VISION RESEARCH

A NATIONAL PLAN: 1999–2003

EXECUTIVE SUMMARY

NATIONAL INSTITUTES OF HEALTH

NATIONAL EYE INSTITUTE

A Report of the National Advisory Eye Council

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Illustration of eye:
Courtesy of Charles M. Blow,
The New York Times

Illustration of brain:
Courtesy of *National Geographic*

A Report of the National Advisory Eye Council

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.

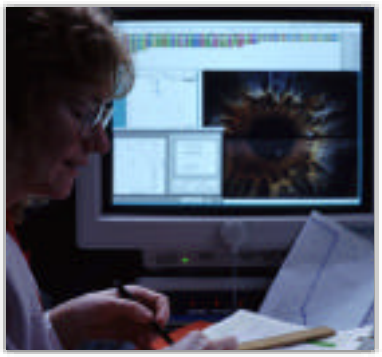
- Identify the genes involved in retinal degenerative diseases, including RP, and determine the pathophysiological mechanisms underlying these mutations.

- 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 immunopathogenic, 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 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 microenvironment through studies of Brüch'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 intercellular 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.

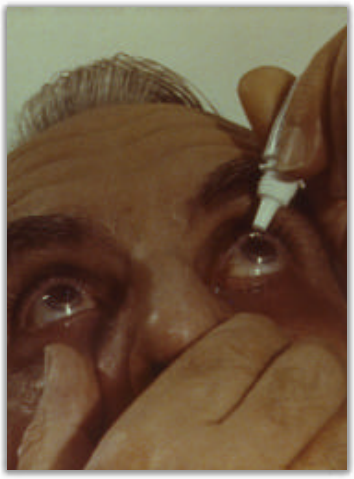
Epidemiological studies conducted in the United States and the West Indies have improved the prevalence and incidence estimates of primary open-angle glaucoma among white and black populations. One strength of these recent studies is the adoption of more inclusive definitions of primary open-angle glaucoma 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:

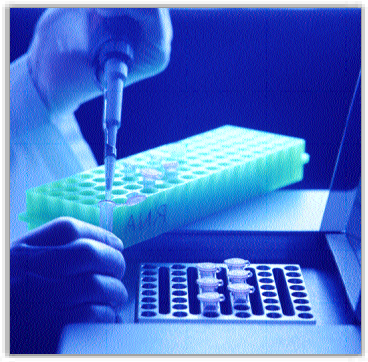
- Identify genes and genetic loci contributing to glaucoma, especially those responsible for the common forms of the disease, and characterize the function and interaction of their gene products.
- Define the molecular and biochemical mechanisms that lead to retinal ganglion cell death in human glaucoma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

Courtesy of J. Pekar, Ph.D.

- 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.

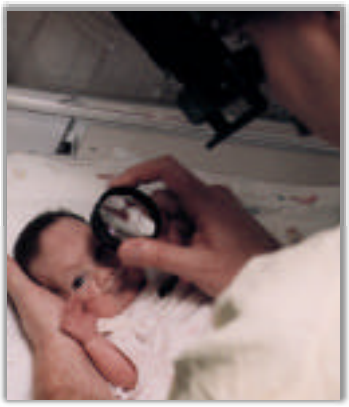
Highlights of Recent Progress

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.



Courtesy of Photography Department
Casey Eye Institute

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.

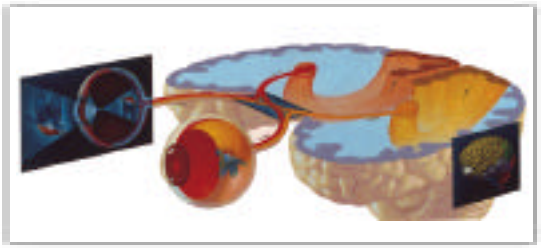
There has been recent progress in the ability of researchers to assess infants as young as 4 months of age and young children who have or are at risk for low vision. The Teller Acuity Card procedure measures the finest grating that a child can resolve by observing the child's eye and head movement responses 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.



Courtesy *National Geographic*

- 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 vision-care 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.

GLOSSARY OF VISION TERMS

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 ACUITY-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.

Acknowledgments

The National Advisory Eye Council extends its sincere gratitude to the cochairs and members of the Vision Research Program Planning Subcommittee; the chairs, cochairs, and members of the planning panels and working groups; the staff of the National Eye Institute; and the numerous consultants and special reviewers from the vision research and healthcare communities. Without the dedication, sacrifice, and significant contributions of these individuals, this vision and plan for the future of eye research would not be possible.

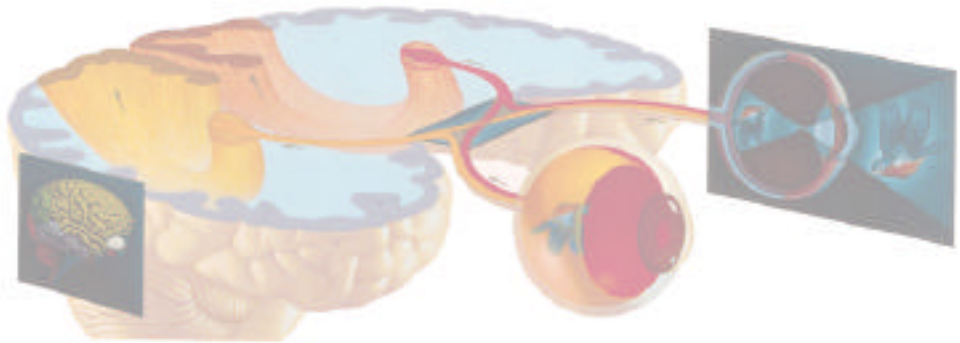


Illustration of eye: Courtesy of Charles M. Blow, *The New York Times*
Illustration of brain: Courtesy of *National Geographic*

For a copy of the full report *Vision Research—A National Plan: 1999–2003*, contact the Office of Science Policy and Legislation, National Eye Institute, Building 31, Room 6A23, 31 Center Drive MSC 2510, Bethesda, MD 20892-2510, telephone (301) 496-4308.

National Advisory Eye Council. *Vision Research—A National Plan: 1999–2003*, *Executive Summary*.

U.S. Department of Health and Human Services

NIH Publication No. 98-4288