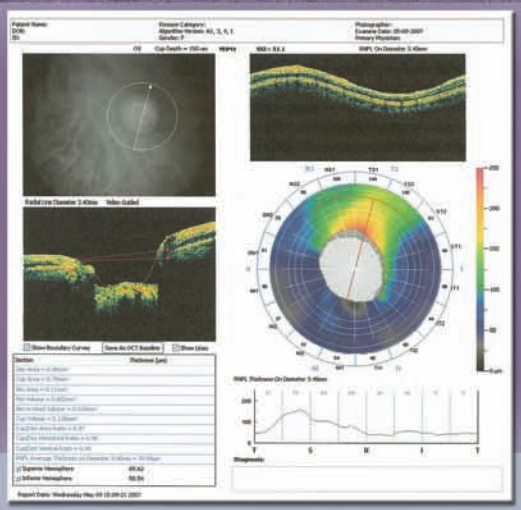
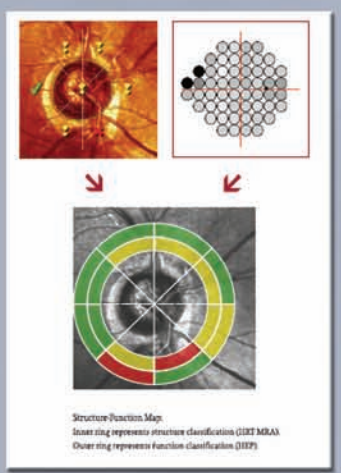
PART 2 OF 2
REVIEW OF OPTOMETRY
AUGUST 2007

THE Glaucoma HANDBOOK





OPTOMETRIC GLAUCOMA SOCIETY

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CHAPTERS

1 | Introduction

I would like to welcome you to the third edition of the Glaucoma Handbook, a publication developed under the auspices of the Optometric Glaucoma Society (OGS). This handbook is meant to serve as a guide to the diagnosis and management of glaucoma. The material includes a review of basics in regards to glaucoma diagnosis and therapy while providing new insights into the condition. Our goal with each new edition is to keep the material fresh and up-to-date. In certain sections, there is a great deal of new information; and in others, little has changed. Thus, certain chapters are brand new and others have been updated. The new sections for this issue relate to angle closure glaucoma and intraocular pressure, while the chapter on new technology has been updated significantly with the introduction of spectral optical coherence tomographers.

Instruments that take an image of the optic nerve and retinal nerve fiber layer have been available for 15 years, with significant changes occurring approximately every 5–6 years. Beginning with confocal scanning laser ophthalmoscopy, refinements led to the introduction of confocal scanning laser polarimetry. Optical Coherence Tomography has been available for a decade with the most recent version, the Stratus OCT, introduced in 2002. The next version of the OCT is being introduced by not one but several companies, who will push each other to develop the best instrument possible. The newest OCTs use Fourier-Domain technology (also called Spectral detection), which allows the entire A-Scan to be acquired at one time rather than being done over a period of time. This leads to faster imaging speed, allowing for a greater amount of information to be obtained in shorter periods, with greater resolution. Retinal histologic details are apparent with Spectral OCT which will allow for improved diagnosis of glaucoma as well as other conditions. This development will be discussed in Chapter 4.

A great deal of new information has recently become available in regards to intraocular pressure (IOP). Much of what was once taken for granted in regards to IOP is being evaluated again, such when it is highest and what are the best tools to measure it. Recent work has highlighted IOP fluctuation may not be the risk factor previously described, in part due to the design of previous studies. Issues of corneal thickness and rigidity are now better understood and, in particular, how they impact on IOP measurements. The Association of International Glaucoma Societies (AIGS) held a consensus meeting on intraocular pressure in May 2007, gathering experts from around the world to discuss this subject. Highlights from this meeting are available at www.globalaigs.org. Chapter 3 discusses new thoughts in regards to IOP, and how we should incorporate this information into our decision making process.

Angle closure glaucoma (ACG) has been described for as long as papers have been written about glaucoma. Still, it is only recently that we have come to understand the natural history and mechanisms, its severity, and how common it is in certain populations. Most optometrists are under the impression that sudden eye pain and intense symptoms are the classic ways that ACG presents. In reality, chronic angle closure glaucoma is the most common form of ACG, with elevated IOP and an extremely narrow angle being present but devoid of symptoms. Gonioscopy is the only way one can differentiate closed from open angle glaucoma, with the prognosis dependent upon the proper diagnosis. The AIGS convened a consensus meeting on angle closure glaucoma in May 2006 with highlights also available online at www.globalaigs.org. Chapter 12 discusses new information in regard to ACG and important points that optometrists should consider whenever one encounters patients with elevated IOP.

I would like to thank the members of the OGS for their support and help in developing these materials. Also, I would like to recommend the OGS on-line e-journal, which is available free of charge. One may sign up for this at www.optometricglaucomasociety.org. On behalf of the OGS, I would like to thank our team of authors, who have contributed to this effort. I would specifically like to welcome the new authors for this edition, David Friedman, Albert Khouri and David Pye. I would also like to thank Karen Fixler, Jill Burdge and Dennis Kowloski from Pfizer for their continuing support of the OGS, and specifically for the unrestricted grant that allowed us to continue with this publication. We hope that you find this handbook useful.

Murray Fingeret, OD
President, Optometric Glaucoma Society
Editor, The Glaucoma Handbook

2 | The Diagnosis of Glaucoma

John G. Flanagan, PhD, MCOptom

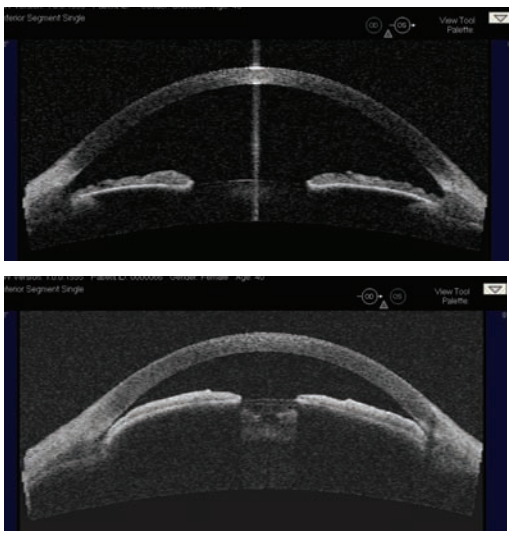
Most glaucomas are asymptomatic until the late stages of the disease, and therefore a careful, comprehensive eye examination, including history, is essential to the early diagnosis. The majority of information important in the patient's history relates to our knowledge of the disease's epidemiology and risk factor analyses. Age and race have clear clinical implications for the risk of developing glaucoma, with peoples of African descent showing a four to five times greater prevalence, a higher risk of blindness and a tendency to be diagnosed at a younger age. More recently it has been shown that while younger Hispanic-Americans develop primary open-angle glaucoma (POAG) at a rate similar to Caucasian-Americans, the ratio increases dramatically in older age, eventually exceeding even African-American rates after the age of 75. Pigmentary glaucoma is more common in Caucasians, as is exfoliative glaucoma—the latter appearing to cluster in certain regions; for example, the Scandinavian countries. Age and ethnicity are also important in regard to the angle closure glaucomas, which will be discussed in Chapter 12. Older age, as well as individuals of Asian heritage, are risk factors for the development of this condition.

Family history is well established as a risk factor for glaucoma. Having a sibling with glaucoma increases a person's chance of developing POAG 3.7-fold, according to some evidence. The prevalence of POAG in people having a first-degree relative with POAG is estimated to be between 4% and 16%. Up to 25% of patients with glaucoma are reported to have a positive family history. The overall proportion of POAG attributable to genetics is thought to be around 16%.

Ocular history is very important, as well. An essential aspect of any initial glaucoma diagnosis is a careful review of previous ocular findings. Ocular hypertension is strongly associated with an increased risk of POAG, as are specific aspects of the optic nerve and nerve fiber layer appearance. Of less diagnostic importance, but still worth documenting, are myopia and a history of systemic disease such as diabetes mellitus, systemic hypertension, vasospastic disease, autoimmune disease and severe hypotension.

TONOMETRY

Intraocular pressure (IOP) remains the single most important risk factor for the development of glaucomatous optic neuropathy, and its measurement is vital in the initial diagnosis and management of the glaucomas. It is also the only major risk factor that can be treated. In recognition of its clinical importance, this edition of the Handbook includes a new chapter dedicated to Tonometry and IOP (see Chapter 3).



1. The anterior chamber as viewed using the Visante OCT. In the top image, the angle is wide open; while in the bottom image, the angle is narrow. (Used with permission Carl Zeiss Meditec, Inc.)

PACHYMETRY

The measurement of corneal thickness, or pachymetry, is generally performed by an ultrasonic device. It should be measured in both eyes prior to gonioscopy, preferably before dilation, and at least two hours after awakening. Additional consideration should be given to the stability of the cornea and pachymetry readings following contact lens wear, cataract, corneal or refractive surgery. The ultrasound probe should be held perpendicular to the cornea and centered on the pupil. Take a minimum of three readings and ensure a standard deviation of 5 microns or less. Device name and time of day should also be recorded.

The normal population mean value for corneal thickness when measured by ultrasound pachymetry is thought to be 544 ±34 microns. Various correction factors for the influence of central corneal thickness (CCT) on IOP have been proposed, but should be considered guidelines rather than absolute corrections. Most corrections are based on values of between 2.5mmHg and 3.5mmHg per 50 microns of CCT from 545 microns. However, it should be noted that the effect is not linear; on thinner corneas, the greater the deviation, the greater the effect. It is increasingly likely that corneal thickness itself is a risk factor for POAG, independent of its tendency to skew tonometry results. The Ocular Hypertension Treatment Study (OHTS) suggested that the influence of CCT as a risk factor was much greater than that predicted by simply correcting the IOP reading for thickness. The relative risk of disease progression per 40 microns of CCT was shown to be 1.71; and the relative risk per 1mmHg of elevated IOP was 1.10. Forty microns would generally be corrected as being equivalent to less than 3mmHg. Therefore, if corneal thickness is viewed only in terms of affecting pressure readings, at least 40% of the relative risk would be unaccounted for.

GONIOSCOPY

The careful examination of the anterior chamber angle is essential in evaluating glaucoma suspects and diagnosing glaucoma. The process is called gonioscopy. Gonioscopy enables the visualization of the anterior angle and its assessment permits the exclusion of angle closure, angle recession, plateau iris or secondary angle block as the cause of raised IOP. Gonioscopy is most commonly performed indirectly by using a contact lens with a mirror system that overcomes the inherent total internal reflection of the angle anatomy. The angle is graded to relate information of its visible anatomical features. Several new, non-contact OCT devices can be used to evaluate the angle; these include the Visante (Carl Zeiss Meditec) and the Slit Lamp (SL)-OCT (Heidelberg Engineering) (Figure 1). Although considerably more expensive than a classic contact goniolens, they have the advantage of being objective and quantitative.

STRUCTURE

Evaluation of the optic nerve head and nerve fiber layer (NFL) is important in identifying early structural damage. Such structural changes frequently occur prior to the presence of repeatable visual function deficits. Clinical evaluation should be performed at the slit lamp using a magnified, stereoscopic view through a dilated pupil. The lens should be handheld. Perform careful, systematic documentation of the neuroretinal rim, including evaluation based on the ISN'T mnemonic device. That is, healthy rim tissue should always be thicker in the inferior (I) region, followed in decreasing thickness by the superior (S), nasal (N) and temporal (T) regions. It has recently been suggested that this clinical schema performs better if the nasal quadrant is ignored, owing to the obscuration of the nasal rim tissue by the nerve head vasculature, resulting in the IST device. Other observations that require documentation include: focal thinning of the rim tissue, vertical elongation of the cup, concentric enlargement of the cup, increased cup depth, saucerization, disc asymmetry, beta-zone parapapillary atrophy and vascular signs such as disc hemorrhage, focal narrowing, baring of circumlinear vessels, bayoneting and nasalization of the vascular tree. The size of the optic disc needs to be evaluated because the cup size correlates directly with the optic disc size. In a healthy individual, the larger the optic disc, the larger the optic cup. The disc size may be qualitatively measured with the small spot of a direct ophthalmoscope, with a fundus lens at the slit lamp or with an optic nerve imaging instrument. Practitioners should use a red-free filter to evaluate the nerve fiber layer (NFL) within two disc diameters of the optic nerve. However, it should be noted that modern digital fundus cameras give unprecedented images of the nerve fiber layer and are highly recommended. Several grading systems have been suggested, with the aim of evaluating the level of diffuse NFL atrophy and the identification of localized wedge or slit defects.

FUNCTION

Visual function is generally evaluated by measuring the visual field via standard automated perimetry. In glaucoma, the central vision is not affected until late in the disease process. Consequently, there is little diagnostic value in evaluating only central visual function by way of visual acuity. Clinical evaluation of automated perimetry charts remains a standard for the detection of glaucoma. Typical glaucomatous visual field defects were first described by von Graefe in 1869 and result from apoptotic death of the retinal ganglion cells. The field defects reflect damage to the NFL bundles as they track toward the optic nerve, although the site of damage is thought to be at the level of the lamina cribrosa within the optic nerve. Classic defects include early isolated paracentral, arcuate, nasal step and occasional temporal wedge defects. It is likely that a generalized defect due to diffuse loss of axons is present in many glaucomatous visual fields, but such defects have limited diagnostic value, as they are difficult to distinguish from the effects of media opacity and pupil size.

The standard clinical application of static threshold automated perimetry entails the assessment of the central 30 degrees. A variety of threshold estimation algorithms are available, with the newer, faster strategies based on Baysian methods—for example, the SITA strategy found on the Humphrey Field Analyzer (HFA). It is important to re-test abnormal-looking visual fields to ensure repeatability, particularly in the naïve patient, as there is a clearly defined learning curve that can mimic early defects. Interpretation can be aided by statistical packages that analyze the data relative to age-matched normal values (Total Deviation), and scan for focal defects by removing the influence of diffuse loss (Pattern Deviation). There are also analyses that judge subjects' intra-test reliability and the symmetry between the upper and lower field, such as the glaucoma hemifield test. It is essential to establish good quality baseline data for both the early diagnosis and the management of manifest disease. There are several specific analyses for glaucomatous progression, the most common being the Humphrey Field Analyzer's Glaucoma Progression Analysis (GPA). The analysis empirically compares serial fields to results collected in a group of patients with stable glaucoma. The original application used age-matched normal data to perform the analysis (Total Deviation), but the Early Manifest Glaucoma Trial found results to be more accurate when based on the Pattern Deviation analysis, by reducing the influence of diffuse loss.

The relationship between structure and function has gained much recent attention and is clearly not as simple as many would hope. However, it is inevitable that we will soon be considering the complexities of this relationship when attempting to diagnose and manage our patients with glaucoma. Indeed, the first available combined analysis of structure and function was recently launched by Heidelberg Instruments by combining results from the Heidelberg Retina Tomograph (HRT3) and the Heidelberg Edge Perimeter (HEP) (see Chapter 4).

The diagnosis of glaucoma requires the clinician to perform a series of tests, including a risk factor analysis, measurement of IOP, assessment of corneal thickness and evaluation of the anterior chamber angle, optic nerve, retinal nerve fiber layer and visual field. The skilled clinician will integrate these results in an attempt to diagnose glaucoma at its earliest manifestation.

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3 | New Thoughts on Tonometry and Intraocular Pressure

David Pye, MOptom

Intraocular pressure (IOP) is a risk factor for the development of glaucoma, though the condition may develop at any IOP level. IOP is the only modifiable risk factor and is determined by the amount of aqueous humor produced along with trabecular outflow, uveoscleral outflow and episcleral venous pressure. IOP shows greater variability in individuals with glaucoma with IOP variation correlated with higher mean pressures, but there is insufficient evidence to support 24-hour IOP fluctuation as an independent risk factor. IOP is higher in individuals in the supine position, and often peaks just before awakening.

It is now 50 years since Goldmann and Schmidt published a paper that described a new method for measuring the intraocular pressure of the eye. The method had considerable appeal, as the IOP could now be measured with the patient in a seated position at a slit lamp. The probe could be relatively easily disinfected and perhaps, above all, the instrument appeared to be based on sound engineering principles. However, in their paper, Goldmann and Schmidt acknowledged that their instrument would not be accurate in all circumstances. In the conclusion to their paper they wrote "under conditions which differ considerably from our measurement conditions (abnormally thick or thin corneas, for example keratoconus, animal eyes, severe epithelial edema), errors of several millimeters are to be expected". In spite of the above, the Goldmann applanation tonometer (GAT) has become the International Standard reference tonometer to which other tonometers are to be compared.

