HOW TO USE NERVE FIBER LAYER EXAMINATION IN THE MANAGEMENT OF GLAUCOMA*

BY *Harry A. Quigley,* MD AND *Alfred Sommer,* MD

INTRODUCTION

WHY DO WE NEED TO LOOK AT THE NERVE FIBER LAYER?

DURING THE PAST 20 YEARS, SHIFTS IN GLAUCOMA DIAGNOSIS AND MANAGEMENT have occurred that affect almost 20 million Americans with intraocular pressure (IOP) above the statistically normal range. Prior to 1960, most such eyes received drop therapy to lower IOP, whether the optic nerve was judged to be damaged or not. Then, it became clear that some glaucoma suspect eyes with elevated IOP had normal visual field tests and continued to test normally for years without therapy. The era of "non-treatment" began. More recently, it has become clear that some glaucoma suspects with normal field tests have already suffered optic nerve damage.[1] These eyes we clearly wish to treat, on the assumption that further damage will be prevented.

This report describes nerve fiber layer (NFL) examination to detect eyes with glaucomatous damage. The method is simple to perform and clearly no more difficult to learn than stereoscopic disk evaluation. Because no response is required from the patient, it is not as subjective as field testing. The equipment necessary is present in every opthalmic office (direct ophthalmoscope and slit lamp/contact lens). NFL examination can reliably identify over 90% of eyes that have a visual field defect.[2-4] Furthermore, it can separate out of the pool of glaucoma suspects a subgroup (about one-fourth) that have damage prior to detectable

*From the Wilmer Institute, Johns Hopkins University School of Medicine, Baltimore, MD. This investigation was supported in part by PHS Research grant EY 02120 (Dr Quigley), EY 03605 (Drs Sommer and Quigley), Core Facility grant EY 01765 (Wilmer Institute), and unrestricted funds provided by the American Health Assistance Foundation, National Glaucoma Research, Washington, DC.

field loss. These eyes are now known to develop optic nerve damage fastest, and thus merit strong consideration for treatment. The NFL examination does not replace field testing, but is a complementary way to gather information.

WHAT IS THE NERVE FIBER LAYER?

In the human eye, there are about 1 million retinal ganglion cells, each sending one axon across the retina to the optic nerve head. As these fibers converge on the disk, their thickness is almost 0.5 mm. The fibers group into bundles and, when they are thick enough, the bundles reflect light back as bright, white lines.[5,6] The thicker the NFL, the brighter are the white striations (Fig 1). The bundles are seen best with a dark background. This is produced by using green illumination. Green light is absorbed by the melanin of the pigment epithelium and choroid, making

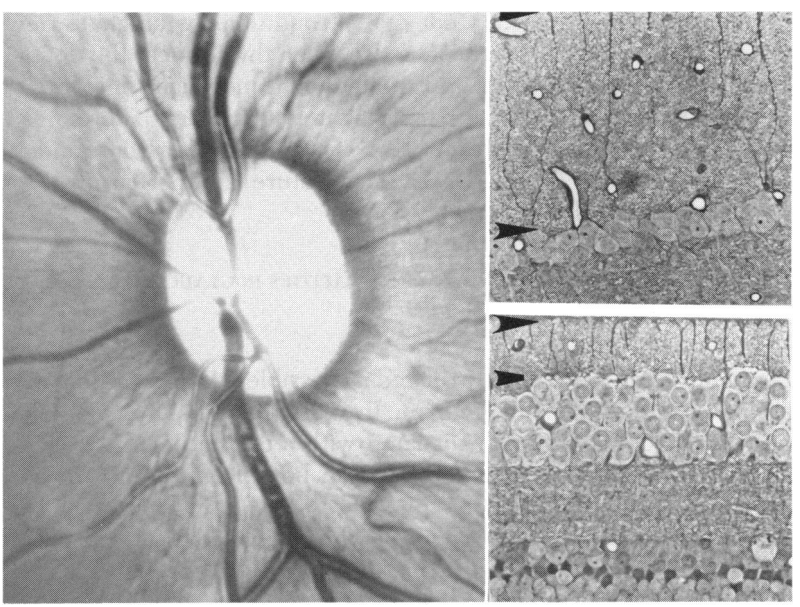


FIGURE 1

Clinical photograph shows normal NFL appearance. Brightest white reflexes are typically at 12 and 6 o'clock positions near disk, with less reflective or darker NFL appearance nasally and toward the macula. This occurs because the brightness of the NFL is proportional to its thickness. Upper right photomicrograph shows normal thickness of NFL at 12 o'clock position (between *arrowheads*), compared to thinner NFL in lower right micrograph taken near temporal disk rim.

the NFL bundles stand out against a black background. The standard green filters on ophthalmoscopes and slit lamps are perfectly adequate for enhancing the NFL view. Since the filters cut down on the total amount of light, the ophthalmoscope or slit lamp should be on their brightest settings.

The NFL bundles make a turn into the optic disk and become the disk rim. Here, their combined thickness determines the disk cup size. NFL examination simply evaluates the state of the fibers of the disk rim back on the retina. Why should that provide any advantage over a stereoscopic disk examination? In some eyes, damage can be easily detected at the disk, and the NFL examination is merely a confirmation. In other eyes, the disk has a normal appearance and the NFL examination again confirms the impression. There are many eyes, however, with disks that are neither clearly normal nor abnormal and the NFL appearance can add useful information.

The NFL is quite thick at the disk, but rapidly thins out going to the periphery. Therefore, the brightest reflections are normally within 1 disk diameter of the nerve head. Under some conditions, wide-angle views of the NFL may be useful. The NFL is also much thicker near the upper and lower poles of the disk than on the horizontal meridian temporally and nasally. The thick the NFL is, the brighter it appears. Therefore, in a normal right eye, the brightest NFL zones are between 10:30 and 12:30 o'clock and between 5:30 and 7:30. This feature is important in recognizing glaucomatous damage.

HOW DO WE FIND NFL ABNORMALITIES IN GLAUCOMA?

