VIEWPOINT

The Department of Ophthalmology Columbia University
at The Edward S. Harkness Eye Institute

Spring / Summer 1999

Stargardt's Gene Discovered

The nature of research is such that it can lead to somewhat unexpected, but potentially rewarding, results. That was precisely the case two years ago, when Dr. Rando L. Allikmets, then an investigator at the National Cancer Institute and now assistant professor of Ophthalmology at Columbia's Eye Institute, was searching for two groups of genes. He and his colleagues wanted to identify genes that might be responsible for resistance to cancer drugs and those involved in human inherited disease—though not necessarily genes involved in problems of the eye. Nevertheless, the process of discovery led Dr. Allikmets and his colleagues to a genetic link for Stargardt's disease, the rare, hereditary vision disorder that bears some similarities to age-related macular degeneration (AMD).

Like AMD, Stargardt's disease is destructive to central vision. But, while AMD is the leading cause of blindness for those over 65, affecting millions of aging Americans, Stargardt's disease strikes only about one in 10,000 people, most of whom are children or adolescents. Stargardt's disease is, consequently, known as juvenile macular degeneration.

The story of 20-year-old Rick Douglas (not his real name) shows the devastating effects that Stargardt's

continued on page three

Dr. Rando L. Allikmets

In This Issue:

Views from the Chair

Dear Friends,

In this issue of *Viewpoint*, we are delighted to bring you news of a major finding that may help efforts to understand, diagnose and prevent blindness caused by inherited macular disorders. Dr. Rando Allikmets, a talented researcher who recently joined our faculty, was one of an NIH team of scientists that identified the gene for a rare disorder called Stargardt's disease. Like age-related macular degeneration (AMD) in adults, Stargardt's disease eventually reduces central vision in children. Dr. Allikmets is currently investigating the Stargardt gene's relationship to AMD, a far more common disorder that affects 700,000 new patients each year. This exciting research is an important first step on a path toward the development of innovative gene therapies to prevent vision loss from inherited retinal diseases.

Today's remarkable technological advances provide us—as never before—with opportunities to better understand and treat many kinds of eye disorders. At the Edward S. Harkness Eye Institute, we have focused on acquiring a wide range of state-of-the-art equipment, some of which is described in this issue of *Viewpoint*. This sophisticated technology is crucial in helping basic and clinical researchers develop improved methods of preventing or managing eyesight problems and also gives our clinicians the ability to locate their patients' damaged eye tissue with the utmost precision.

We are also pleased to report on important work by Dr. David Maberley, a Columbia research fellow, whose studies on nearsightedness should provide a new perspective and valuable information on lifestyle and health issues that may contribute to problems with distance vision. And, finally, we offer some health tips we hope you'll heed to protect your precious gift of sight.

With thanks for your continuing interest and support and best wishes for a healthy and happy summer,

Sincerely,

Stanley Chang, M.D.
Edward S. Harkness Professor
Department of Ophthalmology Chairman

Stargardt's
from page one

disease can cause. A patient of Columbia Professor of Ophthalmology Peter Gouras, M.D., since childhood, Rick began to lose his eyesight at the age of eight after failing a routine school eye exam. When the deterioration of his vision could not be corrected with a simple prescription for eyeglasses, the family sought further help. The result was a diagnosis of Stargardt's disease, which made it necessary for Rick to accept a whole new outlook on life—both literally and figuratively.

In spite of Rick's unexpected and severe loss of vision, his father speaks proudly of the "remarkable strengths and talents" that helped the young boy turn "what we once thought of as a handicap" into just an "inconvenience." In spite of problems that might have seemed insurmountable to a young boy eager to join in every possible activity, Rick succeeded in keeping up with both his studies and his friends. He earned top grades and played basketball and even made the all-league football team. Rick's father says his son's chief complaint during these years was, "not being able to see the numerals on his teammates' jerseys!"

continued on page four

"IDENTIFICATION OF THE STARGARDT'S DISEASE GENE IS A FIRST STEP TOWARD BEING ABLE TO SUBSTITUTE A HEALTHY GENE FOR ONE THAT IS DEFECTIVE...THE TECHNOLOGY IS RIGHT AROUND THE CORNER!"

