programs with respect to blinding eye diseases, visual disorders, mechanisms of visual function, preservation of sight, and the special health problems and requirements of the blind.”

Inherent in this mission is the investigation of normal tissue and normal visual processes, so that a more complete understanding may be gained of the abnormal processes that lead to diseases of the eye and disorders of vision. These investigations are conducted in hundreds of extramural laboratories and clinics throughout the United States and in the NEI’s intramural facilities in Bethesda, Maryland.

TRANSLATIONAL RESEARCH

Also inherent in the NEI mission is the application of the knowledge gained through research to benefit those who suffer from diseases of the eye or disorders of vision. This translational research is a critical component of NEI research programs. It is defined as the application of fundamental scientific discoveries and novel technologies to the development and testing of solutions for clinically relevant problems and thus may be relevant to the prevention, treatment, or diagnosis of eye diseases.

There are several aspects to translational research: (1) It may involve the development of techniques to diagnose or better characterize disease and therefore may not be hypothesis-driven; (2) it should be based on recognized biological principles but may not lead to new biological insights; (3) it can involve knowledge transfer among scientific fields; (4) it may bring together already-established technologies, biological models, and/or conceptual approaches to solve a specific disease-related problem; and (5) it



may ultimately result in clinical trials following nonhuman animal experimentation and initial human testing.

Because translational research focuses on preventing disease and developing treatments and diagnoses for diseases, the scientific principles on which it is based may vary in depth. Thus, while it is desirable to have a complete understanding of the basic biological mechanisms underlying a specific disease process, this may not always be possible or necessary to develop or achieve a successful treatment for a disease. The collaboration between basic scientists and clinicians is an essential aspect of translational research, and the NEI will continue to promote and support this collaboration to encourage high-quality, innovative translational research. Also, the diverse, nontraditional, and multifactorial nature of translational research should be recognized, as well as the fact that it can differ significantly from the traditional, hypothesis-driven research typically funded by the National Institutes of Health.

RETINAL DISEASES PROGRAM

The retina is a complex tissue in the back of the eye that contains specialized photoreceptor cells called rods and cones. The photoreceptors connect to a network of nerve cells for the local processing of visual information. This information is sent to the brain for decoding into a visual image. The adjacent retinal pigment epithelium (RPE) supports many of the retina's metabolic functions.

The retina is susceptible to a variety of diseases, including age-related macular degeneration (AMD), diabetic retinopathy (DR), retinitis pigmentosa (RP) and other inherited retinal degenerations, uveitis, retinal detachment, and eye cancers (ocular melanoma and retinoblastoma). Each of these can lead to visual loss or complete blindness.

The leading cause of visual loss among elderly persons is AMD, which has an increasingly important social and economic impact in the United States. As the size of the elderly population increases in this country, AMD will become a more prevalent cause of blindness than both DR and glaucoma combined. Although laser treatment has been shown to reduce the risk of extensive macular scarring from the “wet” or neovascular form of the disease, there are currently no effective treatments for the vast majority of patients with AMD.

DR is also a major cause of blindness. In the proliferative stage of the disease, newly formed, abnormal blood vessels can break through the retinal surface and hemorrhage into the normally transparent, gelatin-like vitreous in the middle of the eye. Scar tissue may subsequently form and pull the retina away from the back of the eye, causing a retinal detachment to occur. Laser treatment (laser photocoagulation) is a highly effective clinical tool for treating proliferative retinopathy.

The inherited retinal degenerations, typified by RP, result in the destruction of photoreceptor cells and the RPE. This group of debilitating conditions affects approximately 100,000 people in the United States.

One of the major achievements in biology has been defining the cellular events involved in the process of visual transduction—the process that captures light by photoreceptor cells and initiates the electrical signals utilized by the brain in processing visual information. This is now a classic model of how signal processing works in other systems. Advances in understanding visual biochemistry have yielded important new insights into the causes of retinal diseases.

The brain decodes and interprets the visual images that we perceive when electrical impulses generated within the retina are transmitted by ganglion cells via the optic nerve to the visual cortex of the brain. The tools of modern neurobiology offer the potential to understand both light adaptation (sensitivity to varying light levels) and inactivation (turning off the sensitivity to



light). A central unanswered question in neurobiology is how the complex retinal network enables the formation of images and the discrimination of colors.

Program Goals

After a thorough evaluation of the entire Program, the Retinal Diseases Panel recommends the following goals for the next 5-year period:

- With regard to macular degeneration, understand the molecular and biochemical bases for its different forms, improve early diagnosis, characterize environmental effects on its etiology, and develop new treatments.
- Understand the pathogenesis of DR and other vascular diseases of the retina and develop strategies for primary prevention and improved treatment.
- Identify the genes involved in both inherited and retinal degenerative diseases (including RP), determine the pathophysiological mechanisms underlying these mutations, and determine new potential therapeutic strategies for treatment such as gene transfer, tissue and cell transplantation, growth factor therapy, and pharmacological intervention.
- Establish the causes and etiology of uveitis and improve methods for its diagnosis, treatment, and prevention.
- Use both molecular and physiological approaches to study light adaptation in photoreceptors, with particular emphasis on the visual cycle, and identify the postphotoreceptor neural components of adaptation.
- Build on knowledge gained from retinal neuroscience to understand how retinal networks process visual images, a central unanswered question of modern neurobiology.

- Understand the genetic, cellular, and immunologic changes characterizing eye cancers and develop innovative methods of diagnosis and treatment.

Highlights of Recent Progress

The Age-Related Eye Disease Study (AREDS), in which nearly 5,000 Americans at high risk for AMD were prescribed high doses of zinc and three antioxidant vitamins (C, E, and beta-carotene), has revealed encouraging effects. The treatment lowered the risk of developing advanced AMD by 25 percent and reduced the risk of vision loss caused by advanced AMD by 19 percent. AREDS is a powerful example of the importance of large-scale clinical trials and a strong indicator of the possible role of oxidative stress as a contributory factor in AMD and other ischemic retinopathies.

The identification of receptors for the binding and ingestion of spent rod outer segments by the RPE has been a long-awaited finding of considerable importance. It has long been suspected that dysfunction in outer segment phagocytosis by the RPE causes retinal degeneration and blindness. The identified receptors are also utilized for the uptake of apoptotic cells by other phagocytes. Therefore, the phagocytic mechanism of the RPE belongs to a group of related clearance mechanisms that share common elements. This is a major conceptual advance.

The most important development of recent decades in the field of visual transduction is the production of a rhodopsin crystal structure. This important achievement should make it possible to understand the molecular basis of some visual dysfunctions at a level enabling the design of strategies for cures.

The disruption of a number of enzymes and binding proteins involved in the metabolism and transport of retinoids was shown

to cause visual dysfunction. The gene RPE-65 was shown to play a critical role in retinoid metabolism and to be essential for the production of 11-cis-retinol, the precursor for the photopigment 11-cis-retinal. Mutations in this gene were discovered in humans and in dogs. This then culminated in a dramatic and successful, adeno-associated virus-vectored gene replacement therapy. The NEI has capitalized on this event by funding additional preclinical investigations intended to take this gene-based therapy into human clinical trials.

It had been assumed that the pathway for regeneration of the visual pigment 11-cis-retinal was the same in both rods and cones. This has been shown not to be the case; recent research indicates that rods and cones use different pathways. Three new enzymatic activities in cone-dominant retinas were discovered that represent a novel retinoid cycle that is apparently required, since visual pigment bleaching in sunlight greatly exceeds the calculated maximal rate of conversion of all-trans-retinal to 11-cis-retinal in the known retinoid cycle. The newly discovered retinoid cycle takes advantage of biochemical pathway-sharing between Müller cells and cones. This new pathway is 20 times faster than the rod cell pathway and selectively supplies cones with 11-cis-retinal, eliminating competition with rod cells for chromophore.

The field of protein kinesis (protein trafficking) has undergone dramatic advances during the past 5 years. This biological process is vital for all eukaryotic cells, but understanding the process has important implications in the retina. In the highly specialized and polarized photoreceptors, rhodopsin moves from its site of synthesis to the outer segment discs of the photoreceptors, where it is available to transduce light into a signal. Along with trafficking, the translocation of proteins involved in the process of phototransduction in light/dark adaptation and in a circadian rhythm is an

important finding that will help unravel the complex regulation of photoreception.

Molecular genetic studies have shown that ABCR gene mutations are the cause of recessive Stargardt disease. A major breakthrough came with the development of an ABCR knockout mouse. This provided a convenient laboratory model for a systematic study of mechanisms underlying recessive Stargardt disease and resulted in fundamental new insights into the retinoid cycle. As a result, scientists are gaining insight into new players and potential new candidate disease genes.

There have been a number of notable accomplishments in retinal neurobiology in recent years. These include detailed biophysical characterization of the mechanisms of synaptic transmission at ribbon synapses, improved understanding of the processing of contrast signals in the retina, and important insights into circadian signaling.

A nonvisual imaging pathway in the central nervous system (CNS) has been identified on the basis of the initial discovery of a subtype of ganglion cell expressing a photopigment. These photoreceptive ganglion cells have been demonstrated to mediate entrainment of the circadian clock in the hypothalamus.

An elemental advance in the area of retinal development is the discovery that the order in which cell types are generated is determined in large part by molecular programs intrinsic to multipotent retinal stem cells. Significant progress has been achieved in understanding the interplay between these factors and the microenvironment in cellular determination.

Another important advance is the discovery that multipotent retinal stem cells persist in the pigmented ciliary margin. Similarly, Müller glia in postnatal chicken retinas, long thought to be incapable of regeneration, behave as retinal stem cells,

generating new retinal neurons after retinal damage. The possibility that mammalian Müller glia may have a similar ability is raised by recent findings that mammalian retinal stem cells and Müller glia share the expression of many genes.

The development of angiostatic agents for the control of blood vessel growth in retinal vascular disease is important in DR and the wet form of AMD. The critical issue of the underlying vessel loss after angiostatic therapy has not received similar attention. A breakthrough came with the discovery of a subset of systemically administered bone marrow-derived hematopoietic stem cells (HSCs) from mice, which can function as blood vessel progenitors during retinal neovascularization. When HSCs were engineered to express an antiangiogenic, angiogenesis was inhibited; these cells also can rescue and stabilize a vasculature destined to degenerate. A positive trophic effect on photoreceptors resulted from HSC injection into mouse eyes, resulting in their increased survival.