Corneal thickness was recognized as a confounding factor for GAT measurements in 1975 when Ehlers et al published a paper where they performed a cannulation study on patients prior to cataract surgery. They found that GAT overestimated the IOP of those patients who had thick corneas and underestimated the true IOP of those patients with thin corneas. They found a linear relationship between the effect of central corneal thickness (CCT) and GAT measurements, suggesting that changes of CCT of 100 microns could affect the GAT measurements by 7mmHg. Interestingly, the next paper published on this matter was 18 years later, in 1993, when Whitacre published a paper that tried to emulate the Ehlers study, but with fewer subjects. Since this time, there have been a number of papers published using either in vivo data, meta-analysis or theoretical models to predict the effects of CCT on GAT and, as a result, a number of algorithms now exist which attempt to predict the "true" IOP of a patient from CCT and GAT data.

A complicating factor is that there may be racial differences in CCT. Whilst a difference has been demonstrated between African-American and Caucasian populations in the Ocular Hypertension Treatment Study, it is difficult to compare results obtained from other countries due to the different instruments used to measure corneal thickness and the reported population samples. However, the measurement of the "true" IOP of a particular patient is now proving to be more complex than allowing for CCT alone. This was initially discussed in a paper in 1999 by Orssengo and Pye, but more graphically illustrated in a paper by Liu and Roberts who developed a theoretical model for investigating the manner in which the material behavior of the cornea may affect GAT results. Liu and Roberts used corneal behavior data published in the literature, and showed that variations in Young's modulus of the human cornea could produce GAT measurements of 13mmHg to 30mmHg for a true IOP of 15mmHg. At this stage, there is no way of measuring the biomechanical properties of the individual human cornea in vivo, although there is a theoretical method which performs a calculation of Young's modulus on the basis that the cornea is normally hydrated. In other words, the use of a correction factor for GAT based on CCT alone may be in considerable error as the biomechanical effects of the individual cornea cannot be included in the calculation. As a result, some authors are recommending that pachymetry be performed on patients who are then considered to have thin, normal or thick corneas rather than using a specific CCT correction nomogram for GAT.

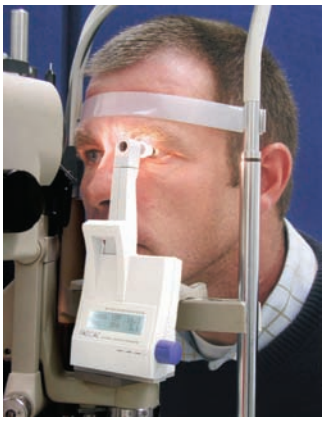

Figure 1. The Pascal Dynamic Contour Tonometer is seen with a measurement being taken. The IOP is displayed in the digital display.

This then leads to two approaches to attempting to measure the IOP. One is to try to measure the biomechanical behavior of the cornea and make an allowance for these material properties to better determine the IOP, and the second is to develop a method of tonometry which directly measures the IOP by being able to overcome the biomechanical influences of the cornea.

The Reichert Ocular Response Analyzer (ORA) is a non-contact tonometer which measures the time delay between the initial applanation, as a result of the puff of air, and the second applanation, which occurs as the cornea begins to regain its shape as a result of the topographical change produced by the initial stimulus. The instrument provides a measure of the corneal behavior, and a "corrected" IOP measurement as a result.

The Pascal tonometer has a tip with a surface contour which, it is claimed, resembles the corneal contour when the pressure on both sides of the probe tip is equal (Figure 1). When this is done, it is suggested that the biomechanical effects of the cornea on IOP are significantly reduced, if not eliminated, and the small pressure sensor located in the probe tip then gives an accurate measure of the IOP. There is a considerable amount of literature which suggests that the Pascal is less affected by corneal properties than GAT.

New tonometers such as the ICare seem to perform similarly to GAT, and other forms of tonometry using acoustic, contact lens or infra-red technologies may appear in the future.

It is difficult to compare studies which have investigated the relative performance of tonometers. Often the protocols vary, the statistical analyses are different, and differing populations are used for the studies. However, Tonnu et al compared the "repeatability

coefficient" which is a measure of how repeatable two readings taken by the same observer will be, and found GAT to be more repeatable than non-contact tonometry, Ocular Blood Flow Tonography and Tonopen.

Another approach has been to investigate the effects of changes in the biomechanical behavior of the cornea on GAT, and this was observed clinically by Kaufman in 1975 who suggested that GAT measurements were often grossly misleading in patients who had only moderate amounts of corneal epithelial edema. There is also evidence from refractive surgery that water in the cornea can significantly reduce GAT measurements. Earlier this year, Hamilton et al reported on the effects on GAT of corneal swelling produced by two hours of eye closure and thick soft contact lens wear. The results seem to suggest that, at low levels of corneal edema, the cornea becomes stiffer and the GAT results may overestimate the true IOP. As the cornea swells beyond 6% to 10%, the cornea may behave as a softer tissue, artificially lowering the GAT measurement.

The direct clinical implications of these results are twofold. One is that if patients wear contact lenses, an estimation of their IOP with GAT will be less affected by corneal material properties if the patient does not wear their contact lenses on the day of measurement. If this is not possible, then trying to measure the IOP of the patient after the same period of contact lens wear at each visit may be appropriate. The second implication of the work relates to the diurnal variation of IOP. On eye opening, the average CCT is thicker than it will be for the rest of the daytime, and the measured IOP with GAT is highest. Interestingly, the CCT and IOP measured in this fashion reduce at a similar rate over the first two hours after eye opening, suggesting a link between the two results. The increase in CCT alone does not explain the increased GAT result, and the soft contact lens swelling results suggest that some of the increased IOP measurement is due to stiffening of the corneal tissue, and it may be that as much as half of the increased GAT measurement of IOP on eye opening may be as a result of increased CCT and Young's modulus of the cornea.

To reduce the corneal effects on IOP measurements obtained with GAT, it would be advisable to ensure that the measurements are taken after the patient has been awake with eyes open for at least two hours.

The biomechanical behavior of the cornea has been reported to be affected by age. Earlier this year, Elsheikh reported on in vitro studies of human corneas that were subjected to relatively slow and rapid rates of corneal inflation to attempt to imitate GAT and non-contact tonometry respectively. Overall, 39 corneas were tested and categorized into three age groups: 50-64, 65-79 and 80-95 years. The results demonstrated that corneas exhibit a time-related behavior to an applied stress, called viscoelasticity, and that the corneas became stiffer with age. The suggested corneal stiffening suggested from this work could significantly affect GAT results.

It is difficult to know what a single IOP measurement actually means and how it should be interpreted, as there seems much more we need to know and understand before a meaningful determination of IOP can be made. While research into the measurement of the true IOP continues, IOP is still an important measurement in clinical practice.

Mr. David Pye, MOptom, is Senior Lecturer and Clinic Director at the School of Optometry and Vision Science, University of New South Wales, Australia.

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4 | New Technologies in the Diagnosis and Management of Glaucoma

John G. Flanagan, PhD, MCOptom

The last decade has seen an explosion of new technologies that have begun to challenge our understanding of the structural and functional relationships in early glaucoma, while at the same time introducing potentially new standards of care. In this chapter, I will review several of the latest technologies and developments.

Methods for the non-invasive, objective, quantitative, structural assessment include scanning laser tomography and optical coherence tomography for the optic nerve (ON) and retinal nerve fiber layer (RNFL); and scanning laser polarimetry for exclusive RNFL analysis. All three technologies are reported to have excellent diagnostic performance in the detection of early glaucoma. These instruments are not meant for stand-alone use but rather support the clinical evaluation of the ON/RNFL. They may provide corroboration of a working diagnosis or require the clinician to re-evaluate his or her assessment of the ON/RNFL.

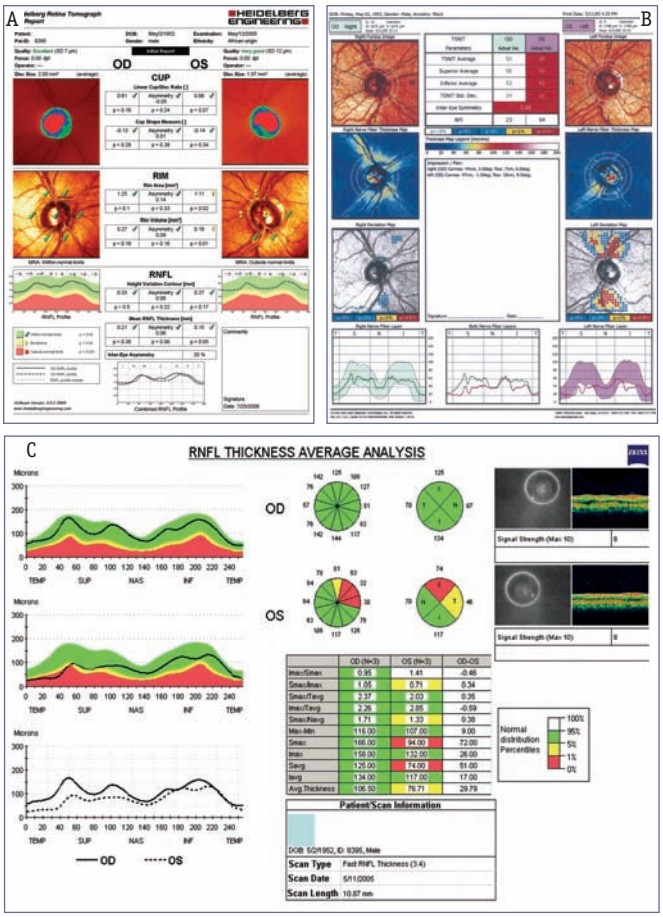


Figure 1a (top left), b (top right), c (bottom). HRT (a), GDx (b) and OCT (c) images of a patient with primary open-angle glaucoma. The loss is in the left eye only. All three technologies reveal the damage to be in the superior portion of the left optic nerve and retinal nerve fiber layer. This is seen as areas in the left eye that are flagged in the superior region. The GDx also shows loss in the inferior portion of the left eye, which does not correspond to the other tests or visual fields.

Scanning laser tomographers (SLT) were first introduced in the late 1980s and are among the most common of the new imaging systems for use in glaucoma. The technology is based on the optical principals of confocal microscopy. A series of images are recorded along the axial axis of the eye, thus enabling three-dimensional reconstruction of the surface of the retina and/or the optic nerve head. The Heidelberg Retina Tomograph (Heidelberg Engineering) is the most common of the SLTs (Figure 1a). The current, third-generation model, the HRT3, was introduced toward the end of 2005. The HRT3 is similar to the previous model in that it operates using a 670nm diode laser light source and a field of view of 15 x 15 degrees, with a two-dimensional resolution for each image plane of 384 x 384 pixels. The scan depth is automatically selected from a range of 1.0mm to 4.0mm, and 16 scans are obtained per millimeter of scan depth. A 2mm scan depth with 32 image scans has a one-second acquisition time (24msec per scan). The HRT3 offers several important developments over its predecessors. A sophisticated image acquisition quality control system has been incorporated. This considerably reduces the learning curve for new users, and helps to ensure adequate image quality for future progression analysis. There is a new alignment algorithm that has reduced the intra-test variability, which in turn enables more sensitive analysis of structural progression. The database for analysis of the stereometric parameters and Moorfields Regression Analysis has been expanded to include 700 of Caucasian descent, 200 of African descent and 200 from Southeast Asia. This database is also used for the new, contour independent Glaucoma Probability Score (GPS), which is based upon automated analysis of the shape of both the optic nerve head and the parapapillary retina in both normal and glaucomatous eyes. The printout reflects these new measures and emphasizes the analysis of cup, rim, retinal nerve fiber layer and ocular asymmetry. There are additional improvements in the Topographic Change Analysis (TCA) that can now display graded levels of significance and Trend Analysis overview plots of cluster vol-

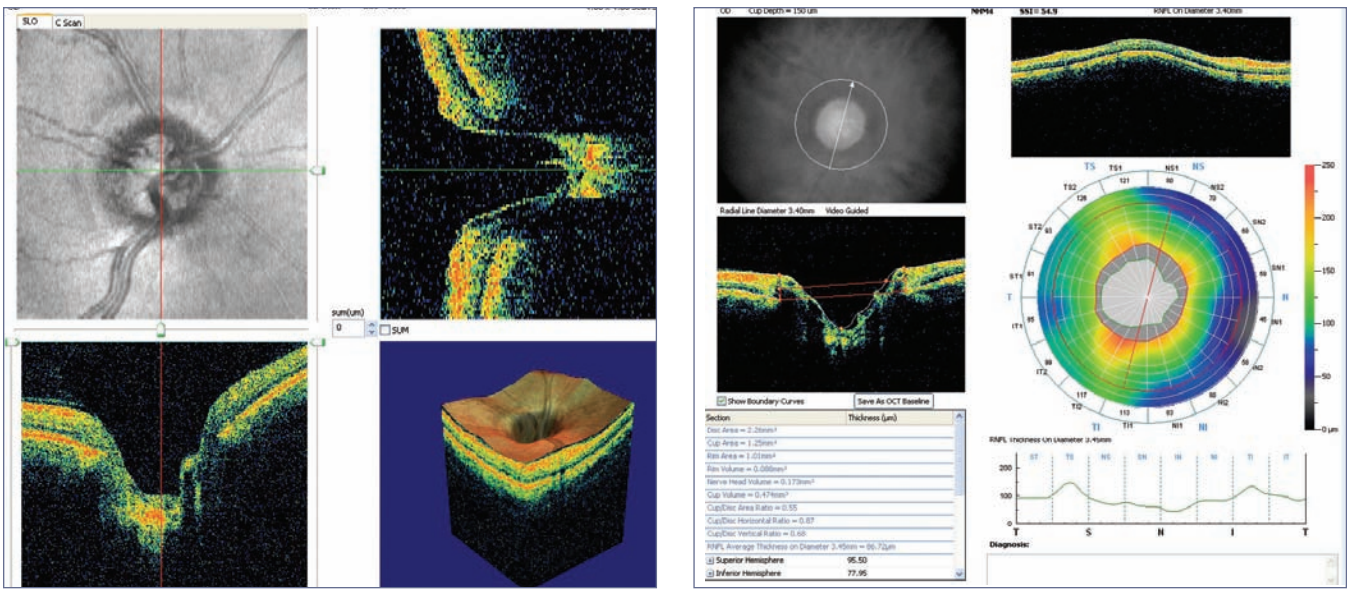


Figure 2a (left). The 3D disk printout as it appears on the computer screen for the RTVue spectral domain OCT. The optic nerve cross-sectional images along with the 3-D view are seen in the printout. Figure 2b (right). The NMH4 printout from the RTVue OCT is seen.

ume and area. The HRT remains the only imaging technology specifically designed to analyze progression, and it has the added advantage of being backwardly compatible to its very first model. This means that some centers now have 15 years of consecutive data. The HRT has the ability to both align and analyze serial images. This is of particular importance, as the greatest potential of the new imaging technologies lies in their detection of subtle structural changes early in the disease, rather than cross sectional classification and staging of the disease. Recent data from the ancillary study of the Ocular Hypertension Treatment Trial has indicated that baseline HRT measures were highly predictive for the development of POAG during the course of the study (Moorfield's Regression Analysis for the temporal inferior sector had a hazard's ratio approaching 6.0).

Scanning laser polarimetry combines scanning laser ophthalmoscopy with polarimetry to measure the retardation of polarized laser light caused by the birefringent properties of the retinal nerve fiber layer (Figure 1b). The commercially available instrument is called the GDx VCC (Carl Zeiss Meditec). It uses an 820nm diode laser source in which the state of polarization is modulated. Image acquisition takes 0.7 seconds and the scan field is 20 degrees. Results are compared to an age-matched normative database, and a machine classifier is used to define the likelihood that a map is normal or glaucomatous. The current GDx is a fifth-generation instrument and uses Variable Corneal Compensation (VCC), which differs from its predecessors in that it performs individual specific compensation of the ocular birefringence, rather than using a fixed, average compensation.