-DR. PETER GOURAS

Here's how a patient with Stargardt's or AMD might see this photo of a pitcher.

"ONCE WE'VE ESTABLISHED A CERTAIN CONNECTION BETWEEN AMD AND ABCR MUTATIONS, PEOPLE WITH THE DEFECTIVE GENE COULD BE ADVISED TO AVOID ANY FACTORS IDENTIFIED AS PUTTING THEM AT RISK OF LOSING THEIR EYESIGHT."

-DR. RANDO ALLIKMETS

Stargardt's

from page three

Rick's determination to surmount the obstacles presented by his condition is typical of most young people with Stargardt's disease. He taught himself to compensate for a lack of central vision by making use of peripheral eyesight and developing his sense of hearing and touch to a high degree. Since his eyes tire easily, Rick also uses books-on-tape and specialized computer software to reduce the stress of visual work.

But, future potential victims of Stargardt's disease may have the opportunity to stop their vision problems before they start, if new treatments based on Dr. Allikmets's genetic find can be successfully developed. As Dr. Gouras explains, "Identification of the Stargardt's disease gene is a first step toward being able to substitute a healthy gene for one that is defective." Such genetically-engineered therapy may, one day, successfully prevent Stargardt's disease in people who are discovered to be at risk for this damaging condition. Speaking with great enthusiasm about this possibility, Dr. Gouras says, "the technology is just around the corner!"

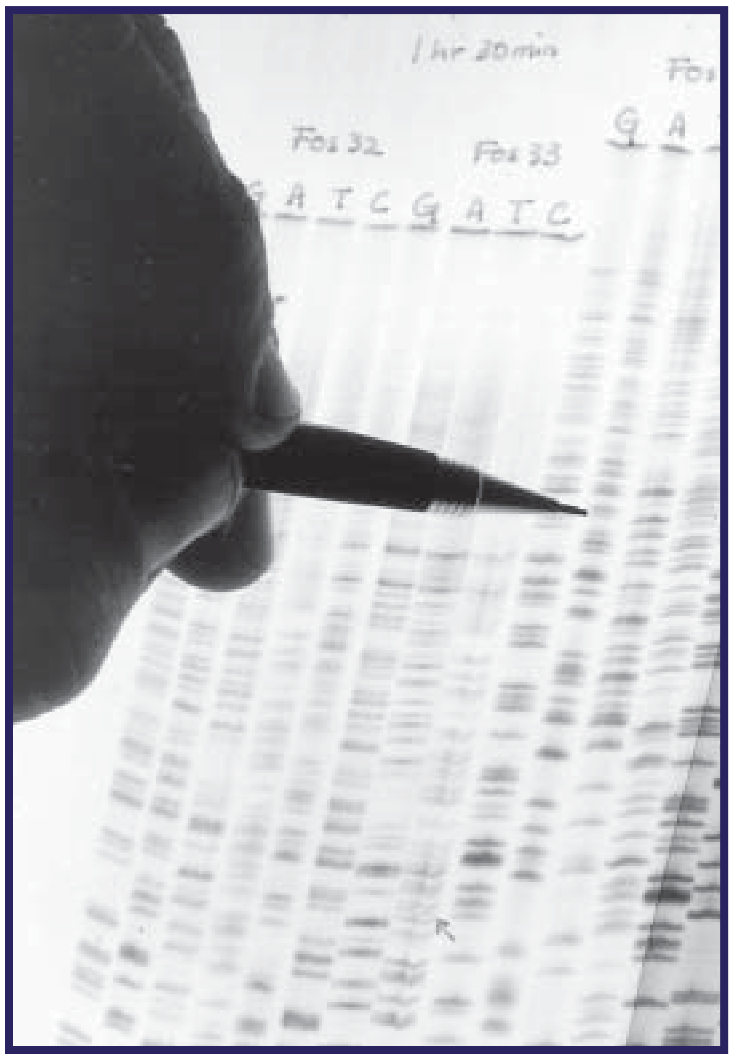
Any ABCR's in AMD?

