

VISION RESEARCH



A NATIONAL PLAN:
1999–2003

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A Report of the National Advisory Eye Council

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A NATIONAL PLAN: 1999–2003

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH
NATIONAL EYE INSTITUTE

A Report of the National Advisory Eye Council



Roy H. Steinberg, M.D., Ph.D.

Not long after the creation of the National Eye Institute (NEI) by Congress in 1968, a young, promising vision research scientist named Roy Steinberg received one of the first NEI Research Career Development Awards. This marked the beginning of

a long and productive association between the NEI and a researcher who served the vision community in many ways.

With his great breadth of knowledge and sharp mind, Roy had a clearer grasp than most of the many facets of retinal research, both clinical and laboratory. Most productive scientists establish a single theme to their research program during their career. Roy was different, adapting to new ideas and seeking challenging new avenues through which to pursue his numerous research interests. His early work led to a greater understanding of the complex active and passive ionic mechanisms governing retinal pigment epithelium (RPE) cell transport properties. He showed how the RPE contributes to the electroretinogram and controls the environment surrounding the photoreceptor cells.

In the late 1980's, while maintaining an interest in retinal physiology, Roy and his colleagues at the University of California at San Francisco became interested in growth factors and their potential use in slowing or preventing retinal degenerations. Roy was instrumental in demonstrating that basic fibroblastic growth factors could act as a survival-promoting neurotrophic factor in hereditary retinal degenerations. At the time of his death, Roy was involved in experiments he believed could lead to treatment of blinding diseases like retinitis pigmentosa and macular degeneration.

Roy's great intellect, careful experimental approach, and keen scientific insights earned him the MERIT Award from the NEI and the Friedenwald Award from the Association for Research in Vision and Ophthalmology. While maintaining an active and vigorous vision research program, Roy also found time to serve as an adviser to the National Institutes of Health and the NEI. He was a member and later Chair of the Visual Disorders Study Section, the forerunner of today's Visual Sciences C. He served as Chair of the Retinal Diseases Panel for the NEI's Vision Research—A National Plan: 1987 Evaluation and Update and as a consultant to the 1978–1982 and the 1994–1998 national plans. He authored the highlights and recommendations from two NEI-sponsored workshops—the first on the Cell Biology of Retinal Detachment in 1986, and the second on Repair and Replacement to Restore Sight in 1991. In 1994, he was appointed to the National Advisory Eye Council, where he served with great distinction until his death.

The NEI and the vision community have lost a dear friend. We are deeply indebted to Roy for his unselfish service and loyalty. The NEI is proud to dedicate *Vision Research—A National Plan: 1999–2003* in his memory.

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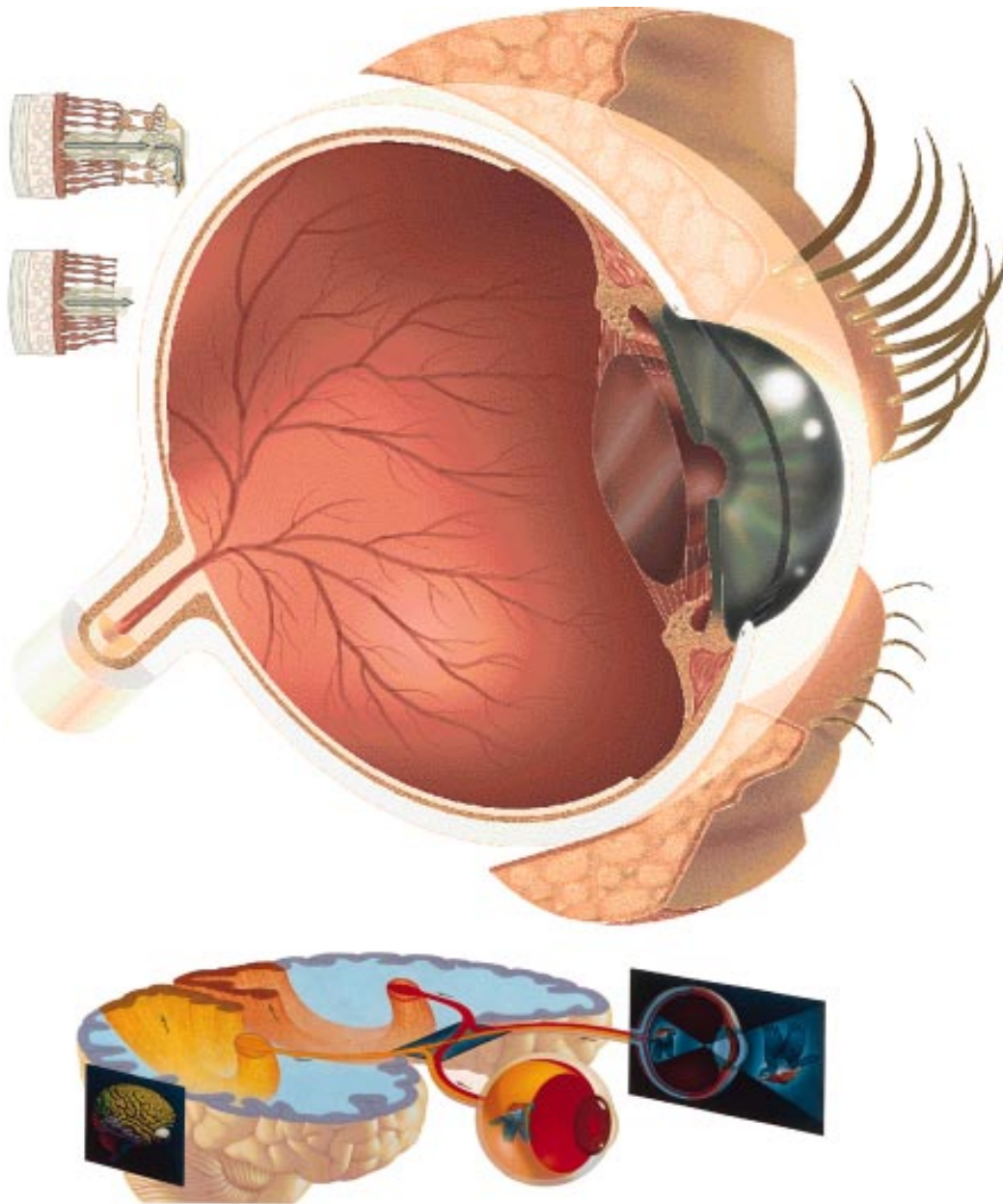


Illustration of the eye: Courtesy of Charles M. Blow/*The New York Times*
Illustration of the brain: Courtesy of *National Geographic*

Over the past few years, there has been increasing interest in priority setting and strategic planning processes throughout the Federal sector. Among the overarching purposes of the Government Performance and Results Act (GPRA), which was passed by Congress and subsequently signed into law in 1993, were provisions to make Federal agencies accountable for achieving program results through the establishment of program goals and objectives against which progress could be measured.

Within the scientific community, concerns have often been voiced that the science cannot be planned, because the course of science is often influenced by unexpected findings. Yet it could be argued that the conduct of science is one of the most carefully planned of all activities funded by the Federal Government. Indeed, the instructions for submitting a research grant application require each applicant to specify: what will be done, why it is important, what has already been done, and how it will be done. These points must be covered in the application's sections on the specific aims, background and significance, preliminary studies and progress report, and research design and methods. Evaluation of the applicant and the proposed research through the peer review process are also key elements of research funding. These components bear great resemblance to the requirements for a strategic plan identified in the GPRA.

While the focus of planning at the individual project level is less global than at the program level, the basic elements are essentially the same—establishment of goals and objectives, assessment of the progress, identification of the needs and/or opportunities, and description of the research approaches to be used. Admittedly, the exact course of scientific research or rate of discovery cannot always be predicted, because both depend greatly on incremental advances in knowledge that often occur over a period of years. Nonetheless, it is incumbent on us to ensure that the investment of public funds is made in areas that are deemed to represent the greatest need and opportunity for progress.

For more than 20 years, the National Eye Institute (NEI) and the National Advisory Eye Council (NAEC), through NAEC's Vision Research Program Planning Subcommittee, have attempted to conscientiously meet their stewardship responsibilities through a comprehensive planning process. During the planning process for their first plan, published in 1975, the NEI and the NAEC stated the need for involving the research community in establishing recommendations for the conduct and evaluation of vision research:

Such recommendations, when formulated with the assistance of respected members of the research community, can be helpful to the investigator in planning the future course of his or her research and to the Federal administrator anxious to assure continuity of high-quality research support in an uncertain period of fluctuating research budgets.

The NEI and the NAEC have long considered the planning and evaluation activities of the program as essential components of the strategic planning process. Panels of experts are assembled to review and make recommendations on NEI research programs. They are also asked to determine where progress was made by identifying the most important research accomplishments that were achieved since publication of the last plan. Not only is this assessment key to evaluating the progress that has been made in achieving the goals and objectives in the previous plan, it is also a vital first step in identifying the future needs and opportunities in each program.

It should be stressed, however, that the NEI and the NAEC have never viewed these plans as blueprints or master plans for research, but rather as vehicles to draw attention to areas of research need and opportunity. Our first priority has been and continues to be funding the highest quality investigator-initiated research applications that will help achieve the goals and objectives outlined in these plans. To that end, the principal factor considered in

determining which applications are funded continues to be the scientific merit of the proposal, as evaluated through the peer review system, combined with the programmatic considerations of the NAEC.

In drafting this sixth formal plan, through the cooperative efforts of members of the vision research community, the NAEC, and the staff of the NEI, special consideration was given to the purpose, intent, and requirements of the GPRA. On behalf of those who

promote, support, and conduct every aspect of science that is related to vision, it is a great privilege to transmit this strategic plan for vision research that conveys the goals and objectives to improve the visual health of our Nation as we move into the 21st century.

Carl Kupfer, M.D.
Director
National Eye Institute

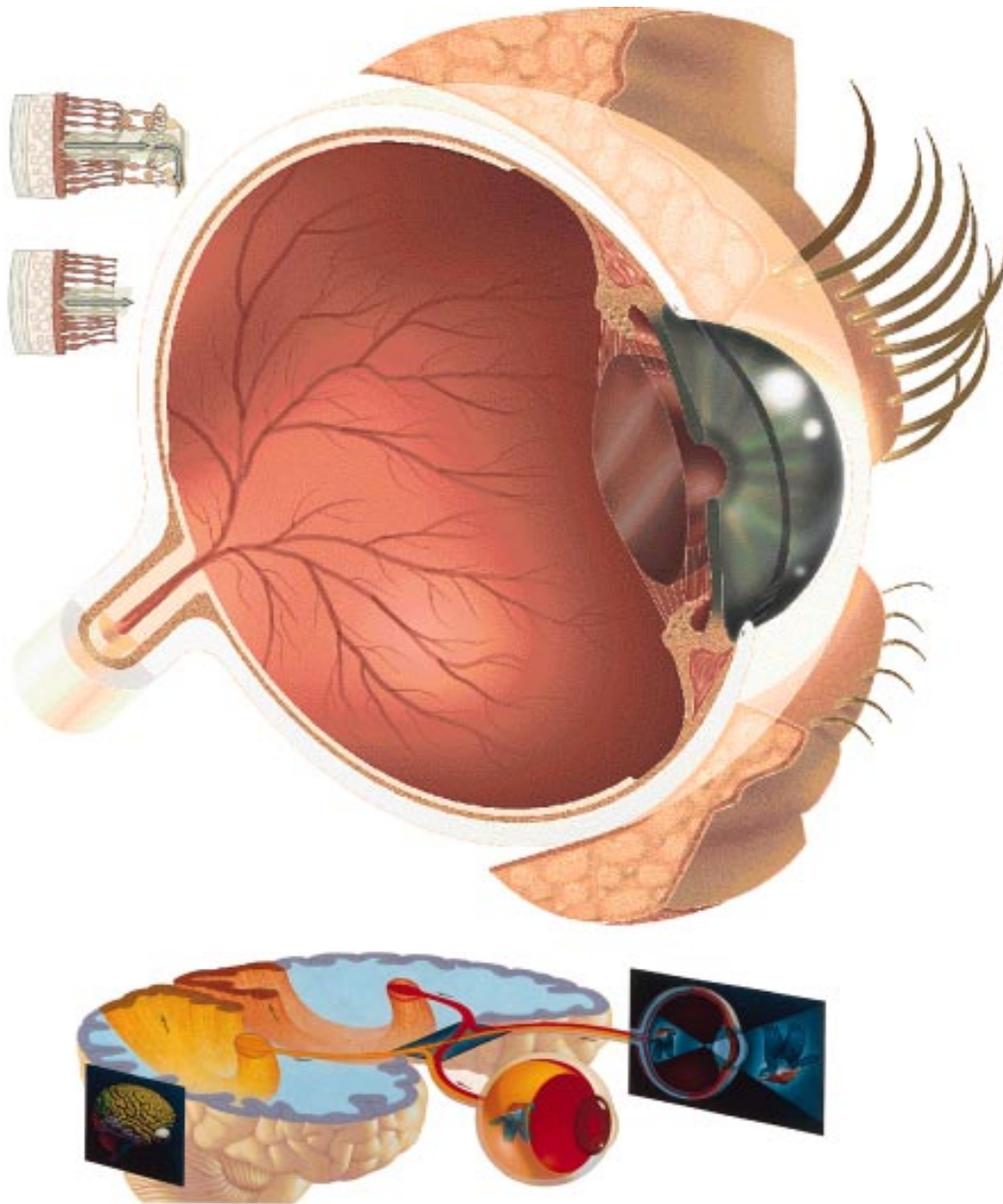


Illustration of the eye: Courtesy of Charles M. Blow/*The New York Times*
Illustration of the brain: Courtesy of *National Geographic*

For more than 20 years, the National Eye Institute (NEI) and the National Advisory Eye Council (NAEC), through its Vision Research Program Planning Subcommittee, have attempted to conscientiously meet their stewardship responsibilities through a comprehensive planning process. This process has resulted in the development and publication of a series of strategic plans that address the most pressing visual health needs of the Nation. These plans have been developed in partnership with the full Council, NEI staff, and numerous members of the vision research community, and with supporters in countless scientific, voluntary, and philanthropic organizations throughout the country. This plan is sixth in the series that dates back to the publication of *Vision Research Program Planning* in 1975.

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 comprise 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 to perform complex tasks for work or pleasure that would otherwise be impossible.

Out of its concern for the eyesight of the American people, 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 own intramural facilities in Bethesda, Maryland.

DEVELOPMENT OF THE 1999–2003 PLAN

In the development of this plan, panels of over 100 experts were assembled to represent each of the NEI’s five formal programs—Retinal Diseases; Corneal Diseases; Lens and Cataract; Glaucoma; and Strabismus, Amblyopia, and Visual Processing—along with specialized groups representing Visual Impairment and Its Rehabilitation and Health Services Research. Information was also solicited for the panels through the NEI homepage (<http://www.nei.nih.gov/>). Visitors to the homepage were provided the opportunity to comment on the most significant accomplishments or advances since the last plan and recommend the most important vision research questions that should be addressed during the next 5 years. This information was then passed along to the panels for consideration in preparing their reports.

Each panel was asked to prepare a report that had the following elements: a program overview and goals; assessment of the progress within the program,

particularly related to the goals and objectives in the last plan; program objectives that are the primary focus for research in the program; the research needs and opportunities that give rise to each objective; and strategic research questions that will lead to achievement of the goals and objectives.

It is important to note, however, that the NEI and the NAEC do not view this plan, nor its predecessors, as blueprints or master plans for research, but rather as vehicles to draw attention to areas of research need and opportunity. Our first priority has been and continues to be funding the highest quality investigator-initiated research applications that will help achieve the goals and objectives outlined in these plans. To that end, the principal factor considered in determining which applications are funded continues to be the scientific merit of the proposal, as evaluated through the peer review system, combined with the programmatic considerations of the NAEC. It is with this in mind that the following summary of the programs, goals, highlights of research progress, and research objectives are presented for Fiscal Years 1999 to 2003.

RETINAL DISEASES PROGRAM

The retina is a complex tissue in the back of the eye that contains specialized photoreceptor cells called rods and cones. They are connected 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 that can lead to visual loss or complete blindness. One such disease, diabetic retinopathy, is 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 two most common forms of cancer that affect the eye are retinoblastoma (RB) and choroidal melanoma. RB is mainly a disease of childhood.

Through the advances achieved over the past few years, RB is now one of the best understood of all solid tumors. It has also opened new opportunities in the etiology of other cancers. Choroidal melanoma primarily affects adults, and its etiology is poorly understood.

The inherited retinal degenerations are typified by retinitis pigmentosa (RP), which results in the destruction of photoreceptor cells, and the RPE. This group of debilitating conditions affects approximately 100,000 people in the United States. The leading cause of visual loss in the elderly is macular degeneration (MD), which has an increasingly important social and economic impact in the United States. As the size of the elderly population increases in this country, age-related macular degeneration (AMD) will become a more prevalent cause of blindness than both diabetic retinopathy 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 MD.

One of the major achievements in all of biology has been in defining cellular events involved in the process of visual transduction—the process that describes the capture of light by the photoreceptor cells and the initiation of 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 of the sensitivity to light). A central unanswered question in neurobiology is how the complex retinal network permits 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 program for the next 5-year period.

- Understand the molecular and biochemical basis for the different forms of MD, improve early diagnosis, characterize environmental effects on the etiology of MD, and develop new treatments.
- Understand the pathogenesis of diabetic retinopathy and other vascular diseases of the retina and develop strategies for primary prevention and improved treatment.
- Identify the genes involved in retinal degenerative diseases, including RP, and determine the pathophysiological mechanisms underlying these mutations.
- Explore new potential therapeutic strategies for inherited retinal diseases, 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, therapy, and prevention.
- Use both molecular and physiological approaches to study light adaptation in photoreceptors, with particular emphasis on the visual cycle.
- Build on knowledge gained from retinal neuroscience to understand how retinal networks process visual images, a central unanswered question of modern neurobiology.

Highlights of Recent Progress

Genes for a number of different forms of heritable macular disease have been mapped to specific chromosomes and, in some cases, the mutated genes have actually been identified. Detection of genes mutated in AMD will permit the development of genetic tests that may identify individuals at risk for the disease.

Aldose reductase, the initial enzyme of the “sorbitol pathway,” may be critical for the development of diabetic retinopathy. A potent new aldose reductase inhibitor has been developed that inhibits the enzyme by approximately 90 percent and prevents vascular endothelial growth factor (VEGF), a factor that has been linked to the abnormal growth of retinal blood vessels or neovascularization, expression in long-term galactosemic rats.

VEGF has become a leading candidate as the agent responsible for neovascularization in retinal and choroidal diseases. This growth factor is present at high concentrations in the vitreous of patients with proliferative diabetic retinopathy and is low to absent in the vitreous of patients with nonvasoproliferative disease.

At least 10 genes causing RP have been identified. At least 24 additional loci causing RP have been placed on the human genome map and are in varying stages of being identified through positional cloning strategies.

Transgenic animals expressing genetic mutations in patients with inherited retinal degenerations have been developed. These animal models are already the subject of intensive study to determine the pathophysiological mechanisms whereby these gene defects lead to photoreceptor degeneration.

Progress has been reported in developing effective strategies for retinal disease, particularly in the area of somatic gene therapy using different delivery systems. Significant slowing of photoreceptor degeneration has been documented in several animal models with the administration of growth factors. Human trials may begin within this year.

A double-masked clinical trial of about 600 patients with RP found that oral vitamin A supplementation slowed the course of retinal degeneration, as measured by the electroretinogram, and that vitamin E hastened it.

Bacterial lipopolysaccharide has recently been exploited as an experimental inducer of uveitis (an intraocular inflammation) in mice and rats, and this newer model has considerably enhanced understanding ocular inflammation due to immuno-pathogenic, rather than autoimmune, processes.

The molecular components of the visual transduction pathway have been described in considerable detail. A significant advance has been the identification and characterization of the guanylate cyclase activating proteins. These proteins regulate the activity of guanylate cyclase and play a role in photorecovery and light adaptation.

The NEI-sponsored clinical trial entitled Studies of the Ocular Complications of AIDS (SOCA) has demonstrated that for AIDS patients with cytomegalovirus (CMV) retinitis a combination therapy with foscarnet and ganciclovir is more effective than either drug alone in controlling it. A recent advance has been the development of a sustained-release ganciclovir device that is surgically implanted into the vitreous cavity and releases drug over several months. There is a significant delay in progression of CMV retinitis for patients receiving the implant.

Progress has been made in signal processing in the retina on two fronts: understanding the codes by which visual information is signaled, and understanding the way the retina transforms incoming information. A new technique for recording signals in the optic nerve has been created that depends on powerful computers. Many optic nerve fibers can now be studied simultaneously, allowing patterns of activity that were once thought insignificant to be analyzed for their information content.

Program Objectives

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

- Explore the pathophysiological heterogeneity of AMD to hasten development of the tools needed for improved diagnosis, prevention, and therapy.
- Investigate the pathogenesis of vascular diseases of the retina and choroid, including diabetic retinopathy, AMD, and retinopathy of prematurity (ROP); develop better methods of prevention and therapy.

- Identify novel causes of inherited retinal degenerations; further examine the cellular and molecular mechanisms whereby identified gene defects cause retinal degenerations.
- Further develop and critically evaluate therapies involving gene delivery, growth factors, and transplantation for the treatment of retinal disease.
- Explore the cellular and molecular basis of the response to retinal injury.
- Identify the factors that dictate the unique properties of intraocular immunity and inflammation and alter systemic immunity to intraocular antigens.
- Develop diagnostic methods and therapeutic approaches that distinguish among infectious, immunopathogenic, and autoimmune posterior segment intraocular inflammation.
- Analyze the mechanisms underlying light adaptation and recovery following photo-transduction.
- Study how visual information is transformed by successive layers of the neural retina and the mechanisms involved.
- Identify and characterize factors important in retinal cell fate determination and differentiation.
- Catalog, map, and functionally characterize genes expressed in the retina and choroid and begin to determine the cellular sites of retinal gene expression in health and disease.
- Probe the control of the retina's micro-environment through studies of Bruch's membrane, the interphotoreceptor matrix, the RPE, glia, choroid, and vitreous.

CORNEAL DISEASES PROGRAM

The cornea is the transparent tissue at the front of the eye that serves two specialized functions: it forms a protective physical barrier that shields the eye from

the external environment, and it serves as the main refractive element of the visual system, directing incoming light onto the lens. Refraction depends on the cornea acquiring transparency during development and maintaining this throughout adult life. In this country, corneal diseases and injuries are the leading cause of visits to eyecare clinicians, and are some of the most painful ocular disorders. In addition, 60 percent of the American population have refractive errors that could be corrected for sharper vision.

Program Goal

After a thorough evaluation of the entire program, the Corneal Diseases Panel recommends the following goal for the program for the next 5-year period.

- Understand the normal function of the cornea and apply this knowledge to the prevention and treatment of traumatic injury and disease.

Highlights of Recent Progress

Recent NEI-funded research has led to great progress in understanding and treating corneal disorders. Much has been learned about new molecular detail of the processes of hydration control that are crucial to maintaining corneal transparency, through the discovery of water-transporting elements called aquaporin proteins. The genes for these transporters have been cloned and sequenced and their functional properties are being determined.

Genetic studies in families afflicted with corneal dystrophies have yielded new insight into the pathogenesis of 13 different corneal dystrophies. Their causative genes have been identified, and the challenge now is to clone the responsible genes to help understand the etiology and pathogenesis of these conditions. This understanding should also lead to improved methods of diagnosis and treatment. The most common corneal dystrophy in the United States is keratoconus, a progressive thinning of the cornea, which causes it to become cone shaped. This disease has become better understood as a result of investigation of its genetic predisposition, detection of early cases through computerized topographic analysis, and initiation of a clinical prospective assessment of the progression of the disease in the Collaborative Longitudinal Evaluation of Keratoconus Study or CLEK.

Using molecular biology techniques, researchers have now determined many of the molecules involved in transparency and how they function. Researchers know the origin of the cells that continuously replace those of the corneal epithelium, and they know some of the factors involved in their regulation. This knowledge was recently applied to restoring the disease-damaged corneal surface of a patient with cells grown from the patient's other, nondiseased eye.

There is mounting evidence that the pathology of many corneal infections is mediated by the immune system. This is particularly clear in the case of infection with herpes simplex virus-1. Infection of T-cell-deficient mouse strains fails to produce corneal inflammation, and mice with corneas purged of antigen-presenting cells develop a milder keratitis than animals with normal corneas. Additionally, individuals infected with the human immunodeficiency virus (HIV) usually do not develop stromal keratitis.

Researchers have improved their understanding of the causes of dry eye in recent years. The nature and regulation of tears is better understood, and much work has been done on the function of mucins (components of tear fluid), hormonal regulation of tear production, and the function of the lipid layer. Changes in lacrimal gland innervation and electrophysiology have been found to precede local autoimmune phenomena in mouse models for Sjögren's Syndrome, an autoimmune disease in which dry eye is a significant symptom. A new autoantigen (cytoskeletal α -fodrin) has been implicated in Sjögren's Syndrome autoimmunity, suggesting improved diagnosis and new therapeutic approaches.

Understanding how the cornea metabolizes lipids (fatty molecules) to form mediators of inflammation and wound healing has advanced in recent years. Recent focus has been on the fatty acid called arachidonic acid. Specific enzymes transform arachidonic acid into prostaglandins, which are substances that can alter blood vessel permeability and platelet aggregation. This transformation is inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs). Several NSAIDs have been introduced into the clinical armamentarium during the past few years. These are beneficial in relieving symptoms of allergic conjunctivitis and in pain and inflammation control following refractive surgery or cataract extraction.

Research on the cornea has generated knowledge that can be applied to problems in other organ systems. For example, studies on the properties of the eye that make the cornea a privileged immune site, i.e., one in which normal immune responses do not occur, raise the possibility that this property can be conferred to other tissues. This may facilitate the transplantation of other organs. Studies on the molecular structure of corneal collagen, a key structural protein, not only provide information on the assembly of this tissue, but also contribute insight into developmental defects of the skeletal system and the skin. Since the cornea is constantly exposed to ultraviolet light and oxidative damage, it has provided information on ways that cells can protect themselves from this damage.

Program Objectives

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

- Explore the molecular basis of corneal transparency.
- Analyze the molecular nature of corneal inflammation and wound healing.
- Delineate the pathogenesis of corneal developmental anomalies and dystrophies.
- Improve the understanding of ocular surface physiology.

LENS AND CATARACT PROGRAM

In contrast to the cellular and molecular complexities present in most other tissues, the lens is a much simpler system, composed of a single layer of epithelial cells that differentiate into fiber cells. The ease of obtaining lens epithelial and fiber cells, plus the relative molecular simplicity of the fully differentiated fiber cells, make the lens one of the best tissues to study events that control aging.

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. Cataract is an immense medical problem, whose eventual cure almost certainly depends on increased understanding of the basic molecular processes occurring in the normal and cataractous lens. By far the most serious problem associated with the lens is its loss of transparency, but most people in midlife face another problem associated with the lens—presbyopia. Presbyopia is the loss of the ability of the lens to focus from distant to near (known as accommodation). By understanding the changes in 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.

The objectives listed in this report have been selected with the assumption that understanding basic lens physiology will provide the framework for learning more about mechanisms involved in presbyopia and cataract and thereby allow researchers to develop more effective treatments.

Program Goals

After a thorough evaluation of the entire program, the Lens and Cataract Panel recommends the following goals for the program for the next 5-year period.

- Understand the physiological basis of lens transparency on the cellular and molecular levels.
- Determine the causes and mechanisms of cataract formation.
- Characterize the controls of lens cell division and differentiation and their roles in the formation of posterior subcapsular and secondary cataracts.
- Understand lens development and the diseases associated with defects in this process.

Highlights of Recent Progress

An important recent discovery has been that α -crystallins, a major structural component of lens cells, prevent damage by denaturation and aggregation of proteins. This novel finding suggested a particularly

significant role for this important class of proteins as a molecular chaperone. Chaperones are proteins that affect protein-protein interactions by stabilizing proteins and preventing other damage when exposed to heat or other environmental stresses.

Progress has also been made in characterizing structural changes that occur to lens proteins during the normal aging process. Advances in technological capabilities have led to the identification of sites where modifications to lens proteins occur. None have yet been specifically associated with age-related cataract, but rather seem to be part of the normal aging process.

Advances in understanding the lens cell cycle have centered around the discovery that the protein made by the RB gene is the central gatekeeper that prevents the lens fiber cells from entering into the cell cycle and, hence, from proliferating. This protein also plays a key role in preventing apoptosis or programmed cell death in the lens and other organs.

Growth factors are involved in all stages of lens development, and their relevance to maintaining a healthy lens has been firmly established. Over the last 5 years, much has been learned about how growth factors signal lens differentiation, regulate the cell cycle, and impact on lens transparency. Experiments indicate that members of the fibroblast growth factor family are prime candidates for the retina-derived inducers of fiber cell differentiation during lens development and the molecules responsible for maintaining the balance between differentiation and division in the mature lens.

The identification of mutations in the Pax-6 gene as being responsible for causing aniridia, a congenital malformation of the eye, was a major breakthrough not only in understanding this disease, but in understanding the developmental processes controlling eye development. This was the first gene to be shown by genetic function to be essential for normal vertebrate eye development.

The identification and characterization of gap junction proteins have also been important in understanding the function of gap junction in the maintenance of lens transparency. Gap junctions contain channels between cells that provide an aqueous pathway between adjacent cells, allowing them to share ions and small molecules. Because

the lens is avascular, it has been hypothesized that gap junctions between lens cells play a crucial role in inter-cellular metabolic support essential for lens survival.

Program Objectives

After carefully considering the research advances that have been made in this program, and based on a careful analysis of the current research needs and opportunities, the Lens and Cataract Panel recommends the following laboratory and clinical research objectives:

- Determine if there are novel markers that differentiate the normal aging process from the diseased (cataractous) state.
- Definitively test hypotheses of cataract.
- Map, identify, and characterize genes which, when mutated, cause congenital or age-related cataract; determine if there are genetic factors that interact with environmental factors to confer susceptibility to age-related cataract.
- Identify genes and pathways that control eye development, especially those critical for lens induction, cell fate determination, and cell differentiation.
- Define the contributions of crystallins to normal lens function.
- Characterize the control of the cell cycle in lens epithelial cells by identifying cell cycle regulators, growth factors, receptors, and signal transduction pathways.
- Characterize, at the molecular level, the ion channels, transporters, and gap junction proteins needed to maintain lens homeostasis; determine what roles perturbations in these systems play in cataract formation.
- Define the mechanisms that regulate the cellular and subcellular architecture of the lens, with special emphasis on the contribution of minor constituents and their progressive modification during aging and opacification.

- Understand the basis of lens accommodation and presbyopia at the molecular and mechanistic levels.

GLAUCOMA PROGRAM

Glaucoma is not a uniform disease but rather a heterogeneous group of disorders that share a distinct type of optic nerve damage that leads to loss of visual function. The disease is manifest as a progressive optic neuropathy that, if left untreated, leads to blindness. It is estimated that as many as 3 million Americans have glaucoma and, of these, as many as 120,000 are blind as a result. Furthermore, it is the number one cause of blindness in African-Americans. Its most prevalent form, primary open-angle glaucoma, can be insidious. This form usually begins in midlife and progresses slowly but relentlessly. If detected early, disease progression can frequently be arrested or slowed with medical and surgical treatment.

The overall emphasis for research in this program is on identifying the biological mechanisms responsible for glaucoma so that improved treatment can be developed. Continued laboratory and clinical research has provided a greater understanding of the normal functions of the ocular tissues involved in this disease. Such studies have led to the introduction of a variety of new drugs to reduce intraocular pressure; the development of new diagnostic tools; better estimates of disease prevalence; and, most importantly, the identification of glaucoma genes.

Program Goals

After a thorough evaluation of the entire program, the Glaucoma Panel recommends the following goals for the program for the next 5-year period.

- Develop improved measures to aid in the clinical diagnosis of glaucoma; monitor progression of disease and treatment effectiveness; and elucidate the pathophysiology and natural history of the disease.
- Understand the molecular and biochemical basis of aqueous humor dynamics, with special emphasis on outflow.

- Identify genetic loci and genes contributing to glaucoma, especially those responsible for the common forms of the disease.
- Determine the mechanisms of optic nerve damage and retinal ganglion cell loss and survival in glaucoma.

Highlights of Recent Progress

The development of new diagnostic and imaging methods provides more reliable and objective methods for early diagnosis of glaucoma and for determining progression of glaucomatous damage. Unlike traditional methods that are based on detection of a small increment of white light on a white background, the new procedures are designed to isolate and measure those visual functions mediated by specific cell populations damaged in glaucoma.

Epidemiological studies conducted in the United States and the West Indies have improved the prevalence and incidence estimates of primary open-angle glaucoma among white and black populations. One strength of these recent studies is the adoption of more inclusive definitions of primary open-angle glaucoma that require the presence of visual field loss or optic disc damage, but do not necessarily require the presence of elevated intraocular pressure.

Over the past 5 years, two new medical therapies for glaucoma have been introduced: latanoprost (Xalatan) and dorzolamide (Trusopt). These are the products of research sponsored by the NEI.

Over the past decade, the use of antifibrotic agents (which inhibit scar tissue formation) to enhance the success of glaucoma filtration surgery in patients has become accepted practice. Filtration surgery is undertaken in the 40 percent to 50 percent of patients whose glaucoma is not amenable to medical therapy. This procedure involves opening a channel through the white of the eye to allow fluid drainage from the eye so that the pressure in the eye does not build up. The surgery frequently failed in the past because an excessive healing response caused scar tissue to be deposited around the site for drainage.

There have been substantial advances in characterizing the pathways that mediate response to drugs in the iris-ciliary body and trabecular

meshwork. Along with the classic neurotransmitters, many neuropeptides have been identified in ocular autonomic and sensory nerves that supply all tissues of the front chamber of the eye.

The genetic linkage mapping of a locus on chromosome 1q to juvenile open-angle glaucoma was a major breakthrough. Since that time, several additional loci have been mapped for glaucomas or ocular diseases associated with secondary glaucomas. This work and mapping of other glaucoma-related loci have substantiated the concept of a genetic component to glaucoma.

In addition to mapping of glaucoma loci by genetic linkage, significant advances in the discovery of glaucoma-causing genes have occurred. A gene for juvenile primary open-angle glaucoma was identified. The gene codes for a protein called trabecular meshwork glucocorticoid response protein was first identified as a protein made by trabecular meshwork cells exposed to glucocorticoid hormones.

Conceptualization that retinal ganglion cell loss in glaucoma is an active cellular process amenable to mechanistic study and to the development of novel therapeutics has been an important step forward in understanding and treating glaucoma. In the last few years, there has been a realization that, in order to understand glaucoma, researchers need to understand how retinal ganglion cells die, irrespective of whether ischemia, mechanical damage, or another mechanism initiates the degeneration. Recent observations have brought new insights into understanding retinal ganglion cell death after axonal damage and have underscored the importance of the need to investigate cellular and molecular mechanisms of neuronal degeneration. Additionally, data have shown that retinal ganglion cells are sensitive to peptides that are known to enhance their survival, thereby suggesting a possible therapeutic opportunity.

Program Objectives

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

- Identify genes and genetic loci contributing to glaucoma, especially those responsible for the common forms of the disease, and characterize the function and interaction of their gene products.
- Define the molecular and biochemical mechanisms that lead to retinal ganglion cell death in human glaucoma and in relevant animal models of related optic nerve injury.
- Enhance understanding of the structure and function of the aqueous humor outflow pathways at the cellular and molecular level.
- Develop a better understanding of anterior segment immunology.
- Improve our understanding of the nature and course of glaucoma, incorporating studies of comorbidity, natural history, and genetics with special emphasis on Hispanic, Native American, and African-American populations.
- Develop improved diagnostic techniques encompassing measures of visual function, optic nerve, and nerve fiber layer structure, *in situ* and for clinical applications of genetics.
- Identify neuroprotective strategies that could prevent retinal ganglion cell death, promote survival, or stimulate regeneration.

STRABISMUS, AMBLYOPIA, AND VISUAL PROCESSING PROGRAM

The Strabismus, Amblyopia, and Visual Processing Program supports both clinical and laboratory research on development, neural processing, eye movement, and associated disorders involving the output of retina and those portions of the brain that serve vision. Studies on normal and impaired vision go hand-in-hand. Detailed knowledge of the normal visual system provides the foundation for understanding the causes of impaired vision and for developing corrective measures.

Over the last three decades visual neuroscience funded by the NEI has exerted a substantial impact on other fields of neuroscience. This is especially true

for developmental and functional studies of the central visual pathways, which have yielded results that have been generalized to the brain as a whole. In developmental neuroscience, the increasing power and sophistication of molecular approaches has led over the past 5 years to an explosion of new information on the basic molecular mechanisms that guide the initial formation and connectivity of the nervous system in general and the visual system in particular. The accessibility of the visual pathways, such as the optic nerve, has enabled the development of powerful models for studying regeneration in the adult central nervous system.

The Strabismus, Amblyopia, and Visual Processing Program has traditionally supported cutting-edge research into the brain systems underlying visual perception and underlying movements of the eyes. The new knowledge resulting from this investment has now brought systems neuroscience to the threshold of a new era in which physiologists can ask incisive questions about how sophisticated visual information, encoded at the highest levels of the cortical visual system, can guide motor planning decisions implemented at the highest levels of the oculomotor system.

Future vision research with emerging technology holds great promise for understanding the development and normal function of the visual and oculomotor systems. Progress in the diagnosis and treatment of clinical disorders that impair vision, such as amblyopia, myopia, nystagmus, and strabismus, depends on laboratory research. Both the future promise and the close link between clinical practice and research are reflected in the overarching program goals of the Strabismus, Amblyopia, and Visual Processing Program.

Program Goals

After a thorough evaluation of the entire program, the Strabismus, Amblyopia, and Visual Processing Panel recommends the following goals for the program for the next 5-year period.

- Determine the etiology of human myopia and identify the risk factors associated with this and other refractive errors so as to prevent their occurrence or progression.

- Understand how the visual system is assembled during development, how its assembly is influenced by endogenous and exogenous factors, and what factors are involved in its regeneration after injury.
- Investigate the development of visual function in children with high risk of amblyopia and strabismus, and develop and disseminate knowledge about effective detection methods and therapeutic interventions to restore 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 and motor mechanisms that control eye movements under natural 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

A key advance in the last 5 years has been the demonstration that the growth of the eye and the development of accurate focus (refractive state) are guided by visual feedback during early life. Myopia, or nearsightedness, is a common condition in which images of distant objects are focused in front of, instead of on, the retina, usually because the eye is too long. Two recent studies have shown that images not focused on the retina guide the developing eye to grow to correct for this lack of focus, and the focusing of images on the retina can cause changes in eye growth directly by a cascade of chemical signals from the retina to the sclera.

Concerted efforts in a number of laboratories over the past two decades have led to the realization that many strabismic and amblyopic states result from abnormal visual experience in early life and

can be prevented or reversed with early detection and intervention.

Molecular, genetic, and neural investigations have been made into disease states affecting the extraocular muscles and the eyelid. Recent evidence suggests that specific genes regulate the development of specific motoneuron pools and that mutations in these genes could be etiologic factors in congenital disorders that affect ocular motility.

Leber's Hereditary Optic Neuropathy (LHON) is a maternally inherited genetic disease that results in substantial loss of central vision in affected patients. The three most common mutations causing LHON have now been identified, providing a useful diagnostic test for LHON as well as new insight into the pathogenesis of the disease.

The Ischemic Optic Neuropathy Decompression Trial was a randomized clinical trial initiated to compare a commonly used surgical procedure against careful observation of patients who had no surgery. This trial has been completed except for long-term followup studies. Results from this study indicate that decompression surgery, a difficult and expensive procedure, is no better than careful followup (in terms of improved vision) and possibly worse. This finding will result in substantial savings in medical costs and will put fewer people at risk to an unnecessary surgical procedure.

Another important advance has been the discovery of molecular and cellular mechanisms that regulate cell growth, survival, and death. In contrast to peripheral nerves, the central nervous system (including the retina and optic nerve) is extremely limited in its capacity for regrowth after injury. Recent experiments in the fruit fly (*Drosophila*), zebrafish, and mouse have identified master control genes for eye formation. In humans, mutations of one of these genes account for a genetic disorder called aniridia, which causes retinal, lens, and iris defects.

Among the most dramatic advances of the last 5 years has been the discovery of specific molecular factors that mediate the formation of topographic order and guide axons to their appropriate targets within the developing visual system. Additional discoveries of fundamental importance in this field are identification of molecules called netrins and

semaphorins, which attract or repel growing axons and form the refined pattern of connections throughout the vertebrate nervous system.

One of the major accomplishments over the past 5 years in the area of functional processing has been the advent of new strategies for minimally invasive optical imaging of the brain. Using what has now become a straightforward technology, it has become possible to visualize the functional organization of exposed visual areas with an unprecedented degree of spatial resolution.

The advent of noninvasive imaging technologies, such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) has, for the first time, allowed researchers to peer inside the living human brain and assess visual function with reasonable spatial and temporal resolution. Several research groups have now identified and topographically mapped visual areas in humans. In addition, several research groups have studied a region called the middle temporal area that may be involved specifically in the analysis of visual motion information.

Central neural mechanisms that govern perceptual sensitivity to visual stimuli continue to be discovered. The past 5 years have yielded a number of behavioral studies that demonstrate that practice on specific perceptual tasks results in increased sensitivity to weak visual signals, as well as increased capacity for discriminating among very similar signals. Furthermore, these capacities can be sharply restricted to the region of space in which the important signal commonly occurs.

Studies have provided novel insights into mechanisms for transforming visual information into signals appropriate for guiding motor behavior. Recent work on perceived self-motion through the environment has led to more insight. Psychophysical and modeling studies have shown that this "optic flow" pattern can be used to compute the observer's future position with respect to obstacles and landmarks. Psychophysical research has shown that humans are exceedingly adept at interpreting these complex flow patterns, and that this capability requires information about the motor signals sent to the eyes and head in addition to the visual flow signals falling on the retina. Physiological studies have identified neural circuits

in a cortical area called MST that receives a combination of visual flow, eye movement, and head position signals appropriate for solving the self-motion problem.

Program Objectives

After carefully considering the research advances that have been made in this program, and based on a careful analysis of the current research needs and opportunities, the Strabismus, Amblyopia, and Visual Processing Panel recommends the following laboratory and clinical research objectives:

- Identify the visual error signals that govern eye growth during correction for refractive error; identify human risk factors for myopia and abnormal eye growth and evaluate promising treatments for preventing the onset of or slowing the progression of myopia, such as special spectacles or contact lenses or pharmacological treatments.
- Investigate the effectiveness of immunomodulating therapies in halting disease progression in optic neuritis; identify the unique characteristics of ocular muscles that render them vulnerable to Graves' ophthalmopathy, myasthenia gravis, orbital myositis, and chronic progressive external ophthalmoplegia.
- Discover how topographic gradients are generated and read out to form retinotopically ordered structures, and identify the sites and mechanisms of action of axon guidance molecules.
- Determine the role of peptide growth factors, such as neurotrophins, in the development, plasticity, and regeneration of the visual pathways; determine how critical periods are regulated; manipulate the molecular signals underlying this regulation to enhance the adaptive and regenerative properties of the adult brain.
- Elucidate the mechanisms by which spontaneous patterns of electrical activity, present before the onset of visual experience, guide the formation of visual structures prior to visual experience.
- Characterize the clinical problems of amblyopia and impaired stereoscopic vision more precisely, and clarify their relationship to strabismus, anisometropia, and other related conditions.
- Study the development and plasticity of neural mechanisms affected in strabismus and amblyopia, including studies in animal models and normal and abnormal human populations.
- Develop innovations in the detection and treatment of strabismus and amblyopia.
- Develop fMRI and related technologies as useful, quantitative tools for exploring the neural basis of human visual processing.
- Understand how neural computations are accomplished and stored within the central visual system.
- Understand plastic mechanisms in the oculomotor system that ensure accurate gaze shifts, precise alignment of the two eyes, steady fixation that can be affected by nystagmus, and a stable visual world during self-movement.
- Extend studies of eye alignment to include vertical and torsional eye movement control; gain insight into the pathogenesis of cyclovertical strabismus.
- Discover how visual information contributes to perceptual decisions, object recognition, internal representations of external space, transformations between different spatial frames of reference, and the formation of neural signals appropriate for guiding behavior.
- Understand the cellular mechanisms that give rise to changes in visual sensitivity associated with attention and perceptual learning.

VISUAL IMPAIRMENT AND ITS REHABILITATION

Vision impairment can be defined as any chronic visual deficit that impairs everyday function and is not correctable by ordinary eyeglasses or contact lenses. Although there have been important strides in the treatment and prevention of eye disease over the past few decades, there still are many causes of vision loss for which there is no cure, and even with the best medical treatment many Americans must live with impaired vision. In the United States, visual impairment is typically 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.

Current estimates indicate that there are more than 3 million Americans with low vision, almost 1 million who are “legally blind,” and roughly 200,000 who are totally blind. Because of their reliance on narrow definitions of vision impairment, these figures underestimate the prevalence of vision impairment. 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 vast majority of the visually impaired population. Vision impairment is included in the 10 most prevalent causes of disability in America.

The leading causes of vision impairment are diseases that are common in the elderly, including AMD, cataract, glaucoma, diabetic retinopathy, and optic nerve atrophy. Over two-thirds of those with vision impairment are over age 65. It is estimated that there were almost 34 million Americans over the age of 65 in 1995, and by the year 2030 this number will more than double. The leading causes of vision impairment among infants and children are retinopathy of prematurity, cortical visual impairment, and structural ocular abnormalities, such as cataract and retinal abnormalities. These conditions occur during infancy and early childhood, when it is difficult to assess their effects on vision and quality of life. In addition, many of these conditions occur with increased prevalence in children with neurodevelopmental delay, further complicating the assessment of level of vision and the evaluation of quality of life.

The next 5 years of research on vision impairment and blindness can lead to great strides in improving the quality of life for the visually disabled population in society. These accomplishments can be realized if the existing research infrastructure is enhanced, and if there is a broad-based program to educate researchers, clinicians, and engineers from a variety of backgrounds about the availability of these resources.

Program Goals

After a thorough evaluation of the entire program, the Visual Impairment and Its Rehabilitation Panel recommends the following goals for the program for the next 5-year period.

- Improve our understanding of structure/function in the visual central nervous system, neural plasticity, and the performance of everyday tasks, so that the visual processing capabilities of the visually impaired 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 among visually impaired persons.
- Determine which interventions are most effective and develop research tools so that these interventions can be scientifically evaluated, ultimately improving the clinical care of the visually impaired population.
- Establish the scope of impaired vision and blindness in our society and its ramifications for everyday life, identifying the prevalence of visual impairment and functional limitation and risk factors for visual disability, so that interventions can be targeted to high-risk subpopulations.

Highlights of Recent Progress

Modern quantitative methods, including anatomical, electrophysiological, and brain imaging approaches (particularly fMRI) are telling researchers a great deal about the visual architecture of the normal brain and the brains of persons with neurological deficits. In

addition, there is an increased understanding of the extent of plastic changes in the adult nervous system, which has implications for rehabilitative training and device development.

Researchers have used the scanning laser ophthalmoscope to assess visual function in patients with central visual impairment. Studies have demonstrated that patients with AMD tend to adopt fixation patterns that avoid placing scotomas (blind spots in the visual field) below or to the left of fixation. This is interesting since placement of scotomas to the right of fixation slows reading more so than any other position.

Research in the past 5 years has clearly indicated that understanding the effects of visual impairment on everyday task performance must include a consideration of cognitive, motor, and other sensory influences. Clinical measures of acuity and contrast sensitivity are not by themselves good predictors of driver safety and performance, which also rely on visual attentional skills, a rapid speed of visual processing, and cognitive skills.

Research is beginning to clarify how visual impairment impacts mobility. Visual impairment can lead to an increased risk of falling and fear of falling, an elevation in crash risk when driving, and reduced mobility and loss of independence in general. Some of these effects appear to be exacerbated under conditions of poor illumination or low contrast.

There has been recent progress in the development and evaluation of rehabilitation programs for the visually impaired. A recent study found that visually impaired veterans report that they benefited from assistive devices that they were trained to use.

A number of new low-vision telescopes have been developed, with most emphasizing more acceptable appearance. Some offer new flexibilities for in-office fitting and demonstration of the device and autofocus capabilities.

Research has explored the efficacy of several methods of presenting magnified text on computer screens, and these approaches have been incorporated into commercially available computer-based reading devices for low vision. In addition, there have been a number of optical and electronic devices employing

new techniques and approaches. Over the past 5 years several new head-mounted electronic low-vision devices have been developed. Research on the utility of these devices is in the preliminary stages.

A key advance, identified as an important priority in the NEI's 1994–1998 national plan, is the development of promising new technology to improve wayfinding in visually impaired persons. Remote signage systems have been developed and commercialized in which installed transmitters serve as signs that can be read and conveyed via electronic voice to users equipped with appropriate handheld receivers. Other developments include a talking map system for route planning that gives voice feedback in response to touch on a touch-sensitive screen and a route planning database system that allows visually impaired travelers to plan travel routes from street maps stored on computer. Personal guidance systems have been developed that utilize computer-based maps and landmark information, in combination with satellite-based global positioning systems, for registering a traveler's present position.

There has been recent progress in the ability of researchers to assess infants as young as 4 months of age and young children who have or are at risk for low vision. The Teller Acuity Card procedure measures the finest grating that a child can resolve by observing the child's eye and head movement responses to black-and-white gratings (stripes) on a gray background. It has successfully been used to measure visual acuity annually in more than 1,000 infants in the NEI's multicenter Cryotherapy for Retinopathy of Prematurity Study.

Epidemiological and survey research on visual impairment is beginning to indicate that the scope of functional impairment and disability from eye conditions is much more prevalent than previously thought. This research, although in its infancy, serves as important groundwork for targeted investigations in this area, and has direct implications for healthcare planning and public health projections.

Program Objectives

After carefully considering the research advances that have been made in this program, and based on a careful analysis of the current research needs and

opportunities, the Visual Impairment and Its Rehabilitation Panel recommends the following laboratory and clinical research objectives:

- Develop a theoretical understanding of normal visual functioning that can be extended to understanding and treating the disabilities experienced by people with low vision.
- Understand the visual requirements of everyday tasks.
- Develop effective assistive devices and techniques to maximize residual vision and/or substitute for visual information.
- Develop environmental designs and modifications that enhance independence among the visually impaired.
- Evaluate the effectiveness of rehabilitation in the visually impaired.
- Ascertain the prevalence and incidence of visual impairment and visual disability in the United States and identify subpopulations at heightened risk for visual impairment and disability.
- Create an effective infrastructure for research on visual impairment and rehabilitation.

HEALTH SERVICES RESEARCH

The provision of health care is a topic of importance to all Americans, as patients and as taxpayers. In this era of changing organization and financing of health care in the United States, additional constraints are being placed on available healthcare resources. It is critical to understand the delivery and use of vision services to best prevent, diagnose, and treat eye conditions and reduce the risk of visual impairment. In order to meet this challenge, the NEI and the NAEC have decided to highlight health services research as a scientific area of interest in vision research for the next 5 years.

The field of health services research is defined broadly by the NEI to include such diverse topics as

increasing patient access to and utilization of visioncare services, improving the delivery of vision services by eyecare professionals, and measuring the visual health of patients receiving eyecare services. Information on the number and characteristics of people with various eye conditions, together with estimates of the economic burden of these conditions, will be needed to understand the full impact of eye disease and visual impairment on the Nation's health. Given the breadth of diseases affecting vision and the differences in age of those afflicted, multiple strategies may be warranted to determine the most appropriate use of diagnostic methods and treatments scientifically demonstrated to improve vision and preserve sight. Increased public awareness of the personal and societal costs of visual impairment will be useful to ensure the allocation of adequate health resources to Americans most in need of visioncare services.

Program Goals

After a thorough evaluation of the entire program, the Health Services Research Working Group recommends the following broad goals for NEI-supported health services research for the next 5-year period.

- Assess the impact of eye disease and visual impairment on the Nation's health.
- Determine the most appropriate use of diagnostic strategies and treatments scientifically demonstrated to improve vision and preserve sight.

Highlights of Recent Progress

A number of important health services research advances have been made in the area of vision research over the past 5 years.

Quality-of-life assessments have been incorporated into the design of several NEI-funded epidemiologic studies and clinical trials, therein recognizing that a patient's quality of life is an important facet to consider in assessing visual health.

In response to the need to more completely understand the impact of clinical interventions specifically on vision-related quality of life from a

patient perspective, the NEI fostered the development and testing of a questionnaire, the NEI-Visual Functioning Questionnaire (NEI-VFQ), to collect this important information.

Findings from recent studies have shown that the majority of people having cataract extraction surgery subsequently report substantial improvement in their ability to see and to perform common, necessary, daily activities.

Numerous studies have reported that a large number of people who have diabetes do not obtain an annual dilated eye examination. Currently funded projects are attempting to identify specific reasons why the medical system is failing to reach this population at increased risk of visual impairment. Other studies are testing specific interventions geared toward the patient or the eyecare provider to increase the rates of ophthalmic screening among people with diabetes.

Program Objectives

After carefully considering the research advances that have been made in this program, and based on a careful analysis of the current research needs and opportunities, the Health Services Research Working Group recommends the following research objectives:

- Determine the number of Americans with eye disease and visual impairment and measure the impact on medical costs and costs to society associated with these conditions.
- Develop effective strategies for screening for eye disease and visual impairment in children and adults.
- Educate eyecare providers and the general public on scientific advances in detecting, preventing, and treating eye diseases and in translating these advances into nationwide clinical practice.
- Identify the factors associated with the most effective delivery and use of visioncare services.

CROSS-CUTTING AND POLICY ISSUES

In addition to establishing goals and objectives for each of the NEI's programmatic and special interest areas, it is important to identify the scientific issues that cut across program lines and the policy issues that are related to operational processes, external factors, and resources, which allow the overall accomplishment of the goals and objectives in this report. They are highlighted here as endorsement by the NAEC of their importance to the programs of the NEI and the vision research community and as an indication of future need.

Cross-Cutting Issues

- Aging Research
- Genetic Research
- Developmental Biology and Regeneration Research
- Drug Delivery
- Trauma
- Systemic Diseases (Immune Disorders and Diabetes)

Policy Issues

- Funding Policies and Priorities
- Laboratory Research
 - Mechanisms of Support
 - Length of Award
 - Downward Negotiations
 - Multiple Grants
 - Interactive Research Project Grants
- Clinical Research
 - Mechanisms of Support
 - Cooperative Agreements
 - Clinical Study Planning Grant
 - Small Research Grants for Data Analysis
 - Clinical Vision Research Development Award
 - Mentored Clinical Scientist Development Award
- Core Grants for Vision Research
- Research Training
 - Summary of Previous Recommendations
 - Recommendations for 1999–2003
- Use of Animals in Vision Research
- Clinical Trials Database
- Resource Requirements

Complete details on all of these cross-cutting and policy issues are found within the pages of this strategic plan.

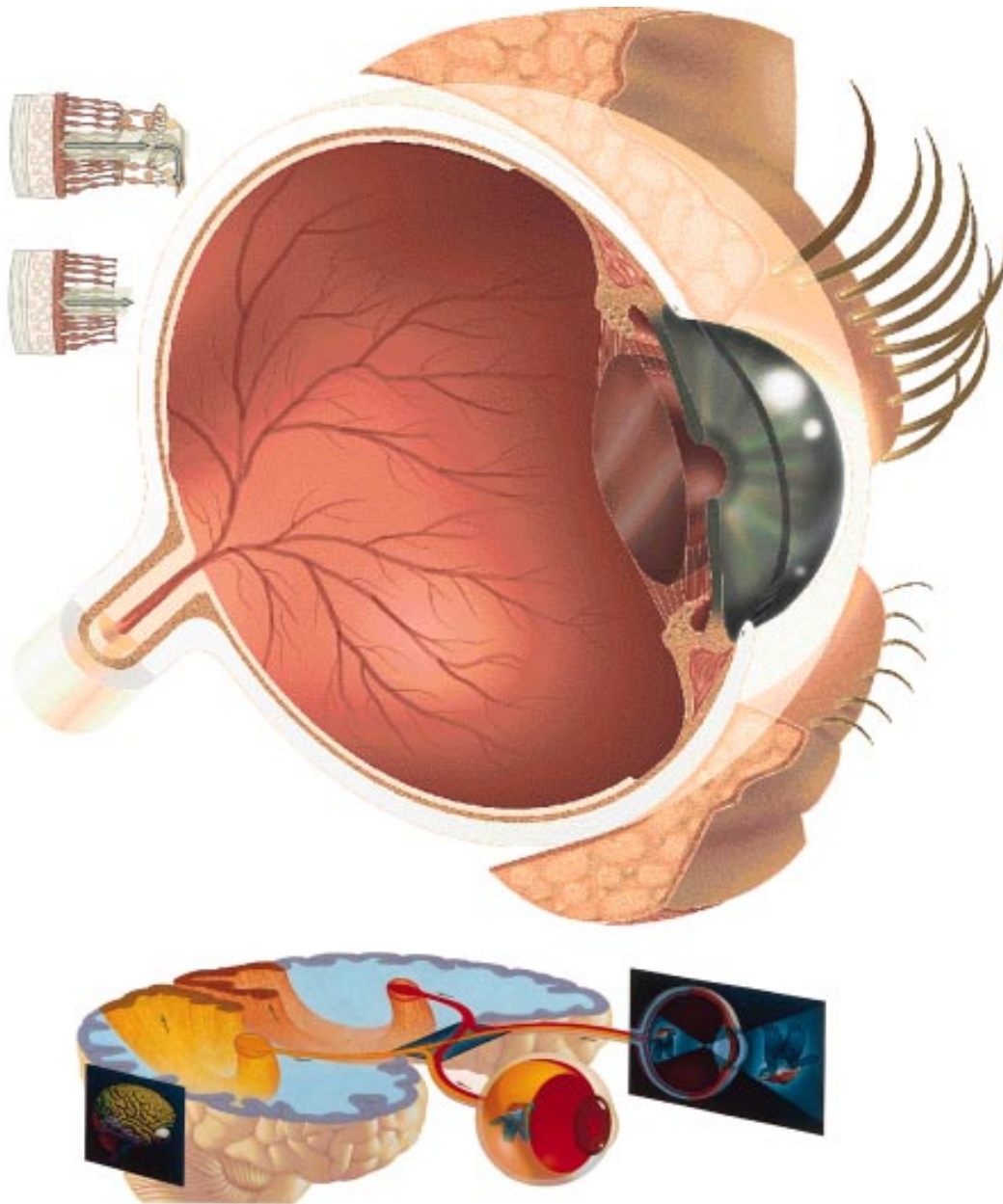


Illustration of the eye: Courtesy of Charles M. Blow/*The New York Times*
Illustration of the brain: Courtesy of *National Geographic*

For nearly 25 years, the National Eye Institute (NEI) and the National Advisory Eye Council (NAEC) have maintained a unique partnership in addressing the most pressing visual health needs through the development and publication of a series of strategic plans at roughly 3- to 5-year intervals. While the NAEC's Vision Research Program Planning Subcommittee (VRPPS) has been charged with the overall responsibility for its development on behalf of the NAEC, this partnership presumes the full participation of other NAEC members, NEI staff, and members of the vision research community and its supporters in numerous scientific, voluntary, and philanthropic organizations throughout the country. Without their cooperation, hard work, and foresight, neither this publication nor its predecessors would have been possible.

Both the NEI and the NAEC took seriously the requirement in the NEI's establishing legislation—to plan for the training of research scientists and the research of disabling eye diseases, with emphasis on the causes of blindness and the loss of visual function. They established a formal planning process that resulted in the publication of the first plan, *Vision Research Program Planning*, in 1975. That first plan set the stage for the process that would guide the development of subsequent plans for more than 20 years by recommending that the planning process be governed by four guiding principles:

1. Research planning procedures must not disrupt extremely successful ongoing programs.
2. Planning procedures must sustain reliance on the investigator-initiated research grant as the primary mechanism for supporting research in the basic biological sciences and ensure that the highest priority is given to the highest quality research.

3. Planning procedures must rely on peer review for assessment of scientific quality and the programmatic considerations of the NAEC.
4. Research program planning must be a prospective, continuing process.

In addition, the need for involving the research community in the development of the recommendations during the planning process was stressed.

The vision research plans have always resulted from a dynamic process. Changes in approach, structure, and format have been made with each plan in an attempt to improve the process and be responsive to the changing needs of the field and existing public health challenges. Although no specific government-wide format has been specified for strategic plans, several common elements have been identified: a comprehensive mission statement covering the organization's major functions and operations; general goals and objectives of the organization (including outcome-related goals and objectives to allow the assessment of success in achieving those goals and objectives); a description of how the goals and objectives are to be achieved, including the operational processes, skills, technology, and resources required; identification of any external factors that could significantly affect the achievement of the goals and objectives; and a description of program evaluations used to establish or revise the goals and objectives.

In this current effort, panels of experts were assembled to represent each of the five formal program areas—Retinal Diseases; Corneal Diseases; Lens and Cataract; Glaucoma; and Strabismus, Amblyopia, and Visual Processing—along with specialized groups representing Visual Impairment and Its Rehabilitation and Health Services Research. Each panel was asked to assess the progress that has been

made in vision research during the preceding 5 years; set realistic goals and objectives; determine research needs and opportunities; and, finally, to develop research strategies for achieving those goals and objectives.

To provide input to the panels, and to solicit views of those who will be affected by or are interested in the plan, two questions were posted on the NEI homepage on the World Wide Web (<http://www.nei.nih.gov/>): *1. Looking back at the past 5 years, what have been the most significant accomplishments or advances that have moved the field of vision research forward? 2. Looking ahead to the next 5 years, what are the most important vision research questions that should be addressed?* The availability of this request for information was announced via letter to grantees and organizations conducting and supporting vision research. Additionally, a request for input was made at a major annual meeting of vision researchers sponsored by the Association for Research in Vision and Ophthalmology in May 1997.

Pertinent information submitted through this solicitation was provided to each of the panels for their consideration. The panels were then asked to prepare a report that had the following elements:

Program Overview and Goals—a brief general overview or description of the research supported within the program, followed by overarching long-range goals.

Assessment of Progress—the most important scientific advances that have taken place within the program, particularly as they relate to the previous plan's goals and objectives, so that scientific progress could be evaluated.

Program Objectives—shorter range and less general than goals, these constitute the areas of primary research focus and are based on the most pressing needs and opportunities in the program for the period covered by the plan.

Research needs and opportunities—identification of the specific needs within the areas of research covered by the each objective and/or the specific opportunities that exist for making significant progress.

Strategic research questions—the strategies or research approaches to be used in addressing the needs and opportunities, stated as the research questions to be asked, with some elaboration on their significance.

Previous plans were much more exhaustive in the detail provided, often at the individual project level. For this round of planning, the VRPPS felt it was necessary to prepare a shorter, more focused document that addressed the plan's most important objectives to be achieved during the period covered by the plan, rather than concentrating on individual projects that should be undertaken to achieve the objective. It should also be emphasized that a great deal of valuable research occurs within each program that may not be covered by a specific objective. This research is the foundation upon which future progress and accomplishment will be built. The objectives in this plan represent those areas in which there is compelling need or unique scientific opportunity to make significant progress over the next 5 years.

It is also important to consider external factors that could significantly affect the achievement of the goals and objectives. In past plans and in this current plan this area has been identified as the Cross-Cutting and Policy Issues. Those areas of research activity that cut across program lines are reiterated in this section, as well as policy issues of importance to the support and conduct of research activities. These include the external influences, such as funding policies, and operational processes, skills (including training), technology, and resources required to achieve the goals and objectives specified in the plan.

The draft panel reports were reviewed by the NAEC at a special subcommittee meeting following the September NAEC meeting. The drafts that contained the comments and suggestions of NAEC members were then returned to the panels for their consideration. Final drafts were then sent to organizations that conduct and support vision research, as well as to the full Council, to solicit their views on the plan's final recommendations. Reviewers were asked specifically to consider whether any important areas of research or specific issues of importance to vision research had been overlooked.

The result of this process is this strategic plan for vision research for Fiscal Years 1999 to 2003. To be sure, it is not a perfect process, for the planning of scientific research is a daunting undertaking. It presumes a vision of where the field should move, based on the needs and opportunities, a knowledge of what has been accomplished, and insight on what might be accomplished in the near future. But it is a sincere effort, undertaken by members of the vision research community on behalf of the entire vision research community and the Nation, to convey the most pressing needs and opportunities in this field and to determine the goals and objectives for the next 5 years.

It has been our pleasure to be associated with and oversee this effort on behalf of the VRPPS of the NAEC. Although our gratitude to those who have so freely given of themselves, their intellect, and their time is scarcely sufficient, it is most humbly offered. We hope the result of this effort will be the improvement in the visual health of our fellow citizens in the years to come.

Eve Higginbotham, M.D.
David Beebe, Ph.D.
Cochairs, Vision Research Program
Planning Subcommittee
National Advisory Eye Council

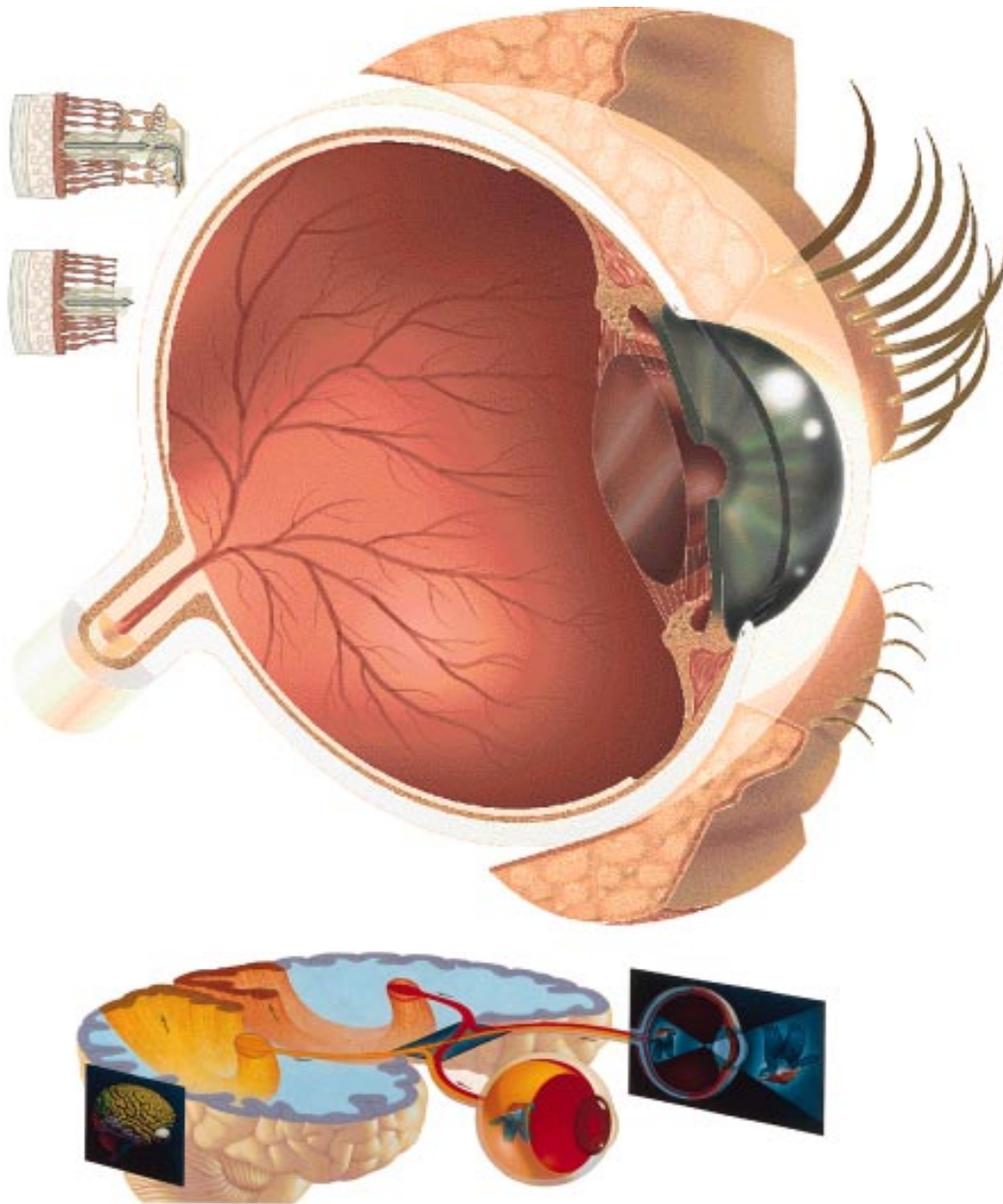


Illustration of the eye: Courtesy of Charles M. Blow/*The New York Times*
Illustration of the brain: Courtesy of *National Geographic*

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.