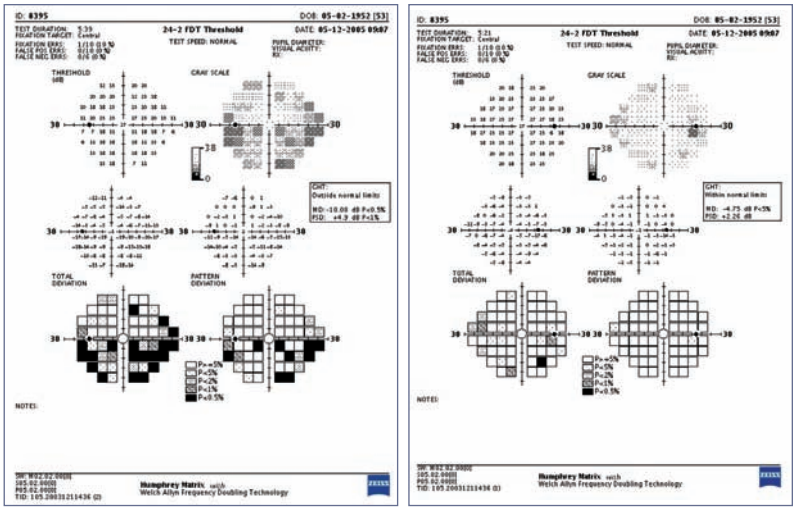


Figure 3a,b. These FDT Matrix 24-2 Full Threshold fields are from the patient seen in Figure 1. The right visual field is within normal limits, and the loss in the left correlates with the images in Figure 1 and SITA SWAP field in Figure 4.

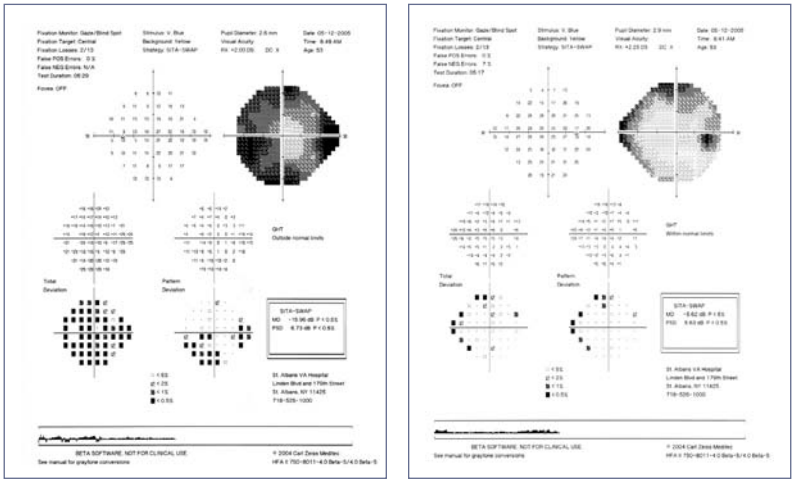


Figure 4. These are SITA SWAP fields for the patient seen in Figure 1 and 3. The loss is in the left eye, with the inferior points being flagged. The field in the right eye is consistent with a trial lens artifact.

The consensus meeting of the Association of International Glaucoma Societies (AIGS) on Glaucoma Diagnosis stated that the VCC reduced the range of normative data, thereby improving detection rates and correlation with other structural measures. Further, recent literature has reported solid reproducibility and an encouraging diagnostic performance in the detection of early disease. There are two anticipated new developments for the GDx. Later this year the long anticipated Guided Progression Analysis (GPA) will be launched, enabling the alignment and analysis of serial data. Next year, the Enhanced Corneal Compensation will replace the VCC, with the idea of further reducing image noise and the effect of atypical scans.

Optical coherence tomography is the one technology that has changed exponentially since the publication of last year's Handbook with the introduction of high resolution, fourier or spectral domain optical coherence tomography (OCT). Presently, the most commonly used of the OCTs is the Stratus OCT (Carl Zeiss Meditec) which is a third generation, time domain OCT that employs low-coherence interferometry to enable high-resolution, cross-sectional imaging of the retina and optic nerve. A superluminescent 830nm diode provides a near infrared, low-coherence source, which is divided and beamed to a reference device in the eye. Each light path goes back to a detector where the reference beam is compared to the measurement beam.

The Stratus can be used in the diagnosis and management of glaucoma by measuring retinal nerve fiber layer (RNFL) thickness around the optic nerve head. Radial tomograms are then used to assess the cross-sectional profile of the optic nerve (Figure 1c). The OCT's RNFL assessment correlates well with the clinical assessment of focal defects and visual fields in patients with glaucoma and demonstrates a significant difference between normal and glaucomatous subjects. Results are compared to an age-matched normative database. Recent studies have suggested that the OCT is capable of detecting early disease progression.

Fourier domain (FD) OCT was recently launched by 9 different companies, including Optovue (RTVue 100), Heidelberg Engineering (Spectralis HRA-OCT), Carl Zeiss Meditec (Cirrus) and Topcon (Figure 2a, b). FD OCT uses a stationary reference mirror, as opposed to the moving reference mirror found in time domain OCT. The interference

between the sample and reference reflections are split into a spectrum, and all wavelengths are simultaneously analyzed using a spectrometer. The resulting spectral interferogram is Fourier transformed to provide an axial scan at a fraction of the time previously required. This has resulted in up to a 100 times increase in the number of A-scans per second (Spectralis at 40,000 scans per second compared to the Stratus at 400 scans per second). The new technologies are paired with complementary imaging modes; for example SLT, to enable registration of all A-scans. This allows accurate image registration and image alignment of serial images, essential for the analysis of progression and therefore overcoming the most significant problems associated with time domain OCT. The new generation instruments are just being delivered and require considerable refinement of their software to ensure good analysis in patients with glaucoma, but they promise to make a substantial contribution to future disease management.

New technologies for visual function have concentrated on selectively testing specific anatomical and/or perceptual pathways. The goal of such an approach is to detect loss of retinal ganglion cells (RGCs) earlier and with improved repeatability.

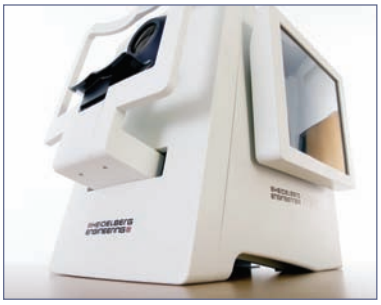
Frequency Doubling Technology perimetry (FDT) is based on the frequency-doubling illusion, whereby a low-spatial frequency grating (<1 cycle/degree) is flickered in counterphase at a high temporal frequency (>15Hz). When this occurs, the spatial frequency of the grating appears to double. The technique has been applied clinically using a grating of 0.25 cycles/degree and temporal frequency of 25Hz. It was initially proposed that the illusion was due to selective processing of the My cells, a subset of magnocellular projecting RGCs. However, this is now thought unlikely, as there is no evidence for such cells in primates—although the illusion does preferentially stimulate the magnocellular system. It is likely that the stimulus, as used clinically, is a flicker contrast threshold task.

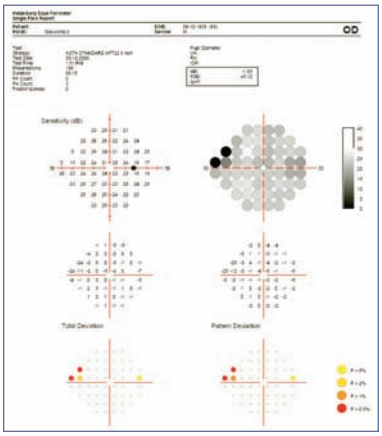
The original FDT tested up to 19 large, 10 degrees x 10 degrees targets in either a threshold mode or a rapid (<1 minute) screening test. During testing, the stimulus flicker and spatial frequency are held constant while the contrast is modified in a stepwise process similar to the bracketing method used in conventional perimetry. In response to concerns over the ability of such large targets to detect subtle, early defects, a second-generation machine was developed, the FDT Matrix, which uses smaller 5-degree targets and measures with a standard 24-2 pattern (Figure 3). A video camera is incorporated for fixation monitoring, and it is possible to view serial fields and perform glaucoma change analysis. A ZEST-like strategy is used to estimate the sensitivity and ensure a standardized test time, regardless of defect.

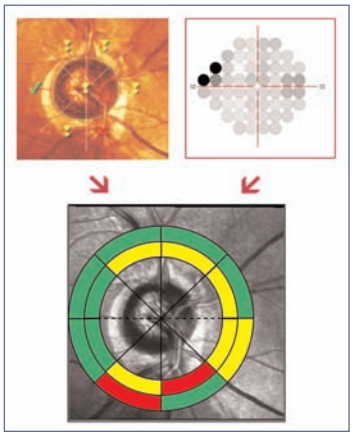
FDT has been reported to have high sensitivity and specificity for the detection of glaucoma. Even when used in the screening mode, it may detect some defects earlier than standard automated perimetry (SAP), and it offers good test-retest characteristics. FDT is relatively resistant to optical blur, small pupils and the influence of ambient illumination—all of which make it ideal in a screening environment. Recent reports on the Matrix suggest that it is capable of diagnosing early disease before SAP and often prior to SWAP. As disease progresses, there is little difference with SAP results.

Short-wavelength automated perimetry (SWAP), or blue-yellow perimetry, uses a large Goldmann size V blue stimulus (centered on 440nm) against a bright yellow background (100 cd/m2) (Figure 4). The rationale is to selectively test the blue cones and their projection through the koniocellular pathway, thus taking advantage of their reduced redundancy. Several longitudinal studies found SWAP to be predictive of early glaucomatous SAP visual field defect, in some cases by up to five years. SWAP is tested, analyzed and displayed in a way intuitively similar to SAP. SWAP is limited by the relatively greater influence of cataracts and other media opacities, a compressed dynamic range, poor test-retest characteristics and increased test time. The clinical application has also been limited by the threshold estimation strategies presently available. SITA SWAP has recently been developed for the HFA and will likely improve its clinical usefulness. However, SWAP will probably not replace SAP and should be considered a complementary test to be used in selected situations, such as high-risk glaucoma suspects with normal SAP results.

Heidelberg Engineering recently launched a new visual function test called the Heidelberg Edge Perimeter (Figure 5A, B). This is based upon an illusionary stimulus called flicker defined form, in which a 5° stimulus region within a background of random dots is flickered at a high temporal frequency (15Hz) in counterphase. This gives rise to an illusionary edge or border that is perceived as







5a (left). The Heidebelberg Engineering HEP perimeter is seen. 5b (center). A nasal step is seen on the printout from the Heidelberg HEP. This printout has similarities to that of the HFA perimeter. 5c (right). One unique feature of the HRT HEP perimeter is the structure function map, which correlates findings of the HRT confocal scanning laser ophthalmoscope with that of the perimeter.

a gray circle against a mean luminance background. The stimulus targets the magnocellular projecting retinal ganglion cells and is proposed for the early detection of glaucomatous damage. Of particular note is the availability of the first ever combined Structure Function Map, in which the HRT's MRA analysis is combined with the visual field analysis of the equivalent ON sectors (Figure 5C).

Current methods for the analysis of visual field progression include an expert inspection of the Overview printout and the Glaucoma Progression Analysis (GPA), an updated version of the original Glaucoma Change Probability (GCP) analysis. Both are empirically based and compare a patient's pattern of change to "typical" change experienced by others with glaucoma. GCP was based on the total deviation normal database, and was criticized for being prone to error in the presence of developing cataract and changing pupil size. The new GPA was developed for the Early Manifest Glaucoma Treatment Trial (EMGT) and uses the pattern deviation normal database, allowing an analysis that is less sensitive to the effects of cataract and reduced pupil size. GPA is available on the Humphrey Field Analyzer (HFA). The analysis uses estimates of the inherent variability of glaucomatous visual fields from data collected at 16 centers. This is combined with the EMGT criterion of three significantly deteriorating points repeated over three examinations. A minimum of two baseline and one follow-up examination are required. Each exam is then compared to baseline and to the two prior visual fields. Points outside the 95th percentile for stability are highlighted, as are points that progress on two or three consecutive examinations. Two additional qualifying statements alert the clinician to the likelihood of "probable progression" (3x2 consecutive) and "likely progression" (3x3 consecutive) (Figure 6a, b, c). An advantage of the GPA is that it permits progression analysis across the full-threshold and SITA-standard threshold estimation strategies, thus allowing analysis of pre-SITA visual fields alongside SITA standard fields.

New technologies have been developed and are gaining clinical acceptance. These new tests complement the examination and allow a better understanding of the visual field, optic nerve or retinal nerve fiber layer. The new technologies supplement tests we have been using for many years. As we gain better understanding of their use and strengths, they will only improve our ability to diagnose and manage glaucoma.

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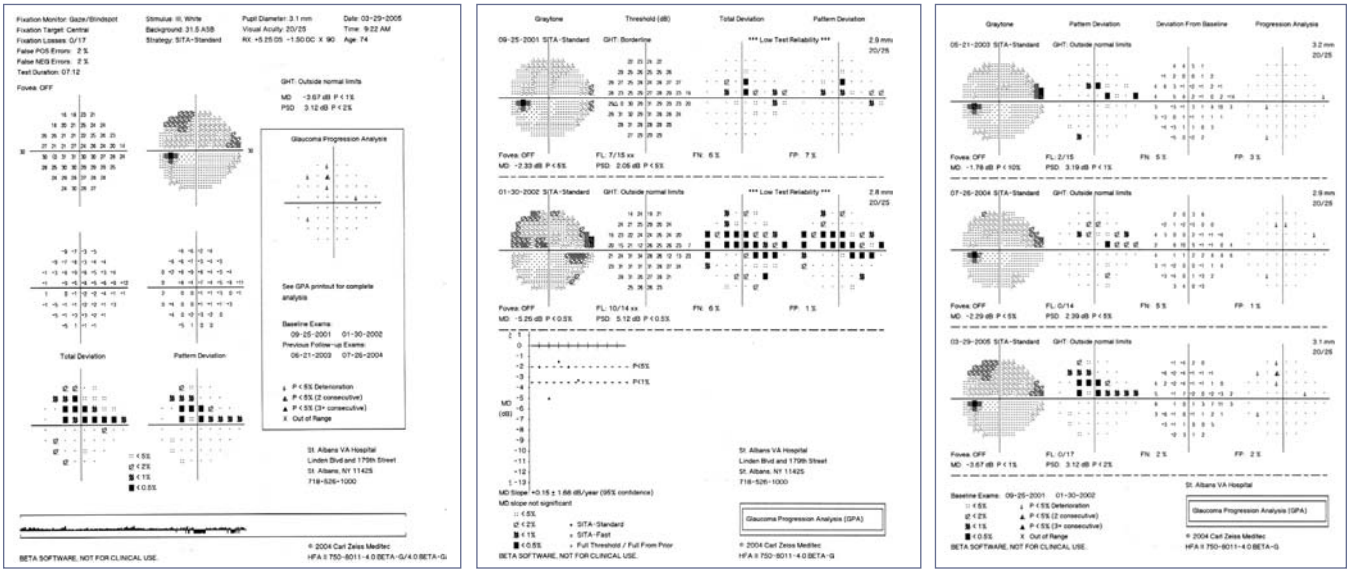

Figure 6a (left) is the left visual field Glaucoma Progression Analysis (GPA) printout for a patient with open-angle glaucoma. Five fields performed between September 2001 and March 2005 are available for analysis. In 6a, the single field summary printout is seen. The box on the right side reveals that a few points have changed once, and one point changed two fields in a row. This is consistent with potential change. In Figure 6b (center), the first page of the overview printout displays the two baseline fields. On the bottom of this page is a table that graphs out each of the fields and displays a regression analysis. Over four years, the fields have improved slightly. Figure 6c (right) shows some progression may have occurred, but this must be confirmed with subsequent field testing.

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5 | Risk Assessment as an Emerging Tool for Glaucoma Care

Robert D. Fechtner, MD, Albert S. Khouri, MD, and Murray Fingeret, OD

The clinician treating patients with glaucoma or glaucoma suspects is faced with the clinical challenges of whom to treat, when to treat and to what extent to treat. Not all patients with glaucoma will lose vision to the extent that quality of life will be compromised. Our current model of diagnosing and treating glaucoma is based on the principles of detecting damage, setting a target intraocular pressure at which we believe the pressure-related component of damage will be reduced or eliminated, then following the patient to monitor for progression. This model has limitations. Early changes are asymptomatic and only as the disease progresses are detectable structural and functional changes observed. Also, changes are irreversible and represent significant damage to the optic nerve.

We treat patients with ocular hypertension and glaucoma by reducing intraocular pressure (IOP). However, it is important to remember that the goal of glaucoma care is not to reduce IOP, not to preserve optic nerve and not to preserve visual field, but rather to preserve sufficient vision for acceptable quality of life. It is the loss of vision from glaucoma that impacts upon the quality of life for our patients. If our tools allow us only to base our treatment decisions on the degree of loss already present or on the detection of additional loss, we are missing an opportunity to identify and treat appropriately patients at greatest risk for losing vision.