Stargardt's disease is an inherited disorder that occurs only in children who receive a copy of the defective gene, known as ABCR, from each parent. Having discovered the ABCR connection to Stargardt's disease, Dr. Allikmets and his colleagues began to wonder whether the gene might also be tied to AMD. "It's a reasonable question to ask because there are similarities between the diseases," explains Dr. Allikmets. "Both cause a build up of cellular debris behind the retina as well as a progressive deterioration of the area near the macula."

So far, their hunch is proving right. In an initial study, reported in "Science," Dr. Allikmets and fellow researchers found mutations in the ABCR genes of one-out-of-six people diagnosed with AMD. Ongoing, larger-scale studies, currently underway in at least 12 different European and American laboratories, also show a significant—though slightly lower—correlation of about 10 percent among people with AMD who also have Stargardt's gene mutations.

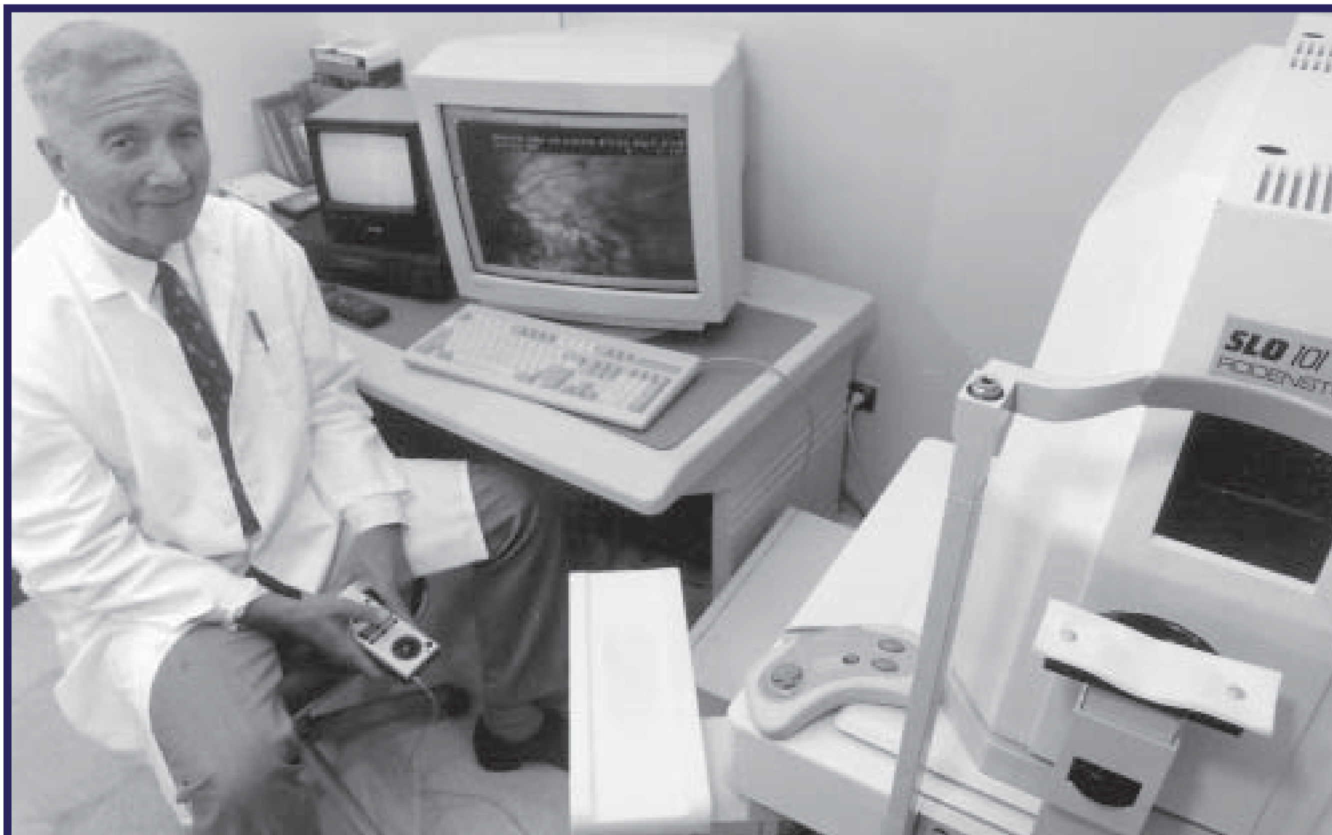
"AMD is a complex disease, caused by multiple genes as well as environmental factors that include exposure to sun, smoking and diet," says Dr. Allikmets. "ABCR is the first and only genetic component discovered in AMD to date. Once we've established a certain connection between AMD and ABCR mutations, people with the defective gene could be advised to avoid any factors identified as putting them at risk of losing their eyesight."