GENERAL TECHNIQUE

The pupil should be as widely dilated as possible. Where chronic miotics or surgery limit pupil enlargement, the direct ophthalmoscope allows a better view. Otherwise, the slit lamp with a contact lens is preferable. With this combination, magnification can be optimized and the illumination is brighter. In addition, the stereoscopic disk appearance can be assessed with the same equipment in white light. One can use a fixation light before the opposite eye to position the view precisely, beginning just above or below the disk margin. The slit beam should be fairly narrow and is often best positioned to one side. One should look for a NFL pattern at the level of the major retinal vessels.

INITIAL EXAMINATION OF THE ARCUATE ZONE

If no pattern is seen, there are three possibilities (Fig 2): (1) the view is

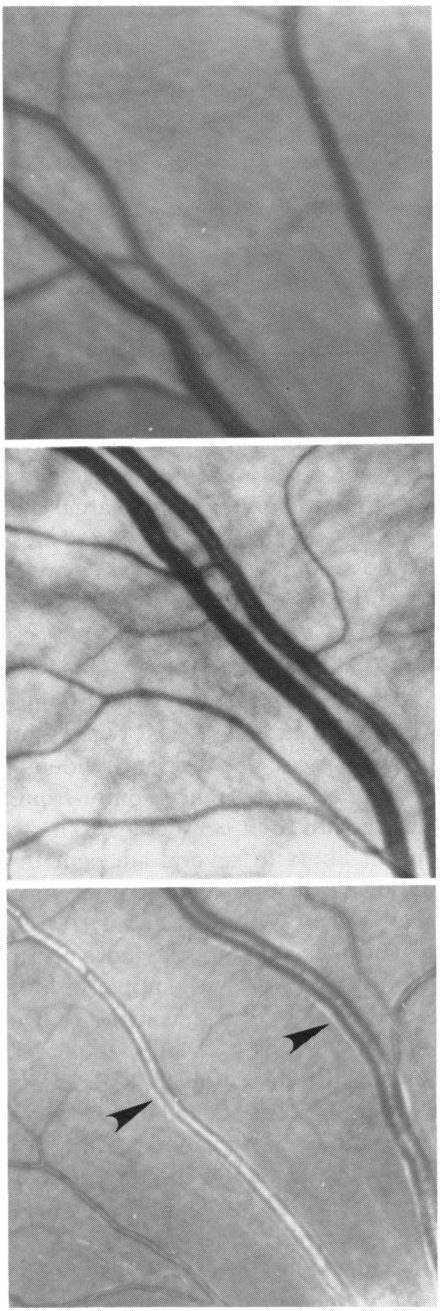


FIGURE 2

When the NFL is poorly seen, there are three possible explanations. Top: Both blood vessels and NFL are blurred when media opacity is in the way (cataract). Middle: Vessels are clearly seen, but background pigmentation is too blonde for green light to be absorbed. Thus, reflection from choroid swamps NFL reflections. Easily visible choroidal vessels indicate that this is the case. Bottom: A poor view of NFL, but vessels are well seen and background is dark. This is true NFL diffuse atrophy. Note that loss of surrounding nerve bundles allows walls of arterioles and venules to be seen (*arrowheads*).

not properly focussed; (2) the fundus is that of a blonde person with too light a background; or, (3) the NFL is atrophic and no pattern is present. If the pigmentation is too light, then NFL examination will not be possible. This is infrequent, but may occur in 5% of eyes. To proceed, one should try to refocus and to reposition the light for a better view. If striations can now be seen, they should be uniformly present and brightest in the 2 hours between 10:30 and 12:30 o'clock (in the right eye), along with its corresponding inferior mirror image area. Occasionally, the normal NFL appearance has 1 or 2 dark, slit-like zones running along the arcuate bundles. These are not abnormal if they are thinner than a small arteriole in width and the rest of the NFL in this zone is bright.

EARLY GLAUCOMA DEFECTS

Perhaps the most easily recognized early defect in glaucoma is *the wedge defect* (Fig 3). A wedge is dark and at least twice as wide as an arteriole, though its width narrows near the disk and widens peripherally, since bundles converge. The dark appearance comes from loss of NFL thickness as fibers die (along with their cell bodies). The wedge defect results from loss of a group of fibers in several adjacent bundles at the nerve head. It is a highly localized injury and may be associated with a local scotoma in the visual field.

While wedges are more easily seen, the more common early finding in glaucoma is *a diffuse loss of fibers*[7] in the upper or lower arcuate area (Fig 4). A wedge is detected because of high contrast between its dark atrophy and bright, white normal NFL on each side. To detect mild diffuse loss of NFL, we must enhance the detection of NFL loss in two ways. First, retinal vessels run within the NFL and all but the largest of them near the disk are normally buried in nerve fibers. This NFL surrounding the vessels blurs our view of the vessel walls. In a normal eye, the first and second branchings of arterioles and venules are always blurred by overlying NFL. Mild diffuse atrophy of the NFL bares the first order branches of vessels, bringing their walls into sharp view. Moderate and severe NFL atrophy uncovers the smaller vessels. Thus, the first method to

