NEI

50YEARS

of Advances in Vision Research

NIH National Eye Institute

From the director

The National Eye Institute was established by Congress in 1968 with an urgent mission: to protect and prolong vision. At the time, millions of Americans were going blind from common eye diseases and facing isolation and a diminished quality of life.

Over the past 50 years, public investment in vision research has paid remarkable dividends. Research supported by NEI and conducted at medical centers, universities, and other institutions across the country and around the world—as well as in laboratory and clinical settings at the National Institutes of Health—has led to breakthrough discoveries and treatments.

Today, many eye diseases can be treated with sight-saving therapies that stabilize or even reverse vision loss. NEI-supported advances have led to major improvements in the treatment of glaucoma, uveitis, retinopathy of prematurity, and childhood amblyopia. We have more effective treatments and preventive strategies for age-related macular degeneration and diabetic retinopathy. Recent successes in gene therapy and regenerative medicine suggest the future looks even brighter for both rare and common eye diseases.

Basic research has revealed new insights about the structure and function of the eye, which also offers a unique window into the brain. In fact, much of what we know about how the brain works comes from studies of the retina. Decades of NEI research on retinal cells has led to fundamental discoveries about how one nerve cell communicates with another, how sets of cells organize into circuits that process different kinds of sensory information, and how neural tissue develops and organizes itself.

People with vision impairment can take advantage of assistive technologies that help them work, read, navigate their home or city, and otherwise remain productive. Many of these technologies have been developed with NEI funding. Ongoing research continues to improve the available options—from prosthetic devices to prism glasses to electronic navigation aids.

This is a remarkable time of discovery. We can view the functioning eye in greater and greater detail and gain a better understanding of the biology, at the level of cells, genes, and proteins, that makes vision possible—and how things can go wrong with disease or trauma.

In this booklet, we provide highlights of key discoveries, initiatives, and clinical trials that over the years have had an impact on the diagnosis and treatment of eye diseases and conditions.

As we look toward the future, I am hopeful we will one day be able to reverse blindness. I believe that our commitment to vision research will get us there.

Paul A. Sieving, M.D., Ph.D.
Director
National Eye Institute

Contents

Making vision a public health priority

The creation of the National Eye Institute (NEI) was a turning point in the treatment of eye disease. At the time of NEI's founding in 1968, cataracts were one of the few blinding eye diseases in the United States that could be treated effectively. However, patients with diseases such as glaucoma, macular degeneration, and diabetic retinopathy were facing a life with progressive loss of vision. Meanwhile, doctors were diagnosing children with inherited forms of blindness, for which there was no treatment.

Millions of Americans were going blind from incurable eye diseases. As a result, patient communities; advocacy groups; and vocal supporters, such as Jules Stein, M.D., Alfred Edward Maumenee Jr., M.D., and Ralph W. Ryan, M.D., convinced members of Congress that this constituted a major public health problem and that action had to be taken.

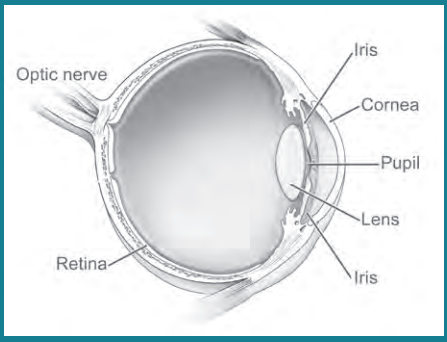
Once NEI was established, the government's investment in vision research provided a steady source of funding to a growing vision research community. For institutions around the country, vision was the focus of discovery research and clinical trials, which elevated the field of ophthalmology among medical specialties.

Fifty years later, NEI continues to pioneer cutting-edge vision research. From supporting the development of drug and biotechnology therapies for age-related macular degeneration (AMD) and diabetic eye disease, to successfully developing gene therapy to treat an inherited form of blindness, to funding assistive technologies that preserve quality of life among those with low vision, NEI improves lives.

The unique features of the eye make it a window into a person's health. During an eye exam, a doctor can see indications of diabetes, high blood pressure, or high cholesterol. The appearance of the eye can also predict cardiovascular disease, multiple sclerosis, or Alzheimer's disease.

The benefits of studying the eye have fostered collaboration among vision scientists, neuroscientists, and researchers studying chronic disease and aging. Basic research into the structure and function of the visual system has helped scientists understand the various elements involved in disease; that is, the cells, molecules, and individual genes and proteins. An increasingly detailed understanding of blinding diseases has led to treatments that prevent eye disease and halt the progression of vision loss.

Today's most common blinding eye diseases include:



- **Age-related macular degeneration** – a disease that damages the macula, the central point of the retina with a high density of light-detecting neurons needed for sharp, central vision
- **Cataracts** – a clouding of the lens of the eye that obstructs the passage of light
- **Diabetic retinopathy** – a complication of diabetes, caused by the abnormal growth and leaking of blood vessels in the retina
- **Glaucoma** – a group of diseases that can damage the eye's optic nerve and result in vision loss and blindness

Ophthalmologist and entertainment magnate Jules Stein, M.D., leads testimony in support of establishing the National Eye Institute at a congressional hearing in 1967.
Illustration courtesy of Research to Prevent Blindness

Attendees convene at the first meeting of the National Advisory Eye Council, April 3–4, 1969. Pictured in the front row, from left: Dr. Glenn Fry, Dr. Edward MacNichol Jr., Dr. Meredith Morgan, and Dr. V. Everett Kinsey; second row, from left: Dr. Kenneth Swan, Dr. Bernard Becker, Dr. David Cogan, and Dr. Noble David; and third row, from left: Dr. James Culver, Dr. John Harris, Dr. John Ferree, Dr. George Smelser, and Dr. Jules Stein. *National Eye Institute, National Institutes of Health (NEI/NIH)*

Helping people with low vision

Low vision is an impairment that cannot be corrected with surgery, glasses, or contact lenses and that hampers people's ability to go about their daily lives. Low vision may involve loss of sharpness or reduced field of vision and may be caused by diseases, such as retinitis pigmentosa or glaucoma, or by a neurological injury due to stroke, trauma, or tumors. Whatever the cause, mobility and navigation are seriously affected, and many individuals with low vision become isolated due to their concern about colliding with other people or objects.

In 1978, NEI established a program dedicated to finding the best approaches to managing severe visual impairment. Over the years, NEI has supported the development of assistive devices and technologies to help people with low vision in reading, writing, navigation, and mobility so that they can remain productive and maintain their independence and quality of life.

Establishing the National Eye Institute

On August 2, 1968, the U.S. Congress passed Public Law 90-489, authorizing the formation of NEI as part of the National Institutes of Health (NIH). President Lyndon B. Johnson signed this legislation two weeks later, and on December 26, 1968, NEI began operations as the first government organization dedicated solely to research on human visual diseases and disorders.

The first step in establishing an administration for the new Institute was appointing an advisory council. Once formed, the National Advisory Eye Council, made up of 12 nationally recognized leaders in ophthalmology, optometry, and basic sciences, embarked on a national search for a director. They selected Carl Kupfer, M.D., chair of ophthalmology at the University of Washington Medical School in Seattle.

The council developed a series of strategic plans that surveyed research efforts in the field and recommended actions necessary to stimulate work in gap areas. In addition, they reviewed and recommended research and training grant applications in the field of vision research.

Simply stated, the mission of NEI was, and still is, to prevent, diagnose, and treat diseases of the visual system, with the goal of preventing and potentially eliminating blindness. To perform its mission, NEI began recruiting top scientists and clinicians to the state-of-the-art facilities at the NIH research campus in Bethesda, Maryland. These scientists would become part of the NEI intramural research program. They would conduct high-risk, high-reward research with access to the world-class NIH Clinical Center, where patients from all over the globe, often with very rare diseases, came to NIH to participate in first-of-their-kind studies.

Prior to the establishment of NEI, the National Institute of Neurological Diseases and Blindness funded eye research at NIH, maintaining a small portfolio of eye-related research grants. As NEI spun off into its own institute, it built on that portfolio, funding research at university laboratories, medical schools, and teaching hospitals around the country. This launched NEI's extramural program, whose grants today account for 85 percent of NEI's budget.

As the new NEI director, Kupfer expanded the scope of the Institute to study the entire visual system, not just the eye. Under his leadership, scientists would conduct research into the neuronal connections that transmit light from the eye to the brain and into the pathologies that cause eye disease.

