

# Progression, Clinical Trials and Prostaglandins:

A Summary of  
the Optometric  
Glaucoma Society's  
Second Annual Meeting

Supported by an  
unrestricted educational grant from



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## INTRODUCTION

On behalf of the Optometric Glaucoma Society (OGS), it is with pleasure that we bring you this supplement containing the proceedings of our second annual meeting, held in December 2003 in Dallas. The OGS has several objectives, including the enhancement of care for patients with glaucoma as well as aid in the glaucoma education for optometrists. The OGS would also like to play a role in developing research related to glaucoma. The Optometric Glaucoma Society is a member of the Association of International Glaucoma Societies (AIGS) with by-laws and membership criteria comparable to the other member societies. Information on membership as well as other programs is available at [www.optometricglaucomasociety.org](http://www.optometricglaucomasociety.org).

The themes for our second annual meeting were "New Developments in Perimetry" and "Clinical Trials in Glaucoma." These areas were explored in talks by Ronald Harwerth, Chris Johnson, Anders Heijl (the 2003 OGS Honoree), Paul Palmberg, Richard Parrish, and Robert Feldman. In addition, at the onset of the meeting, a scientific session was held with papers presented by Thomas Freddo, Leo Semes, Mitchell Dul, William Swanson, Murray Fingeret and Shaban Demirel. John Flanagan was chair of the program with John McSoley serving as meeting chairman.

We would like to thank Drs. Anders Heijl, Paul Palmberg, Richard Parrish, Robert Feldman, Ronald Harwerth and Chris Johnson for allowing us to share their material with you. We would also like to thank Drs. Tony Litwak, Shaban Demirel, Mitchell Dul and Michael Chaglasian for their help in preparation of this supplement. We would also like to thank Pfizer Ophthalmics for providing an unrestricted educational grant to support the development of this supplement. We hope that this information proves useful in your care of patients with glaucoma.

**Murray Fingeret, OD**  
*President, Optometric Glaucoma Society*

*“In eyes with glaucoma, retinal nerve fiber layer injury often involves the superior and inferior optic nerve, even when achromatic field defects are limited to one hemifield.”*

*—Murray Fingeret, OD*



## New Science

### **Protein and Aqueous Outflow Resistance** *Study suggests plasma-derived proteins in aqueous humor are added after aqueous is secreted.*

**BY THOMAS FREDDO, OD, PHD**

Since the early 1950s, it has been assumed that glycosaminoglycans (GAGs) are the principal material causing resistance to outflow through the trabecular meshwork. However, in the last 10 years, this theory has been questioned because of its failure to stand up to experimental analysis. For example, we now know that the concentration of GAGs in virtually every body tissue diminishes with age, whereas it was once thought to increase with age in the outflow pathways. Also, after removing the GAG hyaluronate from the trabecular meshwork of experimental models, we saw no decreases in IOP. Nevertheless, other studies indicate there are components in the aqueous that contribute to outflow resistance, though what they are is unclear. We know the aqueous contains a small amount of plasma-derived protein, and that material drew our suspicion. Other experiments convinced us that plasma-derived proteins were probably not entering into the posterior chamber as part of the aqueous production. We theorized that protein entry and aqueous entry might be wholly separate events. MRI investigations corroborated this theory.

It appears the plasma-derived proteins diffuse from the ciliary body stroma, through the continuous stromal pathway, to the surface of the iris in the angle. From here, they enter the anterior chamber directly, bypassing the posterior chamber. In this way, more protein is added to the aqueous humor just as it enters the trabecular meshwork, where it could play a role in aqueous outflow resistance. If our findings are correct, they would explain the flare associated with medications that suppress aqueous production, such as beta blockers. When timolol was first introduced, there was concern that the flare it produced in patients represented a breakdown of the blood-aqueous barrier. Viewed in the light of our new findings, it is more likely the flare was caused by a higher concentration of proteins in the aqueous. Although aqueous production is

reduced by the drug, proteins continue to enter through the pathway I have described above, causing a concentration effect in the anterior chamber.

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### **Polarimetry May Detect Early Nerve Damage** *Full fields are no guarantee of a healthy optic nerve head.*

**BY MURRAY FINGERET, OD**

In a recent study that attempted to grow our understanding of the structure-function relationship, we set out to assess the ability of polarimetry to detect early retinal nerve fiber layer (RNFL) injury. We chose to study glaucomatous eyes with field defects limited to one portion of the visual field. Eligible patients had a glaucoma hemifield test outside normal limit along with a cluster of three contiguous abnormal points, with at least one point greater than 0.5 percent level and no points greater than 0.5 percent level in the normal hemifield. Eyes with any other ocular abnormality or unreliable visual field were excluded. We enrolled 26 patients with open-angle glaucoma, 15 males and 11 females. In total, we looked at 30 eyes.

We performed polarimetry using a variable corneal compensator, the GDx-VCC TM (Laser Diagnostic Technologies, Inc., San Diego, CA). The polarimetry data was considered abnormal if the RNFL map parameter was at the  $p < 2$  percent significance level, or the deviation map showed at least three contiguous points at the  $p < 0.5$  percent significance level. We used the GDx normative database to determine abnormality.

Mean corrected pattern standard deviation was 7.94 dB. Corresponding RNFL defect was associated with 86.7 percent of the patients with abnormal hemifields. Some 53 percent of the regions with normal achromatic hemifields had RNFL defects.

We concluded that in eyes with glaucoma, retinal nerve fiber layer injury often involves the superior and inferior optic nerve, even when achromatic field defects are limited to one hemifield. A normal achromatic visual field or hemifield does not necessarily imply

the absence of glaucomatous optic nerve injury.