The eyes and the parts of the central nervous system devoted to visual processing comprise a truly 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 it lets us perform complex tasks for work or pleasure that would otherwise be impossible. It is the sense that provides additional meaning to the input of the other senses and binds them together in a profound way. From a technical point of view, sight is a biological representation of the physical world around us that results from the input of millions of neural signals. For these reasons, there is little wonder that Gallup polls in the last three decades indicate that outside of mental incapacity, the disability Americans fear most is blindness.

In recognizing of the importance of sight to the American people, in 1968 Congress passed a law to create the National Eye Institute (NEI). Since its inception, the NEI has conducted an active program of laboratory and clinical research into the major causes of blindness and visual disability. Research has also focused on the normal development of the eye and visual system and the normal processes that result in

vision. For it is only in understanding the elements of normal vision that researchers can interpret and interrupt or intervene in the abnormal events that cause visual loss.

Significant progress has been made in the last 30 years in elucidating the visual process, in understanding and treating many of the diseases of the eye and visual system, and ultimately in preserving eyesight. As we move into the next century, powerful new tools have increased this understanding of the nature of the disease process at the genetic and molecular level. To be sure, even newer and more powerful tools will be developed that will allow us to gain the knowledge that still eludes us.

A great deal remains to be done. As scientists and as those who support the conduct of science, we understand that progress does not always occur as quickly as we would like. But we put ahead of us this vision for the new century. With the continued support of the American people (as provided by Congress) and the research priorities outlined in this strategic plan, we will endeavor to protect this most precious sense of sight for all Americans and all of humanity.

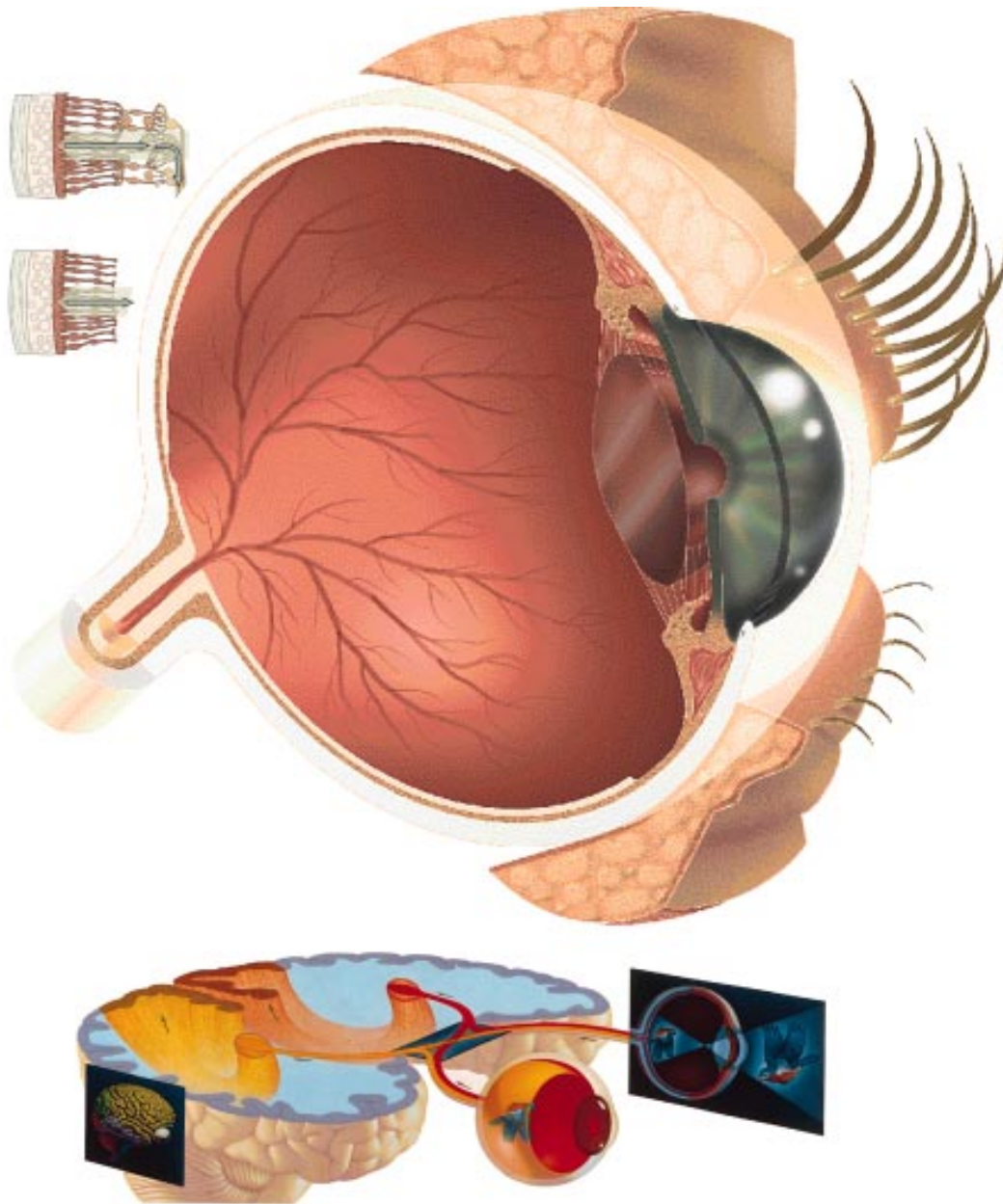


Illustration of the eye: Courtesy of Charles M. Blow/*The New York Times*
Illustration of the brain: Courtesy of *National Geographic*

MISSION

To demonstrate its commitment to the support of research related to blinding eye diseases and visual disorders, Congress established the National Eye Institute (NEI) in 1968 by passing Public Law 90-489. This law amended the Public Health Service Act, stating that the purpose or mission of the newly created Institute was 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 the NEI's 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 own intramural facilities in Bethesda, Maryland.

Health information dissemination activities were added to the mission of the NEI in 1985, and funding for the National Eye Health Education Program (NEHEP) was included in the appropriations bill in Fiscal Year 1988. This allowed the NEI to expand its activities related to the prevention of blindness through public and professional education programs and through the encouragement of regular eye examinations. The NEHEP has already provided valuable information to patients and health professionals alike on diabetic eye disease and glaucoma, two significant causes of adult blindness in this country.

CHALLENGES FOR VISION RESEARCH

In the United States, an estimated 80 million Americans have potentially blinding eye diseases, and 1.1 million people are legally blind. Approximately 12 million people have some degree of visual impairment that cannot be corrected by glasses, and more than 100 million people need corrective lenses to see properly. In 1981, the economic impact of visual disorders and disabilities was approximately \$14.1 billion per year. By 1995, this figure was estimated to have risen to more than \$38.4 billion—\$22.3 billion in direct costs and another \$16.1 billion in indirect costs each year.

While progress in understanding and treating many diseases of the eye and disorders of vision has been enormous over the last two decades, the means to prevent or successfully treat some of the most devastating eye diseases still eludes researchers. Yet, powerful new technological tools afford unique opportunities to discover the causes of these diseases and prevent the development of disease or its sight-threatening consequences. These are not only our greatest opportunities, but also our greatest challenges.

Within this report, the most pressing challenges—posed as research needs and opportunities—are specified within the context of the NEI's programmatic structure and special interest areas. Objectives are set out that summarize these challenges, and research strategies are defined for accomplishing these objectives. The following sections are not all-inclusive summaries of the research conducted within each of these programs and interest areas. They simply highlight a few of the ongoing research activities designed to meet current needs and opportunities.

Retinal Diseases. The retina is the thin, transparent, light-sensitive neural tissue that lines the inside of the back of the eye. The retina originates from central nervous system tissue during embryonic development. This tissue contains photoreceptor cells (both rods and cones) and neurons that convert the light images entering the eye into electrical signals that are transmitted to the brain. The choroid is the underlying layer of blood vessels that nourishes the retina. Diseases and disorders of the retina and the choroid account for most of the blindness and visual disability in the United States; the most important include age-related macular degeneration (AMD), diabetic retinopathy, retinitis pigmentosa (RP), retinal detachment, uveitis, and retinal tumors (choroidal melanoma and retinoblastoma).

To meet the challenges of prevention and treatment posed by these blinding diseases and disorders, the NEI supports studies on the development, molecular and cell biology, molecular genetics, and metabolism of the photoreceptor cells and their dependence on the underlying retinal pigment epithelium; the mechanism of the retina's response to light and the initial processing of information that is transmitted to the visual centers of the brain; the pathogenesis of diabetic retinopathy; the fundamental causes of and etiologic factors responsible for uveitis; the molecular genetic mechanisms responsible for producing retinoblastoma and ocular melanoma; the identification of the genes and pathogenic mechanisms causing RP, AMD, and related disorders; and the cellular and molecular events that accompany retinal detachment.

Corneal Diseases. The cornea is the transparent tissue at the front of the eye that plays an important role in refracting or bending light to focus visual images sharply on the retina. The normal cornea has no blood vessels and is nourished by the fluids that bathe it. Because the cornea is the most exposed surface of the eye, it is especially vulnerable to damage from injury or infection. The leading causes of corneal blindness are herpes and other infections, corneal opacification, and inherited and degenerative diseases.

The NEI supports laboratory, preventative, and therapeutic studies to meet the challenges posed by corneal diseases on a wide range of research topics, including: the regulation of genes that express proteins unique to corneal tissue; the details of the

macromolecular and supramolecular assembly of extracellular corneal matrices; the characterization of cytokines and cell surface receptors that interact with corneal cells, pathogens, and blood-borne cells; the mechanisms that maintain corneal hydration and transparency; the physiologic basis for immune privilege in the cornea; corneal wound healing; the biomechanics of the cornea; the cellular and molecular mechanisms by which corneal transplants are rejected; and the role of specific viral genes in the establishment, maintenance, and reactivation of corneal herpetic infections.

Lens and Cataract. A cataract is an opacity of the eye's normally clear lens that interferes with vision. Cataract may develop at any time during life, although it is most often associated with advancing age. In addition to aging, cataract may be a consequence of diabetes and other metabolic disorders, trauma, exposure to ionizing radiation, or it may be inherited or congenital in nature. Worldwide, 50 percent of all blindness is due to cataract. Cataract treatment in this country is one of the most successful of all surgical procedures. Each year an estimated \$3.4 billion is spent on this procedure through the Medicare program alone. At this time, surgery to remove the opaque lens is the only effective way of treating cataract, and an estimated 1.4 million procedures are performed each year.

The NEI supports research that will ultimately lead to improved treatment or the means to prevent cataract. These include studies of the development and aging of the normal lens of the eye; the identification, at the cellular and molecular level, of those components that maintain the transparency and proper shape of the lens; the control of lens cell division and differentiation; the delineation of the structural and regulatory sequences of crystallin and noncrystallin lens genes; and the impact of continual oxidative insult on the lens.

Glaucoma. Glaucoma is a group of disorders that share a distinct type of optic nerve damage that can lead to blindness. This damage causes death of the retinal ganglion cells that comprise the optic nerve. Glaucoma is often associated with increased pressure within the eye caused by a buildup of aqueous humor, the fluid produced by the ciliary body that nourishes the cornea and lens. Although researchers once thought that glaucoma resulted solely from increased

pressure, they now know that the elevation in the pressure within the eye is only one of the risk factors for the disease. Although glaucoma is primarily a disease of the aging, it may occur at any age or at birth. It can occur as a primary disorder or it can be secondary to other ocular or systemic conditions. Glaucoma is a major health problem and the number one cause of blindness in African-Americans. Approximately 3 million Americans have glaucoma; at least half of all those who have glaucoma are unaware of their condition; and as many as 120,000 are now blind from the disease. Blindness from glaucoma is estimated to impose significant costs on the U.S. Government in Social Security benefits, lost tax revenues, and healthcare expenditures.

To meet the challenges in improving treatment for or preventing visual loss from glaucoma, the NEI supports clinical trials that assess the role of medical and surgical therapy in the treatment of the disease. The NEI also supports studies on the gene expression and regulation of the extracellular matrix proteins of the trabecular meshwork; identification and characterization of genes that are involved in the development of glaucoma; the basic mechanisms that control aqueous humor dynamics; the design of better pharmacologic agents to modulate aqueous humor secretion and outflow; and the pathological processes that lead to glaucomatous neuropathy.

Strabismus, Amblyopia, and Visual Processing.

Research in this program encompasses a broad range of clinical and laboratory studies concerned with the structure and function of the neural pathways from the retina to the brain, the central processing of visual information, visual perception, the control of ocular muscles, and refraction. A large number of congenital, developmental, and degenerative abnormalities affect the visual sensorimotor system, but three disorders are of primary concern: (1) strabismus or the misalignment of the eyes; (2) amblyopia, or lazy eye, in which one eye has reduced vision due to misalignment or unequal refraction; and (3) refractive errors, especially myopia (nearsightedness) and hyperopia (farsightedness). These are frequent causes of visual impairment in children that may persist throughout life. Strabismus occurs in 3 percent to 4 percent of the U.S. population, and amblyopia in 2 percent to 4 percent. Refractive errors—myopia (nearsightedness), hyperopia (farsightedness), and presbyopia

(difficulty focusing on near objects with advancing age)—occur in an estimated 60 percent of the population, who need some form of corrective lenses.

The NEI supports a broad range of laboratory, therapeutic, and preventative studies that are concerned with the development and function of the neural pathways from the eye to the brain; the central processing of visual information; visual perception; optical properties of the eye; oculomotor function; functioning of the pupil; and control of the ocular muscles. Additional emphasis is on research on optic neuropathies, eye movement disorders, and the development of myopia.

Visual Impairment and Its Rehabilitation.

Each of the formal programs encompasses research on diseases and disorders that can produce blindness and on a broad range of lesser degrees of visual impairment that may also be disabling. Some individuals require simple optical or mechanical aids to perform daily functions adequately, while others may need more specialized devices. Although not one of the five formal disease-oriented programs at the NEI, this area of research in the NEI strategic plan is a measure of its importance as a means of ameliorating the effects of blindness and impaired vision. The leading causes of visual impairment are diseases that are common among the elderly, such as AMD, cataract, glaucoma, diabetic retinopathy, and optic nerve atrophy. As noted earlier, an estimated 1.1 million people in this country are legally blind, and approximately 12 million have some degree of uncorrected visual impairment.

The NEI supports research to understand the origins of visual impairment and assist in the rehabilitation of those who have such disabilities. To meet the research challenges in this field, the NEI supports projects aimed at improving the methods of specifying, measuring, and categorizing loss of visual function; devising strategies to help visually impaired people maximize the use of their residual vision; systematically evaluating new and existing visual aids; developing an adequate epidemiological base to understand the causes of blindness, partial loss of sight, and visual anomalies; and studying the optical, electronic, and other rehabilitative needs of people with visual impairments.

Health Services Research. Because health care is important to all Americans—as taxpayers and as patients—the NEI and the NAEC felt compelled to devote a section specifically to this vital topic. As defined by the NEI, the field of health services research includes a broad range of diverse issues, such as increasing patient access to and utilization of visioncare services, improving the delivery of vision services by eyecare professionals, and measuring the visual health of patients receiving eyecare services. The challenges in this area include increasing public awareness of the personal and societal costs of visual impairment and ensuring that visioncare services are allocated to those most in need.

The sections that follow are the reports from each of the seven panels described earlier. These reports:

- Provide greater detail in each area of research.
- Identify the goals and objectives on which the research will be focused over the coming 5 years.
- Identify the needs and opportunities that give rise to these goals and objectives.
- Specify the strategies that will be used to accomplish them.

We at the NEI fully recognize the many challenges that lie ahead as we attempt to accomplish our mission. We believe that this strategic plan charts a course for continued progress in vision research in the new millennium.



PANEL REPORTS

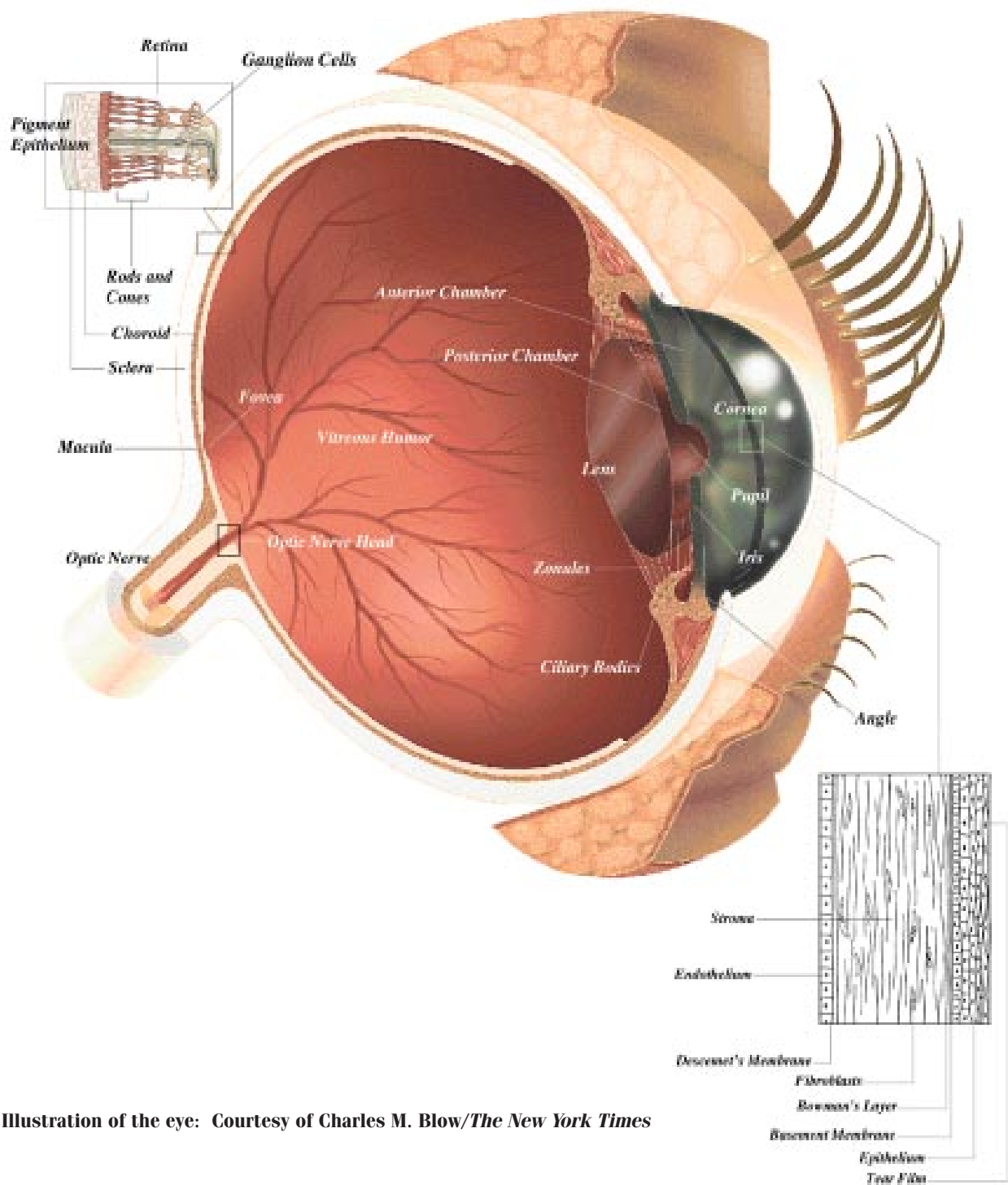


Illustration of the eye: Courtesy of Charles M. Blow/*The New York Times*

PROGRAM OVERVIEW AND GOALS

The retina is a specialized light-sensitive tissue that contains photoreceptor cells (rods and cones) and neurons connected to a neural network for the processing of visual information. This information is sent to the brain for decoding into a visual image. The accessibility of and diversity within the retina make it an ideal system to study. Such studies have a wealth of information on fundamental mechanisms that can be applied to the nervous system. The retina depends on cells of the adjacent retinal pigment epithelium (RPE) for support of its metabolic functions. Photoreceptors in the retina, perhaps because of their huge energy requirements and highly differentiated state, are sensitive to a variety of genetic and environmental insults. The retina is thus susceptible to an array of diseases that result in visual loss or complete blindness.

Two major systems of blood vessels nourish the retina. The retinal circulation feeds the inner layers of the retina (nearest the vitreous), while the choroidal circulation feeds the outer retina comprised of the RPE and photoreceptor cells. Vessels of the retinal circulation have endothelial tight junctions, like capillaries of the brain, serving as a barrier to the diffusion of large molecules. This is the cellular basis of the blood-retinal barrier. The retinal vasculature can be affected by three pathological processes: excessive permeability, vascular closure, and proliferation of newly formed blood vessels (neovascularization).

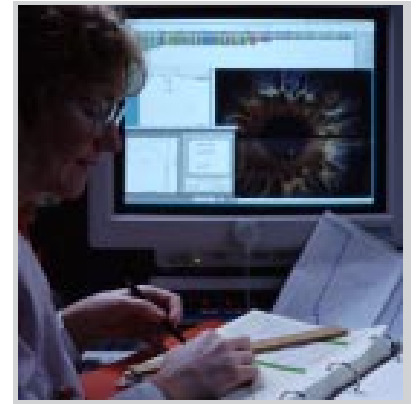
Diabetic retinopathy is a major cause of excessive permeability and is typically accompanied by neovascularization with ballooning of the retinal capillaries to form microaneurysms. The blood-retinal barrier may break down within these microaneurysms, causing leakage of blood proteins with subsequent hemorrhage into the retina and visual loss. Newly formed blood vessels tend to break through the retinal surface, which may result in hemorrhage into the vitreous and in traction retinal detachment, where the retina is pulled away from the underlying choroid.

Because of the prevalence of diabetes, diabetic retinopathy is a major cause of blindness. Laser photocoagulation is a useful clinical tool for treating proliferative retinopathy. Unfortunately, it is estimated that as many as 50 percent of patients are not diagnosed at a stage early enough for this treatment to be effective.

Ocular inflammatory diseases (uveitis) represent another category of retinal vascular disorders. Uveitis can be categorized as infectious and noninfectious types. Infectious agents, such as viruses and bacteria, can be very destructive when they enter the eye. Non-infectious inflammation is caused by problems with immune regulation. Uveitis is usually associated with painless but rapid visual loss.

The acquired immunodeficiency syndrome (AIDS) has had a dramatic impact on the field of ophthalmology. The majority of AIDS patients have ocular manifestations, most commonly a noninfectious microangiopathy called AIDS retinitis or cytomegalovirus (CMV) retinitis. About one-quarter of AIDS patients have compromised vision due to CMV activation. Untreated, CMV retinitis is progressive, resulting in ultimate destruction of the entire retina. Drugs such as ganciclovir and foscarnet have been effective in treating CMV retinitis and have helped AIDS patients preserve their vision in spite of the serious nature of their illness.

The two most common forms of cancer that affect the eye are retinoblastoma (RB) and choroidal melanoma. RB is mainly a disease of childhood. Thanks to the efforts of many vision scientists, RB is now one of the best understood of all solid tumors. Ninety percent of individuals who inherit specific mutations in the RB gene will develop the tumor. Each year, 300 to 400 new cases of RB are diagnosed in the United States. Unfortunately, the most prevalent treatment for RB at this time is surgical removal of the affected



eye. Choroidal melanoma primarily affects adults and its etiology is poorly understood. Nearly 1,500 new cases of choroidal melanoma are diagnosed annually in the United States, and the optimal therapy for this disorder is still unclear.

The inherited retinal degenerations are typified by retinitis pigmentosa (RP), which results in the destruction of photoreceptor cells, the RPE, and choroid. This group of debilitating conditions affects approximately 100,000 people in the United States. Knowledge gained from studies of the structure, function, and metabolism of the normal retina and RPE have had a large impact on scientists' ability to understand what goes wrong in diseases like RP. A great deal of the progress made in dealing with this important clinical problem has depended on advances in research on photoreceptor cell biology, molecular biology, molecular genetics, and biochemistry over the past two decades. Animal models of hereditary retinal disease have been vital in helping unravel the specific genetic and biochemical defects that underlie abnormalities in human retinal diseases. It now seems clear that both genetic and clinical heterogeneity underlie many hereditary retinal diseases.

The leading cause of visual loss in the elderly is macular degeneration (MD). The social and economic impact of this disease in the United States is increasing. The macula is a structure near the center of the retina that contains the fovea. This specialized portion of the retina is responsible for the high-resolution vision that permits activities such as reading. The loss of central vision in MD is devastating. Degenerative changes to the macula (maculopathy) can occur at almost any time in life but are much more prevalent with advancing age. With growth in the aged population, age-related macular degeneration (AMD) will become a more prevalent cause of blindness than both diabetic retinopathy and glaucoma combined. Laser treatment has been shown to reduce the risk of extensive macular scarring from the "wet" or neovascular form of the disease. The effects of this treatment are short-lived, however, due to recurrent choroidal neovascularization. Recently, important new strides have been made in understanding the molecular basis of several forms of MD. Sorsby's fundus dystrophy, a rare form of MD, has been found to respond to vitamin A supplementation. There are currently no effective treatments for the vast majority of MD patients.

Retinal detachments are important clinically and can be divided into three basic types: (1) rhegmatogenous detachment, in which a tear or hole occurs in the retina; (2) serous detachment, resulting from subretinal fluid collection; and (3) traction retinal detachment (TRD), in which the retina is pulled away from the RPE by contractile tissue in the vitreous body or on the retinal surface itself. Rhegmatogenous detachments are the most common and the greatest threat to vision. TRD usually occurs in proliferative retinopathies, most commonly proliferative diabetic retinopathy or proliferative vitreoretinopathy (PVR). Although significant advances have been made in the management of retinal detachments, they remain an important cause of visual morbidity.

One of the major achievements in all of biology has been defining cellular events involved in the process of visual transduction. This has become a classic model that has led the way toward researchers' current understanding of signal processing in other systems. Advances in understanding visual biochemistry have yielded important new insights into the causes of retinal diseases. The majority of these diseases affect photoreceptors and the RPE. For some inherited retinal diseases the affected gene and protein have been identified. Scientists are beginning to understand the early effects on photoreceptors of proteins that are abnormal or that have lost their function. However, they have yet to make the definitive connection between the abnormal function of individual proteins and the death of photoreceptor cells.

The visual images that fall on the retina are sent to the brain to be decoded and interpreted. The visual images that are perceived result from integration of electrical impulses generated within the retina that are in turn transmitted by ganglion cells via the optic nerve to the part of the brain called the visual cortex. Remarkably, the visual system can function over a hundred-millionfold range in illumination. Individual photoreceptor cells are responsive to light intensities varying between sunlight and candlelight. Yet when the lights are turned off, the perception of darkness is nearly instantaneous. What makes this possible? The tools of modern neurobiology offer the potential to understand the cellular mechanisms of both light adaptation (sensitivity to varying light levels) as well as inactivation (turning off the sensitivity to light). At birth, our eyes have their full complement of 300 million retinal cells, with all 10 billion synaptic

contacts already established. Most of the known neurotransmitters and neuropeptides involved in cell-cell communications are represented in the retina. A central unanswered question in neurobiology is how this complex network permits the formation of images and the discrimination of colors.

In Fiscal Year 1997, the National Eye Institute (NEI) funded approximately 600 extramural research projects in the Retinal Diseases Program at a total cost of \$128,316,000.

The goals for laboratory and clinical research conducted within the Retinal Diseases Program for the next 5 years are to:

- Understand the molecular and biochemical basis for the different forms of MD, improve early diagnosis, characterize environmental effects on the etiology of MD, and develop new treatments.
- Understand the pathogenesis of diabetic retinopathy and other vascular diseases of the retina and develop strategies for primary prevention and improved treatment.
- Identify the genes involved in retinal degenerative diseases, including RP, and determine the pathophysiological mechanisms underlying these mutations.
- Explore new potential therapeutic strategies for inherited retinal diseases, 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, therapy, and prevention.
- Use both molecular and physiological approaches to study light adaptation in photoreceptors, with particular emphasis on the visual cycle.
- Build on knowledge gained from retinal neuroscience to understand how retinal networks process visual images, a central unanswered question of modern neurobiology.

ASSESSMENT OF PROGRESS

Within the Retinal Diseases Program, significant progress has been made in the last 5 years in understanding the fundamental and pathogenic processes in the retina and in improving the diagnosis and treatment of a variety of retinal diseases.

Epidemiological, cell biological, and molecular genetic studies of MD. In the past decade, it has become increasingly apparent that the clinical entity known as AMD is actually a heterogeneous group of disorders with multiple pathophysiological mechanisms. Recent epidemiological, cell biological, and genetic studies of MD have incorporated standardized, detailed classification schemes into their study design. The recent development of an international classification and grading system for AMD should allow improved comparisons to be made across different studies.

Recent epidemiologic studies have identified factors, such as cigarette smoking, that increase the risk of AMD. Conversely, antioxidants have been suggested to decrease the risk, raising the possibility that a combination of treatments and behavioral changes could further decrease the risk of AMD (see Development of effective treatments for retinal diseases on page 18). Encouraging results have also emerged from studies that suggest a protective effect of antioxidants.

Progress has also been made in the area of the molecular genetics of various types of MD. Since 1992, the genes for a number of different forms of heritable macular disease have been mapped to specific chromosomes. These include: North Carolina macular dystrophy, Best's disease, Stargardt's disease (both dominant and recessive forms), pattern dystrophy, Sorsby's fundus dystrophy, bifocal chorioretinal atrophy, and autosomal dominant radial drusen (Malattia Leventinese). In three cases (pattern dystrophy, Sorsby's fundus dystrophy, and recessive Stargardt's disease), the mutated genes (RDS, TIMP-3, and ABCR, respectively) have actually been identified. An animal model for the RDS mutation is already available for experiments aimed at improved understanding of the associated pathophysiology, as well as experiments designed to evaluate novel treatment methods with potential application to human disease. Recently, it has been found that the ABCR gene mutated in Stargardt's disease appears to be altered in some patients with AMD. Studies are

ongoing to determine the prevalence of ABCR gene mutations in large cohorts of patients with AMD. Detection of genes mutated in patients with AMD will permit the development of genetic tests that may identify individuals at risk for the disease.

Given the high prevalence of AMD in the older population, it is hoped that inexpensive, safe medications can be identified that will be efficacious for the prevention and treatment of common forms of MD. Severe visual loss in patients with MD is associated with the development of neovascularization. Thus, most treatment trials have been aimed at treating this complication. While the results of the macular photocoagulation study showed some promise regarding laser photocoagulation for treatment of certain patients with neovascularization, the benefits of this treatment are limited. Other treatments are also being explored, but to date none have been found to be effective for the majority of these patients.

Pathogenesis of vascular diseases of the retina.

Vascular endothelial growth factor (VEGF) has become a leading candidate for the long-sought agent responsible for neovascularization in retinal diseases. Retinal neovascularization is often associated with retinal ischemia and hypoxia. Hypoxia induces VEGF production. VEGF is present at high concentrations in the vitreous fluid of patients with proliferative diabetic retinopathy and is low to absent in the vitreous of patients with nonvasoproliferative disease. VEGF levels are high in the retina and vitreous of animals with experimental retinal or iris neovascularization, and methods that block VEGF action (e.g., neutralizing antibodies, soluble receptors, or antisense DNA) prevent neovascularization. In human eyes with retinal and choroidal vascular diseases, and in experimental animals, VEGF is localized primarily in the glial cells of the retina and optic nerve, and in the RPE cells. Although hypoxia has not been identified in choroidal neovascular diseases, VEGF has been reported in the RPE cells of choroidal neovascular membranes. While macular edema and neovascularization apparently result when VEGF is upregulated during certain pathologic processes, the normal function of VEGF may be to stimulate blood vessel growth in fetal development. Mice with a targeted disruption of the VEGF gene die in embryo due to defective vascular development.

An enzyme that may be critical for the development of diabetic retinopathy is aldose reductase, the initial

enzyme of the sorbitol pathway. Although extensive laboratory studies have shown that aldose reductase inhibitors (ARIs) can prevent the development of diabetic retinopathy in experimental animal models, clinical studies using ARIs have not shown significant impact on the development or progression of retinopathy. However, a recent result involving the effect of a potent new ARI in the retinas of experimental animals may be cause for renewed optimism. A new and highly potent ARI that inhibits aldose reductase by approximately 90 percent can prevent VEGF expression in long-term galactosemic rats. It appears that, to be effective, ARIs must penetrate the retina sufficiently to inhibit nearly all of the aldose reductase present. Currently available ARIs have not been able to achieve this level of penetration at safe doses, but newer drugs appear promising.

In diabetic retinopathy, glucose may exert its deleterious effects by directly modifying the expression of genes. Cultured retinal pericytes grown in high glucose show differences in gene expression when compared to cells grown in normal glucose. Basement membranes of blood vessels from diabetic or galactosemic animals contain a profile of collagens different than basement membranes of control animals, suggesting altered expression of genes. Similarly, when animals in poor diabetic “control” or those maintained on high galactose diets for a short time are switched to “tight” control or a normal diet, they develop retinopathy after a delay of several years. The diabetes control and complications trial and its followup showed that the delay of onset and possible prevention of diabetic eye disease was due to tight control of glycemic levels. This study has made a significant contribution to patient welfare and quality of life.

Data from the multicenter Cryotherapy for Retinopathy of Prematurity Study showed that the incidence of severe retinopathy of prematurity (ROP) in very low birth weight premature infants is about double in Caucasian children when compared to African-American children. The reasons for this disparity may include genetic differences and the effects of increased ocular pigmentation in preventing oxidative damage to the retina.

A role for pituitary-associated factor in diabetic retinopathy has been appreciated for many years. Several decades ago, retinal neovascularization was found to regress after pituitary ablation in

diabetic patients that appeared to be related to postsurgical growth hormone (GH) deficiency. In addition, insulin-like growth factor-1 (IGF-1) appears to be associated with proliferative retinopathy. To study the role of GH and IGF-1 in ischemia-induced retinal neovascularization and its interaction with VEGF, transgenic mice were studied. It was found that systemic inhibition of GH, IGF-1, or both may have therapeutic potential in preventing some forms of retinopathy.

Morphological, cellular, and molecular events that accompany retinal wound healing. The retina is composed of a complex and elaborate network of neuronal and nonneuronal cells. Retinal tissue can be exposed to a range of insults from a variety of diseases, including PVR, diabetic retinopathy, maculopathy, AMD, and RP. Physical trauma, environmental insults, and even surgery itself can damage the retina. These insults can often result in a specific biological response to injury called wound healing, which in the case of PVR is characterized by macrophage infiltration, RPE cell transformation, and the deposition of extracellular matrix components. The attempt by the retina to repair damage after injury can result in fibrosis, scar formation, neovascularization, and proliferation of glial cells (gliosis) within the retina. As such, retinal wound healing is often a fundamentally undesirable event with respect to the visual consequences.

Regardless of the cause of the initial damage, retinal wound healing shares important features with wound healing in other tissues. However, because of the retina's unique character as a highly differentiated and specialized tissue, it is not equipped to repair itself in such a way as to restore its own specialized properties. The result is activation of a wound repair process that is incompatible with the retina's function as a neurosensory tissue. Attempts at repair are an ordered process involving complex cell-cell interactions, but ultimately can result in partial or complete loss of vision.

A variety of overlapping biological processes, including abnormal cellular migration, cellular proliferation, cellular transformation, cellular death, invasion, inflammation, fibrosis, gliosis, scarring, and neovascularization, are associated with the retina's attempt to repair itself. Macrophages and other leukocytes are typically attracted to the site of initial

damage, playing a crucial role as regulators of cellular migration and growth, stimulating additional cellular activities, and modulating local cellular activities. Macrophages also produce a variety of biologic response modifiers, most notably fibroblast growth factor (FGF), transforming growth factor (TGF), and platelet-derived growth factor (PDGF).

The exact role of retinal cells, RPE cells, and other cells recruited to the wound site is unclear. There is some indication that RPE cells are one of the sources of regulatory factors involved in the process of wound healing. Studies have shown that a vast number of growth factors, cytokines, and their receptors are secreted or expressed by the RPE, although the precise mechanisms that regulate and modulate their expression remains to be determined. A significant finding related to the potential role of the RPE in wound healing has been the demonstration that there are multiple, self-regulatory, or autocrine loops in RPE cells. Both PDGF and VEGF autocrine loops have been demonstrated. Upregulation of PDGF and its receptors in wounded RPE cells has been documented *in vitro*. The autocrine loop is also modulated *in vivo* and appears to be a potent stimulus for upregulation of PDGF by RPE cells following retinal detachment. Photoreceptor cells or other cells in the retina may play a role in the modulation of these autocrine loops, which is consistent with the finding that the RPE proliferates and becomes more responsive to growth factors following injuries such as retinal detachment. Perhaps similar modulation occurs in the VEGF autocrine loop since VEGF, PDGF, and their receptors can be detected when RPE cells participate in wound repair, as occurs during formation of epiretinal membranes. A better understanding of these regulatory pathways may be useful in developing therapies for controlling the proliferation of RPE and other cells during wound healing.

Genetic etiology of RP and allied diseases. Since 1990, 10 genes causing RP have been identified (rhodopsin, RDS, α - and β -subunits of rod cGMP-phosphodiesterase, ROM1, α -subunit of the rod cGMP-gated channel, RP GTPase regulator, cellular retinaldehyde-binding protein, myosin VIIA, and PE65). Furthermore, at least 24 additional loci causing RP have been placed on the human genome map and are in varying stages of being identified through positional cloning strategies. Progress is being made in the elucidation of genes causing other hereditary diseases

of the retina. These diseases include congenital stationary night blindness (some forms of which are caused by mutations in the genes encoding rhodopsin and the β -subunit of rod cGMP-phosphodiesterase), Oguchi disease (arrestin and rhodopsin kinase), and juvenile hereditary MDs (TIMP-3 and ABCR, a rod photoreceptor-specific protein). Finally, numerous candidate genes (narrowly defined here as genes with known function in the retina and specifically expressed by the retina) have been isolated and are available for chromosomal mapping (to determine if they map to chromosomal regions with known retinal degeneration loci) or for direct mutation analysis in large cohorts of patients with forms of hereditary retinal degeneration, dysfunction, or developmental anomalies.

With regard to RP, each identified gene accounts for a few percent of cases, and rhodopsin, which accounts for about 10 percent of cases. In total, all identified genes to date account only for about one-third of cases. It is uncertain at the present time what proportion of cases are due to defects in the 24 or more unidentified genes known only through linkage studies in one or a few families each. It is possible that there may be 50 to 100 or more human loci that can confer hereditary retinal disease phenotypes. This estimate is consistent with genetic mapping and cloning studies in *Drosophila*, which have provided firm evidence for well over 80 retinal degeneration and dysfunction loci. Therefore, there is little reason to doubt that the set of genes causing retinal degeneration in humans is of comparable size.

Gene identifications in humans have allowed scientists to identify or create animal models with retinal degeneration due to defects in the same gene homologs. In particular, the genes responsible for retinal degeneration in the naturally arising RD and RDS mouse strains (the β -subunit of phosphodiesterase and peripherin/RDS, respectively) are now known to be causes of RP and other retinal degenerations in humans. Transgenic mice, rats, and pigs expressing dominant rhodopsin mutations have been developed, as have transgenic mice with dominant and digenic RDS and ROM1 mutations. These animal models are already the subject of intensive study to determine the pathophysiological mechanisms whereby these gene defects lead to photoreceptor degeneration and hopefully will lead to pilot studies of novel therapies for retinal degenerative diseases.

Developing *Drosophila* as a model for studying hereditary human diseases that cause progressive retinal degeneration such as RP has provided exciting information. The availability of eye mutants in *Drosophila* provides models for dissecting the molecular bases of retinal degeneration. The relevance of this work for humans with RP and allied diseases is illustrated by the fact that mutations in the human homologs of some of the *Drosophila* genes, such as rhodopsin and arrestin, have been found to cause RP or stationary night blindness. It is likely that future evaluation of the human homologs of other *Drosophila* retinal degeneration genes will lead to the identification of novel causes of human hereditary retinal diseases.

The identification of the genes causing some forms of retinal degeneration and retinal dysfunction has permitted advances in understanding the corresponding visual dysfunctions. Studies of dominant rhodopsin mutations using *in vitro*, transgenic mouse, and transgenic *Drosophila* systems, for example, have provided evidence suggesting that, at least for some mutations, the transport of mutant rhodopsin to the rod outer segments is defective. Null mutations in the genes encoding the catalytic subunits of rod phosphodiesterase likely are deleterious because of a secondary increase in the cytoplasmic level of cGMP. The proteins RDS and ROM1 form heterotetramers that accumulate at the rim regions of outer segment discs and perhaps have a key structural role there; without this complex, outer segment discs do not form properly. Regardless of the underlying genetic defect and the early biochemical steps leading to photoreceptor degeneration, the final common pathway for cell death has been found to be apoptosis.

Development of effective treatments for retinal diseases. During the past decade, important insights have been gained into the molecular etiologies of several inherited retinal and macular dystrophies. Studies from many laboratories have defined several promising therapeutic strategies. Progress has been reported in the area of somatic gene therapy with recombinant adenoviral and adenoviral-associated viral vectors. Several laboratories have shown significant slowing of photoreceptor degeneration in several animal models with the administration of basic FGF and neurotrophic agents. Another promising strategy involves directly targeting the

mutant gene or its mRNA product while leaving the normal allele unaltered. Current strategies include ribozymes, antisense nucleic acids, and triplex-forming oligonucleotides. Of the three, the mode of action for ribozymes is best understood. Specific cleavage of single-base substituted mutant mRNAs without degradation of the wild-type mRNA has been demonstrated *in vitro*.

Some advances have been made in the area of retinal transplantation. Cells of the RPE have been grafted into the subretinal space of Royal College of Surgeons (RCS) rat eyes, prolonging the survival of photoreceptors. Embryonic mouse retinal tissue has been grafted into brains of adult mice. These grafts sent out neurites that established synaptic contacts with neurons of the recipient's brain and developed recognizable retinal cell types.

New knowledge about the molecular defects underlying inherited blindness in animals and humans has shown that the retinal degenerations are a highly heterogeneous group of diseases. It is likely that photoreceptors die for different reasons in the different mutants. A rhodopsin mutation resulting in a trafficking defect, for example, may represent a completely distinct cellular lesion from a mutation that causes constitutive activation of the phototransduction cascade. Multiple animal models involving spontaneous mutations in retinal genes have been defined. In addition, several transgenic models of both recessive and dominant human inherited retinal dystrophies have been generated.

A double-masked clinical trial of about 600 patients with RP found that oral vitamin A supplementation slowed the course of retinal degeneration, as measured by electroretinogram (ERG), and that vitamin E hastened the course of degeneration. Reduction in light exposure appears to modulate the severity of disease in some but not all mouse models of RP; a large-scale clinical trial of the possible therapeutic benefit of reduction of light exposure (e.g., sunglasses) has not yet been carried out.

Unique properties of intraocular immunity and inflammation. The intraocular spaces in which immunity and inflammation can occur include the anterior (and posterior) chamber(s), the vitreous cavity, and the subretinal space. Recent evidence indicates that the phenomenon of immunologic

privilege exists in each of these compartments because allogeneic grafts of tumors and of retinal tissues (neuronal retina, RPE) placed within these sites have been seen to display prolonged (even indefinite) survival. However, observations regarding the subretinal space are largely qualitative and require further refinement. For technical reasons, much more has been learned about modulation of immunity and inflammation within the anterior chamber than within the other compartments. In that regard, an ever-expanding list of immunosuppressive and anti-inflammatory factors has been generated by examining aqueous humor. These factors include TGF- β_2 , α -melanocyte stimulating hormone, vasoactive intestinal peptide, calcitonin gene related peptide, macrophage migration inhibitory factor (MIF), and soluble inhibitors of complement activation. In addition, a natural defensin that has been demonstrated to be an antibiotic for gram-positive cocci has been described in aqueous humor. Along with these soluble immunomodulatory factors, the cells that surround the anterior chamber and the subretinal space constitutively express membrane bound forms of Fas ligand and the complement inhibitors, CD59, DAF and CD46. Moreover, cultured epithelial cells of the iris and ciliary body, as well as RPE, have been found constitutively to secrete immunosuppressive factors *in vitro*.

Anti-inflammatory and immunomodulatory factors in the ocular microenvironment affect two phenomena: the existence of intraocular immunologic privilege and the induction of systemic immune deviation or anterior chamber associated immune deviation (ACAID) to intraocular antigens, and the ability of the eye to resist blinding intraocular inflammation in response to injury and infection. The mechanisms by which specific factors in the ocular microenvironment induce ACAID are beginning to be elucidated.

The multiplicity of immunomodulatory factors in aqueous humor has important effects on immune and inflammatory effector mechanisms. TGF- β_2 , as well as other factors in the aqueous humor, inhibit macrophage activation and prevent these cells from acquiring certain effector function (cytotoxicity, generation of oxygen free radicals, and nitric oxide). MIF is a powerful inhibitor of natural killer cells in the eye. Moreover, factors in aqueous humor also have profound effects on certain T-lymphocytes. Primed

T-cells are inhibited from proliferating *in vitro* in response to antigen or T-cell receptor ligand stimulation, and the cells are also prevented from secreting proinflammatory cytokines such as γ -interferon. But not all immunosuppression in the eye depends on soluble molecules in the fluid phase. The recent dramatic demonstration of constitutive expression of Fas ligand on numerous cell types within the eye indicates that a mechanism of peripheral deletion of Fas+T-lymphocytes (via apoptosis) operates to limit intraocular immune expression. Recent studies confirm that intraocular expression of Fas ligand accounts, at least in part, for the extraordinary success of orthotopic corneal allografts in mice, and there is evidence suggesting that Fas ligand also contributes to the generation of the ACAID-inducing signal.

Intraocular inflammation of the posterior segment. Posterior segment intraocular inflammation is an important cause of blindness. The inflammation can display one or more of four distinct clinical features: variably sized focal chorioretinal infiltrate of inflammatory cells; retinal vessel inflammation; vitreous cellular infiltrates; and edema of the macula, optic nerve head, or the entire retina, producing a subretinal posterior segment inflammation. When an infectious agent is identified, the cause is straightforward and appropriate therapy can be instituted. But in many instances, no such agent can be found, and attempts to sort out unknown infectious causes from immunopathogenic processes, and these in turn from autoimmune mechanisms, are usually unsuccessful.

For many years, the laboratory model of choice has been experimental autoimmune uveoretinitis (EAU), evoked in laboratory animals by immunization with one of several autoantigens produced by the adult retina (arrestin, interphotoreceptor retinol binding protein [IRBP], rhodopsin). In certain genetically defined strains of mice (B10.A), immunization with retinal S-antigen (arrestin) produces a disease similar to human ocular histoplasmosis, whereas in rats, similar immunization leads to an exudative retinal detachment resembling Vogt-Koyanagi-Harada disease. Arrestin immunization of monkeys produces a retinal vasculitis. This set of observations makes the following points: the posterior segment of the eye responds to insults, whether infectious, autoimmune, or immunopathogenic, in a limited set of patterns, and these patterns are dictated in part by the host's

genetic makeup, the nature of the insult, and the status of the host's immunologic history.

Immunodominant peptides derived from retinal autoantigens have been identified for arrestin and for IRBP in genetically defined experimental animals. CD4 positive T-cells have emerged as the primary initiators of intraocular inflammation in EAU, and γ -interferon is believed to be the major proinflammatory cytokine involved. To that end, transgenic mice have been produced in which the γ -interferon gene has been inserted under the control of the rhodopsin promoter, and the eyes of these mice develop a blinding posterior segment inflammation. However, confusion about the role of γ -interferon has emerged as investigators have discovered that exogenous administration of γ -interferon reduces the incidence and severity of EAU in experimental animals, and neutralizing antibodies against this cytokine make the experimental disease more intense. Similarly, exogenous interleukin-12 (IL-12), the cytokine most critical to activation of γ -interferon-producing CD4 positive T-cells, also mitigates against intense uveoretinitis. At the same time, inducing oral tolerance by feeding retinal antigens to experimental animals has proven to prevent or greatly diminish the severity of EAU, and a recent report from a pilot human clinical trial suggests the same conclusion. Similarly, induction of ACAID with retinal antigens has been shown to prevent EAU and reduce the severity of extent disease.

By switching from retinal antigens to molecules associated with melanin pigment in the uveal tract, a new model of ocular inflammation has been produced, called experimental anterior autoimmune uveitis (EAAU). The pertinent antigen appears to be a protein or proteins associated with the insoluble fraction of melanin granules, and the pattern of disease caused by immunization with this antigen differs from EAU. The inflammation of EAAU is located primarily within the anterior segment of the eye, emphasizing the fact that the localization of autoimmune-based intraocular inflammation depends, in part, on the nature (and presumably the source) of the antigen within the eye.

Bacterial lipopolysaccharide has recently been exploited as an experimental inducer of endotoxin-induced uveitis in mice and rats, and this newer model has considerably enhanced researchers' understanding of ocular inflammation due to

immunopathogenic, rather than autoimmune, processes. The vessels of the uveal tract are uniquely susceptible to mediators released upon endotoxin stimulation, especially IL-1, IL-6, and tumor necrosis factor- α . As a consequence, the uveal tract itself becomes inflamed and infiltrated with blood-borne cells; the blood-ocular barrier is breached.

One of the most severe forms of posterior segment inflammation is caused by CMV, a common opportunistic infection in patients with AIDS. CMV retinitis accounts for about 85 percent of CMV disease in patients with AIDS and is a significant cause of morbidity. CMV retinitis is a progressive and destructive infection that, left untreated, causes blindness. The NEI-sponsored clinical trial called Studies of the Ocular Complications of AIDS (SOCA) has demonstrated that for AIDS patients with CMV retinitis a combination therapy with foscarnet and ganciclovir is more effective than either of these drugs alone in controlling CMV retinitis. However, there can be complications of intravitreal therapy injection, including endophthalmitis and retinal detachment. A recent advance has been the development of a sustained-release ganciclovir device that is surgically implanted into the vitreous cavity and releases drug over several months. An NEI intramural clinical trial demonstrated a prolonged delay in progression of retinitis for patients receiving the implant when compared to controls.

The molecular basis of visual transduction pathway. Proteins in rod and cone photoreceptor cells that are responsible for the capture of light and its conversion into electrical signals have been identified and characterized in considerable detail. The genes for the photoreceptor proteins, rhodopsin and cone opsins, from a variety of species including human, have been cloned and sequenced. This information has been used with biochemical and biophysical studies to identify specific amino acids and structural regions of these proteins that play key roles in spectral sensitivity and color discrimination, initiation and termination of the photoresponse, and protein folding and stability. This has led to the development of mathematical models that accurately simulate the photoexcitation phase of the visual response in rod cells.

A high-resolution, three-dimensional structure of transducin obtained by X-ray crystallography has been used to understand the mechanism by which guanosine

diphosphate bound to transducin is exchanged for guanosine triphosphate following photoactivation of rhodopsin; it has also provided a glimpse of how transducin subsequently interacts with phosphodiesterase to catalyze the hydrolysis of cGMP. The end target of the visual cascade pathway, the cGMP-gated channel, has also been characterized at molecular and physiological levels. These studies have provided important new insight into how the activity of this channel is controlled by cGMP and extracellular divalent cations and modulated by calmodulin. Considerable progress has also been made toward analyzing the molecular structure, function, and regulation of proteins that play central roles in the termination of the photoresponse and the recovery of the rod cell to its dark-adapted state. These proteins include rhodopsin kinase, arrestin, guanylate cyclase, and several key regulatory calcium-binding proteins. A particularly significant development has been the identification and characterization of the guanylate cyclase activating proteins. These proteins have been shown to regulate the activity of guanylate cyclase activity in a calcium-dependent manner and play a crucial role in photorecovery and light adaptation in photoreceptor cells. Studies have also led to a more complete understanding of the function of the Na/Ca exchanger in maintaining calcium homeostasis in rod cells and the role of glucose metabolism in the production of energy for phototransduction. Disruption of metabolic function and homeostasis in the retina may have serious consequences and contribute to photoreceptor degeneration.

Signal processing in the retina. The retina is a biological image processor. It receives light from images in the world, transforms each image into electrical signals, codes these signals by extracting the essential information from the image, and finally sends this code as patterns of spikes down the optic nerve to the brain. Normal vision requires the retina to operate over illumination conditions that span 10 orders of magnitude (10 billion to one), a feat well beyond the capabilities of any of the most sophisticated optical instruments. During the last 5 years, researchers have gained insight into many areas related to how the retina is “wired” to function and how it is able to adapt to whatever the ambient illumination might be. This progress has been made possible by applying techniques that look at the activity of many cells

simultaneously, by using ever more sophisticated molecular and cellular approaches, and by adopting techniques perfected in nonmammalian retinal studies to study mammalian and primate retinal preparations.

By recording the spike activity of many ganglion cells simultaneously, using arrays of electrodes and powerful computer-based analysis, it has been possible to discover the correlated firing of many cells. This suggests that visual signals transmitted to the brain do not simply reflect the firing in single axons but in combinations of axons. These multielectrode studies have also shown that waves of electrical activity course across the retinas of mammals and reptiles during postnatal development. A great deal has been learned of the synaptic transmitter molecules and the network on cell-to-cell connections that generates these waves. These waves are believed to be important for generating synchronized signals to permit the proper “wiring” of higher visual centers in the brain. Numerous important insights into normal and pathophysiological function of the photoreceptors and other retinal cells have been gained from sophisticated analysis of ERG recordings, the massed electrical response of the retinal neurons that is routinely measured from the cornea of patients.

Over the last 5 years, it has become increasingly apparent that cells of all types in the retina can be electrically coupled to similar or different cell types. Studies of the coupling of fluorescent dyes between these cells show conclusively that not only do the size and nature of the gap junction proteins differ, but that these coupling junctions can be regulated by different “neuromodulator” chemicals that may diffuse through the retina in response to different lighting conditions. Although the synaptic neurotransmitters released by each cell class is close to being identified, it is becoming increasingly evident that many different isoforms of the receptors to these neurotransmitters are expressed on the postsynaptic cells. Each may serve a different function. Moreover, postsynaptic receptors may gate an ion channel or activate intracellular signaling pathways within the same cell. Thus, one neurotransmitter can “drive” a cell in many ways, some of them through rapid activating pathways and some through slower, modulatory pathways. These slower pathways probably serve to adapt cellular function to fit ambient light conditions.

The newly discovered information about the control of neurotransmitter from the ribbon synapses of bipolar and photoreceptor cells has become the exemplar model of how glutamate is released from most neurons in the central nervous system. These studies have been made feasible by newly developed techniques that measure the release of endogenous glutamate from either a specially prepared sheet of photoreceptors or from single cells and/or that measure exocytosis employing electrophysiologically based capacitance measurements. Researchers now know much more about how calcium influx controls glutamate release and how there are “pools” of readily releasable glutamate-containing vesicles that can meet the needs of very fast signaling and “pools” of more slowly releasable vesicles that supply transmitter over longer periods of time. Exquisite correlations have been made between the biophysically measured release rates and the quantity and positioning of neurotransmitter-laden vesicles at the ribbon synapses.

Microelectrode studies formerly restricted to retinas of cold-blooded species are now enjoying success in revealing fundamental concepts of how mammalian and primate retinas function. With these microelectrodes it is possible to record the responses of individual cells to light or neurotransmitters, and then inject dyes into the same cells to illuminate their morphology and connections to other cells. It is becoming increasingly apparent that many of the neurotransmitter receptors are expressed in similar cell types in all vertebrate species. Dye injections viewed with advanced microscopy reveals that the microcircuitry of rabbits, rats, or cats is very similar to that of monkeys and humans. Surprisingly, however, the processing of color information by primate retinas is very distinctive from that of reptilian and fish retinas.

The former promise of molecular biology has proven itself extremely useful in helping to dissect the “wiring” of the retina. Two of the most important retina-specific neurotransmitter receptors, the mGluR6 and the GABA_c, have been cloned. Structure function studies on these proteins are just beginning. A mouse line lacking the mGluR6 receptor has been made and used to verify the role of the rod ON bipolar cell in the conduction of low-light level, rod-driven responses to the ganglion cells. In other studies, transgenic mice have been created with cell type-specific markers. One use of this technique has been to use intense light to

photoablate these specific cells and thereby “drop” these cells from a functioning retinal circuit. This has allowed investigators to unravel roles of individual cell types without having to deal with some of the complexities inherent in pharmacological methods.

Retinal development: establishing and specifying various retinal cell types. Cell lineage analysis has shown that retinal cells are generated from multipotent progenitors throughout development. The cell types generated *in vitro* can be influenced by the environment, and certain growth factors added to retinal cell cultures can lead to shifts in the types of cells produced. Growth factors can also influence the survival of retinal cells *in vitro* or *in vivo*. For example, members of the ciliary neurotrophic factor family of cytokines can reduce the number of rods formed early in development, but prevent their degeneration later in development. FGFs have a number of effects, including effects on cell division, rod development, and survival. In addition to the effect of extrinsic cues, intrinsic properties of progenitors contribute to the genesis of retinal cell types as well. Factors that affect the development of retinal cells may also affect their survival and function and have implications for developing effective treatments for retinal degenerative diseases such as RP.

One aspect of the progress in retinal development that should be noted is the value of model systems like *Drosophila*, *Xenopus*, and zebrafish to understanding vertebrate systems. The overall strategy of retinal cell fate determination and differentiation is the same in the vertebrate and *Drosophila* retina, as are many of the molecules employed. For example, the extracellular receptor Notch and its ligand Delta are crucial for the development of all retinal neurons in *Drosophila* and vertebrates. The basic helix-loop-helix genes are important for both, as are homeobox genes. The eyeless gene encodes a *Drosophila* Pax-6 and specifies eyes in *Drosophila*. In addition, vertebrate Pax-6 molecules can specify ectopic eyes in *Drosophila*, providing strong support for similarities in the development of visual systems. Although the true homology of the systems is still being debated, there is no doubt that the work that has been carried out in animal models has greatly contributed to and continues to enhance scientists’ understanding of the development and function of many classes of genes.

Genes expressed in the retina and choroid.

Major progress has been made in cataloging and mapping genes expressed in the retina and choroid with the advent of the field of genomics and the associated technology. Systematic sequencing of the entire genome of model organisms is underway, and several have been completed. Of particular relevance for understanding the human visual system is the human genome sequencing project. In addition to generating a genome sequence, a genetic map of various organisms has been made, using primarily polymorphic DNA markers and polymerase chain reaction technology. These databases will be invaluable in the work ahead and have already been a major force in changing the way that studies of disease and function have been conducted.

The goal of sequencing the mRNAs expressed in various tissues is also underway. These sequences, known as expressed sequence tags (ESTs), now allow recognition of which genes are expressed in various tissues and allow recognition of transcriptional units among genomic sequences. The “chip” technology that has recently been applied to molecular biology provides tools that will afford a more rapid accumulation of data concerning which cells express which ESTs and will provide for rapid sequencing of genes for diagnostic purposes.

With respect to progress on gene expression in the visual system, the accomplishments have been outstanding. Some of the genes specific to the visual system have been isolated (see Genetic etiology of RP and allied diseases on page 17). Biochemical isolation of proteins and the acquisition of their sequences, as well as the search for genes expressed in the visual system using homology to genes operative in other systems, have provided most of these genes. These genes have supplied a wealth of sequences for use in candidate gene approaches for the identification of mutations in various visual system diseases and for developing strategies for treatment.

Maintenance of a healthy neurosensory retina.

The RPE performs a variety of transport functions that impact on the maintenance of a healthy neurosensory retina. Considerable amounts of lactate are formed by the photoreceptor cells as a product of anaerobic metabolism. The RPE removes this lactate from the

neurosensory retina by transporting it into the choroidal circulation. Water movement is coupled to lactate transport via an H^+ /lactate cotransporter in the apical plasma membrane of the RPE. This system may account for a large fraction of the fluid absorption across the RPE. At light onset, the volume of the extracellular compartment surrounding the photoreceptors increases by 20 percent to 60 percent, much of which is due to changes in RPE transport. The subretinal K^+ concentration decreases at light onset as a result of a change in photoreceptor activity, and this serves as the paracrine signal that triggers the transport of K^+ and Cl^- , which are responsible for changes in subretinal volume. The K and Cl channels that mediate these changes have been characterized, as has their pharmacological regulation. The RPE secretes TIMP-3 into Bruch's membrane. Mutations in the TIMP-3 gene cause Sorsby's fundus dystrophy, an autosomal-dominant inherited disease with a phenotype similar to AMD.

The K^+ channels of Müller cells have been shown to play important roles in regulating the concentration of K^+ in the extracellular space. Müller cells possess neurotransmitter transporters that contribute to neurotransmitter reuptake, glutamate recycling, and protection of neurons against excitotoxicity. In addition, Müller cells have acid/base transport systems that play a role in regulating external pH within the retina.

The *Xenopus* (African clawed frog) neurosensory retina, reduced experimentally to a single neuronal population of rod and cone photoreceptor cells, displays a persistent rhythm in the synthesis and release of the circadian hormone melatonin and in the activity of N-acetyltransferase, the rate-limiting enzyme responsible for melatonin synthesis. In the isolated intact neurosensory retina, retinal melatonin rhythms are, in turn, controlled by dopamine, which is presumably synthesized and released by amacrine cells to interact with dopamine class 2 receptors located on the photoreceptors. Recently, it has been shown that a photoreceptor-specific protein called nocturnin is encoded by



a circadian clock-regulated gene. Thus, with the *Xenopus* retina at least, a circadian clock resides within the photoreceptors. In addition, cyclic melatonin synthesis has been found in retinas of rats and hamsters.

Vision scientists continue to characterize the enzymes and transport proteins involved in the cycling and utilization of vitamin A (retinol) and its derivatives (retinoids) within the retina. This process is called the visual cycle. The retinoid 11-cis retinaldehyde is attached to a class of proteins called opsins. These opsins plus 11-cis retinaldehyde form the rod and cone photoreceptor visual pigments that trap light (photons) and initiate the visual process in the retina. The enzyme that produces 11-cis retinaldehyde from 11-cis retinol, called 11-cis retinol dehydrogenase, has now been characterized by recombinant DNA methods. This protein is found in the retinal pigment epithelium where 11-cis retinol is formed.

The characterization of proteins involved in the visual cycle has been useful for understanding the fundamental processes of retinol uptake, processing, and utilization in the retina, but it also serves the practical purpose of identifying mutations in the genes coding for these proteins. Very recently, mutations have been found in specific genes that encode for proteins involved in the visual cycle in retinal degenerative diseases.

PROGRAM OBJECTIVES

Program objectives for the next 5 years in the area of retinal diseases include both laboratory and applied research.

- Explore the pathophysiological heterogeneity of AMD to hasten development of the tools needed for improved diagnosis, prevention, and therapy.
- Investigate the pathogenesis of vascular diseases of the retina and choroid, including diabetic retinopathy, AMD, and ROP; develop better methods of prevention and therapy.

- Identify novel causes of inherited retinal degenerations; further examine the cellular and molecular mechanisms whereby identified gene defects cause retinal degenerations.
- Further develop and critically evaluate therapies involving gene delivery, growth factors, and transplantation for the treatment of retinal disease.
- Explore the cellular and molecular basis of the response to retinal injury.
- Identify the factors that dictate the unique properties of intraocular immunity and inflammation and alter systemic immunity to intraocular antigens.
- Develop diagnostic methods and therapeutic approaches that distinguish among infectious, immunopathogenic, and autoimmune posterior segment inflammation.
- Analyze the mechanisms underlying light adaptation and recovery following phototransduction.
- Study how visual information is transformed by successive layers of the neural retina and the mechanisms involved.
- Identify and characterize factors important in retinal cell fate determination and differentiation.
- Catalog, map, and functionally characterize genes expressed in the retina and choroid and begin to determine the cellular sites of retinal gene expression in health and disease.
- Probe the control of the retina's micro-environment through studies of Bruch's membrane, the interphotoreceptor matrix, the RPE, glia, choroid, and vitreous.

The needs and opportunities related to each of these objectives and the strategies for accomplishing them will now be considered.

Objective 1: Explore the pathophysiological heterogeneity of AMD to hasten development of the tools needed for improved diagnosis, prevention, and therapy.

Research Needs and Opportunities

Progress has been made in the last 5 years in different areas of AMD. It will now be important to identify the cellular, molecular, and systemic factors that are involved in the pathophysiological cascade of AMD. This can best be accomplished with a combination of approaches including epidemiology, morphology, cell and molecular biology, and genetics. In the area of molecular genetics, studies need to be undertaken to identify genes responsible for late-onset AMD using a combination of linkage and candidate gene approaches. The availability of human donor eyes affected with AMD will be extremely valuable and will create a special opportunity to identify candidate molecules involved in the pathogenesis of AMD which, in turn, can be further evaluated by genetic, biochemical, and epidemiological approaches. Developing animal models of MD, including transgenic technology, of the more prevalent forms of human AMD, will provide the opportunity to elucidate the pathophysiological mechanisms involved in AMD and will allow researchers to develop methods for interrupting or mitigating the disease process. Therapies found to be most promising in the AMD animal models should be considered for human clinical trials. Some strategies may involve genetic detection of presymptomatic individuals followed by treatment designed to prevent or delay the onset of the disease. Additional epidemiologic studies are needed to investigate the association of AMD with other systemic diseases and potentially modifiable risk factors (e.g., diet and vitamin supplements).

Strategic Research Questions

What genes are responsible for significant proportions of typical late-onset AMD? There are a number of dystrophies that affect the macula, whose heritability is undisputed. Some of these are clinically similar enough to AMD that distinction from the latter is sometimes difficult in affected persons over age 50. But, as more families with a history of late-onset AMD are identified and analyzed for genetic mutations, the greater the likelihood that genes causing this disease will be discovered.

Can animal models of the more prevalent genetic forms of human AMD be identified or developed to test the efficacy of existing or novel therapies? Both naturally occurring and transgenic animals have played important roles in understanding many eye diseases. This will certainly be true for AMD.

Can systematic genotyping be accomplished to identify high-risk groups for early detection and treatment? A variety of pathogenic mechanisms are likely to be involved in AMD, and it is unlikely that any given treatment will be effective for all of them. It is essential to develop genotyping methods to reliably subdivide patients into pathophysiologically similar groups. This will allow identification of disease-causing mechanisms in presymptomatic individuals so that specific therapy can be administered at the earliest possible stages of the disease.

