

Questioning Glaucoma Therapy

Despite recent comments to the contrary, there is strong evidence in favor of glaucoma treatment.

BY PAUL PALMBERG, MD, PhD

In May, *Business Week* ran a story¹ alleging that “from heart surgery to prostate care, the health industry knows little about which common treatments really work.” The article chronicles the career of David Eddy, MD, PhD, who is credited with coining the term *evidence-based medicine*. He has made a career of identifying healthcare practices that he believes are based upon physicians’ theories and intuition rather than solid clinical studies.

One example of Dr. Eddy’s work cited by the article’s author, John Carey, involves a search of the literature in 1987 to evaluate the effectiveness of the medical treatment of glaucoma²: Dr. Eddy “ferreted out decades of research evaluating treatment of high pressure in the eyeball, a condition that can lead to glaucoma and blindness. He found about a dozen studies that looked at outcomes with pressure-lowering medications used on millions of people. The studies actually suggested that the 100-year-old treatment was harmful, causing more cases of blindness, not fewer.” Mr. Carey goes on to state that Dr. Eddy submitted a paper to the *Journal of the American Medical Association* and that the publication’s editors sent it out to specialists for review who “marshaled a counterattack.”

My perspective on what occurred in 1987 and all that has transpired in the field of glaucoma since differs significantly from Mr. Carey’s depiction. I believe that glaucoma treatment greatly benefits our patients, and my contention has the support of conclusive research.

WHAT REALLY HAPPENED

Dr. Eddy did indeed write that medical therapy had not been proven effective in preventing progressive visual field loss, but he did not state that treatment caused blindness.² His simple point was that we needed to know whether or not treatment yielded a better outcome than the natural history of glaucoma.

Some ophthalmologists’ responses may have been

defensive, but Dr. Eddy also received a phone call from me in 1988. I asked him to attend a regional meeting of the AAO in Miami that I had organized. Specifically, I invited him to discuss the existing evidence about the effectiveness of glaucoma treatment, because his review had missed key articles³⁻⁵ that provided evidence of its effectiveness. I also suggested that he participate in discussions with several glaucoma specialists who were launching clinical trials of glaucoma therapy. We did not have the funds to pay Dr. Eddy’s appearance fee of several thousand dollars, and he declined my invitation.

Regardless, Dr. Eddy’s challenge helped to invigorate an already developing interest in clinical trials within the field of glaucoma. Douglas Gaasterland, MD, and Fred Ederer were ready to launch the NIH-sponsored Advanced Glaucoma Intervention Study (AGIS, 1988 to 2003), and Stephen Drance, MD, and Douglas Anderson, MD, had planned the Collaborative Normal Tension Glaucoma Study. In 1989, I organized and moderated the AAO/National Society for the Prevention of Blindness Glaucoma Symposium under the theme The Rationale and Effectiveness of Glaucoma Therapy. A new era in glaucoma had arrived.

WHAT WE KNOW NOW

Overview

Today, we know that adequate glaucoma therapy is extremely effective and that it can markedly reduce or halt glaucomatous damage at any stage of the disease. Several recent clinical trials⁶⁻¹³ have provided useful information about the relationship between IOP and the risk of future visual field loss in patients with specific types of glaucoma. The guidance obtained from studying the outcomes of similar patients can help us to set a treatment goal—the “target pressure”—that is likely to prevent that portion of damage that is pressure dependent.¹⁴ Because, epidemiologically, elevated IOP alone accounts for a minority of the damage in the glaucomas,^{15,16} it was surprisingly good news

that a large majority of glaucomatous damage nevertheless depends on pressure. The implication of the studies' findings is that a lower-than-normal IOP can compensate to a large degree for whatever else is harmful in some patients, especially those with normal-tension glaucoma (NTG)¹¹ or advanced primary open-angle glaucoma (POAG).¹²

As a member of the writing team for the AAO's original *Preferred Practice Pattern for Primary Open-Angle Glaucoma* in 1989, my task was to write a chapter on the rationale for and effectiveness of glaucoma therapy.¹⁷ After reviewing the literature on the long-term outcomes of therapy, it appeared to me that patients with advanced damage did best when their IOP was less than 15 mm Hg, as Paul Chandler, MD, had demonstrated in 1959.³ To focus thinking on the management of advanced glaucoma, I coined the term *target pressure*. Now, we have much more detailed information about outcomes to guide us, not only in managing advanced POAG, but also mild, initial POAG, NTG, and ocular hypertension.