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## **Possible Evidence of RGC Dysfunction in Glaucoma**

*Lowering contrast may shed light on problem ganglion cells before they die.*

**BY SHABAN DEMIREL, PHD**

The literature shows a discrepancy between structure and function in glaucomatous damage. Often when we look at the results of structural measures (optic nerve evaluation) and compare them to visual function measures, we find the two do not correlate. Clinically in glaucoma patients, structural damage is evident before visual dysfunction is observed. In the laboratory, primate studies of glaucoma models show evidence that retinal ganglion cell (RGC) dysfunction exists before cells are lost. With this in mind, we attempted to design a study that would evaluate whether RGCs perform abnormally before they die. To accomplish this, we used a vision test with theoretical links between RGC numbers and vision test results. Our test was based on “sampling theory,” which postulates that if one measures the highest frequency that can pass through a system, one can tell how many units are sampling that frequency. In this case, we dealt with spatial frequency. In our design, we measured peripheral resolution acuity, doubled the measure in cycles per degrees, then squared it. This gave us an estimate of how many RGCs are participating in the task. Our study also took advantage of the fact that in peripheral resolution, visual acuity scarcely changes when contrasts are reduced on grating patterns. The resolution demonstrated at 100 percent contrast is almost identical to the resolution demonstrated at 10 percent contrast. However, we theorized that dysfunctional retinal ganglion cells may exhibit reduced contrast sensitivity.

We recruited six normal patients and three early glaucoma cases. We evaluated peripheral drifting grating resolution acuity at two locations for a range of grating contrasts. In the early glaucoma patients, visual defects were no deeper than 5 dB. In this small sample at 10 percent contrast, 99 percent of the RGCs in normal patients were active. Conversely, at the same contrast, only 70 percent of the RGCs in early glaucoma patients were active. It is possi-

ble those missing 30 percent of cells were malfunctioning. While these results are extremely preliminary, they may represent psychophysical evidence for RGC dysfunction in early glaucoma.

DR. DEMIREL IS AN ASSISTANT SCIENTIST AT THE DEVERS EYE INSTITUTE IN PORTLAND.

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## **Device Squeezes More Drops from Latanoprost Bottle**

*A clinical trial of the Xal-Ease delivery system.*

**BY LEO SEMES, OD**

A group of researchers including myself set out to evaluate a new delivery system intended to facilitate topical instillation of latanoprost. In a small clinical trial, we compared this system, called Xal-Ease, to standard manual drop dispensing.

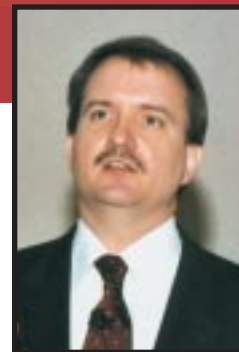
We obtained 24 bottles of latanoprost, provided by our local sales rep who had no knowledge they would be used in a study. Twelve of the bottles were administered using the device, and 12 were used without the dispenser. We also studied two different dispensing techniques. One was to keep the bottle in the inverted position between dispensing drops, which we called the maintained technique. The other was to return the bottle to the upright position after each drop was dispensed, which we called the returned technique.

Two investigators dispensed the medication from bottles; half used the Xal-Ease device and the other half did not. The drops were counted as they were dispensed into a test tube. We determined volume to the nearest 10 ul using a graduated micropipette system. We calculated drop volume based on the total drops and total volume of each test tube. The mean total volume for the 24 bottles was 2850 ul. The mean number of drops per bottle was 90.33. When using the Xal-Ease device, the mean number of drops was 93.3. When using manual dispensing, the mean number of drops was 87.67.

We noted a five-drop difference that favors the delivery device. Part of the difference was attributed to diminished waste when using the delivery device. The remainder of the difference may be accounted for by the smaller drop volume produced by the device, about 1 microliter smaller per drop. By producing an five extra drops per bottle, the device would save the average patient \$20 per year. Also, the returned technique of delivering the drops was more efficient, possibly because it reduced “streaming.” We recommend

***“Each patient had some degree of diffuse visual field loss. This suggests that diffuse loss may appear prior to or concurrent with focal visual field defects.”***

***—M.W. Dul, OD, FAAO***



that our patients use the Xal-Ease device, and that they pause briefly between each eye but without returning the bottle to an upright position.

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### **Two Studies on Macular Perimetry** ***Is measurable diffuse loss present prior to or concurrent with focal defects and can pupil size and different algorithms influence results?***

**BY M.W. DUL, OD, MS, FAAO**

Because macular perimetry is important in evaluating loss in patients with advanced glaucoma, we created two studies that look at factors that might influence these perimetric results. In addition, we set out to determine if the apparently “normal” regions of the central visual field in these glaucoma patients were similar to an age matched normal sample.

The first study measured the effects of pupil dilation and stimulus size on test-retest variability using macular perimetry in patients with advanced glaucoma. In the glaucoma patients, we tested one eye with natural pupils using size III and V stimuli. In the other eye, we used a size III stimuli with and without dilation of the pupil. Normal subjects were tested twice within two weeks with size III stimulus only, with natural pupils.

After comparing the various results, we concluded that dilation of the pupil has minimal effect on sensitivity except in areas of dense scotomas. In these patients, a small pupil and very advanced visual field loss may create a testing scenario where the Weber’s law no longer applies. As a result, dilation of the pupil actually increased sensitivity. We also concluded that increased stimulus size diminished test-retest variability for points with low sensitivity. This means that in fields where size III is not seen in many locations, the use of size V may allow an evaluation of change. Because sensitivity may be much higher for stimulus size V than for size III, changes in retinal sensitivity due to progression may be masked by such a large stimulus.

In the second study, we compared the sensitivities of full threshold (FT) algorithms to SITA algorithms in terms of test-retest variability. There was no significant difference between the two algorithms in test-retest variability for either group, and the amount of diffuse loss was comparable for the two tests. The only significant differences were in test duration and subject preference. For all subjects, test duration was shorter for SITA than for FT, with a mean of 6.7 minutes compared to 12.6 minutes. All the subjects said they preferred the SITA over the FT and universally cited the shorter test duration as the reason. The central visual fields of each of the glaucoma patients differed from the age-similar norms in that each patient had some degree of diffuse visual field loss. This suggests that diffuse loss may appear prior to or concurrent with focal visual field defects.

