LIGHT at the END of the TUNNEL

Visionary research probes the genesis of glaucoma

By KATHY A. FACKELMANN

It wasn't the first time 29-year-old Alan Rogers had sought surgery to treat his fading peripheral vision. Doctors near his Illinois hometown had repeatedly denied his request, saying surgery was too hasty and too drastic an option for someone so young. But when Rogers finally reached the University of Iowa eye clinic, he had proof of his dire need for aggressive treatment. The standard drug therapy had not helped other members of his family, he told the Iowa doctors.

To bolster his case, he whipped out a legal pad with a crudely drawn pedigree. That family tree documented the blinding eye disease that had ripped through his family for five generations.

Rogers got his sight-saving surgery. And ophthalmologists at the University of Iowa in Iowa City got their first tantalizing clue to the genetic origin of a very aggressive form of glaucoma.

Now, those same researchers have homed in on the gene linked to this family's glaucoma legacy.

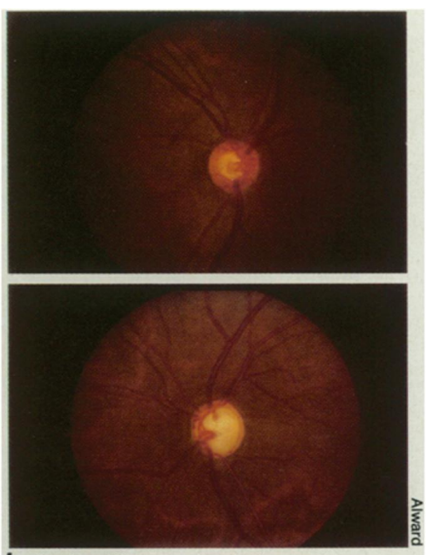
The hope is that the gene can be linked to the thousands of other cases of glaucoma reported in the United States each year.

"Certainly every time a glaucoma gene is discovered by anybody it has the potential to be the big guy: a gene that causes 40 or 50 percent of what we consider to be regular glaucoma," says Edwin M. Stone, an ophthalmologist and geneticist at the University of Iowa.

Stone described his team's findings in April at the Science Writers Seminar in Ophthalmology, held in Universal City, Calif., and sponsored by Research to Prevent Blindness. The researchers also detail their work in the May NATURE GENETICS.

In most forms of glaucoma, the fluid pressure in the eye is abnormally elevated. Researchers believe the pressure may damage the optic nerve, the bundle of fibers carrying messages from the retina to the brain.

That optic nerve damage causes a deterioration in sight at the fringes of the field of vision. Even though central vision can remain sharp, the loss of peripheral vision can prove debilitating, notes ophthalmologist Wallace L.M. Alward, one of the Iowa researchers. Glaucoma patients may trip over objects that remain beyond their narrowed visual field. Everyday activities, like crossing a busy street, become potentially dangerous.



In the healthy eye (top), the optic nerve appears as a pink doughnut of tissue. In the eye with glaucoma (bottom), that pink tissue is nearly gone.

"It's like looking through a soda straw," Alward says. Without treatment, even central vision is lost and people with glaucoma can become completely blind, he adds.

The Rogers family suffers from a rare subtype of primary open-angle glaucoma. As in other forms of glaucoma, the fluid in the eye doesn't drain properly. Normally, this liquid flows out of the eye through a meshwork of drainage canals around the outer edge of the iris. In primary open-angle glaucoma – the most common form of glaucoma in Western countries – the canals become clogged and pressure in the eye soars. Usually, this blockage occurs gradually as a person ages. The Rogers family is unusual because their glaucoma strikes early in life.

At the same seminar, ophthalmologist David L. Epstein of Duke University Medical Center in Durham, N.C., presented data on a novel drug treatment for primary open-angle glaucoma. Right now, people with this form of the disease are treated with drugs or surgery to lower the pressure in the eye. Most of the medications work by slowing the production of fluid inside the eye. The new drug is one of the first to target the eye's drainage system, an approach that may provide long-lasting vision relief for many elderly victims of glaucoma, says Epstein.