In 1970, the National Advisory Eye Council selected Carl Kupfer, M.D., as the first NEI director. *National Eye Institute, National Institutes of Health (NEI/NIH)*

NEI Director Paul A. Sieving, M.D., Ph.D., has set new, ambitious, and urgent goals for the visual sciences. *National Eye Institute, National Institutes of Health (NEI/NIH)*

NEI's extramural program, which began with one vision research program, now comprises 10 programs. These programs include research on the retina, cornea, lens, and visual processing; research into conditions such as glaucoma and low vision; clinical research; and research training and resources. Under the leadership of the current NEI director, Paul A. Sieving, M.D., Ph.D., the extramural portfolio expanded to include new topic areas such as genetics, ocular inflammation, and myopia. The portfolio also includes grants that support basic and translational research, small business innovation research, and research infrastructure. There is also an emphasis on developing the next generation of vision researchers through individual fellowships, clinician-scientist career development, and institutional research training. Through these efforts, NEI fosters scientific breakthroughs at the frontiers of vision research.

The NEI Division of Extramural Research awards about 1,500 research and training grants every year.

Early success in clinical trials improves patient care

Today, the randomized clinical trial is considered the gold standard for testing the safety and efficacy of new treatments in patients. Such a study requires that participants be divided randomly into separate groups to compare different medications, treatments, or interventions. The NEI Division of Epidemiology and Clinical Applications was instrumental in designing clinical trial methods that are now standard practice. For example, testing whether a new drug prevents vision loss does not have to take years. Clinical trials can use surrogate biomarkers and endpoints, such as vision on an eyechart, to determine whether a treatment works. They also can analyze retinal images instead of using subjective exams to evaluate the results of a trial more quickly.

In the early 1970s, the first NEI clinical trials addressed diabetic retinopathy, a disease characterized by the abnormal growth and leaking of blood vessels in the retina. This condition affected approximately 300,000 Americans in 1975. NEI initiated a multicenter clinical trial to test the safety and effectiveness of photocoagulation, a procedure that uses a laser beam to shrink or destroy abnormal blood vessels. The study treated more than 1,700 patients at 16 U.S. medical centers. Initially intended to last five years, NEI ended the study early because the procedure quickly demonstrated its effectiveness in mitigating vision loss.

The Early Treatment Diabetic Retinopathy Study, which began in 1979 as a follow-up to the initial clinical trials, established the optimal conditions to introduce lasers and other medical therapies for diabetic retinopathy. The study identified procedures that gave patients with advanced retinopathy a 95 percent chance of maintaining vision by preventing new blood vessel growth.

IN 1975, APPROXIMATELY

300,000

AMERICANS HAD DIABETIC RETINOPATHY, AN EYE CONDITION THAT CAN LEAD TO **BLINDNESS.**

IN RESPONSE, NEI DEVELOPED CLINICAL TRIALS TO TEST MEDICAL THERAPIES USED TO TREAT **MORE THAN**

1,720

PATIENTS.

BY 1979, SEVERAL ROUNDS OF CLINICAL TRIALS HAD ESTABLISHED PROCEDURES THAT GAVE PATIENTS WITH ADVANCED RETINOPATHY A

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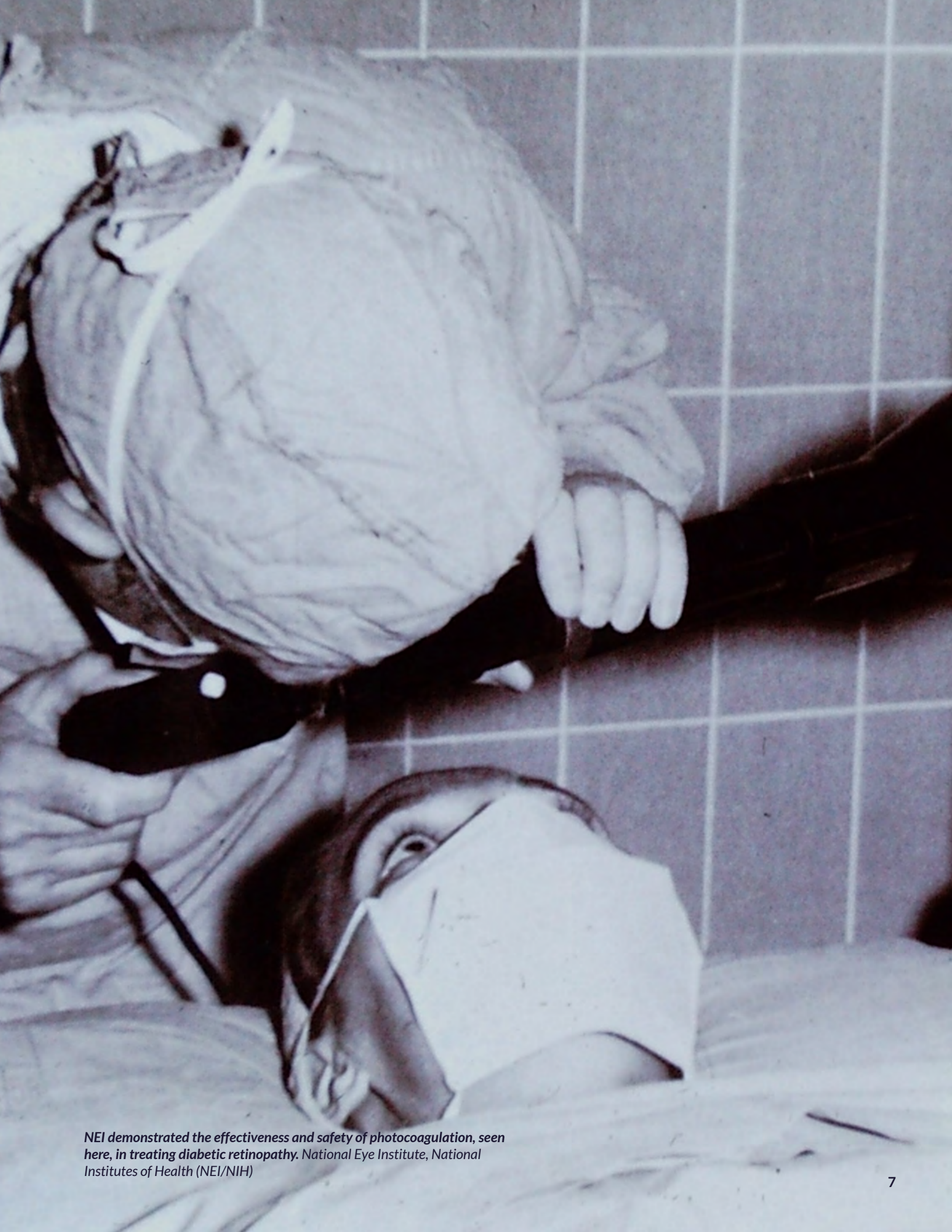
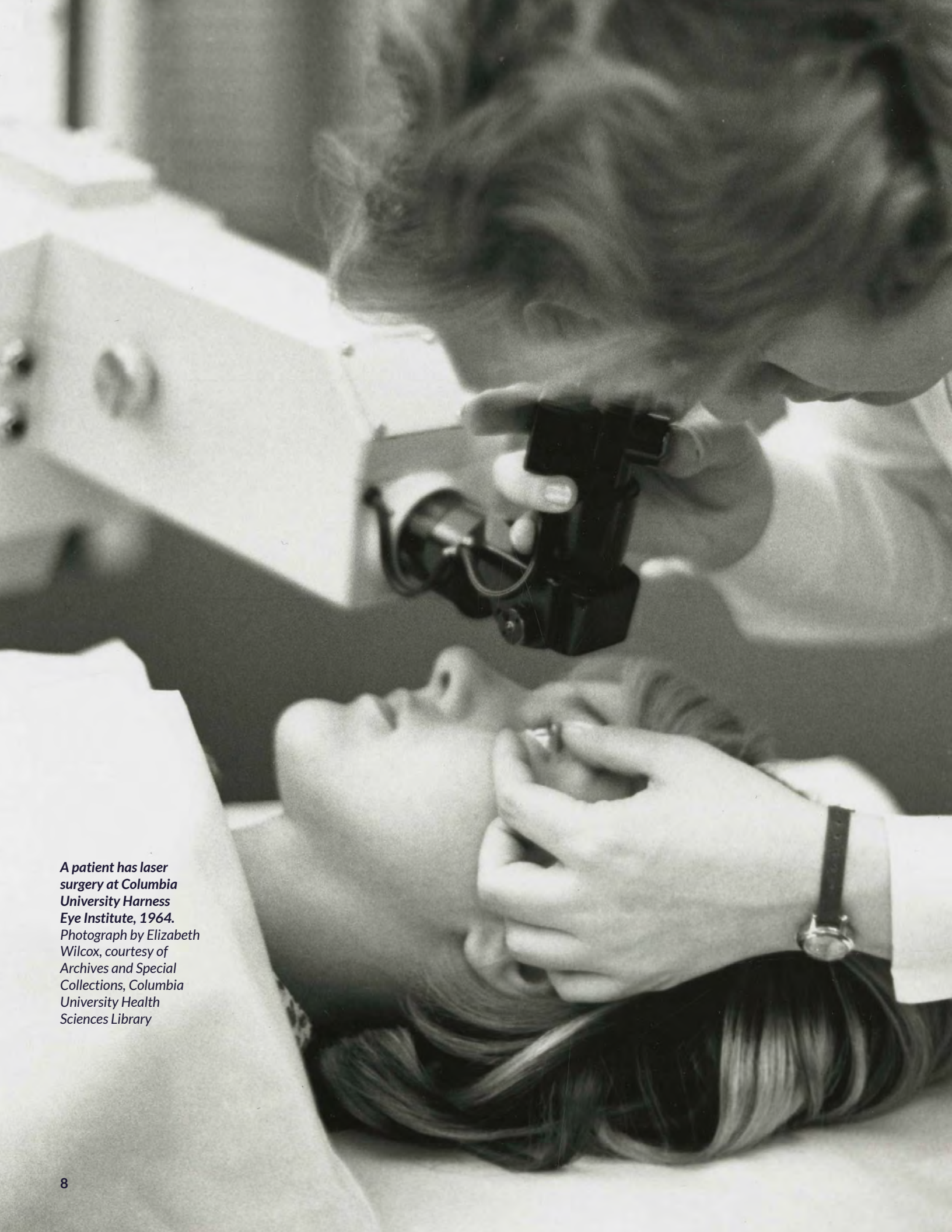