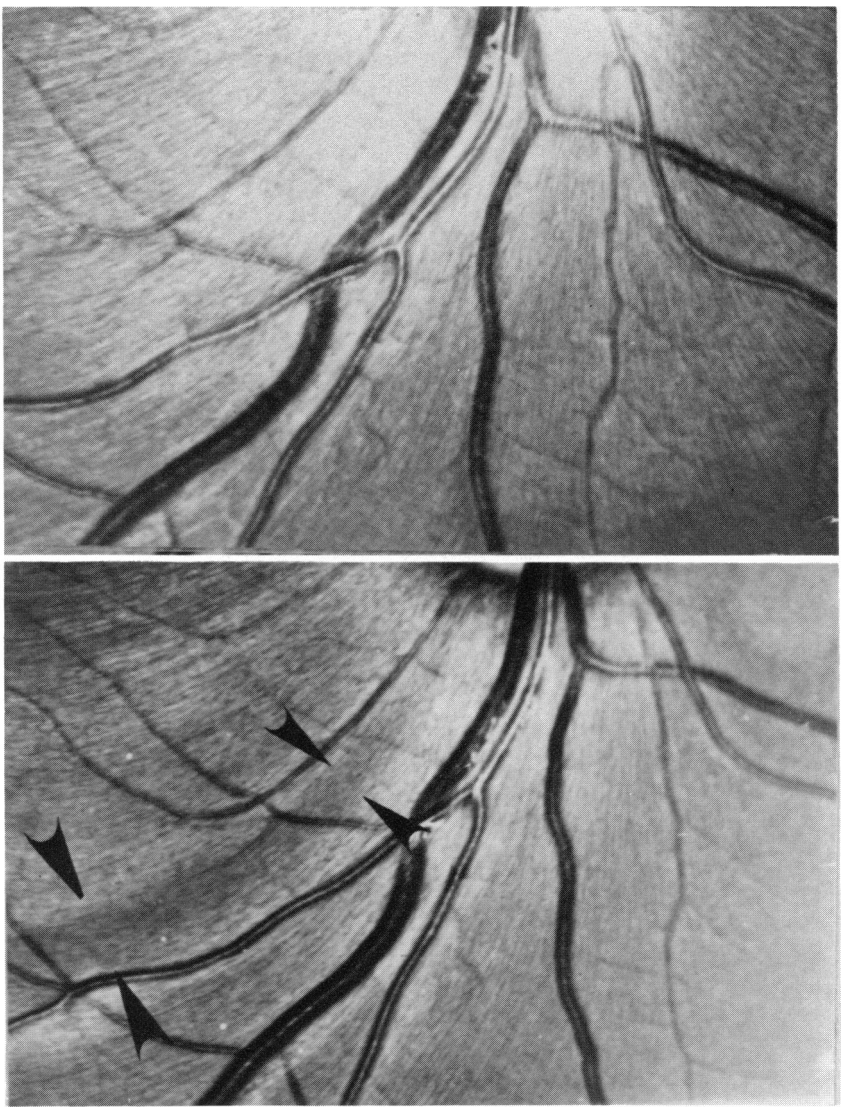


FIGURE 3

This photographic pair shows a monkey eye before (above) and after (below) development of a wedge-shaped NFL defect in inferior arcuate area (between *arrowheads*). Notice that in darker (hence thinner) NFL zone of wedge, arteriolar branch crossing just below *arrowheads* is seen much more easily due to loss of overlying nerve fiber bundles.

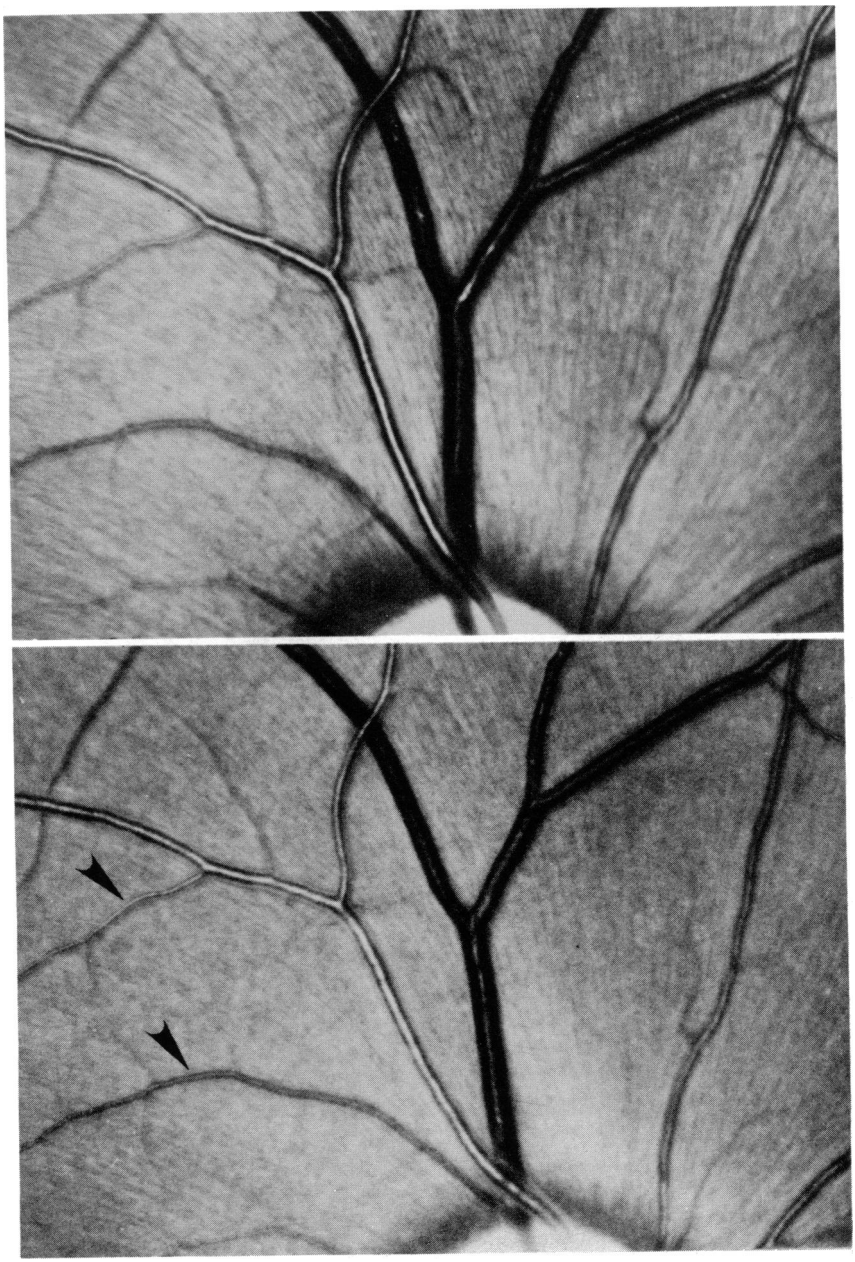


FIGURE 4
Before (above) and after (below) development of mild diffuse NFL atrophy, the most common finding in early glaucoma. In the lower picture, NFL is still seen, but bundle lines appear more sharply drawn (finely etched). Vessels indicated by *arrowheads* are good examples of those that were formerly more covered by nerve fibers in the normal photograph above. Their easy visibility in what should be the thickest NFL zone (near pole) points to atrophy.

detect mild NFL loss is to examine the clarity of blood vessel walls (Fig 2).