POAG

For patients with POAG and moderate-to-severe damage (average -10.5 dB mean deviation on Humphrey perimetry [Carl Zeiss Meditec, Inc., Dublin, CA]), the AGIS found that an optimal IOP is approximately 12 mm Hg (no net progression in a group of 105 patients followed for 8 years).⁶ In contrast, glaucomatous damage occurred at an increasing frequency and severity for groups of patients in whom the IOP was above 18 mm Hg at times and averaged 15, 17, and 20 mm Hg, respectively. My colleagues and I conducted a study of 205 patients in Miami with advanced glaucoma who underwent initial glaucoma surgery with 5-fluorouracil or mitomycin C.⁷ No net progression occurred in this group of patients with a baseline mean deviation of -14.6 dB during a mean of 7 years' follow-up. The mean IOP decreased from 26 to 11 mm Hg throughout the 10-year study.

In patients initially diagnosed with POAG who have mild damage (average mean deviation of -4.8 dB on Humphrey visual field testing), the NIH-sponsored Collaborative Initial Treatment of Glaucoma Study (CIGTS) showed that an average 37% reduction in IOP (27 to 17.5 mm Hg) with medication and added laser therapy when needed resulted in no net visual field progression in 5 years.⁸ The study's protocol required an advancement in treatment until an aggressive target pressure was achieved. I have been on the monitoring committees of the AGIS and CIGTS.

In the NIH-sponsored Early Manifest Glaucoma Trial (EMGT) in Sweden,^{9,10} newly diagnosed patients with POAG were randomized to treatment or observation without treatment—the randomized trial of therapy versus nat-

ural history that Dr. Eddy would have favored. An average 29% reduction in IOP in POAG patients achieved a 50% decrease in their relative risk of progression. The considerably worse outcome in the EMGT (2.2 dB mean deviation progression in the treated subjects vs 3.9 dB in the untreated controls) compared with the CIGTS (0.0 dB net worsening on treatment) may have been due to a difference in protocol. In the EMGT, the treated subjects received a standardized treatment regardless of its effect on IOP. Subjects received Betoptic (Alcon Laboratories, Inc., Fort Worth, TX) b.i.d. and underwent argon laser trabeculoplasty with no advancement of therapy unless their IOP was consistently higher than 25 mm Hg.

The EMGT did show an increased hazard rate of 13% per 1 mm Hg higher average IOP during the study period. An alternative explanation for the difference in outcomes could be the subjects' older age (mean 68 vs 58 years) in the EMGT compared with the CIGTS.

NTG

The Collaborative Normal Tension Glaucoma Study showed that lowering the IOP by 30% (from 16 to 11 mm Hg) reduced the risk of progression in high-risk NTG (previous progression or split fixation documented) from 60% in untreated controls to 20% in treated subjects at 5 years.¹¹

Ocular Hypertension

In the Ocular Hypertension Treatment Study,^{12,13} high IOPs (> 25 mm Hg), large cup-to-disc ratios, older age, and normal-to-thin central corneal thickness (< 555 μ m on ultrasound pachymetry) were predictive of the development of POAG. The risk was as high as 36% in 5 years. Treatment that decreased the IOP by only approximately 20% reduced the relative risk of white and black subjects' progressing to glaucoma to 36% and 58%, respectively, as much as in controls. A recently presented assessment of the relationship of IOP to the risk of glaucomatous progression in the controls found that the relative risk increased by 24% for each millimeter of mercury.¹⁸ This analysis suggests that lowering the IOP to a greater degree further reduces the risk of glaucomatous progression.