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### **How to Compare Cell Loss and Function** ***Study finds degree of visual dysfunction can be relatively independent of the extent of rim loss.***

**BY WILLIAM H. SWANSON, PHD, FAAO**

When we measure visual function and structural damage in glaucoma, we often use different units. Linear units are typically used for electrophysiological (function) and imaging (structure) measure: microvolts of amplitude, microns of thickness or square millimeters of area. For perimetry (function) we use decibels (dB), a logarithmic unit, for measuring sensitivity.

It is widely considered that 6 dB of perimetric loss is the minimum needed to establish a definite clinical defect. A 6 dB visual field loss means a decline by 0.6 log unit, which equals 75 percent loss of visual sensitivity. It may seem a little odd that a 75 percent loss in sensitivity can be considered “minimum” or “early”, but that is how much loss is needed with current clinical methods. The use of a logarithmic scale for perimetric data versus linear scale for imaging data gives a misleading impression that structural loss precedes visual functional loss. Now that assumption is being chal-

lenged. The current debate sweeping glaucoma studies is whether structural damage precedes visual loss. Several of us have suggested that it is more appropriate to use the same type of units when comparing the two measurements. The debate can then take place on a level playing field, so to speak.

As it stands now, comparing dB metric measurements to percentage of rim loss produces a curvilinear relation between the two values. We obtain a more linear relation between mean deviation and percentage of rim loss when both axes are plotted in linear units as “percent remaining.” In other words, instead of presenting visual field loss in dB, we present it in terms of the percentage of normal sensitivity, where 100 percent is mean normal and 0 percent is an absolute defect.

At the SUNY State College of Optometry, we have created a theoretical model to account for linear relationships between ganglion cell loss and decreases in perimetric sensitivity. To test this model, we conducted a preliminary study of 20 glaucoma patients to assess the role of cell dysfunction in structure-function relationships. In the patients we tested, the degree of visual dysfunction was relatively independent of the extent of rim loss.

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## Evaluation of Progression

### A Link Between Visual Function Loss and Structural Damage

*Monkey models help researchers understand the correlation.*

**BY RONALD S. HARWERTH, OD, PHD**

At the University of Houston College of Optometry, we have spent a lot of time studying the structure-function relationship in glaucoma. Specifically, we have asked the question: Can the density of ganglion cells be predicted based on the sensitivity of a visual field measured by perimetry? Recent experiments have convinced us the answer is yes.

In the process we have also learned a great deal about experimental glaucoma models, specifically those provided by macaque monkeys. While not perfect, these models are an excellent preparation for investigating psychophysical and histo-pathologic proper-

ties of optic neuropathy. Here is a look at some of our most recent findings.

### Experimental Models

All of the studies of the structural and functional properties of macaque monkeys' visual system have demonstrated a strong similarity to those of humans. It follows that if the healthy monkey system is similar to a human's, then the compromised system should be similar as well. Of course, no animal model is going to be 100 percent identical to a human. But, on the other hand, there are benefits to animal models over humans as well.

First, neural and sensitivity losses can be assessed by differences between the treated and control eyes of each subject. Second, without treatment, the time course and full extent of visual field defects can be evaluated. Third, repeated measurements from the monkeys cause them to become highly trained and proficient at taking perimetry tests, which makes for highly reliable data—much better than what is achieved with human subjects. Data collected from a human who takes these tests once every other year is not going to be as reliable as data collected from animals who take the test five days a week every day of the year. Finally, histological material can be obtained immediately after the animal is sacrificed.

In a recent study, we began with 16 monkeys: 14 were unilaterally treated, and two were bilaterally treated. Conditions of glaucoma were simulated using laser-induced ocular hypertension. We treated the trabecular meshwork with an Argon laser until IOP was elevated.

The monkeys were trained to fixate and respond to visual stimuli, both central and peripheral. A computer in the Humphrey Field Analyzer controlled the testing data analysis algorithms. The perimetry data from monkeys can be interpreted by standard clinical procedures and is identical to what you expect to see from a human patient.

Another advantage of this experimental glaucoma model is that the visual field defects advance very rapidly. Only a few weeks after elevating pressures, we began to see visual field defects that were easy to identify and locate.

### Conclusions

There are differences between clinical and experimental glaucoma. The glaucoma we created was a model of progressive optic neuropathy caused by highly elevated intraocular pressure. This is an excellent preparation for investigating psychophysical and histopathological properties of optic neuropathy, but it does not mirror many of the clinical characteristics of glaucoma. In some cases, the

***“I believe seven or eight visual fields are necessary to make an informed and accurate decision as to whether a patient has shown consistent progression or has remained stable.”***

***—Chris A. Johnson, PhD***



rapid progression of this model masks differences between testing methods that are important in the early diagnosis of glaucoma.

However, when this noise was accounted for, we did find neural losses correlated with visual losses in standard clinical perimetry. We concluded that similar structure-function relationships must hold true for other forms of perimetry.

If sensitivity losses precede ganglion cell death, as has been suggested in other studies, visual sensitivity measures may represent a truer evaluation of the patient's visual functional status.

We then applied what we learned from the experimental models to human subjects. We found that in clinical patients, as in experimental monkeys, the pathological neural losses from glaucoma are predictable from sensitivity measurements taken with clinical perimetry. However, the variance of the structure-function relationship is larger for patients than for monkeys. This reduced precision may be related to experimental difficulties in obtaining perimetry data and retinal tissue rather than the inherent differences in the structure-function relationship between monkey and man.

The bottom line is that in clinical application, changes in visual sensitivity that are greater than the normal variability should not occur without correlating neural loss. Thus visual sensitivity alone may be a sufficient measure for diagnosis and progression of glaucoma.