A second approach to confirm the impression of diffuse atrophy is to compare the area in question with the remainder of the NFL in the same eye. The pattern should be bright above, dim toward the fovea, then bright again inferiorly. If there is a discontinuity in this bright—dim—bright pattern, or if the upper arcuate zone is not as bright as the lower one, diffuse atrophy is present. This is identical to comparing the upper and lower disk rim for a local narrowing or notch (Fig 5a, b, c).

One can also compare the two eyes for NFL asymmetry (Fig 5b and c). If we suspect upper arcuate diffuse atrophy in the right eye, then the upper left eye arcuate zone should be examined. Alternation between the two eyes is sometimes necessary; this is easier with the direct ophthalmoscope, but is possible with the slit lamp. It is comparable to looking for cup/disk ratio asymmetry between the two eyes.

HOW SENSITIVE IS NFL EXAMINATION?

Histologic studies have shown that 50 μ of NFL thickness produces a bright enough reflex to be visible, while striations become indistinct when NFL is thinner than this. Likewise, a wedge defect can be seen when the atrophic area loses more than 50 μ of NFL adjoining a 50 μ of tissue loss would mean 15,000 fibers dead. This is about 1% of the optic nerve's total fiber number. Usually, however, a more diffuse pattern is seen (Fig 6a and b) and atrophy would have progressed beyond this point before detection. The method clearly has sufficient sensitivity to find glaucomatous damage at an early stage.

FURTHER PATTERNS OF NFL LOSS

As NFL atrophy worsens, there is sometimes a mixture of 2 or 3 *local wedge defects superimposed on moderate diffuse atrophy* (Fig 5c). One's eye is often drawn in this circumstance to the wedges, but careful inspection of the intervening areas shows that blood vessels are not adequately covered.

Where diffuse atrophy is uniform, the NFL pattern not only thins, but the lines between white linear stripes become more organized, almost as

if drawn by hand. This *finely etched appearance* should be recognized as a stage of moderate to severe atrophy (Fig 4).

When there is *severe diffuse atrophy*, no striations at all are seen. All blood vessels stand out in sharp relief. Their white walls are now easily seen as well as their red blood columns (Fig 2). These white walls are

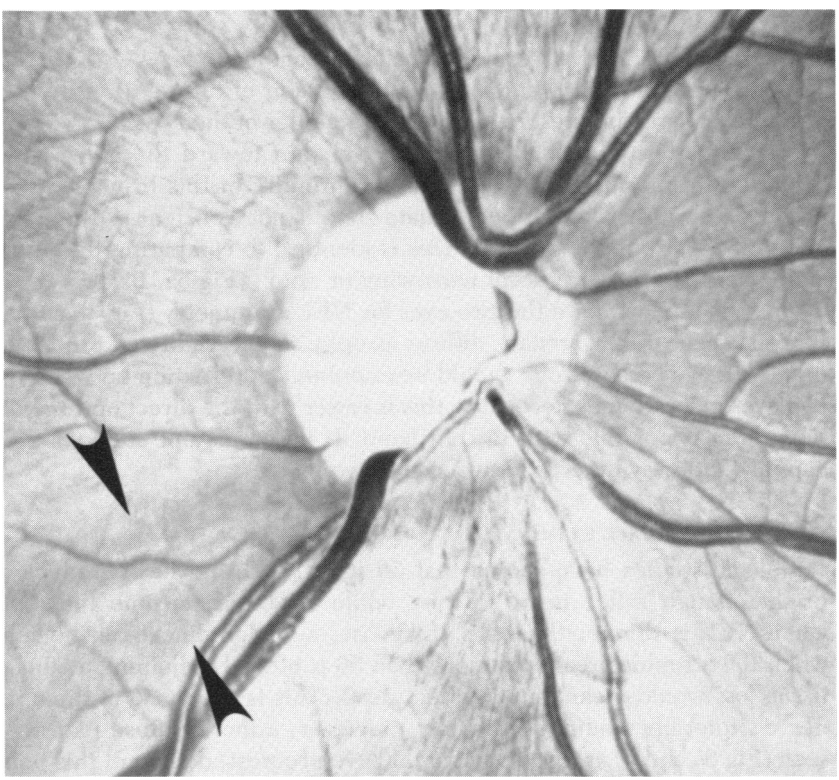
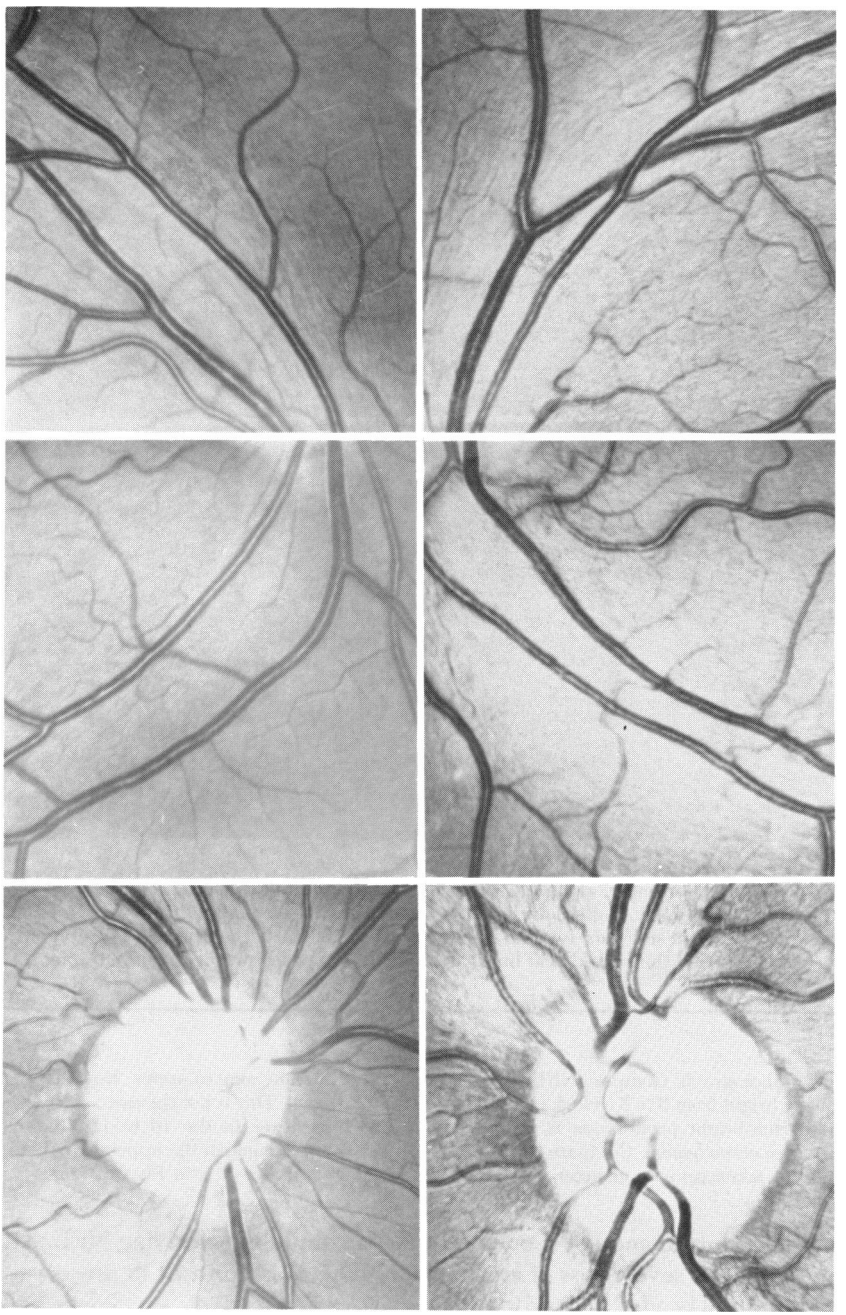


