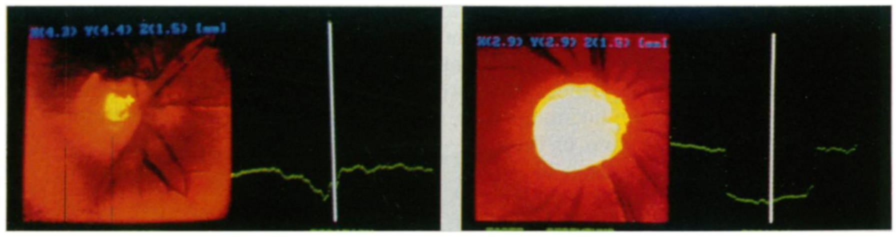
Eyeing the Optic Nerve

Laser finds early signs of blinding glaucoma

By RICK WEISS



Computer images created with the laser tomographic scanner allow easy interpretation of optic nerve-head deformation, an early indicator of glaucoma. Nerve head in a normal eye (left) has a shallow depression. The depression in a glaucomatous eye (right) is larger and deeper.

First came the headaches, and the halos around electric lights. Later, it was the loss of peripheral vision — having to turn her head to see things once visible out of the corner of her eye — that led her to an optometrist.

Expecting nothing more than a change in her eyeglass prescription, the 37-year-old woman was startled to learn the real source of her problems. Higher-than-normal fluid pressures within her left eye had resulted in subtle changes in its optic nerve head, the button-shaped structure in the back of the eye where retinal nerve fibers converge to carry visual messages to the brain.

Diagnosing the condition as glaucoma — a degenerative disease afflicting 2 to 3 million people in the United States — was easy. But her eye had already deteriorated considerably. Indeed, by the time the visual-field defects of glaucoma show up, many people have already suffered irreversible damage to as many as half the ganglion cells and nerve fibers in the affected retina, says Robert N. Weinreb, an ophthalmologist at the University of California, San Diego. This degeneration, if left untreated, destroys peripheral vision and eventually brings total blindness.

Medicated eyedrops can slow glaucoma's progression. And in cases that don't respond to drugs, surgery can temporarily stanch the progressive nerve damage. But the ideal management of glaucoma depends on early detection, Weinreb says; when treatment begins early enough, loss of vision may be prevented altogether.

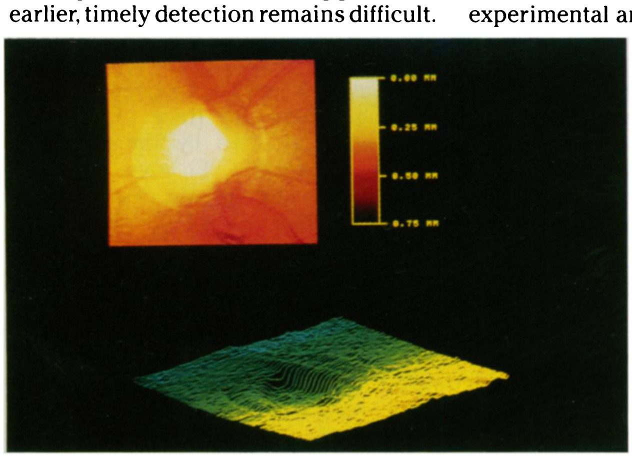
Unfortunately, while regular checkups can improve the odds of finding glaucoma earlier, timely detection remains difficult. That's because high fluid pressure within the eye — popularly considered a hallmark of the disease — never occurs in one-third of glaucoma victims, Weinreb says. And subtle deformations of the optic nerve head — changes truly characteristic of glaucoma — prove difficult to spot and measure.

The inadequacy of classical methods for mapping the topography of the optic nerve head inspired Weinreb and his colleagues to adapt space-age digital imaging techniques to the ocular environment. Three years of trials in hundreds of eyes in glaucoma patients now indicate that the laser-based system they developed — called the laser tomographic scanner — provides a sensitive and precise tool for measuring and tracking nerve-head deformations, Weinreb reported in September at an ophthalmology seminar for science writers in Universal City, Calif.