NEI demonstrated the effectiveness and safety of photocoagulation, seen here, in treating diabetic retinopathy. *National Eye Institute, National Institutes of Health (NEI/NIH)*



A patient has laser surgery at Columbia University Harness Eye Institute, 1964. *Photograph by Elizabeth Wilcox, courtesy of Archives and Special Collections, Columbia University Health Sciences Library*

Lasers have become an indispensable tool for vision care. As a bladeless tool, lasers are now used for refractive surgery (e.g., LASIK), to correct nearsightedness, and cataract surgery, as well as to repair retinal tears before they become detachments. With the success of laser therapies for diabetic retinopathy, clinicians considered applying the technique to other retinal diseases involving abnormal blood vessels, including AMD. That condition is characterized by the deterioration of the macula—the central part of the retina—and vision loss. In 1979, NEI launched the Macular Photocoagulation Study, intended to continue for five years, to determine whether laser photocoagulation treatment could prevent or delay visual acuity loss in patients with AMD. Like the diabetic retinopathy study, NEI halted the AMD study after only three years because it demonstrated the vision-saving capabilities of photocoagulation. Similarly, laser therapy is effective for retinal vein occlusion, a blinding disease caused by the blockage of small veins in the retina.

By 1990, the Glaucoma Laser Trial established that laser therapy was safe and effective for the treatment of open-angle glaucoma. Glaucoma is a major cause of blindness stemming from the progressive degeneration of the optic nerve, which transmits neural signals from the eye to the brain. In the most common form, open-angle glaucoma, normal drainage of fluid in the eye is inhibited, leading to a harmful buildup of pressure in the eye (ocular hypertension). Treatment options now include medicated eye drops and surgery, as well as laser therapy. Each of these treatments helps the eye drain fluid, reducing the pressure buildup and, in turn, reducing the number of neurons that die in the optic nerve.

Reducing blindness through disease prevention

Benjamin Franklin, who invented bifocal glasses, is famous for saying, “An ounce of prevention is worth a pound of cure.” Over the past 50 years, the prevalence of blinding diseases has shifted. Some diseases have an increased burden, largely due to an aging population, but others that were once major public health issues can now be effectively treated or prevented. For example, trachoma, an infectious corneal disease, was once a leading cause of blindness in the United States and worldwide. The development of preventive measures, such as antibiotic treatment and improved sanitation, has since eradicated trachoma in this country.

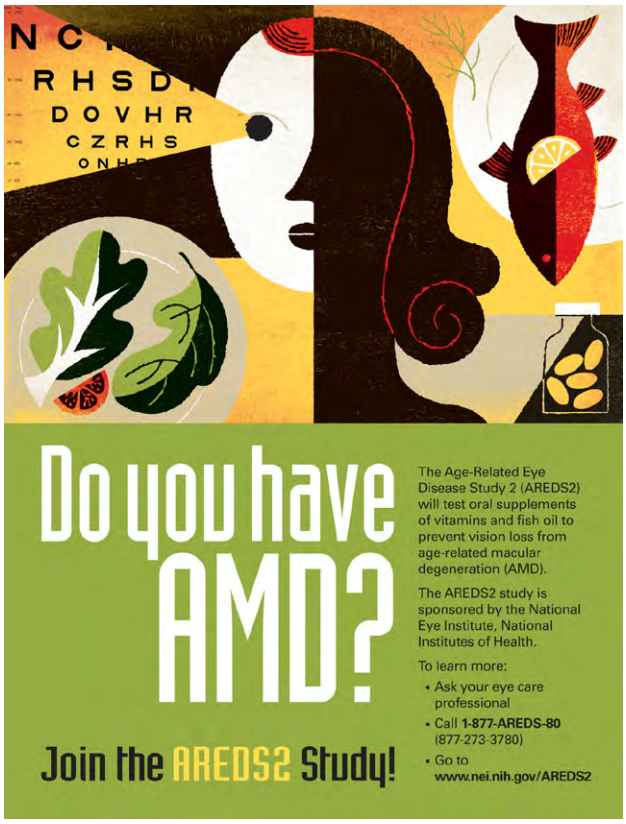
Another example of preventive measures at work involves retinopathy of prematurity (ROP), which was a leading cause of irreversible blindness in children in the 1950s. The condition resulted when oxygen administered to very premature babies in incubators caused toxicity to the retina. Research showing how to optimize the timing and concentration of oxygen rapidly reduced the incidence of ROP. Between 1952 and 1958, the number of cases dropped drastically, from 1,900 to only 28, a statistic cited in congressional hearings on the need for a national institute devoted to vision and the eye in 1968.

Later NEI trials identified therapies to treat ROP. Prompt ROP diagnosis and treatment is critical for preventing blindness. Today, patients living in some rural and underserved areas lack access to trained pediatric ophthalmologists. In 2014, an NEI telemedicine trial called the e-ROP Study demonstrated that retina photographs electronically transmitted to trained technicians for remote screening could correctly identify ROP 98 percent of the time.

During the AIDS epidemic in the 1980s, opportunistic eye infections—infections that occur because of a weakened immune system—such as cytomegalovirus retinitis led to a potentially blinding inflammation in up to 40 percent of AIDS patients. NEI initiated the Longitudinal Study of Ocular Complications of AIDS in 1998 to observe the effects of antiviral agents in 2,392 participants. The study monitored the prevalence of complications as antiretroviral therapies were administered to patients. With the development of highly active antiretroviral therapy to treat HIV, the prevalence of ocular complications of AIDS dropped sharply.

NIH-sponsored epidemiological studies led to the growth of preventive medicine as a field by the late 1980s. From its beginning, NEI conducted its own epidemiological studies. The first, the Framingham Eye Study, carried out between 1971 and 1974, examined how social and environmental factors, such as smoking and alcohol consumption, contributed to the risk of age-related eye diseases. The Baltimore Eye Survey, conducted in the early 1980s, found that African Americans were more than six times as likely as whites to have visual impairment due to open-angle glaucoma. African Americans also had nearly double the impairment from unoperated cataracts.

The Wisconsin Epidemiologic Study of Diabetic Retinopathy and the Beaver Dam Eye Study also made major contributions to understanding the natural progression of diabetic retinopathy, cataracts, and AMD. These epidemiological studies paved the way for NEI to test the effectiveness of nutritional supplements and medical treatments among communities at risk. Two of these studies—the Age-Related Eye Disease Study (AREDS) and the Ocular Hypertension Treatment Study—have transformed ophthalmic medicine.



The Age-Related Eye Disease Study (AREDS) led to a formulation of dietary supplements to help prevent advanced forms of age-related macular degeneration. *National Eye Institute, National Institutes of Health (NEI/NIH)*

Initiated in 1993, AREDS examined the clinical course and prognosis for cataracts and AMD—as well as risk factors, such as obesity, smoking, and diet—among more than 4,700 participants aged 55 to 78. Researchers specifically tested combinations of dietary supplements that had the potential to prevent either disease. Although researchers did not find any supplements to prevent cataracts, in 2001, they announced a preventive formulation for advanced forms of AMD. A high-dose combination of vitamin C, vitamin E, beta-carotene, zinc, and copper reduced disease progression and the likelihood of vision loss by 25 percent in AMD patients. In a follow-up study, lutein and zeaxanthin replaced beta-carotene, after researchers determined that beta-carotene could increase cancer risk in smokers.