The painstaking process of unravelling genetic codes.



Seeing the Eye as Never Before

Only a short time ago, ophthalmologists relied on their scalpels to reveal the root cause of vision disorders that were beyond the reach of simple X-ray photography. Today's technology, however, makes it possible to examine even the most remote recesses of the eye without invasive exploratory surgery. With this advanced equipment, detailed information from three-dimensional images and comprehensive computerized analyses help clinicians to diagnose, monitor and treat eye disease. Leaders in innovative eye care at Columbia University's Department of Ophthalmology are using such sophisticated instruments as the scanning laser ophthalmascope, optical coherence tomography and 3-D ultrasound to help prevent sight loss from eye disease or injury.



Dr. Peter Gouras demonstrating the SLO.

Scanning Laser Ophthalmascope (SLO):

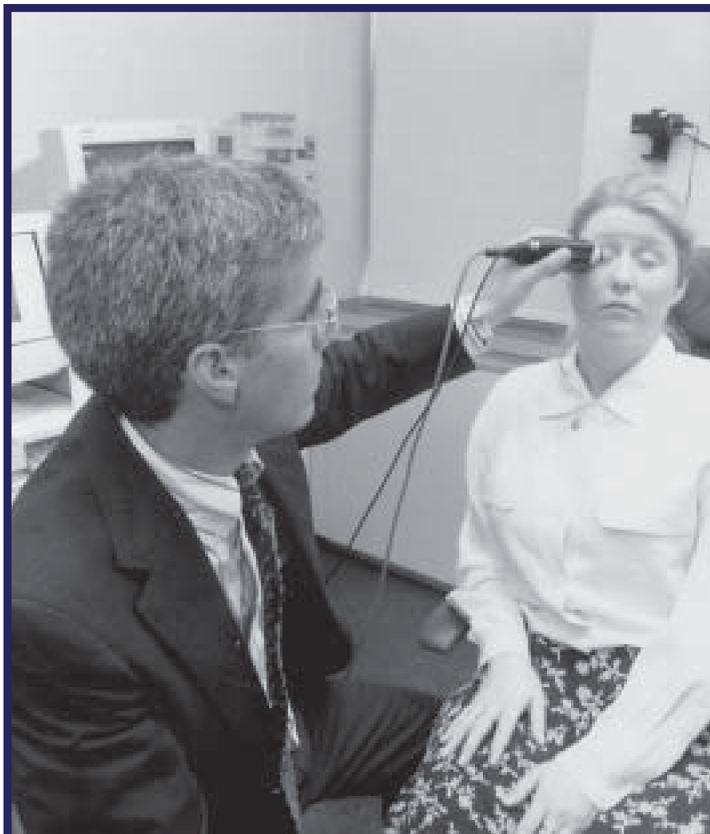
The SLO focuses a laser on any area of retinal tissue to rapidly scan and capture images point-by-point. The SLO's pencil-thin beam instantly returns to a tiny detector aperture along the identical path from which it is projected, transmitting a clear, precise, high-resolution image—without interference from extraneous scattered light. This image can then be recorded or viewed on a monitor in real time. The use of different laser wavelengths makes it possible to visualize each of the retina's individual cellular layers. For example, infrared light provides images of retinal epithelial tissue, important for the diagnosis of macular disorders, and blue light, which helps to visualize the optic nerve, can be used to detect or monitor glaucoma.