FIGURE 5A

Compare upper to lower NFL in this eye. There is a broad wedge-shaped defect in inferior NFL. This is most easily seen by comparing the upper to the lower NFL (one use of symmetry to detect NFL change). This patient had the defect during 2 years of follow-up with normal quantitative fields, then developed an upper field defect while being followed with mildly elevated IOP.

FIGURE 5B

Compare the upper to the lower NFL, the right to the left eye. The right eye pictures (left side) show generally less reflective NFL (diffuse atrophy). The lower right eye (middle left photo) can be seen to have a slightly greater degree of atrophy than the upper right eye (upper left photo).



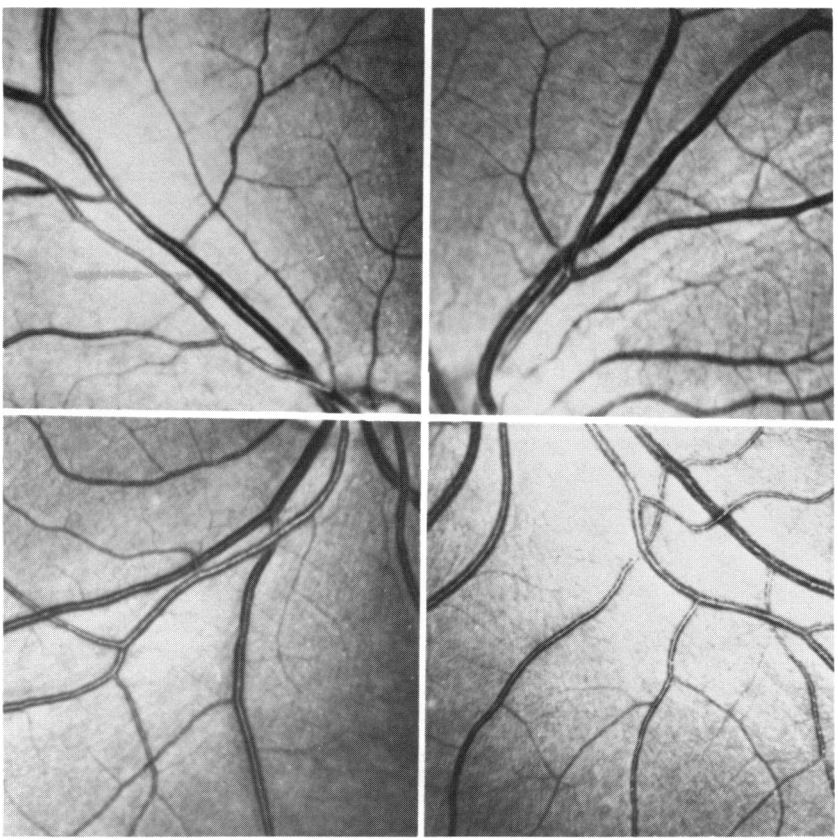
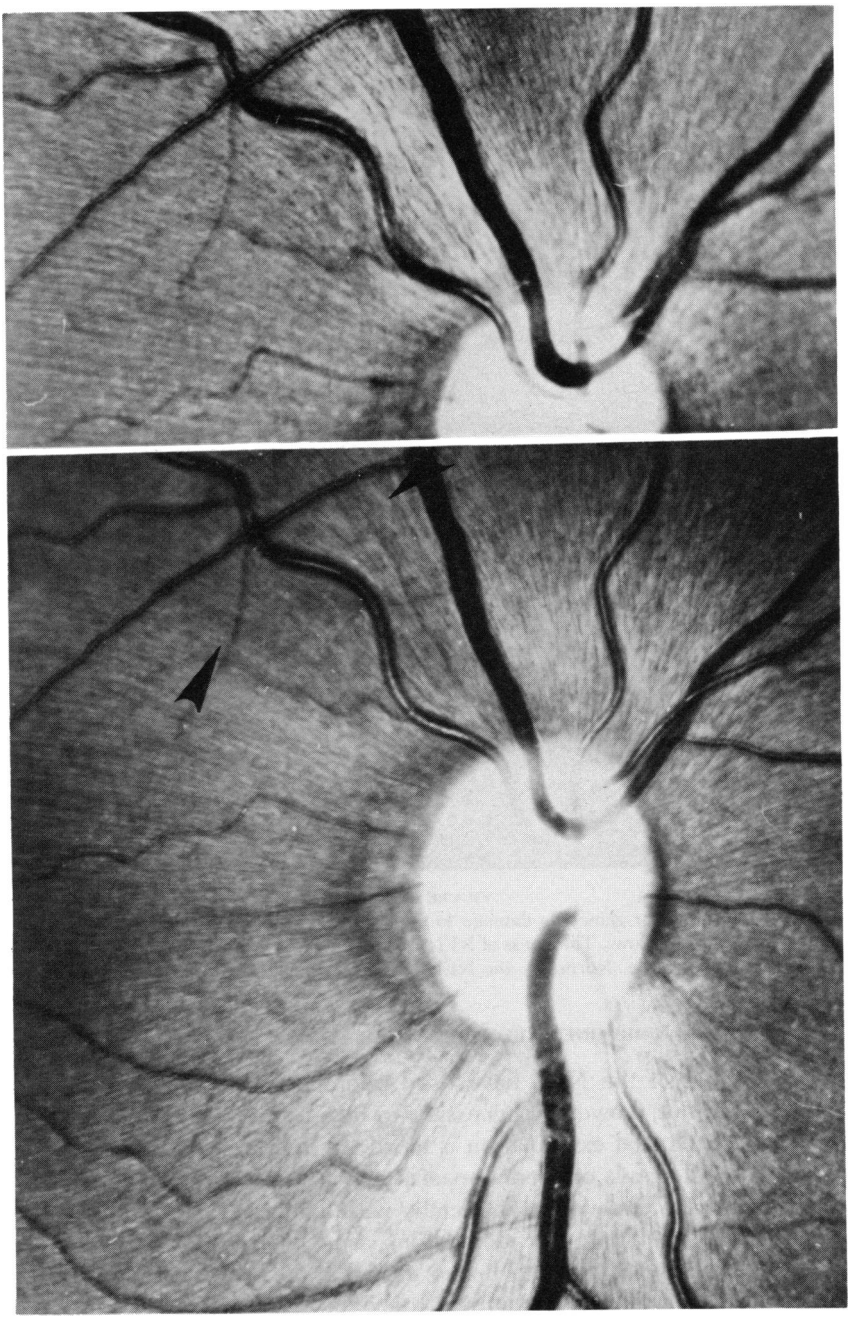