Former Secretary of Health and Human Services Louis W. Sullivan, right, receives an eye exam at Howard University Hospital to promote the launch of the National Eye Health Education Program, 1989. *National Eye Institute, National Institutes of Health (NEI/NIH)*

Preventing blindness through education

In 1988, Congress directed NEI to "increase its commitment to the prevention of blindness through public and professional education programs and the encouragement of regular eye examinations." In response, NEI established the National Eye Health Education Program (NEHEP), which oversees education programs on eye disease, low vision, and vision and aging. NEHEP educates providers and patients about prevention strategies such as early disease detection through regular comprehensive eye exams.

In 1994, NEI initiated the Ocular Hypertension Treatment Study to prevent or delay glaucoma. The study enrolled 1,500 individuals with elevated ocular pressure, but whose condition had not progressed to the optic nerve damage characteristic of glaucoma. The group included 400 African-American participants because of their high risk for glaucoma. By 2002, results from the study had led to new guidelines covering when to initiate treatment for ocular hypertension. Two years later, the study confirmed that eye drops reduced the incidence of glaucoma among African Americans by 50 percent. A 20-year follow-up study is underway to determine the long-term impact of this treatment.

One NEI study demonstrated that eye drops reduced the incidence of glaucoma among African Americans by 50 percent.

A History of the National Eye Institute

The National Eye Institute (NEI) celebrated its 50th anniversary in 2018! Take a look back at the progress made in diagnosing and treating eye disease and vision impairment over the last 50 years.

Carl Kupfer, M.D., becomes the first director of NEI.

The **Diabetic Retinopathy Study** finds laser therapy to be an effective treatment for diabetic retinopathy.

1968

1970

1971

1976

1978

Congress mandates the establishment of NEI to protect and prolong the vision of the American people.

NEI begins **major clinical trials** to find an effective treatment for **diabetic retinopathy**.

NEI begins the **Framingham Eye Study** to examine how social and environmental factors, such as smoking and alcohol consumption, contribute to the risk of age-related eye diseases.

NEI establishes a **low vision program** dedicated to finding the best approaches for managing severe visual impairment.

Neurophysiologists **David Hubel, M.D., and Torsten Wiesel, M.D., receive the Nobel Prize** for work, much of it supported by NEI, illuminating how the brain processes visual signals and how the brain develops and is organized.

1981

1983

The **Macular Photocoagulation Study** establishes laser therapy as an effective treatment for advanced wet macular degeneration.

NEI supports research to isolate and characterize the **retinoblastoma gene**, the first tumor-suppressor gene scientists identified.

1987

1990

The **Glaucoma Laser Trial** demonstrates that laser therapy may be a safe and effective first treatment for patients with newly diagnosed open-angle glaucoma.

Peter Agre, M.D., discovers **aquaporin**, the first known channel facilitating the transport of water between cells. He later wins the Nobel Prize in Chemistry for this discovery.

1991

NEI clones the ***RPE65* gene**, a protein that helps process vitamin A in the visual cycle. This eventually leads to the first FDA-approved human gene therapy for vision disorder.

NEI establishes the **Pediatric Eye Disease Investigator Group** to facilitate multicenter clinical trials on strabismus, amblyopia, and other pediatric eye disorders.

Paul A. Sieving, M.D., Ph.D., becomes the new NEI director.

The **Age-Related Eye Disease Study (AREDS)** finds that high levels of antioxidants and zinc dietary supplements significantly reduce the risk of advanced age-related macular degeneration and its associated vision loss.

1997

2001

2006

1993

2000

2002

NEI-funded researchers solve the 3-D structure of **rhodopsin**, the light-sensitive protein that makes vision possible.

NEI establishes the **Diabetic Retinopathy Clinical Research Network**, which comprises academic research centers and community clinics across 49 states, to develop new therapies for diabetic eye disease.

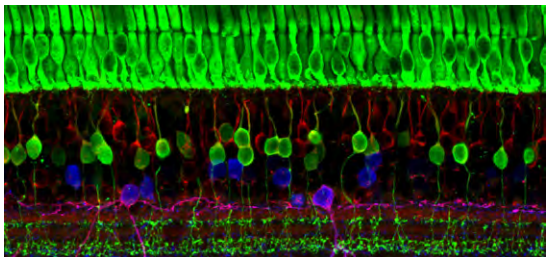
2008

The first application of **new genomics tools** identifies a common gene variant underlying age-related macular degeneration.

2013

NEI launches the National Ophthalmic Disease Genotyping and Phenotyping Network (**eyeGENE®**) to facilitate research into the causes of rare inherited eye diseases and accelerate pathways to treatments.

2014



Neurons and neural connections in the eye and visual system

NEI's **Audacious Goals Initiative** catalyzes research to restore vision through neuroregeneration of the retina.

The **Argus® II retinal prosthesis** becomes the first implanted device that allows patients with an inherited form of blindness to regain partial vision.

2015

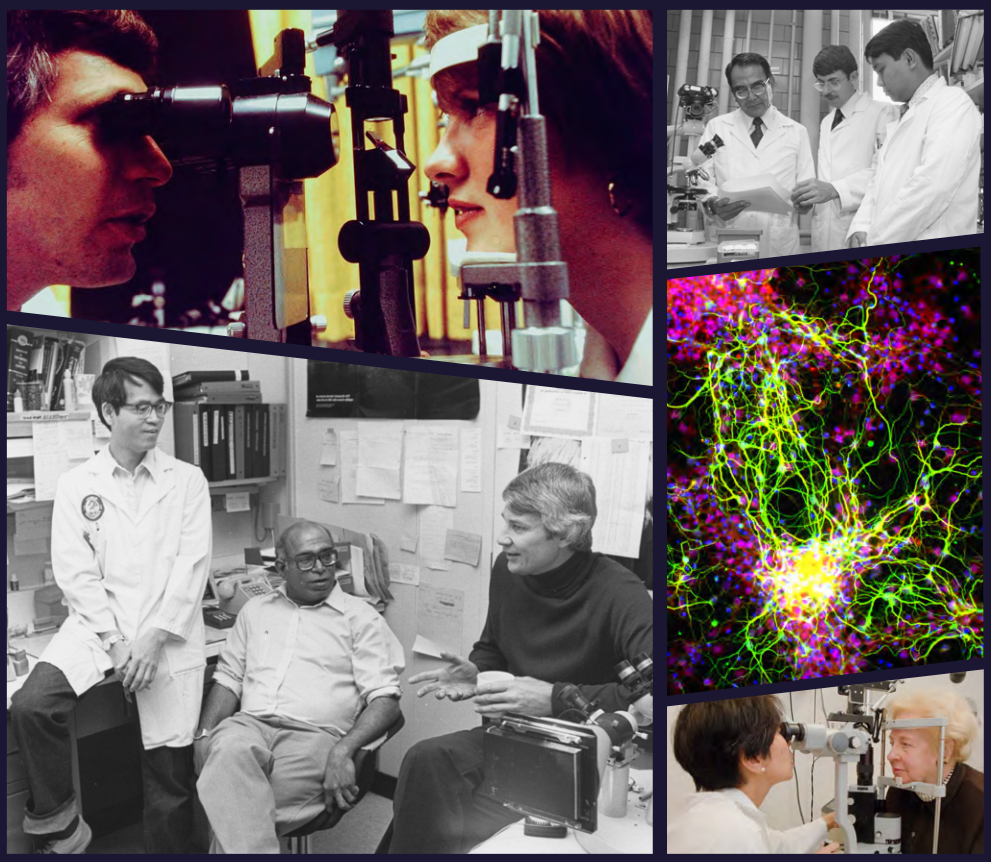
Researchers determine anti-VEGF drugs are effective in **reversing lost vision in advanced cases of diabetic retinopathy.**

2017

An NEI telemedicine clinical trial demonstrates that **remote screening can effectively diagnose retinopathy of prematurity**, a blinding disease in very premature infants, expanding eye care options for rural and underserved communities.

NEI establishes the **NEIGHBOR** (**NEI G**laucoma **H**uman genetic colla**BOR**ation) consortium to identify genetic variants associated with primary open-angle glaucoma.

NEI launches the **3-D Retina Organoid Challenge** to spur the development of a robust 3-D retina organoid system.



