

NATIONAL EYE INSTITUTE

NIH Comprehensive Strategic Plan and Budget To Reduce and Ultimately Eliminate Health Disparities

NEI MISSION/VISION STATEMENT

Congress established the National Eye Institute (NEI) in 1968 with the 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 individuals who are visually impaired. Inherent in the NEI's mission is the investigation of normal visual processes and health information dissemination activities to conduct activities related to the prevention of blindness through public and professional education programs and through the encouragement of regular eye examinations.

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.

OVERVIEW OF THE NEI STRATEGY FOR ADDRESSING HEALTH DISPARITIES

The National Eye Institute's latest strategic plan, Vision Research-A National Plan: 1999-2003, was developed under the auspices of the National Advisory Eye Council. Over 100 experts from all fields of vision research were assembled to make recommendations on research priorities over the period covered by the plan. Among the priorities identified by these experts were several related to health disparities. These priorities included research on glaucoma, diabetic retinopathy, myopia, and health services delivery and use. Recommendations were also made regarding training and attracting minority scientists into vision research. During the review of the strategic plan, the draft was sent to over 50 professional, scientific, or advocacy organizations that support vision research. They were asked to consider whether any important areas of research or specific issues of importance to vision research had been overlooked. The final document reflects the comments and input received during that process.

For this comprehensive strategic plan and budget to reduce and ultimately eliminate health disparities the background, recent progress, and current research were updated. The areas of research priority and research needs and opportunities related to health disparities that were identified in the full strategic plan were extracted. These areas form the core elements for the NEI comprehensive strategic plan and budget to reduce and ultimately eliminate health disparities. In addition, the NEI's National Eye Health Education Program and its activities as a

co-lead agency for the new focus area on Vision and Hearing in the Department's Healthy People 2010 are highlighted.

Future strategic plans for reducing health disparities will be integrated into the formal planning process the NEI has used over the past 25 years. However, additional emphasis will be given by highlighting health disparities as a specific focus area within the overall institute strategic plan. By creating a focus area for reducing health disparities, all research and policy issues can be considered together rather than within each programmatic area, thereby facilitating the development of recommendations that cut across the formal NEI programs.

Areas of Research Emphasis

Glaucoma

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 by 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.

Rationale and Priority

Primary open-angle glaucoma, the most common form of the disease, is 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. Although there are a number of other forms of glaucoma, the major focus of NEI supported research 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. The disease is manifest as a progressive optic neuropathy that, if left untreated, leads to blindness. 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.

An estimated 66.8 million people worldwide have glaucoma and nearly 6.7 million will be bilaterally blind as a result.¹ Glaucoma is a major public health problem in this country, as well. It is estimated that as many as 3 million Americans² have the disease and as many as 120,000³ are blind. Furthermore, it is the number one cause of blindness in African-Americans.⁴

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.⁵ 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.⁶ The Barbados Eye Study, which studied over 4,000 black Barbadians ages 40 to 84, reported a prevalence rate of 7 percent⁷. 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.

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 condition⁸. Glaucoma is three to four times as common in blacks as in whites, and blindness from glaucoma is six times as common in blacks than in whites. In its early stages, glaucoma is usually treated with drugs in daily eye drops. In some patients, the beneficial effect of the eye drops lessens with time, and “advanced glaucoma” develops. Recent findings from the NEI-supported Advanced Glaucoma Intervention Study suggest that black and white patients with advanced glaucoma respond differently to two surgical treatments for the disease. Although both groups benefit from treatment, scientists found that blacks with advanced glaucoma benefit more from a regimen that begins with laser surgery, while whites benefit more from one that begins with an operation called a trabeculectomy⁹.