Risk assessment is a well-accepted tool in other fields of medicine. Perhaps the best known example is cardiovascular medicine. Most adults are at least aware that elevated blood pressure and abnormal blood lipid profile increase the risk of coronary heart disease (CHD). Many have had blood pressure measured and a lipid profile tested. Risk assessment and modification is the fundamental tool for preventing coronary heart disease. No one wishes to learn of their risk by having the first heart attack! True, the consequence of gradual atherosclerosis is a cardiovascular event—quite dramatic compared with the chronic optic neuropathy and gradual loss of vision of glaucoma, but there are some parallels in the underlying principles of risk assessment. We can use the example of cholesterol and IOP.

The understanding of cholesterol as a risk factor has dramatically evolved over time. Early in the evolution of risk assessment for CHD, cholesterol was identified as a risk factor. Initially, normal cholesterol levels were defined as being within 2 standard deviations (SDs) of the mean (200 mg/dL to 310 mg/dL). Later, it was appreciated that there was a continuous effect, even within normal ranges. It soon became evident that subjects with the "normal range" of cholesterol levels included an excessively high incidence of CHD. In fact, the correlation between cholesterol levels and CHD

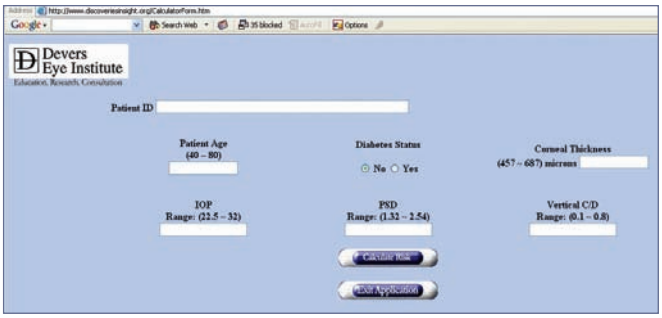

Figure 1. The Discoveries in Sight risk calculator, available on the Internet at www.discoveriesinsight.org.

occurred in a continuous, graded fashion, and normal cholesterol levels were still associated with increased risk of CHD.

For glaucoma, abnormal IOP was described as two standard deviations from the mean (21 mmHg). We have subsequently learned that IOP is a continuous risk factor, even at statistically normal levels. Further, it is clear that one can have high IOP without glaucoma and one can have glaucoma with statistically normal IOP.

With the emerging evidence from large, prospective glaucoma trials, we are beginning to amass the data to allow us to be able to identify risk factors for both the development of and the progression of glaucoma. By applying risk assessment, we can begin to develop models to identify those patients at highest risk of progression. Models allow the creation of risk calculators, tools to estimate individual rather than population risk. We can then determine who is at greatest risk and offer earlier or more aggressive intervention.

The results of recent large-scale trials have encouraged a reassessment of the way clinicians evaluate and manage patients with ocular hypertension (OHT) or glaucoma. The potential benefits of IOP reduction have been clearly demonstrated. The Ocular Hypertension Treatment Study (OHTS) investigated the effect of lowering IOP on progression to open-angle glaucoma (OAG) in over 1600 subjects with OHT but no evidence of glaucomatous damage. Treatment with topical ocular-hypotensive medication reduced the risk of progression to glaucoma by approximately half, from 9.5% in untreated patients to 4.4% in patients receiving treatment. It should be noted that the European Glaucoma Prevention Study (EGPS) found no benefit from treatment of ocular hypertension with dorzolamide compared with placebo (vehicle of dorzolamide). However, the IOP reduction in the placebo group was nearly the same as that in the dorzolamide treated group, a curious finding that has not been fully explained.

A recent study to test the generalizability of the OHTS prediction model for the development of primary open-angle glaucoma in a large independent sample of untreated ocular hypertensive individuals was reported. A prediction model was developed from the observation group of the OHTS that was then tested on the placebo group of the European Glaucoma Prevention Study (EGPS). A calculator to estimate the 5-year risk of developing POAG, based on the pooled OHTS-EGPS predictive model was found to have high precision in assisting clinicians deciding on the frequency of tests and examinations during follow-up and the advisability of initiating preventive treatment.

Similarly, in subjects with early glaucoma (Early Manifest Glau-

coma Trial [EMGT]) who were randomized to either treatment or observation, IOP reduction slowed the rate of progression from 62% in controls to 45% in the treated population (median follow-up of 6 years). Despite these encouraging findings, individualizing therapy based on the results from large-scale clinical trials is difficult. Although IOP reduction may decrease risk of glaucoma and vision loss, treatment costs and potential side effects also need to be considered. It would be helpful to know who is at greatest risk and most likely to benefit from treatment.

For many, it is not surprising to get confirmation that lowering IOP prevents or delays the progression from OHT to glaucoma or from glaucoma to further visual field loss. Perhaps more important than the clear demonstration of the benefits of IOP lowering was the identification of risk factors for the development of glaucomatous damage. Several risk factors were identified at baseline in OHTS for the group who developed glaucoma. Older age was associated with increased risk of developing the disease over the course of the 5 year study. Despite this correlation, it is important to remember that glaucoma takes many years to progress to visual loss. Though increasing age is a risk factor, younger patients should have frequent eye exams, since they have a greater remaining life span over which to develop vision loss.

Higher untreated IOP in OHTS was also associated with a greater frequency of developing glaucoma. This is not surprising since IOP is a consistent risk factor in many studies. In the recent analysis of the Early Manifest Glaucoma Trial with a median follow-up of 8 years, the results confirmed earlier findings that elevated IOP is a strong factor for glaucoma progression, with a hazard ratio increasing by 11% for every 1 mmHg of higher IOP (95% confidence interval 1.06-1.17; P<0.0001). Patients with a greater cup-to-disc diameter (a measure of optic nerve damage) were more likely to develop glaucoma. It is not clear if some of the subjects with the larger cup-to-disc diameters already had early glaucoma without demonstrable visual field defects when they entered the study. In a recent analysis of OHTS data, optic disc hemorrhages were associated with a 6-fold increase (95% CI 3.6-10.1; p<0.001) in risk of developing POAG in ocular hypertensive subjects. A new and fascinating observation was that subjects with thinner corneas were at higher risk for glaucoma. While we know that the thickness of the cornea affects IOP measurements, this alone did not account for the increased risk. Thinner central corneal thickness was an independent risk factor. This has prompted clinicians to measure corneal thickness in patients with ocular hypertension-and glaucoma-on a routine basis.

The OHTS publication included two 3 x 3 tables that included central corneal thickness and either IOP or C/D ratios. We could consider these as the first crude risk calculators. It was possible to combine two risk factors to derive an individual risk for the development of glaucoma. Steven Mansberger, MD, MPH, at Devers Eye Institute, posted an interactive risk calculator on the internet at www.discoveriesinsight.org/GlaucomaRisk.htm (Figure 1). This calculator was based on the OHTS publication. It has undergone modification since it was originally introduced. A version is available for download.

The first validated risk calculation model was published in 2005. This was also based on the OHTS risk model. The calculator was tested on an independent population of ocular hypertensive subjects followed at the University of California, San Diego. With support from Pfizer Ophthalmics, a cardboard slide rule and then a digital handheld risk calculator were produced (Figures 2 and 3). To be used precisely as designed, these calculators require input of data just as it was collected in the OHTS study. This data includes the age, intraocular pressure, central corneal thickness, vertical cup-to-disc ratio, pattern standard deviation (PSD) from a HFA II threshold visual field and diabetes status. However, in clinical practice, a less stringent use should still provide reasonable estimates of risk.

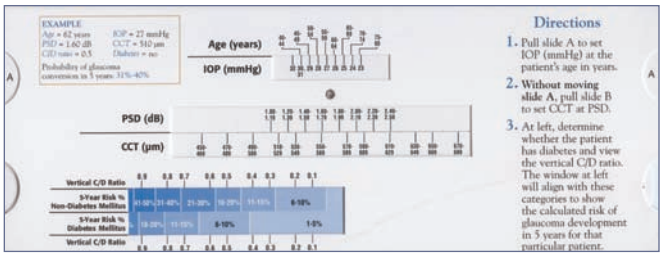

Figure 2. The paper STAR risk calculator that is distributed by Pfizer, Inc.

As mentioned earlier, a validated risk model from the OHTS study was introduced in 2006 (http://ohts.wustl.edu/risk). This prediction model was developed from the observation group of the OHTS and then tested on the placebo group of the EGPS. The calculator was tested and found useful in estimating the 5-year risk of developing POAG, based on the pooled OHTS-EGPS predictive model.

One question when the risk calculator is used is whether to input diabetes status. OHTS found having diabetes to be protective of developing glaucoma, but only diabetics without retinopathy were allowed into the study. Diabetes being protective of developing glaucoma has not been validated in other studies; and until further data is available, it may be better to ignore the diabetes panel on the risk calculator and always keep it checked as "no." Diabetes was not found to be a risk factor in the analysis of pooled OHTS-European Glaucoma Prevention Study dataset. Thus the effect of diabetes on the development of POAG remains controversial.

How can a risk calculator add to the quality of clinical care? At the very least, we should be able to better determine whom to treat and whom to follow without treatment. One consensus group published suggestions that we should observe low-risk patients, consider treatment for moderate risk patients, and treat those at highest risk. The exact treatment threshold has not been clearly determined, but this group selected ranges of <5% for low risk, 5-15% for moderate risk, and >15% for high risk. The rationale is that a glaucoma patient at highest risk to progress from OHT to glaucoma is also probably at relatively high risk for developing a glaucomatous visual disability in his or her lifetime. Other factors will influence the decisions regarding treatment.

The EMGT study identified factors present at the baseline visit that predicted who would progress. These included higher IOP, eligibility in both eyes (glaucoma in both eyes), presence of exfoliation material, worsening visual field (mean defect) and older age. Once the patients returned for follow-up, factors that predicted progression included initial response to treatment (better initial response was protective), IOP at first visit and mean IOP at all follow-

Figure 3. The STAR risk calculator, distributed by Pfizer, Inc.

up visits, as well as percentage of visits at which a disc hemorrhage was detected. Corneal thickness was not identified as a risk factor in this study, but these individuals already had glaucomatous damage, not OHT.

Risk calculators have not yet been developed for progression once a patient has glaucoma. For now, we should evaluate our patients for known or suspected risk factors and either test for progression more frequently or treat more aggressively those we consider at higher risk.

Can we predict which glaucoma patient is at risk for progressing and ultimately developing a visual disability? OHTS identified risk factors for the progression from OHT to open-angle glaucoma (OAG). Risk calculators are now available to help the clinician estimate individual risk of progression. The EMGT study identifies some of the risk factors for progression of OAG. As we refine models of risk, we will be able to better determine which patients are at highest risk and may need aggressive treatment. Conversely, we should identify patients at low risk who can be followed closely without treatment. This requires a fundamental change in our view of glaucoma treatment. Rather than think of it simply as IOP-lowering treatment, we might start to consider it as risk reduction. Of course, we must consider patient preferences and views about risk in making these determinations.

Well-designed clinical trials in glaucoma will continue to advance our understanding of the spectrum of this disease. It is not only reassuring that many of our cherished traditions are now supported by evidence, but also intriguing to explore new concepts about glaucoma based on large, well designed studies. At first, we will make qualitative determinations by identifying risk factors in our patients and altering our treatment decisions. Eventually, we can expect to have risk calculators as tools to help decide whom to treat, when to treat and to what extent.

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6 | Understanding Glaucoma Medications

Murray Fingeret, OD

Medical therapy is the most common method used for the reduction of the intraocular pressure (IOP) associated with ocular hypertension (OHT) and open-angle glaucoma (OAG). Several classes of drugs (prostaglandin derivatives, beta-adrenergic antagonists, carbonic anhydrase inhibitors, adrenergic agonists and cholinergic agonists) may be used to reduce the IOP. Medications are classified based upon several areas: efficacy, safety, tolerability and patient acceptance. Efficacy refers to how well the medication reduces IOP, both in the short- and long-term. What is the drug's response rate? For example, how many individuals will have their IOPs reduced from the baseline level by 15%, 20%, 25%, 30% or more? How often will the IOP creep back towards pre-treatment levels months to years later? Tolerability refers to how well the drug is tolerated and accepted. How often does the patient or doctor feel that side effects preclude continuing the medication? In the perfect world, the clinician would like to select an agent that shows excellent efficacy and persistency, as well as being safe and well-tolerated.

Cholinergic agents, such as pilocarpine, were the drug of choice

for many years. In 1978, beta-adrenergic antagonists were introduced and soon thereafter became the drug of choice. Their popularity stemmed from improved efficacy, reduced dosing schedule and a favorable side effect profile. Over the next two decades, other drug classes (topical carbonic anhydrase inhibitors, adrenergic agonists, cholinergic agents) were used to complement beta-adrenergic blockers. During this period, adrenergic agonists (epinephrine, dipivefrin) became obsolete as newer drugs with significant advantages came to the market. In 1996, a further evolution occurred with the introduction of prostaglandins (PGs). The first PG introduced, latanoprost (Xalatan), soon replaced beta-adrenergic blockers, such as timolol, as the primary agent for the treatment of OHT and open-angle glaucoma. With the use of PGs, IOPs once obtainable with multiple medications were within reach using a single agent. In addition, compliance improved, and diurnal IOP variation was reduced.

Beta-adrenergic antagonists were introduced in 1978 with the introduction of timolol maleate. Since then, additional beta-adrenergic antagonists include levobunolol, betaxolol, metipranolol and carteolol. Betaxolol is different from other medications in this class in that it is a cardio-selective agent that primarily blocks beta1 adrenergic receptors. Carteolol is also unique in that, in addition to being a nonselective beta-adrenergic antagonist, it has intrinsic sympathomimetic activity (ISA).

Nonselective adrenergic antagonists are available in both solution and gel formulations. A gel formulation increases the drug's contact time, enhances efficacy and reduces systemic absorption, but it is usually uncomfortable. Istalol is a specific formulation of timolol maleate that increases the drug's penetration into the eye, allowing it to be used once per day. The beta-adrenergic antagonists reduce IOP between 22 -28% by inhibiting the production of aqueous humor. While the dosage for solutions is listed as bid, the nighttime dosage has little impact on IOP reduction. The morning instillation is the more important for the patient to remember to perform. Topically, the drugs are well-tolerated. The larger concern with the use of topical adrenergic antagonists is their systemic absorption and potential side effects. Side effects include confusion, lethargy, fatigue, bronchospasm and bradycardia. While beta-adrenergic blockers appear to be safe as long as patients with known contraindications (such as pulmonary conditions) avoid them, their use nonetheless has declined over the past decade with the introduction of PGs. PGs are more efficacious with fewer side effects and a better dosing schedule. Also, oral adrenergic antagonists are increasingly being used by internists and cardiologists to treat many cardiovascular conditions. When given systemically, they often reduce the IOP, minimizing the impact if a topical beta blocker is also utilized. In most situations when patients requiring IOP reduction are on oral beta-adrenergic antagonists, PGs become the drug of choice. Still, one advantage of this drug class is that drugs such as timolol or levobunolol are available as generics, which are less expensive than branded medications.

Apraclonidine (Iopidine) was the first drug in a class known as adrenergic agonists. Brimonidine is the other member of this category. Adrenergic agonists inhibit the production of aqueous humor and enhance outflow mechanisms, which leads to an IOP reduction of 22% to 28%. Several side effects occur with apraclonidine, including the development of an allergic follicular conjunctivitis and loss of effect over time (tachyphylaxis). Brimonidine is still affected to some extent by these same side effects, but it has replaced Apraclonidine as the adrenergic agonist of choice. One important difference between adrenergic agonists and beta-adrenergic antagonists is the duration of action. The short duration of action of adrenergic agonists requires that they be used on a tid dosage when they are the only medication utilized. This peak-and-trough effect associated with adrenergic agonists is one reason why they are commonly used in a secondary role. When used in conjunction with other agents, they can be used on a bid basis. Brimonidine is available in a branded product (Alphagan P, 0.10%, 0.15%) and a generic formulation (0.2%). Adrenergic agonists are relatively safe medications, though they should not be used in children due to concerns regarding lethargy. Other side effects include dry mouth, fatigue and drowsiness.