What is the interplay between genetic versus environmental factors in AMD development? AMD may be precipitated or exacerbated by cumulative damage from environmental factors such as light toxicity. But it seems clear that at some point in the process, genetic mechanisms come into play. At what stage this occurs and the precipitating events that are involved will not be clarified until more is known about the interaction between genetics and the environment.

Can effective treatment strategies be developed for the most common forms of AMD? Within families with AMD there are some patients who do relatively well clinically while others do poorly. This suggests that dietary, physical, or additional genetic factors are capable of modulating the effects of the disease gene. Such modulators have the potential to be the basis of effective therapy. If modulators of the disease can be discovered, they would be effective if they altered the rate of progression of the disease by only 15 percent, making a significant number of patients asymptomatic for their entire lives.

What factors or methods can retard the growth of choroidal neovascular membranes, and can this lead to effective treatment strategies? Growth factors such as VEGF are thought to be important modulators of neovascularization. If AMD leads to growth of new blood vessels, it is important to consider growth factors as targets for treatment strategies that can slow or prevent this form of the disease.

Are there modifiable risk factors for AMD to prevent or reduce the risk or progression? Some risk factors for AMD, such as smoking, are modifiable through changes in smoking habits. There may be other factors conferring risk, such as micronutrients, behavioral, and other environmental factors, which may be amenable to modification.

Objective 2: Investigate the pathogenesis of vascular diseases of the retina and choroid, including diabetic retinopathy, AMD, and ROP; develop better methods of prevention and therapy.

Research Needs and Opportunities

Recent advances have provided the identification and characterization of factors and proteins that may play a critical role in the management of diabetic retinopathy. There is a need to test new therapeutic approaches with potentially useful agents such as VEGF neutralizing agents, inhibitors of isoform of protein kinase C (PKC), aminoguanidine, and inhibitors of aldose reductase. Collaborations between National Institutes of Health investigators and the private sector should be encouraged. Since neuron and glial cells in the retina are primary sources of vasoactive compounds such as VEGF, it will be important to understand the metabolism of these cells in diabetes. To increase the pace of discovery of genetic factors involved in diabetic retinopathy, both molecular techniques and animals models need to be developed to allow study of genetic factors involved in the disease. It is important to identify key genes and as well as the mechanisms involved in hyperglycemia. Chronic hyperglycemia is the hallmark event for the development and progression of the disease, and hyperglycemia can act through its effect on genetically controlled mechanisms. The blood-retinal barrier is often compromised in the diabetic state; therefore, it is important to undertake molecular studies of the embryonic development of the blood-retinal barrier, the molecular mechanisms of its maintenance in adult life, and its breakdown in diseased states. Since oxidative processes may be involved in diabetic retinopathy, the measurement of toxic oxidation products in tissues and evaluation of antioxidant enzymes by direct enzyme assay of small

tissue samples are needed. The preventive effects of antioxidant compounds on lesions putatively caused by toxic oxidation products need to be tested in experimental animals or in human clinical trials.

Strategic Research Questions

What pharmacological agents can be developed to prevent or cause the regression of retinal or choroidal neovascularization? Among the candidates that should be tested in the laboratory and, if appropriate, by controlled clinical trials are: VEGF isoform of PKC, aminoguanidine, and ARIs.

What is the role of tissue hypoxia in VEGF upregulation and expression? The role of tissue oxygen could be tested by a new method using magnetic resonance imaging to evaluate quantitatively retinal oxygenation.

Do smaller amounts of VEGF lead to vascular leakage and macular edema, while a larger amount produces neovascularization? Is hypoxia involved in VEGF expression in choroidal neovascularization? VEGF may have different actions solely on the basis of the amount of factor present in the tissues.

Do toxic oxidation products play a role in the pathogenesis of retinal vascular diseases? If so, can antioxidants be used therapeutically to retard this pathogenesis? Measurements of toxic products of oxidation can be carried out in tissues, and levels of antioxidant enzymes can be evaluated by direct enzyme assay of small tissue samples.

Objective 3: Identify novel causes of inherited retinal degenerations; further examine the cellular and molecular mechanisms whereby identified gene defects cause retinal degenerations.

Research Needs and Opportunities

Great strides have been made in identifying genetic defects in inherited retinal degenerations. Efforts should continue toward identifying mutations that cause retinal degeneration or dysfunction in humans by evaluating genes encoding proteins in the phototransduction cascade and other retinal-specific pathways, including the visual cycle, posi-

tional cloning, and evaluating human homologs of genes found to cause retinal degeneration or dysfunction in animals. Since the molecular tools to localize and identify mutated genes for retinal degenerative diseases are available, the genetic defects in different forms of RP have been rapidly forthcoming. Research strategies must now actively be pursued to search for the molecular mechanisms of the pathophysiology of genetic mutations in human retinal degenerations. Specific animal models and in vitro systems with gene defects homologous to those known to cause human retinal degenerative diseases will be valuable in this pursuit. Since the final common pathway for cell death has been found to be apoptosis, continuing research of the mechanisms of cell death and their role in retinal degeneration may provide clues on whether the interference of the cell death pathway is therapeutic. In addition, implementing large-scale mutation-screening technologies to genotype large cohorts of patients will permit clinical studies aimed at finding shared clinical features of patients with similar genetic defects and potentially the evaluation of gene-specific treatments.

Strategic Research Questions

What is the pathophysiology of human retinal degenerative diseases? Many mutations have been discovered in photoreceptor genes, and these have been shown to be associated with RP. As a major component of rod photoreceptor cells, rhodopsin is easily the best studied retinal protein. There are over 90 mutations in rhodopsin, but information is needed on how these mutations actually cause cellular damage.

Can human diseases that are genetically or biochemically homologous to those found in animal models be identified? Animal models form the basis for understanding disease at the most basic level, but the animal model must mimic the human disease if it is to be useful.

Can novel methods be developed and evaluated to slow the progress of retinal degeneration in animal models, and can the promising therapies be evaluated in genetically characterized sets of patients? Neurotrophic factors have been shown to slow photoreceptor degeneration in animal studies, but the reason is unclear. Growth factor therapy may be one way of slowing the rate

of degeneration in humans, but they will, in all probability, be most useful initially in genetically well-characterized patients.

What is the degree of clinical and genetic heterogeneity in different forms of RP and retinal degenerative diseases? Now that molecular genetics and molecular biology techniques are revealing the precise genetic mutations causing retinal degenerations, it is becoming clear that clinically distinct entities may overlap etiologically. Some diseases clinically categorized under a single heading are genetically heterogeneous. It is important for potential therapies to ascertain a patient's genetic status so that nutritional or pharmacologic therapy or transplantation will be most effective.

Objective 4: Further develop and critically evaluate therapies involving gene delivery, growth factors, and transplantation for the treatment of retinal disease.

Research Needs and Opportunities

Molecular etiologies of several inherited retinal and macular dystrophies have been discovered in the past decade. Studies from many laboratories have developed several promising therapeutic strategies. Neurotrophic factors are assuming increasing importance as potential therapeutic agents for retinal disease. Methods for their delivery and study of their efficacy in rescuing degenerative photoreceptor diseases need to be explored.

Similarly, gene replacement therapy for retinal disease offers great potential for ameliorating the consequences of retinal degeneration. To make progress in this area, new methods and vector systems for gene delivery need to be developed. This will require delivery systems to have: reasonable efficiency, low cytotoxicity and immunogenicity, the ability to carry a DNA-insert of practical size, and long-term passenger-gene expression.

There are other cutting-edge approaches that may be potentially useful in treating retinal degeneration. These include studies of antiapoptotic proteins as potential therapeutic agents as well as ribozymes, antisense nucleic acids, and triplex-

forming oligo-nucleotides. The latter should be studied for their in vivo efficacy using relevant animal models of human retinal disease.

Strategic Research Questions

Can combination treatments be explored that are effective in treating cell death in different forms of retinal degeneration? In several rodent animal models of RP, mutations in rhodopsin and other genes cause rapid rod cell death by apoptosis. Photoreceptors in animal models that overexpress bcl-2 have decreased apoptosis and survived environmental and genetic insults longer than cells with normal levels of bcl-2. Thus, bcl-2 appears to protect against retinal degeneration. FGF signaling appears to be associated with progressive photoreceptor degeneration, suggesting it may act as a survival factor.

What are the underlying molecular and cellular defects in retinal degenerative diseases, since understanding the basic mechanisms of retinal degeneration is critical to the development of effective therapy? Many mutations in many proteins of retinal cells have been identified and linked to photoreceptor degeneration. Most cases of RP are monotonic, but digenic inheritance of RP has been demonstrated. Apoptosis appears to be a final common pathway used by cells that are targeted to die.

Can researchers understand why the adult retina is incapable of regeneration following damage, injury, ischemia, or degenerative disease? Transplanted fetal rat retinal cells grafted into the subretinal space in the eye of light-blinded rats develop, differentiate as photoreceptors, and form synaptic contacts. In animals, when fetal RPE cells are transplanted into the subretinal space, they will survive and protect photoreceptors from degeneration.

How well do retinal transplants work (i.e., degree of visual function maintained or restored and length of survival)? Adult photoreceptors from mouse retinas can be isolated and injected into the subretinal space. These cells survive with normal-appearing synaptic terminals, but the outer segments degenerate. Other experiments have used slices of retinas or fetal retinal cells injected into the subretinal space in an effort to promote survival and rescue, all with mixed success, in part because the status of the outer segments is unclear.

Fetal or neonatal transplants do lead to maintenance of photoreceptor outer segment structure, but they have an altered morphology, appearing as “rosettes” or centrally placed photoreceptors surrounded by the remaining retinal cells.

What immunologic issues govern transplant survival in the subretinal space (immune privilege and immunogenicity of transplantation antigens)? Virtually no effort has been made to understand the immune barriers to transplantation of allogeneic and xenogeneic tissues, especially those derived from the retina, into the posterior compartment of the eye. Animal studies aimed at understanding the immunogenetic and immunologic rules of transplantation into the posterior segment are important.

What are the effects of experimental and surgical manipulations and of disease on the immunological microenvironment of the graft site? The short- and long-term immunologic consequences of transplantation into the posterior segment of the eye are unknown.

Objective 5: Explore the cellular and molecular basis of the response to retinal injury.

Research Needs and Opportunities

The process of retinal wound healing has unique molecular and cellular properties. Retinal wound healing is an ordered, albeit undesirable, process involving complex cell-cell interactions. The cellular and molecular events associated with retinal wound healing need careful evaluation to identify the key processes that are involved. Extraretinal cells may influence the retinal wound response through an array of mitogenic, chemotactic, and trophic factors. It is important to know how they interact with their receptors, initiating the migration, proliferation, and phenotypic alteration of retinal cells. In this regard, researchers need to know more about the complex control mechanisms involved in the interaction of retinal growth factors with their receptors under normal conditions and during wound healing. Since mechanical wounding of retinal cells can promote the rescue and survival of photoreceptor and other retinal cells, this mechanism should be unraveled.

Because of the difficulty of studying the retinal wound healing process in patients, the development and availability of animal models will allow the determination of the sequence of molecular and cellular events. Animal models will permit the study of regulatory molecules and provide a means of evaluating new therapies to prevent the retinal wound healing response and neovascularization. Investigating possible genetic factors involved in these diseases, with particular attention to hereditary factors, may be useful.

Strategic Research Questions

What structural, functional, and molecular interactions exist between retinal cells, especially between glial cells and neurons, in the normal retina and in retinal wound healing response? In the ocular wound healing response, cells migrate and proliferate into the subretinal space, the retinal surface, and the vitreous cavity. These cells produce a collagen matrix and avascular membranes that contain a heterogeneous population of cells.

How is the normal retinal environment regulated, and how does this environment change following retinal injury and during retinal wound healing? Cytokines such as the interleukins, interferons, and the chemokines, as well as growth factors like basic FGF, TGF, and epidermal growth factor (EGF) are thought to play some role in wound healing events. There is increasing evidence that the normal process of wound healing, including cell proliferation, migration, collagen synthesis, arachidonic acid metabolism, and angiogenesis are coordinated by a complex array of cytokines.

Why and how do retinal injuries increase the survivability of photoreceptor cells and perhaps other cells in some instances? Studies have shown that injury itself is sufficient to increase the survival of retinal cells, but the basis for this phenomenon is unclear.

What molecular factors are associated with stages of retinal wound healing events, which include gliosis, edema, fibrosis, scar formation, and neovascularization? There is a constellation of events that surround retinal wound healing, and the RPE cell appears to be an important player as a source of biologically active molecules like cytokines, chemokines, and growth factors. RPE cells produce IL-1, M-CSF,

and MGSA, and monocytes can influence the expression of multiple RPE-derived cytokines.

Can reliable animal models be developed that accurately mimic human retinal wound healing? The development of animal models that specifically mimic wound healing would hasten progress toward understanding the retinal wound response.

Can effective therapies be developed to arrest or prevent the retinal wound response in humans? Development of effective therapies will likely be dependent on a more indepth knowledge of the various biologically active molecules involved in the wound healing response. It remains to be determined which cytokines and growth factors are major players in the wound response or whether they all participate equally.

Objective 6: Identify the factors that dictate the unique properties of intraocular immunity and inflammation and alter systemic immunity to intraocular antigens.

Research Needs and Opportunities

Eye-derived immunosuppressive and anti-inflammatory factors play critical roles in ocular immunology, and there is a need to understand how they mediate intraocular immunity and inflammation. Naturally occurring molecules like defensins are important in intraocular immunity and inflammation. The intraocular cellular sources of natural defensins need to be identified, and the molecular mechanisms that enable these factors to be expressed constitutively need to be defined. The immunosuppressive, anti-inflammatory, and natural defensins that are expressed on ocular cells and are present within privileged ocular compartments need to be fully described and characterized.

Novel genetic programs that dictate the creation and maintenance of ocular immune privilege are expressed in the eye by a unique set of genes, including those encoding immunosuppressive and anti-inflammatory factors and their receptors. More information on these genes and their expression and control is needed. In this regard, transgenic animal technology should be employed and will provide an opportunity to elucidate the molecular mechanisms by which immune privilege operates.

Strategic Research Questions

What intraocular factors, soluble or membrane bound, can inhibit immunogenic inflammation within the eye and enable ocular antigens to create a systemic immune-deviant response? The eye is one of several specialized organs or tissues that display immune privilege (i.e., sites that permit foreign tissue grafts to enjoy prolonged survival). Immune privilege is an active rather than a passive process, and knowledge of its molecular basis will facilitate understanding of the underlying mechanism.

Which ocular cells produce intraocular factors, and what is the nature of gene regulation that enables their constitutive production? The microenvironment within the eye contains important immunomodulatory molecules that alter the manner in which ocular antigens are first perceived by the immune system. It also modifies the extent to which immune effectors can mediate protection in the eye.

How do intraocular factors interact with lymphoreticular cells and vascular endothelial cells to regulate the expression of immunity and inflammation within the eye? Immunomodulatory factors within the eye interact with target receptors on the cell surface to regulate immunity. One important mechanism by which immune privilege molds the systemic immune response is by promoting antigen-specific tolerance among peripheral T-cells.

What are the cellular and molecular mechanisms that enable antigenic signals arising from the eye to induce systemic immune deviation? Antigens injected intraocularly have a significant impact on the systemic immune response. One expression of that impact is the emergence of regulatory cells in the spleens of recipients.

Can the principles of immune privilege and immune deviation be used to influence the course of ocular inflammatory and immune diseases? One important mechanism by which immune privilege molds the systemic immune response is by inducing or prompting antigen-specific tolerance among peripheral T-cells. At least four mechanisms are considered relevant to privilege related tolerance: clonal selection, clonal anergy, immune deviation, and suppression.

Objective 7: Develop diagnostic methods and therapeutic approaches that distinguish among infectious, immunopathogenic, and autoimmune posterior segment intraocular inflammation.

Research Needs and Opportunities

Posterior segment intraocular inflammation is an important cause of blindness and can display distinct clinical features. Fundamental knowledge on the extent to which infectious, immunopathogenic, and autoimmune processes interact in producing ocular inflammation is needed. Experimental autoimmune ocular inflammation is a convenient model for the study of ocular inflammation, and the molecules that can induce this condition need to be characterized. The genes that contribute to the susceptibility and resistance to ocular inflammation and that are induced by immunization with ocular autoantigens also need to be identified.

The two major impediments to understanding the pathogenesis of posterior segment intraocular inflammation and for developing treatment and prevention strategies are: (1) lack of knowledge concerning the etiologic factors that cause the disease, and (2) inability to sample the inflamed eye for accurate diagnosis and evaluation of disease status. In many cases it is unclear whether the inflammation results from infectious, immunopathogenic, or autoimmune processes. Information is needed on the extent to which these three pathogenic events interact in producing ocular inflammation. Technical barriers to invasive procedures for acquisition of tissue and fluids for analysis should be overcome and will provide an opportunity to learn more about infectious agents and inflammation-producing immune effector cells and molecules. Opportunities to develop diagnostic approaches and criteria to distinguish among these infectious, autoimmune, and immunopathogenic mechanisms of ocular inflammation will result from these investigations.

Strategic Research Questions

What molecules uniquely expressed in the posterior segment of the eye can function as autoantigens in the pathogenesis of uveitis? Experimental autoimmune ocular inflammation has

been an effective model for the study of ocular inflammation. Immunodominant peptides derived from retinal autoantigens have been identified and shown to induce uveitis. The function of these molecules in the pathogenesis of the disease needs to be elucidated.

What immune effectors (T-cell subsets, types of antibodies, effectors of innate immunity) trigger and participate in inflammation in the posterior segment of the eye? How is inflammation in the posterior segment of the eye triggered? To what extent do silent or unsuspected infections within the eye or extraocular processes act as triggers? What are the offending pathogens? The fundamental mechanisms on triggering the inflammation response in the eye are not known. Recent experimental evidence has shown the involvement of effectors and mediators. The role of T-cells as the primary initiator of inflammation needs to be further investigated.

Which polymorphic host genes confer susceptibility and resistance to inflammation of the posterior segment of the eye? Do these genes encode proteins involved in the adaptive immune response? In the innate immune response? The specific genes and genetic mechanisms involved in both susceptibility and resistance to inflammation need to be identified. Emerging molecular immunological technology will aid in this search.

Which proinflammatory mediators, cytokines, and chemokines mediate intraocular inflammation? The observations concerning mediators in the eye need to be expanded to identify both the mediators and the specific intraocular cells that release these mediators. Mediators can be identified by means of a variety of methods, including *in situ* hybridization.

Can samples of intraocular fluids or tissues and cells be obtained for evaluation of the etiology and pathogenesis of intraocular inflammation? The ability to obtain a sample of an ocular tissue or fluid will serve both to identify the infectious agent for accurate diagnosis and treatment and to evaluate the pathogenesis of the posterior segment inflammation. Advances in surgical procedures for invasive procedures, coupled with sensitive molecular probes, will allow infectious causes and immunopathogenic processes to be sorted out.

Objective 8: Analyze the mechanisms underlying light adaptation and recovery following phototransduction.

Research Needs and Opportunities

During the past decade, biochemical, molecular biological, physiological, and structure-function studies have produced a detailed understanding of the phototransduction cascade. Explorations have established the molecular description and key components of the pathway. Although the activation limb of phototransduction is now fairly well understood, inactivation is less so. There is a need to understand the detailed molecular mechanism by which both rod and cone photoreceptors recover to their dark state following the photoexcitation. The detailed mechanisms for the termination and recovery phase of the photoresponse in photoreceptors cells (rods and cones) need to be determined. In addition, the control of reactions responsible for light adaptation in photoreceptor cells and feedback pathways from horizontal cells need to be defined.

To solve this problem, the mechanisms by which photoreceptors adapt to different light intensities must be discovered. This will require a more indepth study of the role of calcium and regulatory reactions, such as protein phosphorylation and protein-protein interactions in individual steps in the visual transduction pathway. The relationship of adaptation mechanisms in photoreceptors to adaptation mechanisms in other retinal neurons also needs to be understood. New, emerging molecular and physiological technologies will provide unique opportunities to identify and characterize the function of novel proteins that are involved in recovery and adaptation reactions. The various proteins and reactions that mediate the photoresponse in cone cells should be identified.

Understanding the cone photoresponse at a molecular level will provide insights into the molecular basis for differences in light sensitivity, response, and recovery of rod and cone photoreceptors. Analyzing the components and mechanisms of phototransduction and light adaptation in cone cells should shed new light on the molecular basis for differences in the phototransduction and adaptation in rod and cone photoreceptors.

Strategic Research Questions

Can current and newly emerging techniques in molecular and cellular biology, biochemistry, physiology, and biophysics be used to enhance scientists' understanding of phototransduction, recovery, and light adaptation? The current task is to elucidate the mechanisms of recovery and light adaptation. The identification of components and mechanisms is mandatory to understanding the detailed molecular basis of visual transduction.

What novel proteins and mechanisms related to phototransduction and adaptation in rods and cone cells remain to be identified? Additional components are needed to account for the termination of the visual signal and for adaptation. Several components have been identified and set the stage for studies that will determine how they participate in the process. Highly sensitive molecular biology and biochemical techniques (i.e., protein expression systems) can be used to characterize these proteins and elucidate their role in the photoresponse.

Can high-resolution structural analysis be used in conjunction with mutagenesis and gene expression to provide detailed information about the important functional domains of proteins, sites of protein-protein interaction, and reaction mechanisms involved in phototransduction, recovery, and adaptation? Biophysical analysis coupled with molecular biological technology is now an exciting tool for exploring the molecular attributes of function. Such information should provide not only a detailed description of the mechanism of the photoresponse but also be valuable for assessing how mutations in these proteins can affect the function of photoreceptors and cause photoreceptor degeneration.

Objective 9: Study how visual information is transformed by successive layers of the neural retina and the mechanisms involved.

Research Needs and Opportunities

Understanding how visual information is processed as it transverses through successive neural layers of the retina is critical to elucidating retinal circuitry and identifying key levels at which therapeutic

intervention may be possible. Work on processing of information by retinal neurons should exploit recent technical advances and move beyond descriptive studies. It is now possible to record from many mammalian retinas, including those of primates, under visual control. This allows selection of the neuron to be studied and identification of its shape and connectivity after characterization of the physiological behavior. New coding of visual information within ganglion cells needs to be determined. The temporal shaping of visual information of retinal ganglion cells should be elucidated. Further technical work should extend these *in vitro* capabilities, particularly in the arena of isolated and cultured cells and whole retinas. New methods for recording from the retina should be extended, including the use of multielectrode arrays and optical indicators of neuronal activity. Physiological, anatomical, and molecular analysis of the transmission of color information in higher vertebrates should be continued.

The biophysics of the retina's ribbon synapses and multisynaptic complexes needs to be understood. The pattern of neural connectivity among the cells should be determined. The activity of the different retinal synapses needs to be understood at a molecular level. In addition, their complements of neurotransmitter receptors and ion channels must be characterized, as it is now clear that each cell class has its own array. These should be studied by both molecular and physiological methods. The role of gap junctions needs further exploration. The search for genes expressed selectively in subclasses of retinal neurons should be pursued, as should methods of controlling the expression of specific genes in targeted retinal neurons.

Strategic Research Questions

What are the transformations of the visual input that occur within each of the retina's neural layers? With the cataloging of neurotransmitters nearly complete, newly emerging molecular and cellular biological techniques must be applied to discover the fundamentals of retinal circuitry and neurotransmitter function. In parallel with the emphasis on the molecular properties of retinal neurons, the way that these cells work together to process visual information must be discovered.

Can optical and electrophysiological methods of multineuronal recording be extended to study retinal interneurons? A multidisciplinary approach must be taken to reveal and understand the fundamental processes of normal retinal function. The multiple recording techniques are powerful because recording simultaneously from many cells is more efficient than studying them one at a time. Important information on waves of retinal activity is emerging that may help the brain "wire" itself correctly during early development.

How does the synaptic connectivity of the neurons control the visual transformations that are accomplished? The basic connectivity, pharmacology, physiology, and cell biology of both the rod and other specific synaptic pathways must be investigated. Determining the regulation of neuromodulators on functional and structural connectivity of cellular pathways in the retina is important.

What are the neurotransmitter receptors and ion channels on each of the retina's cell types? The diversity of retinal functions requires multiple types of neurotransmitter molecules and receptors. A great deal of information has been obtained on the identification and localization of neurotransmitters and their receptors. Additional emphasis must be placed on the investigations of how neurotransmitters and their receptors exert their specific actions. Identifying the ion channels and their specific role in transmitting visual information in the retina is of particular interest.

What role in visual processing is served by the retina's ribbon synapses, multisynaptic complexes, and gap junctions? The regulation of the number and function of gap junctions in retinal neurons and the role of ribbon synapses must be explored using multifaceted approaches, thereby extending the anatomical identification.

Can molecules and their function, specific to individual types of cells or synapses, be identified? Can cell-specific molecules (or whole classes of cells) be modified or manipulated by genetic techniques in a way useful for dissecting retinal function? Retinal neuroscience can capitalize on the development of molecular technology for probing cellular functions. Molecular probes will continue to be useful in identifying the presence of specific molecules in the neural retina and in localizing the molecules within cells.

Objective 10: Identify and characterize factors in retinal cell fate determination and differentiation.

Research Needs and Opportunities

Researchers currently do not know how many types of progenitor cells exist, or how their properties might contribute to the genesis of different cell types. They do not know if there are any “stem cells” in the retina that could be exploited for transplantation therapies. The different types of progenitor cells need to be identified and described.

Studies on signaling mechanisms in cell fate determination using both cell culture systems and analyses *in vivo* need to be emphasized. Culture systems that allow assay of factors on both cell fate determination and differentiation have been developed in the past, but they need to be expanded and made more sophisticated. For example, many studies have examined rod photoreceptor development, but very few have examined cone development. Potential extrinsic cues that affect development will be identified.

Systems amenable to genetic analysis are invaluable for *in vivo* studies of signaling pathways such as the EGF, Hedgehog, and Wingless signaling pathways. Important questions are how the signaling pathways are integrated and used in cell fate decisions in the eye. Animal models such as *Drosophila*, zebrafish, *Xenopus*, and mouse each offer a different set of advantages and disadvantages for studies of function *in vivo*. Knockouts, particularly conditional knockouts, and transgenic mice should prove to be critical for these studies. When researchers have made progress in understanding the progenitors and know more about the extrinsic cues that affect them, they will be in a position to use this information for transplantation therapies.

Very little is known about how retinal cells adopt their final cell shapes, structures, and polarity. Studies on the roles of membrane biogenesis, integrins, microtubules, actin, myosin, protein targeting, and transport in photoreceptor cell morphogenesis should be emphasized. In addition, mechanisms that regulate the proliferation of retinal precursor cells and subsequently lock them in a postmitotic state when they differentiate are poorly understood.

Understanding these mechanisms is of obvious significance to developmental processes and to many human retinal diseases. The adult retina is incapable of regeneration following damage, injury, ischemia, or degenerative disease.

Strategic Research Questions

What are the properties of progenitors that contribute to the genesis of different cell types? Are there totipotent stem cells in the retina that could be exploited for transplantation therapies? Can mechanisms that regulate the proliferation of retinal precursor cells and subsequently lock them in a postmitotic state when they differentiate be understood? Visual system development involves the production and specification of individual neurons and glial cells that are necessary for assembling the retina. Intrinsic and extrinsic cues that affect development should be identified. Molecular and cellular biological techniques provide powerful tools for dissecting mechanisms of retinal developmental events.

Can tissue-culture systems be developed and expanded that allow assay of factors on both cell fate determination and differentiation, especially for cone development? By applying growth factors, small molecules, and other secreted gene products to cells grown *in vitro*, cell biological screens can be conducted. The types of effects assayed *in vitro* include changes in cell fate, effects on differentiation, and effects on survival. Perturbation of expression or function of molecules with effects *in vitro* can then be expanded to *in vivo* studies.

Can systems amenable to genetic analysis of development, such as *Drosophila*, zebrafish, and *Xenopus*, be pursued? The overall strategy of retinal cell fate determination and differentiation is the same in the vertebrate and *Drosophila* retina, as are many of the molecules employed. For example, the extracellular receptor Notch, and its ligand Delta, are crucial for the development of all retinal neurons in *Drosophila* and vertebrates.

How do retinal cells adopt their final cell shapes, structures, and polarity? Retinal cells have remarkable structure, shape, and polarity. Fundamental retinal processes that both create and maintain retinal organization are unknown.

A detailed understanding of the components and mechanisms that play a role in retinal organization will lead to insights in both the normal and the degenerative retina.

Can cell-specific markers be developed and used to stage the differentiation pathways of each cell type? Antibodies and molecular probes specific for receptors and proteins that may be involved in retinal developmental stages have enormous potential for sorting out differentiation pathways. Genes that are expressed in specific cell types can be used as a basis for making antisera for rapid identification and manipulation of different cell types.

Can animal models (i.e., knockouts, particularly conditional knockouts and transgenic mice) be used specifically for providing critical information on the molecular mechanisms of retinal development? Animal models will provide an opportunity to study retinal development *in vivo*. For such studies, it would be helpful to have reagents for manipulating gene expression in the retina. For example, promoters that could be regulated to control the onset of expression of genes and strains of mice with reporter genes for identifying particular cell populations would be important tools for understanding the molecular mechanisms involved in retinal development.

How are the signaling pathways integrated and used in cell fate decisions? Cell culture and *in vivo* systems are available for studying signaling mechanisms. Studies on rod developmental pathways need to be expanded to include cone development and may include developing more molecular markers to identify cell types.

Objective 11: Catalog, map, and functionally characterize genes expressed in the retina and choroid and begin to determine the cellular sites of retinal gene expression in health and disease.

Research Needs and Opportunities

The opportunity to identify all genes expressed in the retina and choroid is now possible through resources developed by the Human Genome Project and related projects for other systems. Determining this complete set of genes and their cellular location

and specificity is critical for understanding retinal structure and function and the cellular interactions during development. It will be possible to map retinal disease genes in specific animal models of human retinal diseases and map human retinal diseases for which there are families of a significant size. The mapped genes can be evaluated that are specific to the retina or choroid as candidate genes for disease.

The next step will include determining the cellular specificity of genes expressed in the retina or choroid and determining the changes in gene expression that occur as a result of disease. It is important to begin to functionally characterize these retinal and choroidal genes to further understand the relationship of their physiology to human disease.

Strategic Research Questions

Can genes expressed in the adult retina and at key developmental times be identified through analysis of normalized cDNA libraries? The retina and choroid offer an ideal set of tissues to identify genes expressed in development and in the adult. It is straightforward to isolate for the preparation of cDNA libraries from different stages. The opportunity to identify all genes expressed in the retina and choroid is now possible through resources developed by the Human Genome Project and other related projects.

Can cDNA libraries from critical retinal regions, such as the macula and ciliary margin, be prepared and used for identifying unique genes and their function? cDNA libraries are being prepared and sequenced in several laboratories. The cataloging of which genes are expressed in what cells will be challenging, and emerging technologies will be useful. Current technologies for mapping sites of gene expression, including immunohistochemistry and *in situ* hybridization, are expensive and time consuming to perform for the many genes that will need to be characterized.

Can ESTs that appear to be unique to the visual system or that have hallmarks of genes that are good candidates for visual system disease be mapped and used as candidate genes for retinal diseases? The availability of ESTs specific for the visual system may provide a valuable tool for identifying genes that are responsible for retinal degenerative diseases. The genetic mapping of the ESTs will be necessary.

Can genes responsible for human retinal disease and development be functionally characterized to elucidate molecular mechanisms of retinal diseases? Can emerging novel technologies, including DNA chips, be employed to provide the best methods for this goal? The mechanism by which a gene identified as the diseased gene results in retinal degeneration is critical to the application of this information to patients with retinal degenerative diseases. Taking advantage of recent technological advances to develop new research strategies should be incorporated in all molecular and cellular approaches, if applicable.

Objective 12: Probe the control of the retina's microenvironment through studies of Bruch's membrane, the interphotoreceptor matrix, the RPE, glia, choroid, and vitreous.

Research Needs and Opportunities

Studying the production, maintenance, and turnover of Bruch's membrane and the interphotoreceptor matrix is important to understanding the normal, healthy retina and its interaction with its microenvironment. The basic biology of the vitreous, including its development and changes in aging, need to be studied. Researchers also need to determine how proteases and protease inhibitors are involved in the aging process of Bruch's membrane, photoreceptor sheaths, and vitreous. The roles of paracrine factors in the function and survival of retinal neurons must be clarified, which includes the mechanisms by which light-induced, circadian, and pathological changes in the concentrations of ions, neurotrophic factors, neuromodulators, and enzymes in the extracellular spaces of the retina affect the physiology and survival of retinal neurons, RPE cells, and Müller cells. In addition, a better understanding of factors produced by the RPE and other retinal and choroidal cells that inhibit neovascularization must be gained. A thorough investigation of the role of Müller and RPE cells in retinoid uptake processing, release, and transport into and within the retina will be critical to understanding the maintenance of the normal retina. This should include the development of a better understanding of the morphogenesis and physiology of Müller cells and astrocytes, particularly the regulation of the ionic and neurotransmitter content of the retinal and subretinal extracellular space, establishment

and maintenance of polarity, extracellular and intracellular signaling mechanisms, metabolic support of retinal neurons, intercellular coupling, and identification of secretory products. The mechanisms for the specific morphology and physiology of the RPE need to be better understood, particularly with regard to blood-retinal barrier selectivity, maintenance of cell polarity, phagocytosis, RPE phenotype plasticity, metabolism, and signaling mechanisms. In addition, a complete understanding of all unidentified or uncharacterized proteins involved in the uptake, processing, transport, and release of retinoids by cells of the retina should be undertaken.

Strategic Research Questions

What are the cellular sites for the synthesis of the molecular components of Bruch's membrane and the rod and cone outer segment sheaths? An intricate network of macromolecules and components completely surround the RPE/neural retina and may play a role in regulating the behavior of the surrounding cells. Once the components are identified, cell biological techniques could be employed to investigate their synthesis.

Can Müller cells and retinal astrocyte cocultures be developed for electrophysiological analysis of interactions between these cells? It will be necessary to develop cocultures that actually express the same characterization as cells *in vivo*. Well-defined *in vivo* systems may provide the first step in characterizing the transporters, receptors, and other genes expressed by Müller cells.

Can the roles of genes in the development and differentiated functions of RPE cells, Müller cells, and retinal astrocytes in their normal environment be examined? Emerging transgenic technologies can be exploited to sort out the specialized functions of the cells surrounding the retina, such as transepithelial flow of ions and nutrients in the RPE.

Can trophic factors and their receptors synthesized by Müller and RPE cells be identified and characterized? The viability of the retinal structures relies on the components secreted by the cells that establish the intercellular matrices. Cellular biological technology should be exploited to identify the trophic factors involved, and their role in the development and morphogenesis of neural retina should be determined.

Can the roles of Müller and RPE cells in paracrine signaling be characterized? The RPE's response to paracrine factors and details of the signaling pathway need to be understood. By applying electrophysiological and molecular methods, the identity of the specific factors and retinal targets involved may be discovered.

Can the remaining, unresolved components of the visual cycle be characterized so researchers can develop a complete understanding of this process and its role in inherited retinal degenerations? What is the role of Müller cells in the processing and recycling of retinoids? The enzymes and proteins of the visual cycle continue to be characterized. Molecular dissection of the pathway will be necessary to fill in the details of the visual cycle and may serve to provide molecular probes for identifying mutations in genes coding proteins of the visual cycle. The role of Müller cells needs further clarification.

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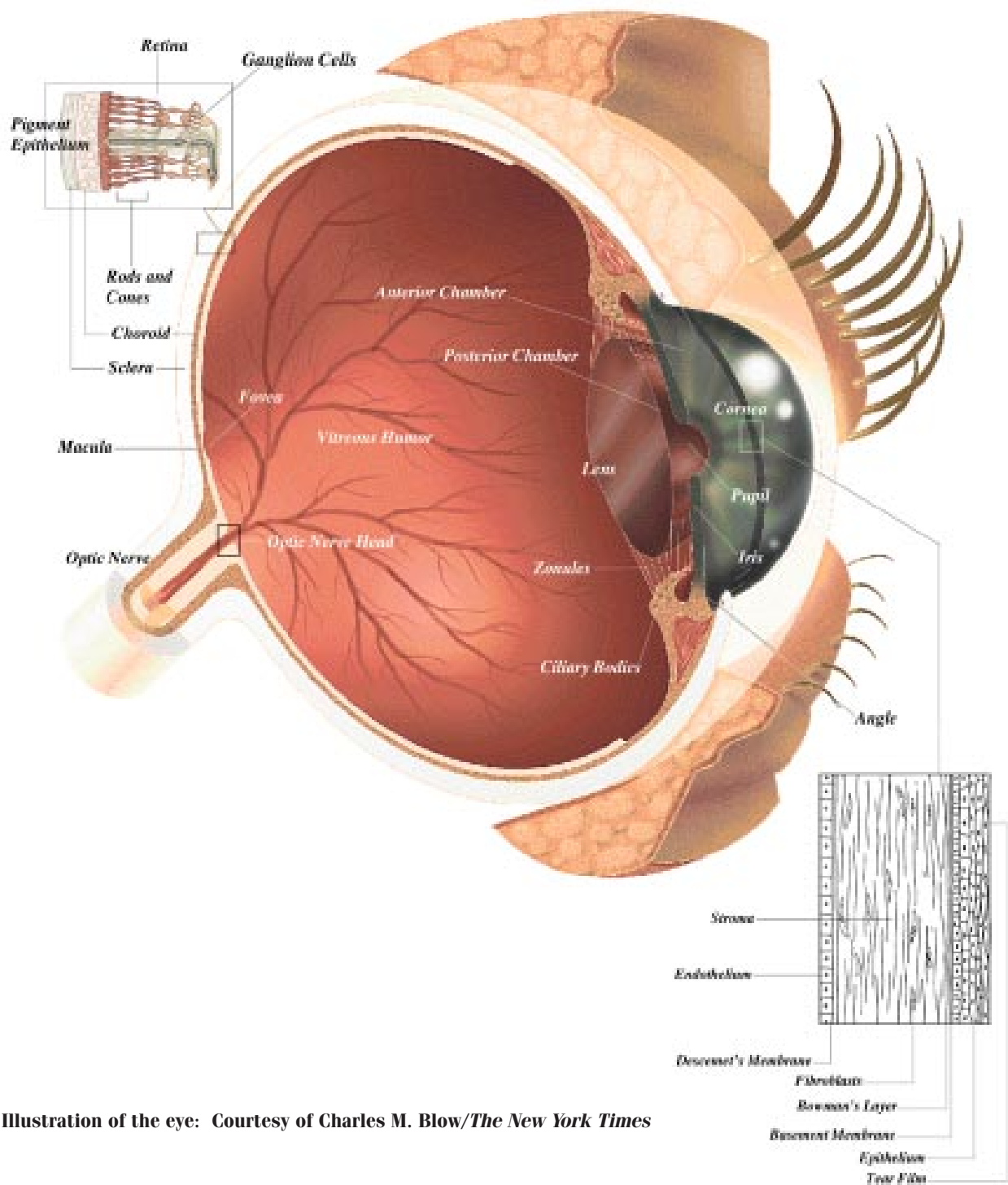


Illustration of the eye: Courtesy of Charles M. Blow/*The New York Times*

PROGRAM OVERVIEW AND GOALS

The cornea is the transparent convex tissue at the front of the eye (Figure 1 on the facing page) that serves two specialized functions. First, it forms, with the sclera, a protective physical barrier that shields the inner eye from the external environment. Equally important is its ability to protect itself from various types of damage, ranging from physical trauma and biochemical injury to infections by myriad pathogenic organisms, to the deleterious effects of long-term exposure to light itself. In protecting itself, the cornea also safeguards many underlying ocular structures from similar damage. Second, the cornea serves as the main refractive element of the visual system, directing incoming light onto the crystalline lens, which focuses it onto the retina. Refraction depends on the cornea acquiring transparency during embryonic development and maintaining it throughout adult life.

Although the cornea, which continues laterally with the layers of the sclera, appears to be one clear membrane, it is composed of several discrete layers (Figure 2 on the facing page):

Conjunctiva—This is the thin, flexible layer of tissue covering both the inner surface of the eyelids and the sclera (the white of the eye). Its elasticity contributes to the ease of eye movements; its goblet cells contribute to the tear film by producing mucus; it heals rapidly with little formation of opaque scar tissue.

Tear film—The liquid tear layer bathing the cornea and conjunctiva performs optical, protective, and lubricative functions. It creates a perfectly smooth liquid outer layer that polishes the corneal surface, mechanically traps and flushes out foreign bodies and chemicals, contains bacteriostatic substances that inhibit the growth of microorganisms, and reduces the surface friction associated with eyelid blinking and eye movement.

Corneal epithelium—

This is a renewable, transparent tissue that, along with the tear film, forms a refracting optical surface. It is the only corneal tissue that is innervated and can signal pain. Like all epithelia, it presents a barrier against the external environment, with intercellular junctions that prevent invasion by pathogens. The epithelium usually must be damaged before an infectious agent can become established.

Corneal stroma—This layer of connective tissue, composed of extracellular matrix molecules and collagen fibrils, is responsible for the strength and shape of the cornea. Although other collagenous structures in the body are opaque (such as cartilage or skin), the corneal stroma is transparent. It is constructed from lamellar collagen fibrils that are small, uniform diameter, and equidistant. Some proteoglycans (PGs) and collagens are unique to the cornea, as is the total lack of blood vessels.

Corneal endothelium—The main physiologic function of this thin inner layer is water transport. Corneal transparency hinges on the precisely controlled hydration required to maintain the stromal matrix structures in their correct spatial organization. The endothelium forms a barrier from the aqueous humor, based on the tight junctions and gap junctions between individual cells, and it maintains a fluid pumping mechanism controlled by a membrane-associated enzyme (Na^+, K^+ -ATPase) that transports excess water out of the stroma. Without this pumping action, the stroma would develop edema, becoming swollen with water and cloudy. The human corneal endothelium has no regenerative and only limited repair capabilities. If endothelial cells are destroyed by disease or trauma, the remaining cells must enlarge and migrate to maintain function. When sufficient endothelial cell loss occurs, corneal edema and blindness ensue, with corneal transplantation as the only available therapy.



In this country, corneal diseases and injuries are the leading cause of visits to eyecare clinicians. These are also some of the most painful ocular disorders. These facts alone underscore the need for laboratory and clinical research aimed at improving treatment for or preventing these diseases and injuries. Corneal problems result largely from the cornea's location as the outermost structure of the eye, but genetic disorders also contribute. Laboratory and clinical research performed during the last 5 years—largely funded by the National Eye Institute (NEI)—has made great progress in understanding and treating corneal disorders. Researchers now know many of the molecules involved in transparency and how these function. They know the origin of the cells that continuously replace those of the corneal epithelium. They also know some of the factors that may be involved in the cells' regulation, which has allowed for the amplification of these cells in culture. This knowledge has recently been applied to restoring the human corneal surface with cells grown from the patient's own eye. This has resulted in treatment for certain conditions that previously resulted in blindness. Procedures such as grafting of placental membrane or corneal limbal epithelial stem cells have aided epithelial healing in other difficult situations.

Research on the cornea has also developed knowledge that can be applied to problems in other organ systems. For example, the cornea has long been known to be favorable for transplantation, and this procedure has become routine. Studies on the properties of the eye that make the cornea such a "privileged" immune site raise the possibility that this property can be conferred to other tissues, thus facilitating the transplantation of other organs. Studies on the molecular structure of collagen fibrils in the corneal stroma have not only provided basic information on the assembly of this tissue, they have also contributed insight into certain developmental defects of the skeletal system and blistering diseases of the skin. Moreover, since the cornea is constantly exposed to ultraviolet (UV) light and oxidative stress, it has provided information on ways that cells can protect themselves from this damage (such as the production of antioxidative enzymes and nuclear ferritin). These mechanisms could provide ways to protect other cells and organs from similar environmental insults.

In Fiscal Year 1997, the NEI funded 179 extramural research projects in the Corneal Diseases Program at a total cost of \$38,610,000. These projects covered six broad areas:

Physiology. These grants are devoted to increasing understanding of fluid and ion transport processes in the cornea and conjunctiva that affect transparency and wound healing. Research was also conducted on the structure and physiology of the tear film and ocular surface to develop rational treatments for dry-eye conditions.

Cell Biology. This area of research supports investigation of corneal growth, development, and wound healing.

Genetics. These projects study corneal gene expression, inheritance of corneal dystrophies, and identification of genes encoding risk factors for the development of corneal anomalies.

Immunobiology. This section supports studies of the etiology of ocular immune privilege and the corneal immune response, corneal transplantation, the nature and regulation of corneal inflammation, and the role of immune cell subpopulations in ocular disease.

Infectious Diseases. Work in this area focuses on the pathogenesis, diagnosis, and treatment of disease caused by potentially blinding agents such as viruses (particularly herpes simplex virus), bacteria, and parasites, and on conditions such as adenoviral epidemic keratoconjunctivitis (commonly known as pink eye), which are associated with very high morbidity and economic costs.

Correction of Refractive Error. Approximately 60 percent of Americans have refractive errors or defects in the ability of their corneas to focus light, which could be corrected to give them sharper vision. This subprogram supports projects to understand the topographic and biomechanical properties of the cornea that result in a normal refraction, to understand the biological effects of contact lens wear on the cornea, to develop instrumentation to measure and correct refractive error, to understand the response of the cornea to refractive surgery, and to investigate the epidemiology of refractive error in the American population.

Thus, the overall goal of the Corneal Diseases Program is to:

Understand the normal function of the cornea and apply this knowledge to the prevention and treatment of traumatic injury and disease.

ASSESSMENT OF PROGRESS

Molecular mechanism of corneal fluid transport. The eye contains a large mass of water and is composed of several specialized cell tissue layers that have fluid movement at the core of their function. The cornea possesses two such layers: the endothelium, which covers the internal side of the cornea, and the epithelium, which covers its external face. Corneal transparency hinges on a precisely controlled degree of hydration that is required to maintain corneal matrix structures in their correct spatial orientation. Although it is known that transport mechanisms present in the endothelium are responsible for corneal dehydration and transparency, details on the coupling between electrolyte transport and water movement have been elusive. The driving force for fluid transport is the osmotic gradient created by the transport of solutes, and it has long been recognized that cell membranes contain specialized structures, or pores, which provide selective passage for water molecules, but the details of solute-solvent coupling have remained obscure.

In the great majority of epithelia, the energy for water transport is derived from the operation of an $\text{Na}^+:\text{K}^+$ pump that, either directly or through activation of secondary transporters and ion channels, produces the appropriate osmotic environment. Although similarities exist between fluid transport among epithelia of various organs, each one presents a particular challenge to the investigator. In epithelial layers the cells are polarized so that the properties and elements of the basolateral and apical membranes are different. Thus, electrolytes and water must cross two distinctive membranes during transepithelial movement. This, and the multiple layers of cells in the corneal epithelium and conjunctiva, represent additional degrees of complexity in the study of these ocular membranes.

A recent major advance in the study of corneal fluid transport has come from the discovery of the aquaporin (AQP) family of water channel or pore proteins. There has been an explosion of work to identify, clone, and sequence the AQP genes; to localize individual transporters; and to determine their function. Other membrane-spanning proteins such as the glucose transporter and K^+ channel proteins exist in sufficient abundance that they might also contribute to the transcellular water movement. The lipid bilayer of the cell membrane also allows a substantial flow of water, but unlike protein channels, the bilayer is less susceptible to solute interaction and regulation.

To date, seven AQPs have been identified and cloned using techniques of molecular biology. AQP-0, which exhibits a lesser degree of water permeability than other family members, is known to be the major intrinsic protein of lens fiber cells. AQP-1 (a small channel-forming integral membrane protein) has been found in various ocular epithelia including the iris, ciliary body, and lens, and is constitutively expressed in the corneal endothelium. AQP-3, which may also transport glycerol, is found in the conjunctiva. AQP-4 is abundant in retinal Müller cells and in the brain, where it appears to function in cerebrospinal fluid absorption. AQP-5 is observed in the secretory lobule of the lacrimal gland and in the corneal epithelium. AQP-5 exhibits a structural feature similar to that in AQP-2, which is now recognized as a critical water-transporting element in the collecting duct of the kidney. AQP-6 is found in the retinal pigment epithelium.

Corneal dystrophies. The corneal dystrophies are a heterogeneous group of conditions that involve abnormal corneal development and result in defects in structure or clarity. These diseases are usually inherited and do not affect other parts of the body. They may begin early in life, but can also manifest with age.

The most common corneal dystrophy in the United States is keratoconus, a progressive thinning process that may be accompanied by scarring. Keratoconus leads to progressive nearsightedness, astigmatism, and a cone-shaped cornea. It has been estimated to occur at a rate of 1 in 2,000 people in the general population. Clinical care for keratoconus is time consuming for patients and doctors because of its chronic progression and the

difficulty of achieving a stable contact lens fit for visual rehabilitation. Keratoconus is the most frequent reason for penetrating keratoplasty in the Western world, and it accounts for \$50 million to \$100 million a year in medical care costs in the United States.

Keratoconus has become better understood during the last 5 years through investigations into the genetic predisposition for the disease, detection of early forms of the disorder through computerized topographic analysis, initiation of an NEI-funded prospective assessment of the progression of the disease (the Collaborative Longitudinal Evaluation of Keratoconus Study or CLEK), and advances in understanding the enzymology that underlies corneal thinning. Diagnosis of the disease may become more certain in the future through the application of noninvasive tests and refinements in corneal topographic analysis. Numerous corneal topography and contact lens innovations are also being introduced to assist in diagnosis and treatment.

Recent biochemical investigation into the pathogenesis of this disorder suggests that the loss of corneal stroma could result from either increased levels of proteases and other catabolic enzymes or decreased levels of proteinase inhibitors. Studies of corneal α -1 proteinase inhibitor and α -2 macroglobulin support the hypothesis that degradative processes may be aberrant in keratoconus. Both inhibitors are markedly diminished in the epithelium of keratoconus corneas.

These biochemical observations may merely reflect a more generalized keratocyte abnormality in keratoconus, since proteinases are released upon cell death from apoptosis (a regulated program of cell death). Compared with normal corneal keratocytes, those from keratoconus corneas have a fourfold greater number of cell surface receptors to the cytokine interleukin-1 (IL-1), an inducer of apoptosis. This increased receptor expression may sensitize keratocytes to IL-1-induced apoptotic death. This hypothesis is consistent with the relationship between keratoconus and eye rubbing, contact lens wear, and allergic hypersensitivity, as trauma could lead to an increased release of IL-1 from the epithelium.

The literature strongly suggests genetic influences in the pathogenesis of keratoconus, including family clusters, twin studies, bilaterality, and the symmetry of topographic alterations between eyes of individual patients. Although recent family studies suggest an autosomal dominant mode of inheritance with variable expression, additional genetic analyses are required to accurately define the role of genetic influences. Studies of families that demonstrate clear inheritance patterns could provide new insights into the pathogenesis of this disorder.

Genetic study of afflicted families has recently yielded new insight into the pathogenesis of other, rarer inherited corneal dystrophies (see Table 1 below).

Table 1. Gene mapping of corneal dystrophies and disorders

<i>Corneal disease</i>	<i>Gene locus</i>
Rieger's Anomaly (iridocorneal mesodermal dysgenesis)	4q
Avellino, lattice type I, Reis Bucklers', and granular dystrophy	5q31
Groenouw type I (keratoepithelin protein)	
Lattice type II dystrophy	9q34
Thiel-Behnke dystrophy	10q23-q24
Peter's Anomaly (Pax-6)	11p
Cornea plana	12
Meesmann's corneal dystrophy (keratin K3, K12)	12q and 17q
X-linked megalocornea	Xq
Fish-eye disease (x-lecithin: cholesterol acyl transferase)	16
Posterior polymorphous dystrophy	20

Linkage analysis has shown that four clinical types of corneal dystrophy result from mutations in a single gene. Granular, Reis Bucklers', lattice type I, and Avellino corneal dystrophies all map to the β ig-h3 gene, which encodes the keratoepithelin adhesion protein. It appears that in these four corneal dystrophies, the mutated keratoepithelin forms amyloidogenic intermediates that precipitate in the cornea, causing a progressive opacification. Three other corneal diseases also involve amyloid-like deposits: polymorphic amyloid degeneration, lattice corneal dystrophy type IIIA, and gelatinous drop-like dystrophy. Keratoepithelin is a good candidate gene for further investigation in these families. Because of the accessibility of the cornea, these disorders represent excellent model systems for study of the molecular details of amyloid deposition in devastating diseases such as Alzheimer's disease.

Several other corneal dystrophies are being explored through genetic studies. Meesmann's corneal dystrophy, in which the cornea accumulates numerous small, round, debris-laden intraepithelial cysts, has been shown to be associated with defects in the cornea-specific keratin K3 or K12 genes on chromosomes 12 and 17. Posterior polymorphous corneal dystrophy, characterized by corneal endothelial vesicles and associated with glaucoma in 15 percent of cases, maps to a site on chromosome 20. Fish-eye disease, associated with large cloudy corneas, is a defect in the α -lecithin:cholesterol acyl transferase gene on chromosome 16. Segregation analysis has shown that severe astigmatism, a refractive error characterized by blurring of vision, is associated with a major autosomal dominant locus.

The challenge now is to refine the genetic loci associated with corneal dystrophies and clone the responsible genes. Continued molecular genetic studies of the corneal dystrophies will improve scientists' understanding of the etiology, pathogenesis, and diagnosis of their dystrophies and hopefully will suggest new avenues for therapy.

Development, growth, and wound healing.

For the cornea, as well as many other ocular structures, the extracellular matrices provide the structural and frequently the functional organization. Virtually every structure of the eye is composed of one or more extracellular matrices or has an extracellular matrix associated with it. In the cornea, the matrices

include the stroma, Bowman's layer, Descemet's membrane, and the corneal epithelial basement membrane. Scientists have made strides toward understanding the molecular composition and the details of the assembly of these matrices. They have also increased their understanding of the degradative enzymes, largely matrix metalloproteinases (MMPs), involved in corneal remodeling during growth and wound healing.

Corneal matrices are chiefly composed of two classes of proteins: collagens and PGs. Many new species have been identified recently, and certain structural features have been deduced using molecular biology techniques. The known collagens now number 20, and at least 13 of these participate in the development and assembly of the different corneal matrices. The number of known PGs is also increasing rapidly, as evidenced by the discovery that the keratan sulfate PGs that characterize the cornea comprise a family of molecules.

Functional studies on corneal collagens and PGs have suggested mechanisms for creating the thin, uniform-diameter collagen fibrils that are characteristic of the corneal stroma and are thought to be a factor essential for transparency. One model, for which there is both structural and functional evidence, involves the formation of heterotypic fibrils, coassemblies of more than one type of collagen, with one type serving a regulatory function. Heterotypic fibrils were first described in the cornea, but are now known to occur in other connective tissues. Other types of collagen, such as the fibril-associated species that bind to the fibril surface, have been identified in the cornea. They are differentially expressed during development and wound healing, and studies suggest that they may alter the interactions between fibrils. Different types of PGs are also known to bind at specific sites along corneal collagen fibrils, and assembly studies suggest that these may also be involved in regulating fibril diameter. The assembly of corneal collagen fibrils in orthogonal arrays undoubtedly also contributes to transparency. Here again, PGs may play a role, but much remains to be learned about the mechanism by which more perfectly arranged fibrils can be induced to form during wound healing.

The MMPs are a family of 18 structurally related enzymes catalyzing cleavage of matrix components. They have recently been implicated in the remodeling that occurs during development, wound healing, or

following laser surgery. They appear in a precisely controlled sequence that suggests they perform specific roles. Cellular sources of MMPs include resident corneal cells and invasive inflammatory cells. Regulation of MMP expression can occur at the level of synthesis, as certain transcription factors have been implicated in differentially regulating their expression. MMP levels can also be controlled by tissue inhibitors of metalloproteinases (TIMPs). Changes in the levels of MMPs and TIMPs have been correlated with pathologic conditions, such as stromal ulceration, keratoconus, and failure to reepithelialize. Animal studies suggest that recombinant TIMPs can ameliorate these conditions. MMP gene expression can be regulated by growth factors, inflammatory cytokines, and constituents of wounds such as fibronectin fragments.

Hemidesmosomes and transmembrane collagen. The hemidesmosome is a complex structure on the basal surface of corneal epithelium. Both the epithelium and the corneal fibroblasts participate in the hemidesmosome's development, the latter by producing matrix components that induce hemidesmosomes to differentiate. The hemidesmosome promotes epithelial attachment to the underlying extracellular matrix through transmembrane receptors that link hemidesmosomal components with keratin fibrils in the cell. New insights into the function of the hemidesmosome have come from the discovery of autoantibodies to a 180 KD protein (BP 180) in the serum of patients with the blistering disease called bullous pemphigoid. BP 180 is a transmembrane component that is associated with a subunit of the hemidesmosome $\alpha 6\beta 4$ integrin. BP 180 is a novel transmembrane ligand of $\alpha 6\beta 4$ that is necessary for normal hemidesmosome formation, and mutations in BP 180 and other hemidesmosomal components are likely to play a role in ocular blistering diseases. It has been suggested that abnormalities in these complexes are involved in persistent epithelial defects or recurrent epithelial erosions of the cornea. These conjectures need to be examined.

Stem cells. Biochemical and biological studies have suggested that the corneal epithelial stem cells necessary for normal regeneration reside in the limbus (see Figure 1), the narrow peripheral zone of cornea bordering the conjunctiva. These stem cells

are postulated to be the progenitor cells necessary for maintaining the normal corneal epithelium. Two recent observations are consistent with this hypothesis. First, removal of the limbal epithelium leads to a spectrum of corneal surface abnormalities such as conjunctival epithelial ingrowth, vascularization, and chronic inflammation. Second, limbal transplants have been shown to result in much better corneal epithelial repair than conjunctival transplants. In a recent report, limbal epithelial cells obtained from a patient's uninvolved eye were cultured, passaged, and grown to confluence to replace conjunctival epithelium removed from the diseased eye. The clinical results were promising, and this technique deserves continued development and evaluation.

An alternate approach that has been recently developed involves transplantation of amniotic membrane cells to cover the perilimbal environment before limbal allograft transplantation. This intervention results in decreased inflammation and vascularization and enhances graft survival.

Regulation of corneal cell division. The discovery of proteins called cyclins, which appear and disappear during the mitotic cycle, has provided a major insight into the mechanism of cell division. Cyclins act as regulatory subunits to activate enzymes known as cyclin-dependent kinases (Cdks). Progression from G_1 to S phase of the mammalian cell cycle is regulated by Cdks and by cyclin E-dependent kinase (Cdk2). Subsequent transition through the cycle requires the action of at least three other cyclins.

Of considerable importance to corneal research is the recent finding that fibrillar collagen inhibits cell proliferation by regulating Cdk2. When smooth-muscle cells are grown on polymerized collagen, phosphorylation of Cdk2 by its kinase is inhibited and levels of Cdk2 inhibitors increase. In contrast, cells grown on monomeric collagen divide normally. Experiments with blocking antibodies indicate that fibrillar collagen specifically regulates Cdk2 activity by stimulating the signaling by extracellular matrix receptors that leads to increased levels of Cdk2 inhibitors and inhibition of proliferation. In the developing cornea, a significant increase in the concentration of fibrillar collagen is associated with dramatic downregulation of keratocyte proliferation. This might be mediated by inhibition of Cdk2, and it is possible that changes in the fibrillar

collagen of the stroma play a role in regulation of corneal fibroblast proliferation during corneal disease. If this is the case, it opens new avenues for therapy.

Corneal gene expression. A molecular analysis of developmental and cellular processes in the cornea has lagged behind that in other ocular tissues, largely from the lack of a tissue-specific promoter. However, progress has been made recently in studies of gene expression involved in creation of the corneal extracellular matrix (section C) and in the differentiation of corneal epithelium, as will be described here. First, at least two keratins (K3 and K12) appear to be produced specifically in the corneal epithelium, and studies are underway to identify the promoter elements that control the expression of their genes. Another opportunity comes from the high expression of certain enzymes in the corneal epithelial cells; the tissue-specific promoters for these genes are candidates for use in directing foreign gene products to the cornea.

The most highly studied abundant enzyme in the corneal epithelium of mammals is aldehyde dehydrogenase class 3 (ALDH3). It comprises up to 40 percent of the soluble corneal protein and can be induced by oxidative stress. Transketolase is another abundant corneal enzyme that is expressed in most other tissues at lower concentrations. Alpha-enolase is also found at unusually high concentrations in the cornea. This enzyme is of special interest because it is preferentially expressed in the circumferential limbal cells of the cornea, where the stem cells reside, with potential implications for delivering gene therapy to the cornea.

There has been less progress in the identification of specific gene products in endothelial cells. Several investigators are presently conducting experiments to identify highly expressed specific genes in the various layers of the cornea. These studies are beginning to be fruitful, and a number of novel genes have been found.

The status of gene expression in cornea differs from the high levels of expression of enzymes and crystallins in the lens, where regulation occurs through developmental processes rather than environmental induction. No specific transcription factors regulating corneal genes have been identified as yet, but Pax-6 is a major candidate for study. Pax-6 is highly expressed

in the developing anterior segment; has been shown to have a direct role in the regulation of crystallin genes in the lens; and induces eye formation in all animals, including invertebrates. Moreover, Pax-6 mutations are associated with human anterior segment diseases such as aniridia (absence of the iris) and Peters' Anomaly (faulty developmental separation of the iris and cornea).

The high expression of enzymes in corneal epithelial cells is reminiscent of the recruitment of enzymes and stress proteins as refractive crystallins in the lens. In the lens, different enzymes are used as crystallins in different species, so the enzyme crystallins are taxon specific. Similarly, the abundant enzymes in the corneal epithelium may differ among species. For example, ALDH3 is found in mammalian corneas but not in chicken or fish corneas. The unexpectedly high concentrations of these corneal enzymes suggest that they may play both enzymatic and nonenzymatic roles in the cornea. This is analogous to the situation in the lens, where the abundant crystallins have refractive and nonrefractive functions—a strategy called gene sharing. ALDH3 appears to protect the corneal epithelium against oxidative damage resulting from the continual surface exposure to the environment, especially to UV light. It has also been suggested that ALDH3 protects the cornea, as well as the rest of the eye, from oxidative stress, by directly absorbing UV radiation. Indeed, since relatively few enzymes comprise the majority of the water-soluble proteins of the corneal epithelial cells, it has been proposed that they be collectively called “absorbins.” Finally, it is even possible that, in addition to being UV filters, the abundant corneal enzymes contribute to transparency by minimizing concentration fluctuations and providing a continuous refractive index within the cytoplasm. The discovery of the possible multiple roles of the abundant corneal enzymes is an exciting challenge for future research.

Immunopathology of corneal infections. A growing body of evidence has demonstrated that the pathology of many corneal infections is mediated by the immune system. This is particularly clear in the case of the host immune response to corneal infection with herpes simplex virus-1 (HSV-1). HSV-1 infection of mouse strains deficient in T-cells (nude mice) fails to produce corneal inflammation or keratitis, and mice whose corneas are purged of antigen-presenting cells develop a milder and briefer keratitis than intact

animals. Individuals infected with the human immunodeficiency virus (HIV) usually do not develop stromal keratitis, even after severe HSV-1 epithelial infection. Results from studies of repeated exposure to trachoma antigens implicate chronic delayed-type hypersensitivity responses in the production of the characteristic lesions in this blinding disease. Studies of corneal bacterial infections with *Pseudomonas* or *Staphylococcus* show that specific subsets of T-lymphocytes are crucial for the development of ocular pathology.

Herpetic disease. The NEI-sponsored Herpetic Eye Disease Study (HEDS) has recently provided valuable new information about the natural history of HSV-1 epithelial keratitis. Patients with a past history of HSV stromal keratitis or iritis were found to be significantly more likely to develop it again after an episode of dendritic keratitis, and thus should be followed closely. These patients should be taught to seek ophthalmic care promptly if they become symptomatic, since past HEDS results demonstrated the efficacy of treatment with topical corticosteroids and prophylactic antivirals. Ongoing HEDS protocols are examining the role of longer term, lower dose, systemic aciclovir in preventing recurrent manifestations of HSV keratitis and determining the risk factors for recurrences.

Corneal HSV-1 infection is potentially blinding, requires frequent office visits, and contributes to a substantial loss of work. Permanent structural damage to the cornea requires surgical intervention and is the cause of over 1,000 penetrating keratoplasties annually in the United States. Acute primary infection of the corneal surface produces virus-induced cell death. In contrast, stromal disease occurs as the result of recurrent infection and involves an immunopathologic process that often leads to scarring, ingrowth of blood vessels, endothelial dysfunction, and vision loss. Understanding the biology of the HSV-1 latency/reactivation/recurrence cycle, and then interfering with reactivation at the molecular level, is likely to be the most efficient means of ameliorating and preventing herpetic keratitis. Recent research has shown that latency-associated transcript (LAT), the only HSV-1 gene abundantly transcribed during latency, is essential for efficient spontaneous reactivation, and that this function maps to the first 20 percent of the LAT transcript.

Recent studies have indicated that the induction of programmed cell death (apoptosis) of lymphocytes by members of the tumor necrosis factor-fas (TNF-fas) receptor family may be a protective mechanism by which the eye limits the extent of inflammation caused by HSV-1 infection. The regulation of interactions between the apoptosis-inducing ligand and its receptor appear especially worthy of study to those interested in ocular immune privilege and the control of extensive ocular immunopathology. The eye remains an ideal organ to study these processes in general. It is readily accessible and mutant strains of small animals with specific genetic defects in members of the fas and TNF receptor families are now available.

Although neutrophils play a role in viral clearance, they also perpetuate T-cell-mediated inflammatory reactions. The cytokine interleukin-2 (IL-2) has recently been shown to mediate corneal inflammation by upregulating the local production of other cytokines that establish a neutrophil-chemotactic gradient and maintain neutrophil viability in the cornea. Molecular studies have recently described a host shutoff mutant of HSV-1 with a restricted ability to invade the corneal epithelium. Recent work in a mouse model suggests that vaccination with HSV glycoprotein gK exacerbates herpetic corneal scarring. This model may be useful in determining and characterizing the protective immune responses generated against HSV-1. Studies in rabbits indicate that local ocular vaccination is much more efficient than systemic vaccination at protecting against both primary and recurrent ocular HSV-1 shedding and corneal disease. This suggests that enhancing local ocular immunity should be targeted in developing a vaccine to combat HSV-1 ocular disease.

Bacterial infection. Corneal infection by *Pseudomonas aeruginosa* often results from contact lens wear and can lead to a highly destructive process resulting in loss of vision. The corneal destruction associated with this organism is thought to be due both to the response of the host and to bacterial proteases acting on corneal tissues. *P. aeruginosa* possesses a number of virulence factors, such as cell-associated pili and extracellular enzymes such as elastases, alkaline protease, and exotoxin A. Once infection has occurred, complex tissue reactions are initiated that include inflammation, formation of new blood vessels, and degradation of the stromal matrix. Various other host factors play a role in this tissue destruction, including enzymes from infiltrating inflammatory cells.

Recent research in an aging mouse model has suggested that failure to upregulate the intercellular adhesion molecule-1 (ICAM-1) in corneal tissues may reflect a reduction of both IL-1 and γ -interferon levels in the infected cornea. This lack of ICAM-1 appears to result in delayed recruitment of neutrophils and other inflammatory cells into the cornea.

Staphylococcus aureus occupies a dominant position in bacterial diseases of the eye. In addition to causing direct infections of the external eye and intraocular tissues, it is also responsible for hypersensitivity diseases of the external eye. Animal models of these entities have been developed in rabbits, where ribitol teichoic acid was found to be the relevant antigen involved in an antibody-mediated immunopathogenesis.