In an effort to understand the genetics of susceptibility to open-angle glaucoma, scientists have been actively pursuing genes responsible for minor forms of the disease that have clear patterns of inheritance. Presently, ten glaucoma loci have been identified and five of the genes are cloned. A major advance came with the cloning of the gene linked to juvenile glaucoma on chromosome 1. This gene, *GLC1A*, encodes a protein that is expressed in a tissue involved in the maintenance of intraocular pressure. Two genes for congenital glaucoma syndromes have been isolated and a third has been mapped to chromosome 1. Three distinct loci associated with Reiger's syndrome, a congenital syndrome that includes glaucoma have been mapped, and one of these has been cloned. Also, the gene for Nail-Patella syndrome, another congenital disorder associated with glaucoma, has been cloned. Other loci mapped include one linked to pigment dispersion glaucoma and two for rare forms of adult onset POAG. Defining roles for these genes with respect to glaucoma should indicate pathways that are disrupted and thereby, help increase our understanding of the pathology of all forms of glaucoma.

Progress has also been made in the development of new pharmacological agents that might protect axons from damage due to glaucoma. Elevated intraocular pressure is frequently associated with glaucoma and explanations for how axons become damaged are usually based on the mechanical effects of elevated intraocular pressure. However, optic nerve damage can occur without abnormally high pressures and conversely, elevated pressure does not necessarily lead to optic nerve damage. Discovering the basis of optic nerve degeneration is essential for the development of the next generation of glaucoma drugs, neuroprotective agents. Scientists now have evidence that the molecule nitric oxide (NO), is directly involved in mediating the degeneration of axons in the optic nerve head¹⁰. Research is being aimed at identifying and developing neuroprotective agents as a new class of glaucoma drugs.

An important aim of current research is to develop methods of 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 a more thorough understanding of the natural history of the disease and whether early treatment can prevent the onset of glaucoma.

In its early stages, glaucoma is usually treated with drugs in daily eye drops. In some patients, the beneficial effect of the eye drops lessens with time, and "advanced glaucoma" develops. However, the role of topical medications in preventing or delaying sight-threatening damage to the eye from glaucoma remains unclear. In order to evaluate the safety and efficacy of topical ocular hypotensive medications in preventing or delaying damage to the optic nerve and loss of vision from primary open angle glaucoma, the NEI has funded the Ocular Hypertension

Treatment Study (OHTS). The OHTS is designed to determine the potential benefit of treatment with ocular hypotensive medications in preventing or delaying damage to the eye from glaucoma. Additionally, the high percentage of African Americans participating will also ensure adequate evaluation of the effectiveness of topical medication in treating African Americans with glaucoma as the study progresses toward conclusion in the coming years.¹¹

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. Clinical and laboratory research will continue to provide a greater understanding of the normal functions of the ocular tissues involved in the disease. Such studies have already led and will continue to lead 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.

Objective

Develop improved measures to aid clinical diagnosis of glaucoma; monitor progression of disease and treatment effectiveness; and elucidate the pathophysiology and natural history of the disease.

Action Plan

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.

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 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 epidemiologic 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.

It is anticipated that significant progress will be made in the next five years to 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.

Performance Measures

The NIH has developed a set of performance measures as a part of its Government Performance and Review Act (GPRA) assessment plan for its research program. The NIH has concluded that strictly numeric goals and measures are neither feasible nor sufficient to capture the breadth and impact of NIH's research program. Therefore, as provisioned for in GRPA, the NIH has defined research performance goals that rely on criteria that are more nearly descriptive in nature ["alternative form" assessment, Sec. 1115 (b)(1)]. These performance measures are: add to the body of knowledge about normal and abnormal biological functions; develop new or improved instruments and technologies

for use in research and medicine; develop new or improved approaches for preventing or delaying the onset of disease and disability; develop new or improved methods for diagnosing disease and disability; and, develop new or improved approaches for treating disease and disability. The NEI will continue to support the very best and highest quality research identified through the peer-review process.

Outcomes Measures

The NEI will support research that will build on the knowledge gained from its investment in the highest quality science and translate the findings of this research program to develop new treatments and diagnosis for glaucoma

Myopia

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. More than 30 years ago, scientists found that raising a variety of animals with a closed eyelid led to the development of myopia, because the eye became elongated. Similar observations were made in human infants in which trauma or some other disorder resulted in neonatal eyelid closure. Over the next three decades a clearer picture of some of the processes involved in the control of refractive error in growing eyes has emerged.