FIGURE 5C
Compare the upper/lower, right/left zones of NFL. In the right eye (left pair), the lower NFL is clearly atrophic. Note both loss of reflexes and easy visibility of small vessels. The upper left eye (right side pair) is not as brightly reflective as the left inferior NFL. Its pattern contains several thin, dark local linear defects superimposed on the overall atrophy.

FIGURE 6A
Lower photograph: Compare NFL appearance in lower arcuate zone to upper. It should be equally bright from 6 to 8 o'clock compared to 10 to 12 o'clock. This is not the case, since the bright-dim-bright progression is broken up by loss of reflexes in the 10 to 11:30 zone (between *arrowheads*). Compare this zone to its original appearance in the upper-half photo taken prior to glaucoma damage. The histology of this eye is in Fig 6B.

normally blurred and not seen due to the surrounding/overlying NFL. At this stage, the severe loss of arcuate zone NFL is in contrast to preservation of fibers headed toward the fovea.



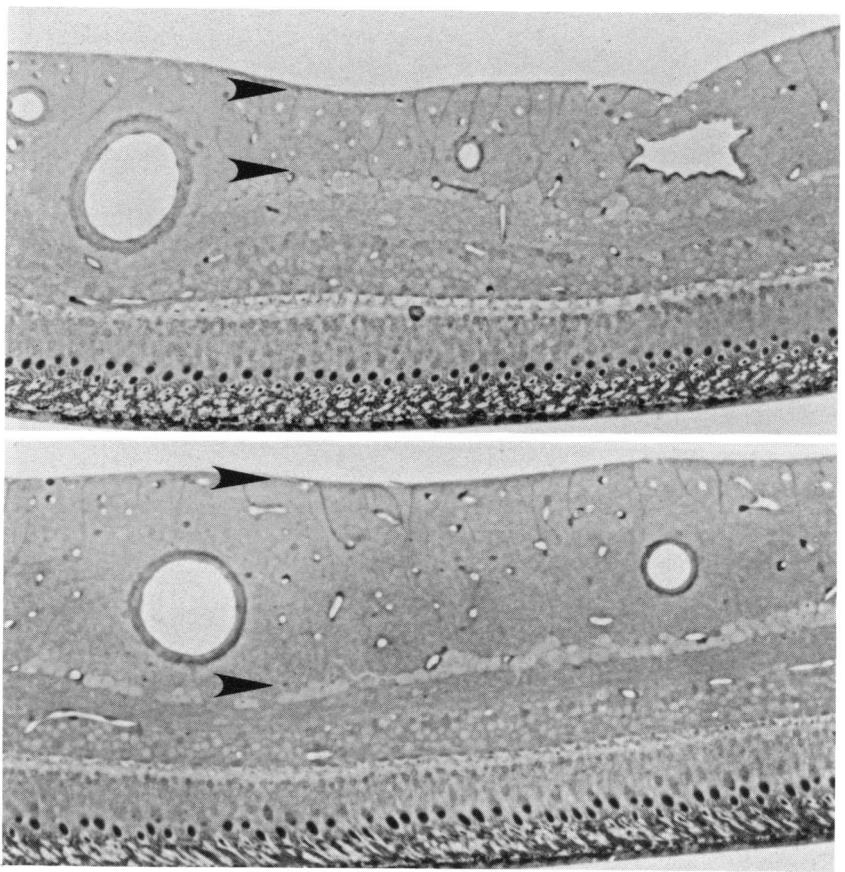


FIGURE 6B
Retina of eye in 6A after glaucoma damage to upper NFL (upper photomicrograph), compared to lower NFL (below). Thickness of NFL (between *arrowheads*) is decreased by more than half in this example. Normally, the NFL would be equally thick in these two areas.