Unlike therapeutic lasers, such as the experimental ultraviolet excimers that cut or shape the cornea to correct vision defects, the scanner's argon-ion laser serves simply as a high-tech measuring stick. Only two of the devices exist in the United States, and for now they remain experimental and too expensive for routine use. But Weinreb foresees a time when laser scanners will become common fixtures in ophthalmologists' examination rooms.

"There's no question in my mind that these are clinical tools that can dramatically change our current management of glaucoma," he says.

Others share his optimism. Carl Kupfer, director of the National Eye Institute in Bethesda, Md., says he's very enthusiastic about the technique. "The potential for the laser tomographic scanner is such that within a matter of milliseconds one can configure the size and contours of the optic nerve head," he says. "If this scanner pays off as we think it will, I think we're going to enter a new era in which lasers are used not only for ocular therapies but for diagnosis as well."



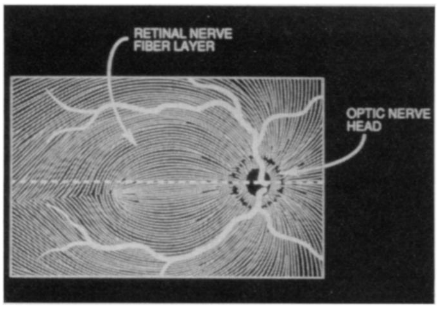
Photos: Weinreb

Another type of display generated by the laser tomographic scanner provides a three-dimensional image of the optic nerve head and measures the precise diameter and depth of the nerve-head depression. Images get stored on optical disks for comparison later, allowing eye doctors to track disease progression.

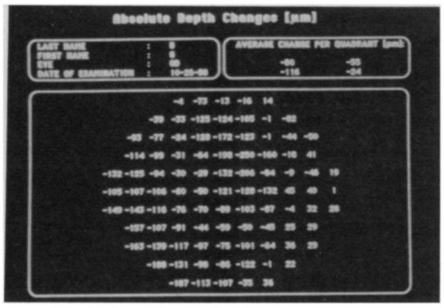
About a million nerve fibers from all over the retina converge at the optic nerve head. There they bend sharply and form a thick bundle, the optic nerve, which exits the back of the eye through a porous back door made of connective tissue.

Optometrists and ophthalmologists can visualize a patient's nerve head by peering into the front of the eye with an ophthalmoscope, and they can photograph the delicate structure to obtain a record of its condition. Viewed through the pupil and lens, the nerve head normally appears round or oval. An area of pallor in the center marks a small depression called the optic cup.

Enlargement and progressive asymmetry of the cup provide telltale signs of glaucoma. But normal cups vary considerably from one individual to another, making detection of these abnormalities difficult at best. Even when given a baseline image for comparison, professionals



Computer simulation shows a pattern of neurons lining the retina. An experimental device called the Fourier ellipsometer detects glaucoma-induced changes in this "fingerprint" as nerve degeneration proceeds.



Display format generated by laser tomographic scanner shows exact depths at different nerve-head regions. With conventional technology, eye doctors can only estimate nerve-head depression depths.

frequently have a hard time documenting gradual changes in a cup's dimensions using an ophthalmoscope or retinal photographic techniques.

Although a few new instruments for surveying nerve-head topography have entered the market in the past few years, including some that analyze digitally acquired images, they still rely on conventional optics, Weinreb notes. And in patients whose pupils won't dilate sufficiently or whose lenses are slightly clouded by developing cataracts — conditions found in up to half of all glaucoma patients — quality images remain elusive.

"Current diagnostic techniques are insensitive and subjective," Weinreb says. "They only allow detection of an abnormality when there has been considerable damage."

Ophthalmologists would like to identify individuals at risk of glaucoma-induced blindness much earlier than that, Kupfer says. For lack of more reliable methods, they resort to measurements of intraocular pressure or examinations to detect loss of peripheral vision — tests that are "time consuming and subjective" he says.

"We have very sophisticated instruments to do these things," Kupfer says, "but it takes 15 to 20 minutes and there are many false positives and false negatives."