Rationale and Priority

Myopia occurs in approximately 25 percent of the population of the United States.¹² Myopia is an important public health problem, which entails substantial societal and personal costs. It is highly prevalent in our society and even more frequent in Asian countries; furthermore, its prevalence may be increasing over time. The most common form of myopia is childhood myopia, which begins after age 6 and progresses rapidly until age 16. Myopia progression results from excessive growth of the eye, primarily by enlargement of the vitreous chamber. Excessive elongation of the eye is a major risk factor for retinal detachment. A clinical study of myopia in first and second generation Hispanic, white, Asian, and black immigrant students in this country demonstrated that Asian immigrants have a significantly higher prevalence of myopia.¹³ Increased prevalence of myopia among Alaskan Eskimos and some American Indian Tribes has also been reported.^{14, 15}

High myopia contributes to significant loss of vision and blindness. At present, the mechanisms involved in the etiology of myopia are unclear, and there is no way to prevent the condition. Current methods of correction require lifelong use of lenses or surgical treatment, which is expensive and may lead to complications.

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.

The NEI is currently conducting a number of studies designed to provide more information on the development and prevention or treatment of myopia. One such study is the Collaborative Longitudinal Evaluation of Ethnicity and Refractive Error (CLEERE) Study. It is a multi-center, observational investigation of ocular development and refractive error development in schoolchildren. It adds three clinical centers to the Orinda Longitudinal Study of Myopia (OLSM), begun in 1989, specifically to describe normal ocular growth in children ages 6 to 14 years, and to develop the ability to predict juvenile onset myopia before it is clinically evident. In addition to the more than 1,300 predominantly Caucasian children enrolled in the OLSM, three additional clinical sites enroll African-American, Hispanic, and Asian children. The children are examined annually for at least four years.

Another ongoing study is the Correction of Myopia Evaluation Trial (COMET), a multicenter, randomized, double-masked clinical trial designed to evaluate whether progressive addition lenses slow the progression of juvenile-onset myopia as compared with single vision lenses. The primary outcome of the study is progression of myopia, defined as the magnitude of the change relative to baseline in spherical equivalent refraction, determined by cycloplegic autorefractometry. The secondary outcome of the study is axial length measured by A-scan ultrasonography.

In a similar study being conducted in Oklahoma, the hypothesis that correction with bifocal spectacle lenses rather than single-vision lenses will slow the progression of myopia in children with near-point esophoria will be tested. The primary outcome variable is refraction as measured with an automated refractor. Axial length is measured with ultrasound in order to test the corollary hypothesis that use of bifocals will slow ocular growth in these myopic children. We will also examine the amount of close work performed by subjects and the degree of parental myopia as factors that may influence myopia progression.

Objective

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.

Action Plan

Identify the visual error signals that govern eye growth during correction for refractive error. And, 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, contact lenses or pharmacological treatments.

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.

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.

It is anticipated that significant progress will be made in the next five years to identify the visual error signals that govern eye growth during correction for refractive error. And, 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, contact lenses or pharmacological treatments.

Performance Measures

The NIH has developed a set of performance measures as a part of its Government Performance and Review Act (GPRA) assessment plan for its research program. The NIH has concluded that strictly numeric goals and measures are neither feasible nor sufficient to capture the breadth and impact of NIH's research program. Therefore, as provisioned for in GRPA, the NIH has defined research performance goals that rely on criteria that are more nearly descriptive in nature ["alternative form" assessment, Sec. 1115 (b)(1)]. These performance measures are: add to the body of knowledge about normal and abnormal biological functions; develop new or improved instrument and technologies for use in research and medicine; develop new or improved approaches for preventing or delaying the onset of disease and disability; develop new or improved methods for diagnosing disease and disability; and, develop new or improved approaches for treating disease and disability. The NEI will continue to support the very best and highest quality research on myopia identified through the peer-review process.

Outcomes Measures

The NEI will support research that will build on the knowledge gained from its investment in the highest quality science and translate the findings of this research program to develop new treatments and preventive strategies for myopia.

Health Services Research

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.

Rationale and Priority

To advance understanding of these issues, the National Eye Institute (NEI) devoted a section to

health services research in its strategic plan, Vision Research-A National Plan: 1999-2003. 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. Various studies have demonstrated the need to ensure patient access and utilization of visioncare services particularly where treatments are available to improve or preserve vision. In blacks undertreatment has been reported for cataract, diabetic retinopathy, and glaucoma.^{16, 17, 18, 19}

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.