Optical Coherence Tomography (OCT):

OCT technology provides high-resolution, cross-sectional images of each area of the eye under study. Two laser beams are projected on the retina to reveal and differentiate between each layer of tissue. The technology pinpoints the exact location of any damaged tissue, making it possible to detect and monitor anatomic changes in the retina, such as macular holes, with much greater accuracy.

3-D Ultrasound:

Three-dimensional ultrasound imaging allows doctors to view the eye's structure and any possible abnormalities volumetrically, giving a clearer understanding of ocular anatomy. Providing an analysis and a display of volume information about the eye within seconds, ultrasound technology offers opportunities for rapid diagnosis, provides detailed monitoring and gives information on which to base appropriate interventional techniques for tumors, retinal detachments, complicated diabetic retinopathy and other vision-threatening conditions.



Dr. William Schiff using 3-D ultrasound.

When Nearsightedness Means More Than a Prescription

One in every four Americans suffers from some degree of nearsightedness. For most of us, eye-glasses, contact lenses, or corrective surgery are all that is needed to restore our vision to the perfect 20/20 score that indicates flawless sight. But, for the five-to-ten million people in the United States whose sight is severely affected, myopia—or nearsightedness—poses a greater than average risk. They may develop vision disorders that are difficult, or even impossible, to correct. In fact, some reports show that severe myopia, which can lead to macular degeneration, glaucoma or retinal detachment, is the fifth leading cause of blindness in the United States.

Nearsightedness occurs when genetic and environmental influences create a progressive elongation of the eye. Because of this lengthening, images cannot completely reach the retina from the focusing mechanisms of the cornea and lens; as a consequence, they appear blurred to the myopic eye. In patients with "high" or severe myopia, usually defined as having a refraction of more than minus 6 diopters—the metric measure of the refractive power of the eye's lens—the eye is able to focus clearly only within a six-inch-distance. By contrast, people with normal vision can focus at any point.

Why are people who are afflicted with severe nearsightedness also prone to other types of eye disorders? Columbia Research Fellow Dr. David Maberley is conducting an investigation, in collaboration with Dr. Stanley Chang, Chairman of the Department of Ophthalmology at Columbia University, to examine the relationship between poor distance vision and

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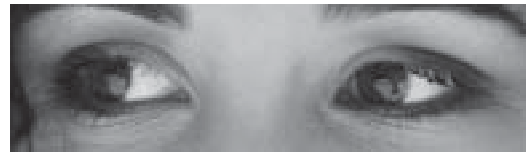
more serious eye diseases. Participants in the study include high myopics, both with and without complications, and provide researchers with information about a broad range of possible risk factors. Researchers will use the data to look for evidence that factors such as a person's family history, educational and employment background, exposure to sunlight, smoking habits and blood pressure levels may be related to his developing complications from nearsightedness.

"There has been little research on myopic macular degeneration and other myopia-related vision loss," says Dr. Maberley, who adds that the probable mechanism for damage is the thinning of the retina and underlying support tissue as the nearsighted eye is stretched and elongated. "If we can learn what factors contribute to tissue breakdown in the retina, we may be able to identify people at risk for myopia-related vision loss. Our ultimate goal is to determine how we can protect this potentially endangered group from becoming blind.