More than 130 genes causing inherited retinopathies in humans have been identified. This makes it possible to identify the cause of RP in approximately 50 percent of patients and the cause of Usher syndrome in 75 percent of patients. Sophisticated analytical techniques such as serial analysis of gene expression (SAGE) have been used to identify over 80 genes that are retina specific or are enriched in the human retina. This genomic information will be useful in identifying candidate genes involved in retinal disease.

Genetically dominant eye diseases are gain-of-function mutations and cannot be corrected by adding a corrective gene. The defective gene first must be inactivated. Progress has been made in this arena by using a mutation-specific, ribozyme-based therapeutic strategy with longstanding rescue in two different lines of transgenic rats, each with its own rhodopsin mutation.

Two classes, hammerhead and hairpin ribozymes, were found to be effective.

Evidence implicating an immune component in the etiology of AMD has been added to genetic evidence as the underlying cause of this disease. Research shows that the RPE is replete with the ability to synthesize molecules involved in the immune response. Drusen, pathological deposits that form between the RPE and Bruch's membrane, are a significant risk factor for AMD development. Immune components include dendritic cells and antigen-presenting cells, and local inflammatory responses have been shown to be closely associated with drusen development. Proteomics has been used to confirm the notion that oxidative mechanisms also contribute to drusen formation. Emerging and evolving lines of evidence are shored up by powerful new tools such as deoxyribonucleic acid (DNA) microarray analysis, microscopic imaging, and proteomics.

Progress in a number of new technologies, methodologies, analyses, and resources have facilitated the advancement of research, including the following:

- High-throughput analysis of retinal expression including microarrays and SAGE are powerful methods to generate complete profiles of specific cell types in the adult retina. These techniques show great promise for revealing new candidate genes that underlie retinal stem cell programs, cell type specification, and retinal disease states.
- High-throughput methodologies for proteomics.
- Genome-wide mutagenesis and phenotype-based screening.
- Large-scale generation, at national and international levels, of resources for genetic analyses.
- Bioinformatics.

- Animal models, including mouse, *Xenopus*, and zebrafish for visual system development, visual behavior, and retinal degeneration.
- Transgenic fish and mice expressing green fluorescent protein (GFP) in specific retinal cell types. Transgenic animals that express GFP specifically in retinal ganglion cells, bipolar cells, rods, or cones have been made in the past few years.
- Electroporation methods to introduce plasmid expression vectors encoding genes of interest or small inhibitory ribonucleic acids (siRNAs) into visual pathway cells *in vivo*, particularly retinal ganglion cells, recently have been developed.
- New methods for achieving loss and gain of function as part of experimental design include the use of morpholinos, conditional knockouts, inducible transgenic animals, and siRNAs.

Program Objectives

After carefully considering the research advances that have been made in this Program and on the basis of a careful analysis of current research needs and opportunities, the Retinal Diseases Panel recommends the following laboratory and clinical research objectives:

- Understand the process and control of circadian shedding of photoreceptor outer segments and their phagocytosis by the RPE.
- Analyze the mechanisms underlying light adaptation and recovery following phototransduction and understand the changes in neural coding in light/dark adaptation.
- Continue to reveal the presence and effects of a circadian clock in photoreceptors. Several metabolic functions and the trafficking of proteins may be regulated or influenced by the circadian clock. These influences may present risk factors for AMD and other retinal disorders.
- Understand the cell biology of cones, including outer segment renewal and shedding, the phototransduction cascade, retinoid metabolism, opsin trafficking, and the regulation of gene expression for cone pigments.
- Understand the basic biology of synaptogenesis. The cellular, molecular, and biophysical determinants of synapse formation have important and far-reaching implications for all aspects of vision, including synaptic remodeling, transplantation, and the development of receptive fields.
- Explore the topographical and regional differences in the organization of the retina and the relationship of this topography to disease progression.
- Continue to develop and apply noninvasive technologies such as functional magnetic resonance imaging (fMRI), ocular coherence tomography, adaptive optics, and confocal imaging to better understand retinal function and changes in disease states.
- Develop strategies to enhance retinal ganglion cell regeneration.
- Understand the role of synchronous activity in sensory coding and the anatomic, functional, and genomic components that regulate neural coding (e.g., finding of synchronicity of firing of retinal ganglion cells).
- Understand the pathogenesis of inherited retinal diseases, DR and other vascular diseases, uveitis, and eye cancers and explore new therapeutic strategies for their treatment.

- Explore the role of glia in the maintenance of retinal neuron function, including photoreceptor rescue and neural remodeling.
- Understand the causes and etiology of uveitis and immune modulation in retinal disorders. Identify the factors that dictate the unique properties of intraocular immunity and inflammation and that alter systemic immunity to intraocular antigens. Investigate possible therapeutic approaches, including gene therapy.
- Study the interacting roles of the environment and genetics in risk factors for retinal disease.
- Examine the genetic component of proliferative vitreoretinopathy and retinal detachment, determine the immune mechanisms involved, and develop antiproliferative drugs.
- Explore the pathophysiological heterogeneity of AMD to hasten development of the tools needed for improved diagnosis, prevention, and therapy.
- Further develop and critically evaluate therapies involving gene delivery, growth factors, and transplantation for the treatment of retinal disease.

The Retinal Diseases Panel recognizes the following additional opportunities/resources that will advance retinal research:

- Standardization of the definitions and characteristics of retinal phenotypes in macular disease. This will allow more precise disease definitions based on genotype-phenotype-environment correlations for the study of disease progression and response to therapy.
- Continued funding of large-scale clinical studies and the comparison of diverse groups and the development of standards for reading centers to compare across studies.
- Expansion of the research resources made available through the NEIBank.
- Continued development of animal models and a coordinated system to share animal model data and resources in the vision community.
- Development of diagnostic methods and therapeutic approaches to distinguish among infectious, immunopathogenic, and autoimmune posterior segment intraocular inflammation.

CORNEAL DISEASES PROGRAM

The cornea is the clear tissue at the front of the eye that serves two specialized functions: It forms a protective barrier that shields the eye from the external environment and serves as the main refractive element of the visual system, directing incoming light through the lens for precise focusing on the retina. Vision depends on the cornea acquiring transparency during development and maintaining clarity throughout adult life. In the United States, corneal diseases and injuries represent some of the most painful ocular disorders and are the leading cause of visits to eye care clinicians. In addition, 60 percent of the U.S. population have refractive errors that need correction for sharper vision. Worldwide, corneal infectious diseases have compromised the vision of more than 250 million people and have blinded over 6 million of them.

Program Goals

After a thorough evaluation of the entire Program, the Corneal Diseases Panel recommends the following goals for the Program for the next 5-year period:

- Explore the biology of the ocular surface as a physiological system, consisting of the tear film, cornea, conjunctiva, lacrimal and meibomian glands, eyelids, and their innervations, to gain a better understanding of the interaction and regulation of these components under normal and pathological conditions.
- Investigate corneal infectious and inflammatory processes and immunological responses to develop treatments to reduce keratitis and prevent blindness.
- Apply the knowledge acquired from discoveries in the basic science of the cornea and other tissues of the ocular

surface to the diagnosis, prevention, and treatment of ocular injury and disease.

Highlights of Recent Progress

Recent NEI-funded research has led to significant progress in defining the composition and function of the tear film and the role of its components in maintaining the health of the ocular surface. It is now recognized that the tear film is a complex, dynamically regulated fluid. Scientists have identified over 500 components in tears. These include innate defense molecules, such as antimicrobial peptides, growth factors, proteases and their inhibitors, and a variety of cytokines. Also found in tears are novel molecules whose functions are beginning to unfold—including lipocalin, which regulates the outermost lipid layer of the tear, and lacritin, a modulator of tight junction permeability. While many of these substances are derived from lacrimal or meibomian gland secretions, the cornea and conjunctiva also contribute a variety of components to the tear film, such as mucins, which are essential for innate defense, surface hydration, and refraction. The actions of these compounds do not occur in isolation and may well be modulated by association with other tear components. New molecular and spectroscopic techniques have been developed and are beginning to unravel the protein-protein and protein-lipid interactions that occur in the tear film.

Recent studies of the causes and mechanisms involved in tear deficiency have led to the suggestion that dry eye syndromes may involve inflammatory processes. Translational research has led to the development of therapeutic strategies that target ocular inflammatory responses and increase tear production as a means of managing dry eye diseases. The importance of hormonal

influences in maintaining lacrimal and meibomian gland function is emerging. Studies of altered protein trafficking in the lacrimal gland suggest that the dry eye in Sjogren syndrome may involve autoantigens misdirected to the plasma membrane from intracellular sites where they are attacked by regulatory lymphocytes.

Significant progress has been made in understanding the pathophysiology of blinding corneal infections. The molecular genetic characteristics of herpes simplex virus type 1 (HSV-1) and the role of the host tissue during the acute and latent periods of infection are being vigorously explored. The NEI-sponsored Herpetic Eye Disease Study demonstrated the efficacy of oral acyclovir in reducing HSV-1 recurrences by 40 percent. River blindness, or onchocerciasis, is a parasitic infection transmitted by black flies. In this immune-mediated disease, Th2 lymphocytes respond not only to the parasite but also to symbiotic bacteria that are released in the cornea from larvae of the parasitic microfilaria. This knowledge likely will lead to more precise diagnoses and more effective treatments for this globally blinding disease. Studies also continue on the immunological response to trachoma, a blinding chlamydial disease prevalent in the tropics. Antibiotic treatment of entire villages over the past 5 years has been proven to be an effective trachoma eradication strategy.

Knowledge about inherited corneal diseases has increased considerably over the past 5 years and will lead to better diagnosis and therapy. The NEI-funded Collaborative Longitudinal Evaluation of Keratoconus Study established that keratoconus is a slowly progressing, asymmetric disease, but when patients are treated with rigid contact lenses, surprisingly good vision is achieved. Along with the discovery of new corneal dystrophies, molecular genetic studies have identified gene loci for more than 30 of these disorders, and a variety of gene mutations are associated with distinctive clinical and histopathological characteristics. For



example, more than 20 mutations of the TGFBI (BIGH3) gene have been found in 14 clinically distinct disorders, including various types of granular and lattice corneal dystrophies. Similarly, a number of phenotypes of macular corneal dystrophy have been attributed to over 70 distinct mutations in the CHST6 gene. Defects in this sulfotransferase gene alter the processing of proteoglycans in the stroma, such as lumican and keratocan, which are essential for optical clarity.

Substantial progress has been made in using a variety of gene knockout models to examine the role of specific stromal molecular components, such as small, leucine-rich proteoglycans, in corneal transparency. Transgenic and knockout studies have established the essential role of the Pax-6 gene during corneal and lacrimal gland development. Proper development of the lens and its signals is required for normal corneal development. Ongoing studies of gene expression changes during development will expand our knowledge of the specific contribution of these molecules in developing and maintaining transparency.