DOES ONE NEED TO PHOTOGRAPH THE NFL?

Clinical studies of the NFL have used photographs to document their findings. It is not, however, necessary to take a picture to evaluate the NFL. In fact, clinical examination is more accurate than photography in eyes with small pupils or media opacity. Sometimes, photographs facilitate routine NFL evaluation, especially with a somewhat uncooperative patient. In such persons, the "stop-action" aspect of photography allows a well-focused view, while the clinical examination is simply frustrating. Furthermore, it is easier to compare the right and left eyes of the same

person with photographs, though this can be done clinically. Without question, it is useful to have documentary photographs for long-term follow-up, just as stereoscopic disk pictures facilitate longitudinal disk cup comparisons.

If one wishes to take photographs of the NFL, the best method uses a 30-degree (standard) fundus camera. With the Zeiss camera (SBG-720 power supply, 480 watt-second, 1.6× magnifier), a short pass 560 cut off filter is placed in the filter slider on the side of the camera (Detric Optics, Hudson, MA). The film is Kodak Technical Pan 2415, developed in D11 (1:1 water, 8 minutes, 70°C). Some use wide angle photographs (60°) with special processing of prints to eliminate excessive contrast.

WHEN IS THE NFL ABNORMAL?

NFL abnormality often appears at an early phase of glaucoma damage. This concept is supported by the following clinical study. A group of glaucoma suspects with elevated eye pressure but no field defects were examined for NFL findings. Then, they were followed for several years with repeated field testing. At the start of the study, about one-fourth of the suspects had detectable NFL abnormality, most commonly this was mild diffuse atrophy. About 1% of suspects per year of follow-up developed their first field defect. Thus far, over 90% of the eyes converting to field loss have come from the suspects with NFL abnormality. When this study is complete, we expect that it will be clear that glaucoma suspects with NFL abnormalities are those eyes that have early optic nerve damage and merit aggressive pressure-lowering therapy.

THE FUTURE

The computer revolution has spread to analysis of the optic disk. Several instruments now are being tested to evaluate the cup/disk ratio automatically via a computer linked to a fundus camera. The most immediate result of this system is to analyze the disk better. For example, we have suspected for some time that the optic disk can vary in its diameter from person to person. If each of us has the same amount of normal disk tissue, but some eyes have bigger disks, then those eyes will have larger cup/disk ratios as a normal finding. We are often presented with eyes that have a 0.6 cup/disk ratio and we wonder whether this is normal for that eye. The disk analysis systems may be able to determine the actual area of the disk rim.[8] If this is reliably specified, then we can say whether a 0.6 cup is normal or represents an eye in which the original cup was 0.2 and atrophy

has occurred.

High level image analysis systems may be able to ascertain whether the NFL and disk appearance are normal or abnormal even better than our eye. If neural atrophy gives tell-tale signs that can be detected by sophisticated computer analysis,[9] Then glaucomatous damage may be detected even earlier. We appear to be only in the infancy of this science.

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DISCUSSION

Dr Robert N. Shaffer. The Glaucoma Service of the Johns Hopkins University has added a great deal of important new information concerning the optic nerve in recent years. Who would have thought that it is possible to lose 40% of the optic nerve without producing a field defect? Who would have thought that all of us have been losing 5000 optic nerve neurons per year through our lives? The authors have now extended the work of Hoyt and Newman in visualizing defects in the nerve-fiber layer.

The authors give a clear description of the nerve-fiber layer and how to examine it. They believe that defects in the layer can have diagnostic and prognostic value. In a group of ocular hypertensive subjects, 25% were found to have nerve-fiber layer defects. In this group, a surprising 1% per year developed field defects. This is a much higher percentage than was found in the Collaborative Glaucoma Study of ocular hypertensives. I wonder if the study groups are truly comparable.

The report brings up a number of questions. How many ocular hypertensive

patients comprised the study group and what was the range of the intraocular pressures? In particular, what happened to the 75% of ocular hypertensives who had no defects in the nerve-fiber layer at the beginning of the study? How many of this group developed defects in the nerve-fiber layer or field loss by the end of the study? In the 25% who had defects in the nerve-fiber layer, could the subsequent development of field loss be due to the inevitable continuing loss of 5000 neurons per year rather than from the increased intraocular pressure?

There is no doubt that the technique is a fascinating research tool. I have some reservations on its clinical use. In a study at the University of California, the accuracy of skilled observers in predicting field loss dropped off markedly when the disc was masked. Without the extensive experience of the authors, borderline normals, and abnormals can look much alike. Are we justified in subjecting our patients to the side-effects, expense, and nuisance of therapy before disc change or field loss occur? There are unconfirmed reports of increased field loss in eyes treated with beta-blocking agents despite significant decrease in intraocular pressure.

Years ago Doctor Oliver Wendell Holmes wrote, "If all the medications known to man were thrown into the ocean, it would be the better for mankind and the worse for the fishes!" Therapeutic decisions must be solidly based. Continued investigation is clearly indicated. I am sure Doctors Quigley and Sommer will have increasingly definitive answers in the near future.

DR MAX FORBES. This is just a brief question. Doctor Quigley has presented this very beautifully and I have listened to his discussion of this previously and attempted to learn this technique. I think I am getting better at it as time passes. It seems to me that I do well with younger patients but when we get up to the 70-year-old group I have a much harder time identifying the nerve fiber layer. I would just like Doctor Quigley to comment on the ability to use this diagnostic technique with respect to the aged patient.

DR BRIAN YOUNGE. I have just one comment to make that I often make to my residents. As a neurophthalmologist this is one of the areas that I have been interested in for a long time. The point that I teach our residents is that the absence of something normally present and subtly seen only with careful examination is much harder to see than the presence of something manifestly abnormal—like a big hemorrhage. So you have to think about what you're looking at in order to see it or notice its absence.