Topical carbonic anhydrase inhibitors (CAI) inhibit the production of aqueous humor and reduce the IOP by 16% to 22%. Originally, CAIs were available only in an oral form (acetazolamide, methazolamide) and were known to induce systemic side effects, such as paresthesias, depression, diarrhea, metallic taste, kidney stones and aplastic anemia. Because CAIs reduce IOP so effectively, a topical formulation was developed. With topical preparations, the inhibition of the carbonic anhydrase enzyme is limited to the eye, dramatically reducing systemic side effects. Dorzolamide 2% (Trusopt) was the original drug in this class, followed by brinzolamide 1% (Azopt). These topical formulations have been shown to be safe, with the most common side effects being local irritation, such as burning and stinging (more pronounced with dorzolamide). However, one concern is that the drugs are from the sulfa family and are therefore contraindicated in individuals with sulfa allergies. CAIs are rarely a primary medication and are almost always used with other agents. Topical CAIs are quite effective when employed in combination with other agents. When combined with timolol to produce Cosopt (timolol-dorzolamide), they form half of the only fixed-combination glaucoma medication approved by the Food and Drug Administration (FDA). Cosopt is used twice per day. Many individuals feel that the topical CAIs are the best secondary agent to be used when the individual's primary drug is effective and tolerated, but further IOP reduction is needed.

Cholinergic agents reduce the IOP by causing the ciliary muscle to contract, leading to improved flow through the trabecular meshwork. Pilocarpine is the most common of the agents making up this class and is available in concentrations ranging from 0.5% to 12%. The most frequently used strengths are 1%, 2% and 4%. Pilocarpine is rarely used due to its qid dosing schedule and commonly induced local side effects, including brow-ache, dim vision, blurred vision and headache. It is an extremely safe drug, systemically, and can reduce IOP up to 25%.

The introduction of timolol led to a quiet revolution in the way glaucoma was managed. Therapy went from an irritating, difficult-to-tolerate agent (pilocarpine) to one that was well-tolerated and effective (timolol). A further revolution occurred in 1996 with the introduction of latanoprost. Dosage was reduced to once per day, IOP reduction enhanced (26% to 34%) and systemic or local side ef-

fects reduced. PGs reduce the IOP by enhancing uveoscleral outflow, leading to IOP levels never before seen with single topical agents. The increase in uveoscleral outflow is caused by the elevated presence of metalloproteinases, which break down the collagen matrix within the uveoscleral region that surrounds the ciliary muscle bundles. New channels for aqueous outflow are created, boosting uveoscleral outflow to greater than 50% of total flow from the eye. Since the introduction of latanoprost, additional PGs have become available, including travoprost (Travatan) and bimatoprost (Lumigan). Both latanoprost and bimatoprost are listed on the drug's package insert as capable of being a primary agent. PGs have a long duration of action, allowing them to be used once per day while still maintaining a flattened diurnal curve throughout a 24-hour period. If needed, other glaucoma agents may be added to PGs. Tachyphlaxis and systemic side effects are rare with local side effects that, while irritating, are not serious. Hyperemia is the most common side effect and is seen least commonly with latanoprost, followed by travoprost, with bimatoprost causing hyperemia most often. Other side effects include iris darkening, which is most commonly seen in individuals with mixed-colored iris, periorbital skin darkening, eyelash growth, anterior uveitis, cystoid macula edema (CME) and irritation. Travatan Z is a new form of travoprost, with Sofzia being used as the preservative instead of benzalkonium chloride (BAK). The intent with the introduction of a non-BAK preserved solution is to reduce symptoms that may be associated with chronic BAK use. CME and anterior uveitis are rare and, when present, almost always occur in eyes with a risk factor, such as prior intraocular surgery or a history of iritis. Eyelash growth is reasonably common, but fortunately is only a cosmetic concern. The iris color change has received a great deal of attention. It is caused by an increase in the size and number of melanin granules within the iris stromal melanocytes. The pigment is contained within the iris, and no signs of increased pigmentation are seen anywhere else in the eye. Periorbital skin darkening is another commonly encountered side effect that typically disappears upon discontinuation of the agent.

There has been controversy as to which of the PGs most effectively reduces IOP. Well-conducted studies have not demonstrated that any of the PGs is superior in reducing IOP. For example, the XLT study, evaluating all the PGs, showed that the three PGs were comparable in regard to efficacy, while hyperemia was most common with bimatoprost. A meta-analysis recently published by van der Valk et al also showed PGs to be similar in efficacy. Another area of question is whether switching PGs within the class is an effective strategy. There are several reasons why a PG may not be effective in a particular patient. Different studies have shown that approximately 9% of individuals will show <15% IOP reduction when any of the PGs are utilized. Will switching from one PG to another lead to a greater IOP drop? Possibly, but the studies used to evaluate this question are confusing. Switch studies have shown that, no matter what the first or second drug is, IOPs will be lower on the second drug. Reasons why the IOP may be reduced include improved compliance or a phenomenon called regression to the mean. Regression to the mean describes the situation in which it takes several IOP readings (data points) to know what the true IOP range is throughout the day (diurnal variation). Whether a switch within class lowers IOP over the long term is still open to question. We do know that if a person is experiencing side effects from one PG, then switching to another is an advisable first step in reducing these symptoms.

Glaucoma medications have evolved over time. We are now at a point where PGs have become the primary agent for therapy, and timolol is used less often in a primary role. Other agents may be used to complement PGs, always with the aim of reducing the IOP to the needed target levels while keeping side effects to a minimum.

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7 | The Management of Glaucoma

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There are many situations that confront the optometrist as he/she decides whether to initiate therapy for ocular hypertension (OHT) or glaucoma. For ocular hypertension, the decision process is discussed in Chapter 5. In regard to glaucoma, when optic nerve and/or visual field damage associated with glaucoma is recognized and other causes of this loss are ruled out, therapy is in order. Before therapy commences, a strategy is developed based upon the stage of disease and IOP level, as well as other factors. A target intraocular pressure (IOP) range is determined and a medication selected. If therapy is not indicated, the patient is often classified as a glaucoma suspect and followed once to twice per year, depending upon the individual's characteristics. The category of glaucoma suspect includes individuals with ocular hypertension as well as suspicious optic nerves or visual fields.

When medical therapy is initiated, the selection of the initial agent usually is decided between two classes of drugs:

prostaglandins (PGs) or topical beta-blockers. PGs have replaced beta-adrenergic antagonists as the most commonly used agent for initial therapy. This is due to their ability to reduce IOP efficiently on a once-per-dosage schedule, without inducing serious side effects, as well as their dampening IOP fluctuations that may occur over a 24-hour period (diurnal curve). Beta-adrenergic antagonists do not reduce IOP as effectively, especially when viewed over a 24-hour period, and have some additional contraindications. Recent information from several clinical trials has highlighted the need for reduced target IOPs, further cementing PG's role as first-line agents.

The initial medication selected is based upon its ability to reduce IOP, its safety profile, tolerability and patient acceptance. The drug needs to be matched to the patient. For example, a patient with a history of anterior uveitis or macula edema would not be a good candidate for PG therapy. Likewise, a patient with pulmonary disease would not be a candidate for beta-adrenergic antagonist therapy. Target IOPs must also be considered as a therapeutic agent is selected. Target pressures refer to the range of IOP that we hope will prevent further glaucomatous damage. A patient's target IOP may change over time, either as new knowledge becomes available, indicating lower IOPs will be advantageous or if progression is confirmed. Target IOPs are a best guess of what IOP will control the condition. The best indicator to show that target IOP has been achieved is when periodic optic nerve and visual field evaluations reveal no change. If change is noted, additional reduction is necessary. Target IOPs are based on the amount of damage present and the highest IOP reading, with greater reduction required as damage worsens. Recent clinical trials have provided evidence that lower target IOPs are important, though no definitive study has shown exactly what IOPs are optimal.

The Ocular Hypertension Treatment Study (OHTS), which had a target IOP reduction of 20%, found that 4.4% of individuals in the therapy group progressed. In a study of glaucoma patients, the Early Manifest Glaucoma Trial (EMGT), in which the goal was 25% IOP reduction, 45% of patients in the therapy group progressed over time. The Collaborative Initial Glaucoma Treatment Study (CIGTS) which had a similar group of patients with early glaucoma as the EMGT, also monitored for progression. CIGTS found little change in the group whose IOP was reduced 38%. In the Advanced Glaucoma Intervention Study (AGIS), groups were broken down based on the percentage of visits in which the IOP was reduced below 18mmHg. One group with a mean IOP of 20.2mmHg showed significant deterioration, while another group with a mean IOP of 12.3mmHg appeared to be stable over an 8-year period. These studies, taken as a group, do not provide proof that IOPs need to be reduced to the low teens for all patients, but they do illustrate the need to reduce IOPs to lower levels than previously thought.

The EMGT recognized that risk factors for glaucomatous progression include higher IOP at the time of diagnosis, pseudoexfoliation, bilateral disease, disc hemorrhages, older age and worse visual field mean deviation. The AGIS found that an additional risk factor is variation in IOP over a 24-hour period. This is a separate risk that describes IOP fluctuation throughout the day, even when IOP is low at certain time points. To recognize diurnal fluctuations, we should record the time of each visit and schedule exams at varying times during the day.

Often it is helpful to begin therapy with a monocular or unilateral trial in which medication is begun in one eye for a few weeks, with the contralateral eye serving as a control. The rationale is that IOP, while often different between the two eyes, will rise and fall over the day to a similar degree. Also, the response to a medication should be similar in both eyes. Since non-responder rates vary from 8% to 25% depending on the class of medication, a monocular trial is one way to ensure the medication is effective as well as determine if side effects are occurring. Realini has questioned the use of the monocular trial, in part because the IOP reduction in one eye does not necessarily predict how the drug will perform in the other. Moreover, monocular trials require at least one additional visit. Nevertheless, many experts continue to recommend the monocular trial, recognizing its limitations but also using it as a way to control the initiation of a new drug.

At the outset of therapy, the patient needs to be educated in regard to the optimal time for drop instillation(s) and potential side effects. Also, it is important to demonstrate proper eyedrop instillation technique and have the patient demonstrate that he/she can properly instill the drops. If eyedrop instillation appears to be a problem, there are devices to aid instillation. Also, a companion or family member may aid in medication insertion. Finally, written dosing schedules should be provided as reminders. The first follow-up visit usually occurs 2 to 4 weeks after therapy commences. At each visit, ask if any side effects have occurred and when the patient last used the medication(s). Patient communication is discussed in Chapter 10. Even when written schedules are provided, some patients misunderstand how to use the medication. Questions that should be addressed at every visit include whether the patient is actually using the drug or if there are any problems or concerns. The IOP is measured to assess whether the medication is effective and pressure is at target level. If the drug is well-tolerated and effective, then the patient is followed over time, watching for medication side effects and/or progression. Patients are seen every 3 to 6 months depending on severity and type of disease. Ocular hypertensives are monitored less often, and individuals with significant loss, more often. Dilated optic nerve evaluation, imaging and visual field testing should be performed at least yearly. Testing more often is recommended in the first year after diagnosis, if a greater degree of loss is present or a question of stability arises.

An important question that should be considered early in the course of follow-up is the rate of change. If a patient is progressing rapidly, we need to recognize this and modify our approach. One way to measure rate of change is to perform perimetry on a 6-month basis for the first 2 years. This is best done with SITA visual fields and the Glaucoma Progression Analysis (GPA) software tool. If the fields are unchanged, the interval between field testing can be increased to yearly. Several fields are needed before a decision can be reached regarding stability, but once 5 fields are available, trends will emerge.

One challenge occurs when a patient does not respond or side effects develop with the initial medication. If side effects occur, what are they? Are they caused by the medication? May they be reduced if a switch occurs within the same class of drugs? An intra-class

switch may work if hyperemia develops with one PG. A more difficult question is if the target IOP level is not reached with the initial medication. In this case, the IOP response needs to be evaluated. For example, if the IOP was very high and/or the damage significant, leading to a target goal of 40% reduction, and the drug provides 25% of the target reduction, then the medication appears to be effective, but a second agent is needed. On the other hand, if the reduction is 15% or less, the patient may be considered a non-responder. Inadequate responses do occur and are not often recognized, leading to unachieved target levels. We should ask if progression may occur in 15 years at the present IOP level. It may be then easier to appreciate the urgency of attempting to achieve target IOP levels.

There are different reasons why the IOP may not have been reduced with the initial agent, including lack of response or poor compliance with the clinician faced with a decision of how to proceed. Switching to a drug within the same class, such as going from one PG to another (intra-class switches) is controversial, since it is not proven that such switches work. Switch studies with PGs have shown that the medication switched to always performs better. However, one problem is that most switch studies have been conducted over only short periods, usually about 30 days. The improved efficacy may be due to the second drug's greater response, but other possible reasons for this reduction include improved compliance or fluctuations in IOP (regression to the mean).

If the medication is effective but further reduction is needed, either because the IOP is above the target goal or progression is identified, the practitioner may choose an additional medication. If a PG is the initial agent, the second agent may be a beta-blocker, alpha agonist or topical CAI. A beta-blocker offers the convenience of once-per-day use; thus the patient would take it in the morning and take the PG at nighttime. When added to a PG, topical CAIs may be more effective at lowering IOP than beta-blockers. But, topical CAIs require twice-per-day dosage. If a patient is on a PG along with a beta-blocker or topical CAI and further IOP reduction is needed, then either of these drugs may be discontinued and a fixed-combination agent containing timolol and dorzolamide (Cosopt) begun. It is important to stress to patients taking two medications that they should wait five minutes before instilling the second agent to avoid washing the first from the eye. Also, remember to instruct patients taking beta-blockers to close their eyes or occlude their punctum for three minutes. This will reduce systemic absorption, improve efficacy and reduce side effects. Argon or Selective Laser Trabeculoplasty and filter surgery become options when the patient is progressing or the IOP is above the target level, and several medical options have been tried (see chapter 8).

In some cases, even with patients who respond well to initial therapy, the IOP may slowly rise over time. Such increases could be due to the glaucoma worsening, problems with compliance or the development of tachyphylaxis. The two questions to ask are: Is the drug effective, and is it being used? If the IOP is elevated, instill the medication and measure the IOP several hours later. Also, observe the patient's drop instillation technique to determine if the drug is getting into the eye. And finally, the reverse monocular trial may be helpful to address whether tachyphylaxis has developed. In this trial, the drug is temporarily discontinued in one eye and continued in the other. If tolerance has developed, there will be little change in the untreated eye's IOP over the next several weeks. However, a rising IOP proves the drug is effective and should be continued, but an additional agent is necessary.

The management of ocular hypertension and glaucoma is an art that requires the clinician to make an ongoing series of decisions and adjustments over the patient's lifetime to ensure the IOP remains at acceptable levels and the condition does not worsen. Periodic monitoring of the optic nerve and visual fields are also necessary. The doctor needs to consider both the short and long-term view to ensure occurs throughout the lifetime of their patient.

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8 | When Medical Therapy Fails: Surgical Options for Glaucoma Management

Kathy Yang-Williams, OD

Surgical intervention becomes an option in the management of open-angle glaucoma when the intraocular pressure (IOP) cannot be sufficiently reduced with medical therapy to prevent progressive optic nerve damage and/or visual field loss. A recent analysis of glaucoma surgery utilization rates in Medicare beneficiaries showed that surgical procedures employed in more advanced glaucoma (trabeculectomy, glaucoma drainage devices, and cyclophotocoagulation) have increased in frequency in the past decade. Recent innovations in glaucoma management, such as the use of prostaglandin analogs and selective laser trabeculoplasty, may have allowed patients to delay more invasive glaucoma procedures.

Selective laser trabeculoplasty (SLT) is a newer procedure performed with a Q-switched 532nm Nd:YAG laser to reduce IOP. Unlike its predecessor, argon laser trabeculoplasty (ALT), SLT

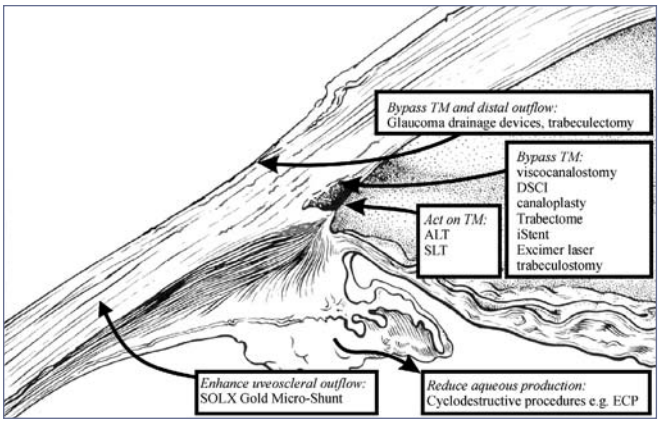

Figure 1. Schematic representation of glaucoma surgery mechanisms. (Modified from Primary Care of the Glaucomas, Fingeret, Lewis: 2001. McGraw Hill, NY).