Corneal trauma, chemical burns, and refractive surgery induce changes in epithelial and stromal cells to repair the wound. Considerable basic knowledge has been acquired regarding regulation of cell-cell and cell-matrix adhesion properties, cell death, signaling molecules invoked during epithelial and stromal cell migration and proliferation, and production of new extra-

cellular matrix by activated stromal cells. The epithelial cells on the corneal surface are continuously replaced by new cells derived from stem cells located in the corneal limbus (corneal periphery). Efforts to identify molecular markers and morphological characteristics of these cells are ongoing. Recent evidence suggests that stem cells exist in a variety of adult tissues, and current studies are examining ocular surface tissues for this possibility. Epithelial stem cells grown on membranes outside the body have been successfully transplanted to restore transparency to the ocular surface damaged by diseases such as Stevens-Johnson syndrome and chemical burns. Unlike most other cells, human corneal endothelial cells generally do not proliferate. However, recent studies of endothelial cell cycle regulation suggest that it may be possible to coax these cells to divide, thus opening a promising avenue for repair of diseased or injured endothelial tissue.

NEI-funded research has contributed to the development of technological innovations that have had a significant impact on clinical care. Silicone hydrogel contact lenses, which allow physiological levels of oxygen to reach the ocular surface, have improved the safety of continuous-wear contact lenses. Progress continues in correcting refractive error by laser-assisted in situ keratomileusis and in understanding the biological consequences of this procedure. Ongoing development of tools to measure higher order aberrations will lead to better vision after refractive surgery. Recent development of the femtosecond laser has encouraged researchers to study partial-thickness keratoplasty, a less invasive surgical procedure that will likely reduce the need for corneal transplantation. Advances in imaging the cornea in vivo, including wavefront imaging, optical coherence tomography, and confocal microscopy, have provided new methods for studying postsurgical and pathological changes in the optical and biomechanical properties of the cornea.

Corneal transplantation has a success rate greater than 90 percent for first-time grafts and remains the most widespread and successful form of solid-tissue transplantation. However, immune rejection remains the leading cause of corneal graft failure. Studies over the past 5 years have revealed the importance of both donor and host antigen-presenting cells and the critical role of minor histocompatibility antigens in provoking corneal graft rejection. Donor age requirements and tissue quality limit the availability of donor corneas. The NEI-funded Cornea Donor Study is a prospective study to determine the graft failure rate over a 5-year followup period by comparing tissues obtained from donors older than 65 years of age with those of younger donors. The NEI also supports tissue bioengineering studies to generate corneal replacements in vitro, thereby supplanting the need for donor eye tissue.

Program Objectives

After carefully considering research progress and current research needs and opportunities, the Corneal Diseases Panel recommends the following objectives to increase knowledge of the ocular surface system and translate this knowledge into clinical practice for the prevention and treatment of corneal disorders:

With respect to the goal of understanding the biology of the ocular surface system:

- Characterize the genes and proteins expressed in tissues of the ocular surface system; determine the functional consequences of changes in expression and molecular interactions; and determine the epigenetic, hormonal, neural, and environmental influences under both normal and pathological conditions.
- Describe intercellular signaling between layers of the cornea as well as between various tissues of the ocular surface sys-

tem to understand its function as a unified physiological system.

- Elucidate the intracellular pathways and diverse effector mechanisms activated by extracellular inputs such as neurotransmitters, hormones, cytokines, and growth factors.
- Probe changes of gene and protein expression in the developing and mature cornea, including the changes in response to signals derived from the lens and other sources.
- Identify and characterize the stem cells of each tissue that make up the ocular surface system, define the ocular stem cell niches, and determine the molecular and structural attributes that maintain stem cells and promote their differentiation.

With respect to the goal of understanding infectious, inflammatory, and immunological processes affecting the cornea:

- Elucidate the pathophysiology of the ocular surface tissues in response to infection, investigate the defensive mechanisms invoked by infectious diseases, and determine the factors that compromise these mechanisms.
- Investigate interactions of the innate and adaptive immune systems with the tis-

sues of the ocular surface system and characterize the impairment of these systems in autoimmune and other corneal diseases.

- Explore, characterize, and analyze the causes of corneal graft rejection and neovascularization and determine the signals that disrupt the immunoregulation of the anterior chamber of the eye.

With respect to the goal of translating discoveries into the prevention and treatment of ocular surface disorders:

- Gain an understanding of the epidemiology of and risk factors for infectious and inflammatory corneal and ocular surface diseases to develop preventive strategies.
- Develop vaccines and other novel therapeutic interventions for blinding viral, bacterial, fungal, and parasitic corneal and ocular surface diseases.
- Develop new technologies for drug delivery, gene therapy, surgery, and tissue bioengineering for treating disorders of the ocular surface system.
- Address the consequences of interventions such as wound healing after refractive surgery and tear film function after drug treatment.

LENS AND CATARACT PROGRAM

In contrast to the cellular and molecular complexities present in most other tissues, the lens is a relatively simple system, composed of a single layer of metabolically active epithelial cells that differentiate into quiescent, but structurally highly differentiated, fiber cells. The ease of obtaining lens epithelial and fiber cells and the relative molecular simplicity of the fully differentiated fiber cells make the lens one of the best tissues to use in the study of events that control aging. Likewise, the lens provides an accessible system for studying the fundamental aspects of embryonic induction.

Nonetheless, it is the transparent properties of the lens and its ability to focus light that present some of the most clinically relevant challenges in eye research. Cataract is an opacity in the normally clear lens that interferes with vision and is by far the most serious problem associated with the lens. The World Health Organization cites cataracts as the leading cause of blindness worldwide. In the United States, cataracts affect an estimated 20.5 million or about one in six Americans older than age 40 years. By the age of 80 years, over one-half of all Americans have cataracts. In spite of readily available effective cataract surgery, cataracts account for a significant amount of vision impairment, particularly among older Americans with limited financial resources. The goals of early detection, prevention, and universal treatment of cataract are central to the Lens and Cataract Program, and advancing these goals requires increased understanding of the basic molecular processes occurring in the normal and cataractous lens.

Most people in midlife face another problem associated with the lens—presbyopia, the loss of the ability of the lens to focus on near objects (known as accommodation). By understanding changes in the physical properties of the normal lens and



its surrounding support structures as a function of age, it may be possible to develop treatments that delay or prevent presbyopia.

Developmental defects in the lens are a major cause of blindness and visual impairment among children. Since many of the pathways required for formation of the lens are also important for lens maintenance, a detailed understanding of lens development will provide a rational basis for the treatment of childhood cataract and could shed light on the diseases of aging associated with the lens. Since lens formation is critical to eye development, these studies will help explain the etiology of common congenital eye malformations such as microphthalmia.

The Lens and Cataract Program objectives listed in this Strategic Plan have been selected with the understanding that basic lens physiology will provide the framework for learning more about the mechanisms involved in presbyopia and cataract, as well as developmental anomalies associated with the lens, thereby allowing researchers to develop more effective treatments.

Program Goals

- Understand the physiological, biochemical, and biophysical bases of lens

transparency on the cellular and molecular levels.

- Determine the causes and mechanisms of age-related changes in the lens that lead to cataracts and presbyopia.
- Understand lens development and the diseases associated with defects in this process.

Highlights of Recent Progress

One of the major highlights in cataract research in the past 5 years was the definitive establishment of an association between smoking and cataract formation. Recent studies also confirm that cataract development may be delayed by protection from ultraviolet ray exposure, for example, by wearing sunglasses and a hat with a brim.

In the area of molecular genetics, a number of new genes for hereditary cataracts have been mapped in humans and laboratory mice. These include some expected genes, such as those encoding lens crystallins, and unexpected genes, such as those encoding membrane proteins and cytoskeletal components. This accomplishment was significantly driven by expanded public genomic DNA and mouse resources, including sequence and mapping reagents and murine cataract alleles recovered from ethylnitrosourea mutagenesis screens.



This work has provided insight into underlying molecular mechanisms leading to opacification. Knowledge that the functional inactivation of genes—whose activity is mainly required during early stages of lens formation—also leads to cataract formation due to their downstream effects in structural lens fiber genes such as crystallins has brought researchers closer to a mechanistic understanding of certain types of cataract. In addition, new genes have been identified for hereditary malformations of the anterior chamber, including Rieger’s anomaly, anterior segment mesodermal dysgenesis, and anophthalmia/microphthalmia.

Pioneering studies using molecular, cellular, and whole-animal approaches have resulted in significant progress in defining the contribution of the crystallins to the function of the lens and to the long-term maintenance of its optical properties. Consistent with molecular and cellular studies demonstrating a critical role for α -crystallin in maintaining lens transparency, mutants of human α A and α B crystallins have been genetically linked to autosomal dominant cataract. Laboratory mice in which the α A crystallin gene has been disrupted have smaller lenses and develop opacity shortly after birth. The nonlenticular role of the crystallins has been highlighted by the identification of mutant α B crystallin associated with desmin-related myopathy, the implication of the involvement of the β -crystallins in development, and the discovery of the expression of the crystallin in the retina.

Investigations into the molecular, structural, and functional properties of α -crystallin have confirmed its role as a molecular chaperone, or “sensor,” of protein stability that recognizes early events in protein unfolding, such as those brought about by age-related damage. Many types of cataract have been traced to protein aggregation and failures of the chaperone machinery. In this regard, they share molecular characteristics with leading aging

pathologies, such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis. Advances in the understanding of cataracts and the development of therapeutic strategies will likely have a far-reaching impact that transcends the lens.

Key to understanding lens function is an understanding of the controls of lens epithelial cell proliferation and differentiation into fiber cells, a process that begins during development and continues throughout life. Advances in the past 5 years demonstrate that control of lens epithelial cell proliferation and differentiation into fiber cells is complex and requires the coordination of multiple growth factor signaling pathways, including those for fibroblast growth factor (FGF), bone morphogenetic protein, and transforming growth factor-beta (TGF β). These growth factor signaling pathways regulate the activity of cell cycle control proteins (including Rb, E2F, and the cyclin-dependent kinases and their inhibitors), which in turn controls epithelial cell proliferation and fiber cell differentiation. Their importance in understanding lens defects is emphasized by the involvement of FGF and TGF β signaling in various types of cataracts.

