

DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

A New Vision for Medical Research
(Part I)

Witness appearing before the
Senate Subcommittee on Labor-HHS-Education Appropriations

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National Eye Institute

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Mr. Chairman and Members of the Committee:

I am pleased to present the Fiscal Year (FY) 2008 President's budget request for the National Eye Institute (NEI). The FY 2008 budget includes \$667,820,000 in the President's request.

As the Director of the NEI, it is my privilege to report on the many research opportunities that exist to reduce the burden of eye disease.

AGE-RELATED MACULAR DEGENERATION

The loss of sight affects us in fundamental ways, threatening independence, mobility and quality of life. Most eye diseases strike later in life. Thus, as life expectancy has increased and the baby boom generation ages, more Americans are becoming susceptible to vision loss and blindness. One such disease, age-related macular degeneration (AMD), is the leading cause of legal blindness. Based on published study data, 8 million older-age Americans are at high risk to develop advanced AMD. AMD causes a progressive loss of central vision, making it difficult to read, recognize faces, drive a car, or perform even simple tasks that require hand-eye coordination.

ANGIOGENESIS AND AMD

Angiogenesis is the term used to describe the growth of new blood vessels. Angiogenesis plays a crucial role in the normal development and maturation of tissues. It also plays a role in many diseases, including eye diseases such as diabetic retinopathy, retinopathy of prematurity and advanced AMD. In advanced AMD, new blood vessels grow abnormally beneath the retina. These abnormal blood vessels leak blood and fluid, producing scarring and severe vision loss.

NEI-supported researchers have established that a protein called vascular endothelial growth factor (VEGF) plays an important role in triggering angiogenesis in AMD and diabetic retinopathy. Thus, VEGF is an important target for drug development. Two anti-VEGF therapies have recently been approved by the FDA for

the treatment of AMD. More recently, NEI-supported researchers have found that in animal models, combination therapies that control diverse elements of angiogenesis can completely inhibit some forms of abnormal blood vessel growth. Anti-VEGF therapies are also being evaluated in clinical trials for diabetic retinopathy. NEI and NIH have invested considerable resources in understanding and controlling angiogenesis. That investment is already paying handsome dividends.

DISEASE MECHANISMS IN AMD

Another critical area in developing treatments of AMD is to identify the causes and mechanisms of the disease early in its pathology. Researchers have long held that AMD can result from the confluence of genetic predisposition and chronic exposure to environmental risk factors, such as diet and smoking. In this scenario, a gene or genes contain subtle variations that hamper cellular function but may not necessarily cause disease directly. However, years of cumulative environmental insult can further strain the underlying genetic predisposition and trigger disease.

On the genetic side of the equation, NEI-supported investigators have identified common variations in four genes that are associated with AMD and may account for 75 percent of the risk of developing AMD. Two of these genes—complement factor H (CFH) and complement factor B (BF)—contain instructions to encode proteins that help regulate the body's immune defense against microbial infections. This defense, called the complement system, provokes inflammation, a common response to foreign pathogens. It is thought that certain variations in these genes result in sub-optimal control of the complement system and cause chronic inflammation. Chronic inflammation may damage tissues of the retina and could lead to AMD.

Chronic inflammation is thought to play a role in many other common diseases beyond the eye, such as Alzheimer's disease, Parkinson's disease, multiple sclerosis, kidney disease, stroke, and atherosclerosis. Although the cells, tissues, and molecular events in these diseases are diverse, they may share some common disease mechanisms that present an opportunity to cross pollinate findings from diverse research areas.

The genetic discovery of the possible role of inflammation and the immune system in AMD is a watershed moment. We have now uncovered a possible central disease mechanism that may lead to a better understanding of this major disease and the development of therapies that prevent vision loss. We now hold the possibility to learn an individual's risk vulnerability well before the disease is detectable clinically, and to intervene effectively, thereby preempting the disease process at its early stages.

PUBLIC HEALTH AND PREVENTION

Another critical and fruitful area of research is the development of public health strategies to prevent or delay AMD. Several epidemiologic studies, published in the 1990s, found evidence to suggest that diets rich in leafy green vegetables, which contain antioxidants, might be associated with a reduced risk of AMD. To leverage these findings, the NEI initiated a large, multi-center prospective study and clinical trial called the Age-Related Eye Disease Study (AREDS). Data from the AREDS study, published in 2001, found that over a 5 year period, a daily formulation of antioxidant vitamins and minerals (vitamins C, E, beta-carotene and zinc with copper) delayed the onset of advanced AMD by 25 percent.

An estimated 8 million older-age Americans are at high risk to develop advanced AMD and vision loss. Of these 8 million, 1.3 million will develop advanced AMD within 5 years. However, now with the successful AREDS treatment, 300,000 of these individuals could be rescued from severe vision loss associated with advanced AMD over a 5-year period. This simple and relatively inexpensive dietary intervention offers to the American public a valuable intervention to prevent severe vision loss and to reduce the need for more aggressive and expensive therapies.

On the heels of this success, the NEI launched AREDS2. One of the primary objectives of AREDS2 is to determine whether oral supplementation with lutein and zeaxanthin and/or omega-3 long-chain polyunsaturated fatty acids will further decrease the progression to advanced AMD or formation of cataract. Previous NIH-funded

studies have found high concentrations of these nutrients in the macula of the eye. Moreover, several studies have found an inverse relationship between dietary intake of these compounds and AMD. AREDS2 could result in a more effective but still inexpensive treatment regimen to prevent severe vision loss.