Recent studies into the role of complement in bacterial endophthalmitis have shown that decomplicated guinea pigs demonstrated impaired host defense against *Staphylococcus*. Additionally, immunologic or chemical injury to human donor corneas showed that terminal components of the complement cascade can be generated in corneal tissue. The results of these studies suggest that complement is important to the host defense against ocular infection.

Immune compromise. Many immune responses are downregulated within the eye. (See Retinal Diseases Panel Report on pages 13–38.) The prevailing teleological explanation is that the eye is designed to restrain inflammatory responses that could inflict collateral damage to innocent bystander cells in the eye, leading to a loss of transparency. This is a unique immunological adaptation because it disarms a major immunological effector mechanism that could be enlisted to protect the eye against myriad pathogens. Thus, limiting the extent of intraocular inflammatory responses represents a compromise in which vision-threatening immune responses are silenced at the risk of opportunistic infection.

Immunological privilege of the anterior chamber and the cornea is multifaceted and involves a large number of adaptations. These include anterior chamber-associated immune deviation; anti-inflammatory and inhibitory effects of aqueous humor constituents, such as transforming growth factor- β on the induction and expression of delayed-type

hypersensitivity; low expression of major histocompatibility complex (MHC) class I antigens; wide expression of FasL (the fas ligand); presence of a potent inhibitor of natural killer cells in the aqueous humor; presence of complement-regulatory proteins in the aqueous humor and on the corneal endothelium; absence of lymphatics draining the anterior chamber; and absence of antigen-presenting cells, especially Langerhans' cells, in the central regions of the cornea.

New information about self-tolerance has emerged from genetic studies. The demonstration that strains of mice with variations in the immunoglobulin-heavy-chain locus are more resistant to HSV-1 keratitis than normal mice represents an important starting point for ocular studies. Analyzing differences in the immunoglobulin-heavy-chain between susceptible and resistant strains demonstrated the involvement of a self-antigen. This self-peptide could be used to confer resistance to HSV-1 keratitis. The importance of this observation relates to a general principle that sequences of peptides of some ocular tissues may be important for the preservation of self-tolerance and autoimmunity. Future studies should be directed at understanding the mechanism of tolerance induction and how to use this information to create new immunologically based pharmaceuticals to treat eye injuries. Recognition that the eye offers an extremely accessible model for study of the immune system is perhaps the most important development in the last several years and should continue as the understanding of immune privilege and tolerance advances.

The aqueous humor may limit pathogenic or autoimmune responses, since molecules found in the aqueous humor appear to dampen lymphocyte functions. How the levels of these molecules are regulated and whether they can be pharmacologically manipulated offer novel therapeutic approaches. Unique features of the accessible surfaces of the eye offer opportunities for development of small molecules that disrupt immunological or inflammatory processes. Wound healing of the cornea may be amenable to treatment with small, rationally designed peptidomimetics derived from receptors involved in inflammation. Study of the TNF family of receptors has recently led to the development of small molecules that interfere with cell death and may be topically active for treating corneal injuries. These studies illustrate the need for detailed structural understanding of the molecules involved in ocular injury and inflammation. Structural analysis of

receptors required for microbial pathogenesis, immunity, and cell-cell contact are all likely to lead to new therapies.

Lacrimal gland physiology. The goals of research in this area have been to understand the causes of lacrimal insufficiency and to develop rational treatments for dry eye. The nature and regulation of tears is becoming better understood, and a great deal of work has been done on the structure and function of mucins, regulation of lacrimation by hormones, and the function of the lipid layer. However, the clinical diagnosis and treatment of dry eye, although often investigated, is still not well understood. Objective and more well-validated, clinically useful tests for dry eye are needed.

Several lines of investigation identified as priorities in the last national plan have progressed significantly. Identification of G proteins and protein kinase isoforms has increased understanding of the pathways that transduce stimulatory nerve signals into the intracellular chemical messages that control lacrimal glandular secretion. Changes in innervation of the lacrimal glands and in aspects of lacrimal gland electrophysiology have been shown to precede local autoimmune phenomena in mouse models for Sjögren's Syndrome. Recognizing the presence of growth factors with potential regulatory actions, both in the lacrimal gland and at the ocular surface, has expanded scientists' view of secretory control. Trophic actions of the innervation of the lacrimal glands have been revealed. A substantial body of evidence has been developed supporting the thesis that androgens and related steroid hormones influence immunosuppressive phenomena in the lacrimal glands.

The hypothesis that lacrimal gland secretory cells actively provoke Sjögren's Syndrome autoimmune responses has gained support from analyses of the intracellular traffic of histocompatibility molecules and autoantigens. This hypothesis appears to be gaining further support from new experiments based on autologous mixed cell reactions that may recreate autoimmune responses under defined cell culture conditions. A new autoantigen (the cytoskeletal component α -fodrin), implicated in Sjögren's Syndrome autoimmunity, has been identified. This autoantigen appears to have considerable specificity, since antibodies to it were found in the serum of 95 percent of patients with Sjögren's Syndrome. No antibodies

were found in normal individuals or in patients with other autoimmune disorders such as systemic lupus erythematosus and rheumatoid arthritis. Thus, it may have considerable diagnostic potential. Moreover, neonatal vaccination with α -fodrin prevented development of the disease in mice, opening the possibility of new therapeutic approaches for Sjögren's Syndrome.

Unexpected discoveries have opened new lines of investigation that may hasten the discovery of more effective therapies for dry eye. Experimental studies with animal models and observational studies with humans have indicated that androgen sex hormones and prolactin modulate the functional status of the lacrimal gland. This work has inspired a general theory that explains why women should be vastly more likely than men to develop both primary lacrimal gland deficiency and Sjögren's autoimmunity, and it suggests hormone modulation therapies that may prevent and treat primary lacrimal deficiency. Moreover, there have been preliminary reports that the androgens modulate the function of the meibomian glands and the lacrimal glands, offering the possibility that hormone treatment may effectively treat dry eye related to lipid-layer deficiency. There have been preliminary reports that androgen withdrawal activates pathways leading to classical apoptotic death of interstitial cells and to nonapoptotic death of secretory epithelial cells in the lacrimal glands. These observations, if substantiated in further work, would help account for the lacrimal gland atrophy that has been reported to follow androgen loss. Moreover, since known autoantigens are present in apoptotic cell fragments, this phenomenon indicates another pathway that may lead to Sjögren's Syndrome autoimmunity.

Lipid mediators of inflammation and nonsteroidal anti-inflammatory drug therapy. Understanding how the cornea metabolizes lipids to form mediators of inflammation and wound healing has advanced markedly in recent years. A major avenue of investigation has focused on the metabolism of the fatty acid arachidonic acid. Arachidonic acid may be oxidized by the cornea using three distinct enzymatic pathways, all of which produce biologically active molecules.

The first pathway, cyclo-oxygenase pathway, transforms arachidonic acid into prostaglandins, thromboxanes, and prostacyclin. These compounds

alter the permeability of blood vessels and the aggregation of platelets (blood cells involved in blood clotting). The enzyme that converts arachidonic acid to the precursor for the prostaglandins is inhibited by nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin, ketorolac, and diclofenac. The anti-inflammatory properties of NSAIDs derives, in major part, from their ability to inhibit prostaglandin production. Several NSAIDs have been introduced into the clinical armamentarium during the past few years. These have proven beneficial in relieving symptoms of allergic conjunctivitis and in controlling pain and inflammation following refractive surgery or cataract extraction.

The second route, lipoxygenase pathways, produce arachidonic acid metabolites that appear to be involved in many aspects of inflammation and wound healing. In the cornea, products of these pathways have been implicated in recruiting inflammatory cells into the cornea and in regulating epithelial wound healing.

The third route for metabolism of arachidonic acid is by epoxygenase pathways. The cornea is a particularly fruitful system for studying these pathways, as evidenced by the seminal contributions to this field using the cornea. Epoxygenase pathway products may be involved in regulating the influx of white blood cells into the cornea following injury and may play a role in the infiltration of blood vessels into the cornea after severe or prolonged injury.

An alternative mechanism by which the cornea may regulate inflammation is by producing platelet-activating factor. Proinflammatory properties ascribed to platelet-activating factor include induction of platelet aggregation, constriction of blood vessels, enhanced release of other mediators that cause dilation and increased permeability of blood vessels, increased arachidonic acid metabolism by other cells, and increased movement of white blood cells.

Ongoing investigations funded through the NEI will further researchers' understanding of the role of these lipids in regulating how the cornea responds to injury. Moreover, pharmacological manipulation of arachidonic acid metabolism and platelet-activating factor production may prove beneficial in ameliorating corneal inflammation and limiting the ingrowth of blood vessels.

PROGRAM OBJECTIVES

The objectives for the Corneal Diseases Program include the following important areas of laboratory and clinical research:

- Explore the molecular basis of corneal transparency.
- Analyze the molecular nature of corneal inflammation and wound healing.
- Delineate the pathogenesis of corneal developmental anomalies and dystrophies.
- Improve the understanding of ocular surface physiology.

The needs and opportunities related to each of these objectives and the strategies for accomplishing them will now be considered.

Objective 1: Explore the molecular basis of corneal transparency.

Researchers must continue to discover the parameters required for transparency and then determine how to achieve these by manipulating the cellular, biochemical, and molecular mechanisms involved in their expression.

Research Needs and Opportunities

Researchers need to learn more about the mechanisms regulating corneal hydration. It is obvious that the various water-channel proteins are widely distributed in ocular tissues. It should now be possible to identify the cell-signaling mechanisms that regulate water permeability either directly through a given AQP channel or via a number of different channels. Their different protein structures suggest that each channel is uniquely regulated. Short-term goals should include measuring water permeability in intact ocular tissues, determining the effects of second messenger systems, and determining the regulation of AQP gene expression. It is important to develop new models to explain the nature of the endothelial fluid pump and to determine whether or not the expression of additional water channels in this cell layer could aid in stromal deturgescence. Longer term work should

include obtaining high-resolution structural data so that the aqueous pathway traversing the water channel can be visualized. Such structural information is needed to develop inhibitors of specific water channels. Similarly, it is possible that increased water permeability in cell membranes of lacrimal, corneal epithelial, or conjunctival cells could aid in moving water into the tears in dry-eye conditions.

Better therapy is needed for corneal edema, which is among the leading indications for corneal transplant surgery in the United States. Corneal edema occurs in a variety of clinical settings, including Fuchs' endothelial dystrophy, trauma, inflammation of the iris, glaucoma, and postsurgical disorders. It is frequently associated with deposition of abnormal proteins, amyloid, and PGs, leading to loss of transparency and decreased visual acuity. Biochemical and molecular studies need to be undertaken to understand these clinically significant conditions. The appearance of growth factors and extracellular matrix abnormalities within these corneas needs to be further understood so that interventions can be developed.

Processes to improve the corneal graft should be developed. Underlying scarring, neovascularization, and tear deficiencies compromise transplant acceptance.

Cell populations for corneal grafting need to be produced, and the means to induce corneal cells to undergo changes facilitating tissue replacement and/or repair need to be discovered. It may even be possible to program other sources of cells to acquire the properties of those of the cornea, thus providing a limitless source of cells for corneal reconstruction and replacement. Unlike the donor corneas currently used for transplantation, such cell populations would always be available when needed, and they would be free of the potential problem of transmission of diseases harbored by a donor.

Strategic Research Questions

Can corneal endothelial cells be induced to divide and repair an injured endothelium? This question requires both cell culture and animal experiments, the use of growth factors, and the molecular analysis of the cyclins and their associated kinases. Transfections with recombinant DNAs and use of viral vectors need to be explored.

Can researchers develop a visual quality-of-life instrument to measure functional corneal transparency? The measure for outcome of therapy for most corneal conditions is high-contrast visual acuity. Yet for many patients visual acuity may be normal even when visual function for real-life conditions (such as night-time driving, hazy conditions, and strenuous physical activity) is compromised. Even though refractive error affects up to 60 percent of the American public, this condition has not been explicitly incorporated into past quality-of-life questionnaires. Improved versions should be developed.

Objective 2: Analyze the molecular nature of corneal inflammation and wound healing.

The cornea is uniquely organized to discourage the induction and expression of inflammatory responses, particularly immune effector mechanisms that inflict significant injury to adjacent cells. The creation of such an immunological blindspot should render the cornea vulnerable to opportunistic infections and neoplasms. However, the conspicuous absence of neoplasms and the relatively low incidence of opportunistic infections suggest the existence of an effective immunological surveillance at the corneal surface. Future work should focus on understanding the molecular mechanisms of corneal immune phenomena, wound healing, cell adhesion, and migration. These studies would prove beneficial for clinical outcomes of infection, refractive surgery, and management of diabetes.

Research Needs and Opportunities

Researchers need to determine which genes are responsible for imparting the characteristics unique to the corneal epithelium, stroma, and endothelium. Knowledge of the mechanisms responsible for their regulation will permit manipulation to correct genetic diseases and physical and chemical injuries. These genes can be identified by screening methods now available, including differential display, a variety of subtractive hybridization procedures, and direct sequencing of transcripts. Once identified, the regulation and roles of these genes can be studied by a variety of means, including cell transfections with gene constructs and retroviral vectors and transgenic mutations and gene knockouts. Using genetic engineering, this knowledge should be applied to correct mutations and alter the behavior of corneal cells during wound healing.

Further study of the mechanisms of mucosal immunity is called for. The IgA secreted on mucosal surfaces is the most abundant immunoglobulin. It has been assumed that tear IgA plays a significant role as a barrier to corneal infections, but direct evidence is lacking. The potential for mucosal vaccines to prevent respiratory and gastrointestinal infections is widely recognized and is a topic of intense research activity. By contrast, only a small number of investigators are actively involved in ocular mucosal vaccine research.

Improved management of herpes simplex keratitis is needed. Recurrent HSV-1 infection is a major cause of corneal blindness. Although antivirals are available to treat primary and recurrent disease, no therapy exists to eradicate recurrences or to protect at-risk populations. Current animal systems and molecular biology tools give researchers the ability to address these problems. The molecular mechanisms of the latency/reactivation/recurrence cycle need to be understood, and the efficacy of HSV-1 glycoproteins as vaccine candidates needs to be explored. Developing successful vaccines will require knowing the immunological parameters involved in resolving primary HSV-1 keratitis in naive animals, protecting previously vaccinated animals against ocular HSV-1 challenge, and protecting against recurrent infection. The focus should be on local ocular immunity and mucosal immunity as they appear more important than systemic immune responses. Developing therapeutic vaccines against recurrent ocular HSV-1 infection and herpetic keratitis should be explored.

Strategic Research Questions

What is the character and function of corneal stem cells? Investigation should be directed toward firmly establishing the location of conjunctival epithelial stem cells, determining the role of goblet cells in homeostasis, identifying molecules that regulate the growth and differentiation of epithelial cells, identifying molecules unique to stem cell populations, and determining the role of corneal nerves in the regenerative process.

What are the immunological sentries of the cornea? T-cells bearing the $\gamma\delta$ cell receptor appear to act as immunological sentries at mucosal and epithelial surfaces, displaying cytotoxicity to a wide variety of tumor target cells and infectious agents. Unlike

conventional effector T-cells, $\gamma\delta$ T-cells kill a wide range of antigenically unrelated targets in an MHC-unrestricted manner. Thus, they appear to be ideally suited to serve as sentinels at the corneal surface. To date, it is not known if $\gamma\delta$ T-cells

are present in the cornea, but their presence could have profound importance in corneal immunobiology. It would also be worth investigating whether antigen-unspecific elements, such as defensins and natural killer cells, function in the cornea.



What are the interactions between stromal keratocytes and epithelial cells? Healing of the cornea following injury or refractive surgery is a complex and poorly understood process. Understanding the interactions between these cell types in the wound healing process is vital to improving the treatment of corneal injuries, including those exacerbated by other diseases such as diabetes, and the outcome of refractive surgery.

What specific host/pathogen interactions occur in ocular infectious disease? Further studies defining the components and mechanisms of host/pathogen interactions are warranted. If molecules used during interactions by the host and the infectious agent can be identified and characterized, molecular biologic methods could duplicate these molecules, leading to new therapeutic strategies.

What are the molecular mechanisms of ocular infectious diseases? Studies that define the molecular pathogenesis of infectious diseases are important. The ability to identify and regulate factors that control the production of inflammatory mediators and molecules may lead to fewer complications and the development of novel therapeutic strategies.

What processes generate immune privilege in the cornea? Regulating the immune response could have important uses in promoting corneal allograft survival. Further exploration and clarification

are needed to determine which anti-inflammatory cytokines function in the cornea, which factors prevent the expression of delayed-type hypersensitivity, and how MHC class I antigen expression is downregulated. It would also be important to determine which antigen-presenting cells promote the development of anterior chamber associated immune deviation and how specific T-cell subtypes prevent the expression of delayed-type hypersensitivity. Investigation is also needed into the role of the spleen and of neuropeptides in sustaining immune privilege.

What cellular and molecular events occur during corneal wound healing? Areas of present interest include the mechanisms of migration, stratification, and differentiation of epithelial cells; apoptosis; migration and differentiation of keratocytes; stromal/epithelial interactions; and deposition and organization of the stroma. These studies should provide new insights into the maintenance of corneal clarity and control of topographic change after corneal surgery, infection, and trauma.

Objective 3: Delineate the pathogenesis of corneal developmental anomalies and dystrophies.

The normal processes of corneal development and differentiation need to be identified and understood at the cellular and molecular levels to be able to unravel their pathogenesis and develop appropriate therapies. A combination of methods using tissue culture, transfection, and transgenic mice will provide valuable new insights.

Research Needs and Opportunities

Resources to archive family pedigrees, tissue specimens, and cell lines from corneal dystrophies need to be established. Family pedigrees of the various corneal dystrophies have been collected by clinicians, many of whom have little access to molecular genetic technology. Conversely, there are many highly sophisticated molecular genetic laboratories that lack the appropriate clinical material to pursue disease studies. Archiving specimens of the various corneal dystrophies would provide a valuable resource to study these disorders in a cost-efficient manner.

Researchers need to determine the corneal mechanisms of inhibition of UV light damage and tumor induction. Primary carcinomas of skin epidermis are common, whereas they are rare in corneal epithelium, even though this tissue is exposed to similar amounts of UV light and other DNA-damaging agents. UV-induced oxidative damage to DNA is mutagenic through a process catalyzed by free iron. It has recently been shown that nuclear ferritin is an important antigen of corneal epithelial cells that protects against UV damage by its iron-sequestering action. Thus, it is important to investigate further the mechanism of action of endogenous ferritins of the cornea and the fluids that bathe it. It is also of interest to define further the putative role of corneal enzymes, such as ALDH3, in protection against UV light. The rarity of primary tumors arising in the cornea suggests that this tissue resists transformation by viral and chemical carcinogens. Does the cornea uniquely regulate the expression of tumor suppressor genes? Does the cornea resist transformation by oncogenes or oncogenic agents? Are apoptosis-inducing genes upregulated in the corneal endothelium? Researchers need to conduct further studies to answer these questions.

Corneal gene therapy should be developed. While the surface location of the cornea is an advantage for experimentation in this area of research, its cellular complexity and large acellular stroma add to the difficulties. Since the corneal epithelium possesses a mitotic potential and is continually renewed from the limbal stem cells, it should be a high-priority target for gene therapy. Because it can be maintained in standard culture conditions for considerable time prior to transplantation, the cornea affords the opportunity for genetic modification in the laboratory. Genetic manipulations could enhance the efficacy of limbal transplants in correcting corneal surface disorders. Appropriate corneal vectors need to be identified for the eventual implementation of gene therapy. Developing genetic engineering in the cornea will have ramifications beyond the actual treatment of disease. It will allow a molecular dissection of cellular processes involved in corneal development and wound healing and open possibilities for the development of disease model systems.

It will be important to increase scientists' knowledge of the structure and function of the

corneal membranes. While much is known about the corneal stroma, little is known about Bowman's layer and Descemet's membrane. Emphasis should be placed on the structure and function of these matrices since they potentially influence epithelial and endothelial attachment. This will be especially significant for Bowman's layer, which may be partially or completely removed during refractive laser surgery.

Strategic Research Questions

What roles do the MMPs play in corneal development? The genes for most of the MMPs and TIMPs are cloned and mapped, and knockout mice are available for many. These resources should greatly facilitate functional studies. MMP inhibitors could potentially be a new way to treat a variety of disorders; however, few studies have examined these agents in detail using animal models of corneal injury.

What are the functions of the metabolic enzymes present at very high concentration in the cornea? The metabolic and detoxification functions of these enzymes should be explored, and the possibility that they might play structural roles should be investigated. Since many of the abundant corneal proteins are encoded by stress-responsive genes, it is important to establish whether inductive events regulate their expression.

What is the molecular genetic basis of keratoconus? Corneal topographic analyses have identified early forms of this disorder. These analyses need to be refined through longitudinal topographic analysis and used to construct pedigrees of the hereditary forms of the disorder. Gene loci should then be identified and cloned to provide clues to the pathogenesis and therapy.

Which gene products are responsible for the inheritance of the various corneal dystrophies and developmental anomalies? Understanding the pathogenesis of these disorders should lead to more effective means of treatment and diagnosis. Strategies to answer this question include differential display and subtractive hybridization. In addition to providing clues to disease processes, corneal-specific gene products will ultimately provide promoters for the use of gene therapy.

Which gene products are specific for corneal development, repair, and wound healing? To manipulate the behavior of corneal cells during development, wound healing, and regeneration, these cells' structure and function at the molecular level must be understood. Emphasis should be placed on regulating components involved in cellular adhesion, migration, and communication. Work should continue on the processes of molecular and supramolecular assembly, which result in the unique architecture of each corneal layer.

Objective 4: Improve the understanding of ocular surface physiology.

There is growing appreciation that the ocular surface and the lacrimal glands are intimately linked in a servomechanism that maintains the comfort and health of the ocular surface. The lacrimal gland interacts with the ocular surface via sensory and secretomotor pathways and lymphocytes trafficking throughout the mucosal immune system. The tear fluid and its many constituents influence the ocular surface and therefore modulate the information that returns to the lacrimal gland. A systemic understanding of these relationships should help unravel the mystifying relationship between the signs and symptoms of dry eye. The present lack of understanding frustrates the diagnosis of dry eye and poses a formidable impediment to epidemiological and interventional studies. Progress in this area should make it possible to more effectively characterize, diagnose, and treat dry-eye conditions.

Research Needs and Opportunities

Researchers need to develop cell lines that maintain lacrimal gland phenotypes. Primary cultures of lacrimal acinar cells that maintain much of the normal differentiated phenotype are being used in several laboratories. However, the use of primary cultures of lacrimal ductal epithelial cells is not yet widespread, and it is not clear whether they can be obtained in quantities large enough for biochemical studies. It will not be possible to exploit the full repertoire of modern molecular biology techniques until immortal cell lines that mimic the differentiated phenotypes are obtained.

The sources of individual variability in the function of the ocular surface-lacrimal gland system need to be determined. These are likely to include initiation of sensory signals, central integration and conscious perception of sensory input, generation of secretomotor output, signal transduction, intracellular signal integration, and functional status of the secretory epithelium. Examining individual variability from such a systemic perspective should make it possible to determine the relationship between signs and symptoms of dry eye.

More information is necessary on the function of tear film components. Relatively little is known about the function of some of the major protein components in the tear film. The interactions between the tear proteins, lipids, and mucins must be elucidated to understand how the tear film protects and lubricates the eye. Increased knowledge of the role of the normal tear components would provide insight into the molecular functional deficiencies in dry-eye disease and could lead to effective treatments.

Strategic Research Questions

Can researchers reconstitute interactions between nerve cells and the lymphoid and epithelial components of the lacrimal gland? It is hoped that progress in cellular and molecular neuroscience will be translated into progress on the physiology of the ocular surface-lacrimal gland system.

What are the details of fluid and electrolyte transport in the conjunctival epithelium? Preliminary reports indicate that the conjunctiva is a Cl^- -secreting and Na^+ -absorbing epithelium, thereby implying that its cells have the potential to contribute toward or modify the composition and tonicity of the tear film. It is not known whether these conjunctival mechanisms coexist in the same cell or if there is a distinct dispersal of functional cell types within the bulbar or palpebral portions of this tissue. This issue needs to be addressed, as does the role of neural regulation.

What cell-cell interactions influence the function of the ocular surface? Coculture systems comprised of primary lacrimal secretory epithelial cells together with autologous lymphocytes offer new opportunities. Such systems could accelerate researchers' efforts to delineate the interactions that ultimately influence the function of the ocular surface-lacrimal gland system.

What is the relationship between early changes in innervation and cellular electrophysiology and the later onset of autoimmune phenomena of Sjögren's Syndrome in animal models? Understanding this relationship may provide important clues to the mechanisms underlying the disease in humans. Similarly, understanding immune regulation at the cellular and molecular levels could provide new medical interventions to control or reverse the autoimmune phenomena of Sjögren's Syndrome.

Can steroid hormones be used as therapy for dry-eye conditions? It is reasonable to explore therapeutic strategies based on steroid hormones. There should be continuing efforts to understand the molecular mechanisms underlying the influence of the hormonal environment on the ocular surface-lacrimal gland system. The lacrimal gland-ocular surface servomechanism has evolved to maintain the homeostasis of the ocular surface, and its function is influenced by systemic factors like hormones and medications, and by local factors like extracellular matrix constituents and cytokines released by infiltrating inflammatory cells. It is possible that the actions of sex hormones are mediated through networks of autocrine and paracrine interactions.

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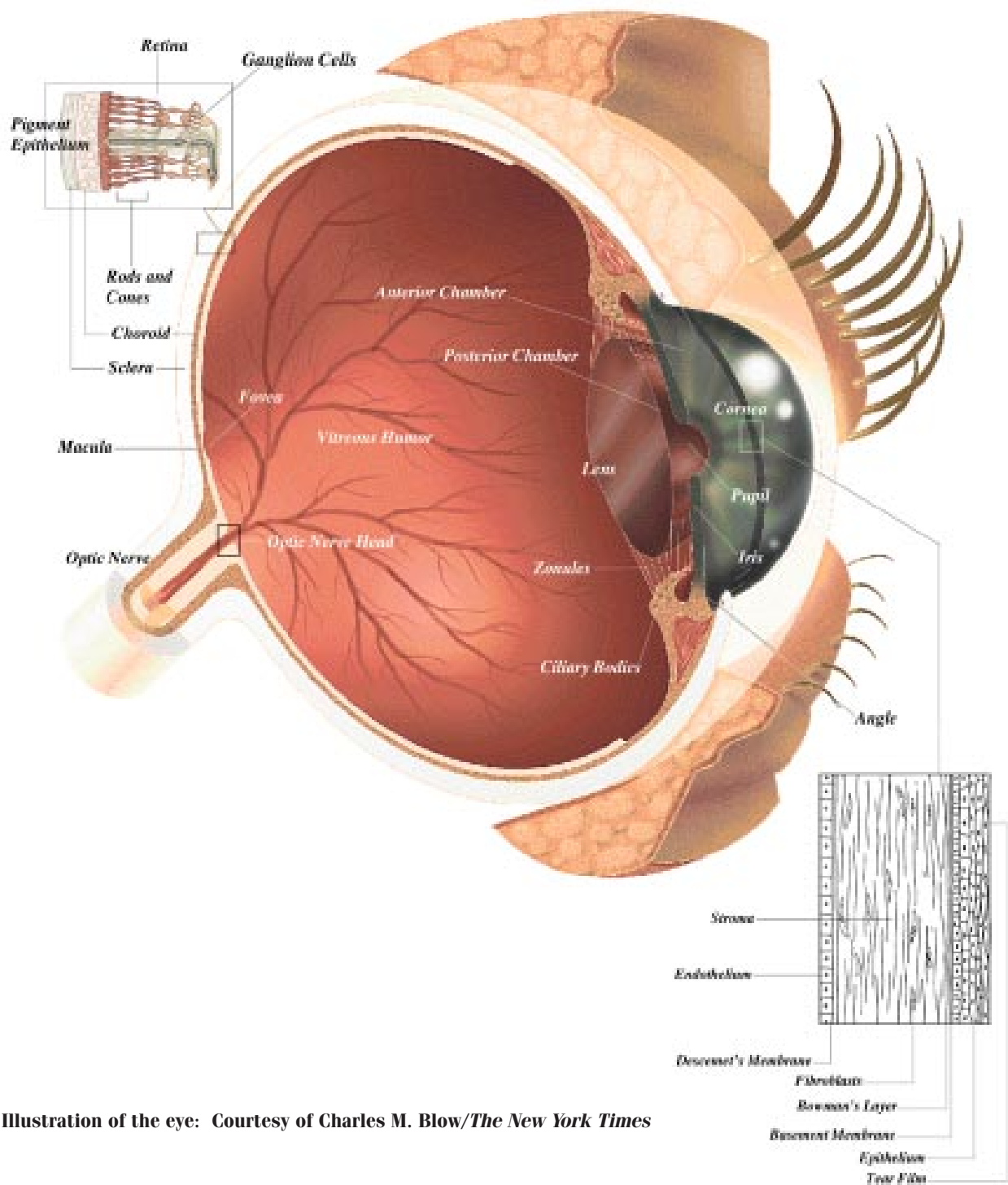


Illustration of the eye: Courtesy of Charles M. Blow/*The New York Times*

PROGRAM OVERVIEW AND GOALS

Although most cells of the body undergo sequential processes of differentiation and aging, the lens cell is perhaps the simplest and most elegant system to study the molecular mechanisms involved in these two fundamental processes. In contrast to the cellular and molecular complexities present in most other tissues, the lens is a much simpler system, comprised of a single layer of epithelial cells that differentiate into fiber cells. Because of the very low turnover of proteins in the differentiated fiber cells, our lenses contain proteins that have been made during all ages of our life. The ease of obtaining lens epithelial and fiber cells, plus the relative molecular simplicity of the fully differentiated fiber cells, make the lens one of the best tissues to study the mechanisms that control the fundamental events of cell differentiation and aging.

Differentiation of epithelial cells to lens fiber cells involves the cessation of proliferation, remodeling of cellular architecture, and significant changes in the collection of genes that are expressed, resulting in a restriction of protein synthesis to the high-level expression of a few classes of proteins. In the last 5 years, it has become evident that differentiation of many cell types involves analogous changes in cellular behavior and a commitment to expression at high levels of cell type-specific genes. Hence, the lens is an excellent system to elucidate the control elements that dictate differentiation in many cell types.

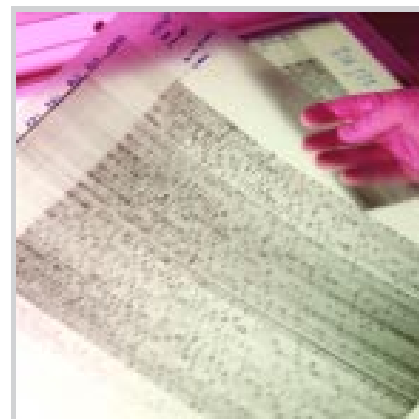
During the later stages of fiber cell differentiation, protein synthesis is essentially terminated and proteolysis is limited. Fiber cells close to the lens center contain aged proteins, while cells close to the lens periphery contain newly synthesized proteins. By carefully peeling away sequential layers of cells, it is possible to obtain proteins of increasing age that date back to before the birth of the organism. Biochemists are just beginning to take advantage of this system to answer fundamental questions on how the aging process changes the nature of proteins.

Based solely on the contribution to understanding differentiation and aging, the lens is indeed an exciting system for study. Nonetheless, it is the transparent properties of the lens and its ability to focus light that present some of the most clinically relevant challenges to scientists involved in eye research.

For most people between the ages of 40 and 50, the ability of the lens to focus from distance to near (accommodate) has been compromised to the point where bifocals are required. The inability to adequately accommodate is known as presbyopia. It is the most common optical disorder of the eye. By understanding the changes in physical properties of the normal lens and its surrounding support structures as a function of age, it may be possible to develop treatments for presbyopia that delay or prevent its onset.

By far, the most serious problem associated with the lens is its loss of transparency. This condition, known as cataract, is the leading cause of blindness in the world. The disorder sometimes occurs in children, but most frequently occurs in adults age 50 and older. To date, there is no universally accepted pharmacological agent to either inhibit or reverse the progression of lens opacity. The only treatment is surgical removal of the lens, followed by implantation of an artificial lens at the time of surgery or the subsequent use of corrective lenses. The following statistics concerning cataract attest to its economic and public health importance:

- Cataract is the leading cause of blindness worldwide, accounting for about 42 percent of all blindness, in spite of the availability of an effective surgical treatment.
- With increasing life expectancy, the number of cases of blindness from this disorder may double by the year 2010.



- Among Medicare beneficiaries, cataract is the most common condition for which eyecare services are sought, accounting for 43 percent of visits to ophthalmologists and optometrists combined.
- In the United States, cataract surgery is the most frequently performed surgical procedure among 30 million Medicare beneficiaries. Approximately 1.35 million cataract operations are performed annually at an estimated cost of \$3.5 billion.

Cataract is an immense medical problem. An eventual cure for cataract strongly depends on increased understanding of the basic molecular processes occurring in the normal and cataractous lens. The objectives listed in this report have been selected based on the assumption that not only are the basic processes of differentiation and aging important reasons for studying the lens, they also provide the framework for learning more about mechanisms involved in presbyopia and cataract. A fundamental understanding of the molecular mechanisms responsible for these two ocular disorders will bring researchers closer to discovering ways to prevent these diseases and developing effective drugs to treat them.

In Fiscal Year 1997, the National Eye Institute (NEI) funded 120 extramural research projects in the Lens and Cataract Program at a total cost of \$25,368,000.

Following are the goals of the Lens and Cataract Program for the next 5 years.

- Understand the physiological basis of lens transparency on the cellular and molecular levels.
- Determine the causes and mechanisms of cataract formation.
- Characterize the controls of lens cell division and differentiation and their roles in the formation of posterior subcapsular and secondary cataracts.
- Understand lens development and the diseases associated with defects in this process.

ASSESSMENT OF PROGRESS

The discovery that α -crystallins have molecular chaperone properties. The discovery that α -crystallins, a major component of lens fiber and epithelial cells, prevent denaturation and aggregation of proteins *in vitro* was unexpected. This novel finding suggested a particularly significant role for this important class of proteins, that of a molecular chaperone. Chaperones are proteins that affect protein-protein interactions by stabilizing protein conformations and preventing nonspecific protein aggregation in the face of heat denaturation or other environmental stresses. Whether the molecular chaperone-like properties of the α -crystallins play a key role in the prevention of protein denaturation and nonspecific aggregation during the aging of the human lens remains to be determined. However, recent findings with knockout mice lacking α -crystallins support the idea that a functional α -crystallin is critical for preventing opacification. Mice in which α A crystallin is missing develop opacities by the age of 7 weeks. Knocking out both α A and α B crystallins in mice results in even more severe cataracts. *In vitro* studies have shown that the molecular chaperone properties of the α -crystallins decrease during aging of the lens perhaps, as studies suggest, as a consequence of environmental insults (e.g., oxidizing agents, ultraviolet [UV] light, glycation) to the human lens. Further support for α -crystallin as a chaperone comes from studies of the central nervous system; α B crystallin expression is greatly enhanced in neurons of patients with neurodegenerative diseases such as Alexander's disease and Alzheimer's disease, where α B crystallin colocalizes with aggregates of aberrant proteins. These findings are consistent with an increase in α -crystallin expression to prevent aggregation in cells that are stressed.

Progress in characterizing changes to lens proteins during human lens aging and cataract.

A great deal of progress has been made in characterizing structural changes that occur to lens proteins during the normal aging process. Identifying sites where posttranslational modifications occur has been aided by mass spectroscopy. Spectroscopic analysis and two-dimensional gel electrophoresis have permitted testing of the hypothesis that specific posttranslational modifications to lens proteins lead to cataract formation. Surprisingly, although many

modifications have been identified, none of these have been specifically associated with age-related cataract. Posttranslational modifications of lens proteins seem to be a function of normal aging rather than cataractogenesis. However, posttranslational protein modifications of α -crystallin may be significant because the physical and chemical properties of the α -crystallins are known to change during aging.

The demonstration that the retinoblastoma protein has a central role in the lens cell cycle.

One goal of understanding cell division in the lens is to identify targets for the development of drug therapies to inhibit the inappropriate cell division that causes posterior secondary cataract following removal of cataract lenses. Advances in this area have centered around the discovery that the retinoblastoma protein pRb is the central gatekeeper that prevents lens fiber cells from entering into the cell cycle and, hence, from proliferating. pRb is a nuclear protein that binds to members of the E2F family of transcription factors, blocking expression of E2F-regulated genes. Not only is pRb involved in cell cycle withdrawal, it also plays a key role in preventing apoptosis or programmed cell death. Mice with homozygous deletions of the Rb gene have provided definitive evidence that inactivation of pRb permits S phase entry and apoptosis in lens fiber cells. Apoptosis in Rb null mice is suppressed when p53, a proapoptotic gene, is deleted along with Rb, suggesting that p53 monitors the cell cycle and prevents tumorigenic proliferation of lens cells.

Progress in defining the role of growth factors in the development and health of the lens.

Growth factors are involved in all stages of lens development, and their relevance to maintaining a healthy lens has been firmly established. Over the last 5 years, much has been learned about how growth factors signal lens differentiation, regulate the cell cycle, and impact on lens transparency. Experiments using transgenic mice and lens explants indicate that members of the fibroblast growth factor (FGF) family are prime candidates for the retina-derived inducers of fiber cell differentiation during lens development and the molecules responsible for maintaining the balance between differentiation and division in the mature lens. Other studies using cultured lens epithelial cells suggest that insulin or insulin-related growth factors (IGFs) act synergistically with FGFs to induce fiber cell differentiation. Studies in transgenic mice point

to a role for platelet-derived growth factor (PDGF) in stimulating epithelial cell proliferation in the mature lens. Lens epithelial cells express receptors for PDGF, whereas adjacent cells in the anterior chamber of the eye synthesize PDGF. Lens epithelial cells exposed to transforming growth factor- β (TGF- β) are induced to assume a spindle shape and synthesize connective tissue proteins, such as collagen type I and α -smooth muscle actin, all characteristics of posterior subcapsular cataracts. Since latent TGF- β is present in the normal eye and can be activated by trauma or surgery, TGF- β may be a significant factor in posterior subcapsular cataracts.

Expanding the understanding of lens development.

Identifying mutations in the Pax-6 gene as being responsible for causing aniridia, a congenital malformation of the eye, was a major breakthrough not only in understanding this disease but also in understanding the developmental processes controlling eye development. This was the first gene to be shown by genetic function to be essential for normal vertebrate eye development. The insight was especially profound because of the nature of the gene: Pax-6 is a member of the homeobox transcription factor family, which is at the heart of the hierarchy of genes controlling formation of the body plan in *Drosophila*. The significance of Pax-6 as a key regulator of eye formation in general, and of determination and differentiation of the lens in particular, has been substantiated in a number of experimental systems. The small-eye mutation *sey* in mice maps to Pax-6. In addition, ectopic expression in *Drosophila* embryos of the *Drosophila* Pax-6 gene *ey* caused formation of extra eyes at a number of sites on these animals. These experiments led researchers to conclude that Pax-6 is a master gene that controls the expression of downstream genes during eye development. This has led to a search for other developmentally regulated genes and promoter elements that are recognized by Pax-6. Recent work suggests that there are a number of regulatory genes, most of which encode transcription factors, that are also essential for normal eye development. These include the homeobox genes *Optx-2* and *Six-3*, and the transcriptional regulator genes *Sox-2* and *Rx-1*.

The identification and characterization of gap junction proteins. Gap junctions contain intercellular channels that provide an aqueous pathway between adjacent cells, allowing them to share ions and small molecules. Because the lens is avascular it has

been hypothesized that gap junctions between lens cells play a crucial role in intercellular metabolic support essential for lens survival. Through molecular biological and immunochemical approaches, three proteins (called connexins) that form lens gap junctions have been identified, cloned, and sequenced. Lens epithelial cells are coupled by channels formed from connexin 43. Mammalian fiber cell gap junctions are formed from connexin 46 and connexin 50. The importance of gap junctions in maintaining transparency has recently been demonstrated with the use of knockout technology. Mutant mice in which the gene for the fiber-specific connexin (connexin 46) has been deleted developed nuclear opacities within 3 weeks of birth. The association of these nuclear cataracts with proteolysis of crystallins underscores the significance of gap junction to the overall homeostasis of the lens.

PROGRAM OBJECTIVES

The objectives for the Lens and Cataract Program over the next 5 years include both laboratory and clinical research.

- Determine if there are novel markers that differentiate the normal aging process from the diseased (cataractous) state.
- Definitively test hypotheses of cataract.
- Map, identify, and characterize genes which, when mutated, cause congenital or age-related cataract; determine if there are genetic factors that interact with environmental factors to confer susceptibility to age-related cataract.
- Identify genes and pathways that control eye development, especially those critical for lens induction, cell fate determination, and cell differentiation.
- Define the contributions of crystallins to normal lens function.
- Characterize the control of the cell cycle in lens epithelial cells by identifying cell cycle regulators, growth factors, receptors, and signal transduction pathways.

- Characterize, at the molecular level, the ion channels, transporters, and gap junction proteins needed to maintain lens homeostasis; determine what roles perturbations in these systems play in cataract formation.
- Define the mechanisms that regulate the cellular and subcellular architecture of the lens, with special emphasis on the contribution of minor constituents and their progressive modification during aging and opacification.
- Understand the basis of lens accommodation and presbyopia at the molecular and mechanistic levels.

The needs and opportunities related to each of these objectives and the strategies for accomplishing them will now be considered.

Objective 1: Determine if there are novel markers that differentiate the normal aging process from the diseased (cataractous) state.

Research Needs and Opportunities

The human age-related cataractous lens is characterized by a lens opacity that is significant enough to decrease the visual acuity of the patient. Although acuity loss is the clinical manifestation of the disorder, the changes in the lens are likely the result of a series of biochemical and biophysical events, occurring over many years, that ultimately lead to opacification. The overall objective is to identify markers in the human lens that will clearly differentiate the processes of aging from cataractogenesis.

Identification and possible quantitation of such markers would significantly aid in understanding the mechanisms that lead to cataractogenesis. This information will help in developing pharmacological agents that can inhibit lens opacification and assist in the early diagnosis of patients who may benefit most from cataract therapy. In addition, identifying novel markers for cataract will permit the development of animal model systems that can approximate the biochemical and biophysical events occurring in the human lens. These animal model

systems will be valuable in the preliminary screening of possible anticataract drugs. Following are general categories of possible markers:

- Biochemical markers of the lens epithelium, especially those involving changes in gene expression or mutations in specific genes.
- Lens protein alterations, especially those involving posttranslational modifications.
- Morphological and optical markers that can be visualized by noninvasive techniques.

Strategic Research Questions

Relative to the normal aging lens, are there differences in DNA coding sequences that may quantitatively or qualitatively affect specific enzymes or structural proteins that are consistently associated with opacification of the human lens? Although there are very small amounts of nucleic acid present in the lens epithelium and lens fiber cells, polymerase chain reaction (PCR) technology has now made it possible to amplify specific DNA or RNA sequences. Primers corresponding to important nucleic acid sequences could be used to amplify and probe for sequences that may be predictive for cataract.

Relative to the normal aging lens, are there qualitative or quantitative changes in posttranslational modifications of lens crystallins or membrane proteins during opacification of the human lens? Recent advances in mass spectrometry and high-pressure liquid chromatography (HPLC) have now made it possible to identify all major posttranslational modifications of proteins from the human cataractous lens. Emphasis should be placed on the use of mass spectral instrumentation connected online with HPLC. After identifying posttranslational modifications, HPLC can be used to quantitate the relative amounts of modification in cataractous versus normal lenses.

Relative to the normal aging lens, are there morphological changes in lens epithelial or lens fiber cells that occur before the onset of opacification of the lens? Advances in confocal microscopy and nuclear magnetic resonance (NMR) imaging have now made it possible to visualize changes in lens morphology and biochemistry before the onset of opacification. These

techniques can be used to monitor various parameters of the lens in a noninvasive manner, make earlier diagnoses of cataract, and identify novel markers that characterize the precataractous human lens.

What optical markers of the eye reflect early cataractous changes, and can such optical signatures be correlated with suspected risk factors for cataract? Until recently, it has been difficult to measure the optical properties of the eye *in vivo*. The marked cost reduction of the high-performance charged coupled device (CCD) camera, together with development of the appropriate software, now make clinical measurement of optical aberrations fast, easy, and noninvasive. These advances provide the opportunity to quantify optical changes in the normal eye indicative of cataract formation and monitor cataract progression.

Objective 2: Definitively test hypotheses of cataract.

Research Needs and Opportunities

Age-related cataracts are the most important types of cataract from a public health perspective. Different types of cataract, classified primarily on whether they are nuclear or cortical, have characteristic morphologies, yet there is a tendency to generalize about cataracts and their causes.

Very little is known about what, in conjunction with age, initiates the formation of cataracts. This is, in part, because the cataractous lens is the end result of processes that occur over many years, even decades. The major initiating factors that have been proposed as a result of epidemiological studies are listed in the following figure. There is no compelling evidence that any of these factors are the primary cause of cataracts. In fact, the initiation of cataracts is probably the result of varying combinations of these factors, which interact in some complex manner.

The modes by which initiating factors affect the lens will be either direct, as in the case of UV exposure, or indirect, by altering levels of metabolites, growth factors, oxidants, antioxidants, autoantibodies, and so forth. Many investigators have suggested that the initial site of action for these factors is the lens epithelia, where altered epithelium function could affect underlying fiber cells. However, it is unclear

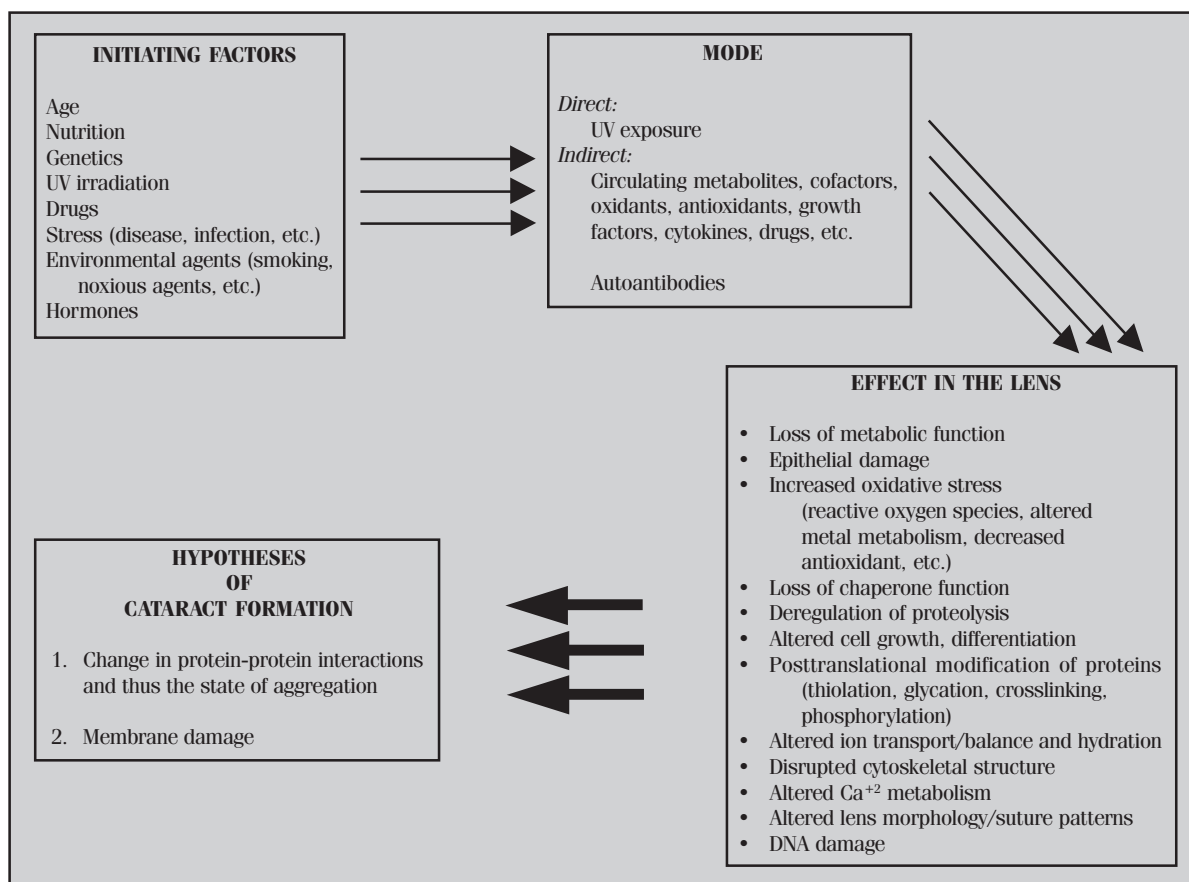


Figure 3. Cataract formation paradigm

if the initial target is the epithelia, the fiber cells, or the surrounding tissues, which secondarily impact the lens.

The major hypotheses proposed to explain age-related cataracts involve either a change in the protein-protein interactions leading to protein aggregation or membrane damage. Processes in the lens thought to affect one or both of these include: oxidative stress; posttranslational modification of crystallins; and, more recently, the loss of chaperone-like activity of α -crystallin. These have been considered key mechanisms leading to age-related cataract. A role for oxidative stress in age-related cataracts has been proposed, but the origin of the stress and the manifestation or relevance to any cataract have not been definitely demonstrated. The major posttranslational modifications of lens proteins seem to be a function of normal aging rather than cataractogenesis. A clear causative association between posttranslational modifications of lens proteins and age-related cataract has not been demonstrated.

Each of the processes in the lens affected by the initiating factors (see Figure 3) has been shown to be related to cataract formation under special conditions or in special model systems. In human lenses, while some of these processes may be critical, there will likely be complex interconnections among them, generating a cascade of events that ultimately lead to cataract. Understanding the interrelationships between these processes will be imperative to elucidating mechanisms involved in cataract formation.

Strategic Research Questions

How can initiating factors be definitively identified? The late onset and likely multifactorial nature of age-related cataracts confounds the identification of initiating factors. The challenge to the scientific community is to design meaningful experiments that test causal agents identified in epidemiological studies. The lack of a well-defined animal model of age-related cataracts has hindered the implementation of such studies.

Do researchers have enough knowledge of the normal human lens to determine the relevant processes in cataracts? Baseline data on normal lens physiology and how it is affected as a result of the aging process are lacking. Large gaps in understanding how the lens maintains its homeostasis exist. Questions relating to cell division and differentiation, transport systems, and maintenance of protein structure are key to enhancing the understanding of normal lens physiology. How these processes change as a function of aging will provide clues as to their relevance to cataract formation.

To understand cataract, do researchers need to focus on tissues surrounding the lens? The initial site of damage in cataractogenesis is unknown. Theories of cataractogenesis postulate a role for agents originating in tissues external to the lens in the etiology of cataracts. The validity of these theories needs to be substantiated by demonstrating an ocular source for these agents. Conversely, the role of growth factors in maintaining the health of the lens is now becoming more apparent. These studies suggest the need to investigate the tissues that produce and secrete growth factors and how the lens utilizes growth factors in pursuing possible mechanisms of cataractogenesis.

What are the major contributing factors to oxidative stress, increased oxidants or decreased antioxidants, or both? A role for oxidative stress in development of age-related cataracts has been accepted. Strategies to determine how oxidative stress is manifested need to be devised to establish its relevance to cataract.

What is the functional relationship between the epithelial cells and fiber cells in normal lenses? Do epithelial cells accumulate altered DNA and subsequently differentiate into defective fiber cells? Many investigators have suggested that the initial site of damage is the lens epithelium, where altered epithelium function could affect underlying fiber cells. Identifying testable mechanisms depends on developing an understanding of the basic functional relationship between lens epithelial and fiber cells.

Objective 3: Map, identify, and characterize genes which, when mutated, cause congenital or age-related cataract; determine if there are genetic factors that interact with environmental factors to confer susceptibility to age-related cataract.

Research Needs and Opportunities

Age-related cataract is a complex disease that appears to be influenced by numerous environmental factors including, but not limited to, diet, UVB radiation, and smoking. While many epidemiological studies have suggested an association between these risk factors and cataract, very little is known concerning the identity of genes that either alone or together with environmental factors may confer susceptibility to cataract. As a start, results from the Beaver Dam Eye Study suggest that a single major gene defect may account for a sizable portion of both nuclear and cortical cataracts in this population.

Congenital cataract is less common than age-related cataract, but it is still responsible for 10 percent to 30 percent of all cases of blindness in children. While treatable, albeit not easily, congenital cataract is associated with a high rate of blindness because of a range of related clinical problems, including amblyopia, glaucoma, and strabismus. To date, nine distinct loci for autosomal dominant cataract have been mapped. The most common inheritance of congenital cataract in humans occurs through autosomal dominant transmission. Mapping of autosomal-dominant families has been important because it has demonstrated the presence of genetic and allelic heterogeneity. Allelic heterogeneity has been suggested by the close linkage of several clinically distinct phenotypes, including the Volkmann and the posterior polar cataract (1p36), the Coppock-like and the polymorphic lamellar cataract (2q33-36), and the Marner and posterior polar cataract (16q22.1). In contrast, genetic heterogeneity of autosomal-dominant cataract families with similar phenotypes has been demonstrated through gene mapping of similar phenotypes to separate loci. These include Cerulean cataract (17q24 and 22q) and anterior polar cataract (17p and a balanced reciprocal 2;14 chromosome translocation).

Finally, two distinctly different inherited cataracts, zonular sutural cataract and zonular pulverulent cataract, have been mapped to 17q11-12 and 1q21-25, respectively.

To circumvent barriers of direct linkage studies in humans, mouse models have also been used to identify genes responsible for cataract development. Approximately 40 mouse mutants with cataract have been reported. Mutants that have had gene mutations identified include Philly (β B2 crystallin), Cat2 (γ E crystallin), Cat Fraser (MIP), K289 (Pax-2), sey (Pax-6), No1 (connexin 50), and To3 (Lim2). The Cat Fraser mutant has been shown to have a splicing defect. The K289 mutant has a 1 bp insertion in the Pax-2 gene, which leads to a frameshift mutation. This mutation was identical to a mutation in a human family with renal-coloboma syndrome, and accentuates the importance of studying the mouse as model for human disease.

During the last 5 years, exciting discoveries have been made concerning the possible involvement of genetic factors in human age-related and congenital cataracts. With the development of sophisticated molecular biological approaches, it is now possible to directly address the hypothesis that defects in specific genes may be at least partially responsible for opacification of the human lens.

Strategic Research Questions

Do genetic mutations contribute to age-related or congenital cataract in humans and, if so, what are the identities of these genes? Linkage analysis for congenital forms of cataracts that are inherited as Mendelian-dominant or -recessive traits is routine. Newly developed methodology to study the genetics of complex diseases increases the likelihood that genetic loci associated with cataract can be directly identified.

Besides the Beaver Dam Eye Study, do other population-based studies also suggest the presence of genes that predispose individuals to cataract and, if so, do certain genes confer susceptibility to certain types of cataracts? What are the identities of these genes? Population-based studies are needed to determine if there is a genetic susceptibility to age-related cataract. If genetics is identified as a factor, studies to map these susceptibility genes need to be implemented.

If genetic mutations play a role in age-related or congenital cataracts, do they confer susceptibility alone, or must they act in the presence of certain environmental insults? With the identification of susceptibility genes, genetic epidemiology studies must be designed to address how and to what degree environmental insults such as UV irradiation, hormones, and nutrition contribute to the etiology of cataracts.

In animal and human cataract systems already partially characterized, what are the exact number of genes and what are the exact nucleotide changes occurring in the genes that are responsible for cataract formation? How do these mutations impair lens function? Complete genotypic and phenotypic characterization of these systems would accelerate genetic mapping studies of congenital and age-related cataracts by providing strong candidate genes.

Does further genetic mapping of mouse and human cataract systems suggest that the same genes may confer susceptibility to cataract in both systems? The use of mouse models has been a productive strategy of identifying candidate genes for human diseases. Continuation of this approach is needed. Studies to characterize the approximately 40 mouse mutants with cataract thus far identified need to be implemented and, once identified, the relevancy of these genes to human disease needs to be ascertained in genetic mapping studies.

Objective 4: Identify genes and pathways that control eye development, especially those critical for lens induction, cell fate determination, and cell differentiation.

Research Needs and Opportunities

Late in the last century, it was observed that the lens formed as a result of the interaction between embryonic ectoderm and the developing retina. This led to a series of classical experiments that suggested that lens formation was a simple process involving inductive signals sent from the presumptive retina, the optic vesicle, to the ectoderm. A number of experiments supported the idea that these signals were sufficient to stimulate lens determination in ectodermal tissue. With the discovery that the genetic disease aniridia is the result of mutations in a key

regulatory gene, Pax-6, lens biologists using molecular techniques and markers have taken a fresh look at early developmental events. Recent studies now suggest that ectoderm acquires a lens bias in a regionalized pattern before the formation of the optic vesicle, and that this lens bias is associated with expression of a lens homeobox gene Pax-6. By the time of contact between the optic vesicle and ectoderm, regions of the ectoderm have already been committed to forming lens. These findings suggest that lens formation is a complex process requiring a number of tissue interactions and the hierarchical expression of a number of genes encoding transcription factors including Sox-2, Rx-1, and the homeobox genes Optx-2 and Pax-6.

These findings have for the first time allowed investigators to hypothesize a conceptual framework for lens determination. However, the interactions among these genes are not understood well enough to know how they coordinate lens formation, and there are likely to be many genes critical for this process that remain to be identified. Many of the identified genes are known to act as transcriptional regulators. While crystallins have been identified as targets of Pax-6 and other transcriptional regulators during lens differentiation, targets of these genes at the earlier stage of lens determination have yet to be defined. Far less is known about the signal transduction pathways that control lens induction and differentiation, though the technology and systems alluded to above can be applied to these questions.

Studies of lens development will benefit from approaches that integrate molecular genetics and embryology by allowing investigators to characterize cell fate genes by the timing of their expression and their place in the developmental hierarchy. As these developmental processes become defined, candidate genes for congenital cataract as well as other congenital diseases affecting the anterior segment will likely be identified. This will allow geneticists to select candidate genes based on their relevance to the developmental characteristics of the syndrome being mapped.

Strategic Research Questions

What are the key transcriptional regulators that control lens determination and differentiation? What is the hierarchical relationship among them and what is their mechanism of action? The identification of Pax-6 as a key regulator in lens determination has reshaped researchers' concepts of lens development. However, the total picture is just emerging, and as genes are discovered, gaps in knowledge will be filled in. Defining interactions among the genes and determining how they coordinate lens formation are critical to completing the picture.

How does the developing lens act to coordinate development of adjacent eye tissues? From studies of Pax-6 it is clear the lens plays a critical role in eye formation. The identification of additional lens-expressed genes and a demonstration of their role in eye development will provide a starting point to ask questions related to the role of the lens in overall eye development.

What are the genetic interactions, as defined by gain of function and loss of function experiments, that define the hierarchy of genes controlling lens determination? Experimental strategies that manipulate gene expression in model systems, either positively or negatively, should be highly useful in defining the gene interactions and determining hierarchical relationships in lens determination.

Do particular gene activities like those of Pax-6 control biologically defined phenomena such as lens specification and differentiation? Functional analysis is needed to identify specific roles for gene products of critical regulatory genes. This will require strategies that integrate classical embryological techniques with genetics and molecular biology.

What are the signals from tissues surrounding the developing lens? What are the receptors and pathways within the lens ectoderm that control its determination? Little is known about the signals and signal transduction pathways that control lens induction and differentiation. With technology advancing at a rapid rate, researchers can now approach these issues.

Objective 5: Define the contributions of crystallins to normal lens function.

Research Needs and Opportunities

The α -, β -, and γ -crystallins make up the bulk of the lens mass and are responsible for the larger refractive index of the lens. The α -crystallins, comprised of two highly related chains (αA and αB), account for approximately 40 percent of lens dry weight, while the families of β - and γ -crystallins, comprised of a least nine related proteins, account for almost all of the remaining dry weight of the lens. The relative contributions of each of the α -, β -, and γ proteins to the total refractile properties of the lens are unknown. In addition, nothing is known concerning the importance of each of the β and γ species in maintaining normal lens transparency, especially under conditions of metabolic stress. The roles of the α -, β -, and γ -crystallins in the possible control of molecular processes that occur during differentiation of the lens epithelial cells also remain undefined.

Recent findings indicate that α -crystallins possess molecular chaperone properties that enable them to inhibit nonspecific protein aggregation. This discovery has demonstrated a physiological role as well as a structural role for α -crystallin. In addition, significant amounts of αB crystallin have been found in other tissues besides the lens, including the retina, the heart, and the brain. Abnormally large amounts of αB crystallin are also found in some human neurological disorders. Both these observations suggest the intriguing possibility that the αB crystallin may also play physiological roles in other tissues.

This discovery of chaperone activity has provided the impetus for conducting further studies to characterize the structural and biochemical properties of this physiologically important process. The ability to perform structure and function studies has been aided by the techniques of molecular biology. The production of large amounts of unmodified crystallins is now possible. Genetic manipulations in mice have permitted the development of animal lines that either lack or overexpress specific α -, β -, or γ -crystallin polypeptides. Recent refinements in the use of cryoelectron microscopy and NMR spectroscopy now make the structural elucidation of large proteins that comprise macromolecular aggregates like α -crystallin feasible.

Strategic Research Questions

What are the molecular structures of the α -crystallins, and what parts of these structures are important in the molecular chaperone properties of the molecules? Technology such as cryoelectron microscopy and NMR spectroscopy now make it possible to address crystallin structure. New labeling techniques allow the spectroscopic identification of specific domains within molecular structures. The information gained from this technology is a first step in defining functional subdomains.

What are the preferred target proteins in the lens for chaperone function? Identifying target proteins will define the physiological role for chaperone function and serve to identify which lens proteins may play a role in cataract formation.

Are some forms of human cataract a direct result of the failure of α -crystallin to act as a molecular chaperone? Strategies such as analysis of loss of function mutants in model systems can be used to provide clues as to the role of this protein in maintaining transparency. From results in these systems, genetic mapping strategies and biochemical analysis can be pursued in humans.

Is the function of αB crystallin in the lens the same as outside the lens, and is this function related to abnormally high levels of expression in certain human disease states? Tissues outside of the lens can potentially reveal new insights into the function of α -crystallin in the lens. Much can be learned from pursuing such studies, particularly in regard to the stress-related role of α -crystallin in the disease process.

What possible roles do the α -, β -, and γ -crystallins play in lens differentiation? The roles of the α -, β -, and γ -crystallins in controlling molecular processes that occur during differentiation of the lens epithelial cells is an area that needs to be investigated.

What are the contributions of each of the β - and γ -crystallins to the transparent and refractile properties of the lens? Even though the crystallins make up the bulk of the lens mass and are responsible for the larger refractive index of the lens, little is known about the relative contributions of each of the α -, β -, and γ proteins to the total refractile properties of the

lens. Nothing is known about the role of each of the β and γ species in maintaining normal lens transparency, especially under conditions of metabolic stress. Strategies to address these questions need to be developed.

Do any of the β - or γ -crystallins have functional roles in tissues other than the lens? Inherent in the concept of gene sharing in regard to the crystallins is the question of whether crystallins have functions in tissues outside of the lens.

Objective 6: Characterize the control of the cell cycle in lens epithelial cells by identifying cell cycle regulators, growth factors, receptors, and signal transduction pathways.

Research Needs and Opportunities

A substantial proportion of people who undergo cataract surgery develop secondary cataracts, a complication that increases the cost of cataract treatment because a second surgical procedure is required. Research has shown that secondary cataract formation is the result of a normal response of the residual lens epithelial cells that often remain after surgery. In the normal adult lens, cell division and differentiation are precisely regulated. After cataract surgery, however, the residual cells appear to be relieved of these controls and begin dividing in an attempt to form a new lens. If this process interferes with vision, laser treatment is required. It is essential to understand the regulation of proliferation and differentiation of these cells in order to devise new cost-effective preventive strategies.

Growth of the lens is regulated by controlled proliferation of lens epithelial cells and precisely localized induction of lens fiber cell differentiation. Lens epithelial cell proliferation appears to be regulated in part by synthesis of PDGF in the anterior chamber of the eye and in part by FGF stimulation near the lens equator. Differentiation into fiber cells appears to be induced by exposure to elevated levels of FGF, which may be acting in concert with IGFs. Signaling through specific integrins may also play a role in this process.

In contrast to the progress that has been made in identifying the extracellular factors that regulate lens growth and differentiation, very little is known about the

specific signal transduction mechanisms they activate. While it is clear that PDGF, different members of the FGF family, and IGFs all act through receptors that have tyrosine kinase activity, the signaling pathways must be distinct in each case. Defining these differences will be crucial to understanding differentiation and cell cycle regulation in the lens. Moreover, since numerous pharmacological agents are available that target signal transduction pathways, information about the relevant signal transduction mechanisms in the lens will open the possibility of pharmacological intervention in situations involving abnormal proliferation or differentiation of lens cells.

Although the specific signaling pathways leading to lens fiber cell differentiation are not yet understood, it is clear that these signals ultimately result in cell cycle withdrawal and changes in gene expression. Several lines of investigation indicate that the active, hypophosphorylated form of the tumor suppressor protein pRb plays a crucial role in this process. Interestingly, however, the expression of Cdk4, the enzyme primarily responsible for phosphorylating pRb and initiating entry into S phase, is not downregulated during normal fiber cell differentiation. Both Cdk4 and its regulatory protein cyclin D are expressed at high levels during fiber cell differentiation. However, activity of the Cdk4/cyclin D complex is suppressed by the Cdk inhibitor p57^{kip2}, thus preventing pRb phosphorylation and leading to cell cycle arrest. The central role of this Cdk inhibitor in normal fiber cell differentiation has recently been demonstrated by homozygous disruption of the p57^{kip2} gene.

In addition to cyclin D/Cdk4, several other cyclins and Cdks are expressed in differentiating lens fiber cells, including p35/Cdk5 and, in the embryonic lens, cyclin B/Cdc2. Since these kinases have also been implicated in apoptosis of certain cell types, their presence in lens fibers raises the possibility that they may be involved in the apoptotic-like events that characterize terminal differentiation of lens fiber cells. Other proteins involved in apoptosis may play roles in terminal differentiation.

Among these are members of the bcl-2 family and the proteases (or capsases) related to the interleukin-1 beta-converting enzyme. Genetic and biochemical analyses of these and other proteins that regulate cell cycle progression and apoptosis

are needed to provide insight into specific genetic defects that lead to aberrant differentiation, inappropriate apoptosis, and cataract. This analysis can also provide an understanding of the uncontrolled lens cell epithelial growth characteristic of secondary cataract.

Strategic Research Questions

What are the growth factors and matrix components that regulate growth and differentiation of the lens *in vivo*? Is growth factor stimulation required throughout the differentiation process or only to initiate the differentiation cascade? Defining individual components involved in growth and differentiation signaling and the mechanistic details of the signaling process is a first step in identifying pathways to target in developing preventative strategies for posterior subcapsular cataract.

Which signal transduction pathways are selectively activated by signals for proliferation or differentiation? Which transcription factors are targeted by the signal transduction pathways? Identifying signaling pathways and transcription factors targeted by these pathways are crucial to understanding differentiation and cell cycle regulation in the lens. Strategies involving pharmacological agents that target signal transduction pathways should provide information about the relevant signal transduction mechanisms in the lens and open the possibility of pharmacological intervention in situations involving abnormal proliferation or differentiation of lens cells.