The availability of genetically altered mouse models has contributed greatly to understanding lens cell cycle regulation and the differentiation of epithelial cells to fiber cells. The foundation of these studies comes from advances in identifying the promoter elements within genes expressed in the lens. Studies of the α and γ crystallin promoters, as well as those from developmentally expressed genes such as Pax-6, have provided critical insights into the structure of promoter elements, which in turn has led to the construction of promoters that allow for targeted tissue and cellular expression of genes that regulate critical functions in the lens.

Optical clarity not only must be achieved by the unique differentiation of lens cells

but also must be maintained for decades after the differentiation process is complete. Identification of mutations in human lens fiber cell cytoskeletal genes, combined with information from studies on genetically engineered mice, establishes that some elements of the lens cytoskeleton are not required to achieve optical clarity but are required to maintain it. These studies suggest that the lens has evolved specific mechanisms with which to resist cataractogenic pressures associated with aging in these postmitotic cells.

Because the lens is avascular, cell-to-cell communication via gap junctions is essential for the maintenance of homeostasis. This is revealed by mutations in human lens fiber connexins, the protein components of gap junctions, resulting in congenital cataracts. Supporting these findings in humans is the demonstration that disruption of connexin genes in mice also results in cataracts, providing experimental models for study. Surprisingly, deletion of one of the fiber connexins, Cx50, results in smaller lenses in the mouse and an accompanying microphthalmia due to a slowing of the cell division rate. Deletion of the other fiber connexin, Cx46, does not have this effect on lens cell growth. Replacement of Cx50 with Cx46 results in rescue of the cataract phenotype, but not slower growth, demonstrating the unique functions of these different gap junction structural proteins. This finding is unique in the area of gap junction study and demonstrates a selectivity provided by the diversity of connexin intercellular channels.

Maintenance of transparency requires that, at the time of differentiation, fiber cells lose their nucleus along with other organelles needed to carry out metabolic processes. Over the past 5 years, the process by which organelles are lost—denucleation—has become better understood because of the recognition that degradation is synchronized and biochemically overlaps with the cell death (apoptotic) cascade.



Defects in development of the lens are a major cause of blindness and visual impairment. Since many of the pathways required for formation of a lens are also important for lens maintenance, a detailed understanding of lens development will provide a sound basis for the treatment of cataracts in both children and adults. In the past 5 years, exceptional progress has been made in defining a gene network critical for early lens development (lens induction) and subsequent lens function. Important findings have confirmed that a single evolutionarily conserved gene, Pax-6, can initiate all of the events required for lens and eye development and demonstrate that the lens is critical for normal development and maintenance of the retina and cornea. The roles of other critical genes in this network were significantly defined, including Prox-1, Sox-2, Maf, Pitx-2, and Pitx-3. These findings were possible because of major breakthroughs in developing new transgenic and conditional knockout lines in both mammalian and nonmammalian model systems, such as those of mouse, zebrafish, and *Xenopus*. In the past 5 years, this basic developmental framework has converged to a remarkable extent with the clinical genetic discoveries noted above, creating a critical synergy between human genetic analysis and developmental analysis in defining the gene networks required for lens development.

Program Objectives

- Determine the extent of visual impairment due to cataract, especially in minority and other selected populations, in the United States and worldwide.
- Map, identify, and characterize genes in people and laboratory mouse models that, when mutated, cause congenital or age-related cataract. Apply population genetics to identify gene-environment interactions that may confer susceptibility to age-related cataract.
- Identify genes, pathways, and cis gene regulatory elements that control eye development, especially those critical for lens formation, cell fate determination, and cell differentiation. Define in molecular terms the classical stages of lens competence, bias, and induction. Exploit new sequence- and phenotype-driven strategies. Investigate the mechanisms by which the lens influences other tissues of the eye, especially during development.
- Characterize the control of the cell cycle in lens epithelial cells by identifying cell cycle regulators, growth factors, receptors, and signal transduction pathways.
- Understand the basis of lens accommodation and presbyopia at the molecular and mechanistic levels.
- Develop a comprehensive bioinformatics infrastructure that will integrate and coordinate all genetic, genomic, and proteomic databases as well as data on animal models that are important for the development of the eye and visual functions. A website with these databases will be the primary vehicle for rapidly disseminating information and making these tools and reagents available to the lens and cataract research community.

GLAUCOMA AND OPTIC NEUROPATHIES PROGRAM

Glaucoma is a group of disorders that shares a distinct type of optic nerve damage that leads to loss of visual function. The disease is manifested as a progressive optic neuropathy that, if left untreated, leads to blindness. It is estimated that as many as 2.2 million Americans have glaucoma, and a similar number may have the disease without knowing it. Of these, as many as 120,000 are blind as a result. Furthermore, glaucoma is the number one cause of blindness in African Americans. Its most prevalent form, primary open-angle glaucoma (POAG), can be insidious. Unfortunately, since quality of life is not significantly affected until the later stages of the disease process, a significant proportion of individuals remain either undiagnosed or undertreated. Glaucoma usually begins in midlife and progresses slowly but relentlessly. If detected early, disease progression can frequently be arrested or slowed with drug and/or surgical treatment. A greater awareness of the deterioration of the optic nerve in the absence of elevation in the intraocular pressure or even functional field loss has reaffirmed the importance of recognizing the disease in its earliest stages.

Continued laboratory and clinical research has provided greater understanding of the normal functions of the ocular tissues involved in glaucoma and other optic neuropathies. Past studies have led to a better understanding of glaucoma etiology and pathophysiology. The results have been the introduction of new glaucoma drugs with still more on the horizon, identification of a number of molecules and genes that play a role—either causative or secondary—in the disease mechanism, development of new diagnostic tools, clarification of the role of intraocular pressure (IOP), and



introduction of new experimental disease models. However, there is still a significant need to improve methods of detecting structural and functional changes and develop new therapeutic options.

More recently, a conceptual change has taken place within the glaucoma research community. Researchers now recognize that to understand glaucoma they need to understand the total neurodegenerative process, including the insults that initiate the neurodegenerative process, the mechanisms by which retinal ganglion cells die, and how these processes relate to end-stage optic nerve damage. In this regard, the workshop “Pathophysiology of Ganglion Cell Death and Optic Nerve Degeneration” was sponsored by the NEI to explore the state of knowledge of neurodegeneration as it applies to glaucoma. The full report *Investigate the Pathophysiology of Ganglion Cell Death and Optic Nerve Degeneration* can be accessed at <http://www.nei.nih.gov/strategicplanning>.

On the basis of the recommendation from both this workshop and the NAEC that glaucoma be viewed as an optic neuropathy and be studied within that context, the Program will be expanded to include research on all optic neuropathies. The current overall emphasis for research in this Program is on identifying the biological mechanisms responsible for the various forms of glaucoma and other optic neuropathies so that improved treatment can be developed. The goals and objectives outlined in this Strategic Plan reflect these changes.

Program Goals

- Develop diagnostic methodologies and treatment regimens that lead to improved patient outcomes and prevent

vision loss from glaucoma and other optic neuropathies.

- Understand the basic biology underlying the pathophysiology of glaucoma and other optic neuropathies.

Highlights of Recent Progress

Over the past 5 years, results from three major clinical trials confirmed the value of reducing IOP in patients with ocular hypertension or glaucoma to prevent the onset of glaucoma in the former case and the progression of disease in the latter. The Ocular Hypertension Treatment Study (OHTS) noted that lowering IOP at least 20 percent produced a 50 percent protective benefit over baseline among those individuals who had elevated IOP without optic disc or visual field deterioration. The Early Manifest Glaucoma Trial determined that patients with newly diagnosed glaucoma progressed less often than untreated patients when IOP was reduced at least 20 percent compared with baseline. The Collaborative Initial Glaucoma Treatment Study demonstrated that patients with glaucoma who undergo either medical or surgical therapy were equally likely to avoid progression of disease after 5 years of followup.

Analyses of key baseline, clinically important factors among ocular hypertensive patients enrolled in the OHTS



uncovered or affirmed a number of risk factors for the development of glaucomatous damage, including IOP, large cup-to-disc ratio, age, and central corneal thickness.

Significant advances in identifying glaucoma-causing or associated genes have been made with the mapping of more than a dozen glaucoma loci and the cloning of more than a half dozen glaucoma genes. New studies involving genome-wide screening are beginning to identify alleles that may play a combinatorial role in complex POAG. Identification of trabecular meshwork glucocorticoid response/myocilin, optineurin, cytochrome P450 1B1 (CYP1B1), and other genes that play a less prominent role in disease causation promises a better understanding of normal eye development and of the molecular pathophysiology of glaucoma in general. The application of genomic technologies has provided an ever-enlarging database of genes/proteins expressed in various anterior segment tissues. Having a rich supply of candidate genes will speed the search for new genes involved in glaucoma pathogenesis.

The introduction of a number of rodent models, both genetic mouse and induced ocular hypertension rat models, has expanded the ability to investigate mechanisms at the molecular and systems levels. One exciting new development in the field of congenital glaucoma is the recent report that tyrosinase modifies the glaucoma phenotype in the CYP1B1 knockout mouse. Significantly, this work supports findings that modifier genes play a role in the etiology of congenital glaucoma in children. Other models have allowed the evaluation of pharmacological approaches that target neurodegenerative processes.

Over the past 5 years, candidates for molecular mediators of the pathophysiology of glaucoma have been identified. This list includes a number of second messengers, stress response proteins, immunologic proteins, and transcription factors. Myocilin

was one of the first proteins to be associated with glaucoma. Much progress has been made on the characterization of myocilin, including an improved understanding of the differences in biochemical and cell biological characteristics between disease-causing and benign forms of the protein.

New applications of technologies, such as the flash and multifocal electroretinogram and multifocal visual evoked potential, allow objective assessment of inner retina functioning in nonhuman animal models as well as in humans. Outcomes of both functional and histologic studies point to a pathological process that does not discriminate between subsets of ganglion cells and involves changes in the glial cells and retinal ganglion cell axons within the optic nerve head, as well as in the dendrites and somas of the retinal ganglion cells in the retina.

Development of new and existing instrumentation for quantification of the retina, retinal nerve fiber layer, and optic nerve head surface has allowed substantial improvement in the clinical detection of structural damage. Algorithms for sensitive and specific screening (detecting glaucomatous damage) and change detection (monitoring glaucomatous progression) are approaching clinical usefulness for several of these instruments.