Anti-VEGF therapies: The search for "Factor X" yields effective treatments for major blinding diseases

As the name suggests, age-related macular degeneration (AMD) affects older adults; its prevalence increases after the age of 50. AMD produces a progressive, often severe loss of vision. Visual tasks like reading, driving a car, or recognizing faces become increasingly difficult as the disease progresses. NEI-funded genetic and epidemiological studies have shown that genetic factors, poor diet, and tobacco use increase a person's risk of developing AMD later in life.

One form of AMD, termed "wet AMD," is characterized by the abnormal growth of blood vessels in the back of the eye. The growth of these blood vessels, termed neovascularization, damages the retina and brings about a rapid and severe loss of vision.

The harmful consequences of ocular neovascularization are not limited to AMD; this destructive process promotes the growth of abnormal, leaky blood vessels that contribute to vision loss in other blinding diseases, including diabetic retinopathy and ROP.

In 1948, ophthalmologist I. C. Michaelson theorized that a soluble molecule might bring about the process of blood vessel formation involved in neovascularization. In the decades that followed, researchers referred to this unidentified agent as "Factor X." NEI-funded research throughout the 1980s and 1990s allowed vision scientists and ophthalmologists to explore the physiological factors that promote neovascularization in patients with diabetic retinopathy, AMD, and ROP.

A breakthrough in the hunt for "Factor X" occurred in the early 1990s, when molecular biologist Napoleone Ferrara isolated the protein vascular endothelial growth factor (VEGF) and described its role in the formation of blood vessels. Tissues naturally produce VEGF during development—or in response to damage—to promote the growth of new blood vessels. However, some diseases increase VEGF release, causing harmful vessels to form. It followed that inhibiting the activity of VEGF would block blood vessel growth. With VEGF clearly identified as a target of therapy, pharmaceutical and biotechnology companies focused their efforts on designing agents to block VEGF activity.

In 2004, the U.S. Food and Drug Administration (FDA) approved the anti-VEGF therapy Macugen® for use in treating AMD. Two years later, the FDA approved another compound, Avastin®, to treat neovascularization in cancer. Doctors soon began using Avastin® in smaller doses to treat AMD, as well. Since then, other anti-VEGF drugs for AMD have hit the market, including LUCENTIS® and EYLEA®.

NEI clinical trials have compared the safety and effectiveness of these anti-VEGF therapies for treating AMD, showing that these drugs not only prevent further vision loss, but in many cases restore vision that already has been lost. NEI supports the Diabetic Retinopathy Clinical Research Network, which facilitates multicenter clinical research on diabetic retinopathy, AMD, hereditary retinal degenerations, and other retinal diseases. The Network compared Avastin, LUCENTIS, and EYLEA in a clinical trial, demonstrating they are also very effective for treating diabetic retinopathy, largely supplanting the use of lasers as a first-line treatment. These NEI trials also explored how often patients should receive treatment and showed that using ocular coherence tomography as an imaging technique can facilitate personalized treatments for individual patients.

Although not a cure, anti-VEGF therapies have revolutionized the treatment of diseases such as wet AMD and diabetic retinopathy, preserving vision for hundreds of thousands of patients. The substantial progress made in treating ocular neovascularization required decades of research and the efforts of scientists, ophthalmologists, and patients. As the search for improved therapies progresses, NEI will continue to support the translation of new scientific discoveries into better outcomes for patients.

Uveitis: Controlling immune reactions in the eye

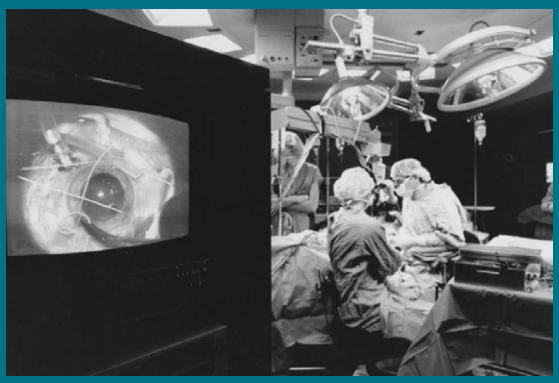
The blood vessel-rich middle layer of the eye, called the uvea, supplies nutrients and immune cells to nourish and repair the eye. Inflammation of the uvea, called uveitis, is a significant cause of blindness worldwide. In the United States, uveitis affects an estimated 2 million Americans and is responsible for 30,000 new cases of blindness each year. Uveitis can strike at any age; three-quarters of uveitis patients are between 20 and 60 years old. Uveitis symptoms include blurred vision, eye pain, redness or inflammation of the eye, and sensitivity to light.

Ophthalmologists identify uveitis as infectious or noninfectious. Bacteria, viruses, or parasitic organisms can trigger inflammation associated with infectious uveitis. In the United States, noninfectious uveitis is more common. It can result from an eye injury or a disease somewhere else in your body. Uveitis also can occur in healthy individuals. Autoimmune uveitis occurs when a patient's immune system loses control and attacks and destroys healthy cells within the eye. In 2005, NEI formed a working group of international uveitis specialists. Their efforts led to the Standardization of Uveitis Nomenclature (SUN) Project. SUN gives physicians worldwide a uniform framework for diagnosing the disease, leading to improved patient care.

Corneal transplants and beyond

The cornea is the clear, outermost surface of the eye, which both serves to protect the eye and to focus the entry of light into the retina. It is devoid of blood vessels and has immune privilege—immune reactions that normally attack harmful invaders are relatively muted in the eye. The cornea is thus an ideal organ for transplantation. In corneal transplant surgery, a surgeon removes the damaged portion of a patient's cornea and replaces it with healthy donor tissue to treat burns, scarring, and advanced cases of corneal disease.

Corneas are the most commonly transplanted tissue worldwide. In 2014, surgeons performed more than 47,000 corneal transplants in the United States. The first successful corneal transplant occurred in 1905. The first eye bank maintaining a supply of corneas for transplant opened in 1944. Yet, a limited supply of donor corneas means that not every patient who could benefit from the surgery is able to have it. The NEI Corneal Donor Study demonstrated that corneas from donors up to 75 years of age had similar rates of survival as tissue from younger donors, greatly expanding the pool of eligible donors. NEI clinical trials have introduced new transplantation techniques, minimizing risks of surgery. NEI also supports the development of artificial corneas made of polymers, expanding the options for patients.



Ophthalmologists perform corneal transplant surgery at Columbia University, 1989. *Photograph by Rene Perez, courtesy of Archives and Special Collections, Columbia University Health Sciences Library*

Identifying the factors that initiate ocular inflammation has been a paramount goal for scientists and clinicians working to improve treatments for uveitis. In the late 1970s, NEI-funded scientists isolated and characterized the S antigen protein and demonstrated its ability to trigger uveitis in guinea pigs. Over the next decade, NEI scientists developed rodent models of uveitis that provided crucial insight into the genes, proteins, and immune cells that initiate and perpetuate the inflammatory processes in the eye. These animal models have allowed vision researchers to shed light on the complex interactions of the immune system in a controlled and reproducible way, revealing novel players in the inflammatory process. The models have also guided strategies to identify improved drugs and other therapeutic agents to help bring intraocular inflammation under control.

Since the 1950s, doctors have used drugs called corticosteroids to treat uveitis. These drugs suppress the immune system reaction responsible for inflammation. However, because these drugs affect the immune system all over the body, they cause many side effects, including osteoporosis and high blood pressure, when used on a long-term basis.

The search for safer and more effective drugs to combat inflammation has led ophthalmologists to evaluate new categories of drugs developed to treat systemic autoimmune disorders like rheumatoid arthritis. The drugs tacrolimus and sirolimus are T-cell inhibitors. Like the immunosuppressant cyclosporine A, they target the activity of T cells—a type of white blood cell actively involved in the immune response—but produce fewer side effects in patients. Large NEI clinical trials have compared methods of administering these drugs, such as by inserting implants or by giving high doses followed by tapering to mimic natural immune reactions.