What regulates expression of the cyclin-dependent kinase inhibitor p57^{kip2}? What target genes other than p57^{kip2} need to be turned on or off to initiate differentiation? A critical step in cell cycle regulation requires the suppression of cell cycle activating proteins. To acquire a complete picture of lens cell growth and differentiation, the details of this step in cell cycle regulation need to be elucidated.

What are the roles of cyclins, Cdks, and other cell cycle regulatory proteins during fiber cell differentiation? Several cyclins and Cdks are expressed in differentiating lens fiber cells. Transgenic and knockout technology should enable investigators to sort out the specific roles for these proteins.

Are apoptosis and terminal differentiation of fiber cells related processes? Genetic and biochemical analyses of proteins that regulate cell cycle progression and apoptosis may provide insight into specific genetic defects that lead to aberrant differentiation, inappropriate cell death, and cataract, as well as an understanding of the uncontrolled lens cell epithelial growth characteristic of secondary cataract.

Objective 7: Characterize, at the molecular level, the ion channels, transporters, and gap junction proteins needed to maintain lens homeostasis; determine what roles perturbations in these systems play in cataract formation.

Research Needs and Opportunities

To perform its refractory function, the lens must be transparent; hence, light-scattering elements are precluded. Consequently, the lens is an avascular tissue that comprises precisely packed multiple layers of cells. Because of the absence of blood vessels, the lens relies on the epithelial cells to take up solutes and ions from the aqueous humor. The epithelial cells then must provide all the necessary metabolic requirements to cells in the lens. To accommodate its unique situation, the lens uses a vast array of channels, pumps, and intercellular connections at gap junctions to distribute nutrients, remove metabolites, and maintain the proper ionic balance for both epithelial and lens fiber cells.

The regional distribution of sodium/potassium pumps, channels, and gap junctions throughout the lens likely creates an internal circulatory system that compensates for the lack of a vasculature system. A system in which ions and water enter the lens along intercellular clefts, cross fiber cell membranes, flow from cell to cell through gap junction channels toward the surface, and cross surface cell membranes to complete the loop has been postulated. The driving force behind the direction of these fluxes is a difference in electromotive potential between outer epithelial cells and inner fiber cells and the distribution of gap junctions in differentiating fiber cells. Because the system of ion fluxes is critical to maintaining transparency, investigators have directed their attention to understanding the details of the various components of the system.

For many years, understanding the molecular mechanisms involved in gap junction function was hampered by a lack of knowledge concerning which membrane polypeptides were directly involved in channel formation. Using methods of modern molecular biology, many of these proteins (called connexins) have been identified and cloned, making it possible to ask the fundamental questions concerning gap junction function. Recently, the tools have been developed that will facilitate definitive examination of the roles and the importance of lens gap junctions. Antibody probes allow the detection of all of the lens connexins. DNA clones permit the detection of the connexin genes and mRNAs and the molecular manipulation of their expression, both in tissue culture systems and in mouse transgenic and knockout lines. Electrophysiological methods are now available for examining lens intercellular communication and studying the biophysical properties of lens gap junction channels.

The importance of gap junctions in maintaining transparency has recently been demonstrated. Experiments were conducted using mice in which deletion of the fiber-specific connexin 46 was introduced. Mice homozygous for the deletion developed nuclear opacities within 3 weeks of birth. The association of these nuclear cataracts with proteolysis of crystallins underscores the significance of gap junctions to the overall homeostasis of the lens.

A number of ion-conducting channels have been identified. Substantial diversity has been discovered in lens potassium channels and suggests that the regulation of transmembrane voltages will likely be complex. Furthermore, several of these channels have been shown by molecular biology to be identical to those from excitable tissues. Asymmetric placement of lens ion transporters has been shown to result in spatially varying standing current flow in the lens. Models of these processes support an internal circulation of fluid in the lens. Chloride channels have been shown to be involved in the lens response to nonisotonic media. However, specific chloride channels have yet to be identified. Sodium conductance in epithelial cells appears to be via a nonselective cation channel. However, the relevance of the leak conductance of sodium by this channel has not been established. Major intrinsic protein (MIP) from lens fiber membranes has been shown to function

as a water channel. Interestingly, lack of this protein occurs in an experimental line of cataractous mice.

Understanding the ion conductance in the lens potentially has clinical relevance. The formation of many kinds of cataracts is accompanied by a rise in both intracellular sodium and calcium with a concomitant loss of intracellular potassium. The molecular nature of the transporting proteins involved in these derangements is essentially unknown. It is clear that lens cell membranes, like other cell membranes, have little permeability to ions in the absence of specific transport proteins; therefore, alterations in these proteins must be involved in the ionic alterations that accompany cataract formation. A detailed structural and functional knowledge of the specific transport proteins involved in these ionic changes is needed, especially in those involved in sodium and calcium movements in the lens. Such movements can occur by adenosine triphosphate (ATP) driven pumps, specific ionic channels, nonspecific ionic channels, and nonchannel-based transporters and can be influenced by transmembrane voltages in the lens. Thus, chloride channels, potassium channels, and electrogenic transporters involved in maintaining lens voltages are critical for controlling lens sodium and calcium movements. It is, therefore, just as important to understand the molecular nature of these transporters as it is to understand those for sodium and calcium movements. Recent advances in molecular biology, electrophysiology, and cellular imaging now allow the molecular nature of these processes to be investigated.

Lastly, the mechanisms that regulate transport need to be understood. Muscarinic and purinergic receptors have been found in lens epithelial cells. Both are involved in intracellular calcium regulation. The signal pathways that are linked to muscarinic and catecholamine receptors, purinoceptors, and other receptors remain to be characterized. As channels are identified and characterized, there will be new opportunities to address questions about their localization, functional integration, and regulation.

Strategic Research Questions

What is the importance of each of the connexins in maintaining lens homeostasis? What is the contribution of each of the connexins to the

maintenance of lens transparency? The opportunity to explore the role of gap junctions in lens in maintaining lens homeostasis and transparency has been made possible by the cloning of connexin proteins. With tools such as antibody probes and cloned genes for transfections, experimental strategies to perform *in situ* histochemical and electrophysiological analyses should provide insight into the function of gap junctions in the lens. Transgenic and knockout technology is proving to be a valuable tool in ascertaining the role of connexins in maintaining lens transparency.

What are the essential molecules that pass through the lens gap junctions, and how is their passage controlled? Identifying the molecules transported by gap junctions and how their passage is regulated will enhance understanding lens physiology. This information should provide significant insights into how changes in levels of essential small molecules, such as glutathione and osmolytes, contribute to age-related and diabetic cataract, respectively.

What is the role of gap junctions in lens development? What molecular mechanisms control expression of connexin genes during lens development? With the availability of cloned genes, connexin-encoding genes can be introduced or deleted in developing embryos *vis-à-vis* transgenic and knockout technology in mice and retroviral technology in the chick. The ability to genetically alter expression of connexins in model systems will allow investigators to pursue strategies to study the role and regulation of connexins in development.

What metabolic factors control opening and closing of the gap junction channels? How do posttranslational modifications and proteolysis contribute to the regulation of gap junctions? Data suggest that posttranslational modifications of connexins regulate gating properties and assembly of gap junctions. Identifying and characterizing posttranslational modifications in gap junctions will expand science's database of knowledge on the role of posttranslational modifications in the maintenance of lens homeostasis.

How are the subunits of gap junctional proteins assembled into functional channels and plaques? How connexins are assembled into functional channels across fiber-fiber, epithelial-epithelial, and fiber-epithelial cell types is unknown. Strategies that

combine the tools of cell and molecular biology should be useful in delineating the critical steps in assembly.

What regulatory signaling pathways exist and how do they alter channel function? Identifying the regulatory pathways that control channel function is critical to understanding how the lens' internal circulatory system functions to maintain lens health.

What are the structural and detailed biophysical properties of each ion channel and pump in lens cells? The lens cells likely contain a complex array of ion channels and pumps in the lens internal circulatory system. Characterization of each individual component is necessary to develop a complete picture of this circulatory system.

How are the channels and pumps targeted to the plasma membrane or to organelle membranes and how is their distribution between epithelium and fibers regulated? Membrane targeting creates an asymmetric distribution of transporters. Presumably this structural distribution reflects a functional specialization that contributes to driving the circulation of ions and fluids. Characterizing membrane targeting of transporters and the distribution of transporters throughout the lens are essential to understanding the driving forces behind the lens circulatory system.

How do changes in ion fluxes apply to cataract models and human cataract studies? Because the formation of many kinds of cataracts is accompanied by a rise in both intracellular sodium and calcium with a concomitant loss of intracellular potassium, strategies to identify the molecular nature of the transporting proteins involved in these derangements are needed. An understanding of ionic changes that accompany cataract formation will require a structural and functional knowledge of the specific transport proteins involved, particularly those subserving sodium and calcium movements in the lens.

Objective 8: Define the mechanisms that regulate the cellular and subcellular architecture of the lens, with special emphasis on the contribution of minor constituents and their progressive modification during aging and opacification.

Research Needs and Opportunities

While cytoskeletal proteins and membrane proteins are minor constituents of lens cells, lens-specific intermediate filaments CP49/phakinin and CP115/filensin and membrane proteins MIP and MP20 may be required for the unique organization of epithelial cells, transparent lens fibers, and lens elasticity. The molecular interactions among cytoskeleton, α -crystallins, and lens cell membranes appear to be modulated by common metabolites (ATP, glutathione, calcium, taurine, and endogenous lens peptides), which influence the symmetric differentiation of lens fibers and the normal development of the transparent lens. Variations in lens metabolites may be a response to regulators of differentiation and growth that are responsible for developing symmetric transparent lenses.

Little is known about the interactions between epithelial and fiber cells that contribute to the symmetry of developing transparent lenses. In lens cells, the preferential expression of CP49/phakinin, CP115/filensin, MIP, and MP20 may be a response to growth factors, signaling pathways, and intercellular communication involved with the regulation of lens cell differentiation that specify normal proliferation and differentiation of lens fiber cells. Defective regulation of growth and differentiation observed in transgenic mice with altered growth factor responses and knockout mice in which Rb is deleted result in asymmetric cellular organization and opacification of lenses. These mice provide an opportunity to investigate not only the contribution of the cytoskeleton and membrane proteins to lens transparency but also the relationship between cytoskeleton integrity, the cytoarchitecture, and cell signaling pathways needed to maintain transparency.

During normal lens growth and development, symmetric shells of fiber cells meet end-to-end along well-defined planes known as lens sutures. Even subtle asymmetry in suture development may be an indicator of potential defects in the cytoarchitecture. Methodology to study lens organization at the tissue

and cellular levels is available. Quantitative analyses are needed to characterize the 3-D organization of lens sutures in normal and abnormal lenses. The use of confocal and other novel microscopic methods in systematic and quantitative analyses of lens cell and tissue structure will enhance researchers' understanding of the cellular organization within the lens tissue and the role of the cytoskeleton and other structural proteins in this organization. Transgenic and knockout mice with altered cytoarchitecture provide an excellent model system for relating structural studies of sutures to the cell biology of the cytoskeleton and the signaling pathways that regulate it. Finally, all such studies must lead to a better understanding of transparency in the human lens. Ultimately, human tissue must be analyzed in order to relate findings in model systems to the processes of aging and cataract formation.

Strategic Research Questions

How is the expression of lens-specific cytoskeletal and membrane components regulated during normal development or during loss of transparency in model systems and human lenses? Aberrations in subcellular architecture may arise as epithelial cells differentiate. Therefore, it is likely that the rearrangements of subcellular structure that occur as epithelial cells differentiate into fiber cells and fiber cells mature are regulated. Transgenic experiments suggest that defective regulation of growth and differentiation is accompanied by defects in cell organization. Technology to probe for differential expression of cytoskeletal and membrane components during normal and defective fiber cell differentiation and maturation is available in model systems. Strategies need to be developed to transfer information from model systems to humans.

Are progressive modifications of the cytoskeleton and cytoarchitecture of human epithelial cells during aging and cataract formation a response to molecular events involving the abnormal expression of growth factors, receptor distribution, and/or signaling functions? Experiments in transgenic mice suggest that defective regulation of growth and differentiation observed in transgenic mice with altered growth factors result in asymmetric cellular organization and opacification of lenses. These mice provide an opportunity to investigate the relationship between cytoskeleton integrity, cytoarchitecture, and cell-signaling pathways.

What changes in suture pattern occur during human cataract formation, normal lens aging, and/or changes in elasticity? Identifying changes in suture pattern during cataract formation and aging will provide structural information at the tissue level that may suggest fundamental underlying changes occurring at the cellular level.

How does the progressive modification of lens epithelial cells as observed *in vivo* result in either quantitative differences in 3-D organization or transparency of lens fiber cells in normal and opaque human lenses? Quantitative analyses are needed to characterize the 3-D organization of lens sutures in normal and abnormal lenses. The use of confocal and other novel microscopic methods in the analyses of lens cell and tissue structure will enhance understanding of the cellular organization within the lens tissue.

Will knockout or overexpression of lens-specific cytoskeletal and membrane components result in decreased or improved lens transparency and elasticity? This technology will enable scientists to answer fundamental questions concerning the contribution that the cytoskeleton and membrane proteins make to the overall functioning of the lens.

Objective 9: Understand the basis of lens accommodation and presbyopia at the molecular and mechanistic levels.

Research Needs and Opportunities

The ability to accommodate progressively decreases with age, eventually requiring many individuals in their midforties to wear reading glasses. This inability to accommodate adequately is termed presbyopia. Presbyopia affects everyone and has enormous economic impact as well as a disconcerting and frustrating impact on quality of life. Consider the fact that in 1997 there were approximately 93.6 million people over the age of 45 in the United States. First, there is the economic cost of increasingly poor work performance from a person's denial of the need for a reading aid. Second is the cost of obtaining an aid. If 25 percent of those age 45 and older received an eye examination (approximately \$60) and bought inexpensive bifocals (about \$150), the economic cost would be \$4.9 billion (ignoring transportation costs

and lost time from work). If another 25 percent solved their near-reading problem by buying nonprescription drugstore readers for \$20, the additional cost would be \$468 million. The economic and quality-of-life improvements of identifying preventive measures or interventions that delay or prevent both the loss of accommodation and the onset of presbyopia are obvious and would be of benefit to everyone, particularly when considering that these may be an individual's most economically productive and influential years.

The exact reasons that the accommodative system fails remain elusive. It has long been suspected that as the lens ages it becomes thicker and less pliable, losing its ability to change shape and consequently its ability to accommodate. There is also some evidence to suggest that the muscle controlling the tension of the zonular attachments to the lens capsule may play a significant if not key role in the failure of the accommodative mechanism to respond adequately with increasing age. In addition, there is preliminary evidence that near-vision can actually be restored by physically changing the relationship between the muscle and lens. Lastly, the role of extralenticular elastic tissues in the ciliary muscle and choroid, in pathophysiology and as therapeutic targets, needs to be explored.

In a somewhat different but related subject, it is known that as the lens ages, the anterior posterior thickness increases and the equatorial diameter decreases, leading to the paradox that a bigger, thicker lens is optically less powerful, as opposed to being more powerful.

In younger adults, malfunctioning of the accommodation mechanism has been implicated as a likely cause of adult-onset myopia. Differential accommodation between the two eyes is also likely to be involved in the development of anisometropia, a condition in which the two eyes have different refractive properties.

Because of recent advancements in measuring objectively the aberrations of the human eye *in vivo*, and because researchers have a better understanding of the biometry of the aging lens, researchers are in a position to accurately model gradient index changes within the lens that could explain the thick lens paradox. Similarly, recent advances in the resolution of a variety of noninvasive measuring techniques like

high-frequency ultrasound should resolve the geometric uncertainties of the relationships between the ciliary muscle, zonules, capsule, and lens during accommodation and as a function of age. These advances suggest ways to delay or prevent presbyopia.

Strategic Research Questions

How do the physical relationships between the ciliary muscle, zonules, capsule, and lens change with accommodation and as a function of age? The resolution of a variety of noninvasive measuring techniques has advanced to the point that they can be used to resolve the relationships between the ciliary muscle, zonules, capsule, and lens. Incorporating these techniques into population-based studies would clarify the role of these issues as they relate to accommodation and age.

Can medical therapy (e.g., antioxidants, lens growth inhibitors) favorably alter the accommodation versus age function? Scientists need to explore innovative approaches to treatment.

What is the role of accommodation in the onset of adult myopia? The etiology of this condition needs to be defined. Studies suggesting that malfunctioning of the accommodation mechanism underlies adult-onset myopia requires confirmation.

LENS AND CATARACT PANEL

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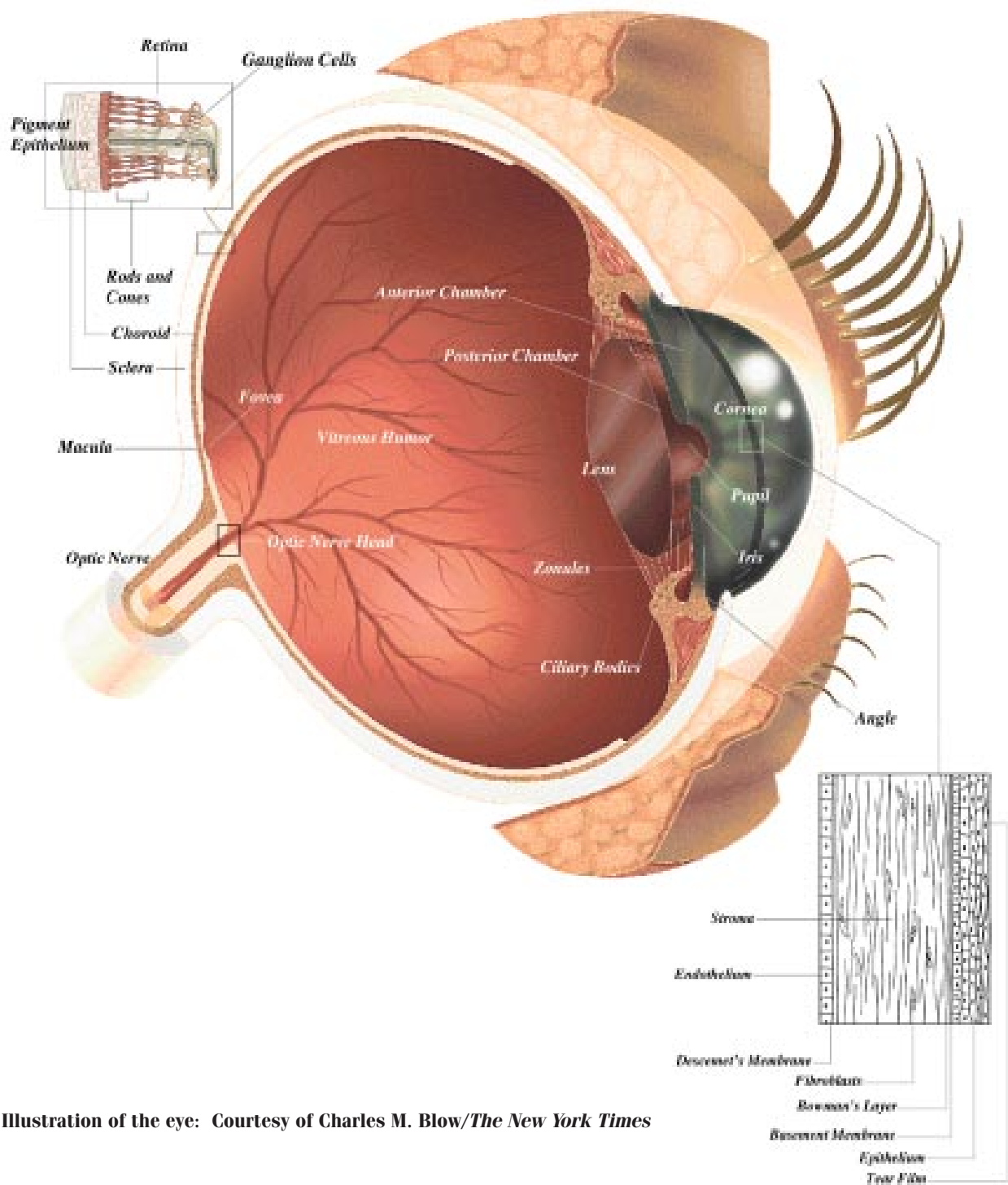


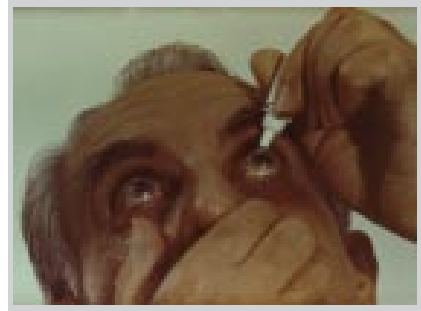
Illustration of the eye: Courtesy of Charles M. Blow/*The New York Times*

PROGRAM OVERVIEW AND GOALS

Glaucoma is a major public health problem in this country. The disease is manifest as a progressive optic neuropathy that, if left untreated, leads to blindness. It is estimated that as many as 3 million Americans have the disease and, of these, as many as 120,000 are blind as a result. Furthermore, it is the number one cause of blindness in African-Americans. Treatments to slow the progression of the disease are available; however, at least half of those who have glaucoma are not receiving treatment because they are unaware of their condition. Blindness from glaucoma is believed to impose significant costs annually on the U.S. Government in Social Security benefits, lost tax revenues, and healthcare expenditures.

Glaucoma is not a single disease but rather a heterogeneous group of disorders that share a distinct type of optic nerve damage that can lead to blindness caused by the death of retinal ganglion cells. These diseases involve several tissues in the front and back of the eye. Commonly, but not always, glaucoma begins with a defect in the front of the eye. Fluid in the anterior portion of the eye, the aqueous humor, forms a circulatory system that brings nutrients and supplies to various tissues. Aqueous humor enters the anterior chamber via the ciliary body epithelium (inflow), flows through the anterior segment bathing the lens, iris, and cornea, and then leaves the eye via specialized tissues known as the trabecular meshwork and Schlemm's canal to flow into the venous system. Intraocular pressure is maintained *vis-à-vis* a balance between fluid secretion and fluid outflow. Almost all glaucomas are associated with defects that interfere with aqueous humor outflow and, hence, lead to a rise in intraocular pressure. The consequence of this impairment in outflow and elevation in intraocular pressure is that optic nerve function is compromised. The result is a distinctive optic nerve atrophy, which clinically is characterized by excavation and cupping of the optic nerve, indicative of loss of optic nerve axons.

Primary open-angle glaucoma is,



by convention, characterized by relatively high intraocular pressures believed to arise from a blockage of the outflow drainage channel or trabecular meshwork in the front of the eye. However, another form of primary open-angle glaucoma, normal-tension glaucoma, is characterized by a severe optic neuropathy in the absence of abnormally high intraocular pressure. Patients with normal-tension glaucoma have pressures within the normal range, albeit often in the high normal range. Both these forms of primary open-angle glaucoma are considered to be late-onset diseases in that, clinically, the disease first presents itself around midlife or later. However, among African-Americans, the disease may begin earlier than middle age. In contrast, juvenile open-angle glaucoma is a primary glaucoma that affects children and young adults. Clinically, this rare form of glaucoma is distinguished from primary open-angle glaucoma not only by its earlier onset but also by the very high intraocular pressure associated with this disease. Angle-closure glaucoma is a mechanical form of the disease caused by contact of the iris with the trabecular meshwork, resulting in blockage of the drainage channels that allow fluid to escape from the eye. This form of glaucoma can be treated effectively in the very early stages with laser surgery. Congenital and other developmental glaucomas in children tend to be severe and can be very challenging to treat successfully. Secondary glaucomas result from other ocular diseases that impair the outflow of aqueous humor from the eye and include pigmentary glaucoma, pseudoexfoliative glaucoma, and glaucomas resulting from trauma and inflammatory diseases. Blockage of the outflow channels by new blood vessels (neovascular glaucoma) can occur in people with retinal vascular disease, particularly diabetic retinopathy. The Glaucoma Program encompasses the study of all glaucomas; however, its major focus remains on primary open-angle glaucoma because of the large number of people affected and its public health impact.

Primary open-angle glaucoma can be insidious. It usually begins in midlife and progresses slowly but relentlessly. If detected, disease progression can frequently be arrested or slowed with medical and surgical treatment. However, without treatment, the disease can result in absolute irreversible blindness. Even though the initial site is believed to occur in the outflow drainage channels at the front of the eye, vision loss from primary open-angle glaucoma is the result of damage to the retinal ganglion cells, whose axons form the optic nerve at the back of the eye.

For many patients, the link between the block in fluid drainage in the front of the eye and retinal ganglion cell death is thought to be an elevation of intraocular pressure. However, as is evident from normal-tension glaucoma, glaucomatous optic nerve damage can occur in the absence of abnormally high intraocular pressures. Conversely, ocular hypertension does not always lead directly to optic nerve damage. Approximately 5 million Americans have elevated intraocular pressures without optic nerve damage or visual field loss. Only some of these ocular hypertensive individuals will actually develop the optic nerve damage that defines glaucoma. Because the relationship between pressure and optic nerve damage is not necessarily direct, high intraocular pressure is now considered to be a risk factor rather than an essential disease characteristic.

An important goal of current research is to develop methods of early diagnosis to detect the disease in the early stages, when treatment is most effective in minimizing irreversible vision loss. This is made more critical by the apparent absence of symptoms in the early stages of glaucoma. Because elevated intraocular pressure is not always accompanied by pathology, nor does elevated intraocular pressure always lead to optic neuropathy, the diagnosis of glaucoma now emphasizes the presence of visual field loss and observable characteristic optic nerve damage. Individuals with ocular hypertension present a unique dilemma for clinicians. In the absence of any overt pathology, clinicians must decide whether or not to treat these individuals with intraocular pressure-lowering medications that can pose a considerable expense and often have side effects. This dilemma can be avoided with more knowledge concerning the natural history of the disease and whether early treatment can prevent the onset of glaucoma.

Because characteristic visual field changes in glaucoma patients are due to degeneration of retinal ganglion cells, clinical progress goes hand-in-hand with progress in understanding how retinal ganglion cell loss occurs and the role played by elevated intraocular pressure in this process. Continued clinical and laboratory research has provided a greater understanding of the normal functions of the ocular tissues involved in the disease. Such studies have led to the introduction of a variety of new drugs to reduce intraocular pressure, the development of new diagnostic tools, better estimates of disease prevalence and incidence, and the identification of glaucoma genes.

In Fiscal Year 1997, the National Eye Institute (NEI) funded 146 extramural research projects in the Glaucoma Program at a total cost of \$29,935,000.

The overall goal of the Glaucoma Program is to identify the biological mechanisms responsible for glaucoma so that improved treatment can be developed. As a means of achieving this overall goal, the Panel recommends the following general goals:

- Develop improved measures to aid in the clinical diagnosis of glaucoma; monitor progression of disease and treatment effectiveness; and elucidate the pathophysiology and natural history of the disease.
- Understand the molecular and biochemical basis of aqueous humor dynamics, with special emphasis on outflow.
- Identify genetic loci and genes contributing to glaucoma, especially those responsible for the common forms of the disease.
- Determine the mechanisms of optic nerve damage and retinal ganglion cell loss and survival in glaucoma.

ASSESSMENT OF PROGRESS

The development of new diagnostic and imaging methods. Developing new visual field test procedures provide more reliable and objective methods for the early diagnosis of glaucoma and for determining the progression of glaucomatous damage. Unlike traditional methods that are based on detecting a small increment of white light on a white

background, the new procedures are designed to isolate and measure those visual functions mediated by specific subsets of ganglion cell populations. The most promising of these new visual field procedures is short-wavelength automated perimetry (SWAP), a procedure that isolates short-wavelength-sensitive vision mechanisms by using a bright yellow background and large blue stimuli.

Longitudinal investigations have established that SWAP can detect glaucomatous visual damage 3 to 5 years earlier than conventional perimetry. Because visual field defects appear earlier with SWAP, earlier detection of glaucoma is a possibility. Standardization of the instrument and its analytical software has made SWAP a viable diagnostic test procedure for future clinical use. Recent quantitative studies have shown a clear correlation between visual function in glaucoma and structural measures of the optic nerve and nerve fiber layer. For instance, information from structure and function analysis has been greatly improved with the introduction of the confocal scanning laser ophthalmoscope. Several new diagnostic instruments using this technology are now commercially available. These instruments are highly reproducible and provide more objective data in much less time than conventional methods, such as stereoscopic fundus photography. Optical coherence tomography is another promising imaging technique currently under evaluation.

Better estimates of the prevalence of glaucoma. Epidemiological studies conducted in the United States and the West Indies have improved the prevalence and incidence estimates of primary open-angle glaucoma among white and black populations. One strength of these studies is the adoption of more inclusive definitions of primary open-angle glaucoma that require the presence of visual field loss or optic disc damage, but do not necessarily require the presence of elevated intraocular pressure. The Beaver Dam (Wisconsin) Eye Study, which studied nearly 5,000 individuals between the ages of 43 and 84, reported a prevalence rate of 2.1 percent in a predominantly Caucasian sample. The Baltimore Eye Study, with over 5,000 participants age 40 and older, reported a prevalence rate of 1.7 percent among Caucasian Americans and 5.6 percent among African-Americans. These prevalence estimates for white Americans are consistent with findings reported in epidemiological studies conducted in Rotterdam and

Australia. The Barbados Eye Study, which studied over 4,000 black Barbadians ages 40 to 84, reported a prevalence rate of 7 percent. The Barbados Eye Study and the Baltimore Eye Study confirm a substantially higher prevalence of primary open-angle glaucoma in Caribbean blacks and African-Americans than in whites.

Introduction of two new drugs to lower intraocular pressure. Over the past 5 years, two new medical therapies for glaucoma have been introduced: latanoprost (Xalatan) and dorzolamide (Trusopt). These are the products of research sponsored by the NEI.

Latanoprost—Initial efforts to use the ocular hypotensive action of naturally occurring prostaglandins (PGs) as a glaucoma therapy were hampered by an inflammatory response they elicited. Recently, a prodrug, an isopropylester of PGF-2 α (latanoprost), was developed as an effective ocular hypotensive agent with clinically acceptable side effects. This esterified analog of PGF-2 α enhances corneal penetration and reduces external side effects without compromising the efficacy of the active moiety.

Dorzolamide—Although orally administered carbonic anhydrase inhibitors (CAIs) have been used clinically for many decades to lower intraocular pressure, their use has been compromised by systemic side effects. By improving lipid solubility and, hence, membrane penetration, without losing water solubility, the topically active CAI dorzolamide (Trusopt) was developed. Topical administration of dorzolamide has far fewer systemic side effects and better patient compliance compared to orally administered CAIs.

The use of antimetabolites to improve filtration surgery outcomes. Over the past decade, the use of antifibrotic agents to enhance the success of glaucoma filtration surgery in patients has become accepted practice. Filtration surgery is often undertaken for the 40 percent to 50 percent of patients whose glaucoma is not amenable to medical therapy. The surgical procedure, which involves opening a channel through the sclera to allow aqueous humor drainage, frequently fails because of an excessive healing response that involves fibroblast proliferation and excessive collagen deposition around the wound site. Two agents that block DNA synthesis—mitomycin-C

and 5-fluorouracil—are effective in reducing the failure rate in trabeculectomy, the most common form of filtration surgery, precisely by inhibiting fibroblast proliferation. Especially in patients with a high clinical risk for surgical failure, these agents have been valuable in increasing the likelihood of a favorable outcome. However, adverse long-term effects of these agents limit their use. Perhaps with a better understanding of the biology of wound healing, new agents that prevent scar formation at the wound site without adverse effects will be discovered.

Progress in characterizing the signaling mechanisms in the diverse tissues of the anterior segment.

The past 5 years have seen substantial advances in characterizing the signal transduction pathways in the iris-ciliary body and trabecular meshwork, which mediate the responses of the eye to endogenous ligands and drugs. Besides the classic neurotransmitters norepinephrine and acetylcholine, many neuropeptides have been identified in the ocular autonomic and sensory nerves that supply all tissues of the anterior segment, including the ciliary processes and trabecular meshwork. The novel neurotransmitter nitric oxide has been implicated in signaling by the ocular parasympathetic nerves. At an intracellular level, isozymes involved in the ocular synthesis (adenyl and guanyl cyclase) and degradation (phosphodiesterases) of cyclic adenosine monophosphate and cyclic guanosine monophosphate, two of the principal second messengers in the ciliary processes and trabecular meshwork, have been identified. In addition, the functions of phospholipids such as phosphatidylinositol and calcium turnover in these ocular tissues are becoming better understood. Advances have been made in understanding the mechanisms by which various agents like peptides, purines, and biogenic amines regulate aqueous humor secretion. In the ciliary body, roles for receptors of adenosine and for peptides such as endothelin, calcitonin gene-related peptide, opioids, natriuretic peptides, and somatostatin are being identified. Several subtypes of $\alpha 2$ adrenoceptors and serotonin receptors are also found in this tissue. In ciliary muscle, endothelin receptors influence calcium mobilization and eicosanoid formation, suggesting receptor linkage to more than one signal transduction pathway.

Quite apart from the descriptive information, several new concepts have become widely accepted. The multiplicity of receptors, second-messenger cascades, and target transport proteins make the second-messenger regulation of transport unique for nearly each cell type. Synergism between parallel hormones or stimuli is likely in regulating ciliary epithelial secretion, a point particularly well documented for the cooperative hormonal actions on intracellular calcium levels. There is increased awareness of possible effects not only on unidirectional secretion but also on reabsorption, leading to the concept that the two processes must be coordinated.

Mapping of multiple genetic loci associated with glaucoma. Progress in understanding the molecular genetics of glaucoma has been achieved in the past few years. A major advance came with the genetic linkage mapping of a locus on chromosome 1q (GLC1A) to juvenile open-angle glaucoma. Subsequent studies confirmed the chromosome 1q linkage and resulted in the fine mapping of the genetic interval. To date, the following glaucoma loci have been mapped for glaucomas or ocular diseases associated with secondary glaucomas:

- ▶ 1q23 - Juvenile-onset primary open-angle glaucoma
- ▶ 1p36 - Congenital glaucoma
- ▶ 2p21 - Congenital glaucoma
- ▶ 2qcen-q13 - Adult-onset, low-tension, primary open-angle glaucoma
- ▶ 3q21-24 - Adult-onset primary open-angle glaucoma
- ▶ 4q25 - Rieger's syndrome (RIEG1)
- ▶ 6p25 - Iridodysgenesis
- ▶ 7q35-q36 - Pigment dispersion syndrome and pigmentary glaucoma
- ▶ 11q13 - Aniridia
- ▶ 13q14 - Rieger's syndrome (RIEG2)

This work and the mapping of other glaucoma-related loci have substantiated the concept of a genetic component to glaucoma.

Identification and characterization of glaucoma-associated genes. In addition to mapping of glaucoma loci by genetic linkage, significant advances in the discovery of glaucoma-causing genes have occurred. A gene for juvenile primary open-angle glaucoma (GLC1A) was identified. The gene codes for a protein called trabecular meshwork glucocorticoid response protein (TIGR) that was first identified as a protein made by trabecular meshwork cells exposed to glucocorticoid hormones. Subsequently, this gene was found to be the same as genes identified from cDNA libraries made from ciliary body and retina. This gene cloned from the retina was named “myocilin” because of the myosin-like domain within the gene. Mutations in this gene have been associated with juvenile-onset primary open-angle glaucoma and, in a small percentage of cases, of adult-onset primary open-angle glaucoma. The normal function of this gene and the role that dysfunctional forms of the gene play in the pathogenesis of glaucoma are unknown.

A gene involved in cases of autosomal recessive congenital glaucoma that maps to 2p21 (GLC3A) has recently been identified. This gene codes for cytochrome P4501B1. The initial mutations identified in this gene appear to be null mutations, implying that loss of function of this gene results in the phenotype. A gene involved in one form of Rieger’s syndrome has also been identified. This gene was identified by cloning a chromosomal translocation breakpoint involving chromosome 4 in a patient with Rieger’s syndrome. The gene called RIEG1 codes for a bicoid homeobox transcription factor, which has been named Solurshin. This same gene has been shown to be involved in some cases of iris hypoplasia with associated glaucoma.

Conceptualization of retinal ganglion cell loss in glaucoma as an active cellular process amenable to mechanistic study and the development of novel therapeutics. Characteristic visual field changes and eventual loss of visual acuity in glaucomatous optic neuropathy are due to degeneration of retinal ganglion cells. The loss of axons of the retinal ganglion cells can be seen clinically as a thinning of the nerve fiber layer and an excavation

of the optic disk, clinically called “cupping.” In many but not all patients this is associated with elevated intraocular pressure. Explanations for how these changes in the glaucomatous optic nerve occur and progress have primarily been based on how elevated intraocular pressure might alter the optic nerve tissue. Two hypotheses have been put forth to explain the effect of high intraocular pressure: one postulates pressure-induced mechanical damage, and a second postulates pressure-induced ischemia.

In the last few years, researchers have determined that, to understand glaucoma, they need to understand how retinal ganglion cells die, irrespective of whether ischemia, mechanical damage, or another mechanism initiates the degeneration. Recent observations have brought new insights into understanding retinal ganglion cell death after axonal damage and have underscored the need to investigate cellular and molecular mechanisms of neuronal degeneration. Evidence that retinal ganglion cells die by apoptosis (programmed cell death) following inner retinal ischemia, optic nerve transection, or elevated intraocular pressure suggests that the molecular components of the cascade of programmed cell death should be investigated in glaucoma. Retinal ganglion cells are sensitive to the excitotoxic action of the neurotransmitter glutamate, and glutamate is present in increased amounts in the vitreous of glaucoma patients and monkeys with experimentally elevated intraocular pressure. Finally, recent data show that retinal ganglion cells are sensitive to peptides that are known to enhance their survival, providing a possible therapeutic opportunity.

PROGRAM OBJECTIVES

Following are the objectives of the Glaucoma Program over the next 5 years.

- Identify genes and genetic loci contributing to glaucoma, especially those responsible for the common forms of the disease, and characterize the function and interaction of their gene products.
- Define the molecular and biochemical mechanisms that lead to retinal ganglion cell death in human glaucoma and in relevant animal models of related optic nerve injury.

- Enhance understanding of the structure and function of the aqueous humor outflow pathways at the cellular and molecular level.
- Develop a better understanding of anterior segment immunology.
- Improve our understanding of the nature and course of glaucoma, incorporating studies of comorbidity, natural history, and genetics, with special emphasis on Hispanic, Native American, and African-American populations.
- Develop improved diagnostic techniques encompassing measures of visual function, optic nerve, and nerve fiber layer structure, *in situ* and for clinical applications of genetics.
- Identify neuroprotective strategies that could prevent retinal ganglion cell death, promote survival, or stimulate regeneration.

The needs and opportunities related to each of these objectives and the strategies for accomplishing them will now be considered.

Objective 1: Identify genes and genetic loci contributing to glaucoma, especially those responsible for the common forms of the disease, and characterize the function and interaction of their gene products.

Research Needs and Opportunities

The application of the theory and technology of molecular genetics to the problems of clinical medicine has produced a wealth of information about the molecular pathogenesis of many human disorders. As with many disorders, identifying specific genes opens up many opportunities to understand glaucoma. Currently, many forms of glaucoma have been shown to be inherited as Mendelian-dominant or -recessive traits, including juvenile open-angle glaucoma, congenital glaucoma, developmental glaucomas (Rieger's syndrome and aniridia), and pigmentary glaucoma. To date, 10 chromosomal loci associated with these glaucomas have been genetically mapped in the human genome, and the genes for juvenile open-angle glaucoma, congenital glaucoma, and Rieger's syndrome have been cloned.

The data on adult-onset primary open-angle glaucoma suggest that susceptibility to the disease may be inherited. For example, twin studies performed 20 to 30 years ago suggested a significant heritability. Other data showed that the incidence of primary open-angle glaucoma in first-degree relatives of affected individuals is 7 to 10 times higher than that of the general population. These studies indicate that there is an association between susceptibility and family history; however, Mendelian patterns in which defined family patterns of inheritance can be discerned were not apparent. Thus, susceptibility to glaucoma is likely a complex trait in which genetic predisposition to the disease is modified by other factors. The etiology of this form of the disease is likely multifactorial, involving the interaction of multiple genes as well as gene-environment interactions, making the genetic analysis of primary open-angle glaucoma extremely challenging. Furthermore, genetic studies are confounded by the late onset of the disease and its clinical variability. The late onset of the disease limits the availability of extended pedigrees. The clinical variability makes it difficult to define the homogenous subgroup of patients required for genetic analysis. All these factors necessitate the use of new statistical methodologies for analysis, well-defined inclusion criteria to increase the likelihood of homogeneity, and aggressive patient recruitment to ensure enough power in the study.

Recent advances in methodology now allow the application of genetic analysis to the study of complex late-onset diseases, increasing the likelihood that genetic loci associated with primary open-angle glaucoma can be identified. Over the next 5 years, these studies can contribute valuable new information about the cause of this blinding condition and present new opportunities for laboratory and clinical research. Genetics may provide insight into the molecular basis underlying the higher prevalence and higher degree of severity of glaucoma in blacks. The identification of glaucoma genes has the potential to define subgroups of glaucoma patients and predict progression rates based on mutations or genetic loci involved. Likewise, it could identify molecular subclasses of disease that respond similarly to specific treatments. The availability of genetics as a diagnostic tool may allow clinicians to customize an intervention strategy based on the risk of blindness for an individual patient and balance treatment with quality-of-life considerations.

At the biochemical and cellular level, collecting sufficient quantities of trabecular meshwork has been a difficult obstacle to understanding the pathology of the disease. Moreover, tissue specimens taken from affected patients undergoing glaucoma surgery have been exposed to prior medical and laser treatments that could obscure the initial abnormalities responsible for the disease. Because genetic analysis investigates the disease process at the DNA level, samples of the actual diseased tissue, or even knowledge about how the disease affects a particular tissue, is not necessary for gene and gene product identification. Thus, the study of the molecular genetics of glaucoma can implicate specific protein products in the development of the disease without requiring direct access to the diseased eye tissue.

Identifying glaucoma-causing genes and their products will give researchers the opportunity to determine whether these genes and gene products function normally and determine how mutations in them cause or increase the susceptibility to glaucoma. With the identification of glaucoma genes, issues such as how an abnormal gene product results in a glaucoma phenotype, whether different mutations in the same gene can explain phenotypic variability, and the possibility of gene-environment interactions can be addressed.

Strategic Research Questions

What is the genetic component(s) of adult-onset primary open-angle glaucoma? Recent advances in methodology now make it possible to perform genetic analysis on complex late-onset diseases like adult-onset primary open-angle glaucoma. Newly developed strategies increase the likelihood that genetic loci associated with primary open-angle glaucoma can be identified. Strategies to characterize the disease at the molecular level are feasible once disease genes are cloned and characterized.

How do gene products responsible for glaucoma cause the disease? As glaucoma causing/susceptibility genes are isolated, strategies to determine whether their gene products are expressed in normal tissue, and how mutations in them cause or increase the susceptibility to glaucoma, must be devised.

How do specific mutations give rise to a specific phenotype? With the identification of glaucoma genes, questions such as how an abnormal gene product

results in a glaucoma phenotype, whether different mutations in the same gene can explain phenotypic variability, and if specific mutations are predictive of progression or response to treatment can be addressed.

Do environmental factors or other gene products modify glaucoma gene products? As genes are identified, prospective studies on how gene-environment interactions affect the natural history and progression of the disease should be implemented.

Can genetic subtypes of primary open-angle glaucoma be recognized clinically? To date, there is no satisfactory explanation as to why there are observed differences in progression rates and response to treatments among glaucoma patients. Likewise, the basis of racial differences has not been elucidated. Genetics may provide insight into the physiological correlates that have been defined in clinical observations and epidemiological studies. With the identification of glaucoma genes, cohort studies should be undertaken to determine if progression rates and response to treatment can be correlated with specific genotypes.

Can transgenic animal models be used to study the function of these genes? Building an animal model with alterations in specific “glaucoma” genes would greatly facilitate progress in understanding the pathophysiology of the disease.

What are the roles of specific glaucoma-causing genes in ocular development and function? Understanding the developmental biology of the anterior segment will be advanced by the identification of genes and gene products for congenital and developmental glaucomas. To study these genes and gene products, models to test the effect of altering gene expression during development must be developed.

Objective 2: Define the molecular and biochemical mechanisms that lead to retinal ganglion cell death in human glaucoma and in relevant animal models of related optic nerve injury.

Research Needs and Opportunities

Over the past century, the primary objective of glaucoma therapy and research has been to lower intraocular pressure. Most research on glaucoma has

addressed either the mechanisms by which intraocular pressure becomes elevated or ways to reduce intraocular pressure. More recently, there has been a greater emphasis on the changes in the optic nerve head and retinal nerve fiber layer as essential features of glaucoma. Furthermore, the existence of normal-tension glaucoma and ocular hypertensives without glaucoma has led to reassessment of the primacy of elevated intraocular pressure in the etiology of the disease. These observations have shown that a more comprehensive understanding of glaucoma etiology necessitates studies of the fundamental processes controlling retinal ganglion cell death. This recognition has stimulated research directed to those cellular components of the posterior segment of the eye that are compromised by the glaucomatous process.

Advances in basic neuroscience have suggested ways that retinal ganglion cells degenerate in glaucoma. During normal neuronal development, including retinal development, cells are programmed to die and do so in a precise manner. Research has shown that this form of cell death (called apoptosis) may be involved in many neurodegenerative conditions, including those involving retinal ganglion cell degeneration. For example, transection of the optic nerve in animal models results in retinal ganglion cell apoptosis, but the molecular program leading to cell death remains to be established. Advances in the molecular genetics of neuronal apoptosis have identified a number of genes that regulate neuronal cell death and survival under normal and pathological conditions. Antiapoptotic genes, proapoptotic genes, transcription factors, neurotrophic factors, and cell cycle regulators have been described in these systems. Further advances may provide a basis for experiments that will lead to an understanding of the signaling cascades that initiate cell death *vis-à-vis* transection and, more importantly, that may be involved in the axonal loss and retinal ganglion cell degeneration that are the hallmarks of glaucoma.

Elevated intraocular pressure remains the most prominent risk factor in the development and progression of glaucoma, yet the mechanisms by which elevated intraocular pressure directly alters homeostasis of retinal ganglion cells and the structure of the optic nerve head are unknown. Mechanical forces created by pressure, flow, and stretch regulate gene expression, cellular activity, and cell proliferation in a

variety of cell types. The signaling mechanisms or the mechanotransducers are the subjects of intense research. Calcium, cyclic AMP, PGs, and growth factors act as signaling molecules in several dynamic models *in vitro*. Moreover, cell matrix interactions may be involved in the response to pressure. Cell adhesion molecules like intercellular adhesion molecule-1 in the vascular endothelium are directly activated by shear stress and appear to be responsible for inducing gene expression after mechanical stress. The techniques used to study the effect of mechanical stress on cells need to be adapted for studying the effect of pressure on the retinal ganglion cells.

Hypoxia due to ischemia and decreased vascular perfusion has been proposed as a factor leading to axonal damage, retinal ganglion cell death, and remodeling of the optic nerve head in glaucoma. Selective neuronal damage due to ischemia in the central nervous system (CNS) is currently the focus of intense research. Neuronal vulnerability to damage may be related to neuronal connectivity, vascularization, blood-brain barrier, and trophic support by astrocytes or neurons. Recent studies have demonstrated that cells respond to hypoxia via cellular oxygen sensors, which regulate gene expression of glycolytic genes and a variety of growth factors that affect vascular perfusion. Reactive oxygen species that can be generated after ischemia may serve as triggers of neuronal apoptosis. By extending this work to the eye, laboratory research aimed at testing the role of vascular perfusion and hypoxia in retinal ganglion cell death may provide mechanistic information and potential pharmacological targets in glaucoma.

Cellular signaling pathways mediate cell-cell interactions, including neuronal-neuronal cell interactions and neuronal and glial cell interactions. These pathways may provide initial or secondary signals for axonal degeneration, glial responses, and vascular perfusion in the glaucomatous optic nerve, and for ganglion cell apoptosis in the retina. Cellular signaling pathways, such as those mediated by nitric oxide, neutrophins, transforming growth factor- β (TGF- β), and other cytokines, may have a role in primary or secondary damage to the axons of the retinal ganglion cells. Secondary responses may involve altering the microenvironment surrounding the axons or modulating the extensive remodeling of the tissue as the chronic disease process proceeds. It is important to explore these and other regulatory pathways that may

be present in the optic nerve to establish their effect on local degenerative and protective neuronal responses. Identification of mediator pathways in the optic nerve is needed because these pathways may represent targets for new therapeutic neuroprotective agents that can be developed for glaucoma.

Primate work has been critical in understanding glaucoma to date. Although the monkey model of laser-induced elevated intraocular pressure is probably the model most closely reflecting the human disease, it is difficult to produce, gives highly variable results, and is expensive. Developing a reliable model in a smaller and more readily accessible laboratory animal in which genetic manipulations are possible would allow experiments on specific aspects of the disease and therefore would greatly facilitate understanding this disease process. Recently, significant strides have been made in developing rodent models of glaucoma. One group has reported a technique for measuring intraocular pressure in the mouse. This methodology has the potential for genetic manipulation, giving researchers techniques for exploring either genes that affect intraocular pressure or genes that retard or accelerate glaucomatous loss. Using mice and other small animals as models must be investigated, but careful attention should be paid to demonstrating the relevance of observations in animals to processes that occur in human tissue. Because glaucoma is a uniquely human disease that ultimately must be studied in humans, access to human tissue must be improved.

Strategic Research Questions

Can an animal model that is more reliable and more accessible than the monkey model be found for the study of retinal ganglion cell death and axonal loss in glaucoma? The use of more accessible and smaller laboratory animals to study the mechanisms of retinal ganglion cell death and axonal degeneration needs to be explored. Criteria for using these animals must include susceptibility to a pressure-induced, chronic, progressive optic neuropathy and an optic nerve structure with enough similarities to that of humans so as to be relevant.

Can an animal model for normal-tension glaucoma be established? The etiology of normal-tension glaucoma is poorly defined. An animal model of normal-tension glaucoma would be highly useful in understanding neuronal cell death in this form of glaucoma.

Can any of the rat or mouse models be used to study optic nerve damage and retinal ganglion cell death caused by elevated intraocular pressure? Existing models must be verified before proceeding with further studies. Issues that must be addressed include whether intraocular pressure in these animals can be measured accurately, whether the disease progression mimics the chronic condition observed in humans, and whether retinal ganglion cell death is caused by elevated intraocular pressure.

Can scientists determine whether the changes in the optic nerve head are the result or the cause of death of retinal ganglion cells? Clinical evidence points to the optic nerve head as the initial site of damage in glaucoma. However, the possibility that structural changes in the optic nerve head are the result rather than the cause of retinal ganglion cell death needs to be considered, and experimental strategies to test this possibility need to be devised.

Are there molecular mechanisms of mechano-transduction that may be important in the regulation of responses to elevated intraocular pressure? Are retinal ganglion cells or the astroglial cells supporting the axons of the optic nerve sensitive to different levels of intraocular pressure? Elevated intraocular pressure remains the most prominent risk factor in the development and progression of glaucoma, yet the mechanisms by which intraocular pressure directly alter the homeostasis of retinal ganglion cells and the structure of the optic nerve head are unknown. Techniques currently used to study the effect of mechanical stress on other cell types need to be adapted for studying the effect of pressure on the retinal ganglion cell.

How can collaborations between neuroscientists with expertise in other neurodegenerative diseases and scientists interested in the neurobiology of glaucoma be encouraged? Strategies to test the relevance of hypotheses of neurodegenerative mechanisms to glaucomatous retinal ganglion cell death need to be pursued. Collaborations with investigators studying other neurodegenerative diseases would facilitate the transfer of generalizable findings related to the neurodegenerative process to models of glaucoma.

Objective 3: Enhance understanding of the structure and function of the aqueous humor outflow pathways at the cellular and molecular level.

Research Needs and Opportunities

The factors that contribute to, influence, and regulate the outflow of aqueous humor are central to understanding glaucoma, yet most of these remain undefined. The continued lack of a suitable experimental model to study the anterior segment components of glaucoma continues to present a formidable challenge to progress in this area. As a direct consequence, the armamentarium of medications available to enhance conventional outflow facility, and thereby reduce intraocular pressure, remains limited. Identifying and evaluating promising candidates for clinically useful outflow drugs remain a high priority.

The long-held view that the increased resistance to trabecular outflow results simply from a progressive accumulation of glycosaminoglycans (GAGs) in the open spaces of the trabecular meshwork has not been borne out. Indeed, most recent studies indicate that a progressive loss of most GAGs in the human trabecular meshwork occurs with age alone, as well as in glaucoma. A consensus still favors a role for GAGs in outflow, but that role must be reevaluated.

As the view of increased outflow resistance caused by a progressive accumulation of GAGs has waned, alternative candidates have been identified. Many of these new candidates are structural or regulatory proteins produced by the trabecular meshwork or are regulatory proteins carried to the meshwork with aqueous flow. Promising avenues for study remain in the area of meshwork constituents that regulate GAGs and related extracellular matrix components, particularly matrix metalloproteinases and their inhibitors. A recently identified shunt pathway that delivers additional plasma-derived proteins from the ciliary body stroma to the aqueous humor via the root of the iris is another potential source of candidate proteins.

Most investigators remain convinced that the solution to the “source of resistance” question resides within the extracellular matrix of the juxtacanalicular region of the trabecular meshwork, either entirely or in conjunction with factors in aqueous humor or in combination with structural features of the inner wall

of Schlemm’s canal. If the extracellular matrix is the key to understanding the mechanisms of outflow resistance, then the cells that produce and maintain this matrix must be the force that turns that key. Understanding the biology of the cells that constitute the trabecular meshwork is essential to understanding the extracellular matrix and its turnover and regulation. Modifications of cell shape, along with an array of receptors and channels, have been recently identified. All of these should be aggressively explored, provided that biologically relevant assays can be demonstrated to have clear meaning for outflow dynamics *in vivo*.

Among the most interesting intrinsic proteins produced by the meshwork is the recently identified TIGR/myocilin protein, a protein whose expression in trabecular meshwork cells *in vitro* is influenced by steroids, a class of compounds known to elevate intraocular pressure in sensitive individuals. Recent linkage of TIGR to the juvenile glaucoma gene, and the subsequent finding that the TIGR protein is identical to myocilin (a protein found in the retina), provide an opportunity to probe for fundamental mechanisms of outflow. In the retina, myocilin is a cytoskeletal protein, suggesting possible mechanisms by which this protein may affect outflow facility. The role of TIGR/myocilin in particular and the cytoskeleton proteins in general requires further investigation.

The biology of the trabecular meshwork presents investigators with a number of experimental challenges. While capable of identifying the constituents and amounts of various tissue components, biochemical studies rarely provide information on the location of the materials being measured. By contrast, histochemical studies can provide information on the location of certain constituents, but the amounts present are difficult to discern. It could easily be the case that both concentration and location of various constituents could be critical in modulating outflow.

Developing newer methods that bridge the critical gap between biochemistry and histochemistry appear to offer promise in addressing basic questions of trabecular cell biology and meshwork matrix biology. *In situ* hybridization and ultrastructural techniques like quick-freeze and deep-etch, which preserve the structure of extracellular matrices, may offer insights previously unattainable. The recent development of several novel organ culture systems has proven a valuable adjunct to the study of the trabecular

meshwork, particularly in the absence of a useful animal model for the anterior segment components of human glaucoma. These systems, when used in conjunction with cell culture and related methods, offer the potential for unraveling the basic questions of trabecular cell function and the respective roles that each function might play in the physiology of outflow. Recent attempts to couple anterior segment perfusion methods with methods of molecular genetics, while in their infancy, might offer the possibility for ultimately providing a means to alter expression of various gene products intrinsic to meshwork cells and then to directly determine the influence of the alterations on outflow facility. Results of such studies could dramatically change mechanistic hypotheses and simultaneously provide a much-needed focus for molecular and population geneticists as they continue their search for the gene or genes that are linked to primary open-angle glaucoma.

An assessment of research needs in the area of aqueous outflow also requires consideration of the uveoscleral outflow pathway. Exploiting this pathway to augment aqueous outflow has proven to be of tremendous clinical value, as evidenced by the clinical efficacy of prostanoid derivatives such as latanoprost in augmenting uveoscleral outflow. With clinical use of this new medication, however, have come questions regarding its mode of action. Clearly, the basic mechanisms underlying uveoscleral outflow need to be understood more fully. To accomplish these goals, more reliable clinical methods for measuring uveoscleral outflow will be needed, and those presently available will need to be refined.

Strategic Research Questions

Can a suitable animal model be found that recreates the anterior segment aspects of primary open-angle glaucoma? Investigations should be undertaken to determine the feasibility of using animal models to study anterior segment aspects of primary open-angle glaucoma. Such models would greatly facilitate understanding outflow physiology and provide a means for evaluating the efficacy of drugs that enhance outflow.

What is the molecular and cellular basis of aqueous outflow resistance? Understanding the molecular factors that contribute to and regulate outflow resistance in the normal pathway is critical to identifying

candidate molecules that contribute to glaucomatous pathology and characterizing pathways amenable to drug intervention.

What are the critical changes in structure and function of cells in the outflow tract that produce a decline in outflow facility? Because almost all forms of glaucoma are associated with an increase in resistance to outflow, determining the site of resistance is central to understanding this disease. Understanding the biology and physiology of the cells and tissue that constitute the site of resistance are essential to understanding the alterations that cause a decrease in outflow facility in glaucomatous tissue.

How can novel findings from cell culture studies be related to outflow? Because no animal model exists, much current knowledge is derived from studies of trabecular meshwork cell culture. The relevancy of findings in cell culture must be pursued in organ culture and other systems, where cellular and tissue interactions can be studied.

Can researchers identify candidate cell products relevant to outflow by coupling organ perfusion with molecular biology? Strategies that couple anterior segment perfusion methods with methods of molecular genetics provide a means to genetically alter expression of proteins in meshwork cells and determine the influence of these alterations on outflow facility. If feasible, this methodology affords the most direct way to test the physiological role of various molecules in outflow.

Can researchers develop clinically useful trabecular outflow drugs for reduction of intraocular pressure? Identifying and evaluating promising candidates for clinically useful outflow drugs are high priorities. As advances in understanding the physiology of outflow are made, strategies based on these advances should be implemented so that they can expand researchers' armamentarium of glaucoma medications to include drugs that enhance conventional outflow facility.

Objective 4: Develop a better understanding of anterior segment immunology.

Research Needs and Opportunities

The immune system protects the eye from destructive infections. (Also see Corneal Diseases Report section on corneal inflammation and wound healing). As in other organ systems, the immune system within the eye must maintain a delicate balance between protection and overreaction, since the latter response can result in ocular diseases such as uveitis. From a clinical perspective, progress has been made in classifying anterior segment inflammation. However, a consensus still does not exist for the nomenclature to describe clinical uveitis. The natural history of uveitis remains poorly characterized.

Vision scientists are beginning to define the complex interactions of cytokines, lipids, and free radicals in anterior segment inflammation and immunoregulation. Improved animal models are emerging, but models of anterior segment inflammation are still limited. These models would be helpful in identifying new and safer ways of enhancing successful filtration surgery. In addition to immune response genes, genetic factors are being recognized in entities like the iritis associated with juvenile rheumatoid arthritis and Blau syndrome. Genes responsible for a predisposition to anterior uveitis need to be sought and characterized. The role of apoptosis as a contributor to immunoregulation within the eye has been recognized and should be further defined.

Marked progress has been made in identifying infectious causes of inflammation, and further effort in this area should provide important new information. Strides have also been made in defining the mechanism by which leukocytes come to the eye. The potential exists to define this system to further understand ocular inflammatory disease and develop improved therapies. Enhanced drug development and delivery are still necessary to control anterior segment inflammation.

Strategic Research Questions

Can a consensus on developing nomenclature and defining outcome measures be found? Consistent classification criteria must be established and incorporated in prospective studies aimed at

determining the natural history and progression of anterior uveitis. A consensus for classification and outcome measurements for uveitis is needed so that the testing of new drugs in clinical trials can proceed.

Can genetic factors that may affect the development and progression of certain inflammatory disorders be identified? Genetic studies need to be expanded beyond secondary inflammations like iritis associated with juvenile rheumatoid arthritis and Blau syndrome. Strategies to carry out studies aimed at identifying genes responsible for a predisposition to anterior uveitis need to be designed.

What do animal models tell us? Improved animal models are emerging, but models of anterior segment inflammation are still limited. Using animal models may provide important insights into treating or preventing inflammation of the anterior segment. Current animal models need to be fully characterized and new models must be developed.

Which cytokines mediate anterior segment inflammation? Candidate cytokines have been identified. Strategies to determine the role that each plays in the inflammatory response are now needed.

Can additional infectious causes be identified? Marked progress has been made in identifying infectious causes of inflammation. Further effort in this area should provide important new information.

Can strategies be developed for improved drug development? Strategies to develop new drug and delivery systems to control anterior segment inflammation need to be devised and implemented.

Objective 5: Improve our understanding of the nature and course of glaucoma, incorporating studies of comorbidity, natural history, and genetics, with special emphasis on Hispanic, Native American, and African-American populations.

Research Needs and Opportunities

Results from the Baltimore Eye Study, the Beaver Dam Eye Study, and the Barbados Eye Study have firmly established race as a significant risk factor for primary

open-angle glaucoma. Though there is variation in estimates that reflects the different populations studied, all of these studies confirm a substantially higher prevalence of primary open-angle glaucoma in blacks. Furthermore, the rates for blindness due to primary open-angle glaucoma in African-Americans are six times higher than the rates for the Caucasian population, reflecting not only an increased rate of the disease but also more severe disease. Other ethnic and racial groups have been studied less rigorously. There is a dearth of information about the prevalence and incidence of glaucoma in Hispanic and Native American populations; therefore, studies need to be initiated in these populations to obtain this critical information.

Questions of comorbidity have not been adequately resolved. Studies that sought to investigate the relationship between glaucoma and myopia have yielded ambiguous results. There is also incomplete and equivocal epidemiologic information available on the relationship between glaucoma and vascular disease. The need to resolve the question of comorbidity is highlighted by the fact that the rate of hypertension is high in minority populations.

Risk factors for glaucoma need to be identified and verified. The question of whether there are susceptibility genes that can affect the course of the disease, especially in regard to ethnic and racial differences, is being actively pursued. With advances in genetics, environmental effects also need to be understood so that researchers can better determine the interaction of genetics and environment in the natural history of this disease. Currently, important known risk factors for glaucoma include elevated intraocular pressure, advanced age, optic disc abnormalities, and family history of primary open-angle glaucoma. However, the contribution each of these known risk factors to the progression of glaucoma is unknown. Questions remain concerning whether or not a compromised vascular system contributes to glaucomatous pathology. The difficulty of adequately measuring ocular blood flow hampers progress in understanding its impact on the survival of retinal neurons and visual function.

The large number of gaps in knowledge about the nature and course of glaucoma point to the need for rigorous epidemiological studies. Well-designed studies that use systematically selected sample sizes (from census tract data, for example) have high rates of

participation by the study sample, and use standard procedures for assessing disease and measuring risk factors needed to address these issues. There is also a critical need for better population-based screening procedures that are simple, inexpensive, portable, and effective. Developing such methods will be useful for testing populations that historically have limited access to formal healthcare systems, for determining more accurately the incidence and prevalence of glaucoma in epidemiologic studies, and for screening large populations in remote regions of the world.

Strategic Research Questions

What is the prevalence and incidence of glaucoma in different ethnic backgrounds? Studies clearly indicate a substantially higher prevalence and incidence of glaucoma in black populations. Prospective studies to obtain prevalence and incidence data in other ethnic groups, particularly Hispanics and Native Americans, are needed to assess the public health impact as it relates to these groups.

How many people have glaucoma and how severe is their visual impairment? Well-designed studies that use systematically selected samples, that have high rates of participation, and that use standard ascertainment procedures are necessary for a more definitive measure of prevalence. These studies will fill in gaps in knowledge about the natural history and course of glaucoma.

How is the course of glaucoma affected by the presence of other diseases/conditions? Prospective studies are called for to resolve questions of comorbidity. Emphasis should be placed on studies that seek to define the natural history and progression of glaucoma in the presence of other diseases associated with aging and/or minority populations, such as adult-onset diabetes and hypertension.

Are environmental risk factors for glaucoma identifiable? Are there genetic risk factors for glaucoma? Prospective studies should be implemented to identify any additional risk factors or physiological correlates associated with the disease to verify the effect of known risk factors and to determine the relative contribution of each risk factor to the etiology of glaucoma. As susceptibility genes are identified, genetic epidemiological studies will be required to sort

out the interaction of genetics and environment to understand the role each plays in the etiology of the disease.

What is the impact of visual impairment on health-related quality of life? Future epidemiological studies must incorporate quality-of-life measurements to provide researchers with a complete picture of the natural history of this disease.

What are the best methods of screening for glaucoma? Screening strategies should center on population-based procedures that are simple, inexpensive, portable, and effective. Implementing these screening methods include testing populations that historically have limited access to formal healthcare systems, determining more accurately the incidence and prevalence of glaucoma in epidemiologic studies, and screening large populations in remote regions of the world.

What is the role of ocular blood flow and micro-circulation of the optic nerve in glaucoma, and how does it relate to visual function? Longitudinal studies that incorporate both blood flow and visual field measurements are necessary to better understand the role of ocular blood flow in glaucoma.

What factors explain why many individuals with high intraocular pressure do not develop glaucoma, while some individuals with normal pressures do develop glaucoma? Epidemiological studies focused on cohorts of ocular hypertensive individuals and normal-tension glaucoma patients should be implemented to identify potential risk factors and other physiological correlates associated with the development of glaucoma in these subpopulations.

Objective 6: Develop improved diagnostic techniques encompassing measures of visual function, optic nerve, and nerve fiber layer structure, in situ and for clinical applications of genetics.

Research Needs and Opportunities

In recent years, the diagnosis of glaucoma has emphasized the presence of visual field loss and observable glaucomatous optic neuropathy, with recognition of high intraocular pressure as a risk factor rather than an essential disease characteristic.

Researchers have achieved a greater ability to identify early functional and structural abnormalities caused by glaucoma. With new statistical analysis packages for visual field and imaging devices, there is more agreement and certainty regarding the presence of abnormal findings. However, the large variability inherent in these measures continues to hamper the identification of disease progression. Developing reliable methods to quantitatively distinguish progression of glaucomatous visual field loss from long-term variability is of critical importance. Such techniques are needed for better outcome measures in clinical treatment trials in glaucoma, for the clinical management of patients, and for clinical research studying the underlying basis of glaucomatous optic nerve damage. Because of the variability of optic nerve topography in normal eyes, well-designed longitudinal studies are needed to learn whether the new diagnostic instruments providing real-time measurements of the optic nerve will improve the ability of clinicians to detect glaucoma and monitor its progression.

The availability of more sensitive visual function tests and new methods of quantifying the topography of the optic nerve head and the retinal nerve fiber layers have provided an opportunity to define the relationship between visual function losses and structural changes in glaucoma. Characterizing these relationships will improve understanding of the clinical course of glaucomatous damage and help to identify the most effective methods for detecting and monitoring pathologic changes. Advances in genetics may be useful in classifying different subtypes of glaucoma and assist in improving diagnosis and treatment. With these opportunities to characterize pathology at a molecular genetic level comes a need for prospective longitudinal studies to expand the search for risk factors in these diseases and improve diagnostic techniques.