"selectively" targets the pigmented cells of the trabecular meshwork (TM) using a larger spot size, lower power setting and less total energy than ALT. These laser settings cause less collateral damage to adjacent TM cells yet reduce the IOP at a rate comparable to ALT. Primary SLT has been shown to be as effective as latanoprost monotherapy in several studies. Advantages of using SLT as compared to ALT include the potential for repeat procedures, the lack of thermal damage to the trabecular meshwork, less post-operative pain and inflammation, and a lower dependence on pigmentation of the angle. However, much like ALT, the success rate of SLT declines over time. Studies of long-term efficacy of SLT have yet to be completed.

Glaucoma filtering surgery is intended to provide long-term control of IOP without medications; to maintain adequate diurnal control with minimal post-operative complications or subjective discomfort. The ideal procedure would be widely available and easily taught without requiring excessive expense for instrumentation. The current gold standard for glaucoma filtering surgery is trabeculectomy, a procedure first popularized by Cairns in 1968. During trabeculectomy, the surgeon creates a partial scleral flap before excising a block of trabecular meshwork. This scleral tunnel allows aqueous to escape from the eye to the subconjunctival space. Trabeculectomy has been associated with a number of complications, including bleb dysesthesia (symptomatic bleb), cataract, bleb failure, hyphema, wound leak, flat anterior chamber, ocular hypotony, hypotony maculopathy, choroidal detachment, suprachoroidal hemorrhage, bleb infection and endophthalmitis. Surgical variations of this procedure have been designed to reduce the frequency of these complications. The use of anti-metabolite therapy, such as 5-fluorouracil (5-FU) and mitomycin-C (MMC), reduces the risk for bleb failure by controlling the formation of scar tissue at the surgical site. Anti-metabolites are indicated for high-risk patients, such as younger patients, those with a history of failed filtration surgery, African-Americans and individuals with aphakic, uveitic, neovascular or secondary angle closure glaucoma. One concern is that anti-metabolites, particularly mitomycin, have been associated with a higher risk for late wound leak, blebitis and endophthalmitis. Patients may present initially with an infected bleb, or "blebitis," associated with a painful red eye, photophobia and discharge. If the infection extends into the eye (bleb-associated endophthalmitis), significant anterior chamber reaction or hypopyon can result. This is an ocular emergency requiring immediate and aggressive antibiotic therapy. Even with treatment, the prognosis for patients with bleb-associated endophthalmitis is poor. Trabeculectomy is a well-established technique, but it poses significant risk for early and late post-operative complications. Frequent post-operative visits are necessary, and additional interventions may be required to ensure the success of the procedure.

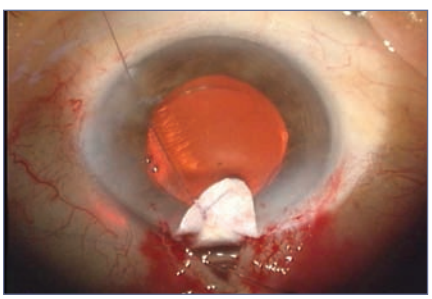

Figure 2. Microcannulation of Schlemm's canal. (Courtesy of iScience Interventional, Menlo Park CA).

Non-penetrating glaucoma surgery reduces the risk of a flat anterior chamber in the immediate post-operative period by creating an alternative outflow pathway without the anterior chamber being penetrated as occurs in trabeculectomy. These procedures are more difficult to teach, and there is often a steep learning curve for surgeons. Non-penetrating glaucoma surgeries do not usually result in the formation of a filtering bleb, and patients have fewer complaints because of the absence of a filtering bleb. However, studies evaluating non-penetrating glaucoma surgery show that intraocular pressure reduction is generally less than what can be achieved with trabeculectomy.

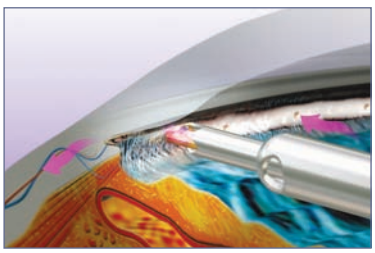

Figure 3. Ablation of TM by Trabectome. (Courtesy of Neomedix Inc, Tustin CA).

Several new glaucoma surgeries intended to reduce IOP without the creation of a filtering bleb are in development. Unlike trabeculectomy and glaucoma drainage devices that shunt aqueous humor to the subconjunctival space where it is resorbed via an episcleral bleb, these procedures either restore or modify existing natural outflow pathways or redirect aqueous via alternative pathways. One group of procedures bypasses TM to re-establish physiologic outflow and avoid the juxtacanalicular TM, while another diverts aqueous away from the anterior chamber into the suprachoroidal space. (Figure 1).

When fluid is directed into the distal outflow channels, the aqueous flows into the sub-scleral space rather than subconjunctival space, as in trabeculectomy, so no bleb is created. There is no risk of hypotony due to the inherent resistance of the distal outflow system and episcleral venous pressure (believed to be in the range of 12 mmHg). Initial results with these procedures suggest that IOP can be significantly reduced although not to the same degree as is achieved with trabeculectomy. But, complica-

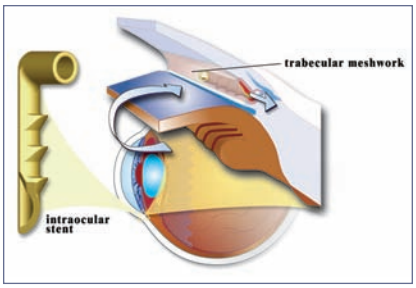

Figure 4. iStent trabecular bypass micro stent. (Courtesy of Glaukos Corp, Laguna Hills CA).

tions such as hypotony and flat anterior chamber are avoided. In canaloplasty with tensioning suture (iScience Interventional, Menlo Park, CA), Schlemm's canal is circumferentially dilated with Healon GV (sodium hyaluronate, Advanced Medical Optics, Santa Ana, CA) using a microcannula 200 microns in diameter. An optic fiber allows the microcatheter to be viewed through the sclera (Figure 2). Once the canal has undergone viscodilation, a 10-0 Prolene suture (Ethicon Inc, Somerville, N.J.) is attached to the cannula and advanced through the canal as the cannula is withdrawn. This suture creates tension on the TM, bringing it anteriorly to reduce resistance to outflow. The Trabectome (NeoMedix, Tustin CA) accesses existing outflow channels by creating a direct communication between the anterior chamber and Schlemm's canal. This ab interno trabeculotomy combines an electrosurgical device with irrigation, aspiration and a protective footplate to ablate and remove TM and the inner wall of Schlemm's canal (Figure 3). Transient intra-operative hyphema due to blood reflux into Schlemm's canal is the most common complication of this procedure. Initial results are promising, with IOP controlled in the 15 to 16 mmHg range. There is no bleb formation or risk for flat anterior chamber, and perilimbal conjunctiva is preserved if further surgical intervention becomes necessary. A new, micro-invasive procedure that restores the conventional outflow pathway by bypassing TM resistance is the iStent (Glaukos Corp., Laguna Hills, CA). This trabecular bypass micro stent is an L-shaped titanium tube measuring 120 microns in diameter that is implanted into Schlemm's canal using a tiny opening through TM (Figure 4). The lumen of the stent restores aqueous flow from the anterior chamber into Schlemm's canal. Prospective clinical studies demonstrate post-operative intraocular pressures of 15mmHg-16mmHg at 12 months. Again, no bleb is formed and the placement of the iStent preserves all future options for glaucoma filtering surgery. Multiple implants may be used to further reduce IOP and to titrate IOP reduction based upon individual patient target pressures. The Solx Gold Shunt (Occulogix Inc, Mississauga, Ontario, Canada) is a 60 micron wafer made of two gold plates that is designed to increase uveoscleral outflow by redirecting fluid from the anterior chamber to the suprachoroidal space. This novel technology takes advantage of a physiologically negative pressure differential between these two areas and explores yet another pathway for aqueous outflow.

A glaucoma drainage device (GDD) consists of an endplate of varying surface area and design that is inserted into the subconjunctival space. The end-plate is attached to a drainage tube inserted into the anterior chamber or the posterior chamber via the pars plana. This drainage tube may offer little resistance to aqueous flow (such as Baerveldt, Molteno) or may be constructed with a unidirectional valve (such as Ahmed, Krupin). Non-valved drainage implants require the insertion of a removable stent within the tube or a ligature around the tube to prevent immediate post-operative hypotony. Drainage implants can reduce IOP 50% below pre-operative levels. However, they are also associated with complications including hypotony, corneal decompensation, encapsulation of end-plate, erosion of tube, suprachoroidal hemorrhage and diplopia. Drainage implants, or tube shunts, have traditionally been reserved for patients who have uncontrolled IOP and a history of failed filtration procedures, scleral buckling surgery, extensive conjunctival scarring or exaggerated inflammatory response (neovascular or uveitic glaucoma). Interestingly, implants are being done more commonly, and some individuals are using them as their primary filtration surgical modality. Early results from the Tube versus Trabeculectomy Study (TVT) indicate that both procedures produced approximately equal IOP reduction at the end of the first year, but patients more often required the use of supplemental medication to reach acceptable IOP following the placement of a non-valved GDD. Future reports from the TVT study will help to evaluate the role of tube surgery in glaucoma management for this specific patient population.

Glaucoma surgery will continue to evolve with the development of new imaging techniques and materials. The ultimate goal of surgical intervention is to achieve long term IOP control with lower risk for surgical complication.

Acknowledgements

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9 | Adherence in Glaucoma Therapy

Steven R. Hahn, MD

Patients do not benefit from medicines they do not take, and most clinicians are aware that patients commonly fail to take all the medication that they are prescribed. Yet, nonadherence does not receive attention proportionate to its recognized importance in clinical practice. Although some physicians may need to be reminded about the magnitude of the problem, it is not a fundamental ignorance of nonadherence that explains the lack of attention it receives. One answer may be that clinicians intuitively know what research on adherence has demonstrated: Nonadherence is difficult to detect, its causes may be hard to identify, and the factors that determine adherence often seem to be beyond the clinician's control or scope of clinical expertise. These beliefs may create a sense of powerlessness that is ultimately rationalized by the feeling that nonadherence is a revelation of the imperfection of human nature and might as well be accepted. The goal of this chapter, and the next one addressing doctor-patient communication, is to reverse this pessimism and empower clinicians by providing necessary information on the prevalence and causes of nonadherence.

"Patient compliance" was the term originally used to describe the extent to which patients take medication and follow lifestyle and behavioral recommendations prescribed by their clinicians. The term "adherence" has largely supplanted "compliance" because the latter carries the connotation of a paternalistic clinician-directed relationship in which patients "comply" with the directives of their doctor. By contrast, adherence connotes a patient's willingness to "stick to" a treatment that they have agreed upon with their clinician. A consensus panel convened by the World Health Organization chose to define adherence as "the extent to which a person's behaviour—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider." Persistence is one aspect of adherence and refers to the extent to which patients sustain use of medication and lifestyle changes and behavioral treatments over time.

The first, and probably most important, problem presented by noncompliance is the difficulty of detecting it. Numerous studies have demonstrated that patients consistently under report and, as discussed in the next chapter, actively conceal nonadherence from their clinicians. A meta analysis of 86 studies revealed that patients consistently overestimated adherence to treatment compared to non-self-report methods of measuring medication taking behavior. Concordance between face to face interview-based self-report was particularly low with electronic event monitors, and somewhat better with adherence questionnaires and diaries, pill counts, insurance claims analyses, and plasma drug concentrations. Clinicians' assessments of adherence also consistently over-estimate adherence. One reason for under detection in addition to relying on patients' self-report may be reliance on measurement of rapidly responsive physiological parameters such as intraocular pressure at the time of a doctor visit, because patients are often more adherent to medication just before their visits to the doctor. This so-called "white coat adherence" has been observed in several therapeutic areas, including glaucoma. Although self-report of nonadherence may be an insensitive measure of the problem, it is reasonably specific. A meta analysis of four studies comparing patient self-report to pill count showed that asking patients if they had missed any doses of any medication detected 55% of patients defined as nonadherent by pill count (sensitivity), and had a specificity of 87%. Nonadherence to treatment is common across therapeutic areas. In a quantitative survey of 569 studies published between 1966 and 1998, adherence ranged from 4.6% to 100%, with a median of 76% and an overall average of 75.2%. Rates of adherence varied significantly with the methods used to measure them, from a low of 66.6% for collateral report and 69% for MEMS caps to a high of 85% for pill count. Rates of adherence to behavioral interventions, such as diet and exercise, are often as low as 10%.

Although there is no gold standard for adherence measurement, the use of surreptitious electronic devices (MEMS recorders) that record the opening of a pill bottle or use of a medication dispenser is one of the most reliable methods. In studies of adherence to glaucoma medications using MEMS devices, almost half of patients (41%) miss 10% of three times daily pilocarpine doses, i.e. one dose in every two days. In another study using the same technology, more than a quarter of patients (27.3%) missed more than a quarter of timolol doses when used either alone or in combination with pilocarpine or another medication; and a small but significant number of patients (8.2% and 15.2%) missed half or more of their medications. Medications that are taken more than once per day are also vulnerable to problems with the timing of doses. Morning medications are taken more reliably than doses later in the day, and noon doses are the most frequently omitted. Studies using MEMS recorders are usually of short duration and typically over sample more persistent patients and under sample those new to treatment. In theory, analysis of pharmacy claims data presents an opportunity to study patients who are new to treatment and to follow adherence behaviors over a longer period of time. An early study using this approach suggested that one quarter of 2,440 patients who filled an initial prescription for glaucoma medication never filled a second one and, overall, patients were without medication for nearly a third (30%) of the 12 month period that was studied. Another study of 3,623 patients with diagnosed glaucoma and 1,677 glaucoma suspects, all apparently newly treated, revealed that nearly half had discontinued all glaucoma medication by the end of one year.

The Glaucoma Adherence and Persistence Study (GAPS), based upon retrospective analysis of the pharmacy and medical claims data of 13,956 patients on glaucoma medication revealed significant problems with nonadherence consistent with previous studies. The principal measure of adherence used in GAPS was the medication possession ratio, or MPR, calculated by dividing the days of supply of medication dispensed by the number of days between prescription fulfillments. The MPR is therefore a ratio expressing the proportion of days for which a patient possesses enough medication to use drops as directed. Although 89% of subjects claimed to take their glaucoma medication "every day," the average medication possession ratio (MPR) observed in GAPS was 0.64 (median 0.57), meaning that the average subject only had enough medication to take 64% of pre-

scribed doses. The most poorly adherent 25% of subjects possessed enough medication to take no more than 36% of their prescribed doses; by contrast, the most adherent 25% possessed enough medication to take 88% of their doses. Over half (55%) of the 10,260 subjects followed for at least one year stopped and restarted medications within that 12-month period. Only 10% of subjects filled prescriptions continuously for 12 months.

Our understanding of the causes of nonadherence has evolved from the original "Health Beliefs Model" which proposes that adherence to treatment is the result of a balance by the patient's perception of their vulnerability to and the threat of the illness, the benefit of the treatment, the cost and burden of the treatment, and social and instrumental support for adherence. This model has evolved to focus on specific elements within these domains. For example, the "Information, Motivation, and Behavioral Skills" (IMB) model asserts that these are the three key independent determinants of adherence. This model makes the observation that patients can be motivated to adhere without being knowledgeable about the illness and vice versa, but they must have the specific information that supports critical behavioral skills, such as those required for administration of drops, or for creating and integrating behavioral triggers that prompt medication taking into their daily routine. The closely related "Therapeutic Decision Model" calls attention to the fact that patients' decisions about adherence are dynamic and incorporate ongoing experience of side effects and efficacy with their providers' recommendations and other sources of information. Most patients engage in an active testing process that usually remains obscure to clinicians because they do not actively explore it with their patients.

Factors influencing adherence have generally been classified into four categories: patient characteristics, provider characteristics, characteristics of the medical regimen, and situational/logistical factors, including cost. Tsai and colleagues identified 71 specific barriers that patients reported interfered with using glaucoma medication. Patients' socio-demographic characteristics have been inconsistently associated; a review of early research in adherence to glaucoma medication found that age and education were not associated with nonadherence, and that ethnicity and male gender probably were, but weakly and inconsistently. With regard to characteristics of the regimen, increased frequency of dosing but not number of medications, total number of medicines for all conditions, and frequency of side effects have been related to nonadherence. Several studies have documented better adherence for prostaglandins compared to other classes of medication. Cost of medication and the need to integrate medication taking with the daily routine have been associated with adherence.

Emerging data from GAPS suggests that provider-patient communication and concern about the future consequences of glaucoma are important factors in driving adherence. Patients who do not have a robust understanding of what glaucoma might do in the future are less likely to adhere to treatment. Patients who passively depend upon their providers and don't actively engage in developing their understanding of the disease are less likely to be successful in sustaining their motivation and in overcoming barriers to adherence.