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.

The NEI is currently supporting the Ophthalmic Complications Prevention Trial designed to evaluate the efficacy of an inexpensive educational intervention to promote annual ophthalmic screening among low-income Black women with diabetes.

Another study entitled Why Preventable Blindness Occurs in Diabetes is attempting to learn why the current health care system is unsuccessful in preventing blindness from diabetic retinopathy, a disease for which effective treatment is available.

The NEI is also supporting a study to develop, implement, and evaluate a comprehensive culture-

specific and community-based education program for the prevention of eye disease in diabetic Oklahoma Indians.

The Diabetic Retinopathy Awareness program is seeking to control visual loss from diabetic retinopathy in the community by evaluating various methods of increasing the use of ophthalmology services among people with diabetes.

The NEI is supporting a major research project in Los Angeles County, California, the Los Angeles Latino Eye Study, to gain a greater understanding of the prevalence and incidence of eye disease among Latinos. Researchers are conducting in-depth interviews with study participants on their medical and ophthalmic histories, use of medications, tobacco and alcohol consumption, and utilization of health care services. Because so little is known about the visual health needs of this segment of the population, the data collected from this study will be instrumental in determining the prevalence of cataract, glaucoma, age-related macular degeneration, and diabetic retinopathy among Latinos in this community. The study will also determine the proportion of blindness and visual impairment that is caused by these diseases, and will explore the association of various risk factors, such as smoking or sun exposure with ocular disease. The study will also examine the effect of eye disease and disorders on quality of life and will assess the cost/benefit of eye care services and the utilization of those services in the Los Angeles Latino community. Continuation of this study should yield results that will assist in setting eye and vision health services priorities in the Los Angeles area and the rest of the country.

Another study supported by the NEI that is designed to improve our understanding of eye disease and visual impairment in the Hispanic population in this country is the Visual Impairment Among Hispanics in Arizona Study. This study is collecting data to determine the prevalence of diabetic retinopathy, cataract, and other causes of blindness and visual impairment in 4,500 Mexican Americans age 40 and older residing in Arizona. The results will provide new information of visual impairment and blindness in the Mexican-American community.

Objective

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

Action Plan

*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.
Identify the factors associated with the most effective delivery and use of visioncare services.*

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.

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.

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.

The NEI anticipates that significant progress will be made in the next five years to 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. And, that the factors associated with the most effective delivery and use of visioncare services will be identified.

Performance Measures

The NIH has developed a set of performance measures as a part of its Government Performance and Review Act (GPRA) assessment plan for its research program. The NIH has concluded that strictly numeric goals and measures are neither feasible nor sufficient to capture the breadth and impact of NIH's research program. Therefore, as provisioned for in GRPA, the NIH has defined research performance goals that rely on criteria that are more nearly descriptive in nature ["alternative form" assessment, Sec. 1115 (b)(1)]. These performance measures are: add to the body of knowledge about normal and abnormal biological functions; develop new or improved instrument and technologies for use in research and medicine; develop new or improved approaches for preventing or delaying the onset of disease and disability; develop new or improved methods for diagnosing disease and disability; and, develop new or improved approaches for treating disease and disability. The NEI will continue to support the very best and highest quality health services research identified through the peer-review process.

Outcomes Measures

The NEI will support health services research that will build on the knowledge gained from its investment in the highest quality science and translate the findings of this research program to improve health services.

Diabetic Retinopathy

Diabetes mellitus is one of the leading causes of death in this country and throughout the world but is also a major cause of blindness. One of the ocular complications of diabetes is diabetic

retinopathy. Diabetic retinopathy causes excessive vascular 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.