DR BENJAMIN SHEPPARD. Doctor Quigley has given us some of the most beautiful pictures in the presentation this morning. The thing I am interested in and want to ask a question in a second or so is related to a similar work I have done on the corneal epithelium fragility. In our research, which has been presented here, it has been found that early diagnostic epithelial changes have been observed suggesting glaucoma before the tonometer. In this study we comparatively used the staining of our fragile epithelial smears with Papanicolaou and Giemsa stains.

The question I would like to ask is this—do you think the increase in intraocular pressure leads to anesthesia affecting the normal function of the corneal epithelium?

Now to digress from this up-to-date paper, but still stick to glaucoma, Doctor Maumenee has presented something this morning that goes into a value of history which stays in the books. History, gentlemen, is relatively permanent. Now we go back a few years to 1938 when we had a train load of physicians leave Chicago for a 3-week trip to our American Medical Association Meeting in San Francisco. To me the outstanding presentation in the ophthalmological section on that medical trip was when Doctor Otto Barkan was doing the first corrective buphthalmic surgery I had ever seen. That was 50 years ago gentlemen.

I know our President, Doctor Frank Newell, presented this morning something on the history of our President's medal. I hope many of you will have a chance to study it as he suggested.

Dr Angelos Dellaporta. I would like to congratulate Doctor Quigley for his excellent work in this field. We have done similar red free nerve fiber studies at Stanford for the last 7 years and we have collected some experience. Doctor Roloff is our expert and I would like to say that it is very difficult sometimes to decide whether the nerve fibers are destroyed or not, as Doctor Quigley mentioned, especially in the situations he enumerated. It is sometimes also very difficult to decide whether the nerve fibers are destroyed, as Doctor Shaffer says, inspite of good photography. I continuously challenge Doctor Roloff to tell me whether a particular eye has glaucoma or not while concealing the disc and sometimes he cannot say so. One question I want to ask Doctor Quigley. How many fibers have to be destroyed to get a visible nerver fiber defect in photography or under examination clinically?

Dr Harry A. Quigley. It certainly was fun to have Doctor Shaffer discuss this paper this morning because much of what I have done in the last 15 years has been chasing ideas that he published and things that he felt were important and this certainly is one of them. He has asked some very important questions. First, whether or not the patients who we are following in our clinical study now are similar or not to those who were in a collaborative glaucoma study. In fact, the two groups were not constituted in the same way. In the collaborative study, as I understand the composition of the patients, there was a lot of family history positive patients who did not at the time they entered the study have glaucoma in the sense of having an elevated eye pressure. So, in fact, there were a lot of normal people who would not have been expected to develop glaucoma damage if it is related to pressure. On the other hand, studies from Europe and one or two studies in the United States now indicate that an unselected group of ocular hypertensive patients with pressures above 21, but generally below 30 (the range of the 900 glaucoma suspects who we follow in our study) develop field loss at a rate of about 1% per year. In our study about 25% of the eyes are presently receiving therapy (whether or not they are taking it no one knows). It appears to

be fairly standard in many studies. We were not surprised that we only had now a total of about 55 patients convert from no field loss to the stage we call field loss. You asked how many patients who did not have nerve fiber abnormalities at the start of the study have developed field loss. Well, we have approximately 200 patients who have nerve fiber layer abnormality among the 900 total. Thirty-five people have developed field loss and 30 of those have an abnormal nerve fiber layer examination. So that 30 out of 200 is the rate of patients who have abnormal nerve fiber layers. Three out of 700 is the rate of field loss development in those who were read as having no nerve fiber layer defect. That has almost achieved statistical significance now that our numbers have reached about 50 or 55 people who develop field loss. So that is why we can say that this is something that predicts which patients are going on to field loss. Now it is very important to distinguish between a study that says how many nerve fibers somebody has in their eye and how somebody's nerve fiber looks and how you behave. It is the reason I began this talk with saying: whether this leads you to follow a patient more carefully or leads you to begin treatment with medicines or surgery is *up to you*. I didn't say that you should treat people who have nerve fiber layer abnormality, I am merely pointing out that this represents a way to distinguish patients who were in an early stage of losing their optic nerve function. We do need to have therapy studies without any question we need to have a serious large scale study to determine whether pressure lowering with each specific agent is good for the patient. But that really isn't an issue here today. The issue today is whether or not this demonstrates damage.

The final issue Doctor Shaffer raised is whether pressure is related to glaucoma or not—an exciting area that I think over the years has been something that is probably the most serious question in glaucoma. If we take a monkey's eye and raise the eye pressure to an average of 32 mm of mercury and leave it there for 18 months, the optic disc becomes indistinguishable from a human eye with glaucoma. The optic nerve loses nerve fibers in a pattern which is identical to the pattern that a human eye with glaucoma loses nerve fibers. So in essence we have fulfilled Koch's postulates with elevated IOP. If you produce an elevated eye pressure, it produces glaucomatous optic neuropathy. How many patients have normal eye pressure and develop glaucomatous neuropathy we are attempting to find out in a prevalence study in Baltimore. What is the true prevalence of low tension glaucoma?

Doctor Forbes' question about age is important; we can still tell the nerve fiber layer finding in aged patients. Our average age of people in the study is about 55 years. It is sometimes harder and sometimes easier in older patients, but we have not detected an age difference in terms of increasing false positives. In the normal group, we studied 150 normals.

Doctor Sheppard, I can't say anything about the cornea. We haven't studied it.

Doctor Dellaporta suggests that it may be difficult to learn to examine the nerve fiber layer. As we teach our residents, they think it is about as hard as learning to examine the stereoscopic and cup appearance. Each of us learned to evaluate the stereoscopic appearance of the disc, and the nerve fiber layer really isn't different.

My thesis gives the figures that Doctor Dellaporta asked about in terms of the number of fibers under ideal conditions you can see. An individual wedge, one of those small wedge defects, could represent a loss of as few as 30,000 fibers. So, under ideal and perfect conditions, you potentially could find that small a loss. It is extremely unlikely that under real conditions you would be able to detect that, and, since the more common pattern is diffuse atrophy of the upper and lower poles, it is more likely that we are not going to see anything less than perhaps 100,000 fibers gone.