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## **Establishing Thresholds with Bayesian Forecasting**

***An introduction to ZEST, a forecasting procedure designed to be quicker than full thresholding methods.***

**BY CHRIS A. JOHNSON, PHD**

The full threshold software included in most automated perimeter employs what is known as the “staircase” method. This is an up/down adaptive method that searches for the threshold based on subject responses in two phases. The first phase of the test moves along in large steps, 4 to 6 dB. Then when the software thinks an endpoint has been reached, it retraces its steps and brackets that

area in smaller intervals, 2 to 3 dB. Usually, two staircase reversals define the threshold. It is an accurate method, but it takes time, 12 to 20 minutes, to perform a central visual field test.

A quicker option is using software that employs Bayesian statistics to forecast expected thresholds. There is no staircasing involved in this method, and visual field tests are completed in fewer steps, partly because the computer estimates responses based on stored data about the population as a whole, including a statistic known as probability density function (PDF). This is the likelihood of a threshold response in the normal and glaucoma populations for a particular stimulus. Using this and other information, Bayesian statistics cut visual field testing time in half.

In addition to the PDF, there are several other factors the software takes into account. For example, in a normal population, sensitivity decreases with age. It is also known that sensitivity is not the same at every eccentricity. Some eccentricities have higher sensitivities than others. Variability is different at central and peripheral locations, as well.

The Swedish Interactive Test Algorithm (SITA) and the new Zippy Estimation of Sequential Thresholds (ZEST) both use the Bayesian method. SITA is a relatively well established method. ZEST is newer and less well known.

### **Differences Between SITA and ZEST**

Obviously, with regard to PDF, there are two kinds of sensitivity, that which the normal population demonstrates and that which the glaucoma population demonstrates. With glaucoma and other types of ocular and neurological diseases, a larger distribution of sensitivity values is produced. To achieve a reading, SITA relies on two different average distributions, one for normal populations and one for glaucomatous populations. After each presentation, the perimeter looks at how well the response behavior up to that point corresponds to either the normal PDF or the glaucomatous PDF and decides which one pertains.

ZEST, on the other hand, combines the two populations, glaucomatous and non-glaucomatous, into one clinical PDF function.

SITA uses the mode of the PDF to establish threshold estimates; ZEST uses the mean of the PDF. The PDFs for SITA are based on population characteristics, while the PDFs for ZEST begin with a flat



pedestal, with all possible thresholds being equally likely.

SITA uses a dynamic termination criterion, which is based on response history. The major caveat of Bayesian methods, human error, comes into play. Human subjects make mistakes. When performing only a small number of presentations, an error early in the process will send the software into the wrong part of a PDF. Now the perimeter must backtrack and perform additional presentations in order to achieve an accurate reading.

The designers of ZEST have tried to avoid this problem by limiting the number of trials and creating a system to catch human mistakes. If a point differs from its neighbors by a certain amount, ZEST re-tests that point. This system creates an increased consistency of test time, regardless of visual field status. Re-testing points that may be mistakes typically takes only an extra 20 seconds of time. Studies have demonstrated that this method does not diminish accuracy or reproducibility.

### Evaluating Progression

While the methods I have described here will save time in establishing thresholds, we still have a long way to go in the accuracy of evaluating the progression of glaucoma. Not all changes in threshold value are due to actual disease progression. Age can cause changes. Points in the human visual field decline at approximately 1 dB per decade. And then there is simple variability to consider, both within an exam and between exams. Variability is the Achilles' heel of evaluating disease progression.

Despite all the advances we have made in the past few years, I believe at least seven or eight visual fields are necessary to make an informed and accurate decision as to whether a patient has shown consistent progression or has remained stable. To achieve better documentation of progression, we need to develop more sensitive tests, methods to lower variability and better analysis methods. However, with Bayesian methods we can at least start off with reliable threshold data at baseline, and that is a major advantage.

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## A New Method for Tracking Progression

*Monitoring pressure alone is not enough; progression rates vary even at the same IOP levels.*

**BY ANDERS HEIJL, MD**

Once we have diagnosed glaucoma, our focus changes from finding the disease to tracking its course. In the past, we were faced with one simple question: is the patient stable or progressing? Now, in light of recent findings, we are faced with an additional question: if the patient is progressing, how fast is that progression? The answer to this last question will be very relevant to long-term management.

Both the Early Manifest Glaucoma Trial (EMGT) and the Collaborative Normal Tension Glaucoma (CNTGS) studies have shown that the rate of progression is extremely variable among patients.

I was involved with the EMGT study.<sup>1</sup> Our aim was to investigate the effect of IOP reduction in the progression of early, newly-detected open-angle glaucoma by comparing a group of patients which received therapy to lower IOP with a group which received no treatment. The study assessed this by measuring increasing visual field loss and optic disc changes.

A group of 129 patients was treated with argon laser trabeculoplasty plus topical betaxolol, and a group of 126 made up the control. Mean IOP was reduced by 5.1 mm Hg from mean a baseline of 20.5 mm Hg in the treated group. The untreated group experienced no change in IOP.

Progression rates varied greatly among patients. Several patients progressed in the first year, but on the other hand, about one-third of the untreated patients have yet to show disease progression after seven years of follow up.

Average deterioration rates were slow: the treated group experienced a rate of 2.3 (median) and 3.5 (mean) dB progression every 10 years; the untreated group experienced a rate of 3.5 dB (median) and 6 dB (mean) progression every 10 years.

Thus some patients fall into a low-risk category. Since patients with early-stage disease and low IOPs experience less positive treatment outcomes anyway, an argument can be made for recommending close follow-up without treatment for these patients. Elderly patients with unilateral disease can also be included in this low-risk group.

However, other patients fall into a high-risk group. These are patients who experience a loss of 3.8 dB per year or greater, which translates to progressing from a visual field with mild damage (4 dB) to serious loss (19.2 dB) or worse in only four years.

It is extremely difficult to predict the fate of an individual patient early in the disease. The levels of variability are simply too high. We can lower variability by taking into account such factors as baseline pressure, age and damage. But even knowing these prognostic factors reduces variability only by half, according to our findings.