CONCLUSION

Unfortunately, readers of the article in *Business Week* might be discouraged from using sight-saving therapy for glaucoma as well as life-saving treatments for diabetes.¹⁹ The results of NIH-sponsored clinical trials have established beyond a doubt the remarkable efficacy of the medical and surgical treatment of glaucoma.²⁰ Those who understand this evidence need to publicize the

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New Paradigms Ahead?

Emerging ideas for detecting and conceptualizing glaucoma gain the spotlight at the IPS' biennial symposium.

BY LINDA ROACH, CONTRIBUTING EDITOR

The quest for visible markers that can separate eyes vulnerable to damage by elevated IOP from those that will remain stable or healthy led members of the International Perimetric Society (IPS) to consider some paradigm-shifting ideas at the group's recent biennial meeting. The IPS' Visual Field & Imaging Symposium, held from July 11 to 14 in Portland, Oregon, could not determine in just a few days if any of the ground-breaking propositions might prove clinically significant. Nevertheless, the more than 60 presentations suggested the roads down which these leading researchers will travel in the next few years, as they try to unite structure and function into a clinically useful picture of glaucoma.

The presentations at the IPS symposium appeared to converge on two main themes. The first was novel techniques for imaging and understanding subtle changes in the optic nerve head and surrounding structures, even at the cellular and molecular levels. The second was ways to use existing imaging and perimetric technologies to aid patients by improving the detection of glaucoma, monitoring the disease's progression better, and predicting in which eyes glaucoma will progress.

Although many presenters dealt with the second theme, the most provocative papers came during a series of speakers—many on the podium together for the first time—who explored novel ways to image and analyze the optic nerve head and associated structures.

SURPRISE IN ADAPTIVE OPTICS

Researchers from the University of California at Davis reported using an adaptive optics, Fourier-domain approach to optical coherence tomography (AO-FdOCT) to achieve images with a 3- μ m lateral resolution and 6- μ m axial resolution.¹ That imaging quality is high enough to reveal individual photoreceptors and other structures that are not visible with currently available commercial devices. The images so far support a conclusion that, if confirmed, would require a re-evaluation of the accepted paradigm for glaucoma.

John S. Werner, PhD, a professor of ophthalmology and vision science at the University of California at Davis, told

the openly skeptical audience that AO-FdOCT has shown patterns of dead cone photoreceptors that correlate with optic nerve damage and visual field defects. He stated that there was a linear correlation between photoreceptors' density and Humphrey visual fields (Carl Zeiss Meditec, Inc., Dublin, CA) in the patients.

"In three optic neuropathies, we have found a very strong correlation between loss of photoreceptors and decreases in the nerve fiber layer and ganglion cell layer thickness, even when the ERGs [electroretinograms] look normal," Dr. Werner said.

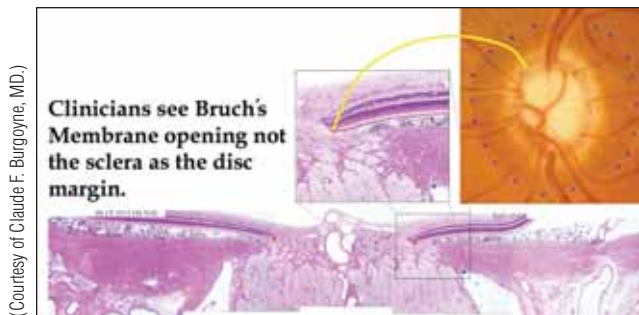
Retinal degeneration has not been a recognized feature of glaucoma, however, and audience members challenged Dr. Werner's results. The AO-FdOCT images must be an artifact of reflectivity changes in the photoreceptors or of alterations in their waveguide properties (the light waves' path within the "missing" photoreceptors). Either situation might make the photoreceptors invisible to the detector but would not really indicate their death, the doubters said. Dr. Werner replied that the missing photoreceptors look the same in retinas damaged by other diseases, but he added that further research is necessary.