What ophthalmologists need, Weinreb explains, is an "accurate, reproducible and sensitive diagnostic technique that would allow both earlier diagnosis and earlier detection of progression. In turn, this would enable initiation of appropriate therapy."

To create a device capable of measuring subtle variations in inner-eye terrain, Weinreb (who earned a degree in electrical engineering before going to medical school) combined forces with Andreas Dreher, an optical scientist and physicist at the University of California, San Diego, and Gerhard Zinser, a physicist in Heidelberg, Germany.

Their laser tomographic scanner utilizes the principle of confocal imaging, which predicts that in a properly constructed optical array, a light detector will selectively "notice" photons originating from a very specific distance. In practice, it involves shining a laser beam into the eye and focusing it on an imaginary plane near the top of the optic nerve head. A computerized control system moves the beam across and down — as though reading lines on a page — until it has scanned the entire plane and stored any reflected points as an array of dots, or pixels, similar to those that illuminate images on computer screens.

The procedure then repeats itself on successively "deeper" planes, storing the reflected points of contact at each level.

Weinreb and his colleagues scan 32 consecutive planes, each deeper than the last by 30 to 60 microns, or less than the diameter of a human hair. In doing so, the team creates a series of images that describe the contours of consecutive "slices" through the optic nerve head. A computer then manipulates those data into full-color images — each one 256 by 256 pixels — and stores them on an optical disk.

"It's fascinating stuff," says Kerry Assil, who uses the nation's other laser tomographic scanner to measure corneal curvatures at the Bethesda Eye Institute in St. Louis. "Bob should be commended. He's got the right idea with glaucoma. Nerve topography is the way to go."

Weinreb concedes that the system remains expensive. But he expects the machine's cost — now more than $100,000 — to come down as the technology improves and more of the devices reach the market. Ten of the laser scanners are now in use in Europe for ophthalmic and other purposes, he notes.

Weinreb also expresses optimism that another experimental device he has helped develop, called a Fourier ellipsometer, will detect even earlier signs of glaucoma. The machine detects changes in the polarization of light reflected from retinal nerve fibers. In doing so, it measures the thickness of these fibers while noting changes in their fingerprint-like pattern along the back of the eye. Studies suggest that such changes often precede nerve-head deformations in pre-glaucomatous eyes, Weinreb says.

Besides allowing earlier detection and treatment of glaucoma, both the laser tomographic scanner and the Fourier ellipsometer should prove helpful in clinical trials of new glaucoma drugs, he adds. With the ability to measure subtle improvements (or progressive declines, when drugs don't work) in glaucoma indicators such as cup depression or nerve fiber patterns, researchers should be able to assess the effectiveness of experimental drugs much more quickly, Weinreb suggests.

Indeed, says Assil, the techniques have already uncovered more details about retinal structure and pathology than researchers know what to do with. "It's providing the ophthalmic community with a whole new set of information, much of which we haven't even figured out how to use," he says. "The science is ahead of our intelligence right now. But we'll catch up." □

Glaucoma's roots and risks

Nobody knows exactly what lies at glaucoma's roots. In many cases, the degenerative syndrome emerges when fluid in the front chamber of the eye fails to drain properly, causing a pressure buildup that gradually destroys sensitive retinal neurons. But in many other cases, high fluid pressures either don't develop or remain transient and undetected, leaving ophthalmologists generally mystified by the progressive loss of vision that ensues.

Beyond the 2 to 3 million U.S. patients already diagnosed with glaucoma, an additional 10 million are considered at risk for the disease by virtue of high intraocular pressure, extreme nearsightedness, diabetes, black race or a family history of glaucoma. Of those patients deemed at risk because of high intraocular pressure, about 1 percent go on to develop the disease each year.

The most common form of glaucoma, chronic open-angle glaucoma, usually strikes after age 30 in people with a family history of the disease. Early symptoms of headaches and blurred vision often get blamed on nervous tension or sinus problems. Without treatment, these individuals will lose peripheral vision and eventually go blind. *— R. Weiss*