At this time, there is little information concerning the impact of visual function loss produced by glaucoma on a person's ability to perform various daily activities. Researchers need to answer a number of questions related to visual loss and quality of life to optimize intervention strategies, such as: At what level of visual field loss is there an impairment of task performance or a negative impact on a person's quality of life? What are the changes in quality of life associated with progression of glaucomatous loss? With visual loss, what other factors influence a person's ability to perform daily activities of living? Will

improved diagnostic and monitoring techniques provide true benefit to the patient in terms of vision or quality of life? The NEI's Visual Functioning Questionnaire (NEI-VFQ) can provide the instrument for some of these investigations.

New clinical measures for early detection of glaucoma have improved specification of the changes found in visual function and optic nerve topography. When correlated with newly identified genetic markers, these clinical measures may help identify the subclasses of glaucoma. The combination of epidemiological, clinical, and laboratory research is fundamental to a better understanding of the disease in humans, which in turn will lead to the development of more effective therapies and improved designs for prospective intervention studies. Clinical studies encompassing visual function, optic nerve and nerve fiber layer structure, and quality-of-life measurements should improve the detection of disease progression and the effects of glaucoma on vision and quality of life.

Strategic Research Questions

What is the best method for determining progression of visual loss in glaucoma? Reliable methods to distinguish progression of visual field loss from long-term variability are needed. Longitudinal studies that directly compare techniques should help scientists discern the most sensitive and specific methodology for determining disease progression.

What is the relationship between visual function loss and structural changes to the optic nerve and retinal nerve fiber layer in glaucoma? To characterize the pathology of glaucomas more comprehensively, prospective longitudinal studies that incorporate existing measures of visual function, optic nerve, and nerve fiber layer structure are needed. Strategies to define the relationship between visual function losses and structural changes in glaucoma should include standard visual function tests, SWAP, and new methods of quantifying the topography of both the optic nerve head and the retinal nerve fiber layers.

What is the relationship of visual loss to task performance, occupational demands, and quality-of-life measures? There is a growing recognition of the importance of evaluating the health outcomes and quality-of-life changes imposed by glaucoma and its treatment. Clinical studies should include quality-of-life

measurements to determine the effects of glaucoma and its treatment on a person's ability to carry out daily tasks. Such information will help clinicians devise more effective intervention strategies.

What is the genetic basis for the different etiologies of glaucomatous optic nerve damage? As glaucoma genes are identified, phenotype descriptions should include detailed optic nerve structure and nerve function assessments to determine if there is a correlation between structural and functional damage with specific genotypes. Correlation of optic nerve damage with genetic markers may assist in classifying subtypes of glaucoma and help predict the course of the disease.

What is the effect of aging on visual function and optic nerve/retinal nerve fiber layer structure? Prospective longitudinal studies to determine optic nerve/retinal nerve fiber layer changes as a function of aging are needed. In addition to improved baseline data against which glaucomatous loss can be measured, this information may provide insight into why aging increases the risk for glaucoma.

Objective 7: Identify neuroprotective strategies that could prevent retinal ganglion cell death, promote survival, or stimulate regeneration.

Research Needs and Opportunities

There is a growing realization that treating glaucoma solely by lowering intraocular pressure is not a comprehensive therapeutic approach. Over the last 5 years, there has been a burgeoning interest in developing agents that will protect neuronal cells from glaucomatous damage. Neuroprotection can be broadly envisioned as a pharmacological means to prevent or slow retinal ganglion cell degeneration or promote regeneration of damaged retinal ganglion cells. Neuroprotection encompasses classic pharmacologic-type molecules, biologics, and gene therapy approaches. To begin thinking about these types of approaches, glaucomatous neurodegenerative processes must first be established and characterized in animal models to identify target pathways where neuroprotective agents can act.

Molecular mechanisms that define the neuroprotective and survival effects of neurotrophic factors and their receptors currently under study in a variety of

in vivo and *in vitro* models need to be expanded to include retinal ganglion cells. Altering cellular homeostasis in the retina or in the optic nerve has been suggested to result in retinal ganglion cell apoptosis and modulation of the apoptotic pathway. This points to a number of targets to investigate. For example, disruption of homeostasis may include glutamate excitotoxicity, production of reactive oxygen species, depletion of intracellular antioxidants, or increase in intracellular calcium. This disruption may, in turn, induce the expression of a number of apoptotic genes/pathways including bcl-2 and the interleukin-1 beta-converting enzyme protease. Ongoing research in neurodegenerative disorders in which apoptosis plays a central pathogenic role should provide new approaches to study the mechanisms of retinal ganglion cell death and neuroprotective strategies in glaucoma.

Glutamate is likely to play an excitotoxic role in the death of retinal ganglion cells, as it does elsewhere in the CNS. Within the retina, photoreceptors and bipolar cells contain high concentrations of glutamate, which they use as a neurotransmitter. Müller cells are actively involved in maintaining extracellular glutamate levels by taking up the released transmitter. Many retinal glutaminergic receptors have been identified: metabotropic receptors, AMPA receptors, kainate receptors, and NMDA receptors. Stimulation of the NMDA receptors in particular leads to activation of a variety of calcium-dependent processes intracellularly and is important for glutamate excitotoxicity and neuronal damage. Several noncompetitive NMDA antagonists and NMDA open-channel blockers have been shown to limit neuronal loss in animal models of neural ischemia and chronic glutamate intoxication and are currently being tested in human neuronal degenerative diseases. Other antagonists that prevent glutamate release from presynaptic storage may also be useful in blocking excitotoxicity. However, glutamate is an essential neurotransmitter. Thus, complete blockade of all glutamate activity seems not to be a viable therapeutic approach. Identifying agents that primarily interfere with the neurotoxic effects of elevated glutamate levels may be pharmacologically useful.

Another molecule that can play a key role in neuronal degeneration in the CNS is nitric oxide. Although at physiological concentrations the molecule acts as a neurotransmitter and vasodilatory agent, nitric oxide is neurodestructive at excessive levels. Since nitric oxide synthase, the biosynthetic enzyme for nitric oxide, is present in the retina and the optic

nerve, nitric oxide may contribute to cell death and glaucomatous pathology. Pharmacological inhibitors of the various forms of nitric oxide synthase are being developed for treating other diseases in which nitric oxide has been implicated and may also prove useful for accomplishing neuroprotection in glaucoma.

Because elevated calcium has been implicated in neuronal cell death, calcium channel blockers have been tried for the treatment of ischemic injury. Adenosine agonists and drugs that increase adenosine appear to reduce neuronal damage in cerebrovascular disease. Experiments have demonstrated that adenosine reduces neuronal damage in reperfusion injury and causes vasodilation of retinal vessels. Conceivably, adenosine agonists could improve blood flow to a compromised optic nerve in glaucoma. To the extent that compromised vascular perfusion of the optic nerve may occur in glaucoma, antagonists at the receptors of these mediators may prove useful in restoring optic nerve blood flow. Production of neurotoxic free fatty acids, such as platelet-activating factor (PAF) from endogenous phospholipids, may occur in the glaucomatous optic nerve. PAF antagonists reduced neuronal damage in experimental models of retinal injury. They may prove to be relevant to glaucoma.

Since neurotrophic factors enhance the survival of retinal ganglion cells and other neurons, these agents or their mediators are interesting candidates for gene therapy approaches. Experiments using transgenic animals and knockout animals have demonstrated that overexpression or underexpression of certain gene products can interfere with the apoptotic mechanism in retinal ganglion cells. Thus, a therapy based on vector-targeted gene transfer to retinal ganglion cells, perhaps through intravitreal administration, may eventually prove useful as a novel therapeutic approach for glaucoma. An example of this therapeutic approach would be to supply retinal ganglion cells with neurotrophic factors that may be in limiting concentration, thereby resulting in activation of the cell death cascade.

Strategic Research Questions

Can the cascade of events leading to retinal ganglion cell death be identified, and can pharmacological interventions that are neuroprotective be identified? Glaucomatous neurodegenerative processes must be established and characterized in animal models in order to identify target pathways where

neuroprotective agents can act. Candidates for neuroprotection being tested to determine their ability to halt or slow the degenerative process in other diseases suggest possible candidate therapeutics that can be tested in glaucoma models.

Can suitable approaches to monitor retinal ganglion cell viability and function in animal models be developed to study the efficacy of neuroprotective agents? Reliable, reproducible endpoints are needed to determine the efficacy of neuroprotective agents in animal models. Ultimately, it must be demonstrated over time that the neuroprotective agent preserves retinal ganglion cells and, hence, visual function. Therefore, inherent in the development of models is developing a way to test cell viability and visual function in the animal.

Can *in vitro* systems used to screen neuroprotective agents for glaucoma be identified? Developing *in vitro* screening systems would facilitate the identification of candidate molecules for neuroprotection strategies.

How can researchers devise strategies to deliver pharmacological agents locally to the retina and optic nerve? A confounding factor in developing neuroprotection strategies for glaucoma is the difficulty in delivering drugs to the retina and optic nerve. Coupled with developing neuroprotective therapies is the need to develop delivery strategies to introduce therapeutics to their target sites.

How can side effects of neuroprotective drugs be minimized? Because it is very likely that any useful neuroprotective drugs may also interfere with normal processes, specificity must be optimized either by modifying the agent or using a targeted drug delivery system. Further complicating the use of these agents is the chronic nature of glaucoma, thus necessitating the need for long-term local exposure of the retinal ganglion cells and increasing the probability of unattended side effects. These confounding factors must be factored into the development of any drug design strategies.

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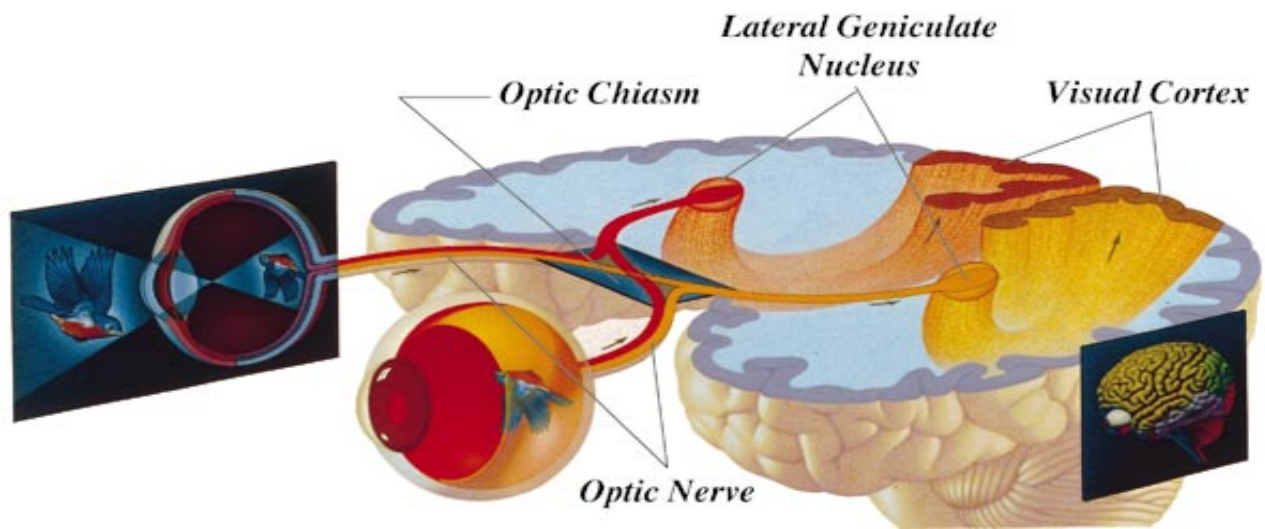


Illustration of the brain: Courtesy of *National Geographic*

PROGRAM OVERVIEW AND GOALS

How do we see? This simple question does not have a simple answer. Vision is a complex series of events that begins when light enters our eyes and ends with perception. We can discriminate between objects of different size, contrast, and color, and we can track moving objects with precision. We routinely perform these tasks over an enormous range of light intensity. Our vision system easily outperforms any manmade machine.

Disruption of any part of the visual system severely impairs our ability to see. Disturbances in neural and ocular development, metabolism, neural processing, and eye movements lead to serious visual impairment such as amblyopia (a developmental abnormality of the central nervous system [CNS] that causes impaired vision in one or both eyes), strabismus (misalignment of the eyes), nystagmus (continuously moving eyes), scotoma (local areas of blindness), myopia (near-sightedness), and other conditions that require strong spectacle lenses. Over 30 million people in the United States suffer from one or more of these visual disorders. These disorders cause substantial visual loss that interferes with learning, working, and overall quality of life.

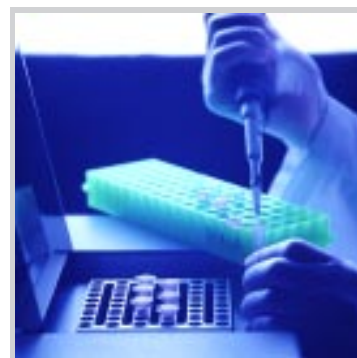
The Strabismus, Amblyopia, and Visual Processing (SAVP) Program of the National Eye Institute (NEI) supports both clinical and laboratory research on development, neural processing, eye movement, and associated disorders involving the output of retina and those portions of the brain that serve vision. Studies on normal and impaired vision go hand-in-hand. Detailed knowledge of the normal visual system provides the foundation for understanding the causes of impaired vision and for developing corrective measures.

Research sponsored by the SAVP Program involves a variety of model species, but the primary goal is to understand the human visual system and alleviate its disorders. Many powerful laboratory

techniques have contributed new knowledge about the visual system, but these methods

are not suitable in humans. Therefore, a variety of animal species are used to simulate human states. Primates are the model system closest to the human, but species ranging from invertebrates, such as flies and horseshoe crabs, to nonprimate mammals, such as cats and rabbits, have yielded and will continue to yield significant information on the fundamental mechanisms of vision common to all species, including humans. Past vision research demonstrated the wisdom of this approach: key insights generally come from model systems that are well suited for exploring a specific research question. Past research also demonstrates the wisdom of using primates for investigations directly related to the human visual system.

Over the last three decades, visual neuroscience has had a substantial impact on other fields of neuroscience. This is especially true for developmental and functional studies of the central visual pathways, which have yielded results that have been generalized to the brain as a whole. In developmental neuroscience, the increasing power and sophistication of molecular approaches has led, over the past 5 years, to an explosion of new information on the basic molecular mechanisms that guide the initial formation and connectivity of the nervous system in general and the visual system in particular. The accessibility of visual pathways, such as the optic nerve, has enabled scientists to develop powerful models for studying regeneration in the adult CNS. Moreover, decades of investment in the study of the structure, function, and development of the visual system—supported in large part by the SAVP Program of the NEI—have made this the system of choice to study the effects of genetic and molecular manipulations like gene deletions (knockouts) or gene insertions (knockins and transgenics). Spurred by new optical and electrical recording techniques, similarly impressive advances



have improved understanding of synaptic and activity-based patterns that guide plastic rearrangements in the developing visual system and the basis of critical periods. These phenomena have provided a conceptual spur to research in childhood developmental disorders and on learning and memory throughout the brain.

In systems neuroscience, the SAVP Program has traditionally supported cutting-edge research into the brain systems underlying visual perception and underlying movements of the eyes. New knowledge resulting from this investment has now brought systems neuroscience to the threshold of a new era in which physiologists can ask incisive questions about how sophisticated visual information, encoded at the highest levels of the cortical visual system, can guide motor planning decisions implemented at the highest levels of the oculomotor system. At this watershed between traditionally defined sensory and motor systems reside many of the higher brain functions that are critical to cognition—attention, memory, volitional decision-making, and the representation and awareness of space. This rapidly developing field encompassing neuroscientific study of these brain functions is known as “cognitive neuroscience,” and vision research will continue to play a leading role in this arena of inquiry. Thus, exciting new dividends are being realized from the substantial investment in basic systems-level research made by this Program over the past several decades.

In Fiscal Year 1997, the NEI funded 340 extramural research projects in the Strabismus, Amblyopia, and Visual Processing Program at a total cost of \$61,316,048.

Future vision research coupled with emerging technology hold great promise for understanding the development and normal function of visual and oculomotor systems. Progress in the diagnosis and treatment of clinical disorders that impair vision, such as amblyopia, myopia, nystagmus, and strabismus, critically depends on laboratory research. Both the future promise and the close link between clinical practice and research are reflected in the overarching goals of the SAVP Program:

- Determine the etiology of human myopia and identify the risk factors associated with this and other refractive errors so as to prevent their occurrence or progression.

- Understand how the visual system is assembled during development, how its assembly is influenced by endogenous and exogenous factors, and what factors are involved in its regeneration after injury.
- Investigate the development of visual function in children with high risk of amblyopia and strabismus, and develop and disseminate knowledge about effective detection methods and therapeutic interventions to restore 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 and motor mechanisms that control eye movements under natural 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.

ASSESSMENT OF PROGRESS

Research in the SAVP Program has been unusually productive during the past 5 years. Important advances have been made in the clinical analysis and treatment of specific diseases, as well as in basic understanding of the development and normal function of the visual and oculomotor systems. Following are a few of the salient advances, particularly those that follow directly from the goals and objectives of the NEI's last 5-year plan.

Demonstration that the growth of the eye and the development of accurate focus (refractive state) are guided by visual feedback during early life. Myopia, or nearsightedness, is a common condition in which images of distant objects are focused in front of, instead of on, the retina, usually because the eye is too long. Myopia occurs in approximately 25 percent of the population of the United States. After

extensive argument about whether to attribute myopia to visual factors or genetic factors, experimentation on animals in the past two decades has provided a clearer, but as yet incomplete, picture of some of the processes involved in the control of refractive error in growing eyes. Two insights are especially important. First, images not focused on the retina guide the developing eye to correct for this defocus. Thus, animals with either hyperopia (farsightedness) or myopia imposed by spectacle lenses alter the shape of their eyes to bring the images back into focus. Second, changes in focus of images on the retina can cause changes in eye growth directly by a cascade of chemical signals from the retina to the sclera. Thus, in animals, normal refractive development and myopia of moderate severity may involve a visual feedback mechanism that controls eye growth. Recent evidence that this feedback occurs in primates suggests that these discoveries have substantial practical implications for the clinical treatment of myopia and other refractive disorders in humans, affording opportunities for testing this hypothesis in clinical trials.

Early detection and intervention in strabismus and amblyopia. Concerted efforts in many laboratories over the past two decades have led to the realization that many strabismic and amblyopic states result from abnormal visual experience in early life that can be prevented or reversed with early detection and intervention. Many barriers still need to be overcome in the national fight against these disorders, including proper education of healthcare professionals and the general population, access to quality health care across socioeconomic classes, and the steady cooperation of families during long-term treatment of infants. In terms of scientific understanding and clinical capability, however, researchers have now arrived at a point where most amblyopias can be successfully treated given early detection and appropriate intervention.

Molecular, genetic, and neural insights into disease states affecting the extraocular muscles and the eyelid. Each eye is served by six extraocular muscles that enable the vast range of eye movements humans make to explore the world and stabilize visual objects on the retina. In addition, each eye is served by an eyelid and blink reflex, which protect the eye from potential injury and ensure that the cornea is regularly moistened. Dysfunction in the

extraocular muscles, the muscles that control the eyelid, or the nerves that serve any of these muscles can result in serious impairment of vision in the affected eye. Researchers have made significant progress in understanding several of these disease states in the last 5 years. For example, the extraocular muscles seem to be immune from the effects of Duchenne muscular dystrophy, even though skeletal muscles degenerate throughout the remainder of the body. Thus, extraocular muscles are structurally and functionally different from those of other motor systems. This unique phenotype raises the possibility that extraocular muscles will respond in a unique manner to many disease states. Recent evidence also suggests that specific genes regulate the development of specific motoneuron pools, and that mutations in these genes could be etiologic factors in congenital disorders that affect ocular motility. A host of clinical disorders affects movements of the eyelid. Fortunately, adaptive “reprogramming” of the neural drive to the muscles of the eyelid can compensate for the effects of these disorders and restore eyeblinks to a near-normal state. New studies have shown, however, that this natural reprogramming can go awry, producing blepharospasm, which results in uncontrollable and prolonged spasms of eyelid closure. Relying on laboratory research concerning the neural mechanism of reprogramming and the details of the neural circuitry controlling the eyelids, researchers have now developed animal models of blepharospasm. These models provide a springboard for testing new treatments for a disorder that afflicts 10 percent of the population over the age of 70.

Discovery of specific gene mutations that cause Leber’s Hereditary Optic Neuropathy. Leber’s Hereditary Optic Neuropathy (LHON) is a maternally inherited genetic disease that results in substantial loss of central vision in affected patients. Most genetic diseases are caused by mutations in chromosomal DNA inside the cell nucleus. LHON, however, is the first disease to be associated with mutations of the small amounts of DNA that reside inside the mitochondria (mtDNA). This DNA encodes for subunits of complex 1 of the respiratory chain, the key biochemical cascade that manufactures the cell’s supply of the high-energy molecule adenosine triphosphate. The three most common mutations causing LHON have now been identified, providing a useful diagnostic test for LHON and new insight into the pathogenesis of the disease.

Completion of the Ischemic Optic Neuropathy Decompression Trial. Ischemic optic neuropathy is the most common pathology of the optic nerve, other than glaucoma, affecting older persons. The Ischemic Optic Neuropathy Decompression Trial was a randomized clinical trial designed to compare patients who received a commonly used surgical procedure with those who were carefully observed but had no surgery. This trial has been completed except for long-term followup studies. Results from this study indicate that decompression surgery, a difficult and expensive procedure, is no better than careful followup (in terms of improved vision) and possibly worse. This finding will result in substantial savings in medical costs and will put fewer people at risk to an unnecessary surgical procedure.

Discovery of molecular and cellular mechanisms that regulate cell growth, survival, and death. In contrast to peripheral nerves, the CNS (including the retina and the optic nerve) is extremely limited in its capacity for regrowth after injury. The primary hope for correcting this situation lies in understanding the underlying mechanisms that mediate cell growth, survival, and death. This field has witnessed explosive growth in the past 5 years, with one exciting discovery following another. For example, experiments in *Drosophila*, zebrafish, and mice have identified master control genes for eye formation. In humans, mutations of one of these genes account for a genetic disorder called aniridia, which causes retinal, lens, and iris defects. Additional developmental studies have uncovered a specific class of molecules (called POU domain transcription factors) that govern the expression of specific genes during development, thereby playing an essential role in establishing different classes of retinal ganglion cells. Proper myelination of the growing nerve appears to be ensured by a different traffic of chemical signals between growing retinal ganglion cells and oligodendrocytes, the cells that ultimately form the myelin sheath around the developing axon. Oligodendrocytes that fail to contact an unmyelinated axon undergo programmed cell death (apoptosis). Many of the genes that underlie this apoptotic “cell suicide” program have been identified and are expressed by most animal cells, including retinal ganglion cells. Survival of retinal neurons is promoted by a class of peptide trophic signals, including the recently discovered bcl-2, which inhibits activation of the cell suicide program. Overexpression of bcl-2 can rescue injured retinal

ganglion cells from almost certain death. Finally, it has become possible in recent years to isolate developing retinal ganglion cells and grow them in tissue culture. This preparation has revealed that survival of retinal ganglion cells requires not only peptide factors such as the neurotrophins, but also intrinsic electrical activity. All of these exciting discoveries have critically important implications for the regeneration of damaged visual pathways, and therefore comprise a high priority area for future research.

Discovery of molecular mechanisms mediating topographic order and axon guidance within the developing visual system. Representation of the visual world in the form of topographic maps is a basic organizational principle of the visual system in all vertebrate animals, including humans. Topographic maps exist in numerous structures throughout the brain and are crucial to the ability to perceive an organized visual world and move in a goal-directed manner within this world. Among the most dramatic advances of the last 5 years has been the discovery of specific molecular factors that mediate the formation of topographic order within the developing visual system. For example, complementary gradients of a specific class of cell surface ligands and their receptors—members of the Eph family of tyrosine kinases—are distributed in a graded manner across topographic maps in the retinotectal system. These gradients are crucial to establishing topographic maps in these structures. Other related molecules are also distributed throughout the visual system and appear to play a fundamental role in guiding growing nerve processes to their targets. Another discovery of fundamental importance in this field is identification of molecules called netrins and semaphorins, which are chemoattractant (or chemorepulsive) molecules that guide growing axons and form the refined pattern of connections throughout the vertebrate nervous system. Research on how these cell surface and diffusible molecules function will be crucial for understanding the inhibitors of regeneration of the optic nerve, the barriers to establishing new nerve connections, and the design of rational therapies to enhance these processes.

Imaging the functional architecture of the visual cortex. One of the major accomplishments over the past 5 years in the area of functional processing has been the advent of new strategies for minimally

invasive optical imaging of the brain. Using what has now become a straightforward technology, it is now possible to visualize the functional organization of exposed visual areas with an unprecedented degree of spatial resolution. This has led to the first complete descriptions of the organization of orientation and ocular dominance domains in striate cortex and the relationship between the two. Increasingly sophisticated stimulus paradigms have allowed investigators to visualize sites of motion and color processing in the striate and extrastriate cortices of carnivores and primates. Optical imaging of intrinsic cortical signals was developed in the visual system, but it was the anatomical and physiological data from decades of vision research that allowed the validity of this approach to be assessed rigorously. Intrinsic signal imaging is now being employed in less well-studied cortical areas, and studies in the visual system have paved the way for clinical investigations to identify epileptic foci in humans. This provides yet another example of how laboratory research on visual processing has enabled an entirely new technology to move into clinical applications. The ability to rapidly visualize the functional architecture of the cortex has allowed the consequences of visual deprivation in strabismus and amblyopic conditions to be assessed directly and provide a further guide for detailed electrophysiological investigations.

Identification and mapping of higher cortical visual areas that serve vision and eye movement control in humans. The human visual cortex is composed of a primary visual area (V1), whose integrity is necessary for functional vision of any sort, and higher order areas that play important roles in more specific aspects of vision, such as object recognition or spatial orientation. These higher visual areas and the pathways that connect them have been investigated in great detail in monkeys and cats, but little progress has been made in analyzing higher regions of the human visual system, because researchers have not been able to carry out appropriate experiments in humans. The advent of noninvasive imaging technologies like positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have now changed this situation dramatically. For the first time, researchers are able to peer inside the living human brain and assess visual function with reasonable spatial and temporal resolution.

Several research groups have now identified and topographically mapped visual areas V2, V3, V3A, and portions of V4 in humans. In addition, several research

groups have studied a region called the middle temporal area (MT or V5), which may be specifically involved in the analysis of visual motion information. The spatial layout and topographic organization of these areas are remarkably similar to the general primate plan deduced over the past 30 years from painstaking studies in several species of monkeys. More recently, similar information has begun to emerge for the control of eye movements by the cerebral cortex, which will certainly be an active area of research in the future. This turn of events is encouraging, not only because of the new knowledge gained concerning the human visual system, but also because it confirms the wisdom of the substantial investment in research on animal models made by the SAVP Program over the past three decades.

The ongoing discovery of central neural mechanisms governing perceptual sensitivity to visual stimuli. The visual system has a limited capacity for processing the vast amounts of visual information that flood the two eyes throughout each day. Exquisitely sensitive mechanisms at several levels of the visual pathway work together to distribute this limited processing capacity to match the organism's most pressing needs. Some of these mechanisms are said to be "bottom-up," in that they are an intrinsic feature of local neural circuits in the visual cortex and operate automatically on all visual information arriving at the cortex. Substantial progress has been made in the past 5 years in understanding the process of contrast gain control, which adjusts the response properties of cortical neurons according to the range of contrasts present in the visual scene during a given epoch of time. Evidence indicates that this scaling of neural sensitivity is achieved by response "normalization," in which the output of each cortical neuron is effectively divided by the pooled activity of a large number of additional neurons that analyze the same small region of visual space. Other mechanisms governing the sensitivity of cortical neurons are said to be "top-down," in the sense that they reflect voluntary decisions made by the organism to pay attention to certain objects, features, or locations in the visual environment.

Visual attention can be manipulated in alert animals using simple behavioral paradigms borrowed from cognitive psychology, and these behavioral manipulations exert dramatic effects on the responses of neurons in higher order regions of the visual cortex. In essence, attention acts as a powerful filter, suppressing unimportant information and passing behaviorally

relevant information on to higher processing stages. Over the past 5 years, powerful attentional effects have been demonstrated at surprisingly early levels of the cortical pathway, and neural correlates have been demonstrated both for spatial attention (the “spotlight” hypothesis) and for feature-based attention. Another major influence on visual sensitivity is perceptual learning. The past 5 years have yielded a flood of behavioral studies demonstrating that practice on specific perceptual tasks results in increased sensitivity to weak visual signals and increased capacity for discriminating among very similar signals, which can be sharply restricted to the region of space in which the important signal commonly occurs. Thus, the adult visual system is not immutable, can change according to behavioral demands, and has implications for potential rehabilitation after injury.

Novel insights into mechanisms for transforming visual information into signals appropriate for guiding motor behavior. Humans use visual information to judge location, size, and shape of objects to predict the future position of those objects. This information is captured by nerve cells in the retina and is therefore represented in a coordinate frame that changes with every movement of the eyes (eye-centered coordinates). To catch, grasp, approach, or avoid such objects, however, information must be transformed from eye-centered coordinates to a body-centered coordinate system appropriate for moving the arms, legs, or hands. Vision researchers have made important strides in the last 5 years in understanding how the brain performs this feat. Psychophysical studies of human observers have shown that visual and nonvisual signals are used to make the coordinate transformations needed to perceive object position with respect to the body. The nonvisual signals are provided by the motor commands sent to the eye and neck muscles and by the commands sent by the vestibular system. Physiological studies suggest that there are a number of intermediate representations of space between visual input and motor output.

Recent work on perceived self-motion through the environment has led to further insight. Psychophysical and modeling studies have demonstrated that this optic flow pattern can be used to compute the observer’s future position with respect to obstacles and landmarks. Psychophysical research has shown that humans are exceedingly adept at interpreting

these complex flow patterns, a capability that requires information about the motor signals sent to the eyes and head in addition to the visual flow signals falling on the retina. Physiological studies have identified neural circuits in a cortical area called MST that receives a combination of visual flow, eye movement, and head position signals appropriate for solving the self-motion problem. These circuits and the role they play in computing self-motion will certainly be a topic of active experimentation in the future.

Combined, these accomplishments illustrate the wide scope and vitality of research in the SAVP Program—from molecular factors underlying the early development of the nervous system, to the neural processes mediating human visual perception, and finally to insights leading to the correction or prevention of visual impairments.

PROGRAM OBJECTIVES

- Identify the visual error signals that govern eye growth during correction for refractive error; identify human risk factors for myopia and abnormal eye growth and evaluate promising treatments for preventing the onset of or slowing the progression of myopia, such as special spectacles or contact lenses or pharmacological treatments.
- Investigate the effectiveness of immunomodulating therapies in halting disease progression in optic neuritis; identify the unique characteristics of ocular muscles that render them vulnerable to Graves’ ophthalmopathy, myasthenia gravis, orbital myositis, and chronic progressive external ophthalmoplegia.
- Discover how topographic gradients are generated and read out to form retinotopically ordered structures, and identify the sites and mechanisms of action of axon guidance molecules.
- Determine the role of peptide growth factors, such as neurotrophins, in the development, plasticity, and regeneration of the visual pathways; determine how critical periods are regulated; manipulate the molecular signals

underlying this regulation to enhance the adaptive and regenerative properties of the adult brain.

- Elucidate the mechanisms by which spontaneous patterns of electrical activity, present before the onset of visual experience, guide the formation of visual structures prior to visual experience.
- Characterize the clinical problems of amblyopia and impaired stereoscopic vision more precisely, and clarify their relationship to strabismus, anisometropia, and other related conditions.
- Study the development and plasticity of neural mechanisms affected in strabismus and amblyopia, including studies in animal models and normal and abnormal human populations.
- Develop innovations in the detection and treatment of strabismus and amblyopia.
- Develop fMRI and related technologies as useful, quantitative tools for exploring the neural basis of human visual processing.
- Understand how neural computations are accomplished and stored within the central visual system.
- Understand plastic mechanisms in the oculomotor system that ensure accurate gaze shifts, precise alignment of the two eyes, steady fixation that can be affected by nystagmus, and a stable visual world during self-movement.
- Extend studies of eye alignment to include vertical and torsional eye movement control; gain insight into the pathogenesis of cyclovertical strabismus.
- Discover how visual information contributes to perceptual decisions, object recognition, internal representations of external space, transformations between different spatial frames of reference, and the formation of neural signals appropriate for guiding behavior.

- Understand the cellular mechanisms that give rise to changes in visual sensitivity associated with attention and perceptual learning.

The needs and opportunities related to each of these objectives and the strategies for accomplishing them will now be considered.

Objective 1(a): Identify the visual error signals that govern eye growth during correction for refractive error.

Research Needs and Opportunities

In animal models, it is now accepted that visual circumstances can influence refractive error, and that this influence involves modification of the growth of the eye. Thus, a feedback mechanism is at work in ocular growth—visual input influences growth, which in turn modifies the visual input. Importantly, the influence of vision on growth can be communicated directly from the retina to the sclera without involvement of the brain. This view of the mechanisms of refractive adjustments has provoked a search for the visual cues the retina uses to discern whether to accelerate or retard the axial growth of the eye and for the signals, presumably chemical, by which the retina communicates to the sclera the appropriate direction of growth. The most provocative candidates are dopamine and acetylcholine because agonists and antagonists, respectively, reduce form-deprivation myopia in both birds and primates.

Strategic Research Questions

What visual signals are used by the retina to regulate growth? What are the chemical signals that permit the retina to communicate with the sclera? How do humoral signals move from the retina through the barrier of the retinal pigment epithelium? If there is a cascade of chemical signals involving several cell types, what is the nature of the cellular interactions involved?

If the etiology of myopia is related to a feedback mechanism that controls normal eye growth, it becomes important to understand what aspect of the visual image signals the eye to elongate and thereby become myopic. Over the next 5 years, it will be important to determine how many

distinct mechanisms of experimentally induced refractive errors exist. The realization that myopia or hyperopia can develop to compensate for defocus imposed by spectacle lenses has created a controversy about whether these refractive changes are produced by the same mechanisms as the myopia resulting from visual deprivation. Resolving this controversy would add significantly to understanding the roles that defocus and other visual feedback play in emmetropization and the development of refractive error. The long-term goal is to learn what visual factors present in the environment may cause children to develop myopia.

Researchers anticipate that the next few years will see rapid progress in the identification of the signal cascades from retina to sclera that cause the eye to increase its rate of elongation, leading to myopia, or to decrease it, leading to hyperopia. Molecular biology techniques will be used to ascertain changes in expression of neurotransmitters, growth factors, and other regulatory proteins in experimentally induced myopia. Understanding these chemical signals may lead to pharmacological agents that might slow myopic progression.

Objective 1(b): Identify human risk factors for myopia and abnormal eye growth and evaluate promising treatments for preventing the onset of or slowing the progression of myopia, such as special spectacles or contact lenses or pharmacological treatments.

Research Needs and Opportunities

As knowledge of the underlying mechanisms that control eye growth and refractive compensation increases, the ability to assess the risk factors that predict the development of myopia in children or adults has increased as well. Reading is the most established risk factor for myopia. More recent observations have strengthened the association of the amount of near work with the rate of myopic progression.

Because the sharpness of the image during reading depends on the precision of accommodation, it is significant that myopic children have poorer accommodation than others. Additional research is needed into how accommodation and convergence are related to myopia. Researchers have also long

suspected that genetic factors play a role in the cause of myopia. The evidence is especially strong in the case of pathological myopia (myopia of high degree). Refractive errors of monozygotic twins are more closely aligned than they are for dizygotic twins. A greater prevalence of myopia exists among the children of myopic parents than among the children of nonmyopic parents. Recent studies of the eye in infancy have also shown that the seeds of myopia may appear early in development. Longitudinal studies of refractive error have suggested that some myopic children may have previously been myopic as infants.

To make the transition from animal studies to clinical studies, there is a pressing need to determine how similar the biological mechanisms of eye growth are in different species, and how similar experimental models of myopia (by visual deprivation or the imposition of hyperopia by spectacle lenses) are to the myopia that develops in schoolchildren. Enough is presently known to begin to evaluate promising treatments for preventing the onset or slowing the progression of myopia and systematically investigate the risk factors associated with the development of myopia.

Strategic Research Questions

What interactions between heredity and environment result in myopia? During the next 5 years, researchers need to bring the biological side of myopia research to the point where the interactions of heredity and environment can be understood, as is beginning to occur with heart disease and obesity. One of the weaknesses of family studies is that it is difficult to separate out the contribution of genes in families from that of a shared environment. Do parents pass on to their children myopic genes or a love for reading? Statistical methods for examining the degree of interaction between heredity and near work should prove useful. These efforts will be strengthened by a genetic analysis of myopia, including linkage analysis or gene mapping. On the environmental side, increasingly sophisticated epidemiological surveys of refractive errors are needed to characterize better potential risk factors. Large-scale population surveys (such as the National Health and Nutrition Examination Survey) could include assessments of refractive errors. Ultimately, studies of visual, cell biological, genetic, and epidemiological factors will inform each other and lead to a better understanding of the etiology of myopia.

The clinical research community should also investigate a number of interesting research questions related to slowing the progression of myopia. Can progressive lenses or bifocals reduce myopic progression in children? Although researchers do not yet know what visual signal causes the retina to signal the eye to elongate, minimizing the blur that a child sees may reduce the impetus toward myopic growth. Can muscarinic agents prevent or reduce myopia? It has been shown in animals that muscarinic antagonists, such as atropine, reduce deprivation myopia, even in species in which these agents do not prevent accommodation. This has given a new rationale for this oldest preventive pharmacological treatment. What effect do rigid, gas-permeable contact lenses have on the progression of myopia? Given the results from some studies, a trial of rigid, gas-permeable contact lenses in children would seem worthwhile, taking into account how such factors as age, degree of myopia, corneal topography, and duration of contact lens wear affect myopia progression. Are there behavioral approaches that could be used to reduce myopia? A well-controlled test of “behavioral” methods of myopia control should be considered. Many patients are convinced that their myopic progression was slowed or reversed by various forms of vision training. If controlled studies confirmed this conviction, it would identify a treatment modality not presently taken seriously by most clinicians. If studies did not confirm it, patients might be deferred from unproved and unsound therapeutic practices. Any of these myopia treatments or prevention studies would be most logically performed in myopes or in children who have been identified to be at moderate to high risk for myopia. Risk-benefit ratios of treatment side effects versus the prevention of myopia will need to be evaluated in each of these studies, as will the reliability of each of the critical measures.

Objective 2(a): Investigate the effectiveness of immunomodulating therapies in halting disease progression in optic neuritis.

Research Needs and Opportunities

Optic neuritis results from inflammation or demyelination of the optic nerve and can lead to serious impairment of vision. Optic neuritis can represent an initial sign of a systemic neural disease such as multiple sclerosis (MS), or it can flare up locally

for unknown reasons. It can occur at any stage of MS, but it is often the initial problem noticed by the patient in the early stages. The underlying mechanisms that cause optic neuritis are unknown, and knowledge has been scanty concerning the long-term natural history of the disease and the exact risk of MS associated with the disease. The Optic Neuritis Trial Treatment (ONTT) was the first multicenter trial sponsored by the NEI that yielded important advances in understanding this disease. The initial results, published in 1992, showed that the standard treatment of oral prednisone alone did not improve the visual outcome and was associated with an increased rate of new attacks of optic neuritis. Treatment with high-dose intravenous followed by oral corticosteroids accelerated visual recovery, but offered no long-term benefit to vision. This treatment produced a short-term reduction in the rate of development of clinically definite MS. This study also demonstrated that the presence of multiple enhancing lesions on the brain MRI scan performed at the time of optic neuritis diagnosis was the single most important predictor of the development of MS within 5 years. The probability of developing MS at 5 years ranged from 16 percent in patients with no lesions to 51 percent in patients with three or more lesions. Patients treated with high-dose methylprednisone had relative protection from developing MS for the first 3 years of followup, but at 5 years the protective effect was no longer observed.

Strategic Research Questions

Can a suitable animal model of optic neuritis be developed to help gain insight in the molecular mechanisms underlying the disease process? Lack of animal models for many neuro-ophthalmological diseases has hampered progress in understanding and treating these diseases. Thus, a very high priority should be the development of suitable, specific models for experimental investigation. Thus far, some insight has emerged from loosely related animal forms of disease, such as allergic encephalomyelitis and viral-induced demyelination. Can such models be used in devising immunomodulating therapies for optic neuritis? Studies of these models have suggested possible strategies to limit optic nerve damage from inflammation, and these need to be pursued. Immunomodulating therapies have shown great promise in slowing the progression of MS and therefore need to be assessed in optic neuritis.

Objective 2(b): Identify the unique characteristics of ocular muscles that render them vulnerable to Graves' ophthalmopathy, myasthenia gravis, orbital myositis, and chronic progressive external ophthalmoplegia.

Research Needs and Opportunities

Thyroid-associated ophthalmopathy (TAO) is a unique pattern of tissue remodeling in the eye orbit (including extensive inflammation and swelling) that is associated with Graves' disease. Graves' disease is an autoimmune condition with three defining symptoms: thyroid enlargement, thyroid overactivity, and a skin condition called dermopathy. Nearly 10 percent of Graves' patients also develop TAO that is severe enough to require treatment. Orbital tissues, including the extraocular muscles and fat, become inflamed, are infiltrated with lymphocytes, and accumulate hyaluronan, a complex carbohydrate. Over the past 5 years, the orbital fibroblast has been characterized extensively and shown to exhibit exaggerated responses to inflammatory signals such as cytokines. In addition, a key enzyme in the prostaglandin synthetic cascade is extremely inducible in orbital fibroblasts compared to many fibroblasts from other regions of the body. The cytokine milieu in orbital tissues, which has been studied with immunohistochemical techniques, suggests the presence of factors such as interleukin-1 and tumor necrosis factor- α , which appear to mediate inflammatory responses. While these findings indicate that orbital tissue may be particularly susceptible to inflammation, the exact molecular events that initiate lymphocyte recruitment and activation are not understood, nor are the links between the thyroid disease and the pathology occurring in the eye orbit. This lack of insight severely limits the development of safe and effective therapeutic strategies for TAO.

Strategic Research Questions

In the field of autoimmune diseases of the eye orbit, of which TAO is a prominent example, what animal models could be used to study the molecular and cellular interactions between the immune system and the orbital connective tissue? High priority should be placed on studies that can yield insight into the initiating events leading to fibroblast activation and tissue remodeling and the cell

signaling events that stimulate the trafficking of immunocompetent cells to the orbit. If possible, the common antigen shared by the thyroid and the orbit should be identified, as it would provide an important target for therapeutic drugs. Treatment strategies will need to be formulated and evaluated, initially in animal models and *in vitro* systems and ultimately in prospective *in vivo* studies. This will probably necessitate multicenter activities if the requisite numbers of subjects are to be included.

Objective 3: Discover how topographic gradients are generated and read out to form retinotopically ordered structures, and identify the sites and mechanisms of action of axon guidance molecules.

Research Needs and Opportunities

The increasing power and sophistication of molecular approaches over the past 5 years has led to an explosion of new information on the basic molecular mechanisms that guide the initial formation, connectivity, and topography of the visual system, and of the nervous system in general. Moreover, decades of investment in the study of the structure, function, and development of the visual system have made this the system of choice to study. The overriding opportunity for the next 5 years is to capitalize on recent advances to achieve a new, substantially more profound level of understanding of the molecular signals underlying both normal development and regeneration.

Strategic Research Questions

What are some of the molecular cues used in the developing visual system to guide growing axons and establish topographic connections? Elegant assays have shown that graded cell surface signals prevent retinal ganglion cell axons from innervating inappropriate regions of central targets. Subsequent studies in mammals have demonstrated that receptors and ligands belonging to the same class of molecules are organized into reciprocal gradients in the retina and tectum. Experiments show that the gradients that these molecules form can confer topographic specificity in the mammalian brain. While the existence of such gradients has been postulated for decades, scientists now have a firm handle on what types of molecules

are involved in constructing such maps. The organization and function of these signaling pathways is likely to be a very rich area for exploration during the next 5 years.

This general approach has also led to the deciphering of some of the basic molecular codes regulating growth cone guidance and patterning of connections in the vertebrate nervous system. Almost 100 years after their existence was first postulated by Cajal, several members of a family of chemoattractant molecules, the netrins, were purified and cloned. These molecules are abundantly expressed in midline structures and, although first described in the spinal cord, are also present at crucial “choice points,” such as the optic chiasm and the optic nerve head. Another class of secreted and membrane-bound guidance molecules, the semaphorins, are involved in the regulation of growth cones by both positive and negative actions. Members of this family induce growth cone collapse and are also likely to be involved in axon guidance. Both the netrins and the semaphorins are found in flies and worms. This discovery highlights the power of using a strategy of molecular homology in genetically tractable animals to identify important vertebrate signaling molecules and subsequently analyzing their functional roles in well-understood vertebrate systems, such as the visual system. From these molecular studies, the idea has emerged that negative regulators of axon guidance are probably at least as important as positive regulators. These different classes of molecules have both positive and negative roles. They are present in adults as well as during normal development, and they are likely to be important cues for determining the regenerative capacity of axon pathways.

High priority should be given to developing new assays that combine *in vitro* accessibility with increasing fidelity to the *in vivo* situation. The past 5 years have witnessed the first molecular insights into long-standing issues, such as the generation of topography within the visual system, but the present state of knowledge regarding the molecular determinants of development and regeneration remains rudimentary. The overriding opportunity for the next 5 years is to capitalize on these recent advances to reveal the molecular signals underlying both normal development and regeneration.

Objective 4: Determine the role of peptide growth factors, such as neurotrophins, in the development, plasticity, and regeneration of the visual pathways; determine how critical periods are regulated; manipulate the molecular signals underlying their regulation to enhance the adaptive and regenerative properties of the adult brain.

Research Needs and Opportunities

There is a pressing need to understand the exact mechanisms of action of known trophic molecules, such as the neurotrophins, which have clear potential as therapeutic agents in the regeneration and plasticity of the nervous system. Much work needs to be done on the functional roles played by these molecules and how their expression and efficacy are regulated by visual experience and activity. More studies are needed on their roles as survival and differentiation factors early in visual development.

Strategic Research Questions

What do researchers know about the molecular substrates governing the development and plasticity of the visual pathways? It is likely that the known molecules represent only the tip of an iceberg of similar molecules involved in regulating growth. Particularly promising approaches to discovering these molecules include cloning by homology and searching the ever-increasing set of known genetic sequences arising from the Human Genome Project and the Nematode Sequencing Project. In this context, large-scale screens of genetically modified organisms (such as flies and worms), with an eye toward molecules specifically involved in mammalian signaling pathways, are also likely to be a fruitful source of new insights. Another major advance in this area has been the discovery that the neurotrophin family of growth factors and the signaling pathways they utilize are likely to be key players in the control of brain plasticity. Although their precise roles are not established, adding or removing neurotrophins alters the normal formation of orientation and ocular dominance columns and responses to visual deprivation. Again, this is an area that opens up many therapeutic possibilities. The availability of powerful reagents to manipulate these growth factors should allow their roles to be rapidly identified. It is especially intriguing that the levels of neurotrophins are regulated by activity and the

development of cortical dendrites and axons is influenced by the specific neurotrophins present at specific ages in the developing cortex.

Because of its accessibility and its relevance to restoration of vision, the optic nerve, which consists of the axons of retinal ganglion cells, is an especially tractable and appropriate model system for the study of the molecular basis of regeneration. Restoring function to the visual system is also easy to assess using electrophysiological, anatomical, and psychophysical techniques, and in many ways is less susceptible to the experimental limitations of other regeneration models such as the spinal cord. Nonetheless, it is almost certain that discoveries that reveal the molecular mechanisms mediating regeneration in the optic nerve will be of great importance elsewhere in CNS regeneration, particularly the spinal cord. Thus, special attention should be given to strategies that seek to identify the normal cues used to grow the optic nerve and to establish connections. These are likely to be useful in the context of regeneration. Additional effort should be invested in determining the molecular constraints in the adult nervous system that prevent axon growth and successful regeneration. The factors controlling neuronal growth are likely to be intimately involved in controlling the windows of time—critical periods when the structure and function of the visual system can be altered by visual experience. Researchers still lack a compelling explanation for the factors that produce closure of critical periods. This has been due in part to the limitations of pharmacological approaches. Developing new model systems, such as visual plasticity in knockout mice, should provide a powerful new tool to approach this issue, especially if expression of relevant genes can be manipulated in space and time.

Objective 5: Elucidate the mechanisms by which spontaneous patterns of electrical activity, present before the onset of visual experience, guide the formation of visual structures prior to visual experience.

Research Needs and Opportunities

In support of the idea that organized patterns of spontaneous activities play a crucial role in organizing the developing visual system, it is now clear that ocular dominance columns are present in

adult-like form even in newborn monkeys. This implies that endogenous activity patterns are a powerful organizing force that operate well before vision is present and are sufficient to structure this important system. Recent work has demonstrated the presence of, and mechanisms underlying, spatiotemporally organized retinal waves in mammals and in turtles. These waves may be important not only for organizing the retinogeniculate and geniculocortical pathways, but also for the development of the retina itself.

Strategic Research Questions

How do spontaneous patterns of activity guide the formation of visual pathways? Little is known about endogenous activity in sites other than the retina, and it is important to establish when such activity exists, whether it is patterned, and whether such patterns carry information necessary to appropriately wire the visual system. This will require the development of multisite recording capabilities in developing systems. With the advent of optical imaging of intrinsic signals, it has become possible to address the role of activity-dependent and nonactivity-dependent cues in the development of orientation selectivity in primary visual cortex. Using this approach, it is clear that organized maps of orientation preference are present prior to eye opening, suggesting that molecular cues or prenatal patterns of activity initially determine pattern orientation columns in the cortex. Single-unit electrophysiology, combined with pharmacological manipulations, suggest that cortical activity plays an important role in determining this property. Moreover, manipulating prenatal patterns of activity also prevent the normal emergence of well-tuned neurons, although the basic maps of orientation tuning are preserved. Understanding of intrinsic cortical circuit formation related to orientation tuning has also advanced significantly. The organization of lateral connections that link orientation columns are profoundly altered by both visual deprivation and other patterns of activity, but they can be established even in the absence of visual input. This implies that activity in other pathways, such as thalamocortical loops, may be providing important cues.

Objective 6: Characterize the clinical problems of amblyopia and impaired stereoscopic vision, and clarify their relationships to strabismus, anisometropia, and other related conditions.

Research Needs and Opportunities

Congenital and early-onset binocular imbalance, including strabismus, unilateral cataract, ptosis, anisometropia, and other unilateral conditions, affect the visual maturation of 3 percent to 5 percent of infants in the United States. Each of these conditions has the potential to cause both amblyopia and other abnormalities in binocular vision. Prevention or treatment of amblyopia through early diagnosis, optical correction, and occlusion therapy is often successful. Binocular sensory function is usually severely compromised by even brief periods of abnormal binocular experience during the first year of life.

Strategic Research Questions

How can researchers improve the visual outcomes for patients with early vision abnormalities? Several issues can only be resolved with rigorous observations of the natural history of these problems within the context of randomized clinical trials, but not on the basis of clinical records alone. Rigorous longitudinal trials of patient characteristics and treatment outcomes for different diseases would be extremely useful. Additional laboratory and clinical research is still needed to determine the etiology of strabismus. Scientists agree that some fraction of cases of strabismus arise from a primary motor anomaly, while others arise from a primary sensory anomaly. Different treatment approaches are clearly needed for different conditions, but there is no well-established agreement on the details for many conditions. In clinical studies, it is very important to concentrate on the two most important patient groups: infantile esotropes (who receive most surgical treatments), and accommodative esotropes (who receive a great deal of optical and orthoptic attention).

The etiology of infantile esotropia is still debated. While early surgical treatment may promote binocular function, it often fails to do so. Surgery may actually facilitate the development of amblyopia by converting the infant from alternating fixation to unilateral fixation, with constant suppression of central vision

in the nonfixing eye. Systematic studies of patient characteristics and outcomes are needed. The etiology of accommodative esotropia is understood in terms of excess accommodative effort to overcome a high hyperopia that does not resolve. The question for these individuals is why they do not emmetropize in the usual way, and whether current strategies of refractive correction are appropriate or cause more long-term problems.

In addition to characterizing these patients and improving the outcomes of clinical trials of conventional treatments, clinical trials of noninvasive treatments (such as orthoptics and vision training) are needed to determine the presence of improvement in eye alignment and visual function. Recent evidence from experiments on cortical plasticity in animals suggests that even after the conventional period of plasticity, CNS function can be altered by patterns of use. What are the limits of neural plasticity in the adult? Experimental evidence documents occasional successes in ameliorating amblyopia in adults through training. Such work provides reason to suppose that some kinds of controlled visual practice regimes might be effective treatments, but these require convincing and systematic investigation under rigorous clinical research protocols.

Objective 7: Study the development and plasticity of neural mechanisms affected in strabismus and amblyopia, including studies in animal models and normal and abnormal human populations.

Research Needs and Opportunities

In parallel with more detailed studies of clinical populations, continued experimental work is needed to characterize the development and developmental plasticity of the specific neural mechanisms that are involved in strabismus and amblyopia. These include mechanisms of stereoscopic vision and visual sensitivity to pattern and form and the role of ocular proprioception.

Strategic Research Questions

How do various aspects of visual function mature in newborns? What is the normal development of eye movements, eye alignment, visual acuity

(measured in different ways), color, motion, and depth perception? How does stereoscopic vision develop in normal subjects? In animals, how are cells that mediate stereoscopic perception organized? Which pathways and areas of the visual cortex are crucial for stereopsis? How do lesions in various portions of the visual pathways affect stereopsis? What defects (anatomical, physiological, and chemical) are seen in animals after misalignment of the visual axes?

Approaches to these issues include psychophysical studies of normal and abnormal human subjects and normal and abnormal behavioral and biological studies of the relevant neural circuits in experimental animals. An important goal for the next 5 years is to study mechanisms of binocular vision in normal and abnormal individuals. Binocular vision is easy to disrupt and difficult to restore after a period of abnormal visual experience, but the neural basis for these properties is unknown. Studies are needed in humans and animals that concentrate on the mechanisms of binocular interaction and binocular suppression, their development in early life, and their susceptibility to abnormal visual input.

Related experiments are also needed during the next 5 years in animal models of amblyopia. It is now well established that amblyopia can be created in animals by artificially producing several of the conditions thought to cause amblyopia in humans. But precise answers to a number of crucial questions are still needed. In general terms, what defects in cortical processing of retinal output are responsible for amblyopia? Early form deprivation causes shrinkage of ocular dominance columns in striate cortex and loss of cells responsive to the amblyopic eye. Work over the past 5 years has further characterized many changes that occur in striate cortex in both deprived animals and animals with other kinds of amblyopia, but very little is known about changes that occur in other regions of the visual cortex or how pathways between various cortical areas are affected in amblyopia. To answer these and related questions will require further use and refinement of animal models of amblyopia. It will also require continued study of these models using advanced techniques, detailed in earlier sections on the functional imaging techniques, to study the neural changes in human and experimental animal amblyopes and may in the long term be a technique of particular value.

Objective 8: Develop innovations in the detection and treatment of strabismus and amblyopia.

Research Needs and Opportunities

Researchers need to improve detection of refractive errors, strabismus, and amblyopia in infants and young children and, once detected, how to treat abnormalities for optimum improvement and avoidance of later problems. It is also important to learn what new diagnostic or surgical techniques for the evaluation or treatment of strabismus are most deserving of further study over the next 5 years.

Strategic Research Questions

Can better public health methods of testing visual function be developed for preverbal children? When children with visual abnormalities are identified, can better methods for detailed clinical office testing be developed? Photographic, video-based, and optoelectronic techniques are being developed for semiautomatic or automatic detection of refractive errors, strabismus, and amblyopia in infants and young children. These or other methods must be developed further to be cost-effective for mass screening. Thresholds must be established for detection of abnormalities, based on the benefits of detection. The effects of populationwide correction of mild or moderate refractive errors, for example, are not yet known, and may in fact be counterproductive by interfering with emmetropization. Proper studies of early intervention methods will be necessary to establish the benefits of early screening.

Automated eye-tracker-based measurement of strabismus in unrestrained children in free space and in different directions of gaze is a worthy goal for technology development. Measurement of fusional vergence potential and vergence amplitudes should also be automated. Surgical procedures, improved methods of botulinum toxin administration, and improved predictors of outcome are needed for common groups of patients, such as those with congenital esotropia, acquired esotropia, and deteriorated intermittent exotropia.

Objective 9: Develop fMRI and related technologies as useful, quantitative tools for exploring the neural basis of human visual processing.

Research Needs and Opportunities

The past 5 years have witnessed an impressive growth in the applicability of imaging technologies to the understanding of human brain function—and in visual function in particular. In the coming 5 years, developments in this area will provide new insight into the organization of brain areas involved in visual perception and in the control of visually guided behaviors. Because of its accessibility and science's large knowledge base, the visual system is already an important area of research in terms of imaging technologies and will undoubtedly continue to serve this role in the coming decades. In the realm of cortical processing, there is an urgent need to improve the spatial capabilities of existing imaging techniques. While optical imaging of intrinsic signals in animals has resolution on the spatial scale of single functional units (e.g., orientation columns), less invasive techniques, such as fMRI, which are much more suitable for use in humans, have not achieved comparable spatial resolution. Thus, an increase in spatial resolution of at least tenfold is required to extend the use of imaging technologies beyond localizing structures involved in various processes. In this case, the hurdles to be overcome are largely technical; attracting physicists, engineers, chemists, and investigators from other related disciplines will be necessary to overcome these technical obstacles. Considerably more work is also needed on understanding the relationship between functional MRI signals and neural activity. Currently, the source of the signals related to brain activity and their precise interpretations remains murky.

In the long term, researchers must consider developing novel, noninvasive techniques for electrically stimulating specific neural circuits within the human brain. Conceptually, progress in neurophysiology has rested on two legs: (1) being able to record, or “listen” to, the activity of nerve cells as they go about their business, and (2) being able to alter the activity of the same cells artificially (electrical stimulation) and observe accompanying changes in behavior. New imaging techniques are beginning to provide the capability to record neural activity in the human brain with useful spatial and

temporal resolution. While transcranial magnetic stimulation holds some promise, radically new approaches will need to be developed, perhaps beginning in highly reduced preparations such as brain slices.

Strategic Research Questions

How can researchers best realize the vast potential of imaging technologies for exploring visual function? First, imaging of the human brain should be performed in parallel with similar studies in nonhuman primates, in which more invasive electrophysiological techniques can be used to confirm or expand findings from imaging studies. Combined imaging and electrophysiological analysis in experimental animals should also facilitate analysis of the actual physiological sources of the signals measured by fMRI. Imaging in nonhuman primates is in its infancy; much more work is needed in this area to allow data from animal experiments to inform those in humans.

Second, fMRI studies in humans should incorporate more rigorous experimental designs, borrowing liberally from the established methodologies of visual psychophysics. It is now clear that reliable fMRI signals can be obtained routinely and that, with additional effort, individual visual areas can be identified in individual human subjects. To exploit these new technical capabilities incisively, investigators must begin to draw on the insights and experimental designs of sensory psychophysics to pose concrete, answerable questions. It is likely that this combined approach holds the greatest potential for gaining novel insights into the neural basis of visual perception.

Third, substantial effort should be devoted to overcoming the current limitations of optical imaging techniques, the most important being limitations in the depth from which signals can be obtained. New techniques to allow areas buried in sulci to be visualized, ideally in awake, behaving animals, will provide insights into the function of brain areas that are currently poorly understood.

Finally, researchers should begin to develop new approaches for stimulating the brain noninvasively at a millimeter level.

Objective 10: Understand how neural computations are accomplished and stored within the central visual system.

Research Needs and Opportunities

At all levels of the visual system, from the retina through the cortex and including the brainstem nuclei involved in control of eye movements, there is an increasing recognition that local circuit processing holds the key to understanding how neural computations are accomplished and stored. Over the next 5 years, understanding how small groups of neurons interact to transform inputs and create behavioral outputs is likely to provide rich insights into the basic codes by which the mammalian brain functions. Investigations of such circuits have implications throughout the range of areas of interest to the SAVP Program, from the earliest stages of visual processing in the retina to the final stages of motor output at the extraocular muscles.

Strategic Research Questions

What new recording techniques, either optical or electrophysiological, can be used to probe activity patterns in small cell assemblies? Considerable effort is needed to develop new theoretical and practical tools for analyzing the voluminous data that will be obtained from such recordings. Progress is needed at several levels: developing new recording technologies, designing new signal processing algorithms, and forming new theoretical frameworks.

All circuits in the visual system on both the sensory processing and motor output branches show considerable plasticity on timescales, ranging from milliseconds to years. The next 5 years should be very rich in terms of understanding both the molecular and cellular bases of the various forms of plasticity and how plastic changes in neural circuits alter the capabilities of those circuits. Currently, most studies of cellular plasticity have concentrated on a restricted number of models and focused primarily on such phenomena as long-term potentiation and long-term depression. As new forms of plasticity emerge, understanding the circumstances under which the various forms are induced and the relationship between plasticity and long-term structural changes in neural circuits will soon increase in importance. Recent

advances in video image processing, confocal microscopy (including multiphoton imaging), vital fluorescent dyes, and time lapse imaging may also be used in brain slices or intact brains to image structural changes in pre- and postsynaptic neuronal processes. This may help to determine what functional changes in visual synapses are actually associated with changes in the morphology of axon terminals or dendrites and the speed with which such changes can occur. At this time, plasticity studies generally focus on the level of single cells and individual synapses; increasing attention needs to be paid to the circuit level consequences of interactions between large numbers of synapses.

As more potential molecular candidates for mediating plasticity are uncovered, molecular genetic approaches need to be supplemented with more sophisticated analysis of signal transduction cascades involved in visual system plasticity. New cell fractionation procedures combined with physiologically relevant stimulation could be used to tease out the earliest events in many signal transduction cascades. Studies identifying important cytoplasmic pathways and distinguishing key posttranslational events and studies aimed at cloning early substrate proteins will be necessary to identify new targets for pharmaceutical development. These pharmaceuticals must be capable of reactivating synaptic plasticity and effective rewiring in the adult brain following childhood visual dysfunction or regeneration of axons following brain trauma. It is also important to determine whether new proteins are synthesized locally to produce synaptic change. More effort should be focused on identifying transcripts localized in dendrites, which could be locally produced during periods of high or curtailed plasticity.

Objective 11: Understand plastic mechanisms in the oculomotor system that ensure accurate gaze shifts, precise alignment of the two eyes, steady fixation that can be affected by nystagmus, and a stable visual world during self-movement.

Research Needs and Opportunities

Eye movement plays a key role in vision. Vision is blurred if the images of objects on the retina move more than a few degrees per second, as could happen during any movement of the head or body. Fortunately,

the nervous system contains gaze stabilization mechanisms (chiefly the vestibulo-ocular and optokinetic systems) that move the eyes precisely to compensate for self-motion. Defects in these stabilization mechanisms lead to markedly reduced visual acuity, mislocalization of objects, and dizziness. Many cases of nystagmus, an uncontrollable back-and-forth movement of the eyes that afflicts many children and adults, can be traced to malfunctions of these stabilization mechanisms. The vestibulo-ocular reflex is primarily responsible for compensating for rapid head movements that would otherwise lead to blurred vision. Most studies of this reflex have been done by fixing the subjects' head rigidly and using a motor to move the head and body passively, as in a rotating chair. It was recently discovered, however, that many neurons in the vestibular system that carry a signal of head velocity during passive rotations of the head or body are silent during voluntary movements of the head (even though the head may be moving at a high velocity). The activity of these neurons is not simply suppressed during voluntary movements, however, because the neurons can still signal the occurrence of passive movement that is superimposed by an experimenter on an ongoing voluntary movement. This indicates that gaze stabilization during voluntary head movements is based on a complex computation that can distinguish between voluntary and passive movements of the head. Remarkably, even the responses of second-order vestibular neurons to head movement appear to be exquisitely sensitive to the behavioral context in which the movement is made. A clear need has emerged to analyze these gaze stabilization systems in a more natural environment, where voluntary and passive head movements may occur in any combination. The stabilization systems are much more complex than researchers recognized earlier.

A great deal of effort has been devoted in recent years to understanding the role of eye and head movements in the computations required to localize an object in space. There is no one-to-one relationship between which region of the retina is active and the location of an object in space. Light reflected from a stationary object can activate nearly any region of the retina, depending on where the eyes and the head are pointing. Thus, information about the site of retinal activity must be combined with information about eye and head position in order to look to or reach for objects of interest. Considerable progress has been made in

understanding the role of the parietal and frontal cortices in these computations. Again, these findings indicate that researchers need to analyze the functioning of these systems in more natural situations, in which animals may look to or reach for a stationary object from any number of starting positions.

Strategic Research Questions

How are the eyes stabilized when a subject is free to move its head and body? In primate experiments, animals will need to be trained to make head, eye, and combined head and eye movements on command to assure proper experimental control. These experiments will be technically difficult but should answer important questions about how the vestibulo-ocular reflex is altered with actively generated eye and head movements. Although findings from these experiments will introduce new complexities of interpretation, experiments at this level are clearly necessary. Other oculomotor systems also need to be studied in a more natural or realistic setting, while still maintaining appropriate experimental control. We rarely shift our gaze without moving our heads; we seldom make a vergence eye movement without also making a saccade. Nonetheless, most studies have used highly restrictive procedures to isolate a particular function.

Recent research has provided far more insightful findings when these systems are studied under more realistic conditions. When saccades occur in conjunction with vergence movements, for example, vergence is speeded while saccades may be slowed. Thus, future studies should involve more natural motor activities, such as active head movement combined with saccades, pursuit, and vergence movements. Better integration between studies of the visual and oculomotor systems is another need. The human oculomotor control system and the visual system evolved together; indeed, the sole function of the oculomotor system is to facilitate good vision. In the past, visual system neurophysiologists have been primarily concerned with preventing eye movements during their experiments. Now there is a growing realization that an adequate description of the visual system must allow for the effects of eye movements. The effects of eye movements will have to be considered if researchers are to discover how to have a coherent view of the world in the face of nearly continuous eye, head, and body movement.

Objective 12: Extend studies of eye alignment to include vertical and torsional eye movement control; gain insight into the pathogenesis of cyclovertical strabismus.

Research Needs and Opportunities

Very precise movements of the eyes are required to maintain proper eye alignment when we shift our gaze between objects that are at different distances from us. Vergence eye movements and accommodation are mechanisms that maintain proper eye alignment and focus so that double vision (diplopia) and blurred vision are avoided. Misalignment of the two eyes, or strabismus, is an extremely common problem, affecting 3 percent to 5 percent of the population. Although there have been significant advances in understanding the basic neural circuits that control the movements of the eyes, the neural circuits involved in stabilizing retinal images by torsional rotations of the eyes—rotations of the eye along the line of sight—are poorly understood. Humans are usually unaware of these torsional movements, but in cases of congenital strabismus, or as a consequence of muscle palsies, the mechanisms that automatically adjust ocular torsion often break down. Single neuron recording experiments and reversible inactivation experiments have permitted identification of some neural systems in the midbrain that govern torsional movements. Much more work is needed, however, to understand how this important class of eye movements is produced and how these movements become defective during disease. Understanding the mechanisms that underlie the perception of the orientation of objects around the line of sight is also needed. A clearer understanding of how orbital connective tissue affects the movement of extraocular muscles is also important for the evaluation of strabismus and the consequences of strabismus surgery.