Program Objectives

- Elucidate the prevalence, pathophysiology, natural history, and history of intervention results of optic neuropathies such as glaucoma and optic neuritis over the full time course of these diseases and within ethnic subgroups.
- Develop improved diagnostic measures to detect optic nerve disease onset, progression, and treatment effectiveness, including development and validation of predictive genetic testing.
- Develop novel therapeutic approaches to optic neuropathies, including stem cell therapy, gene therapy, vaccination, and other neuroprotective strategies, and develop safe and effective surgical procedures, pharmaceuticals, and delivery systems for treatment.
- Continue mapping genetic loci contributing to diseases of the optic nerve, with expanded efforts to enlarge the base of well-characterized patient collections. Exploit new paradigms to explore gene-environment interactions.
- Identify and characterize the genes, gene products, developmental regulatory signals, and pathways responsible for disease of the optic nerve; modulation of their phenotypes; and variable treatment responses using gene mapping, genotype/phenotype studies, animal models, gene expression profiling, and proteomics.
- Determine the mechanisms of optic nerve damage and retinal ganglion cell loss and survival in optic nerve diseases such as glaucoma, as well as their functional correlates. Characterize glaucomatous neurodegeneration and other optic neuropathies within the entire visual pathway at the cellular, structural, and functional levels.
- Develop transgenic and other genetic animal models of optic nerve disease, with emphasis on the principal clinical subtypes of glaucoma (especially open-angle glaucoma), that display key disease features such as optic nerve head cupping and ischemia, retinal ganglion cell loss, and increased IOP.
- Enhance understanding of the structure and function of the aqueous humor outflow pathways at the cellular and molecular levels.
- Exploit genomics and proteomics, as well as cellular and molecular methodologies,

to further characterize the response of the optic nerve and optic nerve head to a variety of physiologic and pathophysiologic perturbations.

- Develop a comprehensive bioinformatics infrastructure that will integrate and coordinate all genetic, genomic, and pro-

teomic databases, as well as data on animal models that are important for the development of the eye and visual functions. A website with these databases will be the primary vehicle for rapidly disseminating information and making these tools and reagents available to the research community.

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING PROGRAM

The Strabismus, Amblyopia, and Visual Processing Program supports clinical and laboratory research on visual development, neural processing, eye movement, and other disorders involving output of the retina and other portions of the brain that serve vision. Knowledge of the normal visual system provides a foundation for understanding the causes of impaired vision and developing corrective measures.

Over the past several decades, visual neuroscience funded by the NEI has exerted a substantial influence on other fields of neuroscience. This is especially true of developmental and functional studies of the central visual pathways, which continue to yield results that can be generalized to the brain as a whole. During the past 5 years, improvements in noninvasive brain imaging techniques, visual testing, and probability-based models of visual perception and new discoveries in axonal guidance and related developmental events have enhanced the understanding of visual function and factors that influence the development, maintenance, and regeneration of the visual system.

Future vision research that employs promising new technologies and collaborations with new disciplines, such as bioengineering, holds great promise for understanding the development and func-



tion of the visual and oculomotor systems. Progress in the diagnosis and treatment of clinical disorders that impair vision, such as amblyopia, strabismus, myopia, and oculomotor disorders, depends on cutting-edge research. The future promise and close link between clinical practice and research are reflected in the overarching Program goals below.

Program Goals

After evaluating the Program, the Strabismus, Amblyopia, and Visual Processing Panel recommends the following goals for the next 5-year period:

- Determine the etiology of myopia in humans, identify the risk factors associated with myopia and other refractive errors, and identify the biochemical pathways associated with the control of eye growth.
- Understand how the visual system develops, its capacity for plasticity, and ways to promote its regeneration.
- Investigate the development of visual function in children at high risk for amblyopia and strabismus, determine underlying mechanisms, and develop and disseminate information about detection methods and therapeutic interventions for restoring normal vision.
- Analyze visual performance in normal and dysfunctional states and develop clinically useful diagnostic tests for assessing visual performance, particularly in infants and young children.
- Understand the neural circuitry and muscular mechanisms that control gaze under environmental conditions and discover the mechanisms that provide plasticity to the oculomotor system.

- Understand how the brain processes visual information, how neural activity is related to visual perception, and how visual processing interacts with other brain systems underlying cognition.

Highlights of Recent Progress

Advances over the past 5 years have had an important influence on understanding the development of the visual system and brain. The visual system has long been an ideal model system for understanding how development sculpts brain organization and for studying CNS regeneration. It is ideal because of its accessibility and high degree of organization in a variety of animal models.

A key advance has been in identifying and describing the molecules in developing visual pathways that guide retinal axonal outgrowth to appropriate targets in the developing nervous system.

An important series of advances have been made in understanding the molecular control of synaptic specificity and topographical mapping. Genetic model systems have begun to reveal the genes necessary for synapse formation and the molecular mechanism by which topographical mapping in the brain is achieved.

There has also been progress in understanding regenerative failure in the CNS. Glial cell molecules that inhibit regeneration of axons have been identified, and there is evidence that they can be neutralized to enhance regeneration.

Another step forward has been a clearer understanding of the mechanisms providing plasticity to the developing visual system, with discoveries of the roles of activity and sleep and of the molecular and cellular mechanisms underlying critical periods of development. Appropriate neurotrophic peptide receptors and electrical activity have been shown to affect cell sur-

vival, rate of dendritic and axonal growth, and the establishment of neural connections. The molecular mechanism by which activity regulates specificity and synaptogenesis in the visual system has been the subject of intensive study over the past several years, illuminating a number of molecular mechanisms.

Progress also has been made over the past 5 years in understanding amblyopia and strabismus. Evidence has emerged showing that patching and penalization treatment regimens can successfully manage amblyopia in children. Recent studies of large populations with amblyopia show distinctive and systematic variations in the patterns of functional loss in amblyopia and the effect of binocularity in these conditions. A better understanding of risk factors and neural mechanisms related to amblyopia and strabismus, plus earlier screening of children, has improved treatment and clinical outcomes.

Progress continues to be made in myopia research, including a refinement in the understanding of visual and biochemical cues and genes involved in the regulation of eye growth and refractive states. Experimental studies have shown, for example, that quality, quantity, and timing of visual stimuli can affect ocular growth, which could influence the development of new treatments. Discovery of the role of circadian rhythms and of the molecular changes in the sclera driven by signals from the retina has increased understanding of eye growth. Clinical studies are examining whether certain optical or pharmacological treatments can slow the progression of myopia in children, while epidemiological studies are identifying risk factors, both environmental and genetic, and are determining the incidence of myopia in the United States and elsewhere.

Also significant is progress in understanding the influence of the oculomotor tissues on eye movements, motor neurons,

extraocular muscles, and connective tissues within the orbit. The orbit contains mechanical relationships that support functions previously thought to require complex neural inputs. The emergence of the concept of pulley arrangements will affect diagnostic, clinical, and surgical approaches to the treatment of oculomotor disorders.

Researchers have acquired new details about the neural mechanisms that control the initiation, direction, and duration of eye movements, including the brainstem mechanisms responsible for saccadic eye movement and the cortical mechanisms responsible for control of gaze. Progress is being made in understanding the relationship between eye movements and the posture or movement of the limbs and head.

New techniques for obtaining intracellular recordings from the intact brain of mammals are increasing the understanding of the circuitry of the visual system. Descriptions of the connectivity between visual areas of the cortex and subcortical afferents continue to be refined and are leading to better descriptions of hierarchical relationships in the brain. Evidence is emerging suggesting that the pattern of visual inputs may play a role in refining developing neural circuits. Parallels between and limits to the presumed homology of the human visual system and that of nonhuman primates also are emerging. It is important to recognize that research on nonhuman primates will continue to play an essential role in understanding the human visual system in health and disease.

A number of studies have shown that contextual cues markedly alter the percept of a given retinal image feature. This has led to the recognition that context plays a fundamental role in the formation of perceptual or "scene-based" representations in the visual system. This transformation is accomplished at relatively early stages in visual processing. A view of perceptual constancy has emerged in which different

retinal stimuli with common environmental causes elicit the same percept. These studies have revealed neuronal responses that vary over time, reflecting the pattern perceived rather than the retinal stimulus.

Studies of visual processing have identified neuronal activity that is correlated with the decision to execute a particular action in response to a particular visual stimulus, rather than simply correlated with either the stimulus or the action alone. These studies have led to promising theories and have identified neuronal substrates in which visual information is mapped to action.

A better understanding of the cell types and their connections in the visual cortical areas has given rise to the idea that there may be fundamental circuits that underlie visual function. This information enhances computational and theoretical approaches to understanding how these circuits function.

Among the advances of the past 5 years has been the refinement of noninvasive neuroimaging technologies. Research using this approach has provided new insights about how the human visual cortex is organized. It has confirmed understanding of the human visual system previously established by anatomical and physiological studies in animals. It has advanced knowledge of the brain processes involved in visual motor function and attention and is providing new insights into neural deficits in abnormalities such as amblyopia and brain reorganization following injury and in oculomotor function. The development and application of imaging technologies at the cellular level have provided important insights into developmental processes, such as axonal guidance, and have led to the discovery of dendritic spine motility underlying both plasticity and development.

Program Objectives

After considering the research advances that have been made in this Program and on the basis of an analysis of research needs and opportunities, the Strabismus, Amblyopia, and Visual Processing Panel recommends the following laboratory and clinical research objectives:

- Determine how stem cells differentiate in the development of the visual system and how they can be used to understand the molecular logic of cell-type-specific identity in the visual system. Develop a clearer understanding of the molecular and cellular signals influencing the growth of axons and the axonal cytoskeleton. Understand how and why axons stop growing once they reach their targets and the mechanisms that control development and maintenance of synapses. Gain an understanding of the mechanisms that control arealization and specification in the visual cortex.
- Elucidate the mechanism of the critical period to determine how experience alters connectivity in the developing visual system. Develop an understanding of how environment and vision influence neural activity in developing circuits and how these interactions alter gene expression and the molecular changes that alter circuit properties.
- Further study the mechanisms that lead to degeneration and regeneration of the central visual pathways, including ganglion cell death and optic nerve regeneration. Determine the basis for CNS regenerative failure. Develop a clearer understanding of the molecular and cellular interactions within the CNS in the context of both normal function and neurodegenerative disorders of the eye and the central visual pathways.
- Develop and apply new recording approaches, electrical or optical, to determine how synaptic input and output give rise to properties such as receptive fields at any level in the visual pathways. Study the function, circuitry, and development of higher order visual areas to determine the effect of attention and top-down influences on visual processing.
- Expand the knowledge of myopia by further characterizing the visual signals that govern eye growth. Identify the genes and gene products associated with these signaling mechanisms. Identify the human risk factors, environmental and genetic, for myopia and abnormal eye growth. Evaluate the efficacy of potential treatments, such as pharmacological approaches, special spectacles, and contact lenses, for slowing the progression of myopia.
- Develop and use innovative approaches to detect and treat strabismus and amblyopia. Develop imaging technologies to further understand the neural basis of amblyopia and related visual deficits. Identify the underlying genetic components related to strabismus and oculomotor disorders. Translate knowledge into tests for reliable screening and early diagnosis.
- Within each processing stage in the visual system, determine the relationships among neuronal cell morphology, laminar position, input patterns, output targets, and encoded sensory information. Understand how the patterns of circuitry within and among visual areas account for the influence of stimulus context on neuronal responsivity. Identify the role that inhibitory circuits play in higher visual processing.
- Determine the cellular mechanisms that give rise to changes in visual sensitivity associated with attention and perceptual learning. Discover the larger role of neuronal plasticity in the formation of visual associative memories and imagery.