Nonadherence to topical glaucoma medication is prevalent and difficult to detect because nonadherence is a socially undesirable behavior that patients are reluctant to reveal. Current understanding of adherence behavior identifies the need for patients to understand the progression of the disease over time in a way that supports concern about future consequences. Patients also need to have the behavioral skills necessary to remember and administer medication. Patients who are actively engaged in learning about glaucoma and interested in participating in decision making are most likely to overcome barriers to adherence. Providers can screen for active engagement in self-care and for the presence of a motivating concern about consequences by asking patients to describe their understanding and concerns about what glaucoma might do in the future. The epidemiology of barriers to adherence support the value of screening for specific barriers to adherence such as cost of medication, taking medications while traveling and away from home, and the mechanics of drop administration. Communication strategies for addressing these factors are addressed in the chapter on communication.

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10 | Communication in the Management of Glaucoma

Steven R. Hahn, MD

A patient's daily decision to use glaucoma medication is the result of a balance between their understanding of the potential risks of glaucoma, their belief in the benefit of medication and the burden of taking their drops. For most patients, the risk of untreated glaucoma is an idea about potential future loss of vision. On the other hand, the burden of treatment is not an idea; it is a tangible daily experience. Although not as burdensome as treatment for many other conditions, glaucoma is vulnerable to all the barriers to adherence associated with any chronic medication and some unique ones as well. In addition to inconvenience, cost, and integration into daily lifestyle, topical glaucoma medication is technically more complex to administer than a pill and often associated with unique nuisance side effects.

If patients' adherence is a balance between the patient's understanding of the risks of glaucoma and the benefits and burdens of treatment, then it is very much the story of the struggle between the effect of episodic communications with their clinicians and the daily experience of taking drops, because the most important and sometimes only source of understanding about glaucoma is what clinicians communicate to them. In short, clinician-patient communication is the foundation of adherence, and adherence is the key factor in treatment outcome, for patients do not benefit from medicines that they do not take.

There are significant barriers to the detection of nonadherence in patients' prescribed chronic medications. Research has demonstrated that physicians have no better than a 50-50 chance of detecting nonadherence in their patients. Three studies of occult nonadherence from studies of chronic diseases are illustrative:

Learned from the first "ASK"

1. What the patient already knows that is correct and important.
2. What the patient doesn't know that they should.
3. The patient's misconceptions and mistaken beliefs.

Focus of the "TELL"

Reinforce what the patient understands correctly, without wasting time.
Prioritize and present the next most important pieces of information.
Correct misconceptions and mistakes.

Learned from the second "ASK"

Assess improvement in confidence, self-efficacy,and commitment.
Assess comprehension and impact of new information.
Assess comprehension and impact of corrected understanding and beliefs.

Patients with "treatment resistant hypertension" who had told their physicians that they were taking their medications consistently were told to continue their current treatment regimen using a pillbox that they knew would record when they took their pills. Subjected to this scrutiny, one-third of the patients were instantly "cured;" however, several had syncopal episodes when they complied with regimens that had previously been intensified in the mistaken belief that they been adherent. Another 20% of the subjects remained uncontrolled, but the recording pill box demonstrated that the cause was nonadherence. In another study using surreptitious micro recording devices, Cramer et al demonstrated that adherence to antiseizure treatment was 88% to 86% during the week before and after a visit to the doctor, but was only 67% one month later. Finally, home glucose diaries were compared to memory chip values in 19 Type I diabetics who were surreptitiously given the first generation of glucometers with a recording memory. Over all, half the patients made up half the values, and physicians had a 50-50 chance of predicting which patients and values were fabricated.

Why should patients conceal nonadherence from their clinicians? Patients realize that providing misinformation may lead to poor decisions about treatment, but their behavior is shaped by a more powerful force: Nonadherence is a "socially undesirable" behavior, and patients want to be seen as "good patients." This desire is often stronger than their concern that concealing nonadherence might lead to bad decisions about treatment. This tendency is exacerbated by the fact that patients expect their clinicians to be judgmental. Unless the clinician does something to alter it, the default perception of the patient is that the clinician will think they are a bad patient and be unsympathetic to any reason they have for not taking medication as directed. Understanding these key features of the psychology of patient self-report of nonadherence is the foundation for a four-step, semi-structured dialogue that reduces barriers to admitting to nonadherence by reversing the judgmental environment and redefining the "good patient" as one who collaborates in solving treatment problems.

THE FOUR STEPS OF THE ADHERENCE DETECTION INTERVIEW

1. Begin with a directive open-ended question: "Tell me how you've been taking your medications." The patient's response will reveal their level of understanding of their regimen. Follow up with a question about how they organize their medication and remember to take them. It is useful to have the patient describe the way they use all of their medications (both topical and systemic), even if the clinician asking is focused on the use of only some of them.

2. Change the patient's expectation that you will be judgmental: Tell the patient that you know that noncompliance is "universal," everyone has difficulty adhering to a medication regime, and it is "normal" or understandable if a dose is missed because of problems such as cost, side effects, inconvenience, etc.

3. Explain how information about adherence will affect decisions about medication: For example, "Your pressure is higher than it should be. Before we change the prescription, let's make sure that you've been able to use the medications you're already on. Taking too much medicine or changing to a second-choice medication would not be the best thing if the real problem has been with taking the medication you've already been prescribed." This intervention is important because it changes the definition of a "good patient" from the unrealistic expectation that the patient will always be adherent, to an understanding that a "good patient" is one who discusses and solve problems with adherence with the clinician.

4. Finally, ask about "forgetting" or "missing" medications: The critical feature of the fourth step in the sequence is that it comes last, after the stage has been set. If the patient claims to be adherent before steps one through three, the task of getting the real story becomes doubly difficult because the patient will have to admit to having not told the whole truth on top of now having to acknowledge their nonadherence.

When problems with adherence are detected, the clinician needs to assess two things: the patient's motivation to take the medicine and the presence of specific barriers to adherence. Even a patient who experiences no burden or barrier to taking a medication will not take it without believing there is a good reason to do so. Therefore, the strategy is to determine that the patient is concerned about the consequences of glaucoma and believes that taking medications will be beneficial. The tactic for this assessment is to use "Open-Ended Questions" about concerns and perceived benefit in an "Ask-Tell-Ask" sequence.

Consider the Following Dialogue:

Optometrist: "Are you concerned about the consequences of glaucoma?"

Patient: "Yes."

Compared With:

Optometrist: "Tell me what you understand about glaucoma, and what your concerns are?"

Patient: "Well, I'm not really sure because I haven't noticed any difference in my vision except for what the new glasses corrected. I mean, my vision is fine when I wear my glasses. I thought glaucoma was where you had real problems seeing. I was told that my pressure is too high by the last doctor who saw me, the one who put me on the drops, but my pressure was high before and I was told there was no need for treatment. So I don't really know what to expect, or whether I should worry or not."

The first question is "closed-ended"; one that calls for a yes or no answer. The second is an "open-ended question"; one that cannot be answered yes or no, but rather calls for a broader response. This open-ended question is still focused. It is a "directed" open-ended question that points the patient's response to a particular domain—concerns about and understanding of glaucoma—but does not constrain the way the patient answers.

The directed open-ended question, "Tell me what you understand about glaucoma, and what your concerns are" is the first "ask" in a three step "ask-tell-ask" pattern that forms the basic building block of all patient education interventions. The first ask of the sequence will tell you three things: What the patient already knows; what the patient doesn't know; and the patient's misconceptions and mistaken beliefs.

In the sample dialogue above, the clinician learns that the patient:

- Knows his "pressure is too high" and that the last doctor recommended medication.
- Doesn't understand why medication was started, specifically why his high intraocular pressure wasn't a reason for starting medication before but is now.
- Has the mistaken belief that he does not have glaucoma unless he is experiencing noticeable vision loss.

It is far better to learn what the patient already knows than it is to launch into a set patient-education speech for at least two reasons. First, the clinician can avoid spending unnecessary time on information the patient already has. Second, asking first allows the clinician to overtly acknowledge the patient's correct understanding, thereby reinforcing his self-confidence, sense of self-efficacy, and praising him for his ability to collaborate in self-care and decision making.

In our sample dialogue, the clinician can tell the patient:

"You're right, your pressure is too high, and that does produce the problem of glaucoma if it is not corrected. It is time for medication in your case…"

The patient's understanding of glaucoma and medication is like a partially assembled jigsaw puzzle. Once the clinician understands which pieces have been connected and which are not yet aligned, it will become clear which piece of the puzzle needs to be put in place next to allow the rest to fall into place. A set speech on glaucoma may include the critical information, but if it is presented along with too much information or at the wrong time the patient will not be able to integrate it.

In our sample dialogue, the clinician can tell the patient:

"…But, high pressure in the fluid in your eye is not the whole story of glaucoma and when you need treatment. The pressure causes damage to the nerve that goes from the eye to the brain, and we detected the beginning of damage in that nerve at the last visit by testing your visual fields, the machine with the flashing lights. That's why we knew that you need treatment." Perhaps the most important benefit of asking before telling is the opportunity to identify the patient's misconceptions and mistaken beliefs. Erroneous beliefs dramatically interfere with patients' motivation to adhere and

self-care behaviors. An undiscovered error in understanding can render all of the correct information a clinician might provide useless. What is truly striking is how prevalent and unpredictable patients' mistaken beliefs can be across all chronic diseases. The only way to discover the patient's mistaken ideas is to ask.

In our sample dialogue, the clinician can tell the patient;

"…A lot of people believe that they don't have glaucoma unless they notice a problem with their vision in everyday life. We can detect the problem of glaucoma before you can yourself, and that's a good thing because it gives us a chance to prevent more serious damage."

If the **first ask** reveals the patient's initial knowledge, missing information, and misconceptions, the "second" ask reveals what has happened to those dimensions of the patient's understanding as a result of the "tell", and also takes the dialogue on to the next step of explanation or instruction. The second ask should take the general form, "What questions or concerns do you have now that you have heard what I just told you?" In our sample dialogue, the patient's response to this second question was: "So you mean I've already got damage to my eye? How bad is it? You said 'prevent more serious damage,' the medicine will do that? And what was that about the visual field test?"

The **second ask** continues the dialogue, and lets the clinician know which parts of the "tell" got through and which didn't. Our patient's response to the second ask makes it clear that the patient needs to learn a little more about the stage and severity of his problem, is ready to hear a reassuring link between medication and preventing vision loss, and didn't quite get the role of visual fields in managing glaucoma.

Adherence is a result of the balance between a patient's concern about the consequences of glaucoma, their belief in the benefit of treatment, and the burden of taking medication. Communication between clinician and patient is the foundation of patients' understanding. Communication about adherence to medication is challenging because patients would rather conceal nonadherence than be perceived as bad patients. This barrier can be lowered by using a four-step semi-structured dialogue that addresses the psychology of acknowledging socially undesirable behavior. Specific barriers can be discovered and addressed using an "ask-tell-ask" interviewing sequence.

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11 | Secondary Glaucomas

Mitchell W. Dul, OD, MS

Secondary glaucomas represent only a small percentage of all glaucomas but these conditions are important to understand as there are critical differences in their diagnosis and management. This section will discuss several of the most common secondary glaucomas.

NEOVASCULAR GLAUCOMA (NVG)

NVG is a condition caused by new blood vessel growth on the iris and in the anterior chamber angle usually resulting from retinal ischemia and hypoxia. NVG is an unusual condition that is more common in older populations. Retinal ischemia and hypoxia associated with conditions such as central retinal vein occlusion and proliferative diabetic retinopathy are implicated in the development of neovascularization of the anterior segment. In the presence of retinal ischemia, angiogenic factors such as vascular endothelial growth factor (VEGF) stimulate the proliferation of new vessels. These angiogenic factors diffuse into the anterior chamber and promote new vessel growth, especially in tissues with prolonged exposure to the aqueous. Obstruction of the angle occurs as a result of the formation of fibrovascular membranes, which serve as scaffolding for the new blood vessels. Subsequent contracture of this membrane can lead to progressive peripheral anterior synechia and subsequent angle closure.

Due to its prolonged contact time with the aqueous, neovascularization usually appears first on the surface of the iris adjacent to the pupillary border. These vessels are fine in caliber and may have aneurism-like out-pouchings. Gonioscopic evaluation may reveal vessels in the anterior chamber angle, even in the absence of iris vessels. One emerging treatment for the management of neovascular glaucoma is the use of bevacizumab (Avastin). Avastin is a monoclonal antibody that works by attaching to and inhibiting the action of vascular endothelial growth factor (VEGF). When VEGF is bound to Avastin, it cannot stimulate the formation and growth of new blood vessels. Injected into the vitreous, this compound has been shown to produce a rapid improvement of retinal and iris neovascularization after a single injection. In addition to this emerging therapy, treatment of the underlying retinal ischemia with panretinal photocoagulation can also prevent anterior chamber neovascularization.

Neovascular glaucoma can lead to a blind, painful eye. Management includes the use of topical atropine 1% to decrease ocular congestion and topical steroids to decrease inflammation along with concurrent use of antiglaucoma medications. Still, surgery remains the main form of therapy. Surgical procedures include cyclocryotherapy, trabeculectomy and tube implant. In general, outcomes are less successful compared to primary open angle glaucoma, although used with Avastin, results may be improved.

GLAUCOMA ASSOCIATED WITH INFLAMMATION

Inflammation associated with different sectors of the eye (scleritis, uveitis, keratitis, trabeculitis) may lead to an increase in IOP substantial enough to cause glaucomatous optic atrophy. In addition, the use of corticosteroid for the treatment of these conditions may also be responsible for increased IOP (steroid responder). In both the pediatric and adult populations, the prevalence of glaucoma associated with uveitis ranges from 5% to 14%, although the etiology of the uveitis varies between these populations. In the general glaucoma population, inflammatory etiologies account for only a small percentage (< 2%) of all glaucomas. Uveitis associated with glaucoma can result from different conditions, such as anterior uveitis (e.g. idiopathic, the spondylarthropathies, juvenile

rheumatoid arthritis associated uveitis), Fuch's Heterochromic uveitis, Posner-Schlossman, Herpetic uveitis, traumatic uveitis, and lens-induced uveitis. In most cases of glaucoma associated with inflammation, the anterior chamber angle is open and the increase in IOP results from direct involvement of the trabecular meshwork as a consequence of local inflammation (e.g. secondary trabeculitis), spill-over from more generalized inflammation (e.g. panuveitis), or as a consequence of accumulation of inflammatory debris. Less commonly, local inflammation causes an increase in IOP as result of a secondary angle closure (see section on angle closure glaucoma).

The pathogenesis of steroid induced glaucoma is not fully understood. Theories include the accumulation of glycosaminoglycans in the anterior chamber angle and increased production of the TIGR/Myoc protein. The result produces increased resistance to aqueous outflow.

In addition to the treatment of the underlying cause of the uveitis, in most cases, the treatment of the ocular component of these conditions will involve both anti-inflammatory (topical corticosteroids) and anti-glaucoma medications (aqueous suppressants). Cycloplegics are used to prevent or manage posterior synechia, secondary neovascular glaucoma and choroidal effusion. Miotics are avoided because their use may exacerbate ciliary spasm, inflammation and increase the likelihood of synechia. Prostaglandins are also avoided, as this group of medications may exacerbate the inflammatory component. If the patient is found to be a steroid responder (IOP elevates over time), the initial consideration is to discontinue or change the steroid medication. If this is not feasible, given the nature of the patient's condition, then more aggressive management of the intraocular pressure may be warranted until the steroid can be discontinued. In general, surgical (trabeculectomy and tube shunts) have less successful outcomes compared to primary open angle glaucoma.

TRAUMATIC GLAUCOMA

Angle recession glaucoma is the most common form of glaucoma associated with trauma. Other forms include: glaucoma associated with hyphema (acute) or later onset (ghost cell glaucoma), trabeculitis, phacolytic glaucoma, and glaucoma associated with lens dislocation. In the acute phase, the presence of blood in the anterior chamber (hyphema) or inflammation as a result of injury (e.g. traumatic iridocyclitis) may cause an increase in intraocular pressure that mandates treatment. The long term effects of ocular trauma associated with the pathogenesis of glaucoma often occur as a result of the initial damage (angle recession) and subsequent healing of the anterior chamber angle (Figure 1). Since most patients with traumatic angle recession will not develop glaucoma (5% to 20% develops glaucoma), and elevated IOP occurs long after the antecedent trauma, it is conceivable that many cases are overlooked. Angle recession glaucoma is relatively uncommon when the recession is less than 180 degrees. Angle recession glaucoma often presents as a unilateral, or asymmetric, glaucoma without symptoms unless in an advanced stage. The patient may not recall a history of blunt ocular trauma. Diagnosis requires a 360 degree gonioscopic assessment of each eye.