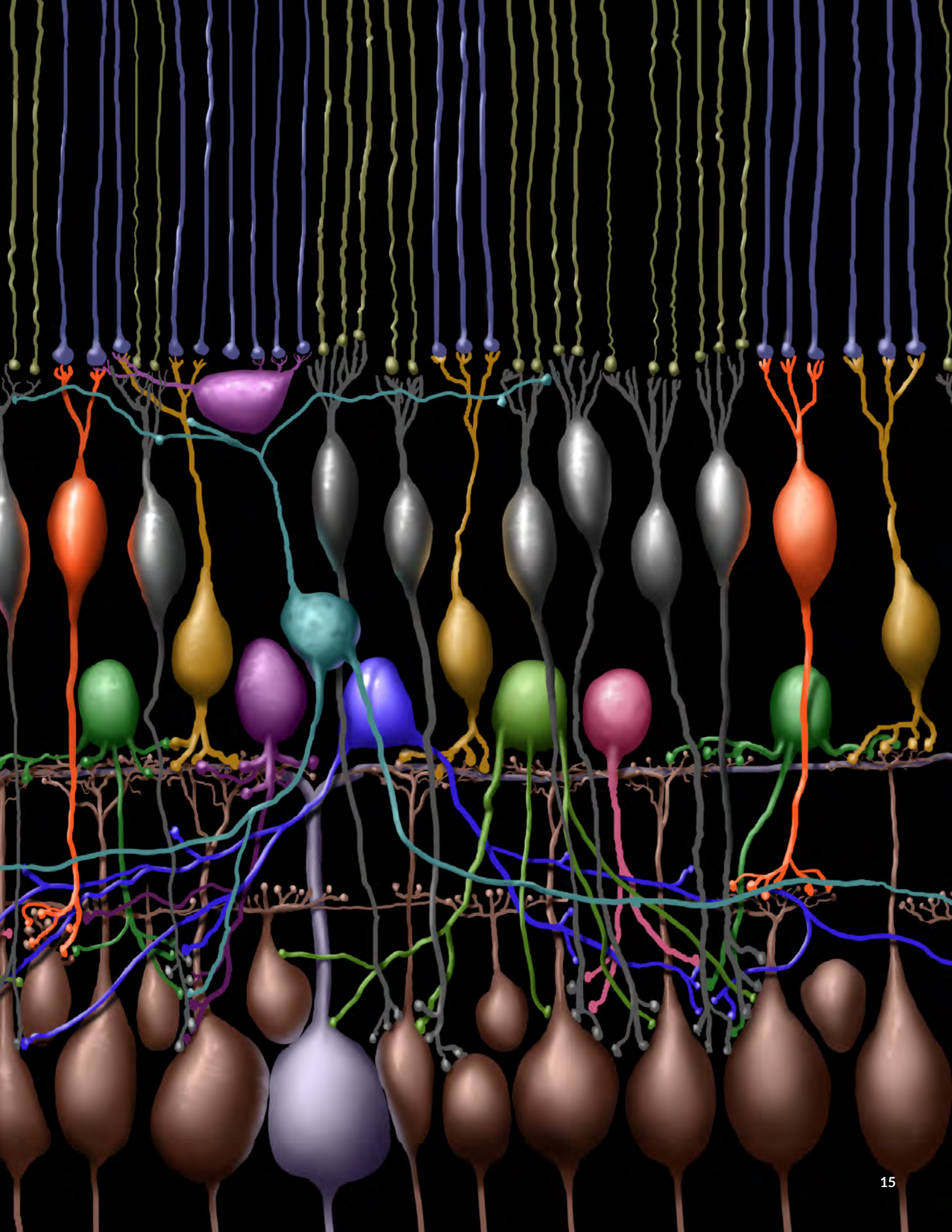
NEI-sponsored trials have also evaluated another category of therapeutic agents called biologics. Biologics are derived from natural components of the immune system and can effectively reduce inflammation with fewer side effects. Interferon beta and antibodies to TNF-alpha are biologics that have emerged as therapies for uveitis.

An eye into the brain

Early in NEI's history, Director Carl Kupfer called for the Institute to not only focus on eye disease, but also to support fundamental research to understand the visual system from eye to brain. Vision begins when light entering the eye reaches the retina, a paper-thin layer of neural tissue lining the back of the eye. Rod and cone photoreceptor cells at the back of the retina absorb the light and convert it into electrical signals that travel to the retinal ganglion cells (RGC), the nerve cells that connect the retina to the brain via the optic nerve, so that we can see.

Unlike other sensory tissues, the retina is part of the central nervous system, along with the brain and spinal cord. Much of what we know about how the brain works comes from studies of the retina. Compared to the brain, housed as it is inside a bony skull, the retina is much more accessible for study. Decades of NEI research on retinal cells has led to fundamental discoveries about how one nerve cell communicates with another, how sets of cells organize into circuits that process different kinds of sensory information (e.g., about brightness, contrast, color), and how neural tissue develops and organizes itself in the first place.

(Right) This illustration shows a slice of the retina, including (at top) nerve fibers that connect to the brain and (below them) ganglion cells, cones, and rods. *National Eye Institute, National Institutes of Health (NEI/NIH)*



Among sensory cells, photoreceptors were the first that scientists understood in great biochemical detail, and photoreceptors continue to serve as an important model for intracellular signaling. Beginning in the late 1950s, neurophysiologists David Hubel, M.D., and Torsten Wiesel, M.D., conducted a series of studies that would profoundly shape our understanding of not only how the brain processes visual signals, but also how it is organized and develops. For this work, much of it supported by NEI, Hubel and Wiesel received the Nobel Prize in 1981.

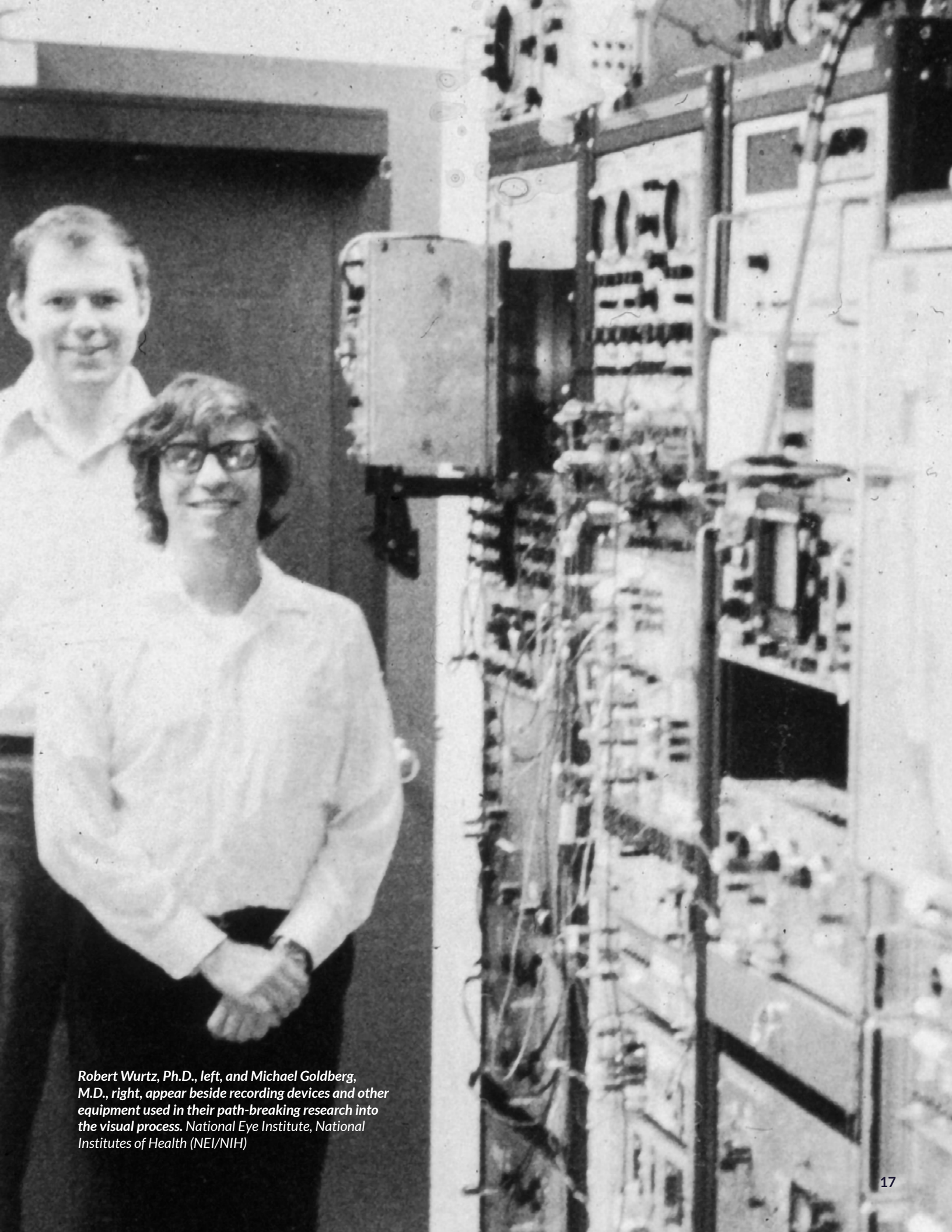
Hubel and Wiesel were the first to study how single nerve cells in the visual cortex respond to visual stimuli. Others' earlier work had shown that any particular RGC responds best to a spot of light (or dark) at a specific location in the visual field. As Hubel and Wiesel studied visually sensitive areas of the brain along the anatomically defined visual pathway, they discovered that cells respond to increasingly complex visual stimuli and, more significantly, that the responses from cells at one stage could plausibly be derived from the input of cells at the previous stage. Their work suggested a hierarchical organization of visual processing—that the brain gradually constructs a complex visual percept or a mental impression from elemental visual features, like edges and boundaries and colors in the scene. The implications were profound, suggesting for the first time a link between visual perception, long studied by psychologists, and the physiological properties of brain cells.