Rationale and Priority

The Centers for Disease Control and Prevention estimate that there are nearly 16 million Americans with diabetes, but that only 10 million have been diagnosed. Almost 800,000 new cases are diagnosed annually. Although the incidence of insulin-dependent diabetes mellitus (IDDM) in whites is nearly twice the incidence in blacks, the prevalence of non-insulin-dependent diabetes mellitus (NIDDM) is between 1.4 and 2.3 times higher in blacks than in whites. Similarly the prevalence of NIDDM is two to three times higher in Hispanics than in non-Hispanic whites. Generally, NIDDM is more common in African Americans, Mexican Americans, Japanese Americans, and Native Americans than in non-Hispanic whites.²⁰ The prevalence of the disease in U.S. Hispanics varies by geographic location and education.^{21,22}

With the increased prevalence of NIDDM in Mexican Americans, studies have shown that there is also a significantly increased risk of severe retinopathy.²³ Diabetic retinopathy has also been shown to occur more often in blacks than in whites, but this difference was not explained by differences in risk factors alone. Rather, the results suggested that the differences may be due to a greater susceptibility to the adverse effects of hyperglycemia and/or blood pressure.²⁴ Although this may help explain the increased prevalence and severity of diabetic retinopathy in blacks, it does not explain the excess prevalence and disease severity in Mexican Americans with NIDDM.²⁵ Previous studies have demonstrated that disease duration, increased hyperglycemia, diagnosis at an earlier age, and the need for insulin treatment is associated with increased prevalence of diabetic retinopathy in both Mexican Americans and Caucasians. Interestingly, no association was found with socioeconomic status.²⁶ The finding that a high percentage of blacks and Hispanics have severe diabetic retinopathy at initial presentation for treatment, strongly argues for earlier referral from primary care physicians and increased public education efforts.²⁷ Although currently recommended treatments are over 95 percent effective in preventing further vision loss, about half of those who could benefit from treatment being treated.

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.

Another growth factor that has been shown promise in the control of angiogenesis is pigment epithelium-derived growth factor (PEDF), a protein found in the healthy eye. PEDF is secreted by the retinal pigment epithelial cells that underlie and nourish the neural retina. Recently, a team of scientists demonstrated that PEDF can transiently delay the death of photoreceptors in mouse models of inherited retinal degenerations. This protein has also been shown to promote neurite-outgrowth and protect spinal cord motor neurons against natural and induced death using cell culture and animal model systems. Another group of scientists has shown that PEDF can prevent the growth of endothelial cells that form new blood vessels. Thus, PEDF behaves as a potent neurotrophic factor for the retina and nerves of the central nervous system, as well as a potent inhibitor of angiogenesis. Continued research to learn how PEDF works may provide information that will contribute to the development of effective treatments for several neural degenerative and angiogenic diseases, such as retinitis pigmentosa, macular degeneration, and diabetic retinopathy.^{28, 29}

Another new therapeutic agent has been developed that may be important in treating blindness in humans caused by diabetic retinopathy or macular degeneration. The new drug, called PKC 412, can be taken orally and appears to have several actions on growth factors and their receptors within the retina. While PKC 412 blocks new abnormal vessel growth, it has no apparent adverse effects on normal, fully mature vessels. Additional research is needed to determine whether PKC 412 is a viable therapeutic alternative in the treatment of diabetic retinopathy.³⁰

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.

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.

Current research efforts continue to focus on the development of improved pharmacologic agents that will prevent or cause the regression of retinal or choroidal neovascularization. Studies are continuing to determine the role of tissue hypoxia in VEGF upregulation and expression. The role of oxidation products in the pathogenesis of retinal vascular diseases is also being studied, as well as the role of antioxidants that may be used therapeutically to retard this pathogenesis.

In spite of the finding that laser therapy has been highly successful in preventing vision loss from proliferative diabetic retinopathy, it has been estimated that up to 50 percent of patients that could benefit from treatment are not receiving appropriate treatment. This suggests that current public and professional education efforts are essential to preserving the vision of diabetic patients.

Objectives

Understand the pathogenesis of diabetic retinopathy and other vascular diseases of the retina and develop strategies for primary prevention and improved treatment.

Action Plan

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

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.

The NEI anticipates that significant progress will be made in the next five years to understand the pathogenesis of vascular diseases of the retina and choroid, including diabetic retinopathy; and develop better methods of prevention and therapy.