The hunt for glaucoma genes is stymied in many cases because most people with the disease have few living relatives showing symptoms of the disease. Geneticists need to study blood samples from many people in order to nab a single gene. Thus, when Rogers walked into the Iowa eye clinic during the summer of 1986 with his legal pad, the doctors took one look and realized they had stumbled upon the genetic equivalent of a winning lottery ticket: The family had enough living members with primary open-angle glaucoma to allow an intensive hunt for the flawed gene.

In 1987, the Iowa investigators began making field trips to Galesburg, Ill., where most of the Rogers clan lived. By conducting home visits, they were able to ask detailed questions about living and long-dead relatives, Alward says. The team also performed eye examinations to look for unrecognized signs of glaucoma and to confirm cases that had already been diagnosed. Finally, they drew blood samples.

The researchers ultimately contacted and examined 21 out of 22 living relatives who had primary open-angle glaucoma. As it turned out, all family members were descendants of a woman who had emigrated from Germany during the late 1800s. The pedigree suggested that the gene causing their severe glaucoma followed a dominant inheritance pattern. Since genes come in pairs, this means that the defective gene dominates its normal counterpart. Even a child who inherits this gene from just one parent will get the disease, says Stone.

Once they had obtained the blood samples, the researchers began combing through DNA extracted from the blood cells of family members. Using a technique called chromosome linkage analysis, they zeroed in on the long arm of chromosome 1. They concluded that the glaucoma gene lies somewhere within that stretch of DNA, a region about 20 million nucleotide base pairs long, Stone says. Nucleotides are the chemical building blocks of DNA.

The next step will be to narrow the search to a much smaller region of the chromosome, Stone says. To do that, the researchers must find more family mem-

bers or identify other people suffering from the same type of early-onset glaucoma. The group has already initiated such an effort, and Stone says he's confident they'll have the precise location of the gene within a few years. Once they identify the gene, they can determine the order of the bases that make up this crucial stretch of DNA, he adds.

Does this gene account for a large number of glaucoma cases, or is it just an anomaly? At this point, no one knows. But even if the gene turns out to be uncommon, it may help scientists direct their hunt for other glaucoma genes, says Eve J. Higginbotham, an ophthalmologist at the University of Michigan in Ann Arbor. Instead of randomly sorting through the entire human genome, investigators can begin to scour the chromosome region identified by the Iowa team. They may find that several genes in the same region play a role in the development of glaucoma, she notes.

More important, she says, the research may pave the way for the development of a simple blood test to identify people at high risk of glaucoma. Right now, physicians have no good method of finding at-risk individuals. Impaired peripheral vision often sneaks up on its victims: Many don't realize they are suffering from glaucoma until destruction of the optic nerve has produced severe, irreversible vision loss, Higginbotham says.

With a blood test, ophthalmologists could identify people who've inherited the disease-causing gene before any damage has occurred, suggests Henry Jampel, an ophthalmologist at Johns Hopkins University in Baltimore. With early treatment, nearly all vision loss from glaucoma can be avoided, he says.

That sight-saving process has already begun for children in the Rogers family. The Iowa researchers have flagged at-risk kids and are now monitoring them. Alan Rogers and other family members who have developed the disease seem to benefit from an operation in which surgeons create a tiny trapdoor in the back of the eye to let the backed-up fluid drain into the surrounding tissue, Alward says. If kids with the bad gene undergo this operation before optic nerve damage occurs, they might never suffer from the blinding disorder, Stone adds.

In the future, geneticists hope to characterize the proteins made by the genes with a link to glaucoma — a move that could lead to new therapies for primary open-angle glaucoma. "If we understood at the exact molecular level what was wrong, then maybe we'd come up with an unbelievably specific drug," Stone says.

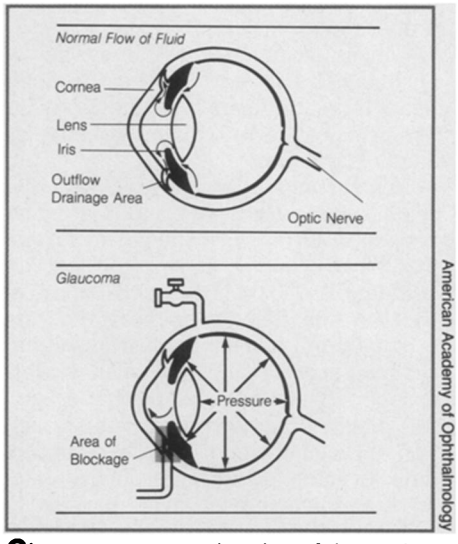
Although their work isn't based on the genetic research conducted by the Iowa team, other investigators have already begun testing a drug that aims to unclog the eye's drainage canals, or trabecular meshwork.