Develop a mechanistic understanding of the origin of the signals that control attention and how they alter the responses of neurons in visual processing and sensorimotor transformations.

- Bridge the knowledge of what happens at the cellular level in the visual system with the knowledge of visual psychophysics. Develop molecular/cellular approaches and imaging technologies to gain an understanding of the role of the cell activity that underlies behavior. Exploit the knowledge of the functional organization of the visual system in animal models with noninvasive imaging studies in humans.
- Attain a clearer understanding of how signals are processed within cortical circuits for voluntary eye movements and characterize the signals that pass from cortical motor circuits to subcortical and cerebellar circuits. Develop a better

understanding of the cellular mechanisms underlying plasticity in the oculomotor system that ensure accurate gaze shift and alignment of the eyes.

- Develop a better understanding of the neural control, biomechanical properties, and anatomical relationships of the tissues around the eye muscles and the roles they play in guiding eye movements.
- Encourage the development and application of emerging technologies that will affect the progress of vision research in the future. Examples include genetic engineering, proteomics, imaging technologies at the cellular and systems levels, development of reagents that signal neural function, and bioinformatics. Encourage collaboration among vision researchers, clinicians, computational scientists, and bioengineers to fully exploit these emerging technologies.

LOW VISION AND BLINDNESS REHABILITATION

Visual impairment can be defined as any chronic visual deficit that impairs everyday functioning and is not correctable by ordinary eyeglasses or contact lenses. Visual impairment can be mild or moderate but also includes total blindness or functional blindness where no useful vision remains. Although there have been important strides over the past few decades in the treatment and prevention of eye diseases that cause visual impairment, there are still many causes of vision loss for which there is no cure. Even with the best medical treatment, many Americans live with impaired vision. In the United States, where normal vision is 20/20, legal blindness is defined as visual acuity with best correction in the better eye worse than or equal to 20/200 or a visual field extent of less than 20 degrees in diameter. In many States, a visual acuity of less than 20/40 disqualifies a person from obtaining a driver's license, as do some visual field deficits. Research in visual impairment and blindness is aimed at developing and assessing new methods for the rehabilitation of visually impaired individuals through assistive technologies, training, and rehabilitation services and education.

Current estimates of the number of people who are visually impaired vary greatly by source and method of measurement, as well as by the inclusion criteria applied. Conservative estimates suggest that there are at least 3.5 to 5 million Americans who are visually impaired, and more than 1 million of these are legally blind. Because of the narrowly defined definitions of visual impairment, these figures undoubtedly underestimate the problem. However, many people experience functional limitations due to vision loss even though they do



not meet the criteria for legal blindness. Even relatively mild impairment of vision can affect the performance of everyday tasks such as driving, reading, and walking. When more broadly defined as visual problems that hamper the performance and enjoyment of everyday activities, other recent estimates indicate that almost 14 million Americans suffer from visual impairment. Older adults represent the majority of the visually impaired population. Visual impairment is included among the 10 most prevalent causes of disability in the United States.

The leading causes of visual impairment are diseases that are common in elderly persons, including AMD, glaucoma, DR, cataract, and optic nerve atrophy. More than two-thirds of people with visual impairment are older than 65 years of age. It is estimated that there were almost 34 million Americans older than age 65 years in 1992 and that by 2030 this number will more than double. Visual impairment in elderly persons decreases independence, increases the risk of falls and fractures, and often leads to isolation and depression.

The leading causes of visual impairment in infants and children are retinopathy of prematurity, deficits in the visual centers of the brain, and structural ocular abnormalities such as cataract and retinal abnormalities. These conditions sometimes have a severe impact on children's quality of life, especially when vision impairment coexists with other impairments, and can have major consequences on education and future opportunities for employment. However, children, like adults, benefit significantly from coordinated and comprehensive services to ameliorate disability.

The next 5 years of research on visual impairment and blindness and their rehabilitation can lead to great strides in improving the quality of life for visually disabled people. These accomplishments can be realized if the existing research infrastructure is enhanced and if there is a broad-based program to educate clinicians, neuroscientists, and engineers from a variety of backgrounds about the research opportunities in low vision and blindness rehabilitation.

The points below are not meant to reflect all opportunities for ameliorating visual impairment. However, they represent a sample of the many opportunities that exist for enriching the base of knowledge in the research and clinical communities and for assisting people with low vision and blindness in improving the quality of their lives.



Program Goals

After a thorough evaluation of the entire Program, the Low Vision and Blindness Rehabilitation Panel recommends the following goals for the Program for the next 5-year period:

- Improve understanding of CNS structure and function, neural plasticity, and the performance of everyday tasks so that the perceptual processing capabilities of people with low vision or blindness can be optimized.

- Develop assistive devices, environmental modifications, and rehabilitation strategies to minimize the impact of visual impairment in everyday life and reduce disability and societal limitations in visually impaired persons.
- Determine which interventions are most effective and develop research tools so that the approaches can be scientifically evaluated, leading to improved clinical and rehabilitative care for the visually impaired population.
- Establish the scope of impaired vision and blindness in U.S. society and its ramifications for everyday life, identifying the prevalence of visual impairment, its functional limitations, and the risk factors for visual disability. These efforts will permit interventions to be targeted to high-risk and underserved subpopulations of individuals with visual impairments and blindness.
- Create a network for the dissemination of research findings to rehabilitation specialists, educators, clinicians, and technology developers. Establish the means and avenues for adapting research for use in clinical and rehabilitation settings.
- Build an infrastructure for developing future generations of researchers who are concerned with a broad range of topics in visual impairment and rehabilitation. Encourage the multidisciplinary collaboration and training of researchers from other areas about issues pertinent to visual impairment.

Highlights of Recent Progress

Important advances have been made in the past 5 years that influence visual impairment and rehabilitation.

Psychometric measures for characterizing disability and assessing quality of life

issues have improved. This has helped researchers recognize the importance of psychosocial factors in vision loss, and the new measures have been applied to rehabilitation research for evaluating the outcomes of intervention programs.

Technologies for low vision enhancement and wayfinding have continued to improve, allowing for advances in mobility research on ways people with normal vision and visual impairment get around using visual, auditory, and haptic cues from the environment. Cognitive factors based on perception of the environment also play an important navigational role in walking and driving.

Progress has been made in leveraging mainstream technologies for people with visual impairments. Accessibility requirements have been incorporated into World Wide Web standards, text-to-speech and speech-to-text software programs have improved, and magnified text is available on most computers. New embossing technologies that produce dynamic tactile cues give people who are blind better access to graphics.

There has been progress in the development and deployment of assistive aids such as the global positioning system-based navigation system, talking signs, auditory signals at street crossings, and barcoding schemes for labeling locations and objects. These location-aware technologies provide detailed information about the environment and a person's whereabouts. Portable assistive devices that enhance residual vision also represent important gains. Some progress has also been made in the development of assistive intraocular aids such as the implantable monocular telescope.

fMRI and other imaging technologies have increased the understanding of changes in the brain related to visual deficits and impairments. Researchers are continuing to learn about the organization of the

brain, which may have implications for rehabilitative training and device development.

Research has identified the incidence of visual impairment in certain segments of the population and its effect on mortality. Earlier epidemiological research revealed that functional impairment and disability from low vision and blindness were much more prevalent than had been thought. More recently, populations have been identified in which visual impairment occurs most frequently. It was learned that visual impairment occurs mostly among people who are underserved by the health care system and among members of minority groups. Additionally, it has been learned that visual impairment is linked to increased mortality independent of comorbid conditions. This research has direct implications for health care planning and public health policy.

There has been progress in raising awareness of visual impairment and rehabilitation. Education and outreach programs in schools, community centers, and elsewhere are teaching ways to prevent vision loss and manage visual impairment. Well-written and targeted educational materials, many on the Web, are helping convey the message that progress is being made to understand and overcome vision loss and develop technologies for managing visual impairment.

Program Objectives

On the basis of a review of the research advances that have been made in this



Program and an analysis of the current research needs and opportunities, the Low Vision and Blindness Rehabilitation Panel recommends the following laboratory and clinical research objectives:

- Evaluate the effectiveness of existing rehabilitation strategies and programs and assess their impact on task performance, psychosocial and psychological factors, and quality of life parameters in people with visual impairment.
- Develop an understanding of visual and nonvisual requirements for performing everyday tasks. Develop comprehensive definitions of visual disabilities.
- Develop an understanding of perceptual and cognitive factors involved in the performance of everyday tasks such as driving, other forms of mobility, and reading.
- Leverage and adapt mainstream technologies such as microelectronics, navigation and location aids, and haptic technologies for use by people with visual impairments. Encourage the development of software for separating content from display format.
- Develop a knowledge base of design requirements for architectural structures, open spaces, and parks and the devices necessary for optimizing the execution of navigation and other everyday tasks by people with visual impairments.
- Focus additional resources on the development of training programs and assistive devices for the rehabilitation of individuals with visual impairments.
- Exploit research opportunities provided by new imaging technologies (especially fMRI) to better understand sensory substitution and visual system and CNS plasticity.
- Encourage and support the development of infrastructure and programs for training researchers in the multidisciplinary components of vision rehabilitation research to ensure continued research in this area.

NATIONAL EYE HEALTH EDUCATION PROGRAM



Eye disease, a major public health problem in the United States, causes significant suffering, disability, loss of productivity, and diminished quality of life for millions of people. The NEI is addressing this public health problem through its National Eye Health Education Program (NEHEP). In 1988 the U.S. Congress appropriated funds for the NEI to “increase its commitment to the prevention of blindness through public and professional education programs and the encouragement of regular eye examinations.” This was the first distinct congressional appropriation designated for eye health promotion and education since the NEI was established in 1968. The three NEHEP program areas are diabetic eye disease, glaucoma, and low vision.