A BIOMECHANICAL EXPLANATION

Less controversial but still unconventional was a biomechanical paradigm for glaucomatous damage to the optic nerve head. The concept would account for much of the heterogeneity ophthalmologists see, including normal-tension glaucoma, healthy optic nerves in the presence of elevated IOP, and the higher incidence of glaucomatous damage at all levels of pressure with aging.

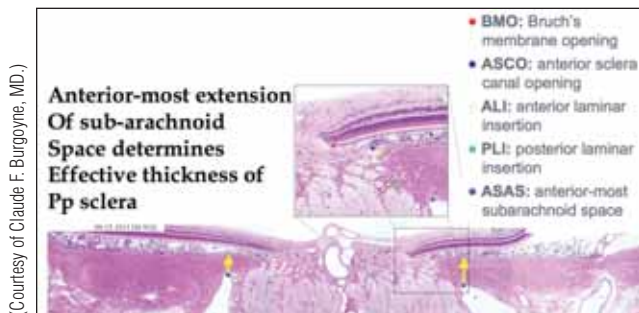
Claude F. Burgoyne, MD, a senior scientist and Van Buskirk Chair of Ophthalmic Research at the Devers Eye Institute in Portland, described support for the hypothesis from monkey studies.² Biomedical engineers J. Crawford Downs, PhD, also of the Devers Eye Institute, and Ian Sigal, PhD, of the University of Toronto buttressed Dr. Burgoyne's presentation with computerized modeling of how changes in tissue's characteristics might affect the eye's behavior in the presence of elevated IOP.³

The optic nerve head's structural relationship to glau-



(Courtesy of Claude F. Burgoyne, MD.)

Figure 1. Bruch's membrane's opening (BMO, red dots) is the histologic correlate to the clinical disc margin. In the future, optic-nerve-head imaging devices may use it to determine a more stable zero-reference plane. Blue dots are a clinical projection of the anterior-most aspect of the sub-arachnoid space, which determines the location of the thinnest portion of the peripapillary sclera (Figure 2). The histology in this figure is not from this actual nerve head but is intended to be representative.

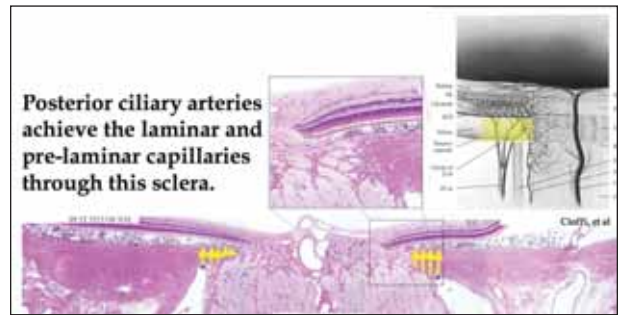


(Courtesy of Claude F. Burgoyne, MD.)

Figure 2. The neural canal is not a cylinder but expands as it passes from Bruch's membrane's opening (BMO, red dots) to the posterior laminar insertion (PLI, light green dots). Its anterior entrance is not defined by the anterior scleral canal's opening (ASCO, dark blue dots) but rather Bruch's membrane's opening. The anterior-most extension of the sub-arachnoid space (ASAS, light blue dots) is not part of the neural canal, but it does determine the thinnest extent of the peripapillary sclera.

coma has been of interest for decades, Dr. Burgoyne noted. Recent improvements in experimental and computerized modeling techniques, however, have allowed him and other scientists to hypothesize ways that connective tissue's stiffness, vascular patency, and molecular signals from astrocytes might interact to influence normal aging and a patient's susceptibility to glaucomatous vision loss.