GENOMIC MEDICINE

AMD research is but one example of genomic medicine, the effort to diagnose and treat patients at the molecular level. Over the past 15 years, NEI-supported researchers have identified more than 450 genes that are involved in various eye and vision diseases. Considerable progress has been made in understanding the resultant disease mechanisms, and treatments are now beginning to emerge. As genomic medicine progresses, we must grapple with the obvious opportunity and challenge of genotyping individuals with eye disease and delivering therapies that are specifically tailored to the individual patient. This personalized approach to medicine is vital to improving the health of all Americans.

The NEI initiated eyeGENE to address this issue. eyeGene is an organized national network of research laboratories to support genetic testing for individuals with eye diseases. As testing services are not routinely available, the diagnostic information from eyeGENE will directly benefit such patients and families. The initiative will significantly aid vision research through a centralized registry that can be used to locate individuals who may wish to participate in clinical trials for new therapies. eyeGENE fills a critical research need that will advance the field. It includes a secure research blood collection and a centralized research repository of disease phenotype features which coupled to genes that cause disease will allow for the creation of the large datasets necessary to identify novel genetic risk factors and other epidemiologic questions. Programs like eyeGENE will drive genomic research and become the necessary fabric for individuals to benefit from advances in genomic medicine.

ADDITIONAL ADVANCES

Recently, a number of developments have added further excitement to the field of vision research. The NEI is supporting projects that address the possible restoration of vision in blinding retinal degenerative diseases by building on recent advances in cell transplantation and precursor cell biology, including the use of bone marrow stem cell transplantation, and on "re-engineering" the production of light-sensitive proteins in retinal neurons.

Research will continue in efforts to control angiogenesis in a number of eye diseases, and will include the conduct of clinical trials in this area. In support of this research is the Diabetic Retinopathy Clinical Research Network (DRCR.net). This collaborative network, supported by the NEI, is dedicated to facilitating multicenter clinical research on diabetic retinopathy, diabetic macular edema and associated conditions. The DRCR.net supports the identification, design, and implementation of multicenter clinical research initiatives focused on diabetes-induced retinal disorders. Principal emphasis is placed on clinical trials, but epidemiologic outcomes and other research may be supported as well. The DRCR.net was formed in September 2002 and currently includes more than 150 participating sites (offices) with more than 500 eye care providers throughout the United States. The success of this new model for bringing improved treatments for diabetic retinopathy more rapidly to patients is dependent upon the active participation of clinical research centers across the U.S., as well as the participation of the patients they treat.

Program plans for FY 2008 include pursuing the research finding of several genes involved in Leber's Hereditary Optic Neuropathy, a genetic disease that frequently results in a substantial loss of central vision. The development of animal models carrying these mutations could lead to successful gene-based therapy for this disease. Research will also pursue remarkable new findings about how the activity of certain brain cells allows us to perceive a stable view of our surroundings despite constant head and eye movements, as highlighted in NEI's strategic plan. This research will help us to understand better the neural control of eye movements and associated disorders, and may have applicability in other sensory systems.

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NATIONAL INSTITUTES OF HEALTH
NATIONAL EYE INSTITUTE
BIOGRAPHICAL SKETCH

PAUL A. SIEVING, M.D., Ph.D.

Director, National Eye Institute, National Institutes of Health, 2001
Member, Institute of Medicine of the National Academies

Education:

B.A., Valparaiso University (Physics with honors), 1970
M.S., Yale University Graduate School (Physics), 1973
Yale Law School, 1973-1974, leave of absence
M.D., University of Illinois Medical School, 1978
Ph.D., University of Illinois (Biomedical Engineering), 1981

Licensure:

National Board of Medical Examiners, 1978
American Board of Ophthalmology, 1983
Medical License: IL, 1978; CA, 1982; MA, 1984; MI, 1985

Professional Experience:

Medical Internship and Ophthalmology Residency, University of Illinois Hospital, 1978-1982. Postdoctoral Fellowship in Retinal Physiology, University of California, San Francisco, 1982-1984. Medical Fellowship in Inherited Retinal Degenerations, Massachusetts Eye and Ear Infirmary, Harvard Medical School, 1984-1985. Faculty, Medical School and Rackham Graduate School, University of Michigan, 1985- 2001.

Academic Appointments and Experience:

At the University of Michigan: Assistant Professor of Ophthalmology, 1985-1989. Faculty, Rackham Graduate School Programs in Neuroscience, 1985-2001; Bioengineering Program, 1985-2001. Associate Professor of Ophthalmology, 1989-1994. Founding Director, Center for Retinal and Macular Degenerations, 1990-2001. Founding Director, Ophthalmic Molecular Diagnostics CLIA Laboratory, University of Michigan, 1999-2001. Professor of Ophthalmology and Visual Sciences, 1994-2001. The Paul R. Lichter Professor of Ophthalmic Genetics, 1990-2001. Director, National Eye Institute, NIH, 2001-present.

Professional Organizations:

Association for Research in Vision and Ophthalmology. International Society for Clinical Electrophysiology of Vision. American Academy of Ophthalmology. American Medical Association. American Ophthalmological Society. Society for Neuroscience. American Society of Human Genetics. Bressler Vision Award Committee. Champalimaud Foundation Award Committee, Portugal.

Honors and Awards:

James Scholar Award and Leon F. Moldavsky Physiology Award, University of Illinois Medical School. Fight-for-Sight Research Award. Career Development Award, National Retinitis Pigmentosa Foundation. Olga Keith Wiess Scholar, Research To Prevent Blindness. Distinguished Alumnus Award, Valparaiso University. American Ophthalmological Society. The Foundation Fighting Blindness, Scientific Advisory Board. Senior Scientific Investigator Award, Research to Prevent Blindness. Alcon Award. Doctor of Science (honorary), Valparaiso University, 2003. The Best Doctors in America. Academia Ophthalmologica Internationalis, elected 2004. Pisart Vision Award, 2005, Institute of Medicine of the National Academies, elected 2006.