Strategic Research Questions

Binocular single vision requires that the two eyes be aligned properly with regard to the horizontal, vertical, and torsional axes of movement. Most work has focused on horizontal disjunctive movements, which may represent a special case because of the association with viewing distance and ocular accommodation. A crucial remaining question is: What are the mechanisms for establishing and maintaining eye alignment in all three axes? Answering the question poses a number of technical difficulties, although the search coil

technique does provide a good means of measuring horizontal, vertical, and torsional movements in animals and cooperative subjects. Alternative eye movement recording techniques should be developed for patients and subjects who cannot use the search coil. A good biomechanical model of the eye that incorporates the latest findings on muscle pulleys, including data from imaging studies, is needed to understand how the central motor commands actually govern eye movement and eye alignment and how the ocular muscles interact to produce accurate, stable gaze.

Objective 13: Discover how visual information contributes to perceptual decisions, object recognition, internal representations of external space, transformations between different spatial frames of reference, and the formation of neural signals appropriate for guiding behavior.

Research Needs and Opportunities

Four decades of research into the central visual system, sponsored largely by the NEI, have now created strategic opportunities for neurobiological investigation of cognitive processes that are based on visual information. Scientists now have some degree of understanding of the way that information is extracted from the retinal image and stored in early areas of cerebral cortex, as well as insight into the organization of processing pathways in higher visual areas of the cortex. They are now in a position to ask considerably more sophisticated questions about how the brain makes decisions on the basis of visual information, how it recognizes objects, how it creates an internal model of external space, how it shifts visual information about the world from one spatial frame of reference to another, and how these cognitive processes ultimately generate signals appropriate for generating behavior.

Strategic Research Questions

How does the brain recognize objects in the visual world? How does it form decisions on the basis of incomplete evidence? How does it maintain an accurate representation of spatial relationships among objects in the world?

Despite variation in the visual image produced by changes in lighting or viewpoint, humans can generally identify familiar objects from many perspectives. The brain is not likely to store detailed three-dimensional representations of the vast numbers of objects that can be recognized by a single person, suggesting that the brain must employ an efficient compression system to store object representations in visual memory. A high research priority is to use both psychophysical and physiological tools to understand how this information compression is accomplished as visual data are processed within the hierarchy of cortical visual areas. Computational scientists have proposed iterative models of object recognition that are fairly successful in machine vision. These models use interactions between stored prototypes and incoming data to improve recognition. It is important to determine whether a similar strategy is employed in biological visual systems. Does feedback from stored information in the human cortex affect information acquisition during early stages of visual processing? Behavioral studies that use traditional psychophysical procedures should test whether these computational models are appropriate for human vision; fMRI measurements of human and monkey visual cortex during performance of object recognition tasks should provide additional data on cortical information flow and storage; and neurophysiological studies on single units should examine how neurons encode distinctive attributes that permit object recognition under a variety of viewing conditions. These diverse experimental approaches could provide information that will assist in diagnosing and treating stroke victims who are impaired in their ability to recognize objects.

Simple forms of decisionmaking can be investigated in animals that are trained to perform forced-choice discrimination tasks. Researchers need to understand how high-level neural circuits use basic sensory signals to form decisions which, in turn, guide behavioral responses. One approach to this problem is to require animals to make decisions near psychophysical threshold, where the sensory evidence is uncertain. Recording at successive levels of sensory processing pathways should allow researchers to determine where and how signals arise that are related unambiguously to the animal's choice rather than to any specific aspect of the stimulus itself. Psychophysicists and cognitive psychologists can contribute to this effort by designing behavioral paradigms that manipulate performance at

the level of decisionmaking rather than the level of sensory processing. A promising example of this type of manipulation is the phenomenon of probability matching, where decisions are influenced not only by the present sensory stimulus but also by the animal's recent history of choice and reward. Neural signals that reflect this history are far more likely to participate in the decision process *per se* than in sensory representation.

The twin issues of spatial representation and coordinate transformation within the central visual pathways are the subject of vigorous investigation and are eminently deserving of continued study. We use our vision to judge the location, size, shape, and future position of objects in our surroundings. Information about these object properties arrives at the retina and is therefore initially represented in a retinal coordinate frame. To interact (grasp, catch, move toward, etc.) with such objects, however, the visual information picked up at the retina must be represented in a coordinate frame that is relevant to the muscles in the arms, legs, and hands. Recent psychophysical studies of human observers have shown that visual and nonvisual signals are used to make the coordinate transformations needed to perceive object position with respect to the body. Recent neurophysiological studies of the extrastriate cortex suggest that there are a number of intermediate representations of space between the visual input and the motor output. These intermediate representations are formed in some instances by modulating responses within a retinally defined receptive field by eye, head, or limb position. In other instances, however, visual receptive fields may actually move in accordance within the movement of the limbs. Much more research needs to be conducted with awake animals so that visual responses can be examined quantitatively during systematic manipulation of eye, head, and limb positions.

Objective 14: Understand the cellular mechanisms that give rise to changes in visual sensitivity associated with attention and perceptual learning.

Research Needs and Opportunities

Physiological work on visual attention has concentrated on exploring the effects of diverse behavioral paradigms on the signals carried by single

neurons at successive stages of the central visual pathways. Attentional modulations of visual signals are more diverse and appear at earlier levels of the visual pathway than previously believed. Exploration and categorization of attentional phenomena at the neuronal level will undoubtedly continue, but new developments are needed in the circuit level analysis of visual attention. Scientists need to determine the cellular mechanisms that mediate the effects of visual attention within local neuronal circuits. It is also important to discover the source of the “control” signals that direct attention to or distract from particular features or locations in the visual environment. The role of feedback connections from higher cortical areas in implementing attentional modulation of sensory processing must also be investigated.

The field of perceptual learning is ripe for physiological investigation. Perhaps the most surprising insight gained from behavioral studies is that the performance gains associated with learning can be remarkably specific for the location in visual space and the exact stimuli for which the subject is trained. Counterintuitively, performance gains do not transfer easily to nearby regions of space or to closely related visual stimuli outside the training set. Some psychophysicists have interpreted this evidence to indicate that the neural changes caused by training are localized to very early stages of the cortical pathway. It is equally possible, however, that the neural changes occur in later stages that read out information from the early stages. The important question here relates to determining the neural mechanisms underlying practice-related gains in basic visual capacities. In principle, considerable insight into this issue can be gained from physiological recordings in trained animals.

Strategic Research Questions

What are the neural mechanisms underlying visual attention and perceptual learning? In the field of visual attention, it would be very useful to develop two or three model paradigms for extended physiological analysis. An ideal paradigm would include straightforward, reliable behavioral methods for controlling attention in nonhuman primates and a visual area (or areas) in which neurons show robust response modulations that correlate with behavioral

manipulations of attention. Pharmacological or thermal inactivation studies could determine whether that visual area contributes causally to attentional behavior. Inactivation of higher cortical areas, in concert with electrophysiological recording in the target area, could begin to provide insight into the sources of attentional control signals. Similarly, multiple electrode recordings may provide insight into interactions between cortical areas underlying attentional phenomena.

In the field of perceptual learning, high priority should be given to studies that promise physiological insight into the loci and mechanisms of learning phenomena. Most perceptual learning paradigms established by psychophysicists in the past few years have involved training periods lasting several days or weeks. Physiological analysis is likely to be most incisive if recording electrodes can be chronically implanted in targeted cortical areas while monkeys undergo training regimes similar to those used with humans. Care must be taken to create an experimental situation in which the neurons studied are most likely to contribute to the behavioral phenomena under analysis. For example, disparity-selective neurons might be the best candidates for physiological analysis of learning phenomena involving stereopsis.

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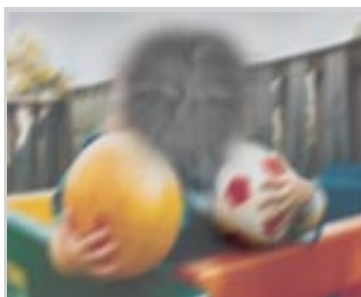
Normal vision



The same scene as it might be viewed by a person with glaucoma



The same scene as it might be viewed by a person with diabetic retinopathy



The same scene as it might be viewed by a person with macular degeneration

PROGRAM OVERVIEW AND GOALS

Visual impairment can be defined as any chronic visual deficit that impairs everyday function and is not correctable by ordinary spectacles or contact lenses. Although there have been important strides in the treatment and prevention of eye disease over the past few decades, there still exist many causes of vision loss for which there is no cure. Even with the best medical treatment, many Americans must live with impaired vision. The term visual impairment is used broadly in this report, covering a wide range of uncorrectable visual disorders including low vision and total blindness. A commonly used definition of low vision, advocated by the World Health Organization, is visual acuity worse than 20/60 with best refractive correction and/or significant visual field loss. In modern society, with its emphasis on reading and driving, some researchers use acuity worse than 20/40 for classifying low vision. "Legal blindness" represents an artificial distinction and has little value for rehabilitation, but it is significant in that it determines eligibility for certain disability benefits from the Federal Government. In the United States, it is typically 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. These overly simple criteria for visual impairment are far from comprehensive in defining the visual function deficits that can cause difficulties with daily living tasks. Many other types of visual impairment are also of concern here because they hamper the performance of everyday activities—problems such as eye movement disorders, visual agnosias, visual processing deficits associated with old age, visual aspects of learning disabilities, and visual disorders of infants and children.

Estimates of the number of Americans with visual impairment depend on how it is defined. Some estimates indicate that there are more than 3 million Americans with low vision, almost 1 million who are "legally blind," and roughly 200,000 who are more severely impaired.

Because of their reliance on narrow definitions of visual impairment, these figures underestimate the prevalence of



Courtesy of J. Pekar, Ph.D.

visual impairment. 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. In adults, visual impairment is associated with loss of personal independence and difficulty maintaining employment, often leading to the need for disability pensions, vocational and social services, and nursing home or assistive living placement. Older adults represent the vast majority of the visually impaired population. Visual impairment is included in the 10 most prevalent causes of disability in America. For older adults, visual problems have a negative impact on quality of life, equivalent to that of life-threatening conditions such as heart disease and cancer. In children, visual impairment is associated with developmental delays and the need for special educational, vocational, and social services, often beyond childhood into adulthood.

The leading causes of visual impairment are diseases that are common in the elderly: age-related macular degeneration (AMD), cataract, glaucoma, diabetic retinopathy, and optic nerve atrophy. Over two-thirds of those with visual impairment are over age 65. Although there are no gender differences in the prevalence of vision problems in older adults, there are more visually impaired women than men because, on average, women live longer than men. However, blacks are twice as likely to be visually impaired than are whites of comparable socioeconomic status. It is estimated that there will be almost 34 million Americans over the age of 65 in 1999, and by the year 2030 this number will more than double.

It is important to emphasize that as the older adult population grows, the number of people with visual impairment and other aging-related disabilities will increase.

The leading causes of visual impairment among infants and children are retinopathy of prematurity (ROP), cortical visual impairment, and structural ocular abnormalities, such as cataract and coloboma. These conditions occur during infancy and early childhood, when it is difficult to assess their effects on vision and quality of life. In addition, many of these conditions occur with increased prevalence in children with neurodevelopmental delay, further complicating the assessment of level of vision and the evaluation of quality of life. More boys than girls are visually impaired. Additionally, increasing numbers of infants are born very prematurely and survive. These children are at high risk for multiple disabilities, including visual deficits, and will substantially increase the number of Americans with visual impairment.

Program Description. The congressional legislation that created the National Eye Institute (NEI) mandates research on amelioration of the impact of impaired vision and blindness on health and well-being. The current NEI research program on visual impairment and its rehabilitation can be divided into six areas. Laboratory research is a fundamental yet often underappreciated pillar of research on visual impairment and blindness. A major goal of this area is to develop a scientific basis for understanding normal visual functioning that can be extended to explain the disabilities experienced by people with low vision, blindness, and other visual processing deficits. Examples include the role of vision in spatial cognition, factors that underlie text legibility and reading performance, and the role of visual attention in impaired vision. Ultimately, such a theory should explain how visual deficits affect performance of everyday activities and how to optimize the visual environment to enhance performance, especially in those with visual impairment. It could guide the development of appropriate rehabilitation strategies, adaptive technology, and assessment tools and indicate when it is more effective to convey information by nonvisual means. A comprehensive understanding will not result from studies only at the sensory “front end” of the visual pathway.

While most forms of visual impairment result from diseases of the ocular media, retina, or optic nerve, the

consequences for everyday life come from the interaction of reduced visual input with other brain systems, including those responsible for motor control and cognition. Nor will a full understanding come from a narrow disciplinary focus. It is likely that the necessary insights for ameliorating the effects of visual impairment will emerge from interdisciplinary studies combining traditional approaches to vision research with methods from research on cognitive science, motor control, development and aging, psychology, neurology, computational modeling, and broader perspectives from neuroscience.

Another primary research area in visual impairment and rehabilitation is visual assessment and everyday task performance. Because vision plays an important role in most everyday activities, people with visual problems are routinely faced with significant challenges in their daily lives, such as recognizing objects and people, getting around (mobility), reading, socializing, working, and taking care of their daily needs (e.g., preparing meals and managing finances). Difficulties with daily activities can lead to conditions that seriously reduce quality of life, including depression, social isolation, educational problems, and employment challenges. All of these underscore the critical importance of research designed to minimize these difficulties among the visually impaired. There is considerable variability among visually impaired persons in their ability to perform everyday tasks, depending on their eye condition, its severity, duration and age of onset, task lighting conditions, as well as compensatory strategies and the existence of other medical problems and disabilities. The challenge for the clinician is to identify which tasks are problematic for a given patient so that a rehabilitation plan can be developed and implemented. Research on valid and reliable assessment tools that allow clinicians to properly identify and treat problems in performing daily visual tasks is absolutely essential to improving clinical care.

The logical partner of visual assessment is the rehabilitation process. Rehabilitation of the visually impaired individual, just as rehabilitation of the physically impaired individual, is directed at optimizing functional capabilities and quality of life. Rehabilitation is a multifaceted process involving the assessment of visual capabilities and the evaluation of functional performance (e.g., reading, writing, and mobility) within the context of lifestyle (e.g., employment, family

activities), attitudes, and psychological well-being. Rehabilitation goals are defined in terms of what matters most in a person's life, and attempts are made to solve functional problems through adaptive options (e.g., vision enhancement and substitution devices, environmental modifications) and coping strategies. The research challenges are to: develop rehabilitation mechanisms that will be effective in enhancing quality of life, determine which approaches are most successful with different types of individuals, and improve the delivery of these services to those in need.

The area of technology and assistive devices is a critically important research area because of its central role in the rehabilitation process. This research focus includes: the development of new devices; application of advanced technologies to visual or sensory substitution aids; and the continuous development and exploitation of new technologies, including communication, information, and computer technology. In addition to developing assistive devices, it is essential that research in this area address how to optimize training in the effective use of devices. This includes a special emphasis on training the elderly, who comprise a substantial portion of the visually impaired population. Other issues central to research in this area are cost, accessibility, cosmesis, personal acceptance of visual rehabilitation devices, and ease of use.

Research on environmental access and modifications addresses the effects of visual impairment on accessing the surroundings in the home, in the workplace, and while traveling, and explores environmental modification strategies for increasing independence of visually impaired persons. Loss of independence, which includes mobility throughout one's own environment, seriously degrades quality of life in far-reaching ways, among them reducing access to social networks and to vision rehabilitation and other health services. Most vision rehabilitation strategies involve prescribing "personal" assistive devices (magnifiers and other optical devices) or providing training or other adaptations to visually impaired individuals. Environmental interventions, however, may serve to allow those with visual impairment to function better in the home, in the workplace, and in environments that are intended for public access, such as shopping malls, hospitals, and transportation facilities. Research on this topic seeks to identify the most effective environmental modifications and evaluate their ease of

implementation, their level of acceptability, and their use by visually impaired persons.

Recent changes in healthcare financing have intensified public interest in the human costs of disability and the effectiveness of treatments and rehabilitation strategies for those affected. It is fully expected that strategies will have to be tailored to the special needs and goals of different subpopulations. To address these issues, research on visual impairment must include outcomes assessment. Outcomes include measures of self-perception of quality of life, assessments of the performance of everyday activities, employment status, independent living status, and educational attainment.

In Fiscal Year 1997, the NEI supported an estimated \$3,800,000 in extramural research projects that emphasized on visual impairment and its rehabilitation.

The program goals for the area of visual impairment and its rehabilitation for the next 5 years are to:

- Improve our understanding of structure/function in the visual central nervous system, neural plasticity, and the performance of everyday tasks, so that the visual processing capabilities of the visually impaired 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 among visually impaired persons.
- Determine which interventions are most effective and develop research tools so that these interventions can be scientifically evaluated, ultimately improving the clinical care of the visually impaired population.
- Establish the scope of impaired vision and blindness in our society and its ramifications for everyday life, identifying the prevalence of visual impairment and functional limitation and risk factors for visual disability, so that interventions can be targeted to high-risk subpopulations.

ASSESSMENT OF PROGRESS

During the past 5 years, there have been a number of accomplishments that span the six research focus areas discussed earlier.

Development and application of brain imaging methods to better understand neurological deficits and brain plasticity in visually impaired persons. Modern quantitative methods, including anatomical, electrophysiological, and brain imaging approaches (particularly functional magnetic resonance imaging [fMRI]) are telling researchers a great deal about the visual architecture of the brains of persons with neurological deficits. In addition, there is an increased understanding of the extent of plastic changes in the adult nervous system, which has implications for rehabilitative training and device development. There is some evidence that visual cortex is recruited for tactile functions for blind subjects. Work on brain plasticity over the past few years lays critical groundwork for addressing questions about neural plasticity in the visually impaired and how it may be exploited during the rehabilitation process.

Application of fundus perimetric methods for the evaluation of visual function in persons with central scotomas. Researchers have used the scanning laser ophthalmoscope (SLO) to assess visual function in patients with central visual impairment. Studies have demonstrated that patients with AMD tend to adopt fixation patterns that avoid placing scotomas below or to the left of fixation. This is interesting since placement of scotomas to the right of fixation slows reading more so than any other position. This fixation preference is different from eyes with macular holes or Stargardt's disease, a juvenile form of macular degeneration (MD), where patients tend to place the scotoma above fixation, and opposite to what would be expected based on reading studies in normally sighted readers. SLO testing has also shown that patients with central scotomas have much less stable fixation and different patterns of eye movements during tasks like visual search and reading than those without central scotomas.

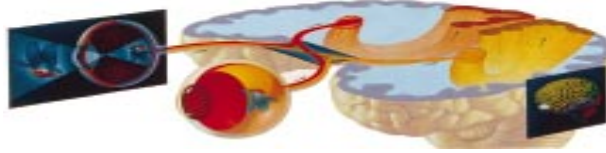
A clearer understanding of the effects of visual impairment on everyday task performance. Research in the past 5 years has clearly indicated that understanding the effects of visual impairment on everyday task performance must include a

consideration of cognitive, motor, and other sensory influences. In reading, visual recognition must be integrated with lexical, syntactic, and semantic knowledge. Clinical measures of acuity and contrast sensitivity are not by themselves good predictors of driver safety and performance, which also rely on visual attentional skills, a rapid speed of visual processing, and cognitive skills. Vision researchers have often tried to decouple visual function from cognition, motor behavior, and other sensory functions, but it has become clear that the role of vision in these tasks cannot be studied in isolation. Both a theoretical and a practical understanding of the complex visual tasks of everyday life will almost certainly require researchers to understand how visual information is integrated with multimodal information in a dynamic manner. Computational modeling approaches are feasible and useful in understanding the component mechanisms of visual behavior, as illustrated by the development of a computational model for reading.

A better understanding of how visual impairment impacts mobility. Recent research is beginning to clarify how visual impairment impacts mobility. For instance, visual impairment reduces walking speed, increases the number of collisions with objects and people in the environment, and increases perceived mobility difficulty, the cognitive demands of walking, and driving difficulty as well. In addition, visual impairment can lead to an increased risk of falling and fear of falling, an elevation in crash risk when driving, and, in general, reduced mobility and loss of independence. Some of these effects appear to be exacerbated under conditions of poor illumination or low contrast. Visual field extent, contrast sensitivity, and motion thresholds are associated with mobility performance, but conventional measures of visual acuity are typically not strong predictors. Knowing how visual impairment affects mobility is essential for developing effective rehabilitative regimens and assistive devices.

Development of rehabilitation strategies and programs for the visually impaired. There has been recent progress in the development and evaluation of rehabilitation programs for the visually impaired. A recent study found that visually impaired veterans report that they use and benefit from assistive devices that they were trained to use. A framework has been proposed that views low vision rehabilitation as a subspecialty of rehabilitation medicine, an established

branch of health care that is sensitive to the multifaceted process of coping and compensating for disability. This broader perspective for vision rehabilitation may assist in integrating it into mainstream health care, facilitating appropriate reimbursement procedures, and ultimately providing more visually impaired persons with access to rehabilitation services. Proposed models of vision rehabilitation need to be evaluated to determine their effectiveness for various patient populations.



Courtesy of National Geographic

Development of improved optical and electronic reading devices. A number of new low-vision telescopes have been developed, with most emphasizing more acceptable appearance. Some offer new autofocus capabilities and flexibilities for in-office fitting and demonstration of the device. New stand magnifiers have been introduced that enhance ergonomics (comfort and ease of use), and the autofocus binocular low-vision telescope has been improved. With the rapid development of speech synthesis, more computerized systems using speech output are being developed for the visually impaired for use with desktop computers and portable handheld devices and for access to the Internet.

Improvements in text navigation and computer access. Research has explored the efficacy of several methods of presenting magnified text on computer screens, and these approaches have been incorporated into commercially available computer-based reading devices for low vision. These devices present text in a variety of formats (e.g., scrolled, rapid serial visual presentation, or spoken synthesized speech), which may be easier for visually impaired people to read and gain access to the World Wide Web, an increasingly important resource in society. Guidelines for making computers and computer-controlled devices accessible for a variety of disabilities, including vision, are available through the University of Wisconsin's Trace Center (<http://www.trace.wisc.edu>).

A common problem encountered by the visually impaired when reading magnified text (such as on a closed-caption television [CCTV]) is locating the

beginning of the next line. Products have been developed that can assist the visually impaired in this challenge. These presentation modes can also be used with text already available in digital forms. In addition, there have been a number of

optical and electronic devices employing new techniques and approaches. Over the past 5 years several new head-mounted electronic low-vision devices have been designed. Research on the utility of these devices is in the preliminary stages. This technology offers the opportunity to provide the high magnification of the CCTV in a portable format, and it may even be possible to provide a wider (virtual) field of view than is practical with a desktop monitor. These devices may offer new advantages in addition to magnification (such as enhancement or field compensation) that could present new visual opportunities. However, much more research and development is needed in this area.

Development of new technologies to enhance wayfinding capabilities of the visually impaired.

A key advance identified as an important priority in the prior plan is the development of promising new technology to improve wayfinding in visually impaired persons. Remote signage systems have been developed and commercialized in which installed transmitters serve as signs that can be read and conveyed via electronic voice to users equipped with appropriate handheld receivers. Other developments include a talking map system for route planning that gives voice feedback in response to touch on a touch-sensitive screen, and a route planning database system that allows visually impaired travelers to plan travel routes from street maps stored on computer. Personal guidance systems have been developed that use computer-based maps and landmark information in combination with satellite-based global positioning systems for registering a traveler's present position. Some of these exciting new developments, while still in need of improvement and evaluation, are already available on a limited basis to consumers.

Progress in the evaluation of infants and children with or at risk for visual impairment.

There has been recent progress in the ability of researchers to assess infants and young children

who have or are at risk for low vision. The Teller Acuity Card procedure, which measures the finest grating that a child can resolve by observing the child's eye and head movement responses to black-and-white gratings (stripes) on a gray background, has been used to measure visual acuity annually in more than 1,000 infants in the NEI's multicenter Cryotherapy for Retinopathy of Prematurity Study. Because the Teller Acuity Card procedure does not require the participant to follow instructions or give a verbal response, it can also be used to test visual acuity in noncommunicative and cognitively impaired elders. Test-retest reliability and interobserver agreement are good, but the validity of the test in these patient groups has not been established.

Another assessment tool developed recently for use with infants and young children is the Low Vision Battery. This instrument assesses functional vision in infants and children whose vision is too low to be measured with the Teller Acuity Card procedure. To date, the Low Vision Battery has been used primarily in children with cicatricial ROP, but it has the potential to provide useful information on functional vision in infants and children whose low vision is caused by other problems.

Increase in the use of epidemiological and survey research methods to understand the scope and impact of visual impairment and disability. Epidemiological and survey research on visual impairment is beginning to indicate that the scope of functional impairment and disability from eye conditions is much more prevalent than previously thought. Certain subpopulations in American society, such as the elderly, are more vulnerable than others, and the diversity of vision problems in terms of their impact on everyday life is broader than originally anticipated. This research, although in its infancy, serves as important groundwork for targeted investigations in this area and has direct implications for healthcare planning and public health projections. There has also been progress toward development of a vision-targeted, health-related, quality-of-life questionnaire that is applicable to the special circumstances of the visually impaired population. These instruments assess the impact of visual impairment in daily life from the individual's own perspective and address a number of important domains, such as difficulty in daily tasks, coping, and general health and functioning. These instruments

are essential for evaluating rehabilitation strategies and understanding the reasons for success or failure of the rehabilitation process.

PROGRAM OBJECTIVES

Program objectives for the next 5 years in the area of visual impairment and its rehabilitation include both basic and applied research.

- Develop a theoretical understanding of normal visual functioning that can be extended to understanding and treating the disabilities experienced by people with low vision.
- Understand the visual requirements of everyday tasks.
- Develop effective assistive devices and techniques to maximize residual vision and/or substitute for visual information.
- Develop environmental designs and modifications that enhance independence among the visually impaired.
- Evaluate the effectiveness of rehabilitation in the visually impaired.
- Ascertain the prevalence and incidence of visual impairment and visual disability in the United States and identify subpopulations at heightened risk for visual impairment and disability.
- Create an effective infrastructure for research on visual impairment and rehabilitation.

The needs and opportunities related to each of these objectives and the strategies for accomplishing them will now be considered.

Objective 1: Develop a theoretical understanding of normal visual functioning that can be extended to understanding and treating the disabilities experienced by people with low vision.

Research Needs and Opportunities

Laboratory and clinical research are important components of the NEI's research program on visual impairment because they provide the knowledge base for improving and enhancing the perceptual processing capabilities of the visually impaired and for designing sensory substitution methods for the profoundly impaired or totally blind person. It is difficult to generalize a theoretical principle to low vision and blindness if it is still poorly understood for normal vision; therefore, the study of the normally sighted does have an important role in the study of visual impairment and its rehabilitation. Research is needed on the visual mechanisms underlying object recognition, mobility, skilled movement, and reading. Many currently popular topics in basic vision research are ripe for addressing issues relevant to visual impairment and its rehabilitation, especially for those with low vision.

Strategic Research Questions

What areas of basic vision research need to be emphasized to improve and enhance the perceptual capabilities of the visually impaired?

Depth Perception and Binocular Processes—It is unclear to what extent those with low vision can benefit from stereo, which is a powerful and routine depth cue for the normally sighted. Anecdotal reports suggest that some persons with low vision make veridical depth judgments under certain circumstances. Additional research is needed to determine the basis for these judgments and how this process could be facilitated in those who have deficient depth perception skills. The relative motion of objects at different distances also provides powerful depth information for people with normal vision. Research has shown that key aspects of motion perception are resistant to blur and contrast reduction, and may therefore be important cues to depth for visually impaired persons. Persons with MD (especially prevalent in the elderly) often read better with one eye covered, yet the reasons for this are not well understood. The conditions

under which those with bilateral macular disease achieve binocular fixation need to be determined.

Multimodal Sensory Integration—There is a need for a more fundamental understanding of multimodal sensory integration in constructing perceptual representation of objects in space. This could be especially helpful for the design of high-tech assistive technology that is designed to provide information through more than one modality. For example, is there a principled way of combining visual and acoustic information to provide access to graphical-user interfaces (GUIs) for people with visual impairment? Similar considerations apply to mobility aids that demand integration of visual, acoustic, or tactile information.

Computational Modeling—Over the past decade there have been many strides in the development of computational models for normal visual processes, such as shape recognition and object recognition. Recent work with computational models of eye movement control during reading have demonstrated the utility of this approach to problems of particular relevance to the understanding of impaired vision. Computational modeling could be useful in understanding the mechanisms underlying visual task performance and visual behavior by incorporating the interaction of vision with motor, cognitive, and other sensory systems. The consequences of visual impairment in task performance could be assessed in terms of its impact in the model's output. Compensations in other aspects of the model could be considered that may offset the effects of impaired vision. In this way, computational models could not only assist in understanding the breakdown in a visual process but also may also suggest rehabilitation approaches.

Field Loss—Researchers need a better theoretical understanding of the information processing characteristics across the full visual field, how these characteristics are perturbed by eye disease, and how the processing capabilities of the remaining visual field, including the visual attention system, can compensate in performing visual tasks. A key unresolved issue is the question of functional equivalence of central and peripheral vision following size scaling (M-scaling). Many simple visual tasks (e.g., target detection) can be performed equally as well in the periphery if targets are suitably increased in size to compensate for differences in spatial resolution. But there is good

evidence that for more complex visual tasks (e.g., reading), central and peripheral vision cannot be made equivalent by size, implying other critical processing differences in central versus peripheral field.

Most of the prior work on field loss has focused on central scotomas, given the high prevalence of AMD among older adults. It is technically difficult to place images at known retinal locations of people with central loss and map their visual fields accurately and reliably. The SLO has played an important role in this area, including the development of macular perimetry techniques that control for eccentric fixation or changes in the direction of gaze. However, there is also a need for simpler techniques that are more widely available.

Peripheral field loss is an often-neglected area of research, despite its importance in a variety of daily tasks such as mobility, driving, and searching for and locating objects of interest. Glaucoma, stroke, and retinal degenerations that cause peripheral vision problems are relatively prevalent in society, and individuals with impaired peripheral fields need rehabilitation options.

Neural Plasticity—Efforts to understand neural plasticity must continue, especially in terms of how the central nervous system is reorganized after visual processing is disrupted or drastically impaired through disease or injury. It is possible that this plasticity could be exploited to enhance the use of residual vision or other sensory and cognitive systems in visually impaired persons. Little is known about whether there are plastic changes in the visual cortex of people with congenital forms of low vision or for those with late-life-onset low vision, such as the elderly. For example, do changes occur in the visual cortex of people suffering from MD? Do training programs that encourage the use of peripheral vision for traditionally central vision tasks (e.g., reading, object recognition) result in changes in the underlying cortical representation? Understanding brain plasticity may also help to explain difficulties encountered by older adults in learning to read by touch (Braille). Answers to these questions are important for understanding long-term adaptation to vision loss, for designing training programs for using peripheral vision and sensory substitution methods, and in evaluating the potential success of therapies for retinal degenerations.

Objective 2: Understand the visual requirements of everyday tasks.

Research Needs and Opportunities

Difficulties with daily activities can lead to serious reductions in quality of life, including depression, social isolation, educational problems, and employment challenges. A better understanding of the role of vision in everyday task performance is critical for designing effective rehabilitation programs. Given the stimulus and environmental complexity of everyday activities and the multiplicity of skills and modalities a person brings to bear on the situation, the study of task performance is not easy. Nevertheless, efforts to develop measurement strategies are not insurmountable as illustrated by recently developed methods for measuring reading skills in those with low vision. Similar efforts need to be extended to a wider variety of daily activities and toward developing a better understanding of why two individuals with similar eye conditions and impairment levels can exhibit very different task performance capabilities.

Strategic Research Questions

What aspects of visual function need to be better understood to determine the requirements of the visually impaired to carry out everyday tasks?

Multidisciplinary Assessment—Visual acuity is the traditional gold standard for visual function evaluation in the clinic, but previous research has indicated that other aspects of visual function are also useful in characterizing problems in visual task performance. For example, contrast is important in predicting mobility skills, and visual processing capabilities across the visual field are important in driving performance. There is widespread sentiment that the search for a battery of visual sensory tests may be an overly simplistic approach to understanding the mechanisms of visual performance deficits among those with low vision. A problem with much of the previous research on task performance is the almost exclusive emphasis on visual predictors in isolation. Future research should focus on the cognitive, motor, and multisensory components of these tasks and examine how visual performance limitations are affected by coexisting deficits in these domains. Older adults and premature infants may be two such groups who

could substantially benefit from this multimodal approach, since they often have cognitive, physical, and/or hearing impairments in addition to their vision loss. Continuing this multidisciplinary theme, there is also a need for research on basic psychosocial processes and dynamics that addresses the motivational factors underlying rehabilitation and the desire for personal independence.

Higher Order Visual Processing—Most previous research has focused on three visual sensory functions—acuity, contrast sensitivity, and visual field sensitivity—and has neglected to closely examine higher order visual processing skills. In preliminary studies, visual processing speed, visual search and attention, motion perception, eye movements, and fundamental components of object recognition appear to have promise in understanding performance problems. The issues need to be addressed as mechanisms underlying visual difficulties in those with low vision.

Visual Requirements for Complex Tasks—Other performance measures in need of development are an orientation and mobility course with standard components, as well as the refinement of definitions of “adverse” mobility measures such as falling, tripping, vehicle crashes, and injuries, which can occur during mobility.

Examples of other common visual tasks that deserve consideration as performance measures include: simulated common settings in which visual tasks can be quantitatively assessed, telephone use, locating objects in cluttered areas, face recognition, filling out a form such as check writing, and use of GUIs on computers and other electronic displays. Researchers embarking in this field may find some guidance from the field of gerontology, where performance-oriented tests have been successfully developed for assessing the instrumental activities of daily living in older adults. These tests are not always visually oriented, but they do demonstrate that complex skills can be analyzed into quantifiable behaviors.

Performance tests for visually impaired infants and children will obviously have to be geared to the specialized everyday activities of these age groups, but are also of high priority if the effects of early interventions on these developmentally challenged populations are to be properly studied.

Objective 3: Develop effective assistive devices and techniques to maximize residual vision and/or substitute for visual information.

Research Needs and Opportunities

There is a high priority for the development of effective assistive devices and techniques to maximize residual vision and/or substitute for visual information to enhance the performance of everyday tasks by the visually impaired. These devices take a variety of forms, including software technology and computer design, optical and electro-optical devices, light and glare control devices, and visual system transplantation techniques. The fundamental rationale underlying these devices is to enable visually impaired persons to function despite their impairment, to be more independent and productive, and to be able to fully participate and enjoy all aspects of society. Special efforts should be directed toward developing rehabilitation options for visual problems for which there is little help available. Some of these areas include small field-of-view telescopes, devices for intermediate-distance tasks, peripheral field expansion, computer-assisted technology heavily based on icons, and coping with and adapting to the use of assistive devices.

Strategic Research Questions

What needs to be considered in the development of assistive devices and related techniques to maximize residual vision?

Many high-priority questions remain with respect to device development. The technology underlying magnifiers is mature, but more ergonomically successful ways to use them must be identified. Can a wide-field telescope be designed and marketed? Are there effective methods for field enhancement? The population least served by low-vision services are persons with restricted visual fields, including both “tunnel vision” and hemianopsia due to glaucoma, retinitis pigmentosa, or stroke. The existing devices for increased field awareness have not proven to be effective on a widespread basis. The problem with most approaches can be traced back to the inadequate model of visual function throughout the peripheral field, and especially for those with field losses. Effective solutions to this problem must go beyond the static concept of the reduced visual field, which neglects the scanning function of eye movements and misrepresents

the actual everyday situation. There is a need to better characterize and understand dynamic visual function in patients with field loss, so that effective devices can be developed.

There is a pressing need to deliver help to the hundreds of thousands of persons who are visually impaired. Researchers should not neglect device development that relies on techniques and methods that can be realistically applied and implemented in existing rehabilitation services. There has been a great deal of emphasis on developing devices that are “low cost,” and this is a laudable goal. However, high cost should not be a deterrent to researchers and engineers if the device shows great promise in solving a significant problem for the visually impaired.

Computer GUIs that are highly visual present a problem for visually impaired persons who need access to computers. The increased use of computer GUIs in many aspects of life (automated tellers, shopping, telephones) and the clear potential for growth in this area require the development of ways of presenting key information in alternative or enhanced formats so that the visually impaired still have access to it. In general, GUI formats are not optimally designed, even for those with normal vision, and therefore provide little guidance for design adaptations for those with visual deficits. Further research in this area will clearly help both normally sighted and visually impaired GUI users.

Objective 4: Develop environmental designs and modifications that enhance independence among the visually impaired.

Research Needs and Opportunities

Environmental modifications must be developed and evaluated to facilitate daily living, improve access to opportunities, and promote active participation by visually impaired persons in society.

Strategic Research Questions

What needs to be considered in the development of environmental designs and modifications to facilitate the daily living needs and independence of the visually impaired?

Tactile Perception—There needs to be a better understanding of the principles underlying tactile discriminability and symbol meaning for those who have never had visual experience and for those who lost vision late in life and are familiar with letter forms and other “visual” conventions. The tactile capabilities of older visually impaired people need to be evaluated, especially those who experience vision loss late in life. For example, are raised letters an effective communications medium to use in public areas such as signage and transaction machines? There has been some work on age-related deficits in tactile sensitivity, but such findings need to be evaluated in terms of their relevance to real-world tasks performance.

Travel—There must be improved understanding of the factors that reduce travel independence in visually impaired persons, especially older adults, when driving, walking, and using public transportation. Reduced mobility is associated with depression and social isolation; thus, improved mobility in the visually impaired is likely to enhance their general health and functioning and their enjoyment of life. Although there has been progress in developing wayfinding technologies, these wayfinding aids must be implemented on a broader basis and evaluated to determine if they are comprehensive enough to allow effective route planning and independent travel, and if visually impaired persons could be trained to use them effectively. Research on wayfinding strategies must not neglect the special needs of people who lose vision in late life, who may find it more difficult to learn to use technically challenging devices. Night driving is a significant problem for increasing numbers of older persons with age-related vision losses and for those with retinal degenerations regardless of age. Research is needed to address this problem both with devices and with environmental modifications that enhance visibility and reduce glare.

Lighting and Interior Design—Visual detection and identification of objects and events in the environment can theoretically be enhanced through improved lighting and interior design in the home and the workplace. Given the wide variability in visual capabilities and needs in visually impaired individuals, methods for evaluating needs and prescribing environmental interventions would be extremely useful, especially those that can be carried out by the visually impaired individual or by untrained family members, friends, or

coworkers. Many persons with low vision have a greatly restricted range of luminances within which they can function effectively. Increased lighting may enhance visibility for some people with low vision, but it can result in glare that diminishes visibility for others. Specific methods are needed for assessing lighting requirements and simple ways of adjusting intensities and contrasts, along with effective ways of disseminating this information to lighting engineers, designers, and the public.



Courtesy of
Photography Department
Casey Eye Institute

Technology—Existing digital technologies may be useful in developing devices to aid in managing everyday “visual” tasks. For example, barcode readers have been successfully developed as shopping aids, allowing price and product information to be presented to the visually impaired consumer in alternative formats. Wider application of this technology to assist visually impaired persons in coping with highly visual yet necessary activities of daily life should be explored and evaluated. Internet-based communication is quickly producing a new kind of environment in which social interaction and commerce can be conducted without travel. While some progress has been made, there still remains the need to develop and evaluate accessible World Wide Web browsers and software technology to ensure accessibility through alternative presentation, such as electronic magnification, voice, and refreshable tactile displays. This would allow visually impaired persons to take advantage of this increasingly important information source in society. Standard interfaces for interactive transaction machines (e.g., banking, vending, transportation ticket purchase) would go far in enhancing access by visually impaired persons.

Objective 5: Evaluate the effectiveness of rehabilitation in the visually impaired.

Research Needs and Opportunities

There is a growing consensus that strategies and procedures designed for the rehabilitation of visually impaired persons must be evaluated for effectiveness,

either through multisite clinical trials or through smaller scale intervention evaluation studies. The emphasis on this type of research in future years stems from the realization that, until now, researchers have accumulated very little scientific data on effectiveness, i.e., “what works versus what doesn’t.” Several studies have reported benefits from rehabilitation programs and training protocols, but without rigorous design features like controls for bias and confounding, these studies are far from conclusive. Survey research on visually impaired patients’ attitudes and beliefs

about the usefulness of visual rehabilitation is informative, but it does not replace clinical trial research that would provide for a “fair test” of the hypothesis that the rehabilitation program under study is effective.

Strategic Research Questions

How do researchers determine if the strategies and procedures designed for rehabilitation of the visually impaired are effective?

Quality-of-Life Outcome Measures—This area has been hampered by a lack of measurement tools for important outcome variables. Reliable and valid outcome measures must be developed before a clinical trial on the effectiveness of rehabilitation programs can be properly evaluated. As discussed previously, there has been progress toward developing a vision-targeted, health-related, quality-of-life measure, but these types of measures are primarily targeted at patients with active disease processes rather than persons with untreatable visual impairment. These quality-of-life measures, such as the NEI-Visual Functioning Questionnaire (NEI-VFQ) must be evaluated with respect to persons whose visual impairment is uncorrectable and untreatable, and tailored so that they are responsive to issues related to rehabilitation and life with an impairment that is not likely to be cured in the future.

Measuring Task Performance—Although a person’s attitudes and beliefs about their own health and

well-being are critical outcome measures in clinical trials, there is also a need for outcome measures that reliably and validly assess the performance of the visual activities of daily living (e.g., reading, mobility, object search and recognition). These performance measures must be standardized and psychometrically sound. There has been some reluctance to develop performance task measures because not only vision but many other functional systems (e.g., physical capabilities, hearing, and cognition) impact the ability to carry out routine daily activities. However, the importance of these measures for determining the effectiveness of various rehabilitation services and approaches underscores the need for persistent research efforts in this area. Also, developing tools to measure visual rehabilitation “potential,” analogous to the Functional Independence Measure widely used in physical rehabilitation, are also needed. This type of prognostic indicator could assist clinicians in more effectively promoting skill development and the use of compensatory strategies.

Assessment of Special Subpopulations—Special attention needs to be directed toward rehabilitation efforts for the aging population, since the prevalence and incidence of visual impairment is highest in this age group. The elderly often have coexisting impairments in hearing, cognition, and movement, which must be taken into account when developing effective rehabilitation strategies for this population. Intervention evaluation should utilize outcome measures that address visual performance as well as quality of life. The evaluation of rehabilitation efforts for visually impaired infants and children is also of high priority and should include an assessment of the role of visual stimulation. Because of the wide range of neurodevelopmental abilities of young children with low vision, studies that evaluate the effectiveness of intervention strategies will need to use assessment tools appropriate to both the visual and the developmental status of children to be studied. For adequate assessment of functional vision, there will need to be continued investigation of nonvisual acuity measures of functional vision in infants and children (e.g., the Low Vision Battery and white sphere kinetic perimetry). Another strategy would be to develop new assessment tools (e.g., a measure of contrast sensitivity for clinical testing of infants and children) and a quality-of-life assessment tool for infants and young children who have low vision.

Objective 6: Ascertain the prevalence and incidence of visual impairment and visual disability in the United States and identify subpopulations at heightened risk for visual impairment and disability.

Research Needs and Opportunities

A great deal of the early work on visual impairment and blindness was carried out with rather small samples, adopting an experimental research design tradition. However, to determine the scope and magnitude of visual impairment and disability in society, large-scale studies must be undertaken. There is a pressing and obvious need to study visual impairment and disability in the elderly, since they represent a large and growing segment of the visually impaired population.

Strategic Research Questions

What is the prevalence and incidence of visual impairment? Epidemiological research tools using larger samples may prove to be critical in addressing questions about the etiology of visual performance problems and quality-of-life reductions among the visually impaired, and for identifying important differences among various subpopulations of visually impaired persons (e.g., children, elderly, totally blind, low vision). The field of epidemiology emphasizes the scientific importance of case definitions for disease, impairment, and disability; the selection of controls; the assessment of bias and confounders; and multi-variable statistical evaluation. All of these are critical issues in research on visual impairment and its rehabilitation.

Epidemiological research in this area serves two important public health functions—it generates information that can be used in population projections for healthcare needs in future years and it identifies potentially underserved populations: infants, children, the elderly, minorities, and the medically uninsured. Epidemiological research also allows for the development of risk factor models of visual disability—identifying the likely causes of visual disability and reduced quality of life among those with visual impairment; determining the diversity in the rehabilitation needs among the visually impaired; and understanding why some people adjust and cope while others are less successful and less likely to benefit from current rehabilitation practices. At a broader level,

epidemiological research is geared at prevention of disease and disability in society, which is a fundamental goal of the National Institutes of Health (NIH). This is an area that needs more work with respect to visual impairment and eye disease.

Objective 7: Create an effective infrastructure for research on visual impairment and rehabilitation.

Research Needs and Opportunities

In previous national plans of the NEI, concerns were expressed about the slow progress of research on visual impairment. The reasons underlying slow progress in prior years are varied, but the thread that runs through all problems in this field is the lack of an effective infrastructure for research on visual impairment and rehabilitation.

Strategic Research Questions

What is the most effective strategy to ensure that these objectives are met? The single most effective strategy that could be implemented to ensure that all the above program objectives are met is to modify the current research infrastructure for funding research on visual impairment and its rehabilitation. A major impediment to attracting researchers to work on visual impairment and blindness has been that both clinical and laboratory vision researchers receive little or no training in research in visual impairment—its theoretical framework, methodology, or analysis. Ophthalmologists, optometrists, and special education and visual rehabilitation professionals understand the medical and visual needs and functional problems of their patients, but they rarely receive comprehensive training in research methods that supports high-quality research. A disproportionately large number of those doing research on visual impairment have been trained as experimental psychologists specializing in visual perception and psychophysics. But even among perception psychologists, impaired vision is usually considered a tangential topic. Furthermore, few psychologists have an opportunity to train in the clinical aspects of visual impairments, epidemiological research methods, and clinical trials, without which it may be difficult to formulate research programs that are both theoretically sound and clinically relevant. One way to address this problem would

be to broaden the scope of funding mechanisms such as the clinician-scientist award (K08) to include those with training in special education, rehabilitation, or engineering, who wish to establish careers as independent scientists in the field of visual impairment and blindness. Conversely, a mechanism to provide laboratory research scientists (e.g., experimental psychologists and neuroscientists) with training in clinical aspects of visual impairment and rehabilitation and epidemiological and clinical trial methodology would provide a critical disciplinary basis for rigorous scientific work on visual impairment.

To attract vision scientists to the field of low vision, the NEI issued a request for applications in 1985. As a result, the number of grants addressing visual impairment and blindness increased from 6 in 1984 to 22 in 1988. With some fluctuation in this figure over the past 8 years, it remained at a similar level (19) in 1996. The majority of these are Small Business Innovative Research (SBIR) grants, with the percentage of R01 proposals addressing visual impairment and rehabilitation decreasing over the years. Peer review panels must be specially attuned to this area during the next 5 years if progress is to accelerate to an acceptable rate.

Research on visual impairment and blindness depends on the multidisciplinary contributions of vision scientists, clinicians, rehabilitation specialists, and engineers. Unfortunately, there are few opportunities for this type of close collaboration. A fundamental problem in this area is that the field is diverse and multidisciplinary, and interested parties do not know how to locate high-quality research expertise. Research organizations studying visual impairment and rehabilitation could go far in stimulating multidisciplinary efforts. Such groups should be encouraged to focus on both intervention development studies (i.e., laboratory research) and intervention evaluation studies (e.g., clinical trials), as well as providing core research support for investigators and information dissemination to the general public.

Research organizations specializing in visual impairment could also foster the much-needed interaction between vision researchers and the engineers and software developers who have been active in developing assistive technology to visually impaired persons, including that funded through

the SBIR and the Small Business Technology Transfer Research programs. These groups could also provide support and access to patients for studies that extend beyond the limitations of traditional clinics. An ongoing problem in research on visual impairment is identifying visually impaired persons who may be interested in participating in research studies. Eye clinics usually deal with patients who are in an acute phase of an often-fluctuating eye disease, rather than patients with stable conditions who may be more amenable to research. Many of the patients seen in low-vision clinics are entrenched in psychosocial adjustments associated with coping with vision loss, making them less likely to be interested in research participation. A facility that is charged with organizing and recruiting visually impaired subjects into research protocols would serve a very valuable research function.

The next 5 years of research on visual impairment and blindness can lead to great strides in improving the quality of life for the visually disabled population in our society. These accomplishments can be realized if the existing research infrastructure is enhanced and there is a broad-based program to educate researchers, clinicians, and engineers from a variety of backgrounds about the availability of these resources.

VISUAL IMPAIRMENT AND ITS REHABILITATION PANEL

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PROGRAM OVERVIEW AND GOALS

With the changing organization and financing of health care in the United States, an understanding of the delivery and use of vision services is important to develop strategies to best prevent, diagnose, and treat eye conditions and reduce the risk of visual impairment. As healthcare resources become more constrained, it is essential to determine the most appropriate use of diagnostic strategies and treatments scientifically demonstrated to improve vision and preserve sight. To understand the impact of eye disease and visual impairment on the Nation's health, data are needed on the number and characteristics of people with various eye conditions, the effects of these conditions on quality of life, and the economic burden of these conditions. This information will serve to increase public awareness of the personal and societal costs of visual impairment and be useful to those who are interested in allocating adequate resources to Americans most in need of visioncare services.

To advance understanding of these issues, the National Eye Institute (NEI) is, for the first time, devoting a section to health services research in its Vision Research National Plan. The NEI defines the field of health services research broadly to include such diverse topics as: increasing patient access to and utilization of visioncare services, improving the delivery of vision services by eyecare professionals, and measuring the visual health of patients receiving eyecare services. A number of different scientific methodologies are used in conducting health services research projects. These include but are not limited to: clinical outcomes research of new or existing data survey research techniques, translational research methods, decision and utility analytic methods, health economics, traditional epidemiologic methods, and randomized clinical trials. The selection of design methodology should be scientifically justified as appropriate for the research objectives of a given study.

In Fiscal Year 1997, the NEI funded six extramural research projects that were related to health services research at a total cost of \$2,467,000.

Two of the broad goals of health services research at the NEI are to:

- Assess the impact of eye disease and visual impairment on the Nation's health.
- Determine the most appropriate use of diagnostic strategies and treatments scientifically demonstrated to improve vision and preserve sight.

ASSESSMENT OF PROGRESS

Although not highlighted in previous plans, the NEI has had a growing interest in health services research. Several important contributions have been made in this area over the past 5 years.

Recognizing that a patient's quality of life is an important facet to consider in assessing visual health, several NEI-funded epidemiologic studies and clinical trials have incorporated a quality-of-life assessment into the study protocol. These quality-of-life data are useful for assessing a patient's acceptance of a scientifically proven treatment regimen. To elucidate the impact of clinical interventions specifically on vision-related quality of life from a patient perspective, the NEI fostered the development and testing of the NEI-Visual Functioning Questionnaire (NEI-VFQ). Based on findings from small groups of patients with specific vision deficits who answered this Questionnaire, diminished visual acuity has been associated with decreased performance of routine daily activities, reduced cognitive ability, and poorer health-related quality of life.

Surgery to remove a cataract and to implant a synthetic lens, one of the most frequently performed procedures among Medicare beneficiaries, was the focus of three large studies. Together, these studies concluded that as a direct benefit of cataract surgery, 77 percent to 92 percent of patients reported substantial improvement in their ability to see and to perform common, necessary daily activities. In

addition, preliminary data indicate that, using patient characteristics assessed prior to surgery, it is possible to reliably predict which patients are most likely to benefit from having their cataract removed. Pre-operative visual acuity in the eye with the cataract was not one of these predictive factors. This finding has important policy implications, since some managed care organizations mandate the use of visual acuity criteria to justify the need for cataract surgery.

People with diabetes mellitus are at risk to develop retinopathy, a leading cause of blindness. Since early diagnosis and treatment has been shown to prevent vision loss in over 90 percent of patients, medical practice guidelines recommend an annual dilated eye examination for all people with diabetes. Recent studies indicate, however, that many people with diabetes do not get an annual dilated eye examination. Several studies have attempted to determine why diabetic patients do not get an annual dilated eye examination and identify the reasons why the medical system is failing to reach this population at increased risk of visual impairment. Other studies have tested specific interventions aimed at the patient or the eyecare provider to increase the rates of ophthalmic screening among people with diabetes.

PROGRAM OBJECTIVES

The following four objectives have been identified as key areas to advance a health services research agenda over the next 5 years. They are:

- Determine the number of Americans with eye disease and visual impairment and measure the impact on medical costs and costs to society associated with these conditions.
- Develop effective strategies for screening for eye disease and visual impairment in children and adults.
- Educate eyecare providers and the general public on scientific advances in detecting, preventing, and treating eye diseases and in translating these advances into nationwide clinical practice.
- Identify the factors associated with the most effective delivery and use of visioncare services.

The needs and opportunities related to each of these objectives and the strategies for accomplishing them will now be considered.

Objective 1: Determine the number of Americans with eye disease and visual impairment and measure the impact on medical costs and costs to society associated with these conditions.

Research Needs and Opportunities

Basic information on the visual health of the U.S. population is critical for increasing public awareness of the effects and costs of visual impairment, assessing the need for eyecare services, evaluating the delivery of vision care, and setting priorities for vision research. However, gathering detailed ophthalmic data on a large, nationally representative sample, while scientifically preferred, is not practical. Over the past decade, studies on three large ethnically and geographically different populations have generated information on the prevalence of and risk factors associated with eye disease and vision loss. Long-term followup of these groups of Caucasians and African-Americans is providing additional information on the frequency of new cases of eye disease. Similar information is needed on children and minority populations of all ages, particularly Hispanics and East Asians.

Even with better estimates of the numbers of Americans with eye disease and visual impairment, complete estimates of the economic and social costs of these conditions are lacking. Previous economic analyses of the costs associated with eye conditions have generally been limited to consideration of direct medical costs to the patient or third-party payers, and to indirect costs to society in the form of tax deductions or disability payments. Given that the onset of visual loss can be gradual and can worsen over time, the true costs of visual impairment are difficult to estimate. The magnitude of direct and indirect medical costs, as well as the costs to society, depends on a number of factors, including: the nature and severity of the visual impairment; the nature and severity of other illnesses; a patient's age, socioeconomic status, and family setting; cultural expectations regarding self-reliance and independence; attitudes about health and health care; and the part of the country where the person lives. All of these factors need to be considered in subsequent research efforts. Also of importance are costs

associated with changes required in the home or workplace that allow visually impaired persons to safely go about their daily activities and income lost by family members who may have to reduce their hours of gainful employment or quit their job to care for a family member who has a visual deficit.

Strategic Research Questions

How many Americans are visually impaired or have eye disease? Estimates of the number of visually impaired Americans and those with one of the major eye diseases are critical to plan future vision research efforts and evaluate the nationwide success of new prevention and treatment interventions. Since there are both genetic and environmental determinants of eye disease, it is particularly important to study ethnically diverse populations. Additional epidemiologic studies on Hispanic, East Asian, and Native American populations are needed to provide regional estimates of disease and to identify risk factors, quality-of-life considerations, and access to care issues, which may differ by ethnic group. National estimates of disease burden among Caucasians and African-Americans may be more readily available using methods like mathematical modeling techniques to extrapolate these data from rates of disease found in NEI-funded, community-based studies.

How many American children have eye disease or vision loss? National estimates of the number of children with vision disorders and their age at onset are critical to design age-appropriate screening programs for the pediatric population and to make adequate followup care available for children at increased risk of an eye disorder. Of particular interest are studies on anisometropia, strabismus, amblyopia, and refractive error. The impact of these disorders on normal child development should be explored in estimating the costs of these conditions in a pediatric population.

What are the direct and indirect medical and social costs associated with visual impairment ($< 20/40$ to $> 20/200$ in the better eye) and blindness ($\leq 20/200$ in the better eye)? Due to differences in the manifestations and age at onset of the major causes of vision loss—glaucoma, age-related macular degeneration and other diseases of the central retina, diabetic retinopathy and maculopathy, unoperated cataract, and CMV retinitis—separate studies may be necessary to

accurately estimate the costs associated with each condition. Computerized administrative databases of expenditure and survey data maintained by governmental agencies and third-party payers often do not have information on the vision status of the participants and, as a result, may only provide a rough estimate of cost. On the other hand, these databases may allow investigators to identify a specific group of patients who can be contacted for further detailed study. The collection of data on the direct and indirect medical costs and social costs may also be obtained in the context of a randomized clinical trial.

Objective 2: Develop effective strategies for screening for eye disease and visual impairment in children and adults.

Research Needs and Opportunities

In an era of limited healthcare resources, it is important to develop cost-effective methods that identify disease in people who may be at increased risk of visual loss for those conditions amenable to treatment. Individuals who are identified by routine screening methods as having possible disease can then be referred to specialists for a more detailed examination and for treatment, should the diagnosis be confirmed. Screening strategies to detect eye disease and visual impairment could be very useful in identifying individuals most in need of comprehensive eyecare services to prevent vision loss and preserve vision-related quality of life.

To advance this objective in a scientific manner, proposed screening strategies directed at assessing visual impairment or eye disease need to be compared to results obtained from a thorough clinical examination. This will determine how well the screening method correctly identifies both people who have the condition and people who do not. Once they have been shown to measure disease or vision loss accurately, screening strategies must then be evaluated to determine whether they can be implemented in practice. In addition, cost-effective screening strategies should be publicly acceptable, relatively inexpensive to implement, targeted to high-risk groups, and able to identify disease at an early stage, when costs associated with treatment might be lower than costs for treating a more advanced stage of the disease.

As a greater number of individuals receive healthcare services in a managed care setting, where preapproval is required before patients can visit eyecare providers, it will become increasingly important to develop and evaluate screening strategies appropriate for implementation in primary care settings and in the community. The goal should be to identify people most in need of specialized care and then to target resources to provide high-quality vision care only to those who need it.

Strategic Research Questions

What screening methods are effective in identifying children most likely to have eye disease or vision loss? Since visual impairment may impact on normal development, it is important to develop screening programs for children to detect and treat eye diseases like strabismus, amblyopia, and significant refractive error. There are a number of issues to consider in designing screening strategies for children. What diseases can be identified using screening methods? At what age is screening optimal? What are age-appropriate considerations in designing the content of screening examinations for use in children? Are there specific settings in which widespread screening is most feasible and practical? Can lay examiners perform the screening? Does screening and subsequent treatment result in improved school performance?

Should there be routine screening for eye disease and visual impairment in adults? Given that the major eye diseases usually affect older Americans, routine screening of young and middle-aged adults for these conditions may not be cost-effective. On the other hand, uncorrected refractive error is an important source of visual impairment in these age groups. Screening methods to identify refractive errors have obvious, important implications for driver and public safety. Several issues deserve scientific investigation. How often should adults have their eyes examined? Should examinations become more frequent with advancing age? What tests should be included as part of these examinations? How often is a dilated eye examination necessary?

Similar information on the frequency and content of eye examinations is necessary to develop screening strategies specifically for persons with systemic conditions or family history, both of which increase the

risk of eye disease or visual impairment. For which disease(s) is screening possible? For which disease(s) is screening cost-effective? How can at-risk groups best be identified? How can screening programs be made culturally appropriate? As genetic markers to predict individuals at increased risk of eye disease or visual impairment become available, how will these influence the content and use of screening methods?

To preserve sight in the oldest group of Americans, it is necessary to develop cost-effective screening programs that can be implemented at in-patient facilities such as rehabilitation hospitals and community-based settings, including nursing homes and adult daycare facilities. Developing low cost, easy to operate, portable equipment would be an asset for such a screening effort.

Can screening for diabetic retinopathy be improved? There is strong evidence that dilated eye examinations are a cost-effective means for detecting treatable retinopathy in people with diabetes mellitus. Nevertheless, many people with diabetes do not get a regular dilated eye examination. It might be possible to develop screening strategies that will minimize the number of exams required and maximize the utility of those performed. What is the optimal interval for comprehensive eye examinations for individuals with diabetes mellitus? Can indicators of risk be identified to tailor the optimal interval for a given individual? Can effective screening with dilation be performed in a primary care setting or by having fundus photographs taken and sent to a reading center for interpretation? Can screening methods be made more culturally appropriate to increase their effectiveness?

Objective 3: Educate eyecare providers and the general public on scientific advances in detecting, preventing, and treating eye diseases and in translating these advances into nationwide clinical practice.

Research Needs and Opportunities

The investment of significant financial and human resources is required to develop new treatments for vision-related conditions and to evaluate their efficacy using randomized, controlled clinical trials. Once an efficacious treatment or prevention strategy is identified, it must be made readily available and utilized before it can be deemed successful.

Implementing research findings into clinical practice is often a difficult task. For example, the benefit of detecting diabetic retinopathy to prevent blindness and the methods used to treat it are well established, yet many people with diabetes become blind. There are many possible reasons why this occurs, including poor access to health care, low prioritization of eye care by people who have diabetes along with many other competing health problems, and lack of coordination among providers who care for patients with diabetes.

With the increasing presence of managed care in America, many more patients are being cared for in primary care settings where there is growing pressure on healthcare providers to see a greater number of patients in less time, and to use fewer resources in caring for their patients. Providers also have limited opportunity to keep up with the fast pace of the scientific literature, especially across medical specialties. This presents a particular problem in educating not only eyecare specialists but also primary care providers on new scientific advances in vision research. On the other hand, managed care organizations may be more receptive to implementing new treatment guidelines if there are cost savings involved.

Research is needed to assess the barriers to translating medical knowledge into practice, and to develop innovative strategies that adapt scientifically proven interventions to the needs and constraints of “real world” settings. To the extent possible, the design of a clinical trial should lend itself to widespread application in the community and allow large numbers of patients with the opportunity to participate in a streamlined study plan.

Strategic Research Questions

How do the American public and the medical community become educated on medical advances related to eye disease and visual impairment? Educating the public and the medical community is one step in translating findings from randomized clinical trials into general clinical practice. Strategies for the effective communication of vision research advances may be different for different populations. A patient’s receptivity depends on a number of factors, including native language, degree of literacy, and cultural expectations. How do patients become educated about their eye condition? How can people

with diabetes be educated most effectively about the need to have a routine, dilated eye examination? How can patients in need of low-vision services be informed about devices that are available to improve their quality of life?

It is critical for healthcare providers to be receptive to new research findings for widespread implementation to be achieved. Their responsiveness may rely on several factors, including specialty training, exposure to scientific literature, experiences with their own patients, and general willingness to incorporate new knowledge into their clinical practice. In a managed care environment, primary care providers need to know how to identify and when to refer patients who need specialized eye care. How can vision research findings be communicated outside the eyecare profession? How can providers be educated on the use of genetic markers of eye disease?

How do patients and providers avail themselves of new treatment options? In designing clinical trials and implementing new interventions outside the research environment, it would be helpful to understand the criteria used by patients and providers in making healthcare decisions. Are there certain characteristics of patients, providers, and healthcare delivery settings that facilitate the incorporation of specific new knowledge into clinical practice? What factors are involved in clinical decisionmaking regarding patient management? What factors determine whether a treatment is acceptable to a given group of patients? How long after publication of study results do research findings become integrated into clinical practice?

Objective 4: Identify the factors associated with the most effective delivery and use of visioncare services.

Research Needs and Opportunities

Given the increasing number of Americans covered by managed care plans, research to examine the delivery and utilization of vision care takes on even greater importance. Little is known about the quantity and quality of eyecare services offered to different segments of the American population, or how the changing patterns of delivering visioncare services influence a person’s access to and utilization of

appropriate, high-quality vision care. With a characterization of the eyecare services offered by providers in different health systems, it may be possible to design and test specific interventions to improve the delivery and utilization of vision care and thereby reduce rates of blindness and visual impairment.

The movement toward fully automated medical records may provide a cost-efficient opportunity to study patterns of care across a variety of healthcare delivery settings. Automated systems may be especially useful for monitoring changes in the content, cost, and use of visioncare services. It is important to note, however, that persons in systems of care with automated records may be different from the general population.

Strategic Research Questions

In what ways do eyecare professionals differ in how they manage patients with a given eye disease or disorder? Although guidelines for providing medical care exist, the practice of medicine has traditionally been left to the judgment of physicians and their patients. While individual customization remains an important part of medical care, large variations in approaches are often associated with wide fluctuations in cost. If alternate clinical management strategies result in similar patient outcomes and with a similar degree of patient satisfaction, widespread application of the most cost-effective strategy could save significant eyecare resources. In this way, resources could be redirected toward other vision-related needs.

To date, cataract surgery has been the topic of most ophthalmic outcomes research because it occurs so frequently and is associated with significant financial expenditure. Outcomes research on the management of a variety of other prevalent ocular disorders is needed. What are the long-term outcomes and costs associated with initial surgery as compared to medical treatment for glaucoma? What are the long-term visual abilities and educational achievements among children whose amblyopia or strabismus was treated using different approaches?

Do variations in clinical practice among eyecare providers in the community result in different patient outcomes as compared to findings from randomized, controlled clinical trials? Variations in practice patterns exist among eyecare providers. Similarly, findings from

randomized, controlled trials become incorporated into clinical practice in a variety of ways. Whether or not a treatment deemed efficacious in a research setting will result in similar patient outcomes in a “real world” setting is unknown. There are many possible reasons for this. Because of stringent eligibility criteria, patients who participate in clinical trials are often fundamentally different from average patients in the community with the same condition. Alternatively, healthcare providers in the community may elect to implement new clinical trial results in ways that are somewhat different from the rigid study protocol required for proper conduct of the clinical trial. Studies are needed on the visual outcomes and patient satisfaction associated with widespread implementation of clinical trial findings. This information may be used to identify subgroups for whom the trial results may not be applicable, to recognize ineffectual implementation of clinical trial findings related to protocol deviations or patient dissatisfaction, and to gather ideas on how to better design future clinical trials.

What are the variations in outcomes, cost, and patient satisfaction associated with various approaches to treat refractive error? Refractive error, a common eye condition, can be corrected by wearing spectacles or contact lenses or by undergoing laser surgery to reshape the cornea. How do persons choose among these corrective options? Given that younger patients have a significant likelihood of further myopic progression, are these corrective modalities associated with similar clinical outcomes and levels of patient satisfaction? Which methods are most cost-effective?

What interventions can be undertaken to increase access to and use of visioncare services among persons at increased risk of eye disease or visual impairment? Even if widespread delivery of eyecare services was available, some patients in need of eye care would not obtain it because of failure to access vision care or failure to comply with the recommendations of eyecare providers. Research is needed to understand how and why patients choose to access or fail to access visioncare services and their reasons for not complying with prescribed services or treatment. This information will provide the basis for designing specific interventions to improve access to and use of appropriate eyecare services.

Several topics are relevant to such research. What is the relationship between a patient’s perspective of

visual ability and actual clinical or psychophysical measures of vision functioning? How does a patient's knowledge of his or her eye disease or visual impairment influence the perceived need to seek out visioncare services? Why do patients who perceive a need for eye care choose not to make use of visioncare services? How do persons prioritize visual health among other medical conditions or quality-of-life considerations? What are the most appropriate methods for measuring quality of life among visually impaired persons with different eye conditions and from different socioeconomic and cultural backgrounds? Are currently available quality-of-life questionnaires sufficient to capture this information or are new questionnaires needed? How do patients decide whether or not they are satisfied with eyecare services? Particular attention should be paid to visually impaired children and their families, adolescents, nursing home residents, persons with a family history of eye disease, and other populations at increased risk of eye disease, visual impairment, or blindness.