The NEHEP is supported by a two-tier advisory structure: the NEHEP Planning Committee and the NEHEP Partnership. The responsibilities of the Planning Committee include recommending program priorities, advising on activities, and facilitating cooperation among the NEHEP Partnership. The Partnership represents over 60 national organizations in the public and private sectors. Partnership members bring vast knowledge of at-risk populations, networks spanning the country, and experience in countless health education efforts.

Under the auspices of the NEHEP, the NEI serves as the lead agency for the *Healthy People 2010* (HP2010) vision

objectives. *HP2010*, a program of the U.S. Department of Health and Human Services, is the Nation’s framework for improving the health of all Americans.

Program Goals

The purpose of the NEHEP is to implement large-scale information, education, and applied research programs. It also seeks to ensure that the results of eye and vision research are used for the benefit of all people. The goals of the NEHEP are to:

- Increase awareness of glaucoma, diabetic eye disease, and low vision in selected high-risk target audiences in the United States.
- Increase awareness of the importance of early detection of glaucoma, diabetic eye disease, and low vision services, with the ultimate goal of effecting appropriate behavior change.
- Increase health care providers’ awareness of the need for regular, comprehensive eye examinations with dilated pupils for those at risk for glaucoma and diabetic eye disease and the need for referrals to low vision services, with the ultimate goal of effecting appropriate behavior change.
- Encourage these groups to take appropriate action based on their increased awareness.

Highlights of Recent Progress

The NEI continues to develop educational materials guided by the NEHEP goals and objectives that target both patients and providers.

The NEI continues to network with community organizations, Federal agencies,

allied health care organizations, health care professional groups, and organizations that assist older adults. The NEI maintains that the community (patients/consumers) and those who support the community (providers, social service advocates, and Federal agencies) are key in educating the public. The NEI uses a multidisciplinary approach to reach both primary and secondary audiences. In an effort to make sure that the general public is reached, the NEI has incorporated the use of conferences, teleconferences, standard and online focus groups, print materials (brochures and pamphlets), TV/radio/print public service announcements, websites, audiovisual materials, interactive multimedia programs, traveling exhibits, and posters.



The NEI strives to provide culturally specific and appropriate messages for all of the NEHEP content areas and materials. The glaucoma materials are being translated into Spanish. The primary low vision booklet has already been translated into Spanish. The NEI is reviewing the diabetes education materials to translate, update, and perform necessary rewrites to reflect the current state of scientific knowledge. Once modified, all diabetes education materials also will be available in both English and Spanish. The NEI also seeks the advice of the Hispanic/Latino community through focus groups and feedback mechanisms to ensure that the educational tools and materials developed are appropriate for the intended audience.

The NEI has begun developing outreach and communication strategies for the American Indian and Alaska Native population. The NEHEP conducted an environmental scan of the vision-related programs and services provided to American Indians and Alaska Natives and identified gaps in eye health information, program services, and materials targeted to these groups.

The NEI maintains an up-to-date website that posts best practices and lessons learned. The NEI encourages NEHEP Partnership members to submit pertinent information or links to websites to assist other NEHEP Partnership members in raising awareness about eye health prevention, education, and treatment. The NEI supports the further development of its website to encompass useful patient-focused information, cutting-edge clinical practices, and lessons-learned approaches to all eye diseases. The NEI has established a Community Awards Program that provides seed money to local communities in establishing eye health initiatives.

It is the NEI's desire to increase the representation of racial and ethnic populations and organizations in the NEHEP Partnership. Having a diverse racial and ethnic representation and diversity of thought and perspective are key to the success of the NEHEP Partnership effort. The NEI encourages NEHEP Partners to share the NEHEP mission, vision, and purpose with their respective peers to promote the inclusion of more racial and ethnic groups. Where necessary, the NEI will continue to identify and invite prospective NEHEP Partners as the program continues to expand.

The NEI is working on a project to educate eye health care professionals about the issues of vision rehabilitation. The NEI is developing a pilot program to enhance referrals of individuals with low vision to vision rehabilitation services. The primary purpose of the program is to increase

patient referrals from eye care professionals to qualified vision rehabilitation services. This program will enable the NEI to develop, test, and evaluate measurable strategies; identify opportunities and barriers; and provide a cadre of health care and eye care professionals and their patients with access to useful sources of information and services. The program also will assist eye care and vision rehabilitation professionals in reaching and providing services to those in need. Once the pilot program has been completed, the NEI will assess its success and utility to eye care professionals and their patients and decide whether to continue the effort. The NEI welcomes any thoughts, suggestions, and/or participation from the NEHEP Partners.

One of the NEI's primary purposes for initiating the NEHEP Partnership was to encourage and enhance collaboration with other Federal agencies. This increased communication with other Federal agencies helps avoid duplication and expands the reach of eye health information.

The *HP2010* Vision Working Group continues discussions centered around strategies to raise awareness about national *HP2010* efforts and how local communities and agencies can become involved. The NEI has provided an *HP2010* vision website link to all Partnership members through the NEI website.

The NEI suggested to all NEHEP Partners that they join in a Memorandum of Understanding with the NEI to work on *HP2010* efforts together. The NEI encourages this type of collaborative effort with all of its NEHEP Partners. This collaboration will provide a forum for the development of a common *HP2010* theme and message for the vision community.

The NEI is developing *HP2010* materials for dissemination to the general public, eye health care professionals, and policymakers. These materials include the *Healthy Vision*

2010 Community Action Guide, Healthy Vision 2010 Toolkit, and the Healthy Vision 2010 Companion Document.

Program Objectives

The NEHEP Partnership met in April 2002 to develop recommendations for the next 5 years. Those recommendations are:

- Ensure that NEHEP goals and objectives are targeted to both patients and providers in providing information on eye health care and vision rehabilitation services.
- Use a multidisciplinary approach to reach secondary target audiences, (allied health professionals, community organizations, etc.).
- Provide culturally specific and appropriate messages for all NEHEP content areas and materials.
- Develop and maintain a website to include best practices and lessons learned.
- Increase the representation of racial and ethnic populations and organizations in the NEHEP Partnership and continue to facilitate the national dialog among current and future NEHEP Partnership members.
- Educate and encourage eye health care professionals about the issues of vision rehabilitation.
- Increase the NEHEP Partnership's collaboration with other Federal agencies.
- Assist Partnership members in reaching out to the vision community to raise awareness about national *HP2010* efforts.
- Provide an *HP2010* vision website link to all Partnership members.
- Develop a common *HP2010* theme and message for the vision community.

- Develop, disseminate, and share *HP2010* materials with the general public, eye health care professionals, and policymakers.

In addition, two new program areas will be reviewed for consideration based on a careful analysis of the scientific research:

- Develop and implement an AMD public education program targeted to providers and patients. This program will focus on disease etiology, risk factors, prevention, intervention, and treatment strategies.

- Coordinate and enhance diverse efforts in children's vision education and outreach. The NEI recognizes the opportunities, national health care mandates, and research conducted to understand the importance of children's eye health care.

ACKNOWLEDGMENTS

The National Eye Institute and the National Advisory Eye Council wish to thank those who contributed suggestions, comments, and recommendations during the development of this Strategic Plan. In particular, we wish to acknowledge the contributions of the members of the program planning panels, including the NEI staff, who so freely gave of their time and expertise and the various organizations that provided advice and assistance in reviewing various drafts of the Plan. The vision research community is indebted to these people for their generous efforts on behalf of those who suffer from visual impairment or blindness due to eye diseases.

Retinal Diseases Panel

***Gary Abrams, M.D.**
Kresge Eye Institute
Detroit, Michigan

***Sally Atherton, Ph.D.**
Medical College of Georgia
Augusta, Georgia

***Joseph Besharse, Ph.D.**
Medical College of Wisconsin
Milwaukee, Wisconsin

Leo Chalupa, Ph.D.
University of California
Davis, California

Martin Friedlander, M.D., Ph.D.
The Scripps Research Institute
La Jolla, California

Bernard Godley, M.D., Ph.D.
Retina Foundation of the Southwest
Dallas, Texas

Carla Green, Ph.D.
University of Virginia
Charlottesville, Virginia

Leslie Hyman, Ph.D.
State University of New York
Stony Brook, New York

Stuart Mangel, Ph.D.
University of Alabama
Birmingham, Alabama

Patsy Nishina, Ph.D.
The Jackson Laboratory
Bar Harbor, Maine

Krzysztof Palczewski, Ph.D.
University of Washington
Seattle, Washington

Donald Zack, M.D., Ph.D.
Johns Hopkins University
Baltimore, Maryland

NEI Program Directors:
Hemin Chen, Ph.D.
Peter Dudley, Ph.D.
Chyren Hunter, Ph.D.
Andrew Mariani, Ph.D.
Grace Shen, Ph.D.

*Trustee of the Association for Research in Vision and Ophthalmology (ARVO)

Corneal Diseases Panel

Dimitri Azar, M.D.
Harvard University
Boston, Massachusetts

Edouard Cantin, Ph.D.
City of Hope Medical Center
Duarte, California

Suzanne Fleiszig, O.D., Ph.D.
University of California
Berkeley, California

Brigid L.M. Hogan, Ph.D.
Duke University Medical Center
Durham, North Carolina

Gordon Klintworth, M.D., Ph.D.
Duke University
Durham, North Carolina

Sandra Masur, Ph.D.
Mount Sinai School of Medicine
New York, New York

Austin Mircheff, Ph.D.
University of Southern California
Los Angeles, California

Jerry Niederkorn, Ph.D.
University of Texas
Dallas, Texas

Steven Sugrue, Ph.D.
University of Florida
Gainesville, Florida

Kirk Wilhelmus, M.D., M.P.H.
Baylor College of Medicine
Houston, Texas

***Steven Wilson, M.D.**
University of Washington
Seattle, Washington

NEI Program Director:
Richard Fisher, Ph.D.

*ARVO Trustee

Lens and Cataract Panel

Steven Bassnett, Ph.D.
Washington University
St. Louis, Missouri

Velia Fowler, Ph.D.
The Scripps Research Institute
La Jolla, California

Thomas Glaser, M.D., Ph.D.
University of Michigan
Ann Arbor, Michigan

Daniel Goodenough, Ph.D.
Harvard Medical School
Boston, Massachusetts

Joseph Horowitz, Ph.D.
University of California
Los Angeles, California

M. Cristina Leske, M.D., M.P.H.
State University of New York
Stony Brook, New York

Richard Mathias, Ph.D.
State University of New York
Stony Brook, New York

Hassane Mchaourab, Ph.D.
Vanderbilt University
Nashville, Tennessee

Guillermo Oliver, Ph.D.
St. Jude Children's Research Hospital
Memphis, Tennessee

***Larry Takemoto, Ph.D.**
Kansas State University
Manhattan, Kansas

NEI Program Director:
Ellen Liberman, Ph.D.