*“In my opinion, lowering patients’ IOPs by 30 to 35 percent is the safest, quickest and most cost effective solution to treat glaucoma.”*

*—Paul Palmberg, MD*



It is only by tracking visual fields over period of time can we measure progression. In the EMGT, we knew we needed a very sensitive yet specific method to identify early glaucoma progression. We based our visual field progression models on Glaucoma Change Probability Maps (GCPM), which we created by retrospectively analyzing about 30,000 fields we had on file at the Malmö University Hospital in Sweden. Based on this analysis, we decided on the number of tests and number of progression points that would define disease progression.

Our GCPMs were different from the original ones available for the Humphrey Perimeter in that ours were based on pattern deviation rather than total deviation. In our model, definite progression was defined as mean deterioration in MD of 1.93 dB or 4.85 highly significant depressed test point locations (the “black boxes” in the pattern deviation probability maps). This translates to 10 to 12 progression points from normal vision to blindness.

Based on our experiences in the EMGT, we have now created the Glaucoma Progression Analysis Program (GPA), designed to be used with the Humphrey Field Analyzer and the SITA program. These pattern deviation GCPMs separate significant change from random change. The program flags reproducible findings and provides clear text messages on whether progression is “possible” or “likely.” The GPA automatically eliminates unreliable fields and first-time fields from untrained patients as well.

The EMGT and other trial data show that glaucoma management needs to be more tailored to the individual than it has been in the past. Risk factors other than IOP should be taken into account, and individual rates of progression should be ascertained as early after diagnosis as possible. We hope our GPA program will help practitioners meet these new challenges to managing glaucoma patients.

1. Leske MC, Heijl A, Hussein M, et al. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol.* 2003 Jan;121(1):48-56.

DR. HEIJL IS AN OPHTHALMOLOGIST AT THE MALMÖ UNIVERSITY HOSPITAL AT THE UNIVERSITY OF LUND, SWEDEN.

## Clinical Trials in Glaucoma

### Evidence-based Target Pressures

*It is only recently that pressure reduction has been linked to better outcomes.*

**BY PAUL PALMBERG, MD, PHD**

For most of the last century glaucoma treatment amounted to little more than groping in the dark. The textbooks had almost nothing to say about the natural history of glaucoma, the effectiveness of treatment or what pressure levels were optimal, and what they did say was often contradictory. Lowering IOP was advocated, but there was little scientific evidence to show that it worked. Not until the late 1980s were several clinical trials launched to evaluate the effectiveness of glaucoma treatment. These studies have recently been published, and we should profit from them.

The Advanced Glaucoma Intervention Study (AGIS) studied patients who had glaucoma for about 10 years and failed medical therapy as it existed between 1988 and 1993.<sup>1</sup> The subjects’ average age was 68, and their average intraocular pressure (IOP) at baseline was 25mm Hg. Mean deviation on visual field testing was -10.6 d/B. The patients were randomized to one of two surgical therapies: laser trabeculoplasty first, followed by filtration surgery, or filtration surgery followed by laser trabeculoplasty. The results of this study debunked the assumption that glaucoma always progresses, and that the best we can hope to do is slow it down. Outcomes showed that when IOP was lowered aggressively—that is, lower than an average of 13mm Hg and always below 18mm Hg—glaucoma progression could be halted.

The Collaborative Normal Tension Treatment Study (CNTGS), conducted in 24 centers around the world, looked at patients with high-risk, normal tension glaucoma that was either progressing or threatening to progress.<sup>2</sup> The pressure goals were strict: each patient’s IOP was to be lowered 30 percent. As long as cataract formation was avoided, reaching these goals reduced progression from a rate of 60 percent in the untreated group to

20 percent in the treated group, a three-fold benefit in favor of treatment.

In the Ocular Hypertension Treatment Study (OHTS), patients with elevated IOP but normal optic nerves and visual fields were randomized into treated and untreated groups.<sup>3</sup> The treated group experienced 18 percent net pressure reduction, usually achieved with a beta blocker. In the untreated group, 9.5 percent of patients went on to develop glaucoma. In the treated group, 4.4 percent of patients went on to develop glaucoma. This confirms the efficacy of lowering the IOP, but is of little use from a patient management standpoint since the number needed to treat (NNT) was 10, which indicates we need to treat 10 patients to benefit one. Of course, a prominent finding of OHTS was identifying corneal thickness of less than 555 microns as a risk factor for developing glaucoma damage, and conversely, identifying corneal thickness greater than 588 microns as a protective factor. Now when I see a patient with 22mm Hg pressure and a cornea of 610 microns, I do not even bother bring up the matter of glaucoma or a follow-up exam. These patients are not at risk. I am convinced all glaucoma patients, not only hypertensive patients, should have the thickness of their corneas measured. In my practice, we have seen normal tension glaucoma patients with corneas of 410 microns who we now realize probably have higher IOPs than we thought.

A study published in 2000 demonstrated the importance of controlling variability in pressure, something also confirmed by AGIS.<sup>4</sup> Pressures that are overly variable correspond to damaged visual fields. Even when IOPs were similar, the eyes with greater IOP variability over a 24-hour period showed an increased risk of field loss by sixfold. This is one of the reasons I am an advocate of beta blockers and prostaglandins as baseline drugs. They maintain the flattest pressure curves. Other drugs may be excellent add-on options, but for a baseline drug, potent pressure-reducing ability and a flat curve are essential.

Finally, as another author in this supplement notes, the Early Manifest Glaucoma Trial (EMGT) has found that some glaucomas progress and some do not.<sup>5</sup> Therefore, we can pick out patients whose risks are high enough to treat. We should approach this paradigm with caution. Yes, in a perfect world we could be more selective in who we treat. Unfortunately, the reality of this health-care system is if do not treat someone, the patient gets the idea there is no danger and disappears rather quickly. In my opinion, lowering patients' IOPs by 30 to 35 percent is the safest, quick-

est and most cost-effective solution to treat glaucoma.