For example, peripapillary scleral thickness not only contributes to the engineering response of the lamina cribrosa beams, but it also influences blood flow through the posterior ciliary arteries. These arteries pass through



(Courtesy of Claude F. Burgoyne, MD.)

Figure 3. Engineers believe that stress and strain within the thin, peripapillary sclera contribute importantly to the behavior of the lamina cribrosa, which spans the canal. Posterior bowing of the peripapillary sclera likely occurs within this region. Stress and strain within these connective tissues should affect the volume of blood flowing through the contained posterior ciliary vessels, which supply the laminar capillaries. (Inset reprinted with permission from Elsevier from Ritch R, Krupin T. *The Glaucomas*. 2nd ed. New York: Mosby; 1996.)

the lamina cribrosa to the choroid and optic nerve head. Thicker sclera and more rigid laminar beams might deform less but, as a result, pass more mechanical load from IOP to contained capillaries and adjacent axon bundles. In contrast, more flexible lamina might reduce these internal effects of IOP but compress nearby axons, ultimately triggering ischemic molecular pathways within the overlying astrocytes that could damage the axon. In older patients whose ocular blood flow can already be compromised by aging and systemic disease, the age-related stiffening of connective tissues might further influence the pressure-related effects on and the clinical appearance of the optic nerve head in glaucoma (Figures 1 through 3).

RETINAL NERVE FIBER LAYER AND VISUAL SENSITIVITY

The meeting's second theme emerged from reports about ways in which to combine or mathematically adjust the results of currently available tests to improve their clinical utility. For instance, a British group led by David F. Garway-Heath, BSc(Hons), MBBS, MD, FRCOphth, of Moorfields Eye Hospital in London reported on a non-linear Bayesian neural network to correlate the retinal nerve fiber layer's thickness, obtained through scanning laser polarimetry, and visual fields measured by standard automated perimetry.⁴ The researchers are seeking to predict visual sensitivity based on the retinal nerve fiber layer's thickness.

The data were from 1,905 eyes from normal subjects, glaucoma patients, and glaucoma suspects in two longitudinal studies, previously reported.^{5,6} In glaucomatous eyes, the investigators reported that the Bayesian neural-

network approach reduced the average error in sensitivity prediction to 4.3 dB compared with 13.2 dB in a linear regression analysis.

A TOUCH OF VIRTUAL REALITY

Ulrich Schiefer, MD, of the University of Tübingen, Germany, presented the early results with a practical method for determining when homonymous scotomata impair driving.⁷ Patients sit in front of a large projection screen covering a 160° X 70° swath of the visual field. Using video game controls, the patient “drives” vertically along a road as cartoon cars move in from the right or left. Collisions and their locations are tracked. They are then counted and correlated to a superimposed perimeter map of the field defects.

Surprisingly, patients in the early testing compensated well for hemifield scotomata by shifting their gaze, even when the defects were large, Dr. Schiefer said. The number of accidents correlated to neither the number nor the location of the defects but to the patient’s reaction time, he stated. This finding perhaps accounts for the improvement in visual performance that glaucoma patients exhibit with various “training” regimens, he said. It also shows how “astonishing” a contribution attention can make to the results of a visual function test, he added.

Dr. Schiefer showed the 148 attendees a video clip of a milling crowd of people passing around a ball. Directed to pay attention to the ball, the experts had their own moment of astonishment when Dr. Schiefer pointed out that they had not noticed the person in a gorilla suit who had walked through the middle of the picture. □

Linda Roach is a freelance medical writer based in Portland, Oregon. She acknowledged no financial interest in the product or company mentioned herein. Ms. Roach may be reached at linda.roach@nasw.org.

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good news. Ensuring that decision makers in the health-care system and the public appreciate the value of glaucoma therapy will ensure its support and improve patients’ adherence to prescribed treatment regimens. □

Editor’s note: David Eddy, MD, declined to respond to this article.

The author wishes to acknowledge that portions of this piece were adapted from one of his earlier articles.²⁰

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