Glaucoma and Optic Neuropathies Panel

Bassem Bejjani, M.D.
Washington State University
Spokane, Washington

Claude Burgoyne, M.D.
Louisiana State University
New Orleans, Louisiana

Laura Frishman, Ph.D.
University of Houston
Houston, Texas

Eve Higginbotham, M.D.
University of Maryland
Baltimore, Maryland

Robert Nickells, Ph.D.
University of Wisconsin
Madison, Wisconsin

Julia Richards, Ph.D.
University of Michigan
Ann Arbor, Michigan

William Swanson, Ph.D.
State College of Optometry
New York, New York

Douglas Vollrath, M.D., Ph.D.
Stanford University
Stanford, California

***Thomas Yorio, Ph.D.**
University of North Texas
Fort Worth, Texas

Beatrice Yue, Ph.D.
University of Illinois
Chicago, Illinois

NEI Program Director:
Ellen Liberman, Ph.D.

*ARVO Trustee

Strabismus, Amblyopia, and Visual Processing Panel

Thomas Albright, Ph.D.
Salk Institute for Biological Studies
San Diego, California

Ben Barres, M.D., Ph.D.
Stanford University School of Medicine
Stanford, California

William Good, M.D.
Smith-Kettlewell Eye Research Institute
San Francisco, California

Dennis Levi, O.D., Ph.D.
University of California
Berkeley, California

Steve Lisberger, Ph.D.
University of California
San Francisco, California

Jeffrey Schall, Ph.D.
Vanderbilt University
Nashville, Tennessee

Carla Shatz, Ph.D.
Harvard Medical School
Boston, Massachusetts

Michael Shadlen, M.D., Ph.D.
University of Washington
Seattle, Washington

David Trolio, Ph.D.
New England College of Optometry
Boston, Massachusetts

Brian Wandell, Ph.D.
Stanford University
Stanford, California

Rafael Yuste, M.D., Ph.D.
Columbia University
New York, New York

NEI Program Directors:
Chyren Hunter, Ph.D.
Michael Oberdorfer, Ph.D.

Low Vision and Blindness Rehabilitation Panel

Aries Arditì, Ph.D.
Lighthouse International
New York, New York

Susana Chung, Ph.D.
University of Houston College of
Optometry
Houston, Texas

Richard Long, Ph.D.
Western Michigan University
Kalamazoo, Michigan

Jack Loomis, Ph.D.
University of California
Santa Barbara, California

Cynthia Owsley, Ph.D.
University of Alabama
Birmingham, Alabama

Eli Peli, O.D.
Schepens Eye Research Institute
Boston, Massachusetts

Noa Rensing, Ph.D.
MicroOptical Engineering Corporation
Westwood, Massachusetts

Kathleen Turano, Ph.D.
Johns Hopkins University School of
Medicine
Baltimore, Maryland

NEI Program Director:
Michael Oberdorfer, Ph.D.

National Eye Health Education Program Planning Committee

Dave Baldrige
National Indian Council on Aging
Albuquerque, New Mexico

W. Lee Ball, Jr., O.D.
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Charles E. Basch, Ph.D.
Columbia University
New York, New York

Norma K. Bowyer, O.D., M.P.H.
Morgantown, West Virginia

Michael R. Duenas, O.D.
Chattahoochee, Florida

David L. Epstein, M.D.
Duke University Medical Center
Durham, North Carolina

George E. Foster, O.D.
Northeastern State University
Tahlequah, Oklahoma

Charles A. Garcia, M.D.
University of Texas Medical School
Houston, Texas

Eve Higginbotham, M.D.
University of Maryland Medical Center
Baltimore, Maryland

Robert E. Kalina, M.D.
University of Washington
Seattle, Washington

Andrew G. Lee, M.D.
University of Iowa Hospital and Clinics
Iowa City, Iowa

Jose S. Pulido, M.D., M.S.
University of Illinois
Chicago, Illinois

(continued on next page)

**National Eye Health Education
Program Planning Committee**
(continued)

Gwen Sterns, M.D.
Rochester General Hospital
Rochester, New York

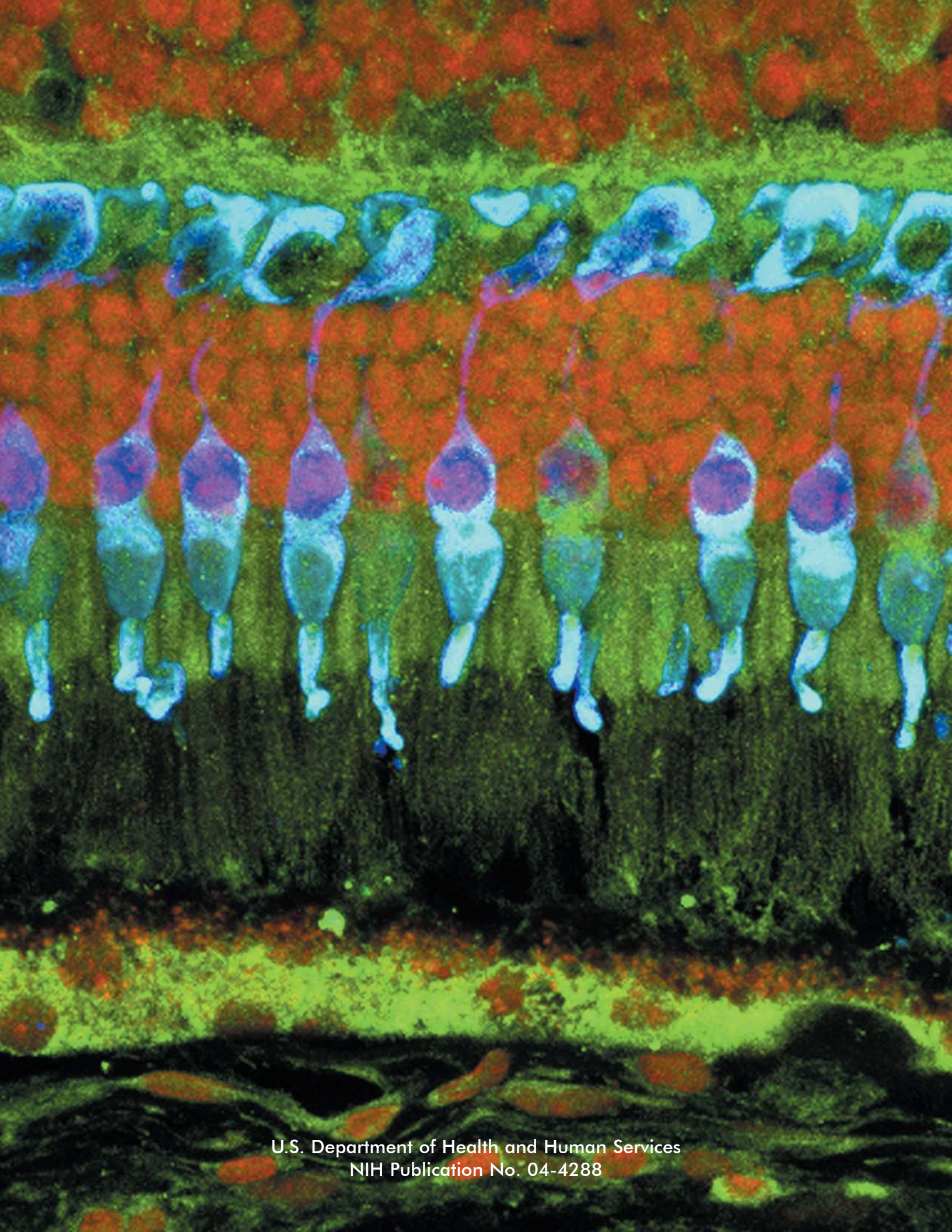
R. Tracy Williams, O.D.
Deicke Center for Visual Rehabilitation
Wheaton, Illinois

Satya Verma, O.D.
Pennsylvania College of Optometry
Elkins Park, Pennsylvania

NEI Staff:
Rosemary Janiszewski
Karen Silver

Reviewers and National Eye Health Education Program Partners

Administration on Aging, U.S. Department of Health and Human Services (DHHS)
 AMD Alliance International
 American Academy of Ophthalmology
 American Academy of Optometry
 American Academy of Physician Assistants
 American Association of Diabetes Educators
 American College of Occupational and Environmental Medicine
 American Diabetes Association
 American Foundation for the Blind
 American Medical Association
 American Optometric Association
 American Pharmaceutical Association
 American Society of Health-System Pharmacists
 American Society of Ophthalmic Registered Nurses
 Association for Education and Rehabilitation of the Blind and Visually Impaired
 Association for Research in Vision and Ophthalmology
 Association of Schools and Colleges of Optometry
 Association of University Professors of Ophthalmology
 Centers for Disease Control and Prevention (CDC), DHHS
 Chi Eta Phi Sorority, Inc.
 Council of Citizens of Low Vision International
 Delta Gamma Foundation
 The Glaucoma Foundation
 Glaucoma Research Foundation
 Helen Keller International
 Illinois Society for the Prevention of Blindness
 InFOCUS
 Joint Commission on Allied Health Personnel in Ophthalmology
 Juvenile Diabetes Research Foundation International
 Lighthouse International
 The Links, Incorporated
 Lions Clubs International
 Lions Eye Health Program (Lions Clubs International Foundation)
 Low Vision Council
 Macular Degeneration Partnership
 Maryland Society for Sight
 National Alliance for Hispanic Health
 National Association for Parents of Children with Visual Impairments, Inc.
 National Association for Visually Handicapped
 National Association of Area Agencies on Aging
 National Association of Hispanic Elderly (Asociación Nacional Por Personas Mayores)
 National Association of Hispanic Nurses
 National Association of Vision Professionals
 National Black Nurses Association
 The National Caucus and Center on Black Aged, Inc.
 National Community Pharmacists Association
 National Council of La Raza
 National Council on Patient Information and Education
 National Council on the Aging, Inc.
 National Diabetes Education Program, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH)/CDC
 National Hispanic Medical Association
 National Institute on Aging, NIH
 National Medical Association
 National Optometric Association
 NIDDK, NIH
 Office of Disease Prevention and Health Promotion, DHHS
 Office of Minority Health, DHHS
 Prevent Blindness America
 Prevention of Blindness Society of the Metropolitan Area
 Research to Prevent Blindness
 Veterans Health Administration, U.S. Department of Veterans Affairs
 Vision Council of America



U.S. Department of Health and Human Services
NIH Publication No. 04-4288