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**What We Don't Know About Glaucoma**  
*To fill the gaps, universal definitions of impairment and risk factors are needed.*

**BY ROBERT M. FELDMAN, MD**

How many times has this happened to you? You diagnose a patient with glaucoma, and he asks, "Doc, am I going blind? How will this disease affect my life?"

How we answer this question is not only important to the patient, it is important to other practitioners as well, because it may influence treatment decisions. It could mean the difference between being satisfied with a 15mm Hg pressure and knowing 10mm Hg is necessary to halt disease progression.

Who is at risk for blindness? Who is more likely to develop symptoms? Whose disease will progress the quickest? In trying to answer these questions, we quickly realize our ignorance outweighs our knowledge. I'll summarize some population studies which have given us what little we do know.

*“Latanoprost, bimatoprost and travoprost are equally potent IOP-lowering treatments. All three are well tolerated, but significantly fewer patients experience hyperemia with latanoprost.”*

*—Richard Parrish, MD*



### Blindness Data

One of the problems with the literature on this subject is the inconsistency of terms. For example, how is blindness defined? In some prospective studies, it is determined by visual acuity only, which I think is a mistake. A glaucoma patient may have a visual acuity of 20/20, but a visual field of 5 degrees. Visual acuity is often the very last attribute to worsen. I suggest we use the same standard the federal government uses to determine legal blindness, which is visual acuity of less than 20/200 in the better eye, and/or visual field of less than 20 degrees.

The Baltimore Eye Survey was a cross-sectional survey of blacks and whites in Baltimore.<sup>1</sup> Of the subjects studied, 13 percent of the black glaucoma patients went blind, while only 3 percent of the white glaucoma patients went blind.

The Blue Mountain Eye Survey, which was conducted in Sydney, Australia, on a white population, found that 8.8 percent of the glaucoma subjects eventually went blind.<sup>2</sup> This was a study that employed visual acuity only as criteria for blindness.

The Proyecto Ver study was a cross-sectional study of 4,774 Hispanic residents in Arizona.<sup>3</sup> Again, based on visual acuity, 5.6 percent of the glaucoma patients went bilaterally blind and 18 percent unilaterally blind. When comparing these data to the Baltimore Eye Survey, blacks show an earlier onset of glaucoma, but when subjects reached the age of 85, the glaucoma rates of the blacks and Hispanics were about the same.

The Rotterdam Eye Survey, which looked at causes of blindness, found that only 8 percent of blindness was caused by glaucoma and only 3 percent of visual impairment was caused by glaucoma.<sup>4</sup> Again, this study illustrates the problem with using visual acuity only to assess blindness; it minimizes glaucoma's threat to public health. "Visual impairment" is another term employed differently among studies. Most define it as visual acuity worse than 20/40. But this does not take into account binocular visual acuity or binocular visual field. Hence, there is a lack of reliable, large-scale population data on visual impairment in glaucoma.

### Progression Data

A retrospective study conducted at Wills Eye Hospital in Philadelphia measured rates of disease progression for a minimum

of 15 years.<sup>5</sup> Researchers created a staging system from one to five to measure progression of field loss and optic disc deterioration—not a perfect system but workable. The study found that 19 percent of eyes remained stable, 43 percent deteriorated one stage, 31 percent deteriorated two stages and 9 percent deteriorated three stages. Some 17 percent deteriorated to visual acuity of 20/200 or worse, but about half of these were due to causes other than glaucoma.

Interestingly, the median time to the first worsening was 7.5 years, to the second, 18.5 years and to the third, 24.5 years. This is probably slower than most practitioners would think. So a patient who goes five years without progression is not necessarily out of the woods.

So what do we tell our inquiring patient? In terms of risk factors for impairment, there is almost nothing we know, other than most patients' vision probably will worsen over time. In terms of blindness, we know risk factors include noncompliance with treatment, poor visual fields at diagnosis and being of a nonwhite race. Our best guess is 3 to 10 percent of glaucoma patients will go blind.

The fundamental unanswered question that emerges is, of patients with glaucoma, who goes blind and who becomes symptomatic? Only by answering this question can we determine who to treat, how aggressively to treat and how to allocate valuable public health resources to this disease.

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## Prostaglandins and the New Glaucoma Therapeutic Paradigm

### Prostaglandins Show Comparable Efficacy but Differences in Tolerability

*Last year's XLT study found the three leading agents to have comparable IOP-lowering abilities.*

BY RICHARD PARRISH, MD

The three leading ocular prostaglandin analogs are comparable in their efficacy but not in their tolerability. These are the conclusions of the XLT study published last spring in the *American Journal of Ophthalmology*.<sup>1</sup> I was part of the XLT study team that compared outcomes in patients with open-angle glaucoma or ocular hypertension who were treated with latanoprost, bimatoprost, or travoprost. I'd like to summarize the study and its results so you can draw your own conclusions.

#### XLT Study

The guiding principles of this 12-week, randomized, masked-evaluator study were to keep the design simple and to focus on outcomes important to physicians and to patients. The primary goal was to measure changes in mean IOP levels from baseline to week 12 at 8:00 AM, the time of each drug's peak effect. In order to get an idea of IOP levels throughout the day, we also measured IOPs at noon, 4:00 PM, and 8:00 PM. We called the average of a patient's four IOP measurements taken across the day the "diurnal IOP," even though it didn't include a nighttime IOP measurement. Our secondary goal was to evaluate tolerability by monitoring adverse events. Occurrences and severity of hyperemia were a primary focus, because hyperemia is known to be a potential side effect of prostaglandin therapy.