Another important concept to emerge from this early work is that the visual system is not simply programmed to "wire up," but depends on early visual activity to develop properly. Hubel and Wiesel discovered a critical period of development after which the wiring of the visual system is more or less permanent. This concept is now recognized as a fundamental feature of the nervous system. An immediately recognized clinical consequence of this discovery was that certain visual disorders, like amblyopia, a neural disorder arising when the two eyes don't point in the same direction, must be treated early, during a defined window of time, to best benefit the patient.

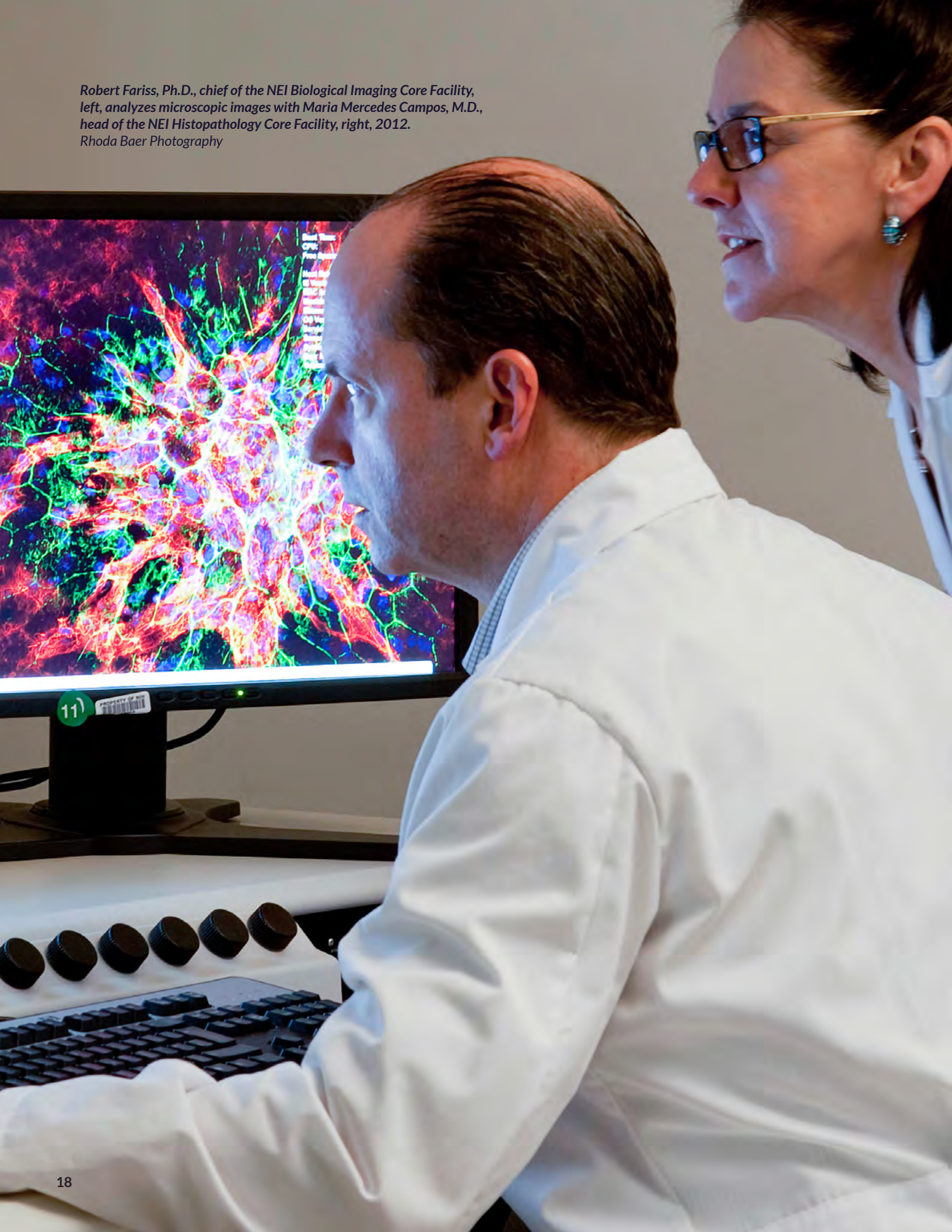
Hubel and Wiesel's early experiments used anesthetized animals. In the late 1960s, Robert H. Wurtz, Ph.D., a researcher in NEI's intramural program, demonstrated that the electrical activity of visual system brain cells could be studied in awake animals. This was a seminal advance: for the first time, investigators could study the brain of a trained animal while it performed a task. This basic paradigm has spawned dozens of research fields and allowed investigators to ask fundamentally new questions about how the brain processes sensory signals that lead to behaviors.

Why is so much cutting-edge research pioneered in the eye?

Unlike our internal organs, the eye is both accessible and transparent, allowing researchers to easily treat the eye with lasers or injections, and to use noninvasive tools to image retinal neurons at a cellular level. The retina, like the brain, is part of the central nervous system. Retinal neural circuits that convert visual images into signals transmitted to the brain are exceedingly complex, but NEI scientists have made great progress decoding their mysteries. The eye also has unique immune properties, such as relative immune privilege, enabling corneal transplants without rejection by the immune system or the need for immunosuppressive drugs. Furthermore, with two eyes, clinical trials can test a therapy in one eye, while leaving the other as an internal control for comparison in the same patient.



Robert Wurtz, Ph.D., left, and Michael Goldberg, M.D., right, appear beside recording devices and other equipment used in their path-breaking research into the visual process. *National Eye Institute, National Institutes of Health (NEI/NIH)*



Robert Fariss, Ph.D., chief of the NEI Biological Imaging Core Facility, left, analyzes microscopic images with Maria Mercedes Campos, M.D., head of the NEI Histopathology Core Facility, right, 2012.
Rhoda Baer Photography

The first steps in seeing

Everyday experience tells us that vision requires light to enter the eye. But how does light interact with the eye to initiate the visual process? The first clues of the chemical steps involved in vision appeared in the late 1800s, when scientists observed that the retina changed color from a dark purple after a prolonged period of time in the dark to a yellowish color when exposed to bright light. Returning the retina to darkness restored its original purple color.

In the 1930s, biochemist George Wald, Ph.D., showed that the change in color from purple to yellow corresponded with a release of vitamin A. With a set of biochemical studies over the next several decades, Wald demonstrated that the light-sensing molecule in rod photoreceptors (later named rhodopsin) consists of vitamin A attached to a protein (opsin). He showed that absorption of light causes the vitamin A molecule to change configuration and dissociate from the opsin, accounting for the observed change in color. For this pioneering work, Wald received the 1967 Nobel Prize in Physiology, along with vision researchers Ragnar Granit, M.D., and Haldan Keffer Hartline, M.D.

Absorption of light by rhodopsin initiates the visual signal in rod photoreceptors. Phototransduction refers to the sequence of biochemical and biophysical events in the rod that immediately follow, generating signals that are communicated to other retinal cells and, ultimately, to the brain. Beginning in the 1970s, a number of techniques rapidly advanced our understanding of the sequence of steps underlying phototransduction. Principal among these was the ability to record the light response from individual rod and cone photoreceptors. The field was further accelerated by the emergence of powerful imaging techniques and genetic engineering methods that allowed scientists to generate animal models with genes of interest mutated or eliminated. As a consequence, the process of rod phototransduction is now understood in detail and stands as the best-characterized signal transduction pathway of its kind.

Still, an important question remained: If light causes rhodopsin to separate into individual components, how does the eye respond to subsequent photons of light? In other words, how does rhodopsin regenerate after the vitamin A and opsin separate? Early on, scientists postulated a visual cycle that restores rhodopsin through a cascade of biochemical reactions. Working out the remaining details of the visual cycle following Wald's initial discoveries would involve many scientists and take the next several decades. The picture that emerged revealed a tightly choreographed set of some half-dozen biochemical steps involving the shuttling of molecules between rods and the neighboring retinal pigment epithelium (RPE), a layer of cells in close proximity to the retina photoreceptor layer and now understood to be critical for maintaining photoreceptor health.