Performance Measures

The NIH has developed a set of performance measures as a part of its Government Performance and Review Act (GPRA) assessment plan for its research program. The NIH has concluded that strictly numeric goals and measures are neither feasible nor sufficient to capture the breadth and impact of NIH's research program. Therefore, as provisioned for in GRPA, the NIH has defined research performance goals that rely on criteria that are more nearly descriptive in nature ["alternative form" assessment, Sec. 1115 (b)(1)]. These performance measures are: add to the body of knowledge about normal and abnormal biological functions; develop new or improved instrument and technologies for use in research and medicine; develop new or improved approaches for preventing or delaying the onset of disease and disability; develop new or improved methods for diagnosing disease and disability; and, develop new or improved approaches for treating disease and disability. The NEI will continue to support the very best and highest quality research on diabetic eye disease identified through the peer-review process.

Outcomes Measures

The NEI will support research that will build on the knowledge gained from its investment in the highest quality science on diabetic retinopathy and translate the findings of this research program to improved treatments and prevention strategies for the ocular complications associated with diabetes.

Training of Minority Scientists

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.

Objective

Ensure the proper resource requirements through Training/Career Development.

Action Plan

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 National Advisory Eye Council's (NAEC) 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.

Performance Measure

The NEI will monitor the number of supplements that are awarded each year to support underrepresented minorities who are pursuing careers in eye and vision research.

Outcomes Measure

The NEI will build on successful strategies that recruited underrepresented minorities into basic and clinical eye and vision research.

Minority Representation in Clinical Trials

The NEI and NAEC fully endorse and support the NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. Because the primary aim of research is to provide scientific evidence leading to a change in health policy or a standard of care, it is imperative to determine whether the intervention or therapy being studied affects women or men or members of minority groups and their subpopulations differently. To this end, the NIH guidelines are intended to ensure that all future NIH-supported biomedical and behavioral research involving human subjects will be carried out in a manner sufficient to elicit information about individuals of both genders and the diverse racial and ethnic groups and, in the case of clinical trials, to examine differential effects on such groups. Increased attention, therefore, must be given to gender, race, and ethnicity in earlier stages of research to allow for informed decisions at the Phase III clinical trial stage. The guidelines reaffirm NIH's commitment to the fundamental principles of inclusion of women and racial and ethnic minority groups and their subpopulations in research. This policy will continue to provide a variety of new research opportunities to address significant gaps in knowledge about health problems that affect women and racial/ethnic minorities and their subpopulations.

The guidelines require that when a Phase III clinical trial is proposed, evidence must be reviewed to show whether or not clinically important gender or race/ethnicity differences in the intervention effect are to be expected. This evidence may include, but is not limited to, data derived from prior animal studies, clinical observations, metabolic studies, genetic studies, pharmacology studies, and observational, natural history, epidemiology and other relevant studies.

Objective

Continue to ensure that all clinical trials that are funded by the NEI adhere to the NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research.

Action Plan

Ensure that all clinical trials funded by the NEI adhere to the NIH Guidelines on the inclusion of Women and Minorities as Subjects in Clinical Research. This will be an ongoing effort that will continue throughout the period of this plan and not incur any significant costs.

Performance Measures

The NEI will closely monitor all clinical trials and applications to assure that appropriate numbers of women and minorities are included.

Outcome Measures

The NEI will strongly enforce the tenants of the NIH Guidelines on the inclusion of women and minorities, and the NEI will communicate to clinical research applicants the need to include women and minorities in their clinical protocols.

National Eye Health Education Program

In 1989, the National Eye Institute (NEI) launched the National Eye Health Education Program (NEHEP), with the goal of increasing awareness among health care professionals and the public of scientifically based health information that can be applied to preserving sight and preventing blindness. Numerous organizations (more than 50 in all) from both the public and private sectors joined in partnership with the NEHEP. Working together, these partners attempted to reach select target audiences, informing them of the importance of early detection and treatment of eye diseases, particularly glaucoma and diabetic retinopathy, and persuading them to make an appropriate change in behavior. The NEHEP currently has three major ongoing education/outreach programs.

Objective

Continue to increase awareness among health care professionals and the public of scientifically based health information that can be applied to preserving sight and preventing blindness.