Patients from 45 sites in the United States were eligible to participate if they had either unilateral or bilateral primary open-angle glaucoma, exfoliative glaucoma, pigmentary glaucoma, or ocular

hypertension defined as an IOP > 21 mm Hg at diagnosis. To be eligible they also had to be treated currently or within the past six months with a topical ocular hypotensive agent either as monotherapy or dual therapy. Up to a month before the start of the study, patients had a screening examination and stopped using all ocular hypotensive agents. An eye was included in the study if the IOP at 8:00 AM at the baseline visit was > 23 mm Hg.

To measure hyperemia, investigators used a four-point grading scale based on standard photographs: 0 for none; 1 for mild; 2 for moderate; 3 for severe. Equally important, we asked patients whether they had developed red eyes and, if so, how much that bothered them. To me, this is a strength of the study because hyperemia is more a cosmetic than a health issue (although hyperemia may complicate future filtration surgery), and patient perception is key. Patients understandably want to avoid the possibility that co-workers, friends and family will comment on their "bloodshot" eyes. Even more importantly, this cosmetic concern may affect whether patients take their medication over the long term. So, we asked: "Have you or anyone else noticed any redness in your eyes since the last visit?" If the answer was yes, we asked to what extent they were bothered by such redness: not at all; a small amount; a moderate amount; or a great deal.

The primary results concerning efficacy were in line with what we expected. All three agents were effective at lowering IOP levels. The mean 8:00 AM IOP at week 12 for latanoprost was 17.1 mm Hg compared with 17.0 mm Hg for bimatoprost and 17.6 mm Hg for travoprost. From baseline to week 12, the average decrease in IOP was 8.6 mm Hg for latanoprost, 8.7 mm Hg for bimatoprost, and 7.9 mm Hg for travoprost. For other mean IOP measurements during the day and for average diurnal IOP levels, we didn't find as much as a millimeter of difference among the three groups.

On the other hand, we found that significantly fewer patients treated with latanoprost experienced eye redness. After 12 weeks, patients treated with latanoprost were least likely to report moderate or severe hyperemia (6.6 percent compared to 11.6 percent with travoprost and 18.2 percent with bimatoprost), and there was no evidence that hyperemia decreased over time. I'm concerned about hyperemia even though only one patient dropped out of the study due to eye redness or irritation. Studies have shown that 50 to 60 percent of newly diagnosed glaucoma patients don't refill their prescriptions as they should, and patients with hyperemia who don't want to put up with it may decide not to refill their prescriptions. Doctors need to discuss possible side effects with their patients and encourage them to report problems so that other treatments can be

***“One can recommend performing perimetry at least twice every year during the first few years after diagnosis. Frequency can be reduced when the patient is not progressing rapidly.”***

***—Anders Heijl, MD***



prescribed if needed.

Like all studies, the XLT study had shortcomings. I think its primary shortcoming was the 12-week time frame. We believed that this time period was adequate to assess the three prostaglandins' IOP-reducing abilities because 12-week findings tend to be almost identical to those at 1 year. But, this relatively limited follow-up precluded the possibility of seeing iris color changes, a known but in my opinion primarily cosmetic side effect of prostaglandin analogs that takes longer to develop.

Overall, I think it's fair to say that the XLT study showed latanoprost, bimatoprost and travoprost are equally potent IOP-lowering treatments. All three agents are generally well tolerated systemically, but significantly fewer patients experience hyperemia with latanoprost.

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## **The Changing Paradigm of Glaucoma Treatment**

***The need for more aggressive pressure reduction is evident; other studies hold out hope of spotting cell damage before it becomes irreversible.***

**BY PAUL PALMBERG, MD, PHD**

Over the last few years, we have witnessed a seismic shift in how glaucoma is treated. Several large-scale studies have indicated the need for a more aggressive stance in decreasing intraocular pressure, with goals of about 20 to 30 percent lower than what we have been taught to seek. Also, this new paradigm calls for a more consistent IOP reduction throughout night and day. A flatter diurnal curve has been shown to prevent visual field progression.

Because we ask our therapeutic agents to accomplish more, prostaglandins have overshadowed beta blockers as the traditional first-line drugs, with 60 percent of patients now beginning therapy on prostaglandins. Other, lesser known breakthroughs indicate loss of visual function can precede structure damage, and it may be possible to identify distressed retinal ganglion cells and treat them before damage becomes permanent.

### **New Targets**

Several studies have supported the thinking that lower pressure goals are necessary. The Advanced Glaucoma Intervention Study (AGIS) advocates a 35 to 50 percent reduction in IOP.<sup>1</sup> The Collaborative Normal-Tension Glaucoma Study (CNTGS) supports a goal of 30 percent reduction.<sup>2</sup> The Collaborative Initial Glaucoma Treatment Study (CIGTS) supports a 35 percent reduction, and preliminary results from the Early Manifest Glaucoma Trial (EMGT) support this conclusion.<sup>3,4</sup> The Ocular Hypertension Treatment Study (OHTS) supports a 20 to 30 percent reduction goal.<sup>5</sup>

Why do such lower pressures result in better outcomes? No one is completely sure. A 20 to 25 percent reduction in IOP appears to work well for many patients, but for others it is not enough. One possible explanation lies in the faulty auto-regulation often seen in elderly patients or those with normal tension glaucoma. In a healthy patient, when pressure in the eye is raised, the body adjusts by increasing the pressure of the blood flow to the optic nerve. At night, when a healthy patient is asleep and IOP naturally decreases, the body adjusts by lowering the pressure of the blood flow to the optic nerve. This phenomenon is called auto-regulation. Patients with auto-regulation problems cannot compensate for elevations in intraocular pressure. In these patients, it may be useful to lower IOP to around 8 to 12mm Hg, which is the average pressure of optic nerve blood flow, rather than traditional goal of 12 to 15mm Hg range. Thus, glaucoma emerges as disease very different from diabetes or systemic hypertension, where the optimal therapeutic goals are in the upper normal regions. To treat the largest percentage of glaucoma patients, goals in the lower normal regions appear more appropriate.