One of the most important and elusive details of the visual cycle is a protein called RPE65. Identified between the late 1990s and early 2000s, RPE65 "resets" the vitamin A molecule to its original structure so that it can reattach to opsin and reconstitute the light-sensing molecule rhodopsin.

This critical role of RPE65 in the visual cycle clearly explained the finding, a number of years earlier, that mutations in the gene coding for RPE65 protein were associated with Leber congenital amaurosis (LCA), an inherited childhood retinal dystrophy affecting 1 in 80,000 people. These fundamental discoveries led to a gene therapy—recently approved by the FDA—in which normal versions of the *RPE65* gene are delivered to the eyes of LCA patients to improve vision.

Genetics in ophthalmology: Impacting clinical care and quality of life

Since the 1980s, researchers have identified hundreds of genes that cause or contribute to eye diseases. Identifying disease-causing mutations in genes is key for screening individuals both before and after they develop symptoms of disease. This is especially important if early intervention can prevent vision loss or even save lives.

The pace of progress in gene discovery accelerated in the mid-1980s and 1990s after the first disease-causing gene was found for retinoblastoma, a rare but deadly form of childhood eye cancer. In the 1980s, scientists believed cancer was caused only by environmental exposure. In a transformative breakthrough, NEI researchers showed that mutations in a single gene, *RB1*, can cause cancer.

RB1 was the first of a class of genes, now known as tumor suppressor genes, that tell the cell when to divide to form new cells. Everyone has two copies of each gene, one inherited from each parent. If both copies of the gene have mutations, cells can start growing out of control because they lack the signals that normally function to suppress cancer. Since the late-1980s, researchers have found many disease-causing mutations for other rare eye diseases.

Progress in genetics was aided by the completion of the Human Genome Project in 2003. The project, an international effort to sequence all the genes of the human body at one time, identified about 30,000 genes in humans. The medical impact of finding disease-causing genetic mutations and applying these findings to clinical care has resulted in the development of gene-based therapies. For example, through early diagnosis and genotyping, modern treatment methods for retinoblastoma now provide a survival rate of more than 96 percent.

An important leap in our understanding of genetic diseases occurred in the disease AMD, the leading cause of blindness in people over the age of 65. In 2005, vision researchers were the first to successfully apply a new gene-identifying technique called genome-wide association study. The study technique combines fast DNA sequencing and powerful computing to compare the DNA of a large population of patients against similar

Genetics

The human body is composed of trillions of cells, which are the basic building blocks of all living things. Cells contain DNA, the body's hereditary material. Locked away within the nucleus of every human cell are the 30,000 genes that control life. Each gene is like a complex computer program containing biologic code that instructs a cell to create a unique protein. Sometimes a piece of genetic code is missing or wrong. This type of change may result in a gene making a damaged protein, an extra protein, or no protein at all. These types of changes are genetic mutations.

Vision requires that a host of genes properly encode the proteins required to see the world throughout our lifetime. A mutation in any one of these genes may interfere with the production of the protein, impair the ability of the cell to function properly, and lead to vision loss. A mutation in one gene or, more commonly, mutations in multiple genes, often acting together with environmental factors, can cause genetic disorders.

individuals without diseases. Five independent, NEI-supported research groups simultaneously identified the *complement factor H (CFH)* gene as being a major risk factor for AMD. The *CFH* gene is responsible for a protein that helps regulate inflammation, implicating the immune system in this disease. In some people with AMD, inflammation in the eyes may trigger a biological process leading to the disease. *CFH* accounts for 40–50 percent of AMD risk. Currently, scientists have identified more than 50 genetic regions as contributing smaller risks for AMD.

Today, researchers have linked more than 500 genes to vision impairment. Most of these genes cause rare retinal eye disease; however, researchers are identifying many additional genes as causing corneal disease, hereditary cataracts, and certain forms of glaucoma.

Commercial genetic testing laboratories have sprung up in response to these genetic discoveries, aiding in diagnosis. Molecular testing can identify carrier status or rule out the presence of familial mutations in non-symptomatic, at-risk relatives. As improved diagnostic technologies become more widely available, reliable, and inexpensive, molecular diagnostic testing for all diseases will become routine in predicting risk and prognosis, and a core component in clinical care. Once individuals with inherited eye diseases have a confirmed genetic diagnosis, they may become candidates for gene-based therapy. This was impossible 50 years ago.

Gene therapy for inherited eye disease

At the time NEI started 50 years ago, doctors were telling individuals with genetic vision disorders that there was nothing they could do to save their vision. Gene therapy has changed that, offering possible cures for genetically inherited diseases by delivering healthy genes or genetic information to affected cells.

With support from NEI, vision researchers have made great strides in the quest to develop gene therapy treatments for eye disease, particularly for retinal degenerative diseases. One particularly promising treatment is called gene replacement therapy, which doctors use for inherited diseases in which both copies of the gene contain mutations. Scientists introduce new, healthy DNA using viruses that act like a fleet of microscopic delivery trucks. Doctors may treat many eye diseases, including Stargardt disease, LCA, and forms of retinitis pigmentosa and glaucoma, with gene replacement therapy.

Today, several clinical trials are testing gene-based therapies for eye disease. One of the biggest success stories involves LCA, caused by mutations in the *RPE* gene. Although vision loss is quite severe in LCA, the structure of the retina remains intact for some time. This feature of the disease presents a window of opportunity to develop therapies that could overcome the *RPE* gene defect before photoreceptor cells degenerate. Scientists first tested LCA gene therapy in Briard dogs, who also carry *RPE65* mutations. NEI researchers injected dogs with a single dose of *RPE65* gene therapy, and, remarkably, they showed significant recovery of vision.

In 2008, three independent clinical trials showed that the treatment was safe for humans and that patients receiving the therapy showed some improvement in their vision. In December 2017, the FDA approved LUXTURNA™, a new gene therapy, to treat individuals with LCA caused by *RPE65* mutations. LUXTURNA is the first directly administered gene therapy approved in the United States that targets a disease caused by genetic mutations. It is also the first and only pharmacologic treatment for an inherited retinal disease. Several other gene-based therapies for inherited eye diseases are undergoing clinical trials today.

NEI Audacious Goals Initiative: A focus on regenerative medicine

In 2012, NEI Director Paul Sieving challenged the National Advisory Eye Council and the vision community to identify a novel and ambitious goal that pushed the boundaries of vision science and tackled the most devastating and difficult-to-treat eye diseases. The resulting NEI Audacious Goals Initiative (AGI) gathered a set of targeted proposals with the overall goal to "restore vision through the regeneration of neurons and neural connections in the eye and visual system."

Regenerative medicine is a new frontier in biomedicine that uses stem cells, engineered biomaterials, and gene editing to repair, replace, or regrow damaged cells, tissues, or organs. AGI builds on the understanding that many leading causes of blindness, such as AMD, diabetic retinopathy, and glaucoma, result from the death of photoreceptor cells and ganglion cells (neurons) in the eye. In the eye and brain, lost and damaged nerve cells must be replaced and coaxed to grow long connections to other nerve cells. This complicated process requires scientists to understand not only biochemical guidance cues but also how to train the visual system to form the right connections.

AGI will greatly influence regenerative approaches to eye diseases as well as to other neurodegenerative diseases, such as Parkinson's disease and Alzheimer's disease.

AGI is designed to be nimble and responsive to rapidly evolving scientific opportunities to reach its goals. It will take a lot of planning, with input from a variety of experts, to be successful. As a first step, NEI assembled several research consortia to tackle the most pressing needs and gaps in science. The first goal is inventing new, noninvasive imaging technology to watch cells grow and form connections over time in animals and, ultimately, in patients responding to therapy. Other AGI consortia are trying to identify new regeneration factors that may be turned into therapy, and to create new models to evaluate the survival of regenerated neurons and cells. Through this initiative, with continuous input from the research community, NEI is supporting the cutting edge of vision science and beyond.

(Right) The NEI Audacious Goals Initiative aims to restore vision by regenerating the neurons and neural connections, illustrated here, in the eye and visual system. *National Eye Institute, National Institutes of Health (NEI/NIH)*

> Given the number of genetic eye diseases and the accessibility of the eye for novel approaches such as stem cell and gene therapy, research on diseases of the visual system has often been at the literal leading edge of biomedicine.
>
> —NIH Director Francis S. Collins, M.D., Ph.D.

U.S. Department of Health & Human Services
National Institutes of Health | National Eye Institute
nei.nih.gov

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