Dr. David Maberley is looking closely at factors affecting distance vision.

What Can You Do To Protect Your Eyesight Against AMD?



- Have your eyes examined regularly.
- Maintain a healthy balanced diet.
- Take vitamin supplements, including vitamins C, E, and beta carotene. These antioxidants may slow down development of age-related macular degeneration (AMD).
- Wear large, yellow-tinted sunglasses to block the sun's damaging ultraviolet rays.
- Don't smoke. It could increase your risk of developing AMD.

Please let us know if you like the size and design of the type—chosen for its readability—that appears in this issue of *Viewpoint*. Send comments to: *Viewpoint*; 100 Haven Avenue, 29D; New York, NY 10032; or call Susan Taylor, 212.304.7200

News Briefs

Miranda Tang, a member of the Department of Ophthalmology's Board of Advisors, has made a gift of $100,000 to Columbia University in support of the Department of Ophthalmology's programs to educate patients about eye disease. Ms. Tang's generous help will fund seminars, lectures and the development of web-based information sites.

The Schering-Plough Corporation recently added $45,000 to their previous support for the Department of Ophthalmology. The corporation's gift will complete the purchase of specialized equipment needed to establish a Biomedical Imaging Facility for the Department's research and clinical activities.

Dr. Pamela Gallin, associate clinical professor of Ophthalmology at Columbia, and health writer, Kathy Matthews, have written *The Savvy Mom's Guide to Medical Care*. The new book is scheduled for publication in October.

DeVoe Lectureship Established

Joan Gilson, a former patient of Dr. Arthur Gerard DeVoe, has made a gift to establish an annual Arthur Gerard DeVoe Lectureship in Columbia's Department of Ophthalmology. Department Chairman Stanley Chang, Edward S. Harkness Professor of Ophthalmology, will present the first DeVoe lecture this fall.

A former chairman of Ophthalmology at Columbia, Dr. DeVoe became the first Edward S. Harkness Professor of Ophthalmology in 1959 and helped to establish the Eye Institute's Corneal Clinic in 1964. Ms. Gilson's generous gift of appreciated securities to endow the lectureship will provide Columbia Ophthalmology faculty with the opportunity to learn from internationally renowned leaders in ophthalmic research and treatment of eye disease. Dr. DeVoe and Ms. Gilson will be honored at a reception immediately following the lecture.

GIVING Well

When Joan Gilson established the DeVoe Lectureship, she chose to do so by making a gift of appreciated securities to Columbia University. Giving securities such as stocks, bonds or mutual funds is a simple way of supporting vital programs in the Department of Ophthalmology and may provide:

-an income tax deduction based on the full fair market value of the securities;
-tax savings that may make the cost of the gift to you less than that of giving the same amount in cash;
-greatly reduced or eliminated capital gains tax; and
-the opportunity to further enhance these tax benefits by funding a life-income gift, like a charitable gift annuity or remainder trust.

We will be pleased to help you and your broker arrange for the transfer of securities, which you have owned for at least 12 months, as a gift to Columbia's Department of Ophthalmology. For more information, please contact:

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Second Annual Ollendorff Lecture

The second annual Ollendorff Visiting Lecture, established in memory of Dr. Ulrich Ollendorff, was held on May 20, 1999. Professor Scheffer Tseng, M.D., Ph.D., who is the Charlotte Breyer Rodgers Chair in Ophthalmology at the University of Miami's Bascom Palmer Eye Institute, discussed ocular surface reconstruction with stem cell transplantation and amniotic membrane transplantation. Dr. Ollendorff's widow, Mrs. Anne Ollendorff, his son and daughter-in-law, Stephen and Bjorg Ollendorff also attended the lecture. Dr. Stanley Chang, Stephen Ollendorff, Dr. Tseng and Bjorg Ollendorff are shown at a dinner following the lecture.