Action Plan

Participants in the NEHEP Planning conference recommended two target audiences for this Program: people with diabetes and health care professionals. They also recommended that messages be directed to family members and other groups, including educators and clergy. Subsequent phases of the Program included groups in which diabetes is more prevalent than in the general population, including Native Americans, Hispanics, and African Americans. The NEHEP has developed the Educating People with Diabetes Kit for health professionals and Ojo con su Visión (Watch Out for Your Vision), a Spanish-language booklet, designed to educate Hispanics with diabetes about the ocular complications of the disease.

Participants in the NEHEP Planning Conference identified three target audiences for glaucoma education: glaucoma patients, the general public, and health care professionals. The current general primary target groups are Blacks over age 40 and anyone over age 60. It also will be important to reach eye and other health care-related professionals to help motivate the at-risk populations to have regular eye exams. Educating the general public

is a means to ensuring long-term success. The Glaucoma Public Education Program consists of a Glaucoma Community Education Kit that community agencies can use to conduct glaucoma awareness activities and comprehensive public service campaigns emphasizing early detection.

In late 1999, the NEHEP launched a new program for the purpose of addressing the impact of low vision on those who have it and to bring the message to them, their families, and the health and service professionals who care for them that information and help are available. The two primary audiences are (1) people age 65 and older who have decreased visual function that interferes with their activities of daily living and (2) people under age 65 who are particularly at risk for low vision--i.e., Hispanic/Latino and African American populations. NEHEP is an ongoing activity of the NEI that will continue on to 2006 and beyond.

Performance Measures

The NEHEP partnership will pretest the materials that it plans to distribute with focus groups to determine the effectiveness of the materials used to communicate NEHEP's message to its target populations. An analysis of public queries to the NEI Office of Health Education, Communication, and Public Liaison will also be conducted to determine if the products that NEHEP produces are having a positive impact on the public's knowledge of eye health.

Outcome Measures

The NEHEP partnership will make changes based on the results of its evaluation of the program to ensure that the program continues to be effective in communicating to the public information about eye health and eye disease.

Healthy People 2010: Vision and Hearing Chapter

Healthy People 2010 represents the ideas and expertise of a diverse range of individuals and organizations concerned about the Nation's health. The Healthy People Consortium--an alliance of more than 350 national organizations and 250 State public health, mental health, substance abuse, and environmental agencies--conducted three national meetings on the development of Healthy People 2010. Members of the voluntary, scientific, and professional organizations that comprise the vision research community joined forces to recommend the inclusion of a section on the visual health needs of the Nation. The NEI agreed to serve as a co-lead agency and support the inclusion of a chapter on vision. Both vision and hearing were selected to share the lead of a new chapter on Vision and Hearing in Healthy People 2010. A workgroup has already been formed and the initial focus of the group is to develop the necessary data sources to assess progress in accomplishing the program's objectives.

Objective

Increase quality and years of healthy life and eliminate health disparities.

Action Plan

Increase the proportion of persons who have a dilated exam at appropriate intervals. Increase the proportion of preschool children aged 5 years and under who receive vision screening. Reduce uncorrected visual impairment due to refractive errors. Reduce blindness and visual impairment in children aged 17 and under. Reduce visual impairment due to diabetic retinopathy. Reduce visual impairment due to glaucoma. Reduce visual impairment due to cataract. Reduce occupational eye injury. Increase the use of appropriate personal protective eyewear in recreational activities and hazardous situations around the home. Increase the use of vision rehabilitation services and adaptive devices by people with visual impairments.

Healthy People 2010 is a ten-year plan to improve the health of the American people.

Performance Measures

A mid-course evaluation will be performed in 2005 to assess of the progress that has been made toward achieving the goals set forth in Healthy People 2010.

Outcome Measures

Based on the results of the mid-course review, strategies for achieving the goals of Healthy People 2010 will be adjusted to enhance the probability of achieving those goals by 2010.

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NEI Health Disparities Budget
(Dollars in Millions)

Institute / Center	FY 2002			FY 2003		
	Research	Infrastructure	Outreach	Research	Infrastructure	Outreach
NEI	\$35.30	\$3.90	\$2.30	\$38.30	\$4.20	\$2.50