"Most glaucoma therapy is nonspecific," says Epstein, who spearheaded the studies of this drug. "Here, for the first time, we've got a drug that is directed at the trabecular meshwork."

Epstein and his co-workers believe that people with primary open-angle glaucoma develop high pressure in the eye because a type of sludge builds up in that meshwork.

The drug in question, ethacrynic acid, has been approved by the Food and Drug Administration as a diuretic but not for the treatment of glaucoma. Yet there are hints that this drug, acting as a powerful clog-buster, lowers eye pressure and could thereby halt vision loss for victims of primary open-angle glaucoma.

Studies of tissue taken from human eyes show that ethacrynic acid doubles or triples the permeability of the trabecular meshwork, allowing more fluid to drain from the eye, Epstein says. His team followed up on these promising laboratory results with animal experiments designed to assess the drug's safety. Monkeys injected with the drug suffered no apparent side effects at doses that would stimulate drainage of eye fluid, Epstein says.



Glaucoma causes clogging of the eye's drainage canals.

The animal studies spurred a very small human trial, which focused on the drug's safety but also provided the scientists with an exciting hint of efficacy. In this pilot study, Epstein collaborated with a group led by Shlomo Melamed of Tel Aviv University in Israel. The researchers tested ethacrynic acid in four men and one woman with very severe open-angle glaucoma. Before treatment, the eye pressures of these patients ranged from 26 to 46 millimeters of mercury. (Normal pressure ranges from 9 to 22 millimeters of mercury.) Using a fine-gauge needle, the researchers carefully injected a small dose of ethacrynic acid directly into one eye of each patient.

"In all five patients, reduction in intraocular pressure was observed after the injection of ethacrynic acid," the team writes in the May 1992 AMERICAN JOURNAL OF OPHTHALMOLOGY. Indeed, eye pressures on the second day after treatment ranged from 12 to 16 millimeters of mercury, well within the healthy range, Epstein says. Furthermore, the drug's pressure-lowering effects lasted for several days without observable side effects.

Epstein speculates that this drug, when given in higher concentrations, may be able to clear the eye's blocked drainage canals for extended periods, perhaps as long as a year. He is the first to admit, however, that many more studies must be conducted in order to prove the drug's efficacy.

"Is this the magic bullet that is going after the defect in glaucoma?" Epstein asks. "We just don't know."

A once-a-year treatment for glaucoma would be a significant advance over the standard regimen, in which patients apply pressure-lowering eye drops twice a day, notes Higginbotham. On the other hand, Jampel points out that the researchers injected ethacrynic acid directly into the eye — a mode of administration that would surely dampen the drug's popularity with patients.

The experiments with ethacrynic acid raise more than a glimmer of hope for millions of people with primary open-angle glaucoma. "It's still too early to really know, but the potential of this drug is certainly very attractive," Higginbotham says.

The genetic investigations, though currently limited to one family, may prove even more revealing in the long run. If the Iowa researchers get their gene — and if that gene turns out to be a major cause of glaucoma — the work may lead to a much better understanding of how this common disease steals peripheral vision, Jampel says. Yet genetics is unlikely to explain this disorder entirely, adds Higginbotham, who believes that environmental factors, such as injury to the eye, may play a role in glaucoma's genesis.

For at least one glaucoma patient, the research is already paying off.

Alan Rogers remembers the first time he drew up his family tree and how it led doctors to develop a more detailed pedigree. Throughout that time, the researchers articulated their dream of finding the gene responsible for his family's struggle with blindness.

Rogers says he was delighted when they announced they were closing in on the genetic roots of glaucoma. That search, if successful, may save children in his and other families from a slowly darkening future.

"That's the hope," Rogers says. "We figure they're on the road now." □