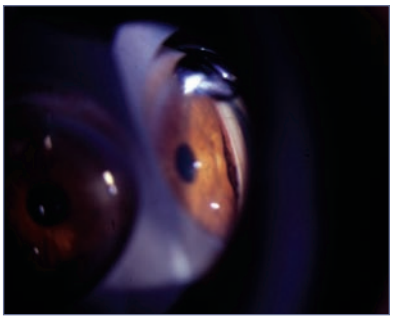

Figure 1. Gonioscopic appearance of angle recession due to blunt trauma.

Since acute increases in intraocular pressure in the setting of blunt trauma may be of short duration, observation and careful follow-up may be all that is required (assuming the presence of a healthy optic nerve prior to injury). If treatment is indicated, aqueous suppressants (e.g. beta blockers, alpha agonists) are the mainstay of treatment. Angle recession glaucoma should be treated in a similar fashion as primary open angle glaucoma (POAG). If customary glaucoma management does not produce an adequate IOP reduction, a course of cycloplegia may produce positive results. Surgical washout of the anterior chamber may be indicated in the presence of hyphema, especially if the corneal endothelium shows signs of compromise (e.g. corneal blood staining), if the hyphema does not resolve over time, or if a subsequent new hypema occurs (rebleed).

For angle recession glaucoma, in general, the results of laser and surgical procedures have less successful outcomes compared to primary open angle glaucoma.

Patients with sickle cell disease are more sensitive to increases in IOP, even of short duration (2 to 4 days). These conditions are capable of occluding the central retinal artery (due, in part, to stagnation of blood in small vessels, excessive deoxygenation of erythrocytes, erythrostasis, sickling and increased blood viscosity). It is, therefore, prudent to order a sickle prep (Sickledex) or hemoglobin electrophoresis on all patients suspected of having sickle cell disease or trait (more common among African Americans and people of Mediterranean descent) in the presence of increased IOP associated with hyphema.

PSEUDOEXFOLIATIVE GLAUCOMA (PXG)

PXG occurs throughout the world. In the United States, the prevalence ranges from 5% to 15% of all glaucoma cases. It is more common in patients >60 y/o and uncommon in patients <40. Pseudoexfoliation syndrome is a systemic disease associated with abnormalities of the basement membrane in epithelial cells, which are found throughout the body. The accumulation of pseudoexfoliative material in the trabecular meshwork and the juxtacanicular tissue next to the Schlemm's canal leads to obstruction of aqueous.

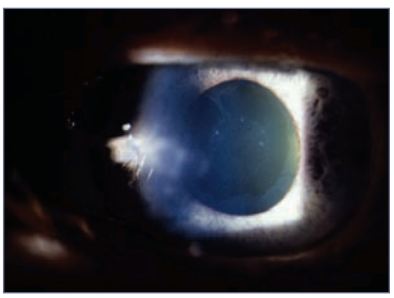

Figure 2. Pseudoexfoliation pattern on the crystalline lens.

Pseudoexfoliation syndrome typically presents unilaterally but may become bilateral and can be an aggressive form of glaucoma that can progress rapidly. The initial signs are usually noted with slit lamp exam by observing

the deposition of white, flaky material on the anterior lens capsule (Figure 3) and iris border.

Treatment of PXG is similar to that of POAG. In general, patients respond well to argon laser trabeculoplasty (ALT). Unfortunately, within five years, approximately half are back to baseline IOPs and some will have a rapid sustained increase in IOP within two years.

PIGMENTARY GLAUCOMA

Figure 3. Pigmentary glaucoma (Courtesy Daniel Roberts, OD).

Pigmentary syndrome and glaucoma tend to occur at a relatively early age (20 to 45 years) with most individuals being myopic (80%), Caucasian and male. Pigment is released from the iris due to lens-iris contact, leaving radially oriented transillumination defects. The pigment circulates in the convection currents of the aqueous before adhering to the corneal endothelium forming Krukenburg's spindle and depositing in the anterior chamber angle. PDS is generally bilateral and asymptomatic. Common signs include a Krukenburg spindle, radially oriented iris transillumination defects, and heavy pigment in the anterior chamber). In some instances, a concave iris may be present (Figure 3).

PDS can resemble postoperative conditions such as IOL-iris chafing and pseudoexfoliation; however, these are often unilateral and present with less and unevenly dispersed pigment.

Treatment should take into account the needs of the patient and the extent of glaucomatous optic neuropathy and/or visual field loss. Like pseudoexfoliative glaucoma, patients typically respond well to ALT at least initially. Laser iridotomy may alter the pressure gradient associated with a concave iris, allowing it to flatten in the anterior chamber thereby decreasing the likelihood of contact. When medical and laser intervention fail, surgical intervention is considered.

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12 | Primary Angle Closure Glaucoma

David S. Friedman, MD

Primary angle closure glaucoma (PACG) is a leading cause of blindness worldwide. In China, it is estimated that nearly one in six individuals over the age of 50 has an angle appearance that puts him/her at risk of PACG and acute angle closure attacks. Asian populations are aging so the number of people with PACG will increase dramatically in the coming decades. While it is often said that Chinese populations (and others in East Asia) have ten times the risk of PACG as Europeans, the truth is that in carefully conducted studies the number is closer to four times as much, and nearly one in 200 Europeans over the age of 40 has PACG. PACG is often missed in these populations, and efforts must be taken to identify it so that needless loss of vision is avoided. Furthermore, it is essential that adequate evaluation is given to the higher risk populations (older persons, Asians, and in particular, older women).

In order to focus this chapter, I will first review the terminology used when referring to patients with PACG and then will discuss the epidemiology of PACG. The remainder of this chapter will cover diagnosis and treatment strategies for PACG. Terminology to describe PACG is confusing, and this lack of clarity influences how we think about the disease. Much of this confusion stems from the literature that developed when gonioscopy first became widely available in the 1950s. Little was known about PACG and the natural history of the disease, so a wide range of terms were used.

In order to allow for more uniform reporting, and to improve how we think about the mechanisms of angle closure, a new terminology was proposed and subsequently modified during a consensus panel meeting involving over 100 glaucoma specialists from around the world. There are currently four categories for describing persons with angle closure, three of which require specific gonioscopic findings. Each of these requires that the pigmented trabecular meshwork is blocked by iris (what is termed "iridotrabecular contact or ITC") in at least one quadrant. There is no firm agreement on how many quadrants must have ITC for angle closure to be present, but current consensus appears to be that at least 180 degrees is required. The amount of ITC is determined in a dark room using a one mm beam on a bright setting while performing gonioscopy. Greater amounts of illumination (a long wide beam, for example) will allow light to enter the pupil which can artificially open the angle.

1. Primary Angle Closure Suspect (PACS): Some people are completely normal except for the fact that the anterior chamber angle has ITC on gonioscopy. There is no "disease" present, and no evidence of harm to the patient. The clinician is concerned by the appearance, but the IOP and the optic nerve are both normal, and there are no peripheral anterior synechiae. How much angle closure must be present to apply this categorization remains controversial, but I typically use 180 degrees or more. Gonioscopy is performed as above, having the patient look straight ahead and only modestly tilting the lens if the view is difficult. Again, this is a somewhat subjective evaluation, but there are no better approaches available. There is ongoing debate about whether or not all these persons require iridotomy to avoid the development of PACG or acute attacks.

2. Primary Angle Closure (PAC): This category includes people

with ITC for 180 degrees or more as described above for PACS. Furthermore, these people have some evidence that the angle appearance is causing harm to the eye. More specifically, they have either peripheral anterior synechiae (PAS) or elevated IOP, but they do not have optic nerve damage and visual field loss. This condition is considered pathologic (although there is almost no long-term data on people with these findings), and most clinicians recommend laser iridotomy for these people.

3. Primary Angle Closure Glaucoma (PACG): This category requires the presence of ITC for 180 degrees or more, as described above, along with glaucomatous optic neuropathy and visual field loss. The glaucoma definition requires the same findings as one would expect for open-angle glaucoma.

3. Primary Angle Closure Attack: This presents with classic signs and symptoms. Patients have very elevated IOP, the angle is closed, the conjunctiva is red, the cornea frequently is cloudy, and the patient has eye pain and may have nausea and vomiting.

PACG occurs in about 0.5% of whites and blacks over the age of 40, and about 1.5% of Chinese and Indian individuals in this age group, but is much more common in older populations. Recent studies indicate that even in high prevalence countries such as China, open angle glaucoma is more common than PACG. However, even though PACG accounts for about a third of all glaucoma cases in China, most of the 5.2 million people blind from glaucoma have PACG. Similar findings were reported for Asian Indians where 41% of those with PACG were blind in one or both eyes from PACG.

PACG is associated with relatively anterior lens position and a proportionally thicker lens, both of which result in a relatively shallow anterior chamber depth, one of the strongest risk factors for PACG. Affected eyes are frequently hypermetropic (although not uniformly so, and PACG frequently occurs in myopic individuals). PACG is also associated with a short axial length and small corneal diameters and radii of curvature. Interestingly, even though PACG is more prevalent in China, one study found that Chinese, blacks and whites had similar mean anterior chamber depths, indicating that other factors (such as the response of the iris to various stimuli) may contribute to higher rates of PACG among Chinese.

While the ocular biometric parameters described are associated with the presence of PACG and acute attacks of angle closure, it is not clear if any of them predicts which PAC suspects would have a poor outcome if left untreated. Other important risk factors that are associated with PACG and AAC attacks are female sex, age, and race.

In order to review the treatment of angle closure I will discuss each of the four sub-categories separately.

1. PACS: As stated above, these individuals have no evidence of disease but have ITC when examined on gonioscopy. There is debate about how to manage such individuals, with some recommending observation and others recommending laser iridotomy (LI) even in cases of ITC for less than 180 degrees.

2. PAC: All those with PAC have evidence of ITC and the presence of either PAS or elevated IOP. There is uniform consensus that LI is indicated for these individuals to help relieve pupil block in order to both prevent acute attacks and to reduce the risk of further progression of angle closure.

3. PACG: Unless PAS are extensive and there is fear of causing a substantial IOP spike while attempting LI, the first procedure for diagnosed PACG is LI. PACG is then treated like any other form of glaucoma with medications, surgery, or a combination of both. If the angle opens after LI and it is possible to perform trabeculoplasty, this is also a treatment option.

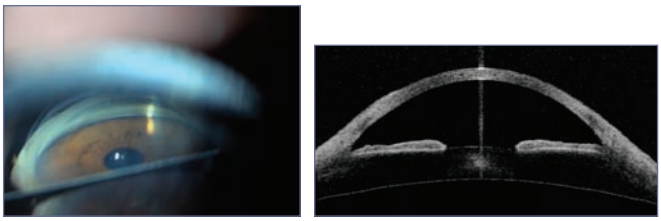

Figure 1a & b. The gonioscopic (a) and anterior segment OCT (b) image of an open angle is seen.

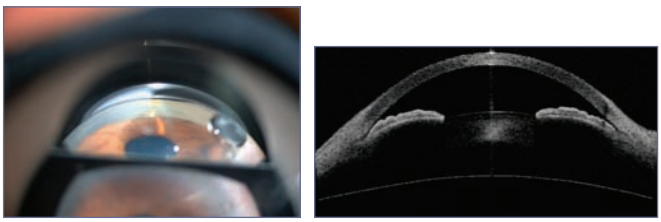

Figure 2a & b. The gonioscopic (a) and anterior segment OCT(b) image of a closed angle, undergoing an angle closure attack is seen.

4. Acute Primary Angle Closure: The mainstay of treatment of acute attacks remains medical therapy. This includes topical ocular hypotensives as well as oral or intravenous carbonic anhydrase inhibitors and in some cases hyperosmotic agents. Some have published findings that acute paracentesis can lower IOP rapidly, but this has the potential of causing damage to intraocular structures. Others have reported that laser iridoplasty can lower IOP acutely, but long-term data showing that this is more or less effective than medical therapy are not yet published. Certainly, if the IOP remains elevated after one to two hours, one can consider performing iridoplasty.

PACG is a leading cause of blindness worldwide. With current technologies, most clinicians can only identify at risk individuals with gonioscopy (Figure 1a and b, 2a and b). Gonioscopy is, therefore, a fundamental part of the evaluation of patients seeking eye-care and needs to be performed routinely. Management of PACG is different from management of open angle glaucoma. For patients to receive proper treatment, all clinicians must provide a complete evaluation of the anterior chamber angle.

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Suggested Readings

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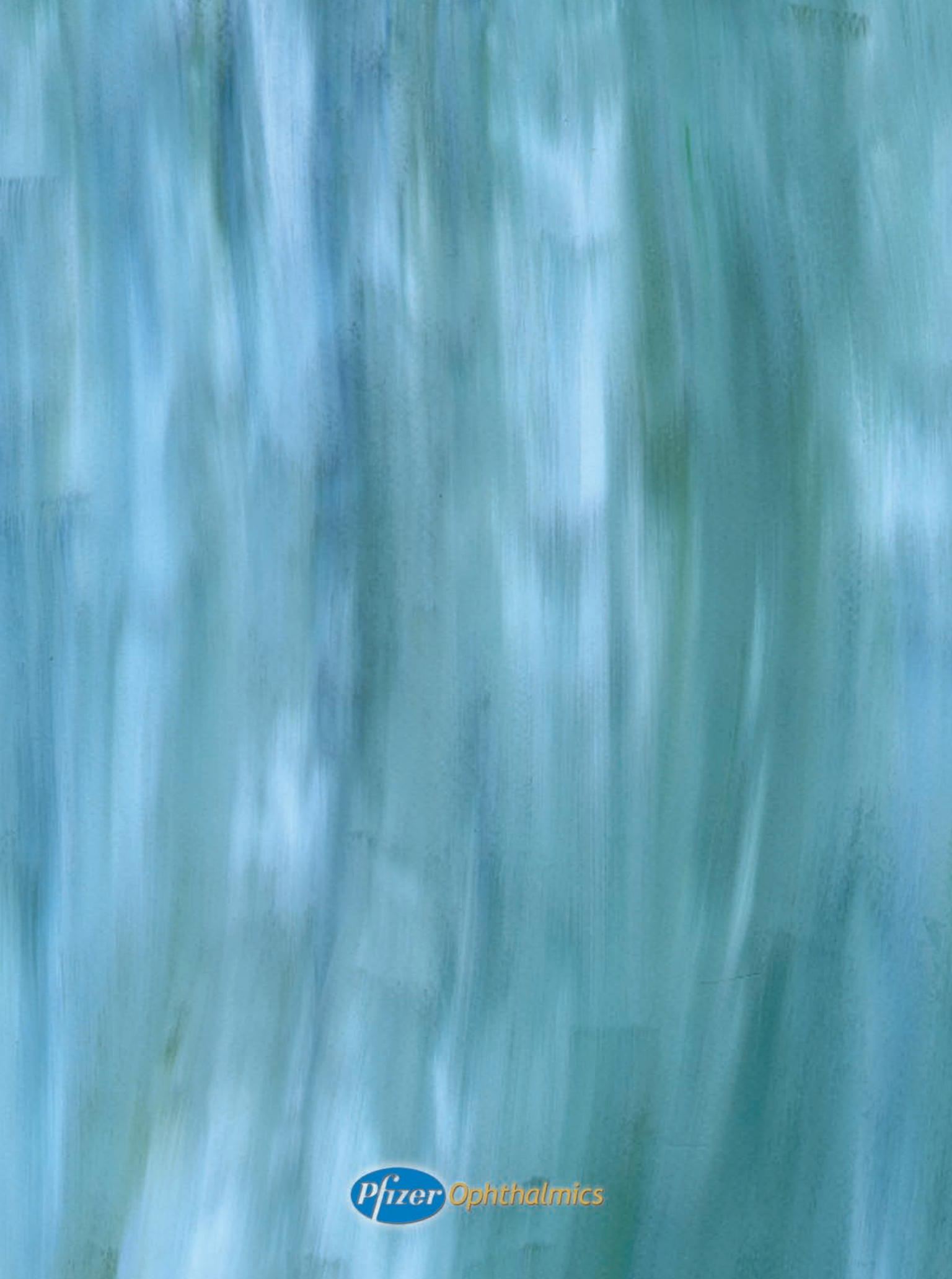
6. Aung T, Ang LP, Chan SP, Chew PT. Acute primary angle-closure glaucoma: long-term intraocular pressure outcome in Asian eyes. Am J Ophthalmol 2001;131:7-12.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