A topical beta blocker will produce an average of 20 to 25 percent IOP reduction, regardless of glaucoma type, while a

prostaglandin will produce a 30 to 35 percent reduction. On average that means an additional reduction of 2 to 3mm Hg for prostaglandins, enough to make a difference. It is estimated that for every millimeter of mercury reduced, the patient receives a 11 percent reduction in the risk of ocular hypertension converting to glaucoma.

Intraocular pressure should remain consistent. Large fluctuations in diurnal pressure are a significant risk factor, even when pressures are within target range for a large part of the day. Over a five-year period, a patient who fluctuates 5.4mmHg has almost six times the risk of developing disease progression when compared to a patient who fluctuates 3.1mmHg.<sup>6</sup> Again, a prostaglandin like latanoprost will outperform timolol (beta blocker) and dorzolamide (topical CAI) in this regard.<sup>7</sup>

### Cell Loss or Field Loss?

We have been taught that irreversible optic nerve damage occurs long before visual function is affected, but how true is that axiom? An interesting result of OHTS was that 38 percent of patients showed reproducible field loss, with no disc damage whatsoever. Studies on animal models have shown that a 6 dB depression in the visual field can precede cell loss. Although not the rule, functional changes can occur before structural ones, especially in patients with recent acute IOP changes. Furthermore, based on studies done by Vittorio Porciatti, MD, and Lori M. Ventura, MD, it appears these early functional changes may be reversible.

It seems logical to assume that retinal ganglion cells will show some signs of distress before they die. In this light, the next question becomes: can we develop a device to detect these distress signals? There are several potential devices and/or strategies: the pattern electroretinogram (PERG), measuring pattern of visual evoked potential (VEP), the Humphrey Frequency Doubling Test (FDT) and shortwave automated perimetry. Such diagnostics could be the future of glaucoma management.

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## Understanding The Early Manifest Glaucoma Trial

*One of the authors of this study clears up some common misconceptions.*

**BY ANDERS HEIJL, MD**

Published 2002 in the Archives of Ophthalmology, the Early Manifest Glaucoma Trial (EMGT) received a great deal of attention.<sup>1</sup> We found that for every millimeter that the intraocular pressure (IOP) was reduced, patients with glaucoma experienced a 10 percent decrease in the risk of disease progression. While these outcomes are heartening (results were better than we would have guessed), they should not be interpreted to mean that every single glaucoma patient must receive the maximum amount of pressure reduction possible. In fact, the take-home lessons from this study are more subtle. The study demonstrated that glaucoma progresses differently in each patient, and that treatment modalities should take these differences into account. For example, maximized efforts to reduce pressure probably should be reserved for patients whose disease is progressing fast or who

are among the younger glaucoma patients (maybe 60 years of age and younger) and, therefore, have many years left.

### Study Summary

The aim of this study was to investigate the effect of IOP reduction in the progression of early, newly-detected open-angle glaucoma by comparing a group of patients that received therapy to lower IOP with a group that received no treatment. We assessed this by carefully watching for increasing visual field loss or optic disc changes.

A group of 129 patients was treated with argon laser trabeculoplasty plus topical betaxolol, and a group of 126 made up the control untreated group. Mean IOP was reduced by 5.1mm Hg from mean baseline of 20.5mm Hg in the treated group. The untreated group experienced no change in IOP. Follow-up exams occurred every three months with perimetry done on every visit and photography twice per year. After six years, a total of 53 percent of patients showed disease progression. The study concluded that treatment cut the risk for progression in half. Positive treatment results were observed in all patient categories, regardless of IOP level, whether exfoliation was present, visual field results or age.<sup>1</sup>

Risk factors for progression included higher intraocular pressure, exfoliation, higher mean deviation as noted on perimetry, having both eyes affected by the disease and advanced age. Exfoliation and bilateral disease doubled the risk of disease progression, we found.<sup>2</sup>

We also looked at a large number of non-ocular risk factors, and found none to be relevant. We tracked hypertension, hypotension, smoking, migraine history, family history of glaucoma, diabetes as well as several others.

It should be noted that our progression criteria was very sensitive. Only a small amount of progression was necessary to qualify. Definite progression was associated with a mean deterioration in MD of 1.93 dB or 4.85 highly significant depressed test point locations.<sup>3</sup> It is interesting to note that in EMGT the great majority of progressions were first identified in the visual fields, not analyses of optic disc photographs.

### Lessons Learned

Progression rates varied greatly among individuals. Several patients progressed in the first year, but on the other hand, about one-third of the untreated patients have yet to show disease progression after seven years of follow up.

Average deterioration rates were slow: the treated group experienced a rate of 2.3 (median) and 3.5 (mean) dB in visual field progression every 10 years; the untreated group experienced a rate of 3.5 dB (median) and 6 dB (mean) progression every 10 years.

Thus some patients fall into a low-risk category. Since patients with early-stage disease and low IOPs experience less dramatic treatment outcomes anyway, an argument can be made for recommending close follow-up without treatment for these patients. Elderly patients with unilateral disease can also be included in this low-risk group.

However, other patients fall into a more high-risk group. These are patients who experience a loss of 3.8 dB per year or greater, which translates to progressing from a visual field with mild damage (4 dB) to serious loss (19.2 dB) or worse in only four years.

These progression variables suggest that newly-diagnosed patients should be followed with visual field testing more often than is now common. One can recommend performing perimetry at least twice every year during the first few years after the patient is diagnosed. The frequency of testing can then be reduced when we have documented that the patient is not progressing rapidly. With this approach, we will identify those relatively few patients with rapid progression, and be able to treat them more vigorously.

Incidentally, now that we have evidence that treatment really does work, we might want to revisit the possibility of glaucoma screening for the population at large. Additionally, we should reconsider the wisdom of diagnosing every single glaucoma case and its effect on quality of life. Patients experience a great deal of anxiety at diagnosis. Given the EMGT results, we usually do no great health service by diagnosing mild, slowly progressing glaucoma in a 78-year-old patient.

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