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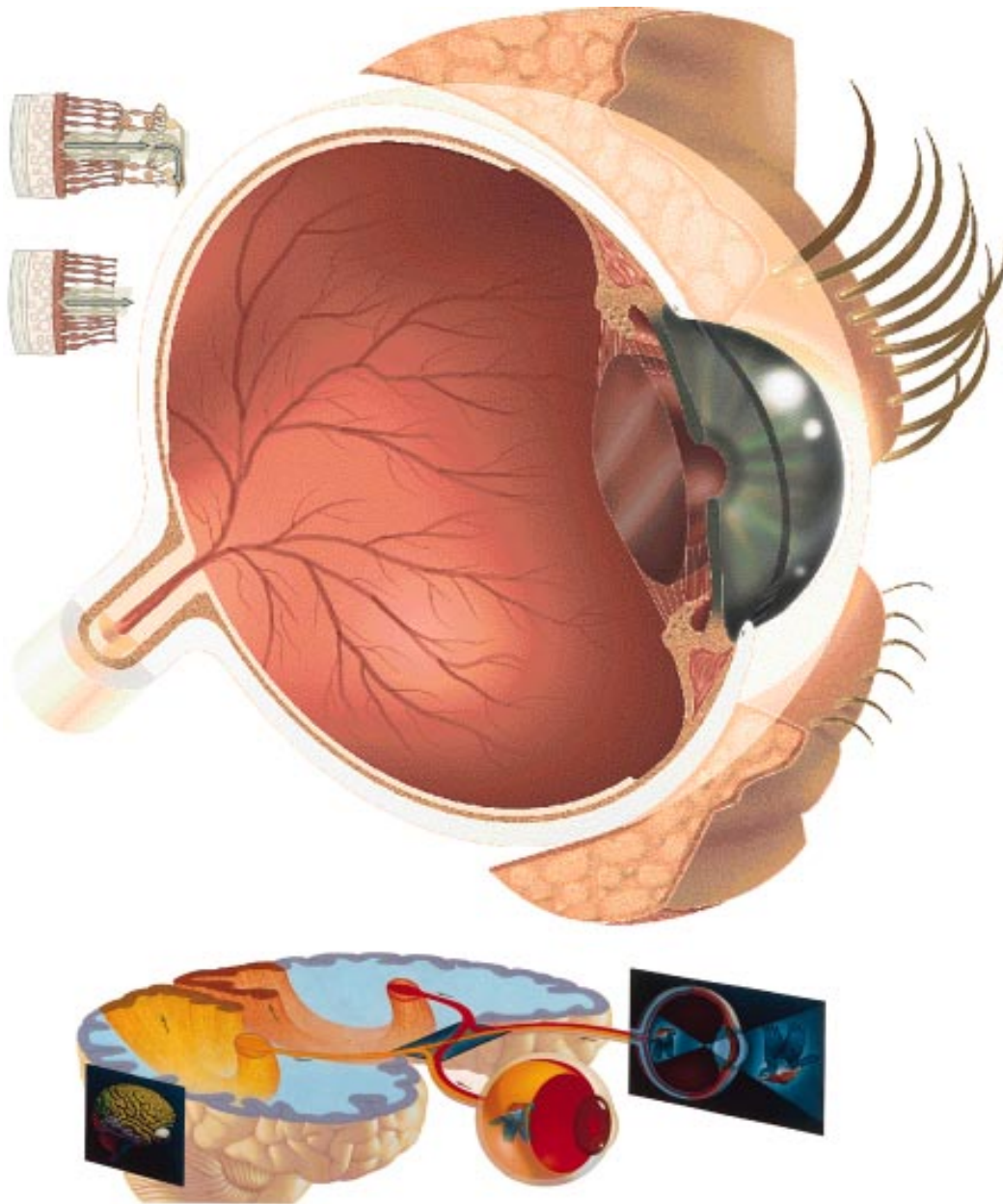


Illustration of the eye: Courtesy of Charles M. Blow/*The New York Times*
Illustration of the brain: Courtesy of *National Geographic*

The following sections deal with scientific issues that cut across programmatic lines and policy issues related to the operational processes, external factors, and resources that affect the overall accomplishment of the goals and objectives in this report. They have been highlighted here as endorsement by the National Advisory Eye Council (NAEC) of their importance to the programs of the National Eye Institute (NEI) and the vision research community and as an indication of future need.

CROSS-CUTTING ISSUES

Aging Research

Many of the most significant causes of blindness and visual disability are associated with the aging process. While improvements in nutrition and health in this country have increased the average lifespan, many Americans are unable to fully enjoy their increased longevity due to visual impairment and its subsequent effect on their quality of life. Indeed, there were approximately 33.9 million Americans age 65 or older in 1995. By the year 2030, that number is expected to double. Improved prevention, diagnosis, and treatment of eye diseases and disorders for this country's older citizens is, therefore, of great importance.

Within each program discussed in this report, the research objectives, needs and opportunities, and research strategies related to many of these diseases and disorders have been identified. In the Retinal Diseases Program, age-related macular degeneration (AMD) and diabetes are the major causes of vision loss in the elderly. Although a highly effective treatment exists for diabetic retinopathy, research indicates only half of those individuals who need treatment currently receive it, and treatment for AMD is available for only the small minority of the cases with the wet form of the disease. Objectives in these areas seek to explore the pathophysiological heterogeneity of AMD and investigate the pathogenesis of these and other vascular diseases of the retina and choroid with the aim of developing better methods of diagnosis, prevention, and treatment.

Diseases that affect the tear film on the surface of the eye, such as Sjögren's Syndrome, are also of concern, particularly among women. An objective within the Corneal Diseases Program is to improve the understanding of ocular surface physiology in hope of finding more treatments for diseases that affect it. Although a highly effective surgical treatment exists for treatment of cataract, the Medicare costs alone are approximately \$3.5 billion per year in this country. Objectives in the Lens and Cataract Program are aimed at finding the genes that cause age-related cataract, and determining if there are genetic factors that interact with environmental factors to confer susceptibility to age-related cataract. Likewise, presbyopia (the inability of the lens to focus or accommodate on near objects as we age) represents a significant economic cost to society. One of the objectives is to understand the basis of lens accommodation and presbyopia at the molecular and mechanistic levels.

The most common types of glaucoma mainly affect older people and increase in prevalence with each decade over age 40. Because those with glaucoma often do not seek medical attention until irreversible loss has occurred, objectives in the Glaucoma Program seek improved methods of early diagnosis and identification of the genes and genetic loci that contribute to glaucoma. Because of the susceptibility of the elderly to these major causes of visual impairment, many of the objectives within the Visual Impairment and Its Rehabilitation section of this report are of special importance to the aging population. These include understanding normal visual functioning so that this knowledge can be extended to treating the problems experienced by people with low vision, and developing effective assistive devices and techniques that will maximize residual vision or substitute for visual information.

Technological advances may also provide the tools for understanding the effect of aging on the levels of expression of the genes in the eye that are normally maintained in balance. Genetic disease research has suggested that in diseases in which only one copy

of a pair of genes is defective, there may be a level of expression below which normal function is lost. In normal cells, there may be a similar decline in expression during the aging process, but the threshold at which the normal function is lost may not be reached until later in life. Intramural researchers will be using microarray technology, a new technology that allows comparison of large numbers of genes. This will allow these researchers to search for genes whose relative levels of expression in the eye decrease or increase disproportionately during normal development, disease, or aging.

In addition to these areas of aging research, the NAEC encourages consideration of the eye as a model of the aging process. The Council feels that collaboration between the NEI and the National Institute on Aging on projects related to the processes involved in aging, as exemplified in eye tissues, would hasten understanding of these processes and development of the means to slow or prevent them.

Genetic Research

Hereditary and congenital diseases are significant causes of blindness and visual disability in the United States. Because the visual impairment often begins early in life, the economic, societal, and personal impact can be enormous. Research is aimed at early diagnosis, development of effective treatments, and ultimately the prevention of these diseases. In addition to known diseases with genetic components, such as retinitis pigmentosa, gyrate atrophy, the corneal dystrophies, and hereditary cataracts, genetic research has also recently identified genes associated with AMD and several forms of glaucoma. The NAEC recommends continuation of the search for genes and genetic loci related to these and other eye diseases and disorders throughout the NEI research program.

Developmental Biology and Regeneration Research

The development and assembly of the visual system have long been an essential part of the neurobiological investigations within the NEI research program. Early investigations into the structure and function of the central visual pathways and how they are modified by early visual experience have been exceedingly important in beginning to understand the plasticity of the central nervous system (CNS) and how the brain selectively responds to stimuli. Among the objectives for the Strabismus, Amblyopia, and Visual

Processing Program are gaining an understanding of how the visual system is assembled during development, how its assembly is influenced by endogenous and exogenous factors, and the factors that are involved in its regeneration after injury. Understanding how the myriad neural connections necessary for a proper visual picture are developed may also lead to the appropriate treatments when these systems are damaged by disease or during the development process.

Regeneration of neural and other ocular tissues is also an area of extreme importance throughout the NEI research program. The adult retina is incapable of regeneration following damage, injury, ischemia, or degenerative disease, as is the case in the visual centers of the brain and other areas of the CNS. Similarly, in glaucoma, damage to the retinal ganglion cells in the optic nerve is irreversible. Research recommended in the Glaucoma Program section of this plan focuses on identifying neuroprotective strategies that could prevent retinal ganglion cell death, promote survival, or stimulate regeneration. The Council believes that research in these areas is important not only to diseases of the eye and visual system, but also for neurodegenerative diseases or damage to CNS tissues, for which regeneration of damaged or diseased neurons would be beneficial.

Drug Delivery

The Council also encourages continued improvement in delivery of drug treatments for ocular disease. Development and testing of devices such as the ganciclovir implant, which demonstrated a significant effect in delaying the progression of retinitis in AIDS patients with cytomegalovirus (CMV) retinitis, may ultimately yield improved treatments for a wide variety of diseases, including bacterial and viral infections, uveitis, glaucoma, and retinal degenerations.

Trauma

Another cross-cutting area closely linked to regeneration is trauma or injury. Because it is the most exposed ocular tissue, the cornea is highly susceptible to trauma from a variety of mechanical, chemical, and environmental insults, in addition to being exposed to a host of microbes capable of inflicting damage to the ocular surface. Retinal tissues, the optic nerve, and the visual pathways and centers in the brain are less exposed, but they too are susceptible to trauma or injury.

Although traumatic damage to tissues can be devastating, often it is the wound healing process itself that upsets the delicate and unique properties of the ocular tissues. For that reason, research throughout the NEI research program is focused on the complex cell-cell interactions and cellular and molecular events associated with wound healing. The hope is that careful evaluation will help identify the key processes that ultimately may be regulated to preclude further damage to vision. Research is also aimed at determining how ocular tissues themselves protect themselves from damage.

Systemic Diseases (Immune Disorders and Diabetes)

Systemic diseases, such as diabetes, can have some of their most devastating consequences in the eye. Diabetes exerts its most harmful ocular effects on the retina, where it causes progressive breakdown of the normal vessels in the eye, a condition called diabetic retinopathy. Diabetics are also at increased risk for other serious eye problems, such as cataract and glaucoma. Studies such as the Diabetes Control and Complications Trial and its followup have made a significant contribution to patient welfare and quality of life by showing that tight control of glycemic levels could delay the onset and possibly prevent diabetic eye disease. Although advances have provided identification and characterization of factors and proteins that may play a critical role in the management of diabetic retinopathy, research is now being focused on testing new therapeutic approaches suggested by the results of this research, as well as newer, more potent aldose reductase inhibitors. Research is also aimed at discovering genetic factors involved in diabetic retinopathy. The Council feels strongly that this research may be beneficial to the entire field of diabetes research and encourages collaboration with the National Institute of Diabetes and Digestive and Kidney Diseases.

Immune disorders of the eye also cut across programmatic lines. Not only does the immune system protect the eye, it must also maintain a delicate balance between protection and overreaction, which can adversely affect the surrounding tissues. Many ocular structures, such as the cornea, lens, and vitreous, do not normally have blood vessels and therefore do not have typical responses to foreign substances, microbes, or transplanted tissues. Within the eye, autoimmune responses such as uveitis can have blinding

consequences. Other autoimmune diseases like Sjögren's Syndrome and Graves' disease can also have sight-impairing consequences. Within the Retinal Diseases Program, objectives seek to identify the factors that dictate the unique properties of intraocular immunity and inflammation and alter systemic immunity to intraocular antigens and to develop diagnostic methods that distinguish among infectious, immunopathogenic, and autoimmune responses. In the Corneal Diseases Program, the focus is on understanding immune regulation at the cellular and molecular levels, which could provide researchers with new medical interventions to control or reverse autoimmune phenomena, such as Sjögren's Syndrome.

POLICY ISSUES

Funding Policies and Priorities

The funding priorities for NEI support are based primarily on the scientific and technical merit of competitive applications as determined by peer review. In making funding decisions, however, issues of program relevance, program balance, and the availability of funds must also be taken into consideration by the NEI. In this regard, the Council reaffirms the value of its designating some applications as having "high program relevance." These applications, which address critical program objectives identified, in most cases, through the planning process, have been judged by scientific review groups to have significant scientific merit. Nonetheless, due to overall constraints on funds, these applications would likely not be funded if priority scores for scientific merit were the sole determinant. The Council's designation of an application as having "high program relevance" is a formal recommendation to the NEI Director to give the application special consideration in making a funding decision. In practice, the NEI has awarded most applications so designated by the Council. During the Fiscal Year (FY) 1992 through FY 1996, approximately 6 percent of all competing awards received the Council designation of "high program relevance."

Laboratory Research

Mechanisms of Support. The Council strongly endorses the NEI's emphasis on maximizing funding opportunities for individual investigators. For support of laboratory research, the NEI's first funding priority should continue to be the individual

investigator-initiated research project grant (R01-type), not program project grants or any other type of “umbrella” mechanism of support. Moreover, the Council continues to urge great restraint in the use of formal Requests for Applications to solicit applications in targeted areas of laboratory research.

Length of Award. The Council believes that the National Institutes of Health (NIH) decision to mandate an average length of 4.0 years for all research project grants should be reconsidered. Throughout most of the 1980’s, the NEI had the longest average length of a research project grant award and the highest “success rate” at the NIH. The relative distribution of competing and noncompeting NEI grants was kept remarkably constant in the process. Thus, the NEI managed to keep the “window of opportunity” open for investigators who submitted competing grant applications during the transition to longer awards. The current mandate decreases overall productivity and creativity as a result of more scientists having to spend valuable time writing and reviewing grant applications. The NEI should be permitted to make longer awards when appropriate.

Downward Negotiations. Downward negotiations are essentially across-the-board cuts to individual grant awards made because of budgetary, not scientific or programmatic considerations. The Council finds the costs awarded on typical NEI grants to be reasonable and not out of line with the costs of biomedical research in today’s environment. Rigorous NEI staff review of individual budget requests, conducted on a grant-by-grant basis subsequent to Initial Review Group and Council recommendations, eliminates unnecessary and unreasonable costs before awards are made. This practice has helped contain the average costs of NEI grants. The Council, therefore, supports the strategy of funding grants at the full levels recommended by NEI staff. It is important that the NEI continue to work toward eliminating the problem of downward negotiations.

Multiple Grants. The Council reviewed data on the distribution of NIH research grant funds, excluding training grants and research and development contracts. For the NIH as a whole, approximately 23 percent of funded investigators held two or more grants. In comparison, the NEI tended to be more conservative regarding multiple awards, with approximately 13 percent of NEI-funded investigators holding two or more grants.

The Council believes that it is reasonable for a principal investigator (PI) to be awarded a second R01-type NIH research project grant when this represents an opportunity for the NEI to support high-quality, programmatically relevant research. The Council expects that, in these cases, the second project would be in a new area of research or be significantly different from that supported by the first grant, and that the PI would have a sufficient level of effort to devote to each project.

The Council recommends that funding a third R01-type NIH research project grant to an individual investigator should occur only in exceptional circumstances and requests that these competing applications be brought to its attention for special consideration. The existence of significant sources of other research support should continue to be among the factors that the NEI considers when making funding decisions. In addition, the Council encourages NEI staff to continue their careful grant-by-grant preaward review of all applications, both competing and noncompeting, to eliminate any scientific and budgetary overlap.

Interactive Research Project Grants. The NIH has traditionally relied on multicomponent awards, such as program projects or center grants, to encourage multidisciplinary collaboration. The NEI does not fund program projects or center grants, but it does support several collaborative research projects. These collaborative projects are funded through individual research project grants to each of several collaborating investigators.

The NIH Interactive Research Project Grant (IRPG) program was first announced in 1993 and later revised. An IRPG group consists of two or more investigator-initiated applications for independent research on related topics, with a formalized agreement to collaborate in specific ways to enhance the accomplishment of the goals of all of the projects. The PIs may be from one or more institutions. The IRPG, therefore, offers a means of promoting collaborative efforts between or among projects that are scientifically related, while providing a record of independently obtained awards and retaining the research autonomy of each PI. Because each research project is an independent application, it must be prepared with the same detail and thoroughness that is required of any other application. The NEI is encouraged to explore the use of the IRPG as an additional, more formal way of facilitating collaborative laboratory research.

Clinical Research

Mechanisms of Support. Unlike many other institutes, the NEI does not use funds contained in the research project grant (R01-type) category of the budget to support clinical research projects like clinical trials and other large epidemiological studies. These types of projects are typically funded as cooperative agreements or cooperative clinical research grants, which appear in the “Other Research” budget category. As these clinical projects are crucial to the NEI’s mission, it must be emphasized to the NIH, the Administration, and the Congress that NIH nonresearch project grant budget categories are important and need to be protected. The distribution of funds among the various budget categories is discussed each year by the Council, and its recommendations are considered by the NEI in setting overall funding policies. At the operational level, this distribution can be fine-tuned to some extent, as funds can be reprogrammed from one category to another, depending on the number, scientific merit, and cost of the different types of applications received in any particular fiscal year.

Cooperative Agreements (U10). The NEI supports investigator-initiated multicenter clinical trials and other large clinical studies using cooperative agreement awards. This mechanism of support is used because NEI staff will be substantially involved with the investigators during the conduct of the clinical trial or study. The role of the NEI is that of a partner, but not a dominant one—the PI has prime responsibility for the project. NEI staff contribute to protocol development, recruitment, data analyses, and dissemination of results. They serve as members of steering committees and participate in a number of activities, including monitoring performance, working closely with data and safety monitoring committees, identifying and selecting additional participating clinics, and preparing and reviewing study publications. They assist in monitoring for quality control and they help coordinate the activities of diverse groups of investigators. The Council strongly supports continued use of cooperative agreements for supporting these types of large-scale clinical studies.

Clinical Study Planning Grant (R21). Investigators who submit applications for large-scale clinical studies for consideration by the NEI are expected to provide detailed information regarding the study rationale, design, protocols and procedures,

analytical techniques, facilities and environment, administrative procedures, and collaborative arrangements. This information is best presented in a well-documented Manual of Procedures (MOP), which is submitted as part of the application. However, preparing an MOP is a time-consuming and expensive activity. The Clinical Study Planning Grant helps support this activity and provides other related assistance. This nonrenewable grant provides a maximum of \$50,000 in direct costs for a period of 1 year.

An important question that each applicant must face is whether to submit a Clinical Study Planning Grant prior to submitting a full-scale, detailed application. The advice given by NEI staff depends on a number of factors, including the relevant experience of the investigators, the resources available to them, the complexity of study protocols, and the extent of preliminary data. The Council recommends that the NEI give further consideration to increasing the maximum amount allotted under this mechanism and extending the length of the grant period beyond 1 year.

Small Research Grants for Data Analysis (R03). The NEI Small Research Grants for Data Analysis provide support for secondary analyses of existing research data that have been generated by clinical trials and other large-scale clinical vision research projects that have been supported by the NEI. The grants can also be used to support analyses of similar types of data derived from other sources, but secondary analyses of data derived from NEI-supported studies are of higher programmatic interest. Applicants may request up to \$50,000 (direct costs) per year for a maximum 2-year grant period for technical assistance, supplies, computer usage, and limited travel for collaborative effort required by the project. This mechanism of support, however, appears underutilized. One explanation may be that the current guidelines for this mechanism permit salary support for the PI “only in unusual circumstances.” Another related explanation may be that the \$50,000 ceiling is too low, and equipment purchases are not allowed. Other issues relate to the relative accessibility of data from NEI-supported studies. The guidelines for this mechanism should be reconsidered as part of an overall NEI review of the accomplishments and status of this program.

Clinical Vision Research Development Award (R21). This award helps institutions acquire the staff and other resources needed to enhance programs of

clinical vision research through the application of epidemiologic and biostatistical methodology to clinical problems. These activities may range from strengthening biostatistician-clinical investigator interactions in the design and conduct of clinical research to developing coordinating center capabilities. A maximum of \$75,000 in direct costs per year for 5 years will be provided. Funds may be requested, for example, for the support of a biostatistician (up to 75 percent effort), for other staff, for computer charges, for supplies, and for equipment. The NEI also supports these kinds of activities through Biostatistics Modules on Core Grants for Vision Research. The Council recommends that the NEI review the accomplishments of the Clinical Vision Research Development Award.

Mentored Clinical Scientist Development Award (K08). The NIH career development mechanisms of support were revised extensively in mid-1995. Applicants were advised that some of the Institutes and Centers would be offering different award provisions, such as salary and research expenses. In the fall of 1995, following discussions with the vision research community and the Council, the NEI revised its Mentored Clinical Scientist Development Award (K08) program. First, the NEI alerted clinical investigators that it had broadened the guidelines of its program to specifically include the disciplines of biostatistics and epidemiology. Second, although grant recipients are subject to a legislatively imposed salary cap (currently \$125,000), the NEI indicated that it would not impose any special cap on salary requests. Salary requests should be reasonable and conform to the established, consistently applied policy of the institution for other staff members of equivalent qualifications, rank, and responsibilities, and reflect no more than the percentage of time actually devoted to the project.

In FY 1995, the NEI supported 20 K-awards at a total cost of \$1,651,000; in FY 1997, the NEI supported 37 K-awards at a total cost of \$4,110,000. In the future, some additional growth in the NEI K08 portfolio seems likely, because the response from the clinical departments has been very enthusiastic. Applications remain of very high quality overall, and for the first time the NEI has begun to attract clinicians in certain subspecialty areas, such as corneal diseases. The Council reaffirms its strong support for the K08 program and the steps that the NEI has taken to improve and strengthen it.

Core Grants for Vision Research

The primary objective of Core Grants for Vision Research is to provide groups of investigators who have achieved independent NEI funding with additional, shared support to enhance their own and their institution's capability for conducting vision research. Secondary objectives of this program include the facilitation of collaborative studies and the attraction of other scientists to research on the visual system.

Core Grants are subdivided into discrete units or modules, each devoted to a specific activity that would be impractical or less efficient to support on an individual research project grant. The primary purpose of each module is to support a service or resource that enhances or facilitates the research efforts of a group of investigators, each having independent NEI funding. This can include the purchase and maintenance of a shared instrument. Examples of such modules include electron microscopy, tissue and cell culture, a hybridoma facility, laboratory animal resources, and image analysis. Some sharing of Core Grant resources and services with other NIH-funded collaborators and with investigators new to vision research is encouraged.

The Council reviewed both the number and size of NEI Core Grants. Consistent with Council recommendations contained in the last plan, the NEI was able to provide some much-needed increases to offset inflation. The number of Core Grants has increased from 30 in 1994 (\$8.1 million in total costs) to 32 in 1997 (\$9.8 million in total costs). This mechanism of support currently utilizes approximately 3.4 percent of the NEI's total extramural research budget. The NEI provides up to \$1,200,000 in direct costs over a 5-year period in support of a Core Grant. The level and duration of support for individual Core Grants are determined on the basis of peer review recommendations and administrative considerations. When considering the vastly increased new opportunities in vision research, the Council has concluded that there is still a clear need to increase further both the number and size of Core Grants. At a minimum, the Council recommends that the NEI continue to increase the size of Core Grants to help offset inflation. If the overall funding situation improves, the Council recommends that the current Core Grant budget ceilings be increased to allow the support of additional modules and to increase the total number of such awards.

Research Training

Introduction

Much of the outstanding progress in every field of vision research has been made possible by a cadre of well-trained laboratory and clinical scientists. It is clear that, to continue this progress, the NEI must train outstanding scientists in individual disciplines who are interested in applying their knowledge and expertise to the study of the visual system and sight-threatening diseases and disorders of vision. As part of the NEI's overall strategy, innovative techniques must be developed for recruiting, nurturing, and training outstanding vision scientists. Applicants for vision training programs should be of the highest quality, and predoctoral and postdoctoral trainees should not be solely admitted to meet the workforce needs of the research laboratories. The strategies of developing a well-trained pool of laboratory and clinical scientists for the future must include the achievement of scientific literacy through innovative science education programs at the elementary level through high school for all students regardless of age or gender or cultural, racial, or ethnic background. The NEI must take full advantage of the changes in the demographic patterns of the workforce and make special efforts to foster the scientific careers of women and minority groups, who will make up the majority of new workers by the year 2000. Programs of support for specific training in visual sciences at graduate and postgraduate levels must convince students that their educational endeavors will be rewarded with opportunities for productive careers and research support. Therefore, the NEI's emphasis on individual investigator-initiated research project grants must continue to be given high priority.

Summary of Previous Recommendations and Implementation

The 1994–1998 national plan set forth the following recommendations: (1) bring young scientists of the highest caliber with expertise in molecular genetics, cell biology, immunology, biostatistics, and epidemiology into vision research; (2) support postdoctoral training primarily by individual fellowships, with the possibility of a short transitional period of support on an institutional training grant as a means to make a transition to another training mechanism of training (i.e., National Research Service Award [NRSA] individual postdoctoral fellowship [F32] or Physician Scientist Award [K11]); (3) support the Physician Scientist Award (K11) as an effective tool

for training clinical researchers; (4) support the First Independent Research and Transition (FIRST) award (R29) and use funds that would have been spent on the discontinued small grants program for these awards; (5) support the need to increase stipends for K11 grant mechanisms and for all NRSA grant mechanisms; and (6) support efforts to recruit and retain women and minorities in science. These recommendations were set forth to ensure that outstanding laboratory and clinical scientists would be trained and available in adequate numbers and in specific scientific disciplines to study the visual system and its diseases.

As a result of these recommendations, a number of changes were made to the NEI research training program. The NEI supported targeted predoctoral training programs, which were developed to assure that outstanding scientists were being trained in molecular biology, genetics, and immunology. Three predoctoral training programs were supported in molecular biology and genetics, three in immunology, and one in molecular biology and biophysics. The program was designed to provide basic science training in specific disciplines and to expose trainees to opportunities in vision research. Overall, these programs provided outstanding research training and supported high-caliber predoctoral trainees.

In addition, the NEI has developed two predoctoral and postdoctoral training programs in biostatistics and epidemiology to train scientists to take leadership roles in designing and conducting clinical trials and epidemiological studies related to ocular diseases. The NEI has also broadened the guidelines on the Mentored Clinical Scientist Award grant mechanism to include training in epidemiology and biostatistics. A course in visual science developed and supported by the NEI in 1992, 1994, and 1996 at the Marine Biological Laboratories (MBL) at Woods Hole, Massachusetts, was aimed at attracting young investigators who were well trained in cellular and molecular biology into vision research. Recruitment was specifically targeted to predoctoral and postdoctoral trainees who were either outside of, or newly entered into, vision research. Early evaluation of this course has shown that outstanding young scientists have attended the course, and some have gone on to apply and receive NEI grant support. The NEI continues to use institutional training grants to support predoctoral trainees and individual fellowships to support postdoctoral trainees. This policy continues to shift the balance of

training positions on institutional training grants (T32s). In 1997, more than 82 percent of the training positions on institutional training grants were occupied with predoctoral trainees, and 77 percent of the postdoctoral trainees supported by the NEI received individual postdoctoral fellowships. The shift toward individual postdoctoral fellowships has resulted in trainees who have the skills necessary to develop into independent investigators.

In 1995, the grant mechanisms to support the development of clinician research scientists was modified, resulting in changes in NIH guidelines. The Physician Scientist Award, the K11 award, became the K08 award, the Mentored Clinical Scientist Award. This is a very similar award to its predecessor, which provides an intensive period of mentored research training. Concurrently, the NEI changed its salary policy for this award and eliminated the salary restriction of \$50,000 per year. Although NEI grantees are subject to a legislatively imposed salary cap (currently \$125,000), the NEI does not impose any additional special cap on salary requests. As a result of this change, the NEI has doubled both the number of K08 grant applications received and supported. There was a noticeable increase in K08 grant applications supporting corneal, epidemiology, and biostatistics research training. Evaluation of these programs revealed that the K08 seems to be an effective grant mechanism for attracting clinicians interested in laboratory and clinically based research careers and provides some advantage to the grantee in subsequently competing for grant support.

The FIRST award grant mechanism (R29) continued to provide 5 years of initial support to new investigators and allowed them to develop an independent laboratory. The NEI continued to support the FIRST award for 5 years, even under the NIH policy of an average of 4 years for grant support. There is an NIH-wide effort to review and evaluate NIH research support and grant mechanisms for new investigators, and it has been recognized that the total direct costs of \$350,000 for a 5-year period are limiting. Recently, the NIH developed a new policy for new investigators, and will no longer accept applications for the R29 grants mechanism. The most significant reason for this policy change was the dollar limitation on the R29. In making this change, the NIH has committed to supporting the same number of new investigators and, if necessary, directing more resources to them.

The NEI continued to support NIH-wide increases in NRSA stipends for institutional training grants and individual postdoctoral fellowships. In 1994 and 1997, stipends increased for predoctoral and postdoctoral trainees supported by NRSA grant mechanisms.

The NEI participated in NIH-wide programs to continue to attract, recruit, and retain women and minorities in research. These included: providing research supplements for underrepresented minorities, promoting reentry into biomedical and behavior research careers, and supporting a predoctoral fellowship program for minority students and students with disabilities. The NEI strongly supported these supplements, and evaluation has shown that excellent candidates have been supported and trained in strong research environments.

Recommendations for 1999–2003

Train high-caliber predoctoral trainees to study the visual system and sight-threatening diseases and disorders of vision. There is a continued need to train vision scientists in basic science areas of immunology, molecular biology, genetics, and cell biology. As part of an overall strategy, the NEI must develop innovative techniques for recruiting, nurturing, and training outstanding vision scientists to study the visual system and its disorders. Applicants for vision training programs should be of the highest level. Graduate programs should allow each applicant's skills to be developed in effective oral and written communication, be completed in no more than 5 or 6 years, and be reviewed annually for progress. The institutional training grant mechanism is seen as the most effective tool for predoctoral training. Even in disciplines that presently are well represented in visual sciences (e.g., neuroscience), it is important to support predoctoral training programs to continue to train highly qualified candidates.

As the NEI develops a strategy for training vision researchers, the Council encourages the NEI to examine and realize economic trends. These trends indicate that, from 1985 to 1995, there was an increase of more than 50 percent in the number of biomedical Ph.D. degrees awarded by U.S. institutions; nearly 70 percent of this increase can be attributed to the increase in the number of noncitizens receiving their Ph.D. degrees in the United States. Even though at the present time there is low unemployment among U.S. citizens with biomedical Ph.D. degrees, the number of

biomedical scientists has grown, while the number of faculty positions has remained stable. Therefore, faculty positions have declined as a percentage of total employment for biomedical scientists. In the future, academic jobs may not be the most prevalent form of employment for U.S. biomedical scientists (FASEB Conference on Graduate Education). The impact of these data on training of vision scientists must be considered in setting the NEI's future training initiatives.

Utilize the individual postdoctoral fellowship for postdoctoral training. Since obtaining an NEI individual postdoctoral fellowship is a competitive process, it is believed that this competition will assure the support of high-quality postdoctoral applicants and research training. A limited number of postdoctoral trainees can be supported on institutional training grants for a short transitional period as a means of attracting promising candidates to vision research and enabling them to make a transition to another mechanism of training or career support.

Encourage training of scientists at the predoctoral and postdoctoral level in the area of corneal, lens and cataract, and glaucoma research. The number of individuals being trained or seeking training in these scientific areas is still inadequate. It is important that the NEI continue to emphasize predoctoral and postdoctoral research training in these areas, always demanding high-quality mentors with outstanding research training experience and environments. The Council recommends continuing the NEI-sponsored vision course at MBL as a means of attracting outstanding young scientists into these scientific disciplines.

Support efforts to increase the stipend level for all NRSA training grant mechanisms. In spite of the recent 1997 NIH increase in stipend levels, they are still low, and well below the recommendations on stipends included in the 1994 National Academy of Sciences report, "Meeting the Nation's Needs for Biomedical and Behavioral Researchers." Predoctoral NRSA stipends are below the estimated salary amounts of NIH-supported graduate research assistants on research grants, as are stipends available from other competitive training programs. In addition, postdoctoral NRSA stipends remain below house staff salaries and salary levels for NIH intramural postdoctoral fellows. Low postdoctoral stipends are frequently cited as a reason for declining an individual NIH NRSA postdoctoral

fellowship offer. Raising the stipend levels is especially important to the postdoctoral trainee, who may be faced with financial and family obligations.

Encourage the use of the Mentored Clinical Scientist Award as an effective tool for training clinician-scientists. The small number of health professionals choosing research careers has been well established. The Mentored Clinical Scientist Award can provide the clinician with an intensive, fulltime research training program in laboratory science and clinical research that is directly relevant to eye diseases. A 4- to-5-year commitment by the applicant is considered necessary to achieve both the applicant's training goals and his or her establishment as an independent clinician-scientist who can compete successfully for independent grant support. The Council believes mentors should be carefully chosen to select the best research and training environment and role model for clinician-scientists. It is hoped that this type of training will increase the number of clinicians who participate in laboratory and clinically based vision research. The well-trained clinician-scientist can be instrumental in translating advances in the laboratory to clinics for patients with ocular diseases.

Establish epidemiological and biostatistical training programs housed in departments of biostatistics, epidemiology, and public health, that have close collaborative arrangements with ophthalmology and optometry departments. The Council supports the development of additional Ph.D. training programs in epidemiology, biostatistics, and clinical trials, with an emphasis on eye diseases. The shortage of trained biostatisticians and epidemiologists impacts the availability of trained personnel for designing, conducting, and managing clinical trials. This would include the training of ophthalmologists and optometrists, with additional quantitative and hands-on training in biostatistics, epidemiology, and clinical trials. Currently, there are only a few formal training programs in the area of clinical trials methodology.

At this time, the NEI is supporting two training programs—one in biostatistics and the other in epidemiology. The goal of the ophthalmological biostatistics training program is to educate predoctoral and postdoctoral trainees in statistical theory and methods applied in laboratory, clinical, and epidemiological studies. The goal of the epidemiology

training program is to provide research training via formal coursework and practical hands-on experience in the design, management, and analysis of data in clinical trials. It is hoped that these two training programs will begin to meet the needs of persons trained to perform leadership roles in conducting and coordinating clinical trials related to eye diseases. In addition, these programs would be designed to foster the development of health professionals into independent investigators capable of designing, conducting, and managing clinical trials.

Develop predoctoral and postdoctoral training programs that provide the opportunity to gain expertise in the methods of health services research and knowledge of the important issues in eye health and disease. There is a severe shortage of individuals with appropriate training to lead efforts in health services research (HSR) in the area of eye health and disease. The changing healthcare system has created a demand for accurate information in many areas that require the methods of HSR, such as access to and utilization of eye care; cost-effectiveness of various approaches to prevention and treatment of eye disease; the outcomes of management strategies for prevention and management of major eye and vision problems; the impact of those outcomes on patients; and the satisfaction of patients with their clinical management. Only a small number of medical doctors have chosen careers in research, and very few have received any training in the methods and approach of HSR. Within the field of health services research, few with Ph.D. degrees have sufficient background and interest in the area of eye care to lead investigations. In addition, very few academic institutions have the resources to provide comprehensive training in both areas. The Council recommends developing training programs that integrate the fields of HSR and eye care. Training should be located in an environment that maximizes the advantages of collaborative relationships of ophthalmologists, optometrists, and vision scientists with those having expertise in HSR. Whether the training program is based in a school of public health or a school of medicine, there should be a close relationship among faculty members. Training programs should involve a continuing effort, stable and committed faculty, and a core of set courses. There should be several ongoing investigations using HSR approaches to problems in health care so that trainees are exposed to a wide array of methodologic approaches. Training opportunities

should be coursework and hands-on experience in design, conduct, and analysis of studies in HSR as applied to eye care.

Continue to attract strong minority scientists into vision research using the NIH-wide program for research supplements for underrepresented minorities. New vision researchers must come in greater measure from members of ethnic minority groups. Members of minorities are markedly underrepresented in science in this country and, therefore, are an increasingly important source of talent for maintaining leadership in this area. Since the NAEC's last major planning effort, lack of marked success to increase the numbers of underrepresented minorities in biomedical science, including vision research, clearly makes the case for the need for new strategies. The NEI has enthusiastically participated in NIH-wide special programs for underrepresented minorities. The Council reaffirms its recognition that progress in this area can come only if potential laboratory and clinical scientists seek and obtain sufficient grounding in fundamental levels of biological, physical, and mathematical sciences. This means that programs must begin at the elementary school and junior high school levels. The vision community must become involved in vision science programs at local schools, sharing the excitement and enthusiasm of science. Vision research organizations may be able to assist with these outreach programs nationwide. A school program called "Vision," for children in grades 4 through 8, was developed by the NEI in cooperation with The Association for Research in Vision and Ophthalmology. This program is a series of three lessons that was designed for vision researchers and eyecare professionals for school classroom visits.

Long-term programs involving promising students, combined with individual mentoring preparing for a career in vision science, should have a positive impact on encouraging minority students to pursue careers in vision research. It is hoped that this will continue to attract and encourage minority individuals to enter and pursue careers in vision research. The Council encourages the use of the research supplement program for underrepresented minorities to provide outstanding research training opportunities for these individuals to develop into independent vision scientists. The Council recommends that mentors be selected who can provide an excellent training environment.

Continue to develop strategies to retain and promote women in vision research careers. Recruitment of women in the field of science has improved steadily, with women being better represented in graduate degree programs, such as medical schools and doctoral studies. Women are not, however, represented well in scientific and academic leadership positions. The commitment to children and other home responsibilities often interrupts a woman scientist's career, especially if she chooses to leave for a period of time, or to work part time, so she can raise her children or attend to other family responsibilities, such as caring for aging parents. In addition, a woman scientist who chooses to reenter a scientific career after fulfilling these obligations often has a difficult time. The Council strongly urges consideration of these factors in designing and implementing training and reentry opportunities for women scientists. The Council supports efforts by the NIH to facilitate full participation by women in all aspects of biomedical research, including developing special strategies that may be necessary to help women combine research training with child rearing and other family responsibilities. There seems to be a disparity in the number of women receiving NRSA research training and the number of recipients of NIH research grants. The Council recommends that the NEI continue to assist women scientists in establishing themselves in productive careers as vision scientists. New ways to retain and promote women in these vision research careers must be identified and implemented.

Support new investigators in vision research and the grant mechanisms that are targeted for vision scientists beginning their independent research careers. There is a continuing concern that increased competition for grants will make it more difficult for new investigators to obtain independent research funding. Analysis of the success rates for first-time grantees and more experienced scientists seeking new grants shows that new investigators continue to fare well in the NIH system. There is no evidence that new investigators have been selectively disadvantaged in obtaining their first research grants. The Council feels that it is extremely important to send a strong signal to new investigators that there is a place for them in the system. Because of the importance of new investigators to the advancement of biomedical and behavioral research, the Council recommends that the NEI support NIH-wide initiatives into the evaluation and development of several mechanisms with the intent of facilitating the entry and retention of new investigators in vision

research. The NEI is initiating a new career development program that is designed to provide an opportunity for new investigators to receive high-quality research training in the NEI intramural program. This program will also facilitate the transition of new investigators to an independent position by offering a research grant. New investigators who provide new ideas and approaches are critical to continuing the progress in vision research.

Evaluate the NEI's training initiatives and programs. The success of the NEI's training programs should be assessed by examining program goals and mission with career outcomes of the trainees. This information should be provided to the trainees, program directors of the institutional training grants, and the Council.

Summary

There is a continuing need for training highly skilled and talented vision researchers who will participate in laboratory and clinical investigations, ultimately leading to new and improved diagnosis, treatment, and prevention of eye diseases. The availability of research funding, employment opportunities, and research costs must be considered in developing future NEI training programs.

Use of Animals in Vision Research

The NAEC strongly endorses the use of animals in research and teaching. Most of the major advances made over the past several decades in the prevention, diagnosis, and treatment of eye diseases and blindness, as well as most of the increases in knowledge about the structure and function of the visual system, have resulted from the study of animals and animal models. Many of these advances have saved or restored the vision of hundreds of thousands of people. Ongoing research offers hope for those still suffering from diseases of the eye.

The Council shares the conviction that animal experiments must be performed humanely, using methods that comply with applicable laws, standards, and policies. Indeed, the Council will not recommend funding any application unless there is a complete and careful justification of the appropriateness of the animal model. The Council applauds the efforts of NEI staff members in helping vision researchers stay abreast of new developments in animal care

by organizing workshops and issuing policy statements about experimental procedures commonly used in studies of the visual system. Vision researchers are encouraged to consult with NEI staff members when issues arise about animal care or experimental procedures.

The Council strongly encourages the vision research community to become familiar with the “Guide for the Care and Use of Laboratory Animals,” published by the Institute of Laboratory Animal Resources of the National Research Council. Vision researchers should be familiar with the policies on the use of animals published by professional societies such as The Association for Research in Vision and Ophthalmology and the Society for Neuroscience, as well as informational guidelines in publications such as *Preparation and Maintenance of Higher Mammals During Neuroscience Experiments*.

The Council encourages and supports the development and use of nonanimal models for vision research. Research projects currently being funded by the NEI include experiments using tissue cultures of animal lens cells that could be instrumental in uncovering the genetic defects associated with human congenital cataracts, and the use of cultured human trabecular cells in glaucoma research.

While nonanimal models avoid the ethical concerns involved in experiments with humans or animals, the Council recommends them as procedures that complement, not replace, the use of animals for research purposes. These models may reduce the number of animals required for research purposes, but they can never eliminate the need for animal research. Simply stated, it is impossible to determine the effectiveness of a drug in reducing intraocular pressure or in slowing the development of cataracts in preparations that do not have eyes. When cell and tissue cultures are used as screening tests for pharmacological agents, results must be validated by animal experiments. Moreover, cells in culture cannot mimic the complicated interaction of physiological systems that occur in living animals. Neither computers nor mathematical models can serve as replacements for animal studies. Computer models that are based on the results of animal experiments and predictions made by these models usually must be verified by additional animal experiments.

An issue that continues to concern the Council is the choice of animal species to be used in research projects. The Council strongly advocates that the species that is best suited to answer the particular research question posed should be selected. Given the mission of the NEI to find new ways to prevent, diagnose, and treat human diseases of the visual system, in the absence of compelling scientific reasons for doing otherwise, preference should be given to using species generating data that will most readily generalize to the human visual system. Of particular concern are cases in which investigators choose species that will not yield results that generalize well, not for scientific reasons, but because of the additional cost of acquisition, housing, or care of the most appropriate species. In the long term, the savings realized by using a less expensive model disappear when the data obtained must then be replicated using the more expensive preparation. Nonhuman primates are the model system closest to the human, but species ranging from invertebrates, such as flies and worms, to nonprimate mammals, such as cats and rabbits, have and will continue to yield significant information on the fundamental mechanisms of vision common to all species, including humans. Thus, the Council encourages applicants to seek the advice of NEI staff when there are questions about the acquisition and animal care components of the budget, about which species is most appropriate for the planned experiments, and to explain the advantages of the particular species to be used in the grant application.

A related issue is the need to convey to the general public, the media, and policymakers an appreciation for how much important information about the human visual system is based on experiments using nonmammalian and invertebrate species. Most of what is known about the anatomical organization of the human retina, about the information processing that occurs in this structure, and about the neurotransmitters used for signal processing were first observed in experiments conducted on frogs, turtles, toads, salamanders, and horseshoe crabs. These animals were used in experiments not because their retinas or visual systems are exactly like the retina or visual system of humans, but because these animal models revealed principles that generalize to humans. Studying a particular photoreceptor type may be enhanced by using an animal that has only that type of photoreceptor. Also, with the use of techniques currently available, it is extremely difficult to record the electrical activity of

certain cells in the mammalian retina. Thus, the role of these cells in processing information (e.g., determining the shape of objects or the direction and rate of movement of objects) must be studied in animals.

Animal activist groups have openly declared their goal of abolishing animal experimentation, and their efforts have been successful. Research projects on human and animal diseases have been delayed or halted by raids on animal laboratories, causing millions of dollars in damages. Efforts to recruit students into health-related careers are being hampered by the climate of fear caused by threats and acts of violence by animal rights activists. Research projects have been shut down and construction of animal facilities delayed by legal actions of the activist groups. New Federal regulations, sometimes passed without benefit of hearings or legislative debate, add tremendously to the cost of animal experimentation. For these reasons, the Council encourages the vision research community to become more active in communicating the value of animal research to the public.

Clinical Trials Database

The ultimate aim of laboratory and clinical research conducted by the NEI is to improve the visual health of the American people. Even though laboratory research may at times seem far removed from the patient's bedside, a tremendous amount of laboratory research must be conducted before new therapies for the prevention or treatment of disease can be developed and tested in a clinical trial setting. Clinical trials are the most effective means of comparing the benefits and risks of new eye disease treatments. Equally important, however, is disseminating the information gained through these clinical trials to researchers, educators, healthcare providers, and most importantly, the American public.

In recognizing the importance of this information, the NEI periodically publishes a book, *Clinical Trials Supported by the National Eye Institute*, which contains information on all of the clinical trials supported by the Institute since 1970. As a means of further disseminating and improving access to information on the results of completed trials, the status of ongoing trials, and the recruitment of patients for trials in progress, a new clinical trials database has been established and is available through the NEI's homepage on the World Wide Web (<http://www.nei.nih.gov/>). This site also provides

a record of the progress and accomplishments in vision research since the Institute was created in 1968.

Resource Requirements

There has been considerable discussion of the Nation's investment in biomedical research in light of the changes in the economic outlook for the country since the publication of the last plan. To be sure, there are few who would argue against continued investment in meeting the health challenges that face us in the modern world; however, it is essential that the investment be made wisely, since choices must still be made between programs competing for the funds available in the discretionary budget.

Within this plan, the goals and objectives for vision research in this country over the next 5 years have been carefully prepared by those with special expertise in the areas of science represented in the NEI's programs. They are the priorities for vision research, representing areas of public health need and scientific opportunity, and are worthy of further investment of precious resources.

The NAEC recognizes that there must also be a careful appraisal of the level of funding that would be realistic and appropriate given the current level of resources (personnel, laboratory space, etc.). The Council feels that doubling the budget over the next 5 years, as proposed by many in Congress, is both a realistic and achievable goal, representing an annual increase of approximately 15 percent. The following table reflects that scenario.

NATIONAL ADVISORY EYE COUNCIL

PLANNING BUDGET
(Dollars in Thousands)

	<u>First-Year Estimate</u>		<u>Second-Year Estimate</u>		<u>Third-Year Estimate</u>		<u>Fourth-Year Estimate</u>		<u>Fifth-Year Estimate</u>	
	<u>No.</u>	<u>Amount</u>	<u>No.</u>	<u>Amount</u>	<u>No.</u>	<u>Amount</u>	<u>No.</u>	<u>Amount</u>	<u>No.</u>	<u>Amount</u>
<u>Research Grants</u>										
Research Projects										
Noncompeting	736	189,058	775	207,174	876	243,463	973	281,217	1,094	328,757
Competing	269	73,862	336	95,748	355	105,463	391	120,609	417	133,900
Subtotal	1,005	262,920	1,111	302,922	1,231	348,926	1,364	401,826	1,511	462,657
SBIR/STTR	56	9,239	62	10,613	69	12,191	76	14,004	84	16,086
Research Centers	35	13,545	36	15,559	40	17,873	41	20,531	45	23,584
Other Research										
Research Careers	52	5,967	57	6,854	63	7,873	70	9,044	77	10,389
Coop. Clinical Research	211	39,705	233	45,609	257	52,391	284	60,182	314	69,131
Other	3	1,068	4	1,227	4	1,410	4	1,620	5	1,861
Subtotal	266	46,740	294	53,690	324	61,674	358	70,846	396	81,381
Total, Research Grants	1,362	332,444	1,503	382,784	1,664	440,664	1,839	507,207	2,036	583,708
<u>Training</u>										
Individual	95	3,616	97	3,833	99	4,063	101	4,307	103	4,565
Institutional	183	6,589	187	6,984	190	7,403	194	7,847	197	8,318
Total	278	10,205	284	10,817	289	11,466	295	12,154	300	12,883
Res. & Dev. Contracts	30	11,837	33	13,597	36	15,619	40	17,942	44	20,610
Intramural Research		40,669		46,716		53,663		61,643		70,809
Res. Mgt. & Support		12,427		14,275		16,398		18,836		21,637
Ext. Construction		1,000		1,149		1,320		1,516		1,741
TOTAL	1,670	408,582	1,820	469,338	1,989	539,130	2,174	619,298	2,380	711,388

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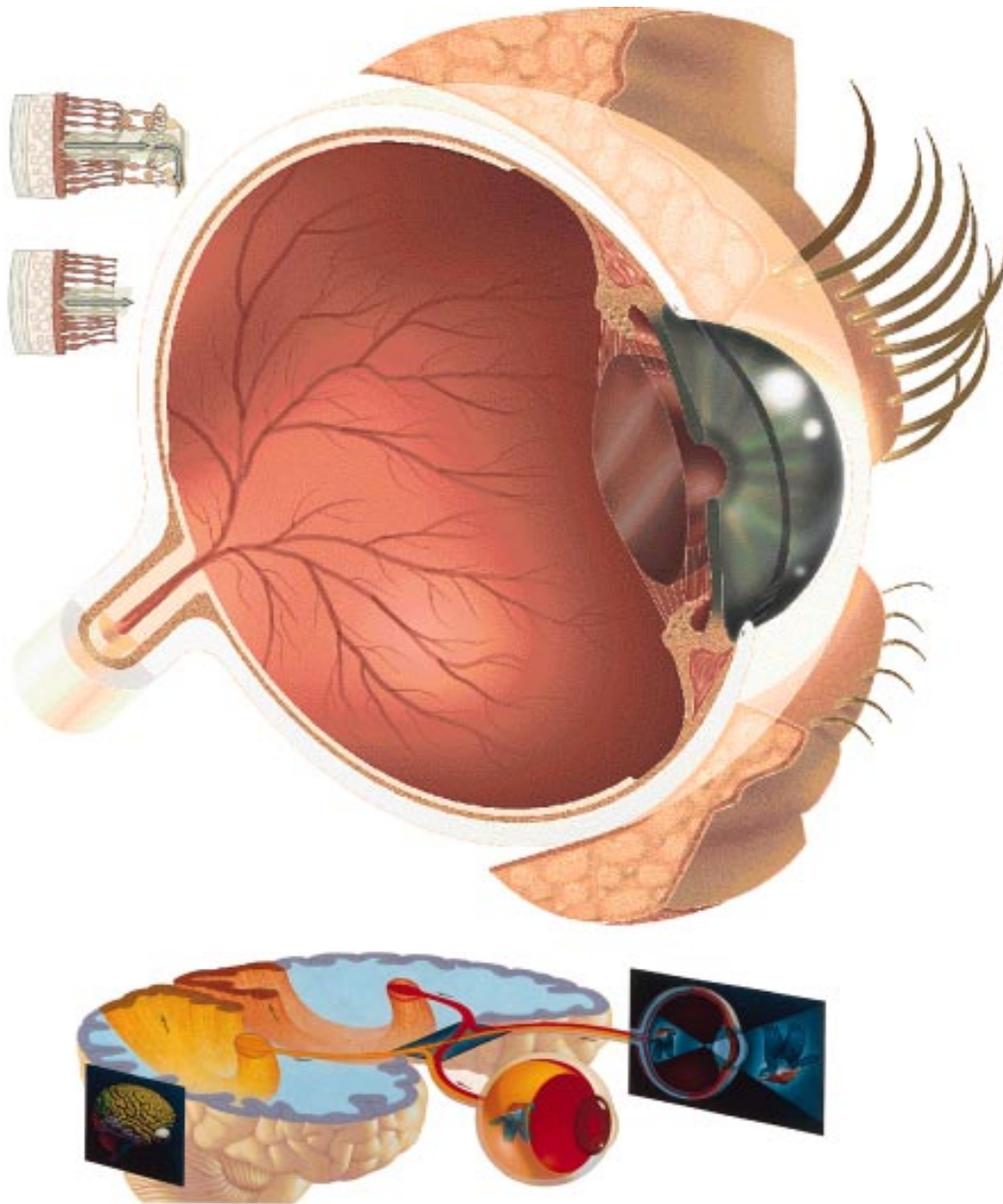


Illustration of the eye: Courtesy of Charles M. Blow/*The New York Times*
Illustration of the brain: Courtesy of *National Geographic*

In August 1993, the 103d Congress passed the Government Performance and Results Act (GPRA), and President Clinton subsequently signed it into law (Public Law 103-62). Among the overarching purposes of the law were provisions to make Federal agencies accountable for achieving program results through the establishment of program goals and objectives against which progress could be measured. The Act called for each Federal agency to develop a strategic plan that would serve as the basis for a process of goal setting and performance measurement throughout the Federal Government. Although the GPRA does not require strategic plans from organizations below the agency level (cabinet-level departments and independent agencies), Senate Report 103-58 suggested that agencies may choose to develop strategic plans for major component organizations with those plans being incorporated into the final agency wide document. In addition to articulating the agency-mission in the strategic plan and identifying the general goals and objectives to be attained in performance or accomplishment of the mission, agencies are required to describe the strategies through which they will meet those goals and objectives.

The National Eye Institute (NEI) and its advisory body the National Advisory Eye Council (NAEC) view the passage of the GPRA as an endorsement of the long-range planning process that was implemented shortly after Congress created the Institute in 1968. The Council believes that this process, while imperfect, is in full accord with the spirit and intent of the GPRA.

The NEI embarked on its first formalized planning effort during internal discussions in 1973, which culminated in the NAEC's publication of the first long-range national plan for vision research in 1975. The issue of accountability, as later stressed in the GPRA, has been a central tenet of the rationale for conducting a formal planning process at the NEI that has remained for more than 20 years of Institute planning activities. That first plan recognized that an essential part of the planning process should be to identify specific program goals, objectives, and

priorities, based on the evaluation of the past accomplishments and future research needs and opportunities.

Strategic Plan Requirements

Although the GPRA does not formally specify a format for strategic plans developed in accordance with the Act, the following requirements were identified: a comprehensive mission statement covering each organization's major functions and operations; general goals and objectives of each organization (including outcome-related goals and objectives that allow assessment of each organization's success in achieving those goals and objectives); a description of how the goals and objectives are to be achieved (including the operational processes, skills, technology, and resources required) identification of any external factors that could significantly affect the achievement of the goals and objectives; and a description of program evaluations that will be used to establish or revise the goals and objectives.

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As a means of addressing these requirements, the mission of the NEI, the goals and objectives for each of the programs, and the strategies for achieving those goals and objectives are contained in the preceding sections of this plan. The GPRA also requires assessment of each organization's success in meeting its goals and objectives, as well as a description of evaluations that will be used in revising the goals and objectives. The NAEC and the NEI have long considered evaluation of the programs as an essential component of the strategic planning process, but it was also recognized that evaluation of scientific progress was a formidable challenge. There are no readily available, reliable measurements that can be used in planning or evaluating scientific endeavors, and caution must be exercised in not focusing on inappropriate (or easier to measure) surrogates that have little to do with the new knowledge gained, which is the most important outcome of scientific inquiry.

Progress in medical research often results from incremental increases in knowledge or understanding of a disease or disease process that accumulates over a long time before a complete understanding is achieved. While a goal or objective may be aimed at gaining a complete understanding, the amount of progress that can be made with available technologies cannot be accurately predicted when dealing with a process of unknown complexity that is not yet fully understood. This makes setting exact milestones for charting progress or measuring the amount of knowledge or understanding gained a difficult if not impossible task. For these reasons, the NEI and the NAEC decided long ago that evaluation of a program (in accomplishing its stated goals and objectives) by panels of experts was the most appropriate method of evaluation in the NEI's strategic planning process.

As part of this process, experts in the various scientific disciplines encompassed by vision research are assembled to evaluate and make recommendations on NEI research programs. They are asked to review where progress has been made by identifying the most important research accomplishments that have been achieved since publication of the last plan. Not only is this assessment key to evaluating the progress that has been made in achieving the goals and objectives in the previous plan, it is also a vital first step in identifying the future needs and opportunities in each program. By asking experts in the field to evaluate the progress that has been made in realizing the goals and objectives in the previous plan, they must also consider whether there are still gaps in knowledge or understanding. They can also judge whether the opportunity exists to make additional progress with currently available technology or resources, or if new technologies or other resources must first become available for additional progress to be made.

Other evaluations of performance at the individual project and program level are also conducted. The peer review process is one of the most rigorous prospective evaluative procedures within the Federal sector. This process depends on expert reviewers to evaluate the past performance and future potential of research proposals. Additionally, in accordance with the provisions of the GPRA, the National Institutes of Health (NIH) will prepare an annual performance plan and an annual performance report for all research and research support activities conducted at the NIH. Both the performance plans and annual

performance reports will be prepared in the aggregate; i.e., a centralized plan and report will be prepared for all components of the NIH. The details of the NIH annual performance plan will be released with the Fiscal Year 1999 budget.

The NIH will assess the performance of its programs based on performance goals and corresponding performance indicators that have been established to encompass the entire NIH research endeavor. These goals and indicators relate to expected program outcomes (the expected results of NIH programs) and program means (the administrative and management activities that support the conduct of scientific research). The goals and objectives in this plan are essential components in preparing the aggregated NIH annual performance plan and in making this assessment process meaningful in evaluating the vision research program of the NEI.

Update Process and Schedule

In preparing this plan, advice and input were solicited on research accomplishments and future directions from scientific and philanthropic organizations that have an interest in the research supported by the NEI. In addition, the opportunity to offer views and recommendations on the NEI programs was provided through the NEI homepage on the World Wide Web (<http://www.nei.nih.gov/>). This information was provided to the program planning panels for their consideration in preparing their reports.

In updating and revising the goals and objectives in this plan, a similar approach will be used in gathering information for the panels to consider. Additionally, NEI contributions to the annual performance reports will be provided to the panels so that they can review the success of NEI programs in meeting the NIH-wide performance goals. The NEI and the NAEC will continue expert panel evaluations of the vision research program as part of the strategic planning process and as a means of assessing the progress within the research programs. It is the intent of the NEI and the NAEC to begin the update and revision process for this 5-year strategic plan 3 years from the time the current plan is published so that the next strategic plan will be in place for the years 2004 to 2009.

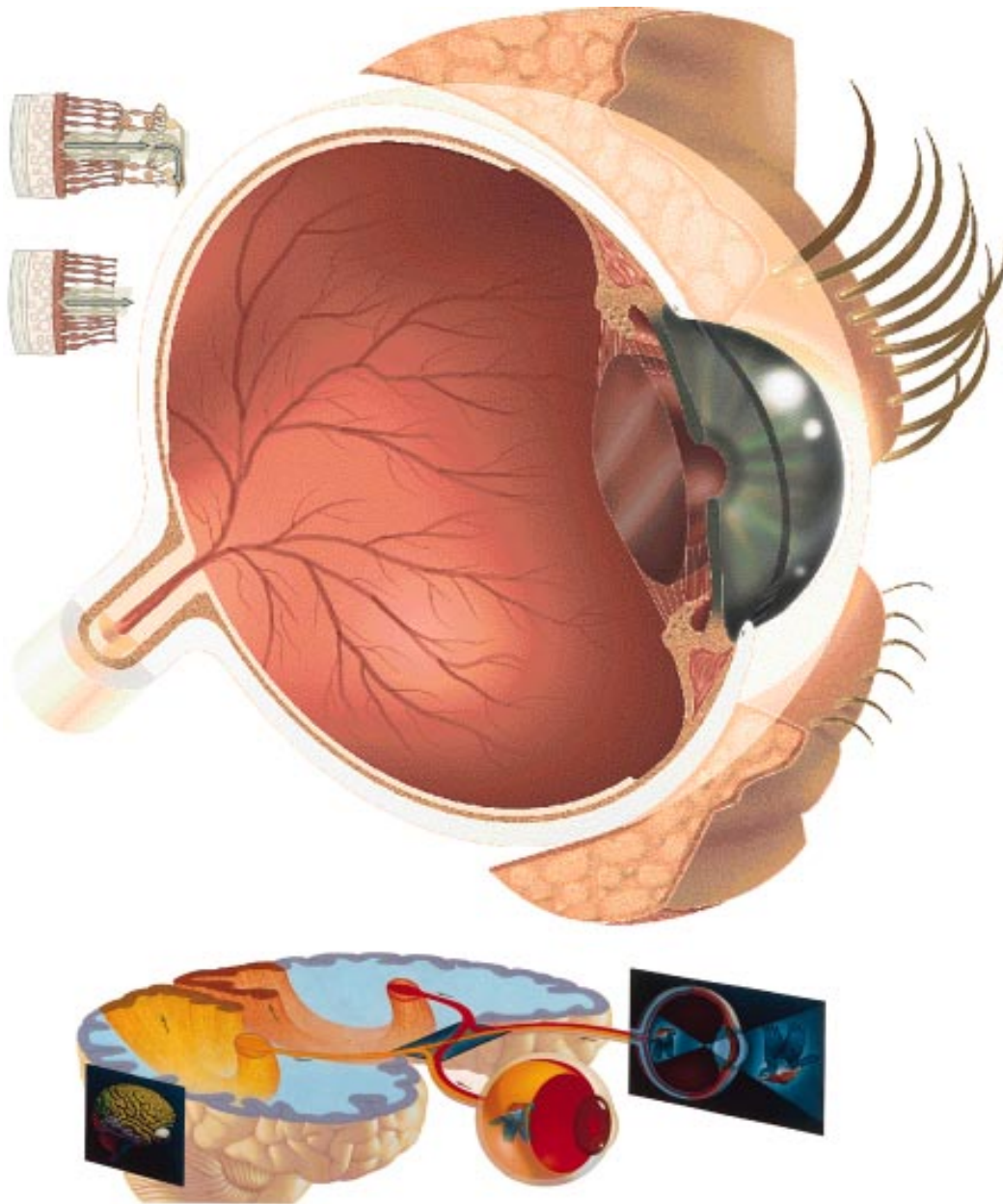


Illustration of the eye: Courtesy of Charles M. Blow/*The New York Times*
Illustration of the brain: Courtesy of *National Geographic*

ACCOMMODATION-The ability of the eye to change focus from distant to near objects; process achieved by the lens changing its shape.

ANTERIOR CHAMBER-The space in front of the iris and behind the cornea.

AQUEOUS HUMOR, AQUEOUS FLUID-Clear, watery fluid that flows between and nourishes the lens and the cornea; secreted by the ciliary processes.

ASTIGMATISM-A condition in which the surface of the cornea is not spherical; causes a blurred image to be received at the retina.

BLIND SPOT-(1) A small area of the retina where the optic nerve enters the eye; occurs normally in all eyes. (2) Any gap in the visual field corresponding to an area of the retina where no visual cells are present; associated with eye disease.

CENTRAL VISION-See **VISUAL ACUITY**.

CHOROID-The layer filled with blood vessels that nourishes the retina; part of the uvea.

CILIARY MUSCLES-The muscles that relax the zonules to enable the lens to change shape for focusing.

CILIARY PROCESSES-The extensions or projections of the ciliary body that secrete aqueous humor.

CONES, CONE CELLS-One type of specialized light-sensitive cells (photoreceptors) in the retina that provide sharp central vision and color vision. Also see **RODS**.

CONJUNCTIVA-The thin, moist tissue (membrane) that lines the inner surfaces of the eyelids and the outer surface of the sclera.

CONTRAST SENSITIVITY-The ability to perceive differences between an object and its background.

CORNEA-The outer, transparent, dome-like structure that covers the iris, pupil, and anterior chamber; part of the eye's focusing system.

DILATION-A process by which the pupil is temporarily enlarged with special eyedrops (mydriatic); allows the eyecare specialist to better view the fundus.

FUNDUS-The interior lining of the eyeball, including the retina, optic disc, and macula; portion of the inner eye that can be seen during an eye examination by looking through the pupil.

HYPEROPIA-Farsightedness; ability to see distant objects more clearly than close objects; may be corrected with glasses or contact lenses.

INTRAOCULAR PRESSURE (IOP)-Pressure of the fluid inside the eye; normal IOP varies among individuals.

IRIS-The colored ring of tissue suspended behind the cornea and immediately in front of the lens; regulates the amount of light entering the eye by adjusting the size of the pupil.

LACRIMAL GLAND-The small, almond-shaped structure that produces tears; located just above the outer corner of the eye.

LEGAL BLINDNESS-In the United States, (1) visual acuity of 20/200 or worse in the better eye with corrective lenses (20/200 means that a person must be at 20 feet from an eyechart to see what a person with normal vision can see at 200 feet), or (2) visual field restricted to 20 degrees diameter or less (tunnel vision) in the better eye.

LENS-The transparent, double-convex (outward curve on both sides) structure suspended between the aqueous and vitreous; helps to focus light on the retina.

MACULA-The small, sensitive area of the central retina; provides vision for fine work and reading.

MYOPIA-Nearsightedness; ability to see close objects more clearly than distant objects; may be corrected with glasses or contact lenses.

OPTIC CUP-The white, cuplike area in the center of the optic disc.

OPTIC DISC/OPTIC NERVE HEAD-The circular area (disc) where the optic nerve connects to the back part of the retina.

OPTIC NERVE-The bundle of over one million nerve fibers that carry visual messages from the retina to the brain.

PERIPHERAL VISION-Side vision; ability to see objects and movement outside the direct line of vision.

POSTERIOR CHAMBER-The space between the back of the iris and the front face of the vitreous; filled with aqueous fluid.

PRESBYOPIA-The gradual loss of the eye's ability to change focus (accommodation) for seeing near objects; caused by the lens becoming less elastic; associated with aging; occurs in almost all people over age 45.

PUPIL-The adjustable opening at the center of the iris that allows varying amounts of light to enter the eye.

RETINA-The light-sensitive layer of tissue that lines the back of the eyeball; sends visual impulses through the optic nerve to the brain.

RETINAL PIGMENT EPITHELIUM (RPE)-The pigment cell layer that nourishes the retinal cells; located just outside the retina and attached to the choroid.

RODS, ROD CELLS-One type of specialized light-sensitive cells (photoreceptors) in the retina that provide side vision and the ability to see objects in dim light (night vision). Also see **CONES**.

SCHLEMM'S CANAL-The passageway for the aqueous fluid to leave the eye.

SCLERA-The tough, white, outer layer (coat) of the eyeball; with the cornea, it protects the entire eyeball.

TRABECULAR MESHWORK-The spongy, meshlike tissue near the front of the eye that allows the aqueous fluid (humor) to flow to Schlemm's canal then out of the eye through ocular veins.

UVEA, UVEAL TRACK-The middle coat of the eyeball, consisting of the choroid in the back of the eye and the ciliary body and iris in front of the eye.

VISUAL ACUTY-The ability to distinguish details and shapes of objects; also called central vision.

VISUAL FIELD-The entire area that can be seen when the eye is forward, including peripheral vision.

VITREOUS-The transparent, colorless mass of gel that lies behind the lens and in front of the retina.

ZONULES-The fibers that hold the lens suspended in position and enable it to change shape during accommodation.



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